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 °C 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.

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حسبنا الله سئوتينا الله من فضلله ورسوله إننا إلى الله راغبون......
Contents

Acknowledgements................................................................................................................................................iv
1. Introduction........................................................................................................................................................1
  1.1 Introduction to Organolithium Chemistry .................................................................................................1
  1.2 Reactions of Organolithiums–Stereochemical Course ..............................................................................2
  1.3 α-Amino Organolithiums .............................................................................................................................6
  1.4 The Complex-Induced Proximity Effect (CIPE) ..........................................................................................7
  1.5 Asymmetric Deprotonation..........................................................................................................................9
  1.6 Determination of configurational stability ..................................................................................................12
  1.7 Configurational Stability of Benzylic α-Amino Organolithiums ...............................................................14
Chapter 2. Synthesis of 1-Substituted Tetrahydroisoquinolines .................................................................19
  2.1 General Introduction to 1-Substituted Tetrahydroisoquinoline (THIQ) ....................................................19
  2.2 The Pictet–Spengler Condensation .............................................................................................................20
  2.3 The Bischler–Napieralski Cyclisation/Reduction .......................................................................................21
  2.4 Synthesis of 1-Substituted-THIQs Using Organolithium Reagents ..........................................................22
  2.5 Synthesis of 1-Substituted N-Boc-tetrahydroisoquinolines Optimization and Scope of Lithiation ........26
    2.5.1 Synthesis and Reaction of N-Boc-6,7-dimethoxytetrahydroisoquinoline ............................................27
    2.5.2 Synthesis and Reaction of N-Boc-[1,3]dioxolo-tetrahydroisoquinoline .............................................30
    2.5.3 Synthesis and Reaction of 7-Chloro-N-Boc-tetrahydroisoquinoline .................................................33
    2.5.4 Synthesis and Reaction of 5-Trifluoromethyl-N-Boc-tetrahydroisoquinoline ..........................36
Chapter 3. Lithiation of N-Boc-3-phenyltetrahydroisoquinoline ..................................................................39
  3.1 Synthesis of N-Boc-3-phenyltetrahydroisoquinoline ..............................................................................39
  3.2 Lithiation of N-Boc-3-Phenyltetrahydroisoquinoline .................................................................................43
  3.3 Density Functional Theory Analysis .........................................................................................................58
  3.4 Conclusion .....................................................................................................................................................62
Chapter 4. Asymmetric Synthesis of Nitrile containing Compounds ............................................................63
  4.1 General Introduction to Nitrile Containing Compounds ...........................................................................63
    4.1.1 Asymmetric Synthesis of Nitriles .........................................................................................................64
    4.1.2 Metallated Nitriles ...............................................................................................................................65
4.1.3 Selective Synthesis Using Organomagnesium Compounds ........................................ 67
4.2 Results and Discussion .................................................................................................. 70
  4.2.1 Synthesis and Reaction of N-Boc-3-cyanotetrahydroisoquinoline ....................... 70
  4.2.2 Synthesis and Reaction of N-Boc-2-cyanopyrrolidine ........................................ 77
4.3 Conclusion .................................................................................................................. 81
5. Experimental ................................................................................................................ 83
  5.1 General Experimental Details .................................................................................... 83
  5.2 Chapter 2 Experimental ............................................................................................ 84
  5.3 Chapter 3 Experimental ............................................................................................ 111
  5.4 Chapter 4 Experimental ............................................................................................ 130
6. Appendices .................................................................................................................... 140
7. References ..................................................................................................................... 156
**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac.</td>
<td>Acetyl</td>
</tr>
<tr>
<td>add.</td>
<td>Addition</td>
</tr>
<tr>
<td>AIDS</td>
<td>Aquired Immune Deficiency Syndrome</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>ax</td>
<td>axial</td>
</tr>
<tr>
<td>Piv</td>
<td>pivaloyl</td>
</tr>
<tr>
<td>Boc</td>
<td><em>tert</em>-butoxycarbonyl</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>C</td>
<td>Celsius</td>
</tr>
<tr>
<td>CIPE</td>
<td>complex induced proximity effect</td>
</tr>
<tr>
<td>cm</td>
<td>centimetre</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>conc.</td>
<td>concentration</td>
</tr>
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<td>COSY</td>
<td>correlation spectroscopy</td>
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<tr>
<td>CPME</td>
<td>cyclopentyl methyl ether</td>
</tr>
<tr>
<td>CSP-GC</td>
<td>chiral stationary phase gas chromatography</td>
</tr>
</tbody>
</table>
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^i  Gibbs energy of activation
h  hour (s)
\Delta H^i  enthalpy of activation
<table>
<thead>
<tr>
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<th>Definition</th>
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<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>HMDS</td>
<td>Hexamethyldisilazane</td>
</tr>
<tr>
<td>HMPA</td>
<td>Hexamethylphosphoramide</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectroscopy</td>
</tr>
<tr>
<td>HSQC</td>
<td>Heteronuclear single quantum coherence spectroscopy</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz</td>
</tr>
<tr>
<td>i.d.</td>
<td>internal diameter</td>
</tr>
<tr>
<td>inv</td>
<td>inversion</td>
</tr>
<tr>
<td>i.pr</td>
<td>isopropyl</td>
</tr>
<tr>
<td>IR</td>
<td>infra-red</td>
</tr>
<tr>
<td>k</td>
<td>reaction rate constant</td>
</tr>
<tr>
<td>K</td>
<td>Kelvin</td>
</tr>
<tr>
<td>kJ</td>
<td>kilojoule (s)</td>
</tr>
<tr>
<td>L</td>
<td>litre (s)</td>
</tr>
<tr>
<td>L*</td>
<td>chiral ligand</td>
</tr>
<tr>
<td>LCT</td>
<td>liquid chromatography tandem</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium diisopropylamide</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>Lithium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>lit.</td>
<td>literature</td>
</tr>
<tr>
<td>LRMS</td>
<td>low resolution mass spectroscopy</td>
</tr>
<tr>
<td>M</td>
<td>molar</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>2-MeTHF</td>
<td>2-methyltetrahydrofuran</td>
</tr>
<tr>
<td>mg</td>
<td>milligram (s)</td>
</tr>
<tr>
<td>min</td>
<td>minute (s)</td>
</tr>
<tr>
<td>mL</td>
<td>millilitre (s)</td>
</tr>
<tr>
<td>mmol</td>
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</tr>
<tr>
<td>mol</td>
<td>mole (s)</td>
</tr>
<tr>
<td>m.p</td>
<td>melting point</td>
</tr>
<tr>
<td>MS</td>
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</tr>
<tr>
<td>m/z</td>
<td>mass to charge ratio</td>
</tr>
<tr>
<td>nm</td>
<td>nanometres</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>nOe</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
<td>nosyl</td>
<td>4-nitrobenzene-1-sulfonyl chloride</td>
</tr>
<tr>
<td>OTf</td>
<td>Trifluoromethanesulfonate</td>
</tr>
<tr>
<td>p-</td>
<td>para</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PMDTA</td>
<td>pentamethyldiethylenetriamine</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>R</td>
<td>alkyl group</td>
</tr>
<tr>
<td>rac-</td>
<td>racemic</td>
</tr>
<tr>
<td>R_{f}</td>
<td>retention factor</td>
</tr>
<tr>
<td>RSM</td>
<td>recovered starting material</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>$R_t$</td>
<td>retention time</td>
</tr>
<tr>
<td>r.t.</td>
<td>room temperature</td>
</tr>
<tr>
<td>S</td>
<td>solvent</td>
</tr>
<tr>
<td>s or sec</td>
<td>second (s)</td>
</tr>
<tr>
<td>$\Delta S^i$</td>
<td>entropy of activation</td>
</tr>
<tr>
<td>SET</td>
<td>single electron transfer</td>
</tr>
<tr>
<td>(−)-sp</td>
<td>(−)-sparteine</td>
</tr>
<tr>
<td>T</td>
<td>temperature</td>
</tr>
<tr>
<td>$t$</td>
<td>time</td>
</tr>
<tr>
<td>$t$-Bu or $t'$Bu</td>
<td>tertiary butyl</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoro acetic acid</td>
</tr>
<tr>
<td>TFAA</td>
<td>trifluoro acetic anhydride</td>
</tr>
<tr>
<td>THIQ</td>
<td>tetrahydroisoquinoline</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>THP</td>
<td>tetrahydropyran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMEDA</td>
<td>$N,N,N,N$-tetramethylethylenediamine</td>
</tr>
<tr>
<td>TMPH</td>
<td>2,2,6,6-Tetramethylpiperidine</td>
</tr>
<tr>
<td>TMPMgCl</td>
<td>2,2,6,6-Tetramethylpiperidinylmagnesium chloride</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>Tos</td>
<td>Toluensulfonyl</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
</tr>
</tbody>
</table>
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.\(^11\),\(^12\)

<table>
<thead>
<tr>
<th>Hexameric</th>
<th>Tetrameric</th>
<th>Dimeric</th>
<th>Monomeric</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$-BuLi</td>
<td>$s$-BuLi</td>
<td>PhCH$_2$Li</td>
<td>-</td>
</tr>
<tr>
<td>EtLi</td>
<td>$i$-PrLi</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$t$-BuLi</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 Et₂O 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

![Ligands for organolithium compounds](image)

**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 Sₐₑ₂ret and Sₐₑ₂inv 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 Sₐₑ₂ret and Sₐₑ₂inv 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 stereospecificity could arise from the presence of the configurationally labile organolithium.
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.\textsuperscript{20} In contrast with a stabilized conjugated system such as a benzylic organolithium, the nearby $\pi$-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 $\sigma$ bond. Figure 1-2 shows the substitution reaction with benzylithiums.\textsuperscript{21–23}

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 \(-78\, ^\circ C\). 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 \(\text{CS}_2\).\(^{22-24}\)

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 \(-78\, ^\circ C\). Although the substitution proceeded through different mechanasisms, they suggested that non-coordinating electrophiles, such as halides gave inversion of configuration. In contrast, coordinating electrophiles like tosylates proceeded with retention.
Gawley reported tin–lithium exchange of N-alkyl 2-tributylstannyl piperidines and pyrrolidines from non-stabilised organolithium species. 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.

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 $\alpha$ 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 $\alpha$ 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.\textsuperscript{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.\textsuperscript{36} A variety of groups, such as amides,\textsuperscript{35} formamides,\textsuperscript{45} carbamates\textsuperscript{36} and nitrosamine\textsuperscript{46} have been used for dipole-stabilization of \(\alpha\)-amino organolithium species.\textsuperscript{38} Mesomerically stabilised organolithiums exist when lithiation occurs adjacent toazaallyl amide, allylic or benzylic amine (Figure 1-3)\textsuperscript{47}.

\[
\begin{align*}
\text{Unstable amino-organo-lithium} & \quad \text{Dipole stabilized amino-organo-lithium} & \quad \text{Mesomerically stabilized amino-organo-lithium} \\
\text{Dipole- and mesomerically} & \quad \text{stabilized organolithium}
\end{align*}
\]

\textbf{Figure 1-3}

\textbf{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 metatalation using an adjacent directing group.\textsuperscript{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\textsuperscript{49}. An investigation in to the CIPE has been carried out, which confirmed the number of reaction steps.\textsuperscript{51,52}
In 1994, Shimaio and Meyers reported the deprotonation reaction of compound 23 using ethoxy vinyl lithium–HMPA (Scheme 1-6), which was prepared from the reaction between t-BuLi, ethyl vinyl ether and HMPA. The reaction was performed at –78 °C, and the use of ethoxy vinyl lithium–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 ethoxy vinyl lithium–HMPA was used. The reason behind this was unclear, they hypothesized that there could be clusters of ethoxy vinyl lithium–HMPA which hindered the deprotonation ortho to the oxazoline group, they also suggested that this reaction could be kinetically controlled.

Furthermore, there are other functional groups that can direct metalation, amide, nitroso, and formamidine and many other directing groups have been widely used by many researchers to direct deprotonation at the α–position (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 Et₂O and TMEDA at −78 °C gave compound 38 in 94% yield after an electrophilic quench with TMSCl. 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.

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 $k_S/k_R$.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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).\textsuperscript{57,58}
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 mechanism. 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 1-11]

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 1-12]

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.

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 CO2 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

Scheme 1-15
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). 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>T (°C)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>−95</td>
<td>10</td>
<td>97</td>
<td>98:2</td>
</tr>
<tr>
<td>2</td>
<td>−95</td>
<td>180</td>
<td>75</td>
<td>94:6</td>
</tr>
<tr>
<td>3</td>
<td>−78</td>
<td>10</td>
<td>95</td>
<td>96:4</td>
</tr>
<tr>
<td>4</td>
<td>−78</td>
<td>180</td>
<td>76</td>
<td>90:10</td>
</tr>
<tr>
<td>5</td>
<td>−78 (DME)</td>
<td>180</td>
<td>54</td>
<td>84:16</td>
</tr>
<tr>
<td>6</td>
<td>−78 (HMPA)</td>
<td>180</td>
<td>50</td>
<td>50:50</td>
</tr>
<tr>
<td>7</td>
<td>−55</td>
<td>120</td>
<td>76</td>
<td>62:38</td>
</tr>
</tbody>
</table>

Table 1-2

![Scheme 1-16](image)

Table 1-3
1.7 Configurational Stability of Benzylic α-Amino Organolithiums

Benzylic α-amino organolithium species are generally configurationally unstable (Figure 1-2, page 3). However, a few secondary benzylithium 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). 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).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>er (R:S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(−)-sparteine</td>
<td>10</td>
<td>83</td>
<td>95:5</td>
</tr>
<tr>
<td>2</td>
<td>(−)-sparteine</td>
<td>0.5</td>
<td>73</td>
<td>95:5</td>
</tr>
<tr>
<td>3</td>
<td>TMEDA</td>
<td>10</td>
<td>81</td>
<td>54:46</td>
</tr>
<tr>
<td>4</td>
<td>TMEDA</td>
<td>0.5</td>
<td>79</td>
<td>70:30</td>
</tr>
</tbody>
</table>

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).

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). 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.

Further work was carried out in 1989 by Meyers and co-workers who investigated the configurational stability of tetrahydroisoquinoline 68 (Scheme 1-21). 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.

In 2013, Coldham and co-workers reported a study on the configurational stability of N-Boc-tetrahydroisoquinoline 72 (Scheme 1-22, Table 1-5). 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 1 hour lithiation time at -78 °C in toluene, product 73 was obtained in a 67% yield and 67:33 er. In comparison, using Et2O 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.
Moving forward, tin-lithium exchange was carried out using racemic 74, n-BuLi and (−)-sparteine in Et₂O at −78 °C (Scheme 1-23). 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.

