UNIVERSITY OF BIRMINGHAM

School of Chemistry

Synthesis of azetidines, γ-lactams, fused furan bispyrrolidines and 2-pyrazolines:

Towards medical application

By

Mariwan A. Hama Salih

A thesis submitted to the University of Birmingham for the degree of

DOCTOR OF PHILOSOPHY

Project supervisor: John S. Fossey

Co-Supervisor: Ferenc Mueller

September 2015

Contents

Acknowledgments

First, I would like to thank my supervisor Dr. John S. Fossey for providing invaluable advice and guidance toward the success of the research project throughout the period of my study in his laboratory.

Special thanks for Human Capacity Development Program in Kurdistan Regional Government (HCDP-KRG) for funding.

I would like to thank [redacted] and [redacted] for collaboration in biological activity screening.

Many thanks are due to Antonio Feula for his help when I first started working on this project.

Special thanks to all members of JSF group present and past to accept work with in all circumstance. Thanks are due to Dr. John Fossey, Daniel Payne, William Britain, Dr. Glenn Lees, Wenlie Zhai, Akina Yoshizawa and Xingjian Li for their comments on writing the thesis.

I wish to express my grateful to the analytical facility for their assistance, especially Dr. Neil Spencer for NMR spectroscopy and Mass spectroscopy, Dr. Louise Male for X-Ray Crystallography and Dr. Chi Tsang for HPLC assistance.

Finally, I would like to express my deepest thanks to my family, sisters and brothers, most importantly, my mother, who I missed all the time, for their patience and continuous encouragement during my study.

This thesis was copy edited for improve language, spelling, grammar and punctuation by proofreading Birmingham team.

Dedicated

To

My beloved Mother

Abbreviations

Bn: benzyl

CAN: ceric ammonium nitrate

Cy: cyclohexyl

DCM: dichloromethane

DMSO: dimethyl sulfoxide

DMF: *N*, *N*- dimethylformamide

DDQ: 2,3-dichloro-5,6-dicyano-1,4-benzoqunone

DIPA: diisopropylamine

DMAP: *N*,*N*-dimethyl aminopyridine

DIEA: diisopropyl ethylamine

DMB: dimethoxybenzyl

DMI: dimethyl imidazolidinone

EtOAc: ethyl acetate

HRMS: high-resolution mass spectra

hpf: hours post fertilisation

LiHMDS: lithium hexamethyldisilylazide

NBS: *N*-bromosuccinamide

NIS: *N*-iodosuccinamide

PPTS: pyrimidinium *p*-toluene sulfonic acid

Pr: propyl

Pyr: pyridine

r.t.: room temperature

TsOH: *p*-toluene sulfonic acid

TEA: triethylamine

THF: tetrahydrofuran

TS: transition state

Abstract

Azetidines have played a significant role in the medicinal arena for many years, and azetidine core is an important building block for the synthesis of β-lactam antibiotics. In this project, a review of the chemistry and literature synthetic routes for azetidine synthesis and its application in organometallic chemistry and medicine was presented. Additionally, the chemistry of γ-lactams, fused tricyclic systems and pyrazolines was discussed. The scope of the iodocyclisation protocol was expanded by introducing heterocyclic and bulky substituents, and through generating azetidine derivatives in good yields. The studies of the iodocyclisation procedure on various homoallylamine derivatives for the synthesis of new heterocyclic compounds for medical applications were presented.

The formation of γ-lactam derivatives in 34-99% yields, as a mixture of diastereomers from iodocyclisation of 3-methyl substituted homoallylamines was described. In addition, the structure and relative stereochemistry of nine single diastereomers were confirmed by single crystal X-ray diffraction. When 3-phenyl substituted homoallylamines were cyclised, intriguing furan bispyrrolidines were obtained stereoselectively in 20-48% yields. Their identity confirmed by X-ray diffraction analysis.

The iodocyclisation of homoallylhydrazine was investigated and a new synthetic method was estabilished to prepare a library of novel pyrazoline derivatives in 61-86% yields.

Intriguing biological responses such as brain haemorrhage and ten other biological features for nine of the synthesised mixture of diastereomers of pyrrolidin-2-ones in zebrafish embryos developmental assays were presented.

Aim of the project

The main goal of this project is to synthesise multi-substituted azetidines from the iodocyclisation of various substituted homoallylamines using the recently established iodocyclisation methodology in Fossey research group, and to study the effect of substitution on regioselectivity of cyclisation of homoallylamines. In addition, the study aims to investigate the synthesis of azetidines or pyrazolidines that could be accessed from the iodocyclisation of homoallylhydrazines, and provide a new synthetic route for their synthesis.

Furthermore, the biological activity of the synthesised compounds is to be investigated in zebrafish developmental assay to provide an early indication of the activity of these compounds in medical arenas.

The substrate scope of the previous work for the synthesis of racemic and enantiopure azetidines from iodocyclisation of racemic and enantiopure homoallylamines will be investigated.

Chapter One

Introduction

1. Introduction

1.1 Azetidine

Azetidine **1** is a four membered saturated heterocyclic nitrogen-containing compound. Azetidine derivatives are an important class of organic compounds in synthetic organic chemistry for drug design, natural products and alkaloids synthesis.[1] Azetidine-2-carboxylic acid **2**,[2] is an analogue of proline, it can be found in the leaves of *Convallarinmajalis*. Sphingosine-derived azetidine alkaloid penaresidin A (**3**) and B (**4**) were extracted from an Okinawan marine sponge[3], and they have been found to be potent actomyocin ATPase activators.

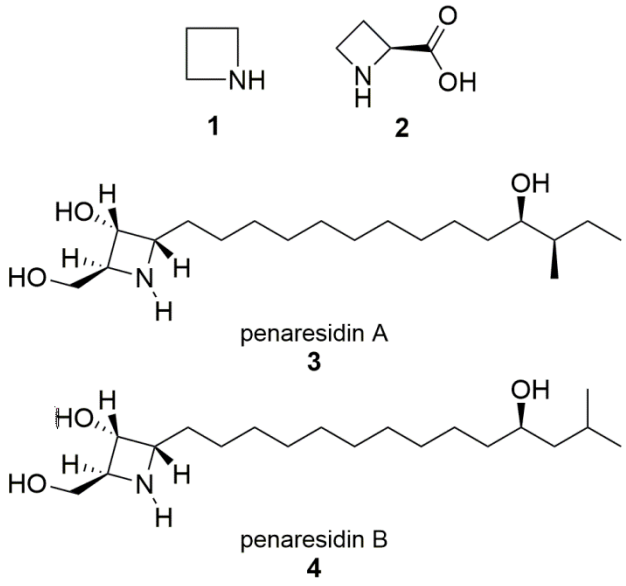


Figure 1: Azetidine and azetidine-containing natural products and alkaloids

Azetidine derivatives are important intermediates for the synthesis of numerous polyamine ligands.[4] Moreover, azetidine derivatives can be used to synthesise metal complexes (Figure 2),

such as chiral ligand **5**, used in asymmetric diethyl zinc additions to aldehydes.[5] It has been found that azetidines could be good ligands for metal complexes such as palladium **7**,[6] and cobalt **6**,[1,4] in catalysis.

The synthesis of azetidines derivatives was challenging due to the unfavourable high energy strained nature of transition states that leads to four-membered rings, [7,8] this makes them difficult and problematic to form. It has also been found that due to the facile ring opening, it is difficult to obtain a high yield of the desired azetidine products.[8] Therefore, the synthesis of azetidine derivatives still needs tobe further developed in order to improve yields and applications.

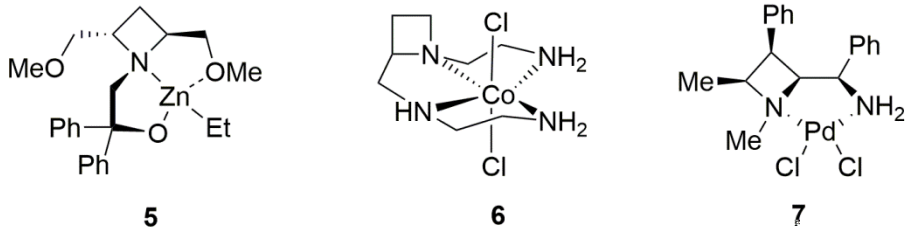


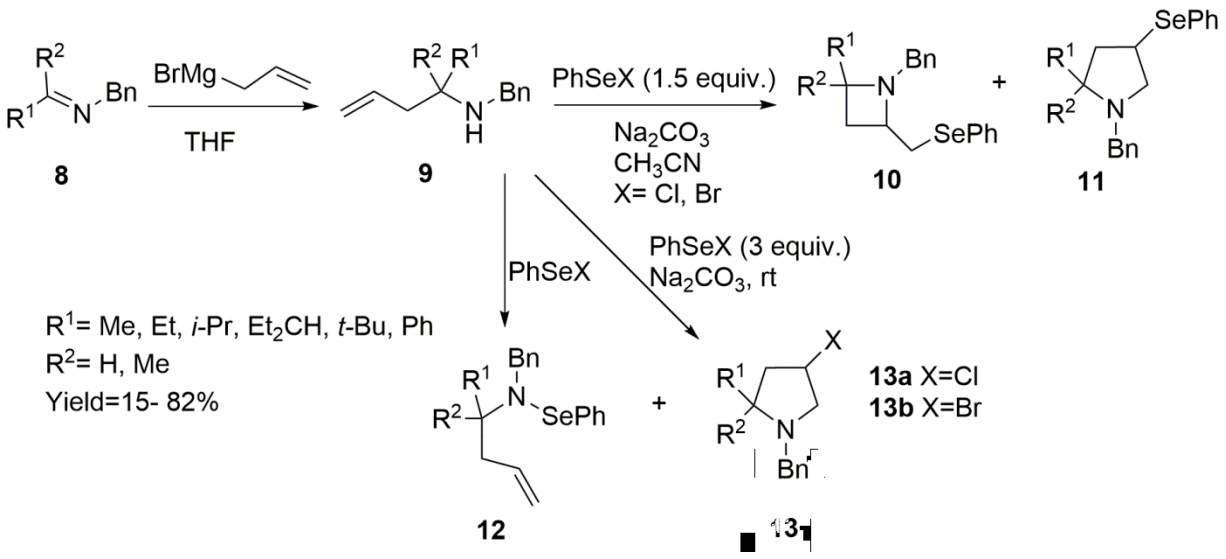
Figure 2: Azetidine metal complexes

1.1.1 Synthesis of azetidine derivatives

Several reports have been published concerning the synthesis of azetidine derivatives.[9] Herein, some of the methods for synthesis and applications in other areas of science, such as medicine, agrochemistry[10] and organometallic chemistry are discussed, along with limitations, such as a low yield for certain azetidine derivatives. In addition, low selectivity, or isomerisation are also discussed.

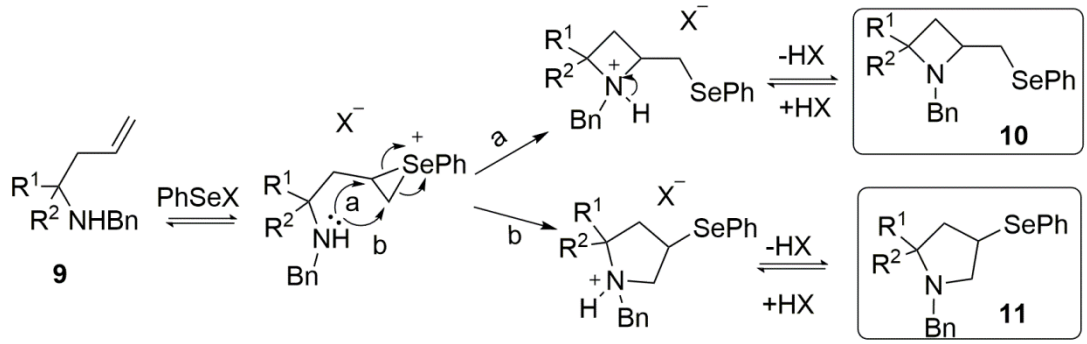
1.1.1.1 Azetidine synthesis *via* selenium-induced cyclisation of homoallylamine derivatives.

Azetidines can be generated from electrophilic cyclisation of homoallylamines *via* 4-*exo*-tet ring cloure.[11] Berthe *et al.*[12] reported an efficient synthetic route to produce 1,2,4-trisubstituted azetidines **10** through a 4-*exo*-tet cyclisation process (Scheme 1). The authors demonstrated that selenium-induced cyclisation of homoallylbenzylamines **9** in acetonitrile at room temperature can deliver a mixture of azetidine **10** and pyrrolidine **11** in 70-100% conversions. When homoallylbenzylamines derived from ketimines were used, the azetidines **10** were isolated as the major products, especially in the case of sterically hindered R groups on the α-carbon. When three equivalents of selenide were used, pyrrolidine compounds **13** were obtained as the major products. The limitations of this methodology include the formation of mixtures of products, which leads to poor yields of azetidines. In the absence of a sufficient amount of selenium reagent, incomplete cyclisation leads to compound **12**, which is hydrolysed during the work up to the corresponding amine **9**. This selenium reagent method benefits from the ready availability of starting materials and the wide scope in terms of the different imines that can be made and used.



Scheme 1: Selenium-induced cyclisation of homoallylamines at room temperature and acetonitrile[11]

The nature of the counter ion (X=Cl or Br, Scheme 1), was found to have a major effect on the ratio of azetidine to pyrrolidine. Only azetidine **10** was produced, when X=Br, but the isolated yield was low. Steric hindrance around α-carbon can affect the result, as in the case of (R^1=Me, R^2=Ph) only azetidine **10** was observed as the major product.

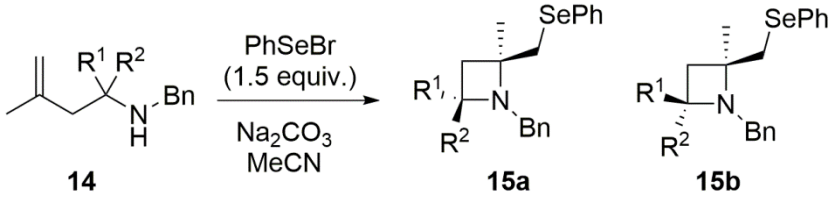


Scheme 2: Reaction mechanism of selenium-induced cyclisation of homoallylamines

The suggested reaction mechanism for both possible products, azetidine and pyrrolidine, include electrophilic addition to the alkenes, followed by two possible pathways for cyclisation (an

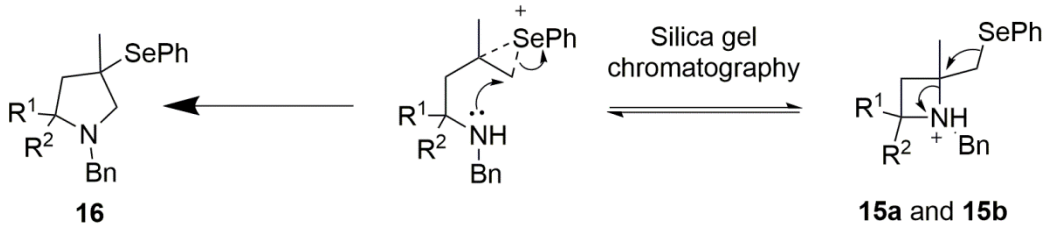
overall 4-*exo*-tet (a) or an overall 5-*endo*-tet (b) cyclisation pathway) which are shown in Scheme 2. The stereochemistry at C2 and C4 of the synthesised azetidine **10** and pyrrolidine **11** were not assigned, and the synthesis of pyrrolidine **11** was direct from cyclisation of homoallylamine **9**, and not *via* ring expansion of azetidine **10**.

The synthesis of a mixture of (*cis*/*trans*)-2,4-azetidines has been reported by Franck *et al*.[8] from the cyclisation of β-methyl substituted homoallylamines **14** using electrophilic selenium bromide. Selenium induced cyclisation of compound **14** can deliver a mixture of (*cis*/*trans*)-azetidines (**15a** and **15b**) in a>80:20 ratio (Scheme 3).



Scheme 3: Selenium mediated cyclisation of methyl substituted homoallylamine

The synthesised azetidines **15a** and **15b** apparently underwent partial acid catalysed isomerisation during silica column purification to deliver pyrrolidine **16**. An addition of 1% TEA and the use of alumina for purification were found to be effective for avoiding such isomerisation (Scheme 4).

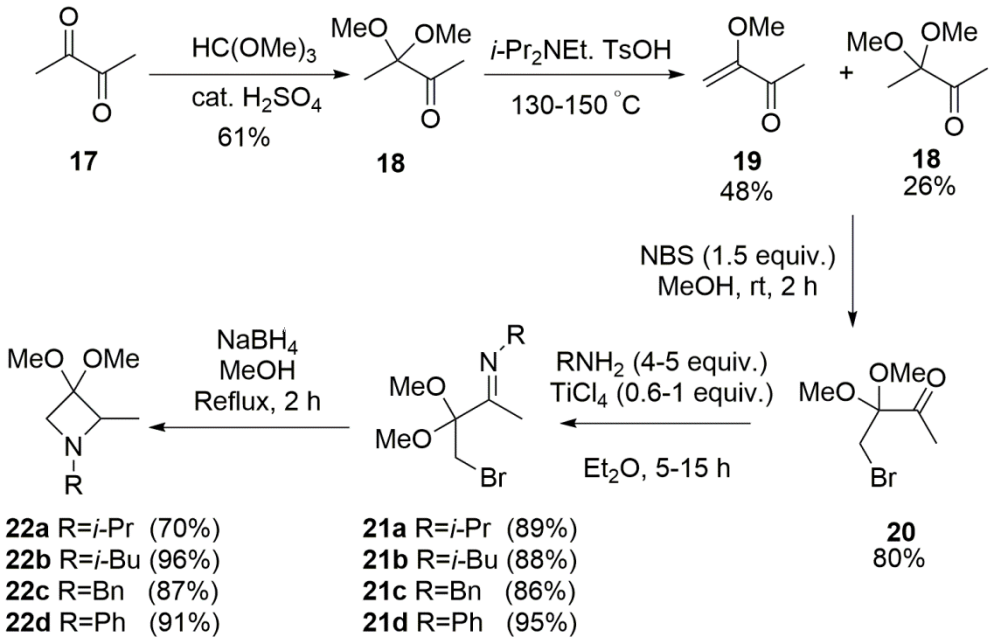


Scheme 4: Acid-catalysed isomerisation of azetidine to pyrrolidine

The yield of **15a** and **15b** were found to be increased with increasing the size of R groups, when R^1=Me to *t*-Bu and R^2=H, the yield was increased from 45% to 68%. When R^1=R^2=H the yield was 35%, and a higher yield was obtained when R^1=R^2=Me (72%).

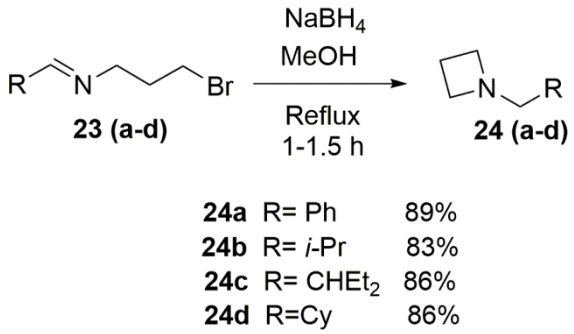
1.1.1.2 Azetidine synthesis *via* reductive cyclisation of imines.

Different research groups have studied the synthesis of azetidines from reductive cyclisation of halogenated imines. Salgado and co-workers[13] proposed that 1,2,3-substituted azetidines (**22a-d**) could be obtained in moderate to high yields from the reductive cyclisation of imines (**21a-d**) using sodium borohydride in refluxing methanol. The reaction starting from selective acylation of readily available diketone **17** to obtain compound **18**, followed by pyrolysis of compound **18** at 130-150 $^{\circ}$C resulted in the formation of enol ether **19** in only 48% yield and recovery of 26% of unreacted **18**. The mixture was treated with 1.5 equivalents of NBS to form 4-bromo-3,3-dimethoxy-2-butanone **20** in an 80% isolated yield. Compounds **21a-d** were synthesised though the reaction of compound **20** with various amines (aliphatic and aromatic). The conditions for some aromatic amines and sterically bulky amines were changed to obtain higher yields. The reductive cyclisation of **21a-d** with two equivalents of sodium borohydride in methanol afforded 1-alkyl-2-methyl-3,3- dimethoxyazetidines **22a-d** in good to excellent yields (Scheme 5).



Scheme 5: Synthesis of azetidines from reductive cyclisation of imines

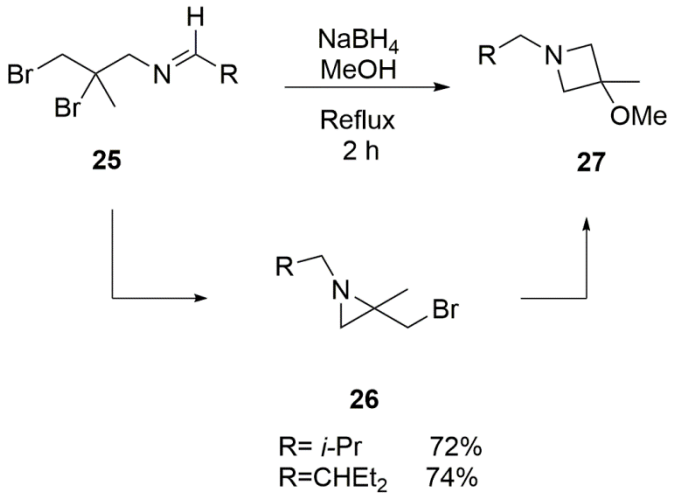
In the cyclisation step, the reaction conditions were changed in order to drive the reaction to completion. For sterically bulky substituents, such as *i*-Bu in **21b**, two equivalents of sodium borohydride were used. In this method, multiple complicated steps were needed to produce azetidines. *N*-Substituted azetidines **24a-d** can be synthesised *via* reductive cyclisation of γ-haloalkyl-imines **23a-d**. Reductive cyclisation of imines were reported previously in 1994 by De Kimpe *et al.*[14], where the synthesis of *N*-substituted azetidines **24a-d** was achieved by treatment of γ-haloalkyl-imines **23a-d**, with an equimolar amount of sodium borohydride in refluxing methanol to form amine, which then intramolecularly cyclised to generate compounds **24a-d** in high yields (Scheme 6).



Scheme 6: Synthesis of azetidines *via* reductive cyclisation of imines

The authors presented that the addition of alkyl and aryl lithium reagents to imines and then subsequent cyclisation in THF at -78 °C could deliver alkyl or aryl substituted azetidines on the benzylic position.

In 2011, De Kimpe and co-workers[15] reported that 3-methoxyazetidines **26** could be synthesised *via* an aziridine to azetidine ring rearrangement upon treatment of *N*-alkylidene-(2,3-dibromo-2-methylpropyl) amines **25** with sodium borohydride through the reductive cyclisation of imines in methanol under reflux conditions (Scheme 7). The authors unexpectedly found that the highly substituted azetidine compounds **24a-d** could be synthesised by variation of the R group. However, the isolated yields were poor due to the unexpected isomerisation that resulted in the formation of three membered rings. This side reaction proceeds through the kinetic aziridines product were followed by ring rearrangement to the thermodynamic azetidines product **27**.



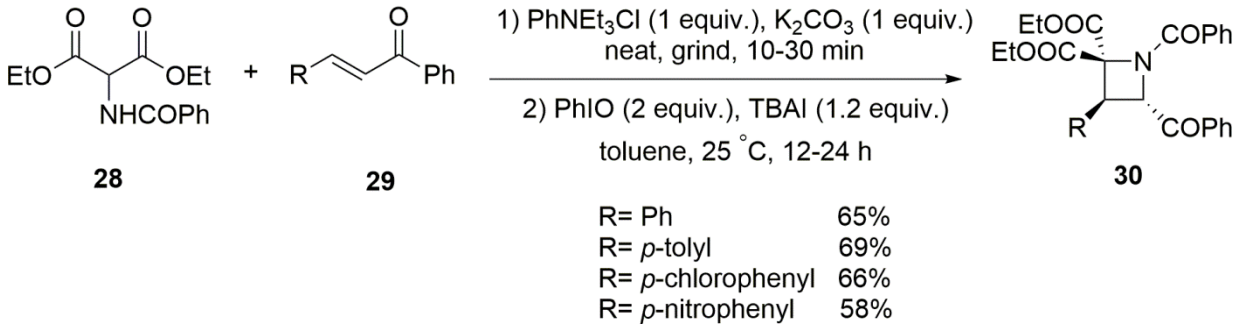
Scheme 7: Synthesis of 3-methoxyazetidine *via* an aziridine to azetidine rearrangement

The reaction of imine **25** proceeds through reduction was followed by subsequent cyclisation *via* an S_N2 mechanism to give aziridine **26**, and finally thermal ring expansion afforded azetidine **27**. This study was not investigated the aromatic substituents on the nitrogen atom to furnish the desired azetidine product, also the undesired ring rearrangement was found to reduce the isolated yield.

1.1.1.3 Azetidine synthesis *via* [2+2]-cycloaddition of 2-aminomalonate.

Ye *et al.*[16] have developed an efficient two-step procedure for the synthesis of highly functionalised chiral azetidines **30** from a [2+2]-cycloaddition of amide protected 2-aminomalonates **28** with two equivalents of chalcones **29**. The reaction proceeds *via* a grind-generation of a Micheal adduct and a subsequent oxidative cyclisation at room temperature to furnish azetidine **30** (Scheme 8). Highly functionalised azetidines containing two stereogenic centres **30**, were synthesised in moderate to good yields (46-75%) and high diastereoselectivitiy (*anti: syn* >95:5). Moreover, it was found that electronic effects of the substituent on the

chalcones played an important role on the reaction outcome. For example, *p*-tolyl and *p*-chloro substituted chalcones produced 69% and 66% yields, respectively, while strongly electron-withdrawing substituent (*p*-nitro) only produced 58% azetidine. The addition of an ammonium salt $PhNEt_3Cl$ as a catalyst was found to increase the yield of Michael adduct up to 90%. In contrast, changing the catalyst to a bulkier one such as $BuNEt_3X$ (X= Br, I) decreased the yield of the Michael adduct 64-18%, respectively. In the case of $BuNEt_3Cl$, the expected azetidine was not obtained.

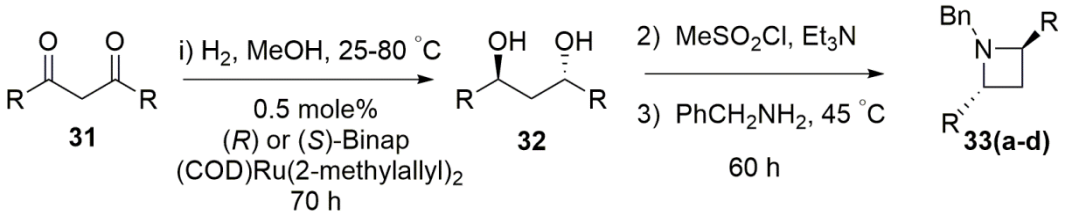


Scheme 8: [2+2]-Cycloaddition to synthesis of highly functionalised azetidines.

1.1.1.4 Azetidine synthesis *via* cyclisation of 1, 3-diol.

Marinetti *et al.*[17] reported a stereoselective synthesis of symmetrically 2,4-disubstituted azetidines (**33a-d**) from optically pure 1,3-diols **32** which are prepared from 1,3-diketones **31** by selective hydrogenation at room temperature in the presence of (*R*) or (*S*)-BINAP as a catalyst. The hydroxyl groups were converted to good leaving group by mesylation in TEA and then the crude material was treated with benzylamine nucleophile, were a subsequent cyclisation leds to corresponding azetidines (**33a-d**) in moderate to high yields (60-85%) and high enantiomeric

excess >95% *ee* (Scheme 9). The synthesised azetidine compounds (**33a-d**) could be employed in the preparation of cyclopalladated complexes (Scheme 26).



Scheme 9: Synthesis of chiral 2,4-disubstituted azetidines.

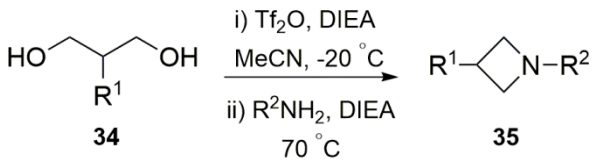
Variation of the R group on **31** caused small changes in the product yields (Table 8). The selectivity was not changed by changing the R group from R=Me, Et and *n*-Pr (Table 1, entries 1, 2 and 3), but when R is an aromatic substituent (Table 1, entry 4), the selectivity was inverted. Variations of *N*-substituents instead of benzyl group were not studied to explore their roles.

Table 1: Synthesised chiral 2,4-disubstituted azetidines

Entry	Compound	R	% *ee*	%yield
1	**31a**	Me	>95(*R*,*R*)	60
2	**31b**	Et	>95(*R*,*R*)	70
3	**31c**	*n*-Pr	>95(*R*,*R*)	85
4	**31d**	Bn	>95(*S*,*S*)	65

Hillier *et al.*[18] reported a one-pot preparation of 1,3-disubstituted azetidines **35** by treatment of 1,3-propane diols **34** with trifluromethanesulfonic anhydride, converting the hydroxyl groups to good leaving groups followed by treatment of the resulting bis-triflates with primary amine

nucleophile *via* intramolecular cyclisation of secondary amine to the triflate leaving group modified carbon to form 1,3-disubstituted azetidines **35** (Scheme 10).



Scheme 10: Azetidine formation *via* bis-triflate activation

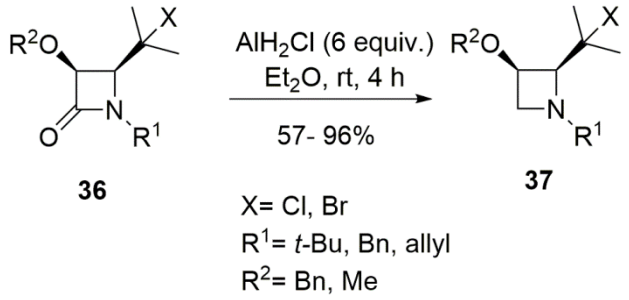
Various substituents at R^1 were studied, and they were found to be intramolecularly cyclised to furnish 1,3-disubstituted azetidines **35** in good to excellent yields (64-92%). When sterically bulky *tert*-butyl at R^1 used (Table 2, entry 5) isolated yield was slightly reduced to (86%). The variation of R^2 using various amine nucleophiles was not studied in detail.

Table 2: Synthesised 3-substituted azetidines

Entry	Compound	R^1	R^2	% yield
1	**34a**	H	$(Ph)_2CH$	64
2	**34b**	Me	Ph	64
3	**34c**	Ph	Bn	92
4	**34d**	OBn	Bn	92
5	**34e**	*t*-Bu	Bn	86

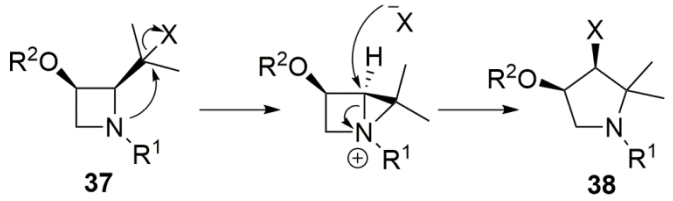
1.1.1.5 Azetidine synthesis *via* reduction of azetidine-2-one.

Chiral haloalkyl azetidines **37** can be synthesised from the reduction of azetidin-2-one **36**. In 2006, Van Brabandt and co-workers[19] reported the reduction of 4-haloalkyl-azetidines by using six equivalents of chloroalane (AlH_2Cl) prepared *in situ* from $AlCl_3$ and $LiAlH_4$ affording new 2-(haloalkyl)azetidines **37** in moderate to high yields 57-98% (Scheme 11). Ring rearrangement was observed at elevated temperature, which reduced the isolated yield of **37**. The authors suggested reactions at room temperature would avoid ring expansion, since rearrangement only occurs at a higher temperature (Scheme 12).



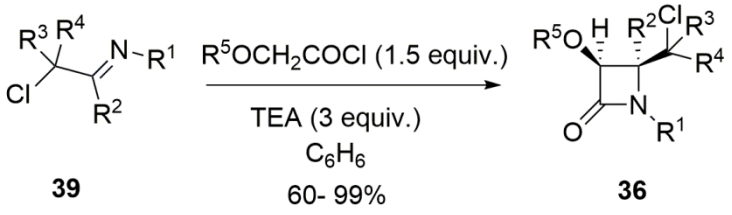
Scheme 11: Synthesis of 2-(haloalkyl) azetidines *via* reduction of 4-(haloalkyl)azetidin-2-ones[18]

The azetidine derivatives synthesised from this route could be useful starting materials for the synthesis of five-membered aza-heterocycles **38** *via* the bicyclic azetidinium ion intermediate formed through rearrangements of the azetidine derivatives **37** without changing the relative stereochemistry (Scheme 12).



Scheme 12: Azetidine ring rearrangement

The limitations of this method lie in the formation of the starting material azetidin-2-one **36**, which involves three steps, starting from the synthesis of imines, α-chlorination of imines and then cyclo condensation of the α-chloroimines **39** with methoxy- or benzyloxyacetyl chloride in the presence of TEA as a base, and benzene at room temperature (Scheme 13).[20]

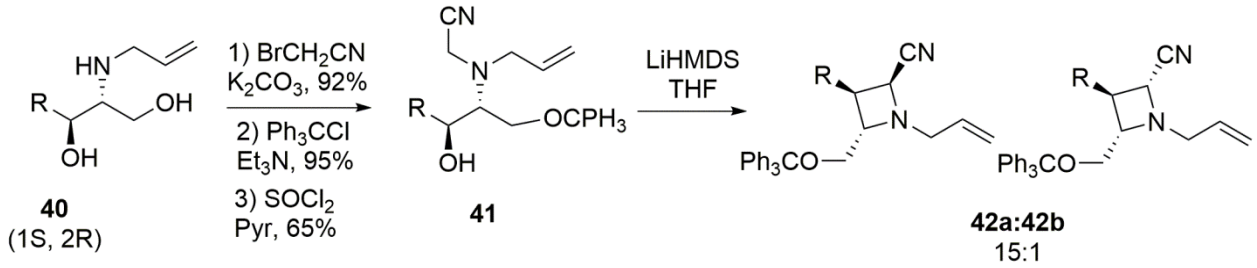


Scheme 13: Reaction of α-chloroimines with acetyl chloride derivatives

1.1.1.6 Miscellaneous methods for synthesis of azetidines:

The densely functionalised epimeric mixture of 2-cyanoazetidine **(42a** and **42b**) is produced starting from β-amino alcohol **40**. Lowe *et al*.[21] presented a four steps synthetic route for the synthesis of chiral azetidines (**42a** and **42b**). This included *N*-alkylation of the secondary amine by treatment of **40** with bromoacetonitrile in the presence of inorganic base to give **41** (R=H) in

high yield (92%). Then the primary alcohol was protected with retention of configuration by treatment with triphenylmethyl chloride in the presence of TEA. Then deprotonation of the α-carbon and subsequent intramolecular cyclisation of **41** by treatment with LiHMDS gave **42a** and **42b** (Scheme 14).



Scheme 14: Azetidine synthesis through β–amino alcohols

The synthesised azetidine compounds could functionalise to provide access to the synthesis of a variety of higher ring systems, such as fused rings, or spirocyclic azetidine compounds. *In silico* analysis means computational simulation of the molecule, which includes calculation of physicochemical properties, such as molecular weight, cLogP, pKa, and HB acceptors and donors. These values for all the synthesised compounds fell in the range of the corresponding CNS drugs. The drawback of this synthetic route is the availability of the starting materials that are not commercially available, and hence needed to be synthesised, which in turn increased the number of steps in an already long synthetic route.

1.1.2 Baldwin rule of ring closure

In 1976, Baldwin[11] suggested three rules for ring closing process and forming ring system. This process is more likely described in three rules: In the tetrahedral systems, only 3- to 7-*exo*-tet are all favoured (Figure 3, i and ii) and 5- to 6-*endo*-tet are disfavoured (Figure 3, iv). In the trigonal

systems, all 3- to 7-*exo*-trig are favoured and 3- to 5-*endo*-trig are disfavoured but 6- to 7-*endo*-trig are favoured. In diagonal systems 3- to 4-*exo*-dig are all disfavoured, but 5- to 7-*exo*-dig and 3- to 7-*endo*-dig are favoured.

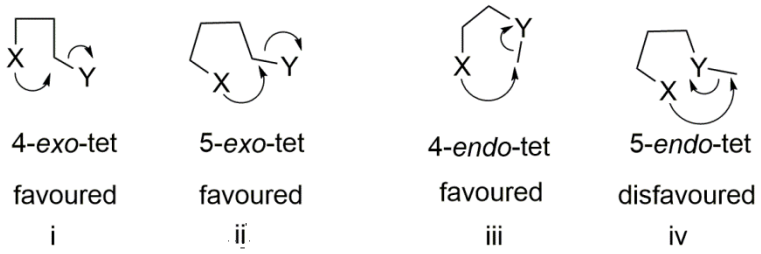
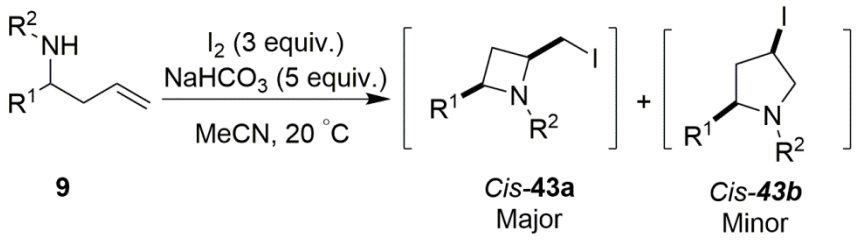


Figure 3: Four and five-member ring forming system according Baldwin rule

Recently our research group has been focusing on the synthesis of azetidines and pyrrolidines for application in both medicinal chemistry and catalysis. A recent report from Feula *et al.*[22] presented a new protocol for the synthesis of 1,2,4-trisubstituted azetidines **43a** bearing a good leaving group, which could be displaced with another nucleophile. This new procedure consists of iodine-mediated cyclisation of homoallylamines through 4-*exo*-tet ring closure system,[11] which requires three equivalents of iodine and five equivalents of $NaHCO_3$ in acetonitrile as a solvent at 20 °C. A racemic mixture of *cis*-iodoazetidines **43a** was obtained as the major product plus trace iodopyrrolidine **43b** as the minor product when the temperature was controlled at less than 20 °C. Iodoazetidines **43a** were not stable above 20 °C. Ring expansion to five membered rings proceeds with ease above 20 °C (Scheme 22). Iodoazetidines can undergo further transformation with different nucleophile to displace iodine and form more stable *cis*-aminoazetidines **44a-o** in a high yield (Table 4). This procedure can be employed for synthesising a wide range of azetidine derivatives.



Scheme 15: Iodine mediated cyclisation of homoallylamine derivatives

It was found that the undesired isomerisation of iodoazetidines occurs during cyclisation of the homoallylamines to form iodopyrrolidine instead of iodoazetidine. Such isomerisation could be avoided by controlling the temperature. Another limitation is the synthesis of 3-substituted azetidines and multi-substituted azetidines, which was not addressed. However, the scope was expanded by changing the R groups by varying the aldehyde and amine sources. The ratio of azetidines to pyrrolidines was found to be R^1 and R^2 substituents dependent. For example, using electron releasing substituents and electron withdrawing substituents at R^2 produced azetidines as the major products, but in different ratios (Table 3).

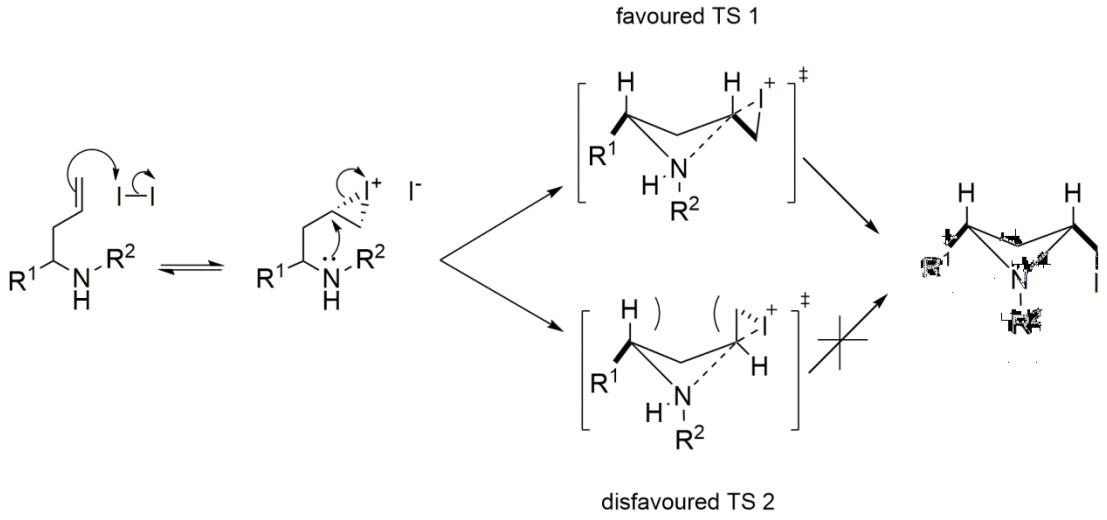
Table 3: Synthesised iodoazetidines *via* iodocyclisation of homoallylamines

Entry	Compound	R^1	R^2	43a:43b[a]	% yield[b]
1	**43a**	Ph	Bn	>99:1	86
2	**43b**	Ph	4-Methoxybenzyl	>99:1	85
3	**43c**	Ph	4-Methylbenzyl	>99:1	93
4	**43d**	3-Pyr	Bn	5:1	91
5	**43e**	4-Pyr	Bn	5:1	95
6	**43f**	4-Nitrophenyl	Bn	3:1	90
7	**43g**	2-Bromophenyl	Bn	3:1	83
8	**43h**	*t*-Bu	Bn	>99:1	87

(a) Conversion based on ^{1}H NMR spectroscopy,(b) yield after purification

It was found that the ratio of azetidine to pyrrolidine is R group dependant (Table 3), which means that the ratio could be varied by replacing phenyl substituent at R^1 and introducing electron withdrawing substituent. For example when R^1=phenyl and 4-nitrophenyl (Table 3, entries 1, 2, 3 and 6) respectively, azetidine *cis*-**43a** was obtained as the major product (>99:1) and the ratio of azetidine was reduced to (3:1) when R=4-nitrophenyl was used. When heterocyclic substituents at R^1 were used (Table 3, entries 4 and 5), the ratio was slightly higher (5:1). Higher yield and selectivity were achieved when substituents R^1 and R^2 were phenyl and benzyl groups respectively (Table 3, entry 1) which also gave a higher conversion with minimum isomerisation (>99:1). The author showed that only *cis*-isomer was formed, as confirmed by nOe and X-ray single crystal structures.

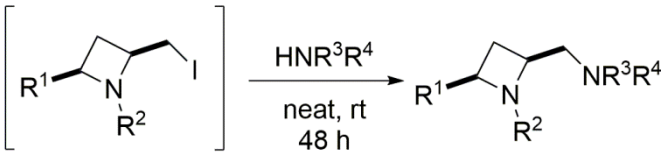
The proposed reaction mechanism and butterfly-like transition states (Scheme 16) are explain the formation of the four membered azetidine rings. At least two possible transition states were suggested to generate azetidine, the transition state TS1 is most favoured because the protons are in the pseudo 1,3-diaxial position, while the transition state TS2 is disfavoured due to an increase in pseudo 1,3-diaxial interaction.



Scheme 16: Reaction mechanism and transition states for azetidine synthesis

This procedure was found to be highly applicable to the synthesis of various new aminoazetidines compounds by simple S_N2 substitution of iodide with different amine nucleophile and it is applicable to alkyl, aryl, heterocycle, and bulky groups (Table 4). Formations of aminoazetidines *cis*-**44a-o** were found slightly affected by changing the amines in the last step. This difference can be explained by employing primary and secondary amines and using the correct method of purification, including number of flash column chromatography attempted and using correct eluent.

Table 4: Synthesised aminoazetidines derivatives



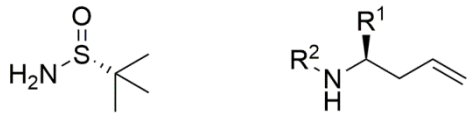
***Cis*-43(a-o)** ***Cis*-44(a-o)**

Entry	Compound	R^1	R^2	R^3	R^4	% yield[a]
1	**44a**	Ph	Bn	Bn	H	86
2	**44b**	Ph	Bn	*n*-Pr	H	87
3	**44c**	Ph	Bn	*i*-Pr	H	69
4	**44d**	Ph	Bn	Pipyridine		83
5	**44e**	Ph	Bn	Morpholine		71
6	**44f**	Ph	Bn	Pipyrazine		81
7	**44g**	Ph	Bn	4-Methoxybenzyl	H	78
8	**44h**	Ph	4-Methoxybenzyl	*n*-Pr	H	74
9	**44i**	Ph	4-Methylbenzyl	Bn	H	75
10	**44j**	3-Pyr	Bn	Bn	H	72
11	**44k**	3-Pyr	Bn	2-hydroxyethyl	H	82
12	**44l**	3-Pyr	Bn	Pyrrolidine		76
13	**44m**	4-Pyr	Bn	Bn	H	71
14	**44n**	4-Bromophenyl	Bn	Bn	H	65
15	**44o**	*t*-Bu	Bn	Bn	H	86

(a)Isolated yield after purification

In Table 4 the variation of R^2 to include heterocyclic and bulky substituents were not studied extensively.

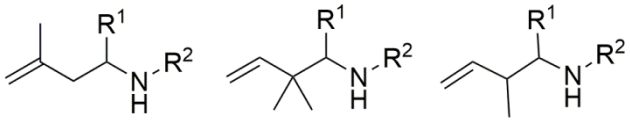
In 2013, Fossey and co-workers showed that it was possible to synthesise enantiopure 2,4-azetidines in high yield (99%) and high enantiomeric excess (>99% *ee*) using an Ellman auxiliary **45** method for the synthesis of enantiopure homoallylamines **46**.[23]



45 **46**

Figure 4: Chiral amine auxiliary and enantiopure homoallylamine

Based on the previous work from our research group, the synthesis of enantiopure azetidines will be continued and the scope of the previous method will be expanded. The study of the iodocyclisation protocol using various homoallylamines, such as 3-methyl substituted homoallylamines **47**, 2-gem-dimethyl substituted homoallylamine **48**, 2-methylhomoallylamine **49** and enantiopure homoallylamines **46**, remains to be investigated (within this project).



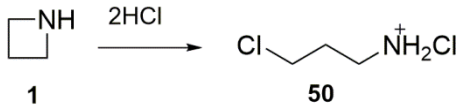
47 **48** **49**

Figure 5: Various homoallylamines

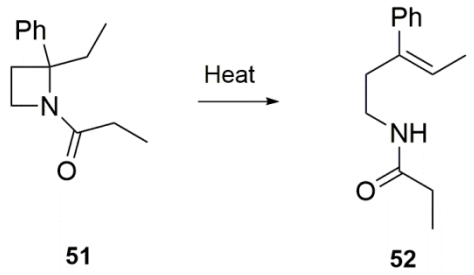
1.1.3 Reactions of azetidines

The ring strain in azetidines makes them excellent candidates for nucleophilic ring opening or ring expansion reactions yielding larger ring systems or obtaining highly substituted acyclic amines. Azetidines are stable compounds under ambient conditions, but they can undergo

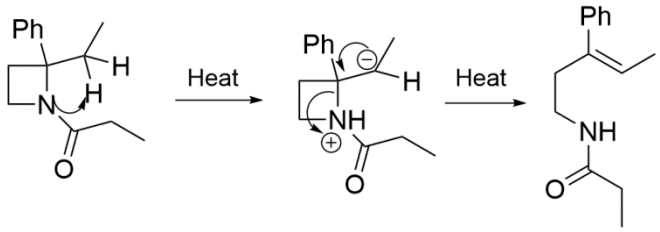
thermal[24] (Scheme 18) and acid-catalysed[7,25] (Scheme 17) ring opening or ring rearrangement to larger ring systems.



Scheme 17: Acid catalysed ring opening of azetidines

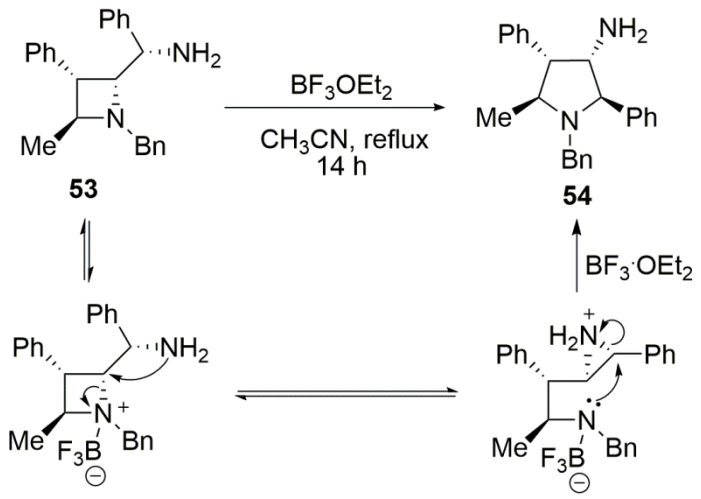


Scheme 18: Thermal catalysed ring opening of azetidines



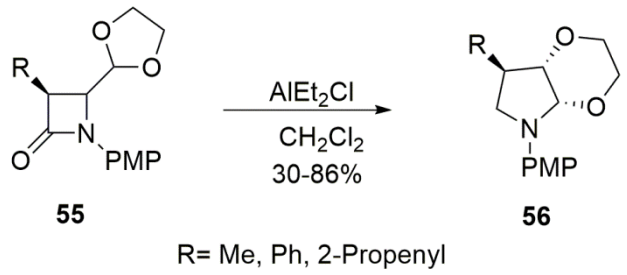
Scheme 19: Plausible mechanism of thermal ring opening of azetidines

Azetidines can undergo ring expansion to form larger ring systems because of ring strain. Vargas-Sanchez *et al.*[26] showed that the *N*-benzylpyrrolidine **54** with four stereogenic centres can be prepared in a quantitative yield with (*dr* 50-95%) *via* Lewis acid catalysed ring rearrangement of *N*-benzyl amino azetidine **53** (Scheme 20).



Scheme 20: Rearrangement of substituted azetidine to pyrrolidine

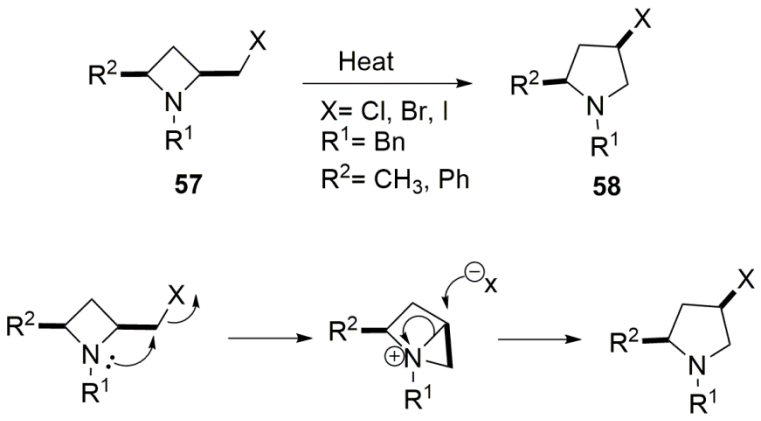
In 2008, Brandi and co-workers[9] reported that ring enlargement occurred in the presence of Lewis acids. The result showed that azetidine carboxaldehyde acetals-2-one **55** under reduction conditions on treatment with chloroalane in DCM were converted to 2,3,4-substituted pyrrolidines **56** in moderate to good yield 30-86% (Scheme 21).



Scheme 21: Azetidines ring enlargement under Lewis acid action.

In 2003, Couty *et al*.[27] reported thermal ring expansion of racemic 2-halomethylazetidines **57** into 3-halopyrrolidine **58** with complete stereo control. Similarly, the same ring enlargement was reported and verified by Feula *et al.*[22] in 2010. It was shown that *cis*-iodomethyl azetidines **57** were converted to the corresponding *cis*-iodopyrrolidines **58** when the reaction mixture was

heated above room temperature (Scheme 22). The proposed mechanism explained the control of stereochemistry during the conversion.



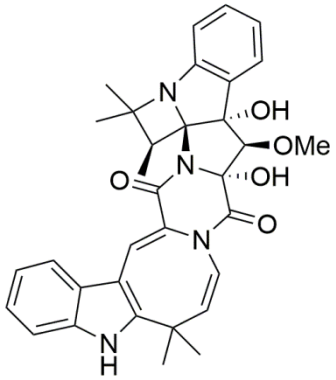
Scheme 22: Thermal ring enlargement of azetidines

1.1.4 Application of azetidines

Azetidines have been discussed in terms of their application in a wide range of areas, such as agrochemistry,[10] metal-ligand complexes in catalysis[6] and medical applications.[26]

1.1.4.1 Agrochemistry of azetidines

Furutani *et al.*[10] found that the azetidine moiety has the potential to enhance the insecticidal activity of alkaloid okaramines. The study was conducted on silkworm larval neurons, and it indicated the activity of okaramine with azetidine moiety **59** over the sixteen other derivatives with no azetidine core. The study also concluded that the azetidine ring has played a major role in the insecticidal activity of the well-known okramine B (Figure 6).

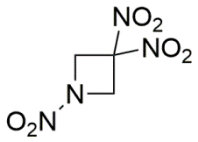


59

Figure 6: Structure of okaramine B

1.1.4.2 Industrial application

Azetidines are widely described for their use as intermediates in the construction of potential energetic molecules.[28] Katritzky showed that 1,3,3-trinitroazetidine (TNAZ) **60** could be a potential energetic material due to the positive heat of formation 26.1K J/mol, that can be employed as an explosive material in military application.[28]



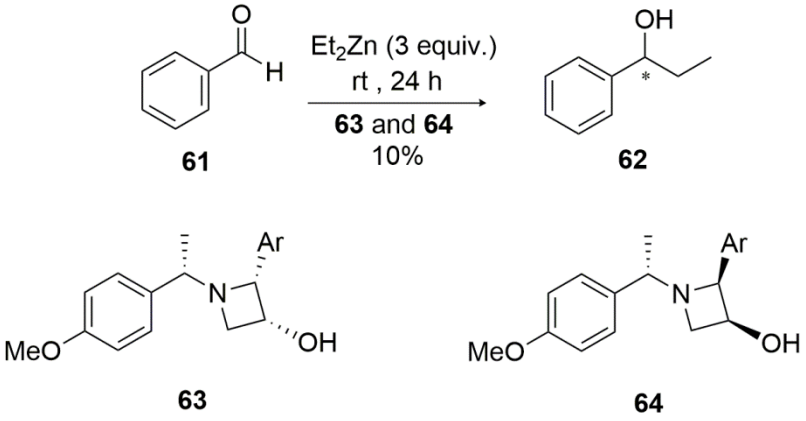
60

Figure 7: Structure of TNAZ

1.1.4.3 Catalytic applications of azetidines

Azetidines could be used as a ligand for the formation of metal complexes,[6] especially when they are functionalised with amine groups. Azetidines have been used as chiral ligand in asymmetric catalysis,[6] and a series of azetidine derivatives have been studied for their catalytic activities and

chiral induction potential. Several researchers used chiral azetidines for asymmetric addition of diethyl zinc to aldehydes.[5,29] For example; Liu *et al*.[29] showed that chiral 3-hydroxyazetidine derivatives **63** and **64** have excellent catalytic activities and enantiomeric selectivity towards asymmetric addition of diethyl zinc to aromatic aldehydes **61** to generate chiral alcohol **62**.[29]



Scheme 23: Azetidine as chiral ligand

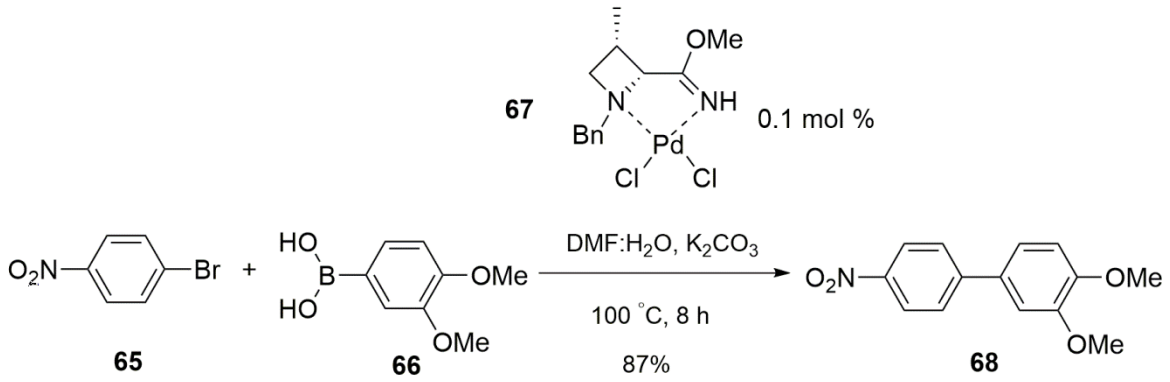
Table 3 details the effects of using ligand **63** and **64** on the selectivity of the produced alcohol **62**. In the presence of ligand (**63a-d**) the (*S*)-**62** was obtained in a 98% isolated yield with enantiomeric excess up to 94% (entry 1). Conversely, (*R*)-**62** produced a 93% yield with up to 97% *ee* as a result of using ligand **64** (entry 5**)**. Moreover, the yield and *ee* was found to be dependent on the substituents on the phenyl ring. For example, the presence of an electron-withdrawing group at the *para*-position of phenyl group leads to lower enantioselectivity compared to the *ortho* and *meta* regio-isomers.

Table 5: Azetidine as chiral ligand

Entry	Compound	Ar	% Yield[a]	% *ee*
1	**63a**	Ph	98	94 (S)
2	**63b**	4-Chlorophenyl	97	89 (S)
3	**63c**	3-Chlorophenyl	96	96 (S)
4	**63d**	2-Chlorophenyl	94	97 (S)
5	**64**	Ph	93	97 (R)

(a) Isolated yield

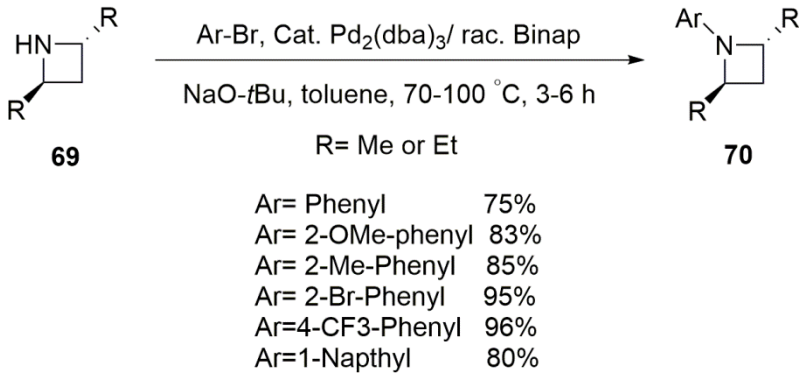
Keller and co-workers[6] showed the efficiency of their synthesised azetidine ligand in catalysis. It was shown that palladium-azetidine complex **67** was a good catalyst in Suzuki cross-coupling reactions for the formation of new carbon-carbon bonds, upon reaction of aryl halide **64** and boronic acid **66**. When the catalyst loading was 0.1% mol, the isolated product **68** was even higher at 87% (Scheme 24).[6]



Scheme 24: Azetidine complex as catalyst for Suzuki cross-coupling reaction

Marinetti and co-workers[17] synthesised chiral 2,4-dimethylazetidine from an efficient coupling of azetidines **69** with aryl halides using palladium complexes as a catalyst to afford chiral *N*-aryl substituted azetidines **70** in 75-96% isolated yields. When R was methyl group, isolated yields of

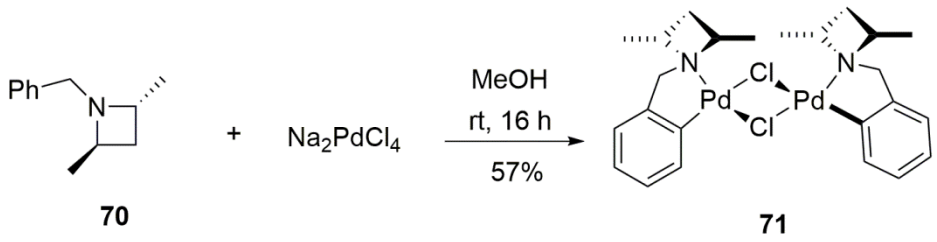
70 was higher than when R is ethyl group. When Ar was a phenyl substituent, compound **70** was obtained in a 75% isolated yield (Scheme 25).



Scheme 25: Synthesis of *N*-aryl azetidines through palladium promoted coupling reaction

When electron releasing substituents at Ar were used (Ar=2-methoxyphenyl and 2-methylphenyl), compound **70** was obtained in a slightly high yield (83-85%). When Ar is electron withdrawing substituent at *para*-position (Ar= 4-CF_3-phenyl), a better yield of product 96% was obtained. When Ar is bulky naphthyl substituent, the product was obtained in an 80% isolated yield. The synthesised azetidine derivatives could be good candidates for the synthesis of palladium containing complexes (Scheme 26).

Cyclopalladated azetidine complexes **71** can be synthesised from the reaction of (*R,R*)-1-benzyl-2,4-dimethylazetidine **70** with Na_2PdCl_4 in methanol at room temperature. A single isomer of *cis*-dimeric complex with two azetidine moieties was obtained in a 57% isolated yield (Scheme 26). The author showed that only *cis*-isomer was formed due to chiral discrimination produced from unusual arrangement of the complex, as the two azetidines were located outside the palladacycle.



Scheme 26: Synthesis of a cyclopalladated *N*-benzylazetidine complex

1.1.4.4 Biological applications of azetidines

Azetidines have played significant roles in pharmaceutical chemistry because of their existence in many biological active natural products[30] and pharmaceuticals.[31]

A number of azetidines have already been used in medicines, such as azelnidipine **72**, as an antihypertensive agent.[31] Some have been used as an antimicrobial,[32] antibacterial, antifungal,[33] analgesics,[34] and anti-depressant agents.[25] The azetidine analogue of nicotine **73** has been reported to be able to bind acetylcholine receptors more effectively than nicotine itself.[35]

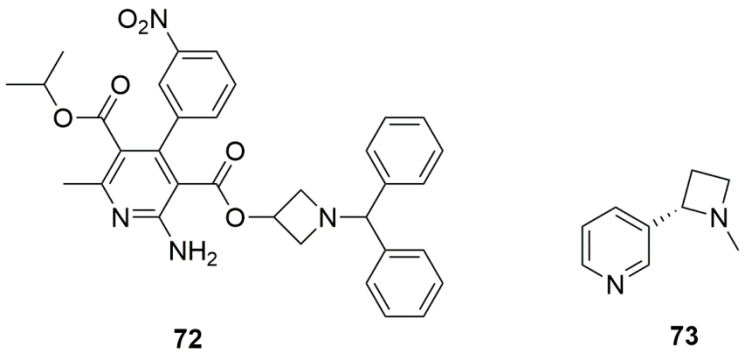
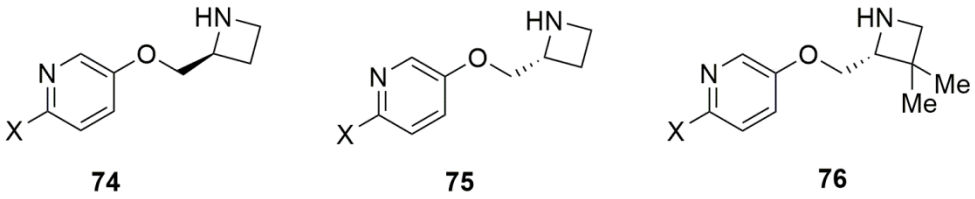


Figure 8: Azelnidipine and azetidine analogue of nicotine

Holladay and co-workers[34] prepared and studied azetidine derivative **74** and its enantiomer **75** (Figure 9) with diverse substitutions on the pyridine ring. It was reported that azetidine **74**

showed analgesic activity in mice. In addition, it had an affinity to nicotinic acetylcholine receptor binding sites in the brain of rats. The synthesised analogue **76** two methyl substituents at the 3-position of the azetidine ring was found to be less active. It was also found that variation of X (X= H, F, Me, Ph, Cl) has only a slight effect on the activity, for example, when X=Cl, the activity slightly increased.

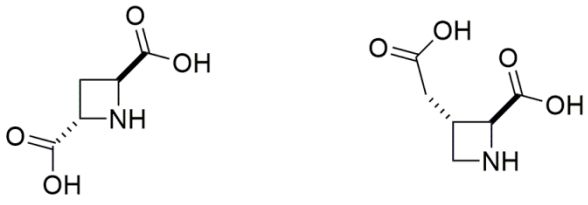


74 **75** **76**

X=H, F, Br, Me, Ph, Cl

Figure 9: Azetidine analogues

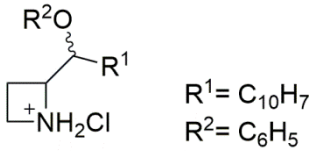
Azetidine amino acids are important examples of biologically active azetidines. Burtoloso and co-workers[36] has investigated some analogues of azetidine-derived glutamate and aspartate. They have been shown to display pharmacological activities. It was reported that azetidine **77** could act as an activator of the metabotropic receptors, while compound **78** could be a potent agonist of the kainite receptor.



77 **78**

Figure 10: Azetidine amino acids

In 2012, Han *et al*.[37] published a new study on antidepressant activity of a group of novel 2-substituted azetidines. In this study, several azetidine derivatives were screened against serotonin, dopamine and noripenephrine transporter, compared with reference drugs such as fluoxetine, nisoxetine and vanoxerine. Azetidine with R^1=$C_{10}H_7$ and R^2=C_6H_5 presented higher activity than reference drugs in enhancing triple reuptake inhibitor.



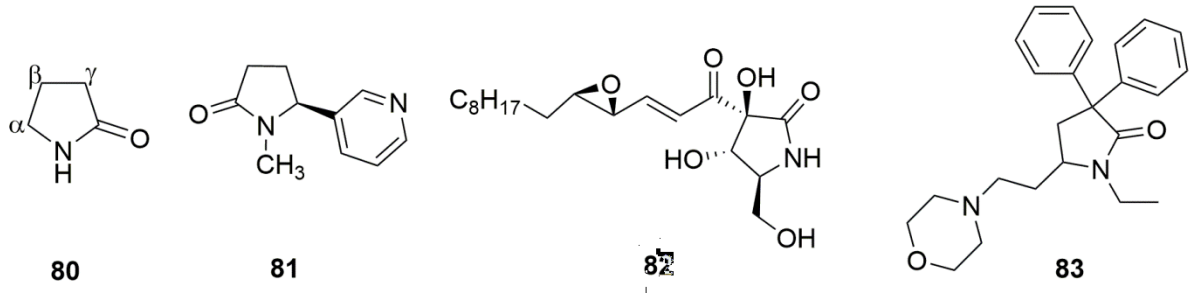
79

Figure 11: 2-Substituted azetidine

In conclusion, the importance of azetidine derivatives was found in the synthesis of natural products, pharmaceuticals and medicine. Azetidines can be synthesised from various procedures, but isolated yields were found to be low, due to purification problems, isomerisation and limited diversifications. In addition, azetidines presented several biological activities, such as triple reuptake inhibitor activity, and binding to acetylcholine receptors activity. Scientists are trying to find a new methodology for their synthesis in order to improve yields and selectivity, and to obtain a higher activity involved with the novel compounds compared to the previously synthesised compounds. In this study, we have tried to synthesise novel multi-substituted azetidines from readily available starting material with improved isolated yields, and have explored their biological activity.

1.2 Pyrrolidin-2-one (γ-lactam)

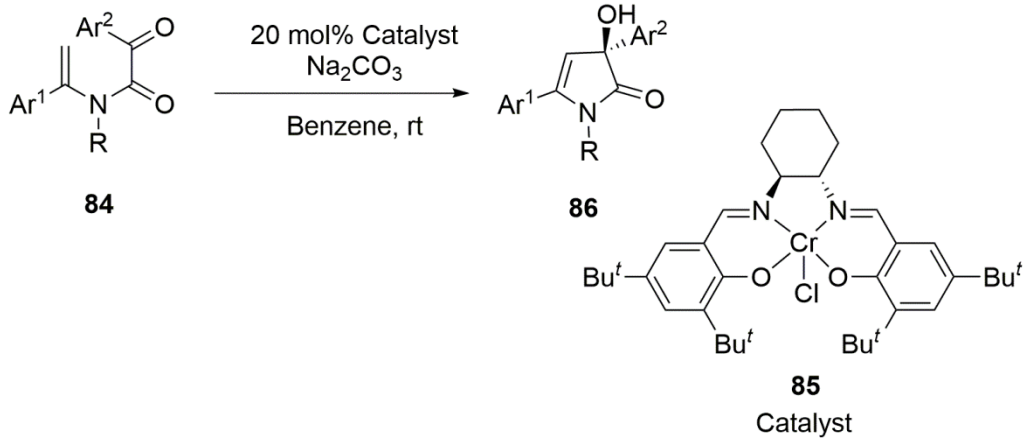
Pyrrolidin-2-ones (γ-lactams) (**80**) are an important class of organic compounds, particularly in synthetic organic chemistry, several biologically active natural products contain γ-lactam cores. [38] They are well known for their therapeutic applications, such as cotinine alkaloid[39] **81** found in tobaccos, which is used as an antidepressant. Natural product (-)-pramancine **82** isolated from fungal genus *Stagonospora* was discovered as an antimicrobial agent.[40] The γ-lactam with morpholine and biphenyl moiety *Doxapram* **83** has been reported as a respiratory stimulant.[41] Significantly, *cis*-1,3,5-γ-lactam derivatives have been found to display as potential α_7 nicotinic acetylcholine receptors (nAChR) agonists.[42] There are several research groups interested in synthesising γ-lactam derivatives. For example, 1,5-disubstituted γ-lactams have been synthesised in good to excellent yields *via* cyclisation of carbinolamide by treatment with trifluoroacetic acid.[43] In 2013, Sun *et al.*[44] synthesised tri-substituted chiral γ-lactams from the reaction of aromatic halide with γ-ketoester through a series of complicated steps. It was found that the synthesised γ-lactam derivatives could be used as a CC chemokine receptor 4 (CCR4) antagonists.[44]



80 **81** **82** **83**

Figure 12: γ-lactam core in natural product and alkaloids

Highly functionalised enantiomerically enriched pyrrolidin-2-one derivatives bearing hydroxylated stereogenic quaternary carbon centres can be prepared, starting from catalytic asymmetric intramolecular nucleophilic addition of tertiary enamides.[45] Yang *et al.* presented the treatment of enamide diketone **84** with sodium carbonate in benzene at room temperature in the presence of catalyst **85** and this resulted in affording hydroxylated 2,3-dihydro-pyrrol-2-ones **86** in very high yields and high selectivity up to 99% *ee*.



