Synthesis and Applications of Derivatives of 1,7-Diazaspiro[5.5]undecane.

A Thesis Submitted by

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In partial fulfilment of the requirements for the degree of

Doctor of Philosophy

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October 2017
Declaration of Originality

I, Joshua Almond-Thynne, certify that the research described in this manuscript was carried out under the supervision of Professor Anthony G. M. Barrett, Imperial College London and Doctor Anastasios Polyzos, CSIRO, Australia. Except where specific reference is made to the contrary, it is original work produced by the author and neither the whole nor any part had been submitted before for a degree in any other institution.

Joshua Almond-Thynne

October 2017

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Abstract

Spiroaminals are an understudied class of heterocycle. Recently, the Barrett group reported a relatively mild approach to the most simple form of spiroaminal; 1,7-diaza[5.5]undecane (I). This thesis consists of the development of novel synthetic methodologies towards the spiroaminal moiety.

The first part of this thesis focuses on the synthesis of aliphatic derivatives of I through a variety of methods from the classic Barrett approach which utilises lactam II, through to de novo bidirectional approaches which utilise diphosphate V and a key Horner-Wadsworth-Emmons reaction with aldehyde VI.

The second part of this thesis concentrates on the synthesis of tetrahydrospirobiquinolines and their derivatives. The methodology developed utilises simple conditions, withstands a range of functional groups, and allows many substrates to be accessed under mild conditions. These compounds showed higher aminal stability relative to their aliphatic counterparts and were further derivatised by bromination, alkylation and cross-coupling techniques, all proceeding with the retention of the aminal centre.
The final part of this thesis details the attempts to complex these newly isolated compounds to a variety of elements across the periodic table, as well as initial investigations into their biological activities.


Acknowledgements

First and foremost, I would like to thank my mentor Professor Tony Barrett. He has taught me an endless amount through my time as an MSci student through to my final days as a PhD student. I know I will continue to learn from him throughout my future career.

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Below are just a selection of people I have had the pleasure of working with, I appreciate them all for their help along the way; Robert Davidson, Alex “De Beers” Brown, Rosa Cookson, Sara Goldstein, Tsz “Freeman” Ma, Dan Elliott, Stefanie Reid, Lam Tran, Luiza Dos Reis Cruz, Hannah Cook, Jiaxu “Linda” Han, Alex Williams, Dan Jones, Taniya Zaman, Lewis Allen, Kath Fletcher, Kate Montgomery, Pete Blencowe, Laurianne Buisson, Milena Czyz, Timothy Connell, Martin Brzozowski, Dean van As, Nenad Micic, James Rushworth, and many, many more.
“There is scarcely any passion without struggle.”

*Albert Camus*
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>([\alpha]^{25}_D)</td>
<td>specific rotation</td>
</tr>
<tr>
<td>(\Delta)</td>
<td>heat</td>
</tr>
<tr>
<td>(\Delta G)</td>
<td>Gibbs free energy</td>
</tr>
<tr>
<td>(\AA)</td>
<td>Angstrom ((10^{-10} \text{ metres}))</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>Acac</td>
<td>acetylacetonate</td>
</tr>
<tr>
<td>Ac(_2)O</td>
<td>acetic anhydride</td>
</tr>
<tr>
<td>AIBN</td>
<td>azobisisobutonitrile</td>
</tr>
<tr>
<td>Anal.</td>
<td>analysis</td>
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<tr>
<td>Aq.</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>Atm</td>
<td>atmosphere (unit)</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-Butyloxycarbonyl</td>
</tr>
<tr>
<td>BINAP</td>
<td>((2,2'\text{-bis(diphenylphosphino)}-1,1'\text{-binaphthyl}))</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>bp</td>
<td>boiling point</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>Bz</td>
<td>benzoyl</td>
</tr>
<tr>
<td>°C</td>
<td>degrees Celsius</td>
</tr>
<tr>
<td>cat.</td>
<td>catalytic</td>
</tr>
<tr>
<td>Cl</td>
<td>chemical ionisation</td>
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<tr>
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<td>concentrated</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shift</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>DCC</td>
<td>(N,N'\text{-dicyclohexylcarbodiimide})</td>
</tr>
<tr>
<td>dd</td>
<td>doublet of doublet</td>
</tr>
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<td>Symbol</td>
<td>Definition</td>
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<td>----------------------------------------</td>
</tr>
<tr>
<td>ddd</td>
<td>doublet of doublet of doublet</td>
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<td>DIBALH</td>
<td>diisopropylaluminium hydride</td>
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<td>$N,N$-diisopropylethylamine</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
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<td>$N,N$-dimethylformamide</td>
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<td>Dess-Martin periodinane</td>
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<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
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<tr>
<td>d.r.</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
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<td>doublet of quartets</td>
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<td>EDC</td>
<td>1-ethyl-3-(3-dimethylaminopropyl)carbodiimide</td>
</tr>
<tr>
<td>e.e</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>EI</td>
<td>electron ionization</td>
</tr>
<tr>
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<td>elemental</td>
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<tr>
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<td>electrospray</td>
</tr>
<tr>
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<td>ethyl</td>
</tr>
<tr>
<td>h</td>
<td>hour</td>
</tr>
<tr>
<td>HBTU</td>
<td>O-(benzotriazol-1-yl)-$N,N,N',N'$-tetramethyluronium hexafluorophosphate</td>
</tr>
<tr>
<td>HMDS</td>
<td>bis(trimethylsilyl)amine</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
</tr>
<tr>
<td>HPLC</td>
<td>high-performance liquid chromatography</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz</td>
</tr>
<tr>
<td>i</td>
<td>iso</td>
</tr>
<tr>
<td>IBX</td>
<td>2-iodoxybenzoic acid</td>
</tr>
<tr>
<td>IC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>half maximal inhibitory concentration</td>
</tr>
<tr>
<td>IPA</td>
<td>2-propanol</td>
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IR  infrared spectroscopy
J  coupling constant
L  litre
LDA  lithium diisopropylamine
LED  light emitting diode
μ  micro
m  multiplet
m  meta
M  molar
Me  methyl
min  minute(s)
 mL  millilitre(s)
mmol  millimole(s)
mol  mole(s)
Mpt  melting point
MS  molecular sieves
Ms  mesylate
NBS  N-bromosuccinimide
NIS  N-iodosuccinimide
NMR  nuclear magnetic radiation
Nu  nucleophile
o  ortho
PCC  pyridinium chlorochromate
PG  general protecting group
pH  potential hydrogen
Phth  phthalimide
Ph  phenyl
PMB  4-methoxybenzyl
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<td>parts per million</td>
</tr>
<tr>
<td>ppy</td>
<td>2-phenyl-pyridine</td>
</tr>
<tr>
<td>PPTS</td>
<td>pyridinium para-toluenesulfonate</td>
</tr>
<tr>
<td>Pr</td>
<td>propyl</td>
</tr>
<tr>
<td>PTSA</td>
<td>para-toluenesulfonic acid</td>
</tr>
<tr>
<td>py</td>
<td>pyridine</td>
</tr>
<tr>
<td>q</td>
<td>quartuplet</td>
</tr>
<tr>
<td>R</td>
<td>general substituent</td>
</tr>
<tr>
<td>RCM</td>
<td>ring-closing metathesis</td>
</tr>
<tr>
<td>Rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
</tr>
<tr>
<td>SM</td>
<td>starting material</td>
</tr>
<tr>
<td>t or tert</td>
<td>tertiary</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
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<td>TEMPO</td>
<td>2,2,6,6-tetramethylpiperidine 1-oxyl</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethanesulfonyl</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
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<td>THF</td>
<td>tetrahydrofuran</td>
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<td>TIPS</td>
<td>triisopropylsilyl</td>
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<td>TLC</td>
<td>thin layer chromatography</td>
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<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>TOF</td>
<td>turnover frequency</td>
</tr>
<tr>
<td>TON</td>
<td>turnover number</td>
</tr>
<tr>
<td>TS</td>
<td>transition state</td>
</tr>
<tr>
<td>UV</td>
<td>ultra-violet light</td>
</tr>
<tr>
<td>Vis</td>
<td>visible spectrum light</td>
</tr>
<tr>
<td>X</td>
<td>halide or pseudohalide</td>
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CHAPTER ONE

GENERAL INTRODUCTION
1. General Introduction

1.1 Spiroyclic Compounds

Modern approaches in medicinal chemistry are increasingly exploring sp$^3$-rich compounds in bioactive discovery programmes. The incorporation of sp$^3$-rich carbons in fragments and lead compounds have shown improved physical properties, from solubility through to reduced entropic protein binding values, relative to conventional sp$^2$-rich structures. Spiroyclic compounds, in particular, have gained significant interest due to their complex three-dimensional shape and fixed conformation of the two rings which combine to generate a wide variety of novel and biologically relevant architectures.

Accordingly, there has been a drive to establish methodology to synthesise and install these spirocyclic centres in a variety of scaffolds. Several laboratories have focused on library based synthesis of novel spirocycles, including the Bode group with SnAP chemistry and the Carreira group with spirocyclic amines (Scheme 1).

**Figure 1:** Spiroyclic pharmaceuticals.

**Scheme 1:** Notable spirocyclic syntheses by Bode and Carreira.
In addition to applications in medicinal chemistry, spirocyclic compounds feature prominently in the field of small molecule catalysis. There is a broad array of spirocyclic derivatives in organo- and metallocatalysts, from the classic Shi epoxidation catalyst 14,10 as well as spirophosphine 17 developed by Zhou11 which has notably used by Fu for photocatalysed C-N cross couplings (Scheme 2).12

![Scheme 2: Examples of spirocycles in catalysis.10,12](image)

With this context, there is a pressing need to investigate new spirocyclic scaffolds in medicinal and synthesis applications, and develop novel methodologies for installing spirocyclic motifs in target compounds.

1.2 Spiroketalas

Spiroketalas are ubiquitous in nature, often found in a wide array of biological sources including insects, marine organisms, fungi and flora.13 Historically, there has been a widespread interest in their synthesis, and efforts have been summarised in several excellent reviews.13,14 There are numerous natural product families that contain the spiroketal moiety, including insect pheromones,15 the milbemycin antibiotics 16 and the highly potent berkelic acid (21), which has potential application in the treatment of ovarian cancer (Figure 2).17
Thus, spiroketals have been identified as a privileged scaffold for novel drug discovery\textsuperscript{18} and several examples of biologically active spiroketals have been reported within the literature (Figure 3). This includes notable work by Ley and his introduction of the spiroketal motif as natural product-like core for sialyl mimic \textsuperscript{22,19} and the highly potent spiroketal adduct \textsuperscript{23} for potential treatment of B-cell chronic lymphocytic leukaemia.\textsuperscript{18} The benzannulated spiroketal, Tofogliflozin (24) was approved in 2014 as a sodium-glucose transport protein (SGLT2) inhibitor for the treatment of diabetes.\textsuperscript{20}

The conformational stability of spiroketals, derived from the anomeric effect, influences their unique biological properties. The anomeric effort is well established and associated with carbohydrate chemistry, where groups containing electronegative atoms favour the axial position on the ring when they are α to a ring heteroatom. This effect is caused by multiple
factors, including hyperconjugation of the lone pair of the ring heteroatom into the $\sigma^*$ orbital of the exocyclic C-X bond $25$-$B$ (Figure 4), as well as a minimisation of dipole moment, and steric repulsion factors when the C-X bond is in this orientation.$^{21}$

![Figure 4: A basic representation of the anomeric effect.](image)

Notable work by Deslongchamp has fully investigated and quantified the anomeric effect in spiroketals, and has demonstrated that it effects the outcome of many acid based methodologies towards these compounds. When utilising thermodynamic conditions for the synthesis of spiroketals there are multiple conformations possible. These conformations are axial-axial ($27$-$A$), axial-equatorial ($27$-$B$) or equatorial-equatorial ($27$-$C$) (Figure 5). $27$-$A$ both the oxygen atoms are antiperiplanar to the opposed C-O bond which allows the stabilisation of the compound in both directions. In contrast, $27$-$B$ has only one bond in the correct conformation and therefore one anomeric effect and $27$-$C$ which in not stabilised by the anomeric effect. Deslongchamps calculated theoretically that only $27$-$A$ should exist, as both steric repulsions and lack of the anomeric effect result in a higher energy for $27$-$B$ and $27$-$C$ of 2.4 and 4.8 kcal mol$^{-1}$ respectively.

![Figure 5: The possible conformations of 27 and their relative calculated energies (Adapted from Deslongchamps$^{21}$).](image)
Delongchamps extended this type of calculation to a variety of substituted spiroketals and more conformationally restrained scaffolds and showed that not all spiroketals adopt this preferred axial-axial conformation. Thus, there are notable examples of “non-anomeric” spiroketals within nature. These “non-anomeric” spiroketals are still investigated today due to their synthetically challenging frameworks and usually require kinetic formation of the spirane centre, alongside substituents to favour the desired orientation.

1.3 Spirohemiaminals

Recently, spiro (N,O) ketals or “spirohemiaminals” have gained further attention. The hemiaminal motif is less common than the (O,O)-ketal equivalent but it is still prevalent in nature from a variety of sources including marine sea sponges, microbes and fungi. Notable examples include azaspiroacid-1 (28), solasodine (29), marineosin A (30), and pandamarinelactone (31).

Figure 6: Examples of spirohemimimal natural products.
Azaspiroacid 28 is infamous for the relatively understudied azaspiracid poisoning caused by the ingestion of contaminated shellfish.30 Solasidine (29) is easily extracted from potato starch product waste streams and is an industrially important precursor to complex steroidal pharmaceuticals such as the progestogens.27 The structurally unique pandamarinelactone-1 (31)29 and marineosin family have gained interest for their biological activity28 and as targets for complex natural product syntheses.25,31

Another important family of synthetic spirohemiaminals is the spiropyran family.32 Spiropyrans 32, due to their facile synthesis and multiple handles for functionalisation and derivatisation, are a well-established class of photoswitch in synthesis of photodynamic materials33 and photodynamic systems.34

![Figure 7: Spiropyran 32 to merocyanine 33 photoswitch.](image)

Spiropyrans 32 are unique photoswitches due to the significant difference in the properties of the two switchable isomers (Figure 7), which can be further influenced or more finely tuned by changing the solvent, temperature, pH or the presence of a metal.32 The spiropyran motif is a spiro-fused indoline and chromene that are perpendicular to each other. These compounds can undergo reversible photoswitching initiated by a photo-induced cleavage of the Cspiro-O bond and subsequent cis-trans isomerisation of the olefin. The dipolar nature of the merocyanine induces stark differences in the physicochemical properties of the merocyanine compared to the spiropyran. The large electric dipole moment renders merocyanines prone to aggregation through dipole-dipole interactions, causing further attenuation of physical properties. These compounds have been used in a variety of applications, most famously, in
Feringa’s work on photo-activated membrane protein channel, one of many papers in the field of mechanical motors/machines which led him to receive the chemistry Nobel prize in 2016.\textsuperscript{34}

### 1.4 Spiroaminals

The \((N,N)\)-spiroketals or “spiroaminals” are even less well studied than their \((O,O)\) or \((N,O)\) analogues. This is predominantly due to the scarcity of spiroaminals derived from natural sources, with only a few spiroaminal natural products reported. The low number of spiroaminal natural products may be attributed to their lack of conformational stability.\textsuperscript{35} However, out of the reported spiroaminal natural products, the indole alkaloid family contain the majority. Some notable examples are \((+)-leuconodine\ F\ (34)\textsuperscript{,36} peganumine A\ (35)\textsuperscript{,37} \((+)-melodinine\ E\ (36)\textsuperscript{,38} as well as the tetrahydroquinoline alkaloid isoschizogamine\ (37) and recently isolated \((\pm)-spiroreticulatine\ (38)\textsuperscript{39} (Figure 8).\textsuperscript{40-43}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure8.png}
\caption{Spiroaminal containing natural products.}
\end{figure}
Compounds 34-37 have all been synthesised by Zhu, with 34 and 36 and a range of other indole alkaloids being derived from a single intermediate. Other notable syntheses of isoschizogamine (37) have been achieved by Heathcock and Fukuyama (see Section 3.1.1). Spiroreticulatine (38) was isolated from Fascaplysinopsis reticulate in 2015 and has shown promising biological activity (see Section 3.1.1). These compounds all follow a general theme that the aminal nitrogens are either substituted or form fenestrane type natural products and all contain α-oxidation at one or more of the aminal nitrogens. These substitutions patterns and oxidation result in aminals that are stabilised both sterically and electronically. Notable spiroaminals that do not follow this trend are the recently isolated pandanusines A (39) and B (40), and pandamarine (41), which are all isolated from Pandanus amaryllifolius, a commonly used ingredient in Asian cuisine (Figure 9).

Figure 9: Spiroaminals extracted from Pandanus amaryllifolius.

A number of other structurally interesting alkaloids have been isolated from the Pandanus genus in addition to compounds 39-41. There has, however, been some scepticism as to whether pandamarine is an artefact of isolation. As very few natural products containing this rare motif have been isolated, and natural products are a primary driving force for the development of novel methodologies, there has been very little work on the synthesis of even relatively simple aminal systems (see Section 2.1). Due to a lack of research on spiroaminals, we sought to investigate these neglected heterocycles.
1.5 Aims of This Project

The aim of this project to expand on the limited number of spiroaminals synthesised to investigate their conformation, properties, and generally improve on our understanding of their chemistry. This project looked to both build upon established methodologies, and develop new methodologies to allow the installation of the spiroaminal motif with user friendly procedures. Once isolated we aim to investigate the biological properties of the isolated compounds as well as attempt to form a variety of metal complexes, to elucidate the aminal coordination chemistry and improve our understanding of this underexplored chemical moiety.
CHAPTER TWO

ALIPHATIC DERIVATIVES OF

1,7-DIAZASPIRO[5.5]UNDECANE
2. Aliphatic Derivatives of 1,7-Diazaspiro[5.5]undecane

2.1 Previous Syntheses

2.1.1 Pre Barrett Group Syntheses

Although there are a few examples of spiroaminals within nature (see chapter 1), there are very few papers on the synthesis of even relatively simple examples. The first reports of these compounds were described by Büchel in 1966, treatment of lactams (42-46) with POCl₃ in refluxing chlorobenzene yielded the intermediate enaminolactams, followed by refluxing in concentrated HCl for 22-48 h afforded the suspected spiroaminals 47-A - 51-A (Scheme 3).

\[
\begin{array}{cccc}
n=1, R = H & 42 & \text{Yield over two steps} & n=1, R = H \quad 47-A \quad ND \\
n=1, R = Me & 43 & & n=1, R = Me \quad 48-A \quad 52\% \\
n=1, R = Ph & 44 & & n=1, R = Ph \quad 49-A \quad 67\% \\
n=2, R = Me & 45 & & n=2, R = Me \quad 50-A \quad 39\% \\
n=2, R = Ph & 46 & & n=2, R = Ph \quad 51-A \quad 46\% \\
\end{array}
\]

**Scheme 3: The Büchel spiroaminal synthesis.**

However, this methodology only tolerated N-Me or N-Ph lactams, with the unsubstituted spiroaminals not being isolated. The exception to this is for the 5 membered 42 which Büchel reports readily underwent spirocyclisation to form spiroaminal 47-A, but this procedure is not mentioned in the experimental section of the paper. The only analysis on the resultant products are IR, UV and microanalysis, so there may some question as to whether the compounds suggested are in fact the spiroaminal compounds. This work was improved upon by Kaupp and co-workers in 1989. Kaupp reported that treatment of δ-valerolactam (52) with lithium hydroxide at elevated temperatures afforded the spiroaminal / amine-imine mixture in increased yields (Scheme 4). This was the first report of spiroaminals where the products were analysed by ¹H and ¹³C NMR spectroscopy as well as by X-ray crystallography. Kaupp utilised spiroaminal 53-A as a precursor to tricyclic diaziridine 54, which was unprecedented at this time.
This methodology was also applicable to butyrolactam (42) and caprolactam (55) starting materials, although the products were only isolated as their amine-imine tautomers 47-B and 56-B respectively (Scheme 5). This is in contrast to Büchel, who reported the spirocyclic product for the [4.4] system 47-A.\(^{48}\)

\[\text{Scheme 5: The amine-imine tautomers 47-B and 56-B reported by Kaupp.}^{49}\]

2.1.2 The Barrett Synthesis

In 2013, the Barrett group reported the synthesis of 1,7-diazaspiro[5.5]undecane (53-A) using the general strategy of the previously reported work by Kaupp and Büchel.\(^{35}\) The route utilised less harsh conditions, and improved yields (Scheme 6). The route consisted of a self-Claisen condensation of \(N\)-Boc lactam 57 upon treatment with lithium bis(trimethylsilyl)amide (LiHMDS). The afforded product was a mixture of \(\beta\)-ketolactam 58-A and the hemiaminal 58-B, prone to decomposition by the competing retro-Claisen. When treated with TFA, deprotection afforded enamino-lactam 59. Subsequent treatment of 59 with concentrated HCl

\[\text{Scheme 4: The Kaupp synthesis of spiroaminal 53-A and diaziridine 54.}^{49}\]
at elevated temperatures, afforded spiroaminal 53-A after purification by chromatography (84% yield, three steps, Scheme 6).

Scheme 6: The Barrett synthesis of spiroaminal 53-A.\(^{35}\)

The final step was proposed to consist of hydrolysis of both the enamine and lactam centres, yielding the \(\alpha\)-keto acid 61, which decarboxylates to afford ketone diamine 62 (Scheme 7). This, upon basification, cyclised to form the amine-imine tautomer 53-B, which spontaneously spirocyclises to form aminal 53-A (Scheme 7). The crude product was found to contain both tautomers, however, after silica gel chromatography, only the spiroaminal 53-A was observed by \(^1\)H and \(^{13}\)C NMR.\(^{35}\)

Scheme 7: Proposed mechanism for the decarboxylation/spirocyclisation of enamine 59.
Aminal 53-A was treated with a range of dielectrophiles to yield a variety of interesting products, that would be difficult to access through any other known chemistry (Scheme 8).  

\[
\begin{align*}
\text{Scheme 8: The reaction of 53 with a range of dielectrophiles.}
\end{align*}
\]

It was also observed that the spiroaminal could bind to both copper and ruthenium to form complexes 67 and 68 as the aminal and amine-imine tautomer respectively (Scheme 9).

\[
\begin{align*}
\text{Scheme 9: Complexation chemistry of spiroaminal 53.}
\end{align*}
\]

2.1.3 Computational Investigations of Thiel

After these initial investigations, spiroaminal 53-A and select derivatives were then studied computationally in collaboration with Thiel. The major focus of this investigation was the equilibrium between the two tautomers of 53-A and 53-B. However, the complexity of these compounds makes this type of study intensive. Spiroaminals are able to access different chair,
half chair, and boat conformations, as well as different conformations depending on the orientation of the N-R bonds with respect to the ring. This results in 3 major conformations, A with both C-N bonds adopting an axial position relative to the opposing ring, B with one nitrogen adopting the axial position and the other adopting the equatorial position, and lastly C with two equatorial nitrogens (Figure 10). Other conformers are accessible during the interchanges between A, B, and C however, with their higher energy boat / half boat structures, they are only transient.

Figure 10: Three possible ring conformations of spiroaminals. Adapted from the work of Thiel.50

Additionally, A-C contain a sub-set of three more conformations per ring conformer depending on the orientation of the N-R bond. Inversely to ring conformations; A-a both N-R bonds adopt a pseudoequatorial position, A-b one pseudoequatorial and one pseudoaxial N-R bond and A-c both N-R bonds are pseudoaxial (Figure 11).

Figure 11: The three possible conformations of A dependent on the N-R bond position.

The orientation of the C-N and N-R bonds can lead to different hyperconjugation effects between n(N) and either σ*(C-N) or σ*(C-C), depending on the orientation of the opposing ring. For example, donation into the σ*(C-N) affords the most stabilisation (13-16 kcal mol⁻¹), as well as playing a key role in the ring opening tautomerisation. For example, conformation A-a both the C-N bonds are axial to the opposing ring leading to n(N)→σ*(C-N) in both directions. Conformation B-a contains one n(N)→σ*(C-N) and one n(N)→σ*(C-C), whereas
all conformations of C contains no anomeric effect and contains two n(N)→σ*(C-C). These donations, although stabilising are just one of many factors within the system. However, it was found that the major conformer A-a was the most stable conformer with the anomeric effect stabilisation for each ring.

Scheme 10: The proposed mechanism of the aminal / amine-imine tautomerisation. Adapted from the work of Thiel.35

The relative free energies of all the transition states and intermediates involved with the ring opening tautomerisation were computationally simulated. The mechanism consists of protonation of one of the aminal nitrogens, which activates the corresponding C-N bond. The same stabilising donation of n(N)→σ*(C-N) now acts as the mechanism for C-N cleavage yielding int2 via TS1. Between int2 and int3 the open ring chain swings to come into proximity to the iminium nitrogen, which helps facilitate the deprotonation affording the amine-imine tautomer (Scheme 10).

It was found that increasing steric bulk on the 4 and/or 10 positions 70-A or 71-A of the carbon backbone, favoured the spirane tautomer, whereas substitution on the nitrogen 69-A made
the ring opening mechanism exergonic. The unsubstituted \textbf{53-A} was shown to be in almost equilibrium with its amine-imine tautomer \textbf{53-B} (Figure 12).

\[ \Delta G_{\text{int1} \rightarrow \text{int4}} = -0.4 \text{ kcal mol}^{-1} \]
\[ \Delta G_{\text{int1} \rightarrow \text{int4}} = -2.6 \text{ kcal mol}^{-1} \]
\[ \Delta G_{\text{int1} \rightarrow \text{int4}} = +1.4 \text{ kcal mol}^{-1} \]
\[ \Delta G_{\text{int1} \rightarrow \text{int4}} = +3.1 \text{ kcal mol}^{-1} \]

\begin{align*}
\text{53-A} & \\
\text{69-A} & \\
\text{70-A} & \\
\text{71-A} & \\
\end{align*}

\textit{Figure 12: The relative free energies of ring opening tautomerisation. Adapted from Thiel.\textsuperscript{50}}

From these results, the focus going forward was on preparing chiral derivatives of spiroaminals. It was envisaged that substitution at the 2,8-positions would yield compounds with chiral cavities to build chiral metal complexes. Further, 4,10-substitutions were predicted by Thiel to increase the stability of the spirane centre.\textsuperscript{50}

\section*{2.2 Lactam Synthesis}

\subsection*{2.2.1 Altering Ring Sizes}

To expand on the number of derivatives accessible by this methodology, we first sought to investigate ring size, similarly to Kaupp.\textsuperscript{49} Lactams \textbf{42, 52, 55} were easily protected under the standard conditions\textsuperscript{52} to yield the precursors to the Claisen reaction in good yields (Scheme 11).

\begin{align*}
\text{n = 1 ; 42} & \\
\text{n = 2 ; 52} & \\
\text{n = 3 ; 55} & \\
\end{align*}

\textit{Scheme 11: Boc-protection of lactams 72, 57 and 73.}
2.2.2 2-Substituted Lactams

Our attention was first directed towards methyl lactam 76. Diastereoselective resolution of 2-methylpiperidine (74) with mandelic acid, followed by Boc protection and ruthenium / sodium periodate-based oxidation afforded lactam 76 in good yields (Scheme 12).54

More complex lactams were accessed through organometallic addition to Ellman sulfinimine 79. Sulfimine 79 was synthesised in two steps from cyclopentene (77) through Schreiber ozonolysis reported by Carreira, and subsequent imine condensation. Treatment with isopropyl or phenyl Grignard reagent afforded sulfinamines 80 and 81 which were treated with methanolic HCl before purification, due to observing decomposition during chromatography, to yield lactams 82 and 83. (Scheme 13). The crude mixtures of organometallic addition reactions showed high diastereoselectivity for the addition of the Grignard reagent to the same face of the sulfinimine oxygen (dr > 20:1) as expected. This is controlled by chelation of oxygen and the metal in the chair like transition state. Boc protection under standard conditions afforded N-Boc lactams 84 and 85.
2.2.3 4-Substituted Lactams

Turning to the findings of Thiel *et al.*, we then focused on installing the isopropyl moiety (see Section 2.1.3) on the 4-position of the spirocyclic backbone via lactam 86. The initial approach was based on the approach developed by Jackman, starting from the naturally occurring terpene, (+)-limonene (88) (Scheme 14).  

![Scheme 14: Jackman’s retrosynthetic analysis of lactam 86.](image)

The isobutylene of 88 was hydrogenated using PtO$_2$ at 1.5 atm of H$_2$. Jackman’s route then proceeded to dehydroxylate and open the ring with chromium mediated oxidation, however this was shortened in our work by implementing ozone for the oxidative cleavage of the cyclic double bond of 89, with an oxidative work up to yield keto acid 90. Acid 90 was methylated to...
aid purification, affording keto ester 91. Oxime formation yielded a mixture of cis and trans isomers (1:1) of 87, which were then treated with various Beckmann rearrangement conditions. In all cases the product afforded was an inseparable mixture of acetyl amine 92 and methyl amide 93 (Scheme 15). Attempts were made to separate the isomers of oxime 87 as well as carry the crude mixture of 92 and 93 through to the lactam, however these attempts were unsuccessful.

Various conditions were tried in an attempt to improve this step; however, these were unsuccessful. Alternative routes were therefore attempted, which would not be limited to having an iso-propyl substituent.

Initially conditions developed by Hayashi for achieving enantioselective 1,4-additions to unsaturated lactam 95 were attempted (Scheme 16). Lactam 95 was prepared from 57 in a one pot procedure using the Mukaiyama methodology. The Hayashi addition of phenyl boroxine with 95 when performed using commercially available (R)-BINAP provided poor yields, and showed little improvement when increasing the scale of the reaction. Thus, with a
desire to produce large quantities of material, the attention turned to more scalable methodologies.

Pigs liver esterase (PLE) is an enzyme commonly utilised in enzymatic resolutions within organic synthesis. In this case PLE was used in the desymmetrisation of 3-substituted dimethyl glutarates (Scheme 17).

3-Substituted glutarates 102 and 103 were obtained through the copper-catalysed addition of Grignard reagents to dimethyl glutaconate as reported by Overman (Scheme 18).

Compounds 102, 103 as well as the commercially available 104 were subjected to the conditions of Jones, consisting of the slow addition of aqueous sodium hydroxide to a solution of substrate and enzyme in a phosphate based buffer, maintaining a pH of 7-8 (Scheme 19). The resultant acid-esters 106-107 were then subjected to borane based reduction, mesylation, azidation, and finally Staudinger reduction with immediate cyclisation.

Scheme 16: Hayashi approach to 4-substituted lactam 96.

Scheme 17: Retrosynthesis of 4-substituted lactams utilising a PLE desymmetrisation.

Scheme 18: Preparation of 3-substituted dimethyl glutarates 102 and 103.
to form lactams 114-116. N-Boc lactams 117, 96, and 118 were afforded after subsequent protection under standard conditions (Scheme 19).

\[
\begin{align*}
\text{Scheme 19: The synthesis of lactams 117, 96 and 118.}
\end{align*}
\]

The ee’s of the acid esters 105-107 were not determined, but were expected to be a maximum of 50%, 54% and 79% ee respectively, as reported by Jones following subsequent lactonization. We hoped that both amplification of ee through recrystallisation, where possible during the synthetic route, and amplification of ee through the Horeau principle would lead to sufficiently high ee’s when the final spiroaminals were isolated.
2.3 Expanding the Barrett Synthesis

With these lactams in hand, the attention turned towards preparing the spiroaminals. Prior to preparing the substituted aminals, the unsubstituted spiroaminal \(53\text{-A}\) was prepared using the conditions previously reported by the Barrett group (Scheme 20).\(^\text{35}\)

![Scheme 20 Synthesis of spiroaminal 53-A.](image)

The product isolated matched the analytical data reported, however it was found that yields varied from the those previously reported within the group. Attempts were made at further shortening the synthetic procedure by performing the Boc deprotection and decarboxylation/spirocyclisation in one step in refluxing HCl for 24 h (Scheme 21). This gave the spiroaminal \(53\text{-A}\) in similar yields, however purification by Kugelrohr distillation was found to be more efficient than the column chromatography purification previously used (see chapter 5 for details).

![Scheme 21: Shortened synthesis of spiroaminal 53-A.](image)

This synthetic procedure was then performed on lactams \(72\), \(73\) and \(76\). Reacting butyrolactam \(72\) under these conditions afforded a mixture of spiroaminal \(47\text{-A}\) and the amine-imine \(47\text{-B}\) in an acceptable yield (Scheme 22). \(47\text{-A}\) and \(47\text{-B}\) are separable by column chromatography, however, spiroaminal \(47\text{-A}\) tautomerises over time to a mixture of the aminal and amine-imine tautomers. This is consistent with the observations of both Büchel\(^\text{48}\) and
Kaupp\textsuperscript{49} who independently claimed to make each tautomer exclusively. Presumably this tautomeration is due to the increased strain on the smaller ring size. The equilibrium could not be influenced by temperature or solvent.


Caprolactam 73 afforded the product as its amine-imine tautomer 56-B (Scheme 23). This corresponds to the findings of Kaupp,\textsuperscript{49} who also reported no spiroaminal formation when starting from 55, most likely due to the larger ring size being less entropically favourable to form relative to the 5 and 6 membered rings.

\[ \text{Scheme 23: Synthesis of amine-imine 56-B.} \]

Methyl lactam 76 when subjected to the Barrett conditions, yielded spiroaminal 119-A in acceptable yields. The structure and conformation of 119-A was confirmed by X-ray crystallography, as the hydrochloride salt (Figure 13).

\[ \text{Scheme 24: Synthesis of spiroaminal 119-A.} \]
The ee of these compounds could not be quantified, as 119-A could not be resolved by various chiral columns. However, with the dimerisation of chiral compounds an amplification of ee is observed, as statistically derived by Horeau.\textsuperscript{66} Additionally a single epimer was observed by \textsuperscript{1}H and \textsuperscript{13}C NMR, we hypothesised the retention of the enantiomeric excess to be high. The solid-state structure revealed the chair-chair conformation with the nitrogens both being axial to the opposed ring as directed by the anomeric effect, as seen in (O,O) spiroketals. The stereochemistry of the newly formed spirane centre is likely controlled by both the anomeric effect, and by the absolute stereochemistry of the adjacent methyl groups. These two factors, along with the reversible formation of the spirocyclic centre, the spirane centre should only form the (R,S,R) epimer, and not the (R,R,R) epimer (Figure 14). This hypothesis is also strengthened by the single diastereomer being observed in the crude reaction mixture, and in the final product as presumably the two epimers would be identifiable by NMR.
With the other 2 and 4-substituted lactams, there was found to be multiple issues with the methodology. The four substituted lactams suffered from a lack of conversion, presumably due to the increased sterics around the site of reactivity. The increased steric strain in the β-keto-lactam / hemiaminal could also accelerate the competing retro-Claisen, affording more starting material.

With low conversions, alongside the inability to purify the reaction mixtures, the second step of the methodology provided complex mixtures of inseparable compounds. For the 2-substituted lactams, conversion was higher but still inhibited. Additionally, due to only obtaining the starting material in moderate ee’s (see section 2.2.3), the crude reaction mixtures became even more complex. Any products being formed were diastereomeric mixtures, meaning analysis of crude reaction mixtures by $^1$H NMR and/or purification became impractical. Investigations into varying solvent, temperature, base and work-ups were conducted to both try and increase starting material conversion and reduce unwanted side reactions. However, it was soon apparent that preparing these lactams and then subjecting them to the harsh acidic conditions was undesirable. The inability to purify the keto-lactam / hemi-aminal 121 mixture led to unreacted starting material 120 being taken through to the
final step, meaning additional deprotection and subsequent side reactions were observed. We therefore turned our attentions to trying to prepare spiroaminals using less harsh conditions. Looking at the reaction mechanism, the final intermediate prior to the spiroaminal formation is the keto-diamine 62 (Section 2.2.1). We believed this compound could be more easily accessed through much milder conditions and potentially still utilise the prepared lactams.

### 2.4 The Failed Approaches for Preparing Spiroaminals

#### 2.4.1 Organometallic Additions to Lactams

The addition of organometallics to N-Boc lactams is well known and, at low temperatures, yields the corresponding ketone. This is most likely due to chelation-based stabilisation of the tetrahedral intermediate before quenching. Several organometallics were screened in order to investigate what functional group manipulations could be used to produce ketodiamine 123 (Scheme 26).

**Scheme 26:** Proposed route to spiroaminals employing an organometallic addition to lactams.

The first attempts were carried out with vinyl and allylmagnesium bromide, yielding the corresponding vinyl and allyl ketones, 124 and 125 respectively (Scheme 27). The decreased yields observed using vinyl Grignard are most likely due to the vinyl ketone being prone to a second 1,4-addition by excess organometallic reagent. Attempts were made to improve upon these yields by using vinyllithium, but yields were not drastically improved upon.
Scheme 27: Synthesis of vinyl ketone 124 and allyl ketone 125.