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). 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.\(^6^9\) 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.\(^7^0\) 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.\(^7^1\) Salsoline 83 has been shown to “regulate prolactin release, neuronal transmission in sympathetic ganglia, and neurotransmission modulation”.\(^6^9\) 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).\(^7^2,7^3\)

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.\(^7^4\)
Usually, biological studies are carried out using racemic THIQs, due to the lack of efficient synthetic approaches to enantiopure THIQs.\textsuperscript{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 $\beta$-phenylethylamine with formaldehyde as shown in Scheme 2-1 (no yield was reported).\textsuperscript{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.\textsuperscript{77}

\[
\text{Scheme 2-1}
\]

Stambuli and co–workers investigated Pictet–Spengler reaction in the presence of Lewis acids (Scheme 2-2).\textsuperscript{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 $[\text{Ca(HFIP)}_2]$. 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.\textsuperscript{78}

\[
\text{Scheme 2-2}
\]
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-tolysulfinyl amine (R)-90 was reacted with simple aldehydes in the presence of BF\(_3\).OEt\(_2\) at \(-78^\circ\text{C}\). 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](image-url)

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.\(^{83}\)
Bischler–Napieralski cyclization was used as a crucial step in the total synthesis of (−)-tejedine (Scheme 2-5).\textsuperscript{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 regioisomers (S)-97\textsubscript{a} and (S)-97\textsubscript{b} in a 40% and 45% yield respectively, each with > 99% dr. The product 97\textsubscript{a} was required for the total synthesis of (−)-tejedine.\textsuperscript{84}

\begin{equation}
\text{Scheme 2-4}
\end{equation}

\begin{equation}
\text{Scheme 2-5}
\end{equation}

**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, \textit{s}-BuLi and \textit{t}-BuLi have been used as bases to complete the lithiation step. Various stabilising groups, including carbamate,\textsuperscript{85} pivaloyl,\textsuperscript{86–88} and formamidine,\textsuperscript{89,90} have been used for dipole–stabilisation of the \(\alpha\)-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).\textsuperscript{91} After the addition of different electrophiles, the mixture was stirred for 1 hour to give compounds 98\textsubscript{a}–\textsubscript{c} in good yields.
Meyers and co-workers reported the lithiation–substitution reaction of $N$-formamidine THIQ 99 at the C–1 position (Scheme 2-7).\textsuperscript{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.

By using oxazolines as auxiliaries, Gawley and co-workers investigated the asymmetric alkylation of THIQ 102 via a lithiation–substitution approach.\textsuperscript{7} A number of substituted oxazolines were tried as the chiral auxiliary. However, only the one from L-valinol was considered to be effective.\textsuperscript{75,93–96} A successful asymmetric alkylation was achieved with up to 97:3 dr (Scheme 2-8).\textsuperscript{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.
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). 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.

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.

Coppola investigated the lithiation of THIQ 113 using t-BuLi in the presence of TMEDA at –78 °C (Scheme 2-11). 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.

Recently, the Coldham group reported the alkylation reaction of N-Boc-THIQs 72 and 113 (Scheme 2-12). 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.

The aim of this chapter is to synthesize 1-substituted-tetrahydroisoquinolines derivatives 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 lithiation–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 Boc₂O to obtain the desired product 113 in a 79% overall yield over two steps (Scheme 2-13). ⁶⁷

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.

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
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 represents a short synthesis of (±)-crispine A from the growing number reported in the literature.\(^{67,100–102}\)

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.\(^{103,104}\)

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 LiAlH₄ gave the desired product (±)-dysoxyline 127 in 75% yield (Scheme 2-18). In order to prepare bromide 129, the acid 128 was reduced to its primary alcohol using NaBH₄. This was transformed directly to the bromide 129 using apple reaction (Scheme 2-19).

Finally, in order to investigate if compound 130 could be synthesized using lithiation-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 BEt₃ was added, followed by the addition of NaOH and H₂O₂. However, no product was isolated, and a complex mixture of products was formed. In an attempt to improve the results, BEt₃ was added at −50 °C followed by the addition of TMSOTf at −78 °C. Later, NaOH and H₂O₂ were added and this gave compounds 131 and 132 in a 90% and 5% yield respectively.
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. 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. 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. However, using trifluoroacetic acid (TFA) in toluene for 16 h at 112 °C gave the cyclised amine in a 74% yield as a salt. Finally, protection using Boc₂O in THF gave only a 23% yield of the targeted molecule 136. Therefore, NaHCO₃ 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:H₂O improved the yield to 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. Recently, there have been several reports explaining the benefit of in-situ ReactIR in optimising reaction conditions. 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. 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 νC=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 νC=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. 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
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 \( \text{137a} \) (\( \nu_{\text{C=O}} \) 1636 cm\(^{-1}\)) after only few minutes. The results are in line with previous work.\(^6\)

\[
\text{136a} \quad \text{(normal) Boc} \quad \overset{-50 \degree \text{C}, \text{THF}}{\longrightarrow} \quad \text{136b} \quad \text{Li}^+ \quad \text{(lithiated)} \quad \nu_{\text{C=O}} 1696 \text{ cm}^{-1} \\
\text{137a} \quad \nu_{\text{C=O}} 1636 \text{ cm}^{-1}
\]

On the basis of the \( \text{in-situ} \) 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 MgBr₂·OEt₂ in THF at −78 °C, followed by addition of benzaldehyde gave no product and only starting material was recovered. Quenching the reaction with benzyl bromide gave compound 138f in a 66% yield. THIQ 138f was reduced using LiAlH₄ 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.
The amine 141 was treated with TFAA in THF to give the acetamide 142 in a 48% yield. 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.

\[
\begin{align*}
\text{Reagents and conditions:} \\
1) & \text{BH}_3, \text{THF} [1 \text{ M}], \text{THF}, 24 \text{ h, then H}_2\text{O}, 30 \text{ min, HCl conc.,} \\
& 1 \text{ h, then NaOH pellets, 1 h (73%);} \\
2) & \text{Raney Ni, NH}_4\text{OH, EtOH 48 h (92%);} \\
3) & \text{pyridine, TFAA, THF, 4 h (79%);} \\
\end{align*}
\]

Scheme 2-26

Pictet–Spengler cyclisation reaction was then carried out, where paraformaldehyde and the amide 142 were mixed in a mixture of H$_2$SO$_4$:AcOH and stirred at room temperature for 48 hours to give the cyclised acetamide 143 in 86% yield. The ratio of H$_2$SO$_4$:AcOH used in the reaction determined the yield of the product 143 as shown in Scheme 2-27.

\[
\begin{align*}
\text{Scheme 2-27} \\
\text{7-Chlorotetrahydroisoquinoline 144 as the hydrochloride salt was prepared in a 69% yield by} \\
\text{hydrolysing amide 143 using potassium carbonate in methanol/H}_2\text{O at 90 °C for 1 hour.} \\
\text{Finally, Boc protection in dioxane/H}_2\text{O obtained the desired THIQ 145 in a 70% yield (Scheme} \\
\text{2-28).}
\end{align*}
\]
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.

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 2-29](image_url)

![Scheme 2-30](image_url)
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. The amine 148 was treated with TFAA in THF to give the acetamide 149 in a 52% yield. Acetamide 149 could then undergo a cyclisation reaction in the presence of paraformaldehyde to give the cyclized product 150 in 86% yield. Hydrolysing the acetamide group using potassium carbonate in MeOH/H$_2$O gave 5-trifluoromethyl-tetrahydroisoquinoline 151 in a 75% yield. Finally protecting THIQ 151 gave the desired THIQ 152 in 89% yield (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$_2$)$_3$Br 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).
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 D8-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 NCH2 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 ΔG‡ ≈ 60.0 kJ/mol at 5 °C. Hence, the half-life was estimated to be about t½ ≈ 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
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 \textit{in-situ} ReactIR spectroscopy, by using \( n \)-BuLi in THF at \(-50 \, ^\circ\text{C}\). The barrier for the Boc group rotation of THIQ 152 was found to be \( \Delta G^\ddagger = 64.0 \, \text{kJ/mol at} \, -50 \, ^\circ\text{C} \), equating to a half–life of approximately 2 minutes at \(-50 \, ^\circ\text{C} \) for the Boc rotation, and this was in line with a previous work done in the coldham group on THIQ 72.\textsuperscript{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 CH₂Cl₂ gave acetamide 156 in 91% yield. This was followed by a cyclisation reaction using a mixture of H₂SO₄:AcOH and paraformaldehyde. The reaction gave only trace amounts of product 157 as was shown by high resolution mass spectrometry. 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).

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 Et3N 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 Et3N and AlMe3. 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:
   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, Et3N, overnight
   c) LDA, −45 °C, amide 159, 20 min, imine 162, −45 °C, 30 min, AlMe3, Et3N, overnight
   d) LDA, −45 °C, amide 159, 20 min, imine 162, −45 °C, 30 min, AlMe3, Et3N, −45 °C, 11 h

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$_4$OH at room temperature for 24 hours. This gave $p$-toluenesulfonamide 166 in a 74% yield, 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).  

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$_2$Cl$_2$ 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).
The amide was treated with oxalyl chloride in the presence of DMF.\textsuperscript{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 \(-15^\circ\text{C}\) 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 spectrometry and \(^1\text{H}\) 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.\textsuperscript{120}

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\(_2\)SO\(_4\) present in the mixture had a crucial effect on the yield of imine 173. When a ratio of 19:1 (MeOH:H\(_2\)SO\(_4\)) 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$_2$SO$_4$) 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. Finally, protection using Boc$_2$O gave the desired product 175 in a 79% yield (Scheme 3-6).

**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 $-50 ^\circ C$ (Scheme 3-7). The IR plot showed a rapid loss of the peak at $\nu_{C=O} 1694 \text{ cm}^{-1}$ assigned for the starting material THIQ 175, with the formation of new peaks at $\nu_{C=O} 1642 \text{ cm}^{-1}$ 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 lithiation 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 around ~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 (CH₃)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 1H NMR spectroscopy. Surprisingly, the ratios of the two regioisomers were electrophile dependent.

![Scheme 3-8](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>E⁺</th>
<th>1-pos:3-pos ratio</th>
<th>Yield %</th>
<th>Recovered 175 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ClSnBu₃</td>
<td>177a:178a</td>
<td>1:1</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>Allyl bromide</td>
<td>177b:178b</td>
<td>2.3:1</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>Benzyl bromide</td>
<td>177c:178c</td>
<td>3:1</td>
<td>69</td>
</tr>
<tr>
<td>4</td>
<td>p-methylbenzyl bromide</td>
<td>177d:178d</td>
<td>3:1</td>
<td>63</td>
</tr>
<tr>
<td>5</td>
<td>MeI</td>
<td>177e:178e</td>
<td>3.9:1</td>
<td>73</td>
</tr>
</tbody>
</table>

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$_3$SnCl gave a 1:1 ratio of products \textbf{177a} and \textbf{178a}. There did seem to be a difference in reactivity between Bu$_3$SnCl 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 \textit{n}-BuLi in THF at $-50$ °C (Scheme 3-9, Table 3-4). Treating the organolithiums with tributyltin chloride gave compounds \textbf{177a} and \textbf{178a} as an inseparable mixture of regioisomers in a 79% yield and about 1:1 ratio with no recovered THIQ \textbf{175}. Only one diastereoisomer of compound \textbf{177a} was obtained, as shown by $^1$H NMR spectroscopy (it was not clear if it was the \textit{cis} or the \textit{trans} isomer). However, when allyl bromide was used as the electrophile, products \textbf{177b} and \textbf{178b} were isolated in about a 2.3:1 ratio with a good yield. This was similar to those from the D$_2$O quench (\textit{vide infra}), whereas using 2.2 equivalents of \textit{n}-BuLi gave a ratio of about 1.6:1 of the two inseparable regioisomers. Reacting THIQ \textbf{175} with 1.5 equivalent of \textit{n}-BuLi, followed by the addition of benzyl bromide and \textit{p}-methylbenzyl bromide gave both regioisomers in a 94% and 78% yield respectively and about a 3:1 ratio with no recovered THIQ \textbf{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 \textbf{177e} and the 1-substituted THIQ \textbf{178e}. Only one diastereoisomer of the 1-substituted product \textbf{177e} was obtained as shown by $^1$H NMR spectroscopy. The two products were separated by recrystallization using hexane/CH$_2$Cl$_2$, and X-ray crystallography showed that the phenyl group and methyl group were \textit{trans} to each other (Figure 3-3). Another electrophile tested was butyl bromide, which gave two inseparable regioisomers \textbf{177f} and \textbf{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.
Table 3-4

<table>
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<tr>
<th>Entry</th>
<th>E⁺</th>
<th>1-pos:3-pos</th>
<th>ratio</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ClSnBu₃</td>
<td>177a:178a</td>
<td>1:1</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td>Allyl bromide</td>
<td>177b:178b</td>
<td>2.3:1</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2.2 eq) n-BuLi</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Benzyl bromide</td>
<td>177c:178c</td>
<td>3:1</td>
<td>66</td>
</tr>
<tr>
<td>4</td>
<td>p-methylbenzyl bromide</td>
<td>177d:178d</td>
<td>3:1</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>177e:178e</td>
<td>4:1</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>Butyl bromide</td>
<td>177f:178f</td>
<td>4:1</td>
<td>97</td>
</tr>
</tbody>
</table>

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, D₂O 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 D₂O 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 D₂O would give a preference for only the 1- substituted product.
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 D₂O quench. The reason behind the 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 D₂O 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 D₂O 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 ClSnBu₃ 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

A variety of other electrophiles were 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 ClSiMe₃ in a 78% yield. Surprisingly, reacting THIQ 175 with bromide 129 gave only recovered starting material. Furthermore, neither 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; the major isomer was the 1-substituted product as shown by ¹H 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 ¹H 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 Rf in comparison to the 1-substituted isomer.
Reacting the organolithium mixture with D$_2$O was then carried out to investigate the ratio of the two organolithiums for the reaction at $-78 \, ^\circ\text{C}$ 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 $-78 \, ^\circ\text{C}$ was calculated to be 11 minutes according to variable temperature NMR studies.

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$_2$O 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.
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 D₂O at –94 °C to the mixture of organolithiums.

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 ¹H 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).