Scheme 27: Catalytic enantioselective reaction of enamides to form pyrrolidin-2-ones

The authors showed that the reaction scope could be explored for different substrates and found that all enamides were consumed to afford the product **86a-k** in an excellent yields 88-99% and high enantioselectivity (87-99% *ee*). When enamides with R=allyl substituent and Ar^1=Ar^2=Phenyl substituent (Table 6, entry 10), the product was obtained in 98%, but the *ee* was slightly decreased to 94%. The *ee* was decreased to 89% and an isolated yield of 99% when enamides with R=methyl and Ar^1=Ar^2=Phenyl (Table 6, entry 11). When enamides bearing phenyl substituents at Ar^1, Ar^2 and R (Table 6, entry 12), the isolated yield of product dropped to 88% and *ee* to 87%.

Table 6: Substrate scope of catalytic enantioselective reaction of enamides

Entry	compound	R	Ar^1	Ar^2	T (h)	Product (%)[a]	*ee* (%)[b]
1	**84a**	Bn	Ph	Ph	16	**86a** (98)	96
2	**84b**	Bn	4-Me-Ph	Ph	4	**86b** (98)	98
3	**84c**	Bn	4-Cl-Ph	Ph	114	**86c** (98)	96
4	**84c**	Bn	4-Cl-Ph	Ph	17	**86c** (98)	97
5	**94d**	Bn	4-Br-Ph	Ph	96	**86d** (98)	99
6	**84e**	Bn	Ph	4-Me-Ph	68	**86e** (98)	97
7	**84f**	Bn	Ph	4-F-Ph	72	**86f** (98)	97
8	**84g**	Bn	Ph	4-Cl-Ph	16	**86g** (98)	97
9	**84h**	PMB	Ph	Ph	11	**86h** (98)	98
10	**84i**	Allyl	Ph	Ph	15	**86i** (98)	94
11	**84j**	Me	Ph	Ph	4	**86j** (99)	89
12	**84k**	Ph	Ph	Ph	4	**86k** (88)	87

(a) Isolated yield, (b) determined with HPLC,

Enamides bearing bulky substituent at Ar^2, such as *tert*-butyl was also probed. When sterically hindered enamide was used, the product was obtained in a 99% yield with (94% *ee*).

Indeed, further improvement in this field is needed, so that readily available starting materials can be used for the synthesis of 1,3,5-trisubstituted pyrrolidin-2-one.

1.3 Fused tricyclic ring system

Fused tricyclic systems are a significant class of organic compounds found in alkaloids, such as Calycanthine (Figure 13).[46] Only a few examples were reported regarding the oxidative dimerisation that leads to the formation of a ring-fused system.[46]

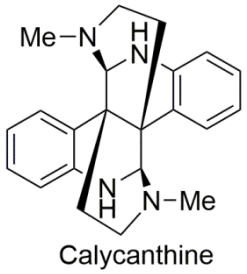
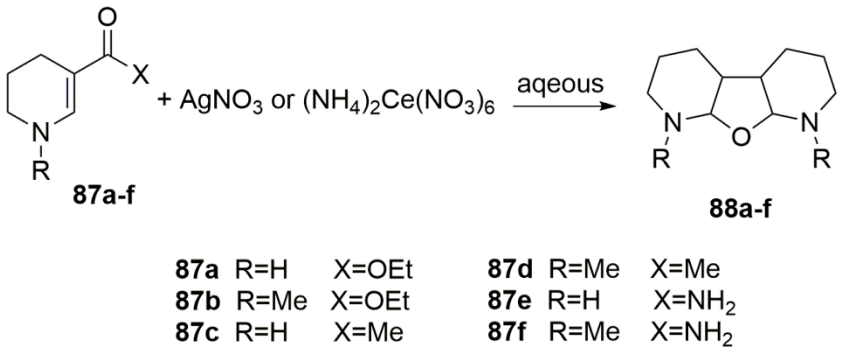


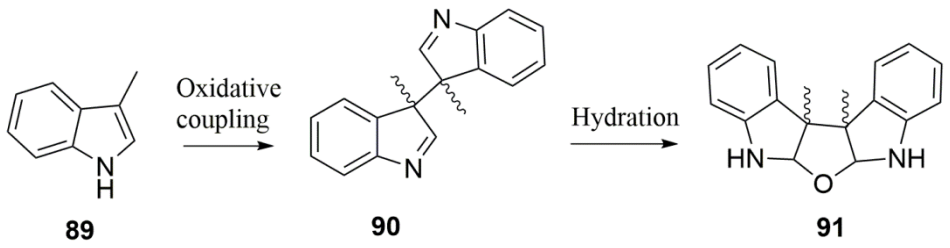
Figure 13: Calycanthine alkaloid

Poulton and co-workers[47] reported the oxidation of enamino-ketones **87a-f** in aqueous solution by using metal salts of Ag^{I} and Ce^{IV}. However, the problematic purification of the product resulted in a poor 30-35% isolated yields of compound **88a-f** (Scheme 28).



Scheme 28: Oxidative dimerisation of enamino-ketones

In 2002, K.-Q. Ling *et al.*[48] reported the formation of a single diastereomer of hexahydrofurodiindole **91** from one-electron oxidation from compound **89** (Scheme 29).

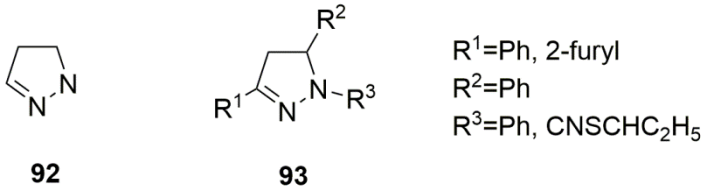


Scheme 29: Oxidative dimerisation of 3-methylindole to form hexahydrofurodiindole

The oxidative coupling of 3-methylindole **89** was found to give oxidative coupled dimer **90**, followed by hydration, which led to the formation of **91**. The stereochemistry of **91** was not assigned, it was believed the two-pyrrolidine ring must have been *cis*-, but the furan ring could be either *cis*- or *trans*-based on the C2 symmetry of the molecule.

1.4 Pyrazoline

2-Pyrazoline **92** is a five membered unsaturated heterocyclic nitrogen-containing compound. Pyrazoline derivatives have been reported as a valuable biological active compounds.[49] 1,3,5-Trisubstituted-2-pyrazoline derivatives **93** have shown to exhibit efficient antidepressant and anticonvulsant activities,[50] antifungal activity,[51] anticancer activity[52] and Cannabinoid CB1 receptor antagonist activity. Additionally, it has been found that pyrazolines are important materials due to their emission properties and ability to chelate with various metals when decorated with appropriate functionality.[53] They have also been investigated as fluorescent whitening agents.[54]

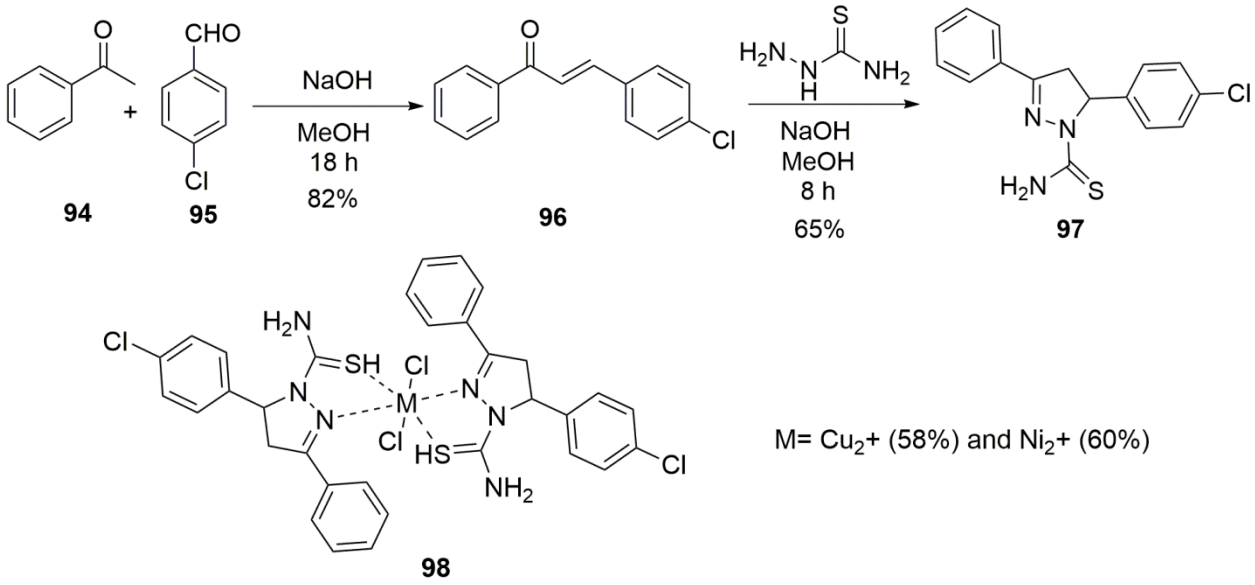


92 **93**

Figure 14: 2-pyrazoline and 2-pyrazoline derivatives

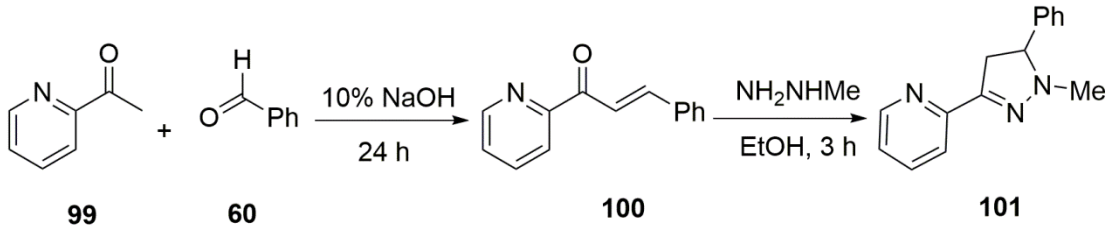
Several procedures for the synthesis of pyrazoline derivatives have been reported,[55] the most commonly employed procedure for the synthesis of pyrazoline derivatives is a base catalysed cyclisation of a chalcone with aryl hydrazine starting with Claisen-Schmidt condensation of acetophenone with aldehydes to form chalcones which are then reacted with aryl hydrazines to form pyrazolines. Recently, in 2012, Manzoor and co-workers[55] synthesised 1,3,5-pyrazoline derivatives through condensation of acetophenone **94** with *p*-chlorobenzaldehyde **95** to form chalcone **96**, followed by base catalysed cyclisation with thiosemicarbazide to form the desired 2-pyrazoline ligand **97** in 65% isolated yield. Coordination of the synthesised ligand was carried

out with copper and nickel to furnish **98** in 58% and 60% yields, respectively. The synthesised metal-ligand was shown to have efficient antifungal activity after coordination with copper and nickel metal **98** (Scheme 30).



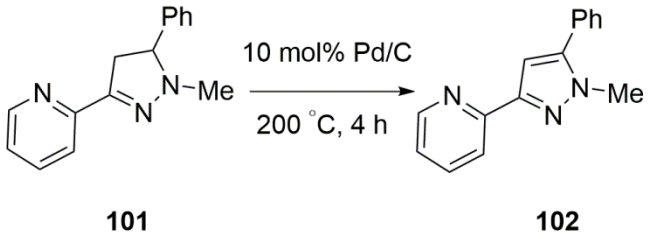
Scheme 30: Synthesis of 2-pyrazoline from Claisen-Schmidt condensation

In 2012, Caggiano and co-workers[56] described a method for the synthesis of a pyrazoline and a pyrazole from condensation of ketone **99** and benzaldehyde **60** to form aza-chalcone **100**, which was further reacted with methyl hydrazine to form pyrazoline **101** in 72% isolated yield (Scheme 31).



Scheme 31: Synthesis of 2-pyrazoline from Claisen-Schmidt condensation

The synthesised pyrazoline **101** was further oxidised to obtain the corresponding pyrazole **102** in the presence of a catalytic amount of palladium on carbon at a high temperature (Scheme 32). The synthesised pyrazolines and pyrazoles were used as selective fluorescent sensors for Cd^{2+} and Zn^{2+}, and they were shown to be capable of distinguishing between these metal ions in acetonitrile.



101 **102**

Scheme 32: Aromatisation of 2-pyrazoline 101 to from the corresponding pyrazole 102

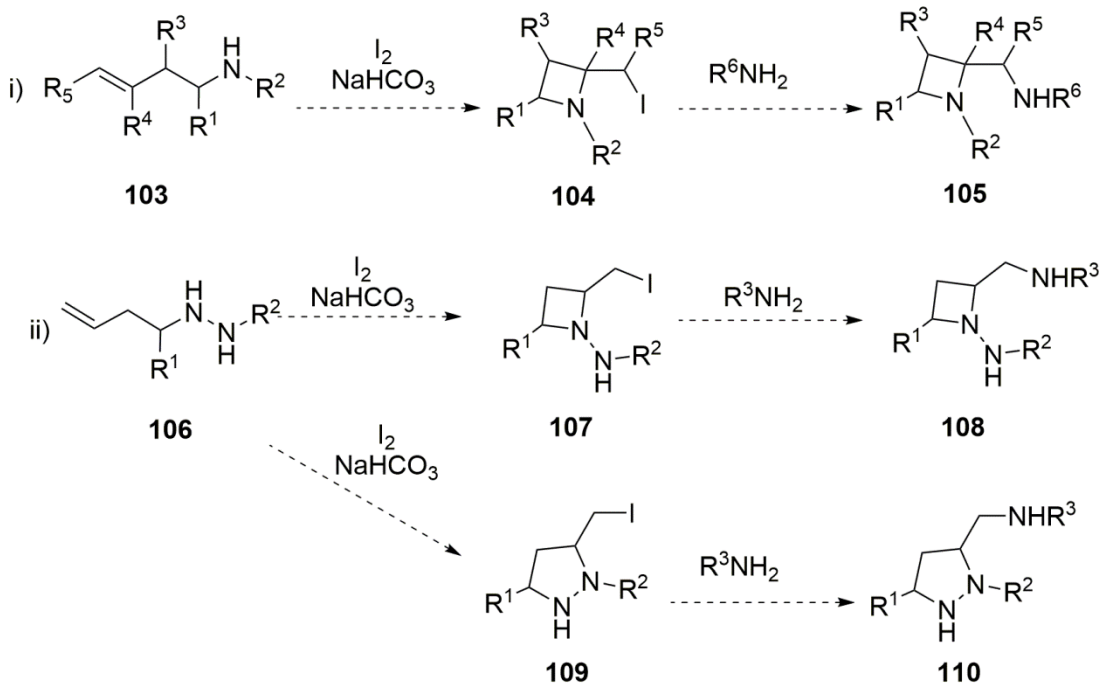
Only one example of pyrazoline was synthesised and employed for application, which could be expanded for further investigation on different substrates.

In conclusion, the synthesis of pyrazoline derivatives featured with a number of limitations in yields and selectivity. The investigation of new methods is needed toward developing efficient procedures in terms of isolated yield and selectivity. These results encouraged our interest towards synthesising compounds with 2-pyrazoline as a core structure, starting from the cyclisation of readily available homoallylhydrazines.

In terms of an overall conclusion of the literature review, several synthetic routes are available for the synthesis of azetidines, pyrrolidin-2-ones, γ-lactams and pyraolines, but not for fused furan bispyrrolidines. In general, they could be synthesised in better yields and selectivity by developing a new strategy starting from readily available starting materials.

The synthesis of multi-substituted azetidines **105** started from iodocyclisation of different homoallylamines **103** using the recently established methodology in Fossey research group (iodine-mediated cyclisation of homoallylamines using iodine and sodium bicarbonate in acetonitrile). The effect of substitution on regioselectively of cyclisation is planned to be investigated.

In addition, a plan has been made to investigate the synthesis of azetidines **108** or pyrazolidines **110**, which can be accessed from the cyclisation of homoallylhydrazines **106** using iodocyclisation protocols to provide a new synthetic route for their synthesis (Scheme 33).



Scheme 33: Proposed routs for the desired target compounds. i) The synthesis of multi-substituted azetidine derivatives *via* iodocyclisation of multi-substituted homoallylamines. ii) The synthesis of azetidine derivatives and pyrazoline derivatives *via* iodocyclisation of homoallylhydrazines

The biological activity of these compounds was probed by screening in a zebrafish embryo developmental assay. Moreover, screening all the newly synthesised compounds in medicinal and agrochemical arenas will be investigated through an ongoing screening partnership by sending samples of the synthesised compounds to two companies, Syngenta and Lilly.

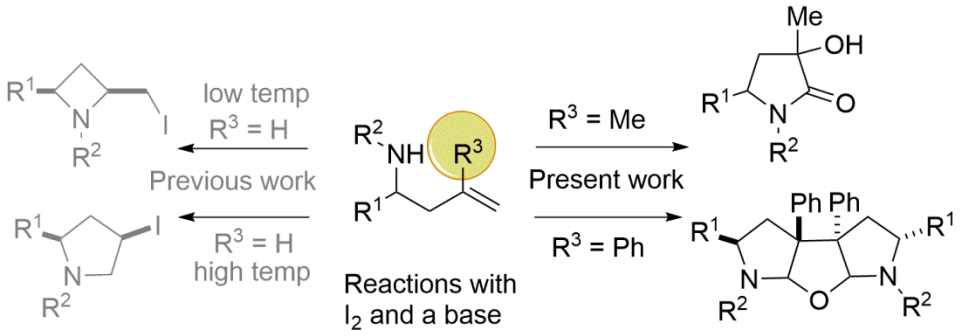
Chapter Two

Results and discussion

Synthesis of Azetidine

2. Results and discussion

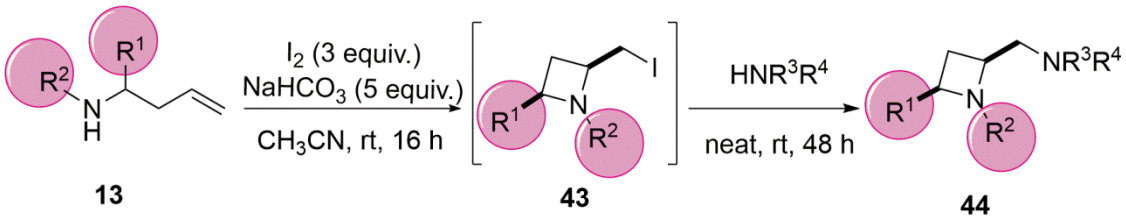
Previous work of Fossey and co-workers showed that the 2,4-*cis*-azetidines can be synthesised *via* iodine-mediated cyclisation of various homoallylamines. Initially, this procedure was employed in this project to expand the scope of the previous studies toward applications in catalysis and biological screening. This led to new findings and chemical understanding, which are explored in this thesis (Scheme 34).



Scheme 34: Summary scheme

2.1 Racemic azetidine synthesis

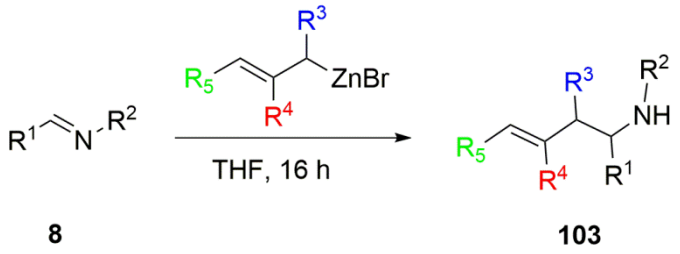
First of all, to continue with the previous work and to expand the scope of R groups, namely the variation of R^1 and R^2 groups were studied (Scheme 35). In order to do this study, the synthesis of intermediates, imines and homoallylamines were started.



Scheme 35: Racemic azetidine synthesis

2.1.1 Synthesis of intermediates

Homoallylamines are important intermediates in organic synthesis. They can be used as building blocks for the synthesis of many natural products, and biologically active compounds.[55,56] It was believed that the majority of the target homoallylamines (Figure 15) could be prepared according to literature protocols.[57] Metal (zinc and magnesium) mediated allylation of imines in dry THF at room temperature was proposed as the ideal methodology (Scheme 36).



Scheme 36: Proposed route for preparation of homoallylamines

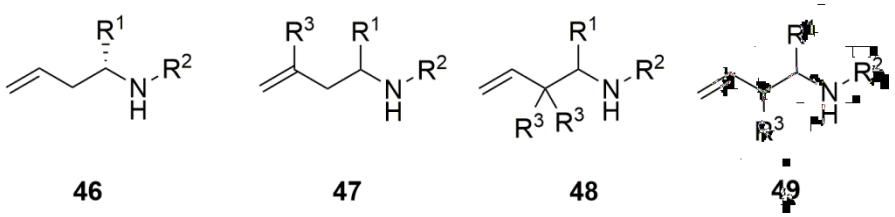
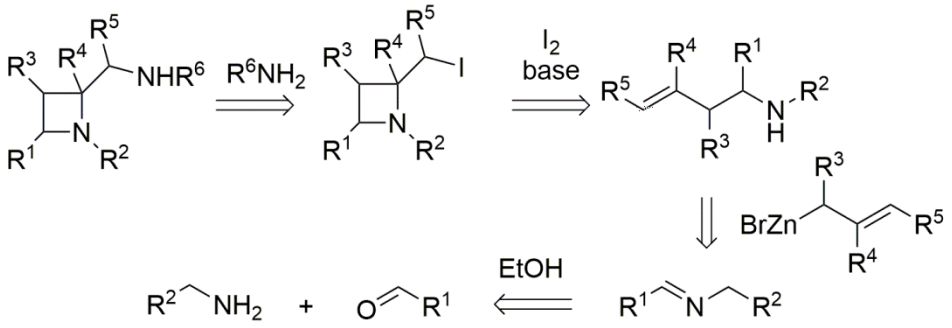


Figure 15: Different substitution patterns of homoallylamines

The syntheses of homoallylamines was planned in order to generate azetidines with different substitution patterns on the rings produced *via* iodine mediated cyclisation protocol (Scheme 37).[22]



Scheme 37: Proposed retrosynthetic route for the synthesis of azetidine using iodocyclisation procedure

The synthesis of azetidine with different substitution patterns was planned in order to study their biological activity and to compare their activities with the previously synthesised azetidines in our research group by using the same strategy. It has been hoped that structure activity relationships (SAR) could be understood.

To prepare these compounds (**46**-**49**), commercially available allyl bromides (**113**, **114**, **115** and **116**) were used to prepare allyl metal species, which were utilised in the allylation of the synthesised imines. Imines were first synthesised, as described in the next section.

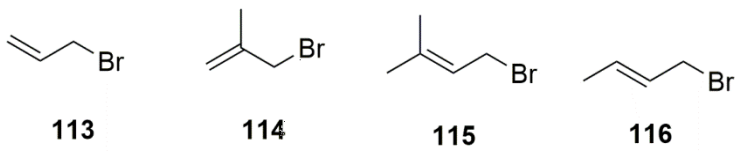
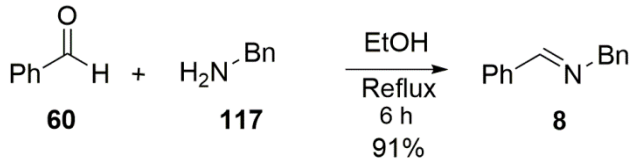


Figure 16: Ally bromide species

2.1.1.1 Synthesis of imines

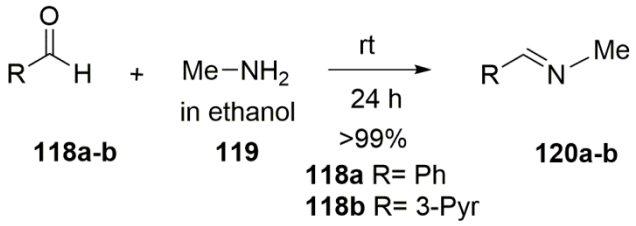
Imines are an important class of organic compounds in synthetic organic chemistry because of the diverse reactivity of the carbon-nitrogen double bond. They were used as a primary substrate for a wide range of syntheses,[58] such as the synthesis of enantiomerically enriched amino phosphoric acids as enzymatic inhibitors from hydrophosphonylation of imines.[59] Initially, the

imine **8** was prepared from condensation of benzaldehyde with benzylamine in refluxing ethanol for six hours.



Scheme 38: Synthesis of imines

The majority of imines used in this project have been prepared using the same protocol except in two cases: *N*-methylimines **120** were prepared by treating aldehydes with methylamine solution **119** and the reaction was performed at room temperature.



Scheme 39: Synthesis ofmethylimines

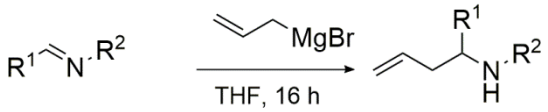
After preparation of imines, the synthesis of homoallylamines was attempted.

2.1.1.2 Synthesis of homoallylamines

Homoallylamines **9a-k** can be prepared by using the two standard literature protocols.[57,60] the first method is through the addition of allyl Grignard reagents, which were prepared *in situ*, to appropriate solutions of the corresponding imines in dry THF at room temperature. The corresponding homoallylamines **9a-k** were synthesised in moderate to good yields (except entries 4 and 9, Table 7) as racemic mixtures by using the same strategy. These homoallylamines were

synthesised in order to apply the cyclisation procedures to synthesise azetidines with various substituents.

Table 7: Synthesised racemic homoallylamines



9 a-j

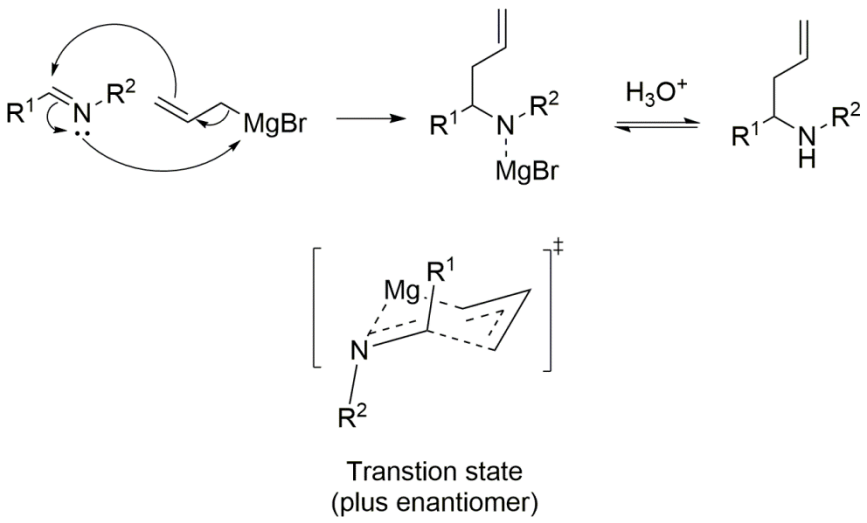
Entry	Product	R^1	R^2	% yield[a]
1	**9a**	Ph	Bn	91
2	**9b**	*t*-Bu	Bn	85
3	**9c**	3-Pyr	Bn	89
4	**9d**	Ph	3-Picolyl	83
5	**9e**	9-Anthracenyl	Bn	<10[b,c]
6	**9f**	Ph	4-Methoxybenzyl	93
7	**9g**	2-Thienyl	Bn	89
8	**9h**	Ph	*n*-Pr	94
9	**9i**	Ph	Allyl	-[d]
10	**9j**	Ph	2-Methylbenzyl	37
11	**9k**	2-Hydroxybenzyl	Bn	-[d]

(a) isolated yield, (b) not purified,(c) reaction time extended to 72 hours, (d) product not observed

Table 7 shows that the different substituent (R) groups affect the formation of the homoallylamines, for example, steric effects are expected to inhibit the allylation process, which can be observed in the case of **9e** (Table 7, entry 5) in which complete conversion was not

obtained despite extending reaction time to 72 hours and heating at reflux. The reaction was unsuccessful when R^1 was an *ortho*-hydroxyl substituted benzyl group **9k** (Table 7, entry 11). A possible explanation for this could be the Grignard being quenched by the phenol, though this is not yet proven. Compound **9i** (Table 7, entry 9) was not obtained as a pure product, due to difficulties faced during purification, as several spots were found on the TLC plate. The allylation of (Table 7, entry 10) was carried out at room temperature, giving a 20% yield. However, by refluxing in dry THF, the yield was slightly improved to 37%.

The expected reaction mechanism and the chair like transition state for the formation of a racemic mixture of homoallylamines are illustrated in Scheme 40.



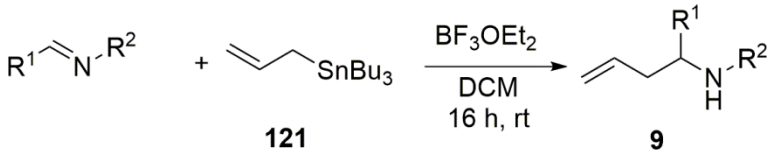
Scheme 40: Reaction mechanism and transition state of homoallylamine

The above reaction mechanism shows that the magnesium metal coordinates to the nitrogen atom of the imine and increases the electrophilicity of the imine carbon, then the ally metal double bond, which acts as a nucleophile and attacks the electrophilic carbon atom of the imine leading to the formation of a racemic mixture of the homoallylamine.

Homoallylamines also could be prepared from the addition of allyltributyltin **121** to the imine solution in dichloromethane in the presence of borontriflouride diethyl etherate as a Lewis acid to activate the imine double bond.[60] This method was used as an alternative route to the formation of homoallylamines **9** due to limitation being reached when Grignard reagents were employed.

Homoallylamines **9a-b** were prepared by dissolving imines **8a-b** in dichloromethane and were treated with boron trifloride diethyl etherate and compound **121** at room temperature. The products **9a-b** were obtained in 75-80% isolated yields (Table 8) and they were comparable with the former procedure, which gives a moderate to good yields. However, this procedure is expensive and involves toxic substances.

Table 8: Synthesis of racemic homoallylamines via addition of allyltributylstannane



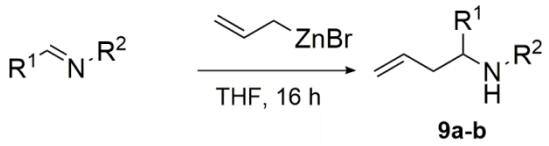
121 9

Entry	Compound	R^1	R^2	% yield[a]
1	**9a**	Ph	Bn	75
2	**9b**	Ph	3-Picolyl	80

[a] Isolated yield

The allylation process could be problematic when using magnesium metal, as a layer of oxide forms on the surface of the metal that is difficult to remove compared to zinc powder. However, the use of activated zinc powder[61] was found to solve this problem and the best yields have been obtained for the corresponding homoallylamines (Table 9).

Table 9: Synthesis of racemic homoallylamines using zinc metal



9a-b

Entry	Compound	R^1	R^2	% yield[a]
1	**9a**	Ph	Bn	91
2	**9k**	Ph	3-Picolyl	89

(a) Isolated yield

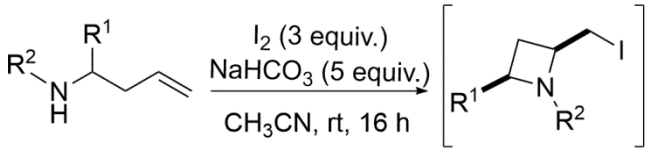
In general, the allylation of imines using zinc metal has been found to be more efficient than using magnesium turning, but not more efficient than using allyltributyltin **121**. The factor that affects the allylation process in general is activation of the metal and the presence of water or air, resulting in the decomposition of the ally metal reagent. Therefore, the reaction has to be carried out in rigorously anhydrous conditions, minimising the presence of water and air, aiding the formation of the organometallic reagents.

2.1.2 Cyclisation of racemic homoallylamines

As discussed earlier, *cis*-2,4-disubsituted iodoazetidines **43** can be prepared by iodine mediated 4-*exo*-trig cyclisation[11] of homoallylamines **9**. The procedure established for the preparation of *cis*-2,4-azetidines, by Fossey and co-workers,[22] utilises three equivalents of iodine and five equivalents of sodium bicarbonate in acetonitrile at 20 °C (Table 10). The synthesised iodoazetidines were not purified due to the undesired isomerisation in to pyrrolidines on silica gel during column chromatography. Despite this, overall good conversion and these unstable iodoazetidines were converted to aminoazetidines **44** (Table 11).

At the starting point of this project, heterocyclic groups in R^2 **9b** (Table 10, entry 2) and bulky groups in R^1 **9c** (Table 10, entry 3) had not been explored. This project aims to develop this methodology through expanding the scope by probing such R groups. Treatment of homoallylamine when R^1=naphthyl and R^2=3-picolyl with the iodocyclisation protocol, gave the desired azetidine generated as the major product in 80- >99% conversion respectively, based on analysis of the proton NMR spectrum.

Table 10 Synthesised racemic iodoazetidines



9 **43**

Entry	Compound	R^1	R^2	%Conv.[a]
1	**9a**	Ph	Ph	>99[b]
2	**9b**	Ph	3-Picolyl	>99
3	**9c**	1-Naphthyl	Bn	80
4	**9d**	Ph	2-Methylbenzyl	-[c]
5	**9e**	Ph	2-Bromobenzyl	-[c]
6	**9f**	Ph	4-Methoxybenzyl	>99[b]

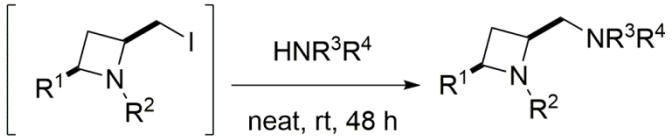
(a) Conversion determined by analysis of crude ^{1}H NMR spectra compared to the starting material, (b)literature compounds, (c)No-product

When R^1 is aromatic and R^2 is benzyl groups, the quantitative conversion to the desired iodoazetidine was achieved. When R^2=3-picolyl (Table 10, entry 2) the corresponding iodoazetidine was obtained in an almost quantitative conversion, while a 1-naphthyl substituent at

R^1 (Table 10, entry 3) delivered only 80% conversion and recovery of 20% starting material. An *ortho*-substituted benzyl was probed. When R^2 is 2-bromo benzyl and 2-methyl benzyl (Table 10, entries 4 and 5), starting materials were recovered without any evidence of cyclisation. This is also observed for a similar substrate discussed later in this thesis (Table 13, entry 7), which suggests that *ortho*-substituted aromatic groups inhibit cyclisation. The reason for the observation may be due to the electronic effect introduced by *ortho*-position substitution of the phenyl group. In contrast, the electronic effect on *para*-position did not affect the cyclisation, for example electron donating substituent such as *para*-methoxybenzyl (Table 10, entry 6) gave a quantitative conversion to azetidine.[22]

The crude product **43a** was then treated with neat benzyl amine as a nucleophile, for 48 hours, delivering aminoazetidine **44a** in a 65% isolated yield. The same strategy was applied for the rest of the synthesised iodoazetidines through treatment with a large excess of piperidine to afford aminoazetidines **44b** in a 76% isolated yield, and through treatment with a large excess of *n*-propylamine to furnish **44c-d** in 50-65% isolated yields (Table 11).

Table 11: Synthesised racemic aminoazetidines



43 **44**

Entry	Compound	R^1	R^2	R^3	R^4	% Yield[a]
1	**44a**	Ph	3-Picolyl	Bn	H	65
2	**44b**	Ph	3-Picolyl	Piperidine		76
3	**44c**	1-Naphthyl	Ph	*n*-Pr	*n*-Pr	50
4	**44d**	Ph	Ph	*n*-Pr	*n*-Pr	65

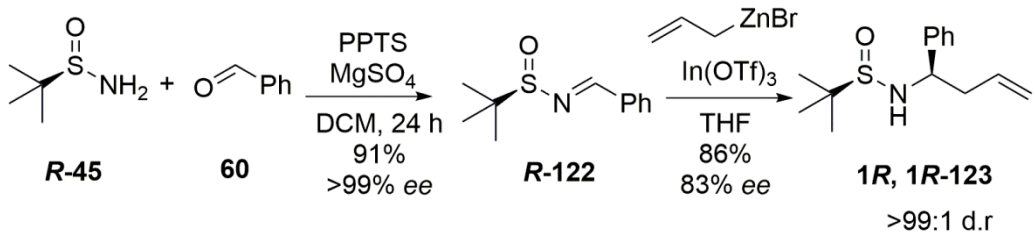
(a) Isolated yield

The analysis of crude proton NMR revealed the recovery of some starting materials, but in all cases *cis*-2,4-aminoazetidine **44a-d** was found to be a major product. Novel azetidine derivatives with a 3-picolyl group were generated in good yields 65-76% (Table 11, entries 1 and 2). When a bulky group was used, R^1= 1-Naphthyl substituent, the desired azetidine **44c** was obtained in only a 50% isolated yield and 30% starting material was recovered (Table 11, entry 3). Additionally homoallylamines with R^2=2-bromobenzyl and 2-methylbenzyl (Table 10, entries 4 and 5) could not be cyclised to deliver azetidines utilising this protocol. Since the scope of the previous method was probed, and the cyclisation of some racemic homoallylamines were clarified, attention then turned to the synthesis of enantiopure azetidines.

2.2 Enantiopure azetidine synthesis

2.2.1 Synthesis of enantiopure homoallylamines

Several reports have been published regarding the synthesis of enantiopure homoallylamine in a high yield with high *ee* (up to >99%) using an Ellman auxiliary **45**.[62,63] (*R*)-*N*-*tert*-butylsulfinylimine **122** was synthesised from the condensation of benzaldehyde **60** with (*R*)-*tert*-butylsulfinamide ***R*-45** in the presence of PPTS and anhydrous $MgSO_4$ using standard literature protocol (Scheme 41).[64] Compound ***R*-122** was obtained in a 91% isolated yield after column chromatography, then it was reacted with ally zinc reagent in the presence of a mild Lewis acid indium triflate, according to a literature procedure.[65] Compound **(1*R*, 1*R*)-123** was obtained in an 86% isolated yield after column chromatography with $[\alpha]_D^{20}$=+120.1 (C. 9.7, $CHCl_3$) and compared with the literature value (+121.6)[23] and high diastereoselectivitiy >99% *d.r* that was confirmed by the analysis of the crude proton NMR spectrum (Scheme 41).



Scheme 41: Preparation of enantiopure (*R*)-2-methyl-*N*-((*S*)-1-phenylbut-3-en-1-yl)propane-2-sulfinamide

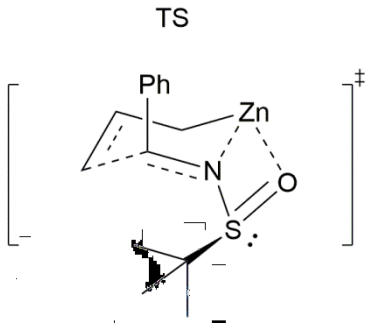
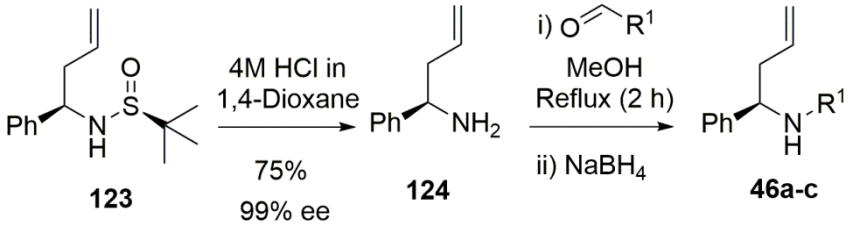


Figure 17: Transition state for the synthesis of enantiopure homoallyl Ellman amine

The transition state involves the metal coordination by the nitrogen of the imine functional group and the oxygen of the sulfinyl oxygen.

The enantiopure amine **124** (99% *ee*) was obtained from the removal of the chiral auxiliary from **123** using 4M hydrochloric acid in 1, 4-dioxane. Compound **46a-c** was generated from reductive amination of **124**. The resulting chiral primary amine was condensed with various readily available aldehydes to obtain imines, which were reduced with sodium borohydride to furnish chiral homoallylamines **46a-c** in 86-91% yields and enantiomeric excess of 93-99% *ee* (Table 12).

Table 12: Synthesised enantiopure homoallylamines



Entry	Compound	R^1	% Yield	*ee* %
1	**46a**	Ph	91	>99[a]
2	**46b**	*t*-Bu	86	91[b]
3	**46c**	3-Picolyl	92	93[b]

(a)Calculated by comparison of literature value of optical rotation, (b) Calculated by HPLC (see experimental data)

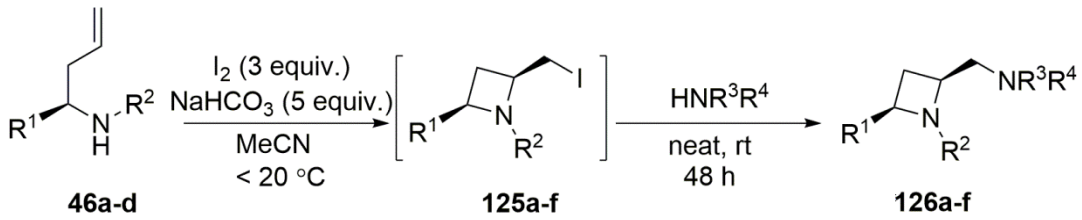
The reductive amination of **124b** with sodium borohydride generated **46b** in 86% yield with 93% *ee* $[\alpha]_D^{20}$= +52 (c.5, DCM) calculated by chiral HPLC (AD column). However, the *ee* obtained for **46a** is **>**99% calculated by comparison of literature value of $[\alpha]^{20}_D$= +56.5 (c.5, $CHCl_3$) (lit. +55.4)[23] and >99% *ee*. The compound **46c** was obtained in a 92% yield with >99% *ee* calculated by chiral HPLC (AD column). Since the synthesised enantiopure homoallylamines in hands, then the cyclisation was investigated.

2.2.2 Cyclisation of enantiopure homoallylamines

Cyclisation of enantiopure homoallylamine **46a** was attempted in order to test the suitability of the cyclisation protocol for the synthesis of single enantiomer azetidines. Treatment of enantiopure homoallylamine **46a** with molecular iodine utilising a previous cyclisation procedure delivered enantiopure iodoazetidines **125a** (Table 13). Further reaction with an amine nucleophile afforded **126a** in a 83% isolated yield and >99% *ee* $[\alpha]_D^{20}$= +97.2 (c.5, $CHCl_3$) (lit. +98.7).[23] This work was published in 2013 and some of the work of this thesis featured in that paper.[23]

Further synthesis of novel enantiopure azetidines was needed for biological activity screening and investigation in catalysis. The same strategy was applied when expanding the scope of the method, and several enantiopure azetidine compounds were prepared (Table 13). Cyclisation of homoallylamines **46a-f** was attempted and aminoazetidines **126a-f** were prepared in 46-82% yields after purification with an enantiomeric excess of 85-99% *ee* calculated by chiral HPLC (AD column was used (see experimental section). The cyclisation of homoallylamines when R^2 is 3-picolyl resulted in quantitative conversion to iodoazetidines. When R^2 is *t*-butyl only 50%, conversion was achieved, as determined by the analysis of crude proton NMR spectrum. When R^2=2-bromobenzyl no product was detected by analysis of the crude proton NMR. The crude products were subjected to the next step without further purification to generate **126a-f**. In the cases of **126b**, **126e** and **126f**, purification was problematic and at least two columns were run for the purification of each compound, which resulted in reducing the isolated yield of the product. When R^2 is 3-picolyl, the conversion to iodoazetidine was quantitative, but after conversion to aminoazetidine **126c-e** and purification using column chromatography, the isolated yield was reduced to 57-82%. When R^1= phenyl and R^2= benzyl, the conversion by analysis of crude proton NMR was 83%, the isolated yield after column chromatography was only 46%.

Table 13: Synthesised enantio enriched azetidines



Entry	Compound	R^1	R^2	R^3	R^4	% Yield	% *ee*
1	**126a**	Ph	Bn	Bn		83	>99[a]
2	**126b**	Ph	Bn	*i*-Pr	H	46	>96[a]
3	**126c**	Ph	3-Picolyl	piperidyl		82	89[b]
4	**126d**	Ph	3-Picolyl	Bn		76	85[b]
5	**126e**	Ph	3-Picolyl	Pyrrolidyl		57	91[b]
6	**126f**	Ph	*t*-Bu	*n*-Pr		50	87[b]
7	**126g**	Ph	2-Bromobenzyl	-	-	-	-[c]

(a) literature compound, (b) calculated by HPLC (see experimental data), (c) Azetidine not observed

The decrease in *ee* can be explained by the thermal stability of the iodoazetidine **125a-f**. When R^2=3-picolyl, the treatment of iodoazetidine **125b** with isopropylamine furnished aminozetidine **126b** (Table 13, entry 2) in a 46% isolated yield with enantiomeric excess >96% *ee* $[\alpha]_D^{20}$= +89.4 (C.5, $CHCl_3$) (lit. +96).[23]When the crude iodoazetidine was treated with pipperidine, benzylamine and pyrrolidine produced aminoazetidine **126c-e** in 82% (89% *ee*), 76% (85% *ee*) and 57% (91% *ee*) (Table 13, entries 3, 4 and 5 respectively). The *ortho*-bromobenzyl substituent (Table 13, entry 6) was not cyclised to furnished azetidine as expected from the previous result, only starting

material was recovered, this result confirms the previous suggestion for cyclisation of *ortho*-substituted group in R^2 restrict cyclisation to form azetidine.

In summary, throughout this section, the scope of the previously developed procedure for the synthesis of azetidines was expanded, to some extent, to include heterocyclic substituents at R^1 and bulky naphthalene group at R^2. The cyclisation was found to be successful and azetidines were obtained in moderate to high yields. In addition, enantiopure azetidines were prepared in 46-83% yields with high enantiomeric excess up to >99% *ee*.

After contributing to complete the study of the scope of R^1 and R^2 and synthesising enantio-enriched azetidines, attention was then turned to work on the allyl part of the homoallylamine. The previous cyclisation protocol was applied to various homoallylamine substrates synthesised from allyl bromide species **113**, **114**, **115** and **116** (Figure 18).

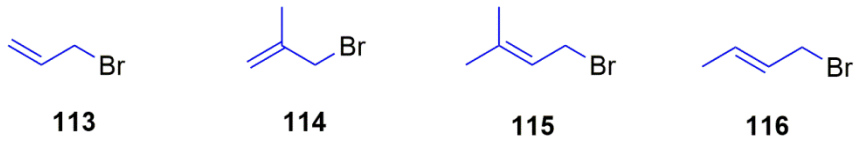


Figure 18: Ally bromide species

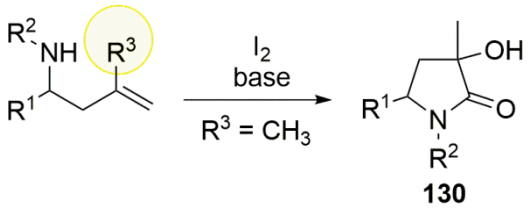
Chapter Two

Results and Discussion

Synthesis of γ-lactam

2.3 γ-Lactams synthesis

To study the possibility of the cyclisation, methyl substituted homoallylamine was cyclised (Scheme 42).



Scheme 42: General scheme for the synthesis of γ-lactams

2.3.1 Synthesis of 3-methyl substituted homoallylamines intermediates

This project aims to probe the effects of substitution on the allyl part for the first time (R^3, Figure 19). First of all, synthesis of homoallylamines with methyl substitution in the 3-position was planned.

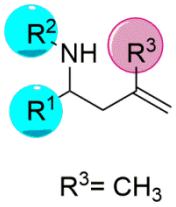
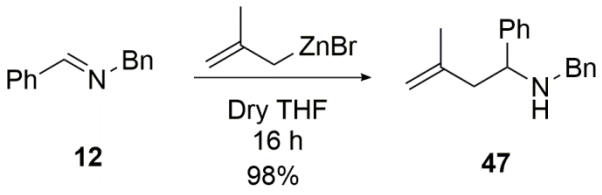


Figure 19: Homoallylamine with methyl substitution in 3-position

The generation of 3-methyl substituted homoallylamine **47** was tried through the treatment of imine **12** with *in situ* prepared methallylzinc reagent in accordance with the literature procedure, [57] the product was obtained as a racemic mixture in 98% isolated yield.



Scheme 43: Synthesis of 3-methylsubstituted homoallylamine

The proposed transition state in Figure 20 shows the possibility of the formation of a racemic mixture of the 3-methyl substituted homoallylamine, which results from the allyl rearrangement.

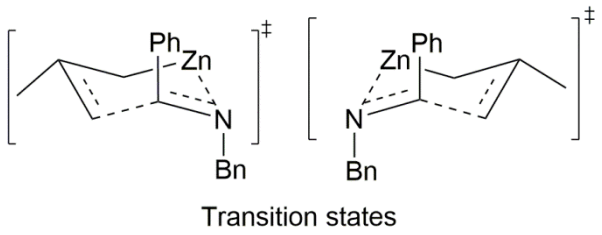
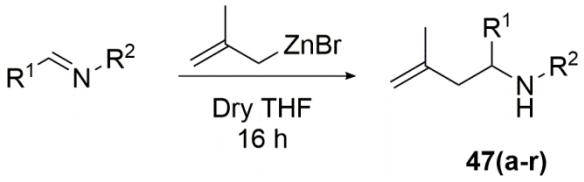


Figure 20: Transition states for the synthesis of racemic 3-methyl substituted homoallylamine

With satisfactory reaction conditions in hand for cyclisation, and to expand the scope of the developed procedure later on, several 3-methyl substituted homoallylamines (**47a-r**) were prepared in 34-98% isolated yields (Table 14). Various imines, including aromatic, benzylic, aliphatic and heterocyclic substituents were employed, in order to obtain comprehensive results on such allylation reaction, and in particular in the cyclisation step.

Table 14: Synthesis of racemic 3-methyl homoallylamines

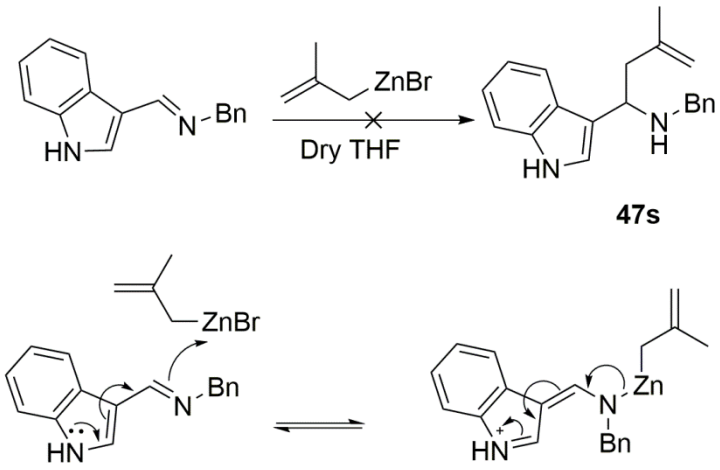


47(a-r)

Entry	Product	R^1	R^2	% yield[a]
1	**47a**	Ph	Bn	98
2	**47b**	Ph	3-Picolyl	74
3	**47c**	Ph	*n*-Pr	41
4	**47d**	3-Pyr	Bn	87
5	**47e**	Ph	2-Methylbenzyl	91
6	**47f**	3-Furyl	Bn	84
7	**47g**	*t*-Bu	Bn	82
8	**47h**	3,4-Dimethoxyphenyl	Bn	66
9	**47i**	Ph	4-Methoxybenzyl	73
10	**47j**	2-Thienyl	Bn	93
11	**47k**	1-Naphthyl	Bn	19
12	**47l**	Ph	Adamantly	81
13	**47m**	2-Bromophenyl	Bn	47
14	**47n**	Ph	4-Chlorobenzyl	34
15	**47o**	4-Nitrophenyl	Bn	57
16	**47p**	3-Pyr	4-Methoxybenzyl	75
17	**47q**	Ph	Me	82
18	**47r**	3-Pyr	Me	67
19	**47s**	3-Indole	Bn	-[b]

(a) Isolated yield, (b) Starting material recovered

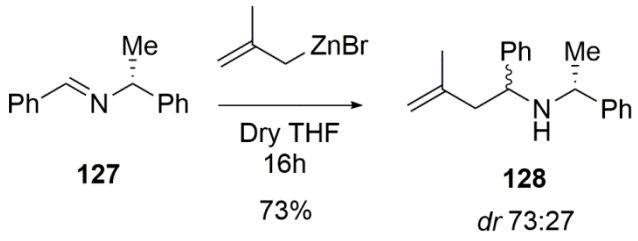
When phenyl substituent at R^1 and Benzyl substituent at R^2 were employed (Table 14, entry 1) the allylated product was obtained in a very high yield 98%. When 3-picolyl substituent was employed at R^2 (Table 14, entry 2), this led to reduction of the allylated product to 74%. Alkyl substituted amine (Table 14, entry 3) gave a low yield of 41%. When R^1=3-pyr (Table 14, entry 4) the isolated yield was increased to 87%. When electron releasing substituents on R^1 and R^2were employed (Table 14, entries 5, 8 and 9) the products were obtained in relatively good yields of 66-91%. Bulky *tert*-butyl substituent (Table 14, entry 7) also gave the allylated product **47g** in (82%) isolated yield. Allylation of imines with the electron withdrawing substituents at R^1 and R^2 in the *ortho*- and *para*-position led to a reduction in the yield to 47%, 34% and 57% for bromo-, chloro- and nitro-substituents respectively (Table 14, entries 13, 14 and 15). The minimum isolated yield of 19% was obtained with a bulky naphthalene substituent **47k** (Table 14, entry 11). When heterocyclic substituents (R^1= 3-Furyl, 2-Thienyl and 3-Pyr) were employed (Table 14, entries 6, 10 and 16), the isolated yield remained high at 75-93%. When R^2= Me (Table 14, entries 17 and 18) the compounds **47q** and **47r** were generated in high isolated yields of 82% and 67%, respectively. The allylated product **47s** (Table 14, entry 19) was not found for indole containing imine, due to the enamine tautomerisation, which results in reducing electrophilicity of the carbon atom in carbon-nitrogen double bond (Scheme 44).



Scheme 44: Indole enamine tautomerisation

The synthesised 3-methyl substituted homoallylamines **47a-r** was used later when expanding the scope of γ-lactam synthesis (Table 16, Page 65).

A mixture of epimers of homoallylamine derived from chiral amine (*R*-methyl-phenylamine) was synthesised from the treatment of enantiopure imine **127** with ally zinc reagent prepared *in situ*. The product was obtained as a mixture of epimers **128** (7:3 *syn*/*anti*), which could not be separated. The ratio was determined by analysis of ^{1}H NMR spectrum of the isolated mixture of the synthesised compound.



127 **128**

dr 73:27

Scheme 45: Formation of diastereometric mixture from enantiopure imine

In Figure 21, the formation of the different ratio of the diastereoisomers, based on the suggested transition states is drawn. The methyl group could result in reducing the amount of one isomer in comparison to the other isomer. The reason could be steric clashes between 1-3 diaxial interaction of the phenyl and the methyl group, which resulted in the formation of two disfavoured transition states: TS II and TS IV.

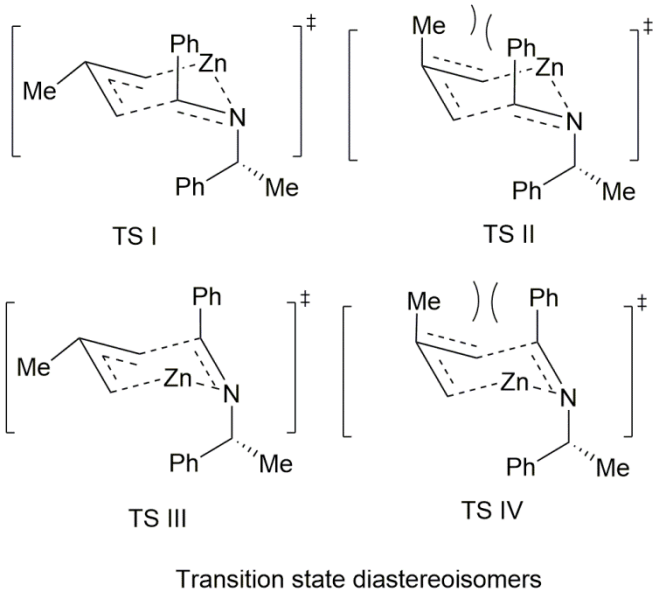
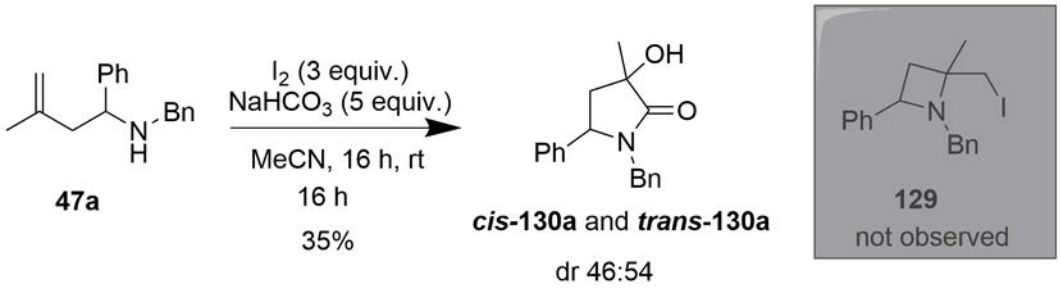


Figure 21: Possible transition states for the formation a mixture of two diastereoisomers

2.3.2 Cyclisation of 3-methyl substituted homoallylamines

The cyclisation of 3-methyl substituted homoallylamines is important because we believed that the cyclisation of 3-methyl substituted homoallylamine could give azetidine **129** (Scheme 46).In order to investigate the synthesis of azetidines bearing a quaternary stereocentre at the 4-position, the cyclisation of 3-methyl substituted homoallylamine had not been attempted by using molecular iodine. However, as mentioned previously the cyclisation by using electrophilic selenium reagent was reported to give a mixture of azetidine and pyrrolidine.[8] The synthesis of

azetidine from the cyclisation of 3-methyl substituted homoallylamine was attempted according to the iodocyclisation protocol.[21] Unlike the cyclisation of homoallylamine to generate azetidine, the desired azetidine was not obtained as envisaged. The analysis of TLC of the material obtained after initial flash chromatography showed no evidence for remaining the starting materials and analysis of the proton NMR spectrum of the crude obtained indicated the formation of a mixture of products, which was supported by the TLC observation. Separation was attempted by using various solvent conditions in flash chromatography. Fortunately, separation was achieved by running longer column chromatography, followed by crystallisations from (20% EtOAc/petroleum ether). The IR spectrum showed a broad peak around 1670 cm^{-1} from an amide (C=O) stretch, but from these analyses alone the actual structure remained elusive. Fortunately, single crystals were formed and the structures were confirmed by X-ray diffraction analysis showing one stereoisomer of a pyrrolidin-2-one (γ-lactam) *cis*-**130**. This was supported with X-Ray diffraction analysis of a crystal of the stereoisomer *trans*-**130** (Scheme 46 and Figure 22).



Scheme 46: Cyclisation of 3-methyl substituted homoallylamine

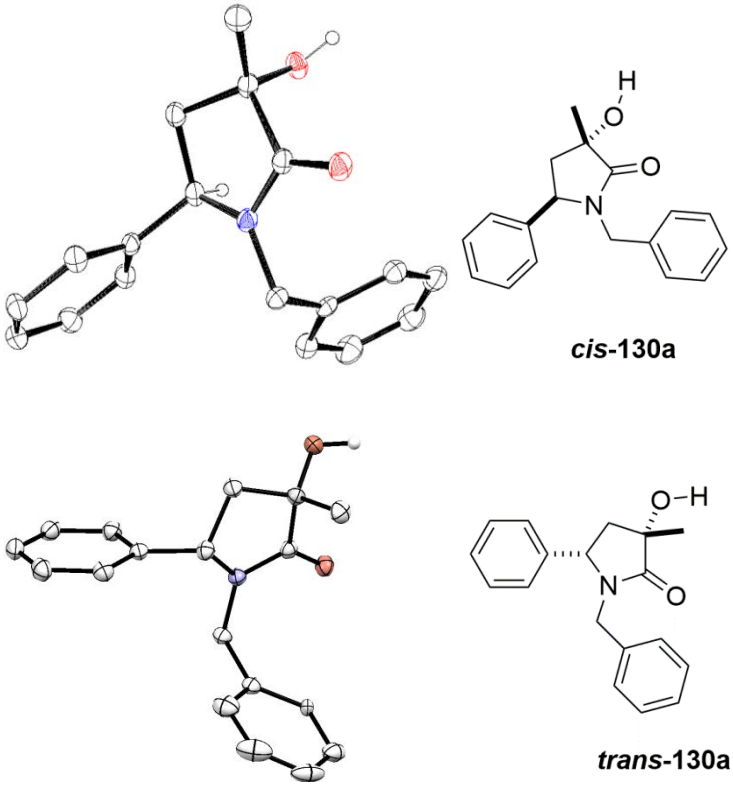


Figure 22: X-Ray crystal structure of *cis*-130 and *trans*-130 with ellipsoids drawn at the 50 % probability level. X-Ray structure analysis performed by Dr. Louise Male at the University of Birmingham.

In addition, with X-ray diffraction results in hand, the relative stereochemistry was more easily assigned for both isomers, using nuclear Over Hauser effect (nOe) experiments (Figure 23). To corroborate this, irradiation of H^a in compound *cis*-**130a** resulted in increasing the H^c signal and the proton of the hydroxyl group, but no nOe was observed between H^a and the phenyl protons. Correspondingly, irradiation of proton H^b in compound *cis*-**130a** led to an increase in the signal of the protons belonging to the methyl group and the phenyl protons, but not the proton of the hydroxyl group. Similarly, irradiation of H^c in compound *trans*-**130a** resulted in increasing the signal of H^b, H^a and protons of the methyl group *trans*-**130a**. As a result, the relative

stereochemistry was found to be *cis*-**130a** and for the *trans*-**130a** was assigned by the same technique and supported by X-ray crystal structure.

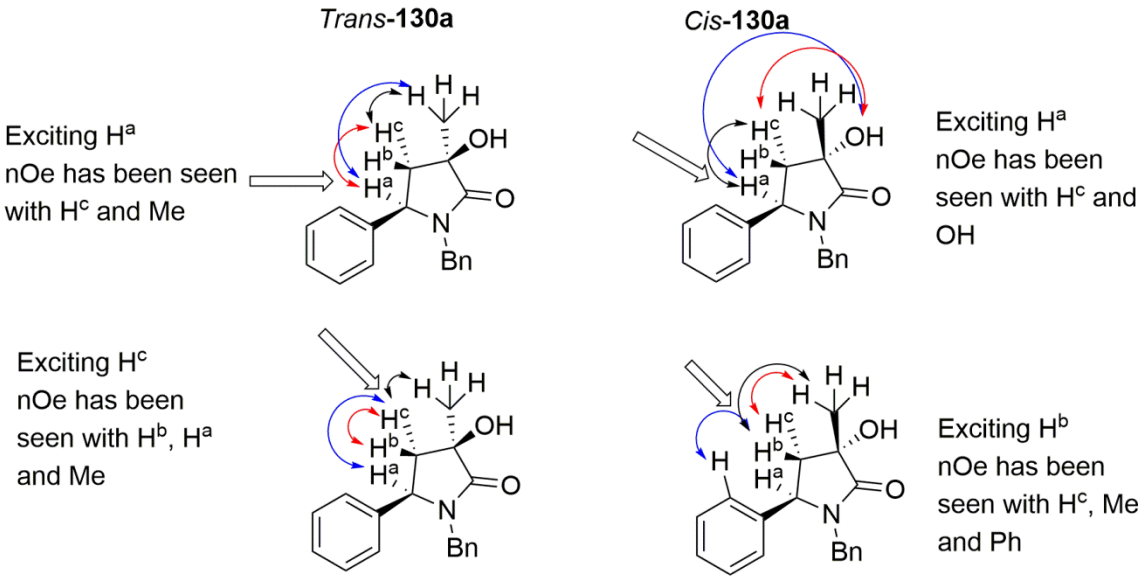
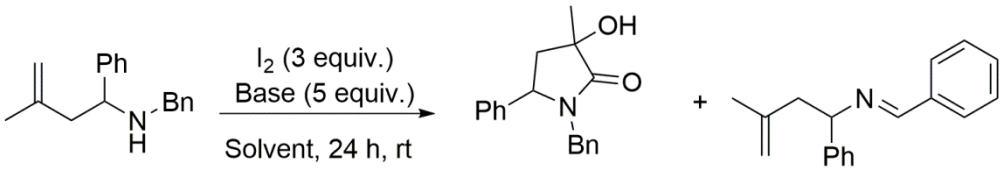


Figure 23: nOe experiments for compound *cis*-130a and *trans*-130a

When the structure and the relative stereochemistry of the unexpected γ-lactam was confirmed, In addition to the literature reports on the significant roles of γ-lactams,[66] particularly in the synthesis of alkaloids and pharmaceutical chemistry,[67] then the separation of diastereomer was performed, followed by the reaction conditions optimisation, and the scope of the method was investigated.

Reaction optimisation of γ-lactam synthesis was carried out by screening various solvents and bases (Table 15).

Table 15: Base and solvent screening for synthesis of γ-lactam



47a **130a** ***cis/trans*** **131**

Entry	Base	Solvent	% yield[b] (130a *cis*/ *trans*)	% 47a	% 130a *cis*/ *trans*	% 131	d.r[a]
1	$NaHCO_3$	CH_3CN	35	35	35	30	57: 43
2	**Cs_2CO_3**	**CH_3CN**	**-**	**27**	**-**	**73**	**-**
3	NaOAc	CH_3CN	20	60	20	20	50: 50
4	NaOH	CH_3CN	18	75	25	-	51: 49
5	Na_2CO_3	CH_3CN	20	43	27	30	60: 40
6	K_2CO_3	CH_3CN	25	33	30	37	43: 57
7	Li_2CO_3	CH_3CN	22	48	22	30	56: 44
8	LiOH	CH_3CN	47	34	47	19	57: 43
9	KOH	CH_3CN	21	53	22	25	54: 46
10	--	CH_3CN	25	65	30	5	56:44
11	$NaHCO_3$	MeCN:H_2O[c]	21	48	30	21	33: 67
12	**$NaHCO_3$**	**EtOAc**	**89**	**0**	**>99**	**0**	**46**: **54**
13	$NaHCO_3$	Dry THF	60	10	60	30	38: 62
14	$NaHCO_3$	MeOH	10	43	40	17	45: 55
15	$NaHCO_3$	DCM	10	90	10	-	50: 50
16	$NaHCO_3$	Dry MeCN	20	60	20	20	48: 52

(a)determined by ^{1}HNMR spectrum of pure product, (b) isolated yield after purification, (c) the ratio was 1:1

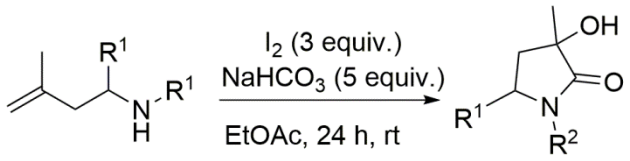
From the reaction conditions optimisation study, it was found that ethyl acetate as a solvent and sodium bicarbonate as a base (Table 15, entry 12) shows a higher yield of *cis*-**130a** and *trans*-**130a** after 24 hours and no by-products were observed. However, in all cases, the ratio of diastereomers was not improved significantly. Interestingly, the oxidation of the amine[68] was noted when cesium carbonate was used as a base and acetonitrile as a solvent (Table 15, entry 2) and no product was observed; instead imine **131** was obtained as a major product (Scheme 48). Sodium acetate and sodium hydroxide (Table 15, entry 3 and 4) gave a 20-25% isolated yield respectively, with a nearly equal diastereomer ratio 1:1. The best diastereomer ratio (60:40) was achieved when sodium carbonate was used as a base (Table 15, entry 5). However, the isolated yield was low (20%). Potassium carbonate (Table 15, entry 6) resulted in a slight increase in the isolated yield 30% and diastereomer ratio also slightly changed to 43:57. Lithium carbonate and potassium carbonate (Table 15, entry 7 and 9) produced no significant change in the isolated yield and diasteroselectivity. Lithium hydroxide (Table 15, entry 8) increased the yield but did not affect the diastereomer ratio. In the case of three equivalents of iodine and no base (Table 15, entry 10), only 25% of γ-lactam was formed after 24 hours and 65% of starting material **47a** was recovered. In the presence of a mixture of acetonitrile and water 1:1, the diastereomer ratio was improved to about 1:3, but the isolated yield was low. When tetrahydrofuran as a solvent (Table 15, entry 13) was used the isolated yield was increased and the diasteroselectivity remained the same, which suggested that the diastereoselectivitiy is not a base nor a solvent dependant, rather the mechanism results in a non-selective cyclisation. What is noteworthy is that formation of compound **131** was found as a minor product in all cases except when sodium hydroxide in acetonitrile and sodium bicarbonate in dichloromethane (Table 15, entry 4 and 15). Cyclisation using different double bond activators such as NBS, Br_2 and NIS were performed, proton NMR

spectra showed a mixture of products, suggesting that none of these reagents is superior to molecular iodine.

2.3.2.1 Expanding the scope of γ-lactam synthesis

With satisfactory reaction conditions in hand, and having various 3-methyl substituted homoallylamines (**47a-r**) synthesised (section 2.3.1), the scope of the developed methodology was probed. Several novel γ-lactam derivatives were synthesised, and in all cases, γ-lactams as a mixture of **(*cis*/*trans*)** were found to be the major product (Table 16).

