DIRECTED LITHIATION OF SUBSTITUTED BENZYLAMINES

THIS THESIS IS SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PhD)

By

AMANY SABER HEGAZY

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SCHOOL OF CHEMISTRY

CARDIFF UNIVERSITY

UNITED KINGDOM

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ProQuest LLC
789 East Eisenhower Parkway
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TO GAMAL, MAHMOUD AND NADA

DECLARATION

ABBREVIATIONS

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Et_2O	Diethyl ether
THF	Tetrahydrofuran
DCM	Dichloromethane
EtOAc	Ethyl acetate
DMF	*N,N*-Dimethylformamide
TEA	Triethylamine
DMA	Dimethylamine
MsCl	Methanesulfonyl chloride
TFAA	Trifluoroacetic anhydride
TFA	Trifluoroacetic acid
RLi	Alkyllithiums
n-BuLi	*n*-Butyllithium
t-BuLi	*tert*-Butyllithium
sec-BuLi	*sec*-Butyllithium
MeLi	Methyl lithium
LDA	Lithium diisopropyl amide
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	Deuteriated dimethylsulfoxide
$CDCl_3$	Deuteriated chloroform
^{1}H NMR	Proton nuclear magnetic resonance
^{13}C NMR	Carbon nuclear magnetic resonance
DEPT	Distortionless Enhancement by Polarization Transfer
COSY	Correlation Spectroscopy
NOE	Nuclear Overhauser effect
J	Coupling constants

δ	Chemical shifts
EI-MS	Electron impact - mass spectra
CI-MS	Chemical ionization - mass spectra
APCI-MS	Atmospheric pressure chemical ionization – mass spectra
ES	Electrospray - mass spectra
IR	Infra red
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

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SUMMARY

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CHAPTER ONE

Chapter one describes the practical consideration of lithiation reactions and preparation of organolithium reagents. It also provides reviews of directed lithiation of substituted aromatics and heterocycles.

CHAPTER TWO

Chapter two describes directed lithiation and substitution of various *N*-benzylpivalamides. Lithiation of *N*-benzylpivalamide with *t*-BuLi in THF at low temperature followed by reaction with benzophenone gave a mixture of *ortho*- and α-substitutions. Ring substitution could be achieved *via* bromine-lithium exchange of *N*-(2-bromobenzyl)pivalamide followed by reactions with electrophiles. Lithiation and substitution of 4-methoxy and 4-methyl derivatives with *t*-BuLi in THF gave *ortho*-substitution. By contrast, lithiation and substitution of the 2-methoxy derivative gave ring substitution, but next to the methoxy group rather than next to the pivaloylaminomethyl group. Under similar reaction conditions lithiation of *N*-(2-methylbenzyl)pivalamide followed by reactions with electrophiles, gave products substituted in the methyl group.

CHAPTER THREE

Chapter three describes lithiation and substitution of various substituted *N'*-benzyl-*N,N*-dimethylureas. Lithiation of unsubstituted, 4-methoxy and 4-methyl derivatives with *t*-BuLi at -78 °C in THF followed by reactions with electrophiles gave *ortho*-substitution. It was found that lithiation of the 2-methyl derivative under similar conditions gave products substituted in the methyl group. By contrast, lithiation and substitution of the 2-methoxy derivative with *t*-BuLi at -20 °C gave a mixture of *o'*- and *o*-substitutions.

CHAPTER FOUR

Chapter four describes cyclization reactions of *N*-(2-substituted benzyl)pivalamides and *N'*-(2-substituted benzyl)-*N,N*-dimethylureas with TFAA as a catalyst in DCM at RT, *via* dehydration from the OH and hydrogen from the NH, to give the corresponding isoindolines in excellent yields. The procedure has been proven to be simple, efficient and general.

CHAPTER FIVE

Chapter five describes cyclization reactions of *N'*-(2-substituted benzyl)-*N,N*-dimethylureas in DCM in the presence of TFAA to produce the corresponding dihydroisoquinolines in excellent yields. However, *N*-(2-(2-hydroxy-2-arylalkyl)benzyl)pivalamides are not cyclised under similar conditions. Instead, esterification of the hydroxyl group with TFAA or dehydration from the OH and a hydrogen from the CH_2 at position 2, takes place to give the corresponding derivatives in high yields.

CHAPTER SIX

Chapter six describes a lithiation procedure that allows the production of 3-substituted isoindolin-1-ones in high yields in only one step *via* lithiation of various substituted *N'*-benzyl-*N,N*-dimethylureas with *t*-BuLi (3.3 mole equivalents) in THF at 0 °C followed by reactions with various electrophiles. The procedure has been proven to be simple, efficient and general.

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CHAPTER ONE

DIRECTED LITHIATION OF AROMATIC COMPOUNDS

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DIRECTED LITHIATION OF AROMATIC COMPOUNDS

1.1 Introduction

Electrophilic aromatic substitution reactions are of great importance in the production of aromatic products, some of which are useful intermediates for the synthesis of valuable industrial, pharmaceutical, agrochemical and fine chemicals. However, most commercial applications still make use of methods developed many years ago, which commonly suffer serious disadvantages, including the requirement for mineral or Lewis acids as activators.[1] Unfortunately, the use of such activators creates a number of environmental problems. The activators may be required in more than stoichiometric amounts and the work-up procedure may lead to hydrolysis of activators and generation of large quantities of corrosive and toxic waste by-products. Moreover, these reactions often lead to mixtures of regioisomers with low selectivity.

In recent years, many efforts have been made to develop clean and environmentally friendly processes for the regioselective production of specific products. It is well recognised that organolithium reagents can play an important role in such cases. Many aromatic compounds undergo lithiation *ortho* to a functional group.[2-17] The organolithium reagents in such reactions are useful intermediates for the synthesis of *ortho*-disubstituted aromatics. Moreover, *ortho*-lithiation has been applied to more complicated heterocycles to produce derivatives that are difficult to prepare by other means.[18-21] This review of organolithium chemistry is not intended to be comprehensive, but rather to summarise the state of the art and provide references to more detailed reviews and primary literature.

1.2 Practical considerations

1.2.1 Choice of solvent

Solvents used in lithiation reactions should be easily purified and free from water and peroxides. They usually have low-enough freezing points that enable them to be used at low temperature without freezing taking place. Also they should not themselves react with organolithium reagents.[4]

Aliphatic hydrocarbons are inert, and easily purified and dried. The isomeric butyllithiums are commercially available in these solvents. However, aryllithiums, methyllithium and reagents such as lithium diisopropylamide (LDA) are insoluble in

aliphatic hydrocarbons in the absence of electron-donating ligands.[4] Aromatic hydrocarbons are also easily purified and dried, but toluene is relatively easily lithiated, and benzene is dangerously toxic and cannot be used at low temperatures because it has a high freezing point (5.5 °C). Therefore ethers are the most commonly used solvents for organolithium reactions. Diethyl ether (Et_2O) is probably the most commonly used solvent for lithiation reactions. It is easily purified and dried, it has an appropriate boiling point and a low enough freezing point. Moreover, most lithium reagents are soluble in diethyl ether and do not cleave the ether too rapidly.

When a more strongly Lewis-basic solvent is required, tetrahydrofuran (THF) is the most widely used alternative to diethyl ether. It does, however, suffer from some disadvantages. It is much more readily attacked by organolithium reagents than diethyl ether; its freezing point is only just above the temperature of evaporating solid carbon dioxide. It is much less easily dried, and more hygroscopic than diethyl ether.

Mixed solvents systems are also the key to working at very low temperatures where it is important not only that the reaction medium should remain liquid, but also its viscosity should remain low. A particularly useful combination is the "Trapp mixture", comprising THF/Et_2O/pentane (or hexane or light petroleum) in a 4/4/1 ratio, which can be used at very low temperatures.[4]

1.2.2 Reactions at low temperatures

Reactions of organolithium reagents are often carried out at low temperatures. In particular it is often stated that a reaction is carried out at -78 °C, the temperature of a solid carbon dioxide-acetone cooling bath. For alternative low temperatures, convenient cooling baths include solvents cooled to slush by stirring with liquid nitrogen. Some examples are listed in Table 1.1.[4]

Table 1.1: Solvents for cooling slush baths

Solvent	Temperature of slush bath (°C)
Tetrachloromethane	-23
Chlorobenzene	-45
Chloroform	-63
Ethyl acetate	-84
Hexane	-94
Methanol	-98
Methylcyclohexane	-126
Pentane	-131

1.2.3 Inert atmospheres

Organolithium reagents are sensitive to moisture in the air. For most preparative applications involving organolithium reagents, a sufficient degree of protection is achieved simply by maintaining a slight positive pressure of an inert gas (nitrogen or argon) over the reaction mixture.

1.2.4 Estimation of organolithium reagents

The best established methods for estimating organolithium reagents in the presence of lithium hydroxide or alkoxides are the Watson[22] and Gilman[23] double titration methods. In these methods, total base is first determined. An aliquot of the test solution is treated with an organic halide of sufficient reactivity to convert the organolithium compound into non-basic lithium halide while leaving any hydroxide or alkoxides unchanged for a second titration. Gilman originally used benzyl chloride, but 1,2-dichloroethane and allyl bromide have been reported to be more generally satisfactory.[23]

1.3 Preparation of organolithium compounds

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. Phenyllithium and methyllithium are highly stable in ethers at room temperature. A list of the most common commercially available organolithium reagents is showed in Table 1.2.

Table 1.2: The most common commercially available organolithium reagents[a]

Organolithium reagent	Solvent	Concentration (M)
n-Butyllithium	Hexanes	1.6, 2.5 and 10.0
	Cyclohexane	2.0
	Pentane	2.0
tert-Butyllithium	Pentane	1.5 and 1.7
sec-Butyllithium	Cyclohexane	1.3
Methyllithium	Diethyl ether	1.4
	Cumene/tetrahydrofuran	1.0
Phenyllithium	Cyclohexane/diethyl ether	1.8

[a] Available from Sigma-Aldrich Chemical Company. Also, some of such reagents are available from Fluka and Alfa Aesar.

Most organolithium compounds exist as clusters both in the solid state and in solution in most solvents. The tendency to aggregate is common for alkylithiums. The aggregates are held together by delocalised covalent bonds between lithium and the terminal carbon of the alkyl chain.[17] In hydrocarbon solvents lithium reagents aggregate to stabilise the electron deficient lithium atom and exist as dimmers, tetramers and hexamers. The state of aggregation was found to be dependent on steric hindrance in organolithiums, so that increasing bulkiness of the organic group in organolithiums tends to decrease the aggregation state.[4,17] Ether solvents such as diethyl ether or THF can provide an alternative electron density source for the lithium atoms.[8] For example, *t*-BuLi is tetrameric in pentane, but becomes, at low temperature, dimeric in diethyl ether and monomeric in THF. Also, a coordinating solvent such as THF, 1,2-dimethoxyethane (DME) or *N,N,N',N'*-tetramethylethylenediamine (TMEDA) increases the reactivity of the organolithium reagents by lowing its aggregation state. The aggregation states for the most common organolithium reagents in different solvents are shown in Table 1.3.[8]

Table 1.3: Aggregation sates for the most common commercially available organolithium reagents

Aggregation state in hydrocarbons		**Aggregation state in Et_2O or THF**		
Hexameric	Tetrameric	Tetrameric	Dimeric	Monomeric
n-BuLi	*sec*-BuLi *t*-BuLi	*n*-BuLi MeLi	*sec*-BuLi *t*-BuLi PhLi	*t*-BuLi[a] PhLi[a]

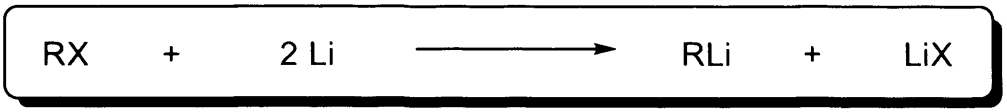
[a] At low temperatures (less than -100 °C).

The majority of organolithiums are prepared by the reaction of organic halides with lithium metal, although halogen-lithium exchange and lithiation methods are also used.

1.3.1 By reaction with lithium metal

Commercially available organolithium reagents are usually produced by reductive lithiation of organic halides with lithium metal (Equation 1.1) at room temperature or above.[4] However, such methods suffer serious disadvantages. For example, the organolithium produced (RLi) could react with alkyl halide (RX) to

produce a coupled product (R-R). Also, problems could arise from the use of lithium metal at the required temperatures.



Equation 1.1

Alkyl chlorides are the best among alkyl halides in reductive lithiation reactions; rate of coupling is fast in the case of alkyl iodides and bromides, but their reductions are also fast.[8]

It should be noted that to obtain a high yield of organolithium compound using this method the following points must be taken into consideration.[4] **Firstly**, the lithium used should be finely divided and free from mineral oil. **Secondly**, the presence of 1-3% of sodium in lithium could increase its reactivity towards alkyl halide (RX) by aiding initiation without significantly affecting the yield or properties of the product (RLi). However, higher concentrations of sodium may lead to low product yields through formation of coupling products (R-R; *via* Wurtz coupling). **Thirdly**, the organic halide should be added slowly with efficient stirring to minimise the formation of coupling product. Table 1.4 shows examples of organolithiums that are routinely prepared using this approach.[4]

Table 1.4: Preparation of organolithiums from reaction of organic halides with lithium metal

Organolithium	Organic halide	Solvent	Yield (%)
n-BuLi	*n*-BuCl	Pentane	93-98
t-BuLi	*t*-BuCl	Pentane	80
MeLi	MeCl	Diethyl ether	70-89
	MeI	Diethyl ether	82
PhLi	PhBr	Diethyl ether	95-99

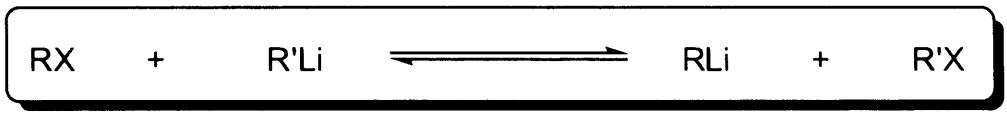
1.3.2 By reaction with lithium salts of radical anions

The reactions of organic halides with lithium metal, leading to organolithium compounds, almost certainly involves electron transfer,[24] so it is not unexpected that under appropriate conditions electron transfer from a radical anion to an organic halide, with lithium as a counter ion, may also give organolithium compounds. With lithium naphthalene yields are variable, but can be high with aryl chlorides.[25] With

lithium 4,4'-di-*tert*-butylbiphenyl excellent yields are reported in several cases,[26] and this reagent gives some organolithiums that are unobtainable by other methods.[27]

1.3.3 By halogen-lithium exchange

The general halogen-lithium exchange reaction (Equation 1.2) has features that make it extremely valuable for preparing organolithium compounds.



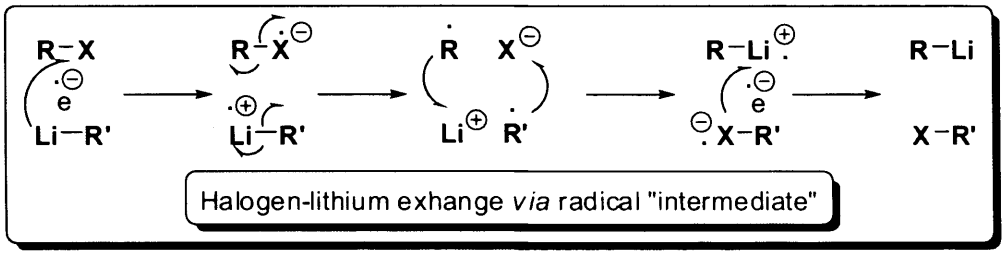
Equation 1.2

The equilibrium lies towards the side having the organolithium compound with the organic group better able to accommodate partial carbanionic character, and it is thus particularly useful for preparing aryllithium compounds by reaction of butyllithium with aryl halides. With iodo and bromo compounds the reaction is general and often proceeds remarkably rapidly even at low temperatures.[4] The reaction is less satisfactory with chloro compounds and does not takes place at all with fluoro derivatives. The solvent used in such processes is normally an ether, though it does take place in hydrocarbon solvents, but more slowly.[4]

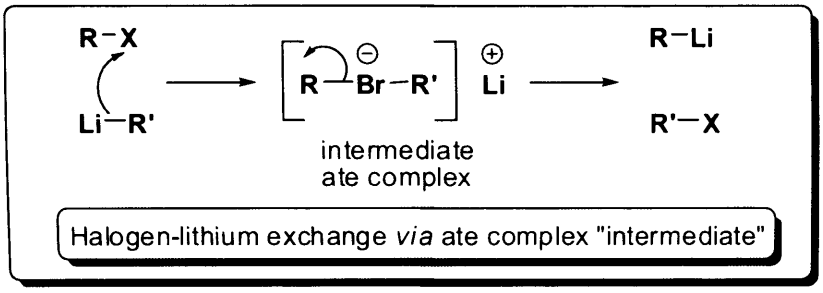
Because halogen-lithium exchange takes place rapidly under mild conditions, potential side-products such as alkylation of the organolithium by the organic halide are not usually troublesome. However, when the desired organolithium reagent is warmed for subsequent reaction it can couple with the alkyl halide, producing a coupled product (R-R').[4] If alkylation is a problem, it can be minimised by use of two mole equivalents of *t*-BuLi. In this case, halogen-lithium exchange is achieved by the first mole equivalent and the second reacts with the *t*-BuX formed to produce isobutane and isobutene.

Halogen-metal exchange processes may involve single electron transfer processes and radical intermediates (Equation 1.3) or proceed through ate complex formation (Equation 1.2) *via* nucleophilic substitution at the halogen.[8] It is believed that alkyl bromides react with alkyllithiums *via* the radical mechanism, while aryl bromides and aryl iodides react *via* ate complexes as intermediates.[8,28] Also, primary

alkyl iodides react *via* a polar mechanism and secondary alkyl iodides react *via* both polar and radical mechanisms.[8,28]



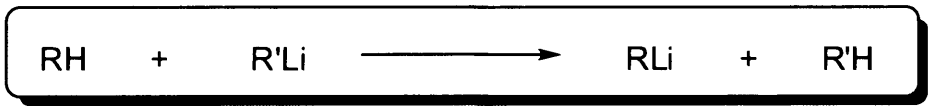
Equation 1.3



Equation 1.4

1.3.4 By lithiation

The replacement of hydrogen by lithium in an organic compound (Equation 1.5) is perhaps the most versatile method for preparing organolithium compounds.[4]



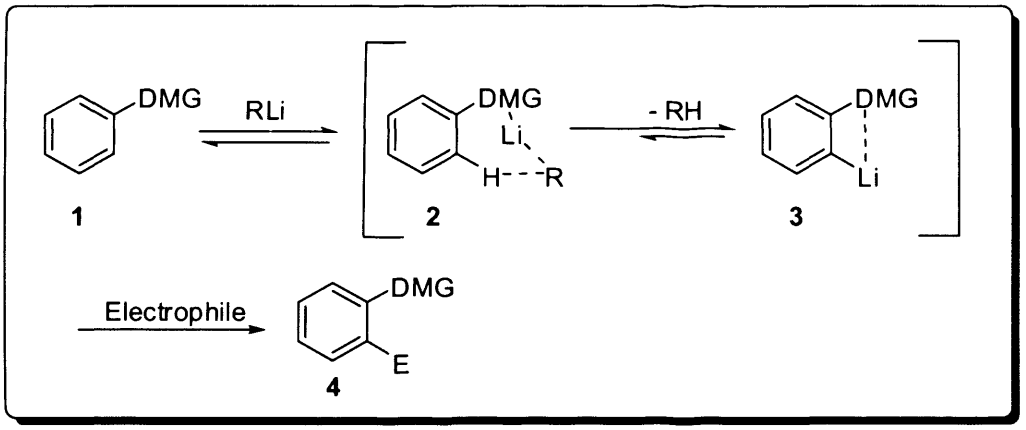
Equation 1.5

The simplest lithiations (deprotonations) are those of relatively acidic hydrocarbons (pKa ≤ *ca.* 33) such as 1-alkynes and triarylmethanes. However, other compounds whose acidities are much lower are also readily lithiated.[4] This happens when activation takes place by the presence of an α- or β-heteroatom that increases the thermodynamic and/or kinetic acidity of a particular hydrogen atom. This type of activation is very useful for the introduction of a substituent *ortho* to an existing functional group (directed ring lithiation) or on an *ortho*-methyl or methylene group (lateral lithiation).[4,8] Directed lithiation of aromatic and heterocycles is discussed in detail in Section 1.4.

1.4 Directed lithiation of aromatic compounds

Regioselective synthesis of *ortho*-disubstituted aromatics is one of the classical problems in synthetic chemistry. Simple electrophilic substitution usually takes place under forcing conditions in the presence of a catalyst and often leads to various isomers and polysubstituted aromatics. A number of alternative approaches have therefore been developed for regioselective *ortho*-disubstitution, and *ortho*-metalation followed by electrophilic substitution is one of the most recognised and efficient.

Directed lithiation of aromatic compounds **1** comprises deprotonation of a site *ortho* to a substituent that possesses a heteroatom (oxygen, nitrogen or sulfur) by use of a base. Such a substituent is known as a directing metallation group (DMG). The base, normally an alkyllithium reagent, leads to an *ortho*-lithiated species **3** (Scheme 1.1). Treatment of **3** with electrophilic reagents produces *ortho*-disubstituted products **4**.[2-21] Apparently, complexation occurs between the substituent group (DMG) and the lithium reagent prior to lithiation to give **2**, and this serves to bring the lithiating agent into closer proximity with the *ortho* proton, which is then selectively removed.[29]



Scheme 1.1

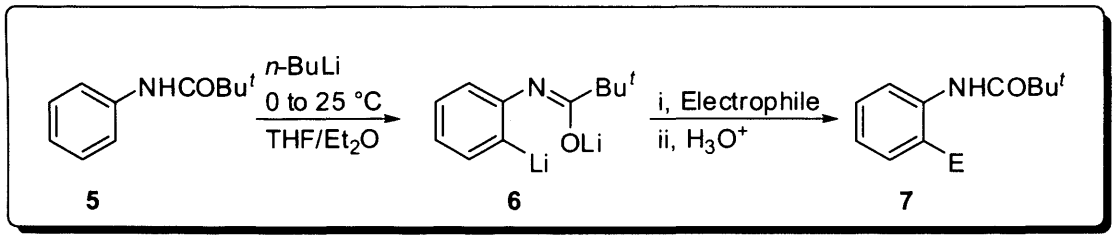
For a successful deprotonation to occur, the DMG must possess the somewhat contrary properties of being a good coordinating site for the lithium reagent and a poor electrophilic site for attack by the lithium reagent. The rate and regioselectivity of *ortho*-lithiation seems to be controlled not only by coordination between the lithium reagent and the heteroatom of the DMG but also by the acidity of the proton at the *ortho*-position. It is not clear which factor has the driving force in *ortho*-lithiation.

However, both of them could play a role for lithiation to be successful. For example, strong activators (DMG) tend to have a mixture of the basic requirements for good coordination to lithium reagent and the electron-withdrawing properties required to cause the *ortho*-protons to become acidic enough to encourage deprotonation efficiently and rapidly.[8]

Groups that encourage such *ortho*-lithiation include: strong activators, SO_2NR_2, NHCOR, $CONR_2$, CSNHR, CONHR, $OCONR_2$, CO_2R, CH_2NHR, OCH_2OMe; moderate activators, OR, NR_2, SR, CF_3, F; and weak activators, CH_2OH, $CH(OR)_2$. The rapid expansion of the list of functionalities capable of directing lithiation has made this approach an important strategy for the synthesis of various regiospecifically substituted benzenes and heterocycles.[30-36]

1.4.1 Directed lithiation of benzene derivatives

Directed lithiation of benzene systems, containing a range of DMGs (*e.g.* $NHCOBu^t$, $NHCO_2Bu^t$, $NHCONMe_2$, CONHR, $CONR_2$, $OCONEt_2$, CH_2NR_2, $CH_2NHCOBu^t$, $CH_2NHCO_2Bu^t$, $CH_2NHCONMe_2$, OMe, SH, CF_3, F, 1*H*-tetrazol-5-yl, *O*-tetrahydropyranyl), with various lithium reagents to produce the corresponding disubstituted benzenes *via* lithium intermediates has been investigated.[37-39] For example, *N*-pivaloylaniline (**5**) has been doubly lithiated, on nitrogen and on the carbon at position 2, with two equivalents of *n*-BuLi at 0 to 25 °C in a THF/Et_2O mixture for 20 h. The *ortho*-dilithiated intermediate **6** thus obtained has been reacted with electrophiles to give the corresponding 2-substituted derivatives **7** (Scheme 1.2) in yields of 53-78%.[37]

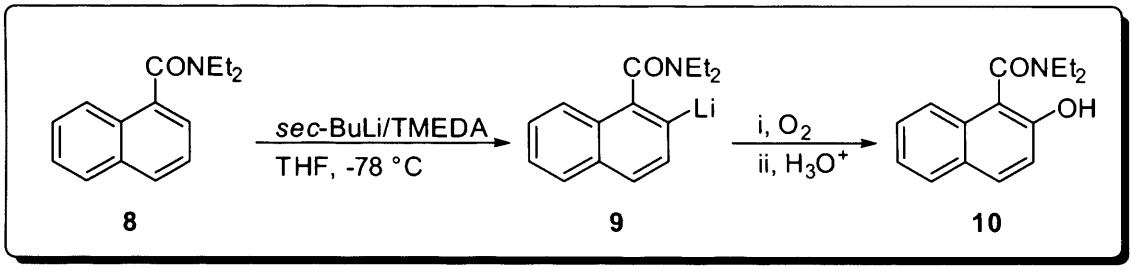


Scheme 1.2

1.4.2 Directed lithiation of naphthalene derivatives

Directed lithiation of naphthalene containing DMGs has received limited attention compared to benzene derivatives. Most of the work reported involves

lithiation of *N,N*-diethyl-1-naphthamide and *N,N*-diethyl-2-naphthamide.[40-43] For example, *N,N*-diethyl-1-naphthamide (**8**) has been lithiated with *sec*-BuLi in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) at -78 °C in THF. The lithium intermediate **9** thus obtained has been reacted with oxygen to give 2-hydroxy-*N,N*-diethyl-1-naphthamides (**10**; Scheme 1.3).[40]



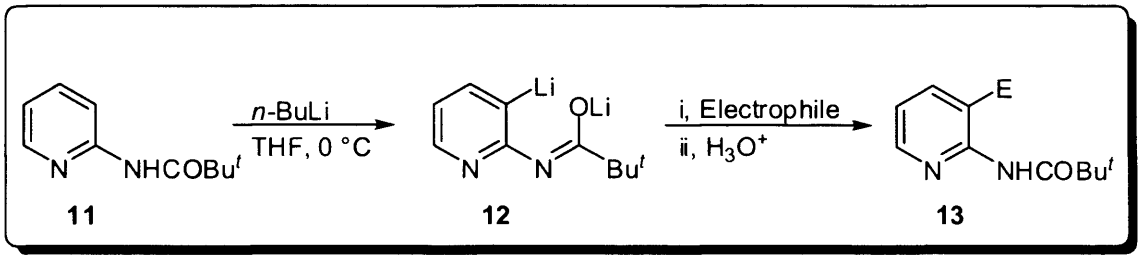
Scheme 1.3

1.4.3 Directed lithiation of heterocycles

The chemistry of heterocyclic compounds is extremely important for the synthesis of valuable bioorganic and pharmaceutical compounds. Lithiation is an important strategy for *ortho*-functionalization of pyridines, quinolines and diazines.[44,45] Unfortunately, in some cases such lithiation reactions with alkyllithiums suffer from nucleophilic addition of the lithium reagent to the azomethine (C=N) bond of azines, even at low temperatures. However, most reactions become completely chemoselective for lithiation by use of less nucleophilic lithium reagents such as LDA and lithium 2,2,6,6-tetramethylpiperidide (LTMP).

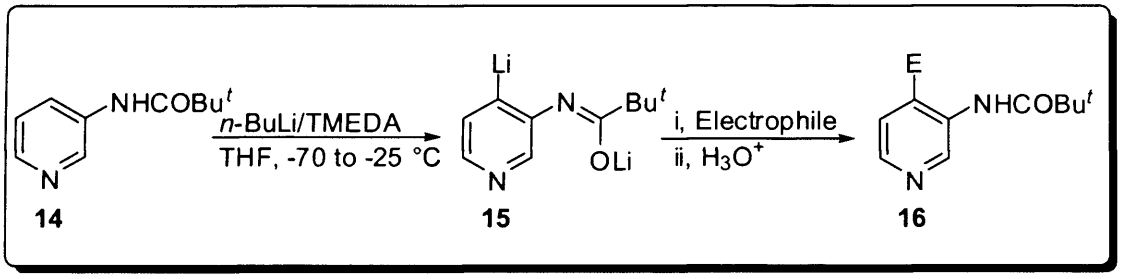
1.4.3.1 Directed lithiation of pyridines

Directed lithiation of pyridines, containing various DMGs (*e.g.* NHCOBu^t, CONHPh, $CONR_2$, SOBu^t, SOAr, CO_2H, OCH_2OEt, OMe, CF_3, F, Cl) at the C-2 position, with various lithium reagents invariably takes place at C-3 to give the corresponding 3-substituted derivatives after reactions of the lithium reagents produced with electrophiles.[46-49] For example, 2-(pivaloylamino)pyridine (**11**) has been lithiated, on nitrogen and on the carbon at position 3, with *n*-BuLi (2 equivalents) in THF at 0 °C. The dilithium reagent **12** thus obtained reacted with a range of electrophiles to give 3-substituted 2-(pivaloylamino)pyridines **13** (Scheme 1.4).[46,47]



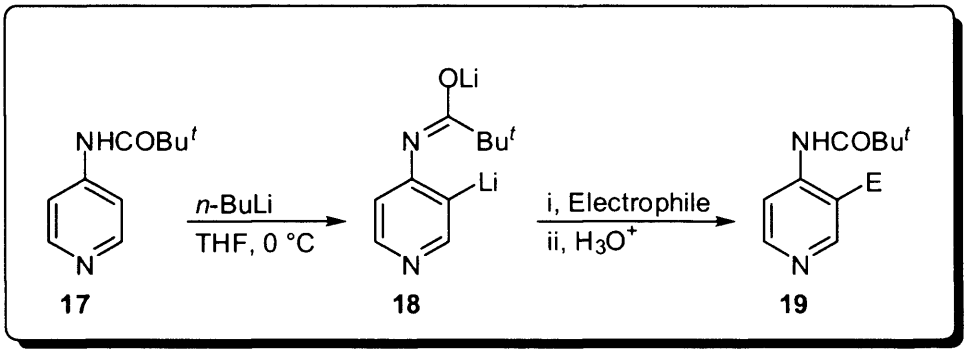
Scheme 1.4

Directed lithiation of pyridines, 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.[50-54] For example, 3-(pivaloylamino)pyridine (**14**) has been lithiated, on nitrogen and on the carbon at position 4, with *n*-BuLi (2 equivalents) in THF at -70 to -25 °C and in the presence of TMEDA. The dilithium reagent **15** thus formed reacted with various electrophiles to give the corresponding 4-substituted 3-(pivaloylamino)pyridines **16** (Scheme 1.5).[50-52]



Scheme 1.5

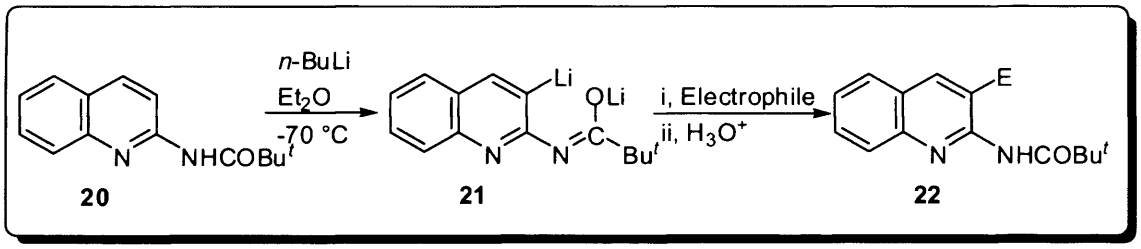
Similarly, directed lithiation of pyridines, containing a DMG (*e.g.* $NHCOBu^t$, $CONR_2$, CONHPh, CO_2H, $CH(OEt)_2$, OMe, Cl) at C-4, takes place at C-3 with various lithium reagents.[46,55-57] For example, 4-(pivaloylamino)pyridine (**17**) has been lithiated, on nitrogen and on the carbon at position 3, with *n*-BuLi in THF at 0 °C. The dilithium reagent **18** obtained reacted with various electrophiles to give the corresponding 3-substituted 4-(pivaloylamino)pyridines **19** (Scheme 1.6).[46,55]



Scheme 1.6

1.4.3.2 Directed lithiation of quinolines

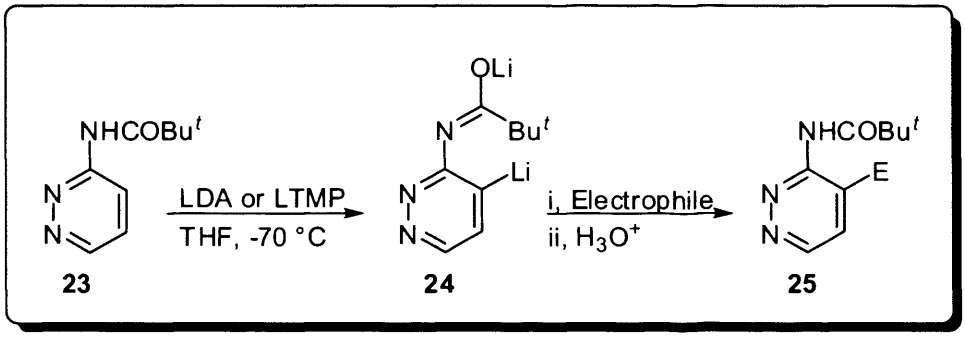
Directed lithiation of quinolines, containing various DMGs (*e.g.* NHCOBu^t, $OCONEt_2$, CO_2H, OR, Cl) at the C-2 position, has been achieved by the use of *n*-BuLi or less nucleophilic lithium reagents (*e.g.* LDA) at low temperatures.[58-60] For example, *ortho*-lithiation of 2-pivaloylaminoquinoline (**20**) has been achieved by use of *n*-BuLi in dry Et_2O at low temperature to give the lithium reagent **21**. Reactions of **21** with various electrophiles afforded the corresponding 3-substituted 2-pivaloylaminoquinolines **22** (Scheme 1.7) in moderate to very good yields.[58]



Scheme 1.7

1.4.3.3 Directed lithiation of pyridazines

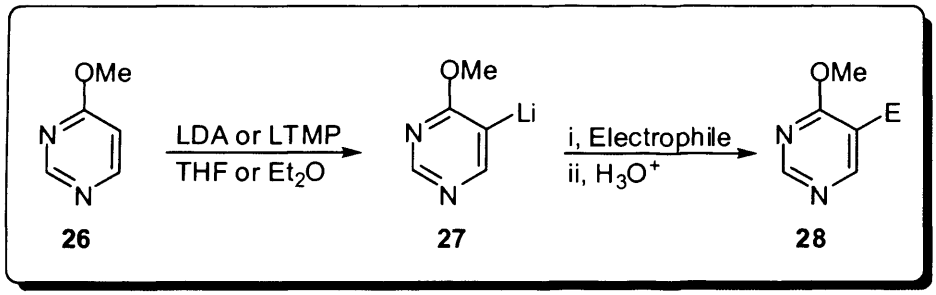
Directed lithiation of pyridazines, containing various DMGs (*e.g.* SO_2NHBu^t, NHCOBu^t, OMe, OCH_2CH_2OMe, Cl) at the C-3 position, has been successfully achieved with less nucleophilic lithium reagents such as LDA and LTMP.[61-63] For example 3-(pivaloylamino)pyridazine (**23**) has been doubly lithiated, on nitrogen and on the carbon at position 4, with LDA or LTMP in THF at -70 °C. The dilithium reagent **24** obtained reacted with various electrophiles to give the corresponding 4-substituted 3-(pivaloylamino)pyridazines **25** (Scheme 1.8).[61]



Scheme 1.8

1.4.3.4 Directed lithiation of pyrimidines

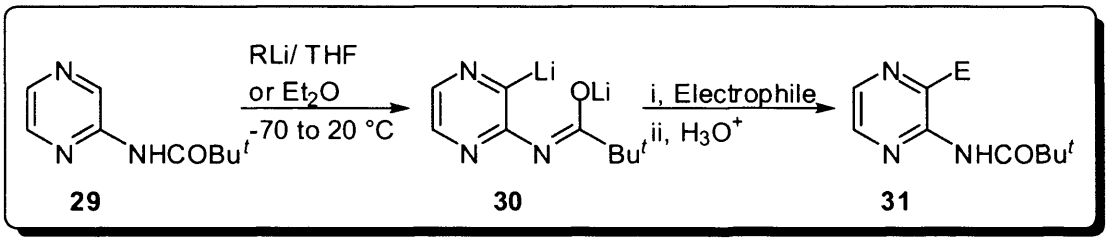
Directed lithiation of pyrimidines, containing a DMG (*e.g.* OMe, F, Cl) at the C-4 position, mainly takes place at C-5 to give the corresponding lithium intermediates, which on reactions with electrophiles produce 4,5-disubstituted pyrimidines.[64-68] For example, lithiation of 4-methoxypyrimidine (**26**) with LDA or LTMP in THF or Et_2O at 0 or -78 °C gave the 5-lithio derivative **27** which reacted with electrophiles to give the corresponding 5-substituted 4-methoxypyrimidines **28** (Scheme 1.9).[64-66]



Scheme 1.9

1.4.3.5 Directed lithiation of pyrazines

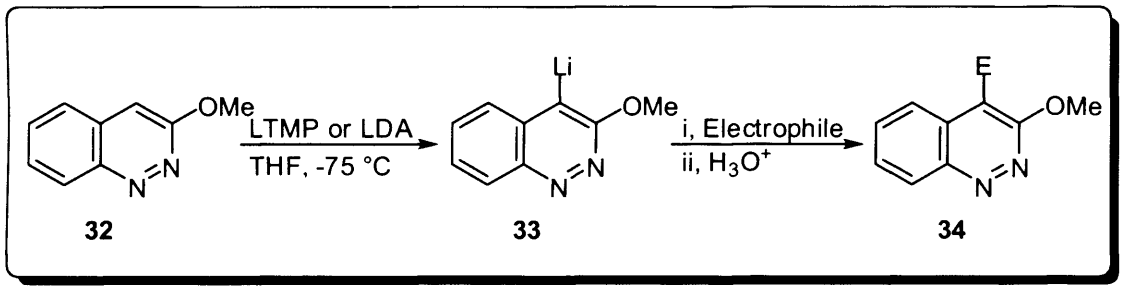
Directed lithiation of pyrazines, containing a DMG (*e.g.* NHCOBu^t, SO_2Bu^t, SO_2Ph, OMe, SR, F, Cl, I) at the C-2 position, invariably takes place at C-3.[69,70] For example, 2-(pivaloylamino)pyrazine (**29**) has been doubly lithiated by the use of alkyllithiums (*n*-BuLi or *t*-BuLi) in THF or Et_2O at -70 to 20 °C. Reactions of the dilithium reagent **30** thus formed with electrophiles produced the corresponding 3-substituted 2-(pivaloylamino)pyrazines **31** (Scheme 1.10).[69]



Scheme 1.10

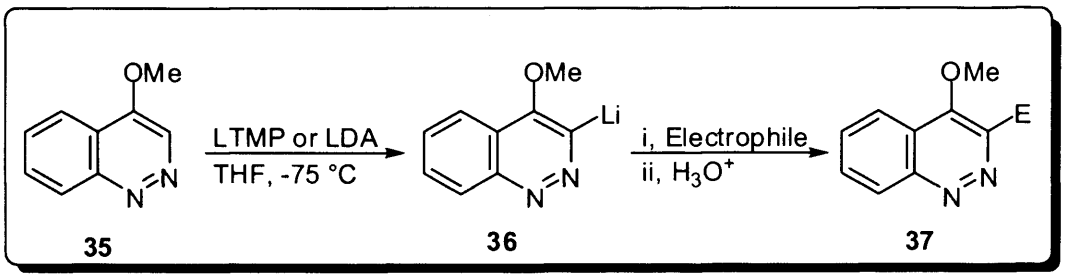
1.4.3.6 Directed lithiation of cinnolines

3-Substituted cinnolines have been lithiated with LTMP or LDA in THF at low temperature at C-4. For example, 3-methoxycinnoline (**32**) has been lithiated at C-4 by use of LTMP or LDA in THF at -75 °C to give the lithium reagent **33** which reacted with various electrophiles to give the corresponding 4-substituted 3-methoxycinnolines **34** (Scheme 1.11).[71]



Scheme 1.11

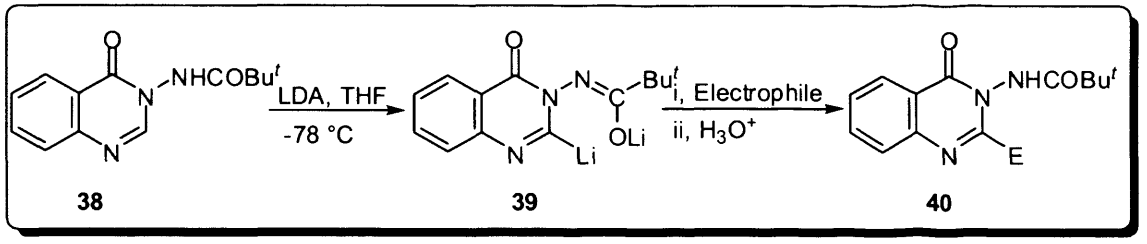
Similarly, the 4-substituted analogues have been lithiated at C-3. For example, 4-methoxycinnoline (**35**) has been lithiated at C-3 by use of LTMP or LDA in THF at -75 °C to give the lithium reagent **36** which reacted with electrophiles to give the corresponding 3-substituted 4-methoxycinnolines **37** (Scheme 1.12).[71]



Scheme 1.12

1.4.3.7 Directed lithiation of quinazolines

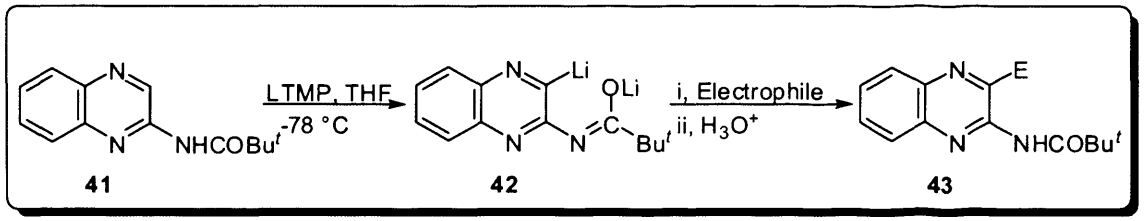
Regioselective lithiation of various quinazoline derivatives has been investigated.[72-81] For example, directed lithiation of 3-pivaloylamino-4(3*H*)-quinazolinone (**38**) was achieved by the use of LDA in THF at –78 °C to give the dilithium intermediate **39**. Reactions of **39** with various electrophiles afforded the corresponding 2-substituted 3-pivaloylamino-4(3*H*)-quinazolinones **40** (Scheme 1.13) in very good yields.[72]



Scheme 1.13

1.4.3.8 Directed lithiation of quinoxalines

Lithiation of various quinoxaline derivatives has been investigated.[82-84] For example, directed lithiation of 2-(pivaloylamino)quinoxaline (**41**) was achieved by the use of LTMP in THF at -78 °C to produce the dilithium reagent **42**.[84] Reactions of the dilithium reagent **42** thus obtained with electrophiles produced the corresponding 3-substituted 2-(pivaloylamino)quinoxalines **43** (Scheme 1.14) in modest yields.[84]



Scheme 1.14

1.5. Conclusion

Directed lithiation offers approaches to *ortho*-disubstituted aromatic products. Directed lithiation of aromatic compounds by lithium reagents at low temperatures and reactions of the lithium reagents thus obtained with electrophiles is useful for the production of *ortho*-disubstituted derivatives. The process has been applied to various aromatics and heterocycles to produce the corresponding *ortho*-disubstituted derivatives that might be difficult to prepare by other means.

CHAPTER TWO

INVESTIGATION OF THE INFLUENCES OF SUBSTITUENTS ON THE LITHIATION SITES OF VARIOUS *N*-BENZYLPIVALAMIDES

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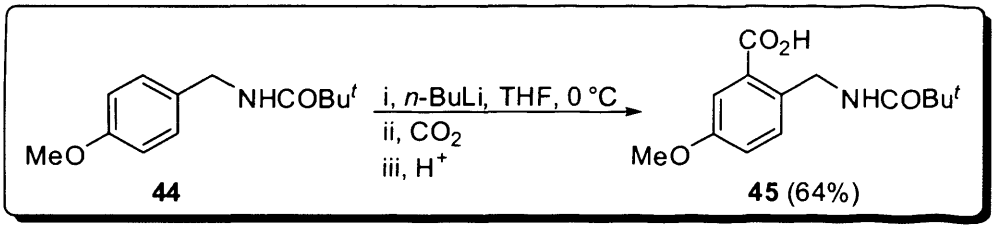
2.1 Introduction

Regioselective synthesis of substituted aromatics is one of the classical problems in synthetic chemistry. Simple electrophilic substitution often leads to various isomers and polysubstituted aromatics and may take place under forcing conditions in the presence of a catalyst. Lithiation of aromatics followed by electrophilic substitution is one of the most efficient approaches for synthesis of substituted and/or modified derivatives.[4-11]

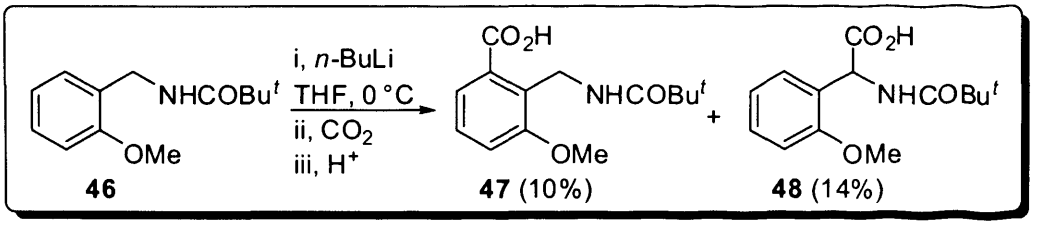
Schlosser has shown that *N*-(4-methoxybenzyl)pivalamide (**44**) undergoes selective lithiation *ortho* to the pivaloylaminomethyl group when treated with *n*-BuLi in anhydrous THF at 0 °C.[85] Reaction of the lithium reagent obtained with carbon dioxide produced the corresponding acid **45** in 64% yield (Scheme 2.1).[85]



44 **45** (64%)

Scheme 2.1

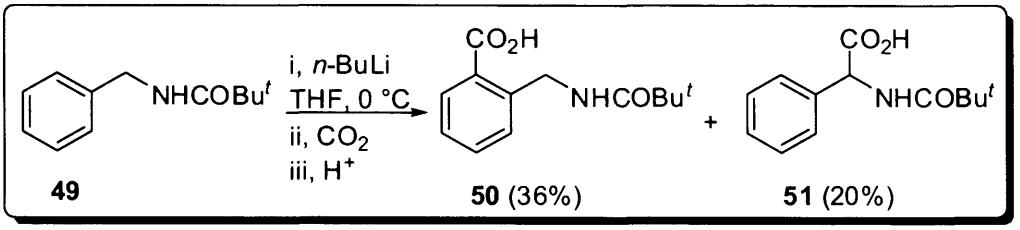
By contrast, *N*-(2-methoxybenzyl)pivalamide (**46**) under similar reaction conditions gave a mixture of two products, one of which involved carboxylation *ortho-* to the pivaloylaminomethyl group (**47**; isolated in 10% yield by fractional crystallization), and the other of which involved carboxylation at the side-chain (**48**; isolated in 14% yield as the methyl ester following treatment of the residue with diazomethane; Scheme 2.2).[85]



46 **47** (10%) **48** (14%)

Scheme 2.2

Similarly, treatment of *N*-benzylpivalamide (**49**) in the same way gave a mixture of two substituted products **50** (*o*-substitution; isolated in 36% yield by fractional crystallization), and **51** (α-substitution; isolated in 20% yield as the methyl ester following treatment of the residue with diazomethane; Scheme 2.3).[85]



Scheme 2.3

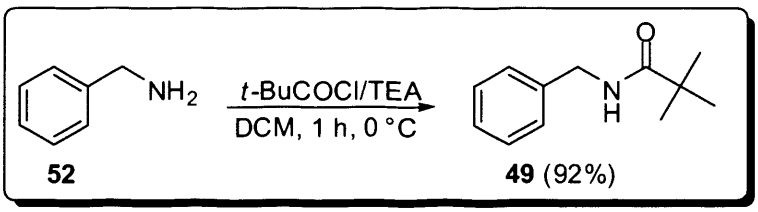
The poor regioselectivity and low yields achieved in the latter reactions render the process unattractive as a synthetic method. However, it was not clear whether the lithiation reaction would proceed in the same way under different reaction conditions (*e.g.* different lithium reagents, reaction temperatures or times) or using electrophiles other than carbon dioxide. These interesting changes in the directing effects of the substituents suggested that further studies on directed lithiation of *N*-(substituted benzyl)pivalamides would be worthwhile.

We therefore decided to investigate lithiation of various *N*-(substituted benzyl)pivalamides to see if the lack of selectivity in such lithiation reactions could be overcome and to examine their scope of applicability and generality. We have selected *N*-benzylpivalamides carrying bromo, methoxy and methyl substituents, as well as the unsubstituted case, as substrates. As shown by Schlosser, unsubstituted *N*-benzylpivalamide could be lithiated at the α-position (on the CH_2) and *o*-position (*ortho* to amidomethyl side chain). In the case of methoxy derivatives, three sites compete for lithiation: α-position (on the CH_2), the *o*-position (*ortho* to amidomethyl side chain) and *o'*-position (*ortho* to methoxy group). In the case of methyl derivatives, four sites compete for lithiation: α-position (on the CH_2), the *o*-position (*ortho* to amidomethyl side chain), on the methyl group itself and *o'*-position (*ortho* to the methyl group), although the last one is unlikely. Therefore, the aim of the work represented in this chapter was to synthesise *N*-(substituted benzyl)pivalamides and investigate their lithiation reactions, to enable convenient syntheses of the corresponding substituted derivatives.

The results, which we now report in this chapter, show consistency with the earlier results reported by Schlosser when *n*-BuLi was used as the lithium reagent at 0 °C.[85] However, variation in the site of lithiation was observed in the case of *N*-(2-methoxybenzyl)pivalamide (**46**) when *t*-BuLi was used at -78 °C. As a result, we have been able to establish conditions for a high-yielding and general ring-substitution, but at the position *ortho*- to the methoxy group rather than *ortho*- to the pivaloylaminomethyl group for this substrate. Lithiation at this site was not reported at all by Simig and Schlosser under their conditions.[85] Also, we found that lithiation of *N*-(4-methylbenzyl)pivalamide takes place smoothly *ortho*- to the pivaloylaminomethyl group, while, lithiation of *N*-(2-methylbenzyl)pivalamide takes place on the methyl group at the 2-position.

2.2 Synthesis of *N*-benzylpivalamide (49)

The first task was to synthesise *N*-benzylpivalamide (**49**) and investigate its lithiation reactions under various reaction conditions. *N*-Benzylpivalamide (**49**) was prepared according to a literature procedure.[86] Reaction with pivaloyl chloride with benzylamine (**52**) in dichloromethane (DCM) and in the presence of triethylamine (TEA) at 0 °C gave **49** in 92% yield after crystallization (Scheme 2.4). The structure of compound **49** was confirmed by various spectroscopic techniques (see Chapter 7; Section 7.2).

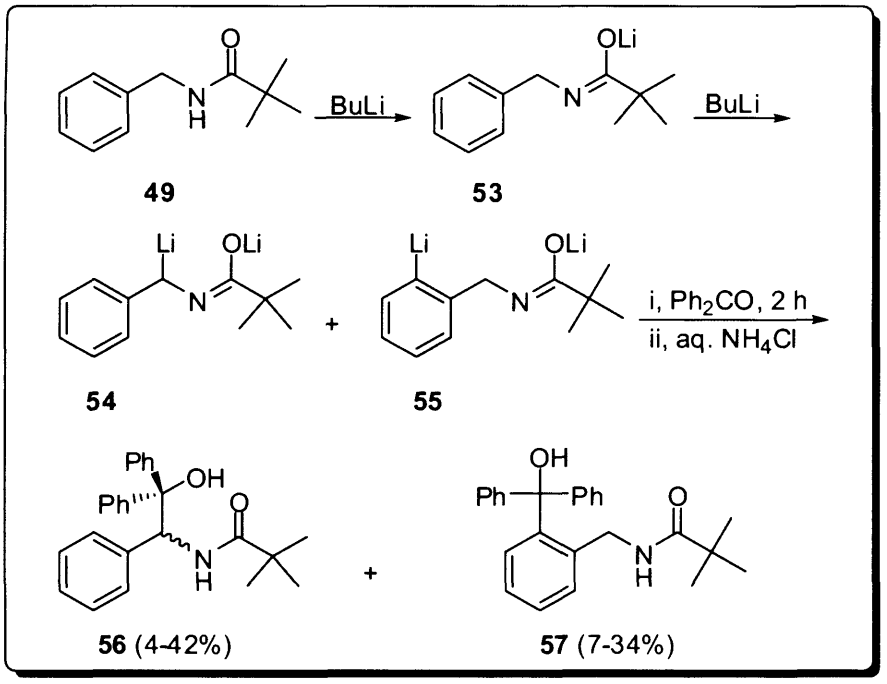


Scheme 2.4

2.3 Lithiation of *N*-benzylpivalamide (49)

Double lithiation of *N*-benzylpivalamide (**49**) has been previously reported (Scheme 2.3).[85] However, the lithiation was not selective, giving a mixture of *o*- and α-lithiation. Therefore, double lithiation of compound **49** was investigated under various reaction conditions in order to see the effect of those conditions on the reaction selectivity and yields of products.

Initially the reaction of **49** with *n*-BuLi (2.2 mole equivalents) was carried out in anhydrous THF under a nitrogen atmosphere at –78 °C. Initial addition of *n*-BuLi provided a yellow solution, presumably because of formation of the monolithium reagent **53**, until approximately one equivalent had been added, then gave a brownish solution as the remaining *n*-BuLi was added, presumably because of formation of the dilithium reagent. The mixture was stirred for 4 h at –78 °C. Benzophenone (1.1 mole equivalents) was added as a solution in anhydrous THF and the mixture was stirred for another 2 h (Scheme 2.5) at –78 °C. The reaction mixture was allowed to warm to room temperature and quenched by addition of saturated aqueous NH_4Cl solution. The product mixture was examined by TLC and showed the formation of two minor new products, along with the starting material **49** and benzophenone, which were isolated by column chromatography (silica gel; Et_2O–hexane, 1:3). The starting material **49** was recovered in 81% yield. The two minor products (Scheme 2.5) were subsequently identified as *N*-(2-hydroxy-1,2,2-triphenylethyl)pivalamide (**56**; 4% yield) and *N*-(2-(hydroxydiphenylmethyl)-benzyl)pivalamide (**57**; 7% yield).



Scheme 2.5

Two mole equivalents of *n*-BuLi were necessary, the first mole to remove the NH proton and the second one to lithiate on the CH_2 at the side-chain or on the ring at the 2-position to produce the dilithium reagents **54** or **55**, respectively (Scheme 2.5).

Compound **56** is the product expected from reaction of the dilithium intermediate **54** with benzophenone (α-substitution), while, compound **57** is the product expected product from the reaction of dilithium intermediate **55** with benzophenone (*ortho*-substitution).

The ^{1}H and ^{13}C NMR spectra of **56** showed the absence of CH_2 signals, indicating that lithiation took place at the CH_2 of the $-CH_2NHCOBu^t$ group. The ^{13}C 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. Compound **56** would of course be present as a racemic mixture. The presence of CH_2 signals in the NMR spectra of **57** indicated that lithiation took place on the ring.

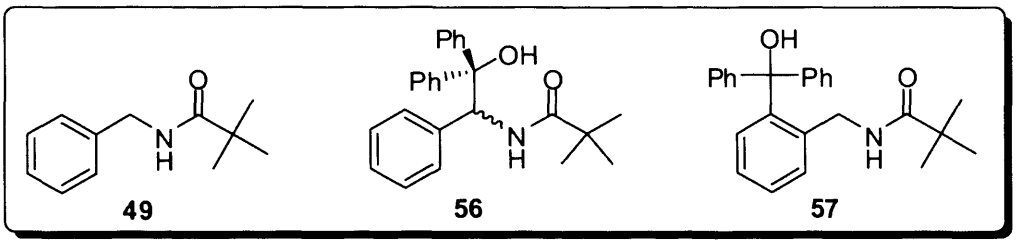
The yields of **56** and **57** were low presumably because the lithiation reaction of **49** with *n*-BuLi at -78 °C was slow. It seems likely that longer reaction time, higher temperature and/or other lithiating reagent might have an effect on the yield. Führer and Gschwend had reported that lithiation of *N*-phenylpivalamide, using *n*-BuLi at 25 °C, was slow and required 20 h as a reaction time to generate the *ortho*-lithiated species.[37] Therefore, it seemed likely that the low yields of the products of lithiation of **49** and treatment with an electrophile observed under the low temperature conditions used here were the result of inefficient lithiation.

It was of interest to see if the reaction would proceed more rapidly with other lithium reagents, and we therefore attempted double lithiation of **49** using *t*-BuLi. It was found that lithiation of **49** with *t*-BuLi (2.2 mole equivalents) under similar reaction conditions to those used with *n*-BuLi, followed by reaction with benzophenone, gave **56** and **57** in slightly better yields (6 and 10%, respectively) after separation by column chromatography (Table 2.1; entry 1) along with **49** (69%). We also attempted double lithiation of **49** using *sec*-BuLi under similar conditions; however, the yields of **56** and **57** were very similar to those obtained using *n*-BuLi as reagent. Therefore, we undertook a more detailed lithiation study of **49** using *t*-BuLi as the lithium reagent.

A series of experiments was conducted to try to find conditions under which only one product would be obtained or to improve the yields of **56** and **57**. Double lithiations of **49** with 2.2 mole equivalents of *t*-BuLi in THF for 2 or 4 h at 0 °C

followed by reaction with benzophenone for 2 h at 0 °C were attempted. Under such conditions the yields of **56** and **57** were in the range of 34–37 and 30–34%, respectively (Table 2.1; entries 2 and 3), while **49** was recovered in 20–28% yield. These results are consistent with Schlosser's findings.[85]

Table 2.1: Yields of **56** and **57** formed by lithiation of **49** using *t*-BuLi (2.2 mole equivalents) and reaction with benzophenone, according to Scheme 2.5



49 **56** **57**

Entry	T (°C)	t (h)	Yield (%)[a]			
			49	**56**	**57**	**overall**
1	-78	4	69 (81)[b]	6 (4)[b]	10 (7)[b]	16 (11)[b]
2	0	2	28	34	30	64
3	0	4	20	37	34	71
4	20	2	30	40	16	56
5	20	4	30	42	17	59

[a] Yield of isolated products after purification by column chromatography.
[b] Figures in parentheses are for similar reactions, but with *n*-BuLi or *sec*-BuLi as a lithium reagent (both reagents gave identical results).

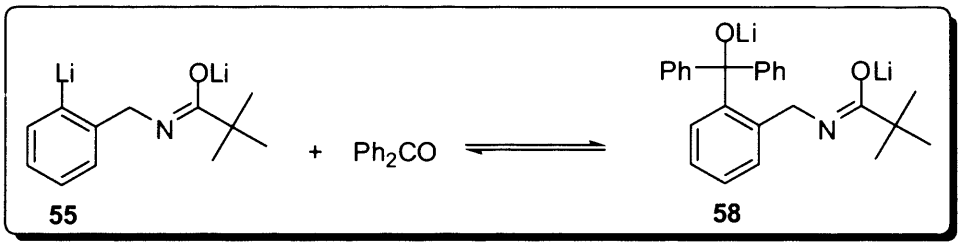
The stability of *n*-BuLi in diethyl ether as a solvent is ten to fifty times greater than in THF at any given temperature.[8] Generally, a temperature increase of 20 °C could shorten the lifetime of BuLi by a factor of 10. It is well recognised that *t*-BuLi decomposes THF more rapidly than *n*-BuLi to produce ethylene and the lithium enolate of acetaldehyde as the most abundant products. Therefore, it is always better to carry out lithiation reactions involving *t*-BuLi and THF below 0 °C.[8] Nevertheless, we decided to attempt double lithiation of **49** with *t*-BuLi in THF at 20 °C to see what effect the temperature could have on both yield and selectivity of products. Lithiations of **49** with *t*-BuLi in THF for 2 or 4 h at 20 °C, followed by reaction with benzophenone for 2 h at 20 °C, were attempted. It was found that the yields of **56** and **57** were in the range of 40–42 and 16–17%, respectively (Table 2.1; entries 4 and 5), while **49** was recovered in 30% yield. It is clear that the overall yields of products formed *via* lithiation were indeed lower at 20 °C than at 0 °C, as would be expected

on the basis of reaction of the *t*-BuLi with the solvent. However, the overall yields, at 56-59%, were still respectable and since **49** and benzophenone were easily recovered the process could be repeated to provide a higher final conversion into products after even 2 cycles. Alternatively, use of a larger excess of *t*-BuLi might lead to an increase in overall yield of products.

More interestingly, the reaction was selective towards the side-chain lithiation product (**56**). At -78 °C the major product (albeit in very low yield) had been the ring-substituted product (**57**), while at 0 °C the two products were formed in more-or-less equal amounts (Table 2.1; entries 2 and 3), but at 20 °C **56** was favoured over **57** by around 2.5:1 (Table 2.1; entries 4 and 5). Indeed, the yield of **56** at 20 °C was actually higher than at 0 °C, despite the likely reaction of the lithiating agent with THF, while the yield of **57** was substantially lower. There are several possible explanations for these observations.

Firstly, lithiation at the *ortho*-position might be slow at 20 °C. However, this explanation is unlikely, since lithiation occurs readily enough at 0 °C.

Secondly, *ortho* and α-lithiations might take place at 20 °C as much as at 0 °C, but at the higher temperature the dilithium intermediate **58**, produced *in-situ* from reaction of **55** and benzophenone, may be unstable, dissociating back to benzophenone and *ortho*-lithiated species **55** (Equation 2.1). The proportion of the adduct **58** present in the mixture when the reaction was quenched would be reflected in the yield of **57** obtained.



Equation 2.1

Since the forward reaction involves ordering, it will have a negative ΔS (Equation 2.2). At higher temperature the TΔS term (Equation 2.2) is greater and -TΔS is therefore more positive, encouraging dissociation. At 0 °C the equilibrium position may favour association, whereas at 20 °C it may favour dissociation. This

possibility was tested by treating **57** with *t*-BuLi (2 equivalents) in dry THF at 20 °C for 2 h. However, following work up **57** was recovered quantitatively (97%), which make this possibility unlikely.

$$\Delta G = \Delta H - T\Delta S$$

Equation 2.2

Thirdly, at 20 °C the *ortho*-lithiated species **55** might be reactive enough to deprotonate the solvent (THF), leading to starting material **49** that cannot react with benzophenone. However, if the lithium reagent **55** is still intact at 20 °C, but the problem is something to do with the way it reacts with the benzophenone at the higher temperature, cooling it down before addition of benzophenone would again lead to formation of **57**. This possibility was tested by carrying out two experiments. The first (Experiment A) involved treatment of **49** with *t*-BuLi (2 equivalents) in dry THF at 20 °C for 2 h. The reaction mixture was then cooled down to 0 °C before benzophenone was added. The reaction mixture was stirred for 2 h at 0 °C, worked up and the product mixture was separated by column chromatography. Under such conditions the yields of **56** and **57** were 41 and 18%, respectively, while **49** was recovered in 30% yield along with benzophenone. These results were virtually identical to those obtained from reactions carried out entirely at 20 °C. The second experiment (Experiment B) involved treatment of **49** with *t*-BuLi (2 equivalents) in dry THF at 0 °C for 2 h to give the mixture of lithium species that led to the products recorded in Entry 2 of Table 2.1. The reaction mixture was then warmed up to 20 °C before benzophenone was added and the reaction mixture was stirred for 2 h at 20 °C. Under such conditions the yields of **56** and **57** were 39 and 20%, respectively, while **49** was recovered in 31% yield along with benzophenone, *i.e.* quite similar to the results of Experiment A, but exhibiting a significantly lower yield of **57** than from reactions conducted entirely at 0 °C (Entries 2 and 3 of Table 2.1). These results clearly indicated that lithium reagent **55** is not very stable at 20 °C and are consistent with its deprotonating the solvent to give back the starting material **49**.

A **fourth** possibility is that the two lithium reagents **54** and **55** are capable of interconverting at 20 °C, presumably through a series of deprotonations and

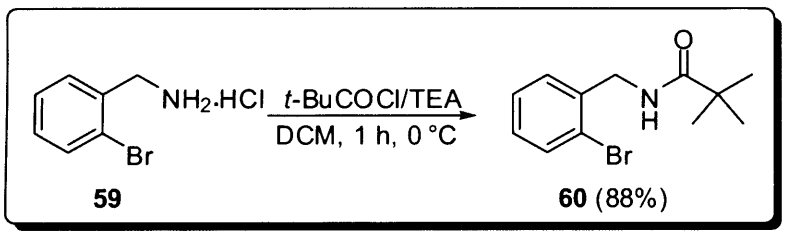
reprotonations, and that **54** is the thermodynamically more stable one. The lower overall yields would be a result of the loss of some *t*-BuLi by reaction with the THF, but the changed proportions of products would reflect the net conversion of **55** into **54**.

Of all the possibilities considered, the third possibility seems the most likely in view of all the results.

Clearly, direct lithiation on the ring without lithiation on the CH_2 of the $CH_2NHCOBu^t$ group was not a realistic hope with *N*-benzylpivalamide (**49**) as substrate. However, ring substitution could presumably be achieved *via* bromine-lithium exchange of *N*-(2-bromobenzyl)pivalamide. Therefore, we decided to synthesise *N*-(2-bromobenzyl)pivalamide.

2.4 Synthesis of *N*-(2-bromobenzyl)pivalamide (60)

N-(2-Bromobenzyl)pivalamide (**60**) was prepared in 88% yield from reaction of pivaloyl chloride with 2-bromobenzylamine hydrochloride (**59**) in the presence TEA in DCM (Scheme 2.6).



Scheme 2.6

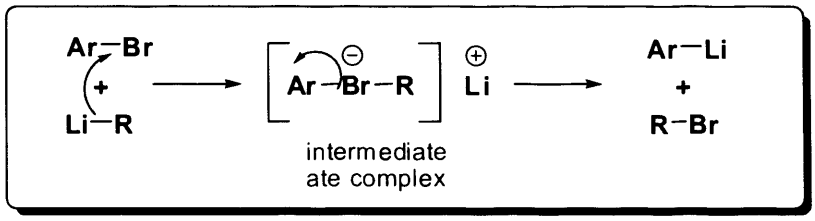
With compound **60** in hand, attention was turned to investigate bromine-lithium exchange of **60** followed by reaction with various electrophiles in an attempt to produce the corresponding 2-substituted derivatives.

2.5 Bromine-lithium exchange of *N*-(2-bromobenzyl)pivalamide (60)

Halogen-lithium exchange of halogenated aromatic compounds is generally favoured over deprotonation (direct lithiation on the ring) at low temperatures. This rapid reaction allows the introduction of a lithium atom at a specific non-activated position on the ring. The rate of halogen-lithium exchange in aryl halides follows the order, ArI > ArBr >> ArCl > ArF. Aryl chlorides and fluorides usually undergo deprotonation at the position next to the halogen producing benzynes.[8] The most

common lithium reagents for halogen-lithium exchange are *t*-BuLi, *n*-BuLi and *sec*-BuLi; however, *t*-BuLi is the most favourable one.

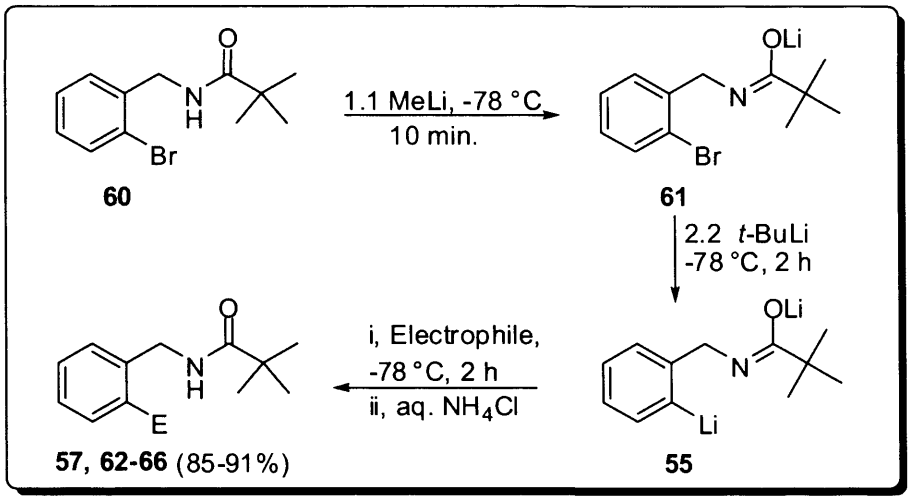
The bromine-lithium exchange in aromatic compounds is likely to proceed through nucleophilic substitution at the bromine *via* formation of ate complex as intermediate (Equation 2.3).[8,87-89] Many examples of halogen-lithium exchange to produce the corresponding aryllithiums have been reported.[8,89]



Equation 2.3

In principle, bromine-lithium exchange of *N*-(2-bromobenzyl)pivalamide (**60**) 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. However, Smith has found that bromine-lithium exchange of *N'*-(2-bromoaryl)-*N,N*-dimethylureas 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.[90] Therefore, bromine-lithium exchange of compound **60** was attempted with MeLi and then *t*-BuLi at -78 °C in THF.

Compound **60** was treated with MeLi (1.1 equivalents) at -78 °C for 10 min to give the lithiated species **61** as a result of deprotonation at the nitrogen (Scheme 2.7). The mixture was then treated with *t*-BuLi (2.2 mole equivalents) and the colourless mixture was stirred for 2 h at -78 °C in an attempt to ensure complete formation of **55**. An electrophile (benzophenone, cyclohexanone, benzaldehyde, 4-anisaldehyde, or deuterium oxide) was added and the mixture was stirred for 2 h at -78 °C (Scheme 2.7). Following work-up, the crude products obtained were crystallized from EtOAc–Et_2O (1:3) to give the corresponding *N*-(2-substituted benzyl)pivalamides **57** and **62-66** (Scheme 2.7) in high yields (Table 2.2). The products were all characterized by standard spectroscopic methods (see Chapter 7; Section 7.5).



Scheme 2.7

Table 2.2: Synthesis of *N*-(2-substituted benzyl)pivalamides **57** and **62-66** according to Scheme 2.7

Product	Electrophile	E	Yield (%)[a]
57	Ph_2CO	$Ph_2C(OH)$	90
62	$(CH_2)_5C=O$	$(CH_2)_5C(OH)$	90
63	PhCHO	PhCH(OH)	86
64	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	87
65	MeI	Me	85
66[b]	D_2O	D	91

[a] Yield of isolated product after crystallization.
[b] Deuteration was almost 100% as indicated by NMR spectra.

As can be seen from Table 2.2, the yields of products were high in all cases. The ^1H NMR spectra of compounds **63** and **64** showed diastereotopicity for the two hydrogens of the CH_2 group at position 1. The diastereotopicity arises from creation of a stereogenic carbon centre, on reaction of lithium intermediate **55** with aldehydes. Compounds **63** and **64** were of course present as racemic mixtures.

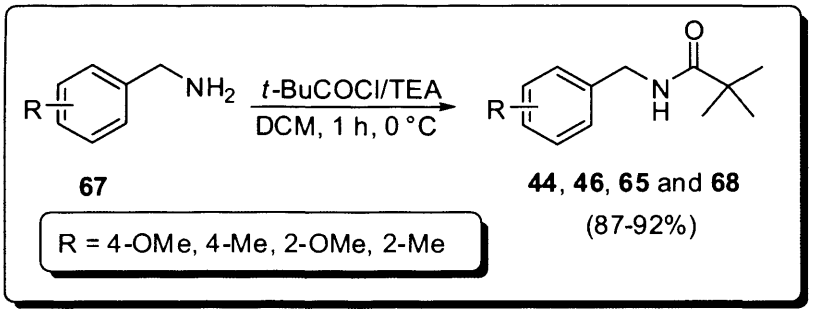
With a method for generating the ring-lithiated species essentially quantitatively now available, the opportunity presented itself to obtain further evidence about the stability of the lithiated species **55** at 20 °C (compare Section 2.3). To understand the reason for the lower yield of **57** obtained from lithiation and substitution of **49** at 20 °C even better two experiments were carried out. The first involved treatment of **60** with MeLi and then *t*-BuLi in THF at -78 °C for 30 min. The mixture was then warmed to 20 °C and stirred for 30 min before benzophenone was added. The reaction mixture was stirred for 2 h at 20 °C and then worked-up. Under

such conditions the isolated yield obtained of **57** was 78%, while unbrominated starting material **49** was obtained in 15% yield along with some benzophenone. The second experiment involved treatment of **60** with MeLi and then *t*-BuLi in dry THF at -78 °C for 30 min. The mixture was warmed to 20 °C and stirred for 30 min and then cooled down to -78 °C before benzophenone was added. The reaction mixture was stirred for 2 h at -78 °C. The yields obtained of **57** and **49** were 82 and 12%, respectively, along with some benzophenone. Again, these results clearly indicated that lithium reagent **55** is not very stable at 20 °C and could be protonated back to **49**.

Attention was next turned to the synthesis of a series of *N*-(substituted benzyl)pivalamides and investigation of their lithiation reactions to see what effect the type and position of the substituent could have on the lithiation site.

2.6 Synthesis of various *N*-benzylpivalamides

Various *N*-benzylpivalamides, namely *N*-(4-methoxybenzyl)pivalamide (**44**), *N*-(2-methoxybenzyl)pivalamide (**46**), *N*-(4-methylbenzyl)pivalamide (**68**) and *N*-(2-methylbenzyl)pivalamide (**65**) were prepared according to Scheme 2.8. The solids obtained after work-up were purified by crystallization to give pure products as white crystals in high yields (Table 2.3).



Scheme 2.8

Table 2.3: Synthesis of *N*-(substituted benzyl)pivalamides **44**, **46**, **65** and **68** according to Scheme 2.8

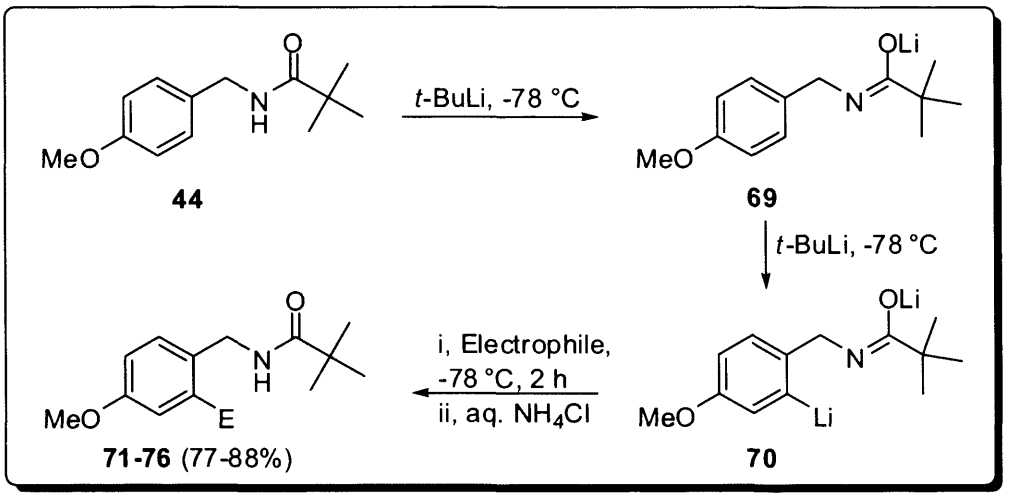
Product	R	Yield (%)[a]
44	4-OMe	87
46	2-OMe	91
65	2-Me	89
68	4-Me	92

[a] Yield of isolated product after crystallization.

Our attention was next turned to investigate the directed lithiation of *N*-(4-methoxybenzyl)pivalamide (**44**) with *t*-BuLi at –78 °C followed by reactions with a range of electrophiles.

2.7 Directed lithiation of *N*-(4-methoxybenzyl)pivalamide (44)

Previous experience with *N*-benzylpivalamide (**49**) suggested that *t*-BuLi might provide higher yields that *n*-BuLi and *sec*-BuLi in reactions involving lithiation. Therefore, reactions similar to those of Schlosser[85] (Scheme 2.1) were carried out with *t*-BuLi in THF at –78 °C. Directed lithiation of *N*-(4-methoxybenzyl)pivalamide (**44**) took place smoothly with *t*-BuLi (2.2 mole equivalents) in THF at –78 °C. Initial addition of *t*-BuLi gave the monolithium reagent **69**, as a yellow solution, then the solution turned brownish red as the remaining *t*-BuLi was added, presumably because of formation of the dilithium reagent **70**. The mixture was stirred for 4 h at –78 °C and then an electrophile (1.1 mole equivalents) was added and the mixture was stirred for 2 h at -78 °C (Scheme 2.9). Following work-up of the reaction mixture the crude products were purified by column chromatography (silica gel; Et_2O–hexane, 1:3) to give the corresponding substituted products in high yields (Table 2.4). The products were all characterised by standard spectroscopic methods (see Chapter 7; Section 7.7). It was difficult from simple ^1H NMR spectra of products to determine whether lithiation had taken place *ortho* to the CH_2NHCO^tBu group or *ortho* to the methoxy group. However, the ^{13}C NMR spectra of compounds **71-76** showed two signals somewhat upfield in the region of 111-117 ppm, which could attributed to C-3 and C-5. Also, they showed a signal somewhat downfield in the δ = 129-134 ppm region, which could be attributed to C-6. These patterns indicated that electrophiles were introduced *ortho*- to the pivaloylaminomethyl group and that the products were *N*-(2-substituted 4-methoxybenzyl)pivalamides **71-76** (Scheme 2.9). Moreover, lithiation next to the $-CH_2NHCO^tBu$ group was expected based on Schlosser's findings using *n*-BuLi at 0 °C.[85]



Scheme 2.9

Table 2.4: Synthesis of *N*-(2-substituted 4-methoxybenzyl)pivalamides **71-76** according to Scheme 2.9

Product	Electrophile	E	Yield (%)[a]
71	MeI	Me	81[b]
72	Ph_2CO	$Ph_2C(OH)$	80
73	$(CH_2)_5C=O$	$(CH_2)_5C(OH)$	77
74	MeCOBu	MeC(OH)Bu	78
75	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	82
76[c]	D_2O	D	88

[a] Yield of isolated product after purification by column chromatography.
[b] *N*-(4-Methoxy-2-methylbenzyl)-*N*-methylpivalamide (**77**) was obtained in 5% yield as side-product due to methylation on the nitrogen. Compound **77** was obtained in 87% yield when the reaction was repeated with 2.2 equivalents of MeI.
[c] Deuteration % was *ca.* 95% as indicated by NMR spectra.

The ^{1}H NMR spectra of compounds **74** and **75** showed diastereotopicity for the two hydrogens of the CH_2 group at position 1 and also for the two hydrogens of the CH_2 group next to the newly created stereogenic carbon at position 2 in compound **74**. Compounds **74** and **75** would, of course, be formed as racemic mixtures.