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 ¹H 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).
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 $-60 \, ^\circ\text{C}$ for 1 hour and by using different electrophiles, good yields were obtained despite the possibility of $\beta$-elimination (Scheme 3-18).123

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 $-50 \, ^\circ\text{C}$ 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).

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 Et₂O 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. 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).
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.

**Scheme 3-21a, b**

1.2 eq n-BuLi, dropwise 63% : 24% (87%, 2.6:1)
1.5 eq n-BuLi 55% : 27% (82%, 2:1)
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-substituted 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\(_2\)Cl\(_2\) gave both regioisomers 182 and 183 in about a 2:1 ratio and a 54% yield (*vida supra*).

![Scheme 3-22a-c](image)

Compound 192 was recrystallized in CH\(_2\)Cl\(_2\)/hexane, and the X-ray crystal structure showed that the *trans* diastereoisomer was isolated (Figure 3-5). It is likely that compounds 190 and
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](image)

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](image)

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\(_2\)O 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 ($R_f$).

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$_2$O$_2$ 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$_2$O$_2$ and NaOH. This gave a 24% yield of the alcohols 203 and 204 in about a 4:1 ratio (Scheme 3-25). 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.

Following on from this, 1-benzyltetrahydroisoquinoline 182 was treated with benzyl bromide in the presence of Et$_3$N to give compound 205 in a 91% yield (Scheme 3-26). Later compound 205 was recrystallized in hexane/CH$_2$Cl$_2$ 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](image)

**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. 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 $-50\,^\circ\mathrm{C}$ and 57:43 at $-72\,^\circ\mathrm{C}$. 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 $-50\,^\circ\mathrm{C}$ (Figure 3-7).
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 $\Delta G^\ddagger \approx 49 \text{ kJ/mol}$, where the phenyl group was in the equatorial position. The second is related to the lithiated intermediate C with $\Delta G^\ddagger \approx 48 \text{ kJ/mol}$ 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.
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).
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 \textit{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 \( \text{D}_2\text{O} \) 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 \( \Delta G^\ddag \approx 68 \text{ KJ/mol} \) and \( \Delta G^\ddag \approx 69 \text{ KJ/mol} \). In comparison the \( \Delta G^\ddag \approx 57 \text{ KJ/mol} \) 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 (\( \Delta G^\ddag \approx 49 \text{ KJ/mol} \) and \( \Delta G^\ddag \approx 48 \text{ KJ/mol} \)). 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.\textsuperscript{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.\textsuperscript{131,132} Two other natural products that contain nitriles are herandia 207 from nymphaefalia and malloapltine 208 from \textit{Mallotus apelta}.\textsuperscript{133,134} Some nitriles have physiological effects in the human body, for example vildagliptin 209 acts as an antibiotic,\textsuperscript{135,136} and bicalutamide 210 is an effective drug used in the treatment of prostate cancer.\textsuperscript{137} Another effective nitrile is milrinone 211, used for the treatment of heart failure.\textsuperscript{138} Escitalopram 212 is used to treat depression.\textsuperscript{139} Anastrazole 213 is used in oestrogen-dependent breast cancer treatment,\textsuperscript{140} and verapamil 214 is used as an antiarrhythmic agent in the treatment of angina.\textsuperscript{138} Lastly, etravirine 215 is a type of non-nucleoside used as an HIV inhibitor in the treatment of AIDS (Figure 4-1).\textsuperscript{141}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4-1.png}
\caption{Figure 4-1}
\end{figure}
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. Therefore several reactions have been reported for the synthesis of racemic and enantioenriched nitriles.

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. Trost and co-workers reported in 2011 the synthesis of nitrile–containing compound 219 (Scheme 4-1). 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.

Another example of an asymmetric synthesis of nitrile–containing compounds has been carried out by the Ruano group (Scheme 4-2). They reported the synthesis of diastereoenriched compounds 221a, b by reacting enantioenriched vinyl sulfoxides 220a, b with Et₂AlCN 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 different diastereoisomers of the starting material.
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.\textsuperscript{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 \textsuperscript{222} will be adopted as Li coordinates to the nitrogen atom. In contrast, C-metallated species \textsuperscript{223} form when less electropositive metals such as Mg, Zn, Pd, and Cu are used (Figure 4-2).\textsuperscript{151,152}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure4-2.png}
\caption{Figure 4-2}
\end{figure}

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 \textsuperscript{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.\textsuperscript{153} Likewise, the X-ray structure of cyclopropanecarbonitrile \textsuperscript{225} in THF contains the Li-N-Li-N dimer. This demonstrated that lithium atoms have an extensive tendency to coordinate to nitrogen.\textsuperscript{154}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure4-3.png}
\caption{Figure 4-3}
\end{figure}

Furthermore, NMR spectroscopic studies on metallated nitriles were carried out using lithiated arylacetonitrile in two different solvents (Figure 4-4).\textsuperscript{155,156} Initially, in Et\textsubscript{2}O, N-metallated species \textsuperscript{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. Likewise, NMR studies on lithiated acetonitrile using a ligand showed that a
ketenimine structure was adopted in THF, due to lithium coordination to the nitrogen.
However, in Et$_2$O the nitrile forms a bridged structure where coordination of N
and C atoms show a rapid equilibrium at $-100 \, ^\circ\text{C}$.\footnote{157,158}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4-4.png}
\caption{Figure 4-4}
\end{figure}

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 determined 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).\footnote{152}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4-5.png}
\caption{Figure 4-5}
\end{figure}

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 $\delta$ 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 $\delta$ 131.2 which indicated that the C-metallated
species was formed. This indicated that metallation is influenced by the carbon scaffold.\footnote{152}
4.1.3 Selective Synthesis Using Organomagnesium Compounds

Enantioselective syntheses of nitrile–containing compounds using magnesium bases have been reported recently. For example, the first enantioselective synthesis of a nitrile–containing compound with microscopic configurational stability was reported by the Carlier group (Scheme 4-3). By subjecting enantiopure bromonitrile 233 to bromine–magnesium exchange at −100 °C for 1 minute, followed by addition of D₂O 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.

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 Et₂O. Also, the reaction was less selective in both THF and 2-MeTHF, while in Et₂O 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 Et₂O showed a saturating dependence of the rate of racemisation (k_rac) on Et₂O. This suggests that in high Et₂O concentrations the structure of intermediate 234 could be either 236 or 237 (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). It was observed that compound 238 underwent highly retentive Mg/Br exchange in Et₂O. 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 Et₂O was 26-fold faster than in 0.12 M Et₂O in toluene, and 800 and 1300 fold faster in 2-MeTHF and THF respectively.

![Scheme 4-4](image)

In 2013, Takeda and co-workers reported enantioselective lithiation–substitution of acyclic enantioenriched nitrile 240 using carbon based electrophiles and \(^{1}\)Pr₂NLi 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 \( \alpha \)-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. Following on from this work, Coldham and co-workers explored the deprotonation of the enantioenriched nitrile 240 using magnesium bases (Scheme 4-5). 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 enantioselectivity 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 \(^{1}\)PrMgCl gave none of the desired products.
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 \(\text{Et}_2\text{O}\) at \(-104\, ^\circ\text{C}\) 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 \(\text{Et}_2\text{O}\) and in a mixture of \(\text{Et}_2\text{O}:\text{THF} (1:1)\). The kinetic data showed that the rate of inversion of the magnesiated intermediate is slightly slower in \(\text{Et}_2\text{O}\) than in THF/\(\text{Et}_2\text{O}\) (the enantiomerisation half–life \(t_{1/2}\) is \(~3\) minutes in \(\text{Et}_2\text{O}\) and only \(~2\) minutes in THF/\(\text{Et}_2\text{O}\)). They hypothesized that this is perhaps because THF helps to solvate the magnesium cation. They also noticed that using \(\text{Et}_2\text{O}\) improves the yields of the products.\(^{165,168}\)

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 focus 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.

\[
\begin{align*}
\text{OH} & \quad \text{1. Et}_3\text{N, CH}_2\text{Cl}_2, 0 ^\circ \text{C} \\
\text{Boc}_2\text{O} & \quad \text{2. Boc}_2\text{O}
\end{align*}
\]

\[
\begin{align*}
\text{OH} & \quad \text{1. Et}_3\text{N, THF} \\
\text{Boc} & \quad \text{2. EtOCOCl, -10 ^\circ C, 30 min} \\
& \quad \text{3. NH}_3, \text{MeOH [7 M], 16 h}
\end{align*}
\]

\[
\begin{align*}
\text{CN} & \quad \text{Et}_3\text{N, THF, 0 ^\circ C} \\
\text{Boc} & \quad \text{TFAA, r.t., 4 h}
\end{align*}
\]

\[
\begin{align*}
\text{NH}_2 & \quad \text{1. Et}_3\text{N, THF} \\
\text{Boc} & \quad \text{2. EtOCOCl, -10 ^\circ C} \\
& \quad \text{3. NH}_3, \text{MeOH [7 M], 16 h}
\end{align*}
\]

\[
\begin{align*}
\text{CN} & \quad \text{Et}_3\text{N, THF, 0 ^\circ C} \\
\text{Boc} & \quad \text{TFAA, r.t., 4 h}
\end{align*}
\]

Initially, THIQ 247 was deprotonated using lithium diisopropylamide (LDA) at \(-78 ^\circ C\) 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 NH₄Cl. 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](image)

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 ν_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 (ν_C=O 1657 cm⁻¹) formed rapidly. This indicated fast lithiation of the enantiopure-247 within ~ 2 minutes (Figure 4-8).

![Scheme 4-9](image)
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\(_4\)Cl. Notably, better yields were obtained when using MeI, PhSSO\(_2\)Ph and MeOCOCN in comparison with both LiHMDS and LDA.

\[
\begin{align*}
\text{(R)- 247} & \quad \text{1. n-BuLi, THF, -78 °C, 2 min} \\
\text{249} & \quad \text{E}^+ \quad \text{-78 °C to r.t.} \\
\text{248a 64\%, E}^+ = \text{MeI} \\
\text{248c 84\%, E}^+ = \text{PhSSO}_2\text{Ph} \\
\text{248d 65\%, E}^+ = \text{MeOCOCN}
\end{align*}
\]

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 \(\nu_{\text{C=O}}\) 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 (\(\nu_{\text{C=O}}\) 1627 cm\(^{-1}\)), indicating fast deprotonation of the nitrile 247 within ~ 2 minutes (Scheme 4-11).
Scheme 4.11. \textit{in-situ} \textit{ReactIR} 3-D and 2-D plots of the deprotonation of 247 at $-104 \, ^\circ \text{C}$; 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 $\alpha$ to nitrile;\textsuperscript{159,167,168} we focused on using TMPMgCl as a base, which was prepared from $^3\text{PrMgCl}$ [2 M] in THF or Et$_2$O 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$_2$O (1:1) at $-104 \, ^\circ \text{C}$. After 10 seconds, methyl cyanoformate was added but no product was obtained. Using PhS-SO$_2$Ph 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, $^3\text{PrMgCl}$ was used instead at $-104 \, ^\circ \text{C}$; unfortunately, no product was formed when using methyl cyanoformate. Therefore, the temperature was changed to $-78 \, ^\circ \text{C}$, using $^3\text{PrMgCl}$ 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$_2$O gave better yields and enantioselectivities (Scheme 4-6). However, the starting material did not dissolve in Et$_2$O and for this reason, a mixture of 2-MeTHF:Et$_2$O was used, and $^3\text{PrMgCl}$ [2 M] in ether was purchased. TMPMgCl in Et$_2$O was added at $-104 \, ^\circ \text{C}$ 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](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>T</th>
<th>base</th>
<th>E⁺ in situ or after 10 min</th>
<th>Yield %</th>
<th>Recovered 247 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF:Et₂O (1:1)</td>
<td>-104 °C</td>
<td>TMPMgCl in THF</td>
<td>MeOCOCN</td>
<td>-</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>THF:Et₂O (1:1)</td>
<td>-104 °C</td>
<td>TMPMgCl in THF</td>
<td>EtOCOCN</td>
<td>-</td>
<td>61</td>
</tr>
<tr>
<td>3</td>
<td>THF:Et₂O (1:1)</td>
<td>-104 °C</td>
<td>TMPMgCl in THF</td>
<td>PhS-SO₂Ph in situ</td>
<td>-</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>THF:Et₂O (1:1)</td>
<td>-78 °C</td>
<td>TMPMgCl in THF</td>
<td>MeOCOCN</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>THF:Et₂O (1:1)</td>
<td>-104 °C</td>
<td>TMPMgCl in Et₂O</td>
<td>MeOCOCN</td>
<td>-</td>
<td>64</td>
</tr>
<tr>
<td>6</td>
<td>THF:Et₂O (1:1)</td>
<td>-104 °C</td>
<td>iPrMgCl in THF</td>
<td>MeOCOCN</td>
<td>-</td>
<td>68</td>
</tr>
<tr>
<td>7</td>
<td>THF:Et₂O (1:1)</td>
<td>-78 °C</td>
<td>iPrMgCl in THF</td>
<td>MeOCOCN</td>
<td>-</td>
<td>72</td>
</tr>
<tr>
<td>8</td>
<td>2-MeTHF:Et₂O (1:1)</td>
<td>-104 °C</td>
<td>TMPMgCl in Et₂O</td>
<td>MeOCOCN</td>
<td>-</td>
<td>63</td>
</tr>
<tr>
<td>9</td>
<td>2-MeTHF:Et₂O (1:1)</td>
<td>-78 °C</td>
<td>TMPMgCl in Et₂O</td>
<td>MeOCOCN</td>
<td>-</td>
<td>59</td>
</tr>
<tr>
<td>10</td>
<td>toluene:Et₂O (1:1)</td>
<td>-104 °C</td>
<td>TMPMgCl in Et₂O</td>
<td>MeOCOCN</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

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 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 KOtBu 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.

![Scheme 4-13](image)

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

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.\textsuperscript{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).

![Scheme 4-14](image)

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\textsubscript{2}O, and after 10 seconds MeOCOCN was added. Quenching the reaction after 30 minutes with aq. NH\textsubscript{4}Cl gave only recovered 247 (Scheme 4-15). (To prepare TMPZnCl, a transmetallation reaction was conducted between TMMPMgCl and ZnCl\textsubscript{2} in ether [2 M] at room temperature for 24 hours).\textsuperscript{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.
The Capriati group has shown how the use of cyclopentylmethyleneether (CPME) had a positive effect on yields when compared to Et₂O in the lithiation of diaryltetrahydrofuran. As a result, TMPMgCl in Et₂O 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-SO₂Ph 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.

