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

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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-diazaspiro[5.5]undecane (**I**).[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**.
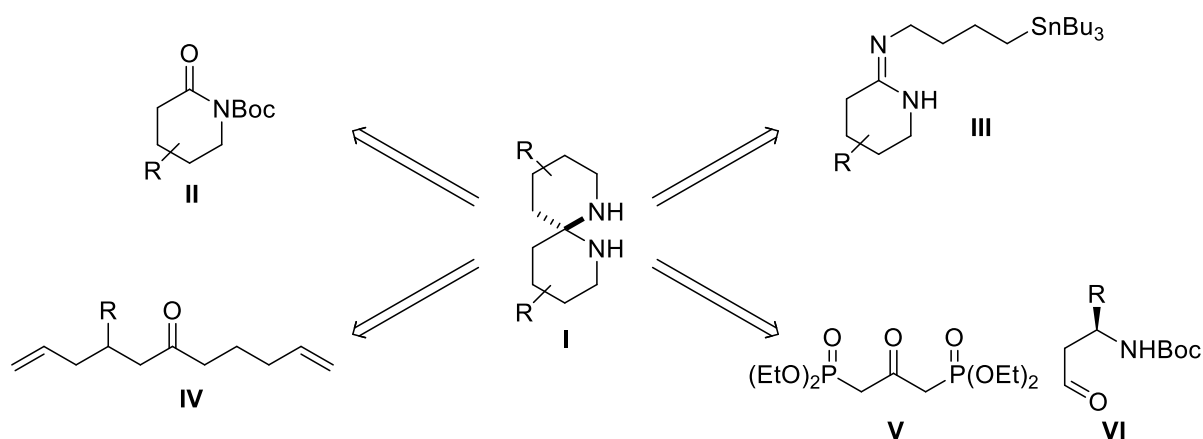
The second part of this thesis concentrates on the synthesis of tetrahydrospirobiquinolines and their derivatives.[ii] The methodology developed utilises simple conditions, withstands a range of functional groups, and allows many substrates to be accessed under mild conditions. These compounds showed 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.

IX
11 examples
34-82% yield
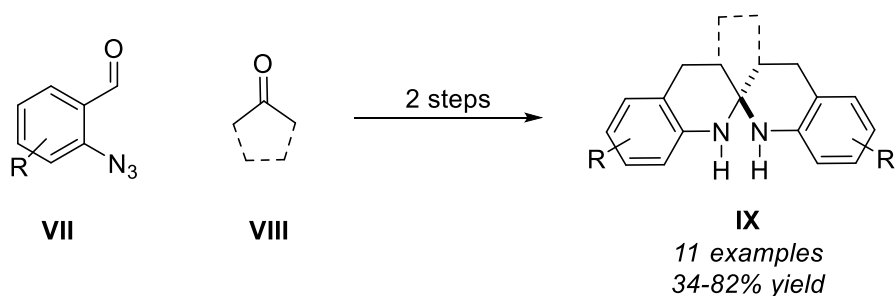
The final part of this thesis details the attempts to complex these newly isolated compounds to a variety of elements across the periodic table, as well as initial investigations into their biological activities.

i) Cordes, J.; Murray, P. R. D.; White, A. J. P.; Barrett, A. G. M. *Org. Lett.* **2013**, *15* (19), 4992.

ii) Almond-Thynne, J.; White, A. J. P.; Polyzos, A.; Rzepa, H. S.; Parsons, P. J.; Barrett, A. G. M. *ACS Omega* **2017**, *2* (7), 3241

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.

Secondly, I thank Doctor Tash Polyzos, he was always ready to talk chemistry even though we were on the other side of the planet to each other. He made my time in Melbourne very enjoyable. I hope to get the chance to visit him, and his amazing group (of PCs) again.

Professor Phil Parsons has become a very close friend to me. When I needed to talk to someone about anything at all, he was always there for me. I will miss working with him day to day but I am sure we will see a lot of each other in the future.

Claire Weston gets my deepest thanks, from proof reading my illiterate gibberish, down to allowing me to talk at her about chemistry for hours on end whenever I needed to. I love you, even if you do not love chemistry anymore.

I also extend my thanks for the huge number of academic staff that have helped me along the way, from casual chats through to helping me with various aspects of my project: Chris Cordier, Mark Crimmin, Virginia Manch, Andrew White, Henry Rzepa, Alan Spivey, Pete Haycock, Andrew Hughes, Don Craig, Chris Braddock, Alan Armstrong, Matt Fuchter and Lisa Haigh.

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

$[\alpha]^{25}_D$	specific rotation
Δ	heat
ΔG	Gibbs free energy
Å	Angstrom (10^{-10} metres)
Ac	acetyl
Acac	acetylacetonate
Ac_2O	acetic anhydride
AIBN	azobisisobutronitrile
Anal.	analysis
Aq.	aqueous
Ar	aryl
Atm	atmosphere (unit)
Boc	*tert*-Butyloxycarbonyl
BINAP	(2,2'-bis(diphenylphosphino)-1,1'-binaphthyl)
Bn	benzyl
bp	boiling point
Bu	butyl
Bz	benzoyl
°C	degrees Celsius
cat.	catalytic
CI	chemical ionisation
conc.	concentrated
δ	chemical shift
d	doublet
DCC	*N,N'*-dicyclohexylcarbodiimide
dd	doublet of doublet

ddd	doublet of doublet of doublet
DIBALH	diisopropylaluminium hydride
DIPEA	*N,N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
d.r	diastereomeric ratio
dt	doublet of triplets
dq	doublet of quartets
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
e.e	enantiomeric excess
EI	electron ionization
Elem.	elemental
equiv.	equivalents
ES	electrospray
Et	ethyl
h	hour
HBTU	O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HMDS	bis(trimethylsilyl)amine
HMPA	hexamethylphosphoramide
HPLC	high-performance liquid chromatography
Hz	hertz
i	iso
IBX	2-iodoxybenzoic acid
IC$_{50}$	half maximal inhibitory concentration
IPA	2-propanol

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

ppm	parts per million
ppy	2-phenyl-pyridine
PPTS	pyridinium para-toluenesulfonate
Pr	propyl
PTSA	para-toluenesulfonic acid
py	pyridine
q	quartuplet
R	general substituent
RCM	ring-closing metathesis
Rt	room temperature
s	singlet
SM	starting material
t or *tert*	tertiary
t	triplet
TBAF	tetrabutylammonium fluoride
TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TOF	turnover frequency
TON	turnover number
TS	transition state
UV	ultra-violet light
Vis	visible spectrum light
X	halide or pseudohalide

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CHAPTER ONE

GENERAL INTRODUCTION

1. General Introduction

1.1 Spirocyclic Compounds

Modern approaches in medicinal chemistry are increasingly exploring sp^3-rich compounds in bioactive discovery programmes.[1] 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.[1] Spirocyclic 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.[2]

Cipargamin (**1**)
Antimalarial

Spironolactone (**2**)
Antiandrogen

Griseofulvin (**3**)
Antifungal
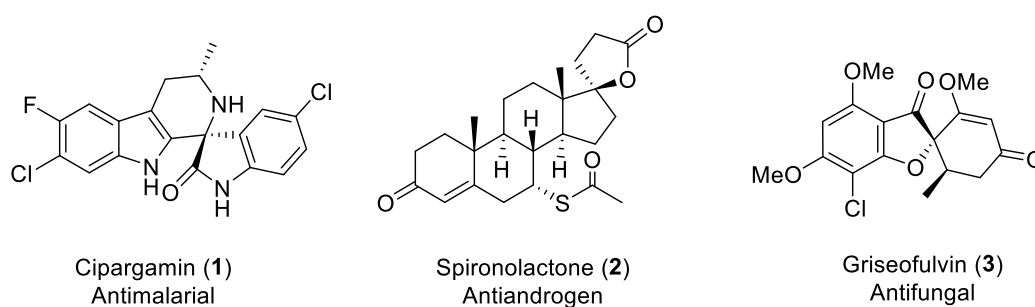
Figure 1: *Spirocyclic pharmaceuticals.*

Accordingly, there has been a drive to establish methodology to synthesise and install these spirocyclic centres in a variety of scaffolds. [3] Several laboratories have focused on library based synthesis of novel spirocycles, including the Bode group with SnAP chemistry[4–6] and the Carreira group with spirocyclic amines[7–9] (Scheme 1).
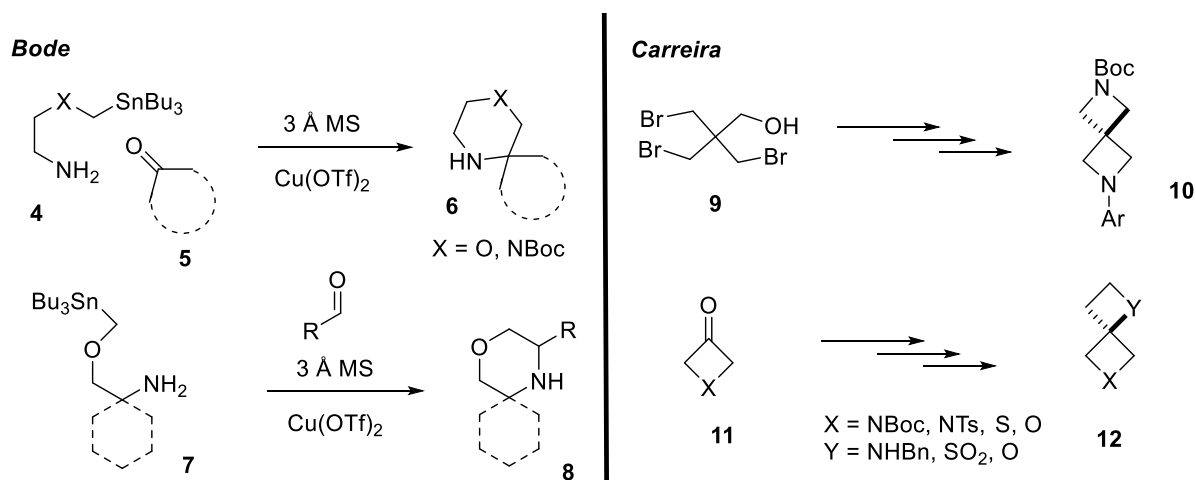
Scheme 1: *Notable spirocyclic syntheses by Bode and Carreira.*[4–9]

In addition to applications in medicinal chemistry, spirocylic 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 Zhou[11] which has notably used by Fu for photocatalysed C-N cross couplings (Scheme 2).[12]
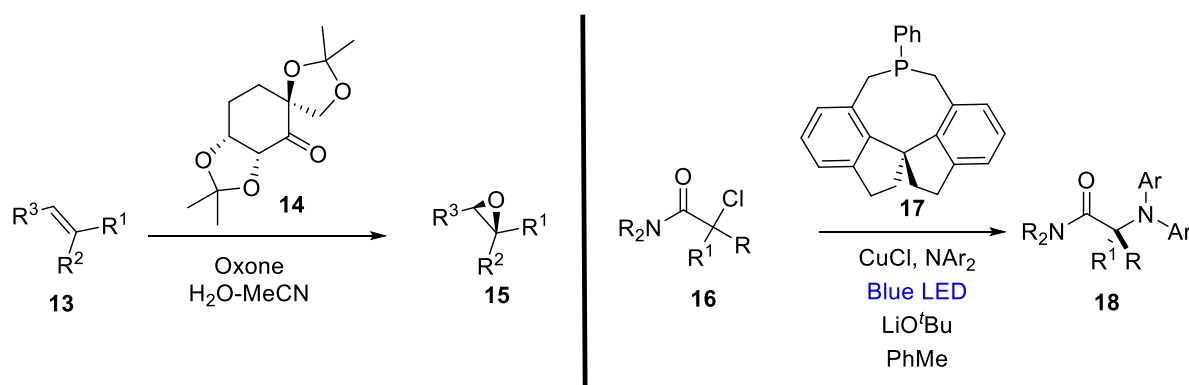
Scheme 2: Examples of spirocycles in catalysis.[10,12]

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 Spiroketals

Spiroketals 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]

(2R,5S,7S)-7-butyl-2-methyl-1,6-
dioxaspiro[4.5]decane (19)
(*Andrena haemorrhoa*)

Milbemycin β3 (20)
(*Streptomyces hygroscopicus*)

Berkelic acid (21)
(*Euglena mutabilis*)
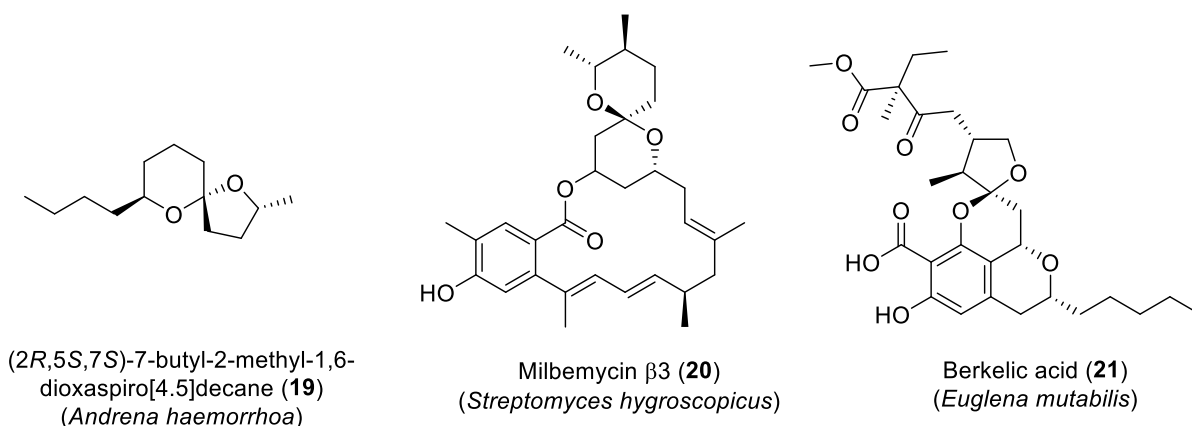
Figure 2: Spiroketal natural products.[13–17]

Thus, spiroketals have been identified as a privileged scaffold for novel drug discovery[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 **22**,[19] and the highly potent spiroketal adduct **23** for potential treatment of B-cell chronic lymphocytic leukaemia.[18] The benzannulated spiroketal, Tofogliflozin (**24**) was approved in 2014 as a sodium-glucose transport protein (SGLT2) inhibitor for the treatment of diabetes.[20]

Sialyl Lewis X mimic (22)
neutrophil/E-selectin binding inhibition

23
*Potential therapeutic agent
for B-cell chronic lymphocytic leukaemia*

Tofogliflozin (24)
SGLT2 Inhibitor
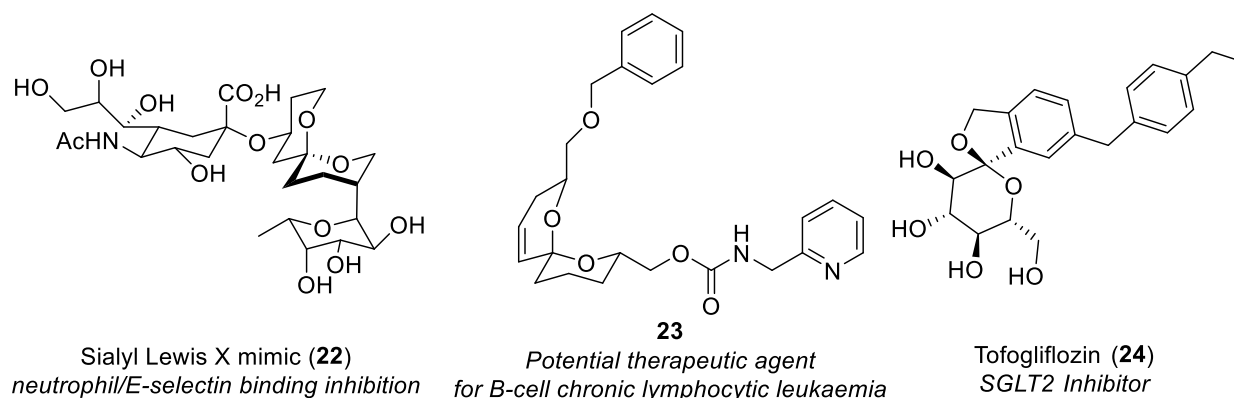
Figure 3: Biologically active spiroketals.[18–20]

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 σ* 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]

25-A   **25-B**   **25-A**   **25-B**
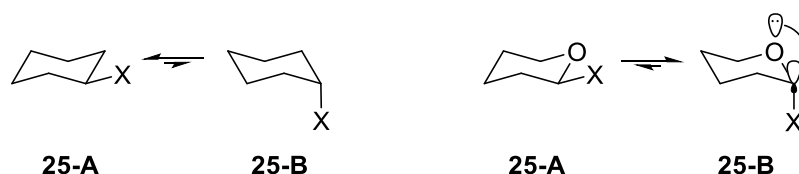
Figure 4: A basic representation of the anomeric effect.

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.

27-A
(0 kcal mol^{-1})

27-B
(+2.4 kcal mol^{-1})

27-C
(+4.8 kcal mol^{-1})
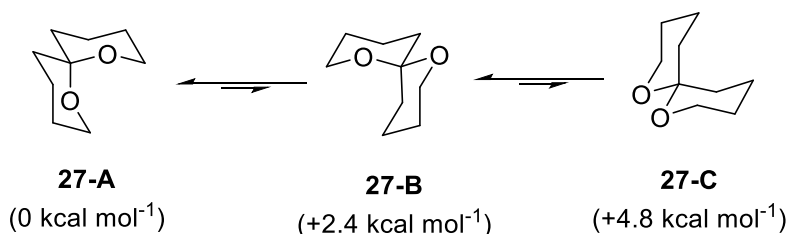
Figure 5: The possible conformations of 27 and their relative calculated energies (Adapted from Deslongchamps[21]).

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.[22,23] 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.[24]

1.3 Spirohemiaminals

Recently, spiro (*N,O*) ketals or "spirohemiaminals" have gained further attention.[25] 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**),[26] solasodine (**29**),[27] marineosin A (**30**),[28] and pandamarinelactone (**31**).[29]

Azaspiracid-1 - **28**

Solasodine - **29**

Marineosin A - **30**

Pandamarinelactone-1 - **31**
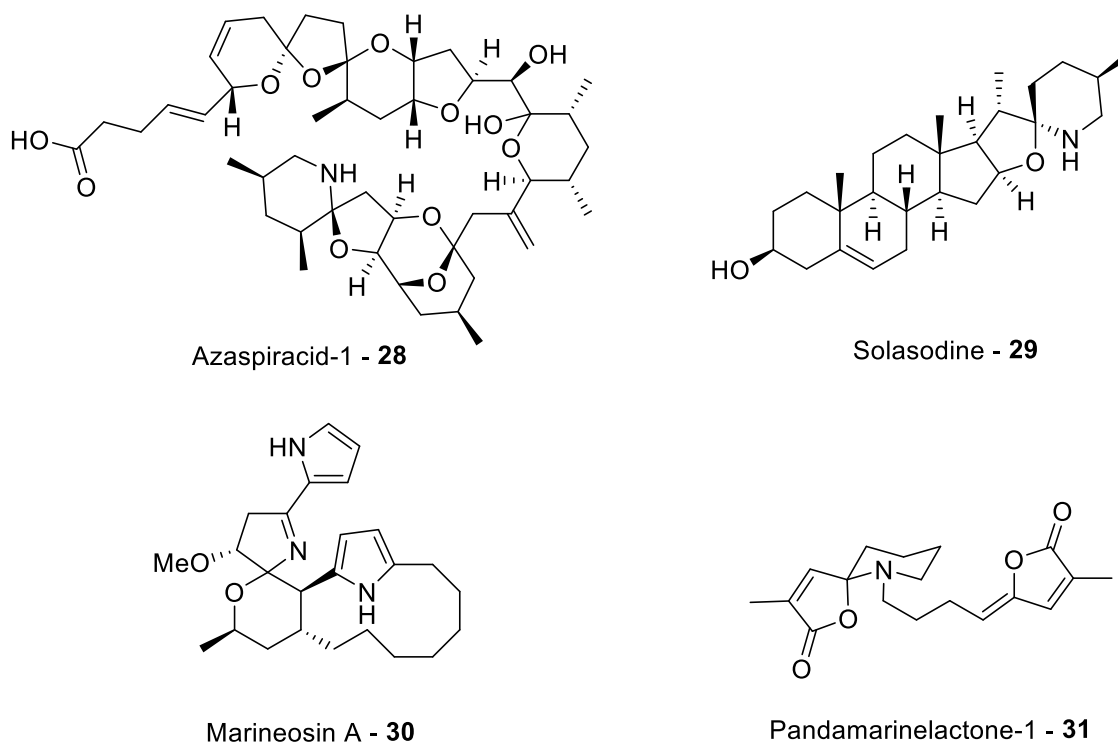
Figure 6: Examples of spirohemiaminal natural products.

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 activity[28] 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 materials[33] and photodynamic systems.[34]
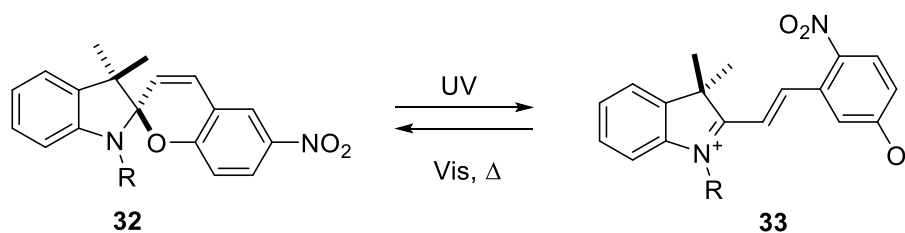
*Figure 7: Spiropyran **32** to merocyanine **33** photoswitch.*

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 C_{spiro}-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.[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.[35] However, out of the reported spiroaminal natural products, the indole alkaloid family contain the majority. Some notable examples are (+)-leuconodine F (**34**),[36] peganimune A (**35**),[37] (+)-melodinine E (**36**),[38] as well as the tetrahydroquinoline alkaloid isoschizogamine (**37**) and recently isolated (±)-spiroreticulatine (**38**)[39] (Figure 8).[40–43]

(+)-Leuconodine F
34

(+)-Peganumine A
35

(+)-Melodinine E
36

(-)-Isoschizogamine
37

(±)-Spiroreticulatine
38
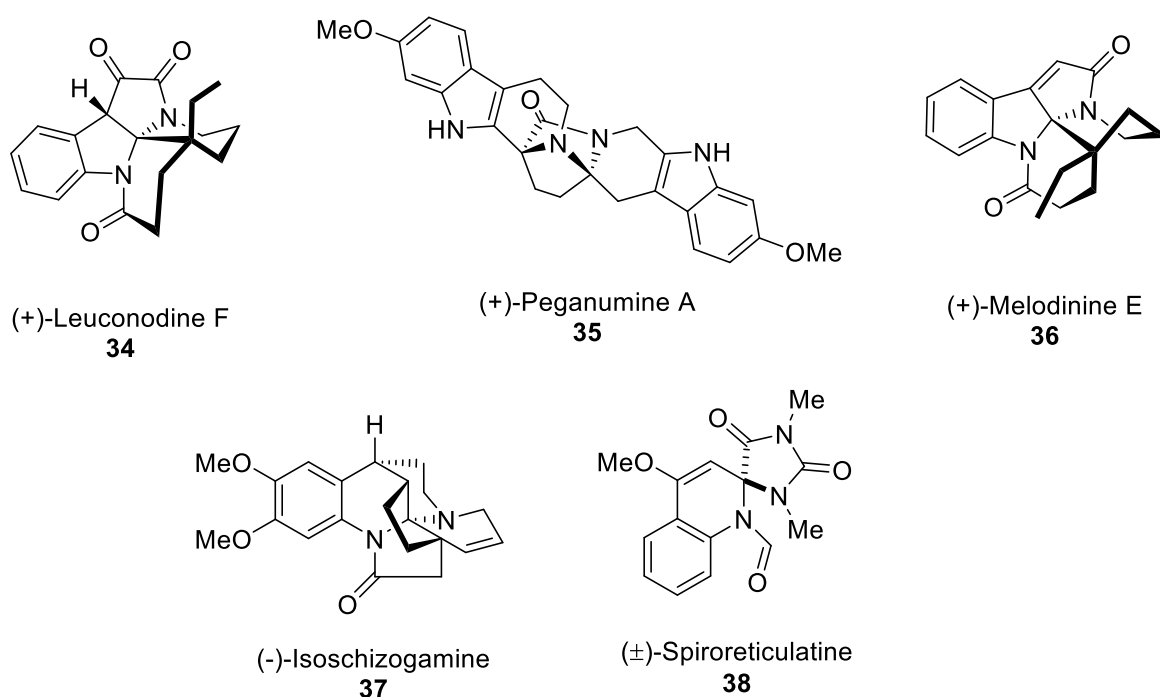
Figure 8: *Spiroaminal containing natural products.*

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.[36,37,40] Other notable syntheses of isoschizogamine (**37**) have been achieved by Heathcock[43] and Fukuyama[42] (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).[39] 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**),[44] and pandamarine (**41**),[45] which are all isolated from *Pandanus amaryllifolius*, a commonly used ingredient in Asian cuisine (Figure 9).[46]

Pandanusines A - **39**   Pandanusines B - **40**   Pandamarine - **41**
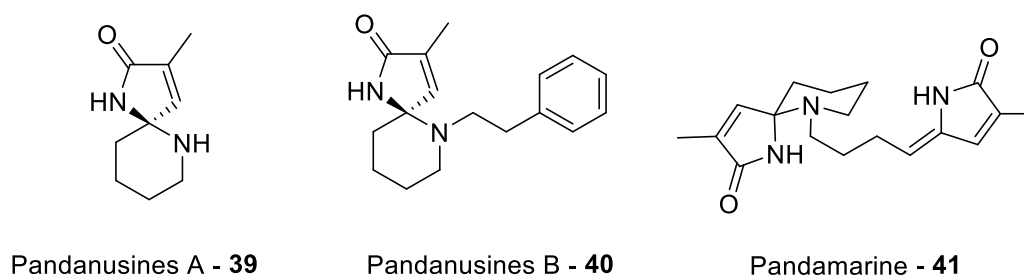
Figure 9: Spiroaminals extracted from Pandanus amaryllifolius.

A number of other structurally interesting alkaloids have been isolated from the *Pandanus* genus in addition to compounds **39**-**41**.[47] There has, however, been some scepticism as to whether pandamarine is an artefact of isolation.[29] 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).[35,48–51] 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,[48] treatment of lactams (**42-46**) with POCl$_3$ in refluxing chlorobenzene yielded the intermediate enamino-lactams, followed by refluxing in concentrated HCl for 22-48 h afforded the suspected spiroaminals **47-A** - **51-A** (Scheme 3).
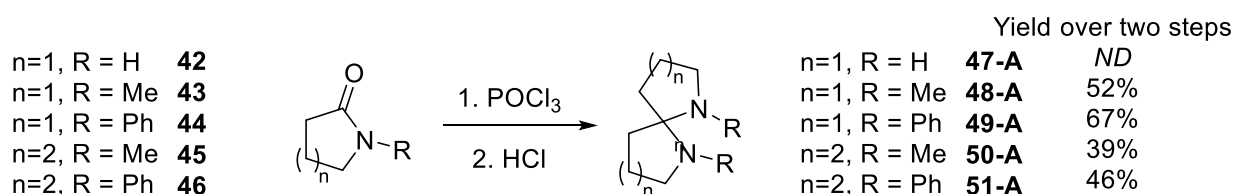
Scheme 3: The Büchel spiroaminal synthesis.[48]

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.[49] 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 ^{1}H and ^{13}C 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.
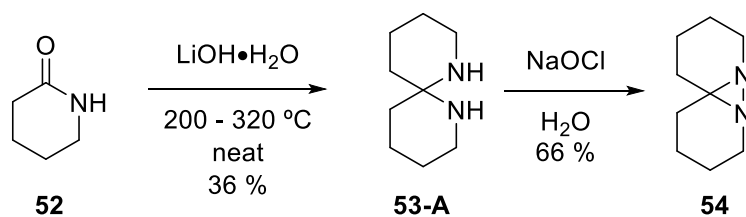
Scheme 4: The Kaupp synthesis of spiroaminal 53-A and diaziridine 54.[49]

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]
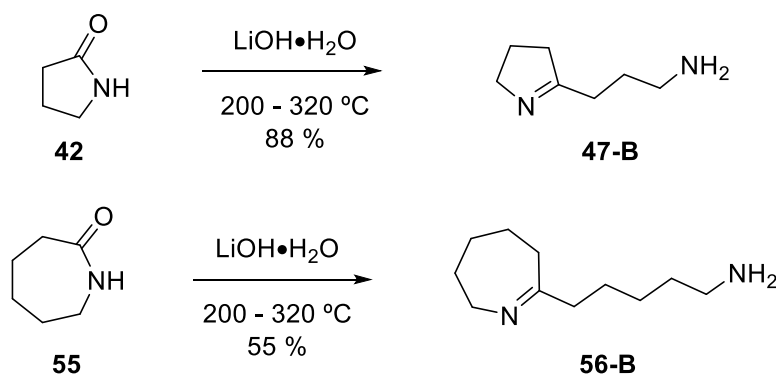
Scheme 5: The amine-imine tautomers 47-B and 56-B reported by Kaupp.[49]

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 β-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

at elevated temperatures, afforded spiroaminal **53-A** after purification by chromatography (84% yield, three steps, Scheme 6).
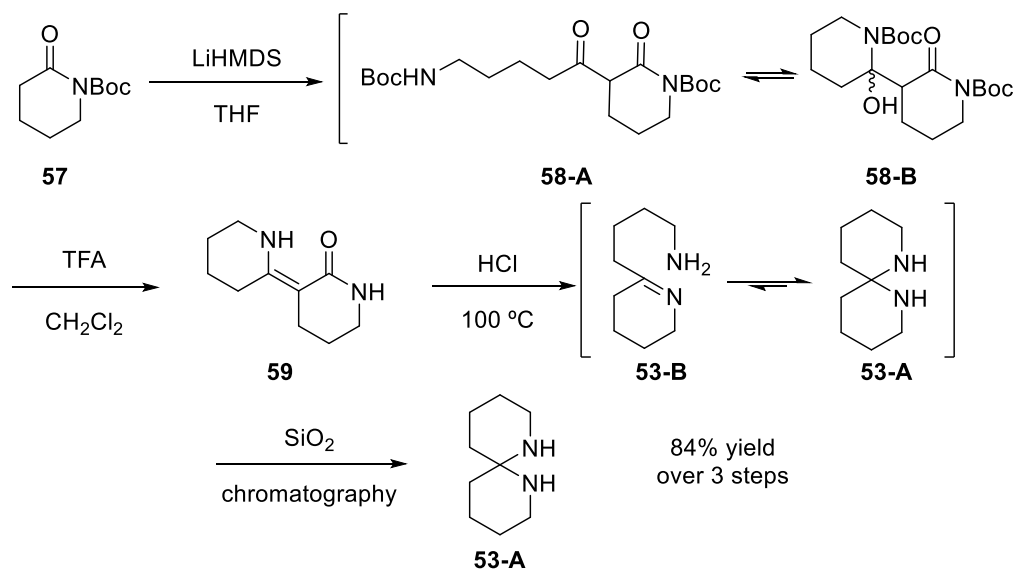
Scheme 6: *The Barrett synthesis of spiroaminal **53-A**.*[35]

The final step was proposed to consist of hydrolysis of both the enamine and lactam centres, yielding the α-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]
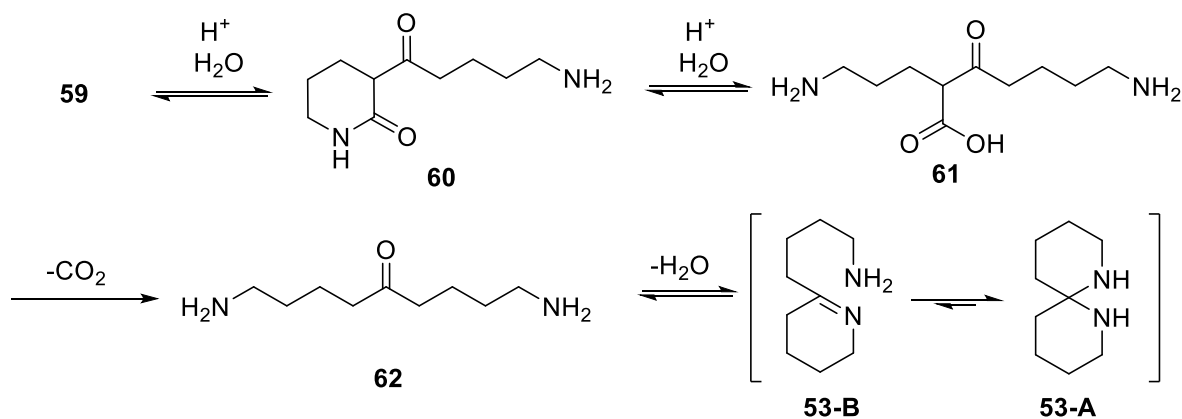
Scheme 7: *Proposed mechanism for the decarboxylation/spirocyclisation of enamine **59**.*

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). [35]
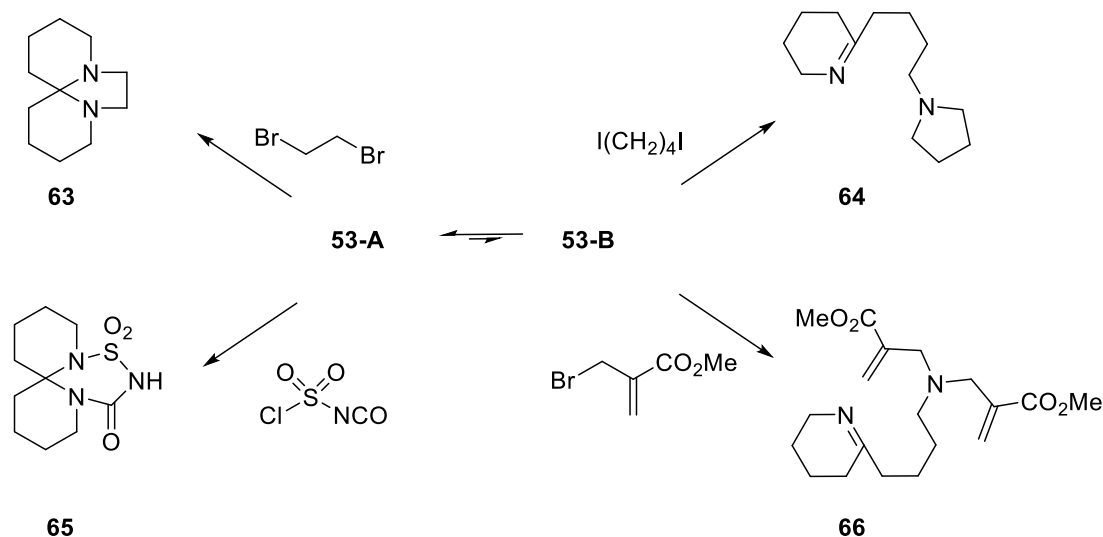
Scheme 8: The reaction of 53 with a range of dielectrophiles.

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).

Scheme 9: Complexation chemistry of spiroaminal 53.

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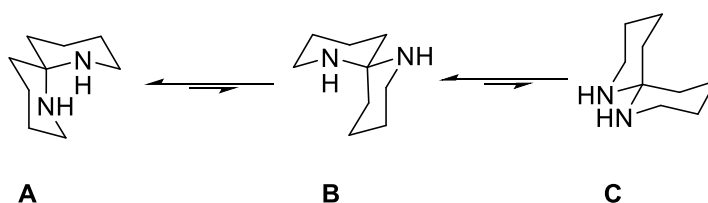
Figure 10: *Three possible ring conformations of spiroaminals. Adapted from the work of Thiel.*[50]

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 $\sigma^*(C-N)$ or $\sigma^*(C-C)$, depending on the orientation of the opposing ring. For example, donation into the $\sigma^*(C-N)$ affords the most stabilisation (13-16 kcal mol^{-1}), as well as playing 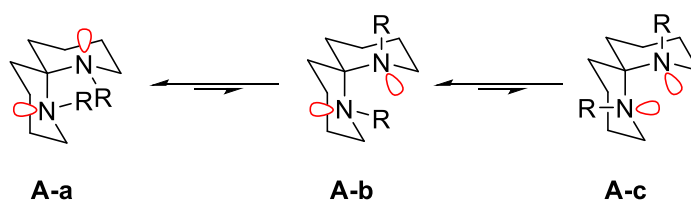a key role in the ring opening tautomerisation. For example, conformation **A-a** both the C-N bonds are axial to the opposing ring leading to $n(N)\rightarrow\sigma^*(C-N)$ in both directions. Conformation **B-a** contains one $n(N)\rightarrow\sigma^*(C-N)$ and one $n(N)\rightarrow\sigma^*(C-C)$, whereas

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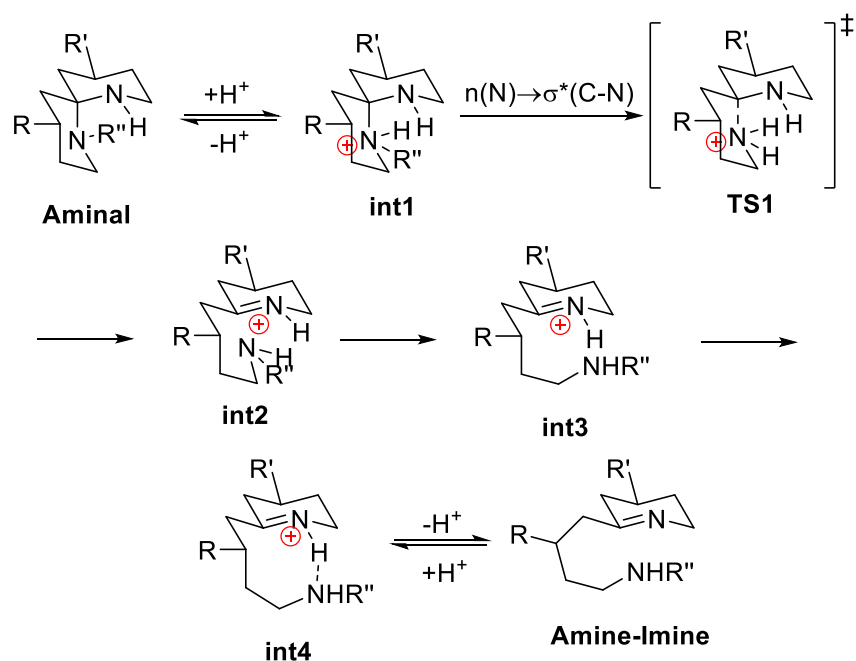
Scheme 10: *The proposed mechanism of the aminal / amine-imine tautomerisation. Adapted from the work of Thiel.*[35]

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 **53-A** was shown to be in almost equilibrium with its amine-imine tautomer **53-B** (Figure 12).

$\Delta G_{int1 \to int4} =$ -0.4 kcal mol-1 $\quad$ $\Delta G_{int1 \to int4} =$ -2.6 kcal mol-1 $\quad$ $\Delta G_{int1 \to int4} =$ +1.4 kcal mol-1a $\quad$ $\Delta G_{int1 \to int4} =$ +3.1 kcal mol-1a

53-A $\quad$ **69-A** $\quad$ **70-A** $\quad$ **71-A**
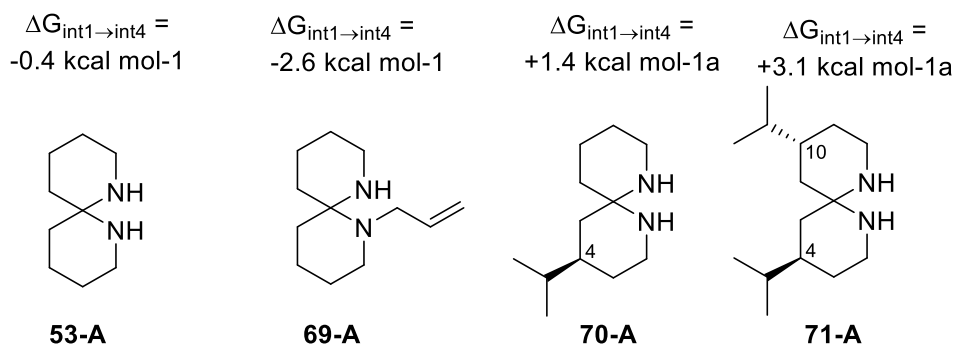
Figure 12: The relative free energies of ring opening tautomerisation. Adapted from Thiel.[50]

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.[50]

2.2 Lactam Synthesis

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.[49] Lactams **42**, **52**, **55** were easily protected under the standard conditions[52] to yield the precursors to the Claisen reaction in good yields (Scheme 11).

n = 1 ; **42**
n = 2 ; **52**
n = 3 ; **55**

Boc$_2$O
DMAP

MeCN

Yield	
n = 1 ; 68%	**72**
n = 2 ; 77%	**57**
n = 3 ; 56%	**73**
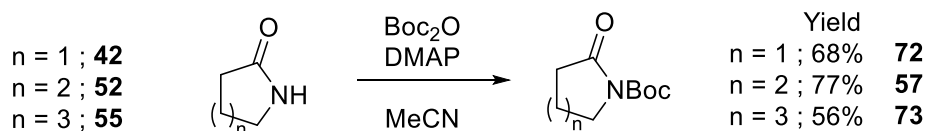
*Scheme 11: Boc-protection of lactams **72, 57** and **73**.*

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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[53] and ruthenium / sodium periodate-based oxidation afforded lactam **76** in good yields (Scheme 12).[54]
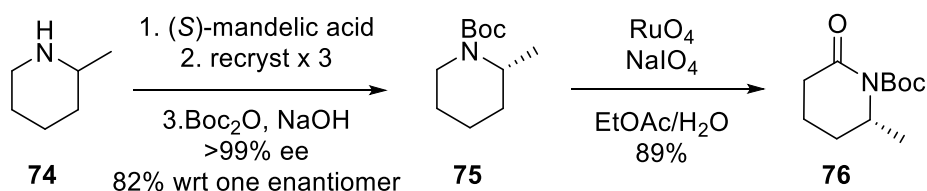
*Scheme 12: The synthesis of (R)-2-methyl lactam **76**.*

More complex lactams were accessed through organometallic addition to Ellman sulfinimine **79**.[55] Sulfinimine **79** was synthesised in two steps from cyclopentene (**77**) through Schreiber ozonolysis,[56] reported by Carreira,[57] 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.[58] Boc protection under standard conditions afforded *N*-Boc lactams **84** and **85**.
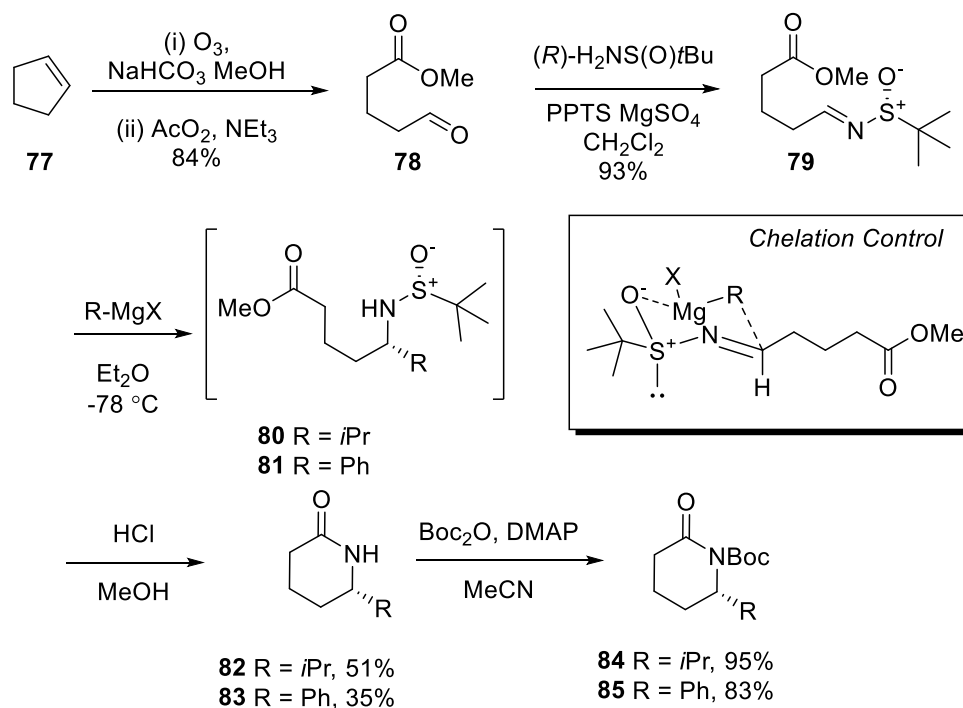
Scheme 13: *The synthesis of 2-substituted lactams via the Ellman sulfinimine **79**.*

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).[59]
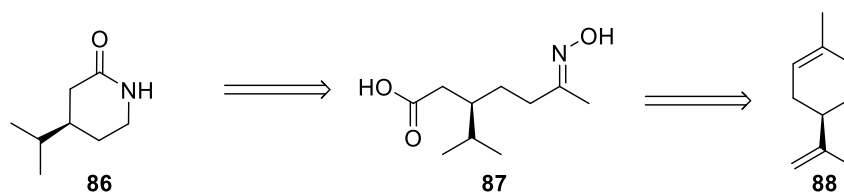
Scheme 14: *Jackman's retrosynthetic analysis of lactam **86**.*[59]

The isobutylene of **88** was hydrogenated using PtO$_2$ at 1.5 atm of H$_2$.[60] 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.
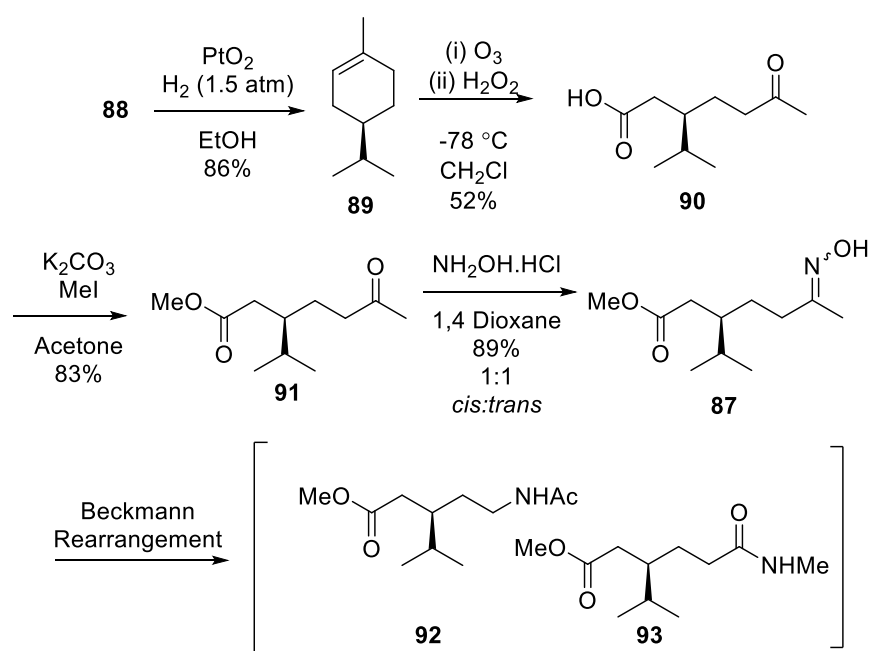
***Scheme 15** Approaches to 86 from (+)-limonene (88).*

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).[61] Lactam **95** was prepared from **57** in a one pot procedure using the Mukaiyama methodology.[62] 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.
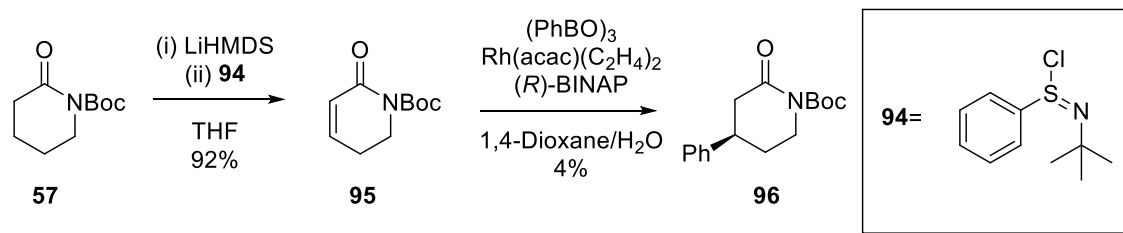
Scheme 16:Hayashi approach to 4-substituted lactam 96.

Pigs liver esterase (PLE) is an enzyme commonly utilised in enzymatic resolutions within organic synthesis.[63] In this case PLE was used in the desymmetrisation of 3-substituted dimethyl glutarates **100** (Scheme 17).[64]
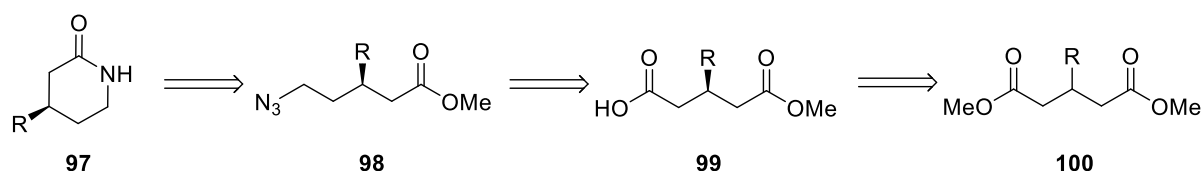
Scheme 17: Retrosynthesis of 4-substituted lactams utilising a PLE desymmetrisation.

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).[65]
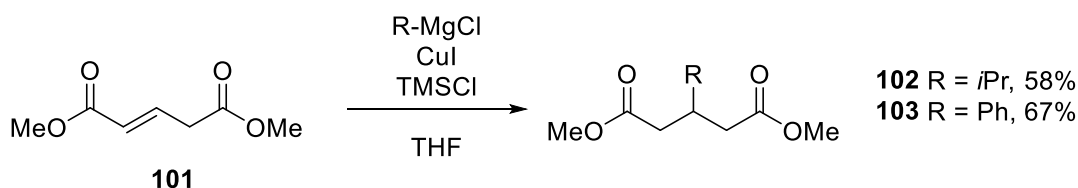
Scheme 18: Preparation of 3-substituted dimethyl glutarates 102 and 103.

