Dearomatising Addition of Tethered Organolithiums to Activated Benzene Derivatives

A thesis submitted to the University of Manchester for the degree of Doctor of Philosophy in the Faculty of Engineering and Physical Sciences

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Contents

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Abstract

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ABSTRACT OF THESIS submitted by Rebecca Harvey 2010

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and entitled Dearomatising Addition of Tethered Organolithiums to Activated Benzene Derivatives

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This thesis describes research carried out on the synthesis of lithiation precursors used to investigate the ability of oxazoline activated benzene derivatives to undergo dearomatising cyclisations.

Chapter 1 illustrates previous work in the area of dearomatising additions, including intra- and inter-molecular dearomatisations. An overview of relevant work conducted within the Clayden group is also described.

Chapter 2 narrates the synthesis of lithiation precursors that contain a (4*R*,5*R*)-*4*,5-diphenyloxazoline activating group on the aromatic ring. The attempts to lithiate and dearomatise these compounds are shown.

Chapter 3 describes the synthesis of achiral oxazoline activated O-allylic pre-lithiation substrates, and their ability to undergo dearomatising cyclisations. Also described is the attempts to find a suitable protecting group for N-allylic dearomatising cyclisations.

Chapter 4 outlines the investigations carried out for the stereoselective synthesis of (4*R*,5*R*)-*4*,5-diphenyloxazolines, which have been used for the activation towards dearomatising cyclisation.

Chapter 5 is an overview of the thesis and outlines possible future work.

Chapter 6 contains the experimental methods and data pertaining to Chapters 2 to 5.

Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning

Notes on Copyright and the Ownership of Intellectual Property rights

Preface

The author graduated from The University of Manchester in July 2006 with First Class honours in the degree of MChem with industrial experience. Their industrial placement was carried out in a medicinal chemistry CEDD at GlaxoSmithKline in Stevenage and the research during the final year project of this course was carried out under supervision of Dr David Berrisford. After graduation she stayed at The University of Manchester to work under the supervision of Prof. Jonathan Clayden. The results of the work carried out during this period are embodied in this thesis. The author is currently working as a chemist at Peakdale Molecular Ltd.

Acknowledgements

Firstly I would like to thank Jonathan for his guidance, support and help throughout the course of my PhD and the opportunity to work in his group.

I am very thankful to all the technical staff at the University of Manchester. Especially Val and Gareth. Also thanks to Rehana for the time she spent teaching me how to use the Prep HPLC and her help with my many attempts at fixing the H-Cube.

I would not have got through my PhD without the support of the research group; with their help in the lab talking through the many problems I have had over the course of these past 4 years and outside where it most often culminated in drinking too much beer. Thanks to the post-docs who I asked far too many questions; Jordi, Julie, Steve, Uli, Damian, Alejandro, Morgan, Gilles, Thomas, Laurent and Wes. The people who settled me in when I arrived; Simon, Abby, Mark, Hazel, Steve and Sean. And finally Everybody else who has made my time doing my PhD so special; Heloise, James S., Paul, Dan, James J., Ol'ga, Jemma, Anne, Julien, Rob, Nadia, Mike, Erik, Alexis, Maxime, Alberto, Michele, Renaud. Thanks also to Ailsa who's summer placement on the benzoyl aziridine rearrangement saved me from spending even more time filtering silica. I am also very appreciative of the people who spent time proof reading this thesis and everything else I have attempted to write, especially a big big thanks to Paul, without you this thesis would not be finished. Outside of the lab I'd like to thank all the people who's fault it is that I wanted to stay in Manchester; Jen, Nick, Laura, Jonathan, Ruth, James, Carpet, Sam, Gi, Ester and Amy. Also thank you to my newest friends who I have met by staying here; Amy, James, Chris, Fiona, Jim, Sarah, Dave, Jenny, Dani, Dave, Michaela, and Sally. Plus everyone from home who I don't get to see as often as I should; Jenna, Louise, Lynne, Sally, Kara, Sarah and Rich.

I'd like to thank my family; for their love, support and most importantly their absolute faith in me even when I have lost all of mine. I am so very lucky to have you all.

Ian; Thank you for putting up with me for the past year, I could not have got to this point without your love, friendship and hugs. Love you forever.

Abbreviations

ATPH	Aluminium tris(2,6-diphenylphenoxide)
AllylBr	Allyl bromide
Ar	Aryl
BHA	2,6-di-*tert*-butyl-4-methoxyphenyl
BIS	*tert*-Butyl sulphinamide
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
Bu	Butyl
n-BuLi	*n*-Butyllithium
s-BuLi	*sec*-Butyllithium
t-Bu	*tert*-Butyl
BUS	*tert*-Butyl sulphonamide
Bz	Benzoyl
CAN	Ceric ammonium nitrate
CI	Chemical ionisation
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DEPT	Distortionless enhancement by polarization transfer
DFT	Density functional theory
DIAD	Diisopropyl azodicarboxylate
DIC	Diisopropylcarbodiimide
DMAP	4-(Dimethylamino)pyridine
DMF	*N,N*-dimethylformamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	Dimethylsulphoxide
d.r.	Diastereomeric ratio
DTBMP	2,6-Di(*tert*-butyl)-4-methylphenol
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
E_a	Activation energy
e.e.	Enantiomeric excess
EI	Election Impact
Ether	Diethyl ether

EtOAc	Ethyl acetate
ES	Electrospray
EWG	Electron withdrawing group
EX	General Electrophile
FTIR	Fourier transform infrared spectroscopy
h	Hours
HMPA	Hexamethylphosphoramide
HOBt	Hydroxybenzotriazole
i-PrLi	*iso*-Propyllithium
K_{eq}	Equilibrium constant
LDA	Lithium *N,N*-diisopropylamide
m-CPBA	*meta*-Chloroperbenzoic acid
Me	Methyl
Min	Minute
mL	Millilitre
mmol	Millimole
MsCl	Methanesulphonyl chloride
NMP	N-Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
Ph	Phenyl
PhH	Benzene
pK_a	Log of acid equilibrium constant
PTSA	*para*-Toluene sulphonic acid
SET	Single electron transfer
SM	Starting material
TBAF	Tetrabutylammonium floride
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMP	2,2,6,6-Tetramethylpiperidine

“I may not have gone where I intended to go, but I think I have ended up where I needed to be”

Douglas Adams, The Long Dark Teatime of the Soul

1 Introduction

1.1 Formation of organolithiums

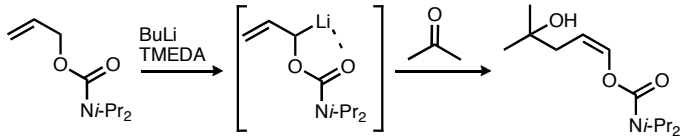
Organolithiums can be formed by a variety of methods;[1] the most common being deprotonations, transmetallation, halogen lithium exchange and carbolithiation. This short review of organolithium formation will not be concerned with transmetallation and carbolithiation, but will concentrate on deprotonations and halogen-lithium exchange.

1.1.1 Deprotonations

In order for a proton to be deprotonated by commercially available alkyllithiums the newly formed organolithium needs to be stabilized.[1] Preferably this can be by the lithium being bonded to a sp-hybridised carbon atom, or the carbon-lithium bond being adjacent to a strongly electron-withdrawing substituent. Less favourable is if the lithium is bonded to a sp^2-hybridised carbon atom, the C-Li bond is in a small ring system (n = 3 or 4), the C-Li bond is α to a sulfur or phosphorus atom or the C-Li bond is in a allylic or benzylic location. Also the organolithium can be stablised if the C-Li bond is adjacent to oxygen or nitrogen, has a nearby heteroatom which is able to stabilize the C-Li bond by co-ordination or if there is a remote acidifying effect (e.g. an electron-withdrawing group *ortho* on an aromatic ring). These stabilising effects are all cumulative, allowing deprotonation to occur if there are several small stabilising conditions in place.

α-Lithiation is when lithiation occurs adjacent to a heteroatom, the mechanisms of these type of reactions are the most studied form of lithiation.[1] A deprotonation α to an oxygen is unfavourable and generally the oxygen's lone pairs need to be delocalized in order to reduce the repulsion of the antibonding interaction of the oxygen's lone pairs with the C-Li bond. An example is the use of carbamates where delocalisation into the carbonyl group can occur. α-Lithiation next to oxygen is also more favourable if the proton is vinylic, allylic or benzylic. A system which shows both these conditions is

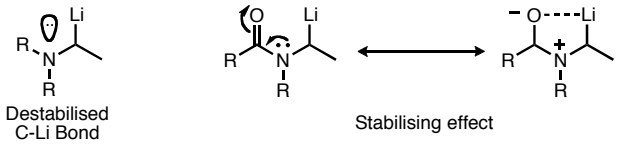
allyl carbamate **1** which is stabilised by the carbonyl. When quenching **2** with aldehydes or ketones the product of γ attack is formed, whereas quenching with alkylating or silylating electrophiles is less regioselective.[2]



1 **2** **3** (75 %)

Scheme 1.1 Regioselective deprotonation of allyl carbamates

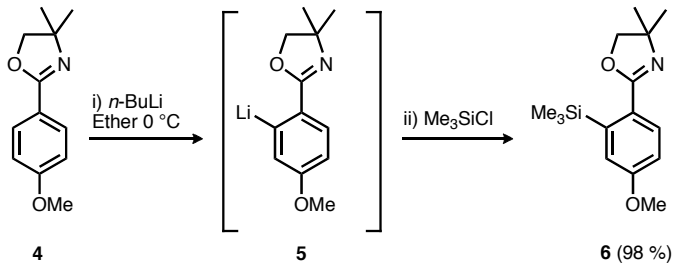
Nitrogen lone pairs have a larger antibonding interaction with adjacent C-Li bonds and therefore conjugation is needed in order to deprotonate α to nitrogen using organolithiums (unless using a superbasic reagent).[3] This can be achieved either by deprotonating amides, carbamates or systems where the lone pair of the nitrogen can be delocalised into an aromatic ring.



a **b**

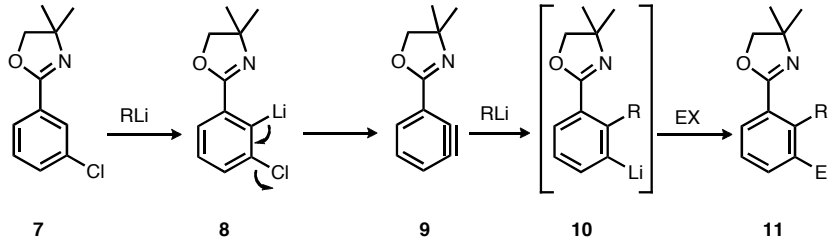
Figure 1.1 Stabilisation of deprotonation α to nitrogen

Ortholithiation is when deprotonation occurs on an activated aromatic ring *ortho* to the activating electron-withdrawing functional group. In general this occurs by the organolithium first forming a complex with the activating group, followed by deprotonation which is often more favoured due to the electron-withdrawing effect of the activating group. Snieckus divided the typical ortholithiation-directing groups into classes, taking into account the ease of lithiation and how well they could be applied to synthesis.[4] The most important class for this body of work is oxazolines, which sit mid table, they act as directing groups for lithiation and are generally unsusceptible to nucleophillic attack by organolithiums. Phenyl oxazolines can be *ortho*-lithiated by *n*-BuLi, an example of which is the lithiation of **4** to form **6** a precursor in a steroid synthesis.[5]



Scheme 1.2 Use of oxazoline directed *ortho*-lithiation

The electron-withdrawing abilities of oxazolines can be exploited in other ways, for example Meyers reported the ortholithiation of **7**, to form **8** which reacts to form an intermediate benzyne **9**. The excess organolithium used in the reaction then adds regioselectively to the 2-position of the benzyne forming **11** after quenching the reaction with an electophile.[6]

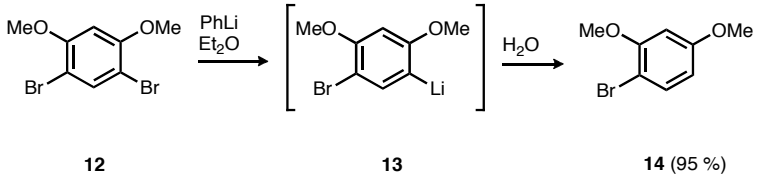


Scheme 1.3 Regioselective benzyne formation

Oxazolines have also been used for their ability to activate aromatic rings towards dearomatising additions (see Sections 1.2.6, 1.3.2.4 and 1.4.2.5).

1.1.2 Halogen-lithium exchange

The first reported halogen-lithium exchange was reported by Wittig in 1938 (the Wittig-Gilman reaction).[1] Wittig described the formation of organolithium **13** when 1,5-dibromo-2,4-dimethoxybenzene (**12**) was treated with phenyllithium, the reaction was quenched using water yielding the debrominated compound **14** (Scheme 1.4).



Scheme 1.4 The first reported halogen-lithium exchange reaction

Gilman went on to show that organolithiums formed by halogen-lithium exchange could be functionalised by reaction with other electrophiles.[1] This work

helped establish that there is an equilibrium between the starting organolithium and the subsequent product and that this equilibrium favoured the organolithium which best stabilised the anionic charge. Figure 1.2 and Table 1.1 show some approximate pK_aH of organolithiums and the equilibrium constants (K_{eq}) of the reaction of the organolithiums with phenyl iodide.

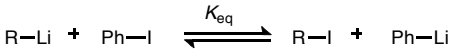


Figure 1.2 K_{eq} of the reaction of organolithiums with phenyl iodide

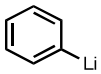
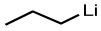
Entry	Organolithium	K_{eq}	Approximate pK_aH of 'carbanion'
1		0.004	36.5
2		1	37
3		10	39
4		3000	42
5		7500	42
6		4×10^4	42
7		5×10^5	42

Table 1.1 K_{eq} of the reaction of organolithiums with phenyl iodide

From this work it was established that *n*-BuLi could be used to cleanly generate aryllithiums (from aryl halides such as Br and I) and alkylithiums (from alkyl idodies). *t*-BuLi can also be used for halogen-lithium exchanges. To achieve this two equivalents of *t*-BuLi are needed for each equivalent of alkyl/aryl halide. The first equivalent is used in the halogen lithium exchange forming the new organolithium and *t*-Butyl halide. The second equivalent converts the *t*-butyl halide produced to 2-methylpropene by elimination of LiX, this prevents protonation of the newly formed organolithium by *t*-butyl halide. These are the most widely used methods for halogen-lithium exchange reactions, but other halogen-lithium exchange reactions are possible.[1]

Two possible mechanisms for halogen-lithium exchange have been proposed. Mechanism 1 (Figure 1.3) involves radical transfers where first a single electron is transferred from lithium to the halide substrate. Radical cleavage then forms the halogen anion which upon combination with the alkyl radical can undergo another

single electron transfer to the R^1 radical which forms an alkyl anion. This then combines with the lithium cation forming the new organolithium.

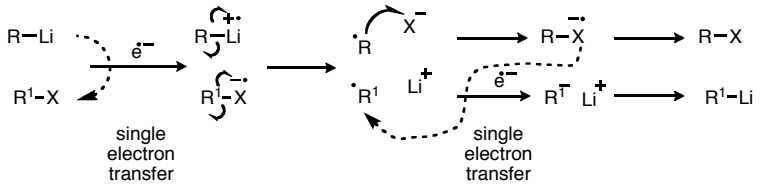


Figure 1.3 Mechanism 1 - Single electron transfer

Mechanism 2 involves a nucleophilic substitution at the halogen (which may either be direct or pass through an intermediate 'ate' complex.

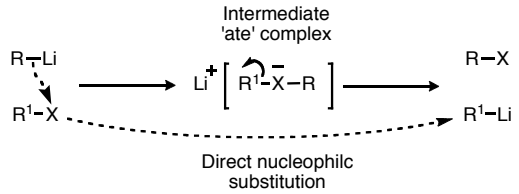


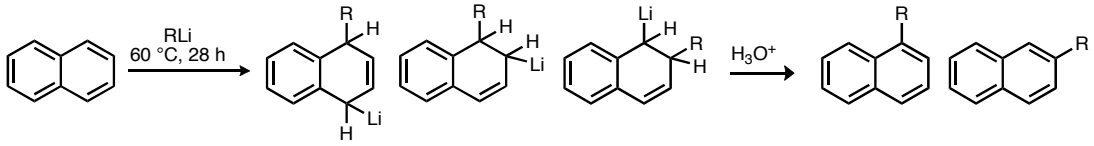
Figure 1.4 Mechanism 2 - Nucleophilic substitution

Experiments designed to elucidate the mechanism of halogen-lithium exchange often give conflicting results. It has been proposed that different mechanisms occur in different circumstances:[1]

- Aryl halide (Br and I) react *via* an 'ate' complex
- Primary alkyl iodides react *via* a polar mechanism (when using *t*-BuLi in ether/pentane solvent mix)
- Secondary alkyl iodides can react *via* either a polar mechanism or a radical mechanism
- Alkyl bromides react via a radical mechanism

1.2 Dearomatising intermolecular additions of organolithiums to naphthalenes

Dixon *et al.*[7] reported that the treatment of unactivated naphthalenes such as **15** with alkyllithiums led to dearomatised adducts **16**, **17** and **18**. These however were unstable to hydrolysis and would form rearomatised addition products **19** and **20**. It was noted that electron withdrawing groups accelerated the reaction.[1]



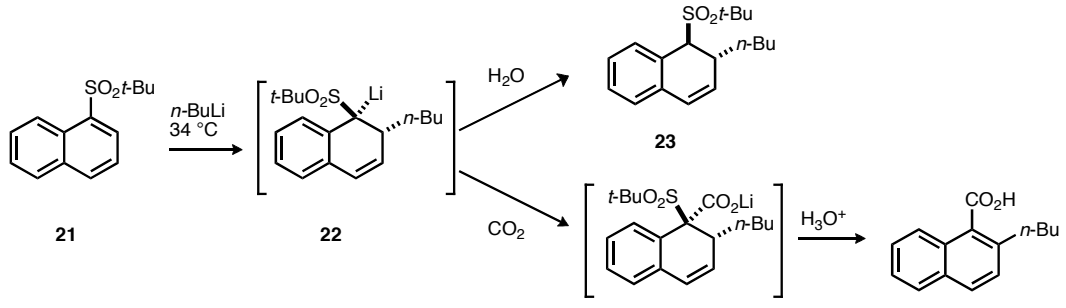
15 **16** **17** **18** **19** **20**

Scheme 1.5 Dearomatisation of unactivated naphthalenes

Since this discovery a wide array of electron withdrawing groups have been studied by different reseach groups. Below is a brief synopsis of these findings.

1.2.1 Sulfone Activation

Stoyanovich *et al.*[8] reported the dearomatisation of sulphone activated naphthalene **21** (Scheme 1.6).



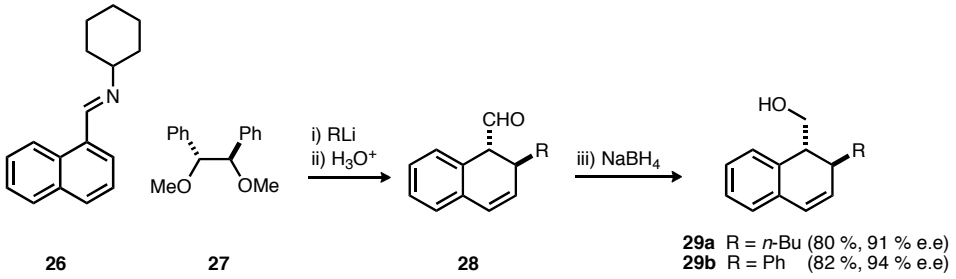
21 **22** **23** **24** **25**

Scheme 1.6 Dearomatisation of sulphone activated naphthalenes

Treatment of **21** with *n*-BuLi in refluxing ether formed dearomatised lithiated intermediate **22**, via addition of the organolithium at the 2-position. Intermediate **22** could then be quenched with water to give the related dihydronaphthalene **23** or trapped with carbon dioxide, allowing the formation of the rearomatised naphthoic acid **25** via *t*-butylsulfinate elimination.

1.2.2 Imine Activation

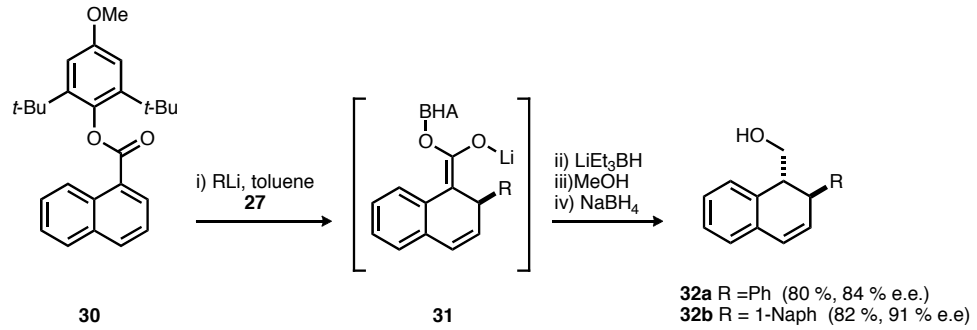
During the 1980's, Meyers and co-workers reported successful 1,4 additions of a range of organolithiums to imine activated naphthalenes forming *cis*-1,2-disubstituted dihydronaphthalenes.[9] This was further developed by Tomioka *et al.* who found that the addition of stoichometric amounts of C^2 symmetric chiral ligand **27** improved both yields and enantioselectivites.[10] This is believed to be due to the formation of a mixed aggregate of the imine, organolithium and chiral catalyst.