Later, an alternative base was prepared in an attempt to improve the yields of the products. Isopropyl magnesium diisopropylamide ([Pr₂N]Mg⁺Pr [0.36 M] 253 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 Et₂O using 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.
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\(_2\)O was conducted at room temperature for 2 hours.\(^{174}\)

\[
\begin{align*}
\text{Nitrile 247} & \quad \xrightarrow{i)} \quad \text{248d, 0\%} \\
\text{[(R)-Nitrile 247]} & \quad \text{Reaction conditions: 1. TMPH, CPME, n-BuLi, 15 min, −78 °C, 2. then −104 °C (R)-247, Et}_2\text{O ZnCl}_2, 1 \text{ hour, 3. MeOCCN, 30 min}
\end{align*}
\]

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

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.

Consequently, the use of other solvents was explored. Firstly, the starting material in Et\(_2\)O 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\(_2\)O, 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.

**Scheme 4-21a**

\[
\begin{align*}
\text{(S)-257} & \xrightarrow{i)} \text{Et}_2\text{O}:\text{THF} \quad (1:1) \quad 10\% \quad 11\% \quad +21\% \text{ RSm} \\
\text{CPME}:\text{THF} \quad (1:1) \quad 21\% \quad 16\% 
\end{align*}
\]

i) Reaction conditions: 1. \(\text{Pr}_2\text{NH}, n\text{-BuLi}, -5\ ^\circ\text{C}, 1\ \text{h}, \text{THF}, 2.\ \text{then (S)-257, 15 min, -78}\ ^\circ\text{C}, \text{solvent}, 3.\ \text{Me}_2\text{CO}, -78\ ^\circ\text{C} \text{to r.t.}

**Scheme 4-21b**

\[
\begin{align*}
\text{(S)-257} & \xrightarrow{i)} \text{Et}_2\text{O}:\text{THF} \quad (1:1) \quad 27\% \quad +11\% \text{ RSm} \\
\text{CPME}:\text{THF} \quad (1:1) \quad 40\% \quad +31\% \text{ RSm} 
\end{align*}
\]

i) Reaction conditions: 1. \(\text{Pr}_2\text{NH}, n\text{-BuLi}, -5\ ^\circ\text{C}, 1\ \text{h}, \text{THF}, 2.\ \text{then (S)-257, 15 min, -78}\ ^\circ\text{C}, \text{solvent}, 3.\ \text{PhCOCl}, -78\ ^\circ\text{C} \text{to r.t.}

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 PhSSO₂Ph 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.

![Scheme 4-22](image)

<table>
<thead>
<tr>
<th>Base</th>
<th>Yield</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrMgCl</td>
<td>8</td>
<td>53:47</td>
</tr>
<tr>
<td>iPrMgCl:LiCl</td>
<td>6</td>
<td>50:50</td>
</tr>
<tr>
<td>TMPMgCl:LiCl</td>
<td>19</td>
<td>50:50</td>
</tr>
<tr>
<td>nBu₂Mg</td>
<td>13</td>
<td>52:48</td>
</tr>
<tr>
<td>TMPMgCl</td>
<td>26</td>
<td>53:47</td>
</tr>
</tbody>
</table>

* All bases were solutions in THF

Table 4-3

As previously stated, using Et₂O gave better yields and enantioselectivities when compared to THF. A project student in the Coldham group under my supervision tried to repeat the reaction above using TMPMgCl in Et₂O. By purchasing a new bottle of iPrMgCl [2 M] in Et₂O to prepare TMPMgCl, an in-situ reaction at −104 °C gave racemic product 258f in only a 5% yield. 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 Et₂O –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. 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 Et₂O 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](image)

* Base was solution in Et₂O

**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 Et₂O 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 Et₂O 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 column, 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. \(^1\)H 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 \( \times \) 3u cellulose–2 column (220 mm \( \times \) 4.60 mm i.d.) or a Chiralpax AD column (220 mm \( \times \) 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·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 Et₂O. The extracts were washed with brine, dried (MgSO₄) 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% NH₄OH (1.08 equiv., 1.08 mmol) in the presence of Raney Ni (0.2 equiv., 0.2 mmol) was stirred vigorously under H₂ (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 (MgSO₄) 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$_2$SO$_4$–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-trifluoro-acetamide derivatives

$N$-(Tetrahydroisoquinoline)-2,2,2-trifluoroacetamide (1 equiv., 1 mmol) was partially dissolved in methanol and water. K$_2$CO$_3$ (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$_2$Cl$_2$, 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$_2$Cl$_2$ (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$_2$Cl$_2$–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 Et₂O (3 × 100 mL), and the organic layers were combined, washed with brine (100 mL), dried (MgSO₄), 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), R₇ 0.12 [petrol–EtOAc (90:10)]; ¹H NMR (400 MHz, CDCl₃, rotamers) δ = 6.64 (1H, s, CH), 6.61 (1H, s, CH), 4.50 (2H, s, NCH₂), 3.87 (6H, s, 2 × OCH₃), 3.65 (2H, t, J 5 Hz, CH₂), 2.77 (2H, t, J 5 Hz, CH₂), 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; R₇ 0.11 [petrol–EtOAc (90:10)]; FTIR ʋ max (film)/cm⁻¹ 3005, 2990, 1675, 1510, 1415; ¹H NMR (400 MHz, CDCl₃, 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, OCH₃), 3.85–3.77 (0.33H, m, CH), 3.80 (3H, s, OCH₃), 3.75 (2H, s, OCH₃), 3.65 (1H, s, OCH₃), 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); ¹³C NMR (100 MHz, CDCl₃, 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 (CH₃), 55.9 & 55.8 (CH₃), 55.7 & 55.6 (CH₃), 55.3 & 55.2 (CH), 42.0 & 41.8 (CH₂), 39.3 & 37.2 (CH₂), 28.5 & 28.3 (CH₃), 28.2 (CH₂); HRMS (ES) Found: MNa⁺, 436.2103. C₂₄H₃₁NO₅Na 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(CH₂)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 120b (2.8 g, 64%) as a separable mixture of diastereoisomers (dr 1:1), each as an oil:

Isomer 120a: (1.4 g, 33%); R₇ 0.27 [petrol–EtOAc (90:10)]; FTIR \( \nu_{\text{max}} \) (film)/cm⁻¹; 2970, 2935, 1685, 1520; \(^1\)H NMR (400 MHz, CDCl₃, rotamers) \( \delta = 6.63–6.55 \) (4H, m, 4 × CH), 5.12–5.10 (1H, m, CH), 4.98–4.96 (1H, m, CH), 4.22–4.19 (0.85H, m, CH), 3.97–3.92 (1.15H, m, CH), 3.85 (12H, br s, 4 × OCH₃), 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, CDCl₃, rotamers) \( \delta = 155.0 & 154.9 \) (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 (CH₃), 55.9 (CH₃), 54.7 & 53.4 (CH), 38.4 & 38.2 (CH₂), 36.9 & 36.2 (CH₂), 28.5 (CH₃), 28.1 & 27.9 (CH₂), 23.5 & 23.2 (CH₂); HRMS (ES) Found: MNa⁺, 649.3533. C₁₉H₂₅NO₄Na requires MNa⁺ 649.3533; LRMS m/z (ES) 649 (100%, MNa⁺).

Isomer 120b: (1.4 g, 33%); R₇ 0.28 [petrol–EtOAc (90:10)]; FTIR \( \nu_{\text{max}} \) (film)/cm⁻¹; 2970, 2935, 1686, 1520 \(^1\)H NMR (400 MHz, CDCl₃, rotamers) \( \delta = 6.63–6.55 \) (4H, m, 4 × CH), 5.12–5.10 (1H, m, CH), 4.98–4.96 (1H, m, CH), 4.22–4.19 (0.8H, m, CH), 4.03–3.94 (1.2H, m, CH), 3.85 (12H, br s, 4 × OCH₃), 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, CDCl₃, rotamers) \( \delta = 155.0 & 154.8 \) (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 (CH₃), 56.0 (CH₃), 54.6 & 53.5 (CH), 38.3 & 38.0 (CH₂), 36.9 & 35.5 (CH₂), 28.5 (CH₃), 28.1 & 27.9 (CH₂), 23.6 & 23.2 (CH₂); HRMS (ES) Found: HRMS (ES) Found: MNa⁺, 649.3533. C₁₉H₂₅NO₄Na 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$_2$)$_4$Br (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 $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2965, 2935, 1680, 1515, 1415; $^1$H NMR (400 MHz, CDCl$_3$) rotamers $\delta = 6.61$–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) $\delta =$ 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$_4$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$_2$Cl$_2$ (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$_2$Cl$_2$ (2 × 5 mL). The combined extracts were dried (MgSO$_4$), evaporated and purified by column chromatography on silica, eluting with CH$_2$Cl$_2$–MeOH (97:3), to give the amine 122 (50 mg, 87%) as an oil; R$_f$ 0.34 [CH$_2$Cl$_2$–MeOH (9:1)]; FTIR $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2990, 2930, 2802, 2750, 1510; $^1$H NMR (400 MHz, CDCl$_3$) $\delta =$ 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$_3$) $\delta =$ 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$^+$).\textsuperscript{101, 102, 100} Data in accordance with the literature.\textsuperscript{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$_2$)$_3$Br (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$_2$Cl$_2$ (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$_2$Cl$_2$ (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; Rp 0.18 [petrol–EtOAc (80:20)]; FTIR $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2935, 2835, 1515, 1460; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 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$_3$) $\delta$ = 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.\textsuperscript{8}

\textit{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; Rp 0.1 [petrol–EtOAc (90:10)]; FTIR $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2970, 2930, 1690, 1520, 1415; $^1$H NMR (400 MHz, CDCl$_3$, rotamers) $\delta$ = 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 × OCH3) 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); 13C NMR (100 MHz, CDCl3, rotamers, CH3 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 (CH3), 53.1 & 52.4 (CH), 39.1 & 37.3 (CH2), 28.4 (CH3), 28.3 & 28.0 (CH2), 26.5 & 26.1 (CH2); HRMS (ES) Found: MNa+, 354.1668. C19H25NO4Na 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), CuSO4·H2O (300 mg, 1.8 mmol), ascorbic acid (300 mg, 1.8 mmol), L-proline (200 mg, 1.8 mmol), and Na2CO3 (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 NH4Cl (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 (MgSO4), 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; Rf 0.11 [petrol–EtOAc (50:50)]; FTIR νmax (film)/cm–1 3000, 2970, 1690, 1365; 1H NMR (400 MHz, CDCl3, 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, OCH3), 3.81 (1.7H, s, OCH3). 3.76 (1.3H, s, OCH3), 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); 13C NMR (100 MHz, CDCl3, rotamers, CH3 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 (CH3), 54.5 & 53.1 (CH), 54.0 (CH2), 38.3 & 36.4 (CH2), 32.8 (CH2), 28.3 & 28.1 (CH3), 28.0 (CH2); HRMS (ES) Found: MNa+, 487.2316. C26H32N4O4Na 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 \(\nu\)max (film)/cm\(^{-1}\) 2970, 2930, 1685, 1515; \(^1\)H NMR (400 MHz, CDCl\(_3\), rotamers) \(\delta = 6.75–6.58\) (5H, m, 5 × CH), 5.93 (2H, s, OCH\(_2\)O), 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) \(\delta = 154.9\) (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 \(m/\mathbf{z}\) (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\(_2\)Cl\(_2\)–MeOH.
(9:1). The filtrate was evaporated. Purification by flash column chromatography on silica gel, eluting with Et₂O–Petrol (97.5:2.5), gave (±)-dysoxyline 127 (60 mg, 75%) as an oil; R\textsubscript{f} 0.12 [petrol–EtOAc (90:10)]; FTIR \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 2935, 2780, 1515, 1490; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta = 6.74–6.69 \) (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\(_2\)O), 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\(_3\)) \( \delta = 147.5 \) (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

![Image of 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\(_2\)Cl\(_2\) (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

![Image of 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\(_2\)Cl\(_2\) (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\(_2\)O (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; Rf 0.32 [petrol–EtOAc (90:10)]; 1H NMR (400 MHz, CDCl₃) δ = 6.79–6.77 (1H, m, CH), 6.72–6.67 (2H, m, 2 × CH), 5.96 (2H, s, OCH₂), 3.35 (2H, t, J 7.5 Hz, CH₂), 3.09 (2H, t, J 7.5 Hz, CH₂). Data in accordance with the literature.¹⁰⁶

**tert-Butyl 6,7-dimethoxy-1-(trimethylsilyl)-3,4-dihydro-1H-isquinoline-2-carboxylate 131 & 1,2,3,4-Tetrahydroisquinolin-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 H₂O₂ (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 CH₂Cl₂ (2 × 20 mL), dried (MgSO₄), 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; Rf 0.6 [petrol–EtOAc (80:20)]; 1H NMR (400 MHz, CDCl₃, 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, SiMe₃), 0.07 (4.5H, s, SiMe₃). data in accordance with the literature.⁶⁷