The results obtained clearly showed that reactions of the lithium reagent with electrophiles is general and substitution had taken place next to the $-CH_2NHCOBu^t$ group, which is consistent with Schlosser's findings with *n*-BuLi at 0 °C.[85] By contrast, Führer and Gschwend had reported that lithiation of *N*-(4-methoxyphenyl)pivalamide, using *n*-BuLi at 25 °C, was not selective.[37] In this case, reactions of the lithium intermediates obtained with an electrophile produced three substitution products, *ortho*- to the $-NHCOBu^t$, *ortho*- to the methoxy group and

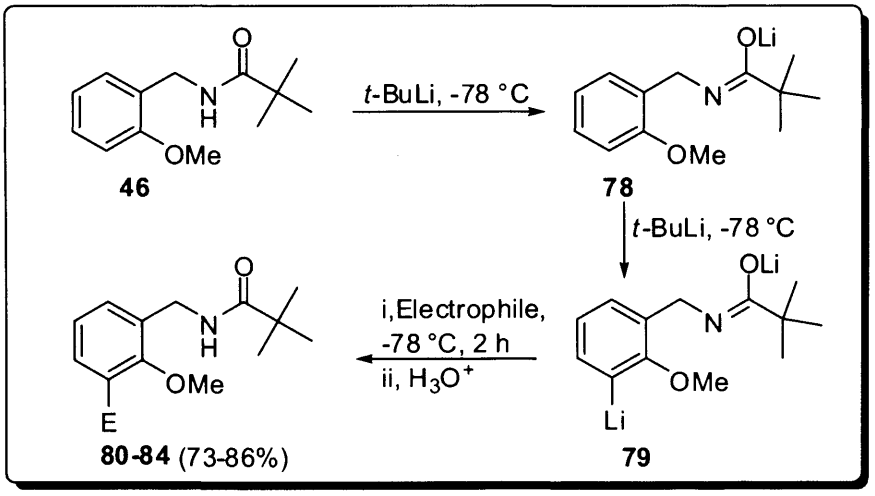
ortho- to both groups.[37] The results of Führer and Gschwend suggest that the pivaloylamino group is slightly superior to a methoxy group in terms of its *ortho*-directing ability.[37] However, our results and those of Schlosser suggest that the pivaloylaminomethyl group is substantially superior to a methoxy group at directing lithiation ortho to itself.

Our attention was next turned to investigate the directed lithiation of *N*-(2-methoxybenzyl)pivalamide (**46**).

2.8 Directed lithiation of *N*-(2-methoxybenzyl)pivalamide (46)

N-(2-Methoxybenzyl)pivalamide (**46**) had been lithiated previously by Schlosser using *n*-BuLi at 0 °C (Scheme 2.2).[85] However, the reaction was not selective. Therefore, we decided to investigate the directed lithiation of **46** under the general conditions used to lithiate compound **44** (Section 2.7; Scheme 2.9).

Therefore, compound **46** was treated with *t*-BuLi (2.2 mole equivalents) at -78 °C in THF under nitrogen (Scheme 2.10). It was found that initial addition of *t*-BuLi provided the monolithium reagent **78** as a yellow solution then turned to the dilithium reagent **79** as a reddish brown solution (Scheme 2.10). The mixture was stirred for 4 h at –78 °C after which an electrophile (1.1 mole equivalents) was added and the mixture was stirred for 2 h at -78 °C (Scheme 2.10) and then allowed to warm to room temperature. Following work-up of the reaction mixture the crude products were purified by column chromatography (silica gel; Et_2O–hexane, 1:3) or direct crystallization from ethyl acetate to give the corresponding *N*-(3-substituted 2-methoxybenzyl)pivalamides **80-85** (Scheme 2.10) in high yields (Table 2.5).



Scheme 2.10

The products were all characterised by standard spectroscopic methods (see Chapter 7; Section 7.9) and clearly indicated that lithiation and substitution took place *ortho-* to the OMe group rather than *ortho-* to the pivaloylaminomethyl group. In some cases, a low yield (2-3%) of a side-product was formed due to side-chain lithiation at the CH_2 to produce dilithium reagent **86** (Figure 2.1). The structures of compounds **80** and **84** were confirmed by X-ray crystallography, as represented in Figures 2.2[91] and 2.3,[92] respectively.

Table 2.5: Synthesis of *N*-(3-substituted 2-methoxybenzyl)pivalamides **80-84** according to Scheme 2.10

Product	Electrophile	E	Yield (%)[a]
80	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	76[b]
81	PhCHO	PhCH(OH)	75
82	Ph_2CO	$Ph_2C(OH)$	73[c]
83[d]	D_2O	D	86
84[e]	CO_2	CO_2H	80[f]

[a] Yield of pure product after column chromatography unless otherwise indicated.
[b] Compound **85** (Figure 2.1) was obtained as a side product in 2% yield due to lithiation and substitution at the side-chain. Also, traces of **46** (3%) were recovered.
[c] Compound **87** (Figure 2.1) was obtained in 3% yield as a side product due to lithiation and substitution at the side-chain.
[d] Deuteration % was *ca.* 95% as indicated by NMR spectra.
[e] Compound **84** was purified by crystallization from ethyl acetate.
[f] The ^1H NMR spectrum of the mother liquor from crystallization showed the presence, in nearly equal proportions, of **46**, the expected product from side chain lithiation **48** (Scheme 2.2) and additional **84**, which were not separated.

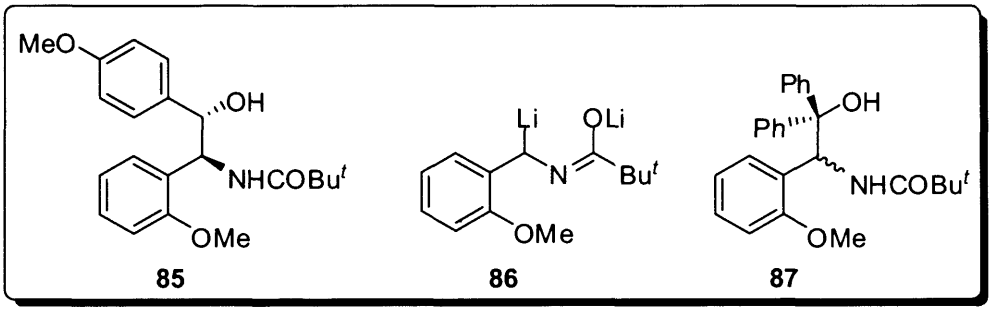


Figure 2.1

The ^1H NMR spectra of **80** and **81** showed that the signals of the two hydrogens of their CH_2 groups appeared separately, as two separated double doublets, verifying that they are diastereotopic. Compounds **80** and **81** would, of course, be

formed as racemic mixtures. Indeed, the X-ray crystallography of compound **80** (Figure 2.2) showed a single type of crystal containing both enantiomers in equal proportions, but the structure displayed (Figure 2.2) shows the structure as *N*-((*S**)-3-(hydroxy(4-methoxyphenyl)methyl)-2-methoxybenzyl)pivalamide. The ^{13}C NMR spectrum of **87** showed that signals of the two phenyl groups appeared separately, verifying that they are diastereotopic. The compound would, of course, be produced as a racemic mixture.

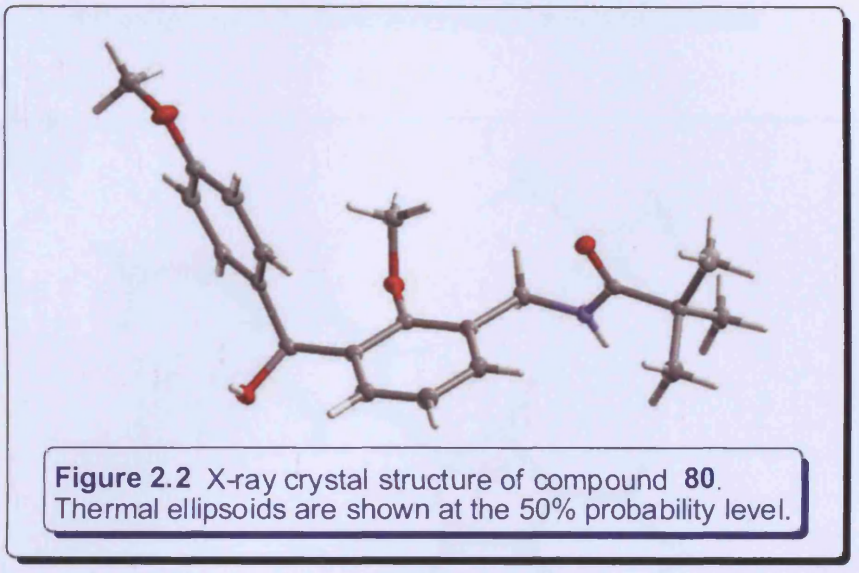


Figure 2.2 X-ray crystal structure of compound **80**. Thermal ellipsoids are shown at the 50% probability level.

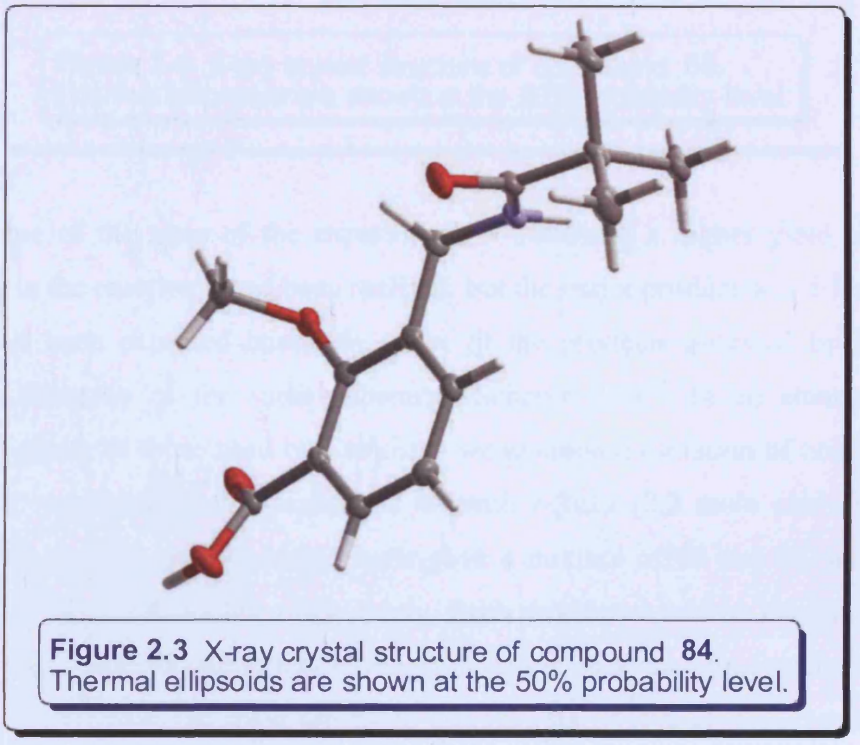


Figure 2.3 X-ray crystal structure of compound **84**. Thermal ellipsoids are shown at the 50% probability level.

Compound **85** could potentially be formed as a pair of racemic diastereoisomers. However, its NMR spectra showed what appeared to be single sets of signals, indicating that the isolated product was probably a single diastereoisomer. However, since this side-product was isolated in only 2% yield, it is possible that a small amount of the other diastereoisomer was formed but not isolated. The X-ray crystallography of compound **85** showed a single type of crystal containing both enantiomers in equal proportions, but the structure displayed (Figure 2.4)[92] shows only one part of the repeating unit, indicating the structure as *N*-((1S*,2S*)-2-hydroxy-1-(2-methoxyphenyl)-2-(4-methoxyphenyl)ethyl)pivalamide.

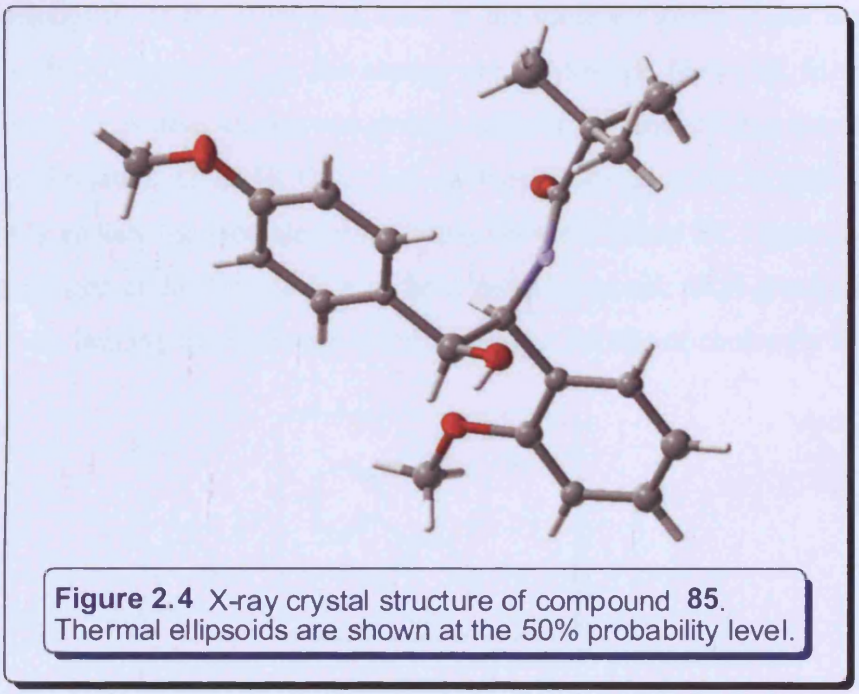
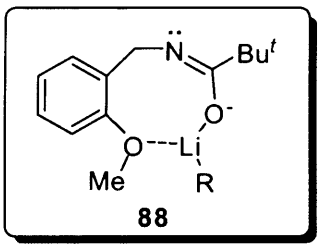


Figure 2.4 X-ray crystal structure of compound **85**. Thermal ellipsoids are shown at the 50% probability level.

Some of the aims of the experiments – obtaining a higher yield and better selectivity in the reaction – had been realised, but the major product was different than would have been expected based on either of the products obtained by Schlosser following lithiation of the same substrate (Scheme 2.2).[85] In an attempt to use conditions closer to those used by Schlosser we attempted lithiation of compound **46** at 0 °C. It was found that lithiation of **46** with *t*-BuLi (2.2 mole equiv.) at 0 °C followed by reaction with 4-anisaldehyde gave a mixture of **80** and **85**, which were isolated in 41 and 39% yields, respectively. Both products could be kinetic, but **80** is formed quicker than **85** and at low temperature is the overwhelming product whereas at higher temperature the rates are more comparable. Although this produced two

products in comparable proportions, as found by Schlosser, the ring-substituted product was still not the one expected based on Schlosser's work.[85]

The results obtained from directed lithiation and substitution of **44** (Section 2.7) and **46** are interesting in that there is a big difference between the situation when the methoxy group is in the 4-position and when it is in the 2-position. When the methoxy group was at the 4-position lithiation took place at the 2-position which is consistent with the results obtained by Schlosser for this substrate.[85] This indicates that the pivaloylaminomethyl group is intrinsically a better directing metallating group than methoxy. However, when the position of the substituent is changed (methoxy at the 2-position) the reaction selectivity is very different, and lithiation occurred selectively at the 3-position, next to the methoxy group rather than next to $-CH_2NHCOBu^t$. The reasons for the change are not known. However, in the case of the 2-methoxy derivative **46** the two groups capable of coordinating the metallating agent (monolithiated $-CH_2NHCOBu^t$ and methoxy) are adjacent to each other and may possibly chelate the incoming metallating agent (structure **88**; Figure 2.5). In this case the hydrogen at the 3-position may be closer to the basic alkyl group than that at the 6-position, making the hydrogen at the 3-position the site of choice for lithiation.



88

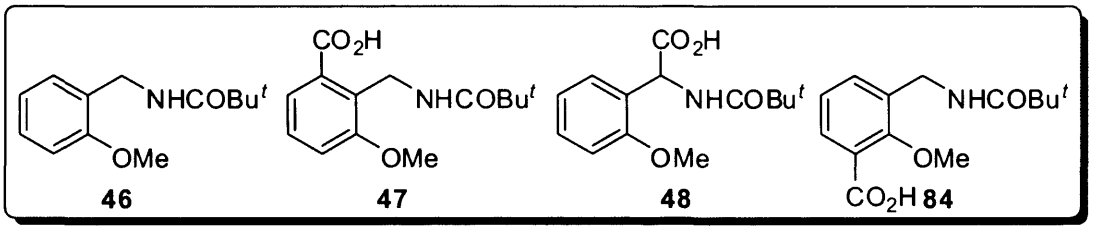
Figure 2.5

Clearly, lithiation of *N*-(2-methoxybenzyl)pivalamide (**46**) with *t*-BuLi in THF at -78 °C, followed by reactions with electrophiles, gave ring substitution, but next to the methoxy group rather than next to the pivaloylaminomethyl group, which was unexpected based on earlier results reported by Schlosser when *n*-BuLi was used at 0 °C.[85] In order to clarify the situation we decided to use carbon dioxide as an electrophile under various reaction conditions.

The lithiation procedure for compound **46** described in Scheme 2.10 was varied by use of different lithium reagents (*t*-BuLi, *sec*-BuLi and *n*-BuLi) and different reaction temperatures (-78 and 0 °C). Compound **46** was treated with RLi (2.2 mole equivalents) at -78 or 0 °C and the mixture was stirred for 2 h at 0 °C or 4 h

at -78 °C. Solid carbon dioxide was added and the reaction mixture was stirred for 30 minutes. The mixture was diluted with ethyl acetate and quenched with dilute HCl. The crude product was crystallized from ethyl acetate to give the pure product and the mother liquor from crystallization was analysed by ^{1}H NMR spectroscopy. The results obtained are recorded in Table 2.6.

Table 2.6: Products from lithiation of **46**, with different alkyllithiums (RLi) at different temperatures (T), followed by reaction with CO_2



Entry	RLi	T (°C)	Yields of isolated compounds (%)[a]		Composition of mother liquor following crystallization (%)[b]			
			47	**84**	**46**	**47**[c]	**48**[d]	**84**
1	*t*-BuLi	-78	—	80[e]	2	—	7	7
2	*t*-BuLi	0	5	40	—	14	26	9
3	*sec*-BuLi	-78	12	—	22	24	34	—
4	*sec*-BuLi	0	25	—	9	23	38	—
5	*n*-BuLi	-78	—	—	97	—	—	—
6	*n*-BuLi	0	11[f]	—	17	19	40	8

[a] Yield of pure product following fractional crystallization of the product mixture.
[b] The approximate % yield of each component in the mother liquor following crystallization, as calculated from ^{1}H NMR spectra and weight of residue.
[c] The structure of **47** was confirmed by X-ray crystallography (Figure 2.6).[92]
[d] No attempt was made to isolate a pure sample of **48**.
[e] Yield obtained under the general conditions.
[f] Yield obtained under Schlosser's conditions.[85]

The ring-substituted product **47** (Figure 2.6),[92] the one expected based on Schlosser's work (Scheme 2.2),[85] was obtained, but in only low yield as a minor product using *t*-BuLi at 0 °C. When *sec*-BuLi was used as the lithium reagent, **47** was isolated in 12-25% yield as white crystals. There was no evidence for the formation of **84** under the conditions tried using *sec*-BuLi. Repeating the same reaction but under Schlosser's conditions using *n*-BuLi at 0 °C gave compound **47** in 11% yield following fractional crystallization of the crude product. Also, the ^{1}H NMR spectrum of the mother liquor from crystallization showed the presence of additional **47**, **48** and

46 in the ratio of 1:1:2 along with traces with **84**. This result is very similar to the one produced by Schlosser and implies that difficulty in isolation of the products from the reaction mixture was the reason for the low yields reported rather than that lithiation was ineffective.[85] Also, it was found that no products were obtained when *n*-BuLi was used at lower temperature (-78 °C), suggesting that lithiation with *n*-BuLi is very slow at low temperature.

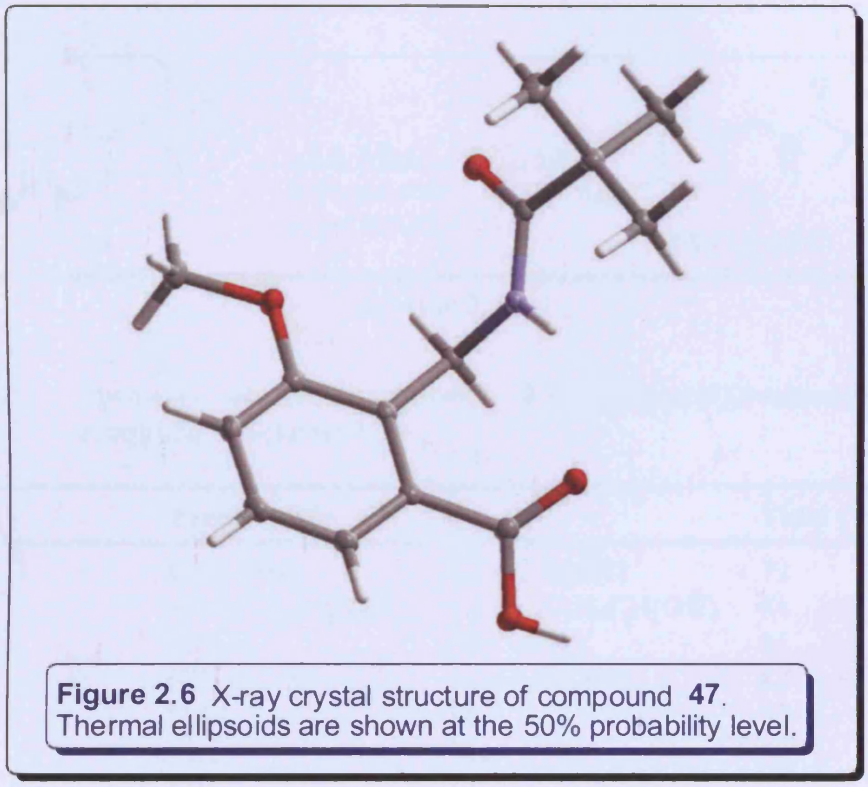


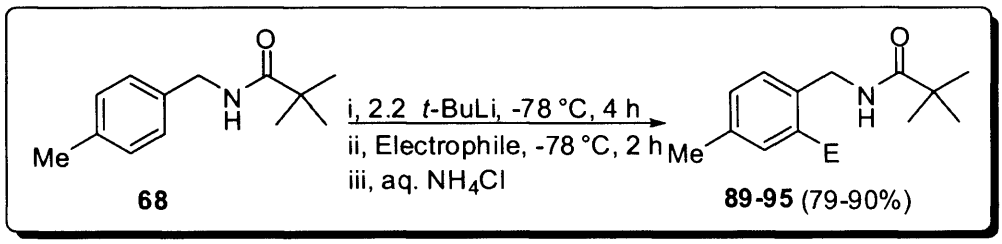
Figure 2.6 X-ray crystal structure of compound **47**. Thermal ellipsoids are shown at the 50% probability level.

It is not clear why lithiation of **46** with *t*-BuLi in THF at -78 °C gives substitution *ortho*- to the methoxy group while a similar procedure with *sec*-BuLi, or use of *n*-BuLi at higher temperature, gives a mixture containing two different substitution products, one of which involves lithiation *ortho*- to the pivaloylaminomethyl group. It could have something to do with the way the lithium reagents aggregate, their ability to chelate the two substituents or the relative bulk of the alkyl groups, but without further information it is not easy to decide. However, whatever, the explanation, the procedure we introduced represents a simple, efficient and high yielding route for substitution of **46** and has practical significance.

Attention was next turned to investigate the directed lithiation of *N*-(4-methylbenzyl)pivalamide (**68**) with *t*-BuLi at -78 °C.

2.9 Directed lithiation of *N*-(4-methylbenzyl)pivalamide (68)

It was found that directed lithiation of *N*-(4-methylbenzyl)pivalamide (**68**), under the general conditions used to lithiate *N*-(4-methoxybenzyl)pivalamide (**44**; Section 2.7) and *N*-(2-methoxybenzyl)pivalamide (**46**; Section 2.8), using *t*-BuLi in THF at -78 °C was general and successful with a range of electrophiles (Scheme 2.11). Various *N*-(2-substituted 4-methylbenzyl)pivalamides **89-95** were obtained in high yields (Table 2.7).



Scheme 2.11

Table 2.7: Synthesis of *N*-(2-substituted 4-methylbenzyl)pivalamides **89-95** according to Scheme 2.11

Product	Electrophile	E	Yield (%)[a]
89	C_6H_5CHO	$C_6H_5CH(OH)$	79
90	$4\text{-}MeOC_6H_4CHO$	$4\text{-}MeOC_6H_4CH(OH)$	81
91	Ph_2CO	$Ph_2C(OH)$	81
92	$(CH_2)_5C{=}O$	$(CH_2)_5C(OH)$	82
93[b]	D_2O	D	88
94	MeI	Me	80[c]
95	EtI	Et	81

[a] Yield of isolated product after purification by column chromatography.
[b] Deuteration % was at least 95% as indicated by NMR spectra.
[c] *N*-(2,4-Dimethylbenzyl)-*N*-methylpivalamide (**96**) was obtained as a side product in 2% yield. Compound **96** was obtained in 88% yield when the reaction was repeated under identical conditions with excess MeI (2.2 equivalents).

The products were all characterised by standard spectroscopic methods (see Chapter 7; Section 7.15) and clearly indicated that substitution had taken place *ortho* to the $-CH_2NHCOBu^t$ which is similar to the case where a methoxy group was present at position 4 (Compound **44**; Section 2.7).

The ^1H NMR spectra of **89** and **90** showed that the signals of the two hydrogens of the CH_2 group appeared separately, as two separated double doublets, verifying that they are diastereotopic. Both compounds would have been formed as racemic mixtures. Indeed, the X-ray crystallography of compound **89** showed a single

type of crystal containing both enantiomers in equal proportions, but the structure portrayed (Figure 2.7)[92] shows just one enantiomeric form, *N*-((*R**)-2-(hydroxy(phenyl)methyl)-4-methylbenzyl)pivalamide. There is significant disorder of the carbons of the *tert*-butyl group.

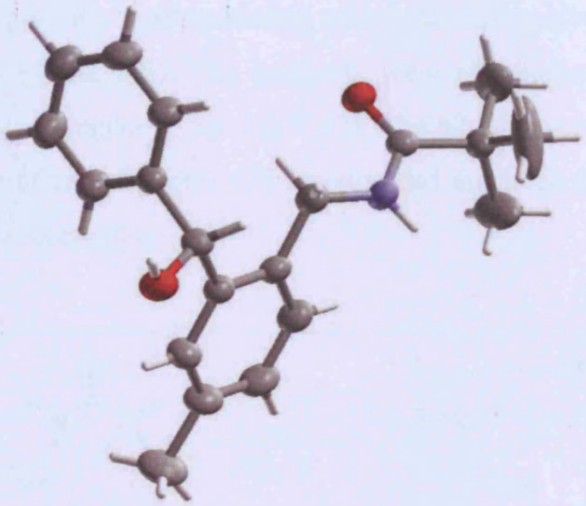


Figure 2.7 X-ray crystal structure of compound **89**. Thermal ellipsoids are shown at the 50% probability level.

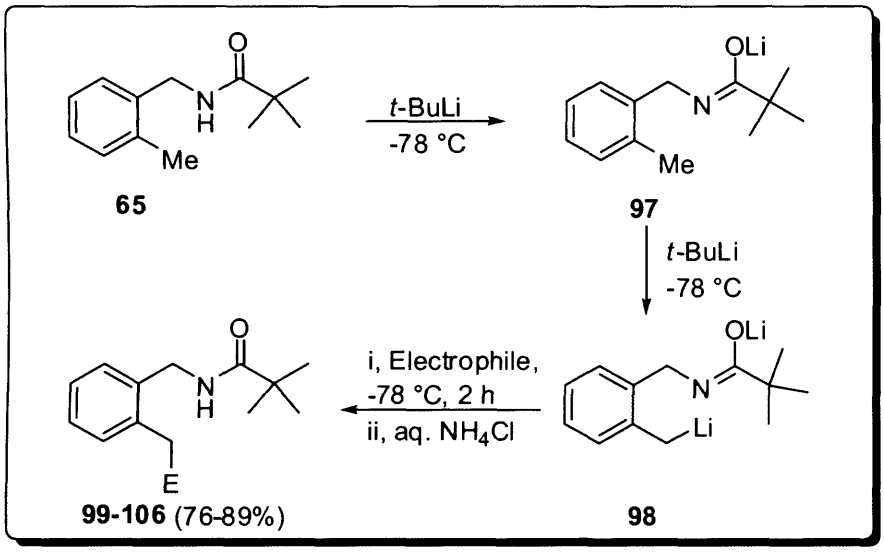
Attention was next turned to investigate the lithiation of *N*-(2-methylbenzyl)pivalamide under the general conditions used for other substrates.

2.10 Lithiation of *N*-(2-methylbenzyl)pivalamide (65)

In the case of *N*-(2-methylbenzyl)pivalamide (**65**) another possibility for lithiation exists that is not available for the other compounds studied so far. This involves lithiation at the methyl group (lateral lithiation). Lithiation of benzylic alkyl groups that are *ortho*-to a directing metallating group is an important methodology in organic synthesis.[8,37] The organolithium intermediates from lateral lithiation usually have significantly greater thermodynamic stability than the corresponding *ortho*-lithiated species obtained by directed lithiation.[8] Lateral lithiation of benzenoid aromatics requires a stabilising group capable of either delocalising negative charge or stabilising an organolithium by coordination.[8] Nitrogen-based stabilising groups placed on the *ortho*-position have been used for a number of lateral lithiations.[8,93-95]

Lateral lithiation of *N*-(2-methylbenzyl)pivalamide (**65**) was attempted with *t*-BuLi (2.2 mole equivalents) at –78 °C in THF under the general conditions used for

other substrates. Addition of the first mole of *t*-BuLi provided the monolithium reagent **97** as a yellow solution and the second mole produced a dilithium reagent (presumed to be **98**) as a reddish brown solution (Scheme 2.12). The dilithium reagent was allowed to react with a range of electrophiles under identical conditions (Scheme 2.12). Following work-up the crude products were purified, by column chromatography, to give the corresponding substituted derivatives **99-106** (Scheme 2.12) in high yields (Table 2.8). The products were all characterised by standard spectroscopic methods (Chapter 7; Section 7.17). The NMR spectra of all compounds showed the presence of two different CH_2 groups and indicated that lateral lithiation to give **98** had indeed taken place.



Scheme 2.12

Table 2.8: Synthesis of *N*-(2-(substituted methyl)benzyl)pivalamides **99-106** according to Scheme 2.12

Product	Electrophile	E	Yield (%)[a]
99	C_6H_5CHO	$C_6H_5CH(OH)$	84
100	$4\text{-}MeOC_6H_4CHO$	$4\text{-}MeOC_6H_4CH(OH)$	89
101	PhCOMe	PhC(OH)Me	80
102	Ph_2CO	$Ph_2C(OH)$	88
103	$(CH_2)_5C{=}O$	$(CH_2)_5C(OH)$	76
104	MeI	Me	87
105	EtI	Et	88
106[b]	D_2O	D	85

[a] Yield of isolated product after purification by column chromatography.
[b] Deuteration was almost complete as indicated by NMR spectra.

As can be seen from Table 2.8, the yields of pure products were high in all cases and the process was general to produce various 2-substituted derivatives.

The ^{1}H NMR spectra of compounds **99-101** showed diastereotopicity for the two hydrogens of the CH_2 groups. They would of course be formed as racemic mixtures. However, the structure of **99** based on X-ray crystallography (Figure 2.8)[92] showed the structure of the specific crystal analysed to be *N*-((*S**)-2-(2-hydroxy-2-phenylethyl)benzyl)pivalamide.

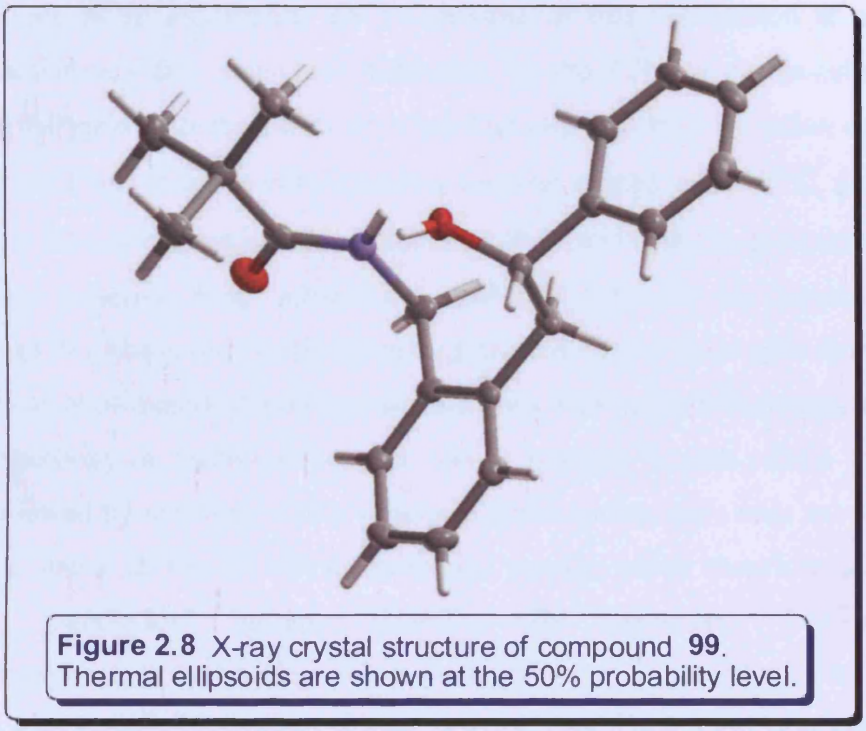


Figure 2.8 X-ray crystal structure of compound **99**. Thermal ellipsoids are shown at the 50% probability level.

The results obtained clearly indicated a big difference between the situation when the methyl group is in the 4-position and when it is in the 2-position. It is presumably because the acidity of the methyl group at the 2-position is higher than that of the ring hydrogens, but when it is in the 4-position the advantage gained from the coordination of the lithium to the directing group encourages lithiation at the ring. Also, when the methyl group is in a position close to the coordination site (*i.e.* position 2), the geometry and/or the acidity of the methyl group made it the site of choice for metallation. The differences in lithiation sites could also arise from the fact that the lithium intermediates obtained from lateral lithiation of *N*-(2-methylbenzyl)pivalamide have greater thermodynamic stability than the corresponding ones produced from *ortho*-lithiation of *N*-(4-methylbenzyl)pivalamide.

Similar observation has been made previously with *N*-(2-methylphenyl)pivalamide with *n*-BuLi at 0 °C.[37]

2.11 Conclusion

A simple, efficient and high yielding lithiation procedure that allows electrophilic substitution of various *N*-benzylpivalamides has been demonstrated to provide various substituted derivatives. Lithiation of unsubstituted *N*-benzylpivalamide with *t*-BuLi in THF at -78–20 °C followed by reactions with benzophenone as an electrophile gave a mixture of ring substitution at position 2 (*ortho*-substitution) and side-chain lithiation of the CH_2 group (α-substitution). However, the yield of *ortho*-substitution product obtained from lithiation carried out at 20 °C was lower than the corresponding reaction carried out at 0 °C, presumably because the lithium reagent is not very stable at 20 °C and could be protonated back to the starting material. Ring substitution could be achieved *via* bromine-lithium exchange of *N*-(2-bromobenzyl)pivalamide followed by reactions with electrophiles. Lithiation of *N*-(4-methoxybenzyl)pivalamide and *N*-(4-methylbenzyl)pivalamide, in which a methoxy or methyl substituent was at position 4, with *t*-BuLi in THF at -78 °C followed by reactions with a variety of electrophiles, gave only substitution at position 2 *ortho* to the pivaloylaminomethyl group, which therefore acted as a directed metallation group (DMG). By contrast, lithiation of *N*-(2-methoxybenzyl)pivalamide, with a methoxy group at position 2, followed by reactions with electrophiles under similar reaction conditions, gave ring substitution, but next to the methoxy group rather than next to the pivaloylaminomethyl group, which was unexpected based on the earlier results reported by Schlosser. Also, lithiation of the 2-methoxy derivative at 0 °C gave a mixture of ring substitution at position 3 (*o'*-substitution) and side-chain lithiation of the CH_2 group (α-substitution), which again was not expected based on Schlosser's findings under similar conditions using *n*-BuLi. It was found that lithiation of *N*-(2-methylbenzyl)pivalamide, where the methyl group was at position 2, at low temperature (-78 °C) followed by reactions with various electrophiles, gave products substituted in the methyl group.

CHAPTER THREE

INVESTIGATION OF THE INFLUENCES OF SUBSTITUENTS ON THE LITHIATION SITES OF VARIOUS *N'*-BENZYL-*N,N*-DIMETHYLUREAS

CHAPTER THREE

INVESTIGATION OF THE INFLUENCES OF SUBSTITUENTS ON THE LITHIATION SITES OF VARIOUS *N'*-BENZYL-*N,N*-DIMETHYLUREAS

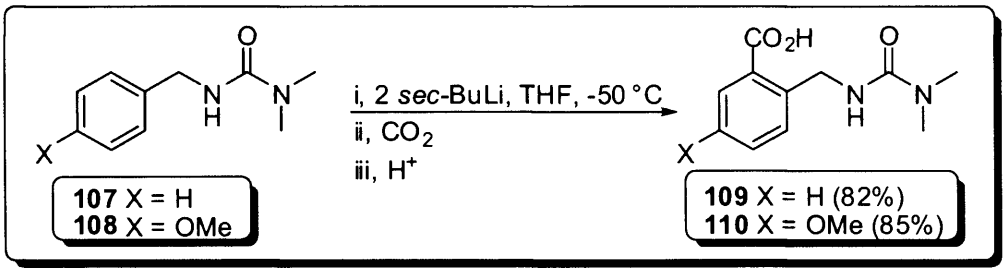
3.1 Introduction

Lithiation of aromatic compounds *ortho* to a directed metallation group has become an invaluable route for the synthesis of various substituted aromatics.[4-11] Various substituents were used as *ortho* directing groups, however, relatively little attention has been paid to ureas. For example, Clayden has shown that *N,N'*-diaryl ureas undergo *ortho*-[12] and lateral lithiations,[13,95] Schlosser lithiated *N'*-benzyl-*N,N*-dimethylureas at the 2-position,[96] Seebach lithiated *N*-allylurea by deprotonation of the methylene group,[97] Beak lithiated *N*-benzyl-*N,N'*-dimethylureas at the benzylic position,[98] Joule has shown that six-membered cyclic ureas have some *ortho* directing ability,[99] Quéguiner lithiated *N,N*-dimethyl-*N'*-(quinolin-3-yl)urea at C-4[100] and Smith lithiated *N'*-aryl-*N,N*-dimethylureas.[101] The reports of Smith and Schlosser are the most relevant ones to the work presented in this chapter.

Smith showed that lithiation of *N'*-aryl-*N,N*-dimethylureas was highly dependent on the nature of substituents on the aryl ring. In favourable cases, the lithium intermediates were generated in high yield *via* directed lithiation.[101] In other cases, lithiation took place on the *N*-methyl groups of the urea moiety or elsewhere on the aryl ring.[101] For example, lithiation of *N'*-(4-chlorophenyl)- and *N'*-(4-trifluoromethylphenyl)-*N,N*-dimethylureas took place *ortho* to the urea containing group, using *n*-BuLi at 0 °C.[101] However, *n*-BuLi failed to lithiate *N'*-(4-fluorophenyl)-*N,N*-dimethylurea under similar conditions, but the use of *t*-BuLi did effect lithiation on the ring next to the urea unit.[101] By contrast, *N'*-(4-methylphenyl)-*N,N*-dimethylurea was lithiated primarily on one of the *N*-methyl groups under similar conditions, while *N'*-(4-methoxyphenyl)-*N,N*-dimethylurea was lithiated *ortho*- to the methoxy group.[101]

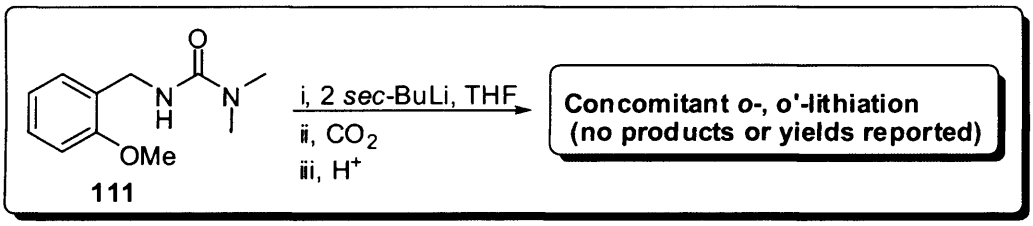
Schlosser has shown that *N'*-benzyl-*N,N*-dimethylurea (**107**) and *N'*-(4-methoxybenzyl)-*N,N*-dimethylurea (**108**) undergo selective lithiation *ortho* to the urea containing group when treated with *sec*-BuLi in THF at –50 °C to give the corresponding carboxylic acid derivatives **109** and **110**, respectively, in high yields

(Scheme 3.1).[96] However, the generality of the process has never been tested, carbon dioxide having been the only electrophile used.



Scheme 3.1

By contrast, directed lithiation of *N'*-(2-methoxybenzyl)-*N,N*-dimethylurea (**111**) under similar reaction conditions was not selective, giving concomitant *o*- and *o'*-lithiation, and no pure products were separated from the reaction mixture after reaction of the lithium reagents formed with carbon dioxide (Scheme 3.2).[96]



Scheme 3.2

In Chapter Two, a simple and convenient lithiation procedure for *N*-benzylpivalamides, followed by reactions of the lithium reagents obtained *in-situ* with various electrophiles, has been developed to produce various substituted products. We therefore decided to investigate the directed lithiation and substitution of various *N'*-(substituted benzyl)-*N,N*-dimethylureas, under conditions similar to those used for directed lithiation of substituted *N*-benzylpivalamides (Chapter Two), in order to examine the products formed and the generality of the process. We have selected *N'*-benzyl-*N,N*-dimethylurea, *N'*-(4-methoxybenzyl)-*N,N*-dimethylurea, *N'*-(2-methoxybenzyl)-*N,N*-dimethylurea, *N'*-(4-methylbenzyl)-*N,N*-dimethylurea and *N'*-(2-methylbenzyl)-*N,N*-dimethylurea as substrates for this study.

Therefore, the aim of the work represented in this chapter was to synthesise various *N'*-benzyl-*N,N*-dimethylureas and investigate their lithiation reactions. In this chapter, the successful syntheses of various *N'*-benzyl-*N,N*-dimethylureas and their

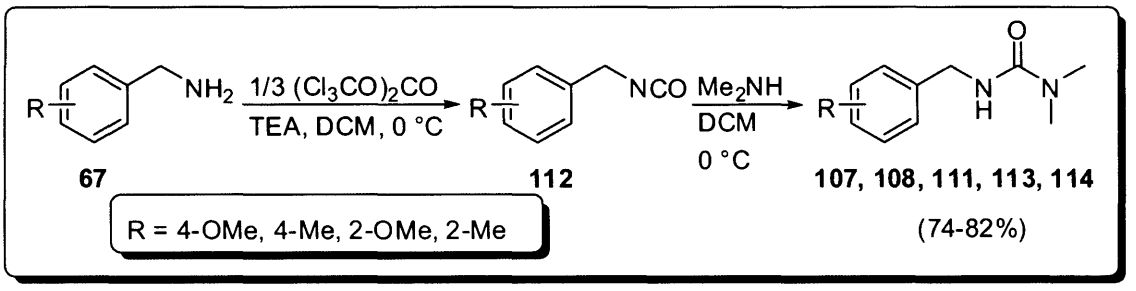
lithiation reactions, with *t*-BuLi (2.2 equivalents) in dry THF, followed by reactions of the lithium intermediates generated *in situ* with various electrophiles to produce the corresponding substituted products in high yields are reported. The results, which we now report in this chapter using *t*-BuLi at low temperature (-78 or -20 °C), show consistency with the earlier results reported by Schlosser when *sec*-BuLi was used as the lithium reagent at -50 °C.[96] Also, we found that lithiation of *N'*-(4-methylbenzyl)-*N,N*-dimethylurea using *t*-BuLi at -78 °C takes place on the ring *ortho*- to the urea unit, while, lithiation of *N'*-(2-methylbenzyl)-*N,N*-dimethylurea *t*-BuLi at -20 °C takes place on the methyl group at the 2-position. Similar observations had been made on lithiation of *N*-(4-methylbenzyl)pivalamide and *N*-(2-methylbenzyl)pivalamide (Chapter Two; Sections 2.9 and 2.10).

3.2 Syntheses of *N'*-benzyl-*N,N*-dimethylureas from the reactions of benzylamines with triphosgene followed by reactions with dimethylamine

N'-(Substituted benzyl)-*N,N*-dimethylureas should be accessible by reactions of substituted benzyl isocyanates with dimethylamine. However, whilst this method can be quite efficient, it suffers from the poor availability and stability of appropriately substituted benzyl isocyanates. These shortcomings prompted us to investigate an approach in which benzyl isocyanates could be generated *in situ* from the corresponding substituted benzylamines, followed by reactions with dimethylamine. Triphosgene is an alternative to phosgene,[102] with the advantages that it is solid, gives three equivalents of phosgene per mole *in situ*, is easy to handle and is much more pleasant to use than phosgene. Triphosgene has been used previously in our group for the synthesis of *N'*-aryl-*N,N*-dimethylureas from the corresponding substituted anilines, followed by reaction with dimethylamine in the presence of triethylamine.[90,101] We decided to use a similar approach for synthesis of *N'*-(substituted benzyl)-*N,N*-dimethylureas directly from readily available substituted benzylamines in a 'one pot' reaction (Scheme 3.3).

Slow addition of a solution of the appropriate benzylamine **67** in DCM to a stirred solution of triphosgene in DCM at 0 °C produced the corresponding benzyl isocyanates **112** *in situ* (Scheme 3.3). A solution of dimethylamine in THF was slowly added to **112** at 0 °C and the reaction mixture was stirred at 0 °C for an extra 1 h. The reaction mixture was worked-up and the products were separated by extraction using

boiling EtOAc/Et_2O (1:3), in which *N'*-benzyl-*N,N*-dimethylureas **107**, **108**, **111**, **113** and **114** dissolved and were obtained in 74-82% yield after crystallizing nicely as colourless crystals from the EtOAc/Et_2O solution. The corresponding dibenzylureas **115** (Figure 3.1) were highly insoluble in hot EtOAc/Et_2O and were collected by filtration as white solids in 2-4% yield (based on **67**). The nature of the products is illustrated in Table 3.1, which also gives the yields obtained. The products were characterized by standard spectroscopic methods (see Chapter 7; Section 7.18).



Scheme 3.3

Table 3.1: Synthesis of *N'*-(substituted benzyl)-*N,N*-dimethylureas **107**, **108**, **111**, **113** and **114** according to Scheme 3.3

R	Yield (%)	
	107, 108, 111, 113 and 114[a]	**115a-e**[b]
H	81	4
4-OMe	82	3
2-OMe	79	2
4-Me	80	3
2-Me	74	4

[a] Yield of pure product.
[b] Based on the amount of benzylamine **67**.

N,N'-Bis(substituted benzyl)ureas **115a-e** (Figure 3.1) were formed as by-products, presumably as a result of reactions of benzylamines **67** with their corresponding benzyl isocyanates **112**, which were generated *in-situ*. The formation of **115** (2-4% yield) was not avoidable even when the addition of benzylamine **67** to a solution of triphosgene was very slow. Dibenzylurea **115a** was obtained as the main product when the mode of addition was reversed, so that a solution of triphosgene was added to **67**.

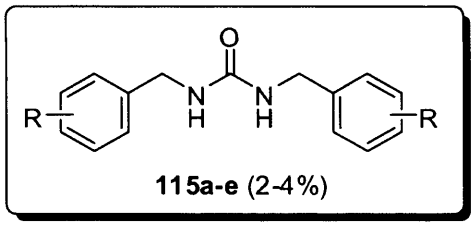
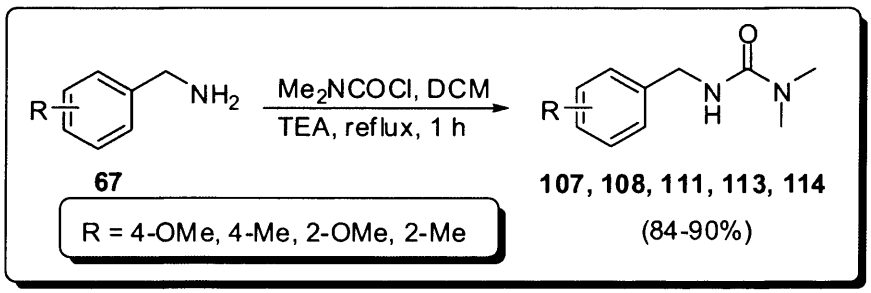


Figure 3.1

As can be seen from Table 3.1, the yields of all compounds were good, proving that the procedure is general for a range of substituents, and this overcomes the poor availability and stability of appropriately substituted benzyl isocyanates. Therefore, it represents a useful one pot procedure for the synthesis of *N'*-(substituted benzyl)-*N,N*-dimethylureas. However, the method always produced *N,N'*-bis(substituted benzyl)ureas **115** as side-products. Therefore, our attention was next turned to the syntheses of *N'*-(substituted benzyl)-*N,N*-dimethylureas from reactions of substituted benzylamines **67** with dimethylcarbamoyl chloride in order to compare the product yields from such a method with the ones obtained using the triphosgene method.

3.3 Syntheses of *N'*-benzyl-*N,N*-dimethylureas from reactions of benzylamines with dimethylcarbamoyl chloride

A mixture of **67** and dimethylcarbamoyl chloride in DCM, in the presence of triethylamine as a base, was heated under reflux conditions for 1 h (Scheme 3.4). The reaction mixture was allowed to cool to room temperature and poured onto water. Following work-up the residue obtained was purified by crystallization from Et_2O or EtOAc/Et_2O mixture (1/3) to give the pure *N'*-(substituted benzyl)-*N,N*-dimethylureas **107**, **108**, **111**, **113** and **114** as white crystals in high yields (Table 3.2). The products were found to be identical in all respects with the ones produced according to Scheme 3.3 using triphosgene.



Scheme 3.4

As can be seen from Table 3.2, the yields were high. Therefore, either of the two methods can be used for synthesis of such compounds. However, the method involving dimethylcarbamoyl chloride gave better yields with no side-products being obtained, but the hazards of the reagents involved in both methods should also be taken into consideration.

Table 3.2: Synthesis of *N'*-(substituted benzyl)-*N,N*-dimethylureas **107**, **108**, **111**, **113** and **114** according to Scheme 3.4

Compound	R	Yield (%)[a]
107	H	88
108	4-OMe	89
111	2-OMe	85
113	4-Me	90
114	2-Me	84

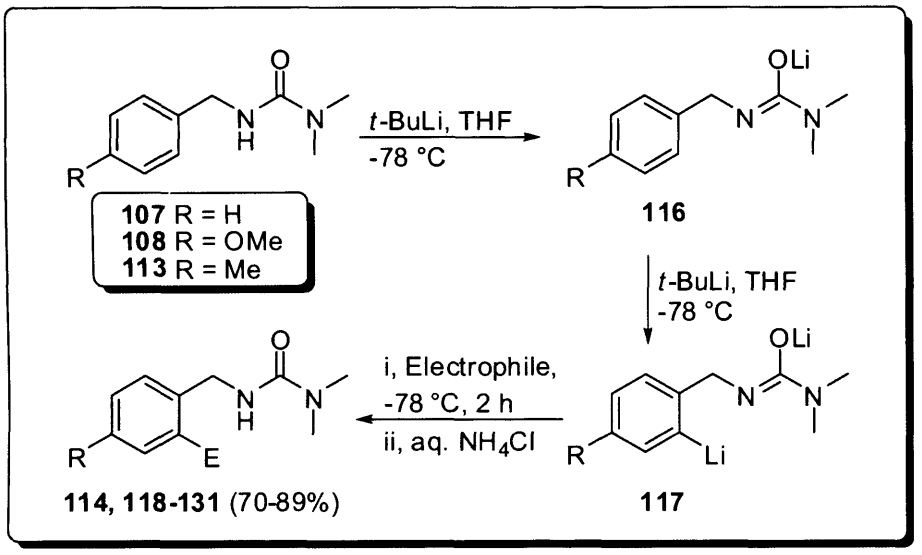
[a] Yield of isolated product after crystallization.

Having successfully synthesized various *N'*-(substituted benzyl)-*N,N*-dimethylureas, our attention was next turned to investigate their lithiation reactions, under the general conditions used for *N*-benzylpivalamides (Chapter Two) using *t*-BuLi at -78 °C, followed by reaction with a range of electrophiles to give the corresponding substituted derivatives.

3.4. Directed lithiation of *N'*-benzyl-*N,N*-dimethylureas 107, 108 and 113

Previous experience with *N*-benzylpivalamides (Chapter Two) suggested that *t*-BuLi might provide higher yields of lithiation products than *sec*- or *n*-BuLi. Therefore, double lithiation of *N'*-benzyl-*N,N*-dimethylurea (**107**), *N'*-(4-methoxybenzyl)-*N,N*-dimethylurea (**108**), and *N'*-(4-methylbenzyl)-*N,N*-dimethylurea (**113**) were attempted under identical conditions using *t*-BuLi (2.2 mole equivalents) at -78 °C in anhydrous THF under nitrogen (Scheme 3.5). Two mole equivalents of *t*-BuLi were required, the first one to deprotonate the urea to form the monolithium reagents **116** as yellow solutions and the second to deprotonate at position 2 to give the dilithium reagents **117** as reddish orange solutions (Scheme 3.5). The mixtures were stirred for 4 h at -78 °C in an attempt to ensure complete formation of dilithium reagents **117**. The general utility of **117** was demonstrated by their further reactions with a range of electrophiles (benzaldehyde, 4-anisaldehyde, benzophenone,

iodomethane, iodoethane, or deuterium oxide) for 2 h at –78 °C under identical conditions (Scheme 3.5). The mixtures were allowed to warm to room temperature and quenched by the addition of aqueous NH_4Cl solution. Following work-up, the crude products were purified by column chromatography (silica gel; Et_2O–hexane, 1:3) to give the corresponding pure products identified as *N'*-(2-substituted benzyl)-*N,N*-dimethylureas **114** and **118-131** (Scheme 3.5) in high yields (Table 3.3). The products were all characterised by standard spectroscopic methods (see Chapter 7; Section 7.20).



Scheme 3.5

The NMR spectra of all compounds showed the presence of CH_2 signals, indicating that lithiation took place on the ring. The ^1H NMR spectra of compound **118**, **119**, **122**, **123**, **127** and **128** showed that the signals of the two hydrogens of the CH_2 group appeared separately, as two separated double doublets, which converted to two doublets after addition of D_2O, verifying that they are diastereotopic and coupling to NH. Such compounds would, of course, be formed as racemic mixtures. Indeed, the X-ray crystallography[92] of compounds **122** (Figure 3.2) and **127** (Figure 3.3) showed a single type of crystal containing both enantiomers in equal proportions in each case, but the structure displayed shows the structure as (*S**)-*N'*-(2-(hydroxy(4-methoxyphenyl)methyl)-4-methoxybenzyl)-*N,N*-dimethylurea and (*R**)-*N'*-(2-(hydroxy(4-methoxyphenyl)methyl)-4-methylbenzyl)-*N,N*-dimethylurea, respectively.

Table 3.3: Synthesis of *N'*-(2-substituted benzyl)-*N,N*-dimethylureas **114** and **118-131** according to Scheme 3.5

Product	R	Electrophile	E	Yield (%)[a]
114	H	MeI	Me	80
118	H	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	86
119	H	PhCHO	PhCH(OH)	82
120	H	Ph_2CO	$Ph_2C(OH)$	84
121[b]	H	D_2O	D	89
122	OMe	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	85
123	OMe	PhCHO	PhCH(OH)	89
124	OMe	Ph_2CO	$Ph_2C(OH)$	84
125[b]	OMe	D_2O	D	86
126	OMe	EtI	Et	88[c]
127	Me	4-$MeOC_6H_4CHOH$	4-$MeOC_6H_4CH(OH)$	76
128	Me	PhCHO	PhCH(OH)	70
129	Me	Ph_2CO	$Ph_2C(OH)$	72
130	Me	EtI	Et	80
131[b]	Me	D_2O	D	86

[a] Yield of isolated product after purification by column chromatography.
[b] Deuteration was at least *ca.* 95% as indicated by NMR spectra.
[c] *N'*-Ethyl-*N'*-(2-ethyl-4-methoxybenzyl)-*N,N*-dimethylurea (**132**) was obtained as a side product in 3% yield due to substitution at nitrogen. Compound **132** was obtained in 90% yield after purification when the reaction was repeated with EtI (2.2 equiv.).

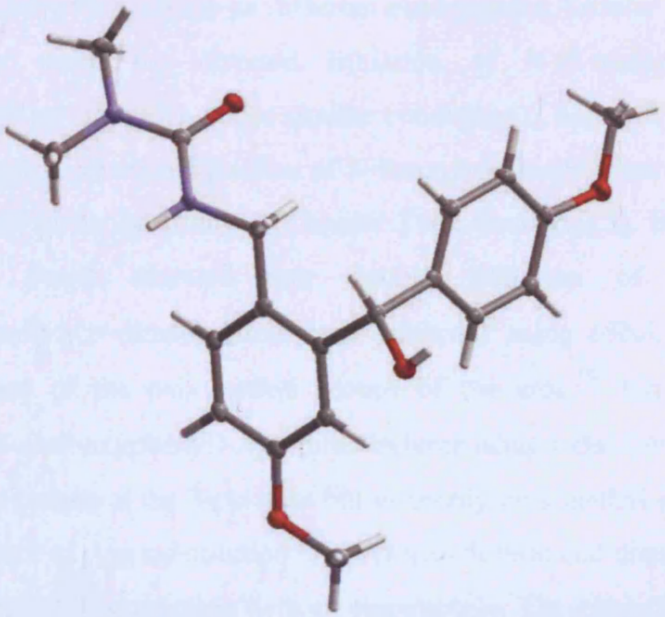


Figure 3.2 X-ray crystal structure of compound **122**. Thermal ellipsoids are shown at the 50% probability level.

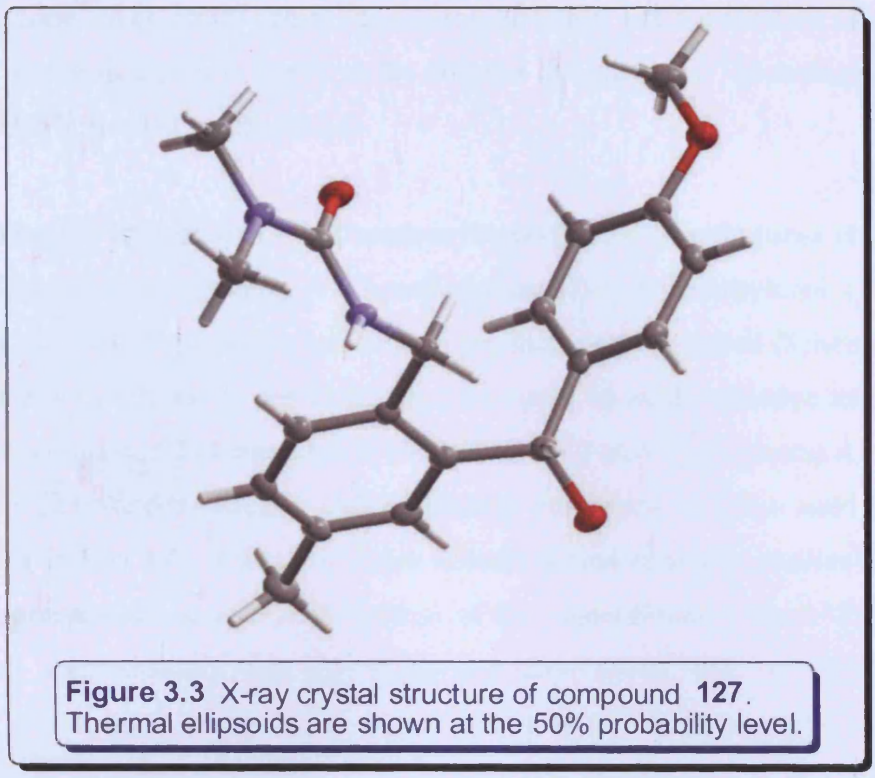


Figure 3.3 X-ray crystal structure of compound **127**. Thermal ellipsoids are shown at the 50% probability level.

From the results in Table 3.3 it is clear that *ortho*-lithiation of *N'*-benzyl-*N,N*-dimethylureas **107**, **108** and **113**, *ortho* to urea containing group, is a general process that can be conducted using *t*-BuLi at –78 °C as well as *sec*-BuLi at –50 °C (as used by Schlosser[96]) and with a variety of different electrophiles. Similar observations had been previously made for directed lithiation of *N*-(4-methoxybenzyl)- and *N*-(4-methylbenzyl)pivalamides under similar conditions (Chapter Two; Sections 2.7 and 2.9, respectively), whereas lithiation of *N*-benzylpivalamide was not selective and gave ring and side chain substitution (Chapter Two; Section 2.3). By contrast to the situation here, Smith showed that double lithiation of *N'*-phenyl and *N'*-(4-methylphenyl)-*N,N*-dimethylureas was achieved using *t*-BuLi at -20 °C and took place on one of the two methyl groups of the urea.[101] On the other hand, lithiation of *N'*-(4-methoxyphenyl)-*N,N*-dimethylurea using *t*-BuLi at 0 or -20 °C took place partially on carbon at the 3-position but primarily on a methyl group of the urea, leading to a mixture of ring substitution, methyl substitution and disubstitution (on the ring and on the methyl) on reaction with an electrophile. The disubstituted derivatives were obtained in high yields when 3 equivalents of *t*-BuLi and excess of the electrophile were used.[101]

Having successfully achieved directed lithiation and substitution of **107**, **108** and **113**, attention was next turned to the directed lithiation of *N'*-(2-methoxybenzyl)-*N,N*-dimethylurea (**111**) with *t*-BuLi.

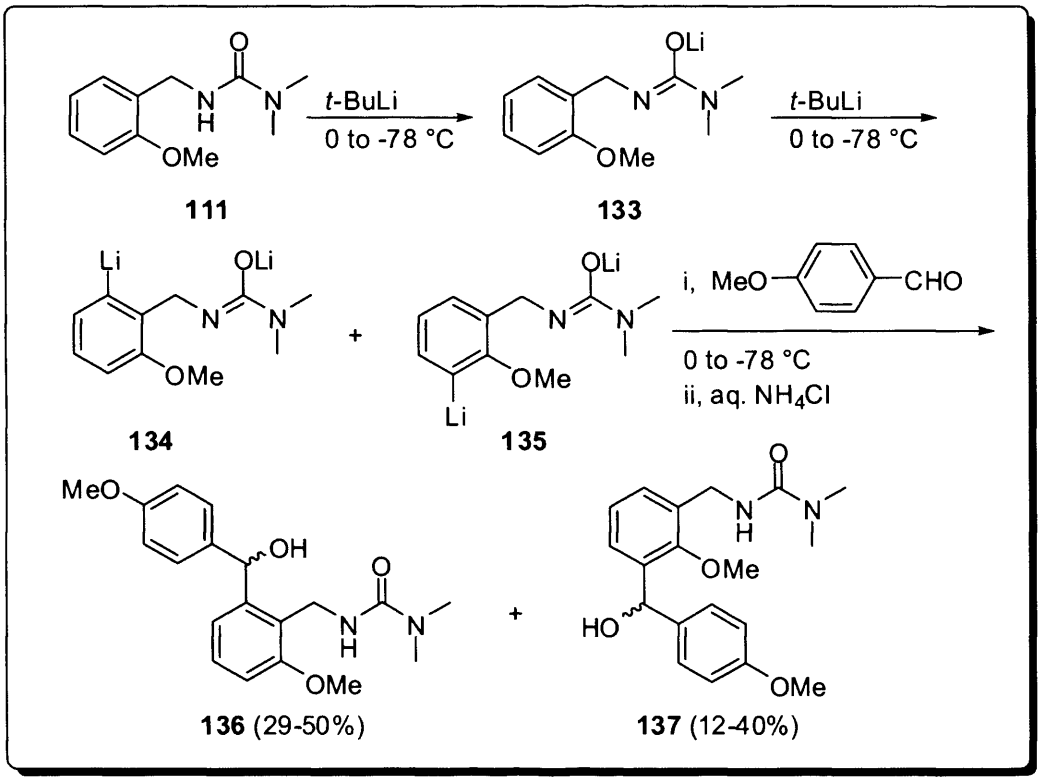
3.5 Directed lithiation of *N'*-(2-methoxybenzyl)-*N,N*-dimethylurea (111)

Schlosser has lithiated *N'*-(2-methoxybenzyl)-*N,N*-dimethylurea (**111**) with *sec*-BuLi, at *o*- and *o'*-positions, but no pure products were separated (Scheme 3.2).[96]

It was of interest to see if the reaction could be made selective and general. Therefore, compound **111** was treated with *t*-BuLi (2.2 mole equivalents) at –78 °C in anhydrous THF under nitrogen under identical conditions to those used for other substrates (Section 3.4). It was found that initial addition of *t*-BuLi provided a yellow solution, presumably because of formation of the monolithium reagent **133** (Scheme 3.6), until approximately one equivalent had been added, then a reddish orange solution was formed as the remaining *t*-BuLi was added, presumably because of formation of a dilithium reagents. The mixture was stirred for 2 h at –78 °C in an attempt to ensure complete formation of the dilithium reagents. 4-Anisaldehyde was added and the mixture was stirred for 2 h at –78 °C. The mixture was worked-up and the product mixture was purified by column chromatography (silica gel; Et_2O–hexane, 1:3) to give two products subsequently identified as *N'*-(2-(hydroxy(4-methoxyphenyl)methyl)-6-methoxybenzyl)-*N,N*-dimethylurea (**136**; 29% yield) and *N'*-(3-(hydroxy-(4-methoxyphenyl)methyl)-2-methoxybenzyl)-*N,N*-dimethylurea (**137**; 26%), along with the starting material **111** (39%) and 4-anisaldehyde.

Compound **136**, having the hydroxy(4-methoxyphenyl)methyl group *ortho*- to the -$CH_2NHCONMe_2$ group, is the expected product from the reaction of 4-anisaldehyde with dilithium intermediate **134** (Scheme 3.6). Compound **137**, having the hydroxy(4-methoxyphenyl)methyl group *ortho*- to the methoxy group, is the expected product from the reaction of dilithium intermediate **135** with 4-anisaldehyde (Scheme 3.6). The sites of lithiations were the ones expected based on Schlosser's findings but in his case no pure products were separated from the reaction mixture.[96]

The ^{1}H NMR spectra of **136** and **137** showed signals for the two hydrogens of a CH_2 group appearing separately, as two separated double doublet, verifying that they were diastereotopic. Compounds **136** and **137** were of course present as racemic mixtures.



Scheme 3.6

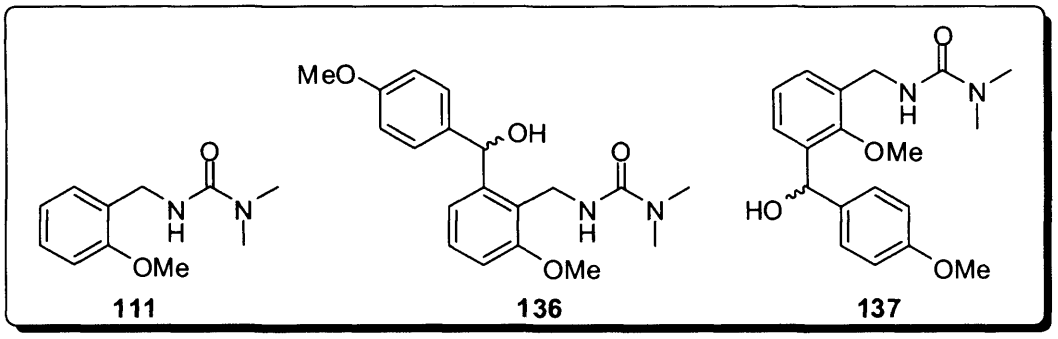
It was of interest to see if the reaction would proceed in the same manner under different reaction conditions. Therefore, a more detailed lithiation study of **111** using *t*-BuLi as the lithium reagent was conducted in an attempt to find conditions under which only one product would be obtained or to improve the yields of **136** and/or **137**. In this study the reaction time and temperature were varied. The results obtained are recorded in Table 3.4. It was found that double lithiation of **111** with *t*-BuLi at –78 °C for 4 h followed by reaction with 4-anisaldehyde for 4 h, gave **136** and **137** in slightly better yields (31 and 27%, respectively) along with residual **111** (34%) after separation by column chromatography (Table 3.4; entry 2).

On lithiation of **111** at –50 °C for 2 h followed by reaction with 4-anisaldehyde for 2 h it was found that yields of **136** and **137** were increased further to 35 and 33%, respectively (Table 3.4; entry 3), while the residual quantity of **111** was less (13%). When the reaction time of the lithium reagents with 4-anisaldehyde was increased to 4 h at –50 °C the yields of **136** and **137** were slightly increased to 36 and 34%, respectively (Table 3.4, entry 4).

It was clear from these results that the temperature had a greater effect on the yields of products than the reaction time. It was found that double lithiation of **111** at -20 °C for 2 h followed by reaction with 4-anisaldehyde for 2 h, gave **136** and **137** in

49 and 40%, respectively, with no starting material **111** being recovered (Table 3.4, entry 5). This result clearly indicated that good overall yields can be achieved from such a reaction.

Table 3.4: Yields of **136** and **137** under various reaction conditions according to Scheme 3.6 under various reaction conditions



Entry	T (°C)	Time (h) Lithiation	Yield (%)[a]		
			111	**136**	**137**
1	–78	2	39	29	26
2	–78	4	34	31	27
3	–50	2	13	35	33
4	–50	4	13	36	34
5	–20	2	—	49	40
6	0[b]	2	12	50	12

[a] Yield of isolated products after purification.
[b] Compound **138** (3%) and compound **139** (11%) were also obtained (Figure 3.4).

Double lithiation of **111** with *t*-BuLi for 2 h at 0 °C followed by reaction with 4-anisaldehyde for 2 h at 0 °C was attempted. Following work-up, the mixture was subjected to TLC, which showed that both products **136** and **137** were present, along with a small quantity of **111**. The TLC also showed the formation of two other minor products, subsequently shown to be **138** and **139** (Figure 3.4).

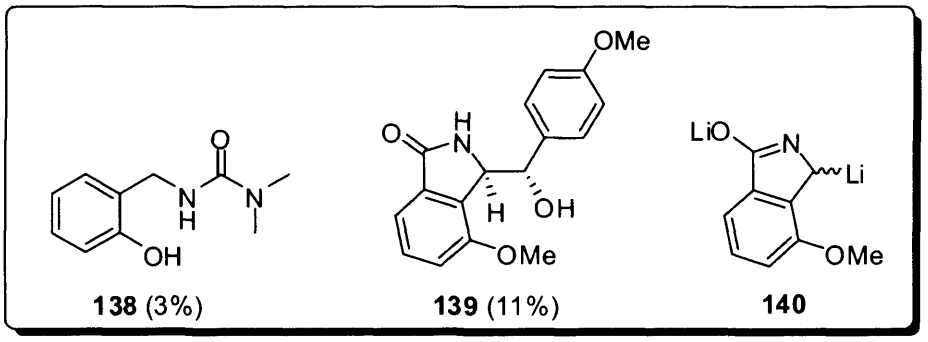


Figure 3.4

All compounds were separated by column chromatography (Table 3.4; entry 6). Compounds **136** and **137** were obtained in 50% and 12% yields, respectively, and **111** was recovered in 12% yield after column chromatography, while **138** and **139** were obtained in yields of 3% and 11%, respectively.

Compound **138** was formed due to cleavage of the ether bond by *t*-BuLi. The formation of **138** was avoided in subsequent experiments by very slow addition of *t*-BuLi. Compound **139** could potentially be formed as a pair of racemic diastereoisomers; however, its NMR spectra showed what appeared to be a single set of signals, indicating that the isolated product was a single racemic diastereoisomer. However, since this compound **139** was isolated in only 11% yield, it is possible that a small amount of the other diastereoisomer was formed but not isolated. The X-ray crystallography of compound **139** showed a single type of crystal containing both enantiomers in equal proportions, but the structure displayed (Figure 3.5)[92] shows only one part of the repeating unit, indicating the structure as 3-(*R**)-3-((*S**)-hydroxy(4-methoxyphenyl)methyl)-4-methoxyisoindolin-1-one. Compound **139** could arise from the reaction of the cyclic lithium intermediate **140** (Figure 3.4), generated *in situ*, with 4-anisaldehyde. Successful syntheses in higher yield of **139** and other related derivatives will be discussed in Chapter Six.

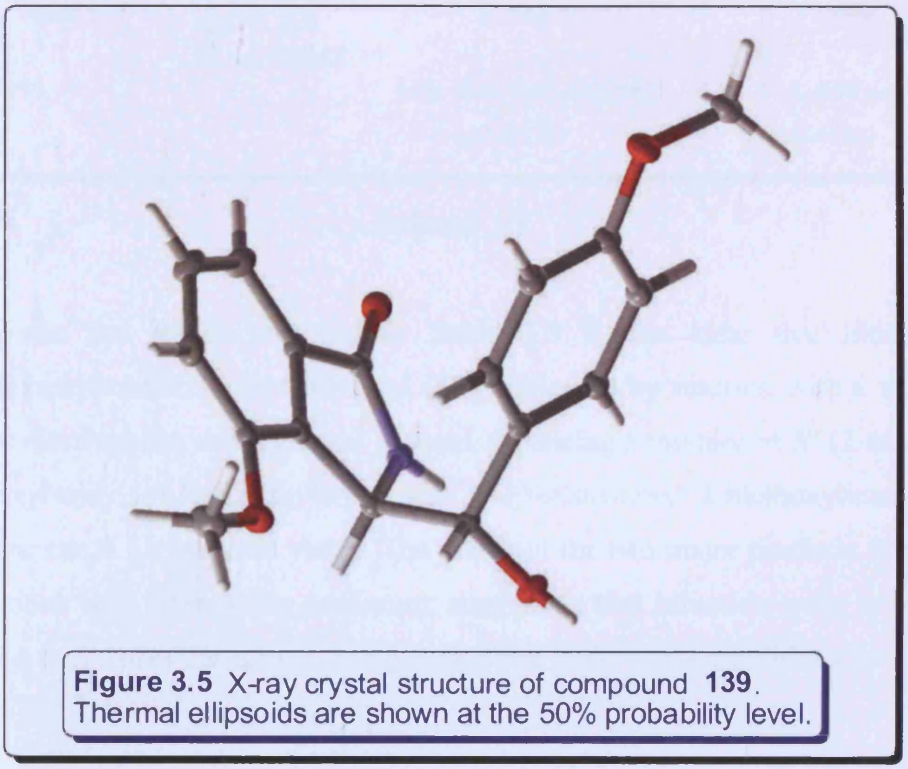
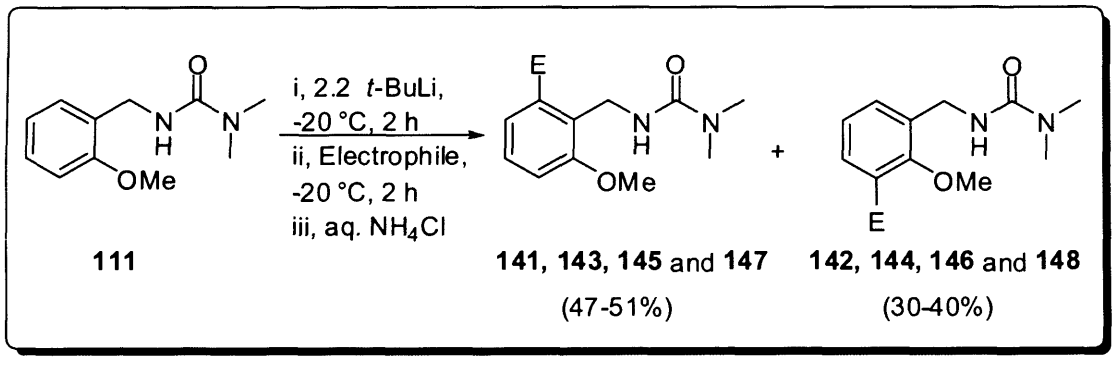


Figure 3.5 X-ray crystal structure of compound **139**. Thermal ellipsoids are shown at the 50% probability level.

Clearly, direct lithiation of **111** on the ring *ortho* to the urea containing group without lithiation *ortho* to the methoxy group was not a realistic hope. Both substitution sites were attacked competitively. It was nevertheless of interest to see if the reaction of the dilithium intermediates **134** and **135** with other electrophiles at -20 °C would be general to produce *N'*-(2-substituted 6-methoxybenzyl)-*N,N*-dimethylureas and *N'*-(3-substituted 2-methoxybenzyl)-*N,N*-dimethylureas. Consequently, reactions of the lithium reagents **134** and **135**, prepared *in-situ* from compound **111**, with a range of electrophiles (benzaldehyde, benzophenone, iodomethane, or iodoethane) were carried out at -20 °C (Scheme 3.7). Each reaction was conducted under identical conditions and then worked-up. The products were separated by column chromatography (silica gel; Et_2O–hexane, 1:3), to give a mixture of the corresponding *N'*-(2-substituted 6-methoxybenzyl)-*N,N*-dimethylureas **141**, **143**, **145** and **147** and *N'*-(3-substituted 2-methoxybenzyl)-*N,N*-dimethylureas **142**, **144**, **146** and **148** (Scheme 3.7) in high overall yields (Table 3.5). The products were characterised by standard spectroscopic methods (see Chapter 7; Section 7.24).



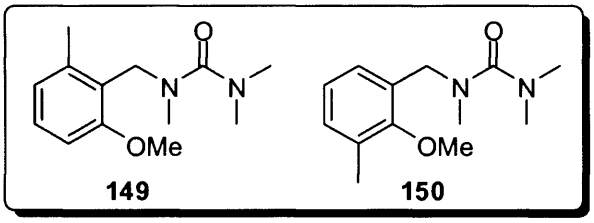
Scheme 3.7

From the results recorded in Table 3.5 it was clear that lithiation of *N'*-(2-methoxybenzyl-*N,N*-dimethylurea (**111**) followed by reaction with a variety of different electrophiles was a general process, producing a mixture of *N'*-(2-substituted 6-methoxybenzyl)-*N,N*-dimethylureas and *N'*-(3-substituted 2-methoxybenzyl)-*N,N*-dimethylureas in high overall yields. The yields of the two major products from all of the reactions were remarkably consistent, suggesting that lithiation *ortho* to methoxy and *ortho* to the urea containing group took place under these conditions in a ratio of around 55:45.

Table 3.5: Synthesis of *N'*-(2-substituted 6-methoxybenzyl)-*N,N*-dimethylureas **141**, **143**, **145** and **147** and *N'*-(3-substituted 2-methoxybenzyl)-*N,N*-dimethylureas **142**, **144**, **146** and **148** according to Scheme 3.7

Electrophile	E	Yield (%)[a]	
		141,[b] 143, 145 and 147	142,[b] 144, 146 and 148
PhCHO	PhCH(OH)	51	38
Ph_2CO[c]	$Ph_2C(OH)$	47	30
MeI[d]	Me	51	40
EtI	Et	51	38

[a] Yield of isolated products after purification.
[b] The ^1H NMR spectra showed diastereotopicity for the two hydrogens of the CH_2 groups.
[c] Starting material **111** (4%) was recovered.
[d] Compounds **149** and **150** (Figure 3.6) were obtained in 5% combined yield, but as a mixture which was difficult to separate. Formation of **149** and **150** clearly indicated that methylation had taken place at both the ring (*o*-/*o'*-) and the nitrogen.