The resultant ketones 124 and 125 were screened against a number of olefin metathesis conditions. However only dimerisation of allyl amine 126 or homo-allyl amine 128 was observed (Table 1 and Table 2).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Equiv.</th>
<th>Solvent</th>
<th>Temp (Time)</th>
<th>Recovered 124 (%)</th>
<th>Yield 127 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Grubbs 2</td>
<td>1.5</td>
<td>CH₂Cl₂</td>
<td>40 °C (16 h)</td>
<td>90</td>
<td>36</td>
</tr>
<tr>
<td>2</td>
<td>Grubbs 2</td>
<td>1.0</td>
<td>CH₂Cl₂</td>
<td>40 °C (16 h)</td>
<td>81</td>
<td>27</td>
</tr>
<tr>
<td>3</td>
<td>Grubbs 2</td>
<td>3.0</td>
<td>CH₂Cl₂</td>
<td>40 °C (16 h)</td>
<td>85</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>Grubbs 2</td>
<td>1.5</td>
<td>CH₂Cl₂</td>
<td>rt (16 h)</td>
<td>69</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>Grubbs 2</td>
<td>1.5</td>
<td>C₆H₆</td>
<td>40 °C (16 h)</td>
<td>94</td>
<td>17</td>
</tr>
<tr>
<td>6</td>
<td>Grubbs 2</td>
<td>1.5</td>
<td>PhMe</td>
<td>110 °C (2 h)</td>
<td>98</td>
<td>39</td>
</tr>
<tr>
<td>7</td>
<td>Grubbs 2</td>
<td>1.5</td>
<td>PhMe</td>
<td>110 °C (16 h)</td>
<td>68</td>
<td>41</td>
</tr>
<tr>
<td>8</td>
<td>GH-2⁺</td>
<td>1.5</td>
<td>CH₂Cl₂</td>
<td>rt (16 h)</td>
<td>93</td>
<td>10</td>
</tr>
<tr>
<td>9</td>
<td>GH-2⁺</td>
<td>1.5</td>
<td>CH₂Cl₂</td>
<td>rt (96 h)</td>
<td>60</td>
<td>25</td>
</tr>
<tr>
<td>10</td>
<td>GH-2⁺</td>
<td>1.5</td>
<td>CH₂Cl₂</td>
<td>40 °C (8 h)</td>
<td>96</td>
<td>12</td>
</tr>
</tbody>
</table>

Table 1: Cross-metathesis conditions attempted between 124 and 126. All reactions carried out on 0.1 mmol scale, with 5 mol% of catalyst. a: Hoveyda-Grubbs Catalyst® 2nd Generation.
The next approach included addition to the lactam of a 4-carbon containing organometallic with a heteroatom-containing terminal functional group, such as a protected alcohol or a STABASE protected amine. Organometallics 130-133 were prone to cyclisation and the corresponding ketones could not be isolated (Table 3). Additionally, the lack of product could be due to the afforded ketones decomposing upon purification as the STABASE protecting groups are susceptible to cleavage under many conditions.
<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product (Yield*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Structure 130" /></td>
<td>134 (ND)</td>
</tr>
</tbody>
</table>
|       | ‘STABASE’ 
(130) |     |
| 2     | ![Structure 131](image2.png) | 135 (ND) |
|       | ‘BENZOSTABASE’ 
(131) |     |
| 3     | ![Structure 132](image3.png) | 136 (ND) |
|       | ‘DPSide’ 
(132) |     |
| 4     | OPMB (133) | 137 (ND) |

Table 3: Organometallic addition to lactam 57. All reactions carried out on 1 mmol scale with 1.2 equiv. of Grignard reagent.
2.4.2 Free-Radical Approaches to Spiroaminals

There have been many reports of utilizing radicals to produce spirocyclic compounds. Most notable in recent years within this field is Bode’s reported tin amine protocol or “SnAP” (see Section 1.1). Inspired by this work, and work within the Polyzos group, we sought to investigate the radical approach to forming aminals. While the addition of radicals to imines and ketones is well known, the analogous chemistry of amidines is relatively less studied.

Scheme 28: Retrosynthesis of spiroaminal 53-A via radical addition to amidines.

Our first approach was in parallel with the work of Bode, but without the presence of a heteroatom alpha to the tin moiety. Amine 142 was prepared in two steps from allyl cyanide (140). Compound 142 was then treated with thioiminium 144, prepared in two steps from lactam 52, to afford amidine 145 (Scheme 29). Amidine 145 which was prone to hydrolysis and therefore used immediately in subsequent reactions.

Scheme 29: Synthesis of tin amidine 145.
When amidine 145 was treated with the conditions developed by Bode, or traditional radical initiating conditions, the desired product 53-A was obtained in very low yields of less than 10% (Scheme 30). Presumably, the absence of an alpha heteroatom that is present in Bode’s system reduces the stability of the resultant primary radical, leading to undesired side-products.

\[
\begin{align*}
\text{When amidine 145 was treated with the conditions developed by Bode,} & \quad \text{or traditional radical initiating conditions, the desired product 53-A was obtained in very low yields of less than 10% (Scheme 30). Presumably, the absence of an alpha heteroatom that is present in Bode’s system reduces the stability of the resultant primary radical, leading to undesired side-products.}
\end{align*}
\]

As a result, our attentions focused on producing a more stable radical intermediate, and with this in mind, iodo-phenethylamine 148 was prepared (Scheme 31). Reduction of the cyanide 146 generated 147 which upon treatment with thioiminium ether 144, afforded amidine 148.

\[
\begin{align*}
\text{As a result, our attentions focused on producing a more stable radical intermediate, and with this in mind, iodo-phenethylamine 148 was prepared (Scheme 31). Reduction of the cyanide 146 generated 147 which upon treatment with thioiminium ether 144, afforded amidine 148.}
\end{align*}
\]

The treatment of 148 with either conditions found within the Polyzos group utilising visible light photoredox catalysis, or traditional radical generators, led solely to the dehalogenated product 149 (Scheme 32).
The spirocyclisation was then attempted using the benzannulated thioiminium ether 154, which was prepared in three steps from tetrahydroisoquinoline (150). Again, only the dehalogenation product was afforded (Scheme 33). A variety of other radical initiation conditions were screened, including prolonged addition of both radical initiator and radical propagating agents, however, none of these afforded the desired product.

While carrying out these reactions, intense colours were observed which completely dissipated upon exposure of the reaction to oxygen during the quench. It was hypothesised that a persistent aminal radical was forming during the reaction. To the best of our knowledge, previous reports of carbon-centred aminal radicals have always included an amide moiety or N-acyl moiety. In view of this, the corresponding N-acyl amidines 156 and 157 were synthesised, however no additional reactivity compared to amidine 153 was observed (Scheme 34).
Our next approach was to replace the ethyl aryl iodide with a simple pendent olefin in the hope that if the aminal radical was formed, it would cyclise onto the alkene. Using the conditions developed by Beaudry, no conversion of starting material 159 was observed and after prolonged reaction times hydrolysis occurred (Scheme 35).

As it was not possible to form the spiroaminal via the routes investigated in satisfactory yields, a novel approach to spiroaminals has been developed.

### 2.5 A Diene Approach to Spiroaminals

#### 2.5.1 Proof of Concept

Due to the symmetrical nature of the targeted spiroaminals, a bidirectional approach was envisaged. With this in mind, the Grignard reagent of bromo-alkane 160 was treated with 0.5 equivalents of ethyl formate to yield the hydroxy-diene 161 which was sequentially oxidised and protected to yield ketal-diene 163 (Scheme 36). This was then treated with ozone and a subsequent triphenylphosphine work-up affording ketal-dialdehyde 164. Dialdehyde 164 was subjected to reductive amination conditions, however, the products were formed in low yields, with the major competing pathway being aldehyde trimerisation.
To bypass this side reaction, a reductive work-up following the ozonolysis of 163 was attempted in order to yield ketal-diol 167. Initially sodium borohydride was used, however this was not a strong enough reducing agent, and ozonide 166 was isolated (Scheme 35). Chemically robust primary ozonides are not uncommon, with several reports in the literature.\cite{78,79} Treatment of 163 with ozone and subsequent excess LiAlH₄ however, yielded alcohol 167 in good yields, without the need for purification (Scheme 37).

Ketal diol 167 was sequentially allowed to react with tolenesulfonyl chloride, and potassium phthalimide, to afford ketal 169. Subsequent treatment with hydrazine yielded the ketal diamine 170, however, all attempts at ketal deprotection were unsuccessful (Scheme 38).
Presumably, this is because the primary amines form aminium ions under the acidic conditions employed for the ketal deprotection. As a positive charge is required on the oxygen to facilitate the removal of the ketal, a compound of such a low molecular weight holding three formal positive charges would be extremely unfavourable. This hypothesis is supported by the facile deprotection of di-phthalimide ketal 169 to yield ketone 171 (Scheme 39). Unsurprisingly, treatment of phthalimide ketone 171 with hydrazine gave inseparable mixtures of by-products, which include the hydrazone and the azine.

As a result, our attentions were directed to the azidation of previously prepared ditosylate 168 (Scheme 40). Ketal diazide 172 was prepared in good yields from diol 167, showing no signs of decomposition and requiring no purification. A mild acidic deprotection of 172 yielded keto diazide 173, which, when treated with Pd/C and 1 atm of hydrogen, afforded the spiroaminal 53-A in good yields (Scheme 40).
Although significantly longer than the original synthetic route, the conditions are considerably milder and the spiroaminal 53-A was afforded without the need for purification after final step. This route allows for the size or substitution of each spiroaminal ring to be varied independently.

### 2.5.2 The First Mono-Substituted Spiroaminal

The first target for a mono-substituted spiroaminal was phenyl substituted 182-A. The synthesis of which precedes via hexenoic Weinreb amide 177, which itself was prepared in three steps from methyl cinnamate (174). A Hosomi-Sakurai addition of allyl trimethylsilane yielded hexenoic ester 175. Subsequent hydrolysis followed by Weinreb amide formation afforded Weinreb amide 177 in good yields (Scheme 41).
Treatment of amide 177 with the Grignard reagent derived from 5-bromo-pentene (160) yielded keto diene 178, Following on from this, utilising the steps described above (see Schemes 34 and 38), intermediate 178 was smoothly taken forward to mono-substituted spiroaminal 182-A in good yields (Scheme 42).

The afforded mono-phenyl 182-A was observed solely as its aminal tautomer. The crude $^1$H NMR and the $^1$H NMR of the purified material showed only one diastereomer was present.
This shows the stereochemistry is being controlled by the anomic effect, as was seen in dimethyl spiroaminal 119-A (see Section 2.3). We propose the phenyl group favours adopting the equatorial or pseudoequatorial position on the ring, resulting in one spirane centre being formed. Therefore, we propose the afforded product is a racemic mixture of \((S,S)\) and \((R,R)\) and contains no \((S,R)\) or \((R,S)\) (Figure 15).

![Figure 15: The possible diastereomers of 182-A.](image)

This prediction is dependent not only on the spirane being able to tautomerise to a thermodynamically preferred product, but additionally the nitrogens adopting the axial-axial position, which would be in agreement with Thiels computational investigation.\(^{50}\)

Although some improvements were made to the route to spiroaminals with respect to robustness and possible substrate scope, the increased number of linear steps was undesirable. A shorter method that avoided the azide moieties yet maintaining a similar bidirectional approach was sought after.

### 2.6 The Horner-Wadsworth-Emmons Approach to Spiroaminals

Inspired by our success in the synthesis of tetrahydrospirobiquinolines\(^{51}\) (see chapter 3), and the previous developed methodology allowing rapid access to the spiroaminal motif, we sought to extend this approach to aliphatic systems.

![Scheme 43: Retrosynthetic approach of 183 using a Horner-Wadsworth Emmons (HWE) reaction.](image)
The use of aromatic aldehydes in the Claisen-Schmidt reaction with acetone is well documented in the literature.\textsuperscript{81} However the use of aliphatic aldehydes is drastically less efficient due to the reduced acidity of the α-proton in the initial aldol product. With this in mind, inspiration was taken from the work of Chen et al.\textsuperscript{82} We envisaged using a Horner-Wadsworth-Emmons (HWE) reaction to replace the Claisen-Schmidt (Scheme 43). The reported diphosphate 190 was easily synthesised from 1,3-dichloroacetone (187) in 3 steps (Scheme 44).\textsuperscript{83} The carbonyl was protected as the hydrazine carboxylate to facilitate the Arbuzov phosphorylation and prevent the competing Perkow reaction.\textsuperscript{84}

![Scheme 44: Synthesis of diphosphate 190.](image)

There was an initial focus on using this significantly milder reaction sequence to introduce chirality within our spiroaminal framework. We initially directed our attention on producing 2,8-disubstituted spiroaminals as the desired aldehydes were readily available with high enantioselectivity using Ellman sulfinimine chemistry.\textsuperscript{58} We first implemented this reaction sequence with benzaldehyde (191) to afford the enantiopure (S)-tert-butyl-sulfinimine 192. Treatment with allyl magnesium bromide afforded allyl sulfinamide 193 with high diastereoselectivity.\textsuperscript{85} The protecting group was easily exchanged to a Boc protecting group utilising a one pot procedure,\textsuperscript{86} yielding homoallylic amine 194 (Scheme 45).

![Scheme 45: Synthesis of homoallylic amine 194.](image)
Ozonolysis of homoallylic amine 194 with a basic work up afforded aldehyde 195 in good yields. Using K$_2$CO$_3$ in a THF/H$_2$O solvent mixture, 195 smoothly underwent the double HWE with diphosphate 190 to afford the dienone 196 in good yields, with the product being isolated solely as the symmetrical diastereomer (Scheme 46).

\[ \begin{align*}
194 & \xrightarrow{(i) O_3 \text{ -78 °C}} \text{NHBOc} \\
& \xrightarrow{(ii) \text{NET}_3 \text{ -78 °C to rt CH}_2\text{Cl}_2 90\%}} \text{195} \\
190 & \xrightarrow{\text{K}_2\text{CO}_3 \text{ THF/H}_2\text{O rt 70\%}} \text{196}
\end{align*} \\
3J_{\text{H}_a-\text{H}_b} = 15\text{Hz}
\]

*Scheme 46: The synthesis of diene 196.*

This dienone was easily hydrogenated under mild conditions, yielding the ketone 197. Treatment with TFA afforded spiroaminal 198-A in good yields (Scheme 47).

\[ \begin{align*}
196 & \xrightarrow{\text{H}_2 (1 \text{ atm}) \text{ Pd/C MeOH}} \left[ \begin{array}{c}
\text{NHBOc} \\
\text{197}
\end{array} \right] \\
& \xrightarrow{\text{TFA CH}_2\text{Cl}_2 76\% \text{ 2 steps}} \text{198-A}
\end{align*} \\
\]

*Scheme 47: Synthesis of phenyl spiroaminal 198-A.*

The spiroaminal was isolated as a single epimer, implying high retention of enantiomeric excess from the previous steps. Attempts were made to recrystallise 198-A in order to confirm the absolute stereochemistry, however, suitable samples have yet to be isolated. We hypothesised that 198-A exists solely as the (R,R,R) epimer (Figure 16), similar to spiroaminal 119-A (see Section 2.3).
In addition to the facile approach to the spiroaminals, the chemistry should be tolerant to a large range of substituents as well as allowing the synthesis of both enantiomers of the final spiroaminals.\textsuperscript{58,87}

In addition, work carried out Jiaxu Han within our group utilising protected aspartic acid \textsuperscript{199}, our group has accessed the unique spiro-di-\(\alpha\)-amino ester \textsuperscript{201-A} (Scheme 48).

\textbf{Scheme 48: Synthesis of spiroaminal \textsuperscript{201-A}. Work carried out by Jiaxu Han.}

The structure of amino ester \textsuperscript{201-A} was confirmed by X-ray crystallography (Figure 17). We hope these further functionalised substrates may exhibit increased complexity for coordination chemistry and biological applications.\textsuperscript{88}
2.7 Conclusions and Future Work

Significant progress has been made towards the synthesis of aliphatic spiroaminals. The HWE approach to spiroaminals utilises mild conditions is high yielding and is experimentally facile (see Section 2.6). The focus going forward is to investigate the robustness of this route in terms of scale and functional group compatibility. There will also be investigations into other substitution patterns using this methodology. The mono HWE reaction of diphosphate 190 has been reported, and this should allow a highly divergent approach to many different spiroaminals including; syn 206, unsymmetrical 207 and 208, and mono substituted 209 (Scheme 49).

*Figure 17: Crystal structure of spiroaminal 201-A, prepared by Jiaxu Han (50% probability ellipsoid).*

*Scheme 49: The possible variations utilising a mono-HWE with diphosphate 190.*
Additionally, the resultant olefins of the HWE could be used to further functionalise the carbon backbone utilising 1,4-additions (Scheme 50).\textsuperscript{90}

\begin{center}
\begin{tikzcd}
\begin{array}{c}
\text{BocHN} \overset{\text{ZnR}_2}{\text{Cu(O Tf)}_2} \overset{\text{L}^*}{\text{NH Boc}} \\
\longrightarrow
\end{array}
\begin{array}{c}
\text{R} \overset{\text{NH}}{\text{R}} \\
\longrightarrow
\end{array}
\begin{array}{c}
\text{R} \overset{\text{NH}}{\text{R}} \\
\end{array}
\end{tikzcd}
\end{center}

\textit{Scheme 50: The possible variation at the 4 and 10 positions utilising 1,4-additions to dienone 210.}

Lastly, the starting diphosphate could be prepared from other α,α'-dichloroketones, such as substituted 213 or cyclic-ketone 214 (Scheme 51). The additional ring could influence the resultant stereochemistry at the aminal centre.\textsuperscript{21} Once the number of isolated spiroaminals has been increased, we will be able to turn our attentions to investigations into their reactivity and medicinal properties.

\begin{center}
\begin{tikzcd}
\begin{array}{c}
\text{R} \overset{\text{NH}}{\text{R}} \\
\end{array}
\begin{array}{c}
\longrightarrow
\end{array}
\begin{array}{c}
\text{Cl} \overset{\text{Cl}}{\text{Cl}} \\
\end{array}
\begin{array}{c}
\end{array}
\end{tikzcd}
\end{center}

\textit{Scheme 51: The possible substitution at the 5 and/or 6 positions utilising different α-α'-dichloroketones 213-214.}
CHAPTER THREE

SYNTHESIS AND REACTIONS OF TETRAHYDROSPIROBIQUINOLINES
3. Synthesis and Reactions of Tetrahydrospirobiquinolines

3.1 Benzannulated Spiroketalts

3.1.1 Natural Products and Biological Activity

Aliphatic spiroketalts have been well studied, and isolated from a plethora of natural products (see chapters 1 and 2). A lesser known compound class, the aryl fused spiroke tals, or benzannulated spiroke talts, is relatively rare when compared to its aliphatic counterpart.\textsuperscript{13,14} Most notable within this structural class are the antitumor antibiotics, the rubromycins 217-220.\textsuperscript{91} These compounds have gained the attention of both biologists for their interesting biological activities,\textsuperscript{92} as well as synthetic chemists for their complex molecular architecture as targets for total synthesis (Figure 18).\textsuperscript{14}

The rubromycins, first isolated from \textit{Streptomyces collinus}, a bacterium isolated from the soil around Baden, Germany, are highly potent inhibitors of Gram-positive bacteria (\textit{Bacillus subtilis}, and \textit{Staphylococcus aureus}) but are ineffective on Gram-negative bacteria, or fungi.\textsuperscript{92,93} Among the spiroke tal members of this family, the first total synthesis of \(\gamma\)-rubromycin.
(219), was reported by Kita,94 followed by a second formal synthesis by Brimble95, and ơ-rubromycin (220) which was synthesised by Li et al.96 There has also been noteworthy work in this field on related natural product heliquinomycin (221) (Figure 19), first synthesised by Danishefsky.97,98 An excellent review on the biological activities of these compounds, and many other benzannulated spiroketalts has been published by Brimble et al.14

![Heliquinomycin - 221](image)

Figure 19: Benzannulated spiroketal natural product Heliquinomycin (221).

The benzannulated spiroaminal core is even less common than the spiroketal, however, it is present in a limited number of natural products. The most notable example is (−)-isoschizogamine (37) (Figure 20), which was isolated from Schizozygia caffaeoides in 1963 by Renner et al.99 The correct structure of 37 was not elucidated until further investigation by Hájiček and co-workers in 1998.100 Isoschizogamine has since been synthesised by several groups including Heathcock (1999),43 Fukuyama (2012),42 Qin (2015),101 and Tokuyama (2015),41 followed by an elegant synthesis by Zhu (2015).102 It is a member of the larger family of alkaloid natural products (see chapter 1). Another example of benzannulated spiroaminal is the immunosuppressant (±)-spiroreticulatine (38) which was isolated by Li et al. in 2015 from Fascaplysinospsis reticulate, a sea sponge found in the South China Sea (Figure 20).39 This natural product shows promising immune-suppressive activities as both the racemate and separated enantiomers against Interleukin (IL-2), while demonstrating little cytotoxicity against normal human cancer cell lines.
3.1.2 Ligands

As well as exhibiting an array of interesting biological activities, benzannulated spiroketals have been developed as ligands for transition metal catalysis. These systems were first reported by van Leeuwen,\textsuperscript{103} who synthesised a range of these compounds, and subsequently found a variety of applications for them in catalysis. Using the bichromane backbone, the van Leeuwan group successfully made the SPANphos family \textsuperscript{222-225},\textsuperscript{104} a C2-symmetric selectively trans-coordinating ligand family, which provided access to an understudied area of unusual steric space around metal centres.\textsuperscript{105} These spiroketals accessed several unique metal complexes, some of which showed activity in methanol carbonylation (Scheme 52).\textsuperscript{106}

\begin{scheme}
\begin{center}
\includegraphics[width=\textwidth]{scheme52.png}
\end{center}
\end{scheme}

\textit{Scheme 52} The SPANPhos family \textsuperscript{222-225}, and their activity in methanol carbonylation.\textsuperscript{106}
This group went on to produce SPANamine (228), a bis-amine bichromane derivative, which was shown to give promising enantioselectivity when applied to the α-fluorination of β-ketoester 229 (Scheme 53), and epoxidation of alkenes. \[ ^{103} \]

More recently the work of Ding, Zang and Zhou allowed rapid access to chiral spiroketals 232 utilising their novel SPINPhox Iridium (I) 233 catalyst under high pressures of hydrogen with dienones 231 (Scheme 54), with the previously reported by van Leeuwan utilising resolution by chiral HPLC or diastereoselective resolution. \[ ^{107} \]

With these spiroketals in hand, the Ding group then published a series of papers on the complexation to metals with these spiroketals, as well as their applications in enantioselective transformations including palladium catalysed allylic amination and gold catalysed olefin cyclopropanation of diazooxindoles (Scheme 55). \[ ^{109} \]
3.2 Route Optimisation

Inspired by the route of Ding, Wang, and Zhou,\textsuperscript{108} We envisaged increasing the structural rigidity of the spiroaminal scaffold of the aliphatic spiroaminals (see chapter two) would reduce or eliminate the amino-imine / aminal tautomerisation.\textsuperscript{50} With the addition of the aromatic π-system we hypothesised the lone pairs on nitrogen would also be electronically restrained, and participate less in the anomeric effect, which could further reduce the energetic favourability of ring opening.\textsuperscript{50} The first attempted approach to the tetrahydrospirobiquinoline 235 was a double aldol condensation of o-nitrobenzaldehyde (238) with acetone to yield the dinitro-dibenzyldieneacetone 237, followed by hydrogen based reduction of both the nitro moieties and the benzylidene olefins (Scheme 56).

Scheme 55: The Zhou cyclopropanation of diazooxindoles.\textsuperscript{110}

\begin{center}
\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme55.png}
\end{figure}
\end{center}

\textit{Scheme 56: Retrosynthetic analysis of tetrahydrospirobiquinoline 235.}
The aldol condensation between 238 and acetone, although described in the literature,\textsuperscript{111} was hard to reproduce in acceptable yields (Scheme 57). This is most likely due to the stability of the resultant olefins in strongly basic aqueous media. Acid catalysed conditions for this transformation are known,\textsuperscript{112} however, they utilised stoichiometric amount of highly toxic reagents.

\begin{center}
\textbf{Scheme 57: The double aldol condensation of 237.}
\end{center}

In addition to this, it was found the hydrogenation of this di-nitro compound yielded multiple products, most likely due to side reactions of the intermediates formed during the reduction of the nitro group.\textsuperscript{113,114} Several conditions were attempted with a variety of metal catalysts, but these were all found to produce complex mixtures of products (Table 4)

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
Entry & Catalyst & Catalyst wt\% & Pressure (atm) & Solvent \\
\hline
1 & PtO$_2$ & 10 & 2 & MeOH \\
\hline
2 & PtO$_2$ & 20 & 2 & MeOH \\
\hline
3 & Pd/C & 10 & 1 & MeOH \\
\hline
4 & Pd/C & 10 & 2 & MeOH \\
\hline
5 & Pd/C & 10 & 4 & MeOH \\
\hline
6 & Pd/C & 20 & 1 & EtOH \\
\hline
\end{tabular}
\end{table}
<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Pd/C</td>
<td>20</td>
<td>1</td>
<td>EtOH</td>
</tr>
<tr>
<td>8</td>
<td>Raney Ni</td>
<td>20</td>
<td>2</td>
<td>EtOH</td>
</tr>
<tr>
<td>9</td>
<td>Raney Ni</td>
<td>20</td>
<td>2</td>
<td>EtOAc</td>
</tr>
</tbody>
</table>

*Table 4: The conditions of the attempted hydrogenation of 237.*

To avoid the nitro group we instead prepared the azido derivative which has been shown to condense well with acetone under basic conditions.\(^{115}\) o-Azidobenzaldehyde (239) was prepared from the analogous nitro compound through S\(_{N}Ar\) with sodium azide (Scheme 58). Although long reaction times were required, these conditions minimised the formation of 2,1-benzisoxazole or anthranil 240,\(^{116}\) and could be scaled up to large quantities, without the risk of exothermic decomposition.\(^{117}\)

![Scheme 58: The synthesis of azide 239.](image)

o-Azidobenzaldehyde (239) was allowed to react with acetone in a 2:1 stoichiometric quantity, in the presence of aqueous sodium hydroxide to provide the diazido dienone 241. Fortuitously, our first conditions for hydrogenation using 10%wt palladium on carbon (Pd/C) at one atmosphere of hydrogen yielded the tetrahydrospirobiquinoline 235 as a single product (Scheme 59).

![Scheme 59: The synthesis of spirobiquinoline 235.](image)
Other metal catalysts and solvents were screened, however the initial conditions were found to be optimal. The structure of spirocycle 235 was confirmed with 2-D NMR spectroscopy and X-ray crystal structure determination (Figure 21).

![Image of spirocycle 235](image)

*Figure 21: The solid-state structure of 235 (50% probability ellipsoids).*

The hydrogenation of 241 is particularly efficient, with global reduction, imine condensation, and aminal formation by nucleophilic attack of the opposing amine on to the resultant imine all occurring in one step. The exact order in which these steps take place has not been studied in detail, however reports in the literature suggest that the reduction of the azide moieties occurs first to yield diamine 242. It is presumed that one of the olefins is then reduced to produce the mono enone 243. At this point there are two possible pathways, A or B. Pathway A occurs by the reduction of the second olefin to yield the saturated diamine 244, followed by a condensation of an aniline onto the ketone to form the amine-imine 246, which then forms the aminal 235. In the second plausible reaction pathway B, the imine formation occurs before the reduction of the second olefin to yield the vinyl dihydroquinoline 245, which then undergoes hydrogenation to yield the common intermediate 246 (Scheme 60).
The methodology is facile, requiring minimal purification. The dienone 241 precipitates from the ethanolic solution and is used in the next step without further purification. After treatment with Pd/C in a hydrogen atmosphere, in many cases the crude product have a purity of >90%. Simple purification through a pad of silica yielded the spiroquinoline as an air stable solid. This methodology has been successfully scaled up to 40 mmol of aldehyde using a Parr shaker apparatus to yield 3.45 g spirobiquinoline 235 (69% yield over two steps).

### 3.3 Synthesis of o-azidobenzaldehydes

1-Azido-2-naphthaldehyde (249) was synthesised from 1-fluoronaphthalene (247) by deprotonation, and subsequent addition of DMF yielding aldehyde 248,\(^{118}\) S\(_{\text{Ar}}\) using a modified procedure of Boswell and Licause\(^{118}\) then afforded azide 249 in good yields. (Scheme 61)

\[ \text{Scheme 61: The synthesis of azide 249.} \]
8-Azidoquinoline-7-carbaldehyde (253) was prepared in 3 steps from 7-methyl-8-nitroquinoline (250). The methyl group was functionalised with N,N-dimethylformamide dimethyl acetal (DMF-DMA) to yield the enamine 251, followed by oxidation cleavage to yield aldehyde 252 with sodium periodate. This was subjected to the standard S\textsubscript{N}Ar conditions to yield the azide 253 (Scheme 62).

\begin{center}
\textbf{Scheme 62: The synthesis of azide 253.}
\end{center}

The synthesis of the additional known o-azidobenzaldehydes 258-261 was accomplished through S\textsubscript{N}Ar of the corresponding nitro derivative. The o-nitrobenzaldehydes 254-257 were commercially available, and were subjected to the conditions of Driver \textit{et al.}\textsuperscript{121,122} to afford the azides 258-261 in good yields, many of which, did not require purification (Scheme 63).

\begin{center}
\textbf{Scheme 63: The preparation of azides 258-261.}
\end{center}

3.4 Substrate Scope

With the o-azidobenzaldehydes in hand, the effect of substituents on the spirocyclisation methodology was investigated. All aldehydes were subjected to reaction under the same
conditions to afford the spirobiquinolines 262-267 in yields ranging from 34-82% over the two steps (Table 5).

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Aldehyde</th>
<th>Product</th>
<th>Yield (%)^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>napthyl</td>
<td>249</td>
<td>262</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>quinoline</td>
<td>253</td>
<td>263</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>3-Me</td>
<td>258</td>
<td>264</td>
<td>53</td>
</tr>
<tr>
<td>4</td>
<td>4-OMe</td>
<td>259</td>
<td>265</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>4-CF₃</td>
<td>260</td>
<td>266</td>
<td>78</td>
</tr>
<tr>
<td>6</td>
<td>5-Cl</td>
<td>261</td>
<td>267</td>
<td>34^b</td>
</tr>
</tbody>
</table>

Table 5: Substrate scope of tetrahydrospirobiquinoline methodology. ^aIsolated yield over two steps, 2 mmol scale wrt aldehyde. ^bSome dehalogenation observed, see main text.

The results showed that the methodology tolerated extended π-systems, electron rich, electron poor, ortho, meta, and para substituted examples. There was little variation in the yields with the exception of 5-chloro (Table 5, Entry 6) where some dehalogenation was observed (Scheme 64) and 3-Me (Table 5, Entry 3) where presumably increased steric congestion at the spirane centre is a contributing factor.

Scheme 64: Dehalogenation during synthesis of spiroquinoline 267.
All the final compounds were only observed as their aminal tautomers, no amine-imine tautomer was detected. They were all found to be stable to both aqueous base, and aqueous acid for over 48 hours, with no decomposition.

### 3.5 Post Spirocyclisation Functionalisation

#### 3.5.1 Aromatic Functionalisation

Following our substrate scope studies, we wished to investigate the stability of the spirane centre towards aromatic functionalisation. Classical nitration conditions, as well as ytterbium(iii) triflate catalysed nitration,\textsuperscript{123} led to decomposition of the spirobiquinoline 235. Decomposition was also observed for classical formylations such as the Vilsmeier-Haack and the Gattermann-Koch reactions (Scheme 65).

![Scheme 65: Failed attempts at aromatic functionalisation of 235.](image)

Treatment of spirobiquinoline 235 with N-bromosuccinimide (NBS) gave the brominated analogues 271 and 272 in good yields (Scheme 65). Dibromination, presumably by an Orton rearrangement,\textsuperscript{124} first occurs \textit{para} to the nitrogens to yield the dibromo spiroquinoline 271 and second, \textit{ortho} to the nitrogens to yield the tetrabromo spiroquinoline 272, with the mono and tribrominated products observed in small quantities (Scheme 66).
The position of the bromo substituents for both 271 and 272 were confirmed by X-ray structural elucidation (Figure 22 and Figure 23).

There is an increase of symmetry with increased substitution in the crystal structures from unsubstituted spiroquinoline 235, dibromo 271, and tetrabromo 272. The aminal nitrogens in all cases are held in an almost co-planar conformation with the mean internal bond angles of 120.8°, 122.3°, and 122.5° respectively. This implies these nitrogens are sp² in terms of orbital hybridisation, which would drastically hinder reactivity (see section 3.5.2). The difference in bond length between the C-N aminal bonds is observed to decrease with the increasing number of bromines, with a difference of 0.026 Å, 0.021 Å, and 0.04 Å respectively. This is
most likely caused by two competing factors. Firstly, the bulky bromines on the ring makes the entire fused ring system expand to accommodate their size, which would explain the large difference between 271 and 272, with the introduction of bromines ortho to the aminal nitrogens. Secondly, the electron withdrawing nature of the bromine atoms will impact the anomeric effect. Increasingly electron deficient aromatics leads to a diminished anomeric effect due to the nitrogen lone pair being further donated the π-system reducing the donation into the opposing σ*(C-N) (see section 2.1.3).

The tetrabromo 272 was subjected to a variety of Suzuki-Miyuara cross coupling conditions in order to synthesise the tetraphenyl spiroquinoline 273 (Table 6). The best conditions were found to be with PdCl₂(PPh₃)₂ as a catalyst, XPhos as a ligand, and K₂CO₃ as a base (Table 6, Entry 7). Other palladium pre-catalysts and ligands also afforded the product in adequate yields.

![Reaction Scheme]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd cat.</th>
<th>Ligand</th>
<th>Base</th>
<th>Solvent (Ratio)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PPh₃)₄</td>
<td>n/a</td>
<td>K₂CO₃</td>
<td>MeCN (n/a)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>[Pd(dppf)Cl₂]</td>
<td>n/a</td>
<td>Ba(OH)₂</td>
<td>DMF-H₂O (6:1)</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>PdCl₂(PPh₃)₂</td>
<td>n/a</td>
<td>K₂CO₃</td>
<td>Dioxane- H₂O-EtOH (5:1:1)</td>
<td>26</td>
</tr>
<tr>
<td>4</td>
<td>PdCl₂(PPh₃)₂</td>
<td>PCy₃</td>
<td>K₂CO₃</td>
<td>DMF-H₂O (6:1)</td>
<td>37</td>
</tr>
<tr>
<td>5</td>
<td>PdCl₂(PPh₃)₂</td>
<td>XPhos</td>
<td>K₂CO₃</td>
<td>DMF-H₂O (6:1)</td>
<td>45</td>
</tr>
<tr>
<td>6</td>
<td>PdCl₂(PPh₃)₂</td>
<td>XPhos</td>
<td>K₂CO₃</td>
<td>DMF-H₂O (8:1)</td>
<td>32</td>
</tr>
<tr>
<td>7</td>
<td>PdCl₂(PPh₃)₂</td>
<td>XPhos</td>
<td>K₂CO₃</td>
<td>DMF-H₂O (4:1)</td>
<td>67</td>
</tr>
<tr>
<td>8</td>
<td>PdCl₂(PPh₃)₂</td>
<td>XPhos</td>
<td>K₂CO₃</td>
<td>DMF-H₂O (4:1)</td>
<td>65</td>
</tr>
<tr>
<td>9</td>
<td>PdCl₂(PPh₃)₂</td>
<td>XPhos</td>
<td>K₂CO₃</td>
<td>DMF-H₂O (4:1)</td>
<td>33</td>
</tr>
</tbody>
</table>
The structure of tetraphenyl spiroquinoine 273 was confirmed by X-ray crystallography (Figure 24). Importantly, this reaction demonstrates the stability of the spiroaminal centre towards palladium cross-coupling, which is one of the most widely used C-C bond forming reactions within industry and academia.\textsuperscript{125}

\textbf{Figure 24: The solid-state structure of 273 (50\% probability ellipsoids).}

\section*{3.5.2 Nitrogen Functionalisation}

We then turned our attention to derivatisation of the nitrogen at the spirane centre. A variety of bases and electrophiles were screened, starting with the conditions previously utilised within the Barrett group for the alkylation and acylation of the aliphatic analogue 53.\textsuperscript{35} Unsurprisingly, weak bases alone led to no conversion, with full recovery for the starting material. This lack of reactivity is presumably due to a mixture of sterics and the electronics of the formally secondary anilines. Spirobiquinoline 235 was also unreactive to alkylation in the presence a variety of stronger bases (Scheme 67).

\textbf{Scheme 67: Failed attempts at nitrogen methylation of 235 with weaker bases.}
Deprotonation with stronger bases was attempted. It was found that while deprotonation with $n$-BuLi was successful, attempts to react with electrophiles were all ineffective (Scheme 68). Deprotonation was confirmed by quenching the lithium species with MeOD, yielding the mono-deuterated 275, with deuterium incorporation $>$95% (Scheme 68).

![Scheme 68: Deprotonation studies of 235.](image)

We expected that aggregation was an issue with the deprotonated spiroquinoline. Attempts were made to isolate the lithium amide utilising the techniques of Collum,\textsuperscript{126} however crystals suitable for X-ray crystallography could not be obtained (see Section 4.2.3). It was found that the addition of HMPA, with methyl iodide or allyl bromide afforded the dimethyl spiroquinoline 274 and diallyl spiroquinoline 276 respectively (Table 7). Reducing the equivalents of HMPA or temperature were found to have detrimental effects on yield. All other electrophiles tested yielded no product (Table 7, Entries 10-12).

<table>
<thead>
<tr>
<th>Entry</th>
<th>R-X</th>
<th>HMPA equiv</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mel</td>
<td>0</td>
<td>THF</td>
<td>-78</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Mel</td>
<td>2.5</td>
<td>THF</td>
<td>-78</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>Mel</td>
<td>5.0</td>
<td>THF</td>
<td>-78</td>
<td>64</td>
</tr>
<tr>
<td>4</td>
<td>Mel</td>
<td>5.0</td>
<td>THF</td>
<td>-40</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>Mel</td>
<td>5.0</td>
<td>THF</td>
<td>-20</td>
<td>48</td>
</tr>
</tbody>
</table>
Table 7: Optimisation of the alkylation/allylation of 235. All reactions were carried out on a 0.2 mmol scale wrt 235. *Isolated yield. **Multiple inseparable products formed, likely carbene formation of BnBr upon treatment with nBuLi.

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Mel</td>
<td>5.0</td>
<td>THF</td>
<td>-78 to 0</td>
</tr>
<tr>
<td>7</td>
<td>Mel</td>
<td>5.0</td>
<td>THF</td>
<td>-78 to rt</td>
</tr>
<tr>
<td>8</td>
<td>AllylBr</td>
<td>5.0</td>
<td>THF</td>
<td>-78</td>
</tr>
<tr>
<td>9</td>
<td>AllylBr</td>
<td>5.0</td>
<td>THF</td>
<td>-78 to rt</td>
</tr>
<tr>
<td>10b</td>
<td>BnBr</td>
<td>5.0</td>
<td>THF</td>
<td>-78</td>
</tr>
<tr>
<td>11b</td>
<td>BnBr</td>
<td>5.0</td>
<td>THF</td>
<td>-100</td>
</tr>
<tr>
<td>12</td>
<td>I(CH₂)₃I</td>
<td>5.0</td>
<td>THF</td>
<td>-78</td>
</tr>
</tbody>
</table>

It was found that the stepwise route, comprising sequential mono deprotonation, electrophile addition, secondary deprotonation, and secondary electrophile addition, also drastically reduced yields. This was highlighted by the instability of the compounds obtained when using a single equivalent of electrophile (Scheme 69). Multiple products were observed, within the crude reaction mixture, however due to the complex mixture of products none could be isolated as analytically pure samples.