Carbamate 132 (0.05 g, 5%) as an oil; Rf 0.1 [petrol–EtOAc (90:10)]; FTIR νmax (film)/cm⁻¹ 3340, 2960, 2930, 1715, 1520; ¹H NMR (400 MHz, CDCl₃) δ = 6.63 (1H, s, CH), 6.60 (1H, s, CH), 4.51 (1H, s, CH), 3.87 (6H, s, 2 × OCH₃), 3.84–3.83 (2H, m, CH₂), 2.78–2.75 (2H, m, CH₂), 1.70 (1H, br s, NH), 1.50 (9H, s, t-Bu); ¹³C NMR (100 MHz, CDCl₃) 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 (CH₂), 55.9 (CH₃), 55.7 (CH), 40.0 (CH₂), 29.6 (CH₂), 28.5 (CH₃); HRMS (ES) Found: MNa⁺, 316.1521. C₁₆H₂₃NO₄Na 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$_2$Cl$_2$–MeOH–conc. NH$_3$ (97.9: 2: 0.1), the amine 134 (4.7 g, 90%) as an oil; R$_f$ 0.1 [CH$_2$Cl$_2$–MeOH–conc. NH$_3$ (90:9:1)]; FTIR $\nu_{\max}$ (film)/cm$^{-1}$ 2965, 2890, 1660, 1485; $^1$H NMR (400 MHz, CDCl$_3$) $\delta =$ 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$_2$O), 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$_3$) $\delta =$ 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$_9$H$_{12}$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$_2$O (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$_2$Cl$_2$ (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$_2$Cl$_2$–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$_2$Cl$_2$ (3 × 50 mL), the combined organic layers were dried (MgSO$_4$), evaporated and purified by flash column chromatography on silica gel, eluting with CH$_2$Cl$_2$–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$_2$Cl$_2$–MeOH–conc. NH$_3$ (90:9:1)]; FTIR
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 into NaOH (50 mL, 1 M), extracted using CH₂Cl₂ (3 × 200 mL), dried (MgSO₄), evaporated and purified by flash column chromatography on silica gel, eluting with CH₂Cl₂–MeOH–conc. NH₃ (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; R₇ 0.5 [petrol–EtOAc (90:10)]; FTIR 𝜈max (film)/cm⁻¹ 2975, 2930, 2900, 1690; ¹H NMR (400 MHz, CDCl₃) δ = 6.60–6.58 (2H, m, 2 × CH), 5.92 (2H, s, OCH₂O), 4.46 (2H, s, NCH₂), 3.62 (2H, t, J 6 Hz, CH₂), 2.74 (2H, t, J 6 Hz, CH₂), 1.51 (9H, s, t-Bu); ¹³C NMR (100 MHz, CDCl₃, 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 (OCH₂O), 79.8 (C), 46.0 & 45.2 (CH₂), 41.8 & 40.6 (CH₂), 28.9 (CH₂), 28.4 (CH₃); HRMS (ES) Found: MNa⁺, 300.1201. C₁₅H₁₉NO₄Na 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 \(\nu_{\text{C}=\text{O}}\). After addition of n-BuLi, a new peak at 1642 cm\(^{-1}\) appeared which was assigned to \(\nu_{\text{C}=\text{O}}\) 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 \(-50^\circ\text{C}\), 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 \(\nu_{\text{C}=\text{O}}\). After addition of n-BuLi, a new peak at 1636 cm\(^{-1}\) appeared which was assigned to \(\nu_{\text{C}=\text{O}}\) 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\(_3\)SnCl (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 \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2960, 2920, 2870, 1700; \(^1\)H NMR (400 MHz, CDCl\(_3\), rotamers) \(\delta = 6.55–6.50\) (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\(_2\)CH\(_2\)CH\(_2\)CH\(_3\)]\(_3\)], 0.57–0.59 [15H, m, Sn(CH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\)]\(_3\)]; \(^{13}\)C NMR (100 MHz, CDCl\(_3\) rotamers) \(\delta = 153.6 \& 153.3 \) (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), 97.7 & 79.1 (C), 49.8 & 49.5 (CH), 41.9 & 40.9 (CH<sub>2</sub>), 29.5 (CH<sub>2</sub>), 29.0 & 28.9 (CH<sub>2</sub>), 28.6 & 28.5 (CH<sub>2</sub>), 27.5 & 27.4 (CH<sub>3</sub>), 13.5 (CH<sub>3</sub>), 10.5 & 10.3 (CH<sub>2</sub>); HRMS (ES) Found: MH<sup>+</sup>, 568.2470. C<sub>27</sub>H<sub>46</sub>NO<sub>4</sub> requires MH<sup>+</sup>, 568.2449; LRMS m/z (ES), 568.2 (40%, MH<sup>+</sup> for <sup>120</sup>Sn), 566.2 (100, MH<sup>+</sup> for <sup>118</sup>Sn).

6-<i>tert</i>-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), <i>n</i>-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<sub>f</sub> 0.4 [petrol–EtOAc (90:10)]; FTIR ʋ<sub>max</sub> (film)/cm<sup>–1</sup> 2960, 2930, 1745, 1695, 1485, 1155, 1040; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 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<sub>3</sub>), 2.90–2.70 (2H, m, 2 × CH), 1.48 (9H, s, Bu); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub> 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<sub>2</sub>), 80.7 & 80.5 (C), 58.6 & 57.5 (CH<sub>3</sub>), 52.4 & 52.3 (CH), 40.8 & 39.8 (CH<sub>2</sub>), 28.9 & 28.7 (CH<sub>2</sub>), 28.4 & 28.3 (CH<sub>3</sub>); HRMS (ES) Found: MH<sup>+</sup>, 336.1453. C<sub>17</sub>H<sub>22</sub>NO<sub>6</sub> requires MH<sup>+</sup> 336.1447; LRMS m/z (ES), 336 (100, MH<sup>+</sup>).

Using general procedure A, tetrahydroisoquinoline 136 (100 mg, 0.36 mmol), <i>n</i>-BuLi (0.17 mL, 0.43 mmol) and MeOCOC1 (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.

<i>tert</i>-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; Rf 0.39 [petrol–EtOAc (90:10)]; FTIR $\tilde{\nu}_{\text{max}}$ (film)/cm$^{-1}$ 2970, 2875, 1670, 1485; $^1$H NMR (400 MHz, CDCl$_3$, rotamers) $\delta = 6.58$–$6.57$ (2H, m, 2 × 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) $\delta = 154.9$ & 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$_4$Na 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; Rf 0.36 [petrol–EtOAc (90:10)]; FTIR $\tilde{\nu}_{\text{max}}$ (film)/cm$^{-1}$ 2965, 2930, 1680, 1480, 836, $^1$H NMR (400 MHz, CDCl$_3$, rotamers ) $\delta = 6.60$ (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) $\delta = 154.4$ (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$_4$SiNa, 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**

![Structure of 138f](image)

Using general procedure A, THIQ 136 (100 mg, 0.36 mmol), n-BuLi (0.17 mL, 0.43 mmol) and PhCH₂Br (0.15 mL, 1.26 mmol) gave after purification by column chromatography on silica gel, eluting with petrol–EtOAc (93:7), the carbamate 138f (87 mg, 66%) as an oil; Rf 0.41 [petrol–EtOAc (90:10)]; FTIR νmax (film)/cm⁻¹ 2975, 2925, 1680, 1485; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃, 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 (CH₂), 79.6 & 79.4 (C), 56.8 & 55.7 (CH), 43.0 & 42.7 (CH₂), 39.3 & 37.0 (CH₂), 29.7 & 28.6 (CH₂), 28.5 & 28.4 (CH₃); HRMS (ES) Found: MNa⁺, 390.1674. C₂₂H₂₆NO₄Na 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**

![Structure of 139](image)

A solution of carbamate 138f (100 mg, 0.24 mmol) in THF (1 mL) was added dropwise to a stirred suspension of LiAlH₄ (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 CH₂Cl₂–MeOH (9:1). The filtrate was evaporated and purified by column chromatography on silica, eluting with CH₂Cl₂–MeOH (95:5), to give the amine 139 (50 mg, 69%) as an oil; Rf 0.4 [CH₂Cl₂–MeOH (9.5:0.5)]; FTIR νmax (film)/ cm⁻¹ 2925, 2775, 1480, 1240; ¹H NMR (250 MHz, CDCl₃, rotamers) δ...
MHz, CDCl$_3$) $\delta = 7.30$–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$_3$) $\delta = 145.8$ (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

![2-(4-Chlorophenyl)ethanamine 141](image)

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$_2$Cl$_2$–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$_2$Cl$_2$–MeOH–conc. NH$_3$ (90:9:1)]; FTIR $\nu_{max}$ (film)/cm$^{-1}$ 3370, 2930, 2860, 1490; $^1$H NMR (400 MHz, CDCl$_3$) $\delta = 7.23$–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$_3$) $\delta = 138.3$ (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$_8$H$_{11}$N$_3$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$_2$O (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$_2$Cl$_2$ (3 × 250 mL), dried (MgSO$_4$), evaporated. Purification by column chromatography on silica gel, eluting with CH$_2$Cl$_2$–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

![$N$-(4-Chlorophenethyl)-2,2,2-trifluoroacetamide 142](image)
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; Rf 0.3 [petrol–EtOAc (90:10)]; FTIR \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 3360, 2970, 2965, 1730; \(^1\)H NMR (400 MHz, CDCl\(_3\), rotamers) \( \delta = 7.34–7.32 \) (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) \( \delta = 157.3 \) (C=O, q, \( J = 37 \) Hz), 136.0 (C), 132.8 (C), 130.0 (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\(_9\)F\(_3\)ClNO requires MH\(^+\) 252.0421; LRMS m/z (ES) 254 (MH\(^+\), 33% for \(^{37}\)Cl), 252 (MH\(^+\), 100% for \(^{35}\)Cl). Data in accordance with the literature.\(^{114}\)

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; Rf 0.41 [petrol–EtOAc (90:10)]; FTIR \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 3005, 2970, 2950, 1690, 1460; \(^1\)H NMR (400 MHz, CDCl\(_3\), rotamers) \( \delta = 7.24–7.20 \) (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) \( \delta = 156.2 \) (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\(_{10}\)F\(_3\)ClNO requires MH\(^+\) 252.0421; LRMS m/z (ES) 266 (34%, MH\(^+\) for \(^{37}\)Cl), 254 (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\(_2\)CO\(_3\) (4.3 g, 32 mmol) gave after purification by column chromatography on silica gel, eluting with CH\(_2\)Cl\(_2\)–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; Rf 0.11 [CH\(_2\)Cl\(_2\)–MeOH–conc. NH\(_3\) (90:10)]; FTIR \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 3315,
2925, 2855, 1485; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.13–7.11\) (1H, m, CH), 7.05–7.02 (2H, m, 2 \times 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\(_3\)) \(\delta = 136.4\) (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\(_9\)H\(_{11}\)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 \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2980, 2935, 1670, 1420; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.16–7.07\) (3H, m, 3 \times CH), 4.55 (2H, s, NCH\(_2\)), 3.65–3.63 (2H, m, 2 \times 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) \(\delta = 154.7\) (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 \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2975, 2930, 1690, 1420; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.15–7.14\) (2H, m, 2 \times 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 \times CH), 1.50 (9H, s, t-Bu); \(^{13}\)C NMR (100 MHz, CDCl\(_3\), rotamers) \(\delta = 154.7 & 154.5\) (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 (CH2), 80.1 & 79.7 (C), 54.2 & 53.3 (CH), 41.3 & 41.0 (CH2), 38.2 & 36.5 (CH2), 28.4 (CH3), 28.2 & 28.0 (CH2); HRMS (ES) Found: MNa+, 330.1223. C17H22ClNO2Na, requires MNa+ 330.1237; LRMS m/z (ES) 332 (33%, MNa+ for 37Cl), 330 (100%, MNa+ for 35Cl).

tert-Butyl 1-butyl-7-chloro-3,4-dihydro-1H-isooquinoline-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; Rf 0.48 [petrol–EtOAc (95:5)]; FTIR $\nu_{\text{max}}$ (film)/cm$^{-1}$, 2960, 2930, 1680, 1460; $^1$H NMR (400 MHz, CDCl3, rotamers) $\delta$ = 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, CDCl3, rotamers, C=O, NCH couldn’t be observed) $\delta$ = 143.5 (C), 135.9 (C), 132.2 (C), 128.9 (CH), 125.7 (CH), 125.6 (CH), 81.2 (C), 43.2 (CH2), 30.1 (CH2), 29.7 (CH2), 28.6 (CH3), 26.0 (CH2), 22.8 (CH2), 14.0 (CH3); HRMS (ES) Found: MH+, 324.1728. C18H27NO2Cl required MH+ 324.1730; LRMS m/z (ES) 324 (100%, MH+ for 35Cl), 326 (35% MH+ for 37Cl).

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

Using general procedure A, THIQ 145 (100 mg, 0.37 mmol), n-BuLi (0.17 mL, 0.44 mmol) and SiMe3Cl (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; Rf 0.36 [petrol–EtOAc (95:5)]; FTIR $\nu_{\text{max}}$ (film)/cm$^{-1}$, 2980, 2930, 1700, 1420, 935; $^1$H NMR (400 MHz, CDCl3, rotamers) $\delta$ = 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, SiMe₃); ¹³C NMR (100 MHz, CDCl₃, 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 (CH₂), 28.5 & 28.4 (CH₂), 28.3 & 28.0 (CH₂), –1.4 & –1.7 (CH₃); HRMS (ES) Found: MNa⁺, 362.1329. C₁₇H₂₆NO₂NaSi₃5Cl requires MNa⁺ 362.1319; LRMS m/z (ES) 364 (33%, MNa⁺ for 37Cl), 362 (100%, MNa⁺ for 35Cl).

**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 ClSnBu₃ (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; Rf 0.6 [petrol–EtOAc (95:5)]; FTIR νmax (film)/cm⁻¹ 2955, 2925, 2855, 1700, 1150; ¹H NMR (400 MHz, CDCl₃, 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, J₁₂, 6 Hz, CH), 3.31 (0.5H, ddd, J₁₂, 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(CH₂CH₂CH₂CH₃)₃], 0.95–0.78 [15H, m, Sn(CH₂CH₂CH₂CH₃)₃]; ¹³C NMR (100 MHz, CDCl₃, 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 (CH₂), 29.0 (CH₂), 28.9 & 28.8 (CH₂), 28.6 & 28.5 (CH₃), 27.4 & 27.3 (CH₂), 13.5 (CH₃), 10.6 & 10.4 (CH₂); HRMS (ES) Found: MH⁺, 558.2134. C₂₆H₃₅NO₃Cl⁵₀Sn requires MH⁺ 558.2161; LRMS m/z (ES) 560 (33%, MH⁺, for 37Cl), 558 (100%, MH⁺ for 35Cl).

