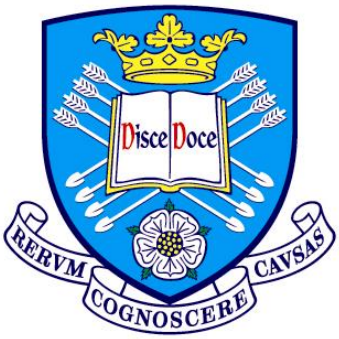
Deprotonation–Substitution of *N*-Boc-tetrahydroisoquinolines

A dissertation submitted for the degree of Doctor of Philosophy in Chemistry



Ruaa Talk

University of Sheffield

September 2017

Dedication

To the most compassionate women in my life Qamar and Mehasin.

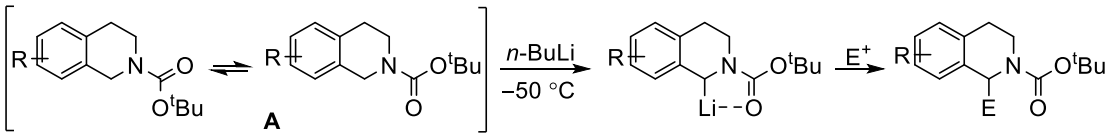
Declaration

This dissertation records the work carried out in the Department of Chemistry, University of Sheffield, between November 2013 and September 2017 and is original except where acknowledged by reference. No part of this work is being, nor has been, submitted for a degree, diploma or any other qualification at any other university.

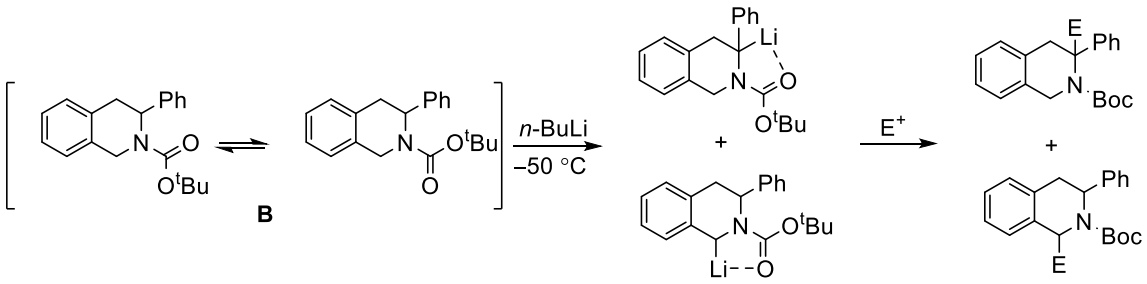
Abstract

Tetrahydroisoquinolines (THIQs) are found in a wide range of natural products and compounds with biological activity. This thesis describes the methodology of deprotonation–substitution as an efficient route to 1-substituted THIQs and 3-substituted THIQs. This methodology was developed by using organolithium and organomagnesium chemistry. Firstly, methods were developed for the lithiation–substitution of tetrahydroisoquinolines by carrying out *in situ* ReactIR spectroscopic monitoring of deprotonation reactions. Moderate to high yields of products were obtained under the optimum reaction conditions.

The lithiation–substitutions of tetrahydroisoquinolines **A** were carried out. This chemistry was applied to a short synthesis of the alkaloids (±)-dysoxyline and (±)-crispine A.



The lithiation–substitution of *N*-Boc-3-phenyltetrahydroisoquinoline **B** was also investigated. Lithiation was found to occur with approximately a 2:1 ratio at C-1 to C-3. NMR studies and DFT analysis were carried out in order to calculate the ratio of the two rotamers of **B**.



Investigations have also focused on *N*-Boc-3-cyanotetrahydroisoquinoline and *N*-Boc-2-cyanopyrrolidine. High enantioselectivities of the forming products could be obtained from the sequence of deprotonation–substitution of these compounds at –104 ºC using magnesium bases. Altering the solvent was shown to have a large impact on the yield and enantioselectivity of the products.

Acknowledgements

First of all, I thank the almighty Allah for the power He has provided me with to complete this work.

I would like to thank my supervisor, Prof. Iain Coldham for giving me the opportunity to carry out a PhD in his research group. I am indebted to HCED Iraq for the scholarship and the generous support. Appreciation goes to the Department of Chemistry, University of Sheffield for offering the recent facilities to perform this research. Thanks go to Sue and Sandra in NMR, Kieth and Rob in HPLC, Nick, Peter, and Sharon in stores, Harry and Craig in X-ray, Simon and Sharon in mass spectrometry.

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I would like finally to thank my wonderful family for all the love and help, as without it I would not continue my work. My Mum, Dad, brothers, sisters, my adorable nieces and nephews. As long as you are breathing I am always fine, safe and happy. may god bless you all.

حَسْبُنَا اللهُ سَيُؤْتِينَا اللهُ مِن فَضْلِهِ وَرَسُولُهُ إِنَّا إِلَى اللهِ رَاغِبُونَ.....

Contents

Abbreviations

Ac.	Acetyl
add.	Addition
AIDS	Aquired Immune Deficiency Syndrome
aq	aqueous
Ar	aryl
ax	axial
Piv	pivaloyl
Boc	*tert*-butoxycarbonyl
Bn	benzyl
br	broad
Bu	butyl
C	Celsius
CIPE	complex induced proximity effect
cm	centimetre
CNS	central nervous system
conc.	concentration
COSY	correlation spectroscopy
CPME	cyclopentyl methyl ether
CSP-GC	chiral stationary phase gas chromatography

CSP-HPLC	chiral stationary phase high performance liquid chromatography
DFT	density functional theory
DG	directing group
DME	1,2-dimethoxyethane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
dr	diastereomeric ratio
E	electrophile
ee	enantiomeric excess
EI	electron impact
epi-	epimer
eq or equiv.	equivalent (s)
eq or equat.	equatorial
er	enantiomeric ratio
ES	electrospray
Et	ethyl
F_{220}	florescence indicator 220
FT	Fourier transform
g	gram (s)
$\Delta G^{\ddagger}$	Gibbs energy of activation
h	hour (s)
$\Delta H^{\ddagger}$	enthalpy of activation

HIV	Human Immunodeficiency Virus
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HRMS	high resolution mass spectroscopy
HSQC	Heteronuclear single quantum coherence spectroscopy
Hz	hertz
i.d.	internal diameter
inv	inversion
^{i}pr	isopropyl
IR	infra-red
k	reaction rate constant
K	Kelvin
kJ	kilojoule (s)
L	litre (s)
L*	chiral ligand
LCT	liquid chromatography tandem
LDA	Lithium diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
lit.	literature
LRMS	low resolution mass spectroscopy
M	molar
Me	methyl

2-MeTHF	2-methyltetrahydrofuran
mg	milligram (s)
min	minute (s)
mL	millilitre (s)
mmol	millimole (s)
mol	mole (s)
m.p	melting point
MS	mass spectra (or spectrum)
m/z	mass to charge ratio
nm	nanometres
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
nosyl	4-nitrobenzene-1-sulfonyl chloride
OTf	Trifluoromethanesulfonate
p-	para
Ph	phenyl
PMDTA	pentamethyldiethylenetriamine
ppm	parts per million
R	alkyl group
rac-	racemic
R_f	retention factor
RSM	recovered starting material

R_t	retention time
r.t.	room temperature
S	solvent
s or sec	second (s)
$\Delta S^{\ddagger}$	entropy of activation
SET	single electron transfer
(–)-sp	(–)-sparteine
T	temperature
t	time
t-Bu or ^{t}Bu	tertiary butyl
TFA	trifluoro acetic acid
TFAA	trifluoro acetic anhydride
THIQ	tetrahydroisoquinoline
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*,*N*-tetramethylethylenediamine
TMPH	2,2,6,6-Tetramethylpiperidine
TMPMgCl	2,2,6,6-Tetramethylpiperidinylmagnesium chloride
TMS	trimethylsilyl
Tos	Toluenesulfonyl
UV	ultraviolet

1. Introduction

1.1 Introduction to Organolithium Chemistry

Organolithium compounds have been used frequently in organic synthesis. The power of organolithium reagents to create new C–C bonds has been used widely, especially in a stereoselective manner. The most common applications in synthesis use organolithium reagents as nucleophiles, strong bases and initiators for polymerization reactions. Also, they have been used widely as starting materials for other organometallic compounds.[1] Baudoin has recently reported the α-arylation of carbamates in high enantiomeric ratio by using sparteine-mediated lithiation in the first step followed by a Negishi cross-coupling.[2] Lithium-halogen exchange is another useful method that has been used in organic synthesis and was discovered by Gilman and Wittig in the early 1930s.[3] Organolithium chemistry has a vast range of applications in organic chemistry, using BuLi as a strong base and nucleophile.

Organolithium reagents are highly reactive bases with pK_a > 35, due to the ionic character of the C–Li bond. While many data suggest that the C–Li bond is ionic, due to the electronegativity difference between the carbon and lithium atoms, it does show covalent features as well.[4,5] For example, most organolithiums are soluble in non-polar solvents. Organolithiums are stable in hydrocarbons and are often stored as solutions in these solvents.[6, 7]

The freezing point measurement, crystal structure, NMR spectroscopic analysis, and calculations all show that in hydrocarbon solvents, organolithiums aggregate as hexamers, tetramers or dimers.[8,9] The steric properties of organolithiums have a crucial effect on their aggregation states. In hydrocarbons, primary organolithiums aggregate as hexamers. Secondary and tertiary organolithiums adopt tetrameric shapes. Bulkier species prefer to exist as dimers (Table 1-1**)**.[10] In fact, the aggregation level of organolithium reagents depends on steric effects and the reactivity of organolithiums is related to the aggregation state.[11,12]

Hexameric	Tetrameric	Dimeric	Monomeric
n-BuLi	*s*-BuLi	$PhCH_2Li$	-
EtLi	*i*-PrLi		
	t-BuLi		

Table 1-1

The reactivity and aggregate structure of organolithium compounds are determined by many factors, such as temperature, concentration, solvent and the presence of ligands. For example, at low temperatures in THF, *t*-BuLi is a dimer, while in Et_2O it is a monomer. The presence of coordinating ligands can stabilize the electron-deficient lithium atom and shift the aggregation to a lower state. These ligands provide an alternative source of electron density for the lithium cation, thus allowing the organolithium to shift to lower aggregates.[13–15] This increases the reactivity of the organolithium. The most common ligands are shown in Figure 1-1.[16]

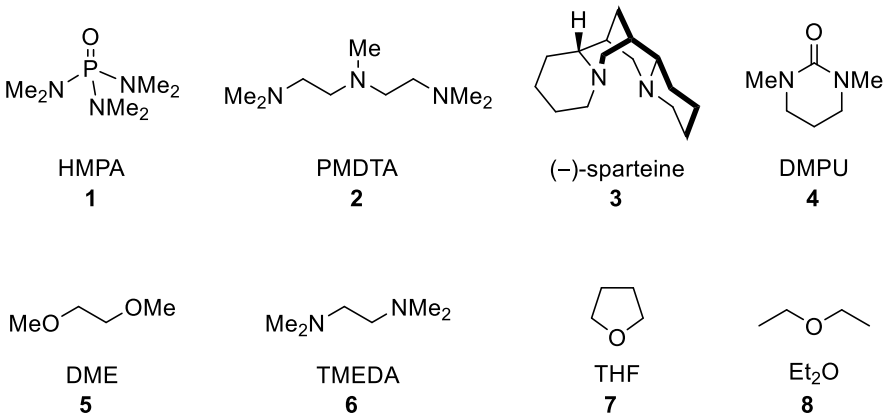


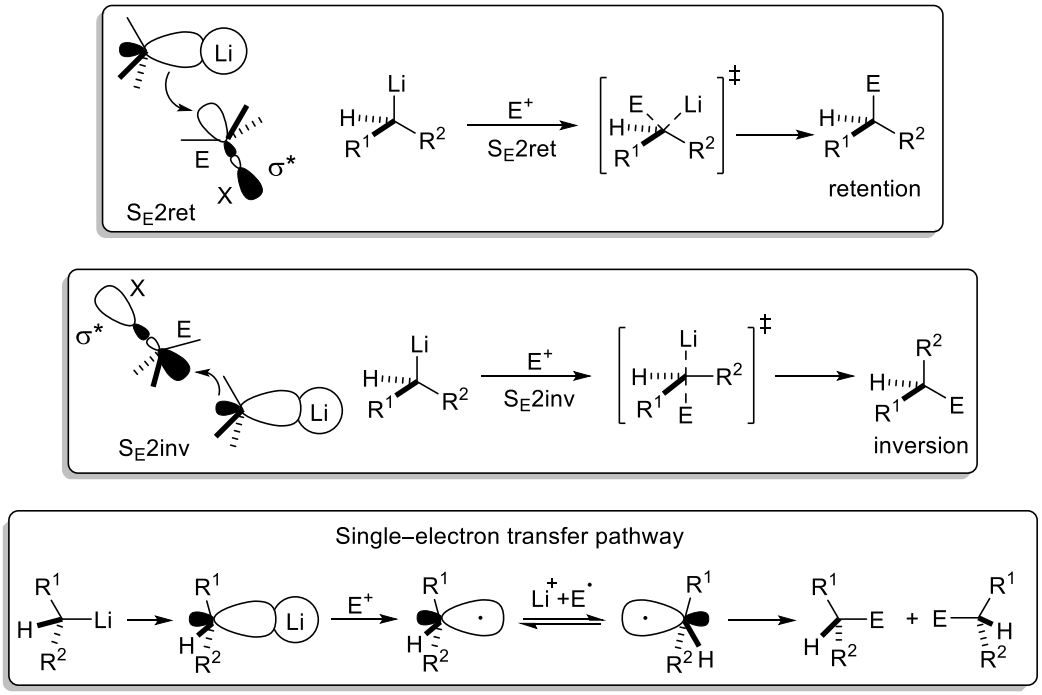
Figure 1-1

1.2 Reactions of Organolithiums–Stereochemical Course

There are several possible pathways for the lithiation–substitution reaction with an electrophile.[17] In 1999, Gawley proposed the terms S_E2ret and S_E2inv as an appropriate means to distinguish two types of reactions (Scheme 1-1).[18] These terms have been used to indicate the concerted formation of the C–E bond and breakage of the C–Li and E–X bonds. Both S_E2ret and S_E2inv require inversion at the electrophilic centre and no interaction between the leaving group and lithium cation. Both reactions are allowed by orbital symmetry and frontier orbital studies that show the reaction could proceed through retention or inversion. Scheme 1-1 shows the electron flow from the organolithium carbanionic orbital HOMO to the orbital of electrophile (alkyl halide) LUMO.

Substitution with complete loss of stereochemistry may occur through a non-concerted single electron transfer, which proceeds through a radical intermediate and hence loss of stereospecificity.[19] When the electrophile is easily reduced, a SET mechanism appears to be predominant.

Alternatively, loss of stereospecifity could arise from the presence of the configurationally labile organolithium.



Scheme 1-1

In the 1950's and 1960's, Seyferth showed that the reaction of vinyllithium species proceeded with retention; either by direct reaction with an electrophile or through a transmetallation–electrophilic quench.[20] In contrast with a stabilized conjugated system such as a benzylic organolithium, the nearby π-system gives the C–Li bond more p-character. This increases the planarity of the organolithium and opens up to a greater scope, both sterically and electronically, the possibility for attack at either lobe of the C–Li σ bond. Figure 1-2 shows the substitution reaction with benzyllithiums.[21–23]

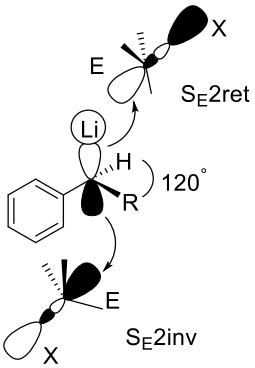
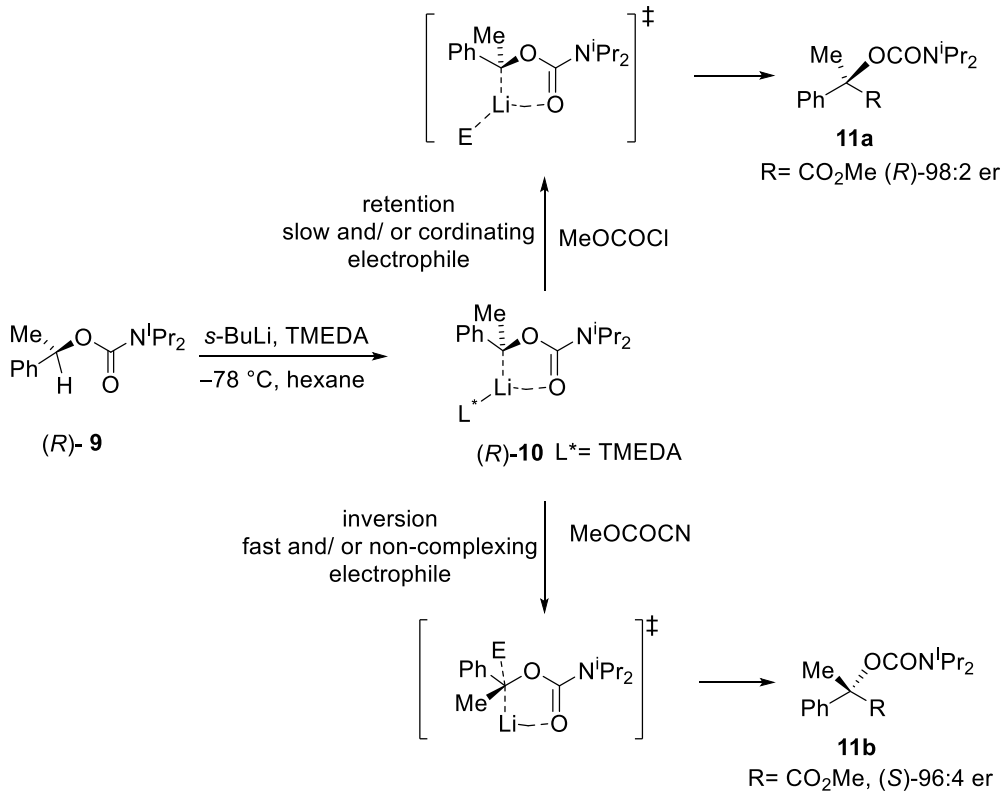


Figure 1-2

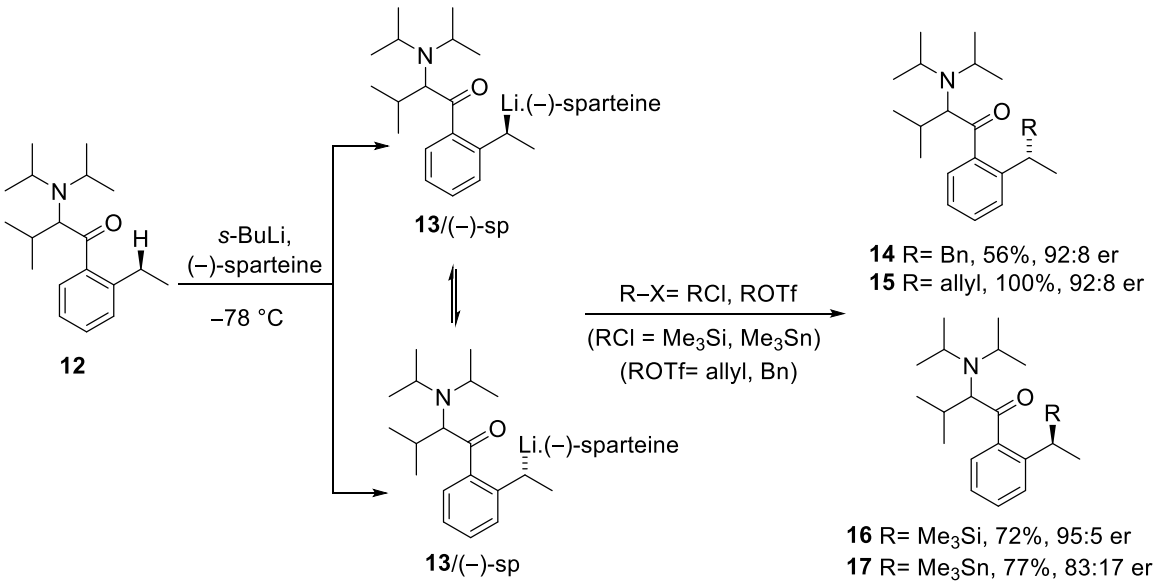
A study on the stereochemical course of these type of reactions was carried out by Hoppe using a configurationally stable tertiary benzylic organolithium with a variety of electrophiles (Scheme 1-2). Hoppe assumed that the deprotonation step proceeded with retention. The stereochemistry of the products was identified through comparison with

known products. Intermediate (*R*)-**10** was formed from the deprotonation of (*R*)-**9** using *s*-BuLi and TMEDA in hexane at –78 °C. Trapping (*R*)-**10** with electrophiles gave products **11a** with retention and **11b** with inversion of configuration (Scheme 1-2). In general, when the electrophilic leaving group coordinates to the lithium atom (such as an oxygen atom), this gives retention of configuration. Inversion occurs with non-coordinating electrophiles that contain leaving groups such as halide or cyanide, or by addition to heterocumulenes, such as CS_2.[22–24]



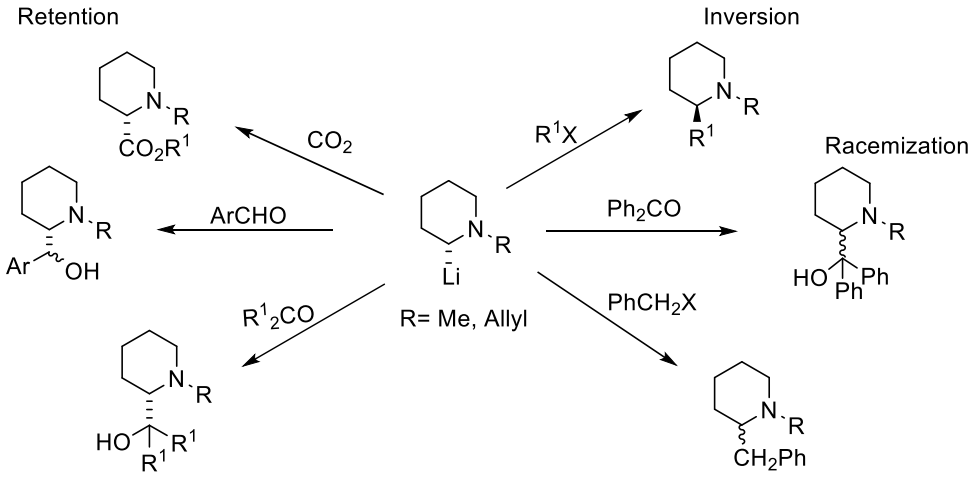
Scheme 1-2

Another study has been reported by Beak and co-workers.[25] The stereochemical behaviour of benzylic substituted organolithiums has been found to be similar to that found by Hoppe and co-workers (Scheme 1-3). They studied the asymmetric substitutions of compound **12** using (–)-sparteine as a ligand at –78 °C. Although the substitution proceeded through different mechanasims, they suggested that non-coordinating electrophiles, such as halides gave inversion of configuration. In contrast, coordinating electrophiles like tosylates proceeded with retention.



Scheme 1-3

Gawley reported tin–lithium exchange of *N*-alkyl 2-tributylstannyl piperidines and pyrrolidines from non-stabilised organolithium species.[19,26,27] He found that reactions of these non-stabilised organolithiums with electrophiles, such as aldehydes, ketones, and acylating agents proceeded with retention. On the other hand, racemisation occurred through single electron transfer with other electrophiles. Scheme 1-4 shows the reaction of *N*-alkyl 2-tributylstannyl piperidines with some electrophiles.



Scheme 1-4

Reactions involving organolithium reagents have a relatively limited scope as electrophiles such as allylic and aryl halides often give poor results. It is hard to alter the electrophilic reduction potential, therefore changing the oxidation potential of the nucleophile helps the reaction to proceed with a wide range of electrophiles. A solution to this is transmetalation of

the organolithium species to other metals, such as copper,[28–31] zinc,[32–34] or palladium.[2] Transmetalation is one of the best ways to halt the SET pathway. The transmetallation is often stereoselective and the subsequent organometallic intermediates often have high configurational stability.[35] Transmetalation offers broader range of reactivity, because each organometallic species reacts with a different scope of electrophiles. For example, organozinc reagents are an attractive option, because of the configurational and chemical stability of the organozinc intermediate. This intermediate can then react with the electrophile, and can transmetallate to other more reactive metals.[36,37]

1.3 *α*-Amino Organolithiums

Hydrocarbons are slow to deprotonate, as protons on hydrocarbons have a high pK_a. However, deprotonation of C–H bonds occurs at an acceptable rate when an organolithium intermediate shows at least one of three features: the electron-rich C–Li bond is stabilised by a nearby electron withdrawing group, an empty orbital, or intramolecular interaction of the lithium atom to a nearby heteroatom. In fact, if the proton to be removed is allylic, benzylic, vinylic, attached to a small saturated ring, or attached to an aromatic ring, its acidity will increase and successful lithiations are more likely to occur. Moreover, lithiation adjacent to sulfur or phosphorus is favoured by acidifying group, for example dialkylphosphonyl or arylsulfonyl. Lithiation also takes place when the proton is adjacent to a nitrogen or oxygen based group.[38]

α-Amino organolithiums can be classified into four types: mesomerically stabilised, dipole-stabilised, mesomerically and dipole-stabilised and non-stabilised organolithiums (Figure 1-3). Deprotonation *α* to nitrogen provides an important method to form *α*-amino-organolithium compounds. This can produce various substituted amines after reaction with different electrophiles.[39]

Unstabilized *α*-amino organolithiums were first reported in the 1970's by Peterson, who found that unstabilized organolithiums could be prepared via tin–lithium exchange.[40–42] Few examples of this kind of organolithium formation have been reported.[43] Organolithium reagents, such as *n*-BuLi could coordinate to the nitrogen lone pair, and this also stabilised the organolithium intermediate. However, interaction of the N lone pair with the adjacent (electron-rich) C–Li bond will be destabilising through a filled-filled orbital interaction between the nitrogen lone pair and the C–Li bond. That's why direct lithiation *α* to nitrogen without an adjacent directing group is usually not possible. However, if an aromatic ring or a

carbonyl is attached to the nitrogen, the repulsive interaction can be relieved through conjugation of the nitrogen lone pair with the directing group.[44]

In 1989, Beak and co-workers described the effect of the carbonyl group on stabilising organolithium intermediates by coordination of the electron rich oxygen with the lithium atom.[36] A variety of groups, such as amides,[35] formamides,[45] carbamates[36] and nitrosamine[46] have been used for dipole-stabilization of α-amino organolithium species.[38] Mesomerically stabilised organolithiums exist when lithiation occurs adjacent to azaallyl amide, allylic or benzylic amine (Figure 1-3).[47]

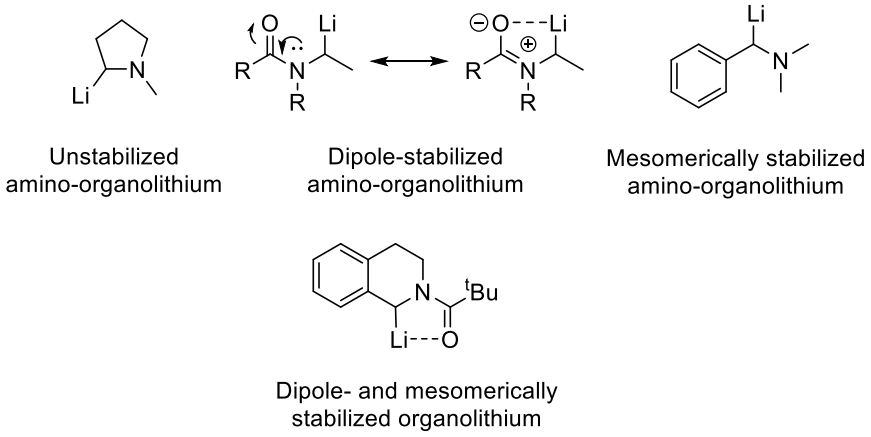
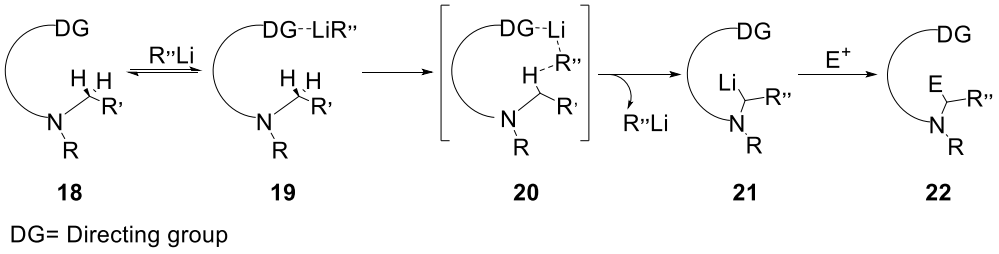


Figure 1-3

1.4 The Complex-Induced Proximity Effect (CIPE)

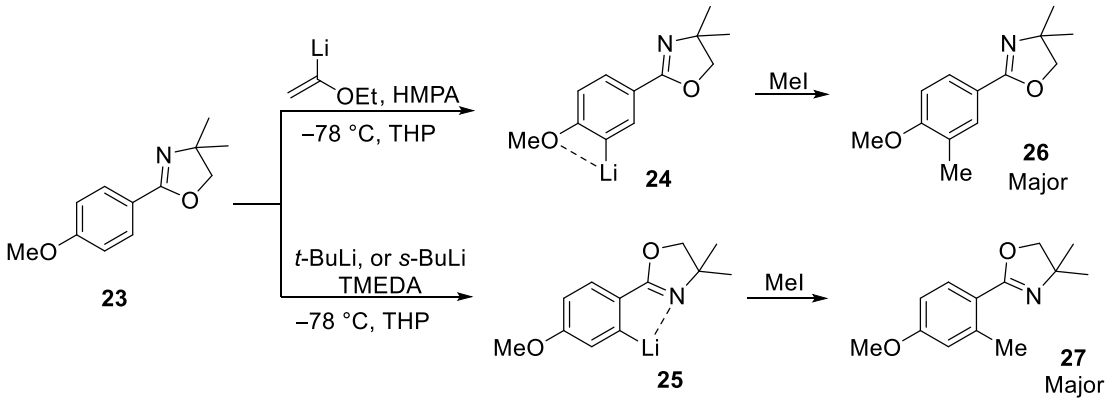
Formation of organolithium species can be explained as a two-step process. These processes include the replacement of a carbon-hydrogen bond by a carbon-lithium bond which can occur chemoselectively, regioselectively, diastereoselectively or enantioselectively. In order for the carbanion intermediate to form, an activating group adjacent to the proton to be removed is needed. This 'activating' group forms a prelithiation complex that is close to the site of deprotonation. This phenomenon is called the complex-induced proximity effect (CIPE). The goal of using the CIPE is to direct metalation using an adjacent directing group.[48–50]

The CIPE is generally used in lithiation–substitution reactions. The reaction proceeds through different steps from **18** to **22** (Scheme 1-5). In the first step, the organolithium base becomes associated with the substrate and forms the pre-lithiation complex **19**. This complex then adopts a suitable conformation **20** to remove a proton, in which the organolithium reagent **21** is formed. Quenching with an electrophile then gives the product **22**.[49] An investigation in to the CIPE has been carried out, which confirmed the number of reaction steps. [51,52]



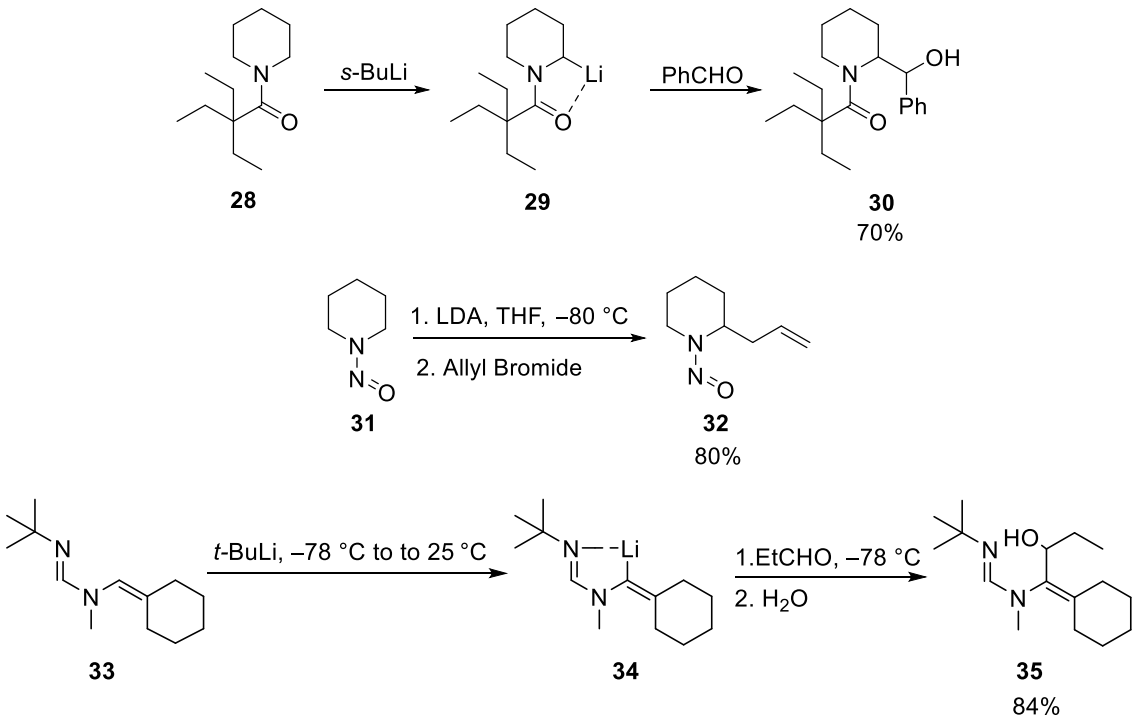
Scheme 1-5

In 1994, Shimaio and Meyers reported the deprotonation reaction of compound **23** using ethoxy vinyllithium–HMPA (Scheme 1-6).[53] which was prepared from the reaction between *t*-BuLi, ethyl vinylether and HMPA. The reaction was performed at –78 °C, and the use of ethoxy vinyllithium–HMPA as a base afforded compound **26** in excellent yield. On the other hand, the use of *s*-BuLi or *t*-BuLi with or without TMEDA led to the formation of compound **27** as the major product. The methoxy group seems to be the dominant directing group when ethyoxyvinyl lithium–HMPA was used. The reason behind this was unclear, they hypothesized that there could be clusters of ethoxy vinyllithium–HMPA which hindered the deprotonation *ortho* to the oxazoline group, they also suggested that this reaction could be kinetically controlled.



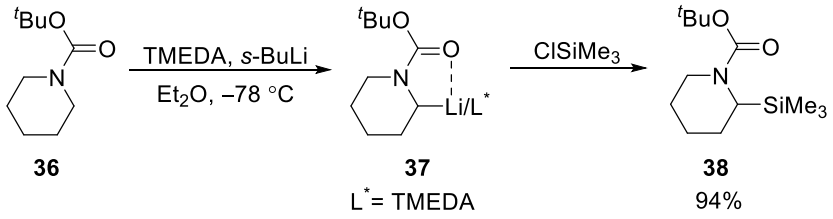
Scheme 1-6

Furthermore, there are other functional groups that can direct metalation, amide,[54] nitroso,[46] and formamidine[45] and many other directing groups have been widely used by many researchers to direct deprotonation at the α–position (Scheme 1-7).



Scheme 1-7

Another well-known directing group is the *tert*-butoxycarbonyl group, which was developed and used by Beak and co-workers in 1989. An example is shown in Scheme 1-8. The reaction of piperidinyl-*t*-butylcarbamate **36** with *s*-BuLi in Et_2O and TMEDA at –78 °C gave compound **38** in 94% yield after an electrophilic quench with TMSCl.[55] In the reaction the *tert*-butoxycarbonyl group directs the lithiation to the 2-position. It also has the advantage of being bulky and sterically hindering nucleophilic attack of *s*-BuLi on to the carbonyl carbon atom.

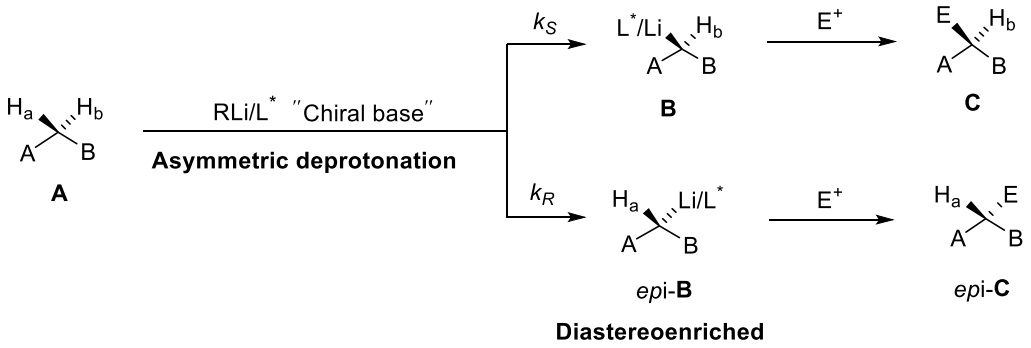


Scheme 1-8

1.5 Asymmetric Deprotonation

The process of asymmetric deprotonation is shown in Scheme 1-9 and involves removing a proton from a prochiral substrate **A** using a chiral base. The base is produced from the complexation of a chiral ligand to an organolithium reagent, and the reaction with the substrate proceeds *via* diastereomeric transition states. These transition states are at different energies

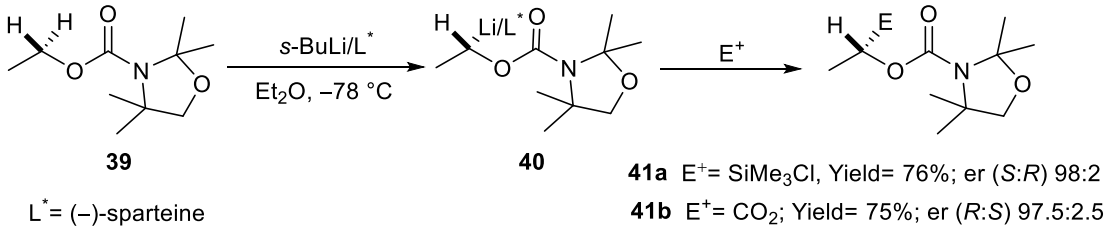
and consequently yield unequal amounts of diastereomeric carbanions **B** and *epi*-**B**. These two intermediates may interconvert, so care needs to be taken to assess this possibility. The deprotonation reaction is kinetically controlled. If there is no equilibration then, after trapping with an electrophile, the enantiomeric ratio of **C** and *epi*-**C** reflects the ratio of k_S/k_R.[44]



Scheme 1-9

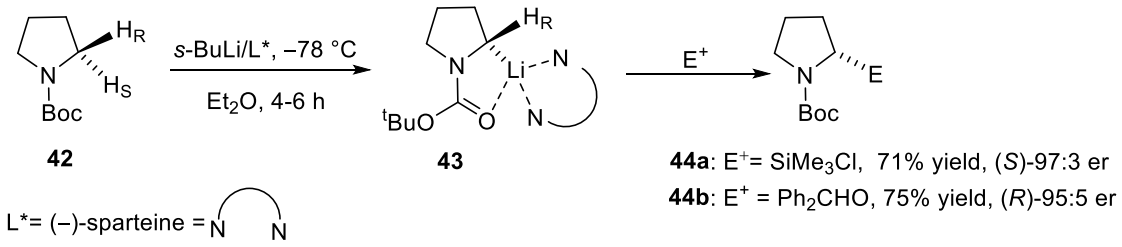
(electrophilic quench assumed retention of configuration)

Hoppe and co-workers were the first group to report the asymmetric deprotonation of chiral substrate **39** using *s*-BuLi/(–)-sparteine, to give the configurationally stable enantioenriched species **40** (Scheme 1-10).[56] They reported that predominantly *pro*-(*S*)-proton had been abstracted. Quenching the intermediate **40** with different electrophiles gave compounds **41a** and **41b** in high enantiomeric ratios with retention of configuration.[56]



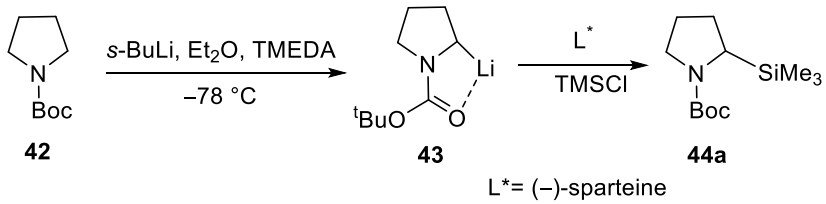
Scheme 1-10

Following on from the work of Hoppe, Beak and co-workers reported the enantioselective synthesis of 2-substituted Boc-pyrrolidines. Using *s*-BuLi/(–)-sparteine, followed by electrophilic quench gave compounds **44a** and **44b** in high enantiomeric ratios (Scheme 1-11).[57,58]



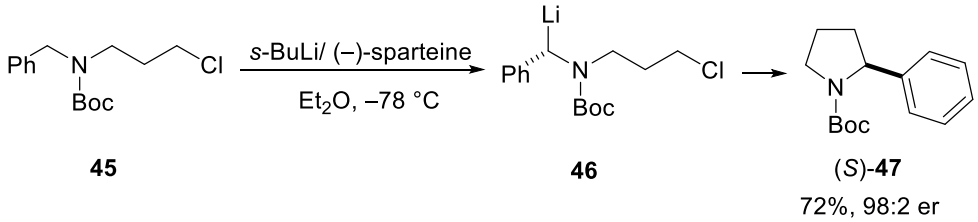
Scheme 1-11

The enantioenrichment of the products **44a** and **44b** may arise from either asymmetric substitution, where asymmetric induction occurs in the post-deprotonation step, or from asymmetric deprotonation were one of the enantiotopic protons is abstracted by the chiral base. Asymmetric deprotonation leads to a configurationally stable intermediate **43**, that reacts stereospecifically with retention or in version of configuration. Tin–lithium exchange experiments were carried out to help clarifying the mechanesim. Racemic **44a** was formed by deprotonation of **42** using *s*-BuLi. Complexation of the racemic intermediate **43** with (–)-sparteine gave compound **44a** as a racemate (Scheme 1-12). This confirmed that the reaction proceeded *via* an asymmetric deprotonation pathway.[57]



Scheme 1-12

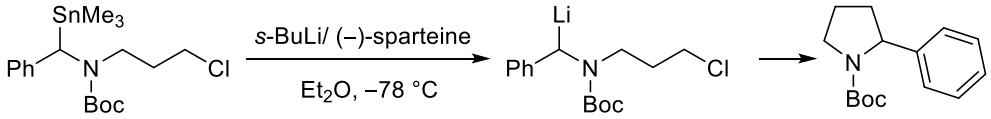
Asymmetric deprotonation was also found to be occurring with the carbamate **45** (Scheme 1-13).[36,59] The intermediate organolithium **46** underwent cyclisation to give the enantioenriched 2-arylpyrrolidine (*S*)-**47** in a 72% yield.



Scheme 1-13

Tin–lithium exchange using racemic substrate **48** in the presence of (–)-sparteine gave racemic product **47** in a 44% yield (Scheme 1-14). This confirmed that the enantioselective step was

the asymmetric deprotonation. Furthermore, cyclisation of organolithium intermediate **46** to (*S*)-**47** must have been faster than the rate of racemization.



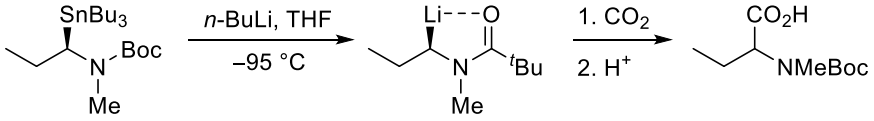
48 **46** **47**
44%

Scheme 1-14

1.6 Determination of configurational stability

Synthesis of enantiopure compounds using organolithium chemistry is related to the configurational stability of the lithium bearing stereogenic centre. The configurational stability can be determined using several ways, such as the synthesis of single enantiomers (by tin-lithium exchange).

Tin-lithium exchange is a rapid, thermodynamically controlled process, it is a stereocontrolled reaction that can be used to indicate the stability of some carbanions.[38] The Chong group have investigated the configurational stability of the enantioenriched organolithium (*R*)-**50** species using different temperatures and times. Enantioenriched (*R*)-**50** was obtained from the transmetallation reaction of the (*R*)-**49** species (98:2 er) using *n*-BuLi at −95 °C in THF (Scheme 1-15, Table 1-2). Quenching the intermediate (*R*)-**50** using CO_2 as an electrophile was carried out to measure the enantioenrichment of the product. They found that at −95 °C and a lithiation time of over 10 minutes, gave a high yield and excellent er (> 98:2) of compound **51**. However, conducting the reaction at a higher temperature of −55 °C resulted in configurational instability (62:38 er) of the intermediate **50** and a 76% yield of compound **51**. Changing the solvent to dimethoxy ethane (DME) increased the epimerisation rate, while adding HMPA in THF resulted in complete racemisation. They have proposed that the effect of HMPA on racemisation could be due to its polarity, or from disrupting the coordination between the directing group and the lithium atom.[60]



(*R*)-**49**
98:2 er

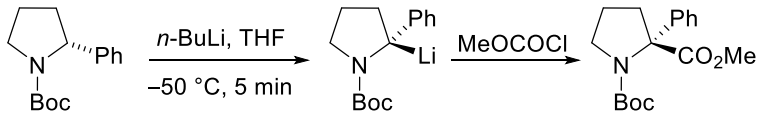
(*R*)-**50** **51**

Scheme 1-15

Entry	T (°C)	Time (min)	Yield (%)	er
1	–95	10	97	98:2
2	–95	180	75	94:6
3	–78	10	95	96:4
4	–78	180	76	90:10
5	–78 (DME)	180	54	84:16
6	–78 (HMPA)	180	50	50:50
7	–55	120	76	62:38

Table 1-2

In 2012, Coldham and O'Brien and co-workers investigated the configurational stability of the enantioenriched substrate (*R*)-**52** (97:3), at different temperatures using *s*-BuLi/(–)-sparteine and MeOCOCl as the electrophile over different times (Scheme 1-16, Table 1-3).[61] By measuring the enantiomeric ratio of the product **54**, they found that temperature had a large impact on the enantiomeric ratio. At a low temperature of –78 °C high enantioenrichment and a low yield of **54** was obtained, meanwhile at 0 °C the reaction generated a better yield of compound **54** due to the rate of Boc group rotation being fast, however the rate of racemisation was also fast. The optimal conditions for lithiation–substitution were found to be –50 °C with a lithiation time of 5 minutes. Different electrophiles were used to give high yields and excellent enantiomeric ratios, as shown in Scheme 1-17.[61]



(*R*)-**52**
97:3 er

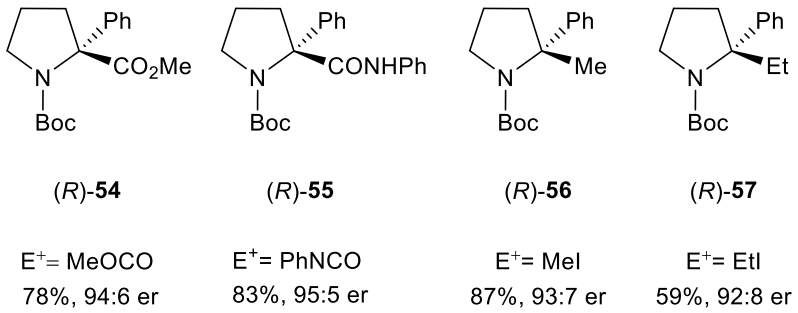
(*R*)-**53**

(*R*)-**54**

Scheme 1-16

Entry	T (°C)	Time (min)	Yield (%)	er (*S*:*R*)
1	–78	60	31	97:3
2	–50	10	74	90:10
3	–50	5	78	94:6
4	–40	5	69	85:15
5	–30	5	79	65:35
6	0	5	82	50:50

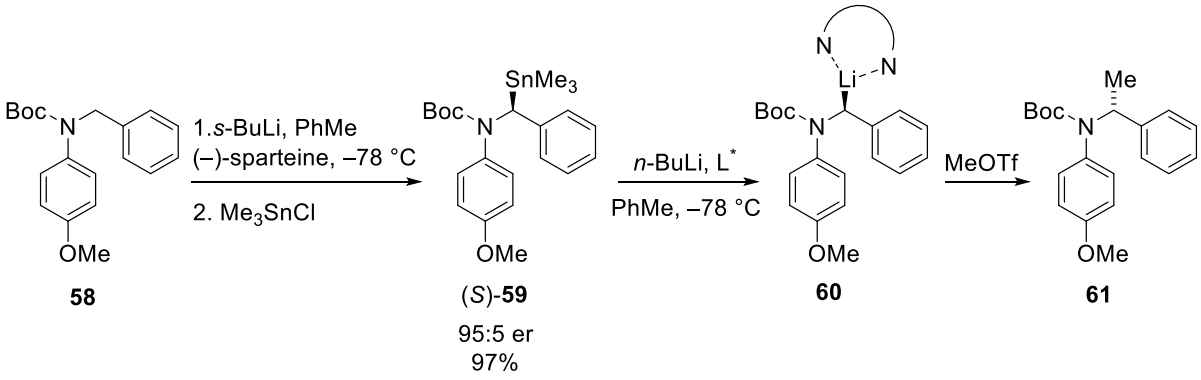
Table 1-3



Scheme 1-17

1.7 Configurational Stability of Benzylic *α*-Amino Organolithiums

Benzylic *α*-amino organolithium species are generally configurationally unstable (Figure 1-2, page 3).[7,21,62,63] However, a few secondary benzyllithium species have been found to be configurationally stable using different solvents and ligands. For example, when (*S*)-**59** was reacted with *n*-BuLi in the presence of (–)-sparteine, it was found to be partially configurationally stable. The high enantiomeric ratio was maintained even after 10 hours. On the other hand, when (*S*)-**59** was reacted with *n*-BuLi in the presence of TMEDA followed by an electrophilic quench, compound **61** was obtained in lower enantiomeric ratios (Scheme 1-18, Table 1-4).[62] It's important to mention that the substrate (*S*)-**59** was prepared by deprotonating compound **58** using s-BuLi/(–)-sparteine at –78 °C. The reaction gave a good yield of (*S*)-**59** and high er **(**95:5).[62]

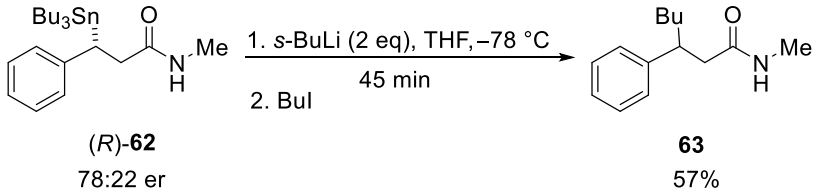


Scheme 1-18

Entry	Ligand	Time (h)	Yield (%)	er (*R*:*S*)
1	(–)-sparteine	10	83	95:5
2	(–)-sparteine	0.5	73	95:5
3	TMEDA	10	81	54:46
4	TMEDA	0.5	79	70:30

Table 1-4

Several techniques have been used to measure the configurational stability of these compounds. For instance, enantioenriched tin compound (*R)*-**62** (78:22) has been transmetalated using *s*-BuLi in THF for 45 minutes. Addition of BuI gave racemic product **63** in a 57% yield (Scheme 1-19).[64]

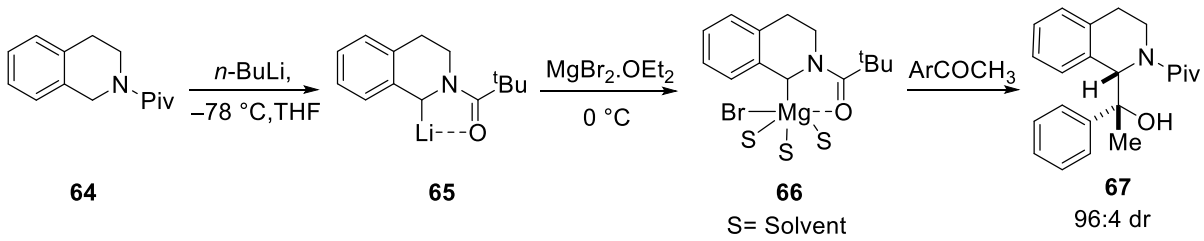


(*R*)-**62**
78:22 er

63
57%

Scheme 1-19

As mentioned previously, another group of α-amino organolithium compounds are dipole and mesomerically stabilised *α*-amino organolithiums (Figure 1-3, page 7). These can be prepared by proton abstraction using an alkyllithium base. Many researchers have questioned the configurational stability of these organolithium species. In 1985, Seebach and co-workers showed that the addition of an aldehyde to lithiated *N*-pivaloyl THIQ **65** in THF resulted in poor diastereoselectivity. However, transmetalation using magnesium bromide gave the magnesiated species **66**, which could then react with an aldehyde to give product **67** with excellent diastereoselectivity (Scheme 1-20).[65] In this case two asymmetric centres were formed simultaneously and selectively. The structure of the major diastereoisomer was only determined by X-ray crystallography. To explain the difference in diastereoselectivity between both metals they suggested that the lithiated intermediate underwent a single electron transfer reaction. As a result low diastereoselectivity was obtained.[65]



64

65

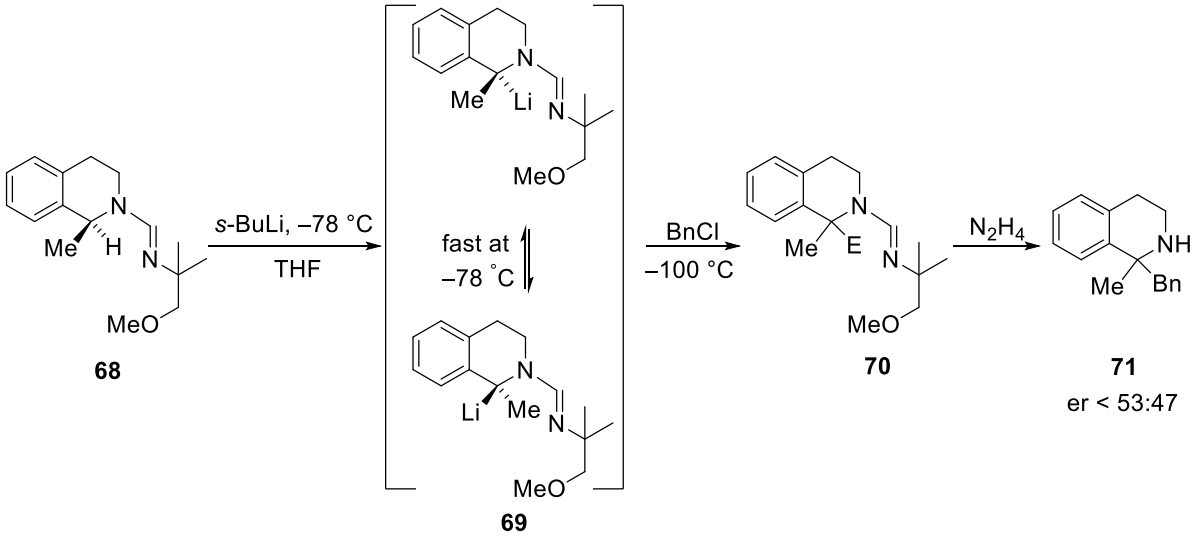
66
S= Solvent

67
96:4 dr

Scheme 1-20

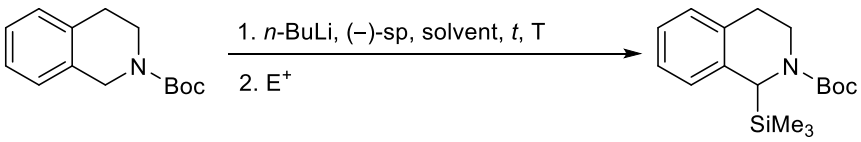
Further work was carried out in 1989 by Meyers and co-workers who investigated the configurational stability of tetrahydroisoquinoline **68** (Scheme 1-21).[63] Lithiation of compound **68** was carried out using *s*-BuLi at –78 °C to generate intermediate **69**. Cooling the reaction mixture to –100 °C, followed by the addition of benzyl chloride gave racemic product **70** that

was converted to compound **71** using hydrazine. This indicated that the organolithium intermediate was configurationally unstable.



Scheme 1-21

In 2013, Coldham and co-workers reported a study on the configurational stability of *N*-Boc-tetrahydroisoquinoline **72** (Scheme 1-22, Table 1-5).[66] Lithiation of substrate **72** using *n*-BuLi/(–)-sparteine was carried out over different times, using different solvents and temperatures, followed by TMSCl trapping. After a 1hour lithiation time at –78 °C in toluene, product **73** was obtained in a 67% yield and 67:33 er. In comparison, using Et_2O as a solvent gave a lower yield and er. The lower yield and er was thought to be due to the coordinating effects of the solvent. Considering the epimerisation of lithium species at high temperature, it was decided to examine the configurational stability at –100 °C using different solvents. Starting with toluene at –100 °C gave a better er (82:18) of **73** in a 48% yield. Enantioselectivity was significantly lost as expected when using 2-MeTHF. Furthermore, lithiation of **72** was investigated at lower temperatures down to –120 °C. Using pentane or a mixture of PhMe and pentane (1:1) at –120 °C gave product **73** in a lower er when compared to carrying the reaction at –100 °C. Finally, slow addition of the electrophile showed a slight improvement in er with low yield. They suggested that in PhMe, there is fairly equal mixture of *n*-BuLi/(–)-sparteine complexes and that they equilibrate at low temperature, but one reacts faster than the other to give the product in up to 85:15 er. They hypothesized that the reaction proceeded through a dynamic kinetic resolution pathway.[66,67]



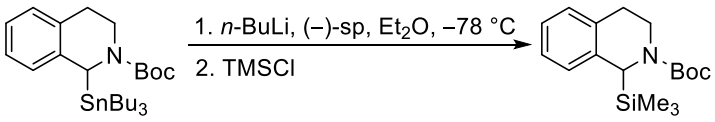
72 **73**

Scheme 1-22

Entry	Time (h)	T (°C)	Solvent	Yield %	er
1	1	–78	PhMe	67	67:33
2	1	–78	Et_2O	54	62:48
3	1	–100	PhMe	48	82:18
4	1	–100	2-MeTHF	26	59:41
5	1	–120	pentane	–	61:39
6	1	–120	PhMe:pentane (1:1)	–	74:26
7	2	–100	PhMe, slow add. of E^+ over 3.5 h	24	85:15

Table 1-5

Moving forward, tin-lithium exchange was carried out using racemic **74**, *n*-BuLi and (–)-sparteine in Et_2O at –78 °C (Scheme 1-23).[66] After 1 hour, transmetalation was completed and the lithiated intermediate was quenched with TMSCl to afford compound **73** with 67:33 er, which was the same as the reaction from direct lithiation. This indicated that the lithiated intermediate derived from compound **74** is configurationally unstable.

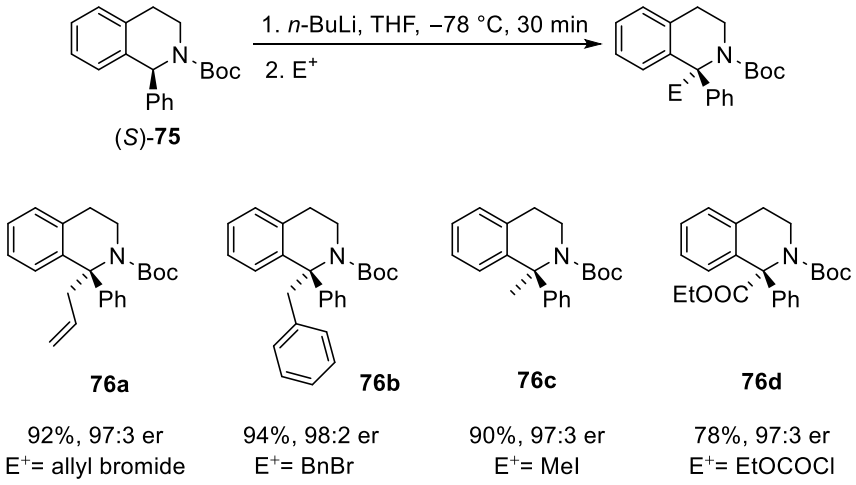


74 **73**
67:33 er

Scheme 1-23

Coldham and Li have reported the lithiation of enantioenriched (*S*)-1-phenyl-*N*-Boc-tetrahydroisoquinoline **75**, using *n*-BuLi at –78 °C (Scheme 1-24).[68] The optimum conditions were found using *in-situ* React IR spectroscopy, which showed that the rotation of the Boc group was fast at –78 °C, and the time required for full lithiation was 30 minutes. High enantioenrichment and good yields of 1,1-disubstituted tetrahydroisoquinolines were isolated without the need to use a chiral ligand. In comparison with THIQ **72**, in which the

organolithium was labile even at a very low temperature, the organolithium derived from 1-Ph-THIQ **75** showed a much higher configurational stability. They have hypothesized that the deprotonation step proceeded with retention of configuration.[68]



Scheme 1-24

Chapter 2. Synthesis of 1-Substituted Tetrahydroisoquinolines

2.1 General Introduction to 1-Substituted Tetrahydroisoquinoline (THIQ)

Tetrahydroisoquinoline (THIQ) alkaloids have become important synthetic targets due to their biological and pharmacological activities, in particular 1-substituted-THIQs. For example, salsolidine **77** and (*S*)-norreticuline **78** are important products, as they act as key intermediates for the synthesis of more complex molecules, such as morphine and (*S*)-xylopinine.[69] Most THIQs have physiological and pathological effects in the human body. For example, (+)-1-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline **79** is an effective anticonvulsant agent.[70] Azapodophyllotoxin **80** is an anti-tumor agent. Another THIQ derivative is 11-hydroxyerythratidine **81**, which "exhibits curare-like, sedative, hypotensive, and central nervous system (CNS) depressant activities". Some THIQs can be found in the structure of natural products like benzylisoquinoline alkaloid **82**, which can be found in the family of *Papaveracea*, known for its antitussive effect.[71] Salsoline **83** has been shown to "regulate prolactin release, neuronal transmission in sympathetic ganglia, and neurotransmission modulation".[69] Tubocurarine **84** is a more complex example and is a non-depolarizing neuromuscular-blocking drug that can be used for skeleton muscle relaxation so its derivatives can be used in anesthesia (Figure 2-1).[72,73]

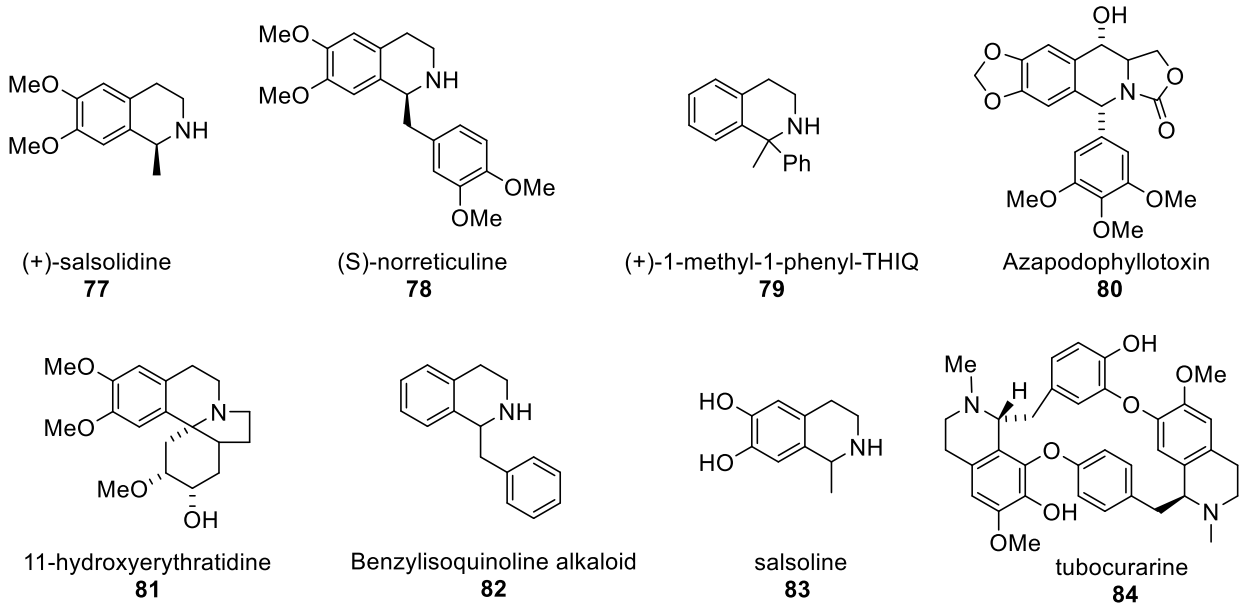


Figure 2-1

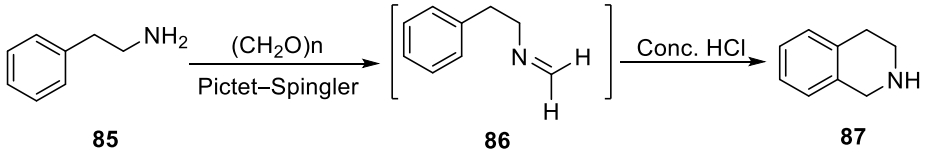
As mentioned above, 1-substituted THIQs have great importance as alkaloids, and as key intermediates in the synthesis of other complex natural products. This has encouraged researchers to develop a number of methodologies for the synthesis of 1-substituted THIQs.[74]

Usually, biological studies are carried out using racemic THIQs, due to the lack of efficient synthetic approaches to enantiopure THIQs.[75]

Generally, the synthesis of THIQ derivatives is achieved using either the Pictet–Spengler or the Bischler–Napieralski reaction. Both approaches provide a way to prepare substituted THIQs with stereoselectivity.