Both the dimethyl spiroquinoline 274 and diallyl spiroquinoline 276 showed complete retention of the spirane centre. This is in contrast to its aliphatic counterpart, which opens to form the amine-imine tautomer when alylated.³⁵ Diallyl spiroquinoline 276 efficiently underwent ring closing metathesis with Hoveyda-Grubbs Catalyst™ 2nd Generation Catalyst (GHII) to yield the pentacyclic 278 (Scheme 70).
3.6 Unsymmetrical Tetrahydrospirobiquinolines

To expand on the number of potential derivatives that can be afforded by this spiroaminal formation methodology, unsymmetrical systems were of high importance. To study the electronics of these compounds, we wished to perturb the electronics of each aromatic ring independently. Although aldol condensations of acetone with two different aldehydes is far less utilised than the synthesis of symmetrical dibenzylideneacetone derivatives, it has been reported by a variety of groups.\textsuperscript{127} In our studies acetone was treated with one equivalent of an o-azidobenzaldehyde 279 under the conditions as previously described for spirobiquinolines 235 and 262-267. The reaction mixture was stirred until it reached completion (TLC), and one equivalent of a second aldehyde 281 was added. This resulted in the precipitation of the unsymmetrical dienone 282, which smoothly underwent hydrogenation-spirocyclisation to afford the tetrahydrospirobiquinoline 283 (Scheme 71).
Both reactions also produced small amounts of the symmetrical spirobiquinolines (<5%), presumably due to competing homo-aldol condensations. This small set of unsymmetrical spirobiquinolines serve as a proof of concept to demonstrate that unsymmetrical systems were easily accessed through this methodology.

### 3.7 Cyclopentanone and Cyclohexanone Derivatives

#### 3.7.1 Synthesis of Cyclic Derivatives

Following from this, our attention turned to replacing acetone as a starting material with cyclic ketones. Cyclopentanone (286) and cyclohexanone (287) were found to afford the spirobiquinolines 288 and 289 respectively in acceptable yields. Interestingly both products were isolated as single epimers (Scheme 72).
The synthesis of cyclic spirobiquinolines 288 and 289.

The stereochemistry of both compounds was assigned by $^1$H and $^{13}$C NMR. Spirocycle 288 was found to exist as the $C_2$ symmetrical trans epimer, whereas spirocycle 289 exists as the unsymmetrical cis epimer, shown by a de-symmetrisation in the NMR. Attempts were made to confirm the stereochemistry of 288 and 289 through X-ray crystallography, however all attempts to obtain suitable crystals were unsuccessful. We expected bromination to increase the crystallinity (see Section 3.5.1), therefore 290 and 291 were prepared (Scheme 73). These analogues were successfully recrystallised to confirm the stereochemistry in both cases.

Scheme 72: The synthesis of cyclic spirobiquinolines 288 and 289.

Scheme 73: The synthesis and solid-state structures of 290 and 291 (50% probability ellipsoids).
3.7.2 Origins of Diastereoselectivity

The origin of the diastereoselectivity was probed computationally with the aid of Professor Henry Rzepa, who carried out the higher-level calculations by implementing dispersion corrected DFT calculations of the relative free energies. The basis set used was B3LYP+D3BJ/Def2-TZVPP/SCRF=ethanol, with an assumption of fast equilibria between the amine-imine and aminal tautomers. No trend was apparent for the relative free energies of both the cyclic and acyclic tautomers of the compounds, with both the aminal tautomers being lower in energy. Natural bond orbital (NBO) analysis indicated the nitrogen lone pair were partially donated into the \( \pi \)-system, as well as participating in the anomeric effect, however the stabilising energies of this effect were similar in both stereoisomers. The calculations, although insightful, did not provide an evident reason for the observed diastereoselectivity.

A possible contributing factor to the stereochemical outcome is the stability of the two intermediate ketones \( \text{293} \) and \( \text{296} \) (Scheme 74). It has been shown that the hydrogenation of cyclic dienones favours the formation of the \textit{cis} compounds.\(^\text{128}\) However it has been shown that \textit{cis}-cyclopentanones \( \text{296} \) can undergo facile isomerisation to its \textit{trans} epimer \( \text{297} \) (Scheme 74).\(^\text{129}\)

Cyclopentanone \( \text{295} \) is more likely to undergo this transformation due to easier access to the enolate due to increased acidity of the \( \alpha \)-proton and increased steric clashing of the two substituents on the smaller ring. Another hypothesis relates to an intermediate within one of

\[ \text{Scheme 74: One possible factor in stereoselectivity.} \]
the proposed pathways for the hydrogenation spirocyclisation (Scheme 60, Section 3.2). If the reaction follows pathway B, it will yield the vinyl tetrahydrophenanthridine 302, with one relative stereocentre already installed, it may be that the cyclisation directs the hydrogenation to a particular face (Scheme 75). One of the analogues may be more prone to forming this cyclic imine intermediate than the other, leading to the opposing selectivity.

Scheme 75: The cyclic imine hypothesis.

Ideally full modelling studies would be carried out on the entire reaction sequence, however due to the number of intermediates present, as well as the opposing diastereomers requiring separate calculations, time constraints did not allow this. Further studies into this diastereoselectivity will be carried out in due course.

3.8 Chiral Resolution

This new methodology has allowed us to access a wide range of derivatives, with an increased spirane stability compared to their aliphatic counterparts. With this higher stability, the compounds could be easily separated by analytical chiral HPLC. It was decided to investigate the stability of the spirane centre once resolved. Initially, analytical data led us to believe there was no tautomerisation occurring. The first attempts at resolution utilised the formation of a diastereomeric salts with a variety of chiral acids. However, all the salts attempted either showed no separation of diastereomers by recrystallisation, or showed decomposition over
prolonged periods. A sample of the napthyl fused 262 was eventually resolved using preparative chiral HPLC (Scheme 76).

\[ \text{IA Column} \]
\[ 2\% \text{ IPA / Hexane} \]
\[ \text{Separation Time 9 minutes} \]

\[ \text{(S)-262} \]
\[ \text{(R)-262} \]
\[ \text{(S,S)-288} \]
\[ \text{(S,S)-305} \]
\[ \text{(S,R,S)-288} \]

Racemisation within 24 h

**Scheme 76** *The chiral resolution and subsequent racemisation of naphthalene 262.*

It was soon apparent that the resolved enantiomers of spirane 262 racemised rapidly in solution (<24 h). This highlighted that the amine-imine tautomer 304 although unobserved by NMR, was accessible at room temperature. The racemisation of enatiopure material would be drastically detrimental to any applications of spiroquinolines as ligands for enantioselective catalysis. Thus, with this preliminary data, our next attempt was the resolution of the cyclic derivative 288. We expected the further rigidified carbon backbone, would hinder the epimerisation at the spirocyclic centre due to the increase cyclic strain and defined stereochemistry on the cyclopentane backbone (Scheme 77).

**Scheme 77** *The proposed barrier for epimerisation in cyclic 288.*
A sample of spiroquinoline 288 was resolved by preparative HPLC and after 72 hours in solution analytical HPLC data showed no epimerisation (Figure 25). This is important if these compounds are to have applications in catalysis or materials at a later date.

3.8 The Helicene Derivative

With interesting optical properties being observed for naphthalene fused 262, our attentions focused on extending the π-system even further. Helicenes have become increasing widespread in the past decade but have been studied for over 100 years.\textsuperscript{130–132} Helicenes are now common motifs in catalysis, materials, and electronic devices.\textsuperscript{133} Thus, there is a need to expand the number of classes of these interesting compounds, for both novel applications, as well as facilitating new methods for their synthesis.

Martin states that “helicenes are characterised by a helical structure made up of ortho-condensed aromatic rings, by the presence of a powerful inherently chiral chromophore, and by the possibility of interactions between overlapping aromatic rings”.\textsuperscript{134} Therefore, spirobiquinoline 307 (Scheme 78), although not technically a helicene, it could be applied as a “helicene surrogate”, if it was to exhibit the desired optical properties.

Scheme 78: The target “helical” spirobiquinoline 307.

Scheme 79: Our initial retrosynthesis of azido aldehyde 306.
Our first approach for preparing azido aldehyde 306 followed a similar route to that of Beringer et al.\textsuperscript{135} (Scheme 79) using the procedures of Lingenfelder and Kellogg,\textsuperscript{136} Friedel-Crafts acylation of naphthalene (312), followed by palladium hydroxide mediated reduction and cyclisation afforded phenanthrone 315. However, all attempts at aromatisation of this compound to give amine 309\textsuperscript{135} were unsuccessful, affording a large mixture of inseparable products (Scheme 80).

\textbf{Scheme 80: Attempted synthesis of phenanthrene 309.}

We then sought to utilise the alkyne cyclisation reported by Furstner,\textsuperscript{137} using the procedure of Alabugin et al.\textsuperscript{138} TMS-acetylene was coupled with 1-bromo-2-benzene (316) under Sonogashira conditions to afford bromide 317. Suzuki coupling with 2-fluorophenylboronic acid yielded the biaryl 318. Removal of the TMS group followed by PtCl\textsubscript{2} mediated cyclisation, using a modified procedure of Eccleshare,\textsuperscript{139} afforded phenanthrene 308 in high yields, and required minimal purification (Scheme 81).
This was easily converted to the azide 306 in analogous fashion to the napthyl aldehyde 249 (see Section 3.3) (Scheme 82). Deprotonation followed by acylation with DMF, and subsequent SNAr with sodium azide under standard conditions afforded azido aldehyde 306.

Acetone, cyclopentanone and cyclohexanone were used to produce the proposed spiroaminals 324-326 (Scheme 83). Due to the poor solubility of 306 in ethanolic solvents, slightly modified procedures were used, utilising THF as a co-solvent for the Claisen-Schmidt and toluene for the hydrogenation/spirocyclisation reaction.
It was found that extended spirocycles 324-326 were more prone to acidic decomposition, compared to the previous spiroquinolines isolated. This decomposition could be initiated by silica or chlorinated solvents that were not pre-treated with base and as such, the yields have yet to be determined. In the cases of 325 and 326, the resultant stereochemistry is believed to be consistent with the previous analogues 288 and 289 (see Section 3.7.1), judging by crude $^1$H NMR (Figure 26).
These compounds decomposed when subjected to silica, alumina or high temperatures for distillation and sublimation, therefore analytically pure samples could not be obtained. Cleaner samples were obtained (Figure 27) and the masses found with mass spectroscopy were in agreement with our proposed structures.
Figure 27: $^1$H NMR of spiroaminal 324 after attempted purification (400 MHz, CDCl$_3$).

The crude reaction mixtures and further isolated products showed intense fluorescence in solution. This property is promising for possible applications in materials. Efforts towards the isolation of these compounds are ongoing within our laboratory.

**3.9 Conclusions and Future Work**

We have developed an experimentally straightforward procedure for the synthesis of novel benzannulated spiroaminals. These compounds show increased spirane stability compared to their aliphatic counterparts and have been derivatised in several ways with retention of the aminal centre.\textsuperscript{51}
In the time that was available, the isolation of analytically pure spirane 324, 325 and 326 was not possible due to their instability towards all purification methods attempted (Figure 28). Efforts at isolation or stabilisation through perturbation of the electronic nature of the aromatic rings will be attempted.

Additionally, investigations will be taken into modifying the photo-physical properties of these systems through the installation of electron rich and electron poor systems on the aromatic rings (Scheme 84). Computational investigations will be carried out to understand the source of fluorescence in these compounds, and whether once resolved, they will emit circularly polarised light upon irradiation for possible applications in materials.
CHAPTER FOUR

THE APPLICATIONS OF DERIVATIVES

OF

1,7-DIAZASPIRO[5.5]UNDECANE
4. The Applications of Derivatives of 1,7-Diazaspiro[5.5]undecane

4.1 Biological Activity

Spirominals are not a common chemical moiety, and therefore little is known about their biological activity and stability. However, the few examples of spiroaminals found within nature (see Sections 1.4 and 3.1.1) have shown some promise as potential lead compounds for anticancer and immunology targets. Peganumine A (35) showed strong inhibition against a variety of cancer cell lines.\textsuperscript{140} Additionally the recently isolated spiroreticulatine (38) showed dose-dependent inhibition of Interleukin (IL-2), but no activity against normal human cancer cell lines (Figure 29).\textsuperscript{39}

![Figure 29: Biological activity of spiroaminal natural products 35 and 38.](image)

With limited information on the biological activity of spiroaminals, all final compounds and key intermediates synthesised by our group were tested against a variety of biological targets in collaboration with the Eli Lilly Open Innovation Drug Discovery (OIDD) program. The compounds tested were inactive against all primary assays except for the Interleukin (IL-17) protein-protein interaction assay. IL-17 has be shown to play an critical role in the inflammation response and contributes to the pathogenesis of autoimmune diseases including psoratic and rheumatoid arthritis.\textsuperscript{141} A selection of spiroaminals were shown to inhibit IL-17 at 100 μM.
The best results were observed for mono-bromo 329 and dimethoxy 265, showing inhibitions of 85% and 96% respectively.

![Chemical structures](image)

**Figure 30**: Biologically active spiroaminals against IL-17 (inhibition% at 100 μM). Data collected by Eli Lilly OIDD.

The primary data for spiroaminals 265 and 329 warranted the collection of a concentration response curve (CRC) against IL-17 generating IC50 values of 37 μM and 29 μM respectively (Figure 31).
This moderate activity shows promise for spiroaminals as potential immunosuppressives, with similar activity against interleukins as naturally occurring spiroreticulatine (38) (Figure 29). Synthesis of further analogues to build up an understanding of structure-activity relationship will be carried out in due course.

4.2 Coordination Chemistry

4.2.1 Diamine Ligands

Diamines are some of the most industrially important and academically renowned classes of ligands to date. They include the Noyori hydrogenation catalyst 330, Jacobson-Katsuki epoxidation catalyst 331, and chemotherapeutic Oxaliplatin 332, recognised as one of the world’s most essential medicines.
Figure 32: A selection of notable diamine containing complexes.

The majority of diamine ligands contain a two carbon chain between the nitrogens, with a few studies looking at extending this to 1,3 and 1,4-diamine ligands. However, the amidate ligand class contains a single carbon spacer between the nitrogens, and acts as a heteroallylic four electron monoanion, generally forming a σ-σ' bidentate bonding structure. The most common synthesis of these compounds is through organometallic addition to a carbodiimide 333, followed by metal salt metathesis of the resultant lithium salt 334 to form a variety of metal complexes (Scheme 85).

Scheme 85: General synthesis of amidate salts.

Amidates have been used for a variety of reactions and materials. In particular, they have been used to make an array of novel synthetically useful lanthanide complexes.
4.2.2 Barrett Spiroaminal Complexes

The Barrett group, when reporting their synthesis of spiroaminal 53 (see Section 2.1.2), also reported the novel coordination chemistry of spiroaminal 53 with ruthenium and copper precursors (Scheme 86).\textsuperscript{35}

Treatment of spiroaminal 53 with [Ru(PPh\textsubscript{3})\textsubscript{3}Cl\textsubscript{2}] afforded monometallic complex \textbf{67} with retention of the spirane centre. In contrast, the treatment of spiroaminal 53 with Cu(OBz)\textsubscript{2} afforded the bimetallic complex \textbf{68}, with the ligand adopting its amine-imine tautomer and forming a 16-membered metallocycle. Both of these structures were confirmed by X-ray crystallography (Figure 33).\textsuperscript{35}

\begin{figure}[h]
  \centering
  \includegraphics[width=\textwidth]{figure33.png}
  \caption{Solid-state structures of \textbf{67} and \textbf{68}, as reported by Barrett.\textsuperscript{35}}
\end{figure}
With both tautomers being accessible, we sought to investigate the coordination chemistry of spiroaminal 53 as well as the synthesised derivatives (see chapters 2 and 3) with a variety of metal precursors.

### 4.2.3 Group One Complexes

The treatment of amines with sodium, lithium, potassium and calcium bases is common place in every laboratory, however, these organometallic systems are not always as simple as they are depicted in traditional organic mechanisms.\(^{126,148}\) Due to the multiple issues found in the alkylation and allylation of tetrahydrospirobiquinoline 235 (see Section 3.5.1), we sought to elucidate the organometallic intermediate formed upon the treatment of 235 with a strong base. Treatment with varying equivalents of \(n\)-BuLi and the addition of MeOD led to deuterium incorporation at the nitrogen of the spirane centre, thus confirming deprotonation (Scheme 87). Further, only mono-deuteration was observed, confirming that only one of the aminal nitrogens can be deprotonated with a base of this strength.

![Scheme 87: Deuteration studies of spiroquinoline 235.](image)

With the observed lack of reactivity of 235 towards electrophiles without the addition of HMPA (see Section 3.5.1), we sought to elucidate the structure of the proposed organometallic aggregates. Treatment of spiroquinoline 235 with a variety of bases and additives did not yield any products suitable for X-ray crystallography (Table 8), however it was shown that the lithium salts were particularly stable even at higher temperatures (Table 8, Entry 4).
### Table 8: The attempted preparation of group 1 salts of 235. 

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Additive</th>
<th>Solvent</th>
<th>Temp</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$n$-BuLi</td>
<td>N/A</td>
<td>THF</td>
<td>-78 °C</td>
<td>Decomp during rexs.</td>
</tr>
<tr>
<td>2</td>
<td>$n$-BuLi</td>
<td>TMEDA</td>
<td>THF</td>
<td>-78 °C</td>
<td>Decomp during rexs.</td>
</tr>
<tr>
<td>3</td>
<td>$n$-BuLi</td>
<td>TRIMEDA</td>
<td>THF</td>
<td>-78 °C</td>
<td>Decomp</td>
</tr>
<tr>
<td>4</td>
<td>$n$-BuLi</td>
<td>N/A</td>
<td>Et$_2$O</td>
<td>0-20 °C</td>
<td>Decomp during rexs.</td>
</tr>
<tr>
<td>5</td>
<td>NaH$^a$</td>
<td>N/A</td>
<td>THF</td>
<td>0 °C</td>
<td>Decomp upon drying.</td>
</tr>
<tr>
<td>6</td>
<td>KH$^a$</td>
<td>N/A</td>
<td>THF</td>
<td>0 °C</td>
<td>Decomp</td>
</tr>
<tr>
<td>7</td>
<td>LiHMDS</td>
<td>N/A</td>
<td>C$_6$D$_6$</td>
<td>-20 °C</td>
<td>Decomp upon drying$^b$</td>
</tr>
<tr>
<td>8</td>
<td>NaHMDS</td>
<td>N/A</td>
<td>C$_6$D$_6$</td>
<td>-20 °C</td>
<td>Decomp upon drying$^b$</td>
</tr>
<tr>
<td>9</td>
<td>KHMDS</td>
<td>N/A</td>
<td>C$_6$D$_6$</td>
<td>-20 °C</td>
<td>Decomp upon drying$^b$</td>
</tr>
<tr>
<td>10</td>
<td>sec-BuLi</td>
<td>TMEDA</td>
<td>THF</td>
<td>-78 °C</td>
<td>Decomp upon drying.</td>
</tr>
<tr>
<td>11</td>
<td>t-BuLi</td>
<td>TMEDA</td>
<td>THF</td>
<td>-78 °C</td>
<td>Decomp upon drying.</td>
</tr>
</tbody>
</table>

As the lithium salt of 235 showed higher stability, with no visible decomposition at room temperature in diethyl ether, further functionalisation of these salts were attempted. Using the conditions reported by Yeoul Lee et al. for the ortho-functionalisation of tetrahydroquinolines, the lithium salt was treated with CO$_2$ at -78 °C to form the proposed lithium carbamate 337 (Scheme 88). Attempts at recrystallisation resulted in decomposition and this structure could therefore not be confirmed.
Scheme 88: The attempted formation of lithium carbamate 337.

With little success in elucidating the structure of the lithium salts, our attentions turned to investigating transition metal complexes in the hope that they would display higher stability and crystallinity.

### 4.2.4 Group Four Complexes

Titanium, hafnium and zirconium have been shown to form extremely active ethylene polymerisation catalysts with the use of diamine ligands. Recently Yeoul Lee et al. have reported the complexation of tetrahydro-[1,10]phenanthroline with zirconium and hafnium. Therefore, we sought to investigate the coordination chemistry of spirotetrahydrophenanthroline 263 with these metals. Attempts at forming these complexes from tetrabenzy precursors were all unsuccessful (Table 9).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal Precursor</th>
<th>Equiv.</th>
<th>Solvent</th>
<th>Temp</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ZrBn₄</td>
<td>1.0</td>
<td>THF</td>
<td>-0 °C</td>
</tr>
<tr>
<td>2</td>
<td>ZrBn₄</td>
<td>0.5</td>
<td>THF</td>
<td>-0 °C</td>
</tr>
<tr>
<td>3</td>
<td>HfBn₄</td>
<td>1.0</td>
<td>THF</td>
<td>-78 °C</td>
</tr>
<tr>
<td>4</td>
<td>HfBn₄</td>
<td>0.5</td>
<td>Et₂O</td>
<td>0-20 °C</td>
</tr>
</tbody>
</table>

*Table 9: The attempted formation of zirconium and hafnium complexes of 263, using the procedure of Yeoul.*
The majority of complexes were coloured oils, and were found by \(^1\)H NMR to be a mixture of multiple products. This is most likely due to the presence of complexes of both the aminal and amine-imine tautomers. As well tautomerisation, formation of monometallic complex 338 and bimetallic complex 339 species could lead to a larger array of products within the crude reaction mixture. The coordination of spirotetrahydrophenanthroline 263 with titanium was then investigated. Pre-treatment of ligand 263 with \(n\)-BuLi followed by the addition of TiCl\(_4\) resulted in decomposition of starting material (Scheme 89).\(^{154}\) Treatment of spirotetrahydrophenanthroline 263 directly with TiCl\(_4\) also led to starting material decomposition.\(^{154}\)

![Scheme 89: Attempted reactions between 263 and TiCl4.](image)

### 4.2.5 Ruthenium Complexes

With the previous success with ruthenium (see Section 4.2.2),\(^{35}\) we sought to investigate a wider range of metal precursors and use a number of the newly prepared spiroaminals. Aliphatic spiroaminals all reacted with RuCl\(_2\)(PPh\(_3\))\(_3\) using the conditions previously reported,\(^{35}\) however, the spiroquinolines showed no reactivity even after prolonged periods of heating (Table 10, Entries 3-4).
<table>
<thead>
<tr>
<th>Entry</th>
<th>ML (Ligand)</th>
<th>Solvent</th>
<th>Temp (Time)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;35&lt;/sup&gt;</td>
<td>RuCl&lt;sub&gt;2&lt;/sub&gt;(PPh&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt; (47)</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>rt (24 h)</td>
<td>Green Oil with small orange micro crystals</td>
</tr>
<tr>
<td>2&lt;sup&gt;35&lt;/sup&gt;</td>
<td>RuCl&lt;sub&gt;2&lt;/sub&gt;(PPh&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt; (56-B)</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>rt (24 h)</td>
<td>Green Oil</td>
</tr>
<tr>
<td>3&lt;sup&gt;35&lt;/sup&gt;</td>
<td>RuCl&lt;sub&gt;2&lt;/sub&gt;(PPh&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt; (235)</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>rt (24 h)</td>
<td>No Reaction&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>4&lt;sup&gt;35&lt;/sup&gt;</td>
<td>RuCl&lt;sub&gt;2&lt;/sub&gt;(PPh&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt; (263)</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>rt (24 h)</td>
<td>No Reaction&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>5&lt;sup&gt;155&lt;/sup&gt;</td>
<td>RuCl&lt;sub&gt;2&lt;/sub&gt;(DMSO)&lt;sub&gt;3&lt;/sub&gt; (53-A)</td>
<td>EtOH</td>
<td>80 °C (4 h)</td>
<td>Black Gum</td>
</tr>
<tr>
<td>6&lt;sup&gt;155&lt;/sup&gt;</td>
<td>RuCl&lt;sub&gt;2&lt;/sub&gt;(DMSO)&lt;sub&gt;3&lt;/sub&gt; (235)</td>
<td>EtOH</td>
<td>80 °C (4 h)</td>
<td>Black Gum</td>
</tr>
<tr>
<td>7&lt;sup&gt;156&lt;/sup&gt;</td>
<td><a href="PF%3Csub%3E6%3C/sub%3E">Ru(C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;6&lt;/sub&gt;)(CH&lt;sub&gt;3&lt;/sub&gt;CN)</a>&lt;sub&gt;2&lt;/sub&gt; (263)</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>rt (48 h)</td>
<td>No Reaction</td>
</tr>
<tr>
<td>8&lt;sup&gt;156&lt;/sup&gt;</td>
<td><a href="PF%3Csub%3E6%3C/sub%3E">Ru(C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;6&lt;/sub&gt;)(CH&lt;sub&gt;3&lt;/sub&gt;CN)</a>&lt;sub&gt;2&lt;/sub&gt; (235)</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>rt 48 h</td>
<td>No Reaction</td>
</tr>
<tr>
<td>9&lt;sup&gt;157&lt;/sup&gt;</td>
<td>[Ru(µ-cymene)Cl&lt;sub&gt;2&lt;/sub&gt;]&lt;sub&gt;2&lt;/sub&gt; (53-A)</td>
<td>IPA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>80 °C 1 h</td>
<td>Brown insoluble solid</td>
</tr>
<tr>
<td>10&lt;sup&gt;157&lt;/sup&gt;</td>
<td>[Ru(µ-cymene)Cl&lt;sub&gt;2&lt;/sub&gt;]&lt;sub&gt;2&lt;/sub&gt; (119-A)</td>
<td>IPA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>80 °C 1 h</td>
<td>Brown insoluble solid</td>
</tr>
</tbody>
</table>

Table 10: The attempted synthesis of spiroaminal ruthenium complexes. All reactions were carried out with 1.0 equiv. of ML. <sup>a</sup>See main discussion, <sup>b</sup>No reaction observed after 24 h at 40 °C.
The products afforded from the aliphatic derivatives 47, 53-A, 119-A and 56-B were extremely sensitive to both water and air, requiring freshly distilled and thoroughly degassed solvents for all manipulations. The majority of recrystallisation attempts of these compounds were unsuccessful, yielding the characteristically green ruthenium oxo decomposition product.\textsuperscript{158} However, spiroaminal 47 afforded a small amount of material suitable for X-ray crystallography after several sequential recrystallisations (Scheme 90).

Scheme 90: Synthesis of bimetallic 333.

The product was identified as a bimetallic compound 340 with the ligand adopting the amine-imine tautomer as seen previously with copper.\textsuperscript{35} Interestingly these ligands adopt a cis configuration pushing the remaining sterically bulky PPh\textsubscript{3} into close proximity (Figure 34).

Figure 34: Solid-state structure of ruthenium complex 340 (50\% probability ellipsoids).
4.2.6 Group 10 Complexes

Palladium and nickel are considered some of the most important transition metals for cross-coupling in chemistry to date.\textsuperscript{125,159} There is therefore a constant need to expand on the number of potential synthetically useful Pd and Ni complexes. Our efforts were first focussed on palladium, due to its plethora of commercially available starting materials.

<table>
<thead>
<tr>
<th>Entry</th>
<th>ML (Ligand)</th>
<th>Solvent</th>
<th>Temp (Time)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{160}</td>
<td>Pd(PPh\textsubscript{3})\textsubscript{4} (47)</td>
<td>C\textsubscript{6}H\textsubscript{6}</td>
<td>rt (24 h)</td>
<td>No reaction</td>
</tr>
<tr>
<td>2\textsuperscript{160}</td>
<td>Pd(PPh\textsubscript{3})\textsubscript{4} (53-A)</td>
<td>C\textsubscript{6}H\textsubscript{6}</td>
<td>rt (24 h)</td>
<td>No reaction</td>
</tr>
<tr>
<td>3\textsuperscript{160}</td>
<td>Pd(PPh\textsubscript{3})\textsubscript{4} (56-B)</td>
<td>C\textsubscript{6}H\textsubscript{6}</td>
<td>rt (24 h)</td>
<td>No reaction</td>
</tr>
<tr>
<td>4\textsuperscript{160}</td>
<td>Pd(PPh\textsubscript{3})\textsubscript{4} (235)</td>
<td>C\textsubscript{6}H\textsubscript{6}</td>
<td>rt (24 h)</td>
<td>No reaction</td>
</tr>
<tr>
<td>5\textsuperscript{161}</td>
<td>Pd(OAc)\textsubscript{2} (53-A)</td>
<td>MeOH</td>
<td>rt (24 h)</td>
<td>No reaction</td>
</tr>
<tr>
<td>6\textsuperscript{161}</td>
<td>Pd(OAc)\textsubscript{2} (235)</td>
<td>MeOH</td>
<td>rt (24 h)</td>
<td>No reaction</td>
</tr>
<tr>
<td>7\textsuperscript{161}</td>
<td>Pd(OAc)\textsubscript{2} (263)</td>
<td>MeOH</td>
<td>rt (24 h)</td>
<td>No reaction</td>
</tr>
<tr>
<td>8\textsuperscript{162}</td>
<td>Pd(TFA)\textsubscript{2} (53-A)</td>
<td>THF</td>
<td>rt 16 h</td>
<td>Unidentified black tar</td>
</tr>
<tr>
<td>9\textsuperscript{162}</td>
<td>Pd(TFA)\textsubscript{2} (235)</td>
<td>THF</td>
<td>rt 16 h</td>
<td>Unidentified black tar</td>
</tr>
</tbody>
</table>
The spiroquinolines 235 and 263 were highly reactive towards Pd(MeCN)$_4$(BF$_4$)$_2$ (Table 11, Entries 10-13), however, the products afforded were completely insoluble in all solvents, even at elevated temperatures. Mass analysis was attempted but no identifiable data could be obtained. One plausible reason for the insolubility observed is that the products formed are polymeric compounds (Figure 35). Although these could still be active catalysts, the lack of solubility led to no analytical data, and therefore the structures cannot be confirmed.
Nickel is known for its particularly high affinity to nitrogen, with many known complexes having a variety of interesting properties and applications. In view of this, our attentions turned to the investigation of reactions of spiroaminals 53-A and 235 with a variety of nickel sources (Table 12). However, no reactions provided any identifiable products.

<table>
<thead>
<tr>
<th>Entry</th>
<th>ML (Ligand)</th>
<th>Solvent</th>
<th>Temp (Time)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;166&lt;/sup&gt;</td>
<td>(DME)NiBr&lt;sub&gt;2&lt;/sub&gt; (53-A)</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>rt (16 h)</td>
<td>No Reaction</td>
</tr>
<tr>
<td>2&lt;sup&gt;166&lt;/sup&gt;</td>
<td>(DME)NiBr&lt;sub&gt;2&lt;/sub&gt; (235)</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>rt (16 h)</td>
<td>No Reaction</td>
</tr>
<tr>
<td>3&lt;sup&gt;166&lt;/sup&gt;</td>
<td>(DME)NiBr&lt;sub&gt;2&lt;/sub&gt; (53-A)</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>40 °C (16 h)</td>
<td>No Reaction</td>
</tr>
<tr>
<td>4&lt;sup&gt;167&lt;/sup&gt;</td>
<td>NiBr&lt;sub&gt;2&lt;/sub&gt; (53-A)</td>
<td>MeCN</td>
<td>85 °C (30 min)</td>
<td>Insoluble brown product. Mass yield (&lt;20%)</td>
</tr>
</tbody>
</table>
Table 12 The attempted synthesis of spiroaminal nickel complexes. All reactions were carried out with 1.0 equiv. of ML.

4.2.7 Platinum Complexes

Diamino platinum complexes are well documented,\textsuperscript{144} and their importance as chemotherapeutics has resulted in world-wide recognition as some of the world’s most important pharmaceuticals.\textsuperscript{168} The original platinate chemotherapeutic, cisplatin (343) has been improved upon by several generations of platinate complexes (Figure 36). The most successful analogues have replaced the two chloro anionic X-type ligands for a chelating bidentate dianionic ligand. One such analogue is carboplatin (344) which is used in the treatment of ovarian and lung cancers.\textsuperscript{169} This was further built upon by oxaliplatin (332), where the amino ligands were replaced by a non-leaving diamine ligand that forms a 5-membered chelate. Oxaliplatin (332) has gained worldwide regulatory approval for the treatment of advanced colon cancer.\textsuperscript{170} Many other improvements have been made by alternating the oxidation state, and by replacing the leaving ligands with biologically active compounds, allowing these scaffolds to be used as prodrugs.\textsuperscript{144,171}
The use of diamine ligands has been shown to increase solubility, activity and selectivity in many cases. Therefore, exploring new diamine ligands is essential for the development of new potential therapeutics. We first turned our attention to the traditional synthesis of bisamino platinates utilising tetraido platinate \( \text{346} \) formed \textit{in situ} from commercially available potassium tetrachloroplatinate (\text{345}). When platinate \( \text{346} \) was treated with spiroaminal \text{53-A} the proposed complex \text{347} precipitated from the solution (Scheme 91). As previously observed with the palladium species and with many platinum complexes,\textsuperscript{171} the products were completely insoluble in all solvents tested.

Conversion of the diodo \text{347} to the dichloro was attempted using a known procedure,\textsuperscript{172} but the lack of solubility resulted in no conversion of starting material. It was also found that the spirobiquinoline derivatives were completely unreactive towards platinum precursors.

At this stage, due to the lack of solubility of all intermediates and extreme light sensitivity of many of the iodo-platinates, our attentions turned to the synthesis of spiroaminals with increased functionality to improve the solubility of the proposed platinate complexes.
4.2.8 Copper Complexes

As with ruthenium, due to the previous success of copper binding to spiroaminal 53,35 we sought to investigate a wider range of copper sources which have shown to be azaphilic and have produced a number of highly reactive catalysts.173 None of the products afforded could be recrystallised to produce crystals suitable for X-ray crystallography, and many were prone to decomposition by adventitious water, exposure to oxygen, or insufficiently degassed solvents (Table 13).

<table>
<thead>
<tr>
<th>Entry</th>
<th>ML (Ligand)</th>
<th>Solvent</th>
<th>Temp (Time)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1174</td>
<td>CuCl₂ (53-A)</td>
<td>CH₂Cl₂</td>
<td>rt (16 h)</td>
<td>No reaction</td>
</tr>
<tr>
<td>2174</td>
<td>CuCl₂ (47)</td>
<td>CH₂Cl₂</td>
<td>rt (16 h)</td>
<td>No reaction</td>
</tr>
<tr>
<td>3174</td>
<td>CuCl₂ (235)</td>
<td>CH₂Cl₂</td>
<td>rt (16 h)</td>
<td>Small amount of red precipitate, non-crystalline</td>
</tr>
<tr>
<td>4175</td>
<td>Cu(OTf)₂ (53-A)</td>
<td>Acetone</td>
<td>rt (15 min)</td>
<td>No reaction</td>
</tr>
<tr>
<td>5175</td>
<td>Cu(OTf)₂ (235)</td>
<td>Acetone</td>
<td>rt (15 min)</td>
<td>No reaction</td>
</tr>
<tr>
<td>6176</td>
<td>Cu(OTf)₂ (53-A)</td>
<td>MeCN</td>
<td>rt (1 min)</td>
<td>Lilac precipitate decomposition upon removal of MeCN</td>
</tr>
<tr>
<td>7176</td>
<td>Cu(OTf)₂ (235)</td>
<td>MeCN</td>
<td>rt (1 min)</td>
<td>Lilac precipitate decomposition upon removal of MeCN</td>
</tr>
</tbody>
</table>
| 8<sup>35</sup> | Cu(OBz)<sub>2</sub>  
(235) | CH<sub>2</sub>Cl<sub>2</sub> | rt | No reaction | MeOH | (16 h) |
| 9<sup>35</sup> | Cu(OBz)<sub>2</sub>  
(263) | CH<sub>2</sub>Cl<sub>2</sub> | rt | No reaction | MeOH | (16 h) |
| 10<sup>35</sup> | Cu(OBz)<sub>2</sub>  
(47) | CH<sub>2</sub>Cl<sub>2</sub> | rt | Recrystallisation did not afford crystalline product | MeOH | (16 h) |
| 11<sup>35</sup> | Cu(OBz)<sub>2</sub>  
(119-A) | CH<sub>2</sub>Cl<sub>2</sub> | rt | Recrystallisation did not afford crystalline product | MeOH | (16 h) |

Table 13: The attempted synthesis of spiroaminal nickel complexes. All reactions were carried out with 1.0 equiv of ML.

4.2.9 Main Group Reactivity

As well as investigating the coordination properties of spiroaminals with a variety of transition metals, we turned our attentions to the reactions of these aminals with a selection of main group elements. In recent years azaboron compounds have become increasing popular due to their facile synthesis,<sup>177</sup> their ability to be finely tuned for specific applications,<sup>178,179</sup> and their bioisosteric nature in biological settings.<sup>180,181</sup> We sought to investigate the reactions of spiroaminals 53-A and 235 with a variety of boron sources (Table 14). Although reaction was observed in some cases, multiple products were observed by <sup>11</sup>B NMR in all cases, highlighting the issues of the coordination of the two tautomers present in the spiroaminal system.
<table>
<thead>
<tr>
<th>Entry</th>
<th>ML (Ligand)</th>
<th>Solvent (Additive)</th>
<th>Temp (Time)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BCl₃·SMe₂</td>
<td>n-hexane (NEt₃)</td>
<td>80 °C (4 h)</td>
<td>Multiple products present by H and B NMR&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>BCl₃·SMe₂</td>
<td>n-hexane (NEt₃)</td>
<td>80 °C (4 h)</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>BCl₃·SMe₂</td>
<td>n-hexane (NEt₃)</td>
<td>80 °C (16 h)</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>BH₃·THF</td>
<td>THF</td>
<td>65 °C (2 h)</td>
<td>Multiple products present by H and B NMR&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>BH₃·THF</td>
<td>THF</td>
<td>65 °C (2 h)</td>
<td>No reaction</td>
</tr>
<tr>
<td>6</td>
<td>BH₃·THF</td>
<td>THF</td>
<td>65 °C (8 h)</td>
<td>No reaction</td>
</tr>
<tr>
<td>7</td>
<td>B₂(NMe₂)₄</td>
<td>PhMe</td>
<td>115 °C (2 h)</td>
<td>No reaction</td>
</tr>
<tr>
<td>8</td>
<td>B₂(NMe₂)₄</td>
<td>PhMe</td>
<td>115 °C (2 h)</td>
<td>No reaction</td>
</tr>
<tr>
<td>9</td>
<td>B₂(NMe₂)₄</td>
<td>PhMe</td>
<td>115 °C (16 h)</td>
<td>No reaction</td>
</tr>
<tr>
<td>10</td>
<td>B₂(NMe₂)₄</td>
<td>PhMe</td>
<td>115 °C (16 h)</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

Table 14: The attempted formations of spiroaminal azaboron compounds. All reactions were carried out with 1.0 equiv of ML. <sup>a</sup>Decomposition of boron compounds upon attempted purification.