Scheme 1.7 Dearomatisation of imine activated naphthalenes

1.2.3 Ester Activation

Tomioka and co-workers also studied the directing ability of 2,6-di-*tert*-butyl-4-methoxyphenyl (BHA) esters.[11-13] They showed that *n*Bu- and phenyl-Li added to naphthyl BHA esters yielding dearomatised addition products in near quantitative yield, but as mixtures of *cis* and *trans* stereoisomers. Use of 1-naphthyllithium gave exclusively the *cis* isomer presumably due to steric interactions.[11, 12] Ligand **27** could also be applied to BHA esters and a one pot process was designed (Scheme 1.8) which could convert the naphthalene **30** to dialkylated dihydronaphthalene **32a-c**.[13]

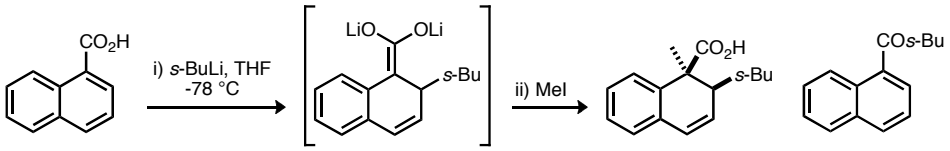


Scheme 1.8 Dearomatisation of BHA ester activated naphthalenes

The reaction could be carried out using a 20 mol % loading of catalyst **27**. However, this led to a reduction of yield along with a decrease in enantiomeric excess to 63-75 %. The overall reaction time was also increased by up to three fold.

1.2.4 Carboxylic Acid Activation[14]

Addition to naphthalenes with a free carboxylic acid at either the 1 or 2 position has been reported. Quenching di-lithiated intermediate **34** with methyl iodide gave the dearomatised product in good yield. The ketone 1,2-addition product **36** was kept to a minimum by carrying out the reaction at -78 °C.

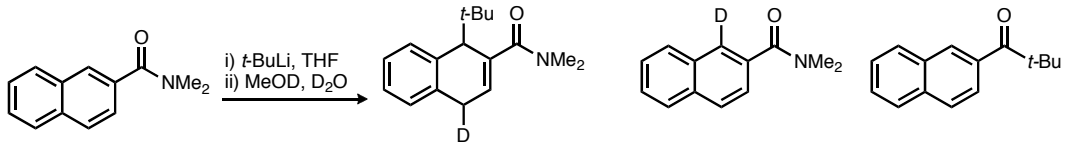


33 **34** **35** (80% 90:10) **36** (8 %)

Scheme 1.9 Dearomatisation of carboxylic acid activated naphthalenes

1.2.5 Amide Activation

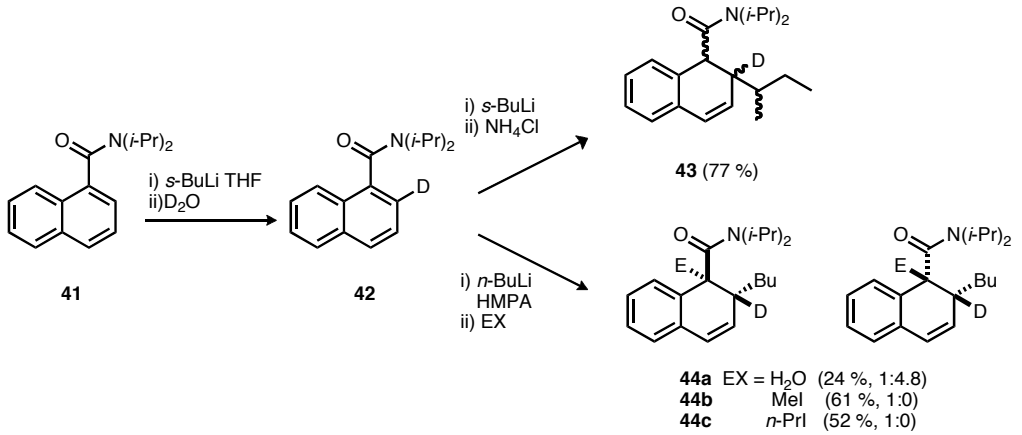
Aryl amides are commonly used to direct *ortho*-lithiation.[4, 15] Meyers *et al.* however, reported the formation of 1,4-adduct **38** when attempting to *ortho*-lithiate naphthamide **37** with *t*-BuLi (Scheme 10).[16] The product showed facile rearomatisation so no further work was carried out.



37 **38** (50 %) **39** (30 %) **40** (10 %)

Scheme 1.10 Dearomatisation of dimethyl amide activated naphthalenes

Within the Clayden group, lithiation and alkylation/protonation of the deuterated amide-activated naphthalene **42** was shown to give dearomatised products.[17] The best diastereoselectivities were obtained when hexamethylphosphoramide (HMPA) was used as a co-solvent in combination with alkylating agents.

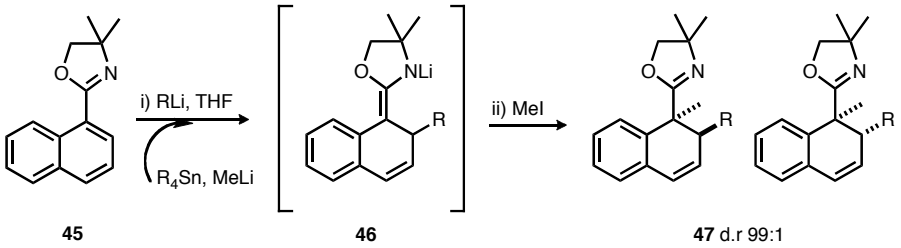


Scheme 1.11 Dearomatisation of *N,N*-diisopropyl amide activated naphthalenes

1.2.6 Oxazoline Activation

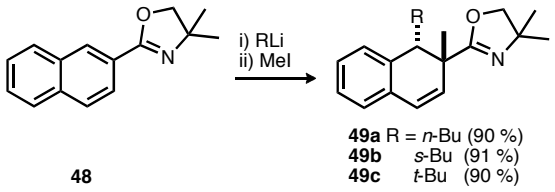
Oxazolines have been widely used for *ortho* lithiation[1, 18, 19] as well as to direct dearomatising additions, where they generally give 1,2 and 1,4 addition products.

Meyers *et al.* has studied dearomatising additions to both pyridyl-[20-22] and naphthyl-[23-26] oxazolines. These studies have been carried out using both achiral and chiral oxazolines. Scheme 1.12 shows the addition of organolithiums to the achiral 1-naphthyloxazoline **45**.



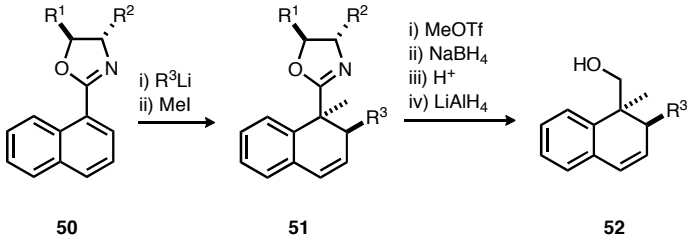
Scheme 1.12 Dearomatisation of 4,4-dimethyloxazoline activated naphthalenes

Organolithiums, which were formed *in situ* using tin-lithium exchange, added to the naphthalene at the *ortho*-position to give aza-enolate **46**. When methyl iodide was used as a quench the *trans* product was formed in greater than 99:1 diastereoselectivity. The *cis* product was only observed when aza-enolate **46** was protonated using isopropanol:water (1:1) or acidic quenches. Similar results were observed for the 4,4-dimethyl-2-(naphthalen-2-yl)oxazoline **48** (Scheme 1.13).[16]



Scheme 1.13 Dearomatisation of 4,4-dimethyl-2-(naphthalen-2-yl)oxazoline

An asymmetric version of this reaction has been achieved using chiral oxazolines as auxiliaries (Scheme 1.14 and Table 1.2).[27] (4*R*,5*R*)-4-(Methoxymethyl)-5-phenyl, valine derived and *tert*-leucinol oxazolines all gave selective dearomatising additions. In order to be efficient as a chiral auxiliary, the oxazoline also needs to be easily removed without racemising the newly formed stereocentres. For both the achiral and chiral oxazolines this can be achieved using a three step, two-pot method. Methylation using methyl triflate quaternizes the nitrogen, the salt is then reduced to form the oxazolidine. Acid hydrolysis cleaves the oxazolidine to the aldehyde, which is then reduced to give the alcohol **52** (Scheme 1.14).



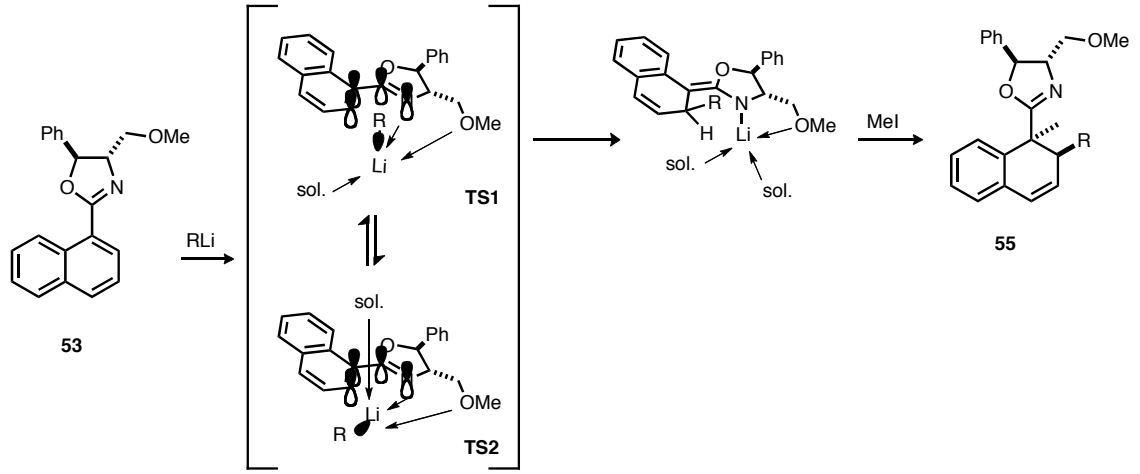
Scheme 1.14 Effect of different oxazolines on the selectivity of the dearomatising addition

Entry	R^1	R^2	R^3	T (°C)	Yield **52** (%)	d.r.
1	Ph	CH_2OMe	*n*-Bu	- 78	73	96:4
2	Ph	CH_2OMe	Ph	- 40	62	83:17
3	H	*i*-Pr	*n*-Bu	- 78	97	97:3
4	H	*i*-Pr	Ph	- 40	87	87:13
5	H	*t*-Bu	*n*-Bu	- 78	99	99:1
6	H	*t*-Bu	Ph	- 40	81	95:5

Table 1.2 Effect of different oxazolines on the selectivity of the dearomatising addition

The best results were observed for the addition of *n*-BuLi to *tert*-leucinol naphthyloxazoline (Entry 5). The lack of any chelating groups in this oxazoline suggests that the control is mainly due to steric bulk.[28] The diastereoselectivity for the (4*R*,5*R*)-4-(methoxymethyl)-5-phenyl oxazoline can be explained by the orbital diagram shown in Scheme 1.15.[24] The chiral oxazoline acts as a bi-dentate ligand by co-ordinating the lithium at both the nitrogen of the oxazoline and the oxygen of the methoxy group.

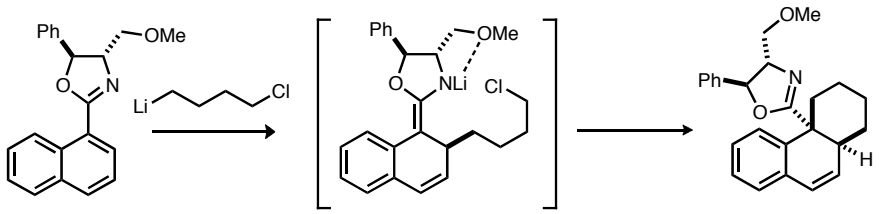
Another co-ordination site is occupied by the R group of the organolithium, the last site is presumed to be filled by a solvent molecule. Two posible conformations can exist, where the R-Li bond is either parallel or orthogonal to the π-system, **TS1** and **TS2** respectively. Meyers suggested that in **TS1** a Woodward-Hoffmann allowed[29] concerted 1,5-sigmatropic rearrangement can occur which gives the aza-enolate **54**.



Scheme 1.15 Meyers' proposed reaction intermediates

In most cases, the electrophile attacks **54** in an *anti*-sense to the incoming nucleophile. When achiral oxazolines which are void of a second co-coordinating group are used, random facial addition is observed followed by *trans* electrophilic trapping, to give racemic dihydronaphthalene products.[30]

Studies have shown a wide range of organolithiums (including vinylLi and MeLi) can be added to chiral naphthyloxazolines, with diastereoselectivites comparable to that of *n*-BuLi and PhLi. As well as methylation with methyl iodide, diphenyl disulphides and carbamates can be used as electrophiles.[28] Interestingly when the organolithium also has an electrophilic centre, a dearomatising addition followed by an intramolecular alkylation can occur (Scheme 1.16).[31] When the intermediate organolithium **56** is warmed, the syn-disposed tricyclic product **57** is formed preferentially in 84% yield, further transformations of **57** showed the d.r to be 98:2 with regard to the initial facial selectivity of the nucleophile.



53 **56** **57** (84 %)

Scheme 1.16 Use of nucleophiles which have an electrophilic centre

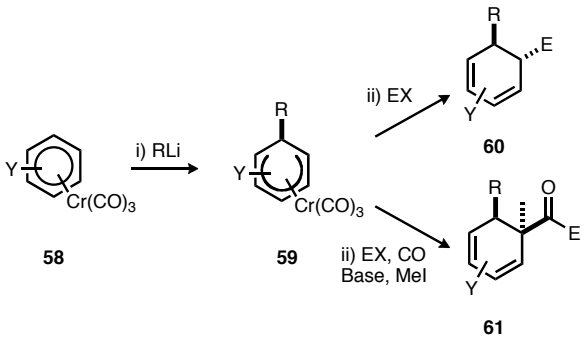
1.3 Dearomatising intermolecular additions of organolithiums to benzenes

1.3.1 Transition Metal Mediated Benzene Dearomatisations

Transition metals have been used for the activation of benzanoid systems towards dearomatising additions.[32] This section highlights the uses of chromium [(η^6-Arene)$Cr(CO)_3$], manganese [(η^6-Arene)$Mn(CO)_3]^+$ and osmium [(η^2-Arene)$Os(NH_3)_5]^{2+}$ complexes.

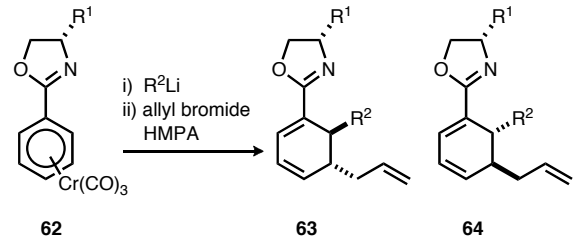
1.3.1.1 Chromium-arene complexes[(η^6-Arene)$Cr(CO)_3$]

Complexation of tricarbonyl chromium to an arene gives an air sensitive electron deficient ring which will readily undergo nucleophilic attack. $Cr(CO)_3$ can also act as a stereodirecting group, directing the attack of nucleophiles and exerting stereocontrol over manipulations of the arene sidechains. Nucleophilic additions of organolithiums are usually highly regioselective and dependent on the directing abilities of subsitituents. Electron donor groups direct attack to the *meta*-position, bulky and electron withdrawing groups lead to *para* addition and groups which can co-ordinate organolithiums (e.g. oxazolines and imines) direct *ortho*.[32] The dearomatising addition occurs by addition of the nucleophile *exo* to the $Cr(CO)_3$ in **58** to give cyclohexadienyl intermediate **59** (Scheme 1.17). Electrophilic attack then occurs at the metal centre followed by *endo* migration[33] to the ring to give diene **60**. In some cases, CO insertion may precede reductive elimination leading to the formation of ketone **61**. In both cases the organolithium nucleophile and electrophile react to give a *trans* relationship.



Scheme 1.17 The selectivity of the addition of organolithiums to chromium-arene complexes

These dearomatising nucleophilic additions can be carried out asymmetrically by using a chiral auxiliary,[34] for example, using a chiral oxazoline such as **62** (Scheme 1.18). The L-*tert*-leucinol oxazoline (Table 1.3, Entries 4-6) shows better diastereoselectivity than the L-valinol derived oxazoline (Entries 1-3), presumed to be due to steric interactions between the nucleophile and the oxazoline R^1 group.[34]

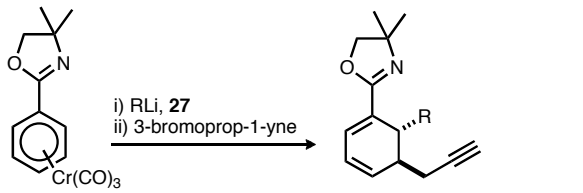


Scheme 1.18 Additions to oxazoline activated chromium-arene complexes

Entry	R^1	R^2	**63**:**64**	Yield (%)
1	*i*-Pr	MeI	96:4	61
2	*i*-Pr	*n*-Bu	95:5	54
3	*i*-Pr	Ph	95:5	48
4	*t*-Bu	Me	>99:1	69
5	*t*-Bu	*n*-Bu	>99:1	62
6	*t*-Bu	Ph	95:5	51

Table 1.3 Additions to oxazoline activated chromium-arene complexes

Other asymmetric methods include use of planar chiral arene complexes[35] and chiral ligands on chromium.[36, 37] Kundig and Tomioka have also demonstrated the use of C_2 chiral catalysts (Scheme 1.19).

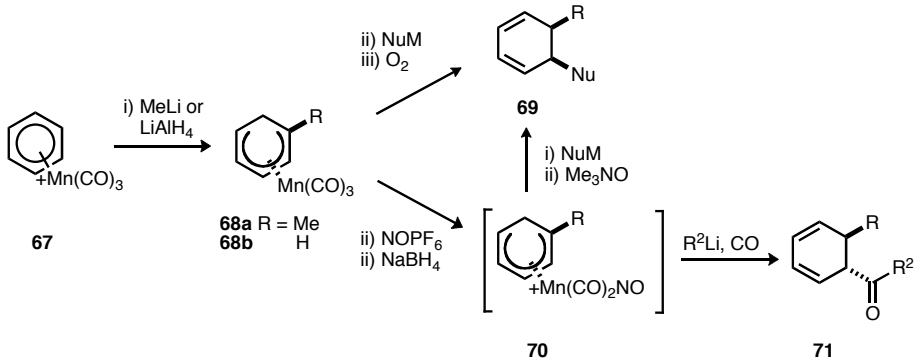


Scheme 1.19 Use of C_2 chiral catalysts in organolithium additions to chromium-arene complexes

Ligand **27** was used in combination with a range of organolithiums to give the 'nucleophile/electrophile addition' products **66a-d** in moderate yields and enantioselectivities.[10]

1.3.1.2 Manganese-arene complexes $[(\eta^6\text{-Arene})Mn(CO)_3]^+$

Manganese-arene complexes behave in a similar way to their chromium counterparts and undergo *exo* nucleophilic attack. However, unlike chromium complexes manganese complexes are positively charged, allowing attack from a broader range of nucleophiles. This increased reactivity means that nucleophilic attack is less selective, with many diene isomers forming. Products are also more likely to rearomatise during the cleavage step. To isolate dearomatised products, complexes can be treated with two nucleophiles as shown in Scheme 1.20.[38]

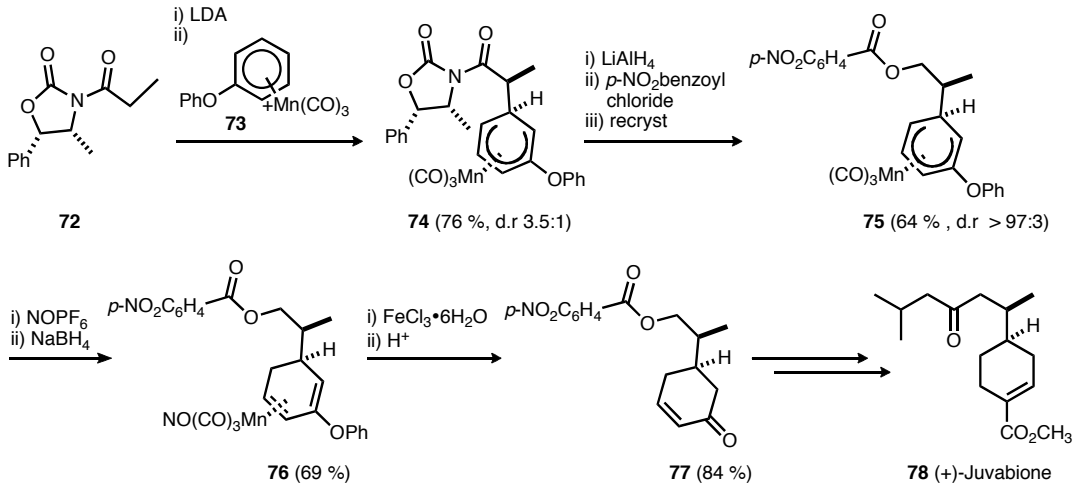


Scheme 1.20 The selectivity of the addition of organolithiums to manganese-arene complexes

Nucleophilic *exo* attack of either an alkyllithium or hydride forms neutral intermediates **68a** or **68b** respectively. These can be treated with a strong nucleophile (NuM) and O_2 to form the *cis* nucleophile/nucleophile product **69**. Exchange of a CO ligand on intermediate **68** with NO (using $NOPF_6$) forms the more reactive electrophilic intermediate **70**.[39] This can then be reacted with much weaker nucleophiles, which add

to a carbon monoxide ligand, then undergo *endo* migration to give acylated *trans*-1,2-disubstituted dienes **71**. Complex **70** can also be treated with strong nucleophiles to give **69**. This methodology is particularly useful when trying to access the single carbon addition product.