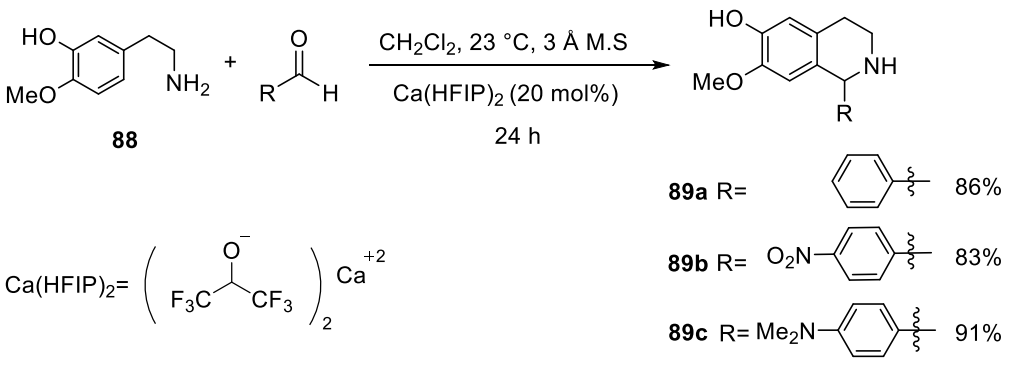
2.2 The Pictet–Spengler Condensation

The Pictet–Spengler reaction is one of the most important ways for the synthesis of isoquinoline alkaloids. Pictet and Spengler found that THIQs can be prepared by reacting β-phenylethylamine with formaldehyde as shown in Scheme 2-1 (no yield was reported).[76] The reaction occurs in two steps. The first step is condensation of the amine and aldehyde to create the intermediate imine **86**, which is carried out under acidic conditions using protic solvent. In the second step, the intermediate imine **86** undergoes a 6-*endo*-trig cyclization to give the cyclized product **87**.[77]



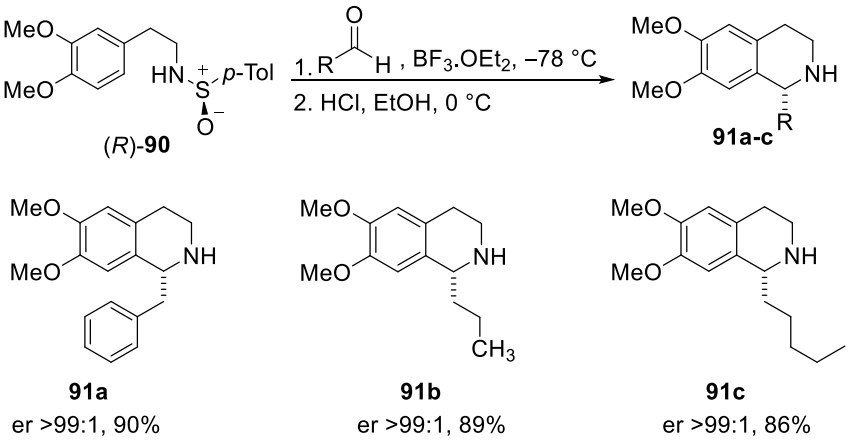
Scheme 2-1

Stambuli and co–workers investigated Pictet–Spengler reaction in the presence of Lewis acids (Scheme 2-2).[78] They studied the use of a 1:1 mixture of different aldehydes with 3-hydroxy-4-methoxyphenethylamine **88** in the presence of calcium 1,1,1,3,3,3-hexafluoroisopropoxide [$Ca(HFIP)_2$]. The use of the Lewis acid allows the reaction to proceed at room temperature with high regioselectivity using a variety of aldehydes. This regioselective reaction provided 1-substituted THIQs **89a–c** in good yields.[78]



Scheme 2-2

Nowadays, stereoselective Pictet–Spengler reactions have become one of the most important approaches for the synthesis of 1-substituted THIQs and their derivatives. Chiral auxiliary promoted methodologies have been used widely, especially attaching a chiral group to the nitrogen atom to achieve stereocontrol for the preparation of enantioenriched compounds.[79] For example, in 2001 Koomen and co–workers reported the synthesis of compounds **91a-c** in high yields and good diastereoselectivities using Pictet–Spengler condensation reaction with the chiral *N*-sulfinyl amine **90** (Scheme 2-3).[80] Enantiopure *N*-*p*-tolylsulfinyl amine (*R*)-**90** was reacted with simple aldehydes in the presence of $BF_3.OEt_2$ at –78 °C. Removing the chiral auxiliary group using mild acidic conditions produced the desired compounds **91a-c** in good overall yields, and in most cases, high enantiomeric ratios.

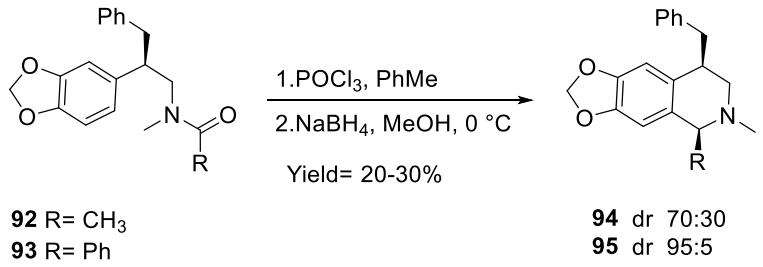


Scheme 2-3

2.3 The Bischler–Napieralski Cyclisation/Reduction

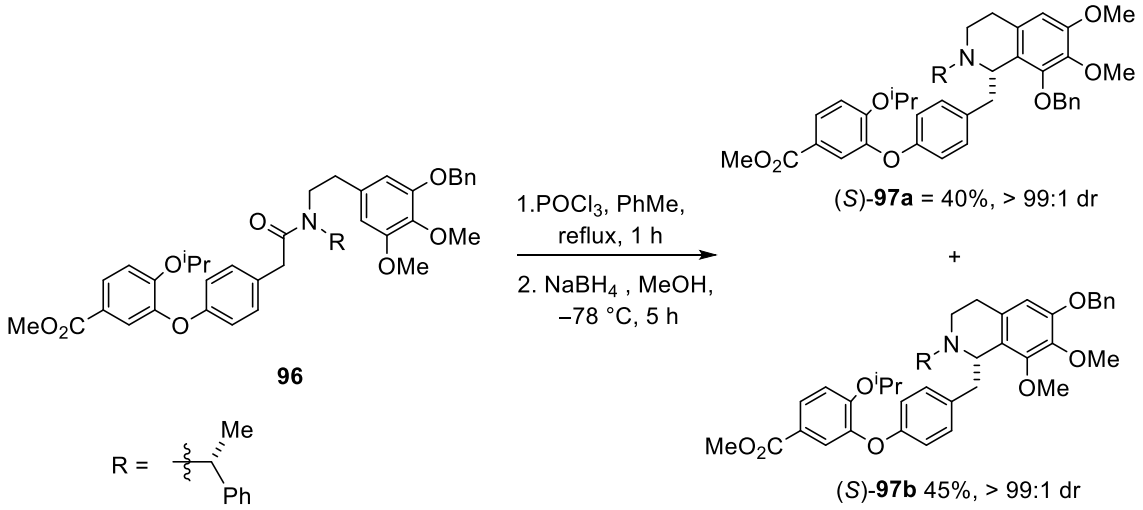
The Bischler–Napieralski reaction is another classical way used for the preparation of THIQ derivatives. The reaction uses the cyclisation of an amide, followed by reduction of the resulting imine.[81] The reduction step is very important for the stereochemical outcome of the synthesis, enabling the formation of a stereogenic centre, thus leading to enantioselective or diastereoselective synthesis.[82]

A Bischler–Napieralski reaction was carried out using enantiopure amides **92** and **93**. Cyclisation followed by *in-situ* reduction for the imine formed using $NaBH_4$ produced compounds **94** and **95** in low yields and diastereoselectivities up to 95:5 (Scheme 2-4). It was observed that the major diastereoisomer was the cis isomer, which results from a stereoselective reduction process.[83]



Scheme 2-4

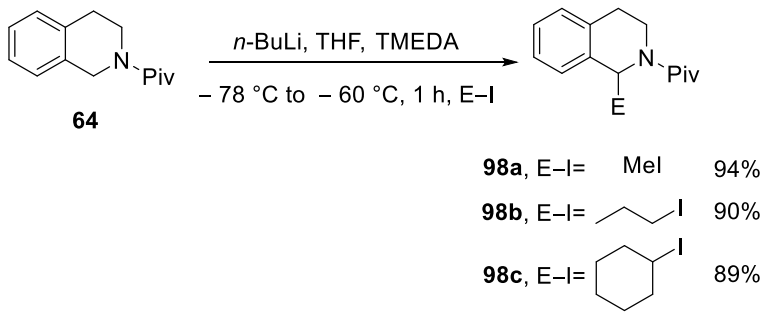
Bischler–Napieralski cyclization was used as a crucial step in the total synthesis of (–)-tejedine (Scheme 2-5).[84] The chiral auxiliary bearing starting material **96** undergoes a typical Bischler–Napieralski cyclisation reaction in benzene, in the presence of phosphorus oxychloride, followed by reduction of the imine formed using $NaBH_4$. The cyclisation reaction gave two regeoisomers (*S*)-**97a** and (*S*)-**97b** in a 40% and 45% yield respectively, each with > 99% dr. The product **97a** was required for the total synthesis of (–)-tejedine.[84]



Scheme 2-5

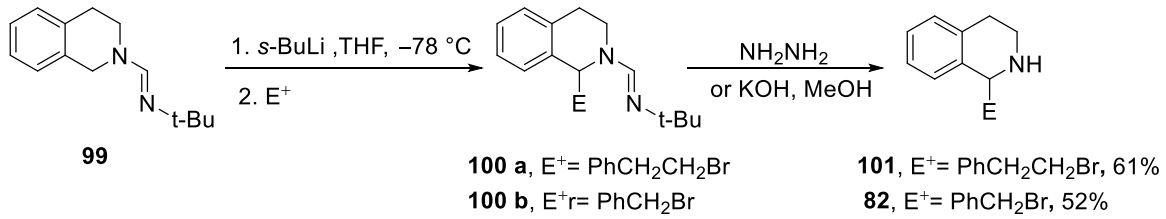
2.4 Synthesis of 1-Substituted-THIQs Using Organolithium Reagents

Lithiation–substitution reactions using organolithium reagents is an interesting approach for the synthesis of tetrahydroisoquinoline derivatives. Generally, *s*-BuLi and *t*-BuLi have been used as bases to complete the lithiation step. Various stabilising groups, including carbamate,[85] pivaloyl,[86–88] and formamidine,[89,90] have been used for dipole–stabilisation of the α-amino organolithium species. Seebach and co-workers reported the lithiation–substitution reaction of THIQ **64** in THF in the presence of TMEDA (Scheme 2-6).[91] After the addition of different electrophiles, the mixture was stirred for 1 hour to give compounds **98a–c** in good yields.



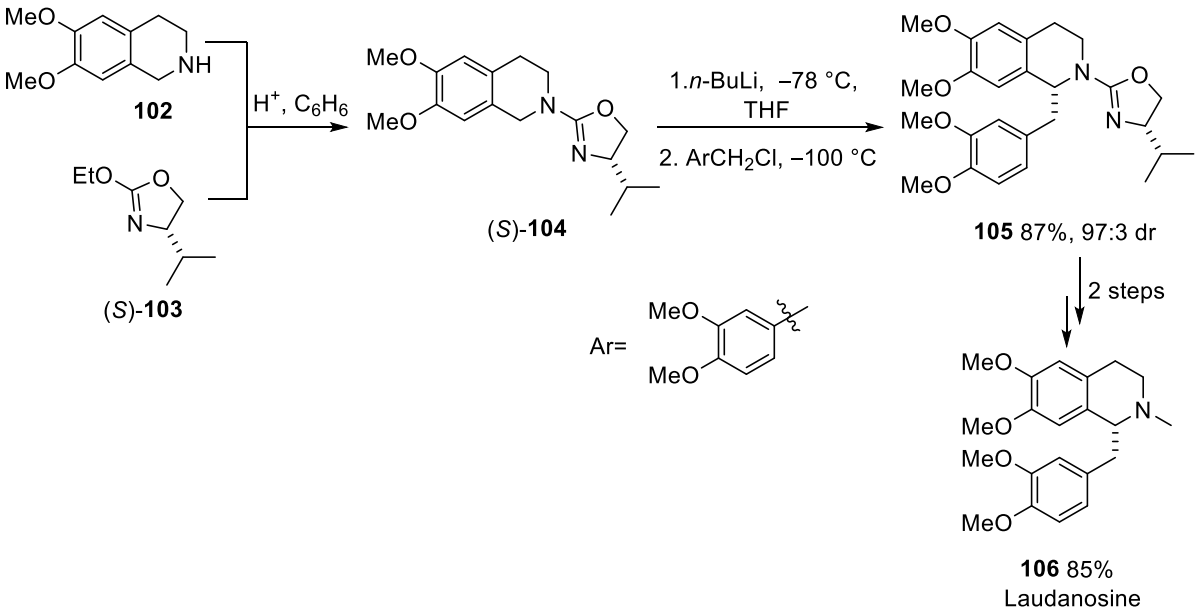
Scheme 2-6

Meyers and co-workers reported the lithiation–substitution reaction of *N*-formamidine THIQ **99** at the C–1 position (Scheme 2-7).[92] The reaction was carried out using *s*-BuLi in THF at –78 °C, followed by introduction of electrophiles. Allowing the reaction mixture to warm to –20 °C over 2–3 hours gave the alkylated products **100a** and **100b**. Later, the formamidine group was removed using potassium hydroxide–methanol or hydrazine to give free amines **101** and **82** in good overall yield over two steps.



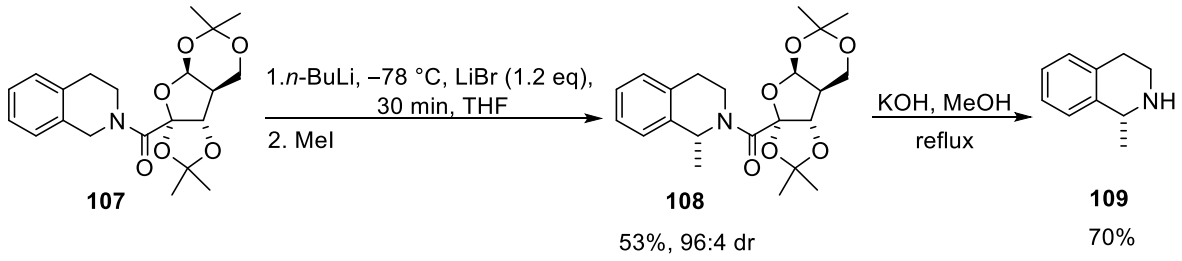
Scheme 2-7

By using oxazolines as auxiliaries, Gawley and co-workers investigated the asymmetric alkylation of THIQ **102** *via* a lithiation–substitution approach.[7] A number of substituted oxazolines were tried as the chiral auxiliary. However, only the one from L-valinol was considered to be effective.[75,93–96] A successful asymmetric alkylation was achieved with up to 97:3 dr (Scheme 2-8).[7] Enantioenriched (*S*)-**104** was prepared from THIQ **102** and oxazoline (*S*)-**103** as chiral auxiliary. Removing the oxazoline chiral auxiliary, followed by further transformation produced laudanosine **106** in 85% yield.



Scheme 2-8

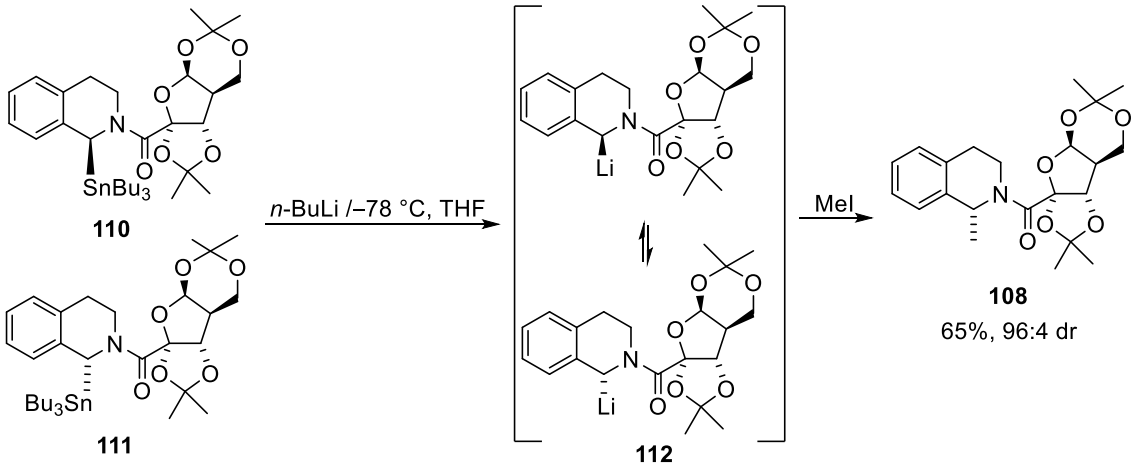
A stereoselective synthesis of 1-substituted THIQs was carried out in 2001 by Quirion and co-workers who investigated the diastereoselective alkylation of THIQ **107** (Scheme 2-9).[97] They reported a general stereoselective approach for 1-substituted THIQs, using electrophilic attack at the corresponding α-amino organolithium species generated from a chiral amide substrate. Using a variety of electrophiles gave 1-substituted compounds in good diastereoselectivities and moderate yields. They found a 5–14% increase in the diastereomeric ratio when using LiBr, resulting in a high level of selectivity. Removing the gluonic acid group using basic conditions was achieved in good yields and the configurational integrity of the products was preserved. This protocol afforded THIQ **109** in a 70% yield and excellent enantioselectivity.



Scheme 2-9

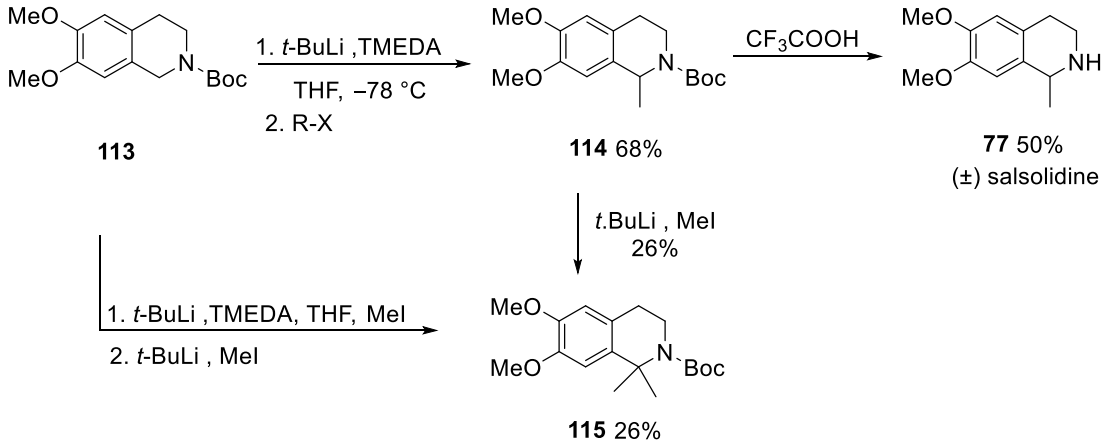
The reaction mechanism was investigated by tin–lithium exchange. Diastereopure stannane **110** or **111** were each treated with *n*-BuLi in THF. Electrophilic quench using MeI in each case gave compound **108** in a 65% yield and dr similar to that observed from direct lithiation (Scheme 2-10). These results suggested that the substitution proceeded through rapid

equilibration of the diastereomeric organolithium intermediates, although there may be a preference for one of these. As a result of the rapid equilibration, the enantioselectivity of the product was determined through the post-metalation step.



Scheme 2-10

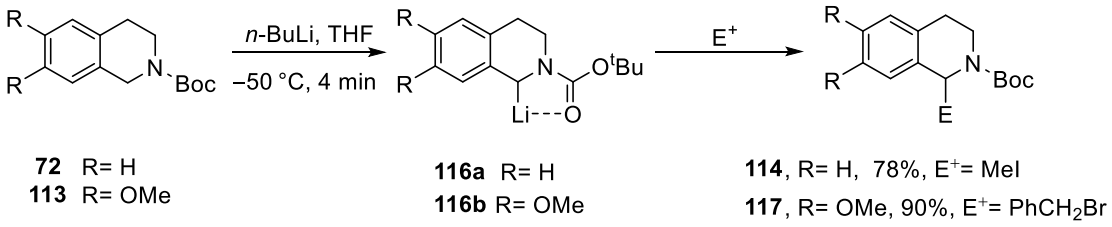
Coppola investigated the lithiation of THIQ **113** using *t*-BuLi in the presence of TMEDA at –78 °C (Scheme 2-11).[85] Subsequent addition of MeI gave compound **114** in a 68% yield. Removing the Boc group using trifluoroacetic acid gave the alkaloid (±) salsolidine in 50% yield. Moving forward, they attempted a one–pot alkylation reaction to form 1,1-disubstituted THIQ **115**. Unfortunately, the reaction was very sluggish even when raising the temperature to 25 °C. Later, they tried to react 1-methyl-THIQ **114** with another equivalent of MeI and *t*-BuLi, but similar results were obtained to the one-pot reaction using starting material **113**.[85]



Scheme 2-11

Recently, the Coldham group reported the alkylation reaction of *N*-Boc-THIQs **72** and **113** (Scheme 2-12).[67] The conditions were optimised using *in-situ* ReactIR. It was found that *N*-

Boc-THIQs **72** and **113** were fully lithiated at –50 °C using *n*-BuLi in THF, and the time required for lithiation was only 4 minutes. These results contrast with, and much simpler than those in Scheme 2-11. In addition, there was no need to use TMEDA as THF was good enough for *n*-BuLi deaggregation. Organolithims **116a** and **b** were quenched with a variety of electrophiles to give good yields of 1-substituted products **114** and **117**.



Scheme 2-12

The aim of this chapter is to synthesize 1-substituted-tetrahydroisoquinole derivetives using lithium reagents. We thought it would be interesting to investigate how substituting the aromatic ring with electron withdrawing groups would affect the lithiation reaction, and whether the previous conditions in Scheme 2-12 would still remain suitable. As can be seen in Scheme 1-22, it was difficult to synthesize enantioenriched 1-substituted *N*-Boc-THIQ derivatives using *n*-BuLi/(–)-sparteine. This was due to the configurational instability of the organolithium intermediate. As a result, only achiral synthesis using *n*-BuLi/THF will be mentioned in this chapter.

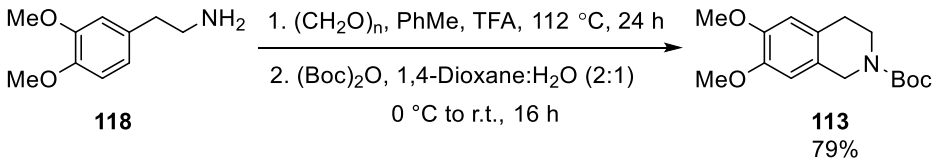
2.5 Synthesis of 1-Substituted *N*-Boc-tetrahydroisoquinolines Optimization and Scope of Lithiation

As mentioned earlier, many researchers were able to effect substitution at C–1 of THIQs by generating a dipole–stabilised carbanion species adjacent to the nitrogen atom, followed by the addition of an electrophile. Different activating groups were used to direct α lithiation such as a Boc group,[85] pivaloyl,[86–88,98,99] and formamidine.[92]

In the light of previous work done in the Coldham group on the synthesis of 1-substituted THIQs, we aimed to prepare more THIQ derivatives using organolithium reagents.[67] As mentioned earlier, THIQs are important due to their biological activity and they are key intermediates in routes to more complex products.

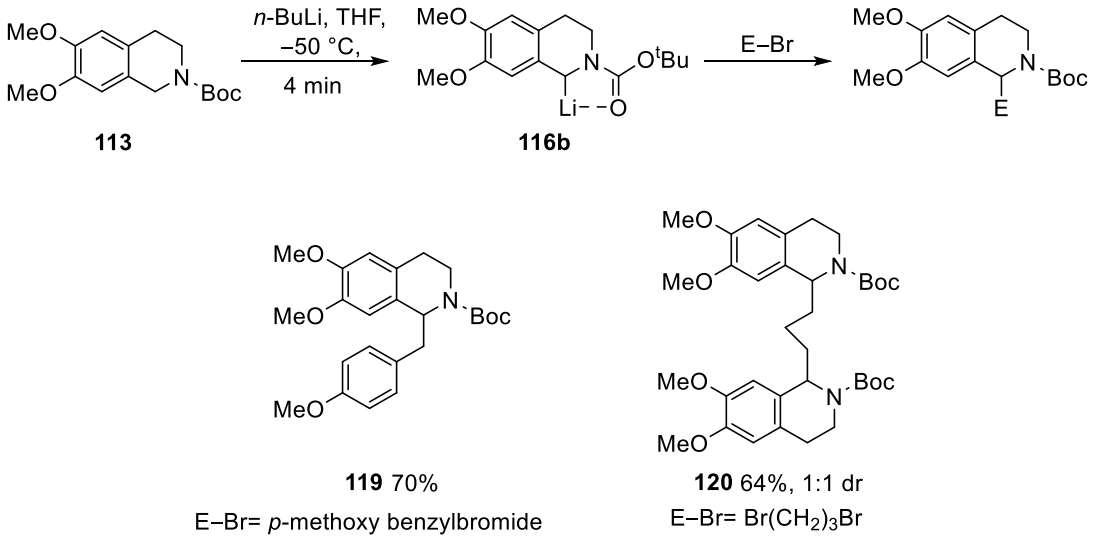
2.5.1 Synthesis and Reaction of *N*-Boc-6,7-dimethoxytetrahydroisoquinoline

Firstly, we decided to continue the work on the lithation–substitution of THIQ **113** as many THIQ alkaloids contain alkoxy or hydroxy groups attached to the aromatic ring. In order to prepare starting material **113**, the amine **118** and paraformaldehyde were mixed in toluene. After heating the reaction mixture for 24 hours, 6,7-dimethoxytetrahydroisoquinoline **102** was formed. The crude mixture was protected using Boc_2O to obtain the desired product **113** in a a 79% overall yield over two steps (Scheme 2-13).[67]



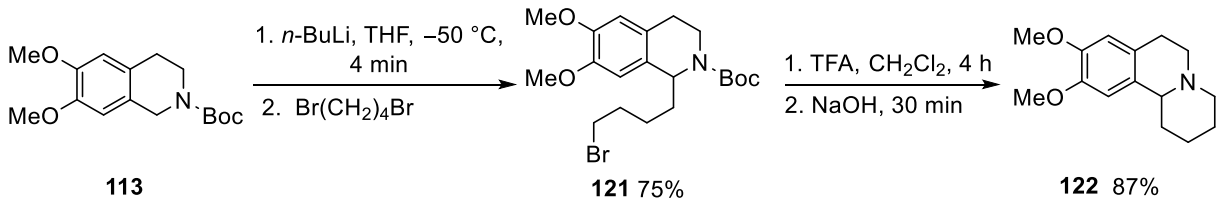
Scheme 2-13

Following from the work done in the Coldham group on THIQ **113**,[67] lithiation was conducted at –50 °C with different electrophiles, and good yields of the desired products were obtained (Scheme 2-14). Addition of 4-methoxybenzyl chloride to the lithiated intermediate **116b** gave compound **119** in a 70% yield. Also, we were able to prepare 1,1′-disubstituted compound **120** in a 64% yield and 1:1 dr, by using 0.5 equiv. of 1,3-dibromopropane.



Scheme 2-14

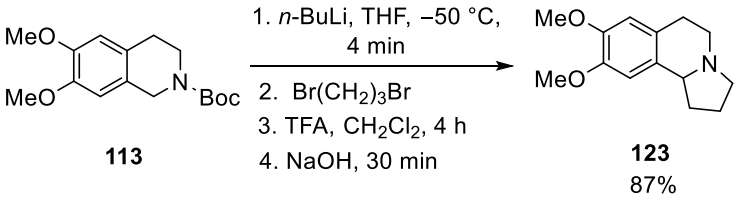
After lithiation–substitution, the THIQ products could potentially be converted to different natural alkaloids and other important products. For example, compound **122** was prepared in 87% yield when adding 1,4-dibromobutane to the lithiated intermediate **116b**, followed by the Boc group removal using TFA at room temperature (Scheme 2-15).[67,100–102]



113 **121** 75% **122** 87%

Scheme 2-15

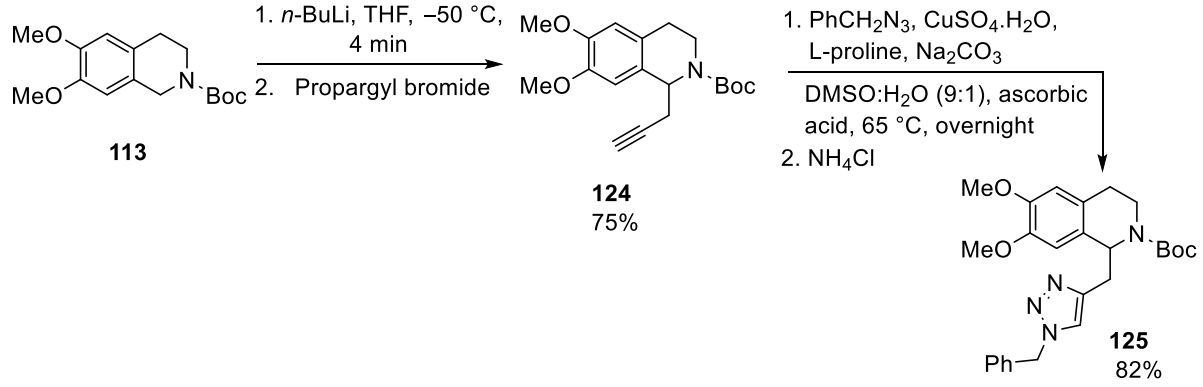
Similarly, addition of 1,3-dibromopropane followed by *in-situ* removal of the Boc group gave the alkaloid (±)-crispine A in 52% yield over two steps, and in only three steps from the commercially available 6,7-dimethoxy tetrahydroisoquinoline **102** (Scheme 2-16). This represent a short synthesis of (±)-crispine A from the growing number reported in the literature.[67,100–102]



113 **123** 87%

Scheme 2-16

In another example, THIQ **113** was treated with propargyl bromide to give compound **124** in a good yield. Compound **124** was treated with benzyl azide and a copper catalyst to obtain the expected triazole **125** in 82% yield (Scheme 2-17). The reaction could give two regioisomers, where the benzyl group and the THIQ are either in a 1,4 or a 1,5 relationship. However, the reaction gave only isomer **125** as judged by ^{1}HNMR spectroscopy. This is likely due to the steric clash that would be present in the other isomer between the benzyl group and the aromatic ring of the THIQ. This reaction proceeded through a copper catalysed click reaction mechanism.[103,104]

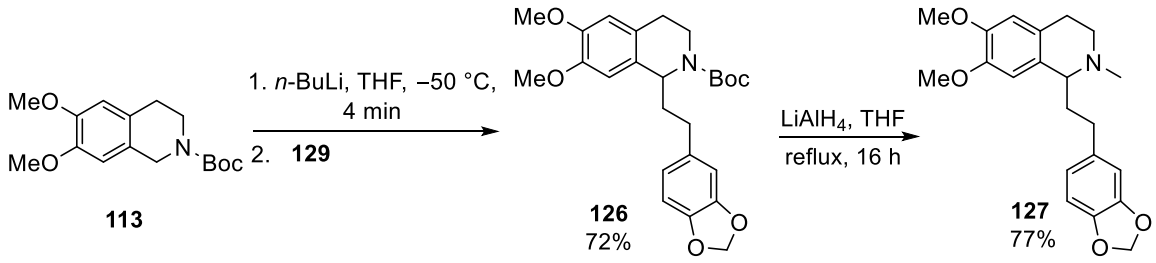


113 **124** 75% **125** 82%

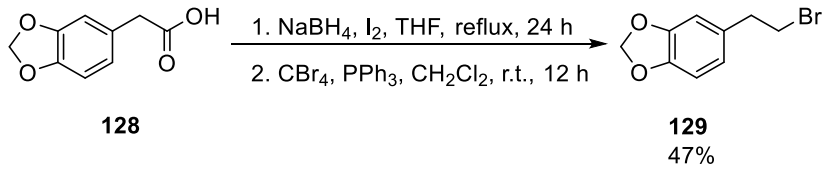
Scheme 2-17

The natural product (±)-dysoxyline was prepared using a lithiation–substitution approach.

Lithiated THIQ **113** was treated with the bromide **129** to give a good yield of compound **126**, despite the potential for β-elimination. The reduction of this compound with $LiAlH_4$ gave the desired product (±)-dysoxyline **127** in 75% yield (Scheme 2-18).[105] In order to prepare bromide **129**, the acid **128** was reduced to its primary alcohol using $NaBH_4$. This was transformed directly to the bromide **129** using apple reaction (Scheme 2-19).[106]

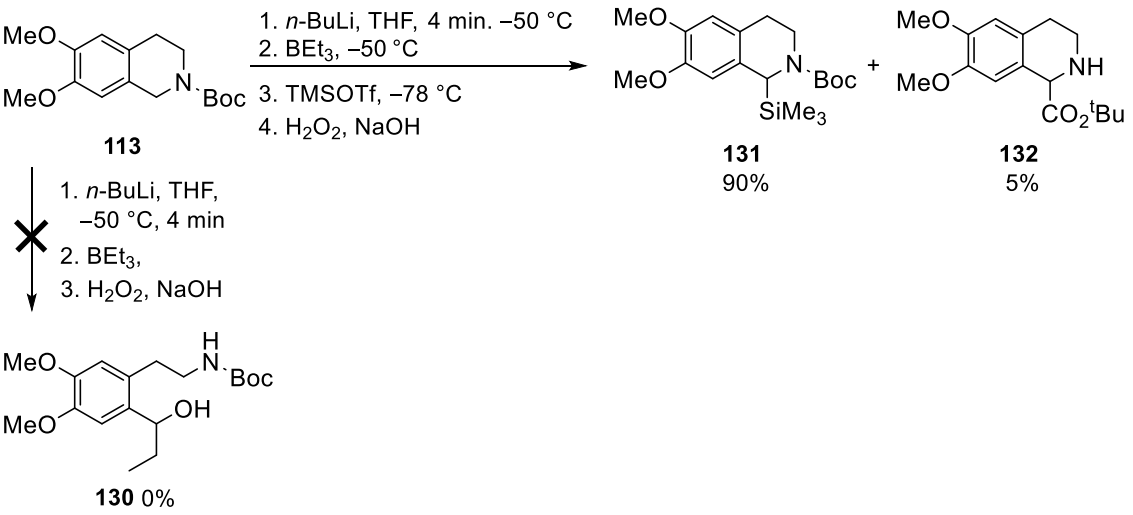


Scheme 2-18



Scheme 2-19

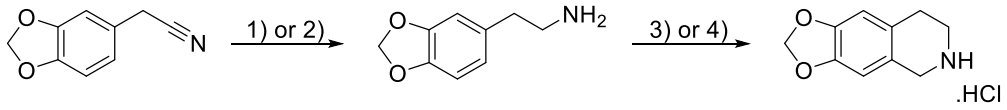
Finally, in order to investigate if compound **130** could be synthesized using lithiaton-substitution approach, *n*-BuLi was added to THIQ **113** in THF at –50 °C (Scheme 2-20). After 4 minutes, the reaction mixture was cooled to –78 °C and BEt_3 was added, followed by the addition of NaOH and H_2O_2. However, no product was isolated, and a complex mixture of products was formed. In an attempt to improve the results, BEt_3 was added at –50 °C followed by the addition of TMSOTf at –78 °C. Later, NaOH and H_2O_2 were added and this gave compounds **131** and **132** in a 90% and 5% yield respectively.[107]



Scheme 2-20

2.5.2 Synthesis and Reaction of *N*-Boc-[1,3]dioxolo-tetrahydroisoquinoline

Since lithiation of THIQ **113** then reaction with a range of electrophiles resulted in good yields of 1-substituted derivatives, we decided to expand the scope to use THIQ **136**, which is another core structure in many natural products. In order to prepare starting material **136**, commercially available nitrile **133** was reduced using borane in THF for 16 hours at 55 °C. After work up, this gave a 75% yield of the amine **134**.[108] However, it was hard to purify the product, as the reaction generated lots of impurities. Therefore, Raney Ni in ethanol in the presence of hydrogen gas was used instead.[109] This method gave a better yield of the amine **134** when compared to using borane. The next step was the Pictet–Spengler cyclisation reaction, where amine **134** and paraformaldehyde were mixed in MeOH in the presence of formic acid. After 24 hours at 50 °C, THIQ **135** was formed in a 67% yield as the hydrochloride salt.[110] However, using trifluoroacetic acid (TFA) in toluene for 16 h at 112 °C gave the cyclised amine in a 74% yield as a salt.[111] Finally, protection using Boc_2O in THF gave only a 23% yield of the targeted molecule **136**. Therefore, $NaHCO_3$ was added to improve the yield, but only a 41% of the protected product **136** was found. Changing the reaction conditions to a mixture of 1,4-dioxane:H_2O improved the yield to 68% (Scheme 2-21).[112]



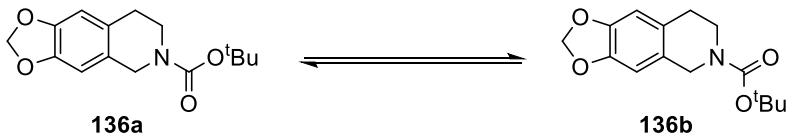
Reagents and conditions:

1) BH_3 [1 M] in THF, THF, 24 h, then H_2O, 30 min, conc. HCl 1 h, then NaOH pellets, 1 h (80%);
2) Raney Ni, NH_4OH, EtOH 48 h (91%);
3) $(CH_2O)_n$, formic acid, MeOH, 55 °C (67%);
4) $(CH_2O)_n$, TFA, PhMe, 112 °C, 16 h (74%);
5) 1,4-Dioxane:H_2O (2:1), Boc_2O, 0 °C to r.t., 16 h (68%).

Scheme 2-21

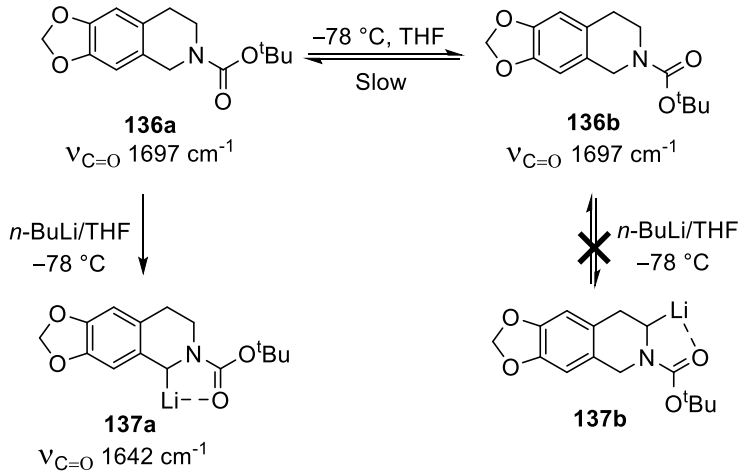
With the *N*-Boc-tetrahydroisoquinoline **136** in hand, the lithiation–substitution reaction conditions were initially investigated using *in-situ* ReactIR, in order to determine if the conditions in Scheme 2-12 would still remain suitable.[67] Recently, there have been several reports explaining the benefit of *in-situ* ReactIR in optimising reaction conditions.[38,61,113] The C–N bond of the Boc group in THIQ molecules rotates slower than the single C–N bond in amines, due to the conjugation between the lone pair of the nitrogen atom and the carbonyl group. As a result of the slow rotation two rotamers can be present (Scheme 2-22). As the Boc

group directs the lithiation by complexation to the base, then only one rotamer (**136a**) undergoes lithiation to give the benzylic lithium intermediate on the 1-position. Also, the amount of the lithiated intermediate could be restricted to the amount of that rotamer. This may be the reason why only 50% of compound **113** was lithiated at –78 °C as previously stated by Coldham and co-workers.[61,67] With this in mind, the lithiation reaction of THIQ **136** was investigated using ReactIR in order to monitor the behaviour of the two rotamers and the lithiation time.



Scheme 2-22

The lithiation reaction of THIQ **136** was first investigated at –78 °C. Compound **136** is suitable for *in-situ* ReactIR, as the carbonyl group stretching frequency and the coordination between the metal and the oxygen atom of the carbonyl group can be easily monitored (Scheme 2-23). THIQ **136** exhibits a peak at $\nu_{C=O}$ 1697 cm^{-1} in the IR spectrum. Addition of *n*-BuLi gave rapid but partial lithiation at this temperature, and at the same time a new peak at $\nu_{C=O}$ 1642 cm^{-1} was observed. These results indicated that the rotation of the Boc group is slow, therefore the two rotamers are interconverting slowly at this temperature (Figure 2-2). This explained why the rate of lithiation was limited at –78 °C. these results are in line with previous work done in the Coldham group.[67] The ReactIR results in Scheme 2-23 are presented in two forms. The three-dimensional plot shows the appearance and disappearance of new signals to be clearly noticed as the reaction progressed. Also, a specific wavelength absorbance can be plotted as a function of time in a 2-D plot.



Scheme 2-23

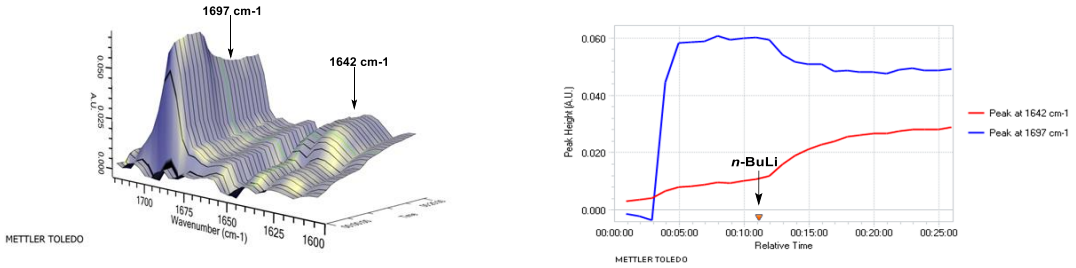
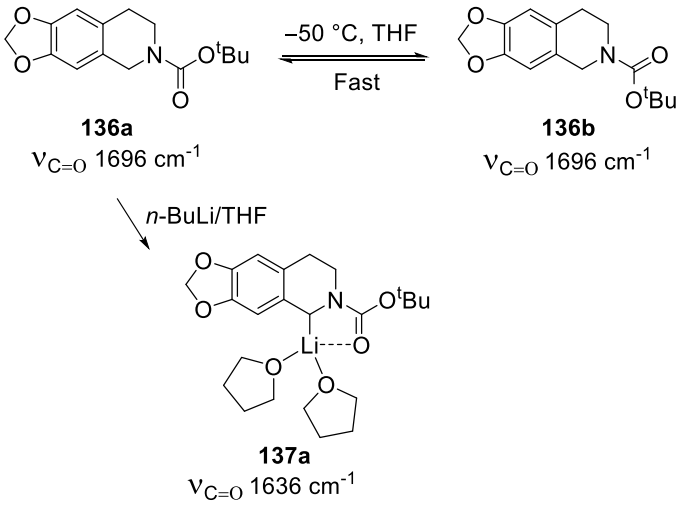
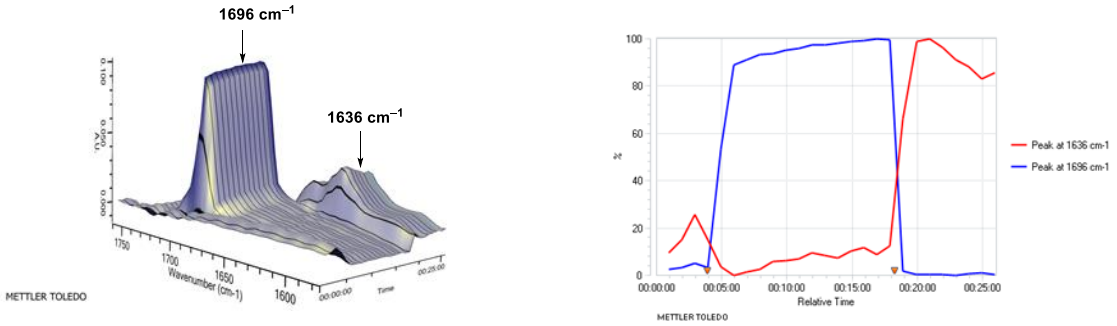


Figure 2-2. *in-situ* ReactIR 3-D and 2-D plots of the lithiation of **136** at –78 °C; Blue Line represents intensity of C=O stretching frequency of **136a** (1697 cm^{-1}) and red line of lithiated **137a** (1642 cm^{-1}) over time. there was ± error when assigning the peaks.

However, conducting the reaction at higher temperature of –50 °C in THF showed rapid and complete lithiation after only 4 minutes, indicating that the rate of rotation of Boc group is fast at this temperature. Scheme 2-24 shows rapid and complete formation of organolithium intermediate **137a** ($\nu_{C=O}$ 1636 cm^{-1}) after only few minutes. the results are in line with previous work.[67]

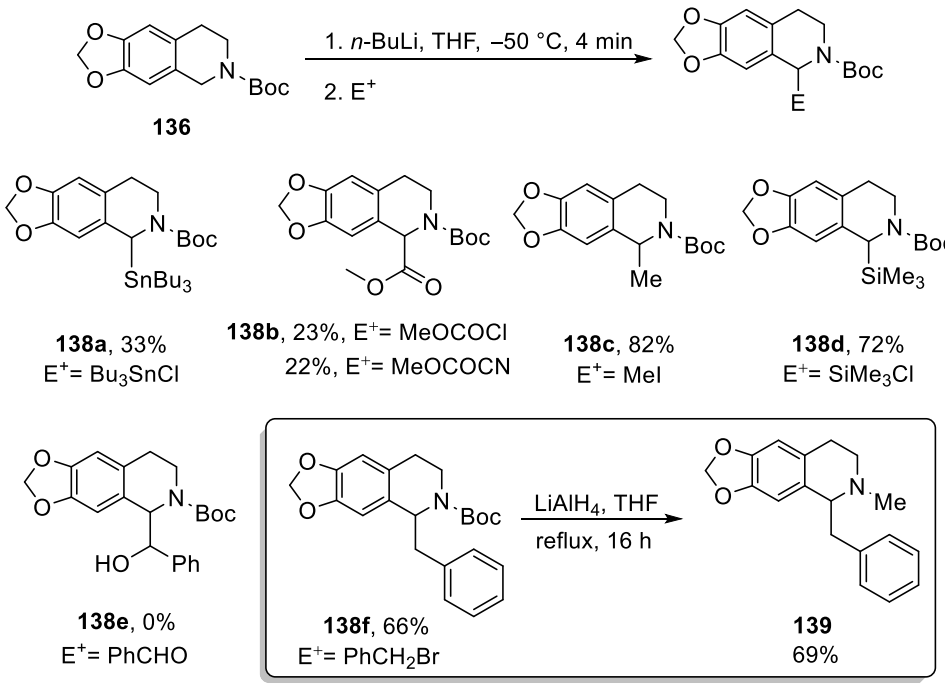




Scheme 2-24. *in-situ* React IR 3-D and 2-D plots of the lithiation of **136** at –50 °C; Blue Line represents intensity of C=O stretching frequency of **136a** (1696 cm^{-1}) and red line of lithiated **137a** (1636 cm^{-1}) over time. there was ± error when assigning the peaks.

On the basis of the *in-situ* ReactIR results obtained, similar conditions to those used for THIQs **72** and **113** were used with THIQ **136**. The optimum conditions for the lithiation reaction of

THIQ **136** involved using *n*-BuLi in THF at –50 °C for 4 min. Addition of electrophiles after this time gave the desired substituted products, although in a variety of yields. Adding tributyltin chloride gave THIQ **138a** in a 33% yield, while THIQ **138b** was formed in only a 22% and 23% yield when quenching with MeOCOCN and MeOCOCl respectively. The reaction with methyl iodide produced THIQ **138c** in 82% yield. TMSCl gave the desired THIQ **138d** in a 72% yield. Finally, both lithiation of compound **136** at –50 °C followed by the addition of benzaldehyde, and lithiation– transmetallation reaction using $MgBr_2.OEt_2$ in THF at –78 °C, followed by addition of benzaldehyde gave no product and only starting material was recovered.[65,96] Quenching the reaction with benzyl bromide gave compound **138f** in a 66% yield. THIQ **138f** was reduced using $LiAlH_4$ to give the *N*-methyl derivative **139** in a 69% yield (Scheme 2-25). Lithiation occurred only in the benzylic position as indicated by ^1H NMR spectroscopy and no other substituted products were observed. It was not clear why the reaction between THIQ **136** and MeOCOCN, MeOCOCl, tributyltin chloride gave low yields.

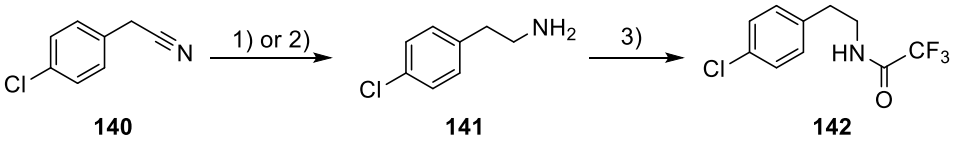


Scheme 2-25

2.5.3 Synthesis and Reaction of 7-Chloro-*N*-Boc-tetrahydroisoquinoline

Having successfully achieved lithiation of THIQ **113** and **136**, lithiation–substitution reactions of THIQs containing electron–withdrawing groups were then investigated. Compound **145** was the first THIQ chosen in order to compare the reactivity with THIQ **113**. To prepare THIQ **145**, commercially available nitrile **140** was first reduced using borane in THF, to give the amine **141** in a 73% yield (Scheme 2-26). In comparison, a 92% yield was obtained using Raney Ni.[109]

The amine **141** was treated with TFAA in THF to give the acetamide **142** in a 48% yield.[114] In an attempt to improve the yield, pyridine was added to the reaction and compound **142** was obtained in a 79% yield as shown in Scheme 2-26.[115]

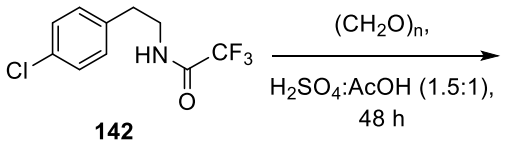


140 **141** **142**

Reagents and conditions:
1) BH_3.THF [1 M], THF, 24 h, then H_2O, 30 min, HCl.conc., 1 h, then NaOH pellets, 1 h (73%);
2) Raney Ni, NH_4OH, EtOH 48 h (92%);
3) pyridine, TFAA, THF, 4 h (79%);

Scheme 2-26

Pictet–Spengler cyclisation reaction was then carried out, where paraformaldehyde and the amide **142** were mixed in a mixture of H_2SO_4:AcOH and stirred at room temperature for 48 hours to give the cyclised acetamide **143** in 86% yield. The ratio of H_2SO_4:AcOH used in the reaction determined the yield of the product **143** as shown in Scheme 2-27.[115]

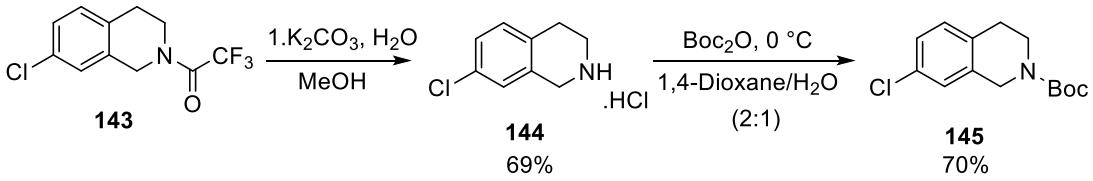


142 **143**

H_2SO_4:AcOH	Yield %
2.5:1	–
2:1	–
1.7:1	17
1.6:1	59
1.5:1	86
1.3:1	32

Scheme 2-27

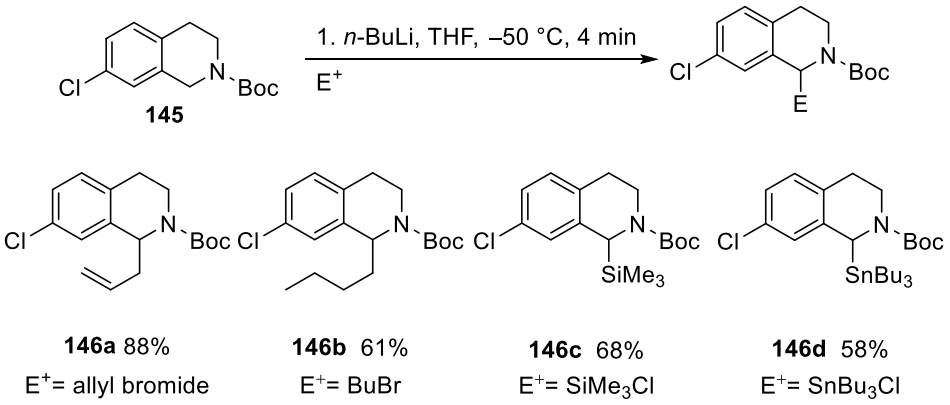
7-Chlorotetrahydroisoquinoline **144** as the hydrochloride salt was prepared in a 69% yield by hydrolysing amide **143** using potassium carbonate in methanol/H_2O at 90 °C for 1 hour. Finally, Boc protection in dioxane/H_2O obtained the desired THIQ **145** in a 70% yield (Scheme 2-28).[112]



143 **144** 69% **145** 70%

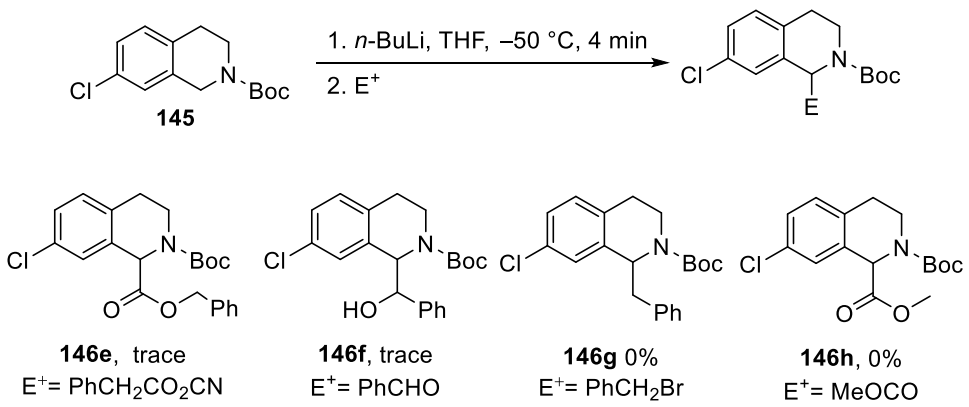
Scheme 2-28

A lithiation–substitution reaction was carried out using similar reaction conditions used for compound **136** in order to investigate if these conditions would remain suitable. As a result, moderate to good yields were obtained with some electrophiles (Scheme 2-29). Only 1-substituted products were found as shown by ^{1}H NMR spectroscopy. This was expected as *n*-BuLi should coordinate to the carbonyl oxygen atom and abstract the more acidic benzylic proton. The chlorine atom dose not compete in this process. Reaction with allyl bromide gave 88% yield of THIQ **146a**, while using butyl bromide gave compound **146b** in a 61% yield. Quenching the reaction with TMSCl or tributyltin chloride gave products **146c** and **146d** in a 68% and 58% yields respectively.



Scheme 2-29

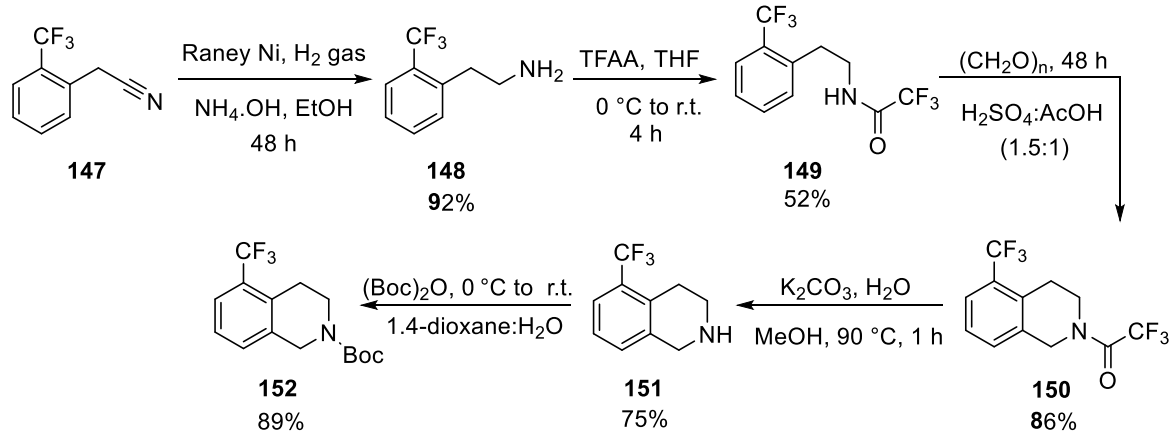
Finally, trace amounts of products **146e** and **146f** were detected by high resolution mass spectrometry after quenching the reaction with benzyl cyanoformate and benzaldehyde, whereas adding benzyl bromide or MeOCOCN gave no products and a complex mixture of products was observed by TLC analysis (Scheme 2-30).



Scheme 2-30

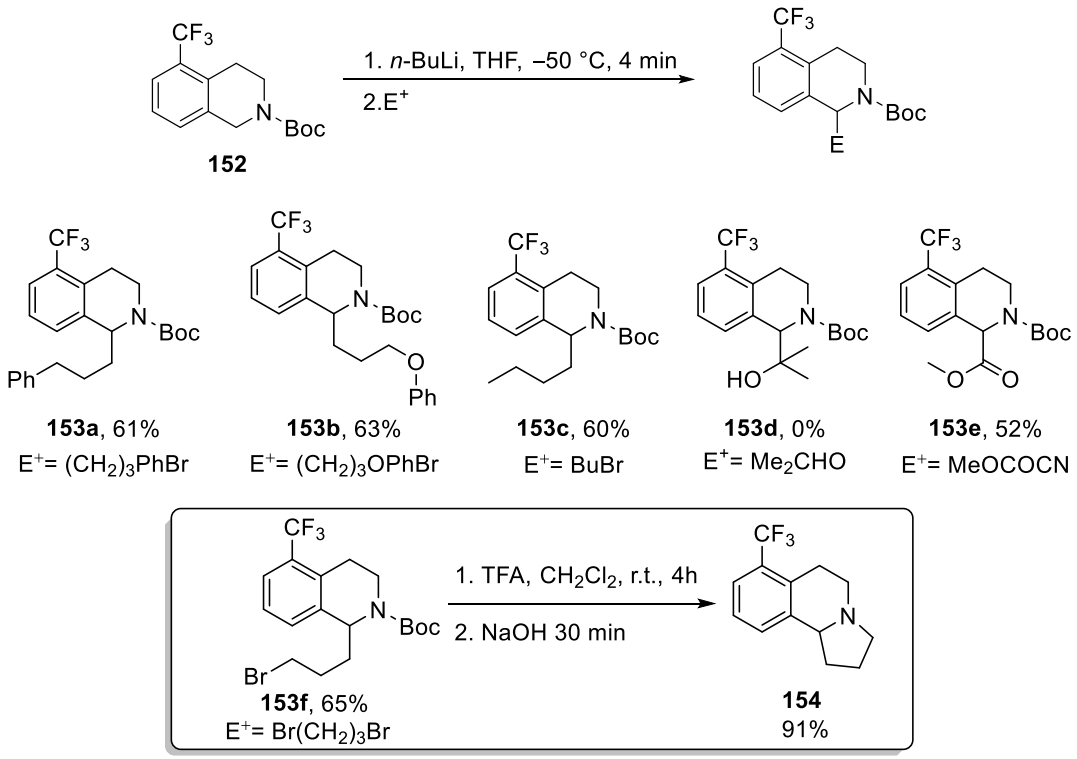
2.5.4 Synthesis and Reaction of 5-Trifluoromethyl-*N*-Boc-tetrahydroisoquinoline

Another THIQ with an electron–withdrawing group attached to the aromatic ring is compound **152**. This was chosen to be investigated as fluorine containing compounds have attracted attention due to their presence in pharmaceuticals. In order to prepare THIQ **152**, nitrile **147** was reduced using Raney Ni and hydrogen gas in ethanol for 48 hours to give the amine **148** in a 92% yield.[109,116] The amine **148** was treated with TFAA in THF to give the acetamide **149** in a 52% yield.[114] Acetamide **149** could then undergo a cyclisation reaction in the presence of paraformaldehyde to give the cyclized product **150** in 86% yield.[115] Hydrolysing the acetamide group using potassium carbonate in MeOH/H_2O gave 5-trifluoromethyl-tetrahydroisoquinoline **151** in a 75% yield. Finally protecting THIQ **151** gave the desired THIQ **152** in 89% yield (Scheme 2-31).[112]



Scheme 2-31

The lithiation reaction of THIQ **152** was conducted using similar conditions to these used for compound **136** (*n*-BuLi in THF at –50 °C for 4 minutes). 1-Substituted derivatives were obtained using some electrophiles as shown in Scheme 2-32. For example, 3-phenyl bromopropane gave THIQ **153a** in a 61% yield. Similarly using $PhO(CH_2)_3Br$ and butyl bromide gave THIQ **153b** and **153c** in 63% and 60% yield, respectively. However, using acetone gave a complex mixture of products. We were pleased to find that using methyl cyanoformate gave the desired product **153d** in a 52% yield. Also, 1,3-dibromopropane was used to obtain compound **153f** in a 65% yield. This was treated later with TFA to give compound **154** in good yield[100–102] (Scheme 2-32).