Compounds **102**, **103** as well as the commercially available **104** were subjected to the conditions of Jones,[63] 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

to form lactams **114-116**.[63] *N*-Boc lactams **117**, **96**, and **118** were afforded after subsequent

protection under standard conditions (Scheme 19).

102 R = *i*Pr
103 R = Ph
104 R = Me

PLE
1 M NaOH

KH$_2$PO$_4$ buff.
pH 7

105 R = *i*Pr - 68% - (*S*) [α]$_D$ = +1.0
106 R = Ph - 67% - (*S*) [α]$_D$ = +44.0
107 R = Me - 65% - (*R*) [α]$_D$ = -3.8

1. BH$_3$•SMe$_2$
2. MsCl, NEt$_3$

108 R = *i*Pr
109 R = Ph
110 R = Me

NaN$_3$

DMF

111 R = *i*Pr
112 R = Ph
113 R = Me

(i) PPh$_3$
(ii) H$_2$O

THF

114 R = *i*Pr   22% *4 steps*
115 R = Ph   7% *4 steps*
116 R = Me   37% *4 steps*

Boc$_2$O
DMAP

MeCN

117 R = *i*Pr 68% [α]$_D$ = -32.4
 96 R = Ph 76% [α]$_D$ = -20.0
118 R = Me 74% [α]$_D$ = +22.2
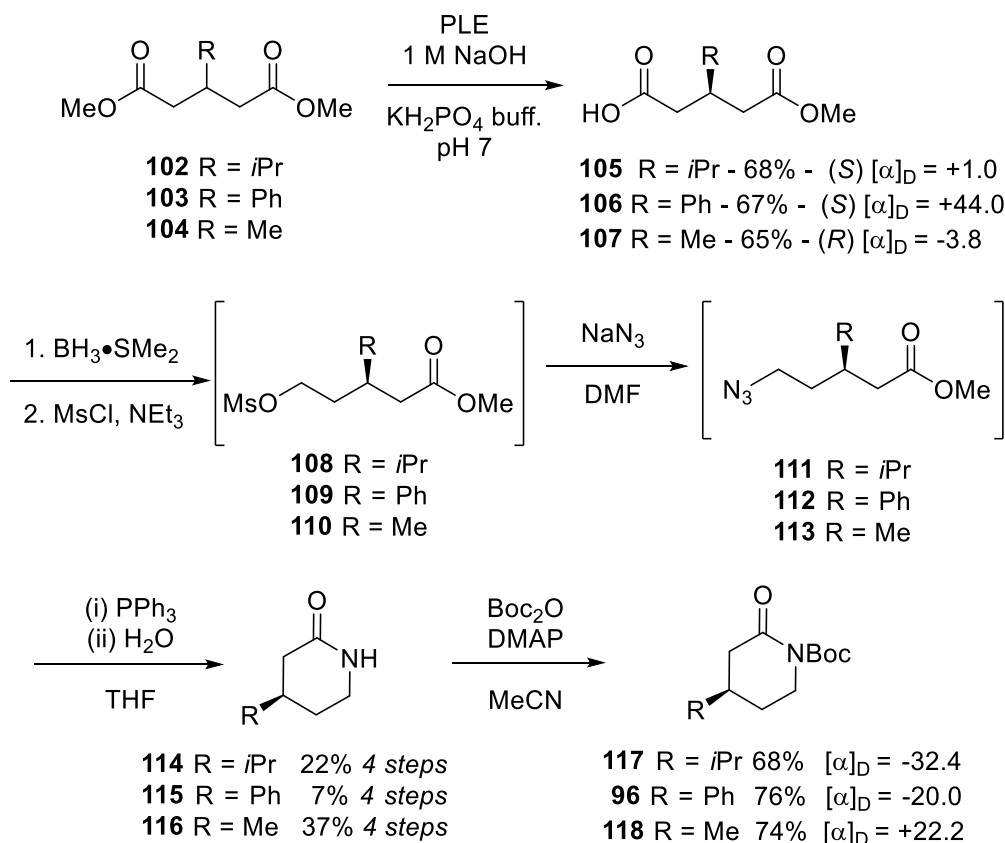
*Scheme 19: The synthesis of lactams **117**, **96** and **118**.*

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.[63] We hoped that both amplification of ee through recrystallisation, where

possible during the synthetic route, and amplification of ee through the Horeau principle[66]

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-A** was prepared using the conditions previously reported by the Barrett group (Scheme 20).[35]
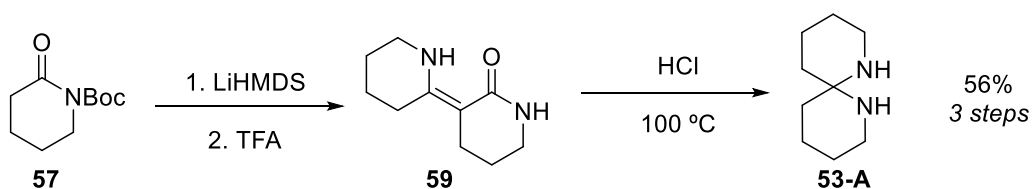
*Scheme 20 Synthesis of spiroaminal **53-A**.*

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-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).
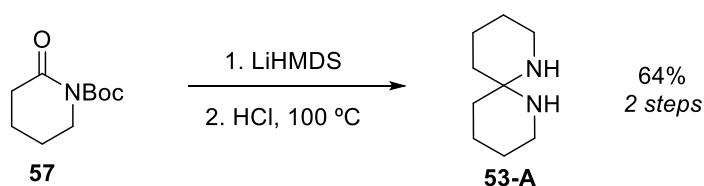
*Scheme 21: Shortened synthesis of spiroaminal **53-A**.*

This synthetic procedure was then performed on lactams **72**, **73** and **76**. Reacting butyrolactam **72** under these conditions afforded a mixture of spiroaminal **47-A** and the amine-imine **47-B** in an acceptable yield (Scheme 22). **47-A** and **47-B** are separable by column chromatography, however, spiroaminal **47-A** tautomerises over time to a mixture of the aminal and amine-imine tautomers. This is consistent with the observations of both Büchel[48] and

Kaupp[49] who independently claimed to make each tautomer exclusively. Presumably this tautomerisation is due to the increased strain on the smaller ring size. The equilibrium could not be influenced by temperature or solvent.
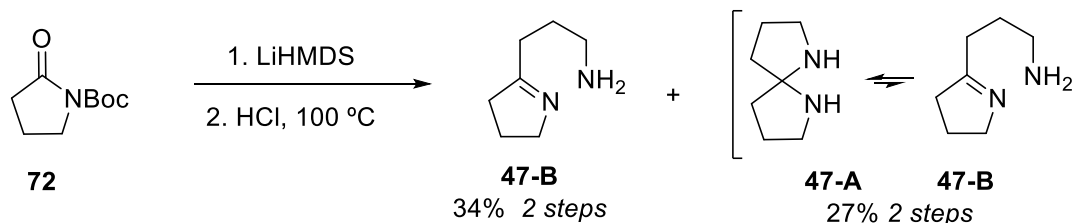
Scheme 22: *Synthesis of [4.4] amine-imine **47-B** and spiroaminal **47-A**.*

Caprolactam **73** afforded the product as its amine-imine tautomer **56-B** (Scheme 23). This corresponds to the findings of Kaupp,[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.
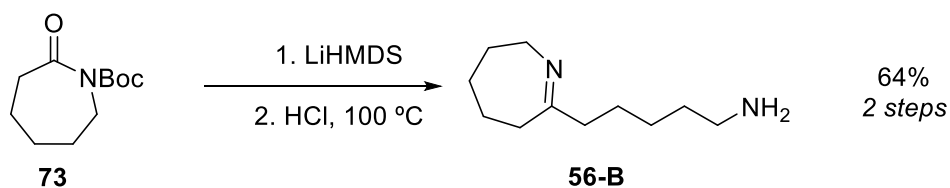
Scheme 23: *Synthesis of amine-imine **56-B**.*

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).
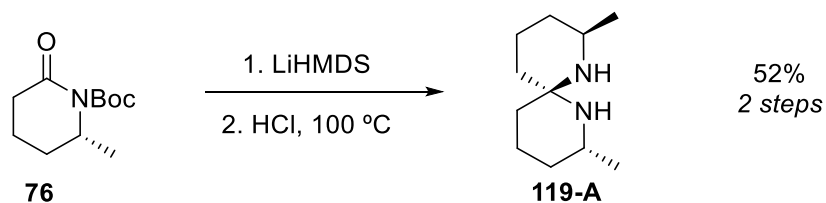
Scheme 24: *Synthesis of spiroaminal **119-A**.*
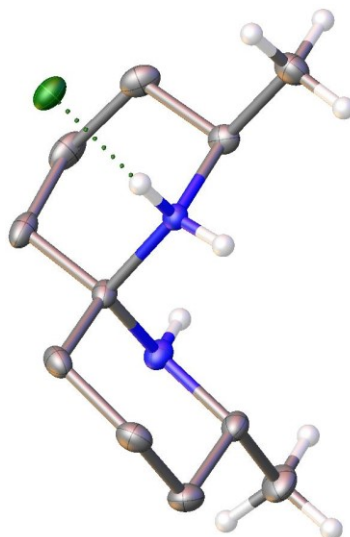
Figure 13: *Crystal structure of spiroaminal **119-A** hydrochloride salt (50% probability ellipsoids).*

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.[66] Additionally a single epimer was observed by ^{1}H and ^{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.
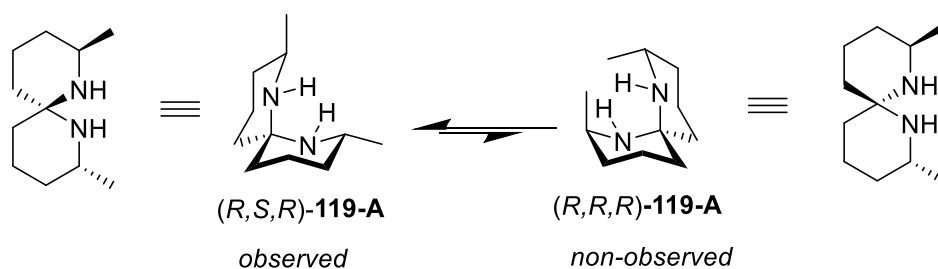
Figure 14: The two possible epimers of spiroaminal **119-A**.

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.
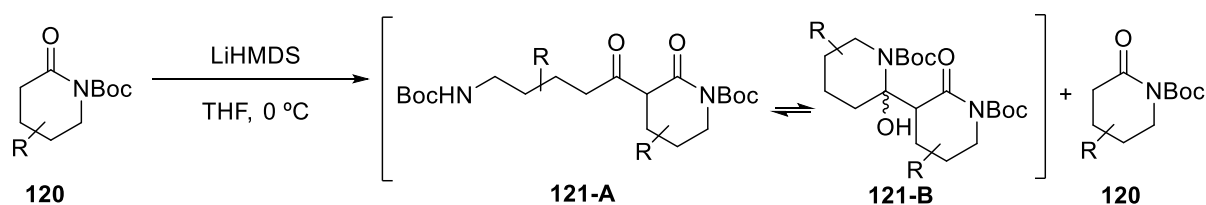
Scheme 25: Failed attempts of the Claisen condensation of substituted lactams.

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.[67] 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).
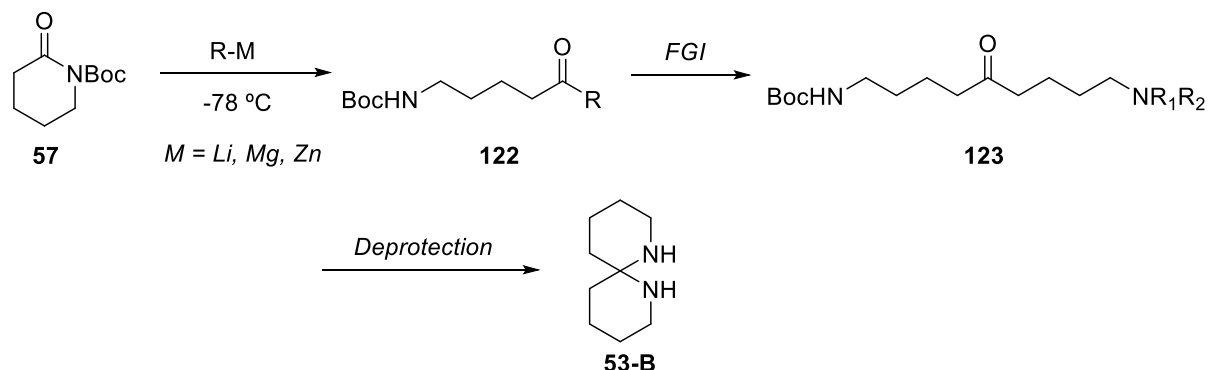
Scheme 26: Proposed route to spiroaminals employing an organometallic addition to lactams.

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.
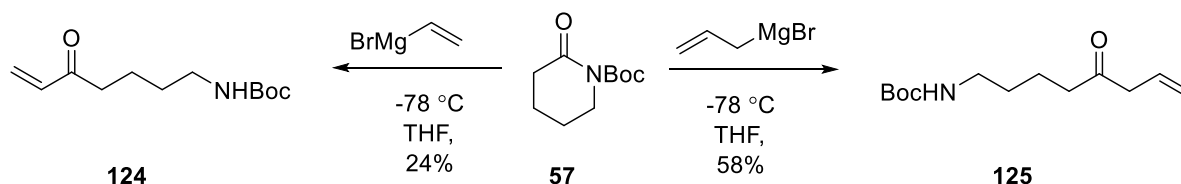
Scheme 27: *Synthesis of vinyl ketone **124** and allyl ketone **125**.*

The resultant ketones **124** and **125** were screened against a number of olefin metathesis conditions.[68] However only dimerisation of allyl amine **126** or homo-allyl amine **128** was observed (Table 1 and Table 2).
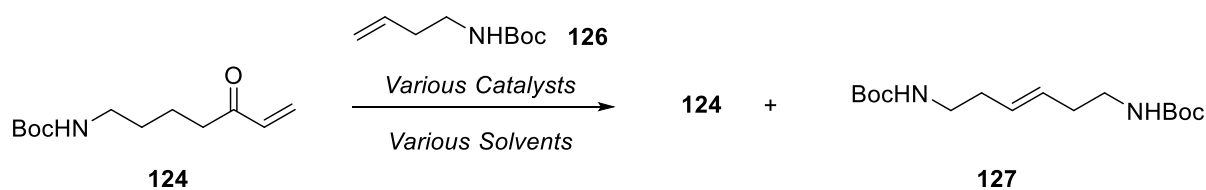
Entry	Catalyst	Equiv. 126	Solvent	Temp (Time)	Recovered 124 (%)	Yield 127 (%)
1	Grubbs 2	1.5	CH_2Cl_2	40 ºC (16 h)	90	36
2	Grubbs 2	1.0	CH_2Cl_2	40 ºC (16 h)	81	27
3	Grubbs 2	3.0	CH_2Cl_2	40 ºC (16 h)	85	35
4	Grubbs 2	1.5	CH_2Cl_2	rt (16 h)	69	25
5	Grubbs 2	1.5	C_6H_6	40 ºC (16 h)	94	17
6	Grubbs 2	1.5	PhMe	110 ºC (2 h)	98	39
7	Grubbs 2	1.5	PhMe	110 ºC (16 h)	68	41
8	GH-2[a]	1.5	CH_2Cl_2	rt (16 h)	93	10
9	GH-2[a]	1.5	CH_2Cl_2	rt (96 h)	60	25
10	GH-2[a]	1.5	CH_2Cl_2	40 ºC (8 h)	96	12

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.*

Table 2 Cross-metathesis conditions attempted between **125** and **128**. All reactions carried out on 0.1 mmol scale, with 5 mol% of catalyst.
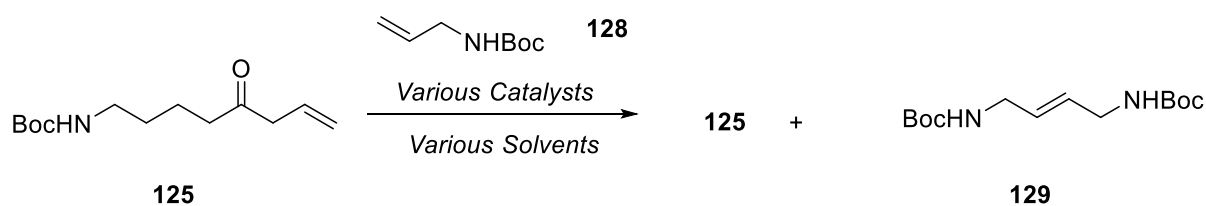
Entry	Catalyst	Equiv. 128	Solvent	Temp (Time)	Recovered 125 (%)	Yield 129 (%)
1	Grubbs 2	1.5	CH$_2$Cl$_2$	40 ºC (8 h)	68	53
2	Grubbs 2	1.5	CH$_2$Cl$_2$	rt (16 h)	90	62
3	Grubbs 2	1.5	CH$_2$Cl$_2$	rt (96 h)	78	53
4	Grubbs 1	1.5	PhMe	rt (16 h)	94	25
5	Grubbs 1	1.5	PhMe	110 ºC (4 h)	80	17

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.[69] 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.[69]
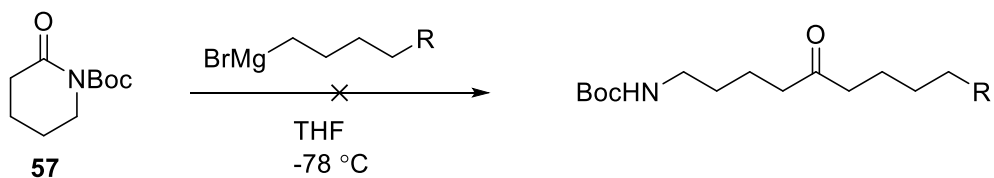
Entry	R	Product (Yield[a])
1	**(130)** 'STABASE' [69]	**134** (ND)
2	**(131)** 'BENZOSTABASE' [70]	**135** (ND)
3	**(132)** 'DPSide' [71]	**136** (ND)
4	OPMB (**133**) [72]	**137** (ND)

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 utilising radicals to produce spirocyclic compounds.[5,73] Most notable in recent years within this field is Bode's reported tin amine protocol or "SnAP" (see Section 1.1).[4,5] 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.[74,75]
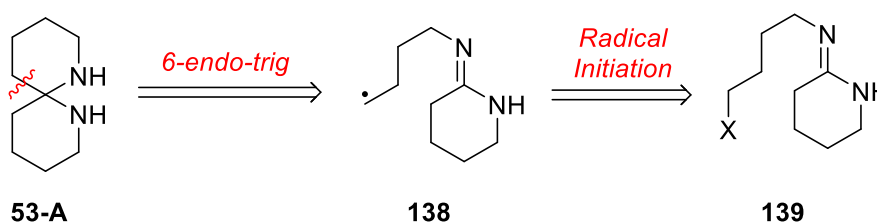
Scheme 28: *Retrosynthesis of spiroaminal 53-A via radical addition to amidines.*

Our first approach was in parallel with the work of Bode, but without the presence of a heteroatom alpha to the tin moiety.[6] 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.
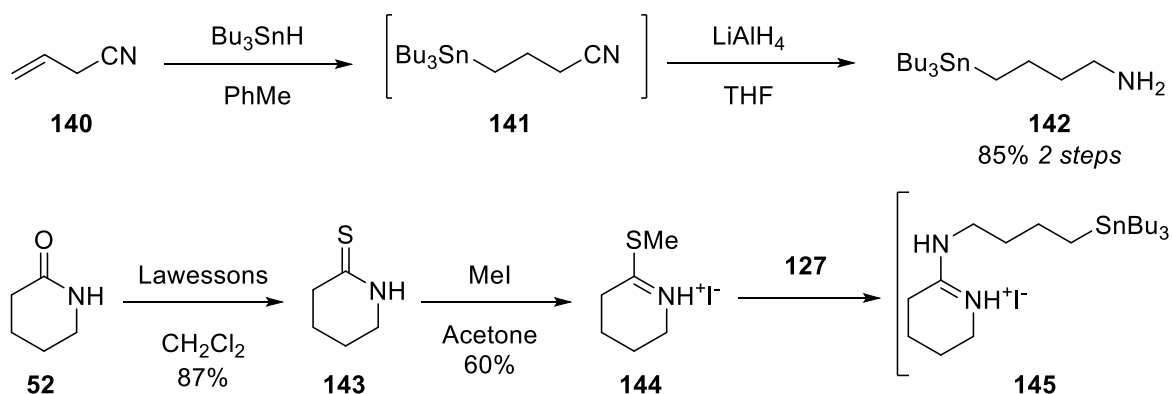
Scheme 29: *Synthesis of tin amidine 145.*

When amidine **145** was treated with the conditions developed by Bode,[6] 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.
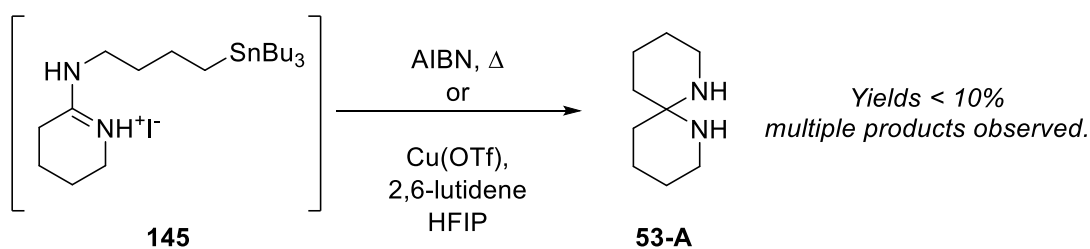
Scheme 30: *Attempted radical cyclisations of **145**.*

As a result, our attentions focused on producing a more stable radical intermediate, and with this is 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**.
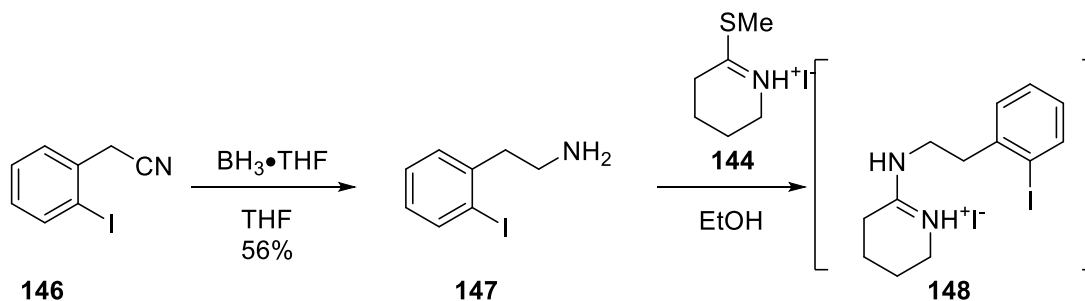
Scheme 31: *Synthesis of amidine **148**.*

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).
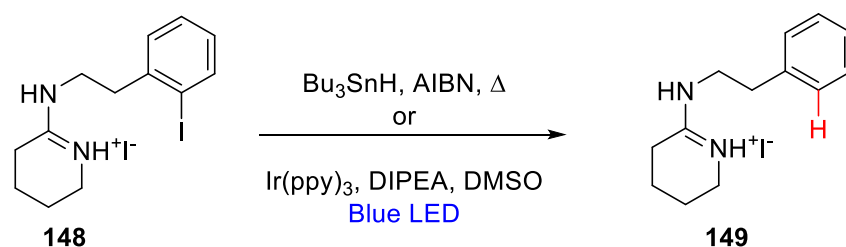
Scheme 32: *Attempted radical cyclisations of 133.*

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,[74] including prolonged addition of both radical initiator and radical propagating agents, however, none of these afforded the desired product.
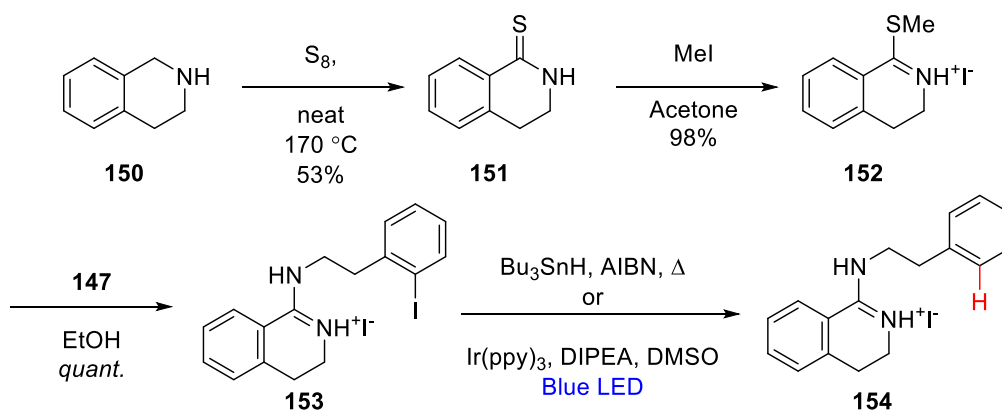
Scheme 33: *Dehalogenation of benzannulated 153.*

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.[76] 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).
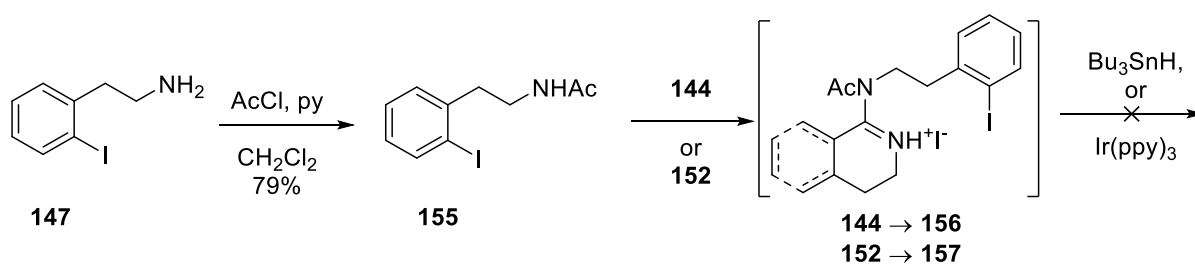
Scheme 34: The synthesis of acylated amidines 156-157.

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,[76] no conversion of starting material **159** was observed and after prolonged reaction times hydrolysis occurred (Scheme 35).
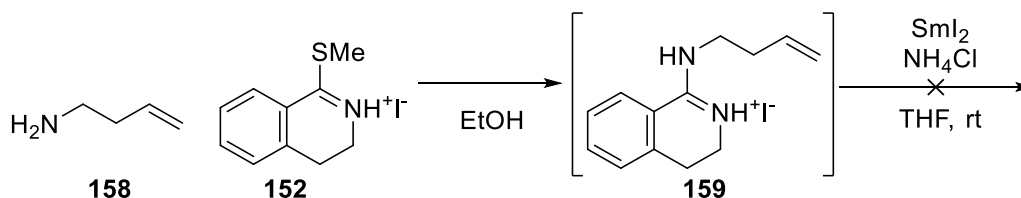
Scheme 35: The attempted radical aminal radical generation of 159.

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 is 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).[77] 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.

49
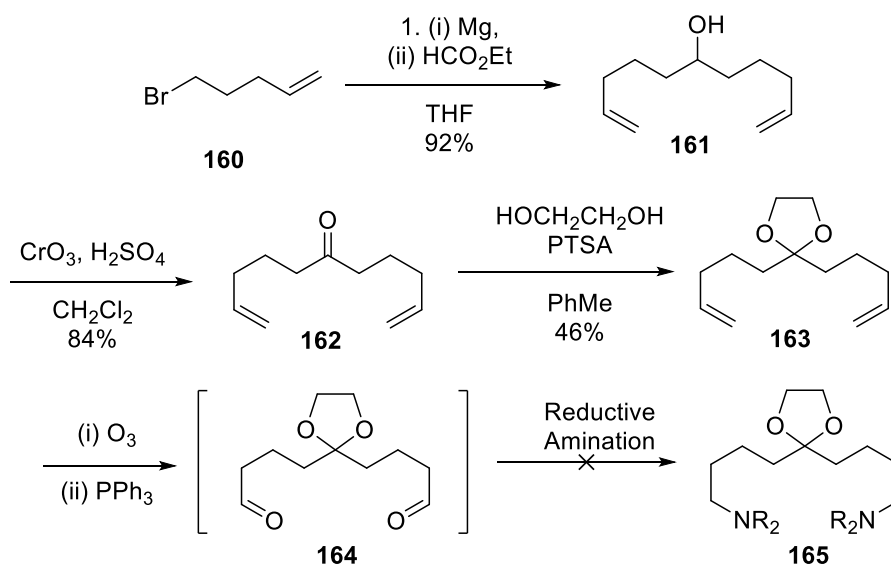
Scheme 36: *Synthesis of ketal diene **163** and attempted reductive amination of **164**.*

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.[78,79] Treatment of **163** with ozone and subsequent excess LiAlH$_4$ however, yielded alcohol **167** in good yields, without the need for purification (Scheme 37).
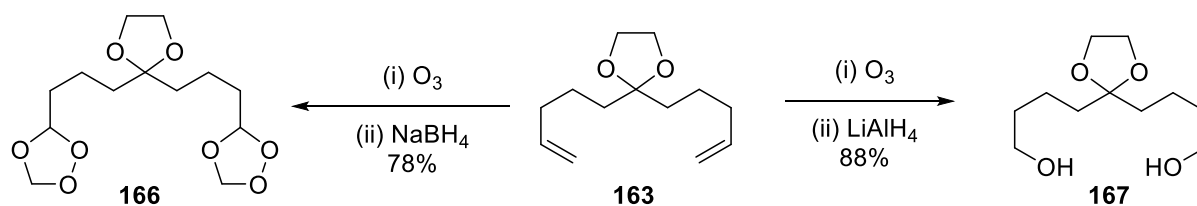
Scheme 37: *Ozonolysis of **163**.*

Ketal diol **167** was sequentially allowed to react with toluenesulfonyl 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).

50
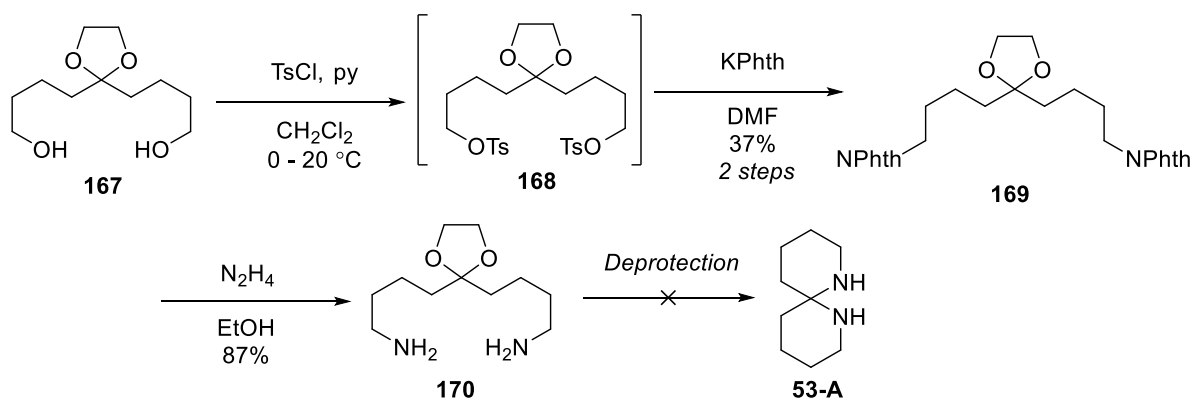
Scheme 38: *Synthesis of ketal diamine 152.*

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.
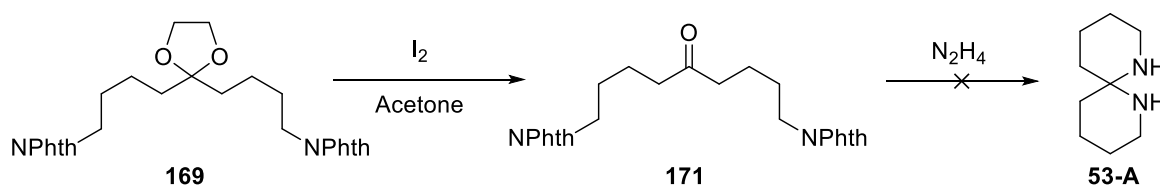
Scheme 39: *Deprotection of ketal 151.*

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).
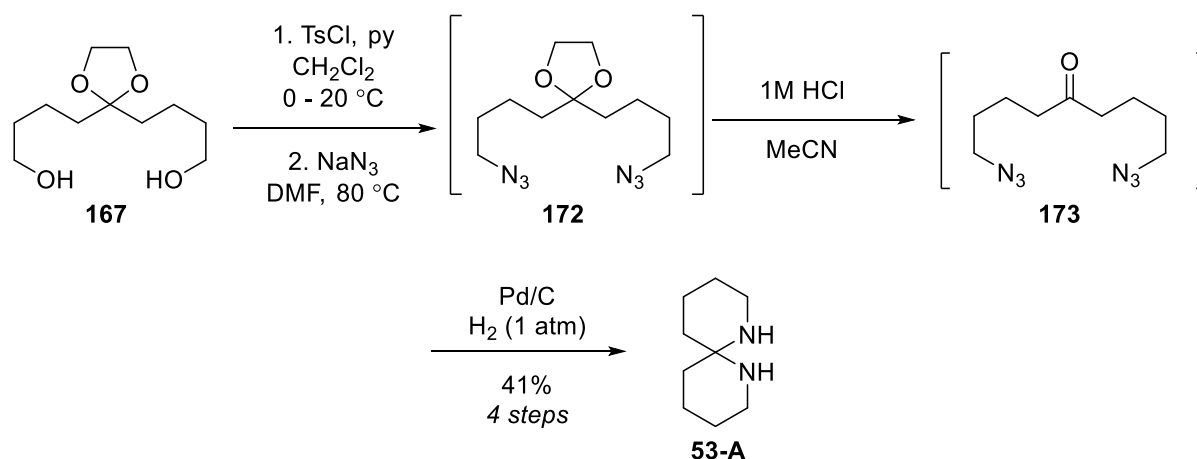
Scheme 40: *The new approach to spiroaminal **53-A**.*

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**.[80] Subsequent hydrolysis followed by Weinreb amide formation afforded Weinreb amide **177** in good yields (Scheme 41).
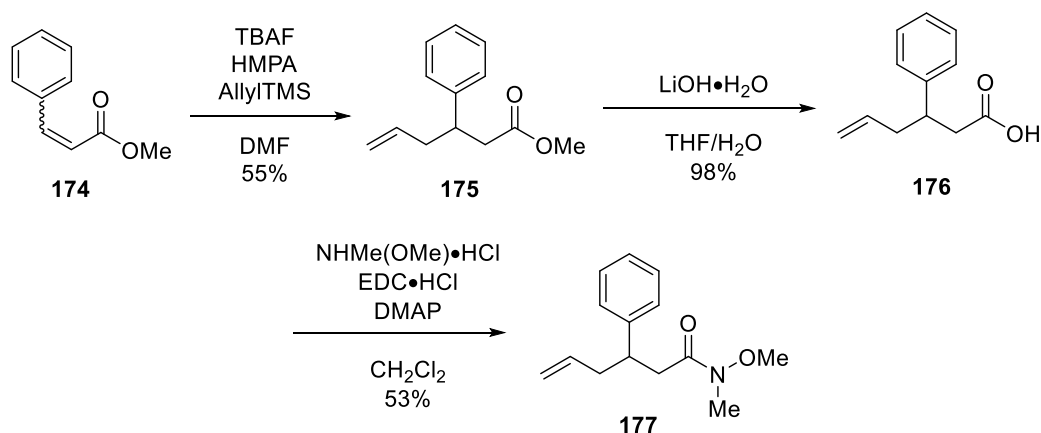
***Scheme 41:** Preparation of Weinreb Amide **177**.*

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).
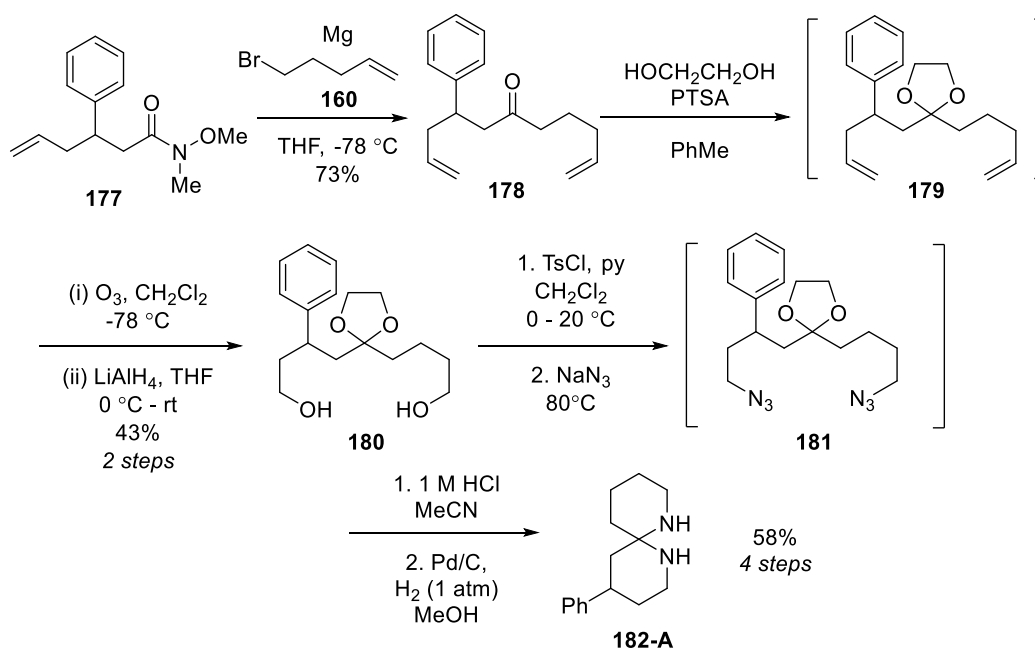
***Scheme 42:** The synthesis of mono-phenyl **182-A**.*

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 anomeric 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).

(R,S)   *(R,R)*   proposed diastereomer   *(S,S)*   *(S,R)*
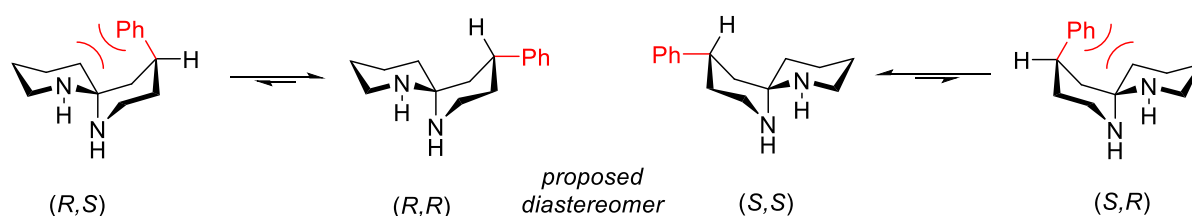
Figure 15: *The possible diastereomers of **182-A**.*

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.
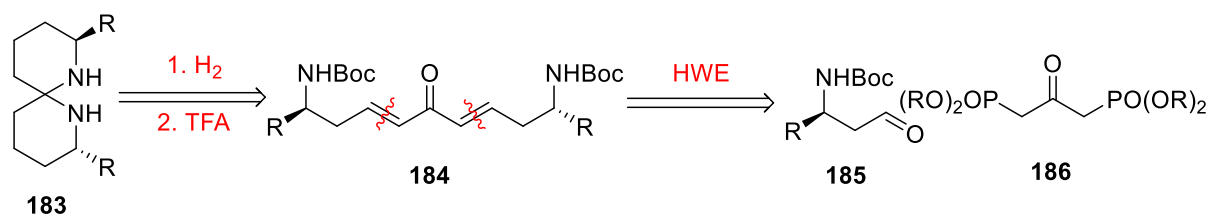
Scheme 43: *Retrosynthetic approach of **183** using a Horner-Wadsworth Emmons (HWE) reaction.*

The use of aromatic aldehydes in the Claisen-Schmidt reaction with acetone is well documented in the literature.[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 is mind, inspiration was taken from the work of Chen *et al.*[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).[83] The carbonyl was protected as the hydrazine carboxylate to facilitate the Arbuzov phosphorylation and prevent the competing Perkow reaction.[84]
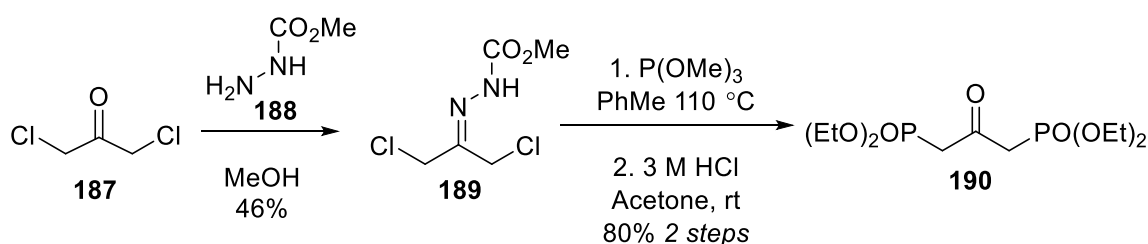
Scheme 44: Synthesis of diphosphate 190.

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-disubstitued spiroaminals as the desired aldehydes were readily available with high enantioselectivity using Ellman sulfinimine chemistry.[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.[85] The protecting group was easily exchanged to a Boc protecting group utilising a one pot procedure,[86] yielding homoallylic amine **194** (Scheme 45).
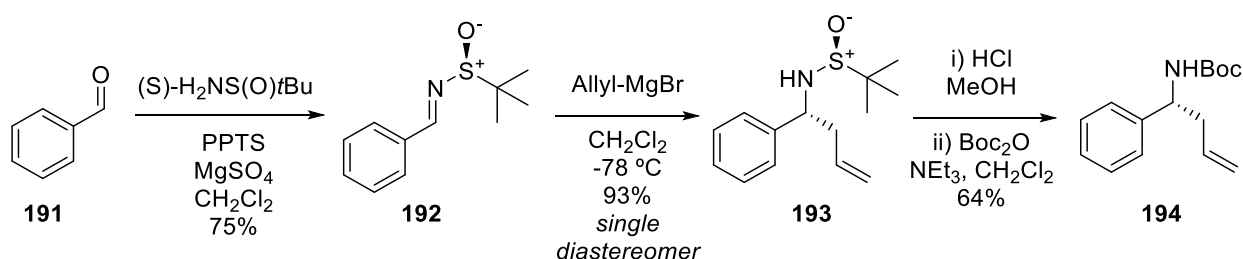
Scheme 45: Synthesis of homoallylic amine 194.

Ozonolysis of homoallylic amine **194** with a basic work up afforded aldehyde **195** in good

yields. Using K_2CO_3 in a THF/H_2O solvent mixture,[83] **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).
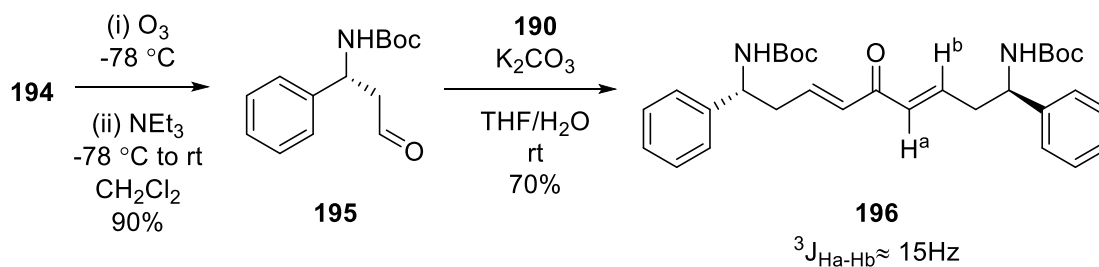
Scheme 46: The synthesis of diene 196.

This dienone was easily hydrogenated under mild conditions, yielding the ketone **197**.

Treatment with TFA afforded spiroaminal **198-A** in good yields (Scheme 47).
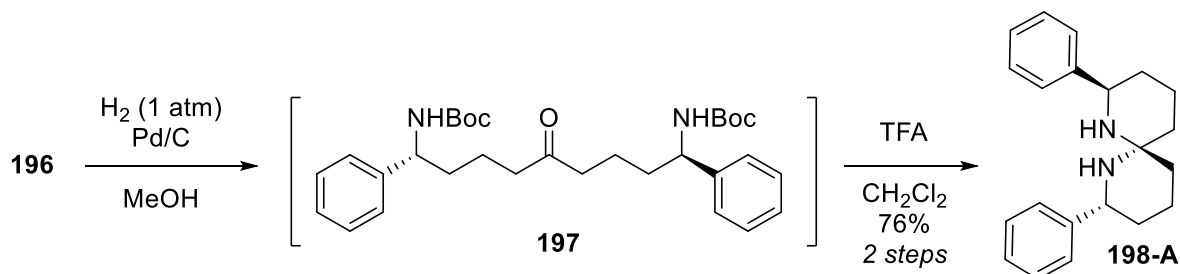
Scheme 47: Synthesis of phenyl spiroaminal 198-A.

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).
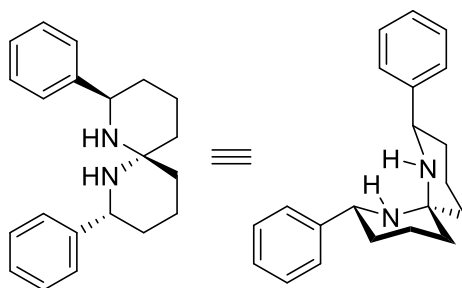
Figure 16: The proposed stereochemistry of 198-A.

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.[58,87]

In addition, work carried out Jiaxu Han within our group utilising protected aspartic acid **199**, our group has accessed the unique spiro-di-α-amino ester **201-A** (Scheme 48).
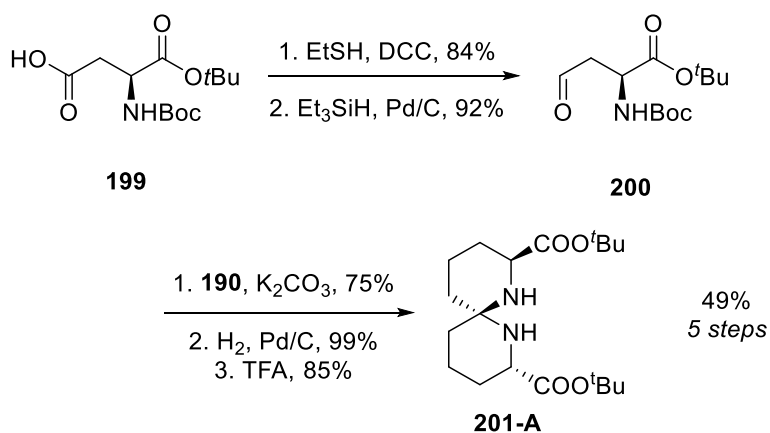
Scheme 48: Synthesis of spiroaminal 201-A. Work carried out by Jiaxu Han.