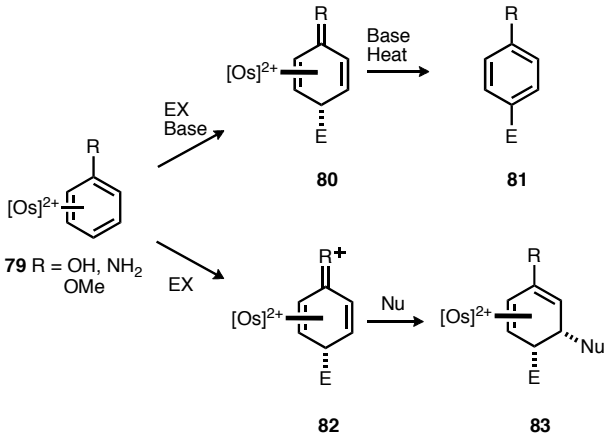
Asymmetric dearomatising addition reactions of Mn-complexes have been developed. Miles *et al.* used the chiral N-acyloxazolidinone nucleophile **72** which, after cleavage and oxidation, gave chiral 2-aryl propionic acids. High diastereoselectivities (>9:1) were obtained with manganese benzene complexes, whereas anisole and 1-phenoxybenzene complexes gave lower diastereoselectivities. The addition of **72** to 1-phenoxybenzene complex **73** gave **74** in 76 % yield (d.r of 3.5:1), this was used as a key step in the asymmetric synthesis of (+)-Juvabione (**78**) as shown in Scheme 1.21.[40]



Scheme 1.21 The use of manganese-arene complexes in the synthesis of (+)-Juvabione

1.3.1.3 Osmium-arene complexes$[(\eta^2\text{-Arene})Os(NH_3)_5]^{2+}$

Osmium complexes have opposing reactivity to manganese and chromium complexes. The (arene)Os^{2+} complex is electron rich due to π back-bonding and is therefore activated to electrophilic attack.[33] Osmium complexes of phenols, anilines and anisoles undergo electrophilic addition at the *para* position, the initial attack is still *exo* to the osmium complex forming either diene **80** if base is present, or cation **82** if not (Scheme 1.22).[32]



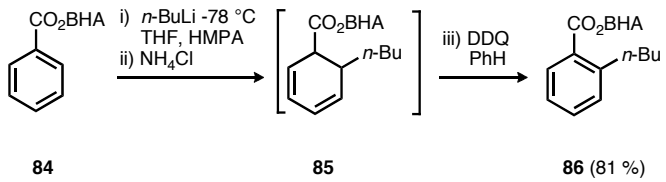
Scheme 1.22 The selectivity of the addition of organolithiums to osmium-arene complexes

Heating diene **80** causes decomplexation and the formation of rearomatised product **81**. Cation **82** is now electrophilic and can be treated with a nucleophile forming a *cis*-1,2-disubstituted cyclohexadiene **83**, which can be demetallated using ceric ammonium nitrate (CAN) or AgOTf. Alternatively, by leaving the osmium complexed to the cyclohexadiene it can be used to direct further reactions. This chemistry is readily applied to heteroaromatics with reports of dearomatisation of furan, pyrrole and thiophene.[41, 42]

1.3.2 Use of electron withdrawing groups for activation

1.3.2.1 Ester activation

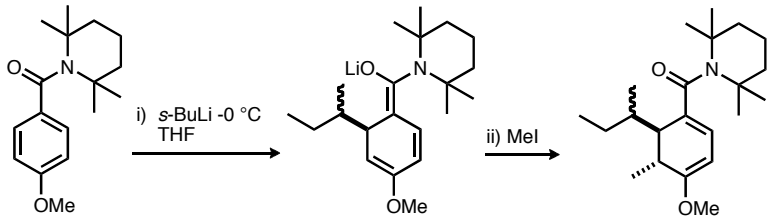
Miyano *et al.* reported the conjugate addition of *n*-BuLi to a BHA activated benzoate nuclei such as **84**. The 2-butyl benzoate addition product **86** was isolated after oxidation of the dearomatised intermediate **85** using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (Scheme 1.23).[43]



Scheme 1.23 Dearomatisation of BHA activated benzenes

1.3.2.2 Amide activation

Clayden has highlighted the ability of amides as activators for dearomatising additions. Use of a hindered 2,2,6,6-tetramethylpiperidine (TMP) benzamide which shields the carbonyl carbon from attack, preventing 1,2-addition. Addition of *s*-BuLi to the *para*-methoxy benzamide **87** gave lithium enolate **88**. Protonation of **88** was non regio- and stereo- selective. Alkylation however, only gave the *trans*-cyclohexadiene product **89** in 71% yield, in a ratio of 3:1 of the epimers at the exocyclic centre (Scheme 1.24).[44]

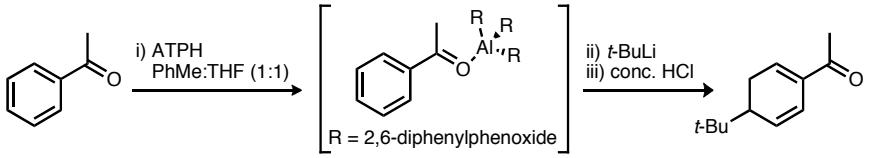


87 **88** **89** (71 %)

Scheme 1.24 Dearomatisation of TMP activated benzenes

1.3.2.3 Carbonyl activation

Yamamoto has showed that aromatic ketones and aldehydes can also promote conjugate addition of organolithiums.[45] Aluminium tris(2,6-diphenyl)phenoxide (ATPH) co-ordination to the carbonyl has the effect of both hindering 1,2-addition and increasing the electrophilicity of the ring (Scheme 1.25).



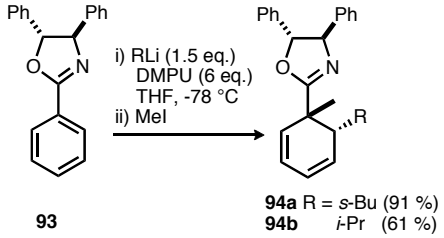
90 **91** **92** (93 %)

Scheme 1.25 Dearomatisation of ATPH activated benzenes

Addition of *t*-BuLi to ATPH co-ordinated acetophenone **91** followed by conc. HCl quench gave the dearomatised 1,6-addition product **92** in good yield.[46] Further studies showed that the reaction was quench dependent, as quenching with 1N HCl gave increased amounts of rearomatised products. This reaction has also been applied to naphthalene analogues, giving high yields of dearomatised products.[45]

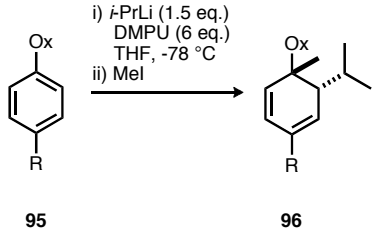
1.3.2.4 Oxazoline activation

Studies by Clayden[47] have shown that (4*R*,5*R*)-4,5-diphenyloxazoline activated benzenoid systems such as **93** can undergo dearomatising additions of organolithiums (Scheme 1.26) akin to those of Meyers (see Section 1.2.6)



Scheme 1.26 Dearomatisation of (4*R*,5*R*)-4,5-diphenyl oxazoline activated benzenes

The scope of the reaction with respect to the oxazoline has been investigated (Table 1.4 and Scheme 1.27).[48, 49] The best results were observed with the original *anti*-diphenyl oxazoline **97**. When the opposing *syn*-diphenyl oxazoline **98** was employed no conversion to product was observed. The phenyl analogue (R=H) gave only decomposition products whereas the anisole analogue (R=OMe) returned 100 % starting material. (4*R*,5*R*)-4-(Methoxymethyl)-5-phenyl oxazoline **99,** which has been utilised by Meyers for dearomatising additions to naphthylenes gave 25 % of diene **96** for both the phenyl and anisole analogues.



Scheme 1.27 The ability of different oxazolines to activate towards dearomatising additions

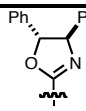
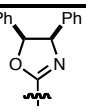
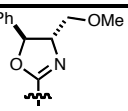
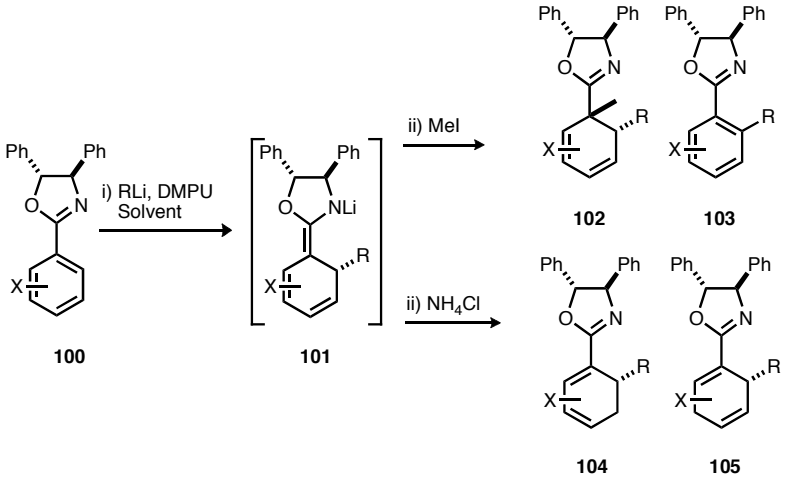
Ox		 97	 98	 99
Entry	R	Yield **96** (%)	Yield **96** (%)	Yield **96** (%)
1	H	61	0	25
2	OMe	64	0	24

Table 1.4 The ability of different oxazolines to activate towards dearomatising additions

The *anti*-diphenyl oxazoline **97** was then used for further investigation of the dearomatising addition with regard to aromatic substitution, organolithium and electrophilic quench. The results are summarised in Scheme 1.28 and Table 1.5).



Scheme 1.28 Ability of different organolithiums to undergo dearomatising additions to 4,5-diphenyl oxazolines activated benzenoid systems

Entry	SM	X	RLi	Quench	Product (%)	**103** (%)
1	**93**	H	*n*-Bu	MeI	-[a]	-
2	**93**	H	*i*-Pr	MeI	**102a** 70	-
3	**93**	H	*s*-Bu	MeI	**102a** 81[b]	-
4	**93**	H	*t*-Bu	MeI	**102a** 17[c]	-
5	**100b**	4-Ph	*i*-Pr	MeI	**102b** 32	30
6	**100c**	3-OMe	*i*-Pr	MeI	**102c** 54[d]	-
7	**100d**	4-OMe	*i*-Pr	MeI	**102d** 70	-
8	**100d**	4-OMe	*s*-Bu	MeI	**102d** 78	7
9	**93**	H	*i*-Pr	NH_4Cl	**104a** 47	5
10	**93**	H	*s*-Bu	NH_4Cl	**104a** 56	9
11	**100d**	4-OMe	*i*-Pr	MeOH	**104d** 30	6
					105d 15	
12[e]	**100e**	4-F	*i*-Pr	NH_4Cl	**105e** 53	7

[a] 95 % recovered SM. [b] The product was formed in as 3:1 mixture of diastereoisomers with respect to the exocyclic stereogenic centre. [c] The product of alkylation of the oxazoline ring was also isolated in 17 % yield. [d] Additional by-product from *ortho* methylation in 9 % yield. [e]Reaction carried out in toluene with racemic **100e**

Table 1.5 The ability of different organolithiums to undergo dearomatising additions to 4,5-diphenyl oxazoline activated benzenoid systems

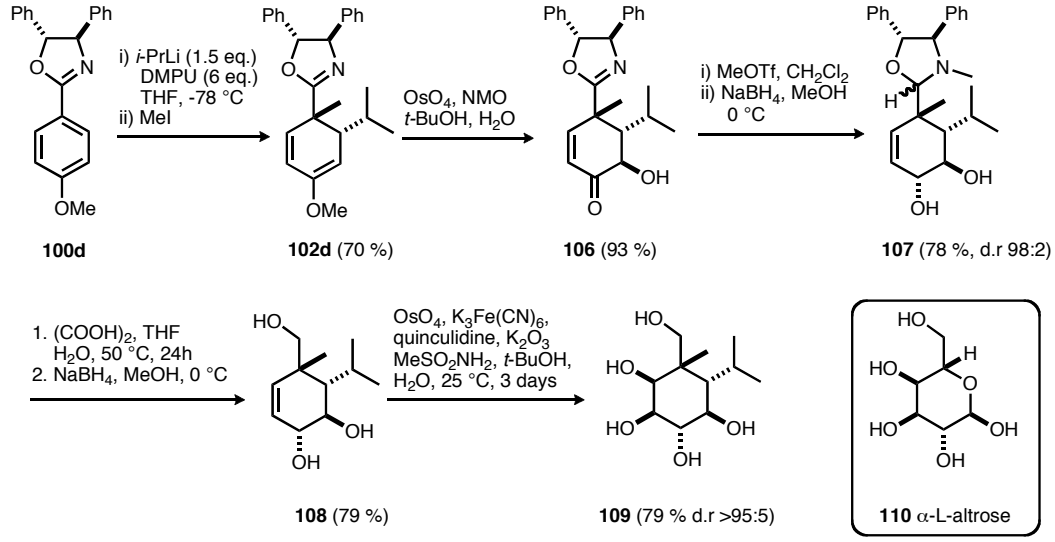
Aromatic substitution was well tolerated. The best results are seen with *para*-substituents, methoxy and fluorine (Entries 7, 8 and 12). Addition to the *meta*-methoxy substrate (Entry 6) takes place solely at the 2-position, when addition to an *ortho*-methoxy substrate was attempted, the methoxy group was displaced with the nucleophile by an S_NAr reaction. A related displacement reaction was observed by Miyano during the lithiation of BHA esters.[43]

Methyl iodide and ammonium chloride electrophiles both give single diasteroisomers of the addition products. Protonation gave either the 1,3-cyclohexadiene **104** or the 1,4-cyclohexadiene **105** depending on the substitution of the starting material. Treatment of azaenolate **101** with allyl bromide or benzyl bromide was not regioselective giving mixtures of 1,2 and 2,3 addition products.[48] With some examples the rearomatised product **103** was formed in low yield as a side product.

A preliminary reactivity pattern for the addition of organolithiums has been formed. The most effective additions are of secondary alkyllithiums *s*-BuLi and *i*-PrLi. *t*-BuLi (Entry 4) gave a small amount of the dearomatised addition product but a low recovery of starting material was observed due to the formation of other addition products. Primary organolithiums (for example, *n*-BuLi, Entry 1) return mainly starting material presumably because they are not basic enough to either undergo nucleophilc addition to or *ortho*-lithiate the ring. Attempts to dearomatise the ring with other organolithiums such as vinyllithium and cyclohexyllithium were unsuccessful.[50]

Due to the specific tolerance shown for the organolithium used, it was initially suggested that the mechanism for this addition had some radical character as primary alkyllithiums do not form stable radical anions. EPR investigations carried out by Karlubikova have since shown that a radical species with a large coupling constant (*cca*. 20 G) was formed under the reaction conditions which is not expected for a radical formed at *ortho* position of **93**. This large coupling did however compare well to the EPR spectra of oxazoline radicals reported by both Placucci[51] and Icli.[52] This suggests that the radicals formed are separate from the reaction pathway and therefore the reaction mechanism is unlikely to have a radical nature.[50]

This methodology has been used to form a key intermediate in the synthesis of carbosugar analogues of α-L-altrose **110** (Scheme 1.29).[43] Addition of *i*-PrLi to **100d** forms cyclohexadiene **102d**, which was oxidised to the hydroxyenone **106.** The oxazoline was removed by a sequential alkylation-reduction-hydrolysis-reduction method to give the alcohol **108**.[25] Finally a diastereoselective dihydroxylation yielded α-L-altrose analogue **109**.



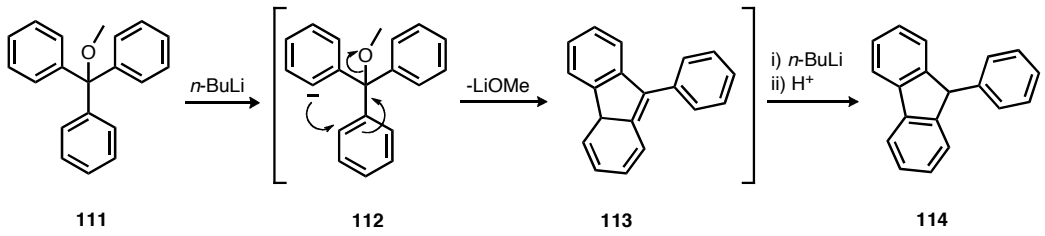
Scheme 1.29 Use of the dearomatising addition in the synthesis of L-altrose analogue 110

This methodology has also been used in the synthesis of an analogue of α-L-mannose and is currently being used in attempts to synthesise amino-carbasugars.[53]

1.4 Dearomatising intramolecular additions of organolithiums to aryls

1.4.1 Dearomatising intramolecular additions onto unactivated aromatic rings

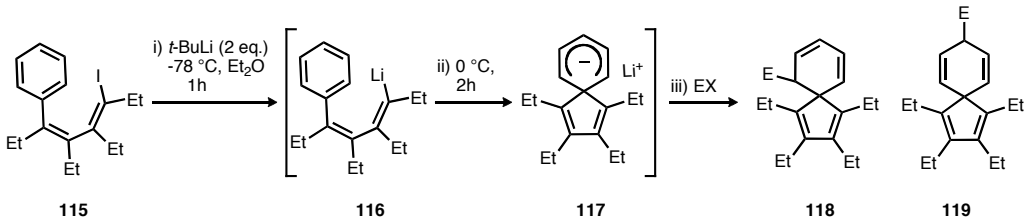
One of the earliest accounts of cyclisations onto unactivated aromatic rings is that of methoxytriphenylmethane **111** (Scheme 1.). Deprotonation of **111** gave lithiated intermediate **112** which cyclised onto an adjacent phenyl ring eliminating LiOMe and forming fluorenyl derivative **113**. Further lithiation and hydrolysis forms 9-phenyl-9*H*-fluorene **114**.[54]



Scheme 1.30 Dearomatising cyclisation of methoxytriphenylmethane

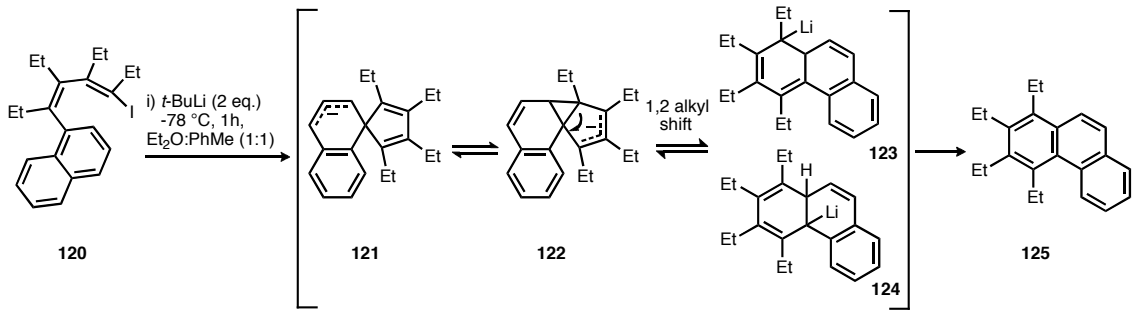
A more recent example is the dearomatising anionic cyclisation of diene **116** (Scheme 1.31) and diene **120** (Scheme 1.32). In both cases, the organolithium undergoes an *ipso* intramolecular attack to give dearomatised intermediates which can

then be reacted with electrophiles to give bi- or tri-spirotricylic products.[55] (-4,5-diethyl-6-phenylocta-3,5-dien-3-yl)lithium **116** was formed by iodo-lithium exchange at -78 °C and was stable at this temperature with protic quenches giving only the de-halogenated product. Warming to 0 °C for two hours led to cyclisation to dearomatised anion **117**, which could then be trapped with a wide range of electrophiles. The ratio of the double bond positional isomers formed is dependent on the electrophile used, for example, ketones gave only the non-conjugated diene **119**.



Scheme 1.31 Dearomatising cyclisation of 4-phenyl-1-lithiobutadiene

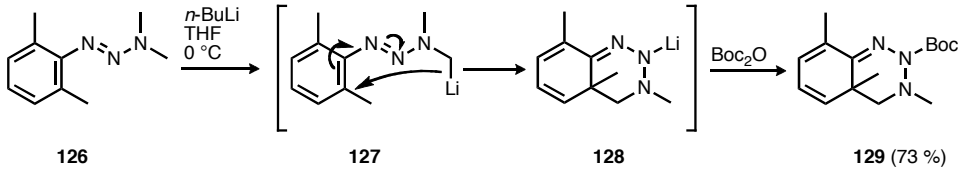
Related cyclisations of the 1-(-4,5-diethyl-6-iodoocta-3,5-dien-3-yl)naphthalene **120** were also observed, **120** demonstrated increased reactivity with cyclisations occurring at -78 °C (Scheme 1.32). In addition to trapping the naphthalene dearomatised anion **121** with electrophiles to give products related to **118** and **119**, it was found that at higher temperatures a rearrangement occured *via* a cyclopropane containing intermediate **122**, which after 1,2-alkyl shift and rearomatisation gave the phenanthrene derivative **125**. This rearrangement as yet has not been observed with the phenyl butadienes.