Efforts were made at purifying these compounds, however the products could not isolated or identified. Our attentions turned towards phosphorous, as many P-N bond containing ligands have important roles in catalysis for both industry and academia. <sup>185</sup> Treatment of spiroaminals...
53-A and 235 with PhPCI₂ under the conditions of Kornev\textsuperscript{185} yielded a complex mixture of compounds by $^1$H and $^{31}$P NMR (Scheme 92). Presumably this is due to the steric strain involved in forming the 4-membered bisamino phosphine ring, leading to multiple side reactions.

![Scheme 92: The attempted synthesis of bisaminophosphines 348 and 349.](image)

4.3 Conclusion and Future Work

Despite the majority of the complexation reactions attempted affording no real insight into the coordination properties of spiroaminal, the ruthenium dimer 333 was synthesised and its structure confirmed by X-ray crystallography (Figure 37).

![Figure 37: The isolated ruthenium dimer 340 and its solid-state structure (50% probability ellipsoids).](image)
Attention is now focused on the synthesis of spiroaminals containing additional chelating groups, utilising the novel methodologies developed within our group (see Sections 2.6 and 3.2). We hope these additional groups would stabilise the spirane centre to prevent tautomerisation and aid purification of these sensitive compounds, as well as increase the stability of the resultant metal complexes.
CHAPTER FIVE

EXPERIMENTAL
5. Experimental

5.1 General Methods

All reactions were carried out under nitrogen or argon and in oven-dried glassware, unless otherwise stated. The following reaction solvents were distilled under nitrogen: Et₂O, THF and PhMe were dried over Na/Ph₂CO; MeOH, CH₂Cl₂, NEt₃ and pyridine were dried over CaH₂. H₂O refers to redistilled H₂O. Other solvents and all reagents were obtained from commercial suppliers and, if purity was >98%, used as obtained. Room temperature was taken as 23 °C, where no external heating or cooling was applied. Prolonged periods of reaction cooling were accomplished through the use of CryoCool apparatus. Hydrogenations with large volumes (>50 mL) or at pressures higher than atmospheric were carried out in a Parr Series 391 Shaker Hydrogenation Apparatus.

¹H NMR spectra were recorded at 400 or 500 MHz. The solvent used in each case is specified and spectra are referenced to residual solvent peaks. Chemical shifts (δ) are quoted to two decimal places in parts per million (ppm) with signal splitting recorded as singlet (s), doublet (d), triplet (t), quartet (q), quintet (qu) and multiplet (m). Coupling constants, J, are quoted to one decimal place in Hertz (Hz). ¹³C NMR spectra were recorded at 101 or 126 MHz. Chemical shifts are quoted to one decimal place in ppm. The solvent used in each case is specified and spectra are referenced to residual solvent peaks. For CDCl₃: δ H =7.26, δ C = 77.16 ppm and d₆-DMSO - δ H = 2.50, δ C = 39.52 ppm.

The numbering of ¹H and ¹³C within this experimental has been allocated for the clarity of the assignment and is independent from IUPAC nomenclature and allocated compound names. Infrared (IR) spectra were recorded on a PerkinElmer FT-IR spectrometer and were recorded neat. Indicative features of spectrum are given with adsorptions reported in wavenumbers (cm⁻¹).

High resolution mass spectra (HRMS) (EI, CI, ESI) were recorded by the Imperial College Mass Spectrometry Service.
Melting points were obtained using a SRS MPA100 Optimelt melting point system and are uncorrected.

Microanalysis data was determined at the London Metropolitan University Analytical Service. Optical rotations were recorded on a Perkin-Elmer 241 Polarimeter with a path length of 0.5 dm. Concentrations (c) are quoted in g/100 mL.

Analytical and preparative chiral HPLC was carried out using a Agilent 1200 series HPLC system fitted with a Chiralpak IA or a Chiralpak IE column.

X-ray diffraction data was recorded by the Imperial College Department of Chemistry X-ray diffraction service by Doctor Andrew J. P. White with the exception of crystal structures 119-A and 340 which were recorded by Professor Jonathan White of the University of Melbourne. Flash column chromatography was performed using Fluorochem or Merck silica gel 60 (particle size 40 - 63 μm) unless otherwise stated. Thin layer chromatography (TLC) was performed on Merck Kiesegel 60 F254 0.25 mm pre-coated aluminium backed plates. Product spots were visualised under UV light (λ_max = 254 nm) and/or by staining with either aqueous potassium permanganate solution, acidic vanillin solution or phosphomolybdic acid solution.

All commercially available organometallic reagents were titrated before use. Organolithiums are titrated using the procedure of Kofron,$^{186}$ whereas organomagnesium reagents were titrated using the procedure of Knochel.$^{187}$
5.2 General Procedures

**General Procedure: Preparation of LiHMDS.**

$n$BuLi (2.5 M in hexanes, 1.0 equiv.) was added dropwise to a solution of HMDS (1.0 equiv.) in THF (1 M) at 0 °C. The solution was stirred for 15 minutes before immediate use. The solution can be diluted or concentrated for other desired molarities.

**General Procedure: Preparation of Grignard reagents.**

A solution of alkyl bromide or iodide (1.0 equiv.) in Et$_2$O or THF (1 M) was added to activated magnesium powder at a rate of which gentle reflux is obtained. If the reaction was not immediately initiated (judged by a lack of dissolution of magnesium powder, or a lack of heat evolution) a single crystal of iodine was added to the suspension and gentle heating is applied. The mixture was then stirred for 4 h and the excess magnesium was removed by cannula filtration. The resultant solution was titrated using the procedure of Knochel,\textsuperscript{187} and used immediately. The solution can be diluted or concentrated for other desired molarities.

**General Procedure A: Boc protection of lactams and amines.**

A lactam or an amine (1.0 equiv.), Boc$_2$O (1.25 equiv.) and DMAP (0.25 equiv.) were stirred in MeCN (0.25 M) for 16 h at room temperature. The solution was concentrated under vacuo to approximately 33% of the original volume. The resultant slurry was diluted with EtOAc (100 mL), washed with half-saturated brine (50 mL) and the aqueous layer was re-extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with 10% citric acid (50 mL), dried over MgSO$_4$, and the solvent removed by rotary evaporation. The purification for each product is given separately.
General procedure B: Lactam formation from ester acids.

5-Methoxy-3-substituted-5-oxopentanoic acid (1.0 equiv.) was stirred in THF (0.66 M) and cooled to -20 ºC. A solution of BH₃●SMe₂ (1.0 M in THF, 1.0 equiv.) was added drop-wise while maintaining a temperature <-10 ºC. After the addition, the ice bath was removed and the solution was stirred for a further 3 h. The solution was then quenched with H₂O, solid K₂CO₃ (1.7 equiv.) was added portion-wise. Once the addition was complete, the mixture was diluted with Et₂O and the organic layer was collected. The aqueous layer was further extracted with Et₂O (x 2), the combined organic layers were washed with brine, dried over MgSO₄ and the solvent removed under vacuum to yield the crude alcohol which was prone to lactonisation and therefore, used immediately.

The crude alcohol and triethylamine (1.5 equiv.) in CH₂Cl₂ (0.30 M) were cooled to 0 ºC and stirred for 10 minutes. MsCl (1.2 equiv.) was then added drop-wise over 1 minute. Once the addition was completed, the solution was left to return to room temperature and stirred for 4 h. After this time, the reaction was quenched with 1 M HCl, the organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (x 2). The combined organic layers were dried over MgSO₄ and the solvent removed by rotary evaporation to yield the crude mesylate.

The crude mesylate and NaN₃ (3.0 equiv.) in DMF (0.33 M) were heated to 60 ºC for 4 h. The reaction was cooled, the solids were removed by filtration and the filtrate was dried extensively under high vacuum. The resultant liquid was dissolved in THF (0.1 M) and PPh₃ (1.0 equiv.) was added in a single portion. This was stirred at 40 ºC until nitrogen evolution had finished (1-2 h). H₂O (2.0 equiv.) was added and this was stirred at 40 ºC for a further 16 h. After this time, the reaction was dried extensively under vacuum. The resultant slurry was triturated in pentane/Et₂O (1:1 40 mL) at -20 ºC for 5 h. The solids were removed by filtration and the solvent removed by rotary evaporation. The purification of the resultant crude lactam is given with each example.
General procedure C: Spiroaminal Formation from N-Boc Lactams.

Using a modified procedure of Barrett\textsuperscript{35}, LiHMDS (0.25 M in THF, 0.55 equiv.) was added dropwise over 3 h to a solution of lactam (1.0 equiv.) in THF (0.5 M) at 0 °C. After the addition, the cooling bath was removed and the solution was left to return to room temperature and stirred for 4 h. The solution was quenched with solid NH\textsubscript{4}Cl (1.1 equiv.), and the suspension was stirred for 10 min before dilution with Et\textsubscript{2}O (4 mL/mmol). This was washed with half sat. aqueous NH\textsubscript{4}Cl (x 1), with the aqueous layer being re-extracted with Et\textsubscript{2}O (x 2), the combined organics were then dried over MgSO\textsubscript{4}, and the solvent removed by rotary evaporation, to yield the crude ketolactam-hemiaminal intermediate.

The crude mixture was cooled to 0 °C before the addition of conc. HCl (1 mL/mmol). The solution was heated to 100 °C for 24 h. The reaction was basified to pH 14 with KOH (10 M) at 0 °C. The resultant mixture was extracted with CH\textsubscript{2}Cl\textsubscript{2} (x 5), the combined organics were dried over MgSO\textsubscript{4}, and the solvent removed by rotary evaporation to afford the crude spiroaminal. The purification is given separately with each example.

General Procedure D; Room temperature S\textsubscript{N}Ar of o-nitro-benzaldehydes.

Using a modified procedure of Driver,\textsuperscript{188} Sodium azide (3.0 equiv.) was added to a solution of nitro aldehyde (1.0 equiv.) in HMPA (0.33 M) at 0 °C. The mixture was warmed to room temperature, and stirred for 24 h. After this time, the solution was diluted with Et\textsubscript{2}O (250 mL) and washed with H\textsubscript{2}O (5 x 50 mL). The solvent was removed by rotary evaporation, followed by drying the crude product under vacuum (1 x 10\textsuperscript{-2} mbar) for 24 h yielding the aryl azide which did not require further purification.
General Procedure E; Synthesis of tetrahydrospirobiquinolines.

o-Azido-benzaldehyde (2.0 mmol, 2.0 equiv.) in absolute EtOH (20 mL) was cooled in an ice bath. Acetone (73 µL, 1.0 mmol, 1.0 equiv.) was added, followed by NaOH (2.5 M, 2.5 mL, 5.0 mmol, 5.0 equiv.), added dropwise over 30 seconds with stirring. The ice bath was removed and after 4 h at room temperature, the resultant precipitate was collected by filtration and washed with ice-cold absolute EtOH. The slurry was re-suspended in EtOH (20 mL) with 10% Pd/C (10 weight%) and was stirred under a hydrogen atmosphere (balloon) for 16 h. The catalyst was removed by filtration, and the solvent removed by rotary evaporation. The purification for each spiro-biquinoline is given separately.

This reaction has been successively scaled up to 40 mmol of aldehyde, it is worth noting that at volumes over 100 mL of solvent, better results were observed using a Parr shaker apparatus at a pressure of 1.5 bar. A balloon can still be used at these scales, however this results in longer reaction times.

General Procedure F; Bromination of tetrahydrospirobiquinolines with NBS.

Freshly recrystallized* NBS (2.0 or 4.0 equiv.) was added in one portion with stirring to spirobiquinoline (1.0 equiv.) in MeCN (0.05 M) at 0 ºC and the resultant solution was allowed to warm up to room temperature. After 16 h, the solvent was removed by rotary evaporation, and the resultant slurry dissolved in CH₂Cl₂ and H₂O (1:1). The layers were separated, and the aqueous layer was further extracted with CH₂Cl₂ (x 2). The combined organic extracts were dried (MgSO₄), the solvent removed by rotary evaporation. The purification for each spiro-biquinoline is given separately.

*5 g of NBS is dissolved in 50 mL of H₂O under reflux before hot filtration and rapid cooling. The precipitate is removed by filtration, washed with cold H₂O and dried before immediate use.
5.3 Procedures and Compound Characterisation

*tert*-Butyl 2-oxopyrrolidine-1-carboxylate - 72

Using general procedure A; lactam 42 (5.0 g, 59 mmol) gave *N*-Boc lactam 72 (7.4 g, 68%) as a colourless liquid after purification by column chromatography (20 → 100% Et₂O in pentane). The data is consistent with that reported in the literature.¹⁸⁹

¹H NMR (400 MHz, CDCl₃) δ 3.71 – 3.66 (m, 2H), 2.44 (t, J = 8.1 Hz, 2H), 1.98 – 1.89 (m, 2H), 1.46 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ 174.2, 150.2, 82.6, 46.5, 32.9, 28.0 (3C), 17.4.

HR-MS (El) calcd for C₉H₁₅O₃N (M⁺): 185.1052, found: 185.1065.
**tert-Butyl 2-oxopiperidine-1-carboxylate - 57**

Using general procedure A; lactam 52 (30.0 g, 303 mmol) gave N-Boc lactam 57 (42.6 g, 77%) as a colourless liquid after purification by column chromatography (20% Et₂O in pentane). The data is consistent with that reported in the literature.¹⁹⁰

¹H-NMR (400 MHz, CDCl₃) δ 3.52-3.54 (m, 2H), 2.37-2.39 (m, 2H), 1.80-1.60 (m, 4H), 1.39 (s, 9H).

¹³C-NMR (101 MHz, CDCl₃) δ 171.1, 152.5, 82.5, 46.1, 34.7, 27.8 (3C), 22.6, 20.3.

HR-MS (ESI) calcd for C₁₂H₂₀N₂O₃Na (M + CH₃CN + Na⁺): 263.1372, found: 263.1380.
tert-Butyl 2-oxoazepane-1-carboxylate - 73

Using general procedure A; lactam 55 (5.0 g, 44 mmol) gave N-Boc lactam 73 (5.3 g, 56%) as a colourless liquid after purification by column chromatography (20 -> 50 % Et₂O in pentane). Analytical data matched the reported data.¹⁹¹

¹H NMR (400 MHz, CDCl₃) δ 3.79 – 3.67 (m, 2H), 2.70 – 2.53 (m, 2H), 1.85 – 1.65 (m, 6H), 1.51 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ 175.7, 153.1, 82.8, 46.2, 39.6, 29.3, 28.8, 28.1 (3C), 23.6.

HR-MS (El) calcd for C₁₁H₁₉O₃N (M⁺): 213.1365, found: 213.1360.
Using the procedure of Nanayakkara\textsuperscript{53}; 2-methylpiperidine (2.4 g, 24 mmol, 1.1 equiv.) was added dropwise to a solution of (S)-mandelic acid (3.4 g, 22 mmol, 1.0 equiv.) in MeOH (10 mL) at 0 °C at a rate to keep the temperature below 5 °C. After the addition was complete, Et\textsubscript{2}O (45 mL) was added dropwise at 0 °C. After this the stirrer bar was removed and the solution was left at -20 °C for 16 h. The resultant precipitate was collected by filtration and then subsequently recrystallised from MeOH/Et\textsubscript{2}O (1:5) three times to yield the mandelic salt as a white crystalline solid (2.36 g, 42%, 84% wrt (R)-enantiomer). This was dissolved in 10% NaOH (10 mL) cooled to 0 °C and a solution of Boc\textsubscript{2}O (2.5 g, 11.5 mmol, 1.15 equiv.) in THF (20 mL) was added dropwise to keep the temperature below 5 °C. Once the addition was complete, the ice bath was removed and the reaction left to stir overnight. After this time, the THF was removed by rotary evaporation. The solution was extracted with Et\textsubscript{2}O (3 x 50 mL). The combined organic were dried over MgSO\textsubscript{4} and the solvent removed by rotary evaporation. The crude product was purified by column chromatography (10% EtOAc in pentane) to afford the product as a colourless liquid (2.0 g, 41% over two steps, 82% wrt one enantiomer). The data is consistent with that reported in the literature.\textsuperscript{192}

\begin{align*}
\text{\textsuperscript{1}H NMR} & \text{ (400 MHz, CDCl\textsubscript{3}) } \delta 4.34 (t, J = 6.1 \text{ Hz}, 1H), 3.89 (dd, J = 13.2 \text{ Hz}, 3.7 \text{ Hz}, 1H), 2.78 (td, J = 3.7, 13.2 \text{ Hz}, 1H), 1.64-1.51 (m, 4H), 1.43 (s, 9H), 1.38-1.29 (m, 2H), 1.09 (d, J = 6.9 \text{ Hz}, 3H). \\
\text{\textsuperscript{13}C NMR} & \text{ (101 MHz, CDCl\textsubscript{3}) } \delta 154.3, 79.1, 46.2, 38.8, 28.6 (3C), 27.5, 25.8, 18.8, 15.8. \\
[\alpha]_D^{22} & : -48.5 \text{ (c, 1.0, CHCl\textsubscript{3})}, \{\text{lit.} \textsuperscript{53} [\alpha]_D^{24} : -50.7 \text{ (c, 1.0, CHCl\textsubscript{3})}\} \\
\text{MS (EI)} & \text{ calcd for C}_{11}\text{H}_{21}\text{NO}_{2} \text{ (M + H\textsuperscript{+})}: 199.1572, \text{ found: 199.1602.}
\end{align*}
Piperidine 75 (1.5 g, 7.5 mmol, 1.0 equiv.) was stirred with ruthenium (IV) oxide hydrate (300 mg, 2.25 mmol, 30 mol% anhydrous basis) in EtOAc (90 mL). This was added to a solution of NaIO₄ (8.0 g, 37.0 mmol, 5.0 equiv.) in water (75 mL) and the biphasic solution was left to stir under argon for 16 h. After this time the phases were separated, with the aqueous phase being further extracted with EtOAc (2 x 100 mL). The combined organic layers were stirred with activated charcoal (2 g) dried over MgSO₄, filtered and the solvent was removed by rotary evaporation. The crude product was purified by column chromatography (20% EtOAc in pentane) to yield the product 76 as a colourless liquid which slowly crystallised to a white solid upon standing (1.42 g, 89%). The data is consistent with that reported in the literature.¹⁹³

¹H NMR (400 MHz, CDCl₃) δ 4.27 (dtd, J = 9.4, 6.6, 3.4 Hz, 1H), 2.55 – 2.37 (m, 2H), 1.98 – 1.84 (m, 2H), 1.80 – 1.62 (m, 2H), 1.50 (s, 9H), 1.25 (d, J = 6.5 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 171.4, 153.1, 82.9, 51.8, 34.3, 29.4, 28.0 (3C), 20.6, 17.4.

[α]D²² : -5.1 (c, 1.0, CHCl₃).

HR-MS (EI) calcd for C₁₁H₁₉O₃N (M⁺): 213.1365, found: 213.1357.
Using the procedure of Carreira\textsuperscript{57}; cyclopentene (77) (7.0 mL, 75.0 mmol) and powdered NaHCO\textsubscript{3} (2.0 g) in CH\textsubscript{2}Cl\textsubscript{2}/MeOH (5:1 300 mL) was cooled to -78 °C. Ozone was bubbled through the solution until a pale blue colour persisted, the solution was sparged with argon until colourless. The reaction mixture was warmed to room temperature, filtered and diluted with C\textsubscript{6}H\textsubscript{6} (80 mL) and concentrated by rotary evaporation to approx. 50 mL. The resultant solution was diluted with CH\textsubscript{2}Cl\textsubscript{2} (225 mL) cooled to 0 °C. To this NEt\textsubscript{3} (16 mL) was added dropwise, followed by the dropwise addition of acetic anhydride (21 mL). The solution was left to stir at 0 °C for 15 min, warmed to room temperature and stirred for a further 4 h. After this time the reaction mixture was washed with 0.1 M HCl (150 mL), 10 % NaOH (150 mL) and H\textsubscript{2}O (150 mL), dried over MgSO\textsubscript{4} and the solvent removed in vacuo. The crude product was purified by column chromatography (15\textrightarrow 20% EtOAc in pentane) to afford the product (8.2 g, 84%) as a colourless liquid. The data is consistent with that reported in the literature.\textsuperscript{57}

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 9.76 (t, \(J = 1.3\) Hz, 1H), 3.66 (s, 3H), 2.52 (td, \(J = 7.2, 1.3\) Hz, 2H), 2.36 (t, \(J = 7.3\) Hz, 2H), 1.94 (t, \(J = 7.2\) Hz, 2H).

\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ 201.8 , 173.5 , 51.8 , 43.0 , 33.0 , 19.9 .

\textit{A mass could not be obtained for this compound through a range of techniques.}
Using the procedure of Chemla\textsuperscript{55}; methyl 5-oxopentanoate (78) (3.16 g, 24.0 mmol, 1.0 equiv.), (S)-(−)-2-methyl-2-propanesulfinamide (2.60 g, 22.0 mmol, 0.9 equiv.), PPTS (630 mg, 2.5 mmol, 0.1 equiv.) and MgSO\textsubscript{4} (12 g) in CH\textsubscript{2}Cl\textsubscript{2} (60 mL) was stirred for 24 h. After this time the reaction mixture was filtered, the solvent removed in \textit{vacuo}, the crude product was purified by column chromatography (50% Et\textsubscript{2}O in pentane) to afford the product 79 (5.25 g, 93%) as a colourless liquid. The data is consistent with that reported in the literature.\textsuperscript{55}

\textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}) δ 8.05 (t, \textit{J} = 4.2 Hz, 1H), 3.65 (s, 3H), 2.59 – 2.49 (m, 2H), 2.43 – 2.31 (m, 2H), 2.02 – 1.87 (m, 2H), 1.16 (s, 9H).

\textbf{\textsuperscript{13}C NMR} (101 MHz, CDCl\textsubscript{3}) δ 173.4, 168.5, 56.7, 51.7, 35.3, 33.2, 22.4, 20.6 (3C)

[\alpha]_D^{22} : +233.0 (c, 1.7, CHCl\textsubscript{3}), {lit.}\textsuperscript{55} [\alpha]_D^{20} : +230.0 (c, 1.7, CHCl\textsubscript{3})

\textbf{HR-MS} (Cl) calcd for C\textsubscript{10}H\textsubscript{20}NO\textsubscript{3}S (M + H\textsuperscript{+}): 234.1164, found: 234.1163.
Using a modified procedure of Chemla and Guijarro: Isopropylmagnesium chloride (2.0 M in Et₂O, 1.00 mL, 2.0 mmol, 2.0 equiv.) was added dropwise to a solution of sulfinimine (233 mg, 1.0 mmol, 1.0 equiv.) in Et₂O (2 mL) at -78 °C. After stirring at -78 °C for 4 h the solution was quenched with 1M HCl (10 mL). The phases were separated, and the aqueous layer was further extracted with Et₂O (2 x 10 mL). The combined organic layers were washed with sat. aqueous NaHCO₃ (15 mL), H₂O (15 mL), brine (15 mL), dried over MgSO₄, and the solvent was removed by rotary evaporation. The crude sulfinamine was dissolved in MeOH (3 mL), cooled to 0 °C and conc. HCl (50 μL) was added. After 2 h, all the volatiles were removed by rotary evaporation, the resultant residue was dissolved in 2 M HCl (10 mL) which was washed with EtOAc (3 x 10 mL). The aqueous layer was basified with a 2 M NH₃/NH₄ chloride buffer (10 mL) and then taken to pH 12 with the dropwise addition of 2 M NaOH. The solution was matured for 10 min, extracted with CH₂Cl₂ (3 x 10 mL), the combined organics were dried over MgSO₄, and the solvent removed by rotary evaporation. Purification by column chromatography (10% EtOAc in pentane + 1% NEt₃) afforded the product (70 mg, 51%) as a colourless oil. The data is consistent with that reported in the literature.

**¹H NMR** (400 MHz, CDCl₃) δ 5.80 (s, 1H), 3.25 – 3.07 (m, 1H), 2.39 (dddd, J = 17.7, 5.7, 2.9, 1.7 Hz, 1H), 2.25 (dddd, J = 17.8, 11.6, 6.2 Hz, 1H), 2.00 – 1.79 (m, 2H), 1.74 – 1.56 (m, 2H), 1.45 – 1.30 (m, 1H), 0.93 (dd, J = 8.0, 6.8 Hz, 6H).

**¹³C NMR** (101 MHz, CDCl₃) δ 172.9, 58.9, 33.0, 31.5, 25.1, 20.2, 18.1, 18.0.

[α]D²⁵: +58.0 (c, 0.4, CHCl₃), {lit.¹⁹⁵ [α]D²⁵: +68.9 (c, 0.4, CHCl₃)}

**HR-MS** (EI) calcd for C₈H₁₅NO (M⁺): 141.1154, found: 141.1160.
**tert-Butyl (S)-2-isopropyl-6-oxopiperidine-1-carboxylate - 84**

Using general procedure A; lactam 82 (60 mg, 0.42 mmol) gave N-Boc lactam 84 (96 mg, 95%) as a colourless liquid after purification by column chromatography (10% EtOAc in pentane).

**H NMR** (400 MHz, CDCl₃) δ 4.03 (dt, J = 8.0, 5.3 Hz, 1H, H¹), 2.61 – 2.36 (m, 2H, H²), 1.98 – 1.85 (m, 2H, H⁴a and H⁵), 1.84 – 1.77 (m, 2H, H³a, H⁴b), 1.77 – 1.68 (m, 1H, H³b), 1.51 (s, 9H, Boc), 0.92 (t, J = 6.6 Hz, 6H, H⁶).

**C NMR** (101 MHz, CDCl₃) δ 172.3 (C=O), 153.5 (Boc C=O), 82.8 (Boc OMe₃), 60.5 (C¹), 34.1 (C²), 31.4 (C³), 28.1 (3C, Boc CH₃), 23.5 (C⁴), 19.5 (C⁵), 18.2 (C⁶), 17.8 (C⁶').

**IR** ν= 2957, 2875, 1702, 1648, 1408, 1351, 1181 cm⁻¹.

[α]₀²⁵: +48.5 (c, 1.0, CHCl₃)

**HR-MS** (El) calcd for C₁₃H₂₃NO₃ (M⁺): 241.1670; found: 241.1681.
Using the procedure described for lactam 82: phenylmagnesium bromide (3.0 M in Et₂O, 660 μL, 2.0 mmol, 2.0 equiv.) was in the place of isopropylmagnesium chloride to afford the lactam 83 (62 mg, 35%) after purification by chromatography (50 % EtOAc in pentane +1 % NEt₃) as a white solid. Analytical data matched the reported data.¹⁹⁶

¹H NMR (400 MHz, CDCl₃) δ 7.40 – 7.34 (m, 2H), 7.30 (tt, \( J = 7.8 \), 1.4 Hz, 3H), 5.86 (s, 1H), 4.61 – 4.47 (m, 1H), 2.57 – 2.37 (m, 2H), 2.17 – 2.07 (m, 1H), 1.98 – 1.88 (m, 1H), 1.86 – 1.75 (m, 1H), 1.74 – 1.65 (m, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 172.4, 142.6, 129.0 (2C), 128.1, 126.2 (2C), 58.0, 32.3, 31.4, 19.9.

\([\alpha]_{D}^{25} : -33.0 (c, 2.0, CHCl₃)\)

HR-MS (ES) calcd for C₁₁H₁₄NO (M + H⁺): 176.1075, found: 176.1077.
**tert-Butyl (S)-2-oxo-6-phenylpiperidine-1-carboxylate - 85**

Using general procedure A; lactam 83 (88 mg, 0.5 mmol) gave N-Boc lactam 85 (114 mg, 83%) as a white solid after purification by column chromatography (10% EtOAc in pentane). Analytical data matched the reported data.¹⁹⁷

¹H NMR (400 MHz, CDCl₃) δ 7.34 (dd, J = 8.1, 6.6 Hz, 2H), 7.28 – 7.19 (m, 3H), 5.22 (t, J = 5.5 Hz, 1H), 2.65 – 2.52 (m, 2H), 2.24 – 2.07 (m, 1H), 1.93 (dtd, J = 13.4, 6.2, 3.5 Hz, 1H), 1.73 (dddt, J = 20.0, 10.5, 6.7, 3.7 Hz, 2H), 1.25 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ 171.5, 142.6, 128.7 (2C), 127.4, 125.9 (2C), 83.1, 60.85, 34.7, 31.8, 27.7 (2C), 17.6.

[α]D²⁰ : -17.0 (c, 0.3, CHCl₃), {lit.¹⁹⁷ [α]D²⁰ : -19.6 (c, 0.24, CHCl₃)}

HR-MS (ES) calcd for C₁₆H₂₂NO₃ (M + H⁺): 276.1600, found: 276.1616.
Using the procedure of Wender\textsuperscript{60}; a mixture of (+)-limonene (88) (65 mL, 0.4 mol), PtO\textsubscript{2} (160 mg) in EtOH (200 mL) was agitated under a hydrogen atmosphere (1 atm) for 10 h. After this time, the catalyst was removed by filtration. The solvent was removed under vacuum, and the product was purified by vacuum distillation (70 °C, 2.0 mbar) to afford the product (89) (48 g, 86\%) as a colourless liquid. The data is consistent with that reported in the literature.\textsuperscript{198}

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 5.38 (ddt, J = 6.3, 3.3, 1.4 Hz, 1H), 2.08 – 1.66 (m, 5H), 1.64 (d, J = 1.4 Hz, 3H), 1.52 – 1.12 (m, 3H), 0.91 – 0.86 (m, 6H)

\textsuperscript{13}C-NMR (101 MHz, CDCl\textsubscript{3}). 133.5, 121.1, 39.7, 32.6, 30.0, 29.2, 26.2, 23.4, 19.7 (2C).

[\alpha]_{D}^{20} : +106.4 (c, 1.0, CHCl\textsubscript{3}), \{lit.\textsuperscript{59} [\alpha]_{D}^{22} : +101.8(c, 1.0, CHCl\textsubscript{3})\}

HR-MS (El) calcd for C\textsubscript{10}H\textsubscript{18} (M\textsuperscript{+}): 138.1409, found: 138.1500.
Ozone was bubbled through a solution of alkene 89 (18.3 g, 133 mmol, 1.0 equiv.) in CH₂Cl₂ (100 mL) at -78 ºC until a blue colour persisted. The solution was sparged with oxygen for 10 min, followed by argon for 10 min. The solution was warmed to 0 ºC, and aqueous hydrogen peroxide (50% wt, 9.9 mL, 146 mmol, 1.1 equiv.) was added drop-wise over 1 h. This was allowed to warm to room temperature and left to stir for 16 h. After this time it was quenched with sat. aqueous Na₂S₂O₅ (50 mL) the solution was basified with 10 M NaOH to pH 14. The aqueous layer was washed with CH₂Cl₂ (2 x 150 mL). The aqueous layer was acidified with conc. HCl to pH 1. This was extracted with CH₂Cl₂ (3 x 300 mL), the combined organic layers were dried over MgSO₄ and the solvent removed by rotary evaporation to afford the crude product 90 (13.8 g, 52%) as a colourless liquid and was then taken through to the next step crude, without further purification.

¹H NMR (400 MHz, CDCl₃) δ 2.46 (t, J = 7.7 Hz, 2H), 2.36 (dd, J = 15.7, 5.3 Hz, 1H), 2.15 (s, 4H), 1.82 – 1.61 (m, 3H), 1.51 (dtd, J = 15.2, 8.0, 5.8 Hz, 1H), 0.93 – 0.83 (m, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 209.0 , 179.4 , 41.8 , 40.3 , 35.6 , 30.1 , 25.2 , 19.5 , 18.5 (2C).

A mass could not be obtained for this compound through a range of techniques.
To a solution of crude acid 90 (700 mg, 3.7 mmol, 1.0 equiv.) in acetone (50 mL) was added K$_2$CO$_3$ (2.6 g, 18.5 mmol, 5.0 equiv.) followed by MeI (3.4 mL, 18.5 mmol, 15.0 equiv.) at room temperature. The suspension was stirred for 16 h, the solids were removed by filtration and the solvents removed by rotary evaporation. The resultant oil was purified by column chromatography (CHCl$_3$) to afford the product 91 (626 mg, 83%) as a colourless liquid. The data is consistent with that reported in the literature.$^{199}$

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.59 (s, 3H), 2.37 (t, $J = 7.8$ Hz, 2H), 2.24 (dd, $J = 15.3$, 5.7 Hz, 1H), 2.09 – 2.03 (m, 4H), 1.74 – 1.34 (m, 4H), 0.79 (dd, $J = 11.3$, 6.8 Hz, 6H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 208.6 , 174.1 , 51.5 , 41.6 , 40.3 , 35.6 , 29.9 , 25.1 , 19.3 , 18.4.

[$\alpha$]$_D^{22}$: +4.0 (c, 1.0, CHCl$_3$), {lit.$^{199}$ [$\alpha$]$_D^{20}$: +3.9 (c, 1.0, CHCl$_3$)}

HR-MS (ESI) calcd for C$_{11}$H$_{20}$O$_3$Na (M + Na$^+$): 223.1310, found: 223.1317.
Using the procedure of Kovacic,\textsuperscript{200} and Barrett\textsuperscript{201}; N,N-Dichloro-tert-butylamine was prepared by the drop-wise addition of HCl (3 M, 100 mL) to a suspension of tert-butylamine (4 mL, 38 mmol) and 75% calcium hypochlorite (16 g, 78.4 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (100 mL). After the addition was completed the biphasic mixture was stirred for 1 h before the phases were separated. The organic layer was washed with H\textsubscript{2}O (1 x 50 mL) and dried over NaSO\textsubscript{4} and the solvent removed by rotary evaporation to yield the crude dichloroamine as a viscous yellow oil. This was added immediately to a solution of PhSAc (5.5 g, 36 mmol) in C\textsubscript{6}H\textsubscript{6} (15 mL), and heated at 80 °C for 20 min. All volatiles were removed by extensive drying under high vacuum to yield the product 94 as a moisture sensitive solid (7.8 g, 95%). The data is consistent with that reported in the literature.\textsuperscript{201}

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 8.11-8.15 (m, 2H), 7.57-7.60 (m, 3H), 1.56 (s, 9H).
tert-Butyl 2-oxo-5,6-dihydropyridine-1(2H)-carboxylate - 95

LiHMDS (1.0 M in THF, 11 mL, 11 mmol, 1.1 equiv.) was added to a solution of lactam 57 (2.0 g, 10 mmol, 1.0 equiv.) in THF (60 mL) at -78 °C. After 10 minutes, a solution of 94 (2.6 g, 12 mmol, 1.2 equiv.) in THF (40 mL) was added dropwise over 10 minutes. After stirring for 30 min at -78 °C, the reaction was quenched with sat. aqueous NaHCO₃ (50 mL) and allowed to warm to room temperature. The resultant solution was extracted with EtOAc (2 x 75 mL), the combined organic layers were washed with brine (100 mL), dried over MgSO₄ and the solvent removed by rotary evaporation. The crude product was purified by column chromatography (20% EtOAc in pentane) to afford the product 95 (1.8 g, 92%) as a yellow liquid. The data is consistent with that reported in the literature.¹⁹⁰

¹H NMR (400 MHz, CDCl₃) δ 6.78 (dt, J = 9.0, 4.2 Hz, 1H), 5.96 (dt, J = 9.8, 1.8 Hz, 1H), 3.86 (t, J = 6.5 Hz, 2H), 2.41 (m 2H), 1.54 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ 169.6, 152.3, 143.3, 127.6, 82.8, 43.5, 28.2, 24.9.

HR-MS (ESI) calcd for C₁₀H₁₅NO₃ (M + H⁺): 198.1125, found: 198.1125.
Dimethyl 3-isopropylpentanedioate - 102

Using the procedure of Overman\textsuperscript{202}, a solution of isopropylmagnesium chloride (1 M in THF, 75 mL, 75 mmol, 4.0 equiv.) was added drop-wise to a suspension of Cul (1.1 g, 5.6 mmol, 0.3 equiv.) in THF (200 mL) at room temperature. This mixture was stirred at room temperature for 10 min before being cooled to -78 °C. TMSCl (9.5 mL, 75 mmol, 4.0 equiv.) and dimethyl glutaconate 101 (3.0 g, 18.75 mmol, 1.0 equiv.) were added consecutively, and this was stirred at -78 °C for 3 h. The solution was warmed to room temperature and quenched slowly with sat. aqueous NH\textsubscript{4}Cl (250 mL) and diluted with EtOAc (250 mL). The organic layer was collected and the aqueous layer was further extracted with EtOAc (2 x 250 mL). The combined organic layers were dried over MgSO\textsubscript{4} and the solvent removed under vacuum to yield the crude product. This was purified by bulb-to-bulb distillation (60 °C, 0.1 mbar) to yield the product 102 (2.2 g, 58%) as a colourless liquid. The data is consistent with that reported in the literature.\textsuperscript{203}

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 3.66 (s, 6H), 2.46-2.10 (m, 5H), 1.73 (m, 1H), 0.88 d, \( J \) = 6.9 Hz, 6H).

\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) 173.6 (2C), 51.7 (2C), 37.9 (2C), 35.9, 30.5, 19.1 (2C).