The structure of amino ester **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.[88]
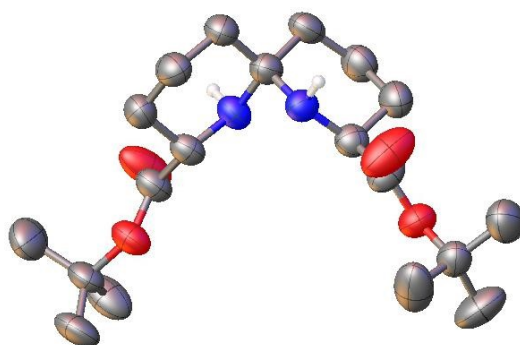
Figure 17: *Crystal structure of spiroaminal 201-A, prepared by Jiaxu Han (50% probability ellipsoid).*

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,[89] 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).
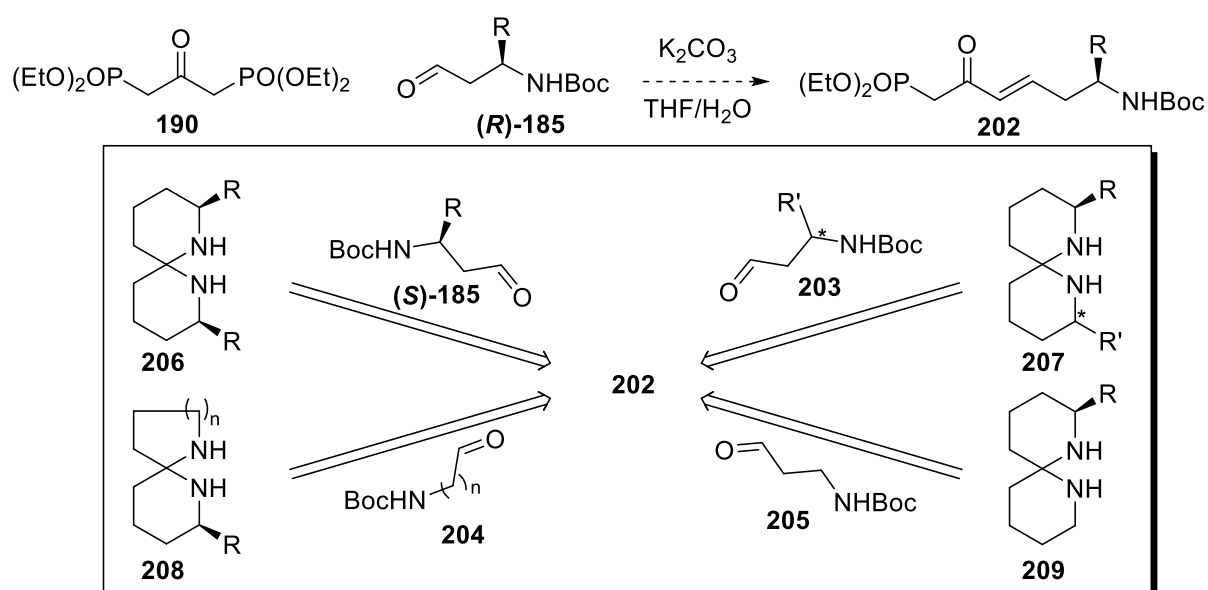
Scheme 49: *The possible variations utilising a mono-HWE with diphosphate 190.*

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Additionally, the resultant olefins of the HWE could be used to further functionalise the carbon backbone utilising 1,4-additions (Scheme 50).[90]
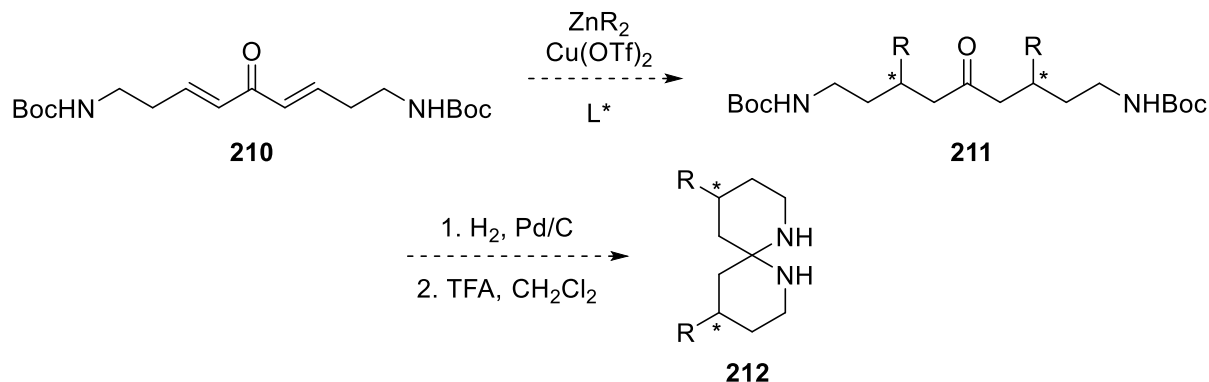
Scheme 50: *The possible variation at the 4 and 10 positions utilising 1,4-additions to dienone **210**.*

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.[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.
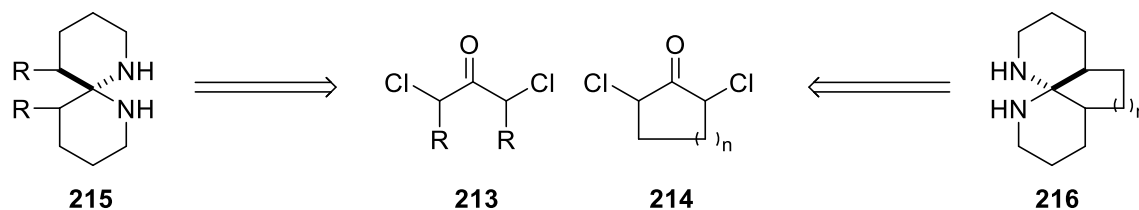
Scheme 51: *The possible substitution at the 5 and/or 6 positions utilising different α-α'-dichloroketones **213**-**214**.*

CHAPTER THREE

SYNTHESIS AND REACTIONS OF TETRAHYDROSPIROBIQUINOLINES

3. Synthesis and Reactions of Tetrahydrospirobiquinolines

3.1 Benzannulated Spiroketals

3.1.1 Natural Products and Biological Activity

Aliphatic spiroketals 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 spiroketal, or benzannulated spiroketal, is relatively rare when compared to its aliphatic counterpart.[13,14] Most notable within this structural class are the antitumor antibiotics, the rubromycins **217-220**.[91] These compounds have gained the attention of both biologists for their interesting biological activities,[92] as well as synthetic chemists for their complex molecular architecture as targets for total synthesis (Figure 18).[14]
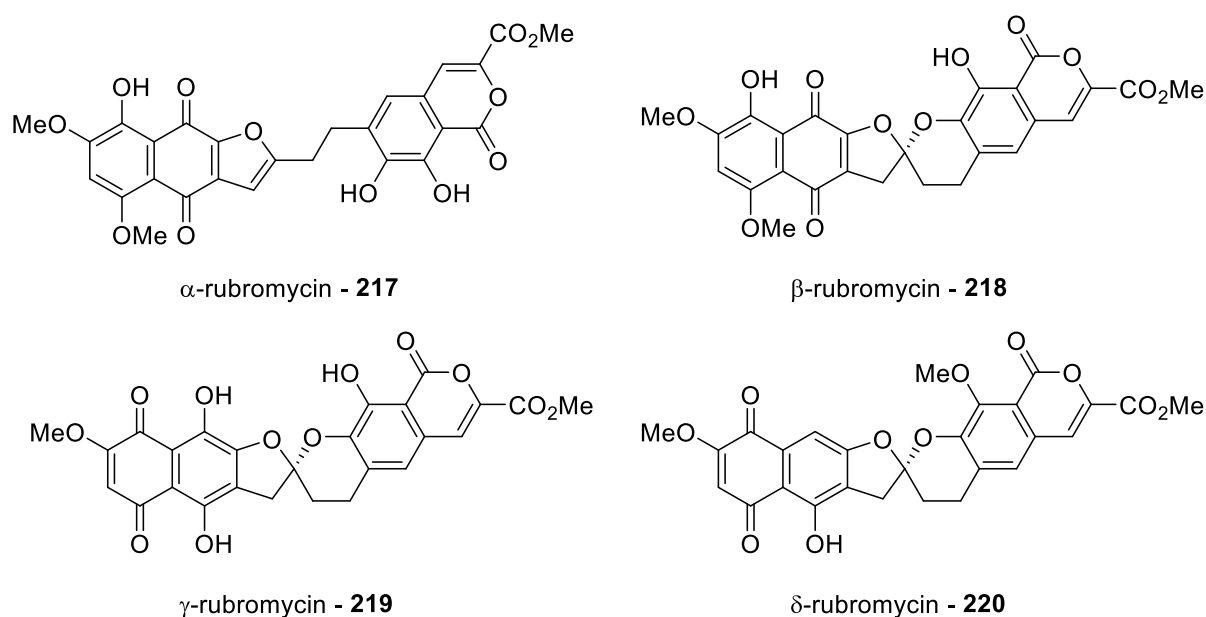
Figure 18: Rubromycin natural product family.

The rubromycins, first isolated from *Streptomyces collinus,* a bacterium isolated from the soil around Baden, Germany, are highly potent inhibitors of Gram-positive bacteria (*Bacillus subtilis,* and *Staphylococcus aureus*) but are ineffective on Gram-negative bacteria, or fungi.[92,93] Among the spiroketal members of this family, the first total synthesis of γ-rubromycin

(**219**), was reported by Kita,[94] followed by a second formal synthesis by Brimble[95], and ∂-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 spiroketals has been published by Brimble *et al*.[14]
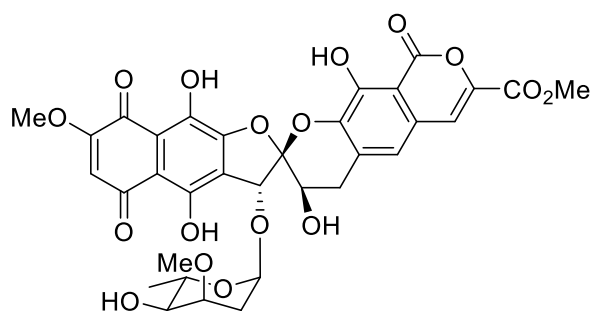
Heliquinomycin - **221**

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 *Fascaplysinopsis 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.
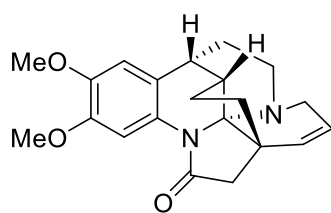
(−)-Isoschizogamine - **37**
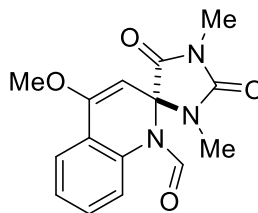
(±)-Spiroreticulatine - **38**

Figure 20: Spiroaminal containing natural products 37 and 38.

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,[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 **222**-**225**,[104] a *C2*-symmetric selectively *trans*-coordinating ligand family, which provided access to a understudied area of unusual steric space around metal centres.[105] These spiroketals accessed several unique metal complexes, some of which showed activity in methanol carbonylation (Scheme 52).[106]
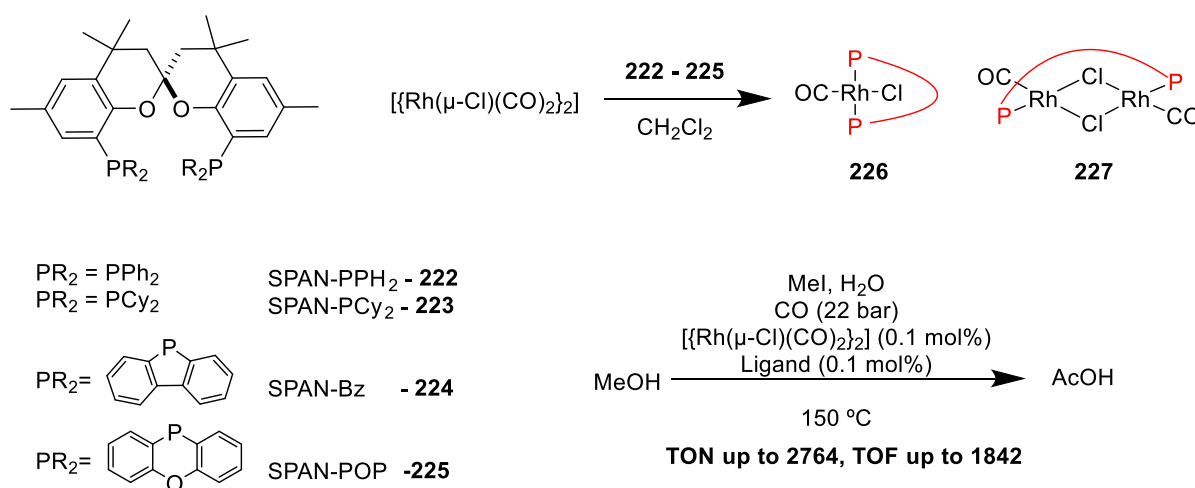
Scheme 52 The SPANPhos family 222-225, and their activity in methanol carbonylation.[106]

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),[107] and epoxidation of alkenes.[103]
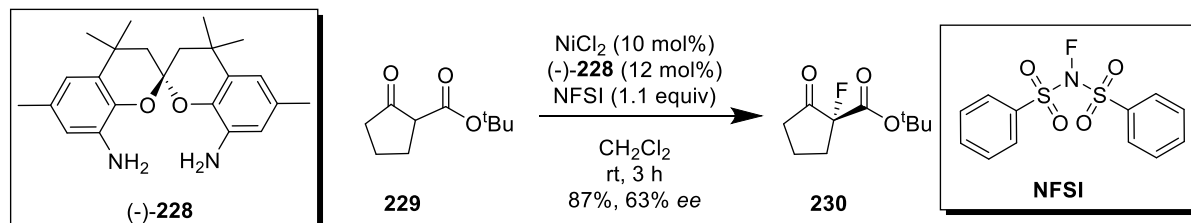
*Scheme 53: The application of SPANamine **228** in α-fluorination of **229** with N-fluorobenzenesulfonimide (NFSI).*[107]

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),[108] with the previously reported by van Leeuwan utilising resolution by chiral HPLC or diastereoselective resolution.[107]
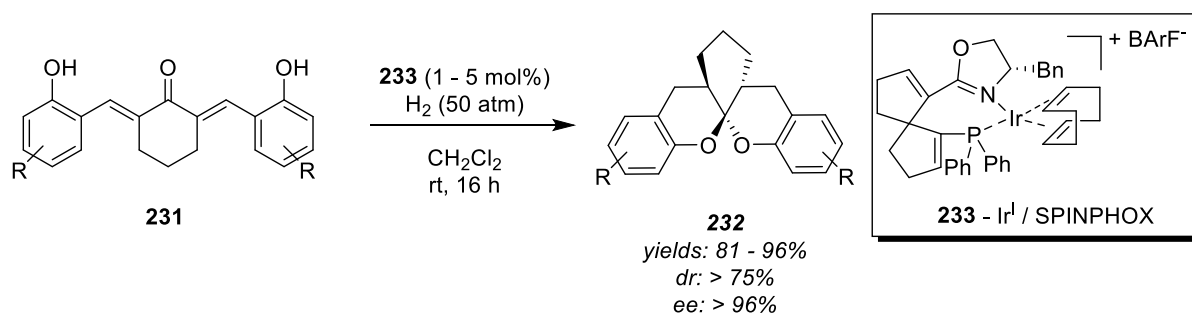
*Scheme 54: Enantioselective synthesis of spiroketals utilising iridium spinphox ligand **233**.*[108]

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[109] and gold catalysed olefin cyclopropanation of diazooxindoles (Scheme 55).[110]
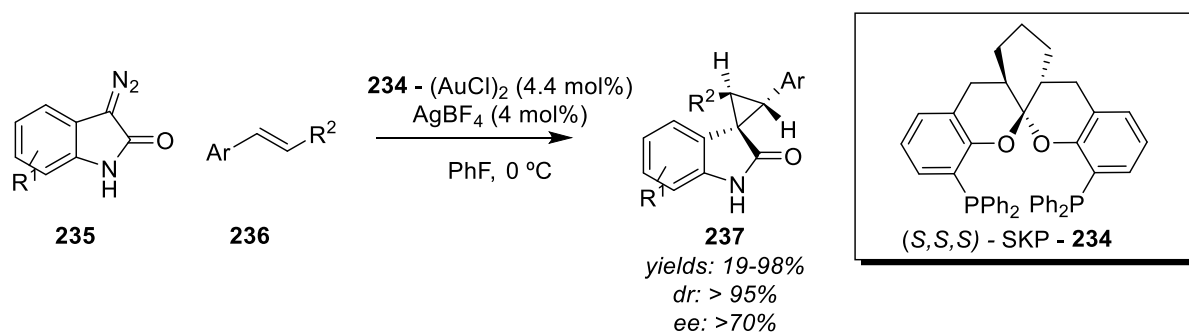
Scheme 55 The Zhou cyclopropanation of diazooxindoles.[110]

3.2   Route Optimisation

Inspired by the route of Ding, Wang, and Zhou,[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.[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.[50] The first attempted approach to the tetrahydrospirobiquinoline **235** was a double aldol condensation of *o*-nitrobenzaldehyde (**238**) with acetone to yield the dinitro-dibenzylideneacetone **237,** followed by hydrogen based reduction of both the nitro moieties and the benzylidene olefins (Scheme 56).
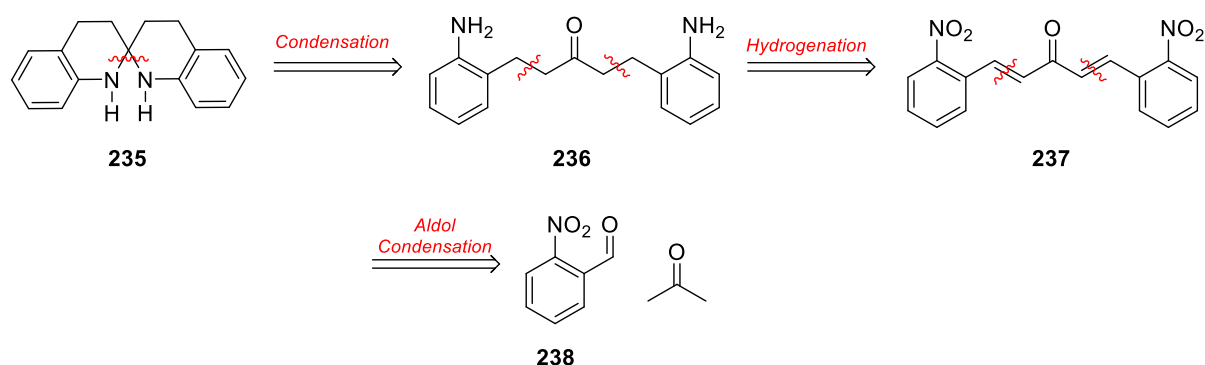
Scheme 56: Retrosynthetic analysis of tetrahydrospirobiquinoline 235.

The aldol condensation between **238** and acetone, although described in the literature,[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,[112] however, they utilised stoichiometric amount of highly toxic reagents.
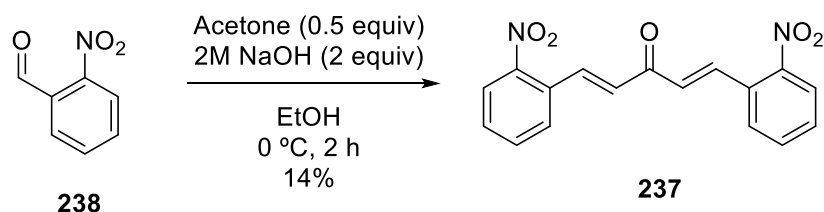
Scheme 57: *The double aldol condensation of **237**.*

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.[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)
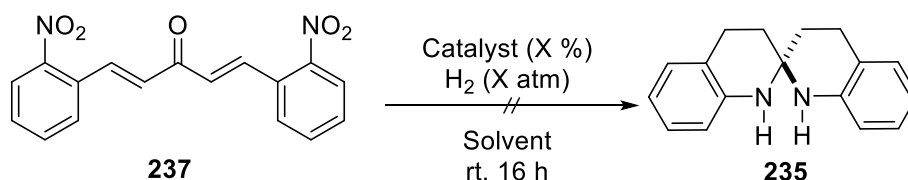
Entry	Catalyst	Catalyst wt%	Pressure (atm)	Solvent
1	PtO$_2$	10	2	MeOH
2	PtO$_2$	20	2	MeOH
3	Pd/C	10	1	MeOH
4	Pd/C	10	2	MeOH
5	Pd/C	10	4	MeOH
6	Pd/C	20	1	EtOH

7	Pd/C	20	1	EtOH
8	Raney Ni	20	2	EtOH
9	Raney Ni	20	2	EtOAc

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_NAr 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]
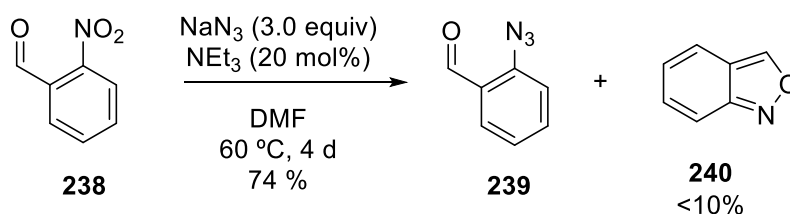
Scheme 58: The synthesis of azide 239.

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).
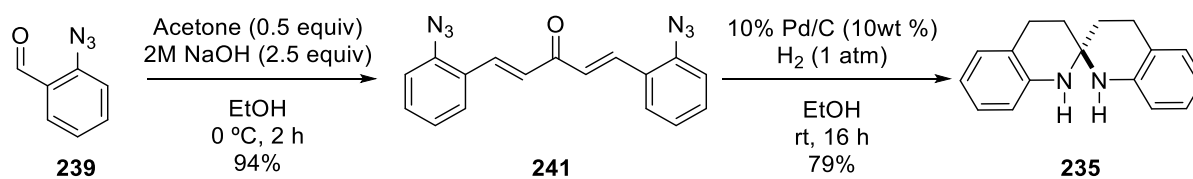
Scheme 59: The synthesis of spirobiquinoline 235.

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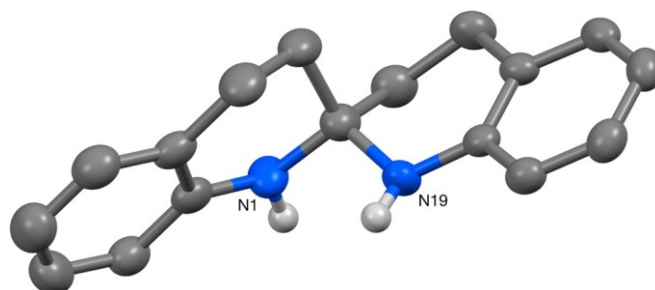
Figure 21: *The solid-state structure of **235** (50% probability ellipsoids).*

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).
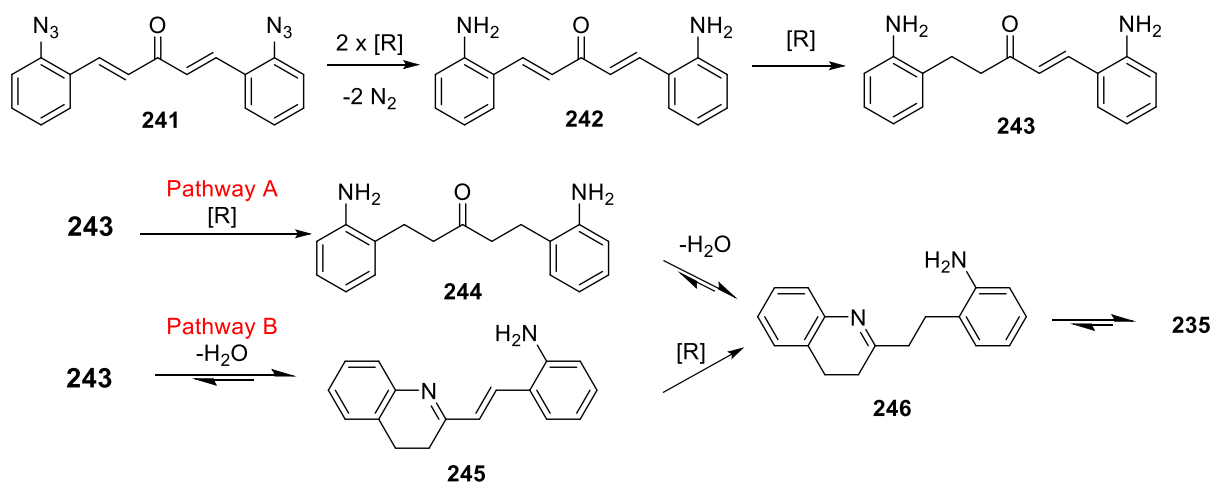
Scheme 60: *The proposed reaction pathways for the hydrogenation/spirocyclisation transformation.*

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$_N$Ar using a modified procedure of Boswell and Licause[119] then afforded azide **249** in good yields. (Scheme 61)
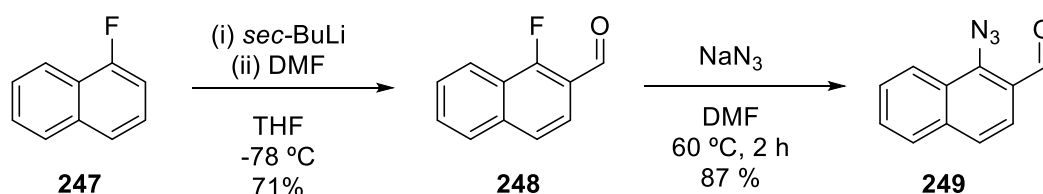
Scheme 61: *The synthesis of azide 249.*

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.[120] This was subjected to the standard S_NAr conditions to yield the azide **253** (Scheme 62).
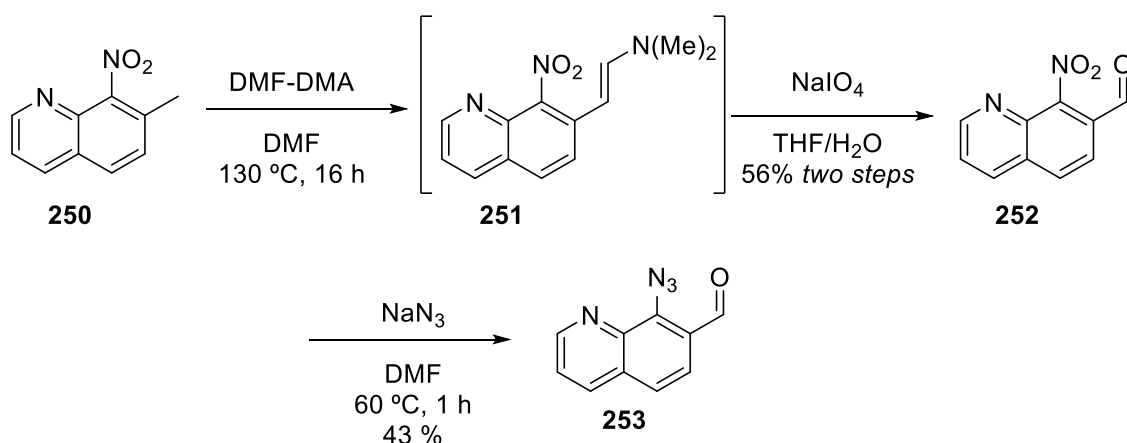
Scheme 62: *The synthesis of azide **253**.*

The synthesis of the additional known *o*-azidobenzaldehydes **258**-**261** was accomplished through S_NAr of the corresponding nitro derivative. The *o*-nitrobenzaldehydes **254**-**257** were commercially available, and were subjected to the conditions of Driver *et al.*[121,122] to afford the azides **258**-**261** in good yields, many of which, did not require purification (Scheme 63).

R			R		Yield
3-Me	**254**		3-Me	**258**	17 %
4-OMe	**255**		4-OMe	**259**	85 %
4-CF₃	**256**		4-CF₃	**260**	76 %
5-Cl	**257**		5-Cl	**261**	64 %
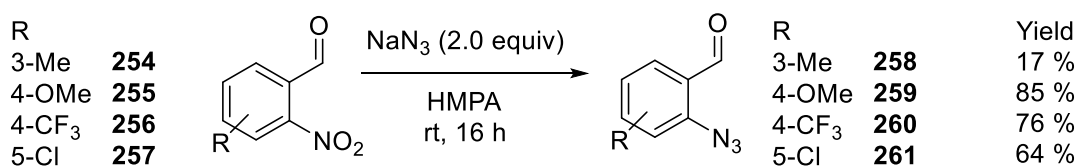
Scheme 63: *The preparation of azides **258**-**261**.*

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).
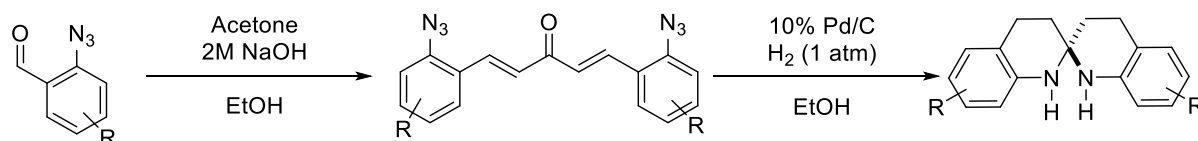
Entry	R	Aldehyde	Product	Yield (%)[a]
1	napthyl	**249**	**262**	67
2	quinoline	**253**	**263**	75
3	3-Me	**258**	**264**	53
4	4-OMe	**259**	**265**	82
5	4-CF$_3$	**260**	**266**	78
6	5-Cl	**261**	**267**	34[b]

Table 5: Substrate scope of tetrahydrospiroquinoline methodology. [a]Isolated yield over two steps, 2 mmol scale wrt aldehyde. [b]Some 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.
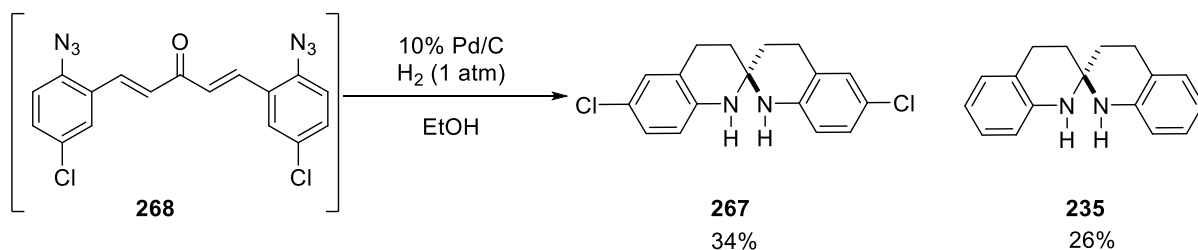
*Scheme 64: Dehalogenation during synthesis of spiroquinoline **267**.*

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,[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).
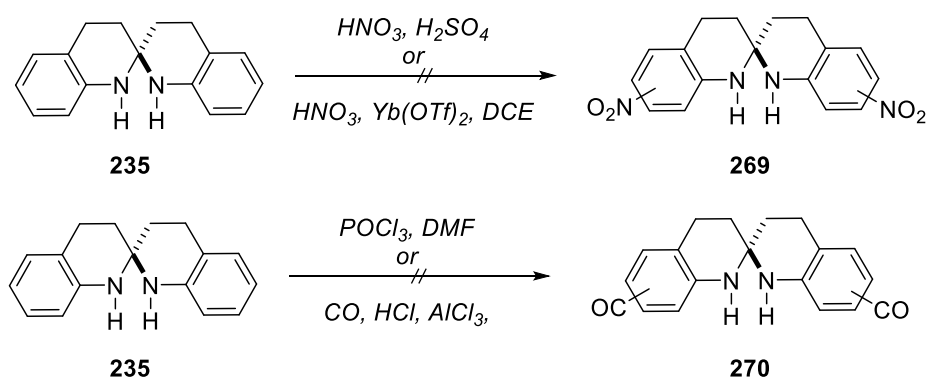
Scheme 65: *Failed attempts at aromatic functionalisation of* **235***.*

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,[124] first occurs *para* to the nitrogens to yield the dibromo spiroquinoline **271** and second, *ortho* to the nitrogens to yield the tetrabromo spiroquinoline **272**, with the mono and tribrominated products observed in small quantities (Scheme 66).
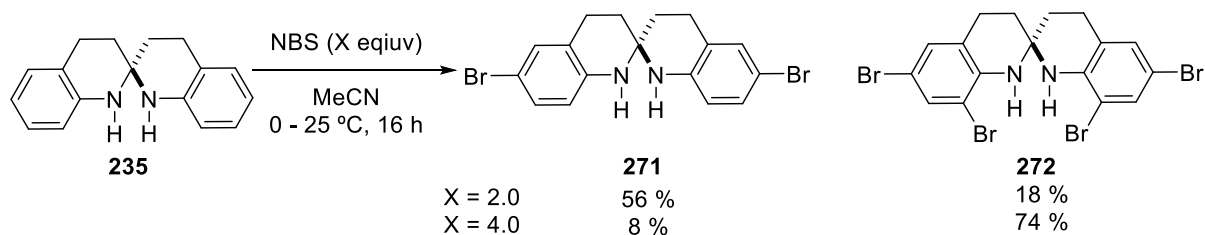
Scheme 66: Bromination of spirobiqunoline **235**.

The position of the bromo substituents for both **271** and **272** were confirmed by X-ray structural elucidation (Figure 22 and Figure 23).
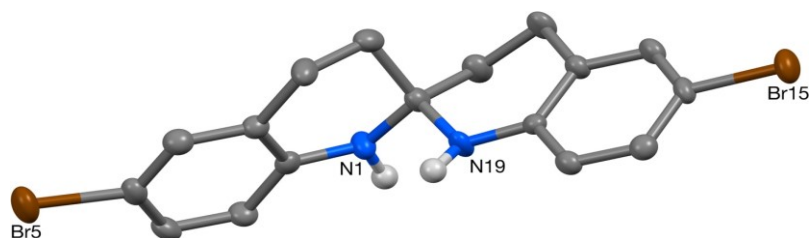
Figure 22: The solid-state structure of **271** (50% probability ellipsoids).
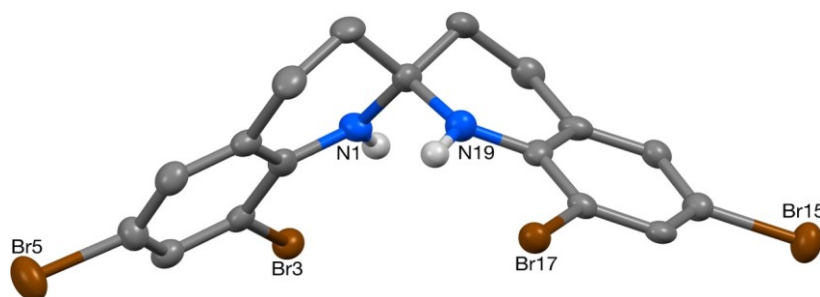
Figure 23: The solid-state structure of **272** (50% probability ellipsoids).

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 120.8º, 122.3º, and 122.5º respectively. This implies these nitrogens are sp^2 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 $PdCl_2(PPh_3)_2$, as a catalyst, XPhos as a ligand, and K_2CO_3 as a base (Table 6, Entry 7). Other palladium pre-catalysts and ligands also afforded the product in adequate yields.
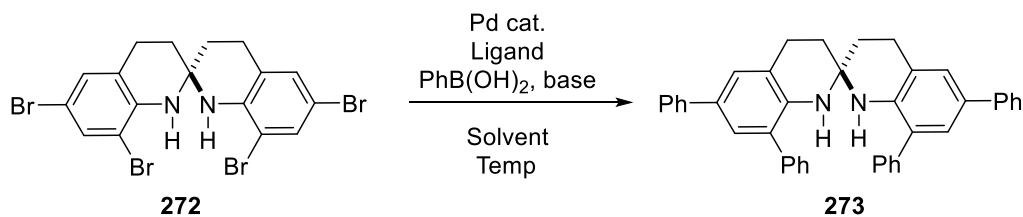
Entry	Pd cat.	Ligand	Base	Solvent (Ratio)	Yield (%)[a]
1	$Pd(PPh_3)_4$	n/a	K_2CO_3	MeCN (n/a)	0
2	$[Pd(dppf)Cl_2]$	n/a	$Ba(OH)_2$	$DMF-H_2O$ (6:1)	14
3	$PdCl_2(PPh_3)_2$	n/a	K_2CO_3	Dioxane- H_2O-EtOH (5:1:1)	26
4	$PdCl_2(PPh_3)_2$	PCy_3	K_2CO_3	$DMF-H_2O$ (6:1)	37
5	$PdCl_2(PPh_3)_2$	XPhos	K_2CO_3	$DMF-H_2O$ (6:1)	45
6	$PdCl_2(PPh_3)_2$	XPhos	K_2CO_3	$DMF-H_2O$ (8:1)	32
7	$\mathbf{PdCl_2(PPh_3)_2}$	**XPhos**	$\mathbf{K_2CO_3}$	$\mathbf{DMF-H_2O}$ **(4:1)**	**67**
8[b]	$PdCl_2(PPh_3)_2$	XPhos	K_2CO_3	$DMF-H_2O$ (4:1)	65
9[c]	$PdCl_2(PPh_3)_2$	XPhos	K_2CO_3	$DMF-H_2O$ (4:1)	33

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.[125]
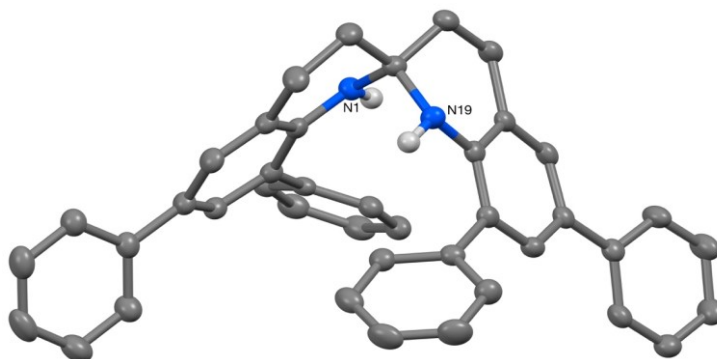
Figure 24: *The solid-state structure of **273** (50% probability ellipsoids).*

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**.[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).
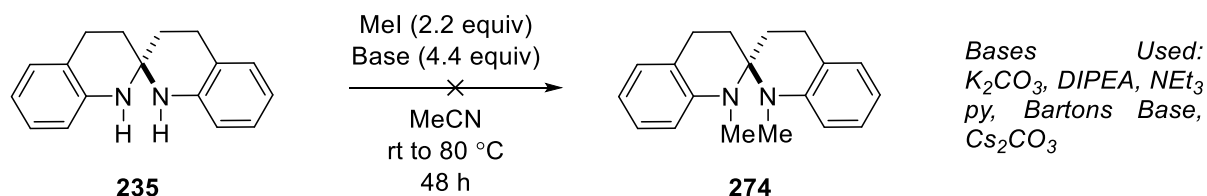
Scheme 67: *Failed attempts at nitrogen methylation of **235** with weaker bases.*

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).
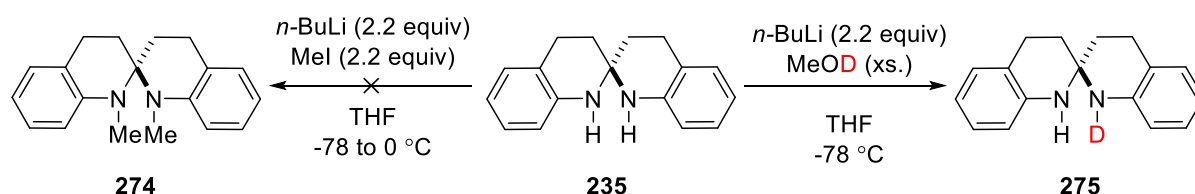
Scheme 68: Deprotonation studies of 235.

We expected that aggregation was an issue with the deprotonated spiroquinoline. Attempts were made to isolate the lithium amide utilising the techniques of Collum,[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).
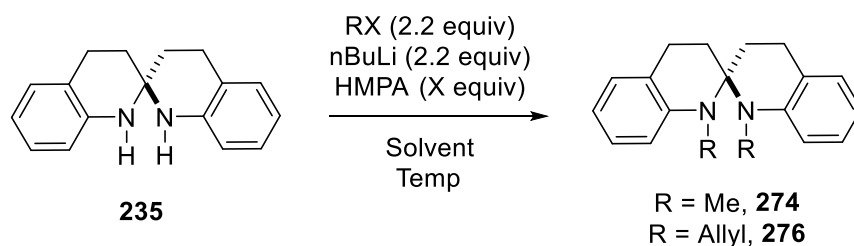
Entry	R-X	HMPA equiv	Solvent	Temp (°C)	Yield (%)[a]
1	MeI	0	THF	-78	0
2	MeI	2.5	THF	-78	23
3	MeI	5.0	THF	-78	64
4	MeI	5.0	THF	-40	50
5	MeI	5.0	THF	-20	48

6	MeI	5.0	THF	-78 to 0	86
7	**MeI**	**5.0**	**THF**	**-78 to rt**	**91**
8	AllylBr	5.0	THF	-78	36
9	**AllylBr**	**5.0**	**THF**	**-78 to rt**	**80**
10[b]	BnBr	5.0	THF	-78	ND
11[b]	BnBr	5.0	THF	-100	ND
12	I(CH$_2$)$_3$I	5.0	THF	-78	0

Table 7: Optimisation of the alkylation/allylation of 235. All reactions were carried out on a 0.2 mmol scale wrt 235. [a]Isolated yield. [b]Multiple inseparable products formed, likely carbene formation of BnBr upon treatment with nBuLi.

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.
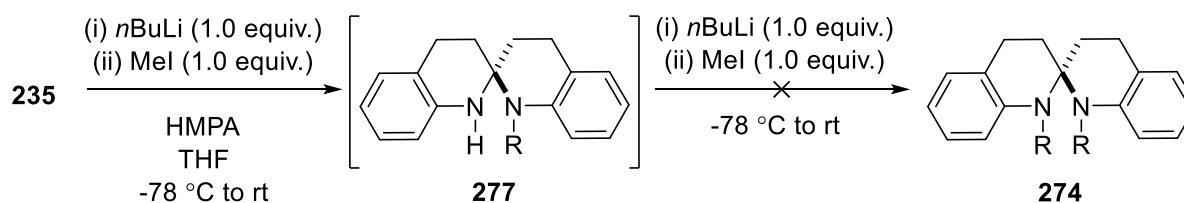
Scheme 69: The attempted stepwise double alkylation of 235.

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 allylated.[35] Diallyl spiroquinoline **276** efficiently underwent ring closing metathesis with Hoveyda-Grubbs Catalyst™ 2nd Generation Catalyst (GHII) to yield the pentacyclic **278** (Scheme 70).
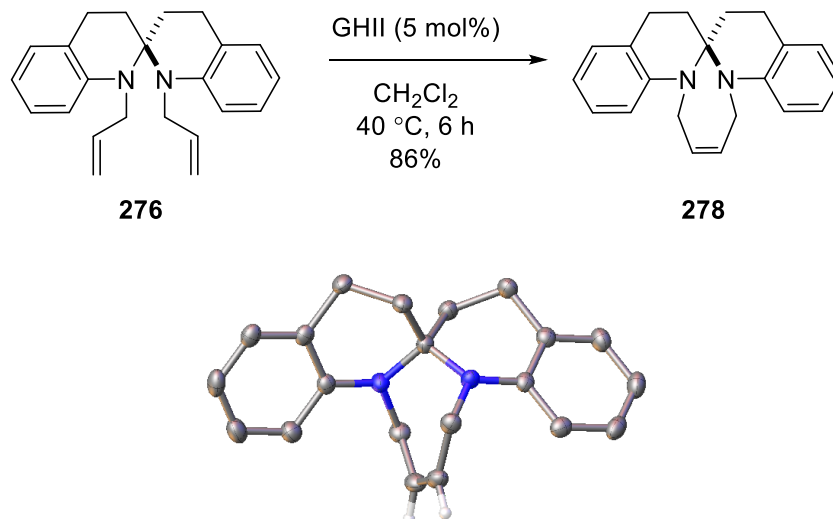
Scheme 70: *Ring closing metathesis of diallyl **276** and the solid-state structure of **278** (50% probability ellipsoids)*

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.[127] In our studies acetone was treated with one equivalent of a *o*-azidobenzaldehyde **279** under the conditions as previously described for spirobiquinoles **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).

78
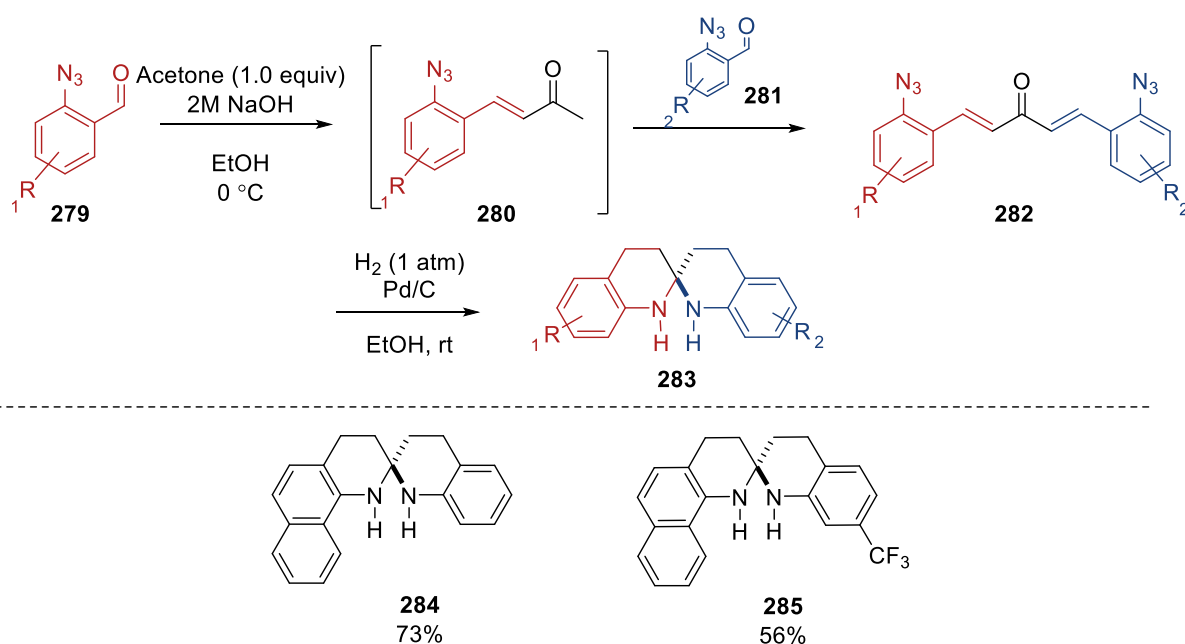
Scheme 71: *The synthesis of unsymmetrical tetrahydrospirobiquinolines 284 and 285.*

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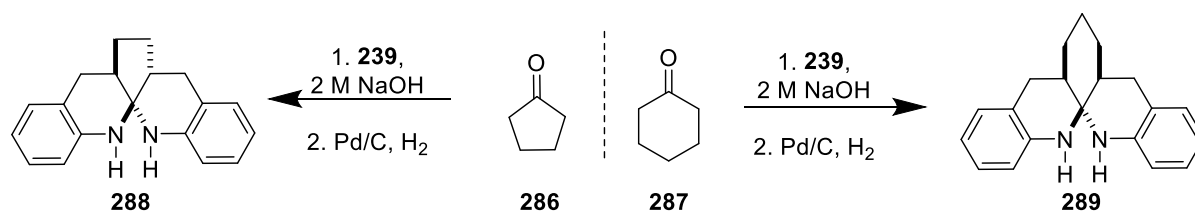
Scheme 72: *The synthesis of cyclic spirobiquinolines **288** and **289**.*

The stereochemistry of both compounds was assigned by ^{1}H and ^{13}C NMR. Spirocycle **288** was found to exist as the *C2* 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.
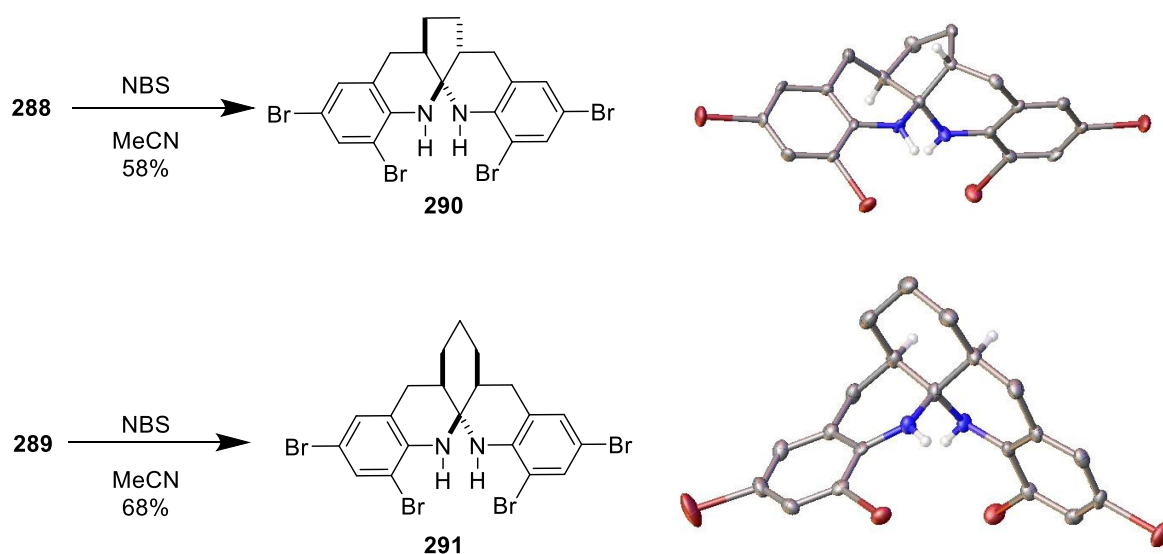
Scheme 73: *The synthesis and solid-state structures of **290** and **291** (50% probability ellipsoids).*

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 π-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 **293** and **296** (Scheme 74). It has been shown that the hydrogenation of cyclic dienones favours the formation of the *cis* compounds.[128] However it has been shown that *cis*-cyclopentanones **296** can undergo facile isomerisation to its *trans* epimer **297** (Scheme 74).[129]
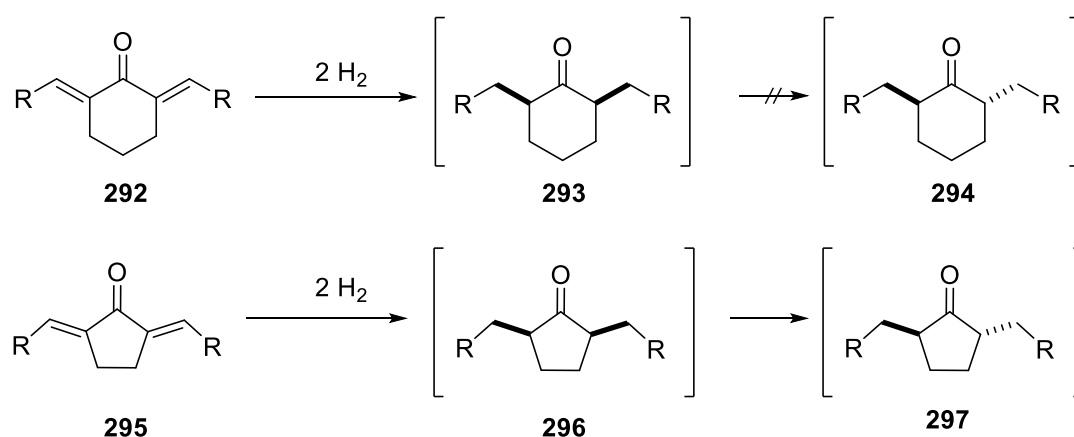
Scheme 74: *One possible factor in stereoselectivity.*

Cyclopentanone **295** is more likely to undergo this transformation due to easier access to the enolate due to increased acidity of the α-proton and increased steric clashing of the two substituents on the smaller ring. Another hypothesis relates to an intermediate within one of

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.
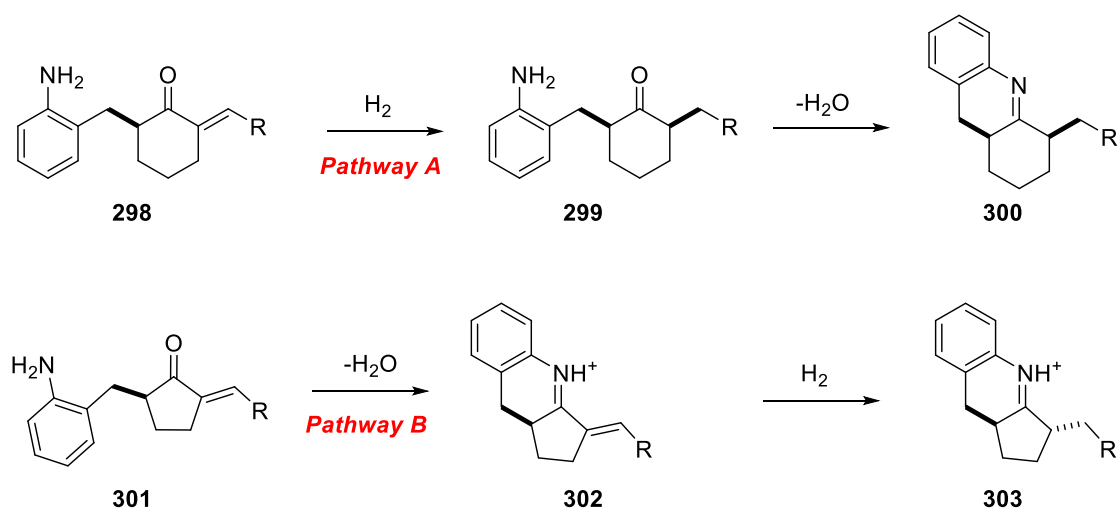
Scheme 75: *The cyclic imine hypothesis.*

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).