Scheme 1.32 Dearomatising cyclisation of 1-lithio-4-naphthyl-1,3-butadienes

Heteroatom containing tethers have also been shown to be able to cyclise onto unactivated rings. Scheme 1.33 shows the cyclisation of (*E*)-1-(2,6-dimethylphenyl)-3,3-dimethyltriaz-1-ene **126**.[56] Lithiation of **126** deprotonates on the methyl α to nitrogen forming a stable organolithium which can cyclise with dearomatisation at the substituted methyl position to give a stable organolithium **128**. This organolithium is

then captured using di-*tert*-butyl dicarbonate to give the Boc protected amine **129** in 73 % yield. When this reaction is carried out using the un-methylated analogue of **126** the cyclised product formed is unstable and no dearomatised products are isolated. As with other dearomatising cyclisations this reaction has been proposed to be an electrocyclic process.[57]



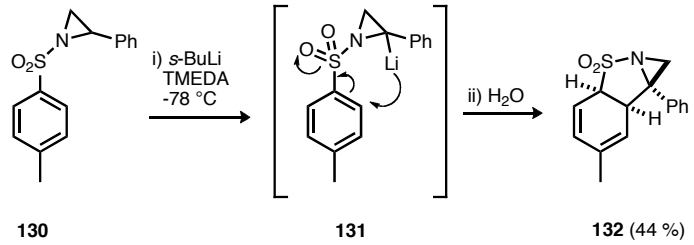
126 **127** **128** **129** (73 %)

Scheme 1.33 Dearomatising cyclisation of 3,3-dimethyltriazene tether

1.4.2 Dearomatising intramolecular additions onto activated aromatic ring

1.4.2.1 Sulfone activated aromatic rings

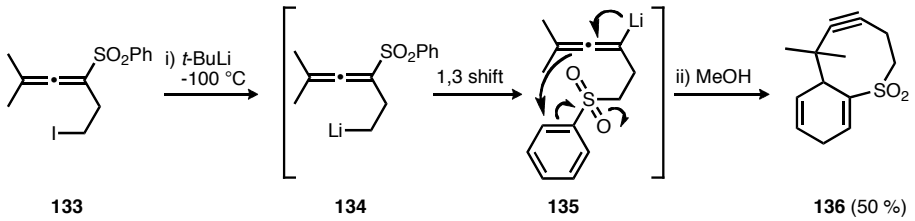
In 1991, Schaumann *et al.* noted a side reaction of ring opening of *N*-tosyl aziridine **130** which gave dearomatised products. From further studies it was found that α-deprotonation of the aziridine gave lithiated species **131** which after cyclisation and quenching with water gave the dearomatised product **132** as a single diastereoisomer.[58]



130 **131** **132** (44 %)

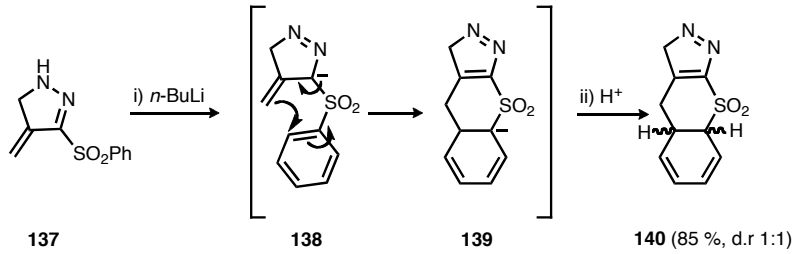
Scheme 1.34 Dearomatising cyclisation of *N*-tosyl aziridines

This side reaction may be considered unsurprising as Stoyanovich had previously reported the use of sulfones as activating groups for the addition of organolithiums to naphthalenes (see Section 1.2.1). The cyclisation of similar silyl substituted aziridines has been reported by Aggarwal.[59] Additional examples of the cyclisation of aromatic sulfones have been reported by Crandall[60] and Padwa.[61] Crandall *et al.* reported a dearomatising addition via the terminal allenyl anion **134** to the phenyl sulfone, yielding bicyclic sulfone **136** after protic quench.[60]



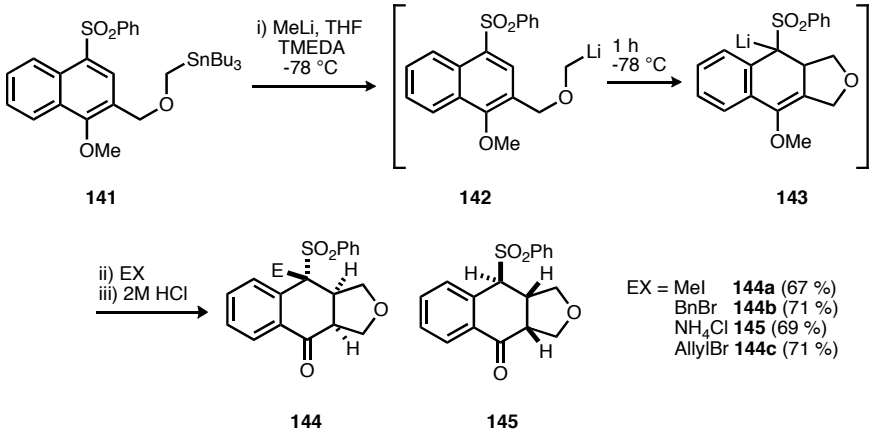
Scheme 1.35 Dearomatising cyclisation onto a phenyl sulfone

Padwa, whilst attempting to aromatise pyrazolephenyl sulfone **137** by nitrogen deprotonation, formed a stable conjugated anion **138**, which cyclised by addition to the *ortho* position of the phenyl sulphone. Protonation gave tricyclic product **140** as a 1:1 mixture of stereoisomers.[61]



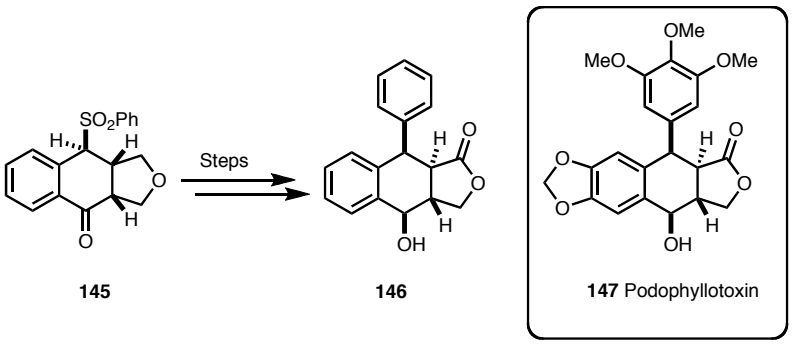
Scheme 1.36 Dearomatising cyclisation onto a pyrazolephenyl sulfone

Clayden[57] has studied the cyclisation of organolithiums which are tethered to sulfone-activated naphthalenes **141** (Scheme 1.37). Tin lithium exchange generated organolithium **142** which cyclised at -78 °C to the sufone-stabilised anion **143**, which was then alkylated using either BnBr, MeI or allylBr. The products were stable to hydrolysis yielding the ketone **144** as a single diastereoisomer.



Scheme 1.37 Dearomatising cyclisation of an ether tethered organolithium onto a sulfone activated naphthalene

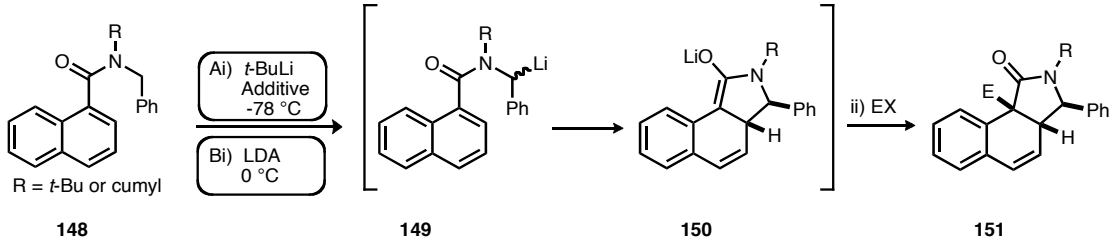
Podophyllotoxin **147** is a lignan natural product. By quenching anion **143** with ammonium chloride yielded sulphone **145**, which has been used as an intermediate in the synthesis of a podophyllotoxin analogue **146** (Scheme 1.38).



Scheme 1.38 Dearomatised intermediate used in the synthesis of Podophyllotoxin analogue 146

1.4.2.2 Amide activated aromatic rings

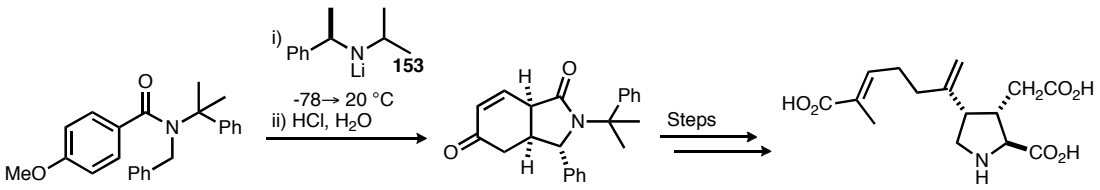
Clayden has extensively studied the use of amide activating groups in intramolecular dearomatising reactions. *N*-Benzylnaphthamide **148** was shown to be deprotonated by *t*-BuLi either at the α-benzylic position or the *ortho* position, using deuterium labelling studies. Trapping experiments using methyl iodide gave a 2:1 ratio of the α-methylated product to the *ortho*-methylated product. By using additives such as HMPA and DMPU the equilibrium between the two deprotonated forms could be shifted towards the α-lithiated species **149**.[62] Studies showed that **149** can cyclise to give the lithium enolate **150**, which can be trapped by electrophiles to give a single diastereoisomer of the product **151** (Scheme 1.39), which suggests that the cyclisation is stereospecific.[57] In the absence of HMPA/DMPU no cyclisation was observed.[57] The discovery that LDA is basic enough to deprotonate at the benzylic position meant cyclisations could be performed at higher temperatures (between -30 and 0 ^{o}C), LDA is also compatible with a wider range of aryl groups (e.g. halogen containing).[63]



Scheme 1.39 Dearomatising cyclisations of *N*-benzylnaphthamides

It has also been shown that *N*-benzylbenzamides undergo the same reaction using either *t*-BuLi and HMPA at -78 ºC or LDA at 0-25 ºC to give the expected isoindolones 26-88 % yield.[63, 64]

Asymmetric versions of the amide activated cyclisations have been established for both benzamides and naphthylamides. The previously reported LDA methodology was developed to use chiral lithium amide **153**, giving cyclised products in good yields and enantiomeric excess after recrystallization (Scheme 1.40). **154** is a key intermediate in the synthesis of the kainoid (-)-isodomoic acid C.[65]

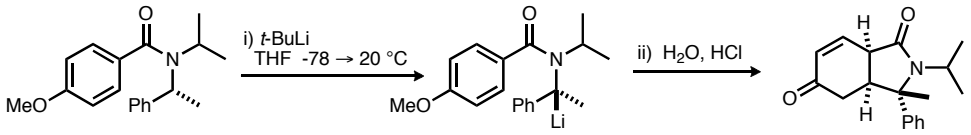


152 **154** (86 %, 62 % e.e) recryst. 99 % e.e **155** (-)-isodomoic acid C

Scheme 1.40 Asymmetric dearomatising cyclisation of *N*-benzyl benzamides

This dearomatising cyclisation methodology has also been used to synthesise other members of the kainoid family including a pyroglutamate analogue,[66] an acromelic acid analogue,[66] (-)-kainic acid,[67] (±)-kaninic acid,[68] and an α-methylated analogue of kainic acid.[69] More recently it has been used in the total synthesis of (–)-isodomoic acid B, (–)-isodomoic acid E and (–)-isodomoic acid F.[70]

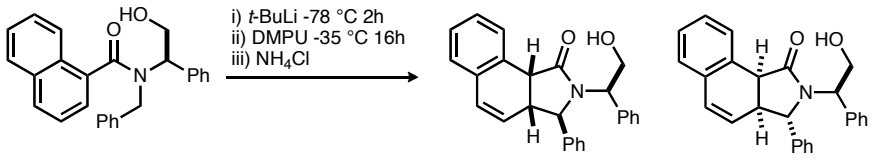
Diastereoselective transformations can also be induced by using a substituent on the benzyl position. For example benzamide **156** cyclises in 80 % yield and 99 % ee via organolithium **157** (Scheme 1.41).[71]



156 **157** **158** (80 %, 99 % e.e)

Scheme 1.41 Dearomatising cyclisation of chiral *N*-benzyl benzamides

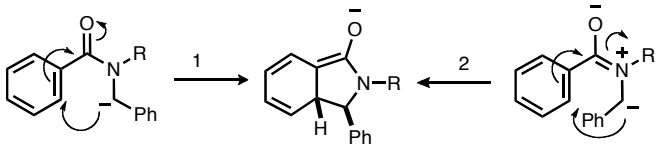
The use of a chiral auxilliary on the nitrogen also imparts stereochemical control on the reaction. Phenylglycinol has been shown to yield cyclised products in a high diastereomeric ratio (Scheme 1.42).[66]



159 **160** (91 %) **161** (9 %)

Scheme 1.42 Use of a chiral protecting group in the dearomatising cyclisation of *N*-benzyl benzamides

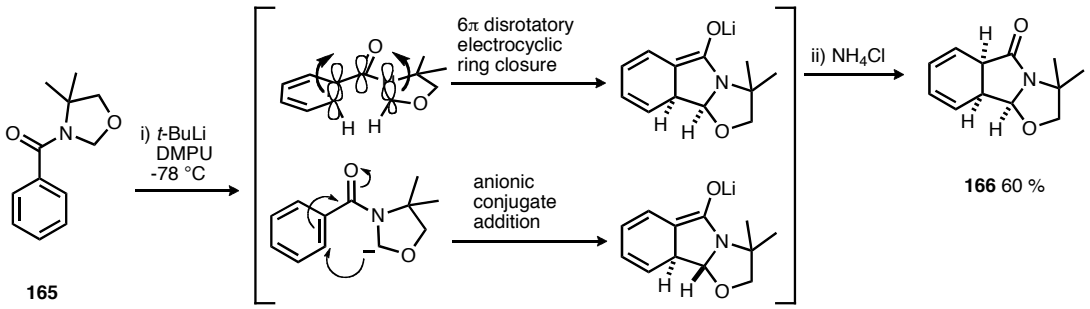
There are two proposed mechanisms for this type of reaction both of which would support the selectivity for the *cis* product (Figure 1.5). The anionic conjugate addition mechanism (Path 1), is a 5-*endo*-trig cyclisation and is therefore a Baldwin-disfavoured process.[72] Even though this is disfavoured, *ab initio* and DFT calculations reported by Lopez-Ortiz and Gonzalez have shown that the cyclisation of benzamide and phosphinamide ions (see Section 1.4.2.3) have Michael-type ionic characteristics.[73] This has been further substantiated by Clayden who reported the 5-*endo*-trig cyclisations of lithiated N-benzyl acrylamides.[74]



163 **162** **164**

Figure 1.5 Possible mechanisms for the dearomatising cyclisations of *N*-benzyl benzamides

Support for the electrocyclic mechanism (**2**) was provided by the cyclisation of *N*-benzoyl oxazolidinone **165** (Scheme 1.43)[72] to *cis*-tricycle **166** as a single diastereoisomer. **166** is the expected product of an electrocyclic disrotary ring closure but not the expected product of the anionic mechanism.



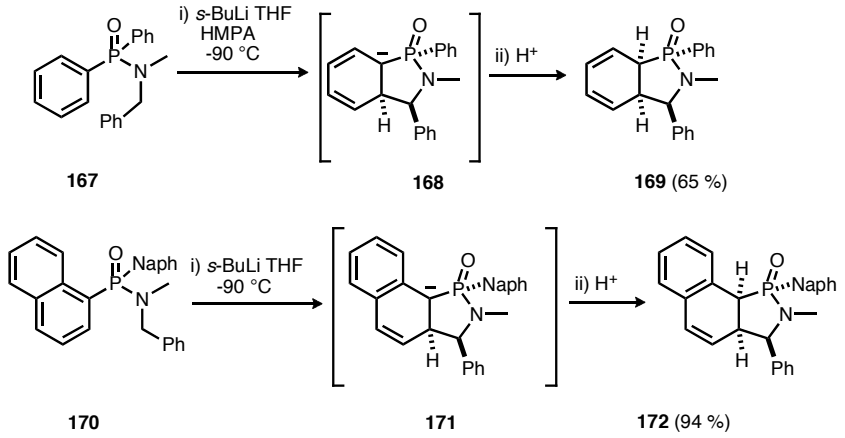
165 **166** 60 %

Scheme 1.43 Dearomatising cyclisation of *N*-benzoyl oxazolidinone activated benzene

It has been shown that a protecting group is needed on nitrogen to give good yields and selectivities. Large protecting groups cause the benzyl to adopt a *trans* configuration to the carbonyl required for cyclisation.[72]

1.4.2.3 Phosphinamide and phosphonamide activated aromatic rings

Lopez-Ortiz and co-workers have investigated the cyclisation of both benzyl (**167**) and naphthyl *N*-benzyl phosphinamides (**170**).[75] The naphthyl phosphinamides show better stereoselectivity with 94 % of a single stereoisomer being formed from the cyclisations (Scheme 1.44).[76]

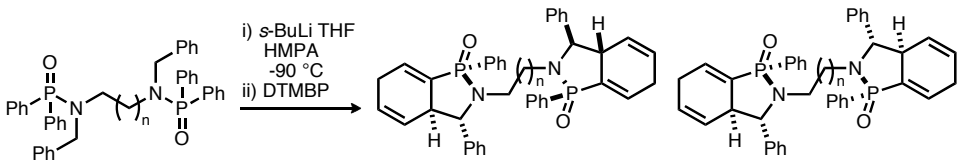


167 **168** **169** (65 %)

170 **171** **172** (94 %)

Scheme 1.44 Dearomatising cyclisations of benzyl and naphthyl *N*-benzyl phosphinamides

A double dearomatisation has also been reported using a one pot strategy to give doubly phosphorylated systems in good yields and with high *regio*- and *stereo*-control.[77]

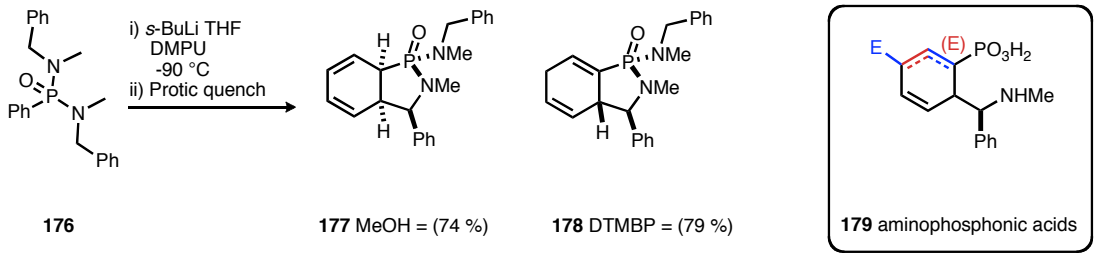


173 n = 1, 2, 3

174a:175a n = 1 (97 % (67:33))
174b:175b 2 (73 % (67:33))
174c:175c 3 (83 % (83:17))

Scheme 1.45 Double dearomatising cyclisation of benzyl *N*-benzyl phosphinamides

They have also shown that *N*-benzyl-P-aryl phosphonamides **176** can undergo the same type of dearomatising cyclisations. For this reaction the selectivity is quench dependent; MeOH introduced the proton at the α carbon with respect to phosphorus to give **177** in 74 %. However 2,6-di(*tert*-butyl)-4-methylphenol (DTBMP) protonated at the γ position yielding **178**.[78]

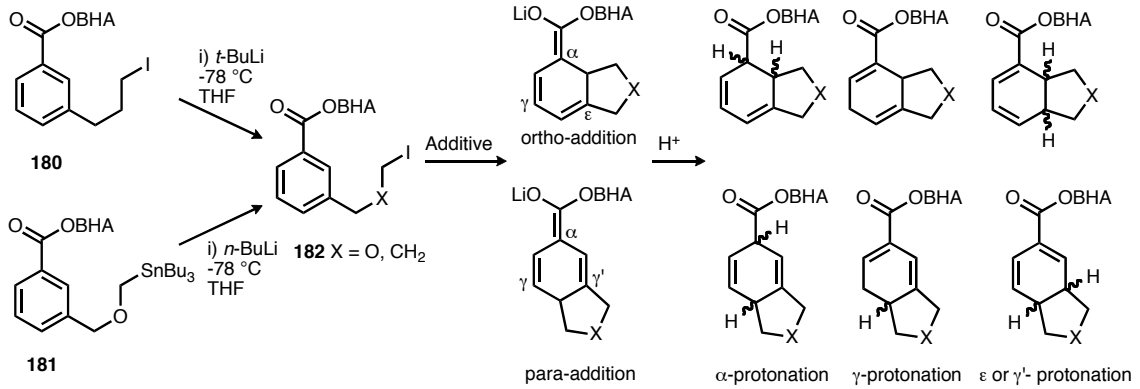


Scheme 1.46 Dearomatising cyclisations of *N*-benzyl-P-aryl phosphonamides

As with the phosphinamides **169** and **172**, **177** and **178** can be deprotected using 2N HCl to furnish γ-(N-methylamino)phosphonic acids e.g. **179** that have shown promising levels of antitumor activity in preliminary screens.

1.4.2.4 Ester activated aromatic rings[57, 79]

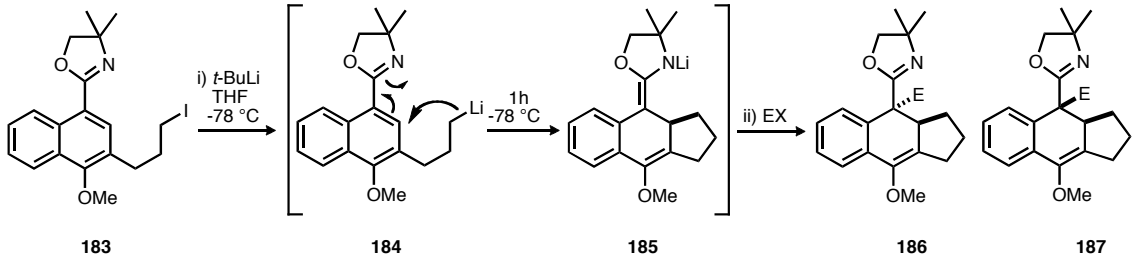
Clayden has also investigated the cyclisation onto BHA ester activated rings. The organolithiums required for the cyclisation were prepared by lithium-halogen exchange and tin-halogen exchange respectively for ester **180** and **181**. In the presence of an additive (either HMPA, DMPU or TMEDA) both of the resultant organolithiums undergo dearomatising cyclisations. This was characterised by loss of benzoate aromatic peaks and the appearance of complex peaks in both the alkene and aliphatic regions of the ^{1}H NMR spectra of the crude reactions. Unfortunately the complexity of the spectra suggested that many stereo- and regioisomers had formed through a non selective addition at both the *ortho*- and *para*-positions, along with non-stereo- and regio-selective enolate protonation which would also give increased amounts of products (Scheme 1.47).



Scheme 1.47 Dearomatising cyclisation of organolithiums tethered to BHA activated benzenes

1.4.2.5 Oxazoline Activated Aromatic Rings[57, 79]

Within the Clayden group, Kenworthy successfully cyclised a variety of tethered alkyllithiums onto naphthalene rings using an activating oxazoline electron withdrawing group to form new fused ring systems. Unlike the related work by Meyers (see Section 1.2.6) the nucleophile is tethered to the naphthalene ring.