HR-MS (ESI) calcd for C\textsubscript{10}H\textsubscript{19}O\textsubscript{4} (M + H\textsuperscript{+}): 203.1283, found: 203.1291.
Dimethyl 3-isophenylpentanedioate - 103

![Structure](image)

Using the procedure described for isopropyl 102; phenylmagnesium bromide was implemented in the place of isopropylmagnesium chloride to afford the phenyl 103 (3.8 g. 67%) as a white solid, after purification by recrystallization from n-hexane. The data is consistent with that reported in the literature.²⁰⁴

³¹H NMR (400 MHz, CDCl₃) δ 7.36 – 7.21 (m, 5H), 3.69 (q, J = 7.4 Hz, 1H), 3.62 (s, 6H), 2.80 – 2.63 (m, 4H).

³¹C-NMR (101 MHz, CDCl₃). δ 171.9 (2C), 142.3, 128.6 (2C), 128.1 (2C), 126.9, 51.4 (2C), 40.4, 38.3 (2C).

m.p. 86-87 °C (hexane) {lit: 87-88 °C}.²⁰⁵

HR-MS (ESI) calcd for C₁₃H₁₆O₄ (M + H⁺): 237.1127, found: 237.1126.
Using the procedure of Jones\textsuperscript{63}; dimethyl 3-methylpentanedioate (104) (20 g, 115 mmol, 1.0 equiv.) and pigs liver esterase (PLE) (0.95 g 8000 U) stirred in KH\textsubscript{2}PO\textsubscript{4} pH 7 buffer (445 mL). Freshly made 1 M NaOH (115 mL, 115 mmol, 1.0 equiv.) was added drop-wise over 10 hours while keeping the pH between 7 and 8. After all the NaOH was added, the solution was cooled -78 °C. The solution was quenched with a saturated brine solution (250 mL). This was filtered, washed with Et\textsubscript{2}O (2 x 250 mL). The aqueous layer was acidified to pH 1 with 1 M HCl, extracted with Et\textsubscript{2}O (4 x 250 mL), the combined organic layers were washed with H\textsubscript{2}O (250 mL) and brine (2 x 250 mL), dried over MgSO\textsubscript{4} and the solvent removed by rotary evaporation to yield the crude product. This was purified by bulb-to-bulb vacuum distillation (100 °C, 0.2 mbar) to yield the product 104 (12 g, 65%) as a colourless liquid. The data is consistent with that reported in the literature.\textsuperscript{206}

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 3.66 (s, 3H), 2.54 – 2.20 (m, 5H), 1.04 (d, J = 6.4 Hz, 3H).

\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ 178.8 , 172.9 , 51.7 , 40.6 , 27.30 , 19.9·

\([\alpha]\)\textsubscript{D}\textsuperscript{20}: +1.0 (c, 1.0, CHCl\textsubscript{3}); {lit.}\textsuperscript{206} \([\alpha]\)\textsubscript{D}\textsuperscript{20}: +0.6 (c, 1.0, CHCl\textsubscript{3}).

HR-MS (EI) calcd for C\textsubscript{7}H\textsubscript{13}O\textsubscript{4} (M + H\textsuperscript{+}): 161.0808, found: 161.0810.
Using the procedure described for methyl acid-ester 107; iso-propyl diester 102 (2.2 g, 10.9 mmol) gave the acid ester 105 (1.4 g, 68%) as a colourless liquid after purification by bulb-to-bulb distillation (105 °C, 0.2 mbar). The data is consistent with that reported in the literature.\(^{207}\)

\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta 9.52\) (s, 1H), 3.65 (s, 3H), 2.52-2.10 (m, 5H), 1.77 (m, 1H), 0.88 (d, \(J=6.7\) Hz, 6H).

\(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)) \(\delta 179.7, 173.4, 51.7, 37.6, 35.9, 30.5, 19.6\) (2C).

\([\alpha]_D^{21}\) : +44.0 (c, 0.25, CHCl\(_3\))

\(\text{HR-MS (EI)}\) calcd for C\(_9\)H\(_{16}\)O\(_4\) (M\(^+\)) : 188.1049, found: 188.1057.
(S)-5-Methoxy-5-oxo-3-phenylpentanoic acid - 106

Using the procedure described for methyl acid-ester 107; phenyl diester 103 (3.8 g. 16.1 mmol) gave the acid ester 106 (2.4 g, 67%) as a white solid after purification by recrystallisation from AcOH. The data is consistent with that reported in the literature.  

**1H NMR** (400 MHz, CDCl₃) δ 7.34-7.10 (m, 5H), 3.55-3.65 (m, 1H), 3.56 (s, 3H), 2.82-2.64 (m, 4H).

**13C- NMR** (100 MHz, CDCl₃), 177.8, 172.2, 142.1, 128.6 (2C), 127.3 (2C), 127.2, 53.5, 40.3, 40.0, 38.1.

m.p. 96-97 °C (AcOH)

[α]₀²² : -3.8 (c, 1.1, CHCl₃), {lit.²⁰ [α]₀²⁰ : -3.6 (c, 1.1, CHCl₃)}.

**HR-MS (EI)** calcd for C₁₂H₁₅O₄ (M + H⁺): 223.0935, found: 223.0930.
Using general method B; methyl acid-ester 107 (12.0 g, 75 mmol) was implemented to afford the methyl lactam 116 (3.2 g, 37%) after purification by column chromatography (10% EtOAc in pentane) as a colourless liquid.

\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta 6.11\) (s, 1H, NH), 3.40 – 3.23 (m, 2H, H\(^4\)), 2.50 – 2.39 (m, 1H, H\(^{1a}\)), 2.01 – 1.91 (m, 2H, H\(^{1b}\) and H\(^2\)), 1.89 – 1.78 (m, 1H, H\(^{3a}\)), 1.41-1.44 (m, 1H, H\(^{3b}\)), 1.03 (d, J = 6.2 Hz, 3H, H\(^5\)).

\(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)) \(\delta 172.4\) (C=O), 41.4 (C\(^1\)), 39.8 (C\(^4\)), 30.2 (C\(^2\)), 27.7 (C\(^3\)), 21.2 (C\(^5\)).

\([\alpha]_D^{21}\) : +24.0 (c, 0.5, CHCl\(_3\))

\(\text{IR} \nu= 3206, 2957, 2872, 1697, 1659, 1497, 1342\ \text{cm}^{-1}\).

\(\text{HR-MS (EI)}\) calcd for C\(_6\)H\(_{11}\)NO (M\(^+\)): 113.0841; found: 113.0836.
tert-Butyl (R)-4-methyl-2-oxopiperidine-1-carboxylate - 118

Using general procedure A; lactam 116 (800 mg, 7.1 mmol) gave N-Boc lactam 118 (1.12 g, 74%) as a colourless liquid after purification by column chromatography (20% EtOAc in pentane). Analytical data matched the reported data.  

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.77 (dt, $J = 12.8, 5.0$ Hz, 1H), 3.48 (ddd, $J = 12.8, 10.9, 4.3$ Hz, 1H), 2.57 (ddd, $J = 16.7, 5.1, 2.1$ Hz, 1H), 2.09 (dd, $J = 16.8, 10.6$ Hz, 1H), 2.00 – 1.87 (m, 2H), 1.51 (s, 9H), 1.01 (d, $J = 6.4$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 171.1, 153.0, 82.90, 45.7, 43.23, 31.0, 28.2 (3C), 27.7, 21.3, 14.31.

$[\alpha]_D^{20}$: +22.2 (c, 0.6, CHCl$_3$), {lit.$^{210}$ $[\alpha]_D^{20}$: +28.3 (c, 0.59, CHCl$_3$)}.

HR-MS (EI) calcd for C$_{11}$H$_{20}$NO$_3$ (M + H$^+$): 214.1438, found: 214.1438.
(S)-4-
isoPropylpiperidin-2-one - 114

Using general method B; isopropyl acid-ester 105 (1.4 g, 7.44 mmol) was implemented to afford isopropyl lactam 114 (230 mg, 22%) after purification by column chromatography (0 → 10% EtOAc in pentane) as a colourless liquid. The data is consistent with that reported in the literature.59

\[ {^1}\text{H NMR} \ (400 \text{ MHz, CDCl}_3) \ \delta \ 6.98 \text{ (s, 1H), } 3.40 \text{ – 3.27 (m, 1H), } 3.20 \text{ (td, } J = 11.8, 4.3 \text{ Hz, 1H), } 2.38 \text{ (ddd, } J = 17.6, 4.9, 2.1 \text{ Hz, 1H), } 1.99 \text{ (dd, } J = 17.5, 11.2 \text{ Hz, 1H), } 1.81 \text{ (ddd, } J = 13.3, 4.6, 2.4 \text{ Hz, 1H), } 1.62 \text{ – 1.43 (m, 2H), } 1.35 \text{ (dt, } J = 13.1, 11.5, 5.5 \text{ Hz, 1H), } 0.87 \text{ (dd, } J = 6.5, 3.1 \text{ Hz, 6H).} \]

\[ {^{13}}\text{C NMR} \ (101 \text{ MHz, CDCl}_3) \ \delta \ 173.3, 41.6, 39.1, 35.4, 31.9, 25.9, 19.3. \]

\[ \text{HR-MS (El) calcd for C}_8\text{H}_{15}\text{NO (M\textsuperscript{+}): 141.1154; found: 141.1150.} \]

\[ [\alpha]_D^{20} : -16.4 (c, 1.0, \text{CHCl}_3), \{\text{lit.} [\alpha]_D^{20} : -35.0 (c, ND, H}_2\text{O)\}. \]
**tert-Butyl (S)-4-isopropyl-2-oxopiperidine-1-carboxylate - 117**

Using general procedure A; lactam 114 (230 mg, 1.63 mmol) gave N-Boc lactam 117 (270 mg, 68%) as a colourless liquid after purification by column chromatography (15% EtOAc in pentane).

**1H NMR** (400 MHz, CDCl$_3$) $\delta$ 3.81 (ddd, $J = 12.8, 5.0, 4.1$ Hz, 1H, $H^{4a}$), 3.47 (ddd, $J = 12.8, 11.0, 4.3$ Hz, 1H, $H^{4b}$), 2.59 (ddd, $J = 17.0, 5.3, 2.1$ Hz, 1H, $H^{1a}$), 2.20 (dd, $J = 16.9, 11.3$ Hz, 1H, $H^{1b}$), 1.94 (dddd, $J = 13.4, 8.5, 4.2, 2.2$ Hz, 1H, $H^2$), 1.52 (s, 9H, Boc), 1.68 – 1.37 (m, 3H, $H^3$ and $H^5$), 0.91 (dd, $J = 6.7, 3.2$ Hz, 6H, H$^6$).

**13C NMR** (101 MHz, CDCl$_3$) $\delta$ 171.7 ($C=O$), 152.8 ($C=O$ Boc), 82.9 (O$\text{CMe}_3$), 45.8 ($C^4$), 39.0 ($C^3$), 36.0 ($C^1$), 32.1 ($C^5$), 28.2 (3C, Boc $\text{CMe}_3$), 27.6 ($C^3$), 19.5 ($C^6$), 19.5 ($C^6'$)

[$\alpha]_D^{20}$: -32.4 (c, 1.0, CHCl$_3$)

**HR-MS** (EI) calcd for C$_{13}$H$_{23}$NO$_3$ ($M^+$): 241.1670; found: 241.1677.

**IR** ν= 2976, 1765, `1709, 1367, 1282, 1248, 1145 cm$^{-1}$. 
Using general method B; phenyl acid-ester 106 (2.4 g, 10.8 mmol) was implemented to afford isopropyl lactam 115 (134 mg, 7%) after purification by column chromatography (10% EtOAc in pentane) as a white solid. The data is consistent with that reported in the literature.\textsuperscript{211}

\textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}) δ 7.41-7.19 (m, 5H), 5.85 (s, 1H), 3.45 (dd, J = 5.9, 3.0 Hz, 2H), 3.14 (m, 1H), 2.73 (ddd, J = 17.6, 5.2, 1.9 Hz, 1H), 2.53 (dd, J = 17.6, 11.0 Hz, 1H), 2.19-1.91 (m, 2H).

\textbf{\textsuperscript{13}C NMR} (101 MHz, CDCl\textsubscript{3}) δ 172.4, 143.5, 128.5, 126.8 (2C), 126.6 (2C), 48.24, 41.2, 38.3, 27.4.

[\alpha]_D^{20} \text{ : } -24.4 (c, 0.5, CHCl\textsubscript{3}), \{\text{lit.}\textsuperscript{212} [\alpha]_D^{25} \text{ : } -20.2 (c, 0.5, CHCl\textsubscript{3})\}.

\textbf{HR-MS} (ES) calcd for C\textsubscript{11}H\textsubscript{14}NO\textsubscript{4} (M + H\textsuperscript{+}) : 176.1075, found: 176.1065.
**tert-Butyl (S)-2-oxo-4-phenylpiperidine-1-carboxylate - 96**

Using general procedure A; lactam 115 (134 mg, 0.76 mmol) gave N-Boc lactam 96 (160 mg, 76%) as a colourless liquid after purification by column chromatography (10% EtOAc in pentane). The data is consistent with that reported in the literature.\textsuperscript{213}

\textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}) δ 7.38 – 7.15 (m, 5H), 3.88 (ddd, J = 12.9, 5.0, 4.1 Hz, 1H), 3.63 (ddd, J = 12.8, 10.9, 4.3 Hz, 1H), 3.12 (dtd, J = 11.1, 5.6, 3.8 Hz, 1H), 2.88 – 2.79 (m, 1H), 2.64 (dd, J = 17.1, 11.2 Hz, 1H), 2.20 (m, 1H), 2.01 – 1.88 (m, 1H), 1.55 (s, 9H).

\textbf{\textsuperscript{13}C NMR} (101 MHz, CDCl\textsubscript{3}) δ 170.5, 152.8, 143.2, 129.0 (2C), 127.1 (2C), 126.5, 83.2, 45.7, 42.2, 38.5, 30.5, 28.2 (3C).

\textbf{HR-MS} (ES) calcd for C\textsubscript{16}H\textsubscript{22}NO\textsubscript{3} (M + H\textsuperscript{+}): 276.1594, found: 276.1584.

\([\alpha]_D^{20}\) : -20.0 (c, 1.0, CHCl\textsubscript{3})
Using general procedure C; lactam 57 (19.9 g, 100 mmol) gave spiroaminal 53-A (4.3 g, 56%) which could be purified to by column chromatography (10% MeOH in CH₂Cl₂ +1% NEt₃) to yield the product as a brown oil. Alternatively, purification by Kugelrohr distillation (125 °C, 9 x 10⁻² mbar) yields aminal 53-A as a colourless oil. The data is consistent with that reported in the literature in both cases.³⁵

¹H NMR (400 MHz, CDCl₃) δ 2.82 (bs 4H), 1.78 (bs, 2H), 1.73-1.23 (m, 12H).

¹³C NMR (100 MHz, CDCl₃) δ 68.3, 40.6 (2C), 37.0 (2C), 26.4 (2C), 20.4 (2C).

HR-MS (ESI) calcd for C₉H₁₉N₂ (M + H⁺): 155.1548, found: 155.1546.
3-(3,4-dihydro-2H-pyrrol-5-yl)propan-1-amine 47-B

and 1,6-diazaspiro[4.4]nonane 47-A

Using general procedure C; Lactam 72 (3.7 g, 20.0 mmol) gave both the amine-imine 47-B (428 mg, 34%) and a mixture of spiroaminal 47-A and amine-imine 47-B (340 mg, 27%) which could be separated and purified by column chromatography (0->15% MeOH in CH₂Cl₂ +1% NEt₃) to yield the products as brown oils

Note: spiroaminal 47-A is particularly volatile.

Amine-imine 47-B, matched the reported data.⁴⁹

¹H NMR (400 MHz, CDCl₃) δ 3.92 – 3.69 (m, 2H), 3.14 – 2.94 (m, 2H), 2.63 (t, J = 8.0 Hz, 1H), 2.59 – 2.39 (m, 2H), 2.20 (dddd, J = 12.9, 9.2, 7.8, 6.9 Hz, 1H), 2.14 – 2.01 (m, 4H), 1.90 – 1.77 (m, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 179.0, 60.7, 53.1, 44.3, 38.6, 29.0, 23.8.

HR-MS (ESI) calcd for C₇H₁₅N₂ (M + H⁺): 127.1235, found: 127.1239.

Aminal 47-A.

¹H NMR (400 MHz, CDCl₃) δ 3.84 – 3.66 (bs, 4H, H¹), 2.40 (m, 6H, H² and N-H), 1.80 (bs, 4H, H²).

¹³C NMR (101 MHz, CDCl₃) δ 64.7 (RHN-CNHR), 51.1 (2C, C¹), 33.8 (2C, C³), 23.0 (2C, C²).

IR ν = 3115, 2936, 1452, 1166, 821 cm⁻¹.

HR-MS (ESI) calcd for C₇H₁₅N₂ (M + H⁺): 127.1235, found: 127.1236.
5-(3,4,5,6-Tetrahydro-2H-azepin-7-yl)pentan-1-amine – 56-B

Using general procedure C; Lactam 73 (3.6 g, 16.9 mmol) gave amine-imine 56-B (1.9 g, 64%) which could be purified by column chromatography (15% MeOH in CH$_2$Cl$_2$ +2% NEt$_3$) to yield the product as a brown oil. The data is consistent with that reported in the literature.$^{49}$

$^1$H NMR (400 MHz, CDCl$_3$) δ 3.59 – 3.52 (m, 2H), 2.68 (dd, J= 7.7, 6.3 Hz, 2H), 2.37 – 2.31 (m, 2H), 2.29 – 2.21 (m, 2H), 1.81 – 1.71 (m, 2H), 1.61 – 1.28 (m, 10H)

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 178.9, 51.9, 42.9, 42.2, 33.8, 33.3, 31.7, 26.9, 26.6, 26.1, 23.7.

HR-MS (ESI) calcd for C$_{11}$H$_{22}$N$_2$Na (M + Na$^+$): 205.1675, found: 205.1680.
Using general procedure C; Lactam 76 (1065 mg, 5.0 mmol) gave spiroaminal 119-A (236 mg, 52%) which was purified by bulb-to-bulb distillation (130 °C, 9 x 10⁻² mbar) to yield the spiroaminal 119-A as a colourless oil, which crystallized slowly upon standing.

**¹H NMR** (400 MHz, CDCl₃) δ 5.90 (s, 2H, NH), 3.53 (dqd, J = 10.0, 6.3, 3.5 Hz, 2H, H⁴), 2.46 – 2.23 (m, 4H, H₃a and H₁a), 1.97 – 1.86 (m, 4H, H³b and H²b), 1.78 – 1.62 (m, 2H, H¹b), 1.37 (m, 2H, H²b), 1.21 (d, J = 6.4 Hz, 6H, C⁵).

**¹³C NMR** (101 MHz, CDCl₃) δ 62.9 (RHN₁CNHR), 49.0 (2C, C⁴), 31.1 (2C, C¹), 30.6 (2C, C³), 23.0 (2C, C⁵), 19.9 (2C C²).

**IR** ν= 3276, 2932, 1648, 1330 cm⁻¹.

**m.p.** 37-40 °C (CHCl₃/pentane).

**HR-MS** (CI) calcd for C₁₁H₂₃N₂ (M + H⁺): 183.1861, found: 183.1860

[α]D²⁰: +16.7 (c, 0.1, CHCl₃)
**tert-Butyl (5-oxohept-6-en-1-yl)carbamate - 124**

Freshly prepared vinylmagnesium bromide (1.0 M in THF, 1.1 mL, 1.1 mmol, 1.0 equiv.) was added dropwise to a solution of lactam 57 (200 mg, 1.0 mmol, 1.0 equiv.) in THF (10 mL) at -78 °C. The solution was stirred for 15 minutes before being quenched with AcOH (1 mL). The mixture was allowed to warm to room temperature, diluted with H₂O (10 mL) the phases were separated and the aqueous layer was further extracted with CH₂Cl₂ (2 x 10 mL). The combined organics were washed with brine, dried over MgSO₄ and the solvent removed by rotary evaporation to afford the crude product. Purification by column chromatography (0 -> 20% Et₂O in pentane) afforded the product 124 (54 mg, 24%) as a colourless oil.

**1H NMR** (400 MHz, CDCl₃) δ 6.37 (dd, J = 17.7, 10.5 Hz, 1H, H²), 6.24 (dd, J = 17.7, 1.3 Hz, 1H, H¹a), 5.84 (dd, J = 10.5, 1.3 Hz, 1H, H¹b), 3.57 (t, J = 6.8 Hz, 2H, H⁶), 2.61 (t, J = 6.9 Hz, 2H, H³), 1.74 – 1.58 (m, 4H, H⁴ and H⁵), 1.50 (s, 9H, Boc).

**13C NMR** (101 MHz, CDCl₃) δ 206.7 (C=O), 152.8 (C=O Boc), 136.6 (C²), 128.1 (C¹), 82.3 (OCMe₃), 46.1 (C⁶), 39.3 (C³), 28.7 (C⁵), 28.2 (3C, Boc CH₃), 21.2 (C⁴).

**HR-MS** (CI) calcd for C₁₂H₂₂NO₃ (M + H⁺): 228.1594, found: 228.1596.
Freshly prepared allylmagnesium bromide (1.0 M in THF, 1.1 mL, 1.1 mmol, 1.0 equiv.) was added dropwise to a solution of lactam 57 (200 mg, 1.0 mmol, 1.0 equiv.) in THF at -78 °C. The solution was stirred for 15 minutes before being quenched with sat. aqueous NH₄Cl (20 mL). The mixture was allowed to warm to room temperature, the phases were separated and the aqueous layer was further extracted with CH₂Cl₂ (2 x 15 mL). The combined organic layers were washed with brine, dried over MgSO₄ and the solvent removed by rotary evaporation to afford the crude product. Purification by column chromatography (20% Et₂O in pentane) afforded the product 125 (140 mg, .58%) as a colourless oil.

**1H NMR** (400 MHz, CDCl₃) δ 5.89 (ddt, J = 17.2, 10.3, 7.0 Hz, 1H, H²), 5.21 – 5.05 (m, 2H, H¹), 4.59 (s, 1H, NH), 3.15 (m, 2H, H⁷), 3.09 (m, 2H, H³), 2.46 (t, J = 7.2 Hz, 2H, C⁴), 1.62 – 1.53 (m, 2H, H⁶), 1.46 – 1.42 (m, 2H, H⁶), 1.42 (s, 9H, Boc).

**13C NMR** (101 MHz, CDCl₃) δ 208.6 (C=O), 156.1 (C=O Boc), 130.7 (C²), 118.9 (C¹), 79.2 (OCMe₃), 47.9 (C³), 41.8 (C⁷), 40.2 (C⁴), 29.58 (C⁶), 28.5 (3C, Boc CH₃), 20.7 (C⁵).

**IR** ν= 3376, 2930, 1698, 1518, 1365, 1248, 1164 cm⁻¹.

**HR-MS** (Cl) calcd for C₁₃H₂₄N₂O₃ (M + H⁺): 242.1751, found: 242.1740.
AIBN (82 mg, 0.5 mmol, 0.1 equiv.) was added to a mixture of allyl cyanide (140) (600 μL, 7.5 mmol, 1.5 equiv.) and Bu₃SnH (1.35 mL, 5.0 mmol, 1.0 equiv.). The solution was heated to 80 °C for 16 h. The resultant homogenous solution was cooled, diluted with Et₂O (60 mL) and transferred via cannula to a suspension of LiAlH₄ (300 mg, 7.9 mmol, 1.6 equiv.) in Et₂O (60 mL) at 0 °C. The suspension was warmed to room temperature before being refluxed at 40 °C for 16 h. The reaction was quenched with MeOH (20 mL) at 0 °C followed by the addition of H₂O (1 mL). The mixture was filtered, dried over MgSO₄, and the solvent removed by rotary evaporation to yield the analytically pure amine 142 (1.55 g, 85%) as a yellow liquid.

\[ \text{4-(Tributylstannyl)butan-1-amine - 142} \]

\[
\text{Bu}_3\text{Sn(CH}_2\text{CH}_2\text{CN)}\text{NH}_2
\]

\(^1\text{H NMR}\) (400 MHz, CDCl₃) δ 2.68 (t, \(J = 6.8 \text{ Hz}, 2\text{H, H}^1\)), 1.56 – 1.40 (m, 10H), 1.34 – 1.23 (m, 8H), 0.88 (t, \(J = 7.3 \text{ Hz}, 9\text{H}\)), 0.84 – 0.76 (m, 8H).

\(^{13}\text{C NMR}\) (101 MHz, CDCl₃) δ 42.0 (C¹), 38.8 (C²), 29.4 (3C), 27.5 (3C), 24.4 (C³), 13.8 (4C), 8.9 (3C).

*Further analysis was not carried out due to suspected toxicity concerns.*
Using the procedure of Hussaini\textsuperscript{214}; a solution of lactam 52 (2.0 g, 20 mmol, 1.0 equiv.) in CH$_2$Cl$_2$ (40 mL) was added dropwise to a suspension of Lawessons reagent (4.0 g, 10 mmol, 0.5 equiv.) in CH$_2$Cl$_2$ (40 mL) at room temperature and stirred for 2 h. The mixture was filtered, the solvent was removed by rotary evaporation and the crude compound was purified by column chromatography (40% EtOAc in pentane) to yield the product 143 (1.9 g, 84%) as a yellow solid. The data is consistent with that reported in the literature.\textsuperscript{214}

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.95 (s, 1H), 3.35 (t, $J = 6.0$ Hz, 2H), 2.88 (t, $J = 6.2$ Hz, 2H), 1.90 – 1.67 (m, 4H).

$^{13}$C-NMR (100 MHz, CDCl$_3$) δ 202.1, 44.7, 39.7, 21.0, 20.3.

HR-MS (Cl) calcd for C$_5$H$_{10}$NS (M + H$^+$): 116.0528, found: 116.0530.
Mel (132 μL, 2.12 mmol, 1.06 equiv.) was added to a solution of thiolactam 143 (230 mg, 2.0 mmol, 1.0 equiv.) in acetone (3 mL) and stirred for 16 h. The resultant precipitate was collected by filtration, washed with Et₂O (10 mL) to afford the product (307 mg, 60%) as a white powder.

\[ \text{MeI} \quad (132 \mu\text{L, 2.12 mmol, 1.06 equiv.}) \]

\[ \text{thiolactam 143} \quad (230 \text{ mg, 2.0 mmol, 1.0 equiv.}) \]

\[ \text{acetone (3 mL)} \]

\[ \text{stirred for 16 h} \]

\[ \text{the product (307 mg, 60%) as a white powder} \]

\[ \text{MeI} \quad (132 \mu\text{L, 2.12 mmol, 1.06 equiv.}) \]

\[ \text{thiolactam 143} \quad (230 \text{ mg, 2.0 mmol, 1.0 equiv.}) \]

\[ \text{acetone (3 mL)} \]

\[ \text{stirred for 16 h} \]

\[ \text{the product (307 mg, 60%) as a white powder} \]

\[ \text{H NMR (400 MHz, DMSO-}d_6\text{)} \quad \delta \text{ 11.87 (s, 1H, NH), 3.58 (t, } J = 5.7 \text{ Hz, 2H, H}^1\text{), 2.91 (t, } J = 5.9 \text{ Hz, 2H, H}^1\text{), 2.65 (s, 3H, C}^5\text{), 1.86 – 1.70 (m, 4H, H}^2\text{ and H}^3\text{).} \]

\[ \text{C NMR (101 MHz, DMSO-}d_6\text{)} \quad \delta \text{ 189.4 (MeS}C=N\text{), 45.8 (C}^1\text{), 30.2 (C}^4\text{), 19.2 (C}^2\text{), 17.3 (C}^5\text{), 13.8 (C}^3\text{).} \]

\[ \text{IR } v = 3117, 3022, 2951, 1635, 1430, 1337, 11-6, 786 \text{ cm}^{-1}. \]

\[ \text{m.p. 178-181 °C (acetone/Et}2\text{O).} \]

\[ \text{A mass could not be obtained for this compound through a range of techniques.} \]
Using the procedure of De Vos\textsuperscript{215}; BH$_3$THF (1 M in THF, 20 mL, 29.0 mmol, 5 equiv.) was added dropwise to a solution of 4-iodophenylacetonitrile (146) (1.0 g, 4.1 mmol) at room temperature. After the addition is complete the solution was heated to 70 $^\circ$C for 2 h. The mixture was cooled in an ice bath and the quenched with 6 M HCl (2 mL). The mixture was stirred for 10 min before being basified with 1 M NaOH to pH 14. The solution was extracted with CH$_2$Cl$_2$ (2 x 20 mL), the combined organics were washed with H$_2$O (20 mL), brine (20 mL), dried over MgSO$_4$, and the solvent removed by rotary evaporation to yield the product 147 (567 mg, 56%) as a colourless oil. The data is consistent with that reported in the literature.\textsuperscript{215}

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.82 (dd, $J =$ 7.9, 1.2 Hz, 1H), 7.30 – 7.25 (m, 1H), 7.22 (dd, $J =$ 7.6, 1.9 Hz, 1H), 6.90 (td, $J =$ 7.6, 1.9 Hz, 1H), 2.95 (ddd, $J =$ 7.4, 6.2, 1.6 Hz, 2H), 2.91 – 2.85 (m, 2H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 142.5, 139.7, 130.0, 128.4, 128.1, 100.9, 44.8, 42.5.

HR-MS (ES) calcd for C$_8$H$_{11}$NI ($M + H^+$): 247.9931, found: 247.9930.
Using the procedure of Keglevich\textsuperscript{216}; tetrahydroisoquinoline (150) (2.00 g, 15 mmol, 1.0 equiv.) and S\textsubscript{8} (0.96 g, 30 mmol, 2.0 equiv.) were irradiated neat to 170 °C in a microwave for 15 min. Once cooled to room temperature, the residue was taken up in CHCl\textsubscript{3} (25 mL), filtered, the solvent removed by rotary evaporation and the crude product was purified by column chromatography (40% EtOAc in pentane) to yield the product 151 (1.3g, 53%) as a yellow solid. The data is consistent with that reported in the literature\textsuperscript{216}.

\textbf{1}^H\textit{NMR} (400 MHz, CDCl\textsubscript{3}) \(\delta\) 9.16 (s, 1H), 8.51 (dd, \(J = 7.9\), 1.2 Hz, 1H), 7.44 (td, \(J = 7.5\), 1.3 Hz, 1H), 7.33 (t, \(J = 7.6\) Hz, 1H), 7.16 (d, \(J = 7.5\) Hz, 1H), 3.54 (td, \(J = 6.8\), 3.5 Hz, 2H), 3.00 (t, \(J = 6.8\) Hz, 2H).

\textbf{13}C\textit{NMR} (101 MHz, CDCl\textsubscript{3}) \(\delta\) 193.9, 134.0, 132.7, 132.4, 132.0, 127.3, 127.1, 41.8, 27.9.

\textbf{HR-MS} (ESI) calcd for C\textsubscript{9}H\textsubscript{10}NS (M + H\textsuperscript{+}): 164.0534, found: 164.0542.
Mel (132 μL, 2.1 mmol, 1.1 equiv.) was added to a solution of thiolactam 151 (326 mg, 2.0 mmol, 1.0 equiv.) in acetone (5 mL) and stirred for 16 h. The resultant precipitate was collected by filtration, washed with Et₂O (10 mL) to afford the product 152 (595 mg, 98%) as a pale-yellow powder.

**¹H NMR** (400 MHz, DMSO-d$_6$) δ 7.98 (d, J = 7.6 Hz, 1H, Ar-H), 7.78 (td, J = 7.5, 1.3 Hz, 1H, Ar-H), 7.61 – 7.46 (m, 2H, Ar-H), 3.84 (t, J = 7.3 Hz, 2H, H$^1$), 3.11 (t, J = 7.3 Hz, 2H, H$^2$), 2.84 (s, 3H, H$^3$).

**¹³C NMR** (101 MHz, DMSO-d$_6$) δ 177.5 (MeS=C=N), 136.6 (Ar), 136.0 (Ar), 128.8 (Ar), 128.1 (Ar), 127.6 (Ar), 125.6 (Ar), 43.1 (C$^1$), 25.0 (C$^2$), 14.1 (C$^3$).

**IR** ν = 2971, 2163, 1614, 122, 772, 718, 699 cm$^{-1}$.

**m.p.** 196 °C {dec} (acetone/Et₂O).

A mass could not be obtained for this compound through a range of techniques.
A solution of amine 147 (246 mg, 1.0 mmol, 1.0 equiv.) in EtOH (5 mL) was added to a suspension of imino thioether 152 (305 mg, 1.0 mmol, 1.0 equiv.) in EtOH (5 mL) at room temperature and stirred for 4 h. The volatiles were removed to yield the amidine 153 (504 mg, 99%) as a pale yellow solid.

\textsuperscript{1}H NMR (400 MHz, DMSO-\textit{d}_6) \delta 9.69 – 9.55 (bs, 2H, NH), 7.88 (dd, \textit{J} = 11.4, 7.9 Hz, 2H, Ar-H), 7.69 (t, \textit{J} = 7.5 Hz, 1H, Ar-H), 7.56 – 7.33 (m, 4H, Ar-H), 7.03 (t, \textit{J} = 7.5 Hz, 1H, Ar-H), 3.63 (t, \textit{J} = 7.3 Hz, 2H, H\textsubscript{1}), 3.55 (t, \textit{J} = 6.6 Hz, 2H, H\textsubscript{3}), 3.12 (t, \textit{J} = 7.2 Hz, 2H, H\textsubscript{2}), 3.02 (t, \textit{J} = 6.6 Hz, 2H, H\textsubscript{4}).

\textsuperscript{13}C NMR (101 MHz, DMSO-\textit{d}_6) \delta 156.6 (N\textsubscript{C}=N), 140.8 (Ar), 139.1 (Ar), 138.8 (Ar), 134.0 (Ar), 130.1 (Ar), 128.8 (Ar), 128.7 (Ar), 128.5 (Ar), 127.3 (Ar), 126.5 (Ar), 122.3 (Ar), 101.2 (Ar-I), 42.2 (C\textsubscript{1} or C\textsubscript{3}), 40.1 (C\textsubscript{3} or C\textsubscript{1}), 37.5 (C\textsubscript{1}), 26.6 (C\textsubscript{2}).

IR \nu = 3094, 1646, 1605, 1556, 1335, 1012, 786, 741 cm\textsuperscript{-1}.

HR-MS (ES) calcd for C\textsubscript{17}H\textsubscript{18}IN\textsubscript{2} (M + H\textsuperscript{+}): 377.0515, found: 377.0517.

\textbf{m.p.} 228-230 °C (EtOH).
Using the procedure of Yoon Chi\textsuperscript{217}: acetyl chloride (300 μL, 3.8 mmol, 1.1 equiv.) was added to a solution of amine 147 (1 g, 3.5 mmol, 1.0 equiv.) and NEt\textsubscript{3} (0.7 mL, 5.3 mmol, 1.5 equiv.) in THF (10 mL) at 0 °C. The solution was stirred for 1 h at room temperature before the solvent was removed by rotary evaporation. The crude mixture was taken up in EtOAc (100 mL), washed with H\textsubscript{2}O (50 mL), brine (50 mL), dried over MgSO\textsubscript{4}, and the solvent removed by rotary evaporation. Purification by column chromatography (40% EtOAc in pentane) yielded the product (865 mg, 79%) as a colourless liquid. The data is consistent with that reported in the literature.\textsuperscript{217}

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.83 (dd, \textit{J} = 8.0, 1.2 Hz, 1H), 7.29 (td, \textit{J} = 7.4, 1.2 Hz, 1H), 7.22 (dd, \textit{J} = 7.7, 1.7 Hz, 1H), 6.92 (td, \textit{J} = 7.6, 1.8 Hz, 1H), 5.54 (s, 1H), 3.50 (q, \textit{J} = 6.7 Hz, 2H), 2.96 (t, \textit{J} = 7.0 Hz, 2H), 1.96 (s, 3H).

\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ 170.2, 141.7, 139.8, 130.1, 128.7, 128.5, 100.8, 40.0, 39.7, 23.5.

HR-MS (ES) calcd for C\textsubscript{10}H\textsubscript{13}INO (M + H\textsuperscript{+}): 290.0042, found: 290.0041.
Using the procedure of Brasholz\textsuperscript{77}; ethyl formate (7.5 mL, 93 mmol, 0.55 equiv.) was added dropwise to a freshly prepared solution of pent-5-enemagnesium bromide (1.0 M in THF, 169 mL, 168 mmol, 1.0 equiv.) at 0 °C. After the addition, the resultant mixture was heated to 40 °C for 4 h. The reaction mixture was cooled, quenched with sat. aqueous NH\textsubscript{4}Cl (300 mL), the phases were separated and the aqueous layer was further extracted with Et\textsubscript{2}O (2 x 300 mL). The combined organics were washed with brine (250 mL), dried over MgSO\textsubscript{4} and the solvent removed by rotary evaporation to yield the crude alcohol. This was purified by bulb-to-bulb distillation (75 °C, 0.1 mbar) to yield the product \textbf{161} (13 g, 92%) as a colourless liquid. The data is consistent with that reported in the literature.\textsuperscript{15}

\textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}) δ 5.80 (ddq, J = 17.0, 10.3, 6.8 Hz, 2H), 5.13 – 4.89 (m, 4H), 3.79 – 3.69 (m, 1H), 2.06 (tdt, J = 6.0, 2.8, 1.4 Hz, 4H), 1.87 – 1.83 (s, 1H), 1.61 – 1.37 (m, 8H).

\textbf{\textsuperscript{13}C NMR} (101 MHz, CDCl\textsubscript{3}) δ 138.8 (2C), 114.7 (2C), 71.8, 37.0 (2C), 33.8 (2C), 25.0 (2C).