Table 16: Synthesised γ-lactams *via* iodine mediated cyclisation of 3-methyl substituted homoallylamine



47a-q **130a-q**

Entry	Compound	R^1	R^2	% yield[a]	d.r.[b]
1	**130a**	Ph	Bn	89	54:46
2	**130b**	Ph	3-Picolyl	91	57:43
3	**130c**	Ph	*n*-Pr	34	56:44
4	**130d**	Ph	2-Me-benzyl	43	60:40
5	**130e**	3-Furyl	Bn	72	54:46
6	**130f**	*t*-Bu	Bn	67	55:45
7	**130g**	3,4-OMe-Ph	Bn	65	56:44
8	**130h**	Ph	4-OMe-benzyl	78	61:39
9	**130i**	Ph	Admantyl	57	30:70
10	**130j**	2-Thio	Bn	73	36:64
11	**130k**	2-Br-Ph	Bn	55	67:33
12	**130l**	Ph	4-Cl-benzyl	64	60:40
13	**130m**	4-NO_2-Ph	Bn	55	45:55
14	**130n**	1-Naph	Bn	72	24:76
15	**130o**	Ph	Me	43	56:44
16	**130p**	3-Pyr	4-OMe-benzyl	99	52:48
17	**130q**	3-Pyr	Me	68	53:47

(a) isolated yield as a mixture of diastereomers, (b) determined by ^{1}H NMR spectrum of the isolated products

The γ-lactams **130a-q** were obtained in moderate to high yields as the major products for all substrates tried. When phenyl substituent at R^1 and a benzyl substituent at R^2 was employed (Table 16, entry 1), the corresponding γ-lactam **130a** was obtained in a high yield 89%. Alkyl

substituent amines (Table 16, entries 3, 15 and 17) can also be cyclised to deliver γ-lactams. However, the cyclisation of a similar substrate was found to not deliver azetidine.[22] When R^2= *n*-Pr (Table 16, entry 3) the isolated yield was slightly low at 34%. In general, alkyl substituents at R^2 gave lower yields compared to the alkyl substituent at R^1=*tert*-butyl (Table 16, entry 6) that gave reasonable yields (67%), suggesting that alkyl group containing substrates are not very reactive under these reaction conditions. *Para*-substituted benzylic substituents at R^2 were probed, such as 4-chlorobenzyl and 4-methoxybenzyl (Table 16, entries 8 and 12), they gave high yield (78 and 64%) respectively. An *ortho*-substituted benzylic substituent 2-tolylbenzyl at R^2 (Table 16, entry 4) led to a redution in the isolated yield (43%). An electronic effect of substituents at R^1 was also employed (Table 16, entries 11 and 13), *ortho*- and *para*-substituents (2-bromophenyl and 4-nitrophenyl) and isolated yield was notably reduced to (55%). Heterocyclic substituents (3-furyl and 2-thienyl) were used at R^1 (Table 16, entries 5 and 10) and the yield was improved to (72 and 73%) respectively. The diastereomer ratios of the products were not improved again by changing R^1 and R^2 substituents. The best diastereomer ratio (67:33 d.r.) was achieved with 2-bromobenzyl substituent at R^1 (Table 16, entry 11), but the isolated yield was low (55%). The diastereomer ratios of the synthesised compounds were calculated by comparison of signals in the analysis of ^{1}H NMR spectra.

Figure 24 gives a representative example of the spectrum of non-separated mixtures of diastereomer of compound **130q**, which shows the two apparent *triplets* next to other at around 4.42 and 4.70 ppm which belong to the (C*H*) of both diastereomer of the product. These are compared to the singlet around 4.84 or singlet at 4.88 ppm each of which belongs to one proton

of the starting material (C=CH_2) homoallylamine, and to another singlet at around 8.1 ppm which belongs to the single proton (C*H*=N) of compound **131**.

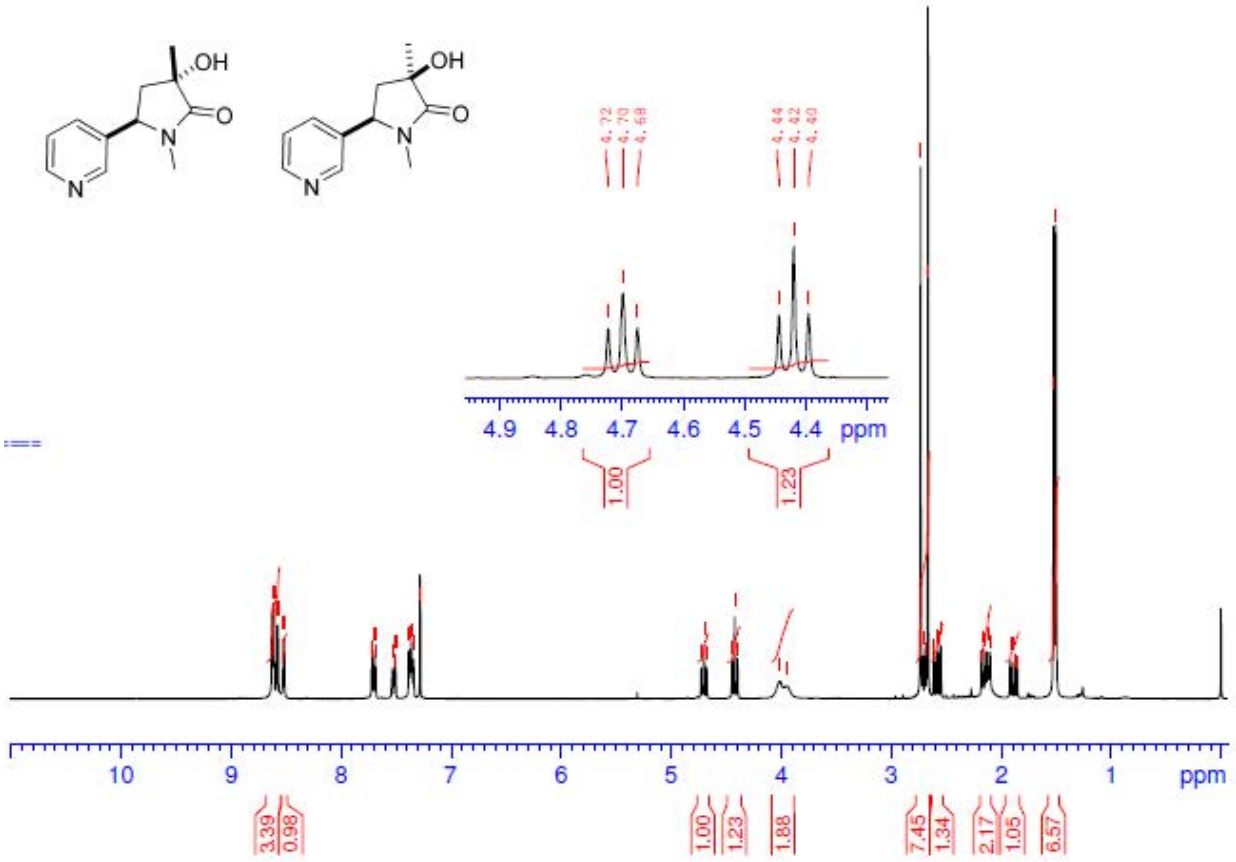


Figure 24: ^{1}H NMR spectrum of a mixture of diastereoisomers of compound *cis*-130q and *trans*-130q

Figure 25 provides an example on the separated mixture of diastereoisomers of the one synthesised compound **130o** into single diastereoisomers. Single diastereoisomers were separated for all the synthesised mixtures by using column chromatography, and the correct solvent mixtures allowed for separation. This could be applied to all the synthesised molecules.

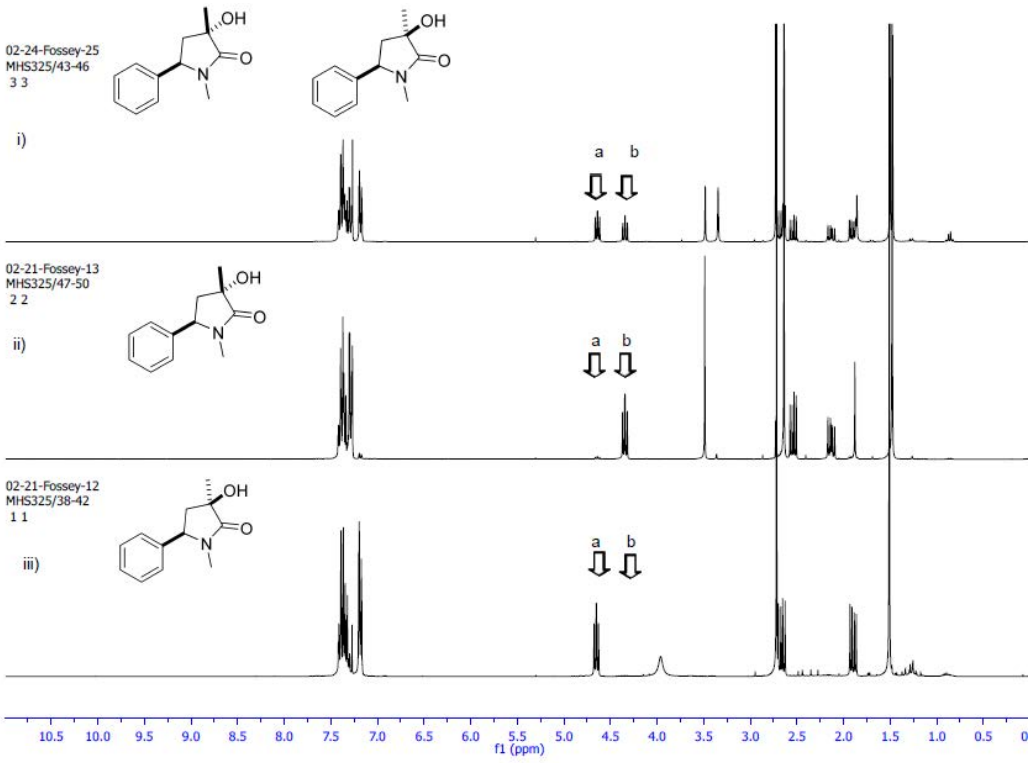


Figure 25: The ^{1}H NMR spectra shown for a mixture and individual diastereoisomers of compound 130o

The relative stereochemistry was assigned to some of the synthesised γ-lactam derivatives (experimental section) by single crystal X-ray diffraction. The crystals of compound *trans*-**130d** were grown in a mixture of ethyl acetate and hexane or ethyl acetate and petroleum ether, and the X-ray crystal structure is shown (Figure 26).

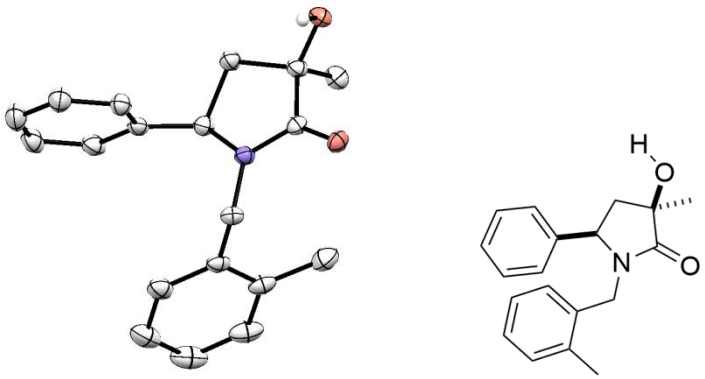
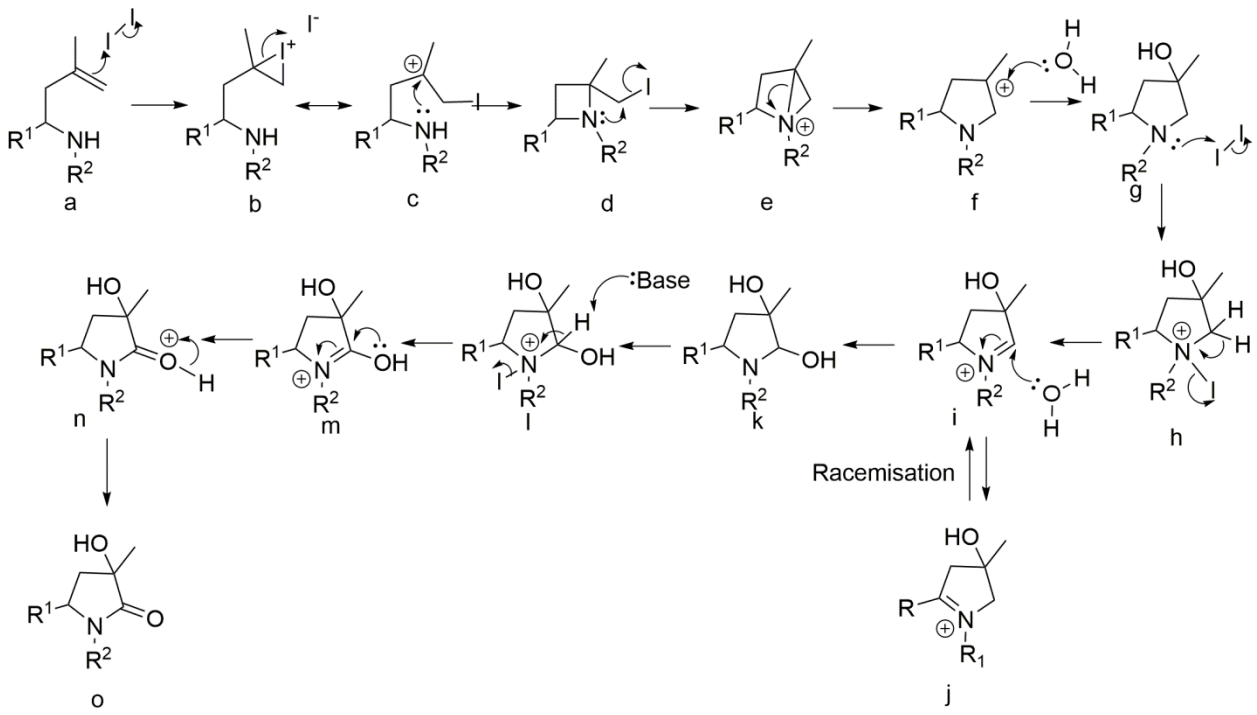


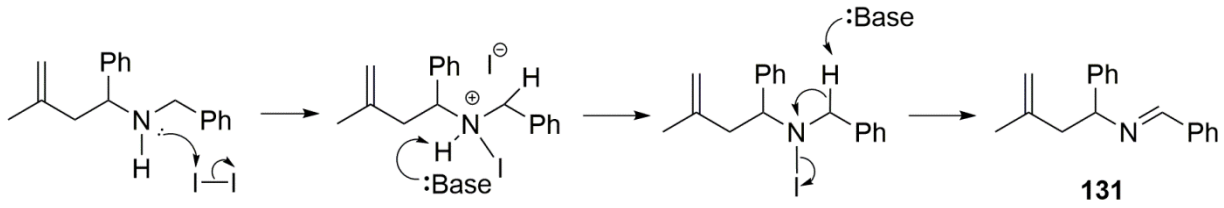
Figure 26: X-ray crystal structures of compound *trans*-130d

Scheme 47 shows the suggested reaction mechanism for the formation of racemic γ-lactams. The reaction was start through the formation of iodonium intermediate **b**, followed by the formation of quaternary carbonium ion **c**, which could then be attacked by the nitrogen lone pair through S_N1 mechanism to form azetidine intermediate **d**. The unstable intermediate is robustly transformed in to a five membered ring pyrrolidines **f** *via* azetidinium intermediate **e**, followed by a series of elimination and addition and finally oxidation of **k** to deliver γ-lactam **o** in the final step (Scheme 47). It is believed that the oxidation of **g** to produce **i** could cause racemisation to from **j** rather than **k**.



Scheme 47: Proposed mechanism pathway to form γ-lactams

The mechanism for the formation of the minor product **131** shows in the Scheme 48, which ends by the elimination of a proton from a less hindered carbon next to nitrogen atom to form the corresponding imine **131**.[68]

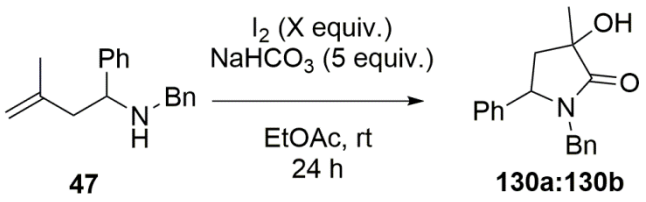


Scheme 48: Mechanism pathway to form the corresponding oxidised form of imine

Based on the proposed mechanism for the formation of γ-lactams, and in order to understand the reaction mechanism through the formation of the intermediate compounds shown in Scheme 47, the equivalents of iodine were probed. When one equivalent of iodine was used, no product was

obtained, but most of the starting material was recovered. When two equivalents of iodine were used, no product was observed and only 20% of the starting material was recovered. When iodine was used in excess (three, four and five equivalents), γ-lactams ***cis*-130** and ***trans*-130** as major products were obtained in more than 98% isolated yields, suggesting that the formation of γ-lactams needs iodine in excess to help the oxidation of the proposed double bond containing intermediates, which are shown in the suggested reaction mechanism (Scheme 45).

Table 17: Iodine screening for synthesis of lactams

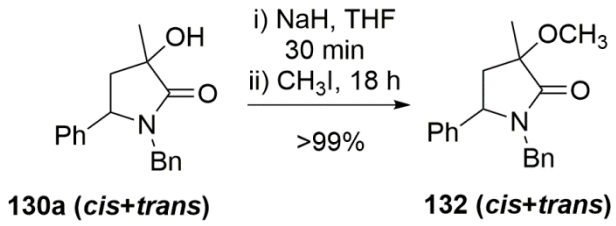


47 **130a:130b**

Entry	Iodine (equivalents)	47 %	% Yield 130a:130b	% by-product[a]
1	1	90	-	10
2	2	20	-	80
3	3	-	98	2
4	4	-	>99	0.5
5	5	-	>99	0.5

2.3.2.2 Modification of γ-lactams

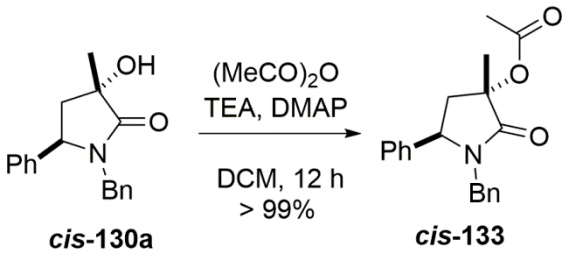
Methylation of the tertiary alcohol of the γ-lactam was attempted for two reasons; firstly to compare the ease of separation of diastereoisomers before and after methylation, and secondly to study the biological activity after methylation. Hence, the mixture of diastereoisomers of compound **130** has been methylated (Scheme 49), the hydroxyl group was deprotonated by treatment with sodium hydride and followed by *O*-methylation gave quantitative conversion to compound **132** as a mixture of diastereoisomers. The separation of diastereoisomers was attempted for the methylated product and no significant improvements were seen, the separation was as laborious with the parent OH.



130a (*cis*+*trans*) **132 (*cis*+*trans*)**

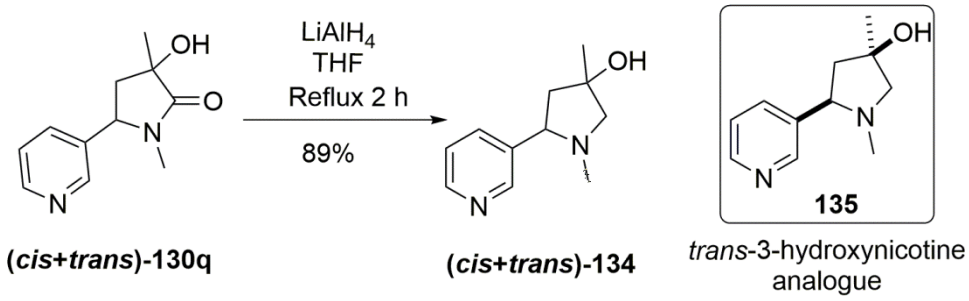
Scheme 49: Methylation of hydroxyl group of (*cis*/*trans*)-130a to give 132

In order to modify hydroxyl group of γ-lactam, acetylation was carried out on a single diastereoisomer of compound ***cis*-130p** (based on the availability of single diastereoisomer of starting material) using acetic anhydride in the presence of DMAP as a nucleophilic catalyst, with triethylamine in dichloromethane as a solvent. The complete conversion was achieved giving a single diastereoisomer of acetylated product ***cis*-133**.



Scheme 50: Acetylation of cis-130a to give *cis*-133

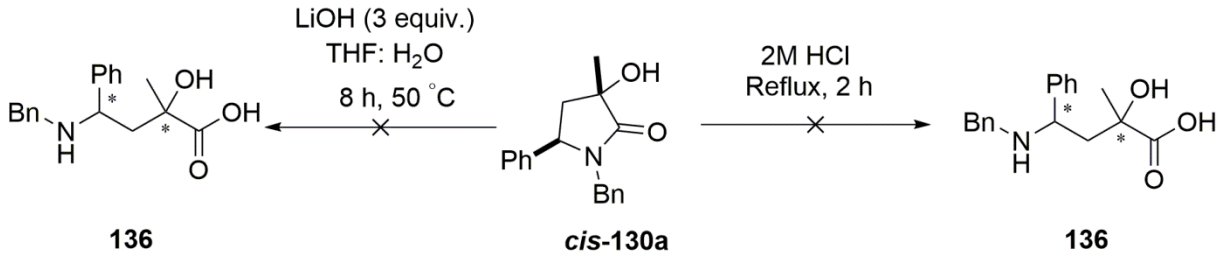
Trans-3-hydroxynicotine **135** has been reported to bind neuronal acetylcholine receptors and enhance cognition function.[69] In order to generate the analogue of **135**, the reduction of carbonyl group of compound **130q** was performed. The carbonyl group in compound **130q** was reduced. Initially, five equivalents of lithium aluminium hydride were used and only 56% of **134q** was isolated, when the amount of reducing agent was increased to ten equivalents, the yield was improved to 89% isolated yield of **134q**. The separation to get the single diastereoisomers was found to be more difficult compared to the starting material. The relative stereochemistry after reduction was confirmed for both single diastereoisomers by nOe experiment.



Scheme 51: Reduction of carbonyl group of compound 130q

The α-hydroxy-γ-amino acids **136** are well known for their interesting role in biology, [70] such as anti-HIV activities.[71] the hydrolysis of γ-lactam would deliver α-hydroxy-γ-amino acids **136**. Therefore, acid and base mediated ring opening were attempted several times on ***cis*-130a**. So far,

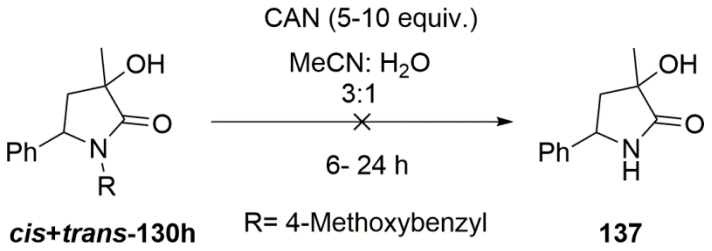
only the starting material was recovered. These results suggest the stability of the synthesised γ-lactams to acid and base conditions.



Scheme 52: Acid and base catalysed ring-opening attempts of γ-lactam 130a

Further work could be done to make the reaction work, such as increasing the reaction temperature, changing the solvent, and controlling the reaction time.

Deprotection of nitrogen group could be important to generate a new version of pyrrolidine compound **137** bearing free nitrogen atom that helps to coordinate better with metal ions. CAN was previously reported as the most widely used reagent for oxidative cleavage of *N*-4-methoxybenzyl group.[72] In order to generate compound **137**, deprotection of *N*-4-methoxybenzyl group from compound **130h** was attempted in the presence of five to ten equivalents of CAN using literature protocol.[45] The reaction was tried several times by changing reaction conditions, such as changing the equivalents of CAN or the ratio of water to acetonitrile, but the product **137** was not observed (Scheme 53). However, the TLC analysis showed consumption of all starting material. The reason for this result is not clear, but it could be a result of degradation of the molecule because of deprotection. The same procedure was applied on the reduced version of **130h**, unfortunately the product was not observed in this case either.

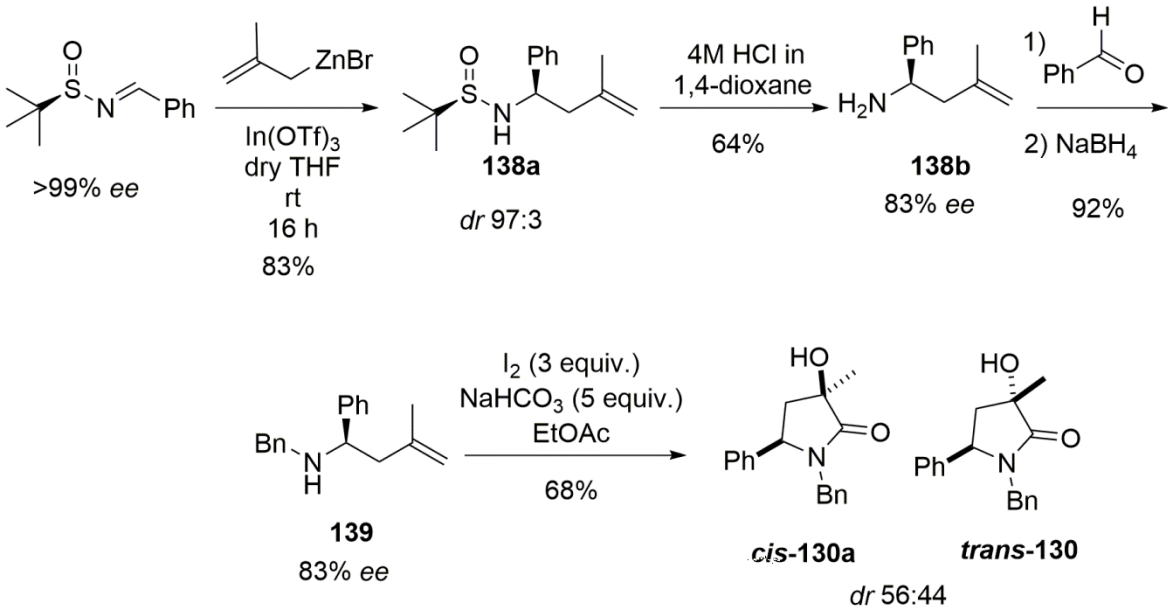


Scheme 53: Deprotection attempt of 4-Methoxybenzyl group from γ-lactam 130h

After several modifications were performed on some of the synthesised γ-lactams, and in order to test the possibility of the preparation of enantiopure γ-lactam compound, attention was then turned in to synthesis of enantiopure homoallylamines first, and cyclisation later on.

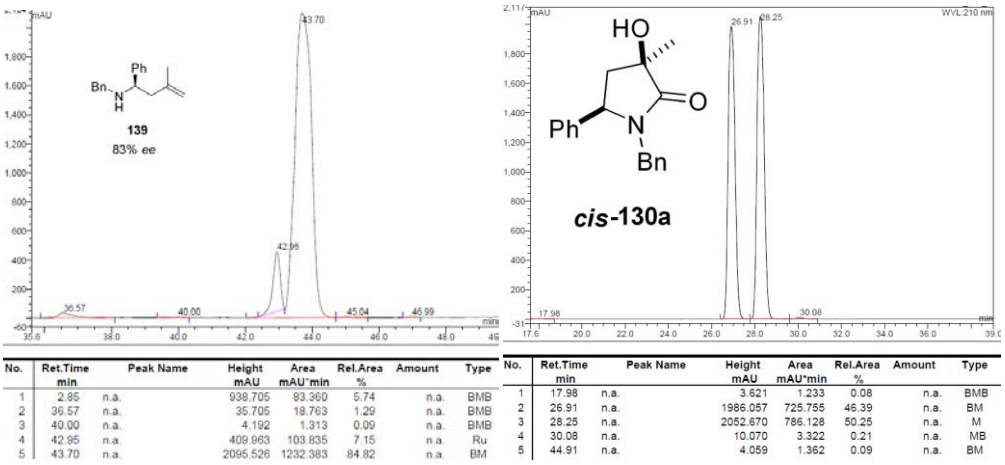
2.3.3 Cyclisation of enantio enriched 3-methyl substituted homoallylamines

The chiral amine auxiliary protocol was used in order to synthesise non-racemic γ-lactams. The reaction was attempted by the synthesis of enantiopure imine, followed by selective allylation in the presence of indium triflate to form **(2*R*, 4*R*)-138a**. Then the chiral auxiliary was removed to form enantiopure allyl amine ***R*-138b** in 64% isolated yield and 83% *ee*, followed by condensation with an aldehyde and subsequent reductive amination with sodium borohydride to obtain ***R*-139** in an 92% isolated yield and 83%*ee*.



Scheme 54: Attempted to synthesis of enantiopure γ-lactam from enantiopure homoallylamine gave racemic products

The cyclisation of compound **139** was attempted using the iodocyclisation protocol for synthesis of non-racemic γ-lactams. The product was purified and crystallised. The X-ray single crystal structure and optical rotation measurements all showed the formation of racemic γ-lactams ***cis*-130a** and ***trans*-130a**.



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	2.85	n.a.	938.705	83.360	5.74	n.a.	BMB
2	36.57	n.a.	35.705	18.763	1.29	n.a.	BMB
3	40.00	n.a.	4.192	1.313	0.09	n.a.	BMB
4	42.95	n.a.	409.963	103.835	7.15	n.a.	Ru
5	43.70	n.a.	2095.526	1232.383	84.82	n.a.	BM

No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	17.98	n.a.	3.621	1.233	0.08	n.a.	BMB
2	26.91	n.a.	1986.057	725.755	46.39	n.a.	BM
3	28.25	n.a.	2052.670	786.128	50.25	n.a.	M
4	30.08	n.a.	10.070	3.322	0.21	n.a.	MB
5	44.91	n.a.	4.059	1.362	0.09	n.a.	BM

Figure 27: Analytical HPLC spectra showed racemic formation of γ-lactam Non-racemic starting material (left hand) and racemic product after diastereoisomer separation (right hand)

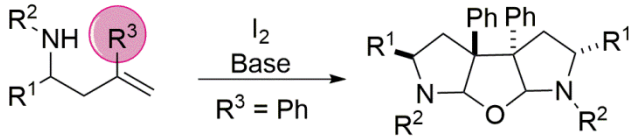
The products **130a** and **130b** were found to have zero optical rotation on polarimeter, this mean that the product is not be enantiopure, this is also confirmed by X-ray diffraction technique which shows molecule as centrosymmetric, which contains an inversion centre, and two of four molecules in the unit cell are (*S*) and the other two are (*R*). For further proving racemisation, the HPLC was run for the starting material and the product, the HPLC spectrum also shows two peaks for the product, while the staring material homoallylamine was found as enantio enriched with 83% *ee* (Figure 27). The reason for such racemisation is defined by the suggested reaction mechanism from the oxidation step to form imine intermediate with the defined stereocentre hydrogen atom (Scheme 47, **j**).

A new efficient synthetic route for the synthesis of 1,3,5-trisubstituted-pyrrolidin-2-one bearing functionalised hydroxylated quaternary carbon centre **130a-q** in a moderate to good yield *via* iodine mediated cyclisation of 3-methyl substituted homoallylamines at room temperature has been presented. Although the mixture of diastereomers are obtained, this method has several promising features; three simple steps, readily available and inexpensive starting materials, and finally, good yields with low by-products.

To expand the scope of this new route, and to improve the selectivity of the developed method to synthesis of γ-lactams, the generation of 3-phenyl substituted pyrrolidine-2-ones (instead of 3-methyl substituted pyrrolidine-2-ones) *via* cyclisation of 3-phenyl substituted homoallylamines was investigated.

2.4 Furan bis-pyrrolidine synthesis

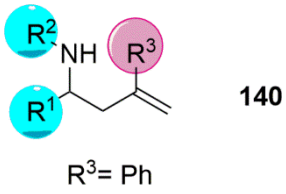
The cyclisation of phenyl substituted homoallylamine was studied in order to expand the scope of the γ-lactam synthesis (Scheme 55).



Scheme 55: General scheme for the synthesis of furan bispyrrolidine

2.4.1 Synthesis of 3-phenyl substituted homoallylamines intermediates

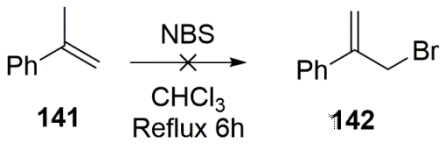
The cyclisation of 3-phenyl substituted homoallylamines was tried to expand the scope of γ-lactam synthesis. It was believed that the cyclisation of such homoallylamines could furnish γ-lactams bearing phenyl substitution at 3-position. We also believed that the phenyl group would improve selectivity of the method for the synthesis of azetidine or pyrrolidine or single diastereoisomer of γ-lactam based on the steric effect produced compared to methyl group. In order to understand this hypothesis, the synthesis of 3-phenyl substituted homoallylamine was attempted. Initially, the search for the existence of compound **140** was started either for readily availability or for synthetic procedure, only two literature references were found for the synthetic procedure regarding the synthesis of compound **140**.[73,74]



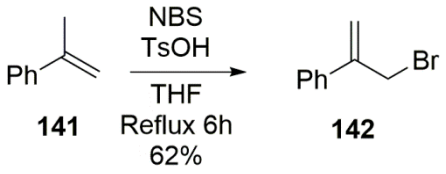
140

Figure 28: Homoallylamine with phenyl substitution at 3-position

The synthesis of 3-phenyl substituted homoallylamines **140** was attempted, from zinc-mediated allylation of imines in dry THF at reflux, using phenallylbromide **142**. Phenallylbromide was prepared by using literature procedure,[73] by the addition of NBS to α-methyl styrene **141** under reflux, in the presence of p-toluene sulfonic acid to give the desired phenallylbromide product **142** in a 62% isolated yield (Scheme 57). The first attempt in the absence of TsOH, utilising literature protocol[74] was unsuccessful, this suggests that the radical initiator TsOH is required.[73]



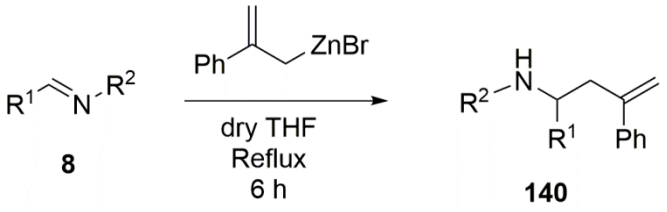
Scheme 56: Preparation of phenallylbromide in the absence of radical initiator



Scheme 57: Preparation of phenallylbromide *via* bromination of α-methyl styrene

A racemic mixture of **140** was obtained in a high yield from treatment of imine **8** with phenallyl zinc reagent prepared *in situ* from **142** in dry THF at reflux temperature. The reaction between imine and phenallyl zinc reagents was not observed at room temperature, however, heating the reaction mixture at reflux gave the desired products **140a-c** in 72-91% isolated yield (Table 18).

Table 18: Synthesised 3 -phenyl substituted homoallylamine



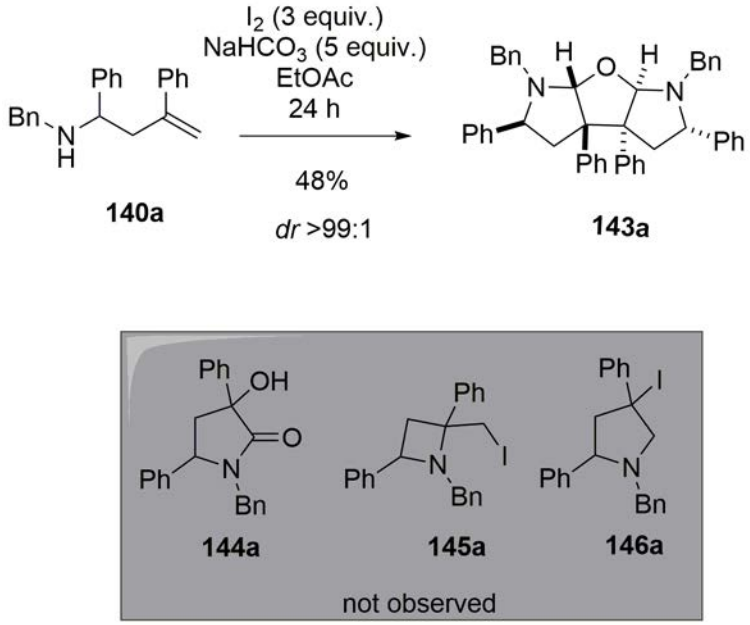
Entry	compound	R^1	R^2	% Yield[a]
1	**140a**	Ph	Bn	72
2	**140b**	Ph	4-Methoxybenzyl	82
3	**140c**	Ph	Me	91

(a) isolated yield after purification

When phenyl substituent was used at R^1 and benzyl at R^2, the product was obtained in 72% (Table 18, entry 1). When electron releasing substituent at R^2 (4-methoxybenzyl) was used (Table 18, entry 2), the isolated yield of **140b** increased to 82%. When alkyl substituent at R^2 was used (Table 18, entry 3), the isolated yield of **140c** was much higher (91%). Then the cyclisation was investigated.

2.4.2 Cyclisation of 3–phenyl substituted homoallylamines

Compound **140a** underwent iodocyclisation using the developed procedure for the synthesis of γ-lactam (Section 2.3, page 55). Analysis by TLC showed formation of the product after 24 hours. After workup, it was found the product could be easily crystallised from hexane or petroleum ether alone. The analysis of proton NMR spectra of the crude mixture showed no evidence for the formation of any of the desired products **144a**, **145a** and **146a**. Hence, the product remained an unexpected compound.



Scheme 58: Iodocyclisation of 3-phenyl substituted homoallylamine

Crystallisation of the product from petroleum ether gave a single crystal for X-ray crystal structure determination. The structure was shown to be a novel fused tricyclic furan bispyrrolidine **143a**.

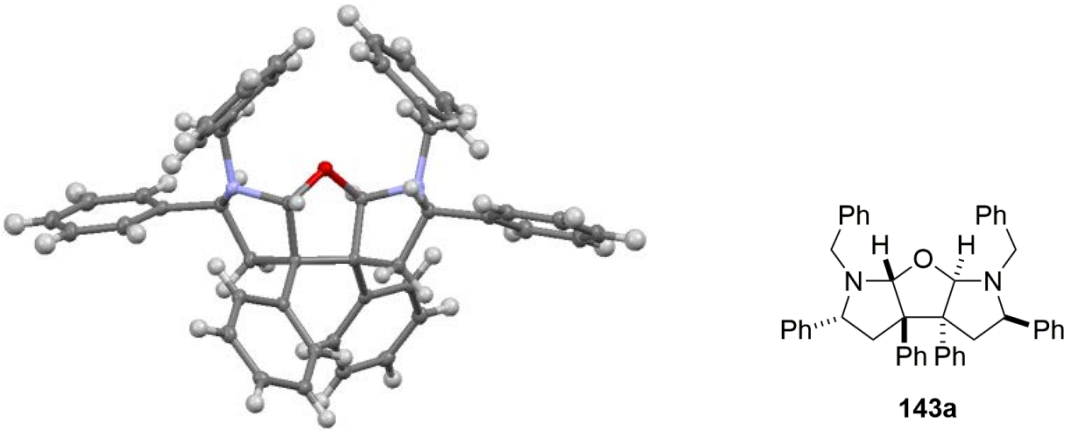
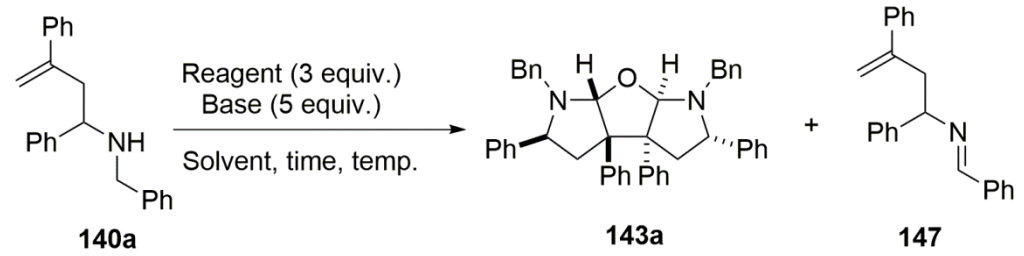


Figure 29: X-ray crystal structure of 143a with ellipsoids drawn at the 50 % probability level

Unexpectedly, Furan bispyrrolidine **143a** was formed as a C2-racemate of the single diastereoisomer, as shown in Figure 29, in an acceptable yield (48%), from oxidative dimerisation of 3-phenyl substituted homoallylamine **140a**.

Compound **140a** was used as a typical substrate for the optimisation of reaction conditions in order to improve the product yield of tricyclic compound **143a**. Several bases and solvents were screened in addition to changing temperature and reagents, the standard reaction condition (Table 19, entry 1) gave a higher yield compared to other reaction conditions that have been tested.

Table 19: Study and optimisation of reaction condition for fused tricyclic compound



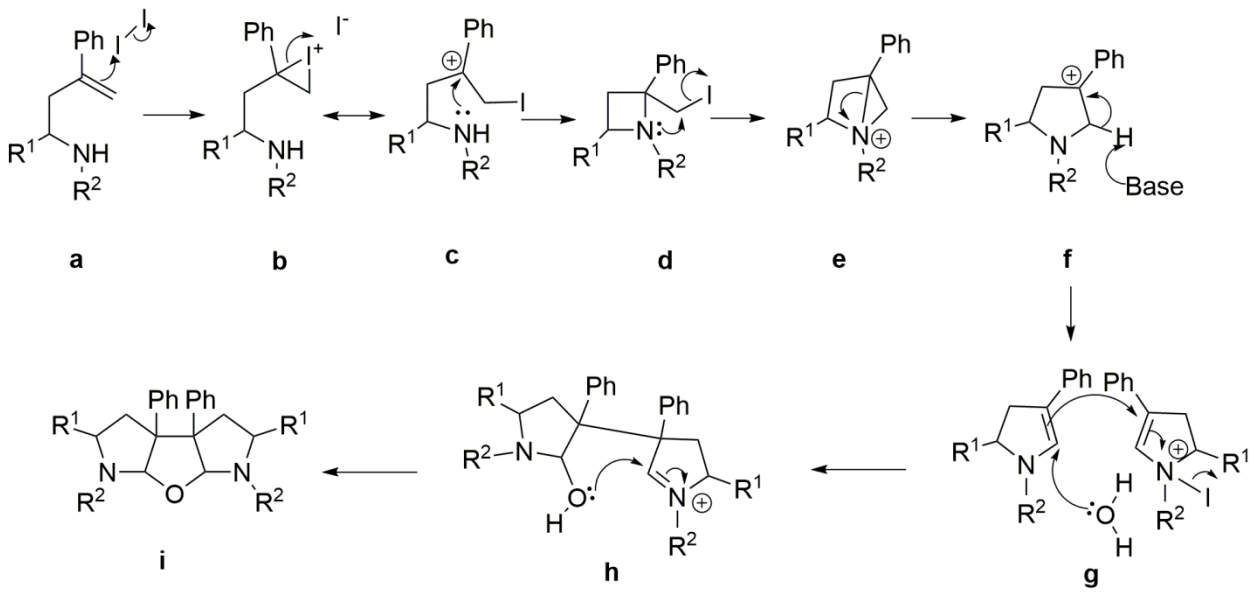
140a **143a** **147**

Entry	Solvent	Base	T/ °C	Time /h	Reagent	140a %	143a %[a]	147 %
1	**EtOAc**	**$NaHCO_3$**	**r.t.**	**24**	**I_2**	**52**	**48**	**-**
2	EtOAc	$NaHCO_3$	Reflux	24	I_2	81	19	-
3	EtOAc	$NaHCO_3$	r.t	48	I_2	83	17	-
4	EtOAc	$NaHCO_3$	r.t	72	I_2	89	11	-
5	EtOAc	LiOH	r.t	24	I_2	80	20	-
6	EtOH	$NaHCO_3$	r.t	24	I_2	>50	-[b]	-
7	MeCN	$NaHCO_3$	r.t	48	I_2	69	31	-
8	EtOAc	Cs_2CO_3	r.t	24	I_2	-	-	>99
9	EtOAc	$NaHCO_3$	r.t	24	NIS	73	27	-
10	EtOAc	$NaHCO_3$	r.t	24	Br_2	82	18	-
11	MeCN	LiOH	r.t	24	I_2	67	33	-
12	$CHCl_3$	$NaHCO_3$	r.t	24	I_2	>99	-	-
13	THF	$NaHCO_3$	r.t	24	I_2	81	19	-

(a) Isolated yield, (b) unidentified product

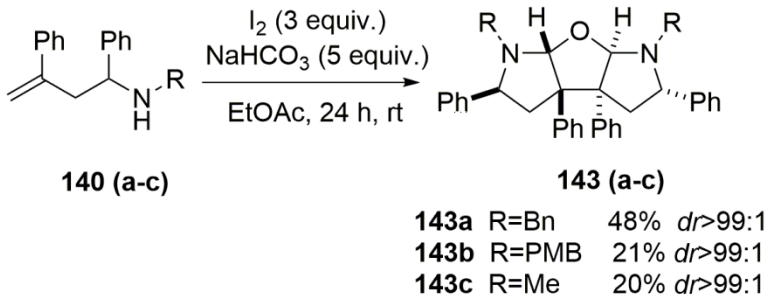
When leaving the reaction longer and increasing the reaction temperature to reflux, this led to a decrease in the isolated yield to 19-11% (Table 19, entry 2, 3 and 4), suggesting that the remaining product in the reaction vessel for a longer time could cause degradation of the molecule. Lithium hydroxide (Table 19, entry 5) did not alter the isolated yield of the product. In the presence of protic solvent ethanol (Table 19, entry 6), compound **143a** was not found, instead, the unidentified product was obtained with recovering >50% of the compound **140a**. Using acetonitrile as a solvent (Table 19, entry 7) gave lower yield 31%. Cesium carbonate (Table 19, entry 8) did not deliver compound **143a** as expected; instead, the corresponding oxidised form of starting material **147** was obtained. Using different cyclisation reagents NIS and Br_2 (Table 19, entry 9 and 10) did not help to improve the product yield. When LiOH in acetonitrile was employed (Table 19, entry 11), no significant improve in the yield was obtained. Employing halogenated solvent chloroform (Table 19, entry 12) led to recovering all of the starting material.

The proposed mechanism suggested the oxidative coupling of the enamine intermediates **g** produced after basic elimination of proton from pyrrolidinium intermediate **f** followed by nucleophilic attack from the nucleophilic carbon of pyrrolidines ring to form **h**, finally cyclisation to form furan ring fused with two molecules of pyrrolidines (Scheme 59).



Scheme 59: Suggested reaction mechanism for the formation of furan bispyrrolidine.

In order to determine the possibility of the formation of the fused tricyclic product from different substrate, the cyclisation of compound **140b** and **140c** were tried, using the same strategy. Compound **143b** and **143c** were obtained in 20% and 21% isolated yields respectively, (Scheme 60).



Scheme 60: Synthesis of fused tricyclic furan bispyrrolidine derivatives

From the results obtained, it was found that compound **143a-c** were obtained as major products. From these examples, it was investigated that variation of substituents R did not increase the

yields, but the selectivity was already solved for all substrates, as only single diastereoisomers were formed in each case.

In conclusion, a new synthetic procedure developed from the cyclisation of phenyl substituted homoallylamine for the preparation of fused tricyclic furan bispyrrolidines functionalised in three positions on each pyrrolidine ring *via* oxidative dimerisation of phenyl-substituted homoallylamines using the iodocyclisation procedure. Suggesting that the synthesis of γ-lactam bearing phenyl substituent instead of methyl substituent at 3- position was not possible using this strategy.

Further work in our research group is ongoing to expand the scope of this discovery, such as changing phenyl group and expanding scope of R to include heterocyclic groups and substituted phenyl groups. Additionally, investigation in to the synthesis of enantiopure furan bispyrrolidine is ongoing from the enantiopure starting material.

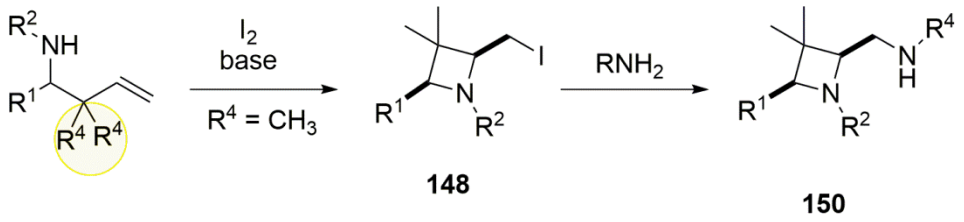
Chapter Two

Result and discussion

Synthesis of 3-substituted azetidine

2.5 Synthesis of 3-gem-dimethyl substituted azetidine

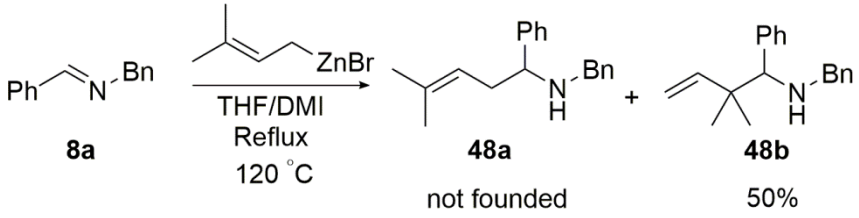
For further study on the cyclisation, the synthesis of 3-gem-dimethyl substituted azetidine from cyclisation of gem-dimethyl substituted homoallylamine was then investigated.



Scheme 61: General scheme for the synthesis of 3-gem-dimethylazetidine

2.5.1 Attempt toward synthesis of 4-gem-dimethyl substituted homoallylamine

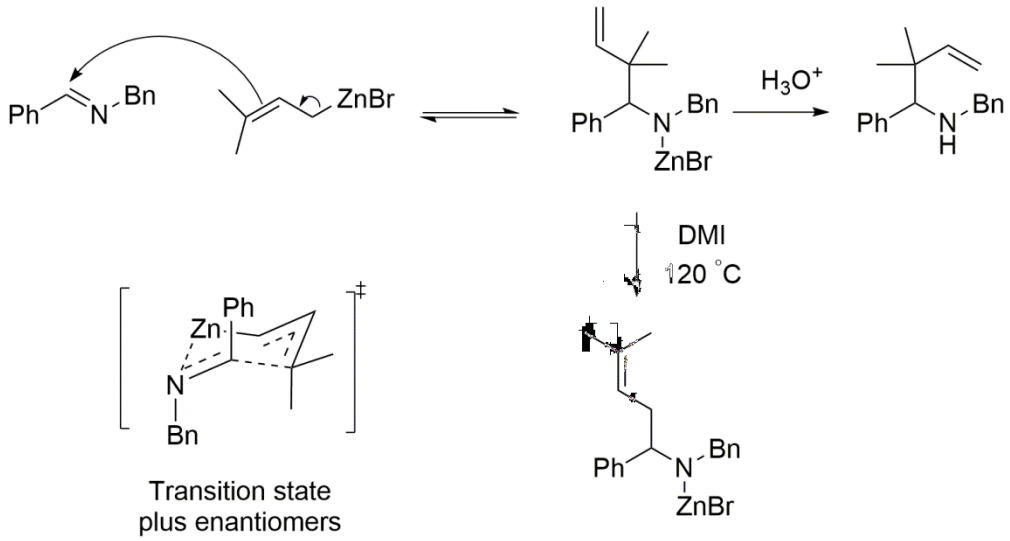
The synthesis of 4-gem-dimethyl substituted homoallylamines **48a** was previously reported that could be obtained regioselectively as a thermodynamic product, through treatment of imine with prenyl zinc bromide in the presence of THF and then DMI according to literature procedure.[75] In order to obtain **48a**, the allylation of imine **8a** was tried using prenyl zinc bromide *in situ* prepared in dry THF and DMI for 24 h. The product **48b** was formed in a 50% yield and recovering 40% of the starting material.



Scheme 62: Synthesis of 2-gem-dimethyl substituted homoallylamine

The expected reaction mechanism suggested for this reaction according to the literature, involves allylic rearrangement,[76] which occurs through a transition state (Scheme 63), or isomerisation of

the homoallylamines **48a** to **48b** in the presence of DMI and another imine molecule because of high temperature, but the formation of only **48b** suggests that the isomerisation did not occur.



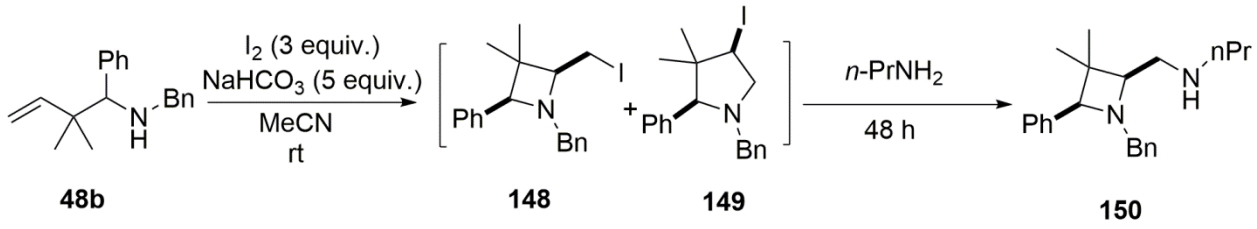
Scheme 63: Transition state and mechanism of synthesis of 2-gem-dimethallylamine

The zinc mediated allylation of imine **8a** to generate 4-gem-dimethyl substituted homoallylamines **48a** was unsuccessful due to the formation of **48b** being faster than **48a**. With 50% of **48b** in hand, then the cyclisation was attempted.

2.5.2 Cyclisation of 2-gem-dimethyl substituted homoallylamines

The iodocyclisation of 2-gem-dimethyl substituted homoallylamines was believed to furnish 2-gem-dimethylazetidines. Despite the difficulties faced during the synthesis of **48b** (section 2.5.1), cyclisation was attempted. After the reaction completed and analysis of the crude ^{1}H NMR spectrum revealed the formation of a mixture of equal amount of iodoazetidine **148** and iodopyrrolidine **149**. The resulting crude mixture was treated with excess propylamine, which

resulted in the recovery of the aminoazetidine **150** in a 50% isolated yield, but purification of aminopyrrolidine was not successful.



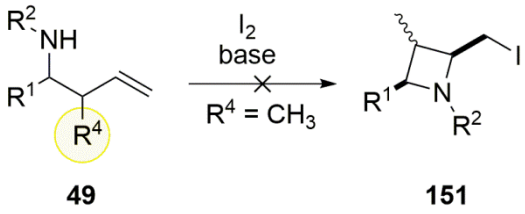
48b **148** **149** **150**

Scheme 64: Iodocyclisation of 2-gem-dimethylsubstitutedhomoallylamine

The synthesis of 2-gem-dimethyl substituted azetidines proved to be problematic by this strategy. Further work is ongoing in our research group towards discovering a new procedure for the synthesis of homoallylamine **48b**.

2.6 Towards the synthesis of 3-substituted azetidines

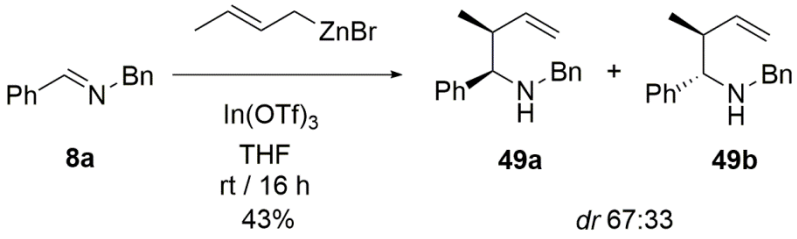
In order to study the cyclisation of 3-methyl substituted homoallylamine and the possibility of the synthesis of chiral 3-methyl substituted azetidine, the iodocyclisation of 2-methyl substituted homoallylamine was investigated.



Scheme 65: Suggested general scheme for the synthesis of 3-methylazetidines

2.6.1 Synthesis of 2-methyl substituted homoallylamine intermediate

The zinc-mediated allylation of imines **8a** utilising crotylbromide can afford **49a** and **49b** as a mixture of diastereomer (syn/anti) in a (7:3) ratio. The reaction was conducted using a combination of two literature procedures, [57,75] treatment of imine **8a** with the *in situ* generated allyl zinc reagent, which was prepared by using two equivalents of crotylbromide and 2.5 equivalents of zinc in dry THF in the presence of indium triflate. A mixture of diastereomers **49a** and **49b** were obtained (*dr* 67:33) in a 43% isolated yield.



Scheme 66: Synthesis of 2-methyl substituted homoallylamine

Several column chromatography methods were attempted for separation, but unfortunately, it was impossible to successfully separate the diastereomers. Analysis of the crude ^{1}H NMR spectrum of the product revealed a mixture of two diastereoisomers in a ratio of 67:33 (syn/anti). The ratio is due to the allylic rearrangement that resulted from the resonance of the transition state (Figure 30), which resulted in a decrease in the ratio of *syn* isomer compared to the *anti* isomer. As a result of the difficulties encountered during the separation of diastereoisomers, the compound was taken forward to the cyclisation step as a mixture of diastereoisomers.

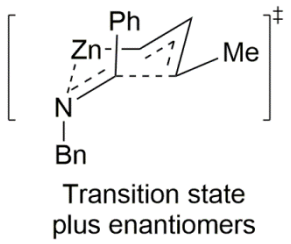
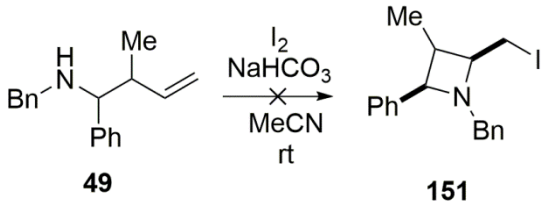


Figure 30: Transition state of 2-methyl homoallylamine formation

2.6.2 Cyclisation attempt of 2-methyl substituted homoallylamines

The cyclisation of 2-methyl substituted homoallylamine **49** was thought to give an azetidine with one extra chiral centre at the position 3 (**151**). The diastereometric mixtures of compound **49** were mixed with three equivalents of iodine and five equivalents of sodium bicarbonate in acetonitrile at room temperature. Analysis of the result confirmed that azetidine **151** was not generated. Instead, the mixture of mostly starting material and unidentified by-products were obtained.

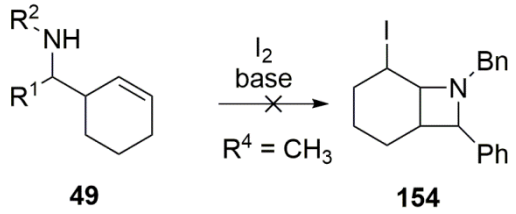


Scheme 67:Iodocyclisation of 2-methyl substituted homoallylamine

In conclusion, based on the results obtained from the cyclisation of 2-methyl substituted homoallylamine, it is proved that the synthesis of chiral 3-substituted azetidine is not possible by using this method. For further investigation, the reaction conditions optimisation could be considered or finding another synthetic route.

2.7 Cyclisation attempt of cyclic homoallylamine

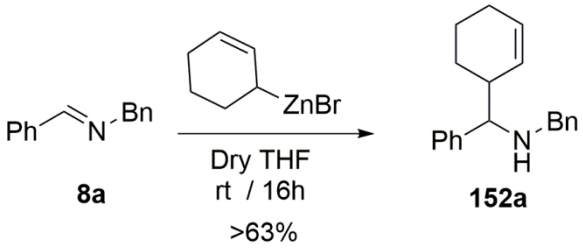
The study on the cyclisation of cyclic homoallylamine to obtain ring fused azetidine was attempted.



Scheme 68: Suggested general scheme for the synthesis of fused azetidines

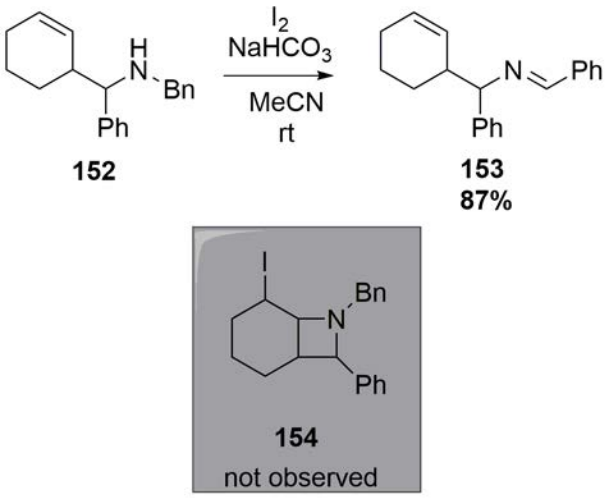
The syntheses of ring-fused azetidines were another goal that was expected that could be achieved from the cyclisation of cyclic homoallylamine **152a** (Scheme 70). In order to achieve this goal, the synthesis of cyclic homoallylamine **152a** was attempted. Homoallylamine **152a** was prepared in a 63% isolated yield, using the standard literature procedure, [57] by treatment of imine

8a with *in situ* prepared cyclohex-2-en-1-ylzinc bromide reagent, followed by an aqueous workup to give the crude product in complete conversion. Purifying **152a** using column chromatography causes degradation of the product. After numerous attempts for purification through traditional chromatographic techniques, including gravity and flash column chromatography utilising several solvent systems and eluent, such as ethyl acetate and hexane, it was found that triturating the crude compound in water overnight resulted in a pure product.



Scheme 69: Synthesis of cyclohexenylallylamine

Cyclisation of **152a** was attempted utilising the iodine mediated cyclisation strategy.[22] Analysis of TLC showed that all the starting material was consumed. The proton NMR spectrum showed no evidence for the formation of the desired fused azetidine **154**. Instead the secondary amine was oxidised to afford the corresponding imine **153** in >87% conversion based on unreacted starting material.



Scheme 70: Iodocyclisation of cyclic homoallylamine

The two possible transition states are proposed TS I and TS II (Figure 31). The formation of unfavourable high-energy transition state TS I, due to 1,3-diaxial interaction, prevented the cyclisation from delivering the desired fused azetidine**154**.

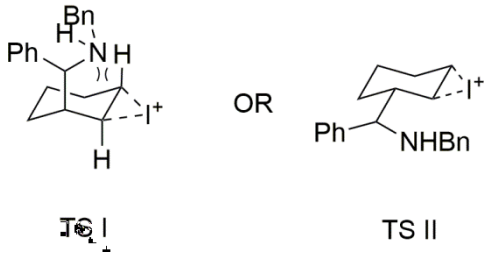
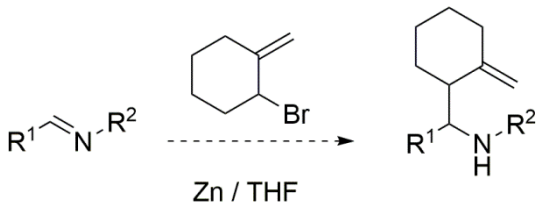


Figure 31: Unfavourable high-energy transition states

In conclusion, the cyclisation of cyclic homoallylamine was unsuccessful to deliver ring fused azetidine, suggests that the synthesis of ring fused azetidine need further servey and study to find a good method. For example, using terminal alkene bonded to aliphatic ring (Scheme 71). This work is currently in process in the Fossey research group, working towards synthesis of fused azetidines.