Scheme 1.48 Dearomatising cyclisation of a hydrocarbon tether onto an oxazoline activated naphthalene

Entry	EX	Product (%)
1	MeI	**186a** (72)
2	BnBr	**186b** (65)
3	NH_4Cl	**187** (63)
4	PhCHO	**186c** (45)[a]
5	AllylBr	**186d** (67)

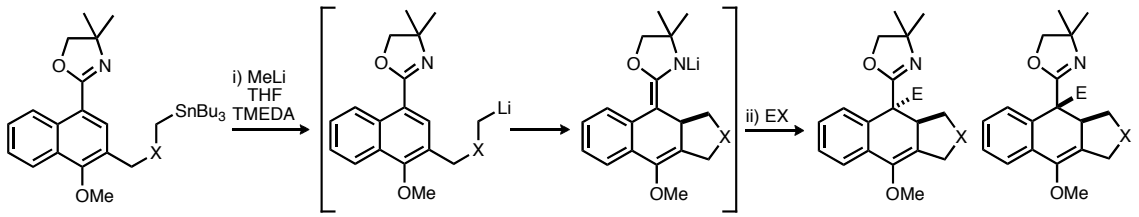
[a] Yield of major epimer of 3:1 mixture

Table 1.6 Dearomatising cyclisation of a hydrocarbon tether onto an oxazoline activated naphthalene

Using the geminal dimethyloxazoline iodo substrate **183,** halogen-lithium exchange gave alkyllithium **184**, which cyclised at -78 °C to form aza-enolate **185** (Scheme 1.48 and Table 1.6). This can then be trapped with a range of electrophiles in moderate to good yield. When the electrophile is an alkylating agent, attack occurs at the *exo* face of the bicyclic system to give the product **186** with the oxazoline on the *endo* face as a single diastereoisomer. Quenching with ammonium chloride gave the opposing *exo* product **187**, as a single diastereoisomer.

Ether and tertiary amine tethers were also studied (Scheme 1.49).[57] The organolithiums of the type **188** were formed by tin-lithium exchange using MeLi. Cyclisation of the amine containing organolithium required a higher temperature of -40 °C compared to the alkyl and the ether tethers which both cyclised at -78 °C. The resultant aza-enolates could be quenched with a range of electrophiles in good yields. The THF fused dihydronaphthalene was formed with the oxazoline on the *exo* face **192**

for both alkylation and protonation except when using BnBr (Entry 2, Table 1.7). This was also observed for the nitrogen tether, with all electrophiles yielding the *exo* product **192**.



Scheme 1.49 Dearomatising cyclisation of ether and amine tethers onto an oxazoline activated naphthalene

Entry	Temp (°C)	X	Quench	Product (%)
1	- 78	O	MeI	**192a** (79)
2	- 78	O	BnBr	**191a** (79)[a]
3	- 78	O	NH_4Cl	**192b** (74)
4	- 78	O	PhCHO	**192c** (41)[b]
5	- 40	NBn	MeI	**192d** (71)
6	- 40	NBn	NH_4Cl	**192e** (73)
7	- 40	NBn	PhCHO	**192f** (80)[b]
8	- 40	NBn	AllylBr	**192g** (57)

[a]Yield of 3:1 mixture of diastereoisomers [b]Yield of major epimer of 2:1 mixture at the alcohol centre [f] Yield of 3:2 epimeric mix at alcohol centre

Table 1.7 Dearomatising cyclisation of ether and amine tethers onto an oxazoline activated naphthalenes

1.5 Project aims

In their recent review, Ortiz et al. cover 16 different functional groups that have promoted dearomatising nucleophilic addition to anthracene, naphthalene and benzene systems.[80] In general the dearomatisation of naphthalene is much more facile than that of benzene as the aromaticity of only one ring is destroyed. Where the dearomatising addition is intramolecular, the work has mainly focused on the cyclisation of organolithiums which are tethered to the ring system by an electron-withdrawing group (EWG), e.g. amides (Figure 1.6a and section 1.3.2.2). Some substrates where the electron-withdrawing group is not part of the organolithium tether and is instead a substituent on the aromatic ring have been investigated (Figure 1.6b). This type of system works well when using a naphthalene ring system (see section 1.4.2.1 and 1.4.2.5). However with benzenoid systems, cyclisations either fail (when using hindered amides or sulphones as the electron-withdrawing group) or are unselective as shown in the use of the BHA esters (see section 1.4.2.4).[79]

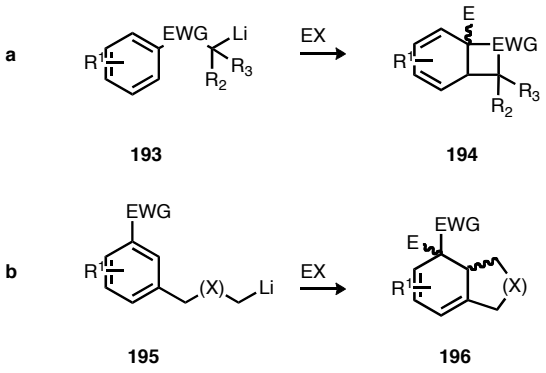


Figure 1.6 Possible placement for the electron-withdrawing group for dearomatising cyclisations

The aim of this project is to further investigate the use of a detached electron-withdrawing group with benzenoid systems in an attempt to improve selectivity in these reactions. The ability of (4*R*,5*R*)-4,5-diphenyloxazolines in intermolecular dearomatising additions to benzenoid systems (Scheme 1.26), has led our interest in developing its use in intramolecular cyclisations. The (4*R*,5*R*)-4,5-diphenyloxazolines showed limited scope with respect to the organolithiums which were able to dearomatise the ring (see section 1.2.6, Table 1.5). As cyclisations are more effective than intermolecular reactions it was hoped that the two together may work better. For this investigation different substrates will be synthesised which vary the substituent on the aromatic ring (to investigate blocking unselective additions), have different

organolithium tethers (to create a variety of fused rings), use alternative methods of organolithium generation and also have different oxazoline electron withdrawing groups in order to determine if any reactions are specific to the (4*R*,5*R*)-4,5-diphenyloxazoline.

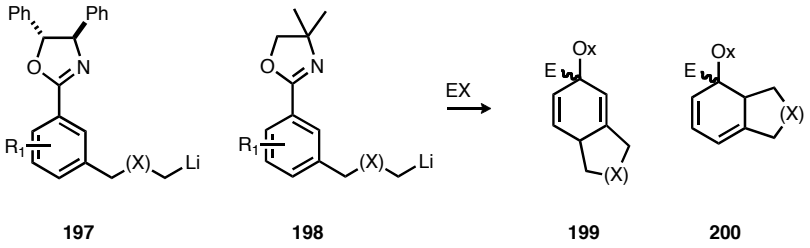


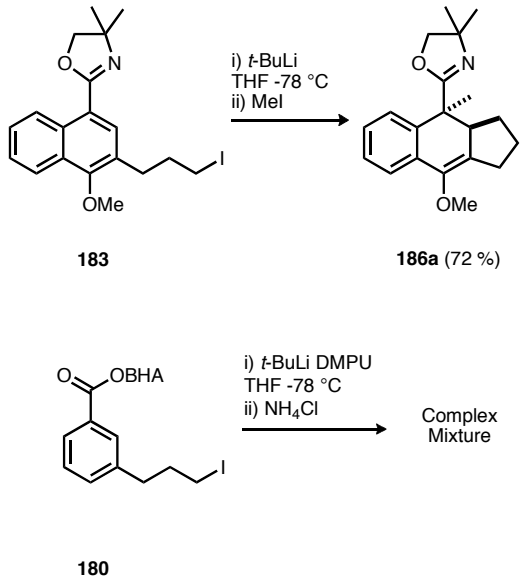
Figure 1.7 Possible substrates for investigation

Depending on the regioselectivity of the reaction the dearomatising addition could take place at either the *ortho* or *para* positions to form either **199** or **200** selectively or mixtures of both. These products are novel fused ring structures and we hope to exploit the different reactivities of the unsaturated bonds and carry out selective transformations such as dihydroxylations. As the oxazoline is an activating group we would also like to investigate its removal.

2 Dearomatising intramolecular additions of organolithiums to (4*R*,5*R*)-4,5-diphenyloxazoline activated benzenoids

2.1 Hydrocarbon tethered organolithiums

The investigations carried out by Kenworthy have shown that simple primary alkyl lithium tethers, formed by halogen-lithium exchange, can undergo dearomatising cyclisation onto activated naphthyl and benzenoid systems (Scheme 2.1 and sections 1.4.2.5 and 1.4.2.4).[79]

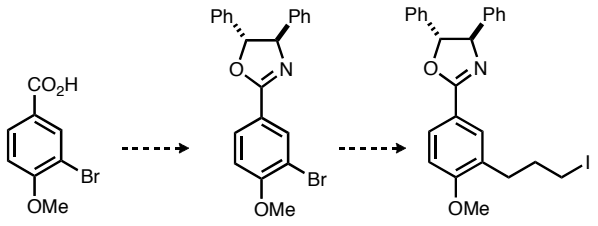


Scheme 2.1 Dearomatising cyclisations of primary alkyl lithium tethers

When used to dearomatise 4,4-dimethyloxazoline activated naphthalene **183** the addition was regioselective, due to a *para* methoxy blocking group, forming **186a** in 72 % yield. However the cyclisation of the hydrocarbon organolithium onto the BHA activated phenyl **180** was not regioselective and protonation of the intermediate anions was non-selective a complex mixture of dearomatised products was observed. As there are already examples of this type of tether undergoing cyclisations, it was felt it would be a suitable tether to investigate the ability of (4*R*,5*R*)-4,5-diphenyloxazolines to direct intramolecular dearomatising cyclisations.

2.1.1 Construction of the hydrocarbon tethered lithiation precursor

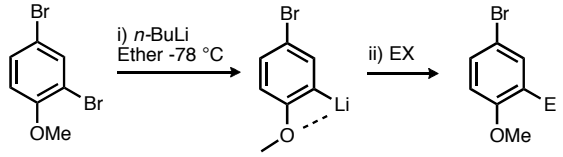
Initial attempts to synthesise the required substrate installed the oxazoline group first, as we envisaged that the tether could be installed by manipulation of the bromine at the *meta*-position of the benzene ring of **202** (Figure 2.1).



201 **202** **203**

Figure 2.1 Retrosynthesis for the hydrocarbon tether construction

The *para*-methoxy group was included for two reasons; firstly to block dearomatising addition to the *para*-position if the addition was not regioselective and secondly, to help to stabilise the lithium anion during the halogen lithium exchange reaction used to install the tether (Scheme 2.). The organolithium **205** is the thermodynamic mono-lithiated product where the *ortho*-methoxy stabilises the organolithium.[a,81]



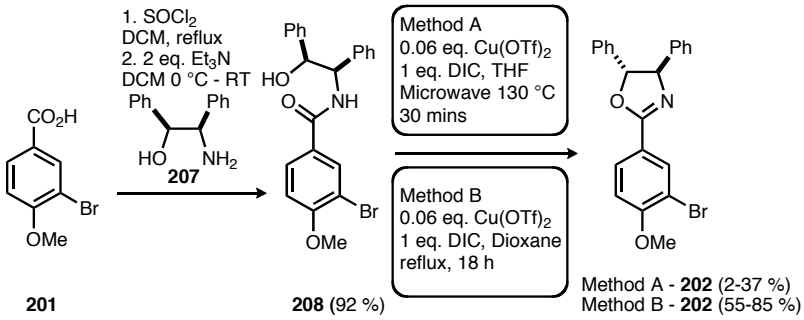
204 **205** **206**

Scheme 2.2 Regioselective bromine-lithium exchange of 2,4-dibromoanisole

The oxazoline was constructed by first forming the β-hydroxy amide **208** (Scheme 2.3). This could be synthesized in 92 % yield by coupling the benzoyl chloride formed from 3-bromo-4-methoxy benzoic acid **201** with (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol (**207**). Cyclisation could then be effected by using the method described by Linclau.[82] The β-hydroxyl group is alkylated with

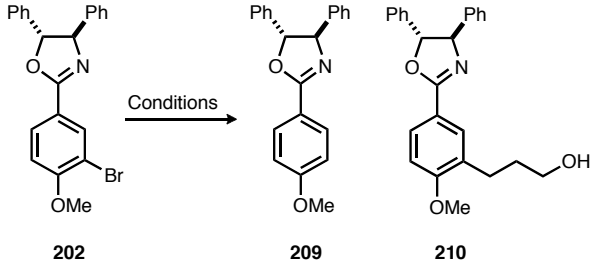
[a] Methoxy substituted extended enolates have been shown to have greater regiocontrol during protonation.[80]

diisopropylcarbodiimide, cyclisation then occurs by elimination of the activated alcohol to form the oxazoline. The reaction proceeds with inversion of stereochemistry at the alcoholic centre, with a d.r. of >99:1.[b] This method was however capricious with yields varying when repeated from 2-37 % when carried out with microwave irradiation, but this yield could be improved to 55-85 % by prolonged thermal heating in 1,4 dioxane.



Scheme 2.3 Synthesis of 2-(3'-bromo-4'-methoxy-phenyl)-4,5-diphenyloxazoline

With the oxazoline group formed it was hoped that the tether could be installed by halogen lithium exchange, quenching with oxetane and BF_3OEt_2.[79] However lithiation attempts failed to incorporate the tether with only the de-halogenated compound **209** seen in the crude ^{1}H NMR spectrum (Table 2.1, Scheme 2.4).



Scheme 2.4 Tether incorporation conditions

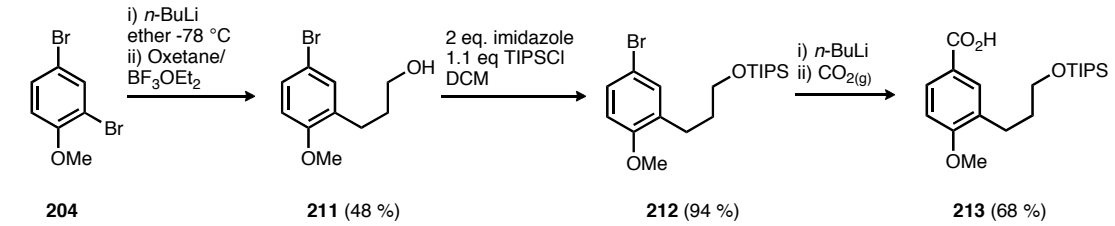
Entry	RLi	Lithiation		Quench	
		Temp (°C)	Time	Temp (°C)	Time
1	*t*-Bu (2 eq.)	- 78	20 mins	- 78	1 h
2	*t*-Bu (2 eq.)	- 78	20 mins	- 78-RT	1 h
3	*n*-Bu (1.5 eq.)	- 78	20 mins	- 78-RT	1 h

Table 2.1 Tether incorporation conditions

Due to the failure to install the tether at the late stage, the halogen lithium exchange was carried out first (Scheme 2.5). Lithiation of 2,4-dibromo anisole (**204**) followed by oxetane and BF_3OEt_2 quench gave the propyl alcohol **213** in 48 %. The alcohol was then protected as the triisopropyl silyl ether to allow manipulation of the

[b] Only one set of oxazoline peaks are seen in the crude ^{1}H NMR spectrum.

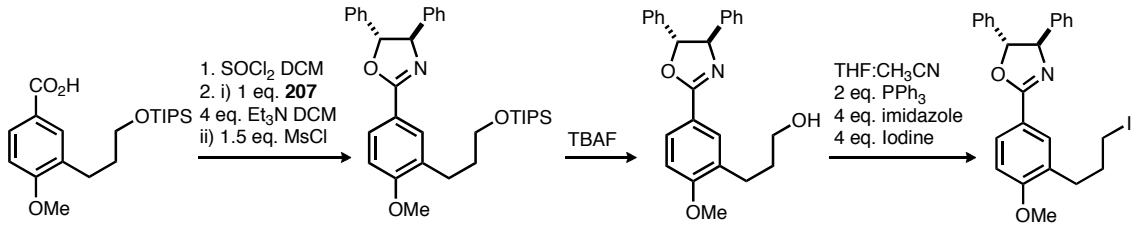
remaining bromine. By again utilising halogen lithium exchange, this time quenching with carbon dioxide, the carboxylic acid **213** was formed in moderate yield.



204 **211** (48 %) **212** (94 %) **213** (68 %)

Scheme 2.5 Installation of the tether for the hydrocarbon tether lithiation precursor

Installation of the oxazoline was achieved by a one-pot amide coupling, mesylation and cyclisation method (Scheme 2.6) (see Chapter 4 for additional details on the development of this method) to give the oxazoline in 88 % yield. The silyl protecting group was removed using tetra-*n*-butylammonium fluoride (TBAF), to afford the primary alcohol **210**, which could then be converted to the dearomatisation precusor (iodide **203**) in 64 % yield.

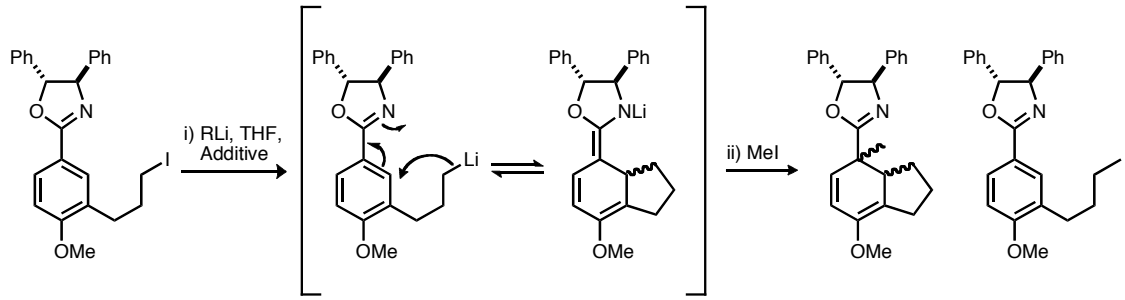


213 **214** (88 %) **210** (79 %) **203** (64 %)

Scheme 2.6 Installation of the oxazoline for the hydrocarbon tether lithiation precursor

2.1.2 Lithiation of hydrocarbon tethered oxazoline activated benzenes

For the cyclisation of the hydrocarbon tether onto the naphthyl oxazoline and BHA ester systems, Kenworthy used *t*-BuLi with and without DMPU to form the cyclised products (Scheme 1.47, Scheme 1.48).[57, 79] These conditions were used as a basis for the lithiation conditions applied to the hydrocarbon tether **203**. The results of these trials are shown in Table 2.2.



203 **215** **216** **217** **218**

Scheme 2.7 Conditions used for the lithiation of the hydrocarbon tether

Entry	Eq. RLi	Eq. Additive	Temp (°C)	Product[a]
1	(2 eq.) *t*-Bu	-	- 78	**218**
2	(2 eq.) *t*-Bu	5 eq. DMPU	- 78	**218**
3	(2 eq.) *t*-Bu	-	- 40	**218**
4	(2 eq.) *t*-Bu	5 eq. DMPU	- 40	**218** (16 mg, 65 %)
5	(2 eq.) *n*-Bu	-	0	**218**
6	(2 eq.) *n*-Bu	5 eq. DMPU	0	**218**

[a] Product seen in the crude ^{1}HNMR spectrum of reaction mixtures (see Appendix 8.1.1 pg. 172)

Table 2.2 Conditions used for the lithiation of the hydrocarbon tether

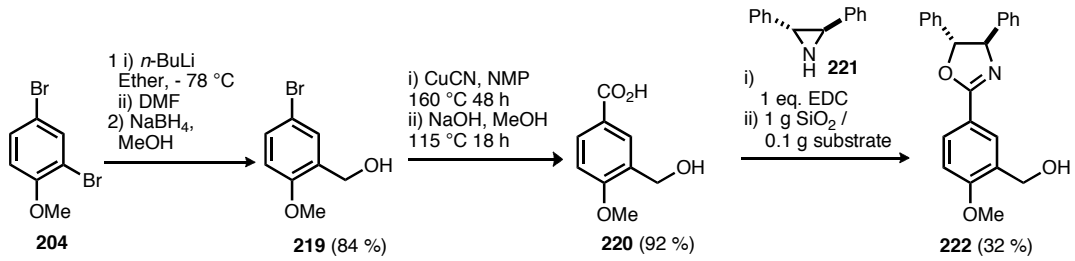
It was hoped that the organolithium formed for the halogen-lithium exchange of **203** would undergo an anionic cyclisation to form aza-enolate **216** which could then be trapped with electrophiles such as methyl iodide to give the dearomatised products e.g. **217**. At low temperatures (Entries 1 and 2), iodine-lithium exchange occurred to give the lithated intermediate **215**, shown by the formation of the product of methylation **218**. This was characterised by the presence of a triplet at 1.87 ppm corresponding to the new CH_3 group and three CH_2 signals at 2.60-2.50, 1.92-1.84 and 1.62-1.53 ppm in the ^{1}H NMR spectrum. In order to try and effect cyclisation, the reaction temperature was increased (Entries 3-6) however at – 40 °C again only methylated starting material was observed. Entries 5 and 6 indicate that the lithiated intermediate **215** is also stable at 0 °C and will form **218** upon methylation. Parris has shown that the highest yields of dearomatised products were observed with the use of secondary alkyl lithiums (*i*-PrLi and *s*-BuLi).[49] Primary alkyl lithiums (e.g. *n*-BuLi) do not undergo intermolecular dearomatising additions to (4*R*,5*R*)-4,5-diphenyloxazoline activated benzenes. This suggests a tether which forms a secondary alkyl lithium upon lithiation may be more successful.

2.2 Ether tethered organolithiums

Kenworthy had also shown that ether-containing tethers could be used for dearomatising cyclisations onto oxazoline activated naphthalene systems (Scheme 1.49).