\textbf{HR-MS} (Cl) calcd for C\textsubscript{11}H\textsubscript{19}O (M - H\textsuperscript{+}): 167.1430, found: 167.1432.
Using the procedure of Brasholz\textsuperscript{77}; H\textsubscript{2}SO\textsubscript{4} (4.2 M, 18.5 mL) was added dropwise to a solution of CrO\textsubscript{3} (5.0 g, 50.0 mmol, 0.7 equiv.) in H\textsubscript{2}O (7.4 mL) and stirred for 5 min. This was added to a solution of alcohol 161 (12.2 g, 72.6 mmol, 1.0 equiv.) in CH\textsubscript{2}Cl\textsubscript{2} (300 mL), and the biphasic solution was stirred for 4 h. The phases were separated and the aqueous layer was further extracted with Et\textsubscript{2}O (2 x 150 mL). The combined organics were filtered through Celite\textsuperscript{®}, dried over MgSO\textsubscript{4} and the solvent was removed by rotary evaporation. The crude ketone was purified by bulb-to-bulb distillation (55 °C, 0.1 mbar) to afford the product 162 (10 g, 84%) as a colourless liquid. The data is consistent with that reported in the literature.\textsuperscript{15}

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 5.88 – 5.71 (m, 2H), 5.05 – 4.91 (m, 4H), 2.39 (t, J = 7.4 Hz, 4H), 2.13 – 1.99 (m, 4H), 1.67 (p, J = 7.4 Hz, 4H).

\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ 211.0 , 138.1 (2C), 115.3 (2C), 42.1 (2C), 33.2 (2C), 22.9 (2C).

HR-MS (Cl) calcd for C\textsubscript{11}H\textsubscript{19}O (M + H\textsuperscript{+}): 167.1430, found: 167.1431.
Ketone 162 (5.3 g, 31.8 mmol, 1.0 equiv.) and PTSA (775 mg, 3.1 mmol, 0.1 equiv.) in PhMe (160 mL) and ethylene glycol (40 mL) were heated to 130 °C in a Dean-Stark apparatus for 16 h. The reaction was cooled to room temperature, diluted with CH₂Cl₂ (100 mL) and washed with sat. aqueous NaHCO₃ (75 mL), 1 M HCl (75 mL), brine (75 mL), dried over MgSO₄, and the solvent removed by rotary evaporation. The crude product was purified by column chromatography (10% Et₂O in pentane) to yield the product 163 (3.06 g, 46%) as a colourless liquid. The data is consistent with that reported in the literature.¹⁵

¹H NMR (400 MHz, CDCl₃) δ 5.80 (ddt, J = 17.0, 10.2, 6.7 Hz, 2H), 5.07 – 4.90 (m, 4H), 3.92 (s, 4H), 2.10 – 2.00 (m, 4H), 1.64 – 1.58 (m, 4H), 1.51 – 1.40 (m, 4H).

¹³C NMR (101 MHz, CDCl₃) δ 138.8 (2C), 114.7 (2C), 111.8 (2C), 65.1 (2C), 36.7 (2C), 34.0 (2C), 23.2 (2C).

HR-MS (CI) calcd for C₁₃H₂₃O₂ (M + H⁺): 211.1698, found: 211.1699.
Ozone was bubbled through a solution of diene 163 (2.1 g, 10 mmol, 1.0 equiv.) in CH$_2$Cl$_2$ (30 mL) at -78 °C until a blue colour persisted. After this the solution was sparged with argon until the colour had dissipated. The solvent was removed in vacuo and the residue re-dissolved in THF (30 mL), cooled to 0 °C, and LiAlH$_4$ (1.9 g, 50 mmol, 5.0 equiv.) was added in several portions. Once the addition was complete the ice bath was removed and the reaction stirred for a further 4 h at room temperature. The suspension was cooled to 0 °C and the following added sequentially in a dropwise manner; MeOH (12 mL), 2 M NaOH (12 mL) and H$_2$O (12 mL). The resultant white precipitate was filtered off and washed with EtOAc. The layers were separated, the organic layer was dried over MgSO$_4$ and solvent removed in vacuo to yield the crude product 167 as a colourless liquid (1.9 g, 88%). This product could be carried on to the next step crude, but an analytically pure sample can be isolated through chromatography (EtOAc). The data is consistent with that reported in the literature.$^{218}$

$^1$H NMR (400 MHz, CDCl$_3$) δ 3.94 (s, 4H), 3.65 (t, $J$ = 6.4 Hz, 4H), 1.68 – 1.60 (m, 4H), 1.60 – 1.54 (m, 4H), 1.50 – 1.39 (m, 6H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 111.7, 65.1 (2C), 62.9 (2C), 36.9 (2C), 33.0 (2C), 20.1 (2C).

HR-MS (EI) calcd for C$_{11}$H$_{22}$O$_4$ (M$^+$): 218.1518, found: 211.1520.
TsCl (3.5g, 18.3 mmol, 4.0 equiv.) was added to a solution of diol 167 (1.0 g, 4.6 mmol, 1.0 equiv.) in pyridine (10 mL) at -10 °C in a single portion. The reaction was stirred for 1 h and quenched with H₂O (50 mL), extracted with CH₃Cl (3 x 50 mL). The combined organic layers were dried over MgSO₄ and the solvent removed by rotary evaporation to yield the crude di-tosylate as a yellow oil. The crude intermediate was dissolved in DMF (12.5 mL) with potassium phthalimide (3.8 g, 20.5 mmol, 4.5 equiv.) and heated to 100 °C for 1 h. After cooling to room temperature, the solution was quenched with H₂O (50 mL). The solution was extracted with CH₃Cl (3 x 50 mL). The combined organic layers were dried over MgSO₄ and the solvent removed by rotary evaporation. The resultant residue was taken up in EtOH and cooled to -20 °C overnight. The precipitate was collected by filtration, and recrystallized from hot EtOH to yield the product 169 (810 mg, 37% two steps) as a white crystalline material.

**1H NMR** (400 MHz, CDCl₃) δ 7.83 (dd, J = 5.4, 3.1 Hz, 4H, Ar-H), 7.70 (dd, J = 5.5, 3.0 Hz, 4H, Ar-H), 3.90 (s, 4H, H⁵), 3.67 (t, J = 7.2 Hz, 4H, H¹), 1.73 – 1.57 (m, 8H, H² and H⁴), 1.47 – 1.35 (m, 4H, H³).

**13C NMR** (101 MHz, CDCl₃) δ 168.5 (4C, NC=O), 133.9 (4C, Ar), 132.3 (4C, Ar), 123.3 (4C, Ar), 111.4 (ROCOR), 65.1 (2C, C⁵), 38.0 (2C, C⁴), 36.8 (2C, C⁴), 28.9 (2C, C²), 21.2 (2C, C³).

**IR** ν= 1769, 1704, 1431, 1370, 1401, 1047, 713 cm⁻¹.

**m.p.** 148-150 °C (EtOH).

Di-phthalimide 169 (476 mg, 1.0 mmol, 1.0 equiv.) was suspended in EtOH (10 mL) and hydrazine hydrate (60%, 200 μL, 2.2 mmol, 2.2 equiv.) was added and heated to 80 °C for 2 h. The mixture was quenched with 2 M NaOH (10 mL) and extracted with CHCl₃ (3 x 25 mL). The combined organic layers were dried over MgSO₄ and the solvent removed in vacuo to yield the crude diamine as a yellow oil (190 mg, 87%) which did not require purification.

\[ \text{HR-MS (Cl)} \text{ calcd for C}_{13}\text{H}_{28}\text{N}_{3}\text{O}_{2} (M + CH}_{3}\text{CN + H}^+): 258.2176, \text{ found: } 258.2175. \]

IR \( \nu = 3352, 1571, 1313, 1047, 948 \text{ cm}^{-1}. \)
Ketal **169** (47 mg, 0.1 mmol, 1.0 equiv.) and I₂ (3 mg, 0.01 mmol, 0.1 equiv.) were stirred in acetone (5 mL) at room temperature for 16 h. The acetone was removed by rotary evaporation and the residue taken up in CH₂Cl₂ (10 mL). The solution was washed with 15% aqueous Na₂S₂O₅ (10 mL), H₂O (10 mL), brine (10 mL), dried over MgSO₄, and the solvent removed by rotary evaporation to afford the ketone **171** (37 mg, 85%) as a pale yellow solid, which did not require further purification.

**¹H NMR** (400 MHz, CDCl₃) δ 7.82 (dd, J = 5.5, 3.1 Hz, 4H, Ar-H), 7.70 (dd, J = 5.4, 3.0 Hz, 4H, Ar-H), 3.67 (t, J = 6.9 Hz, 4H, H¹), 2.45 (t, J = 7.1 Hz, 4H, H⁴), 1.77 – 1.52 (m, 8H, H² and H³).

**¹³C NMR** (101 MHz, CDCl₃) δ 210.0 (C=O), 168.5 (4C, Phth C=O), 134.0 (4C, Ar), 132.2 (4C, Ar), 123.3 (4C, Ar), 42.1 (2C, C¹), 37.6 (2C, C¹'), 28.1 (2C, H² or H³), 20.9 (2C, H² or H³).

**IR** ν= 1770, 1701, 1463, 1394, 1367, 1048, 719, 710 cm⁻¹.

**m.p.** 89-90 °C (EtOH).

**HRMS** (ES) calcd for C₂₅H₂₅N₂O₅ (M + H⁺): 433.1763, found: 433.1772.
1,7-Diazaspiro[5.5]undecane – 53-A

TsCl (3.5 g, 18.3 mmol, 4.0 equiv.) was added to a solution of diol 167 (1.0 g, 4.6 mmol, 1.0 equiv.) in pyridine (10 mL) at -10 °C in a single portion. The reaction was stirred for 1 h and quenched with H₂O (50 mL), extracted with CH₃Cl (3 x 50 mL). The combined organic layers were dried over MgSO₄ and the solvent removed by rotary evaporation to yield the crude di-tosylate as a yellow oil. The crude intermediate was dissolved in DMF (12.5 mL) with NaN₃ (1.3 g, 20.5 mmol, 4.5 equiv.) and heated to 80 °C for 1 h. After cooling to room temperature, the reaction was quenched with H₂O (50 mL). This was extracted with CH₃Cl (3 x 50 mL). The combined organic layers were dried over MgSO₄ and the solvent removed by rotary evaporation. The crude product was taken up in MeOH (20 mL) and flushed with Argon. 10 wt.% Pd/C (100 mg) was added and the suspension is stirred under an atmosphere of hydrogen (1 atm) for 4 h. The catalyst was removed by filtration, and the solvent removed by rotary evaporation. The crude product 53-A (289 mg, 41%) was afforded as a colourless liquid and sufficiently pure (>95%) but can be purified further as described previously. The analytical data was identical to previous methods described within this report.
Using the procedure of Majetich\textsuperscript{219}; TBAF (1 M, 1 mL, 1 mmol, 0.16 equiv.) was added to a suspension of 4 Å MS (1.0 g) and methyl cinnamate (175) (1.0 g, 6.2 mmol, 1.0 equiv.) in DMF (10 mL). To this, a solution of HMPA (3.2 mL, 17.3 mmol, 2.8 equiv.), Allyltrimethylsilane (3.0 mL, 18.9 mmol, 3.0 equiv.) and DMF (20 mL) was added dropwise at room temperature and stirred for 30 minutes. After this time, MeOH (9 mL) and 12 M HCl (1 mL) were added and stirred for a further 15 minutes. The resultant solution was diluted with H\textsubscript{2}O (200 mL), filtered and extracted with CH\textsubscript{2}Cl\textsubscript{2} (2 x 250 mL). The combined organic layers were washed with H\textsubscript{2}O (2 x 150 mL), brine (150 mL), dried over MgSO\textsubscript{4} and solvent removed by rotary evaporation to yield the crude reaction mixture. Purification by column chromatography (5% EtOAc in pentane) afforded the product 175 (689 mg, 55%) as colourless oil. The data is consistent with that reported in the literature.\textsuperscript{80}

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 7.30 (m, 2H), 7.20 (m, 3H), 5.70-5.60 (m, 1H), 5.03-4.96 (m, 2H), 3.58 (s, 3H), 3.25-3.18 (m, 1H), 2.75-2.55 (m, 2H), 2.42-2.38 (m, 2H).

\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \( \delta \) 172.9, 143.7, 136.0, 128.5 (2C), 127.5 (2C), 126.7, 117.0, 51.6, 41.9, 40.7, 40.5.

HR-MS (CI) calcd for C\textsubscript{12}H\textsubscript{15}O\textsubscript{2} (M + H\textsuperscript{+}): 191.1067, found: 191.1067.
3-Phenylhex-5-enoic acid -176

LiOH·H₂O (200 mg, 4.8 mmol, 1.9 equiv.) was added to a solution of methyl ester 175 (500 mg, 2.5 mmol, 1.0 equiv.) in THF/H₂O (3:1 25 mL) and stirred at room temperature for 16 h. The reaction was acidified to pH 1 with 1 M HCl, extracted with Et₂O (3 x 25 mL). The combined organic layers were dried over MgSO₄ and solvent removed by rotary evaporation to yield the crude product, which was purified by column chromatography (20% CH₂Cl₂ in Et₂O +1% AcOH) to yield the product 176 (460 mg, 98%) as a colourless liquid. The data is consistent with that reported in the literature.²²⁰

¹H NMR (400 MHz, CDCl₃) δ 7.33-7.19 (m, 5H), 5.71-5.61 (m, 1H), 5.01 (m, 2H), 3.24-3.17 (m, 1H), 2.77-2.59 (m,2H), 2.41 (m, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 178.3, 143.42 , 135.8, 128.6 (2C), 127.5 (2C), 126.8 , 117.2, 41.5, 40.7, 40.2.

HR-MS (Cl) calcd for C₁₂H₁₅O₂ (M + H⁺): 191.1067, found: 191.1074.
**N-Methoxy-N-methyl-3-phenylhex-5-enamide - 177**

Acid 176 (380 mg, 2.0 mmol, 1.0 equiv.), NHMe(OMe)·HCl (291 mg, 3.0 mmol, 1.5 equiv.), EDC·HCl (573 mg, 3.0 mmol, 1.5 equiv.) and DMAP (366 mg, 3.0 mmol, 1.5 equiv.) in CH₂Cl₂ (12 mL) were stirred at room temperature for 16 h. The solvent was removed by rotary evaporation, the resultant slurry was taken up in EtOAc (25 mL) and washed sequentially with H₂O (25 mL), sat. aqueous NaHCO₃ (25 mL), brine (25 mL), dried over MgSO₄ and the solvent removed by rotary evaporation. Purification by column chromatography (20% EtOAc in pentane) afforded the product 177 (246 mg, 53%) as a colourless oil.

**¹H NMR** (400 MHz, CDCl₃) δ 7.34 – 7.28 (m, 2H, Ar-H), 7.27 – 7.18 (m, 3H, Ar-H), 5.70 (ddt, J = 17.1, 10.2, 7.0 Hz, 1H, H⁴), 5.05 – 4.99 (m, 1H, H⁵a), 4.99 – 4.94 (m, 1H, H⁵b), 3.57 (s, 3H, NOMe), 3.39 – 3.30 (m, 1H, H²), 3.12 (s, 3H, NMe), 2.75-2.77 (m, 2H, H¹), 2.44-2.47 (m, 2H, H³).

**¹³C NMR** (101 MHz, CDCl₃) δ 173.0 (C=O), 143.4 (Ar), 136.4 (C⁴), 128.3 (2C, Ar), 127.6 (2C, Ar), 126.3 (Ar), 116.5 (C⁵), 61.1 (NOMe), 41.1 (C²), 40.4 (C³), 38.0 (C¹), 32.1 (NMe).

**IR** ν = 1655, 1543, 1383, 994, 761, 699 cm⁻¹.

**HR-MS** (ESI) calcd for C₁₄H₂₀O₂N (M + H⁺): 234.1494, found: 234.1480.
Freshly prepared solution of pent-5-enemagnesium bromide (1.0 M in THF, 1.7 mL, 1.7 mmol, 1.0 equiv.) was added to a solution of Weinreb amide 177 (396 mg, 1.7 mmol, 1.0 equiv.) in THF (10 mL) at -78 °C. Stirring at this temperature was continued for 2 h before the reaction was quenched with sat. aqueous NH₄Cl (15 mL). The phases were separated and the aqueous layer was further extracted with Et₂O (2 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO₄ and solvent removed by rotary evaporation to yield the crude reaction mixture. Purification by column chromatography (10% Et₂O in pentane) afforded the product 178 (282 mg, 73%) as colourless oil.

$^{1}$H NMR (400 MHz, CDCl₃) δ 7.32 – 7.25 (m, 2H, Ar-H), 7.22 – 7.13 (m, 3H, Ar-H), 5.67 (m, 2H, H² and H⁸), 5.19 – 4.85 (m, 4H, H¹ and H¹⁰), 3.33 – 3.22 (m, 1H, H⁷), 2.80 – 2.58 (m, 2H, H⁶), 2.45 – 2.15 (m, 4H, H⁶ and H⁸), 1.99 – 1.85 (m, 2H, H³), 1.65 – 1.41 (m, 2H, H⁴).

$^{13}$C NMR (101 MHz, CDCl₃) δ 209.7 (C=O), 144.3 (Ar), 138.1 (C² or C⁹), 136.4 (C² or C⁹), 128.6 (2C, Ar), 127.6 (2C, Ar), 126.5 (Ar), 116.8 (C¹ or C¹⁰), 115.2 (C¹ or C¹⁰), 48.9 (C⁶), 42.8 (C⁵), 40.9 (C⁵), 40.8 (C⁷), 33.1 (C³), 22.7 (C⁴).

4-(2-(4-Hydroxybutyl)-1,3-dioxolan-2-yl)-3-phenylbutan-1-ol - 180

Using the procedure described for 163; ketone 178 (143 mg, 0.5 mmol) gave the ketal 179 as an inseparable mixture of product and starting material (6:4) Therefore, the crude product was used without further purification.

Using the procedure as described for 167; the crude ketal diene gave the product 180 (63 mg, 42% over two steps) as a colourless oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.31 – 7.26 (m, 2H, Ar-H), 7.23 – 7.15 (m, 3H, Ar-H), 3.94 – 3.80 (m, 4H, H$^9$ and H$^{10}$), 3.60 – 3.38 (m, 4H, H$^1$ and H$^6$), 2.94 (ddt, $J = 9.5$, 7.4, 5.3 Hz, 1H, H$^6$), 2.09 (dd, $J = 14.6$, 7.3 Hz, 1H, H$^{5a}$), 2.03 – 1.92 (m, 2H, H$^7$), 1.86 – 1.75 (m, 1H, H$^{5a}$), 1.59 (s, 1H, OH), 1.56 – 1.31 (m, 6H, H$^2$, H$^3$ and H$^4$), 1.25 (s, 1H, OH).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 146.3 (Ar), 128.6 (2C, Ar), 127.7 (2C, Ar), 126.2 (Ar), 111.8 (ROCOR), 64.7 (C$^9$ or C$^{10}$), 64.6 (C$^9$ or C$^{10}$), 62.8 (C$^1$ or C$^8$), 61.0 (C$^1$ or C$^8$), 43.0 (C$^5$), 40.9 (C$^7$), 37.8 (C$^6$), 37.2 (C$^4$), 32.9 (C$^2$), 20.1 (C$^3$).

IR ν = 3363, 1454, 1047, 702 cm$^{-1}$.

HRMS (EI) calcd for C$_{17}$H$_{26}$O$_4$ (M$^+$): 294.1831, found: 294.1827.
4-Phenyl-1,7-diazaspiro[5.5]undecane – 182-A

Using the procedure as described for 53-A; the ketal diol 180 (50 mg, 0.2 mmol) gave the product 182-A (22 mg, 58% over two steps) as a colourless oil.

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.33 – 7.27 (m, 2H, Ar-H), 7.23 – 7.16 (m, 3H, Ar-H), 3.12 (bs, 2H, H$_1$), 2.94 – 2.87 (m, 1H, H$_3$), 2.84 (bs, 2H, H$_3$), 2.12 – 2.06 (m, 1H, H$_{4a}$), 1.90 (bs, 2H, NH), 1.89 – 1.82 (m, 1H, H$_{2a}$), 1.80 – 1.71 (m, 2H, H$_6$), 1.70 – 1.61 (m, 3H, H$_6$ and H$_{2b}$), 1.57 – 1.47 (m, 2H, H$_7$).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 146.3 (Ar-C$_3$), 128.6 (2C, Ar), 127.0 (2C, Ar), 126.4 (Ar-C$_2$), 63.0 (RHN$_2$NHR), 41.1 (3C, C$_1$ overlapping C$_4$ and C$_8$), 37.9 (C$_3$), 33.5 (C$_2$), 27.9 (C$_7$), 21.1 (C$_7$).

IR $\nu =$ 3275, 1775, 1452, 757 cm$^{-1}$.

HR-MS (EI) calcd for C$_{15}$H$_{22}$N$_2$ ($M^+$): 231.1861, found: 231.1861.
Methyl 2-(1,3-dichloropropan-2-yldene)hydrazine-1-carboxylate - 189

Using the procedure of Fairlamb, 1,3-dichloroacetone (187) (14.0 g, 110 mmol, 1.0 equiv.) was added in 3 portions to a solution of methyl hydrazinocarboxylate (9.8 g, 108 mmol, 1.0 equiv.) in MeOH (200 mL) at room temperature. The reaction was stirred for 4 h before the solution was concentrated to approx. 20 mL by rotary evaporation. The resultant precipitate was collected by filtration and washed with Et₂O (3 x 50 mL) to afford the product 189 (9.7 g 46%) as a white solid. The data is consistent with that reported in the literature. 83

\[^{1}\text{H NMR}\ (400 \text{ MHz, CDCl}_3) \delta 8.38 (s, 1H), 4.32 (s, 2H), 4.18 (s, 2H), 3.88 (s, 3H).\]

\[^{13}\text{C NMR}\ (101 \text{ MHz, CDCl}_3) \delta 153.7, 143.7, 53.6, 45.9, 33.3.\]

\[^{\text{HRMS (El)}}\ (\text{calcd for C}_5\text{H}_8\text{N}_2\text{O}_2\text{Cl}_2 (M^+)): 197.9963, \text{ found: 197.9971.}\]
Using the procedure of Fairlamb, P(OEt)$_3$ (11.2 mL, 64 mmol, 2.2 equiv.) was added dropwise to a suspension of dichloro hydrazinecarboxylate 189 (5.8 g, 29 mmol, 1.0 equiv.) in PhMe (50 mL). Once the addition was complete, the resultant mixture was heated to 130 °C for 16 h. The solvent was removed by rotary evaporation, the residue taken up in H$_2$O (40 mL), and the product extracted with EtOAc (3 x 20 mL). The volatiles were removed by rotary evaporation and high vaccum (1 x 10$^{-2}$ mbar) for 16 h. The resultant yellow liquid was dissolved in acetone (20 mL), and 3 M HCl (20 mL) was added. The reaction mixture was stirred for 6 h before being diluted with H$_2$O (40 mL), and the acetone removed by rotary evaporation. The product was extracted with CHCl$_3$ (3 x 20 mL), which was dried over MgSO$_4$ and the solvent removed by rotary evaporation to afford the product 190 (7.6 g, 80%) as a yellow liquid. The product did not require further purification. The data is consistent with that reported in the literature.

$^1$H NMR (400 MHz, CDCl$_3$) δ 4.18 – 4.06 (m, 8H), 3.32 (d, $J_{HP} = 22.9$ Hz, 4H), 1.31 (t, $J = 7.0$ Hz, 12H).

$^{13}$C NMR (101 MHz,) δ 193.9, 63.2 – 62.3 (m, 4C), 43.3 (d, $J_{CP} = 126.4$ Hz, 2C), 16.8 – 15.5 (m, 4C).

$^{31}$P NMR (162 MHz, CDCl$_3$) δ 18.90.

HRMS (EI) calcd for C$_{11}$H$_{24}$O$_7$P$_2$ (M$^+$): 330.0997, found: 330.0988.
(S,E)-N-Benzylidene-2-methylpropane-2-sulfinamide - 192

Benzaldehyde (191) (12.6 mL, 125 mmol, 1.25 equiv.), (R)-2-methylpropane-2-sulfinamide (9.7 g, 80 mmol, 1.0 equiv.), PTSA (1.05 g, 4 mmol, 5 mol%) and MgSO₄ (50 g) in CH₂Cl₂ (150 ml) were stirred at room temperature for 16 h. After this time, the solids were removed by filtration and the solvent removed by rotary evaporation. The crude product purified by column chromatography (10% EtOAc in pentane) to yield the product 192 (12.5 g, 75%) as a colourless liquid. The data is consistent with that reported in the literature. ⁸⁵

¹H NMR (400 MHz, CDCl₃) δ 8.59 (s, 1H), 7.85 (d, J = 6.6 Hz, 2H), 7.56 – 7.43 (m, 3H), 1.27 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ 162.9, 134.3, 132.5, 129.5, 129.1, 57.9, 22.8

[α]D ²² : +99.0 (c, 1.0, CHCl₃), {lit.²²¹ [α]D ²⁵ : +97.5 (c, 1.15, CHCl₃)}

Allylmagnesium bromide (1.0 M in Et$_2$O, 18.25 mL, 18.25 mmol, 2.0 equiv.) was added dropwise to a solution of sufinimine 192 (1.9 g, 9.13 mmol, 1.0 equiv.) in CH$_2$Cl$_2$ (50 mL) at -78°C. After 30 minutes of stirring with cooling, the reaction was quenched with sat aq NH$_4$Cl (50 mL). The phases were separated, with the aqueous layer being further extracted with CH$_2$Cl$_2$ (2 x 50 mL). The combined organic layers were washed with brine, dried over MgSO$_4$, and the solvent removed by rotary evaporation. The crude product was purified by column chromatography (25% EtOAc in pentane) to give the product 193 (2.14 g, 93%) as a white solid, as a single diastereomer. The data is consistent with that reported in the literature.$^{85}$

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.37 – 7.27 (m, 5H), 5.73 (dddd, $J$ = 16.5, 10.3, 8.3, 5.8 Hz, 1H), 5.23 – 5.12 (m, 2H), 4.47 (ddd, $J$ = 8.1, 5.5, 2.4 Hz, 1H), 3.69 – 3.62 (m, 1H), 2.60 (dtt, $J$ = 14.1, 5.6, 1.5 Hz, 1H), 2.48 (dt, $J$ = 14.1, 8.3 Hz, 1H), 1.19 (s, 9H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 141.9, 134.3, 128.6, 127.8, 127.6, 119.4, 57.2, 55.8, 43.5, 22.7.

$\lbrack \alpha \rbrack$$_D^{22}$ : +143.0 (c, 1.0, CHCl$_3$)

HRMS (El) calcd for C$_{14}$H$_{22}$NOS (M + H$^+$): 252.1422, found: 252.1410.
Using the procedure reported by Corte of Bristol-Myers Squibb; conc. HCl (1 mL) was added to a solution of sulfinamide (2.1 g, 8.4 mmol, 1.0 equiv.) in MeOH (80 mL) at 0 °C. The solution was stirred for 4 h, before the volatiles were removed by rotary evaporation. The resultant solid was dissolved in CH₂Cl₂ (80 mL) and cooled to 0 °C. NEt₃ (4.5 mL, 32 mmol, 3.8 equiv.) was added dropwise, followed by the addition of Boc₂O (2.0 g, 9.2 mmol, 1.1 equiv.). The solution was stirred overnight at room temperature before being diluted with H₂O (80 mL). The phases were separated, and the aqueous layer being further extracted with CH₂Cl₂ (80 mL), the combined organics were washed with brine (50 mL), dried over MgSO₄, and the solvent was removed by rotary evaporation. The crude product was purified by column chromatography (0 → 50% EtOAc in pentane) to yield the product (1.3 g, 64%) as a white solid. The data is consistent with that reported in the literature.

**¹H NMR (400 MHz, CDCl₃)** δ 7.37 – 7.32 (m, 2H), 7.26 (s, 3H), 5.70 (ddt, J = 17.2, 10.2, 7.0 Hz, 1H), 5.16 – 5.06 (m, 2H), 4.88 (s, 1H), 4.75 (s, 1H), 2.54 (t, J = 6.8 Hz, 2H), 1.43 (s, 9H).

**¹³C NMR (101 MHz, CDCl₃)** δ 155.3, 142.6, 134.1, 128.6, 127.2, 126.3, 118.3, 79.6, 54.2, 41.3, 28.5.

[α]₀²² : +42.0 (c, 1.0, CHCl₃), {lit.²²³ [α]₀²⁴ : +45 (c, 1.00, CHCl₃)}.

*A mass could not be obtained for this compound through a range of techniques.*
Ozone was bubbled through a solution of homoallylic amine 194 (157 mg, 0.64 mmol) and Sudan III (trace) in CH$_2$Cl$_2$/MeOH (1:1 60 mL) at -78 ºC until the solution became colourless. The solution was sparged with oxygen for 10 min, followed by argon for 10 min. NEt$_3$ (265 μL, 1.9 mmol, 3.0 equiv.) was added in a single portion and the reaction was allowed to slowly warm to rt. The volatiles were removed by rotary evaporation, and the resultant solid was purified by column chromatography (2% MeOH in CH$_2$Cl$_2$) to yield the product 195 (143 mg, 90%). The data is consistent with that reported in the literature.$^{224}$

$^1$H NMR (400 MHz, CDCl$_3$) δ 9.71 (t, $J$ = 2.0 Hz, 1H), 7.36 – 7.21 (m, 5H), 5.21 – 5.03 (m, 2H), 2.90 (tdd, $J$ = 17.1, 8.8, 6.1 Hz, 2H), 1.39 (s, 9H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 200.2, 155.2, 141.1, 129.0, 127.9, 126.4, 80.2, 50.0, 28.4.

$[\alpha]_D$: $^{22}$ +70.0 (c, 1.0, CHCl$_3$), $^{25}$ [lit.$^{225}$ $[\alpha]_D$: $^{25}$ +27.5 (c, 0.08, CHCl$_3$)]

HRMS (El) calcd for C$_{14}$H$_{18}$NO$_3$ (M - H$^+$): 248.1287, found: 248.1297.
Di-tert-butyl ((1R,3E,6E,9R)-5-oxo-1,9-diphenylnona-3,6-diene-1,9-diyl)dicarbamate -

K$_2$CO$_3$ (207 mg, 1.5 mmol, 3.0 equiv.) was added in a single portion to a solution of aldehyde 195 (126 mg, 0.5 mmol, 1.8 equiv.), and diphosphate 190 (93 mg, 0.28 mmol, 1.0 equiv.) in THF/H$_2$O (10 mL, 1:1) at room temperature. The resultant solution was stirred for 16 h before being quenched with brine (20 mL) and extracted with EtOAc (3 x 20 mL). The organic layers were washed with brine (25 mL), dried over MgSO$_4$, the solvent removed in vacuo, and the crude product purified by column chromatography (2% MeOH in CH$_2$Cl$_2$) followed by a second column chromatography (30% EtOAc in PhMe) to afford the product 196 (108 mg, 70%) as a colourless oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.45 – 7.25 (m, 10H, Ar-H), 6.72 (dt, $J = 14.8$, 7.0 Hz, 2H, H$^2$), 6.30 (d, $J = 15.7$ Hz, 2H, H$^1$), 4.97 – 4.77 (m, 6H, H$^4$ and NH), 2.77 – 2.67 (m, 4H, C$^3$), 1.43 (s, 18H, Boc).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 194.4 (C=O), 155.18 (4C, Boc C=O overlapping C$^2$), 143.0 (2C, Ar-C$^4$), 131.2 (2C, C$^1$), 128.9 (4C, Ar), 127.7 (2C, Ar), 126.4 (4C, Ar), 79.9 (2C, Boc O(C(Me)$_3$)$_3$, 54.0 (2C, C$^4$), 40.0 (2C, C$^3$), 28.5 (6C, Boc CMe$_3$).

IR ν= 3354, 1682, 1617, 1247, 1164 cm$^{-1}$.

[$\alpha$]$^D_{22}$: +90.0 (c, 0.2, CHCl$_3$)

HRMS (ES) calcd for C$_{31}$H$_{41}$N$_2$O$_5$ (M + H$^+$): 521.3015, found: 521.3012.
Diene 196 (50 mg, 0.1 mmol) and Pd/C (10 mg) in MeOH (5 mL) was a stirred under an atmosphere of H₂ (1 atm) for 4 h before the catalyst was removed by filtration and the solvent removed by rotary evaporation. The resultant residue was dissolved in CH₂Cl₂ (5 mL) and cooled to 0 °C. TFA (500 μL) was added dropwise, the cooling bath was removed and the solution was stirred at rt for 16 h. The solution was diluted with CH₂Cl₂ (15 mL), washed with sat. aqueous NaHCO₃ (2 x 10 mL), brine (10 mL), dried over MgSO₄ and the volatiles removed by rotary evaporation. The crude product was purified by preparative TLC (3% MeOH in CH₂Cl₂) to afford the aminal 198-A (22 mg, 76% over two steps) as a white foam.

¹H NMR (400 MHz, CDCl₃) δ 7.47 – 7.40 (m, 4H, Ar-H), 7.39 – 7.31 (m, 4H, Ar-H), 3.83 – 3.66 (m, 2H, H¹), 2.35 – 2.02 (m, 2H, NH), 1.83 – 1.60 (m, 12H, H², H³ and H⁴).

¹³C NMR (101 MHz, CDCl₃) δ 145.5 (Ar-C¹), 128.6 (2C, Ar), 127.3 (Ar), 127.1 (2C, Ar), 67.9 (RHN-CNHR), 54.4 (C¹), 37.9 (C²), 34.5 (C³), 20.5 (C⁴).

IR ν= 3332, 3027, 2926, 1450, 756 cm⁻¹.

[α]D²²: +34.0 (c, 0.1, CHCl₃)

2-Nitrobenzaldehyde (238) (7.0 g, 46 mmol, 1.0 equiv.), NaN₃ (9.0 g, 138 mmol 3.0 equiv.) and NEt₃ (1.3 mL, 9.2 mmol, 0.2 equiv.) in DMF (60 mL) were stirred at 60 °C for 96 h. The reaction mixture is cooled, diluted with H₂O (150 mL), extracted with CH₂Cl₂ (3 x 150 mL). The combined organics were washed with H₂O (2 x 150 mL), 5% LiCl solution (4 x 100 mL) and brine (150 mL), dried over MgSO₄ and the solvent removed in vacuo. The crude product is purified by column chromatography (10% EtOAc in pentane) to yield the product 239 as a pale yellow crystalline solid (5 g, 74%). The data is consistent with that reported in the literature.¹²¹

¹H NMR (400 MHz, CDCl₃) δ 10.34 (s, 1H), 7.88 (dd, J = 7.8, 1.7 Hz, 1H), 7.66 – 7.54 (m, 1H), 7.29-7.23 (m, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 188.7, 143.0, 135.5, 129.1, 127.1, 125.0, 119.2.

A mass could not be obtained for this compound through a range of techniques.
Using general procedure E; α-azidobenzaldehyde (239) gave the spiro-biquinoline 235 (185 mg, 74%), as a colourless crystalline solid after purification by chromatography on silica (50% CH₂Cl₂ in pentane).

**¹H NMR** (400 MHz, CDCl₃) δ 7.11 – 6.96 (m, 4H, H³ and H⁶), 6.70 (td, J = 7.4, 1.2 Hz, 2H, H⁴), 6.48 (dd, J = 7.9, 1.2 Hz, 2H, H⁵), 4.27 (s, 2H, NH), 2.91 (t, J = 6.8 Hz, 4H, H²), 2.10 – 1.90 (m, 4H, H¹).

**¹³C NMR** (101 MHz, CDCl₃) δ 142.6 (2C, Ar-N), 129.2 (2C, H³ or H⁶), 127.24 (2C, H³ or H⁶), 120.2 (2C, Ar-C²), 117.8 (2C, H⁴), 114.8 (2C, H⁵), 63.5 (RHN-CNR), 33.3 (2C, C¹), 23.4 (2C, C²).

**m.p.** 131-132 °C (CH₂Cl₂).

**IR** ν= 3372, 3047, 1600, 1488, 1468, 743 cm⁻¹.

**HR-MS** (ESI) calcd for C₁₇H₁₉N₂ (M + H⁺): 251.1548, found: 251.1546.

**Microanalysis**, calcd for C₁₇H₁₈N₂: C, 81.56; H, 7.25; N, 11.19; Found: C, 81.44; H, 7.37; N, 11.08.
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Using the procedure of Schlosser\textsuperscript{118}: sec-BuLi (1.3 M in hexanes, 15 mL, 20 mmol, 1.0 equiv.) was added dropwise to a solution of 1-fluoronaphthalene (247) (2.6 mL, 20 mmol, 1.0 equiv.) in THF (40 mL) at −78 \(^\circ\)C. The solution was stirred at this temperature for 2 h before the addition of DMF (3.2 mL). The reaction was stirred for 5 min before dilution with Et\(_2\)O (50 mL), quenched with NH\(_4\)Cl (50 mL), the phases were separated and the aqueous layer was further extracted with Et\(_2\)O (2 x 50 mL). The combined organics were dried over MgSO\(_4\), and the solvent removed by rotary evaporation. The crude product was purified by column chromatography (5% EtOAc in pentane) to yield the aldehyde 248 (2.5 g, 71%) as a white crystalline solid. The data is consistent with that reported in the literature.\textsuperscript{226}

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 10.56 (d, \(J = 0.8\) Hz, 1H), 8.20 (dd, \(J = 8.3, 1.2\) Hz, 1H), 7.87 – 7.76 (m, 2H), 7.71 – 7.57 (m, 3H).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 187.1 (d, \(J_{CF} = 8.7\) Hz), 163.1 (d, \(J_{CF} = 267.7\) Hz), 138.0 (d, \(J_{CF} = 6.2\) Hz), 130.1, 127.9 (d, \(J_{CF} = 3.2\) Hz), 127.3, 124.3 (d, \(J_{CF} = 4.3\) Hz), 123.2 (d, \(J_{CF} = 15.5\) Hz), 122.0 (d, \(J_{CF} = 6.1\) Hz), 121.9 (d, \(J_{CF} = 2.1\) Hz), 118.9 (d, \(J_{CF} = 5.9\) Hz).

\(^{19}\)F NMR (377 MHz, CDCl\(_3\)) \(\delta\) -127.3.