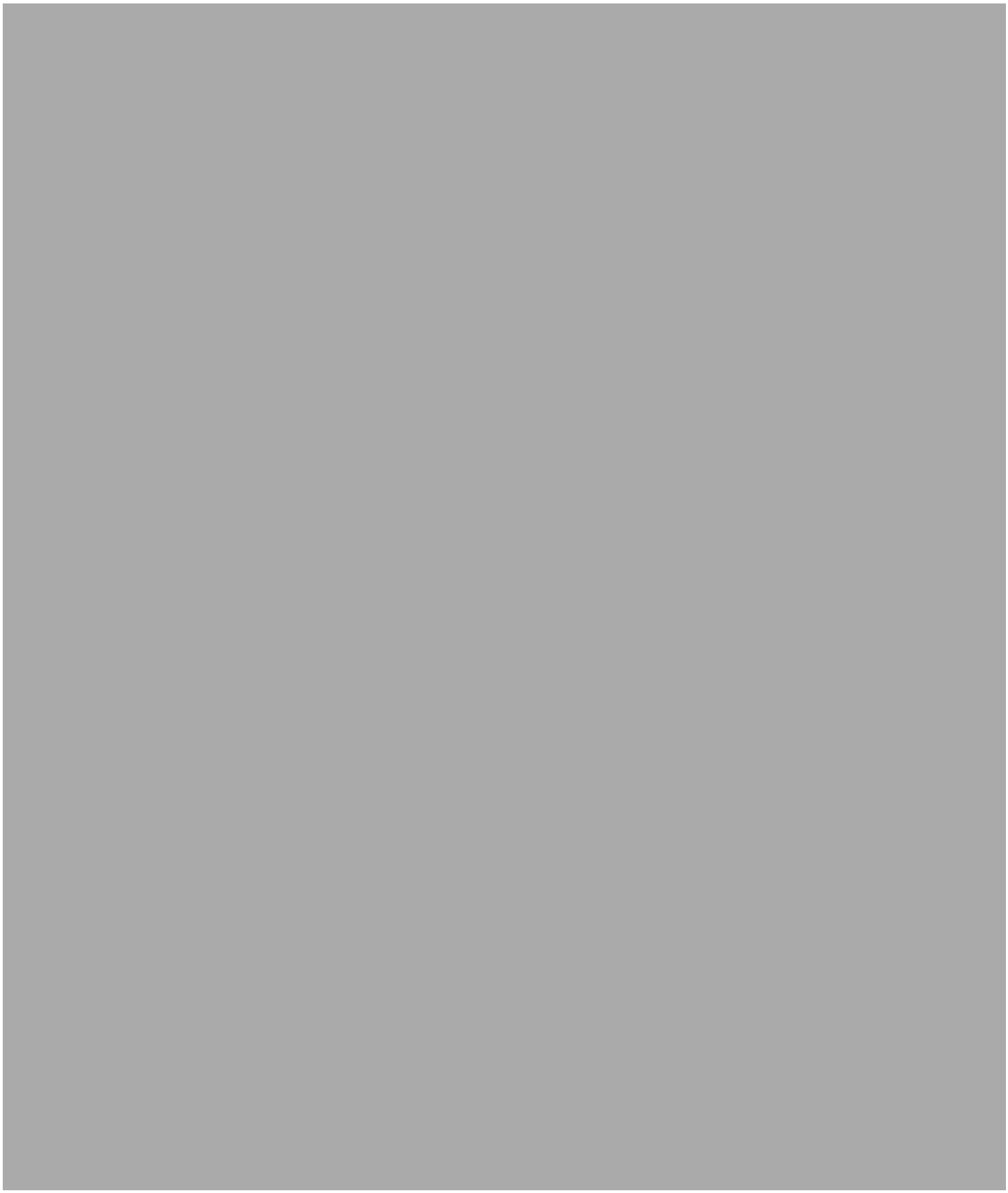


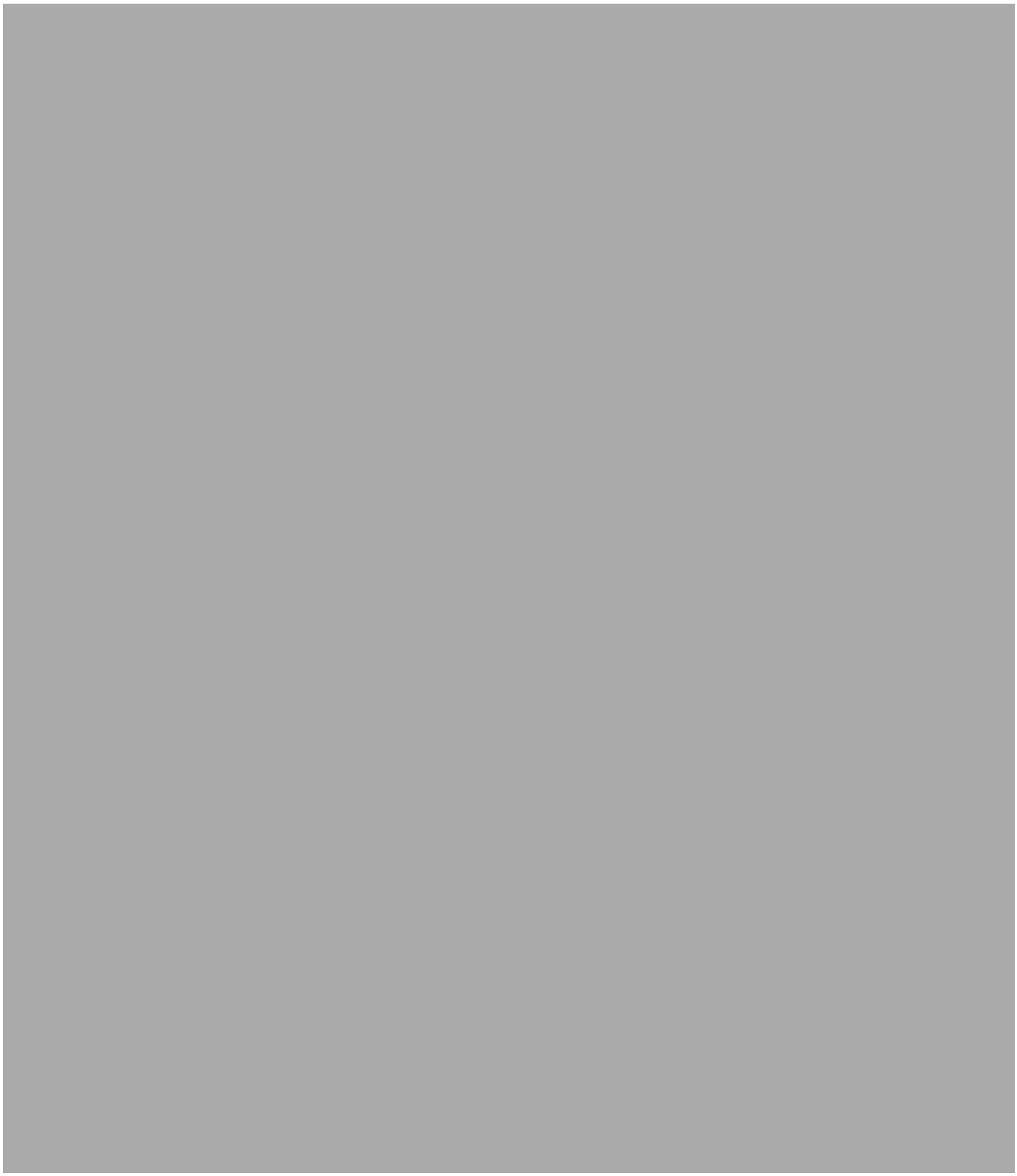
Scheme 71: Proposed synthetic route for the synthesis of cyclic terminal alkene homoallylamine

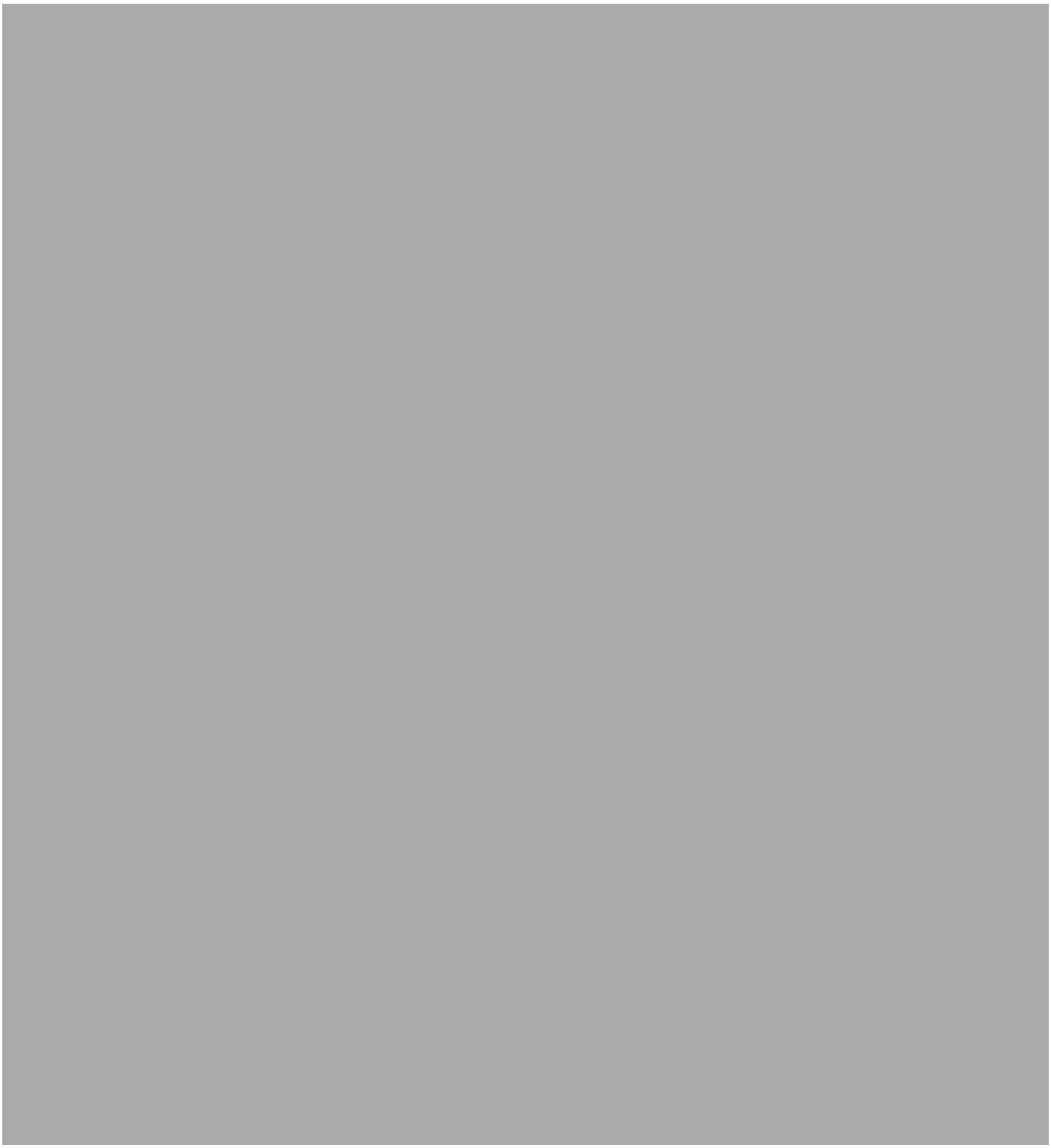
Chapter Two

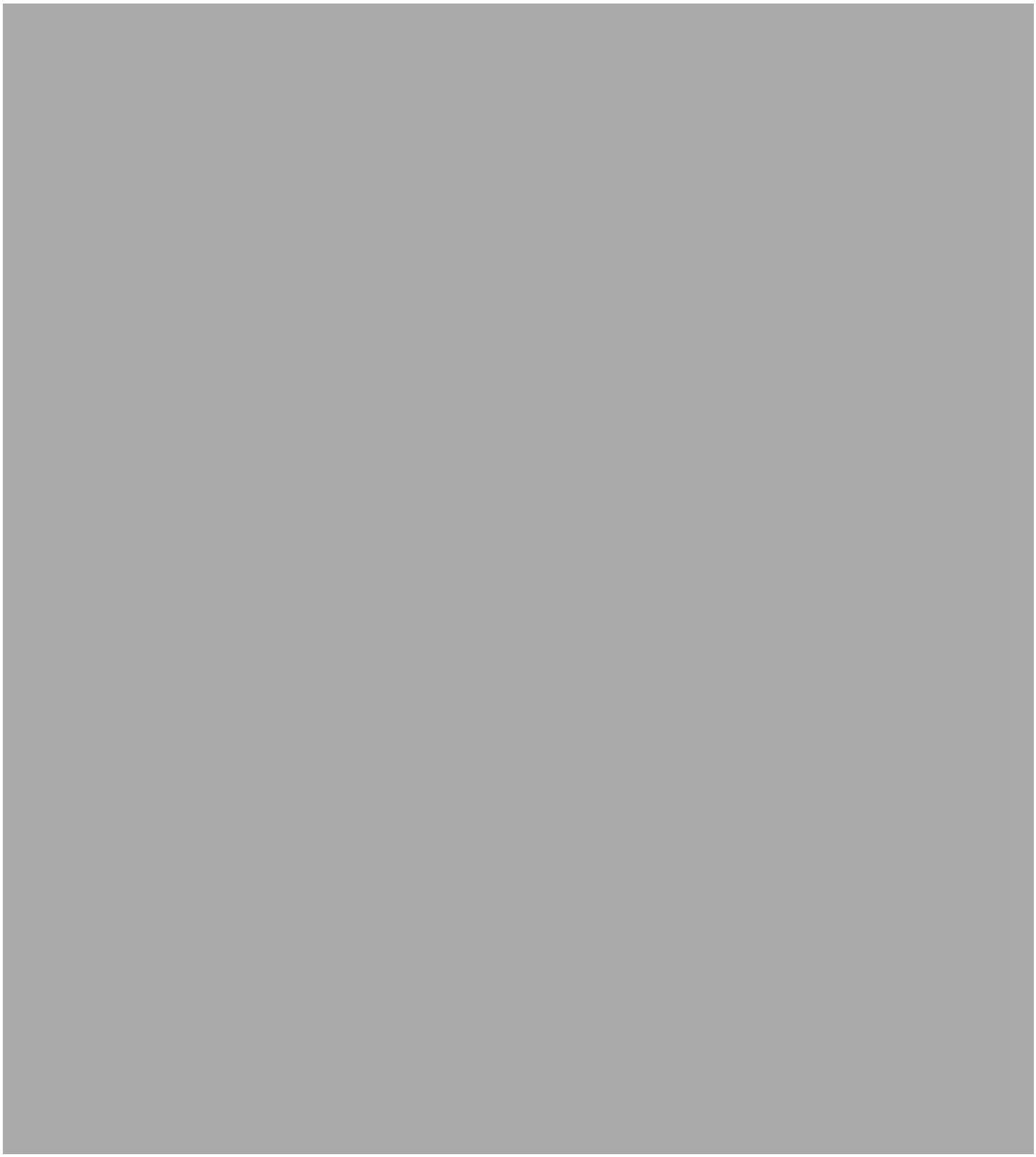
Results and Discussion

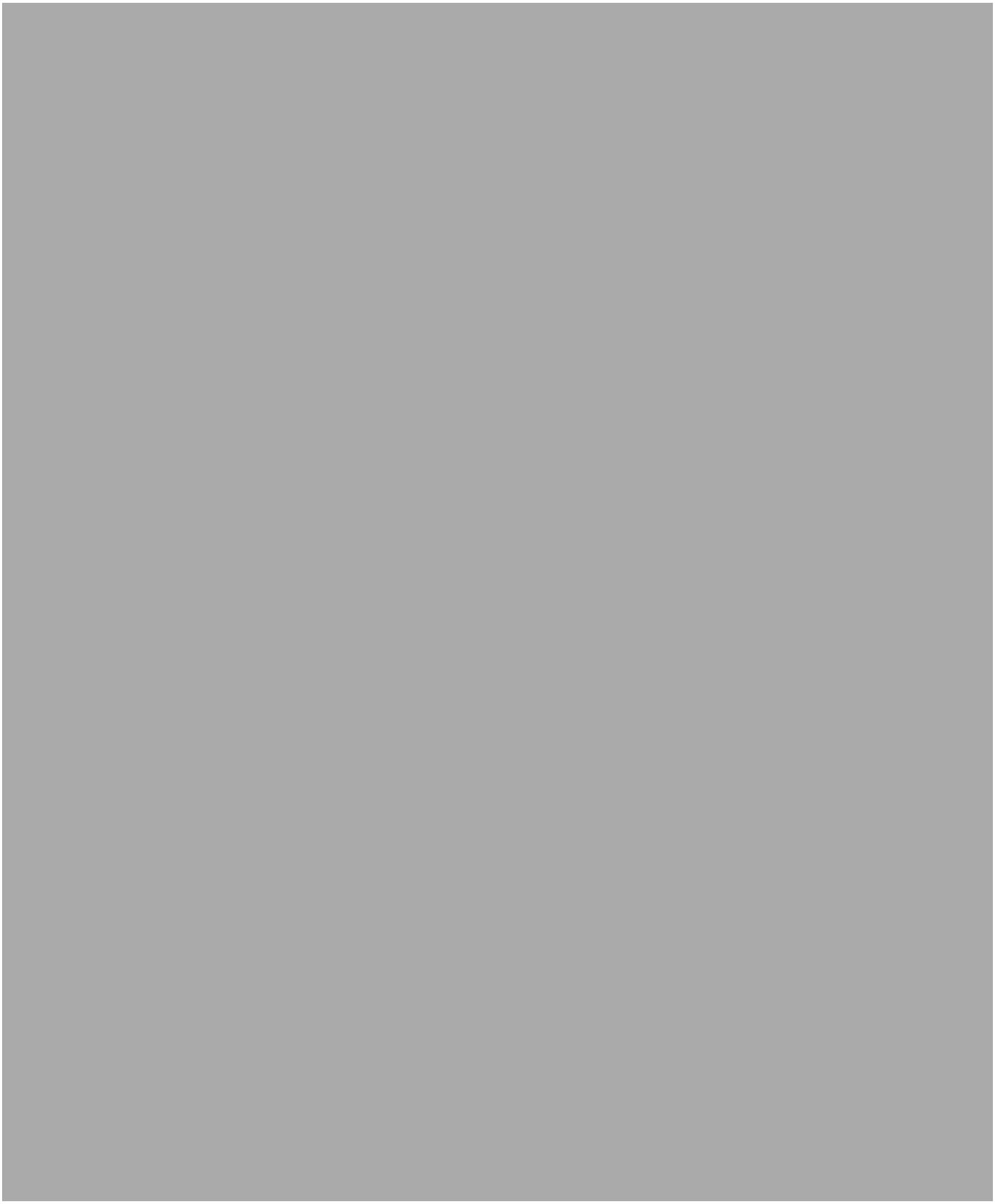
Synthesis of 2-Pyrazoline

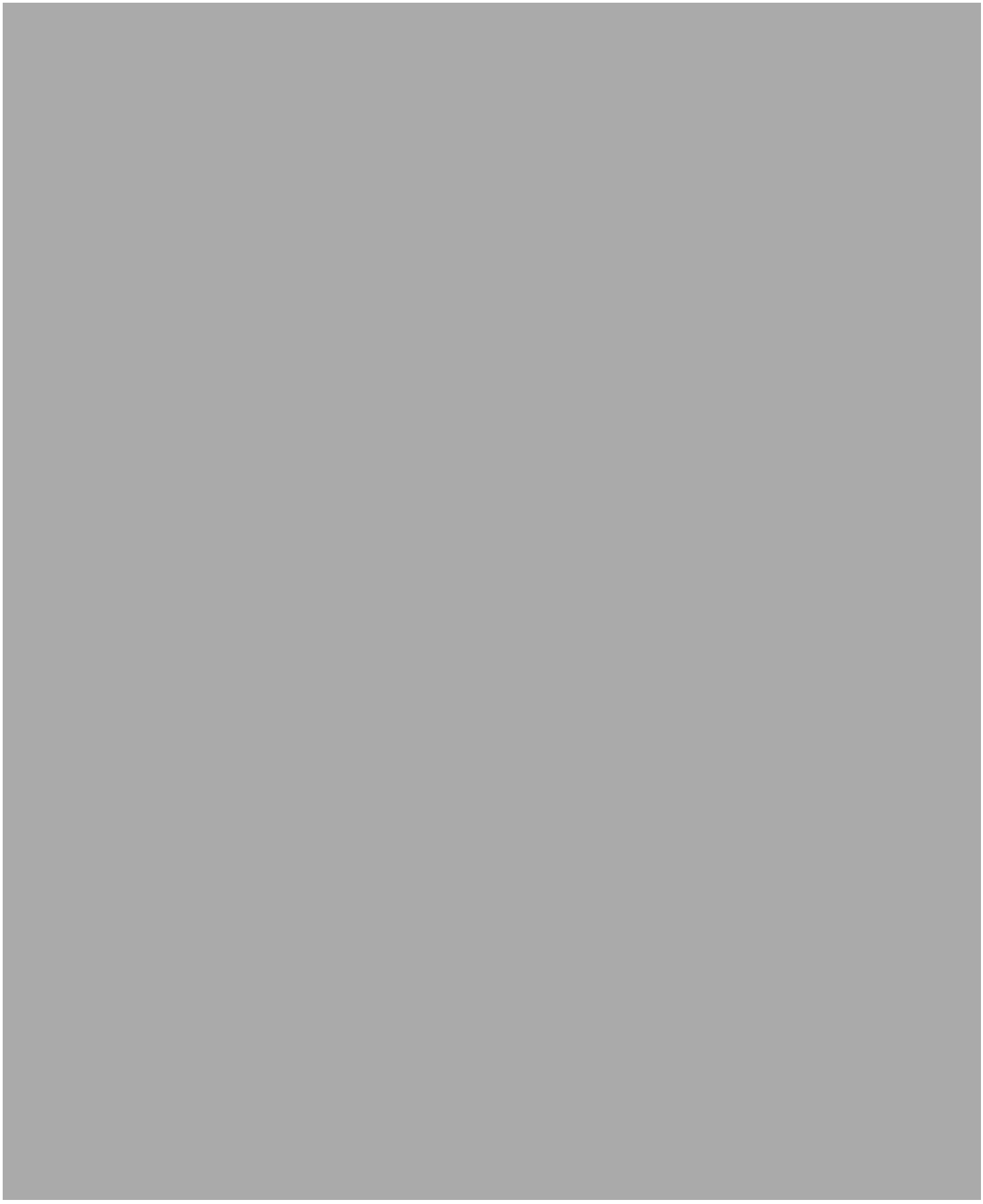


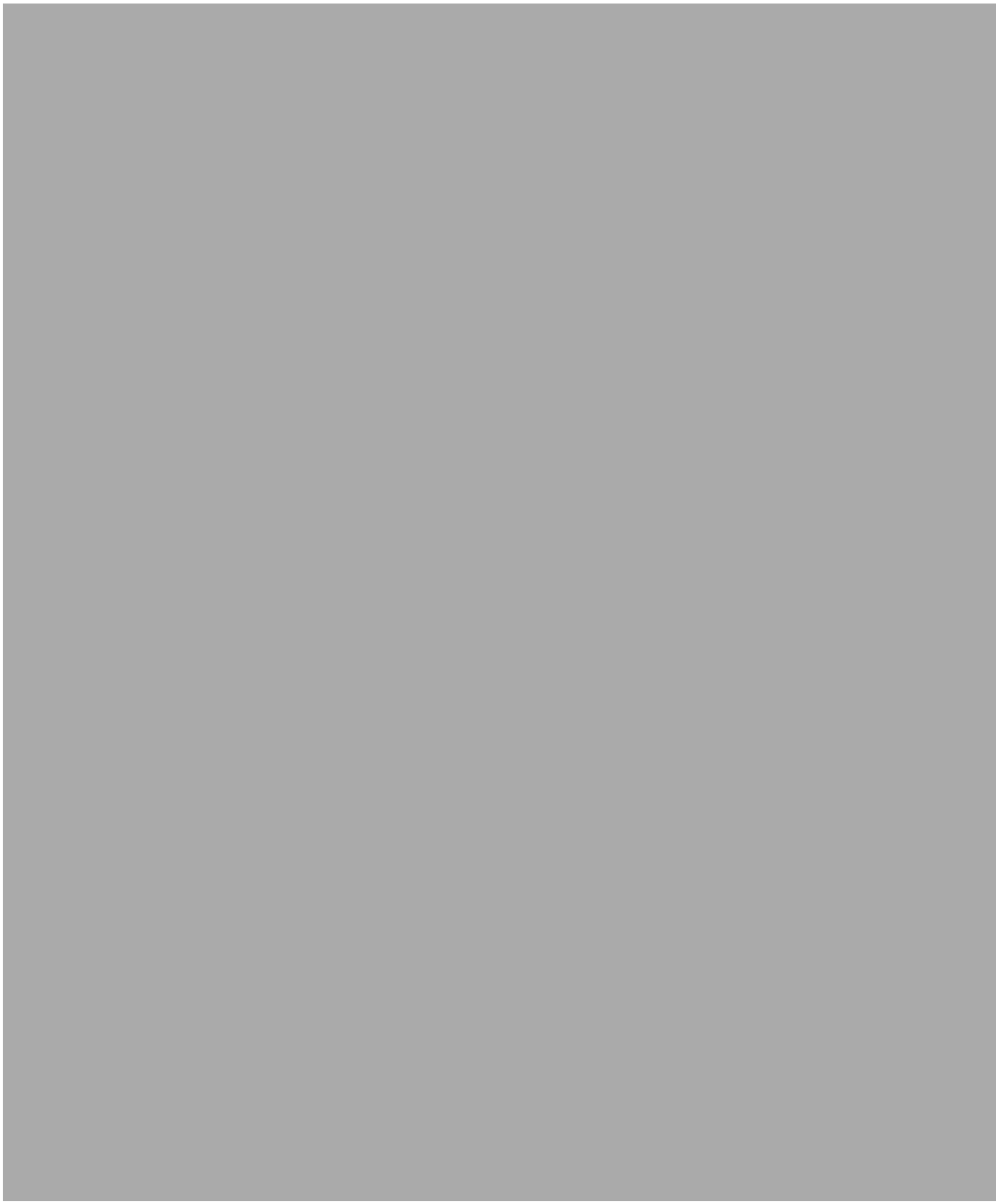


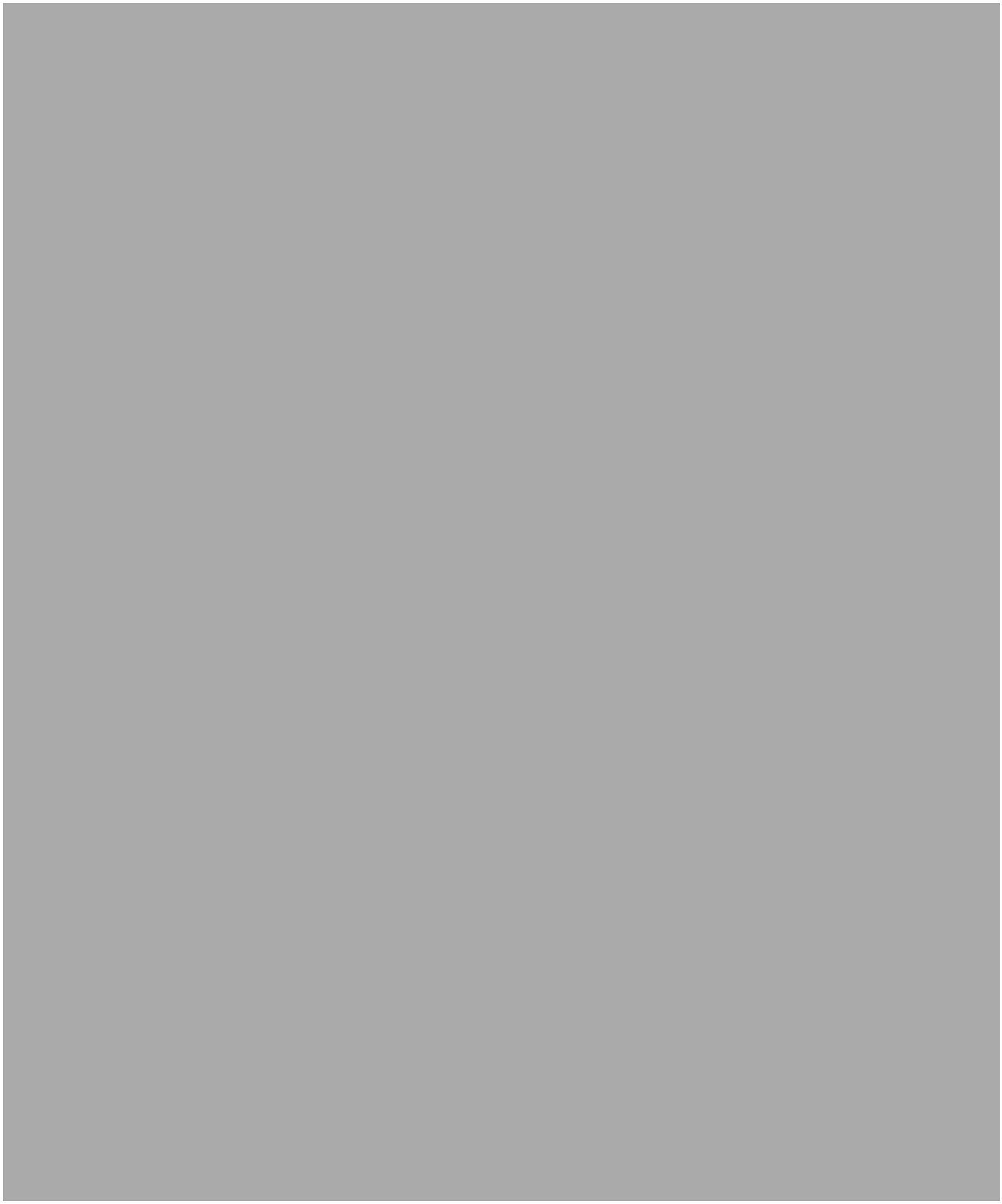


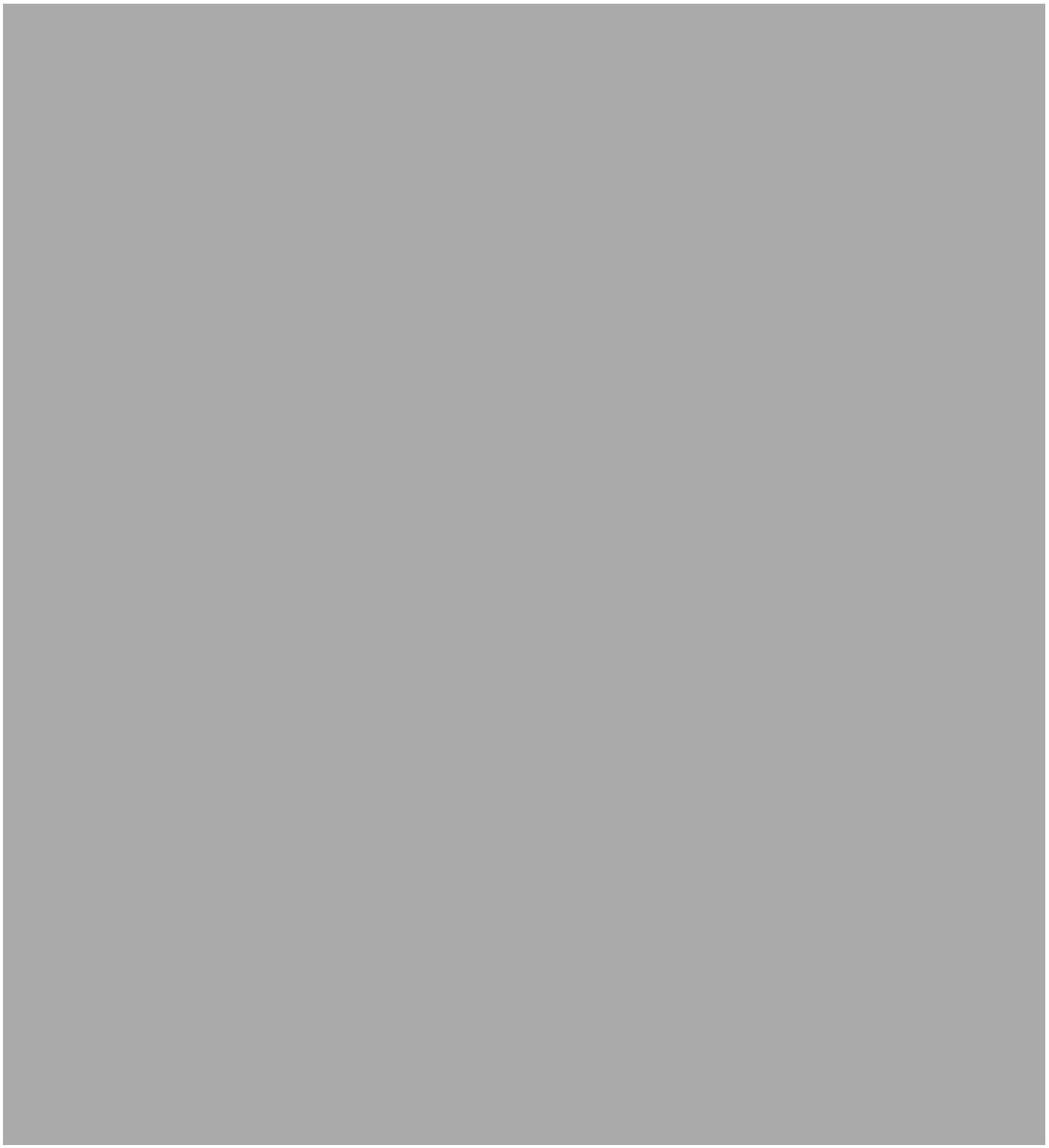


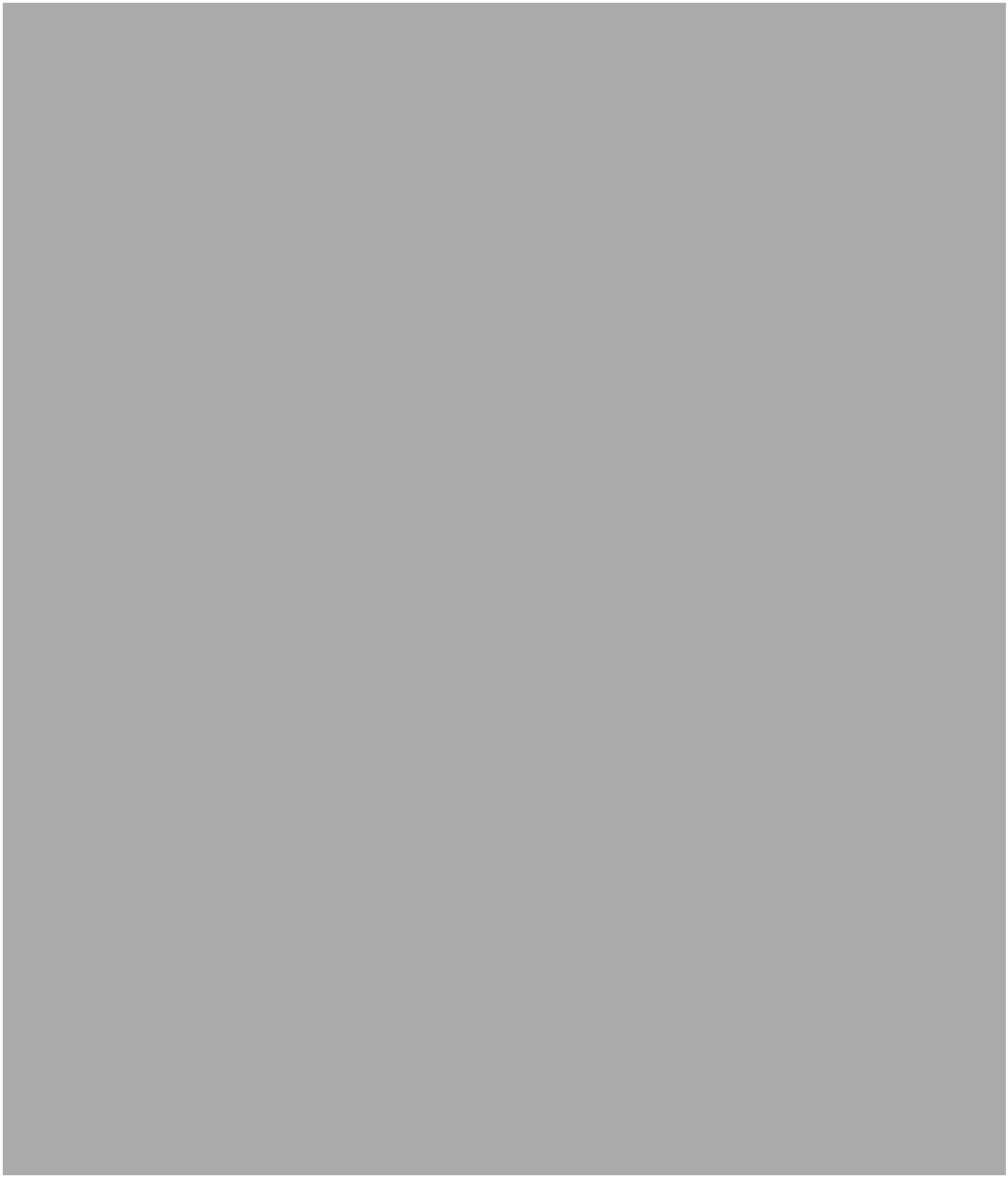






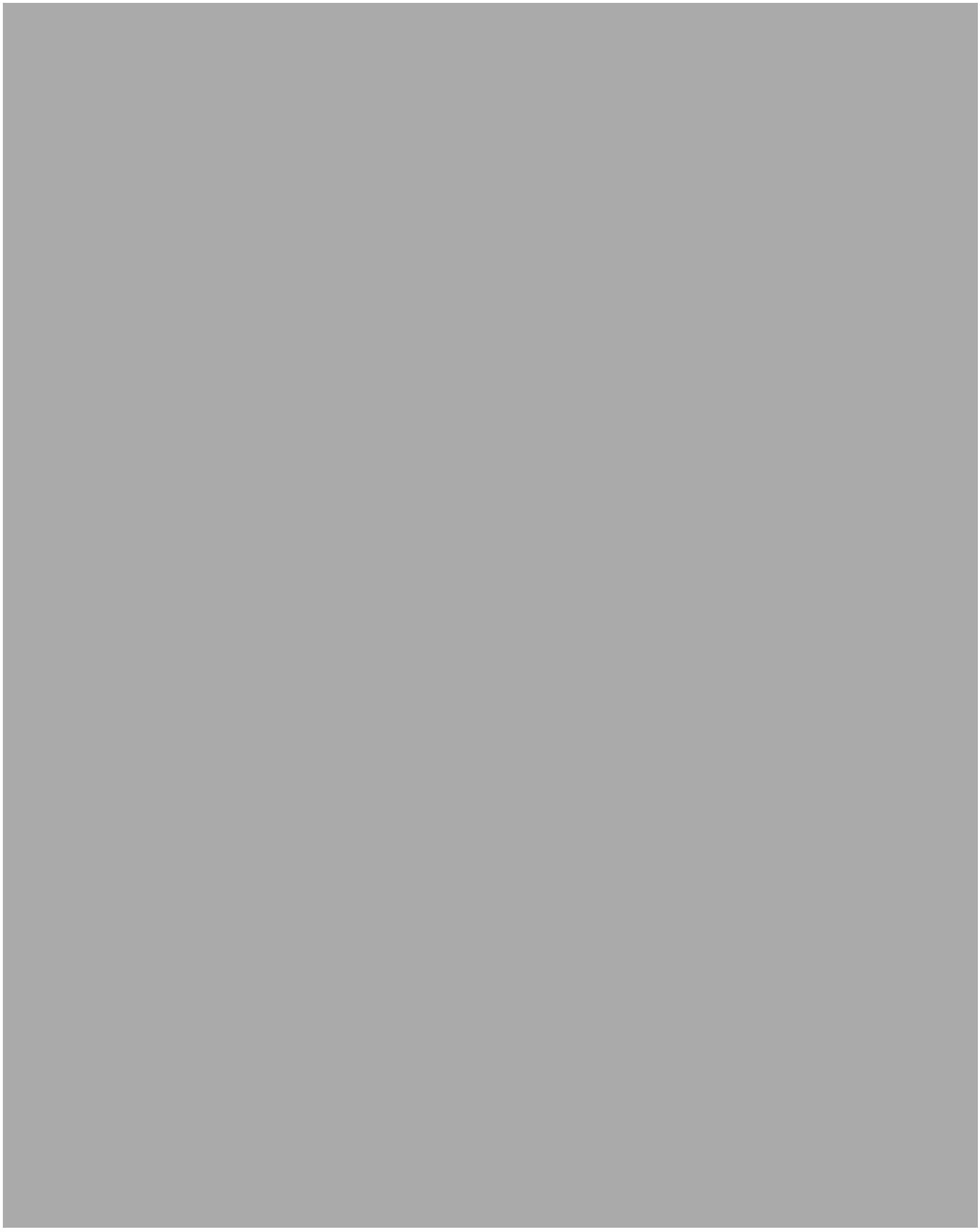


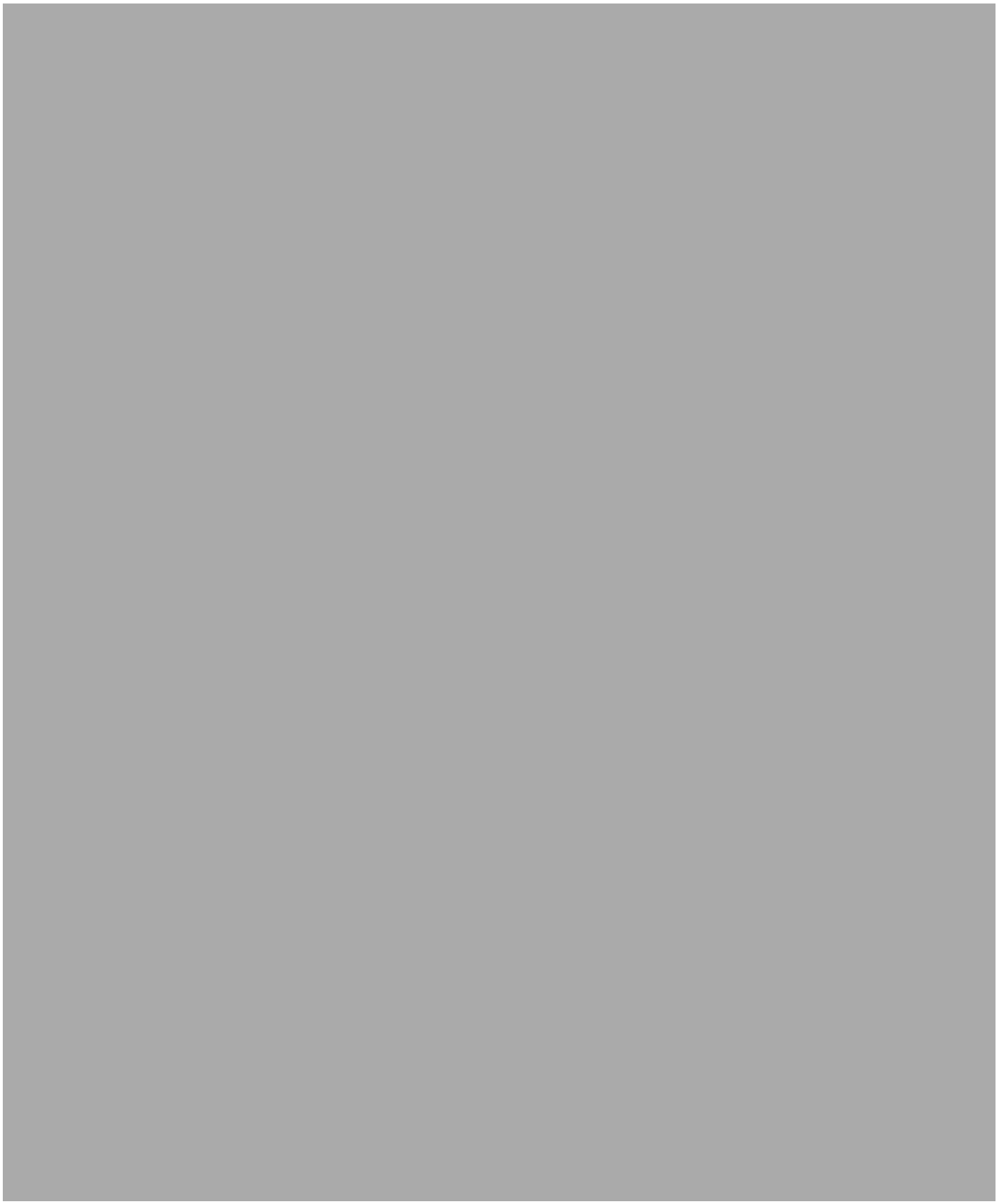


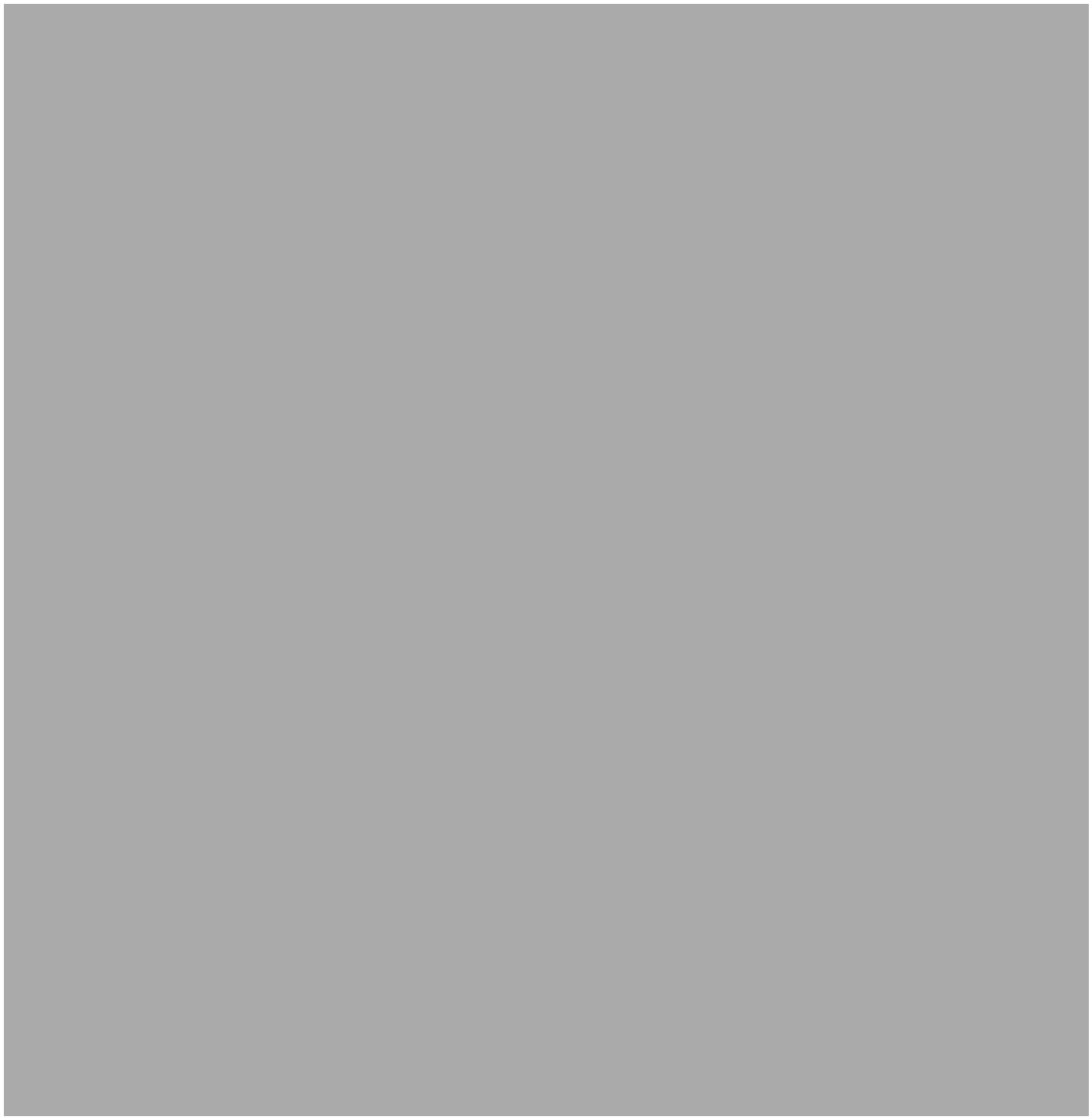


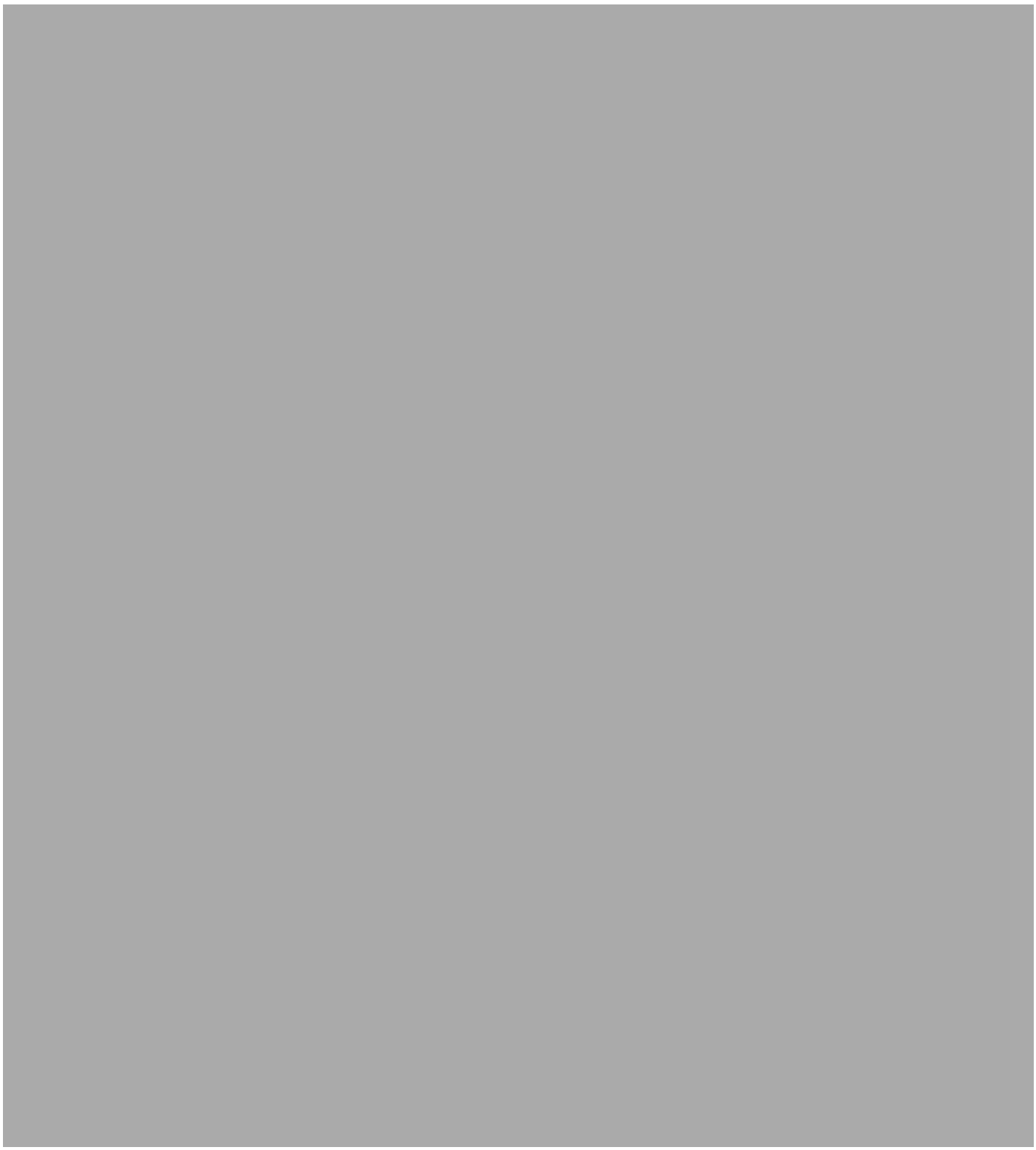
Chapter Three

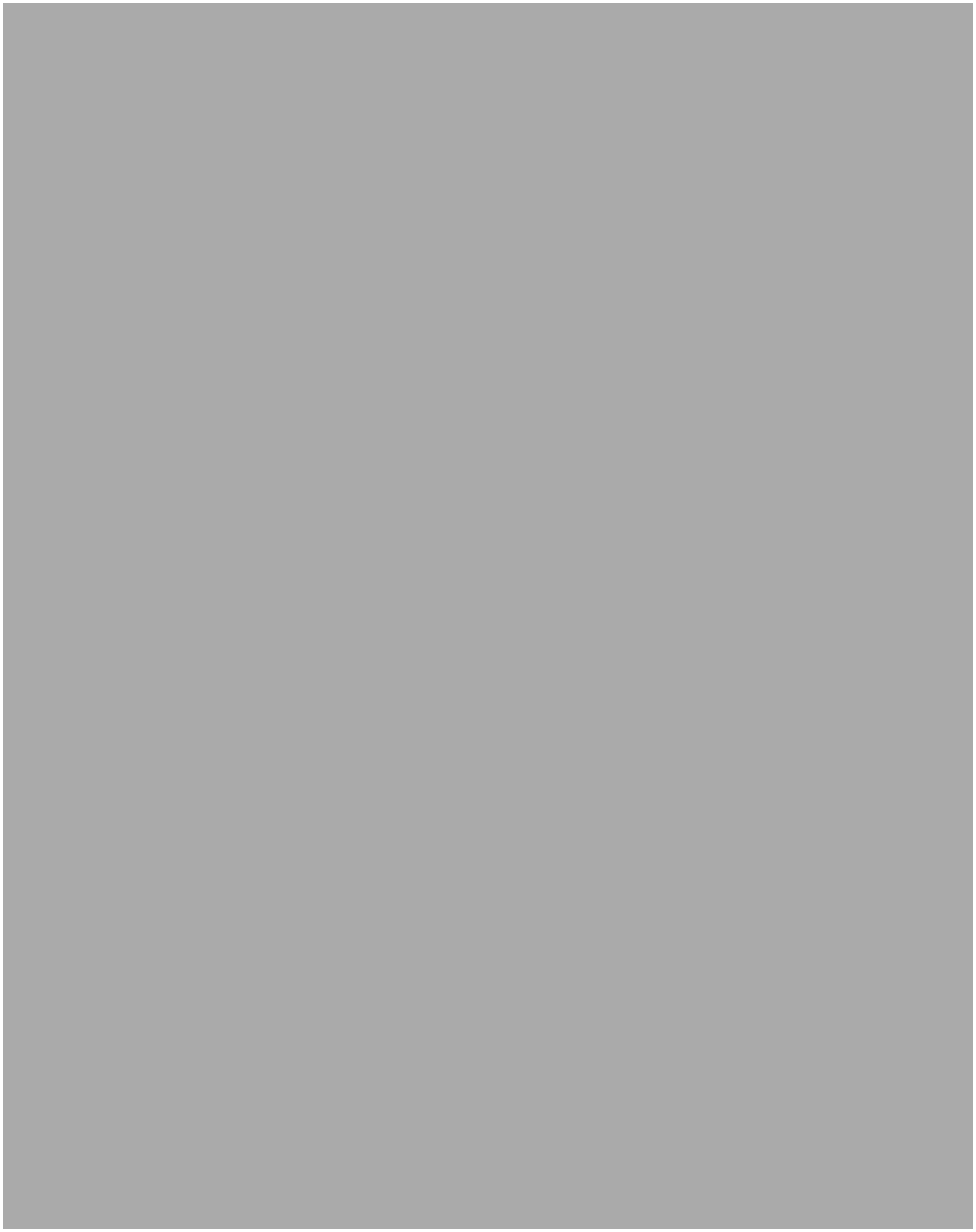
Biological applications

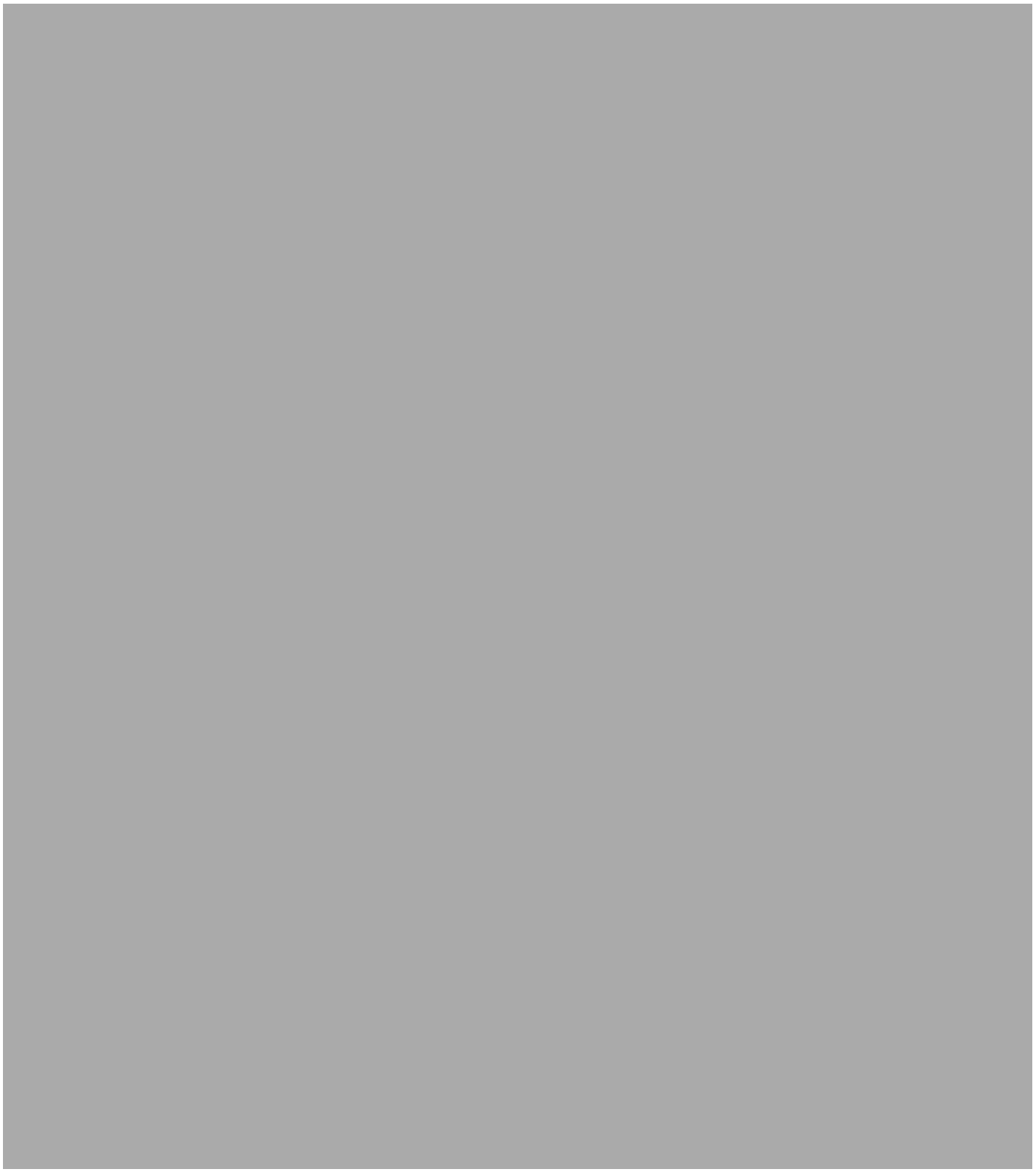


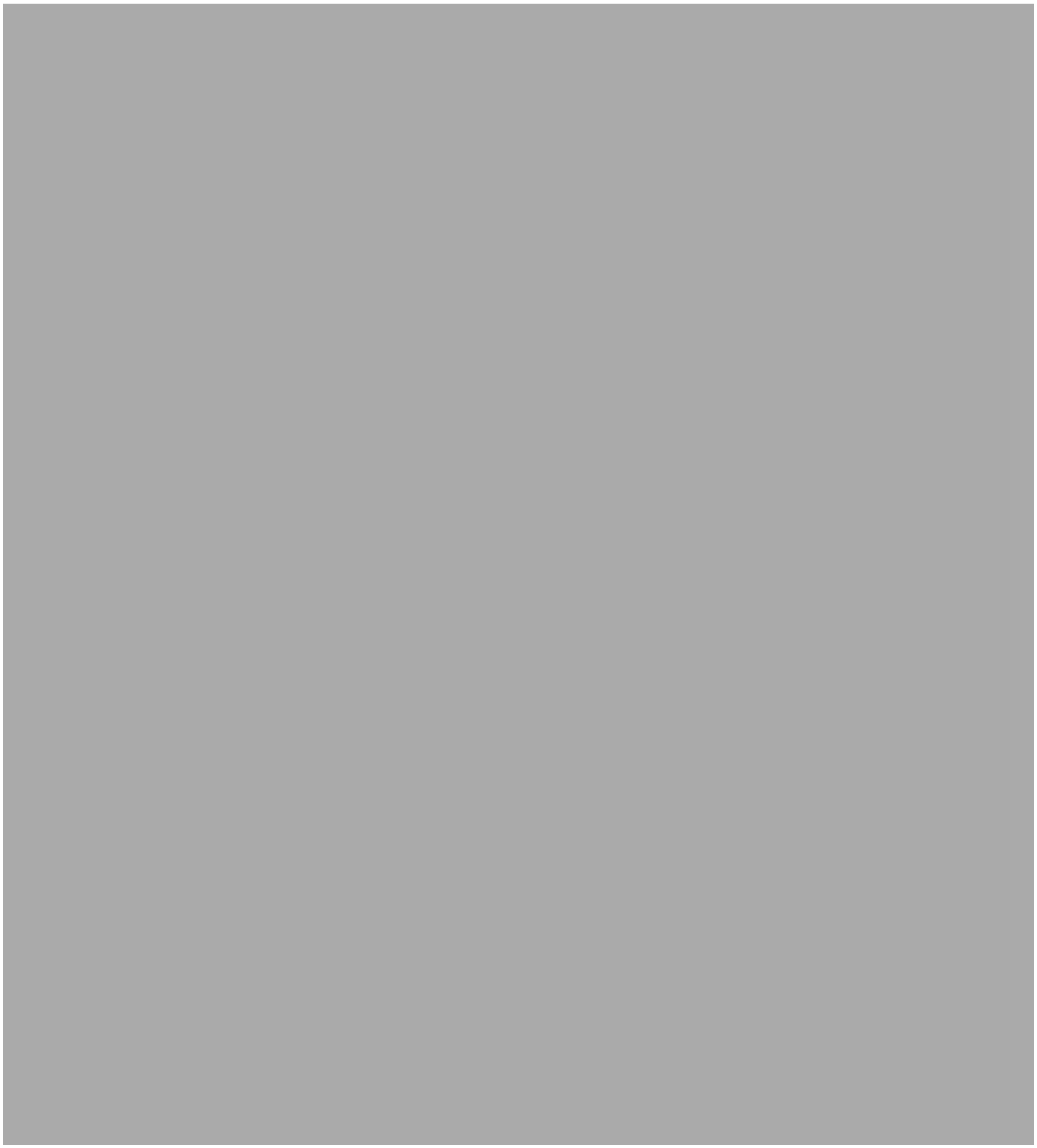


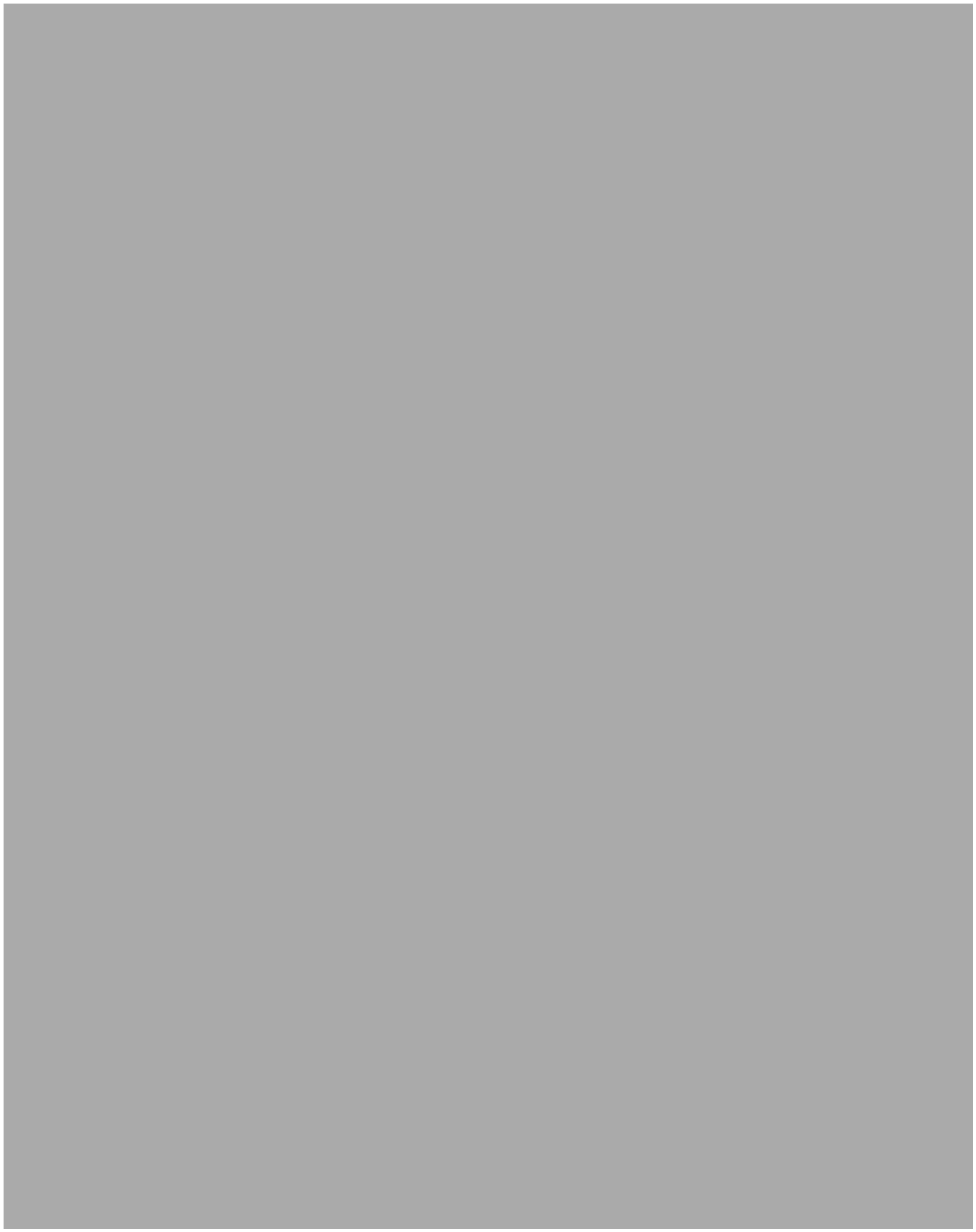


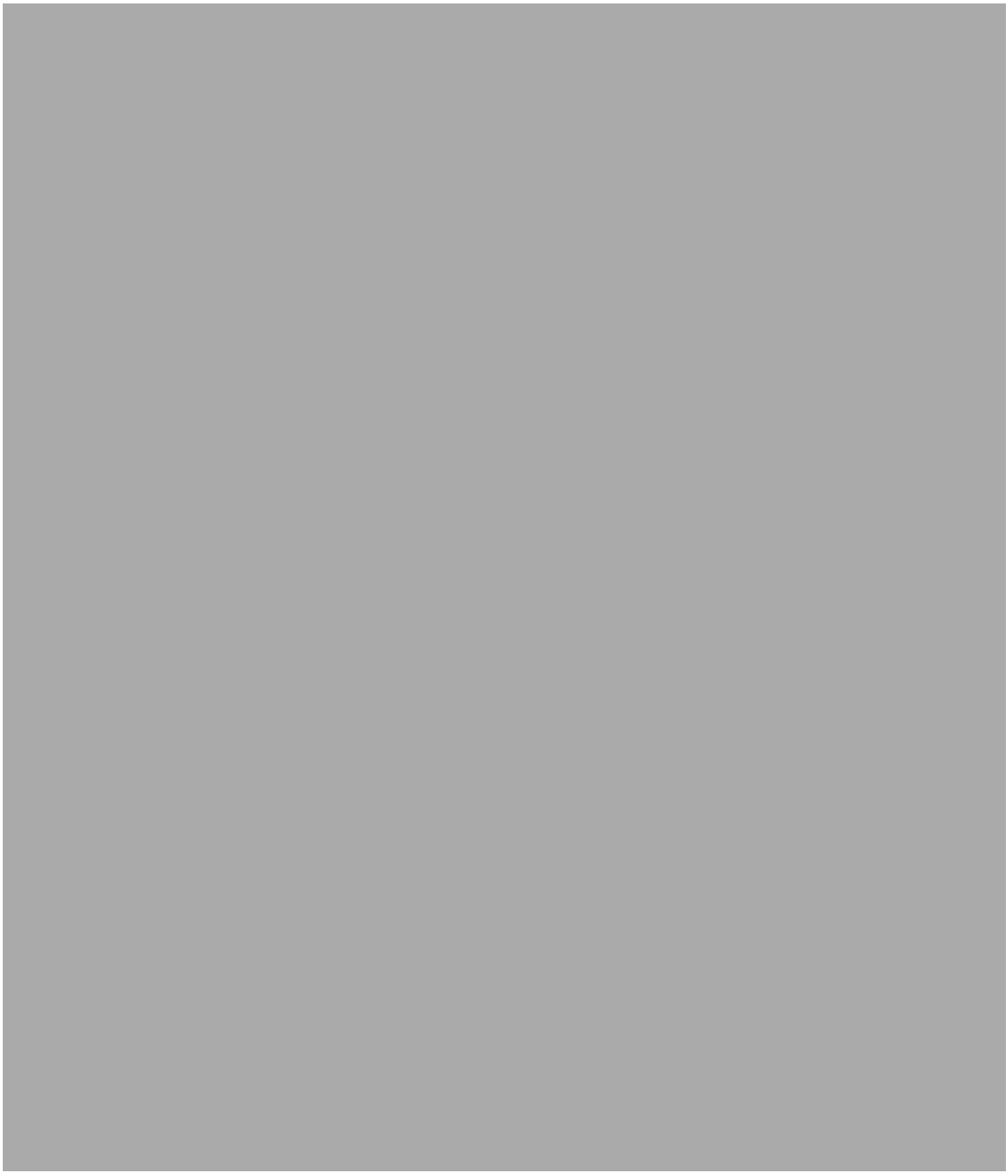


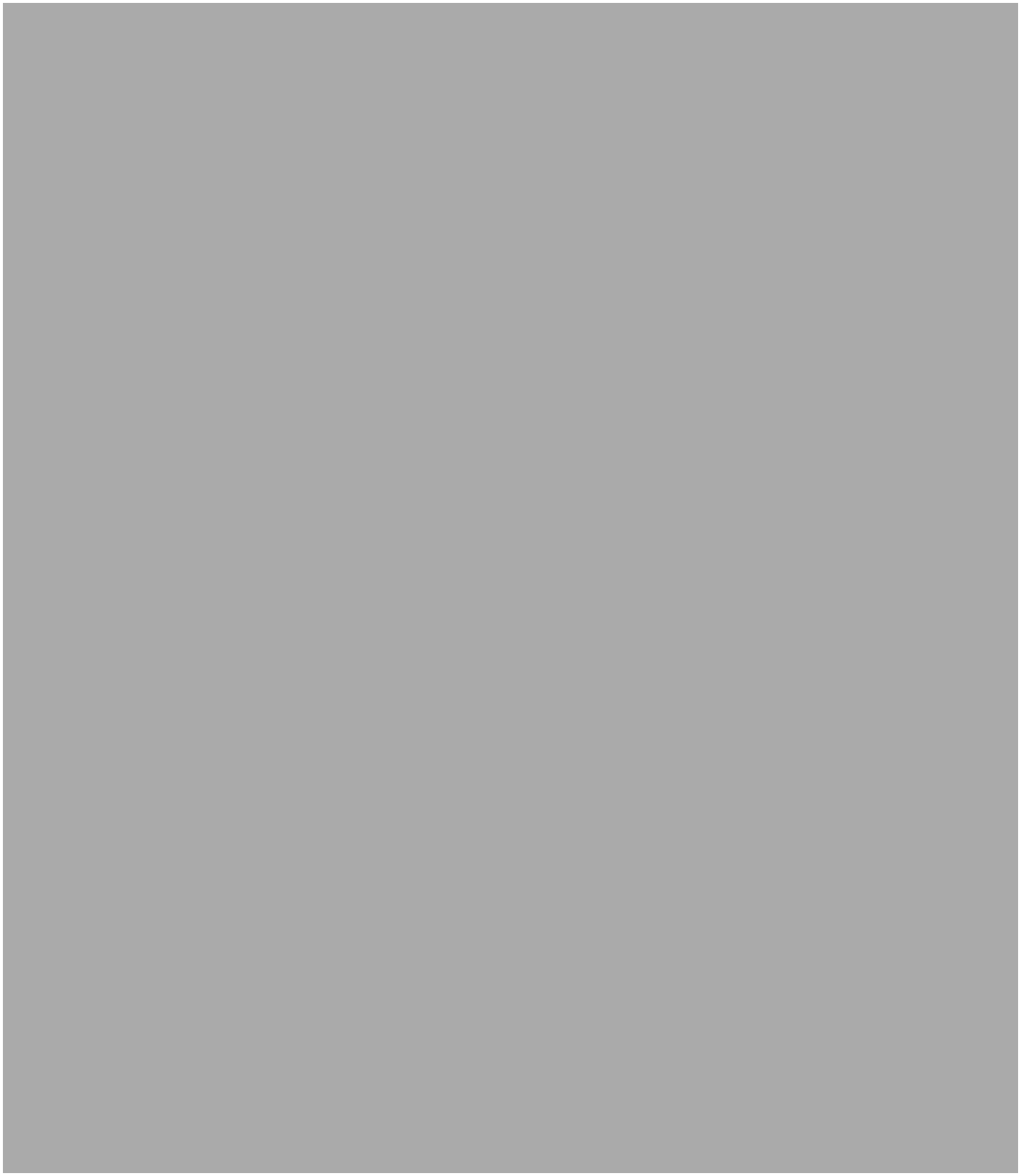


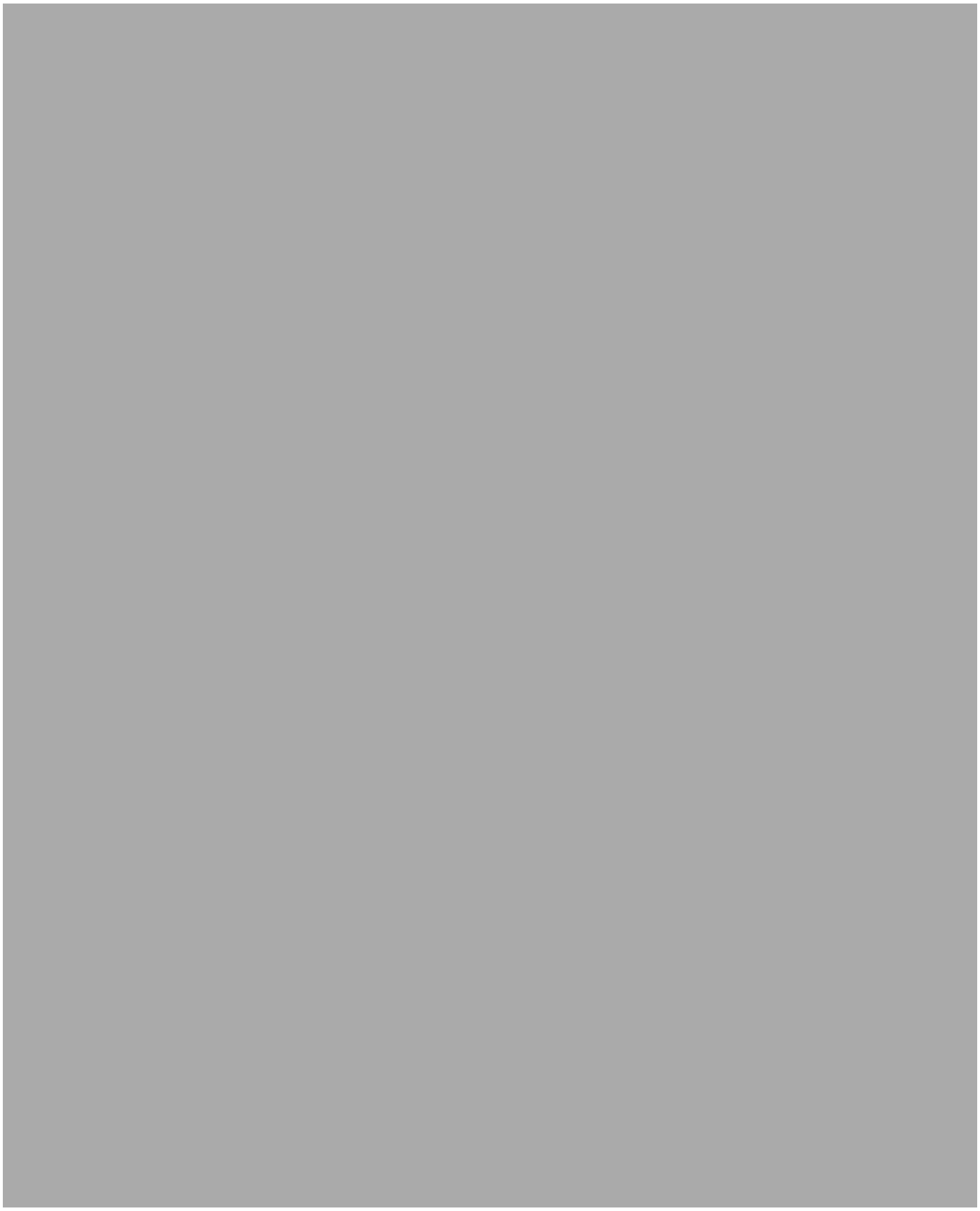












Chapter Four

Conclusion

4. Conclusion

In conclusion, the synthesis of a symmetric chiral *cis*-2,4-azetidines in 50-83% yields and up to 99% *ee* from cyclisation of enantiopure homoallylamines was reported, employing iodine-mediated cyclisation methodology established by the Fossey research group for the synthesis of racemic *cis*-2,4-azetidine. The substrate scope of the previous methodology was also expanded.

An efficient new procedure for the synthesis of γ-lactams, as a mixture of diastereomers in 34-99% yields has been developed from the cyclisation of 3-methyl substituted homoallylamines, using three equivalents of iodine and five equivalents of sodium bicarbonate in ethyl acetate at room temperature. Single diastereomers were separated using column chromatography. In addition, some modifications were made in the synthesis of nicotine analogues. As a result, a new class of the hydroxylated pyrrolidine derivatives was generated from the reduction of pyrrolidin-2-ones. The optimisation of the reaction conditions for the synthesis of γ-lactam, led to another important route for oxidation of secondary amines using caesium carbonate as a base with iodine in ethyl acetate.

Biological activity tests for the synthesised γ-lactam derivatives, such as *cis*+*trans*-**130a** and *cis*+*trans*-**130j** have shown intriguing activities, particularly in the brain and liver of zebrafish embryos. Anti-inflammatory activity was investigated for some of the synthesised γ-lactam derivatives, such as **130a**, **130g**, **130h**, **130k**, **130m** and **130n** and only compounds **130g** and **130n** showed to have anti-inflammation activity. Anti-bacterial activity for a mixture of diastereomers of compounds **130a**, **130g**, **130n**, and **130j** was measured, and interestingly, **130g** and **130j** proved to be active against gram-positive *E-Coli* bacteria.

A new efficient methodology was established for the synthesis of fused tricyclic furan bispyrrolidines stereoselectively in 20-48% yields, from iodine-mediated cyclisation of 3-phenyl substituted homoallylamines, using the same protocol as for the synthesis of γ-lactams.