149 **150**

Figure 3.6

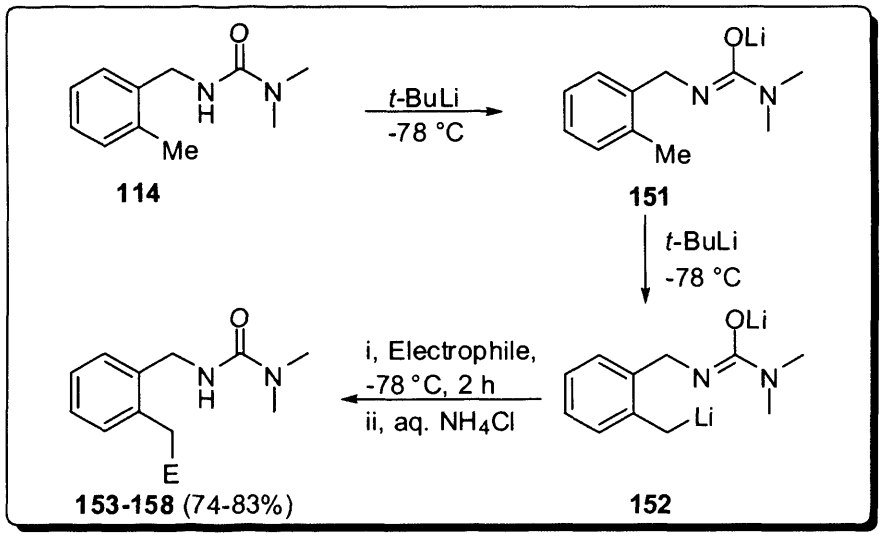
The results obtained from directed lithiation and substitution of **108** (Section 3.4) and **111** are consistent with the results obtained by Schlosser for both substrates.[96] When the methoxy group was at the 4-position lithiation took place at the 2-position. This indicates that the urea containing group is intrinsically a better directing metallating group than methoxy. However, when the methoxy was at the 2-position lithiation occurred on the ring competitively at the 3-position, next to the methoxy group, and at the 6-position, next to $-CH_2NHCONMe_2$. The reasons for the change are not known. However, in the case of the 2-methoxy derivative **111** the two groups capable of coordinating the metallating agent (monolithiated $-CH_2NHCONMe_2$ and methoxy) are adjacent to each other and may possibly chelate the incoming metallating agent.

Finally, attention was next turned to lateral lithiation of *N'*-(2-methylbenzyl)-*N,N*-dimethylurea (**114**) using t-BuLi at -78 °C.

3.6 Lateral lithiation of *N'*-(2-methylbenzyl)-*N,N*-dimethylurea (114)

An activating group with the ability to coordinate and to acidify is important in benzylic lithiation as well as *ortho*-lithiation. However, the acidifying groups in *ortho*-lithiation operate by inductive effects, since the C-Li bond is in the same plane as the aromatic ring, while, for lateral lithiation involving formation of a benzylic C-Li bond, the acidifying group works best by conjugation.[8] Lateral lithiation of various aromatics containing nitrogen-based stabilising groups on the *ortho*-position has been reported previously.[8,13,93-95] Also, we have shown that lateral lithiation of *N*-(2-methylbenzyl)pivalamide took place smoothly on the methyl group with *t*-BuLi at -78 °C (Chapter Two; Section 2.10). Therefore, it was of interest to test the possibility of lateral lithiation of *N'*-(2-methylbenzyl)-*N,N*-dimethylurea (**114**) under similar conditions.

Indeed, treatment of **114** with *t*-BuLi (2.2 mole equivalents) at –78 °C in THF gave a yellow solution presumed to be the monolithium reagent **151** and then turned to a reddish orange solution presumed to be the dilithium reagent **152** (Scheme 3.8). The mixture was stirred for 4 h at -78 °C and then the dilithium reagent was allowed to react with a range of electrophiles (benzaldehyde, 4-anisaldehyde, benzophenone, acetophenone, iodoethane, or deuterium oxide). Each reaction was conducted under identical conditions and then worked-up. The crude products were purified by column chromatography (silica gel; Et_2O–hexane, 1:3), to give the corresponding *N'*-(2-(substituted methyl)benzyl)-*N,N*-dimethylureas **153-158** (Scheme 3.8) in good yields (Table 3.6). The products were all characterised by standard spectroscopic methods (see Chapter 7; Section 7.25).



Scheme 3.8

Table 3.6: Synthesis of *N'*-(2-(substituted methyl)benzyl)-*N,N*-dimethylureas **153-158** according to Scheme 3.8

Product	Electrophile	E	Yield (%)[a]
153	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	79
154	PhCHO	PhCH(OH)	77
155	PhCOMe	PhCH(OH)Me	74
156	Ph_2CO	$Ph_2C(OH)$	76
157	EtI	Et	82
158[b]	D_2O	D	83

[a] Yield of isolated product after purification by column chromatography.
[b] Deuteration was over *ca.* 90% as indicated by NMR spectra.

The NMR spectra of all compounds showed the presence of two different CH_2 groups. The ^1H NMR spectra of compounds **153-155** showed that the signals of the two protons of the two CH_2 groups, $-CH_2NHCONMe_2$ and the CH_2 group at the 2-position, appeared separately, verifying that they are diastereotopic. Such compounds were of course present as racemic mixtures.

As can be seen from Table 3.6, it is clear that lateral lithiation of **114** is a general process that can be conducted using *t*-BuLi and with a variety of different electrophiles. The difference in lithiation site in the case of *N'*-(4-methylbenzyl)-*N,N*-dimethylurea and *N'*-(2-methylbenzyl)-*N,N*-dimethylurea is presumably because the acidity of the 2-methyl group is higher than that of the ring hydrogens, but when it is in the 4-position the advantage gained from the coordination of the lithium to the directing group encourages lithiation at the ring. Also, when the methyl group is in a position close to the coordination site (*i.e.* position 2), the geometry and/or the acidity of the methyl group made it the site of choice for metallation.

3.7 Conclusion

Various substituted *N'*-benzyl-*N,N*-dimethylurea derivatives have been synthesized in high yield *via* simple and efficient lithiation procedures of *N'*-benzyl-*N,N*-dimethylureas followed by reactions with a range of electrophiles. Lithiation of unsubstituted *N'*-benzyl-*N,N*-dimethylurea, *N'*-(4-methoxybenzyl)-*N,N*-dimethylurea and *N'*-(4-methylbenzyl)-*N,N*-dimethylurea with *t*-BuLi at -78 °C in THF followed by reactions with various electrophiles gave ring substitution at position 2 *ortho* to the urea containing group, which therefore acted as a directed metallating group (DMG). By contrast, lithiation of *N'*-(2-methoxybenzyl)-*N,N*-dimethylurea with *t*-BuLi at

-20 °C in THF, with a methoxy group at position 2, followed by reactions with a range of electrophiles gave mixtures of ring substitution next to the methoxy group (*o'*-substitution) and next to the urea containing group (*o*-substitution). The yields of the two products from all of the reactions were remarkably consistent, suggesting that lithiation *ortho* to methoxy and *ortho* to the urea containing group took place under these conditions in a ratio of around 55:45. It was found that lithiation of *N'*-(2-methylbenzyl)-*N,N*-dimethylurea, where the methyl group was at position 2, with *t*-BuLi at -78 °C in THF, followed by reactions with various electrophiles, gave products substituted in the methyl group, with no evidence for ring or side-chain substitution.

CHAPTER FOUR

SYNTHESIS OF SUBSTITUTED ISOINDOLINES

CHAPTER FOUR

SYNTHESIS OF SUBSTITUTED ISOINDOLINES

4.1 Introduction

Isoindoles show significant applications and useful properties since this ring system can be found in a number of valuable compounds including alkaloids and drugs.[103-105] Isoindoles are commercially less important than indoles, at least partly because of a lack of good synthetic methods. Simple isoindoles can be prepared from the cyclization of 1,2-bis(bromomethyl)benzene, phthalaldehyde or 2-cyanobenzyl chloride with amines or alkoxides or by condensation reactions of carbonyl compounds with amines.[106,107] However, these are particularly applicable to produce isoindole compounds with no substituents on the benzenoid ring. Moreover, such synthetic methods involve various steps and/or provide low yields. However, Clayden has developed a very useful approach to dihydroisoindolones with particular substitution patterns using dearomatising cyclization of lithiated *N*-benzylbenzamides and demonstrated its utility for synthesis of natural products such as kainic acid.[108-112]

Other substitution patterns would be potentially available from reactions studied by Schlosser,[85,96] but the reported reactions were not always highly regioselective and their generality has never been tested. Therefore, we became interested to develop a new approach for the synthesis of various dihydroisoindole derivatives, whereby highly selective processes for *ortho*-lithiation would allow production of specifically substituted isoindolines.

In Chapters 2 and 3, we have reported convenient procedures for the directed lithiation of compounds of the general formula **159** (Figure 4.1) using *t*-BuLi in anhydrous THF at -78 °C followed by reactions with carbonyl compounds (aldehydes and ketones) to give the corresponding *ortho*-disubstituted products **160** (Figure 4.1) in high yields. The general utility of compounds **160** would be demonstrated by their cyclization to the corresponding dihydroisoindoles (or isoindolines) **161** (Figure 4.1). Therefore, the aim of the work presented in this chapter was to investigate if cyclization of **160** could be achieved and would be general. In this chapter, the successful cyclizations of **160** with trifluoroacetic anhydride (TFAA) in DCM at room temperature to give the corresponding isoindolines **161** in excellent yields are reported.

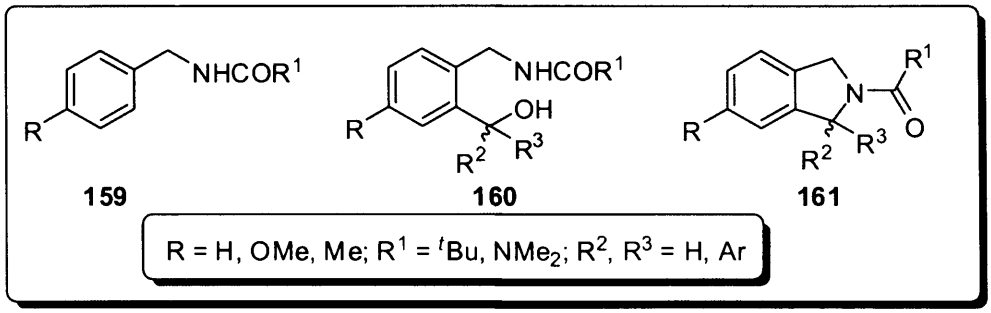
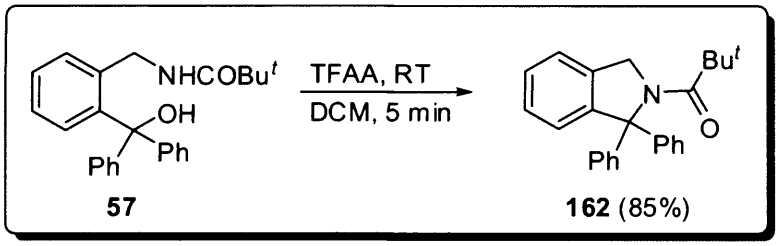


Figure 4.1

4.2 Synthesis of 1,1-diphenyl-2-pivaloylisoindoline (162)

It was hoped that cyclization of *N*-(2-(hydroxydiphenylmethyl)benzyl)-pivalamide (**57**) could be achieved *via* dehydration. Therefore, an initial reaction was carried out between compound **57** and few drops of TFAA at room temperature in DCM (Scheme 4.1). TLC was used to monitor the progress of the reaction, and indicated the formation of a new product, the formation of which was complete within 5 minutes. The mixture was quenched by the addition of water and worked-up. The residue obtained was subjected to flash column chromatography (silica gel; Et_2O–hexane, 1:3) to give the pure product, identified as compound **162**, in 85% yield.



Scheme 4.1

The chemical ionization (CI) mass spectrum showed a very high intensity (100%) pseudo molecular ion (MH^+) at m/z = 356. The accurate mass of the pseudo molecular ion confirmed the formula as $C_{25}H_{26}NO$ (MH^+), indicating the loss of 18 from the molecular weight of the starting material **57**. Moreover the microanalysis confirmed the formula of compound **162** as $C_{25}H_{25}N_2O$. The IR spectrum of compound **162** showed no absorption band corresponding to the stretching vibrations of the NH or OH group. Also, in the ^1H NMR spectrum there were no exchangeable hydrogens. Clearly, cyclization of **57** *via* dehydration had taken place and the structure of **162** was further confirmed by X-ray crystallography (Figure 4.2).[92]

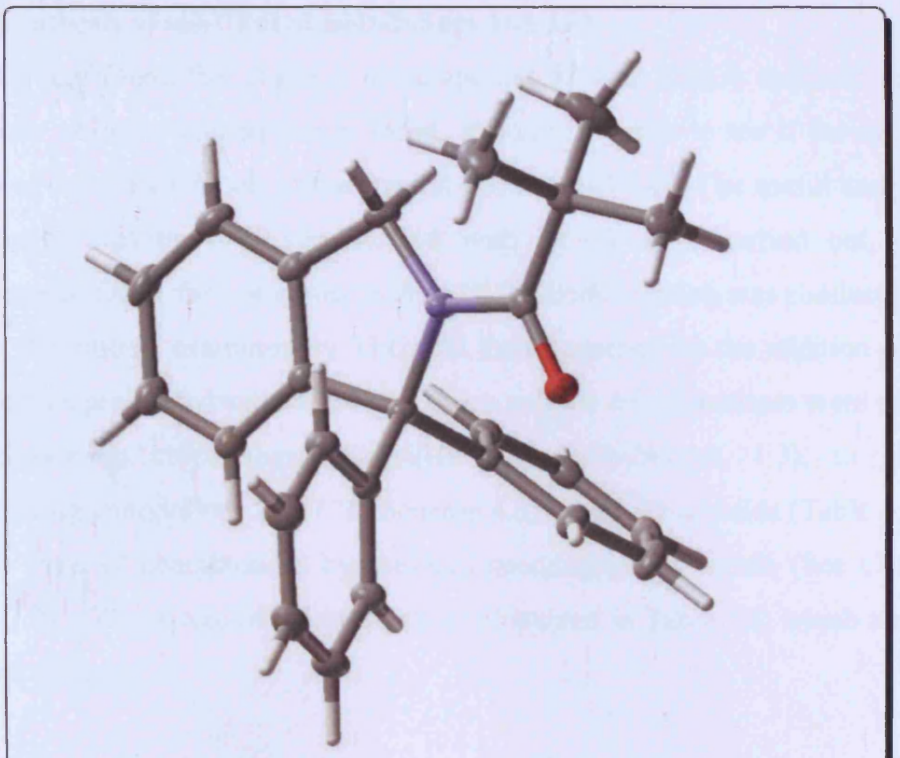
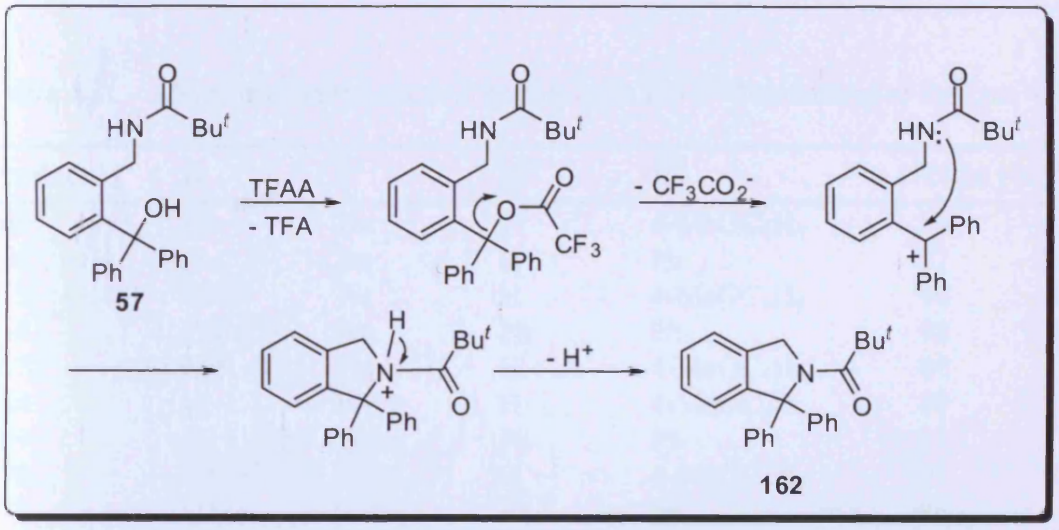


Figure 4.2 X-ray crystal structure of compound **162**. Thermal ellipsoids are shown at the 50% probability level.

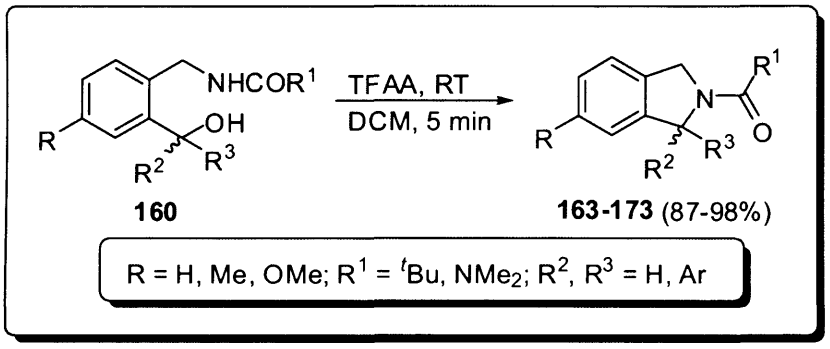
The cyclization would be consistent with Baldwin's rules as 5-exo-tet,[113,114] but it is far more likely that it occurs by an S_N1 mechanism (Scheme 4.2).



Scheme 4.2

4.3 Synthesis of substituted isoindolines 163-173

Having found that reaction of compound **57** with TFAA occurred smoothly and rapidly at room temperature in DCM, it was of interest to see if the cyclization reaction of other compounds of the general formula **160** would be useful and general. Consequently, reactions of various **160** with TFAA were carried out at room temperature in DCM for 5 minutes (Scheme 4.3). Each reaction was conducted under identical conditions, examined by TLC and then quenched by the addition of water. The reactions proceeded smoothly in all cases and the crude products were subjected to flash column chromatography (silica gel; Et_2O–hexane, 1:3), to give the corresponding isoindolines **163-173** (Scheme 4.3) in excellent yields (Table 4.1). The products were all characterised by standard spectroscopic methods (See Chapter 7; Section 7.27). The nature of the products is illustrated in Table 4.1, which also gives the yields obtained.



Scheme 4.3

Table 4.1: Synthesis of substituted isoindolines **163-173** according to Scheme 4.3

Product	R	R^1	R^2	R^3	Yield (%)[a]
163	H	^{t}Bu	H	4-$MeOC_6H_4$	89
164	H	^{t}Bu	H	Ph	87
165	OMe	^{t}Bu	H	4-$MeOC_6H_4$	90
166	OMe	^{t}Bu	Ph	Ph	98
167	Me	^{t}Bu	H	4-$MeOC_6H_4$	88
168	H	NMe_2	H	4-$MeOC_6H_4$	89
169	H	NMe_2	Ph	Ph	91
170	OMe	NMe_2	H	4-$MeOC_6H_4$	91
171	OMe	NMe_2	Ph	Ph	88
172	Me	NMe_2	H	4-$MeOC_6H_4$	91
173	Me	NMe_2	Ph	Ph	88

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

The ^{1}H NMR spectra of compounds **163-165**, **167**, **168**, **170** and **172** showed diastereotopicity for the two hydrogens of the CH_2 group at position 3 of the isoindoline ring. Such compounds would have been formed as racemic mixtures. However, the X-ray crystallography of compound **165** (Figure 4.3)[92] showed that the structure of the specific crystal looked at was (*S**)-6-methoxy-1-(4-methoxyphenyl)-2-pivaloylisoindoline. By contrast, the X-ray crystallography of compound **170** showed a single type of crystal containing both enantiomers in equal proportions, but the structure displayed (Figure 4.4)[92] shows only one part of the repeating unit, indicating the structure as (*R**)-2-dimethylaminocarbonyl-6-methoxy-1-(4-methoxyphenyl)isoindoline.

The two-dimensional NMR correlation spectroscopy (COSY) for compound **170** showed that one of the hydrogens at the 3-position was also coupled to H-1. It also showed that there was no coupling between H-4 and either of the hydrogens at position 3 or between H-1 and H-7.

Figure 4.3 X-ray crystal structure of compound **165**. Thermal ellipsoids are shown at the 50% probability level.

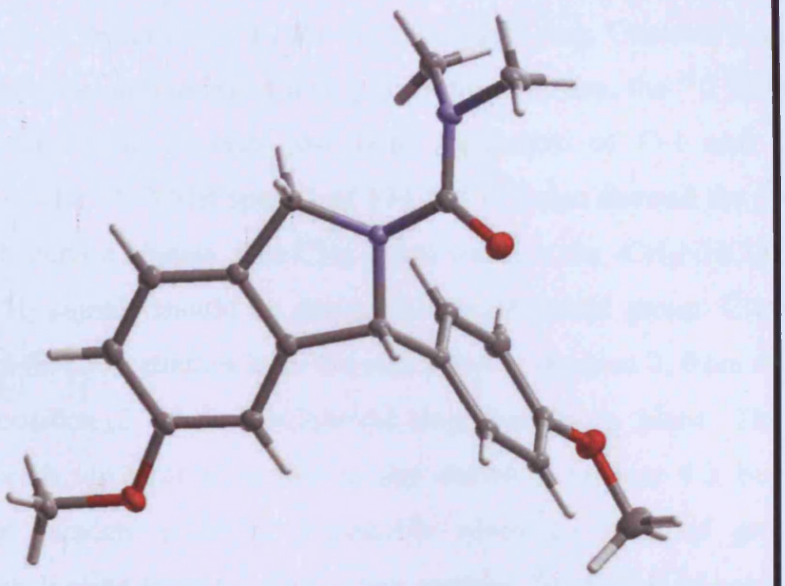
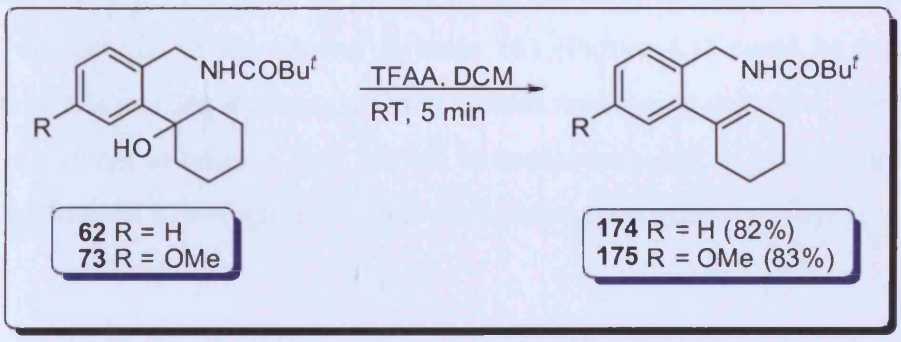


Figure 4.4 X-ray crystal structure of compound **170**. Thermal ellipsoids are shown at the 50% probability level.

4.4 Synthesis of *N*-(2-cyclohexenylbenzyl)pivalamides 174 and 175

It was found that reactions of *N*-(2-(1-hydroxycyclohexyl)benzyl)pivalamide (**62**) and *N*-(2-(1-hydroxycyclohexyl)-4-methoxybenzyl)pivalamide (**73**), where the substituent at position 2 was a hydroxycyclohexyl group, with TFAA in DCM at room temperature proceeded in a different manner (Scheme 4.4). Both reactions were conducted under conditions identical to those described in Schemes 4.1 and 4.3. The reaction mixtures were worked-up and the crude products were subjected to flash column chromatography (silica gel; Et_2O–hexane, 1:3), to give pure products, subsequently identified as **174** (82% yield) and **175** (83% yield), respectively (Scheme 4.4).



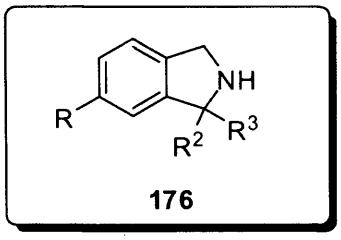
Scheme 4.4

The ^{1}H NMR spectra of compounds **174** and **175** showed the presence of only nine proton signals of the expected 10 for the cyclohexyl ring. One was a multiplet at relatively very low field suggestive of a vinylic hydrogen. Also, the ^{13}C NMR spectra showed signals resonating at very low field suggestive of C-1 and C-2 of a cyclohexenyl ring. The ^{13}C NMR spectra of **174** and **175** also showed the presence of five different CH_2 carbon signals. One CH_2 signal was due the $-CH_2NHCO^tBu$, while the other four CH_2 signals should be due to the cyclohexenyl group. Clearly, these patterns indicated that dehydration from the side chain at position 2, from the OH and a hydrogen at position 2 of the cyclohexyl ring, had taken place. The reaction presumably proceeds *via* a cation similar to that shown in Scheme 4.2, but loss of a proton from the adjacent position, impossible when the attached groups were aromatic, is easier, leading to an E1 elimination process. The failure of compounds **62** and **73** to cyclise was presumably because the carbenium ions formed by loss of water from the protonated species could easily eliminate a proton from the α-position of the cyclohexyl group to produce **174** and **175**, respectively, which is impossible in the case of aryl substituents.

In an attempt to convert compounds **62** and **73** to the corresponding cyclic products, we have attempted reactions of **62** and **73** with TFAA at room temperature but for longer reaction times up to 24 h. However, products **174** and **175** were obtained, respectively, in yields comparable to those obtained from reactions shown in Scheme 4.4. No further attempts were made to try to find conditions under which cyclization of **62** and **73** to the corresponding substituted isoindolines could be effective.

4.5. Attempted synthesis of 1-substituted isoindolines

In order to render the synthetic approach described in Sections 4.2 and 4.3 even more valuable, it would be useful if the pivaloyl or dimethylaminocarbonyl group in compounds of the general formula **161** (Figure 4.1) could be removed to reveal a free NH without the isoindole ring system itself being damaged. We therefore decided to attempt to remove such groups in compounds **161** to provide products of the general formula **176** (Figure 4.5) that would have even greater utility.



176

Figure 4.5

Using compounds **162** and **168** as models, these compounds were treated with a few drops of TFA at room temperature in DCM for 2 h. However, the quantitative recovery of starting materials indicated that no reactions took place under the conditions tried. Therefore, compounds **162** and **168** were treated with TFA, in the presence or absence of water, in DCM under reflux conditions for 20 minutes, at which time TLC indicated the presence of a complex mixture of products. Purification of the product mixtures by column chromatography on silica gel proved to be difficult and no pure products were separated. We have also attempted removal of the pivaloyl or dimethylaminocarbonyl group by the use of dilute hydrochloric acid but again there was no product obtained. No further attempts were made to try to find conditions under which removal of the pivaloyl group from **162** or the dimethylaminocarbonyl group from **168** could be effective.

4.6 Conclusion

Cyclization *via* dehydration of *N*-(2-substituted benzyl)pivalamides and *N'*-(2-substituted benzyl)-*N*,*N*-dimethylureas with trifluoroacetic anhydride as a catalyst in dichloromethane at room temperature takes place to give the corresponding isoindolines. The process is general, simple and convenient for compounds having aromatic groups attached to the carbinol carbon atom to produce various derivatives in excellent yields. However, when a hydroxycyclohexyl group is present at position 2, cyclization is not successful and dehydration from the OH group and the hydrogen at position 2 of the cyclohexyl ring takes place to produce cyclohexenyl derivatives in high yield. Attempts to remove the pivaloyl or dimethylaminocarbonyl group from position 1 of the isoindoline ring using trifluoroacetic acid were not successful.

CHAPTER FIVE

SYNTHESIS OF SUBSTITUTED TETRAHYDROISOQUINOLINES

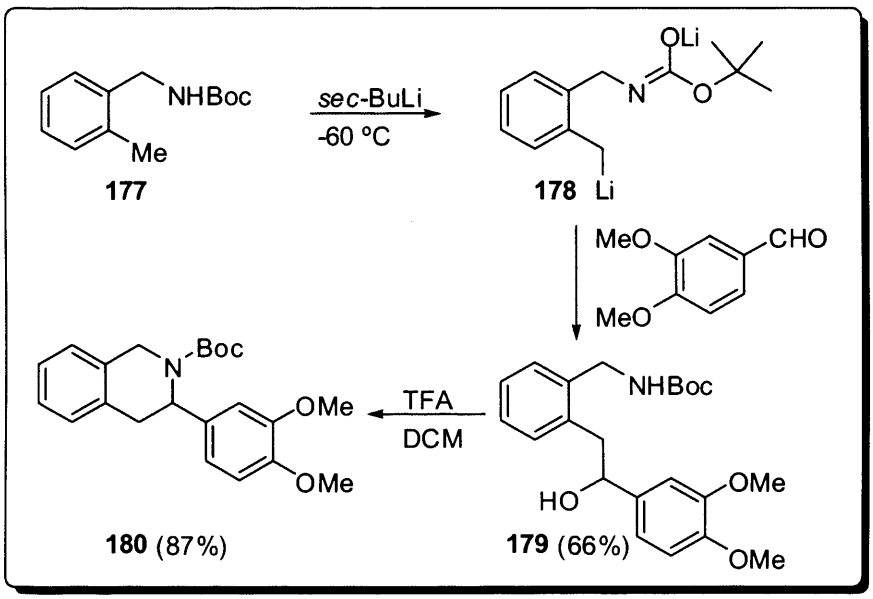
CHAPTER FIVE

SYNTHESIS OF SUBSTITUTED TETRAHYDROISOQUINOLINES

5.1 Introduction

Dihydroisoquinoline is an important and useful skeleton in organic synthesis.[115] A number of approaches to the synthesis of dihydroisoquinolines has been developed.[116-118] However, most of the reported syntheses require multiple steps. Considerable effort has been directed toward the development of efficient syntheses of these compounds using a wide range of transition-metal catalysts. Recently, transition-metal-catalyzed cyclizations of 2-(1-alkynyl)arylaldimines were used as tools for the syntheses of isoquinolines,[119,120] and they were also successfully applied to the total synthesis of natural products.[121] Unfortunately, some of the syntheses would create a number of environmental disadvantages, such as the production of large quantities of toxic or corrosive waste, if used on a large scale.

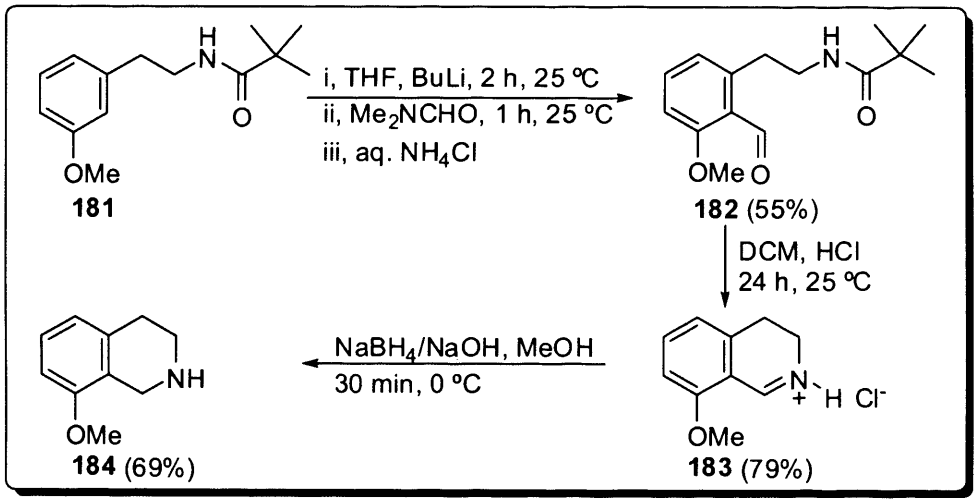
Two useful approaches to the synthesis of 1,2,3,4-tetrahydroisoquinolines, involving lithiation procedures, have been reported (Schemes 5.1 and 5.2).[122,123] One method simply involves lithiation of *N*-(*tert*-butoxycarbonyl)-2-methylbenzylamine (**177**) with *sec*-BuLi at -60 °C to give the lithium intermediate **178** which on reaction with veratraldehyde produces **179** in 66% yield. Treatment of **179** with TFA gives the corresponding tetrahydroisoquinoline **180** in 87% yield (Scheme 5.1).[122]



Scheme 5.1

However, the cyclization appears to require the presence of the 4-methoxy group in the electrophile, presumably through stabilization of the intermediate carbenium ion, as the corresponding unsubstituted phenyl compound (when benzaldehyde was used as the electrophile) failed to cyclise under similar, or more strongly acidic, conditions. Also, no cyclization took place when other carbonyl compounds were used, *e.g.* benzophenone and cyclohexanone.[122]

The other approach, reported by Schlosser, involved lithiation of 2-(3-methoxyphenyl)-*N*-pivaloylethylamine (**181**) at room temperature with BuLi at the aromatic position flanked by the two substituents (OMe and $-CH_2CH_2NHCO^tBu$) and the lithium reagent thus formed was reacted with *N*,*N*-dimethylformamide (DMF) to produce the corresponding aldehyde **182** in 55% yield (Scheme 5.2).[123] Acid catalysed cyclization of **182** gave 8-methoxy-3,4-dihydroisoquinoline hydrochloride (**183**) in 79% yield, which on treatment with sodium hydroxide and sodium borohydride afforded 8-methoxy-1,2,3,4-tetrahydroisoquinoline (**184**) in 69% yield (Scheme 5.2).[123] However, the generality of the reaction has never been tested. Therefore, we became interested in developing a new approach for the synthesis of tetrahydroisoquinoline derivatives, whereby regioselective lithiation would allow production of specifically substituted tetrahydroisoquinolines.



Scheme 5.2

In Chapters 2 and 3, we have reported convenient procedures for the lateral lithiation of compounds of the general formula **185** (Figure 5.1) using *t*-BuLi in anhydrous THF at -78 °C followed by reactions with carbonyl compounds (aldehydes

and ketones) to give the corresponding *ortho*-disubstituted products **186** (Figure 5.1) in high yields. The general utility of **186** would be demonstrated by their cyclization to the corresponding 1,2,3,4-tetrahydroisoquinolines **187** (Figure 5.1). It was of interest to see if cyclization of **186** could be achieved and would be general. Therefore, reactions of **186** were carried out with trifluoroacetic anhydride (TFAA) in DCM at room temperature. In this chapter, we report on the attempts to cyclise **186** under mild conditions to produce the corresponding tetrahydroisoquinolines **187**.

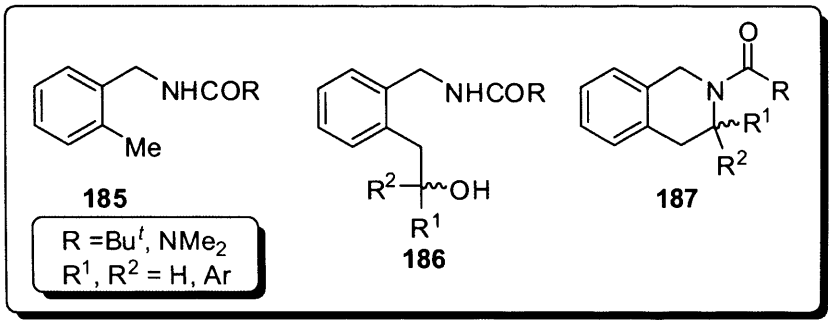


Figure 5.1

5.2 Attempted cyclizations of *N*-(2-(2-hydroxy-2-arylalkyl)benzyl)pivalamides

It was hoped that cyclization of *N*-(2-(2-hydroxy-2-arylalkyl)benzyl)-pivalamides could be achieved *via* dehydration. Three compounds were tested, namely compounds **99-101** (Figure 5.2)

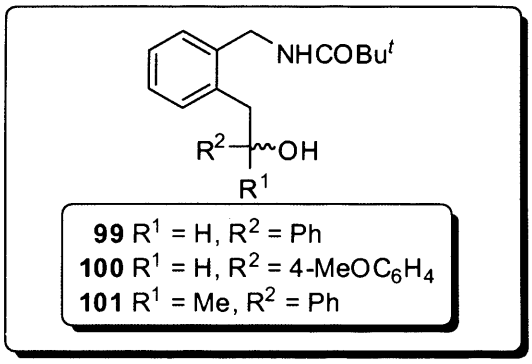
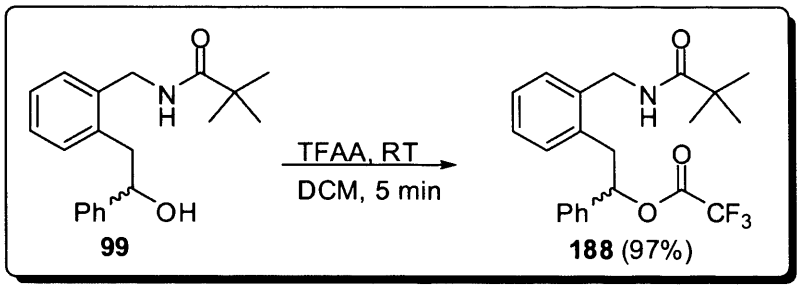


Figure 5.2

The first reaction was carried out between *N*-(2-(2-hydroxy-2-phenylethyl)benzyl)pivalamide (**99**) and TFAA at room temperature in DCM (Scheme 5.3). TLC indicated the formation of a new product, the formation of which was

complete within 5 minutes. The mixture was quenched by the addition of water and worked-up. The residue obtained was purified by flash column chromatography to give the pure product, identified as *N*-(2-(2-phenyl-2-trifluoroacetoxyethyl)benzyl)-pivalamide (**188**), obtained in 97% yield.

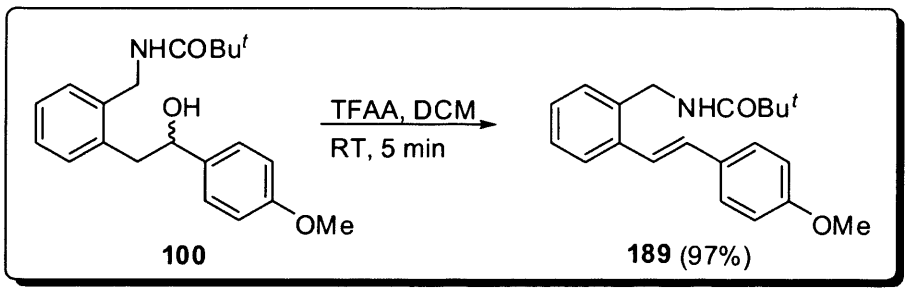


Scheme 5.3

The ^{13}C NMR spectrum of **188** showed that the carbonyl carbon atom of the $CF_3C{=}O$ group resonated as a quartet (J = 42 Hz) at δ = 156.9 ppm, while the CF_3 carbon resonated as a quartet (J = 284 Hz) at δ = 114.8 ppm. Its ^1H NMR spectrum showed that the signals of the two protons of the two CH_2 groups, the CH_2NHCO^tBu and the CH_2 at position 2 group, appeared separately, as two separated double doublets, indicating that they are diastereotopic. Compound **188** was of course present as a racemic mixture.

Compound **99** had evidently failed to cyclise and instead **188**, which seemed to be stable, was produced. The stability of **188** could be due to the fact that the carbenium ion that could be formed if the trifluoroacetate anion was lost would not be highly stabilized.

Attempted cyclization of *N*-(2-(2-hydroxy-2-(4-methoxyphenyl)ethyl)benzyl)-pivalamide (**100**) under conditions similar to those used in Scheme 5.3 gave a new product, identified as compound **189** (Scheme 5.4), which was obtained in 97% yield after purification by flash column chromatography.



Scheme 5.4

The ^{1}H NMR spectrum of **189** showed the presence of two doublets at 7.06 and 6.88 ppm with a high coupling constant (each with $J = 16$ Hz), indicating a *trans*-disubstituted double bond. The ^{13}C NMR spectrum of **189** showed unsaturated carbon signals resonating downfield at 126.2 and 123.5 ppm. Clearly dehydration, from the OH and hydrogen of the CH_2 group at position 2, had taken place. The structure of **189** was confirmed further by X-ray crystallography (Figure 5.3)[92] and was identified as (*E*)-*N*-(2-(4-methoxystyryl)benzyl)pivalamide.

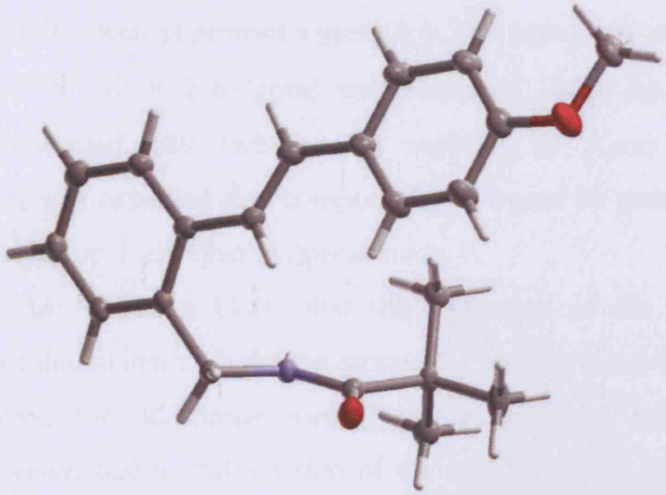
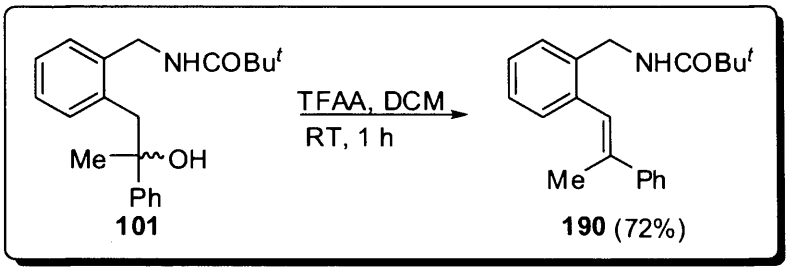


Figure 5.3 X-ray crystal structure of compound **189**. Thermal ellipsoids are shown at the 50% probability level.

It is interesting that different types of products were produced when compounds **99** and **100** were treated with TFAA. It is clear that the 4-methoxy group, in the case of compound **100**, would stabilize the carbenium ion produced *in-situ* due to elimination of trifluoroacetate anion from the ester initially formed from **100**, compared to the corresponding compound lacking the methoxy group. Loss of a proton from the α-position of the carbenium ion would produce **189**.

Similarly, treatment of *N*-(2-(2-(hydroxy-2-phenylpropyl)benzyl)pivalamide (**101**) with TFAA at room temperature in DCM (Scheme 5.5) for 5 minutes gave compound **190** but in only 14% yield, along with 79% of starting material **101**. We attempted to improve the yield of **190** under various reaction conditions and indeed, the yield was improved to 72% when the reaction time was 1 h.



Scheme 5.5

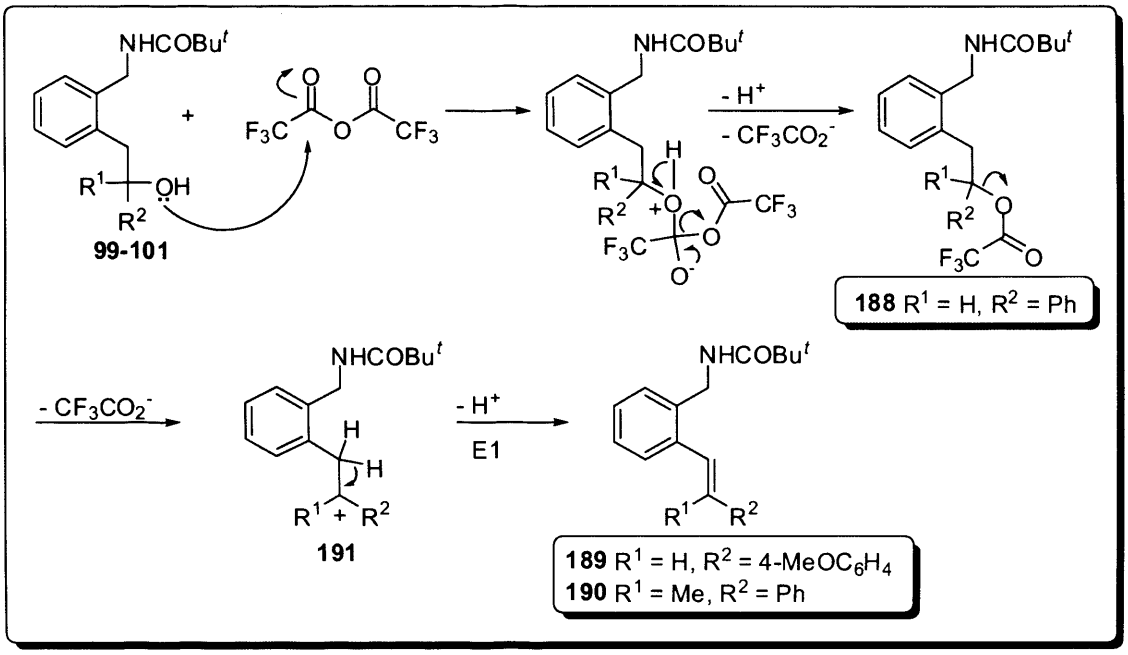
Product **190** was characterised by standard spectroscopic methods (see Chapter 7; Section 7.31). The Nuclear Overhauser Effect (NOE) experiment clearly showed that when the methyl protons signal (δ = 2.05 ppm) was irradiated the signal corresponding to H-3 (δ = 7.46 ppm) was enhanced. Also, by analogy with the structure of compound **189** (which was verified by X-ray crystal structure determination), it was expected that compound **190** would be present in the E-form, (*E*)-*N*-(2-(2-phenylprop-1-enyl)benzyl)pivalamide.

In this case it seems likely that the formation of the trifluoroacetate is somewhat slower due to steric hindrance around the tertiary alcohol group in **101**, but that once formed the additional methyl group tends to help elimination of trifluoroacetate anion due to stabilization of the carbenium ion produced, which on loss of a proton produces **190**.

Clearly, cyclization reactions of compounds **99-101**, having a pivaloylaminomethyl group at position 1, with TFAA were not successful under the conditions tried. In such compounds the *tert*-butyl of the $-CH_2NHCOBu^t$ group only weakly donates electron density to the carbonyl group, while the carbonyl group pulls electron density from the NH and therefore leaves the NH less nucleophilic, which tends to make the cyclization process less likely. However, such compounds might still cyclise under more forcing conditions.

Esterification or dehydration was observed when compounds **99-101** were treated with TFAA to produce the corresponding trifluoroacetate ester **187** or alkenes **189** and **190**, respectively. Dehydration from compounds **100** and **101** probably occurs *via* the relatively stable cations **191** (Scheme 5.6). Such cations are secondary (R^1 = H, R^2 = 4-$MeOC_6H_4$) or tertiary (R^1 = Me, R^2 = Ph) and at least one of the groups is aromatic so the cations also receive benzylic stabilisation. Therefore, elimination (E1) to produce an alkene, as seen with compounds **189** and **190**, is not surprising. On the other hand, compound **188** (R^1 = H, R^2 = Ph), which will give a

somewhat less stable cation, produces the trifluoroacetate ester rather than the alkene. In the light of the results obtained the following general reaction mechanism is suggested (Scheme 5.6).



Scheme 5.6

In principle it is quite likely that given more time for the reaction of **99** with TFAA that the trifluoroacetate group ($CF_3CO_2^-$) could be eliminated from **188** to give the corresponding cation **192** (Figure 5.4), which would either eliminate a hydrogen to form the corresponding alkene **193** or cyclise to produce the corresponding tetraisoquinoline **194**.

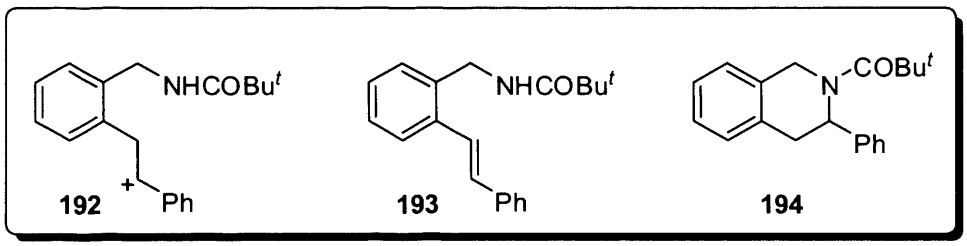
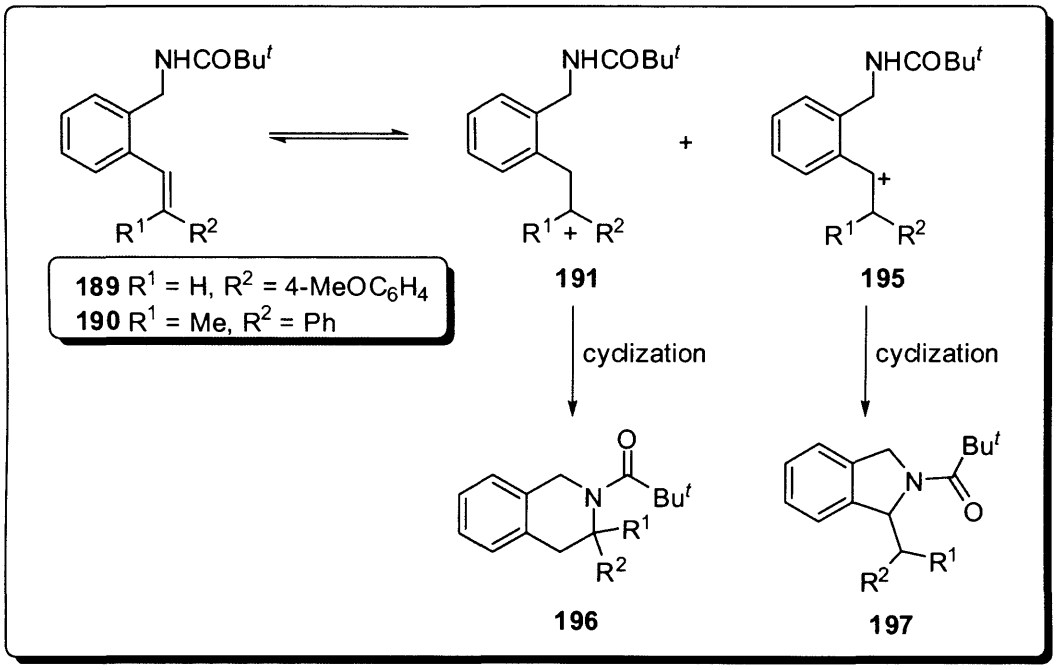


Figure 5.4

However, increasing the reaction time (up to 24 h) and the reaction temperature (reflux conditions) still gave mostly the trifluoroacetate ester **188** with little evidence for the formation of the corresponding alkene **193** (*via* elimination of a

proton) or the cyclization product **194** (Figure 5.4). Also, when **188** was treated with TFA for 4 h under reflux conditions there was little evidence for formation of either **193** or **194** and 91% of **188** was recovered.

In the cases when elimination occurred (*i.e.* production of **189** and **190** from reactions of TFAA with **100** and **101**, respectively), it is possible that re-protonation by trifluoroacetic acid (TFA) produced in the reaction would have given cation **191** in equilibrium (Scheme 5.7), along with cation **195**. In principle, cations **191** and **195** could undergo cyclization to produce **196** and **197**, respectively (Scheme 5.7).



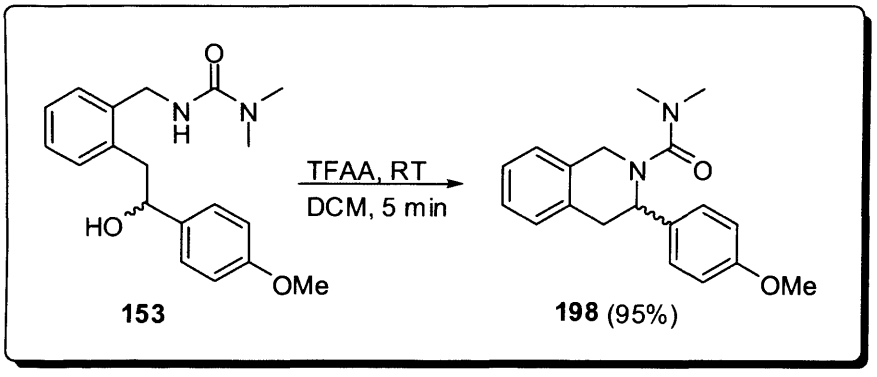
Scheme 5.7

However, treatment of compounds **189** and **190** with TFA under various reaction conditions (various reaction times and temperatures) gave no cyclised products. The quantitative recovery of **189** and **190** indicated that no reactions had taken place under the conditions tried.

No further attempts were made to try to find conditions under which cyclization could be effective. However, it was of interest to see if the cyclization reactions of related compounds, with a $-CH_2NHCONMe_2$ group at position 1 instead of a pivaloylaminomethyl group, could be possible. Consequently, our attention was next turned to possible cyclization of *N'*-(2-(2-hydroxy-2-arylalkyl)benzyl)-*N*,*N*-dimethylureas.

5.3 Synthesis of 3-(4-methoxyphenyl)-2-dimethylaminocarbonyl-1,2,3,4-tetrahydroisoquinoline (198)

Initially, a cyclization reaction of *N'*-(2-(2-hydroxy-2-(4-methoxyphenyl)-ethyl)benzyl)-*N*,*N*-dimethylurea (**153**) was attempted under conditions similar to those described in Scheme 5.3. It was hoped that cyclization of **153** could be achieved *via* elimination of water, from the OH and NH hydrogen. Therefore, reaction between compound **153** and TFAA at room temperature in DCM for 5 minutes was carried out (Scheme 5.8). The mixture was quenched by the addition of water and worked-up. The residue obtained was purified by flash column chromatography (silica gel; Et_2O–hexane, 1:3) to give the pure product, subsequently identified as compound **198**, obtained in 95% yield.



Scheme 5.8

The ^{1}H NMR spectrum of **198** showed that the signals of the two hydrogens of the CH_2 groups, at positions 1 and 4 of the isoquinoline ring, appear separately, as two separated doublets, verifying that they are diastereotopic. Compound **198** would, of course, be formed as a racemic mixture. Indeed, the X-ray crystallography of compound **198** showed a single type of crystal containing both enantiomers in equal proportions, but the structure displayed (Figure 5.5)[92] shows the structure as (*S**)-3-(4-methoxyphenyl)-2-dimethylaminocarbonyl-1,2,3,4-tetrahydroisoquinoline. Clearly, cyclization of **153** *via* dehydration, from OH and the NH hydrogen, had taken place.

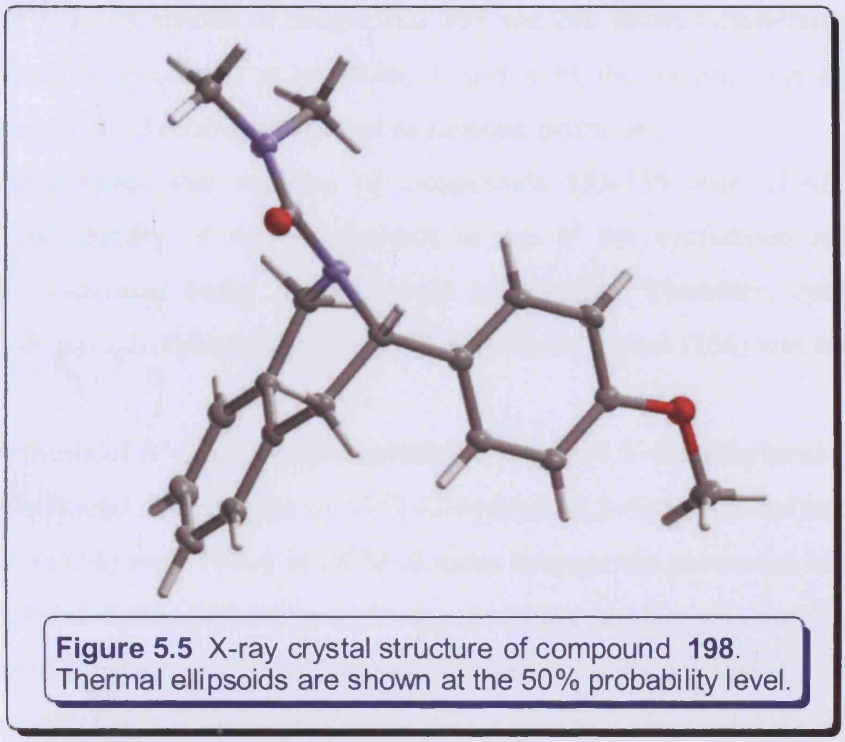
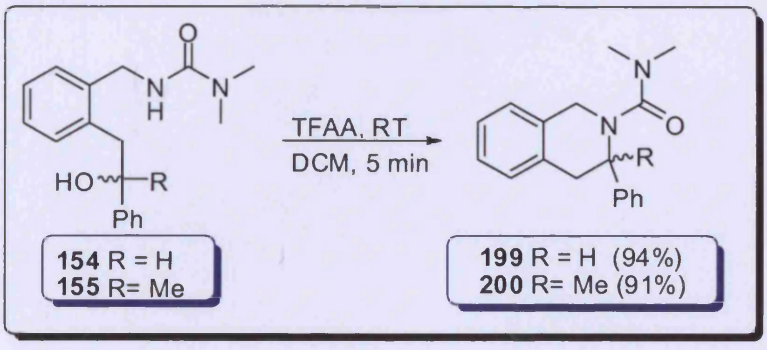


Figure 5.5 X-ray crystal structure of compound **198**. Thermal ellipsoids are shown at the 50% probability level.

5.4 Synthesis of substituted tetrahydroisoquinolines 199 and 200

Having found that reaction of compound **153** with TFAA occurred smoothly and rapidly at room temperature in DCM, it was of interest to see if the cyclization reaction of other compounds related to **153** would be successful. Consequently, reactions of compounds **154** and **155** with TFAA were carried out at room temperature in DCM for 5 minutes (Scheme 5.9). The reactions proceeded smoothly in both cases and the crude products were subjected to flash column chromatography, to give the pure products, identified as 3-phenyl-2-dimethylaminocarbonyl-1,2,3,4-tetrahydroisoquinoline (**199**; 94% yield) and 3-methyl-3-phenyl-2-dimethylaminocarbonyl-1,2,3,4-tetrahydroisoquinoline (**200**; 91% yield).



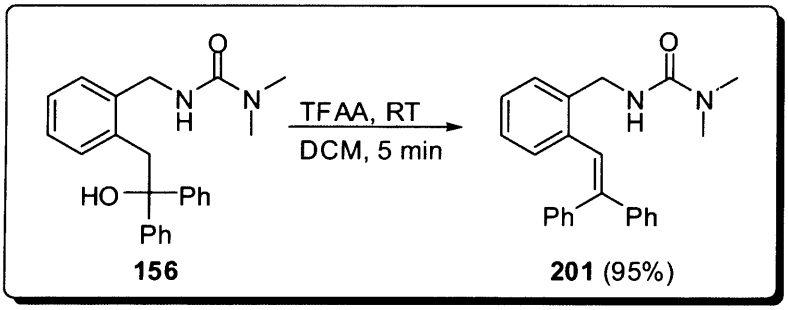
Scheme 5.9

The ^{1}H NMR spectra of compounds **199** and **200** showed diastereotopicity for the two pairs of hydrogens at positions 1 and 4 of the isoquinoline rings. Both compounds would, of course, be formed as racemic mixtures.

Having found that reaction of compounds **153-155** with TFAA occurred smoothly and rapidly, it was of interest to see if the cyclization reactions of compounds containing bulky groups would be possible. Therefore, cyclization of *N'*-(2-(2-hydroxy-2,2-diphenylethyl)benzyl)-*N,N*-dimethylurea (**156**) was attempted.

5.5 Synthesis of *N'*-(2-(2,2-diphenylvinyl)benzyl)-*N,N*-dimethylurea (201)

It was found that reaction of *N'*-(2-(2-hydroxy-2,2-diphenylethyl)benzyl)-*N,N*-dimethylurea (**156**) with TFAA in DCM at room temperature proceeded in a different manner (Scheme 5.10). Following work-up, the crude product was purified by flash column chromatography to give pure product, subsequently identified as *N'*-(2-(2,2-diphenylvinyl)benzyl)-*N,N*-dimethylurea (**201**), which was obtained 95% yield.



Scheme 5.10

Product **201** was characterised by standard spectroscopic methods and X-ray crystallography (Figure 5.6).[92] Clearly, dehydration from the OH and a hydrogen from the CH_2 group had taken place.

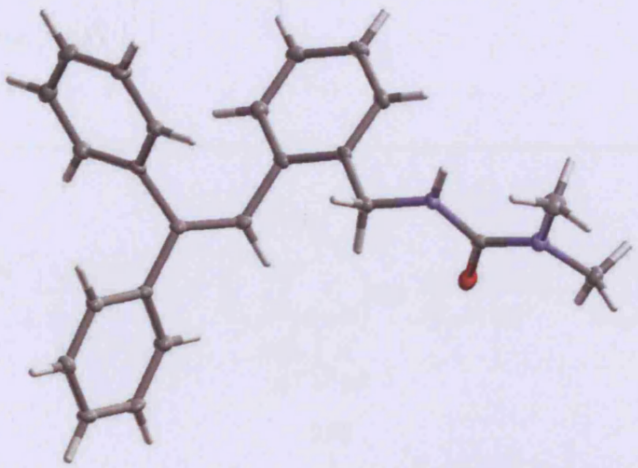
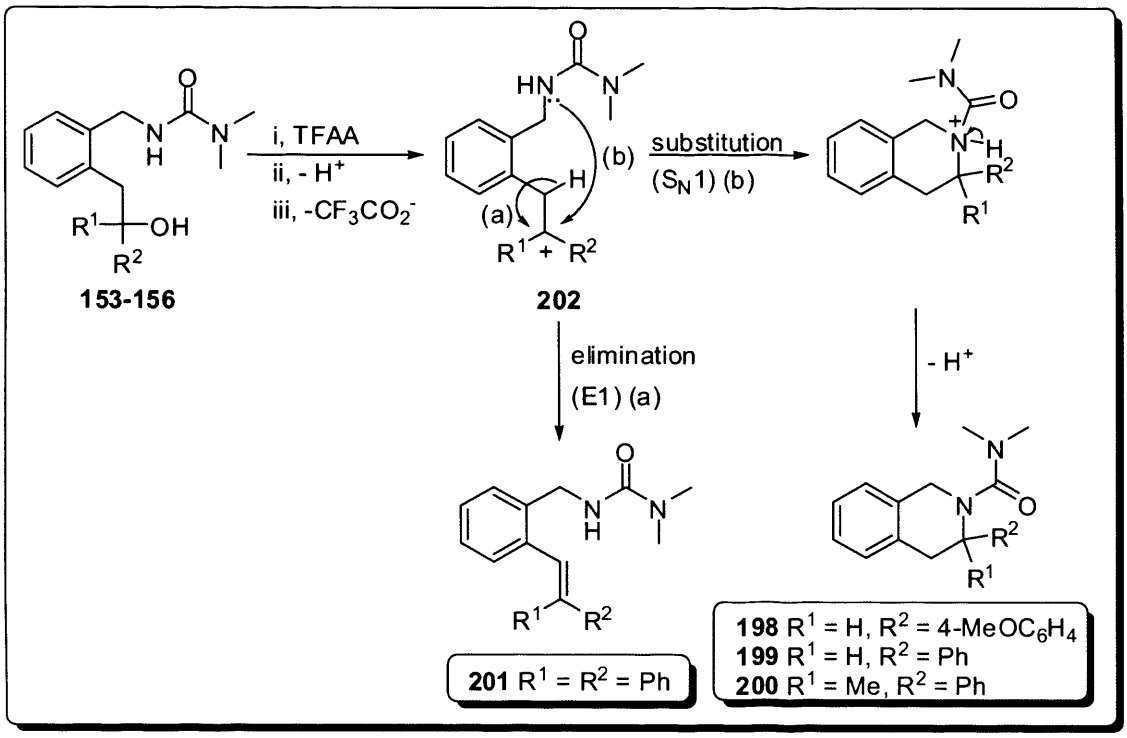


Figure 5.6 X-ray crystal structure of compound **201**. Thermal ellipsoids are shown at the 50% probability level.

Clearly, cyclization reactions of compounds having a $-CH_2NHCONMe_2$ group at position 1 (compounds **153-155**) with TFAA were successful to produce the corresponding tetrahydroisoquinolines **198-200**, respectively. In the case of such compounds the dimethylamino part of the $-CH_2NHCONMe_2$ group donates electron density to the carbonyl group. Therefore, the carbonyl group does not pull electron density to the same extent from the NH and leaves the NH more nucleophilic than in the pivaloylamino case, and therefore more likely to cyclise, as observed. However, in the case when the hydroxydiphenylethyl group is present at position 2 (compound **156**), cyclization is not successful and elimination of water takes place to produce the corresponding alkene **201**.

Dehydration, either with cyclization or to form an alkene, probably goes *via* the relatively stable cations **202** (Scheme 5.11). Such cations are at least secondary and sometimes tertiary (if neither R^1 nor R^2 is hydrogen) and in all cases at least one of the groups is aromatic so the cation also has benzylic stabilisation. Cyclization *via* substitution (S_N1) is more likely to take place than in the pivaloylamino case because of the greater nucleophilicity of the N atom and is observed in the cases of products **198-200**. However, in the most stable case ($R^1 = R^2 = Ph$; compound **156**) the cation formed is tertiary, doubly benzylic and very hindered so that cyclization is not so likely to occur and elimination (E1) takes place to produce the corresponding alkene

201. In the light of these results the following general reaction mechanism is suggested (Scheme 5.11).



Scheme 5.11

5.6 Attempted synthesis of 2-unsubstituted 1,2,3,4-tetrahydroisoquinolines

In order to render the synthetic approach described in Sections 5.3 and 5.4 even more valuable, it would be useful if the dimethylamino group in compounds of the general formula **203** (Figure 5.7) could be removed to reveal a free NH without the isoquinoline ring system itself being damaged. We therefore decided to attempt to remove the dimethylamino group in compounds **203** to provide products of the general formula **204** (Figure 5.7).

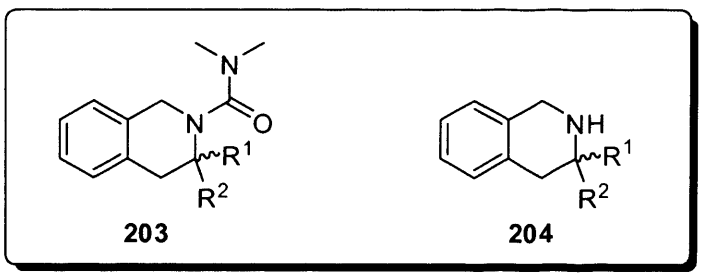


Figure 5.7

Using compound **198** as the model, we attempted removal of the dimethylaminocarbonyl group at position 2 by treatment with a few drops of TFA in DCM at room temperature or under reflux conditions for 2 h. However, TLC and NMR indicated the presence of mainly starting material in the reaction mixture. We also attempted to use TFA under reflux conditions for 1 h with no DCM. The reaction mixture turned deep red but no pure products were separated from the reaction mixture by column chromatography on silica gel. Finally, reactions of **198** with dilute HCl were attempted at room temperature and under reflux conditions for up to 24 h. However, the quantitative recovery of **198** indicated that hydrolysis was not successful under the conditions tried. No further attempts were made to try to find conditions under which removal of the dimethylaminocarbonyl group from compound **198** could be successful.

5.7 Conclusion

N-(2-(2-Hydroxy-2-arylalkyl)benzyl)pivalamides are not cyclised on reaction with trifluoroacetic anhydride in DCM at room temperature. Instead, esterification of the hydroxyl group with TFAA or dehydration from the OH and a hydrogen from the CH_2 at position 2, takes place to give the corresponding derivatives in high yields. In contrast, reactions of TFAA with *N'*-(2-substituted benzyl)-*N*,*N*-dimethylureas in DCM under identical conditions produced the corresponding tetrahydroisoquinolines in excellent yields (91-95%) for the derivatives tried. However, when a bulky group, such as hydroxydiphenylethyl, is present at position 2, cyclization is not successful and dehydration, from OH and a hydrogen from the CH_2 group at position 2, takes place to produce an unsaturated derivative in high yield. Attempts to remove the dimethylaminocarbonyl group at position 1 of the isoquinoline ring using trifluoroacetic acid or dilute HCl were not successful.

CHAPTER SIX

SYNTHESIS OF SUBSTITUTED ISOINDOLIN-1-ONES

CHAPTER SIX

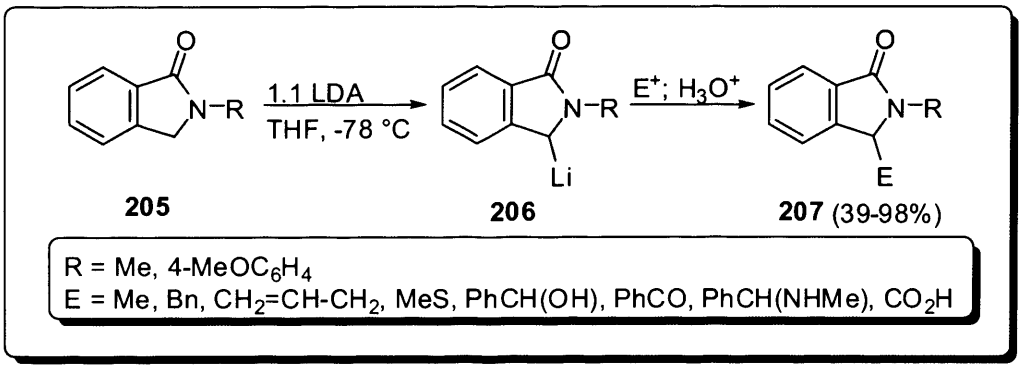
SYNTHESIS OF SUBSTITUTED ISOINDOLIN-1-ONES

6.1 Introduction

Although the isoindolinone (2,3-dihydro-1*H*-isoindol-l-one) skeleton was not commonly encountered in the past, in recent years there has been a great deal of interest in such compounds since they represent the core unit of numerous naturally occurring substances.[103-105] Also, several members belonging to this family are new nonpeptidic low molecular weight broad-spectrum inhibitors of Human Rhinovirus (HRV).[124]

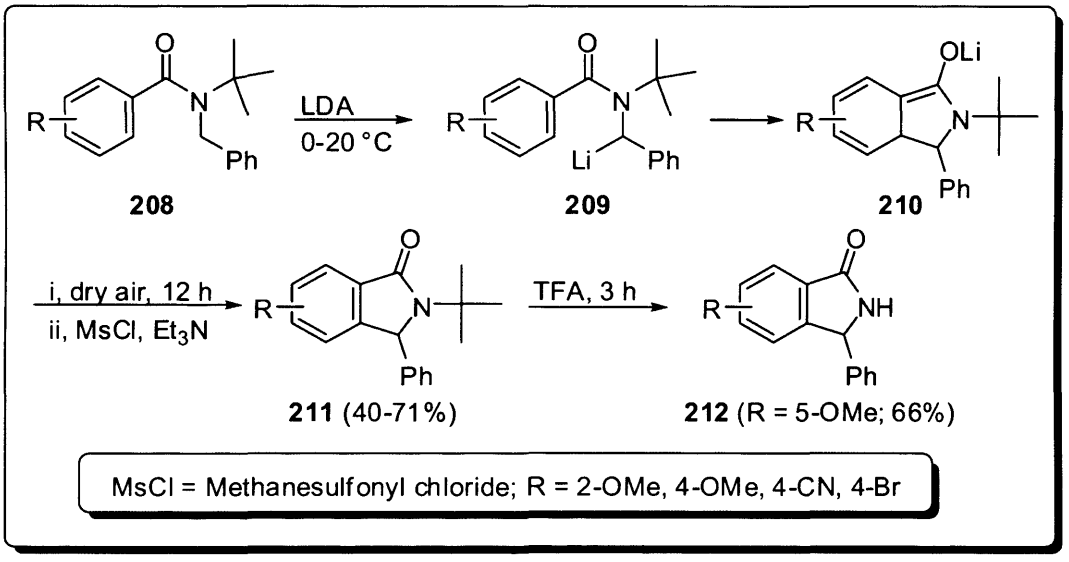
Several traditional methods are available for the synthesis of isoindolinones.[125,126] However, such methods generally require multiple reaction steps, and are unsatisfactory, both in yield and generality. In recent years a number of new approaches have been developed for the synthesis of substituted isoindolines, of which the most generally useful involve palladium-catalysed reactions[127] and lithiation procedures.[108-112,128-130]

In particular, among the methods involving lithiation two useful approaches to the synthesis of 2,3-dihydroisoindolin-1-ones have been reported (Schemes 6.1 and 6.2).[108,128] One method simply involves lithiation of a preformed 2,3-dihydroisoindol-l-one ring system, **205**, at the 3-position using one equivalent of LDA at -78 °C, to produce the lithium intermediate **206**, which on treatment with an electrophile gives the corresponding **207** (Scheme 6.1).[128] Clearly, the general utility of this approach depends on the availability of appropriately substituted analogues of the dihydroisoindolin-1-one ring system **205**.



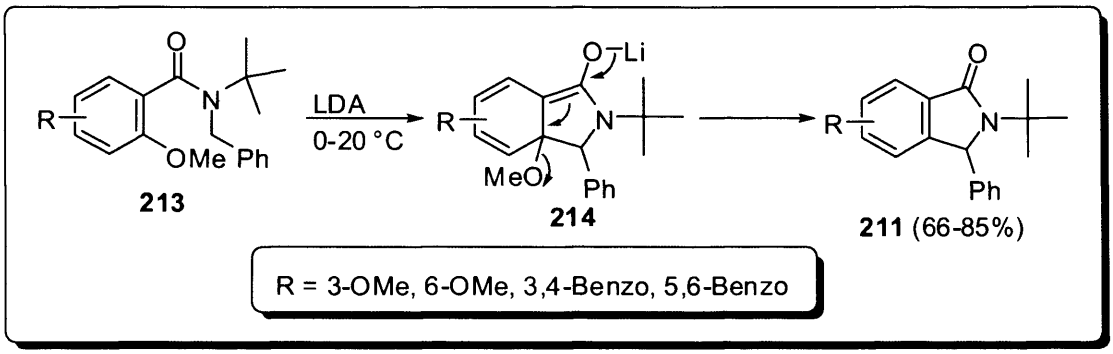
Scheme 6.1

The other, potentially more useful, approach reported by Clayden involves generation of the isoindolin-1-one ring system during the lithiation step. For example, lithiation of *N-tert*-butyl-*N*-benzylbenzamides **208** with LDA gives intermediates **209** that cyclise to form a dearomatised species **210**. Oxidation to re-aromatise the system gives the corresponding 2,3-dihydroisoindolin-1-ones **211** (Scheme 6.2; cyclization - rearomatisation).[108] Treatment of **211** (R = 5-OMe; Scheme 6.2) with trifluoroacetic acid (TFA) to remove the *tert*-butyl group gives the corresponding 2,3-dihydroisoindolin-1-one **212** in 66% yield.[108] However, this approach gives more modest yields, requires the additional step to remove the Bu^t group, and also involves incorporating the eventual C-3 substituent into the starting material, which limits the generality.



Scheme 6.2

Clayden has improved the yield of 2,3-dihydroisoindolin-1-ones such as **211** using 2-methoxy amides **213** as the starting materials; in this case the methoxy group acts as a leaving group, avoiding the need for an oxidation step.[108] Thus, lithiation of **213** with LDA gave lithium intermedaies **214** which cyclised to produce **211** in good to excellent yields (Scheme 6.3; cyclization - substitution).[108] However, this approach still requires an additional step to remove the Bu^t group.



Scheme 6.3

Therefore, with the aim of developing a methodology for the synthesis of 3-substituted isoindolin-1-ones, *N'*-benzyl-*N,N*-dimethylureas were subjected to lithiation reactions with *t*-BuLi, and subsequently with electrophiles. In this chapter, we describe a novel and efficient synthetic approach to 3-substituted isoindolin-1-ones that involves both cyclization to give the ring system and incorporation of a C-3 substituent in a single synthetic step *via* lithiation of *N'*-benzyl-*N,N*-dimethylureas with *t*-BuLi in THF at 0 °C followed by reactions of the cyclic dilithium intermediates thus formed with various electrophiles.

6.2 Synthesis of (*R**)-3-((*S**)-hydroxy(4-methoxyphenyl)methyl)-4-methoxy-isoindolin-1-one (139)

In Chapter 3 (Section 3.5), we have shown that lithiation of *N'*-(2-methoxybenzyl)-*N,N*-dimethylurea (**111**) with two equivalents of *t*-BuLi at -20 °C followed by reaction with 4-anisaldehyde gave a mixture of ring substitution products; *o*-substitution (next to the dimethylaminocarbonylaminomethyl group, 49% yield) and *o'*-substitution (next to the methoxy group, 40% yield). The *o*-substitution product was obtained from reaction of dilithium reagent **134**, produced *in-situ* from **133** (Figure 6.1), with 4-anisaldehyde, while the *o'*-substitution product was produced from reaction of **135** (Figure 6.1) with 4-anisaldehyde.

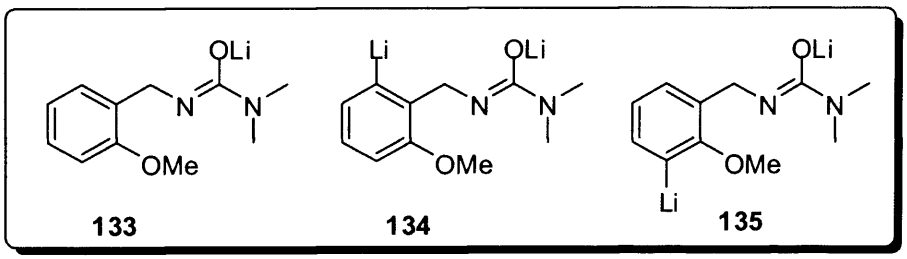
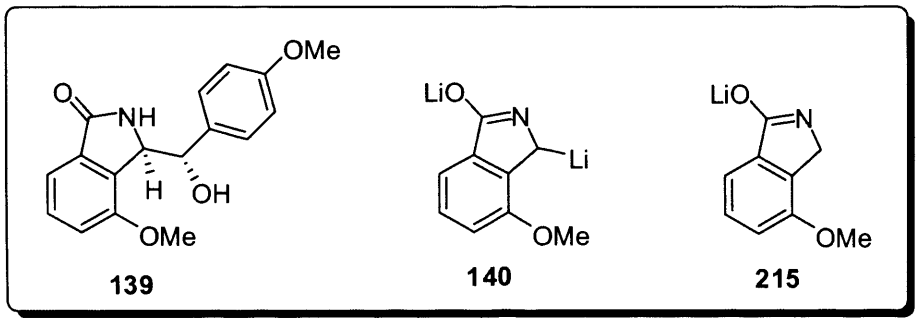


Figure 6.1

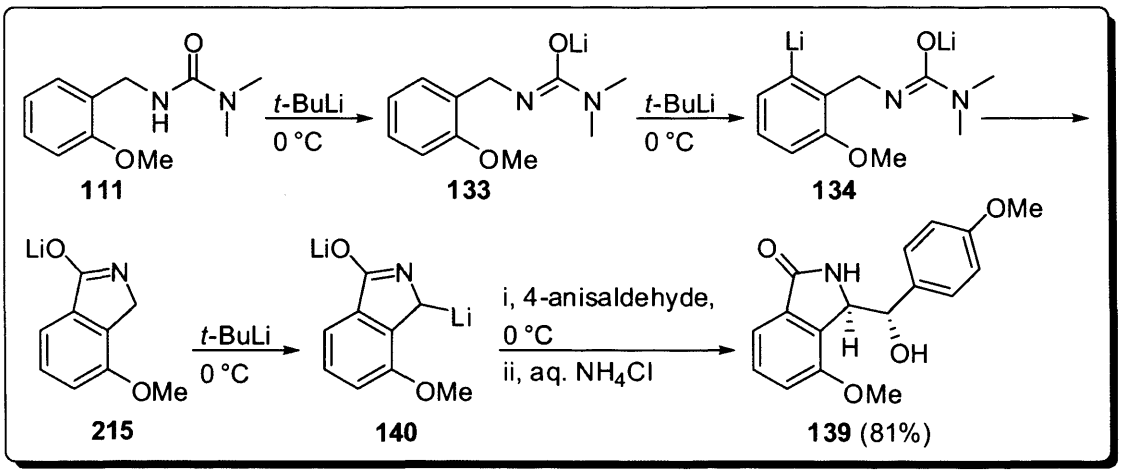
However, when the reaction was carried out at 0 °C rather than at -20 °C it produced *o*-substitution product (50% yield), *o'*-substitution product (12% yield) and an isoindolin-1-one derivative (**139**; Figure 6.2, 11% yield). Also, some of the starting material **111** (12%) was recovered under the conditions tried. Compound **139** would arise by cyclization of **134**, produced *in-situ* from **133** (Figure 6.1), to give **215**, followed by further lithiation to give **140** (Figure 6.2), which on reaction with 4-anisaldehyde gives **139** (Figure 6.2). Therefore, it appeared likely that the yield of **139** could be increased by use of a larger quantity of *t*-BuLi (three equivalents).