HR-MS (EI) calcd for C\(_{11}\)H\(_7\)FO (M\(^+\)): 174.0481, found: 174.0481.
1-Azido-2-naphthaldehyde – 249

Using a modified procedure of Boswell and Licause;\textsuperscript{119} 1-fluoro-2-naphthaldehyde 248 (2.4 g, 13.9 mmol, 1.0 equiv.) in anhydrous DMF (21 mL) was cooled to 0 °C under argon. NaN\textsubscript{3} (1.8 g, 27.7 mmol, 2.0 equiv.) was added in one portion and the resultant solution was heated to 60 °C with constant argon sparging for 2 h. After this time, the mixture was cooled to room temperature, diluted with H\textsubscript{2}O (50 mL), and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed sequentially with 5% aqueous LiCl (3 x 50 mL) and brine (50 mL) and dried over MgSO\textsubscript{4}. The solvent was rotary evaporated to give the azide 249 (2.4 g, 87%) without need for further purification as a yellow crystalline solid. The data is consistent with that reported in the literature.\textsuperscript{119}

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 10.54 (s, 1H), 8.41 – 8.33 (m, 1H), 7.92 – 7.84 (m, 2H), 7.77 (d, \(J = 8.6\) Hz, 1H), 7.71 – 7.61 (m, 2H).

\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ 189.8, 140.4, 137.1, 129.8, 128.70, 128.1, 127.7, 126.5, 125.5, 125.0, 124.0.

HR-MS (El) calcd for C\textsubscript{11}H\textsubscript{7}N\textsubscript{3}O (M\textsuperscript{+}): 197.0589; found: 197.0582;

Microanalysis, calcd for C\textsubscript{11}H\textsubscript{7}N\textsubscript{3}O: C, 67.00; H, 3.58; N, 21.31; Found: C, 66.78; H, 3.39; N, 21.12.
Using the procedure of Thummel;\textsuperscript{120} 7-methyl-8-nitroquinoline (250) (5.0 g, 26 mmol, 1.0 equiv.), DMF.DMA (4.2 mL, 39 mmol, 1.5 equiv.) in DMF (2.5 mL) were heated to 140 °C for 16 h. The reaction was then cooled to 0 °C and diluted with H$_2$O (10 mL). The precipitate was removed by filtration and washed with H$_2$O (10 mL). The solid was dissolved in THF/H$_2$O (1:1 350 mL) and NaIO$_4$ (20.0 g, 94 mmol, 3.6 equiv.) was added in one portion, the resultant suspension was stirred for 2 hours before being filtered. The solution was diluted with EtOAc (200 mL), the phases were separated, the organic phase were washed with sat. aqueous NaHCO$_3$ (2 x 100 mL), brine (100 mL), dried over MgSO$_4$, and the solvent removed by rotary evaporation. The crude product was purified by column chromatography (80% CH$_2$Cl$_2$ in pentane) to afford the product 252 (3.0 g, 56%) as a white solid at a purity of 90% with an impurity that could not be identified. The data is consistent with that reported in the literature.\textsuperscript{120}

$^1$H NMR (400 MHz, CDCl$_3$) δ 10.24 (d, $J = 0.5$ Hz, 1H), 9.12 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.32 (dd, $J = 8.4, 1.7$ Hz, 1H), 8.09 (d, $J = 2.7$ Hz, 2H), 7.68 (dd, $J = 8.4, 4.2$ Hz, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 186.4, 153.7, 152.3, 136.0, 132.4, 130.6, 125.7, 125.0, 123.7, 122.2.

HR-MS (ES) calcd for C$_{10}$H$_7$N$_2$O$_3$ (M+ H$^+$): 203.0451; found: 203.0450.
8-Azidoquinoline-7-carbaldehyde – 253

NaN₃ (1.8 g, 27.4 mmol, 3.0 equiv.) was added to 8-nitroquinoline-7-carbaldehyde (252) (1.9 g, 9.13 mmol, 1.0 equiv.) in anhydrous DMF (14 mL) and NEt₃ (260 µL, 1.82 mmol, 0.2 equiv.) under argon and heated at 60 ºC with argon sparging. After 1 h, the mixture was allowed to cool, diluted with H₂O (50 mL), and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed sequentially with 5% aqueous LiCl (3 x 50 mL) and brine (1 x 50 mL) and dried over MgSO₄. After rotary evaporation, the residue was chromatographed on silica (gradient; 0 → 50% CH₂Cl₂ in pentane) to give azide 253 (785 mg, 43%) as a yellow solid.

¹H NMR (400 MHz, CDCl₃) δ 10.68 (s, 1H, H⁶), 8.95 (d, J = 4.0 Hz, 1H, H¹), 8.18 (d, J = 8.3 Hz, 1H, H³ or H⁴), 7.93 (d, J = 8.6 Hz, 1H, H³ or H⁴), 7.63 – 7.50 (m, 2H, H² and H⁵).

¹³C NMR (101 MHz, CDCl₃) δ 189.3 (C⁶), 148.9, 143.5, 141.8, 136.6, 132.4, 125.7, 124.1, 123.8, 123.7.

m.p. 125-126 ºC (CH₂Cl₂).

IR 2125, 1675, 1384, 1295, 1256, 837 cm⁻¹.

HR-MS (ES+) calcd for C₁₀H₆N₄O (M + H⁺): 199.0620; found: 199.0628.

Microanalysis, calcd for C₁₀H₆N₄O: C, 60.60; H, 3.05; N, 28.27; Found: C, 60.38; H, 3.17; N, 28.09.
2-Azido-3-methylbenzaldehyde - 258

Using general procedure D; 3-methyl-2-nitrobenzaldehyde (254) (1000 mg, 6.1 mmol) gave the product 258 (168 mg, 17%) as a tan solid after chromatography on silica (10% EtOAc in pentane). The data is consistent with that reported in the literature.\textsuperscript{122}

\textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}) $\delta$ 10.34 (s, 1H), 7.72 (dd, $J = 7.6$, 1.6 Hz, 1H), 7.43 (ddd, $J = 7.5$, 1.7, 0.8 Hz, 1H), 7.27 – 7.21 (m, 2H), 2.47 (s, 3H).

\textbf{\textsuperscript{13}C NMR} (101 MHz, CDCl\textsubscript{3}) $\delta$ 189.9, 140.3, 137.6, 133.3, 129.2, 129.1, 126.0, 18,1.

\textit{A mass could not be obtained for this compound through a range of techniques.}
4-Methoxy-2-azidobenzaldehyde - 259

Using general procedure D; 4-methoxy-2-nitrobenzaldehyde (255) (471 mg, 2.6 mmol) gave the product 259 (389 mg, 84%) as an off-white solid. The data is consistent with that reported in the literature. An impurity of the starting material (<10%) could not be removed by column chromatography.

$^1$H NMR (400 MHz, CDCl$_3$) δ 10.18 (d, $J = 0.8$ Hz, 1H), 7.85 (d, $J = 8.7$ Hz, 1H), 6.75 (ddd, $J = 8.7$, 2.3, 0.8 Hz, 1H), 6.69 (d, $J = 2.3$ Hz, 1H), 3.90 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 187.4, 165.5, 145.0, 131.3, 121.2, 111.2, 104.0, 55.9.

A mass could not be obtained for this compound through a range of techniques.
2-Azido-4-(trifluoromethyl)benzaldehyde - 260

Using general procedure D; 2-nitro-4-(trifluoromethyl)benzaldehyde (256) (995 mg, 4.5 mmol) gave the product 260 (742 mg, 76%) as a white solid. The data is consistent with that reported in the literature.\textsuperscript{122}

\textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}) \(\delta\) 10.38 (d, \(J = 0.8\) Hz, 1H), 8.00 (dt, \(J = 8.0, 0.8\) Hz, 1H), 7.54 – 7.42 (m, 2H).

\textbf{\textsuperscript{13}C NMR} (101 MHz, CDCl\textsubscript{3}) \(\delta\) 187.6, 143.6, 136.9 (q, \(J_{CF} = 33.3\) Hz), 129.9, 124.4, 121.7 (q, \(J = 3.6\) Hz), 118.9 (d, \(J_{CF} = 277.3\) Hz), 116.4 (q, \(J_{CF} = 3.5\) Hz).

\emph{A mass could not be obtained for this compound through a range of techniques.}
2-Azido-5-chlorobenzaldehyde - 261

Using general procedure D; 5-chloro-2-nitrobenzaldehyde (257) (453 mg, 2.4 mmol) gave the product 261 (284 mg, 64 %) as a yellow solid. The data is consistent with that reported in the literature.$^{188}$

$^1$H NMR (400 MHz, CDCl$_3$) δ 10.24 (d, $J = 0.8$ Hz, 1H), 7.90 (d, $J = 8.4$ Hz, 1H), 6.90 (ddd, $J = 8.4$, 2.0, 0.8 Hz, 1H), 6.82 (d, $J = 2.0$ Hz, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 187.1, 147.5, 144.9, 131.0, 124.1, 115.6, 109.3.

HRMS (El) calcd for C$_7$H$_4$O$_7$N$_3$Cl (M$^+$): 181.0043, found: 181.0038.
General Procedure D; 1-azido-2-naphthaldehyde (249) gave the spiro-biquinoline 262 as a white amorphous solid (235 mg, 67%) after purification by chromatography on silica (gradient; 20 → 50% CH₂Cl₂ in pentane).

**¹H NMR** (400 MHz, CDCl₃) δ 7.80 – 7.74 (m, 2H, H₈), 7.72 – 7.65 (m, 2H, H₅), 7.42 – 7.38 (m, 4H), 7.28 – 7.23 (m, 4H), 4.92 (s, 2H, NH), 3.20 – 3.05 (m, 4H, H₂), 2.29 – 2.06 (m, 4H, H¹).

**¹³C NMR** (101 MHz, CDCl₃) δ 136.9 (2C, Ar-N), 133.3 (2C), 128.7 (2C), 128.1 (2C), 125.3 (2C), 125.1 (2C), 123.1 (2C), 119.4 (2C), 117.7 (2C), 114.4 (2C), 64.3 (RHN-CNHR), 32.9 (2C, C¹'), 24.4 (2C, C²).

**m.p.** 169-170 °C (pentane).

**IR** ν= 3373, 1574, 1473, 1396, 745 cm⁻¹.

**HR-MS** (ES+) calcd for C₂₅H₂₃N₂ (M + H⁺): 351.1861, found: 351.1872.

**Microanalysis**, calcd for C₂₅H₂₂N₂: C, 85.68; H, 6.33; N, 7.99; Found: C, 85.57; H, 6.40; N, 7.90.
General Procedure D: 8-azidoquinoline-7-carbaldehyde (253) gave the spiro-biquinoline 263 (264 mg, 75%) as a yellow solid after purification by chromatography on silica (gradient; 0 → 10% MeOH in CH₂Cl₂).

¹H NMR (400 MHz, CDCl₃) δ 8.66 (dd, J = 4.2, 1.7 Hz, 2H, H⁸), 8.05 (dd, J = 8.2, 1.7 Hz, 2H, H⁷), 7.33 – 7.28 (m, 4H, H⁴ and H⁷), 7.10 (d, J = 8.2 Hz, 2H H³), 6.55 (s, 2H, NH), 3.23 (ddd, J = 17.3, 9.1, 5.7 Hz, 2H, H²a), 3.11 (dt, J = 17.1, 6.0 Hz, 2H, H²b), 2.37 – 2.27 (m, 2H, H¹a), 2.16 (ddd, J = 12.7, 9.1, 5.7 Hz, 2H, H¹a).

¹³C NMR (101 MHz, CDCl₃) δ 147.3 (2C, Ar-N), 138.7 (2C, C⁹), 137.6 (2C, C⁹), 135.9 (2C, C⁵), 128.7 (2C, C³), 127.6 (2C, C³), 120.8 (2C, C⁷), 116.0 (2C, Ar-C²), 114.2 (2C, C⁴), 63.0 (RHN-CNHR, 33.3 (2C, C¹), 24.0 (2C, C²).

m.p. 153-155 °C (CH₂Cl₂).

IR ν = 3402, 1508, 1472, 1325, 819, 793 cm⁻¹.

HR-MS (ES+) calcd for C₂₃H₂₂N₄ (M + H⁺): 353.1766, found: 353.1772.

Microanalysis, calcd for C₂₃H₂₂N₄: C, 78.38; H, 5.72; N, 15.90; Found: C, 78.19; H, 5.81; N, 15.73.
General Procedure D: 2-azido-6-methylbenzaldehyde (258) gave the spiro-biquinoline 264 (147 mg, 53%) as a colourless oil after purification by chromatography on silica (60% CH$_2$Cl$_2$ in pentane).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.00 – 6.91 (m, 4H, Ar-H), 6.67 (t, $J$ = 7.5 Hz, 2H, Ar-H), 2.91 (t, $J$ = 6.8 Hz, 4H, H$_2$), 2.11 (s, 6H, Ar-Me), 2.05 (t, $J$ = 6.8 Hz, 4H, H$_1$).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 140.7 (2C, Ar-N), 128.4 (2C, C$_5$), 127.1 (2C, C$_3$) 121.4 (2C, Ar-Me), 119.6 (2C, Ar-C$_2$), 117.1 (2C, C$_4$), 64.4 (RHN_CNR), 33.2 (2C, C$_1$), 24.0 (2C, C$_2$), 17.4 (2C, Ar-Me).

IR $\nu$ = 3392, 1658, 1541, 1514, 769 cm$^{-1}$.

HR-MS (ESI) calcd for C$_{19}$H$_{23}$N$_2$ (M + H$^+$): 279.1856, found: 279.1977.

Microanalysis, calcd for C$_{19}$H$_{22}$N$_2$: C, 81.97; H, 7.97; N, 10.06; Found: C, 82.08; H, 8.05; N, 9.85
General Procedure D; 2-azido-4-methoxybenzaldehyde (259) gave the spiro-biquinoline 265 (241 mg, 77%) as a white solid after purification by chromatography on silica (50% CH₂Cl₂ in pentane).

\(^1\)H NMR (400 MHz, CDCl₃) δ 6.94 (d, J = 8.2 Hz, 2H, H²), 6.28 (dd, J = 8.3, 2.5 Hz, 2H, H⁴ or H⁵), 6.04 (d, J = 2.4 Hz, 2H, H⁴ or H⁵), 4.27 (s, 2H, NH), 3.73 (s, 6H, OMe), 2.83 (t, J = 6.7 Hz, 4H, C²), 2.03 – 1.90 (m, 4H, H¹).

\(^{13}\)C NMR (101 MHz, CDCl₃) δ 159.2 (2C, Ar-O), 143.5 (2C, Ar-N), 130.0 (2C, C³), 112.7 (2C, Ar-C₂), 104.0 (2C, C⁴), 99.9 (2C, C⁵), 63.3 (RHN-CNHR), 55.32 (2C, OMe), 33.5 (2C, C¹), 22.6 (2C, C²).

m.p. 159-161 °C (CHCl₃).

IR ν= 3382, 1613, 1479, 1325, 1199, 828 cm⁻¹.

HR-MS (ESI) calcd for C₁₉H₂₃N₂O₂ (M + H⁺): 311.1760, found: 311.1773.

Microanalysis, calcd for C₁₇H₁₈N₂: C, 73.52; H, 7.14; N, 9.03; Found: C, 73.33; H, 6.98; N, 8.80.
7,7'-Bis(trifluoromethyl)-3,3',4,4'-tetrahydro-1H,1'H-2,2'-spirobi[quinoline] – 266

General Procedure D: 2-azido-4-(trifluoromethyl)benzaldehyde (260) gave the spiro- biquinoline 266 (316 mg, 82%) as a white solid after purification by chromatography on silica (20% CH2Cl2 in pentane).

\[ \text{IR } \nu = 3401, 1508, 1467, 1325, 1103, 818 \text{ cm}^{-1}. \]

\[ \text{HR-MS (ESI) calcd for C}_{19}\text{H}_{17}\text{N}_{2}\text{F}_{6} (M + H^+): 387.1296, found: 387.1294.} \]

Microanalysis, calcd for C_{19}H_{16}N_{2}F_{6}: C, 59.07; H, 4.17; N, 7.25; Found: C, 58.93; H, 4.24; N, 7.21.
General Procedure D; 2-azido-5-chlorobenzaldehyde (261) gave the spiroquinoline 267 (108 mg, 34%) as a colourless oil after purification by chromatography on silica (50% CH₂Cl₂ in pentane).

**¹H NMR** (400 MHz, CDCl₃) δ 7.02 (d, J = 2.4 Hz, 2H, H₃), 6.96 (dd, J = 8.4, 2.5 Hz, 2H, H⁴), 6.40 (d, J = 8.5 Hz, 2H, H⁵), 4.21 (s, 2H, NH), 2.85 (m, 4H, H²), 2.03 – 1.84 (m, 4H, H¹).

**¹³C NMR** (101 MHz, CDCl₃) δ 141.1 (2C, Ar-N), 128.9 (2C, C³), 127.2 (2C, C⁴), 122.4 (2C, Ar-C² or Ar-Cl), 121.7 (2C, Ar-C² or Ar-Cl), 115.8 (2C, C⁵), 63.7 (RHN̵CNHR), 32.9 (2C, C¹), 23.3 (2C, C²).

**IR** ν = 3398, 2936, 1480, 1291, 850 cm⁻¹.


**Microanalysis**, calcd for C₁₇H₁₈N₂Cl₂: C, 63.96; H, 5.05; N, 8.78; Found: C, 64.00; H, 5.10; N, 8.71.
General Procedure F; Using 2.0 equiv. of NBS, spiropiquinoine 235 (500 mg, 2.0 mmol) gave the dibromide 271 (509 mg, 56%) as a white crystalline solid after purification by chromatography on silica (25% CH₂Cl₂ in pentane).

**¹H NMR** (400 MHz, CDCl₃) δ 7.19 (d, J = 2.3 Hz, 2H, H₃), 7.11 (dd, J = 8.5, 2.3 Hz, 2H, H⁴), 6.38 (d, J = 8.5 Hz, 2H, H⁵), 4.25 (s, 2H, NH), 2.87 (t, J = 6.8 Hz, 4H, H²), 1.97–1.92 (m, 4H, H¹).

**¹³C NMR** (101 MHz, CDCl₃) δ 141.5 (2C, Ar-N), 131.7 (2C, C³), 130.0 (2C, C⁵), 122.2 (2C, Ar-C²), 116.2 (2C, C⁴), 109.5 (2C, Ar-Br), 63.6 (RHN-CNHR), 32.8 (2C, C¹), 23.2 (2C, C²).

**m.p.** 178-181 °C (CH₂Cl₂);

**IR** ν = 3403, 2928, 1467, 1290, 856, 801 cm⁻¹

**HR-MS** (ESI) calcd for C₁₇H₁₇N₂⁷⁸Br⁸¹Br (M + H⁺): 408.9660, found: 408.9748.

**Microanalysis**, calcd for C₁₇H₁₆N₂Br₂: C, 50.03; H, 3.95; N, 6.86; Found: C, 50.17; H, 3.92; N, 6.63.
General Procedure F; Using 4.0 equiv. of NBS, spirobiquinoline 235 (500 mg, 2.0 mmol) gave the tetrabromide 272 (830 mg, 74%) as a white crystalline solid after purification by chromatography on silica (10% CH$_2$Cl$_2$ in pentane).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.42 (d, J = 2.2 Hz, 2H, H$^4$), 7.14 (d, J = 2.2 Hz, 2H, H$^3$), 4.80 (s, 2H, NH), 2.88 (td, J = 6.5, 1.5 Hz, 4H, H$^2$), 2.06 – 1.96 (m, 2H, H$^{1a}$), 1.93 – 1.82 (m, 2H, H$^{1b}$).
$^{13}$C NMR (101 MHz, CDCl$_3$) δ 138.7 (2C, Ar-N), 132.5 (2C, C$^3$), 130.9 (2C, Ar-Br), 123.2 (2C, Ar-C$^2$), 109.3 (2C, Ar-Br$^2$), 108.7 (2C, C$^4$), 64.8 (RHN$^1$CNR), 32.9 (2C, C$^1$), 23.9 (2C, C$^3$).

m.p. 172-173 ºC (CHCl$_3$).

IR ν = 3397, 1691, 1480, 1449, 1173, 859 cm$^{-1}$.

HR-MS (ESI) calcd for C$_{17}$H$_{15}$N$_2$Br$_2$ (M + H$^+$): 566.7928, found: 566.7924.

Microanalysis, calcd for C$_{17}$H$_{14}$N$_2$Br$_4$: C, 36.08; H, 2.49; N, 4.95; Found: C, 35.93; H, 2.52; N, 5.08.
6,6',8,8'-Tetraphenyl-3,3',4,4'-tetrahydro-1H,1'H-2,2'-spirobi[quinoline] – 273

6,6',8,8'-Tetrabromo-3,3',4,4'-tetrahydro-1H,1'H-2,2'-spirobi[quinoline] (272) (28 mg, 0.05 mmol, 1.0 equiv.), phenylboronic acid (30 mg, 0.25 mmol, 5.0 equiv.), K$_2$CO$_3$ (28 mg, 0.20 mmol, 4.0 equiv.), and XPhos (5 mg, 0.01 mmol, 0.2 equiv.) were loaded into a vial. DMF and H$_2$O (4:1, 500 µL) were added and the mixture was sparged for 20 min with argon. PdCl$_2$(PPh$_3$)$_2$ (4 mg, 57 µmol, 11 mol%) was added and the mixture was heated at 90 ºC for 16 h. The mixture was cooled to room temperature, the solvent was removed in vacuo, and the residue chromatographed on silica (20 → 50% CH$_2$Cl$_2$ in pentane) to afford the spiro-biquinoline 273 (19 mg, 67%) as a white solid.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.56 (d, $J = 7.2$ Hz, 2H, H$_3$), 7.41-7.35 (m, 8H, Ph-H and H$_4$), 7.32 – 7.24 (m, 14H, Ph-H), 4.67 (s, 2H, NH), 2.99 (dt, $J = 16.4, 6.5$ Hz, 2H, H$_{2a}$), 2.83 (ddd, $J = 16.4, 8.6, 6.5$ Hz, 2H, H$_{2b}$), 2.00 (m, 4H, H$_1$).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 141.2 (2C, Ar-N), 139.2 (2C, Ar), 139.0 (2C, Ar), 130.4 (2C, Ar), 129.2 (4C, Ar), 129.2 (4C, Ar) 129.8 (4C, Ar), 127.8 (2C, Ar), 127.5 (2C, Ar), 127.3 (2C, Ar), 127.0 (2C, Ar), 126.5 (4C, Ar), 126.4 (2C, Ar), 121.3 (2C, Ar), 64.6 (RHN$_2$NHR), 33.8 (2C, C$^1$), 24.1 (2C, C$^2$).

m.p. 167-171 ºC (CHCl$_3$).

IR ν = 3391, 1599, 1462, 1207, 943, 761, 698 cm$^{-1}$.

HR-MS (ESI) calcd for C$_{41}$H$_{35}$N$_2$ (M + H$^+$): 555.2800, found: 555.2813.

Microanalysis, calcd for C$_{41}$H$_{24}$N$_2$: C, 88.77; H, 6.18; N, 5.05; Found: C, 89.05; H, 6.05; N, 4.87.
Spirobiquinoline 235 (50 mg, 0.2 mmol, 1.0 equiv.) was dissolved in a mixture of THF (2 mL) and HMPA (170 µL, 1.0 mmol, 5.0 equiv.) and cooled to –78 °C. n-BuLi (2.5 M in hexanes; 160 µL, 0.4 mmol, 2.0 equiv.) was added dropwise with stirring over 30 sec. After 5 min, Mel (28 µL, 0.44 mmol) in THF (1 mL) was added dropwise with stirring over 5 min. After a further 5 min at -78 °C, the cooling bath was removed and the solution was warmed to room temperature. The reaction was quenched with sat. aqueous NH₄Cl (5 mL), and the resultant mixture extracted with CH₂Cl₂ (2 x 10 mL). The combined organic extracts were dried over MgSO₄, the solvent removed by rotary evaporation and the residue chromatographed on silica (20% CH₂Cl₂ in pentane +1% NEt₃) to afford the product 274 (50 mg, 91%) as a white solid.

\[ \text{1H NMR (400 MHz, CDCl}_3\text{)} \delta 7.23 - 7.14 (m, 2H, H^6), 7.08 - 7.01 (m, 2H, H^3), 6.72 - 6.68 (m, 4H, H^6 and H^4), 2.99 - 2.87 (m, 2H, H^{2a}), 2.80 (s, 6H, N-Me), 2.73 (t, J = 4.4 Hz, 1H, H^{2b}), 2.69 (t, J = 4.4 Hz, 1H, H^{2b}), 2.12 (ddd, J = 12.5, 5.0, 1.2 Hz, 2H, H^{1a}), 2.02 (ddd, J = 13.4, 5.1, 3.9 Hz, 2H, H^{1b}). \]

\[ \text{13C NMR (101 MHz, CDCl}_3\text{)} \delta 146.1 (2C, Ar-N), 128.3 (2C, C^3 or C^5), 127.5 (2C, C^3 or C^5), 122.4 (2C, Ar-C^2), 116.4 (2C, C^4), 111.7 (2C, C^6), 74.2 (R₂NCNR₂), 30.9 (2C, N-Me), 28.9 (2C, C^1), 24.7 (2C, C^2). \]

\[ \text{m.p. 107-108 °C (CH}_2\text{Cl}_2). \]

\[ \text{IR ν = 1599, 1490, 1009, 740 cm}^{-1}. \]

\[ \text{HR-MS (ESI) calcd for C}_{19}\text{H}_{23}\text{N}_2\text{ (M + H)}^{+}: 279.1861, \text{ found: 279.1857.} \]

\[ \text{Microanalysis, calcd for C}_{19}\text{H}_{23}\text{N}_2: C, 81.97; H, 7.97; N, 10.06; \text{ Found: C, 81.92; H, 8.12; N, 9.95.} \]
1,1’-Diallyl-3,3’,4,4’-tetrahydro-1H,1’H-2,2'-spirobi[quinoline] – 276

Spirobiquinoline 235 (50 mg, 0.2 mmol, 1.0 equiv.) was dissolved in a mixture of THF (2 mL) and HMPA (170 µL, 1.0 mmol, 5.0 equiv.) and cooled to –78 °C. n-BuLi (2.5 M in hexanes; 160 µL, 0.4 mmol, 2.0 equiv.) was added dropwise with stirring over 30 sec. After 5 min, allyl bromide (38 µL, 0.44 mmol) in THF (1 mL) was added dropwise with stirring over 5 min. After a further 5 min at -78 °C, the cooling bath was removed and the solution warmed to room temperature. The solution was quenched with sat. aqueous NH₄Cl (5 mL), and the resultant mixture extracted with CH₂Cl₂ (2 x 10 mL). The combined organic extracts were dried over MgSO₄, the solvent removed by rotary evaporation, and the residue chromatographed on silica (20% CH₂Cl₂ in pentane +1% NEt₃) to afford the product 276 (53 mg, 80%) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ 7.09 (td, J = 7.8, 1.7 Hz, 2H, H⁵), 7.01 (dd, J = 7.3, 1.5 Hz, 2H, H²), 6.71 – 6.61 (m, 4H, H⁶ and H⁴), 5.77 (ddt, J = 17.4, 9.5, 4.6 Hz, 2H, H⁸), 5.16 – 5.05 (m, 4H, H⁹), 3.86 (dt, J = 4.3, 2.0 Hz, 2H, H⁷), 2.86 (ddd, J = 16.5, 9.9, 6.9 Hz, 2H, H²a), 2.72 – 2.61 (m, 2H, H²b), 2.14 – 2.06 (m, 4H, H¹).

¹³C NMR (101 MHz, CDCl₃) δ 145.0 (2C, Ar-N), 136.2 (2C, C⁸), 128.3 (2C, C⁷), 127.1 (2C, C⁵), 123.4 (2C, Ar-C²), 116.8 (2C C⁹), 115.9 (2C, C⁵), 113.2 (2C, C⁶), 76.2 (R₂NČN₁), 46.3 (2C, C⁷), 31.5 (2C, C¹), 24.9 (2C, C²).

IR ν= 2942, 2845, 1601, 1490, 1458, 910, 743 cm⁻¹.

HR-MS (ESI) calcd for C₂₃H₂₇N₂ (M - H⁺): 331.2169, found: 331.2164.

Microanalysis, calcd for C₂₃H₂₆N₂: C, 83.59; H, 7.93; N, 8.48; Found: C, 83.54; H, 8.09; N, 8.33.
Diallyl spiroquinoline 276 (50 mg, 0.15 mmol, 1.0 equiv.) was dissolved in CH$_2$Cl$_2$ (1 mL) and sparged for 10 min with argon. Hoveyda-Grubbs™ 2$^{\text{nd}}$ generation catalyst (4.6 mg, 7 µmol, 5 mol%) was added, and the mixture was heated to 40 ºC for 6 h. The mixture was cooled to room temperature and chromatographed on silica (15 $\rightarrow$ 20% CH$_2$Cl$_2$ in pentane +1% NEt$_3$) to give 278 (39 mg, 86%) as a white solid.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.13 – 7.00 (m, 4H, H$^3$ and H$^5$), 6.66 (td, $J = 7.3$, 1.0 Hz, 2H, H$^6$), 6.49 (dd, $J = 8.1$, 0.9 Hz, 2H, H$^8$), 5.86 – 5.77 (m, 2H, H$^9$), 4.06 – 3.91 (m, 2H, H$^{7a}$), 3.63 (ddd, $J = 16.4$, 3.5, 1.9 Hz, 2H, H$^{7b}$), 2.99 – 2.82 (m, 2H, H$^{2a}$), 2.61 (dt, $J = 15.4$, 3.4 Hz, 2H, H$^{2b}$), 2.30 (dt, $J = 13.3$, 3.4 Hz, 2H, H$^{1a}$), 2.17 – 2.03 (m, 2H, H$^{1b}$).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 144.2 (2C, Ar-N), 127.7 (2C, C$^3$ or C$^5$), 127.3 (2C, C$^3$ or C$^5$), 127.2 (2C, C$^6$), 124.6 (2C, Ar-C$^2$), 116.6 (2C, C$^4$), 111.0 (2C, C$^6$), 77.2 (R$_2$NCNR$_2$), 42.6 (2C, C$^7$), 31.6 (2C, C$^1$), 24.8 (2C, C$^2$).

m.p. 230-231 ºC (CH$_2$Cl$_2$).

IR ν = 1597, 1488, 1451, 1360, 735 cm$^{-1}$.

HR-MS (ESI) calcd for C$_{21}$H$_{23}$N$_2$ (M - H$^+$): 303.1861, found: 303.1869.

Microanalysis, Calcd for C$_{21}$H$_{22}$N$_2$: C, 83.40; H, 7.33; N, 9.26; Found: C, 83.45; H, 7.56; N, 9.19.
Using a modified general procedure E, o-azidobenzaldehyde (239) (147 mg, 1.0 mmol, 1.0 equiv.) was dissolved in absolute EtOH (20 mL) and cooled in an ice bath. Acetone (73 µL, 1.0 mmol, 1.0 equiv.) was added followed by the dropwise addition of 2 M NaOH (2.5 mL, 5.0 mmol, 5.0 equiv.) with stirring. After 2 h, the aldehyde was consumed (TLC) and at this time 1-azido-2-naphthaldehyde (249) (197 mg, 1.0 mmol, 1.0 equiv.) was added in one portion. After a further 2 h, the resultant precipitate was collected by filtration and washed with ice-cold absolute EtOH. The slurry was re-suspended in EtOH (20 mL) with 10% Pd/C (10 wt.%) and stirred under a hydrogen atmosphere (1 atm) for 16 h. The catalyst was removed by filtration, and the solvent removed by rotary evaporation. The residue was chromatographed on silica (0 → 50% CH₂Cl₂ in pentane) to give the unsymmetrical spiro-biquinoline 284 (219 mg, 73%) as an orange oil.

\(^1\)H NMR (400 MHz, CDCl₃) δ 7.79 – 7.74 (m, 1H, Ar-H), 7.69 – 7.66 (m, 1H, Ar-H), 7.43 – 7.38 (m, 2H, Ar-H), 7.22 (q, J = 8.4 Hz, 2H, Ar-H), 7.10 – 6.98 (m, 2H, Ar-H), 6.71 (td, J = 7.4, 1.2 Hz, 1H, Ar-H), 6.50 (dd, J = 8.1, 1.1 Hz, 1H, Ar-H), 4.80 (s, 1H, N-H), 4.37 (s, 1H, N-H), 3.05 (t, J = 6.8 Hz, 2H, H⁴), 2.96 (d, J = 12.1 Hz, 2H, H¹), 2.13 – 2.03 (m, 4H, H² and H³).

\(^{13}\)C NMR (101 MHz, CDCl₃) δ 142.6, 137.0, 133.3, 129.2, 128.7, 128.0, 127.3, 125.3, 125.1, 123.1, 120.4, 119.4, 117.8, 117.7, 114.6, 114.3, 64.0, 33.3, 32.9, 24.2, 23.5.

IR ν= 3389, 1473, 1398, 797, 748 cm⁻¹.

HR-MS (ESI) calcd for C₂₁H₁₉N₂ (M - H⁺): 299.1548, found: 299.1542.

Microanalysis, Calcd for C₂₁H₂₀N₂: C, 83.96; H, 6.71; N, 9.33; Found: C, 83.84; H, 6.67; N, 9.48.
7’-(Trifluoromethyl)-3,3’,4,4’-tetrahydro-1H,1’H-spiro[benzo[h]quinoline-2,2’-quinoline]  

Using the procedure described for spiro-biquinoline 284; 2-azido-4-(trifluoromethyl)benzaldehyde (260) (215 mg, 1.0 mmol, 1.0 equiv.) and 1-azido-2-naphthaldehyde (249) (197 mg, 1.0 mmol, 1.0 equiv.) were converted into the spiro-biquinoline 285 (206 mg, 56%) as an orange oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.79 – 7.75 (m, 1H, Ar-H), 7.69 – 7.64 (m, 1H, Ar-H), 7.43 – 7.39 (m, 2H, Ar-H), 7.26 (m, 1H, Ar-H), 7.20 (d, $J = 8.4$ Hz, 1H, Ar-H), 7.15 (d, $J = 7.8$ Hz, 1H, Ar-H), 6.94 – 6.89 (m, 1H, Ar-H), 6.72 (d, $J = 1.6$ Hz, 1H, Ar-H), 4.73 (s, 1H), N-H, 4.55 (s, 1H, N-H), 3.06 (t, $J = 6.8$ Hz, 2H, H$^4$), 3.01 – 2.89 (m, 2H, H$^1$), 2.18 – 1.95 (m, 4H, H$^2$ and H$^3$).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 142.8 (2C), 136.6, 133.3, 129.9, 129.5, 128.8, 128.0, 125.4, 125.2, 124.0, 123.1, 119.3, 118.1, 114.3, 114.1, 110.9, 64.1, 33.3, 32.6, 24.1, 23.6.

$^{19}$F NMR (377 MHz, CDCl$_3$) δ -62.63.

IR ν = 3397, 1473, 1332, 1114, 799 cm$^{-1}$.

HR-MS (ESI) calcd for C$_{22}$H$_{18}$N$_2$F$_3$ (M - H$^+$): 367.1422, found: 367.1428.

Microanalysis, calcd for C$_{22}$H$_{19}$N$_2$F$_3$: C, 71.73; H, 5.20; N, 7.60; Found: C, 71.53; H, 4.97; N, 7.86.
**5,5a,6,7,7a,8,13,14-Octahydrocyclopenta[1,2-b:1,5-b]diquinoline - 288**

General Procedure E; cyclopentanone (286) (89 µL, 1.0 mmol, 1.0 equiv.) was used instead of acetone with o-azidobenzaldehyde (239), to afford the spiroquinoline 18 (115 mg, 42%) as a white solid. The product was chromatographed on silica (50% CH₂Cl₂ in pentane).

**¹H NMR** (400 MHz, CDCl₃) δ 7.13 – 7.00 (m, 4H, Ar-H), 6.71 (td, J = 7.4, 1.2 Hz, 2H, Ar-H), 6.50 (dd, J = 7.8, 1.1 Hz, 2H, Ar-H), 4.12 (s, 2H, N-H), 2.90 (dd, J = 15.9, 5.7 Hz, 2H, H¹a), 2.65 (dd, J = 15.9, 7.2 Hz, 2H, H¹b), 2.20 (td, J = 7.3, 5.5 Hz, 2H, H²), 2.01 – 1.88 (m, 2H, H³a), 1.51 – 1.38 (m, 2H, H³b).

**¹³C NMR** (101 MHz, CDCl₃) δ 142.7 (2C, Ar-N), 128.9 (2C, Ar), 127.1 (2C, Ar), 121.3 (2C, Ar-C¹), 117.7 (2C, Ar), 113.6 (2C), 75.3 (RHN=CNHR), 43.8 (2C, C²), 30.1 (2C, C¹), 27.78 (2C, C²).

**m.p.** 109-111 °C (pentane)

**IR** ν= 3384, 1605, 1474, 1261, 748 cm⁻¹.


**Microanalysis**, calcd for C₁₉H₂₀N₂: C, 82.57; H, 7.29; N, 10.14; Found: C, 82.45; H, 7.35; N, 9.98.
General Procedure E: cyclohexanone (287) (103 µL, 1.0 mmol, 1.0 equiv.) was used instead of acetone with o-azidobenzaldehyde (239), to afford the spiro-biquinoline 289 (175 mg, 48%) as a white solid. A sample was chromatographed on silica (50% CH₂Cl₂ in pentane).

¹H NMR (400 MHz, CDCl₃) δ 7.07 – 7.03 (m, 2H, Ar-H), 7.02 – 6.96 (m, 2H, Ar-H), 6.69 (tdd, J = 7.6, 5.2, 1.3 Hz, 2H, Ar-H), 6.44 (dd, J = 8.1, 1.2 Hz, 2H, Ar-H), 4.47 (s, 1H, N-H), 4.22 (s, 1H, N-H), 3.24 (dd, J = 17.3, 5.9 Hz, 1H, H¹a or H⁷a), 2.80 (dd, J = 17.2, 5.8 Hz, 1H, H¹b or H⁷b), 2.70 – 2.50 (m, 2H, H¹ab or H⁷ab), 2.13 – 1.32 (m, 8H, H₂, H₃, H₄, and H₅).