Scheme 2-32

As outlined in Scheme 2-32, moderate yields of 1-substituted THIQs were obtained. We expected that the rotation of the Boc group was fast at –50 °C. As the rate of lithiation depends on the rate of Boc group rotation then having an appreciation of this rate would help understanding the lithiation reaction. Therefore, we decided to obtain the kinetics for the Boc group rotation and compare the results to previous work done in the Coldham group using *N*-Boc-tetrahydroisoquinoline **72**. Variable temperature NMR spectroscopy was conducted in order to determine the barrier for the Boc group rotation. A sample of 5-trifluoromethyl-*N*-Boc-tetrahydroisoquinoline **152** in D_8-THF was warmed to observe coalescence of the benzylic protons. The coalescence occurred at about 5 °C (Figure 2-3). The rotamers of THIQ **152** were found to exist in 49:51 ratio, with the benzylic NCH_2 as singlets at δ = 4.65 and 4.68 ppm. From the difference in chemical shift between the rotamers, and coalescence temperature, the barrier for the Boc group rotation was calculated to be $\Delta G^{\ddagger} \approx 60.0$ kJ/mol at 5 °C. Hence, the half-life was estimated to be about $t_{½} \approx 2$ minutes at –50 °C. This explained why the lithiation needed only few minutes for completion at this temperature. These results were consistent with the experimental data from *in-situ* React IR spectroscopy. Also, they were in line with what was found previously within the Coldham group using *N*-Boc THIQ **72**.[67]

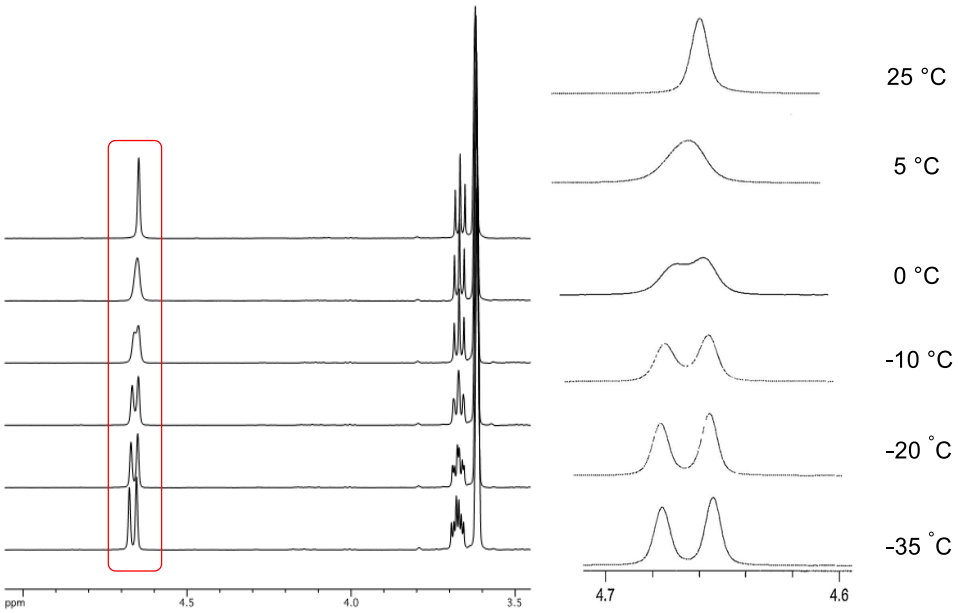


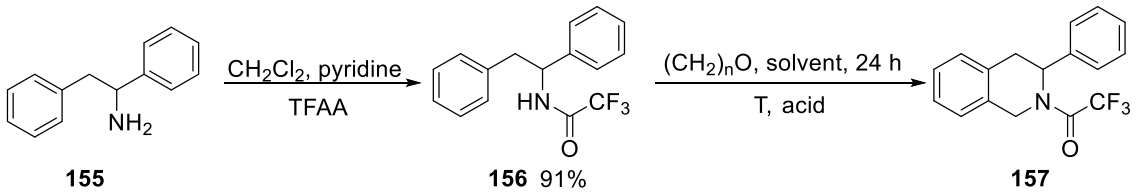
Figure 2-3: Variable temperature ^{1}HNMR spectroscopy of THIQ 152
Showing region 5.0–3.5 ppm

In conclusion, lithiation of *N*-Boc-tetrahydroisoquinoline has been extended to a selection of different substituted derivatives using the same conditions that was found previously for compound **113**. The lithiated intermediate could then be trapped using a wide range of electrophiles to obtain 1-substituted THIQs in good yields. The lithiation of THIQ **136** was optimised using *in-situ* ReactIR spectroscopy, by using *n*-BuLi in THF at –50 °C. The barrier for the Boc group rotation of THIQ **152** was found to be $\Delta G^{\ddagger} \approx 64.0$ kJ/mol at –50 °C, equating to a half–life of approximately 2 minutes at –50 °C for the Boc rotation, and this was in line with a previous work done in the coldham group on THIQ **72**.[67]

Chapter 3. Lithiation of *N*-Boc-3-phenyltetrahydroisoquinoline

3.1 Synthesis of *N*-Boc- 3-phenyltetrahydroisoquinoline

Since lithiation–substitution of *N*-Boc-THIQs in chapter 2 resulted in good yields of 1-substituted products, we decided to investigate the lithiation–substitution reactions of THIQ **175** (*vida infra*), in order to determine if the lithiation–substitution reaction would give both regioisomers, namely the 1-substituted and the 3-disubstituted products or if only one of these regioisomers could be obtained. To start our investigations, we tried to synthesize the target THIQ **175** using the method shown in Scheme 2-31. Treating the commercially available amine **155** with TFAA in CH_2Cl_2 gave acetamide **156** in 91% yield. This was followed by a cyclisation reaction using a mixture of H_2SO_4:AcOH and paraformaldehyde.[114] The reaction gave only trace amounts of product **157** as was shown by high resolution mass spectrometry.[115] Different ratios of the acid mixture were investigated in the hope that this would improve the results, but no product was formed (Scheme 3-1, Table 3-1).



155 **156** 91% **157**

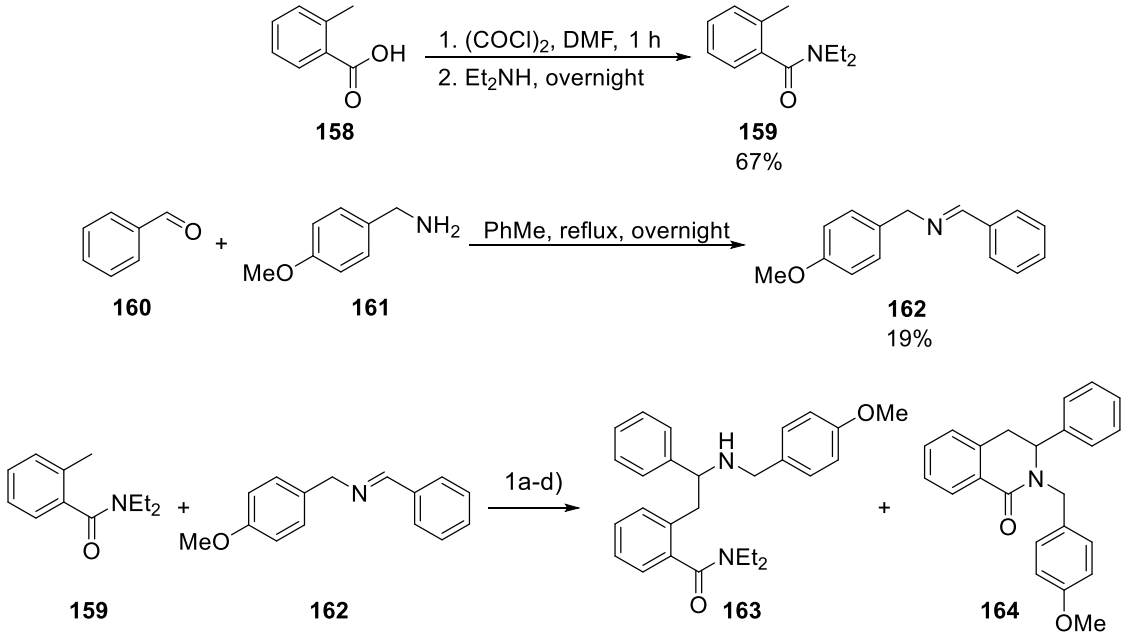
Scheme 3-1

Acid	T °C	Solvent	**157**%
AcOH:TFA (50:50)	112	PhMe	–
HCl:AcOH (50:50)	112	PhMe	–
HCl:AcOH (50:50)	r.t.	–	–
H_2SO_4:AcOH (50:50)	r.t.	THF	–
H_2SO_4:AcOH (65:35)	r.t.	THF	–
H_2SO_4:AcOH (25:9)	r.t.	–	trace
H_2SO_4:AcOH (25:9)	112	PhMe	–
H_2SO_4:AcOH (30:70)	r.t.	–	–
H_2SO_4:AcOH (10:90)	r.t.	–	–
H_2SO_4:AcOH (2:98)	r.t.	–	–
H_2SO_4:AcOH (2:98)	112	PhMe	–

Table 3-1

Another possible method to prepare 3-phenyltetrahydroisoquinoline **175** was by reacting amide **159** with imine **162** in the presence of lithium diisopropylamide (LDA). First, amide **159** was

prepared by adding oxalyl chloride to acid **158** in the presence of DMF. Meanwhile, imine **162** was prepared from the reaction between benzaldehyde and *p*-methoxybenzylamine. Amide **159** was deprotonated with LDA in THF at –78 °C. After 20 minutes, imine **162** was added and the mixture was allowed to warm to –60 °C and aqueous HCl [2 M] was added. The mixture was left stirring overnight but no product was obtained. Rather than adding acid, we wondered whether the addition of a base might help cyclisation and produce compound **164**, so Et_3N was added to the reaction. However, this gave a very poor yield of compound **163**. Similarly, the reaction was repeated at –45 °C in the presence of Et_3N and $AlMe_3$. This gave compound **163** in a low yield with trace amounts of compound **164**. In each case, it was noticed that the reaction produced a complex mixture of products. Therefore, the reaction was repeated by maintaining the temperature at –45 °C for 11 hours, but only trace amounts of compound **164** and a low yield of compound **163** were formed (Scheme 3-2).[117]

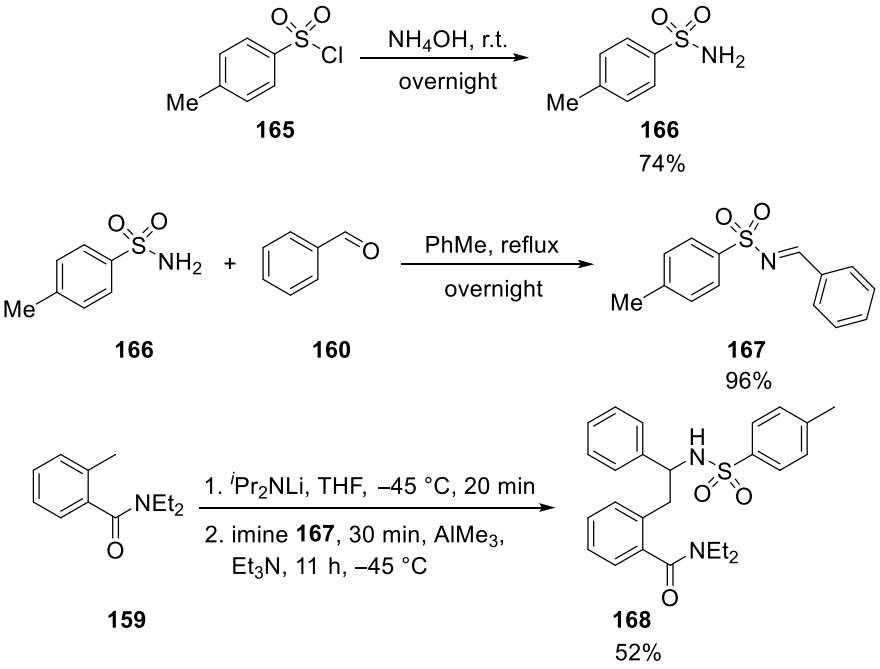


1) ***Reaction and Conditions:***	**163**		**164**
a) LDA, –78 °C, amide **159**, 20 min, imine **162**, –60 °C, HCl [2 M], overnight	–	:	–
b) LDA, –78 °C, amide **159**, 20 min, imine **162**, –60 °C, 30 min, Et_3N, overnight	2%	:	–
c) LDA, –45 °C, amide **159**, 20 min, imine **162**, –45 °C, 30 min, $AlMe_3$, Et_3N, overnight	5%	:	–
d) LDA, –45 °C, amide **159**, 20 min, imine **162**, –45 °C, 30 min, $AlMe_3$, Et_3N, –45 °C, 11 h	17%	:	trace

Scheme 3-2

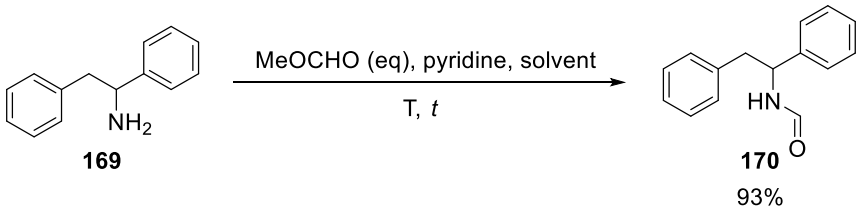
It was thought that changing the imine may improve the results and lead to cyclisation. Therefore, imine **167** was used instead, which was prepared from a 24 hours reaction between

p-toluenesulfonyl chloride and NH_4OH at room temperature for 24 hours. This gave *p*-toluenesulfonamide **166** in a 74% yield,[118] which was reacted with benzaldehyde to give imine **167** in excellent yield. A similar procedure to reaction 1d in Scheme 3-2 was then used to obtain compound **168** in a moderate yield. It may have been possible to remove the tosyl group (or use an alternative sulfonamide that could be cleaved such as nosyl) but we stopped investigating this method (Scheme 3-3).[117,119]



Scheme 3-3

As our previous attempts to obtain THIQ **175** were unsuccessful, a Pictet–Spengler condensation reaction was used to synthesize 3-phenyltetrahydroisoquinoline **175** through intermediate **172**. In the first step, amine **169** was converted to amide **170** using methyl formate. Unfortunately, using 1.5 equivalents of methyl formate in CH_2Cl_2 in the presence of pyridine at room temperature for 16 hours gave no product. However, using 1,4-dioxane as a solvent and heating the reaction mixture for 16 hours gave compound **170** in a 40% yield. Adding 2 equivalents of methylformate and leaving the mixture to stir for 24 hours improved the yield to 50%. Forcing the reaction further by heating at 105 °C for 48 hours using 20 equivalents of methylformate gave an excellent yield of amide **170** (Scheme 3-4, Table 3-2).

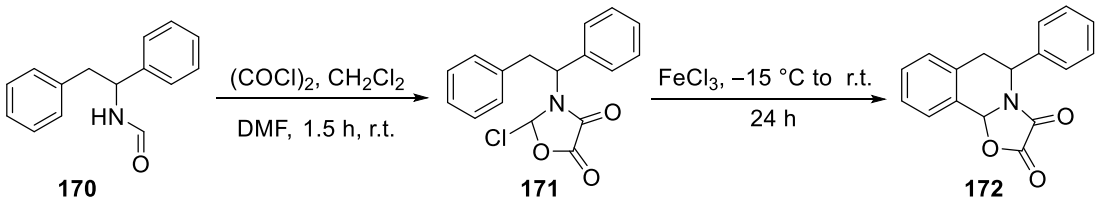


Scheme 3-4

MeOCHO (eq)	T °C	Solvent	*t* (h)	Yield%
1.5	r.t	CH_2Cl_2	16	–
1.5	110	1.4-Dioxane	16	40
2	110	1.4-Dioxane	24	50
10	110	1.4-Dioxane	36	78
15	110	1.4-Dioxane	36	81
20	110	1.4-Dioxane	48	93

Table 3-2

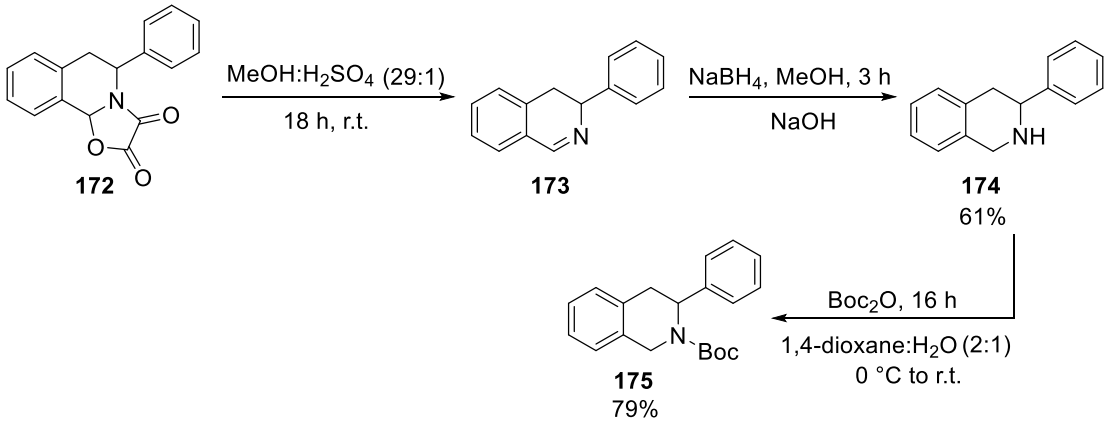
The amide was treated with oxalyl chloride in the presence of DMF.[120] The reaction was monitored using FTIR spectroscopy, where new peaks appeared at 1836 cm^{-1} & 1750 cm^{-1} and the amide peak at 1680 cm^{-1} disappeared after 90 minutes. This indicated that dicarbonyl **171** had formed. The reaction mixture was cooled to –15 °C and $FeCl_3$ was added in one portion causing the reaction to overheat. Therefore, the reaction was repeated and the Lewis acid was added in small portions over three hours to give intermediate **172**. The progress of the reaction was monitored using TLC analysis, mass sepctrometery and ^1H NMR spectroscopy, which showed complete conversion of dicarbonyl **171** to intermediate **172** after 24 hours. Also, it was observed that a large amount of solvent was required in order to dissolve the Lewis acid completely (Scheme 3-5). Furthermore, the intermediate **172** was not stable for more than 24 hours.[120]



Scheme 3-5

The next step was to hydrolyse the oxazolo group using a mixture of MeOH and concentrated sulfuric acid. It was noticed that the amount of H_2SO_4 present in the mixture had a crucial effect on the yield of imine **173**. When a ratio of 19:1 ($MeOH:H_2SO_4$) was used, the reaction severely overheated. Similarly, using a ratio of 25:1 obtained no product. However, using a ratio of 29:1

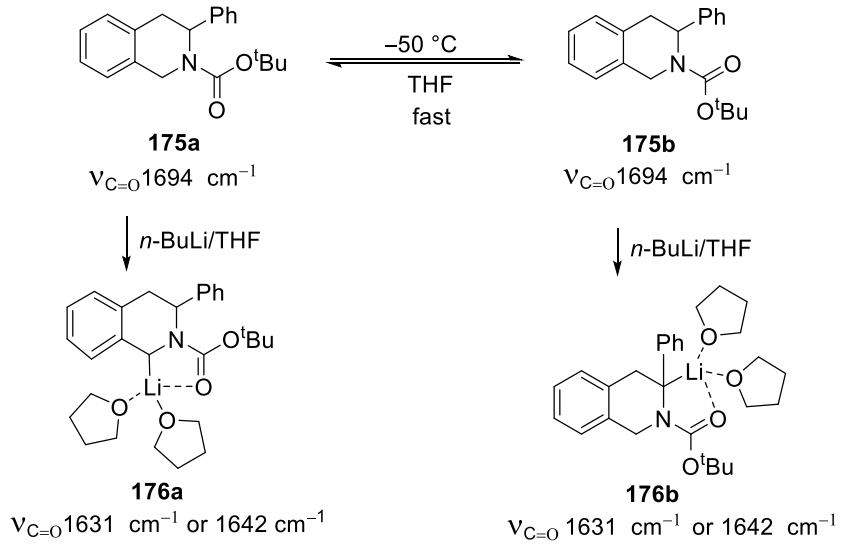
(MeOH:H_2SO_4) gave imine **173** as shown by TLC analysis. Reduction of imine **173** was carried out using $NaBH_4$ to give THIQ **174** in a 61% yield over four steps.[120] Finally, protection using Boc_2O gave the desired product **175** in a 79% yield (Scheme 3-6).[112]



Scheme 3-6

3.2 Lithiation of *N*-Boc-3-Phenyltetrahydroisoquinoline

With THIQ **175** in hand, the optimum conditions for lithiation–substitution reaction were investigated using *in-situ* ReactIR spectroscopy. Not surprisingly, a full and rapid lithiation was observed in under 2 minutes using 1.2 equivalents of *n*-BuLi in THF at –50 °C (Scheme 3-7). The IR plot showed a rapid loss of the peak at $\nu_{C=O}$ 1694 cm^{-1} assigned for the starting material THIQ **175**, with the formation of new peaks at $\nu_{C=O}$ 1642 cm^{-1} and 1632 cm^{-1} which were assigned to lithiated intermediates **176a** and **176b**. The rotation of the Boc group seemed slightly faster than in THIQ **136**. The ReactIR distinguished between the two possible sites of lithation and two peaks at 1642 cm^{-1} and 1631 cm^{-1} were observed for $\nu_{C=O}$ of the lithiated intermediates (Figure 3-1).



Scheme 3-7

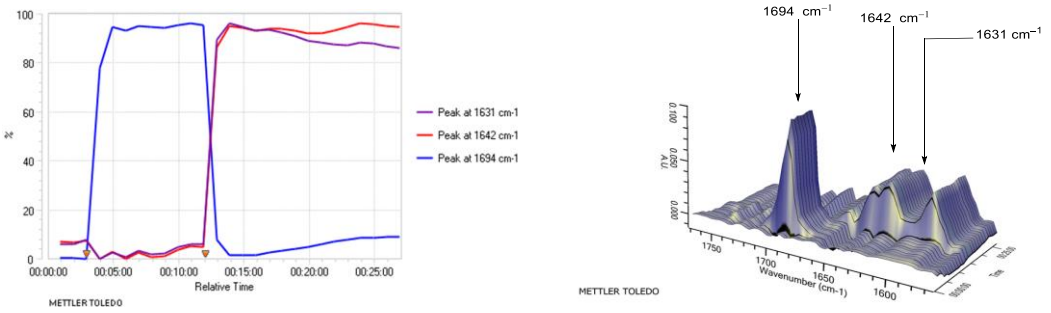


Figure 3-1. *in-situ* ReactIR 3-D and 2-D plots of the lithiation of **175** at –50 °C; Blue Line represents intensity of C=O stretching frequency of **175** (1694 cm^{-1}), red line of lithiated **176a** or **176b** (1642 cm^{-1}) and purple line for lithiated **176a** or **176b** (1632 cm^{-1}) over time. there was ± error when assigning the peaks.

Next, variable temperature NMR spectroscopy was carried out to determine the coalescence temperature of the two rotamers. This could be used later to calculate the $t_{1/2}$ at a certain temperature. According to these studies the coalescence temperature of the two *tert*-butyl Boc group rotamers was determined to be arround ~10 °C as shown in Figure 3-2. This figure shows only the region from 1.00–2.00 ppm with the rotamers of THIQ **175** in a ratio of approximately 1.2:1 from the $(CH_3)_3$ peak and a broad singlet peak for THF.

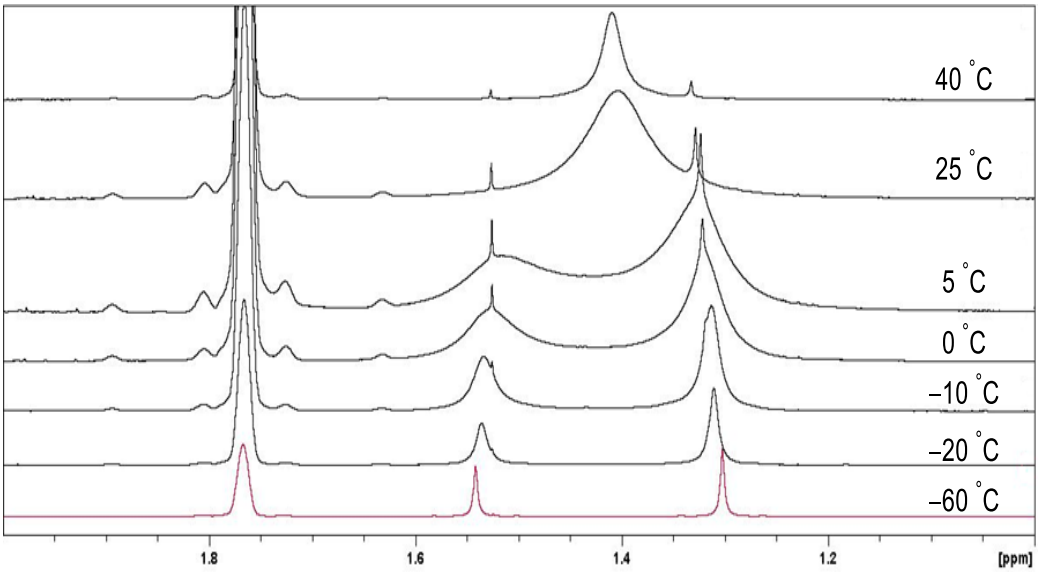
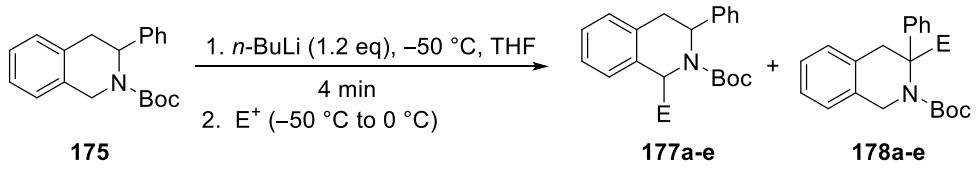


Figure 3-2 shows the region from 1.0-2.0 ppm

Line shape analysis was carried out using these spectra in order to calculate the two parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ (Appendix 2). $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were found to be approximately 61.3 kJ/mol and 15.9 J/K·mol respectively. This gave $\Delta G^{\ddagger} \approx 57$ kJ/mol at 0 °C, and $\Delta G^{\ddagger} \approx$ 58 kJ/mol at –50 °C. The half-life for the rotation of the Boc group at –50 °C can be calculated to be only $t_{1/2} \approx 5.1$

seconds. Hence, the lithiation requires less than a minute at this temperature. These results match the *in-situ* ReactIR results in Figure 3-1.

On the basis of the *in-situ* ReactIR studies, the lithiation reaction of THIQ **175** was conducted using 1.2 equivalents of *n*-BuLi in THF at –50 °C for 4 minutes (Scheme 3-8, Table 3-3). A range of electrophiles was explored, allowing 1-substituted and 3-substituted THIQ derivatives to be isolated in good yields, however between 11–23% starting material was recovered. Trapping the mixture of organolithiums with tributyltin chloride gave the inseparable regioisomers in a 52% yield with 23% recovery of THIQ **175**. In comparison, using allyl bromide gave a 79% yield of products **177b** and **178b** in a ratio of 2.3:1, and an 11% yield of recovered THIQ **175**. Quenching the organolithiums with benzyl bromide, *p*-methylbenzyl bromide and MeI gave 69%, 63% and 73% yields respectively in different ratios with similar amounts of recovered THIQ **175**. It was noticed that only one diastereoisomer of the 1-substituted compounds was observed, as shown by ^{1}H NMR spectroscopy. Surprisingly, the ratios of the two regioisomers were electrophile dependent.



175 **177a-e** **178a-e**

Scheme 3-8

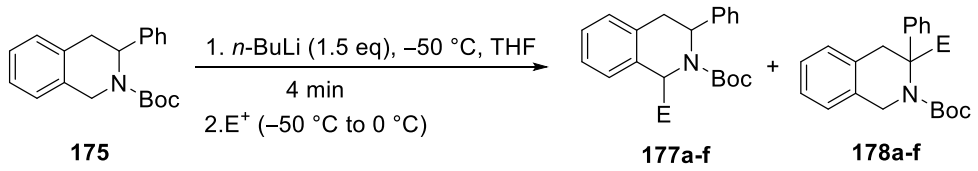
Entry	E^+	1-pos:3-pos	ratio	Yield %	Recovered **175** %
1	$ClSnBu_3$	**177a:178a**	1:1	52	23
2	Allyl bromide	**177b:178b**	2.3:1	79	11
3	Benzyl bromide	**177c:178c**	3:1	69	23
4	*p*-methylbenzyl bromide	**177d:178d**	3:1	63	14
5	MeI	**177e:178e**	3.9:1	73	12

Table 3-3

As shown in the Scheme above, the ratios obtained did not correspond to the 1.2:1 ratio of the two rotamers found in the NMR studies. The 1-substituted THIQ was often the major isomer and this could be due to the acidity of the proton on C-1 being slightly higher than that on C-3. Another point to mention is that the ReactIR showed full lithiation at –50 °C using 1.2 equivalent of *n*-BuLi in THF, however recovered THIQ **175** was found from the reactions with the electrophiles above. This suggested that the organolithium C-3 intermediate could be

unstable and decompose before reacting with the electrophiles. However, this would not explain why Bu_3SnCl gave a 1:1 ratio of products **177a** and **178a**. There did seem to be a difference in reactivity between Bu_3SnCl and the other carbon–based electrophiles in Table 3-3, and/or a difference in stability of the tributyltin product (s). This suggests that the ratio of 1:1 in this case could be due to a decomposition of C-3 or C-1 tin compounds.

Next, the ratio between the two regioisomers was investigated using 1.5 equivalents of *n*-BuLi in THF at –50 °C (Scheme 3-9, Table 3-4). Treating the organolithiums with tributyltin chloride gave compounds **177a** and **178a** as an inseparable mixture of regioisomers in a 79% yield and about 1:1 ratio with no recovered THIQ **175**. Only one diastereoisomer of compound **177a** was obtained, as shown by ^{1}H NMR spectroscopy (it was not clear if it was the *cis* or the *trans* isomer). However, when allyl bromide was used as the electrophile, products **177b** and **178b** were isolated in about a 2.3:1 ratio with a good yield. This was similar to those from the D_2O quench (*vide infra*), whereas using 2.2 equivalents of *n*-BuLi gave a ratio of about 1.6:1 of the two inseparable regioisomers. Reacting THIQ **175** with 1.5 equivalent of *n*-BuLi, followed by the addition of benzyl bromide and *p*-methylbenzyl bromide gave both regioisomers in a 94% and 78% yield respectively and about a 3:1 ratio with no recovered THIQ **175**. Using the same conditions, MeI was used to quench the mixture of organolithiums and this gave an 88% yield and about a 1:4 ratio of the 3-substituted compound **177e** and the 1-substituted THIQ **178e**. Only one diastereoisomer of the 1-substituted product **177e** was obtained as shown by ^{1}H NMR spectroscopy. The two products were separated by recrystallization using hexane/CH_2Cl_2, and X-ray crystallography showed that the phenyl group and methyl group were *trans* to each other (Figure 3-3). Another electrophile tested was butyl bromide, which gave two inseparable regioisomers **177f** and **178f** in excellent yield and a ratio similar to that obtained from the MeI quench. The 1-substituted products were the major isomers, and only one diastereoisomer was obtained as shown by ^{1}H NMR spectroscopy.



Scheme 3-9

Entry	E^+	1-pos:3-pos	ratio	Yield %
1	$ClSnBu_3$	**177a:178a**	1:1	79
2	Allyl bromide	**177b:178b**	2.3:1	82
		(2.2 eq) *n*-BuLi	1.6:1	
3	Benzyl bromide	**177c:178c**	3:1	66
4	*p*-methylbenzyl bromide	**177d:178d**	3:1	94
5	MeI	**177e:178e**	4:1	88
6	Butyl bromide	**177f:178f**	4:1	97

Table 3-4

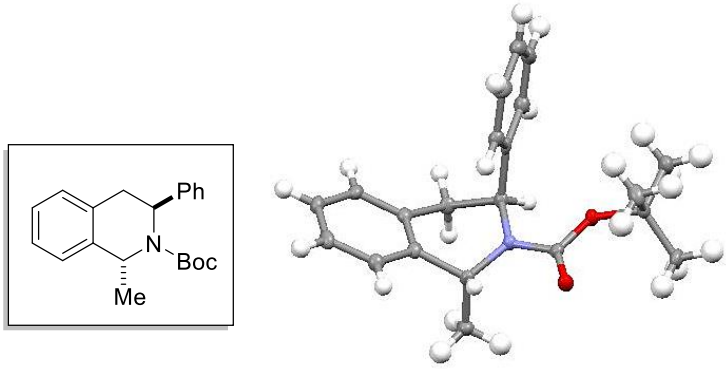
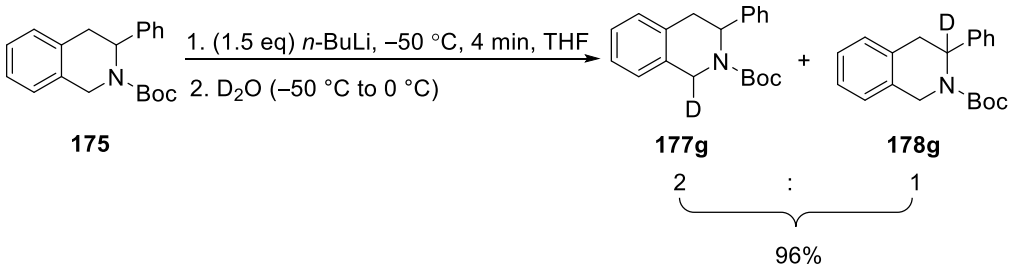


Figure 3-3: X-ray crystal of compound 177e
structure shows the *trans* diastereoisomer

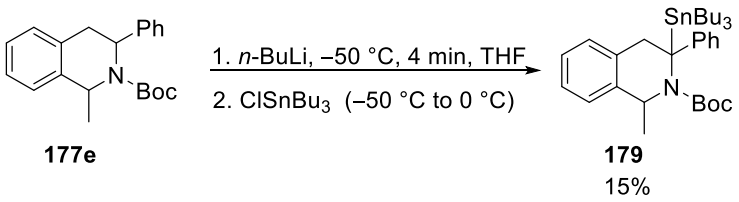
To investigate the ratio of the organolithiums for the reaction at –50 °C using 1.5 equivalents of *n*-BuLi, D_2O was used and the reaction gave a 96% yield and about a 2:1 ratio of the inseparable regioisomers **177g** and **178g (**Scheme 3-10). No non-deuterated starting material was observed as shown by ^1H COSY and HSQC NMR spectroscopy. It was surprising to find a different ratio than that from the two rotamers found from the NMR studies when adding D_2O to the mixture of organolithiums. However, as the Boc group rotates quickly at –50 °C, then the *n*-BuLi has a choice for which proton to remove. Therefore, there could be a different ratio of organolithiums (and hence deuterated products) from Boc rotamers (1.2:1), as the reaction kinetically favoured to lithiate C-1 over C-3. Future work could involve investigating whether the addition of 0.5 equivalents of *n*-BuLi, followed by the addition of D_2O would give a preference for only the 1- substituted product.



Scheme 3-10

As can be seen in Table 3-4, the ratio of the two regioisomers from the reaction with some electrophiles did not match the 2:1 ratio of the two organolithiums found from D_2O quench. The reason behind the a 4:1 ratio in case of MeI could be because this electrophile was slow to react with the organolithium intermediates, hence decomposition of the C-3 organolithium may have occurred upon warming the reaction mixture before reacting fully with MeI.[121] It could be possible in a future work to try the addition of D_2O to the mixture of organolithiums after partially warming to see if there is an increase in the ratio of 1-substituted to 3-substituted product. Another experiment would be carrying out lithiation at –78 °C, followed by the addition of D_2O 30 minutes after the MeI addition.

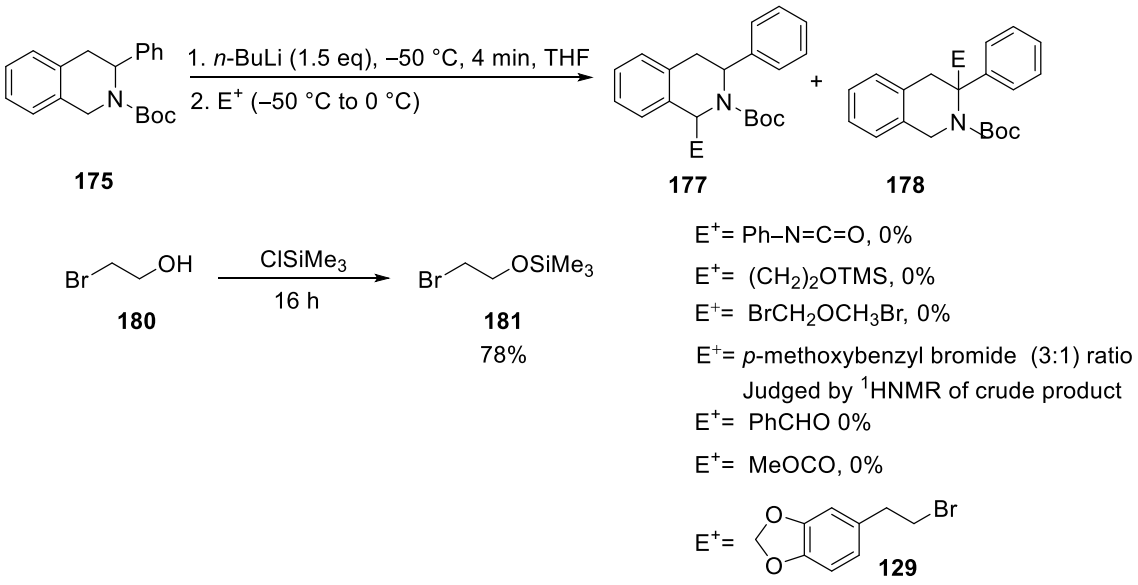
We were also interested to investigate whether treating compound **177e** with 1.5 equivalent of *n*-BuLi followed by electrophilic quench would form the 1,1,3-trisubstituted product or the 1,3,3-trisubstituted isomer (Scheme 3-11). The reaction of THIQ **177e** was conducted using *n*-BuLi in THF at –50 °C. Addition of $ClSnBu_3$ gave compound **179** in only a 15% yield. The low yield could be accounted by the reduced reactivity at C-1 due to the presence of the methyl group, and the possibility that this group could be deprotonated to give another by-product although this product was isolated, but not identified.[66]



Scheme 3-11

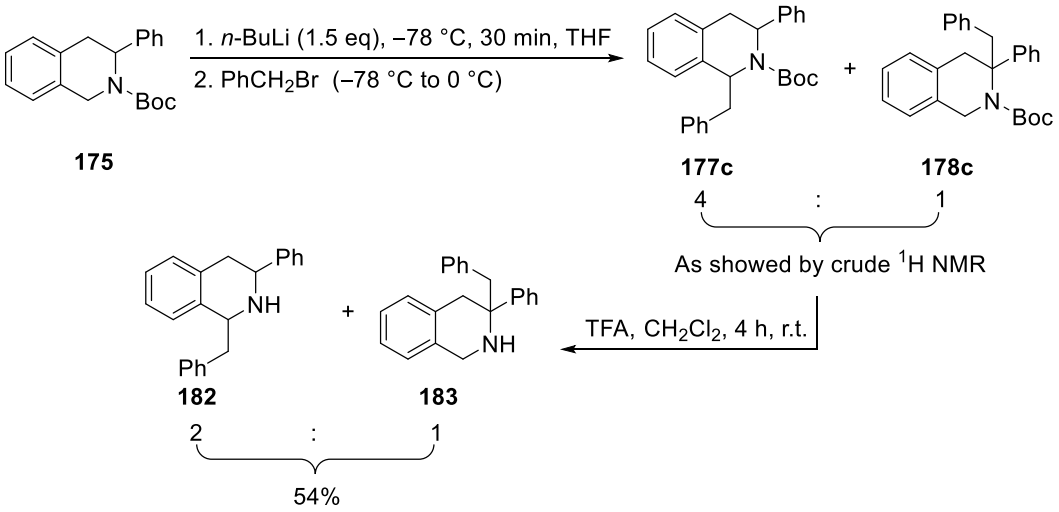
A variety of other electrophiles weas used for the lithiation–substitution reaction of THIQ **175** but no products were obtained. For instance, reactions with benzaldehyde, (2-bromoethoxy)trimethylsilane **181** and phenyl isocyanate each gave complex mixtures of products. The electrophile (2-bromoethoxy)trimethylsilane **181** was prepared from the alcohol

180 and $ClSiMe_3$ in a 78% yield.[122] Surprisingly, reacting THIQ **175** with bromide **129** gave only recovered starting material. Furthermore, nither methyl cyanoformate, nor bromomethoxy methane gave any of the desired products, and only recovered starting material was isolated. Finally, quenching the reaction with *p*-methoxybenzyl bromide gave products in a 3:1 ratio were the major isomer was the 1-subsituted product as shown by ^{1}H NMR spectroscopy, which could not be purified (Scheme 3-12). It was not known why these electrophiles gave poor results, however they were found not to be suitable in reactions with THIQ **175.**



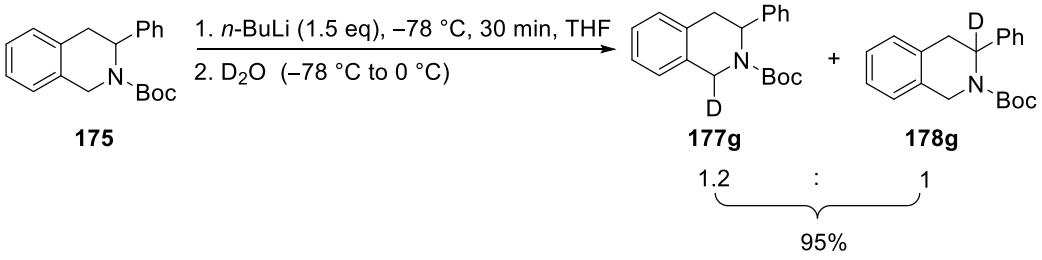
Scheme 3-12

Next, the lithiation reaction was tried at a lower temperature of –78 °C to investigate if the reaction would proceed with better selectivity. *n*-BuLi was added at –78 °C and the reaction mixture was stirred for 30 minutes before the addition of benzyl bromide. This reaction gave about a 4:1 ratio of products **177c** and **178c** as shown by the crude ^{1}H NMR spectra (Scheme 3-13), which was similar to that at –50 °C. Removing the Boc group in an attempt to separate the two regioisomers using TFA gave compounds **182** and **183** in a 72% yield and about a 2:1 ratio. The reason behind the 2:1 ratio of amines **182** to **183** could be due to losing some of the 1-substituted amine during purification. It was noticed that the 3-substituted product had a much lower retention factor R_f in comparision to the 1-substitued isomer.



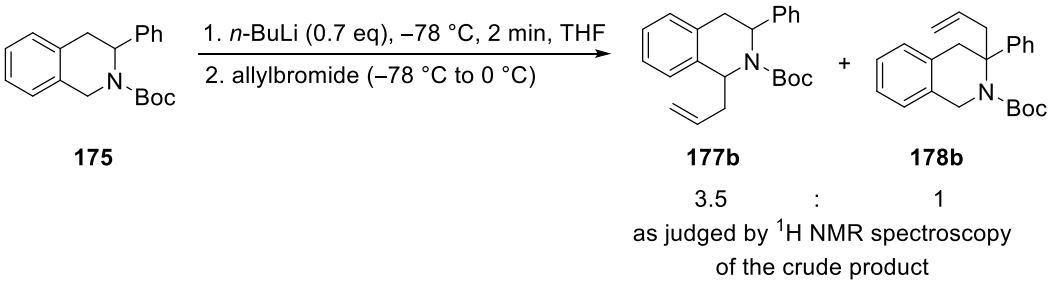
Scheme 3-13

Reacting the organolithium mixture with D_2O was then carried out to investigate the ratio of the two organolithiums for the reaction at –78 °C using 1.5 equivalents of *n*-BuLi. A ratio of about 1.2:1 of the two inseparable regioisomers **177g** and **178g** in a 95% yield was obtained after a lithiation time of 30 minutes (Scheme 3-14). These results corroborate with the 1.2:1 ratio of rotamers observed from the variable temperature NMR spectroscopic measurements. The lithiation reaction was completed and no non-deuterated starting material was observed as shown by ^{1}H COSY and HSQC NMR spectroscopy. The half-life for the rotation at –78 °C was calculated to be 11 minutes according to variable temperature NMR studies.



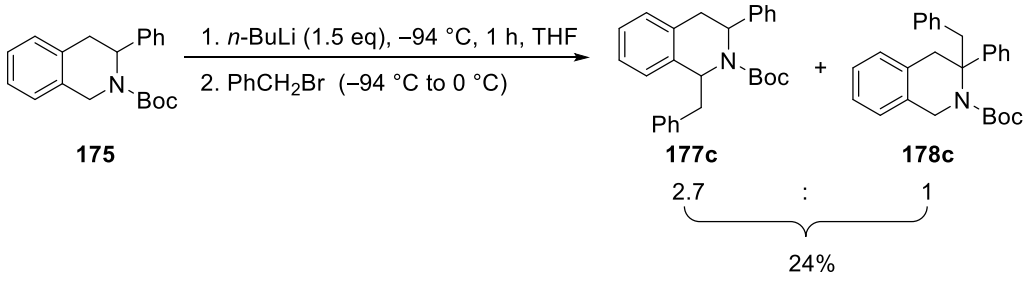
Scheme 3-14

It was thought that, using less than 1 equivalent of *n*-BuLi for 2 minutes would give a preference for one regioisomer over the other as both rotamers are present. Therefore, 0.7 equivalents of *n*-BuLi was used, however the electrophile was changed from D_2O to allyl bromide to make it easier to determine the ratio of the two regioisomers. The allyl bromide was added after 2 minutes to the mixture of organolithiums. A ratio of about 3.5:1 of the 1-substituted **177b** and 3-substituted **178b** was produced as shown by the crude ^{1}H NMR (Scheme 3-15). These results showed that there was a preference to lithiate on C-1.



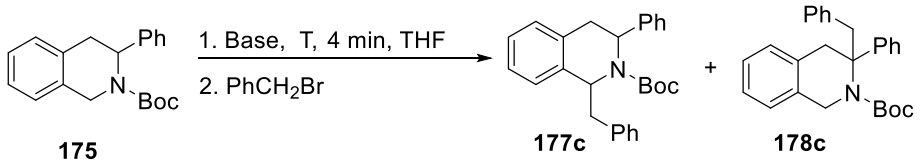
Scheme 3-15

Next, the lithiation reaction was carried out at a much lower temperature than –78 °C to investigate if the ratio of the two regioisomers would match the ratio of rotamers (1.2:1). The lithiation reaction was conducted at –94 °C for one hour using 1.5 equivalents of *n*-BuLi, followed by the addition of benzyl bromide. The products **177c** and **178c** were isolated in only a 24% yield and a 2.7:1 ratio (Scheme 3-16). It was clear from the ratio obtained that there was a preference to lithiate at C-1. At this temperature, the rate of lithiation should be faster than the rate of rotation. This should lead to a ratio of 1.2:1 although a yield of a 24% is not very informative. It could be possible in future work to investigate the addition of D_2O at –94 °C to the mixture of organolithiums.



Scheme 3-16

Since the lithiation reactions at –78 °C and –50 °C with the electrophiles above showed no selectivity, the reaction was then conducted at a higher temperature of 0 °C, in the hope that this may give better selectivity than that at –50 °C. Addition of benzyl bromide gave about a 3:1 ratio of compounds **177c** and **178c** as shown by the crude ^{1}H NMR spectrum. Hydrolysing the Boc group using TFA obtained compounds **182** and **183** in a 64% and about a 2:1 ratio. This was similar to the reaction at –50 °C which indicated that the reaction was kinetically controlled. Therefore, the base was changed to *s*-BuLi to investigate if different ratios would be obtained, and THIQ **175** was deprotonated at –50 °C in THF followed by the addition of benzyl bromide. This reaction gave about a 3:1 ratio of the two regioisomers in a 62% yield. Finally, 2.2 equivalents of *s*-BuLi was used to investigate if there was any difference in selectivity. However, this gave a complex mixture of products (Scheme 3-17).

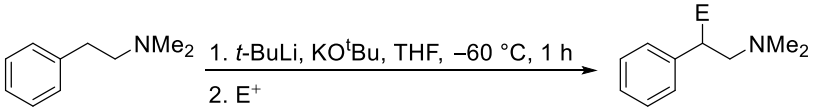


175 **177c** **178c**

Base	T °C	Yield %	ratio (**177c:178c**)
n-BuLi	0 °C	-	3:1 Judjed by crude NMR
s-BuLi	–50 °C	62	3:1 Judjed by crude NMR
s-BuLi (2.2 eq)	–50 °C	-	-

Scheme 3-17

Moving on from this work, we decided to carry out deprotonation using Schlosser's base, hoping that the reaction would obtain better selectivity. Strohmann and co-workers had recently reported a regioselective synthesis of phenethylamine derivatives using a Schlosser type base. By conducting the reaction at –60 °C for 1 hour and by using different electrophiles, good yields were obtained despite the possibility of β-elimination (Scheme 3-18).[123]



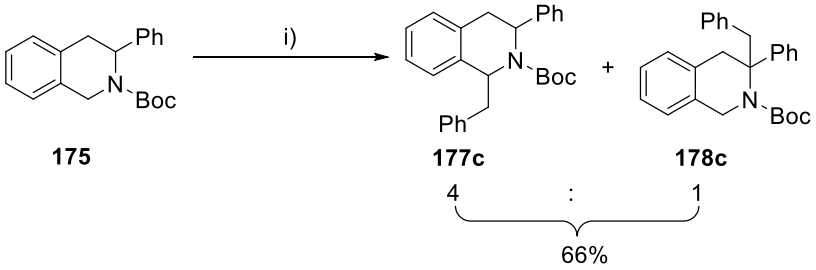
184

185a, E^+= BuBr, 92%

185b, E^+= $ClMe_3SiCl$, 84%

Scheme 3-18

Treatment of THIQ **175** with Schlosser's base was disappointing as only a slight increase in selectivity was observed in comparison to earlier reactions. The deprotonation reaction was conducted at –50 °C in THF, where benzyl bromide was added 3 seconds after the addition of THIQ **175**. The reaction produced a 66% yield of both regioisomers in about a 4:1 ratio (Scheme 3-19).



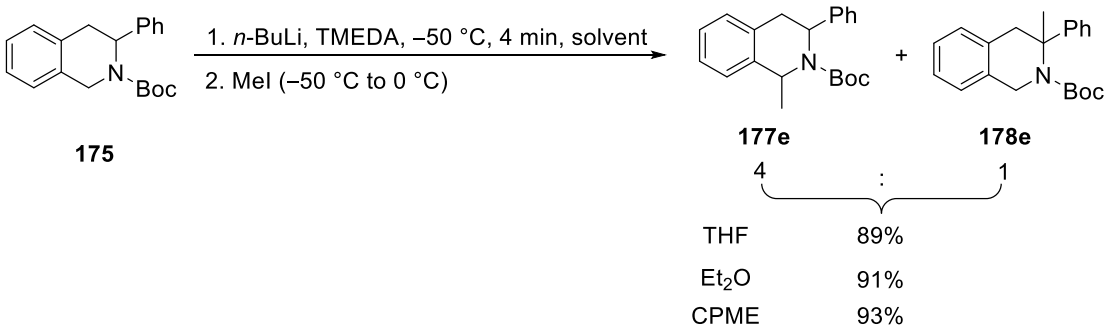
175 **177c** **178c**

i) ***Reaction conditions:*** 1. *n*-BuLi, KO^{t}Bu, –50 °C, 2 min, THF, 3 sec, THIQ **175**, 3 sec, 3. $PhCH_2Br$ (–50 °C to 0 °C)

Scheme 3-19

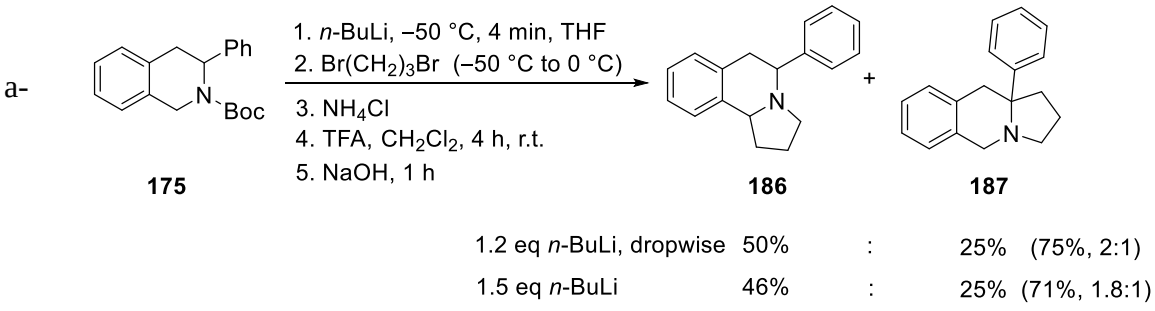
Following on from this, to try and obtain different selectivities TMEDA was used, which would allow a steric clash between the organolithium complex and the phenyl group on C-3 to take

place. This could give a preference for the 1-substituted isomer over the 3-substituted one. Firstly, 1.5 equivalents of *n*-BuLi was added to a mixture of starting material **175** and 1.5 equivalents of TMEDA in THF. After 4 minutes, MeI was added to obtain a 90% yield of both regioisomers **177e** and **178e** in about a 4:1 ratio. The use of the solvents Et_2O and CPME was also explored. However, the reaction using these solvents gave a 4:1 ratio which was the same ratio obtained when TMEDA was not used (Scheme 3-20). These results indicated that no steric clash was affecting the ratio of the two regioisomers.

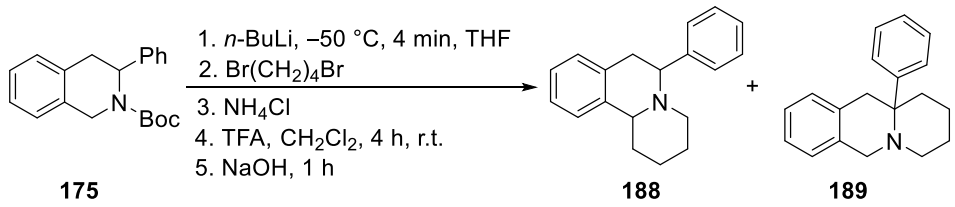


Scheme 3-20

We then decided to prepare the compounds in Scheme 3-21a,b following the same method that was used to prepare (±)-crispine A (Scheme 2-16). These compounds are known for their biological activity, for instance compound **186** is known as an anti-depressant.[124,125] 1,3-Dibromopropane and 1,4-dibromobutane were used as electrophiles, good yields and about a 2:1 ratio of the separable 1-substituted compounds and 3-substituted derivatives were obtained over two steps with both electrophiles. Assuming that the reaction was kinetically controlled, slow addition of 1.2 equivalents of *n*-BuLi was tried in the hope that better selectivity would be obtained. Notably, dropwise addition using 1.2 equivalents of *n*-BuLi gave slightly higher yields and similar ratios in comparison to the fast addition using 1.5 equivalents of the same base (Scheme 3-21a,b).[105]



b-

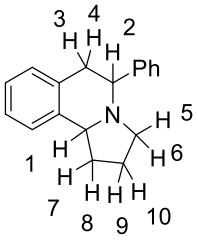


175 188 189

1.2 eq *n*-BuLi, dropwise	63%	:	24% (87%, 2.6:1)
1.5 eq *n*-BuLi	55%	:	27% (82%, 2:1)

Scheme 3-21a, b

In order to determine the stereochemistry of compound **186**, an nOe NMR experiment was carried out. Irradiation of proton no. 1 gave an enhancement to protons no. 3 and 5, these protons are possibly *cis* to proton no. 1. If the *cis* isomer was isolated, irradiating proton no. 1 would give an enhancement of proton no. 2 as well but this was not observed. The results combined with proton no. 2 irradiation; this gave an enhancement of proton no's. 3,4 and 6, suggested that the stereochemistry of the product was *trans*. Figure 3-4 shows the nOe spectra of compound **186**. Overall, the nOe results were not conclusive and we suggested that the *trans* isomer was isolated, however this was not verified.



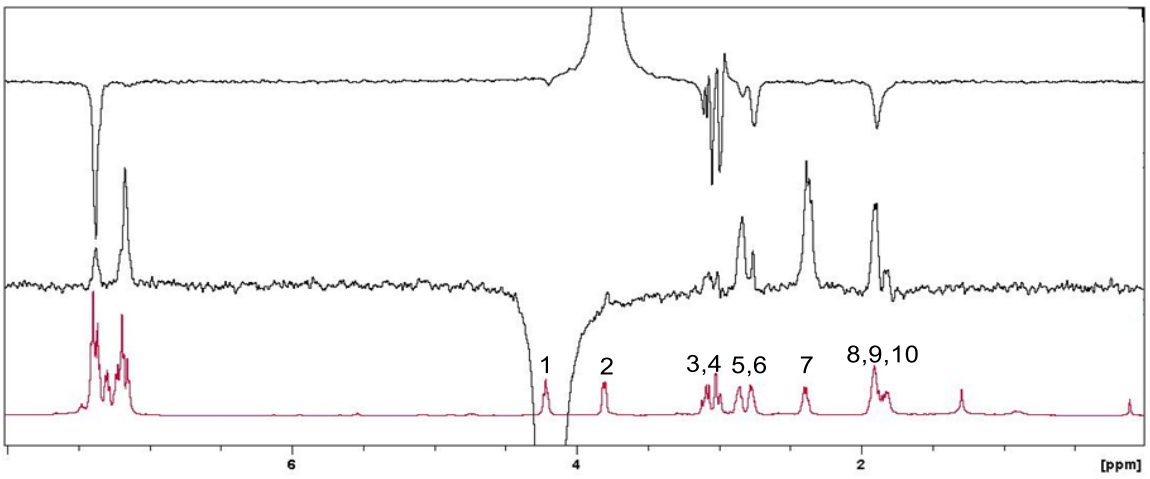
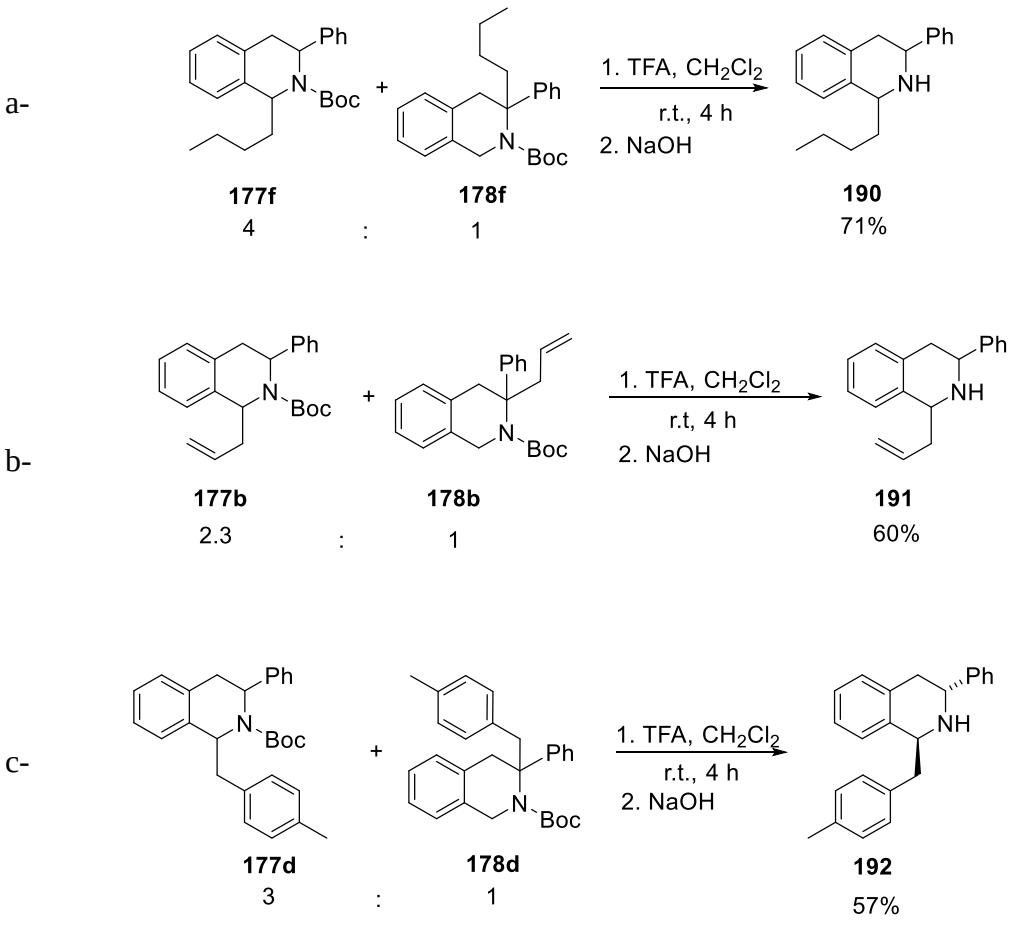


Figure 3-4

Similarly, the stereochemistry of compound **188** was assumed to be *trans* by comparison with the NMR data of the *cis* isomer in the literature.[126]

Following on from this, 2 equivalents of TFA was used to remove the Boc group from the products in Scheme 3-9 in order to try and separate the two regioisomers. However, only one of the regioisomers (1-substituted) was isolated. Scaling up these reactions in order to try and make the process easier was unsuccessful and only the 1-substitued products **190** (71%), **191** (60%), and **192** (57%) were obtained (Scheme 3-22 a to c).[105] On the other hand, treating the mixture of compounds **177a** and **178a** with TFA (2 or 5 equivalents) gave a complex mixture of products, while adding TFA (2 or 5 equivalents) to the mixture of compounds **177e** and **178e** gave only recovered starting material. However, reacting a 3:1 mixture of compounds **177c** and **178c** with 2 equivalents TFA in CH_2Cl_2 gave both regioisomers **182** and **183** in about a 2:1 ratio and a 54% yield (*vida supra*).