IA Column
2% IPA / Hexane
Separation Time 9 minutes

(*S*)-**262** **304** (*R*)-**262**

Racemisation within 24 h
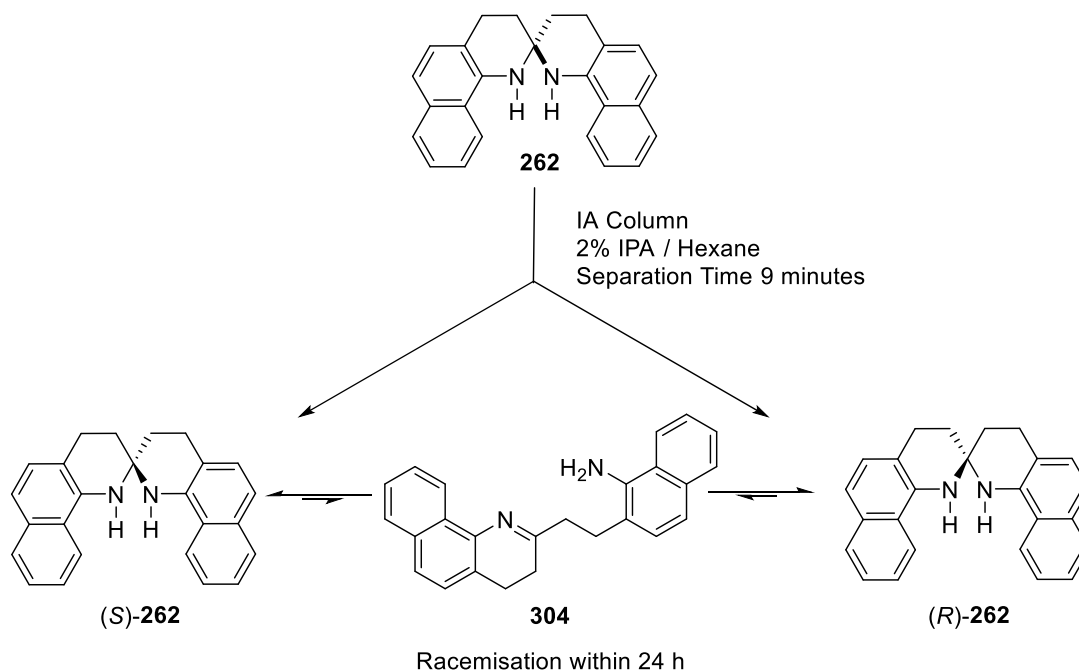
Scheme 76 The chiral resolution and subsequent racemisation of naphthalene 262.

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).

(*S*,*S*,*S*)-**288** (*S*,*S*)-**305** (*S*,*R*,*S*)-**288**
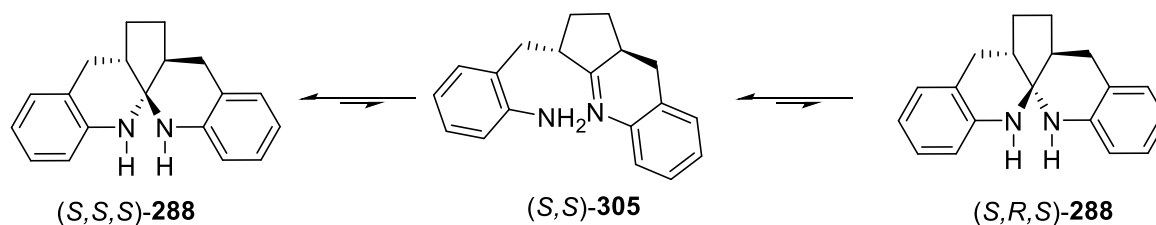
Scheme 77: The proposed barrier for epimerisation in cyclic 288.

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.

A – Unresolved **288**

| B – **288-A** t= 0 h | C – **288-B** t= 72 h |
| D - **288-B** t= 0 h | E - **288-B** t= 72 h |
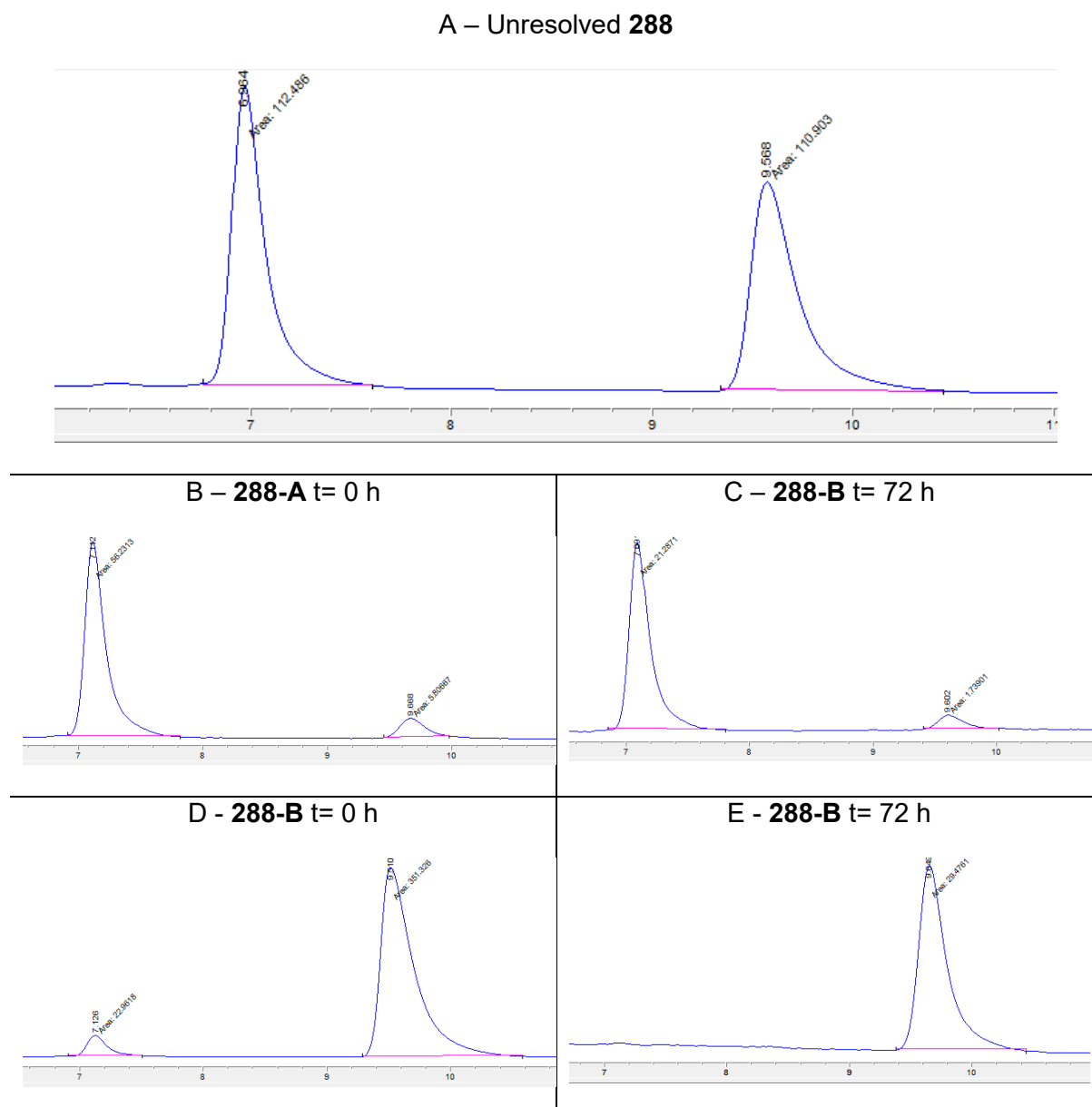
Figure 25: *The HPLC traces of the resolution of **288**. A – Unresolved material. B – Enantiomer A, 0 h after resolution. C – Enantiomer A, 72 h after resolution. D – Enantiomer B, 0 h after resolution. E – Enantiomer B, 72 h after resolution. Method: Chiralpak IE Column, 2% IPA/Hexane.*

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.[130–132] Helicenes are now common motifs in catalysis, materials, and electronic devices.[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.

306   **307**
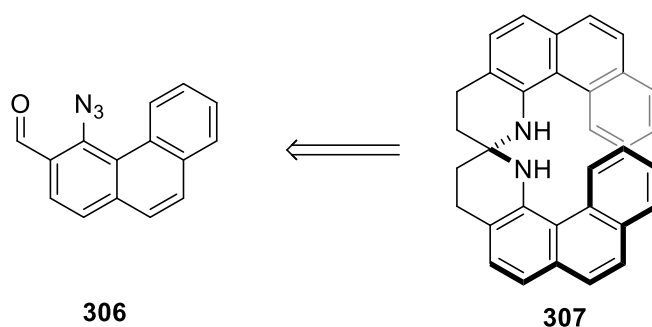
*Scheme 78: The target "helical" spirobiquinoline **307**.*

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*".[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.

306   **308**   **309**

310
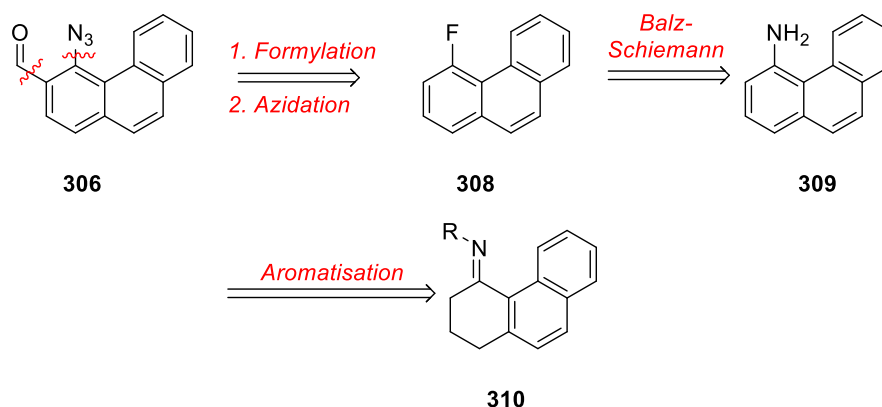
*Scheme 79: Our initial retrosynthesis of azido aldehyde **306**.*

85

Our first approach for preparing azido aldehyde **306** followed a similar route to that of Beringer *et al.*[135] (Scheme 79) using the procedures of Lingenfelder and Kellogg,[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**[135] were unsuccessful, affording a large mixture of inseparable products (Scheme 80).
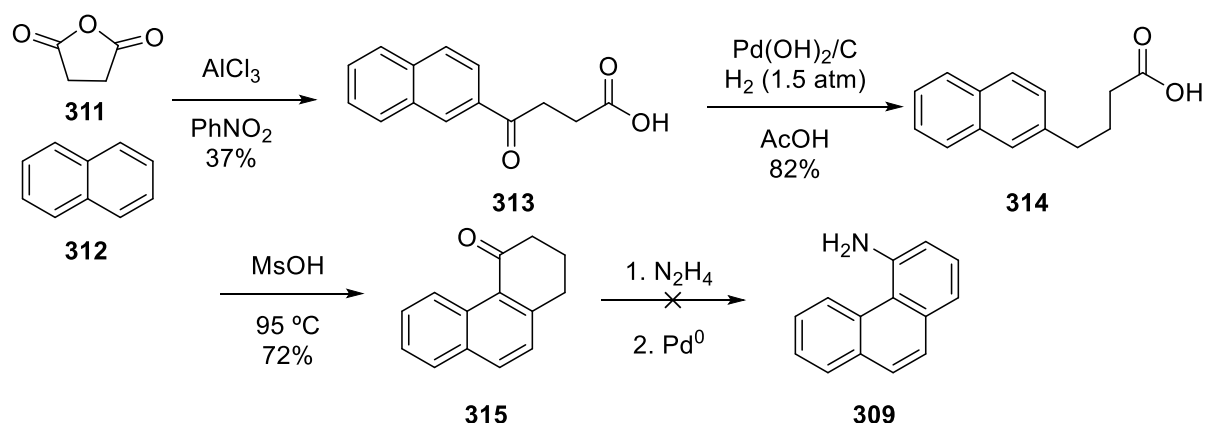
Scheme 80: *Attempted synthesis of phenanthrene 309.*

We then sought to utilise the alkyne cyclisation reported by Furstner,[137] using the procedure of Alabugin *et al.*[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 $PtCl_2$ mediated cyclisation, using a modified procedure of Eccleshare,[139] afforded phenanthrene **308** in high yields, and required minimal purification (Scheme 81).
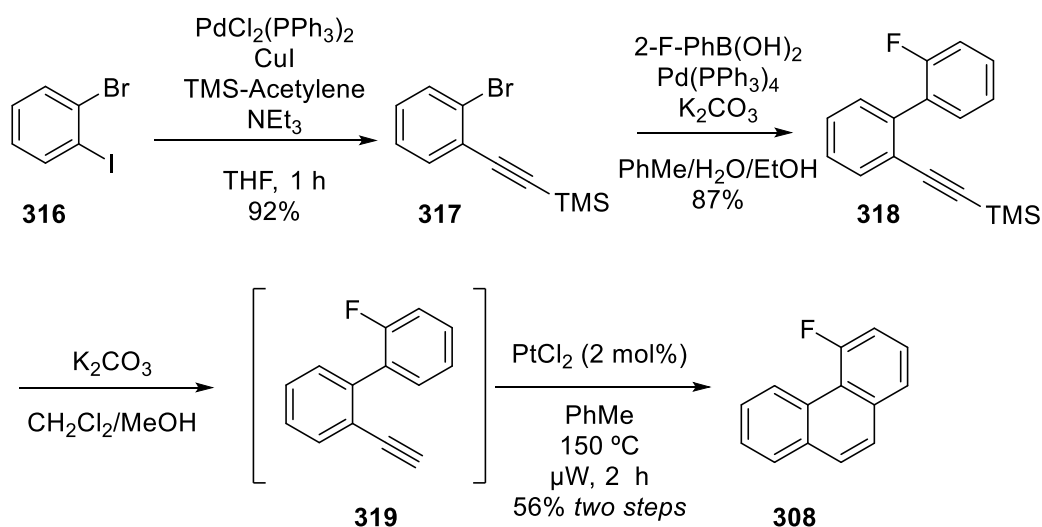
Scheme 81: *Synthesis of 4-fluorophenanthrene (308).*

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 S_NAr with sodium azide under standard conditions afforded azido aldehyde **306**.
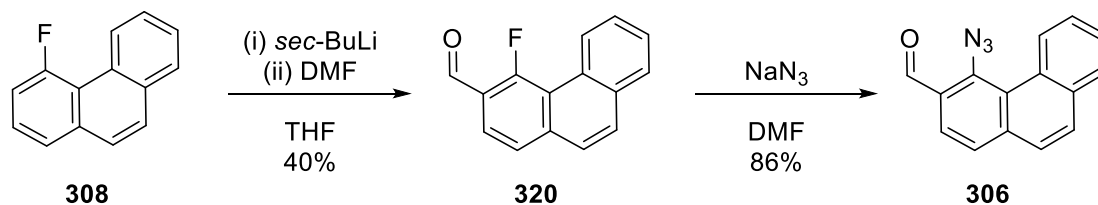
Scheme 82: *Synthesis of azido-benzaldehyde 306.*

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.
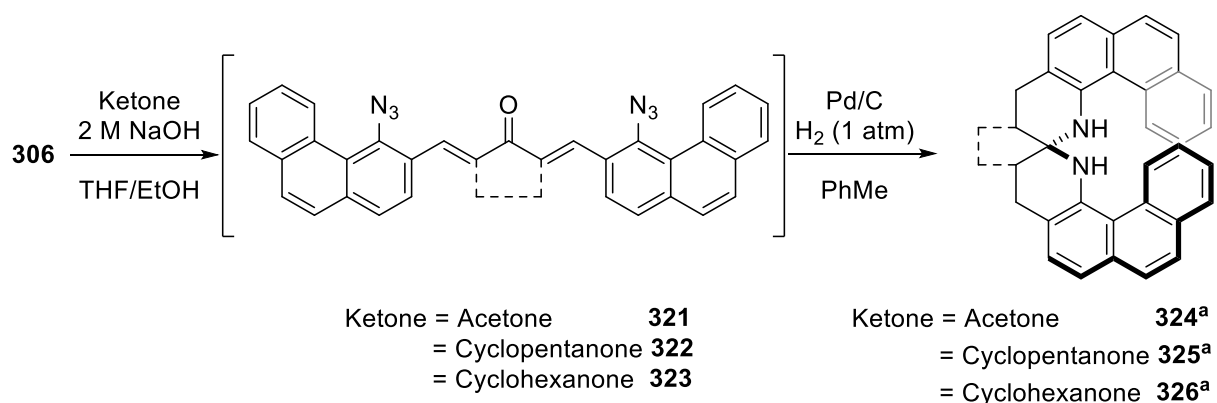
Scheme 83: *Modified procedure for the synthesis of **324-326**. [a]:Observed by ^{1}H NMR and HRMS (ES).*

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).
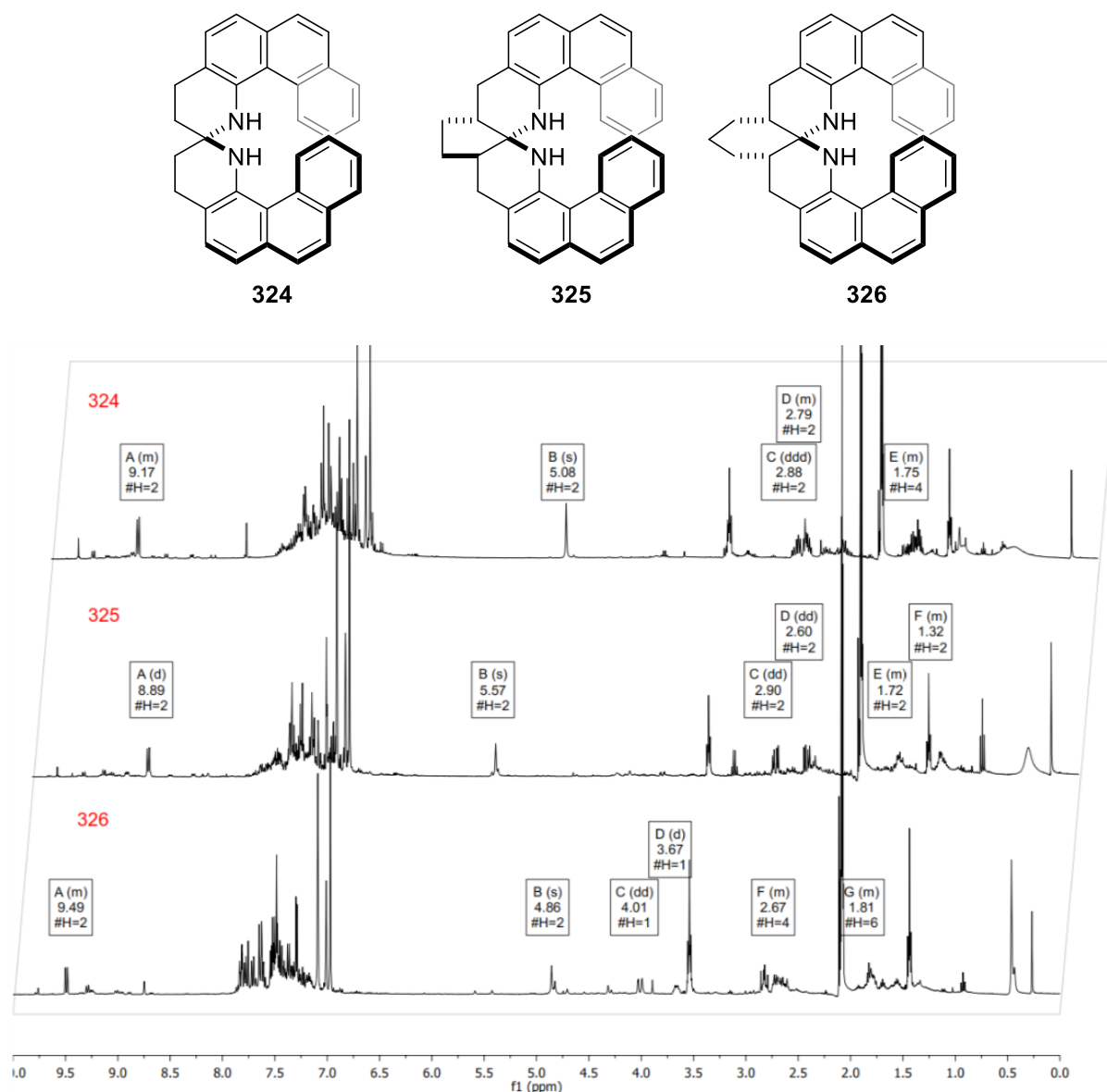
Figure 26: *Top*: *proposed spiroaminals **324**-**326**. Bottom: ^{1}H NMR of crude reaction mixtures after filtration of catalyst with characteristic protons labelled (400 MHz, PhMe-d$_8$).*

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.
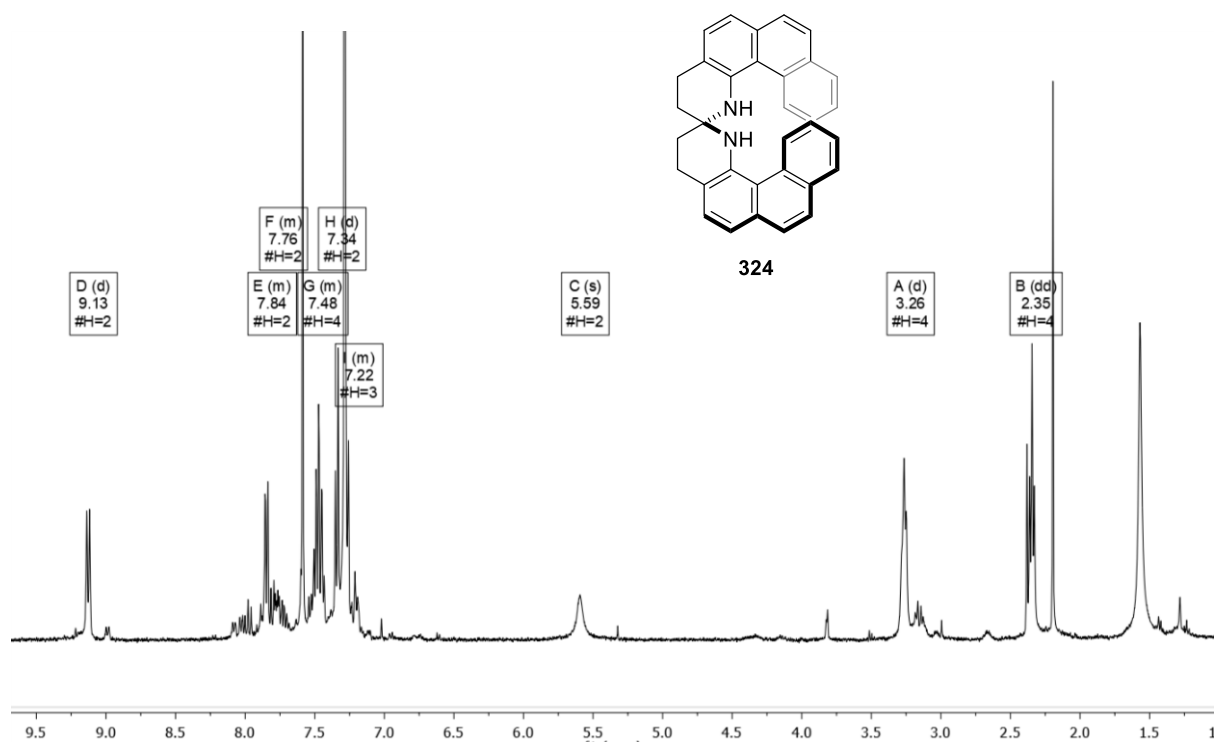
Figure 27: *^{1}H NMR of spiroaminal **324** after attempted purification (400 MHz, CDCl$_3$).*

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.[51]
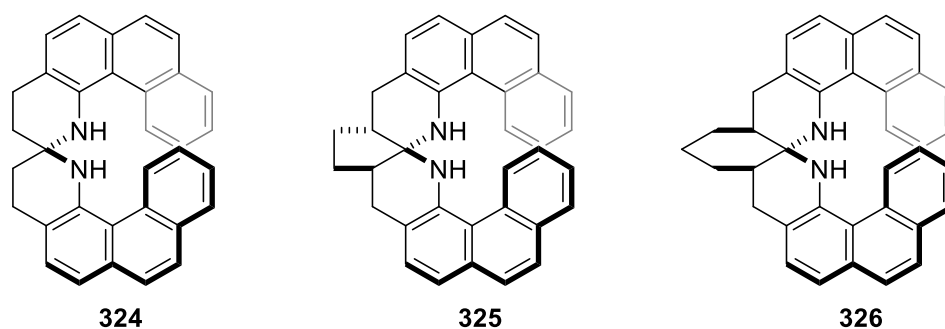
Figure 28: *The target spiroquinolines **324, 325** and **326**.*

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.
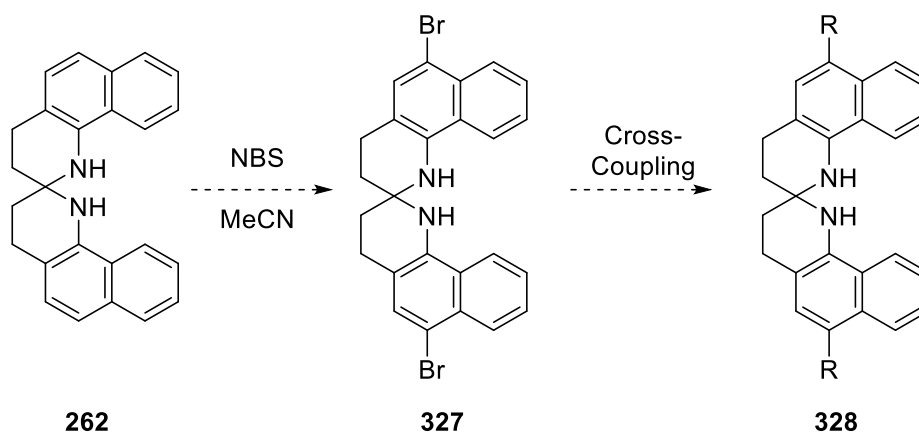
Scheme 84: *One possible synthetic route for derivatisation of spiroaminal **262**.*

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.[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).[39]

Cell	IC$_{50}$	Interleukin (IL-2)	
		Conc.	Inhibition
HL-60	5.5 μM		
MCF-7	38.5 μM	5 μM	26%
PC-3	40.2 μM	25 μM	38%
HepG2	55.4 μM	50 μM	44%
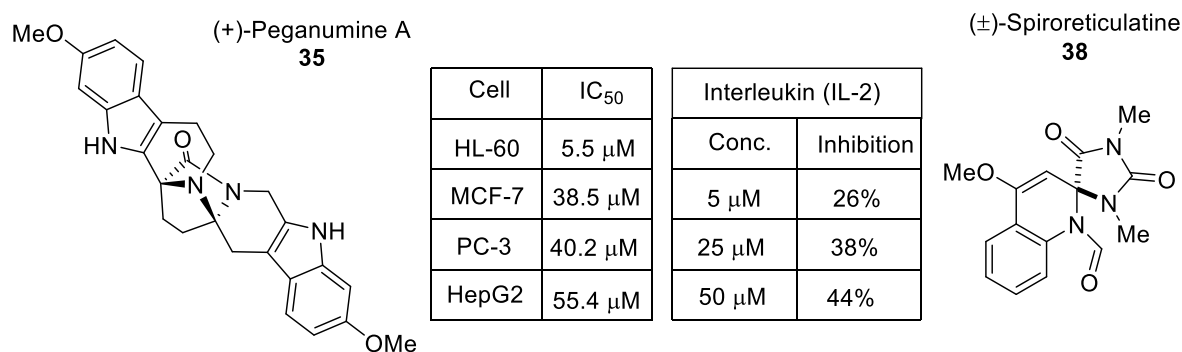
Figure 29: Biological activity of spiroaminal natural products 35 and 38.

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.[141] A selection of spiroaminals were shown to inhibit IL-17 at 100 μM

(Figure 30). The best results were observed for mono-bromo **329** and dimethoxy **265**, showing

inhibitions of 85% and 96% respectively.
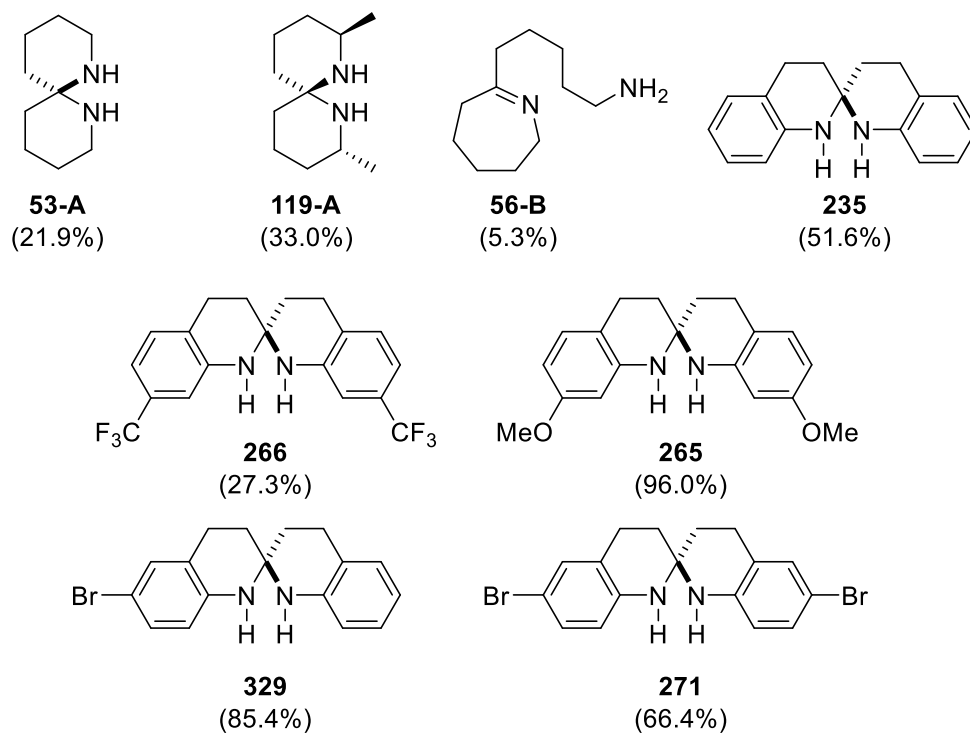
Figure 30: *Biologically active spiroaminals against IL-17 (inhibition% at 100 μM). Data collected by Eli Lilly OIDD.*

The primary data for spiroaminals **265** and **329** warranted the collection of a concentration

response curve (CRC) against IL-17 generating IC_{50} values of 37 μM and 29 μM respectively

(Figure 31).
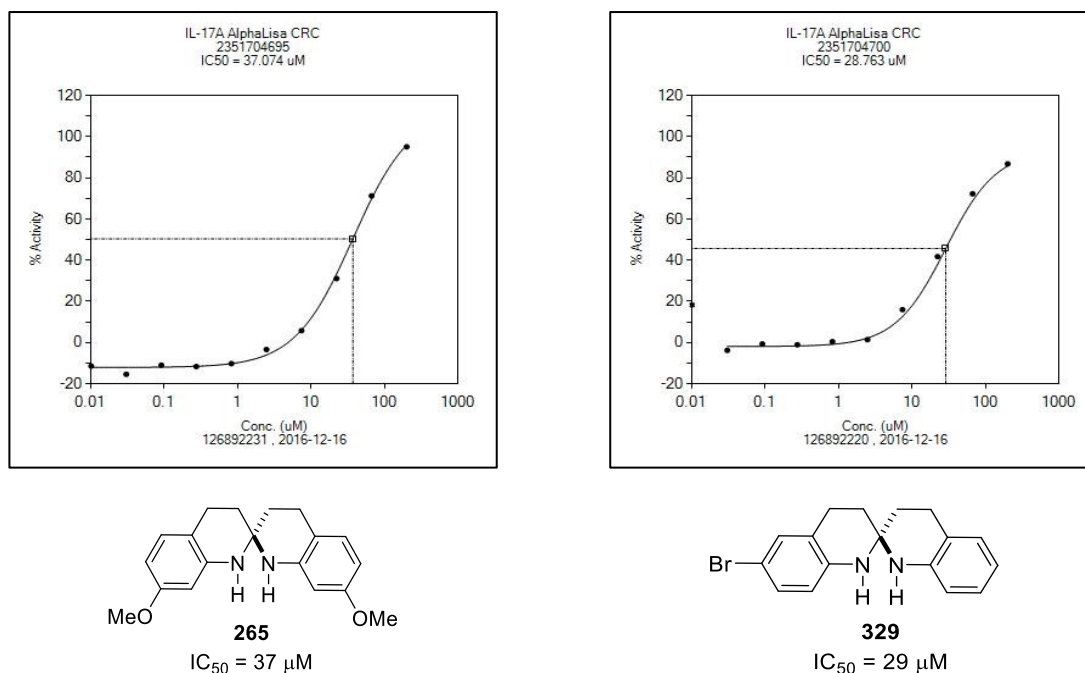
Figure 31: *CRC plots and IC$_{50}$ values of **265** and **323** against IL-17. Data collected by Eli Lilly OIDD.*

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**,[142] Jacobson-Katsuki epoxidation catalyst **331**,[143] and chemotherapeutic Oxaliplatin **332**, recognised as one of the world's most essential medicines.[144]

330
Ar = 3,5-DiMePh

331

332
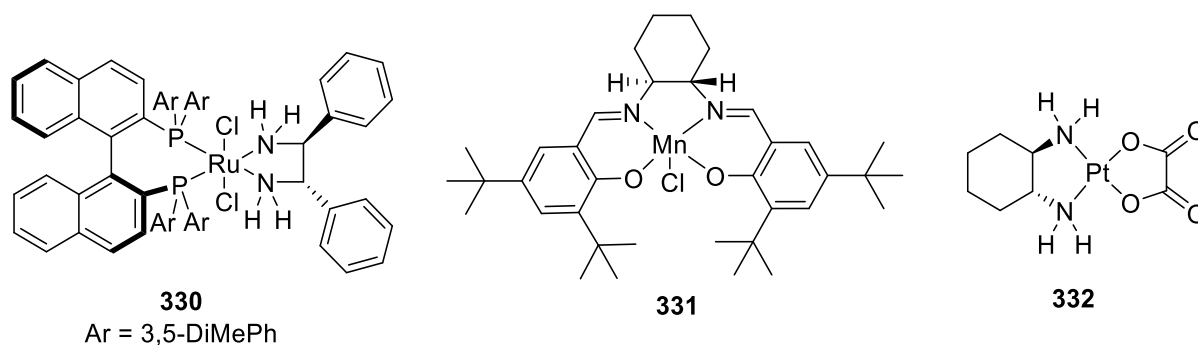
Figure 32: A selection of notable diamine containing complexes.

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.[145] 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).[146]

333

334

335
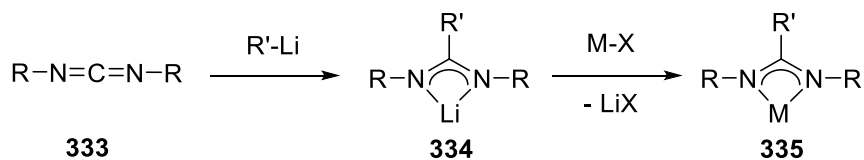
Scheme 85: General synthesis of amidate salts.

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.[147]

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).[35]
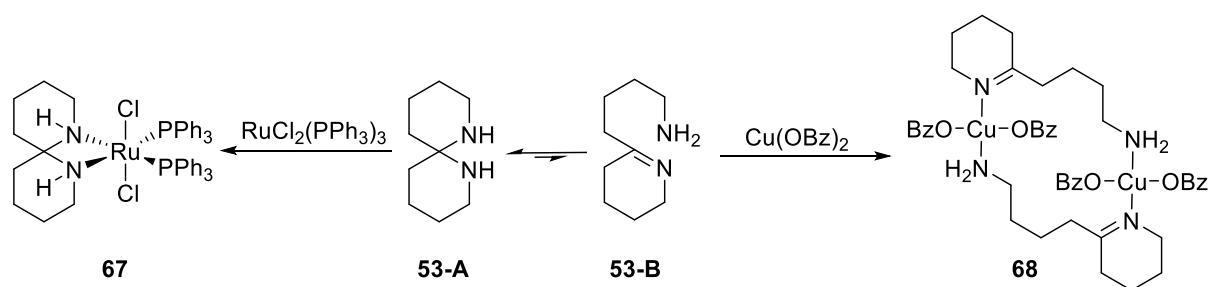
Scheme 86: *The synthesis of ruthenium complex **67** and copper complex **68**.*

Treatment of spiroaminal **53** with [Ru(PPh$_3$)$_3$Cl$_2$] afforded monometallic complex **67** with retention of the spirane centre. In contrast, the treatment of spiroaminal **53** with Cu(OBz)$_2$ afforded the bimetallic complex **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).[35]
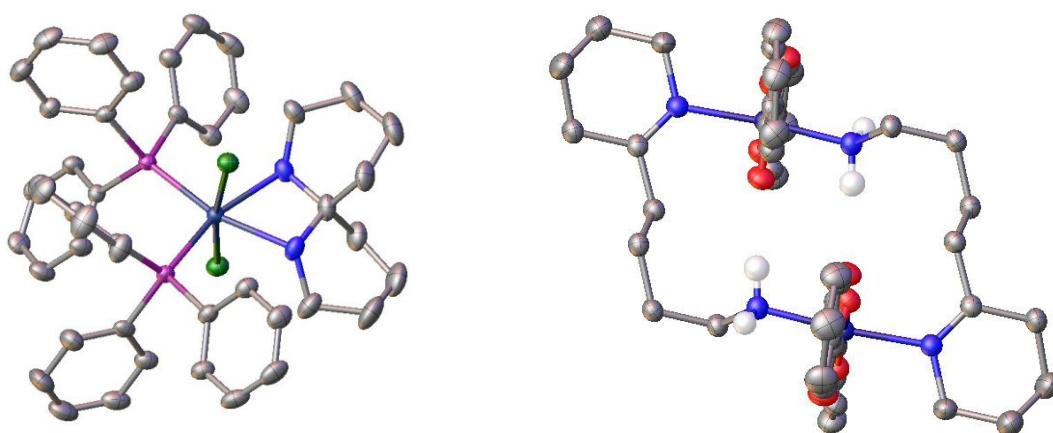
Figure 33: *Solid-state structures of **67** and **68**, as reported by Barrett.*[35]

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.
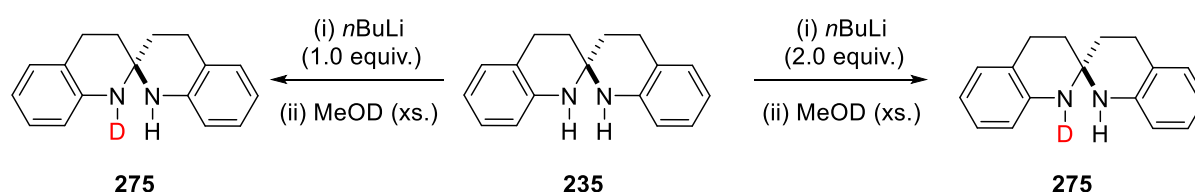
Scheme 87: Deuteration studies of spiroquinoline 235.

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. [a];100% purity, removal of mineral oil by washing with hexanes. [b]; Full deprotonation observed by ^1H NMR.
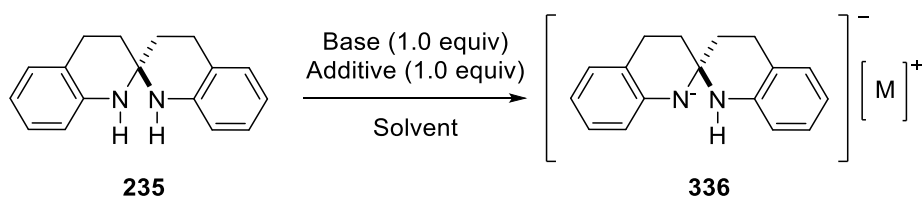
Entry	Base	Additive	Solvent	Temp	Result
1[149]	*n*-BuLi	N/A	THF	-78 ºC	Decomp during rexs.
2[149]	*n*-BuLi	TMEDA	THF	-78 ºC	Decomp during rexs.
3[149]	*n*-BuLi	TRIMEDA	THF	-78 ºC	Decomp
4[150]	*n*-BuLi	N/A	Et$_2$O	0-20 ºC	Decomp during rexs.
5	NaH[a]	N/A	THF	0 ºC	Decomp upon drying.
6	KH[a]	N/A	THF	0 ºC	Decomp
7[151]	LiHMDS	N/A	C$_6$D$_6$	-20 ºC	Decomp upon drying[b]
8[151]	NaHMDS	N/A	C$_6$D$_6$	-20 ºC	Decomp upon drying[b]
9[151]	KHMDS	N/A	C$_6$D$_6$	-20 ºC	Decomp upon drying[b]
10[149]	*sec*-BuLi	TMEDA	THF	-78 ºC	Decomp upon drying.
11[149]	*t-BuLi*	TMEDA	THF	-78 ºC	Decomp upon drying.

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,[150] the lithium salt was treated with CO_2 at -78 ºC to form the proposed lithium carbamate **337** (Scheme 88). Attempts at recrystallisation resulted in decomposition and this structure could therefore not be confirmed.
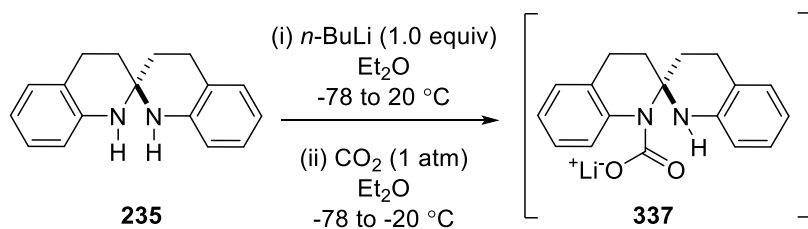
*Scheme 88: The attempted formation of lithium carbamate **337**.*

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.[152] Recently Yeoul Lee *et al.* have reported the complexation of tetrahydro-[1,10]phenanthroline with zirconium and hafnium.[153] Therefore, we sought to investigate the coordination chemistry of spirotetrahydrophenanthroline **263** with these metals. Attempts at forming these complexes from tetrabenzyl precursors were all unsuccessful (Table 9).

Proposed Structures
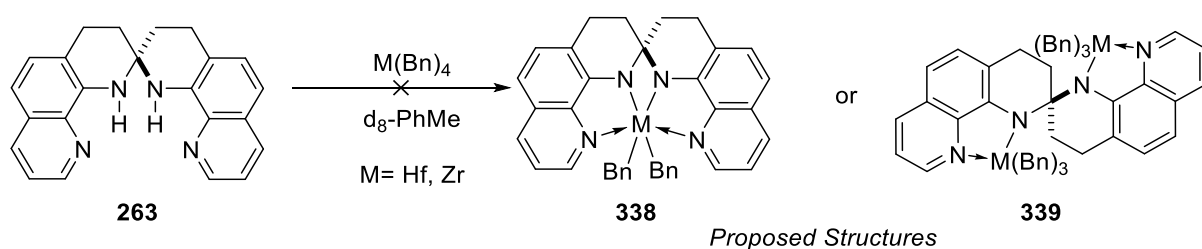
Entry	Metal Precursor	Equiv.	Solvent	Temp
1	ZrBn$_4$	1.0	THF	-0 ºC
2	ZrBn$_4$	0.5	THF	-0 ºC
3	HfBn$_4$	1.0	THF	-78 ºC
4	HfBn$_4$	0.5	Et$_2$O	0-20 ºC

***Table 9:** The attempted formation of zirconium and hafnium complexes of **263**, using the procedure of Yeoul.[153]*

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]

263
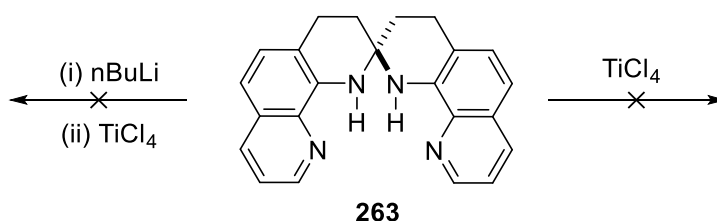
Scheme 89: *Attempted reactions between **263** and TiCl$_4$.*

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).

Entry	ML (Ligand)	Solvent	Temp (Time)	Result
1[35]	RuCl₂(PPh₃)₃ (47)	CH₂Cl₂	rt (24 h)	*Green Oil with small orange micro crystals*
2[35]	RuCl₂(PPh₃)₃ (56-B)	CH₂Cl₂	rt (24 h)	*Green Oil*
3[35]	RuCl₂(PPh₃)₃ (235)	CH₂Cl₂	rt (24 h)	*No Reaction[b]*
4[35]	RuCl₂(PPh₃)₃ (263)	CH₂Cl₂	rt (24 h)	*No Reaction[b]*
5[155]	RuCl₂(DMSO)₃ (53-A)	EtOH	80 ºC (4 h)	*Black Gum*
6[155]	RuCl₂(DMSO)₃ (235)	EtOH	80 ºC (4 h)	*Black Gum*
7[156]	[Ru(C₆H₆)(CH₃CN)](PF₆)₂ (263)	CH₃CN	rt (48 h)	*No Reaction*
8[156]	[Ru(C₆H₆)(CH₃CN)](PF₆)₂ (235)	CH₃CN	rt 48 h	*No Reaction*
9[157]	[Ru(p-cymene)Cl₂]₂ (53-A)	IPA[a]	80 ºC 1 h	*Brown insoluble solid*
10[157]	[Ru(p-cymene)Cl₂]₂ (119-A)	IPA[a]	80 ºC 1 h	*Brown insoluble solid*
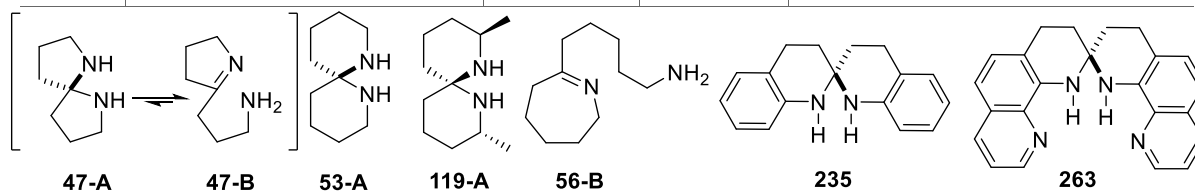
Table 10: *The attempted synthesis of spiroaminal ruthenium complexes. All reactions were carried out with 1.0 equiv. of ML. [a];See main discussion, [b];No reaction observed after 24 h at 40 ºC.*

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.[158] However, spiroaminal **47** afforded a small amount of material suitable for X-ray crystallography after several sequential recrystallisations (Scheme 90).
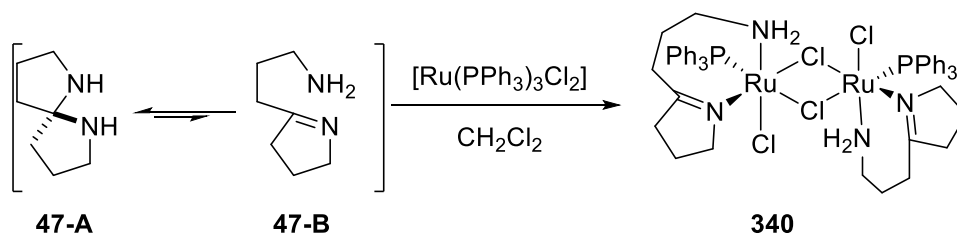
Scheme 90: *Synthesis of bimetallic* **333.**

The product was identified as a bimetallic compound **340** with the ligand adopting the amine-imine tautomer as seen previously with copper.[35] Interestingly these ligands adopt a *cis* configuration pushing the remaining sterically bulky PPh$_3$ into close proximity (Figure 34).
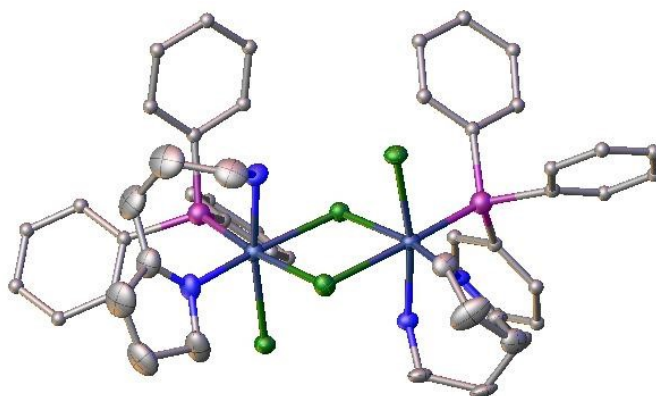
Figure 34: *Solid-state structure of ruthenium complex* **340** *(50% probability ellipsoids).*

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.[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.