**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 CH₂Cl₂: MeOH: conc. NH₃ (93.75:6:0.25), the amine 148 (13.2 g, 92%) as an oil; Rf 0.18 [CH₂Cl₂:MeOH:conc. NH₃ (90:9:1)]; FTIR νmax (film)/cm⁻¹ 3315, 2970, 1450; ¹H NMR (400 MHz, CDCl₃) 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), 3.12 (2H, t, J 8 Hz, CH); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ = 138.5 (C), 131.8 (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. \(\text{C}_9\text{H}_{11}\text{NF}_3\) requires MH\(^+\) 190.0844; LRMS \(m/\zeta\) (ES) 190 (100%, MH\(^+\)). Data in accordance with the literature, only mass spectrum and \(^1\)H NMR were reported.\(^{191}\)

\(N\)-(2-(Trifluoromethyl)phenethyl)-2,2,2-trifluoroacetamide 149

![Chemical Structure](image)

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 \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 3315, 1700, 1560; \(^1\)H 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. \(\text{C}_{11}\text{H}_{9}\text{F}_6\text{NO}\) requires M\(^+\) 285.0583; LRMS \(m/\zeta\) (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

![Chemical Structure](image)

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 \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2970, 1695, 1465; \(^1\)H 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$_2$CO$_3$ (5.3 mL, 38.5 mmol) gave after purification by column chromatography on silica gel, eluting with CH$_2$Cl$_2$–MeOH–conc. NH$_3$ (93.4:6:0.25), the amine 151 (1.44 g, 75%) as an oil; R$_f$ 0.16 [CH$_2$Cl$_2$:MeOH:conc. NH$_3$ (90:9:1)]; FTIR $\nu_{\text{max}}$ (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 $\nu_{\text{max}}$ (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$_2$F$_3$Na 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$_2$)$_3$Ph (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 $\upsilon_{\text{max}}$ (film)/cm$^{-1}$ 2970, 2930, 1690, 1420; $^1$H NMR (400 MHz, CDCl$_3$, rotamers) $\delta$ = 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) $\delta$ = 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$_2$F$_3$Na 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$_2$)$_3$OPh (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 $\upsilon_{\text{max}}$ (film)/cm$^{-1}$ 2970, 1685, 1420; $^1$H NMR (400 MHz,
CDCl$_3$, rotamers) $\delta = 7.52$–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) $\delta = 159.0$ (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$_3$F$_3$Na 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$_2$)$_3$CH$_3$ (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 $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2965, 2930, 1690, 1425; $^1$H NMR (400 MHz, CDCl$_3$, rotamers) $\delta = 7.52$–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) $\delta = 154.8$ (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$_2$F$_3$Na 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; Rf 0.19 [petrol–EtOAc (95:5)]; FTIR \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 2990, 2935, 1750, 1660, 1390; \(^1\)H NMR (400 MHz, CDCl\(_3\), rotamers) \( \delta = 7.70 – 7.68 \) (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) \( \delta = 171.6 & 171.2 \) (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\(_4\)F\(_3\) 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\(_2\))\(_3\)Br (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; Rf 0.4 [petrol–EtOAc (80:20)]; FTIR \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 2975, 2925, 1690, 1420; \(^1\)H NMR (400 MHz, CDCl\(_3\), rotamers) \( \delta = 7.55–7.53 \) (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) \( \delta = 154.9 & 154.2 \) (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\(_2\)).
Trifluoroacetic acid (0.28 mL, 3.66 mmol) was added to a solution of carbamate 153f (400 mg, 0.95 mmol) in CH₂Cl₂ (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 CH₂Cl₂ (2 × 5 mL). The combined extracts were dried (MgSO₄), 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; Rf 0.5 [petrol–EtOAc (80:20)]; FTIR νmax (film)/ cm⁻¹ 2920, 2850, 1470, 1375; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) δ = 140.5 (C), 133.0 (C), 129.6 (CH), 128.1 (C, q, J 25 Hz), 125.7 (CH), 124.5 (CF₃, q J 276 Hz), 123.9 (CH, q, J 7 Hz), 63.5 (CH), 53.5 (CH₂), 47.9 (CH₂), 30.6 (CH₂), 25.4 (CH₂), 22.1 (CH₂); HRMS (ES) Found: MH⁺, 242.1147. C₁₃H₁₅NF₃ requires MH⁺ 242.1147; LRMS m/z (ES) 242 (100%, MH⁺). ³⁰¹, ³⁰², ¹⁰⁰
5.3 Chapter 3 Experimental

\[ N-(1,2\text{-Diphenylethyl})\text{-}2,2,2\text{-trifluoroacetamide} \] 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 petrol–EtOAc (96.5:3.5), the acetamide 156 (7.1 g, 96%) as an oil; \( R_f \) 0.2 [petrol–EtOAc (90:10)]; FTIR \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 3335, 3005, 2915, 1695, 1550; \(^1\)HNMR (400 MHz, CDCl\(_3\), rotamers) \( \delta \) = 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) \( \delta \) = 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\(_3\)NO, requires MH\(^+\) 294.1133; LRMS m/z (ES) 294 (100%, MH\(^+\)). Data in accordance with the literature.\(^{192}\)

\[ N,N\text{-Diethyl-2-methylbenzamide} \] 159

O-Toluic acid (0.5 g, 3.7 mmol) and \( N,N\text{-dimethylformamide} \) (0.05 mL, 0.07 mmol) in CH\(_2\)Cl\(_2\) (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\(_3\),) \( \delta \) = 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\(_3\)), 1.8 (3H, t, \( J \) 7 Hz, CH\(_3\)), 1.05 (3H, t, \( J \) 7, CH\(_3\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\),) \( \delta \) = 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](phenylmethylene)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)]; ^1H NMR (400 MHz, CDCl_3) δ = 8.40 (1H, s, CH), 7.81–7.79 (2H, m, 3 × 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); ^13C 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 mixture 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 ν_{max} (film)/cm\(^{-1}\) 3225, 3010, 2980, 2935, 1750, 1610 1600; ^1H 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); ^13C 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), 61.5 (OCH$_3$), 55.2 (CH), 50.3 (CH), 43.4 (CH), 43.2 (CH), 39.3 (CH), 14.0 (CH), 12.7 (CH); HRMS (ES) Found: MH$^+$, 417.2533. C$_{27}$H$_{32}$N$_2$O$_2$ requires MH$^+$ 417.2537; LRMS m/z (ES) 417 (100%, MH$^+$).

**p-Toluenesulfonamide 166**

![Structure of p-Toluenesulfonamide](image)

*p*-Toluensulfonyl chloride (3.0 g, 15.8 mmol) was added in portions to NH$_4$OH [2.6 mL, 47.3 mmol, 18 M in H$_2$O]. 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$_2$Cl$_2$–MeOH (80:20)]; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 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**

![Structure of 1-Methyl-4-[(E)-2-phenylethenesulfonyl]benzene](image)

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$_2$O (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$_2$Cl$_2$ (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$_2$Cl$_2$ (20:80)]; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 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

\[ \text{\includegraphics[width=0.2\textwidth]{amide168.png}} \]

$n$-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$_3$N (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$_4$Cl (10 mL) was added. The solvent was evaporated and the residue was extracted using CH$_2$Cl$_2$ (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.\textsuperscript{119} 133–135 °C); R$_f$ 0.45 [petrol–EtOAc (50:50)]; FTIR $\nu_{max}$ (film)/cm$^{-1}$ 2835, 1600, 1575; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 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.\textsuperscript{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$_2$Cl$_2$ (2 × 100 mL). The combined extracts were dried (MgSO$_4$), evaporated and purified by column chromatography on silica, eluting with CH$_2$Cl$_2$–MeOH (92:8), gave the amide 170 (5.3 g, 93%) as an amorphous solid; mp 117–120 °C (lit.\textsuperscript{120} 111.5–112.5 °C); R$_f$ 0.18 [CH$_2$Cl$_2$–MeOH (90:10)]; FTIR $\nu_{max}$ (film)/cm$^{-1}$ 3275, 3030, 2920, 1660, 1535; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 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\(_3\)) \(\delta = \) 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

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

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\(_2\)Cl\(_2\) (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

![3-Phenyl-3,4-dihydroisoquinoline 173](image)

The crude intermediate 172 (10.5 g, 37.6 mmol) was dissolved in MeOH (140 mL) and H\(_2\)SO\(_4\) (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 \(\times\) 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

NaBH₄ (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 CH₂Cl₂ (150 mL × 2), dried (MgSO₄), evaporated and the residue was purified by column chromatography on silica, eluting with CH₂Cl₂–MeOH (92:8), to give the amine 174 (6.1 g, 61% over four steps) as an oil; Rᶠ 0.21 [CH₂Cl₂–MeOH (90:10)]; ¹H NMR (400 MHz, CDCl₃) 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.

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; Rᶠ 0.23 [petrol–EtOAc (90:10)]; FTIR νmax (film)/cm⁻¹ 3005, 2975, 1690, 1455; ¹H NMR (400 MHz, CDCl₃, 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); ¹³C NMR (100 MHz, CDCl₃, 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 (CH₂), 35.9 (CH₂), 28.4 (CH₃); HRMS (ES) Found: MNa⁺, 332.1614. C₂₀H₂₃NO₂Na 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 \(\nu_{\text{C=O}}\). After addition of n-BuLi, new peaks at \(\nu_{\text{C=O}}\) 1642 cm\(^{-1}\) and 1632 cm\(^{-1}\) appeared which was assigned to \(\nu_{\text{C=O}}\) 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-isooquinoline-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 \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 3005, 2975, 1685, 1515, 1150; \(^1\)H NMR (400 MHz, CDCl\(_3\), rotamers) \(\delta = 7.14–7.08\) (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, \(J_{\text{16 Hz}}\), CH), 4.35 (0.5H, d, \(J_{\text{16 Hz}}\), CH), 3.59 (0.5H, d, \(J_{\text{16 Hz}}\), CH), 3.43 (0.5H, d, \(J_{\text{16 Hz}}\), 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\(_2\)CH\(_2\)CH\(_2\)CH\(_3\))], 0.89–0.73 [15H, m, (SnCH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\))]; \(^{13}\)C NMR (100 MHz, CDCl\(_3\), rotamers, C=O) \(\delta = 157.1\) (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 \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2970, 2945, 2930, 1690, 1495, 1170; \(^1\)H NMR (400 MHz, CDCl\(_3\), rotamers) \(\delta = 7.24–7.07\) (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) \(\delta = 155.1\) (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), 127.3 & 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\(_2\)Na 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 \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 2970, 2930, 2920, 1685, 1495, 1170; \(^1\)H NMR (400 MHz, CDCl\(_3\), rotamers) \( \delta = 7.36–7.35 \) (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) \( \delta = 155.1 \) & 154.6 (2 × C=O), 145.2 (C), 143.0 (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), 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\(_3\)).

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 \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 3025, 2970, 2925, 1690, 1120; \(^1\)H NMR (400 MHz, CDCl\(_3\), rotamers) \( \delta = 7.26–7.24 \) (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\(_3\)).
(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$_2$), 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$_2$Na requires MNa$^+$ 436.2247; LRMS m/z (ES) 436 (100%, MNa$^+$).

tert-Butyl (1R,3S)-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 Mel (0.07 mL, 1.16 mmol) gave after recrystallisation using hexane–CH$_2$Cl$_2$, 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 $\nu_{\text{max}}$ (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$_2$Na 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 $\nu_{\text{max}}$ (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 (CH2), 46.3 (CH2), 28.0 (CH3), 25.1 (CH3); HRMS (ES) Found: MNa+, 346.1789. C21H25NO2Na, requires MNa+; 346.1780, LRMS m/z (ES) 346 (100%, MNa+).

tert-Butyl 1-butyl-3-phenyl-3,4-dihydro-1H-isquinoline-2-carboxylate 177f and tert-Butyl 3-butyl-3-phenyl-1,4-dihydroisquinoline-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; Rf 0.57 [petrol–EtOAc (80:20)]; FTIR \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 3005, 2955, 2925, 1685, 1170; \(^1\)H NMR (400 MHz, CDCl3, rotamers) \( \delta = 7.21–7.07 \) (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, tert-Bu), 0.99–0.88 (4H, m, 4 × CH); \(^13\)C NMR (100 MHz, CDCl3, rotamers) \( \delta = 155.1 \) (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 (CH2), 44.4 (CH2), 43.7 & 43.1 (CH2), 40.6 & 39.9 (CH2), 37.0 (CH2), 36.2 (CH2), 29.3 & 28.9 (CH2), 28.5 & 28.3 (CH3), 28.0 (CH3), 27.3 & 26.6 (CH2), 23.2 & 22.7 (CH2), 14.2 (CH3), 14.1 (CH3); HRMS (ES) Found: MNa+, 388.2240. C24H31NO2Na requires MNa+ 388.2247; LRMS m/z (ES) 388 (100%, MNa+).

tert-Butyl 3-phenyl-3,4-dihydro(1-²H1)-1H-isquinoline-2-carboxylate 177g tert-Butyl 3-phenyl-1,4-dihydro(3-²H)isquinoline-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 \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 3005, 2970, 2925, 1690, 1160; \(^1\)H NMR (400 MHz, CDCl\(_3\), rotamers) \( \delta = 7.13 - 7.03 \) (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) \( \delta = 155.3 \) (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: M\( \text{Na}^+ \), 333.1682. \( C_{20}H_{22}DNO_2 \text{Na} \) requires M\( \text{Na}^+ \) 333.1684; LRMS \( m/z \) (ES) 333 (100%, M\( \text{Na}^+ \)); Found: C, 76.91; H, 7.57; N, 4.07. \( C_{20}H_{22}DNO_2 \text{Na} \) 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 \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 2955, 2925, 2890, 1670, 1455, 1155; \(^1\)H NMR (400 MHz, CDCl\(_3\), rotamers) \( \delta = 6.95 - 6.90 \) (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\(_3\) & \( \text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \)], 1.24–1.18 [6H, m, \( \text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \)], 0.81–0.74 [15H, m, \( \text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\), rotamers) \( \delta = 156.1 \) (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: M\( \text{Na}^+ \), 636.2841. \( C_{33}H_{51}NO_2^{120}\text{SnNa} \) requires M\( \text{Na}^+ \) 636.2839; LRMS \( m/z \) (ES) 636 (100%, M\( \text{Na}^+ \).
1-Benzyl-3-phenyl-1,2,3,4-tetrahydroisoquinoline 182 and 3-benzyl-3-phenyl-2,4-dihydro-1H-isooquinoline 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 CH₂Cl₂ (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 CH₂Cl₂ (2 × 20 mL). The combined extracts were dried (MgSO₄) 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; R₇ 0.2 [petrol–EtOAc (90:10)]; FTIR v_max (film)/ cm⁻¹ 3330, 3060, 3020, 1500; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 (CH₂), 38.1 (CH₂); HRMS (ES) Found: MH⁺, 300.1719. C₂₂H₂₁N requires MH⁺ 300.1746; LRMS m/z (ES) 300 (100%, MH⁺). No data were available.