Scheme 3-22a-c

Compound **192** was recrystallized in CH_2Cl_2/hexane, and the X-ray crystal structure showed that the *trans* diastereoisomer was isolated (Figure 3-5). It is likely that compounds **190** and

191 are also the *trans* isomer, and each existed as a single diastereoisomer as was shown by ^{1}H NMR spectroscopy.

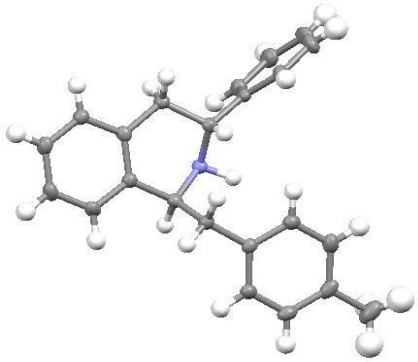
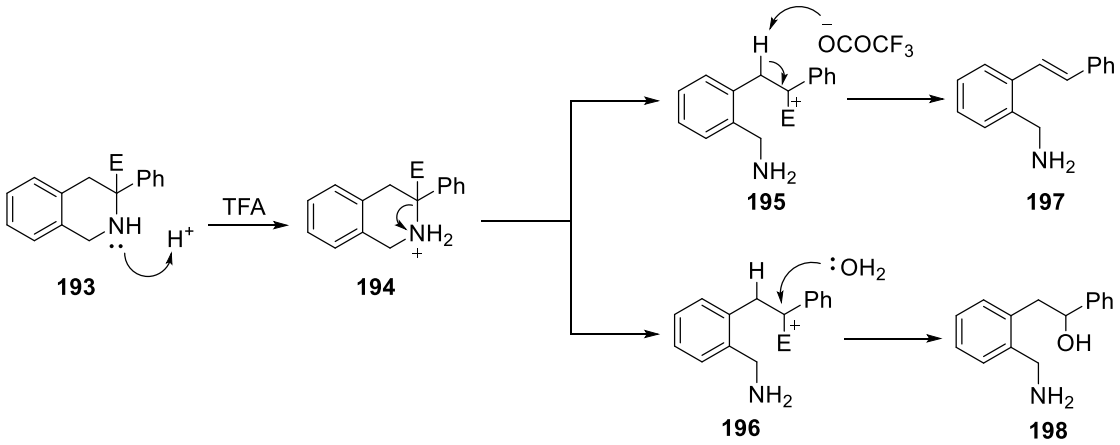


Figure 3-5: X-ray crystal structure of compound 192 shows the *trans* diastereoisomer

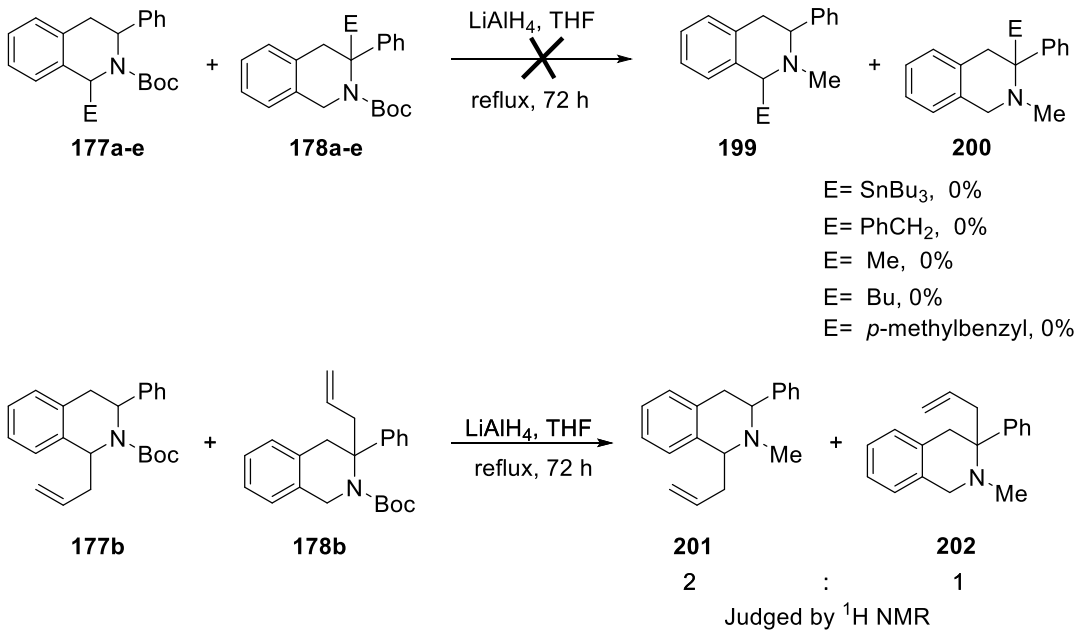
It was disappointing to lose one of the regioisomers in some of the reactions in Scheme 3-22 through Boc group removal. It was assumed that this may have been due to further protonation of the secondary amine **193**, which led to the formation of acyclic products **197** and/or **198** (Scheme 3-23). The hydrolysis reaction generated a complex mixture of products as shown by both TLC analysis and the crude ^{1}H NMR spectrum.



Scheme 3-23

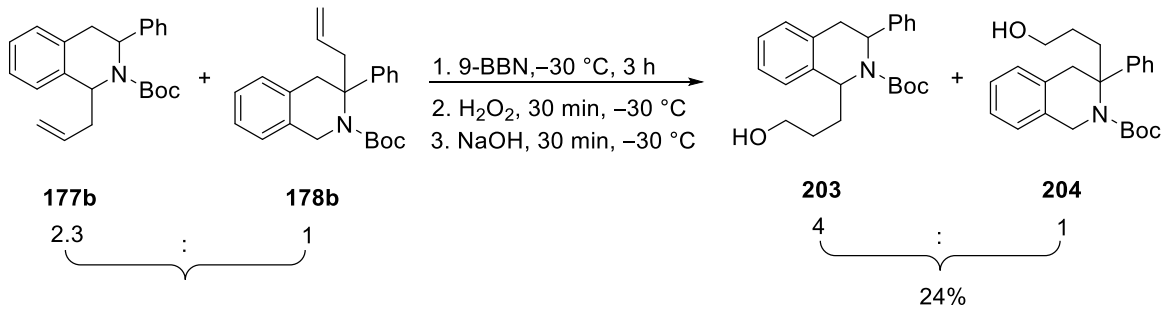
Due to the disappointment of losing one of the regioisomers after hydrolysing the Boc group using TFA, we tried to reduce the Boc group using $LiAlH_4$. However, no products were produced and only recovered THIQ **175** was found with almost all cases. Trying to change the solvent to Et_2O did not improve the results. Also, heating the reaction mixture for 72 hours gave no product (Scheme 3-24). However, when the allylic derivatives **177b** and **178b** in about a 2.3:1 ratio was used, the reaction gave about a 2:1 ratio of the inseparable isomers as shown by ^{1}H NMR spectroscopy of the crude product. Separating the reduced species **201** and **202**

from the recovered starting material was difficult, as all the components had the same retention factor (R_f).



Scheme 3-24

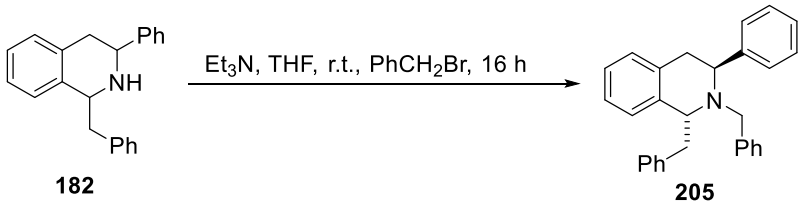
To expand the range of substituted THIQs, a mixture of compounds **177b** and **178b** in about a 2.3:1 ratio was treated with 9-BBN in order to produce alcohols **203** and **204**. First, the reaction mixture was left to stir at –20 °C for 6 hours, followed by the addition of H_2O_2 and NaOH, but a complex mixture of products was obtained. Therefore, the reaction was conducted at –30 °C for 3 hours, followed by the addition of H_2O_2 and NaOH. This give a 24% yield of the alcohols **203** and **204** in about a 4:1 ratio (Scheme 3-25).[127] The reason behind the 4:1 ratio could be due to a steric clash between the 9-BBN and the phenyl group at C-3 position.



Scheme 3-25

Following on from this, 1-benzyltetrahydroisoquinoline **182** was treated with benzyl bromide in the presence of Et_3N to give compound **205** in a 91% yield (Scheme 3-26). Later compound **205** was recrystallized in hexane/CH_2Cl_2 and the *trans* diastereoisomer was isolated as shown

by the X-ray crystal structure (Figure 3-6). This confirmed that the lithiation–substitution reaction of THIQ **175** formed the *trans* diastereoisomer of the compounds in Scheme 3-8.



Scheme 3-26

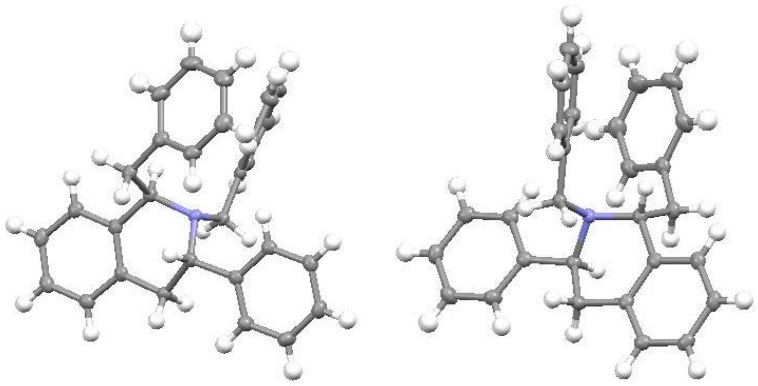


Figure 3-6: X-ray crystal structure of compound 205 shows the *trans* diastereoisomer

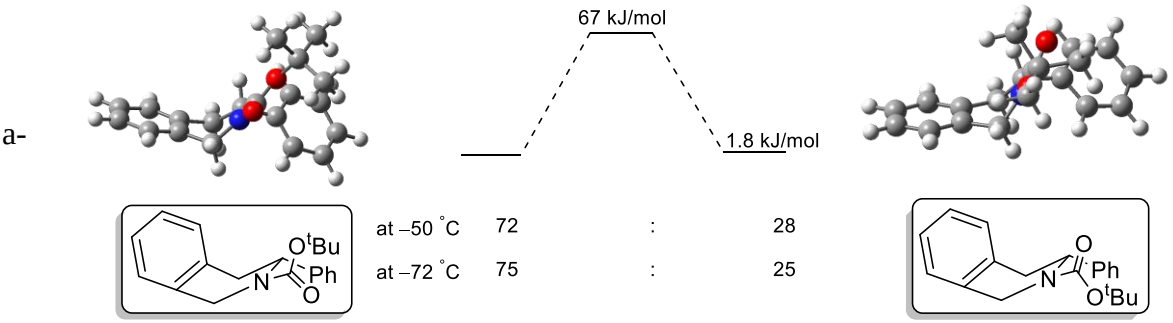
3.3 Density Functional Theory Analysis

In order to investigate further the lithiation substitution reaction of tetrahydroisoquinoline **175** and the ratio of the two regioisomers, computational DFT studies have been carried out by Mathew Dwyer within the Department of Chemistry at the University of Sheffield.[128] The calculations were performed using the 6-311G (d,p) basis set with B3LYP functional. The solvent was included via the PCM method with the default parameter for THF. Firstly, orientations of the starting material were modelled, and four relatively low energy structures were found (Figure 3-7 a-d). The lowest energy conformation was related to the boat structure with the phenyl group in the equatorial position with $\Delta G^{\ddagger} \approx 67$ kJ/mol (Figure 3-7a). For this conformation the rotation of the Boc group, which is fast at the calculated temperatures showed that the distribution between the two rotamers was 72:28 at –50 °C and 75:25 at –72 °C. The second lowest energy conformation also had a boat structure but with the phenyl group in the axial position; the energy barrier for this structure was calculated to be $\Delta G^{\ddagger} \approx 68$ kJ/mol, with a distribution ratio of 60:40 at –50 °C and –72 °C between the two rotamers (Figure 3-7b). Another conformation with a relatively low energy barrier is the chair structure with the phenyl

group in the equatorial position (Figure 3-7c). This structure possessed a slightly higher energy barrier than the boat conformation with $\Delta G^{\ddagger} \approx 70$ kJ/mol. The distribution between the two rotamers for this structure was calculated to be 56:44 at –50 °C and 57:43 at –72 °C. These results showed that the DFT calculations did not match the experimental results, which showed that the ratio of the two regioisomers is around 2:1 at –50 °C (Figure 3-7).

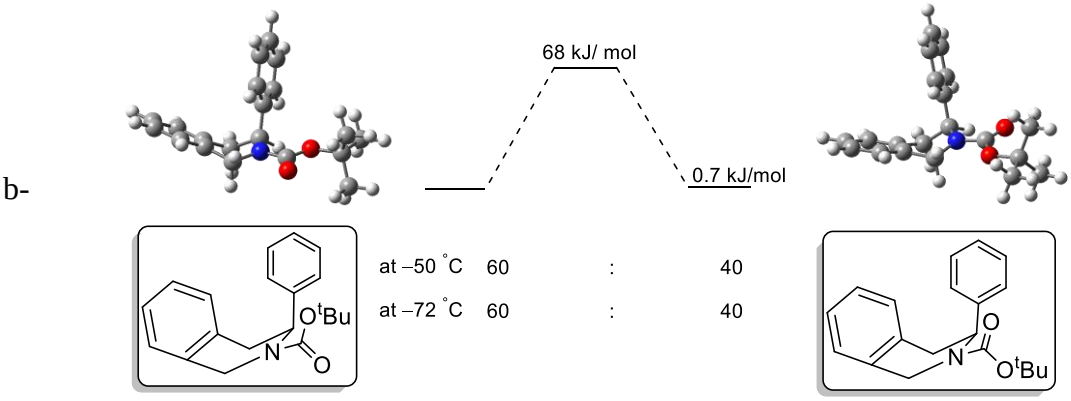
A **B**

a-



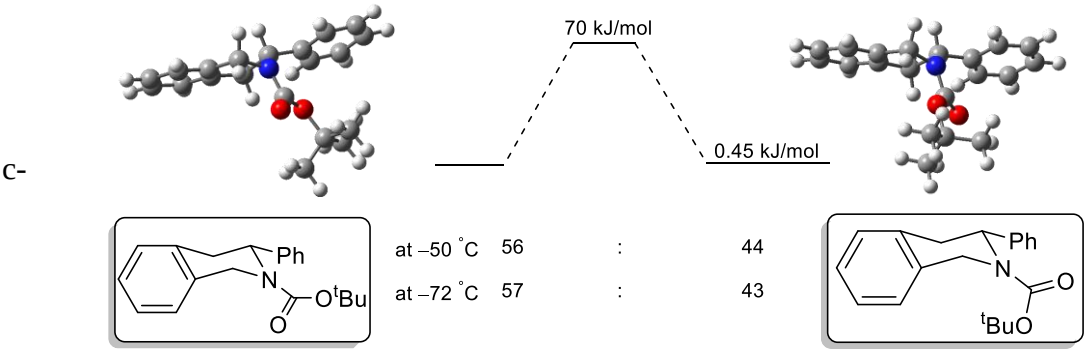
Boat conformation with Ph group in the eq position

b-



Boat conformation with Ph group in the ax position

c-



Chair conformation with Ph group in the eq position

d-

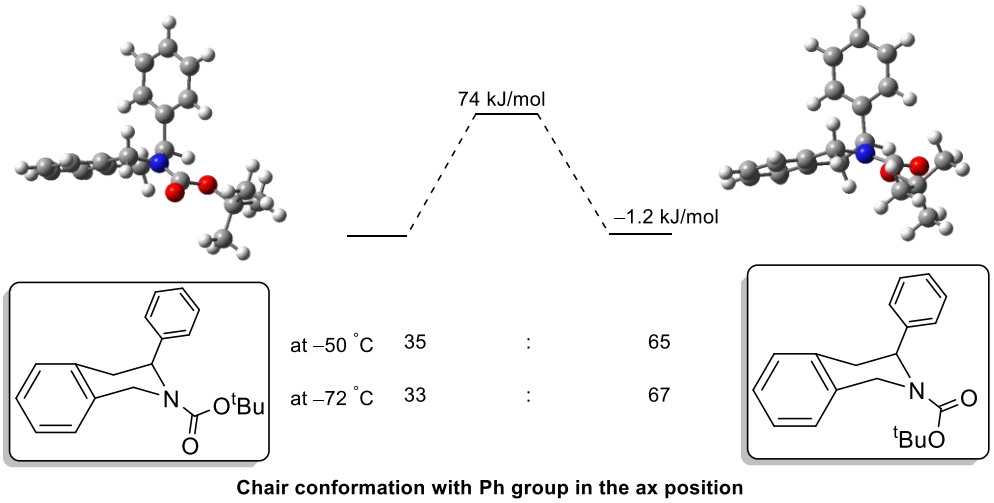


Figure 3-7a-d

Furthermore, the calculations showed as expected that THIQ **175** should exist as two rotamers. Two possible conformations could be formed, either the conformation pointing towards the 1-carbon to give the 1-lithiated intermediate **C** or the conformation to give the 3-lithiated intermediate **D**. The energies of these lithium complexes were calculated, and two structures were found to have the lowest energies. The first is related to the lithiated intermediate **D** with $\Delta G^{\ddagger} \approx 49$ kJ/mol, where the phenyl group was in the equatorial position. The second is related to the lithiated intermediate **C** with $\Delta G^{\ddagger} \approx 48$ kJ/mol where the phenyl group was in the axial position (Figure 3-8). This showed that the energy barrier for lithiation on both positions was relatively similar.

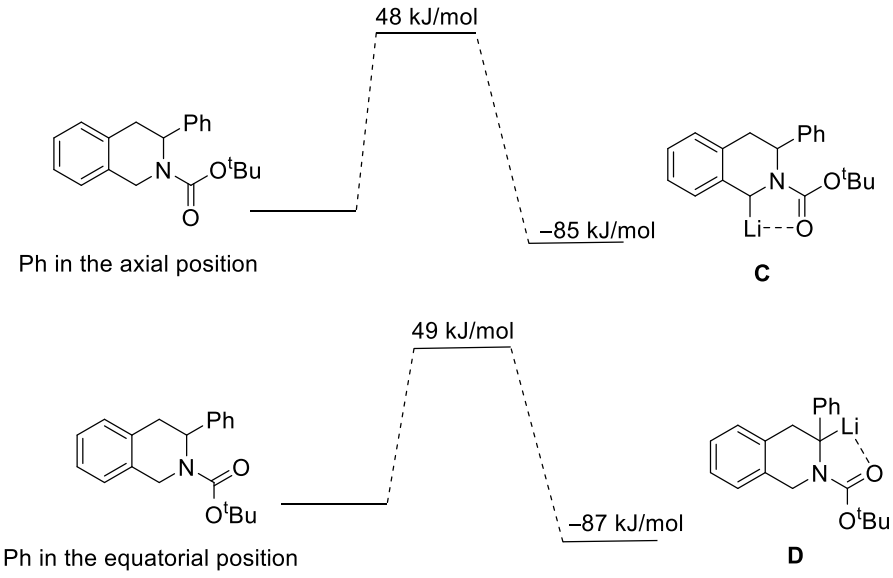


Figure 3-8

Finally, the DFT calculations were calculated at –50 °C and –72 °C. These showed that the boat conformation with the phenyl group in the equatorial position pointing toward C-1 possessed the lowest energy structure. The results suggested it was likely for compound **175** to adopt the boat conformation with the phenyl in either the equatorial or axial position as these had similar energies. The calculations showed that the chair conformation with the phenyl group in the equatorial position adopted the highest energy structure, which was 18 kJ/mol higher than the lowest energy conformation. Therefore, the chair conformation is more likely to adopt the structure with the phenyl group in the axial position. In addition, these calculations showed the ratio between the chair to boat structures with the phenyl group in the equatorial position to be 53:47. The ratio between the boat structures with the phenyl group in the equatorial position to the axial one is 60:40. On the other hand, calculations showed the ratio between the boat to chair with axial phenyl group to be 53:47 (Figure 3-9).[128]

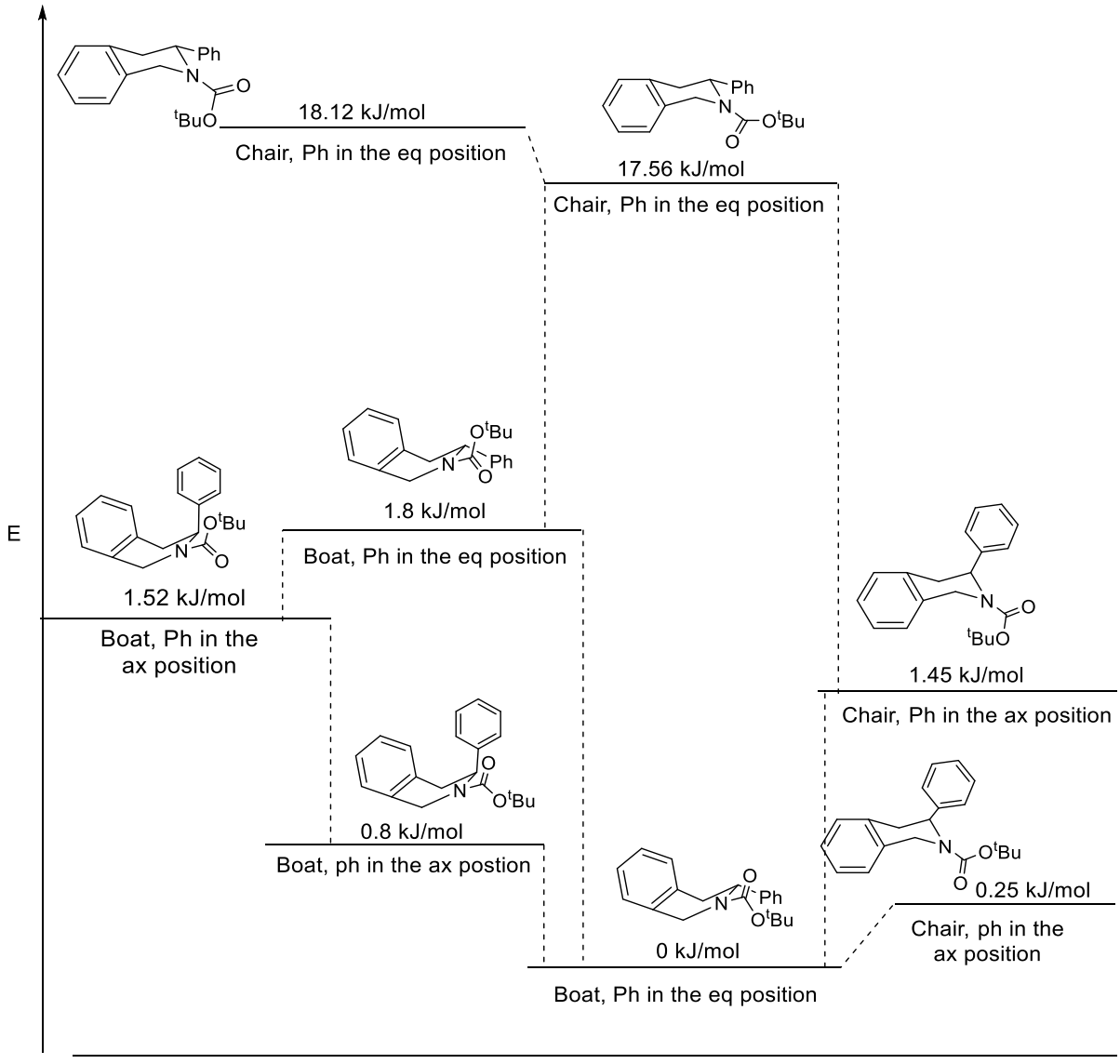


Figure 3-9

3.4 Conclusion

To summarize, it was found that *N*-Boc-3-phenyl-tetrahydroisoquinoline **175** can be deprotonated using *n*-BuLi. The lithiation reaction of this compound was optimised using *in-situ* ReactIR spectroscopy. The optimum conditions were found to be *n*-BuLi in THF at –50 °C for 4 min, which was the same as tetrahydroisoquinolines **113**, **136**, **145** and **152**. The lithiated intermediates were reacted with a number of electrophiles at –50 °C to give the 1-substituted and the 3-substituted products with an average ratio of 2:1 according to a D_2O quench, whereas the ratio was approximately 1.2:1 at –78 °C. Variable temperature NMR studies were carried out to calculate the energy barrier for the Boc group rotation between the two rotamers. This was found to be very fast, even faster than tetrahydroisoquinoline **152**. Also, DFT calculations were carried out in order to determine the ratio between the two rotamers, and these were found to be different from the experimental and the spectroscopic data. For THIQ **175**, the calculated energy barriers for the lowest energy conformation were found to be $\Delta G^{\ddagger} \approx 68$ KJ/mol and $\Delta G^{\ddagger} \approx 69$ KJ/mol. In comparision the $\Delta G^{\ddagger} \approx 57$ KJ/mol from variable temperature NMR. On the other hand, calculations showed that the energy barrier of the first and third positions of lithiated **175** were similar ($\Delta G^{\ddagger} \approx 49$ KJ/mol and $\Delta G^{\ddagger} \approx 48$ KJ/mol). This indicated that both position could react similarly to give similar ratios after an electrophilic quench. However, the experimental data showed different results.

Chapter 4. Asymmetric Synthesis of Nitrile containing Compounds

4.1 General Introduction to Nitrile Containing Compounds

Nitrile–containing compounds are known for their pharmaceutical importance. They have been used widely in the treatment of a diverse range of conditions and are found in more than 120 natural products.[129,130] For instance, cyanogenic glycosides such as linamarine **206** is one of the most common natural nitriles and they have been isolated extensively from plants, fungi, and bacteria.[131,132] Two other natural products that contain nitriles are herandia **207** from nymphaefalia and malloapltine **208** from *Mallotus apelta*.[133,134] Some nitriles have physiological effects in the human body, for example vildagliptin **209** acts as an antibiotic,[135,136] and bicalutamide **210** is an effective drug used in the treatment of prostate cancer.[137] Another effective nitrile is milrinone **211**, used for the treatment of heart failure.[138] Escitalopram **212** is used to treat depression.[139] Anastrazole **213** is used in oestrogen-dependent breast cancer treatment,[140] and verapamil **214** is used as an antiarrhythmic agent in the treatment of angina.[138] Lastly, etravirine **215** is a type of non-nucleoside used as an HIV inhibitor in the treatment of AIDS (Figure 4-1).[141]

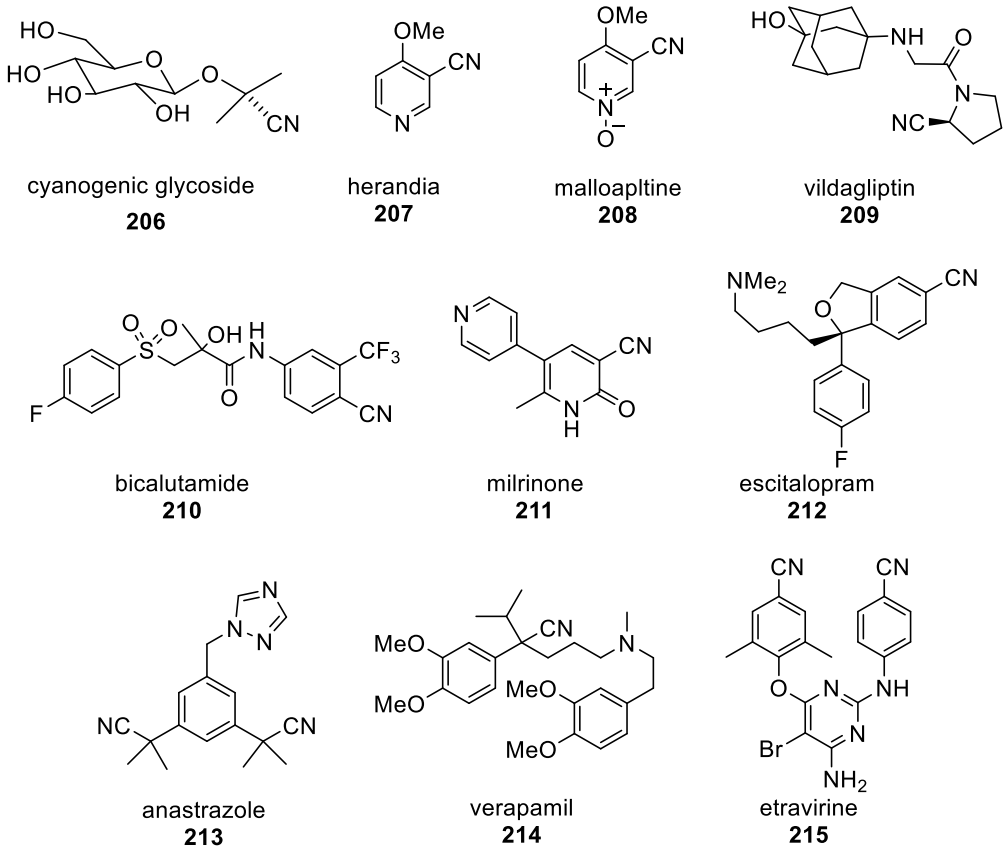
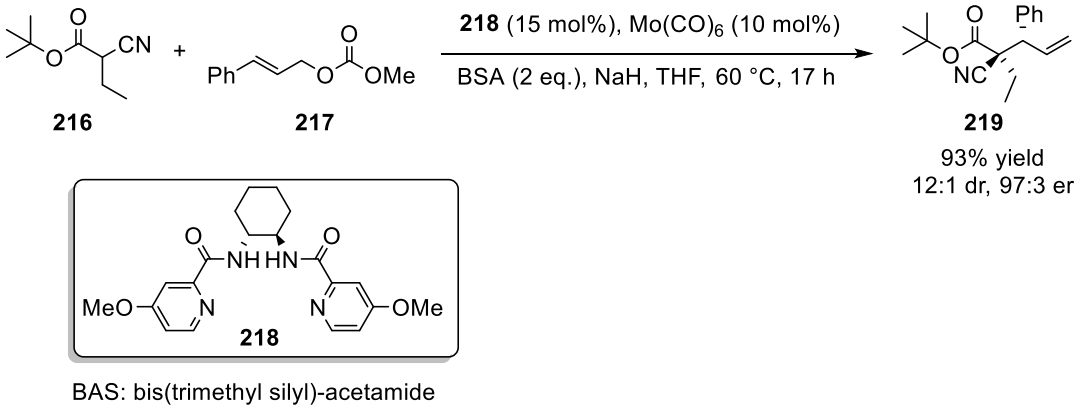


Figure 4-1

Nitriles are an important class of compounds that can be easily converted into a range of other functional groups such as carboxylic acids, amides, ketones and aldehydes using relatively simple reactions.[142] Therefore several reactions have been reported for the synthesis of racemic and enantioenriched nitriles.[143–147]

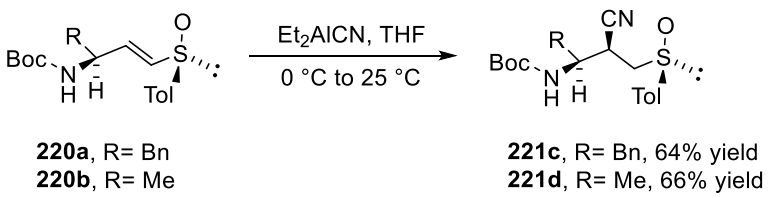
4.1.1 Asymmetric Synthesis of Nitriles

Generally, asymmetric synthesis of nitriles is important due to the chiral nature of most naturally occurring nitrile molecules.[148] Trost and co-workers reported in 2011 the synthesis of nitrile–containing compound **219** (Scheme 4-1).[149] Asymmetric allylic alkylation of ester **216** was carried out using carbamate **217** in the presence of molybdenum–catalyst and ligand **218**, this gave good yield and high diastereoselectivity of the formed product **219**.



Scheme 4-1

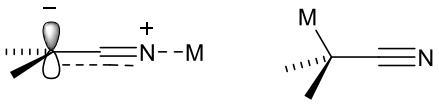
Another example of an asymmetric synthesis of nitrile–containing compounds has been carried out by the Ruano group (Scheme 4-2).[150] They reported the synthesis of diastereoenriched compounds **221a, b** by reacting enantioenriched vinyl sulfoxides **220a, b** with Et_2AlCN in THF. The stereochemistry of the starting material determined the stereochemical outcome of the product, the use of such precursors could direct the addition of the cyanide group to produce products with a single diastereoisomer. This has been proven by carrying out the reaction using diffirent diastereoisomers of the starting material.[150]



Scheme 4-2

4.1.2 Metallated Nitriles

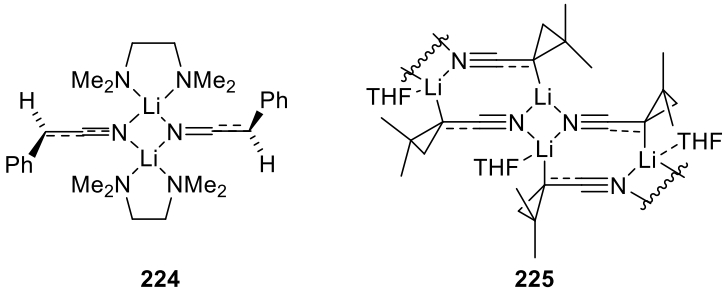
Obtaining high levels of enantio and diastereoselectivity can be achieved using chiral ligands. Only a few examples in the literature describe the asymmetric alkylation of metallated nitriles, as they represent a continuing synthetic challenge. Metallated nitriles have been used for carbon–carbon bond formation, since they are powerful nucleophiles due to the small steric demand of the nitrile group.[151] The natural identity of metallated nitriles depends on the nature of the metal, solvent, temperature and the structure of the nitrile containing substrate. For example, when coordinated to highly electropositive metals, such as Li, a planar intermediate **222** will be adopted as Li coordinates to the nitrogen atom. In contrast, *C*-metallated species **223** form when less electropositive metals such as Mg, Zn, Pd, and Cu are used (Figure 4-2).[151,152]



222 **223**

Figure 4-2

X-ray crystallography studies were reported by Boche and co–workers to show the inductive effect of a metallated CN group (Figure 4-3). They obtained an X–ray structure of lithiated phenyl acetonitrile **224** using benzene as a solvent in the presence of TMEDA. This showed that the lithium atom was bonded to the nitrogen atom in a dimeric structure.[153] Likewise, the X–ray structure of cyclopropanecarbonitrile **225** in THF contains the Li-N-Li-N dimer. This demonstrated that lithium atoms have an extensive tendency to coordinate to nitrogen.[154]

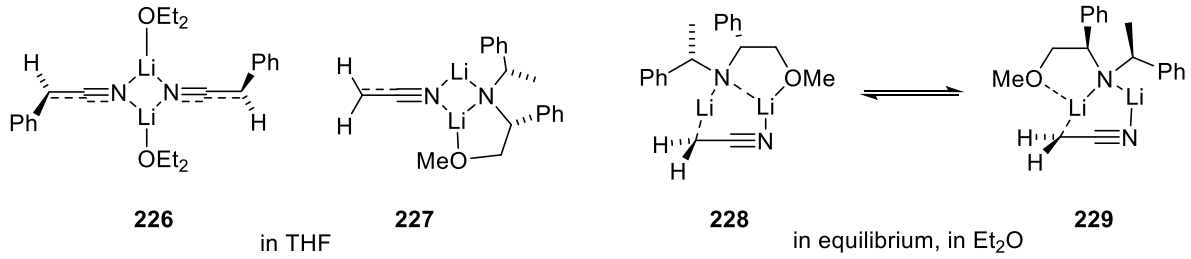


224 **225**

Figure 4-3

Furthermore, NMR spectroscopic studies on metallated nitriles were carried out using lithiated arylacetonitrile in two different solvents (Figure 4-4).[155,156] Initially, in Et_2O, *N*-metallated species **226** was formed. However, in THF, the determination of the lithiated structure was unsuccessful. This may have been due to the formation of a contact ion pair structure with THF,

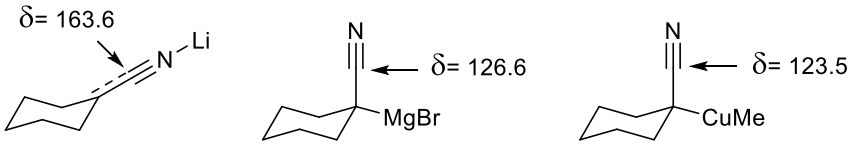
facilitating fast chemical exchange. It was assumed that in THF the structure could be monomeric.[155,156] Likewise, NMR studies on lithiated acetonitrile using a ligand showed that a ketenimine structure **227** was adopted in THF, due to lithium coordination to the nitrogen. However, in Et_2O the nitrile forms a bridged structure **228** and **229** where coordination of N and C atoms show a rapid equilibrium at –100 °C.[157,158]



226 **227** **228** **229**

Figure 4-4

More recently, NMR spectroscopic studies on metallated nitriles were carried out by Fleming and co-workers to determine the metal coordination geometry. This could be det`ermined by signal positions in the ^{13}C NMR spectrum. Using cyclohexanecarbonitrile, peaks at 126.6 and 123.5 ppm were observed in the ^{13}C NMR *via* deprotonation using magnesium or copper bases respectively. This indicated that both metals coordinate to the carbon. However, a signal at 163.6 ppm was observed when an organolithium reagent was added, showed that the nitrile was *N*-lithiated (Figure 4-5).[152]



230 **231** **232**

Figure 4-5

They also carried out studies on metallated phenylacetonitrile and these showed that the lithiated and the magnesiated species were *N*-metallated. They also investigated the metalation of 2-(2-methoxyphenyl)acetonitrile in order to determine if the metallation could be promoted towards carbon when using the methoxy directing group. As shown in Figure 4-6, deprotonation using magnesium and lithium bases showed a resonance at δ 141.1 and 147.6 respectively in the ^{13}C NMR spectrum, which was consistent with *N*-metallation. However, the more electronegative copper showed a signal at δ 131.2 which indicated that the *C*-metallated species was formed. This indicated that metallation is influenced by the carbon scaffold.[152]

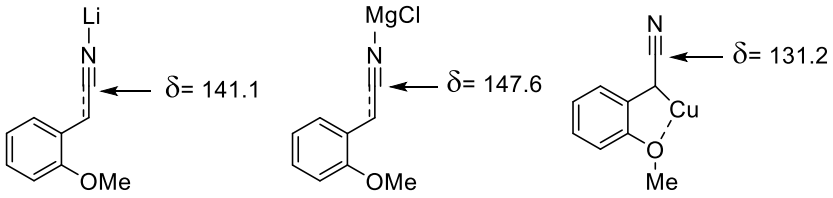
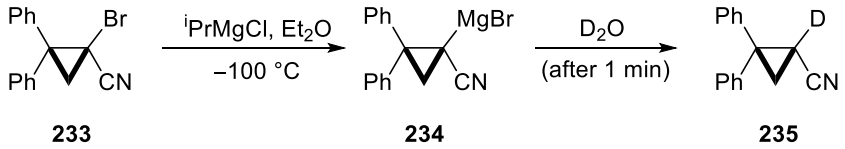


Figure 4-6

4.1.3 Selective Synthesis Using Organomagnesium Compounds

Enantioselective syntheses of nitrile–containing compounds using magnesium bases have been reported recently.[152,159–162] For example, the first enantioselective synthesis of a nitrile–containing compound with microscopic configurational stability was reported by the Carlier group (Scheme 4-3).[163] By subjecting enantiopure bromonitrile **233** to bromine–magnesium exchange at –100 °C for 1 minute, followed by addition of D_2O gave deuterated nitrile **235** in a 97% yield and 90:10 er. The reaction proceeded with retention of configuration. They found that the rate of racemisation for intermediate **234** was slow at –100 °C with a half-life of 11.4 ±1 hour.



Scheme 4-3

Further investigations were carried out to explore the role of solvent on the racemisation of intermediate **234**. It was found that the rate of racemisation in THF and 2-MeTHF was approximately seven to eightfold faster than in Et_2O. Also, the reaction was less selective in both THF and 2-MeTHF, while in Et_2O the stereochemistry of bromine–magnesium exchange was highly retentive. These results show a significant effect of solvents on the enantiomerization process. Investigations into the reaction order in Et_2O showed a saturating dependence of the rate of racemisation (k_{rac}) on Et_2O. This suggests that in high Et_2O concentrations the structure of intermediate **234** could be either **236** or **237** (Figure 4-7).[164]

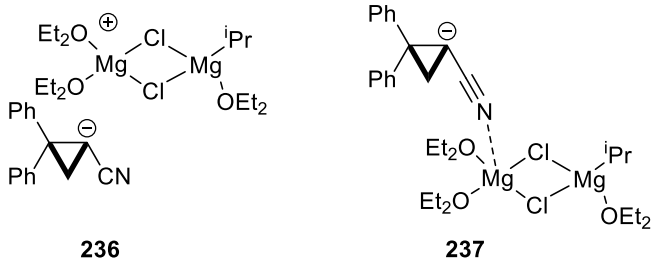
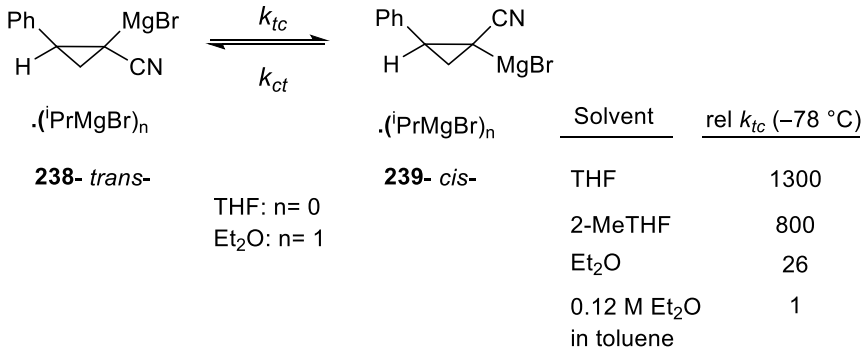


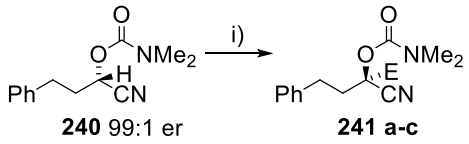
Figure 4-7

Following from the investigations above, a study regarding solvent effects on epimerization of chiral Grignard reagent **238** has been reported (Scheme 4-4).[165] It was observed that compound **238** underwent highly retentive Mg/Br exchange in Et_2O. There was a noticeable dynamic range in the epimerization rate constants (k_{tc}) when changing solvent. The concentration and the identity of the ethereal solvents has a dramatic effect on configurational stability of nitrile **238**. Notably, epimerization in Et_2O was 26–fold faster than in 0.12 M Et_2O in toluene, and 800 and 1300 fold faster in 2-MeTHF and THF respectively.



Scheme 4-4

In 2013, Takeda and co-workers reported enantioselective lithiation–substitution of acyclic enantioenriched nitrile **240** using carbon based electrophiles and $^iPr_2NLi$ at –114 °C. They found that using an *in-situ* deprotonation of the starting material, the product was obtained in high yield and enantioselectivity using ethyl cyanoformate as the electrophile. They hypothesised that the ability of the carbamoyl group to stabilise the α-nitrile carbanion is the reason behind the high enantiomeric ratios. They reported that the electrophilic quench proceeded with inversion of configuration. However, with more bulky electrophiles or with alkyl halides, racemic products were formed.[166] Following on from this work, Coldham and co-workers explored the deprotonation of the enantioenriched nitrile **240** using magnesium bases (Scheme 4-5).[167] Investigation was carried out using either normal addition, where *in-situ* deprotonation occurred *via* addition of a nitrile **240** and MeOCOCN mixture to the base at –107 °C, or inverse addition where nitrile **240** was added to the base followed by electrophilic quench of MeOCOCN after 10 sec. Better enantioselctivity was achieved when using the inverse addition procedure, especially in the absence of LiCl. The magnesiated nitrile showed high configurational stability at –107 °C, but at –78 °C the rate of racemization was fast and only the *in-situ* process gave high enantioenrichment. Regarding magnesium bases, using TMPMgCl gave excellent results even at –78 °C while ^{i}PrMgCl gave none of the desired products.[167]



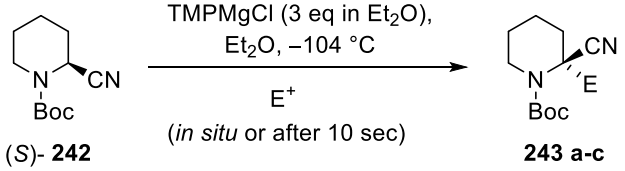
240 99:1 er **241 a-c**

E^+		Yield %	er
MeOCO	**241a**	66	97:3
EtOCOCl	**241b**	75	92:8
PhCOCl	**241c**	73	82:18

Reagent and conditions i): Nitrile **240** and electrophile added to TMPMgCl in THF (3 equiv) in Et_2O/THF (1:1), –107 °C over 4 min, then, after 10 min, NH_4Cl (aq).

Scheme 4-5

As mentioned earlier, solvents have a great impact on the rate of racemisation and epimerization. Recently, Coldham and co-workers reported deprotonation–substitution of enantiopure nitrile (*S*)-**242** using TMPMgCl in Et_2O at –104 °C using different electrophiles (Scheme 4-6). [168] This gave high yields and excellent enantioselectivities of the products. They conducted a kinetic experiment in order to determine the rate of epimerisation of magnesiated (*S*)-**242** in Et_2O and in a mixture of Et_2O:THF (1:1). The kinetic data showed that the rate of inversion of the magnesiated intermediate is slightly slower in Et_2O than in THF/Et_2O (the enantiomerisation half–life $t_{1/2}$ is ~3 minutes in Et_2O and only ~2 minutes in THF/Et_2O). They hypothesized that this is perhaps because THF helps to solvate the magnesium cation. They also noticed that using Et_2O improves the yields of the products.[165,168]



(*S*)- **242** **243 a-c**

E^+		Yield %	er
$PhSSO_2Ph$	**243a**	67	98:2
Me_2CO	**243b**	63	96:4
cyclobutanone	**243c**	68	95:5

Scheme 4-6

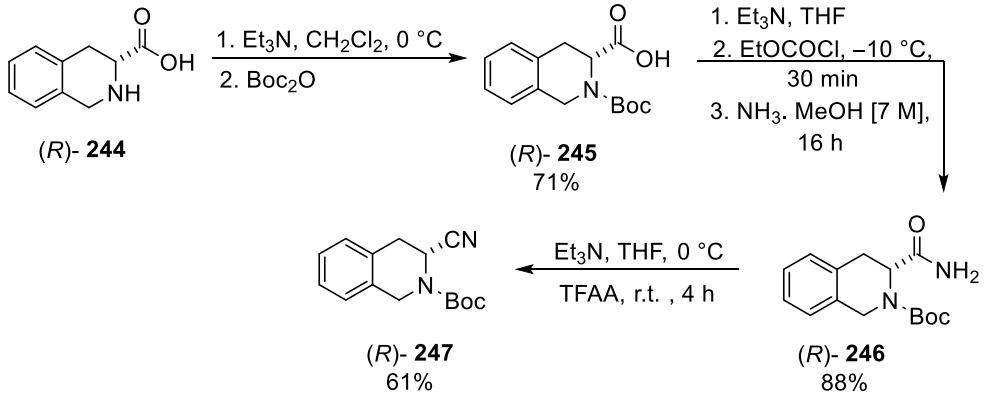
The Aim of this chapter is to synthesize *N*-Boc-3,3-disubstituted-cyanotetrahydroisoquinoline and *N*-Boc-2,2-disubstituted-cyanopyrrolidine *via* deprotonation-substitution approach using mainly organomagnesium bases. As mentioned earlier solvent has a great effect on the rate of epimerisation of the nitrile group.[165] We thought it would be interesting to investigate how changing solvent would effect the rate of epimerisation of the nitrile group in the main

substrates under investigation. Investigations will focuse on the enantioselective synthesis, and the enantioselectivity of the forming products will be determined using chiral HPLC.

4.2 Results and Discussion

4.2.1 Synthesis and Reaction of *N*-Boc-3-cyanotetrahydroisoquinoline

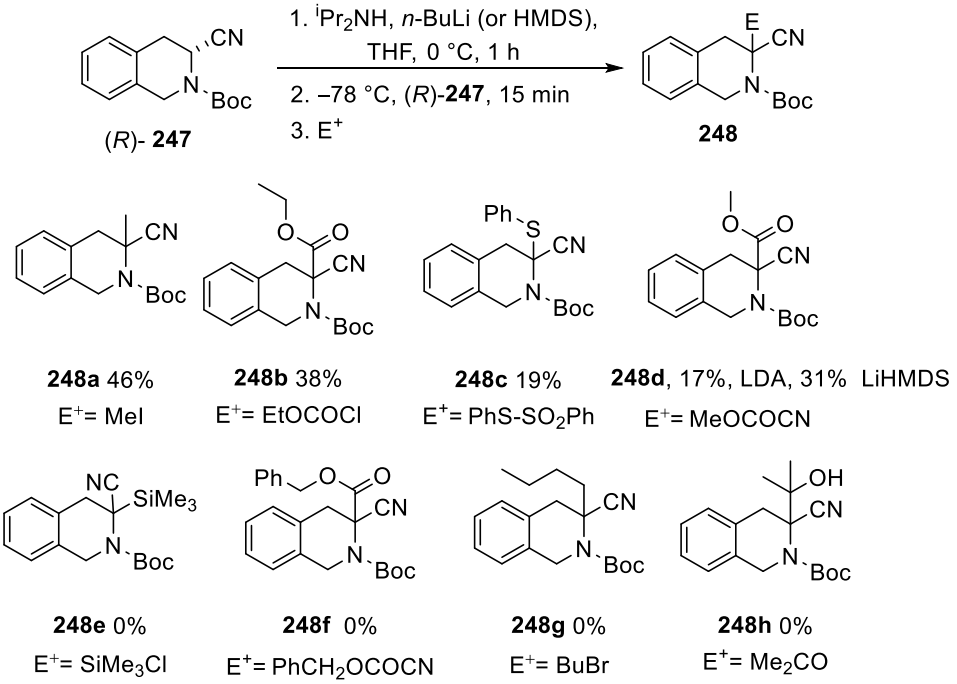
Since tetrahydroisoquinolines have great importance as alkaloids and as key intermediates in the synthesis of other complex natural products, we investigated the deprotonation–substitution of enantioenriched (*R*)-nitrile **247**. In order to prepare nitrile **247**, commercially available enantioenriched carboxylic acid **244** was first *N*-protected with Boc_2O (Scheme 4-7). Initially, this was attempted using DMAP as the base in THF but gave only recovered starting material.[169] Therefore, NaOH [1 M] was used in THF and a 23% of the protected acid **245** was formed. It had been noticed that the solubility of the starting material was very poor in NaOH [1 M]/THF. As a result, a mixture of bases was used to promote the reaction and saturated $NaHCO_3$:NaOH [1 M] 1:1 was added to the starting material in THF. Using a mixture of these bases dissolved the acid directly to give a 53% yield of compound **245**. Another method involved using Et_3N in CH_2Cl_2 to give the desired product in a 71% yield.[170] In the next step, the carboxylic acid was converted to the amide **246**.[171] Finally, the amide was dehydrated to give the nitrile **247** using TFAA in a 61% yield (Scheme X).[171] The nitrile was enantioenriched, as verified from the specific rotation $[\alpha]_D^{25}$ +14 (1, $CHCl_3$). It was assumed that the nitrile had 100:0 er, but this was not proven.



Scheme 4-7

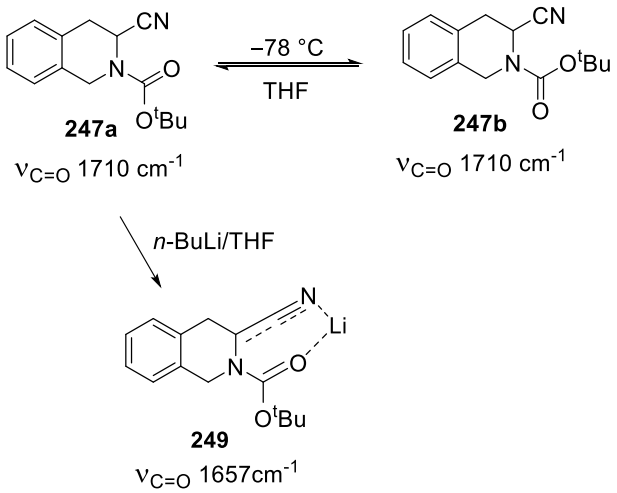
Initially, THIQ **247** was deprotonated using lithium diisopropylamide (LDA) at –78 °C followed by the addition of different electrophiles after 15 minutes. The reaction mixture was allowed to warm to room temperature before adding aqueous NH_4Cl. Unfortunately, poor yields of racemic products were obtained with the electrophiles used and different ratios of recovered starting material was observed (Scheme 4-8). In an attempt to improve the results,

LiHMDS was used at –78 °C in THF. After 15 minutes methyl cyanoformate was added, the reaction mixture was allowed to warm to room temperature before adding aqueous NH_4Cl. However, only a 31% yield of the racemic product **248d** was obtained and recovered starting material. The products found to be racemic by chiral HPLC.



Scheme 4-8

Therefore, lithiation–substitution reaction of nitrile **247** was investigated using *in-situ* ReactIR spectroscopy at –78 °C using *n*-BuLi/THF (Scheme 4-9). Nitrile **247** exhibited a peak for $\nu_{c=o}$ at 1710 cm^{-1} in the IR spectrum. Rapid and complete loss of this peak was observed when *n*-BuLi was added and a new peak for a carbonyl ($\nu_{c=o}$ 1657 cm^{-1}) formed rapidly. This indicated fast lithiation of the enantiopure-**247** within ~ 2 minutes (Figure 4-8).



Scheme 4-9

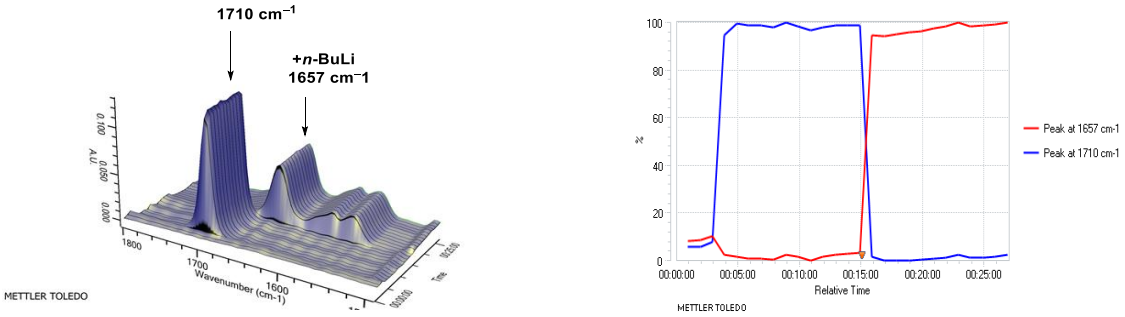
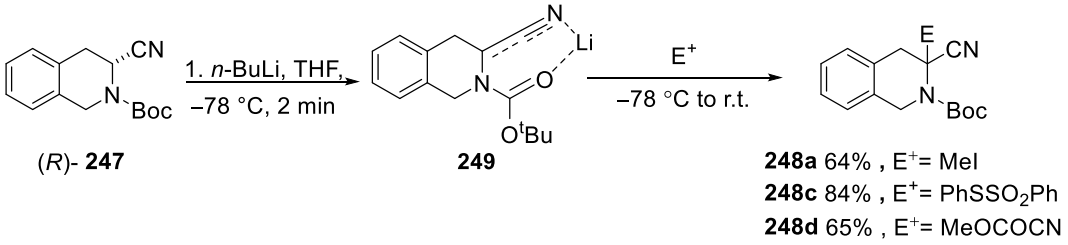


Figure 4-8. *in-situ* ReactIR 3-D and 2-D plots of the lithiation of **247** at –78 °C; Blue Line represents intensity of C=O stretching frequency of **247** (1710 cm^{-1}) and red line of lithiated **249** (1657 cm^{-1}) over time. . there was ± error when assigning the peaks.

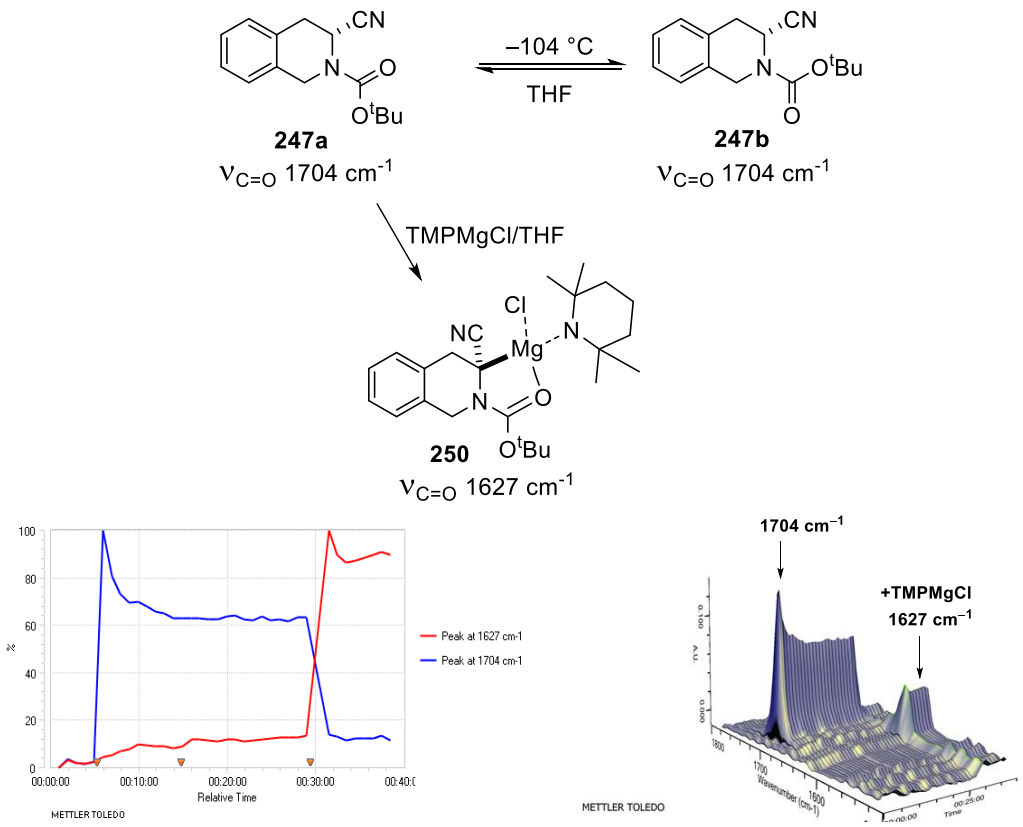
n-BuLi was used next based on the *in-situ* ReactIR results obtained, and the electrophiles were added to lithiated **249** after 2 min at –78 °C in THF (Scheme 4-10). The reaction mixture was allowed to warm to room temperature before adding NH_4Cl. Notably, better yields were obtained when using MeI, $PhSSO_2Ph$ and MeOCOCN in comparison with both LiHMDS and LDA.



Scheme 4-10

Chiral stationary phase gas chromatography was used to determine the enantiomeric ratio of compounds **24a**, **c**, and **d**, and these were found to be racemic.

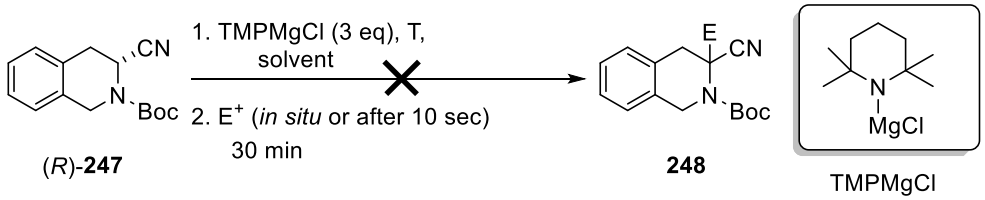
As previously stated, magnesium bases can provide *C*-metallated nitrile species, and as a result this may allow the chiral integrity to be maintained. Therefore, an *in situ* ReactIR study was carried out using TMPMgCl (2.5 eq)/THF at –104 °C, in order to optimise the reaction conditions using magnesium bases. Nitrile **247** exhibited a peak for $\nu_{c=o}$ at 1704 cm^{-1} in the IR spectrum. Rapid and complete loss of this peak was observed, when adding 2.5 equivalents of TMPMgCl with the formation of magnesiated intermediate **250** ($\nu_{c=o}$ 1627 cm^{-1}), indicating fast deprotonation of the nitrile **247** within ~ 2 minutes (Scheme 4-11).



Scheme 4-11. *in-situ* ReactIR 3-D and 2-D plots of the deprotonation of **247** at –104 °C; Blue Line represents intensity of C=O stretching frequency of **247** (1704 cm^{-1}) and red line of the magnesiated **250** (1627 cm^{-1}) over time.