The generation of gem-dimethyl substituted azetidine was found to be problematic when using this strategy, because of the difficulties faced in the synthesis of the starting materials. In addition, the iodocyclisation of cyclic homoallylamine for the synthesis of fused azetidine was investigated and it was found that obtaining azetidine was not possible and the cyclisation was not successful, instead the starting material was oxidised to form the corresponding imine in >87% conversion.

Finally, a new straightforward route for the preparation of novel 2-pyrazoline derivatives was designed from cyclisation of homoallylhydrazines, using three equivalents of iodine and five equivalents of sodium bicarbonate in acetonitrile, at room temperature. A library of novel aminopyrazoline derivatives has been prepared in 61-86% yields. The study found evidence for the fluorescence property of the synthesised pyrazoline derivatives and proved the role of substituents on the fluorescence property.

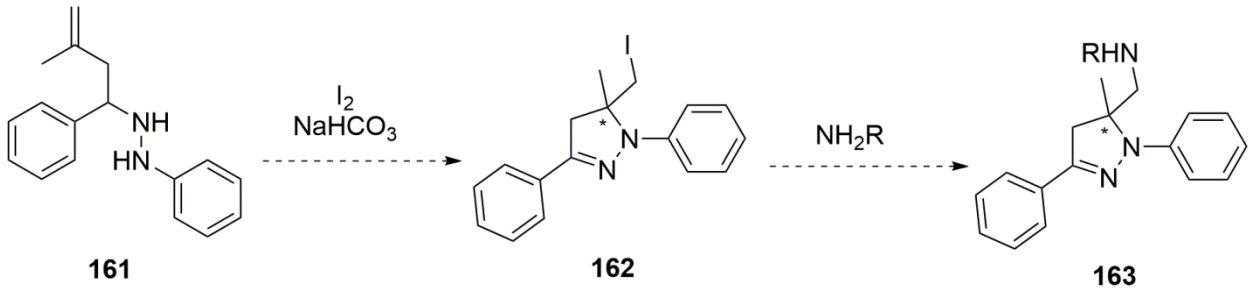
The application of the synthesised compounds in biology and catalytic activity are under investigation by the Fossey research group. In addition, some of the synthesised γ-lactams and pyrazoline molecules were sent to Syngenta and are currently under investigation in agrochemistry. Several of the synthesised pyrazoline and γ-lactam compounds were submitted for biological screening to Lilly Company and are currently under investigation.

Chapter Five

Future work

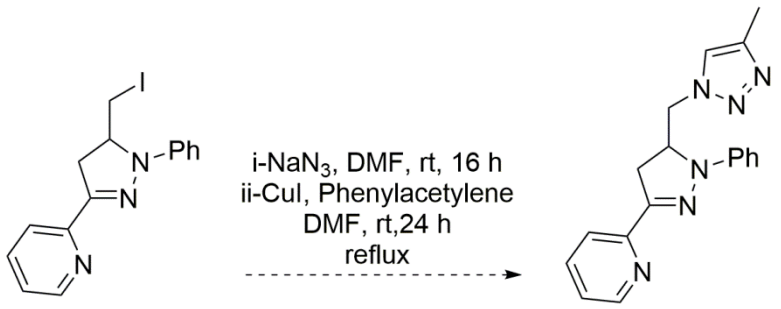
5. Future work

2-pyrazoline derivatives bearing stereogenic quaternary carbon centre could be obtained from the iodocyclisation of 3-Methyl substituted homoallylhydrazine **159**, which could be synthesised from zinc mediated allylation of imine.



161 **162** **163**

In addition, a click-reaction could be performed to displace iodine from the synthesised iodopyrazoline to form triazole linked with pyrazoline.

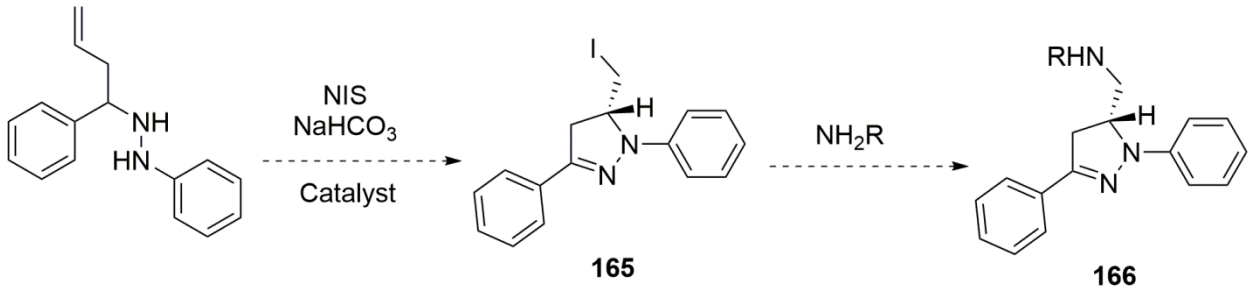


164

From the proved fluorescence properties of pyrazoline derivatives,[54] the comprehensive study could be undertaken to investigate their uses as a selective sensor.

Synthesis of enantiopure pyrazoline derivatives could be attempted by using chiral auxiliary technique, or by using a different cyclisation agent and a catalyst, such as that reported by

Tripathy *etal*.[86] and applying a similar protocol on cyclisation of homoallylhydrazines to access the synthesis of enantiopure pyrazoline.



Biological activity could be investigated for the synthesised 2-pyrazoline derivatives through screening zebrafish embryos developmental assays, and the structure activity relationships (SAR) with azetidines derivatives could be analysed.

Chapter Six

Experimental part

6. Experimental Part

All reagents and solvents used are commercially available, from Sigma-Aldrich or Fisher, unless otherwise stated. ^{1}HNMR spectroscopy was performed at 300 MHz on a Bruker AVIII300 NMR spectrometer, and at 400 MHz on an AV400 NMR spectrometer. Proton decoupled ^{13}CNMR spectroscopy was recorded at 10 MHz on a Bruker AVIII400 NMR spectrometer at room temperature. Chemical shifts (δ) were recorded in ppm relative to TMS (δ 0.00) for ^{1}HNMR or residual solvent and to chloroform (δ 77.0) for the ^{13}CNMR measurements, coupling constant *J* are expressed in Hertz. The PENDANT technique was used to aid ^{13}CNMR assignment in some cases. Mass spectra were recorded by Electrospray MS waters LCT Time of flight Mass Spectrometer and with EI (GC/MS) waters GCT premier time of flight mass spectrometer. IR spectroscopy was recorded on a PerkinElmer 100FT-IR spectrometer at room temperature. Column chromatogram was obtained from combiflash machine Rf300. Melting points were measured by the Stuart^{TM} digital melting point apparatus (SMP10).

General Procedures

General procedure for preparation of imines (a1)

Aldehyde (1 equiv.) and amine (1.1 equiv.) were mixed in ethanol (30 mL) and the reaction mixture was stirred at reflux temperature for six hours. After the reaction was completed, then the solvent was removed *in vacue* and the crude product was purified by rapid flash chromatography.

General procedure for preparation of hydrazone imines (a2)

Aldehyde (1 equiv.) and phenylhydrazine (1.05 equiv.) were mixed in ethanol (10 mL) and the reaction mixture was stirred at room temperature for two hours (if the reaction did not start, it needed to be refluxed for 2 hours). After the reaction was completed, the reaction mixture was cooled to room temperature, it was filtered under vacuum, and the solid products were collected and dried under vacuum.

General procedure for preparation of homoallylamines (b1)

Magnesium turning (2 equiv.) under nitrogen, was mixed with ally bromide (1.5 equiv.) in dry THF (10 mL) and stirred at room temperature for 30 minutes. An appropriate amount of imines (1 equiv.) in dry THF (2 mL) was added. The reaction mixture was stirred for 16 hours at room temperature. After the reaction was completed, it was quenched with a saturated solution of sodium bicarbonate (5mL) and was extracted with ethyl acetate (3x 20 mL), the product was obtained after column chromatography (ethyl acetate/ hexane 1:9).

General procedure for preparation of homoallylamines (b2)

Imine (1 equiv.) in dichloromethane (20 mL) was mixed with boron triflouride diethyl etherate (3 equiv.) and the reaction mixture was stirred at room temperature for 30 minutes. Then allyltributyltin (1.5 equiv.) was added. The reaction mixture was stirred for 16 hours at room temperature with TLC monitoring, when the reaction was completed, it was quenched with brine and was extracted with (3x 20 mL) ethyl acetate, the combined organic layers were concentrated *in vacue* and dried with $MgSO_4$, and the crude was purified with column chromatography ethyl acetate / hexane 1:9.

General procedure for preparation of enantiopure Ellman homoallylamines (c1)

Activated zinc powder (3 equiv.) under nitrogen, was mixed with indium triflate (2 equiv.) and ally bromide (2 equiv.) in dry THF (10 mL), and then stirred for 30 minutes at room temperature. (R)-(+)-*tert*-butaylsulfinimine (1 equiv.) in dry THF (10 mL) was added, the reaction mixture was stirred at room temperature for 24 hours with TLC monitoring. After the reaction was completed then the reaction was quenched with brine and extracted with ethyl acetate (3x 20 mL), the pure product was obtained after column chromatography ethyl acetate/ hexane 1:9.

General procedure for preparation of enantiopure amine (deprotection of Ellman auxiliary) (c2)

Ellman homoallylamine (1 equiv.) was mixed with (2 equiv.) of (1:1) 4M hydrochloric acid in dioxane and methanol prepared *in situ*. The reaction mixture was stirred for 24 hours at room temperature. Afetr the reaction was completed then the solvent was removed *in vacue*, the residue was washed with diethyl ether (3x 5mL), the aqueous layer was neutralized and re-extracted with diethyl ether (3x 10 mL), the combined organic layers were dried using $MgSO_4$ and the solvent was removed *in vacuo*.

General procedure for preparation of enantiopure homoallylamines (c3)

Aldehyde (1 equiv.) in methanol (10 mL) was mixed with (1.1 equiv.) of enantiopure amine stirred at reflux temperature for 6 hours and cooled at room temperature, then sodium borohydried (2 equiv.) was added and stirred for 24 hours at room temperature. Methanol was removed *in vacue*, washed with water (3x 5 mL), extracted with DCM (3x 10 mL). The combined

organic layers were dried with $MgSO_4$. The pure product was obtained after column chromatography (ethyl acetate/ hexane 2/8).

General procedure for preparation of 3-methyl-substituted homoallylamines (d)

Activated zinc powder (2 equiv.) under nitrogen, was mixed with methallylbromide (1.5 equiv.) in dry THF (10 mL) and stirred for 30 minutes at room temperature. An appropriate amount of imines (1 equiv.) in dry THF (2 mL) was added and the reaction mixture was stirred for 16 hours at room temperature. After the reaction was completed as judged by TLC, it was quenched with a saturated solution of sodium bicarbonate (5 mL) and extracted with ethyl acetate (3x 20 mL), the combined organic layers were concentrated *in vacuo* and the product was purified by column chromatography ethyl acetate/ hexane 1:9.

General procedure for preparation of 3-phenyl-substituted homoallylamines (e)

Activated zinc powder (2 equiv.) under nitrogen, was mixed with phenyl-substituted allybromide (2.5 equiv.) in dry THF (10 mL) and stirred for 30 minutes (heat to 50 $^{\circ}$C). An appropriate amount of imines (1 equiv.) in dry THF (2 mL) was added. The reaction mixture was heated at reflux temperature for one hour, and then the reflux was removed and was stirred for another 16 hours at room temperature. After the reaction was completed as judged by TLC, it was quenched with a saturated solution of sodium bicarbonate (5mL) and extracted with ethyl acetate (3x 20 mL), the combined organic layers were combined and concentrated *in vacuo* and the pure product was obtained after column chromatography ethyl acetate/ hexane 1/9.

General procedure for preparation of homoallylhydrazines (f)

Activated zinc powder (2 equiv.) under nitrogen, was mixed with ally bromide (2.5 equiv.) in dry THF (10 mL) and was stirred for 30 minutes. An appropriate amount of hydrazone imines (1 equiv.) in dry THF (2 mL) was added. The reaction mixture was stirred for 6 hours at room temperature. After the reaction was completed as judged by TLC, it was quenched with a saturated solution of sodium bicarbonate (5 mL) and extracted with ethyl acetate (3x 20 mL), the combined organic layers were concentrated *in vacuo* and the pure product was obtained after column chromatography ethyl acetate/hexane 1:1.

General procedure for preparation of 2-gem-dimethyl-substituted homoallylamines (g)

Activated zinc powder (2 equiv.) under nitrogen, was mixed with prenyl bromide (2.5 equiv.) in dry THF (10 mL) and was stirred for 30 minutes at room temperature. An appropriate amount of imines (1 equiv.) in dry THF (2 mL) was added. The reaction mixture was stirred for an hour. Then DMI (5mL) was added and the mixture was heated to 120 $^{\circ}$C for overnight. After the reaction was completed as judged by TLC, it was quenched with a saturated solution of sodium bicarbonate (5mL) and extracted with (3x 20 mL) ethyl acetate, the pure product was obtained after column chromatography ethyl acetate/hexane 1:9.

General procedure for azetidines synthesis (h)

Homoallylamines (1 equiv.) in acetonitrile (50 mL), were mixed with iodine (3 equiv.) and sodium bicarbonate (5 equiv.) and was stirred for 16 hours at 0-20 $^{\circ}$C. After the reaction was completed, the the reaction was quenched by a saturated solution of sodium thiosulfate, then washed with brine (3x10 mL) and water (3x10 mL) and extracted with diethyl ether (3x20 mL)

then dried by $MgSO_4$. The crude iodoazetidine was mixed with excess of amine (3 mL) in neat, and was stirring at room temperature for 48 hours, the reaction was quenched by (2M NaOH) solution, and extracted with dichloromethane and washed with brine and water, the product was obtained after column chromatography.

General procedure for synthesis of γ-lactams (i)

Methyl substituted homoallylamines (1 equiv.) in ethyl acetate (25 mL) were mixed with iodine (3 equiv.) and sodium bicarbonate (5 equiv.), the mixture was stirred at room temperature for 24 hours. After the reaction was completed as judged by TLC, then it was quenched with sodium thiosulfate (5mL) and extracted with ethyl acetate (3x20 mL). The combined organic layers were concentrated *in vacuo* and purified by column chromatography. Separation of diastereomers was performed by further column chromatography.

General procedure for synthesis of furan bispyrrolidines (j)

Phenyl substituted homoallylamines (1 equiv.) in ethyl acetate (25 mL) were mixed with iodine (3 equiv.) and sodium bicarbonate (5 equiv.), the reaction mixture was stirred at room temperature for 24 hours. After the reaction was completed as judged by TLC, then it was quenched with sodium thiosulfate (5mL) and extracted with ethyl acetate (3x20 mL). The combined organic layers were concentrated *in vacue* and the product was purified by column chromatography.

General procedure for synthesis of iodopyrazolines (k)

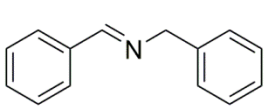
Homoallylhydrazines (1 equiv.) in acetonitrile (25 mL) were mixed with iodine (3quiv.) and sodium bicarbonate (5 equiv.), the reaction mixture was stirred at room temperature for 24 hours, After the reaction was completed as judged by TLC, then it was quenched with sodium thiosulfate (5mL) and extracted with ethyl acetate (3x20 mL). The combined organic layers were concentrated under reduced pressure.

General procedure for synthesis of aminopyrazolines (l)

The crude iodopyrazolines were mixed in neat with an excess amount of amines, the reaction mixture was stirred at room temperature for 48 hours with TLC monitoring, then it was quenched with 2M NaOH, and extracted with dichloromethane (3x20 mL) and washed with brine (3x10 mL), and the combined organic layers were concentrated *in vacuo*, and dried over $MgSO_4$. The crude product was purified by combiflash chromatography machine.

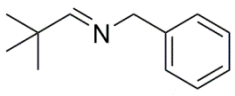
Characterisation data

***N*-benzylidene-1-phenylmethanamine (8a)**



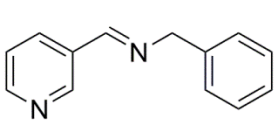
General procedure (**a1**) was used, benzaldehyde (1.0 gm, 9.40 mmol), benzylamine (1.1 gm, 9.00 mmol), colourless oil, 180 mg 99% yield. IR 3084, 3063, 2795, 1652, 1576, 1478, 1450, 1422, 1379, 1308, 1283, 1224, 1166, 1026, 834, 725, 670.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 4.83 (2H, s, C*H*$_2$), 7.20- 7.35 (8H, m, ArC*H*), 7.71-7.82 (2H, m, ArC*H*), 8.45 (1H,s, C*H*=N).^{13}C NMR (δ; 100 MHz $CDCl_3$); 65.2 (CH_2), 127.2 (ArCH), 128.2 (ArCH), 128.6 (ArCH), 131.5 (ArC), 139.0 (ArC), 162.5 (CH=N). MS (ES+) calculated for formula $C_{14}H_{13}N$: 195.2; found: 195.1. The spectral data are comparable with literature.[22]

***N*-benzyl-2,2-dimethylpropan-1-imine (8b)**



General procedure (**a1**) was used, pivaldehyde (1.0 gm, 11.6 mmol), benzylamine (0.8 gm, 6.00 mmol), yellow oil, 174 mg 91% yield. IR 2889, 1890, 1642, 1430, 1023.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.05 (9H, s,C*H*$_3$), 4.45 (2H, s, ArC*H*$_2$), 7.10-7.25 (5H, m, ArC*H*), 7.55 (1H, s, C*H*=N).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 12.6 ($3CH_3$), 27.1 (CH), 45.6 (CH_2), 126.9 (2ArCH), 127.5 (2ArCH), 1128.1 (ArCH), 133.3 (ArC), 151.9 (CH=N). The spectral data are comparable with literature.[59]

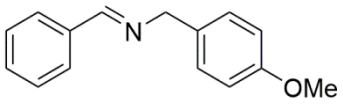
***N*-benzyl-1-(pyridin-3-yl)methanimine (8c)**



General procedure (**a1**) was used, 3-Pyridinecarboxaldehyde (1.0 gm, 9.30 mmol), benzylamine (1.0 gm, 9.00 mmol), pale yellow oil, 168 mg 90% yield. IR; 3060, 3029, 2882, 1646, 1586, 1567, 1467, 1435, 1364, 992, 771, 739, 698.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 4.90 (2H, d, *J* 1.4, ArC*H*$_2$), 7.26-7.42 (5H, m, ArC*H*), 8.16 (2H, dt,

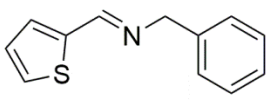
*J*7.6, 1.5, PyrC*H*), 8.44 (1H, d, *J* 7.9, PyrC*H*), 8.68 (1H, d, *J* 7.1, PyrC*H*), 8.9 (1H, s, C*H*=N), ^{13}C NMR (δ; 100 MHz, $CDCl_3$); 55.3 (CH_3), 64.7 (CH_2), 113.9 (2ArCH), 123.7 (ArCH), 129.3 (2ArCH), 130.8 (ArC), 131.8 (PyrC), 134.6 (PyrCH), 150.3 (PyrCH), 151.5 (PyrCH), 158.5 (CH=N), 158.8 (PyrCH). MS (ES+) calculated for formula $C_{13}H_{12}N_2^+$: 197.2; found: 197.2. The spectral data are comparable with literature.[59]

_N_-benzylidne-1-(4-methoxyphenyl)methanamine (8e)



General procedure (**a1**) was used, benzaldehyde (1.0 gm, 9.40 mmol), 4-methoxybenzylamine (1.2 gm, 6.90 mmol), yellow oil, 172 mg 94% yield. IR 3016, 2664, 1602, 1525, 1459, 1395, 1389, 1356, 1308, 1285, 1222, 1190, 1134, 1087, 1035, 896, 890, 868, 814, 777, 763, 710, 680. ^{1}H NMR (δ; 300 MHz, $CDCl_3$); 3.75 (3H, s, OC*H*$_3$), 4.75 (2H, s, ArC*H*$_2$), 6.85 (2H, dd, *J* 15, 1.3, ArC*H*), 7.25 (2H, dd, *J* 15, 1.8, ArC*H*), 7.35 (5H, m, ArC*H*), 8.25 (1H, s, C*H*=N).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 55.3 (OCH_3), 64.5 (CH_2), 114.0 (2ArCH), 128.3 (2ArCH), 128.6 (2ArCH), 129.3 (2ArCH), 130.8 (ArCH), 131.4 (ArC), 136.2 (ArC), 158.7 (ArCOMe), 161.7 (CH=N). The spectral data are comparable with literature.[22]

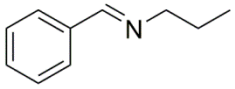
_N_-benzyl-1-(thiophen-2-yl)methanimine (8f)



General procedure (**a1**) was used, thiophencarboxaldehyde (1.0 gm, 9.0 mmol), benzylamine (1.2 gm, 10.0 mmol), brown yellow oil, 175 mg 92% yield. IR 3063, 3027, 2869, 1631, 1495, 1430, 1345, 1219, 1044, 835, 697.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 4.83 (2H, s, ArC*H*$_2$), 7.11 (1H, dd, *J* 5.0, 3.6, ThioC*H*), 7.26- 7.45 (7H, m, ArCH, ThioCH), 8.49 (1H, s, C*H*=N).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 64.4 (CH_2), 127.0 (ThioCH),

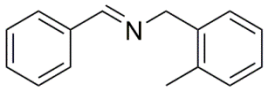
127.4 (ArCH), 128.0 (2ArCH), 128.5 (2ArCH), 129.0 (ThioCH), 130.7 (ThioCH), 139.0 (ThioC), 142.4 (ArC), 155.2 (CH=N). MS (ES+) calculated for formula $C_{12}H_{12}NS$: 202.1; found: 202.2. The spectral data are comparable with literature.[87]

1-Phenyl-*N*-propylmethanimine (8g)



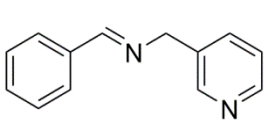
General procedure (**a1**) was used, benzaldehyde (1.0 gm, 9.40 mmol), propylamine (50 mg, 9.40 mmol), yellow oil, 121 mg 92% yield. IR 3027, 3062, 2960, 2930, 2873, 2832, 1646. ^{1}H NMR (δ; 300 MHz, $CDCl_3$); 0.96 (3H, t, *J* 17.0, C*H*$_3$), 1.75 (2H, m, C*H*$_2$), 3.58 (2H, t, *J* 9.0, C*H*$_2$), 7.35-7.45 (2H, m, ArCH), 7.65-7.72 (3H, m, ArCH), 8.25 (1H, s, C*H*=N).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 11.9 (CH_3), 24.1 (CH_2), 63.5 (CH_2), 128.1 (2ArCH), 128.6 (2ArCH), 131.2 (ArCH), 136.4 (ArC), 160.9 (CH=N). The spectral data are comparable with literature.[22]

***N*-benzylidene-1-(o-tolyl)methanamine (8j)**



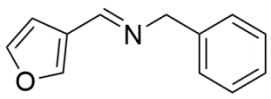
General procedure (**a1**) was used, benzaldehyde (1.0 gm, 9.40 mmol), 2-methylbenzylamine (1.1 gm, 9.40 mmol), pale yellow oil, 178 mg 90% yield. IR 2835, 2823, 1605, 1576, 1492, 1364, 1311, 1127, 1035, 898, 830, 762, 704, 689.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 2.35 (3H, s, C*H*$_3$), 4.35 (2H, s, ArC*H*$_2$), 7.25-7.55 (8H, m, ArCH), 7.75 (1H, d, *J* 4.5, ArC*H*), 8.35 (1H, s, C*H*=N).^{13}C NMR (δ; 100 MHz $CDCl_3$); 19.4 (CH_3), 62.7 (CH_2), 126.2 (ArCH), 127.2 (ArCH), 128.3 (2ArCH), 128.5 (ArCH), 128.7 (2ArCH), 130.2 (ArCH), 130.8 (ArCH), 136.3 (ArC), 137.6 (ArC), 161.9 (CH=N). MS (ES+) m/z= 192.1. The spectral data are comparable with literature.[58]

***N*- benzylidene-1-pyridine-3-yl)methanamine (8k)**



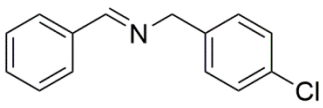
General procedure (**a1**) was used, benzaldehyde (1.0 gm, 9.40 mmol), 3-picolylamine (1.1 gm, 9.40 mmol), yellow oil, 170 mg, 95% yield. IR 3027, 2844, 1642, 1576, 1478, 1450, 1422, 1379, 1308, 1293, 1217, 1170, 1124, 1066, 1025, 963, 923, 858, 824, 787, 753, 711, 692. ^{1}H NMR (δ; 300 MHz, $CDCl_3$); 4.75 (2H, s, PyrCH_2), 7.22-7.45 (5H, m, ArC*H*), 7.65 (1H, d, *J* 13.1, PyrC*H*), 8.45 (1H, s, PyrC*H*), 8.51 (1H, dd, *J* 6.1, 2.0, PyrC*H*), 8.65 (C*H*=N).^{13}C NMR (δ; 100MHz, $CDCl_3$); 62.3 (CH_2), 123.4 (PyrCH), 128.3 (2ArCH), 128.7 (2ArCH), 131.0 (ArCH), 134.9 (PyrCH), 135.5 (ArC), 135.9 (PyrC), 148.4 (PyrCH), 149.4 (PyrCH), 162.7(CH). MS (ES+) M/z= 197.1. The spectral data are comparable with literature.[88]

***N*-benzyl-1-(furan-3-yl)methanimine (8l)**



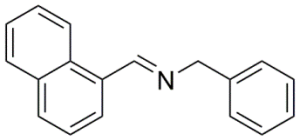
General procedure (**a1**) was used, furancarboxaldehyde (1 gm, 10.0 mmol), benzylamine (1.2 gm, 10.0 mmol), brown oil, 172 mg 95% yield. ^{1}H NMR (δ; 300 MHz, $CDCl_3$); 4.73 (2H, s, ArCH_2), 6.85 (1H, s, FurC*H*), 7.72 (1H, s, FurC*H*), 7.41 (1H,s, FurC*H*), 7.22-7.38 (5H, m, ArC*H*), 8.33 (1H, s, C*H*=N).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 65.2 (CH_2), 108.0 (FurCH), 125.5 (FurC), 127.0 (ArCH). 128.0 (2ArCH), 128.4 (2ArCH), 139.2 (ArC), 144.1 (FurCH), 145.4 (FurCH), 153.6 (CH=N). MS (ES+) m/z= 185.1. The spectral data are comparable with literature.[59]

***N*-(4-chlorobenzyl)-1-phenylmethanimine (8m)**



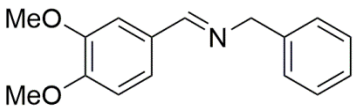
General procedure (**a1**) was used, benzaldehyde (1.0 gm, 9.40 mmol), 4-chlorobenzylamine (1 gm, 9.40 mmol), yellow oil, 195 mg 92% yield. IR 3027, 2841, 1892, 1643, 1490, 1090, 1014, 798, 753, 691.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 4.76 (2H, *s*, ArCH_2), 7.22-7.38 (5H, m, ArC*H*), 7.35-7.45 (2H, m, ArC*H*), 7.72- 7.78 (2H, m, ArC*H*), 8.35 (1H, s, C*H*=N).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 64.2 (CH_2), 128.4 (2ArCH), 128.6 (2ArCH), 129.0 (2ArCH), 129.5 (2ArCH), 131.0 (ArCH), 132.8 (ArC), 136.0 (ArC), 137.9 (ArC), 162.4 (CH=N). The spectral data are comparable with literature.[59]

***N*-benzylidne-1-(naphthyl)methanamine (8n)**



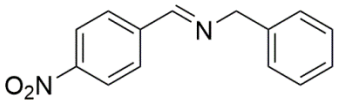
General procedure (**a1**) was used, 1-naphthalenecarboxaldehyde (1 gm, 6.40 mmol), benzylamine (1.2 gm, 6.4 mmol), yellow oil, 149 mg 95% yield. IR 3023, 2860, 1631, 1587, 1497, 1411, 1302, 1355, 1315, 1302, 1342, 1224, 1119, 1090, 1024, 875, 850, 810, 755, 730, 710, 680.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 5.02 (2H, s, ArCH_2), 7.28-7.71 (4H, m, ArC*H*), 7.90-8.06 (2H, m, ArC*H*), 9.05 (1H, d, *J* 8.4, ArC*H*), 9.10 (1H, s, C*H*=N).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 66.1 (CH_2), 124.4 (ArCH), 125.3 (ArCH), 126.1 (ArCH), 127.0 (ArCH), 127.1 (ArCH), 127.2 (ArCH), 128.0 (ArCH), 128.6 (ArCH), 128.7 (ArCH), 129.2 (ArCH), 131.2 (ArCH), 131.4 (ArCH), 131.6 (ArC), 133.9 (ArC), 139.6 (ArC), 161.8 (CH=N). The spectral data are comparable with literature.[59]

***N*-benzyl-1-(3,4-dimethoxyphenyl)methanimine (8o)**



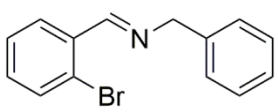
General procedure (**a1**) was used, 3,4- methoxycarboxaldehyde (1 gm, 7.20 mmol), benzylamine (1.1 gm, 6.02 mmol), yellow oil, 140 mg 92% yield.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 3.93 (3H, s, OC*H*$_3$), 3.95 (3H, s, OC*H*$_3$), 4.83 (2H, s, ArC*H*$_2$), 6.89 (1H, s, ArC*H*), 6.91 (1H, s, ArC*H*), 7.21 (1H, dd, *J* 8.2, 1.9, ArC*H*), 7.28-7.41 (2H, m, ArC*H*), 7.52 (1H, d, *J* 1.9, ArC*H*), 8.32 (1H, s, C*H*=N).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 55.9 ($2CH_3$), 64.9 (CH2), 108.8 (ArCH), 110..4 (ArCH), 123.3 (ArCH), 126.9 (ArCH), 127.0 (ArCH), 128.0 (ArCH), 128.4 (ArCH), 129.4 (ArC), 139.4 (ArC), 149.3 (ArC), 151.4 (ArC), 161.5 (CH=N). MS (ES^+) m/z 256 ($M+H^+$). The spectral data are comparable with literature.[89]

***N*-benzyl-1-(4-nitrophenyl)methanimine (8p)**



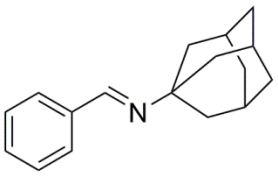
General procedure (**a1**) was used, 4-nitrocarboxaldehyde (1.0 gm, 6.30 mmol), benzylamine (1.1 gm, 6.30 mmol), brown oil, 133 mg 92% yield. IR 3063, 3029, 2850, 1644, 1600, 1517, 1375, 1339, 1107, 1027, 838, 698.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 4.88 (2H, s, ArC*H*$_2$), 7.22-7.39 (5H, m, ArC*H*), 7.92 (2H, dd, *J* 7.8, 2.0, ArC*H*), 8.24 (2H, dd, *J* 7.9, 1.9, ArC*H*), 8.46 (1H, s, C*H*=N).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 65.2 (*C*H_2), 123.9 (2ArCH), 127.3(ArCH), 128.1 (2ArCH), 128.7 (2ArCH), 129.0 (2ArCH), 138.5 (ArC), 141.6 (ArC), 149.1 ($ArCNO_2$), 159.5 (CH=N). MS (ES^+) m/z 241.2 ($M+H^+$).

***N*-benzyl-1-(2-bromophenyl)methanimine (8q)**



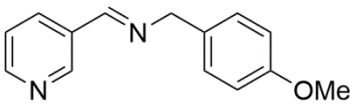
General procedure (**a1**) was used, 2-bromocarboxaldehyde (1.0 gm, mmol), benzylamine (1.0 gm, 6.4 mmol), yellow oil, 124 mg 92% yield. ^{1}H NMR (δ; 300 MHz, $CDCl_3$); 4.76 (2H, s, ArC*H*$_2$), 7.13-7.26 (7H, m, ArC*H*), 7.45-7.48 (1H, m, ArC*H*), 7.97 (1H, dd, *J* 7.7, 1.9, ArC*H*), 8.68 (1H, s, C*H*=N).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 66.2 (CH_2), 125.2 (ArCH), 127.1(ArCH), 128.0 (ArCH), 128.2 (ArCH), 128.5 (ArCH), 131.9 (ArCH), 133.0 (ArCH), 134.5 (ArC), 139.0 (ArC), 161.0 (CH=N). MS (ES^+) m/z 273.0 ($M+H^+$). The spectral data are comparable with literature.[87]

***N*-((1*s*,3*s*)-adamantan-1-yl)-1-phenylmethanimine (8r)**



General procedure (**a1**) was used, benzaldehyde (1 gm, 9.40 mmol), admatamine (1.2 gm, 9.80 mmol), white precipitate, 146 mg 93% yield. IR 3027, 2841, 1892, 1643, 1490, 1090, 1014, 798, 753, 691.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.66-1.81 (15H, m, 6C*H*$_2$, 3C*H*), 7.35-7.45 (2H, m, ArCH), 7.70-7.80 (3H, m, ArCH), 8.8.29 (1H, s, C*H*=N).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 29.6 (3CH), 36.6 ($3CH_2$), 43.2 ($3CH_2$), 57.5 (C), 127.9 (2ArCH), 128.5 (2ArCH), 130.1 (ArCH), 137.3 (ArC), 155.0 (CH=N). HRMS $[M+H]^+$ calculated for formula $C_{17}H_{22}N$: 240.1752; found: 240.1752.

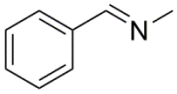
***N*-(4-methoxybenzyl)-1-(pyridin-3-yl)methanimine (8s)**



General procedure (**a1**) was used, 3-pyridinecarboxaldehyde (1 gm, 9.30 mmol), 4-methoxybenzylamine (1.2 gm, 9.30 mmol), yellow oil 90% yield. IR 3386, 2958, 2836, 1610, 1589, 1511, 1246, 1029, 817, 706.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 4.73 (2H, *s*, ArC*H*$_2$), 5.01 (3H, s, OC*H*$_3$), 7.21-7.31 (2H, m, ArCH), 7.35- 7.45

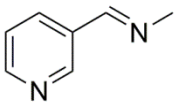
(2H, m, ArC*H*), 7.7 (1H, d, *J* 7.1, PyrC*H*), 7.75 (1H, m, PyrC*H*), 8.4 (1H, s, PyrC*H*), 8.5 (1H, d, *J* 6.9, PyrC*H*), 8.55 (C*H*=N).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 55.3 (CH_3), 64.7 (CH_2), 113.9 (2ArCH), 123.7 (PyrCH), 129.2 (2ArCH), 131.8 (ArC), 132.0 (PyrC), 134.6 (PyrCH), 150.3 (PyrCH), 151.5 (PyrCH), 158.5 (CH=N), 158.8 (ArCOMe). HRMS ($M+H^+$) calculated for formula $C_{14}H_{15}N_2O^+$: 227.2722; found: 227.2787. The spectral data are comparable with literature.[87]

_N_-methyl-1-phenylmethanimine (8t)



Benzaldehyde (1gm, 9.4 mmol) was mixed with methylamine solution (5 mL) and stirred at room temperature for 24 hours, the solvent was removed to give pure imine. Pale yellow oil, 110 mg 99% yield.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 3.51 (3H, s, C*H*$_3$), 7.39-7.41 (3H, m, ArC*H*), 7.69-7.72 (2H, m, ArC*H*), 8.26 (1H, s, C*H*=N).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 48.2 (CH_3), 127.9 (ArCH), 128.2 (ArCH), 128.6 (ArCH), 129.7 (ArCH), 130.5 (ArCH), 136.2 (ArC), 162.6 (CH=N). MS (ES+) calculated for formula $C_{14}H_{13}N$: 120.1; found: 120.1. The spectral data are comparable with literature.[90]

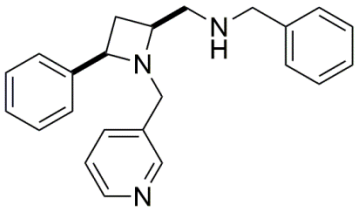
_N_-methyl-1-(pyridin-3-yl)methanimine (8u)



3-Pyridinecarboxaldehyde (1gm, 9.30 mmol) was mixed with methylamine solution (5 mL) and stirred at room temperature for 24 hours, the solvent was removed to give pure imine, yellow oil, 115 mg 99% yield. ^{1}H NMR (δ; 300 MHz, $CDCl_3$); 3.55 (3H, s, C*H*$_3$), 7.32-7.36 (1H, m, PyrC*H*), 8.06-8.09 (1H, m, PyrC*H*), 8.32 (1H, s, PyrC*H*), 8.63-8.65 (1H, m, PyrC*H*), 8.86 (1H, s, C*H*=N).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 48.4 (CH_3), 123.6 (PyrCH), 131.7 (PyrC), 134.2 (PyrCH), 149.9 (PyrCH), 151.3 (PyrCH), 159.5 (CH=N). MS

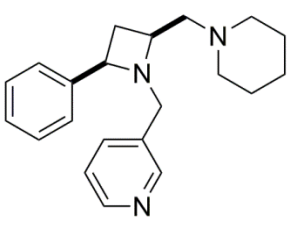
(ES+) calculated for formula $C_{14}H_{13}N$: 121.1; found: 121.1. The spectral data are comparable with literature.[91]

_N_-benzyl-1-((2_S_, 4_R_)-4-phenyl-1-(pyridin-3-ylmethyl)azetidin-2-yl)methanamine (44a)



General procedure (**h**) was used, 1-phenyl-*N*-(pyridin-3-ylmethyl)but-3-en-1-amine (280 mg, 0.83 mmol), flash chromatography (DCM/Methanol= 9.5/0.5), yellow brown oil, 200 mg 65% yield. IR 3020, 2822, 1670, 1567, 1470, 1454, 1421, 1354, 1260.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 2.01 (2H, dd, *J* 18.8, 8.7, CHC*HH*N), 2.39-2.49 (2H, m, CHC*HH*CH), 2.56 (1H, dd, *J* 12.1, 4.3, CH), 3.32 (1H, m, CH), 3.67 (ABq, 2H, J_{AB}13.2, J_{AB}13.2, PyrCH_2), 3.64 (2H, s, ArCH_2), 3.99 (1H, app.t, *J* 8.2, C*H*CHH), 7.08 (2H, ddd, *J* 7.7, 4.8, 0.6, ArC*H*), 7.13-7.44 (10H, overlapping m, ArC*H*, PyrC*H*), 8.39 (1H, dd, *J* 4.8, 1.6, PyrC*H*), 8.49 (1H, d, *J* 1.8, PyrCH).^{13}C NMR (δ; 100 MHz, $CDCl_3$), 31.3 (CH_2), 53.3 (CH_2), 54.0 (CH_2), 58.8 (CH_2), 62.6 (CH), 65.8 (CH), 123 (PyrCH), 126.9 (2ArCH), 127.2 (ArCH), 127.2 (ArCH), 128.2 (2ArCH), 128.4 (2ArCH), 128.7 (2ArCH), 134.1 (ArC), 136.7 (PyrCH), 140.0 (PyrC), 143.0 (ArC), 148.5 (PyrCH), 150.2 (PyrCH).HRMS $[M+H]^+$calculated for formula $C_{23}H_{26}N_3^+$344.2120; found 344.2121.

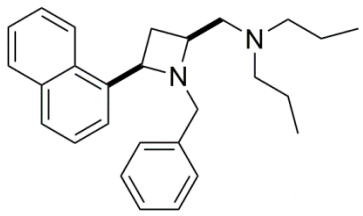
3-((2-Phenyl-4-(piperidin-1-ylmethyl)azetidin-1-yl)methyl)pyridine (44b)



General procedure (**h**) was used, 1-phenyl-*N*-(pyridin-3-ylmethyl)but-3-en-1-amine (130 mg, 0.53 mmol), flash chromatography (DCM/Methanol= 9.5/0.5 and 9/1), 100 mg 76% yield. IR 3028, 2934, 2852, 2803,1576, 1492, 1454, 1424, 1354, 1326, 1303, 1157, 1122,

1026, 998, 860, 752, 714, 699.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 0.91 (2H, dd, *J* 13.0, 5.8, $CH_2CH_2CH_2$), 1.23-1.49 (4H, m, 2x CH_2), 1.60 (4H, dt, *J* 10.9, 5.4, 2x CH_2), 1.80 (2H, dt, *J* 10.1, 8.5, NCH_2CH), 3.46 (1H, dt, *J* 13.6, 6.9, CH_2CHCH_2), 3.72 (2H, d, *J* 2.6, PyrCH_2), 4.00 (1H, app.t, *J* 8.1, CHCHH), 7.10 (2H, dd, *J* 7.4, 4.8, ArCH), 7.15-7.39 (3H, m, ArCH), 7.59 (1H, dt, *J* 7.8, 1.8, PyrCH), 8.39 (1H, dd, *J* 4.8, 1.4, PyrCH), 8.49 (1H, d, *J* 1.5, PyrCH).^{13}C NMR (δ; 100 MHz, $CDCl_3$), 23.7 (CH_2), 25.2 ($2CH_2$), 35.4 (CH_2), 54.9 ($2CH_2$), 58.5 (CH_2), 60.3 (CH), 64.8 (CH_2), 66.3 (CH), 123.0 (PyrCH), 126.8 (2ArCH), 127.2 (ArCH), 128.2 (2ArCH), 133.8 (PyrC), 137.0 (PyrCH), 142.9 (ArC), 148.3 (PyrCH), 150.4 (PyrCH). High resolution MS [$M+H^+$] calculated for formula $C_{21}H_{27}N_3^+$: 321.2205 found 321.2207.

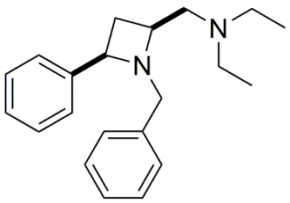
_N_-(((2_S_,4_R_)-1-benzyl-4-(naphthalen-1-yl)azetidin-2-yl)methyl)-_N_-propylpropan-1-amine (44c)



General procedure (**h**) was used, *N*-benzyl-1-(naphthalen-1-yl)but-3-en-1-amine (210 mg, 0.72 mmol), flash chromatography (Ethyl acetate/Hexane= 1/1), yellow brown oil, 120 mg 50% yield. IR 2956, 2924, 1666, 1454, 799, 778, 699.^{1}H-NMR (δ; 300 MHz, $CDCl_3$); 0.80 (3H, t, *J* 7.3, CH_3), 1.25 (3H, t, *J* 8.9, CH_3), 1.22-1.43 (4H, m, 2x CH_2CH_3), 1.76 (2H, dd, *J* 18.6, 8.6, $CHCH_2N$), 2.16-2.40 (4H, m, 2x $NCH_2CH_2CH_3$), 2.8-2.97 (1H, m, CH_2CHCH_2), 3.81 (ABq, 2H, J_{AB}12.6, J_{AB}12.6, ArCH_2), 4.73 (1H, app.t, *J* 8.5, CHCHH), 7.55-7.57 (10H, m, ArCH), 7.74 (2H, d, ArCH).^{13}CNMR (δ; 100 MHz, $CDCl_3$), 11.9 ($2CH_3$), 20.1 (CH_2), 29.7 ($2CH_2$), 35.2 ($2CH_2$), 56.9 ($2CH_2$), 60.0 (CH), 62.0 (CH), 62.3 (CH_2), 62.7 (2CH), 122.9 (ArCH), 123.0 (ArCH), 124.4 (ArCH), 124.9 (ArCH), 125.4 (ArCH), 125.6 (ArCH), 125.8 (ArCH), 126.1 (ArCH), 126.7 (ArCH), 127.1 (ArCH), 128.1 (ArCH), 129.6 (ArCH), 133.6

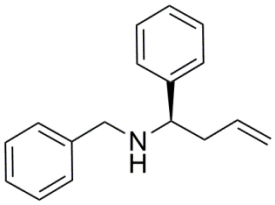
(2ArC), 138.8 (ArC), 139.6 (ArC). High resolution MS [M+H$^+$] calculated for formula $C_{27}H_{35}N_2^+$: 387.2800 found 387.2819.

***N*-(((2*S*,4*R*)-1-benzyl-4-phenylazetidin-2-yl)methyl)-N-ethylethanamine (44e)**



General procedure (**f**) was used, *N*-benzyl-1-phenylbut-3-en-1-amine (200 mg, 8.5 mmol), flash chromatography (DCM/Methanol= 9.5/0.5), yellow brown oil, 80 mg 65% yield. IR 3024, 2820, 1666, 1523, 1450, 1342, 1260.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 0.93 (6H, t, *J* 7.1, 2x C*H*$_3$), 1.78 (2H, dd, *J* 17.9, 9.3, C*H*$_2$CH$_3$), 2.29 (1H, dd, *J* 13.2, 3.5, CH$_2$C*H*CH$_2$), 2.36-2.52 (2H, m, C*H*$_2$CH$_3$), 2.61 (2H, dt, *J* 10.1, 7.4, CHC*HH*CH), 3.70 (ABq, 2H, J_{AB}12.8, J_{AB}12.8, ArC*H*$_2$), 4.01 (1H, app.t, *J* 8.2, C*H*CHH), 7.20-7.47 (10H, m, ArCH).^{13}C NMR (δ; 100 MHz, $CDCl_3$), 21.1 (2CH$_3$), 31.3 (CH$_2$), 50.0 (CH$_2$), 54.8 (CH$_2$), 58.2 (CH), 64.1 (CH), 64.5 (CH), 124.3 (ArCH), 124.9 (ArCH), 126.9 (2ArCH), 127.1 (2ArCH), 127.5 (2ArCH), 128.1 (2ArCH), 142.1 (ArC), 143.5 (ArC).HRMS [M+H]$^+$calculated for formula $C_{21}H_{29}N_2^+$309.4116; found 309.4119.

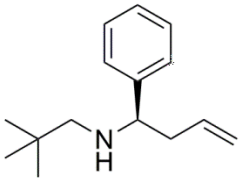
(*R*)-*N*-benzyl-1-phenylbut-3-en-1-amine (46a)



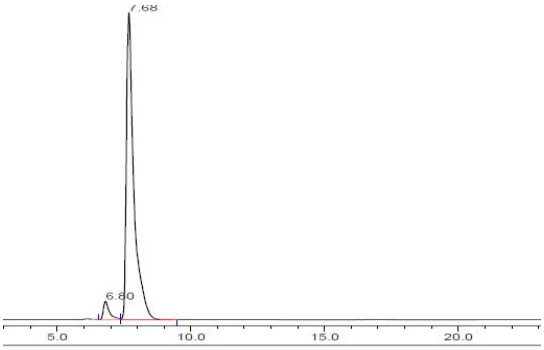
General procedure (**c3**) was used. *N*-benzyl-1-phenylbut-3-en-1-amine (1 gm, 2.40 mmol), 3-bromo-1-propene (1.2 gm, 10.0 mmol) and zinc powder (400 mg, 7.2 mmol) in dry THF (10 mL), pale yellow oil, 1.45 gm 91% yield.^{1}H NMR (δ; 300 MHz, $CDCl_3$);1.82 (1H, s, NH), 2.25-2.35 (1H, m, NHC*H*CHH), 3.41 (1H, d, *J*13.3, PhCH*H*), 3.56-3.61 (ABq, 2H, *m*, PhCH*H*),4.90-5.10 (2H, m, olefine C*HH*), 5.50-5.60 (1H, m, C*H*=CH$_2$), 7.05-7.25 (10H, m, ArCH).^{13}C NMR (δ; 100MHz , $CDCl_3$); 43.3 (CH$_2$), 51.5 (CH$_2$), 61.5 (CH), 117.7 (CH$_2$), 126.9 (CH), 127.2 (ArCH), 128.2 (ArCH), 128.3

(2ArCH), 128.4 (2ArCH), 128.5 (2ArCH), 128.7 (2ArCH), 135.6 (ArC), 141.0 (ArC), 144.0 (C). HRMS $[M+H]^+$ calculated for the formula $C_{17}H_{20}N^+$ 238.1592; found 238.1584. $[\alpha]^{20}_D$= +56.5 (C 5, $CHCl_3$) (lit. +55.4). >99% *ee*.[23]

(*R*)-*N*-neopentyl-1-phenylbut-3-en-1-amine (46b)



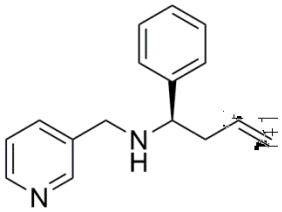
General procedure (**c3**) was used. *N*-neopentyl-1-phenylmethanimine (1 gm, 5.70 mmol), 3-bromo-1-propene (1.3 gm, 11.4 mmol) and zinc powder (900 mg,14.2 mmol) in dry THF (10 mL), pale yellow oil, 985 mg 93% yield.[1]H NMR (δ; 300 MHz, $CDCl_3$);1.52 (9H, s, CH_3), 2.22-2.32 (1H, m, NHC*H*CHH), 3.46 (2H, d, *J*12.4, CC*HH*),5.10-5.25 (2H, m, olefine C*HH*), 5.60-5.80 (1H, m, C*H*=CH_2), 7.15-7.20 (5H, m, ArCH).[13]C NMR (δ; 100MHz , $CDCl_3$); 23.1 (CH_3), 23.1 (CH_3), 23.1 (CH_3), 43.3 (CH_2), 51.5 (CH_2), 61.5 (CH), 117.7 (CH_2), 128.5 (2ArCH), 128.7 (ArCH), 135.6 (ArCH), 140.5 (ArC), 144.0 (C). HRMS $[M+H]^+$calculated for the formula $C_{15}H_{24}N^+$ 218.1832; found 218.1824. $[\alpha]^{20}_D$=+26.5 (c 5, DCM). HPLC (AD column), hexane/isopropanol 99:1, flow rate=0.2 mL/ minutes, 91% *ee*.



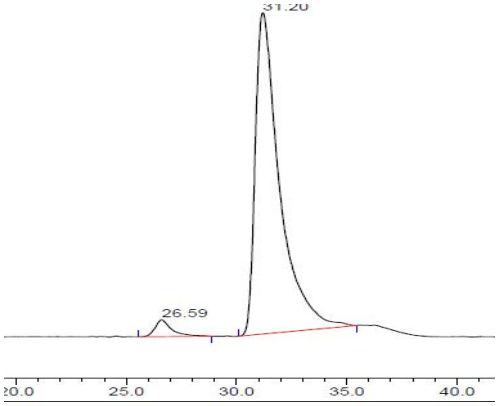
ime n	Peak Name	Height mAU	Area mAU*min	Rel.Area %
30	n.a.	29.637	7.778	4.61
68	n.a.	497.787	160.938	95.39
		527.423	168.716	100.00

Figure 44: HPLC data for ***R*-46b**

(*R*)-1-phenyl-*N*-(pyridin-3-ylmethyl)but-3-en-1-amine (46c)



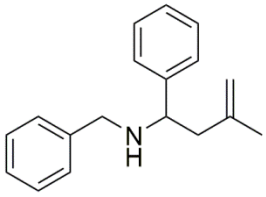
General procedure (**c3**) was used, 1-phenyl-*N*-(pyridin-3-ylmethyl)methanimine (1 gm, 2.40 mmol), 3-bromo-1-propene (1.2 gm, 10.0 mmol) and zinc powder (400 mg,7.2 mmol) in dry THF (10 mL), yellow oil, 1.40 gm 92% yield.^{1}H NMR (δ; 300 MHz, $CDCl_3$);1.80 (1H, s, NH), 2.42-2.45 (1H, m, NHC*H*CHH), 3.42 (1H, d, *J*13.1, PhCH*H*), 3.26-3.41 (2H, *m*, PhC*HH*), 4.86-5.00 (2H, m, olefine C*HH*), 5.40-5.50 (1H, m, C*H*=CH_2), 7.05-7.25 (6H, m, ArCH), 8.35-8.45 (2H, m, PyCH), 8.50 (1H, s, PyCH).^{13}C NMR (δ; 100MHz , $CDCl_3$); 43.3 (CH_2), 51.5 (CH_2), 61.5 (CH), 117.7 (CH_2), 126.9 (CH), 127.2 (ArCH), 128.2 (ArCH), 128.3 (2ArCH), 128.4 (ArCH), 128.5 (PyrCH), 128.7 (PyrCH), 135.6 (ArC), 141.0 (PyrC). HRMS $[M+H]^+$ calculated for the formula $C_{16}H_{19}N_2^+$ 239.1502; found 239.1504. $[\alpha]^{20}_D$=+41.3 (C 5, DCM). HPLC (AD column), hexane/isopropanol 99:1, flow rate=0.2 mL/minutes, >93% *ee*.



Height mAU	Area mAU*min	Rel.Area %	Amount
4.062	3.564	3.46	n.a.
77.131	99.287	96.54	n.a.
81.192	102.851	100.00	0.000

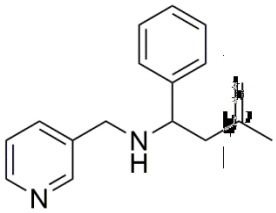
Figure 45: HPLC data for ***R*-46c**

***N*-benzyl-3-methyl-1-phenylbut-3-en-1-amine (47a)**



General procedure (**d)** was used. *N*-benzylidene-1-phenylmethanamine (1000 mg, 5.0 mmol), 3-bromo-2-methylprop-2-ene (1000 mg, 10 mmol) and zinc powder (838 mg, 10 mmol) in dry THF (10 mL). Pale yellow oil, 2.0 gm 99% yield. IR 3450, 3026, 2933, 1492. ^{1}H NMR (δ; 300 MHz, $CDCl_3$) ;1.72 (3H, s, C*H*$_3$),1.85 (1H, s, N*H*), 2.37 (1H, dd, J_{ab}14.0, J_{ac}4.7, CHC*H*H), 2.45 (1H, dd, J_{ab}14.0, J_{bc} 9.5, CHCH*H*), 3.56 (ABq, 1H, J_{AB}13.5, ArC*H*H), 3.78 (ABq, 1H, J_{AB}13.5, ArCH*H*), 3.84 (1H, dd, J_{bc}9.5, J_{ac}4.7, NC*H*CHH), 4.84 (1H, s, olefine C*H*H), 4.88 (1H, s, olefine CH*H*), 7.25-7.50 (10H, m, ArCH).^{13}C NMR (δ; 100MHz , $CDCl_3$); 22.1 (CH_3), 47.6 (CH_2), 51.5 (CH_2), 59.3 (CH), 113.4 (CH_2), 126.8 (2ArCH), 127.0 (2ArCH), 127.3 (2ArCH), 128.1 (2ArCH), 128.3 (ArCH), 128.4 (ArCH), 140.6 (ArC), 142.7 (ArC), 144.3 (C). HRMS $[M+H]^+$ calculated for the formula $C_{18}H_{22}N^+$ 252.1762; found 252.1752.[92]

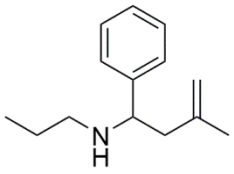
3-Methyl-1-phenyl-N-(pyridin-3-ylmethyl)but-3-en-1-amine (47b)



General procedure (**d**) was used. *N*-benzyl-1-(pyridin-3-yl)methanimine(1.0 gm, 5.0 mmol), 3-bromo-2-methylprop-2-ene (1.0 gm, 10 mmol) and zinc powder (838 mg, 10 mmol) in dry THF (10 mL), yellow oil, 0.7 gm 74% yield. IR 3319, 3061, 3028, 2968, 2844, 1645, 1576, 1453, 1423, 1026, 892, 757, 701.^{1}H NMR (δ; 300MHz, $CDCl_3$); 1.68 (3H, s, C*H*$_3$), 2.24-2.45 (2H, m, CHC*HH*), 3.61 (ABq, 2H, J_{AB}13.7, J_{AB}13.7, PyrC*HH*), 3.75 (1H, dd, *J*8.2, 4.1, NC*H*CHH), 4.77 (1H, s, olefine C*H*H), 4.83 (1H, s, olefine CH*H*), 7.15-7.47 (6H, m, ArC*H*), 7.55 (2H, d, *J* 13.0, PyrC*H*), 8.47 (2H, d, *J* 8.3, PyrC*H*).^{13}C NMR (δ; 100 MHz, CDCl3); 22.1 (CH_3), 47.6 (CH_2), 48.8 (CH_2),

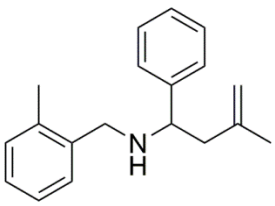
59.5 (CH), 113.6 (=CH_2), 123.3 (PyrCH), 127.2 (3ArCH), 128.5 (2ArCH), 135.8 (PyrCH), 135.9 (C), 142.60 (PyrC), 143.92 (ArC), 148.38 (PyrCH), 149.70 (PyrCH). HRMS [M+H^+] calculated for formula $C_{17}H_{21}N_2^+$; 253.1705; found 253.1709.

3-Methyl-1-phenyl-*N*-propylbut-3-en-1-amine (47c)



General procedure (**d**) was used. 1-phenyl-*N*-propylmethanimine(1.0 gm, 5.0 mmol), 3-bromo-2-methylprop-2-ene (1.0 gm, 10 mmol) and zinc powder (838 mg, 10 mmol) in dry THF (10 mL), yellow oil, 0.6 gm 41% yield. IR 3066, 3026, 3028, 2960, 2866 , 1646, 1602, 1454, 1375, 1309, 1142, 8, 893, 755.^{1}H NMR (δ; 300 MHz, $CDCl_3$) ; 0.85 (3H, t, *J* 7.4, C*H*$_3$), 1.38-1.55 (2H, m, CHC*HH*), 1.74 (3H, s, C*H*$_3$), 4.24-4.46 (4H, m, 2C*H*$_2$), 3.75 (1H, dd, *J* 14.4, 1.2, NC*H*CHH), 4.72 (1H, s, olefine C*H*H), 4.80 (1H, s, olefine CH*H*), 7.16-7.39 (5H, m, ArC*H*).^{13}C NMR (δ; 100MHz , $CDCl_3$); 11.8 (CH_3), 22.2 (CH_3), 23.1 (CH_2), 47.4 (CH_2), 49.9 (CH_2), 60.7 (CH), 113.4 (=CH_2), 127.0 (ArCH), 127.2 (2ArCH), 128.3 (2ArCH), 142.7 (ArC), 144.3 (C). HRMS [M+H^+] calculated for formula $C_{14}H_{22}N^+$; 204.1752; found 204.1753.

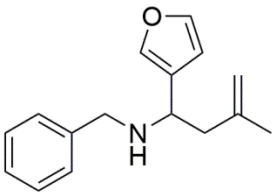
3-Methyl-N-(2-methylbenzyl)-1-phenylbut-3-en-1-amine (47e)



General procedure (**d**) was used. *N*-(2-methylbenzyl)-1-phenylmethanimine (1.0 gm, 5.0 mmol), 3-bromo-2-methylprop-2-ene (1.0 gm, 10.0 mmol) and zinc powder (838 mg, 10 mmol) in dry THF (10 mL). Pale yellow oil, 1.6 gm 91% yield. IR 3061, 2940, 1635, 1453, 890, 698.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.69 (3H, s, C*H*$_3$), 2.26 (3H, s, C*H*$_3$), 2.32-2.52 (3H, m, overlapping NH, C*H*$_2$), 3.60 (ABq, 2H, J_{AB}13.6, J_{AB}13.6, ArC*HH*), 3.82 (1H, dd, *J* 11.9, 5.9, NC*H*CHH), 4.69 (1H, s,

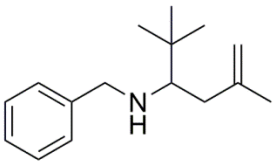
olefine C*H*H),4.72 (1H, s, olefine CH*H*), 7.15-7.49 (9H, m, ArC*H*).[13]C NMR (δ; 100 MHz, CDCl3); 18.9 (CH_3), 22.0 (CH_3), 47.4 (CH_2), 49.4 (CH_2), 59.9 (CH), 113.6 (=CH_2), 125.8 (ArCH), 127.1 (ArCH), 127.3 (2ArCH), 128.3 (2ArCH), 128.9 (2ArCH), 130.3 (ArCH), 136.5 (ArCCH_3), 138.0 (ArC), 142.7 (ArC), 144.0 (C). HRMS [M+H^+] calculated for formula $C_{19}H_{24}N^+$; 266.1909; found 266.1907.

_N_-benzyl-1-(furan-3-yl)-3-methylbut-3-en-1-amine (47f)



General procedure (**d**) was used, *N*-benzyl-1-(furan-3-yl)methanimine(1 gm, 5.4 mmol), brown oil, 110 mg, 84% yield. IR 3063, 2950, 1450, 1369, 889, 678.[1]H NMR (δ; 300 MHz, $CDCl_3$); 1.65 (3H, s, C*H*$_3$), 2.21-2.52 (2H, m, CHC*HH*), 3.52-3.84 (3H, m, C*H* overlapping CH_2), 4.78 (1H, s, olefine C*H*H), 4.81 (1H, s, olefine CH*H*), 6.47 (1H, s, FurC*H*), 7.22-7.46 (7H, m, ArC*H* overlapping FurC*H*).[13]C NMR (δ; 100 MHz, $CDCl_3$); 22.0 (CH_3), 45.9 (CH_2), 50.4 (CH), 51.2 (CH_2), 109.1 (FurCH), 113.5 (=CH_2), 126.9 (ArCH), 127.0 (2ArCH), 127.2 (2ArCH), 128.2 (C), 139.8 (FurCH), 140.5 (ArC), 142.5 (FurC), 143.2 (FurCH). HRMS [M+H^+] calculated for formula $C_{16}H_{20}NO^+$; 242.1545; found 242.1543.

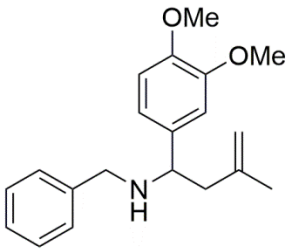
_N_-benzyl-2,2,5-trimethylhex-5-en-3-amine (47g)



General procedure (**d**) was used, pale yellow oil 82% yield. IR 3064, 3031, 2946, 1646, 1453, 1374, 890, 698.[1]H NMR (δ; 300 MHz, $CDCl_3$); 0.89 (9H, *s*, CH_3), 1.62 (3H, s, CH_3), 1.85 (1H, dd, J_{ab}13.6, J_{ac}6.9, C*H*H), 2.33 (1H, dd, J_{ab}13.6, J_{bc}6.7, CH*H*), 3.55 (ABq, 2H, J_{AB}12.9, J_{AB}12.9, ArCH_2), 3.72 (1H, dd, J_{ac}6.9, J_{bc}6.7, C*H*), 4.72 (1H, s, olefine C*H*H), 4.80 (1H, s, olefine CH*H*), 7.19-7.42 (5H, m,

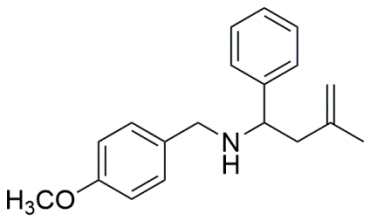
ArC*H*).[13]C NMR (δ; 100 MHz, $CDCl_3$); 22.0 (CH_3), 26.9 ($3CH_3$), 40.7 (CH_2), 47.6 (CH_2), 51.5 (C), 64.1 (CH), 112.8 (CH_2), 126.8 (ArCH), 127.9 (ArCH), 128.2 (2ArCH), 128.3 (2ArCH), 140.6 (ArC), 141.4 (C). HRMS [$M+H^+$] calculated for formula $C_{16}H_{26}N^+$; 232.2065; found 232.2064.

_N_-benzyl-1-(3,4-dimethoxyphenyl)-3-methylbut-3-en-1-amine (47h)



General procedure (**d**) was used, *N*-benzyl-1-(3,4-dimethoxyphenyl)methanimine (50 mg, 0.25 mmol), pale yellow oil, 62 mg 66% yield. [1]H NMR (δ; 300 MHz, $CDCl_3$); 1.45 (3H, s, C*H*$_3$), 1.88 (1H, s, N*H*), 2.13-2.38 (2H, m, CHC*HH*), 3.60 (ABq, 2H, J_{AB}14.1, J_{AB}14.1, PhC*HH*), 3.75 (1H, dd, *J* 13.1, 8.6, C*H*CHH), 4.64 (1H, s, olefine C*H*H), 4.70 (1H, s, olefine CH*H*), 6.71 (2H, m, ArC*H*), 6.88 (1H, s, ArC*H*), 7.05- 7.18 (5H, m, ArC*H*). [13]C NMR (δ; 100 MHz, $CDCl_3$); 22.1 (CH_3), 47.8 (CH_2), 51.4 (CH_2), 55.9 ($2OCH_3$), 58.9 (CH),), 110.0 (ArCH), 111.0 (ArCH), 113.5 (=CH_2), 119.5 (2ArCH), 126.9 (ArCH), 128.0 (2ArCH), 128.2 (2ArCH), 136.9 (ArC), 140.6 (ArC), 142.8 (C), 148.0 (ArCOMe), 149.2 (ArCOMe). HRMS [$M+H^+$] calculated for formula $C_{20}H_{25}NO_2Na^+$; 334.1783; found 334.1788.

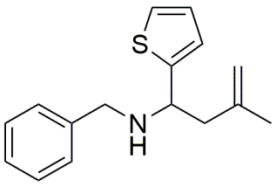
_N_-(4-methoxybenzyl)-3-methyl-1-phenylbut-3-en-1-amine (47i)



General procedure (**d**) was used, yellow oil 73% yield. IR 2926, 1611, 1511, 1453, 1301, 1245, 1036, 701. [1]H NMR (δ; 300 MHz, $CDCl_3$); 1.66 (3H, s, C*H*$_3$), 1.78 (1H, s, N*H*), 2.25-2.42 (2H, m, CHC*HH*), 3.59 (ABq, 2H, J_{AB}13.7, J_{AB}13.7, ArC*HH*), 3.74 (1H, dd, *J* 9.3, *J*4.9, C*H*CHH), 4.77 (1H, s, olefine C*H*H), 4.81 (1H, s, olefine CH*H*), 7.18-7.43 (3H,

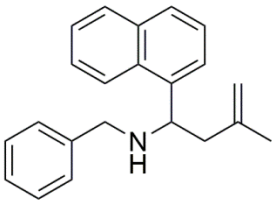
m, ArC*H*), 7.56-7.60 (1H, m, ArC*H*), 8.51 (1H, s, ArC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 22.1 (CH_3), 47.6 (CH_2), 50.9 (CH_2), 55.3 (CH), 59.2 (CH), 113.4 (=CH_2), 113.7 (2ArCH), 127.0 (ArCH), 127.3 (2ArCH), 128.4 (2ArCH), 129.3 (2ArCH), 132.8 (ArCOMe), 142.8 (ArC), 144.4 (ArC), 158.6 (C). HRMS [M+H$^+$] calculated for formula $C_{19}H_{24}NO^+$; 282.1858; found 282.1856.

_N_-benzyl-3-methyl-1-(thiophen-2-yl)but-3-en-1-amine (47j)



General procedure (**d**) was used, *N*-benzyl-1-(thiophen-2-yl)methanimine (1 gm, 5.6 mmol), yellow oil, 1.2 mg, 93% yield. IR 2922, 1645, 1494, 1453, 1373, 1317, 1109, 894, 695.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.64 (3H, s, C*H*$_3$), 2.35-2.51 (2H, m, CHC*HH*), 3.7 (ABq, 2H, J_{AB}12.9, J_{AB}12.9, ArC*H*$_2$), 4.15 (1H, dd, J_{bc}7.9, J_{ac}4.4, C*H*CHH), 4.74 (1H, s, olefine C*H*H), 4.80 (1H, s, olefine CH*H*), 6.94-7.03 (3H, m, 3xThioC*H*), 7.15-7.42 (5H, m, ArC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 21.9 (CH_3), 47.9 (CH_2), 51.1 (CH_2), 54.9 (CH), 113.9 (=CH_2), 124.1 (ThioCH), 124.4 (ThioCH), 126.4 (ThioCH), 127.1 (ArCH), 128.4 (4ArCH), 138.9 (ThioC), 142.1 (C), 142.1 (ArC). HRMS [M+H] calculated for formula $C_{16}H_{20}NS^+$ 258.1316; found 258.1315.

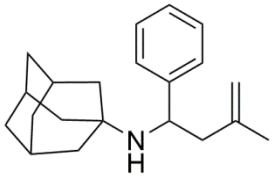
_N_-benzyl-3-methyl-1-(naphthalen-1-yl)but-3-en-1-amine (47k)



General procedure (**d**) was used, white solid precipitate, 0.3 gm 19%. yield.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.84 (3H, s, C*H*$_3$), 2.10 (1H, s, N*H*), 2.55 (2H, ddd, *J* 24.4, 14.2, 6.9, CHC*H*H), 3.75 (ABq, 2H, J_{AB}13.4, J_{AB}13.4, ArC*HH*), 4.75 (1H, dd, *J*10.1, *J*3.3, C*H*CHH), 4.95 (1H, d, *J* 6.7, C*H*CHH), 7.30-7.43 (3H, m, ArC*H*), 7.52-7.65 (2H, m, ArC*H*), 7.86 (1H, d, *J* 8.1, naphC*H*), 7.93-8.06 (2H, m, naphC*H*), 8.26 (1H, d, *J* 4.7, naphC*H*).^{13}C NMR (δ; 100 MHz, CDCl3); 22.1 (CH_3), 46.7 (CH_2),

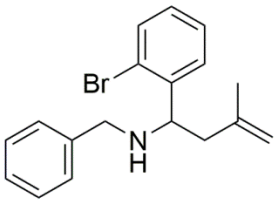
51.8 (CH_2), 113.6 (=CH_2), 122.8 (ArCH), 123.9 (ArCH), 125.3 (ArCH), 125.8 (ArCH), 125.9 (ArCH), 126.9 (ArCH), 127.4 (ArCH), 128.3 (ArCH), 128.4 (ArCH), 129.2 (ArCH), 131.6 (ArC), 134.2 (ArC), 139.5 (ArC), 140.7 (ArC), 143.0 (C). HRMS [M+H^+] calculated for formula $C_{22}H_{24}N^+$; 302.1909; found 302.1908.

***N*-(3-methyl-1-phenylbut-3-en-1-yl)adamantan-1-amine (47l)**



General procedure (**d**) was used, white solid precipitate 81% yield. IR 2904, 2848, 1645, 1452,700.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.30-2.20 (15H, overlapping m, 6xCH_2 & 3x admantyl C*H*), 4.03 (1H, dd, *J*9.9, *J*4.1, C*H*CHH), 4.78 (1H, s, olefine C*H*H), 4.83 (1H, s, olefine CH*H*), 7.15-7.48 (5H, m, ArCH).^{13}C NMR (δ; 100 MHz, CDCl3); 21.8 (CH_3), 29.6 (3CH), 35.8 (CH_2), 36.6 (3CH_2), 43.8 (2CH_2), 49.7 (CH_2), 51.1 (C), 52.6 (CH), 114.0 (=CH_2), 126.3 (ArCH), 126.9 (2ArCH), 128.0 (2ArCH), 143.1 (ArC), 148.5 (C). HRMS [M+H^+] calculated for formula $C_{21}H_{30}N^+$; 296.2378; found 296.2366.