Amine 183 (21 mg, 22%) as an oil; R₇ 0.2 [petrol–EtOAc (80:20)]; FTIR v_max (film)/cm⁻¹ 3330, 3060, 3020, 1500; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 (CH₂), 36.8 (CH₂), 29.7 (CH₂); HRMS (ES) Found: MH⁺, 300.1717. C₂₂H₂₁N requires MH⁺ 300.1746; LRMS m/z (ES) 300 (100%, MH⁺).
Using general procedure A, THIQ 175 (0.15 g, 0.48 mmol), n-BuLi (0.24 mL, 0.57 mmol), and Br(CH₂)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 CH₂Cl₂ (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 CH₂Cl₂ (2 × 50 mL), the combined extracts were dried (MgSO₄), 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; Rₜ 0.22 [petrol–EtOAc (80:20)]; FTIR vₑₑₓₐₜ (film)/cm⁻¹ 3000, 2990, 2950, 1450; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 (CH₂), 38.6 (CH₂), 32.0 (CH₂), 23.1 (CH₂); HRMS (ES) Found: MH⁺, 250.1591. C₁₈H₁₉N 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; Rₜ 0.25 [petrol–EtOAc (80:20)]; FTIR vₑₑₓₐₜ (film)/cm⁻¹ 2950, 2920, 1600, 1450; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 (CH₂), 50.0 (CH₂), 41.6 (CH₂), 36.7
Using general procedure A, THIQ 175 (0.15 g, 0.48 mmol), n-BuLi (2.4 mL, 0.57 mmol), and Br(CH₂)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 CH₂Cl₂ (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 CH₂Cl₂ (2 × 20 mL). The combined extracts were dried (MgSO₄), 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; R₇ 0.22 [petrol–EtOAc (80:20)]; FTIR ʋmax (film)/cm⁻¹ 3005, 2970, 1480; ¹H NMR (400 MHz, CDCl₃) 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, CH₂), 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)]; ¹³C NMR (100 MHz, CDCl₃) 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 (CH₂), 36.0 (CH₂), 31.2 (CH₂), 25.0 (CH₂), 23.3 (CH₂); HRMS (ES) Found: MH⁺, 264.1748. C₁₅H₂₁N requires MH⁺ 264.1747; LRMS m/z (ES) 264 (100%, MH⁺).
Amine 189 (30 mg, 24%) as a gum; Rf 0.54 [petrol–EtOAc (80:20)]; FTIR \( \nu_{\text{max}} \) (film)/cm\(^{-1}\): 2960, 2940, 1450; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta = 7.56–7.55 \) (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), 1.72–1.61 (3H, m, 3 × CH); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta = 147.0 \) (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 carbamates 177f and 178f in (4:1) ratio (0.1 g, 0.27 mmol) in CH\(_2\)Cl\(_2\) (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\(_2\)Cl\(_2\) (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; Rf 0.45 [petrol–EtOAc (80:20)]; FTIR \( \nu_{\text{max}} \) (film)/cm\(^{-1}\): 3315, 2955, 2920, 1490, 1450; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta = 7.51–7.48 \) (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\(_3\)) \( \delta = 149.4 \) (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 CH₂Cl₂ (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 CH₂Cl₂ (2 × 50 mL). The combined extracts were dried (MgSO₄), 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; Rf 0.37 [petrol–EtOAc (80:20)]; FTIR νmax (film)/cm⁻¹ 3350, 2955, 2920, 1630, 1490; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 (CH₂), 55.7 (CH), 51.6 (CH), 41.3 (CH₂), 37.8 (CH₂); HRMS (ES) Found: MH⁺, 250.1593. C₁₈H₁₉N requires MNH⁺ 250.1590; LRMS m/z (ES) 250 (100%, MNa⁺).

(1S,3R)-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 CH₂Cl₂ (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 CH₂Cl₂ (2 × 50 mL). The combined extracts were dried (MgSO₄), 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; Rf 0.4 [petrol–EtOAc (80:20)]; FTIR νmax (film)/cm⁻¹ 3315, 3020, 2920, 1515, 1490; ¹H NMR (400
MHz, CDCl$_3$) $\delta = 7.48$–$7.46$ (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), 3.11–2.98 (3H, m, 3 × CH), 2.35 (3H, s, CH$_3$), 1.94 (1H, br s, NH); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta = 144.1$ (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-isooquinoline-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$_2$O$_2$ (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 $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3460, 3005, 2920, 1690, 1450, 1170, 1160; $^1$H NMR (400 MHz, CDCl$_3$, rotamers) $\delta = 7.21$–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) $\delta = 155.5$ & 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 × CH₃); HRMS (ES) Found: MNa⁺, 390.2044. C₂₅H₂₉NO₃Na requires MNa⁺ 390.2040; LRMS m/z (ES) 390 (100%, MNa⁺).

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

![Structure of 1,2-Dibenzyl-3-phenyl-3,4-dihydro-1H-isoquinoline 205](image)

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 (MgSO₄), 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; Rₐ 0.48 [petrol–EtOAc (90:10)]; FTIR νmax (film)/cm⁻¹ 3060, 3025, 2925, 1600, 1490; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 (CH₂), 43.1 (CH₂), 27.1 (CH₂); HRMS (ES) Found: MH⁺, 390.2219. C₂₀H₂₇N 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 \(\text{tBu}_2\text{NH}\) (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\(_4\)Cl (2 mL) was added. The mixture was extracted with CH\(_2\)Cl\(_2\) (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 \(\text{tPrMgCl}\) (9 mL, 18 mmol, 2 M in Et\(_2\)O) under Argon at room temperature and left to stir for 18 hours in the dark. Et\(_2\)O (6 mL) was added, the mixture was titrated against iodine to determine the concentration.

General procedure I: Deprotonation and electrophilic quench using TMPMgCl

TMPMgCl (0.6 mmol, 3 equiv., 0.45 M in Et\(_2\)O) 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 \textit{in situ} or after 10 seconds. After 30 min, NH\(_4\)Cl (2 mL) was added. The solvent was evaporated and the residue was extracted using CH\(_2\)Cl\(_2\) (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.
(3R)-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 evaporated under vacuum, and the residue was extracted using CH₂Cl₂ (3 x 250 mL), the organic layer was washed with brine (2 x 60 mL) then water (60 mL x 2), the combined organic layer was dried (MgSO₄), and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with CH₂Cl₂–MeOH (90:10), to give the acid 245 (4.8 g, 71%) as an oil; Rf 0.6 [CH₂Cl₂–MeOH (80:20)]; [α]D²⁵ +16.5 (1, MeOH) [lit.²⁰³ [α]D ²² +20.9 (0.50, MeOH)]; ¹H NMR (400 MHz, CDCl₃, 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 (3R)-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 (MgSO₄), and the solvent was evaporated. Purification by column chromatography on silica, eluting with CH₂Cl₂–MeOH (95:5), gave the amide 246 (2.6 g, 88%), as an oil; Rf 0.55 [CH₂Cl₂–MeOH (90:10)]; [α]D²⁵ + 3.1 (1, CHCl₃); FTIR νmax (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, NH₂), 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, CDCl₃, 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 (CH₂), 31.7 & 30.4 (CH₂), 28.3 (CH₃);
HRMS (ES) Found: MH⁺, 277.1552. C₁₅H₂₁N₂O₃ 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

\[
\begin{array}{c}
\text{CN} \\
N_{\text{Boc}} \\
\text{Ph}
\end{array}
\]

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 extracted with CH₂Cl₂ (40 mL × 2), then washed with aqueous HCl (10 mL, 0.1 M) and NaOH (10 mL, 0.1 M), dried (MgSO₄) 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; [α]D²⁵ +14 (1, CHCl₃); Rₖ 0.40 [petrol–EtOAc (80:20)]; FTIR 𝜈max (film)/cm⁻¹ 2980, 2945, 2240, 1700, 1170; ¹H NMR (400 MHz, CDCl₃, 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, CDCl₃, 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 (CH₂), 41.6 (CH), 32.4 (CH₂), 28.3 (CH₃); HRMS (ES) Found: MH⁺, 259.1456. C₁₅H₁₉N₂O₂ requires MH⁺ 259.1447; LRMS m/z (ES) 259 (100%, MH⁺).

ReactIR monitoring of the lithiation of tert-Butyl (3R)-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 𝜈C=O. After addition of n-BuLi, a new peak at 1657 cm⁻¹ appeared which was assigned to 𝜈C=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 (3R)-3-cyano-3,4-dihydro-1H-tetrahydroisoquinoline-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 Et2O) 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 ν\(_{C=O}\). After addition of TMPMgCl, a new peak at 1627 cm\(^{-1}\) appeared which was assigned to ν\(_{C=O}\) 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), \(^3\)Pr\(_2\)NH (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 \(\nu_{\text{max}}\) (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, CDCl\(_3\), 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\(_2\)O\(_2\) 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), tPr₂NH (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 ν_max (film)/cm⁻¹ 3005, 2985, 1750, 1700, 1165; ¹H NMR (400 MHz, CDCl₃, rotamers) δ = 7.35–7.29 (4H, m, CH), 4.86 (1H, d, J 15 Hz, CH), 4.31 (2H, q, J 7 Hz, CH₂), 3.42 (1H, d, J 15 Hz, CH), 3.15 (1H, d, J 15 Hz, CH), 1.50 (9H, s, t-Bu), 1.33 (3H, t, J 7 Hz, CH₃); NMR (400 MHz, CDCl₃, 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 (CH₂), 38.7 (CH₂); FTIR ν_max (film)/cm⁻¹ 3000, 2960, 2240, 1700, 1160; HRMS (ES) Found: MH⁺, 330.1620. C₁₈H₂₂N₂O₄ 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), tPr₂NH (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 ν_max (film)/cm⁻¹; 3000, 2960, 2240, 1700, 1160; ¹H NMR (400 MHz, CDCl₃, 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, CDCl₃, 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 (CH₂), 41.3 (CH₂), 28.3 & 28.1 (CH₃); HRMS (ES) Found: MH⁺, 367.1483. C₂₁H₂₃N₂O₂S 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), tPr$_2$NH (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; Rf 0.23 [petrol–EtOAc (90:10)]; FTIR $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3010, 2980, 2245, 1760, 1705, 1160; $^1$H NMR (400 MHz, CDCl$_3$, rotamers) $\delta = 7.35$–7.28 (4H, m, 4 $\times$ 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) $\delta = 168.0$ (C=O), 152.7 (C=O), 134.8 (C), 130.4 (C), 128.3 (2 $\times$ 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$_2$O$_4$ 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$_4$Cl (3 mL) was added, the solvent was evaporated and the residue was extracted using CH$_2$Cl$_2$ (3 $\times$ 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 KOtBu (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$_4$Cl (3 mL) was added, solvent was evaporated and the residue was extracted using CH$_2$Cl$_2$ (3 $\times$ 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 \( \text{^3} \text{Pr}_2 \text{NH} \) (0.07 mL, 0.58 mmol) in \( \text{Et}_2 \text{O} \) (2 mL) at \(-5^\circ \text{C} \). After 1 h, \( \text{^3} \text{PrMgCl} \) [0.29 ml, 0.58 mmol, 2 M in \( \text{Et}_2 \text{O} \)] was added, the mixture was allowed to warm to room temperature. After 2 h, the mixture was cooled to \(-104^\circ \text{C} \) and nitrile 247 (50 mg, 0.19 mmol) in \( \text{CPME} \) (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 \( \text{NH}_4 \text{Cl} \) (3 mL) was added. The organic solvents were removed, and the residue was extracted using \( \text{CH}_2\text{Cl}_2 \) (3 \( \times \) 10 mL), the combined extracts were dried (\( \text{MgSO}_4 \)), 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 \( \text{Et}_2 \text{O} \)) was added to nitrile 247 (50 mg, 0.19 mmol) in \( \text{CPME} \) (1 mL) at \(-104^\circ \text{C} \). 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), gave compound 248d (21 mg, 34%) with enantiomeric ratio of 87:13; \( [\alpha]_D^{25} + 20 \) (1, \( \text{CHCl}_3 \)). Other data as above.

**tert-Butyl (2S)-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 \(^\circ \text{C} \) and di-\( \text{t} \)-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 \( \text{CH}_2\text{Cl}_2 \) (3 \( \times \) 100 mL), the organic layer was washed with water (50 mL), dried (\( \text{MgSO}_4 \)), and the solvent was evaporated to give without further purification acid 255 (1.51 g, 80%) as an amorphous solid; m.p. 130–132 \(^\circ \text{C} \) [lit.\textsuperscript{205} 133–136 \(^\circ \text{C} \)]; \( [\alpha]_D^{23} \) –64 (1, \( \text{CH}_3\text{COOH} \)) [lit.\textsuperscript{206} \( [\alpha]_D^{22} \) –61.1 (1, \( \text{CH}_3\text{COOH} \))]; \(^1\text{H} \) NMR (400 MHz, \( \text{CDCl}_3 \), rotamers) \( \delta = 9.55 \) (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 \( \times \) CH), 1.49 (4H, s, \( \text{t} \)-\( \text{Bu} \)), 1.43 (5H, s, \( \text{t} \)-\( \text{Bu} \)). Data in accordance with the literature.\textsuperscript{206}
**tert-Butyl (2S)-2-carbamoylpyrrolidine-1-carboxylate 256**

![Chemical Structure](image)

Ethyl chloroformate (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 NH₄ [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 (MgSO₄), and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with MeOH–CH₂Cl₂ (95:5), gave amid 256 (6.4 g, 80%) as an amorphous solid; m.p 97–99 °C [lit. 103.6–107.7 °C]; [α]₀²³̼⁰⁰ –46.0 (1, CHCl₃) [lit. 0.2⁰⁰ [α]₀²⁵̼⁰⁰ –42.4 (1, MeOH)]; Rₐ 0.52 [MeOH–CH₂Cl₂ (30:70)]; FTIR νₘₐₓ (film)/cm⁻¹ 3365, 3200, 2975, 1670, 1660; ¹H NMR (400 MHz, CDCl₃, rotamers) δ = 6.84 (0.5H, br s, NH₂), 6.24–5.80 (1.5H, m, NH₂), 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); ¹³C NMR (400 MHz, CDCl₃, rotamers) δ = 176.1 & 175.0 (C=O), 155.9 & 154.7 (C=O), 80.6 (C), 61.1 & 59.8 (CH), 47.2 (CH₂), 31.2 (CH₂), 28.5 (CH₃), 24.6 & 23.9 (CH₂); HRMS (ES) Found: MH⁺, 215.1392. C₁₀H₁₉N₂O₃ requires MH⁺ 215.1396; LRMS m/z (ES) 215 (100%, MH⁺). Data in accordance with the literature, only [α]₀, ¹H NMR and m.p. were reported.¹⁷⁹

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

![Chemical Structure](image)

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 CH₂Cl₂ (50 mL) and washed with aqueous NaOH (20 mL, 0.1 M), the organic layer was dried (MgSO₄), 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; [α]₀²⁵̼⁰⁰ –94 (1.3, MeOH) [lit. 0.2⁰⁰ [α]₀²⁵̼⁰⁰ –95.5 (1.5, MeOH); Rₐ 0.45 [petrol–EtOAc (70:30)]; FTIR νₘₐₓ (film)/cm⁻¹ 2975, 2160, 2230, 1700; ¹H NMR (400 MHz, CDCl₃, 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); ¹³C NMR (400 MHz, CDCl₃, 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$_2$O$_2$ 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$_2$NH (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 $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2985, 2925, 2235, 1760, 1160, 1065; $^1$H NMR (400 MHz, CDCl$_3$, rotamers) $\delta$ = 3.86–3.79 (1H, m, CH), 3.46–3.40 (1H, m, CH), 2.30–2.20 (4H, m, 4 $\times$ CH), 1.79 (3H, s, CH$_3$), 1.54 (3H, s, CH$_3$); $^{13}$C NMR (400 MHz, CDCl$_3$, rotamers) $\delta$ = 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$_9$H$_{12}$N$_2$O$_2$ 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 $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3350, 2970, 2245, 1670; $^1$H NMR (400 MHz, CDCl$_3$, rotamers) $\delta$ = 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 $\times$ 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) $\delta$ = 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$_2$O$_3$ 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 tPr₂NH (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 \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 3005, 2990, 2250, 1720, 1695, 1165; \(^1\)H NMR (400 MHz, CDCl\(_3\), rotamers) \(\delta = 8.00–7.95\) (2H, m, 2 \(\times\) CH), 7.66–7.62 (1H, m, CH), 7.53–7.49 (2H, m, 2 \(\times\) 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 \(\times\) CH), 1.26 (9H, s, t-Bu); \(^{13}\)C NMR (400 MHz, CDCl\(_3\), rotamers) \(\delta = 171.1\) (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: M\(\text{Na}^+\), 323.1368. \(\text{C}_{17}\text{H}_{20}\text{N}_{2}\text{O}_{3}\text{Na}\) requires M\(\text{Na}^+\) 323.1366; LRMS \(m/z\) (ES) 323 (100%, M\(\text{Na}^+\)).