139 **140** **215**

Figure 6.2

It was of interest to see if the production of **139** in high yield could be achieved. Therefore, compound **111** was treated with *t*-BuLi (3.3 mole equivalents) at 0 °C in anhydrous THF under nitrogen (Scheme 6.4). Initial addition of *t*-BuLi provided a yellow solution, presumably because of formation of the monolithium reagent **133**, until approximately one equivalent had been added, then a reddish orange solution was formed as the second *t*-BuLi was added, presumably because of formation of the dilithium reagent **134**, which could cyclize to produce lithium intermediate **215**. Reaction of the third mole of *t*-BuLi with **215** could produce the corresponding cyclic dilithium reagent **140**. The mixture was stirred for 6 h at 0 °C in an attempt to ensure complete formation of the **140**. 4-Anisaldehyde (1.1 mole equivalents) was added (Scheme 6.4) and the mixture was stirred for 2 h at 0 °C. The mixture was allowed to warm to room temperature and quenched by the addition of aqueous NH_4Cl solution. The solid obtained following work-up was washed with diethyl ether to give pure product identified as **139** which was isolated in 81% yield. Compound **139** was found to be identical in all respects with the one produced previously (Chapter 3; Section 3.5).



Scheme 6.4

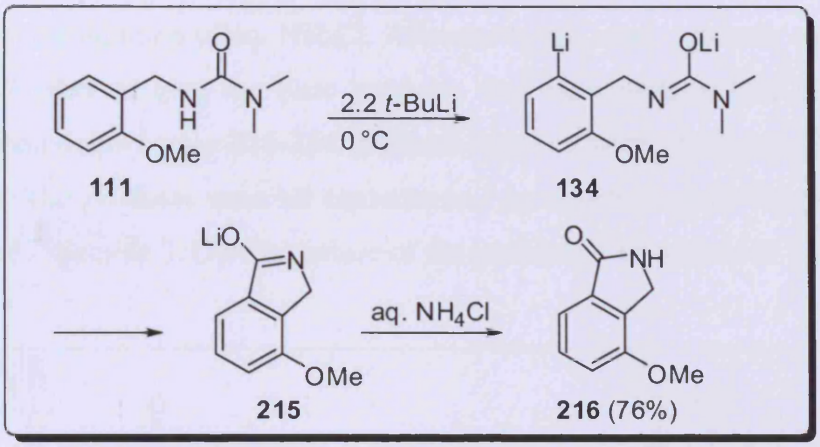
Compound **139** could potentially be formed as a pair of racemic diastereoisomers; however, its NMR spectra showed what appeared to be a single set of signals, indicating that the isolated product was a single diastereoisomer. However, although this compound was isolated in high yield (81%), it is possible that a small amount of the other diastereoisomer was formed but washed out during the purification process. The X-ray crystallography of compound **139** confirmed the crystal structure as (*R**)-3-((*S**)-hydroxy(4-methoxyphenyl)methyl)-4-methoxy-isoindolin-1-one (Figure 3.5: Chapter 3, Section 3.5).[92]

Clearly, lithiation of **111** with *t*-BuLi (3.3 mole equivalents) in anhydrous THF at 0 °C for 6 h, followed by treatment with 4-anisaldehyde (1.1 mole equivalents) gave **139** in high yield. While an increased yield of **139** was expected, the disappearance of *o'*-substitution product was a surprise. It would appear that at 0 °C, not only does **134** cyclise to give **215**, but **135** (Figure 6.1) is also in equilibrium with **134**, allowing its eventual conversion into **215** and then **140** (Scheme 6.4).

6.3 Synthesis of 4-methoxyisoindolin-1-one (216)

It was of interest to prove that cyclic lithium reagent **215** was formed as an intermediate during the reaction described in Scheme 6.4. Therefore, compound **111** was treated with *t*-BuLi (2.2 mole equivalents) at 0 °C in anhydrous THF under nitrogen for 6 h (Scheme 6.5). The mixture was allowed to warm to room temperature and quenched by the addition of aqueous NH_4Cl solution. Following work-up, the solid obtained was washed with diethyl ether to give the pure product, identified as 4-methoxyisoindolin-1-one (**216**) and was obtained in 76% yield. Clearly, reaction of

111 with *t*-BuLi (2.2 equivalents) produced the dilithium reagent **134** which could cyclize to produce lithium intermediate **215** and on protonation gave **216** (Scheme 6.5).



Scheme 6.5

Compound **216** was characterised by standard spectroscopic methods and X-ray crystallography (Figure 6.3).[92]

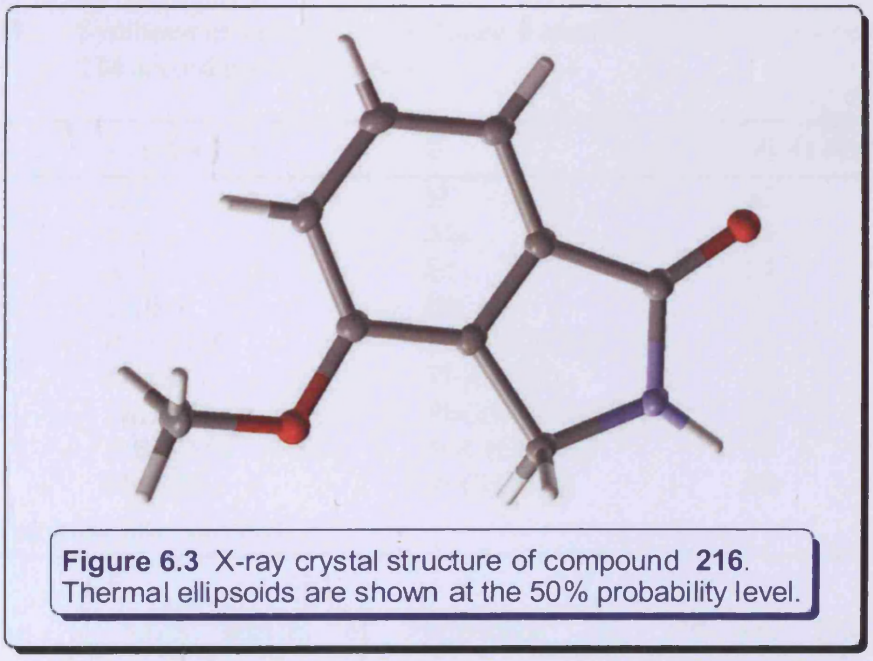
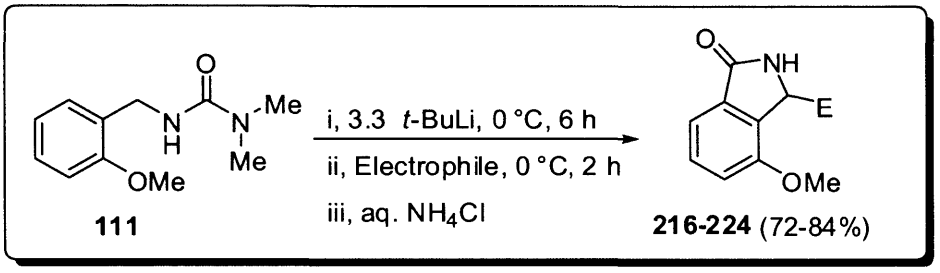


Figure 6.3 X-ray crystal structure of compound **216**. Thermal ellipsoids are shown at the 50% probability level.

6.4 Synthesis of various 3-substituted 4-methoxyisoindolin-1-ones 216-224

It was of interest to see if the reaction of the cyclic dilithium intermediate **140** with other electrophiles would be useful and general. Consequently, reactions of the

cyclic dilithium intermediate **140**, prepared *in-situ* from compound **111**, with a range of electrophiles (H_2O, iodomethane, iodoethane, bromobutane, cyclohexanone, benzophenone, acetophenone, 2-hexanone, or benzaldehyde) were carried out (Scheme 6.6). Each reaction was conducted under identical conditions and then quenched by the addition of aq. NH_4Cl. Afterwards, the crude products were washed with diethyl ether to give the pure products that were identified as 3-substituted 4-methoxyisoindolin-1-ones **216-224** (Scheme 6.6) and were obtained in high yields (Table 6.1). The products were all characterised by standard spectroscopic methods (see Chapter 7; Section 7.37). The nature of the products is illustrated in Table 6.1.



Scheme 6.6

Table 6.1: Synthesis of various 3-substituted 4-methoxyisoindolin-1-ones **216-224** according to Scheme 6.6

Product	Electrophile	E	Yield (%)[a]
216	H_2O	H	82
217	MeI	Me	79
218	EtI	Et	84
219	BuBr	Bu	72
220	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	78
221	Ph_2CO	$Ph_2C(OH)$	81
222	PhCOMe	PhC(OH)Me	81
223	BuCOMe	BuC(OH)Me	78
224	PhCHO	PhCH(OH)	80

[a] Yield of isolated pure product.

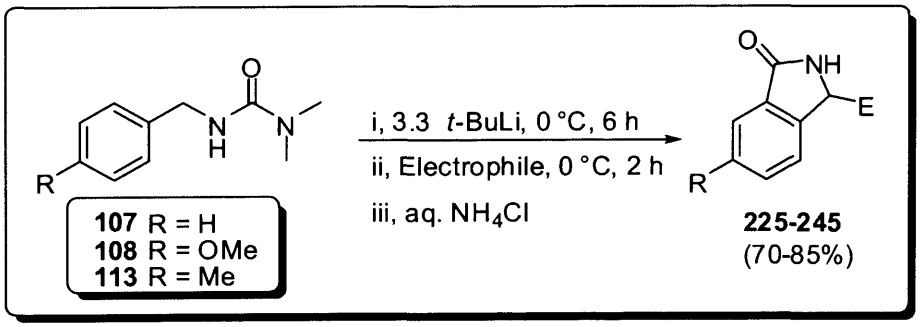
The ^1H NMR spectra of compounds **218**, **219** and **223** showed diastereotopicity for the two hydrogens of the CH_2 group attached to position 3 (**218** and **219**) or to the C(OH)Me carbon attached to position 3 (**223**) of the isoindolone ring. In the ^{13}C NMR spectrum of compound **220** the two sides of the cyclohexane ring appeared as separated signals, and for compound **221** the two phenyl groups appeared as separated signals in the ^{13}C NMR spectrum, verifying that they are

diastereotopic. Compounds **217-221** would of course be formed as racemic mixtures. Compounds **222-224** could potentially be formed as pair of racemic diastereoisomers; however, their NMR spectra showed what appeared to be one set of signals, indicating that the isolated product in each case was a single diastereoisomer. However, although these compounds were isolated in high yields (72-84%), it is possible that small amounts of the other diastereoisomers were formed but washed out during purification of the crude products by washing with diethyl ether. We have not determined the stereochemistry of compounds **222-224**, however, by analogy with the structure of compound **139** (which was verified by x-ray crystal structure determination as (*R**)-3-((*S**)-hydroxy(4-methoxyphenyl)methyl)-4-methoxy-isoindolin-1-one; Figure 3.5, Chapter 3), it was expected that such compounds would be present as (*R**)-3-(*S**)-diastereoisomers.

From the results recorded in Table 6.1 it was clear that lithiation of *N'*-(2-methoxybenzyl-*N,N*-dimethylurea (**111**) with *t*-BuLi (3.3 mole equivalents) at 0 °C followed by reaction with a variety of different electrophiles was a general process, producing 3-substituted 4-methoxyisoindolin-1-ones **216-224** in high yields.

6.5 Synthesis of various substituted isoindolin-1-ones 225-245

The generality of the process was tested further using other ring-substituted *N'*-benzyl-*N,N*-dimethylureas **107**, **108** and **113**. Each substrate was lithiated according to the standard procedure shown in Schemes 6.4 and 6.6, and then treated with various electrophiles. The crude products were washed with diethyl ether to give the pure products that were identified as substituted isoindolin-1-ones **225-245** (Scheme 6.7) and were obtained in high yields (Table 6.2). The products were all characterised by standard spectroscopic methods (see Chapter 7; Section 7.38). The nature of the products is illustrated in Table 6.2.



Scheme 6.7

Table 6.2: Synthesis of various substituted isoindolin-1-ones **225-245** according to Scheme 6.7

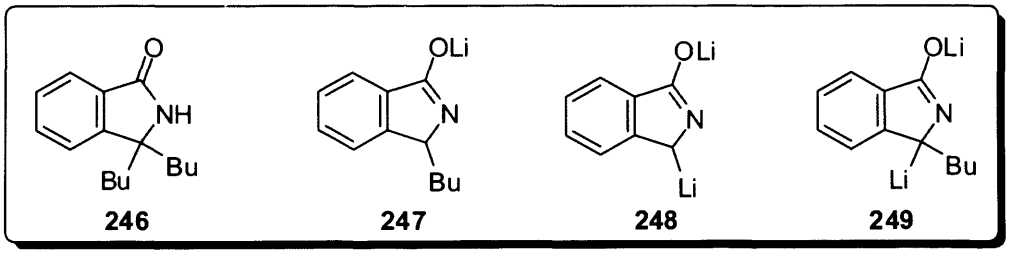
Product	R	Electrophile	E	Yield (%)[a]
225	H	H_2O	H	71
226	H	MeI	Me	75
227	H	EtI	Et	77
228	H	BuBr	Bu	76[b]
229	H	Ph_2CO	$Ph_2C(OH)$	74
230	H	PhCHO	PhCH(OH)	73
231	H	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	78
232	OMe	H_2O	H	70
233	OMe	MeI	Me	76
234	OMe	EtI	Et	78
235	OMe	BuBr	Bu	77
236	OMe	Ph_2CO	$Ph_2C(OH)$	72
237	OMe	PhCHO	PhCH(OH)	75
238	Me	H_2O	H	75
239	Me	MeI	Me	78
240	Me	EtI	Et	75
241	Me	$(CH_2)_5C=O$	$(CH_2)_5C(OH)$	72
242	Me	Ph_2CO	$Ph_2C(OH)$	85
243	Me	MeCOBu	MeC(OH)Bu	77
244	Me	PhCHO	PhCH(OH)	79
245	Me	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	83

[a] Yield of isolated pure product.
[b] Compound **246** (Figure 6.4) was obtained in 5% yield.

The ^{1}H NMR spectra of compounds **227**, **228**, **234**, **235** and **240** showed diastereotopicity for the two hydrogens of the CH_2 group attached to position 3 of the isoindolinone ring, while the spectrum of **243** showed it for the CH_2 group next to the $CH_3C(OH)$ group, verifying that all are diastereotopic. For compounds **229**, **236** and **242** the two phenyl groups appeared as separated signals in their ^{13}C NMR spectra, verifying that they are diastereotopic. The two sides of the cyclohexane ring in compound **241** should appear as separated signals; however, we were unable to record its ^{13}C NMR spectrum due to its poor solubility. Compounds **226-229**, **233-236** and **239-242** would of course be formed as racemic mixtures. Compounds **230**, **231**, **237**, **243-245** could potentially be formed as pairs of racemic diastereoisomers. Indeed, the ^{1}H and ^{13}C NMR spectra of compound **231** showed the expected presence of two diastereoisomers in the ratio of 6:1 according to the ^{1}H NMR spectrum. The isomers were not separated but based on the structure of compound **139**, it is believed that the major diastereoisomer would be present as (*R**)-3-(*S**)- and the minor one as (*R**)-3-

(*R**)-. However, the NMR spectra of **230**, **237**, **243-245** showed what appeared to be one set of signals, indicating that the isolated product in each case was probably a single diastereoisomer, and we have not determined which one. However, although these compounds were isolated in high yields (70-85%), it is possible that small amounts of the other diastereoisomers were formed but washed out during the purification process. Again, we have not determined the stereochemistry of such compounds, however, it seems likely that they would be present as (*R**)-3-(*S**)-diastereoisomers by analogy with the structure of compound **139**.

Compound **246** (Figure 6.4) was obtained as a side product in 5% yield when 1-bromobutane was used as the electrophile. It was characterised by standard spectroscopic methods (see Chapter 7; Section 7.38). Compound **246** could be obtained due to further lithiation of **247**, produced *in situ* from **248**, at position 3, to produce cyclic lithium intermediate **249** (Figure 6.4) followed by reaction with a further equivalent of 1-bromobutane.



246 **247** **248** **249**

Figure 6.4

From the results recorded in Table 6.2 it was clear that lithiation of *N'*-benzyl)-*N,N*-dimethylureas **107, 108** and **113** with *t*-BuLi (3.3 mole equivalents) at 0 °C followed by cyclization and reactions with a variety of electrophiles was a general process, producing various substituted isoindolin-1-ones **225-245** in high yields (70-86%).

6.6 Attempted cyclization of *N*-benzylpivalamide (49)

Having successfully synthesized various isoindolin-1-ones *via* lithiation and substitution of *N'*-benzyl-*N,N*-dimethylureas (Sections 6.2-6.5), attention was next turned to investigate whether the corresponding *N'*-benzylpivalamides could be cyclized in the same manner. Therefore, *N'*-benzylpivalamide (**49**; Figure 6.5) was treated with *t*-BuLi (2.2 mole equivalents) at 0 °C in anhydrous THF under nitrogen

and the mixture was stirred for 6 h, in an attempt to produce compound **250** (Figure 6.5). The mixture was allowed to warm to room temperature and quenched by the addition of aqueous NH_4Cl solution. The product mixture was examined by TLC and showed that no new product was formed; instead, only starting material was recovered (98%).

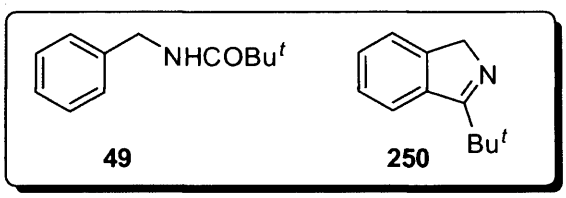


Figure 6.5

We attempted to vary the length of reaction time with *t*-BuLi (up to 24 h) but no cyclic product was formed indicating that no cyclization took place under the conditions tried. No further attempts were made to try to find conditions under which cyclization of *N'*-benzylpivalamide could be successful.

6.7 Attempted synthesis of 1,2-dihydroisoquinolin-3(4*H*)-ones

Having successfully synthesized various isoindolin-1-ones from *N'*-benzyl-*N,N*-dimethylureas (Sections 6.2-6.5), attention was next turned to investigate whether *N'*-(2-methylbenzyl)-*N,N*-dimethylurea (**114**) could be lithiated and cyclised in the same manner under similar conditions to produce 1,2-dihydroisoquinolin-3(4*H*)-one (**251**; Figure 6.6). Therefore, **114** was treated with *t*-BuLi (2.2 mole equivalents) at 0 °C in anhydrous THF under nitrogen and the mixture was stirred for 6 h. The mixture was allowed to warm to room temperature and quenched by the addition of aqueous NH_4Cl solution. The product mixture was examined by TLC and showed the presence of only starting material. Compound **114** was recovered quantitatively, which is an indication that no cyclization took place under these conditions. We attempted to vary the length of reaction time of **114** with *t*-BuLi (up to 18 h) at 0 °C but no cyclic product was formed.

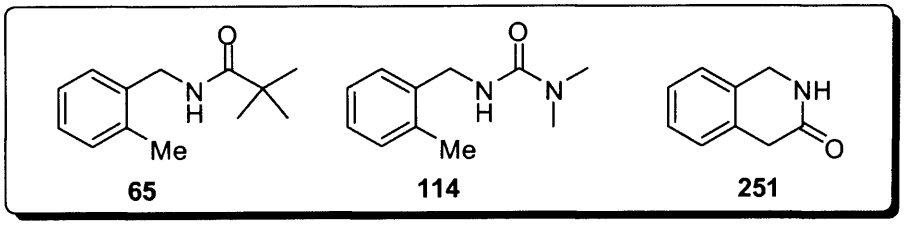


Figure 6.6

Compound **65** was also treated with *t*-BuLi (2.2 mole equivalents) in THF at 0 °C for 24 h. The product mixture was examined by TLC and showed the presence of only **65**. The quantitative recovery of starting material indicated that no cyclization took place under these conditions. This result was expected since *N'*-benzylpivalamide (**49**; Figure 6.5) had also proved to be difficult to cyclize.

No further attempts were made to try to find conditions under which cyclization of **114** or **65** could be successful. It seems that the formation of six-membered rings is relatively difficult compared to the corresponding five-membered rings.

6.8 Conclusion

A lithiation procedure has been developed that allows the production of 3-substituted isoindolin-1-ones in high yields in only one step *via* lithiation of various substituted *N'*-benzyl-*N,N*-dimethylureas with *t*-BuLi (3.3 mole equivalents) in THF at 0 °C followed by reactions with various electrophiles. The procedure has been proven to be simple, efficient and general. However, *N*-(substituted benzyl)pivalamides on treatment with *t*-BuLi for a longer reaction time failed to produce the corresponding cyclic products. Also, lithiation of *N'*-(2-methylbenzyl)-*N,N*-dimethylurea and *N*-(2-methylbenzyl)pivalamide followed by reaction with an electrophile under similar conditions failed to produce the corresponding cyclized six-membered ring compounds and instead simple lithiation and substitution took place on the methyl group at position 2.

CHAPTER SEVEN

EXPERIMENTAL

CHAPTER SEVEN
EXPERIMENTAL

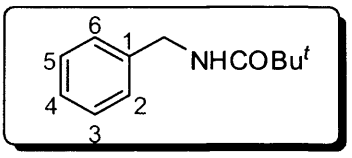
7.1 General experimental

Melting point determinations were performed by the open capillary method using a Gallenkamp melting point apparatus and are reported uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV400 (Swansea University) or Bruker AV500 (Cardiff University) spectrometer operating at 400 or 500 MHz for ^{1}H and 100 or 125 MHz for ^{13}C measurements, respectively. 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. ^{13}C multiplicities are based on DEPT signals and are reported s (C), d (CH), t (CH_2) and q (CH_3). Assignments of signals are based on 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 Quattro II spectrometer, electron impact (EI) at 70 eV and chemical ionization (CI) at 50 eV by the use of NH_3 as ionization gas. Accurate mass data were obtained on a MAT900 instrument. Electrospray (ES) analyses were performed on a ZQ4000 spectrometer in positive and negative ionisation modes. IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer. Microanalyses were performed by Warwick analytical service at the University of Warwick. X-ray analyses were obtained from the EPSRC National Crystallography Service, Department of Chemistry, Southampton University, Southampton and the X-Ray Crystallography Service, School of Chemistry, Cardiff University, Cardiff, UK. In all the figures, the thermal ellipsoids are displayed at 50% probability. 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.[22] Other chemicals were obtained from Aldrich Chemical Company and used without further purification. THF was distilled from sodium benzophenone ketyl. Other solvents were purified by standard procedures.[131,132]

7.2 Synthesis of *N*-benzylpivalamide (49)

To a cooled solution (0 °C) of benzylamine (**52**; 4.28 g, 40.0 mmol) and triethylamine (8.0 mL) in CH_2Cl_2 (100 mL) pivaloyl chloride (5.3 g, 44.3 mmol) was

slowly added in a drop-wise manner over 30 min. The reaction mixture was stirred at 0 °C for an extra 1 h. The mixture was poured onto H_2O (100 mL) and the organic layer was separated, washed with H_2O (2 x 50 mL), and dried ($MgSO_4$) and the solvent was then removed under reduced pressure. The solid obtained was purified by crystallization from Et_2O–hexane (2:1) to give *N*-benzylpivalamide (**49**; 7.03 g, 36.8 mmol; 92%) as white crystals.



Mp: 79–80 °C (lit.[86] 76–78 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.16 (m, 5 H, Ph), 5.98 (br, exch., 1 H, NH), 4.34 (d, *J* = 6 Hz, 2 H, CH_2), 1.14 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.7 (s, C=O), 139.1 (s, C-1), 129.1 (d, C-3/C-5), 128.0 (d, C-2/C-6), 127.8 (d, C-4), 43.9 (t, CH_2), 39.1 [s, $C(CH_3)_3$], 28.0 [q, $C(CH_3)_3$].

EI–MS: *m/z* (%) = 191 (M^+, 7), 91 ($PhCH_2^+$, 88), 77 (Ph^+, 19), 57 ($^tBu^+$, 100).

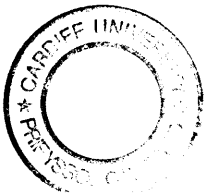
CI–MS: *m/z* (%) = 209 ($M + NH_4^+$, 27), 192 (MH^+, 100).

HRMS: *m/z* calc. for $C_{12}H_{18}NO$ (MH^+), 192.1383; found, 192.1385.

FT–IR: ν_{max} = 3303 (NH), 2961 (CH), 1636 (C=O), 1544 (aromatic C=C), 1217, 1000 cm^{-1}.

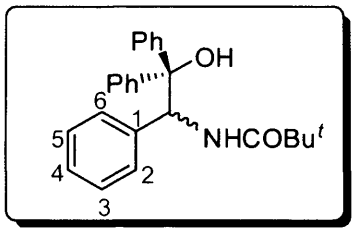
7.3 Lithiation and substitution of *N*-benzylpivalamide (49)

A solution of *t*-BuLi in pentane (2.6 mL, 1.7 M, 4.4 mmol) was added to a stirred solution of **49** (0.38 g, 2.0 mmol) at the appropriate temperature (–78, 0 or 20 °C) in anhydrous THF (20 mL) under N_2. Formation of the monolithium reagent **53** was observed as a yellow solution and the dilithium reagents were observed as brownish solution. The mixture was stirred at the appropriate temperature for 2–4 h and a solution of benzophenone (0.40 g, 2.2 mmol) in anhydrous THF (8 mL) was added. The reaction mixture was stirred for 2 h at the appropriate temperature, and then allowed to warm to r.t. if the reaction was carried out at low temperature. It was then diluted with EtOAc (20 mL) and quenched with aq. sat. NH_4Cl (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; Et_2O–hexane, 1:3) to give the pure products **56** and **57**.



The yields obtained were in the range of 6-42% for **56** and 10-34% for **57**. A significant quantity of the starting material **49** (20–69%) was also recovered. The yields obtained under various reaction conditions are recorded in Table 2.1.

_N_-(2-Hydroxy-1,2,2-triphenylethyl)pivalamide (56)



Yield: 44 mg–0.31 g (0.12–0.83 mmol, 6–42%); see Table 2.1.

Mp: 229–230 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.58 (d, J = 9 Hz, exch., 1 H, NH), 7.55–7.02 (m, 15 H, 3 Ph), 6.21 (br, exch., 1 H, OH), 5.88 (d, J = 9 Hz, 1 H, CH), 0.92 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, DMSO-d_6): δ = 177.0 (s, C=O), 147.5 (s, C-1 of Ph), 145.9 (s, C-1 of Ph), 140.6 (s, C-1), 129.9 (d, C-3/C-5), 128.6, 128.2 (2 d, C-3/C-5 of 2 Ph), 127.6 (d, C-2/C-6), 127.4 (d, C-4), 127.1, 126.7 (2 d, C-2/C-6 of 2 Ph), 127.0, 126.9 (2 d, C-4 of 2 Ph), 80.7 (s, C-OH), 59.9 (d, CH), 38.8 [s, $C(CH_3)_3$], 27.9 [q, $C(CH_3)_3$].

EI–MS: *m/z* (%) = 355 (M^+ - H_2O, 8), 330 (35), 312 (18), 296 (M^+ – Ph, 11), 270 (48), 256 (M^+ – NHCO^{t}Bu – OH, 32), 252 (100), 239 (81), 226 (34), 215 (35).

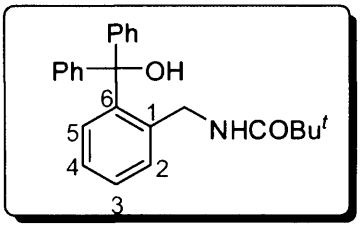
CI–MS: *m/z* (%) = 374 (MH^+, 42), 356 (MH^+ – H_2O, 100).

HRMS: *m/z* calc. for $C_{25}H_{28}NO_2$ (MH^+), 374.2115; found, 374.2114.

FT–IR: ν_{max} = 3329 (NH and OH), 2922 (CH), 1614 (C=O), 1562 (aromatic C=C), 1514, 1470, 1240 cm^{-1}.

Anal. calc. for $C_{25}H_{27}NO_2$: C, 80.40; H, 7.29; N, 3.75. Found: C, 80.41; H, 7.27; N, 3.76.

_N_-(2-(Hydroxydiphenylmethyl)benzyl)pivalamide (57)



Yield: 74 mg–0.25 g (0.20–0.67 mmol, 10–34%); see Table 2.1.

Mp: 218–219 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.85 (t, J = 6 Hz, exch., 1 H, NH), 7.35–7.32 (m, 5 H, H-4 and H-3/H-5 of 2 Ph), 7.28–7.23 (m, 7 H, H-6 and H-2/H-6/H-4 of 2 Ph), 7.08–7.04 (m, 2 H, H-5 and OH), 6.53 (d, J = 8 Hz, 1 H, H-3), 4.02 (d, J = 6 Hz, 2 H, CH_2), 1.08 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, DMSO-d_6): δ = 178.5 (s, C=O), 148.5 (s, C-1 of 2 Ph), 145.3 (s, C-1), 140.2 (s, C-2), 129.7 (d, C-3), 129.4 (d, C-6), 128.6 (d, C-3/C-5 of 2 Ph), 128.4 (d, C-4), 128.3 (d, C-2/C-6 of 2 Ph), 127.6 (d, C-4 of 2 Ph), 126.4 (d, C-5), 82.3 (s, C-OH), 41.9 (t, CH_2), 38.8 [s, $C(CH_3)_3$], 28.2 [q, $C(CH_3)_3$].

EI–MS: *m/z* (%) = 373 (M^+, 31), 355 ($M^+ - H_2O$, 47), 330 (11), 313 (25), 312 (100).

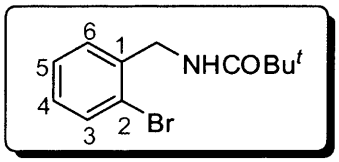
CI–MS: *m/z* (%) = 374 (MH^+, 4), 358 ($M^+ - CH_3$, 71), 356 ($MH^+ - H_2O$, 100), 296 (12), 243 (22), 200 (25), 192 ($M^+ - Ph_2CO$, 48), 183 (Ph_2COH^+, 22), 119 (46), 102 (35).

HRMS: *m/z* calc. for $C_{25}H_{27}NO_2$ (M^+), 373.2036; found, 373.2043.

FT–IR: ν_{max} = 3359 (NH and OH), 2967 (CH), 1599 (C=O), 1526 (aromatic C=C), 1364, 1210, 1027 cm^{-1}.

7.4 Synthesis of *N*-(2-bromobenzyl)pivalamide (60)

The procedure was identical with that described for the synthesis of *N*-benzylpivalamide (**49**; Section 7.2) except that 2-bromobenzylamine hydrochloride (**59**; 8.86 g, 40.0 mmol) was used instead of benzylamine (**52**). The reaction mixture was worked-up and the solid obtained was purified by crystallization from Et_2O–hexane (2:1) to give **60** (9.47 g, 35.2 mmol, 88%) as white crystals.



Mp: 101-102 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (dd, J = 2, 8 Hz, 1 H, H-3), 7.33 (dd, J = 2, 8 Hz, 1 H, H-6), 7.28 (app. dt, J = 2, 8 Hz, 1 H, H-4), 7.14 (app. dt, J = 2, 8 Hz, 1 H, H-5), 6.22 (br, exch., 1 H, NH), 4.47 (d, J = 6 Hz, 2 H, CH_2), 1.22 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.7 (s, C=O), 138.0 (s, C-1), 133.2 (d, C-3), 130.7 (d, C-6), 129.5 (d, C-4), 128.1 (d, C-5), 124.1 (s, C-2), 44.3 (t, CH_2), 39.2 [s, $C(CH_3)_3$], 28.0 [q, $C(CH_3)_3$].

EI–MS: *m/z* (%) = 190 [M^+ – Br or $PhCH_2NHCO^tBu^+$, 73], 171 [M^+ (^{81}Br) – $NHCO^tBu$, 70], 169 [M^+ (^{79}Br) – $NHCO^tBu$, 71], 107 (50), 90 (79), 89 (85), 77 (72), 57 ($^tBu^+$, 100).

CI–MS: *m/z* (%) = 289 [M (^{81}Br) + NH_4^+, 71], 287 [M (^{79}Br) + NH_4^+, 73], 272 [MH^+ (^{81}Br), 100], 270 [MH^+ (^{79}Br), 99], 209 (68), 192 (48), 190 (18).

HRMS: *m/z* calc. for $C_{12}H_{17}BrNO$ (MH^+ (^{79}Br)), 270.0488; found, 270.0488.

FT–IR: ν_{max} = 3334 (NH), 2935 (CH), 1635 (C=O), 1532 (aromatic C=C), 1228, 1020, 701 cm^{-1}.

7.5 Synthesis of *N*-(2-substituted benzyl)pivalamides 57 and 62-66 *via* bromine-lithium exchange of *N*-(2-bromobenzyl)pivalamide (60)

To a cooled solution (–78 °C) of *N*-(2-bromobenzyl)pivalamide (**60**; 0.54 g, 2.0 mmol) in anhydrous THF (20 mL) under a nitrogen atmosphere was added a solution of MeLi in Et_2O (2.2 mL, 1.0 M, 2.2 mmol), in order to deprotonate the nitrogen to form the monolithium reagent **61**. The mixture was stirred for 10 min at -78 °C. Bromine-lithium exchange was then effected by the addition of *t*-BuLi in heptane (2.6 mL, 1.7 M, 4.4 mmol). The mixture was stirred at -78 °C for 2 h, to ensure the complete formation of the dilithium reagent **55**, after which an electrophile (2.2 mmol), in anhydrous THF (8 mL) if solid, otherwise neat, was added. The mixture was stirred for 2 h at -78 °C then the cooling bath was removed and the mixture allowed to warm to room temperature. The mixture was diluted with EtOAc (10 mL) and then quenched with aq. sat. NH_4Cl solution (15 mL). The organic layer was separated, dried ($MgSO_4$), and evaporated under reduced pressure. The crude product obtained was purified by crystallization from EtOAc–Et_2O (1:3) to give pure *N*-(2-substituted benzyl)pivalamides **57** and **62-66** as white crystals. The yields obtained are recorded in Table 2.2.

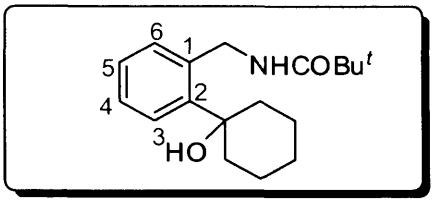
N-(2-(Hydroxydiphenylmethyl)benzyl)pivalamide (57)

Yield: 0.67 g (1.80 mmol, 90%).

Mp: 218–219 °C.

Compound **57** was found to be identical in all respects with the one produced from ring lithiation of *N*-benzylpivalamide (**49**) followed by reaction with benzophenone at low temperature (0 or –78 °C; Section 7.3). See Section 7.3 for spectral data.

_N_-(2-(1-Hydroxycyclohexyl)benzyl)pivalamide (62)



Yield: 0.52 g (1.80 mmol, 90%).

Mp: 127–128 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.35 (m, 2 H, H-3 and H-5), 7.28–7.19 (m, 2 H, H-4 and H-6), 6.67 (br, exch., 1 H, NH), 4.73 (d, J = 5 Hz, 2 H, CH_2), 2.89 (s, exch., 1 H, OH), 2.00-1.68 [m, 10 H, $(CH_2)_5$], 1.16 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.5 (s, C=O), 146.7 (s, C-2), 137.7 (s, C-1), 132.5 (d, C-6), 127.7 (d, C-3), 127.6 (d, C-4), 126.0 (d, C-5), 75.0 (s, C-1 of cyclohexyl), 43.2 (t, CH_2NH), 39.2 (t, C-2/C-6 of cyclohexyl), 38.9 [s, $C(CH_3)_3$], 27.9 [q, $C(CH_3)_3$], 25.7 (t, C-4 of cyclohexyl), 22.4 (t, C-3/C-5 of cyclohexyl).

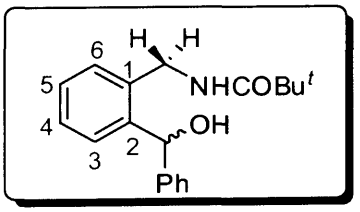
EI–MS: *m/z* (%) = 289 (M^+, 11), 246 (22), 204 (25), 170 (46), 145 (43), 129 (23), 115 (20), 91 (21), 57 (^{t}Bu$^+$, 100).

CI–MS: *m/z* (%) = 290 (MH^+, 22), 272 ($MH^+ - H_2O$, 100), 192 (4).

HRMS: *m/z* calc. for $C_{18}H_{28}NO_2$ (MH^+), 290.2115; found, 290.2116.

FT–IR: ν_{max} = 3329 (NH and OH), 2923 (CH), 1613 (C=O), 1520 (aromatic C=C), 1239, 1023 cm^{-1}.

_N_-(2-(Hydroxyphenylmethyl)benzyl)pivalamide (63)



Yield: 0.51 g (1.72 mmol, 86%).

Mp: 138–139 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.90 (app. t, J = 6 Hz, exch., 1 H, NH), 7.45 (dd, J = 2, 8 Hz, 1 H, H-6), 7.33–7.14 (m, 8 H, H-3, H-4, H-5 and Ph), 5.95 (d, J = 5 Hz, exch., 1 H, OH), 5.91 (d, J = 5 Hz, 1 H, CH), 4.34 (dd, J = 6, 16 Hz, 1 H, 1 H of CH_2), 4.17 (dd, J = 6, 16 Hz, 1 H, 1 H of CH_2), 1.13 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, DMSO-d_6): δ = 178.1 (s, C=O), 145.2 (s, C-1 of Ph), 143.1 (s, C-1), 137.4 (s, C-2), 128.9 (d, C-3/C-5 of Ph), 127.8 (d, C-2/C-6 of Ph), 127.7 (d, C-4 of Ph), 127.6 (d, C-3), 127.5 (d, C-4), 127.4 (d, C-5), 127.3 (d, C-6), 71.7 (d, CH), 40.2 (t, CH_2), 38.9 [s, $C(CH_3)_3$], 28.3 [q, $C(CH_3)_3$].

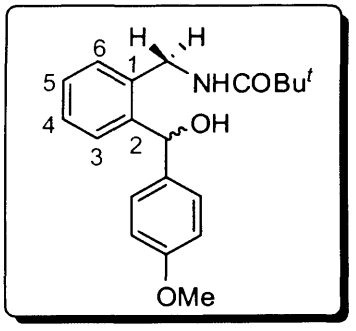
EI–MS: *m/z* (%) = 297 (M^+, 8), 280 (M^+ + 1 – H_2O, 22), 279 (M^+ - H_2O, 17), 236 (12), 222 (M^+ - H_2O - ^{t}Bu, 23), 197 (M^+ – NHCO^{t}Bu, 41), 196 (50), 195 (85), 180 (52), 178 (82), 165 (79), 152 (55), 119 (62), 115 (81), 102 (79), 91 ($PhCH_2^+$, 80), 77 (Ph^+, 88), 65 (46), 57 (^{t}Bu$^+$, 100).

CI–MS: *m/z* (%) = 315 (M + NH_4^+, 4), 298 (MH^+, 26), 280 (MH^+ – H_2O, 100), 119 (6).

HRMS: *m/z* calc. for $C_{19}H_{24}NO_2$ (MH^+), 298.1802; found, 298.1805.

FT–IR: ν_{max} = 3305 (NH and OH), 2956 (CH), 1628 (C=O), 1543 (aromatic C=C), 1453, 1299, 1207, 1020 cm^{-1}.

N-(2-(Hydroxy-(4-methoxyphenyl)methyl)benzyl)pivalamide (64)



Yield: 0.57 g (1.74 mmol, 87%).

Mp: 164–166 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.87 (app. t, J = 5 Hz, exch., 1 H, NH), 7.48 (dd, J = 2, 8 Hz, 1 H, H-6), 7.27–7.20 (m, 4 H, H-4, H-5 and H-2/H-6 of 4-methoxyphenyl), 7.13 (d, J = 8 Hz, 1 H, H-3), 6.89 (d, J = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 5.88 (d, J = 4 Hz, exch., 1 H, OH), 5.79 (d, J = 4 Hz, 1 H, CH), 4.33 (dd, J = 5, 16 Hz, 1 H, 1 H of CH_2), 4.10 (dd, J = 5, 16 Hz, 1 H, 1 H of CH_2), 3.73 (s, 3 H, OCH_3), 1.13 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, DMSO-d_6): δ = 177.6 (s, C=O), 158.5 (s, C-4 of 4-methoxyphenyl), 142.8 (s, C-1), 142.7 (s, C-2), 136.7 (s, C-1 of 4-methoxyphenyl), 128.6 (d, C-2/C-6 of 4-methoxyphenyl), 127.0 (d, C-3), 126.9 (d, C-6), 126.8 (d, C-4), 126.7 (d, C-5), 114.1 (d, C-3/C-5 of 4-methoxyphenyl), 70.8 (d, CH), 55.4 (q, OCH_3), 39.8 (t, CH_2), 38.4 [s, $C(CH_3)_3$], 27.8 [q, $C(CH_3)_3$].

EI–MS: *m/z* (%) = 327 (M^+, 7), 309 ($M^+ - H_2O$, 81), 294 ($M^+ - H_2O$ - Me, 13), 278 (38), 252 ($M^+ - H_2O - {}^tBu$, 100), 240 (51).

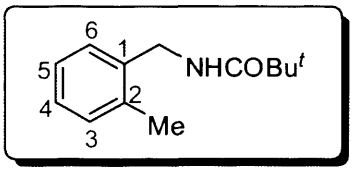
CI–MS: *m/z* (%) = 328 (MH^+, 6), 326 (M^+ –1, 18), 311 ($MH^+ - H_2O$, 45), 310 ($M^+ - H_2O$, 100), 220 (14), 192 (20), 119 (46), 102 (34).

HRMS: *m/z* calc. for $C_{20}H_{25}NO_3$ (MH^+), 328.1907; found, 328.1908.

FT–IR: ν_{max} = 3316 (NH and OH), 2932 (CH), 1636 (C=O), 1531 (aromatic C=C), 1462, 1226, 1020 cm^{-1}.

Anal. calc. for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.71; N, 4.22. Found: C, 73.37; H, 7.70; N, 4.28.

_N_-(2-Methylbenzyl)pivalamide (65)



Yield: 0.35 g (1.70 mmol, 85%).

Mp: 108–109 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.07–7.02 (m, 4 H, H-3, H-4, H-5 and H-6), 5.65 (br, exch., 1 H, NH), 4.29 (d, *J* = 5 Hz, 2 H, CH_2), 2.17 (s, 3 H, CH_3), 1.09 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.5 (s, C=O), 136.9 (s, C-1), 136.6 (s, C-2), 130.9 (d, C-3), 128.8 (d, C-6), 128.1 (d, C-4), 126.6 (d, C-5), 42.3 (t, CH_2), 39.2 [s, $C(CH_3)_3$], 28.0 [q, $C(CH_3)_3$], 19.3 (q, CH_3).

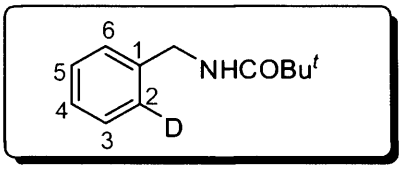
EI–MS: *m/z* (%) = 205 (M^+, 17), 105 ($M^+ - NHCO{}^tBu$, 78), 91 ($PhCH_2^+$, 23), 77 (30), 57 ($^tBu^+$, 100).

CI–MS: *m/z* (%) = 411 (2 M^+ + 1, 16), 223 ($M + NH_4^+$, 24), 206 (MH^+, 100).

HRMS: *m/z* calc. for $C_{13}H_{20}NO$ (MH^+), 206.1539; found, 206.1542.

FT–IR: ν_{max} = 3316 (NH), 2959 (CH), 1637 (C=O), 1538 (aromatic C=C), 1221, 1005 cm^{-1}.

_N_-(2-Deuteriobenzyl)pivalamaide (66)



Yield: 0.35 g (1.82 mmol, 91%).

Mp: 79–80 °C (Mp of undeuteriated analogue 76–78 °C[86]).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.23 (m, 2 H, H-3 and H-5), 7.21–7.17 (m, 2 H, H-4 and H-6), 5.92 (br, exch., 1 H, NH), 4.35 (d, J = 4 Hz, 2 H, CH_2), 1.15 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.6 (s, C=O), 139.0 (s, C-1), 129.1 (d, C-4), 129.0 (d, C-6), 128.0 (d, C-3), 127.8 (d, C-5), 127.5 (seen as three lines, 1:1:1, because of coupling to D, C-2), 43.8 (t, CH_2), 39.1 [s, $C(CH_3)_3$], 28.0 [q, $C(CH_3)_3$].

EI–MS: *m/z* (%) = 192 (M^+, 19), 92 (M^+ – NHCO^{t}Bu, 96), 57 (^{t}Bu$^+$, 100).

CI–MS: *m/z* (%) = 210 (M + NH_4^+, 32), 193 (MH^+, 100).

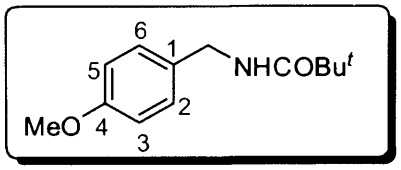
HRMS: *m/z* calc. for $C_{12}H_{17}DNO$ (MH^+), 193.1446; found, 193.1445.

FT–IR: ν_{max} = 3305 (NH), 2967 (CH), 1620 (C=O), 1525 (aromatic C=C), 1439, 1225 cm^{-1}.

7.6 Synthesis of _N_-(substituted benzyl)pivalamides

The procedure was identical with that described for the synthesis of *N*-benzylpivalamide (**49**; Section 7.2) except that the appropriate substituted benzylamine (**67**; 40.0 mmol) was used. The reaction mixture was worked-up and the solid obtained was purified by crystallization from Et_2O–hexane (2:1) to give the pure *N*-(substituted benzyl)pivalamides **44**, **46**, **65** and **68** as white crystals. The yields obtained are reported in Table 2.3.

_N_-(4-Methoxybenzyl)pivalamide (44)



Yield: 7.69 g (34.8 mmol, 87%).

Mp: 90–91 °C (lit.[133,134] 88–90 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19 (d, *J* = 8 Hz, 2 H, H-3 and H-5), 6.86 (d, *J* = 8 Hz, 2 H, H-2 and H-6), 5.97 (br, exch., 1 H, NH), 4.36 (d, *J* = 6 Hz, 2 H, CH_2), 3.79 (s, 3 H, OCH_3), 1.21 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.6 (s, C=O), 159.3 (s, C-4), 131.2 (s, C-1), 129.4 (d, C-2/C-6), 114.5 (d, C-3/C-5), 55.7 (q, OCH_3), 43.4 (t, CH_2), 39.1 [s, $C(CH_3)_3$], 28.0 [q, $C(CH_3)_3$].

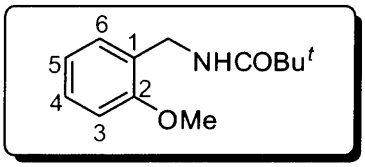
EI–MS: *m/z* (%) = 221 (M^+, 47), 136 (M^+ – CO^{t}Bu, 28), 121 ($MeOC_6H_4CH_2^+$, 100), 91 ($PhCH_2^+$, 35), 77 (65), 57 (^{t}Bu$^+$, 96).

CI–MS: *m/z* (%) = 239 (M + NH_4^+, 8), 222 (MH^+, 100), 121 (11).

HRMS: *m/z* calc. for $C_{13}H_{20}NO_2$ (MH^+), 222.1489; found, 222.1487.

FT–IR: ν_{max} = 3332 (NH), 2965 (CH), 1635 (C=O), 1539 (aromatic C=C), 1517, 1254, 1218, 1031 cm^{-1}.

N-(2-Methoxybenzyl)pivalamide (46)



Yield: 8.04 g (36.4 mmol, 91%).

Mp: 103–104 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.24 (m, 2 H, H-3 and H-5), 6.94–6.88 (m, 2 H, H-4 and H-6), 6.25 (br, exch., 1 H, NH), 4.42 (d, *J* = 6 Hz, 2 H, CH_2), 3.86 (s, 3 H, OCH_3), 1.20 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.4 (s, C=O), 158.0 (s, C-2), 130.0 (d, C-6), 129.1 (d, C-4), 126.9 (s, C-1), 121.1 (d, C-5), 110.7 (d, C-3), 55.7 (q, OCH_3), 40.0 (t, CH_2), 39.1 [s, $C(CH_3)_3$], 28.0 [q, $C(CH_3)_3$].

EI–MS: *m/z* (%) = 221 (M^+, 19), 136 (M^+ – CO^{t}Bu, 43), 121 ($MeOC_6H_4CH_2^+$, 78), 91 ($PhCH_2^+$, 70), 77 (21), 57 (^{t}Bu$^+$, 100), 41 (80).

CI–MS: *m/z* (%) = 222 (MH^+, 100), 119 (9).

HRMS: *m/z* calc. for $C_{13}H_{20}NO_2$ (MH^+), 222.1489; found, 222.1490.

FT–IR: ν_{max} = 3338 (NH), 2964 (CH), 1637 (C=O), 1532 (aromatic C=C), 1517, 1242, 1113, 1026 cm^{-1}.

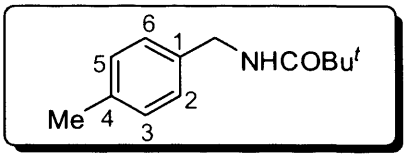
_N_-(2-Methylbenzyl)pivalamide (65)

Yield: 7.30 g (35.6 mmol, 89%).

Mp: 108–109 °C.

Compound **65** was found to be identical in all respects with the one produced *via* bromine-lithium exchange of *N*-(2-bromobenzyl)pivalamide (**60**) followed by reaction with iodomethane as an electrophile (Section 7.5). See Section 7.5 for spectral data.

_N_-(4-Methylbenzyl)pivalamide (68)



Yield: 7.54 g (36.8 mmol, 92%).

Mp: 96–97 °C (lit.[134] 94–96 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16 (br, 4 H, H-2, H-3, H-5 and H-6), 6.00 (br, exch., 1 H, NH), 4.40 (d, *J* = 6 Hz, 2 H, CH_2), 2.35 (s, 3 H, CH_3), 1.23 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.6 (s, C=O), 137.5 (s, C-1), 136.1 (s, C-4), 129.8 (d, C-3/C-5), 128.1 (d, C-2/C-6), 43.7 (t, CH_2), 39.1 [s, $C(CH_3)_3$], 28.0 [q, $C(CH_3)_3$], 21.5 (q, CH_3).

EI–MS: *m/z* (%) = 205 (M^+, 15), 105 (M^+ – NHCO^{t}Bu, 95), 91 ($PhCH_2^+$, 46), 77 (49), 57 (^{t}Bu$^+$, 100).

CI–MS: *m/z* (%) = 223 (M + NH_4^+, 12), 206 (MH^+, 100), 122 (5).

HRMS: *m/z* calc. for $C_{13}H_{20}NO$ (MH^+), 206.1539; found, 206.1541.

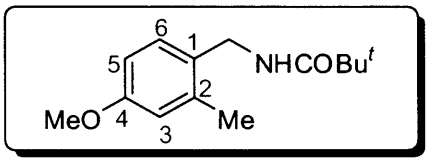
FT–IR: ν_{max} = 3318 (NH), 2958 (CH), 1637 (C=O), 1537 (aromatic C=C), 1220, 1005 cm^{-1}.

7.7 Synthesis of *N*-(2-substituted 4-methoxybenzyl)pivalamides 71-76 *via* directed lithiation of *N*-(4-methoxybenzyl)pivalamide (44)

A solution of *t*-BuLi in heptane (2.6 mL, 1.7 M, 4.4 mmol) was added to a cold (-78 °C), stirred solution of *N*-(4-methoxybenzyl)pivalamide (**44**; 0.44 g, 2.0 mmol) in anhydrous THF (20 mL) under N_2. Formation of the monolithium reagent **69** was observed as a yellow solution and the dilithium reagent **70** was observed as a brownish solution. The mixture was stirred at –78 °C for 4 h, to ensure the complete

formation of the dilithium reagent **70**, after which an electrophile (2.2 mmol), in anhydrous THF (8 mL) if solid, otherwise neat, was added. The mixture was stirred for 2 h at -78 °C then the cooling bath was removed and the mixture allowed to warm to room temperature. It was then diluted with Et_2O (10 mL) and quenched with aq. sat. 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 residue obtained was purified by column chromatography (silica gel; Et_2O–hexane, 1:3) to give pure products. The yields obtained are reported in Table 2.4.

_N_-(4-Methoxy-2-methylbenzyl)pivalamide (71)



Yield: 0.38 g (1.62 mmol, 81%).

Mp: 93–94 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.04 (d, J = 8 Hz, 1 H, H-6), 6.66 (d, J = 2 Hz, 1 H, H-3), 6.62 (dd, J = 2, 8 Hz, 1 H, H-5), 5.64 (br, exch., 1 H, NH), 4.27 (d, J = 5 Hz, 2 H, CH_2), 3.70 (s, 3 H, OCH_3), 2.20 (s, 3 H, CH_3), 1.12 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.4 (s, C=O), 159.5 (s, C-4), 138.5 (s, C-2), 130.4 (d, C-6), 128.7 (s, C-1), 116.7 (d, C-3), 115.5 (d, C-5), 55.6 (q, OCH_3), 41.9 (t, CH_2), 39.1 [s, $C(CH_3)_3$], 28.0 [q, $C(CH_3)_3$], 19.6 (q, CH_3).

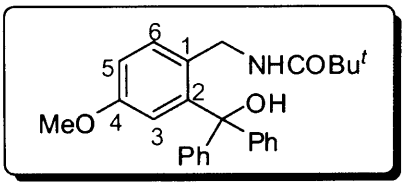
EI–MS: *m/z* (%) = 235 (M^+, 8), 135 (M^+ – NHCO^{t}Bu, 67), 134 (52), 91 ($PhCH_2^+$, 33), 77 (12), 57 (^{t}Bu$^+$, 100).

CI–MS: *m/z* (%) = 253 (M + NH_4^+, 3), 236 (MH^+, 100), 135 (M^+ – NHCO^{t}Bu, 21), 119 (12), 102 (15), 52 (47).

HRMS: *m/z* calc. for $C_{14}H_{22}NO_2$ (MH^+), 236.1645; found, 236.1646.

FT–IR: ν_{max} = 3306 (NH), 2959 (CH), 1627 (C=O), 1532 (aromatic C=C), 1493, 1244, 1024 cm^{-1}.

_N_-(2-(Hydroxydiphenylmethyl)-4-methoxybenzyl)pivalamide (72)



Yield: 0.64 g (1.60 mmol, 80%).

Mp: 205–207 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.25 (m, 11 H, H-6 and 2 Ph), 6.79 (dd, *J* = 2, 8 Hz, 1 H, H-5), 6.41 (t, *J* = 6 Hz, exch., 1 H, NH), 6.26 (d, *J* = 2 Hz, 1 H, H-3), 5.22 (s, exch., 1 H, OH), 4.08 (d, *J* = 6 Hz, 2 H, CH_2), 3.63 (s, 3 H, OCH_3), 1.05 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.8 (s, C=O), 158.1 (s, C-4), 147.7 (s, C-1 of 2 Ph), 146.7 (s, C-2), 132.8 (d, C-6), 131.1 (s, C-1), 128.4 (d, C-3/C-5 of 2 Ph), 128.2 (d, C-2/C-6 of 2 Ph), 127.6 (d, C-4 of 2 Ph), 117.1 (d, C-3), 112.8 (d, C-5), 82.9 (s, C-OH), 55.4 (q, OCH_3), 41.9 (t, CH_2), 38.8 [s, $C(CH_3)_3$], 27.8 [q, $C(CH_3)_3$].

EI–MS: *m/z* (%) = 385 ($M^+ - H_2O$, 43), 328 ($M^+ - H_2O - {}^tBu$, 33), 300 ($M^+ - H_2O - CO^tBu$, 100).

CI–MS: *m/z* (%) = 402 (M^+ - 1, 2), 388 ($M^+ - CH_3$, 46), 386 ($MH^+ - H_2O$, 42), 273 (12), 222 (84), 200 (27), 183 (Ph_2COH^+, 40), 119 (63), 102 (100).

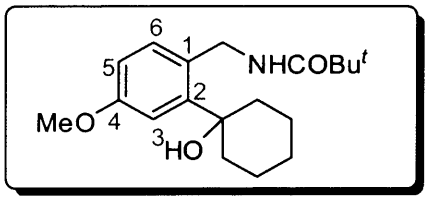
ES^+–MS: *m/z* (%) = 426 ($M + Na^+$, 25), 386 ($MH^+ - H_2O$, 62), 285 (100).

ES^-–MS: *m/z* (%) = 403 (M^-, 10), 402 ($M^- - 1$, 24), 220 (100).

HRMS: *m/z* calc. for $C_{26}H_{29}NO_3Na$ ($M + Na^+$), 426.2040; found, 426.2041.

FT–IR: ν_{max} = 3323 (NH and OH), 2964 (CH), 1623 (C=O), 1531 (aromatic C=C), 1493, 1242, 1034 cm^{-1}.

_N_-(2-(1-Hydroxycyclohexyl)-4-methoxybenzyl)pivalamide (73)



Yield: 0.49 g (1.54 mmol, 77%).

Mp: 109–110 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 8 Hz, 1 H, H-6), 6.83 (d, *J* = 2 Hz, 1 H, H-3), 6.64 (dd, *J* = 2, 8 Hz, 1 H, H-5), 6.56 (br t, exch., 1 H, NH), 4.55 (d, *J* = 6 Hz, 2 H, CH_2), 3.70 (s, 3 H, OCH_3), 2.72 (s, exch., 1 H, OH), 1.89–1.61 [m, 10 H, $(CH_2)_5$], 1.06 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.4 (s, C=O), 158.9 (s, C-4), 148.4 (s, C-2), 133.8 (d, C-6), 129.8 (s, C-1), 113.1 (d, C-3), 111.5 (d, C-5), 74.9 (s, C-1 of

cyclohexyl), 55.6 (q, OCH_3), 42.7 (t, CH_2NH), 39.1 (t, C-2/C-6 of cyclohexyl), 38.9 [s, $C(CH_3)_3$], 27.9 [q, $C(CH_3)_3$], 25.7 (t, C-4 of cyclohexyl), 22.4 (t, C-3/C-5 of cyclohexyl).

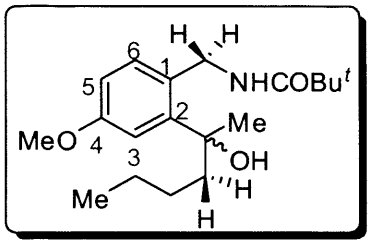
EI–MS: *m/z* (%) = 319 (M^+, 13), 301 ($M^+ - H_2O$, 18), 276 (10), 234 (30), 216 (100).

CI–MS: *m/z* (%) = 320 (MH^+, 17), 302 ($MH^+ - H_2O$, 53), 222 (52), 201 (22), 189 (19), 116 (68), 102 (100), 52 (74).

HRMS: *m/z* calc. for $C_{19}H_{30}NO_3$ (MH^+), 320.2220; found, 320.2225.

FT–IR: ν_{max} = 3330 (NH and OH), 2924 (CH), 1612 (C=O), 1530 (aromatic C=C), 1238, 1025 cm^{-1}.

_N_-(2-(2-Hydroxyhexan-2-yl)-4-methoxybenzyl)pivalamide (74)



Yield: 0.50 g (1.56 mmol, 78%).

Mp: 102–103 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 (d, *J* = 8 Hz, 1 H, H-6), 6.72 (d, *J* = 2 Hz, 1 H, H-3), 6.68 (br, exch., 1 H, NH), 6.64 (dd, *J* = 2, 8 Hz, 1 H, H-5), 4.54 (dd, *J* = 6, 14 Hz, 1 H, 1 H of CH_2NH), 4.50 (dd, *J* = 5, 14 Hz, 1 H, 1 H of CH_2NH), 3.71 (s, 3 H, OCH_3), 2.83 (s, exch., 1 H, OH), 1.85 (m, 1 H, 1 H of CH_2COH), 1.74 (m, 1 H, 1 H of CH_2COH), 1.55 (s, 3 H, CH_3COH), 1.25–1.11 (m, 4 H, $CH_2CH_2CH_3$), 1.05 [s, 9 H, $C(CH_3)_3$], 0.78 (t, *J* = 7 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.3 (s, C=O), 158.7 (s, C-4), 146.9 (s, C-2), 134.1 (d, C-6), 129.5 (s, C-1), 114.1 (d, C-3), 111.3 (d, C-5), 77.0 (s, C-OH), 55.6 (q, OCH_3), 44.7 (t, $CH_2CH_2CH_2CH_3$), 42.9 (t, CH_2NH), 38.9 [s, $C(CH_3)_3$], 31.5 (q, CH_3COH), 27.9 [q, $C(CH_3)_3$], 26.9 (t, $CH_2CH_2CH_3$), 23.5 (t, CH_2CH_3), 14.4 (q, CH_2CH_3).

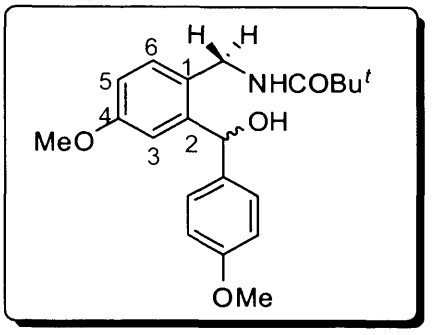
EI–MS: *m/z* (%) = 321 (M^+, 6), 303 ($M^+ - H_2O$, 41), 264 ($M^+ - {}^t$Bu, 100), 246 ($M^+ - H_2O - {}^t$Bu, 36).

CI–MS: *m/z* (%) = 322 (MH^+, 53), 304 ($MH^+ - H_2O$, 100), 264 ($M^+ - {}^t$Bu, 9), 222 (12), 219 (33), 119 (36), 102 (23).

HRMS: *m/z* calc. for $C_{19}H_{32}NO_3$ (MH^+), 322.2377; found, 322.2379.

FT–IR: ν_{max} = 3315 (NH and OH), 2933 (CH), 1635 (C=O), 1531 (aromatic C=C), 1462, 1352, 1227, 1020, 1000 cm^{-1}.

_N_-(2-(Hydroxy-(4-methoxyphenyl)methyl)-4-methoxybenzyl)pivalamide (75)



Yield: 0.58 g (1.64 mmol, 82%).

Mp: 130–132 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.76 (app. t, J = 6 Hz, exch., 1 H, NH), 7.22 (d, J = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 7.08 (d, J = 2 Hz, 1 H, H-3), 7.07 (d, J = 8 Hz, 1 H, H-6), 6.88 (d, J = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 6.80 (dd, J = 2, 8 Hz, 1 H, H-5), 5.86 (s, 1 H, CH), 5.81 (s, exch., 1 H, OH), 4.26 (dd, J = 6, 15 Hz, 1 H, 1 H of CH_2), 3.98 (dd, J = 6, 15 Hz, 1 H, 1 H of CH_2), 3.74 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 1.11 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, DMSO-d_6): δ = 177.5 (s, C=O), 158.5 (s, C-4), 158.4 (s, C-4 of 4-methoxyphenyl), 144.3 (s, C-2), 136.6 (s, C-1 of 4-methoxyphenyl), 136.5 (s, C-1), 128.7 (d, C-6), 128.6 (d, C-2/C-6 of 4-methoxyphenyl), 113.8 (d, C-3/C-5 of 4-methoxyphenyl), 112.8 (d, C-3), 111.9 (d, C-5), 70.8 (d, CH), 55.4 (q, OCH_3), 55.3 (q, OCH_3), 39.2 [s, $C(CH_3)_3$], 39.4 (t, CH_2), 27.8 [q, $C(CH_3)_3$].

EI–MS: m/z (%) = 357 (M^+, 17), 339 ($M^+ - H_2O$, 100), 324 (15), 308 (12), 296 (13).

CI–MS: m/z (%) = 358 (MH^+, 1), 356 ($M^+ - 1$, 9), 340 ($MH^+ - H_2O$, 100), 250 (12), 222 (28), 154 (11), 137 (8), 119 (15), 102 (23).

ES^+–MS: m/z (%) = 380 ($M + Na^+$, 25), 340 ($MH^+ - H_2O$, 67), 239 ($MH^+ - CO^tBu - H_2O - Me$, 100).

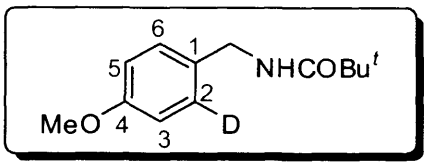
ES^-–MS: m/z (%) = 357 (M^-, 9), 356 ($M^- - 1$, 39), 220 (100).

HRMS: m/z calc. for $C_{21}H_{27}NO_4Na$ ($M + Na^+$), 380.1832; found, 380.1832.

FT–IR: ν_{max} = 3313 (NH and OH), 2933 (CH), 1635 (C=O), 1531 (aromatic C=C), 1462, 1352, 1227, 1020 cm^{-1}.

Anal. calc. for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.63; H, 7.64; N, 3.89%.

_N_-(2-Deuterio-4-methoxybenzyl)pivalamide (76)



Yield: 0.39 g (1.76 mmol, 88%).

Mp: 90–91 °C (Mp of undeuteriated analogue 88–90 °C[133,134]).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18 (d, *J* = 8 Hz, 1 H, H-6), 6.88–6.76 (m, 2 H, H-3 and H-5), 5.96 (br t, exch., 1 H, NH), 4.34 (d, *J* = 6 Hz, 2 H, CH_2), 3.79 (s, 3 H, OCH_3), 1.21 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.6 (s, C=O), 159.3 (s, C-4), 131.1 (s, C-1), 129.4 (d, C-6), 129.1 (seen as three lines, 1:1:1, because of coupling to D, C-2), 114.5 (d, C-3), 114.4 (d, C-5), 55.7 (q, OCH_3), 43.4 (t, CH_2), 39.1 [s, $C(CH_3)_3$], 28.0 [q, $C(CH_3)_3$].

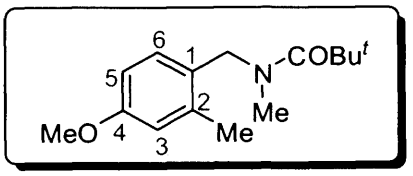
EI–MS: *m/z* (%) = 222 (M^+, 11), 122 (M^+ – NHCO^{t}Bu, 100), 79 (21), 57 (^{t}Bu$^+$, 88).

CI-MS: *m/z* (%) = 240 (M + NH_4^+, 7), 223 (MH^+, 100), 122 (M^+ – NHCO^{t}Bu, 12), 102 (10), 52 (6).

HRMS: *m/z* calc. for $C_{13}H_{19}DNO_2$ (MH^+), 223.1551; found, 223.1553.

FT–IR: ν_{max} = 3332 (NH), 2932 (CH), 1633 (C=O), 1531 (aromatic C=C), 1494, 1238, 1033 cm^{-1}.

_N_-(4-Methoxy-2-methylbenzyl)-_N_-methylpivalamide (77)



Yield: 25 mg (0.10 mmol, 5%).

Colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.87 (d, *J* = 8 Hz, 1 H, H-6), 6.61-6.59 (m, 2 H, H-3 and H-5), 4.47 (s, 2 H, CH_2), 3.66 (s, 3 H, OCH_3), 2.85 (s, 3 H, NCH_3), 2.14 (s, 3 H, CH_3), 1.21 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.9 (s, C=O), 159.0 (s, C-4), 137.8 (s, C-2), 128.8 (s, C-1), 127.6 (d, C-6), 116.6 (d, C-3), 111.4 (d, C-5), 55.6 (q, OCH_3), 50.7 (t, CH_2), 39.5 [s, $C(CH_3)_3$], 36.4 (q, NCH_3), 28.8 [q, $C(CH_3)_3$], 19.6 (q, CH_3).

EI–MS: *m/z* (%) = 249 (M^+, 4), 135 (M^+ – NMeCO^{t}Bu, 100), 91 ($PhCH_2^+$, 34), 77 (12), 57 ($^tBu^+$, 90).

CI–MS: *m/z* (%) = 250 (MH^+, 100), 135 (M^+ – NHCO^{t}Bu, 27), 116 (22).

HRMS: *m/z* calc. for $C_{15}H_{24}NO_2$ (MH^+), 250.1802; found, 250.1804.

FT–IR: ν_{max} = 2956 (CH), 1633 (C=O), 1536 (aromatic C=C), 1490, 1240, 1011cm^{-1}.

7.8 Synthesis of *N*-(4-methoxy-2-methylbenzyl)-*N*-methylpivalamide (77) *via* directed lithiation of *N*-(4-methoxybenzyl)pivalamide (44)

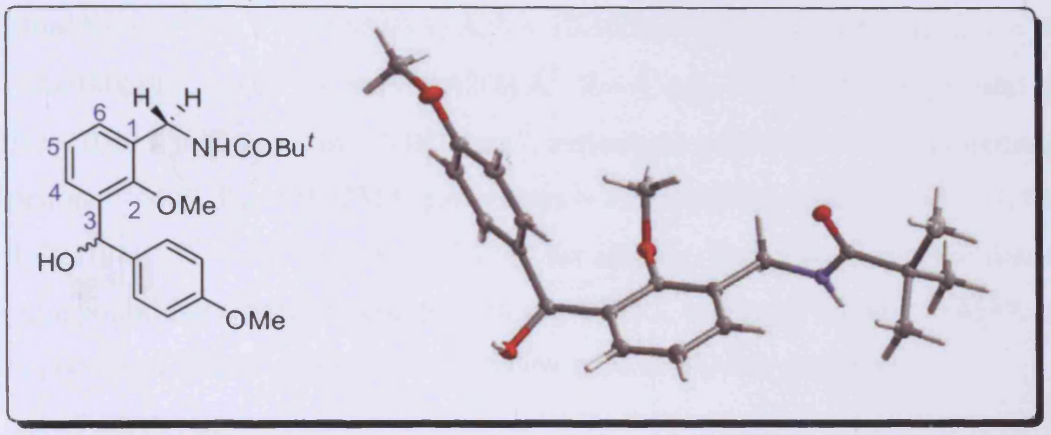
The procedure was identical with that described in Section 7.7 except that excess iodomethane (0.63 g, 4.4 mmol) was used. The reaction mixture was worked-up and purified by column chromatography (silica gel; Et_2O–hexane, 1:3) to give **77** (0.43 g, 1.74 mmol, 87%) as a colourless oil. Compound **77** was found to be identical in all respects with the one produced as a side product from reaction of dilithium reagent of compound **44** with 1.1 equivalents of iodomethane (Section 7.7).

7.9 Synthesis of *N*-(3-substituted 2-methoxybenzyl)pivalamides 80-84 *via* directed lithiation of *N*-(2-methoxybenzyl)pivalamide (46)

A solution of *t*-BuLi in heptane (2.6 mL, 1.7 M, 4.4 mmol) was added to a cold (-78 °C), stirred solution of *N*-(2-methoxybenzyl)pivalamide (**46**; 0.44 g, 2.0 mmol) in anhydrous THF (20 mL) under N_2. Formation of the monolithium reagent **78** was observed as a yellow solution and the dilithium reagent **79** was observed as a brownish solution. The mixture was stirred at –78 °C for 4 h, to ensure the complete formation of the dilithium reagent, after which an electrophile (2.2 mmol), in anhydrous THF (8 mL) if solid, otherwise neat, was added. The mixture was stirred for 2 h at –78 °C then the cooling bath was removed and the mixture allowed to warm to room temperature. It was then diluted with Et_2O (10 mL) and quenched with aq. sat. 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 residue obtained was purified by column chromatography (silica gel; Et_2O–hexane, 1:3) to give pure products **80-84**. In the case of carbon dioxide as electrophile the cooling bath was

removed before solid carbon dioxide was added and the mixture was stirred for 30 minutes while the temperature rose, and then quenched with HCl (2 M; 5 mL). The crude product was crystallised from ethyl acetate to give pure **84**. The yields obtained are recorded in Table 2.5.

_N_-(3-(Hydroxy-(4-methoxyphenyl)methyl)-2-methoxybenzyl)pivalamide (80)



Yield: 0.54 g (1.52 mmol; 76%).

Mp: 144–145 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.04 (app. t, J = 6 Hz, exch., 1 H, NH), 7.39 (dd, J = 2, 8 Hz, 1 H, H-4), 7.28 (d, J = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 7.13 (app. t, J = 8 Hz, 1 H, H-5), 7.08 (dd, J = 2, 8 Hz, 1 H, H-6), 6.89 (d, J = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 5.98 (d, J = 4 Hz, exch., 1 H, OH), 5.72 (d, J = 4 Hz, 1 H, CH), 4.40 (dd, J = 6, 16 Hz, 1 H, 1 H of CH_2), 4.28 (dd, J = 6, 16 Hz, 1 H, 1 H of CH_2), 3.75 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 1.19 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, DMSO-d_6): δ = 178.4 (s, C=O), 158.9 (s, C-2), 154.9 (s, C-4 of 4-methoxyphenyl), 139.4 (s, C-1 of 4-methoxyphenyl), 138.3 (s, C-1), 133.5 (s, C-3), 128.5 (d, C-2/C-6 of 4-methoxyphenyl), 127.0 (d, C-4), 126.8 (d, C-6), 124.7 (d, C-5) 114.1 (d, C-3/C-5 of 4-methoxyphenyl), 68.7 (d, CH), 61.9 (q, OCH_3), 55.9 (q, OCH_3), 38.9 [s, $C(CH_3)_3$], 37.5 (t, CH_2), 28.3 [q, $C(CH_3)_3$].

EI–MS: *m/z* (%) = 357 (M^+, 2), 339 ($M^+ - H_2O$, 29), 324 ($M^+ - H_2O$ – Me, 38), 254 ($M^+ - H_2O$, – CO^{t}Bu, 51), 240 (M^+ – NHCO^{t}Bu – OH, 63), 238 ($M^+ - MeOC_6H_4C^+$, 100), 225 (30), 211 ($MeOC_6H_4CH(OH)Ph^+$, 25), 195 (30), 181 (29), 165 (56), 152 (62), 146 (82).

CI–MS: *m/z* (%) = 375 ($M + NH_4^+$, 11), 358 (MH^+, 14), 340 ($MH^+ - H_2O$, 100), 222 (57), 154 (30), 119 (72), 102 (37).

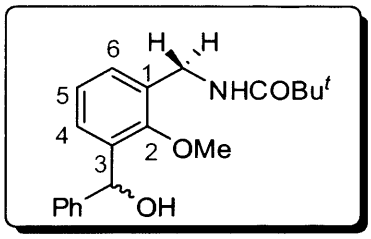
HRMS: *m/z* calc. for $C_{21}H_{28}NO_4$ (MH^+), 358.2013; found, 358.2014.

FT–IR: ν_{max} = 3329 (NH and OH), 2923 (CH), 1614 (C=O), 1562 (aromatic C=C), 1469, 1241, 1037, 1001 cm^{-1}.

Anal. calc. for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.56; H, 7.64; N, 4.09%.

Selected crystallographic data: $C_{21}H_{27}NO_4$, FW = 357.44, T = 150(2) K, λ = 0.71073 Å, Monoclinic, $P2_1/a$, a = 12.6540(3) Å, b = 10.5000(2) Å, c = 14.5990(4) Å, α = 90°, β = 92.0180(10)°, γ = 90°, V = 1938.52(8) $Å^3$, Z = 4, $\rho_{calc.}$ = 1.225 Mg/m^3, crystal size = 0.40 × 0.40 × 0.10 mm^3, m = 0.084 mm^{-1}, reflections collected = 7167, independent reflections = 4407, R_{int} = 0.07314, parameters = 239, final R_1 = 0.0530, wR_2 = 0.1239 for $I>2\sigma(I)$ and R_1 = 0.0759, wR_2 = 0.1364 for all data. Full crystallographic data for this compound have been deposited with the CCDC, reference number 736587, and can be obtained free of charge *via* http://www.ccdc.ac.uk/data_request/cif.

_N_-(3-(Hydroxyphenylmethyl)-2-methoxybenzyl)pivalamide (81)



Yield: 0.49 g (1.50 mmol, 75%).

Mp: 133–135 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 7 Hz, 2 H, H-3/H-5 of Ph), 7.36–7.32 (m, 3 H, H-2/H-4/H-6 of Ph), 7.27 (dd, *J* = 2, 8 Hz, 1 H, H-4), 7.19 (dd, *J* = 2, 8 Hz, 1 H, H-6), 7.13 (app. t, *J* = 8 Hz, 1 H, H-5), 6.12 (br t, exch., 1 H, NH), 6.10 (s, 1 H, CH), 4.51 (dd, *J* = 6, 15 Hz, 1 H, 1 H of CH_2), 4.44 (dd, *J* = 5, 15 Hz, 1 H, 1 H of CH_2), 3.59 (s, 3 H, OCH_3), 2.97 (br, exch., 1 H, OH), 1.21 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.9 (s, C=O), 156.1 (s, C-2), 144.1 (s, C-1 of Ph), 137.8 (s, C-1), 132.0 (s, C-3), 129.2 (s, C-4), 128.8 (d, C-3/C-5 of Ph), 128.1 (d, C-4 of Ph), 127.8 (d, C-6), 126.9 (d, C-2/C-6 of Ph), 125.2 (d, C-5), 71.8 (d, CH), 62.1 (q, OCH_3), 39.1 (t, CH_2), 39.0 [s, $C(CH_3)_3$], 28.0 [q, $C(CH_3)_3$].

ES^+–MS: *m/z* (%) = 357 ($M + Na^+$, 100), 328 (MH^+, 16), 311 ($MH^+ - OH$, 15), 310 ($MH^+ - H_2O$, 68), 281 (12).

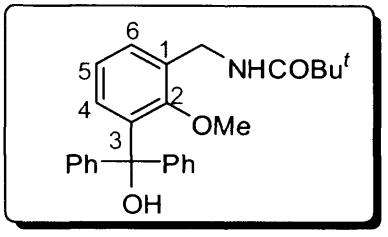
ES^-–MS: *m/z* (%) = 327 (M^-, 8), 326 ($M^- - 1$, 22), 220 (100), 188 (13), 131 (30).

HRMS: *m/z* calc. for $C_{20}H_{26}NO_3$ (MH^+), 328.1907; found, 328.1905.

FT–IR: ν_{max} = 3319 (NH and OH), 2929 (CH), 1639 (C=O), 1528 (aromatic C=C), 1492, 1344, 1234, 1006 cm^{-1}.

Anal. calc. for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28. Found: C, 73.39; H, 7.72; N, 4.26%.

_N_-(3-(Hydroxydiphenylmethyl)-2-methoxybenzyl)pivalamide (82)



Yield: 0.59 g (1.46 mmol, 73%).

Mp: 173–174 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.80 (t, J = 6 Hz, exch., 1 H, NH), 7.10–7.01 (m, 10 H, 2 Ph), 6.90 (d, J = 8 Hz, 1 H, H-4), 6.76 (app. t, J = 8 Hz, 1 H, H-5), 6.48 (dd, J = 2, 8 Hz, 1 H, H-6), 5.74 (s, exch., 1 H, OH), 4.04 (d, J = 6 Hz, 2 H, CH_2), 3.12 (s, 3 H, OCH_3), 0.92 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, DMSO-d_6): δ = 178.5 (s, C=O), 156.4 (s, C-2), 147.9 (s, C-1 of 2 Ph), 141.2 (s, C-1), 134.5 (s, C-3), 128.4 (d, C-2/C-6 and C-3/C-5 of 2 Ph), 128.4 (d, C-4), 128.3 (d, C-6), 127.7 (d, C-4 of 2 Ph), 123.7 (d, C-5), 81.5 (s, C-OH), 61.2 (q, OCH_3), 40.0 [s, $C(CH_3)_3$], 37.8 (t, CH_2), 28.3 [q, $C(CH_3)_3$].