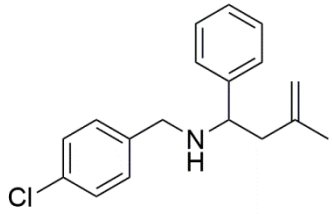
***N*-(2-bromobenzyl)-3-methyl-1-phenylbut-3-en-1-amine (47m)**



General procedure (**d**) was used, *N*-benzyl-1-(2-bromophenyl)methanimine (1 gm, 3.6 mmol), pale yellow oil, 0.58 gm 47% yield. IR 3064, 3027, 2918, 2850, 1645, 1566, 1454, 1121, 1022, 895, 753, 698.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.69 (3H, *s*, CH_3), 1.86 (1H, s, N*H*), 2.09 (1H, dd, J_{ab}14.1, J_{ac}4.0, CHC*H*H), 2.40 (1H, dd, J_{ab}14.1, J_{bc} 4.7, CHCH*H*), 3.58 (ABq, 2H, J_{AB}13.7, J_{AB}13.7, ArC*HH*), 4.25 (1H, dd, J_{ac}4.0, J_{bc}4.7, C*H*CHH), 4.78 (1H, s,olefine C*H*H), 4.82 (1H, s, olefine CH*H*), 7.05-7.62 (1H, m, ArC*H*), 7.20-7.38 (5H, m, ArC*H*), 7.52 (1H, d, *J* 8.1, ArC*H*),

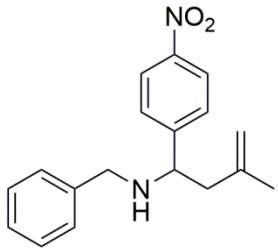
7.75 (1H, d, *J* 8.7, ArC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 21.6 (CH_3), 45.9 (CH_2), 51.7 (CH_2), 57.7 (CH), 113.7 (=CH_2), 124.0 (ArCBr), 126.9 (ArCH), 127.8 (ArCH), 128.2 (ArCH), 128.3 (2ArCH), 128.4 (ArCH), 132.8 (ArCH), 140.5 (C), 142.8 (ArC), 142.8 (ArC). HRMS [M+H^+] calculated for formula $C_{18}H_{21}NBr^+$; 331.2120; found 331.2122.

_N_-(4-chlorobenzyl)-3-methyl-1-phenylbut-3-en-1-amine (47n)



General procedure (**d**) was used, *N*-(4-chlorobenzyl)-1-phenylmethaniminepale (1 gm, 4.3 mmol), yellow oil, 0.45 gm 34% yield. IR 3027, 3063, 2929, 1646, 1490, 1453, 1090, 700.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.66 (3H, s, C*H*$_3$), 2.20-2.41 (2H, m, CHC*HH*), 3.54 (ABq, 2H, J_{AB}13.7, J_{AB}13.7, ArC*HH*), 3.69 (1H, dd, J_{bc}11.9, J_{ac}5.9, C*H*CHH), 4.77 (1H, s, olefine C*H*H), 4.79 (1H, s, olefine CH*H*), 7.10-7.40 (9H, m, ArC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 22.1 (CH_3), 47.6 (CH_2), 50.7 (CH_2), 59.3 (CH), 113.5 (=CH_2), 127.1 (ArCH), 127.3 (ArCH), 128.4 (ArCH), 129.5 (ArCH), 132.5 (ArC), 139.1 (ArC), 142.7 (ArC), 144.1 (C). HRMS [M+H^+] calculated for formula $C_{18}H_{21}NCl^+$; 286.1363; found 286.1354.

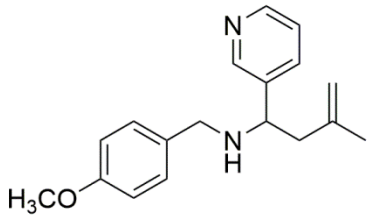
_N_-benzyl-3-methyl-1-(4-nitrophenyl) but-3-en-1-amine (47o)



General procedure (**d**) was used, brown yellow oil, 0.34 gm 57% yield. IR 3020, 2912, 2840, 1640, 1445, 1120, 895, 697.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.68 (3H, s, C*H*$_3$), 2.22-2.35 (2H, m, CHC*HH*), 3.58 (ABq, 2H, J_{AB}13.7.6, J_{AB}13.7, ArC*HH*), 3.88 (1H, dd, J_{bc}11.9, J_{ac}5.9, C*H*CHH), 4.77 (1H, s, olfine C*H*H), 4.83 (1H, s, olefine CH*H*), 7.20-7.38 (5H, m, ArC*H*), 7.62 (2H, d, *J*8.1, ArC*H*), 8.20 (2H, d, *J*8.1, ArCH). ^{13}C NMR (δ; 100 MHz, $CDCl_3$); 21.9 (CH_3), 47.5 (CH_2), 51.7

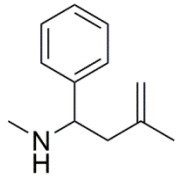
(CH_2), 58.9 (CH), 114.3 (=CH_2), 123.8 (2ArCH), 127.1 (ArCH), 128.0 (2ArCH), 128.1 (2ArCH), 128.5 (2ArCH), 139.9 (C), 141.7 (ArC), 147.2 ($ArCNO_2$), 152.5 (ArC). HRMS [$M+H^+$] calculated for formula $C_{18}H_{21}N_2O_2^+$; 296.3700; found 296.3703.

***N*-(4-methoxybenzyl)-3-methyl-1-(pyridin-3-yl)but-3-en-1-amine (47p)**



General procedure (**d**) was used, *N*-(4-methoxybenzyl)-1-(pyridin-3-yl)methanimine (50 mg, 0.22 mmol), brown yellow oil, 60 mg 75% yield. IR 3327, 3066, 2917, 1645, 1589, 1453, 1433, 1116, 892, 748, 698.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.65 (3H, s, C*H*$_3$), 2.21-2.41 (1H, m, CHC*HH*), 3.51 (ABq, 2H, J_{AB}13.2,J_{AB}13.2, $ArCH_2$), 3.80 (3H, s, OC*H*$_3$), 4.78 (1H, app.t, *J* 24.9, C*H*CHH), 6.99 (4H, dd, *J* 85.1, 8.6, ArC*H*), 7.28 (1H, dd, *J* 7.9, 4.7, ArC*H*), 7.76 (1H, dt, *J* 7.8, 1.9, ArC*H*), 8.51 (1H, dd, *J* 4.8, 1.6, ArC*H*), 8.58 (1H, *s,* ArC*H*).^{13}C NMR (δ; 100 MHz, CDCl3); 21.9 (CH_3), 47.4 (CH_2), 50.8 (CH_2), 55.2 (CH), 56.8 (CH), 113.8 (2ArCH), 114.0 (=CH_2), 123.6 (ArCH), 129.2 (ArCH), 132.2 (C), 134.78 (PyrCH), 139.6 (PyrC), 147.0 (C), 148.6 (PyrCH), 149.5 (PyrCH), 158.6 (COMe). HRMS [$M+H^+$] calculated for formula $C_{14}H_{15}N_2O^+$; 227.1184; found 227.1175.

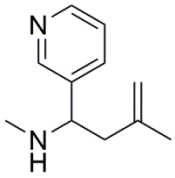
1,4-Mimethyl-1-phenylbut-3-en-1-amine (47q)



General procedure (**d**) was used, *N*-methyl-1-phenylmethanimine (50 mg, 0.41 mmol), yellow oil, 0.57 mg 82% yield. IR 3322, 3060, 3026, 2932, 2821, 1946, 1807, 1645.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.64 (3H, s, C*H*$_3$), 2.16 (3H, s, C*H*$_3$), 2.18-2.33 (2H, m, CHC*HH*), 3.52 (1H, dd, J_{ac}9.1, J_{bc}5.2, C*H*CHH), 4.68 (H, s, olefine C*H*H), 4.71 (1H, s, olefine CH*H*), 7.09-7.29 (5H, m, ArCH).^{13}C NMR (δ; 100 MHz, CDCl3); 22.2

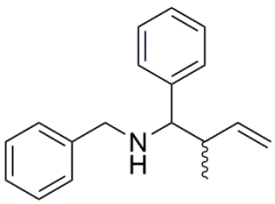
(CH_3), 34.7 (CH_3), 47.3 (CH_2), 62.8 (CH), 113.4 (=CH_2), 127.0 (ArCH), 127.2 (2ArCH), 128.4 (2ArCH), 142.7 (ArC), 143.7 (C). HRMS calculated for formula $C_{12}H_{18}N^+$; 176.1439; found 176.1446.

1,4-Mimethyl-1-(pyridin-3-yl)but-3-en-1-amine (47r)



General procedure (**d**) was used, *N*-methyl-1-(pyridin-3-yl)methanimine (50 mg, 0.41 mmol) brown yellow oil, 48 mg 67% yield. IR 3322, 3060, 3026, 2932, 1946, 1807, 1645.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.75 (3H, s, C*H*$_3$), 2.26 (3H, s, C*H*$_3$), 2.31 (2H, m, CHC*HH*), 3.69 (1H, dd, *J*9.1, *J*5.3, C*H*CHH), 4.71 (1H, s, olefine C*H*H), 4.81 (1H, s, olefine CH*H*),7.29-7.36 (1H, m, PyrC*H*), 7.74- 7.79 (1H, m, PyrC*H*), 8.5-8.63 (2H, m, 2x PyrC*H*).^{13}C NMR (δ; 100 MHz, CDCl3); 22.0 (CH_3), 34.6 (CH_3), 47.6 (CH_2), 60.2 (CH), 114.1 (=CH_2), 123.9 (PyrCH), 135.5 (PyrCH), 139.8 (PyrC), 141.7 (PyrCH), 148.3 (PyrCH), 149.1 (C). HRMS calculated for formula $C_{11}H_{17}N_2^+$; 177.1392; found 177.1402.

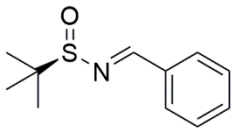
***N*-benzyl-2-methyl-1-phenylbut-3-en-1-amine (46a-cis and 46b-trans)**



General procedure (**f**) was used, *N*-benzyl-1-phenylmethanimine (50 mg, 4.7 mmol), yellow oil, 21 mg 43% yield. IR 3063, 3026, 2973, 1638, 1602, 1493, 1453, 916. ^{1}H NMR (δ; 300 MHz, $CDCl_3$); 0.81 (3H, d, *J* 6.8, $CH_{3\ min}$), 1.04 (3H, d, *J* 6.9, $CH_{3\ maj}$), 2.43 (1H, q, *J* 7.1, 3.6, C*H*$CH_{3\ maj}$), 2.59 (1H, q, *J* 6.8, 5.6, C*H*$CH_{3\ min}$), 3.33-3.58 (4H, m, 2x Ar$CH_{2\ maj+min}$), 3.66-3.80 (2H, m, 2x C*H*=$CH_{2\ maj+min}$), 4.99-5.29 (4H, m, 2x olefine C*HH* $_{maj+min}$), 5.66-5.85 (2H, m, 2x NC*H*CH $_{maj+min}$), 7.25-7.46 (20H, m, ArC*H*).^{13}C NMR (δ; 100MHz , $CDCl_3$); 15.4 (CH_3), 17.9 (CH_3), 43.8 (CH), 45.7 (CH), 51.5 (CH_2), 51.5 (CH_2), 66.2 (CH), 66.7 (CH), 114.9 (=CH_2), 116.1 (=CH_2), 126.8 (ArCH), 126.8

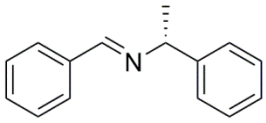
(ArCH),126.9 (ArCH), 127.2 (ArCH), 128.0 (2ArCH), 128.1 (2ArCH), 128.2 (2ArCH), 128.2 (2ArCH), 128.3 (2ArCH), 128.5 (2ArCH), 140.8 (2ArC), 141.2 (2ArCH), 141.9 (2ArC), 142.3 (2ArCH), 142.5 (2C). HRMS calculated for formula $C_{18}H_{22}N^+$; 252.0038; found 252.001631.

(*R*)-*N*-benzylidene-2-methylpropane-2-sulfinamide (112)



(*R*)-*tert*-butylsulfinamide (1g, 7.2 mmol) in dichloromethane, was mixed with (3 gm, 21.9 mmol) of benzaldehyde and (5 gm, 36.5 mmol) of magnesium sulphate and (0.1 gm, 0.1 mmol) of PPTs and stirred at room temperature for 24 hours. The product filtered and purified by column chromatography. Yellow oil, 120 mg 92% yield. ^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.25 (9H, s,C*H*$_3$), 7.45-7.51 (3H, m, ArC*H*), 7.80 (1H, d, *J* 5.9, ArC*H*), 8.15 (1H, d, *J* 4.9, ArC*H*), 8.60 (C*H*=N).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 12.6 ($3CH_3$), 27.1 (CH), 45.6 (CH_2), 126.9 (2ArCH), 127.5 (2ArCH), 1128.1 (ArCH), 133.3 (ArC), 151.9 (CH=N). HRMS $[M+H]^+$ calculated for formula $C_{11}H_{15}NOSNa^+$: 232.0772; found: 232.0773. The spectral data are comparable with literature.[93]

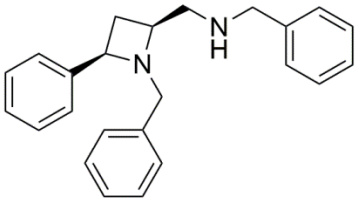
(*R*)-1-phenyl-*N*-(1-phenylethyl)methanimine (119)



General procedure (**a1**) was used, benzaldehyde (1 gm, 9.4 mmol), colourless oil, 1.81 gm 92% yield. IR 2851, 1889, 1623, 1480, 1091, 1015.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.61 (3H, s, C*H*$_3$), 4.51 (1H, q, *J* 13.9, 10.1, C*H*), 7.17-7.41 (8H, m, ArC*H*), 7.77 (2H, m, ArC*H*), 8.35 (C*H*=N).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 24.9 (CH_3), 69.8 (CH), 126.2 (2ArCH), 126.7 (ArCH), 128.3 (2ArCH), 128.5 (2ArCH), 128.6 (2ArCH), 130.7 (ArCH), 136.5 (ArC), 145.3 (ArC), 159.6 (CH=N). The spectral data are comparable with literature.[94]

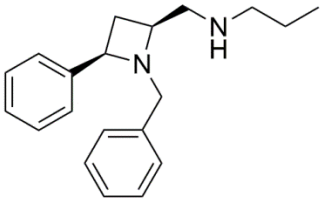
Characterisation data for the synthesised enantiopure azetidine compounds:

***N*-benzyl-1-((2S, 4R)-1-benzyl-4-phenylazetidin-2-yl)methanamine**



General procedure (**h**) was used, (*R*)-*N*-benzyl-1-phenylbut-3-en-1-amine (100 mg, 0.33 mmol), flash chromatography (EA/hexane 1:1), yellow brown oil, 85 mg 83% yield. IR 3027, 2929, 2850, 2808, 1570, 1440, 1421, 1320, 1302, 1150.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 2.29 (1H, q, *J* 9.7, PhCHC*H*H), 2.51 (1H, dd, *J* 12.5, 6.2, CHCH*H*), 2.61-2.88 (2H, m, NC*H*), 3.50-3.95 (3H, overlapping m, NCH_2, CH_2CHCH_2), 4.15 (1H, app.t, *J* 7.2, C*H*CHH), 7.09-7.62 (10H, m, ArC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 18.3 (CH_3), 19.2 (CH_3), 32.0 (CH_2), 48.0 (CH_2), 51.0 (CH), 58.4 (CH), 60.7 (CH_2), 65.6 (CH), 126.8 (2ArCH), 127.6 (ArCH), 127.8 (ArCH), 128.7 (2ArCH), 128.8 (2ArCH), 129.5 (2ArCH), 137.9 (ArC), 139.0 (ArC). High resolution MS $[M+H]^+$calculated for formula $C_{24}H_{27}N_2^+$: 343.2174 found 343.2176. $[\alpha]_D^{20}$ = +95.7 (c 5, $CHCl_3$) lit. (+94.5), >99% ee.[23]

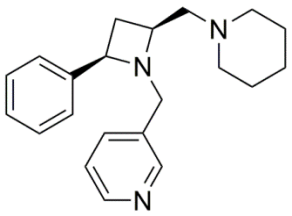
***N*-(((2S,4R)-1-benzyl-4-phenylazetidin-2-yl)methyl)propan-1-amine (126b)**



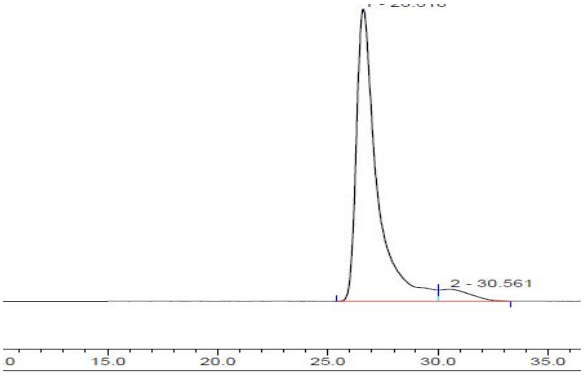
General procedure (**h**) was used, (*R*)-*N*-benzyl-1-phenylbut-3-en-1-amine (200 mg, 8.5 mmol), flash chromatography (DCM/Methanol= 9.5/0.5), yellow brown oil, 112 mg 46% yield. IR 3027, 2929, 2850, 2808,1570, 1440, 1421, 1320, 1302, 1150.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.18 (3H, d, *J* 6.5, CH_3), 1.23 (3H, d, *J* 6.5, CH_3), 2.29 (1H, dd, *J* 12.5, 8.2, CHC*H*H), 2.51 (1H, dd, *J* 12.5, 6.2, CHCH*H*), 2.61-2.88 (2H, m, NC*H*), 3.50-3.95 (3H, overlapping m, NCH_2, CH_2CHCH_2), 4.15 (1H, app.t, *J* 7.2, C*H*CHH), 7.09-7.62 (10H, m, ArC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 18.3 (CH_3), 19.2 (CH_3), 32.0 (CH_2), 48.0 (CH_2), 51.0 (CH), 58.4 (CH), 60.7 (CH_2), 65.6 (CH), 126.8

(2ArCH), 127.6 (ArCH), 127.8 (ArCH), 128.7 (2ArCH), 128.8 (2ArCH), 129.5 (2ArCH), 137.9 (ArC), 139.0 (ArC). High resolution MS $[M+H]^+$calculated for formula $C_{20}H_{27}N_2^+$: 295.2174 found 295.2176. $[\alpha]_D^{20}$ = +89.4 (c 5, $CHCl_3$) lit. (+96.4). 96% *ee*.[23]

3-(((2*R*,4*S*)-2-phenyl-4-(piperidin-1-ylmethyl)azetidin-1-yl)methyl)pyridine (126c)



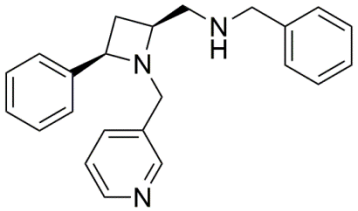
General procedure (**h**) was used, (*R*)-1-phenyl-N-(pyridin-3-ylmethyl)but-3-en-1-amine (98 mg, 0.42 mmol), flash chromatography (DCM/Methanol= 9.5/0.5), yellow oil, 105 mg 82% yield. IR 3028, 2934, 2852, 2803,1576, 1492, 1454, 1424, 1354, 1326, 1303, 1157, 1122, 1026, 998, 860, 752, 714, 699.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 0.91 (2H, dd, *J* 13.0, 5.8, CH_2), 1.23-1.49 (2H, m, CH_2), 1.60 (2H, dt, *J* 10.9, 5.4, 2x CH_2), 1.80 (2H, dt, *J* 10.1, 8.5, CHCH_2CH), 3.46 (1H, dt, *J* 13.6, 6.9, C*H*), 3.72 (ABq, 2H, J_{AB} 2.6,J_{AB} 2.6,PyrC*HH*), 4.00 (1H, app.t, *J* 8.1, C*H*CHH), 7.10 (2H, dd, *J* 7.4,4.8, ArCH), 7.15-7.39 (3H, m, ArCH), 7.59 (1H, dt, *J*7.8, 1.8, PyrCH), 8.39 (1H, dd, *J* 4.8, 1.4, PyrCH), 8.49 (1H, d, *J* 1.5, PyrCH).^{13}C NMR (δ; 100 MHz, $CDCl_3$), 23 (CH_2), 25 (CH_2), 35 (CH_2), 54 (CH_2), 58 (CH_2), 60 (CH), 64 (CH_2), 66 (CH), 123 (CH), 127 (ArCH), 133 (ArC), 137 (CH), 143 (ArC), 148 (CH), 150 (CH). High resolution MS $[M+H]^+$calculated for formula $C_{21}H_{28}N_3^+$: 322.2283 found 322.2284. $[\alpha]_D^{20}$ = +84 (c 5.0, DCM). HPLC (AD column was used), hexane/isopropanol 98:2, flow rate=0.25 ml/min, 89% *ee*.



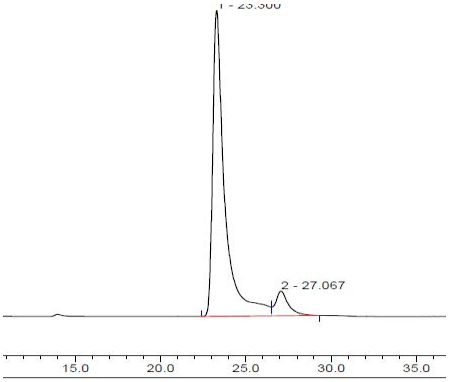
Peak Name	Height mAU	Area mAU*min	Rel.Area %	Ar
	121.961	132.751	94.46	
	4.951	7.793	5.54	
	126.912	140.544	100.00	

Figure 46: HPLC data for **2*R*,4*S*-126d**

_N_-benzyl-1-((2*R*,4*S*)-4-phenyl-1-(pyridin-3-ylmethyl)azetidin-2-yl)methanamine (126d)



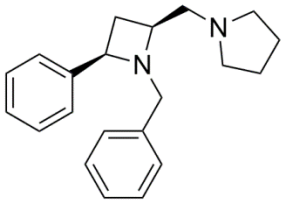
General procedure (**h**) was used, (*R*)-1-phenyl-*N*-(pyridin-3-ylmethyl)but-3-en-1-amine (132 mg, 0.55 mmol), flash chromatography (DCM/Methanol= 9.5/0.5), yellow oil, 150 mg 76% yield. IR 3027, 2824, 1673, 1260, 1157, 696. ^{1}H NMR (δ; 300 MHz, $CDCl_3$); 2.01 (1H, dd, *J* 18.8, 8.7, CHC*H*HCH), 2.39-2.49 (2H, m, CHCH*H*CH), 2.56 (1H, dd, *J* 12.1, 4.3, C*H*CHH), 3.32 (1H, m, CHHC*H*CHH), 3.67 (ABq, 2H, J_{AB} 13.2, J_{AB}13.2, PyrC*HH*), 3.64 (2H, s, ArCH_2), 3.99 (1H, app.t, *J* 8.2, C*H*CHH), 7.08 (2H, ddd, *J* 7.7, 4.8, 0.6, ArCH),7.13-7.44 (10H, *m*, ArCH, PyrCH), 8.39 (1H, dd, *J* 4.8,1.6, PyrCH), 8.49 (1H, d, *J* 1.8, PyrCH).^{13}C NMR (δ; 100 MHz, $CDCl_3$), 31(CH_2), 46 (CH_2), 53 (CH_2), 54 (CH_2), 58 (CH_2), 62 (CH), 65 (CH), 123 (CH), 126-128 (10ArCH), 134 (PyrC), 136 (2PyrCH), 140 (ArC), 143 (ArC), 148 (PyrCH), 150 (PyrCH). HRMS $[M+H]^+$ calculated for formula $C_{23}H_{26}N_3^+$344.2127; found 344.2122. $[\alpha]_D^{20}$ = +82 (c 5.0, DCM). HPLC (AD column was used), hexane/isopropanol 98:2, flow rate=0.25 ml/min, 85% *ee*.



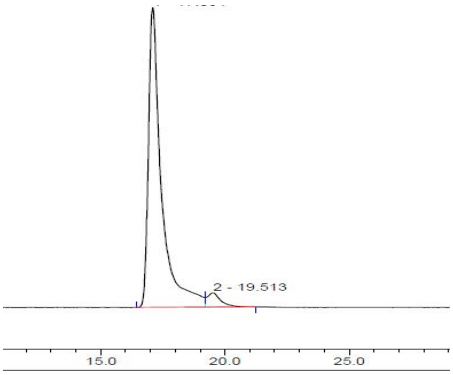
eak Name	Height mAU	Area mAU*min	Rel.Area %	An
	155.904	127.311	92.06	
	12.565	10.979	7.94	
	168.469	138.290	100.00	

Figure 47: HPLC data for 2R, 4s-126d

1-(((2R,4S)-1-benzyl-4-phenylazetidin-2-yl)methyl)pyrrolidine (126e)



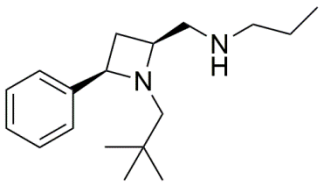
General procedure (**h**) was used, (*S*)-*N*-benzyl-1-phenylbut-3-en-1-amine (200 mg, 8.5 mmol), flash chromatography (DCM/Methanol= 9.5/0.5), yellow brown oil, 80 mg 57% yield. IR 3024, 2905, 2834, 2805,1560, 1482, 1454, 1420, 1150.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.52-1.70 (4H, overlapping m, 2x CH_2), 2.22 (4H, overlapping m, 2x CH_2), 2.41-2.55 (2H, m, NCH_2), 3.13-3.28 (2H, m, CHCH_2CH), 3.62 (ABq, 2H, J_{AB} 14.1, J_{AB}14.1, ArCH_2), 3.89 (1H, app.t, *J*13.1, C*H*CHH), 7.07-7.38 (10H, m, ArC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$), 23.3 ($2CH_2$), 34.9 (CH_2), 54.5 ($2CH_2$), 58.5 (CH_2), 60.4 (CH), 61.3 (CH_2), 66.1 (CH), 123.1 (ArCH), 126.7 (3ArCH), 127.1 (ArCH), 128.3 (3ArCH), 137.1 (ArCH), 148.5 (ArC), 150.5 (ArC). High resolution MS $[M+H]^+$calculated for formula $C_{21}H_{27}N_2^+$: 307.2127 found 307.2128. $[\alpha]_D^{20}$ = +66 (c 5.0, DCM). HPLC (AD column was used), hexane/isopropanol 98:2, flow rate=0.25 ml/min, 91% *ee*.



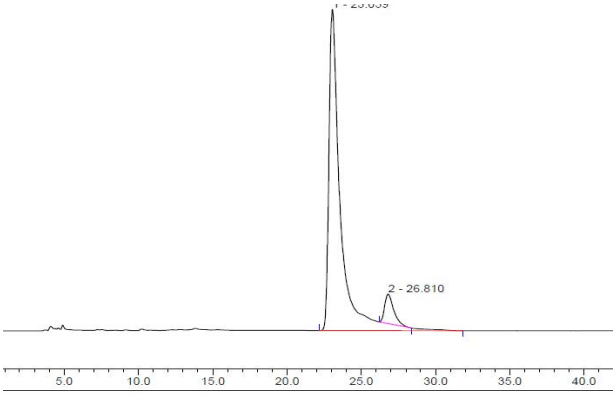
ıe	Height mAU	Area mAU*min	Rel.Area %	Amc
	71.941	43.713	95.25	
	3.427	2.181	4.75	
	75.369	45.894	100.00	

Figure 48: HPLC data for 2R, 4S-126e

N-(((2*R*,4*S*)-1-neopentyl-4-phenylazetidin-2-yl)methyl)propan-1-amine (126f)



General procedure (**h**) was used, (*R*)-*N*-neopentyl-1-phenylbut-3-en-1-amine (120 mg, 0.55 mmol), flash chromatography (Hexane/EtOAc = 9/1 Rf = 0.3), yellow brown oil, 80 mg 50% yield. IR 3675, 2957, 2925, 1668, 1455, 1394, 1258, 1066, 1027, 867, 795, 751, 698.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 0.64 (9H, s, C*H*$_3$), 0.98 (3H, t, *J* 7.4, C*H*$_3$), 1.60 (2H, dq, *J* 14.6, 7.4, C*H*$_2$CH$_3$), 1.95 (2H, dt, *J* 10.4, 8.4, NC*H*$_2$CH$_2$), 2.39 (2H, s, NC*H*$_2$C), 2.47 (1H, dt, *J* 10.5, 7.8, CHC*H*HCH), 2.61-2.68 (1H, m, CHCH*H*CH), 2.78 (2H, ddd, *J* 17.6, 11.9, 4.8, NHC*H*$_2$CH), 3.16-3.27 (1H, m, CHHC*H*CHH), 3.85 (1H,app.t, *J* 8.1, C*H*CHH),7.21-7.55 (5H, m, ArC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 11.8 (CH_3), 23.2 (CH_2), 28.4 ($3CH_3$), 31.3 (CH_2), 31.5 (C), 52.3 (CH), 54.2 (CH_2), 63.3 (CH_2), 69.7 (CH_2), 73.4 (CH), 127.0 (ArCH), 127.5 (2ArCH), 128.0 (2ArCH), 144.9 (ArC). HRMS [M+ H^+] calculated for formula $C_{18}H_{30}N_2^+$: 275.2430; found: 275.2431. $[\alpha]_D^{20}$ = +93 (c 5.0, DCM).HPLC (AD column was used), hexane/isopropanol 99:1, flow rate=0.2 ml/min, 87% *ee*.

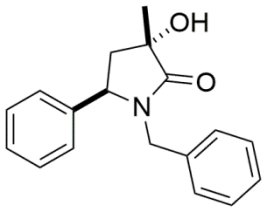


Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount
23.06	n.a.	419.668	378.792	93.30	n.a.
26.81	n.a.	38.407	27.188	6.70	n.a.
		458.075	405.980	100.00	0.000

Figure 49: HPLC data for 2R,4S-126f

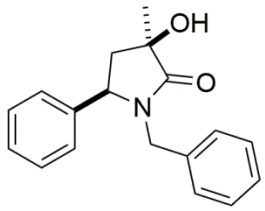
Characterisation data for the synthesised pyrrolidin-2-one compounds:

***N*-benzyl-3-hydroxy-3-methyl-5-phenylpyrrolidin-2-one (*cis*-130a)**



General procedure (**b**) was used. *N*-Benzyl-3-methyl-1-phenylbut-3-en-1-amine **44a** (156 mg, 0.60 mmol), iodine (460 mg, 1.80 mmol), sodium bicarbonate (254 mg, 3.03 mmol), ethyl acetate/petroleum ether 40%, Rf=0.23, white crystal (mpt 155-156 ˚C), 63 mg 46% yield. IR 3286, 3030, 2933, 1671 (s), 1576.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.55 (3H, s, CH_3), 1.92 (1H, dd, J_{ab}13.0, J_{ac}8.5, CHC*H*H), 2.59 (1H, dd, J_{ab}13.0, J_{bc}6.8, CHCH*H*), 3.57 (ABq,1H, J_{AB}14.6, ArCH*H*), 4.53 (1H, dd, J_{ac}8.5, J_{bc}6.8, C*H*CHH), 5.09 (ABq,1H, J_{AB}14.6, ArC*H*H), 7.04-7.43 (10H, m, ArC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 24.5 (CH_3), 44.0 (CH_2), 44.5 (CH_2), 57.8 (CH), 74.0 (COH), 126.9 (ArCH), 127.6 (ArCH), 127.9 (ArCH), 128.4 (ArCH), 128.6 (ArCH), 129.0 (ArCH), 135.8 (ArC), 139.0 (ArC), 177.1 (CO). HRMS $[M+H]^+$ calculated for the formula $C_{18}H_{19}NO_2^+$282.3519; found 282.3514.

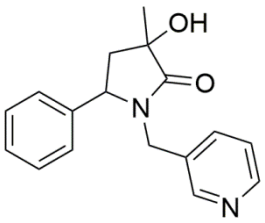
***N*-benzyl-3-hydroxy-3-methyl-5-phenylpyrrolidin-2-one (*trans*-130a)**



General procedure (**b**) was used. *N*-Benzyl-3-methyl-1-phenylbut-3-en-1-amine **44a** (156 mg, 0.60 mmol), iodine (460 mg, 1.80 mmol), sodium bicarbonate (254 mg, 3.03 mmol), ethyl acetate/ petroleum ether 40%, Rf= 0.25, white crystal (mpt 161-162 ˚C), 78 mg, 54% yield. IR 3286, 3030, 2933, 1671, 1576.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.44 (3H, s, CH_3), 2.14 (1H, dd, J_{ab}13.1, J_{ac}8.4, CHC*H*H), 2.46 (1H, dd, J_{ab}13.1, J_{bc}6.0, CHCH*H*), 3.47 (ABq, 1H, J_{AB}14.4, ArC*H*H), 4.16 (1H, dd, J_{ac}8.4, J_{bc}6.0, C*H*CHH), 5.06 (ABq, 1H, J_{AB}14.4, ArCH*H*), 7.01-7.42 (10H, m, ArC*H*).^{13}C NMR (δ; 100 MHz,

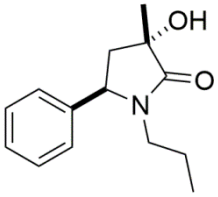
$CDCl_3$); 25.2 (CH_3), 43.9 (CH_2), 44.5 (CH_2), 58.1 (CH), 74.3 (COH), 126.9 (ArCH), 127.6 (ArCH), 127.9 (ArCH), 128.2 (ArCH), 128.3 (ArCH), 128.6 (ArCH),129.0 (ArCH), 135.5 (ArC), 139.7 (ArC), 176.9 (CO). HRMS $[M+H]^+$ calculated for the formula $C_{18}H_{19}NO_2^+$282.3519; found 282.3514.

_N_-(3-Pyridyl)-3-hydroxy-3-methyl-5-phenyl-pyrrolidin-2-one (_cis_-130b and _trans_-130b)



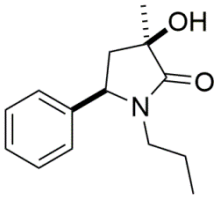
(Mixture of diastereoisomers maj/min) General procedure (**b**) was used. 3-Methyl-1-phenyl-*N*-(pyridin-3-ylmethyl)butan-1-amine **44b** (255 mg, 1.01 mmol), iodine (769 mg, 3.03 mmol), sodium bicarbonate (424 mg, 5.05 mmol), ethyl acetate 100%. Rf=0.2, yellow oil (gum), 0.25 g 91% yield. IR 3323, 2927, 1668(s).^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.43 (3H, s, C$H_{3\ min}$), 1.56 (3H, s, C$H_{3\ maj}$), 1.94 (1H, dd, J_{ab}13.8, J_{ac}7.1, CHCHH$_{maj}$), 2.19 (1H, dd, J_{ab}13.1, J_{ac}7.7, CHCHH_{min}), 2.49 (1H, dd, J_{ab}13.1,J_{bc}6.8, CHCHH$_{min}$), 2.59 (1H, dd,J_{ab}13.8, J_{bc}7.4,CHCHH_{maj}), 3.64 (ABq, 1H, J_{AB}17.1, PyrCHH_{maj}), 4.18 (1H, dd, J_{ac}7.7, J_{bc}6.8, CHCHH$_{min}$), 4.50 (1H, dd, J_{ac}7.1, J_{bc}7.4, CHCHH$_{maj}$), 4.97 (ABq, 1H, J_{AB}15.4, PyrCHH$_{min}$) 7.06-7.46 (12H, m, ArCH), 7.49 (2H, dt, J 1.9, 7.9, PyrCH), 8.17 (1H, d, J 2.0, PyrCH), 8.24(1H, d, J 2.0, PyrCH), 8.52 (2H, m, overlapping, PyrCH).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 24.5 (CH_3), 25.0 (CH_3), 42.1 (CH_2), 42.1 (CH_2), 43.9 (CH_2), 44.0 (CH_2), 58.2 (CH), 58.5 (CH), 73.9 (COH), 74.2 (COH), 123.6 (ArCH), 127.0 (ArCH), 127.7 (ArCH), 128.5 (ArCH), 128.8 (ArCH), 129.2(ArCH), 131.5 (PyrC), 135.4 (ArCH),136.1(ArCH), 136.2 (ArC), 138.5 (ArC), 139.2 (ArCH), 139.2 (ArCH), 149.1 (PyrCH), 149.1 (PyrCH), 149.2 (PyrCH), 149.2 (PyrCH), 149.7(PyrCH), 149.7 (PyrCH), 149.9 (PyrCH), 149.9 (PyrCH), 150.7 (CO), 152.9 (CO). HRMS $[M+H]^+$ calculated for the formula $C_{17}H_{19}N_2O_2^+$ 283.1450; found 283.1447.

***N*-propyl-3-hydroxy-3-methyl-5-phenylpyrrolidin-2-one (*cis*-130c)**



General procedure (**b**) was used. *N*-Propyl-3-methyl-1-phenylbut-3-en-1-amine **44c** (800 mg, 3.9 mmol), iodine (300 mg, 11.8 mmol), sodium bicarbonate (1650 mg, 19.6 mmol), ethyl acetate/ hexane 50%, Rf= 0.25, yellow solid (mpt 95-96˚C), 200 mg, 22% yield. IR 3348, 2965, 1673 (s), 1457, 1366.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 0.84 (3H, t, *J* 7.2, CH_2CH_3), 1.39-1.48 (2H, m, CH_2CH_3), 1.49 (3H, s, CH_3), 1.88 (1H, dd, J_{ab}13.7, J_{ac}6.6, CHC*H*H), 2.55-2.70 (2H, m, NCH_2), 3.63 (1H, dt, J_{ab}13.7, J_{bc}6.6, CHCH*H*), 4.76 (1H, app.t, *J*7.1, C*H*CHH), 7.14-7.43 (5H, m, ArC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 11.1 (CH_3), 19.9 (CH_2), 25.1 (CH_3), 42.4 (CH_2), 44.2 (CH_2), 58.8 (CH), 74.2 (C-OH), 126.7 (ArCH), 128.1 (ArCH), 129.0 (ArCH), 140.2 (ArC), 176.8 (CO). HRMS $[M+Na]^+$ calculated for the formula $C_{14}H_{19}NO_2Na^+$ 256.1318; found 256.1313.

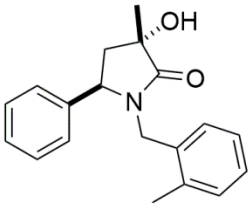
***N*-propyl-3-hydroxy-3-methyl-5-phenylpyrrolidin-2-one (*trans*-130c)**



General procedure (**b**) was used. *N*-Propyl-3-methyl-1-phenylbut-3-en-1-amine **44c** (800 mg, 3.9 mmol), iodine (300 mg, 11.8 mmol), sodium bicarbonate (1.65 gm, 19.6 mmol), ethyl acetate/hexane 50%. Rf= 0.27, yellow solid (mpt 84-85 ˚C), 120 mg, 13% yield. IR3348, 2965, 1673 (s), 1457, 1366.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 0.84 (3H, t, *J* 7.4, CH_2CH_3), 1.38-1.48 (2H, m, CH_2CH_3), 1.49 (3H, s, CH_3), 1.88 (1H, dd, J_{ab}13.0, J_{ac}7.0, CHC*H*H), 2.55-2.70 (2H, m, NCH_2), 3.55-3.65 (1H, m, CHCH*H*), 4.46 (1H, app.t, *J*7.0, C*H*CHH), 7.24-7.45 (5H, m, ArC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 11.2 (CH_3), 20.0 (CH_2), 24.9 (CH_3), 42.2 (CH_2), 44.5 (CH_2), 58.7 (CH), 74.0 (COH),

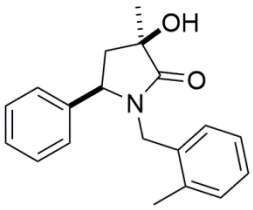
127.4 (ArCH), 128.5 (ArCH), 129.0 (ArCH), 139.4 (ArC), 176.8 (CO). HRMS $[M+Na]^+$ calculated for the formula $C_{14}H_{19}NO_2Na^+$ 256.1318; found 256.1313.

_N_-(2-methylbenzyl)-3-hydroxy-3-methyl-5-phenylpyrrolidin-2-one (_cis_-130d)



General procedure (**i**) was used, *N*-(2-methylbenzyl)-3-methyl-1-phenylbut-3-en-1-amine **44e** (245 mg, 0.92 mmol), iodine (703 gm, 2.77 mmol), sodium bicarbonate (388 gm, 4.60 mmol), ethyl acetate/petroleum ether 30%, Rf= 0.27, white solid (mpt 161-162 °C), 68 mg 25% yield. IR 3370, 2928, 1675(s), 1456.^{1}H NMR (δ; 300 MHz, $CDCl_3$);1.55 (3H, s, CH_3), 1.91 (1H, dd, J_{ab}13.8, J_{ac}6.0, CHC*H*H), 2.09 (3H, s, ArCH_3), 2.60 (1H, dd, J_{ab}13.8, J_{bc}8.1, CHCH*H*), 3.69 (ABq, 1H, J_{AB}14.8, ArC*H*H), 4.44 (1H, dd, J_{ac}6.0, J_{bc}8.1, C*H*CHH),5.10 (ABq,1H, J_{AB}15.0, ArCH*H*),6.80 (1H, d, *J* 7.4, ArC*H*), 6.94-7.41 (8H, m, ArC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 19.0 (CH_3), 25.4 (CH_3), 42.5 (CH_2), 43.8 (CH_2), 58.0 (CH), 74.4 (COH), 125.8 (ArCH), 126.7 (ArCH), 127.7 (ArCH), 128.0 (ArCH), 129.0 (ArCH), 129.1(ArCH), 130.4 (ArCH), 133.0 (ArC),136.9 (ArC), 140.0 (ArC), 176.2 (CO). HRMS $[M+Na]^+$calculated for the formula $C_{19}H_{21}NO_2Na^+$318.1469; found 318.1470.

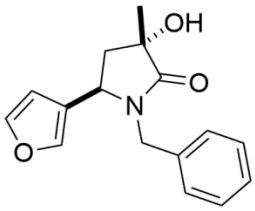
_N_-(2-methylbenzyl)-3-hydroxy-3-methyl-5-phenylpyrrolidin-2-one (_trans_-130d)



General procedure (**i**) was used. *N*-(2-methylbenzyl)-3-methyl-1-phenylbut-3-en-1-amine **44e** (245 mg, 0.92 mmol), iodine (703 gm, 2.77 mmol), Sodium bicarbonate (388 gm, 4.60 mmol), ethyl acetate/petroleum ether 30%, Rf= 0.27, colourless crystals (mpt 132-133°C), 50 mg 18% yield. IR 3370, 2926, 1675(s), 1456.^{1}H NMR (δ; 300 MHz, $CDCl_3$);1.49 (3H, s, CH_3), 1.96 (1H, dd, J_{ab}13.8, J_{ac}6.1, CHC*H*H), 2.14 (3H, s, ArCH_3), 2.48 (1H, dd, J_{ab}13.8, J_{bc}8.0, CHCH*H*), 3.69 (ABq, 1H, J_{AB}14.8,

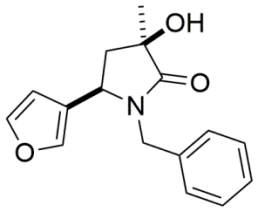
ArC*H*H), 4.13 (1H, dd, J_{ac}6.1, J_{bc}8.0, C*H*CHH), 4.44 (ABq, 1H, J_{AB}14.8, ArCH*H*), 6.79 (1H, d, *J* 7.4, ArC*H*), 6.94-7.41 (8H, m, ArC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$);18.9 (CH_3), 25.0 (CH_3), 42.1 (CH_2), 44.2 (CH_2), 58.0 (CH), 74.2 (COH), 125.8 (ArCH), 127.6 (ArCH), 127.8 (ArCH), 128.4 (ArCH), 128.9 (ArCH), 129.5 (ArCH), 130.5(ArCH), 133.2 (ArC), 136.8 (ArC), 139.4 (ArC), 176.9 (CO). HRMS $[M+Na]^+$ calculated for the formula $C_{19}H_{21}NO_2Na^+$318.1469; found 318.1470.

_N_-benzyl-5-(furan-3-yl)-3-hydroxy-3-methylpyrrolidin-2-one (_cis_-130e)



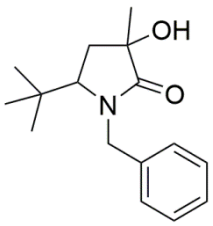
General procedure (**i**) was used. *N*-benzyl-3-methyl-1-(furan-3-yl) but-3-en-1-amine **44f** (300 mg, 1.24 mmol), iodine (950 mg, 3.70 mmol), sodium bicarbonate (520 mg, 6.20 mmol), ethyl acetate/petroleum ether 30%, Rf=0.27, light yellow crystals (mpt 131-132°C), 60 mg 40% yield. IR 3356, 2932, 1663(s).^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.55 (3H, s, CH_3), 1.95 (1H, dd, J_{ab}13.2, J_{ac}8.1, CHC*H*H), 2.50 (1H, dd,J_{ab}13.2, J_{bc}6.9, CHCH*H*), 3.68 (ABq, 1H, J_{AB}14.8, ArC*H*H), 4.55 (1H, J_{ac}8.1, J_{bc}6.9, C*H*CHH), 5.03(ABq,1H, J_{AB}14.8, ArCH*H*), 6.23 (1H, dd, *J*0.6, 1.5, FurC*H*), 7.08-7.48 (5H, overlapping m, ArC*H*, FurC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 25.1 (CH_3), 42.3 (CH_2), 44.4 (CH_2), 49.6 (CH), 74.2 (COH), 108.3 (FurCH), 124.3 (FurC), 127.6 (ArCH), 128.2 (ArCH), 128.7 (ArCH), 135.8 (ArC), 140.8 (FurCH), 144.3 (FurCH), 176.3 (CO). HRMS $[M+Na]^+$calculated for the formula $C_{16}H_{17}NO_3Na^+$294.1105; found 294.1106.

***N*-benzyl-5-(furan-3-yl)-3-hydroxy-3-methylpyrrolidin-2-one (*trans*-130e)**



General procedure (**i**) was used, *N*-benzyl-3-methyl-1-(furan-3-yl) but-3-en-1-amine **44f** (300 mg, 1.24 mmol), iodine (950 mg, 3.70 mmol), sodium bicarbonate (520 mg, 6.20 mmol), ethyl acetate/petroleum ether 30%, Rf=0.25, white crystals (mpt 120-121 °C), 40 mg 35% yield. IR 3356, 2932, 1663(s).^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.44 (3H, s, CH_3), 2.17 (1H, dd, J_{ab}13.2, J_{ac}8.1, CHC*H*H), 2.38 (1H, dd, J_{ab}12.9, J_{bc}6.9, CHCH*H*), 3.61 (ABq,1H, J_{AB}14.6, ArC*H*H), 4.25 (1H, dd, J_{ac}8.1, J_{bc}6.9, C*H*CHH), 5.02 (ABq, 1H, J_{AB}14.6, ArCH*H*), 6.39 (1H, dd, *J*0.6, 1.5, FurC*H*), 7.02-7.35 (5H, m, ArC*H*), 7.44 (2H, t, *J* 1.5, FurC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 24.4 (CH_3), 42.4 (CH_2), 44.3 (CH_2), 48.9 (CH), 73.9 (COH), 108.8 (FurCH), 123.7 (FurC), 127.7 (ArCH), 128.3 (ArCH), 128.7 (ArCH), 136.1 (ArC), 141.3 (FurCH), 144.3 (FurCH), 176.8 (CO). HRMS $[M+Na]^+$calculated for the formula $C_{16}H_{17}NO_3Na^+$ 294.1105; found 294.1106.

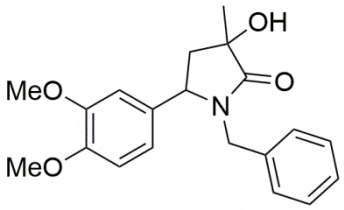
***N*-benzyl-5-(tert-butyl)-3-hydroxy-3-methylpyrrolidin-2-one (*cis*-130f and *trans*-130f)**



(Mixture of diastereoisomers maj/min) General procedure (**i**) was used. N-Benzyl-2,2,5-trimethylhex-5-en-3-amine **44g** (100 mg, 0.68 mmol), iodine (520 mg, 2.06 mmol), sodium bicarbonate (288 mg, 3.43 mmol), ethyl acetate/petroleum ether 80%, Rf=0.65, pale yellow crystal, 120 mg, 67% yield. IR 3352, 2902, 1662(s).^{1}HNMR (δ; 300 MHz, $CDCl_3$); 0.89 (9H, s,C$H_{3\ min}$), 0.93 (9H, s, C$H_{3\ maj}$), 1.45 (3H, s, C$H_{3\ min}$), 1.56 (3H, s, CH_{3maj}),1.77 (1H, dd, J_{ab}14.1, J_{ac}7.3, CHC*H*H$_{min}$), 2.03 (1H, dd, J_{ab}4.8, J_{bc}8.2, CHCH*H*$_{min}$), 2.45 (1H, dd, J_{ab}13.1, J_{ac}6.9, CHC*H*H$_{maj}$), 2.59 (1H, dd, J_{ab}13.1, J_{bc}7.8, CHCH*H*$_{maj}$), 3.21 (1H,dd, J_{ac}7.3, J_{bc}8.2, C*H*CHH$_{min}$), 4.17 (1H, app.t, *J*7.3,

C*H*CHH$_{maj}$), 5.06 (ABq, 2H, J_{AB}14.4, ArC*HH*$_{maj}$), 5.30 (ABq, 2H, J_{AB}15.7, ArC*HH* $_{min}$), 6.87-7.44 (10H, m, ArCH).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 22.1 (CH_3), 22.6 (CH_3), 26.9 (CH_3), 27.1 (CH_3), 36.6 (CH), 37.1 (CH), 44.3 (CH_2), 44.4 (CH_2), 62.3 (CH), 63.0 (CH), 74.1 (COH), 74.3 (COH), 127.0 (ArCH), 127.4 (ArCH), 127.7 (ArCH), 128.3 (ArCH), 128.5 (ArCH), 128.7 (ArCH), 129.0 (2ArCH), 139.1 (ArC), 139.8 (ArC), 177.0 (CO), 177.5 (CO). MS(ES+) $[M+Na]^+$ formula $C_{16}H_{23}NO_2Na^+$ found 284.15.

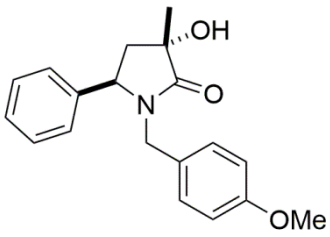
_N_-benzyl-5-(3,4-dimethoxyphenyl)-3-hydroxy-3-methylpyrrolidin-2-one (*cis*-130g and *trans*-130g)



(Mixture of diastereoisomers maj/min) General procedure (**i**) was used. *N*-benzyl-1-(3,4-dimethoxyphenyl)-3-methylbut-3-en-1-amine **44h** (155 mg, 0.49 mmol), iodine (379 mg, 1.49 mmol), sodium bicarbonate (209 mg, 2.48 mmol), methanol/dichloromethane 5%, pale yellow precipitate, 110 mg, 65% yield. IR 3380, 1680(s), 1682(s).^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.45 (3H, s, C*H*$_{3min}$), 1.58 (3H, s, C*H*$_{3\ maj.}$),1.92 (1H, dd, J_{ab}13.8, J_{ac}6.8, CHC*H*H$_{maj.}$), 2.18 (1H, dd,J_{ab}13.0,J_{bc}8.2, CHCH*H*$_{maj.}$), 2.45 (1H, dd, J_{ab}13.8, J_{ac}6.8, CHC*H*H$_{min}$), 2.58 (1H, dd, J_{ab}13.8, J_{bc}7.5, CHCH*H*$_{min}$), 3.53 (ABq, 1H, J_{AB}14.8, PhC*HH*$_{min}$), 3.64 (ABq, 1H, J_{AB}14.8, PhC*HH*$_{maj}$), 3.83 (6H, s, OC*H*$_{3\ min}$), 3.92 (6H, s, OC*H*$_{3\ maj}$), 4.14 (1H, dd, J_{ac}6.8, J_{bc}7.5, C*H*CHH$_{min}$), 4.49 (1H, app.t, *J*6.8, C*H*CHH $_{maj}$), 5.02 (1H, t, *J* 13.8, ArC*H*H $_{maj+min}$), 6.54 (2H, d, *J* 1.6, ArC*H*), 6.65-6.76 (2H, m, ArC*H*),6.86 (2H, dd, J_{ab}3.0,J_{ac}8.2, ArC*H*), 6.98-7.03 (2H, m, ArC*H*), 7.05-7.11 (2H, m, ArCH), 7.28 (6H, d, *J* 3.7, ArCH).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 24.4 (CH_3), 25.2 (CH_3), 29.7 (CH_2), 43.8 (CH_2), 43.9 (CH_2), 44.6 (CH), 44.7 (CH), 55.9 (2OCH_3), 57.9 (CH), 58.2 (CH), 74.1 (COH), 74.4 (COH), 109.6 (ArCH), 110.0 (ArCH), 110.8 (ArCH), 111.0 (ArCH), 111.3 (ArCH), 119.5 (ArCH), 120.5 (ArCH), 127.6 (ArCH), 128.0 (2ArCH), 128.4 (ArCH), 128.5 (ArC), 128.6

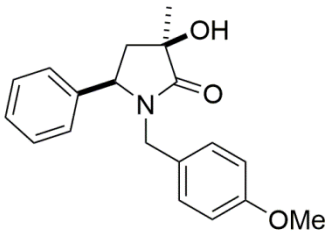
(ArCH), 128.9 (ArCH), 129.0 (ArC), 148.9 (Ar*C*OCH_3), 149.1(ArC), 149.5 (Ar*C*OCH_3), 176.6 (CO), 177.1 (CO). HRMS $[M+H]^+$ calculated for the formula $C_{20}H_{23}NO_4Na$ $^+$364.1525; found 364.1519.

_N_-(4-methoxybenzyl)-3-hydroxy-3-methyl-5-phenylpyrrolidin-2-one (*cis*-130h)



General procedure (**i**) was used. *N*-(4-Methoxylbenzyl)-3-methyl-1-phenylbut-3-en-1-amine **44i** (280 mg, 0.99 mmol), iodine (758 mg, 2.98 mmol), sodium bicarbonate (417 mg, 4.97 mmol), ethyl acetate/petroleum ether 40%, RF=0.23, colourless crystal (mpt 141-142 $^\circ$C), 70 mg, 35% yield. IR 3377, 2929, 1680(s).^{1}H NMR (δ; 300 MHz, $CDCl_3$);1.55 (3H, s, CH_3), 1.90 (1H, dd, J_{ab}13.7, J_{ac}6.6, CHC*H*H), 2.57 (1H, dd, J_{ab}13.8,J_{bc}7.8, CHCH*H*), 3.51 (ABq, 1H, J_{AB}14.5, ArC*H*H), 3.77 (3H, s,OCH_3), 4.51 (1H, app.t, *J* 7.2, C*H*CHH), 5.04 (ABq, 1H, J_{AB}14.5, ArCH*H*), 6.78 (2H, d, *J*8.6, ArC*H*), 6.98 (2H, d, *J* 8.6,ArC*H*), 7.06-7.17 (2H, m, ArC*H*), 7.29-7.43(3H, m, ArC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 25.2(CH_3), 44.0(CH_2), 55.2(CH), 58.1(CH), 74.3(COH), 114.0 (ArCH), 127.0 (ArCH), 127.7(ArC), 128.2 (ArCH), 129.0 (ArCH), 129.8 (ArCH), 140.0(ArC), 159.0(ArC), 176.8 (CO). HRMS $[M+Na]^+$ calculated for the formula $C_{19}H_{21}NO_3Na^+$334.1421; found 334.1419.

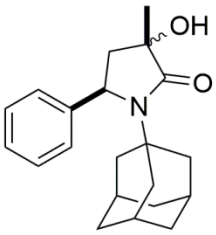
_N_-(4-methoxybenzyl)-3-hydroxy-3-methyl-5-phenylpyrrolidin-2-one (*trans*-130h)



General procedure (**i**) was used. *N*-(4-Methoxylbenzyl)-3-methyl-1-phenylbut-3-en-1-amine **44i** (280 mg, 0.99 mmol), iodine (758 mg, 2.98 mmol), sodium bicarbonate (417 mg, 4.97 mmol), ethyl acetate/

petroleum ether 40%, Rf=0.25, colourless crystal (mpt 159-160 °C), 51 mg, 45% yield. IR 3377, 2929, 1680(s).^{1}H NMR (δ; 300 MHz, $CDCl_3$);1.43 (3H, s, CH_3), 2.13 (1H, dd, J_{ab}13.0, J_{ac}6.6, CHC*H*H), 2.45 (1H, dd, J_{ab}13.0, J_{bc}6.8, CHCH*H*), 3.41 (ABq, 1H, J_{AB}14.4, ArC*H*H), 3.78 (3H, s, OCH_3), 4.14 (1H, dd, J_{ac}6.6, J_{bc}6.8, C*H*CHH), 5.01 (ABq, 1H, J_{AB}14.4, ArCH*H*), 6.79 (2H, d, *J* 8.7, ArC*H*), 6.90 (2H, d, *J* 8.6, ArC*H*), 7.17-7.24 (2H, m, ArC*H*), 7.29-7.37(3H, m, ArC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 24.4(CH_3), 43.9(CH_2), 44.2(CH_2), 55.2(CH_3), 74.1(COH), 114.0(ArCH), 127.7 (ArCH), 128.0(ArC), 128.4 (ArCH), 129.0 (ArCH), 129.8 (ArCH), 139.2(ArC), 159.1(ArC), 177.30 (CO). HRMS $[M+Na]^+$ calculated for the formula $C_{19}H_{21}NO_3Na^+$334.1421; found 334.1419.

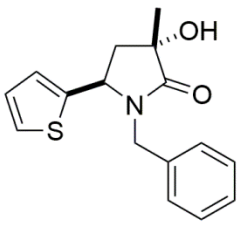
_N_-(adamantan-1-yl)-3-hydroxy-3-methyl-5-phenylpyrrolidin-2-one (*cis*-134i and *trans*-130i)



General procedure (**i**) was used. *N*-(Admantan-1-yl) phenylbut-3-ene **44l** (237 mg, 0.80 mmol), iodine (610 mg, 2.40 mmol), sodium bicarbonate (337 mg, 4.00 mmol), ethyl acetate (50 mL), ethyl acetate/hexane 50%, white precipitate, 150 mg, 57% yield. IR 2904, 2849, 1657(s).^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.20-2.30 (24H, overlapping m, AdmantCH_2), 2.44 (1H, dd, J_{ab}13.4, J_{ac}8.3, CHC*H*H_{maj}), 2.63 (1H, dd, J_{ab}12.9, J_{ac}10.0, CHC*H*H_{min}), 2.73 (1H, dd, J_{ab}13.4, J_{bc}8.3, CHCH*H*$_{maj}$), 4.19 (1H, dd, J_{ab}12.9, J_{bc}9.8, CHCH*H*$_{min}$), 4.47-4.55 (1H, m, C*H*), 4.63-4.71 (1H, m, C*H*), 4.74 (1H, dd, J_{ac}8.3, J_{bc}8.3, C*H*CHH_{maj}), 4.77 (1H, d, J_{ac}10.0, J_{bc}9.8, C*H*CHH_{min}), 5.04 (3H, d, *J* 9.6, C*H*), 7.08-7.53 (10H, m, ArC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 19.9 (CH_3), 26.5 (CH_3), 29.5 (CH), 29.7 (CH), 29.9 (CH), 36.2 (CH), 36.7 (CH), 41.8 ($2CH_2$), 42.2 ($2CH_2$), 49.5 (CH_2), 49.6 (CH_2), 54.6 (CH_2), 57.3 (CH), 59.3(CH), 77.8 (CH_2), 87.0 (CH), 88.7 (CH), 125.4 (ArCH), 126.1 (ArCH), 126.2 (ArCH), 126.6 (ArCH), 127.1 (ArCH), 127.2 (ArCH), 127.4

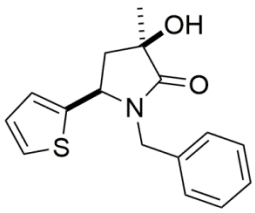
(ArCH), 127.8 (ArCH), 127.9 (ArCH), 128.0 (ArCH), 128.2 (ArCH), 128.7 (ArCH),144.9 (ArC), 149.0 (ArC), 177.3 (CO), 177.8 (CO). HRMS $[M+H]^+$ calculated for the formula $C_{21}H_{28}NO_2^+$ 326.2122; found 326.2120.

_N_-benzyl-3-hydroxy-3-methyl-5-(thiophen-2-yl) pyrrolidin-2-one (*cis*-130j)



General procedure (**i**) was use.*N*-Benzyl-3-methyl-1-(thiophen-2-yl) but-3-en-1-amine**44j** (156 mg, 0.6 mmol), iodine (460 mg, 1.80 mmol), sodium bicarbonate (254 mg, 3.03 mmol), ethyl acetate/ petroleum ether 40%, Rf=0.35, white crystal (mpt 142-143°C), 27 mg 36% yield. IR 3292, 2940, 1671 (s).^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.45 (3H, s, C*H*$_3$), 2.31 (1H, dd, J_{ab}13.0, J_{ac}8.6, CHC*H*H), 2.53 (1H, dd, J_{ab}13.0, J_{bc}6.7, CHCH*H*), 3.59 (ABq, 1H, J_{AB}14.7, ArC*H*H), 4.52 (1H, dd, J_{ac}8.6, J_{bc}6.7, C*H*CHH), 5.05 (ABq, 1H, J_{AB}14.7, ArC*H*H), 6.88-7.12 (3H, m, ThioC*H*), 7.22-7.39 (5H, m, ArC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 24.2(CH_3), 44.4 (CH_2), 44.9 (CH_2), 53.1 (CH), 73.8 (COH), 126.4 (ArCH), 126.8 (ArCH), 127.5 (ArCH), 127.7 (ArCH), 128.4 (ThioCH), 128.7 (ThioCH), 129.0 (ThioCH), 136.0 (ThioC), 142.7 (ArC), 176.9 (CO). HRMS $[M+Na]^+$calculated for the formula $C_{16}H_{17}NO_2NaS^+$ 310.0876; found 310.0878.

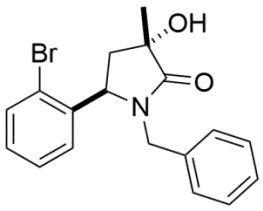
_N_-benzyl-3-hydroxy-3-methyl-5-(thiophen-2-yl) pyrrolidin-2-one (*trans*-130j)



General procedure (**i**) was used. *N*-Benzyl-3-methyl-1-(thiophen-2-yl) but-3-en-1-amine **44j** (156 mg, 0.60 mmol), iodine (460 mg, 1.80 mmol), sodium bicarbonate (254 mg, 3.03 mmol), ethyl acetate/ petroleum ether 40%, Rf=0.25, white crystal (mpt 134-135 °C), 23 mg 30% yield. IR 3292, 2940, 1671 (s).^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.62 (3H, s, CH_3), 2.09 (1H, dd, J_{ab}13.1, J_{ac}6.3, CHC*H*H), 2.65 (1H,

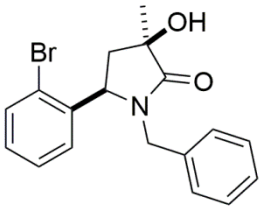
dd, J_{ab}13.1, J_{bc}7.7, CHCH*H*), 3.63 (ABq,1H, J_{AB}14.7, ArC*H*H), 4.86 (1H, app.t, *J*7.1, C*H*CHH), 5.20 (ABq,1H, J_{AB}14.7, ArCH*H*), 6.80-7.36 (3H, m, ThioC*H*), 7.36-7.38 (5H, m, ArC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 24.0 (CH_3), 44.2 (CH_2), 44.7 (CH_2), 53.0 (CH), 73.9 (COH), 126.9 (ArCH), 127.0 (ArCH), 127.3 (ArCH), 127.9 (2ArCH), 128.5 (ThioCH), 128.6 (ThioCH), 129.0 (ThioCH), 136.4 (ThioC), 142.9 (ArC), 177.1 (CO). HRMS $[M+Na]^+$calculated for the formula $C_{16}H_{17}NO_2NaS^+$ 310.0876; found 310.0878.

_N_-benzyl-5-(2-bromophenyl)-3-hydroxy-3-methylpyrrolidin-2-one (*cis*-130k)



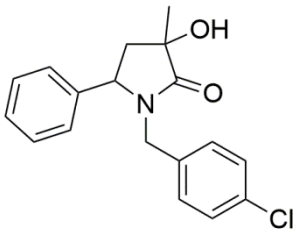
General procedure (**i**) was used. *N*-Benzyl-3-methyl-1-(2-bromophenyl)but-3-en-1-amine **44k** (200 mg, 0.60 mmol), iodine (460 mg, 1.8 mmol), sodium bicarbonate (250 mg, 3.0 mmol), ethyl acetate/petroleum ether 40%, Rf= 0.18, white crystal (mpt 125-126°C), 74 mg, 34% yield. IR 3327, 2926, 1679(s).^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.45 (3H, s,CH_3), 1.89 (1H, dd, J_{ab}13.5, J_{ac}3.7, CHC*H*H), 2.66 (1H, dd, J_{ab}13.5, J_{bc}8.9, CHCH*H*), 3.67 (ABq, 1H, J_{AB}14.5, ArC*H*H), 4.91 (1H, dd, J_{ac}3.7, J_{bc}8.9, C*H*CHH), 5.16 (ABq, 1H, J_{AB}14.5, ArC*H*H), 7.01-7.42 (8H, m, ArC*H*), 7.59 (1H, dd, *J* 8.0, 1.0, ArC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 24.8 (CH_3), 42.6 (CH_2), 45.0 (CH_2), 56.3 (COH), 123.4 (ArC), 127.8 (ArCH), 128.0 (ArCH), 128.3 (ArCH), 128.6 (ArCH), 128.7 (ArCH), 129.4 (ArCH), 133.1 (ArCH), 135.3 (ArC), 147.0 (ArC), 176.5 (CO). HRMS $[M+Na]^+$calculated for the formula $C_{18}H_{18}NO_2BrNa^+$282.0410; found 282.0419.

***N*-benzyl-5-(2-bromophenyl)-3-hydroxy-3-methylpyrrolidin-2-one (*trans*-130k)**



General procedure (**i**) was used. *N*-Benzyl-3-methyl-1-(2-bromophenyl)but-3-en-1-amine **44k** (200 mg, 0.60 mmol), iodine (460 mg, 1.8 mmol), sodium bicarbonate (250 mg, 3.0 mmol), ethyl acetate/petroleum ether 40%, Rf= 0.25, white crystal (mpt 112-113 °C), 48 mg 21% yield. IR 3327, 2926, 1679(s).^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.43 (3H, s, C*H*$_3$), 1.94 (1H, dd, J_{ab}13.2, J_{ac}7.3, CHC*H*H), 2.52 (1H, dd, J_{ab}13.2, J_{bc}7.3, CHCH*H*),3.58 (ABq, 1H, J_{AB} 14.4, ArC*H*H), 4.73 (1H, app.t, *J*7.2, C*H*CHH), 5.09 (ABq, 1H, J_{AB}14.4, ArCH*H*), 6.99 (2H, dd, *J* 6.5, 2.8, ArC*H*), 7.15-7.45 (5H, m,ArC*H*), 7.55 (1H, d, *J* 7.3, ArC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 24.8 (CH_3), 42.6 (CH_2), 45.0 (CH_2), 56.3 (COH), 123.4 (ArC), 127.8 (ArCH), 128.0 (ArCH), 128.3 (ArCH), 128.6 (ArCH), 128.7 (ArCH), 129.4 (ArCH), 133.1 (ArCH), 135.3 (ArC), 147.0 (ArC), 176.5 (CO). HRMS $[M+Na]^+$calculated for the formula $C_{18}H_{18}NO_2BrNa^+$282.0410; found 282.0419.

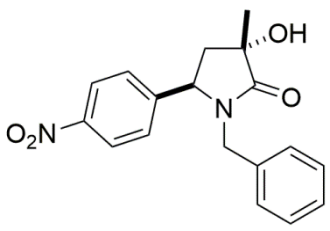
***N*-(4-chlorobenzyl)-3-hydroxy-3-methyl-5-phenylpyrrolidin-2-one (*cis*-130l and *trans*-130l)**



(Mixture of diastereoisomers maj/min) General procedure (**i**) was used. *N*-(4-Chlorobenzyl)-3-methyl-1-phenylbut-3-en-1-amine **44l** (160 mg, 0.56 mmol), iodine (426 mg, 1.68 mmol), sodium bicarbonate (235 mg, 2.79 mmol), ethyl acetate/hexane 50%, white precipitate, 113mg, 64% yield. IR 3286, 1681(s).^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.43 (3H, s, C$H_{3\ min}$), 1.58 (3H, s, C$H_{3\ maj}$), 1.94 (1H, dd, J_{ab}13.8,J_{ac}7.0, CHC*H*H$_{maj}$), 2.16 (1H, dd, J_{ab}13.1, J_{ac}8.5, CHCH*H*$_{min}$), 2.48 (1H, dd, J_{ab}13.1, J_{bc}8.3, CHC*H*H$_{min}$),2.61 (1H, dd, J_{ab}13.8, J_{bc}7.5, CHCH*H*$_{maj}$), 3.47(ABq, 1H, J_{AB}14.5, ArC*H*H$_{min}$), 3.57 (ABq, 1H, J_{AB}14.5, ArC*H*H$_{maj}$), 4.14(1H, dd, J_{ac}8.5, J_{bc}8.3,

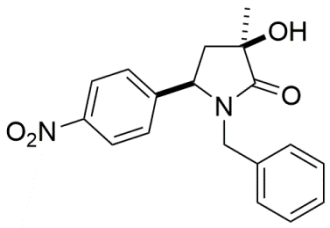
C*H*CHH$_{min}$), 4.54 (1H, dd, J_{ac}7.0, J_{bc}7.5, C*H*CHH$_{maj}$), 4.97 (ABq, 1H, J_{AB} 9.6, ArCH*H*$_{min}$), 5.02(ABq, 1H, J_{AB}9.8, ArCH*H*$_{maj}$), 6.91 (2H, d, *J* 8.5, ArC*H*), 7.00 (2H, d, *J* 8.5, ArC*H*), 7.10 (2H, d, *J* 8.1, ArC*H*), 7.12-7.38 (12H, m, ArC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 24.5 (CH_3), 25.1 (CH_3), 43.9 (CH_2), 44.1 (CH_2), 58.0 (CH), 58.3 (CH), 74.0 (COH), 74.3 (COH), 127.0 (ArCH), 127.7 (ArCH), 128.4 (ArCH), 128.6 (ArCH), 128.8 (ArCH), 129.1 (ArCH), 129.7 (ArCH), 129.9 (ArCH), 133.5 (ArC), 133.6 (ArC), 134.2 (ArC), 134.4 (ArC), 138.7 (ArC), 139.4 (ArC), 176.7 (CO), 176.8 (CO). HRMS $[M+H]^+$calculated for the formula $C_{18}H_{19}ClNO_2^+$316.1110; found 316.1104.