In the light of previous work in the Coldham group using magnesium bases for enantioselective metallation *α* to nitrile;[159,167,168] we focused on using TMPMgCl as a base, which was prepared from ^{i}PrMgCl [2 M] in THF or Et_2O and TMPH. We hoped that the magnesiated intermediate would be configurationally stable on the reaction time scale, and therefore it would be possible to obtain enantioenriched products. TMPMgCl was added to enantiopure nitrile **247** in a mixture of THF:Et_2O (1:1) at –104 °C. After 10 seconds, methyl cyanoformate was added but no product was obtained. Using PhS-SO_2Ph gave only recovered starting material. It is important to understand that these results may have been related to the solvent, base or temperature. With this in mind, ^{i}PrMgCl was used instead at –104 °C; unfortunately, no product was formed when using methyl cyanoformate. Therefore, the temperature was changed to –78 °C, using ^{i}PrMgCl and TMPMgCl respectively, this gave no desired product. As mentioned earlier, Carlier and co-workers investigated the effect of solvent on epimerisation (Scheme 4-4). Also, Coldham and co-workers reported that changing the solvent from THF to Et_2O gave better yields and enantioselectivities (Scheme 4-6). However, the starting material did not dissolve in Et_2O and for this reason, a mixture of 2-MeTHF:Et_2O was used, and ^{i}PrMgCl [2 M] in ether was purchased. TMPMgCl in Et_2O was added at –104 °C followed by addition of

methyl cyanoformate after 10 sec. Unfortunately, no product was formed. The same reaction was repeated at a higher temperature of –78 °C, but gave similar results. It was found that the starting material dissolved in toluene, and so the reaction was next attempted in a mixture of toluene:ether (1:1), TMPMgCl in ether was added at –104 °C and methyl cyanoformate was added after 10 seconds, this resulted in a complex mixture of products (Scheme 4-12, Table 4-1).



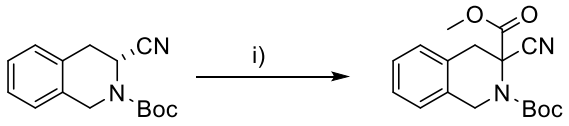
Scheme 4-12

Entry	Solvent	T	base	E^+ *in situ* or after 10 min	Yield %	Recovered **247** %
1	THF:Et_2O (1:1)	–104 °C	TMPMgCl in THF	MeOCOCN	–	72
2	THF:Et_2O (1:1)	–104 °C	TMPMgCl in THF	EtOCOCN	–	61
3	THF:Et_2O (1:1)	–104 °C	TMPMgCl in THF	PhS-SO_2Ph *in situ*	–	81
4	THF:Et_2O (1:1)	–78 °C	TMPMgCl in THF	MeOCOCN		78
5	THF:Et_2O (1:1)	–104 °C	TMPMgCl in Et_2O	MeOCOCN	–	64
6	THF:Et_2O (1:1)	–104 °C	^{i}PrMgCl in THF	MeOCOCN	–	68
7	THF:Et_2O (1:1)	–78 °C	^{i}PrMgCl in THF	MeOCOCN	–	72
8	2-MeTHF:Et_2O (1:1)	–104 °C	TMPMgCl in Et_2O	MeOCOCN	–	63
9	2-MeTHF:Et_2O (1:1)	–78 °C	TMPMgCl in Et_2O	MeOCOCN	–	59
10	toluene:Et_2O (1:1)	–104 °C	TMPMgCl in Et_2O	MeOCOCN	–	–

Table 4-1

We were disappointed to find no positive results using magnesium bases when changing solvents and temperature. This may be due to either the low reactivity of magnesiated **250** toward the electrophiles used or the stability of the magnesiated species. We suspected in each case in Table 4-1 there was a deprotonation of nitrile **247**, as shown by the ReactIR in Scheme 4-11.

Therefore, the base was changed to TMPK. This could be prepared from a reaction between TMPH and K^{t}OBu in the presence of *n*-BuLi. The product was formed in a 35% yield as a racemate (Scheme 4-13). Changing the solvent to 2-MeTHF gave no improvement in the yield or enantiomeric ratio. This may have been due to the formation of a planar *N*-metallated species, which resulted in a racemate.



(*R*)- **247** **248d**

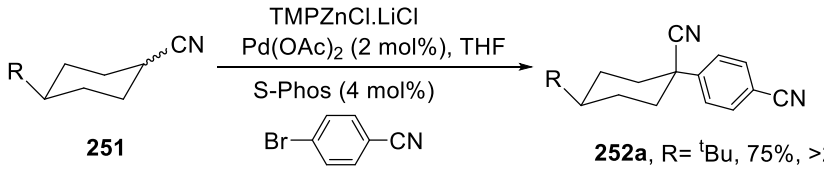
THF, 35%, 48:52 er

2-MeTHF, 37%, 46:54 er

i) Reaction conditions: 1. KO^{t}Bu, TMPH, *n*-BuLi, –78 °C, 15 min, solvent, 2. then –104 °C (*R*)-**247** was added, 3. MeOCOCN, 30 min

Scheme 4-13

Our attention then switched to another well-known base, TMPZnCl.LiCl. This is another important type of organometallic compound that has been used widely in organic synthesis. Fleming and Knochel reported the use of TMPZnCl.LiCl in the deprotonation of a variety of cyclohexanecarbonitriles.[172] These were then transmetallated using palladium, followed by the addition of an aryl bromide to give high yields of the products. High diastereoselectivities were obtained in the presence of bulky groups in the 4-position, or a methyl group in the 2-position (Scheme 4-14).



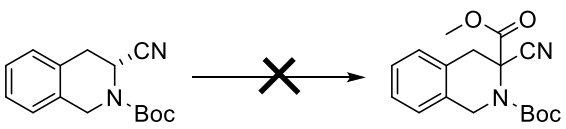
251

252a, R= ^{t}Bu, 75%, >20:1 dr

252b, R= ^{t}BuMe$_2$Si, 71%, >20:1 dr

Scheme 4-14

Therefore, we tried to deprotonate enantiopure nitrile **247** using TMPZnCl in the hope that good selectivity and better yields would be obtained. TMPZnCl was added to nitrile **247** at –104 °C in a mixture of 2-MeTHF:Et_2O, and after 10 seconds MeOCOCN was added. Quenching the reaction after 30 minutes with aq. NH_4Cl gave only recovered **247** (Scheme 4-15). (To prepare TMPZnCl, a transmetallation reaction was conducted between TMPMgCl and $ZnCl_2$ in ether [2 M] at room temperature for 24 hours).[173,174] It was not clear why no product was obtained when using the organozinc base, however it could be because nitrile **247** was very sluggish to react with the base.

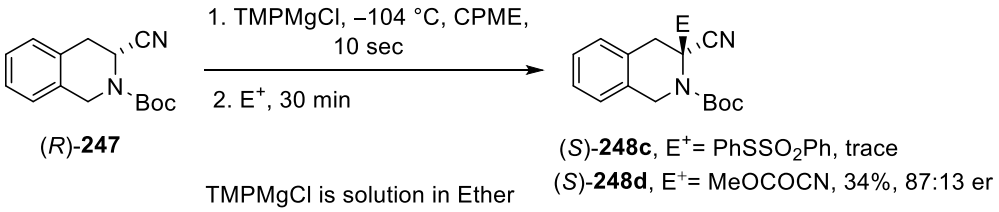


(*R*)- **247** **248d** 0%

i) Reaction conditions: 1. TMPMgCl, Et_2O, r.t., $ZnCl_2$. Et_2O [2 M], 24 h, then –104 °C (*R*)-**247,** 10 sec, 2-MeTHF:Et_2O (1:1) was added, 3. MeOCOCN, 30 min

Scheme 4-15

The Capriati group has shown how the use of cyclopentylmethylether (CPME) had a positive effect on yields when compared to Et_2O in the lithiation of diaryltetrahydrofuran.[175] As a result, TMPMgCl in Et_2O was added to enantioenriched nitrile (*R*)-**247** in CPME at –104 °C followed by addition of MeOCOCN after 10 seconds. This gave compound **248d** in a 34% yield and an 87:13 enantiomeric ratio (Scheme 4-16). Later, PhS-SO_2Ph was used as electrophile where *in-situ* addition obtained trace amounts of product **248c**, which was detected by high resolution mass spectroscopy. However, the product was lost over the column (Scheme 4-16). The reaction was assumed to proceed *via* retention of configuration, but this has not been proven. As can be seen, using CPME gave better results than THF and 2-MeTHF. This could be because in these two solvents the reactivity of magnesium bases changes as the aggregation states change as well.



(*R*)-**247**

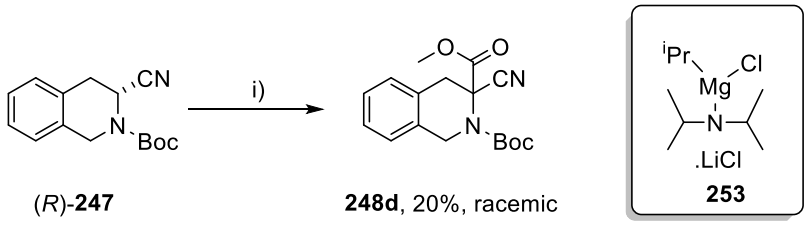
(*S*)-**248c**, E^+= $PhSSO_2Ph$, trace

(*S*)-**248d**, E^+= MeOCOCN, 34%, 87:13 er

TMPMgCl is solution in Ether

Scheme 4-16

Later, an alternative base was prepared in an attempt to improve the yields of the products. isopropyl magnesium diisopropylamide (^{i}Pr$_2$N)Mg^{i}Pr [0.36 M] **253**[174,176] was added to nitrile **247** at –104 °C in CPME, followed by an electrophilic quench of MeOCOCN to give compound **248d** in a 20% yield as a racemate (Scheme 4-17).(The base **253** was prepared from a transmetalation reaction of lithium diisopropylamide in Et_2O using ^{i}PrMgCl [2 M] at room temperature for 2 hours). The absence of any selectivity could be because the base **253** exists as monomer in CPME, which may not be as bulky as TMPMgCl. It could be possible in a future work to investigate if the structure of base **253** is a monomer.

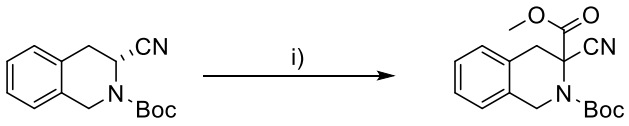


(*R*)-**247** **248d**, 20%, racemic Base **253** is solution in Ether

i) *Reaction conditions:* 1.$^{i}Pr_2NLi$, Et_2O, $^{i}PrMgCl$, 2 h, r.t., 2. then –104 °C (*R*)-**247**, CPME, 10 sec, 3. MeOCOCN, 30 min

Scheme 4-17

To try and further improve the yield of product **248d**, TMPZnCl.LiCl in CPME was used instead. TMPZnCl.LiCl [0.4 M] was added to nitrile **247** at –104 °C in CPME, and after 10 seconds MeOCOCN was added (Scheme 4-18). However, no product was formed and this may be due to the fact that organozinc reagents are less reactive bases than organomagnesium bases.[177] To prepare TMPZnCl a transmetallation reaction of TMPLi and $ZnCl_2$ [2 M] in Et_2O was conducted at room temperature for 2 hours.[174]



(*R*)- **247** **248d**, 0%

i) *Reaction conditions:* 1. TMPH, CPME, *n*-BuLi, 15 min, –78 °C, 2. then –104 °C (*R*)-**247**, Et_2O $ZnCl_2$, 1 hour, 3. MeOCOCN, 30 min

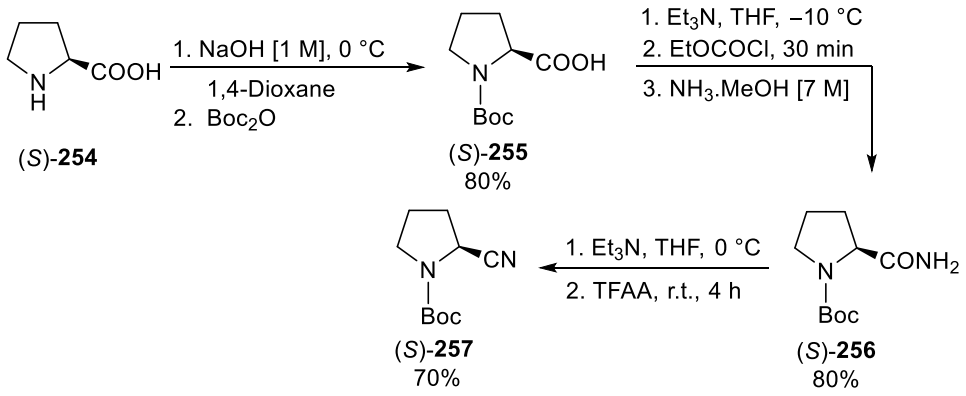
Scheme 4-18

As can be seen, using TMPMgCl gave the most promising results. However, low yields were obtained, and we decided to stop our investigations.

4.2.2 Synthesis and Reaction of *N*-Boc-2-cyanopyrrolidine

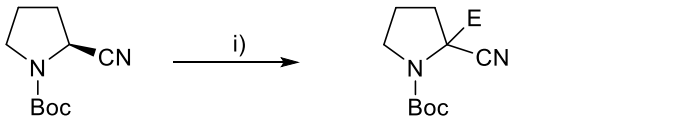
Since the deprotonation–substitution of nitrile **247** using magnesium bases resulted in poor yields, we investigated the synthesis of enantiopure nitrile **257**, which is of importance as it could provide a route to unnatural proline derivatives after hydrolysing the nitrile group to the carboxylic acid.[129] In the light of previous work done in the Coldham group by Skilbeck on enantiopure proline derived nitrile **257** (*vide infra*), further investigations were carried out in an attempt to improve the results.[159] To prepare nitrile **257**, commercially available L-proline was firstly protected to give **255** in an 80% yield. The acid was converted to the amide **256** in an 80% yield.[171,178] Finally, the amide was dehydrated using trifluoroacetic anhydride to give nitrile **247** (Scheme 4-19).[179] The nitrile was formed as a single enantiomer and its absolute stereochemistry was verified from the specific rotation $[\alpha]_D^{25}$ –94 (1.3, MeOH) in comparison

to the literature [lit.[179] for the (*S*)-enantiomer $[\alpha]_D^{22}$ –95.5 (1.5, MeOH)]. It was assumed that the nitrile has 100:0 er, but this was not proven.



Scheme 4-19

After the enantiopure nitrile **257** was isolated, it was deprotonated using lithium diisopropylamide (LDA), followed by electrophilic quench to prepare racemic products (Scheme 4-20). Skilbeck tried to deprotonate (*S*)-**257** using LDA, but poor results were obtained using some electrophiles. For example, a 17 % yield of **258b** was obtained using acetone, however when we repeated the same reaction no product was found.[159] We also tried using acid chlorides as electrophiles but found that acetyl chloride and benzoyl chloride gave no products. Benzaldehyde gave a trace amount of product that could not be purified. It was not clear why these reactions did not proceed.

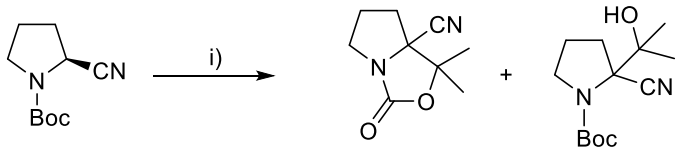


i) Reaction conditions: 1. $^{i}Pr_2NH$, *n*-BuLi, –5 °C, 1 h, THF. 2. then (*S*)-**257**, 15 min, –78 °C 3. electrophile, –78 °C to r.t.

Scheme 4-20

Consequently, the use of other solvents was explored. Firstly, the starting material in Et_2O was added to LDA in THF, followed by addition of acetone after 15 minutes. This gave compounds **258a** and **258b** in a 11% and a 10% yield respectively. Using benzoyl chloride gave product **258c** in 27% yield. We tried conducting the reaction in pure Et_2O, but a complex mixture of products was obtained when using acetone. Therefore, LDA was prepared using THF and the starting material was added in CPME. This showed slightly better results with acetone, and compounds **258a** and **258b** were obtained in a 21% and a 16% yields respectively.[159] By using benzoyl chloride as the electrophile under these conditions, the nitrile **258c** was formed in 40%

yield (Scheme 4-21a and b). Surprisingly, by-products from a reaction between LDA and the electrophiles were found in all cases. These by-products were characterised by NMR spectroscopy and the structure of product **259**, formed from the addition of PhCOCl was confirmed by single crystal X-ray analysis (Figure 4-9). However, no such products were found when using nitrile **247**. It was not clear why LDA reacted with the electrophiles. Unfortunately, the enantiomers of products **258a** and **258b** could not be separated using CSP-GC or CSP-HPLC.

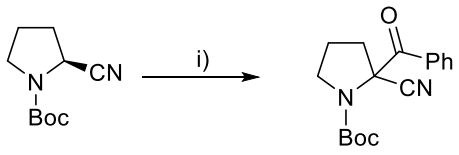


(*S*)-**257** **258a** **258b**

Et_2O:THF (1:1)	10%	11%	+ 21% RSm
CPME:THF (1:1)	21%	16%	

i) Reaction conditions: 1. $^{i}Pr_2NH$, *n*-BuLi, –5 °C, 1 h, THF, 2. then (*S*)-**257**, 15 min, –78 °C, solvent, 3. Me_2CO, –78 °C to r.t.

Scheme 4-21a

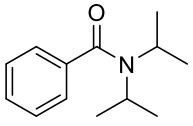


(*S*)-**257** **258b**

Et_2O:THF (1:1)	27%	+ 11% RSm
CPME:THF (1:1)	40%	+ 31% RSm

i) Reaction conditions: 1. $^{i}Pr_2NH$, *n*-BuLi, –5 °C, 1 h, THF, 2. then (*S*)-**257**, 15 min, –78 °C, solvent, 3. PhCOCl, –78 °C to r.t.

Scheme 4-21b



259

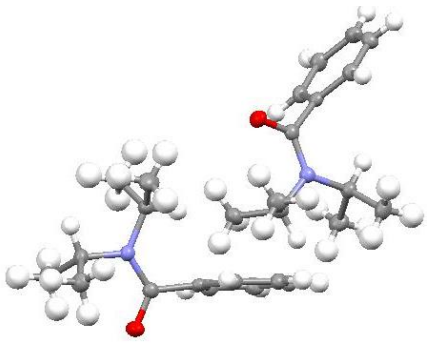
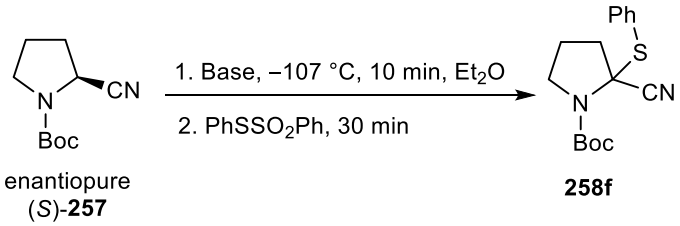


Figure 4-9: Shows the dimeric structure of the by-product 259

To obtain high enantioselectivity *via* a deprotonation–substitution process, magnesium bases were used. Previously in the Coldham group Skilbeck used different magnesium bases to deprotonate (*S*)-nitrile **257** in the hope that this would provide good yields and enantioselectivities. The reaction was carried out using $PhSSO_2Ph$ as an electrophile, however a low yield of racemic product **258f** was obtained (Scheme 4-22, Table 4-3). Skilbeck assumed that the reason for lack of enantioselectivity was because the reaction proceeded *via* a single electron transfer process.[159]



enantiopure (*S*)-**257** — **258f**

Scheme 4-22

Base	Yield %	er
^{i}PrMgCl	8	53:47
^{i}PrMgCl.LiCl	6	50:50
TMPMgCl.LiCl	19	50:50
$^{n}Bu_2Mg$	13	52:48
TMPMgCl	26	53:47

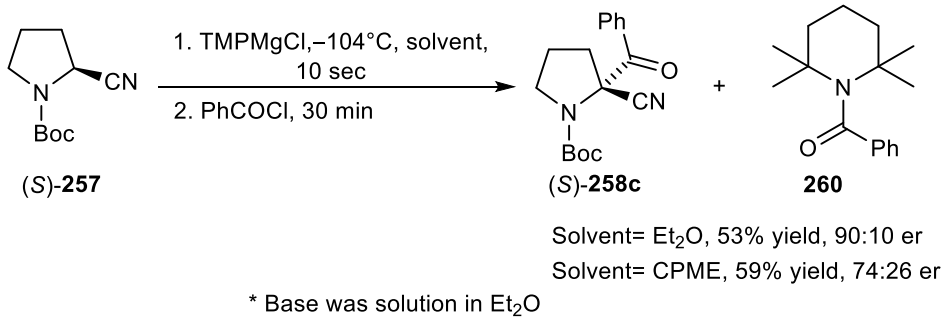
* All bases were solutions in THF

Table 4-3

As previously stated, using Et_2O gave better yields and enantioselectivities when compared to THF.[168] A project student in the Coldham group under my supervision tried to repeat the reaction above using TMPMgCl in Et_2O. By purchasing a new bottle of ^{i}PrMgCl [2 M] in Et_2O to prepare TMPMgCl, an *in-situ* reaction at –104 °C gave racemic product **258f** in only a 5% yield.[180] This indicated that sulfur containing electrophiles were not ideal.

A further reaction was then carried out in my project with the enantioenriched nitrile **257**, which was deprotonated using TMPMgCl in Et_2O –104 °C followed by the addition of benzoyl chloride after 10 seconds to the reaction mixture of nitrile **257** (Scheme 4-23). As a result, compound **258c** was obtained in a 53% yield and a 90:10 enantiomeric ratio. In the meantime, changing solvent to CPME using the same conditions gave compound **258c** in a 59% yield and a 74:26 er. The crystal structure was determined by X-ray crystallography (Figure 4-10), but the absolute configuration was inconclusive. However, the reaction was assumed to proceed with retention of configuration due to previous studies.[168] Also, a by-product was formed from

reaction between the base and the electrophile, and this was verified by NMR spectroscopy and high resolution mass spectrometry. The low yields obtained from the reaction with TMPMgCl in Et_2O could be because nitrile **257** is poorly reactive toward magnesium bases. Therefore, future studies may focus on using other organometallics in order to generate *C*-metallated species, which may give better yields and good selectivities.



Scheme 4-23

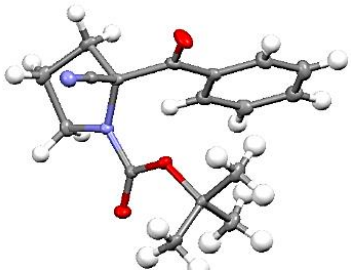


Figure 4-10: shows the structure of Compound 258c. Flack parameter 0.39 (3)

Notably, it was hard to synthesise and purify the racemic derivatives of nitrile **257**. The results when using TMPMgCl as a base were not promising. For this reason, we decided to stop these investigations.

4.3 Conclusion

To summarise, both proline derived nitrile **257** and *N*-Boc-3-cyano tetrahydroisoquinoline **247** were synthesised as enantiopure compounds. Several bases and solvents were used for the asymmetric deprotonation of nitrile **247**, and the deprotonated intermediate was trapped with MeOCOCN. Only low yields were obtained, however in one case a high enantiomeric ratio was found when using TMPMgCl in Et_2O and CPME as a solvent. For proline derived nitrile **257**, low yields were obtained using both LDA and TMPMgCl with different electrophiles. Changing solvent in the lithiation reaction to generate the racemic products improved the

yields. Notably, using TMPMgCl as a solution in Et_2O instead of THF gave moderate yields and high enantiomeric ratio when trapping the reaction with benzoyl chloride.

5. Experimental

5.1 General Experimental Details

All reagents were obtained from commercial suppliers and were used without further purification unless otherwise specified. Solvents were obtained from Grubbs dry solvent system (model: SPS-200-6). Electrophiles were freshly distilled. *n*-BuLi and *sec*-BuLi were titrated before use.[181] Flash column chromatography was performed using DAVISIL silica gel (40-63 micron mesh). The purification of products for 1 mmol scale reaction, a 1 cm coloumn, filled to a depth of 10 cm, was used. Thin layer chromatography was performed on Macherey–nagel–Alugram Sil G/UV 254 silica plates and visualised by UV irradiation at 254 nm or by staining with an alkaline $KMnO_4$ dip. ^1H NMR spectra were recorded on either a Bruker AC250 (250 MHz) or a Bruker AC400 (400 MHz) instrument. Chemical shifts are reported in ppm with respect to the residual solvent peaks, with multiplicities given as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Coupling constants (*J* values) are quoted to the nearest 0.5 Hz with values in Hertz (Hz) and were corrected. ^{13}C NMR were recorded on the above instruments at either 63 MHz or 100 MHz. Melting points were recorded on a Gallenkamp hot stage and were uncorrected. Low and high resolution (accurate mass) mass spectra were recorded on a Micromass Autospec for Electron Impact (EI) and on a Walters LCT instrument for Electro–Spray (ES). Specific rotations were calculated from optical rotations recorded on an AA-10 automatic polarimeter. Infra–Red spectra were recorded on a Perkin Elmer Spectrum RX Fourier Transform–IR System. Only selected peaks are reported and absorption maxima are given in cm^{-1}. ReactIR infra-red spectroscopic monitoring was performed on a Mettler-Toledo ReactIR iC 4000 spectrometer equipped with a diamond-tipped (DiComp) probe. *In-situ* X-ray data was measured on a Bruker Smart CCD area detector with Oxford Cryosystems Resolution between the enantiomers was achieved using a Beckman system fitted with a Phenomenex Lux × 3u cellulose–2 column (220 mm × 4.60 mm i.d.) or a Chiralpax AD column (220 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane: isopropanol as the mobile phase at a flow rate of 1 $mL \cdot min^{-1}$, ambient temperature, detection by UV absorbance at 220 nm. low temperature system. Elemental analysis was carried out using a Perkin Elmer 2400 CHNS/0 Series II Elemental Analyser.

5.2 Chapter 2 Experimental

General procedure A: Lithiation and electrophilic quench of the *N*-Boc-tetrahydroisoquinolines 113, 136, 145, 152, 175 at –50 °C

n-BuLi (1.2 equiv., 2.5 M in hexane) was added to a stirred solution of *N*-Boc-tetrahydroisoquinoline (1.0 equiv.) in THF (2 mL) at –50 °C (1 mmol). After 4 min, the electrophile (3 mmol, 3.0 equiv.) was added dropwise. The mixture was allowed to warm to room temperature over 16 h and MeOH (1 mL) was added. The solvent was evaporated, and the residue was purified by column chromatography on silica gel as described below.

General Procedure B: *N*-Boc-Protection of Amines

Di-*tert*-butyl dicarbonate (1.2 equiv.) was added dropwise to the amine (1 equiv., 1 mmol) in a mixture of water (1 mL) and 1,4-dioxane (2 mL) at 0 °C. After 4 h, the mixture was allowed to warm to room temperature over 16 h. The mixture was extracted with Et_2O. The extracts were washed with brine, dried ($MgSO_4$) and the solvent was evaporated. The crude product was purified by column chromatography to give the carbamate.

General Procedure C: Reduction of Nitrile Using Raney Nickel

A solution of nitrile (1 equiv.) in ethanol (1 mmol) and 29% NH_4OH (1.08 equiv., 1.08 mmol) in the presence of Raney Ni (0.2 equiv., 0.2 mmol) was stirred vigorously under H_2 (1 atm) for 48 h. The reaction mixture was filtered through Celite, then the filtrate was concentrated under reduced pressure to give the amine. The crude mixture was purified by column chromatography on silica gel, as described below.

General Procedure D: Formation of 2,2,2-trifluoro-*N*-phenethylacetamide derivatives

Pyridine (2 equiv.) was added to the amine (1 equiv.) in THF (1 mL) and a solution of trifluoroacetic anhydride (4 equiv.) was added dropwise at 0 °C. The reaction mixture was stirred for 4 h at room temperature, then quenched by addition of water (2 mL) at 0 °C. The mixture was extracted with EtOAc, and the extracts were washed with brine, dried ($MgSO_4$) and the solvent was evaporated. The crude mixture was purified by column chromatography to give the acetamide.

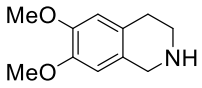
General Procedure E: Cyclisation of acetamides using Pictet-Spengler Condensation Reaction.

A mixture composed of H_2SO_4–AcOH (1.5:1) was added at room temperature in one portion to a mixture of acetamide (1 equiv.) and paraformaldehyde (1.5 equiv.). The reaction mixture was stirred for 48 h at room temperature. The mixture was poured in ice–water (200 mL) and was extracted with EtOAc. The organic phases were combined, washed with water (25 mL), aqueous saturated $NaHCO_3$ (25 mL), and then dried ($MgSO_4$,) filtered and concentrated. The residue was purified by silica gel column chromatography.

General procedure F: Hydrolysis of tetrahydroisoquinoline-*N*-trifiuoro-acetamide derivatives

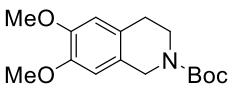
N-(Tetrahydroisoquinoline)-2,2,2-trifluoroacetamide (1 equiv., 1 mmol) was partially dissolved in methanol and water. K_2CO_3 (4 equiv.) was added in one portion and the reaction mixture was stirred at 90 °C for 1 h. The mixture was extracted using CH_2Cl_2, and the combined extracts were dried ($MgSO_4$). The mixture was filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography.

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline 102



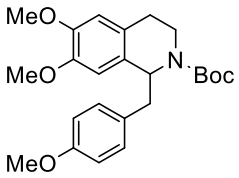
A mixture of amine **118** (10.0 g, 55.2 mmol), paraformaldehyde (1.9 g, 66.2 mmol) and TFA (12.7 mL, 114 mmol) in toluene (100 mL) was heated under reflux. After 24 h, excess TFA was removed under reduced pressure and the residue was poured into aqueous NaOH (100 mL, 2 M), The solution was extracted using CH_2Cl_2 (3 × 250 mL), the organic layers were combined, dried ($MgSO_4$), and the solvent was evaporated. Purification by flash column chromatography on silica gel, eluting with CH_2Cl_2–MeOH–conc. NH_3 (94.9:5:0.1), gave the amine **102** (13.0 g) as an oil used crude in the next step.

***tert*-Butyl 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-carboxylate 113**



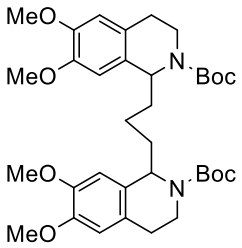
Using general procedure B, di-*tert*-butyl dicarbonate (14.3 g, 66 mmol) was added to 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (10.6 g, 55 mmol) in a mixture of water (60 mL) and 1,4-dioxane (120 mL) at 0 °C. After 4 h, the mixture was warmed to room temperature over 16 h. The mixture was extracted with Et_2O (3 × 100 mL), and the organic layers were combined, washed with brine (100 mL), dried ($MgSO_4$), evaporated and purified by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), to give the carbamate **113** (12.7 g, 79%) as an amorphous solid, m.p. 128–130 °C (lit.[182] 128–130 °C), R_f 0.12 [petrol–EtOAc (90:10)]; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 6.64 (1H, s, CH), 6.61 (1H, s, CH), 4.50 (2H, s, NCH_2), 3.87 (6H, s, 2 × OCH_3), 3.65 (2H, t, *J* 5 Hz, CH_2), 2.77 (2H, t, *J* 5 Hz, CH_2), 1.51 (9H, s, *t*-Bu). Data in accordance with the literature.[182]

tert-Butyl-6,7-dimethoxy-1-[(4-methoxyphenyl)methyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate 119



Using general procedure A, THIQ **113** (1.0 g, 3.4 mmol), *n*-BuLi (1.6 mL, 4.1 mmol) and *p*-methoxybenzylchloride (0.6 mL, 4.1 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (92:8), the carbamate **119** (980 mg, 70%) as an oil; R_f 0.11 [petrol–EtOAc (90:10)]; FTIR υ_{max} (film)/cm^{-1} 3005, 2990, 1675, 1510, 1415; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.05–7.02 (2H, m, 2 × CH), 6.85–6.80 (2H, m, 2 × CH), 6.63 (0.67H, s, CH), 6.60 (0.33H, s, CH), 6.34 (0.67H, s, CH), 6.20 (0.33H, s, CH), 5.22 (0.33H, t, *J* 7 Hz CH), 5.07 (0.67H, t, *J* 7 Hz, CH), 4.15 (0.67H, ddd, *J* 12, 5, 3 Hz, CH), 3.87 (3H, s, OCH_3), 3.85–3.77 (0.33H, m, CH), 3.80 (3H, s, OCH_3), 3.75 (2H, s, OCH_3), 3.65 (1H, s, OCH_3), 3.37–3.22 (1H, m, CH), 3.10–3.00 (1H, m, CH), 2.96–2.72 (2H, m, 2 × CH), 2.65–2.55 (1H, m, CH), 1.45 (3H, s, *t*-Bu), 1.35 (6H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 158.3 & 158.1 (C), 154.6 & 154.5 (C=O), 147.6 & 147.5 (C), 146.9 & 146.7 (C), 130.8 & 130.6 (CH), 130.7 & 130.5 (C), 128.8 & 128.6 (C), 126.6 & 126.3 (C), 113.7 & 113.5 (CH), 111.3 & 111.0 (CH), 110.7 & 110.3 (CH), 79.5 & 79.4 (C), 56.5 (CH_3), 55.9 & 55.8 (CH_3), 55.7 & 55.6 (CH_3), 55.3 & 55.2 (CH), 42.0 & 41.8 (CH_2), 39.3 & 37.2 (CH_2), 28.5 & 28.3 (CH_3), 28.2 (CH_2); HRMS (ES) Found: MNa^+, 436.2103. $C_{24}H_{31}NO_5Na$ requires MNa^+ 436.2103; LRMS *m/z* (ES) 436 (100%, MNa^+).

***tert*-Butyl 1-(3-(2-(*tert*-butoxycarbonyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolin-1-yl) propyl)-3,4-dihydro-6,7-dimethoxyisoquinoline-2(1H)-carboxylate 120**

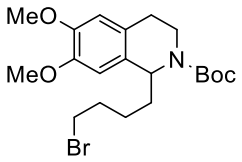


Using general procedure A, THIQ **113** (2.0 g, 6.8 mmol), *n*-BuLi (3.2 mL, 8.2 mmol) and $Br(CH_2)_3Br$ (0.3 ml, 3.4 mmol) gave after purification by column chromatography on silica gel, eluting with petrol–EtOAc (99:1), the carbamates **120a** and 120**b** (2.8 g, 64%) as a separable mixture of diastereoisomers (dr 1:1), each as an oil:

Isomer **120a**: (1.4 g, 33%); R_f 0.27 [petrol–EtOAc (90:10)]; FTIR υ_{max} (film)/cm^{-1}; 2970, 2935, 1685, 1520; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 6.63–6.55 (4H, m, 4 × CH), 5.12–5.10 (1H, m, CH), 4.98–4.96 (1H , m, CH), 4.22–4.19 (0.85 H, m, CH), 3.97–3.92 (1.15H, m, CH), 3.85 (12H, br s, 4 × OCH_3), 3.27–3.15 (2H, m, CH), 2.86–2.81 (2H, m, CH), 2.63–2.59 (2H, m, CH), 1.93–1.72 (4H, m, 2 × CH), 1.63–1.53 (2H, m, CH), 1.47 (18H, br s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 155.0 & 154.9 (C=O), 147.6 (C) & 147.3 (C), 130.6 & 130.1 (C), 126.4 & 126.0 (C), 111.6 & 111.4 (CH), 110.3 & 110.0 (CH), 79.7 & 79.2 (C), 56.1 (CH_3), 55.9 (CH_3), 54.7 & 53.4 (CH), 38.4 & 38.2 (CH_2), 36.9 & 36.2 (CH_2), 28.5 (CH_3), 28.1 & 27.9 (CH_2), 23.5 & 23.2 (CH_2); HRMS (ES) Found: MNa^+, 649.3533. $C_{19}H_{25}NO_4Na$ requires MNa^+ 649.3533; LRMS *m/z* (ES) 649 (100%, MNa^+).

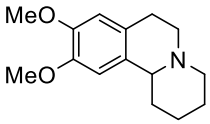
Isomer **120b**: (1.4 g, 33%); R_f 0.28 [petrol–EtOAc (90:10)]; FTIR υ_{max} (film)/cm^{-1}; 2970, 2935, 1686, 1520 ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 6.63–6.55 (4H, m, 4 x CH), 5.12–5.10 (1H, m, CH), 4.98–4.96 (1H, m, CH), 4.22–4.19 (0.8H, m, CH), 4.03–3.94 (1.2H, m, CH), 3.85 (12H, br s, 4 × OCH_3), 3.27–3.15 (2H, m, CH), 2.86–2.81 (2H, m, CH), 2.63–2.59 (2H, m, CH), 1.93–1.72 (4H, m, 2 × CH), 1.63–1.53 (2H, m, CH), 1.47 (18H, br s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 155.0 & 154.8 (C=O), 147.5 (C), 147.3 (C), 130.5 & 130.0 (C), 126.3 & 125.8 (C), 111.6 & 111.4 (CH), 110.3 & 109.9 (CH), 79.7 & 79.2 (C), 56.1 (CH_3), 56.0 (CH_3), 54.6 & 53.5 (CH), 38.3 & 38.0 (CH_2), 36.9 & 35.5 (CH_2), 28.5 (CH_3), 28.1 & 27.9 (CH_2), 23.6 & 23.2 (CH_2); HRMS (ES) Found: HRMS (ES) Found: MNa^+, 649.3533. $C_{19}H_{25}NO_4Na$ requires MNa^+ 649.3533; LRMS *m/z* (ES) 649 (100%, MNa^+).

***tert*-Butyl 1-(4-bromobutyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-carboxylate 121**



Using general procedure A, THIQ **113** (700 mg, 2.38 mmol), *n*-BuLi (1.24 mL, 2.86 mmol) and $Br(CH_2)_4Br$ (0.34 mL, 2.86 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (98:2), the carbamate **121** (760 mg, 75%) as an oil; R_f 0.21 [petrol–EtOAc (80:20)]; FTIR υ_{max} (film)/cm^{-1} 2965, 2935, 1680, 1515, 1415; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 6.61–6.60 (2H, m, 2 × CH), 5.12–5.08 (0.5H, m, CH), 4.98–4.95 (0.5H, m, CH), 4.27–4.23 (0.5H, m, CH), 4.01–3.98 (0.5H, m, CH), 3.88 (6H, br s, 2 × CH_3), 3.48–3.42 (2H, m, 2 × CH), 3.27–3.22 (0.5H, m, CH), 3.15–3.08 (0.5H, m, CH), 3.00–2.79 (1H, m, CH), 2.65–2.61 (1H, m, CH), 2.06–1.54 (6H, m, 6 × CH), 1.51 (9H, br s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 154.8 (C=O), 147.8 (C), 147.4 (C), 130.2 & 129.8 (C), 126.5 & 126.0 (C), 111.6 (CH), 110.2 & 109.9 (CH), 79.9 & 79.5 (C), 56.1 (CH_3), 55.9 (CH_3), 54.2 & 53.4 (CH), 38.3 & 36.5 (CH_2), 36.2 & 35.7 (CH_2), 33.6 (CH_2), 32.5 (CH_2), 28.4 (CH_3), 27.9 (CH_2), 25.4 & 25.1 (CH_2); Found: MNa^+, 450.1247. $C_{20}H_{30}NO_4{}^{79}BrNa$ requires MNa^+ 450.1247; LRMS *m/z* (ES) 452 (97%, MNa^+). 450 (100%, MNa^+).

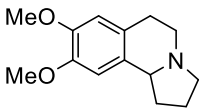
9,10-Dimethoxy-1H,2H,3H,4H,6H,7H,11bH-pyrido[2,1-a]isoquinoline 122



Trifluoroacetic acid (0.1 mL, 1.48 mmol) was added to a solution of carbamate **121** (100 mg, 0.24 mmol) in CH_2Cl_2 (5 mL). After 4 h, the solvent was evaporated and aqueous NaOH (5 mL,1M) was added. After 30 min the mixture was extracted with CH_2Cl_2 (2 × 5 mL). The combined extracts were dried ($MgSO_4$), evaporated and purified by column chromatography on silica, eluting with CH_2Cl_2–MeOH (97:3), to give the amine **122** (50 mg, 87%) as an oil; R_f 0.34 [CH_2Cl_2–MeOH (9:1)]; FTIR υ_{max} (film)/cm^{-1} 2990, 2930, 2802, 2750, 1510; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.71 (1H, s, CH), 6.59 (1H, s, CH), 3.86 (6H, s, 2 × OCH_3), 3.20–2.96 (4H, m, 4 × CH), 2.66–2.50 (2H, m, 2 × CH), 2.38–2.27 (2H, m, 2 × CH), 1.97–1.92 (1H, m, CH), 1.76–1.70 (2H, m, 2 × CH), 1.56–1.42 (2H, m, 2 × CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 147.3 (C), 147.1 (C), 130.2 (C), 126.6 (C), 111.4 (CH), 108.1 (CH), 63.2 (CH), 56.9 (CH_2),

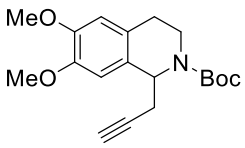
56.0 (CH_3), 55.8 (CH_3), 52.8 (CH_2), 31.5 (CH_2), 29.0 (CH_2), 25.4 (CH_2), 25.0 (CH_2); HRMS (ES) Found: MH^+, 248.1645. $C_{15}H_{21}NO_2$ requires MH^+ 248.1645; LRMS *m/z* (ES) 248 (100%, MH^+).[101, 102, 100] Data in accordance with the literature[8]

(±)-Crispine A 123



Using general procedure A, THIQ **113** (1.0 g, 3.4 mmol), *n*-BuLi (1.63 mL, 4.1 mmol) and $Br(CH_2)_3Br$ (0.41 mL, 4.1 mmol) gave the crude reaction mixture. Trifluoroacetic acid (0.37 mL, 4.9 mmol) was added to a solution of the crude mixture (0.68 g, 1.64 mmol) in CH_2Cl_2 (15 mL) and the mixture was stirred at room temperature. After 4 h, the solvent was evaporated and aqueous NaOH (30 mL, 1 M) was added. After 30 min, the mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined extracts were dried ($MgSO_4$), evaporated and purified by flash column chromatography on silica, eluting with petrol–EtOAc (92:8) gave (±)-Crispine A **123** (410 mg, 52%) as an oil; R_f 0.18 [petrol–EtOAc (80:20)]; FTIR υ_{max} (film)/cm^{-1} 2935, 2835, 1515, 1460; ^{1}H NMR (400 MHz, $CDCl_3$,) δ = 6.63 (1H, s, CH), 6.58 (1H, s, CH), 4.12–4.05 (1H, m, CH), 3.86 (6H, s, 2 × OCH_3), 3.21–3.17 (2H, m, 2 × CH), 3.12–3.05 (2H, m, CH), 2.97–2.96 (2H, m, 2 × CH), 2.56–2.48 (1H, m, CH), 2.07–1.99 (2H, m, 2 × CH), 1.93–1.83 (1H, m, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.1 (C), 148.0 (C), 127.3 (C), 124.8 (C), 111.1 (CH), 108.8 (CH), 61.9 (CH), 56.0 (CH_3), 55.9 (CH_3), 53.1 (CH_2), 47.6 (CH_2), 31.5 (CH_2), 26.3 (CH_2), 22.4 (CH_2); Data in accordance with the literature.[8]

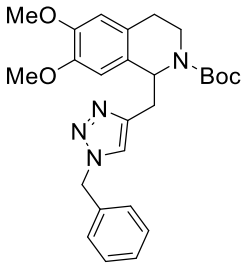
***tert*-Butyl 6,7-dimethoxy-1-(prop-2-yn-1-yl)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate 124**



Using general procedure A, THIQ **113** (1.0 g, 3.4 mmol), *n*-BuLi (1.63 mL, 4.08 mmol) and propargyl bromide (0.36 ml, 4.1 mmol) gave after purification by column chromatography on silica gel, eluting with petrol–EtOAc (99:1) the carbamate **124** (0.88 g, 78%) as an oil; R_f 0.1 [petrol–EtOAc (90:10)]; FTIR υ_{max} (film)/cm^{-1} 2970, 2930, 1690, 1520, 1415; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 6.78 (1H, s, CH), 6.61 (1H, s, CH), 5.27–5.24 (0.5H, m, CH), 5.14

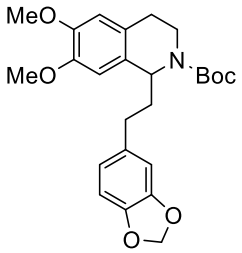
(0.5H, t, *J* 6 Hz, CH), 4.21–4.18 (0.5H, m, CH), 3.97–3.93 (0.5H, m, CH), 3.87 (6H, s, 2 × OCH_3) 3.47–3.42 (0.5H, m, CH), 3.31–3.26 (0.5H, m, CH), 2.87–2.71(4H, m, 4 × CH), 2.02–2.00 (1H, m, CH), 1.50 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers, CH_3 could be missing) δ = 154.6 & 154.4 (C=O), 147.9 & 147.8 (C), 147.3 (C), 127.8 & 127.6 (C), 126.7 & 126.5 (C), 111.4 & 111.2 (CH), 110.5 &110.1 (CH), 81.5 (C), 80.1 & 79.8 (C), 55.9 & 55.8 (CH_3), 53.1 & 52.4 (CH), 39.1 & 37.3 (CH_2), 28.4 (CH_3), 28.3 & 28.0 (CH_2), 26.5 & 26.1 (CH_2); HRMS (ES) Found: MNa^+, 354.1668. $C_{19}H_{25}NO_4Na$ requires MNa^+ 354.1668; LRMS *m/z* (ES) 354 (100%, MNa^+).

tert-Butyl 1-[(1-benzyl-1H-1,2,3-triazol-4-yl) methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-carboxylate 125



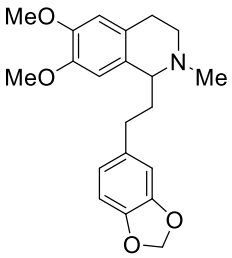
A solution of carbamate **113** (500 mg, 1.5 mmol) and benzyl azide (200 mg, 1.8 mmol), $CuSO_4.H_2O$ (300 mg, 1.8 mmol), ascorbic acid (300 mg, 1.8 mmol), L-proline (200 g, 1.8 mmol), and Na_2CO_3 (100 mg, 1.8 mmol) were heated in DMSO/water (10 mL, 9:1) for 18 h. The mixture was cooled to room temperature and saturated aqueous NH_4Cl (30 mL) was added. The precipitate was filtered and washed with distilled water (100 mL), extracted with EtOH (3 × 200 mL), the combined extracts were dried ($MgSO_4$), and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (60:40), gave the carbamate **125** (570 mg, 83%) as an oil; R_f 0.11 [petrol–EtOAc (50:50)]; FTIR υ_{max} (film)/cm^{-1} 3000, 2970, 1690, 1365; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.35–7.15 (6H, m, 6 × CH), 6.66–6.56 (2H, m, 2 × CH), 5.55–5.36 (3H, m, 3 × CH), 4.28–4.21 (0.5H, m, CH), 3.98–3.91 (0.5H, m, CH), 3.85 (3H, s, OCH_3), 3.81 (1.7H, s, OCH_3). 3.76 (1.3H, s, OCH_3), 3.21–3.02 (2.5H, m, CH), 3.02–2.76 (1H, m, CH), 2.62–2.57 (1H, m, CH), 1.99–1.84 (0.5H, m, CH), 1.38 (3H, s, *t*-Bu), 1.26 (6H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers, CH_3 could be missing) δ = 154.8 & 154.4 (C=O), 147.8 (C), 147.4 (C), 145.2 & 144.8 (C), 135.0 & 134.6 (C), 129.1 (CH), 128.8 (CH), 128.7 & 128.6 (CH), 128.0 & 127.9 (CH), 126.2 (2 × C), 121.9 (CH), 111.4 (CH), 109.9 (CH), 79.7 & 79.5 (C), 56.0 & 55.9 (CH_3), 54.5 & 53.1 (CH), 54.0 (CH_2), 38.3 & 36.4 (CH_2), 32.8 (CH_2), 28.3 & 28.1 (CH_3), 28.0 (CH_2); HRMS (ES) Found: MNa^+, 487.2316. $C_{26}H_{32}N_4O_4Na$ requires MNa^+ 487.2321; LRMS *m/z* (ES) 487(100%).

***tert*-Butyl 1-[2-(2H-1,3-benzodioxol-5-yl)ethyl]-6,7-dimethoxy-1,2,3,4 tetrahydroisoquinoline-2-carboxylate 126**



Using general procedure A, THIQ **113** (1.0 g, 3.4 mmol), *n*-BuLi (1.63 mL, 4.08 mmol) and 5-(2-bromoethyl)-2H-1,3-benzodioxole (0.9 g, 1.6 mmol) gave after purification by column chromatography on silica gel, eluting with petrol–EtOAc (92:8), the carbamate **126** (1.08 g, 72%) as an oil; R_f 0.12 [petrol–EtOAc (80:20)]; FTIR υ_{max} (film)/cm^{-1} 2970, 2930, 1685, 1515; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 6.75–6.58 (5H, m, 5 × CH), 5.93 (2H, s, OCH_2O), 5.18–5.01 (1H, m, CH), 4.28–4.26 (0.5H, m, CH), 4.05–4.00 (0.5H, m, CH), 3.86 (6H, s, 2 × OCH_3), 3.29–3.17 (1H, m, CH), 2.98–2.59 (4H, m, 4 × CH), 2.10–2.00 (2H, m, 2 × CH), 1.50 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 154.9 (C=O), 147.7 (C), 147.4 (C), 145.6 (C), 136.0 & 135.7 (C), 130.1 (C), 129.6 (C), 126.3 & 125.9 (C), 120.9 (CH), 111.6 (CH), 110.2 & 109.9 (CH), 108.7 (CH), 108.1 (CH), 100.7 (CH_2), 79.9 & 79.4 (C), 56.0 (CH_3), 55.9 (CH_3), 54.4 & 53.6 (CH), 39.1 & 38.7 (CH_2), 36.9 (CH_2), 32.7 (CH_2), 28.5 (CH_3), 28.1 & 27.9 (CH_2); HRMS (ES) Found: MNa^+, 464.2032. $C_{25}H_{31}NO_6$ Na requires MNa^+ 464.2032; LRMS *m/z* (ES) 464 (100%, MNa^+).

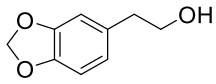
(±) Dysoxyline 127



A solution of carbamate **126** (100 mg, 0.24 mmol) in THF (2 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (500 mg, 1.2 mmol) in THF (10 mL) at 0 °C. The resulting solution was stirred at room temperature for 1 h then heated under reflux for 16 h. The solution was allowed to cool to room temperature, then aqueous NaOH (5 mL, 1 M) was added dropwise. The solid was removed by filtration though Celite and washed with CH_2Cl_2–MeOH

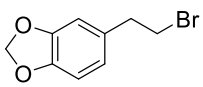
(9:1). The filtrate was evaporated. Purification by flash column chromatography on silica gel, eluting with Et_2O–Petrol (97.5:2.5), gave (±)-dysoxyline **127** (60 mg, 75%) as an oil; R_f 0.12 [petrol–EtOAc (90:10)]; FTIR υ_{max} (film)/cm^{-1} 2935, 2780, 1515, 1490; ^1H NMR (400 MHz, $CDCl_3$) δ = 6.74–6.69 (2H, m, 2 × CH), 6.66–6.62 (1H, m, CH), 6.58 (1H, s, CH), 6.55 (1H, s, CH), 5.92 (2H, s, OCH_2O), 3.85 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.42 (1H, t, *J* 5 Hz, CH), 3.20–3.12 (1H, m, CH), 2.82–2.63 (4H, m, 4 × CH), 2.54–2.46 (1H, m, CH), 2.48 (3H, s, NCH_3), 2.05–2.00 (2H, m, 2 × CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 147.5 (C), 147.3 (C), 147.2 (C), 145.4 (C), 136.8 (C), 129.7 (C), 126.7 (C), 121.0 (CH), 111.2 (CH), 110.0 (CH), 108.9 (CH), 108.1 (CH), 100.7 (CH_2), 62.6 (CH), 56.0 (CH_3), 55.8 (CH_3), 48.2 (CH_2), 42.7 (CH_3), 37.1 (CH_2), 31.3 (CH_2), 25.4 (CH_2); HRMS (ES) Found: MH^+, 356.1862. $C_{21}H_{26}NO_4$ requires MH^+ 356.1862; LRMS *m/z* (ES) 349 (100%, MNa^+), 356 (50%, MH^+). Data in accordance with the literature.[183]

2-(2H-1,3-Benzodioxol-5-yl) ethanol 128



2H-1,3-Benzodioxol-5-ylacetic acid (1.0 g, 5.5 mmol) and $NaBH_4$ (0.5 g, 14.4 mmol) were dissolved in THF (10 mL), and the mixture cooled to 0 °C. A solution of iodine (1.4 g, 5.6 mmol) in THF (5 mL) was added dropwise over 15 min, and the resulting solution was heated at reflux. After 24 h the mixture was cooled to room temperature and methanol was added until evolution of H_2 had ceased. The clear solution was stirred at 20 °C for 30 min, and the solvent was evaporated. The resulting paste was taken up with aqueous NaOH (20 mL, 5 M) and was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried ($MgSO_4$), and evaporated, to give the alcohol **128** (0.97 g) as an oil, used crude in the next step.

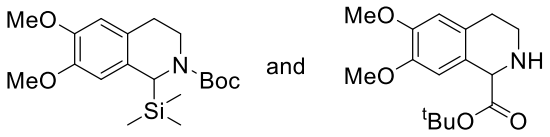
5-(2-Bromoethyl)-1,3-benzodioxole 129



Triphenylphosphine (1.9 g, 7.4 mmol) was added to a solution of alcohol **128** (0.97 g, 5.9 mmol) in CH_2Cl_2 (20 mL) in the presence of carbon tetrabromide (3.3 g, 7.0 mmol) at room temperature. After 12 h the white precipitate was filtered, and the resulting paste was taken up in Et_2O (50 mL). The combined organic layer was concentrated, and the excess of carbon tetrabromide was removed under vacuum. After purification by column chromatography on

silica gel, eluting with petrol–EtOAc (95:5), gave the bromide **129** (0.63 g, 47%) as an oil; R_f 0.32 [petrol–EtOAc (90:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.79–6.77 (1H, m, CH), 6.72–6.67 (2H, m, 2 × CH), 5.96 (2H, s, OCH_2O), 3.35 (2H, t, *J* 7.5 Hz, CH_2), 3.09 (2H, t, *J* 7.5 Hz, CH_2). Data in accordance with the literature.[106]

***tert*-Butyl 6,7-dimethoxy-1-(trimethylsilyl)-3,4-dihydro-1H-isoquinoline-2-carboxylate 131 & 1,2,3,4-Tetrahydroisoquinolin-1-yl 2,2-dimethylpropanoate 132**

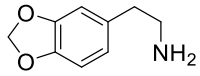


n-BuLi (0.75 mL, 1.89 mmol) was added to THIQ **113** (0.4 g, 1.6 mmol) in THF (10 mL) at –50 °C, after 4 min triethylborane (5.1 mL, 5.1 mmol, 1 mL in THF) was added. After 30 min, the mixture was cooled to –78 °C and TMSOTf (0.28 mL, 1.57 mmol) was added. After 30 min H_2O_2 (0.5 Ml, 30%) was added, the mixture was allowed to warm to 0 °C. After 30 min, NaOH (2 mL, 1 M) was added, the mixture was extracted using CH_2Cl_2 (2 × 20 mL), dried ($MgSO_4$), evaporated and purified by column chromatography on silica gel, eluting with petrol–EtOAc (95:5) to give the carbamates **131 and 132** in 95 % yield.

Carbamate **131**(0.51 g, 90%) as an oil; R_f 0.6 [petrol–EtOAc (80:20)]; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 6.62 (0.5H, s, CH), 6.60 (0.5H, s, CH), 6.50 (0.5H, s, CH), 6.45 (0.5H, s, CH), 4.89 (0.5H, s, CH), 4.72 (0.5H, s, CH), 4.30 (0.5H, dddd, *J* 13, 6, 3, 1 Hz, CH), 4.03 (0.5H, dddd, *J* 13, 6, 3, 1 Hz, CH), 3.86 (5H, s, 5 × CH), 3.84 (1H, s, CH), 3.22 (0.5H, ddd, *J*, 13, 10, 4 Hz, CH), 3.04 (0.5H, ddd, *J* 13, 10, 4 Hz, CH), 2.95–2.80 (1H, m, CH), 2.63 (1H, ddd, *J* 13, 9.5, 4 Hz, CH), 1.51 (4.5H, s, *t*-Bu), 1.49 (4.5H, s, *t*-Bu), 0.08 (4.5H, $SiMe_3$), 0.07 (4.5H, s, $SiMe_3$). data in accordance with the literature.[67]

Carbamate **132** (0.05 g, 5%) as an oil; R_f 0.1 [petrol–EtOAc (90:10)]; FTIR υ_{max} (film)/cm^{-1} 3340, 2960, 2930, 1715, 1520; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.63 (1H, s, CH), 6.60 (1H, s, CH), 4.51 (1H, s, CH), 3.87 (6H, s, 2 × OCH_3), 3.84–3.83 (2H, m, CH_2), 2.78–2.75 (2H, m, CH_2), 1.70 (1H, br s, NH), 1.50 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.6 (C=O), 147.6 (C), 147.4 (C), 122.3 (C), 121.2 (C), 111.7 (CH), 111.5 (CH), 79.7 (C), 56.0 (CH_3), 55.9 (CH_3), 55.7 (CH), 40.0 (CH_2), 29.6 (CH_2), 28.5 (CH_3); HRMS (ES) Found: MNa^+, 316.1521. $C_{16}H_{23}NO_4Na$ requires MNa^+ 316.1519; LRMS *m/z* (ES) 316 (100%, MNa^+).

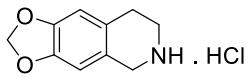
2-(Benzo[d][1,3]dioxol-6-yl)ethanamine 134



Using general procedure C, nitrile **133** (5.7 g, 32 mmol) and Raney Ni (0.4 g, 7.6 mmol) gave after purification by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH–conc. NH_3 (97.9: 2: 0.1), the amine **134** (4.7 g, 90%) as an oil; R_f 0.1 [CH_2Cl_2–MeOH–conc. NH_3 (90:9:1)]; FTIR υ_{max} (film)/cm^{-1} 2965, 2890, 1660, 1485; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.75 (1H, d, *J* 7 Hz, CH), 6.70 (1H, s, CH), 6.69 (1H, d, *J* 7 Hz, CH), 5.95 (2H, s, OCH_2O), 2.92 (2H, t, *J* 7 Hz, CH_2), 2.66 (2H, t, *J* 7 Hz, CH_2), 1.24 (2H, br s, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 147.7 (C), 145.9 (C), 133.6 (C), 121.6 (CH), 109.3 (CH), 108.2 (CH), 100.8 (OCH_2), 43.7 (CH_2), 39.8 (CH_2); HRMS (ES) Found: MH^+, 166.0861. $C_9H_{12}NO_2$ requires MH^+ 166.0868; LRMS *m/z* (ES) 166.0 (100%, MH^+). Data in accordance with the literature, only ^{1}H NMR spectra was reported.[184]

Borane in THF (12.4 mL, 6.2 mmol, 1 M) was added to the nitrile **133** (1.0 g, 6.2 mmol) in THF (15 mL) at room temperature. After 1 h, the mixture was heated to 66 °C for 24 h, then the mixture was cooled to 0 °C and H_2O (3 mL) was added dropwise over 5 min. After 30 min conc. HCl (8 mL, 12 M) was added. After 1 h, NaOH (3 g) was added as pellets to the mixture, the solvent was evaporated and the residue was extracted using CH_2Cl_2 (3 × 100 mL), the combined organic layers were dried ($MgSO_4$), evaporated and was purified by flash column chromatography on silica gel, eluting with CH_2Cl_2–MeOH–conc. NH_3 (97.9: 2: 0.1), to give the amine **134** (0.76 g, 75%). Data as above

5,6,7,8-Tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline 135

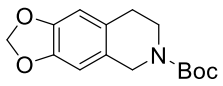


A mixture of amine **134** (3.9 g, 24.2 mmol), paraformaldehyde (0.70 g, 26.5 mmol) and TFA (23 mL, 303 mmol) in toluene (30 mL) was heated under reflux. After 24 h, excess TFA was evaporated and the residue was poured into aqueous NaOH (25 mL, 2 M). The solution was extracted using CH_2Cl_2 (3 × 50 mL), the combined organic layers were dried ($MgSO_4$), evaporated and purified by flash column chromatography on silica gel, eluting with CH_2Cl_2–MeOH–conc. NH_3 (94.9:5:0.1), to give the amine **135** as it's hydrochloric salt (3.8 g, 74%) as an amorphous solid; m.p. 189–191 °C; R_f 0.12 [CH_2Cl_2–MeOH–conc. NH_3 (90:9:1)]; FTIR

υ_{max} (film)/cm^{-1} 2890, 2840, 1680, 1480; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.56 (1H, s, CH), 6.48 (1H, s, CH), 5.90 (2H, s, OCH_2O), 3.92 (2H, s, NCH_2), 3.10 (2H, t, *J* 6 Hz, CH_2), 2.70 (2H, t, *J* 6 Hz, CH_2), 2.14 (2H, br s, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 144.8 (C), 144.6 (C), 127.7 (C), 126.5 (C), 108.0 (CH), 105.1 (CH), 100.0 (CH_2), 47.3 (CH_2), 42.8 (CH_2), 28.2 (CH_2); HRMS (ES) Found: MH^+, 178.0860. $C_{10}H_{12}NO_2$ required MH^+ 178.0868; LRMS *m/z* (ES) 178 (100%, MH^+).[185] No data were reported.

A mixture of the amine **134** (2.7 g, 6.0 mmol) and paraformaldehyde (0.18 g, 6.05 mmol) were dissolved in a mixture of formic acid–MeOH (10:1) mL and the mixture was heated under reflux for 16 h. The solvent was evaporated and the residue was poured in to NaOH (50 mL, 1 M), extracted using CH_2Cl_2 (3 × 200 mL), dried ($MgSO_4$), evaporated and purified by flash column chromatography on silica gel, eluting with CH_2Cl_2–MeOH–conc. NH_3 (94.9:5:0.1), to give the amine **135** (3.5 g, 67%). Data as above.

tert-Butyl 7,8-Dihydro-[1,3]dioxolo[4,5-g]isoquinoline-6(5H)-carboxylate 136



Using general procedure B, di-*tert*-butyl dicarbonate (4.4 g, 20 mmol) and the amine **135** (3.0 g, 17 mmol) gave after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the carbamate **136** (3.2 g, 68%) as an oil; R_f 0.5 [petrol–EtOAc (90:10)]; FTIR υ_{max} (film)/ cm^{-1} 2975, 2930, 2900, 1690; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.60–6.58 (2H, m, 2 × CH), 5.92 (2H, s, OCH_2O), 4.46 (2H, s, NCH_2), 3.62 (2H, t, *J* 6 Hz, CH_2), 2.74 (2H, t, *J* 6 Hz, CH_2), 1.51 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers, aromatic C couldn't be observed) δ = 154.8 (C=O), 146.1 (C), 127.7 (C), 108.5 (CH), 106.4 & 106.1 (CH), 100.7 (OCH_2O), 79.8 (C), 46.0 & 45.2 (CH_2), 41.8 & 40.6 (CH_2), 28.9 (CH_2), 28.4 (CH_3); HRMS (ES) Found: MNa^+, 300.1201. $C_{15}H_{19}NO_4Na$ requires MNa^+ 300.1212; LRMS *m/z* (ES) 300 (100%, MNa^+).