EI–MS: *m/z* (%) = 385 ($M^+ - H_2O$, 100), 370 ($M^+ - H_2O$ – Me, 35).

CI–MS: *m/z* (%) = 421 ($M + NH_4^+$, 5), 405 (MH^+ + 1, 12), 404 (MH^+, 3), 388 ($M^+ - CH_3$, 48), 386 ($MH^+ - H_2O$, 100), 343 (11), 273 (13), 222 (34), 200 (24), 183 (Ph_2COH^+, 14), 119 (100), 102 (45).

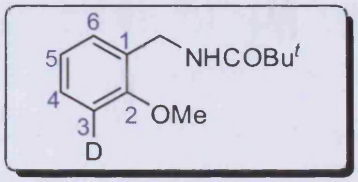
ES^+–MS: *m/z* (%) = 426 ($M + Na^+$, 38), 421 ($M + NH_4^+$, 100), 404 (MH^+, 13), 386 ($MH^+ - H_2O$, 88).

ES^-–MS: *m/z* (%) = 403 (M^-, 32), 402 ($M^- - 1$, 100), 388 ($M^- - CH_3$, 40), 241 (18), 206 (22).

HRMS: *m/z* calc. for $C_{26}H_{30}NO_3$ (MH^+), 404.2220; found, 404.2219.

FT–IR: ν_{max} = 3334 (NH and OH), 2938 (CH), 1635 (C=O), 1533 (aromatic C=C), 1462, 1238, 1019 cm^{-1}.

_N_-(3-Deuterio-2-methoxybenzyl)pivalamide (83)



Yield: 0.38 g (1.72 mmol, 86%).

Mp: 103–104 °C (Mp of undeuteriated analogue 103–104 °C; **46**, Section 7.6).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.15 (m, 2 H, H-5 and H-6), 6.83 (m, 1 H, H-4), 6.14 (br, exch., 1 H, NH), 4.36 (d, J = 6 Hz, 2 H, CH_2), 3.78 (s, 3 H, OCH_3), 1.11 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.4 (s, C=O), 158.0 (s, C-2), 130.1 (d, C-6), 129.1 (d, C-4), 129.0 (s, C-1), 121.1 (d, C-5), 110.5 (seen as three lines, 1:1:1, because of coupling to D, C-3), 55.7 (q, OCH_3), 40.0 (t, CH_2), 39.1 [s, $C(CH_3)_3$], 28.0 [q, $C(CH_3)_3$].

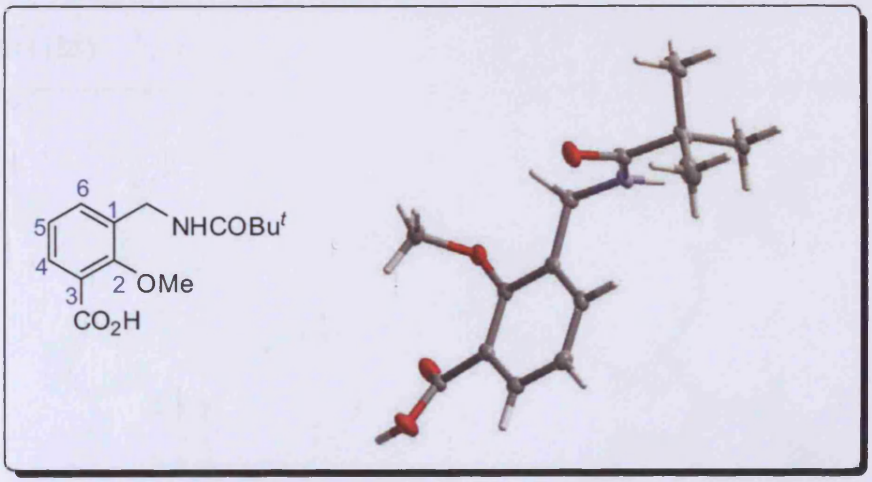
EI–MS: *m/z* (%) = 222 (M^+, 12), 137 (M^+ – CO^{t}Bu, 28), 122 (M^+ – NHCO^{t}Bu, 71), 92 ($C_6H_4O^+$, 91), 79 (22), 77 (17), 57 (^{t}Bu$^+$, 100).

CI–MS: *m/z* (%) = 223 (MH^+, 100), 137 (M^+ – CO^{t}Bu, 4), 119 (5), 102 (3).

HRMS: *m/z* calc. for $C_{13}H_{19}DNO_2$ (MH^+), 223.1551; found, 223.1550.

FT–IR: ν_{max} = 3340 (NH), 2969 (CH), 1626 (C=O), 1538 (aromatic C=C), 1481, 1418, 1224 cm^{-1}.

2-Methoxy-3-(pivalamidomethyl)benzoic acid (84)



Yield: 0.42 g (1.58 mmol, 80%).

Mp: 156–157 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.03 (t, J = 6 Hz, exch., 1 H, NH), 7.57 (dd, J = 2, 8 Hz, 1 H, H-6), 7.32 (dd, J = 2, 8 Hz, 1 H, H-4), 7.16 (app. t, J = 8 Hz, 1 H, H-5), 4.32 (d, J = 6 Hz, 2 H, CH_2), 3.79 (s, 3 H, OCH_3), 1.15 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, DMSO-d_6): δ = 178.1 (s, C=O), 167.8 (s, CO_2H), 157.1 (s, C-2), 134.6 (s, C-3), 131.5 (d, C-4), 129.6 (d, C-6), 126.1 (s, C-1), 123.9 (d, C-5), 62.1 (q, OCH_3), 38.6 [s, $C(CH_3)_3$], 37.3 (t, CH_2), 27.9 [q, $C(CH_3)_3$].

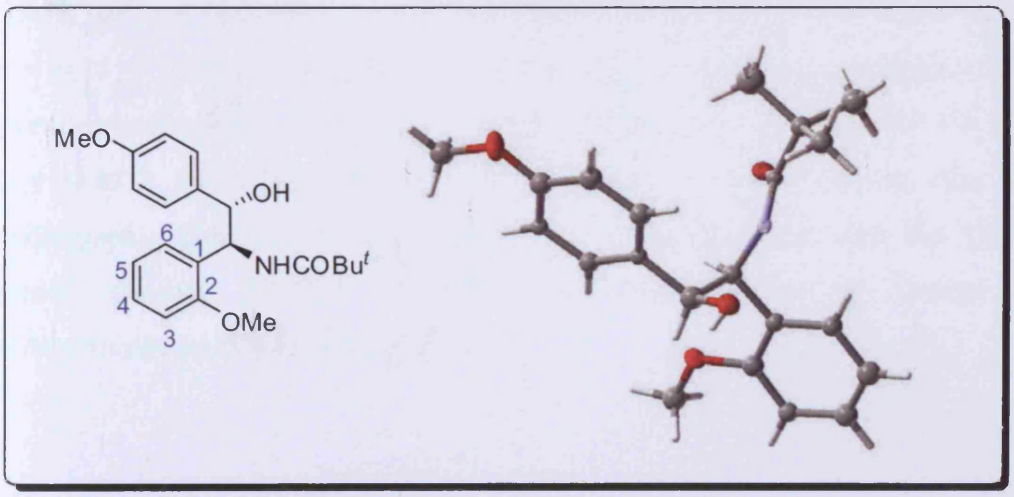
ES^+–MS: m/z (%) = 569 (2 M + K^+, 12), 553 (2 M + Na^+, 100), 548 (2 M + NH_4^+, 32), 329 (M + $MeCNNa^+$, 25), 304 (M + K^+, 27), 288 (M + Na^+, 70), 266 (MH^+, 71).

HRMS: m/z calc. for $C_{14}H_{20}NO_4$ (MH^+), 266.1392; found, 266.1386.

FT–IR: ν_{max} = 3377 (NH and OH), 2972 (CH), 1698 (CO_2), 1610 (C=O), 1540 (aromatic C=C), 1427, 1368, 1247 cm^{-1}.

Selected crystallographic data: $C_{14}H_{19}NO_4$, FW = 265.30, T = 150(2) K, λ = 0.71073 Å, Monoclinic, $P2_1/c$, a = 13.9970(5) Å, b = 13.9230(5) (2) Å, c = 15.0940(8) Å, α = 90°, β = 106.480(2)°, γ = 90°, V = 2820.7(2) $Å^3$, Z = 8, $\rho_{calc.}$ = 1.249 Mg/m^3, crystal size = 0.40 × 0.30 × 0.06 mm^3, m = 0.091 mm^{-1}, reflections collected = 10912, independent reflections = 6430, R_{int} = 0.0712, parameters = 353, final R_1 = 0.0750, wR_2 = 0.1406 for I>2σ(I) and R_1 = 0.1497, wR_2 = 0.1673 for all data. Full crystallographic data for this compound have been deposited with the CCDC, reference number 736584, and can be obtained free of charge *via* http://www.ccdc.ac.uk/data_request/cif.

_N_-((1S*,2S*)-2-hydroxy-1-(2-methoxyphenyl)-2-(4-methoxyphenyl)ethyl)-pivalamide (85)



Yield: 14 mg (0.04 mmol, 2%).

Mp: 203–205 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.25 (d, J = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 7.23–7.19 (m, 3 H, NH, H-4 and H-6), 6.96 (d, J = 8 Hz, 1 H, H-3), 6.91 (app. t, J = 8 Hz, 1 H, H-5), 6.86 (d, J = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 5.52 (d, J = 4 Hz, exch., 1 H, OH), 5.24 (dd, J = 3, 6 Hz, 1 H, CH), 4.78 (dd, J = 4, 3 Hz, 1 H, C*H*OH), 3.83 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 1.05 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, DMSO-d_6): δ = 176.5 (s, C=O), 158.4 (s, C-4 of 4-methoxyphenyl), 156.5 (s, C-2), 136.2 (s, C-1 of 4-methoxyphenyl), 130.3 (s, C-1), 128.1 (d, C-6), 127.6 (d, C-4), 127.2 (d, C-2/C-6 of 4-methoxyphenyl), 120.3 (d, C-5), 113.3 (d, C-3/C-5 of 4-methoxyphenyl), 110.9 (d, C-3), 73.1 (d, CHOH), 55.8 (q, OCH_3), 55.3 (q, OCH_3), 53.8 (d, CH), 38.5 [s, *C*$(CH_3)_3$], 27.6 [q, C(*C*$H_3)_3$].

EI–MS: *m/z* (%) = 339 (M^+ – H_2O, 3), 254 (M^+ – H_2O – CO^{t}Bu, 4), 222 (M^+ – $MeOC_6H_4CO$, 10), 221 [M^+ – $MeOC_6H_4CHO$ or $MeOC_6H_4CH(OH)Ph^+$, 81], 220 [M^+ – $MeOC_6H_4CHOH$ or $MeOC_6H_4C(OH)Ph^+$, 22], 203 (8), 137 (29), 136 (72), 121 (48), 109 (18), 94 (28), 91 (22), 77 (47), 57 (^{t}Bu$^+$, 100).

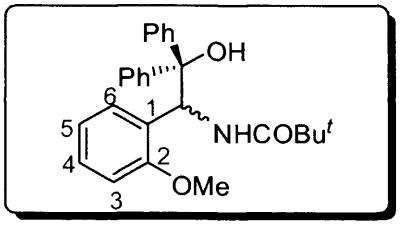
CI–MS: *m/z* (%) = 358 (MH^+, 8), 340 (MH^+ – H_2O, 56), 222 (M^+ – $MeOC_6H_4CO$, 100), 154 (61), 137 (63), 119 (75), 102 (90), 86 (15).

HRMS: *m/z* calc. for $C_{21}H_{28}NO_4$ (MH^+), 358.2013; found, 358.20124.

FT–IR: ν_{max} = 3451 (NH and OH), 3258 (CH), 1635 (C=O), 1560 (aromatic C=C), 1513, 1252, 1027 cm^{-1}.

Selected crystallographic data: $C_{21}H_{27}NO_4$, FW = 357.44, T = 150(2) K, λ = 0.71073 Å, Triclinic, P1, a = 7.403(2) Å, b = 16.774(3) Å, c = 18.372(4) Å, α = 62.537(7)°, β = 77.658(10)°, γ = 76.021(15)°, V = 1950.4(8) Å^3, Z = 4, $\rho_{calc.}$ = 1.214 Mg/m^3, crystal size = 0.25 × 0.06 × 0.06 mm^3, m = 0.084 mm^{-1}, reflections collected = 5162, independent reflections = 3239, R_{int} = 0.1707, parameters = 270, final R_1 = 0.2028, wR_2 = 0.4072 for I>2σ(I) and R_1 = 0.2559, wR_2 = 0.4390 for all data. Full crystallographic data for this compound have been deposited with the CCDC, reference number 736588, and can be obtained free of charge *via* http://www.ccdc.ac.uk/data_request/cif.

N-(2-Hydroxy-1-(2-methoxyphenyl)-2,2-diphenylethyl)pivalamide (87)



Yield: 24 mg (0.06 mmol, 3%).

Mp: 203–204 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.54–6.99 (m, 13 H, 2 Ph, H-4, H-6 and NH), 6.86 (app. t, J = 8 Hz, 1 H, H-5), 6.54 (d, J = 8 Hz, 1 H, H-3), 6.34 (d, J = 9 Hz, 1 H, CH), 6.15 (s, exch., 1 H, OH), 3.14 (s, 3 H, OCH_3), 0.91 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, DMSO-d_6): δ = 176.6 (s, C=O), 157.0 (s, C-2), 147.5, 145.3 (2 s, C-1 of Ph), 130.8 (d, C-6), 128.9 (s, C-1), 128.52, 128.49 (2 d, C-3/C-5 of 2 Ph), 127.51, 127.41 (2 d, C-2/C-6 of 2 Ph), 127.4, 127.1 (2 d, C-4 of 2 Ph), 126.6 (d, C-4), 120.1 (d, C-5), 110.4 (d, C-3), 80.9 (s, C-OH), 55.4 (q, OCH_3), 52.1 (d, CH), 38.7 [s, $C(CH_3)_3$], 27.9 [q, $C(CH_3)_3$].

EI–MS: *m/z* (%) = 386 ($MH^+ - H_2O$, 10), 360 (13), 300 (24), 286 (34), 270 (90), 252 (41), 241 (62), 239 (100).

CI–MS: *m/z* (%) = 405 (MH^+ + 1, 4), 404 (MH^+, 8), 386 ($MH^+ - H_2O$, 10), 222 (100), 220 ($M^+ - Ph_2COH$, 41), 183 (Ph_2COH^+, 43), 136 (27), 119 (22), 102 (11).

HRMS: *m/z* calc. for $C_{26}H_{30}NO_3$ (MH^+), 404.2220; found, 404.2221.

FT–IR: ν_{max} = 3338 (NH and OH), 2932 (CH), 1631 (C=O), 1528 (aromatic C=C), 1242, 1172, 1022 cm^{-1}.

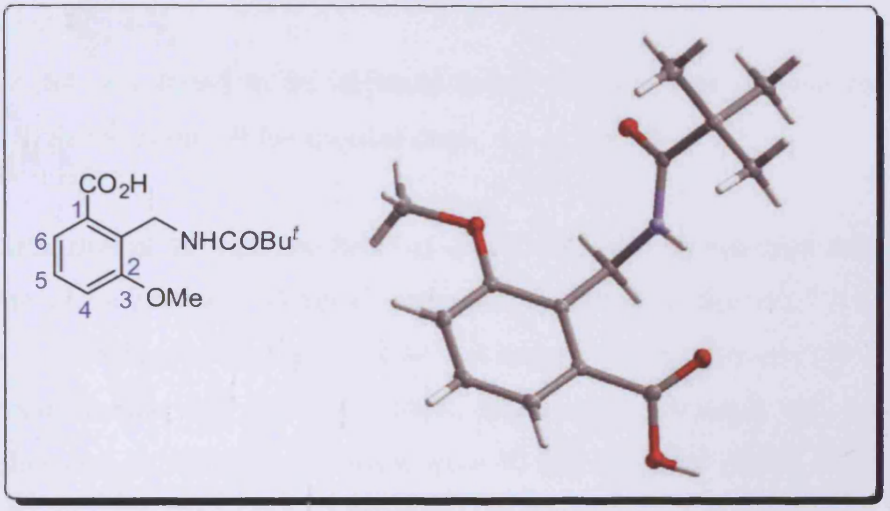
7.10 Lithiation of 46 with *t*-BuLi at 0 °C followed by reaction with 4-anisaldehyde

The procedure was identical with that described in Section 7.9 except that the reaction was carried out at 0 °C and 4-anisaldehyde was the electrophile. The reaction mixture was worked-up and purified by column chromatography (silica gel; Et_2O–hexane, 1:3) to give **80** (0.28 g, 0.78 mmol, 39%) and **85** (0.29 g, 0.81 mmol, 41%). Compounds **80** and **85** were identical in all respects with the ones produced from reaction of the dilithium reagents of compound **46** with 4-anisaldehyde (Section 7.9).

7.11 Lithiation of 46 with *t*-BuLi at 0 °C followed by reaction with CO_2

The procedure was identical with that described in Section 7.9 except that the reaction was carried out at 0 °C and solid carbon dioxide was the electrophile. The reaction mixture was worked-up and the product mixture was purified by fractional crystallization using ethyl acetate to give **47** (26 mg, 0.098 mmol, 5%) and **84** (0.21 g, 0.79 mmol, 40%) as white crystals. No attempts were made to isolate **48**.

3-Methoxy-2-(pivalamidomethyl)benzoic acid (47)



Mp: 170-171 °C (lit.[85] 168-169 °C).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.43 (t, J = 6 Hz, exch., 1 H, NH), 7.34 (app. t, J = 8 Hz, 1 H, H-5), 7.27 (dd, J = 2, 8 Hz, 1 H, H-6), 7.19 (dd, J = 2, 8 Hz, 1 H, H-4), 4.47 (d, J = 6 Hz, 2 H, CH_2), 3.82 (s, 3 H, OCH_3), 1.05 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, DMSO-d_6): δ = 177.5 (s, C=O), 169.7 (s, CO_2H), 158.4 (s, C-3), 134.3 (s, C-2), 128.7 (d, C-5), 126.7 (s, C-1), 121.6 (d, C-6), 114.6 (d, C-4), 56.5 (q, OCH_3), 38.4 [s, $C(CH_3)_3$], 35.7 (t, CH_2), 27.8 [q, $C(CH_3)_3$].

ES$^+$–MS: *m/z* (%) = 553 (2 M + Na$^+$, 34), 531 (2 M + H$^+$, 42), 329 (M + MeCNNa$^+$, 32), 304 (M + K$^+$, 3), 266 (MH^+, 100).

HRMS: *m/z* calc. for $C_{14}H_{20}NO_4$ (MH^+), 266.1392; found, 266.1392.

FT–IR: ν_{max} = 3401 (NH and OH), 2965 (CH), 1698 (CO_2), 1611 (C=O), 1539 (aromatic C=C), 1467, 1385, 1219 cm^{-1}.

Selected crystallographic data: $C_{14}H_{19}NO_4$, FW = 265.30, T = 150(2) K, λ = 0.71073 Å, Triclinic, P1, a = 7.6270(4) Å, b = 8.3440(5) Å, c = 11.1510(6) Å, α = 98.759(3)°, β = 95.311(4)°, γ = 92.118(2)°, V = 697.42(7) Å^3, Z = 2, $\rho_{calc.}$ = 1.263 Mg/m^3, crystal

size = 0.40 × 0.16 × 0.11 mm^3, m = 0.092 mm^{-1}, reflections collected = 4551, independent reflections = 3160, R_{int} = 0.0347, parameters = 177, final R_1 = 0.0534, wR_2 = 0.1177 for $I>2\sigma(I)$ and R_1 = 0.0797, wR_2 = 0.1316 for all data. Full crystallographic data for this compound have been deposited with the CCDC, reference number 736585, and can be obtained free of charge *via* http://www.ccdc.ac.uk/data_request/cif.

2-Methoxy-3-(pivalamidomethyl)benzoic acid (84)

Mp: 156–157 °C.

Compound **84** was found to be identical in all respects with the one produced in Section 7.9. See Section 7.9 for spectral data.

7.12 Lithiation of 46 with *sec*-BuLi at -78 °C followed by reaction with CO_2

The procedure was identical with that described in Section 7.9 except that *sec*-BuLi in cyclohexane (3.2 mL, 1.4 M, 4.4 mmol) was used instead of *t*-BuLi and solid carbon dioxide was the electrophile. The residue obtained was treated with diethyl ether and on standing overnight gave **47** (63 mg, 0.24 mmol, 12%) as white crystals. No attempt was made to isolate **48**.

7.13 Lithiation of 46 with *sec*-BuLi at 0 °C followed by reaction with CO_2

The procedure was identical with that described in Section 7.9 except that *sec*-BuLi in cyclohexane (3.2 mL, 1.4 M, 4.4 mmol) was used instead of *t*-BuLi and the reaction was carried out at 0 °C instead of -78 °C in which solid carbon dioxide was the electrophile. The residue obtained was treated with diethyl ether and on standing overnight gave **47** (0.13 g, 0.49 mmol, 25%) as white crystals. No attempt was made to isolate **48**.

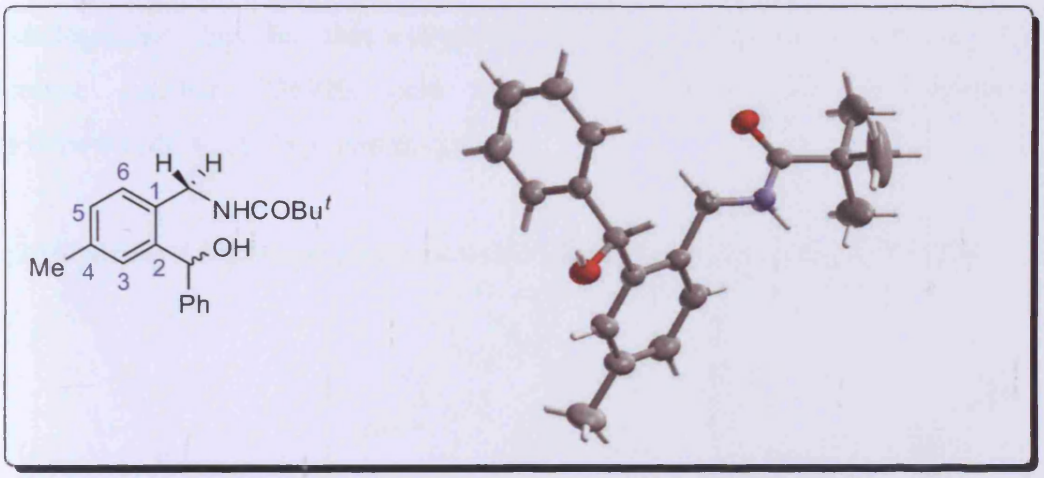
7.14 Lithiation of 46 with *n*-BuLi at 0 °C followed by reaction with CO_2

The procedure was identical with that described in Section 7.9 except that *n*-BuLi in hexanes (2.8 mL, 1.6 M, 4.5 mmol) was used instead of *t*-BuLi and the reaction was carried out at 0 °C instead of -78 °C in which solid carbon dioxide was the electrophile. The residue obtained was treated with diethyl ether to give **47** (58 mg, 0.22 mmol, 11%) as white crystals. No attempts were made to isolate **48** or **84**.

7.15 Synthesis of *N*-(2-substituted 4-methylbenzyl)pivalamides 89-95 *via* directed lithiation of *N*-(4-methylbenzyl)pivalamide (68)

A solution of *t*-BuLi in heptane (2.6 mL, 1.7 M, 4.4 mmol) was added to a cold (-78 °C), stirred solution of **68** (0.41 g, 2.0 mmol) in anhydrous THF (20 mL) under N_2. The mixture was stirred at –78 °C for 4 h, after which an electrophile (2.2 mmol), in anhydrous THF (8 mL) if solid, otherwise neat, was added. The mixture was stirred for 2 h at –78 °C and then worked-up as usual. The crude product obtained was purified by column chromatography (silica gel; Et_2O–hexane, 1:3) to give pure products as white solids. The yields obtained are recorded in Table 2.7.

N-(2-(Hydroxyphenymethyl)-4-methylbenzyl)pivalamide (89)



Yield: 0.49 g (1.58 mmol, 79%).

Mp: 150–151 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.06 (m, 7 H, Ph, H-3 and H-6), 7.00 (dd, *J* = 2, 8 Hz, 1 H, H-5), 5.99 (br t, exch., 1 H, NH), 5.92 (br, 1 H, CH), 4.29 (dd, *J* = 5, 14 Hz, 1 H, 1 H of CH_2), 4.16 (dd, *J* = 5, 14 Hz, 1 H, 1 H of CH_2), 3.40 (br, exch., 1 H, OH), 2.23 (s, 3 H, CH_3), 0.97 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.7 (s, C=O), 143.9 (s, C-1 of Ph), 141.8 (s, C-2), 137.9 (s, C-1), 133.7 (s, C-4), 130.7 (d, C-3), 129.4 (d, C-6), 129.3 (d, C-5), 128.9 (d, C-3/C-5 of Ph), 127.8 (d, C-4 of Ph), 127.1 (d, C-2/C-6 of Ph), 74.1 (d, CH), 41.1 (t, CH_2), 38.9 [s, $C(CH_3)_3$], 27.8 [q, $C(CH_3)_3$], 21.6 (q, CH_3).

ES^+–MS: *m/z* (%) = 334 ($M + Na^+$, 89), 312 (MH^+, 8), 295 ($MH^+ - OH$, 21), 294 ($MH^+ - H_2O$, 100), 208 (12), 193 (78), 102 (27), 57 ($^tBu^+$, 81).

ES^-–MS: *m/z* (%) = 311 (M^-, 2), 310 ($M^- - 1$, 23), 204 [$M^- - C_6H_4CH(OH)$, 100].

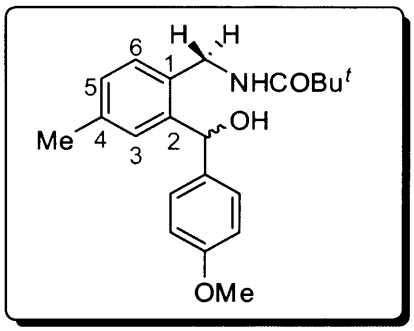
HRMS: *m/z* calc. for $C_{20}H_{26}NO_2$ (MH^+), 312.1958; found, 312.1960.

FT–IR: ν_{max} = 3339 (NH and OH), 2906 (CH), 1630 (C=O), 1549 (aromatic C=C), 1495, 1356, 1235, 1020 cm^{-1}.

Anal. calc. for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 77.23; H, 8.14; N, 4.45%.

Selected crystallographic data: $C_{20}H_{25}NO_2$, FW = 311.410, T = 296(2) K, λ = 0.71073 Å, Monoclinic, $P2_1/c$, a = 10.7160(7) Å, b = 15.0800(7) Å, c = 11.2900(11) Å, α = 90°, β = 94.234(3)°, γ = 90°, V = 1819.5(2) $Å^3$, Z = 4, $\rho_{calc.}$ = 1.137 Mg/m^3, crystal size = 0.32 × 0.32 × 0.12 mm^3, m = 0.073 mm^{-1}, reflections collected = 9766, independent reflections = 3353, R_{int} = 0.0728, parameters = 214, final R_1 = 0.0751, wR_2 = 0.1741 for $I>2\sigma(I)$ and R_1 = 0.1621, wR_2 = 0.2090 for all data. Full crystallographic data for this compound have been deposited with the CCDC, reference number 736920, and can be obtained free of charge *via* http://www.ccdc.ac.uk/data_request/cif.

_N_-(2-(Hydroxy-(4-methoxyphenyl)methyl)-4-methylbenzyl)pivalamide (90)



Yield: 0.55 g (1.61 mmol, 81%).

Mp: 184–186 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.55 (app. t, J = 6 Hz, exch., 1 H, NH), 7.05 (s, 1 H, H-3), 6.96 (d, J = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 6.78 (br, 2 H, H-5 and H-6), 6.62 (d, J = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 5.60 (d, J = 4 Hz, 1 H, CH), 5.51 (d, J = 4 Hz, exch., 1 H, OH), 4.02 (dd, J = 6, 15 Hz, 1 H, 1 H of CH_2), 3.79 (dd, J = 6, 15 Hz, 1 H, 1 H of CH_2), 3.48 (s, 3 H, OCH_3), 2.03 (s, 3 H, CH_3), 0.86 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, DMSO-d_6): δ = 178.0 (s, C=O), 158.9 (s, C-4 of 4-methoxyphenyl), 143.2 (s, C-2), 137.3 (s, C-1), 136.1 (s, C-4), 134.2 (s, C-1 of 4-methoxyphenyl), 129.0 (d, C-2/C-6 of 4-methoxyphenyl), 128.1 (d, C-3), 128.0 (d,

C-6), 127.7 (d, C-5), 114.2 (d, C-3/C-5 of 4-methoxyphenyl), 71.3 (d, CH), 55.9 (q, OCH_3), 40.0 (t, CH_2), 38.9 [s, $C(CH_3)_3$], 28.3 [q, $C(CH_3)_3$], 21.8 (q, CH_3).

EI–MS: *m/z* (%) = 323 ($M^+ - H_2O$, 17), 266 ($M^+ - H_2O - {}^tBu$, 62), 238 ($M^+ - H_2O - CO^tBu$, 33), 209 ($M^+ - H_2O - CH_2NHCO^tBu$, 50), 165 (55), 130 (44), 92 (46), 77 (100).

CI–MS: *m/z* (%) = 341 (M^+, 6), 340 ($M^+ - 1$, 17), 326 (M^+ – Me, 48), 324 ($MH^+ - H_2O$, 100), 206 (66), 154 (22), 137 [$MeOC_6H_4CH(OH)^+$, 17], 119 ($MeC_6H_3CH_2NH^+$, 37), 102 [$^tBuCOH(NH_2)^+$, 22].

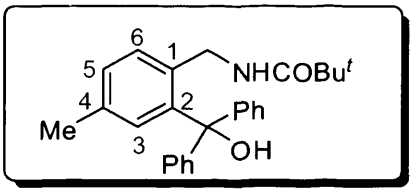
ES^+–MS: *m/z* (%) = 364 ($M + Na^+$, 82), 325 ($MH^+ - H_2O$, 22), 324 ($M^+ - H_2O$, 79), 223 ($M^+ - H_2O - NHCO^tBu$, 100).

ES^-–MS: *m/z* (%) = 341 (M^-, 12), 340 ($M^- - 1$, 52), 204 [M^- – $MeOC_6H_4CH(OH)$, 100].

HRMS: *m/z* calc. for $C_{21}H_{26}NO_3$ ($M^- - 1$), 340.1918; found, 340.1908.

FT–IR: ν_{max} = 3328 (NH and OH), 2923 (CH), 1613 (C=O), 1563 (aromatic C=C), 1469, 1242, 1026 cm^{-1}.

_N_-(2-(Hydroxydiphenylmethyl)-4-methylbenzyl)pivalamide (91)



Yield: 0.63 g (1.63 mmol, 81%).

Mp: 244–246 °C.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.81 (br t, exch., 1 H, NH), 7.34–7.24 (m, 10 H, 2 Ph), 7.17 (d, *J* = 8 Hz, 1 H, H-6), 7.08 (d, *J* = 8 Hz, 1 H, H-5), 7.05 (s, 1 H, H-3), 6.36 (s, exch., 1 H, OH), 3.93 (d, *J* = 5 Hz, 2 H, CH_2), 2.08 (s, 3 H, CH_3), 1.07 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, DMSO-d_6): δ = 178.4 (s, C=O), 148.6 (s, C-1 of 2 Ph), 145.3 (s, C-2), 137.1 (s, C-1), 135.2 (s, C-4), 130.4 (d, C-3), 129.7 (d, C-6), 129.0 (d, C-5), 128.6 (d, C-3/C-5 of 2 Ph), 128.3 (d, C-2/C-6 of 2 Ph), 127.5 (d, C-4 of 2 Ph), 82.2 (s, C-OH), 41.7 (t, CH_2), 38.7 [s, $C(CH_3)_3$], 28.2 [q, $C(CH_3)_3$], 21.8 (q, CH_3).

EI–MS: *m/z* (%) = 370 ($MH^+ - H_2O$, 8), 369 ($M^+ - H_2O$, 28), 368 ($M^+ - H_2O$ – H, 9), 312 ($M^+ - H_2O - {}^tBu$, 51), 310 (48), 285 ($MH^+ - H_2O - CO^tBu$, 83), 284 ($M^+ - H_2O - CO^tBu$, 100).

CI–MS: *m/z* (%) = 388 (MH^+, 21), 370 ($MH^+ - H_2O$, 40), 206 (72), 200 ($M^+ - 2$ Ph – H_2O – Me, 22), 183 (Ph_2COH^+, 35), 119 ($MeC_6H_3CH_2NH^+$, 81), 102 [$^tBuCOH(NH_2)^+$, 100].

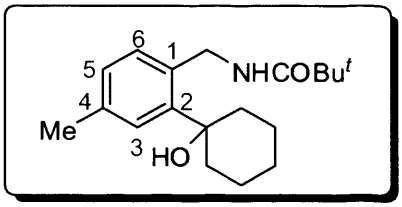
ES^+–MS: *m/z* (%) = 410 (M + Na^+, 22), 370 ($MH^+ - H_2O$, 100), 270 ($MH^+ - H_2O$ – $NHCO^tBu$, 7), 269 ($M^+ - H_2O - NHCO^tBu$, 37).

ES^-–MS: *m/z* (%) = 432 (100), 387 (M^-, 20), 386 ($M^- - 1$, 72).

HRMS: *m/z* calc. for $C_{26}H_{30}NO_2$ (MH^+), 388.2271; found, 388.2266.

FT–IR: ν_{max} = 3334 (NH and OH), 2941 (CH), 1635 (C=O), 1532 (aromatic C=C), 1461, 13377, 1237, 1020 cm^{-1}.

_N_-(2-(1-Hydroxycyclohexyl)-4-methylbenzyl)pivalamide (92)



Yield: 0.50 g (1.65 mmol, 82%).

Mp: 127–129 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.15 (d, *J* = 8 Hz, 1 H, H-6), 7.08 (s, 1 H, H-3), 6.93 (d, *J* = 8 Hz, 1 H, H-5), 6.57 (br t, exch., 1 H, NH), 4.59 (d, *J* = 5 Hz, 2 H, CH_2), 2.85 (br s, exch., 1 H, OH), 2.24 (s, 3 H, CH_3), 1.89–1.59 [m, 10 H, $(CH_2)_5$], 1.06 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.4 (s, C=O), 146.6 (s, C-2), 137.1 (s, C-1), 134.6 (s, C-4), 132.6 (d, C-3), 128.3 (d, C-6), 126.8 (d, C-5), 75.0 (s, C-1 of cyclohexyl), 43.0 (t, CH_2NH), 39.2 (t, C-2/C-6 of cyclohexyl), 38.9 [s, $C(CH_3)_3$], 27.9 [q, $C(CH_3)_3$], 25.8 (t, C-4 of cyclohexyl), 22.4 (t, C-3/C-5 of cyclohexyl), 21.7 (q, CH_3).

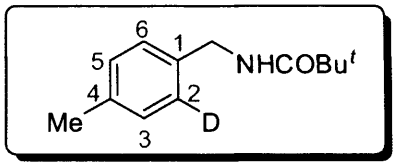
EI–MS: *m/z* (%) = 303 (M^+, 3), 184 (8), 159 (10), 105 (12), 91 (13), 57 ($^tBu^+$, 100).

CI–MS: *m/z* (%) = 304 (MH^+, 18), 286 ($MH^+ - H_2O$, 100), 206 (9).

HRMS: *m/z* calc. for $C_{19}H_{30}NO_2$ (MH^+), 304.2271; found, 304.2275.

FT–IR: ν_{max} = 3329 (NH and OH), 2925 (CH), 1611 (C=O), 1564 (aromatic C=C), 1514, 1241, 1028 cm^{-1}.

_N_-(2-Deuterio-4-methylbenzyl)pivalamide (93)



Yield: 0.39 g (1.76 mmol, 88%).

Mp: 96–97 °C (Mp of undeuteriated analogue 94–96 °C[133,134]).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.05 (m, 3 H, H-3, H-5 and H-6), 5.84 (br, exch., 1 H, NH), 4.03 (d, J = 5 Hz, 2 H, CH_2), 2.26 (s, 3 H, CH_3), 1.14 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.6 (s, C=O), 137.5 (s, C-1), 135.9 (s, C-4), 129.8 (d, C-3), 129.7 (d, C-5), 128.1 (d, C-6), 127.8 (seen as three lines, 1:1:1, because of coupling to D, C-2), 43.7 (t, CH_2), 39.1 [s, $C(CH_3)_3$], 28.0 [q, $C(CH_3)_3$], 21.5 (q, CH_3).

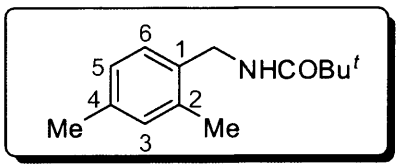
EI–MS: *m/z* (%) = 206 (M^+, 17), 106 (M^+ – NHCO^{t}Bu, 100), 92 (M^+ – CH_2NHCO^tBu, 18), 78 (19), 77 (17), 57 ($^tBu^+$, 92).

CI–MS: *m/z* (%) = 224 ($M + NH_4^+$, 12), 207 (MH^+, 100).

HRMS: *m/z* calc. for $C_{13}H_{19}DNO$ (MH^+), 207.1602; found, 207.1598.

FT–IR: ν_{max} = 3332 (NH), 2970 (CH), 1625 (C=O), 1538 (aromatic C=C), 1482, 1417, 1219 cm^{-1}.

_N_-(2,4-Dimethylbenzyl)pivalamide (94)



Yield: 0.35 g (1.60 mmol, 80%).

Mp: 95–97 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.01 (d, J = 8 Hz, 1 H, H-6), 6.93 (s, 1 H, H-3), 6.90 (d, J = 8 Hz, 1 H, H-5), 5.63 (br, exch., 1 H, NH), 4.30 (d, J = 5 Hz, 2 H, CH_2), 2.23 (s, 3 H, CH_3), 2.19 (s, 3 H, CH_3), 1.13 [s, 9 H, $C(CH_3)_3$].

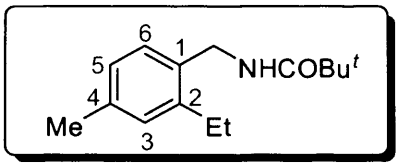
^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.4 (s, C=O), 137.8 (s, C-1), 136.9 (s, C-2), 133.5 (s, C-4), 131.8 (d, C-3), 129.1 (d, C-6), 127.2 (d, C-5), 42.2 (t, CH_2), 39.1 [s, $C(CH_3)_3$], 28.1 [q, $C(CH_3)_3$], 21.4 (q, CH_3), 19.3 (q, CH_3).

CI–MS: *m/z* (%) = 237 ($M + NH_4^+$, 12), 220 (MH^+, 100), 119 (10), 102 (5).

HRMS: *m/z* calc. for $C_{14}H_{22}NO$ (MH^+), 220.1696; found, 220.1693.

FT–IR: ν_{max} = 3329 (NH), 2969 (CH), 1638 (C=O), 1533 (aromatic C=C), 1362, 1302, 1220, 1006 cm^{-1}.

_N_-(2-Ethyl-4-methylbenzyl)pivalamide (95)



Yield: 0.38 g (1.63 mmol, 81%).

Mp: 88–89 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.03 (d, *J* = 8 Hz, 1 H, H-6), 6.97 (s, 1 H, H-3), 6.92 (d, *J* = 8 Hz, 1 H, H-5), 5.60 (br, exch., 1 H, NH), 4.33 (d, *J* = 5 Hz, 2 H, CH_2NH), 2.54 (q, *J* = 7 Hz, 2 H, CH_2CH_3), 2.26 (s, 3 H, CH_3), 1.13 [s, 9 H, $C(CH_3)_3$], 1.11 (t, *J* = 7 Hz, 3 H, CH_2CH_3).

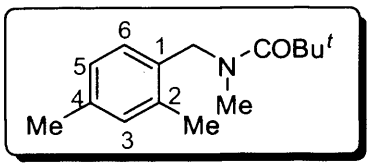
^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.4 (s, C=O), 143.0 (s, C-1), 138.1 (s, C-2), 132.8 (s, C-4), 130.1 (d, C-3), 129.5 (d, C-6), 126.8 (d, C-5), 41.6 (t, CH_2NH), 39.1 [s, $C(CH_3)_3$], 28.0 [q, $C(CH_3)_3$], 25.7 (t, CH_2CH_3), 21.5 (q, CH_3), 16.0 (q, CH_2CH_3).

CI–MS: *m/z* (%) = 251 ($M + NH_4^+$, 8), 234 (MH^+, 100), 218 (6), 206 (12), 132 (9), 119 (10), 116 (11), 52 (40).

HRMS: *m/z* calc. for $C_{15}H_{24}NO$ (MH^+), 234.1852; found, 234.1854.

FT–IR: ν_{max} = 3326 (NH), 2963 (CH), 1635 (C=O), 1534 (aromatic C=C), 1266, 1220, 1009 cm^{-1}.

_N_-(2,4-Dimethylbenzyl)-_N_-methylpivalamide (96)



Yield: 9.5 mg (0.04 mmol, 2%).

Colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.04–6.85 (m, 3 H, H-3, H-5 and H-6), 4.49 (s, 2 H, CH_2), 2.86 (s, 3 H, NCH_3), 2.18 (s, 3 H, CH_3), 2.12 (s, 3 H, CH_3), 1.21 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.0 (s, C=O), 137.0 (s, C-2), 136.2 (s, C-4), 133.5 (s, C-1), 131.6 (d, C-3), 129.7 (d, C-6), 127.1 (d, C-5), 51.1 (t, CH_2), 39.4 (q, NCH_3), 36.6 [s, $C(CH_3)_3$], 28.8 [q, $C(CH_3)_3$], 21.3 (q, CH_3), 19.3 (q, CH_3).

EI–MS: *m/z* (%) = 233 (M^+, 9), 119 (M^+ – NMeCO^{t}Bu or $MeC_6H_3CH_2NH^+$, 93), 105 (M^+ – $CH_2N(Me)CO^tBu$, 15), 91 ($MeC_6H_4^+$, 33), 77 (21), 57 ($^tBu^+$, 100).

CI–MS: *m/z* (%) = 234 (MH^+, 100), 220 (MH^+ – CH_2, 17).

HRMS: *m/z* calc. for $C_{15}H_{24}NO$ (MH^+), 234.1852; found, 234.1853.

FT–IR: ν_{max} = 2970 (CH), 1626 (C=O), 1504 (aromatic C=C), 1479, 1401, 1364, 1188, 1023 cm^{-1}.

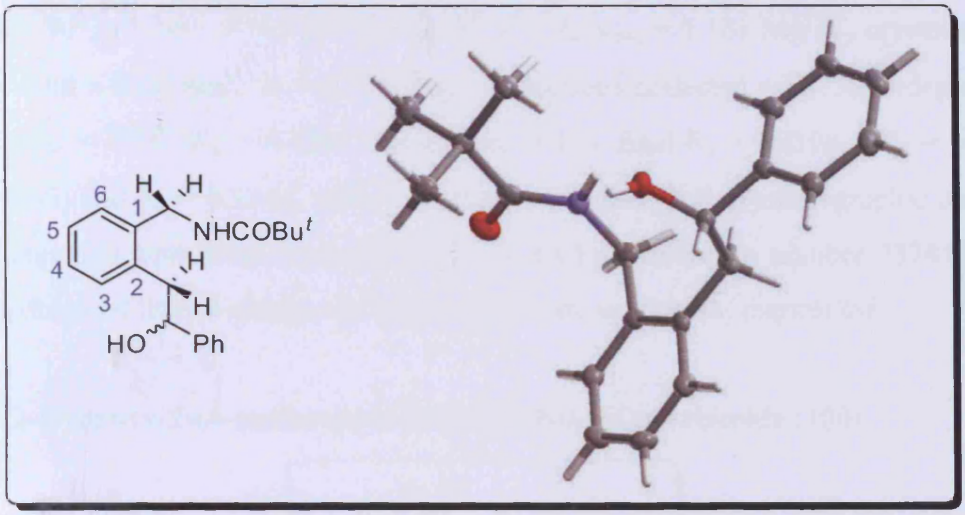
7.16 Synthesis of *N*-(2,4-dimethylbenzyl)-*N*-methylpivalamide (96) *via* directed lithiation of *N*-(4-methylbenzyl)pivalamide (68)

The procedure was identical with that described in Section 7.15 except that excess iodomethane (0.63 g, 4.4 mmol) was used. The reaction mixture was worked-up and purified by column chromatography (silica gel; Et_2O–hexane, 1:3) to give **96** (0.41 g, 1.76 mmol, 88%) as a colourless oil. Compound **96** was identical in all respects with the one produced as a side product from reaction of the dilithium reagent of compound **68** with 1.1 equivalents of iodomethane (Section 7.15).

7.17 Synthesis of *N*-(2-substituted methyl)benzylpivalamides 99-106 *via* lateral lithiation of *N*-(2-methylbenzyl)pivalamide (65)

A solution of *t*-BuLi in heptane (2.6 mL, 1.7 M, 4.4 mmol) was added to a cold (-78 °C), stirred solution of *N*-(2-methylbenzyl)pivalamide (**65**; 0.41 g, 2.0 mmol) in anhydrous THF (20 mL) under N_2. Formation of the monolithium reagent **97** was observed as a yellow solution and the dilithium reagent **98** was observed as a brownish solution. The mixture was stirred at –78 °C for 4 h, to ensure the complete formation of the dilithium reagent **98**, after which an electrophile (2.2 mmol), in anhydrous THF (8 mL) if solid, otherwise neat, was added. The mixture was stirred for 2 h at –78 °C then the cooling bath was removed and the mixture allowed to warm to room temperature. The reaction mixture was worked-up as usual and purified by column chromatography (silica gel; Et_2O–hexane, 1:3) to give the pure products as white solids. The yields obtained are recorded in Table 2.8.

N-(2-(2-Hydroxy-2-phenyethyl)benzyl)pivalamide (99)



Yield: 0.52 g (1.67 mmol, 84%).

Mp: 133–134 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.21 (m, 9 H, Ph, H-3, H-4, H-5 and H-6), 6.69 (br t, exch., 1 H, NH), 4.94 (dd, 1 H, *J* = 9, 4 Hz, CH), 4.53 (dd, *J* = 6, 14 Hz, 1 H, 1 H of C*H*$_2$NH), 4.33 (dd, *J* = 2, 14 Hz, 1 H, 1 H of C*H*$_2$NH), 3.10 (dd, *J* = 9, 14 Hz, 1 H, 1 H of CH_2), 3.01 (dd, *J* = 4, 14 Hz, 1 H, 1 H of CH_2), 2.78 (br, exch., 1 H, OH), 1.19 [s, 9 H, C(CH_3)$_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.7 (s, C=O), 144.6 (s, C-1), 137.7 (s, C-1 of Ph), 137.6 (s, C-2), 130.8 (d, C-3), 130.3 (d, C-6), 128.9 (d, C-3/C-5 of Ph), 128.3 (d, C-4 of Ph), 128.1 (d, C-4), 127.4 (d, C-5), 126.2 (d, C-2/C-6 of Ph), 76.2 (d, CH), 42.5 (t, CH_2), 41.8 (t, CH_2), 39.1 [s, *C*(CH_3)$_3$], 28.0 [q, C(*C*H$_3$)$_3$].

EI–MS: *m/z* (%) = 311 (M^+, 6), 295 (MH^+ – OH, 31), 294 (M^+ – OH, 100), 278 (M^+ – OH – Me, 8).

CI–MS: *m/z* (%) = 329 (M + NH_4^+, 9), 313 (MH^+ + 1, 13), 312 (MH^+, 78), 294 (MH^+ – H_2O or M^+ - OH, 100), 234 (M^+ – Ph, 8), 206 [M^+ – PhCH(OH), 12], 205 (M^+ – PhCHO, 17), 192 (7), 119 (10), 102 (9).

HRMS: *m/z* calc. for $C_{20}H_{26}NO_2$ (MH^+), 312.1958; found, 312.1955.

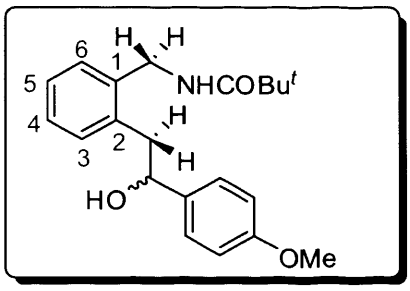
FT–IR: ν_{max} = 3314 (NH and OH), 2971 (CH), 1627 (C=O), 1542 (aromatic C=C), 1367, 1216, 1055 cm^{-1}.

Anal. calc. for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 77.21; H, 8.14; N, 4.54%.

Selected crystallographic data: $C_{20}H_{25}NO_2$, FW = 311.41, T = 150(2) K, λ = 0.71073

Å, Orthorhombic, $Pca2_1$, a = 10.4480(3) Å, b = 11.3910(3) Å, c = 29.4400(9) Å, α = 90°, β = 90°, γ = 90°, V = 3503.75(17) $Å^3$, Z = 8, $\rho_{calc.}$ = 1.181 Mg/m^3, crystal size = 0.50 × 0.08 × 0.06 mm^3, m = 0.075 mm^{-1}, reflections collected = 20758, independent reflections = 7296, R_{int} = 0.1196, parameters = 423, final R_1 = 0.0598, wR_2 = 0.1025 for I>2σ(I) and R_1 = 0.1544, wR_2 = 0.1288 for all data. Full crystallographic data for this compound have been deposited with the CCDC, reference number 737412, and can be obtained free of charge *via* http://www.ccdc.ac.uk/data_request/cif.

_N_-(2-(2-Hydroxy-2-(4-methoxyphenyl)ethyl)benzyl)pivalamide (100)



Yield: 0.61 g (1.79 mmol, 89%).

Mp: 124–126 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 7.28–7.20 (m, 4 H, H-3, H-4, H-5 and H-6), 6.88 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 6.83 (br, exch., 1 H, NH), 4.87 (dd, *J* = 4, 9 Hz, 1 H, CH), 4.49 (dd, *J* = 6, 14 Hz, 1 H, 1 H of C*H*$_2$NH), 4.30 (dd, *J* = 4, 14 Hz, 1 H, 1 H of C*H*$_2$NH), 3.80 (s, 3 H, OCH_3), 3.22 (br, exch., 1 H, OH), 3.07 (dd, *J* = 9, 14 Hz, 1 H, 1 H of CH_2), 2.94 (dd, *J* = 4, 14 Hz, 1 H, 1 H of CH_2), 1.17 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.8 (s, C=O), 159.4 (s, C-4 of 4-methoxyphenyl), 137.9 (s, C-1), 137.5 (s, C-2), 137.0 (s, C-1 of 4-methoxyphenyl), 130.8 (d, C-3), 130.2 (d, C-6), 128.2 (d, C-4), 127.6 (d, C-2/C-6 of 4-methoxyphenyl), 127.3 (d, C-5), 114.2 (d, C-3/C-5 of 4-methoxyphenyl), 75.7 (d, CH), 55.7 (q, OCH_3), 42.5 (t, CH_2), 41.9 (t, CH_2), 39.01 [s, *C*$(CH_3)_3$], 28.0 [q, C(*C*$H_3)_3$].

EI–MS: *m/z* (%) = 341 (M^+, 5), 324 (M^+ – OH, 63), 323 (M^+ – H_2O, 79), 308 (5), 266 (M^+ – H_2O – ^{t}Bu, 21), 254 (13), 238 (M^+ – H_2O – CO^{t}Bu, 100).

CI–MS: *m/z* (%) = 357 (M + NH_4^+, 4), 342 (MH^+, 8), 341 (M^+, 20), 325 (MH^+ – OH, 24), 324 (MH^+ – H_2O, 100), 251 (4), 234 (6), 205 (7), 154 (8), 119 (15), 102 (7), 52 (10).

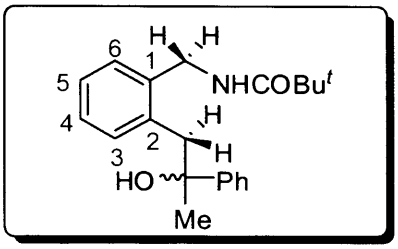
ES^+–MS: *m/z* (%) = 364 ($M + Na^+$, 19), 324 ($M^+ - H_2O$, 33), 223 ($M^+ - H_2O$ – NHCO^{t}Bu, 100).

ES^-–MS: *m/z* (%) = 340 ($M^- - 1$, 12), 205 ($M^- - MeOC_6H_4CHO$, 12), 204 [M^- – $MeOC_6H_4CH(OH)$, 100], 100 (28).

HRMS: *m/z* calc. for $C_{21}H_{28}NO_3$ (MH^+), 342.2064; found, 342.2065.

FT–IR: ν_{max} = 3321 (NH and OH), 2954 (CH), 1629 (C=O), 1555 (aromatic C=C), 1463, 1370, 1220, 1035 cm^{-1}.

_N_-(2-(2-Hydroxy-2-phenylpropyl)benzyl)pivalamide (101)



Yield: 0.52 g (1.60 mmol, 80%).

Mp: 135–137 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 8 Hz, 2 H, H-2/H-6 of Ph), 7.35 (t, *J* = 8 Hz, 2 H, H-3/H-5 of Ph), 7.30–7.26 (m, 2 H, H-4 of Ph and H-6), 7.20 (app. dt, *J* = 2, 8 Hz, 1 H, H-4), 7.12 (app. dt, *J* = 2, 8 Hz, 1 H, H-5), 6.87 (dd, *J* = 2, 8 Hz, 1 H, H-3), 6.55 (br app. t, exch., 1 H, NH), 4.44 (dd, *J* = 5, 14 Hz, 1 H, 1 H of C*H*$_2$NH), 4.37 (dd, *J* = 5, 14 Hz, 1 H, 1 H of C*H*$_2$NH), 3.17 (d, *J* = 14 Hz, 1 H, 1 H of CH_2), 3.12 (d, *J* = 14 Hz, 1 H, 1 H of CH_2), 2.42 (s, exch., 1 H, OH), 1.68 (s, 3 H, CH_3), 1.21 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.6 (s, C=O), 149.2 (s, C-1 of Ph), 138.7 (s, C-1), 135.8 (s, C-2), 132.4 (d, C-3), 130.0 (d, C-6), 128.5 (d, C-3/C-5 of Ph), 127.5 (d, C-4), 127.3 (d, C-4 of Ph), 127.2 (d, C-2/C-6 of Ph), 125.4 (d, C-5), 75.5 (s, C-OH), 46.6 (t, CH_2), 41.7 (t, CH_2), 39.1 [s, *C*$(CH_3)_3$], 30.3 (q, CH_3), 29.5 [q, C(*C*$H_3)_3$].

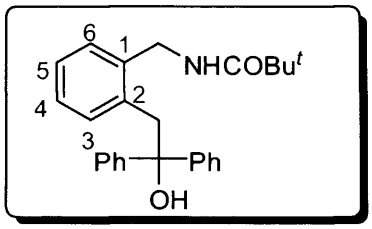
EI–MS: *m/z* (%) = 325 (M^+, 1), 308 (M^+ – OH, 77), 307 ($M^+ - H_2O$, 34), 292 (12), 282 (23), 264 (31), 248 (19), 229 (60), 222 ($M^+ - H_2O$ – CO^{t}Bu, 100).

CI–MS: *m/z* (%) = 343 ($M + NH_4^+$, 2), 326 (MH^+, 34), 309 ($MH^+ - H_2O$ or M^+ – OH, 36), 308 ($MH^+ - H_2O$, 100), 248 (5), 306 (MH^+ – PhCOMe, 17), 205 (MH^+ – PhC(OH)Me, 22), 138 (7), 119 (9), 102 (9), 52 (7).

HRMS: *m/z* calc. for $C_{21}H_{28}NO_2$ (MH^+), 326.2115; found, 326.2115.

FT–IR: ν_{max} = 3324 (NH and OH), 2964 (CH), 1623 (C=O), 1493 (aromatic C=C), 1242, 1025 cm^{-1}.

_N_-(2-(2-Hydroxy-2,2-diphenylethyl)benzyl)pivalamide (102)



Yield: 0.68 g (1.76 mmol, 88%).

Mp: 94–95 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.23 (m, 11 H, 2 Ph and H-6), 7.17 (app. dt, *J* = 2, 8 Hz, 1 H, H-4), 6.97 (app. dt, *J* = 2, 8 Hz, 1 H, H-5), 6.56 (dd, *J* = 2, 8 Hz, 1 H, H-3), 6.38 (br t, exch., 1 H, NH), 4.36 (d, *J* = 5 Hz, 2 H, C*H*$_2$NH), 3.75 (s, 2 H, CH_2), 2.72 (s, exch., 1 H, OH), 1.18 [s, 9 H, C(CH_3)$_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.6 (s, C=O), 147.1 (s, C-1 of 2 Ph), 139.0 (s, C-1), 134.8 (s, C-2), 132.3 (d, C-3), 129.7 (d, C-6), 128.5 (d, C-4), 128.3 (d, C-3/C-5 of 2 Ph), 127.6 (d, C-4 of 2 Ph), 127.2 (d, C-5), 126.8 (d, C-2/C-6 of 2 Ph), 79.0 (s, C-OH), 43.8 (t, CH_2), 42.3 (t, CH_2), 39.1 [s, *C*(CH_3)$_3$], 29.5 [q, C(*C*H_3)$_3$].

EI–MS: *m/z* (%) = 370 (M^+ – H_2O, 7), 284 (M^+ – H_2O – CO^{t}Bu, 12), 269 (M^+ – H_2O – NHCO^{t}Bu, 39), 268 (M^+ – H_2O – H_2NCO^{t}Bu, 100), 252 (13).

CI–MS: *m/z* (%) = 405 (M + NH_4^+, 5), 388 (MH^+, 18), 387 (M^+, 33), 370 (MH^+ – H_2O or M^+ – OH, 100), 310 (M^+ – Ph, 11), 285 (5), 257 (7), 223 (12), 206 (MH^+ – Ph_2CO, 41), 200 (M^+ – 2 Ph – H_2O – Me, 52),183 (Ph_2CHO^+, 17), 119 ($PhCH_2CO^+$, 29), 102 [^{t}BuCOH(NH_2)$^+$, 12], 52 (16).

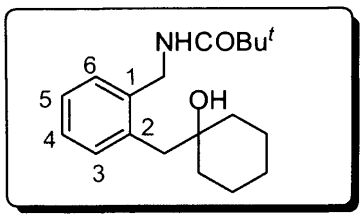
ES$^+$–MS: *m/z* (%) = 410 (M + Na^+, 23), 370 (MH^+ – H_2O, 72), 270 (M^+ – OH – NHCO^{t}Bu, 22), 269 (M^+ – H_2O – NHCO^{t}Bu, 100), 191 (47), 102 (49), 91 (47).

ES$^-$–MS: *m/z* (%) = 388 (MH^-, 3), 387 (M^-, 21), 386 (M^- – 1, 100).

HRMS: *m/z* calc. for $C_{26}H_{33}N_2O_2$ (M + NH_4^+), 405.2537; found, 405.2534.

FT–IR: ν_{max} = 3310 (NH and OH), 2933 (CH), 1635 (C=O), 1531 (aromatic C=C), 1449, 1227, 1020 cm^{-1}.

_N_-(2-((1-Hydroxycyclohexyl)methyl)benzyl)pivalamide (103)



Yield: 0.46 g (1.52 mmol, 76%).

Mp: 93–96 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23-7.09 (m, 4 H, H-3, H-4, H-5 and H-6), 6.77 (br t, exch., 1 H, NH), 4.41 (br d, 2 H, C*H*$_2$NH), 2.75 (s, 2 H, CH_2), 1.86 (br s, exch., 1 H, OH), 1.51-1.43 [m, 10 H, $(CH_2)_5$], 1.10 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.7 (s, C=O), 138.6 (s, C-1), 136.3 (s, C-2), 132.3 (d, C-3), 130.3 (d, C-6), 127.4 (d, C-4), 127.3 (d, C-5), 72.2 (s, C-1 of cyclohexyl), 45.0 (t, CH_2NH), 42.2 (t, CH_2NH), 39.1 [s, *C*$(CH_3)_3$], 38.3 (t, C-2/C-6 of cyclohexyl), 28.0 [q, C(*C*$H_3)_3$], 26.1 (t, C-4 of cyclohexyl), 22.4 (t, C-3/C-5 of cyclohexyl).

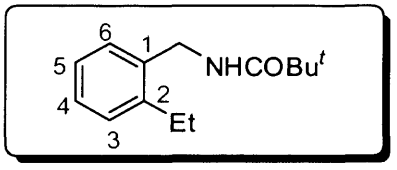
EI–MS: *m/z* (%) = 303 (M^+, 7), 286 (M^+ – OH, 39), 285 (M^+ – H_2O, 87), 270 (M^+ – H_2O – Me, 12), 260 (M^+– Me – C_2H_4, 100), 242 (40), 228 (M^+ – H_2O – ^{t}Bu, 77), 218 (M^+ – CO^{t}Bu, 71).

CI–MS: *m/z* (%) = 321 (M + NH_4^+, 3), 304 (MH^+, 100), 286 (MH^+ – H_2O, 58), 205 (9), 119 (5), 52 (11).

HRMS: *m/z* calc. for $C_{19}H_{30}NO_2$ (MH^+), 304.2271; found, 304.2272.

FT–IR: ν_{max} = 3341 (NH and OH), 2929 (CH), 1634 (C=O), 1529 (aromatic C=C), 1449, 1208 cm^{-1}.

_N_-(2-Ethylbenzyl)pivalamide (104)



Yield: 0.38 g (1.74 mmol, 87%).

Mp: 64–65 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.08 (m, 4 H, H-3, H-4, H-5 and H-6), 5.69 (br t, exch., 1 H, NH), 4.37 (d, *J* = 5 Hz, 2 H, C*H*$_2$NH), 2.58 (q, *J* = 7 Hz, 2 H, C*H*$_2$CH$_3$), 1.14 (t, *J* = 7 Hz, 3 H, CH_2CH_3), 1.13 [s, 9 H, $C(CH_3)_3$].

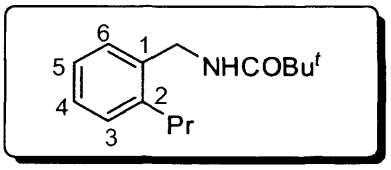
^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.5 (s, C=O), 143.0 (s, C-1), 135.9 (s, C-2), 129.3 (d, C-3), 129.2 (d, C-6), 128.4 (d, C-4), 126.6 (d, C-5), 41.8 (t, CH_2NH), 39.1 [s, *C*$(CH_3)_3$], 28.0 [q, C(*C*$H_3)_3$], 25.7 (t, *C*H_2CH_3), 15.8 (q, CH_2CH_3).

ES$^+$–MS: *m/z* (%) = 237 (M + NH_4^+, 15), 220 (MH^+, 100).

HRMS: *m/z* calc. for $C_{14}H_{22}NO$ (MH^+), 220.1696; found, 220.1694.

FT–IR: ν_{max} = 3331 (NH), 2963 (CH), 1632 (C=O), 1531 (aromatic C=C), 1217, 1008 cm^{-1}.

_N_-(2-Propylbenzyl)pivalamide (105)



Yield: 0.41 g (1.76 mmol, 88%).

Mp: 66–67 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.08 (m, 4 H, H-3, H-4, H-5 and H-6), 5.68 (br t, exch., 1 H, NH), 4.37 (d, *J* = 5 Hz, 2 H, CH_2NH), 2.52 (t, *J* = 7 Hz, 2 H, $CH_2CH_2CH_3$), 1.53 (app. sextet, *J* = 7 Hz, 2 H, CH_2CH_3), 1.14 [s, 9 H, $C(CH_3)_3$], 0.98 (t, *J* =7 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.4 (s, C=O), 141.5 (s, C-1), 136.1 (s, C-2), 130.1 (d, C-3), 129.2 (d, C-6), 128.1 (d, C-4), 126.6 (d, C-5), 41.8 (t, CH_2NH), 39.1 [s, $C(CH_3)_3$], 34.9 (t, $CH_2CH_2CH_3$), 28.0 [q, $C(CH_3)_3$], 24.8 (t, CH_2CH_3), 15.8 (q, CH_3).

EI–MS: *m/z* (%) = 233 (M^+, 9), 204 (M^+ – Et, 5), 190 (M^+ – Pr, 4), 133 (M^+ – Pr – ^{t}Bu, 14), 132 (M^+– Pr – ^{t}BuH, 97), 117 (M^+– NHCO^{t}Bu – CH_4, 100), 105 ($PhCH_2N^+$, 81), 91 ($PhCH_2^+$, 24), 57 (^{t}Bu, 49).

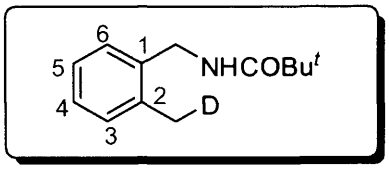
CI–MS: *m/z* (%) = 251 (M + NH_4^+, 45), 334 (MH^+, 100), 206 (18), 132 (M^+– CO^{t}Bu – CH_4, 20), 119 (8), 102 (6).

ES^+–MS: *m/z* (%) = 251 (M + NH_4^+, 7), 234 (MH^+, 42), 133 (17), 114 (18), 106 ($PhCH_2NH^+$, 32), 105 ($PhCH_2N^+$, 100), 104 ($PhCHN^+$, 95).

HRMS: *m/z* calc. for $C_{15}H_{24}NO$ (MH^+), 234.1852; found, 234.1852.

FT–IR: ν_{max} = 3331 (NH), 2963 (CH), 1633 (C=O), 1530 (aromatic C=C), 1363, 1218, 1008 cm^{-1}.

_N_-(2-(Deuteriomethyl)benzyl)pivalamide (106)



Yield: 0.35 g (1.70 mmol, 85%).

Mp: 108–109 °C (Mp of undeuteriated analogue 108–109 °C; **65**, Section 7.5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13–7.09 (m, 4 H, H-3, H-4, H-5 and H-6), 5.70 (br t, exch., 1 H, NH), 4.34 (d, *J* = 5 Hz, 2 H, CH_2NH), 2.21 [(1:1:1) t, *J* = 2 Hz, 2 H, CH_2D], 1.14 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.5 (s, C=O), 136.9 (s, C-1), 136.5 (s, C-2), 131.0 (d, C-3), 128.8 (d, C-6), 128.1 (d, C-4), 126.6 (d, C-5), 42.3 (t, CH_2NH), 39.2 [s, $C(CH_3)_3$], 28.1 [q, $C(CH_3)_3$], 19.1 (seen as three lines, 1:1:1, because of coupling to D, CH_2D).

EI–MS: *m/z* (%) = 207 (M^+ + 1, 4), 206 (M^+, 13), 109 (M^+ – CH_2D, 2), 107 ($PhCH_2NH_2^+$, 20), 106 ($PhCH_2NH^+$, 60), 105 ($PhCH_2N^+$, 37), 92 (10), 78 (12), 57 ($^tBu^+$, 92).

CI–MS: *m/z* (%) = 224 (M + NH_4^+, 12), 208 (MH^+ + 1, 32), 207 (MH^+, 100).

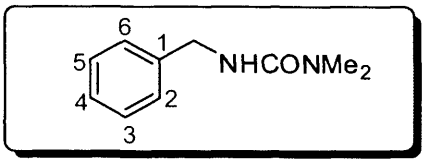
HRMS: *m/z* calc. for $C_{13}H_{19}DNO$ (MH^+), 207.1602; found, 207.1602.

FT–IR: ν_{max} = 3328 (NH), 2924 (CH), 1612 (C=O), 1532 (aromatic C=C), 1238, 1024 cm^{-1}.

7.18 Synthesis of *N'*-benzyl-*N*,*N*-dimethylureas from reactions of benzylamines with triphosgene followed by reactions with dimethylamine

To a cooled (0 °C) stirred solution of triphosgene (4.72 g, 16.0 mmol) in CH_2Cl_2 (60 mL) a solution of the appropriate substituted benzylamine (**67**, 40.0 mmol) and triethylamine (8.88 g, 88.0 mmol) in CH_2Cl_2 (60 mL) was slowly added in a drop-wise manner over 30 min. The reaction mixture was stirred at 0 °C for 2 h, after which a solution of dimethylamine in THF (24.0 mL, 2.0 M, 48.0 mmol) was added. The reaction mixture was stirred at 0 °C for an extra 1 h. The mixture was poured onto H_2O (50 mL) and the organic layer was separated, washed with H_2O (2 x 25 mL), and dried ($MgSO_4$) and the solvent was then removed under reduced pressure. The products were separated by extraction using boiling EtOAc/Et_2O (1:3), from which *N'*-benzyl-*N*,*N*-dimethylureas crystallized nicely as white crystals on cooling. The white solids that were highly insoluble in hot EtOAc/Et_2O were collected by filtration and identified as *N*,*N'*-dibenzylureas **115**. The yields obtained are reported in Table 3.1.

_N'_-Benzyl-_N,N_-dimethylurea (107)



Yield: 5.77 g (32.4 mmol, 81%).

Mp: 76–77 °C (lit.[135] 77 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.15 (m, 5 H, Ph), 4.75 (br, exch., 1 H, NH), 4.33 (d, J = 6 Hz, 2 H, CH_2), 2.83 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8 (s, C=O), 140.2 (s, C-1), 129.0 (d, C-3/C-5), 128.1 (d, C-2/C-6), 127.6 (d, C-4), 45.4 (t, CH_2), 36.7 [q, $N(CH_3)_2$].

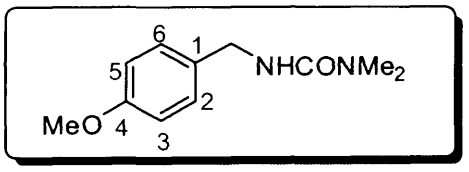
EI–MS: *m/z* (%) = 178 (M^+, 22), 106 ($PhCH_2NH^+$, 21), 91 ($PhCH_2^+$, 78), 77 (Ph^+, 51), 72 (Me_2NCO^+, 75), 65 (31), 56 (19), 51 (26), 44 (Me_2N^+, 93), 42 (CON^+, 100).

CI–MS: *m/z* (%) = 196 ($M + NH_4^+$, 6), 179 (MH^+, 100), 106 ($PhCH_2NH^+$, 8), 46 (29), 44 (18).

HRMS: *m/z* calc. for $C_{10}H_{15}N_2O$ (MH^+), 179.1179; found, 179.1181.

FT–IR: ν_{max} = 3319 (NH), 2924 (CH), 1621 (C=O), 1538 (aromatic C=C), 1343, 1216 cm^{-1}.

_N'_-(4-Methoxybenzyl)-_N,N_-dimethylurea (108)



Yield: 6.82 g (32.8 mmol, 82%).

Mp: 81–82 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.09 (d, J = 8 Hz, 2 H, H-2/H-6), 6.71 (d, J = 8 Hz, 2 H, H-3/H-5), 4.54 (br, exch., 1 H, NH), 4.19 (br, 2 H, CH_2), 3.64 (s, 3 H, OCH_3), 2.76 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2 (s, C=O), 158.7 (s, C-4), 132.2 (s, C-1), 129.5 (d, C-2/C-6), 114.4 (d, C-3/C-5), 55.7 (q, OCH_3), 44.9 (t, CH_2), 36.6 [q, $N(CH_3)_2$].

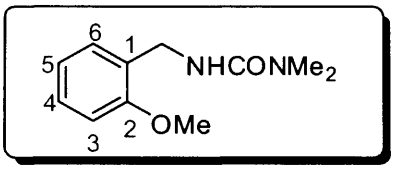
EI–MS: *m/z* (%) = 208 (M^+, 23), 136 ($MeOC_6H_4CH_2NH^+$, 25), 121 ($MeOC_6H_4CH_2^+$, 87), 109 (9), 78 (34), 77 (37), 72 (Me_2NCO^+, 100), 65 (17), 51 (21), 46 (44), 44 (69), 42 (52).

CI–MS: *m/z* (%) = 226 ($M + NH_4^+$, 3), 209 (MH^+, 100), 136 ($MeOC_6H_4CH_2NH^+$, 4), 121 ($MeOC_6H_4CH_2^+$, 5).

HRMS: *m/z* calc. for $C_{11}H_{17}N_2O_2$ (MH^+), 209.1285; found, 209.1283.

FT–IR: ν_{max} = 3318 (NH), 2927 (CH), 1622 (C=O), 1537 (aromatic C=C), 1378, 1351, 1229, 1027 cm^{-1}.

_N'_-(2-Methoxybenzyl)-_N,N_-dimethylurea (111)



Yield: 6.57 g (31.6 mmol, 79%).

Mp: 97–98 °C.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.20 (dt, *J* = 2, 8 Hz, 1 H, H-4), 7.14 (d, *J* = 8 Hz, 1 H, H-6), 6.94 (d, *J* = 8 Hz, 1 H, H-3), 6.90 (t, *J* = 8 Hz, 1 H, H-5), 6.60 (t, *J* = 6 Hz, exch., 1 H, NH), 4.21 (d, *J* = 6 Hz, 2 H, CH_2), 3.80 (s, 3 H, OCH_3), 2.84 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.1 (s, C=O), 157.1 (s, C-2), 129.4 (s, C-1), 128.2 (d, C-6), 127.7 (d, C-4), 120.8 (d, C-5), 111.0 (d, C-3), 56.0 (q, OCH_3), 39.2 (t, CH_2), 36.8 [q, $N(CH_3)_2$].

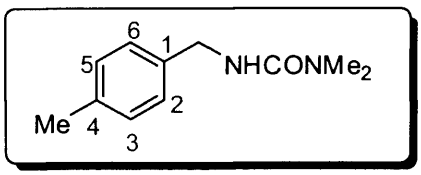
EI–MS: *m/z* (%) = 208 (M^+, 43), 136 ($MeOC_6H_4CH_2NH^+$, 84), 121 ($MeOC_6H_4CH_2^+$, 56), 91 ($PhCH_2^+$, 90), 109 (12), 107 (12), 78 (30), 77 (36), 72 (Me_2NCO^+, 100), 65 (35), 51 (24), 46 (48), 44 (77), 42 (46).

CI–MS: *m/z* (%) = 209 (MH^+, 100), 52 (7).

HRMS: *m/z* calc. for $C_{11}H_{17}N_2O_2$ (MH^+), 209.1285; found, 209.1284.

FT–IR: ν_{max} = 3327 (NH), 2924 (CH), 1622 (C=O), 1534 (aromatic C=C), 1376, 1241, 1228, 10267 cm^{-1}.

_N'_-(4-Methylbenzyl)-_N,N_-dimethylurea (113)



Yield: 6.14 g (32.0 mmol, 80%).

Mp: 94–95 °C (lit.[136] 93 °C).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.14 (d, J = 8 Hz, 2 H, H-3/H-5), 7.09 (d, J = 8 Hz, 2 H, H-2/H-6), 6.82 (t, J = 6 Hz, exch., 1 H, NH), 4.18 (d, J = 6 Hz, 2 H, CH_2), 2.81 [s, 6 H, $N(CH_3)_2$], 2.27 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.1 (s, C=O), 139.1 (s, C-1), 136.1 (s, C-4), 129.4 (d, C-3/C-5), 127.8 (d, C-2/C-6), 44.1 (t, CH_2), 36.8 [q, $N(CH_3)_2$], 21.5 (q, CH_3).

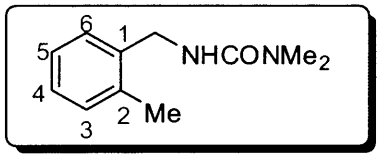
EI–MS: *m/z* (%) = 192 (M^+, 36), 120 ($MeC_6H_4CH_2NH^+$, 38), 105 ($MeC_6H_4CH_2^+$, 68), 91 ($MeC_6H_4^+$, 68), 77 (40), 72 (Me_2NCO^+, 100), 65 (23), 51 (17), 46 (33), 44 (88), 42 (55).

CI–MS: *m/z* (%) = 385 (2 M^+ + 1, 3), 210 (M + NH_4^+, 5), 193 (MH^+, 100).

HRMS: *m/z* calc. for $C_{11}H_{17}N_2O$ (MH^+), 193.1335; found, 193.1338.

FT–IR: ν_{max} = 3318 (NH), 2923 (CH), 1618 (C=O), 1534 (aromatic C=C), 1372, 1227, 1025 cm^{-1}.

N'-(2-Methylbenzyl)-N,N-dimethylurea (114)



Yield: 5.68 g (29.6 mmol, 74%).

Mp: 82–83 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.01 (m, 4 H, Ar), 4.48 (br, exch., 1 H, NH), 4.31 (br, 2 H, CH_2), 2.82 [s, 6 H, $N(CH_3)_2$], 2.26 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.7 (s, C=O), 137.5 (s, C-1), 136.8 (s, C-2), 130.8 (s, C-3), 128.8 (d, C-6), 127.9 (d, C-4), 126.5 (d, C-5), 43.6 (t, CH_2), 36.7 [q, $N(CH_3)_2$], 19.45 (q, CH_3).

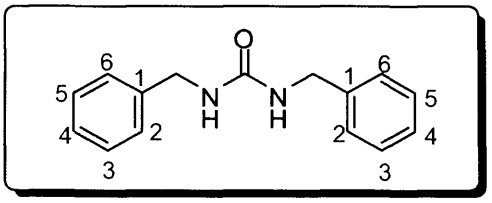
EI–MS: *m/z* (%) = 192 (M^+, 35), 177 (M^+ – Me, 5), 148 (7), 120 ($MeC_6H_4CH_2NH^+$, 49), 105 ($MeC_6H_4CH_2^+$, 88), 104 ($MeC_6H_4CH_2^+$, 94) 91 ($MeC_6H_4^+$, 40), 77 (40), 72 (Me_2NCO^+, 100), 65 (17), 46 (16), 44 (46), 42 (16).

CI–MS: *m/z* (%) = 210 (M + NH_4^+, 4), 193 (MH^+, 100), 122 (14), 120 ($MeC_6H_4CH_2NH^+$, 20), 103 (15), 89 (12), 52 (27), 46 (39), 44 (16).

HRMS: *m/z* calc. for $C_{11}H_{17}N_2O$ (MH^+), 193.1335; found, 193.1335.

FT–IR: ν_{max} = 3317 (NH), 2925 (CH), 1635 (C=O), 1533 (aromatic C=C), 1353, 1231 cm^{-1}.

_N,N'_-Dibenzylurea (115a)



Yield: 0.38 g (1.58 mmol, 4%).

Mp: 175–176 °C (lit.[137] 175–176 °C).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.34–7.23 (m, 10 H, 2 Ph), 6.47 (t, J = 6 Hz, exch., 2 H, 2 NH), 4.25 (d, J = 6 Hz, 4 H, 2 CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.0 (s, C=O), 141.8 (s, C-1), 129.1 (d, C-3/C-5), 127.9 (d, C-2/C-6), 127.4 (d, C-4), 43.9 (t, CH_2).

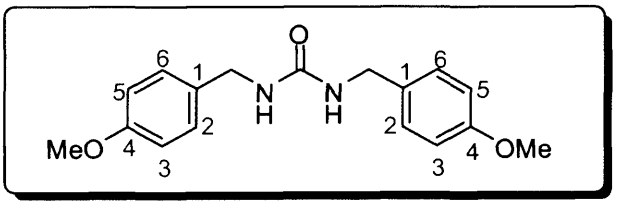
EI–MS: *m/z* (%) = 240 (M^+, 16), 149 (M^+ – $PhCH_2$, 20), 106 ($PhCH_2NH^+$, 53), 91 ($PhCH_2^+$, 100), 77 (Ph^+, 34), 65 (32), 51 (27).