_N_-benzyl-3-hydroxy-3-methyl-5-(4-nitrophenyl) pyrrolidin-2-one (*cis*-130m)



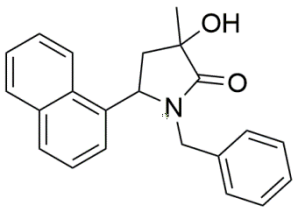
General procedure (**i**) was used. *N*-Benzyl-3-methyl-1-(4-nitrophenyl)but-3-en-1-amine **44m** (300 mg, 1.0 mmol), iodine (770 mg, 3.0 mmol), sodium bicarbonate (425 mg, 5.0 mmol), ethyl acetate/petroleum ether 60%, Rf= 0.25, light brown precipitate (mpt 238-239˚C), 88 mg 25% yield. IR 3386, 2928, 1681(s), 1527, 1349, 698.^{1}H NMR (δ; 300 MHz, $CDCl_3$);1.57 (3H, s, CH_3), 1.88 (1H, dd, J_{ab}13.8, J_{ac}6.7, CHC*H*H), 2.65 (1H, dd, J_{ab}13.8, J_{bc}7.8, CHCH*H*), 3.60 (ABq,1H, J_{AB}14.7, ArC*H*H), 4.63 (1H, app.t, *J* 7.2, C*H*CHH), 5.16 (ABq, 1H, J_{AB}14.7, ArCH*H*), 6.99-7.09 (2H, m, ArC*H*), 7.24- 7.37 (5H, m, ArC*H*), 8.26 (2H, d,*J*8.7, ArC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 25.2 (CH_3), 43.7 (CH_2), 45.0 (CH_2), 57.6 (CH), 74.1 (COH), 124.4 (2ArCH), 127.7 (2ArCH), 127.9 (2ArCH), 128.2 (2ArCH), 128.8 (ArCH), 134.9 (ArC), 147.4 (ArC), 147.8 ($ArCNO_2$), 176.7 (CO). HRMS $[M+Na]^+$calculated for the formula $C_{18}H_{18}N_2O_4Na^+$349.1166; found 349.1164.

***N*-benzyl-3-hydroxy-3-methyl-5-(4-nitrophenyl) pyrrolidin-2-one (*trans*-130m)**



General procedure (**i**) was used. *N*-benzyl-3-methyl-1-(4-nitrophenyl)but-3-en-1-amine **44m** (300 mg, 1.0 mmol), iodine (770 mg, 3.0 mmol), sodium bicarbonate (425mg, 5.0 mmol), ethyl acetate/ petroleum ether 60%, yellow oil, 100 mg, 30% yield. IR 3386, 2928, 1681(s), 1527, 1349, 698.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.47 (3H, s, CH_3), 2.10 (1H, dd, J_{ab}13.2, J_{ac}7.6, CHC*H*H), 2.50 (1H, dd, J_{ab}13.3, J_{bc}7.3, CHCH*H*), 3.54 (ABq, 1H, J_{AB}14.6, ArC*H*H), 4.28 (1H, app.t, *J*7.4, C*H*CHH), 5.16 (ABq,1H, J_{AB}14.6, ArCH*H*), 7.17- 7.50 (2H, m, ArC*H*), 7.35-7.15 (5H, m, ArC*H*), 8.24 (2H, d, *J* 6.9, ArC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 25.2 (CH_3), 43.6 (CH_2), 44.9 (CH_2), 57.6 (CH), 74.0 (COH), 124.3 (2ArCH), 127.7 (2ArCH), 127.9 (2ArCH), 128.2 (2ArCH), 128.8 (ArCH), 134.9 (ArC), 147.4 (ArC), 147.8 (ArC), 176.7 (CO). HRMS $[M+Na]^+$calculated for the formula $C_{18}H_{18}N_2O_4Na^+$349.1166; found 349.1164.

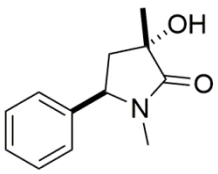
***N*-benzyl-3-hydroxy-3-methyl-5-(naphthalen-1-yl)pyrrolidin-2-one (*cis*-130n and *trans*-130n)**



General procedure (**i**) was used. *N*-benzyl-3-methyl-1-(naphthalen-1-yl)but-3-en-1-amine **44n** (126 mg, 0.418 mmol), iodine (318 mg, 1.2 mmol), sodium bicarbonate (175 mg, 2.09 mmol), ethyl acetate/hexane 50%, white precipitate, 100 mg, 72% yield. IR 3355, 2985, 1676(s).^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.53 (3H, s, C$H_{3maj.}$), 1.95 (3H, s, CH_{3min}), 2.17 (1H, dd, J_{ab}13.4,J_{ac}7.2, CHC*H*H $_{maj}$), 2.50 (1H, dd, J_{ab}13.1,J_{ac}7.1, CHC*H*H$_{min}$), 2.64 (1H, dd, J_{ab}13.4,J_{bc}7.4, CHCH*H*$_{maj}$), 2.82 (1H, dd, J_{ab}13.1,J_{bc}9.9, CHCH*H*$_{min}$), 3.35 (1H, dd, *J*14.4, ArC*H*H$_{min}$), 3.70 (2H, d, *J*14.4,ArC*H*H$_{maj}$), 4.61 (1H, dd, J_{ac}7.1,J_{bc}9.9, C*H*CHH$_{min}$), 5.41 (1H, dd, J_{ac}7.2,J_{bc}7.4, C*H*CHH$_{maj}$), 5.23 (2H, d,

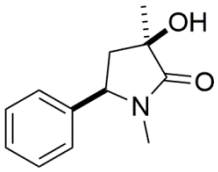
*J*14.5,ArCHH_{maj}), 5.34 (2H, d, *J*14.5,ArCHH_{min}), 6.93 (4H, t, *J* 7.5, NaphC*H*), 7.06- 8.24 (20H, m, ArC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 24.9 (CH_3), 25.0 (CH_3), 41.4 (CH_2), 44.0 (CH_2), 44.9 (CH_2), 45.0 (CH_2), 45.3 (CH_2), 52.3 (CH), 60.5 (CH), 74.3 (COH), 121.7 (ArCH), 123.1 (ArCH), 123.8 (ArCH), 124.9 (ArCH), 125.8 (ArCH), 126.4 (ArCH), 126.6 (ArCH), 127.0 (ArCH), 127.7 (ArCH), 128.4 (ArCH), 128.5 (ArCH), 128.6 (ArCH), 128.7 (ArCH), 129.0 (ArCH), 129.5 (ArCH), 130.1 (ArC), 131.0 (ArC), 133.9 (ArC), 135.6 (ArC), 135.9 (ArC), 177.4 (2CO). HRMS $[M+H]^+$ calculated for the formula $C_{22}H_{22}NO_2^+$ 332.4150; found 332.4131.

1,3-Dimethyl-3-hydroxy-5-phenylpyrrolidin-2-one (*cis*-130o)



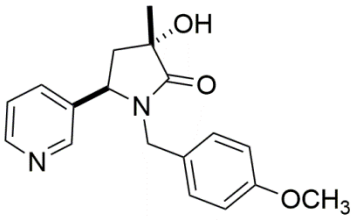
General procedure (**i**) was used. 1,3-dimethyl-1-phenylbut-3-en-1-amine **44q** (500 mg, 2.80 mmol), iodine (2.15 mg, 8.5 mmol), sodium bicarbonate (118 mg, 14.1 mmol), ethyl acetate/petroleum ether 70%, Rf= 2.28, white crystal (mpt 159-160 ˚C). 135mg, 24% yield. IR 3306, 2928, 1668, 1454, 1256.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.48 (3H, s, CH_3), 2.13 (1H, dd, J_{ab}13.2, J_{ac}8.1, CHC*H*H), 2.54 (1H, dd, J_{ab}13.2, J_{bc}6.9, CHCH*H*), 2.65 (3H, s, NCH_3), 4.34 (1H, dd, J_{ac}8.1, J_{bc}6.9, C*H*CHH), 7.22-7.43 (5H, m, ArC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 25.3 (CH_3), 28.7 (CH_3), 44.3 (CH_2), 61.4 (CH), 74.1 (COH), 126.5 (ArCH), 128.1 (ArCH), 129.1 (ArCH), 140.3 (ArC), 177.0 (CO). HRMS $[M+Na]^+$calculated for the formula $C_{12}H_{15}NO_2Na^+$228.0996; found 228.1000.

1,3-Dimethyl-3-hydroxy- 5-phenylpyrrolidin-2-one (*trans*-130o)



General procedure (**i**) was used. *N*, 3-dimethyl-1-phenylbut-3-en-1-amine **44q** (500 mg, 2.80 mmol), iodine (2150 mg, 8.47 mmol), sodium bicarbonate (1180 mg, 14.10 mmol), ethyl acetate/petroleum ether 70%, Rf= 0.29, white crystal (mpt 168-169 ˚C), 118 mg 19% yield. IR 3306, 2928, 1668, 1454, 1256.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.51 (3H, s, CH_3), 1.90 (1H, dd, J_{ab}13.2, J_{ac}7.0, CHC*H*H), 2.66 (1H, dd, J_{ab}13.8, J_{bc}7.7, CHCH*H*), 2.72 (3H, s, NCH_3), 4.65 (1H, dd, J_{ac}7.0, J_{bc}7.7, C*H*CHH), 7.12-7.44 (5H, m, ArC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 24.8 (CH_3), 28.4 (CH_3), 44.4 (CH_2), 61.0 (CH), 74.1 (COH), 127.3(ArCH), 128.5 (ArCH), 129.0 (2ArCH), 139.6 (ArC), 177.3(CO). HRMS $[M+Na]^+$calculated for the formula $C_{12}H_{15}NO_2Na^+$228.0996; found 228.1000.

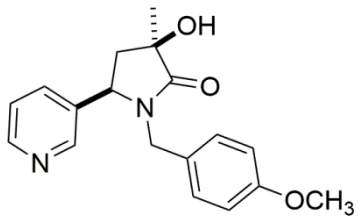
***N*-(4-methoxybenzyl)-3-hydroxy-3-methyl-5-(pyridin-3-yl)pyrrolidin-2-one (*cis*-130p)**



General procedure (**i**) was used. *N*-benzyl-3-methyl-1-phenylbut-3-en-1-amine **44p** (350 mg, 1.24 mmol), iodine (940 mg, 3.70 mmol), sodium bicarbonate (520 mg, 6.19 mmol), the product was separated with crystallisation from dichloromethane/petroleum ether 50%, white crystal (mpt 172-173 ˚C), 150 mg, 51% yield. IR 2934, 1689 (s), 1611, 1512, 1431, 1245.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.39 (3H, s, CH_3), 2.08 (1H, dd, J_{ab}13.8, J_{ac}6.9, CHC*H*H), 2.41 (1H, dd, J_{ab}13.8, J_{bc}7.6, CHCH*H*), 3.35 (ABq, 1H, J_{AB}14.5, ArC*H*H), 3.71 (3H, s, OCH_3), 4.13 (1H, app.t, *J* 7.5, C*H*CHH), 4.96 (ABq,1H, J_{AB}14.5, ArCH*H*), 6.77 (4H, dt, *J* 1.9, 1.9,ArC*H*), 7.38 (2H, dt, *J* 1.9 ,1.9, PyrC*H*), 8.38(1H, d, *J* 1.9,PyrC*H*), 8.55 (1H, dd, *J* 4.7, 1.6, PyrC*H*).^{13}C NMR (δ; 100 MHz, CDCl3); 24.9 (CH_3), 43.9 (CH_2), 44.1 (CH_2), 55.2 (CH_3), 55.9 (OCH_3), 74.0 (COH), 114.1

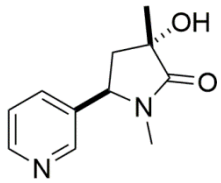
(ArCH), 123.9 (ArCH), 127.1 (ArC), 129.6 (ArCH), 134.6 (ArCH), 135.4 (ArC), 149.0 (ArCH), 149.7 (ArCH), 159.1 (ArC), 176.8 (CO). HRMS $[M+H]^+$calculated for the formula $C_{18}H_{21}N_2O_3^+$313.1541; found 313.1552.

_N_-(4-methoxybenzyl)-3-hydroxy-3-methyl-5-(pyridin-3-yl)pyrrolidin-2-one (*trans*-130p)



General procedure (**i**) was used. *N*-(4-methoxybenzyl)-3-methyl-1-3-pyridylbut-3-en-1-amine **44p** (350 mg, 1.24mmol), iodine (940 mg, 3.70 mmol), sodium bicarbonate (520 mg, 6.19 mmol), dichloromethane/petroleum ether 50%, yellow oil, 140 mg, 48% yield. IR 2934, 1689 (s), 1611, 1512, 1431, 1245. ^{1}H NMR (δ; 300 MHz, $CDCl_3$);1.55 (3H, s, CH_3),1.88 (1H, dd, J_{ab}13.7, J_{ac}6.9, CHC*H*H), 2.58 (1H, dd, J_{ab}13.7, J_{bc}7.0, CHCH*H*), 3.51 (ABq,1H, J_{AB}14.5, ArC*H*H), 3.78 (1H, s, OCH_3), 4.53 (1H, app.t, *J* 7.3, C*H*CHH), 5.04 (ABq,1H, J_{AB}14.5, ArCH*H*), 6.83 (4H, dt, *J*1.9,1.9, ArC*H*), 7.39 (1H, dt, *J* 1.9, 1.9, PyrC*H*), 8.38 (1H, d, *J* 1.9, PyrC*H*), 8.61 (1H, dd, *J*1.6,4.7, PyrC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 24.9 (CH_3), 43.9 (CH_2), 44.1 (CH_2), 55.2 (CH), 55.9 (CH), 74.0 (COH), 114.1 (ArCH), 123.9 (ArCH), 127.1 (ArC), 129.6 (ArCH), 134.4 (ArCH), 135.4 (ArC), 149.0 (ArCH), 149.7 (ArCH), 159.1 (ArC), 176.8 (CO). HRMS $[M+H]^+$calculated for the formula $C_{18}H_{21}N_2O_3^+$313.1541; found 313.1552.

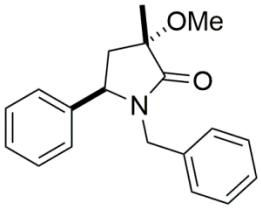
1,3-Dimethyl-3-hydroxyl-5-(pyridin-3-yl)pyrrolidin-2-one (*cis*-130q)



General procedure (**i**) was used. 1,3-dimethyl-1-(pyridin-3-yl)but-3-en-1-amine **44r** (400 mg, 2.27 mmol), iodine (1730 mg, 1.80 mmol), sodium bicarbonate (950 mg, 11.30mmol), methanol/ dichloromethane 5%, Rf= 0.24, pale yellow crystal (mpt 168-169 ˚C), 150 mg, 36% yield. IR 3356, 2927, 1679(s).^{1}H NMR (δ;

300 MHz, $CDCl_3$); 1.51 (3H, s, CH_3), 1.89 (1H, dd, J_{ab}13.8, J_{ac}6.7, CHC*H*H), 2.62-2.77 (4H, overlapping, CHCH*H*, NCH_3), 4.69 (1H, app t, *J* 7.2, C*H*CHH), 7.36 (1H, dd, *J*4.8,7.9, PyrC*H*), 7.51 (1H, dt, *J* 7.9, 1.9, PyrC*H*), 8.52 (1H, s, PyrC*H*), 8.62 (1H, d, *J* 3.8, PyrC*H*).^{13}C NMR (δ; 100 MHz, CDCl3);25.2 (CH_3), 28.7 (CH_3), 43.9 (CH_2), 59.1 (CH), 73.9 (COH), 124.0 (ArCH), 133.8 (ArCH), 135.7 (ArC), 148.6 (ArCH), 149.8 (ArCH), 176.7 (CO). HRMS $[M+H]^+$calculated for the formula $C_{11}H_{15}N_2O_2^+$ 207.1134 found 207.1136.

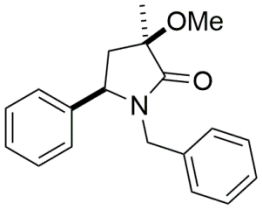
_N_-benzyl-3-methoxy-3-methyl-5-phenylpyrrolidin-2-one (*cis*-137a)



N-Benzyl-3-hydroxy-3-methyl-5-phenylpyrrolidin-2-one *cis*-**130a** and *trans*-**130a** (0.07 g, 0.25 mmol) in dry DMF (10 mL), was added sodium hydride (0.01g, 0.5mmol), the reaction mixture was stirred for 30 minutes, then iodomethane (0.7 mL, 0.5 mmol) was added and stirred for another 18 hours at room temperature (TLC was monitored), quenched by addition of (10 mL) water and extracted with ethyl acetate, the combined organic layer was washed with brine and dried with magnesium sulfate to give the alkylated product in quantitative yield, the single diastereoisomer was separated by column chromatography using silica gel and ethyl acetate/petroleum ether 30%, Rf=0.21, colourless solid (mpt 82-83 ˚C), 34 mg, 50% yield. IR 3360, 2928, 1683 (s).^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.51 (3H, s, CH_3), 1.85 (1H, dd, J_{ab}13.9, J_{ac}7.6, CHC*H*H), 2.55 (1H, dd, J_{ab}13.9, J_{bc}7.1, CHCH*H*), 3.36 (3H, s, CH_3), 3.50 (ABq,1H, J_{AB} 14.6, ArC*H*H), 4.46 (1H, app.t, *J* 7.3, C*H*CHH), 5.13 (ABq, 1H, J_{AB}14.6, ArCH*H*), 6.94- 7.47 (10H, m, ArC*H*). ^{13}C NMR (δ; 100 MHz, $CDCl_3$); 21.5 (CH_3), 40.2 (CH_2), 44.5 (CH_2), 51.7 (CH_3), 57.2 (CH), 79.3 (*C*OCH_3), , 127.3 (ArCH), 127.5 (ArCH), 128.1 (ArCH), 128.3 (ArCH), 128.6 (ArCH), 129.0 (ArCH), 136.0

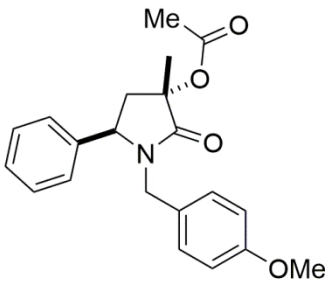
(ArC), 139.7 (ArC), 174.7 (CO). HRMS $[M+Na]^+$ calculated for the formula $C_{19}H_{21}NO_2Na^+$ 318.1470; found 318.1478.

_N_-benzyl-3-methoxy-3-methyl-5-phenylpyrrolidin-2-one (*trans*-137b)



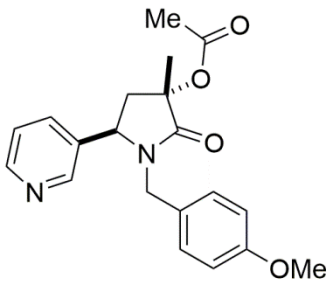
N-Benzyl-3-hydroxy-3-methyl-5-phenylpyrrolidin-2-one *cis*-**130a** and *trans*-**130a** (0.07g, 0.25mmol) in dry DMF (10 mL), was added sodium hydride (0.01 g, 0.5 mmol), the reaction mixture was stirred for 30 minutes, then iodomethane (0.7 mL, 0.5 mmol) was added and stirred for an other 18 hours at room temperature (TLC was monitored), quenched by addition of (10 mL) water and extracted with ethyl acetate, the combined organic layer was washed with brine and dried with magnesium sulfate to give the alkylated product, the single diastereoisomer was separated by column chromatography using silica gel and ethyl acetate/petroleum ether 30%, Rf=0.25, colourless solid (mpt 75-76˚C), 33 mg 49% yield. IR 3360, 2928, 1683.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.42 (3H, s, CH_3), 2.17 (1H, dd, J_{ab} 13.3, J_{ac}7.9,CHC*H*H), 2.26 (1H, dd, J_{ab} 13.3, J_{bc}7.3,CHCH*H*),, 3.43 (3H, s, OCH_3), 3.47 (ABq, 1H, J_{AB}14.5, ArC*H*H), 4.12 (1H, app.t, *J* 7.6, C*H*CHH), 5.12 (ABq, 1H, J_{AB}14.5, ArCH*H*), 6.92-7.46 (10H, m, ArC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 20.0 (CH_3), 40.2 (CH_2), 44.5 (CH_2), 51.7 (CH_3), 58.3 (CH), 78.5 (*C*OCH_3), 126.8 (ArCH), 127.1 (ArCH), 127.7 (ArCH), 128.4 (ArCH), 128.4 (ArCH), 128.6 (ArCH), 136.0 (ArC), 139.8 (ArC), 173.7 (CO). HRMS$[M+Na]^+$ calculated for the formula $C_{19}H_{21}NO_2Na^+$ 318.1470; found 318.1478.

***N*-(4-methoxybenzyl)-3-methyl-2-oxo-5-phenylpyrrolidin-3-yl acetate (*cis*-138a)**



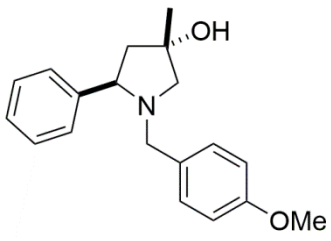
N-(4-Methoxybenzyl)-3-hydroxy-3-methyl-5-phenylpyrrolidin-2-one **134h** (35 mg,0.11 mmol), triethylamine (22 mg, 0.22 mmol), DMAP (5.80 mg, 0.011 mmol) and acetic anhydride (22 mg, 0.22 mmol) were added in (10 mL) dry dichloromethane under nitrogen and stirred at room temperature for 24 hours with TLC monitoring. The reaction was quenched with (30mL) brine extracted with ethyl acetate (3x 25 mL) and the combined organic layer was washed with water and dried with $MgSO_4$ and the product was obtained as colourless crystals after recrystallised from dichloromethane/petroleum ether 10%, colourless crystals (mpt 121-122˚C), 36 mg, 92% yield. IR 3286, 3030, 2933, 1671(s), 1669(s).^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.56 (3H, s, CH_3), 1.89(1H, dd, J_{ab}14.4, J_{ac}4.8, CHC*H*H), 2.03 (3H, s, COCH_3), 2.73 (1H, dd, J_{ab}14.4, J_{bc}9.6, CHCH*H*), 3.44 (ABq,1H,J_{AB}14.5, ArC*H*H),3.71 (3H, s, OCH_3), 4.44 (1H, dd, J_{ac}4.8, J_{bc}9.6, C*H*CHH), 5.02 (ABq, 1H, J_{AB}14.5, ArCH*H*), 6.85 (4H, dt, *J*2.9, 2.6, ArC*H*), 7.00-7.33 (5H, m, ArC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 20.2 (CH_3), 24.7 (CH_3), 40.0 (CH_2), 43.4 (CH_2), 54.1 (CH), 56.7 (*C*OCH_3), 79.0 ($COCOCH_3$), 112.6 (ArCH), 125.7 (ArCH), 126.0 ($ArCOCH_3$), 127.0 (ArCH), 128.0 (ArCH), 129.2 (ArCH), 139.5 (ArC), 158.0 (ArC), 169.0 (CO), 171.9 (CO). HRMS $[M+H]^+$calculated for the formula $C_{21}H_{23}NO_4^+$353.4116; found 354.4115.

***N*-(4-methoxybenzyl)-3-methyl-2-oxo-5-(pyridin-3-yl)pyrrolidin-3-ylacetate (*cis*-138b)**



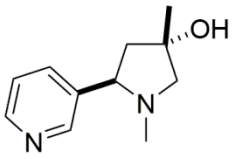
N-(4-Methoxybenzyl)-3-hydroxy-3-methyl-5-phenylpyrrolidin-2-one *cis*-**134a** (135 mg, 0.43 mmol), triethylamine (80 mg, 0.86 mmol), DMAP (23 mg, 0.043 mmol) and acetic anhydride (88 mg, 0.86 mmol) were added in (10 mL) dry dichloromethane under nitrogen and stirred at room temperature for 24 h with TLC monitoring. The reaction was quenched with (5 mL) brine extracted with ethyl acetate and the combined organic layer was washed with water and *in vacuo* evaporated solvent gave yellow solid (mpt 193-194˚C), 123 mg, 56% yield. IR 3457, 2931, 1736 (s), 1701 (s).^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.56 (3H, s, CH_3), 1.89 (1H, dd, J_{ab}14.4, J_{ac}4.8, CHC*H*H), 2.03 (3H, s, COCH_3), 2.73 (1H, dd, J_{ab}14.4, J_{bc}4.8, CHCH*H*), 3.44 (ABq, 1H, J_{AB}14.5, ArC*H*H), 3.71 (3H, s, COCH_3), 4.44 (1H, dd, J_{ac}4.8, J_{bc}4.8, C*H*CHH), 5.02 (ABq, 1H, J_{AB}14.5, ArCH*H*), 6.85 (4H, dd, J_{ab}8.6, J_{ac}69.4, ArC*H*), 7.00-7.33 (6H, m, ArC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 20.2 (CH_3), 24.7 (CH_3), 40.0 (CH_2), 43.4 (CH_2), 54.1 (CH), 56.7 (*C*OCH_3), 79.0 (*C*$OCOCH_3$), 112.6 (2ArCH), 125.7 (ArCH), 126.0 (Ar$COCH_3$), 127.0 (ArCH), 128.0 (ArCH), 129.2 (ArCH), 139.5 (ArC), 158.0 (ArC), 169.0 (CO), 171.9 (CO). HRMS $[M+H]^+$calculated for the formula $C_{20}H_{23}N_2O_4^+$355.1661; found 355.1658.

***N*-(4-methoxybenzyl)-3-methyl-5-phenylpyrrolidin-3-ol (*cis*-139a)**



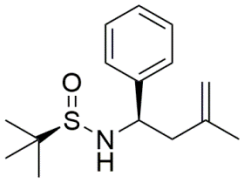
N-(4-Methoxybenzyl)-3-hydroxy-3-methyl-5-phenylpyrrolidin-2-one *cis*-**134l** (30 mg, 0.096mmol) in dry THF (5 mL) was added drop wise to the refluxed solution of $LiAlH_4$ (18 mg, 0.48mmol) in dry THF (5 mL) for three hours, the reaction was quenched with (20 mL) water and extracted with dichloromethane (3 x 20 mL) the combined organic layer was washed with brine and dried with magnesium sulfate and *in vacuo* evaporated solvent and column chromatography ethyl acetate/hexane 30% gave colourless oil 16 mg 56% yield. IR 3393, 2925, 1510, 1245.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.44 (3H, s, C*H*$_3$), 1.82 (1H, J_{ab}12.0, J_{ac}9.0, CHC*H*H), 2.20 (1H, J_{ab}12.0, J_{bc}6.0, CHCH*H*), 2.43 (1H, d, *J*10.0,C*H*H),3.11 (1H, d, *J*10.8, CH*H*), 3.72-3.84 (6H, m, OCH_3, ArC*H*$'$*H*$''$&C*H*CHH), 6.83 (2H, d, *J* 8.6, ArC*H*), 7.18 (2H, d, *J* 8.5, ArC*H*), 7.23-7.53 (5H, m, ArC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 29.3 (CH_3), 51.8 (CH_2), 55.2 (CH), 56.9 ($2CH_2$), 67.4 (CH_2), 113.5 ($ArOCH_3$), 127.2 (ArCH), 127.4 (ArCH), 128.4 (ArCH), 129.6 (ArCH), 131.4 (ArC), 158.4 (ArC). HRMS $[M+H]^+$ calculated for the formula $C_{19}H_{24}NO_2^+$ 298.1802; found 298.1807.

***N*-methyl-3-methyl-5-(pyridin-3-yl)pyrrolidin-3-ol (*cis*-139b)**



3-Hydroxy-1,3-dimethyl-5-phenylpyrrolidin-2-one *cis*-**134q** (70 mg, 0.34 mmol) in dry THF (5 mL) was added to refluxed solution of $LiAlH_4$ (128 mg, 3.4 mmol) in dry THF (5 mL) for three hours with TLC monitoring (methanol/DCM 10%), the reaction was quenched with (20 mL) water and extracted with dichloromethane (3 x 20 mL) the combined organic layers were washed with brine and dried with magnesium sulfate and *in vacuo* evaporated solvent and column chromatography (methanol/ dichloromethane/ petroleum ether 1:7:2) gave yellow oil 58 mg, 89% yield. IR 3361, 2966, 2777.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.39 (3H, s,CH_3), 1.90 (1H, dd, J_{ab}7.7, J_{ac}1.6, CHC*H*H), 1.92 (1H, dd, J_{ab}7.7, J_{bc}1.6, CHCH*H*), 2.19 (3H, s, NCH_3), 2.32-2.43 (2H, m, NC*H*H),3.07 (1H, dd, *J*1.5,9.7, NCH*H*), 3.22 (1H, dd, J_{ac} 1.6, J_{bc}1.6, C*H*CHH), 7.29 (2H, dd, *J* 6.7, 3.8, PyrC*H*), 7.74 (1H, dt, *J* 7.8, 1.8, PyrC*H*), 8.53 (1H, s, PyrC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 24.9 (CH_3), 39.9 (CH_3), 51.2 (CH_2), 53.8 (COH), 68.2 (CH), 70.7 (CH_2), 123.7 (PyrCH), 134.9 (PyrCH), 138.0 (PyrC), 148.8 (PyrCH), 149.43 (PyrCH). HRMS $[M+H]^+$calculated for the formula $C_{11}H_{17}N_2O^+$193.1344; found 193.1341.

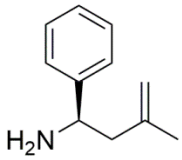
(*R*)-2-methyl-*N*-((*S*)-3-methyl-1-phenylbut-3-en-1-yl)propane-2-sulfinamide (138a)



General procedure (**f**) was used, yellow oil 50 mg, 80% yield. IR 2963, 1709, 1453, 1024, 897.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.18 (9H, s, 3x CH_3), 1.77 (3H, s, CH_3), 2.45 (2H, dd, *J* 8.1, 4.1,C*HH*), 3.70 (1H, s, NH), 4.55 (1H, dd, *J* 8.9, *J*5.2, C*H*CHH), 4.85 (1H, s, olefine C*H*H), 4.96 (1H, s, olefine CH*H*), 7.23-7.39 (5H, m, ArC*H*).^{13}C NMR (δ; 100MHz , $CDCl_3$); 21.8 (CH_3), 22.6 (3CH_3), 47.9 (CH_2), 54.5

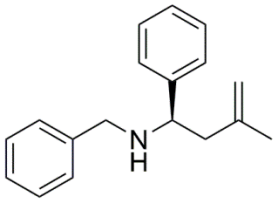
(CH), 55.6 (C), 115.0 (=CH_2), 127.5 (2ArCH), 127.6 (ArCH), 128.5 (2ArCH), 142.1 (ArC),142.2 (C). $[\alpha]_D^{20}$ =+76 (c 5.0, DCM) (lit. +74).[95] HRMS [M+H^+] calculated for formula $C_{15}H_{24}NOS^+$; 266.1579; found 266.1576.

(*R*)-3-Methyl-1-phenylbut-3-en-1-amine (138b)



General procedure (**f**) was used, colourless oil, 20 mg, 72% yield. IR 2932, 1646, 1453, 1376, 893, 756, 700.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.76 (3H, s, CH_3), 2.56 (2H, s, NH_2), 3.58-3.64 (1H, m, CHC*H*H), 3.68-3.76 (1H, m, CHCH*H*), 4.09 (1H, dd, *J*8.9, *J*5.2, C*H*CHH), 4.80 (1H, s, olefine C*H*H), 4.81 (1H, s, olefine CH*H*), 7.20-7.39 (5H, m, ArC*H*).^{13}C NMR (δ; 100MHz , $CDCl_3$); 22.3 (CH_3), 42.9 (CH_2), 48.5 (CH), 113.3 (=CH_2), 126.3 (2ArCH), 127.0 (ArCH), 128.4 (2ArCH), 142.9 (ArC), 146.1 (C). $[\alpha]_D^{20}$=+34 (c 5.0, DCM) (lit. +41). MS (ES+) calculated for formula $C_{11}H_{16}N^+$; 161.2; [M+H^+] found 162.1.

(*S*)-*N*-benzyl-3-methyl-1-phenylbut-3-en-1-amine (139)

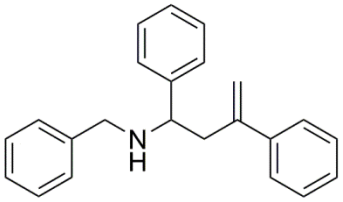


General procedure (**f**) was used, (*R*)-1-phenylbut-3-en-1-amine (20 mg, 0.13 mmol), colourless oil, 65 mg, 92% yield. IR 3324, 3063, 3026, 2968, 2933, 2841, 1946, 1807, 1645, 1602, 1493, 1453, 1027, 697.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.63 (3H, s, CH_3), 1.77 (1H,s, NH), 2.26 (1H, dd, J_{ab}14.0, J_{ac}4.8, CH_2), 2.37 (1H, dd, J_{ab}14.0, J_{bc}4.8, CH_2), 3.57 (ABq, 2H, J_{AB}13.4, J_{AB}13.4, ArC*HH*), 3.80 (1H, dd, J_{ac}4.8, J_{bc}4.8, NCH), 4.79 (1H, s, olefine C*H*H), 4.84 (1H, s, olefine CH*H*), 7.26-7.36 (10H, m, ArC*H*).^{13}C NMR (δ; 100 MHz, CDCl3); 22.1 (CH_3), 47.7 (CH_2), 51.5 (CH_2), 59.3 (CH), 113.5 (=CH_2), 126.9 (ArCH), 127.1 (ArCH), 127.4 (2ArCH), 128.4 (2ArCH), 128.5 (2ArCH), 128.8 (2ArCH), 140.7 (ArC), 142.8 (ArC), 144.3 (C). $[\alpha]_D^{20}$ (c

5.0, DCM) =+54.5. HRMS $[M+H]^+$ calculated for formula $C_{18}H_{22}N^+$; 252.1752; found 252.1762. HPLC (AD column was used), hexane/isopropanol 98:2, flow rate=0.25 ml/min, 83% *ee*.

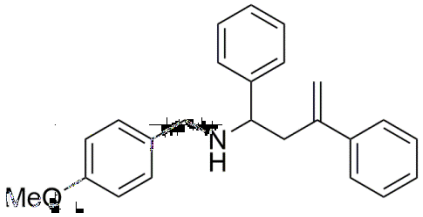
Characterisation data for the synthesised intermediates and fused tricyclic compounds:

***N*-benzyl-1,3-diphenylbut-3-en-1-amine (140a)**



General procedure (**e**) was used, *N*-benzyl-1-phenylmethanimine (1 gm, 5.1 mmol), pale yellow oil, 2.2 gm, 72% yield. IR 3060, 3023, 3024, 2980, 2920, 1630, 1363. ^{1}H NMR (δ; 300 MHz, $CDCl_3$) ; 1.78 (1H, s, NH), 2.76 (1H, ddd, *J* 14.2, 9.3, 0.6, CHC*H*H), 2.89 (1H, ddd, J 14.1, 4.7, 1.1,CHCH*H*), 3.74 (ABq, 2H, J_{AB}8.7, J_{AB}8.7, ArC*HH*), 3.68 (1H, dd, *J* 9.4, *J*4.7, C*H*CHH), 5.07 (1H, s, olefine CH*H*), 5.29 (1H, s, olefine C*H*H), 7.07-7.39 (15H, m, ArC*H*).^{13}C NMR (δ; 100MHz , $CDCl_3$); 45.3 (CH_2), 51.5 (CH_2), 60.1 (CH), 115.4 (C), 126.4 (ArCH), 126.7 (ArCH), 127.1 (ArCH), 127.3 (ArCH), 127.6 (ArCH), 128.0 (ArCH), 128.3 (ArCH), 128.5 (ArCH), 142.2 (ArC), 146.2 (ArC), 147.3 (ArC). HRMS [M+H$^+$] calculated for formula $C_{23}H_{24}N^+$; 314.1909; found 314.19112.

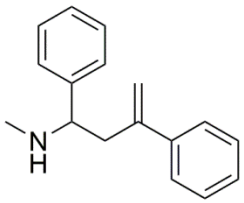
***N*-(4-methoxybenzyl)-1,3-diphenylbut-3-en-1-amine (140b)**



General procedure (**e**) was used, *N*-(4-methoxybenzyl)-1-phenylmethanimine (1 gm, 4.4 mmol), yellow oil, 1.7 gm, 82% yield. IR 3066, 3026, 3028, 2960, 2932, 2866, 2799, 1646, 1602, 1454, 1375. ^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.80 (1H, s, NH), 2.69-2.93 (2H, m, CHC*HH*), 3.41 (ABq, 2H, J_{AB}13.1, J_{AB}13.1, ArC*HH*), 3.66 (1H, dd, *J*9.2, *J* 4.8, C*H*CHH), 3.76 (3H, s, OCH_3), 5.06 (1H, s, olefine C*H*H), 5.28 (1H, s, olefine CH*H*), 6.75 (2H, d, *J* 8.6, ArC*H*), 7.02 (2H, dd, *J* 8.6, ArC*H*), 7.22-7.45 (10H, m, ArC*H*).^{13}C NMR (δ; 100MHz , $CDCl_3$); 45.2 (CH_2), 50.9 (CH_3), 55.3 (CH), 59.8 (CH), 113.7 (2ArCH), 115.5 (C), 126.1 (ArCH), 126.4

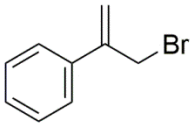
(ArCH), 127.1 (ArCH), 127.3 (ArCH), 127.6 (ArCH), 128.0 (ArCH), 128.4 (ArCH), 128.6 (ArCH), 129.1 (ArCH), 132.6 (ArC), 140.5 (ArC), 144.1 (ArC), 145.7 (C), 158.4 (ArCOMe). HRMS [M+H$^+$] calculated for formula $C_{24}H_{26}NO^+$; 344.2014; found 344.2003.

_N_-methyl-1,3-diphenylbut-3-en-1-amine (140c)



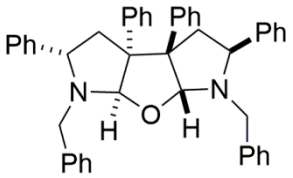
General procedure (**e**) was used, *N*-methyl-1-phenylmethanimine (1 gm, 8.4 mmol), yellow oil, 1.9 gm, 91% yield. IR 3045, 3024, , 2968, 2930, 2854, 2707, 1640, 1618.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 2.16 (3H, s, C*H*$_3$), 2.83 (2H, m, CHC*HH*), 3.50 (1H, dd, *J* 8.6, *J* 5.3, C*H*CHH), 5.06 (1H, s, olefine C*H*H), 5.30 (1H, s, olefine CH*H*), 7.19-7.44 (10H, m, ArC*H*).^{13}C NMR (δ; 100MHz , $CDCl_3$); 34.6 (CH_3), 44.9 (CH_2), 63.0 (CH), 115.3 (CH_2), 126.3 (ArCH), 127.0 (ArCH), 127.2 (ArCH), 127.6 (ArCH), 128.3 (ArCH), 128.4 (ArCH), 140.5 (ArC), 128.5 (ArCH), 143.7 (ArC), 145.6 (C). HRMS [M+H$^+$] calculated for formula $C_{17}H_{20}N^+$; 238.1596; found 238.1593.

3-bromoprop-1-en-2-yl)benzene (142)



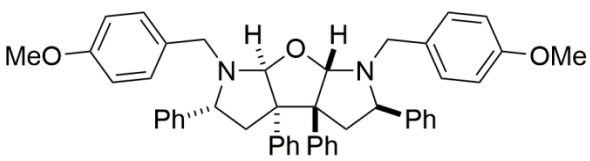
The literature procedure was used, [73] yellow oil, 2 gm, 62% yield. ^{1}H NMR (δ; 300 MHz, $CDCl_3$); 4.38 (2H, s, C*H*$_2$), 5.52 (2H, d, *J* 20.8, olefine C*H*$_2$), 7.29-7.41 (3H, m, ArC*H*), 7.47-7.53 (2H, m, ArC*H*). ^{13}C NMR (δ; 100 MHz, $CDCl_3$); 34.2 (CH_2), 117.2 (=CH_2), 126.1 (2ArCH), 128.3 (ArCH), 128.5 (2ArCH), 137.6 (ArC), 144.3 (C). MS [m/z] calculated for formula C_9H_9Br; 197.0; found 197.0. The spectral data was comparable with literature.[73]

***N*,*N*-dibenzyl-2,3a,3b,5-tetraphenyldecahydrofuro[2,3-b:5,4-b']dipyrrole (143a)**



General procedure (**j**) was used. *N*-Benzyl-1,3-diphenylbut-3-en-1-amine **10a** (500 mg, 1.5 mmol), iodine (1. 21 gm, 4.78 mmol), sodium bicarbonate (4.67 gm, 7.97 mmol), column chromatography ethyl acetate/ hexane 10%, Rf= 0.7, crystallisation with ethyl acetate/ petroleum ether 10%, colourless crystal (mpt 190-192 ˚C), 266 mg 48% yield. IR 3060, 2850, 1601, 1493, 1454, 1365, 1142.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.85 (2H, dd, J_{ab}13.8, J_{ac}7.6, CHC*H*H), 2.67 (2H, dd, J_{ab}13.8, J_{bc}8.4, CHCH*H*), 3.60 (ABq, 2H, J_{AB}12.9, ArC*H*H),3.87 (ABq, 2H, J_{AB}12.9, ArC*HH*), 3.99 (2H, app.t, *J* 8.0, C*H*CHH), 5.61 (2H, s, OC*H*), 7.06-7.48 (30H, overlapping m, ArC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 47.4 (CH_2), 50.8 (CH_2), 61.8 (C), 65.9 (CH), 98.0 (CH), 126.3 (ArCH), 126.9 (ArCH), 127.0 (ArCH), 127.5 (ArCH), 128.2 (ArCH), 128.3 (ArCH), 128.9 (ArCH), 129.1 (ArCH), 139.4 (ArC), 143.3 (ArC), 144.2 (ArC). HRMS $[M+H]^+$calculated for formula $C_{46}H_{43}N_2O^+$639.3360; found 639.3375.

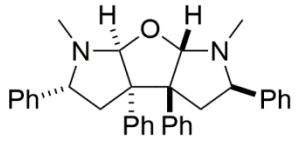
***N*, *N*-bis(4-methoxybenzyl)-2,3a,3b,5-tetraphenyldecahydrofuro[2,3-b:5,4-b']dipyrrole (143b)**



General procedure (**j**) was used. *N*-(4-Methoxybenzyl)-1,3-diphenylbut-3-en-1-amine **10b** (310 mg, 0.90 mmol), iodine (687 mg, 2.70 mmol), sodium bicarbonate (379 mg, 4.50 mmol), column chromatography ethyl acetate/ hexane 10%, Rf= 0.7, crystallisation with ethyl acetate/ petroleum ether 10%, colourless crystal (mpt 215-216 ˚C), 120 mg, 20% yield. IR 2858, 1614, 1512.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.84 (2H, dd,J_{ab}13.8, J_{ac}7.6, CHC*H*H), 2.67 (2H, dd,J_{ab}13.8, J_{bc}8.4, CHCH*H*), 3.53 (ABq, 2H, J_{AB}12.6,ArC*H*H), 3.66 (ABq, 2H, J_{AB}12.6, ArCH*H*), 3.87 (6H, s, OCH_3), 3.97 (2H, app.t, *J* 8.0,

C*H*CHH), 5.58 (2H, s, OC*H*), 6.93 (4H, d, *J* 8.6, ArC*H*), 7.06-7.28 (20H, overlapping m, ArC*H*), 7.37 (4H, d, *J* 8.5, ArC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 47.5 (CH_2), 50.2 (CH_2), 55.3 (CH_3), 61.7 (C), 65.8 (CH), 98.0 (CH), 113.6 (ArCH), 126.2 (ArCH), 126.9 (ArCH), 127.5 (ArCH), 128.3 (ArCH), 128.9 (ArCH), 130.2 (ArCH), 131.4(ArC), 143.4 (ArC), 144.2 (ArC), 158.6 (ArC). HRMS $[M+H]^+$calculated for the formula $C_{48}H_{47}N_2O_3^+$ 699.3587; found 699.3591.

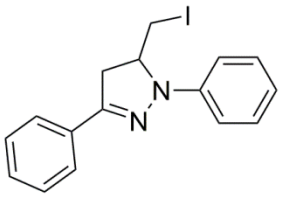
_N_-1,6-dimethyl-2,3a,3b,5-tetraphenyldecahydrofuro[2,3-b:5,4-b']dipyrrole (143c)



General procedure (**j**) was used. *N*-Methyl-1,3-diphenylbut-3-en-1-amine **10c** (265 mg, 1.12 mmol), iodine (850 mg, 3.34 mmol), sodium bicarbonate (468 mg, 5.58 mmol), ethyl acetate/ hexane 10%, Rf= 0.7, crystallisation with ethyl acetate/ petroleum ether 10%, colorless crystal (mpt 195-196 ˚C), 120 mg 22% yield. IR 3050, 2800, 1602, 1491.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.93 (2H, dd, J_{ab}13.8, J_{ac}7.6, CHC*H*H), 2.44 (6H, s, NCH_3), 2.82 (2H, dd, J_{ab}13.8, J_{bc}8.5, CHCH*H*), 3.97 (2H, app.t, *J* 8.0, C*H*CHH), 5.82 (2H, s, OC*H*), 7.04-7.36 (20H, m, ArC*H*).^{13}C NMR (δ; 100 MHz, $CDCl_3$); 34.6 (CH_3), 47.7 (CH_2), 62.0 (PhC), 66.8 (CH), 103.1 (CH), 126.3 (ArCH), 127.0 (ArCH), 127.5 (ArCH), 127.6 (ArCH), 128.2 (ArCH), 129.0 (ArCH), 143.0 (ArC), 144.0 (ArC). HRMS $[M+H]^+$calculated for the formula $C_{34}H_{35}N_2O^+$ 487.2728; found 487.2749.

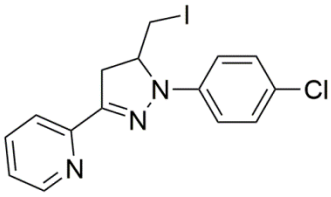
Characterisation data for the synthesised 2-pyrazoline compounds:

5-iodo-1,3-diphenylhexahydropyridazine (157a)



General procedure (**k**) was used. *N*-phenyl-2-(1-phenylbut-3-en-1-yl)hydrazine (400 mg, 1.67 mmol), iodine (1270 mg, 5.00 mmol), sodium bicarbonate (705 mg, 8.40 mmol), dark green oil (gum). IR 2922, 2852, 1686, 1597 (s), 1499, 1458(m), 1366 (m), 766.^{1}H NMR (δ; 300 MHz, $CDCl_3$) ; 3.06 (1H, app.t, *J* 10.2, C*H*HCH), 3.15 (1H, dd, J_{ab}17.3, J_{ac}4.2, CH*H*CH), 3.45 (1H, dd, *J* 11.8, 5.6, CHC*H*H), 3.51 (1H, dd, *J* 9.9, 2.7, CHCH*H*), 4.66 (1H, tdd, *J* 10.7, 4.2, 2.7, CHHC*H*CHH), 6.80-6.97 (2H, m, ArC*H*), 7.66-7.81 (1H, m, ArC*H*),^{13}C NMR (δ; 100MHz, $CDCl_3$);23.2 (CH_2), 37.5 (CH_2), 60.0 (CH), 113.2 (2ArCH), 126.7 (ArCH), 127.9 (2ArCH), 128.0 (2ArCH), 128.1 (2ArCH), 128.2 (ArCH),133.0 (ArC=N), 140.2 (ArC), 141.9 (ArC).HRMS $[M+H]^+$ calculated for the formula $C_{16}H_{16}IN_2^+$: 363.0364; found 363.00358.

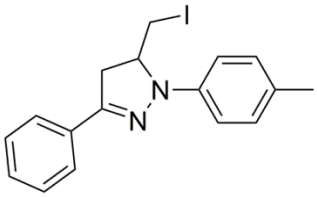
2-(1-(4-chlorophenyl)-5-(iodomethyl)-4,5-dihydro-1H-pyrazol-3-yl)pyridine (157f)



General procedure (**k**) was used. 2-(1-(2-(4-chlorophenyl)hydrazinyl)but-3-en-1-yl)pyridine (671 mg, 2.45 mmol), iodine (1860 mg, 7.35 mmol), sodium bicarbonate (1029 mg, 12.20 mmol), yellow brown oil. IR 2928, 1686, 1597(S), 1499, 1456(m), 1366(m).^{1}H NMR (δ; 300 MHz, $CDCl_3$); 312 (1H, app.t, *J* 10.0, CHC*H*H), 3.39 (1H, dd, J_{ab}18.3, J_{bc} 4.5 CHCH*H*), 3.47 (1H, dd, *J* 10.1, 2.5, C*H*HCH), 3.62 (1H, dd, J_{ab}18.3, J_{ac}11.2, CH*H*CH), 4.63-4.75 (1H, m, CHHC*H*CHH), 7.05-7.14 (2H, m, ArC*H*), 7.15-7.32 (3H, m, ArC*H*), 7.66-7.72 (2H, m, PyrC*H*), 8.05 (1H, dt, *J* 8.1, 1.0, PyrC*H*), 8.59 (1H, ddd, *J* 4.9, 1.7, 0.9, PyrC*H*).^{13}C NMR (δ; 100MHz,

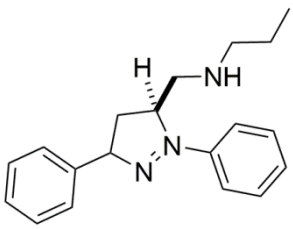
$CDCl_3$); 7.6 (CH_2), 39.6 (CH_2), 61.0 (CH), 114.5 (2ArCH), 120.7 (ArCH), 123.1 (ArCH), 124.9 (ArCCl), 129.4 (2ArCH), 136.1 (PyrCH), 141.6 (ArC), 148.8 (ArC=N), 149.2 (PyrCH), 151.5 (PyrC). HRMS $[M+H]^+$ calculated for the formula $C_{15}H_{14}ICIN_3^+$: 397.9921; found 397.9906.

5-(iodomethyl)-3-phenyl-1-(p-tolyl)-4,5-dihydro-1H-pyrazole (157e)



General procedure (**k**) was used. 1-(1-phenylbut-3-en-1-yl)-2-(p-tolyl)hydrazine (550 mg, 2.20 mmol), iodine (1680 mg, 6.60 mmol), sodium bicarbonate (920 mg, 10.90 mmol), pale yellow oil. IR 2922, 2852, 1686, 1597(s), 1499, 1458(m), 1366(m), 766.^{1}H NMR (δ; 300 MHz, $CDCl_3$); 2.29 (1H, s, C*H*$_3$), 3.06 (1H, app.t, *J* 10.2, C*H*HCH), 3.14 (1H, dd, *J* 17.3, 4.5, CH*H*CH), 3.49 (1H, ddd, *J* 20.1, 10.8, 6.8, CHC*HH*), 4.63 (1H, tdd, *J* 10.7, 4.4, 2.7, CHHC*H*CHH), 7.00-7.15 (2H, m, ArC*H*), 7.30-7.44 (5H, m, ArCH), 7.68-7.76 (2H, m, ArCH).^{13}C NMR (δ; 100MHz, $CDCl_3$); 8.9 (CH_2), 20.6 (CH_3), 39.7 (CH_2), 61.4 (CH), 113.5 (2ArCH), 125.8 (2ArCH), 128.8 (2ArCH), 128.9 (2ArCH), 129 ($ArCCH_3$), 130.0 (2ArCH), 132.6 (ArC), 141.4 (ArC), 146.6 (ArC=N). HRMS $[M+H]^+$ calculated for the formula $C_{17}H_{18}IN_2^+$: 377.0515; found 377.0503.

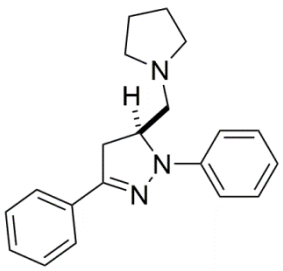
2,6-Diphenyl-*N*-propylhexahydropyridazin-4-amine (158a)



General procedure (**l**) was used. *N*-phenyl-2-(1-phenylbut-3-en-1-yl)hydrazine (400 mg, 1.67 mmol), iodine (1270 mg, 5.00 mmol), sodium bicarbonate (705 mg, 8.40 mmol). Column chromatography 60% ethyl acetate Rf= 0.2, yield was calculated over two steps, yellow oil, 0.15 gm 80% yield. IR 3450, 3026, 2924, 2853, 1596(S), 1493, 1393(m), 1129(m).^{1}H NMR (δ; 300 MHz, $CDCl_3$); 0.87 (3H, t, *J* 7.4, CH_3), 1.38-1.52 (2H, m, C*H*$_2$CH$_3$), 2.58 (2H, dd, *J* 8.5,

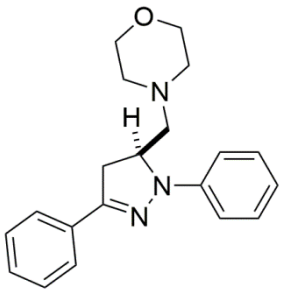
6.0, NHCH_2), 2.78 (1H, dd, J_{ab}12.0, J_{ac}7.3, C*H*HCH), 2.94 (1H, dd, J_{ab} *J* 12.0, J_{bc}3.4, CH*H*CH), 3.27 (1H, dd, *J* 16.9, 5.6, CHC*H*H), 3.41 (1H, dd, *J* 16.9, 11.2, CHCH*H*), 4.46 (1H, m, CHHC*H*CHH), 6.83 (1H, dt, *J* 7.4, 1.2, ArCH), 7.15-7.40 (7H, m, ArC*H*), 7.69-7.78 (2H, dd, *J* 8.3, 1.4, ArC*H*).^{13}C NMR (δ; 100MHz, $CDCl_3$); 11.7 (CH_3), 23.2 (CH_2), 37.5 (CH_2), 50.9 (CH_2), 52.0 (CH_2), 60.1 (CH), 113.3 (2ArCH), 119.1 (ArCH), 125.8 (2ArCH), 128.5 (3ArCH), 129.2 (2ArCH), 133.0 (ArC=N), 144.9 (ArCH), 148.4 (ArCH). HRMS $[M+H]^+$ calculated for the formula $C_{19}H_{24}N_3^+$: 294.1967; found 294.1970.

1,3-Diphenyl-5-(pyrrolidin-1-ylmethyl)-4,5-dihydro-1H-pyrazole (158b)



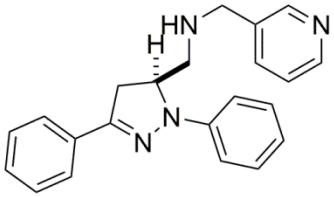
General procedure (**I**) was used. *N*-phenyl-2-(1-phenylbut-3-en-1-yl)hydrazine (200 mg, 0.84 mmol), iodine (640 mg, 2.50 mmol), sodium bicarbonate (350 mg, 4.20 mmol). Column chromatography 80% ethyl acetate/hexane Rf= 0.5, yield was calculated over two steps, yellow oil, 0.16 gm 63% yield. IR 3350, 2921, 2860, 1592(S), 1487, 1392(m), 1128(m).^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.75 (4H, dt, *J* 7.4, 6.8, 2x CH_2), 2.35 (2H, dd, *J* 11.7, 8.7, C*HH*CH), 2.56-2.85 (4H, m, 2x CH_2), 3.55 (2H, dd, *J* 12.3, 7.7, CH_2N),4.50 (1H, m, CHHC*H*CHH), 6.85 (1H, dd, *J* 10.2, 4.2, ArC*H*), 7.05-7.45 (7H, m, ArCH), 7.70 (1H, t, *J* 8.4, ArCH), 7.87 (1H, dd, *J* 6.8, 1.7, ArC*H*).^{13}C NMR (δ; 100MHz, $CDCl_3$); 23.6 ($2CH_2$), 37.9 (CH_2), 54.7 ($2CH_2$), 57.3 (CH_2), 59.0 (CH), 113.2 (2ArCH), 118.8 (ArCH), 125.0 (ArCH), 125.8 (2ArCH), 128.5 (2ArCH), 128.6 (ArCH), 129.2 (ArCH), 133.1 (ArC), 144.5 (ArC), 148.1 (ArC=N). HRMS $[M+H]^+$ calculated for the formula $C_{20}H_{24}N_3^+$: 306.1970; found 306.1956.

4-((1,3-diphenyl-4,5-dihydro-1H-pyrazol-5-yl)methyl)morpholine (158c)



General procedure (**l**) was used. *N*-phenyl-2-(1-phenylbut-3-en-1-yl)hydrazine (294 mg, 1.24 mmol), iodine (900 mg, 3.70 mmol), sodium bicarbonate (500 mg, 6.15 mmol). Column chromatography 30% ethyl acetate/ hexane Rf= 0.25, yellow solid (mpt 98-99 $^{\circ}$C), yield over two steps= 0.26 gm 80% yield. IR 3382, 2925, 1596(m), 1499, 1455(m), 1123(m). ^{1}H NMR (δ; 300 MHz, $CDCl_3$); 2.36 (1H, dd, *J*12.7, 9.3, C*H*HN), 2.41-2.52 (2H, m, CH_2), 2.55-2.67 (2H, m, CH_2), 2.73 (1H, dd, *J* 12.7, 3.5, CH*H*N), 3.37 (2H, dd, *J* 7.8, 3.5, C*HH*CH), 3.66-3.79 (4H, m, 2x CH_2), 3.45-4.55 (1H, m, CHHC*H*CHH), 6.81-6.86 (1H, m, ArC*H*), 7.10-7.47 (7H, m, ArC*H*), 7.76 (2H, dd, *J* 8.3, 1.4, ArC*H*).^{13}C NMR (δ; 100MHz, $CDCl_3$); 37.7 (CH_2), 54.2 ($2CH_2$), 57.6 (CH), 59.5 (CH_2), 67.0 ($2CH_2$), 113.2 (2ArCH), 119.0 (ArCH), 125.8 (2ArCH), 128.6 (3ArCH), 129.2 (2ArCH), 133.1 (ArC=N), 144.5 (ArC), 148.1 (ArC). HRMS $[M+H]^+$ calculated for the formula $C_{20}H_{24}N_3O^+$: 322.1912; found 322.1919.

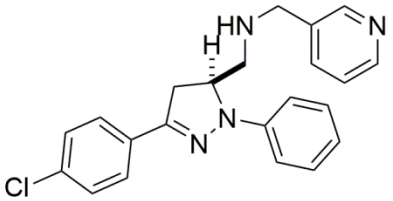
1-(1,3-diphenyl-4,5-dihydro-1H-pyrazol-5-yl)-N-(pyridin-3-ylmethyl)methanamine (158d)



General procedure (**l**) was used. *N*-phenyl-2-(1-phenylbut-3-en-1-yl)hydrazine (588 mg, 2.47 mmol), iodine (1880 mg, 7.40 mmol), sodium bicarbonate (1036 mg, 12.30 mmol). Column chromatography 100% ethyl acetate Rf=0.25, yellow oil (Gum), yield over two steps= 0.28 gm 75% yield. IR 3325, 2921, 1598(s), 1491, 1398(m), 1125(m). ^{1}H NMR (δ; 300 MHz, $CDCl_3$); 2.79 (1H, dd, *J* 12.1, 3.2, C*H*HNH), 2.93 (1H, d, *J* 12.1, 5.9, CH*H*NH), 3.2-3.42 (2H, m, ArCH_2), 3.66-3.81 (2H, m, PyrCH_2), 4.39 (1H, m, CHHC*H*CHH), 6.78-6.88 (H, m, ArC*H*), 7.12-7.20

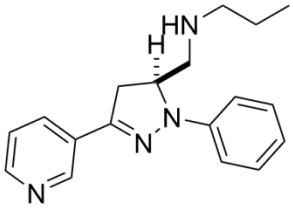
(2H, m, ArC*H*), 7.21-7.41 (7H, m, ArC*H*), 7.48-7.59 (1H, m, PyrC*H*), 7.65-7.77 (2H, m, ArC*H*), 8.45 (1H, dd, *J* 4.8, 1.6, ArC*H*), 8.49 (1H, d, *J* 1.7, PyrC*H*).^{13}C NMR (δ; 100MHz, $CDCl_3$); 37.3 (CH_2), 50.2 (CH_2), 51.2 (CH_2), 59.9 (CH), 113.3 (2ArCH), 119.2 (ArCH), 123.4 (PyrCH), 125.8 (2ArCH), 128.6 (2ArCH), 128.7 (2ArCH), 129.2 (2ArCH), 132.8 (ArC=N), 135.6 (ArC), 135.7 (PyrCH), 144.9 (PyrC), 148.5 (PyrCH), 148.6 (ArC), 149.7 (PyrCH). HRMS $[M+H]^+$ calculated for the formula $C_{22}H_{23}N_4^+$: 343.1920; found 343.1923.

1-(3-(4-chlorophenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-5-yl)-N-(pyridin-3-ylmethyl)methanamine (158e)



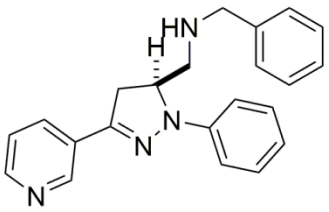
General procedure (**I**) was used. 1-(1-(4-chlorophenyl)but-3-en-1-yl)-2-phenylhydrazine (382 mg, 1.40 mmol), iodine (1066 mg, 4.20 mmol), sodium bicarbonate (580 mg, 7.00 mmol). Column chromatography 100% ethyl acetate Rf=0.2, yellow oil, 0.182 gm 78% yield. IR 2923, 1597(s), 1491(s), 1389, 1127(m), 828(m). ^{1}H NMR (δ; 300 MHz, $CDCl_3$); 2.80 (1H, dd, *J* 12.1, 3.0, C*H*HNH), 2.96 (1H, dd, *J* 12.1, 5.8, CH*H*NH), 3.20-3.41 (2H, m, C*HH*CH), 3.68-3.94 (2H, m, PyrCH_2), 4.42-4.52 (1H, m, CHHC*H*CHH), 6.82-6.88 (1H, m, ArC*H*), 7.13-7.21 (3H, m, ArC*H*), 7.23-7.36 (4H, m, ArC*H*), 7.55 (1H, dt, *J* 7.8, 1.8, PyrC*H*), 7.60-7.66 (2H, m, ArC*H*), 8.46 (1H, dd, *J* 4.8, 1.6, PyrC*H*), 8.50 (1H, d, *J* 2.0, PyrC*H*).^{13}C NMR (δ; 100MHz, $CDCl_3$); 37.1 (CH_2), 50.0 (CH_2), 51.1 (CH_2), 60.0 (CH), 113.3 (2ArCH), 119.2 (ArCH), 123.4 (PyrCH), 128.7 (2ArCH), 128.9 (2ArCH), 129.3 (2ArCH), 130.0 (ArC=N), 134.3 (ArC), 135.4 (ArC), 135.7 (PyrCH), 144.5 (ArC), 147.4 (ArC), 148.5 (PyrCH), 149.6 (PyrCH). HRMS $[M+H]^+$ calculated for the formula $C_{22}H_{22}N_4Cl^+$: 377.1533; found 377.1526.

***N*-((1-phenyl-3-(pyridin-3-yl)-4,5-dihydro-1H-pyrazol-5-yl)methyl)propan-1-amine (158f)**



General procedure (**l**) was used.3-(1-(2-phenylhydrazinyl)but-3-en-1-yl)pyridine (583 mg, 2.46 mmol), iodine (1850 mg, 7.30 mmol), sodium bicarbonate (1020 mg, 12.18 mmol). Column chromatography 5% methanol/dichloromethane Rf= 0.5, yellow oil, yield over two steps= 0.20 gm 61% yield. IR 3285, 2925, 1597(s), 1499, 1389(m), 1125(m).^{1}H NMR (δ; 300 MHz, $CDCl_3$) ; 0.88 (3H, t, *J* 7.4, CH_3), 1.39-1.53 (2H, m, C*H*$_2$CH$_3$), 2.59(2H, dd, *J* 8.5, 6.0, NHC*H*$_2$), 2.84 (1H, dd, *J* 12.2, 7.0, C*H*HNH), 2.95 (1H, dd, *J* 12.1, 3.3, CH*H*NH), 3.33 (1H, dd, *J* 17.0, 5.9, C*H*HCH), 3.43 (1H, dd, *J* 16.9, 11.1, CH*H*CH), 4.47-4.62 (1H, m, CHHC*H*CHH), 6.87 (1H, dt, *J* 7.4, 1.2, ArC*H*), 6.84-6.90 (5H, m, ArC*H*), 8.04-8.10 (1H, m, PyrC*H*), 8.53 (1H, dd, *J* 4.8,1.6, PyrC*H*), 8.87 (1H, *J* 2.2, 0.7, PyrC*H*).^{13}C NMR (δ; 100MHz, $CDCl_3$); 11.6 (CH_3), 22.9 (CH_2), 37.0 (CH_2), 50.5 (CH_2), 51.9 (CH_2), 59.9 (CH), 113.4 (2ArCH), 119.6 (ArCH), 123.4 (ArCH), 128.9 (PyrC), 129.3 (2ArCH), 132.6 (ArCH), 144.3 (ArC=N), 145.4 (ArC), 147.1 (PyCH), 149.3 (PyrCH).HRMS $[M+H]^+$ calculated for the formula $C_{18}H_{23}N_4^+$: 295.1923; found 295.1912.

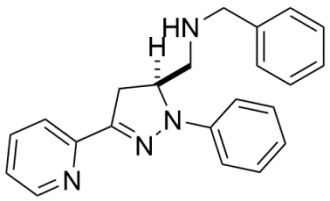
***N*-benzyl-1-(1-phenyl-3-(pyridin-3-yl)-4,5-dihydro-1H-pyrazol-5-yl)methanamine (158g)**



General procedure (**l**) was used. 3-(1-(2-phenylhydrazinyl)but-3-en-1-yl)pyridine (583 mg, 2.46 mmol), iodine (1850 mg, 7.30 mmol), sodium bicarbonate (1020 mg, 12.18 mmol), column chromatography 100% ethyl acetate. Rf= 0.35, yellow oil, yield over two steps= 0.20 gm 71% yield. IR 3340, 2953, 1591(s), 1489, 1391(m), 1123(m).^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.61 (1H, dd, *J* 14.8, 7.4, C*H*HNH), 2.87 (1H, dd, *J* 10.4, 4.7, CH*H*NH), 3.32 (2H, dd, *J* 8.6, 6.0,

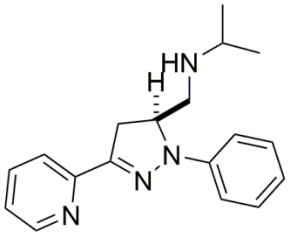
C*HH*CH), 3.76 (2H, d, *J* 2.0, ArCH_2), 4.39-4.55 (1H, m, CHHC*H*CHH), 6.85 (1H, t, *J* 7.2, ArC*H*), 7.11-7.33 (7H, m, ArC*H*), 8.04 (1H, dt, *J* 8.0, 1.9, PyrC*H*), 8.52 (1H, dd, *J* 4.8, 1.6, PyrC*H*), 8.85 (1H, d, *J* 1.7, PyrC*H*).^{13}C NMR (δ; 100MHz, $CDCl_3$); 36.8 (CH_2), 49.9 (CH_2), 53.8 (CH_2), 60.1 (CH), 113.4 (2ArCH), 119.6 (ArCH), 123.4 (ArCH), 127.1 (ArCH), 128.1 (2ArCH), 128.4 (2ArCH), 128.6 (2ArCH), 129.0 (PyrC), 129.3 (2ArCH), 132.6 (PyrCH), 140.1 (ArC=N), 144.3 (ArC), 145.5 (ArC), 147.1 (PyrCH), 149.3 (PyrCH). HRMS $[M+H]^+$ calculated for the formula $C_{22}H_{23}N_4^+$: 343.1923; found 343.1926.

_N_-benzyl-1-(1-phenyl-3-(pyridin-2-yl)-4,5-dihydro-1H-pyrazol-5-yl)methanamine (158h)



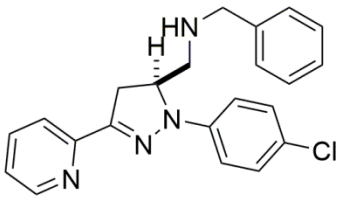
General procedure (**I**) was used. 2-(1-(2-phenylhydrazinyl)but-3-en-1-yl)pyridine (305 mg, 1.25 mmol), iodine (970 mg, 3.80 mmol), sodium bicarbonate (535 mg, 6.35 mmol), column chromatography 10% Methanol/ dichloromethane, Rf= 0.35, yellow brown oil, yield over two steps= 0.28 gm 65% yield. IR 3281, 2923, 1597(m), 1499, 1389(m), 1126(m).^{1}H NMR (δ; 300 MHz, $CDCl_3$); 2.89 (1H, t, *J* 6.3, C*H*HNH), 3.43-3.56 (2H, m, C*HH*CH), 3.78 (2H, s, ArCH_2), 4.46-4.58 (1H, m, CHHC*H*CHH), 6.85 (1H, tt, *J* 13.7, 6.2, ArC*H*), 7.09-7.33 (7H, m, ArCH), 7.60-7.68 (1H, m, PyrCH), 8.05 (1H, dt, *J* 8.1, 0.9, PyrCH), 8.51-8.64 (1H, m, PyrCH). ^{13}C NMR (δ; 100MHz, $CDCl_3$); 32.2 (CH_2), 50.1 (CH_2), 53.9 (CH_2), 60.3 (CH), 113.5 (2ArCH), 119.6 (ArCH), 120.6 (PyrCH), 122.6 (PyrCH), 127.0 (ArCH), 128.0 (2ArCH), 128.3 (2ArCH), 129.2 (2ArCH), 135.9 (PyrCH), 140.2 (ArC=N), 144.2 (ArC), 149.1 (PyrCH), 149.5 (ArC), 152.3 (PyrC). HRMS $[M+H]^+$ calculated for the formula $C_{22}H_{23}N_4^+$: 343.1923; found 343.1927.