ReactIR monitoring of the lithiation of _tert_-Butyl 2H,5H,7H,8H-[1,3]dioxolo[4,5-g]isoquinoline-6-carboxylate 136 by _n_-BuLi in THF (Figure 2-2)

THF (12 mL) was added to a flask equipped with a stirrer bar and ReactIR probe at room temperature under Ar. After cooling to –78 °C, a solution of *N*-Boc-tetrahydroisoquinoline **136** (0.5 g, 2.0 mmol) in THF (2.0 mL) was added. The solution was stirred for 10 min to verify

the stability of the readout on the ReactIR. *n*-BuLi (1.0 mL, 2.5 mmol, 2.5 M in hexane) was added, and the solution stirred for 5 min.

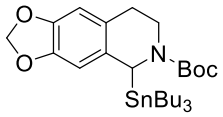
For *N*-Boc-tetrahydroisoquinoline **136**, a peak at 1697 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *n*-BuLi, a new peak at 1642 cm^{-1} appeared which was assigned to $\nu_{C=O}$ of the lithiated intermediate **137**. After a lithiation time of 30 sec, partial lithiation of *N*-Boc-tetrahydroisoquinoline **136** to lithiated intermediate **137** was observed. After 5 min no further lithiation was observed.

ReactIR monitoring of the lithiation *tert*-Butyl 2H,5H,7H,8H-[1,3]dioxolo[4,5-g]isoquinoline-6-carboxylate 136 by *n*-BuLi in THF (Scheme 2-24)

THF (12 mL) was added to a flask equipped with a stirrer bar and ReactIR probe at room temperature under Ar. After cooling to –50 °C, a solution of *N*-Boc-tetrahydroisoquinoline **136** (0.5 g, 2.0 mmol) in THF (2 mL) was added. The solution was stirred for 10 min to verify the stability of the readout on the ReactIR. *n*-BuLi (1.0 mL, 2.5 mmol, 2.5 M in hexane) was added, and the solution was stirred for 10 min.

For *N*-Boc-tetrahydroisoquinoline **136**, a peak at 1696 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *n*-BuLi, a new peak at 1636 cm^{-1} appeared which was assigned to $\nu_{C=O}$ of lithiated intermediate **137**. After a lithiation time of 4 min, the lithiation of *N*-Boc-tetrahydroisoquinoline **136** to intermediate **137** was completed.

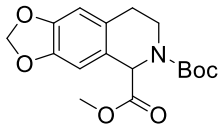
***tert*-Butyl 5-(tributylstannyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinoline-6(5H)-carboxylate 138a**



Using general procedure A, THIQ **136** (100 mg, 0.36 mmol), *n*-BuLi (0.17 mL, 0.43 mmol) and Bu_3SnCl (0.5 mL, 1.26 mmol) gave after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the carbamate **138a** (67 mg, 33%) as an oil; R_f 0.65 [petrol–EtOAc (90:10)]; FTIR υ_{max} (film)/cm^{-1} 2960, 2920, 2870, 1700; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 6.55–6.50 (1H, m, CH), 6.37–6.31 (1H, m, CH), 5.88–5.87 (2H, m, 2 × CH), 5.23–5.10 (1H, m, CH), 4.24–4.16 (0.5H, m, CH), 3.81–3.74 (0.5H, m, CH), 3.28 (0.5H, ddd *J* 12, 8, 4 Hz, CH), 2.98–2.80 (1.5H, m, CH), 2.65–2.55 (1H, m, CH), 1.50 (4.5H, s, *t*-Bu), 1.48 (4.5H, s, *t*-Bu), 1.45–1.22 [12H, m, $Sn(CH_2\mathit{CH_2CH_2}\ CH_3)_3$], 0.57–0.59 [15H, m, $Sn(\mathit{CH_2}\ CH_2CH_2\mathit{CH_3})_3$]; ^{13}C NMR (100 MHz, $CDCl_3$ rotamers) δ = 153.6 & 153.3 (C=O), 146.2 &

146.1 (C), 144.4 & 144.2 (C), 133.1 & 132.6 (C), 124.3 & 124.2 (C), 108.6 & 108.1 (CH), 104.1 & 103.7 (CH), 100.5 & 100.4 (OCH_2O), 79.8 & 79.1 (C), 49.8 & 49.5 (CH), 41.9 & 40.9 (CH_2), 29.5 (CH_2), 29.0 & 28.9 (CH_2), 28.6 & 28.5 (CH_2), 27.5 & 27.4 (CH_3), 13.5 (CH_3), 10.5 & 10.3 (CH_2); HRMS (ES) Found: MH^+, 568.2470. $C_{27}H_{46}NO_4{}^{120}Sn$ requires MH^+, 568.2449; LRMS *m/z* (ES), 568.2 (40%, MH^+ for ^{120}Sn), 566.2 (100, MH^+ for ^{118}Sn).

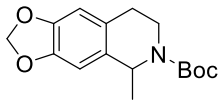
6-*tert*-Butyl 5-methyl 7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinoline-5,6(5H)-dicarboxylate 138b



Using general procedure A, THIQ **136** (100 mg, 0.36 mmol), *n*-BuLi (0.17 mL, 0.43 mmol) and MeOCOCN (0.1 mL, 1.26 mmol) gave after purification by column chromatography on silica gel, eluting with petrol–EtOAc (92:8), the carbamate **138b** (22 mg, 19%) as an oil; R_f 0.4 [petrol–EtOAc (90:10)]; FTIR υ_{max} (film)/cm^{-1} 2960, 2930, 1745, 1695, 1485, 1155, 1040; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ = 6.96–6.94 (1H, m, CH), 6.64–6.62 (1H, m, CH), 5.95–5.94 (2H, m, 2 × CH), 5.48–5.32 (1H, m, CH), 3.77–3.69 (5H, m, 2 × CH and OCH_3), 2.90–2.70 (2H, m, 2 × CH), 1.48 (9H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$ rotamers) δ = 172.2 & 171.9 (C=O), 155.3 & 154.9 (C=O), 147.1 & 147.2 (C), 146.3 & 146.1 (C), 129.0 & 128.7 (C), 123.6 & 122.8 (C), 108.4 & 108.2 (CH), 107.7 (CH), 101.1 & 101.0 (CH_2), 80.7 & 80.5 (C), 58.6 & 57.5 (CH_3), 52.4 & 52.3 (CH), 40.8 & 39.8 (CH_2), 28.9 & 28.7 (CH_2), 28.4 & 28.3 (CH_3); HRMS (ES) Found: MH^+, 336.1453. $C_{17}H_{22}NO_6$ requires MH^+ 336.1447; LRMS *m/z* (ES), 336 (100, MH^+).

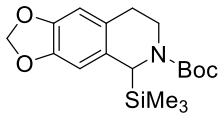
Using general procedure A, tetrahydroisoquinoline **136** (100 mg, 0.36 mmol), *n*-BuLi (0.17 mL, 0.43 mmol) and MeOCOCl (0.07 mL, 1.26 mmol) gave after purification by column chromatography on silica gel, eluting with petrol–EtOAc (92:8), the carbamate **138b** (28 mg, 23%). data as above.

***tert*-Butyl 7,8-dihydro-5-methyl-[1,3]dioxolo[4,5-g]isoquinoline-6(5H)-carboxylate 138c**



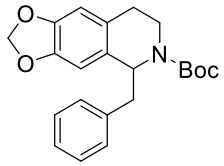
Using general procedure A, THIQ **136** (100 mg, 0.36 mmol), *n*-BuLi (0.17 mL, 0.43 mmol) and MeI (0.08 mL, 1.26 mmol) gave after purification by column chromatography on silica gel, eluting with petrol–EtOAc (92:8), the carbamate **138c** (85 mg, 81%) as an amorphous solid; m.p. 81–82 °C; R_f 0.39 [petrol–EtOAc (90:10)]; FTIR υ_{max} (film)/cm^{-1} 2970, 2875, 1670, 1485; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 6.58–6.57 (2H, m, 2 × CH), 5.80 (2H, s, OCH_2O), 5.18–4.96 (1H, br m, CH), 4.27–3.91 (1H, br m, CH), 3.67–2.60 (3H, br m, 3 × CH), 1.50 (9H, s, *t*-Bu), 1.40 (3H, d, *J* 7 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 154.9 & 154.4 (C=O), 146.1 (C), 146.0 (C), 127.3 (C), 127.1 (C), 108.4 (CH), 106.7 (CH), 100.7 (CH_2), 79.6 (C), 50.5 & 49.8 (CH), 38.0 & 36.6 (CH_2), 29.6 (CH_2), 29.0 & 28.0 (CH_3), 22.0 (CH_3); HRMS (ES) Found: MNa$^+$, 314.1369. $C_{16}H_{22}NO_4Na$ requires MNa$^+$ 314.1360; LRMS *m/z* (ES) 314 (100, MNa$^+$).

tert-Butyl 7, 8-dihydro-5-(trimethylsilyl)-[1,3] dioxolo[4,5-g]isoquinoline-6(5H)-carboxylate 138d



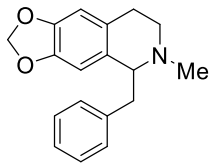
Using general procedure A, THIQ **136** (100 mg, 0.36 mmol), *n*-BuLi (0.17 mL, 0.43 mmol) and $ClSiMe_3$ (0.16 mL, 1.2 mmol) gave after purification by column chromatography on silica gel, eluting with petrol–EtOAc (92:8), the carbamate **138d** (90 mg, 72%) as an oil; R_f 0.36 [petrol–EtOAc (90:10)]; FTIR υ_{max} (film)/cm^{-1} 2965, 2930, 1680, 1480, 836, ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 6.60 (0.5H, s, CH), 6.57 (0.5H, s, CH), 6.46 (0.5H, s, CH), 6.45 (0.5H, s, CH), 5.92–5.89 (2H, m, 2 × CH), 4.83 (0.5H, br m, CH), 4.67 (0.5H, br m, CH), 4.18 (0.5H, dt, *J* 12, 5 Hz, CH), 3.93 (0.5H, dt, *J* 12, 5 Hz, CH), 3.25 (0.5H, ddd, *J* 12, 9, 5 Hz, CH), 3.11–3.05 (0.5H, m, CH), 2.90–2.78 (1H, m, CH), 2.65–2.55 (1H, m, CH), 1.50 (4.5H, s, *t*-Bu), 1.49 (4.5H, s, *t*-Bu), 0.06 (4.5H, s, $SiMe_3$), 0.05 (4.5H, s, $SiMe_3$); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 154.4 (C=O), 145.9 & 144.8 (C), 145.1 & 144.9 (C), 130.3 & 129.7 (C), 125.7 & 125.6 (C), 108.9 & 108.6 (CH), 105.4 & 105.1 (CH), 100.7 & 100.6 (CH_2), 79.7 & 79.2 (C), 49.9 & 49.0 (CH), 41.0 & 39.8 (CH_2), 28.9 & 28.55 (CH_2), 28.5 (CH_3), –1.4 & –1.6 (CH_3); HRMS (ES) Found: MNa$^+$, 372.1603. $C_{18}H_{28}NO_4SiNa$, requires MNa$^+$ 372.1607; LRMS *m/z* (ES) 372 (100%, MNa$^+$).

***tert*-Butyl 5-benzyl-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinoline-6(5H)-carboxylate 138f**



Using general procedure A, THIQ **136** (100 mg, 0.36 mmol), *n*-BuLi (0.17 mL, 0.43 mmol) and $PhCH_2Br$ (0.15 mL, 1.26 mmol) gave after purification by column chromato-graphy on silica gel, eluting with petrol–EtOAc (93:7), the carbamate **138f** (87 mg, 66%) as an oil; R_f 0.41 [petrol–EtOAc (90:10)]; FTIR υ_{max} (film)/cm^{-1} 2975, 2925, 1680, 1485; ^1H NMR (400 MHz , $CDCl_3$) δ = 7.36–7.20 (3H, m, 3 × CH), 7.15–7.04 (2H, m, 2 × CH), 6.61–6.54 (2H, m, 2 × CH), 5.94–5.90 (2H, m, 2 × CH), 5.27 (0.35H, t, *J* 7 Hz, CH), 5.13–5.10 (0.65H, m, CH), 4.20–4.12 (0.65H, m, CH), 3.81–3.72 (0.35H, m, CH), 3.34–3.23 (1H, m, CH), 3.06–2.95 (2H, m, 2 × CH), 2.91–2.81 (0.65 H, m, CH), 2.74–2.67 (0.35H, m, CH), 2.63–2.57 (0.65H, m, CH), 2.52–2.46 (0.35H, m, CH), 1.26 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 154.5 & 154.3 (C=O), 146.3 & 146.1 (C), 145.8 & 145.7 (C) 138.3 & 138.1 (C), 130.1 & 130.0 (C), 129.7 & 129.6 (CH), 129.0 & 128.8 (CH), 128.3 & 128.1 (CH), 127.8 & 127.7 (CH), 126.4 & 126.2 (C), 108.6 & 108.2(CH), 107.6 & 107.2 (CH), 100.8 & 100.7 (CH_2), 79.6 & 79.4 (C), 56.8 & 55.7 (CH), 43.0 & 42.7 (CH_2), 39.3 & 37.0 (CH_2), 29.7 & 28.6 (CH_2), 28.5 & 28.4 (CH_3); HRMS (ES) Found: MNa^+, 390.1674. $C_{22}H_{26}NO_4Na$ requires MNa^+ 390.1618; LRMS *m/z* (ES) 390 (100, MNa^+).

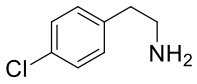
5-Benzyl-6-methyl-2H, 5H, 6H, 7H, 8H-[1, 3] dioxolo[4,5-g]isoquinoline 139



A solution of carbamate **138f** (100 mg, 0.24 mmol) in THF (1 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (500 mg, 1.2 mmol) in THF (5 mL) at 0 °C under nitrogen. The mixture was stirred at room temperature for 1 h then was heated under reflux. After 16 h, the mixture was allowed to cool to room temperature. Aqueous NaOH (5 mL,1 M) was added dropwise. The solids were removed by filtration though Celite and were washed with CH_2Cl_2–MeOH (9:1). The filtrate was evaporated and purified by column chromatography on silica, eluting with CH_2Cl_2–MeOH (95:5), to give the amine **139** (50 mg, 69%) as an oil; R*f* 0.4 [CH_2Cl_2–MeOH (9.5:0.5)]; FTIR υ_{max} (film)/ cm^{-1} 2925, 2775, 1480, 1240; ^1H NMR (250

MHz, $CDCl_3$) δ = 7.30–7.26 (2H, m, 2 × CH), 7.23–7.19 (1H, m, CH), 7.16–7.14 (2H, m, 2 × CH), 6.56 (1H, s, CH) , 6.22 (1H, s, CH), 5.91–5.87 (2H, m, 2 × CH), 3.74 (1H, t, *J* 6 Hz, CH), 3.24–3.11 (2H, m, 2 × CH), 2.90–2.73 (3H, m, 3 × CH), 2.59–2.53 (1H, m, CH), 2.49 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 145.8 (C), 145.3 (C), 139.9 (C), 130.6 (C), 129.5 (CH), 128.1 (CH), 127.2 (C), 126.0 (CH), 108.4 (CH), 107.8 (CH), 100.5 (CH_2), 65.2 (CH_3), 46.6 (CH_2), 42.6 (CH), 41.6 (CH_2), 25.7 (CH_2); HRMS (ES) Found: MH^+, 282.1491. $C_{18}H_{20}NO_2$ requires MH^+ 282.1491; LRMS *m/z* (ES) 282 (100%, MH^+).[186,187]

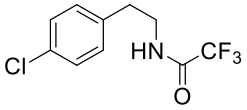
2-(4-Chlorophenyl)ethanamine 141



Using general procedure C, nitrile **140** (10 g, 66 mmol) and Raney Ni (0.9 g, 15.8 mmol) gave after purification by flash column chromatography on silica gel, eluting with CH_2Cl_2–MeOH–conc.NH_3 (93.75:6:0.25), gave the amine **141** (9.4 g, 92%) as an oil; R_f 0.09 [CH_2Cl_2–MeOH–conc. NH_3 (90:9:1)]; FTIR υ_{max} (film)/cm^{-1} 3370, 2930, 2860, 1490; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.23–7.21 (2H, m, 2 × CH), 7.10–7.07 (2H, m, 2 × CH), 2.90 (2H, t, *J* 7 Hz, CH_2), 2.66 (2H, t, *J* 7 Hz, CH_2), 1.10 (1H, br s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 138.3 (C), 131.7 (C), 130.1 (CH), 128.4 (CH), 43.4 (CH_2), 39.4 (CH_2); HRMS (ES) Found: MH^+, 156.0584. $C_8H_{11}N^{35}Cl$ requires MH^+ 156.0580; LRMS *m/z* (ES) 158 (34%, MH^+ for ^{37}Cl), 156 (100%, MH^+ for ^{35}Cl). Data in accordance with the literature.[116,188]

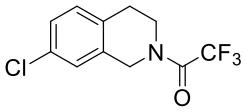
Borane (94 mL, 94 mmol, 1 M in THF) was added to the nitrile **140** (10 g, 72.7 mmol) in dry THF (120 mL) at room temperature, the mixture was stirred at reflux. After 24 h the mixture was cooled to 0 °C and H_2O (23 mL) was added dropwise over 5 min. After 30 min conc. HCl (29 mL, 12 M) was added. After 1 h NaOH (12 g) was added as pellets. The solvent was evaporated and the residue was extracted using CH_2Cl_2 (3 × 250 mL), dried ($MgSO_4$), evaporated. Purification by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH–conc. NH_3 (97.9: 2: 0.1), to give the amine **141** (8.3 g, 73%) as an oil. Data as above.

***N*-(4-Chlorophenethyl)-2,2,2-trifluoroacetamide 142**



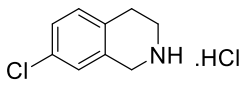
Using general procedure D, amine **141** (1.0 g, 6.4 mmol) and trifluoroacetic anhydride (1.1 mL, 7.7 mmol) and pyridine (0.37 mL, 12.8 mmol) gave after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the amide **142** (1.3 g, 79%) as an amorphous solid; m.p. 101–103 °C; R_f 0.3 [petrol–EtOAc (90:10)]; FTIR υ_{max} (film)/cm^{-1} 3360, 2970, 2965, 1730; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.34–7.32 (2H, m, 2 × CH), 7.15–7.13 (2H, m, 2 × CH), 6.32–6.31 (1H, br m, NH), 3.62 (2H, q, *J* 7 Hz, CH_2), 2.88 (2H, t, *J* 7 Hz, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 157.3 (C=O, q, *J* 37 Hz), 136.0 (C), 132.8 (C), 130.0 (CH), 129.0 (CH), 115.7 (CF_3, q, *J* 288 Hz), 40.9 (CH_2), 34.3 (CH_2); LRMS found: MH$^+$, 252.0401. $C_{10}H_9{}^{35}ClF_3NO$ requires MH$^+$ 252.0421; LRMS 254 (MH$^+$, 33% for ^{37}Cl), 252 (MH$^+$, 100% for ^{35}Cl). Data in accordance with the litrature.[114]

1-(7-Chloro-3,4-dihydroisoquinolin-2(1H)-yl)-2,2,2-trifluoroethanone 143



Using general procedure E, amide **142** (0.9 g, 3.7 mmol) and paraformaldehyde (0.17 mL, 5.6 mmol) gave after purification by flash column chromatography on silica gel, eluting with petrol–EtOAc (94:6), the amide **143** (0.83 g, 86%) as an amorphous solid; m.p. 61–61.5 °C; R_f 0.41 [petrol–EtOAc (90:10)]; FTIR υ_{max} (film)/cm^{-1} 3005, 2970, 2950, 1690, 1460; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.24–7.20 (1H, m, CH), 7.17–7.10 (2H, m, 2 × CH), 4.78–4.73 (2H, m, 2 × CH), 3.91–3.84 (2H, m, 2 × CH), 2.96–2.92 (2H, m, 2 × CH); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 156.2 (C=O, q, *J* 37 Hz), 133.1 & 133.0 (C), 132.6 & 132.4 (C), 131.6 (C), 130.2 & 129.9 (CH), 127.7 & 127.3 (CH), 126.4 & 126.0 (CH), 116.4 (CF_3, q, *J* 287 Hz), 46.6 & 45.1 (CH_2), 43.2 & 41.6 (CH_2), 28.7 & 27.3 (CH_2); HRMS (ES) Found: MH$^+$, 264.0413. $C_{11}H_{10}{}^{35}Cl\,NOF_3$ requires MH$^+$ 264.0403; LRMS m/z (ES) 266 (34%, MH$^+$ for ^{37}Cl), 264 (100%, MH$^+$ for ^{35}Cl). Data in accordance with the literature.[189]

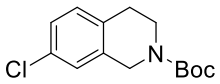
7-Chloro-1,2,3,4-tetrahydroisoquinoline 144



Using general procedure F, amide **143** (2.1 g, 7.9 mmol) and K_2CO_3 (4.3 g, 32 mmol) gave after purification by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH–conc. NH_3 (97.4:2.5:0.1), the amine **144** as the hydrochloride salt (1.1 g, 69%) as an amorphous solid; m.p. 51–52 °C; R_f 0.11 [CH_2Cl_2–MeOH–conc. NH_3 (90:10)]; FTIR υ_{max} (film)/cm^{-1} 3315,

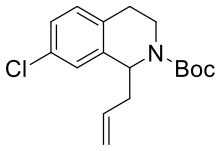
2925, 2855, 1485; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.13–7.11 (1H, m, CH), 7.05–7.02 (2H, m, 2 × CH), 4.01 (2H, s, NCH_2), 3.16 (2H, t, *J* 6 Hz, CH_2), 2.80 (2H, t, *J* 6 Hz, CH_2), 2.55 (2H, br s, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 136.4 (C), 132.7 (C), 131.4 (C), 130.6 (CH), 126.5 (CH), 126.1 (CH), 47.4 (CH_2), 43.3 (CH_2), 28.0 (CH_2); HRMS (ES) Found: MH^+, 168.0582. $C_9H_{11}N^{35}Cl$ requires MH^+ 168.0580. Data in accordance with the literature.[190]

tert-Butyl 7-chloro-3,4-dihydroisoquinoline-2(1H)-carboxylate 145



Using general procedure B, di-*tert*-butyl dicarbonate (1.7 g, 7.9 mmol) and amine **144** (1.1 g, 6.6 mmol) gave after purification by flash column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the carbamate **145** (1.48 g, 70%) as an oil; R_f 0.27 [petrol–EtOAc (95:5)]; FTIR υ_{max} (film)/cm^{-1} 2980, 2935, 1670, 1420; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.16–7.07 (3H, m, 3 × CH), 4.55 (2H, s, NCH_2), 3.65–3.63 (2H, m, 2 × CH), 2.80 (2H, t, *J* 5 Hz, CH_2), 1.50 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers, C=O couldn't be observed) δ = 154.7 (C=O), 135.4 (C), 133.1 (C), 131.7 (C), 130.7 (CH), 129.3 & 129.1 (CH), 126.5 & 126.1 (CH), 80.0 (C), 45.7 & 44.9 (CH_2), 41.5 & 40.5 (CH_2), 28.5 (CH_3, *t*-Bu), 28.3 (CH_2); HRMS (ES) Found: MNa^+, 290.0933. $C_{10}H_{11}NO_2{}^{35}ClNa$ requires MNa^+ 290.0924; LRMS m/z (ES) 292 (33%, MNa^+, for ^{37}Cl), 290 (100, MNa^+, for ^{35}Cl).

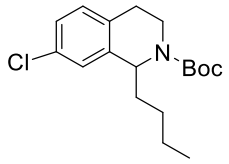
tert-Butyl 1-allyl-7-chloro-3,4-dihydroisoquinoline-2(1H)-carboxylate 146a



Using general procedure A, THIQ **145** (100 mg, 0.37 mmol), *n*-BuLi (0.17 mL, 0.44 mmol) and allyl bromide (0.13 mL, 1.3 mmol) gave after purification by column chromatography on silica gel, eluting with petrol–EtOAc (98:2), the carbamate **146a** (100 mg, 91%) as plates; m.p. 94–96 °C; R_f 0.6 [petrol–EtOAc (90:10)]; FTIR υ_{max} (film)/cm^{-1} 2975, 2930, 1690, 1420; ^{1}H NMR (400 MHz, $CDCl_3$,) δ = 7.15–7.14 (2H, m, 2 × CH), 7.08–7.06 (1H, m, CH), 5.85–5.80 (1H, m, CH), 5.26–5.24 (0.4H, m, CH), 5.10–5.06 (2.6H, m, CH), 4.25–4.22 (0.6H, m, CH) 4.01–3.96 (0.4H, m, CH), 3.30–3.13 (1H, m, CH), 2.93–2.85 (1H, m, CH), 2.73–2.70 (1H, m, CH), 2.56–2.52 (2H, m, 2 × CH), 1.50 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 154.7 & 154.5 (C=O), 139.1 & 138.9 (C), 134.6 (CH), 132.9 & 132.7 (C), 131.5 (C), 130.4

& 130.0 (CH), 127.1 (CH), 126.8 & 126.7 (CH), 117.7 & 117.3 (CH_2), 80.1 & 79.7 (C), 54.2 & 53.3 (CH), 41.3 & 41.0 (CH_2), 38.2 & 36.5 (CH_2), 28.4 (CH_3), 28.2 & 28.0 (CH_2); HRMS (ES) Found: MNa^+, 330.1223. $C_{17}H_{22}{}^{35}ClNO_2Na$, requires MNa^+ 330.1237; LRMS *m/z* (ES) 332 (33%, MNa^+ for ^{37}Cl), 330 (100%, MNa^+ for ^{35}Cl).

***tert*-Butyl 1-butyl-7-chloro-3,4-dihydro-1H-isoquinoline-2-carboxylate 146b**



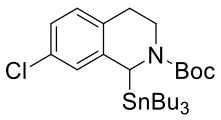
Using general procedure A, THIQ **145** (100 mg, 0.37 mmol), *n*-BuLi (0.17 mL, 0.44 mmol) and butyl bromide (0.13 mL, 1.3 mmol) gave after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the carbamate **146b** (73 mg, 61%) as oil; R_f 0.48 [petrol–EtOAc (95:5)]; FTIR υ_{max} (film)/cm^{-1}, 2960, 2930, 1680, 1460; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.26–7.25 (1H, m, CH), 7.12–7.10 (1H, m, CH), 7.00–6.99 (1H, m, CH), 3.72–3.68 (2H, m, 2 × CH), 2.71 (3H, m, 3 × CH), 1.53 (9H, s, *t*-Bu), 1.27–1.16 (9H, m, 9 × CH); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers, C=O, NCH couldn't be observed) δ = 143.5 (C), 135.9 (C), 132.2 (C), 128.9 (CH), 125.7 (CH), 125.6 (CH), 81.2 (C), 43.2 (CH_2), 30.1 (CH_2), 29.7 (CH_2), 28.6 (CH_3), 26.0 (CH_2), 22.8 (CH_2), 14.0 (CH_3); HRMS (ES) Found: MH^+, 324.1728. $C_{18}H_{27}NO_2{}^{35}Cl$ required MH^+ 324.1730; LRMS *m/z* (ES) 324 (100%, MH^+ for ^{35}Cl), 326 (35% MH^+ for ^{37}Cl).

***tert*-Butyl 7-chloro-3,4-dihydro-1-(trimethylsilyl)-isoquinoline-2(1H)-carboxylate 146c**

Using general procedure A, THIQ **145** (100 mg, 0.37 mmol), *n*-BuLi (0.17 mL, 0.44 mmol) and $SiMe_3Cl$ (0.13 mL, 1.0 mmol) gave after purification by column chromatography on silica gel, eluting with petrol–EtOAc (98:2), the carbamate **146c** (85 mg, 68%) as plates; m.p. 115-116 °C; R_f 0.36 [petrol–EtOAc (95:5)]; FTIR υ_{max} (film)/cm^{-1}, 2980, 2930, 1700, 1420, 935; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.05–7.03 (2H, m, 2 × CH), 6.96–6.95 (1H, m, CH), 4.95 (0.5H, s, CH), 4.78 (0.5H, s, CH), 4.30–4.20 (0.5H, m, CH), 4.03–3.97 (0.5H, m, CH), 3.25 (0.5H, dt, *J* 9, 5 Hz CH), 3.10–3.05 (0.5H, m, CH), 2.95–2.82 (1H, m, CH), 2.72–

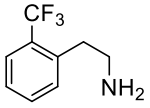
2.65 (1H, m, CH), 1.50 (4.5H, s, *t*-Bu), 1.48 (4.5H, s, *t*-Bu), 0.09–0.06 (9H, m, $SiMe_3$); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 154.4 & 154.3 (C=O), 139.2 & 138.7 (C), 131.4 & 131.3 (C), 131.2 & 131.1 (C), 130.8 & 130.4 (CH), 129.9 & 128.8 (CH), 125.0 & 124.6 (CH), 79.9 & 79.4 (C), 49.7 & 48.9 (CH), 40.8 & 39.5 (CH_2), 28.5 & 28.4 (CH_3), 28.3 & 28.0 (CH_2), –1.4 & –1.7 (CH_3); HRMS (ES) Found: MNa^+, 362.1329. $C_{17}H_{26}NO_2NaSi^{35}Cl$ requires MNa^+ 362.1319; LRMS *m/z* (ES) 364 (33%, MNa^+ for ^{37}Cl), 362 (100%, MNa^+ for ^{35}Cl).

tert-Butyl 1-(tributylstannyl)-7-chloro-3,4-dihydroisoquinoline-2(1H)-carboxylate 146d



Using general procedure A, THIQ **145** (100 mg, 0.37 mmol), *n*-BuLi (0.17 mL, 0.44 mmol) and $ClSnBu_3$ (0.36 mL, 1.3 mmol) gave after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the carbamate **146d** (120 mg, 58%) as an oil; R_f 0.6 [petrol–EtOAc (95:5)]; FTIR υ_{max} (film)/cm^{-1} 2955, 2925, 2855, 1700, 1150 ; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.00–6.95 (2H, m, 2 × CH), 6.85–6.80 (H, m, CH), 5.34–5.17 (1H, m, CH), 4.35–4.25 (0.5H, m, CH), 3.85 (0.5H, dt, *J* 12, 6 Hz, CH), 3.31 (0.5H, ddd, *J* 12, 8, 4 Hz, CH), 3.01–2.85 (1.5H, m, CH), 2.75–2.65 (1H, m, CH), 1.60 (4.5H, s, *t*-Bu), 1.59 (4.5H, s, *t*-Bu), 1.45–1.20 [12H, m, $Sn(CH_2\mathit{CH_2CH_2}CH_3)_3$], 0.95– 0.78 [15H, m, $Sn(\mathit{CH2}CH_2CH_2\mathit{CH_3})_3$]; ^{13}C NMR (100 MHz, $CDCl_3$, rotamers, C=O couldn't be observed) δ = 131.8 (C), 130.1 & 129.5 (CH), 130.0 (C), 129.9 & 129.8 (C), 123.9 & 123.7 (CH), 123.4 (CH), 79.4 (C), 49.6 & 49.3 (CH), 41.7 & 40.6 (CH_2), 29.0 (CH_2), 28.9 & 28.8 (CH_2), 28.6 & 28.5 (CH_3), 27.4 & 27.3 (CH_2), 13.5 (CH_3), 10.6 & 10.4 (CH_2); HRMS (ES) Found: MH^+, 558.2134. $C_{26}H_{45}NO_2{}^{35}Cl^{120}Sn$ requires MH^+ 558.2161; LRMS *m/z* (ES) 560 (33%, MH^+, for ^{37}Cl), 558 (100%, MH^+ for ^{35}Cl).

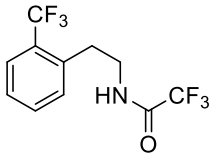
2-(2-(Trifluoromethyl)phenyl)ethanamine 148



Using general procedure C, nitrile **147** (14.0 g, 76 mmol) and Raney Ni (1.1 mL, 18 mmol) gave after purification by column chromatography on silica gel, eluting with CH_2Cl_2: MeOH: conc. NH_3 (93.75:6:0.25), the amine **148** (13.2 g, 92%) as an oil; R_f 0.18 [CH_2Cl_2:MeOH:conc. NH_3 (90:9:1)]; FTIR υ_{max} (film)/cm^{-1} 3315, 2970, 1450; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.65

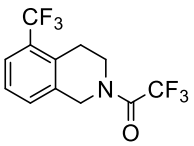
(1H, d, *J* 8 Hz, CH), 7.51–7.42 (1H, m, CH), 7.38 (1H, t, *J* 8 Hz, CH), 7.32 (1H, t, *J* 8 Hz, CH), 3.48 (2H, t, *J* 8 Hz, CH_2), 3.12 (2H, t, *J* 8 Hz, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 138.5 (C), 131.8 (CH), 131.3 (CH), 131.3 (CH), 128.7 (C, q, *J* 18 Hz), 126.2 (CH, q, *J* 6 Hz), 124.2 (CF_3, q, *J* 270 Hz), 43.6 (CH_2), 37.1 (CH_2); HRMS (ES) Found: MH^+, 190.0839. $C_9H_{11}NF_3$ requires MH^+ 190.0844; LRMS *m/z* (ES) 190 (100%, MH^+). Data in accordance with the literature, only mass spectrum and ^1H NMR were reported.[191]

_N_-(2-(Trifluoromethyl)phenethyl)-2,2,2-trifluoroacetamide 149



Using general procedure D, amine **148** (2 g, 10.5 mmol), trifluoroacetic anhydride (2.5 mL, 12.6 mmol) and pyridine (0.6 mL, 21 mmol) gave after purification by flash column chromatography on silica gel, eluting with petol–EtOAc (98:2), the amide **149** (1.56 g, 52%) as an amorphous solid; m.p. 72–73 °C; R_f 0.1 [petrol–EtOAc (95:5)]; FTIR υ_{max} (film)/cm^{-1} 3315, 1700, 1560; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.68 (1H, d, *J* 8 Hz, CH), 7.54 (1H, t, *J* 8 Hz, CH), 7.41–7.36 (2H, m, 2 × CH), 6.64–6.63 (1H, br m, NH), 3.63 (2H, q, *J* 7 Hz, CH_2), 3.10 (2H, t, *J* 7 Hz, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 157.6 (C=O, q, *J* 36.0 Hz), 136.4 (C), 132.0 (CH),131.5 (CH), 128.7 (C, q, *J* 30 Hz), 126.9 (CH), 126.6 (CH, q, *J* 6 Hz), 124.6 (CF_3, q, *J* 270 Hz), 116.4 (CF_3, q, *J* 280 Hz), 46.8 & 45.3 (CH_2), 42.5 & 41.0 (CH_2); HRMS Found: M^+, 285.0580. $C_{11}H_9F_6NO$ requires M^+, 285.0583; LRMS *m/z* (ES) 285 (100% M^+). Only mass spectrum was recorded. [191]

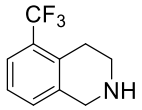
2,2,2-Trifluoro-1-(5-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl)ethanone 150



Using general procedure E, amide **149** (2.1 g, 7.3 mmol) and paraformaldehyde (0.3 g, 10.9 mmol) gave after purification by flash column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the amide **150** (1.8 g, 86%) as an amorphous solid; m.p. 57–57.5 °C; R_f 0.14 [petrol–EtOAc (95:5)]; FTIR υ_{max} (film)/cm^{-1} 2970, 1695, 1465; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.63–7.59 (1H, m, CH), 7.37–7.34 (2H, m, 2 × CH), 4.86–4.81 (2H, m,

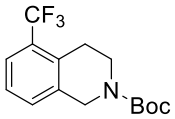
2 × CH), 3.91–3.88 (2H, m, 2 × CH), 3.15–3.14 (2H, m, 2 × CH); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 155.8 (C=O, q, *J* 36 Hz), 133.4 & 132.9 (C), 132.0 (C), 130.4 & 129.8 (CH), 128.7 (C, q, *J* 36 Hz), 126.7 & 126.6 (CH), 125.1 & 124.6 (CH, each q, *J* 7 Hz)), 124.1 (CF_3, q, *J* 274 Hz), 116.4 (CF_3, q, *J* 287 Hz), 46.80 & 45.3 (CH_2), 42.52 & 42.5 (CH_2), 26.0 & 24.6 (CH_2); HRMS (ES) Found: MH^+, 298.0681. $C_{12}H_{10}NOF_6$, requires MH^+ 298.0667; LRMS *m/z* (ES) 298 (100 %, MH^+). Only mass spectrum was reported.[191]

5-(Trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline 151



Using general procedure F, amide **150** (2.9 g, 9.6 mmol) and K_2CO_3 (5.3 mL, 38.5 mmol) gave after purification by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH–conc. NH_3 (93.4:6:0.25), the amine **151** (1.44 g, 75%) as an oil; R_f 0.16 [CH_2Cl_2:MeOH:conc. NH_3 (90:9:1)]; FTIR υ_{max} (film)/cm^{-1} 3050, 3040, 1465, 1430; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.50 (1H, d, *J* 7 Hz, CH), 7.25–7.20 (2H, m, 2 × CH), 4.10 (2H, s, NCH_2), 3.18 (2H, t, *J* 6 Hz, CH_2), 2.97 (2H, t, *J* 6 Hz, CH_2), 1.75 (1H, br s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 137.4 (C), 133.6 (C), 130.1 (CH), 129.0 (C, q, *J* 30 Hz), 125.4 (CH), 124.5 (CF_3, q, *J* 280 Hz), 123.9 (CH, q, *J* 6 Hz), 48.7 (CH_2), 43.3 (CH_2), 26.0 (CH_2); HRMS (ES) Found: MH^+, 202.0853. $C_{10}H_{11}NF_3$, requires MH^+ 202.0844; LRMS *m/z* (ES) 202 (100%, MH^+). Data in accordance with the literature, only mass spectrum and ^{1}H NMR were reported.[191]

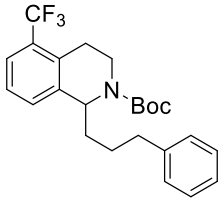
***tert*-Butyl 5-(trifluoromethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate 152**



Using general procedure B, di-*tert*-butyl dicarbonate (1.9 g, 8.9 mmol) and THIQ **151** (1.5 g, 7.4 mmol) gave after purification by flash column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the carbamate **152** (1.5 g, 67%) as an oil; R_f 0.41 [petrol–EtOAc (95:5)]; FTIR υ_{max} (film)/cm^{-1} 2975, 2930, 1695, 1420; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.52–7.51 (1H, m, CH), 7.29–7.28 (2H, m, 2 × CH), 4.63 (2H, s, NCH_2), 3.65 (2H, t, *J* 6 Hz, CH_2), 3.10 (2H, t, *J* 6 Hz, CH_2), 1.51 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 154.6 (C=O), 135.5 (C), 133.6 (C), 130.1 (CH), 126.2 (C), 125.9 (CH), 124.1 (CH, q, *J* 6 Hz), 124.4 (CF_3, q, *J* 274 Hz), 80.1 (C), 46.1 & 45.1 (CH_2) 41.1 & 40.8 (CH_2), 28.4 (CH_3),

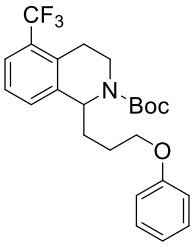
25.7 (CH_2); HRMS (ES) Found: (MNa^+), 324.1201. $C_{15}H_{18}NO_2F_3Na$ requires MNa^+ 324.1187; LRMS *m/z* (ES) 324 (100%, MNa^+).

***tert*-Butyl 5-(trifluoromethyl)-3,4-dihydro-1-(3-phenylpropyl)isoquinoline-2(1H)-carboxylate 153a**



Using general procedure A, THIQ **152** (100 mg, 0.33 mmol), *n*-BuLi (0.19 mL, 0.49 mmol) and $Br(CH_2)_3Ph$ (0.17 mL, 1.16 mmol) gave after purification by column chromatography on silica gel, eluting with petrol–EtOAc (99:1), the carbamate **153a** (84 mg, 61%) as an oil; R_f 0.25 [petrol–EtOAc (90:10)]; FTIR υ_{max} (film)/cm^{-1} 2970, 2930, 1690, 1420; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.53–7.52 (1H, m, CH), 7.30–7.19 (7H, m, 7 × CH), 5.30–5.25 (0.5H, m, CH), 5.09–5.00 (0.5H, m, CH), 4.30–4.16 (0.5H, m, CH), 4.00–3.97 (0.5H, m, CH), 3.26–3.16 (1H. m, CH), 3.05–2.92 (2H, m, 2 × CH), 2.75–2.67 (2H, m, 2 × CH), 1.90–1.72 (4H, m, 4 × CH), 1.51 (4.5H, s, *t*-Bu), 1.49 (4.5H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers, aromatic C could be missing) δ = 154.8 & 154.6 (C=O), 142.2 & 141.8 (C), 140.1 & 139.8 (C), 133.3 & 133.0 (C), 131.2 (CH), 130.9 (CH), 128.3 (2 × CH), 125.8 (CH), 124.3 (CF_3, q, *J* 270 Hz), 124.2 (CH), 80.1 & 79.8 (C), 54.9 & 53.8 (CH), 37.6 (CH_2), 36.4 (CH_2), 36.0 (CH_2), 35.4 (CH_2), 28.4 & 27.9 (CH_3), 25.2 & 25.1 (CH_2); HRMS (ES) Found: MNa^+, 442.1961. $C_{24}H_{28}NO_2F_3Na$ requires MNa^+ 442.1970; LRMS *m/z* (ES) 442 (100%, MNa^+).

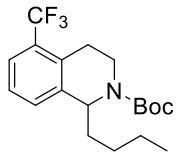
***tert*-Butyl 5-(trifluoromethyl)-3,4-dihydro-1-(3-phenoxypropyl)isoquinoline-2(1H)-carboxylate 135b**



Using general procedure A, THIQ **152** (100 mg, 0.33 mmol), *n*-BuLi (0.19 mL, 0.49 mmol) and $Br(CH_2)_3OPh$ (0.17 mL, 1.16 mmol) gave after purification by column chromatography on silica gel, eluting with petrol–EtOAc (99:1), the carbamate **153b** (90 mg, 63%) as an oil; R_f 0.22 [petrol–EtOAc (90:10)]; FTIR υ_{max} (film)/cm^{-1} 2970, 1685, 1420; ^{1}H NMR (400 MHz,

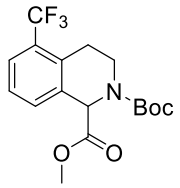
$CDCl_3$, rotamers) δ = 7.52–7.45 (1H, m, CH), 7.37–7.25 (4H, m, 4 × CH), 6.96–6.90 (3H, m, 3 × CH), 5.30–5.27 (0.5H, m, CH), 5.15–5.12 (0.5H, m, CH), 4.30–4.25 (0.5H, m, CH), 4.10–4.02 (2.5H, m, CH), 3.37–3.20 (1H, m, CH), 3.08–2.98 (2H, m, 2 × CH), 2.03–1.90 (4H, m, 4 × CH), 1.50 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 159.0 (C–O), 154.9 & 154.5 (C=O), 140.2 & 139.7 (C), 133.3 & 133.0 (C), 131.2 & 130.9 (CH), 129.4 (CH), 128.6 (C, q, *J* 31 Hz), 125.8 (CH), 124.3 (CH), 121.0 (CF_3, q, *J* 274 Hz), 120.7 & 120.6 (CH), 114.5 (CH), 80.2 & 79.9 (C), 67.2 (CH_2), 54.6 & 53.7 (CH), 37.6 & 36.0 (CH_2), 33.5 & 33.1 (CH_2), 29.7 & 28.4 (CH_3), 26.2 (CH_2) 25.2 & 25.0 (CH_2); HRMS (ES) Found: MNa^+, 458.1919. $C_{24}H_{29}NO_3F_3Na$ requires MNa^+ 458.1918; LRMS *m/z* (ES) 458 (100%, MNa^+).

tert-Butyl 1-butyl-5-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate 153c



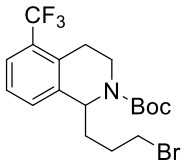
Using general procedure A, THIQ **152** (100 g, 0.33 mmol), *n*-BuLi (0.19 mL, 0.49 mmol) and $Br(CH_2)_3CH_3$ (0.12 mL, 1.16 mmol) gave after purification by column chromatography on silica gel, eluting with petrol–EtOAc (98:2), the carbamate **153c** (70 mg, 60%) as an oil; R_f 0.36 [petrol–EtOAc (90:10)]; FTIR υ_{max} (film)/cm^{-1} 2965, 2930, 1690, 1425; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.52–7.51 (1H, m, CH), 7.29–7.28 (2H, m, 2 × CH), 5.21–5.18 (0.5H, br m, CH), 5.07–5.05 (0.5H, br m, CH), 4.25–4.22 (0.5H, br m, CH), 4.00–3.97 (0.5H, br m, CH), 3.36–3.15 (1H, br m, CH), 3.05–2.93 (2H, br m, 2 × CH), 1.89–1.66 (2H, m, 2 × CH), 1.50 (9H, s, *t*-Bu), 1.45–1.29 (4H, m, 4 × CH), 0.94–0.89 (3H, m, 3 × CH); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 154.8 (C=O), 140.3 & 140.1 (C), 133.3 & 133.0 (C), 131.2 & 130.9 (CH), 128.3 (C, q, *J* 28.5 Hz), 125.6 (CH), 124.1 (CH), 121.7 (CF_3, q *J* 269 Hz) , 80.0 & 79.7 (C), 54.9 & 54.1 (CH), 37.7 & 36.9 (CH_2), 36.5 & 35.9 (CH_2), 29.7 & 28.7 (CH_2), 28.4 (CH_3), 25.2 & 25.1 (CH_2), 22.5 (CH_2), 14.0 (CH_3); HRMS (ES) Found: MNa^+, 380.1795. $C_{19}H_{26}NO_2F_3Na$, requires MNa^+ 380.1813; LRMS *m/z* (ES) 380 (100%, MNa^+).

2-*tert*-Butyl 1-methyl 5-(trifluoromethyl)-3,4-dihydroisoquinoline-1,2(1H)-dicarboxylate 153e



Using general procedure A, THIQ **152** (100 mg, 0.33 mmol), *n*-BuLi (0.19 mL, 0.49 mmol) and MeOCOCl (0.09 mL, 1.16 mmol) gave after purification by column chromatography on silica gel, eluting with petrol–EtOAc (99:1), the carbamate **153e** (35 mg, 30%) as an oil; R_f 0.19 [petrol–EtOAc (95:5)]; FTIR υ_{max} (film)/cm^{-1} 2990, 2935, 1750, 1660, 1390; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.70–7.68 (1H, m, CH), 7.62–7.60 (1H, m, CH), 7.36–7.32 (1H, m, CH), 5.54 (0.5H, s, CH), 5.50 (0.5H, s, CH), 3.84–3.76 (2H, m, 2 × CH), 3.75 (3H, s, OCH_3), 3.12–3.05 (2H, m, 2 × CH), 1.52 (4.5H, s, *t*-Bu), 1.49 (4.5H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 171.6 & 171.2 (C=O), 155.1 & 154.4 (C=O), 134.7 & 134.4 (C), 133.3 & 133.0 (C), 130.1 (C, q, *J* 30 Hz), 132.1 & 313.7 (CH), 126.2 (CH), 125.4 (CH, q, *J* 6 Hz), 124.1 (CF_3, q, *J* 270 Hz), 81.1 & 80.8 (C), 58.7 & 57.5 (CH_3), 52.7 & 52.5 (CH), 40.1 & 39.0 (CH_2), 28.4 & 28.3 (CH_3), 25.4 & 25.3 (CH_2); HRMS (ES) Found: MH^+, 360.1408. $C_{17}H_{21}NO_4F_3$ requires MH^+ 360.1408; LRMS *m/z* (ES) 360 (100%, MH^+).

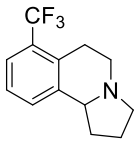
***tert*-Butyl 1-(3-bromopropyl)-5-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate 153f**



Using general procedure A, THIQ **152** (200 mg, 0.66 mmol), *n*-BuLi (0.31 mL, 0.78 mmol) and $Br(CH_2)_3Br$ (0.08 mL, 0.79 mmol), gave after purification by column chromatography on silica gel, eluting with petrol–EtOAc (99:1), the carbamate **153f** (180 mg, 68%) as an oil; R_f 0.4 [petrol–EtOAc (80:20)]; FTIR υ_{max} (film)/cm^{-1} 2975, 2925, 1690, 1420; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.55–7.53 (1H, m, CH), 7.35–7.30 (2H, m, 2 × CH), 5.26–5.23 (0.5H, m, CH), 5.10–5.08 (0.5H, m, CH), 4.33–4.27 (0.5H, m, CH), 4.08–4.06 (0.5H, m, CH), 3.68–3.51 (2H, m, 2 × CH), 3.31–3.15 (1H, m, CH), 3.00–2.97 (2H, m, 2 × CH), 2.05–1.95 (4H, m , 4 × CH), 1.50 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 154.9 & 154.2 (C=O), 139.7 (C), 139.2 (C), 133.6 & 132.6 (C), 131.3 & 130.8 (CH), 125.9 & 125.8 (CH), 124.4 (CH), 124.3 (CF_3, q, *J* 280 Hz), 80.5 & 80.0 (C), 54.1 & 52.9 (CH), 37.6 & 35.9 (CH_2),

35.2 & 34.7 (CH_2), 33.5 & 33.0 (CH_2), 29.8 & 29.2 (CH_2), 28.4 (CH_3), 25.6 & 25.0 (CH_2); HRMS (ES) Found: MNa^+, 444.0754. $C_{18}H_{23}NO_2F_3{}^{79}BrNa$ requires MNa^+ 444.0762; LRMS *m/z* (ES) 446 (97% MNa^+), 444 (100%, MNa^+).

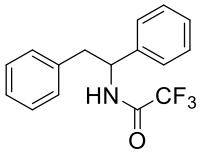
7-(Trifluoromethyl)-1H, 2H, 3H, 5H, 6H, 10bH-pyrrolo [2, 1-a] isoquinoline 154



Trifluoroacetic acid (0.28 mL, 3.66 mmol) was added to a solution of carbamate **153f** (400 mg, 0.95 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at room temperature. After 4 h, the solvent was evaporated and aqueous NaOH (30 mL, 1 M) was added. After 30 min, the mixture was extracted with CH_2Cl_2 (2 × 5 mL). The combined extracts were dried ($MgSO_4$), evaporated, and the residue was purified by flash column chromatography on silica, eluting with petrol–EtOAc (92:8), to give the amine **154** (210 mg, 91%) as an amorphous solid; mp 76–78 °C; R_f 0.5 [petrol–EtOAc (80:20)]; FTIR υ_{max} (film)/ cm^{-1} 2920, 2850, 1470, 1375; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.52–7.50 (1H, m, CH), 7.29–7.23 (2H, m, 2 × CH), 3.27–3.04 (4H, m, 4 × CH), 2.69–2.54 (2H, m, 2 × H), 2.45–2.37 (1H, m, CH), 2.01–1.71 (4H, m, 4 × CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 140.5 (C), 133.0 (C), 129.6 (CH), 128.1 (C, q, *J* 25 Hz), 125.7 (CH), 124.5 (CF_3, q *J* 276 Hz), 123.9 (CH, q, *J* 7 Hz), 63.5 (CH), 53.5 (CH_2), 47.9 (CH_2), 30.6 (CH_2), 25.4 (CH_2), 22.1 (CH_2); HRMS (ES) Found: MH^+, 242.1147. $C_{13}H_{15}NF_3$ requires MH^+ 242.1147; LRMS *m/z* (ES) 242 (100%, MH^+). [101, 102,100]

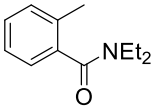
5.3 Chapter 3 Experimental

N-(1,2-Diphenylethyl)-2,2,2-trifluoroacetamide 156



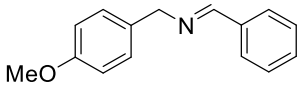
Using general procedure D, 1,2-diphenylethylamine **155** (5.00 g, 25.3 mmol), trifluoroacetic anhydride (5.9 mL, 30.4 mmol) and pyridine (1.5 mL, 50.7 mmol) gave after purification by flash column chromatography on silica gel, eluting with petol–EtOAc (96.5:3.5), the acetamide **156** (7.1 g, 96%) as an oil; R_f 0.2 [petrol–EtOAc (90:10)]; FTIR υ_{max} (film)/cm^{-1} 3335, 3005, 2915, 1695, 1550; ^{1}HNMR (400 MHz, $CDCl_3$, rotamers) δ = 7.37–7.33 (3H, m, 3 × CH), 7.28–7.21 (5H, m, 5 × CH), 7.07–7.05 (2H, m, 2 × CH), 6.54 (1H, br d, *J* 7 Hz, NH), 5.28 (1H, q, *J* 7 Hz, CH), 3.25–3.16 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers, C=O couldn't be observed) δ = 139.2 (C), 135.9 (C), 129.4 (CH), 128.9 (CH), 128.6 (CH), 128.2 (CH), 127.0 (CH), 126.5 (CH) 115.6 (q, *J* 242 Hz, CF_3), 55.2 (CH), 41.9 (CH_2); HRMS (ES) Found: MH$^+$, 294.1105. $C_{16}H_{14}F_3NO$, requires MH$^+$ 294.1133; LRMS *m/z* (ES) 294 (100%, MH$^+$). Data in accordance with the literature.[192]

N,*N*-Diethyl-2-methylbenzamide 159



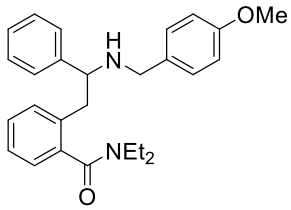
O-Toluic acid (0.5 g, 3.7 mmol) and *N*,*N*-dimethylformamide (0.05 mL, 0.07 mmol) in CH_2Cl_2 (10 mL) were cooled to 0 °C and oxalyl chloride (0.37 mL, 4.4 mmol) was added dropwise over 15 minutes. The mixture was stirred for 30 min, and diethylamine was added dropwise, and the mixture was allowed to warm to room temperature. After 16 h the mixture was washed with aqueous HCl (20 mL, 2 M), water (50 mL), dried ($MgSO_4$), and evaporated. Purification by column chromatography on silica, eluting with petrol–EtOAc (97:3), gave the amide **159** (0.5 g, 67%) as an oil; R_f 0.32 [petrol–EtOAc (80:20)]; ^{1}H NMR (400 MHz, $CDCl_3$,) δ = 7.28–7.25 (1H, m, CH), 7.22–7.18 (3H, m, 3 × CH), 3.17–3.11 (4H, m, 2 × CH_2), 2.30 (3H, s, CH_3), 1.28 (3H, t, *J* 7 Hz, CH_3), 1.05 (3H, t, *J* 7, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.8 (C=O), 137.1 (C), 133.8 (C), 131.7 (CH), 130.2 (CH), 128.5 (CH), 125.4 (CH), 42.5 (CH_2), 38.6 (CH_2), 18.7 (CH_3), 13.9 (CH_3), 12.8 (CH_3); HRMS (ES) Found: MH$^+$, 192.1385. $C_{12}H_{17}NO$ requires MH$^+$ 192.1383; LRMS *m/z* (ES) 192 (100%, MH$^+$). Data in accordance with the literature.[193]

(*E*)-[(4-Methoxyphenyl)methyl](phenylmethylidene)amine 162



Benzaldehyde (2.00 g, 18.8 mmol), and 4-methoxy-benzene methanamine (3.90 g, 28.3 mmol) were heated in toluene (15 mL) using a Dean–Stark apparatus. After 16 h, the solvent was evaporated, to give the imine **162** (1.2 g, 19%) as an amorphous solid; m.p. 59–61 °C; R_f 0.16 [CH_2Cl_2–MeOH (90:10)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.40 (1H, s, CH), 7.81–7.79 (2H, m, 2 × CH), 7.45–7.42 (3H, m, 3 × CH), 7.29–7.27 (2H, m, 2 × CH), 6.92–6.90 (2H, m, 2 × CH), 4.80 (2H, s, CH_2), 3.82 (3H, s, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.1 (CH), 158.7 (C), 146.1 (C), 131.3 (C), 130.7 (CH), 129.2 (CH), 128.6 (CH), 128.2 (CH), 113.9 (CH), 64.5 (CH_2), 55.3 (CH_3); HRMS (ES) Found: MH^+, 226.1236. $C_{15}H_{16}NO$ requires MH^+ 226.1232; LRMS *m/z* (ES) 226 (100%, MH^+). Data in accordance with the literature.[194]

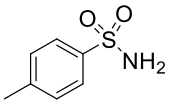
***N*,*N*-Diethyl-2-(2-{[(4-methoxyphenyl)methyl]amino}-2-phenylethyl)benzamide 163**



n-BuLi (3.0 mL, 6.7 mmol) was added to diisopropylamine (0.94 mL, 6.73 mmol) in THF (10 mL) at 0 °C. After 30 min the mixure was cooled to –45 °C and *N*,*N*-diethyl-2-methylbenzamide **159** (0.5 g, 6.12 mmol) in THF (5 mL) was added. The mixture was stirred for 20 min (the colour of the mixture turned to deep red after a few minutes), then (1E)-1-(4-methoxyphenyl)-N-phenylmethanimine **162** (1.29 g, 6.12 mmol) in THF (5 mL) was added. After 1 h at –45 °C, $AlMe_3$ (0.97 g, 7.34 mmol) and Et_3N (1.02 mL, 7.34 mmol) were added. After 10 h at –45 °C, the solvent was evaporated and the residue was extracted with EtOAc (3 × 50 mL), dried ($MgSO_4$), evaporated and purified by column chromatography on silica, eluting with petrol–EtOAc (90:10), to give amine **163** (47 mg, 17%) as an oil; R_f 0.11 [petrol–EtOAc (50:50)]; FTIR υ_{max} (film)/cm^{-1} 3225, 3010, 2980, 2935, 1750, 1610 1600; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.47–7.45 (1H, m, CH), 7.41–7.40 (1H, m, CH), 7.39–7.35 (3H, m, 3 × CH), 7.33–7.31 (2H, m, 2 × CH), 7.29–7.26 (2H, m, 2 × CH), 7.25–7.20 (2H, m, 2 × CH), 6.96–6.94 (1H, m, CH), 6.80–6.78 (1H, m, CH), 4.54 (2H, s, CH_2), 4.06–3.99 (1H, m, CH), 3.79 (3H, s, OCH_3), 3.60–3.34 (3H, m, 3 × CH), 3.26–3.19 (3H, m, 3 × CH), 2.19 (1H, br s, NH), 1.29 (3H, t, *J* 7 Hz, CH_3), 1.11 (3H, t, *J* 7 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ =

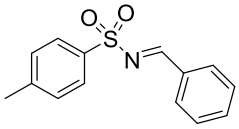
164.2 (C–O), 158.4 (C=O), 140.8 (C), 138.7 (C), 136.2 (C), 132.2 (C), 129.9 (CH), 129.6 (CH), 129.1 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 127.6 (CH), 127.5 (CH), 125.8 (CH), 64.0 (CH_2), 61.5 (OCH_3), 55.2 (CH), 50.3 (CH_2), 43.4 (CH_2), 39.3 (CH_2), 14.0 (CH_3), 12.7 (CH_3); HRMS (ES) Found: MH^+, 417.2533. $C_{27}H_{32}N_2O_2$ requires MH^+ 417.2537; LRMS *m/z* (ES) 417 (100%, MH^+).