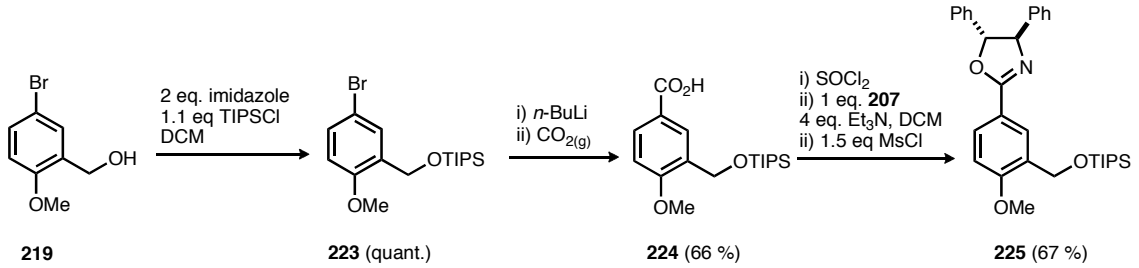
2.2.1 Construction of ether tethered organolithiums

To install the ether tether we used the same lithiation conditions as with the formation of the hydrocarbon tether but quenched the reaction with DMF, to give the 5-bromo-2-methoxy-*N,N*-dimethylbenzamide which could be reduced using $NaBH_4$ to give the alcohol **219**. The carboxylic acid could then be installed by displacement of the bromine with cyanide followed by hydrolysis to give the required carboxylic acid **220** for use in the benzoyl aziridine one pot coupling rearrangement reaction. However, the yield for the oxazoline **222** was very poor, this is presumed to be due to the poor solubility of **222**.



Scheme 2.8 Synthesis of intermediate 222 for the construction of the ether tether

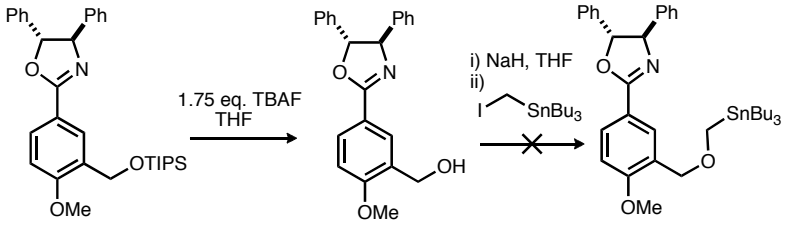
To improve the yield of the oxazoline **222**, **219** was first protected as the triisopropyl silyl ether under standard conditions to give **223** quantitatively (Scheme 2.9). The carboxylic acid functionality was installed by lithiation and carbon dioxide quench, this gave the required substrate **224** in 66 % yield. The oxazoline formation was more successful using the 1 pot coupling, mesylation and cyclisation conditions forming **225** in 67 % yield.



219 **223** (quant.) **224** (66 %) **225** (67 %)

Scheme 2.9 Synthesis of intermediate 225 for the construction of the ether tether

Deprotection using TBAF gave the alcohol **222** in 83 % yield. However, attempts to alkylate **222** with iodomethyltributyltin (prepared by the method of Seitz)[83] to form the tether **226** failed, therefore no further work was carried out on this tether.

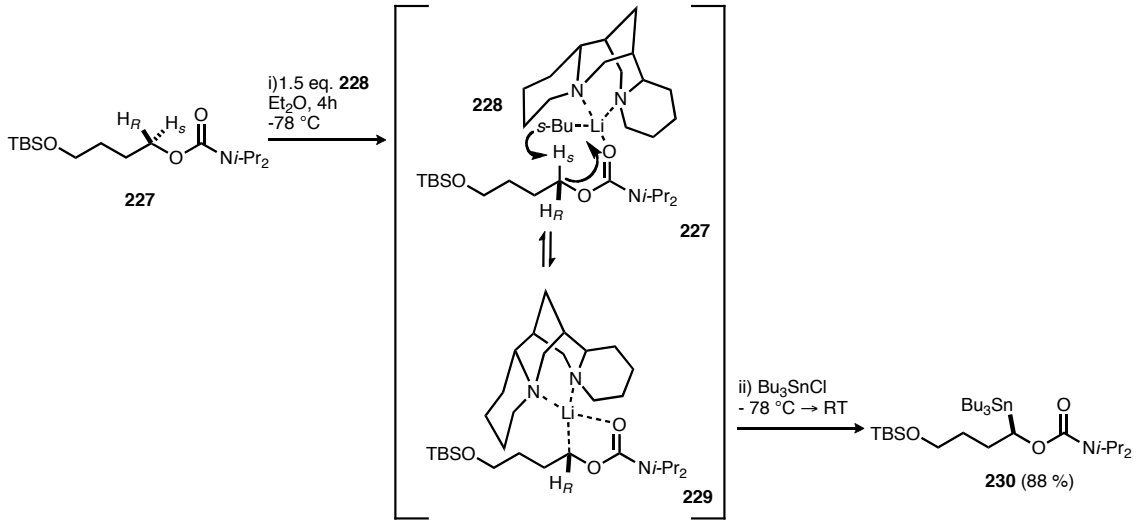


225 **222** (83 %) **226**

Scheme 2.10 Attempt to alkylate 222 with iodomethyltributyltin

2.3 Carbamate stabilised organolithium tether

With the hydrocarbon tether failing to undergo dearomatising additions and as the attempts to form the ether-tethered organolithium failed, we turned our attentions to other methods to form a secondary alkyl lithium. Work by Hoppe and co-workers has involved the stereoselective deprotonation at the α-position of *N,N*-diisopropyl carbamates, an example of which is shown in Scheme 2.11.



Scheme 2.11 (-) Sparteine mediated deprotonation or carbamates

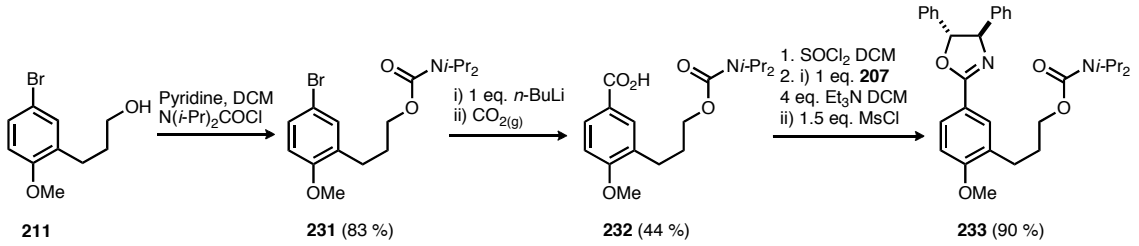
Here the *s*-BuLi-sparteine complex **228** removes the *pro-S*-hydrogen preferentially from **227**.[84, 85, 86] This gives a configurationally stable organolithium **229**, which after quenching with *tri*-butyltin chloride yields the enantiopure stannane **230** in 88 % yield.

We wanted to explore whether this method of deprotonation could be used in our system to form an organolithium capable of undergoing dearomatising cyclisations.

2.3.1 Construction of a carbamate tethered to an oxazoline activated benzene

To construct the lithiation precursor, 3-(5-bromo-2-methoxyphenyl)propan-1-ol (**211**) was coupled with *N,N*-diisopropyl carbomylchloride to give carbamate **231**. As with the hydrocarbon tether, the carboxylic acid needed for the oxazoline formation, could be installed by halogen-lithium exchange followed by carbon dioxide quench.

After forming the benzoyl chloride, the one-pot oxazoline formation method was used to give the carbamate lithiation precursor **226** (Scheme 2.12).

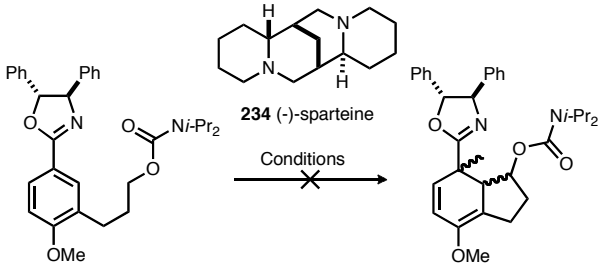


211 **231** (83 %) **232** (44 %) **233** (90 %)

Scheme 2.12 Synthesis of the carbamate tether lithiation precursor

2.3.2 Lithiation of a carbamate tethered oxazoline activated benzene

Initially as we did not need to deprotonate the lithiation precursor selectively we used *n*-BuLi in a range of solvents (THF, Et_2O and toluene) with and without additives (DMPU and HMPA) to attempt to lithiate **233** followed by methyl iodide quench. In all cases crude reaction mixtures showed that the precursor was not deprotonated as no methylated precursor was isolated. We then attempted to utilise Hoppe's conditions for the lithiation of **227** with the hope that these would be more successful (Scheme 2.13, Table 2.3).



233 **235**

Scheme 2.13 Attempted conditions for the lithiation of the carbamate tether

Entry	RLi Eq.	Additive 1.4 Eq.	Solvent	Time (min)	Observations
1[a]	1.4 *n*Bu	**234**	Et_2O	60	SM returned
2[a]	1.4 *s*Bu	**234**	Et_2O	60	SM returned
3[b]	1.4 *s*Bu	-	Et_2O	300	SM returned
4[b]	1.4 *s*Bu	**234**	Et_2O	300	Complex products
5[b]	1.4 *n*Bu	-	Et_2O	300	SM returned
6[b]	1.4 *n*Bu	**234**	Et_2O	300	Complex products

[a] Addition of premixed RLi and **234** to substrate, [b] Additions of RLi to pre-mixed **234** and substrate.

Table 2.3 Attempted conditions for the lithiation of the carbamate tether

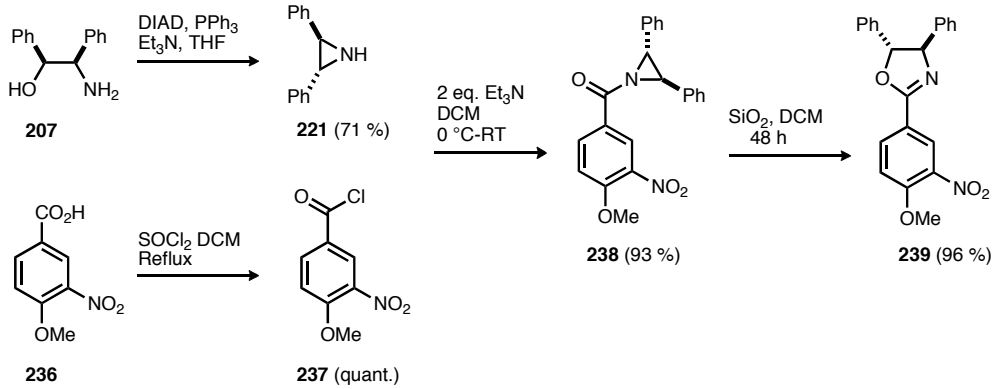
The lithiations were carried out with and without (-)-sparteine (**238**) to allow direct comparison. In the cases where no (-)-sparteine was present or reaction times were shorter (Entries 1-3 and 5) only starting material was returned. When the organolithium was added to a pre-mixed solution of the substrate **233** and (-)-sparteine, the ^{1}H NMR spectrum of the crude reaction mixture showed a mixture of starting material and additional products. However no products of methylation or dearomatisation were isolated by flash column chromatography.

2.4 1-Benzyl-1,3-dimethylurea tethered organolithiums

Due to the apparent un-reactivity of both the hydrocarbon and the carbamate tethers towards dearomatising cyclisations, our attention was turned towards other methods of secondary organolithium synthesis. We want to attempt to use a benzylic lithiation site, as they have been used successfully for the intramolecular dearomatising addition of organolithium tethers that contain a benzylic amide or phosphonamide (see sections 1.4.2.2 and 1.4.2.3). We decided to tether the benzylic position to the activated ring via a 1,3-dimethylurea as work by Beak has shown that benzylic positions next to ureas can be successfully deprotonated.[87, 88] To ensure that the *para*-methoxy group is not preventing cyclisation, the *des*-methoxy analogue was also synthesised along with the *para*-methoxy substrate for a direct comparison of reactivity.

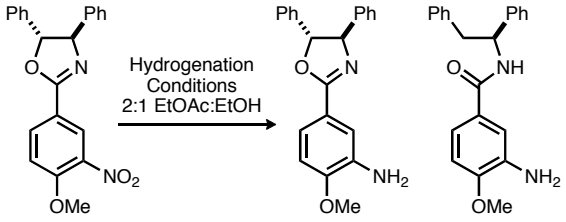
2.4.1 Construction of a 1-benzyl-1,3-dimethylurea tethered to a activated methoxyphenyl

Our initial route to the lithiation precusor installed the (4*R*,5*R*)-4,5 diphenyloxazoline first (Scheme 2.14). The highest yielding oxazoline formation method was that of the selective rearrangement on silica of benzoyl aziridine **238** (other routes to **239** are more fully described in Chapter 4). The benzoyl aziridine **237** was made by amide coupling of (2*R*,3*R*)-2,3-diphenylaziridine **221**, that was formed by a simple Mitsunobu reaction from the corresponding amino alcohol **207**, with the pre-formed 4-methoxy-3-nitrobenzoylchloride **237**. The benzoyl aziridine was then used in the silica-mediated rearrangement without further purification.



Scheme 2.14 Synthesis of 2-(4'methoxy-3'-nitro-phenyl)-4,5-diphenyloxazoline

Formation of the aniline by hydrogenation was initially troublesome. The ring-opening product **241** was observed when using standard hydrogenation conditions, which was characterised by loss of the CH doublets seen at 5.45 and 5.26 ppm for **239** and 5.29 and 5.09 ppm for amine **240** (Entry 1, Table 2.4). Method development using the H-Cube™ flow hydrogenation reactor showed that by using Lindlar catalyst (5 % Pd/C with Pb and $CaCO_3$) with a low flow rate (Entry 3) or at increased pressure (Entry 4) only aniline **240** was isolated. These results could be repeated without the flow reactor with atmospheric hydrogen, but the reaction time was greatly increased (Entry 5).



239 **240** **241**

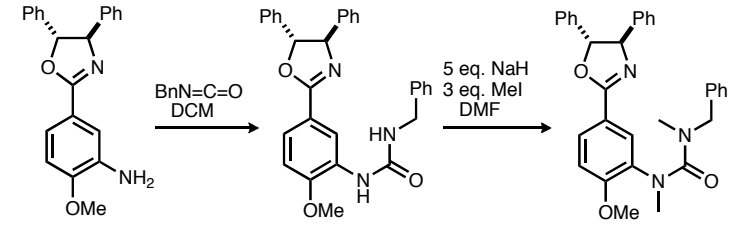
Scheme 2.15 Hydrogenation of 2-(4'methoxy-3'-nitro-phenyl)-4,5-diphenyloxazoline

Entry	Conditions	Flow rate ml/min	Pressure	Time	Product (yield)
1	10 % Pd/C, H_2	3	-	-	**241**
2	5 % Lindlar catalyst, H_2	3	-	-	**239**
3	5 % Lindlar catalyst, H_2	0.1	-	-	**240**
4[a]	5 % Lindlar catalyst, H_2	0.5	50 bar	-	**240** (88 %)
5[b]	5 % Lindlar catalyst, H_2	-	-	8 days	**240** (100 %)

[a] Passed through the flow reactor twice [b] Carried out under atmospheric hydrogen

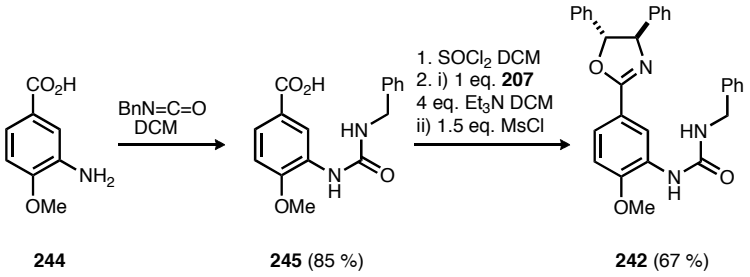
Table 2.4 Hydrogenation of 2-(4'methoxy-3'-nitro-phenyl)-4,5-diphenyloxazoline

Aniline **240** could now be coupled with benzyl isocyanate under standard conditions, the low yield (57 %) was due to self-condensation of the benzyl isocyanate (Scheme 2.16). Purification of **242** was complicated by the co-elution of the self-condensation product with the desired compound in flash column chromatography. The final methylation step to give the required lithiation precusor **243** was carried out using 5 eq. of sodium hydride, as at lower equivalencies mixtures of mono- and di-methylated ureas formed.



Scheme 2.16 Construction of the 1-benzyl-1,3-dimethylurea tethered activated methoxyphenyl

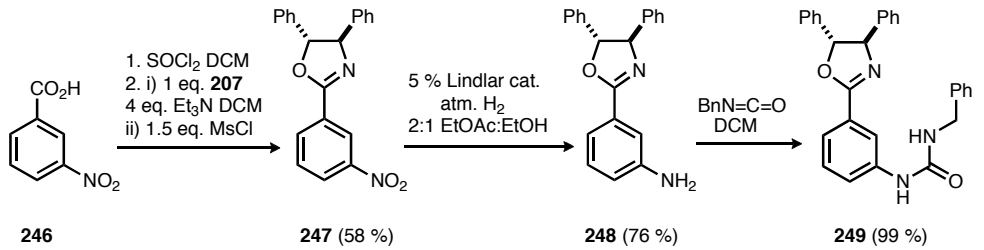
The route to the 1-benzyl-1,3-dimethylurea tethered system was simplified when it was discovered that 3-(3-benzylureido)-4-methoxy benzoic acid (**245**), formed by treating commercially available **244** with benzyl isocyanate, could be used in the one-pot oxazoline synthesis method. This gave the methylation precursor **242** in two steps.



Scheme 2.17 Shorter synthesis of the 1-benzyl-1,3-dimethylurea tethered activated methoxyphenyl

2.4.1.1 Construction of a 1-benzyl-1,3-dimethylurea tethered to activated benzene

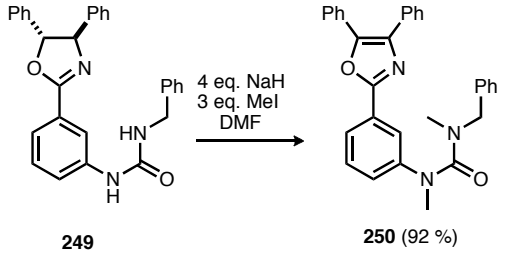
As with the first route to the *para*-methoxy substrate **243** the oxazoline of the *des*-methoxy substrate was installed first, this time using the one-pot method applied to 3-nitrobenzoic acid (**246**) to give oxazoline **247** (Scheme 2.18). The reduction of the nitro functionality to the aniline was achieved again using hydrogenation with 5 % Lindlar catalyst. The aniline was then coupled to benzyl isocyanate to give the urea **249**.



Scheme 2.18 Synthesis of the 1-benzyl-1,3-dimethylurea tethered activated benzene

The methylation of the urea **249** was first attempted on a trial scale in DMF (Scheme 2.19), but in crude ^{1}H NMR spectrum characteristic signals for the oxazoline CH protons were not present, these are usually observed as doublets at 5.47 and 5.28

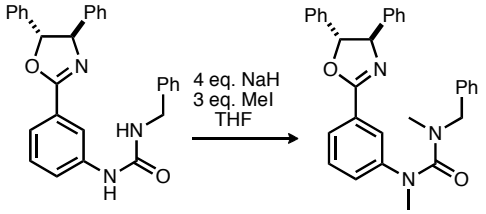
ppm. Therefore the major product from this reaction was presumed to be the oxazole **250**, thought to be formed via an elimination of hydrogen across the benzylic positions of the oxazoline.



249 **250** (92 %)

Scheme 2.19 Formation of undesired oxazole 250

By changing the solvent to THF, this side reaction was eliminated giving methylated urea **251** in 89 % (Scheme 2.20).

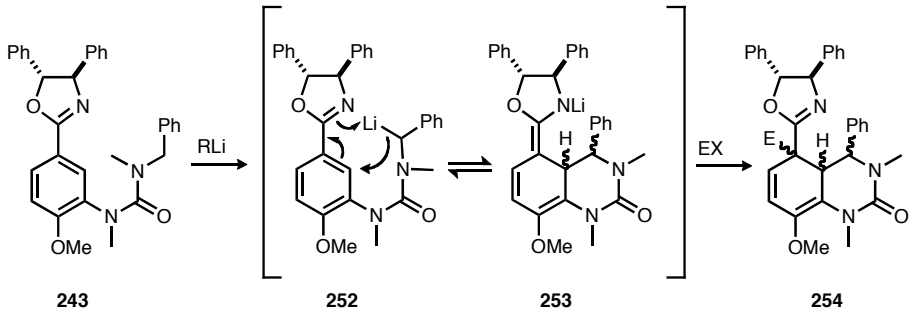


249 **251** (89 %)

Scheme 2.20 Conditions used for the urea methylation to form the 1-benzyl-1,3-dimethylurea

2.4.2 Lithiation of the 1-benzyl-1,3-dimethylurea tethers

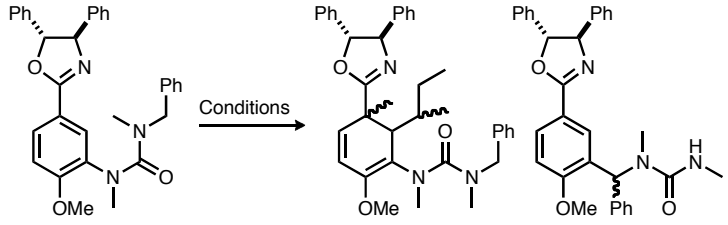
With the substrates in hand, our attention was focused on the products of lithiation. It was hoped that deprotonation at the benzyl position of the urea would form a stable secondary organolithium **252** which could cyclise to give aza-enolate **253**. Quenching intermediate **253** with electrophiles (EX) would yield cyclohexadienes such as **254** (Scheme 2.21). As there are three new stereocentres being formed from this reaction, eight different stereoisomers may be formed. The *des*- methoxy substrate could be further complicated by the cyclisation at both the *para*- and *ortho*-positions.



243 252 253 254

Scheme 2.21 Expected product of the lithiation of the 1-benzyl-1,3-dimethylurea urea tethers

The substrates were subjected to a wide range of lithiation conditions; varying the organolithium, additive used and temperature (Scheme 2.22, Table 2.5).