CI–MS: *m/z* (%) = 258 (M + NH_4^+, 2), 241 (MH^+, 36), 108 ($PhCH_2NH_3^+$, 82), 106 ($PhCH_2NH^+$, 100), 78 (13), 52 (47).

HRMS: *m/z* calc. for $C_{15}H_{17}N_2O$ (MH^+), 241.1335; found, 241.1340.

FT–IR: ν_{max} = 3330 (NH), 2922 (CH), 1614 (C=O), 1563 (aromatic C=C), 1514, 1470, 1240 cm^{-1}.

_N,N'_-Bis(4-methoxybenzyl)urea (115b)



Yield: 0.36 g (1.2 mmol, 3%).

Mp: 173-174 °C (lit.[138] 171–173 °C).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.17 (d, J = 8 Hz, 4 H, H-2/H-6), 6.87 (d, J = 8 Hz, 4 H, H-3/H-5), 6.32 (t, J = 6 Hz, exch., 2 H, 2 NH), 4.15 (d, J = 6 Hz, 4 H, 2 CH_2), 3.73 (s, 6 H, 2 OCH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.9 (s, C=O), 158.9 (s, C-4), 133.7 (s, C-1), 129.2 (d, C-2/C-6), 114.5 (d, C-3/C-5), 55.9 (q, OCH_3), 43.3 (t, CH_2).

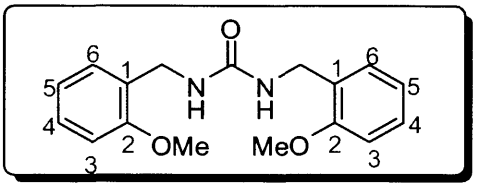
EI–MS: *m/z* (%) = 300 (M^+, 10), 179 (M^+ – $MeOC_6H_4CH_2$, 27), 136 ($MeOC_6H_4CH_2NH^+$, 86), 121 ($MeOC_6H_4CH_2^+$, 100), 109 (26), 91 ($PhCH_2^+$, 18), 77 (42), 65 (17), 51 (14).

CI–MS: *m/z* (%) = 318 ($M + NH_4^+$, 4), 301 (MH^+, 100), 198 (11), 181 (17), 179 (M^+ – $MeOC_6H_4CH_2$, 7), 138 ($MeOC_6H_4CH_2NH_3^+$, 22), 136 ($MeOC_6H_4CH_2NH^+$, 56), 121 ($MeOC_6H_4CH_2^+$, 50), 52 (23).

HRMS: *m/z* calc. for $C_{17}H_{21}N_2O_3$ (MH^+), 301.1547; found, 301.1547.

FT–IR: ν_{max} = 3327 (NH), 2922 (CH), 1624 (C=O), 1562 (aromatic C=C), 1509, 1236, 1029 cm^{-1}.

_N,N'_-Bis(2-methoxybenzyl)urea (115c)



Yield: 0.24 g (0.8 mmol, 2%).

Mp: 202–204 °C.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.22 (t, *J* = 8 Hz, 2 H, H-4), 7.19 (d, *J* = 8 Hz, 2 H, H-6), 6.95 (d, *J* = 8 Hz, 2 H, H-3), 6.89 (t, *J* = 8 Hz, 2 H, H-5), 6.30 (t, *J* = 6 Hz, exch., 2 H, 2 NH), 4.18 (d, *J* = 6 Hz, 4 H, 2 CH_2), 3.78 (s, 6 H, 2 OCH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.4 (s, C=O), 157.1 (s, C-4), 128.6 (s, C-1), 128.3 (d, C-6), 128.1 (d, C-4), 120.4 (d, C-5), 110.7 (d, C-3), 55.6 (q, OCH_3), 38.6 (t, CH_2).

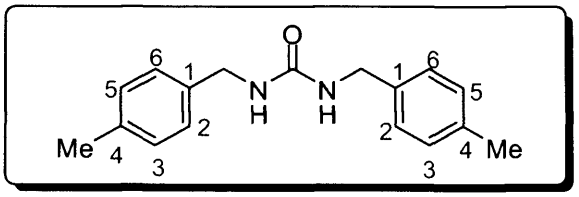
EI–MS: *m/z* (%) = 300 (M^+, 11), 179 (M^+ – $MeOC_6H_4CH_2$, 21), 163 (28), 136 ($MeOC_6H_4CH_2NH^+$, 100), 121 ($MeOC_6H_4CH_2^+$, 52), 104 (20), 91 ($PhCH_2^+$, 76), 77 (32), 65 (31), 51 (17).

CI–MS: *m/z* (%) = 301 (MH^+, 42), 151 (4), 138 ($MeOC_6H_4CH_2NH_3^+$, 41), 136 ($MeOC_6H_4CH_2NH^+$, 23), 122 (36), 121 ($MeOC_6H_4CH_2^+$, 18), 108 ($MeOC_6H_5^+$, 100) 106 (35), 94 (28).

HRMS: *m/z* calc. for $C_{17}H_{21}N_2O_3$ (MH^+), 301.1547; found, 301.1546.

FT–IR: ν_{max} = 3318 (NH), 2922 (CH), 1617 (C=O), 1584 (aromatic C=C), 1464, 1235, 1021 cm^{-1}.

N,N'-Bis(4-methylbenzyl)urea (115d)



Yield: 0.32 g (1.2 mmol, 3%).

Mp: 226–227 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.15–7.01 (m, 8 H, 2 Ar), 6.37 (t, J = 6 Hz, exch., 2 H, 2 NH), 4.18 (d, J = 6 Hz, 4 H, 2 CH_2), 2.28 (s, 6 H, 2 CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.9 (s, C=O), 138.7 (s, C-1), 136.4 (s, C-4), 130.0 (d, C-3/C-5), 127.9 (d, C-2/C-6), 43.6 (t, CH_2), 21.5 (q, CH_3).

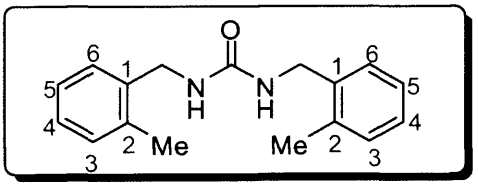
EI–MS: *m/z* (%) = 268 (M^+, 14), 163 ($M^+ - MeC_6H_4CH_2$, 12), 120 ($MeC_6H_4CH_2NH^+$, 63), 105 ($MeC_6H_4CH_2^+$, 100), 91 ($PhCH_2^+$, 61), 77 (52), 65 (22), 51 (13).

CI–MS: *m/z* (%) = 286 ($M + NH_4^+$, 4), 269 (MH^+, 57), 179 (13), 165 (17), 139 (16), 122 ($MeC_6H_4CH_2NH_3^+$, 95), 120 ($MeC_6H_4CH_2NH^+$, 100), 105 ($MeC_6H_4CH_2^+$, 15), 78 (14), 52 (79).

HRMS: *m/z* calc. for $C_{17}H_{21}N_2O$ (MH^+), 269.1648; found, 269.1650.

FT–IR: ν_{max} = 3326 (NH), 2921 (CH), 1611 (C=O), 1558 (aromatic C=C), 1512, 1468, 1237, 1066 cm^{-1}.

N,N'-Bis(2-methylbenzyl)urea (115e)



Yield: 0.43 g (1.6 mmol, 4%).

Mp: 223–225 °C.

^{1}H NMR (MHz, DMSO-d_6): δ = 7.25–7.12 (m, 8 H, 2 Ar), 6.32 (t, J = 6 Hz, exch., 2 H, 2 NH), 4.23 (d, J = 6 Hz, 4 H, 2 CH_2), 2.22 (s, 6 H, 2 CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.8 (s, C=O), 139.3 (s, C-1), 136.2 (s, C-2), 130.7 (d, C-3), 128.1 (d, C-6), 127.5 (d, C-4), 126.6 (d, C-5), 42.0 (t, CH_2), 19.4 (q, CH_3).

EI–MS: *m/z* (%) = 268 (M^+, 26), 163 ($M^+ - MeC_6H_4CH_2$, 33), 120 ($MeC_6H_4CH_2NH^+$, 77), 105 ($MeC_6H_4CH_2^+$, 100), 91 ($PhCH_2^+$, 78), 77 (84), 65 (38), 51 (14).

CI–MS: *m/z* (%) = 286 ($M + NH_4^+$, 7), 269 (MH^+, 100), 182 (12), 179 (33), 165 (21), 122 ($MeC_6H_4CH_2NH_3^+$, 47), 120 ($MeC_6H_4CH_2NH^+$, 43), 52 (53).

HRMS: *m/z* calc. for $C_{17}H_{21}N_2O$ (MH^+), 269.1648; found, 269.1647.

FT–IR: ν_{max} = 3316 (NH), 2933 (CH), 1635 (C=O), 1531 (aromatic C=C), 1462, 1227, 1020 cm^{-1}.

7.19 Synthesis of *N'*-benzyl-*N,N*-dimethylureas from reactions of substituted benzylamines with dimethylcarbamoyl chloride

A stirred mixture of **67** (40.0 mmol), dimethylcarbamoyl chloride (4.83 g, 45 mmol) and triethylamine (5.05 g, 55.0 mmol) in CH_2Cl_2 (60 mL) was heated under reflux for 1 h. The mixture was poured onto H_2O (50 mL) and the organic layer was separated, washed with H_2O (2 x 25 mL), and dried ($MgSO_4$) and the solvent was then removed under reduced pressure. The solid obtained was purified by crystallization from EtOAc/Et_2O (1/3) to give pure *N'*-(substituted benzyl)-*N,N*-dimethylureas as white crystalline solids. The yields obtained are reported in Table 3.2. The products were found to be consistent in all respects with the ones produced using triphosgene method (Sections 7.18). See Section 7.18 for spectral data.

7.20 Synthesis of *N'*-(2-substituted benzyl)-*N,N*-dimethylureas 114 and 118-131 *via* directed lithiation of *N'*-benzyl-*N,N*-dimethylureas 107, 108 and 113

A solution of *t*-BuLi in heptane (2.6 mL, 1.7 M, 4.4 mmol) was added to a cold (-78 °C), stirred solution of the appropriate *N'*-benzyl-*N,N*-dimethylurea (**107**, **108** or **113**; 2.0 mmol) in anhydrous THF (20 mL) under N_2. Formation of the monolithium reagent **116** was observed as a yellow solution and the dilithium reagent **117** was observed as a brownish solution. The mixture was stirred at –78 °C for 4 h, to ensure the complete formation of the dilithium reagent **117**, after which an electrophile (2.2 mmol), in anhydrous THF (8 mL) if solid, otherwise neat, was added. The mixture was stirred for 2 h at –78 °C then the cooling bath was removed and the mixture allowed to warm to room temperature. It was then diluted with Et_2O (10 mL) and quenched with aq. sat. 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 residue obtained was purified by column chromatography (silica gel; Et_2O–hexane, 1:3) to give the corresponding *N'*-(2-substituted benzyl)-*N,N*-dimethylureas **114** and **118-131**. The yields obtained are recorded in Table 3.3.

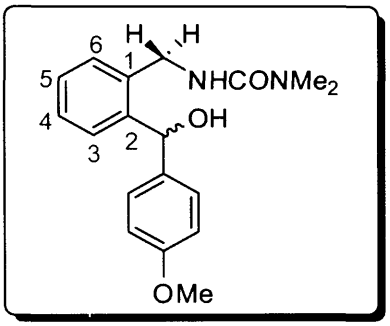
N'-(2-Methylbenzyl)-N,N-dimethylurea (114)

Yield: 0.31 g (1.61 mmol, 80%).

Mp: 82–83 °C.

Compound **114** was found to be identical in all respects with the one produced either from reaction of 2-methylbenzylamine (**67e**) with triphosgene followed by reaction with dimethylamine (Section 7.18) or with dimethylcarbamoyl chloride in the presence of triethylamine as a base (Section 7.19). See Section 7.18 for spectral data.

N'-(2-(Hydroxy-(4-methoxyphenyl)methyl)benzyl)-N,N-dimethylurea (118)



Yield: 0.54 g (1.72 mmol, 86%).

Mp: 185–186 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.44 (app. dt, J = 2, 8 Hz, 1 H, H-4), 7.27-7.21 (m, 5 H, H-3, H-5, H-6 and H-2/H-6 of 4-methoxyphenyl), 6.87 (d, J = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 6.66 (t, J = 6 Hz, exch., 1 H, NH), 5.92 (d, J = 4 Hz, 1 H, CH), 5.80 (d, J = 4 Hz, exch., 1 H, OH), 4.30 (dd, J = 6, 16 Hz, 1 H, 1 H of CH_2), 4.09 (dd, J = 6, 16 Hz, 1 H, 1 H of CH_2), 3.73 (s, 3 H, OCH_3), 2.79 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.0 (s, C=O), 158.9 (s, C-4 of 4-methoxyphenyl), 143.3 (s, C-1), 138.3 (s, C-2), 137.4 (s, C-1 of 4-methoxyphenyl), 129.0 (d, C-2/C-6 of 4-methoxyphenyl), 128.1 (d, C-3), 127.4 (d, C-6), 127.3 (d, C-4), 127.1 (d, C-5) 114.2 (d, C-3/C-5 of 4-methoxyphenyl), 71.2 (d, CH), 55.9 (q, OCH_3), 44.4 (t, CH_2), 36.7 [q, $N(CH_3)_2$].

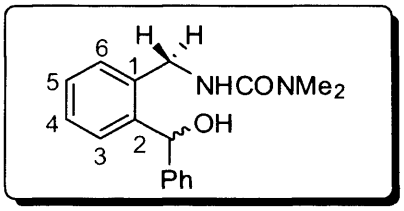
ES$^+$–MS: *m/z* (%) = 337 ($M + Na^+$, 62), 315 (MH^+, 7), 297 ($MH^+ - H_2O$, 58), 209 ($M^+ - H_2O$ – $NHCONMe_2$, 100), 89 (84), 72 (78).

HRMS: *m/z* calc. for $C_{18}H_{23}N_2O_3$ (MH^+), 315.1703; found, 315.1700.

FT–IR: ν_{max} = 3331 (NH and OH), 2924 (CH), 1616 (C=O), 1563 (aromatic C=C), 1510, 1238, 1023 cm^{-1}.

Anal. calc. for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.55; H, 7.14; N, 8.84%.

_N'_-(2-(Hydroxyphenylmethyl)benzyl)-_N,N_-dimethylurea (119)



Yield: 0.47 g (1.65 mmol, 82%).

Mp: 138–140 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37-7.23 (m, 9 H, ArH), 6.05 (d, *J* = 4 Hz, 1 H, CH), 5.00 (t, *J* = 6 Hz, exch., 1 H, NH), 4.71 (d, *J* = 4 Hz, exch., 1 H, OH), 4.38 (dd, *J* = 6, 14 Hz, 1 H, 1 H of CH_2), 4.27 (dd, *J* = 6, 14 Hz, 1 H, 1 H of CH_2), 2.71 [s, 6 H, $N(CH_3)_2$].

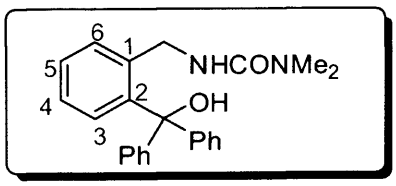
^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.7 (s, C=O), 144.1 (s, C-1 of Ph), 142.2 (s, C-1), 137.8 (s, C-2), 130.6 (d, C-3), 128.9 (d, C-6), 128.7 (d, C-3/C-5 of Ph), 128.4 (d, C-4), 128.0 (d, C-5), 127.6 (d, C-4 of Ph), 127.1 (d, C-2/C-6 of Ph), 73.8 (d, CH), 42.6 (t, CH_2), 36.4 [q, $N(CH_3)_2$].

ES^+–MS: *m/z* (%) = 285 (MH^+, 44), 268 (MH^+ – OH, 18), 267 (MH^+ – H_2O, 100), 179 (4), 60 (8).

HRMS: *m/z* calc. for $C_{17}H_{21}N_2O_2$ (MH^+), 285.1598; found, 285.1600.

FT–IR: ν_{max} = 3289 (NH and OH), 2925 (CH), 1645 (C=O), 1545 (aromatic C=C), 1352, 1231, 1019 cm^{-1}.

_N'_-(2-(Hydroxydiphenylmethyl)benzyl)-_N,N_-dimethylurea (120)



Yield: 0.61 g (1.69 mmol, 84%).

Mp: 235–236 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.43-7.23 (m, 13 H, 2 Ph, H-4, H-6 and OH), 7.04 (dt, J = 2, 8 Hz, 1 H, H-5), 6.80 (t, J = 6 Hz, exch., 1 H, NH), 6.49 (dd, J = 2, 8 Hz, 1 H, H-3), 3.86 (d, J = 6 Hz, 2 H, CH_2), 2.76 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.3 (s, C=O), 149.0 (s, C-1 of 2 Ph), 145.3 (s, C-1), 141.2 (s, C-2), 130.5 (d, C-3), 129.5 (d, C-6), 128.9 (d, C-3/C-5 of 2 Ph), 128.6 (d, C-5), 128.4 (d, C-2/C-6 of 2 Ph), 127.4 (d, C-4 of 2 Ph), 126.3 (d, C-4), 82.0 (s, C-OH), 43.0 (t, CH_2), 36.7 [q, $N(CH_3)_2$].

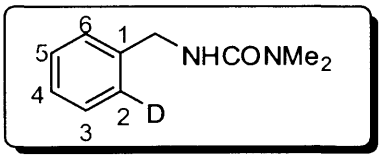
ES^+–MS: *m/z* (%) = 383 ($M + Na^+$, 48), 343 ($MH^+ - H_2O$, 27), 255 (100), 89 (84).

ES^-–MS: *m/z* (%) = 360 (M^-, 5), 359 ($M^- - 1$, 41), 177 [$M^- - Ph_2C(OH)$, 100], 132 (20), 104 (40).

HRMS: *m/z* calc. for $C_{23}H_{24}N_2O_2Na$ ($M + Na^+$), 383.1730; found, 383.1731.

FT–IR: ν_{max} = 3329 (NH and OH), 2928 (CH), 1621 (C=O), 1530 (aromatic C=C), 1264, 1029 cm^{-1}.

_N'_-(2-Deuteriobenzyl)-_N,N_-dimethylurea (121)



Yield: 0.32 g (1.79 mmol, 89%).

Mp: 76–77 °C (Mp of undeuteriated analogue lit.[135] 77 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.24 (m, 4 H, H-3, H-4, H-5 and H-6), 4.84 (br, exch., 1 H, NH), 4.41 (br, 2 H, CH_2), 2.91 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8 (s, C=O), 140.2 (s, C-1), 128.9 (d, C-3), 128.8 (seen as three lines, 1:1:1, because of coupling to D, C-2), 128.1 (d, C-5), 127.8 (d, C-6), 127.6 (d, C-4), 45.4 (t, CH_2), 36.6 [q, $N(CH_3)_2$].

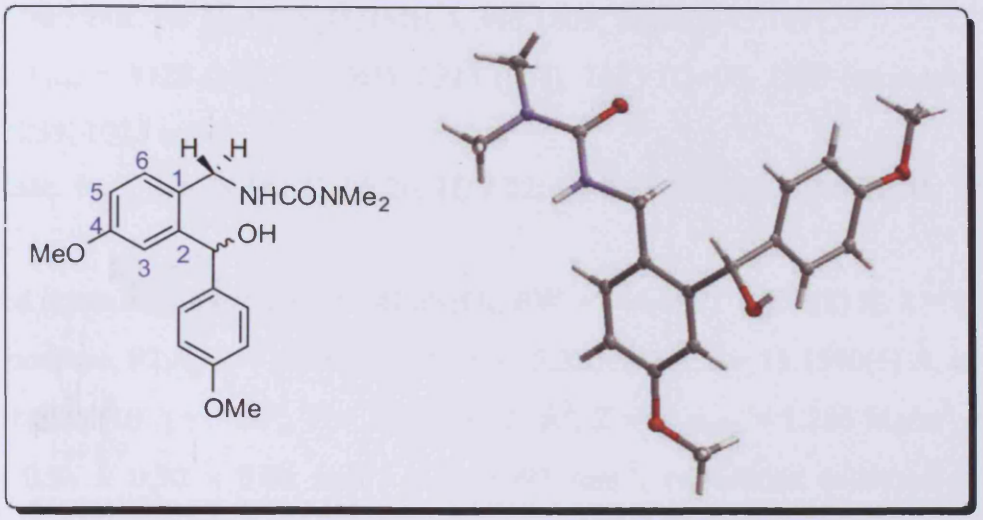
EI–MS: *m/z* (%) = 179 (M^+, 25), 106 (36), 92 ($C_6H_4O^+$, 48), 91 ($C_6H_3O^+$, 57), 77 (41), 72 (92), 44 (100).

CI–MS: *m/z* (%) = 197 ($M + NH_4^+$, 23), 180 (MH^+, 100), 179 (M^+, 88), 106 ($PhCH_2NH^+$, 25), 52 (30), 46 (31).

HRMS: *m/z* calc. for $C_{10}H_{14}DN_2O$ (MH^+), 180.1242; found, 180.1243.

FT–IR: ν_{max} = 3320 (NH), 2925 (CH), 1622 (C=O), 1533 (aromatic C=C), 1512, 1375, 1232, 1035 cm^{-1}.

N'-(2-(Hydroxy-(4-methoxyphenyl)methyl)-4-methoxybenzyl)-N,N-dimethylurea (122)



Yield: 0.59 g (1.71 mmol; 85%).

Mp: 137–138 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.21 (d, J = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 7.14 (d, J = 8 Hz, 1 H, H-6), 7.03 (d, J = 2 Hz, 1 H, H-3), 6.86 (d, J = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 6.78 (dd, J = 2, 8 Hz, 1 H, H-5), 6.53 (app. t, J = 6 Hz, exch., 1 H, NH), 5.88 (d, J = 5 Hz, 1 H, CH), 5.81 (d, J = 5 Hz, exch., 1 H, OH), 4.21 (dd, J = 6, 14 Hz, 1 H, 1 H of CH_2), 3.96 (dd, J = 6, 14 Hz, 1 H, 1 H of CH_2), 3.73 (s, 6 H, 2 OCH_3), 2.77 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.0 (s, C=O), 158.9 (s, C-4), 158.8 (s, C-4 of 4-methoxyphenyl), 144.8 (s, C-2), 137.3 (s, C-1 of 4-methoxyphenyl), 130.3 (s, C-1), 129.9 (d, C-6), 129.0 (d, C-2/C-6 of 4-methoxyphenyl), 114.2 (d, C-3/C-5 of 4-methoxyphenyl), 113.2 (d, C-3), 112.4 (d, C-5), 71.2 (d, CH), 55.9 (q, OCH_3), 55.8 (q, OCH_3), 41.2 (t, CH_2), 36.7 [q, $N(CH_3)_2$].

EI–MS: m/z (%) = 344 (M^+, 7), 326 ($M^+ - H_2O$, 11), 282 ($M^+ - H_2O - NMe_2$, 21), 254 ($M^+ - H_2O - CONMe_2$, 66), 243 (96), 239 (75), 225 (92), 210 (12), 195 (13), 181 (10), 165 (20), 152 (31), 135 (100), 121 (82), 102 (80), 89 (78).

CI–MS: m/z (%) = 345 (MH^+, 1), 343 ($M^+ - 1$, 6), 327 ($MH^+ - H_2O$, 51), 260 (8), 246 (11), 209 (22), 154 (31), 137 (22), 121 (25), 106 (65), 103 (98), 91 (51), 89 (100), 74 (24), 63 (87).

ES^+–MS: m/z (%) = 367 ($M + Na^+$, 71), 345 (MH^+, 6), 327 ($MH^+ - H_2O$, 66), 239 (100), 89 (22), 72 (27).

ES$^-$–MS: *m/z* (%) = 344 (M^-, 15), 343 (M^- – 1, 70), 298 (31), 207 [M^- – $MeOC_6H_4CH(OH)$, 100], 190 (12), 162 (15), 120 (20).

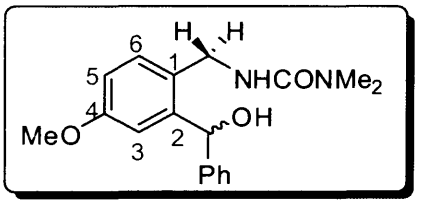
HRMS: *m/z* calc. for $C_{19}H_{25}N_2O_4$ (MH^+), 345.1809; found, 345.1811.

FT–IR: ν_{max} = 3328 (NH and OH), 2923 (CH), 1633 (C=O), 1563 (aromatic C=C), 1511, 1239, 1023 cm^{-1}.

Anal. calc. for $C_{19}H_{24}N_2O_4$: C, 66.26; H, 7.02; N, 8.13. Found: C, 66.23; H, 7.04; N, 8.05%.

Selected crystallographic data: $C_{19}H_{24}N_2O_4$, FW = 344.40, T = 150(2) K, λ = 0.71073 Å, Monoclinic, $P2_1/c$, a = 10.9920(4) Å, b = 15.3230(5) Å, c = 11.1540(5) Å, α = 90°, β = 108.7900(10)°, γ = 90°, V = 1778.55(12) $Å^3$, Z = 4, $\rho_{calc.}$ = 1.286 Mg/m^3, crystal size = 0.38 × 0.30 × 0.06 mm^3, m = 0.091 mm^{-1}, reflections collected = 7298, independent reflections = 4046, R_{int} = 0.0483, parameters = 231, final R_1 = 0.0599, wR_2 = 0.1267 for I>2σ(I) and R_1 = 0.1008, wR_2 = 0. 0.1444 for all data. Full crystallographic data for this compound have been deposited with the CCDC, reference number 736581, and can be obtained free of charge *via* http://www.ccdc.ac.uk/data_request/cif.

_N'_-(2-(Hydroxyphenylmethyl)-4-methoxybenzyl)-_N,N_-dimethylurea (123)



Yield: 0.56 g (1.78 mmol, 89%).

Colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.12 (m, 6 H, Ph and H-6), 6.81 (d, *J* = 2 Hz, 1 H, H-3), 6.66 (dd, *J* = 2, 8 Hz, 1 H, H-5), 5.89 (d, *J* = 4 Hz, 1 H, CH), 4.80 (app. t, *J* = 6 Hz, exch., 1 H, NH), 4.68 (d, *J* = 4 Hz, exch., 1 H, OH), 4.21 (dd, *J* = 6, 14 Hz, 1 H, 1 H of CH_2), 4.08 (dd, *J* = 6, 14 Hz, 1 H, 1 H of CH_2), 3.64 (s, 3 H, OCH_3), 2.58 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3 (s, C=O), 158.7 (s, C-4), 144.0 (s, C-1 of Ph), 143.8 (s, C-2), 132.1 (d, C-6), 129.8 (s, C-1), 128.7 (d, C-3/C-5 of Ph), 127.6 (d, C-4 of Ph), 127.2 (d, C-2/C-6 of Ph), 114.6 (d, C-5), 113.3 (d, C-3), 73.7 (d, CH), 55.6 (q, OCH_3), 42.1 (t, CH_2), 36.4 [q, $N(CH_3)_2$].

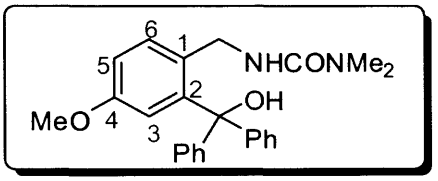
EI–MS: *m/z* (%) = 314 (M^+, 5), 297 ($MH^+ - H_2O$, 12), 252 ($M^+ - H_2O - NMe_2$, 11), 225 (71), 224 ($M^+ - H_2O - CONMe_2$, 82), 208 [MH^+ – PhCH(OH), 100], 180 (22), 165 (36), 148 (24), 121 (40), 102 (77), 89 (67), 77 (Ph^+, 85), 72 (Me_2NCO^+, 92), 44 (70).

CI–MS: *m/z* (%) = 315 (MH^+, 13), 299 (100), 297 ($MH^+ - H_2O$, 82), 241 (23), 226 (31).

HRMS: *m/z* calc. for $C_{18}H_{23}N_2O_3$ (MH^+), 315.3869; found, 315.3866.

FT–IR: ν_{max} = 3321 (NH and OH), 2836 (CH), 1627 (C=O), 1525 (aromatic C=C), 1494, 1229, 1033 cm^{-1}.

_N'_-(2-(Hydroxydiphenylmethyl)-4-methoxybenzyl)-_N,N_-dimethylurea (124)



Yield: 0.66 g (1.69 mmol, 84%).

Mp: 223–224 °C.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.48 (s, exch., 1 H, OH), 7.36–7.18 (m, 11 H, H-6 and 2 Ph), 6.78 (dd, *J* = 2, 8 Hz, 1 H, H-5), 6.64 (t, *J* = 6 Hz, exch., 1 H, NH), 6.01 (d, *J* = 3 Hz, 1 H, H-3), 3.75 (d, *J* = 6 Hz, 2 H, CH_2), 3.54 (s, 3 H, OCH_3), 2.76 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.3 (s, C=O), 157.6 (s, C-4), 148.9 (s, C-1 of 2 Ph), 146.9 (s, C-2), 132.8 (s, C-1), 132.4 (d, C-6), 128.3 (d, C-3/C-5 of 2 Ph), 128.1 (d, C-2/C-6 of 2 Ph), 127.2 (d, C-4 of 2 Ph), 116.8 (d, C-3), 112.3 (d, C-5), 81.8 (s, C-OH), 55.4 (q, OCH_3), 42.5 (t, CH_2), 36.6 [q, $N(CH_3)_2$].

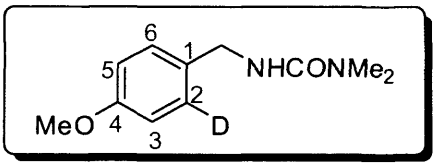
ES^+–MS: *m/z* (%) = 413 ($M + Na^+$, 12), 391 (MH^+, 8), 372 ($M^+ - H_2O$, 100), 285 (22), 209 (10), 101 (11), 89 (12).

ES^-–MS: *m/z* (%) = 390 (M^-, 14), 389 ($M^- - 1$, 61), 157 (13), 115 (15), 101 (13), 62 (100).

HRMS: *m/z* calc. for $C_{24}H_{26}N_2O_3Na$ ($M + Na^+$), 413.1836; found, 413.1837.

FT–IR: ν_{max} = 3322 (NH and OH), 2964 (CH), 1622 (C=O), 1531 (aromatic C=C), 1446, 1243, 1025 cm^{-1}.

N'-(2-Deuterio-4-methoxybenzyl)-N,N-dimethylurea (125)



Yield: 0.36 g (1.72 mmol, 86%).

Mp: 81–82 °C (Mp of undeuteriated analogue 81-82 °C; **108**, Section 7.18).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18 (d, *J* = 8 Hz, 1 H, H-6), 6.80–6.77 (m, 2 H, H-3 and H-5), 4.30 (br t, exch., 1 H, NH), 4.28 (d, *J* = 6 Hz, 2 H, CH_2), 3.72 (s, 3 H, OCH_3), 2.83 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3 (s, C=O), 158.7 (s, C-4), 132.0 (s, C-1), 29.5 (d, C-6), 129.2 (seen as three lines, 1:1:1, because of coupling to D, C-2), 114.4 (d, C-3), 114.3 (d, C-5), 55.7 (q, OCH_3), 44.9 (t, CH_2), 36.7 [s, $N(CH_3)_2$].

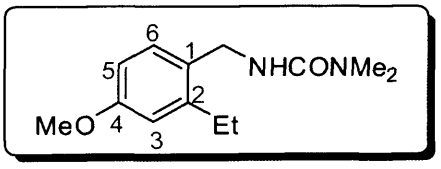
EI–MS: *m/z* (%) = 209 (M^+, 23), 163 (M^+ – OMe – Me, 6), 137 (M^+ – $CONMe_2$, 32), 122 (M^+ – $NHCONMe_2$, 100), 110 (9), 92 (12), 72 (Me_2NCO^+, 96), 52 (28), 44 (100).

CI-MS: *m/z* (%) = 227 (M + NH_4^+, 6), 210 (MH^+, 100), 122 (M^+ – $NHCONMe_2$, 2), 52 (6).

HRMS: *m/z* calc. for $C_{11}H_{16}DN_2O_2$ (MH^+), 210.1347; found, 210.1349.

FT–IR: ν_{max} = 3317 (NH), 2926 (CH), 1618 (C=O), 1532 (aromatic C=C), 1495, 1377, 1226, 1031 cm^{-1}.

N'-(2-Ethyl-4-methoxybenzyl)-N,N-dimethylurea (126)



Yield: 0.42 g (1.78 mmol, 89%).

Mp: 90–91 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 8 Hz, 1 H, H-6), 6.78 (d, *J* = 2 Hz, 1 H, H-3), 6.73 (dd, *J* = 2, 8 Hz, 1 H, H-5), 4.38 (br, 3 H, CH_2N and NH), 3.81 (s, 3 H, OCH_3), 2.91 [s, 6 H, $N(CH_3)_2$], 2.68 (q, *J* = 7 Hz, 2 H, CH_2CH_3), 1.24 (t, *J* = 7 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.6 (s, C=O), 158.6 (s, C-4), 144.7 (s, C-2), 130.9 (d, C-6), 129.0 (s, C-1), 115.0 (d, C-3), 111.3 (d, C-5), 55.6 (q, OCH_3), 42.7 (t, NCH_2), 36.6 [q, $N(CH_3)_2$], 26.0 (t, CH_2CH_3), 15.8 (q, CH_2CH_3).

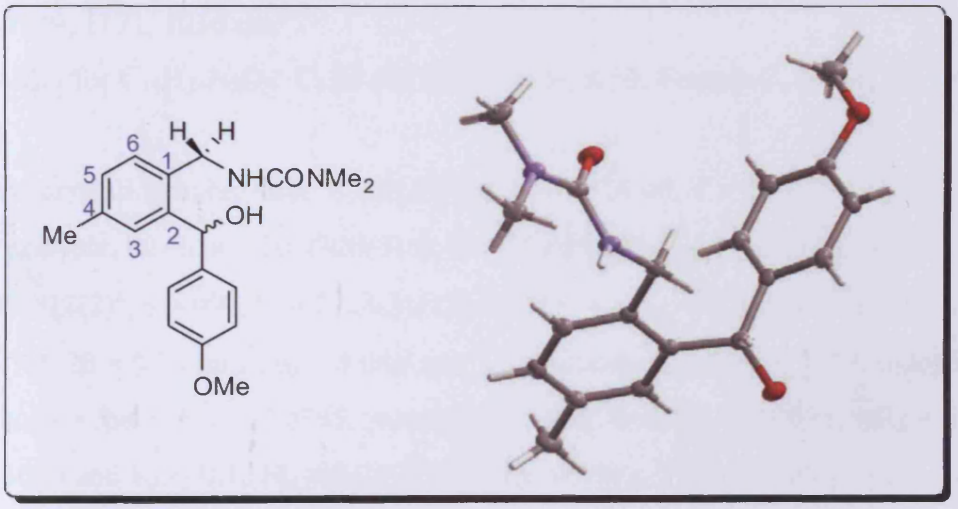
EI–MS: *m/z* (%) = 236 (M^+, 6), 164 (M^+ – $CONMe_2$, 8), 162 (10), 149 (M^+ – $HNCONMe_2$, 32), 148 (M^+ – $H_2NCONMe_2$, 21), 134 (12), 117 (21), 101 (16), 90 (30), 72 (Me_2NCO^+, 74), 44 (18).

CI–MS: *m/z* (%) = 237 (MH^+, 66), 179 (8), 149 (M^+ – $HNCONMe_2$, 21), 89 (51), 46 (100), 44 (10).

HRMS: *m/z* calc. for $C_{13}H_{21}N_2O_2$ (MH^+), 237.1598; found, 237.1599.

FT–IR: ν_{max} = 3320 (NH), 2932 (CH), 1627 (C=O), 1533 (aromatic C=C), 1502, 1371, 1240, 1193, 1029 cm^{-1}.

_N'_-(2-(Hydroxy-(4-methoxyphenyl)methyl)-4-methylbenzyl)-_N,N_-dimethylurea (127)



Yield: 0.50 g (1.52 mmol, 76%).

Mp: 174–175 °C.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.26 (s, 1 H, H-3), 7.21 (d, *J* = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 7.11 (d, *J* = 8 Hz, 1 H, H-6), 7.01 (d, *J* = 8 Hz, 1 H, H-5), 6.86 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 6.58 (t, *J* = 6 Hz, exch., 1 H, NH), 5.89 (d, *J* = 5 Hz, 1 H, CH), 5.78 (d, *J* = 5 Hz, exch., 1 H, OH), 4.25 (dd, *J* = 6, 16 Hz, 1 H, 1 H of CH_2), 4.03 (dd, *J* = 6, 16 Hz, 1 H, 1 H of CH_2), 3.72 (s, 3 H, OCH_3), 2.78 [s, 6 H, $N(CH_3)_2$], 2.58 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.0 (s, C=O), 158.9 (s, C-4 of 4-methoxyphenyl), 143.2 (s, C-2), 137.5 (s, C-1), 136.0 (s, C-4), 135.3 (s, C-1 of 4-methoxyphenyl), 128.9 (d, C-2/C-6 of 4-methoxyphenyl), 128.5 (d, C-3), 128.0 (d, C-6), 127.8 (d, C-5) 114.2 (d, C-3/C-5 of 4-methoxyphenyl), 71.2 (d, CH), 55.9 (q, OCH_3), 41.4 (t, CH_2), 36.7 [q, $N(CH_3)_2$], 21.8 (q, CH_3).

EI–MS: *m/z* (%) = 328 (M^+, 1), 310 ($M^+ - H_2O$, 14), 266 ($M^+ - H_2O - NMe_2$, 57), 239 ($M^+ - H_2O - CONMe_2$, 49), 227 (47), 209 ($M^+ - H_2O - CH_2NHCONMe_2$, 79), 178 (22), 165 (58), 152 (35), 130 (28), 109 (48), 92 ($CH_3C_6H_5^+$, 100), 90 (85).

CI–MS: *m/z* (%) = 329 (MH^+, 3), 328 (M^+, 6), 327 ($M^+ - 1$, 16), 311 ($MH^+ - H_2O$, 100), 240 ($MH^+ - H_2O - CONMe_2$, 22), 203 (14), 193 ($MH^+ - MeOC_6H_4CO$, 47), 154 (18), 137 (10), 118 (11), 106 (30), 89 (33), 72 (5), 63 (22).

ES^+–MS: *m/z* (%) = 351 ($M + Na^+$, 30), 329 (MH^+, 12), 312 ($MH^+ - OH$, 17), 311 ($MH^+ - H_2O$, 100).

ES^-–MS: *m/z* (%) = 328 (M^-, 19), 327 ($M^- - 1$, 100).

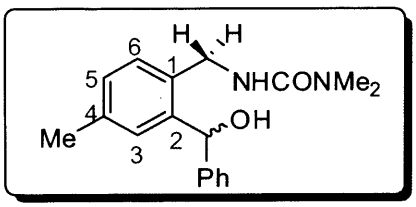
HRMS: *m/z* calc. for $C_{19}H_{25}N_2O_3$ (MH^+), 329.1860; found, 329.1852.

FT–IR: ν_{max} = 3318 (NH and OH), 2962 (CH), 1627 (C=O), 1606 (aromatic C=C), 1533, 1239, 1171, 1010 cm^{-1}.

Anal. calc. for $C_{19}H_{24}N_2O_3$: C, 69.49; H, 7.37; N, 8.53. Found: C, 69.44; H, 7.40; N, 8.58%.

Selected crystallographic data: $C_{19}H_{24}N_2O_3$, FW = 328.40, T = 150(2) K, λ = 0.71073 Å, Monoclinic, $P2_1/n$, a = 10.3320(5) Å, b = 14.8650(7) Å, c = 12.1720(7) Å, α = 90°, β = 112.812(2)°, γ = 90°, V = 1723.21(15) $Å^3$, Z = 4, $\rho_{calc.}$ = 1.266 Mg/m^3, crystal size = 0.22 × 0.20 × 0.08 mm^3, m = 0.086 mm^{-1}, reflections collected = 7279, independent reflections = 3943, R_{int} = 0.0795, parameters = 222, final R_1 = 0.0698, wR_2 = 0.1335 for $I>2\sigma(I)$ and R_1 = 0.1574, wR_2 = 0.1653 for all data. Full crystallographic data for this compound have been deposited with the CCDC, reference number 736583, and can be obtained free of charge *via* http://www.ccdc.ac.uk/data_request/cif.

_N'_-(2-(Hydroxyphenylmethyl)-4-methylbenzyl)-_N,N_-dimethylurea (128)



Yield: 0.41 g (1.39 mmol, 70%).

Mp: 135–136 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.13 (m, 10 H, ArH, NH and OH), 5.97 (br s, 1 H, CH), 4.27 (d, *J* = 14 Hz, 1 H, 1 H of CH_2), 4.17 (d, *J* = 14 Hz, 1 H, 1 H of CH_2), 2.64 [s, 6 H, $N(CH_3)_2$], 2.21 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.7 (s, C=O), 144.2 (s, C-1 of Ph), 142.2 (s, C-2), 138.5 (s, C-1), 134.7 (s, C-4), 130.8 (d, C-3), 129.6 (d, C-6), 129.1(d, C-5), 128.9 (d, C-3/C-5 of Ph), 127.7 (d, C-4 of Ph), 127.1 (d, C-2/C-6 of Ph), 73.9 (d, CH), 42.4 (t, CH_2), 36.5 [q, $N(CH_3)_2$], 21.6 (q, CH_3).

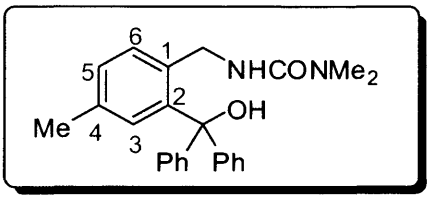
EI–MS: *m/z* (%) = 298 (M^+, 11), 281 (M^+ – OH or MH^+ – H_2O, 42), 280 (M^+ – H_2O, 32), 236 (M^+ – H_2O – NMe_2, 100), 235 (M^+ – OH – NMe_2, 83), 220 (48).

CI–MS: *m/z* (%) = 299 (MH^+, 24), 282 (MH^+ – OH, 43), 281 (MH^+ – H_2O, 100), 221 (M^+ – Ph, 7), 210 (10), 193 (14), 106 (11), 89 (27), 52 (75), 46 (40).

HRMS: *m/z* calc. for $C_{18}H_{23}N_2O_2$ (MH^+), 299.1754; found, 299.1753.

FT–IR: ν_{max} = 3218 (NH and OH), 2934 (CH), 1630 (C=O), 1606 (aromatic C=C), 1533, 1234, 1171, 1010 cm^{-1}.

_N'_-(2-(Hydroxydiphenylmethyl)-4-methylbenzyl)-_N,N_-dimethylurea (129)



Yield: 0.54 g (1.44 mmol, 72%).

Mp: 225–227 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.40 (s, exch., 1 H, OH), 7.34–7.22 (m, 11 H, 2 Ph and H-6), 7.09 (dd, *J* = 1, 8 Hz, 1 H, H-5), 6.76 (t, *J* = 6 Hz, exch., 1 H, NH), 6.31 (d, *J* = 1 Hz, 1 H, H-3), 3.79 (d, *J* = 6 Hz, 2 H, CH_2), 2.75 [s, 6 H, $N(CH_3)_2$], 2.08 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.3 (s, C=O), 149.1 (s, C-1 of 2 Ph), 145.3 (s, C-2), 138.2 (s, C-1), 135.1 (s, C-4), 130.7 (d, C-3), 130.2 (d, C-6), 129.4 (d, C-5), 128.9 (d, C-3/C-5 of 2 Ph), 128.5 (d, C-2/C-6 of 2 Ph), 127.4 (d, C-4 of 2 Ph), 81.9 (s, C-OH), 42.8 (t, CH_2), 36.7 [q, $N(CH_3)_2$], 21.8 (q, CH_3).

EI–MS: *m/z* (%) = 374 (M^+, 6), 357 (M^+ – OH, 12), 356 (M^+ – H_2O, 46), 312 (M^+ – H_2O – NMe_2, 13), 311 (M^+ – H_2O –$NHMe_2$, 22), 297 (33), 285 (MH^+ – H_2O – $CONMe_2$, 73), 284 (M^+ – H_2O – $CONMe_2$, 100).

CI–MS: *m/z* (%) = 374 (M^+, 1), 373 (M^+ – 1, 6), 359 (24), 357 (MH^+ – H_2O, 100), 286 (MH^+ – OH – $CONMe_2$, 46), 284 (M^+ – H_2O – $CONMe_2$, 22), 257 (MH^+ – H_2O – $CHNHCONMe_2$, 20).

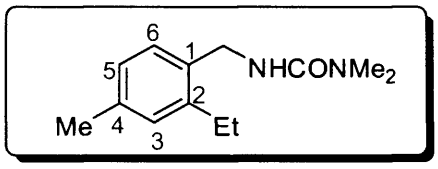
ES^+–MS: *m/z* (%) = 397 ($M + Na^+$, 12), 375 (MH^+, 8), 358 ($MH^+ - OH$, 32), 357 ($MH^+ - H_2O$, 100), 169 (20), 193 (12), 89 (23).

ES^-–MS: *m/z* (%) = 374 (M^-, 27), 373 ($M^- - 1$, 100).

HRMS: *m/z* calc. for $C_{24}H_{27}N_2O_2$ (MH^+), 375.2067; found, 375.2072.

FT–IR: ν_{max} = 3323 (NH and OH), 2959 (CH), 1636 (C=O), 1530 (aromatic C=C), 1243, 1024 cm^{-1}.

_N'_-(2-Ethyl-4-methylbenzyl)-_N,N_-dimethylurea (130)



Yield: 0.35 g (1.59 mmol, 80%).

Mp: 60–62 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.08 (d, *J* = 8 Hz, 1 H, H-6), 6.95 (s, 1 H, H-3), 6.91 (d, *J* = 8 Hz, 1 H, H-5), 4.38 (br, exch., 1 H, NH), 4.31 (br, 2 H, CH_2NH), 2.58 (q, *J* = 7 Hz, 2 H, CH_2CH_3), 2.25 [s, 6 H, $N(CH_3)_2$], 2.25 (s, 3 H, CH_3), 1.14 (t, *J* = 7 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.6 (s, C=O), 142.9 (s, C-1), 137.8 (s, C-2), 133.7 (s, C-4), 130.0 (d, C-3), 129.5 (d, C-6), 127.2 (d, C-5), 42.9 (t, CH_2NH), 36.6 [q, $N(CH_3)_2$], 25.8 (t, CH_2CH_3), 21.5 (q, CH_3), 16.0 (q, CH_2CH_3).

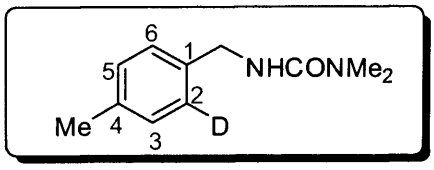
EI–MS: *m/z* (%) = 220 (M^+, 7), 191 ($M^+ - Et$, 5), 133 ($M^+ - NHCONMe_2$, 12), 132 ($M^+ - H_2NCONMe_2$, 33), 117 ($M^+ - Me - H_2NCONMe_2$, 25), 91 ($MeC_6H_4^+$, 22), 77 (13), 72 (Me_2NCO^+, 100), 65 (8), 46 (16), 44 (62), 42 (34).

CI–MS: *m/z* (%) = 238 ($M + NH_4^+$, 8), 221 (MH^+, 100).

HRMS: *m/z* calc. for $C_{13}H_{21}N_2O$ (MH^+), 221.1648; found, 221.1649.

FT–IR: ν_{max} = 3317 (NH), 2964 (CH), 1634 (C=O), 1606 (aromatic C=C), 1532, 1239, 1010 cm^{-1}.

_N'_-(2-Deuterio-4-methylbenzyl)-_N,N_-dimethylurea (131)



Yield: 0.33 g (1.71 mmol, 86%).

Mp: 94–95 °C (Mp of undeuteriated analogue lit.[136] 93 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.14 (m, 3 H, H-3, H-5 and H-6), 4.73 (br, exch., 1 H, NH), 4.38 (br, 2 H, CH_2), 2.92 [s, 6 H, $N(CH_3)_2$], 2.35 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8 (s, C=O), 137.3 (s, C-1), 137.0 (s, C-4), 129.6 (d, C-3), 129.5 (d, C-5), 128.2 (d, C-6), 127.9 (seen as three lines, 1:1:1, because of coupling to D, C-2), 45.2 (t, CH_2), 36.7 [q, $N(CH_3)_2$], 21.5 (q, CH_3).

EI–MS: *m/z* (%) = 193 (M^+, 63), 192 (M^+ – 1, 33), 121 (M^+ – $CONMe_2$, 36), 120 (M^+ – H – $CONMe_2$, 28), 106 (M^+ – $NHCONMe_2$, 50), 105 (M^+ – $H_2NCONMe_2$, 37), 92 ($MeC_6H_5^+$, 18), 91 ($MeC_6H_4^+$, 16), 77 (25), 72 (Me_2NCO^+, 100), 46 (46), 44 (91), 42 (23).

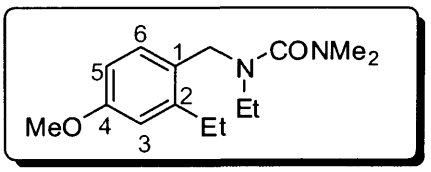
CI–MS: *m/z* (%) = 211 (M + NH_4^+, 21), 194 (MH^+, 100), 179 (M^+, 61).

HRMS: *m/z* calc. for $C_{11}H_{16}DN_2O$ (MH^+), 194.1398; found, 194.1398.

FT–IR: ν_{max} = 3331 (NH), 2952 (CH), 1612 (C=O), 1563 (aromatic C=C), 1510, 1239, 1024 cm^{-1}.

7.21 Synthesis of *N'*-ethyl-*N'*-(2-ethyl-4-methoxybenzyl)-*N,N*-dimethylurea (132) *via* directed lithiation of 108

A solution of *t*-BuLi in heptane (2.6 mL, 1.7 M, 4.4 mmol) was added to a cold (-78 °C), stirred solution of *N'*-(4-methoxybenzyl)-*N,N*-dimethylurea (**108**; 0.42 g, 2.0 mmol) in anhydrous THF (20 mL) under N_2. The mixture was stirred at –78 °C for 4 h, after which iodoethane (0.69 g, 4.4 mmol) was added. The mixture was stirred for 2 h at –78 °C then the cooling bath was removed and the mixture allowed to warm to room temperature. The reaction mixture was worked-up as described in Section 3.10.5. The product was purified by column chromatography (silica gel; Et_2O–hexane, 1:3) to give **132** (0.48 g, 1.81 mmol, 90%) as a colourless oil.



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10 (d, *J* = 8 Hz, 1 H, H-6), 6.68 (d, *J* = 2 Hz, 1 H, H-3), 6.63 (dd, *J* = 2, 8 Hz, 1 H, H-5), 4.24 (s, 2 H, CH_2N), 3.71 (s, 3 H, OCH_3), 3.04 (q, *J* = 7 Hz, 2 H, NCH_2CH_3), 2.74 [s, 6 H, $N(CH_3)_2$], 2.52 (q, *J* = 7 Hz, 2 H, CH_2CH_3), 1.31 (t, *J* = 7 Hz, 3 H, NCH_2CH_3), 1.02 (t, *J* = 7 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8 (s, C=O), 159.2 (s, C-4), 144.0 (s, C-2), 129.4 (d, C-6), 127.9 (s, C-1), 114.9 (d, C-3), 110.9 (d, C-5), 55.6 (q, OCH_3), 48.6 (t, CH_2N), 42.8 (t, NCH_2CH_3), 39.1 [q, $N(CH_3)_2$], 25.7 (t, CH_2CH_3), 15.0 (q, CH_2CH_3), 13.0 (q, CH_2CH_3).

EI–MS: *m/z* (%) = 264 (M^+, 8), 235 (M^+ – Et, 7), 190 (20), 162 (39), 149 [M^+ – $N(Et)CONMe_2$, 100], 148 [M^+ – $NH(Et)CONMe_2$, 54], 129 (33), 121 (20), 91 (35), 72 (71).

CI–MS: *m/z* (%) = 265 (MH^+, 100), 149 [M^+ – $N(Et)CONMe_2$, 50], 129 (34), 117 (68), 72 (Me_2NCO^+, 25), 46 (47), 44 (40).

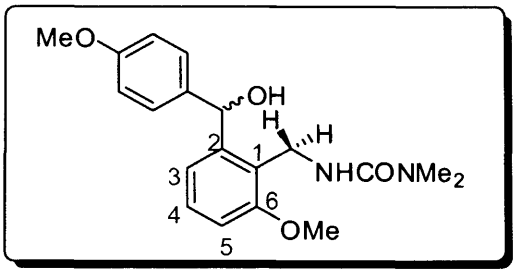
HRMS: *m/z* calc. for $C_{15}H_{25}N_2O_2$ (MH^+), 265.3713; found, 265.3713.

FT–IR: ν_{max} = 2964 (CH), 1639 (C=O), 1578 (aromatic C=C), 1492, 1394, 1238, 1121, 1029 cm^{-1}.

7.22 Synthesis of *N'*-(2-(hydroxy(4-methoxyphenyl)methyl)-6-methoxybenzyl)-*N,N*-dimethylurea (136) and *N'*-(3-(hydroxy(4-methoxyphenyl)methyl)-2-methoxybenzyl)-*N,N*-dimethylurea (137) *via* lithiation of *N'*-(2-methoxybenzyl)-*N,N*-dimethylurea (111) at -20 °C

A solution of *t*-BuLi in heptane (2.6 mL, 1.7 M, 4.4 mmol) was added to a cold (-20 °C), stirred solution of *N'*-(2-methoxybenzyl)-*N,N*-dimethylurea (**111**; 0.42 g, 2.0 mmol) in anhydrous THF (20 mL) under N_2. Formation of the monolithium reagent **133** was observed as a yellow solution and the dilithium reagents **134** and **135** were observed as a reddish orange solution. The mixture was stirred at –20 °C for 2 h, to ensure the complete formation of the dilithium reagents, after which 4-anisaldehyde (0.30 g, 2.2 mmol) was added. The mixture was stirred for 2 h at -20 °C then the cooling bath was removed and the mixture allowed to warm to room temperature. It was then diluted with Et_2O (10 mL) and quenched with aq. sat. 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 product mixture was separated by column chromatography (silica gel; Et_2O–hexane, 1:3) to give **136** (0.34 g, 0.99 mmol, 49%) and **137** (0.28 g, 0.81 mmol, 40%) as white solids.

_N'_-(2-(Hydroxy-(4-methoxyphenyl)methyl)-6-methoxybenzyl)-_N,N_-dimethylurea (136)



Yield: 0.34 g (0.99 mmol, 49%).

Mp: 139–140 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 7.10 (app. t, *J* = 8 Hz, 1 H, H-4), 6.78–6.72 (m, 4 H, H-3, H-5 and H-3/H-5 of 4-methoxyphenyl), 6.12 (d, *J* = 6 Hz, exch., 1 H, OH), 6.02 (d, *J* = 6 Hz, 1 H, CH), 5.23 (app. t, *J* = 6 Hz, exch., 1 H, NH), 4.30 (dd, *J* = 6, 16 Hz, 1 H, 1 H of CH_2), 4.22 (dd, *J* = 6, 16 Hz, 1 H, 1 H of CH_2), 3.78 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 2.72 [s, 6 H, $N(CH_3)_2$].

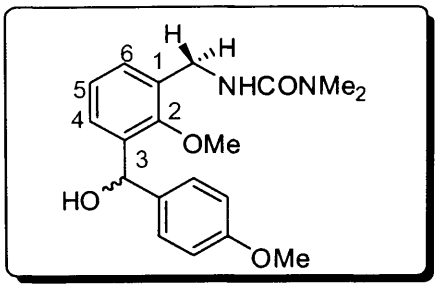
^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2 (s, C=O), 158.9 (s, C-6), 158.7 (s, C-4 of 4-methoxyphenyl), 144.6 (s, C-2), 137.1 (s, C-1 of 4-methoxyphenyl), 128.8 (d, C-4), 127.8 (d, C-2/C-6 of 4-methoxyphenyl), 126.1 (s, C-1), 122.4 (d, C-3), 113.8 (d, C-3/C-5 of 4-methoxyphenyl), 110.2 (d, C-5), 73.3 (d, CH), 56.0 (q, OCH_3), 55.6 (q, OCH_3), 37.2 (t, CH_2), 36.5 [q, $N(CH_3)_2$].

ES^+–MS: *m/z* (%) = 689 ($2M^+ + 1$, 12), 345 (MH^+, 47), 327 ($MH^+ - H_2O$, 100), 239 (6), 219 (5).

HRMS: *m/z* calc. for $C_{19}H_{25}N_2O_4$ (MH^+), 345.1809; found, 345.1807.

FT–IR: ν_{max} = 3308 (NH and OH), 2934 (CH), 1630 (C=O), 1611 (aromatic C=C), 1509, 1242, 1029 cm^{-1}.

_N'_-(3-(Hydroxy-(4-methoxyphenyl)methyl)-2-methoxybenzyl)-_N,N_-dimethylurea (137)



Yield: 0.28 g (0.81 mmol, 40%).

Mp: 140–141 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (dd, *J* = 2, 8 Hz, 1 H, H-4), 7.19 (d, *J* = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 7.16 (br d, *J* = 8 Hz, 1 H, H-6), 7.01 (app. t, *J* = 8 Hz, 1 H, H-5), 6.75 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 5.96 (s, 1 H, CH), 5.44 (s, exch., 1 H, OH), 4.81 (app. t, *J* = 6 Hz, exch., 1 H, NH), 4.36 (dd, *J* = 6, 16 Hz, 1 H, 1 H of CH_2), 4.32 (dd, *J* = 6, 16 Hz, 1 H, 1 H of CH_2), 3.69 (s, 3 H, OCH_3), 3.49 (s, 3 H, OCH_3), 2.78 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3 (s, C=O), 158.9 (s, C-2), 156.0 (s, C-4 of 4-methoxyphenyl), 137.8 (s, C-1 of 4-methoxyphenyl), 136.4 (s, C-1), 133.0 (s, C-3), 129.3 (d, C-4), 128.3 (d, C-2/C-6 of 4-methoxyphenyl), 127.6 (d, C-6), 125.0 (d, C-5), 114.1 (d, C-3/C-5 of 4-methoxyphenyl), 71.2 (d, CH), 62.1 (q, OCH_3), 55.6 (q, OCH_3), 40.3 (t, CH_2), 36.6 [q, $N(CH_3)_2$].

CI–MS: *m/z* (%) = 345 (MH^+, 6), 344 (M^+, 2), 343 (M^+ – 1, 5), 329 (M^+ – Me, 82), 327 ($MH^+ - H_2O$, 56), 301 ($MH^+ - NMe_2$, 12), 282 ($M^+ - H_2O - NMe_2$, 16), 256 (8), 237 (7), 209 (10), 137 (53), 121 (16), 101 (11), 89 (58), 72 (Me_2NCO^+, 25), 46 (100).

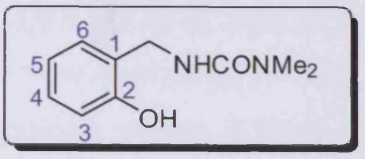
HRMS: *m/z* calc. for $C_{19}H_{25}N_2O_4$ (MH^+), 345.1809; found, 345.1813.

FT–IR: ν_{max} = 3344 (NH and OH), 2935 (CH), 1625 (C=O), 1611 (aromatic C=C), 1509, 1461, 1242, 1170, 1031 cm^{-1}.

7.23 Lithiation of *N'*-(2-methoxybenzyl)-*N,N*-dimethylurea (111) at 0 °C followed by reaction with 4-anisaldehyde

The procedure was identical to that described in Section 7.22 except that the reaction was carried out at 0 °C for 2 h followed by reaction with 4-anisaldehye at 0 °C for 2 h. The reaction mixture was worked-up and the product mixture was examined by TLC to show a mixture of four products, **136**, **137**, **138**, **139**, and starting material **111**. A white solid was obtained from treatment of the product mixture with diethyl ether (20 mL) which was filtered and washed with diethyl ether (2 x 15 mL) to give **139** (66 mg, 0.22 mmol, 11%). The filtrate was concentrated and subjected to column chromatography (silica gel; Et_2O–hexane, 1:3) to give **136** (0.35 g, 1.02 mmol, 50%), **137** (0.08 g, 0.24 mmol, 12%), **138** (12 mg, 0.06 mmol, 3%) and **111** (50 mg, 0.24 mmol, 12%). Compounds **136** and **137** were found to be identical in all respects with the ones produced from similar reactions carried out at low temperatures (–78 to –20 °C).

N′-(2-Hydroxybenzyl)-N,N-dimethylurea (138)



Yield: 12 mg (0.06 mmol, 3%).

Mp: 152–153 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.44 (s, exch., 1 H, OH), 7.23 (dt, *J* = 2, 8 Hz, 1 H, H-4), 7.06 (dd, *J* = 2, 8 Hz, 1 H, H-6), 6.94 (dd, *J* = 2, 8 Hz, 1 H, H-3), 6.80 (app. dt, *J* = 2, 8 Hz, 1 H, H-5), 5.29 (br, exch., 1 H, NH), 4.34 (d, *J* = 6 Hz, 2 H, CH_2), 2.91 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3 (s, C=O), 156.7 (s, C-2), 131.1 (d, C-6), 130.2 (d, C-4), 126.2 (s, C-1), 119.8 (d, C-5), 118.2 (d, C-3), 42.1 (t, CH_2), 36.7 [q, $N(CH_3)_2$].

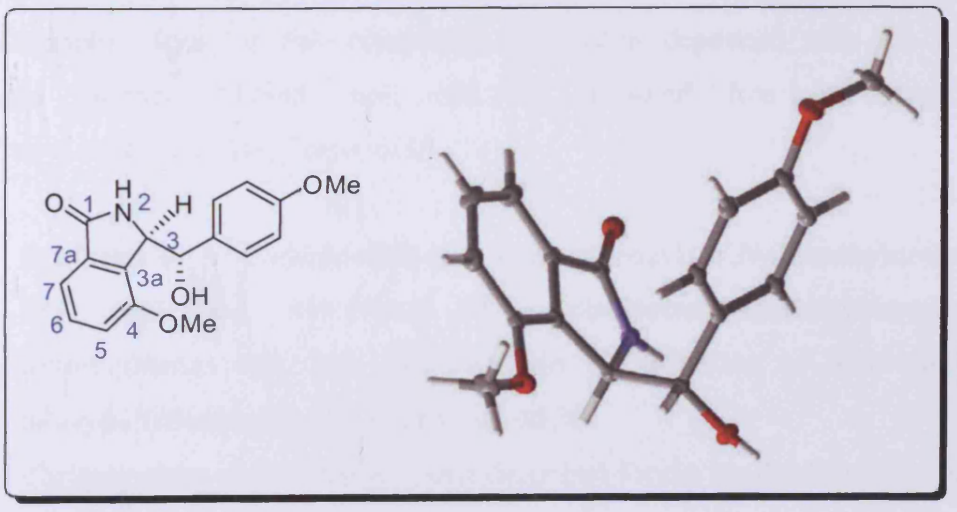
EI–MS: *m/z* (%) = 194 (M^+, 22), 149 (8), 122 (M^+ – Me_2NCO, 20), 107 (M^+ – Me_2NCONH, 24), 106 (M^+ – Me_2NCO NH_2, 31), 78 (30), 77 (32), 72 (Me_2NCO^+, 100), 46 (24), 44 (47).

CI–MS: *m/z* (%) = 195 (MH^+, 22), 106 (M^+ – Me_2NCO NH_2, 33), 89 ($Me_2NCONH_3^+$, 100).

HRMS: *m/z* calc. for $C_{10}H_{15}N_2O_2$ (MH^+), 195.1128; found, 195.1127.

FT–IR: ν_{max} = 3393 (NH and OH), 2763 (CH), 1682 (C=O), 1583 (aromatic C=C), 1534, 1387, 1226 cm^{-1}.

(R*)-3-((S*)-Hydroxy(4-methoxyphenyl)methyl)-4-methoxyisoindolin-1-one (139)



Yield: 66 mg (0.22 mmol, 11%).

Mp: 199–201 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.77 (s, exch., 1 H, NH), 7.31 (app. t, J = 8 Hz, 1 H, H-6), 7.16 (d, J = 8 Hz, 1 H, H-5), 6.93 (d, J = 8 Hz, 1 H, H-7), 6.89 (d, J = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl group), 6.58 (d, J = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl group), 5.73 (d, J = 3 Hz, exch., 1 H, OH), 5.39 (app. t, J = 3 Hz, 1 H, H-3), 4.89 (d, J = 3 Hz, 1 H, C*H*OH), 3.97 (s, 3 H, OCH_3), 3.60 (s, 3 H, OCH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.7 (s, C-1), 158.4 (s, C-4 of 4-methoxyphenyl), 155.0 (s, C-4), 134.9 (s, C-1 of 4-methoxyphenyl), 131.6 (s, C-7a), 131.5 (s, C-3a), 130.1 (d, C-6), 128.3 (d, C-2/C-6 of 4-methoxyphenyl), 114.9 (d, C-7), 113.6 (d, C-5), 112.5 (d, C-3/C-5 of 4-methoxyphenyl), 71.6 (d, CHOH), 61.5 (d, C-3), 56.0 (q, OCH_3), 55.1 (q, OCH_3).

EI–MS: *m/z* (%) = 163 (46), 136 (M^+ – $MeOC_6H_4CH(OH)CHN$, 54), 135 (M^+ – $MeOC_6H_4CH(OH)CHNH$, 100), 119 (8), 107 (10), 92 (11), 77 (15).

CI–MS: *m/z* (%) = 300 (MH^+, 100), 284 ($M^+ - NH_2$, 8), 237 (24).

HRMS: *m/z* calc. for $C_{17}H_{18}NO_4$ (MH^+), 300.1230; found, 300.1231.

FT–IR: ν_{max} = 3304 (NH and OH), 2872 (CH), 1677 (C=O), 1604 (aromatic C=C), 1512, 1273, 1048 cm^{-1}.

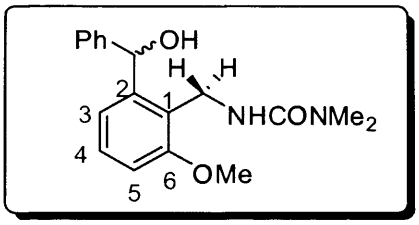
Selected crystallographic data: $C_{17}H_{17}NO_4$, FW = 299.32, T = 293(2) K, λ = 0.71073 Å, Triclinic, P1, a = 7.5240(3) Å, b = 9.4100(3) Å, c = 11.9960(5) Å, α = 83.877(2)°, β = 77.311(2)°, γ = 68.559(2)°, V = 770.92(5) $Å^3$, Z = 2, $\rho_{calc.}$ = 1.289 Mg/m^3, crystal size = 0.20 × 0.15 × 0.15 mm^3, m = 0.092 mm^{-1}, reflections collected = 5071, independent reflections = 3513, R_{int} = 0.0334, parameters = 202, final R_1 = 0.0570, wR_2 = 0.1277 for I>2σ(I) and R_1 = 0.0855, wR_2 = 0.1433 for all data. Full crystallographic data for this compound have been deposited with the CCDC, reference number 737415, and can be obtained free of charge *via* http://www.ccdc.ac.uk/data_request/cif.

7.24 Synthesis of *N'*-(2-(substituted-6-methoxybenzyl)-*N*,*N*-dimethylureas 141, 143, 145 and 147 and *N'*-(3-(substituted-2-methoxybenzyl)-*N*,*N*-dimethylureas 142, 144, 146 and 148 *via* lithiation of *N'*-(2-methoxybenzyl)-*N*,*N*-dimethylurea (111) at –20 °C

The procedure was identical to that described for the synthesis of **136** and **137** (Section 7.22) except that an electrophile (2.2 mmol), in anhydrous THF (8 mL) if

solid, otherwise neat, was used instead of 4-anisaldehyde. The reaction mixture was worked-up and the product mixture was separated by column chromatography (silica gel; Et_2O–hexane, 1:3) to give pure products. The yields of products **141-148** are recorded in Table 3.5.

_N'_-(2-(Hydroxyphenylmethyl)-6-methoxybenzyl)-_N,N_-dimethylurea (141)



Yield: 0.32 g (1.02 mmol, 51%).

Mp: 126–127 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 8 Hz, 2 H, H-2/H-6 of Ph), 7.34 (app. t, *J* = 8 Hz, 2 H, H-3/H-5 of Ph), 7.32–7.20 (m, 2 H, H-4 and H-4 of Ph), 6.86 (dd, *J* = 1, 8 Hz, 1 H, H-3), 6.82 (dd, *J* = 1, 8 Hz, 1 H, H-5), 6.41 (d, *J* = 6 Hz, exch., 1 H, OH), 6.18 (d, *J* = 6 Hz, 1 H, CH), 5.36 (app. t, *J* = 6 Hz, exch., 1 H, NH), 4.41 (dd, *J* = 6, 16 Hz, 1 H, 1 H of CH_2), 4.32 (dd, *J* = 6, 16 Hz, 1 H, 1 H of CH_2), 3.90 (s, 3 H, OCH_3), 2.85 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2 (s, C=O), 159.0 (s, C-6), 144.9 (s, C-1 of Ph), 144.5 (s, C-2), 128.8 (d, C-4), 128.4 (d, C-3/C-5 of Ph), 126.9 (d, C-4 of Ph), 126.7 (d, C-2/C-6 of Ph), 126.3 (s, C-1), 122.8 (d, C-3), 110.3 (d, C-5), 73.7 (d, CH), 56.0 (q, OCH_3), 37.3 (t, CH_2), 36.5 [q, $N(CH_3)_2$].

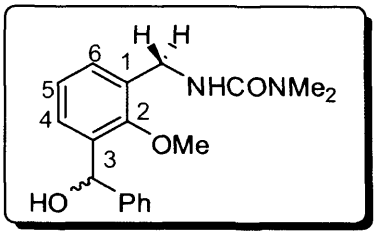
EI–MS: *m/z* (%) = 314 (M^+, 2), 296 ($M^+ - H_2O$, 61), 252 ($M^+ - H_2O - NMe_2$, 5), 224 ($M^+ - H_2O - CONMe_2$, 33), 209 ($M^+ - H_2O - NHCONMe_2$, 13), 208 ($M^+ - H_2O - H_2NCONMe_2$, 23), 180 (9), 165 (12), 148 (19), 89 (17), 77 (Ph^+, 24), 72 (Me_2NCO^+, 100), 44 (33).

CI–MS: *m/z* (%) = 315 (MH^+, 42), 299 ($M^+ - Me$, 22), 297 ($MH^+ - H_2O$, 100), 226 (12), 225 ($MH^+ - H_2O - CONMe_2$, 11), 224 ($M^+ - H_2O - CONMe_2$, 10), 209 ($M^+ - H_2O - NHCONMe_2$, 82), 197 (12), 103 (15), 89 (85), 72 (Me_2NCO^+, 38), 46 (45), 44 (26).

HRMS: *m/z* calc. for $C_{18}H_{23}N_2O_3$ (MH^+), 315.1703; found, 315.1702.

FT–IR: ν_{max} = 3311 (NH and OH), 2851 (CH), 1622 (C=O), 1550 (aromatic C=C), 1460, 1381, 1235, 1041 cm^{-1}.

N'-(3-Hydroxyphenylmethyl)-2-methoxybenzyl)-N,N-dimethylurea (142)



Yield: 0.24 g (0.76 mmol, 38%).

Mp: 146–147 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (d, J = 8 Hz, 2 H, H-2/H-6 of Ph), 7.26 (app. t, J = 8 Hz, 2 H, H-3/H-5 of Ph), 7.21–7.15 (m, 4 H, H-4, H-5, H-6 and OH), 7.01 (t, J = 8 Hz, 1 H, H-4 of Ph), 6.00 (s, 1 H, CH), 4.75 (app. t, J = 6 Hz, exch., 1 H, NH), 4.37 (dd, J = 6, 16 Hz, 1 H, 1 H of CH_2), 4.34 (dd, J = 6, 16 Hz, 1 H, 1 H of CH_2), 3.51 (s, 3 H, OCH_3), 2.80 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8 (s, C=O), 156.1 (s, C-2), 144.2 (s, C-1 of Ph), 137.6 (s, C-1), 133.1 (s, C-3), 129.5 (d, C-4), 128.7 (d, C-3/C-5 of Ph), 127.9 (d, C-4 of Ph), 127.8 (d, C-6), 127.0 (d, C-2/C-6 of Ph), 125.1 (d, C-5), 71.8 (d, CH), 62.2 (q, OCH_3), 40.4 (t, CH_2), 36.6 [q, $N(CH_3)_2$].

EI–MS: *m/z* (%) = 314 (M^+, 1), 297 ($MH^+ - H_2O$, 4), 296 ($M^+ - H_2O$, 8), 252 ($M^+ - H_2O - NMe_2$, 6), 236 (8), 226 (12), 209 ($M^+ - H_2O - NHCONMe_2$, 14), 208 ($M^+ - H_2O - H_2NCONMe_2$, 32), 181 (8), 165 (18), 152 (13), 133 (16), 105 ($PhCH_2N^+$, 29), 91 ($PhCH_2^+$, 62), 77 (Ph^+, 60), 72 (Me_2NCO^+, 100), 44 (69).

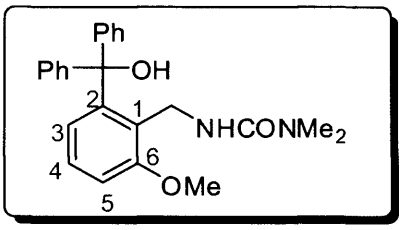
CI–MS: *m/z* (%) = 315 (MH^+, 6), 299 ($M^+ - Me$, 23), 297 ($MH^+ - H_2O$, 7), 237 (12), 209 ($M^+ - H_2O - NHCONMe_2$, 82), 197 (8), 103 (15), 89 (85), 72 (Me_2NCO^+, 23), 46 (100), 44 (43).

HRMS: *m/z* calc. for $C_{18}H_{23}N_2O_3$ (MH^+), 315.1703; found, 315.1700.

FT–IR: ν_{max} = 3303 (NH and OH), 2835 (CH), 1607 (C=O), 1552 (aromatic C=C), 1461, 1378, 1233, 1023 cm^{-1}.

Anal. calc. for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.74; H, 7.06; N, 8.90%.

N'-(2-(Hydroxydiphenylmethyl)-6-methoxybenzyl)-N,N-dimethylurea (143)



Yield: 0.37 g (0.95 mmol, 47%).

Mp: 218–219 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.98 (s, exch., 1 H, OH), 7.64 (d, J = 8 Hz, 4 H, H-2/H-6 of 2 Ph), 7.31 (t, J = 8 Hz, 4 H, H-3/H-5 of 2 Ph), 7.21 (t, J = 8 Hz, 2 H, H-4 of 2 Ph), 7.07 (app. t, J = 8 Hz, 1 H, H-4), 6.88 (br d, J = 8 Hz, 1 H, H-3), 6.31 (dd, J = 3, 8 Hz, 1 H, H-5), 5.48 (br t, exch., 1 H, NH), 4.04 (d, J = 6 Hz, 2 H, CH_2), 3.91 (s, 3 H, OCH_3), 2.85 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.8 (s, C=O), 159.4 (s, C-6), 149.2 (s, C-1 of 2 Ph), 147.9 (s, C-2), 128.2 (d, C-3/C-5 of 2 Ph), 128.0 (d, C-2/C-6 of 2 Ph), 127.7 (d, C-4), 126.9 (s, C-1), 126.8 (d, C-4 of 2 Ph), 123.5 (d, C-3), 110.6 (d, C-5), 81.4 (s, C-OH), 56.1 (q, OCH_3), 39.5 (t, CH_2), 36.5 [q, $N(CH_3)_2$].

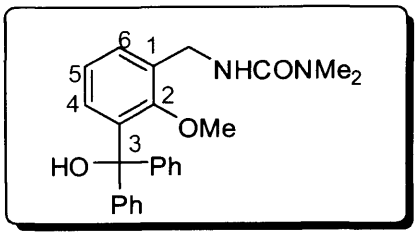
EI–MS: *m/z* (%) = 390 (M^+, 4), 372 ($MH^+ - H_2O$, 9), 313 (M^+ – Ph, 8), 284 (18), 224 (15), 178 (12), 161 (16), 105 (45), 91 ($PhCH_2^+$, 25), 77 (Ph^+, 46), 72 (Me_2NCO^+, 100), 44 (22).

CI–MS: *m/z* (%) = 391 (MH^+, 7), 373 ($MH^+ - H_2O$, 100), 306 (22), 292 (30), 273 (42), 235 (15).

HRMS: *m/z* calc. for $C_{24}H_{29}N_2O_3$ (MH^+), 391.2016; found, 391.2013.

FT–IR: ν_{max} = 3399 (NH and OH), 3025 (CH), 1630 (C=O), 1569 (aromatic C=C), 1500, 1443, 1243, 1025 cm^{-1}.

N'-(3-(Hydroxydiphenylmethyl)-2-methoxybenzyl)-N,N-dimethylurea (144)



Yield: 0.24 g (0.61 mmol, 30%).

Mp: 207–209 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27-6.81 (m, 13 H, 2 Ph, OH, H-4 and H-5), 6.42 (dd, *J* = 2, 8 Hz, 1 H, H-6), 4.88 (br, exch., 1 H, NH), 4.40 (d, *J* = 6 Hz, 2 H, CH_2), 3.79 (s, 3 H, OCH_3), 2.86 [s, 6 H, $N(CH_3)_2$].

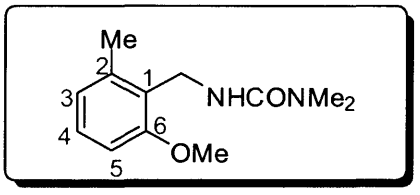
^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8 (s, C=O), 158.0 (s, C-2), 147.0 (s, C-1 of 2 Ph), 133.5 (s, C-1), 128.7 (s, C-3), 128.4 (d, C-3/C-5 of 2 Ph), 128.3 (d, C-2/C-6 of 2 Ph), 128.2 (d, C-4), 128.1 (d, C-4 of 2 Ph), 127.7 (d, C-6), 124.0 (d, C-5), 82.6 (s, C-OH), 61.6 (q, OCH_3), 40.4 (t, CH_2), 36.7 [q, $N(CH_3)_2$].

CI–MS: *m/z* (%) = 391 (MH^+, 100), 373 ($MH^+ - H_2O$, 47), 292 (46), 72 (Me_2NCO^+, 76), 44 (46).

HRMS: *m/z* calc. for $C_{24}H_{29}N_2O_3$ (MH^+), 391.2016; found, 391.2015.

FT–IR: ν_{max} = 3368 (NH and OH), 2998 (CH), 1632 (C=O), 1559 (aromatic C=C), 14980, 1445, 1246, 1029 cm^{-1}.

_N'_-(2-Methoxy-6-methylbenzyl)-_N,N_-dimethylurea (145)



Yield: 0.23 g (1.03 mmol, 51%).

Colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.07 (app. t, *J* = 8 Hz, 1 H, H-4), 6.72 (d, *J* = 8 Hz, 1 H, H-5), 6.66 (d, *J* = 8 Hz, 1 H, H-3), 4.81 (br, exch., 1 H, NH), 4.38 (d, *J* = 6 Hz, 2 H, CH_2), 3.77 (s, 3 H, OCH_3), 2.78 [s, 6 H, $N(CH_3)_2$], 2.37 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8 (s, C=O), 158.7 (s, C-2), 138.9 (s, C-6), 128.4 (d, C-4), 126.4 (s, C-1), 124.8 (d, C-5), 108.5 (d, C-3), 55.9 (q, OCH_3), 37.3 (t, CH_2), 36.6 [q, $N(CH_3)_2$], 20.2 (q, CH_3).