_p_-Toluenesulfonamide 166



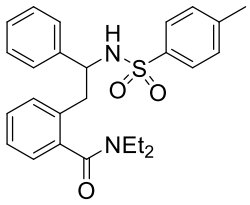
P-Toluensulfonyl chloride (3.0 g, 15.8 mmol) was added in portions to NH_4OH [2.6 mL, 47.3 mmol, 18 M in H_2O]. After 6 h, the product was formed as a white solid, filtered and washed with cold water (2 mL), to give the amide **166** (2 g, 74%) as an amorphous solid; m.p 135–137 °C, [lit[195], 134–137 °C]; R_f 0.18 [CH_2Cl_2–MeOH (80:20)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.84 (2H, d, *J* 8 Hz, 2 × CH), 7.34 (2H, d, *J* 8 Hz, 2 × CH), 4.78 (2H, br s, NH_2), 2.45 (3H, s, CH_3). Data in accordance with the literature.[195]

1-Methyl-4-[(E)-2-phenylethenesulfonyl]benzene 167



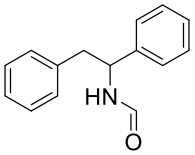
4-Methylbenzenesulfonamide **166** (1.7 g, 9.8 mmol) was added to a mixture of titanium (IV) isopropoxide (3.2 mL, 10.8 mmol) and benzaldehyde (1.0 mL, 9.8 mmol) in Et_2O (10 mL) and the mixture was heated to 40 °C. After 24 h saturated aqueous $NaHCO_3$ (5 mL) was added and the solid was filtered. The filtrate was evaporated and the residue was extracted with CH_2Cl_2 (3 × 50 mL) and dried ($MgSO_4$). The solvent was evaporated to give the imine **167** (2.43 g, 96%) as an amorphous solid; m.p. 101–103 °C [lit[196] 101.3–102.7 °C]; R_f 0.2 [MeOH–CH_2Cl_2 (20:80)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.09 (1H, s, CH), 7.96–7.90 (4H, m, 4 × CH), 7.66–7.62 (1H, m, CH), 7.51 (2H, t, *J* 8 Hz, 2 × CH), 7.38–7.33 (2H, m, 2 × CH), 2.46 (3H, s, CH_3). Data in accordance with the literature.[197]

***N*,*N*-Diethyl-2-[2-(4-methylbenzenesulfonamido)-2-phenylethyl]benzamide 168**



n-BuLi (1.56 mL, 3.74 mmol, 2 M in hexane) was added to *N*,*N*-diisopropylamine (0.5 mL, 3.7 mmol) in THF (5 mL) at 0 °C. After 30 min, the mixture was cooled to –45 °C and the amide **159** (0.5 g, 3.1 mmol) in THF (5 mL) was added. After 20 minutes, imine **167** (0.8 g, 3.1 mmol) in THF (10 ml) was added. After 15 min Et_3N (0.87 ml, 6.24 mmol) and $AlMe_3$ (0.2 mL, 6.24 mmol) were added. After 6 h, the mixture was allowed to warm to room temperature, then saturated aqueous NH_4Cl (10 mL) was added. The solvent was evaporated and the residue was extracted using CH_2Cl_2 (3 × 50 ml), the combined organic layers were dried ($MgSO_4$), and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (60:40), gave the amide **168** (0.73 g, 52%) as an amorphous solid; m.p 132–135 °C (lit.[119] 133–135 °C); R_f 0.45 [petrol–EtOAc (50:50)]; FTIR υ_{max} (film)/cm^{-1} 2835, 1600, 1575; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.44 (1H, s, NH), 7.84–7.82 (2H, m, 2 × CH), 7.45–7.43 (2H, m, 2 × CH), 7.34–7.30 (2H, m, 2 × CH), 7.26–7.22 (3H, m, 2 × CH), 7.08–7.05 (2H, m, 2 × CH), 6.90–6.80 (2H, m, 2 × CH), 4.12–4.10 (1H, m, CH), 3.66–3.60 (2H, m, CH), 3.19–3.10 (2H, m, CH), 2.86–2.82 (1H, m, CH), 2.66–2.59 (1H, m, CH), 2.45 (3H, s, CH_3), 1.30 (3H, t, *J* 7 Hz, CH_3), 1.01 (3H, t, *J* 7Hz, CH_3). Data in accordance with the literature.[119]

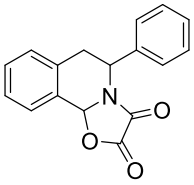
***N*-(1,2-Diphenylethyl)formamide 170**



A mixture of 1,2-diphenylethylamine **169** (5.0 g, 25 mmol), pyridine (3.7 mL, 126 mmol), and methylformate (18.3 mL, 506 mmol) in 1,4-dioxane was heated to 105 °C. After 48 h, the solvent was evaporated and the residue was washed with aqueous HCl (30 mL, 2 M), then with aqueous NaOH (30 mL, 1 M). The mixture was extracted using CH_2Cl_2 (2 × 100 mL). The combined extracts were dried ($MgSO_4$), evaporated and purified by column chromatography on silica, eluting with CH_2Cl_2–MeOH (92:8), gave the amide **170** (5.3 g, 93%) as an amorphous solid; mp 117–120 °C (lit.[120] 111.5–112.5 °C); R_f 0.18 [CH_2Cl_2–MeOH (90:10)]; FTIR υ_{max} (film)/cm^{-1} 3275, 3030, 2920, 1660, 1535; ^{1}H NMR (400 MHz, $CDCl_3$,) δ = 8.17 (1H, s, CH),

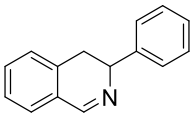
7.34–7.23 (8H, m, 8 × CH), 7.10–7.08 (2H, m, 2 × CH), 5.86 (1H, br d, *J* 7 Hz, NH), 5.38 (1H, q, *J* 7 Hz, CH), 3.19–3.11 (2H, m, 2 × CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.3 (C=O), 140.9 (C), 136.8 (C), 129.3 (CH), 128.6 (CH), 127.6 (CH), 126.7 (CH), 126.5 (CH), 126.3 (CH), 53.1 (CH), 42.5 (CH_2); HRMS (ES) Found: MH^+, 226.1230. $C_{15}H_{15}NO$, requires MH^+ 226.1226; LRMS *m/z* (ES) 226 (100%, MH^+). Data in accordance with the literature.[120]

5-Phenyl-5H,6H,10bH-[1,3]oxazolo[2,3-a]isoquinoline-2,3-dione 172



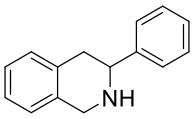
Oxalyl chloride (12.3 mL, 71 mmol) was added dropwise over 30 min to a mixture of amide **170** (8.0 g, 35 mmol) and DMF (0.1 mL) in CH_2Cl_2 (100 mL) at 0 °C. The progress of the reaction was followed by IR spectroscopy, which showed two new carbonyl peaks at 1836 cm^{-1} & 1750 cm^{-1} and the amide peak at 1680 cm^{-1} disappeared after 90 min. After 2 h, the mixture was cooled to –15 °C and $FeCl_3$ (6.9 g, 42.6 mmol) was added in very small portions over 3 h, then the mixture was allowed to warm to room temperature. After 24 h, aqueous HCl (10 mL, 2 M) was added dropwise and the mixture was stirred for 1 h. The organic layer was separated, washed with brine, dried ($MgSO_4$), and evaporated to give intermediate **172** (10.5 g) as an oil, R_f 0.45 [petrol–EtOAc (50:50)]; used crude in the next step.

3-Phenyl-3,4-dihydroisoquinoline 173



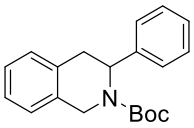
The crude intermediate **172** (10.5 g, 37.6 mmol) was dissolved in MeOH (140 mL) and H_2SO_4 (4.6 mL, 18 M) and was stirred for 30 min at room temperature before heating at 90 °C. After 24 h, the solvent was evaporated and the residue was basified using NaOH (100 mL, 2 M) until it reached pH 7. The mixture was extracted using EtOAc (250 mL × 3), dried ($MgSO_4$), and evaporated to give the imine **173** (9.9 g) as an oil, used crude in the next step.

3-Phenyl-1,2,3,4-tetrahydroisoquinoline 174



$NaBH_4$ (3.6 g, 95.6 mmol) was added in portions to a solution of the crude imine **173** (9.9 g, 47.8 mmol) in methanol (100 mL) at 0 °C. After 3 h, aqueous NaOH (20 mL, 2 M) was added, and the solvent was evaporated. The residue was extracted using CH_2Cl_2 (150 mL × 2), dried ($MgSO_4$), evaporated and the residue was purified by column chromatography on silica, eluting with CH_2Cl_2–MeOH (92:8), to give the amine **174** (6.1 g, 61% over four steps) as an oil; R_f 0.21 [CH_2Cl_2–MeOH (90:10)]; ^{1}H NMR (400 MHz, $CDCl_3$,) δ = 7.47–7.45 (1H, m, CH), 7.41–7.37 (2H, m, 2 × CH), 7.33–7.30 (2H, m, 2 × CH), 7.20–7.10 (4H, m, 4 × CH), 4.31 (1H, d, *J* 16 Hz, CH), 4.21 (1H, d, *J* 16 Hz, CH), 4.07–4.03 (1H, m, CH), 3.02–3.00 (2H, m, 2 × CH), 1.90 (1H, br s, NH). Data in accordance with the literature.[198]

***tert*-Butyl 3-phenyl-3,4-dihydro-1H-isoquinoline-2-carboxylate 175**



Using general procedure B, di-*tert*-butyl dicarbonate (0.4 g, 1.9 mmol) and amine **174** (0.5 g, 2.3 mmol) gave after purification by flash column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the carbamate **175** (0.5 g, 79%) as an amorphous solid; m.p 70–73 °C; R_f 0.23 [petrol–EtOAc (90:10)]; FTIR υ_{max} (film)/cm^{-1} 3005, 2975, 1690, 1455; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.25–7.14 (9H, m, 9 × CH), 5.38 (1H, br s, CH), 4.87–4.84 (1H, d, *J* 16 Hz, CH), 4.31–4.27 (1H, m, CH), 3.36–3.31 (1H, m, CH), 3.14–3.10 (1H, m, CH), 1.40 (9H, br s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers, aromatic C, CH could not be observed) δ = 155.2 (C=O), 142.4 (C), 133.8 (C), 128.2 (2 × CH), 126.9 (CH), 126.8 (CH), 126.4 (CH), 126.0 (CH), 80.0 (C), 54.4 (CH), 43.8 (CH_2), 35.9 (CH_2), 28.4 (CH_3); HRMS (ES) Found: MNa^+, 332.1614. $C_{20}H_{23}NO_2Na$ requires MNa^+332.1626; LRMS *m/z* (ES) 332 (100%, MNa^+).

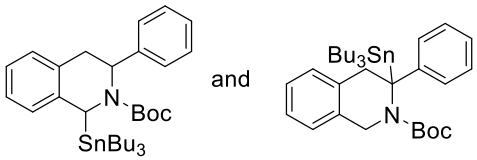
ReactIR monitoring of the lithiation *N*-Boc-3-phenylTetrahydroisoquinoline 175 by *n*-BuLi in THF (Figure 3-1)

THF (12 mL) was added to a flask equipped with a stirrer bar and ReactIR probe at room temperature under Ar. After cooling to –50 °C, a solution of *N*-Boc-tetrahydroisoquinoline **175** (0.6 g, 2.0 mmol) in THF (2 mL) was added. The solution was stirred for 10 min to verify the

stability of the readout on the ReactIR. *n*-BuLi (1.0 mL, 2.5 mmol, 2.5 M in hexane) was added. The solution was stirred for 10 min.

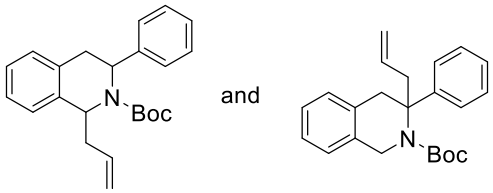
For *N*-Boc-3-phenyl-tetrahydroisoquinoline **175**, a peak at 1694 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *n*-BuLi, new peaks at $\nu_{C=O}$ 1642 cm^{-1} and 1632 cm^{-1} appeared which was assigned to $\nu_{C=O}$ of lithiated intermediate **176a** or **176b**. After a lithiation time of > 1 min, the lithiation of *N*-Boc-tetrahydroisoquinoline **175** to intermediate **176a** and **176b** was completed.

tert-Butyl 3-phenyl-1-(tributylstannyl)-3,4-dihydro-1H-isoquinoline-2-carboxylate 177a and _tert_-butyl 3-phenyl-3-(tributylstannyl)-1,4-dihydroisoquinoline-2-carboxylate 178a



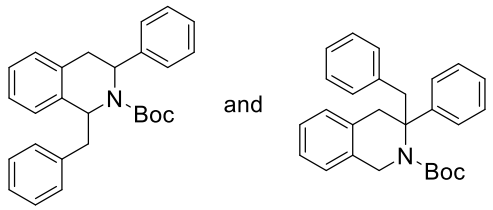
Using general procedure A, THIQ **175** (0.1 g, 0.32 mmol), *n*-BuLi (0.3 mL, 7.7 mmol), and $ClSnBu_3$ (0.3 mL, 1.12 mmol) gave after purification by column chromatography on silica gel, eluting with petrol–EtOAc (96:4), the carbamates **177a** and **178a** as inseparable regioisomers**,** ratio 1:1 (0.15 g, 79%) as an oil; R_f 0.6 [petrol–EtOAc (80:20)]; FTIR υ_{max} (film)/cm^{-1} 3005, 2975, 1685, 1515, 1150; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.14–7.08 (5H, m, 5 × CH), 6.95–6.89 (4H, m, 4 × CH), 5.46–5.36 (0.5H, m, CH), 5.28–5.23 (0.5H, m, CH), 4.83 (0.5H, d, *J* 16 Hz, CH), 4.35 (0.5H, d, *J* 16 Hz, CH), 3.59 (0.5H, d, *J* 16 Hz, CH), 3.43 (0.5H, d, *J* 16 Hz, CH), 3.16–3.11 (0.5H, m, CH), 3.01–2.98 (0.5H, m, CH), 1.55 (9H, s, *t*-Bu), 1.42–1.16 [12H, m, ($SnCH_2\mathit{CH_2CH_2}CH_3$)], 0.89–0.73 [15H, m, ($Sn\mathit{CH_2}CH_2CH_2\mathit{CH_3}$)]; ^{13}C NMR (100 MHz, $CDCl_3$, rotamers, C=O) δ = 157.1 (2 × C=O), 145.0 & 144.8 (C), 140.3 (C), 136.3 & 135.7 (C), 134.8 (C), 134.0 & 133.9 (C), 133.4 (C), 129.0 & 128.8 (CH), 128.7 (CH), 128.4 (CH), 128.2 (CH), 128.0 & 127.8 (CH), 127.7 (CH), 127.3 & 127.2 (CH), 126.4 & 126.2 (CH), 126.1 (CH), 125.8 (CH), 125.7 (CH), 125.4 & 125.3 (CH), 124.8 & 124.7 (CH), 123.9 (CH), 80.3 (C), 80.0 (C), 60.3 (C), 58.5 & 57.5 (CH), 56.5 & 55.5 (CH), 43.6 & 41.3 (CH_2), 36.3 & 35.9 (CH_2), 35.0 & 34.1 (CH_2), 29.1 & 29.0 (CH_2), 28.4 (2 × CH_3), 28.0 & 27.9 (CH_2), 27.6 (CH_2), 27.2 & 27.1 (CH_2), 15.6 & 15.3 (CH_2), 14.3 & 14.2 (CH_3), 13.7 & 13.6 (CH_3), 13.3 (CH_2); HRMS (ES) Found: MNa^+, 622.2706. $C_{32}H_{49}NO_2\,^{120}SnNa$ requires MNa^+ 622.2683; LRMS *m/z* (ES) 622 (100%, MNa^+).

***tert*-Butyl 3-phenyl-1-(prop-2-en-1-yl)-3,4-dihydro-1H-isoquinoline-2-carboxylate 177b and *tert*-Butyl 3-phenyl-3-(prop-2-en-1-yl)-1,4-dihydroisoquinoline-2-carboxylate 178b**



Using general procedure A, THIQ **175** (0.5 g, 1.6 mmol), *n*-BuLi (1.0 mL, 2.4 mmol), and allyl bromide (0.42 mL, 2.9 mmol) gave after purification by column chromatography on silica gel, eluting with petrol–EtOAc (90:10), the carbamates **177b** and **178b** in 2.3:1 ratio as inseparable regioisomers (0.46 g, 82%) as an oil; R_f 0.58 [petrol–EtOAc (80:20)]; FTIR υ_{max} (film)/cm^{-1} 2970, 2945, 2930, 1690, 1495, 1170; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.24–7.07 (6H, m, 6 × CH), 6.89–6.80 (3H, m, 3 × CH), 5.94–5.88 (0.3H, m, CH), 5.81–5.72 (0.7H, m, CH), 5.33–5.15 (2H, m, 2 × CH), 5.04–4.97 (1.7H, m, CH), 4.27–4.26 (0.3H, m, CH), 3.61–3.53 (1H, m, CH), 3.41 (0.3H, d, *J*, 14.5 Hz, CH), 2.92–2.76 (1.7H, m, CH), 2.68 (0.3H, d, *J* 14.5 Hz, CH), 2.50–2.43 (0.7H, m, CH), 1.18–1.13 (9H, m, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 155.1 (2 × C=O), 145.2 (C), 137.4 (C), 137.2 (C), 136.0 (C), 135.3 (C), 134.8 (CH), 134.1 (CH), 132.1 (C), 128.6 & 128.5 (CH), 128.3 (CH), 128.2 & 128.1 (CH), 127.8 & 127.7 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 127.3 & 127.2 (CH), 127.1 (CH), 126.5 (CH), 126.3 & 126.1 (CH), 125.8 (CH), 125.5 & 125.4 (CH), 124.4 (CH), 119.0 (CH_2), 117.6 (CH_2), 79.9 (C), 79.7 (C), 61.9 & 60.4 (C), 57.0 & 56.7 (CH), 56.6 & 55.9 (CH), 49.5 (CH_2), 46.8 (CH_2), 44.1 (CH_2), 41.7 (CH_2), 36.4 & 36.2 (CH_2), 28.5 (CH_3), 28.0 & 27.6 (CH_3); HRMS (ES) Found: MNa^+, 372.1942. $C_{23}H_{27}NO_2Na$ requires MNa^+ 372.1943; LRMS *m/z* (ES) 372 (100%).

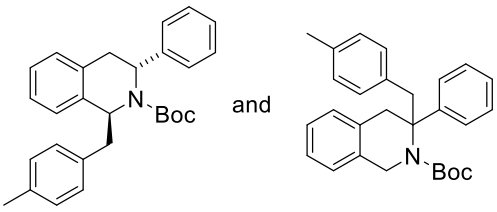
***tert*-Butyl 1-benzyl-3-phenyl-3,4-dihydro-1H-isoquinoline-2-carboxylate 177c and *tert*-Butyl 3-benzyl-3-phenyl-1,4-dihydroisoquinoline-2-carboxylate 178c**



Using general procedure A, THIQ **175** (0.15 g, 0.48 mmol), *n*-BuLi (0.3 mL, 0.7 mmol) and benzyl bromide (0.4 mL, 1.44 mmol) gave after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the carbamates **177c** and **178c** in 3:1 ratio as

inseparable regioisomers (0.15 g, 78%) as an oil; R_f 0.28 [petrol–EtOAc (90:10)]; FTIR υ_{max} (film)/cm^{-1} 2970, 2930, 2920, 1685, 1495, 1170; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.36–7.35 (1H, m, CH), 7.22–7.21 (3H, m, 3 × CH), 7.17–7.13 (1H, m, CH), 7.08–7.03 (4H, m, 4 × CH), 6.96–6.87 (5H, m, 5 × CH), 5.47–5.42 (0.75H, m, CH), 5.29–5.23 (0.75H, m, CH), 5.05 (0.25H, d, *J* 15 Hz, CH), 4.18 (0.25H, d, *J* 15 Hz, CH), 3.48 (0.25H, d, *J* 15 Hz, CH), 3.39–3.30 (1H, m, CH), 3.20–2.96 (1.75H, m, CH), 2.79 (0.25H, d, *J* 15 Hz, CH), 2.70–2.62 (0.75H, m, CH), 1.29–1.18 (9H, m, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 155.1 & 154.6 (2 × C=O), 145.2 (C), 144.0 (C), 138.1 & 137.9 (C), 137.7 (C), 136.7 (C), 136.4 & 136.2 (C), 135.2 & 135.0 (C), 132.6 & 132.2 (C), 131.2 (CH), 130.1 (CH), 129.9 (CH), 128.3 & 128.2 (CH), 128.0 (CH), 127.9 (CH), 127.6 & 127.5 (CH), 127.4 (CH), 127.3 (CH), 127.1 (CH), 127.0 & 126.9 (CH), 126.7 & 126.6 (CH), 126.4 (CH), 126.2 & 126.1 (CH), 126.0 (CH), 125.8 & 125.7 (CH), 125.5 (CH), 125.3 (CH), 125.1 (CH), 124.4 (CH), 80.3 & 80.1 (C), 79.7 (C), 62.7 (C), 59.5 & 58.7 (CH), 56.6 & 56.0 (CH), 46.3 & 44.3 (CH_2), 43.7 & 43.4 (CH_2), 42.8 & 42.7 (CH_2), 36.1 & 35.9 (CH_2), 29.7 (CH_2), 28.6 & 28.3 (CH_3), 28.2 & 28.1 (CH_3); HRMS (ES) Found: MH^+, 422.2083. $C_{27}H_{29}NO_2Na$ requires MNH^+ 422.2096; LRMS *m/z* (ES) 422 (100%, MNa^+).

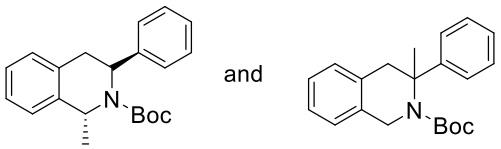
tert-Butyl 1-[(4-Methylphenyl) methyl]-3-phenyl-3,4-dihydro-1H-isoquinoline-2-carboxylate 177d and _tert_-Butyl 3-[(4-Methylphenyl)methyl]-3-phenyl-1,4-dihydroisoquinoline-2-carboxylate 178d



Using general procedure A, THIQ **175** (0.30 g, 0.96 mmol), *n*-BuLi (0.6 mL, 1.44 mmol), and 4-methylbenzylbromide (0.5 g, 2.9 mmol) gave after purification by column chromatography on silica gel, eluting with petrol–EtOAc (94:5), the carbamates **177d** and **178d** as inseparable regioisomers, ratio 3:1 (0.37 g, 94%) as an oil; R_f 0.3 [petrol–EtOAc (90:10)]; FTIR υ_{max} (film)/cm^{-1} 3025, 2970, 2925, 1690, 1120; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.26–7.24 (1H, m, CH), 7.19–7.12 (2H, m, 2 × CH), 7.09–7.02 (5H, m, 5 × CH), 6.93–6.91 (0.5H, m, CH), 6.85–6.79 (4H, m, 4 × CH), 6.71–6.69 (0.5H, m, CH), 5.49–5.42 (0.75H, m, CH), 5.29–5.22 (0.75H, m, CH), 5.07 (0.25H, d, *J* 15 Hz, CH), 4.15 (0.25H, d, *J* 15 Hz, CH), 3.49 (0.25H, d, *J* 15 Hz, CH), 3.62–3.22 (1H, m, CH), 3.17–2.94 (1.75H, m, CH), 2.79 (0.25H, d, *J* 15 Hz, CH), 2.71–2.60 (0.75H, m, CH), 2.37 (0.75H, s, CH_3), 2.34 (2.25H, s, CH_3), 1.30–1.19

(9H, m, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 155.1 & 154.6 (2 × C=O), 145.3 (C), 144.1 (C), 136.9 & 136.6 (C), 136.3 (C), 136.2 (C), 135.7 & 135.6 (C), 135.4 (C), 135.0 & 134.8 (C), 134.5 (C), 132.6 & 132.3 (C), 131.1 (CH), 129.9 & 129.7 (CH), 129.0 (CH), 128.7 & 128.6 (CH), 128.4 (CH), 128.2 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 127.3 & 127.2 (CH), 127.1 & 127.0 (CH), 126.3 (CH), 126.1 (CH), 126.0 (CH), 125.8 (CH), 125.5 & 125.3 (CH), 125.1 (CH), 124.4 (CH), 80.3 & 80.0 (C), 79.7 (C), 62.7 (C), 59.6 & 58.7 (CH), 56.6 & 56.1 (CH), 46.3 & 43.8 (CH_2), 42.9 (CH_2), 42.6 & 42.3 (CH_2), 36.1 & 36.0 (CH_2), 29.7 (CH_2), 28.6 & 28.3 (CH_3), 28.2 & 28.1 (CH_3), 21.1 (CH_3), 21.0 (CH_3); HRMS (ES) Found: MNa^+, 436.2227. $C_{28}H_{31}NO_2Na$ requires MNa^+ 436.2247; LRMS *m/z* (ES) 436 (100%, MNa^+).

tert-Butyl (1*R*,3*S*)-1-methyl-3-phenyl-3,4-dihydro-1H-isoquinoline-2-carboxylate 177e and _tert_-Butyl 3-methyl-3-phenyl-1,4-dihydroisoquinoline-2-carboxylate 178e



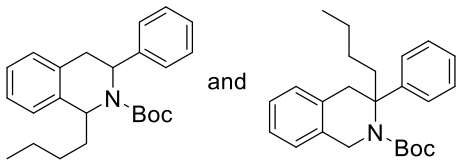
Using general procedure A, THIQ **X** (100 mg, 0.32 mmol), *n*-BuLi (0.2 mL, 0.48 mmol), and MeI (0.07 mL, 1.16 mmol) gave after recrystallisation using hexane–CH_2Cl_2, the carbamates **177e** and **178e** as separated regioisomers, ratio 4:1 (92 mg, 88%).

Carbamate **177e** (75 mg, 72%), as cubes; m.p. 84–87 °C; R_f 0.41 [petrol–EtOAc (90:10)]; FTIR υ_{max} (film)/cm^{-1} 3000, 2920, 1690, 1455; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.21–7.20 (2H, m, 2 × CH), 7.11–7.06 (4H, m, 4 × CH), 6.89–6.83 (3H, m, 3 × CH), 5.50–5.19 (2H, m, 2 × CH), 3.59–3.55 (1H, m, CH), 2.87–2.83 (1H, m, CH), 1.52 (3H, d, *J* 7 Hz, CH_3), 1.19 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 155.0 (C=O), 145.1 (C), 140.0 (C), 131.7 (C), 128.5 (CH), 127.6 (CH), 127.0 (CH), 126.9 (CH), 126.1 (CH), 125.9 (CH), 125.5 (CH), 79.6 (C), 56.6 (CH), 56.4 (CH), 36.0 (CH_2), 28.5 & 28.1 (CH_3), 14.1 (CH_3); HRMS (ES) Found: MNa^+, 346.1790. $C_{21}H_{25}NO_2Na$ requires MNa^+ 346.1783; LRMS *m/z* (ES) 346 (100%, MNa^+).

Carbamate **178e** (17 mg, 18%) as an oil; R_f 0.41 [petrol–EtOAc (80:20)]; FTIR υ_{max} (film)/ cm^{-1} 3000, 2920, 1690, 1455; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.32–7.27 (7H, m, 7 × CH), 7.09–7.08 (2H, m, 2 × CH), 4.91 (1H, d, *J* 15 Hz, CH), 4.67 (1H, d, *J* 15 Hz, CH), 3.06 (1H, d, *J* 14.5 Hz, CH), 2.83 (1H, d, *J* 14.5 Hz, CH), 1.67 (3H, s, CH_3), 1.09 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 152.1 (C=O), 149.5 (C), 136.0 (C), 135.8 (C), 127.9

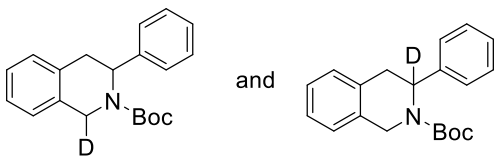
(CH), 127.4 (CH), 127.1 (CH), 126.7 (CH), 126.0 (CH), 125.8 (CH), 124.5 (CH), 79.7 (C), 60.3 (C), 48.0 (CH_2), 46.3 (CH_2), 28.0 (CH_3), 25.1 (CH_3); HRMS (ES) Found: MNa^+, 346.1789. $C_{21}H_{25}NO_2Na$, requires MNa^+; 346.1780, LRMS *m/z* (ES) 346 (100%, MNa^+).

tert-Butyl 1-butyl-3-phenyl-3,4-dihydro-1H-isoquinoline-2-carboxylate 177f and _tert_-Butyl 3-butyl-3-phenyl-1,4-dihydroisoquinoline-2-carboxylate 178f



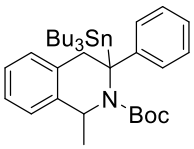
Using general procedure A, THIQ **175** (0.12 g, 0.4 mmol), *n*-BuLi (0.24 mL, 0.58 mmol), and butyl bromide (0.13 mL, 1.2 mmol) gave after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the carbamates **177f** and **178f** in 4:1 ratio as inseparable regioisomers (0.14 g, 97%) as an oil; R_f 0.57 [petrol–EtOAc (80:20)]; FTIR υ_{max} (film)/cm^{-1} 3005, 2955, 2925, 1685, 1170; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.21–7.07 (6H, m, 6 × CH), 6.89–6.80 (3H, m, 3 × CH), 5.48–5.19 (1.6H, m, CH), 4.99–4.96 (0.2H, m, CH), 4.34 (0.2H, d, *J* 14.5 Hz, CH), 3.65–3.57 (0.8H, m, CH), 3.35 (0.2H, d, *J* 14.5 Hz, CH), 2.89–2.52 (1H, m, CH), 2.19–2.03 (1H, m, CH), 1.68–1.60 (1H, m, CH), 1.47–1.36 (3H, m, 3 × CH), 1.18–1.06 (9H, s, *t*-Bu), 0.99–0.88 (4H, m, 4 × CH); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 155.1 (2 × C=O), 145.3 (C), 138.3 (C), 136.0 (C), 135.6 (C), 133.8 & 133.5 (C), 132.2 (C), 128.7 & 128.6 (CH), 128.2 & 128.1 (CH), 128.0 & 127.9 (CH), 127.6 (CH), 127.4 (CH), 127.3 (CH), 127.1 & 127.0 (CH), 126.5 & 126.4 (CH), 126.2 (CH), 126.1 (CH), 125.6 (CH), 125.5 & 125.4 (CH), 124.7 (CH), 124.5 (CH), 76.6 & 76.5 (2 × C), 62.3 (C), 57.9 & 57.0 (CH), 56.6 & 55.9 (CH), 46.9 (CH_2), 44.4 (CH_2), 43.7 & 43.1 (CH_2), 40.6 & 39.9 (CH_2), 37.0 (CH_2), 36.2 (CH_2), 29.3 & 28.9 (CH_2), 28.5 & 28.3 (CH_3), 28.0 (CH_3), 27.3 & 26.6 (CH_2), 23.2 & 22.7 (CH_2), 14.2 (CH_3), 14.1 (CH_3); HRMS (ES) Found: MNa^+, 388.2240. $C_{24}H_{31}NO_2Na$ requires MNa^+ 388.2247; LRMS *m/z* (ES) 388 (100%, MNa^+).

tert-Butyl 3-phenyl-3,4-dihydro(1-$^2H_1$)-1H-isoquinoline-2-carboxylate 177g _tert_-Butyl 3-phenyl-1,4-dihydro(3-^2H)isoquinoline-2-carboxylate 178g



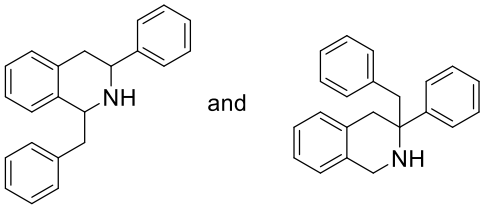
Using general procedure A, THIQ **175** (100 mg, 0.32 mmol), *n*-BuLi (0.2 mL, 0.5 mmol), and deuterium oxide (0.02 mL, 0.97 mmol) gave after purification by column chromatography on silica gel, eluting with petrol–EtOAc (99:1), the carbamates **177g** and **178g** in 2:1 ratio as inseparable regioisomers (93 mg, 96%) as an oil; R_f 0.23 [petrol–EtOAc (90:10)]; FTIR υ_{max} (film)/cm^{-1} 3005, 2970, 2925, 1690, 1160; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.13–7.03 (9H, m, 9 × CH), 5.25 (0.65H, br s, CH), 4.77 (0.35H, d *J* 16 Hz, CH), 4.17–4.15 (1H, br m, CH), 3.22–3.20 (1H, m, CH), 3.02–2.98 (1H, m, CH), 1.30 (9H, br s, *t*-Bu); ^{13}C NMR (126 MHz, $CDCl_3$, rotamers, one CH could not be observed) δ = 155.3 (C=O), 142.8 (C), 134.4 (C),133.8 (C), 128.2 (2 × CH), 126.9 (CH), 126.8 (CH), 126.4 (CH), 126.0 (CH), 80.0 (C), 54.4 (C), 43.4 (2 × CH, t, *J* 22 Hz), 35.0 (CH_2), 28.4 (CH_3); HRMS (ES) Found: MNa$^+$, 333.1682. $C_{20}H_{22}DNO_2Na$ requires MNa$^+$ 333.1684; LRMS *m/z* (ES) 333 (100%, MNa$^+$); Found: C, 76.91; H, 7.57; N, 4.07. $C_{20}H_{22}DNO_2$ requires C, 77.39; H, 7.79; N, 4.5.

tert-Butyl 1-methyl-3-phenyl-3-(tributylstannyl)-1,4-dihydroisoquinoline-2-carboxylate **179**



Using general procedure A, carbamate **177e** (46 mg, 0.14 mmol), *n*-BuLi (0.09 mL, 0.21 mmol), and $ClSnBu_3$ (0.11 mL, 0.42 mmol) gave after purification by column chromatography on silica gel, eluting with petrol–EtOAc (98:2), the carbamate **179** (30 mg, 15%) as an oil; R_f 0.38 [petrol–EtOAc (90:10)]; FTIR υ_{max} (film)/cm^{-1} 2955, 2925, 2890, 1670, 1455, 1155; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 6.95–6.90 (6H, m, 6 × CH), 6.81–6.79 (1H, m, CH), 6.57–6.71 (1H, m, CH), 6.67–6.63 (1H, m, CH), 5.07 (1H, q, *J* 6 Hz, CH), 3.39 (2H, s, CH_2), 1.50 (9H, s, *t*-Bu), 1.46–1.30 [9H, m, CH_3 & ($SnCH_2\mathit{CH_2CH_2}CH_3)_3$], 1.24–1.18 [6H, m, ($SnCH_2\mathit{CH_2CH_2}CH_3)_3$], 0.81–0.74 [15H, m, ($Sn\mathit{CH_2}CH_2CH_2\mathit{CH_3})_3$]; ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 156.1 (C=O), 146.8 (C), 139.5 (C), 139.4 (C), 127.8 (CH), 127.7 (CH), 126.5 (CH), 126.2 (CH), 125.6 (CH), 123.9 & 123.8 (CH), 123.6 (CH), 80.0 (C), 59.6 (C), 53.5 (CH), 39.9 (CH_2), 29.2 (CH_2), 28.6 (CH_3), 27.7 (CH_2), 13.7 (CH_3), 13.0 (CH_2); HRMS (ES) Found: MNa$^+$, 636.2841. $C_{33}H_{51}NO_2{}^{120}SnNa$, requires MNa$^+$ 636.2839; LRMS *m/z* (ES) 636 (100%, MNa$^+$).

1-Benzyl-3-phenyl-1,2,3,4-tetrahydroisoquinoline 182 and 3-benzyl-3-phenyl-2,4-dihydro-1H-isoquinoline 183

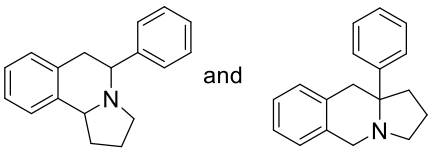


Trifluoroacetic acid (0.05 mL, 0.63 mmol) was added to a 3:1 mixture of carbamates **177c** and **178c** in a 3:1 ratio (0.12 g, 0.31 mmol) in CH_2Cl_2 (5 mL) at room temperature. After 4 h, the solvent was evaporated and aqueous NaOH (5 mL, 1 M) was added. After 1 h, the mixture was extracted using CH_2Cl_2 (2 × 20 mL). The combined extracts were dried ($MgSO_4$) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (75:25), gave the amines **182** and **183** in 2:1 ratio as separable regioisomers (65 mg, 69%).

Amine **182** (44 mg, 47%) as an oil; R_f 0.2 [petrol–EtOAc (90:10)]; FTIR υ_{max} (film)/cm^{-1} 3330, 3060, 3020, 1500; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.50–7.47 (2H, m, 2 × CH), 7.39–7.36 (2H, m, 2 × CH), 7.34–7.30 (3H, m, 3 × CH), 7.28–7.21 (6H, m, 6 × CH), 7.18–7.16 (1H, m, CH), 4.44–4.37 (2H, m, 2 × CH), 3.26–3.20 (1H, m, CH), 3.16–3.10 (1H, m, CH), 3.06–3.00 (2H, m, 2 × CH), 2.03 (1H, br s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 144.1 (C), 139.1 (C), 137.9 (C), 134.7 (C), 129.3 (CH), 129.1 (CH), 128.8 (CH), 128.6 (CH), 127.4 (CH), 127.2 (CH), 126.8 (CH), 126.5 (CH), 126.4 (CH), 125.8 (CH), 58.3 (CH), 51.8 (CH), 42.9 (CH_2), 38.1 (CH_2); HRMS (ES) Found: MH^+, 300.1719. $C_{22}H_{21}N$ requires MH^+ 300.1746; LRMS *m/z* (ES) 300 (100%, MH^+). No data were available.[199]

Amine **183** (21 mg, 22%) as an oil; R_f 0.2 [petrol–EtOAc (80:20)]; FTIR υ_{max} (film)/ cm^{-1} 3330, 3060, 3020, 1500; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37–7.35 (2H, m, 2 × CH), 7.28–7.24 (3H, m, 3 × CH), 7.21–7.18 (4H, m, 4 × CH), 7.13–7.06 (2H, m, 2 × CH), 6.88–6.87 (3H, m, 3 × CH), 4.00 (1H, d, *J* 16 Hz, CH), 3.79 (1H, d, *J* 16 Hz, CH), 3.25 (1H, d, *J* 16 Hz, CH), 3.11–3.01 (3H, m, 3 × CH), 1.79 (1H, br s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 143.2 (C), 136.7 (C), 135.1 (C), 134.0 (C), 130.6 (CH), 129.1 (CH), 126.0 (CH), 127.7 (CH), 127.2 (CH), 126.5 (CH), 126.4 (CH), 125.9 (CH), 125.7 (CH), 125.6 (CH), 44.3 (CH_2), 36.8 (CH_2), 29.7 (CH_2); HRMS (ES) Found: MH^+, 300.1717. $C_{22}H_{21}N$ requires MH^+ 300.1746; LRMS *m/z* (ES) 300 (100%, MH^+).

(5*S*,10b*R*)-5-Phenyl-1H,2H,3H,5H,6H,10bH-pyrrolo[2,1-a]isoquinoline 186 and 10a-Phenyl-1H,2H,3H,5H,10H-pyrrolo[1,2-b]isoquinoline 187



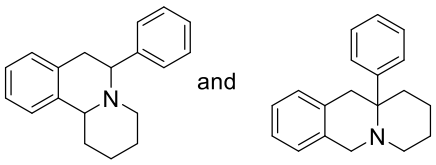
Using general procedure A, THIQ **175** (0.15 g, 0.48 mmol), *n*-BuLi (0.24 mL, 0.57 mmol), and $Br(CH_2)_3Br$ (0.14 mL, 1.44 mmol) gave the protected carbamates as inseparable products. Trifluoroacetic acid (2.6 mL, 0.20 mmol) was added to a solution of the crude carbamates (0.22 g, 0.52 mmol) in CH_2Cl_2 (5 mL) and the mixture was stirred at room temperature. After 4 h, the solvent was evaporated and aqueous NaOH (20 mL, 1 M) was added. After 1 h, the mixture was extracted using CH_2Cl_2 (2 × 50 mL), the combined extracts were dried ($MgSO_4$), and the solvent was evaporated. purification by column chromatography on silica, eluting with petrol–EtOAc (95:5), gave the amines **186** and **187** as separable regioisomers in (2:1) ratio (86 mg, 75%).

Amine **186** (56 mg, 50%) as a gum; R_f 0.22 [petrol–EtOAc (80:20)]; FTIR υ_{max} (film)/cm^{-1} 3000, 2990, 2950, 1450; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41–7.34 (4H, m, 4 × CH), 7.32–7.28 (1H, m, CH), 7.25–7.13 (4H, m, 4 × CH), 4.23 (1H, t, *J* 8 Hz , CH), 3.88 (1H, dd, *J* 9.5, 4 Hz, CH), 3.15–3.08 (1H, m, CH), 3.02–2.97 (1H, m, CH), 2.88–2.83 (1H, m, CH), 2.80–2.74 (1H, m, CH), 2.42–2.34 (1H, m, CH), 1.92–1.80 (3H, m, 3 × CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 143.1 (C), 138.6 (C), 134.8 (C), 128.4 (CH), 127.8 (CH), 127.7 (CH), 127.2 (CH), 126.2 (CH), 126.1 (CH), 126.0 (CH), 60.8 (CH), 60.5 (CH), 52.4 (CH_2), 38.6 (CH_2), 32.0 (CH_2), 23.1 (CH_2); HRMS (ES) Found: MH^+, 250.1591. $C_{18}H_{19}N$ requires MH^+ 250.1590; LRMS *m/z* (ES) 250 (100%, MH^+). The compound is commercially available, data has not been provided.[200]

Amine **187** (30 mg, 25%) as a gum; R_f 0.25 [petrol–EtOAc (80:20)]; FTIR υ_{max} (film)/cm^{-1} 2950, 2920, 1600, 1450; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.58–7.56 (2H, m, 2 × CH), 7.32–7.28 (2H, m, 2 × CH), 7.20–7.10 (5H, m, 5 × CH), 3.90 (1H, d, *J* 16 Hz, CH), 3.79 (1H, d, *J* 16 Hz, CH), 3.24 (1H, t, *J* 7.5 Hz, CH), 3.14 (1H, d, *J* 16 Hz, CH), 2.95 (1H, d, *J* 16 Hz, CH), 2.70 (1H, q, *J* 7.5 Hz, CH), 2.15–2.09 (1H, m, CH), 1.85–1.69 (3H, m, 3 × CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.4 (C), 136.5 (C), 135.4 (C), 128.4 (CH), 127.9 (CH), 126.5 (CH),126.4 (CH), 126.0 (CH), 125.8 (CH), 125.4 (CH), 65.4 (C), 53.0 (CH_2), 50.0 (CH_2), 41.6 (CH_2), 36.7

(CH_2), 22.1 (CH_2); HRMS (ES) Found: MH^+, 250.1591. $C_{18}H_{19}N$ requires MH^+ 250.1589; LRMS *m/z* (ES) 250 (100%, MH^+). Data in accordance with the literature.[201]

(6*S*,11b*R*)-6-Phenyl-1H,2H,3H,4H,6H,7H,11bH-pyrido[2,1-a]isoquinoline 188 and 11a-Phenyl-1H,2H,3H,4H,6H,11H-pyrido[1,2-b]isoquinoline 189

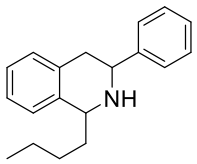


Using general procedure A, THIQ **175** (0.15 g, 0.48 mmol), *n*-BuLi (2.4 mL, 0.57 mmol), and $Br(CH_2)_4Br$ (0.17 mL, 1.44 mmol) gave the protected carbamates as inseparable products. Trifluoroacetic acid (2.7 mL, 0.20 mmol) was added to a solution of the crude products (0.24 g, 0.54 mmol) in CH_2Cl_2 (5 mL) and the mixture was stirred at room temperature. After 4 h, the solvent was evaporated and aqueous NaOH (5 mL, 1 M) was added. After 1 h, the mixture was extracted using CH_2Cl_2 (2 × 20 mL). The combined extracts were dried ($MgSO_4$), and the solvent was evaporated. Purification by column chromatography on silica, eluting with petrol–EtOAc (95:5), gave the amines **188** and **189** as separable regioisomers in 2:1 ratio (0.11 g, 87%).

Amine **188** (80 mg, 63%) as a gum; R_f 0.22 [petrol–EtOAc (80:20)]; FTIR υ_{max} (film)/cm^{-1} 3005, 2970, 1480; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.33–7.32 (3H, m, 3 × CH), 7.21–7.15 (6H, m, 6 × CH), 4.24 (1H, t, *J* 6 Hz, CH), 3.60–3.58 (1H, m, CH), 3.49–3.44 (1H, m, CH), 3.10–2.97 (2H, m, 2 × CH), 2.45–2.39 (1H, m, CH), 2.15–2.12 (1H, m, CH), 1.89–1.86 (1H, m, CH), 1.73–1.60 (2H, m, 2 × CH), 1.50–1.43 (2H, m, 2 × CH); [lit.[126] (for cis-isomer) 7.42–7.36 (4H, m, 4 × CH), 7.32–7.29 (2H, m, 2 × CH), 7.22 (2H, dd, *J* 8.1, 7.3 Hz, CH_2), 7.16 (3H, dd, *J* 8.1, 7.3 Hz, 3 × CH), 7.05 (1H. d, *J* 7.3 Hz, CH), 3.51 (1H, dd, *J* 11.4 Hz, CH), 3.41 (1H, d, *J* 10.7 Hz, CH), 3.26 (1H. dd, *J* 16, 11.4 Hz, CH), 2.90–2.86 (2H, m, 2 × CH), 2.44 (1H, dd, *J* 16, 3.2 Hz, CH), 1.94–1.91 (1H, m, CH), 1.87–1.82 (1H, m, CH), 1.67–1.48 (4H, m, 4 × CH)]; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 144.9 (C), 139.5 (C), 133.6 (C), 128.7 (CH), 128.6 (CH), 128.1 (CH), 127.4 (CH), 126.2 (CH), 125.7 (CH), 125.5 (CH), 60.3 (CH), 57.7 (CH), 52.3 (CH_2), 36.0 (CH_2), 31.2 (CH_2), 25.0 (CH_2), 23.3 (CH_2); HRMS (ES) Found: MH^+, 264.1748. $C_{19}H_{21}N$ requires MH^+ 264.1747; LRMS *m/z* (ES) 264 (100%, MH^+).

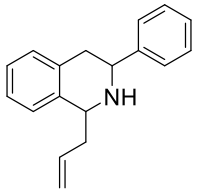
Amine **189** (30 mg, 24%) as a gum; R_f 0.54 [petrol–EtOAc (80:20)]; FTIR υ_{max} (film)/cm^{-1} 2960, 2940, 1450; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56–7.55 (2H, m, 2 × CH), 7.28–7.21 (3H, m, 3 × CH), 7.18–7.13 (2H, m, 2 × CH), 7.10–7.05 (1H, m, CH), 6.87–6.85 (1H, m, CH), 3.83 (1H, d, *J* 17 Hz, CH), 3.58 (1H, d, *J* 17 Hz, CH), 3.41 (1H, d, *J* 17 Hz, CH), 3.02 (1H, d, *J* 17 Hz, CH), 2.88–2.83 (2H, m, 2 × CH), 1.88–1.78 (3H, m, 3 × CH), 1.72–1.61 (3H, m, 3 × CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 147.0 (C), 134.1 (C), 133.5 (C), 128.6 (CH), 128.1 (CH), 126.7 (CH), 126.5 (CH), 126.4 (CH), 125.8 (CH), 125.7 (CH), 58.8 (C), 53.3 (CH_2), 49.2 (CH_2), 40.1 (CH_2), 26.2 (CH_2), 25.8 (CH_2), 21.1 (CH_2); HRMS (ES) Found: MH$^+$, 264.1748. $C_{19}H_{21}N$ requires MH$^+$ 264.1745; LRMS *m/z* (ES) 264 (100%, MH$^+$).

1-Butyl-3-phenyl-1,2,3,4-tetrahydroisoquinoline 190



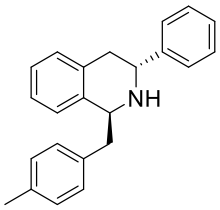
Trifluoroacetic acid (0.06 mL, 0.54 mmol) was added to a 4:1 mixture of crbamates **177f** and **178f** in (4:1) ratio (0.1 g, 0.27 mmol) in CH_2Cl_2 (5 mL) at room temperature. After 4 h, the solvent was evaporated and aqueous NaOH (10 mL, 1 M) was added. After 1 h, the mixture was extracted with CH_2Cl_2 (2 × 50 mL). The combined extracts were dried ($MgSO_4$), and the solvent was evaporated. Purification by column chromatography on silica, eluting with petrol–EtOAc (95:5), gave the amine **190** (51 mg, 71%) as an oil; R_f 0.45 [petrol–EtOAc (80:20)]; FTIR υ_{max} (film)/cm^{-1} 3315, 2955, 2920, 1490, 1450; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.51–7.48 (2H, m, 2 × CH), 7.42–7.38 (2H, m, 2 × CH), 7.34–7.30 (1H, m, CH), 7.20–7.11 (4H, m, 4 × CH), 4.28–4.24 (1H, m, CH), 4.15–4.12 (1H, m, CH), 3.01–2.99 (2H, m, 2 × CH), 2.10 (1H, br s, NH), 1.99–1.93 (1H, m, CH), 1.77–1.71 (1H, m, CH), 1.52–1.28 (7H, m, 4 × CH & CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 149.4 (C), 139.3 (C), 134 (C), 129.0 (CH), 128.6 (CH), 127.4 (CH), 127.0 (CH), 126.8 (CH), 126.1 (CH), 125.7 (CH), 56.4 (CH), 51.6 (CH), 37.7 (CH_2), 36.3 (CH_2), 29.1 (CH_2), 22.6 (CH_2), 14.1 (CH_3); HRMS (ES) Found: MH$^+$, 266.1902. $C_{19}H_{24}N$, requires MH$^+$; 266.1909, LRMS *m/z* (ES) 266 (100%, MH$^+$).

3-Phenyl-1-(prop-2-en-1-yl)-1,2,3,4-tetrahydroisoquinoline 191



Trifluoroacetic acid (0.20 mL, 2.63 mmol) was added to a 2.3.:1 mixture of carbamates **177b** and **178b** (0.46 g, 1.31 mmol) in CH_2Cl_2 (12 mL). The mixture was stirred for 4 h at room temperature, the solvent was evaporated and aqueous NaOH (10 mL, 1 M) was added. After 1 h, the mixture was extracted with CH_2Cl_2 (2 × 50 mL). The combined extracts were dried ($MgSO_4$), evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (65:35), to give the amine **191** (0.17 g, 60%) as an oil; R_f 0.37 [petrol–EtOAc (80:20)]; FTIR υ_{max} (film)/cm^{-1} 3350, 2955, 2920, 1630, 1490; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.48–7.46 (2H, m, 2 × CH), 7.41–7.37 (2H, m, 2 × CH), 7.34–7.30 (1H, m, CH), 7.20–7.12 (4H, m, 4 × CH), 5.92 (1H, dddd, *J* 15, 9, 6, 3 Hz, CH), 5.21–5.16 (2H, m, 2 × CH), 4.33–4.14 (2H, m, 2 × CH), 3.09–2.96 (2H, m, 2 × CH), 2.77–2.68 (1H, m, CH), 2.62–2.56 (1H, m, CH), 2.12 (1H, br s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 144.3 (C), 138.0 (C), 135.9 (CH), 134.8 (C), 129.0 (CH), 128.6 (CH), 127.4 (CH), 127.0 (CH), 126.9 (CH), 126.3 (CH), 125.8 (CH), 118.4 (CH_2), 55.7 (CH), 51.6 (CH), 41.3 (CH_2), 37.8 (CH_2); HRMS (ES) Found: MH^+, 250.1593. $C_{18}H_{19}N$ requires MNH^+ 250.1590; LRMS *m/z* (ES) 250 (100%, MNa^+).

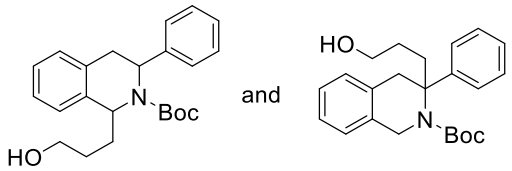
(1*S*,3*R*)-1-(4-Methylbenzyl)-3-phenyl-1,2,3,4-tetrahydroisoquinoline 192



Trifluoroacetic acid (0.13 mL, 1.78 mmol) was added to a 3:1 mixture of tetrahydroisoquinolines **177d** and **178d** (0.37 g, 0.9 mmol) in CH_2Cl_2 (10 mL) at room temperature. After 4 h, the solvent was evaporated and aqueous NaOH (5 mL, 1 M) was added. After 1 h, the mixture was extracted with CH_2Cl_2 (2 × 50 mL). The combined extracts were dried ($MgSO_4$), evaporated and purified by column chromatography on silica gel, eluting with petrol–EtOAc (60:40), gave the amine **192** (0.16 g, 57%) as plates; m.p 71–73 °C; R_f 0.4 [petrol–EtOAc (80:20)]; FTIR υ_{max} (film)/cm^{-1} 3315, 3020, 2920, 1515, 1490; ^{1}H NMR (400

MHz, $CDCl_3$) δ = 7.48–7.46 (2H, m, 2 × CH), 7.40–7.37 (2H, m, 2 × CH), 7.34–7.22 (4H, m, 4 × CH), 7.18–7.13 (5H, m, 5 × CH), 4.40–4.37 (2H, m, 2 × CH), 3.21–3.15 (1H, m, CH), 3.11–2.98 (3H, m, 3 × CH), 2.35 (3H, s, CH_3), 1.94 (1H, br s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 144.1 (C), 137.9 (C), 136.0 (C), 135.9 (C), 134.7 (C), 129.5 (CH), 129.1 (CH), 129.0 (CH), 128.6 (CH), 127.4 (CH), 127.2 (CH), 126.9 (CH), 126.4 (CH), 125.8 (CH), 58.4 (CH), 51.8 (CH), 42.4 (CH_2), 38.1 (CH_2), 21.0 (CH_3); HRMS (ES) Found: MH^+, 314.1914. $C_{23}H_{23}N$ requires MH^+ 314.1903; LRMS *m/z* (ES) 314 (100%, MH^+).

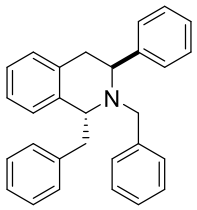
***tert*-Butyl 1-(3-hydroxypropyl)-3-phenyl-3,4-dihydro-1H-isoquinoline-2-carboxylate 203 and *tert*-Butyl 3-(3-hydroxypropyl)-3-phenyl-1,4-dihydroisoquinoline-2-carboxylate 204**



9-BBN [(1.14 mL, 0.57 mmol), 0.5 M in THF] was added to a mixture of compounds **177b** and **178b** in 2.3:1 ratio (0.1 g, 0.28 mmol) in THF (3 mL) at –30 °C. After 3 h, aqueous H_2O_2 (30%, 0.2 mL) was added. After 1 h, aqueous NaOH (0.28 mL, 1 M) was added and the mixture was allowed to warm to room temperature. After 24 h, brine (3 mL) was added, and the mixture was extracted using EtOAc (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (93:7), gave the alcohols **203** and **204** as inseparable regioisomers in 4:1 ratio (21 mg, 24%) as an oil; R_f 0.2 [petrol–EtOAc (80:20)]; FTIR υ_{max} (film)/cm^{-1} 3460, 3005, 2920, 1690, 1450, 1170, 1160; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.21–7.20 (2H, m, 2 × CH), 7.10–7.07 (4H, m, 4 × CH), 6.90–6.88 (1H, m, CH), 6.80–6.78 (2H, m, 2 × CH), 5.32–5.30 (0.8H, m, CH), 5.24–5.22 (0.8H, m, CH) 5.14 (0.2H, d, *J* 15 Hz, CH), 4.40 (0.2H, d, *J* 15 Hz, CH), 3.81–3.75 (2H, m, 2 × CH), 3.57 (0.8H, dd, *J* 15, 6 Hz, CH), 3.30 (0.2H, d, *J* 15 Hz, CH), 2.84 (0.8H, d, *J* 15 Hz, CH), 2.75 (0.2H, d, *J* 15 Hz, CH), 2.55 (1H, br s, OH), 2.15–2.12 (1H, m, CH), 1.76–1.67 (3H, m, 3 × CH), 1.30–1.18 (9H, m, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers, 2 aromatic CH and one C (*t*-Bu) couldn't be observed) δ = 155.5 & 155.3 (2 × C=O), 146.4 & 144.9 (C), 138.0 (C), 136.8 (C), 135.4 (C), 132.2 (C), 131.5 (C), 128.8 (CH), 127.7 (CH), 127.6 (CH), 127.3 (CH), 126.9 (CH), 126.6 (CH), 126.5 (CH), 126.2 (CH), 125.8 (CH), 125.5 (2 × CH), 124.5 (CH), 80.0 (C), 63.2 (C), 62.0 (CH_2), 60.8 (CH_2), 56.6 (CH), 55.6 (CH), 44.5 (CH_2), 36.3 (CH_2), 35.8 (CH_2), 33.7 (CH_2), 32.5 (CH_2), 29.7 (CH_2), 28.8 (CH_2),

28.0 (2 × CH_3); HRMS (ES) Found: MNa^+, 390.2044. $C_{23}H_{29}NO_3Na$ requires MNa^+ 390.2040; LRMS *m/z* (ES) 390 (100%, MNa^+).

1,2-Dibenzyl-3-phenyl-3,4-dihydro-1H-isoquinoline 205



Benzyl bromide (0.05 mL, 0.4 mmol) was added to a mixture of triethylamine (0.06 mL, 0.4 mmol) and amine **182** (60 mg, 0.2 mmol) in THF (3 mL) at room temperature. After 16 h, the mixture was washed with saturated aqueous citric acid (2 mL), and dried ($MgSO_4$), the solvent was evaporated and the residue was purified by column chromatography on silica, eluting with petrol–EtOAc (97:3), to give the amine **205** (71 mg, 91%) as an amorphous solid; m.p 65–68 °C; R_f 0.48 [petrol–EtOAc (90:10)]; FTIR υ_{max} (film)/cm^{-1} 3060, 3025, 2925, 1600, 1490; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60–7.58 (2H, m, 2 × CH), 7.39–7.35 (2H, m, 2 × CH), 7.31–7.30 (3H, m, 3 × CH), 7.25–7.20 (4H, m, 4 × CH), 7.13–7.10 (3H, m, 3 × CH), 7.07–7.03 (3H, m, 3 × CH), 6.79–6.78 (2H, m, 2 × CH), 4.78 (1H, dd, *J* 11, 5 Hz, CH), 4.03 (1H, dd, *J* 11, 5 Hz, CH), 3.51 (1H, d, *J* 14 Hz, CH), 3.37–3.17 (4H, m, 4 × CH), 3.02 (1H, dd, *J* 14, 5 Hz, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 142.4 (C), 140.0 (C), 139.4 (C), 137.7 (C), 134.1 (C), 130.5 (CH), 129.7 (CH), 129.4 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 128.0 (CH), 127.8 (CH), 127.3 (CH), 126.8 (CH), 126.2 (CH), 126.0 (CH), 61.5 (CH), 52.9 (CH), 50.1 (CH_2), 43.1 (CH_2), 27.1 (CH_2); HRMS (ES) Found: MH^+, 390.2219. $C_{29}H_{27}N$ requires MH^+ 390.2216; LRMS *m/z* (ES) 390 (100%, MH^+).

5.4 Chapter 4 Experimental

General procedure G: Deprotonation and electrophilic quench using LDA

n-BuLi (1.2 equiv., 2.5 M in hexane) was added to a stirred solution of $^{i}Pr_2NH$ (1.2 equiv., 0.24 mmol) in THF (2 mL) at 0 °C. After 1 h, the mixture was cooled to –78 °C and nitrile (1.0 equiv.) in solvent (0.2 M) was added. After 15 min, the electrophile (0.6 mmol, 3 equiv.) was added. The mixture was allowed to warm to room temperature and aqueous NH_4Cl (2 mL) was added. The mixture was extracted with CH_2Cl_2 (2 mL), the combined extracts were dried ($MgSO_4$), the solvent was evaporated, and the residue was purified by column chromatography on silica gel as described below.

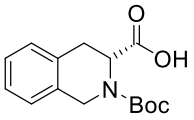
General procedure H: Preparation of TMPMgCl

TMPH (3 mL, 18 mmol) was added to $^{i}PrMgCl$ (9 mL, 18 mmol, 2 M in Et_2O) under Argon at room temperature and left to stir for 18 hours in the dark. Et_2O (6 mL) was added, the mixture was titrated against iodine to determine the concentration.[202]

General procedure I: Deprotonation and electrophilic quench using TMPMgCl

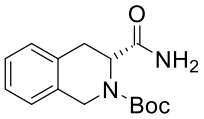
TMPMgCl (0.6 mmol, 3 equiv., 0.45 M in Et_2O) was added to the nitrile (0.2 mmol, 1 equiv.) in Ether or CPME (1 mL) at –104 °C, then the electrophile (0.6 mmol, 3 equiv) was present *in situ* or after 10 seconds. After 30 min, NH_4Cl (2 mL) was added. The solvent was evaporated and the residue was extracted using CH_2Cl_2 (10 mL x 3), the combined extracts were dried ($MgSO_4$), the solvent was evaporated and the residue purified by column chromatography on silica gel as described below.

(3*R*)-2-(*tert*-Butoxycarbonyl)-3,4-dihydro-1H-isoquinoline-3-carboxylic acid 245



Triethylamine (7.4 mL, 53 mmol) was added to carboxylic acid **244** (4.3 g, 24 mmol) in THF (30 mL) at room temperature. The mixture was cooled to 0 °C and di-tert-butyl dicarbonate (5.8 g, 26.7 mmol) was added dropwise over 10 min. After 4 h saturated citric acid solution was added until the mixture reached pH 2, THF was evaborated uder vacume, and the residue was extracted using CH_2Cl_2 (3 x 250 mL), the organic layer was washed with brine (2 × 60 mL) then water (60 mL × 2), the combined organic layer was dried ($MgSO_4$), and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH (90:10), to give the acid **245** (4.8 g, 71%) as an oil; R_f 0.6 [CH_2Cl_2–MeOH (80:20)]; $[\alpha]_D^{25}$ +16.5 (1, MeOH) [lit.[203] $[\alpha]_D$ [22] +20.9 (0.50, MeOH)]; ^{1}HNMR (400 MHz, $CDCl_3$, rotamers) δ = 10.10 (1H, br s, OH), 7.20–7.10 (4H, m, CH), 5.15 (0.5H, br s, CH), 4.77–4.66 (1.5H, m, CH), 4.54–4.46 (1H, m , CH), 3.29–3.17 (2H, m, 2 × CH), 1.53 (4.5H, s, *t*-Bu), 1.42 (4.5H, s, *t*-Bu). Data in accordance with the literature.[203]

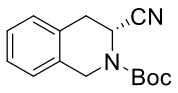
***tert*-Butyl (3*R*)-3-carbamoyl-3,4-dihydro-1H-isoquinoline-2-carboxylate 246**



Triethyl amine (1.5 mL, 10.8 mmol) was added to a solution of the acid **245** (3.0 g, 10.8 mmol) in THF (30 mL), the mixture was allowed to cool to –10 °C and ethyl chloroformate (2.4 mL, 24.9 mmol) was added dropwise over 10 min. After 30 min, ammonia in methanol [10.8 mL, 21.6 mmol, 2 M] was added. After 16 h, the solvent was evaporated, EtOAc (30 mL) was added and the mixture was filtered. The filtrate was washed with brine (20 mL), dried ($MgSO_4$), and the solvent was evaporated. Purification by column chromatography on silica, eluting with CH_2Cl_2–MeOH (95:5), gave the amide **246** (2.6 g, 88%), as an oil; R_f 0.55 [CH_2Cl_2– MeOH (90:10)]; $[\alpha]_D^{23}$ + 3.1 (1, $CHCl_3$); FTIR υ_{max} (film)/ cm^{-1} 3010, 2960, 1680, 1670, 1390; 1H NMR (400 MHz, CDCl3, rotamers) δ = 7.19–7.16 (4H, m, 4 × CH), 6.13–6.01 (2H, m, NH_2), 5.04–4.88 (0.5H, m, CH), 4.61–4.52 (2.5H, m, CH), 3.25–3.06 (2H, m, 2 × CH), 1.46 (9H, s, *t*-Bu); NMR (400 MHz, $CDCl_3$, rotamers) δ = 175.1 & 174.1 (C=O), 155.1 & 154.4 (C=O), 133.8 (C), 133.5 & 133.0 (C), 128.3 & 127.8 (CH), 127.4 & 127.2 (CH), 126.9 & 126.5 (CH), 126.1 & 125.8 (CH), 81.2 (C), 56.3 (CH), 44.9 & 44.2 (CH_2), 31.7 & 30.4 (CH_2), 28.3 (CH_3);

HRMS (ES) Found: MH^+, 277.1552. $C_{15}H_{21}N_2O_3$ requires MH^+; 277.1544, LRMS *m/z* (ES) 277 (100%, MH^+). No data were reported. [204]

***tert*-Butyl (3R)-3-cyano-3,4-dihydro-1H-isoquinoline-2-carboxylate 247**



Trifluoroacetic anhydride (1.8 mL, 12.9 mmol) was added to the amide **246** (3.0 g, 10.8 mmol) and triethylamine (1.5 mL, 10.8 mmol) in THF (15 mL) at 0 °C. The mixture was allowed to warm to room temperature. After 4 h, water (20 mL) was added and THF was evaporated. The aqueous layer was extructed with CH_2Cl_2 (40 mL × 2), then washed with aqueous HCl (10 mL, 0.1 M) and NaOH (10 mL, 0.1 M), dried ($MgSO_4$) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (96:6), gave the nitrile **247** (1.7 g, 61%) as an amorphous solid; m.p 105–108 °C; $[\alpha]_D^{25}$ +14 (1, $CHCl_3$); R_f 0.40 [petrol–EtOAc (80:20)]; FTIR υ_{max} (film)/cm^{-1} 2980, 2945, 2240, 1700, 1170; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.31–7.24 (2H, m, 2 × CH), 7.22–7.18 (2H, m, 2 × CH), 5.60 (0.6H, br s, CH), 5.28 (0.4H, br s, CH), 4.81 (1H, d, *J* 17 Hz, CH), 4.51 (1H, d, *J* 17 Hz, CH), 3.30–3.28 (0.4H, m, CH), 3.26–3.24 (0.6H, m, CH), 3.11–3.10 (0.6H, m, CH), 3.07–3.06 (0.4H, m, CH), 1.55 (9H, s, *t*-Bu); NMR (400 MHz, $CDCl_3$, rotamers) δ = 153.9 (C=O), 131.8 (C), 130.1 (C), 128.9 (CH), 127.4 (CH), 127.2 (CH), 126.4 (CH), 117.8 (C), 81.9 (C), 43.7 (CH_2), 41.6 (CH), 32.4 (CH_2), 28.3 (CH_3); HRMS (ES) Found: MH+, 259.1456. $C_{15}H_{19}N_2O_2$ requires MH^+ 259.1447; LRMS *m/z* (ES) 259 (100%, MH^+).