243 255 256

Scheme 2.22 Products of lithiation of the 1-benzyl-1,3-dimethylurea tethers

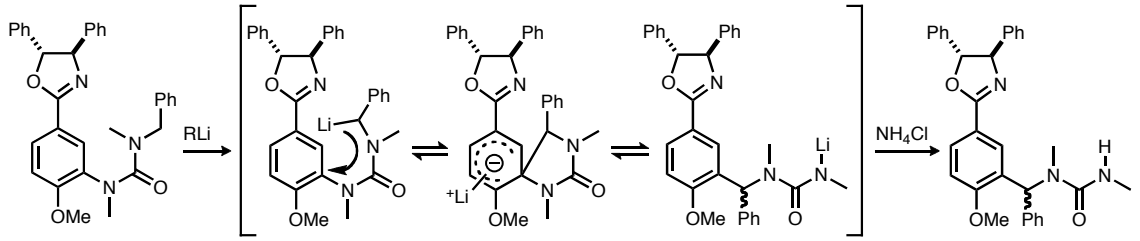
Entry	RLi	Additive	Temp (°C)	Time (mins)	Quench	Product
1	2.5 eq. *s*-BuLi	5 eq. DMPU	- 78	60	MeI	**255**
2	2.5 eq. *s*-BuLi	-	- 78	72	MeI	**255**
3	1.2 eq. LDA	-	- 78	105	MeOD	**243**
4	1.2 eq. LDA	-	- 78 to 0	105	MeOD	**243**
5	2 eq. LDA	5 eq. DMPU	- 78	60	MeI	**243**
6	1.1 eq. *n*-BuLi	-	- 78	10	MeI	**243**
7	5 eq. *n*-BuLi	-	- 78	5	NH_4Cl	**243**:**256** (6:1)
8	5 eq. *n*-BuLi	5 eq. DMPU	- 78	5	NH_4Cl	**243**:**256** (1:7) (13 mg, 65 %)
10	5 eq. *n*-BuLi	5 eq. DMPU	- 78	5	MeI	complex mixture of products

Table 2.5 Conditions used for the lithiation of the 1-benzyl-1,3-dimethylurea tethers

Under the standard conditions used for the intermolecular dearomatising addition to (4*R*,5*R*)-diphenyloxazoline activated benzenoids (Entries 1 and 2),[49] the products seen resulted from the dearomatising addition of *s*-BuLi to the aromatic ring (**255**) characterised by the presence of *s*-Bu peaks and coupling between the two unsaturated protons of the dearomatised ring in the crude ^{1}H NMR spectrum. The organolithium used was therefore changed to lithium diisopropylamide (LDA) in order to favour deprotonation of the benzylic position (Entries 3-5), but these attempts were

unsuccessful with only the starting material recovered. By using a large excess of both *n*-BuLi and DMPU deprotonation of the benzylic position was successful. The organolithium formed did not undergo dearomatising addition onto the *ortho*-position as expected, instead the product of a C-N rearrangement **256** was isolated, when quenching with NH_4Cl (Entry 8, Table 2.5), along with remaining **243**. As the two compounds are close running by column chromatography we were unable to isolate **256** cleanly. The same conditions were trialled with methyl iodide quench but this gave a complex mixture of products, which we were unable to separate cleanly enough by column chromatography for complete analysis.

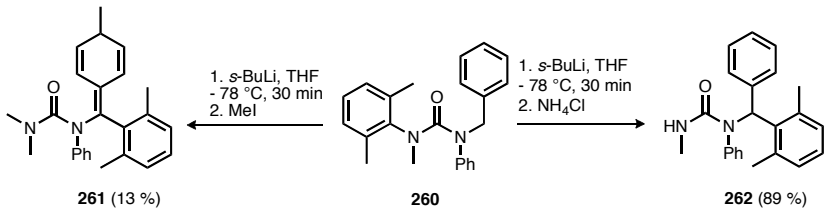
This type of N→C migration of the aryl group has been extensively studied within the Clayden group, with studies on the migration of benzyl, naphthyl and pyridyl rings onto benzylic and allylic positions.[89-91] The products of the C-N benzyl migration are typically characterised by a singlet at approximately 6.8 ppm for the CH next to the phenyl ring. For **256** there is two singlets, which together integrate to 1H, they are in a ratio of (~1:1), showing that the rearrangement in this instance is not stereospecific. This unselectivity is either due to an unselective rearrangement or racemisation of the new stereocentre by the additional equivalents of *n*-BuLi used in the reaction conditions. In the mechanism for the rearrangement the organolithium **257** attacks the *meta*-position forming a dearomatised spiro intermediate **258**, the C-N bond then breaks forming the more stable anion on the nitrogen (**259**). Upon quenching, intermediate **259** is trapped by the electrophile, which in this case was $NH_4Cl_{(aq)}$ (Entries 7 and 8, Scheme 2.23).



Scheme 2.23 Suggested mechanism for urea rearrangement

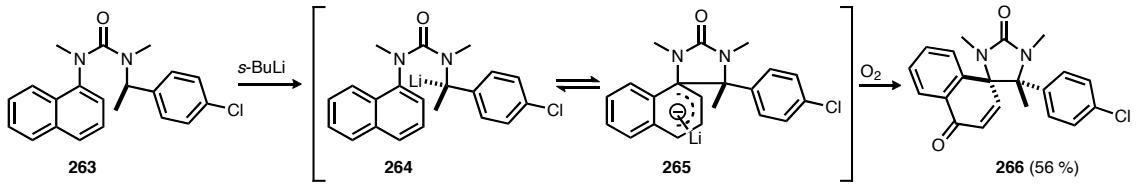
This type of rearrangement was discovered during attempts to determine the favoured site of lithiation of **260**. When quenching the reaction with methyl iodide a small amount of dearomatised product **261** was isolated resulting from the N→C migration followed by a second deprotonation and electrophilic quench. By changing

the quench to NH_4Cl or H_2O the product of N→C migration **262** could be isolated in good yield.



Scheme 2.24 The first examples of N→C urea aryl migration

The mechanism of the reaction has been investigated by trapping the spirocyclic intermediate **265**, which is formed from the lithiation of **263**, using oxygen (Scheme 2.25).



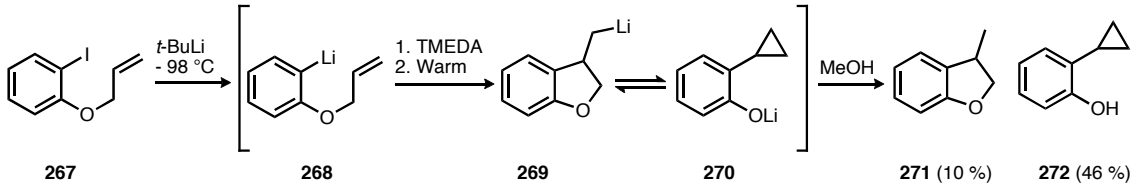
Scheme 2.25 The trapping of dearomatised intermediates from the urea rearrangement

Attempts to trap out similar dearomatised intermediates from the lithiation of **243** by bubbling air through the reaction mixture failed to yield any dearomatised products.

Trial lithiations were carried out on the *des*-methoxy analogue **251** using the same conditions as used for Entry 10, of Table 2.5. However the reaction mixtures from these were extremely complex giving seven different spots by TLC that could not be separated cleanly by column chromatography. Due to the propensity of the urea to undergo this rearrangement and the lack of stereoselectivity in the rearrangement even with the presence of a chiral auxiliary, no further lithiation attempts were carried out on substrates **243** and **251**.

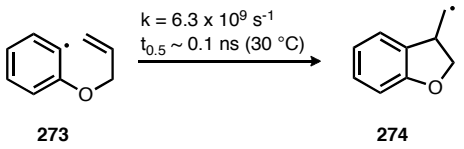
2.5 O-Allylic organolithium tethers

Work by Bailey has shown that 2-(2-propenoxy)phenyllithium **268**, formed from the halogen-lithium exchange of **267** using *t*-BuLi, followed by addition of TMEDA and warming resulted in the formation of the cyclised intermediate **269**.[92] A small amount of **269** was trapped by quenching with methanol to give **271** in 10 %, but the majority of **269** underwent an elimination before the quench to give anion **270**, which upon quenching yields the 2-(cyclopropyl)phenol **272**.



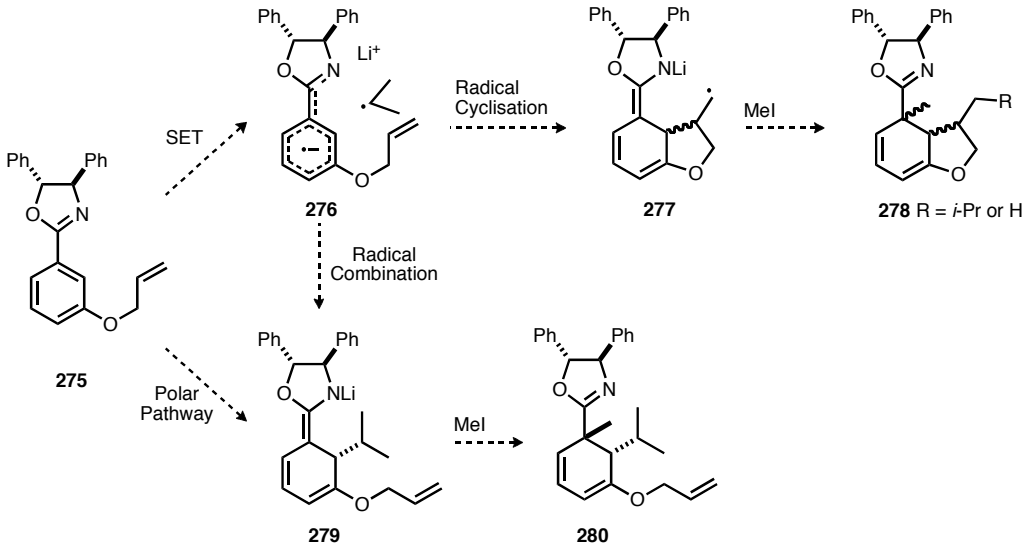
Scheme 2.26 The tandem anionic cyclisation-γ-elimination of 2-(2-propenoxy)phenyllithium

As well as being able to undergo anionic cyclisations, allyl aryl ethers can be used as radical clocks for determination of the lifetime of radicals. Allyl aryl ether **273** has a half life of approximately 0.1 ns at 30 °C making it one of the fastest cyclisation probes.[93]



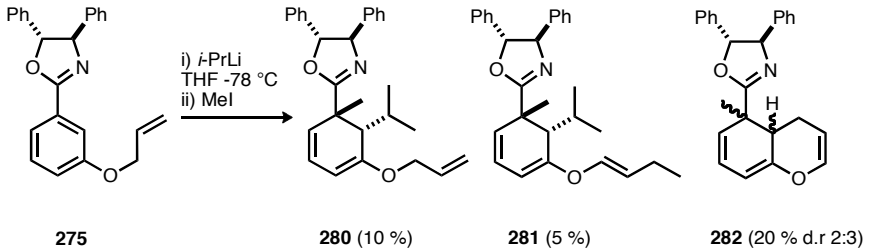
Scheme 2.27 Radical cyclisation of allyl aryl ether 268

In order to investigate whether the mechanism for the dearomatising intermolecular addition onto (4*R*,5*R*)-4,5-diphenyloxazoline activated benzenoids had any radical nature, Parris synthesised **275** which has an allyl ether radical probe tethered at the *meta*-position of the benzenoid ring.[48] Depending on the mechanism taking place either **278** or **280** was expected to be formed. The probe would only discount the SET mechanism if the radical cyclisation to form **277** was faster than the radical combination to give **279**.



Scheme 2.28 Expected products of the single electron transfer and polar pathway mechanism for the lithiation of 275

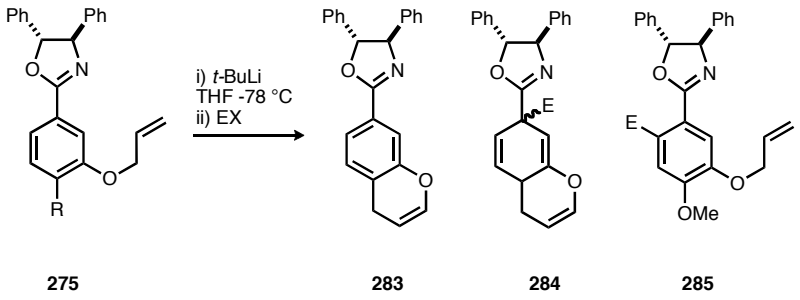
When attempted by Parris,[48] the lithiation of **275** formed the products of both the intermolecular addition of *i*-PrLi and the intramolecular dearomatising addition of the allyl tether (Scheme 2.29). Due to the general reactivity of the (4*R*,5*R*)-4,5-diphenyloxazoline activated benzenoids to undergo intermolecular dearomatising addition at the *ortho* position, it was first proposed that this dearomatising cyclisation also occurred at the *ortho*-position to give chromene **282** in 20 % yield.



Scheme 2.29 Postulated products of the lithiation of an O-allylic tether

Karlubikova went on to further improve this reaction.[50] By quenching with NH_4Cl she has been able to show that nucleophilic attack of the lithiated allyl ether occurs at the *para*-position to give the rearomatised product **283** (Entry 1, Table 2.6). The ^1H NMR spectrum of **283** has a signal at 7.6 ppm for H8 of the aromatic ring. The peak is a doublet with a small *J* value of 1.5 Hz due to fine W coupling to the H6 proton. By using *t*-BuLi to deprotonate the O-allylic system the yield of the dearomatised product **284** could be increased to 84 % (Entry 2) from Parris's initial 20 %. This is presumed to be due to *t*-BuLi being unable to undergo dearomatising intermolecular addition.[48] To further investigate the regioselectivity of the cyclisation substrate **275b**, which has a blocking methoxy group in the para position, was

synthesised and subjected to the lithiating conditions (Entry 4). No products of dearomatising cyclisation were observed in the crude reaction mixture. Only **285** the product of *ortho*-metalation was isolated, again showing that the addition is taking place solely at the *para* position.



Scheme 2.30 Further investigations into dearomatising additions of O-allylic systems

Entry	SM	R	EX	Product
1	**275**	H	NH_4Cl	**283** (84 %)
2	**275**	H	MeI	**284a** (84 %, d.r. 3:2 at H4a)
3	**275**	H	BnBr	**284b** (92 %, d.r. 1:1 at H4a)
4	**275b**	OMe	MeI	**285** 13 %

Table 2.6 Further investigations into dearomatising additions of O-allylic systems

Unfortunately as with the original result of Parris, the dearomatising addition is not selective with the four possible diastereoisomers formed. This lack of facial selectivity observed for the nucleophile can only be attributed to the distance between the site of attack and the oxazoline directing group. For the intermolecular dearomatising additions the (4*R*,5*R*)-4,5-diphenyloxazoline controls the stereoselectivity via its steric bulk.

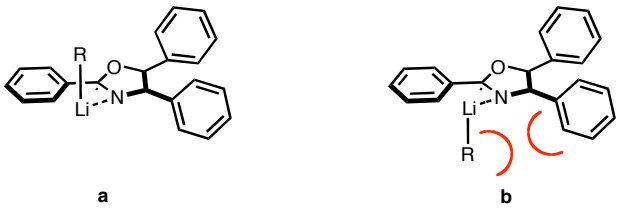
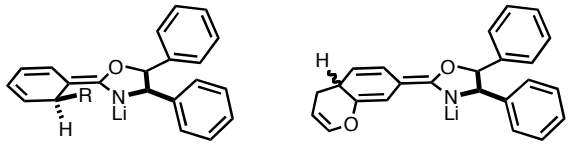


Figure 2.2 Stereochemical rationale for the addition to (4*R*,5*R*)-4,5-diphenyloxazolines

As the nitrogen lone pair lies in the plane of the oxazoline it therefore allows co-ordination of the lithium in the same manner with the R group either above (Figure 2.2a) or below (Figure 2.2b) the plane of the ring. The phenyl group adjacent to the nitrogen favours delivery as shown in Figure 2.2a preventing the unfavourable steric interactions shown in Figure 2.2b. This attack of the organolithium *via* complexation

with nitrogen is consistent with the complex-induced proximity effect (CIPE)[94] and also the mechanism described by Meyers for the mono-dentate oxazolines.[28]

The selectivity of the quench is dependent on the steric hindrance displayed by the intermediate azaenolate. With the 1,2 additions the site of nucleophile attack and electrophilic quench are close, forcing the electrophilic quench to add to the less hindered face, *trans* with respect to the nucleophile (Figure 2.3a). For these 1,4 additions the sites are more distant reducing the steric hinderance caused by the addition of the nucleophile, therefore the facial selectivity is reduced (Figure 2.3b).



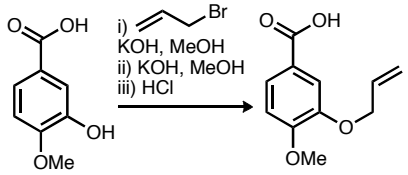
a b

Figure 2.3 Proposed rationale for the lack of facial selectivity for the electophilic quench in the dearomatising cyclisation

Attempts were made to increase the selectivity by use of a more bulky electrophilic quench with BnBr (Entry 3), which gave an excellent yield of dearomatised products however the selectivity was still poor at about 1:1 at H4a.

2.5.1 Construction of O-allylic organolithium tethers

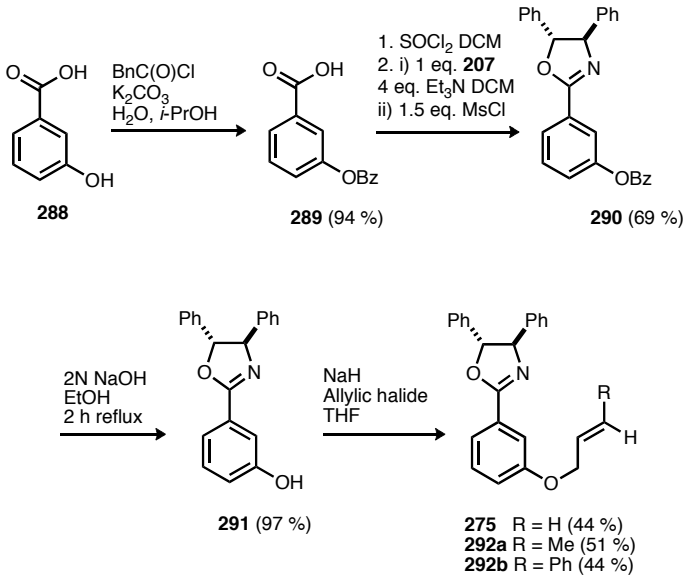
Due to the success of the allyl ether tether we wanted to investigate whether other allylic ether systems could be cyclised in a similar fashion. In Karlubikova's synthesis of the O-allyl tethered substrate the method of Meakins was employed.[95] The tether was installed by joint esterification and ether formation of 3-hydroxy benzoic acid, followed by saponification of the ester to return the carboxylic acid **287**. This worked well when using allyl bromide giving **287** in 71 % yield. However when using other allylic halides the reaction failed returning unreacted 3-hydroxy benzoic acid and the product of alkylated methanol (Scheme 2.31).



286 **287** (71 %)

Scheme 2.31 Karlubikova's synthesis of the O-allyl tether

Due to this issue we needed to find a different method that would preferably install the allylic ether linkage last so as to allow the synthesis of different allylic ether substrates from a common intermediate. In order to synthesise the required phenol we first protected 3-hydroxybenzoic acid as a benzoyl ester (Scheme 2.31). This protection was chosen as we had already established that deprotection of benzyl protecting groups was problematic due to the easily cleaved benzylic positions of the (4*R*,5*R*)-4,5-diphenyloxazoline (Scheme 2.15). The now protected benzoic acid **289** was then subjected to the one-pot oxazoline synthesis to give the oxazoline **290** in 69 % yield. Deprotection was easily achieved by saponification of the ester in NaOH.[a] The resulting phenol **291** was then alkylated with a range of allylic halides to give the lithiation precursors (Scheme 2.32).

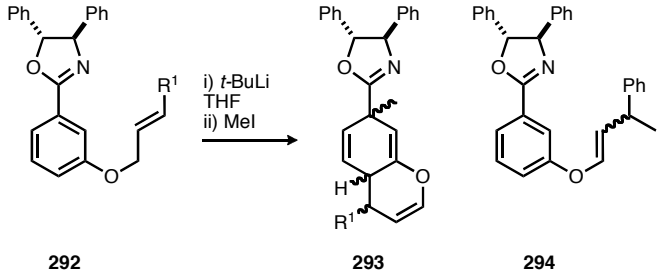


Scheme 2.32 Synthesis of O-allylic tethers

2.5.2 Lithiation of the O-allylic organolithium tethers

With the precursors in hand we then investigated their ability to undergo dearomatising additions (Scheme 2.33, Table 2.7).

[a] No epimerization of the chiral centers of the oxazoline was observed by ^{1}H NMR spectroscopy.



292 293 294

Scheme 2.33 Lithiation of O-crotyl and cinnamyl tethers

Entry	SM	R^1	Temp (°C)	EX	Product
1	**292a**	Me	-78	MeI	**293a** (37 %, d.r. 1:1 at H4a)
2	**292b**	Ph	-78	MeI	**294** (37 %)
3	**292b**	Ph	-78→-40	MeI	**293b** (28 %, d.r. 1:0.6 at H4a)

Table 2.7 Lithiation of the O-crotyl and cinnamyl tethers

Like the O-allyl system **270** both **292a** and **292b** undergo a dearomatising addition at the *para*-position, but the yields are greatly decreased compared to the cyclisation of **275**. In order to get the O-cinnamyl tether to cyclise, the reaction needed to be warmed to - 40 °C after lithiation. At -78 °C lithiation takes places shown by the isolation of **294**, which no longer has a signal corresponding to the CH_2 group in the ^1H NMR spectrum, instead there is a signal for a CH group, which couples, to an allylic CH and a CH_3 group by correlation spectroscopy. These peaks appear as multiples in the ^1H NMR spectrum therefore the geometry of the allylic system cannot be determined.