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\(_2\)O] and nitrile 257 (50 mg, 0.25 mmol) in Et\(_2\)O (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\(_2\)O] 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 a solid; 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 region 5.0–3.5 ppm are shown below, which includes two singlet of NCH$_2$ plus a triplet for partially undeuterated THF).

From the spectra, coalescence for the benzylic CH$_2$ at 4.65 ppm occurred at T$_c$ ~ 5 °C.

The difference in chemical shift ($\Delta\nu^{0}_{AB}$) 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, $t_{1/2} = (\ln2)/k = 0.035$ s

And, at 5 °C, $\Delta G^\ddagger = RT[\ln(k_0T/h) - \lnk] = 61.0$ kJ/mol

These data are very similar to the parent N-Boc-tetrahydroisoquinoline, 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.

**pre-coalescence, slow exchange:**

$$k = \frac{\pi}{\sqrt{2}} \left[ (\Delta v_{A})_{1/2}^q - (\Delta v_{A})_{1/2}^0 \right]$$

**pre-coalescence, intermediate exchange:**

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

**coalescence:**

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

**post-coalescence:**

$$k = \frac{\pi \Delta v_0^2}{2} \frac{1}{(\Delta v_{1/2})^e - (\Delta v_{A})_{1/2}^0}$$

**Raw data:**

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These values provided the following (approximate) parameters:

\[ \Delta H^\ddagger \approx \pm 81 \text{ kJ/mol} \]

\[ \Delta S^\ddagger \approx \pm 77 \text{ J/K·mol} \]

These values suggest that \( \Delta G^\ddagger \approx 60 \text{ kJ/mol at } 5 \text{ °C and } \Delta G^\ddagger \approx 64 \text{ kJ/mol at } -50 \text{ °C.} \)

This equates to \( t_{1/2} \approx 2.5 \text{ min at } -50 \text{ °C.} \) The lithiation reactions were carried out at \(-50 \text{ °C} \) 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 around ~ 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$$\nu$$_{AB}^0$) 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:*

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

*pre-coalescence, intermediate exchange:*

$$k = \frac{\pi}{\sqrt{2}} \left[ \Delta\nu_0^2 - \Delta\nu_e^2 \right]^{1/2}$$
coalescence:

\[ k = \frac{\pi \Delta v_0}{\sqrt{2}} \]

post-coalescence:

\[ k = \frac{\pi \Delta v_0^2}{2} \left( \frac{1}{(\Delta v_{1/2})^e} - (\Delta v_A)^{0}_{1/2} \right) \]

Raw data:

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Eyring plot of 1/T against ln (k/T):
These values provided the following (approximate) parameters:

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

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

These values suggest that $$\Delta G^\ddagger \approx 57 \text{ kJ/mol}$$ at 0 °C and $$\Delta G^\ddagger \approx 58 \text{ kJ/mol}$$ at −50 °C. This equates to $$t_{1/2} \approx 5.13 \text{ sec}$$ 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

(S)-248d

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

rac-258c
**Boc**

**(S)-258c**

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

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**Boc**

**(S)-258c**

From: TMPMgCl, Et₂O, –104 °C, and PhCOCI

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<tbody>
<tr>
<td>1</td>
<td>18.090</td>
<td>122.649</td>
<td>90.5</td>
<td>92.3</td>
<td>1.65</td>
</tr>
<tr>
<td>2</td>
<td>21.260</td>
<td>10.804</td>
<td>8.2</td>
<td>7.8</td>
<td>0.77</td>
</tr>
<tr>
<td>Total</td>
<td>195.847</td>
<td>137.450</td>
<td>100.0</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>

---

**Recrystallized (S)-258c**

From: TMPMgCl, Et₂O, –104 °C, and PhCOCI

<table>
<thead>
<tr>
<th>Reten. Time</th>
<th>Area [mm^2]</th>
<th>Height [mm]</th>
<th>Area [%]</th>
<th>Height [%]</th>
<th>WRS [min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18.137</td>
<td>33.759</td>
<td>83.8</td>
<td>86.7</td>
<td>0.93</td>
</tr>
<tr>
<td>2</td>
<td>21.397</td>
<td>7.642</td>
<td>2.0</td>
<td>4.3</td>
<td>0.89</td>
</tr>
<tr>
<td>Total</td>
<td>1297.837</td>
<td>32.104</td>
<td>100.0</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 5: X-ray crystal structure determination of compound trans-177e

Table 3. Crystal data and structure refinement for OIC274_0m.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification code</td>
<td>OIC274_0m</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>C21 H25 N O2</td>
</tr>
<tr>
<td>Formula weight</td>
<td>323.42</td>
</tr>
<tr>
<td>Temperature</td>
<td>100(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>1.54178 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Orthorhombic</td>
</tr>
<tr>
<td>Space group</td>
<td>P2(_1)2(_1)2(_1)</td>
</tr>
</tbody>
</table>
| Unit cell dimensions          | \(a = 6.3372(2) \text{ Å} \) \(\alpha = 90^\circ\) \(\text{, } \)
                                | \(b = 9.2748(3) \text{ Å} \) \(\beta = 90^\circ\) \(\text{, } \)
                                | \(c = 30.5375(10) \text{ Å} \) \(\gamma = 90^\circ\) \(\text{, } \)
| Volume                        | 1794.88(10) \(\text{ Å}^3\)          |
| 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                  | \(-7 \leq h \leq 7, -11 \leq k \leq 11, -36 \leq l \leq 36\) |
| Reflections collected         | 26794                                |
| Independent reflections       | 3181 \([R(int) = 0.1243]\)           |
| Completeness to theta = 66.681° | 99.9 %                              |
Absorption correction  
Max. and min. transmission  
Refinement method  
Data / restraints / parameters  
Goodness-of-fit on $F^2$  
Final R indices [$I>2\sigma(I)$]  
R indices (all data)  
Absolute structure parameter  
Extinction coefficient  
Largest diff. peak and hole

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

![Chemical structure](image)

**Table 2. Crystal data and structure refinement**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification code</td>
<td>rtalk1_0m</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>C23 H23 N</td>
</tr>
<tr>
<td>Formula weight</td>
<td>313.42</td>
</tr>
<tr>
<td>Temperature</td>
<td>100(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>1.54178 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P21</td>
</tr>
</tbody>
</table>

or rtalk1_0m.
Unit cell dimensions

\[
a = 9.1774(5) \text{ Å} \\
b = 6.1797(3) \text{ Å} \\
c = 15.8672(9) \text{ Å}
\]
\[
\alpha = 90^\circ \\
\beta = 101.832(3)^\circ \\
\gamma = 90^\circ.
\]

Volume 880.76(8) Å³

Z 2

Density (calculated) 1.182 Mg/m³

Absorption coefficient 0.512 mm⁻¹

F(000) 336

Crystal size 0.320 x 0.210 x 0.120 mm³

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 F²

Data / restraints / parameters 3056 / 1 / 218

Goodness-of-fit on F² 1.063

Final R indices [I>2σ(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.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification code</td>
<td>OIC276_a</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>C29 H27 N</td>
</tr>
<tr>
<td>Formula weight</td>
<td>389.51</td>
</tr>
<tr>
<td>Temperature</td>
<td>100(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>1.54178 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P21/c</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 19.2008(5) Å, α = 90°.</td>
</tr>
<tr>
<td></td>
<td>b = 15.7338(4) Å, β = 90.5540(10)°.</td>
</tr>
<tr>
<td></td>
<td>c = 7.1805(2) Å, γ = 90°.</td>
</tr>
<tr>
<td>Volume</td>
<td>2169.14(10) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.193 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.516 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>832</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.120 x 0.080 x 0.060 mm³</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>2.301 to 66.606°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-22≤h≤22, -18≤k≤17, -8≤l≤8</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>47341</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>3847 [R(int) = 0.0641]</td>
</tr>
<tr>
<td>Completeness to theta = 66.606°</td>
<td>99.9 %</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Semi-empirical from equivalents</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.65 and 0.43</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>3847 / 0 / 272</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>1.048</td>
</tr>
<tr>
<td>Final R indices [I&gt;2sigma(I)]</td>
<td>R1 = 0.0398, wR2 = 0.0972</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.0516, wR2 = 0.1031</td>
</tr>
</tbody>
</table>
Extinction coefficient 0.0015(3)
Largest diff. peak and hole 0.237 and -0.180 eÅ⁻³

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

![Chemical Structure](image)

**Table X: Crystal data and structure refinement for oic291v.**

<table>
<thead>
<tr>
<th>Identification code</th>
<th>oic291v</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C₁₇H₂₀N₂O₃</td>
</tr>
<tr>
<td>Formula weight</td>
<td>300.35</td>
</tr>
<tr>
<td>Temperature/K</td>
<td>99.96</td>
</tr>
<tr>
<td>Crystal system</td>
<td>orthorhombic</td>
</tr>
<tr>
<td>Space group</td>
<td>P2₁2₁2₁</td>
</tr>
<tr>
<td>a/Å</td>
<td>8.6352(4)</td>
</tr>
<tr>
<td>b/Å</td>
<td>10.1913(5)</td>
</tr>
<tr>
<td>c/Å</td>
<td>17.8369(8)</td>
</tr>
<tr>
<td>α/°</td>
<td>90</td>
</tr>
<tr>
<td>β/°</td>
<td>90</td>
</tr>
<tr>
<td>γ/°</td>
<td>90</td>
</tr>
<tr>
<td>Volume/Å³</td>
<td>1569.72(13)</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>ρ calc/g/cm³</td>
<td>1.271</td>
</tr>
<tr>
<td>μ/mm⁻¹</td>
<td>0.713</td>
</tr>
<tr>
<td>F(000)</td>
<td>640.0</td>
</tr>
<tr>
<td>Crystal size/mm³</td>
<td>0.22 x 0.2 x 0.1</td>
</tr>
<tr>
<td>Radiation</td>
<td>CuKα (λ = 1.54178)</td>
</tr>
<tr>
<td>2θ range for data collection</td>
<td>9.918 to 133.12</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-10 ≤ h ≤ 10, -12 ≤ k ≤ 12, -21 ≤ l ≤ 21</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>45809</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>2769 [R(int) = 0.0255, R_sym = 0.0094]</td>
</tr>
<tr>
<td>Data/restraints/parameters</td>
<td>2769/0/202</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>1.116</td>
</tr>
<tr>
<td>Final R indexes [I&gt;2σ(I)]</td>
<td>R₁ = 0.0252, wR₂ = 0.0641</td>
</tr>
<tr>
<td>Final R indexes [all data]</td>
<td>R₁ = 0.0253, wR₂ = 0.0642</td>
</tr>
<tr>
<td>Largest diff. peak/hole / e Å⁻³</td>
<td>0.12/-0.23</td>
</tr>
<tr>
<td>Flack parameter</td>
<td>0.39(3)</td>
</tr>
</tbody>
</table>
Appendix 9: X-ray crystal structure determination of compound 259

![Diagram of the molecular structure](image)

Table 1. Crystal data and structure refinement for RHUR1_a.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification code</td>
<td>RHUR1_a</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>C13 H19 N O</td>
</tr>
<tr>
<td>Formula weight</td>
<td>205.29</td>
</tr>
<tr>
<td>Temperature</td>
<td>100(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>1.54178 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P21/c</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 22.6148(10) Å</td>
</tr>
<tr>
<td></td>
<td>b = 7.4345(3) Å</td>
</tr>
<tr>
<td></td>
<td>c = 14.6142(7) Å</td>
</tr>
<tr>
<td>Volume</td>
<td>2456.79(19) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>8</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.110 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.540 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>896</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.210 x 0.180 x 0.180 mm³</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>3.910 to 66.652°.</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-26&lt;=h&lt;=26, -8&lt;=k&lt;=8, -17&lt;=l&lt;=17</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>31811</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>4339 [R(int) = 0.0552]</td>
</tr>
<tr>
<td>Completeness to theta</td>
<td>99.9 %</td>
</tr>
<tr>
<td>Description</td>
<td>Value</td>
</tr>
<tr>
<td>-------------------------------------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Semi-empirical from equivalents</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.7528 and 0.6874</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F^2</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>4339 / 0 / 279</td>
</tr>
<tr>
<td>Goodness-of-fit on F^2</td>
<td>1.055</td>
</tr>
<tr>
<td>Final R indices [I&gt;2sigma(I)]</td>
<td>R1 = 0.0414, wR2 = 0.1023</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.0479, wR2 = 0.1070</td>
</tr>
<tr>
<td>Extinction coefficient</td>
<td>n/a</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.173 and -0.211 eÅ^-3</td>
</tr>
</tbody>
</table>
7. References


(128) Dwyer, M. DFT Analysis, University of Sheffield, 2017.