Entry	ML (Ligand)	Solvent	Temp (Time)	Result
1[160]	$Pd(PPh_3)_4$ (**47**)	C_6H_6	rt (24 h)	*No reaction*
2[160]	$Pd(PPh_3)_4$ (**53-A**)	C_6H_6	rt (24 h)	*No reaction*
3[160]	$Pd(PPh_3)_4$ (**56-B**)	C_6H_6	rt (24 h)	*No reaction*
4[160]	$Pd(PPh_3)_4$ (**235**)	C_6H_6	rt (24 h)	*No reaction*
5[161]	$Pd(OAc)_2$ (**53-A**)	MeOH	rt (24 h)	*No reaction*
6[161]	$Pd(OAc)_2$ (**235**)	MeOH	rt (24 h)	*No reaction*
7[161]	$Pd(OAc)_2$ (**263**)	MeOH	rt (24 h)	*No reaction*
8[162]	$Pd(TFA)_2$ (**53-A**)	THF	rt 16 h	*Unidentified black tar*
9[162]	$Pd(TFA)_2$ (**235**)	THF	rt 16 h	*Unidentified black tar*

10[163]	Pd(MeCN)$_4$(BF$_4$)$_2$ (**235**)	MeOH/ MeCN	rt 1 min	*Insoluble off-white precipitate. Mass yield >90%[a]*
11[163]	Pd(MeCN)$_4$(BF$_4$)$_2$ (**263**)	MeOH/ MeCN	rt 1 min	*Insoluble off-white precipitate. Mass yield >90% [a]*
12	Pd(MeCN)$_4$(BF$_4$)$_2$ (**235**)	MeCN	0 ºC 1 min	*Insoluble off-white precipitate. Mass yield >90% [a]*
13	Pd(MeCN)$_4$(BF$_4$)$_2$ (**235**)	MeCN	-20 to 0 ºC 1 min	*No reaction at -20 ºC for 4 h, then precipitation of product at 0 ºC, insoluble off white solid. [a]*
14	Pd(MeCN)$_4$(BF$_4$)$_2$ (**53-A**)	MeCN	rt 16 h	*No reaction*
15[164]	PdCl$_2$(MeCN)$_2$ (**53-A**)	Acetone/ H$_2$O	80 ºC 16 h	*Complex mixture of products by ^{1}H NMR*
16[164]	PdCl$_2$(MeCN)$_2$ (**235**)	Acetone/ H$_2$O	80 ºC 16 h	*Complex mixture of products by ^{1}H NMR*

47-A **47-B** **53-A** **56-B** **235** **263**
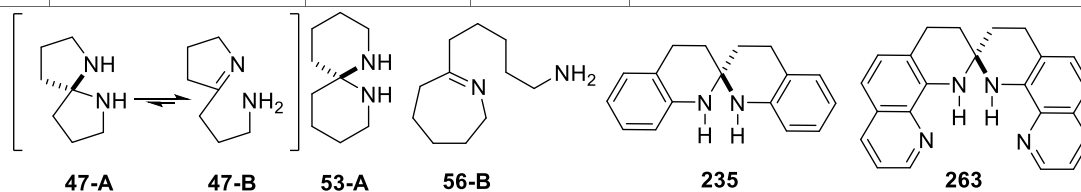
Table 11: The attempted synthesis of spiroaminal palladium complexes. All reactions were carried out with 1.0 equiv. of ML. [a];See main discussion, [b];No reaction observed after 24 h at 40 ºC.

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,[165] the lack of solubility led to no analytical data, and therefore the structures cannot be confirmed.

341 **342**
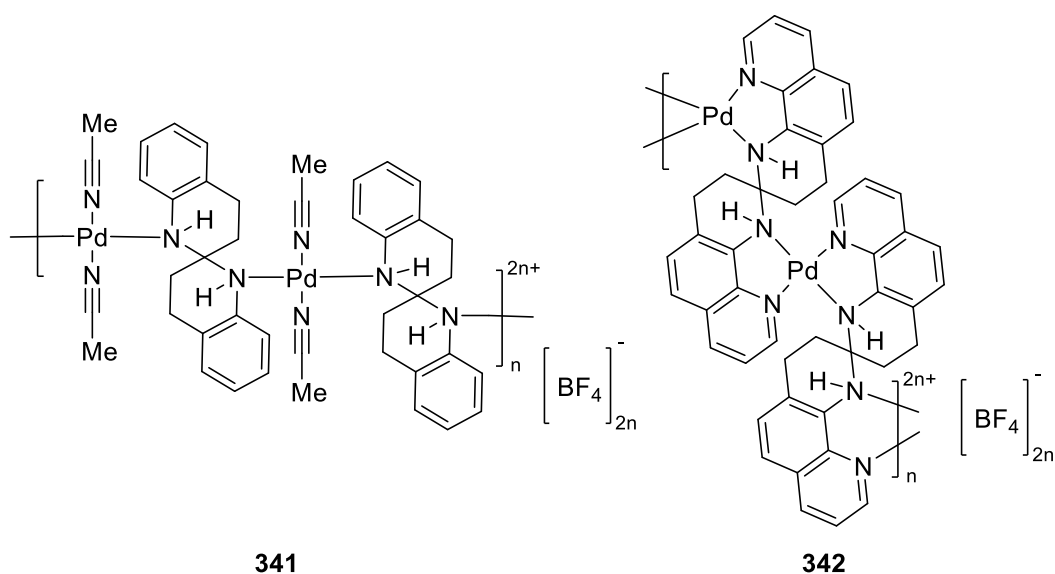
Figure 35: Possible polymeric palladium complexes 334 and 335.

Nickel is known for its particularly high affinity to nitrogen, with many known complexes having a variety of interesting properties and applications.[159] 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.

Entry	ML (Ligand)	Solvent	Temp (Time)	Result
1[166]	(DME)NiBr$_2$ (**53-A**)	CH$_2$Cl$_2$	rt (16 h)	*No Reaction*
2[166]	(DME)NiBr$_2$ (**235**)	CH$_2$Cl$_2$	rt (16 h)	*No Reaction*
3[166]	(DME)NiBr$_2$ (**53-A**)	CH$_2$Cl$_2$	40 ºC (16 h)	*No Reaction*
4[167]	NiBr$_2$ (**53-A**)	MeCN	85 ºC (30 min)	*Insoluble brown product. Mass yield (<20%)*

5[167]	NiBr$_2$ (**235**)	MeCN	85 ºC (30 min)	*Insoluble green product. Mass yield (<10%)*
6[167]	NiBr$_2$ (**53-A**)	MeCN	85 ºC (30 min)	*No reaction*
7[167]	NiBr$_2$ (**235**)	MeCN	85 ºC (30 min)	*No reaction*

53-A   **235**
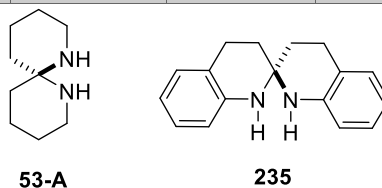
Table 12 *The attempted synthesis of spiroaminal nickel complexes. All reactions were carried out with 1.0 equiv. of ML.*

4.2.7 Platinum Complexes

Diamino platinum complexes are well documented,[144] and their importance as chemotherapeutics has resulted in world-wide recognition as some of the world's most important pharmaceuticals.[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 bidentante dianionic ligand. One such analogue is carboplatin (**344**) which is used in the treatment of ovarian and lung cancers.[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.[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.[144,171]
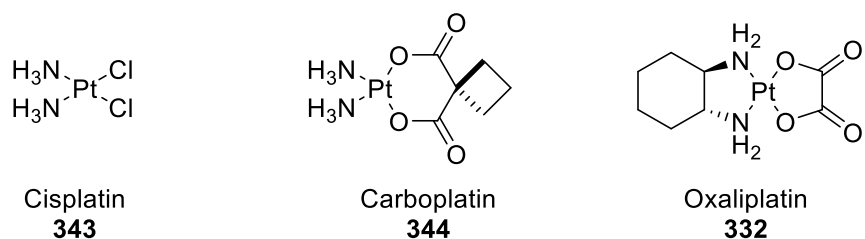
Figure 36: *Approved platinate chemotherapeutics.*

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 tetraiodo platinate **346** formed *in situ* from commercially available potassium tetrachloroplatinate (**345**). When platinate **346** was treated with spiroaminal **53-A** the proposed complex **347** precipitated from the solution (Scheme 91). As previously observed with the palladium species and with many platinum complexes,[171] the products were completely insoluble in all solvents tested.
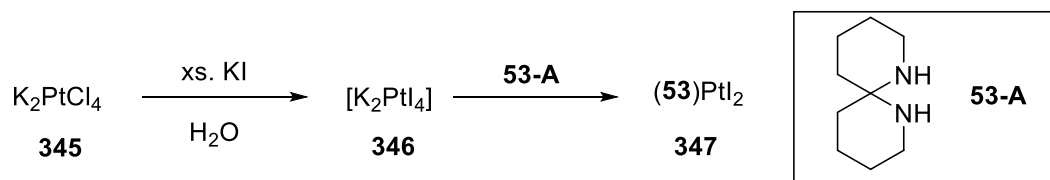
Scheme 91: *Synthesis of proposed diiodoplatinate 347.*

Conversion of the diiodo **347** to the dichloro was attempted using a known procedure,[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).

Entry	ML (Ligand)	Solvent	Temp (Time)	Result
1[174]	CuCl$_2$ (**53-A**)	CH$_2$Cl$_2$	rt (16 h)	*No reaction*
2[174]	CuCl$_2$ (**47**)	CH$_2$Cl$_2$	rt (16 h)	*No reaction*
3[174]	CuCl$_2$ (**235**)	CH$_2$Cl$_2$	rt (16 h)	*Small amount of red precipitate, non-crystalline*
4[175]	Cu(OTf)$_2$ (**53-A**)	Acetone	rt (15 min)	*No reaction*
5[175]	Cu(OTf)$_2$ (**235**)	Acetone	rt (15 min)	*No reaction*
6[176]	Cu(OTf)$_2$ (**53-A**)	MeCN	rt (1 min)	*Lilac precipitate Decomposition upon removal of MeCN*
7[176]	Cu(OTf)$_2$ (**235**)	MeCN	rt (1 min)	*Lilac precipitate Decomposition upon removal of MeCN*

8[35]	Cu(OBz)$_2$ (**235**)	CH$_2$Cl$_2$ MeOH	rt (16 h)	*No reaction*
9[35]	Cu(OBz)$_2$ (**263**)	CH$_2$Cl$_2$ MeOH	rt (16 h)	*No reaction*
10[35]	Cu(OBz)$_2$ (**47**)	CH$_2$Cl$_2$ MeOH	rt (16 h)	*Recrystallisation did not afford crystalline product*
11[35]	Cu(OBz)$_2$ (**119-A**)	CH$_2$Cl$_2$ MeOH	rt (16 h)	*Recrystallisation did not afford crystalline product*

47-A   47-B   53-A   119-A   235   263
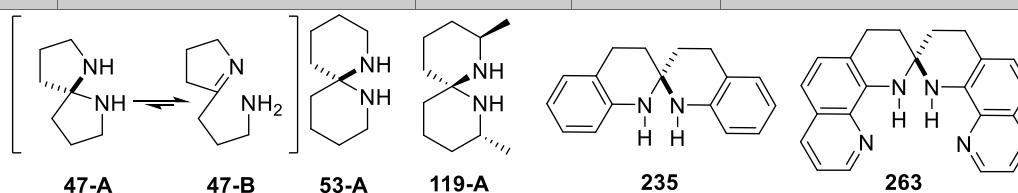
Table 13: *The attempted synthesis of spiroaminal nickel complexes. All reactions were carried out with 1.0 equiv of ML.*

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,[177] their ability to be finely tuned for specific applications,[178,179] and their bioisosteric nature in biological settings.[180,181] 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 ^{11}B NMR in all cases, highlighting the issues of the coordination of the two tautomers present in the spiroaminal system.

Entry	ML (Ligand)	Solvent (Additive)	Temp (Time)	Result
1[182]	BCl$_3$•SMe$_2$ (**53-A**)	*n*-hexane (NEt$_3$)	80 ºC (4 h)	*Multiple products present by ^{1}H and ^{11}B NMR*[a]
2[182]	BCl$_3$•SMe$_2$ (**235**)	*n*-hexane (NEt$_3$)	80 ºC (4 h)	*No reaction*
3[182]	BCl$_3$•SMe$_2$ (**235**)	*n*-hexane (NEt$_3$)	80 ºC (16 h)	*No reaction*
4[183]	BH$_3$•THF (**53-A**)	THF	65 ºC (2 h)	*Multiple products present by ^{1}H and ^{11}B NMR*[a]
5[183]	BH$_3$•THF (**235**)	THF	65 ºC (2 h)	*No reaction*
6[183]	BH$_3$•THF (**235**)	THF	65 ºC (8 h)	*No reaction*
7[184]	B$_2$(NMe$_2$)$_4$ (**53-A**)	PhMe	115 ºC (2 h)	*No reaction*
8[184]	B$_2$(NMe$_2$)$_4$ (**235**)	PhMe	115 ºC (2 h)	*No reaction*
9[184]	B$_2$(NMe$_2$)$_4$ (**53-A**)	PhMe	115 ºC (16 h)	*No reaction*
10[184]	B$_2$(NMe$_2$)$_4$ (**53-A**)	PhMe	115 ºC (16 h)	*No reaction*

Table 14: *The attempted formations of spiroaminal azaboron compounds. All reactions were carried out with 1.0 equiv of ML. [a]Decomposistion 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.[185] Treatment of spiroaminals

53-A and **235** with PhPCl$_2$ under the conditions of Kornev[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.
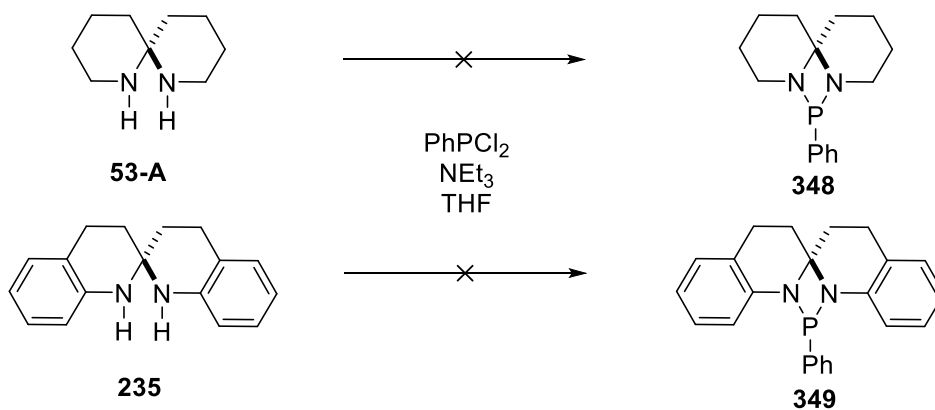
*Scheme 92: The attempted synthesis of bisaminophosphines **348** and **349**.*

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).
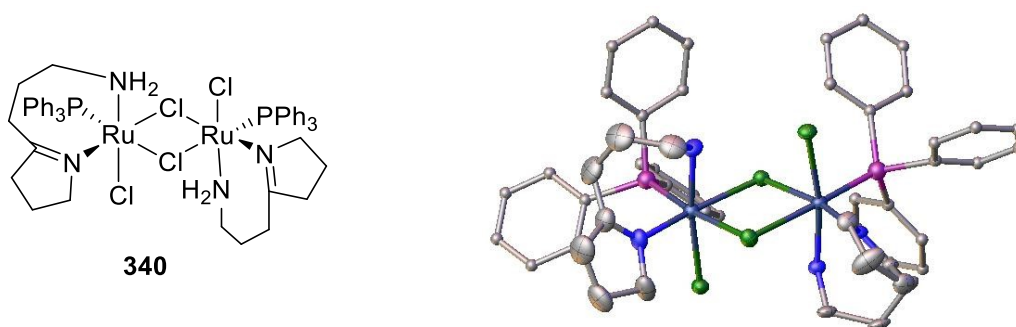
*Figure 37: The isolated ruthenium dimer **340** and its solid-state structure (50% probability ellipsoids).*

Attentions are now focussed 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: Et_2O, THF and PhMe were dried over Na/Ph_2CO; MeOH, CH_2Cl_2, NEt_3 and pyridine were dried over CaH_2. H_2O refers to redistilled H_2O. 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.

^{1}H 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). ^{13}C 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 $CDCl_3$: δ H =7.26, δ C = 77.16 ppm and d_6-DMSO - δ H = 2.50, δ C = 39.52 ppm.

The numbering of ^{1}H and ^{13}C 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 ºC. 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,[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 $BH_3 \bullet SMe_2$ (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 H_2O, solid K_2CO_3 (1.7 equiv.) was added portion-wise. Once the addition was complete, the mixture was diluted with Et_2O and the organic layer was collected. The aqueous layer was further extracted with Et_2O (x 2), the combined organic layers were washed with brine, dried over $MgSO_4$ 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 CH_2Cl_2 (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 CH_2Cl_2 (x 2). The combined organic layers were dried over $MgSO_4$ and the solvent removed by rotary evaporation to yield the crude mesylate.

The crude mesylate and NaN_3 (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 PPh_3 (1.0 equiv.) was added in a single portion. This was stirred at 40 ºC until nitrogen evolution had finished (1-2 h). H_2O (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/Et_2O (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[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 ºC. 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_4Cl (1.1 equiv.), and the suspension was stirred for 10 min before dilution with Et_2O (4 mL/mmol). This was washed with half sat. aqueous NH_4Cl (x 1), with the aqueous layer being re-extracted with Et_2O (x 2), the combined organics were then dried over $MgSO_4$ and the solvent removed by rotary evaporation, to yield the crude ketolactam-hemiaminal intermediate.

The crude mixture was cooled to 0 ºC before the addition of conc. HCl (1 mL/mmol). The solution was heated to 100 ºC for 24 h. The reaction was basified to pH 14 with KOH (10 M) at 0 ºC. The resultant mixture was extracted with CH_2Cl_2 (x 5), the combined organics were dried over $MgSO_4$, 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_NAr of *o*-nitro-benzaldehydes.

Using a modified procedure of Driver;[188] Sodium azide (3.0 equiv.) was added to a solution of nitro aldehyde (1.0 equiv.) in HMPA (0.33 M) at 0 ºC. The mixture was warmed to room temperature, and stirred for 24 h. After this time, the solution was diluted with Et_2O (250 mL) and washed with H_2O (5 x 50 mL). The solvent was removed by rotary evaporation, followed by drying the crude product under vacuum (1×10^{-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 CH_2Cl_2 and H_2O (1:1). The layers were separated, and the aqueous layer was further extracted with CH_2Cl_2 (x 2). The combined organic extracts were dried ($MgSO_4$), 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 H_2O under reflux before hot filtration and rapid cooling. The precipitate is removed by filtration, washed with cold H_2O and dried before immediate use.

5.3 Procedures and Compound Characterisation

tert-Butyl 2-oxopyrrolidine-1-carboxylate - 72
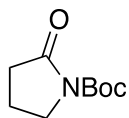
Using general procedure **A**; lactam **42** (5.0 g, 59 mmol) gave *N*-Boc lactam **72** (7.4 g, 68%) as a colourless liquid after purification by column chromatography (20 → 100% Et$_2$O in pentane). The data is consistent with that reported in the literature.[189]

¹H NMR (400 MHz, CDCl$_3$) 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, CDCl$_3$) δ 174.2, 150.2, 82.6, 46.5, 32.9, 28.0 (3C), 17.4.

HR-MS (EI) calcd for C$_9$H$_{15}$O$_3$N (M$^{\cdot+}$): 185.1052, found: 185.1065.

tert-Butyl 2-oxopiperidine-1-carboxylate - 57
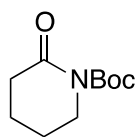
Using general procedure **A**; lactam **52** (30.0 g, 303 mmol) gave *N*-Boc lactam **57** (42.6 g, 77%) as a colourless liquid after purification by column chromatography (20% Et$_2$O in pentane). The data is consistent with that reported in the literature.[190]

^{1}H-NMR (400 MHz, CDCl$_3$) δ 3.52-3.54 (m, 2H), 2.37-2.39 (m, 2H), 1.80-1.60 (m, 4H), 1.39 (s, 9H).

^{13}C-NMR (101 MHz, CDCl$_3$) δ 171.1, 152.5, 82.5, 46.1, 34.7, 27.8 (3C), 22.6, 20.3.

HR-MS (ESI) calcd for C$_{12}$H$_{20}$N$_2$O$_3$Na (M + CH$_3$CN + Na$^+$): 263.1372, found: 263.1380.

tert-Butyl 2-oxoazepane-1-carboxylate - 73
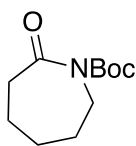
Using general procedure **A**; lactam **55** (5.0 g, 44 mmol) gave *N*-Boc lactam **73** (5.3 g, 56%) as a colourless liquid after purification by column chromatography (20 -> 50 % Et$_2$O in pentane). Analytical data matched the reported data.[191]

¹H NMR (400 MHz, CDCl$_3$) 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, CDCl$_3$) δ 175.7, 153.1, 82.8, 46.2, 39.6, 29.3, 28.8, 28.1 (3C), 23.6.

HR-MS (EI) calcd for C$_{11}$H$_{19}$O$_3$N (M$^{.+}$): 213.1365, found: 213.1360.

(R)-tert-Butyl 2-methylpiperidine-1-carboxylate - 75
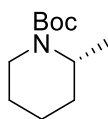
Using the procedure of Nanayakkara[53]; 2-methylpiperidine (2.4 g, 24 mmol, 1.1 equiv.) was added dropwise to a solution of (S)-mandelic acid (3.4 g, 22 mmol, 1.0 equiv.) in MeOH (10 mL) at 0 °C at a rate to keep the temperature below 5 °C. After the addition was complete, Et_2O (45 mL) was added dropwise 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_2O (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_2O (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_2O (3 x 50 mL). The combined organic were dried over $MgSO_4$ 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.[192]

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34 (t,J = 6.1 Hz, 1H), 3.89 (dd, J = 13.2 Hz, 3.7 Hz, 1H), 2.78 (td, J = 3.7, 13.2 Hz, 1H), 1.64-1.51 (m, 4H), 1.43 (s, 9H), 1.38-1.29 (m, 2H), 1.09 (d, J = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3, 79.1, 46.2, 38.8, 28.6 (3C), 27.5, 25.8, 18.8 , 15.8.

$[\alpha]_D^{22}$: -48.5 (c, 1.0, $CHCl_3$), {lit. [53] $[\alpha]_D^{24}$: -50.7 (c, 1.0, $CHCl_3$)}

MS (EI) calcd for $C_{11}H_{21}NO_2$ (M + H$^+$): 199.1572, found: 199.1602.

(*R*)-*tert*-Butyl 2-methyl-6-oxopiperidine-1-carboxylate - 76
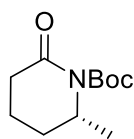
Piperidine **75** (1.5 g, 7.5 mmol, 1.0 equiv.) was stirred with ruthenium (IV) oxide hydrate (300 mg, 2.25 mmol, 30 mol% anhydrous basis) in EtOAc (90 mL). This was added to a solution of NaIO$_4$ (8.0 g, 37.0 mmol, 5.0 equiv.) in water (75 mL) and the biphasic solution was left to stir under argon 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 MgSO$_4$, 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, CDCl$_3$) 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, CDCl$_3$) δ 171.4, 153.1, 82.9, 51.8, 34.3, 29.4, 28.0 (3C), 20.6, 17.4.

$[\alpha]_D^{22}$: -5.1 (*c*, 1.0, CHCl$_3$).

HR-MS (EI) calcd for C$_{11}$H$_{19}$O$_3$N (M$^{\cdot+}$): 213.1365, found: 213.1357.

Methyl 5-oxopentanoate - 78
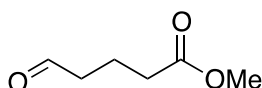
Using the procedure of Carreira[57]; cyclopentene (**77**) (7.0 mL, 75.0 mmol) and powdered NaHCO$_3$ (2.0 g) in CH$_2$Cl$_2$/MeOH (5:1 300 mL) was cooled to -78 ºC. Ozone was bubbled through the solution until a pale blue colour persisted, the solution was sparged with argon until colourless. The reaction mixture was warmed to room temperature, filtered and diluted with C$_6$H$_6$ (80 mL) and concentrated by rotary evaporation to approx. 50 mL. The resultant solution was diluted with CH$_2$Cl$_2$ (225 mL) cooled to 0 ºC. To this NEt$_3$ (16 mL) was added dropwise, followed by the dropwise addition of acetic anhydride (21 mL). The solution was left to stir at 0 ºC 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$_2$O (150 mL), dried over MgSO$_4$ and the solvent removed in *vacuo.* The crude product was purified by column chromatography (15→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.[57]

¹H NMR (400 MHz, CDCl$_3$) 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).

¹³C NMR (101 MHz, CDCl$_3$) δ 201.8 , 173.5 , 51.8 , 43.0 , 33.0, 19.9 .

A mass could not be obtained for this compound through a range of techniques.

(*S,E*)-Methyl 5-((*tert*-butylsulfinyl)imino)pentanoate - 79
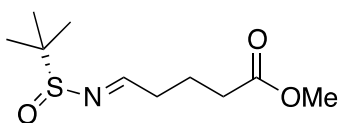
Using the procedure of Chemla[55]; methyl 5-oxopentanoate (**78**) (3.16 g, 24.0 mmol, 1.0 equiv.), (*S*)-(−)-2-methyl-2-propanesulfinamide (2.60 g, 22.0 mmol, 0.9 equiv.), PPTS (630 mg, 2.5 mmol, 0.1 equiv.) and $MgSO_4$ (12 g) in CH_2Cl_2 (60 mL) was stirred for 24 h. After this time the reaction mixture was filtered, the solvent removed in *vacuo,* the crude product was purified by column chromatography (50% Et_2O 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.[55]

¹H NMR (400 MHz, $CDCl_3$) δ 8.05 (t, *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).

¹³C NMR (101 MHz, $CDCl_3$) 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, $CHCl_3$), {lit.[55] $[\alpha]_D^{20}$: +230.0 (*c*, 1.7, $CHCl_3$)}

HR-MS (CI) calcd for $C_{10}H_{20}NO_3S$ (M + H⁺): 234.1164, found: 234.1163.

(S)-6-*iso*Propylpiperidin-2-one - 82
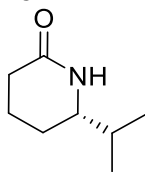
Using a modified procedure of Chemla[55] and Guijarro[194]: Isopropylmagnesium chloride (2.0 M in Et_2O, 1.00 mL, 2.0 mmol, 2.0 equiv.) was added dropwise to a solution of sulfinimine **79** (233 mg, 1.0 mmol, 1.0 equiv.) in Et_2O (2 mL) at -78 ºC. After stirring at -78 ºC for 4 h the solution was quenched with 1M HCl (10 mL). The phases were separated, and the aqueous layer was further extracted with Et_2O (2 x 10 mL). The combined organic layers were washed with sat. aqueous $NaHCO_3$ (15 mL), H_2O (15 mL), brine (15 mL), dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The crude sulfinamine was dissolved in MeOH (3 mL), cooled to 0 ºC 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 t basified with a 2 M NH_3/NH_4 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 CH_2Cl_2 (3 x 10 mL), the combined organics were dried over $MgSO_4$, and the solvent removed by rotary evaporation. Purification by column chromatography (10% EtOAc in pentane + 1% NEt_3) afforded the product **83** (70 mg, 51%) as a colourless oil. The data is consistent with that reported in the literature.[195]

^{1}H NMR (400 MHz, $CDCl_3$) 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 (ddd, 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).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 58.9, 33.0, 31.5, 25.1, 20.2, 18.1, 18.0.

$[\alpha]_D^{25}$: +58.0 (c, 0.4, $CHCl_3$), {lit.[195] $[\alpha]_D^{25}$: +68.9 (c, 0.4, $CHCl_3$)}

HR-MS (EI) calcd for $C_8H_{15}NO$ (M$^+$): 141.1154, found: 141.1160.

tert-Butyl (*S*)-2-isopropyl-6-oxopiperidine-1-carboxylate - 84
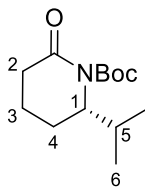
Using general procedure **A**; lactam **82** (60 mg, 0.42 mmol) gave *N*-Boc lactam **84** (96 mg, 95%) as a colourless liquid after purification by column chromatography (10% EtOAc in pentane).

^{1}H NMR (400 MHz, CDCl$_3$) δ 4.03 (dt, *J* = 8.0, 5.3 Hz, 1H. H^1), 2.61 – 2.36 (m, 2H, H^2), 1.98 – 1.85 (m, 2H, H^{4a} and H^5), 1.84 – 1.77 (m, 2H, H^{3a}, H^{4b}), 1.77 – 1.68 (m, 1H, H^{3b}), 1.51 (s, 9H, Boc), 0.92 (t, *J* = 6.6 Hz, 6H, H^6).

^{13}C NMR (101 MHz, CDCl$_3$) δ 172.3 (C=O), 153.5 (Boc C=O), 82.8 (Boc OCMe$_3$), 60.5 (C^1), 34.1 (C^2), 31.4 (C^5), 28.1 (3C, Boc CH$_3$), 23.5 (C^4), 19.5 (C^3), 18.2 (C^6), 17.8 (C$^{6'}$).

IR ν= 2957, 2875, 1702, 1648, 1408, 1351, 1181 cm^{-1}.

$[\alpha]_D^{25}$: +48.5 (*c*, 1.0, CHCl$_3$)

HR-MS (EI) calcd for C$_{13}$H$_{23}$NO$_3$ (M$^{+\cdot}$): 241.1670; found: 241.1681.

(*S*)-6-Phenylpiperidin-2-one - 83
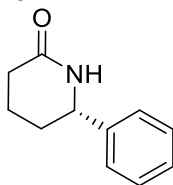
Using the procedure described for lactam **82**; phenylmagnesium bromide (3.0 M in Et_2O, 660 µL, 2.0 mmol, 2.0 equiv.) was in the place of isopropylmagnesium chloride to afford the lactam **83** (62 mg, 35%) after purification by chromatography (50 % EtOAc in pentane +1 % NEt_3) as a white solid. Analytical data matched the reported data.[196]

¹H NMR (400 MHz, $CDCl_3$) 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, $CDCl_3$) 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, $CHCl_3$)

HR-MS (ES) calcd for $C_{11}H_{14}NO$ (M + H⁺): 176.1075, found: 176.1077.

tert-Butyl (*S*)-2-oxo-6-phenylpiperidine-1-carboxylate - 85
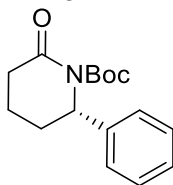
Using general procedure **A**; lactam **83** (88 mg, 0.5 mmol) gave *N*-Boc lactam **85** (114 mg, 83%) as a white solid after purification by column chromatography (10% EtOAc in pentane). Analytical data matched the reported data.[197]

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.

$[\alpha]_D^{20}$: -17.0 (*c*, 0.3, CHCl₃), {lit.[197] $[\alpha]_D^{20}$: -19.6 (*c*, 0.24, CHCl₃)}

HR-MS (ES) calcd for $C_{16}H_{22}NO_3$ (M + H⁺): 276.1600, found: 276.1616.

(*R*)-4-Isopropyl-1-methylcyclohex-1-ene - 89
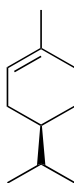
Using the procedure of Wender[60]; a mixture of (+)-limonene (**88**) (65 mL, 0.4 mol), PtO_2 (160 mg) in EtOH (200 mL) was agitated under a hydrogen atmosphere (1 atm) for 10 h. After this time, the catalyst was removed by filtration. The solvent was removed under vacuum, and the product was purified 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.[198]

^{1}H NMR (400 MHz, $CDCl_3$) 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)

^{13}C-NMR (101 MHz, $CDCl_3$). 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, $CHCl_3$), {lit.[59] $[\alpha]_D^{22}$: +101.8(*c*, 1.0, $CHCl_3$)}

HR-MS (EI) calcd for $C_{10}H_{18}$ (M^{+}): 138.1409, found: 138.1500.

(R)-3-Isopropyl-6-oxoheptanoic acid - 90
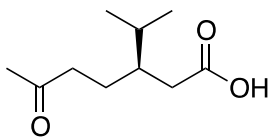
Ozone was bubbled through a solution of alkene **89** (18.3 g, 133 mmol, 1.0 equiv.) in CH_2Cl_2 (100 mL) at -78 ºC until a blue colour persisted. The solution was sparged with oxygen for 10 min, followed by argon for 10 min. The solution was warmed to 0 ºC, and aqueous hydrogen peroxide (50% wt, 9.9 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 NaS_2O_8 (50 mL) the solution was basified with 10 M NaOH to pH 14. The aqueous layer was washed with CH_2Cl_2 (2 x 150 mL). The aqueous layer was acidified with conc. HCl to pH 1. This was extracted with CH_2Cl_2 (3 x 300 mL), the combined organic layers were dried over $MgSO_4$ 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.

(R)-Methyl 3-isopropyl-6-oxoheptanoate - 91
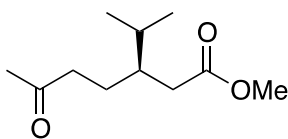
To a solution of crude acid **90** (700 mg, 3.7 mmol, 1.0 equiv.) in acetone (50 mL) was added K_2CO_3 (2.6 g, 18.5 mmol, 5.0 equiv.) followed by MeI (3.4 mL, 18.5 mmol, 15.0 equiv.) at room temperature. The suspension was stirred for 16 h, the solids were removed by filtration and the solvents removed 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]

¹H NMR (400 MHz, CDCl₃) δ 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).

¹³C NMR (101 MHz, CDCl₃) δ 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, CHCl₃), {lit.[199] $[\alpha]_D^{20}$: +3.9 (*c*, 1.0, CHCl₃)}

HR-MS (ESI) calcd for $C_{11}H_{20}O_3Na$ (M + Na⁺): 223.1310, found: 223.1317.

N-tert-Butyl-phenylsulfinimidoyl chloride - 94
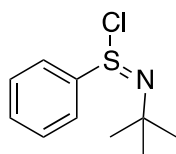
Using the procedure of Kovacic,[200] and Barrett[201]; *N,N*-Dichloro-*tert*-butylamine was prepared by the drop-wise addition of HCl (3 M, 100 mL) to a suspension of *tert*-butylamine (4 mL, 38 mmol) and 75% calcium hypochlorite (16 g, 78.4 mmol) in CH_2Cl_2 (100 mL). After the addition was completed the biphasic mixture was stirred for 1 h before the phases were separated. The organic layer was washed with H_2O (1 x 50 mL) and dried over $NaSO_4$ 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_6H_6 (15 mL), and heated at 80 ºC 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.[201]

¹H NMR (400 MHz, $CDCl_3$) 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(2*H*)-carboxylate - 95
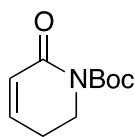
LiHMDS (1.0 M in THF, 11 mL, 11 mmol, 1.1 equiv.) was added to a solution of lactam **57** (2.0 g, 10 mmol, 1.0 equiv.) in THF (60 mL) at -78 ºC. After 10 minutes, a solution of **94** (2.6 g, 12 mmol, 1.2 equiv.) in THF (40 mL) was added dropwise over 10 minutes. After stirring for 30 min at -78 ºC, the reaction was quenched with sat. aqueous NaHCO$_3$ (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 MgSO$_4$ 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]

^{1}H NMR (400 MHz, CDCl$_3$) 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).

^{13}C NMR (101 MHz, CDCl$_3$) δ 169.6, 152.3, 143.3, 127.6, 82.8, 43.5, 28.2, 24.9.

HR-MS (ESI) calcd for C$_{10}$H$_{16}$NO$_3$ (M + H$^+$): 198.1125, found: 198.1125.

Dimethyl 3-isopropylpentanedioate - 102
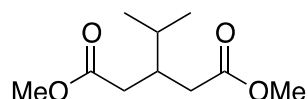
Using the procedure of Overman[202]; a solution of *iso*propylmagnesium chloride (1 M in THF, 75 mL, 75 mmol, 4.0 equiv.) was added drop-wise to a suspension of CuI (1.1 g, 5.6 mmol, 0.3 equiv.) in THF (200 mL) at room temperature. This mixture was stirred at room temperature for 10 min before being cooled to -78 ºC. 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 ºC for 3 h. The solution was warmed to room temperature and quenched slowly with sat. aqueous NH$_4$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$_4$ and the solvent removed under vacuum to yield the crude product. This was purified by bulb-to-bulb distillation (60 ºC, 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.[203]

¹H NMR (400 MHz, CDCl$_3$) δ 3.66 (s, 6H), 2.46-2.10 (m, 5H), 1.73 (m, 1H), 0.88 d, *J*= 6.9 Hz, 6H).

¹³C NMR (101 MHz, CDCl$_3$) 173.6 (2C), 51.7 (2C), 37.9 (2C), 35.9 , 30.5, 19.1 (2C).

HR-MS (ESI) calcd for C$_{10}$H$_{19}$O$_4$ (M + H$^+$): 203.1283, found: 203.1291.

Dimethyl 3-isophenylpentanedioate - 103
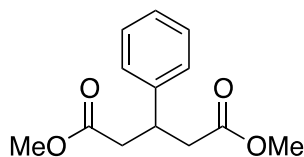
Using the procedure described for *iso*propyl **102**; phenylmagnesium bromide was implemented in the place of isopropylmagnesium chloride to afford the phenyl **103** (3.8 g. 67%) as a white solid, after purification by recrystallization from *n*-hexane. The data is consistent with that reported in the literature.[204]

¹H 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).

¹³C-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 ºC}.[205]

HR-MS (ESI) calcd for $C_{13}H_{16}O_4$ (M + H⁺): 237.1127, found: 237.1126.

(*R*)-5-Methoxy-3-methyl-5-oxopentanoic acid - 107
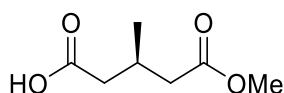
Using the procedure of Jones[63]; dimethyl 3-methylpentanedioate (**104**) (20 g, 115 mmol, 1.0 equiv.) and pigs liver esterase (PLE) (0.95 g 8000 U) stirred in KH_2PO_4 pH 7 buffer (445 mL). Freshly made 1 M NaOH (115 mL, 115 mmol, 1.0 equiv.) was added drop-wise over 10 hours while keeping the pH between 7 and 8. After all the NaOH was added, the solution was cooled -78 ºC. The solution was quenched with a saturated brine solution (250 mL). This was filtered, washed with Et_2O (2 x 250 mL). The aqueous layer was acidified to pH 1 with 1 M HCl, extracted with Et_2O (4 x 250 mL), the combined organic layers were washed with H_2O (250 mL) and brine (2 x 250 mL), dried over $MgSO_4$ and the solvent removed by rotary evaporation to yield the crude product. This was purified by bulb-to-bulb vacuum distillation (100 ºC, 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.[206]

**^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.66 (s, 3H), 2.54 – 2.20 (m, 5H), 1.04 (d, J = 6.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 178.8 , 172.9 , 51.7 , 40.6 , 27.30 , 19.9 .

$[\alpha]_D^{20}$: +1.0 (*c*, 1.0, $CHCl_3$), {lit.[206] $[\alpha]_D^{20}$: +0.6 (*c*, 1.0, $CHCl_3$)}.

HR-MS (EI) calcd for $C_7H_{13}O_4$ (M + H^+): 161.0808, found: 161.0810.

(S)-3-isoPropyl-5-methoxy-5-oxopentanoic acid – 105
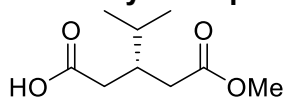
Using the procedure described for methyl acid-ester **107**; *iso*propyl diester **102** (2.2 g. 10.9 mmol) gave the acid ester **105** (1.4 g, 68%) as a colourless liquid after purification by bulb-to-bulb distillation (105 ºC, 0.2 mbar). The data is consistent with that reported in the literature.[207]

¹H NMR (400 MHz, CDCl$_3$) δ 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).

¹³C NMR (101 MHz, CDCl$_3$) δ 179.7, 173.4, 51.7, 37.6, 35.9, 30.5, 19.6 (2C).

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

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
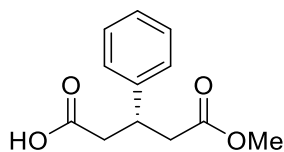
Using the procedure described for methyl acid-ester **107**; phenyl diester **103** (3.8 g. 16.1 mmol) gave the acid ester **106** (2.4 g, 67%) as a white solid after purification by recrystallisation from AcOH. The data is consistent with that reported in the literature.[208]

¹H NMR (400 MHz, CDCl$_3$) 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, CDCl$_3$), 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)

$[\alpha]_D^{22}$: -3.8 (c, 1.1, CHCl$_3$), {lit.[209] $[\alpha]_D^{20}$: -3.6 (c, 1.1, CHCl$_3$)}.

HR-MS (EI) calcd for C$_{12}$H$_{15}$O$_4$ (M + H$^+$): 223.0935, found: 223.0930.

(R)-4-Methylpiperidin-2-one - 116
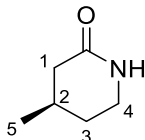
Using general method **B**; methyl acid-ester **107** (12.0 g, 75 mmol) was implemented to afford the methyl lactam **116** (3.2 g, 37%) after purification by column chromatography (10% EtOAc in pentane) as a colourless liquid.

^{1}H NMR (400 MHz, CDCl$_3$) δ 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}C NMR (101 MHz, CDCl$_3$) δ 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$_3$)

IR ν= 3206, 2957, 2872, 1697, 1659, 1497, 1342 cm^{-1}.

HR-MS (EI) calcd for C$_6$H$_{11}$NO (M$^{+\cdot}$): 113.0841; found: 113.0836.

tert-Butyl (_R_)-4-methyl-2-oxopiperidine-1-carboxylate - 118
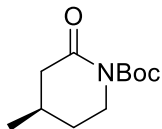
Using general procedure **A**; lactam **116** (800 mg, 7.1 mmol) gave _N_-Boc lactam **118** (1.12 g, 74%) as a colourless liquid after purification by column chromatography (20% EtOAc in pentane). Analytical data matched the reported data.[210]

¹H NMR (400 MHz, CDCl$_3$) δ 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).

¹³C NMR (101 MHz, CDCl$_3$) δ 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
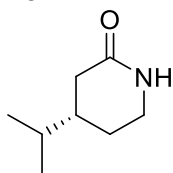
Using general method **B**; isopropyl acid-ester **105** (1.4 g, 7.44 mmol) was implemented to afford isopropyl lactam **114** (230 mg, 22%) after purification by column chromatography (0 → 10% EtOAc in pentane) as a colourless liquid. The data is consistent with that reported in the literature.[59]

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

^{13}C NMR (101 MHz, CDCl$_3$) δ 173.3, 41.6, 39.1, 35.4, 31.9, 25.9, 19.3.

HR-MS (EI) calcd for C$_8$H$_{15}$NO (M$^{+\cdot}$): 141.1154; found: 141.1150.

$[\alpha]_D^{20}$: -16.4 (c, 1.0, CHCl$_3$), {lit.[59] $[\alpha]_D^{20}$: -35.0 (c, ND, H$_2$O)}.

tert-Butyl (*S*)-4-isopropyl-2-oxopiperidine-1-carboxylate - 117
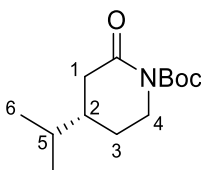
Using general procedure **A**; lactam **114** (230 mg, 1.63 mmol) gave *N*-Boc lactam **117** (270 mg, 68%) as a colourless liquid after purification by column chromatography (15% EtOAc in pentane).

^{1}H NMR (400 MHz, CDCl$_3$) δ 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).

^{13}C NMR (101 MHz, CDCl$_3$) δ 171.7 (C=O) , 152.8 (C=O Boc) , 82.9 (OCMe$_3$) , 45.8 (C^4) , 39.0 (C^2) , 36.0 (C^1) , 32.1 (C^5) , 28.2 (3C, Boc CH$_3$) , 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$^{+\cdot}$): 241.1670; found: 241.1677.

IR ν= 2976, 1765, `1709, 1367, 1282, 1248, 1145 cm^{-1}.

(*S*)-4-Phenylpiperidin-2-one - 115
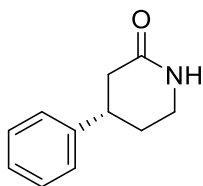
Using general method **B**; phenyl acid-ester **106** (2.4 g, 10.8 mmol) was implemented to afford isopropyl lactam **115** (134 mg, 7%) after purification by column chromatography (10% EtOAc in pentane) as a white solid. The data is consistent with that reported in the literature.[211]

¹H NMR (400 MHz, CDCl$_3$) δ 7.41-7.19 (m, 5H), 5.85 (s, 1H), 3.45 (dd, J = 5.9, 3.0 Hz, 2 H), 1H), 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).

¹³C NMR (101 MHz, CDCl$_3$) δ 172.4, 143.5, 128.5, 126.8 (2C), 126.6 (2C), 48.24, 41.2, 38.3, 27.4.

$[\alpha]_D^{20}$: -24.4 (*c*, 0.5, CHCl$_3$), {lit.[212] $[\alpha]_D^{25}$: -20.2 (*c*, 0.5, CHCl$_3$)}.

HR-MS (ES) calcd for C$_{11}$H$_{14}$NO$_4$ (M + H$^+$): 176.1075, found: 176.1065.

tert-Butyl (*S*)-2-oxo-4-phenylpiperidine-1-carboxylate - 96
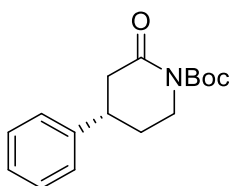
Using general procedure **A**; lactam **115** (134 mg, 0.76 mmol) gave *N*-Boc lactam **96** (160 mg, 76%) as a colourless liquid after purification by column chromatography (10% EtOAc in pentane). The data is consistent with that reported in the literature.[213]

¹H NMR (400 MHz, CDCl₃) 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).

¹³C NMR (101 MHz, CDCl₃) 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).

HR-MS (ES) calcd for $C_{16}H_{22}NO_3$ (M + H⁺): 276.1594, found: 276.1584.

$[\alpha]_D^{20}$: -20.0 (*c*, 1.0, CHCl₃)

1,7-Diazaspiro[5.5]undecane – 53-A
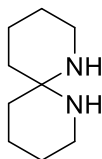
Using general procedure **C**; lactam **57** (19.9 g, 100 mmol) gave spiroaminal **53-A** (4.3 g, 56%) which could be purified to by column chromatography (10% MeOH in CH_2Cl_2 +1% NEt_3) to yield the product as a brown oil. Alternatively, purification by Kugelrohr distillation (125 ºC, 9 x 10^{-2} mbar) 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 $C_9H_{19}N_2$ (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
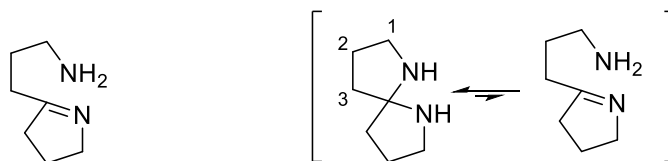
Using general procedure **C**; Lactam **72** (3.7 g, 20.0 mmol) gave both the amine-imine **47-B** (428 mg, 34%) and a mixture of spiroaminal **47-A** and amine-imine **47-B** (340 mg, 27%) which could be separated and purified by column chromatography (0->15% MeOH in CH_2Cl_2 +1% NEt_3) to yield the products as brown oils

Note: spiroaminal **47-A** is particularly volatile.

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

¹H NMR (400 MHz, $CDCl_3$) 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, $CDCl_3$) δ 179.0, 60.7, 53.1, 44.3, 38.6, 29.0, 23.8.

HR-MS (ESI) calcd for $C_7H_{15}N_2$ (M + H⁺): 127.1235, found: 127.1239.

Aminal **47-A**.

¹H NMR (400 MHz, $CDCl_3$) δ 3.84 – 3.66 (bs, 4H, H¹), 2.40 (m, 6H, H³ and N-H), 1.80 (bs, 4H, H²).

¹³C NMR (101 MHz, $CDCl_3$) δ 64.7 (RHN<u>C</u>NHR), 51.1 (2C, C¹), 33.8 (2C, C³), 23.0 (2C, C²).

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

HR-MS (ESI) calcd for $C_7H_{15}N_2$ (M + H⁺): 127.1235, found: 127.1236.

5-(3,4,5,6-Tetrahydro-2H-azepin-7-yl)pentan-1-amine – 56-B
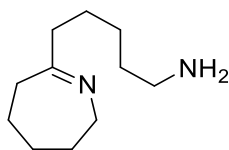
Using general procedure **C**; Lactam **73** (3.6 g, 16.9 mmol) gave amine-imine **56-B** (1.9 g, 64%) which could be purified by column chromatography (15% MeOH in CH_2Cl_2 +2% NEt_3) to yield the product as a brown oil. The data is consistent with that reported in the literature.[49]

¹H 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)

¹³C 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 $C_{11}H_{22}N_2Na$ (M + Na^+): 205.1675, found: 205.1680.

(*2R,6S,8R*)-2,8-Dimethyl-1,7-diazaspiro[5.5]undecane – 119-A
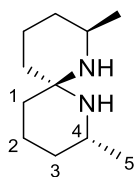
Using general procedure **C**; Lactam **76** (1065 mg, 5.0 mmol) gave spiroaminal **119-A** (236 mg, 52%) which was purified by bulb-to-bulb distillation (130 ºC, 9 x 10^{-2} mbar) to yield the spiroaminal **119-A** as a colourless oil, which crystallized slowly upon standing.

^{1}H NMR (400 MHz, CDCl$_3$) δ 5.90 (s, 2H, NH), 3.53 (dqd, *J* = 10.0, 6.3, 3.5 Hz, 2H, H^4), 2.46 – 2.23 (m, 4H, H^{3a} and H^{1a}), 1.97 – 1.86 (m, 4H, H^{3b} and H^{2a}), 1.78 – 1.62 (m, 2H, H^{1b}), 1.37 (m, 2H, H^{2b}), 1.21 (d, *J* = 6.4 Hz, 6H, C^5).