***N*-((1-phenyl-3-(pyridin-2-yl)-4,5-dihydro-1H-pyrazol-5-yl)methyl)propan-2-amine (158i)**



General procedure (**l**) was used. 2-(1-(2-phenylhydrazinyl)but-3-en-1-yl)pyridine (305 mg, 1.25 mmol), iodine (970 mg, 3.80 mmol), sodium bicarbonate (535 mg, 6.35 mmol), column chromatography 100% ethyl acetate Rf= 0.5, yellow oil, yield over two steps= 0.260 gm 70% yield. IR 3300, 2962, 1597, 1561(s), 1500, 1390(m), 1128(m).^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.03 (6H, dd, *J* 6.2, 3.3, $2CH_3$), 2.66-2.84 (2H, m, C*HH*NH), 2.99 (1H, dd, *J* 15.9, 8.0, NHC*H*), 3.41 (1H, dd, *J* 17.7, 5.7, CH*H*CH), 3.55 (1H, dd, *J* 17.7, 11.4, CH*H*CH), 4.48-4.59 (1H, m, CHHC*H*CHH), 6.80-6.92 (1H, m, ArC*H*), 7.12-7.35 (6H, m, ArC*H*), 7.66 (1H, dt, *J* 12.8, 6.2, PyrC*H*), 8.03-8.10 (1H, m, PyrC*H*), 8.49-8.61 (1H, m, PyrC*H*).^{13}C NMR (δ; 100MHz, $CDCl_3$); 23.0 (CH_3), 23.1 (CH_3), 37.1 (CH_2), 48.2 (CH_2), 48.9 (CH), 60.5 (CH), 113.5 (2ArCH), 119.6 (ArCH), 120.6 (PyrCH), 122.6 (2ArCH), 129.2 (2ArCH), 135.9 (PyrCH), 144.2 (ArC=N), 149.1 (PyrCH), 149.2 (ArC), 152.3 (ArC). HRMS $[M+H]^+$ calculated for the formula $C_{18}H_{23}N_4^+$: 295.1923; found 295.1917.

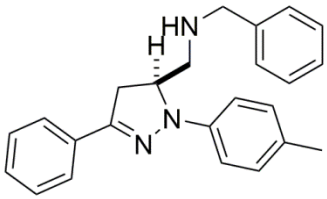
***N*-benzyl-1-(1-(4-chlorophenyl)-3-(pyridin-2-yl)-4,5-dihydro-1H-pyrazol-5-yl)methanamine (158j)**



General procedure (**l**) was used. 2-(1-(2-(4-chlorophenyl) hydrazinyl)but-3-en-1-yl)pyridine (335 mg, 1.22 mmol), iodine (930 mg, 3.67 mmol), sodium bicarbonate (500 mg, 6.10 mmol). Column chromatography 100% ethyl acetate Rf=0.45, yellow brown oil, yield over two steps= 0.230 gm 86% yield. IR 3281, 2923, 1597(m), 1499, 1389(m), 1126(m).^{1}H NMR (δ; 300 MHz, $CDCl_3$); 2.82 (2H, t, *J* 6.2, C*HH*NH), 3.49 (2H, dd, *J* 8.5, 5.6, C*HH*CH), 3.76 (2H, s, ArCH_2), 4.40-4.50 (1H, m, CHHC*H*CHH), 7.04-7.11 (2H, m, ArC*H*), 7.14-7.33 (8H, m, ArC*H*), 7.60-7.67 (2H, m,

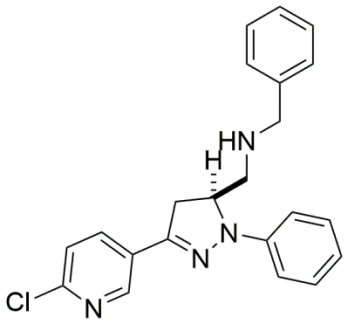
PyrC*H*), 8.02 (1H, dt, *J* 8.0, 0.9, PyrC*H*), 8.55 (1H, ddd, *J* 4.9, 1.7, 0.9, PyrC*H*).^{13}C NMR (δ; 100MHz, $CDCl_3$); 37.2 (CH_2), 49.8 (CH_2), 53.8 (CH_2), 60.3 (CH), 114.6 (2ArCH), 120.7 (ArCH), 122.8 (PyrCH), 124.2 (ArCCl), 127.1 (ArCH), 128.0 (2ArCH), 128.4 (2ArCH), 129.1 (2ArCH), 136.0 (PyrCH), 140.1 (ArC=N), 142.8 (ArC), 149.2 (PyrCH), 150.1 (ArC), 152.0 (PyrC). HRMS $[M+H]^+$ calculated for the formula $C_{22}H_{22}ClN_4^+$: 377.1533; found 377.1530.

_N_-benzyl-1-(3-phenyl-1-(p-tolyl)-4,5-dihydro-1H-pyrazol-5-yl)methanamine (158k)



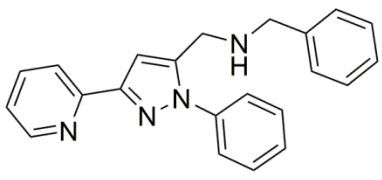
General procedure (**l**) was used. 1-(1-phenylbut-3-en-1-yl)-2-(p-tolyl) hydrazine (275 mg, 1.10 mmol), iodine (840 mg, 3.30 mmol), sodium bicarbonate (460 mg, 5.45 mmol). Column chromatography 20% ethyl acetate/hexane Rf= 0.35, yellow brown oil, yield over two steps= 0.30 gm 76% yield. IR 3450, 3026, 2924, 2853, 1596(S), 1493, 1393(m), 1129(m). ^{1}H NMR (δ; 300 MHz, $CDCl_3$); 2.28 (3H, s, CH_3), 2.85 (2H, d, *J* 4.9, C*HH*NH), 3.21-3.40 (2H, m, C*HH*CH), 3.76 (2H, s, ArCH_2), 4.33-4.44 (1H, m, CHHC*H*CHH), 7.14-7.49 (10H, m, ArCH), 7.65-7.81 (4H, m, ArCH).^{13}C NMR (δ; 100MHz, $CDCl_3$); 20.7 (CH_3), 37.4 (CH_2), 50.2 (CH_2), 53.9 (CH_2), 60.5 (CH), 113.7 (2ArCH), 125.8 (2ArCH), 127.1 (2ArCH), 128.5 (2ArCH), 128.6 (3ArCH), 129.8 (2ArCH), 133.1 ($ArCCH_3$), 133.1 (ArC), 140.3 (ArC), 142.9 (ArC), 148.2 (ArC=N). HRMS $[M+H]^+$ calculated for the formula $C_{24}H_{26}N_3^+$: 356.2127; found 356.2122.

***N*-benzyl-1-(3-(6-chloropyridin-3-yl)-1-phenyl-4,5-dihydro-1H-pyrazol-5-yl)methanamine (158l)**



General procedure (**l**) was used. 2-chloro-5-(1-(2-phenylhydrazinyl) but-3-en-1-yl)pyridine (500 mg, 1.8 mmol), iodine (139 mg, 5.47 mmol), sodium bicarbonate (767 mg, 9.13 mmol). Column chromatography 80% ethyl acetate/hexane Rf= 0.45, yellow brown oil, yield over two steps= 0.33 gm 75% yield. IR 3452, 3021, 2924, 2852, 1599(S), 1490, 1392(m), 1125(m).^{1}H NMR (δ; 300 MHz, $CDCl_3$); 2.82 (1H, dd, *J* 12.3, 3.1, C*H*HCH), 2.92 (1H, dd, *J* 12.3, 6.2, CH*H*CH), 3.29 (2H, dd, *J* 8.6, 6.7, C*HH*NH), 3.76 (2H, d, *J* 2.0, $ArCH_2$), 4.49 (1H, dtd, *J* 9.7, 6.4, 3.1, CHHC*H*CHH), 6.83-6.90 (1H, m, ArC*H*), 7.13 (2H, dd, *J* 8.7, 1.0, ArC*H*), 7.19-7.32 (7H, m, ArC*H*), 8.03 (2H, dd, *J* 8.4, 2.4, 2xPyrC*H*), 8.54 (1H, d, *J* 0.5, PyrC*H*).^{13}C NMR (δ; 100MHz, $CDCl_3$); 36.7 (CH_2), 49.7 (CH_2), 53.8 (CH_2), 60.2 (CH), 113.5 (2ArCH), 119.8 (ArCH), 124.2 (PyrCH), 127.1 (ArCH), 128.1 (2ArCH), 128.5 (2ArCH), 129.0 (2ArCH), 135.3 (PyrCH), 140.1 (ArC), 144.0 (ArC), 144.3 (ArC=N), 146.6 (PyrCH), 150.6 (PyrCCl). HRMS $[M+H]^+$ calculated for the formula $C_{22}H_{22}N_4Cl^+$: 377.1533; found 377.1538.

***N*-benzyl-1-(1-phenyl-3-(pyridin-2-yl)-1H-pyrazol-5-yl)methanamine (159)**



N-benzyl-1-(1-phenyl-3-(pyridin-2-yl)-4,5-dihydro-1H-pyrazol-5-yl)methanamine (50 mg, 0.146 mmol) was dissolved in toluene (20 mL), then DDQ (9.9 mg, 0.438 mmol) was added, the reaction mixture was refluxed for 6 hours, when the reaction completed judged by TLC then cooled to room temperature and filtered to remove the excess of DDQ. The crude product was purified by column chromatography 10% Methanol/ dichloromethane, Rf= 0.38, pale yellow oil,

yield= 0.025 gm 50% yield. IR 3280, 2923, 1660(m), 1592(m), 1490, 1125(m).^{1}H NMR (δ; 300 MHz, $CDCl_3$); 2.89 (4H, m, C*HH*NC*HH*), 5.28 (1H, s, olefin C*H*), 7.25-7.32 (5H, m, PhC*H*),), 7.35-7.40 (5H, m, PhC*H*), 7.68 (2H, m, PyrC*H*), 8.05 (1H, dt, *J* 8.1, 0.9, PyrC*H*), 8.64 (1H, d, *J*0.5, PyrC*H*). ^{13}C NMR (δ; 100MHz, $CDCl_3$); 31.2 (CH_2), 45.1 (CH_2), 110.0 (CH), 113.5 (ArCH), 113.4 (ArCH), 119.6 (ArCH), 120.6 (PyrCH), 122.6 (PyrCH), 127.0 (ArCH), 128.0 (2ArCH), 128.3 (2ArCH), 129.2 (2ArCH), 134.0 (PyrCH), 140.5 (ArC=N), 144.0 (ArC), 147.0 (C=C), 149.2 (PyrCH), 149.8 (ArC), 151.2 (PyrC). HRMS $[M+H]^+$ calculated for the formula $C_{22}H_{21}N_4^+$: 341.1920; found 341.1928.

X-Ray crystallographic data

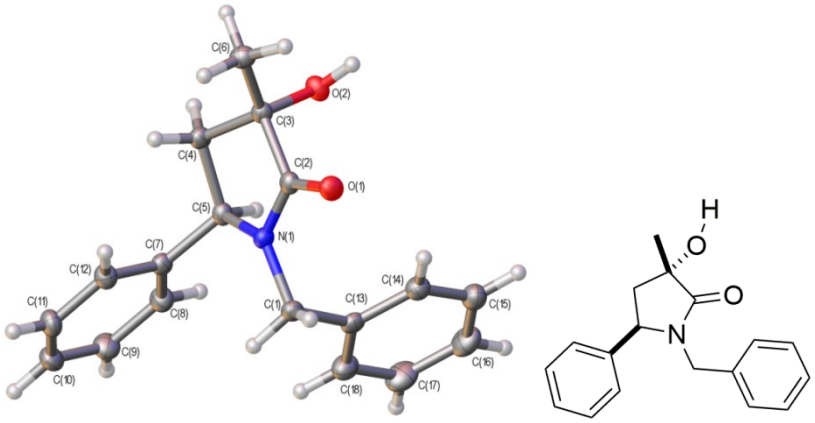


Figure 50: X-ray crystal structure of *cis*-130a with ellipsoids drawn at the 50 % probability level.

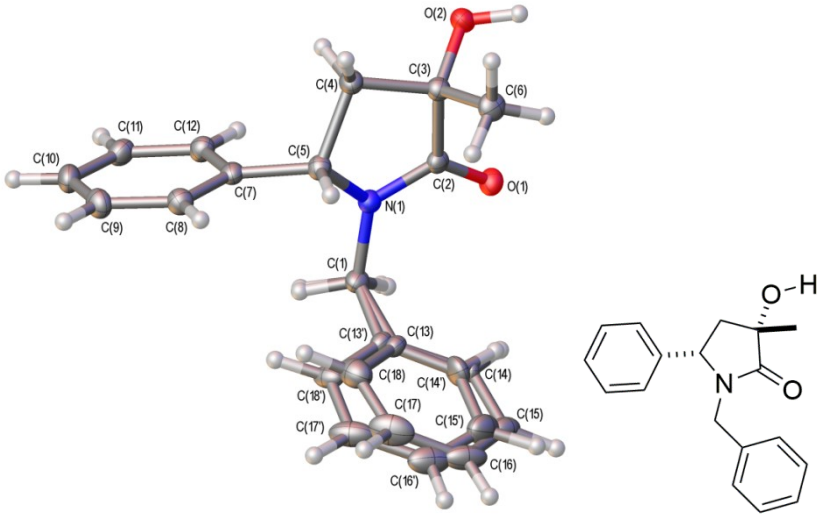


Figure 51: X-ray crystal structure of *trans*-130a with ellipsoids drawn at the 50 % probability level. The phenyl group C (13)-C (18)/C (13')-C (18') is disordered over two positions with a refined occupancy ratio of 54(1):46(1).

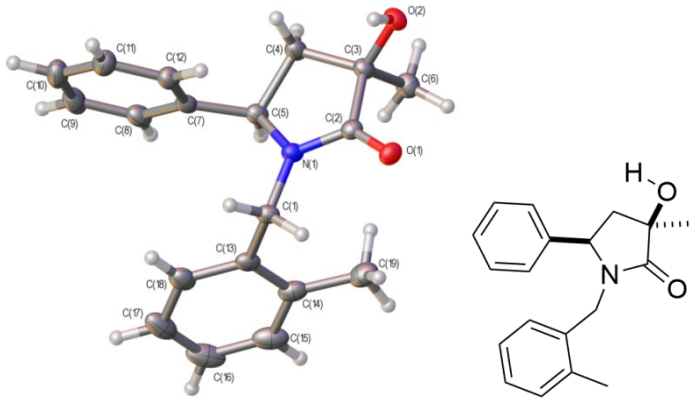


Figure 52: X-ray crystal structure of *trans*-130d with ellipsoids drawn at the 50 % probability level.

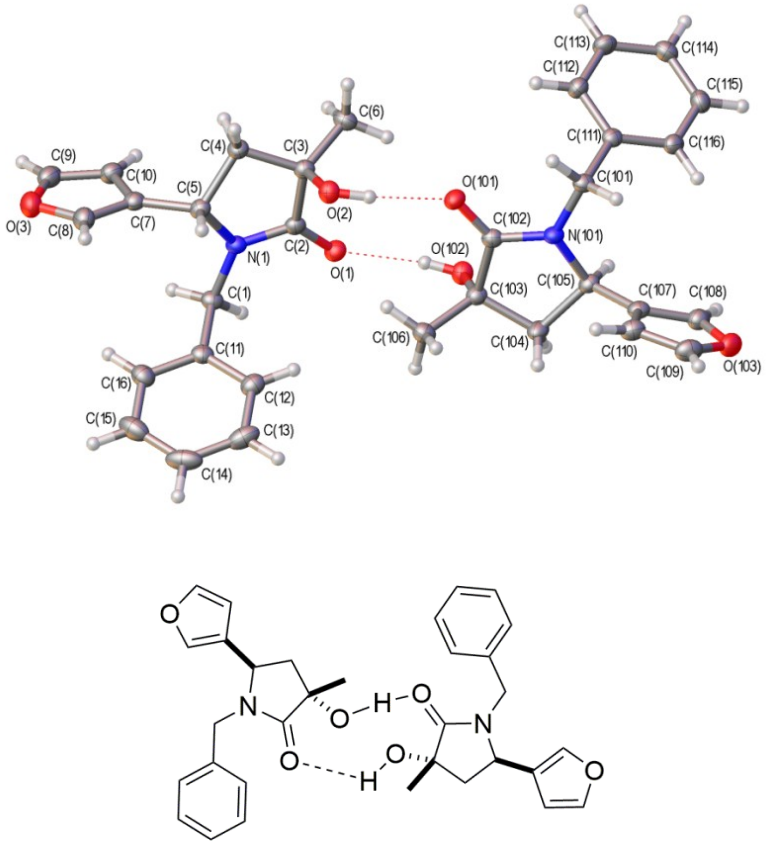


Figure 53: X-ray crystal structure of *cis*-130e with ellipsoids drawn at the 50 % probability level. The structure contains two crystalographically-independent molecules in the asymmetric unit.

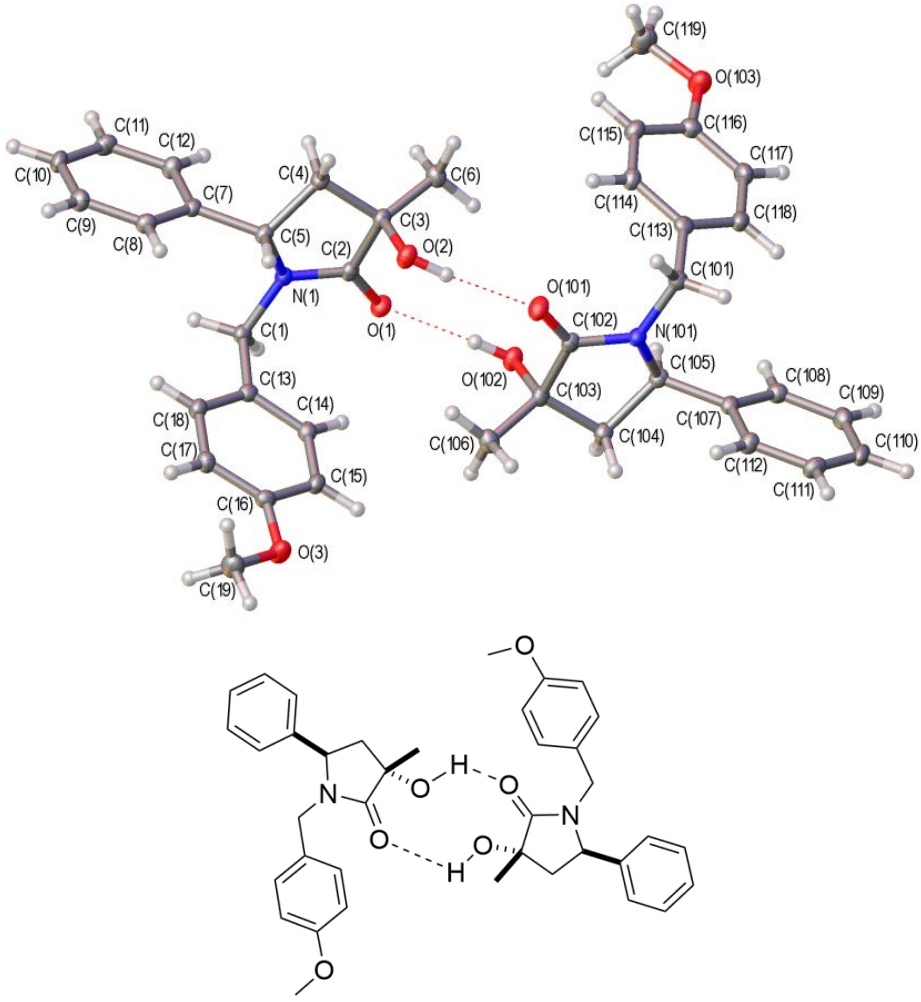


Figure 54: X-ray crystal structure of *cis*-130h with ellipsoids drawn at the 50 % probability level. The structure contains two crystalographically-independent molecules in the asymmetric unit.

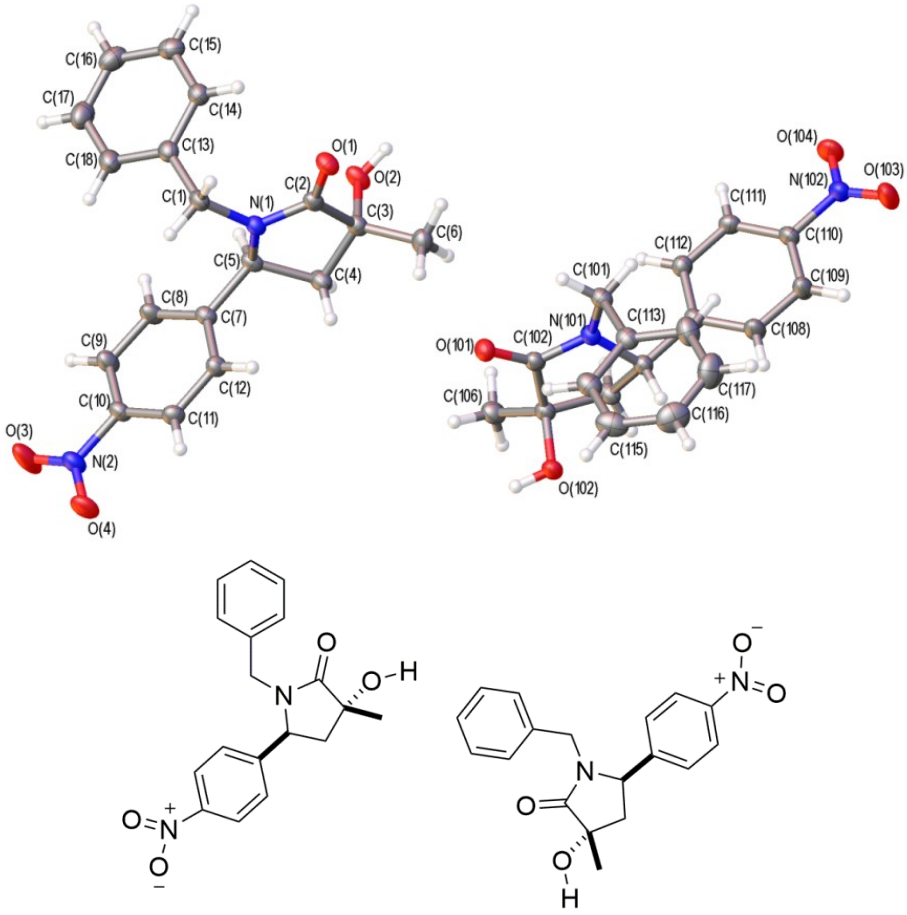


Figure 55: X-ray crystal structure of *cis*-130m with ellipsoids drawn at the 50 % probability level. The structure contains two crystallographically-independent molecules in the asymmetric unit.

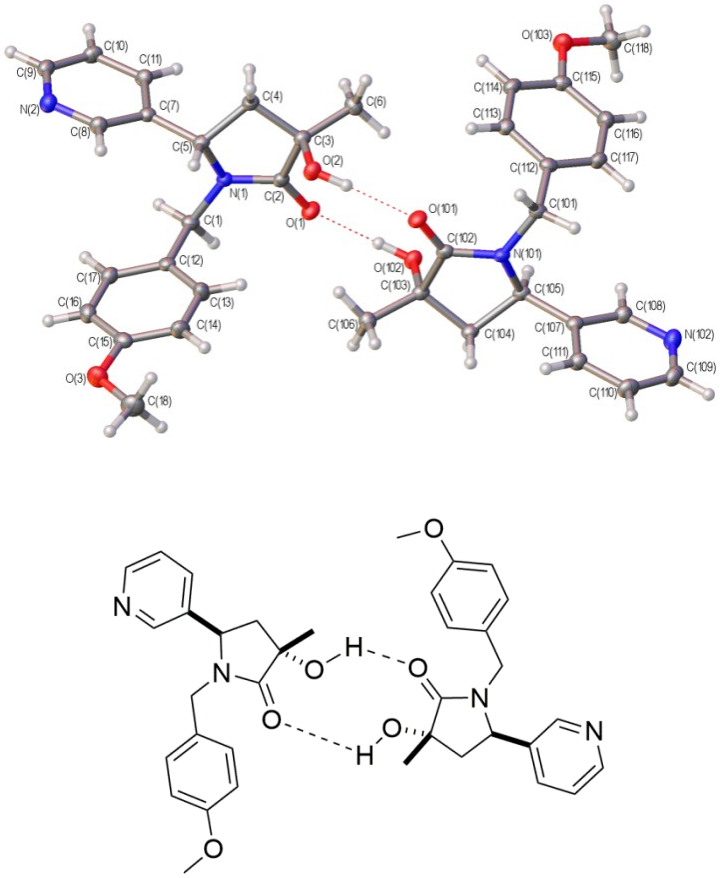


Figure 56: X-ray crystal structure of *cis*-130pwith ellipsoids drawn at the 50 % probability level. The structure contains two crystalographically-independent molecules in the asymmetric unit.

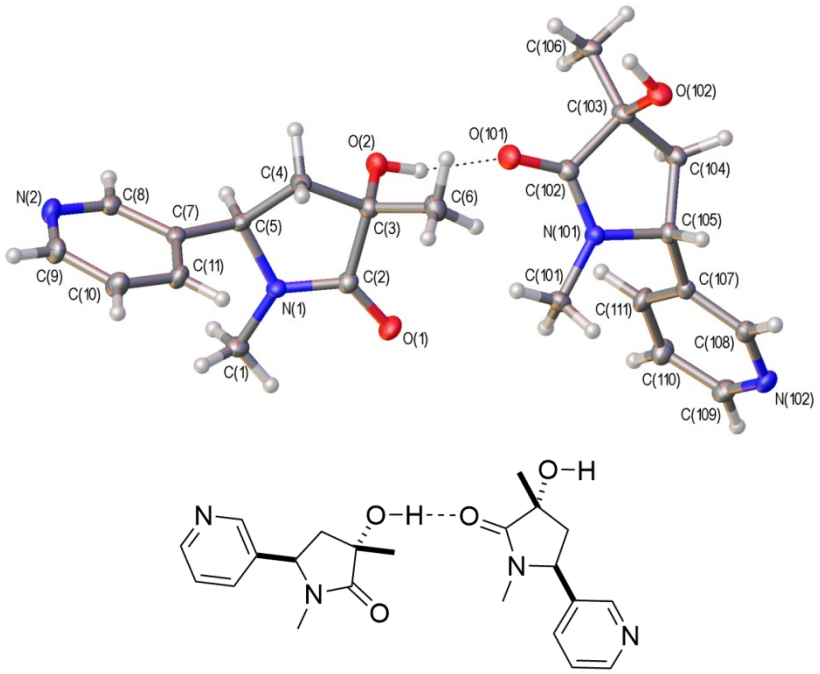
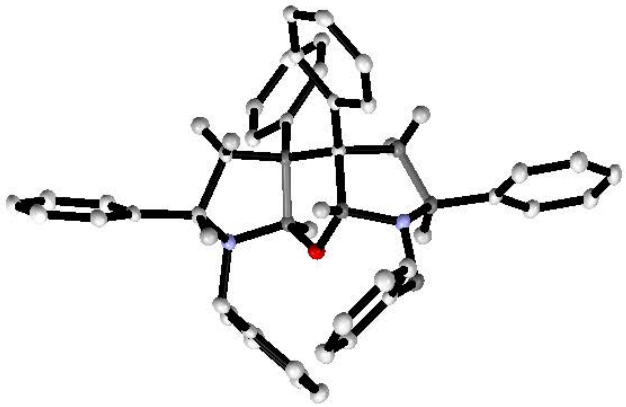


Figure 57: X-ray crystal structure of *cis*-130q with ellipsoids drawn at the 50 % probability level. The structure contains two crystalographically-independent molecules in the asymmetric unit.



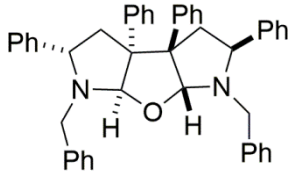


Figure 58: X-ray crystal structure of 143a with ellipsoids drawn at the 50 % probability level.

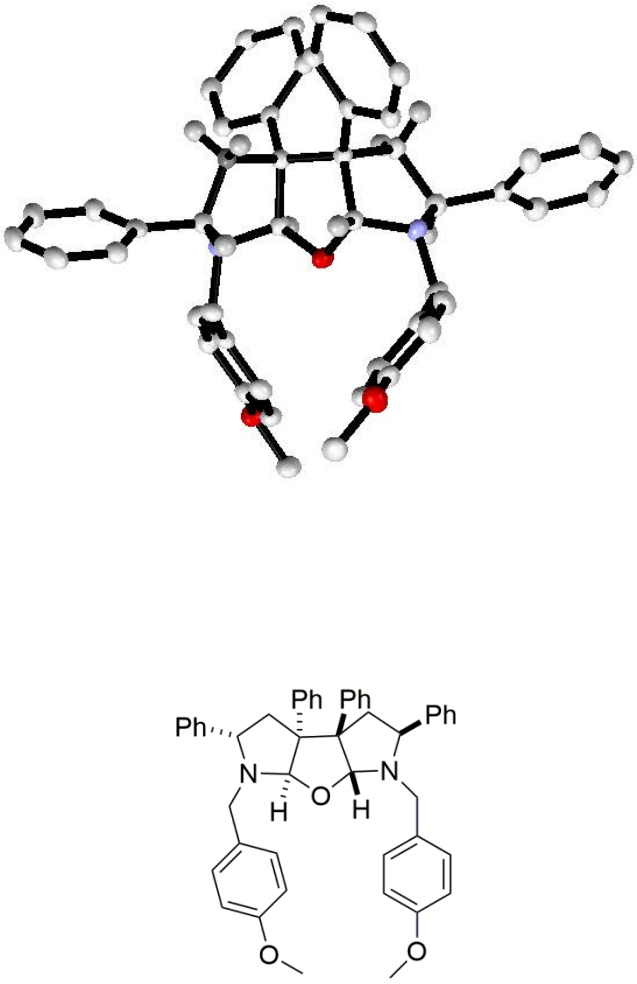


Figure 59: X-ray crystal structure of 143b with ellipsoids drawn at the 50 % probability level.

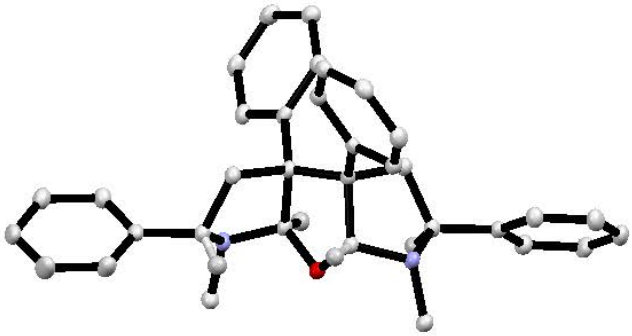


Figure 60: X-ray crystal structure of 143c with ellipsoids drawn at the 50 % probability level.

Crystal structure determination of *cis*-130a:

$C_{18}H_{19}NO_2$ (M =281.34): monoclinic, space group $P2_1/c$ (no. 14), a = 7.63367(18) Å, b = 29.2305(5) Å, c = 6.84862(15) Å, β = 102.295(2)°, V = 1493.12(6) Å^3, Z = 4, T = 99.94(19) K, μ(CuKα) = 0.646 mm^{-1}, *Dcalc* = 1.252 g/mm^3, 10140 reflections measured (11.866 ≤ 2θ ≤ 148.962), 2899 unique (R_{int} = 0.0248, R_{sigma} = 0.0231) which were used in all calculations. The final R_1 was 0.0367 (I>2σ (I)) and wR_2 (F_2) was 0.0934 (all data).[96, 97]

Crystal structure determination of *trans*-130a:

$C_{18}H_{19}NO_2$ (M =281.34): monoclinic, space group $C2/c$ (no. 15), a = 20.2930(2) Å, b = 6.84225(8) Å, c = 22.5979(2) Å, β = 90.8593(9)°, V = 3137.36(5) Å^3, Z = 8, T = 99.94(17) K, μ(CuKα) = 0.615 mm^{-1}, *Dcalc* = 1.191 g/mm^3, 28439 reflections measured (7.826 ≤ 2θ ≤ 149.016), 3181 unique (R_{int} = 0.0244, R_{sigma} = 0.0109) which were used in all calculations. The final R_1 was 0.0343 (I>2σ (I)) and wR_2 (F_2) was 0.1396 (all data).[97, 97]

Crystal structure determination of *trans*-130d:

$C_{19}H_{21}NO_2$ (M =295.37): orthorhombic, space group Pbca (no. 61), a = 12.4972(2) Å, b = 14.1613(2) Å, c = 17.5538(3) Å, V = 3106.62(9) Å^3, Z = 8, T = 100.01(10) K, μ(CuKα) = 0.645 mm^{-1}, *Dcalc* = 1.263 g/cm^3, 15485 reflections measured (10.078° ≤ 2θ ≤ 148.89°), 3132 unique (R_{int} = 0.0249, R_{sigma} = 0.0184) which were used in all calculations. The final R_1 was 0.0379 (I>2σ (I)) and wR_2 (F_2) was 0.0966 (all data). [96, 97]

Crystal structure determination of *cis*-130e:

$C_{16}H_{17}NO_3$ (M =271.30): orthorhombic, space group $P2_12_12_1$ (no. 19), a = 6.86998(8) Å, b = 15.21957(20) Å, c = 27.0563(4) Å, V = 2828.95(6) Å^3, Z = 8, T = 100.00(10) K, μ(CuKα) = 0.717 mm^{-1}, *Dcalc* = 1.274 g/mm^3, 15654 reflections measured (6.534 ≤ 2θ ≤ 148.936), 5473 unique (R_{int} = 0.0239, R_{sigma} = 0.0248) which were used in all calculations. The final R_1 was 0.0289 ($I>2\sigma(I)$) and wR_2 (F_2) was 0.0703 (all data).[96, 97]

Crystal structure determination of *cis*-130h:

$C_{19}H_{21}NO_3$ (M =311.37): triclinic, space group P-1 (no. 2), a = 6.98428(14) Å, b = 15.3845(4) Å, c = 16.6168(4) Å, α = 110.497(2)°, β = 97.0023(18)°, γ = 102.2736(19)°, V = 1596.16(7) Å^3, Z = 4, T = 100.00(10) K, μ(CuKα) = 0.703 mm^{-1}, *Dcalc* = 1.296 g/mm^3, 30499 reflections measured (5.814 ≤ 2θ ≤ 149.132), 6446 unique (R_{int} = 0.0314, R_{sigma} = 0.0265) which were used in all calculations. The final R_1 was 0.0420 ($I>2\sigma(I)$) and wR_2 (F_2) was 0.1611 (all data). [96, 97]

Crystal structure determination of *cis*-130m:

$C_{18}H_{18}N_2O_4$ (M = 326.34): triclinic, space group P-1 (no. 2), a = 7.87442(17) Å, b = 13.1736(2) Å, c = 15.8461(3) Å, α = 88.7943(13)°, β = 76.7697(16)°, γ = 88.4490(15)°, V = 1599.38(5) Å^3, Z = 4, T = 100.01(10) K, μ(CuKα) = 0.798 mm^{-1}, *Dcalc* = 1.355 g/cm^3, 55778 reflections measured (5.73° ≤ 2θ ≤ 148.794°), 6470 unique (R_{int} = 0.0294, R_{sigma} = 0.0141) which were used in all calculations. The final R_1 was 0.0380 ($I>2\sigma(I)$) and wR_2 was 0.1058 (all data). [96, 97]

Crystal structure determination of *cis*-130p-:

$C_{18}H_{20}N_2O_3$ (M =312.36): triclinic, space group P-1 (no. 2), a = 6.8071(3) Å, b = 15.0202(7) Å, c = 15.8559(8) Å, α = 90.798(4)°, β = 101.156(4)°, γ = 100.035(4)°, V = 1564.30(13) Å^3, Z = 4, T = 99.98(10) K, μ(CuKα) = 0.739 mm^{-1}, $Dcalc$ = 1.326 g/cm^3, 11128 reflections measured (5.688° ≤ 2θ ≤ 149.102°), 6195 unique (R_{int} = 0.0285, R_{sigma} = 0.0384) which were used in all calculations. The final R_1 was 0.0391 (I>2σ (I)) and wR_2 (F_2) was 0.1067 (all data). [96, 97]

Crystal structure determination of *cis*-130q:

$C_{11}H_{14}N_2O_2$ (M =206.24): triclinic, space group P-1 (no. 2), a = 7.5414(3) Å, b = 11.8446(5) Å, c = 12.2635(5) Å, α = 80.154(4)°, β = 88.093(4)°, γ = 88.519(3)°, V = 1078.48(8) Å^3, Z = 4, T = 100.00(10) K, μ(CuKα) = 0.724 mm^{-1}, $Dcalc$ = 1.270 g/mm^3, 7212 reflections measured (7.32 ≤ 2θ ≤ 148.982), 4221 unique (R_{int} = 0.0222, R_{sigma} = 0.0333) which were used in all calculations. The final R_1 was 0.0399 (I>2σ (I)) and wR_2 (F_2) was 0.1031 (all data).[96, 97]

Crystal structure determination of 143a:

$C_{46}H_{42}N_2O$ (M =638.81): monoclinic, space group C2/c (no. 15), a = 12.55604(14) Å, b = 15.09459(13) Å, c = 18.96430(17) Å, β = 105.8657(10)°, V = 3457.35(6) Å^3, Z = 4, T = 99.9(2) K, μ(CuKα) = 0.557 mm^{-1}, $Dcalc$ = 1.227 g/cm^3, 32364 reflections measured (9.378° ≤ 2θ ≤ 148.662°), 3515 unique (R_{int} = 0.0309, R_{sigma} = 0.0135) which were used in all calculations. The final R_1 was 0.0364 (I>2σ (I)) and wR_2 (F_2) was 0.0919 (all data).[96, 97]

Crystal structure determination of 143b:

$C_{48}H_{46}N_2O_3$ (M =698.87): triclinic, space group P-1 (no. 2), a = 10.1705(3) Å, b = 10.2903(3) Å, c = 19.4528(5) Å, α = 99.778(2)°, β = 99.679(2)°, γ = 106.888(2)°, V = 1868.03(9) Å^3, Z = 2, T = 99.99(11) K, μ(CuKα) = 0.600 mm^{-1}, $Dcalc$ = 1.242 g/cm^3, 31249 reflections measured (14.244° ≤ 2θ ≤ 140.124°), 7054 unique (R_{int} = 0.0352, R_{sigma} = 0.0246) which were used in all calculations. The final R_1 was 0.0863 (I>2σ (I)) and wR_2 (F_2) was 0.2339 (all data). [96, 97]

Crystal structure determination of 143c:

$C_{34}H_{34}N_2O$ (M =486.63): monoclinic, space group $P2_1/c$ (no. 14), a = 11.9986(2) Å, b = 10.60180(16) Å, c = 20.9045(4) Å, β = 104.8514(19)°, V = 2570.37(8) Å^3, Z = 4, T = 100.00(10) K, μ(CuKα) = 0.580 mm^{-1}, $Dcalc$ = 1.258 g/cm^3, 17451 reflections measured (7.622° ≤ 2θ ≤ 148.838°), 5186 unique (R_{int} = 0.0340, R_{sigma} = 0.0268) which were used in all calculations. The final R_1 was 0.0404 (I> 2σ (I)) and wR_2 (F_2) was 0.1100 (all data). [96, 97]

The datasets were measured on an Agilent SuperNova diffractometer using an Atlas detector. The data collections were driven and processed and numerical absorption corrections based on Gaussian integration over multifaceted crystal models were applied using CrysAlisPro (CrysAlisPro, Agilent Technologies Version 1.171.36.28, 2013). The structures were solved using ShelXS [2] and refined by a full-matrix least-squares procedure on F^2 in ShelXL[94] All non-hydrogen atoms were refined with anisotropic displacement parameters. For ***cis*-130a**, ***trans*-130a**, ***trans*-130d**, ***cis*-130e**, ***cis*-130h**, ***cis*-130m**, ***cis*-130p** and ***cis*-130q** the hydrogen atoms belonging to the hydroxyl group(s) (O (2) and O (102)) were located in the electron density and freely refined. All remaining hydrogen atoms for all ten structures were added at calculated

positions and refined by use of a riding model with isotropic displacement parameters based on the equivalent isotropic displacement parameter (U_{eq}) of the parent atom.

In ***cis*-130e**, ***cis*-130h**, ***cis*-130m**, ***cis*-130p** and ***cis*-130q** there are two crystalographically-independent molecules in the asymmetric unit. In ***trans*-130a** the phenyl group C (13)-C (18)/C (13')-C (18') is disordered over two positions with a refined occupancy ratio of 54(1):46(1). Figures were produced using OLEX2.[95]The CIFs for ***trans*-130a**, ***cis*-130a**, ***trans*-130d**, ***cis*-130e**, ***cis*-130h**, ***cis*-130p**, ***cis*-130q**, **143a**, **143b**, **143c** and ***cis*-130m** have been deposited with the CCDC and have been given the deposition numbers 1028121-1028130 and 1038737 respectively.

In **158a** the space group is centrosymmetric such that in four of the molecules in the unit cell C (4) is *S* and in the other four molecules in the unit cell C (4) is *R*. The relative stereochemistry is the same in all the molecules in the unit cell. The hydrogen atoms belonging to N (3) were located in the electron density and freely refined (with a DFIX restraint applied to N (3)-H (3d)). All remaining hydrogen atoms were added at calculated positions and refined by use of a riding model with isotropic displacement parameters based on the equivalent isotropic displacement parameter (U_{eq}) of the parent atom.

Biological experimental part

Ethical statement

Adult zebrafish from the wild-type AB* strain were maintained and used according to animal experimentation licensing requirements of the Scientific Procedures Act 1986 (UK) under standard conditions with a 14 hour light and 10 hour dark cycle in a Tecniplast flow-through system.[82]

Zebrafish breeding and embryo collection

Adult zebrafish were divided into separate crossing cages consisting of one male and one female zebrafish the night before embryo collection. Zebrafish embryos were then collected the next morning within four hours following fertilization. The unfertilized eggs and dead or abnormal embryos were removed and the normally developed embryos were placed in E3 embryo medium and stored in an incubator at 28°C until required for use.[82]

Toxicity testing

Zebrafish embryos were exposed to nine derivatives of gamma lactam family. Zebrafish embryos were tested in 96 well plates with one embryo in each well. One row was allocated for each concentration, in total six concentrations were tested per drug. One row per plate was also assigned to the solvent control and one row to the E3 control. Treatment was initiated at six hours post fertilization (hpf) and embryos were exposed to compound over five days without compound renewal.[82]

Compound stock solutions were prepared using DMSO and subsequent dilutions were prepared using E3 medium with no dilutions exceeding 1% DMSO.

In the first part of the toxicity, testing embryos were exposed to each compound at 6 different concentrations (0.01, 0.1, 1, 10, 100 and 1000 μM). For compound 3 however, the range was adjusted to 0.001, 0.01, 0.1, 1, 10 and 100 μM due to solubility problems at 1000 μM.

In this first phase the mortality rate was documented every 24 hours. Additionally small selections of general phenotypes were also scored using the following scoring criteria: ++++ = very severe, +++ = severe, ++ = moderate, + = mild, +/- = slight/no effect and - = no effect.

For the second phase a narrower concentration range was used to score a wide variety of morphological defects with 33 features scored in total. The features were scored using a defined scoring criteria with 5 = normal, 4 = slight effect/almost normal, 3 = mild, 2 = moderate, 1 = severe, 0.5 = very severe and 0 = not applicable.

Oil Red O staining

Samples were fixed overnight in 4% PFA, before being infiltrated with a graded series of propylene glycol (25%, 50%, 75% and 100%) and being stained with 0.5% Oil Red O commercially available solution in 100% propylene glycol overnight at room temperature. The following day washes in decreasing concentrations of propylene glycol (100%, 75%, 50% and 25%) and two washes in PBS were then performed before the samples were finally stored in 75% glycerol. [82]

Alizarin red S staining

Samples were fixed overnight in 4% PFA and then stained for 2-3 hours with Alizarin Red S commercially available staining solution. To stop the reaction, samples were washed twice with PBS and then stored in 75% glycerol. [82]

O-dianisidine staining

Samples were fixed overnight in 4% PFA. The next day the samples were washed once with PBS and then stained with O-dianisidine commercially available staining solution for 15 minutes in the dark at room temperature. After staining samples were washed once with PBS and then stored in 75% glycerol. [82]

Acridine orange staining

Live embryos were exposed to 5 µg/ml of commercially available acridine orange solution for 30 minutes in the dark. Samples were then washed twice in 20 ml of E3 embryo medium before being immediately imaged. [82]

Sudan black staining

For the tail fin wounding assay, zebrafish larvae at 3 dpf in groups of 10 were exposed to each compound at 10 µM for 1 hour. After the 1 hour exposure period the larvae were anaesthetized and the caudal fin tips were cut. The larvae were then allowed to recover in E3 embryo medium for 3 hours before being fixed in 4% PFA overnight. The next day the larvae were washed twice with PBST and then stained with 60 µL Sudan Black reagent for 20 [82]

References

(1) Starmans, W. *Synthesis and Application of the functionalised Azetidines [online]*; 2st ed, UB, Nijmegen, 1997; Vol. 1.

(2) Andreu, I.; Delgado, J.; Espinos, A.; Peres, R.; Jimenez, M. C.; Miranda, M. A. *Org. Lett.* **2008**, *10*, 5207.

(3) Yoda, H.; Oguchi, T.; Takabe, K. *Tetrahedron Lett.* **1997**, *38*, 3283.

(4) Harrowfield, J. M.; Jang, G. H.; Kim, Y.; Thuery, P.; Vicens, J. *J. Chem. Soc., Dalton Trans.* **2002**, 1241.

(5) Shi, M.; Jiang, J.-K. *Tetrahedron: Asymmetry* **1999**, *10*, 1673.

(6) Keller, L.; Sanchez, M. V.; Prim, D.; Couty, F.; Evano, G.; Marrot, J. *J. Organometallic Chem.* **2005**, *690*, 2306.

(7) Reusch, W. In *Heterocyclic Compounds [online]*; Michigan State University: 2013.

(8) Franck, X.; Leleu, S.; Outurquin, F. *Tetrahedron Lett.* **2010**, *51*, 4437.

(9) Brandi, A.; Cicchi, S.; Cordero, F. *Chem. Rev.* **2008**, *108*, 3988.

(10) Furutani, S.; Nakatani, Y.; Miura, Y.; Ihara, M.; Kai, K.; Hayashi, H.; Matsuda, K. *Sci. Rep.* **2014**, *4*.

(11) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

(12) Berthe, B.; Quturquin, F.; Paulmier, C. *Tetrahedron Lett.* **1997**, *38*, 1393.

(13) Salgado, A.; Dejaegher, Y.; Boeykens, M. *Tetrahedron* **2003**, *59*, 2231.

(14) De Kimpe, N.; De Smaele, D. *Tetrahedron Lett.* **1994**, *35*, 8023.

(15) Stanković, S.; Catak, S.; D'hooghe, M.; Goossens, H.; Abbaspour Tehrani, K.; Bogaert, P.; Waroquier, M.; Van Speybroeck, V.; De Kimpe, N. *J Org Chem* **2011**, *76*, 2157.

(16) Ye, Y.; Wang, H.; Fan, R. *Org. Lett.* **2010**, *12*, 2802.

(17) Marinetti, A.; Hubert, P.; Genet, J. *Eur. J. Org. Chem.* **2000**, 1815.

(18) Hillier, M. C.; Chen, C.-y. *J. Org. Chem.* **2006**, *71*, 7885.

(19) Van Brabandt, W.; Van Landeghem, R.; De Kimpe, N. *Org. Lett.* **2006**, *8*, 1105.

(20) D'hooghe, M.; Dekeukeleire, S.; Leemans, E.; De Kimpe, N. *Pure and Appl. Chem.* **2010**, *82*, 1749.

(21) Lowe, J. T.; Lee, M. D.; Akella, L. B.; Davoine, E.; Donckele, E. J.; Durak, L.; Duvall, J. R.; Gerard, B.; Holson, E. B.; Joliton, A.; Kesavan, S.; Lemercier, B. C.; Liu, H.; Marié, J.-C.; Mulrooney, C. A.; Muncipinto, G.; Welzel-O'Shea, M.; Panko, L. M.; Rowley, A.; Suh, B.-C.; Thomas, M.; Wagner, F. F.; Wei, J.; Foley, M. A.; Marcaurelle, L. A. *J. Org. Chem.* **2012**, *77*, 7187.

(22) Feula, A.; Male, L.; Fossey, J. S. *Org. Lett.* **2010**, *12*, 5044.

(23) Feula, A.; Dhillon, S. S.; Byravan, R.; Sangha, M.; Ebanks, R.; Hama Salih, M. A.; Spencer, N.; Male, L.; Magyary, I.; Deng, W. P.; Muller, F.; Fossey, J. S. *Org. Biomol. Chem.* **2013**, *11*, 5083.

(24) Hassner, A. *Heterocyclic compounds small ring heterocycles [online]*; 2nd ed.; New York, 1983; Vol. 42.

(25) Dwivedi, S. K.; Gandhi, S.; Rastogi, N.; Singh, V. K. *Tetrahedron Lett.* **2007**, *48*, 5375.

(26) Vargas-Sanchez, M.; Couty, F.; Evano, G.; Prim, D.; Marrot, J. *Org. Lett.* **2005**, *7*, 5861.

(27) Couty, F.; Durrat, F.; Prim, D. *Tetrahedron Lett.* **2003**, *44*, 5209.

(28) Katritzky, A. R. In *Comprehensive Heterocyclic Chemistry [online]*; 2nd ed. 2008; Vol. 3.

(29) Liu, R.; Bai, X.; Zhang, Z.; Zi, G. *Appl. Organometalic Chem.* **2008**, *22*, 671.

(30) Yoda, H.; Uemura, T.; Takabe, K. *Tetrahedron Lett.* **2003**, *44*, 977.

(31) Yamagishi, T. *Hypertens Res* **2006**, *29*, 767.

(32) Sharma, M. C.; Sahu, N. K.; Kohli, D. V.; Chaturvedi, S. C. *Dig. J. Nanomaterials and Biostructures* **2009**, *4*, 339.

(33) Sharma, M. C.; Sahu, N. K.; Kohli, D. V.; Chaturvedi, S. C. *Dig. J. Nanomaterials and Biostructures* **2009**, *4*, 361.

(34) Holladay, M. W.; Bai, H.; Li, Y.; Lin, N.; Daanen, J. F.; Ryther, K. B.; Wasicak, J. T.; Kincaid, J. F.; He, Y.; Hettinger, A. M.; Huang, P.; Anderson, D. J.; Bannon, A. W.; Buckley, M. J.; Campbell, J. E.; Donnelly-Roberts, D. L.; Gunther, K. L.; Kim, D. J. B.; Kuntzweiler, T. A.; Sullivan, J. P.; Decker, M. W.; Arneric, S. P. *Bioorg. & Med. Chem. Lett.* **1998**, *8*, 2797.

(35) Abood, L. G.; Lu, X.; Banerjee, S. *Biochem. Pharmacol.* **1987**, *36*, 2337.

(36) Burtoloso, A. C. B.; Correia, C. R. D. *Tetrahedron* **2008**, *64*, 9928.

(37) Han, Y.; Han, M.; Shin, D.; Song, C.; Hahn, H.-G. *J. Med. Chem.* **2012**, *55*, 8188.

(38) Li, J.; Liu, S.; Niu, S.; Zhuang, W.; Che, Y. *J. Nat. Prod.* **2009**, *72*, 2184.

(39) Dubon, P.; Farwick, A.; Helmchen, G. *Synlett* **2009**, 1413.

(40) Schwartz, R. E.; Helms, G. L.; Bolessa, E. A.; Wilson, K. E.; Giacobbe, R. A.; Tkacz, J. S.; Bills, G. F.; Liesch, J. M.; Zink, D. L.; Curotto, J. E.; Pramanik, B.; Onishi, J. C. *Tetrahedron* **1994**, *50*, 1675.

(41) Singh, P.; Dimitriou, V.; Mahajan, R. P.; Crossley, A. W. *Br. J. Anaesth.* **1993**, *71*, 685.

(42) Enz, A.; Feuerbach, D.; Frederiksen, M. U.; Gentsch, C.; Hurth, K.; Müller, W.; Nozulak, J.; Roy, B. L. *Bioorg. & Med. Chem. Lett.* **2009**, *19*, 1287.

(43) Katritzky, A. R.; Mehta, S.; He, H.-Y.; Cui, X. *J. Org. Chem.* **2000**, *65*, 4364.

(44) Sun, W.; Tian, L.; Qi, H.; Jiang, D.; Wang, Y.; Li, S.; Xiao, J.; Yang, X. *Chin. J. Chem.* **2013**, *31*, 1144.

(45) Yang, L.; Wang, D.-X.; Huang, Z.-T.; Wang, M.-X. *J. Amer. Chem. Soc.* **2009**, *131*, 10390.

(46) Takamizawa, M.; Takahashi, H.; Sakakibara, H.; Kobayashi, T. *Tetrahedron* **1967**, *23*, 2959.

(47) Herten, B. W.; Poulton, G. A. *J. Chem. Soc., Chem. Commun.* **1975**, 456.

(48) Ling, K.-Q.; Ren, T.; Protasiewicz, J. D.; Sayre, L. M. *Tetrahedron Lett.* **2002**, *43*, 6903.

(49) Adhikari, A.; Kalluraya, B.; Sujith, K. V.; Gouthamchandra, K.; Jairam, R.; Mahmood, R.; Sankolli, R. *Eur. J. Med. Chem.* **2012**, *55*, 467.

(50) Özdemir, Z.; Kandilci, H. B.; Gümüşel, B.; Çalış, Ü.; Bilgin, A. A. *Eur. J. Med. Chem.* **2007**, *42*, 373.

(51) Ali, I.; Wani, W. A.; Khan, A.; Haque, A.; Ahmad, A.; Saleem, K.; Manzoor, N. *Microbial Pathogenesis* **2012**, *53*, 66.

(52) Taj, T.; Kamble, R. R.; Gireesh, T. M.; Hunnur, R. K.; Margankop, S. B. *Eur.J. Med. Chem.* **2011**, *46*, 4366.

(53) Ciupa, A.; Mahon, M. F.; De Bank, P. A.; Caggiano, L. *Org. Biomol. Chem.* **2012**, *10*, 8753.

(54) Chase, B. H.; Evans, J. M. *J. Chem. Soc. (Resumed)* **1964**, 4825.

(55) Sankappa Rai, U.; Isloor, A.; Shetty, P.; Isloor, N.; Padaki, M.; Fun, H.-K. *Med Chem Res* **2012**, *21*, 1090.

(56) Gómez-Barrio, A.; Montero-Pereira, D.; Nogal-Ruiz, J.; Escario, J.; Muelas-Serrano, S.; Kouznetsov, V.; Vargas Méndez, L.; Urbina Gonzáles, J.; Ochoa, C. *Acta Parasit.* **2006**, *51*, 73.

(57) Wang, D.; Dai, L.; Hou, X.; Zhang, Y. *Tetrahedron Lett.* **1996**, *37*, 4187.

(58) Anderson, J. C.; Blake, A. J.; Howell, G. P.; Wilson, C. *J. Org. Chem.* **2004**, *70*, 549.

(59) Joly, G. D.; Jacobsen, E. N. *J. Amer. Chem. Soc.* **2004**, *126*, 4102.

(60) Keck, G. E.; Enholm, E. J. *J. Org. Chem.* **1985**, *50*, 146.

(61) Liu, M.; Shen, A.; Sun, X.-W.; Deng, F.; Xu, M.-H.; Lin, G.-Q. *Chem. Commun.* **2010**, *46*, 8460.

(62) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984.

(63) Guo, T.; Song, R.; Yuan, B.-H.; Chen, X.-Y.; Sun, X.-W.; Lin, G.-Q. *Chem. Commun.* **2013**, *49*, 5402.

(64) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278.

(65) Sun, X. W.; Xu, M. H.; Lin, G. Q. *Org. Lett.* **2006**, *8*, 4979.

(66) Baussanne, I.; Royer, J. *Tetrahedron Lett.* **1998**, *39*, 845.

(67) Nay, B.; Riache, N.; Evanno, L. *Nat. Prod. Rep.* **2009**, *26*, 1044.

(68) Feula, A.; Fossey, J. S. *RSC Advances* **2013**, *3*, 5370.

(69) Lin, N.-H.; Carrera, G. M.; Anderson, D. J. *J. Med. Chem.* **1994**, *37*, 3542.

(70) Shon, M.; Shanmugavel, R.; Shin, G.; Mathew, S.; Lee, S.-H.; Yun, H. *Chem. Commun.* **2014**, *50*, 12680.

(71) Vara Prasad, J. V. N.; Loo, J. A.; Boyer, F. E.; Stier, M. A.; Gogliotti, R. D.; Turner, W. J.; Harvey, P. J.; Kramer, M. R.; Mack, D. P.; Scholten, J. D.; Gracheck, S. J.; Domagala, J. M. *Bioorg. Med. Chem.* **1998**, *6*, 1707.

(72) Bull, S. D.; Davies, S. G.; Kelly, P. M.; Gianotti, M.; Smith, A. D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3106.

(73) Tripathi, C. B.; Mukherjee, S. *Angew. Chem. Int. Ed.* **2013**, *52*, 8450.

(74) Ohmura, T.; Masuda, K.; Takase, I.; Suginome, M. *J. Am. Chem. Soc.* **2009**, 16624.

(75) Zhao, L.; Zhang, S.; Jin, H.; Wan, L.; Dou, F. *Org. Lett.* **2012**, *14*, 886.

(76) Carey, F. A. *Adv. Org. Chem.: Part B: Reactions and Synthesis*; Springer US, 2013.

(77) Ternon, M.; Outurquin, F.; Paulmier, C. *Tetrahedron* **2001**, *57*, 10259.

(78) Husain, K.; Abid, M.; Azam, A. *Eur. J. Med. Chem.* **2008**, *43*, 393.

(79) Ananthnag, G. S.; Adhikari, A.; Balakrishna, M. S. *Catalysis Commun.* **2014**, *43*, 240.

(80) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Del. Rev.* **1997**, *23*, 3.

(81) Delvecchio, C.; Tiefenbach, J.; Krause, H. M. *Assay Drug Dev. Technol.* **2011**, *9*, 354.

(82) Dhillion, S. S. PhD thesis, University of Birmingham, 2014.

(83) Ashby, J. *Environmental Health Perspec.* **1996**, *104*, 1101.

(84) Liu, J.; Zeng, L.; Kennedy, R. M.; Gruenig, N. M.; Childs, S. J. *Devel. Bio.* **2012**, *363*, 95.

(85) Kar, G. K.; Roy, B. C.; Das Adhikari, S.; Ray, J. K.; Brahma, N. K. *Bioorg. Med. Chem.* **1998**, *6*, 2397.

(86) Tripathi, C. B.; Mukherjee, S. *Org. Lett.* **2014**, *16*, 3368.

(87) Seayad, A. M.; Ramalingam, B.; Yoshinaga, K.; Nagata, T.; Chai, C. L. L. *Org. Lett.* **2009**, *12*, 264.

(88) Padilla, S.; Tejero, R. n.; Adrio, J.; Carretero, J. C. *Org. Lett.* **2010**, *12*, 5608.

(89) Curtin, N. J.; Barlow, H. C.; Bowman, K. J.; Calvert, A. H.; Davison, R.; Golding, B. T.; Huang, B.; Loughlin, P. J.; Newell, D. R.; Smith, P. G.; Griffin, R. J. *J. Med. Chem.* **2004**, *47*, 4905.

(90) Radulović, N. S.; Miltojević, A. B.; Vukićević, R. D. *Comptes Rendus Chim.* **2013**, *16*, 257.

(91) Kumata, K.; Yui, J.; Hatori, A.; Fujinaga, M.; Yanamoto, K.; Yamasaki, T.; Kawamura, K.; Wakizaka, H.; Nengaki, N.; Yoshida, Y.; Ogawa, M.; Fukumura, T.; Zhang, M.-R. *J. Med. Chem.* **2011**, *54*, 6040.

(92) Rodríguez, S.; Castillo, E.; Carda, M.; Marco, J. A. *Tetrahedron* **2002**, *58*, 1185.

(93) Xu, H.-C.; Chowdhury, S.; Ellman, J. A. *Nat. Protocols* **2013**, *8*, 2271.

(94) Bourzat, J. D.; Commerçon, A. *Tetrahedron Lett.* **1993**, *34*, 6049.

(95) Foubelo, F.; Yus, M. *Tetrahedron: Asymm.* **2004**, *15*, 3823.

(96) Sheldrick, G. *Acta Crystallogr. Sec. A* **2008**, *64*, 112.

(97) Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A.; Puschmann, H. *J. Appl. Crystallogr.* **2009**, *42*, 339.

Appendix

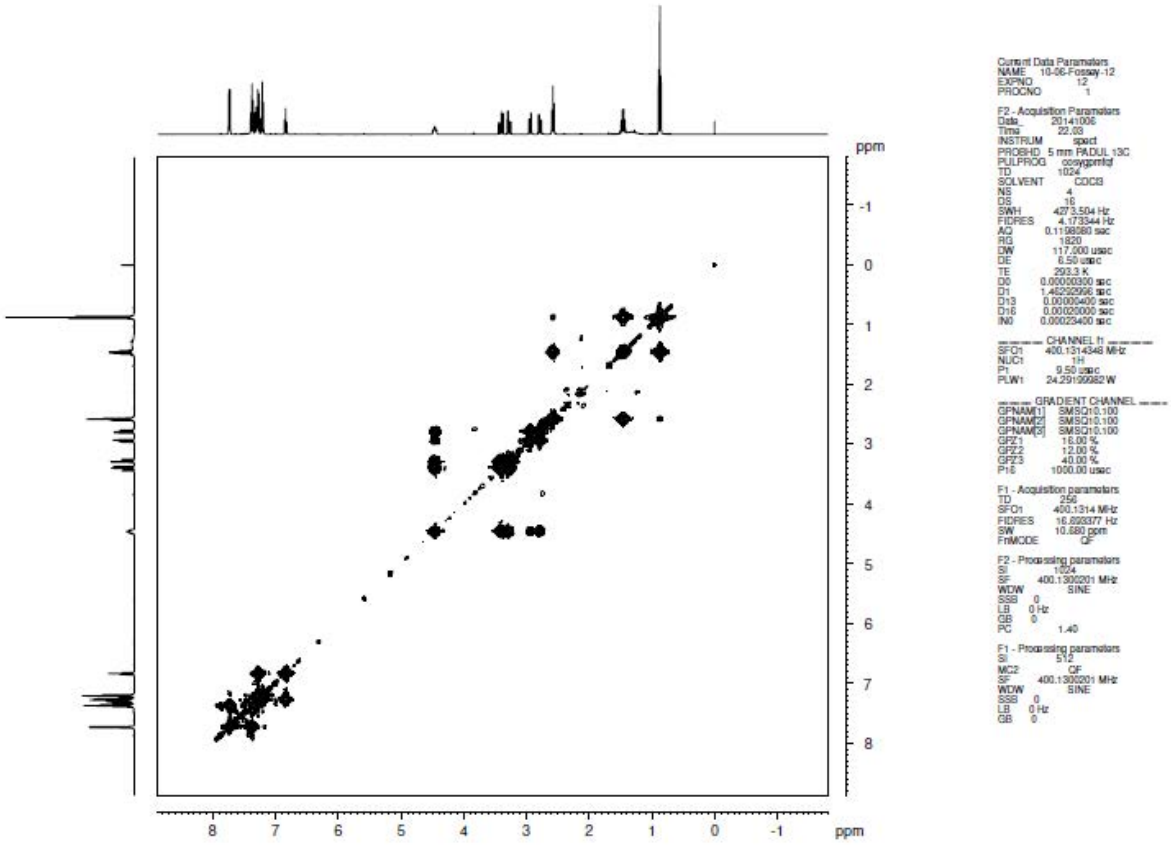


Figure 61: COSY 2D-NMR for compound 158a

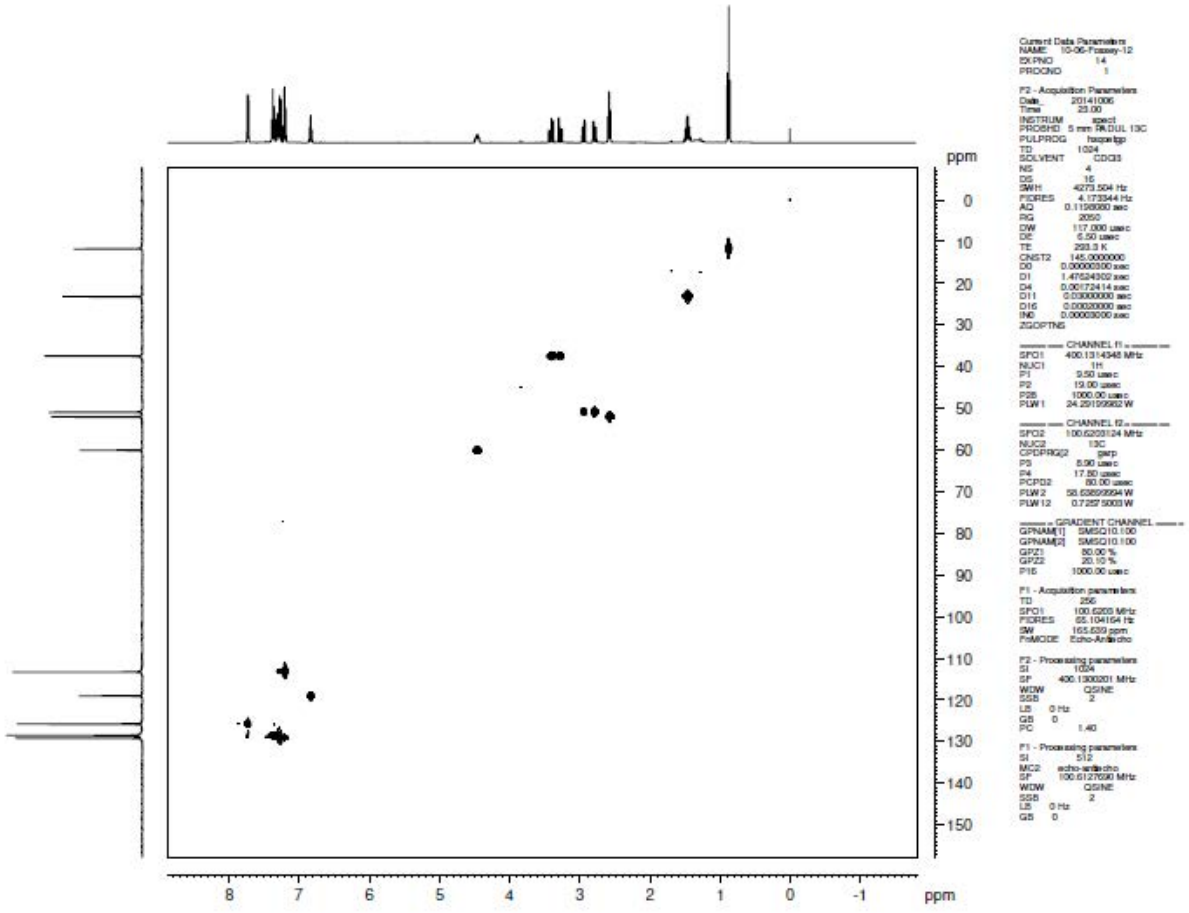


Figure 62: HSQC 2D-NMR for compound 158a

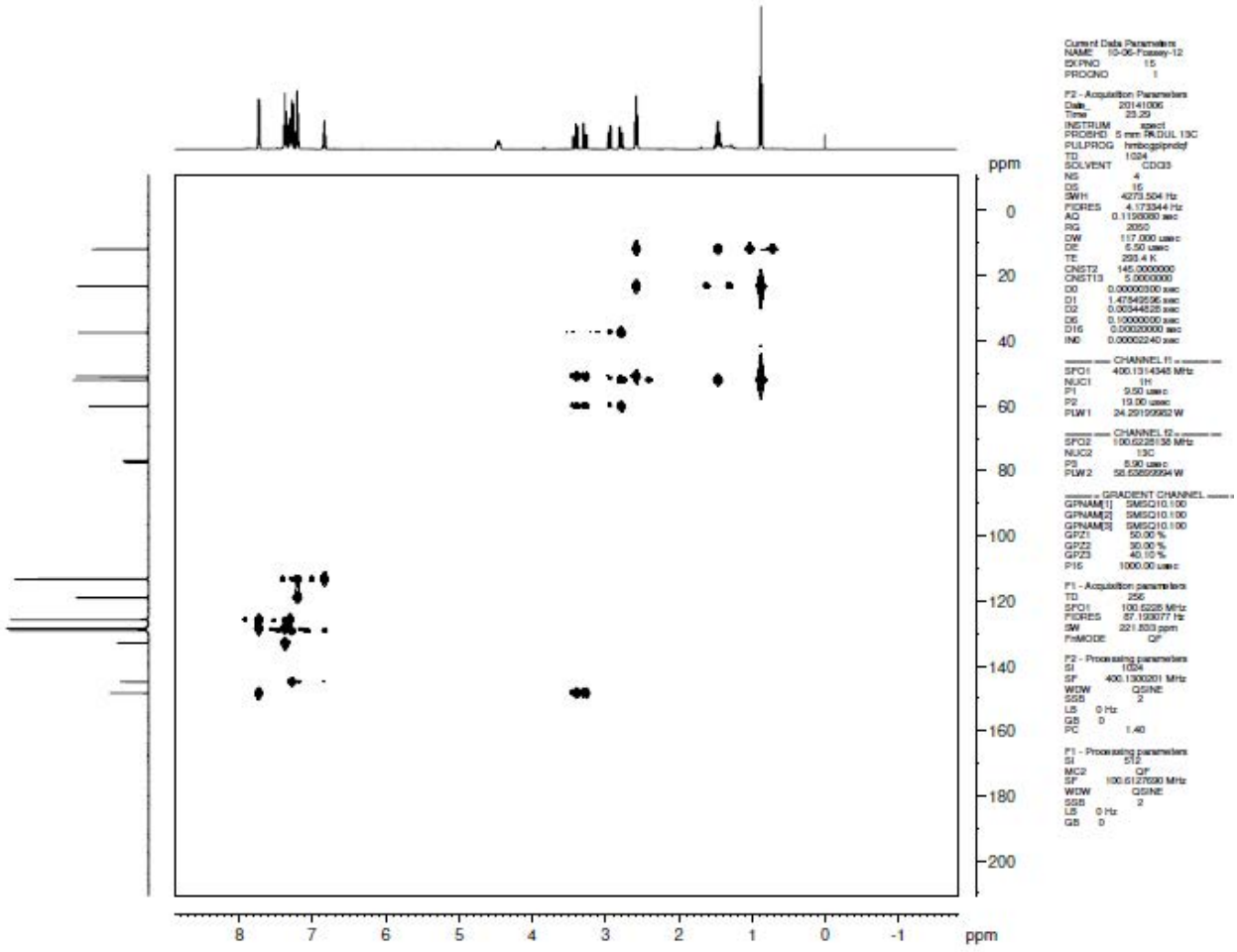


Figure 63: HMBC 2D-NMR for compound 158a