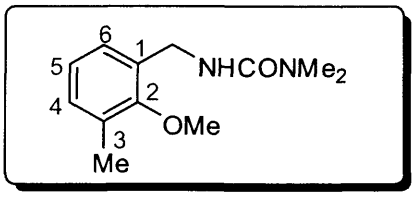
EI–MS: *m/z* (%) = 222 (M^+, 12), 207 (M^+ – Me, 3), 150 ($M^+ - Me_2NCO$, 40), 135 ($M^+ - Me_2NCONH$, 35), 105 (21), 91 ($PhCH_2^+$, 20), 77 (12), 72 (Me_2NCO^+, 100), 44 (72).

CI–MS: *m/z* (%) = 445 (2 M^+ + 1, 2), 223 (MH^+, 100), 222 (M^+, 13), 150 ($M^+ - Me_2NCO$, 12), 135 ($M^+ - Me_2NCONH$, 11), 72 (Me_2NCO^+, 12), 46 (9).

HRMS: *m/z* calc. for $C_{12}H_{19}N_2O_2$ (MH^+), 223.1441; found, 223.1441.

FT–IR: ν_{max} = 3341 (NH), 2932 (CH), 1635 (C=O), 1540 (aromatic C=C), 1471, 1264, 1090 cm^{-1}.

N'-(2-Methoxy-3-methylbenzyl)-*N*,*N*-dimethylurea (146)



Yield: 0.18 g (0.81 mmol, 40%).

Colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.09 (dd, *J* = 1, 8 Hz, 1 H, H-4), 7.02 (br d, *J* = 8 Hz, 1 H, H-6), 6.91 (app. t, *J* = 8 Hz, 1 H, H-5), 4.84 (br, exch., 1 H, NH), 4.37 (d, *J* = 6 Hz, 2 H, CH_2), 3.69 (s, 3 H, OCH_3), 2.82 [s, 6 H, $N(CH_3)_2$], 2.22 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8 (s, C=O), 157.2 (s, C-2), 132.7 (s, C-1), 131.5 (s, C-3), 131.0 (d, C-4), 127.8 (d, C-6), 124.7 (d, C-5), 60.8 (q, OCH_3), 40.9 (t, CH_2), 36.6 [q, $N(CH_3)_2$], 16.4 (q, CH_3).

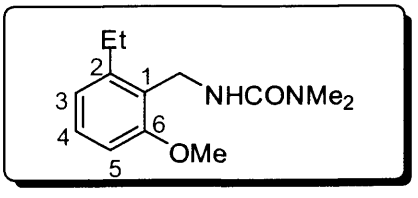
EI–MS: *m/z* (%) = 222 (M^+, 12), 191 (6), 150 (M^+ – Me_2NCO, 31), 135 (M^+ – Me_2NCONH, 16), 105 (12), 91 ($PhCH_2^+$, 18), 77 (11), 72 (Me_2NCO^+, 100), 44 (54).

CI–MS: *m/z* (%) = 223 (MH^+, 100), 209 (8), 150 (M^+ – Me_2NCO, 6), 72 (Me_2NCO^+, 7), 46 (9).

HRMS: *m/z* calc. for $C_{12}H_{19}N_2O_2$ (MH^+), 223.1441; found, 223.1443.

FT–IR: ν_{max} = 3341 (NH), 2928 (CH), 1633 (C=O), 1528 (aromatic C=C), 1469, 1372, 1206, 1007 cm^{-1}.

N'-(2-Ethyl-6-methoxybenzyl)-*N*,*N*-dimethylurea (147)



Yield: 0.24 g (1.02 mmol, 51%).

Colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.14 (m, 2 H, H-4 and NH), 6.86 (d, *J* = 8 Hz, 1 H, H-3), 6.68 (d, *J* = 8 Hz, 1 H, H-5), 4.30 (br, 2 H, CH_2NH), 3.74 (s, 3 H, OCH_3), 3.07 (q, *J* = 7 Hz, 2 H, CH_2CH_3), 2.72 [s, 6 H, $N(CH_3)_2$], 1.06 (t, *J* = 7 Hz, 3 H, CH_3).

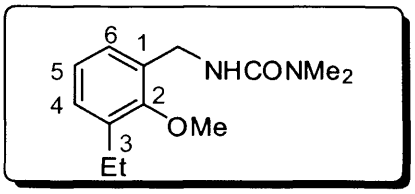
^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.5 (s, C=O), 156.3 (s, C-6), 126.9 (d, C-4), 126.8 (s, C-2), 125.4 (s, C-1), 119.4 (d, C-3), 109.0 (d, C-5), 54.2 (q, OCH_3), 45.4 (t, CH_2NH), 41.5 (t, CH_2CH_3), 37.7 [q, $N(CH_3)_2$], 11.8 (q, CH_2CH_3).

EI–MS: *m/z* (%) = 236 (M^+, 13), 207 (M^+ – Et, 7), 164 (M^+ – Me_2NCO, 52), 134 (M^+ – Me_2NCONH – Me, 51), 121 (M^+ – Me_2NCO – Et, 87), 115 (17), 91 ($PhCH_2^+$, 51), 72 (Me_2NCO^+, 100), 44 (30).

HRMS: *m/z* calc. for $C_{13}H_{21}N_2O_2$ (MH^+), 237.1598; found, 237.1598.

FT–IR: ν_{max} = 3340 (NH), 2937 (CH), 1632 (C=O), 1490 (aromatic C=C), 1397, 1239, 1028 cm^{-1}.

_N'_-(3-Ethyl-2-methoxybenzyl)-_N,N_-dimethylurea (148)



Yield: 0.18 g (0.76 mmol, 38%).

Colourless oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.11 (app. t, *J* = 8 Hz, 1 H, H-5), 6.75 (d, *J* = 8 Hz, 1 H, H-6), 6.67 (d, *J* = 8 Hz, 1 H, H-4), 4.84 (br, exch., 1 H, NH), 3.89 (d, *J* = 6 Hz, 2 H, CH_2NH), 3.78 (s, 3 H, OCH_3), 2.77 [s, 6 H, $N(CH_3)_2$], 2.73 (q, *J* = 7 Hz, 2 H, CH_2CH_3), 1.12 (t, *J* = 7 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8 (s, C=O), 158.7 (s, C-2), 130.7 (s, C-1), 130.7 (d, C-4), 127.7 (s, C-3), 124.7 (d, C-6), 121.9 (d, C-5), 55.9 (q, OCH_3), 36.9 (t, CH_2NH), 36.6 [q, $N(CH_3)_2$], 26.6 (t, CH_2CH_3), 16.5 (q, CH_2CH_3).

EI–MS: *m/z* (%) = 236 (M^+, 12), 207 (M^+ – Et, 9), 164 (M^+ – Me_2NCO, 32), 149 (M^+ – Me_2NCO – Me, 51), 148 (M^+ – Me_2NCONH_2, 95), 135 (15), 117 (34), 101 (24), 91 ($PhCH_2^+$, 56), 77 (25), 72 (Me_2NCO^+, 100), 44 (67).

CI–MS: *m/z* (%) = 237 (MH^+, 100), 164 (M^+ – Me_2NCO, 5), 148 (M^+ – Me_2NCONH_2, 11), 89 (13), 72 (Me_2NCO^+, 10), 46 (19), 44 (12).

HRMS: *m/z* calc. for $C_{13}H_{21}N_2O_2$ (MH^+), 237.1598; found, 237.1599.

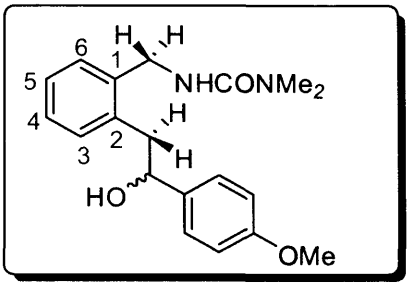
FT–IR: ν_{max} = 3329 (NH), 2965 (CH), 1636 (C=O), 1520 (aromatic C=C), 1470, 1270, 1095 cm^{-1}.

7.25 Synthesis of _N'_-(2-substituted methylbenzyl)-_N,N_-dimethylureas 153-158 *via* directed lithiation of _N'_-(2-methylbenzyl)-_N,N_-dimethylurea (114)

The procedure was identical with that described in Section 7.20 except that _N'_-(2-methylbenzyl)-_N,N_-dimethylurea (**114**) was used instead of compound **107**, **108**

or **113**. The reaction mixture was worked-up and purified by column chromatography (silica gel; Et_2O–hexane, 1:3) to give pure products as white solids. The yields obtained are recorded in Table 3.6.

_N'_-(2-(2-(Hydroxy-2-(4-methoxyphenyl)ethyl)benzyl)-_N,N_-dimethylurea (153)



Yield: 0.52 g (1.58 mmol, 79%).

Mp: 108–109 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 7.29–7.22 (m, 5 H, H-3, H-4, H-5, H-6 and NH), 6.89 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 5.32 (s, exch., 1 H, OH), 4.88 (dd, *J* = 4, 9 Hz, 1 H, CH), 4.44 (d, *J* = 14 Hz, 1 H, 1 H of C*H*$_2$NH), 4.35 (d, *J* = 14 Hz, 1 H, 1 H of C*H*$_2$NH), 3.81 (s, 3 H, OCH_3), 3.12 (dd, *J* = 9, 14 Hz, 1 H, 1 H of CH_2), 2.94 (dd, *J* = 4, 14 Hz, 1 H, 1 H of CH_2), 2.85 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4 (s, C=O), 158.9 (s, C-4 of 4-methoxyphenyl), 138.4 (s, C-1), 137.8 (s, C-2), 137.0 (s, C-1 of 4-methoxyphenyl), 130.7 (d, C-3), 130.4 (d, C-6), 128.1 (d, C-4), 127.4 (d, C-2/C-6 of 4-methoxyphenyl), 127.3 (d, C-5), 114.2 (d, C-3/C-5 of 4-methoxyphenyl), 75.7 (d, CH), 55.7 (q, OCH_3), 43.3 (t, CH_2), 42.5 (t, CH_2), 36.6 [q, $N(CH_3)_2$].

EI–MS: *m/z* (%) = 328 (M^+, 2), 311 (M^+ – OH, 100), 310 (M^+ – H_2O, 51), 308 (20), 265 (63).

CI–MS: *m/z* (%) = 328 (M^+, 3), 327 (M^+ – 1, 3), 312 (MH^+ – OH, 17), 311 (MH^+ – H_2O, 100), 240 (MH^+ – H_2O – $CONMe_2$, 11), 193 (28), 179 (14), 154 (28), 137 (22), 135 (17), 106 (58), 89 (81), 63 (20).

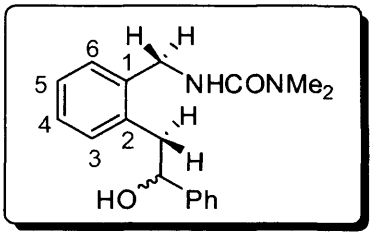
ES$^+$–MS: *m/z* (%) = 351 (M + Na^+, 58), 329 (MH^+, 2), 312 (MH^+ – OH, 22), 311 (MH^+ – H_2O, 100).

ES$^-$–MS: *m/z* (%) = 328 (M^-, 14), 327 (M^- – 1, 100).

HRMS: *m/z* calc. for $C_{19}H_{25}N_2O_3$ (MH^+), 329.1860; found, 329.1864.

FT–IR: ν_{max} = 3314 (NH and OH), 2933 (CH), 1632 (C=O), 1530 (aromatic C=C), 1510, 1243, 1024 cm^{-1}.

N'-(2-(2-Hydroxy-2-phenylethyl)benzyl)-N,N-dimethylurea (154)



Yield: 0.46 g (1.54 mmol, 77%).

Mp: 116–117 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.12 (m, 10 H, Ph, H-3, H-4, H-5, H-6 and NH), 5.44 (br s, exch., 1 H, OH), 4.82 (dd, *J* = 4, 9 Hz, 1 H, CH), 4.33 (d, *J* = 14 Hz, 1 H, 1 H of C*H*$_2$NH), 4.25 (d, *J* = 14 Hz, 1 H, 1 H of C*H*$_2$NH), 3.02 (dd, *J* = 9, 14 Hz, 1 H, 1 H of CH_2), 2.88 (dd, *J* = 4, 14 Hz, 1 H, 1 H of CH_2), 2.75 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9 (s, C=O), 144.8 (s, C-1), 138.5 (s, C-1 of Ph), 137.7 (s, C-2), 130.7 (d, C-3), 130.4 (d, C-6), 128.9 (d, C-3/C-5 of Ph), 128.1 (d, C-4), 128.0 (d, C-5), 127.3 (d, C-4 of Ph), 126.2 (d, C-2/C-6 of Ph), 76.1 (d, CH), 43.3 (t, CH_2), 42.5 (t, CH_2), 36.6 [q, $N(CH_3)_2$].

EI–MS: *m/z* (%) = 299 (M^+ + 1, 6), 298 (M^+, 1), 281 (M^+ – OH or $MH^+ - H_2O$, 51), 280 ($M^+ - H_2O$, 14), 209 (33), 208 (100).

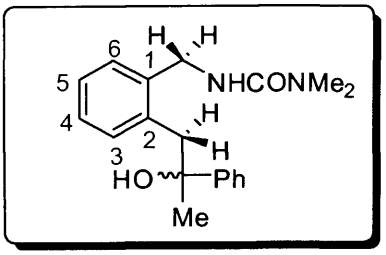
CI–MS: *m/z* (%) = 316 (M + NH_4^+, 3), 299 (MH^+, 100), 282 (MH^+ – OH, 26), 281 ($MH^+ - H_2O$, 100), 193 (44), 179 (12), 106 (41), 89 (64), 52 (68), 46 (78).

HRMS: *m/z* calc. for $C_{18}H_{23}N_2O_2$ (MH^+), 299.1754; found, 299.1755.

FT–IR: ν_{max} = 3230 (NH and OH), 2938 (CH), 16310 (C=O), 1586 (aromatic C=C), 1530, 1212, 1018 cm^{-1}.

Anal. calc. for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.50; H, 7.47; N, 9.40%.

N'-(2-(2-Hydroxy-2-phenylpropyl)benzyl)-N,N-dimethylurea (155)



Yield: 0.45 g (1.47 mmol, 74%).

Mp: 82–83 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (d, *J* = 8 Hz, 2 H, H-2/H-6 of Ph), 7.26–7.22 (m, 3 H, H-3, H-4 and H-5 of Ph), 7.17 (d, *J* = 8 Hz, 1 H, H-3), 7.14 (br, exch., 1 H, NH), 7.08 (app. t, *J* = 8 Hz, 1 H, H-5), 6.99 (app. t, *J* = 8 Hz, 1 H, H-4), 6.74 (d, *J* = 8 Hz, 1 H, H-6), 5.35 (s, exch., 1 H, OH), 4.31 (d, *J* = 14 Hz, 1 H, 1 H of C*H*$_2$NH), 4.23 (d, *J* = 14 Hz, 1 H, 1 H of C*H*$_2$NH), 3.09 (d, *J* = 14 Hz, 1 H, 1 H of CH_2), 3.04 (d, *J* = 14 Hz, 1 H, 1 H of CH_2), 2.78 [s, 6 H, $N(CH_3)_2$], 1.6 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9 (s, C=O), 148.5 (s, C-1 of Ph), 139.6 (s, C-1), 135.8 (s, C-2), 132.3 (d, C-3), 130.2 (d, C-6), 128.5 (d, C-3/C-5 of Ph), 127.4 (d, C-4 of Ph), 127.1 (d, C-5), 126.5 (d, C-4), 125.4 (d, C-2/C-6 of Ph), 75.4 (s, C-OH), 46.6 (t, CH_2), 43.2 (t, CH_2), 36.7 [q, $N(CH_3)_2$], 30.3 (q, CH_3).

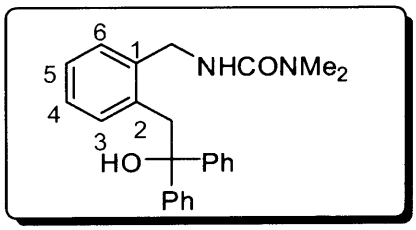
EI–MS: *m/z* (%) = 312 (M^+, 1), 295 (M^+ – OH, 12), 294 (M^+ – H_2O, 10), 222 (M^+ – H_2O – $CONMe_2$, 25), 207 (M^+ – H_2O – $NHCONMe_2$, 32), 206 (MH^+ – H_2O – $NCONMe_2$, 100).

CI–MS: *m/z* (%) = 313 (MH^+, 33), 297 (24), 296 (MH^+ – OH, 20), 295 (MH^+ – H_2O, 100), 235 (M^+ – Ph, 13), 193 (78), 179 (9), 138 (39), 106 ($PhCHO^+$, 42), 89 (78), 52 (58), 46 (67), 44 (24).

HRMS: *m/z* calc. for $C_{19}H_{25}N_2O_2$ (MH^+), 313.1911; found, 313.1912.

FT–IR: ν_{max} = 3329 (NH and OH), 2928 (CH), 1611 (C=O), 1531 (aromatic C=C), 1246, 1026 cm^{-1}.

N'-(2-(2-Hydroxy-2,2-diphenylethyl)benzyl)-N,N-dimethylurea (156)



Yield: 0.57 g (1.52 mmol, 76%).

Mp: 119–120 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.41 (d, *J* = 8 Hz, 4 H, H-2/H-6 of 2 Ph), 7.27 (app. t, *J* = 8 Hz, 4 H, H-3/H-5 of 2 Ph), 7.19–6.86 (m, 6 H, H-3, H-4, H-5, H-6 and H-4 of 2 Ph), 6.66 (t, *J* = 6 Hz, exch., 1 H, NH), 5.83 (s, exch., 1 H, OH), 3.99 (d, *J* = 6 Hz, 2 H, C*H*$_2$NH), 3.68 (s, 2 H, CH_2), 2.79 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.5 (s, C=O), 148.5 (s, C-1 of 2 Ph), 140.9 (s, C-1), 135.4 (s, C-2), 131.8 (d, C-3), 128.0 (d, C-6), 127.9 (d, C-3/C-5 of 2 Ph), 126.8 (d, C-2/C-6 of 2 Ph), 126.6 (d, C-4 of 2 Ph), 126.0 (d, C-4), 125.4 (d, C-5), 77.8 (s, C-OH), 42.9 (t, CH_2), 41.3 (t, CH_2), 36.3 [q, $N(CH_3)_2$].

EI–MS: *m/z* (%) = 374 (M^+, 2), 357 (M^+ – OH, 11), 268 (MH^+ – OH – $CONMe_2$, 100), 252 (16), 239 (12), 206 (25).

CI–MS: *m/z* (%) = 375 (MH^+, 12), 374 (M^+, 6), 373 (M^+ – 1, 5), 359 (33), 357 (MH^+ – H_2O, 89), 286 (MH^+ – OH – $CONMe_2$, 10), 257 (MH^+ – H_2O – $CHNHCONMe_2$, 12), 200 (81), 193 (100), 183 (Ph_2COH^+, 71), 179 (17), 118 (24), 106 (55), 89 (87), 63 (15).

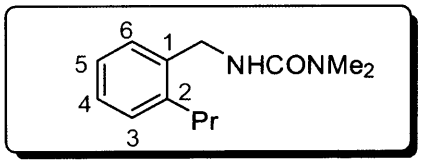
ES^+–MS: *m/z* (%) = 397 (M + Na^+, 100), 375 (MH^+, 4), 358 (MH^+ – OH, 13), 357 (MH^+ – H_2O, 69), 270 (MH^+ – H_2O – $NHCONMe_2$, 14), 269 (M^+ – H_2O – $NHCONMe_2$, 52), 191(34), 89 (78).

ES^-–MS: *m/z* (%) = 374 (M^-, 2), 373 (M^- – 1, 8), 191 (100), 146 (9), 118 (21), 87 (25).

HRMS: *m/z* calc. for $C_{24}H_{30}N_3O_2$ (M + NH_4^+), 392.2333; found, 392.2330.

FT–IR: ν_{max} = 3331 (NH and OH), 2927 (CH), 1621 (C=O), 1531 (aromatic C=C), 1246, 1026 cm^{-1}.

_N'_-(2-Propylbenzyl)-_N,N_-dimethylurea (157)



Yield: 0.36 g (1.64 mmol, 82%).

Mp: 59–61 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.05 (m, 4 H, H-3, H-4, H-5 and H-6), 4.58 (br, exch., 1 H, NH), 4.33 (br, 2 H, C*H*$_2$NH), 2.80 [s, 6 H, $N(CH_3)_2$], 2.54 (t, *J* = 7 Hz, 2 H, C*H*$_2$$CH_2CH_3$), 1.53 (app. sextet, *J* = 7 Hz, 2 H, C*H*$_2$$CH_3$), 0.89 (t, *J* = 7 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.6 (s, C=O), 141.3 (s, C-1), 137.1 (s, C-2), 129.9 (d, C-3), 129.1 (d, C-6), 127.8 (d, C-4), 126.5 (d, C-5), 42.9 (t, CH_2NH), 36.6 [q, $N(CH_3)_2$], 34.9 (t, *C*$H_2CH_2CH_3$), 24.8 (t, *C*H_2CH_3), 14.5 (q, CH_3).

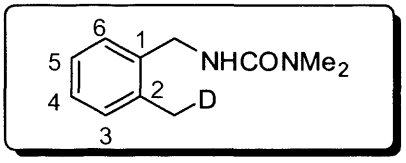
EI–MS: *m/z* (%) = 220 (M^+, 31), 177 (M^+ – Pr, 13), 148 (M^+ – $CONMe_2$, 10), 132 (M^+ – $H_2NCONMe_2$, 47), 117 (M^+ – Me – $H_2NCONMe_2$, 82), 105 (M^+ – $CONMe_2$ – Pr, 53), 91 ($MeC_6H_4^+$, 22), 89 (34), 77 (24), 72 (Me_2NCO^+, 100), 65 (15), 46 (23), 44 (69), 42 (33).

CI–MS: *m/z* (%) = 441 (2 M^+ + 1, 12), 238 (M + NH_4^+, 13), 221 (MH^+, 100).

HRMS: *m/z* calc. for $C_{13}H_{21}N_2O$ (MH^+), 221.1648; found, 221.1648.

FT–IR: ν_{max} = 3325 (NH), 2957 (CH), 1631 (C=O), 1529 (aromatic C=C), 1375, 1227 cm^{-1}.

_N'_-(2-Deuteriomethylbenzyl)-_N,N_-dimethylurea (158)



Yield: 0.32 g (1.66 mmol, 83%).

Mp: 73–75 °C (Mp of undeuteriated analogue 73–75 °C; **114**, Section 7.18).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.12 (m, 4 H, H-3, H-4, H-5 and H-6), 4.61 (br, exch., 1 H, NH), 4.42 (br, 2 H, CH_2NH), 2.91 [s, 6 H, $N(CH_3)_2$], 2.31 [(1:1:1) t, *J* = 2 Hz, 2 H, CH_2D].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.7 (s, C=O), 137.5 (s, C-1), 136.8 (s, C-2), 130.8 (d, C-6), 128.7 (d, C-3), 127.8 (d, C-5), 126.5 (d, C-4), 43.6 (t, CH_2NH), 36.6 [q, $N(CH_3)_2$], 19.4 (seen as three lines, 1:1:1, because of coupling to D, CH_2D).

EI–MS: *m/z* (%) = 194 (M^+ + 1, 15), 193 (M^+, 43), 149 (M^+ – NMe_2, 11), 121 (M^+ – $CONMe_2$, 37), 106 (M^+ – $NHCONMe_2$, 71), 105 (M^+ – $H_2NCONMe_2$, 66), 92 ($MeC_6H_5^+$, 21), 78 (24), 77 (Ph^+, 21), 72 (Me_2NCO^+, 100), 46 (32), 44 (79), 42 (27).

CI–MS: *m/z* (%) = 211 (M + NH_4^+, 17), 195 (23), 194 (MH^+, 100), 52 (20).

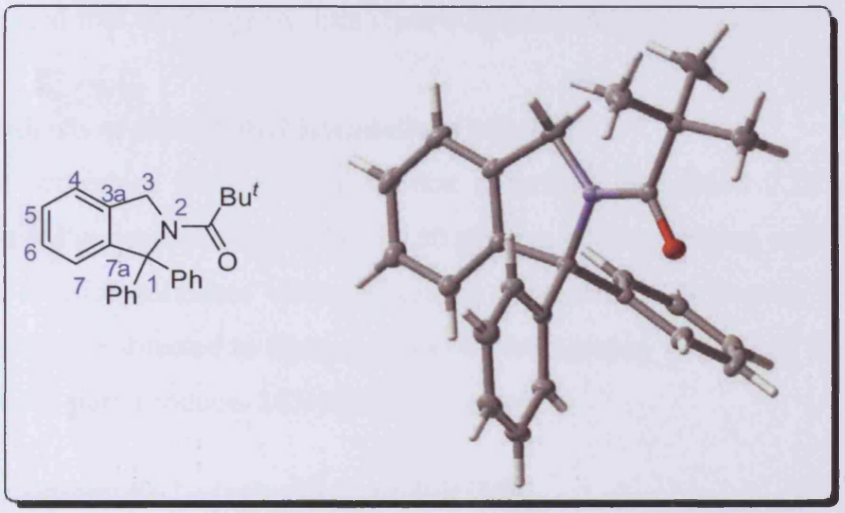
HRMS: *m/z* calc. for $C_{11}H_{16}DN_2O$ (MH^+), 194.1398; found, 194.1398.

FT–IR: ν_{max} = 3315 (NH), 2926 (CH), 1622 (C=O), 1537 (aromatic C=C), 1512, 1376, 12.35, 1027 cm^{-1}.

7.26 Synthesis of 1,1-diphenyl-2-pivaloylisoindoline (162) *via* cyclization of *N*-(2-(hydroxydiphenylmethyl)benzyl)pivalamide (57)

Trifluoroacetic anhydride (0.5 mL) was added to a stirred solution of *N*-(2-(hydroxydiphenylmethyl)benzyl)pivalamide (**57**; 0.50 g, 1.34 mmol) in DCM

(10 mL) at room temperature. The mixture was stirred for 5 min at room temperature, after which TLC showed the formation of a single product. The reaction mixture was quenched with H_2O (10 mL). The organic layer was separated, washed with aq. sat. $NaHCO_3$ (10 mL), H_2O (2 x 10 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue obtained was subjected to flash column chromatography (silica gel; Et_2O–hexane, 1:3) to give pure **162** (0.40 g, 1.14 mmol, 85%) as a white solid.



Mp: 149–150 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.23 (m, 13 H, 2 Ph, H-4, H-5 and H-6), 7.04 (d, *J* = 8 Hz, 1 H, H-7), 5.30 (s, 2 H, H-3), 1.35 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.8 (s, C=O), 146.5 (s, C-7a), 143.1 (s, C-1 of 2 Ph), 135.7 (s, C-3a), 128.8 (d, C-2/C-6 of 2 Ph), 128.5 (d, C-4), 128.0 (d, C-7), 127.9 (d, C-3/C-5 of 2 Ph), 127.0 (d, C-4 of 2 Ph), 125.1 (d, C-6), 122.2 (d, C-5), 80.9 (s, C-1), 53.9 (t, C-3), 40.1 [s, *C*$(CH_3)_3$], 28.0 [q, C(*C*$H_3)_3$].

EI–MS: *m/z* (%) = 355 (M^+, 22), 298 (M^+ – ^{t}Bu, 55), 278 (M^+ – Ph, 20), 255 (M^+ – ^{t}BuCONH, 42), 239 (21), 220 (19), 206 (12), 194 (40), 178 (28), 165 (32), 116 (11), 105 ($PhCH_2N^+$, 23), 91 ($PhCH_2^+$, 9), 77 (Ph^+, 20), 57 (^{t}Bu$^+$, 100), 41 (27).

CI–MS: *m/z* (%) = 356 (MH^+, 100).

HRMS: *m/z* calc. for $C_{25}H_{26}NO$ (MH^+), 356.2009; found, 356.2010.

FT–IR: ν_{max} = 2957 (CH), 1618 (C=O), 1510 (aromatic C=C), 1371, 1348, 1242, 1173, 1030 cm^{-1}.

Anal. calc. for $C_{25}H_{25}NO$: C, 84.47; H, 7.09; N, 3.94. Found: C, 84.35; H, 7.03; N, 3.83%.

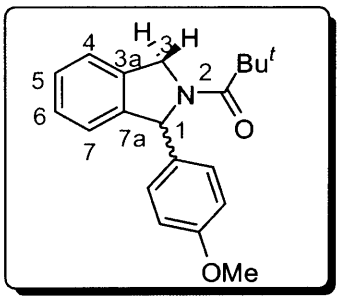
Selected crystallographic data: $C_{25}H_{25}NO$, FW = 355.46, T = 150(2) K, λ = 0.71073

Å, Orthorhombic, $Pna2_1$, a = 19.5940(2) Å, b = 10.8450(2) Å, c = 9.2270(5) Å, α = 90°, β = 90°, γ = 90°, V = 1960.71(11) $Å^3$, Z = 4, $\rho_{calc.}$ = 1.204 Mg/m^3, crystal size = 0.40 × 0.34 × 0.30 mm^3, m = 0.072 mm^{-1}, reflections collected = 4301, independent reflections = 3656, R_{int} = 0.0300, parameters = 247, final R_1 = 0.0481, wR_2 = 0.1016 for I>2σ(I) and R_1 = 0.0616, wR_2 = 0.1085 for all data. Full crystallographic data for this compound have been deposited with the CCDC, reference number 737413, and can be obtained free of charge *via* http://www.ccdc.ac.uk/data_request/cif.

7.27 Synthesis of substituted isoindolines 163-173

The procedure was identical to that described in Section 7.26 except that compounds of the general formula **160** (0.50 g) were used as starting materials instead of **57**. The reaction mixtures were worked-up as described in Section 7.26 and the residues obtained subjected to flash column chromatography (silica gel; Et_2O–hexane, 1:3) to give the pure products **163-173** as white solids.

1-(4-Methoxyphenyl)-2-pivaloylisoindoline (163)



Yield: 0.42 g (1.36 mmol, 89%).

Mp: 112–114 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (app. t, *J* = 8 Hz, 1 H, H-6), 7.29 (d, *J* = 8 Hz, 1 H, H-4), 7.25 (app. t, *J* = 8 Hz, 1 H, H-5), 7.19 (d, *J* = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 7.09 (d, *J* = 8 Hz, 1 H, H-7), 6.83 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 6.32 (s, 1 H, H-1), 5.26-5.16 (m, 2 H, H-3), 3.78 (s, 3 H, OCH_3), 1.24 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.8 (s, C=O), 159.0 (s, C-4 of 4-methoxyphenyl), 141.4 (s, C-7a), 136.3 (s, C-3a), 128.3 (d, C-4 and C-7), 128.1 (s, C-1 of 4-methoxyphenyl), 128.0 (d, C-2/C-6 of 4-methoxyphenyl), 123.9 (d, C-6), 122.7 (d, C-5), 114.3 (d, C-3/C-5 of 4-methoxyphenyl), 69.0 (d, C-1), 55.6 (q, OCH_3), 54.0 (t, C-3), 39.7 [s, $C(CH_3)_3$], 28.0 [q, $C(CH_3)_3$].

EI–MS: *m/z* (%) = 309 (M^+, 12), 294 (M^+ – Me, 3), 278 (M^+ – OMe, 7), 252 (M^+ – ^{t}Bu, 15), 224 (M^+ – ^{t}BuCO, 12), 209 (M^+ – ^{t}BuCO – Me, 23), 194 (8), 165 (9), 135 (7), 116 (6), 57 (^{t}Bu$^+$, 100), 41 (73).

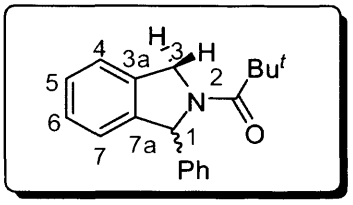
CI–MS: *m/z* (%) = 310 (MH^+, 100).

HRMS: *m/z* calc. for $C_{20}H_{24}NO_2$ (MH^+), 310.1802; found, 310.1802.

FT–IR: ν_{max} = 2958 (CH), 1616 (C=O), 1510 (aromatic C=C), 1371, 1357, 1242, 1117 cm^{-1}.

Anal. calc. for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.65; H, 7.54; N, 4.52%.

1-Phenyl-2-pivaloylisoindoline (164)



Yield: 0.41 g (1.47 mmol, 87%).

Mp: 110–111 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.11 (m, 8 H, Ph, H-4, H-5 and H-6), 7.00 (d, *J* = 8 Hz, 1 H, H-7), 6.24 (s, 1 H, H-1), 5.17-5.07 (m, 2 H, H-3), 1.24 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.2 (s, C=O), 143.9 (s, C-1 of Ph), 141.0 (s, C-7a), 136.2 (s, C-3a), 129.0 (d, C-3/C-5 of Ph), 128.4 (d, C-4), 128.1 (d, C-2/C-6 of Ph), 127.6 (d, C-4 of Ph), 126.7 (d, C-7), 123.9 (d, C-6), 122.7 (d, C-5), 69.7 (d, C-1), 54.2 (t, C-3), 39.8 [s, $C(CH_3)_3$], 28.0 [q, $C(CH_3)_3$].

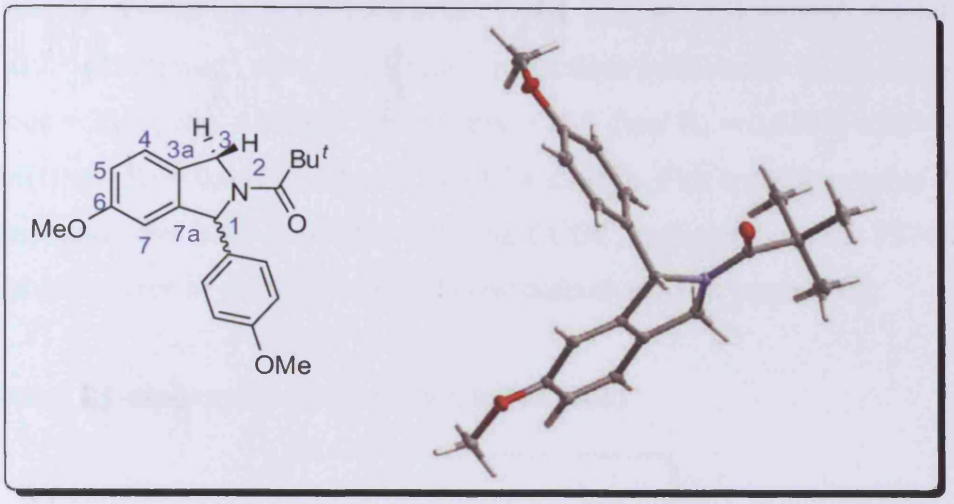
EI–MS: *m/z* (%) = 279 (M^+, 11), 222 (M^+ – ^{t}Bu, 10), 194 (M^+ – ^{t}BuCO, 11), 179 (M^+ – ^{t}BuCONH, 32), 178 (M^+ – ^{t}BuCONH$_2$, 29), 165 (M^+ – ^{t}BuCONHCH$_2$, 16), 116 (12), 105 ($PhCH_2N^+$, 6), 91 ($PhCH_2^+$, 9), 89 (15), 77 (Ph^+, 18), 57 (^{t}Bu$^+$, 100), 41 (95).

CI–MS: *m/z* (%) = 297 ($M + NH_4^+$, 2), 280 (MH^+, 100).

HRMS: *m/z* calc. for $C_{19}H_{22}NO$ (MH^+), 280.1696; found, 280.1694.

FT–IR: ν_{max} = 2962 (CH), 1616 (C=O), 1510 (aromatic C=C), 1410, 1369, 1357, 1209, 1093 cm^{-1}.

6-Methoxy-1-(4-methoxyphenyl)-2-pivaloylisoindoline (165)



Yield: 0.43 g (1.26 mmol, 90%).

Mp: 133–134 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 8 Hz, 1 H, H-4), 7.18 (d, *J* = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 6.85 (dd, *J* = 2, 8 Hz, 1 H, H-5), 6.83 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 6.58 (d, *J* = 2 Hz, 1 H, H-7), 6.25 (s, 1 H, H-1), 5.20-5.09 (m, 2 H, H-3), 3.78 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 1.32 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.7 (s, C=O), 160.2 (s, C-6), 159.0 (s, C-4 of 4-methoxyphenyl), 142.8 (s, C-7a), 136.2 (s, C-1 of 4-methoxyphenyl and C-3a), 128.2 (d, C-4), 123.5 (d, C-7), 114.9 (d, C-5), 114.3 (d, C-2/C-6 of 4-methoxyphenyl), 108.5 (d, C-3/C-5 of 4-methoxyphenyl), 69.1 (d, C-1), 55.9 (q, OCH_3), 55.6 (q, OCH_3), 53.5 (t, C-3), 39.7 [s, $C(CH_3)_3$], 28.0 [q, $C(CH_3)_3$].

EI–MS: *m/z* (%) = 339 (M^+, 8), 282 (M^+ – ^{t}Bu, 41), 254 (M^+ – ^{t}BuCO, 12), 239 (M^+ – ^{t}BuCONH, 16), 238 (M^+ – ^{t}BuCONH$_2$, 20), 224 (7), 208 (6), 195 (5), 165 (8), 152 (8), 139 (7), 104 (8), 92 (5), 77 (14), 57 (^{t}Bu$^+$, 100), 41 (73).

CI–MS: *m/z* (%) = 340 (MH^+, 100).

HRMS: *m/z* calc. for $C_{21}H_{26}NO_3$ (MH^+), 340.1907; found, 340.1913.

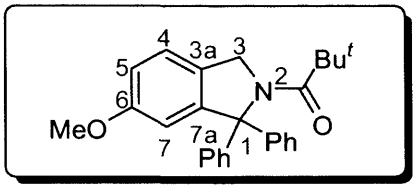
FT–IR: ν_{max} = 2959 (CH), 1615 (C=O), 1511 (aromatic C=C), 1477, 1400, 1358, 1243, 1171, 1023 cm^{-1}.

Anal. calc. for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.42; H, 7.46; N, 4.08%.

Selected crystallographic data: $C_{21}H_{25}NO_3$, FW = 339.42, T = 150(2) K, λ = 0.71073

Å, Orthorhombic, $P2_12_12_1$, a = 5.85700(10) Å, b = 16.4960(4) Å, c = 18.6450(6) Å, α = 90°, β = 90°, γ = 90°, V = 1801.43(8) $Å^3$, Z = 4, $\rho_{calc.}$ = 1.251 Mg/m^3, crystal size = 0.25 × 0.25 × 0.20 mm^3, m = 0.083 mm^{-1}, reflections collected = 4120, independent reflections = 3365, R_{int} = 0.0606, parameters = 231, final R_1 = 0.0504, wR_2 = 0.1003 for I>2σ(I) and R_1 = 0.0699, wR_2 = 0.1090 for all data. Full crystallographic data for this compound have been deposited with the CCDC, reference number 737410, and can be obtained free of charge *via* http://www.ccdc.ac.uk/data_request/cif.

6-Methoxy-1,1-diphenyl-2-pivaloylisoindoline (166)



Yield: 0.47 g (1.22 mmol, 98%).

Mp: 119–121 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.10 (m, 11 H, 2 Ph and H-4), 6.73 (dd, *J* = 2, 8 Hz, 1 H, H-5), 6.37 (d, *J* = 2 Hz, 1 H, H-7), 5.11 (s, 2 H, H-3), 3.56 (s, 3 H, OCH_3), 1.20 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.2 (s, C=O), 160.2 (s, C-6), 147.6 (s, C-7a), 142.7 (s, C-1 of 2 Ph), 128.7 (d, C-3/C-5 of 2 Ph), 128.4 (s, C-3a), 127.9 (d, C-2/C-6 of 2 Ph), 127.15 (d, C-4 of 2 Ph), 123.0 (d, C-4), 114.8 (d, C-7), 110.0 (d, C-5), 81.2 (s, C-1), 55.8 (q, OCH_3), 53.5 (t, C-3), 40.2 [s, $C(CH_3)_3$], 27.88 [q, $C(CH_3)_3$].

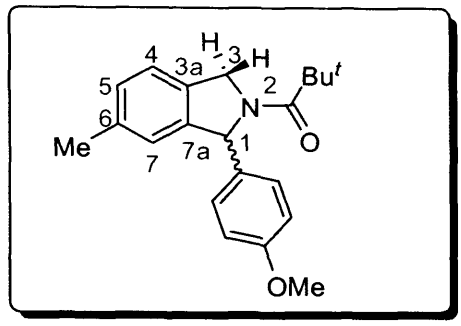
EI–MS: *m/z* (%) = 386 (M^+ + 1, 22), 385 (M^+, 81), 328 (M^+ – ^{t}Bu, 100), 308 (42), 300 (M^+ – ^{t}BuCO, 38), 292 (21), 220 (16).

CI–MS: *m/z* (%) = 386 (MH^+, 100), 328 (M^+ – ^{t}Bu, 3), 303 (19), 284 (5).

HRMS: *m/z* calc. for $C_{26}H_{28}NO_2$ (MH^+), 386.2115; found, 386.2113.

FT–IR: ν_{max} = 2957 (CH), 1638 (C=O), 1599 (aromatic C=C), 1490, 1444, 1351, 1210, 1172 cm^{-1}.

1-(4-Methoxyphenyl)-6-methyl-2-pivaloylisoindoline (167)



Yield: 0.42 g (1.29 mmol, 88%).

Mp: 148–149 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8 Hz, 1 H, H-4), 7.18 d, *J* = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 7.10 (d, *J* = 8 Hz, 1 H, H-5), 6.90 (s, 1 H, H-7), 6.84 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 6.26 (s, 1 H, H-1), 5.21-5.11 (m, 2 H, H-3), 3.78 (s, 3 H, OCH_3), 2.30 (s, 3 H, CH_3), 1.33 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.7 (s, C=O), 159.0 (s, C-4 of 4-methoxyphenyl), 141.5 (s, C-7a), 138.1 (s, C-1 of 4-methoxyphenyl), 136.5 (s, C-6), 133.4 (s, C-3a), 128.9 (d, C-2/C-6 of 4-methoxyphenyl), 128.1 (d, C-7), 124.3 (d, C-4), 122.4 (d, C-5), 114.3 (d, C-3/C-5 of 4-methoxyphenyl), 70.0 (d, C-1), 55.6 (q, OCH_3), 53.8 (t, C-3), 39.7 [s, $C(CH_3)_3$], 28.0 [q, $C(CH_3)_3$], 21.7 (q, CH_3).

EI–MS: *m/z* (%) = 323 (M^+, 4), 266 (M^+ – ^{t}Bu, 3), 238 (M^+ – ^{t}BuCO, 8), 223 (M^+ – ^{t}BuCONH, 13), 208 (9), 194 (6), 165 (8), 130 (7), 77 (14), 57 (^{t}Bu$^+$, 100), 41 (77).

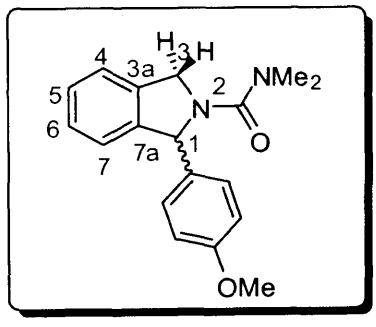
CI–MS: *m/z* (%) = 324 (MH^+, 100), 266 (3), 216 (5).

HRMS: *m/z* calc. for $C_{21}H_{26}NO_2$ (MH^+), 324.1958; found, 324.1953.

FT–IR: ν_{max} = 2958 (CH), 1637 (C=O), 1535 (aromatic C=C), 1357, 1231 cm^{-1}.

Anal. calc. for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79; N, 4.33. Found: C, 77.84; H, 7.83; N, 4.41%.

1-(4-Methoxyphenyl)-2-dimethylaminocarbonylisoindoline (168)



Yield: 0.42 g (1.42 mmol, 89%).

Mp: 111–112 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.21 (m, 5 H, H-4, H-5, H-6 and H-2/H-6 of 4-methoxyphenyl), 7.03 (d, *J* = 8 Hz, 1 H, H-7), 6.83 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 6.37 (d, *J* = 3 Hz, 1 H, H-1), 5.10 (dd, *J* = 3, 14 Hz, 1 H, 1 H of H-3), 4.66 (d, *J* = 14 Hz, 1 H, 1 H of H-3), 3.78 (s, 3 H, OMe), 2.90 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.4 (s, C=O), 159.2 (s, C-4 of 4-methoxyphenyl), 142.2 (s, C-7a), 136.6 (s, C-3a), 136.3 (s, C-1 of 4-methoxyphenyl), 128.8 (d, C-2/C-6 of 4-methoxyphenyl), 128.0 (d, C-4), 127.8 (d, C-7), 123.9 (d, C-6), 122.4 (d, C-5), 114.3 (d, C-3/C-5 of 4-methoxyphenyl), 67.8 (d, C-1), 55.6 (q, OMe), 55.5 (t, C-3), 38.7 [q, $N(CH_3)_2$].

EI–MS: *m/z* (%) = 296 (M^+, 7), 252 ($M^+ - Me_2N$, 11), 224 ($M^+ - Me_2NCO$, 23), 208 (13), 194 (4), 180 (5), 165 (7), 135 (5), 116 (8), 87 (Me_2NCONH^+, 12), 72 (Me_2NCO^+, 100), 44 (22).

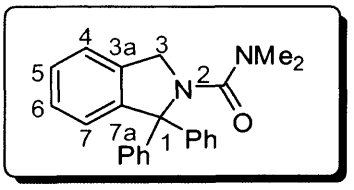
CI–MS: *m/z* (%) = 297 (MH^+, 100), 91 (14).

HRMS: *m/z* calc. for $C_{18}H_{21}N_2O_2$ (MH^+), 297.1598; found, 297.1598.

FT–IR: ν_{max} = 2959 (CH), 1613 (C=O), 1510 (aromatic C=C), 1371, 1357, 1243, 1028 cm^{-1}.

Anal. calc. for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.80; H, 6.78; N, 9.30%.

2-Dimethylaminocarbonyl-1,1-diphenylisoindoline (169)



Yield: 0.43 g (1.26 mmol, 91%).

Mp: 161–163 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.09 (m, 13 H, 2 Ph, H-4, H-5 and H-6), 6.90 (d, *J* = 8 Hz, 1 H, H-7), 4.90 (s, 2 H, H-3), 2.61 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.7 (s, C=O), 146.1 (s, C-7a), 142.3 (s, C-1 of 2 Ph), 134.7 (s, C-3a), 127.6 (d, C-2/C-6 of 2 Ph), 126.7 (d, C-4), 126.5 (d, C-3/C-5 of 2 Ph), 126.3 (d, C-7), 125.7 (d, C-4 of 2 Ph), 123.4 (d, C-6), 120.9 (d, C-5), 80.0 (s, C-1), 52.5 (t, C-3), 38.0 [q, $N(CH_3)_2$].

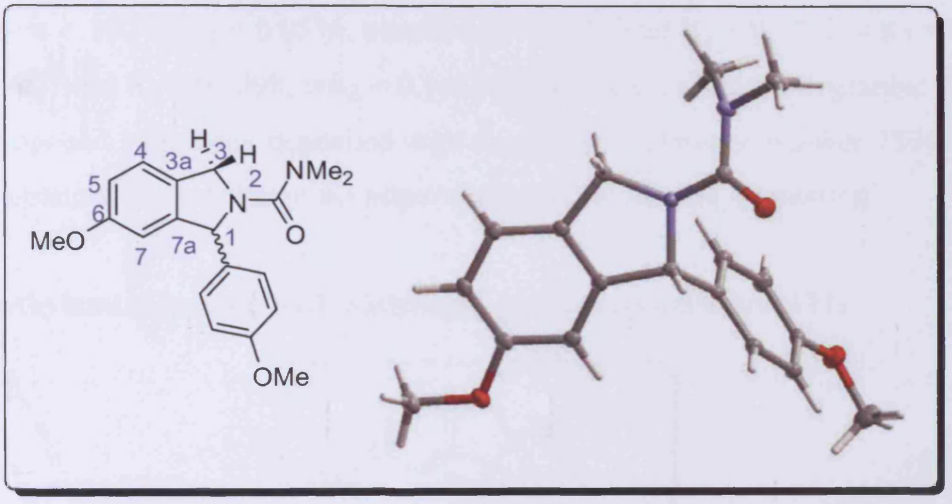
EI–MS: *m/z* (%) = 342 (M^+, 10), 265 (M^+ – Ph, 22), 254 (M^+ – Me_2NCONH_2, 24), 239 (9), 193 (M^+ – Ph – Me_2NCO, 7), 178 (M^+ – Ph – Me_2NCONH, 15), 165 (M^+ – Ph – $Me_2NCONCH_2$, 20), 72 (Me_2NCO^+, 100), 42 (10).

CI–MS: *m/z* (%) = 343 (MH^+, 100), 272 (10), 106 (12), 89 (16), 63 (17), 52 (89), 46 ($Me_2NH_2^+$, 47).

HRMS: *m/z* calc. for $C_{23}H_{23}N_2O$ (MH^+), 343.1805; found, 343.1809.

FT–IR: ν_{max} = 2957 (CH), 1617 (C=O), 1510 (aromatic C=C), 1371, 1358, 1242, 1173, 1037 cm^{-1}.

2-Dimethylaminocarbonyl-6-methoxy-1-(4-methoxyphenyl)isoindoline (170)



Yield: 0.43 g (1.32 mmol, 91%).

Mp: 98–100°C.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.12 (d, *J* = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 7.05 (d, *J* = 8 Hz, 1 H, H-4), 6.74–6.71 (m, 3 H, H-5 and H-3/H-5 of 4-methoxyphenyl), 6.42 (d, *J* = 2 Hz, 1 H, H-7), 6.23 (d, *J* = 3 Hz, 1 H, H-1), 4.90 (dd, *J* = 3, 13 Hz, 1 H, 1 H of H-3), 4.46 (d, *J* = 13 Hz, 1 H, 1 H of H-3), 3.67 (s, 3 H, OCH_3), 3.61 (s, 3 H, OCH_3), 2.77 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.4 (s, C=O), 160.0 (s, C-6), 159.3 (s, C-4 of 4-methoxyphenyl), 143.6 (s, C-7a), 136.2 (s, C-1 of 4-methoxyphenyl), 129.7 (d, C-2/C-6 of 4-methoxyphenyl), 129.1 (s, C-3a), 123.5 (d, C-4), 115.0 (d, C-7), 114.7 (d, C-3/C-5 of 4-methoxyphenyl), 108.9 (d, C-5), 67.9 (d, C-1), 55.8 (q, OCH_3), 55.7 (q, OCH_3), 55.0 (t, C-3), 38.7 [q, $N(CH_3)_2$].

EI–MS: *m/z* (%) = 326 (M^+, 3), 282 (M^+ – Me_2N, 5), 254 (M^+ – Me_2NCO, 10), 238 (M^+ – Me_2NCONH_2, 16), 218 (5), 146 (4), 72 (Me_2NCO^+, 100), 44 (10).

CI–MS: *m/z* (%) = 327 (MH^+, 100), 105 (5), 91 (6), 52 (8), 46 ($Me_2NH_2^+$, 13).

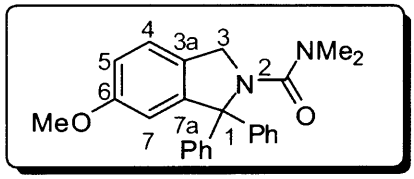
HRMS: *m/z* calc. for $C_{19}H_{23}N_2O_3$ (MH^+), 327.1703; found, 327.1702.

FT–IR: ν_{max} = 2931 (CH), 1616 (C=O), 1511 (aromatic C=C), 1400, 1370, 1251, 1023 cm^{-1}.

Anal. calc. for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 69.97; H, 6.73; N, 5.42%.

Selected crystallographic data: $C_{19}H_{22}N_2O_3$, FW = 326.39, T = 150(2) K, λ = 0.71073 Å, Monoclinic, $P2_1/c$, a = 13.9310(5) Å, b = 6.0890(2) Å, c = 20.0590(8) Å, α = 90°, β = 91.349(2)°, γ = 90°, V = 1701.05(11) $Å^3$, Z = 4, $\rho_{calc.}$ = 1.274 Mg/m^3, crystal size = 0.40 × 0.20 × 0.10 mm^3, m = 0.087 mm^{-1}, reflections collected = 6476, independent reflections = 3877, R_{int} = 0.0534, parameters = 222, final R_1 = 0.0571, wR_2 = 0.1237 for I>2σ(I) and R_1 = 0.1098, wR_2 = 0.1460 for all data. Full crystallographic data for this compound have been deposited with the CCDC, reference number 737418, and can be obtained free of charge *via* http://www.ccdc.ac.uk/data_request/cif.

2-Dimethylaminocarbonyl-1,1-diphenyl-6-methoxyisoindoline (171)



Yield: 0.42 g (1.13 mmol, 88%).

Mp: 157–158 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.11 (m, 10 H, 2 Ph), 7.08 (d, *J* = 8 Hz, 1 H, H-4), 6.70 (dd, *J* = 2, 8 Hz, 1 H, H-5), 6.42 (d, *J* = 2 Hz, 1 H, H-7), 4.85 (s, 2 H, H-3), 3.58 (s, OCH_3), 2.61 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.0 (s, C=O), 159.9 (s, C-6), 148.9 (s, C-7a), 143.6 (s, C-1 of 2 Ph), 129.3 (d, C-3/C-5 of 2 Ph), 128.2 (s, C-3a), 128.0 (d, C-2/C-6 of 2 Ph), 127.2 (d, C-4 of 2 Ph), 123.1 (d, C-4), 114.3 (d, C-5), 109.9 (d, C-7), 79.5 (s, C-1), 55.8 (q, OCH_3), 53.6 (t, C-3), 39.5 [q, $N(CH_3)_2$].

EI–MS: *m/z* (%) = 372 (M^+, 20), 295 (M^+ – Ph, 6), 284 (M^+ – Me_2NCONH_2, 41), 165 (7), 91 (8), 88 (19), 72 (Me_2NCO^+, 100), 42 (22).

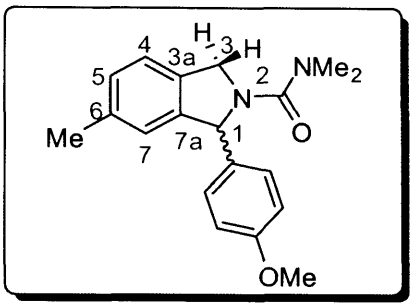
CI–MS: *m/z* (%) = 373 (MH^+, 100).

HRMS: *m/z* calc. for $C_{24}H_{25}N_2O_2$ (MH^+), 373.1911; found, 373.1911.

FT–IR: ν_{max} = 2997 (CH), 1617 (C=O), 1510 (aromatic C=C), 1371, 1242, 1172, 1029 cm^{-1}.

Anal. calc. for $C_{24}H_{24}N_2O_2$: C, 77.39; H, 6.49; N, 7.52. Found: C, 77.37; H, 6.51; N, 7.47%.

2-Dimethylaminocarbonyl-1-(4-methoxyphenyl)-6-methylisoindoline (172)



Yield: 0.43 g (1.39 mmol, 91%).

Mp: 125–126 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.13 (d, *J* = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 7.05 (d, *J* = 8 Hz, 1 H, H-4), 6.97 (d, *J* = 8 Hz, 1 H, H-5), 6.75–6.73 (m, 3 H, H-7 and H-3/H-5 of 4-methoxyphenyl), 6.22 (d, *J* = 2 Hz, 1 H, H-1), 4.94 (dd, *J* = 2, 14 Hz, 1 H, 1 H of H-3), 4.50 (d, *J* = 14 Hz, 1 H, 1 H of H-3), 3.68 (s, 3 H, OCH_3), 2.78 [s, 6 H, $N(CH_3)_2$], 2.18 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.4 (s, C=O), 159.2 (s, C-4 of 4-methoxyphenyl), 142.3 (s, C-7a), 137.7 (s, C-6), 136.4 (s, C-1 of 4-methoxyphenyl), 133.6 (s, C-3a), 128.5 (d, C-2/C-6 of 4-methoxyphenyl), 128.2 (d, C-7), 124.3 (d, C-4), 122.2 (d, C-5), 114.3 (d, C-3/C-5 of 4-methoxyphenyl), 67.8 (d, C-1), 55.6 (q, OCH_3), 55.3 (t, C-3), 38.7 [q, $N(CH_3)_2$], 15.7 (q, CH_3).

EI–MS: *m/z* (%) = 310 (M^+, 5), 266 ($M^+ - Me_2N$, 14), 238 ($M^+ - Me_2NCO$, 22), 222 ($M^+ - Me_2NCONH_2$, 19), 165 (13), 130 (12), 72 (Me_2NCO^+, 100), 44 (15), 42 (23).

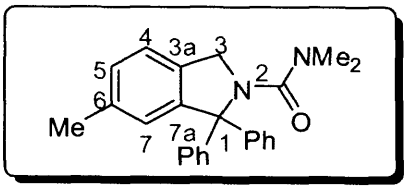
CI–MS: *m/z* (%) = 311 (MH^+, 100), 52 (22).

HRMS: *m/z* calc. for $C_{19}H_{23}N_2O_2$ (MH^+), 311.1754; found, 311.1749.

FT–IR: ν_{max} = 2958 (CH), 1616 (C=O), 1511 (aromatic C=C), 1371, 1358, 1243, 1029 cm^{-1}.

Anal. calc. for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03. Found: C, 73.50; H, 7.15; N, 9.01%.

2-Dimethylaminocarbonyl-1,1-diphenyl-6-methylisoindoline (173)



Yield: 0.42 g (1.18 mmol, 88%).

Mp: 158–160 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.13 (m, 10 H, 2 Ph), 7.07 (d, *J* = 8 Hz, 1 H, H-4), 6.95 (d, *J* = 8 Hz, 1 H, H-5), 6.72 (s, 1 H, H-7), 3.25 (s, 2 H, H-3), 2.61 [s, 6 H, $N(CH_3)_2$], 2.15 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.9 (s, C=O), 147.6 (s, C-7a), 143.8 (s, C-1 of 2 Ph), 137.9 (s, C-6), 133.1 (s, C-3a), 129.0 (d, C-3/C-5 of 2 Ph), 128.8 (d, C-7), 127.9 (d, C-2/C-6 of 2 Ph), 127.1 (d, C-4 of 2 Ph), 125.2 (d, C-4), 122.1 (d, C-5), 79.4 (s, C-1), 53.8 (t, C-3), 39.5 [q, $N(CH_3)_2$], 21.9 (q, CH_3).

EI–MS: *m/z* (%) = 356 (M^+, 7), 279 (M^+ – Ph, 13), 268 (M^+ – Me_2NCONH_2, 31), 253 (M^+ – $Me_2NCONHCH_2$, 7), 165 (13), 72 (Me_2NCO^+, 100), 42 (15).

CI–MS: *m/z* (%) = 357 (MH^+, 100), 193 (12), 106 (14), 89 (16), 46 ($CONH_2^+$, 30).

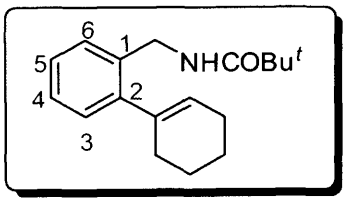
HRMS: *m/z* calc. for $C_{24}H_{25}N_2O$ (MH^+), 357.1961; found, 357.1960.

FT–IR: ν_{max} = 2852 (CH), 1619 (C=O), 1520 (aromatic C=C), 1363, 1340, 1218 cm^{-1}.

7.28 Synthesis of *N*-(2-(cyclohexenyl)pivalamides 174 and 175

The procedure was identical with that described in Section 7.26 except that compounds **62** and **73** (0.50 g) were used as starting materials instead of **57**. The reaction mixtures were worked-up and the residues obtained were subjected to flash column chromatography (silica gel; Et_2O–hexane, 1:3) to give the pure products **174** and **175** as white solids.

N-(2-Cyclohexen-1-ylbenzyl)pivalamide (174)



Yield: 0.38 g (1.42 mmol, 82%).

Mp: 118–119 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.03 (m, 4 H, H-3, H-4, H-5 and H-6), 5.78 (br, exch., 1 H, NH), 5.52 (m, 1 H, H-2 of cyclohexenyl), 4.34 (d, *J* = 5 Hz, 2 H, CH_2), 2.15–2.07 (m, 4 H, H-3 and H-6 of cyclohexenyl), 1.71–1.58 (m, 4 H, H-4 and H-5 of cyclohexenyl), 1.13 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.4 (s, C=O), 144.8 (s, C-1 of cyclohexenyl), 138.4 (s, C-1), 135.5 (s, C-2), 129.3 (d, C-5), 128.9 (d, C-6), 127.7 (d, C-3), 127.4 (d, C-4), 127.2 (d, C-2 of cyclohexenyl), 42.2 (t, CH_2NH), 39.1 [s, $C(CH_3)_3$], 31.0 (t, C-6 of cyclohexenyl), 28.0 [q, $C(CH_3)_3$], 25.8 (t, C-3 of cyclohexenyl), 23.4 (t, C-5 of cyclohexenyl), 22.4 (t, C-4 of cyclohexenyl).

EI–MS: *m/z* (%) = 271 (M^+, 4), 186 (M^+ – ^{t}BuCO, 8), 171 (M^+ – ^{t}BuCONH, 17), 170 (M^+ – ^{t}BuCONH$_2$, 56), 157 (M^+ – ^{t}BuCONHCH$_2$, 11), 142 (50), 128 (32), 115 (26), 102 (12), 91 ($PhCH_2^+$, 11), 77 (5), 57 (^{t}Bu$^+$, 100), 41 (71).

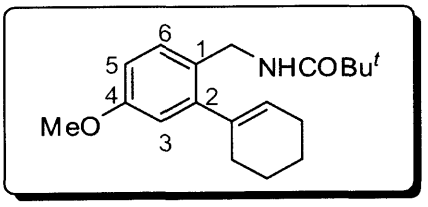
CI–MS: *m/z* (%) = 543 (2 M^+ + 1, 4), 289 (M + NH_4^+, 6), 272 (MH^+, 100), 170 (15), 119 (17), 102 (9), 52 (24).

HRMS: *m/z* calc. for $C_{18}H_{26}NO$ (MH^+), 272.2009; found, 272.2012.

FT–IR: ν_{max} = 3328 (NH), 2921 (CH), 1638 (C=O), 1512 (aromatic C=C), 1540, 1368, 1210, 1003 cm^{-1}.

Anal. calc. for $C_{18}H_{25}NO$: C, 79.66; H, 9.28; N, 5.16. Found: C, 79.73; H, 9.33; N, 5.09%.

N-(2-Cyclohexen-1-yl-4-methoxybenzyl)pivalamide (175)



Yield: 0.39 g (1.30 mmol, 83%).

Mp: 99–100 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.09 (d, *J* = 8 Hz, 1 H, H-6), 6.68 (dd, *J* = 2, 8 Hz, 1 H, H-5), 6.58 (d, *J* = 2 Hz, 1 H, H-3), 5.70 (br, exch., 1 H, NH), 5.52 (m, 1 H, H-2 of cyclohexenyl), 4.26 (d, *J* = 5 Hz, 2 H, CH_2), 3.71 (s, 3 H, OCH_3), 2.15–2.06 (m, 4 H, H-3 and H-6 of cyclohexenyl), 1.71–1.58 (m, 4 H, H-4 and H-5 of cyclohexenyl), 1.11 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.2 (s, C=O), 159.1 (s, C-4), 146.2 (s, C-1 of cyclohexenyl), 138.5 (s, C-2), 130.5 (d, C-6), 127.7 (s, C-1), 127.1 (d, C-2 of cyclohexenyl), 114.7 (d, C-5), 112.7 (d, C-3), 55.7 (q, OCH_3), 41.8 (t, CH_2NH), 39.0 [s, $C(CH_3)_3$], 30.9 (t, C-6 of cyclohexenyl), 28.0 [q, $C(CH_3)_3$], 25.7 (t, C-3 of cyclohexenyl), 23.4 (t, C-5 of cyclohexenyl), 21.9 (t, C-4 of cyclohexenyl).

EI–MS: *m/z* (%) = 301 (M^+, 2), 200 (22), 172 (13), 159 (9), 128 (6), 115 (8), 77 (5), 57 ($^tBu^+$, 100), 41 (93).

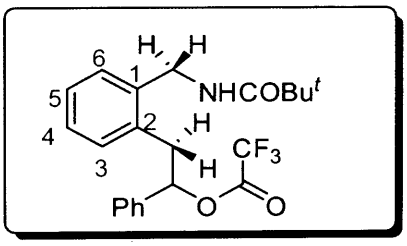
CI–MS: *m/z* (%) = 319 ($M + NH_4^+$, 3), 302 (MH^+, 100), 200 (11), 119 (17), 102 (12), 52 (15).

HRMS: *m/z* calc. for $C_{19}H_{28}NO_2$ (MH^+), 302.2115; found, 302.2115.

FT–IR: ν_{max} = 3347 (NH), 2940 (CH), 1647 (C=O), 1505 (aromatic C=C), 1492, 1330, 1207, 1029 cm^{-1}.

7.29 Synthesis of *N*-(2-(2-phenyl-2-trifluoroacetoxyethyl)benzyl)pivalamide (188)

Trifluoroacetic anhydride (0.5 mL) was added to a stirred solution of *N*-(2-(2-hydroxy-2-phenylethyl)benzyl)pivalamide (**99**; 0.50 g, 1.61 mmol) in DCM (10 mL) at room temperature. The mixture was stirred for 5 min at room temperature, at which time TLC showed the formation of a pure product. The reaction mixture was quenched with H_2O (10 mL). The organic layer was separated, washed with aq. sat. $NaHCO_3$ (10 mL) and H_2O (2 x 10 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue obtained was subjected to flash column chromatography (silica gel; Et_2O–hexane, 1:3) to give pure **188** (0.63 g, 1.55 mmol, 97%) as a white solid.



Mp: 127–128 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.07 (m, 9 H, H-3, H-4, H-5, H-6 and Ph), 6.01 (dd, *J* = 6, 8 Hz, 1 H, CH), 5.80 (br app. t, exch., 1 H, NH), 4.38 (dd, *J* = 6, 15 Hz, 1 H, 1 H of CH_2NH), 4.29 (dd, *J* = 6, 15 Hz, 1 H, 1 H of CH_2NH), 3.24 (dd, *J* = 8,

15 Hz, 1 H, 1 H of CH_2CH), 3.19 (dd, J = 6, 15 Hz, 1 H, 1 H of CH_2CH), 1.13 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.7 (s, C=O), 156.9 (q, J = 42 Hz, CF_3C=O), 137. 8 (s, C-1), 137.1 (s, C-1 of Ph), 134.5 (s, C-2), 131.6 (d, C-3), 129.9 (d, C-4), 129.5 (d, C-5), 129.4 (d, C-6), 129.3 (d, C-3/C-5 of Ph), 128.3 (d, C-4 of Ph), 126.7 (d, C-2/C-6 of Ph), 114.8 (q, J = 284 Hz, CF_3), 80.9 (d, CH), 41.5 (t, CH_2NH), 39.9 (t, CH_2CH), 39.1 [s, $C(CH_3)_3$], 27.9 [q, $C(CH_3)_3$].

EI–MS: *m/z* (%) = 407 (M^+, 4), 310 ($M^+ - CF_3CO$, 4), 294 ($M^+ - CF_3CO_2$, 85), 293 ($M^+ - CF_3CO_2H$, 100), 278 (3).

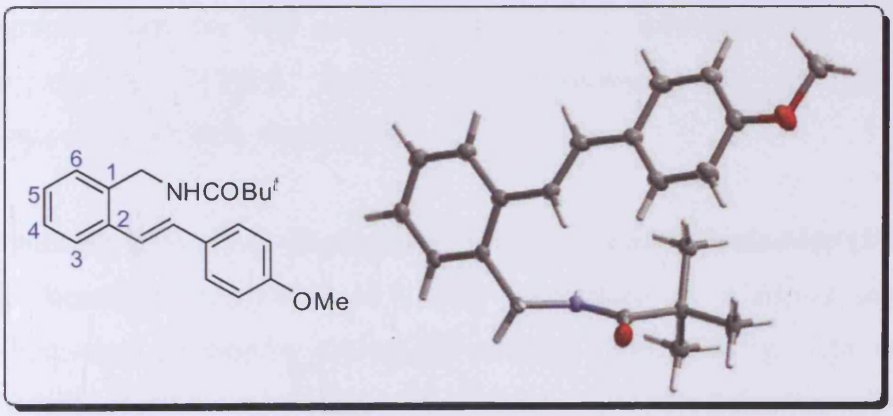
CI–MS: *m/z* (%) = 425 ($M + NH_4^+$, 6), 408 (MH^+, 5), 329 (11), 312 (42), 294 ($M^+ - CF_3CO_2$, 100), 192 (10), 119 (19), 52 (16).

HRMS: *m/z* calc. for $C_{22}H_{25}F_3NO_3$ (MH^+), 408.1781; found, 408.1789.

FT–IR: ν_{max} = 3313 (NH), 2933 (CH), 1635 (C=O), 1531 (aromatic C=C), 1462, 1227, 1030, 1020, 1000 cm^{-1}.

7.30 Synthesis of (*E*)-*N*-(2-(4-methoxystyryl)benzyl)pivalamide (189)

The procedure was identical with that described in Section 7.29 except that *N*-(2-(2-hydroxy-2-(4-methoxyphenyl)ethyl)benzyl)pivalamide (**100**; 0.50 g, 1.47 mmol) was used as starting material instead of **99**. The reaction mixture was worked-up and the residue obtained subjected to flash column chromatography (silica gel; Et_2O–hexane, 1:3) to give the pure product **100** (0.46 g, 1.35 mmol, 97%) as a white solid.



Mp: 113–115 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, J = 8 Hz, 1 H, H-3), 7.37 (d, J = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 7.24 (app. dt, J = 2, 8 Hz, 1 H, H-4), 7.18–7.12 (m,

2 H, H-5 and H-6), 7.06 (d, J = 16 Hz, 1 H, CH), 6.88 (d, J = 16 Hz, 1 H, CH), 6.80 (d, J = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 5.67 (br t, exch., 1 H, NH), 4.50 (d, J = 5 Hz, 2 H, CH_2), 3.74 (s, 3 H, OCH_3), 1.05 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.1 (s, C=O), 159.9 (s, C-4 of 4-methoxyphenyl), 137.4 (s, C-1), 135.6 (s, C-2), 130.9 (d, C-5), 130.4 (s, C-1 of 4-methoxyphenyl), 130.2 (d, C-6), 128.7 (d, C-4), 128.4 (d, C-2/C-6 of 4-methoxyphenyl), 127.7 (d, C-3), 126.2 (d, CH), 123.5 (d, CH), 114.5 (d, C-3/C-5 of 4-methoxyphenyl), 55.7 (q, OCH_3), 42.7 (t, CH_2), 39.1 [s, $C(CH_3)_3$], 27.9 [q, $C(CH_3)_3$].

EI–MS: *m/z* (%) = 323 (M^+, 10), 222 ($M^+ - {}^tBuCONH_2$, 88), 207 ($M^+ - {}^tBuCONH_2$ – Me, 21), 191 ($M^+ - {}^tBuCONH_2$ – OMe, 22), 165 (15), 115 (13), 57 ($^tBu^+$, 100).

CI–MS: *m/z* (%) = 341 ($M + NH_4^+$, 12), 324 (MH^+, 100), 222 ($M^+ - {}^tBuCONH_2$, 7), 119 (18), 52 (17).

HRMS: *m/z* calc. for $C_{21}H_{29}N_2O_2$ ($M + NH_4^+$), 341.2224; found, 341.2225.

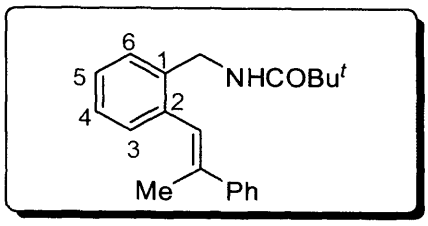
FT–IR: ν_{max} = 2961 (CH), 1628 (C=O), 1512 (aromatic C=C), 1453, 1225, 1037 cm^{-1}.

Anal. calc. for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79; N, 4.33. Found: C, 77.89; H, 7.81; N, 4.30%.

Selected crystallographic data: $C_{21}H_{25}NO_2$, FW = 323.42, T = 150(2) K, λ = 0.71073 Å, Triclinic, P1, a = 5.4050(5) Å, b = 10.0960(9) Å, c = 16.5930(18) Å, α = 91.891(4)°, β = 98.280(4)°, γ = 95.537(5)°, V = 890.83(15) $Å^3$, Z = 2, $\rho_{calc.}$ = 1.206 Mg/m^3, crystal size = 0.36 × 0.20 × 0.20 mm^3, m = 0.077 mm^{-1}, reflections collected = 5471, independent reflections = 3957, R_{int} = 0.0471, parameters = 221, final R_1 = 0.0847, wR_2 = 0.1573 for $I>2\sigma(I)$ and R_1 = 0.1734, wR_2 = 0.1886 for all data. Full crystallographic data for this compound have been deposited with the CCDC, reference number 737414, and can be obtained free of charge *via* http://www.ccdc.ac.uk/data_request/cif.

7.31 Synthesis of (*E*)-*N*-(2-(2-phenylprop-1-enyl)benzyl)pivalamide (190)

Trifluoroacetic anhydride (0.5 mL) was added to a stirred solution of *N*-(2-(2-(hydroxy-2-phenylpropyl)benzyl)pivalamide (**101**; 0.50 g, 1.54 mmol) in DCM (10 mL) at room temperature. The mixture was stirred for 1 h before being worked-up and the residue obtained was then purified by column chromatography (silica gel; Et_2O–hexane, 1:3) to give the pure product **190** (0.34 g, 1.11 mmol, 72%) as a white solid.



Mp: 85–86 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 8 Hz, 1 H, H-3), 7.31-7.18 (m, 8 H, H-4, H-5, H-6 and Ph), 6.79 (s, 1 H, CH), 5.76 (br t, exch., 1 H, NH), 4.38 (d, *J* = 6 Hz, 2 H, CH_2), 2.05 (s, 3 H, CH_3), 1.06 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.4 (s, C=O), 143.2 (s, C-1), 139.0 (s, C-2), 137.7 (s, C-1 of Ph), 136.9 (s, *C*-CH_3), 130.5 (d, C-5), 129.0 (d, C-6), 128.8 (d, C-3/C-5 of Ph), 128.5 (d, C-4), 128.3 (d, C-3), 128.2 (d, C-4 of Ph), 127.4 (d, C-2/C-6 of Ph), 126.3 (d, CH), 42.5 (t, CH_2), 39.1 [s, *C*$(CH_3)_3$], 28.0 [q, C(*C*$H_3)_3$], 17.6 (q, CH_3).

EI–MS: *m/z* (%) = 307 (M^+, 7), 222 (M^+ – ^{t}BuCO, 4), 206 (M^+ – ^{t}BuCONH$_2$, 38), 191 (M^+ – ^{t}BuCONH$_2$ – Me, 18), 178 (8), 165 (6), 128 (15), 115 (8), 91 (22), 77 (Ph^+, 8), 57 (^{t}Bu$^+$, 100), 41 (58).

CI–MS: *m/z* (%) = 325 (M + NH_4^+, 23), 308 (MH^+, 100), 206 (6), 119 (32), 102 (22), 52 (60).

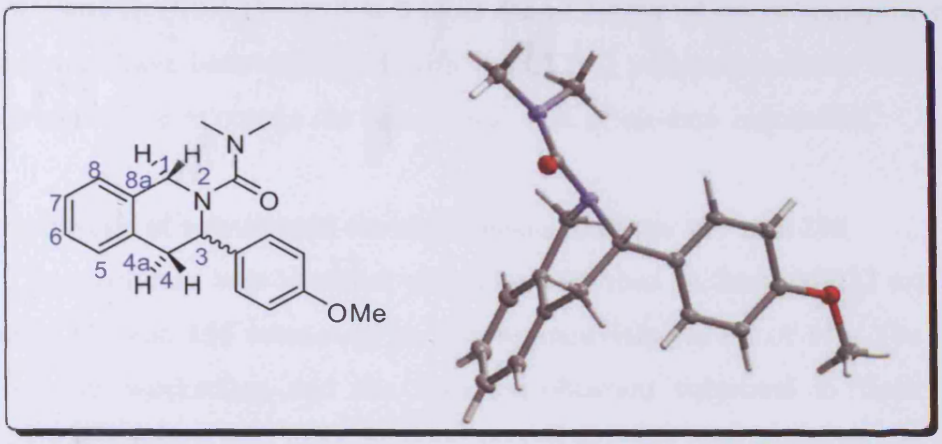
HRMS: *m/z* calc. for $C_{21}H_{26}NO$ (MH^+), 308.2009; found, 308.2006.

FT–IR: ν_{max} = 3329 (NH), 2921 (CH), 1638 (C=O), 1539 (aromatic C=C), 1357, 1210 cm^{-1}.

7.32 Synthesis of 3-(4-methoxyphenyl)-2-dimethylaminocarbonyl-1,2,3,4-tetrahydroisoquinoline (198) *via* cyclization *N'*-(2-(2-hydroxy-2-(4-methoxyphenyl)ethyl)benzyl)-*N*,*N*-dimethylurea (153)

Trifluoroacetic anhydride (0.5 mL) was added to a stirred solution of *N'*-(2-(2-hydroxy-2-(4-methoxyphenyl)ethyl)benzyl)-*N*,*N*-dimethylurea (**153**; 0.50 g, 1.52 mmol) in DCM (10 mL) at room temperature. The mixture was stirred for 5 min at room temperature, by which time TLC showed the formation of a pure product. The reaction mixture was quenched with H_2O (10 mL). The organic layer was separated, washed with aq. sat. $NaHCO_3$ (10 mL) and H_2O (2 x 10 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue obtained was subjected to flash

column chromatography (silica gel; Et_2O–hexane, 1:3) to give pure **198** (0.45 g, 1.45 mmol, 95%) as a white solid.



Mp: 102–103 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.07 (m, 3 H, H-6, H-7 and H-8), 7.04 (d, *J* = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 6.90 (d, *J* = 8 Hz, 1 H, H-5), 6.69 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 5.18 (dd, *J* = 3, 6 Hz, 1 H, H-3), 4.34 (d, *J* = 16 Hz, 1 H, 1 H of H-1), 4.00 (d, *J* = 16 Hz, 1 H, 1 H of H-1), 3.65 (s, 3 H, OCH_3), 3.36 (dd, *J* = 6, 16 Hz, 1 H, 1 H of H-4), 3.13 (dd, *J* = 3, 16 Hz, 1 H, 1 H of H-4), 2.80 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.2 (s, C=O), 158.9 (s, C-4 of 4-methoxyphenyl), 134.3 (s, C-4a), 133.1 (s, C-8a), 129.1 (s, C-1 of 4-methoxyphenyl), 128.7 (d, C-8), 128.4 (d, C-2/C-6 of 4-methoxyphenyl), 127.2 (d, C-5), 126.4 (d, C-6), 126.2 (d, C-7), 114.1 (d, C-3/C-5 of 4-methoxyphenyl), 55.6 (q, OCH_3), 54.0 (d, C-3), 46.3 (t, C-1), 39.0 [q, $N(CH_3)_2$], 32.2 (t, C-4).

EI–MS: *m/z* (%) = 310 (M^+, 12), 266 ($M^+ - Me_2N$, 9), 238 ($M^+ - Me_2NCO$, 32), 222 ($M^+ - Me_2NCONH_2$, 62), 202 (15), 189 (23), 178 (11), 165 (13), 121 (31), 104 ($C_6H_4CH_2N^+$, 100), 91 ($PhCH_2^+$, 17), 72 (Me_2NCO^+, 93), 44 (17).

CI–MS: *m/z* (%) = 311 (MH^+, 100), 89 (17), 52 (33), 46 (28).

HRMS: *m/z* calc. for $C_{19}H_{23}N_2O_2$ (MH^+), 311.1754; found, 311.1751.

FT–IR: ν_{max} = 2958 (CH), 1618 (C=O), 1510 (aromatic C=C), 1399, 1370, 1348, 1242, 1173, 1033 cm^{-1}.