^{13}C NMR (101 MHz, CDCl$_3$) δ 62.9 (RHN$\underline{C}$NHR), 49.0 (2C, C^4), 31.1 (2C, C^1), 30.6 (2C, C^3), 23.0 (2C, C^5), 19.9 (2C C^2).

IR ν= 3276, 2932, 1648, 1330 cm^{-1}.

m.p. 37-40 ºC (CHCl$_3$/pentane).

HR-MS (CI) calcd for C$_{11}$H$_{23}$N$_2$ (M + H$^+$): 183.1861, found: 183.1860

$[\alpha]_D^{20}$: +16.7 (*c*, 0.1, CHCl$_3$)

tert-Butyl (5-oxohept-6-en-1-yl)carbamate - 124
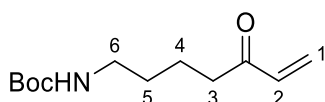
Freshly prepared vinylmagnesium bromide (1.0 M in THF, 1.1 mL, 1.1 mmol, 1.0 equiv.) was added dropwise to a solution of lactam **57** (200 mg, 1.0 mmol, 1.0 equiv.) in THF (10 mL) at -78 ºC. The solution was stirred for 15 minutes before being quenched with AcOH (1 mL). The mixture was allowed to warm to room temperature, diluted with H_2O (10 mL) the phases were separated and the aqueous layer was further extracted with CH_2Cl_2 (2 x 10 mL). The combined organics were washed with brine, dried over $MgSO_4$ and the solvent removed by rotary evaporation to afford the crude product. Purification by column chromatography (0 -> 20% Et_2O in pentane) afforded the product **124** (54 mg, 24%) as a colourless oil.

¹H NMR (400 MHz, $CDCl_3$) δ 6.37 (dd, J = 17.7, 10.5 Hz, 1H, H^2), 6.24 (dd, J = 17.7, 1.3 Hz, 1H, H^{1a}), 5.84 (dd, J = 10.5, 1.3 Hz, 1H, H^{1b})., 3.57 (t, J = 6.8 Hz, 2H, H^6), 2.61 (t, J = 6.9 Hz, 2H, H^3), 1.74 – 1.58 (m, 4H, H^4 and H^5), 1.50 (s, 9H, Boc).

¹³C NMR (101 MHz, $CDCl_3$) δ 206.7 ($\underline{C}$=O), 152.8 ($\underline{C}$=O Boc), 136.6 (C^2), 128.1 (C^1), 82.3 (O$\underline{C}Me_3$), 46.1 (C^6), 39.3 (C^3), 28.7 (C^5), 28.2 (3C, Boc $\underline{C}H_3$), 21.2 (C^4).

HR-MS (CI) calcd for $C_{12}H_{22}NO_3$ (M + H⁺): 228.1594, found: 228.1596.

tert-Butyl (5-oxooct-7-en-1-yl)carbamate - 125
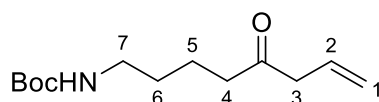
Freshly prepared allylmagnesium bromide (1.0 M in THF, 1.1 mL, 1.1 mmol, 1.0 equiv.) was added dropwise to a solution of lactam **57** (200 mg, 1.0 mmol, 1.0 equiv.) in THF at -78 ºC. The solution was stirred for 15 minutes before being quenched with sat. aqueous NH_4Cl (20 mL). The mixture was allowed to warm to room temperature, the phases were separated and the aqueous layer was further extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent removed by rotary evaporation to afford the crude product. Purification by column chromatography (20% Et_2O in pentane) afforded the product **125** (140 mg, .58%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (ddt, J = 17.2, 10.3, 7.0 Hz, 1H, H^2), 5.21 – 5.05 (m, 2H, H^1), 4.59 (s, 1H, NH), 3.15 (m, 2H, H^7), 3.09 (m, 2H, H^3), 2.46 (t, J = 7.2 Hz, 2H, C^4), 1.62 – 1.53 (m, 2H, H^6), 1.46 – 1.42 (m, 2H, H^5), 1.42 (s, 9H, Boc).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.6 ($\underline{C}$=O), 156.1 ($\underline{C}$=O Boc), 130.7 (C^2), 118.9 (C^1), 79.2 (O$\underline{C}Me_3$), 47.9 (C^3), 41.8 (C^7), 40.2 (C^4), 29.58 (C^6), 28.5 (3C, Boc $\underline{C}H_3$), 20.7 (C^5).

IR ν= 3376, 2930, 1698, 1518, 1365, 1248, 1164 cm^{-1}.

HR-MS (CI) calcd for $C_{13}H_{24}N_2O_3$ (M + H$^+$): 242.1751, found: 242.1740.

4-(Tributylstannyl)butan-1-amine - 142
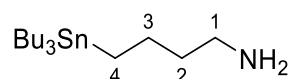
AIBN (82 mg, 0.5 mmol, 0.1 equiv.) was added to a mixture of allyl cyanide (**140**) (600 µL, 7.5 mmol, 1.5 equiv.) and Bu_3SnH (1.35 mL, 5.0 mmol, 1.0 equiv.). The solution was heated to 80 ºC for 16 h. The resultant homogenous solution was cooled, diluted with Et_2O (60 mL) and transferred via cannula to a suspension of $LiAlH_4$ (300 mg, 7.9 mmol, 1.6 equiv.) in Et_2O (60 mL) at 0 ºC. The suspension was warmed to room temperature before being refluxed at 40 ºC for 16 h. The reaction was quenched with MeOH (20 mL) at 0 ºC followed by the addition of H_2O (1 mL). The mixture was filtered, dried over $MgSO_4$, and the solvent removed by rotary evaporation to yield the analytically pure amine **142** (1.55 g, 85%) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.68 (t, *J* = 6.8 Hz, 2H, H^1), 1.56 – 1.40 (m, 10H), 1.34 – 1.23 (m, 8H), 0.88 (t, *J* = 7.3 Hz, 9H), 0.84 – 0.76 (m, 8H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 42.0 (C^1), 38.8 (C^2), 29.4 (3C), 27.5 (3C), 24.4 (C^3), 13.8 (4C), 8.9 (3C).

Further analysis was not carried out due to suspected toxicity concerns.

Piperidine-2-thione - 143
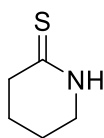
Using the procedure of Hussaini[214]; a solution of lactam **52** (2.0 g, 20 mmol, 1.0 equiv.) in CH$_2$Cl$_2$ (40 mL) was added dropwise to a suspension of Lawessons reagent (4.0 g, 10 mmol, 0.5 equiv.) in CH$_2$Cl$_2$ (40 mL) at room temperature and stirred for 2 h. The mixture was filtered, the solvent 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.[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 (CI) calcd for C$_5$H$_{10}$NS (M + H$^+$): 116.0528, found: 116.0530.

6-(Methylthio)-2,3,4,5-tetrahydropyridin-1-ium iodide - 144
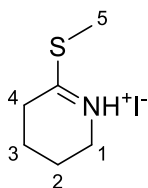
MeI (132 μL, 2.12 mmol, 1.06 equiv.) was added to a solution of thiolactam **143** (230 mg, 2.0 mmol, 1.0 equiv.) in acetone (3 mL) and stirred for 16 h. The resultant precipitate was collected by filtration, washed with Et$_2$O (10 mL) to afford the product (307 mg, 60%) as a white powder.

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

^{13}C NMR (101 MHz, DMSO-d_6) δ 189.4 (MeS$\underline{C}$=N), 45.8 (C^1), 30.2 (C^4), 19.2 (C^2), 17.3 (C^5), 13.8 (C^3).

IR ν= 3117, 3022, 2951, 1635, 1430, 1337, 11-6, 786 cm^{-1}.

m.p. 178-181 ºC (acetone/Et$_2$O).

A mass could not be obtained for this compound through a range of techniques.

2-(2-Iodophenyl)ethan-1-amine - 147
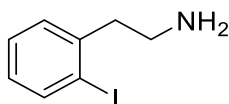
Using the procedure of De Vos[215]; BH$_3$•THF (1 M in THF, 20 mL, 29.0 mmol, 5 equiv.) was added dropwise to a solution of 4-iodophenylacetonitrile (**146**) (1.0 g, 4.1 mmol) at room temperature. After the addition is complete the solution was heated to 70 ⁰C for 2 h. The mixture was cooled in an ice 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.[215]

^{1}H NMR (400 MHz, CDCl$_3$) δ 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$_3$) δ 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.

4-Dihydroisoquinoline-1(2H)-thione - 151
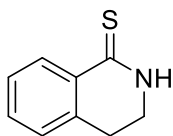
Using the procedure of Keglevich[216]; tetrahydroisoquinoline (**150**) (2.00 g, 15 mmol, 1.0 equiv.) and S_8 (0.96 g. 30 mmol, 2.0 equiv.) were irradiated neat to 170 ºC in a microwave for 15 min. Once cooled to room temperature, the residue was taken up in $CHCl_3$ (25 mL), filtered, the solvent removed 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.[216]

¹H NMR (400 MHz, $CDCl_3$) δ 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).

¹³C NMR (101 MHz, $CDCl_3$) δ 193.9, 134.0, 132.7, 132.4, 132.0, 127.3, 127.1, 41.8, 27.9.

HR-MS (ESI) calcd for $C_9H_{10}NS$ (M + H⁺): 164.0534, found: 164.0542.

1-(Methylthio)-3,4-dihydroisoquinolin-2-ium iodide - 152
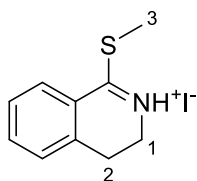
MeI (132 μL, 2.1 mmol, 1.1 equiv.) was added to a solution of thiolactam **151** (326 mg, 2.0 mmol, 1.0 equiv.) in acetone (5 mL) and stirred for 16 h. The resultant precipitate was collected by filtration, washed with Et$_2$O (10 mL) to afford the product **152** (595 mg, 98%) as a pale-yellow powder.

^{1}H 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).

^{13}C NMR (101 MHz, DMSO-d_6) δ 177.5 (MeS$\underline{C}$=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 ºC {dec} (acetone/Et$_2$O).

A mass could not be obtained for this compound through a range of techniques.

1-((2-Iodophenethyl)amino)-3,4-dihydroisoquinolin-2-ium iodide - 153
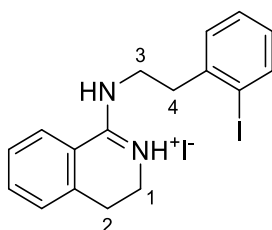
A solution of amine **147** (246 mg, 1.0 mmol, 1.0 equiv.) in EtOH (5 mL) was added to a suspension of imino thioether **152** (305 mg, 1.0 mmol, 1.0 equiv.) in EtOH (5 mL) at room temperature and stirred for 4 h. The volatiles were removed to yield the amidine **153** (504 mg, 99%) as a pale yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.69 – 9.55 (bs, 2H, NH), 7.88 (dd, J = 11.4, 7.9 Hz, 2H, Ar-H), 7.69 (t, J = 7.5 Hz, 1H, Ar-H), 7.56 – 7.33 (m, 4H, Ar-H), 7.03 (t, J = 7.5 Hz, 1H, Ar-H), 3.63 (t, J = 7.3 Hz, 2H, H^1), 3.55 (t, J = 6.6 Hz, 2H, H^3), 3.12 (t, J = 7.2 Hz, 2H, H^2), 3.02 (t, J = 6.6 Hz, 2H, H^4).

^{13}C NMR (101 MHz, DMSO-d_6) δ 156.6 (N$\underline{C}$=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^1 or C^3), 40.1 (C^3 or C^1), 37.5 (C^4), 26.6 (C^2).

IR ν= 3094, 1646, 1605, 1556, 1335, 1012, 786, 741 cm^{-1}.

HR-MS (ES) calcd for C$_{17}$H$_{18}$IN$_2$ (M + H$^+$): 377.0515, found: 377.0517.

m.p. 228-230 ºC (EtOH).

N-(2-Iodophenethyl)acetamide - 155
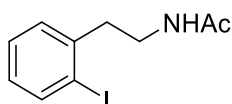
Using the procedure of Yoon Chi[217]: acetyl chloride (300 μL, 3.8 mmol, 1.1 equiv.) was added to a solution of amine **147** (1 g, 3.5 mmol, 1.0 equiv.) and NEt$_3$ (0.7 mL, 5.3 mmol, 1.5 equiv.) in THF (10 mL) at 0 ºC. The solution was stirred for 1 h at room temperature before the solvent was removed by rotary evaporation. The crude mixture was taken up in EtOAc (100 mL), washed with H$_2$O (50 mL), brine (50 mL), dried over MgSO$_4$, 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.[217]

¹H NMR (400 MHz, CDCl$_3$) δ 7.83 (dd, J = 8.0, 1.2 Hz, 1H), 7.29 (td, J = 7.4, 1.2 Hz, 1H), 7.22 (dd, J = 7.7, 1.7 Hz, 1H), 6.92 (td, J = 7.6, 1.8 Hz, 1H), 5.54 (s, 1H), 3.50 (q, J = 6.7 Hz, 2H), 2.96 (t, J = 7.0 Hz, 2H), 1.96 (s, 3H).

¹³C NMR (101 MHz, CDCl$_3$) 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$_{10}$H$_{13}$INO (M + H$^+$): 290.0042, found: 290.0041.

Undeca-1,10-dien-6-ol - 161

OH
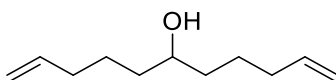
Using the procedure of Brasholz[77]; ethyl formate (7.5 mL, 93 mmol, 0.55 equiv.) was added dropwise to a freshly prepared solution of pent-5-enemagnesium bromide (1.0 M in THF, 169 mL, 168 mmol, 1.0 equiv.) at 0 ºC. After the addition, the resultant mixture was heated to 40 ºC for 4 h. The reaction mixture was cooled, quenched with sat. aqueous NH_4Cl (300 mL), the phases were separated and the aqueous layer was further extracted with Et_2O (2 x 300 mL). The combined organics were washed with brine (250 mL), dried over $MgSO_4$ and the solvent removed by rotary evaporation to yield the crude alcohol. This was purified by bulb-to-bulb distillation (75 ºC, 0.1 mbar) to yield the product **161** (13 g, 92%) as a colourless liquid. The data is consistent with that reported in the literature.[15]

¹H NMR (400 MHz, $CDCl_3$) 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).

¹³C NMR (101 MHz, $CDCl_3$) δ 138.8 (2C), 114.7 (2C), 71.8 , 37.0 (2C), 33.8 (2C), 25.0 (2C).

HR-MS (CI) calcd for $C_{11}H_{19}O$ (M - H⁺): 167.1430, found: 167.1432.

Undeca-1,10-dien-6-one - 162
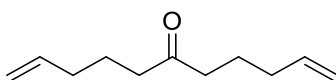
Using the procedure of Brasholz[77]; H_2SO_4 (4.2 M,18.5 mL) was added dropwise to a solution of CrO_3 (5.0 g, 50.0 mmol, 0.7 equiv.) in H_2O (7.4 mL) and stirred for 5 min. This was added to a solution of alcohol **161** (12.2 g, 72.6 mmol, 1.0 equiv.) in CH_2Cl_2 (300 mL), and the biphasic solution was stirred for 4 h. The phases were separated and the aqueous layer was further extracted with Et_2O (2 x 150 mL). The combined organics were filtered through Celite®, dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The crude ketone was purified by bulb-to-bulb distillation (55 ºC, 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.[15]

¹H NMR (400 MHz, CDCl$_3$) 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).

¹³C NMR (101 MHz, CDCl$_3$) δ 211.0 , 138.1 (2C), 115.3 (2C), 42.1 (2C), 33.2 (2C), 22.9 (2C).

HR-MS (CI) calcd for $C_{11}H_{19}O$ (M + H$^+$): 167.1430, found: 167.1431.

2,2-Di(pent-4-en-1-yl)-1,3-dioxolane - 163
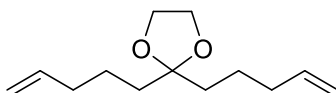
Ketone **162** (5.3 g, 31.8 mmol, 1.0 equiv.) and PTSA (775 mg, 3.1 mmol, 0.1 equiv.) in PhMe (160 mL) and ethylene glycol (40 mL) were heated to 130 ºC in a Dean-Stark apparatus for 16 h. The reaction was cooled to room temperature, diluted with CH_2Cl_2 (100 mL) and washed with sat. aqueous $NaHCO_3$ (75 mL), 1 M HCl (75 mL), brine (75 mL), dried over $MgSO_4$, and the solvent removed by rotary evaporation. The crude product was purified by column chromatography (10% Et_2O 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]

^{1}H NMR (400 MHz, $CDCl_3$) 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).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.8 (2C), 114.7 (2C), 111.8 , 65.1 (2C), 36.7 (2C), 34.0 (2C), 23.2 (2C).

HR-MS (CI) calcd for $C_{13}H_{23}O_2$ (M + H$^+$): 211.1698, found: 211.1699.

4,4'-(1,3-Dioxolane-2,2-diyl)bis(butan-1-ol) - 167
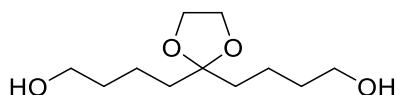
Ozone was bubbled through a solution of diene **163** (2.1 g, 10 mmol, 1.0 equiv.) in CH_2Cl_2 (30 mL) at -78 °C until a blue colour persisted. After this the solution was sparged with argon until the colour had dissipated. The solvent was removed in *vacuo* and the residue re-dissolved in THF (30 mL), 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_2O (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.

2,2'-((1,3-Dioxolane-2,2-diyl)bis(butane-4,1-diyl))bis(isoindoline-1,3-dione) - 169
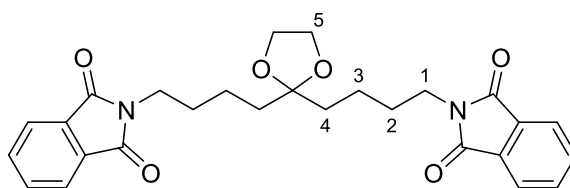
TsCl (3.5g, 18.3 mmol, 4.0 equiv.) was added to a solution of diol **167** (1.0 g, 4.6 mmol, 1.0 equiv.) in pyridine (10 mL) at -10 °C in a single portion. The reaction was stirred for 1 h and quenched with H_2O (50 mL), extracted with CH_3Cl (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ 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 H_2O (50 mL). The solution was extracted with CH_3Cl (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ 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

^{1}H NMR (400 MHz, $CDCl_3$) 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, H^5), 3.67 (t, J = 7.2 Hz, 4H, H^1), 1.73 – 1.57 (m, 8H, H^2 and H^4), 1.47 – 1.35 (m, 4H, H^3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5 (4C, N$\underline{C}$=O), 133.9 (4C, Ar), 132.3 (4C, Ar), 123.3 (4C, Ar), 111.4 (RO$\underline{C}$OR), 65.1 (2C, C^5), 38.0 (2C, C^4), 36.8 (2C, C^4), 28.9 (2C, C^2), 21.2 (2C, C^3).

IR ν= 1769, 1704, 1431, 1370, 1401, 1047, 713 cm^{-1}.

m.p. 148-150 ºC (EtOH).

HR-MS (CI) calcd for $C_{27}H_{29}N_2O_6$ (M + H$^+$): 477.2026, found: 477.2022.

4,4'-(1,3-Dioxolane-2,2-diyl)bis(butan-1-amine) - 170
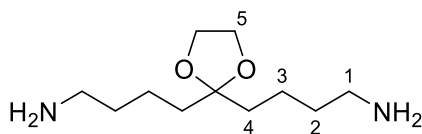
Di-phthalimide **169** (476 mg, 1.0 mmol, 1.0 equiv.) was suspended in EtOH (10 mL) and hydrazine hydrate (60%, 200 μL, 2.2 mmol, 2.2 equiv.) was added and heated to 80 °C for 2 h. The mixture was quenched with 2 M NaOH (10 mL) and extracted with $CHCl_3$ (3 x 25 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed in *vacuo* to yield the crude diamine as a yellow oil (190 mg, 87%) which did not require purification.

¹H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 4H, H^5), 2.66 (t, J = 6.7 Hz, 4H, H^1), 1.62 – 1.55 (m, 4H, H^4), 1.51 – 1.30 (m, 12H, H^2, H^3, NH_2).

¹³C NMR (101 MHz, $CDCl_3$) δ 111.7 (RO$\underline{C}$OR), 65.0 (2C, C^5), 42.2 (2C, C^1), 37.0 (2C, C^4), 34.10 (2C, C^2), 21.2 (2C,bC^3).

HR-MS (CI) calcd for $C_{13}H_{28}N_3O_2$ (M + CH_3CN + H^+): 258.2176, found: 258.2175.

IR ν= 3352, 1571, 1313, 1047, 948 cm⁻¹.

2,2'-(5-Oxononane-1,9-diyl)bis(isoindoline-1,3-dione) - 171
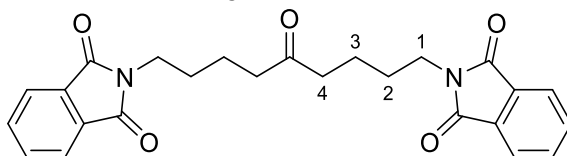
Ketal **169** (47 mg, 0.1 mmol, 1.0 equiv.) and I_2 (3 mg, 0.01 mmol, 0.1 equiv.) were stirred in acetone (5 mL) at room temperature for 16 h. The acetone was removed by rotary evaporation and the residue taken up in CH_2Cl_2 (10 mL). The solution was washed with 15% aqueous $Na_2S_2O_3$ (10 mL), H_2O (10 mL), brine (10 mL), dried over $MgSO_4$, 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.

^{1}H NMR (400 MHz, CDCl$_3$) 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, H^1), 2.45 (t, *J* = 7.1 Hz, 4H, H^4), 1.77 – 1.52 (m, 8H, H^2 and H^3).

^{13}C NMR (101 MHz, CDCl$_3$) δ 210.0 ($\underline{C}$=O), 168.5 (4C, Phth $\underline{C}$=O), 134.0 (4C, Ar), 132.2 (4C, Ar), 123.3 (4C, Ar), 42.1 (2C, C^4), 37.6 (2C, C^1), 28.1 (2C, H^2 or H^3), 20.9 (2C, H^2 or H^3).

IR ν= 1770, 1701, 1463, 1394, 1367, 1048, 719, 710 cm^{-1}.

m.p. 89-90 ºC (EtOH).

HRMS (ES) calcd for $C_{25}H_{25}N_2O_5$ (M + H$^+$): 433.1763, found: 433.1772.

1,7-Diazaspiro[5.5]undecane – 53-A
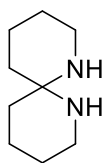
TsCl (3.5 g, 18.3 mmol, 4.0 equiv.) was added to a solution of diol **167** (1.0 g, 4.6 mmol, 1.0 equiv.) in pyridine (10 mL) at -10 °C in a single portion. The reaction was stirred for 1 h and quenched with H_2O (50 mL), extracted with CH_3Cl (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ 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 NaN_3 (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 H_2O (50 mL). This was extracted with CH_3Cl (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ 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 .

Methyl 3-phenylhex-5-enoate - 175
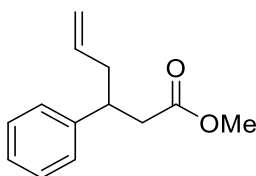
Using the procedure of Majetich[219]; TBAF (1 M, 1 mL, 1 mmol, 0.16 equiv.) was added to a suspension of 4 Å MS (1.0 g) and methyl cinnamate (**175**) (1.0 g, 6.2 mmol, 1.0 equiv.) in DMF (10 mL). To this, a solution of HMPA (3.2 mL, 17.3 mmol, 2.8 equiv.), Allyltrimethylsilane (3.0 mL, 18.9 mmol, 3.0 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_2O (200 mL), filtered and extracted with CH_2Cl_2 (2 x 250 mL). The combined organic layers were washed with H_2O (2 x 150 mL), brine (150 mL), dried over $MgSO_4$ 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.[80]

^{1}H NMR (400 MHz, CDCl$_3$) δ 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).

^{13}C NMR (101 MHz, CDCl$_3$) δ 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 $C_{12}H_{15}O_2$ (M + H$^+$): 191.1067, found: 191.1067.

3-Phenylhex-5-enoic acid -176
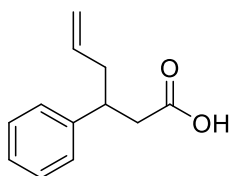
LiOH·H$_2$O (200 mg, 4.8 mmol, 1.9 equiv.) was added to a solution of methyl ester **175** (500 mg, 2.5 mmol, 1.0 equiv.) in THF/H$_2$O (3:1 25 mL) and stirred at room temperature for 16 h. The reaction was acidified to pH 1 with 1 M HCl, extracted with Et$_2$O (3 x 25 mL). The combined organic layers were dried over MgSO$_4$ and solvent removed by rotary evaporation to yield the crude product, which was purified by column chromatography (20% CH$_2$Cl$_2$ in Et$_2$O +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, CDCl$_3$) 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, CDCl$_3$) 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 (CI) calcd for C$_{12}$H$_{15}$O$_2$ (M + H$^+$): 191.1067, found: 191.1074.

N-Methoxy-*N*-methyl-3-phenylhex-5-enamide - 177
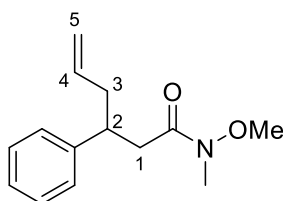
Acid **176** (380 mg, 2.0 mmol, 1.0 equiv.), NHMe(OMe)·HCl (291 mg, 3.0 mmol, 1.5 equiv.), EDC·HCl (573 mg, 3.0 mmol, 1.5 equiv.) and DMAP (366 mg, 3.0 mmol, 1.5 equiv.) in CH_2Cl_2 (12 mL) were stirred at room temperature for 16 h. The solvent was removed by rotary evaporation, the resultant slurry was taken up in EtOAc (25 mL) and washed sequentially with H_2O (25 mL), sat. aqueous $NaHCO_3$ (25 mL), brine (25 mL), dried over $MgSO_4$ 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.

^{1}H NMR (400 MHz, $CDCl_3$) 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, H^4), 5.05 – 4.99 (m, 1H, H^{5a}), 4.99 – 4.94 (m, 1H, H^{5b}), 3.57 (s, 3H, NOMe), 3.39 – 3.30 (m, 1H, H^2), 3.12 (s, 3H, NMe), 2.75-2.77 (m, 2H, H^1), 2.44-2.47 (m, 2H, H^3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0 (C=O), 143.4 (Ar), 136.4 (C^4), 128.3 (2C, Ar), 127.6 (2C, Ar), 126.3 (Ar), 116.5 (C^5), 61.1 (NOMe), 41.1 (C^2), 40.4 (C^3), 38.0 (C^1), 32.1 (NMe).

IR ν= 1655, 1543, 1383, 994, 761, 699 cm^{-1}.

HR-MS (ESI) calcd for $C_{14}H_{20}O_2N$ (M + H$^+$): 234.1494, found: 234.1480.

4-Phenylundeca-1,10-dien-6-one - 178
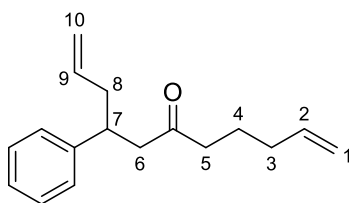
Freshly prepared solution of pent-5-enemagnesium bromide (1.0 M in THF, 1.7 mL, 1.7 mmol, 1.0 equiv.) was added to a solution of Weinreib amide **177** (396 mg, 1.7 mmol, 1.0 equiv.) in THF (10 mL) at -78 ºC. Stirring at this temperature was continued for 2 h before the reaction was quenched with sat. aqueous NH_4Cl (15 mL). The phases were separated and the aqueous layer was further extracted with Et_2O (2 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and solvent removed by rotary evaporation to yield the crude reaction mixture. Purification by column chromatography (10% Et_2O in pentane) afforded the product **178** (282 mg, 73%) as colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.25 (m, 2H, Ar-H), 7.22 – 7.13 (m, 3H, Ar-H), 5.67 (m, 2H, H^2 and H^9), 5.19 – 4.85 (m, 4H, H^1 and H^{10}), 3.33 – 3.22 (m, 1H, H^7), 2.80 – 2.58 (m, 2H, H^6), 2.45 – 2.15 (m, 4H, H^5 and H^8), 1.99 – 1.85 (m, 2H, H^3), 1.65 – 1.41 (m, 2H, H^4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.7 ($\underline{C}$=O), 144.3 (Ar), 138.1 (C^2 or C^9), 136.4 (C^2 or C^9), 128.6 (2C, Ar), 127.6 (2C, Ar), 126.5 (Ar), 116.8 (C^1 or C^{10}), 115.2 (C^1 or C^{10}), 48.9 (C^6), 42.8 (C^5), 40.9 (C^8), 40.8 (C^7), 33.1 (C^3), 22.7 (C^4).

HR-MS (EI) calcd for $C_{17}H_{22}O$ (M^{+}): 242.1671, found: 242.1677.

4-(2-(4-Hydroxybutyl)-1,3-dioxolan-2-yl)-3-phenylbutan-1-ol - 180
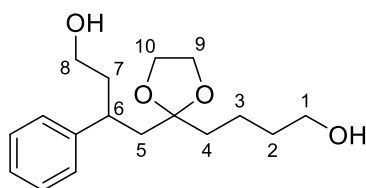
Using the procedure described for **163**; ketone **178** (143 mg, 0.5 mmol) gave the ketal **179** as an inseparable mixture of product and starting material (6:4) Therefore, the crude product was used without further purification.

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^8), 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 (RO$\underline{C}$OR), 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
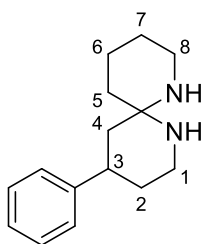
Using the procedure as described for **53-A**; the ketal diol **180** (50 mg 0.2 mmol) gave the product **182-A** (22 mg, 58% over two steps) as a colourless oil.

¹H 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^8), 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^5), 1.70 – 1.61 (m, 3H, H^6 and H^{2b}), 1.57 – 1.47 (m, 2H, H^7).

¹³C NMR (126 MHz, CDCl$_3$) δ 146.3 (<u>Ar</u>-C^3), 128.6 (2C, Ar), 127.0 (2C, Ar), 126.4 (<u>Ar</u>-C^2), 63.0 (RHN<u>C</u>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 ν= 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-ylidene)hydrazine-1-carboxylate - 189
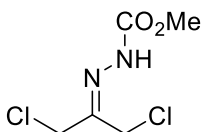
Using the procedure of Fairlamb;[83] 1,3-dichloroacetone (**187**) (14.0 g, 110 mmol, 1.0 equiv.) was added in 3 portions to a solution of methyl hydrazinocarboxylate (9.8 g, 108 mmol, 1.0 equiv.) in MeOH (200 mL) at room temperature. The reaction was stirred for 4 h before the solution was concentrated to approx. 20 mL by rotary evaporation. The resultant precipitate was collected by filtration and washed with Et$_2$O (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}H NMR (400 MHz, CDCl$_3$) δ 8.38 (s, 1H), 4.32 (s, 2H), 4.18 (s, 2H), 3.88 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 153.7, 143.7, 53.6, 45.9, 33.3.

HRMS (EI) calcd for C$_5$H$_8$N$_2$O$_2$Cl$_2$ (M$^{.+}$): 197.9963, found: 197.9971.

Tetraethyl (2-oxopropane-1,3-diyl)bis(phosphonate) - 190
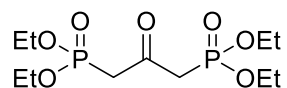
Using the procedure of Fairlamb;[83] P(OEt)$_3$ (11.2 mL, 64 mmol, 2.2 equiv.) was added dropwise to a suspension of dichloro hydrazinecarboxylate **189** (5.8 g, 29 mmol, 1.0 equiv.) in PhMe (50 mL). Once the addition was complete, the resultant mixture was heated to 130 ºC for 16 h. The solvent was 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.[83]

¹H 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).

¹³C 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).

³¹P 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
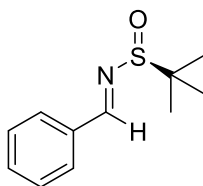
Benzaldehyde (**191**) (12.6 mL, 125 mmol, 1.25 equiv.), (*R*)-2-methylpropane-2-sulfinamide (9.7 g, 80 mmol, 1.0 equiv.), PTSA (1.05 g, 4 mmol, 5 mol%) and $MgSO_4$ (50 g) in CH_2Cl_2 (150 ml) were stirred at room temperature for 16 h. After this time, the solids were removed by filtration and the solvent 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

$[\alpha]_D^{22}$: +99.0 (*c*, 1.0, CHCl₃), {lit.[221] $[\alpha]_D^{25}$: +97.5 (*c*, 1.15, CHCl₃)}

HRMS (EI) calcd for $C_{11}H_{16}NOS$ (M + H⁺): 210.0953, found: 210.0950.

(*S*)-2-Methyl-*N*-((*R*)-1-phenylbut-3-en-1-yl)propane-2-sulfinamide - 193
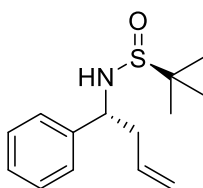
Allylmagnesium bromide (1.0 M in Et$_2$O, 18.25 mL,18.25 mmol, 2.0 equiv.) was added dropwise to a solution of sufinimine **192** (1.9 g, 9.13 mmol, 1.0 equiv.) in CH$_2$Cl$_2$ (50 mL) at -78ºC. After 30 minutes of stirring with cooling, the reaction was quenched with sat aq NH$_4$Cl (50 mL). The phases 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]

¹H 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).

¹³C 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.

$[\alpha]_D^{22}$: +143.0 (*c*, 1.0, CHCl$_3$)

HRMS (EI) calcd for C$_{14}$H$_{22}$NOS (M + H⁺): 252.1422, found: 252.1410.

(R)-tert-Butyl (1-phenylbut-3-en-1-yl)carbamate -194
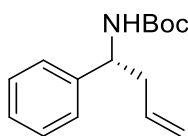
Using the procedure reported by Corte of Bristol-Myers Squibb;[86] conc. HCl (1 mL) was added to a solution of sulfinamide **193** (2.1 g, 8.4 mmol, 1.0 equiv.) in MeOH (80 mL) at 0 °C. The solution was stirred for 4 h, before the volatiles were removed by rotary evaporation. The resultant solid was dissolved in CH_2Cl_2 (80 mL) and cooled to 0 °C. NEt_3 (4.5 mL, 32 mmol, 3.8 equiv.) was added dropwise, followed by the addition of Boc_2O (2.0 g, 9.2 mmol, 1.1 equiv.). The solution was stirred overnight at room temperature before being diluted with H_2O (80 mL). The phases were separated, and the aqueous layer being further extracted with CH_2Cl_2 (80 mL), the combined organics were washed with brine (50 mL), dried over $MgSO_4$, 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 **194** (1.3 g, 64%) as a white solid. The data is consistent with that reported in the literature. [222]

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.

$[\alpha]_D^{22}$: +42.0 (c, 1.0, CHCl₃), {lit.[223] $[\alpha]_D^{24}$: +45 (c, 1.00, CHCl₃)}.

A mass could not be obtained for this compound through a range of techniques.

(*R*)-*tert*-Butyl (3-oxo-1-phenylpropyl)carbamate - 195
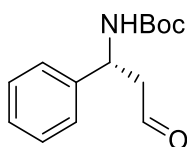
Ozone was bubbled through a solution of homoallylic amine **194** (157 mg, 0.64 mmol) and Sudan III (trace) in CH_2Cl_2/MeOH (1:1 60 mL) at -78 °C until the solution became colourless. The solution was sparged with oxygen for 10 min, followed by argon for 10 min. NEt_3 (265 µL, 1.9 mmol, 3.0 equiv.) 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_2Cl_2) to yield the product **195** (143 mg, 90%). The data is consistent with that reported in the literature.[224]

¹H NMR (400 MHz, CDCl₃) 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).

¹³C NMR (101 MHz, CDCl₃) 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, CHCl₃), {lit.[225] $[\alpha]_D^{25}$: +27.5 (*c*, 0.08, CHCl₃)}

HRMS (EI) 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 - 196
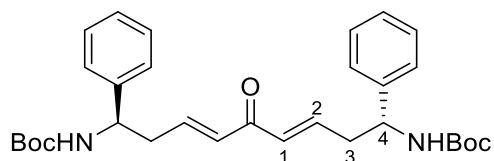
K_2CO_3 (207 mg, 1.5 mmol, 3.0 equiv.) was added in a single portion to a solution of aldehyde **195** (126 mg, 0.5 mmol, 1.8 equiv.), and diphosphate **190** (93 mg, 0.28 mmol, 1.0 equiv.) in THF/H_2O (10 mL, 1:1) at room temperature. The resultant solution was stirred for 16 h before being quenched 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_2Cl_2) followed by a second column chromatography (30% EtOAc in PhMe) to afford the product **196** (108 mg, 70%) as a colourless oil.

¹H 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).

¹³C NMR (101 MHz, $CDCl_3$) δ 194.4 (C=O), 155.18 (4C, Boc C=O *overlapping* C^2), 143.0 (2C, A̲r-C^4), 131.2 (2C, C^1), 128.9 (4C, Ar), 127.7 (2C, Ar), 126.4 (4C, Ar), 79.9 (2C, Boc OC̲(Me)$_3$, 54.0 (2C, C^4), 40.0 (2C, C^3), 28.5 (6C, Boc CM̲e$_3$).

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

$[\alpha]_D^{22}$: +90.0 (*c*, 0.2, $CHCl_3$)

HRMS (ES) calcd for $C_{31}H_{41}N_2O_5$ (M + H$^+$): 521.3015, found: 521.3012.

(2R,6R,8R)-2,8-Diphenyl-1,7-diazaspiro[5.5]undecane – 198-A
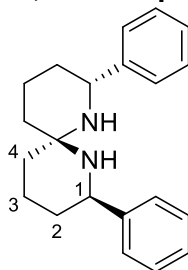
Diene **196** (50 mg, 0.1 mmol) and Pd/C (10 mg) in MeOH (5 mL) was a stirred under an atmosphere of H_2 (1 atm) for 4 h before the catalyst was removed by filtration and the solvent removed by rotary evaporation. The resultant residue was dissolved in CH_2Cl_2 (5 mL) and cooled to 0 ºC. TFA (500 µL) was added dropwise, the cooling bath was removed and the solution was stirred at rt for 16 h. The solution was diluted with CH_2Cl_2 (15 mL), washed with sat. aqueous $NaHCO_3$ (2 x 10 mL), brine (10 mL), dried over $MgSO_4$ and the volatiles removed by rotary evaporation. The crude product was purified by preparative TLC (3% MeOH in CH_2Cl_2) to afford the aminal **198-A** (22 mg, 76% over two steps) as a white foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.40 (m, 4H, Ar-H), 7.39 – 7.31 (m, 4H, Ar-H), 3.83 – 3.66 (m, 2H, H^1), 2.35 – 2.02 (m, 2H, NH), 1.83 – 1.60 (m, 12H, H^2, H^3 and H^4)

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.5 (Ar-C^1), 128.6 (2C, Ar), 127.3 (Ar), 127.1 (2C, Ar), 67.9 (RHN$\underline{C}$NHR), 54.4 (C^1), 37.9 (C^4), 34.5 (C^2), 20.5 (C^3).

IR ν= 3332, 3027, 2926, 1450, 756 cm^{-1}.

$[\alpha]_D^{22}$: +34.0 (*c*, 0.1, $CHCl_3$)

HRMS (ESI) calcd for $C_{21}H_{27}N_2$ (M + H$^+$): 307.2174, found: 307.2181.

2-azidobenzaldehyde - 239
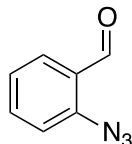
2-Nitrobenzaldehyde (**238**) (7.0 g, 46 mmol, 1.0 equiv.), NaN$_3$ (9.0 g, 138 mmol 3.0 equiv.) and NEt$_3$ (1.3 mL, 9.2 mmol, 0.2 equiv.) in DMF (60 mL) were stirred at 60 ºC for 96 h. The reaction mixture is cooled, diluted with H$_2$O (150 mL), extracted with CH$_2$Cl$_2$ (3 x 150 mL). The combined organics were washed with H$_2$O (2 x 150 mL), 5% LiCl solution (4 x 100 mL) and brine (150 mL), dried over MgSO$_4$ 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, CDCl$_3$) 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, CDCl$_3$) 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

3,3',4,4'-Tetrahydro-1H,1'H-2,2'-spirobi[quinoline] – 235
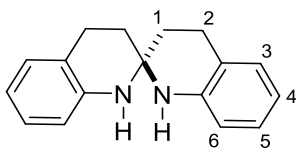
Using general procedure **E**; *o*-azidobenzaldehyde (**239**) gave the spiro-biquinoline **235** (185 mg, 74%), as a colourless crystalline solid after purification by chromatography on silica (50% CH_2Cl_2 in pentane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 – 6.96 (m, 4H, H^3 and H^6), 6.70 (td, *J* = 7.4, 1.2 Hz, 2H, H^4), 6.48 (dd, *J* = 7.9, 1.2 Hz, 2H, H^5), 4.27 (s, 2H, NH), 2.91 (t, *J* = 6.8 Hz, 4H, H^2), 2.10 – 1.90 (m, 4H, H^1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.6 (2C, Ar-N), 129.2 (2C, H^3 or H^6), 127.24 (2C, H^3 or H^6), 120.2 (2C, Ar-C^2), 117.8 (2C, H^4), 114.8 (2C, H^5), 63.5 (RHNCNHR), 33.3 (2C, C^1), 23.4 (2C, C^2).

m.p. 131-132 ºC (CH_2Cl_2).

IR ν= 3372, 3047, 1600, 1488, 1468, 743 cm^{-1}.

HR-MS (ESI) calcd for $C_{17}H_{19}N_2$ (M + H$^+$): 251.1548, found: 251.1546.

Microanalysis, calcd for $C_{17}H_{18}N_2$: C, 81.56; H, 7.25; N, 11.19; Found: C, 81.44; H, 7.37; N, 11.08.

1-Fluoro-2-naphthaldehyde-248
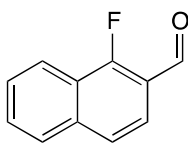
Using the procedure of Schlosser[118]: *sec*-BuLi (1.3 M in hexanes, 15 mL, 20 mmol, 1.0 equiv.) was added dropwise to a solution of 1-fluoronapthalene (**247**) (2.6 mL, 20 mmol, 1.0 equiv.) in THF (40 mL) at – 78 ºC. The solution was stirred at this temperature for 2 h before the addition of DMF (3.2 mL). The reaction was stirred for 5 min before dilution with Et_2O (50 mL), quenched with NH_4Cl (50 mL), the phases were separated and the aqueous layer was further extracted with Et_2O (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.[226]

^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ -127.3.

HR-MS (EI) calcd for $C_{11}H_7FO$ (M$^{·+}$): 174.0481, found: 174.0481.

1-Azido-2-naphthaldehyde – 249
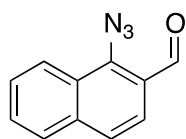
Using a modified procedure of Boswell and Licause;[119] 1-fluoro-2-naphthaldehyde **248** (2.4 g, 13.9 mmol, 1.0 equiv.) in anhydrous DMF (21 mL) was cooled to 0 ºC under argon. NaN_3 (1.8 g, 27.7 mmol, 2.0 equiv.) was added in one portion and the resultant solution was heated to 60 ºC with constant argon sparging for 2 h. After this time, the mixture was cooled to room temperature, diluted with H_2O (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 $MgSO_4$. 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.[119]

1H NMR (400 MHz, $CDCl_3$) 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).

13C NMR (101 MHz, $CDCl_3$) 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 (EI) calcd for $C_{11}H_7N_3O$ (M⁺·): 197.0589; found: 197.0582;

Microanalysis, calcd for $C_{11}H_7N_3O$: C, 67.00; H, 3.58; N, 21.31; Found: C, 66.78; H, 3.39; N, 21.12.

8-Nitroquinoline-7-carbaldehyde - 252
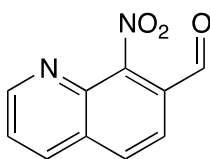
Using the procedure of Thummel;[120] 7-methyl-8-nitroquinoline (**250**) (5.0 g, 26 mmol, 1.0 equiv.), DMF.DMA (4.2 mL, 39 mmol, 1.5 equiv.) in DMF (2.5 mL) were heated to 140 ºC for 16 h. The reaction was then cooled to 0 ºC and diluted with H_2O (10 mL). The precipitate was removed by filtration and washed with H_2O (10 mL). The solid was dissolved in THF/H_2O (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_2Cl_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. [120]

¹H NMR (400 MHz, CDCl₃) 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).

¹³C NMR (101 MHz, CDCl₃) 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 $C_{10}H_7N_2O_3$ (M+ H⁺·): 203.0451; found: 203.0450.

8-Azidoquinoline-7-carbaldehyde – 253
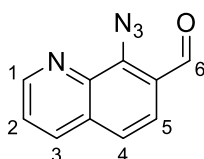
NaN$_3$ (1.8 g, 27.4 mmol, 3.0 equiv.) was added to 8-nitroquinoline-7-carbaldehyde (**252**) (1.9 g, 9.13 mmol, 1.0 equiv.) in anhydrous DMF (14 mL) and NEt$_3$ (260 µL, 1.82 mmol, 0.2 equiv.) under argon and heated at 60 ºC with argon sparging. After 1 h, the mixture was allowed to cool, diluted with H$_2$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 (1 x 50 mL) and dried over MgSO$_4$. After rotary evaporation, the residue was chromatographed on silica (gradient; 0 → 50% CH$_2$Cl$_2$ in pentane) to give azide **253** (785 mg, 43%) as a yellow solid.

^{1}H NMR (400 MHz, CDCl$_3$) δ 10.68 (s, 1H, H^6), 8.95 (d, J = 4.0 Hz, 1H, H^1), 8.18 (d, J = 8.3 Hz, 1H, H^3 or H^4), 7.93 (d, J = 8.6 Hz, 1H, H^3 or H^4), 7.63 – 7.50 (m, 2H, H^2 and H^5).

^{13}C NMR (101 MHz, CDCl$_3$) δ 189.3 (C^6), 148.9 , 143.5 , 141.8 , 136.6 , 132.4 , 125.7 , 124.1 , 123.8 , 123.7 .

m.p. 125-126 ºC (CH$_2$Cl$_2$).

IR 2125, 1675, 1384, 1295, 1256, 837 cm^{-1}.

HR-MS (ES+) calcd for C$_{10}$H$_7$N$_4$O (M + H$^+$): 199.0620; found: 199.0628.

Microanalysis, calcd for C$_{10}$H$_6$N$_4$O: C, 60.60; H, 3.05; N, 28.27; Found: C, 60.38; H, 3.17; N, 28.09.

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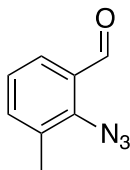
Using general procedure **D**; 3-methyl-2-nitrobenzaldehyde (**254**) (1000 mg, 6.1 mmol) gave the product **258** (168 mg, 17%) as a tan solid after chromatography on silica (10% EtOAc in pentane). The data is consistent with that reported in the literature.[122]

^{1}H NMR (400 MHz, CDCl$_3$) δ 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).

^{13}C NMR (101 MHz, CDCl$_3$) δ 189.9 140.3, 137.6, 133.3, 129.2, 129.1, 126.0, 18,1.

A mass could not be obtained for this compound through a range of techniques.

4-Methoxy-2-azidobenzaldehyde - 259
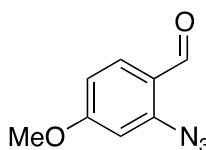
Using general procedure **D**; 4-methoxy-2-nitrobenzaldehyde (**255**) (471 mg, 2.6 mmol) gave the product **259** (389 mg, 84%) as an off-white solid. The data is consistent with that reported in the literature.[122] An impurity of the starting material (<10%) could not be removed by column chromatography.

¹H 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).

¹³C 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
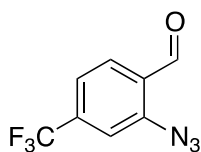
Using general procedure **D**; 2-nitro-4-(trifluoromethyl)benzaldehyde (**256**) (995 mg, 4.5 mmol) gave the product **260** (742 mg, 76%) as a white solid. The data is consistent with that reported in the literature.[122]

¹H NMR (400 MHz, CDCl₃) δ 10.38 (d, J = 0.8 Hz, 1H), 8.00 (dt, J = 8.0, 0.8 Hz, 1H), 7.54 – 7.42 (m, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 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).

A mass could not be obtained for this compound through a range of techniques.

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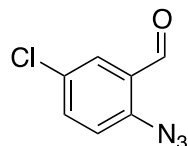
Using general procedure **D**; 5-chloro-2-nitrobenzaldehyde (**257**) (453 mg, 2.4 mmol) gave the product **261** (284 mg, 64 %) as a yellow solid. The data is consistent with that reported in the literature.[188]

^{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 (EI) calcd for C$_7$H$_4$O$_7$N$_3$Cl (M$^{.+}$): 181.0043, found: 181.0038.

3,3',4,4'-Tetrahydro-1*H*,1'*H*-2,2'-spirobi[benzo[*h*]quinoline] – 262
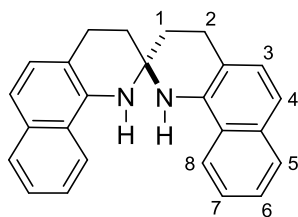
General Procedure **D**; 1-azido-2-naphthaldehyde (**249**) gave the spiro-biquinoline **262** as a white amorphous solid (235 mg, 67%) after purification by chromatography on silica (gradient; 20 → 50% CH_2Cl_2 in pentane).

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<u>C</u>NHR), 32.9 (2C, C¹), 24.4 (2C, C²).

m.p. 169-170 ºC (pentane).

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

HR-MS (ES+) calcd for $C_{25}H_{23}N_2$ (M + H⁺): 351.1861, found: 351.1872.

Microanalysis, calcd for $C_{25}H_{22}N_2$: C, 85.68; H, 6.33; N, 7.99; Found: C, 85.57; H, 6.40; N, 7.90.