¹³C NMR (101 MHz, CDCl₃) δ 142.3 (Ar-N), 141.1 (Ar-N), 129.9 (Ar), 129.1 (Ar), 127.1 (Ar), 126.9 (Ar), 120.2 (Ar-C¹⁷), 118.4 (Ar-C¹⁷), 117.9 (Ar), 117.6 (Ar), 115.7 (Ar), 115.4 (Ar), 64.4 (RHN-CNHR), 39.7 (C² or C⁶), 38.5 (C² or C⁶), 29.4 (C¹ or C⁷), 29.2 (C¹ or C⁷), 29.0 (C³ or C⁵), 28.7 (C³ or C⁵), 25.3 (C⁴).

m.p. 140-141 ºC (pentane).

IR ν = 3372, 1586, 1477, 1251, 748 cm⁻¹.

HR-MS (ESI) calcd for C₂₀H₂₃N₂ (M + H⁺): 291.1861, found: 291.1875.

Microanalysis, calcd for C₂₀H₂₃N₂: C, 82.72; H, 7.64; N, 9.65; Found: C, 82.70; H, 7.73; N, 9.66.
1,3,10,12-tetrabromo-5,5a,6,7,7a,8,13,14-octahydrocyclopenta[1,2-b:1,5-b]diquinoline – 290

![Structure](image)

General Procedure F; spiroquinoline 288 (5 mg, 18 µmol) and freshly recrystallized NBS (13 mg, 72 µmol, 4.0 equiv.) gave the tetra-bromo 290 (6 mg, 58%) as a white solid. A sample was purified by silica pad chromatography (20% CH$_2$Cl$_2$ in pentane)

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.44 (d, $J = 2.2$ Hz, 2H, Ar-H), 7.13 (d, $J = 2.1$ Hz, 2H, Ar-H), 4.68 (s, 2H, N-H), 2.88 (dd, $J = 16.0$, 5.4 Hz, 2H, H$_{1a}$), 2.63 (dd, $J = 16.0$, 7.1 Hz, 2H, H$_{1b}$), 2.21 (t, $J = 6.4$ Hz, 2H, H$_2$), 1.93 – 1.83 (m, 2H, H$_{3a}$), 1.34 (m, 2H, H$_{3b}$)

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 138.8 (2C, Ar-N), 132.2 (2C, Ar), 130.6 (2C), 123.9(2C), 108.6 (2C, Ar), 108.5 (2C, Ar), 76.2 (RHN-CNHR), 43.2 (2C, C$^2$), 30.0 (2C, C$^1$), 26.8 (2C, C$^3$).

HR-MS (ESI) calcd for C$_{19}$H$_{17}$N$_2$Br$_2$: 592.8079, found: 592.8085.
General Procedure F; spiroquinoline 291 (5 mg, 17 µmol) and freshly recrystallized NBS (13 mg, 72 µmol, 4.0 equiv.) gave the tetra-bromo 291 (7 mg, 68%) as a white solid after purification by chromatography on silica (20% CH₂Cl₂ in pentane).

**¹H NMR** (400 MHz, CDCl₃) δ 7.39 (s, 2H, Ar-H), 7.18 – 7.10 (m, 2H, Ar-H), 4.95 (s, 1H, N-H), 4.76 (s, 1H, N-H), 3.23 (dd, J = 17.4, 5.6 Hz, 1H, H¹a or H⁷a), 2.89 – 2.63 (m, 2H, H¹ab or H⁷ab), 2.58 (d, J = 17.4 Hz, 1H, H¹a or H⁷a), 2.09 – 1.88 (m, 2H, H² and H⁶), 1.80 – 1.65 (m, 2H, H³a and H⁵a), 1.52 – 1.36 (m, 4H, H³b, H⁵b and H⁴).

**¹³C NMR** (101 MHz, CDCl₃) δ 138.4 (Ar-N), 137.09 (Ar-N), 132.6 (Ar), 132.4 (Ar), 131.7 (Ar), 131.0 (Ar), 123.0 (Ar), 121.5 (Ar), 110.3 (Ar), 110.1 (Ar), 109.0 (Ar), 108.7 (Ar), 64.7 (RHNCNHR), 39.6 (C² or C⁶), 37.8 (C² or C⁵), 29.5 (C¹ or C⁷), 29.2 (C¹ or C⁷), 28.6 (C⁵ or C³), 28.1 (C⁵ or C³), 25.0 (C⁴).

**HR-MS** (ESI) calcd for C₂₀H₁₉N₂Br₂⁻Br₂ (M + H⁺): 606.8236, found: 606.8163.
Using the procedure of Lingenfelder and Kellogg,\textsuperscript{136} under an atmosphere of argon, naphthalene (312) (21 g, 164 mmol, 1.5 equiv.) and succinic anhydride (311) (11 g, 109 mmol, 1.0 equiv.) was added in one portion to a rapidly stirred solution of AlCl\textsubscript{3} (42 g, 315 mmol, 2.9 equiv.) in PhNO\textsubscript{2} (90 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 16 h. The resultant mixture was poured into ice water (250 g), this was acidified with 6 M HCl (20 mL). The resultant precipitate was collected by filtration, washed with water (50 mL), and n-hexane (50 mL), and recrystallised from hot AcOH to yield the keto-acid 313 as a white solid (9.1 g, 37%). The analytical data matched the previously reported data.\textsuperscript{136}

\textsuperscript{1}H NMR (400 MHz, DMSO-\textit{d}\textsubscript{6}) \(\delta\) 12.20 (s, 1H), 8.71 (s, 1H), 8.15 (d, \(J = 8.0\) Hz, 1H), 8.01 (app - q, \(J = 6.9, 4.7\) Hz, 3H), 7.65 (dt, \(J = 19.1, 7.1\) Hz, 2H), 3.53 – 3.30 (m, 2H, \textit{overlapping with H\textsubscript{2}O}), 2.65 (t, \(J = 6.3\) Hz, 2H).

\textsuperscript{13}C NMR (101 MHz, DMSO-\textit{d}\textsubscript{6}) \(\delta\) 198.5, 173.9, 135.1, 133.7, 132.2, 129.8, 129.7, 128.7, 128.3, 127.7, 127.0, 123.5, 33.2, 28.0.

HR-MS (El) calcd for C\textsubscript{14}H\textsubscript{12}O\textsubscript{3} (M\textsuperscript{+}): 228.0786, found: 228.0786.
Using the procedure of Lingenfelder and Kellogg,\textsuperscript{136} ketone 313 (4.2 g, 18.4 mmol) and Pd(OH)$_2$/C (10% wt, 400 mg) in AcOH (40 mL) was agitated under a atmosphere of hydrogen (1.5 bar) for 48 h. The catalyst was removed by filtration through Celite®. The filtrate was poured into H$_2$O (200 mL) with cooling. The resulting precipitate was collected by filtration, and washed with PhMe to yield the acid 314 as a white solid (3.3 g, 82%). The analytical data matched the previously reported data.\textsuperscript{136} An impurity of starting material (<10%) could not be removed by recrystallisation.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.82 (dd, $J = 10.4, 7.7$ Hz, 3H), 7.65 (s, 1H), 7.47 (qt, $J = 7.7, 3.8$ Hz, 2H), 7.36 (dd, $J = 8.4, 1.7$ Hz, 1H), 2.88 (t, $J = 7.6$ Hz, 2H), 2.44 (t, $J = 7.4$ Hz, 2H), 2.10 (p, $J = 7.4$ Hz, 2H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 179.6, 138.8, 133.7, 132.2, 128.2, 127.7, 127.6, 127.3, 126.8, 126.1, 125.4, 35.3, 33.4, 26.2.

HR-MS (EI) calcd for C$_{14}$H$_{12}$O$_2$ (M$^+$): 214.0994, found: 214.0999.
2,3-Dihydrophenanthren-4(1H)-one - 315

Using the procedure of Lingenfelder and Kellogg, \textsuperscript{136} acid 313 (1.0 g, 4.67 mmol) was added to MsOH (25 mL) at 90 °C. The solution was stirred at this temperature for 2 h. After cooling to room temperature, the solution was diluted with cold H$_2$O (100 mL). The aqueous solution was extracted with Et$_2$O (3 X 100 mL), the combined organic layers were washed sequentially with sat. aqueous NaHCO$_3$ (100 mL), H$_2$O (100 mL), brine (100 mL), dried over MgSO$_4$ and the solvent removed under by rotary evaporation affording the ketone 315 as a brown solid, that did not require further purification. The analytical data matched the previously reported data. \textsuperscript{136}

$^1$H NMR (400 MHz, CDCl$_3$) δ 9.47 – 9.31 (m, 1H), 7.92 (d, $J$ = 8.6 Hz, 1H), 7.81 (dd, $J$ = 8.3, 1.6 Hz, 1H), 7.63 (ddd, $J$ = 8.6, 6.8, 1.5 Hz, 1H), 7.49 (ddd, $J$ = 8.1, 6.8, 1.2 Hz, 1H), 7.33 (d, $J$ = 8.4 Hz, 1H), 3.13 (t, $J$ = 6.1 Hz, 2H), 2.84 – 2.75 (m, 2H), 2.20 (tt, $J$ = 7.4, 5.9 Hz, 2H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 200.6, 146.9, 134.3, 132.9, 131.5, 129.0, 128.4, 127.5, 127.1, 126.8, 126.0, 41.3, 31.8, 23.2.

HR-MS (ESI) calcd for C$_{14}$H$_{13}$O (M + H$^+$): 197.0966, found: 197.0963.
Using the procedure of Yamada\textsuperscript{227}; PdCl$_2$(PPh$_3$)$_2$ (685 mg, 0.9 mmol, 2 mol\%) and Cul (185 mg, 1.0 mmol, 2 mol\%) were suspended in PhMe (150 mL) and sparged with argon for 5 minutes. NEt$_3$ (27 mL), 1-bromo-2-iodobenzene (310) (6.5 mL, 50.6 mmol, 1.0 equiv.) and TMS-acetylene (8.5 mL, 60.0 mmol, 1.2 equiv.) were added sequentially and stirred for 1 h. The reaction was diluted with Et$_2$O (200 mL), filtered through Celite® and the solvent removed by rotary evaporation. The crude product was purified by silica pad (pentane) to yield the product as a colourless liquid (11.7 g, 92\%). The data is consistent with that reported in the literature.\textsuperscript{227}

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.57 (dd, $J = 8.1$, 1.3 Hz, 1H), 7.49 (dd, $J = 7.7$, 1.8 Hz, 1H), 7.24 (td, $J = 8.0$, 7.6, 1.6 Hz, 2H), 7.15 (td, $J = 7.7$, 1.8 Hz, 1H), 0.28 (s, 9H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 133.7, 132.5, 129.7, 127.0, 125.9, 125.4, 103.2, 99.8 HR-MS (EI) calcd for C$_{11}$H$_{13}$BrSi (M$^+$): 241.1670; found: 241.1681.
Using the procedure of Alabugin,\textsuperscript{138} aryl bromide 311 (6.3 g, 25 mmol, 1.0 equiv.), (2-fluorophenyl)boronic acid (12.5 g, 90 mmol, 3.5 equiv.) and K$_2$CO$_3$ (35 g, 250 mmol, 10 equiv.) in PhMe (160 mL), H$_2$O (40 mL) and EtOH (40 mL) was sparged with argon for 15 minutes before the addition of freshly prepared\textsuperscript{228} Pd(PPh$_3$)$_4$ (1.4 g, 1.25 mmol, 5 mol%). The reaction was heated to 120 °C for 16 h, cooled to room temperature and diluted with H$_2$O (100 mL). The layers were separated and the aqueous layer was further extracted with CH$_2$Cl$_2$ (2 x 200 mL). The combined organics were dried over MgSO$_4$, the solvent removed by rotary evaporation, and the crude product purified by silica pad (pentane), to yield the product 312 (5.82 g, 87\%) as a colourless liquid.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.58 (dt, $J$ = 7.5, 1.0 Hz, 1H), 7.43 (td, $J$ = 7.5, 1.8 Hz, 1H), 7.39 - 7.29 (m, 4H), 7.20 - 7.10 (m, 2H), 0.08 (s, 9H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 161.6 , 158.5 , 138.9 , 132.4 , 131.9 (d, $J$ = 3.8 Hz), 130.0 , 129.3 (d, $J$ = 7.9 Hz), 128.3 , 127.5 , 123.4 (d, $J$ = 3.7 Hz), 115.5 , 115.3 , 103.9 , 97.5 , -0.4 (3C).

$^{19}$F NMR (377 MHz, CDCl$_3$) $\delta$ -114.78

IR $\nu$ = 2159, 1471, 1248, 864, 846, 751 cm$^{-1}$.

HRMS (ESI) calcd for C$_{17}$H$_{17}$SiF (M$^+$): 268.1084, found: 268.1090.
4-Fluorophenanthrene - 308

Using the procedure of Alabugin,\textsuperscript{138} Biaryl 312 (1.34 g, 5.0 mmol, 1.0 equiv.) and K$_2$CO$_3$ (69 mg, 0.5 mmol, 0.1 equiv.) in MeOH (50 mL) and CH$_2$Cl$_2$ (50 mL) was stirred for 4 h. The reaction was diluted with H$_2$O (50 mL), the layers were separated, the aqueous layer was extracted with CH$_2$Cl$_2$ (50 mL). The combined organics were dried over MgSO$_4$ and the solvent removed by rotary evaporation, to yield the intermediate as a yellow liquid, which was used immediately.

Using the procedure of Eccleshare,\textsuperscript{139} the crude alkyne 313 and PtCl$_2$ (65 mg, 0.25 mmol, 5mol%) in PhMe (15 mL) under an argon blanket was sealed in a microwave vial. This was heated to 150 °C for 90 min using microwave irradiation. The solvent was removed by rotary evaporation and the crude product purified by silica pad (pentane), to yield the product 308 (552 mg, 56% over two steps) as a white crystalline solid. The data is consistent with that reported in the literature.\textsuperscript{229}

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.16 – 9.11 (m, 1H), 7.91 (dd, $J = 7.7$, 1.7 Hz, 1H), 7.79 – 7.62 (m, 5H), 7.54 (td, $J = 7.8$, 4.9 Hz, 1H), 7.37 (ddd, $J = 14.3$, 7.8, 1.3 Hz, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 161.6 (d, $J = 252.5$ Hz), 134.9 (d, $J = 4.6$ Hz), 132.7 , 128.6 , 128.4 , 128.0 , 127.7 , 127.3 (d, $J = 2.1$ Hz), 126.9 (d, $J = 1.7$ Hz), 126.7 (d, $J = 9.9$ Hz), 126.6 (d, $J = 3.1$ Hz), 124.6 (d, $J = 3.8$ Hz), 119.7 , 113.5 (d, $J = 24.6$ Hz).

HR-MS (EI) calcd for C$_{14}$H$_9$F ($M^+$): 196.0688; found: 196.0670.

Microanalysis, calcd for C$_{14}$H$_9$F: C, 85.69; H, 4.62; Found: C, 85.53; H, 4.52.
Using the procedure of Schlosser,\textsuperscript{118} sec-BuLi (1.3 M in hexanes, 1.50 mL, 2.0 mmol, 1.0 equiv.) was added dropwise to a solution of 4-fluorophenanthrene 308 (400 mg, 2.0 mmol, 1.0 equiv.) in THF (5 mL) at –78 °C. The solution was stirred at this temperature for 2 h before the addition of DMF (350 μL). After 5 min, the reaction was diluted with Et₂O (15 mL) and quenched with H₂O (5 mL). The phases were separated and the aqueous layer further extracted with Et₂O (3 x 20 mL), the combined organics were dried over MgSO₄, and the solvent removed by rotary evaporation. The crude product was purified by column chromatography (5% EtOAc in pentane) to yield the aldehyde 314 as a white crystalline solid (180 mg, 40%). Analysis was consistent with the reported literature data,\textsuperscript{230} as well as recovering a sample of starting material 308 (110 mg, 26%).

\textsuperscript{1}H NMR (400 MHz, CDCl₃) δ 10.69 (d, J = 0.9 Hz, 1H), 9.17 – 9.05 (m, 1H), 8.01 (dd, J = 8.3, 6.3 Hz, 1H), 7.96 (dd, J = 7.8, 1.6 Hz, 1H), 7.92 (d, J = 8.8 Hz, 1H), 7.80 – 7.65 (m, 5H).

\textsuperscript{13}C NMR (101 MHz, CDCl₃) δ 187.6 (d, J = 12.0 Hz), 165.3 (d, J = 267.2 Hz), 139.2 (d, J = 6.0 Hz), 132.8 , 131.9 , 129.1 , 128.7 (d, J = 4.4 Hz), 128.3 , 127.8 , 127.6 , 126.3 (d, J = 3.0 Hz), 125.1 (d, J = 3.9 Hz), 124.1 (d, J = 3.4 Hz), 121.8 (d, J = 8.9 Hz).

\textsuperscript{19}F NMR (377 MHz, CDCl₃) δ -119.60.

HR-MS (EI) calcd for C₁₅H₉OF (M⁺): 224.0637; found: 224.0630.

Microanalysis, Calcd for C₁₅H₉FO: C, 80.35; H, 4.05; Found: C, 80.21; H, 4.23.
Using a modified procedure of Boswell, a solution of aryl fluoride 314 (180 mg, 0.8 mmol, 1.0 equiv.), NaN₃ (156 mg, 2.4 mmol, 3.0 equiv.) in DMF (3 mL) and NEt₃ (25 μL) stirred at 60 °C for 16 h, with constant argon sparging. After this time the reaction was cooled to room temperature, quenched with H₂O (20 mL) and extracted with Et₂O (3 x 25 mL). The combined organics were washed sequentially with H₂O (2 x 25 mL), 5% LiCl (2 x 25 mL) and brine (25 mL), dried over MgSO₄ and the solvent removed by rotary evaporation to afford the product 306 (170 mg, 86%) as a yellow solid, which did not require further purification.

**1H NMR** (400 MHz, CDCl₃) δ 10.64 (s, 1H, H¹), 9.56 – 9.48 (m, 1H, H⁹), 8.05 (d, J = 8.2 Hz, 1H, H³ or H⁴), 7.96 (dd, J = 7.9, 1.6 Hz, 1H, H³ or H⁴), 7.91 (d, J = 8.8 Hz, 1H, H⁵), 7.86 (d, J = 8.1 Hz, 1H, H⁶ or H⁸), 7.78 (ddd, J = 8.7, 7.1, 1.7 Hz, 1H, H⁶ or H⁸), 7.75 – 7.67 (m, 2H, H⁷ and H⁸).

**13C NMR** (101 MHz, CDCl₃) δ 189.9 (C¹), 141.1, 138.3, 133.5, 131.7, 129.5, 129.2, 128.2, 127.8, 127.6, 127.3, 127.2, 127.1, 126.6, 124.7.

**IR** ν= 3348, 2110, 1681, 1185, 1137, 747, 735 cm⁻¹.

*A mass could not be obtained for this compound through a range of techniques*
Using a modified procedure of Barrett,\textsuperscript{35} A solution of spiroaminal 47 (13 mg, 0.1 mmol, 1.0 equiv.) in freshly degassed* CH$_2$Cl$_2$ (1.0 mL) was added to a solution of [RuCl$_2$(PPh$_3$)$_3$] (96 mg, 0.1 mmol, 1.0 equiv.) in freshly degassed CH$_2$Cl$_2$ (4.0 mL). The solution was stirred for 16 h before the reaction was placed inside a Schlenk-flask containing freshly distilled degassed n-hexane (5 mL) and the seal was pierced with a wide gauge needle. After 4 days the remaining solution was decanted and the recrystallisation process was repeated twice. This afforded the product 333 (24 mg, 42%) as orange platelets which were suitable for X-ray crystallography.

HR-MS (EI) calcd for C$_{50}$H$_{59}$Cl$_4$N$_4$P$_2$Ru$_2$ (M +H$^+$): 1121.1051; found: 1121.1000.

\* Degassing was carried out with 3 iterations of freeze-pump-thaw.
APPENDICES
6. Appendix

6.1 Crystal structure of (2R,6S,8R)-2,8-dimethyl-1,7-diazaspiro[5.5]undecan-1-ium chloride (119-A•HCl)

Empirical formula \( \text{C}_{11}\text{H}_{23}\text{ClN}_{2} \)
Formula weight 218.76
Temperature/K 293(2)
Crystal system orthorhombic
Space group P2\(_1\)2\(_1\)2\(_1\)
a/Å 9.966(2)
b/Å 14.167(3)
c/Å 8.8630(18)
\( \alpha/° \) 90
\( \beta/° \) 90
\( \gamma/° \) 90
Volume/Å\(^3\) 1251.4(4)
\( \rho_{\text{calc}} \)/g/cm\(^3\) 1.161
\( \mu/\text{mm}^{-1} \) 0.274
F(000) 480.0
Radiation MoK\( \alpha \) (\( \lambda = 0.71073 \))
2\( \Theta \) range for data collection/° 8.426 to 55.806
Index ranges \(-13 \leq h \leq 13, -16 \leq k \leq 18, -11 \leq l \leq 11 \)
Reflections collected 8344
Independent reflections 2858 [\( R_{\text{int}} = 0.0433, R_{\text{sigma}} = 0.0355 \)]
Data/restraints/parameters 2858/0/141
Goodness-of-fit on \( F^2 \) 1.085
Final R indexes [\( I \geq 2\sigma (I) \)] \( R_1 = 0.0281, wR_2 = 0.0708 \)
Final R indexes [all data] \( R_1 = 0.0283, wR_2 = 0.0709 \)
Largest diff. peak/hole / e Å\(^{-3} \) 0.23/-0.14
Flack parameter -0.02(2)
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6.2 Crystal structure of 1-(phenethylamino)-3,4-dihydroisoquinolin-2-ium iodide (154)

Formula \( \text{C}_{17}\text{H}_{19}\text{N}_2\text{I} \)
Formula weight 378.24
Temperature 173(2) K
Diffractometer, wavelength Agilent Xcalibur 3 E, 0.71073 Å
Crystal system, space group Monoclinic, P2\(_1\)/c
Unit cell dimensions
\( a = 11.4746(2) \text{ Å} \)
\( b = 9.1217(2) \text{ Å} \)
\( c = 15.3811(3) \text{ Å} \)
\( a = 90° \)
\( b = 92.4144(19)° \)
\( g = 90° \)
Volume, \( Z \) 1608.47(6) Å\(^3\), 4
Density (calculated) 1.562 Mg/m\(^3\)
Absorption coefficient 1.984 mm\(^{-1}\)
F(000) 752
Crystal colour / morphology Colourless plates
Crystal size 0.25 x 0.22 x 0.06 mm\(^3\)
q range for data collection 2.597 to 28.257°
Index ranges -15<=h<=15, -11<=k<=10, -11<=l<=19
Refins collected / unique 5593 / 3233 \([R(int) = 0.0183]\)
Refins observed \([F>4s(F)]\) 2719
Absorption correction Analytical
Max. and min. transmission 0.889 and 0.681
Refinement method Full-matrix least-squares on F\(^2\)
Data / restraints / parameters 3233 / 2 / 189
Goodness-of-fit on F\(^2\) 2.1.037
Final R indices \([F>4s(F)]\) R1 = 0.0287, wR2 = 0.0510
R indices (all data) R1 = 0.0382, wR2 = 0.0546
Largest diff. peak, hole 0.551, -0.558 eÅ\(^{-3}\)
Mean and maximum shift/error 0.000 and 0.001
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6.3 Crystal structure of 3,3',4,4'-tetrahydro-1H,1'H-2,2'-spirobi[quinoline]

(235)

Formula \( \text{C}_{17} \text{H}_{18} \text{N}_{2} \)
Formula weight 250.33
Temperature \( 173(2) \) K
Diffractometer, wavelength Agilent Xcalibur 3 E, 0.71073 Å
Crystal system, space group Tetragonal, I-4
Unit cell dimensions \( a = 18.6804(6) \) Å \( a = 90^\circ \)
\( b = 18.6804(6) \) Å \( b = 90^\circ \)
\( c = 7.6330(4) \) Å \( g = 90^\circ \)
Volume, \( Z \) 2663.6(2) Å³, 8
Density (calculated) 1.249 Mg/m³
Absorption coefficient 0.074 mm⁻¹
\( F(000) \) 1072
Crystal colour / morphology Colourless tablets
Crystal size 0.52 x 0.42 x 0.18 mm³
q range for data collection 2.883 to 28.028°
Index ranges \( -24<=h<=16, -19<=k<=22, -10<=l<=9 \)
Refins collected / unique 7724 / 2775 [R(int) = 0.0251]
Refins observed \([F>4s(F)]\) 2305
Absorption correction Analytical
Max. and min. transmission 0.990 and 0.974
Refinement method Full-matrix least-squares on F²
Data / restraints / parameters 2775 / 2 / 180
Goodness-of-fit on F² 1.044
Final R indices \([F>4s(F)]\) \( R1 = 0.0400, wR2 = 0.0718 \)
R indices (all data) \( R1 = 0.0533, wR2 = 0.0771 \)
Absolute structure parameter -1.2(10)
Largest diff. peak, hole 0.100, -0.134 eÅ⁻³
Mean and maximum shift/error 0.000 and 0.001
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6.4 Crystal structure of 3,3',4,4'-tetrahydro-1H,1'H-2,2'-spirobi[benzo[h]quinoline] (262)

Identification code AB1714
Formula C_{25}H_{22}N_{2}
Formula weight 350.44
Temperature 173(2) K
Diffractometer, wavelength Agilent Xcalibur PX Ultra A, 1.54184 Å
Crystal system, space group Monoclinic, P2\textsubscript{1}/c
Unit cell dimensions 
\begin{align*}
  &a = 8.8728(6) \text{ Å} & a = 90^\circ \\
  &b = 14.3163(12) \text{ Å} & b = 97.202(7)^\circ \\
  &c = 14.4169(12) \text{ Å} & c = 90^\circ 
\end{align*}

Volume, Z 1816.9(2) Å\textsuperscript{3}, 4
Density (calculated) 1.281 Mg/m\textsuperscript{3}
Absorption coefficient 0.574 mm\textsuperscript{-1}
F(000) 744
Crystal colour / morphology Purple blocky needles
Crystal size 0.27 x 0.06 x 0.05 mm\textsuperscript{3}
\(\text{\&} \) range for data collection 4.370 to 74.091°
Index ranges -10<=h<=10, -17<=k<=17, -17<=l<=17
Refins collected / unique 11055 / 11055 [R(int) = 0.0569]
Refins observed [F>4\(\sigma\)(F)] 5890
Absorption correction Analytical
Max. and min. transmission 0.975 and 0.920
Refinement method Full-matrix least-squares on F\textsuperscript{2}
Data / restraints / parameters 11055 / 2 / 255
Goodness-of-fit on F\textsuperscript{2} 0.933
Final R indices [F>4\(\sigma\)(F)] R1 = 0.0569, wR2 = 0.1407
R indices (all data) R1 = 0.1100, wR2 = 0.1649
Largest diff. peak, hole 0.254, -0.246 eÅ\textsuperscript{-3}
Mean and maximum shift/error 0.000 and 0.001
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6.5 Crystal structure of 6,6'-dibromo-3,3',4,4'-tetrahydro-1H,1'H-2,2'-spirobi[quinoline] (271)

Identification code AB1609
Formula $\text{C}_{17}\text{H}_{15}\text{Br}_{2}\text{N}_{2}$
Formula weight 408.14
Temperature 173(2) K
Diffractometer, wavelength Agilent Xcalibur 3 E, 0.71073 Å
Crystal system, space group Triclinic, P-1
Unit cell dimensions $a = 8.2840(6)$ Å $a = 68.118(6)^\circ$
$b = 10.2385(6)$ Å $b = 71.449(7)^\circ$
$c = 10.3631(8)$ Å $g = 87.541(6)^\circ$
Volume, $Z$ 770.38(10) Å$^3$, 2
Density (calculated) 1.759 Mg/m$^3$
Absorption coefficient 5.256 mm$^{-1}$
$F(000)$ 404
Crystal colour / morphology Colourless blocks
Crystal size 0.38 x 0.35 x 0.20 mm$^3$
q range for data collection 2.448 to 27.935°
Index ranges $-9\leq h\leq 8$, $-13\leq k\leq 12$, $-13\leq l\leq 9$
Refins collected / unique 4432 / 3027 [R(int) = 0.0222]
Refins observed [F>4s(F)] 2411
Absorption correction Analytical
Max. and min. transmission 0.472 and 0.274
Refinement method Full-matrix least-squares on F$^2$
Data / restraints / parameters 3027 / 2 / 199
Goodness-of-fit on F$^2$ 1.007
Final R indices [F>4s(F)] $R1 = 0.0305$, $wR2 = 0.0592$
R indices (all data) $R1 = 0.0457$, $wR2 = 0.0649$
Largest diff. peak, hole 0.387, -0.400 eÅ$^{-3}$
Mean and maximum shift/error 0.000 and 0.001
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6.6 Crystal structure 6,6',8,8'-tetrabromo-3,3',4,4'-tetrahydro-1H,1'H-2,2'-spirobi[quinoline] (272)

Identification code AB1608b
Formula \( \text{C}_{17}\text{H}_{14}\text{Br}_4\text{N}_2 \)
Formula weight 565.94
Temperature 173(2) K
Diffractometer, wavelength Agilent Xcalibur PX Ultra A, 1.54184 Å
Crystal system, space group Monoclinic, P2\(1\)/c
Unit cell dimensions \( a = 8.7964(3) \) Å \( a = 90^\circ \)
\( b = 12.5727(4) \) Å \( b = 100.818(3)^\circ \)
\( c = 15.8234(5) \) Å \( c = 90^\circ \)
Volume, Z 1718.88(10) Å\(^3\), 4
Density (calculated) 2.187 Mg/m\(^3\)
Absorption coefficient 11.422 mm\(^{-1}\)
\( F(000) \) 1080
Crystal colour / morphology Colourless tablets
Crystal size 0.24 x 0.09 x 0.08 mm\(^3\)
\( \theta \) range for data collection 4.523 to 73.815°
Index ranges -10<=h<=9, -15<=k<=9, -19<=l<=17
Refins collected / unique 5495 / 3310 [R(int) = 0.0295]
Refins observed [F>4\(\sqrt{\sigma(F)}\)] 2760
Absorption correction Analytical
Max. and min. transmission 0.533 and 0.257
Refinement method Full-matrix least-squares on F\(^2\)
Data / restraints / parameters 3310 / 2 / 217
Goodness-of-fit on F\(^2\) 1.097
Final R indices [F>4\(\sqrt{\sigma(F)}\)] R1 = 0.0354, wR2 = 0.0790
R indices (all data) R1 = 0.0469, wR2 = 0.0846
Largest diff. peak, hole 0.447, -0.575 eÅ\(^{-3}\)
Mean and maximum shift/error 0.000 and 0.001
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6.7 Crystal structure 6,6',8,8'-tetraphenyl-3,3',4,4'-tetrahydro-1H,1'H-2,2'-spirobi[quinoline] (273)
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C(42)-C(43)-C(38)  120.83(15)
6.8 Crystal structure 1,4,10,11,12,13-hexahydro-[1,3]diazepino[1,2-a:3,2-a']diquinoline (278)

Formula \( C_{21} H_{22} N_2 \)
Formula weight 302.40
Temperature 173(2) K
Diffractometer, wavelength Agilent Xcalibur 3 E, 0.71073 Å
Crystal system, space group Monoclinic, \( P2_1/n \)
Unit cell dimensions
\[
\begin{align*}
    a &= 8.4668(4) \text{ Å} & a &= 90^\circ \\
    b &= 8.8098(4) \text{ Å} & b &= 91.110(4)^\circ \\
    c &= 20.8081(9) \text{ Å} & g &= 90^\circ
\end{align*}
\]
Volume, \( Z \) 1551.81(12) Å\(^3\), 4
Density (calculated) 1.294 Mg/m\(^3\)
Absorption coefficient 0.076 mm\(^-1\)
\( F(000) \) 648
Crystal colour / morphology Pale yellow blocks
Crystal size 0.54 x 0.49 x 0.40 mm\(^3\)
q range for data collection 2.615 to 28.072°
Index ranges \(-11\leq h\leq10, -11\leq k\leq10, -27\leq l\leq17\)
Refins collected / unique 5349 / 3097 [\( R(int) = 0.0185 \)]
Refins observed [\( F>4s(F) \)] 2549
Absorption correction Analytical
Max. and min. transmission 0.977 and 0.971
Refinement method Full-matrix least-squares on \( F^2 \)
Data / restraints / parameters 3097 / 0 / 209
Goodness-of-fit on \( F^2 \) 1.033
Final \( R \) indices [\( F>4s(F) \)] \( R1 = 0.0427, wR2 = 0.0932 \)
\( R \) indices (all data) \( R1 = 0.0548, wR2 = 0.1009 \)
Largest diff. peak, hole 0.206, -0.190 eÅ\(^-3\)
Mean and maximum shift/error 0.000 and 0.000
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6.9 Crystal structure 1,3,10,12-tetrabromo-5,5a,6,7,7a,8,13,14-octahydrocyclopenta[1,2-b:1,5-b']diquinoline (290)

Formula  C\textsubscript{19} H\textsubscript{16} Br\textsubscript{4} N\textsubscript{2}
Formula weight  591.98
Temperature  173(2) K
Diffractometer, wavelength  Agilent Xcalibur 3 E, 0.71073 Å
Crystal system, space group  Monoclinic, P\textsubscript{2}\textsubscript{1}/c
Unit cell dimensions  a = 12.6560(8) Å  a = 90°
  b = 8.9013(6) Å  b = 97.911(6)°
  c = 16.6514(11) Å  g = 90°
Volume, Z  1858.0(2) Å\textsuperscript{3}, 4
Density (calculated)  2.116 Mg/m\textsuperscript{3}
Absorption coefficient  8.669 mm\textsuperscript{-1}
F(000)  1136
Crystal colour / morphology  Colourless plates
Crystal size  0.48 x 0.29 x 0.07 mm\textsuperscript{3}
q range for data collection  2.600 to 28.292°
Index ranges  -8<=h<=16, -10<=k<=11, -21<=l<=19
Refins collected / unique  6314 / 3719 [R(int) = 0.0335]
Refns observed [F>4s(F)]  2465
Absorption correction  Analytical
Max. and min. transmission  0.537 and 0.105
Refinement method  Full-matrix least-squares on F\textsuperscript{2}
Data / restraints / parameters  3719 / 2 / 235
Goodness-of-fit on F\textsuperscript{2}  2.1.012
Final R indices [F>4s(F)]  R1 = 0.0436, wR2 = 0.0553
R indices (all data)  R1 = 0.0906, wR2 = 0.0656
Largest diff. peak, hole  0.693, -0.702 eÅ\textsuperscript{-3}
Mean and maximum shift/error  0.000 and 0.001
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6.10 Crystal structure 1,3,11,13-tetrabromo-5,5a,6,8,8a,9,14,15-octahydro-7H-quinolino[3,2-d]acridine (291)

Formula \( C_{20} H_{18} Br_4 N_2 \)
Formula weight 606.00
Temperature 173(2) K
Diffractometer, wavelength Agilent Xcalibur 3 E, 0.71073 Å
Crystal system, space group Triclinic, P-1
Unit cell dimensions \( a = 8.6429(5) \) Å \( a = 80.017(4)^\circ \)
\[ \begin{align*}
  b &= 9.5129(5) \text{ Å} \\
  c &= 12.9337(6) \text{ Å} \\
  g &= 77.318(5)^\circ 
\end{align*} \]
Volume, \( Z \) 984.87(10) Å³, 2
Density (calculated) 2.043 Mg/m³
Absorption coefficient 8.180 mm⁻¹
\( F(000) \) 584
Crystal colour / morphology Colourless blocks
Crystal size 0.40 x 0.29 x 0.26 mm³
\( q \) range for data collection 2.611 to 28.152°
Index ranges -10<=h<=11, -12<=k<=12, -13<=l<=17
Refins collected / unique 5645 / 3873 [R(int) = 0.0178]
Refins observed \( [F>4s(F)] \) 3033
Absorption correction Analytical
Max. and min. transmission 0.272 and 0.151
Refinement method Full-matrix least-squares on \( F^2 \)
Data / restraints / parameters 3873 / 2 / 244
Goodness-of-fit on \( F^2 \) 21.039
Final R indices \( [F>4s(F)] \) \( R1 = 0.0335, wR2 = 0.0595 \)
R indices (all data) \( R1 = 0.0531, wR2 = 0.0648 \)
Largest diff. peak, hole 0.485, -0.478 eÅ⁻³
Mean and maximum shift/error 0.000 and 0.001
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6.11 Crystal structure of dichloro(3-(3,4-dihydro-2H-pyrrol-5-yl)propan-1-amine)triphenylphosphineruthenium(II) dimer (340)

Empirical formula \( C_{50}H_{55}N_4P_2Ru_2 \)
Formula weight 1120.10
Temperature/K 293(2)
Crystal system orthorhombic
Space group Pbca
\( a/\text{Å} \) 17.494(4)
\( b/\text{Å} \) 19.879(4)
\( c/\text{Å} \) 27.534(6)
\( \alpha/^{\circ} \) 90
\( \beta/^{\circ} \) 90
\( \gamma/^{\circ} \) 90
Volume/\( \text{Å}^3 \) 9575(3)
\( Z \) 12
\( \rho_{\text{calc}} \text{g/cm}^3 \) 1.5550
\( \mu/\text{mm}^{-1} \) 0.961
\( F(000) \) 4563.7
Crystal size/mm\(^3\) N/A × N/A × N/A
Radiation Mo K\( \alpha \) (\( \lambda = 0.71073 \))
2\( \Theta \) range for data collection/\( ^{\circ} \) 2.96 to 55.86
Index ranges \(-11 \leq h \leq 11, \ -26 \leq k \leq 26, \ -35 \leq l \leq 35 \)
Reflections collected 111614
Independent reflections 7829 [\( R_{\text{int}} = 0.0581, \ R_{\text{sigma}} = 0.0194 \)]
Data/restraints/parameters 7829/0/575
Goodness-of-fit on \( F^2 \) 1.051
Final R indexes [\( I \geq 2\sigma (I) \)] \( R_1 = 0.0325, \ wR_2 = 0.0782 \)
Final R indexes [all data] \( R_1 = 0.0386, \ wR_2 = 0.0820 \)
Largest diff. peak/hole / \( e \text{ Å}^{-3} \) 0.65/-1.00
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References


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“One must imagine Sisyphus happy.”

*Albert Camus*