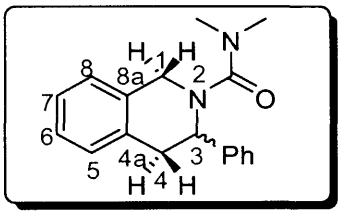
Selected crystallographic data: $C_{19}H_{22}N_2O_2$, FW = 310.39, T = 150(2) K, λ = 0.71073 Å, Monoclinic, $P2_1/n$, a = 13.0240(9) Å, b = 8.9900(7) Å, c = 15.2990(13) Å, α = 90 °, β = 112.974(3)°, γ = 90°, V = 1649.2(2) $Å^3$, Z = 4, $\rho_{calc.}$ = 1.250 Mg/m^3, crystal size

= 0.40 × 0.20 × 0.16 mm^3, m = 0.082 mm^{-1}, reflections collected = 6302, independent reflections = 3737, R_{int} = 0.0516, parameters = 211, final R_1 = 0.0658, wR_2 = 0.1379 for I>2σ(I) and R_1 = 0.1237, wR_2 = 0.1613 for all data. Full crystallographic data for this compound have been deposited with the CCDC, reference number 737417, and can be obtained free of charge *via* http://www.ccdc.ac.uk/data_request/cif.

7.33 Synthesis of substituted tetrahydroisoquinolines 199 and 200

The procedure was identical with that described in Section 7.32 except that compounds **154** and **155** were used as starting materials instead of **153**. The reaction mixtures were worked-up and the residues obtained subjected to flash column chromatography (silica gel; Et_2O–hexane, 1:3) to give the pure products **199** and **200** as white solids.

3-Phenyl-2-dimethylaminocarbonyl-1,2,3,4-tetrahydroisoquinoline (199)



Yield: 0.44 g (1.57 mmol, 94%).

Mp: 96–98 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.08 (m, 9 H, H-5, H-6, H-7, H-8 and Ph), 4.78 (dd, *J* = 4, 9 Hz, 1 H, H-3), 4.31 (d, *J* = 14 Hz, 1 H, 1 H of H-1), 4.21 (d, *J* = 14 Hz, 1 H, 1 H of H-1), 2.96 (dd, *J* = 9, 14 Hz, 1 H, 1 H of H-4), 2.83 (dd, *J* = 4, 14 Hz, 1 H, 1 H of H-4), 2.72 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8 (s, C=O), 144.5 (s, C-4a), 137.9 (s, C-8a), 137.2 (s, C-1 of Ph), 130.0 (d, C-8), 129.6 (d, C-4 of Ph), 129.3 (d, C-3/C-5 of Ph), 128.9 (d, C-5), 128.2 (d, C-6), 127.5 (d, C-7), 126.9 (d, C-2/C-6 of Ph), 76.3 (d, C-3), 43.5 (t, C-1), 42.6 (t, C-4), 38.1 [q, $N(CH_3)_2$].

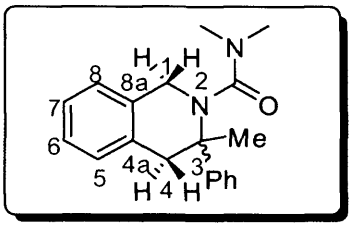
EI–MS: *m/z* (%) = 280 (M^+, 2), 208 (M^+ – Me_2NCO, 4), 192 (44), 177 (6), 148 (7), 120 (18), 104 ($PhCHN^+$, 100), 91 ($PhCH_2^+$, 25), 77 (Ph^+, 61), 72 (Me_2NCO^+, 66), 44 (26).

CI–MS: *m/z* (%) = 299 (M + NH_4^+, 62), 281 (MH^+, 72), 271 (9), 193 (22), 179 (15), 118 (16), 106 (32), 89 (36), 72 (Me_2NCO^+, 7), 63 (12), 46 (100).

HRMS: *m/z* calc. for $C_{18}H_{21}N_2O$ (MH^+), 281.1648; found, 281.1647.

FT–IR: ν_{max} = 2935 (CH), 1636 (C=O), 1523 (aromatic C=C), 1512, 1455, 1203, 1174, 1037 cm^{-1}.

3-Methyl-3-phenyl-2-dimethylaminocarbonyl-1,2,3,4-tetrahydroisoquinoline (200)



Yield: 0.43 g (1.46 mmol, 91%).

Mp: 122–124 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.04 (m, 8 H, H-6, H-7, H-8 and Ph), 6.89 (d, *J* = 8 Hz, 1 H, H-5), 4.28 (d, *J* = 16 Hz, 1 H, 1 H of H-1), 4.14 (d, *J* = 16 Hz, 1 H, 1 H of H-1), 3.42 (d, *J* = 16 Hz, 1 H, 1 H of H-4), 3.23 (d, *J* = 16 Hz, 1 H, 1 H of H-4), 2.82 [s, 6 H, $N(CH_3)_2$], 1.59 (s, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.6 (s, C=O), 147.7 (s, C-1 of Ph), 135.6 (s, C-4a), 134.1 (s, C-8a), 129.4 (d, C-5), 128.8 (d, C-3/C-5 of Ph), 127.9 (d, C-6), 127.1 (d, C-7), 126.5 (d, C-4 of Ph), 125.6 (d, C-8), 125.5 (d, C-2/C-6 of Ph), 59.4 (s, C-3), 49.8 (t, C-4), 43.6 (t, C-1), 39.8 [q, $N(CH_3)_2$], 28.1 (q, CH_3).

EI–MS: *m/z* (%) = 294 (M^+, 22), 279 (M^+ – Me, 24), 222 (M^+ – Me_2NCO, 52), 206 (M^+ – Me_2NCONH_2, 100).

CI–MS: *m/z* (%) = 295 (MH^+, 100), 222 (M^+ – Me_2NCO, 7), 193 (8), 89 (12), 52 (28), 46 (52).

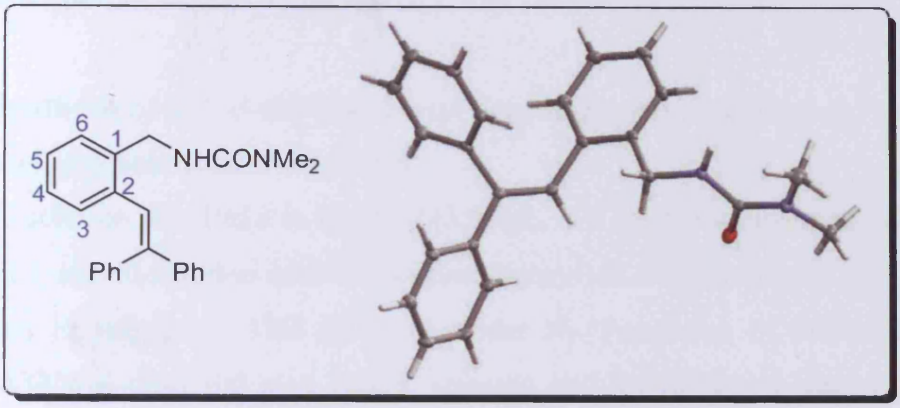
HRMS: *m/z* calc. for $C_{19}H_{23}N_2O$ (MH^+), 295.1805; found, 295.1807.

FT–IR: ν_{max} = 2973 (CH), 1645 (C=O), 1522 (aromatic C=C), 1492, 1381, 1361, 1174, 1107 cm^{-1}.

7.34 Synthesis of *N'*-(2-(2,2-diphenylvinyl)benzyl)-*N,N*-dimethylurea (201)

The procedure was identical with that described in Section 7.32 except that compound **156** was used as starting material instead of **153**. The reaction mixture was worked-up and the residue obtained subjected to flash column chromatography (silica

gel; Et_2O–hexane, 1:3) to give the pure product **201** (0.45 g, 1.26 mmol, 95%) as a white solid.



Mp: 106–108 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.05 (m, 13 H, H-5, H-6, CH and 2 Ph), 6.87 (app. t, *J* = 8 Hz, 1 H, H-4), 6.83 (t, *J* = 6 Hz, exch., 1 H, NH), 6.71 (d, *J* = 8 Hz, 1 H, H-3), 4.31 (d, *J* = 6 Hz, 2 H, CH_2), 2.77 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.4 (s, C=O), 143.0 (s, C-1 of 2 Ph), 142.9 (s, *C*-CH), 140.0 (s, C-1), 136.0 (s, C-2), 130.7 (d, C-3/C-5 of 2 Ph), 129.7 (d, C-3), 128.7 (d, C-4 of 2 Ph), 128.6 (d, C-4), 127.9 (d, C-2/C-6 of 2 Ph), 127.6 (d, C-5), 127.0 (d, C-6), 126.1 (d, CH), 42.2 (t, CH_2), 36.2 [q, $N(CH_3)_2$].

EI–MS: *m/z* (%) = 356 (M^+, 12), 312 ($M^+ - Me_2N$, 7), 284 (10), 268 (100), 252 (8), 206 (12), 178 (13), 167 (33), 152 (18), 91 ($PhCH_2^+$, 13), 72 (Me_2NCO^+, 71), 44 (22).

CI–MS: *m/z* (%) = 374 ($M + NH_4^+$, 100), 357 (MH^+, 81), 331 (6), 301 (5), 276 (7), 167 (15), 118 (19), 106 (25), 89 (33), 46 (100).

HRMS: *m/z* calc. for $C_{24}H_{25}N_2O$ (MH^+), 357.1961; found, 357.1960.

FT–IR: ν_{max} = 3316 (NH), 2958 (CH), 1637 (C=O), 1538 (aromatic C=C), 1352, 1230 cm^{-1}.

Anal. calc. for $C_{24}H_{24}N_2O$: C, 80.87; H, 6.79; N, 7.86. Found: C, 80.90; H, 6.89; N, 7.63%.

Selected crystallographic data: $C_{72}H_{76}N_6O_5$, FW = 1105.39, T = 150(2) K, λ = 0.71073 Å, Monoclinic, $P2_1/n$, a = 19.0960(3) Å, b = 10.8300(2) Å, c = 30.7660(5) Å, α = 90°, β = 107.7660(10)°, γ = 90°, V = 6059.27(18) $Å^3$, Z = 4, $\rho_{calc.}$ = 1.212 Mg/m^3, crystal size = 0.32 × 0.20 × 0.06 mm^3, m = 0.076 mm^{-1}, reflections collected = 26316, independent reflections = 8712, R_{int} = 0.0683, parameters = 770, final R_1 = 0.0836, wR_2 = 0.2243 for I >2σ(I) and R_1 = 0.1130, wR_2 = 0.2492 for all data. Full

crystallographic data for this compound have been deposited with the CCDC, reference number 737416, and can be obtained free of charge *via* http://www.ccdc.ac.uk/data_request/cif.

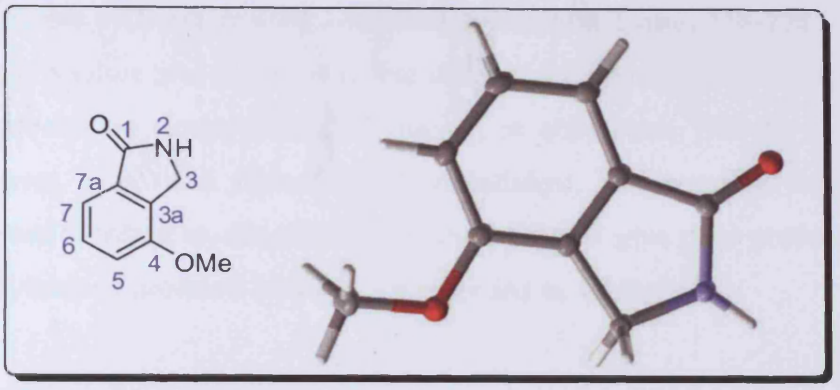
7.35 Synthesis of (*R**)-3-((*S**)-hydroxy(4-methoxyphenyl)methyl)-4-methoxyisoindolin-1-one (139)

A solution of *t*-BuLi in heptane (3.9 mL, 1.7 M, 6.6 mmol) was added to a cold (0 °C), stirred solution of *N'*-(2-methoxybenzyl)-*N,N*-dimethylurea (**111**; 0.42 g, 2.0 mmol) in anhydrous THF (20 mL) under N_2. Formation of the monolithium reagent **133** was observed as a yellow solution and the dilithium reagent **134** was observed as a reddish orange solution, after which the colour changed to deep red. The mixture was stirred at 0 °C for 6 h after which 4-anisaldehyde (0.30 g, 2.2 mmol) was added. The mixture was stirred for 2 h at 0 °C then the cooling bath was removed and the mixture allowed to warm to room temperature. It was then diluted with Et_2O (10 mL) and quenched with aq. sat. 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 residue obtained was treated with diethyl ether (20 ml) and gave a white solid which was filtered and then washed with diethyl ether. The pure product was identified as **139** (0.49 g, 1.63 mmol, 81%).

Compound **139** was found to be identical in all respects with the one produced previously in Chapter 3; Section 3.5. See Section 7.23 for spectral data.

7.36 Synthesis of 4-methoxyisoindolin-1-one (216)

A solution of *t*-BuLi in heptane (2.6 mL, 1.7 M, 4.4 mmol) was added to a cold (0 °C), stirred solution of *N'*-(2-methoxybenzyl)-*N,N*-dimethylurea (**111**; 0.42 g, 2.0 mmol) in anhydrous THF (20 mL) under N_2. The mixture was stirred at 0 °C for 6 h then the cooling bath was removed and the mixture allowed to warm to room temperature. The mixture was stirred at room temperature overnight. The reaction mixture was worked-up and purified as described in Section 7.35 to give **216** (0.25 g, 1.53 mmol, 76%) as a white solid.



Mp: 190–192 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.60 (s, exch., 1 H, NH), 7.46 (app. t, J = 8 Hz, 1 H, H-6), 7.26 (d, J = 8 Hz, 1 H, H-7), 7.19 (d, J = 8 Hz, 1 H, H-5), 4.29 (s, 2 H, H-3), 3.88 (s, 3 H, OCH_3).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 170.3 (s, C-1), 154.9 (s, C-4), 134.6 (s, C-3a), 131.8 (s, C-7a), 129.9 (d, C-6), 115.2 (d, C-7), 113.5 (d, C-5), 55.8 (q, OCH_3), 43.0 (t, C-3).

EI–MS: *m/z* (%) = 163 (M^+, 100), 162 (M^+ – 1, 42), 135 (M^+ – CO, 12), 134 (M^+ – CH_2NH, 22), 132 (44), 119 (22), 104 (18), 92 (15), 77 (26).

CI–MS: *m/z* (%) = 327 (2 M^+ + 1, 6), 181 (M + NH_4^+, 14), 164 (MH^+, 100), 134 (M^+ – CH_2NH, 10).

HRMS: *m/z* calc. for $C_9H_{10}NO_2$ (MH^+), 164.0706; found, 164.0707.

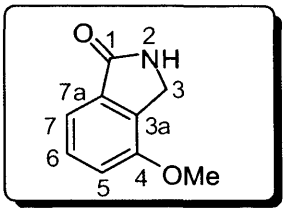
FT–IR: ν_{max} = 3286 (NH and OH), 2870 (CH), 1682 (C=O), 1585 (aromatic C=C), 1440, 1266, 1052 cm^{-1}.

Selected crystallographic data: $C_9H_9NO_2$, FW = 163.17, T = 150(2) K, λ = 0.71073 Å, Triclinic, P1, a = 7.2640(5) Å, b = 7.8940(6) Å, c = 8.3280(8) Å, α = 104.845(3)°, β = 114.462(4)°, γ = 103.622(5)°, V = 387.21(5) $Å^3$, Z = 2, $\rho_{calc.}$ = 1.400 Mg/m^3, crystal size = 0.25 × 0.24 × 0.18 mm^3, m = 0.0301 mm^{-1}, reflections collected = 2379, independent reflections = 1714, R_{int} = 0.0301, parameters = 110, final R_1 = 0.0512, wR_2 = 0.1220 for I>2σ(I) and R_1 = 0.0735, wR_2 = 0.1361 for all data. Full crystallographic data for this compound have been deposited with the CCDC, reference number 737411, and can be obtained free of charge *via* http://www.ccdc.ac.uk/data_request/cif.

7.37 Synthesis of 3-substituted 4-methoxyisoindolin-1-ones 216-224

The procedure was identical to that described for the synthesis of **139** (Section 7.35) except that an electrophile (2.2 mmol), in anhydrous THF (8 mL) if solid, otherwise neat, was used instead of 4-anisaldehye. The reaction mixtures were worked-up and purified as described in Section 7.35 to give pure products as white solids. The yields of products **216-224** are recorded in Table 6.1.

4-Methoxyisoindolin-1-one (216)

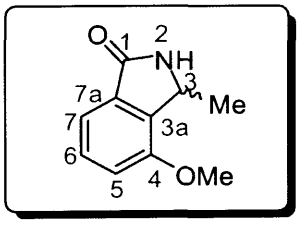


Yield: 0.27 g (1.65 mmol, 82%).

Mp: 190–192 °C.

Compound **216** produced using the general procedure was found to be identical in all respects with the one produced previously using 2.2 mole equivalents of *t*-BuLi (Section 7.36). See Section 7.36 for spectral data.

4-Methoxy-3-methylisoindolin-1-one (217)



Yield: 0.28 g (1.58 mmol, 79%).

Mp: 153–154 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26 (br s, exch., 1 H, NH), 7.47 (t, J = 8 Hz, 1 H, H-6), 7.24 (d, J = 8 Hz, 1 H, H-7), 7.15 (d, J = 8 Hz, 1 H, H-5), 4.73 (q, J = 7 Hz, 1 H, H-3), 3.92 (s, 3 H, OCH_3), 1.55 (d, J = 7 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2 (s, C-1), 155.3 (s, C-4), 136.8 (s, C-7a), 133.9 (s, C-3a), 130.1 (d, C-6), 116.0 (d, C-7), 113.6 (d, C-5), 55.8 (q, OCH_3), 52.0 (d, C-3), 19.3 (q, CH_3).

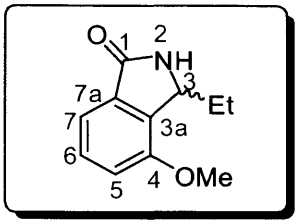
EI–MS: *m/z* (%) = 177 (M^+, 24), 162 (M^+ – Me, 100), 146 (10), 119 (8), 105 (9), 91 (11), 84 (8), 49 (15).

CI–MS: *m/z* (%) = 195 ($M + NH_4^+$, 30), 178 (MH^+, 100), 162 ($M^+ - Me$, 8), 94 (11), 52 (50), 44 (41).

HRMS: *m/z* calc. for $C_{10}H_{12}NO_2$ (MH^+), 178.0863; found, 178.0864.

FT–IR: ν_{max} = 3071 (NH and OH), 2971 (CH), 1680 (C=O), 1602 (aromatic C=C), 1493, 1267, 1057 cm^{-1}.

3-Ethyl-4-methoxyisoindolin-1-one (218)



Yield: 0.32 g (1.68 mmol, 84%).

Mp: 150–152 °C.

^1H NMR (500 MHz, DMSO-d_6): δ = 7.72 (s, exch., 1 H, NH), 7.44 (app. t, *J* = 8 Hz, 1 H, H-6), 7.23 (d, *J* = 8 Hz, 1 H, H-7), 7.18 (d, *J* = 8 Hz, 1 H, H-5), 4.57 (dd, *J* = 3, 7 Hz, 1 H, H-3), 3.87 (s, 3 H, OCH_3), 2.08 (ddq, *J* = 3, 14, 7 Hz, 1 H, 1 H of CH_2), 1.59 (app. d quintet, *J* = 14, 7 Hz, 1 H, 1 H of CH_2), 0.73 (app. t, *J* = 7 Hz, 3 H, CH_3).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 169.7 (s, C-1), 155.1 (s, C-4), 134.8 (s, C-7a), 134.4 (s, C-3a), 130.1 (d, C-6), 115.0 (d, C-7), 113.8 (d, C-5), 56.1 (d, C-3), 55.9 (q, OCH_3), 25.0 (t, CH_2), 9.2 (q, CH_3).

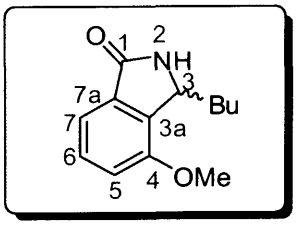
EI–MS: *m/z* (%) = 191 (M^+, 7), 162 ($M^+ - Et$, 100), 149 (5), 132 (6).

CI–MS: *m/z* (%) = 209 ($M + NH_4^+$, 9), 192 (MH^+, 100), 176 ($M^+ - Me$, 12), 162 ($M^+ - Et$, 28), 94 (11), 59 (33), 44 (40).

HRMS: *m/z* calc. for $C_{11}H_{14}NO_2$ (MH^+), 192.1019; found, 192.1018.

FT–IR: ν_{max} = 3303 (NH and OH), 2922 (CH), 1679 (C=O), 1602 (aromatic C=C), 1493, 1271, 1049 cm^{-1}.

3-Butyl-4-methoxyisoindolin-1-one (219)



Yield: 0.32 g (1.45 mmol, 72%).

Mp: 130–131 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.57 (s, exch., 1 H, NH), 7.47–7.41 (m, 2 H, H-6 and H-7), 7.22 (dd, *J* = 2, 8 Hz, 1 H, H-5), 4.69 (dd, *J* = 3, 7 Hz, 1 H, H-3), 3.91 (s, 3 H, OCH_3), 2.20 (m, 1 H, 1 H of $CH_2CH_2CH_2CH_3$), 1.65 (m, 1 H, 1 H of $CH_2CH_2CH_2CH_3$), 1.39–1.22 (m, 4 H, $CH_2CH_2CH_3$), 0.88 (t, *J* = 7 Hz, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.5 (s, C-1), 155.3 (s, C-4), 135.6 (s, C-7a), 134.2 (s, C-3a), 130.0 (d, C-6), 116.1 (d, C-7), 113.5 (d, C-5), 56.4 (d, C-3), 55.8 (q, OCH_3), 32.4 (t, $CH_2CH_2CH_2CH_3$), 27.9 (t, $CH_2CH_2CH_3$), 23.0 (t, CH_2CH_3), 14.3 (q, CH_3).

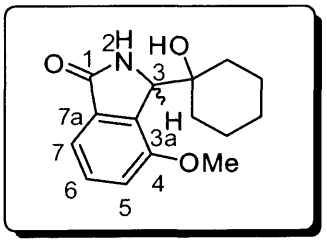
EI–MS: *m/z* (%) = 219 (M^+, 4), 188 (M^+ – Me, 3), 162 (M^+ – Bu, 100), 148 (4), 132 (5), 119 (4), 91 (4), 77 (6).

CI–MS: *m/z* (%) = 237 (M + NH_4^+, 8), 220 (MH^+, 100), 204 (9), 190 (11), 164 (18), 162 (M^+ – Bu, 17), 86 (17), 72 (38), 58 (41), 44 (39).

HRMS: *m/z* calc. for $C_{13}H_{18}NO_2$ (MH^+), 220.1332; found, 220.1332.

FT–IR: ν_{max} = 3314 (NH and OH), 2955 (CH), 1678 (C=O), 1600 (aromatic C=C), 1490, 1276, 1053 cm^{-1}.

3-(1-Hydroxycyclohexyl)-4-methoxyisoindolin-1-one (220)



Yield: 0.41 g (1.57 mmol, 78%).

Mp: 206–207 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.45 (s, exch., 1 H, NH), 7.43 (app. t, *J* = 8 Hz, 1 H, H-6), 7.25 (d, *J* = 8 Hz, 1 H, H-7), 7.22 (d, *J* = 8 Hz, 1 H, H-5), 4.46 (s, 1 H, H-3), 4.32 (s, exch., 1 H, OH), 3.88 (s, 3 H, OCH_3), 1.54–0.96 (m, 10 H, cyclohexyl group).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 169.8 (s, C-1), 155.0 (s, C-4), 135.9 (s, C-7a), 132.0 (s, C-3a), 130.2 (d, C-6), 115.5 (d, C-7), 114.6 (d, C-5), 73.5 (s, C-1 of cyclohexyl group), 65.5 (d, C-3), 56.1 (q, OCH_3), 38.8, 33.7 (2 t, C-2/C-6 of

cyclohexyl group), 25.8 (t, C-4 of cyclohexyl group), 21.5, 21.4 (2 t, C-3/C-5 of cyclohexyl group).

EI–MS: *m/z* (%) = 262 (MH^+, 11), 262 (M^+, 2), 244 ($MH^+ - H_2O$, 32), 243 ($M^+ - H_2O$, 100), 214 (33), 212 (21), 188 (M^+ – NCO – OMe, 48), 177 (19), 176 (34), 175 (55).

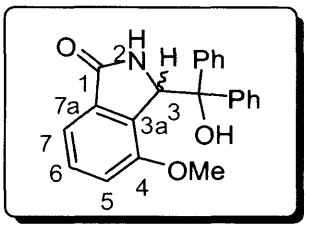
CI–MS: *m/z* (%) = 279 ($M + NH_4^+$, 2), 262 (MH^+, 29), 244 ($MH^+ - H_2O$, 4), 181 (35), 164 ($M^+ - C_6H_{10}OH$, 100), 134 (12), 116 (88), 98 (12), 55 (13).

HRMS: *m/z* calc. for $C_{15}H_{20}NO_3$ (MH^+), 262.1438; found, 262.1435.

FT–IR: ν_{max} = 3301 (NH and OH), 2952 (CH), 1690 (C=O), 1590 (aromatic C=C), 1470, 1240, 1047 cm^{-1}.

Anal. calc. for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.13; H, 7.34; N, 5.48%.

3-(Hydroxydiphenylmethyl)-4-methoxyisoindolin-1-one (221)



Yield: 0.56 g (1.62 mmol, 81%).

Mp: 206–208 °C.

^1H NMR (500 MHz, DMSO-d_6): δ = 7.89 (s, exch., 1 H, NH), 7.52–7.18 (m, 11 H, H-6 and 2 Ph), 7.10 (d, *J* = 8 Hz, 1 H, H-7), 6.94 (d, *J* = 8 Hz, 1 H, H-5), 5.84 (s, exch., 1 H, OH), 5.76 (s, 1 H, H-3), 3.19 (s, 3 H, OCH_3).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 169.7 (s, C-1), 155.0 (s, C-4), 145.8, 144.4 (2 s, C-1 of 2 Ph), 136.2 (s, C-7a), 131.9 (s, C-3a), 130.2 (s, C-6), 128.0, 127.4 (2 d, C-3/C-5 of 2 Ph), 127.1, 126.9 (2 d, C-2/C-6 of 2 Ph), 127.0, 126.8 (2 d, C-4 of 2 Ph), 115.0 (d, C-7), 113.9 (d, C-5), 79.7 (s, C-OH), 64.3 (d, C-3), 55.5 (q, OCH_3).

EI–MS: *m/z* (%) = 182 ($PhCO^+$, 22), 163 (12), 105 (100), 77 (Ph^+, 89), 51 (33).

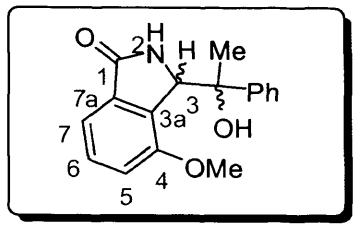
CI–MS: *m/z* (%) = 346 (MH^+, 100).

ES^+-MS: *m/z* (%) = 691 (2 MH^+ + 1, 12), 346 (MH^+, 31), 164 (100).

HRMS: *m/z* calc. for $C_{22}H_{20}NO_3$ (MH^+), 346.1438; found, 346.1440.

FT–IR: ν_{max} = 3301 (NH and OH), 2981 (CH), 1690 (C=O), 1599 (aromatic C=C), 1491, 1267, 1038 cm^{-1}.

3-(1-Hydroxy-1-phenylethyl)-4-methoxyisoindolin-1-one (222)



Yield: 0.43 g (1.62 mmol, 81%).

Mp: 235–236 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.61 (s, exch., 1 H, NH), 7.32 (app. t, J = 8 Hz, 1 H, H-6), 7.26 (d, J = 7 Hz, 2 H, H-2/H-6 of Ph), 7.15 (app. t, J = 7 Hz, 2 H, H-3/H-5 of Ph), 7.11–7.05 (m, 3 H, H-5, H-7 and H-4 of Ph), 5.42 (s, exch., 1 H, OH), 4.83 (s, 1 H, H-3), 3.67 (s, 3 H, OCH_3), 1.51 (s, 3 H, CH_3).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 169.8 (s, C-1), 154.7 (s, C-4), 154.2 (s, C-1 of Ph), 135.5 (s, C-7a), 131.9 (s, C-3a), 130.2 (d, C-6), 127.5 (d, C-3/C-5 of Ph), 126.8 (d, C-4 of Ph), 115.3 (d, C-7), 114.2 (d, C-5), 76.0 (s, C-OH), 65.7 (d, C-3), 56.1 (q, OCH_3), 26.6 (q, CH_3).

EI–MS: *m/z* (%) = 265 ($M^+ - H_2O$, 100), 238 (22), 187 (35).

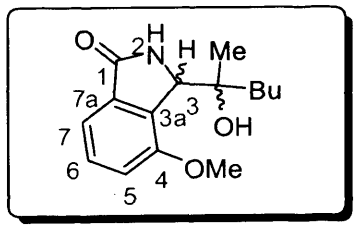
CI–MS: *m/z* (%) = 301 ($M + NH_4^+$, 3), 284 (MH^+, 100), 268 (12).

HRMS: *m/z* calc. for $C_{17}H_{18}NO_3$ (MH^+), 284.1281; found, 284.1281.

FT–IR: ν_{max} = 3373 (NH and OH), 3010 (CH), 1687 (C=O), 1594 (aromatic C=C), 1488, 1367, 1263, 1044 cm^{-1}.

Anal. calc. for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.98; H, 6.03; N, 4.94%.

3-(2-Hydroxyhexyl)-4-methoxyisoindolin-1-one (223)



Yield: 0.41 g (1.56 mmol, 78%).

Mp: 186–187 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.83 (s, exch., 1 H, NH), 7.54 (dd, J = 1, 8 Hz, 1 H, H-7), 7.49 (app. t, J = 8 Hz, 1 H, H-6), 7.12 (dd, J = 1, 8 Hz, 1 H, H-5), 4.72 (s, exch.,

1 H, OH), 4.08 (s, 1 H, H-3), 3.99 (s, 3 H, OCH_3), 1.34 (s, 3 H, CH_3), 1.39–1.33 (m, 2 H, $CH_2CH_2CH_2CH_3$), 1.29–0.94 (m, 4 H, $CH_2CH_2CH_3$), 0.79 (t, J = 7 Hz, 3 H, CH_2CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.1 (s, C-1), 154.3 (s, C-4), 135.5 (s, C-7a), 132.5 (s, C-3a), 130.6 (d, C-6), 117.5 (d, C-7), 114.2 (d, C-5), 74.7 (s, C-OH), 66.9 (d, C-3), 56.5 (q, OCH_3), 36.8 (t, $CH_2CH_2CH_2CH_3$), 25.6 (t, $CH_2CH_2CH_3$), 24.8 (q, CH_3), 23.6 (t, CH_2CH_3), 14.4 (q, CH_2CH_3).

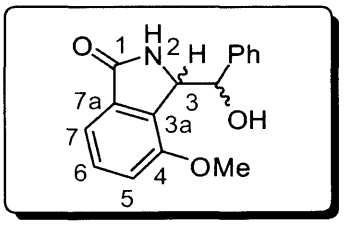
EI–MS: *m/z* (%) = 163 (M^+ – BuCOMe, 100), 148 (10), 132 (13), 119 (11), 58 (15), 43 (18).

CI–MS: *m/z* (%) = 264 (MH^+, 30), 181 (7), 164 (MH^+ – BuCOMe, 18), 118 (100).

HRMS: *m/z* calc. for $C_{15}H_{22}NO_3$ (MH^+), 264.1600; found, 264.1596.

FT–IR: ν_{max} = 3490 (NH and OH), 3073 (CH), 1682 (C=O), 1593 (aromatic C=C), 1263, 1046 cm^{-1}.

3-(Hydroxy(phenyl)methyl)-4-methoxyisoindolin-1-one (224)



Yield: 0.43 g (1.60 mmol, 80%).

Mp: 213–214 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.79 (s, exch., 1 H, NH), 7.31 (app. t, J = 8 Hz, 1 H, H-6), 7.16 (d, J = 8 Hz, 1 H, H-7), 7.03–6.97 (m, 5 H, Ph), 6.91 (d, J = 8 Hz, 1 H, H-5), 5.82 (d, J = 4 Hz, exch., 1 H, OH), 5.43 (app. t, J = 4 Hz, 1 H, CH), 4.92 (d, J = 3 Hz, 1 H, H-3), 3.98 (s, 3 H, OCH_3).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 175.0 (s, C-1), 160.3 (s, C-4), 144.8 (s, C-1 of Ph), 140.1 (s, C-7a), 136.8 (s, C-3a), 135.4 (d, C-6), 132.6 (d, C-4 of Ph), 132.5 (d, C-2/C-6 of Ph), 132.4 (d, C-3/C-5 of Ph), 120.1 (d, C-7), 118.8 (d, C-5), 77.2 (d, CHOH), 66.6 (d, C-3), 61.2 (q, OCH_3).

EI–MS: *m/z* (%) = 163 (M^+ – PhCHO, 22), 132 (5), 116 (15), 105 (14), 86 (24), 84 (30), 51 (56), 49 (100).

CI–MS: *m/z* (%) = 270 (MH^+, 15), 181 (7), 164 (MH^+ – PhCHO, 100), 148 (8), 134 (7), 124 (14), 105 (23), 94 (13), 78 (12), 58 (28), 44 (27).

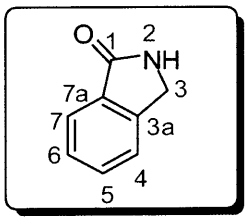
HRMS: *m/z* calc. for $C_{16}H_{16}NO_4$ (MH^+), 270.1125; found, 270.1125.

FT–IR: ν_{max} = 3201 (NH and OH), 3070 (CH), 1672 (C=O), 1603 (aromatic C=C), 1492, 1269, 1053 cm^{-1}.

7.38 Synthesis of various substituted isoindolin-1-ones 225-245

A solution of *t*-BuLi in heptane (3.9 mL, 1.7 M, 6.6 mmol) was added to a cold (0 °C), stirred solution of the appropriate substituted *N'*-benzyl-*N,N*-dimethylureas **107**, **108** and **113** (2.0 mmol) in anhydrous THF (20 mL) under N_2. The mixture was stirred at 0 °C for 6 h after which an electrophile (2.2 mmol), in anhydrous THF (8 mL) if solid, otherwise neat, was added. The mixture was stirred for 2 h at 0 °C then the cooling bath was removed and the mixture allowed to warm to room temperature. It was then diluted with Et_2O (10 mL) and quenched with aq. sat. 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 residue obtained was treated with diethyl ether (20 ml) to give a white solid which was filtered and washed with diethyl ether. The pure products were identified as substituted isoindolin-1-ones **225-245**. The yields of products are recorded in Table 6.2.

Isoindolin-1-one (225)



Yield: 0.19 g (1.43 mmol, 71%).

Mp: 153–154 °C (lit.[139] 149–151 °C).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 8 Hz, 1 H, H-7), 7.66 (br, exch., 1 H, NH), 7.49 (dt, *J* = 2, 8 Hz, 1 H, H-5), 7.43–7.40 (m, 2 H, H-4 and H-6), 4.41 (s, 2 H, H-3).

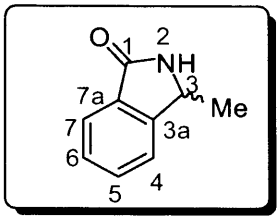
^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.0 (s, C-1), 143.7 (s, C-3a), 132.2 (s, C-7a), 131.8 (d, C-5), 128.0 (d, C-4), 123.8 (d, C-7), 123.2 (d, C-6), 45.7 (d, C-3).

APCI–MS: *m/z* (%) = 134 (MH^+, 100).

HRMS: *m/z* calc. for C_8H_8NO (MH^+), 134.0606; found, 134.0604.

FT–IR: ν_{max} = 3288 (NH and OH), 2964 (CH), 1676 (C=O), 1570 (aromatic C=C), 1458, 1272, 1052 cm^{-1}.

3-Methylisoindolin-1-one (226)



Yield: 0.22 g (1.50 mmol, 75%).

Mp: 117–118 °C (lit.[140] 115–116 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.35 (br, exch., 1 H, NH), 7.77 (d, *J* = 8 Hz, 1 H, H-7), 7.49 (dt, *J* = 2, 8 Hz, 1 H, H-5), 7.38–7.34 (m, 2 H, H-4 and H-6), 4.63 (q, *J* = 7 Hz, 1 H, H-3), 1.43 (d, *J* = 7 Hz, 3 H, CH_3).

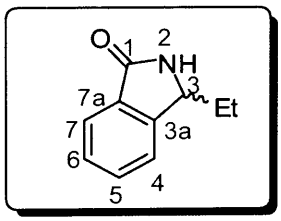
^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.3 (s, C-1), 149.0 (s, C-3a), 131.8 (s, C-7a), 131.7 (d, C-5), 128.0 (d, C-4), 123.6 (d, C-7), 122.2 (d, C-6), 52.8 (d, C-3), 20.2 (q, CH_3).

ES^+–MS: *m/z* (%) = 295 (2 M^+, 9), 189 (M + $MeCNH^+$, 100), 148 (MH^+, 34).

HRMS: *m/z* calc. for $C_9H_{10}NO$ (MH^+), 148.0762; found, 148.0762.

FT–IR: ν_{max} = 3176 (NH and OH), 2934 (CH), 1678 (C=O), 1602 (aromatic C=C), 1457, 1265, 1043 cm^{-1}.

3-Ethylisoindolin-1-one (227)



Yield: 0.25 g (1.55 mmol, 77%).

Mp: 103–105 °C (lit.[140] 104–105 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.46 (br, exch., 1 H, NH), 7.76 (d, *J* = 8 Hz, 1 H, H-7), 7.46 (app. dt, *J* = 2, 8 Hz, 1 H, H-5), 7.35 (app. t, *J* = 8 Hz, 1 H, H-6), 7.21 (d, *J* = 8 Hz, 1 H, H-4), 4.52 (dd, *J* = 5, 7 Hz, 1 H, H-3), 1.94 (ddq, *J* = 5, 14, 7 Hz, 1 H, 1 H of CH_2), 1.62 (app. d quintet, *J* = 14, 7 Hz, 1 H, 1 H of CH_2), 0.87 (app. t, *J* = 7 Hz, 3 H, CH_3).

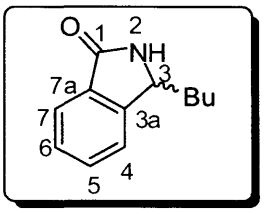
^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.6 (s, C-1), 147.6 (s, C-3a), 132.3 (s, C-7a), 131.7 (d, C-5), 128.5 (d, C-4), 123.6 (d, C-7), 122.4 (d, C-6), 58.2 (d, C-3), 27.3 (t, CH_2), 9.5 (q, CH_3).

APCI–MS: *m/z* (%) = 203 ($M + MeCNH^+$, 37), 162 (MH^+, 100).

HRMS: *m/z* calc. for $C_{10}H_{12}NO$ (M^+), 162.0913; found, 162.0919.

FT–IR: ν_{max} = 3312 (NH and OH), 2945 (CH), 1677 (C=O), 1589 (aromatic C=C), 1472, 1267, 1043 cm^{-1}.

3-Butylisoindolin-1-one (228)



Yield: 0.29 g (1.53 mmol, 76%).

Mp: 88–89 °C (lit.[140] 88–89 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 8 Hz, 1 H, H-7), 7.66 (br, exch., 1 H, NH), 7.49 (app. dt, *J* = 2, 8 Hz, 1 H, H-5), 7.40–7.36 (m, 2 H, H-4 and H-6), 4.55 (dd, *J* = 4, 7 Hz, 1 H, H-3), 1.88 (m, 1 H, 1 H of $CH_2CH_2CH_2CH_3$), 1.59 (m, 1 H, 1 H of $CH_2CH_2CH_2CH_3$), 1.30–1.23 (m, 4 H, $CH_2CH_2CH_3$), 0.82 (t, *J* = 7 Hz, 3 H, CH_3).

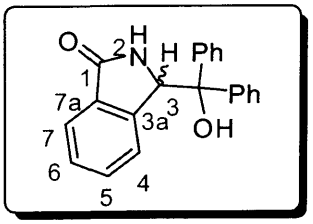
^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.2 (s, C-1), 147.8 (s, C-3a), 132.0 (s, C-7a), 131.7 (d, C-5), 128.0 (d, C-4), 123.7 (d, C-7), 122.4 (d, C-6), 57.0 (d, C-3), 34.3 (t, $CH_2CH_2CH_2CH_3$), 27.6 (t, $CH_2CH_2CH_3$), 22.6 (t, CH_2CH_3), 13.9 (q, CH_3).

ES^+–MS: *m/z* (%) = 189 (M^+, 25), 177 (56), 132 (M^+ – Bu, 100), 104 (23), 72 (32).

HRMS: *m/z* calc. for $C_{12}H_{15}NO$ (M^+), 189.1154; found, 189.1154.

FT–IR: ν_{max} = 3312 (NH and OH), 2960 (CH), 1677 (C=O), 1596 (aromatic C=C), 1475, 1272, 1045 cm^{-1}.

3-(Hydroxydiphenylmethyl)isoindolin-1-one (229)



Yield: 0.47 g (1.49 mmol, 74%).

Mp: 189–191 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.20 (br, exch., 1 H, NH), 7.60 (d, J = 8 Hz, 1 H, H-7), 7.52 (app. t, J = 8 Hz, 1 H, H-5), 7.35 (d, J = 8 Hz, 1 H, H-4), 7.30–7.00 (m, 11 H, H-6 and 2 Ph), 6.44 (d, J = 6 Hz, 1 H, H-3), 6.19 (s, exch., 1 H, OH).

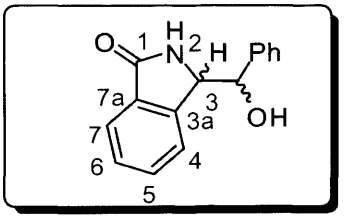
^{13}C NMR (125 MHz, DMSO-d_6): δ = 170.3 (s, C-1), 145.2, 145.1 (2 s, C-1 of 2 Ph), 141.2 (s, C-3a), 134.2 (s, C-7a), 130.9 (d, C-5), 129.6 (d, C-4), 128.3, 128.2 (2 d, C-3/C-5 of 2 Ph), 127.4, 127.3 (2 d, C-2/C-6 of Ph), 126.4, 126.3 (2 d, C-4 of 2 Ph), 124.6 (d, C-7), 122.8 (d, C-6), 79.1 (s, C-OH), 67.5 (d, C-3).

ES$^+$–MS: *m/z* (%) = 316 (MH^+, 3), 315 (M^+, 2), 297 ($M^+ - H_2O$, 37), 268 (10), 182 (Ph_2CO^+, 100), 133 (95), 105 (97).

HRMS: *m/z* calc. for $C_{21}H_{18}NO_2$ (MH^+), 316.1338; found, 316.1338.

FT–IR: ν_{max} = 3202 (NH and OH), 2990 (CH), 1678 (C=O), 1590 (aromatic C=C), 1491, 1252, 1025 cm^{-1}.

3-(Hydroxyphenylmethyl)isoindolin-1-one (230)



Yield: 0.35 g (1.46 mmol, 73%).

Mp: 174–175 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.69 (br, exch., 1 H, NH), 7.48 (d, J = 8 Hz, 1 H, H-7), 7.31 (app. dt, J = 2, 8 Hz, 1 H, H-5), 7.37 (app. t, J = 8 Hz, 1 H, H-6), 7.21 (br, 5 H, Ph), 7.07 (d, J = 8 Hz, 1 H, H-4), 5.92 (d, J = 4 Hz, exch., 1 H, OH), 4.81 (d, J = 6 Hz, 1 H, H-3), 4.73 (dd, J = 4, 6 Hz, 1 H, CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.5 (s, C-1), 144.5 (s, C-1 of Ph), 141.1 (s, C-3a), 133.6 (s, C-7a), 131.0 (d, C-5), 128.3 (d, C-4), 127.8 (d, C-3/C-5 of Ph), 127.7 (d, C-2/C-6 of Ph), 127.6 (d, C-4 of Ph), 124.7 (d, C-7), 122.8 (d, C-6), 74.8 (d, CHOH), 61.9 (d, C-3).

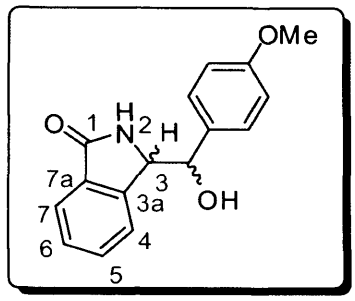
EI–MS: *m/z* (%) = 239 (M^+, 4), 221 ($M^+ - H_2O$, 100), 220 (51), 193 (33), 165 (89), 149 (86).

CI–MS: *m/z* (%) = 257 ($M + NH_4^+$, 12), 240 (MH^+, 100), 224 (24).

HRMS: *m/z* calc. for $C_{15}H_{14}NO_2$ (MH^+), 240.1019; found, 240.1018.

FT–IR: ν_{max} = 3237 (NH and OH), 2957 (CH), 1669 (C=O), 1599 (aromatic C=C), 1512, 1050 cm^{-1}.

3-(Hydroxy(4-methoxyphenyl)methyl)isoindolin-1-one (231)



Yield: 0.42 g (1.56 mmol, 78%).

Mp: 196–198 °C.

Compound **231** was a mixture of diastereoisomers, which were not separated; however, many individual NMR signals could be identified; **231a**:**231b** = 6:1 (by ^{1}H NMR).

ES^+–MS: *m/z* (%) = 561 (2 M + Na^+, 12), 539 (2 M^+ + 1, 100), 311 (M + $MeCNNa^+$, 17), 270 (M + $MeCNH^+$, 17), 270 (MH^+, 100), 252 ($M^+ - H_2O$, 58), 175 (6).

HRMS: *m/z* calc. for $C_{16}H_{16}NO_3$ (MH^+), 270.1130; found, 270.1121.

FT–IR: ν_{max} = 3301 (NH and OH), 2886 (CH), 1678 (C=O), 1602 (aromatic C=C), 1510, 1271, 1042 cm^{-1}.

Compound 231a:

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.55 (br, exch., 1 H, NH), 7.51–7.37 (m, 4 H, H-4, H-5, H-6 and H-7), 7.13 (d, *J* = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl group), 6.77 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl group), 5.69 (d, *J* = 4 Hz, exch., 1 H, OH), 4.95 (app. t, *J* = 4 Hz, 1 H, H-3), 4.83 (d, *J* = 4 Hz, 1 H, C*H*OH), 3.70 (s, 3 H, OCH_3).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 170.0 (s, C-1), 158.8 (s, C-4 of 4-methoxyphenyl), 145.1 (s, C-3a), 133.6 (s, C-1 of 4-methoxyphenyl), 133.1 (s, C-7a), 131.2 (d, C-5), 128.6 (d, C-2/C-6 of 4-methoxyphenyl), 128.3 (d, C-7), 124.5 (d, C-4), 122.9 (d, C-6), 113.3 (d, C-3/C-5 of 4-methoxyphenyl), 73.9 (d, CHOH), 62.5 (d, C-3), 55.4 (q, OCH_3).

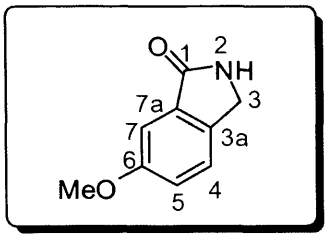
Compound 231b:

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.67 (br, exch., 1 H, NH), 7.51–7.38 (m, 4 H, H-4, H-5, H-6 and H-7), 7.06 (d, *J* = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl group),

6.79 (d, J = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl group), 5.82 (d, J = 4 Hz, exch., 1 H, OH), 4.77 (d, J = 4 Hz, 1 H, C*H*OH), 4.66 (app. t, J = 4 Hz, 1 H, H-3), 3.68 (s, 3 H, OCH_3).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 170.3 (s, C-1), 159.3 (s, C-4 of 4-methoxyphenyl), 145.0 (s, C-3a), 133.7 (s, C-1 of 4-methoxyphenyl), 133.4 (s, C-7a), 131.1 (d, C-5), 128.9 (d, C-2/C-6 of 4-methoxyphenyl), 128.4 (d, C-7), 124.8 (d, C-4), 122.9 (d, C-6), 113.4 (d, C-3/C-5 of 4-methoxyphenyl), 74.7 (d, CHOH), 62.1 (d, C-3), 55.4 (q, OCH_3).

6-Methoxyisoindolin-1-one (232)



Yield: 0.23 g (1.41 mmol, 70%).

Mp: 189–190 °C.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.21 (br, exch., 1 H, NH), 7.38 (d, J = 2 Hz, 1 H, H-7), 7.35 (d, J = 8 Hz, 1 H, H-4), 7.14 (dd, J = 2, 8 Hz, 1 H, H-5), 4.42 (s, 2 H, H-3), 3.87 (s, 3 H, OCH_3).

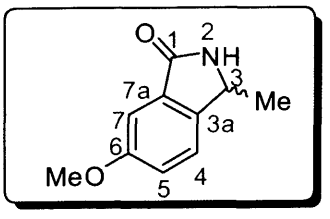
^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.2 (s, C-1), 160.0 (s, C-6), 135.9 (s, C-3a), 133.5 (s, C-7a), 124.0 (d, C-4), 120.3 (d, C-5), 106.3 (d, C-7), 55.7 (q, OCH_3), 45.4 (d, C-3).

ES^+–MS: m/z (%) = 205 ($M + MeCNH^+$, 100), 164 (MH^+, 68).

HRMS: m/z calc. for $C_9H_{10}NO_2$ (MH^+), 164.0706; found, 164.0709.

FT–IR: ν_{max} = 3294 (NH and OH), 2976 (CH), 1678 (C=O), 1577 (aromatic C=C), 1472, 1265, 1049 cm^{-1}.

6-Methoxy-3-methylisoindolin-1-one (233)



Yield: 0.27 g (1.52 mmol, 76%).

Mp: 160–161 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.21 (br, exch., 1 H, NH), 7.33 (d, *J* = 2 Hz, 1 H, H-7), 7.31 (d, *J* = 8 Hz, 1 H, H-4), 7.13 (dd, *J* = 2, 8 Hz, 1 H, H-5), 4.66 (q, *J* = 7 Hz, 1 H, H-3), 3.86 (s, 3 H, OCH_3), 1.48 (d, *J* = 7 Hz, 3 H, CH_3).

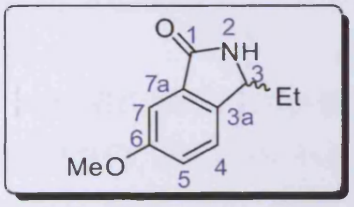
^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.2 (s, C-1), 160.0 (s, C-6), 141.3 (s, C-3a), 133.0 (s, C-7a), 123.1 (d, C-4), 120.2 (d, C-7), 106.3 (d, C-5), 55.7 (q, OCH_3), 52.4 (d, C-3), 20.4 (q, CH_3).

ES^+–MS: *m/z* (%) = 219 ($M + MeCNH^+$, 96), 178 (MH^+, 100).

HRMS: *m/z* calc. for $C_{10}H_{12}NO_2$ (MH^+), 178.0863; found, 178.0862.

FT–IR: ν_{max} = 3165 (NH and OH), 2979 (CH), 1679 (C=O), 1600 (aromatic C=C), 1487, 1261, 1046 cm^{-1}.

3-Ethyl-6-methoxyisoindolin-1-one (234)



Yield: 0.30 g (1.57 mmol, 78%).

Mp: 137–138 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.16 (br, exch., 1 H, NH), 7.33 (d, *J* = 8 Hz, 1 H, H-4), 7.31 (s, 1 H, H-7), 7.12 (dd, *J* = 2, 8 Hz, 1 H, H-5), 4.56 (dd, *J* = 5, 7 Hz, 1 H, H-3), 3.87 (s, 3 H, OCH_3), 1.96 (ddq, *J* = 5, 14, 7 Hz, 1 H, 1 H of CH_2), 1.70 (app. d quintet, *J* = 14, 7 Hz, 1 H, 1 H of CH_2), 0.97 (app. t, *J* = 7 Hz, 3 H, CH_3).

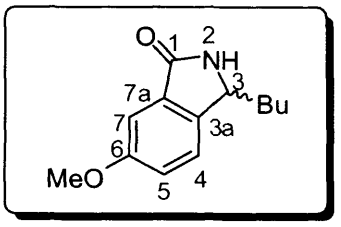
^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.4 (s, C-1), 160.0 (s, C-6), 139.8 (s, C-3a), 133.6 (s, C-7a), 123.2 (d, C-4), 120.1 (d, C-5), 106.3 (d, C-7), 57.8 (d, C-3), 55.7 (q, OCH_3), 27.5 (t, CH_2), 9.5 (q, CH_3).

EI–MS: *m/z* (%) = 191 (M^+, 21), 162 (M^+ – Et, 100), 147 (M^+ – Et – Me, 13), 134 (15), 119 (16).

HRMS: *m/z* calc. for $C_{11}H_{13}NO_2$ (M^+), 191.0946; found, 191.0943.

FT–IR: ν_{max} = 3300 (NH and OH), 2942 (CH), 1678 (C=O), 1598 (aromatic C=C), 1475, 1270, 1045 cm^{-1}.

3-Butyl-6-methoxyisoindolin-1-one (235)



Yield: 0.34 g (1.55 mmol, 77%).

Mp: 145–147 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.71 (br, exch., 1 H, NH), 7.44 (d, J = 8 Hz, 1 H, H-4), 7.15–7.03 (m, 2 H, H-5 and H-7), 4.48 (dd, J = 3, 7 Hz, 1 H, H-3), 3.81 (s, 3 H, OCH_3), 1.84 (m, 1 H, 1 H of $CH_2CH_2CH_2CH_3$), 1.48 (m, 1 H, 1 H of $CH_2CH_2CH_2CH_3$), 1.31–1.21 (m, 4 H, $CH_2CH_2CH_3$), 0.84 (t, J = 7 Hz, 3 H, CH_3).

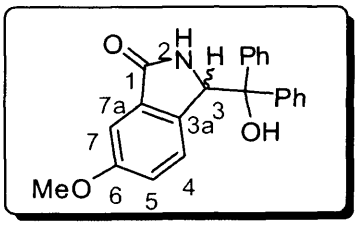
^{13}C NMR (125 MHz, DMSO-d_6): δ = 169.6 (s, C-1), 159.5 (s, C-6), 140.4 (s, C-3a), 134.3 (s, C-7a), 124.3 (d, C-4), 119.4 (d, C-5), 106.5 (d, C-7), 56.0 (d, C-3), 55.9 (q, OCH_3), 34.4 (t, $CH_2CH_2CH_2CH_3$), 27.3 (t, $CH_2CH_2CH_3$), 22.6 (t, CH_2CH_3), 14.3 (q, CH_3).

ES$^+$–MS: *m/z* (%) = 261 (M + MeCNH$^+$, 100), 220 (MH$^+$, 46), 204 (9), 164 (21)

HRMS: *m/z* calc. for $C_{13}H_{18}NO_2$ (MH$^+$), 220.1338; found, 220.1347.

FT–IR: ν_{max} = 3305 (NH and OH), 2967 (CH), 1680 (C=O), 1597 (aromatic C=C), 1477, 1277, 1051 cm^{-1}.

3-(Hydroxydiphenylmethyl)-6-methoxyisoindolin-1-one (236)



Yield: 0.50 g (1.45 mmol, 72%).

Mp: 159–160 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.12 (br, exch., 1 H, NH), 7.71–7.16 (m, 10 H, 2 Ph), 6.93 (d, J = 2 Hz, 1 H, H-7), 6.75 (s, exch., 1 H, OH), 6.69 (dd, J = 2, 8 Hz, 1 H, H-5), 5.78 (d, J = 8 Hz, 1 H, H-4), 5.40 (s, 1 H, H-3), 3.68 (s, 3 H, OCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.0 (s, C-1), 160.0 (s, C-6), 146.5, 144.7 (2 s, C-1 of 2 Ph), 136.4 (s, C-3a), 135.1 (s, C-7a), 128.6, 128.5 (2 d, C-3/C-5 of 2 Ph),

127.4, 127.4 (2 d, C-4 of 2 Ph), 126.3, 126.2 (2 d, C-2/C-6 of Ph), 124.6 (d, C-4), 119.2 (d, C-5), 106.6 (d, C-7), 78.4 (s, C-OH), 64.4 (d, C-3), 55.7 (q, OCH_3).

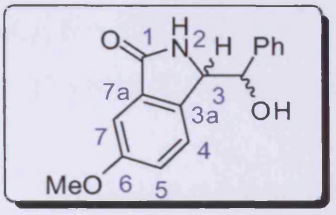
EI–MS: *m/z* (%) = 346 (M^+ + 1, 33), 345 (M^+, 10), 328 ($MH^+ - H_2O$, 45), 327 ($M^+ - H_2O$, 100).

CI–MS: *m/z* (%) = 346 (MH^+, 100).

HRMS: *m/z* calc. for $C_{22}H_{20}NO_3$ (MH^+), 346.1438; found, 346.1443.

FT–IR: ν_{max} = 3205 (NH and OH), 2994 (CH), 1677 (C=O), 1594 (aromatic C=C), 1493, 1255, 1027 cm^{-1}.

3-(Hydroxyphenylmethyl)-6-methoxyisoindolin-1-one (237)



Yield: 0.45 g (1.50 mmol, 75%).

Mp: 164–165 °C.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.86 (br, exch., 1 H, NH), 7.32–7.23 (m, 6 H, Ph and H-7), 7.16 (d, *J* = 8 Hz, 1 H, H-4), 6.91 (d, *J* = 8 Hz, 1 H, H-5), 5.82 (d, *J* = 4 Hz, exch., 1 H, OH), 5.43 (app. t, *J* = 4 Hz, 1 H, CH), 4.33 (d, *J* = 4 Hz, 1 H, H-3), 3.68 (s, 3 H, OCH_3).

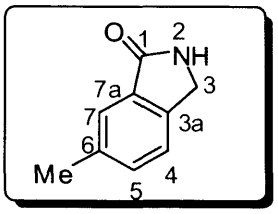
^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.0 (s, C-1), 160.2 (s, C-6), 140.8 (s, C-1 of Ph), 135.4 (s, C-3a), 133.7 (s, C-7a), 128.7 (d, C-3/C-5 of Ph), 128.4 (d, C-4 of Ph), 127.5 (d, C-2/C-6 of Ph), 124.9 (d, C-4), 119.6 (d, C-5), 114.0 (d, C-7), 78.6 (d, CHOH), 62.8 (d, C-3), 55.6 (q, OCH_3).

ES^+–MS: *m/z* (%) = 561 (2 M + Na^+, 23), 539 (2 M^+ + 1, 62), 333 (M + $MeCNNa^+$, 51), 311 (M + $MeCNH^+$, 100), 270 (MH^+, 74), 252 ($M^+ - H_2O$, 71), 209 (27).

HRMS: *m/z* calc. for $C_{16}H_{16}NO_4$ (MH^+), 270.1130; found, 270.1133.

FT–IR: ν_{max} = 3300 (NH and OH), 2923 (CH), 1679 (C=O), 1600 (aromatic C=C), 1504, 1270, 1052 cm^{-1}.

6-Methylisoindolin-1-one (238)



Yield: 0.22 g (1.50 mmol, 75%).

Mp: 211–213 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.51 (br, exch., 1 H, NH), 7.48 (s, 1 H, H-7), 7.44 (d, J = 8 Hz, 1 H, H-5), 7.39 (d, J = 8 Hz, 1 H, H-4), 4.32 (s, 2 H, H-3), 2.39 (s, 3 H, CH_3).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 170.5 (s, C-1), 141.7 (s, C-3a), 137.6 (s, C-6), 133.2 (s, C-7a), 132.6 (d, C-5), 123.8 (d, C-7), 123.4 (d, C-4), 45.1 (t, C-3), 21.3 (q, CH_3).

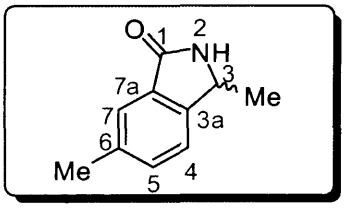
ES$^+$–MS: *m/z* (%) = 295 (2 M$^+$ + 1, 41), 189 (M + MeCNH$^+$, 92), 148 (MH$^+$, 100).

HRMS: *m/z* calc. for $C_9H_{10}NO$ (MH$^+$), 148.0755; found, 148.0762.

FT–IR: ν_{max} = 3286 (NH and OH), 2972 (CH), 1676 (C=O), 1570 (aromatic C=C), 1467, 1261, 1047 cm^{-1}.

Anal. calc. for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.32; H, 6.14; N, 9.41%.

3,6-Dimethylisoindolin-1-one (239)



Yield: 0.25 g (1.55 mmol, 78%).

Mp: 161–162 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.59 (br, exch., 1 H, NH), 7.45 (s, 1 H, H-7), 7.44 (d, J = 8 Hz, 1 H, H-5), 7.39 (d, J = 8 Hz, 1 H, H-4), 4.56 (q, J = 6 Hz, 1 H, H-3), 2.38 (s, 3 H, CH_3), 1.33 (d, J = 6 Hz, 3 H, CH_3CH).

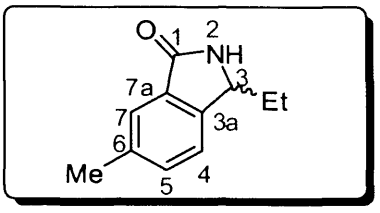
^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.4 (s, C-1), 146.9 (s, C-3a), 137.7 (s, C-6), 132.8 (d, C-5), 132.7 (s, C-7a), 123.3 (d, C-7), 122.9 (d, C-4), 51.9 (d, C-3), 21.3 (q, CH_3), 20.8 (q, CH_3).

ES^+–MS: *m/z* (%) = 323 ($2\ M^+ + 1$, 22), 203 ($M + MeCNH^+$, 96), 162 (MH^+, 100).

HRMS: *m/z* calc. for $C_{10}H_{12}NO$ (MH^+), 162.0925; found, 162.0925.

FT–IR: ν_{max} = 3187 (NH and OH), 2986 (CH), 1677 (C=O), 1598 (aromatic C=C), 1478, 1266, 1042 cm^{-1}.

3-Ethyl-6-methylisoindolin-1-one (240)



Yield: 0.26 g (1.49 mmol, 75%).

Mp: 165-166 °C.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.27 (br, exch., 1 H, NH), 7.58 (s, 1 H, H-7), 7.28 (d, *J* = 8 Hz, 1 H, H-5), 7.23 (d, *J* = 8 Hz, 1 H, H-4), 4.49 (dd, *J* = 5, 7 Hz, 1 H, H-3), 2.36 (s, 3 H, CH_3), 1.91 (ddq, *J* = 5, 14, 7 Hz, 1 H, 1 H of CH_2), 1.62 (app. d quintet, *J* = 14, 7 Hz, 1 H, 1 H of CH_2), 0.89 (app. t, *J* = 7 Hz, 3 H, CH_3CH_2).

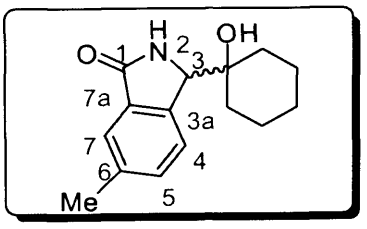
^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.7 (s, C-1), 144.8 (s, C-3a), 137.9 (s, C-6), 132.7 (d, C-5), 132.4 (s, C-7a), 123.8 (d, C-4), 122.1 (d, C-7), 58.0 (d, C-3), 27.4 (t, CH_2), 21.3 (q, CH_3), 9.5 (q, CH_3CH_2).

APCI–MS: *m/z* (%) = 175 (M^+, 11), 146 (M^+ – Et, 100), 118 (12).

HRMS: *m/z* calc. for $C_{11}H_{13}NO$ (M^+), 175.0997; found, 175.1000.

FT–IR: ν_{max} = 3307 (NH and OH), 2949 (CH), 1679 (C=O), 1597 (aromatic C=C), 1470, 1272, 1049 cm^{-1}.

3-(1-Hydroxycyclohexyl)-6-methylisoindolin-1-one (241)



Yield: 0.35 g (1.43 mmol, 72%).

Mp: 235–237 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.72 (br, exch., 1 H, NH), 6.56 (d, J = 8 Hz, 1 H, H-5), 6.53 (s, 1 H, H-7), 6.42 (d, J = 8 Hz, 1 H, H-4), 4.00 (s, exch., 1 H, OH), 3.42 (s, 1 H, H-3), 2.27 (s, 3 H, CH_3), 0.65–0.33 (m, 10 H, cyclohexyl).

Compound **34** was highly insoluble in DMSO so that its ^{13}C NMR spectrum was not recorded.

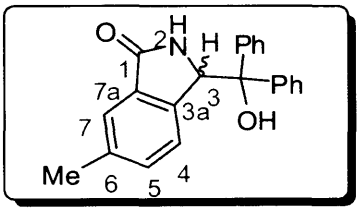
ES$^+$–MS: *m/z* (%) = 491 (2 M$^+$ + 1, 10), 287 (M + MeCNH$^+$, 79), 246 (MH$^+$, 100), 228 (M$^+$ – H_2O, 18).

HRMS: *m/z* calc. for $C_{15}H_{20}NO_2$ (MH$^+$), 264.1494; found, 246.1498.

FT–IR: ν_{max} = 3307 (NH and OH), 2943 (CH), 1681 (C=O), 1596 (aromatic C=C), 1472, 1246, 1043 cm^{-1}.

Anal. calc. for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.81; H, 7.85; N, 5.80%.

3-(Hydroxydiphenylmethyl)-6-methylisoindolin-1-one (242)



Yield: 0.56 g (1.70 mmol, 85%).

Mp: 236–264 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.12 (br, exch., 1 H, NH), 7.61–7.19 (m, 11 H, 2 Ph and H-7), 7.11 (d, J = 8 Hz, 1 H, H-5), 6.26 (d, J = 8 Hz, 1 H, H-4), 5.81 (s, exch., 1 H, OH), 5.72 (s, 1 H, H-3), 2.33 (s, 3 H, CH_3).

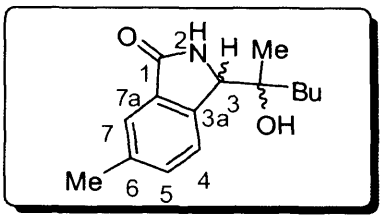
^{13}C NMR (125 MHz, DMSO-d_6): δ = 172.40 (s, C-1), 145.5, 145.2 (2 s, C-1 of 2 Ph), 142.4 (s, C-3a), 137.6 (s, C-6), 134.4 (s, C-7a), 131.8 (d, C-5), 128.3, 128.2 (2 d, C-3/C-5 of 2 Ph), 127.3, 127.2 (2 d, C-4 of 2 Ph), 127.1, 127.0 (2 d, C-2/C-6 of 2 Ph), 124.3 (d, C-4), 123.0 (d, C-7), 79.0 (s, C-OH), 63.4 (d, C-3), 21.2 (q, CH_3).

ES$^+$–MS: *m/z* (%) = 659 (2 M$^+$ + 1, 12), 371 (M + MeCNH$^+$, 71), 330 (MH$^+$, 100), 312 (M$^+$ – H_2O, 36), 189 (8).

HRMS: *m/z* calc. for $C_{22}H_{20}NO_2$ (MH$^+$), 330.1494; found, 330.1487.

FT–IR: ν_{max} = 3278 (NH and OH), 3000 (CH), 1678 (C=O), 1591 (aromatic C=C), 1493, 1251, 1040 cm^{-1}.

3-(2-Hydroxyhexyl)-4-methylisoindolin-1-one (243)



Yield: 0.38 g (1.54 mmol, 77%).

Mp: 88–89 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.47 (br, exch., 1 H, NH), 7.53 (d, J = 8 Hz, 1 H, H-5), 7.42 (s, 1 H, H-7), 7.35 (d, J = 8 Hz, 1 H, H-4), 4.79 (s, exch., 1 H, OH), 4.39 (br, 1 H, H-3), 2.38 (s, 3 H, CH_3), 1.33–1.09 (m, 6 H, $CH_2CH_2CH_2CH_3$), 1.06 (s, 3 H, CH_3C-OH), 0.79 (t, J = 7 Hz, 3 H, CH_3CH_2).

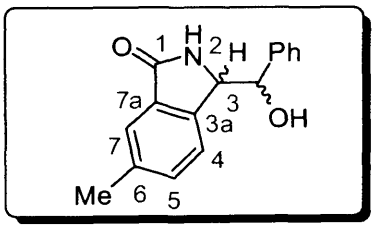
^{13}C NMR (125 MHz, DMSO-d_6): δ = 170.3 (s, C-1), 142.8 (s, C-3a), 137.7 (s, C-6), 133.9 (s, C-7a), 132.4 (d, C-5), 125.0 (d, C-4), 123.1 (d, C-7), 73.6 (s, C-OH), 65.5 (d, C-3), 36.3 (t, $CH_2CH_2CH_2CH_3$), 25.4 (t, $CH_2CH_2CH_3$), 24.6 (q, CH_3), 23.3 (t, CH_2CH_3), 21.3 (q, CH_3), 14.5 (q, CH_3CH_2).

ES$^+$–MS: *m/z* (%) = 517 (2 M + Na$^+$, 9), 495 (2 M$^+$ + 1, 44), 289 (M + MeCNH$^+$, 32), 248 (MH$^+$, 100), 230 (M$^+$ – H_2O, 41), 148 (9), 100 (8).

HRMS: *m/z* calc. for $C_{15}H_{22}NO_2$ (MH$^+$), 248.1651; found, 248.1646.

FT–IR: ν_{max} = 3467 (NH and OH), 3042 (CH), 1680 (C=O), 1590 (aromatic C=C), 1269, 1041 cm^{-1}.

3-(Hydroxyphenylmethyl)-6-methylisoindolin-1-one (244)



Yield: 0.40 g (1.58 mmol, 79%).

Mp: 228–229 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.01 (br, exch., 1 H, NH), 7.41 (d, J = 2 Hz, 1 H, H-7), 7.31–7.22 (m, 5 H, Ph), 7.03 (dd, J = 2, 8 Hz, 1 H, H-5), 6.33 (d, J = 8 Hz, 1 H, H-4), 5.62 (d, J = 3 Hz, exch., 1 H, OH), 4.67 (d, J = 8 Hz, 1 H, H-3), 4.39 (dd, J = 3, 8 Hz, 1 H, C*H*OH), 2.32 (s, 3 H, CH_3).

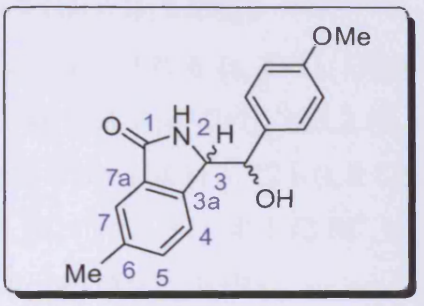
^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.3 (s, C-1), 141.1 (s, C-3a), 140.9 (s, C-1 of Ph), 137.9 (s, C-6), 133.3 (s, C-7a), 131.9 (d, C-5), 128.2 (d, C-7), 128.1 (d, C-3/C-5 of Ph), 127.7 (d, C-2/C-6 of Ph), 124.1 (d, C-4 of Ph), 123.2 (d, C-4), 76.9 (d, CHOH), 62.7 (d, C-3), 21.3 (q, CH_3).

APCI–MS: *m/z* (%) = 529 (2 M + Na^+, 61), 507 (2 M^+ + 1, 93), 317 (M + $MeCNNa^+$, 15), 295 (M + $MeCNH^+$, 22), 254 (MH^+, 89), 236 ($M^+ - H_2O$, 100), 100 (22).

HRMS: *m/z* calc. for $C_{16}H_{16}NO_2$ (MH^+), 254.1181; found, 254.1182.

FT–IR: ν_{max} = 3312 (NH and OH), 2943 (CH), 1678 (C=O), 1602 (aromatic C=C), 1500, 1272, 1045 cm^{-1}.

3-(Hydroxy(4-methoxyphenyl)methyl)-6-methylisoindolin-1-one (245)



Yield: 0.47 g (1.66 mmol, 83%).

Mp: 211–213 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.47 (br, exch., 1 H, NH), 7.31–7.29 (m, 3 H, H-4, H-5 and H-7), 7.12 (d, *J* = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 6.76 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 5.65 (d, *J* = 4 Hz, exch., 1 H, OH), 4.92 (app. t, *J* = 4 Hz, 1 H, C*H*OH), 4.77 (d, *J* = 4 Hz, 1 H, H-3), 3.69 (s, 3 H, OCH_3), 2.33 (s, 3 H, CH_3).

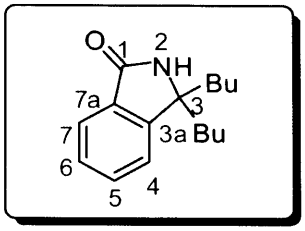
^{13}C NMR (125 MHz, DMSO-d_6): δ = 170.1 (s, C-1), 158.8 (s, C-4 of 4-methoxyphenyl), 142.3 (s, C-3a), 137.7 (s, C-6), 133.8 (s, C-7a), 133.2 (s, C-1 of 4-methoxyphenyl), 132.1 (d, C-5), 128.6 (d, C-2/C-6 of 4-methoxyphenyl), 124.2 (d, C-7),123.1 (d, C-4), 113.3 (d, C-3/C-5 of 4-methoxyphenyl), 73.9 (d, CHOH), 62.3 (d, C-3), 55.4 (q, OCH_3), 21.3 (q, CH_3).

ES^+–MS: *m/z* (%) = 589 (2 M + Na^+, 37), 567 (2 M^+ + 1, 64), 325 (M + $MeCNH^+$, 65), 284 (MH^+, 100), 266 ($MH^+ - H_2O$, 46).

HRMS: *m/z* calc. for $C_{17}H_{18}NO_3$ (MH^+), 284.1287; found, 284.1290.

FT–IR: ν_{max} = 3301 (NH and OH), 2896 (CH), 1677 (C=O), 1601 (aromatic C=C), 1519, 1271, 1042 cm^{-1}.

3,3-Dibutylisoindolin-1-one (246)



Yield: 25 mg (0.10 mmol, 5%).

Mp: 88–89 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 8 Hz, 1 H, H-7), 7.47 (app. t, *J* = 8 Hz, 1 H, H-5), 7.36 (app. t, *J* = 8 Hz, 1 H, H-6), 7.23 (d, *J* = 8 Hz, 1 H, H-4), 7.16 (br s, exch., 1 H, NH), 1.85–1.72 (m, 4 H, 2 $CH_2CH_2CH_2CH_3$), 1.18–1.09 (m, 8 H, 2 $CH_2CH_2CH_3$), 0.74 (t, *J* = 7 Hz, 6 H, 2 CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.6 (s, C-1), 150.8 (s, C-3a), 133.3 (s, C-7a), 131.8 (d, C-5), 127.8 (d, C-4), 123.7 (d, C-7), 121.2 (d, C-6), 65.1 (s, C-3), 39.0 (t, 2 $CH_2CH_2CH_2CH_3$), 25.6 (t, 2 $CH_2CH_2CH_3$), 22.8 (t, 2 CH_2CH_3), 13.8 (q, 2 CH_3).

ES^+–MS: *m/z* (%) = 513 (2 M + Na^+, 12), 491 (2 M^+ + 1, 3), 309 (M + $MeCNNa^+$, 24), 287 (M + $MeCNH^+$, 97), 246 (MH^+, 100).

HRMS: *m/z* calc. for $C_{16}H_{24}NO$ (MH^+), 246.1858; found, 246.1858.

FT–IR: ν_{max} = 3300 (NH and OH), 2960 (CH), 1681 (C=O), 1591 (aromatic C=C), 1473, 1273, 1046 cm^{-1}.

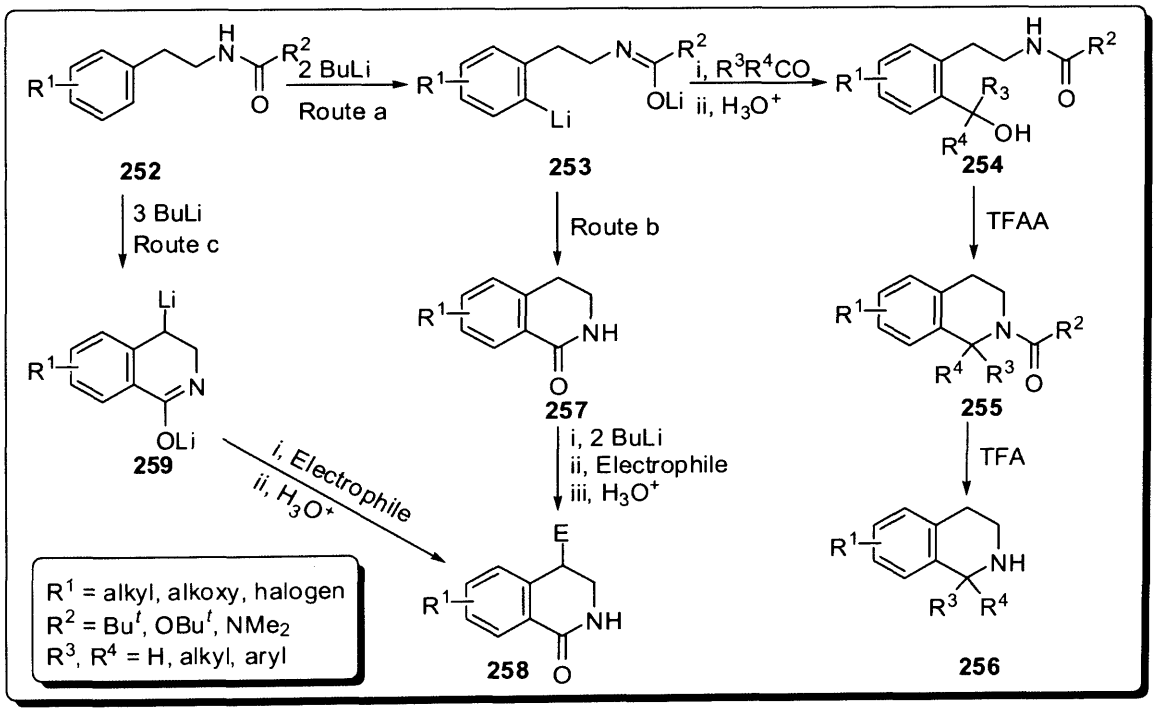
FINAL CONCLUSION AND FUTURE WORK

FINAL CONCLUSION AND FUTURE WORK

A simple, efficient and high yielding lithiation procedure that allows electrophilic substitution of various *N*-benzylpivalamides and *N'*-benzyl-*N,N*-dimethylureas has been demonstrated to provide various substituted derivatives. Catalytic cyclization reactions of some of the products with TFAA, *via* dehydration from the OH and hydrogen from the NH, takes place to give the corresponding isoindolines and tetrahydroisoquinolines in excellent yields.

Also, a lithiation procedure has been developed that allows the production of 3-substituted isoindolin-1-ones in high yields in only one step *via* lithiation of various substituted *N'*-benzyl-*N,N*-dimethylureas with *t*-BuLi (3.3 mole equivalents) in THF at 0 °C followed by reactions with various electrophiles. The procedure has been proven to be simple, efficient and general.

However, *N*-(2-(2-hydroxy-2-arylalkyl)benzyl)pivalamides are not cyclised to produce the corresponding tetrahydroisoquinolines on reaction with TFAA under the conditions tried. Therefore, future work could aim for the production of such compounds *via* lithiation procedures as shown in the Scheme below. It is hoped that lithiation of *N*-substituted 2-arylethylamines **252** would give the corresponding dilithium reagents **253** which on reaction with carbonyl compounds would give the corresponding *ortho*-substituted derivatives **354** (Route a). Catalytic cyclization of **254** with TFAA could produce **255** which on reaction with TFA could give the corresponding **256** (Route a). Also, isoquinolin-1-ones **257** and **258** could be synthesized *via* Routes b and c.



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