3,3',4,4'-Tetrahydro-1*H*,1'*H*-2,2'-spirobi[[1,10]phenanthroline] – 263
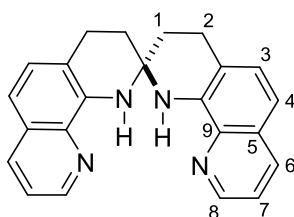
General Procedure **D**; 8-azidoquinoline-7-carbaldehyde (**253**) gave the spiro-biquinoline **263** (264 mg, 75%) as a yellow solid after purification by chromatography on silica (gradient; 0 → 10% MeOH in CH_2Cl_2).

¹H NMR (400 MHz, $CDCl_3$) 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, $CDCl_3$) δ 147.3 (2C, Ar-N), 138.7 (2C, C⁹), 137.6 (2C, C⁸), 135.9 (2C, C⁵), 128.7 (2C, C³), 127.6 (2C, C⁵), 120.8 (2C, C⁷), 116.0 (2C, <u>Ar</u>-C²), 114.2 (2C, C⁴), 63.0 (RHN<u>C</u>NHR, 33.3 (2C, C¹), 24.0 (2C, C²).

m.p. 153-155 °C (CH_2Cl_2).

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

HR-MS (ES+) calcd for $C_{23}H_{20}N_4$ (M + H⁺): 353.1766, found: 353.1772.

Microanalysis, calcd for $C_{23}H_{20}N_4$: C, 78.38; H, 5.72; N, 15.90; Found: C, 78.19; H, 5.81; N, 15.73.

8,8'-Dimethyl-3,3',4,4'-tetrahydro-1*H*,1'*H*-2,2'-spirobi[quinoline] – 264
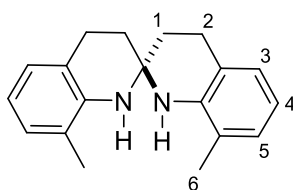
General Procedure **D***;* 2-azido-6-methylbenzaldehyde (**258**) gave the spiro-biquinoline **264** (147 mg, 53%) as a colourless oil after purification by chromatography on silica (60% CH$_2$Cl$_2$ in pentane).

^{1}H NMR (400 MHz, CDCl$_3$) δ 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-<u>Me</u>), 2.05 (t, *J* = 6.8 Hz, 4H, H^1).

^{13}C NMR (101 MHz, CDCl$_3$) δ 140.7 (2C, Ar-N), 128.4 (2C, C^5),127.1 (2C, C^3) 121.4 (2C, <u>Ar</u>-Me), 119.6 (2C, <u>Ar</u>-C^2), 117.1 (2C, C^4), 64.4 (RHN<u>C</u>NHR), 33.2 (2C, C^1), 24.0 (2C, C^2), 17.4 (2C, Ar-<u>Me</u>).

IR ν= 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

7,7'-Dimethoxy-3,3',4,4'-tetrahydro-1H,1'H-2,2'-spirobi[quinoline] – 265
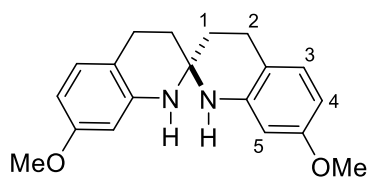
General Procedure **D**; 2-azido-4-methoxybenzaldehyde (**259**) gave the spiro-biquinoline **265** (241 mg, 77%) as a white solid after purification by chromatography on silica (50% CH_2Cl_2 in pentane)

^{1}H NMR (400 MHz, CDCl$_3$) δ 6.94 (d, J = 8.2 Hz, 2H, H^3), 6.28 (dd, J = 8.3, 2.5 Hz, 2H, H^4 or H^5), 6.04 (d, J = 2.4 Hz, 2H, H^4 or H^5), 4.27 (s, 2H, NH), 3.73 (s, 6H, OMe), 2.83 (t, J = 6.7 Hz, 4H, C^2), 2.03 – 1.90 (m, 4H, H^1).

^{13}C NMR (101 MHz, CDCl$_3$) δ 159.2 (2C, <u>Ar</u>-O), 143.5 (2C, Ar-N), 130.0 (2C, C^3), 112.7 (2C, <u>Ar</u>-C$_2$), 104.0 (2C, C^4), 99.9 (2C, C^5), 63.3 (RHN<u>C</u>NHR), 55.32 (2C, O<u>Me</u>), 33.5 (2C, C^1), 22.6 (2C, C^2).

m.p. 159-161 °C (CHCl$_3$).

IR ν= 3382, 1613, 1479, 1325, 1199, 828 cm^{-1}.

HR-MS (ESI) calcd for C$_{19}$H$_{23}$N$_2$O$_2$ (M + H$^+$): 311.1760, found: 311.1773.

Microanalysis, calcd for C$_{17}$H$_{18}$N$_2$: 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-1*H*,1'*H*-2,2'-spirobi[quinoline] – 266
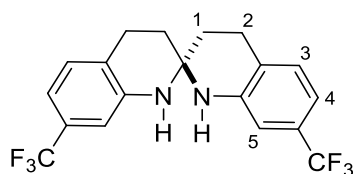
General Procedure **D**;. 2-azido-4-(trifluoromethyl)benzaldehyde (**260**) gave the spiro-biquinoline **266** (316 mg, 82%) as a white solid after purification by chromatography on silica (20% CH_2Cl_2 in pentane).

¹H NMR (400 MHz, CDCl₃) δ 7.13 (d, *J* = 7.8 Hz, 2H, H³), 6.92 (dd, *J* = 7.8, 1.7 Hz, 2H, H⁴), 6.71 (d, *J* = 1.6 Hz, 2H, H⁵), 4.40 (s, 2H, NH), 2.98 – 2.84 (m, 4H, H²), 2.09 – 1.87 (m, 4H, H¹).

¹³C NMR (101 MHz, CDCl₃) δ 142.6 (2C, Ar-N), 129.6 (2C, Ar-CF³), 123.6 (2C, CF₃), 114.3 (2C, C³), 114.3 (2C, Ar-C²), 111.1 (2C, CF⁴), 111.0 (2C, C⁵), 63.7 (RHNCNHR), 33.0 (2C, C¹), 23.4 (2C, C²).

¹⁹F NMR (377 MHz, CDCl₃) δ -62.67.

m.p. 132-133 ºC (CHCl₃).

IR ν= 3401, 1508, 1467, 1325, 1103, 818 cm⁻¹.

HR-MS (ESI) calcd for $C_{19}H_{17}N_2F_6$ (M + H⁺): 387.1296, found: 387.1294.

Microanalysis, calcd for $C_{19}H_{16}N_2F_6$: C, 59.07; H, 4.17; N, 7.25; Found: C, 58.93; H, 4.24; N, 7.21.

6,6'-Dichloro-3,3',4,4'-tetrahydro-1*H*,1'*H*-2,2'-spirobi[quinoline] – 267
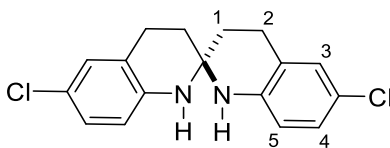
General Procedure **D**; 2-azido-5-chlorobenzaldehyde (**261**) gave the spiroquinoline **267** (108 mg, 34%) as a colourless oil after purification by chromatography on silica (50% CH_2Cl_2 in pentane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, *J* = 2.4 Hz, 2H. H^3), 6.96 (dd, *J* = 8.4, 2.5 Hz, 2H. H^4), 6.40 (d, *J* = 8.5 Hz, 2H, H^5), 4.21 (s, 2H, NH), 2.85 (m, 4H, H^2), 2.03 – 1.84 (m, 4H, H^1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.1 (2C, Ar-N), 128.9 (2C, C^3), 127.2 (2C, C^4), 122.4 (2C, Ar-C^2 or Ar-Cl), 121.7 (2C, Ar-C^2 or Ar-Cl), 115.8 (2C, C^5), 63.7 (RHNCNHR), 32.9 (2C, C^1), 23.3 (2C, C^2).

IR ν= 3398, 2936, 1480, 1291, 850 cm^{-1}.

HR-MS (ESI) calcd for $C_{17}H_{18}N_2Cl$ (M + H$^+$ - Cl): 285.1159, found: 285.1164.

Microanalysis, calcd for $C_{17}H_{16}N_2Cl_2$: C, 63.96; H, 5.05; N, 8.78; Found: C, 64.00; H, 5.10; N, 8.71.

6,6'-Dibromo-3,3',4,4'-tetrahydro-1H,1'H-2,2'-spirobi[quinoline] – 271
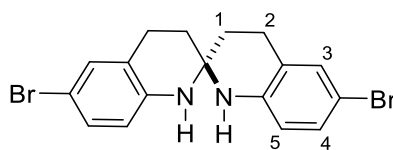
General Procedure **F**; Using 2.0 equiv. of NBS, spirobiquinoine **235** (500 mg, 2.0 mmol) gave the dibromide **271** (509 mg, 56%) as a white crystalline solid after purification by chromatography on silica (25% CH_2Cl_2 in pentane).

1H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, J = 2.3 Hz, 2H, H^3), 7.11 (dd, J = 8.5, 2.3 Hz, 2H, H^4), 6.38 (d, J = 8.5 Hz, 2H, H^5), 4.25 (s, 2H, NH), 2.87 (t, J = 6.8 Hz, 4H, H^2), 1.97 – 1.92 (m, 4H, H^1).

13C NMR (101 MHz, $CDCl_3$) δ 141.5 (2C, Ar-N), 131.7 (2C, C^3), 130.0 (2C, C^5), 122.2 (2C, Ar-C^2), 116.2 (2C, C^4), 109.5 (2C, Ar-Br), 63.6 (RHN$\underline{C}$NHR), 32.8 (2C, C^1), 23.2 (2C, C^2).

m.p. 178-181 ºC (CH_2Cl_2);

IR ν= 3403, 2928, 1467, 1290, 856, 801 cm^{-1}

HR-MS (ESI) calcd for $C_{17}H_{17}N_2{}^{79}Br^{81}Br$ (M + H$^+$): 408.9660, found: 408.9748.

Microanalysis, calcd for $C_{17}H_{16}N_2Br_2$: C, 50.03; H, 3.95; N, 6.86; Found: C, 50.17; H, 3.92; N, 6.63.

6,6',8,8'-Tetrabromo-3,3',4,4'-tetrahydro-1*H*,1'*H*-2,2'-spirobi[quinoline] – 272
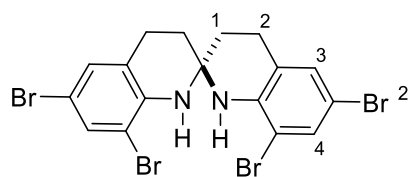
General Procedure **F**; Using 4.0 equiv. of NBS, spirobiquinoline **235** (500 mg, 2.0 mmol) gave the tetrabromide **272** (830 mg, 74%) as a white crystalline solid after purification by chromatography on silica (10% CH_2Cl_2 in pentane).

^{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<u>C</u>NHR), 32.9 (2C, C^1), 23.9 (2C, C^2).

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$_2$^{79}Br$_2$^{81}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
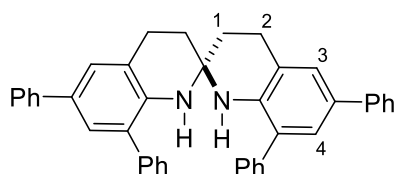
6,6',8,8'-Tetrabromo-3,3',4,4'-tetrahydro-1H,1'H-2,2'-spirobi[quinoline] (**272**) (28 mg, 0.05 mmol, 1.0 equiv.), phenylboronic acid (30 mg, 0.25 mmol, 5.0 equiv.), K_2CO_3 (28 mg, 0.20 mmol, 4.0 equiv.), and XPhos (5 mg, 0.01 mmol, 0.2 equiv.) were loaded into a vial. DMF and H_2O (4:1, 500 µL) were 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_2Cl_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, <u>Ar</u>-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<u>C</u>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.

1,1'-Dimethyl-3,3',4,4'-tetrahydro-1*H*,1'*H*-2,2'-spirobi[quinoline] – 274
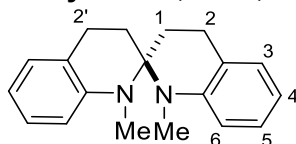
Spirobiquinoline **235** (50 mg, 0.2 mmol, 1.0 equiv.) was dissolved in a mixture of THF (2 mL) and HMPA (170 µL, 1.0 mmol, 5.0 equiv.) and cooled to – 78 ºC. *n*-BuLi (2.5 M in hexanes; 160 µL, 0.4 mmol, 2.0 equiv.) was added dropwise with stirring over 30 sec. After 5 min, MeI (28 µL, 0.44 mmol) in THF (1 mL) was added dropwise with stirring over 5 min. After a further 5 min at -78 ºC, the cooling bath was removed and the solution was warmed to room temperature. The reaction was quenched with sat. aqueous NH$_4$Cl (5 mL), and the resultant mixture extracted with CH$_2$Cl$_2$ (2 x 10 mL). The combined organic extracts were dried over MgSO$_4$, the solvent removed by rotary evaporation and the residue chromatographed on silica (20% CH$_2$Cl$_2$ in pentane +1% NEt$_3$) to afford the product **274** (50 mg, 91%) as a white solid.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.23 – 7.14 (m, 2H, H^5), 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}).

^{13}C NMR (101 MHz, CDCl$_3$) δ 146.1 (2C, <u>Ar</u>-N), 128.3 (2C, C^3 or C^5), 127.5 (2C, C^3 or C^5), 122.4 (2C, <u>Ar</u>-C^2), 116.4 (2C, C^4), 111.7 (2C, C^6), 74.2 (R$_2$N<u>C</u>NR$_2$), 30.9 (2C, N-<u>Me</u>), 28.9 (2C, C^1), 24.7 (2C, C^2).

m.p. 107-108 ºC (CH$_2$Cl$_2$).

IR ν= 1599, 1490, 1009, 740 cm^{-1}.

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

Microanalysis, calcd for C$_{19}$H$_{22}$N$_2$: C, 81.97; H, 7.97; N, 10.06; 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
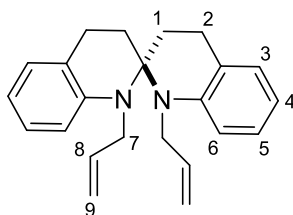
Spirobiquinoline **235** (50 mg, 0.2 mmol, 1.0 equiv.) was dissolved in a mixture of THF (2 mL) and HMPA (170 µL, 1.0 mmol, 5.0 equiv.) and cooled to – 78 ºC. *n*-BuLi (2.5 M in hexanes; 160 µL, 0.4 mmol, 2.0 equiv.) was added dropwise with stirring over 30 sec. After 5 min, allyl bromide (38 µL, 0.44 mmol) in THF (1 mL) was added dropwise with stirring over 5 min. After a further 5 min at -78 ºC, the cooling bath was removed and the solution warmed to room temperature. The solution was quenched with sat. aqueous NH$_4$Cl (5 mL), and the resultant mixture extracted with CH$_2$Cl$_2$ (2 x 10 mL). The combined organic extracts were dried over MgSO$_4$, the solvent removed by rotary evaporation, and the residue chromatographed on silica (20% CH$_2$Cl$_2$ in pentane +1% NEt$_3$) to afford the product **276** (53 mg, 80%) as a colourless oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.09 (td, *J* = 7.8, 1.7 Hz, 2H, H^5), 7.01 (dd, *J* = 7.3, 1.5 Hz, 2H, H^3), 6.71 – 6.61 (m, 4H, H^6 and H^4), 5.77 (ddt, *J* = 17.4, 9.5, 4.6 Hz, 2H, H^8), 5.16 – 5.05 (m, 4H, H^9), 3.86 (dt, *J* = 4.3, 2.0 Hz, 2H, H^7), 2.86 (ddd, *J* = 16.5, 9.9, 6.9 Hz, 2H, H^{2a}), 2.72 – 2.61 (m, 2H, H^{2b}), 2.14 – 2.06 (m, 4H, H^1).

^{13}C NMR (101 MHz, CDCl$_3$) δ 145.0 (2C, <u>Ar</u>-N), 136.2 (2C, C^8), 128.3 (2C, C^3), 127.1 (2C, C^5), 123.4 (2C, <u>Ar</u>-C^2), 116.8 (2C C^9), 115.9 (2C, C^5), 113.2 (2C, C^6), 76.2 (R$_2$N<u>C</u>NR$_2$), 46.3 (2C, C^7), 31.5 (2C, C^1), 24.9 (2C, C^2).

IR ν= 2942, 2845, 1601, 1490, 1458, 910, 743 cm^{-1}.

HR-MS (ESI) calcd for C$_{23}$H$_{27}$N$_2$ (M - H$^+$): 331.2169, found: 331.2164.

Microanalysis, calcd for C$_{23}$H$_{26}$N$_2$: C, 83.59; H, 7.93; N, 8.48; Found: C, 83.54; H, 8.09; N, 8.33.

1,4,10,11,12,13-Hexahydro-[1,3]diazepino[1,2-*a*:3,2-*a'*]diquinoline - 278
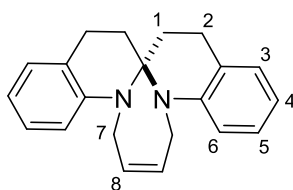
Diallyl spiroquinoline **276** (50 mg, 0.15 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (1 mL) and sparged for 10 min with argon. Hoveyda-Grubbs™ 2nd generation catalyst (4.6 mg, 7 µmol, 5 mol%) was added, and the mixture was heated to 40 ºC for 6 h. The mixture was cooled to room temperature and chromatographed on silica (15 → 20% CH_2Cl_2 in pentane +1% NEt₃) to give **278** (39 mg, 86%) as a white solid.

¹H NMR (400 MHz, CDCl₃) 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^4), 5.86 – 5.77 (m, 2H, H^8), 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}).

¹³C NMR (101 MHz, CDCl₃) 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^8), 124.6 (2C, Ar-C^2), 116.6 (2C, C^4), 111.0 (2C, C^6), 77.2 (R₂NCNR₂), 42.6 (2C, C^7), 31.6 (2C, C^1), 24.8 (2C, C^2).

m.p. 230-231 ºC (CH₂Cl₂).

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.

3,3',4,4'-Tetrahydro-1*H*,1'*H*-spiro[benzo[*h*]quinoline-2,2'-quinoline] - 284
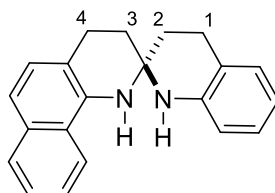
Using a modified general procedure **E**, *o*-azidobenzaldehyde (**239**) (147mg, 1.0 mmol, 1.0 equiv.) was dissolved in absolute EtOH (20 mL) and cooled in an ice bath. Acetone (73 µL, 1.0 mmol, 1.0 equiv.) was added followed by the dropwise addition of 2 M NaOH (2.5 mL, 5.0 mmol, 5.0 equiv.) with stirring. 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% CH_2Cl_2 in pentane) to give the unsymmetrical spiro-biquinoline **284** (219 mg, 73%) as an orange oil.

¹H NMR (400 MHz, CDCl$_3$) 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).

¹³C NMR (101 MHz, CDCl$_3$) 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 $C_{21}H_{19}N_2$ (M - H⁺): 299.1548, found: 299.1542.

Microanalysis, Calcd for $C_{21}H_{20}N_2$: 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-1*H*,1'*H*-spiro[benzo[*h*]quinoline-2,2'-quinoline]

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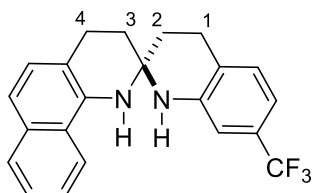
Using the procedure described for spiro-biquinoline **284**; 2-azido-4-(trifluoromethyl)benzaldehyde (**260**) (215 mg, 1.0 mmol, 1.0 equiv.) and 1-azido-2-naphthaldehyde (**249**) (197 mg, 1.0 mmol, 1.0 equiv.) were converted into the spiro-biquinoline **285** (206 mg, 56%) as an orange oil.

¹H NMR (400 MHz, CDCl₃) 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, H⁴), 3.01 – 2.89 (m, 2H, H¹), 2.18 – 1.95 (m, 4H, H² and H³).

¹³C NMR (101 MHz, CDCl₃) 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.

¹⁹F NMR (377 MHz, CDCl3) δ -62.63.

IR ν= 3397, 1473, 1332, 1114, 799 cm⁻¹.

HR-MS (ESI) calcd for $C_{22}H_{18}N_2F_3$ (M - H⁺): 367.1422, found: 367.1428.

Microanalysis, calcd for $C_{22}H_{19}N_2F_3$: 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
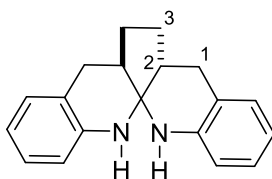
General Procedure **E**; cyclopentanone (**286**) (89 μL, 1.0 mmol, 1.0 equiv.) was used instead of acetone with *o*-azidobenzaldehyde (**239**), to afford the spiroquinoline **18** (115 mg, 42%) as a white solid. The product was chromatographed on silica (50% CH_2Cl_2 in pentane).

¹H NMR (400 MHz, CDCl$_3$) 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, H^{1a}), 2.65 (dd, J = 15.9, 7.2 Hz, 2H, H^{1b}), 2.20 (td, J = 7.3, 5.5 Hz, 2H, H^2), 2.01 – 1.88 (m, 2H, H3^a), 1.51 – 1.38 (m, 2H, H^{3b}).

¹³C NMR (101 MHz, CDCl$_3$) δ 142.7 (2C, <u>Ar</u>-N), 128.9 (2C, Ar), 127.1 (2C, Ar), 121.3 (2C, <u>Ar</u>-C^1), 117.7 (2C, Ar), 113.6 (2C), 75.3 (RHN<u>C</u>NHR), 43.8 (2C, C^2), 30.1 (2C, C^1), 27.78 (2C, C^3).

m.p. 109-111 ºC (pentane)

IR ν= 3384, 1605, 1474, 1261, 748 cm^{-1}.

HR-MS (ESI) calcd for C$_{19}$H$_{21}$N$_2$ (M + H$^+$): 277.1705, found: 277.1710.

Microanalysis, calcd for C$_{19}$H$_{20}$N$_2$: C, 82.57; H, 7.29; N, 10.14; Found: C, 82.45; H, 7.35; N, 9.98.

5a,6,7,8,8a,9,14,15-Octahydro-5*H*-quinolino[3,2-*d*]acridine - 289
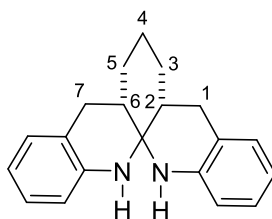
General Procedure **E***;* cyclohexanone (**287**) (103 µL, 1.0 mmol, 1.0 equiv.) was used instead of acetone with *o*-azidobenzaldehyde (**239**), to afford the spiro-biquinoline **289** (175 mg, 48%) as a white solid. A sample was chromatographed on silica (50% CH_2Cl_2 in pentane).

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, H^{1a} or H^{7a}), 2.80 (dd, *J* = 17.2, 5.8 Hz, 1H, H^{1b} or H^{7b}), 2.70 – 2.50 (m, 2H, H^{1ab} or H^{7ab}), 2.13 – 1.32 (m, 8H, H^2, H^3, H^4, and H^5).

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-C$^{1/7}$), 118.4 (Ar-C$^{1/7}$), 117.9 (Ar), 117.6 (Ar), 115.7 (Ar), 115.4 (Ar), 64.4 (RHN<u>C</u>NHR), 39.7 (C^2 or C^6), 38.5 (C^2 or C^6), 29.4 (C^1 or C^7), 29.2 (C^1 or C^7), 29.0 (C^3 or C^5), 28.7 (C^3 or C^5), 25.3 (C^4).

m.p. 140-141 ºC (pentane).

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

HR-MS (ESI) calcd for $C_{20}H_{23}N_2$ (M + H⁺): 291.1861, found: 291.1875.

Microanalysis, calcd for $C_{20}H_{23}N_2$: 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
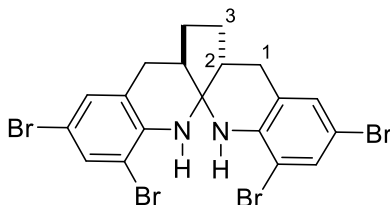
General Procedure **F***;* spiroquinoline **288** (5 mg, 18 µmol) and freshly recrystallized NBS (13 mg, 72 µmol, 4.0 equiv.) gave the tetra-bromo **290** (6 mg, 58%) as a white solid. A sample was purified by silica pad chromatography (20% CH_2Cl_2 in pentane)

^{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$\underline{C}$NHR), 43.2 (2C, C^2), 30.0 (2C, C^1), 26.8 (2C, C^3).

HR-MS (ESI) calcd for $C_{19}H_{17}N_2{}^{79}Br_2{}^{81}Br_2$ (M + H$^+$): 592.8079, found: 592.8085.

1,3,11,13-tetrabromo-5a,6,7,8,8a,9,14,15-octahydro-5*H*-quinolino[3,2-*d*]acridine – 291
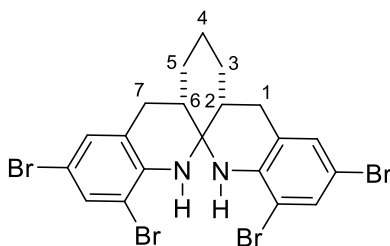
General Procedure **F**; spiroquinoline **291** (5 mg, 17 μmol) and freshly recrystallized NBS (13 mg, 72 μmol, 4.0 equiv.) gave the tetra-bromo **291** (7 mg, 68%) as a white solid after purification by chromatography on silica (20% CH_2Cl_2 in pentane).

¹H NMR (400 MHz, $CDCl_3$) 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, H^{1a} or H^{7a}), 2.89 – 2.63 (m, 2H, H^{1ab} or H^{7ab}), 2.58 (d, *J* = 17.4 Hz, 1H, H^{1a} or H^{7a}), 2.09 – 1.88 (m, 2H, H^2 and H^6), 1.80 – 1.65 (m, 2H, H^{3a} and H^{5a}), 1.52 – 1.36 (m, 4H, H^{3b}, H^{5b} and H^4).

¹³C NMR (101 MHz, $CDCl_3$) 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 (RHN$\underline{C}$NHR), 39.6 (C^2 or C^6), 37.8 (C^2 or C^6), 29.5 (C^1 or C^7), 29.2 (C^1 or C^7), 28.6 (C^5 or C^3), 28.1 (C^5 or C^3), 25.0 (C^4).

HR-MS (ESI) calcd for $C_{20}H_{19}N_2{}^{79}Br_2{}^{81}Br_2$ (M + H⁺): 606.8236, found: 606.8163.

4-(Naphthalen-2-yl)-4-oxobutanoic acid - 313
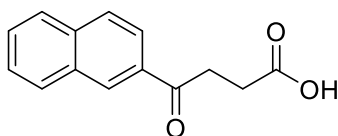
Using the procedure of Lingenfelder and Kellogg;[136] under an atmosphere of argon, napthalene (**312**) (21 g, 164 mmol, 1.5 equiv.) and succinic anhydride (**311**) (11 g, 109 mmol, 1.0 equiv.) was added in one portion to a rapidly stirred solution of $AlCl_3$ (42 g, 315 mmol, 2.9 equiv.) in $PhNO_2$ (90 mL) at 0 ºC. 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.[136]

¹H NMR (400 MHz, DMSO-d_6) δ 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, *overlapping with* H₂O), 2.65 (t, *J* = 6.3 Hz, 2H).

¹³C NMR (101 MHz, DMSO-d_6) δ 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 (EI) calcd for $C_{14}H_{12}O_3$ (M⁺): 228.0786, found: 228.0786.

4-(Naphthalen-2-yl)butanoic acid - 314
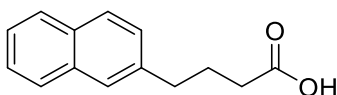
Using the procedure of Lingenfelder and Kellogg;[136] ketone **313** (4.2 g, 18.4 mmol) and Pd(OH)$_2$/C (10% wt, 400 mg) in AcOH (40 mL) was agitated under a atmosphere of hydrogen (1.5 bar) for 48 h. The catalyst was removed by filtration through Celite®. The filtrate was poured into H$_2$O (200 mL) 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.[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$^{\cdot+}$): 214.0994, found: 214.0999.

2,3-Dihydrophenanthren-4(1H)-one - 315
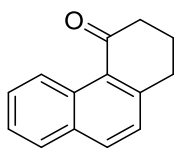
Using the procedure of Lingenfelder and Kellogg;[136] acid **313** (1.0 g, 4.67 mmol) was added to MsOH (25 mL) at 90 ºC. The solution was stirred at this temperature for 2 h. After cooling to room temperature, the solution was diluted with cold H_2O (100 mL). The aqueous solution was extracted with Et_2O (3 X 100 mL), the combined organic layers were washed sequentially with sat. aqueous $NaHCO_3$ (100 mL), H_2O (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.[136]

¹H NMR (400 MHz, CDCl₃) 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).

¹³C NMR (101 MHz, CDCl₃) 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.

((2-Bromophenyl)ethynyl)trimethylsilane -317
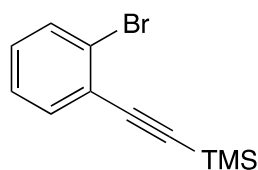
Using the procedure of Yamada[227]; PdCl$_2$(PPh$_3$)$_2$ (685 mg, 0.9 mmol, 2 mol%) and CuI (185 mg, 1.0 mmol, 2 mol%) were suspended in PhMe (150 mL) and sparged with argon for 5 minutes. NEt$_3$ (27 mL), 1-bromo-2-iodobenzene (**310**) (6.5 mL, 50.6 mmol, 1.0 equiv.) and TMS-acetylene (8.5 mL, 60.0 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. [227]

¹H NMR (400 MHz, CDCl$_3$) δ 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).

¹³C NMR (101 MHz, CDCl$_3$) δ 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$^{+ \cdot}$): 241.1670; found: 241.1681.

((2'-Fluoro-[1,1'-biphenyl]-2-yl)ethynyl)trimethylsilane - 318
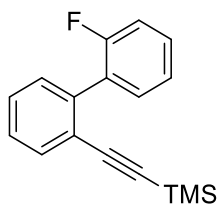
Using the procedure of Alabugin;[138] aryl bromide **311** (6.3 g, 25 mmol, 1.0 equiv.). (2-fluorophenyl)boronic acid (12.5 g, 90 mmol, 3.5 equiv.) and K_2CO_3 (35 g, 250 mmol, 10 equiv.) in PhMe (160 mL), H_2O (40 mL) and EtOH (40 mL) was sparged with argon for 15 minutes before the addition of freshly prepared[228] $Pd(PPh_3)_4$ (1.4 g, 1.25 mmol, 5 mol%). The reaction was heated to 120 ºC for 16 h, cooled to room temperature and diluted with H_2O (100 mL). The layers were separated and the aqueous layer was further extracted with CH_2Cl_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.

¹H NMR (400 MHz, CDCl₃) δ 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).

¹³C NMR (101 MHz, CDCl₃) δ 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) .

¹⁹F NMR (377 MHz, CDCl₃) δ -114.78

IR ν= 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
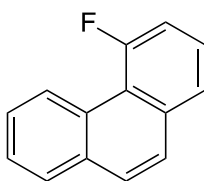
Using the procedure of Alabugin;[138] Biaryl **312** (1.34 g, 5.0 mmol, 1.0 equiv.) and K_2CO_3 (69 mg, 0.5 mmol, 0.1 equiv.) in MeOH (50 mL) and CH_2Cl_2 (50 mL) was stirred for 4 h. The reaction was diluted with H_2O (50 mL), the layers were separated, the aqueous layer was extracted with CH_2Cl_2 (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;[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 ºC 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.[229]

¹H NMR (400 MHz, $CDCl_3$) δ 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).

¹³C NMR (101 MHz, $CDCl_3$) δ 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 $C_{14}H_9F$ (M$^{+\cdot}$): 196.0688; found: 196.0670.

Microanalysis, calcd for $C_{14}H_9F$: C, 85.69; H, 4.62; Found: C, 85.53; H, 4.52.

4-Fluorophenanthrene-3-carbaldehyde - 320
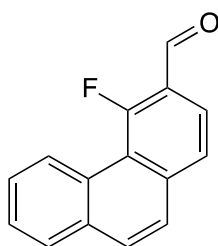
Using the procedure of Schlosser;[118] *sec*-BuLi (1.3 M in hexanes, 1.50 mL, 2.0 mmol, 1.0 equiv.) was added dropwise to a solution of 4-fluorophenanthrene **308** (400 mg, 2.0 mmol, 1.0 equiv.) in THF (5 mL) at − 78 °C. The solution was stirred at this temperature for 2 h before the addition of DMF (350 µL). After 5 min, the reaction was diluted with Et_2O (15 mL) and quenched with H_2O (5 mL). The phases were separated and the aqueous layer further extracted with Et_2O (3 x 20 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 **314** as a white crystalline solid (180 mg, 40%). Analysis was consistent with the reported literature data,[230] as well as recovering a sample of starting material **308** (110 mg, 26%).

¹H NMR (400 MHz, $CDCl_3$) 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).

¹³C NMR (101 MHz, $CDCl_3$) 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).

¹⁹F NMR (377 MHz, $CDCl_3$) δ -119.60.

HR-MS (EI) calcd for $C_{15}H_9OF$ (M⁺·): 224.0637; found: 224.0630.

Microanalysis, Calcd for $C_{15}H_9FO$: C, 80.35; H, 4.05; Found: C, 80.21; H, 4.23.

4-Azidophenanthrene-3-carbaldehyde - 306
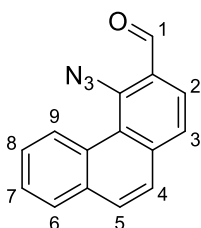
Using a modified procedure of Boswell;[119] a solution of aryl fluoride **314** (180 mg, 0.8 mmol, 1.0 equiv.), NaN_3 (156 mg, 2.4 mmol, 3.0 equiv.) in DMF (3 mL) and NEt_3 (25 µL) stirred at 60 ºC for 16 h, with constant argon sparging. After this time the reaction was cooled to room temperature, quenched with H_2O (20 mL) and extracted with Et_2O (3 x 25 mL). The combined organics were washed sequentially with H_2O (2 x 25 mL), 5% LiCl (2 x 25 mL) and brine (25 mL), dried over $MgSO_4$ 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.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.64 (s, 1H, H^1), 9.56 – 9.48 (m, 1H, H^9), 8.05 (d, J = 8.2 Hz, 1H, H^3 or H^4), 7.96 (dd, J = 7.9, 1.6 Hz, 1H. H^3 or H^4), 7.91 (d, J = 8.8 Hz, 1H, H^2), 7.86 (d, J = 8.1 Hz, 1H, H^5 or H^6), 7.78 (ddd, J = 8.7, 7.1, 1.7 Hz, 1H, H^5 or H^6), 7.75 – 7.67 (m, 2H, H^7 and H^8).

^{13}C NMR (101 MHz, $CDCl_3$) δ 189.9 (C^1), 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

Dichloro(3-(3,4-dihydro-2H-pyrrol-5-yl)propan-1-amine)triphenylphosphineruthenium(II) dimer 340
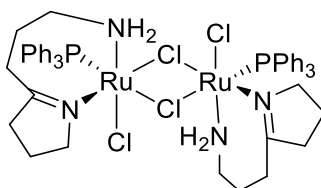
Using a modified procedure of Barrett;[35] A solution of spiroaminal **47** (13 mg, 0.1 mmol, 1.0 equiv.) in freshly degassed* CH_2Cl_2 (1.0 mL) was added to a solution of $[RuCl_2(PPh_3)_3]$ (96 mg, 0.1 mmol, 1.0 equiv.) in freshly degassed CH_2Cl_2 (4.0 mL). The solution was stirred for 16 h before 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 $C_{50}H_{59}Cl_4N_4P_2Ru_2$ (M +H$^{+\cdot}$): 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)
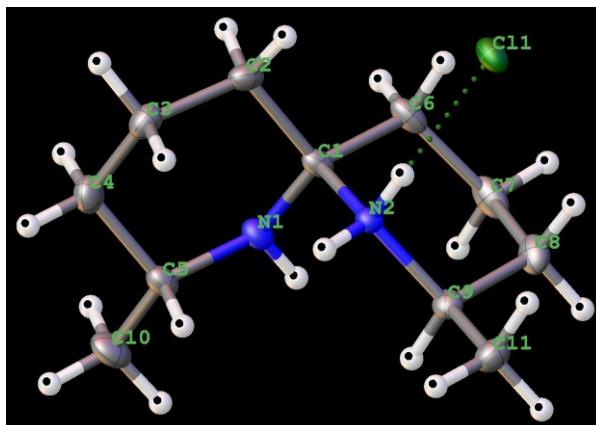
Empirical formula	$C_{11}H_{23}ClN_2$
Formula weight	218.76
Temperature/K	293(2)
Crystal system	orthorhombic
Space group	$P2_12_12$
a/Å	9.966(2)
b/Å	14.167(3)
c/Å	8.8630(18)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1251.4(4)
Z	4
ρ_{calc}g/cm^3	1.161
μ/mm^{-1}	0.274
F(000)	480.0
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	8.426 to 55.806
Index ranges	-13 ≤ h ≤ 13, -16 ≤ k ≤ 18, -11 ≤ l ≤ 11
Reflections collected	8344
Independent reflections	2858 [R_{int} = 0.0433, R_{sigma} = 0.0355]
Data/restraints/parameters	2858/0/141
Goodness-of-fit on F^2	1.085
Final R indexes [I>=2σ (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)

Bond lengths [Å]			Bond Angles [º]	
C(1)-N(1)	1.4355(19)		N(1)-C(1)-C(6)	110.3(13)
C(1)-C(6)	1.523(2)		N(1)-C(1)-C(2)	110.1(13)
C(1)-C(2)	1.527(2)		C(6)-C(1)-C(2)	111.4(13)
C(1)-C(2)	1.5560(19)		N(1)-C(1)-N(2)	112.4(12)
C(2)-C(3)	1.528(2)		C(6)-C(1)-N(2)	105.8(12)
C(3)-C(4)	1.529(3)		C(2)-C(1)-N(2)	106.8(12)
C(4)-C(5)	1.520(2)		C(1)-C(2)-C(3)	113.1(13)
C(5)-N(1)	1.469(2)		C(2)-C(3)-C(4)	110.0(14)
C(5)-C(10)	1.524(2)		C(5)-C(4)-C(3)	110.7(14)
C(6)-C(7)	1.527(3)		N(1)-C(5)-C(4)	109.4(14)
C(7)-C(8)	1.524(3)		N(1)-C(5)-C(10)	107.8(14)
C(8)-C(9)	1.523(2)		C(4)-C(5)-C(10)	112.1(14)
C(9)-N(2)	1.5049(19)		C(1)-C(6)-C(7)	113.3(13)
C(9)-C(11)	1.517(2)		C(8)-C(7)-C(6)	109.7(13)
			C(9)-C(8)-C(7)	112.5(14)
			N(2)-C(9)-C(11)	109.9(13)
			N(2)-C(9)-C(8)	108.7(13)
			N(11)-C(9)-C(8)	111.7(13)
			C(1)-N(1)-C(5)	117.6(13)
			C(9)-N(2)-C(1)	114.2(12)

6.2 Crystal structure of 1-(phenethylamino)-3,4-dihydroisoquinolin-2-ium iodide (154)
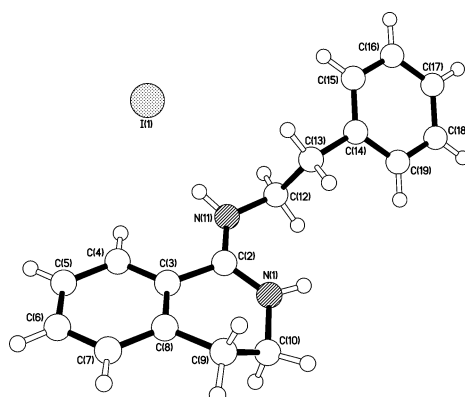
Formula $C_{17}H_{19}N_2$, I
Formula weight   378.24
Temperature   173(2) K
Diffractometer, wavelength   Agilent Xcalibur 3 E, 0.71073 Å
Crystal system, space group Monoclinic, P2$_1$/c
Unit cell dimensions   a = 11.4746(2) Å   a = 90°
        b = 9.1217(2) Å   b = 92.4144(19)°
        c = 15.3811(3) Å   g = 90°
Volume, Z   1608.47(6) Å3, 4
Density (calculated)   1.562 Mg/m3
Absorption coefficient 1.984 mm-1
F(000) 752
Crystal colour / morphology   Colourless plates
Crystal size   0.25 x 0.22 x 0.06 mm3
q range for data collection   2.597 to 28.257°
Index ranges   -15<=h<=15, -11<=k<=10, -11<=l<=19
Reflns collected / unique   5593 / 3233 [R(int) = 0.0183]
Reflns observed [F>4s(F)]   2719
Absorption correction Analytical
Max. and min. transmission   0.889 and 0.681
Refinement method   Full-matrix least-squares on F2
Data / restraints / parameters 3233 / 2 / 189
Goodness-of-fit on F2 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

Bond lengths [Å]

N(1)-C(2)	1.311(4)
N(1)-C(10)	1.468(4)
C(2)-N(11)	1.315(4)
C(2)-C(3)	1.483(4)
C(3)-C(8)	1.394(4)
C(3)-C(4)	1.396(4)
C(4)-C(5)	1.380(4)
C(5)-C(6)	1.378(4)
C(6)-C(7)	1.382(4)
C(7)-C(8)	1.386(4)
C(8)-C(9)	1.501(4)
C(9)-C(10)	1.506(4)
N(11)-C(12)	1.476(4)
C(12)-C(13)	1.491(4)
C(13)-C(14)	1.535(4)
C(14)-C(15)	1.368(5)
C(14)-C(19)	1.397(5)
C(15)-C(16)	1.376(5)
C(16)-C(17)	1.360(5)
C(17)-C(18)	1.374(5)
C(18)-C(19)	1.382(4)

Bond Angles [º]

C(2)-N(1)-C(10)	122.9(2)
N(1)-C(2)-N(11)	121.9(3)
N(1)-C(2)-C(3)	118.4(3)
N(11)-C(2)-C(3)	119.6(3)
C(8)-C(3)-C(4)	120.6(3)
C(8)-C(3)-C(2)	118.3(3)
C(4)-C(3)-C(2)	121.1(3)
C(5)-C(4)-C(3)	119.6(3)
C(6)-C(5)-C(4)	119.9(3)
C(5)-C(6)-C(7)	120.7(3)
C(6)-C(7)-C(8)	120.3(3)
C(7)-C(8)-C(3)	118.9(3)
C(7)-C(8)-C(9)	122.3(3)
C(3)-C(8)-C(9)	118.8(3)
C(8)-C(9)-C(10)	109.8(3)
N(1)-C(10)-C(9)	109.7(2)
C(2)-N(11)-C(12)	126.6(3)
N(11)-C(12)-C(13)	111.5(3)
C(12)-C(13)-C(14)	111.2(3)
C(15)-C(14)-C(19)	117.9(3)
C(15)-C(14)-C(13)	121.0(3)
C(19)-C(14)-C(13)	121.0(3)
C(14)-C(15)-C(16)	120.9(3)
C(17)-C(16)-C(15)	121.0(3)
C(16)-C(17)-C(18)	119.5(3)
C(17)-C(18)-C(19)	119.8(3)
C(18)-C(19)-C(14)	120.8(3)

6.3 Crystal structure of 3,3',4,4'-tetrahydro-1H,1'H-2,2'-spirobi[quinoline] (235)
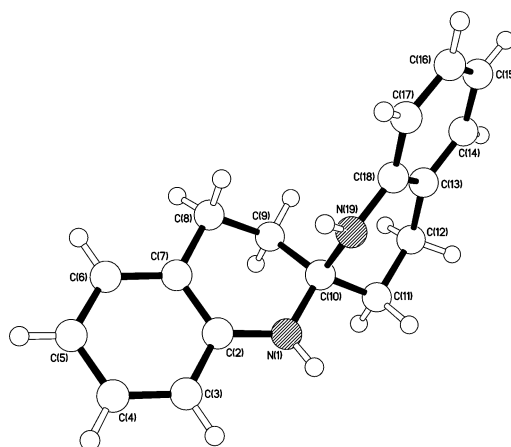
Formula $C_{17}H_{18}N_2$
Formula weight   250.33
Temperature   173(2) K
Diffractometer, wavelength   Agilent Xcalibur 3 E, 0.71073 Å
Crystal system, space group Tetragonal, I-4
Unit cell dimensions   a = 18.6804(6) Å   a = 90°
        b = 18.6804(6) Å   b = 90°
        c = 7.6330(4) Å   g = 90°
Volume, 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
Reflns collected / unique   7724 / 2775 [R(int) = 0.0251]
Reflns 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

.
Bond lengths [Å]

N(1)-C(2)	1.386(3)
N(1)-C(10)	1.447(3)
C(2)-C(3)	1.393(3)
C(2)-C(7)	1.403(3)
C(3)-C(4)	1.371(4)
C(4)-C(5)	1.390(4)
C(5)-C(6)	1.387(4)
C(6)-C(7)	1.382(3)
C(7)-C(8)	1.509(3)
C(8)-C(9)	1.522(4)
C(9)-C(10)	1.523(3)
C(10)-N(19)	1.473(3)
C(10)-C(11)	1.519(3)
C(11)-C(12)	1.528(3)
C(12)-C(13)	1.500(3)
C(13)-C(14)	1.393(3)
C(13)-C(18)	1.401(3)
C(14)-C(15)	1.374(3)
C(15)-C(16)	1.388(3)
C(16)-C(17)	1.382(3)
C(17)-C(18)	1.393(3)
C(18)-N(19)	1.394(3)

Bond Angles [º]

C(2)-N(1)-C(10)	123.19(18)
N(1)-C(2)-C(3)	120.6(2)
N(1)-C(2)-C(7)	120.6(2)
C(3)-C(2)-C(7)	118.7(2)
C(4)-C(3)-C(2)	121.4(2)
C(3)-C(4)-C(5)	120.4(3)
C(6)-C(5)-C(4)	118.3(3)
C(7)-C(6)-C(5)	122.2(2)
C(6)-C(7)-C(2)	119.0(2)
C(6)-C(7)-C(8)	121.7(2)
C(2)-C(7)-C(8)	119.4(2)
C(7)-C(8)-C(9)	110.8(2)
C(8)-C(9)-C(10)	111.5(2)
N(1)-C(10)-N(19)	109.47(18)
N(1)-C(10)-C(11)	109.75(19)
N(19)-C(10)-C(11)	106.24(19)
N(1)-C(10)-C(9)	107.77(19)
N(19)-C(10)-C(9)	111.60(19)
C(11)-C(10)-C(9)	112.0(2)
C(10)-C(11)-C(12)	111.0(2)
C(13)-C(12)-C(11)	113.8(2)
C(14)-C(13)-C(18)	118.2(2)
C(14)-C(13)-C(12)	121.2(2)
C(18)-C(13)-C(12)	120.5(2)
C(15)-C(14)-C(13)	122.4(2)
C(14)-C(15)-C(16)	118.8(2)
C(17)-C(16)-C(15)	120.4(2)
C(16)-C(17)-C(18)	120.6(2)
C(17)-C(18)-N(19)	120.5(2)
C(17)-C(18)-C(13)	119.6(2)
N(19)-C(18)-C(13)	119.9(2)
C(18)-N(19)-C(10)	118.57(18)

6.4 Crystal structure of 3,3',4,4'-tetrahydro-1H,1'H-2,2'-spirobi[benzo[h]quinoline] (262)
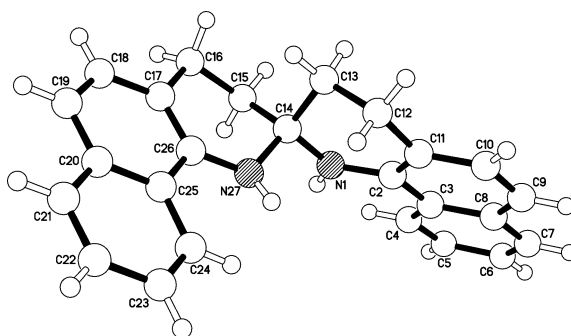
Identification code   AB1714

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, $P2_1/c$

Unit cell dimensions   a = 8.8728(6) Å   a = 90°

      b = 14.3163(12) Å   b = 97.202(7)°

      c = 14.4169(12) Å   c = 90°

Volume, Z   1816.9(2) Å^3, 4

Density (calculated)   1.281 Mg/m^3

Absorption coefficient 0.574 mm^{-1}

F(000) 744

Crystal colour / morphology   Purple blocky needles

Crystal size   0.27 x 0.06 x 0.05 mm^3

□ range for data collection   4.370 to 74.091°

Index ranges   -10<=h<=10, -17<=k<=17, -17<=l<=17

Reflns collected / unique   11055 / 11055 [R(int) = 0.0569]