ReactIR monitoring of the lithiation of *tert*-Butyl (3*R*)-3-Cyano-3,4-dihydro-1H-isoquinoline-2-carboxylate 247 by *n*-BuLi in THF (Figure 4-8)

THF (12 mL) was added to a flask equipped with a stirrer bar and ReactIR probe at room temperature under Ar. After cooling to –78 °C, a solution of 3-cyano-*N*-Boc-tetrahydroisoquinoline **247** (0.5 g, 2.0 mmol) in THF (2 mL) was added. The solution was stirred for 10 min to verify the stability of the readout on the ReactIR. *n*-BuLi (1.0 mL, 2.5 mmol, 2.5 M in hexane) was added. The solution was stirred for 10 min.

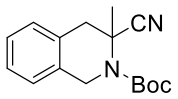
For 3-cyano-*N*-Boc-tetrahydroisoquinoline **247**, a peak at 1710 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of *n*-BuLi, a new peak at 1657 cm^{-1} appeared which was assigned to $\nu_{C=O}$ of lithiated intermediate **249**. After a lithiation time of 2 min, the lithiation of 3-cyano-*N*-Boc-tetrahydroisoquinoline **247** to intermediate **249** was completed.

ReactIR monitoring of the deprotonation of *tert*-Butyl (3*R*)-3-cyano-3,4-dihydro-1H-isoquinoline-2-carboxylate X by TMPMgCl in THF (Scheme 4-11)

THF (12 mL) was added to a flask equipped with a stirrer bar and ReactIR probe at room temperature under Ar. After cooling to –104 °C, a solution of 3-cyano-*N*-Boc-tetrahydroisoquinoline **247** (0.5 g, 2.0 mmol) in THF (2 mL) was added. The solution was stirred for 10 min to verify the stability of the readout on the ReactIR. TMPMgCl (11.1 mL, 5.0 mmol, 0.45 M in Et_2O) was added. The solution was stirred for 10 min.

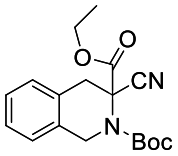
For 3-cyano-*N*-Boc-tetrahydroisoquinoline **247**, a peak at 1704 cm^{-1} was observed which was assigned to $\nu_{C=O}$. After addition of TMPMgCl, a new peak at 1627 cm^{-1} appeared which was assigned to $\nu_{C=O}$ of magnesiated intermediate **250**. After a deprotonation time of 7 min, the deprotonation of *N*-Boc-tetrahydroisoquinoline **247** to intermediate **250** was completed.

***tert*-Butyl 3-cyano-3-methyl-1,4-dihydroisoquinoline-2-carboxylate 248a**



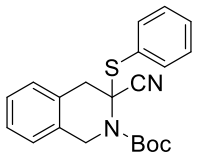
Using general procedure G, *n*-BuLi (0.18 mL, 0.46 mmol), $^{i}Pr_2NH$ (0.06 mL, 0.46 mmol), nitrile **247** (100 mg, 0.38 mmol) and MeI (0.06 mL, 1.14 mmol) gave after purification by column chromatography on silica gel, eluting with petrol–EtOAc (99:1), compound **248a** (47 mg, 46%) as an amorphous solid; m.p 126–128 °C; R_f 0.36 [petrol–EtOAc (90:10)]; FTIR υ_{max} (film)/cm^{-1} 2980, 2950, 2930, 2230, 1700, 1160; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.33–7.28 (3H, m, 3 × CH), 7.25–7.22 (1H, m, CH), 4.57 (1H, d, *J* 15 Hz, CH), 4.51 (1H, d, *J* 15 Hz, CH), 3.39 (1H, d, *J* 15 Hz, CH), 3.08 (1H, d, *J* 15 Hz, CH), 1.66 (3H, s, CH_3), 1.57 (9H, s, t-Bu); NMR (400 MHz, CDCl3, rotamers) δ = 153.7 (C=O), 135.0 (C), 132.4 (C), 128.1 (CH), 127.8 (CH), 127.6 (CH), 126.0 (CH), 121.3 (C), 82.4 (C), 52.0 (C), 44.8 (CH_2), 42,3 (CH_2), 28.4 (CH_3), 26.1 (CH_2) ; HRMS (ES) Found: MH+, 273.1612. $C_{16}H_{21}N_2O_2$ requires MH^+ 273.1603; LRMS *m*/*z* (ES) 273 (100%, MH^+). Enantiomers were resolved by chiral stationary phase HPLC using cellulose1 column with 3% IPA in hexane at 1 mL/min, detection at 220 nm. The enantiomers had a retention time of 11.3 and 12.7 min.

2-*tert*-Butyl 3-Ethyl 3-Cyano-1,4-dihydroisoquinoline-2,3-dicarboxylate 248b



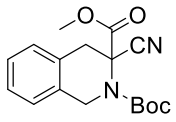
Using general procedure G, *n*-BuLi (0.12 mL, 0.27 mmol), $^{i}Pr_2NH$ (0.04 mL, 0.27 mmol), nitrile **247** (60 mg, 0.23 mmol) and EtOCOCl (0.07 ml, 0.69 mmol) gave after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), nitrile **248b** (29 mg, 38%) as an oil; R_f 0.38 [petrol–EtOAc (80:20)]; FTIR υ_{max} (film)/cm^{-1} 3005, 2985, 1750, 1700, 1165; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.35–7.29 (4H, m, CH), 4.86 (1H, d, *J* 15 Hz, CH), 4.43 (1H, d, *J* 15 Hz, CH), 4.31 (2H, q, *J* 7 Hz, CH_2), 3.42 (1H, d, *J* 15 Hz, CH), 3.31 (1H, d, *J* 15 Hz, CH), 1.50 (9H, s, *t*-Bu), 1.33 (3H, t, *J* 7 Hz, CH_3); NMR (400 MHz, $CDCl_3$, rotamers, aromatic CH could be missing) δ = 167.3 (C=O), 152.8 (C=O), 133.8 (C), 130.6 (C), 128.2 (2 × CH), 127.3 (CH), 126.2 (CH), 117.4 (C), 83.4 (C), 63.3 (C), 44.2 (CH_2), 38.7 (CH_2), 29.7 (CH_2), 28.1 (CH_3), 14.0 (CH_3); HRMS (ES) Found: MH$^+$, 330.1620. $C_{18}H_{22}N_2O_4$, requires MH$^+$; 333.1624, LRMS *m*/*z* (ES) 333 (100%, MH$^+$). Enantiomers were resolved by chiral stationary phase HPLC using cellulose1 column with 7% IPA in hexane at 1 mL/min, detection at 220 nm. The enantiomers had a retention time of 10.4 min and 11.6 min.

tert-Butyl 3-cyano-3-[(phenylsulfanyl)methyl]-1,4-dihydroisoquinoline-2-carboxylate 248c



Using general procedure G, *n*-BuLi (0.19 mL, 0.45 mmol), $^{i}Pr_2NH$ (0.06 mL, 0.46 mmol), nitrile **247** (100 mg ,0.38 mmol) and *S*-Phenyl benzenethiosulfonate (0.5 g, 2.03 mmol) gave after purification by column chromatography on silica gel, eluting with petrol–EtOAc (99:1), nitrile **248c** as an oil (41 mg, 19%); R_f 0.35 [petrol–EtOAc (80:20)]; FTIR υ_{max} (film)/cm^{-1}; 3000, 2960, 2240, 1700, 1160; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.61–7.58 (1H, m, CH), 7.57–7.55 (1H, m, CH), 7.53–7.51 (2H, m, 2 × CH), 7.54–7.42 (3H, m, 3 × CH), 7.24–7.23 (1H, m, CH), 7.17–7.13 (1H, m, CH), 4.66 (1H, d, *J* 15 Hz, CH), 4.44 (1H, d, *J* 15 Hz, CH), 3.40 (1H, d, *J* 15 Hz, CH), 3.27 (1H, d, *J* 15 Hz, CH), 1.59 (9H, s, *t*-Bu); NMR (400 MHz, $CDCl_3$, rotamers) δ = 153.0 (C=O), 137.5 (2 × CH), 134.0 (C), 131.0 (C), 130.5 (CH), 129.6 (C), 129.4 (CH), 127.9 (2 × CH), 126.0 (CH), 118.4 (C), 83.4 (C), 61.2 (C), 45.2 (CH_2), 41.3 (CH_2), 28.3 & 28.1 (CH_3); HRMS (ES) Found: MH$^+$, 367.1483. $C_{21}H_{23}N_2O_2S$ requires MH$^+$ 367.1480; LRMS m/z (ES) 367 (100%, MH$^+$). Enantiomers were resolved by chiral stationary phase HPLC using cellulose1 column with 3% IPA in hexane at 1 mL/min, detection at 220 nm. The enantiomers had a retention time of 9.9 min and 11.5 min.

2-*tert*-Butyl 3-methyl 3-cyano-1,4-dihydroisoquinoline-2,3-dicarboxylate 248d



Using general procedure G, *n*-BuLi (0.18 mL, 0.46 mmol, 2.5 M in hexane), $^{i}Pr_2NH$ (0.06 mL, 0.46 mmol), nitrile **247** (100 mg, 0.38 mmol) and MeOCOCN (0.1 mL, 1.35 mmol) gave after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), nitrile **248d** (21 mg, 17%) as an amorphous solid; m.p 128–131 °C; R*f* 0.23 [petrol–EtOAc (90:10)]; FTIR υ_{max} (film)/cm^{-1} 3010, 2980, 2245,1760, 1705, 1160; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.35–7.28 (4H, m, 4 × CH), 4.90 (1H, d, *J* 15 Hz, CH), 4.39 (1H, d, *J* 15 Hz, CH), 3.89 (3H, s, CH_3), 3.42 (1H, d, *J* 15 Hz, CH), 3.30 (1H, d, *J* 15 Hz, CH), 1.50 (9H, s, *t*-Bu); ^{13}C NMR (400 MHz, $CDCl_3$, rotamers) δ = 168.0 (C=O), 152.7 (C=O), 134.8 (C), 130.4 (C), 128.3 (2 × CH), 127.4 (CH), 126.3 (CH), 117.3 (C), 83.4 (C), 59.9 (C), 53.9 (CH_3), 44.2 (CH_2), 38.6 (CH_2), 28.1 (CH_3); HRMS (ES) Found: MH$^+$, 317.1499. $C_{17}H_{21}N_2O_4$ requires MH$^+$ 317.1501; LRMS m/z (ES) 317 (100%, MH$^+$). Enantiomers were resolved by chiral stationary phase HPLC using AD column with 5% IPA in hexane at 1 mL/min, detection at 220 nm. The enantiomers had a retention time of 14.7 and 16.3 min.

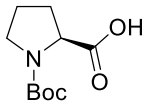
n-BuLi (0.11 mL, 0.27 mmol) was added to HMDS (0.05 mL, 0.25 mmol) in THF (2 mL) at –78 °C. After 15 min nitrile **247** (60 mg, 0.23 mmol) in THF (1 mL) was added. After 10 min MeOCOCN (0.05 mL, 0.69 mmol) was added. The mixture was allowed to warm to room temperature and NH_4Cl (3 mL) was added, the solvent was evaporated and the residue was extracted using CH_2Cl_2 (3 x 10 mL), the combined extracts were dried ($MgSO_4$), and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), gave nitrile **248d** (23 mg, 31%). Other data as above.

n-BuLi (0.14 mL, 0.32 mmol) was added to a mixture of KO^{t}Bu (30 mg, 0.32 mmol), and TMPH (0.05 mL, 0.29 mmol) in 2-MeTHF (2mL) at –78 °C. After 15 min the mixture was cooled to –104 °C and nitrile **247** (70 mg, 0.27 mmol) was added. After 10 sec, MeOCOCN (0.06 mL, 0.81 mmol) was added. After 30 min, aqueous NH_4Cl (3 mL) was added, solvent was evaporated and the residue was extracted using CH_2Cl_2 (3 × 10 mL), the combined extracts were dried ($MgSO_4$), the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), gave nitrile **248d** (32 mg, 37%) with enantiomeric ratio 50:50. Other data as above.

n-BuLi (0.23 mL, 0.58 mmol) was added to $^{i}Pr_2NH$ (0.07 mL, 0.58 mmol) in Et_2O (2 mL) at –5 °C. After 1 h, $^{i}PrMgCl$ [0.29 ml, 0.58 mmol, 2 M in Et_2O] was added, the mixture was allowed to warm to room temperature. After 2 h, the mixture was cooled to –104 °C and nitrile **247** (50 mg, 0.19 mmol) in CPME (1 mL) was added. After 10 sec, MeOCOCN (0.05 mL, 0.58 mmol) was added, the mixture was stirred for 30 min and aqueous NH_4Cl (3 mL) was added. The organic solvents were removed, and the residue was extracted using CH_2Cl_2 (3 × 10 mL), the combined extracts were dried ($MgSO_4$), and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), gave nitrile **248d** (12 mg, 20%) with enantiomeric ratio 48:52. Other data as above.

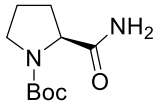
Using general procedure I, TMPMgCl (1.29 mL, 0.58 mmol, 0.45 M in Et_2O) was added to nitrile **247** (50 mg, 0.19 mmol) in CPME (1 mL) at –104 °C. After 10 seconds MeOCOCN (0.05 mL, 0.58 mmol) was added. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), gavecompound **248d** (21 mg, 34%) with enantiomeric ratio of 87:13; $[\alpha]_D^{25}$ + 20 (1, $CHCl_3$). Other data as above.

tert-Butyl (2*S*)-2-cyanopyrrolidine-1-carboxylate 255



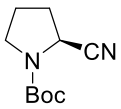
Aqueous NaOH [17.4 mL, 17.4 mmol, 1 M] was added to a solution of L-proline (1 g, 8.7 mmol) in 1,4-dioxane (6.4 mL). The mixture was stirred until L-proline began to dissolve. The mixture was allowed to cool to 0 °C and di-*tert*-butyl dicarbonate (2.3 g, 10.4 mmol) in 1,4-dioxane was added dropwise. After 30 min, the ice bath was removed and the mixture was allowed to warm to room temperature. After 4 h, 1,4-dioxane was evaporated, and saturated citric acid (20 mL) was added until the mixture reached pH 2. The mixture was extracted using CH_2Cl_2 (3 × 100 mL), the organic layer was washed with water (50 mL), dried ($MgSO_4$), and the solvent was evaporated to give without further purification acid **255** (1.51 g, 80%) as an amorphous solid; m.p. 130–132 °C (lit.[205] 133–136 °C); $[\alpha]_D^{23}$ –64 (1, CH_3COOH) [lit.[206] $[\alpha]D^{22}$ –61.1 (1, CH_3COOH)]; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ = 9.55 (1H, br s, OH), 4.38–4.35 (0.5H, m, CH), 4.27–4.24 (0.5H, m, CH), 3.60–3.55 (0.5H, m, CH), 3.51–3.45 (1H, m, CH), 3.40–3.34 (0.5H, m, CH), 2.34–2.25 (1H, m, CH), 2.16–2.03 (1H, m, CH), 2.00–1.87 (2H, m, 2 × CH), 1.49 (4H, s, *t*-Bu), 1.43 (5H, s, *t*-Bu). Data in accordance with the literature.[206]

***tert*-Butyl (2*S*)-2-carbamoylpyrrolidine-1-carboxylate 256**



Ethyl chlorofomate (7.1 mL, 74.3 mmol) was added to a mixture of carboxylic acid **255** (8.0 g, 37.2 mmol) and triethylamine (8.1 mL, 74.3 mmol) in THF (100 mL) at –10 °C. After 30 min, aqueous NH_4 [10.6 mL, 74.3 mmol, 7 M in MeOH] was added and the mixture was left to warm to room temperature. After 16 hours, the solvent was evaporated and EtOAc (60 mL) was added. The mixture was filtered, the filtrate was evaporated, dried ($MgSO_4$), and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with MeOH–CH_2Cl_2 (95:5), gave amid **256** (6.4 g, 80%) as an amorphous solid; m.p 97–99 °C [lit.[179] 103.6–107.7 °C]; $[\alpha]_D^{23}$ –46.0 (1, $CHCl_3$) [lit.[207] $[\alpha]_D^{25}$ –42.4 (1, MeOH)]; R_f 0.52 [MeOH–CH_2Cl_2 (30:70)]; FTIR υ_{max} (film)/cm^{-1} 3365, 3200, 2975, 1670, 1660; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 6.84 (0.5H, br s, NH_2), 6.24–5.80 (1.5H, m, NH_2), 4.32–4.11 (1H, m, CH), 3.51–3.27 (2H, m, 2 × CH), 2.33–1.81 (4H, m, 4 × CH), 1.43 (9H, s, t-Bu); ^{13}C NMR (400 MHz, $CDCl_3$, rotamers) δ = 176.1 & 175.0 (C=O), 155.9 & 154.7 (C=O), 80.6 (C), 61.1 & 59.8 (CH), 47.2 (CH_2), 31.2 (CH_2), 28.5 (CH_3), 24.6 & 23.9 (CH_2); HRMS (ES) Found: MH^+, 215.1392. $C_{10}H_{19}N_2O_3$ requires MH^+ 215.1396; LRMS *m*/*z* (ES) 215 (100%, MH^+). Data in accordance with the literature, only $[\alpha]_D$, ^{1}H NMR and m.p. were reported.[179]

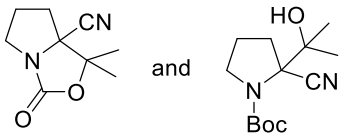
***tert*-Butyl (2*S*)-2-cyanopyrrolidine-1-carboxylate 257**



Trifluoroacetic anhydride (3.97 mL, 28.0 mmol) was added to amide **256** (5.0 g, 23.3 mmol) and triethylamine (6.50 mL, 46.7 mmol) in THF (25 mL) at 0 °C. The mixture was allowed to warm to room temperature. After 4 h, water (10 mL) was added, and THF was evaporated. The residue was taken in CH_2Cl_2 (50 mL) and washed with aqueous NaOH (20 mL, 0.1 M), the organic layer was dried ($MgSO_4$), and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), gave nitrile **257** (3.2 g, 70%) as an oil; $[\alpha]_D^{25}$ –94 (1.3, MeOH) [lit.[207] $[\alpha]_D^{22}$ –95.5 (1.5, MeOH]; R_f 0.45 [petrol–EtOAc (70:30)]; FTIR υ_{max} (film)/cm^{-1} 2975, 2160, 2230, 1700; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 4.36–4.28 (1H, m, CH), 3.34–3.26 (1H, m, CH), 3.20–3.11 (1H, m, CH), 2.11–2.02 (2H, m, 2 × CH), 1.92–1.83 (2H, m, 2 × CH), 1.32 (5H, s, *t*-Bu), 1.29 (4H, s, *t*-Bu); ^{13}C NMR (400 MHz, $CDCl_3$, rotamers) δ = 153.4 (C=O), 119.5 (C), 81.8 & 81.4 (C), 47.6 & 47.5 (CH), 46.4

& 46.1 (CH_2), 32.1 & 31.2 (CH_2), 28.7 (CH_3), 25.1 & 24.2 (CH_2); HRMS (ES) Found: MH^+, 197.1289. $C_{10}H_{17}N_2O_2$ requires MH^+ 197.1290; LRMS *m*/*z* (ES) 197 (100%, MH^+). Data in accordance with the literature. [179]

1,1-Dimethyl-3-oxo-dihydro-5H-pyrrolo[1,2-c][1,3]oxazole-7a-carbonitrile 258a & *tert*-Butyl 2-cyano-2-(2-hydroxypropan-2-yl) pyrrolidine-1-carboxylate 258b

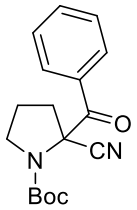


Using general procedure G, *n*-BuLi (0.31 mL, 0.76 mmol) and $^iPr_2NH$ (0.1 mL, 0.76 mmol) in THF (1 mL), nitrile **257** (100 mg, 0.5 mmol) in CPME (1 mL) and acetone (0.11 mL, 1.5 mmol) gave after purification by column chromatography on silica gel, eluting with petrol–EtOAc (70:30) the nitriles **258a** and **285b** in 37% yield.

Nitrile 258a (19 mg, 21%) as an oil; R_f 0.25 [petrol–EtOAc (50:50)]; FTIR υ_{max} (film)/cm^{-1} 2985, 2925, 2235, 1760, 1160, 1065; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ = 3.86–3.79 (1H, m, CH), 3.46–3.40 (1H, m, CH), 2.30–2.20 (4H, m, 4 × CH), 1.79 (3H, s, CH_3), 1.54 (3H, s, CH_3); ^{13}C NMR (400 MHz, $CDCl_3$, rotamers) δ = 154.8 (C=O), 118.0 (C), 73.1 (C), 61.2 (C), 46.0 (CH_2), 33.1 (CH_2), 28.2 (CH_3), 27.4 (CH_3), 22.8 (CH_2); HRMS (ES) Found: MNa^+, 203.0787. $C_9H_{12}N_2O_2$ requires MNa^+ 203.0796; LRMS m/z (ES) 203 (100%, MNa^+). No resolution conditions for the enantiomers were found

Nitrile **258b** (20 mg, 16%) as an amorphous solid; m.p 84–86 °C; R_f 0.3 [petrol–EtOAc (50:50)]; FTIR υ_{max} (film)/cm^{-1} 3350, 2970, 2245, 1670; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ = 6.68 (1H, br s, OH), 3.83–3.78 (1H, m, CH), 3.30–3.23 (1H, m, CH), 2.45–2.40 (1H, m, CH), 2.06–1.89 (3H, m, 3 × CH), 1.48 (9H, s, *t*-Bu), 1.32 (3H, s, CH_3), 1.13 (3H, s, CH_3); ^{13}C NMR (400 MHz, $CDCl_3$, rotamers) δ = 156.0 (C=O), 118.9 (C), 82.7 (C), 73.8 (C), 70.6 (C), 49.7 (CH_2), 38.4 (CH_2), 28.4 (CH_3), 26.7 (CH_3), 23.0 (CH_2), 22.9 (CH_3); HRMS (ES) Found: MH^+, 225.1706. $C_{13}H_{23}N_2O_3$ requires MH^+ 225.1709; LRMS *m*/*z* (ES) 225 (100%, MH^+). No resolution conditions for the enantiomers were found.

***tert*-Butyl 2-cyanopyrrolidine-1-carboxylate 258c**



Using general procedure G, *n*-BuLi (0.31 mL, 0.76 mmol) and $^{i}Pr_2NH$ (0.1 mL, 0.76 mmol) in THF (1 mL), nitrile **257** (100 mg, 0.5 mmol) in CPME (1 mL) and benzoyl chloride (0.17 mL, 1.5 mmol) gave after purification by column chromatography on silica gel, eluting with petrol–EtOAc (70:30), the nitrile **248c** (60 mg, 40%) as an amorphous solid; m.p 84–87 °C; R_f 0.3 [petrol–EtOAc (50:50)]; FTIR υ_{max} (film)/cm^{-1} 3005, 2990, 2250, 1720, 1695, 1165; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 8.00–7.95 (2H, m, 2 × CH), 7.66–7.62 (1H, m, CH), 7.53–7.49 (2H, m, 2 × CH), 3.90–3.84 (1H, m, CH), 3.76–3.69 (1H, m, CH), 2.83–2.77 (1H, m, CH), 2.62–2.54 (1H, m, CH), 2.23–2.17 (2H, m, 2 × CH), 1.26 (9H, s, *t*-Bu); ^{13}C NMR (400 MHz, $CDCl_3$, rotamers) δ = 171.1 (C=O), 152.1 (C=O), 133.9 & 133.4 (CH), 132.2 (C), 128.8 & 128.7 (CH), 128.5 & 128.3 (CH), 119.1 & 118.8 (C), 82.6 & 81.8 (C), 68.0 (C), 47.0 (CH_2), 39.0 & 38.2 (CH_2), 28.3 & 28.2 (CH_3), 23.8 & 23.5 (CH_2); HRMS (ES) Found: MNa^+, 323.1368. $C_{17}H_{20}N_2O_3Na$ requires MNa^+ 323.1366; LRMS *m*/*z* (ES) 323 (100%, MNa^+). Enantiomers were resolved by chiral stationary phase HPLC using cellulose 1 column with 3% IPA in hexane at 1 mL/min, detection at 220 nm. The enantiomers had a retention time of 19.3 and 22.6 min.

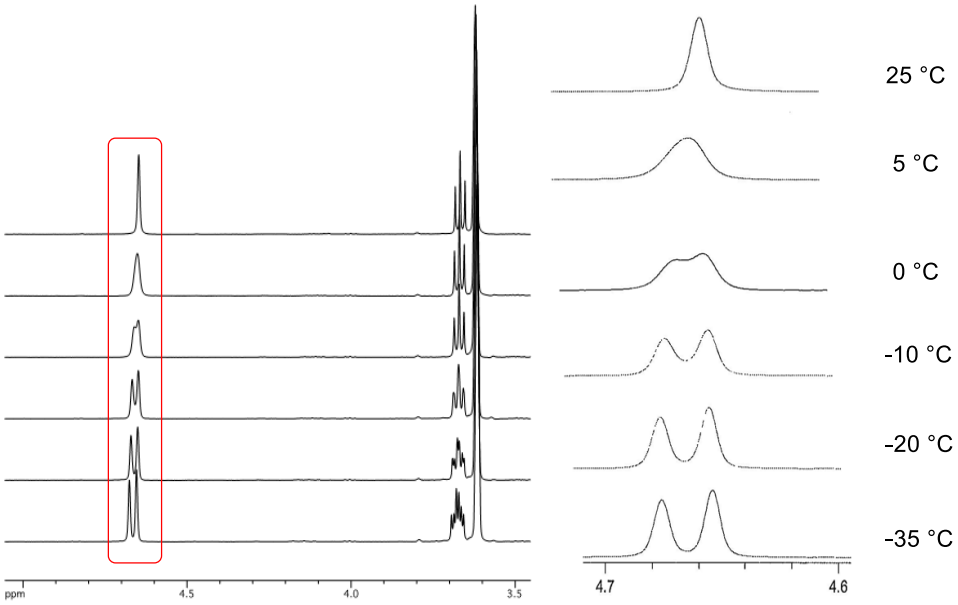
Using general procedure I, TMPMgCl [1.7 mL, 0.75 mmol, 0.45 M in Et_2O] and nitrile **257** (50 mg, 0.25 mmol) in Et_2O (1 mL) at –104 °C. After 10 seconds benzoyl chloride (0.09 mL, 0.75 mmol) was added. Purification as above gave nitrile **258c** (40 mg, 53%) as a solid; enantiomeric ratio 90:10; $[\alpha]_D^{25}$ –25.3 (1, $CHCl_3$). Other data as above.

Using general procedure I, TMPMgCl [1.7 mL, 0.75 mmol, 0.45 M in Et_2O] was added to nitrile **257** (50 mg, 0.25 mmol) in CPME (1 mL) at –104 °C. After 10 seconds benzoyl chloride (0.09 mL, 0.75 mmol) was added. Purification as above gave nitrile **258c** (45 mg, 59%) as asolid; enantiomeric ratio 74:26. Other data as above.

6.Appendices

Appendix 1: VT-NMR spectra and data for *N*-Boc-tetrahydroisoquinoline **152**

A sample of the tetrahydroisoquinoline **152** (15 mg) in D_8-THF (0.7 mL) was placed in an NMR tube; the tube was transferred to a cooled NMR spectrometer (400 MHz, temperature coil recording –35 °C). The NMR spectrometer was warmed gradually and spectra were recorded as shown below. Warming allowed coalescence of the signals for the benzylic NCH_2 protons at 4.67 ppm, which occurred at approximately 5 °C (only peaks in the reagon 5.0–3.5 ppm are shown below, which includes two singlet of NCH_2 plus a triblet for partially undeuterated THF).



From the spectra, coalescence for the benzylic CH_2 at 4.65 ppm occurred at $T_c \sim 5$ °C.

The difference in chemical shift ($\Delta\nu^o_{AB}$) between the rotamers at low temperature was ~8.9 Hz.

So, at 5 °C, $k = (\pi \times 8.9)/\sqrt{2} = 19.8\ s^{-1}$

So, at 5 °C, $t_{1/2} = (\ln 2)/k = 0.035$ s

And, at 5 °C, $\Delta G^{\ddagger} = RT[\ln(k_bT/h) - \ln k] = 61.0$ kJ/mol

These data are very similar to the parent *N*-Boc-tetrahydroisoquinoline,[67] which has a barrier to rotation of the Boc group, $\Delta G^{\ddagger} \approx 60.8$ kJ/mol at 5.5 °C.

Using line shape analysis, values for *k* were calculated using formulas shown below.[208]

pre-coalescence, slow exchange:

$$k = \frac{\pi}{\sqrt{2}}[(\Delta v_A)^{e}_{1/2} - (\Delta v_A)^{0}_{1/2}]$$

pre-coalescence, intermediate exchange:

$$k = \frac{\pi}{\sqrt{2}}[{\Delta v_0}^2 - {\Delta v_e}^2]^{1/2}$$

coalescence:

$$k = \frac{\pi \Delta v_0}{\sqrt{2}}$$

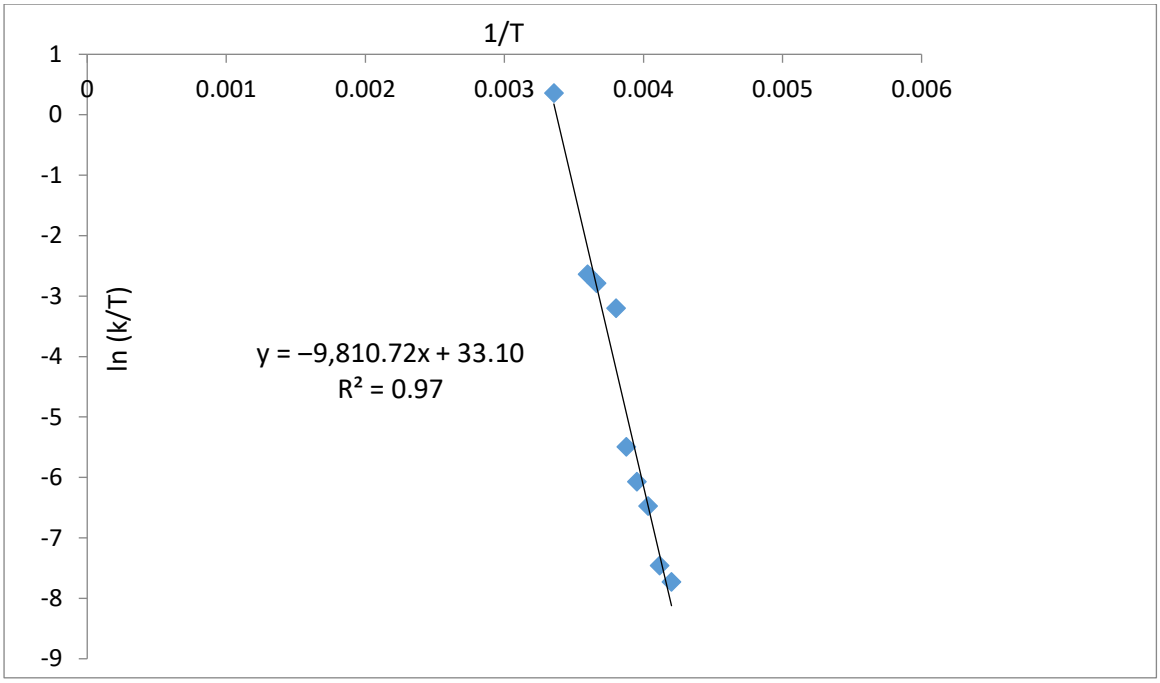
post-coalescence:

$$k = \frac{\pi {\Delta v_o}^2}{2} \frac{1}{(\Delta v_{1/2})^e - (\Delta v_A)^0_{1/2}}$$

Raw data:

T/K	1/T	Δv_0	$(\Delta v_A)^{e}_{1/2}$	$(\Delta v_A)^{0}_{1/2}$	Δv_e	*k*	In(*k*/T)
238	0.004201	8.9	2.944	2.897		0.10441	–7.7317
243	0.004115	8.9	2.96	2.897		0.13995	–7.4595
248	0.004032	8.9	3.069	2.897		0.38209	–6.4755
253	0.003952	8.9	3.16	2.897		0.58424	–6.0708
258	0.003876	8.9	3.373	2.897		1.05740	–5.4971
263	0.003802	8.9	4.03	2.897	7.48	10.7136	–3.2006
273	0.003663	8.9	5.56	2.897	4.68	16.8167	–2.7870
278	0.003597	8.9	7.38	2.897		19.7708	–2.6434
298	0.003356	8.9	3.19	2.897		424.651	0.3542

Eyring plot of 1/T against ln(*k*/T):



These values provided the following (approximate) parameters:

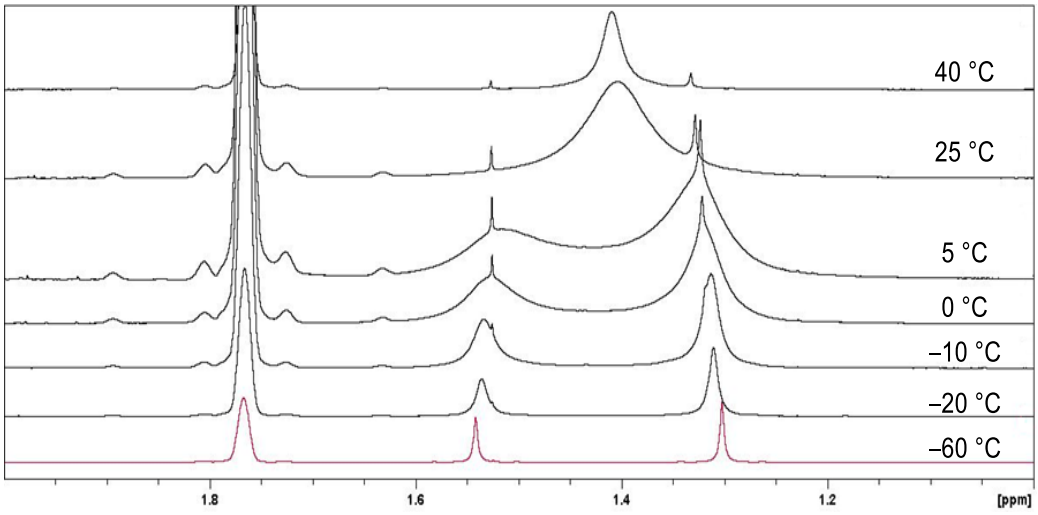
$\Delta H^{\ddagger} \approx \pm 81$ kJ/mol

$\Delta S^{\ddagger} \approx \pm 77$ J/K·mol

These values suggest that $\Delta G^{\ddagger} \approx 60$ kJ/mol at 5 °C and $\Delta G^{\ddagger} \approx 64$ kJ/mol at –50 °C.
This equates to $t_{1/2} \approx 2.5$ min at –50 °C. The lithiation reactions were carried out at –50 °C and we allowed a few minutes for the rotation of the Boc group, so these data approximately match the experimental and the ReactIR results (see Scheme 2-32).

Appendix 2: VT-NMR spectra and data of *N*-Boc-3-phenyl tetrahydroisoquinoline **175**

A sample of the THIQ **175** (15 mg) in D_8-THF (0.7 mL) was placed in an NMR tube; the tube was transferred to a cooled NMR spectrometer (500 MHz, temperature coil recording –60 °C). The NMR spectrometer was warmed gradually, and spectra were recorded as shown below. Warming allowed coalescence of the signals for the Boc $(CH_3)_3$ protons at 1.54 and 1.30 ppm, which occurred arround ~ 10 °C (only the region from 1.0–2.0 ppm with the rotamers of $(CH_3)_3$ are shown below plus broad singlet for partially undeuterated THF).



From the spectra, coalescence for the Boc CH_3 at 1.40 ppm occurred at T_C ~ 10 °C.

The difference in chemical shift ($\Delta\upsilon^0_{AB}$) between the rotamers at low temperature was ~ 118 Hz.

So, at 0 °C, $k = (\pi \times 118)/\sqrt{2} = 155.48\ s^{-1}$

So, at 0 °C, $t_{1/2}$ (ln2)/ $k = 4 \times 10^{-3}$ s

And, at 0 °C, $\Delta G^{\ddagger} = RT[\ln (k_bT/h)] - \ln k] \approx$ 56.99 kJ/mol

Using line shape analysis, values for *k* were calculated using formulae shown below.[208]

pre-coalescence, slow exchange:

$$k = \frac{\pi}{\sqrt{2}}[(\Delta v_A)^e_{1/2} - (\Delta v_A)^0_{1/2}]$$

pre-coalescence, intermediate exchange:

$$k = \frac{\pi}{\sqrt{2}}[\Delta {v_0}^2 - \Delta {v_e}^2]^{1/2}$$

coalescence:

$$k = \frac{\pi \Delta v_0}{\sqrt{2}}$$

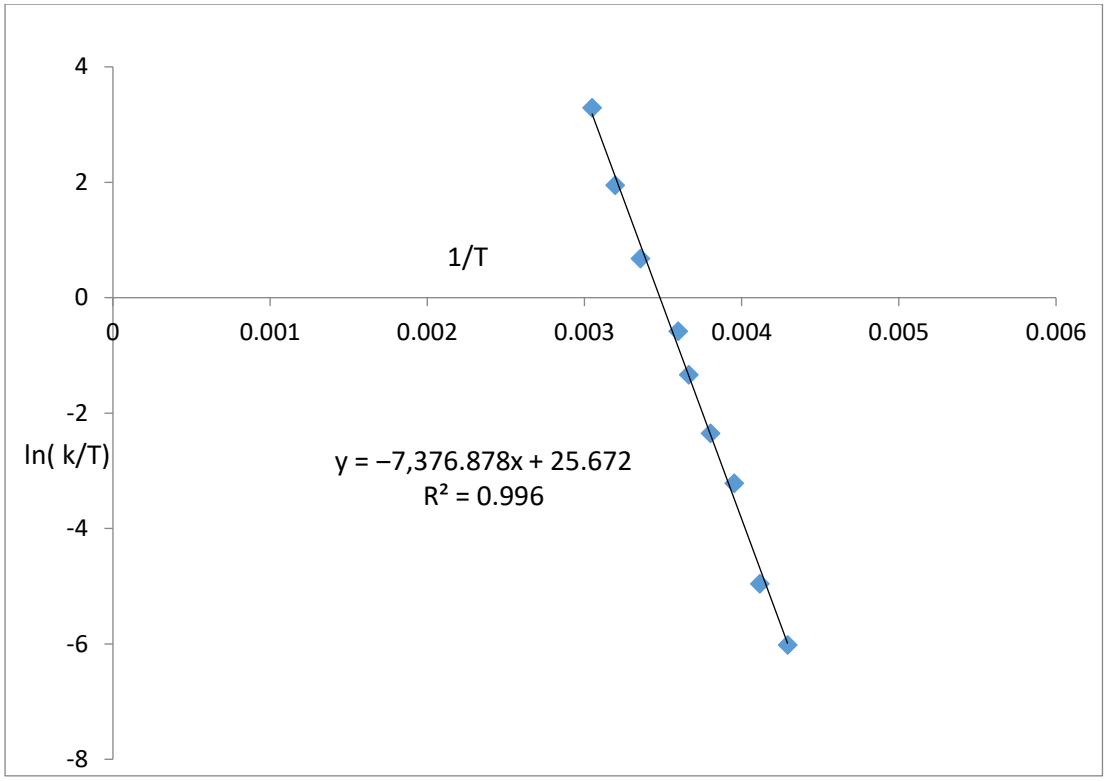
post-coalescence:

$$k = \frac{\pi \Delta {v_o}^2}{2} \frac{1}{(\Delta v_{1/2})^e - (\Delta v_A)^0_{1/2}}$$

Raw data:

T/K	1/T	Δ υ_0	$(\Delta\upsilon_A)^e_{1/2}$	$(\Delta\upsilon_A)^0_{1/2}$	$\Delta\upsilon_e$	k	ln(k/T)
223	0.004484	118	1.65	1.65		0	
233	0.004292	118	1.905	1.65		0.566467	–6.01937474
243	0.004115	118	2.42	1.65		1.710508	–4.95627076
253	0.003953	118	6.218	1.65		10.14754	–3.21615857
263	0.003802	118	12.925	1.65		25.04673	–2.3514107
273	0.003663	118	33.896	1.65	102.5	71.63254	–1.33792234
278	0.003597	118	77.352	1.65	95	155.4849	–0.58107247
298	0.003356	118	38.976	1.65		585.9655	0.676167488
313	0.003195	118	11.603	1.65		2197.503	1.948873906
328	0.003049	118	4.13	1.65		8819.254	3.291678941

Eyring plot of 1/T against ln (*k*/T):



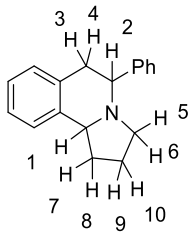
These values provided the following (approximate) parameters:

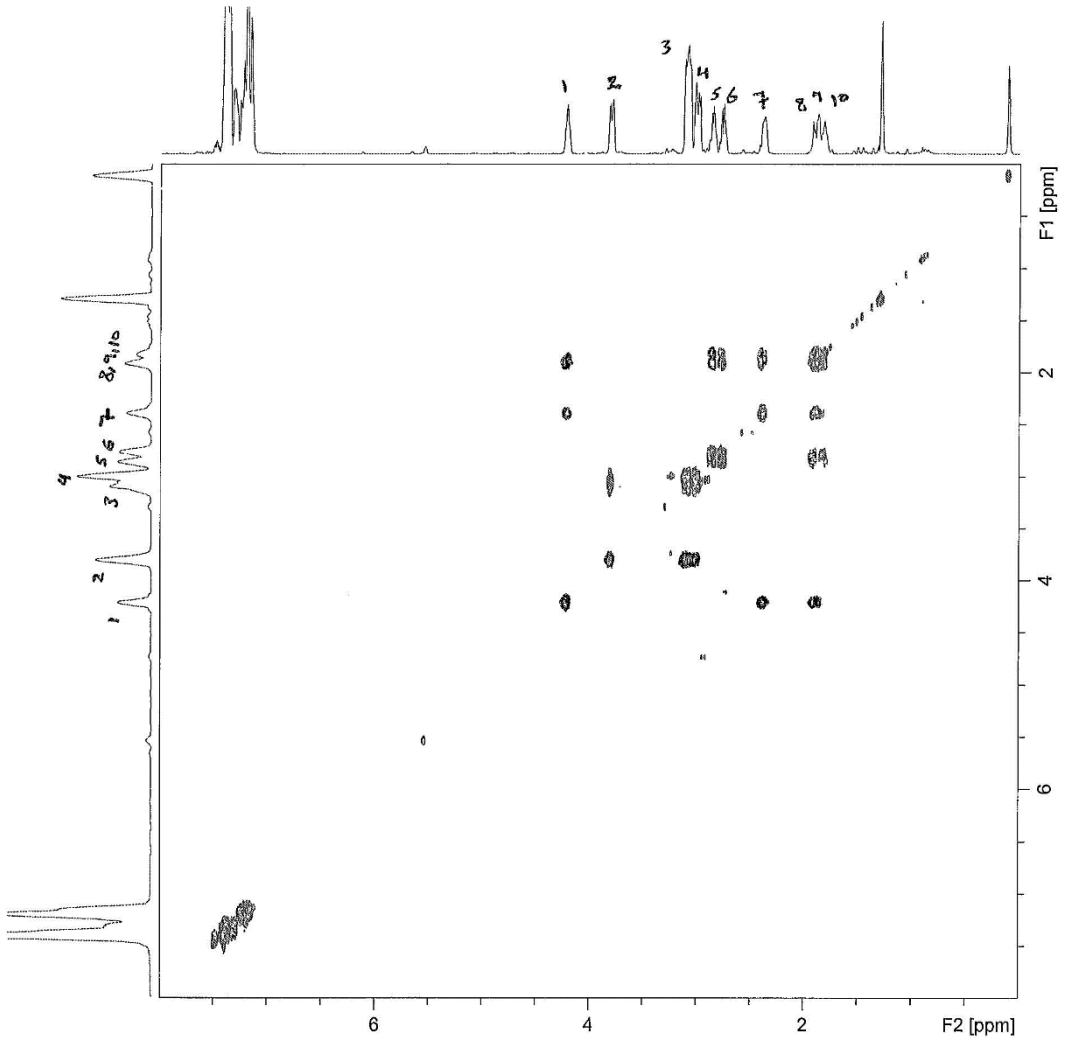
$\Delta H^{\ddagger} \approx \pm 61.33$ kJ/mol

$\Delta S^{\ddagger} \approx \pm 15.90$ J/K·mol

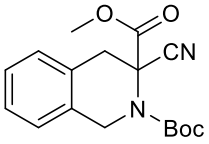
These values suggest that $\Delta G^{\ddagger} \approx 57$ kJ/mol at 0 °C and $\Delta G^{\ddagger} \approx 58$ kJ/mol at –50 °C. This equates to $t_{1/2} \approx 5.13$ sec at –50 °C. The lithiation reactions were carried out at –50 °C and we allow a few minutes for the rotation of the Boc group, so these data approximately match the experimental results and the ReactIR (Scheme 3-9).

Appendix 3: The 2D-COSY NMR for compound **186**





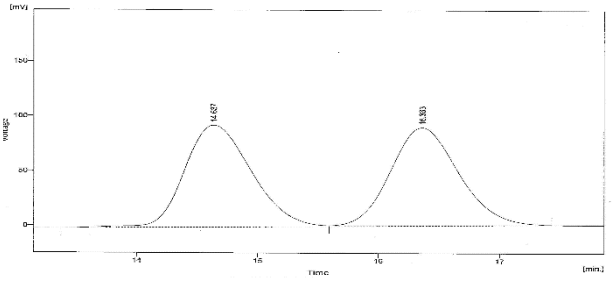
Appendix 4: HPLC traces for a selection of compounds

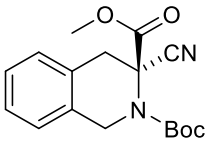


rac-**248d**

Result Table - Calculation Method Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	14.637	3579.799	93.130	50.3	50.8	0.60
2	16.363	3517.261	89.740	49.4	49.0	0.61
3	42.437	18.446	0.390	0.3	0.2	0.74
	Total	7115.506	183.260	100.0	100.0	



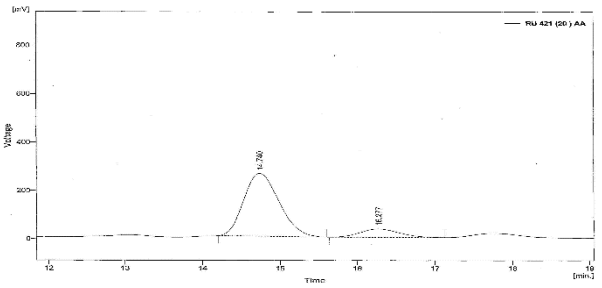


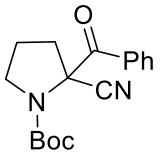
(*S*) -**248d**

From: TMPMgCl, CMPE, −104 °C, and MeOCOCN

Result Table - Calculation Method Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	14.740	8275.452	260.412	87.1	88.1	0.51
2	16.277	1215.598	35.022	12.8	11.8	0.54
3	26.877	9.482	0.248	0.1	0.1	0.64
	Total	9500.532	295.682	100.0	100.0	

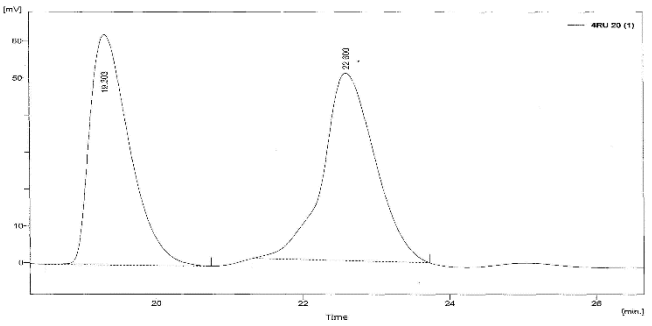


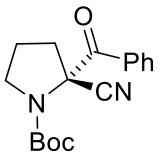


rac-**258c**

Result Table - Calculation Method Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	19.303	2372.761	62.413	48.4	55.1	0.59
2	22.600	2533.159	50.766	51.6	44.9	0.72
	Total	4905.920	113.179	100.0	100.0	



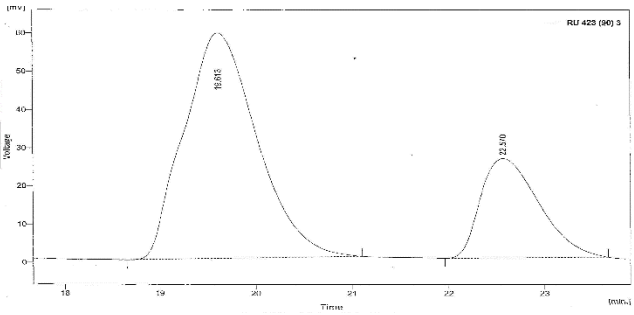


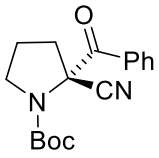
(*S*)-**258c**

From: TMPMgCl, CPME, –104 °C, and PhCOCl

Result Table - Calculation Method Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	19.613	3098.618	59.028	73.8	69.4	0.84
2	22.570	1101.066	25.972	26.2	30.6	0.68
	Total	4199.684	84.999	100.0	100.0	



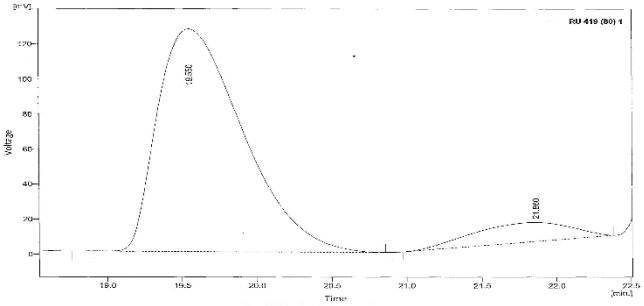


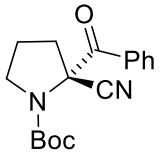
(*S*)-**258c**

From: TMPMgCl, Et_2O, –104 °C, and PhCOCl

Result Table - Calculation Method Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	19.550	5037.328	127.096	90.8	92.2	0.63
2	21.860	512.489	10.814	9.2	7.8	0.77
	Total	5549.817	137.910	100.0	100.0	



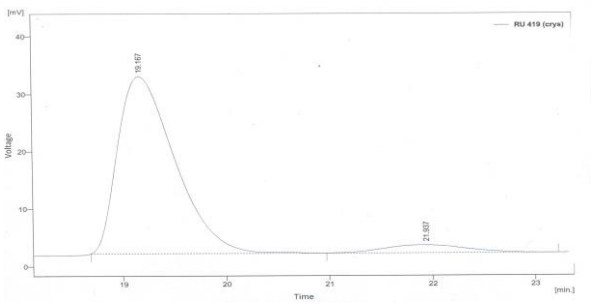


Recrystallized (*S*)-**258c**

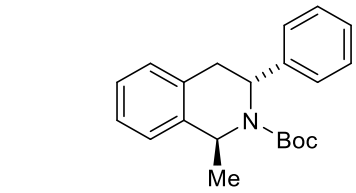
From: TMPMgCl, Et_2O, –104 °C, and PhCOCl

Result Table - Calculation Method Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	19.167	1189.256	30.787	93.8	95.7	0.60
2	21.937	78.642	1.397	6.2	4.3	0.89
	Total	1267.897	32.184	100.0	100.0	



Appendix 5: X-ray crystal structure determination of compound *trans*-**177e**



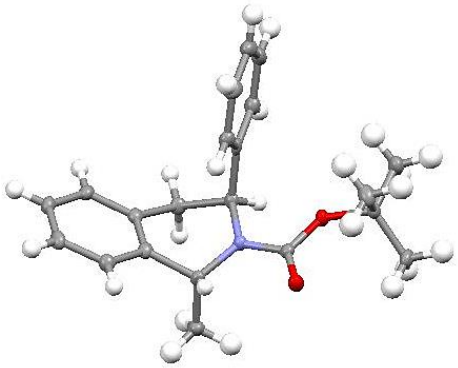
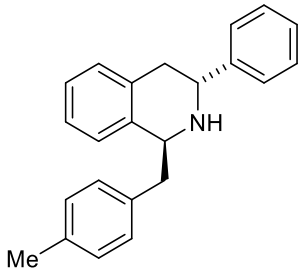


Table 3. Crystal data and structure refinement for OIC274_0m.

Identification code	OIC274_0m	
Empirical formula	C21 H25 N O2	
Formula weight	323.42	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 6.3372(2) Å	α= 90°.
	b = 9.2748(3) Å	β= 90°.
	c = 30.5375(10) Å	γ = 90°.
Volume	1794.88(10) $Å^3$	
Z	4	
Density (calculated)	1.197 Mg/m^3	
Absorption coefficient	0.598 mm^{-1}	
F(000)	696	
Crystal size	0.250 x 0.120 x 0.120 mm^3	
Theta range for data collection	2.894 to 66.681°.	
Index ranges	-7<=h<=7, -11<=k<=11, -36<=l<=36	
Reflections collected	26794	
Independent reflections	3181 [R(int) = 0.1243]	
Completeness to theta = 66.681°	99.9 %	

Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.753 and 0.547
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3181 / 0 / 221
Goodness-of-fit on F^2	1.057
Final R indices [I>2sigma(I)]	R1 = 0.0421, wR2 = 0.0938
R indices (all data)	R1 = 0.0558, wR2 = 0.1008
Absolute structure parameter	0.02(19)
Extinction coefficient	n/a
Largest diff. peak and hole	0.185 and -0.253 e.$Å^{-3}$

Appendix 6: X-ray crystal structure determination of compound *trans*-**192**



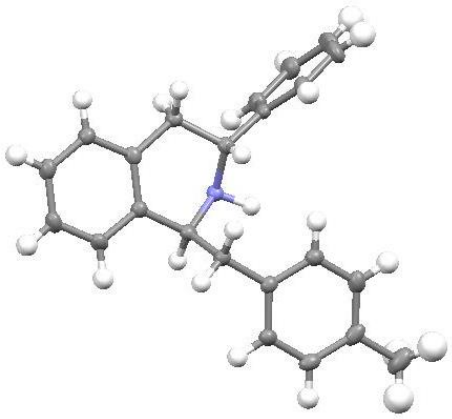


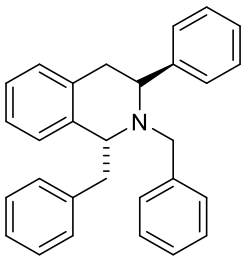
Table 2. Crystal data and structure refinement f

or rtalk1_0m.

Identification code	rtalk1_0m
Empirical formula	C23 H23 N
Formula weight	313.42
Temperature	100(2) K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	$P2_1$

Unit cell dimensions	a = 9.1774(5) Å	α= 90°.
	b = 6.1797(3) Å	β= 101.832(3)°.
	c = 15.8672(9) Å	γ = 90°.
Volume	880.76(8) $Å^3$	
Z	2	
Density (calculated)	1.182 Mg/m^3	
Absorption coefficient	0.512 mm^{-1}	
F(000)	336	
Crystal size	0.320 x 0.210 x 0.120 mm^3	
Theta range for data collection	2.845 to 66.570°.	
Index ranges	-10<=h<=10, -7<=k<=7, -18<=l<=18	
Reflections collected	11320	
Independent reflections	3056 [R(int) = 0.0526]	
Completeness to theta = 66.570°	99.5 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3056 / 1 / 218	
Goodness-of-fit on F^2	1.063	
Final R indices [I>2sigma(I)]	R1 = 0.0403, wR2 = 0.0924	
R indices (all data)	R1 = 0.0486, wR2 = 0.0976	
Absolute structure parameter	0.1(5)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.160 and -0.184 $e.Å^{-3}$	

Appendix 7: X-ray crystal structure determination of compound *trans*-**205**



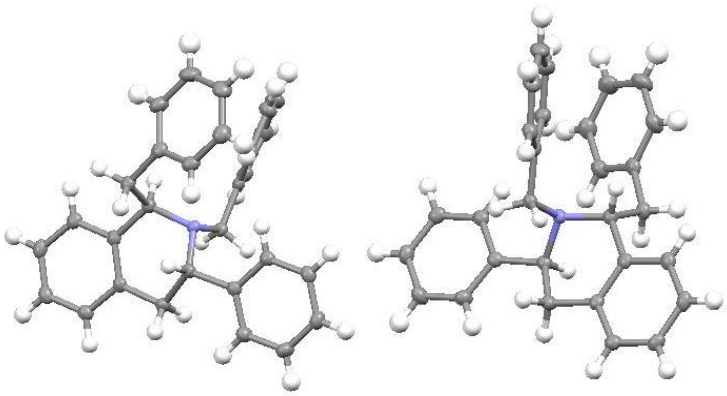
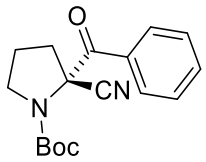


Table 4. Crystal data and structure refinement for OIC276_a.

Identification code	OIC276_a	
Empirical formula	C29 H27 N	
Formula weight	389.51	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 19.2008(5) Å	α= 90°.
	b = 15.7338(4) Å	β= 90.5540(10)°.
	c = 7.1805(2) Å	γ= 90°.
Volume	2169.14(10) $Å^3$	
Z	4	
Density (calculated)	1.193 Mg/m^3	
Absorption coefficient	0.516 mm^{-1}	
F(000)	832	
Crystal size	0.120 x 0.080 x 0.060 mm^3	
Theta range for data collection	2.301 to 66.606°.	
Index ranges	-22<=h<=22, -18<=k<=17, -8<=l<=8	
Reflections collected	47341	
Independent reflections	3847 [R(int) = 0.0641]	
Completeness to theta = 66.606°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.65 and 0.43	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3847 / 0 / 272	
Goodness-of-fit on F^2	1.048	
Final R indices [I>2sigma(I)]	R1 = 0.0398, wR2 = 0.0972	
R indices (all data)	R1 = 0.0516, wR2 = 0.1031	

Extinction coefficient	0.0015(3)
Largest diff. peak and hole	0.237 and -0.180 e.Å^{-3}

Appendix 8: X-ray crystal absolute structure determination of compound (*S*)-**258c**



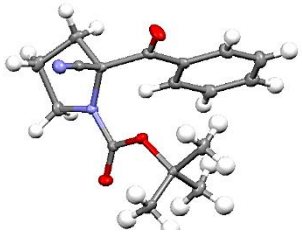
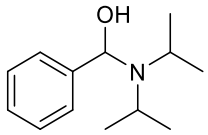


Table X: Crystal data and structure refinement for oic291v.

Identification code	oic291v
Empirical formula	$C_{17}H_{20}N_2O_3$
Formula weight	300.35
Temperature/K	99.96
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	8.6352(4)
b/Å	10.1913(5)
c/Å	17.8369(8)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1569.72(13)
Z	4
ρ_{calc}g/cm^3	1.271
μ/mm^{-1}	0.713
F(000)	640.0
Crystal size/mm^3	0.22 × 0.2 × 0.1
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection	/° 9.918 to 133.12
Index ranges	$-10 \leq h \leq 10$, $-12 \leq k \leq 12$, $-21 \leq l \leq 21$
Reflections collected	45809
Independent reflections	2769 [R_{int} = 0.0255, R_{sigma} = 0.0094]
Data/restraints/parameters	2769/0/202
Goodness-of-fit on F^2	1.116
Final R indexes [I>=2σ (I)]	R_1 = 0.0252, wR_2 = 0.0641
Final R indexes [all data]	R_1 = 0.0253, wR_2 = 0.0642
Largest diff. peak/hole / e Å^{-3}	0.12/-0.23
Flack parameter	0.39(3)

Appendix 9: X-ray crystal structure determination of compound **259**



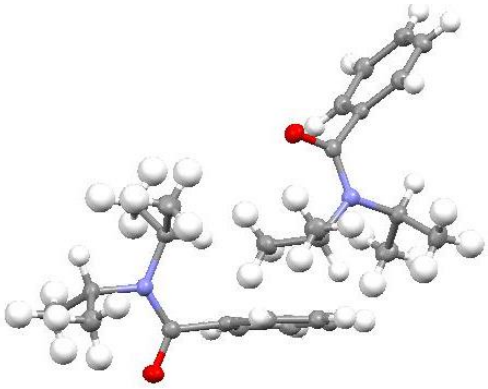


Table 1. Crystal data and structure refinement for RHUR1_a.

Identification code	RHUR1_a	
Empirical formula	C13 H19 N O	
Formula weight	205.29	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 22.6148(10) Å	α= 90°.
	b = 7.4345(3) Å	β= 90.884(2)°.
	c = 14.6142(7) Å	γ= 90°.
Volume	2456.79(19) $Å^3$	
Z	8	
Density (calculated)	1.110 Mg/m^3	
Absorption coefficient	0.540 mm^{-1}	
F(000)	896	
Crystal size	0.210 x 0.180 x 0.180 mm^3	
Theta range for data collection	3.910 to 66.652°.	
Index ranges	-26<=h<=26, -8<=k<=8, -17<=l<=17	
Reflections collected	31811	
Independent reflections	4339 [R(int) = 0.0552]	
Completeness to theta = 66.652°	99.9 %	

Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7528 and 0.6874
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4339 / 0 / 279
Goodness-of-fit on F^2	1.055
Final R indices [I>2sigma(I)]	R1 = 0.0414, wR2 = 0.1023
R indices (all data)	R1 = 0.0479, wR2 = 0.1070
Extinction coefficient	n/a
Largest diff. peak and hole	0.173 and -0.211 e.Å^{-3}

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