Reflns observed [F>4□(F)]   5890

Absorption correction Analytical

Max. and min. transmission   0.975 and 0.920

Refinement method   Full-matrix least-squares on F^2

Data / restraints / parameters 11055 / 2 / 255

Goodness-of-fit on F^2 0.933

Final R indices [F>4□(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^{-3}

Mean and maximum shift/error   0.000 and 0.001

Bond lengths [Å]			Bond Angles [°]	
N(1)-C(2)	1.393(4)		C(2)-N(1)-C(14)	123.2(3)
N(1)-C(14)	1.445(4)		C(11)-C(2)-N(1)	121.2(3)
C(2)-C(11)	1.390(5)		C(11)-C(2)-C(3)	119.8(3)
C(2)-C(3)	1.438(5)		N(1)-C(2)-C(3)	119.0(3)
C(3)-C(4)	1.418(5)		C(4)-C(3)-C(8)	118.1(3)
C(3)-C(8)	1.426(5)		C(4)-C(3)-C(2)	122.6(3)
C(4)-C(5)	1.371(5)		C(8)-C(3)-C(2)	119.3(3)
C(5)-C(6)	1.408(6)		C(5)-C(4)-C(3)	121.5(4)
C(6)-C(7)	1.358(6)		C(4)-C(5)-C(6)	120.1(4)
C(7)-C(8)	1.422(5)		C(7)-C(6)-C(5)	120.1(4)
C(8)-C(9)	1.417(6)		C(6)-C(7)-C(8)	121.5(4)
C(9)-C(10)	1.360(6)		C(9)-C(8)-C(7)	122.2(4)
C(10)-C(11)	1.417(5)		C(9)-C(8)-C(3)	119.1(4)
C(11)-C(12)	1.505(5)		C(7)-C(8)-C(3)	118.7(4)
C(12)-C(13)	1.534(5)		C(10)-C(9)-C(8)	120.4(4)
C(13)-C(14)	1.528(5)		C(9)-C(10)-C(11)	122.0(4)
C(14)-N(27)	1.481(4)		C(2)-C(11)-C(10)	119.3(4)
C(14)-C(15)	1.523(5)		C(2)-C(11)-C(12)	119.4(3)
C(15)-C(16)	1.522(5)		C(10)-C(11)-C(12)	121.1(3)
C(16)-C(17)	1.505(5)		C(11)-C(12)-C(13)	110.0(3)
C(17)-C(26)	1.386(5)		C(14)-C(13)-C(12)	111.2(3)
C(17)-C(18)	1.410(5)		N(1)-C(14)-N(27)	108.6(3)
C(18)-C(19)	1.370(5)		N(1)-C(14)-C(15)	109.0(3)
C(19)-C(20)	1.409(5)		N(27)-C(14)-C(15)	106.9(3)
C(20)-C(21)	1.420(5)		N(1)-C(14)-C(13)	109.1(3)
C(20)-C(25)	1.422(5)		N(27)-C(14)-C(13)	110.8(3)
C(21)-C(22)	1.363(6)		C(15)-C(14)-C(13)	112.4(3)
C(22)-C(23)	1.399(6)		C(16)-C(15)-C(14)	112.1(3)
C(23)-C(24)	1.375(5)		C(17)-C(16)-C(15)	112.8(3)
C(24)-C(25)	1.416(5)		C(26)-C(17)-C(18)	119.0(3)
C(25)-C(26)	1.440(5)		C(26)-C(17)-C(16)	121.2(3)
C(26)-N(27)	1.397(4)		C(18)-C(17)-C(16)	119.7(3)
			C(19)-C(18)-C(17)	122.2(4)
			C(18)-C(19)-C(20)	120.1(3)
			C(19)-C(20)-C(21)	121.5(4)
			C(19)-C(20)-C(25)	119.5(3)
			C(21)-C(20)-C(25)	118.9(4)
			C(22)-C(21)-C(20)	121.2(4)
			C(21)-C(22)-C(23)	120.2(4)
			C(24)-C(23)-C(22)	120.2(4)
			C(23)-C(24)-C(25)	121.3(4)
			C(24)-C(25)-C(20)	118.1(3)
			C(24)-C(25)-C(26)	123.1(3)
			C(20)-C(25)-C(26)	118.8(3)
			C(17)-C(26)-N(27)	120.4(3)
			C(17)-C(26)-C(25)	120.3(3)
			N(27)-C(26)-C(25)	119.2(3)
			C(26)-N(27)-C(14)	119.3(3)

6.5 Crystal structure of 6,6'-dibromo-3,3',4,4'-tetrahydro-1H,1'H-2,2'-spirobi[quinoline] (271)
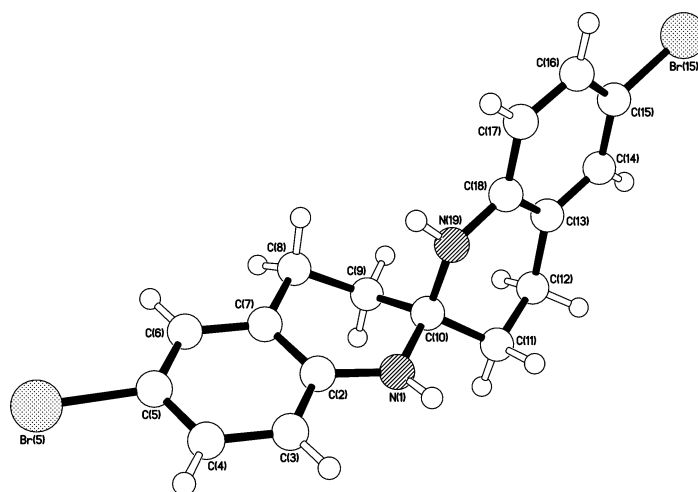
Identification code   AB1609
Formula $C_{17}H_{16}Br_2N_2$
Formula weight   408.14
Temperature   173(2) K
Diffractometer, wavelength   Agilent Xcalibur 3 E, 0.71073 Å
Crystal system, space group Triclinic, P-1
Unit cell dimensions   a = 8.2840(6) Å   a = 68.118(6)°
         b = 10.2385(6) Å   b = 71.449(7)°
         c = 10.3631(8) Å   g = 87.541(6)°
Volume, Z   770.38(10) Å3, 2
Density (calculated)   1.759 Mg/m3
Absorption coefficient 5.256 mm-1
F(000) 404
Crystal colour / morphology   Colourless blocks
Crystal size   0.38 x 0.35 x 0.20 mm3
q range for data collection   2.448 to 27.935°
Index ranges   -9<=h<=8, -13<=k<=12, -13<=l<=9
Reflns collected / unique   4432 / 3027 [R(int) = 0.0222]
Reflns observed [F>4s(F)]   2411
Absorption correction Analytical
Max. and min. transmission   0.472 and 0.274
Refinement method   Full-matrix least-squares on F2
Data / restraints / parameters 3027 / 2 / 199
Goodness-of-fit on F2 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

Bond lengths [Å]

N(1)-C(2)	1.395(3)
N(1)-C(10)	1.443(3)
C(2)-C(7)	1.392(4)
C(2)-C(3)	1.393(4)
C(3)-C(4)	1.374(4)
C(4)-C(5)	1.377(4)
C(5)-C(6)	1.381(4)
C(5)-Br(5)	1.907(3)
C(6)-C(7)	1.384(4)
C(7)-C(8)	1.508(4)
C(8)-C(9)	1.515(4)
C(9)-C(10)	1.534(4)
C(10)-N(19)	1.464(3)
C(10)-C(11)	1.526(4)
C(11)-C(12)	1.519(4)
C(12)-C(13)	1.511(4)
C(13)-C(14)	1.379(4)
C(13)-C(18)	1.412(4)
C(14)-C(15)	1.377(4)
C(15)-C(16)	1.385(4)
C(15)-Br(15)	1.913(3)
C(16)-C(17)	1.373(4)
C(17)-C(18)	1.395(4)
C(18)-N(19)	1.382(3)

Bond angles [°]

C(2)-N(1)-C(10)	123.1(2)
C(7)-C(2)-C(3)	119.8(3)
C(7)-C(2)-N(1)	120.8(3)
C(3)-C(2)-N(1)	119.3(3)
C(4)-C(3)-C(2)	121.0(3)
C(3)-C(4)-C(5)	118.8(3)
C(4)-C(5)-C(6)	121.2(3)
C(4)-C(5)-Br(5)	119.3(2)
C(6)-C(5)-Br(5)	119.5(2)
C(5)-C(6)-C(7)	120.3(3)
C(6)-C(7)-C(2)	118.9(3)
C(6)-C(7)-C(8)	121.5(3)
C(2)-C(7)-C(8)	119.6(3)
C(7)-C(8)-C(9)	111.2(3)
C(8)-C(9)-C(10)	112.2(2)
N(1)-C(10)-N(19)	109.0(2)
N(1)-C(10)-C(11)	108.5(2)
N(19)-C(10)-C(11)	107.2(2)
N(1)-C(10)-C(9)	107.7(2)
N(19)-C(10)-C(9)	111.8(3)
C(11)-C(10)-C(9)	112.4(2)
C(12)-C(11)-C(10)	112.4(3)
C(13)-C(12)-C(11)	111.6(2)
C(14)-C(13)-C(18)	119.2(3)
C(14)-C(13)-C(12)	121.4(2)
C(18)-C(13)-C(12)	119.3(3)
C(15)-C(14)-C(13)	120.6(3)
C(14)-C(15)-C(16)	121.1(3)
C(14)-C(15)-Br(15)	120.0(2)
C(16)-C(15)-Br(15)	118.9(2)
C(17)-C(16)-C(15)	118.7(3)
C(16)-C(17)-C(18)	121.6(3)
N(19)-C(18)-C(17)	120.2(2)
N(19)-C(18)-C(13)	121.0(2)
C(17)-C(18)-C(13)	118.7(3)
C(18)-N(19)-C(10)	122.6(2)

6.6 Crystal structure 6,6',8,8'-tetrabromo-3,3',4,4'-tetrahydro-1H,1'H-2,2'-spirobi[quinoline] (272)
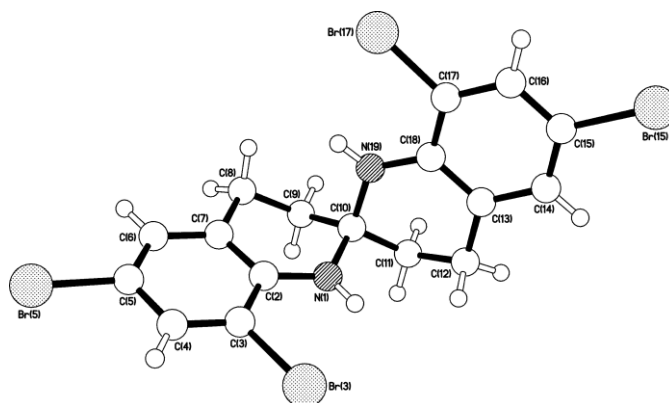
Identification code   AB1608b

Formula $C_{17}H_{14}Br_4N_2$

Formula weight   565.94

Temperature   173(2) K

Diffractometer, wavelength   Agilent Xcalibur PX Ultra A, 1.54184 Å

Crystal system, space group Monoclinic, P2₁/c

Unit cell dimensions   a = 8.7964(3) Å α = 90°

      b = 12.5727(4) Å β = 100.818(3)°

      c = 15.8234(5) Å γ = 90°

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

θ range for data collection   4.523 to 73.815°

Index ranges   -10<=h<=9, -15<=k<=9, -19<=l<=17

Reflns collected / unique   5495 / 3310 [R(int) = 0.0295]

Reflns observed [F>4σ(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>4σ(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

Bond lengths [Å]

N(1)-C(2)	1.384(6)
N(1)-C(10)	1.474(6)
C(2)-C(7)	1.399(7)
C(2)-C(3)	1.418(7)
C(3)-C(4)	1.360(7)
C(3)-Br(3)	1.900(5)
C(4)-C(5)	1.389(7)
C(5)-C(6)	1.385(8)
C(5)-Br(5)	1.897(5)
C(6)-C(7)	1.384(8)
C(7)-C(8)	1.529(7)
C(8)-C(9)	1.515(8)
C(9)-C(10)	1.516(7)
C(10)-N(19)	1.470(6)
C(10)-C(11)	1.522(7)
C(11)-C(12)	1.525(7)
C(12)-C(13)	1.501(7)
C(13)-C(14)	1.401(7)
C(13)-C(18)	1.414(7)
C(14)-C(15)	1.392(7)
C(15)-C(16)	1.375(7)
C(15)-Br(15)	1.898(5)
C(16)-C(17)	1.373(7)
C(17)-C(18)	1.403(6)
C(17)-Br(17)	1.894(5)
C(18)-N(19)	1.371(6)

Bond angles [°]

C(2)-N(1)-C(10)	121.6(4)
N(1)-C(2)-C(7)	122.0(5)
N(1)-C(2)-C(3)	120.6(4)
C(7)-C(2)-C(3)	117.3(5)
C(4)-C(3)-C(2)	122.9(5)
C(4)-C(3)-Br(3)	119.4(4)
C(2)-C(3)-Br(3)	117.8(4)
C(3)-C(4)-C(5)	118.4(5)
C(6)-C(5)-C(4)	120.7(5)
C(6)-C(5)-Br(5)	120.6(4)
C(4)-C(5)-Br(5)	118.6(4)
C(7)-C(6)-C(5)	120.7(5)
C(6)-C(7)-C(2)	120.0(5)
C(6)-C(7)-C(8)	121.1(5)
C(2)-C(7)-C(8)	118.9(5)
C(9)-C(8)-C(7)	110.9(4)
C(8)-C(9)-C(10)	112.4(4)
N(19)-C(10)-N(1)	112.3(4)
N(19)-C(10)-C(9)	108.7(4)
N(1)-C(10)-C(9)	107.3(4)
N(19)-C(10)-C(11)	108.1(4)
N(1)-C(10)-C(11)	108.1(4)
C(9)-C(10)-C(11)	112.5(4)
C(10)-C(11)-C(12)	112.2(4)
C(13)-C(12)-C(11)	112.2(4)
C(14)-C(13)-C(18)	119.8(4)
C(14)-C(13)-C(12)	121.6(5)
C(18)-C(13)-C(12)	118.6(5)
C(15)-C(14)-C(13)	120.1(5)
C(16)-C(15)-C(14)	120.4(5)
C(16)-C(15)-Br(15)	119.9(4)
C(14)-C(15)-Br(15)	119.7(4)
C(17)-C(16)-C(15)	120.0(4)
C(16)-C(17)-C(18)	121.9(4)
C(16)-C(17)-Br(17)	119.4(4)
C(18)-C(17)-Br(17)	118.7(4)
N(19)-C(18)-C(17)	120.7(4)
N(19)-C(18)-C(13)	121.5(4)
C(17)-C(18)-C(13)	117.8(4)
C(18)-N(19)-C(10)	123.4(4)

6.7 Crystal structure 6,6',8,8'-tetraphenyl-3,3',4,4'-tetrahydro-1H,1'H-2,2'-spirobi[quinoline] (273)
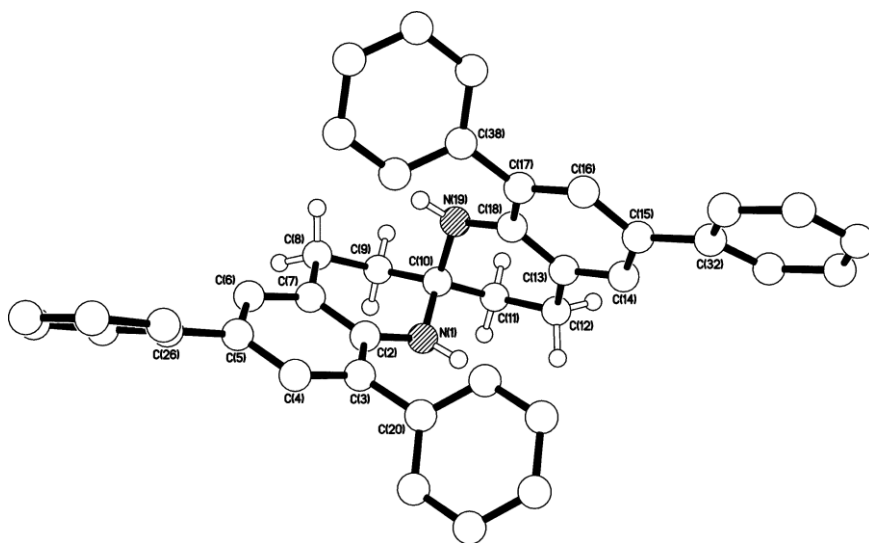
Formula $C_{41} H_{34} N_2$
Formula weight   554.70
Temperature   173(2) K
Diffractometer, wavelength   Agilent Xcalibur 3 E, 0.71073 Å
Crystal system, space group Orthorhombic, Pbca
Unit cell dimensions   a = 18.7174(5) Å   a = 90°
          b = 12.0319(4) Å   b = 90°
          c = 26.3744(7) Å   g = 90°
Volume, Z   5939.6(3) Å3, 8
Density (calculated)   1.241 Mg/m3
Absorption coefficient 0.072 mm-1
F(000) 2352
Crystal colour / morphology   Pale yellow blocks
Crystal size   0.55 x 0.29 x 0.28 mm3
q range for data collection   2.864 to 28.296°
Index ranges   -15<=h<=24, -14<=k<=8, -35<=l<=20
Reflns collected / unique   13823 / 6138 [R(int) = 0.0221]
Reflns observed [F>4s(F)]   4594
Absorption correction Analytical
Max. and min. transmission   0.986 and 0.979
Refinement method   Full-matrix least-squares on F2
Data / restraints / parameters 6138 / 2 / 397
Goodness-of-fit on F2 1.026
Final R indices [F>4s(F)]   R1 = 0.0439, wR2 = 0.0887
R indices (all data)   R1 = 0.0674, wR2 = 0.0992
Largest diff. peak, hole   0.204, -0.171 eÅ-3
Mean and maximum shift/error   0.000 and 0.001

| Bond lengths [Å]		Bond Angles [°]	
N(1)-C(2)	1.3940(18)	C(2)-N(1)-C(10)	118.45(11)
N(1)-C(10)	1.4640(18)	N(1)-C(2)-C(7)	119.46(12)
C(2)-C(7)	1.4058(19)	N(1)-C(2)-C(3)	121.29(12)
C(2)-C(3)	1.4142(19)	C(7)-C(2)-C(3)	119.24(13)
C(3)-C(4)	1.391(2)	C(4)-C(3)-C(2)	119.06(13)
C(3)-C(20)	1.4936(19)	C(4)-C(3)-C(20)	117.51(12)
C(4)-C(5)	1.397(2)	C(2)-C(3)-C(20)	123.32(13)
C(5)-C(6)	1.392(2)	C(3)-C(4)-C(5)	122.46(13)
C(5)-C(26)	1.484(2)	C(6)-C(5)-C(4)	117.14(13)
C(6)-C(7)	1.387(2)	C(6)-C(5)-C(26)	121.46(13)
C(7)-C(8)	1.517(2)	C(4)-C(5)-C(26)	121.29(13)
C(8)-C(9)	1.526(2)	C(7)-C(6)-C(5)	122.62(13)
C(9)-C(10)	1.520(2)	C(6)-C(7)-C(2)	119.45(13)
C(10)-N(19)	1.4752(19)	C(6)-C(7)-C(8)	119.67(13)
C(10)-C(11)	1.519(2)	C(2)-C(7)-C(8)	120.81(13)
C(11)-C(12)	1.524(2)	C(7)-C(8)-C(9)	113.34(12)
C(12)-C(13)	1.517(2)	C(10)-C(9)-C(8)	112.01(12)
C(13)-C(14)	1.382(2)	N(1)-C(10)-N(19)	112.02(11)
C(13)-C(18)	1.400(2)	N(1)-C(10)-C(11)	109.55(12)
C(14)-C(15)	1.395(2)	N(19)-C(10)-C(11)	106.24(12)
C(15)-C(16)	1.3958(19)	N(1)-C(10)-C(9)	107.09(12)
C(15)-C(32)	1.487(2)	N(19)-C(10)-C(9)	110.28(12)
C(16)-C(17)	1.391(2)	C(11)-C(10)-C(9)	111.73(12)
C(17)-C(18)	1.410(2)	C(10)-C(11)-C(12)	111.70(12)
C(17)-C(38)	1.492(2)	C(13)-C(12)-C(11)	113.59(12)
C(18)-N(19)	1.4034(18)	C(14)-C(13)-C(18)	119.78(13)
C(20)-C(25)	1.396(2)	C(14)-C(13)-C(12)	118.91(13)
C(20)-C(21)	1.398(2)	C(18)-C(13)-C(12)	121.28(13)
C(21)-C(22)	1.385(2)	C(13)-C(14)-C(15)	122.72(13)
C(22)-C(23)	1.387(2)	C(14)-C(15)-C(16)	116.48(13)
C(23)-C(24)	1.382(2)	C(14)-C(15)-C(32)	121.68(13)
C(24)-C(25)	1.388(2)	C(16)-C(15)-C(32)	121.82(13)
C(26)-C(31)	1.390(2)	C(17)-C(16)-C(15)	122.72(13)
C(26)-C(27)	1.396(2)	C(16)-C(17)-C(18)	119.13(13)
C(27)-C(28)	1.387(2)	C(16)-C(17)-C(38)	117.96(13)
C(28)-C(29)	1.378(2)	C(18)-C(17)-C(38)	122.82(13)
C(29)-C(30)	1.381(3)	C(13)-C(18)-N(19)	119.20(13)
C(30)-C(31)	1.385(2)	C(13)-C(18)-C(17)	119.02(13)
C(32)-C(33)	1.393(2)	N(19)-C(18)-C(17)	121.78(12)
C(32)-C(37)	1.398(2)	C(18)-N(19)-C(10)	115.43(11)
C(33)-C(34)	1.381(2)	C(25)-C(20)-C(21)	118.21(13)
C(34)-C(35)	1.378(2)	C(25)-C(20)-C(3)	120.44(14)
C(35)-C(36)	1.378(2)	C(21)-C(20)-C(3)	120.97(13)
C(36)-C(37)	1.386(2)	C(22)-C(21)-C(20)	120.77(14)
C(38)-C(39)	1.390(2)	C(21)-C(22)-C(23)	120.37(16)
C(38)-C(43)	1.398(2)	C(24)-C(23)-C(22)	119.43(14)
C(39)-C(40)	1.389(2)	C(23)-C(24)-C(25)	120.50(15)
C(40)-C(41)	1.382(2)	C(24)-C(25)-C(20)	120.69(16)
C(41)-C(42)	1.377(2)	C(31)-C(26)-C(27)	118.31(14)
C(42)-C(43)	1.385(2)	C(31)-C(26)-C(5)	120.43(14)
		C(27)-C(26)-C(5)	121.22(14)
		C(28)-C(27)-C(26)	120.56(15)
		C(29)-C(28)-C(27)	120.41(16)

C(28)-C(29)-C(30)	119.63(15)
C(29)-C(30)-C(31)	120.28(16)
C(30)-C(31)-C(26)	120.82(16)
C(33)-C(32)-C(37)	117.04(14)
C(33)-C(32)-C(15)	121.18(13)
C(37)-C(32)-C(15)	121.73(13)
C(34)-C(33)-C(32)	121.62(14)
C(35)-C(34)-C(33)	120.46(15)
C(36)-C(35)-C(34)	119.13(15)
C(35)-C(36)-C(37)	120.59(15)
C(36)-C(37)-C(32)	121.16(14)
C(39)-C(38)-C(43)	118.14(14)
C(39)-C(38)-C(17)	121.17(14)
C(43)-C(38)-C(17)	120.42(13)
C(40)-C(39)-C(38)	120.69(16)
C(41)-C(40)-C(39)	120.44(16)
C(42)-C(41)-C(40)	119.49(15)
C(41)-C(42)-C(43)	120.42(16)
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)
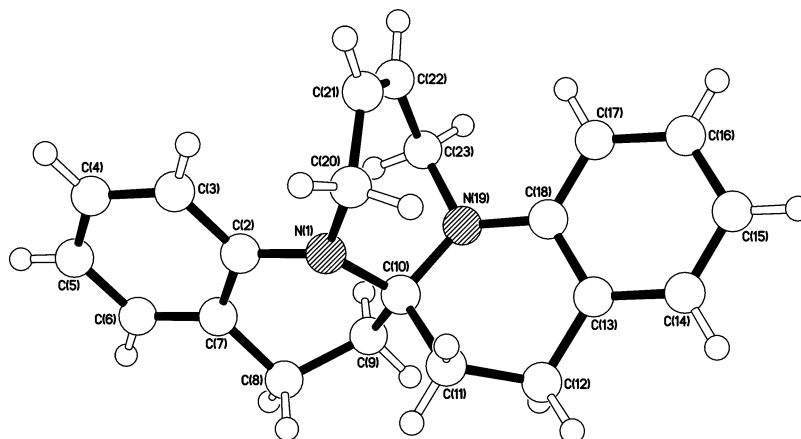
Formula $C_{21} H_{22} N_2$
Formula weight   302.40
Temperature   173(2) K
Diffractometer, wavelength   Agilent Xcalibur 3 E, 0.71073 Å
Crystal system, space group Monoclinic, $P2_1/n$
Unit cell dimensions   a = 8.4668(4) Å   a = 90°
        b = 8.8098(4) Å   b = 91.110(4)°
        c = 20.8081(9) Å   g = 90°
Volume, Z   1551.81(12) Å3, 4
Density (calculated)   1.294 Mg/m3
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 mm3
q range for data collection   2.615 to 28.072°
Index ranges -11<=h<=10, -11<=k<=10, -27<=l<=17
Reflns collected / unique   5349 / 3097 [R(int) = 0.0185]
Reflns observed [F>4s(F)]   2549
Absorption correction Analytical
Max. and min. transmission   0.977 and 0.971
Refinement method   Full-matrix least-squares on F2
Data / restraints / parameters 3097 / 0 / 209
Goodness-of-fit on F2 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

Table 2. Bond lengths [Å]   Bond angles [°]

N(1)-C(2)	1.3900(17)	C(2)-N(1)-C(20)	119.02(11)
N(1)-C(20)	1.4538(17)	C(2)-N(1)-C(10)	123.43(11)
N(1)-C(10)	1.4791(17)	C(20)-N(1)-C(10)	115.27(11)
C(2)-C(3)	1.4017(19)	N(1)-C(2)-C(3)	121.54(13)
C(2)-C(7)	1.406(2)	N(1)-C(2)-C(7)	119.75(12)
C(3)-C(4)	1.388(2)	C(3)-C(2)-C(7)	118.63(13)
C(4)-C(5)	1.375(2)	C(4)-C(3)-C(2)	120.36(14)
C(5)-C(6)	1.389(2)	C(5)-C(4)-C(3)	121.01(14)
C(6)-C(7)	1.383(2)	C(4)-C(5)-C(6)	118.80(14)
C(7)-C(8)	1.4988(19)	C(7)-C(6)-C(5)	121.63(15)
C(8)-C(9)	1.5163(19)	C(6)-C(7)-C(2)	119.52(13)
C(9)-C(10)	1.5312(19)	C(6)-C(7)-C(8)	122.73(13)
C(10)-N(19)	1.4818(17)	C(2)-C(7)-C(8)	117.76(13)
C(10)-C(11)	1.5332(19)	C(7)-C(8)-C(9)	109.02(12)
C(11)-C(12)	1.5209(19)	C(8)-C(9)-C(10)	112.84(11)
C(12)-C(13)	1.499(2)	N(1)-C(10)-N(19)	108.24(11)
C(13)-C(14)	1.3818(19)	N(1)-C(10)-C(9)	110.70(11)
C(13)-C(18)	1.4085(19)	N(19)-C(10)-C(9)	108.56(11)
C(14)-C(15)	1.386(2)	N(1)-C(10)-C(11)	108.60(11)
C(15)-C(16)	1.379(2)	N(19)-C(10)-C(11)	110.80(11)
C(16)-C(17)	1.388(2)	C(9)-C(10)-C(11)	109.94(11)
C(17)-C(18)	1.398(2)	C(12)-C(11)-C(10)	112.29(12)
C(18)-N(19)	1.3953(17)	C(13)-C(12)-C(11)	108.84(11)
N(19)-C(23)	1.4623(17)	C(14)-C(13)-C(18)	119.84(13)
C(20)-C(21)	1.508(2)	C(14)-C(13)-C(12)	122.83(13)
C(21)-C(22)	1.318(2)	C(18)-C(13)-C(12)	117.33(12)
C(22)-C(23)	1.503(2)	C(13)-C(14)-C(15)	121.56(14)
		C(16)-C(15)-C(14)	118.76(14)
		C(15)-C(16)-C(17)	120.91(15)
		C(16)-C(17)-C(18)	120.59(15)
		N(19)-C(18)-C(17)	122.24(13)
		N(19)-C(18)-C(13)	119.38(12)
		C(17)-C(18)-C(13)	118.30(13)
		C(18)-N(19)-C(23)	118.35(11)
		C(18)-N(19)-C(10)	122.78(11)
		C(23)-N(19)-C(10)	115.26(11)
		N(1)-C(20)-C(21)	114.00(12)
		C(22)-C(21)-C(20)	123.67(13)
		C(21)-C(22)-C(23)	124.22(13)
		N(19)-C(23)-C(22)	115.16(12)

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)
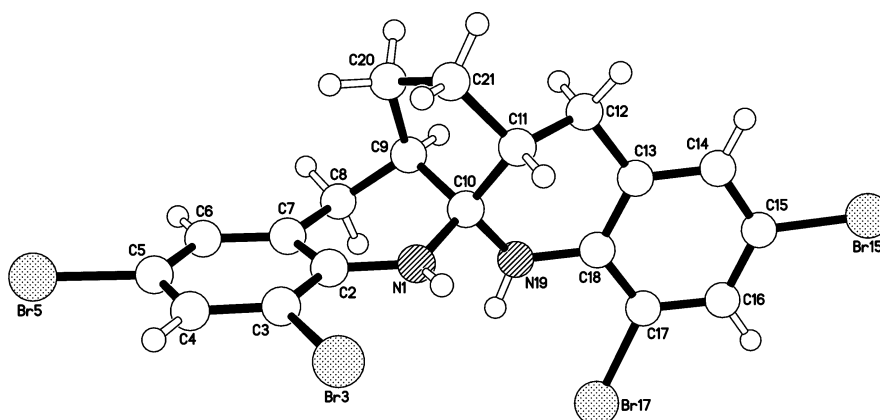
Formula $C_{19} H_{16} Br_4 N_2$
Formula weight 591.98
Temperature 173(2) K
Diffractometer, wavelength Agilent Xcalibur 3 E, 0.71073 Å
Crystal system, space group Monoclinic, P2₁/c
Unit cell dimensions a = 12.6560(8) Å a = 90°
     b = 8.9013(6) Å b = 97.911(6)°
     c = 16.6514(11) Å g = 90°
Volume, Z 1858.0(2) Å3, 4
Density (calculated) 2.116 Mg/m3
Absorption coefficient 8.669 mm-1
F(000) 1136
Crystal colour / morphology Colourless plates
Crystal size 0.48 x 0.29 x 0.07 mm3
q range for data collection 2.600 to 28.292°
Index ranges -8<=h<=16, -10<=k<=11, -21<=l<=19
Reflns collected / unique 6314 / 3719 [R(int) = 0.0335]
Reflns observed [F>4s(F)] 2465
Absorption correction Analytical
Max. and min. transmission 0.537 and 0.105
Refinement method Full-matrix least-squares on F2
Data / restraints / parameters 3719 / 2 / 235
Goodness-of-fit on F2 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-3
Mean and maximum shift/error 0.000 and 0.001

Table 2. Bond lengths [Å]

N(1)-C(2)	1.381(5)
N(1)-C(10)	1.465(6)
C(2)-C(3)	1.374(6)
C(2)-C(7)	1.410(7)
C(3)-C(4)	1.391(6)
C(3)-Br(3)	1.904(5)
C(4)-C(5)	1.374(7)
C(5)-C(6)	1.374(6)
C(5)-Br(5)	1.905(5)
C(6)-C(7)	1.377(6)
C(7)-C(8)	1.498(6)
C(8)-C(9)	1.522(6)
C(9)-C(20)	1.535(7)
C(9)-C(10)	1.536(6)
C(10)-N(19)	1.453(6)
C(10)-C(11)	1.532(7)
C(11)-C(12)	1.514(6)
C(11)-C(21)	1.536(6)
C(12)-C(13)	1.504(6)
C(13)-C(14)	1.394(6)
C(13)-C(18)	1.399(6)
C(14)-C(15)	1.386(6)
C(15)-C(16)	1.382(6)
C(15)-Br(15)	1.904(4)
C(16)-C(17)	1.377(6)
C(17)-C(18)	1.386(6)
C(17)-Br(17)	1.898(5)
C(18)-N(19)	1.384(5)
C(20)-C(21)	1.547(6)

Bond angles [°]

C(2)-N(1)-C(10)	125.9(4)
C(3)-C(2)-N(1)	122.5(5)
C(3)-C(2)-C(7)	118.2(4)
N(1)-C(2)-C(7)	119.2(4)
C(2)-C(3)-C(4)	122.5(5)
C(2)-C(3)-Br(3)	120.2(4)
C(4)-C(3)-Br(3)	117.4(4)
C(5)-C(4)-C(3)	117.8(4)
C(6)-C(5)-C(4)	121.4(5)
C(6)-C(5)-Br(5)	120.1(4)
C(4)-C(5)-Br(5)	118.5(4)
C(5)-C(6)-C(7)	120.5(5)
C(6)-C(7)-C(2)	119.6(4)
C(6)-C(7)-C(8)	123.4(5)
C(2)-C(7)-C(8)	117.0(4)
C(7)-C(8)-C(9)	109.7(4)
C(8)-C(9)-C(20)	115.9(4)
C(8)-C(9)-C(10)	111.4(4)
C(20)-C(9)-C(10)	104.8(4)
N(19)-C(10)-N(1)	108.3(4)
N(19)-C(10)-C(11)	112.6(4)
N(1)-C(10)-C(11)	109.5(4)
N(19)-C(10)-C(9)	113.5(4)
N(1)-C(10)-C(9)	109.1(4)
C(11)-C(10)-C(9)	103.7(4)
C(12)-C(11)-C(10)	110.4(4)
C(12)-C(11)-C(21)	114.1(4)
C(10)-C(11)-C(21)	103.1(4)
C(13)-C(12)-C(11)	110.9(4)
C(14)-C(13)-C(18)	120.6(4)
C(14)-C(13)-C(12)	121.8(4)
C(18)-C(13)-C(12)	117.6(4)
C(15)-C(14)-C(13)	119.3(4)
C(16)-C(15)-C(14)	121.4(4)
C(16)-C(15)-Br(15)	119.3(4)
C(14)-C(15)-Br(15)	119.3(4)
C(17)-C(16)-C(15)	117.9(4)
C(16)-C(17)-C(18)	123.2(4)
C(16)-C(17)-Br(17)	117.2(4)
C(18)-C(17)-Br(17)	119.6(4)
N(19)-C(18)-C(17)	122.1(4)
N(19)-C(18)-C(13)	120.3(4)
C(17)-C(18)-C(13)	117.6(4)
C(18)-N(19)-C(10)	123.3(4)
C(9)-C(20)-C(21)	106.9(4)
C(11)-C(21)-C(20)	105.0(4)

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)
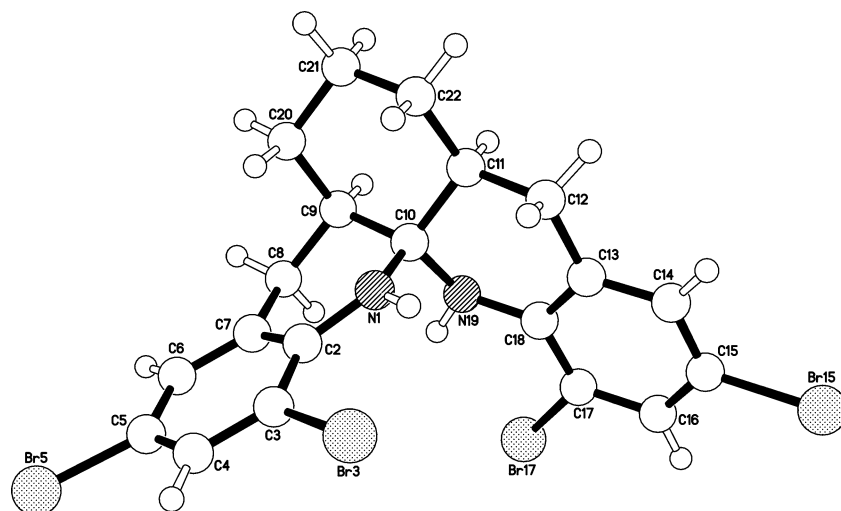
Formula $C_{20}H_{18}Br_4N_2$
Formula weight   606.00
Temperature   173(2) K
Diffractometer, wavelength   Agilent Xcalibur 3 E, 0.71073 Å
Crystal system, space group Triclinic, P-1
Unit cell dimensions   a = 8.6429(5) Å   a = 80.017(4)°
        b = 9.5129(5) Å   b = 72.909(5)°
        c = 12.9337(6) Å   g = 77.318(5)°
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
Reflns collected / unique   5645 / 3873 [R(int) = 0.0178]
Reflns observed [F>4s(F)]   3033
Absorption correction Analytical
Max. and min. transmission   0.272 and 0.151
Refinement method   Full-matrix least-squares on F2
Data / restraints / parameters 3873 / 2 / 244
Goodness-of-fit on F2 1.039
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

Table 2. Bond lengths [Å]

		Bond angles [°]	
N(1)-C(2)	1.384(4)	C(2)-N(1)-C(10)	122.1(3)
N(1)-C(10)	1.454(4)	N(1)-C(2)-C(3)	122.0(3)
C(2)-C(3)	1.398(5)	N(1)-C(2)-C(7)	120.4(3)
C(2)-C(7)	1.413(5)	C(3)-C(2)-C(7)	117.4(3)
C(3)-C(4)	1.379(5)	C(4)-C(3)-C(2)	122.2(3)
C(3)-Br(3)	1.893(4)	C(4)-C(3)-Br(3)	118.3(3)
C(4)-C(5)	1.371(5)	C(2)-C(3)-Br(3)	119.5(3)
C(5)-C(6)	1.375(5)	C(5)-C(4)-C(3)	118.7(3)
C(5)-Br(5)	1.896(4)	C(4)-C(5)-C(6)	120.9(3)
C(6)-C(7)	1.374(5)	C(4)-C(5)-Br(5)	119.2(3)
C(7)-C(8)	1.506(5)	C(6)-C(5)-Br(5)	119.9(3)
C(8)-C(9)	1.525(5)	C(7)-C(6)-C(5)	120.9(4)
C(9)-C(20)	1.536(5)	C(6)-C(7)-C(2)	119.7(3)
C(9)-C(10)	1.536(5)	C(6)-C(7)-C(8)	121.1(3)
C(10)-N(19)	1.469(4)	C(2)-C(7)-C(8)	119.3(3)
C(10)-C(11)	1.536(5)	C(7)-C(8)-C(9)	111.8(3)
C(11)-C(22)	1.520(5)	C(8)-C(9)-C(20)	110.6(3)
C(11)-C(12)	1.533(5)	C(8)-C(9)-C(10)	110.2(3)
C(12)-C(13)	1.512(5)	C(20)-C(9)-C(10)	110.8(3)
C(13)-C(14)	1.382(5)	N(1)-C(10)-N(19)	112.1(3)
C(13)-C(18)	1.410(5)	N(1)-C(10)-C(9)	109.1(3)
C(14)-C(15)	1.370(5)	N(19)-C(10)-C(9)	109.1(3)
C(15)-C(16)	1.377(5)	N(1)-C(10)-C(11)	110.3(3)
C(15)-Br(15)	1.896(4)	N(19)-C(10)-C(11)	106.5(3)
C(16)-C(17)	1.376(5)	C(9)-C(10)-C(11)	109.8(3)
C(17)-C(18)	1.398(5)	C(22)-C(11)-C(12)	111.4(3)
C(17)-Br(17)	1.896(4)	C(22)-C(11)-C(10)	112.8(3)
C(18)-N(19)	1.389(4)	C(12)-C(11)-C(10)	110.7(3)
C(20)-C(21)	1.517(5)	C(13)-C(12)-C(11)	113.0(3)
C(21)-C(22)	1.517(6)	C(14)-C(13)-C(18)	120.5(4)
		C(14)-C(13)-C(12)	120.1(3)
		C(18)-C(13)-C(12)	119.4(3)
		C(15)-C(14)-C(13)	120.5(4)
		C(14)-C(15)-C(16)	121.0(4)
		C(14)-C(15)-Br(15)	119.7(3)
		C(16)-C(15)-Br(15)	119.3(3)
		C(17)-C(16)-C(15)	118.4(4)
		C(16)-C(17)-C(18)	123.0(3)
		C(16)-C(17)-Br(17)	118.0(3)
		C(18)-C(17)-Br(17)	119.0(3)
		N(19)-C(18)-C(17)	122.0(3)
		N(19)-C(18)-C(13)	121.4(3)
		C(17)-C(18)-C(13)	116.6(3)
		C(18)-N(19)-C(10)	118.9(3)
		C(21)-C(20)-C(9)	112.6(3)
		C(22)-C(21)-C(20)	111.4(3)
		C(21)-C(22)-C(11)	111.2(3)

6.11 Crystal structure of dichloro(3-(3,4-dihydro-2H-pyrrol-5-yl)propan-1-amine)triphenylphosphineruthenium(II) dimer (340)
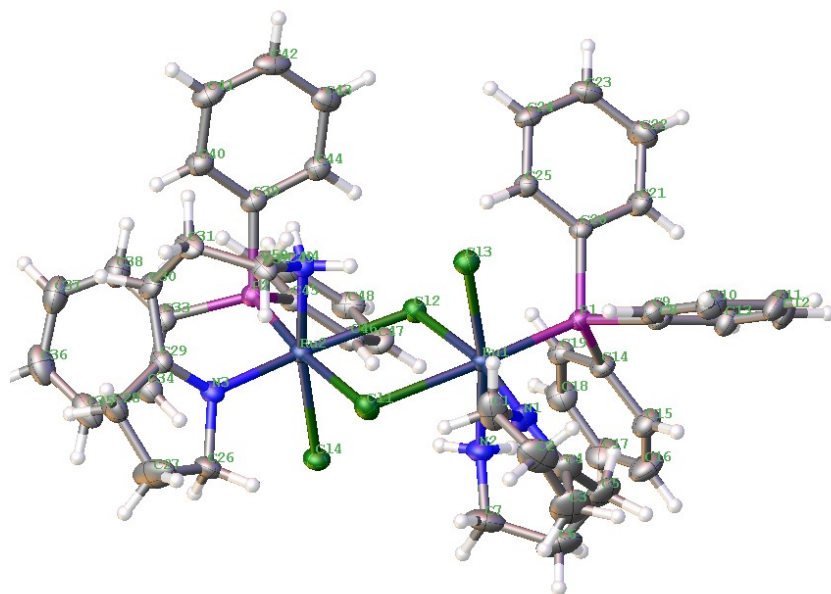
Empirical formula	$C_{50}H_{55}N_4P_2Ru_2$
Formula weight	1120.10
Temperature/K	293(2)
Crystal system	orthorhombic
Space group	Pbca
a/Å	17.494(4)
b/Å	19.879(4)
c/Å	27.534(6)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	9575(3)
Z	12
ρ_{calc}g/cm^3	1.5550
μ/mm^{-1}	0.961
F(000)	4563.7
Crystal size/mm^3	N/A × N/A × N/A
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	2.96 to 55.86
Index ranges	-11 ≤ h ≤ 11, -26 ≤ k ≤ 26, -35 ≤ l ≤ 35
Reflections collected	111614
Independent reflections	7829 [R_{int} = 0.0581, R_{sigma} = 0.0194]
Data/restraints/parameters	7829/0/575
Goodness-of-fit on F^2	1.051
Final R indexes [I>=2σ (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 Å^{-3}	0.65/-1.00

Bond lengths [Å]				Bond Angles [°]			
C1	C2	1.526(5)		N1	C1	C2	104.4(4)
C30	C31	1.535(5)		C3	C2	C1	103.8(4)
C1	N1	1.483(5)		C4	C3	C2	101.6(4)
C31	C32	1.524(5)		C5	C4	C3	122.0(4)
C2	C3	1.511(7)		N1	C4	C3	114.4(5)
C32	N4	1.476(5)		N1	C4	C5	123.3(3)
C3	C4	1.493(5)		C6	C5	C4	112.2(4)
C33	C34	1.402(5)		C7	C6	C5	113.7(4)
C4	C5	1.474(7)		N2	C7	C6	113.3(3)
C33	C38	1.389(5)		C13	C8	C9	118.9(3)
C4	N1	1.279(5)		P1	C8	C9	116.9(3)
C33	P2	1.845(3)		P1	C8	C13	123.9(3)
C5	C6	1.533(7)		C10	C9	C8	120.3(4)
C34	C35	1.390(4)		C11	C10	C9	120.5(4)
C6	C7	1.517(6)		C12	C11	C10	119.6(3)
C35	C36	1.367(6)		C13	C12	C11	120.7(4)
C7	N2	1.489(4)		C12	C13	C8	119.9(4)
C36	C37	1.385(6)		C19	C14	C15	117.4(4)
C8	C9	1.380(5)		P1	C14	C15	124.7(3)
C37	C38	1.398(5)		P1	C14	C19	116.4(3)
C8	C13	1.392(5)		C16	C15	C14	121.1(3)
C39	C40	1.390(5)		C17	C16	C15	120.4(4)
C8	P1	1.844(3)		C18	C17	C16	119.6(4)
C39	C44	1.398(4)		C19	C18	C17	120.1(3)
C9	C10	1.395(4)		C18	C19	C14	121.2(3)
C39	P2	1.852(4)		C25	C20	C21	118.6(3)
C10	C11	1.373(6)		P1	C20	C21	119.6(3)
C40	C41	1.397(5)		P1	C20	C25	121.8(2)
C11	C12	1.365(6)		C22	C21	C20	120.4(4)
C41	C42	1.382(5)		C23	C22	C21	120.2(3)
C12	C13	1.398(5)		C24	C23	C22	119.9(3)
C42	C43	1.367(6)		C25	C24	C23	120.1(3)
C14	C15	1.397(5)		C24	C25	C20	120.8(3)
C43	C44	1.391(5)		N3	C26	C27	105.0(3)
C14	C19	1.403(4)		C28	C27	C26	105.9(3)
C45	C46	1.383(5)		C29	C28	C27	102.1(3)
C14	P1	1.837(4)		C30	C29	C28	122.4(4)
C45	C50	1.407(4)		N3	C29	C28	114.2(3)
C15	C16	1.380(6)		N3	C29	C30	123.4(3)
C45	P2	1.857(4)		C31	C30	C29	112.8(3)
C16	C17	1.381(5)		C32	C31	C30	112.9(3)
C46	C47	1.391(5)		N4	C32	C31	113.3(3)
C17	C18	1.382(6)		C38	C33	C34	118.7(3)
C47	C48	1.384(5)		P2	C33	C34	115.8(3)
C18	C19	1.381(5)		P2	C33	C38	124.8(3)
C48	C49	1.382(6)		C35	C34	C33	119.9(4)
C20	C21	1.393(4)		C36	C35	C34	121.2(4)
C49	C50	1.381(6)		C37	C36	C35	119.6(3)
C20	C25	1.373(5)		C38	C37	C36	120.2(4)
N1	Ru1	2.078(2)		C37	C38	C33	120.4(4)
C20	P1	1.856(3)		C44	C39	C40	118.5(3)
N2	Ru1	2.128(3)		P2	C39	C40	124.7(2)
C21	C22	1.391(4)		P2	C39	C44	116.1(3)
N3	Ru2	2.078(3)					

C22	C23	1.374(6)	C41	C40	C39	120.8(3)
N4	Ru2	2.141(3)	C42	C41	C40	119.3(4)
C23	C24	1.368(5)	C43	C42	C41	120.9(3)
Ru1	P1	2.2528(9)	C44	C43	C42	120.0(3)
C24	C25	1.398(4)	C43	C44	C39	120.6(4)
Ru1	Cl1	2.5265(9)	C50	C45	C46	117.8(3)
C26	C27	1.501(6)	P2	C45	C46	122.9(2)
Ru1	Cl2	2.4269(8)	P2	C45	C50	119.3(3)
C26	N3	1.496(4)	C47	C46	C45	120.9(3)
Ru1	Cl3	2.4525(11)	C48	C47	C46	120.6(4)
C27	C28	1.502(6)	C49	C48	C47	119.2(4)
Ru2	P2	2.2472(9)	C50	C49	C48	120.3(3)
C28	C29	1.507(4)	C49	C50	C45	121.1(4)
Ru2	Cl1	2.5187(8)	C4	N1	C1	109.5(3)
C29	C30	1.476(5)	Ru1	N1	C1	119.1(2)
Ru2	Cl2	2.4256(8)	Ru1	N1	C4	130.2(3)
C29	N3	1.283(5)	Ru1	N2	C7	120.2(3)
Ru2	Cl4	2.4441(10)	C29	N3	C26	109.4(3)
			Ru2	N3	C26	119.4(3)
			Ru2	N3	C29	130.4(2)
			Ru2	N4	C32	119.32(19)
			N2	Ru1	N1	92.13(12)
			P1	Ru1	N1	100.14(8)
			P1	Ru1	N2	94.41(10)
			Cl1	Ru1	N1	86.43(8)
			Cl1	Ru1	N2	82.36(10)
			Cl1	Ru1	P1	172.83(3)
			Cl2	Ru1	N1	168.53(8)
			Cl2	Ru1	N2	83.39(8)
			Cl2	Ru1	P1	90.76(3)
			Cl2	Ru1	Cl1	82.52(2)
			Cl3	Ru1	N1	90.11(10)
			Cl3	Ru1	N2	171.10(10)
			Cl3	Ru1	P1	93.67(3)
			Cl3	Ru1	Cl1	89.19(3)
			Cl3	Ru1	Cl2	92.79(3)
			N4	Ru2	N3	92.45(12)
			P2	Ru2	N3	99.52(7)
			P2	Ru2	N4	95.25(8)
			Cl1	Ru2	N3	86.63(7)
			Cl1	Ru2	N4	81.91(8)
			Cl1	Ru2	P2	173.37(3)
			Cl2	Ru2	N3	168.88(7)
			Cl2	Ru2	N4	82.98(8)
			Cl2	Ru2	P2	91.01(3)
			Cl2	Ru2	Cl1	82.71(2)
			Cl4	Ru2	N3	90.65(10)
			Cl4	Ru2	N4	169.57(8)
			Cl4	Ru2	P2	94.05(3)
			Cl4	Ru2	Cl1	88.34(3)
			Cl4	Ru2	Cl2	92.16(3)
			C14	P1	C8	105.15(16)
			C20	P1	C8	99.80(13)
			C20	P1	C14	101.08(15)
			Ru1	P1	C8	119.04(11)

Ru1	P1	C14	110.81(10)
Ru1	P1	C20	118.67(11)
C39	P2	C33	106.36(16)
C45	P2	C33	96.74(15)
C45	P2	C39	100.11(15)
Ru2	P2	C33	119.32(11)
Ru2	P2	C39	111.79(10)
Ru2	P2	C45	119.83(11)
Ru2	Cl1	Ru1	94.85(3)
Ru2	Cl2	Ru1	99.93(3)

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"One must imagine Sisyphus happy."

Albert Camus