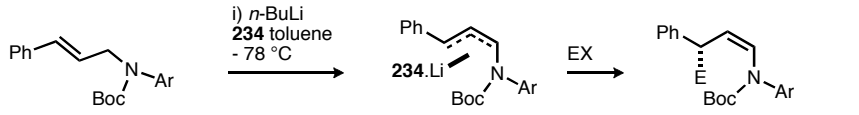
During the dearomatising cyclisation three new stereocentres are formed meaning there may be up to four diastereomeric pairs formed dependent on the selectivity of the reaction. The stereoisomers co-elute during column chromatography it has not been possible to separate any stereoisomers present to allow for full assignment. In the ^1H NMR spectra of **293a** the signals for the stereoisomers overlap except for the signals for H4a, which has a 1:1 ratio of signals at 2.69-2.65 and 2.62-2.58 ppm in the ^1H NMR. For **293b** there is a 1:0.6 ration of signals for H4a. This is comparable to the cyclisation of **275**, which was unselective with regard to the addition of the nucleophile.

The regioselectivity of the reaction is as yet unexplained, this cyclisation is novel as all the reported dearomatising cyclisations (as described in the introduction of this thesis) occur at the *ortho*-position with regard to the electron-withdrawing group.

The presence of stereoisomers at the H4 position rules out a pericyclic type mechanism as that would be stereoselective at both H4 and H4a.

2.6 N-Allylic organolithium tethers

Due to the success of the O-allylic system we wanted to investigate whether the cyclisation could be achieved with another heteroatom. Beak and co-workers have widely studied the lithiation of *N*-Boc allylic systems.[96-98] For example the lithiation of *N*-(Boc)-*N*-(*p*-methoxyphenyl)cinnamylamine **295**,[99, 100] using a (-)-sparteine (**234)**/*n*-BuLi chiral base complex selectively deprotonates the *pro*-R proton to form the stable intermediate **296**.[101] The organolithium **296** can then be quenched with a range of carbon based electrophiles, which react selectively at the γ-position to give products of the type **297** in good yield and e.r.



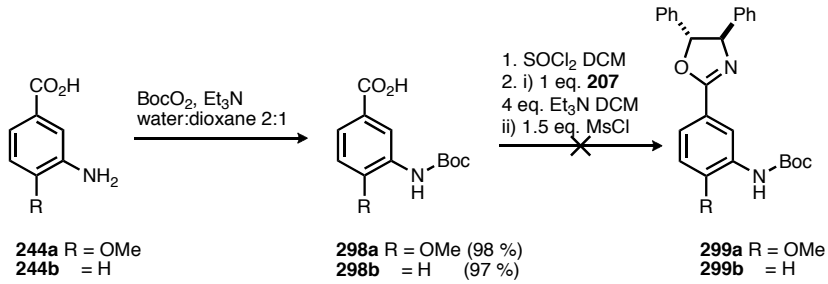
295 **296** **297** (72-97 %, e.r >97:3)

Scheme 2.34 Lithiation of *N*-(Boc)-*N*-(*p*-methoxyphenyl)cinnamylamine

This precedence led us to investigate whether lithiated *N*-Boc allylic systems could act as a nucleophile in our novel dearomatising cyclisation. We decided to synthesise the *para*-methoxy (**302a**) and *des*-methoxy analogues (**302b**), in order to further corroborate the inability to cyclise shown by the *para*-methoxy containing O-allyl system **275b** (Scheme 2.30).

2.6.1 Construction of the N-allylic organolithium tethers

Both of the analogues were synthesized in the same fashion. First the starting benzoic acids **244a** and **244b** were Boc protected using literature methods.[102,103] Attempts to install the (4*R*,5*R*)-4,5-diphenyloxazoline using the one-pot method gave the desired oxazoline but the products formed no longer had a Boc protecting group. This is presumably due to the Boc protecting group's instability under the benzoyl chloride formation step.



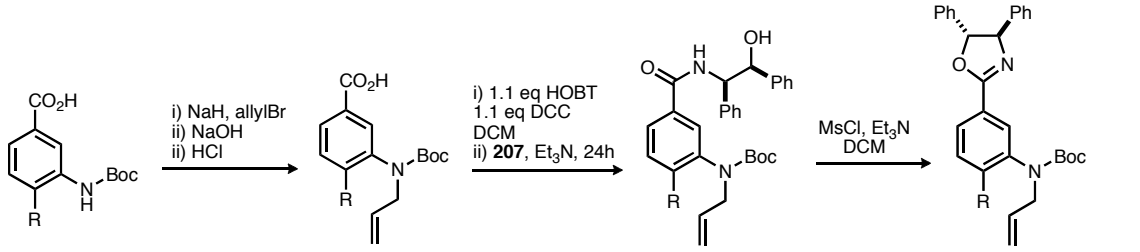
244a R = OMe
244b = H

298a R = OMe (98 %)
298b = H (97 %)

299a R = OMe
299b = H

Scheme 2.35 Attempt to install the oxazoline for the N-allyl tether via the one-pot coupling, mesylation and cyslisation

To prevent this deprotection an adapted method of the Meakins alkylation,[95] esterification and saponification was utilized to give the 3-(allyl(*tert*-butoxycarbonyl)amino)-4-methoxy benzoic acid **300a** and 3-(allyl(*tert*-butoxycarbonyl)amino)benzoic acid **300b** in 96 % and 81 % respectively over the two steps. The oxazoline formation was then split into separate steps. First the β-hydroxyamide was formed under amide coupling conditions using dicyclohexylcarbodiimide (DCC) and hydroxybenzotriazole (HOBt) with the amino alcohol **207**. Cyclisation was then effected using methanesulfonyl chloride to give the lithiation precursors **302a** and **302b** in good yields (Scheme 2.36).



298a R = OMe
298b = H

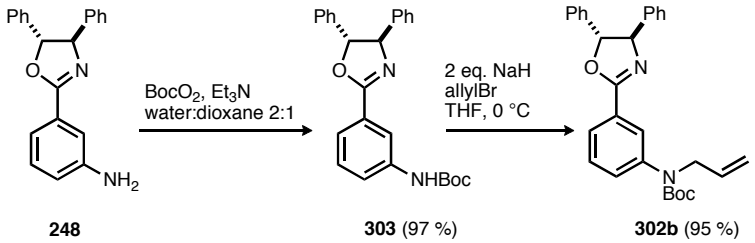
300a R = OMe (96 %)
300b = H (81 %)

301a R = OMe (98%)
301b = H (70 %)

302a R = OMe (84 %)
302b = H (89 %)

Scheme 2.36 Construction of the methoxy and *des*-methoxy *N* (Boc)-allyl systems

The *des*-methoxy analogue could also be accessed by utilizing the 3-((4*R*,5*R*)-4,5-diphenyloxazoline)aniline **248**, synthesized for use in the formation of the benzyl urea tether (Section 2.4.1.1). Both the Boc protection and the alkylation are high yielding reactions, which allowed access to the required lithiation precursor **297a** in four steps from the commercial starting material. As the final step is the alkylation this route allows easier access to other allylic systems, that maybe problematic to form using the Meakins alkylation method as highlighted by Karlubikova (Scheme 2.31).[50]

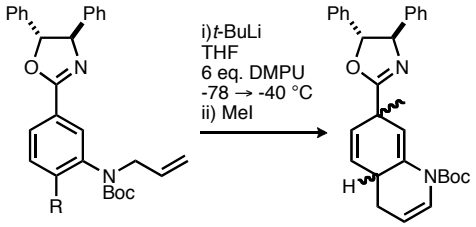


248 **303** (97 %) **302b** (95 %)

Scheme 2.37 Alternative synthesis of the N-allylic tethered *des*-methoxy system

2.6.2 Lithiation of the N-allylic systems

With the lithiation precursor in hand we could now investigate whether the N-allyl tethered systems behaved in a similar way to the O-allyl system.



302a R = OMe
302b = H

304 (39 %)

Scheme 2.38 The lithiation of the N-allyl tethered benzenoid systems

Initially the conditions used for the cyclisation of the O-allyl tether were attempted, but no dearomatised products were isolated. By warming the reaction mixture of lithiated **302b** to – 40 °C for 25 mins, dearomatised products could be seen in the ^{1}H NMR spectrum of the crude reaction mixture when quenching with NH_4Cl. Unfortunately these products co-eluted with the starting material during column chromatography so could not be isolated cleanly.

Using the same conditions but quenching with MeI the dearomatised product could be isolated as a mixture of diastereoisomers in 39 % (see appendix 8.1.5 pg. 176), two new stereocentres are formed during the reaction meaning four possible stereoisomers could be formed, the ^{1}H NMR spectra of **304** is further complicated by the presence of rotamers. By running the sample in deuterated toluene at 90 °C, the ^{1}H NMR spectra was sharper however the signals for H4a are seen as a multiplet at 2.78-2.75 ppm so no d.r. can be determined for this position. The *para*-methoxy substrate **302a** did not cyclise under these conditions as there are no characteristic signals for the H2 and H3 protons, which are usually at 5.6 and 4.7 ppm respectively and would show a strong correlation using correlation spectroscopy. We therefore believe lithiation of **302a** under these conditions has formed a mixture of allyl isomerised and methylated starting

material. This is further evidence that this type of cyclisation occurs solely at the *para*-position.

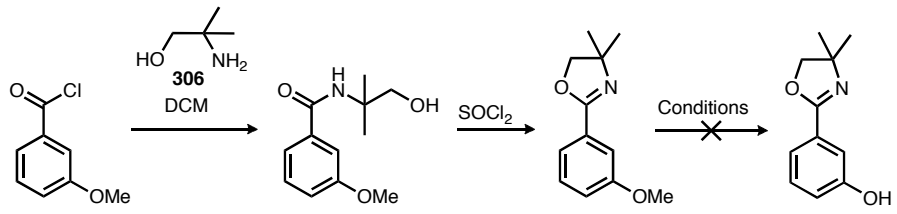
3 Dearomatising intramolecular additions to 4,4-dimethyloxazoline activated benzenoids

The intermolecular dearomatising addition is specific to the (4*R*, 5R)-4,5-diphenyl oxazoline.[48] Exchanging the oxazoline for the *syn*-diphenyl oxazoline or (4*R*,5*R*)-4-(methoxymethyl)-5-phenyl oxazoline gave no or reduced yields of dearomatised products (Section 1.3.2.4, Scheme 1.27). In order to establish whether this type of dearomatising cyclisation is equally specific to the (4*R*,5*R*)-4,5-diphenyl oxazoline we wanted to change the oxazoline used for the activation. As the dearomatising cyclisation of the allyl tethers described in Chapter 2 is not stereospecific, giving mixtures of diastereoisomers, we wanted to focus on an achiral oxazoline. 4,4-Dimethyloxazolines have been utilised in intermolecular dearomatisation of naphthalenes by Meyers (Section 1.2.6, Scheme 1.12)[20] and also for the intramolecular dearomatisation of naphthalenes by Kenworthy (Section 1.4.2.5, Scheme 1.48).[57] On the basis of this previous work we wanted to investigate its ability to promote this intramolecular benzene dearomatisation.

3.1 O-allylic organolithium tethers

3.1.1 Construction of O-allylic organolithium tethers

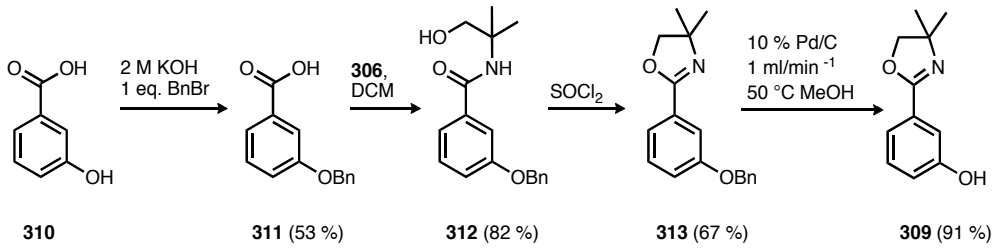
To enable the synthesis of different allylic systems we wanted to install the oxazoline on an aryl ring which has a protected *meta*-phenol moiety, which would allow late stage functionalisation after deprotection. Initially we turned to methyl ether protection, envisaging a simple BBr_3 mediated deprotection of **308** (Scheme 3.1). The 4,4-dimethyloxazoline could be easily installed by first coupling 3-methoxybenzoyl chloride with 4 eq. of 2-amino-2-methylpropan-1-ol (**306**) to give the β-hydroxyamide **307**. Intermediate **307** could then be cyclised by drop-wise addition of excess $SOCl_2$ to give the 2-(3-methoxyphenyl)-4,4-dimethyloxazoline (**308**) in 84 % yield.



Scheme 3.1 Installation of the 4,4-dimethyloxazoline on the methyl ether protected substrate

Several methods were trialed for the deprotection of **308**, but none were successful. Attempts using BBr_3 appeared to form a complex with the substrate,[a] but this could not be hydrolysed to form the phenol. Other deprotection attempts used $BF_3{\cdot}Et_2O$ and propane-1,3-dithiol, but again none of the desired product **309** was isolated.

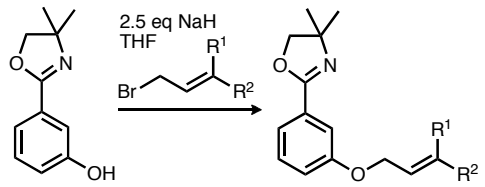
As the 4,4-dimethyloxazoline has been shown to be stable under hydrogenation conditions,[104] the benzyl ether was chosen as a suitable protecting group. The synthesis was approached by first protecting 3-hydroxy benzoic acid under standard conditions to give the protected acid **310** in 53 % yield.[105] The oxazoline could then be installed as before to give the benzyl ether **313** in 74 % yield over the two steps. Debenzylation using standard hydrogenation conditions using the H-Cube™ gave the required phenol **309** in 91 % yield (Scheme 3.2).



Scheme 3.2 Synthesis of the 4,4-dimethyloxazoline activated phenol 304

Alkylation of **309** with the required allylic bromide gave the allyl **314a**, crotyl **314b** and prenyl **314c** ethers in excellent yields (Scheme 3.3, Table 3.1). The yield of the cinnamyl ether **314d** was decreased due to the excess cinnamyl bromide present in the reaction conditions co-eluting with the product during purification by column chromatography.

[a] The spot corresponding to **308** disappeared by TLC and a new spot appeared on the baseline. ^{1}H NMR spectrum showed a shift of the oxazoline protons, and a peak corresponding to the methylene group. The complex broke down over time when left in the NMR tube to return **308**.



309 314

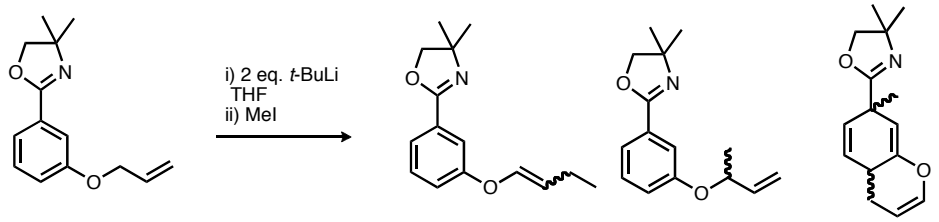
Scheme 3.3 Alkylation of the phenol 309 to give the O-allylic lithiation precursors

Entry	R^1	R^2	Yield
1	H	H	**314a** (89 %)
2	H	Me	**314b** (87 %)
3	Me	Me	**314c** (89 %)
4	H	Ph	**314d** (25 %)

Table 3.1 Alkylation of phenol 309

3.1.2 Lithiation of the O-allylic systems

In order to establish conditions for the dearomatisation of the 4,4-dimethyloxazoline activated allylic ether substrates, investigations were first carried out using the O-allylic substrate. These are shown in Table 3.2.



314a 315 316 317

Scheme 3.4 Development of the lithiation conditions for the allyl ether 4,4-dimethyloxazoline activated benzenoids

Entry	Additive (eq.)	Temp (°C)	Time (min)	Products
1	DMPU (6)	- 78	30	**315** + **316**
2	-	- 78	30	**315** + **316**
3	DMPU (6)	- 78 → - 40	5/25	**315** + **316** + **317**
4	-	- 78 → - 40	5/25	**315** + **316** + **317**
5	-	- 78 → 0	5/25	**317** 62 % (d.r. 4:1 at H4a)[a]

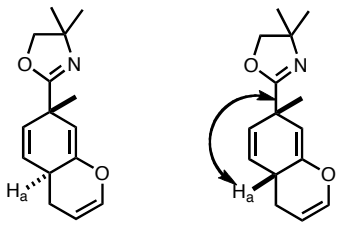
[a] d.r. Determined by the ratio in the crude ^{1}H NMR spectrum after aqueous work up.

Table 3.2 Development of the lithiation conditions for the O-allylic tethered 4,4-dimethyloxazoline activated benzenoids

Under the conditions used for the cyclisation of the O-allylic tether in the (4*R*,5*R*)-4,5-diphenyloxazoline activated system (Entry 1) no products of

dearomatisation were observed shown by the presence of peaks in the aromatic region of the crude ^{1}H NMR spectrum of the crude reaction mixture. However the reaction did not return unreacted starting material, instead mixtures of the methylated products such as **315** and **316** were present which were characterised by complication of the allylic and aliphatic regions of the ^{1}H NMR. By warming the reaction mixture to – 40 °C mixtures of the same methylated products were present along with possible dearomatised product which could be characterised by the presence of the H4a proton which coupled to both the allylic H5 proton and the H4 CH_2 signal by correlation spectroscopy of the crude reaction mixture. When carrying out the reactions with DMPU present the crude reaction mixtures were less clean due to the formation of additional uncharacterised side products. By warming the reaction further to 0 °C (Entry 5) 62 % of the dearomatised product **317** was isolated with a d.r. of (4:1) at H4a. Purification by column chromatography allowed the separation of the diastereomeric pairs **317a** (25 %) and **317b** (2 %). Total separation of the two diastereomeric pairs was not achieved as the two pairs had similar polarity on silica, therefore mixed fractions were combined to give a further 36 % of a 2:1 mixture of **317a** and **317b**. Purification by preparative HPLC was attempted but this gave a very low mass recovery. The low recovery observed for both HPLC and flash column chromatography is attributed to the instability of the dearomatised products. Degradation of samples was observed both in NMR sample tubes, which were left, to run overnight and also in round bottom flasks that were kept in the freezer under argon for a week.

With the two diastereomeric pairs isolated, the relative stereochemistry of the major and minor pairs could be established by NOE spectroscopy. When irradiating H_a of **317a** no enhancement was seen to the methyl group, suggesting they are on opposing sides of the ring and therefore have an *anti* relationship. However when irradiating H_a of **317b** enhancement to the methyl group was observed suggesting that the minor diastereomeric pair has a *syn* relationship (Scheme 3.5).

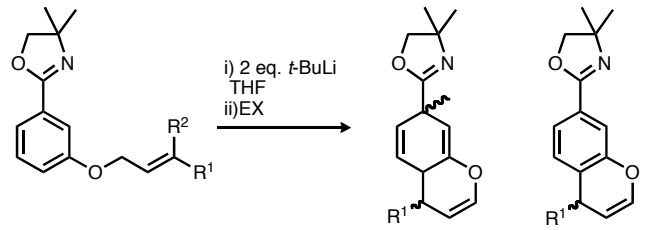


317a (26 %) **317b** (2 %)

Scheme 3.5 NOE spectroscopy on 317a and 317b

These results do not fit with the results observed for the intermolecular dearomatising additions to (4*R*,5*R*)-4,5-diphenyloxazoline activated benzenoid systems where alkylating electrophiles always add *anti* to the attack of the organolithium nucleophile. For the dearomatising cyclisation of **314a** the product of *syn* addition, where the electrophile adds *syn* to the attack of the organolithium nucleophile, is favoured to give **317a** as the major product. However this dearomatising addition is less selective, shown by the formation of the *anti* product **317b**. When the lithiation of **314a** was repeated on a 0.5 g scale purification was more successful yielding **317a** (180 mg, 35 %) and **317b** (85 mg, 16 %).

With these developed conditions now in hand these were applied to the other O-allylic substrates. As well as quenching with methyl iodide we also used saturated aqueous ammonium chloride solution and oxygen to give the rearomatised addition products in order to establish if the attack was still occurring at the *para*-position. The results of the investigations are shown in Table 3.3.



314 318 319

Scheme 3.6 Lithiation of the O-allylic tethered 4,4-dimethyloxazoline activated benzenoids

Entry	Substrate	R^1	R^2	EX	Products
1	**314a**	H	H	NH_4Cl	**319a** (18 %)
2	**314a**	H	H	O_2	**319a** (7 %)
3	**314b**	Me	H	MeI	**318b** (34 % d.r. 1:0.4)
4	**314b**	Me	H	NH_4Cl	**319b** (6 %)
5	**314b**	Me	H	O_2	**319b** (22 %)
6	**314c**	Me	Me	MeI	No dearomatised products isolated
7	**314d**	Ph	H	MeI	**318d** (12 % d.r. 1:0.6 at H4a)
8	**314d**	Ph	H	NH_4Cl	Inseparable mixture of **314d** and **319d**

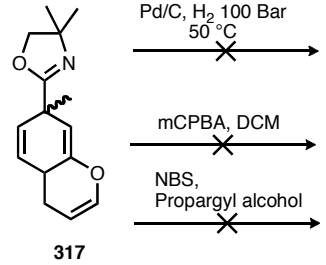
Table 3.3 Lithiation of the O-allylic tethered 4,4-dimethyloxazoline activated benzenoids

Alkylation of the azaenolates formed by the dearomatising cyclisation using methyl iodide gave the chromene type dearomatised products **318**. As with the chiral variant decreased yields were observed for the O-crotyl and O-cinnamyl tethers. Either quenching with aqueous saturated ammonium chloride solution or oxygen formed the rearomatised products of type **319**. The ^{1}H NMR spectra for the rearomatised products **319a** and **319b** have doublets with small *J* values for the W coupling of the H-8 with the H-6 proton, showing that the dearomatisation was taking place solely at the *para*-position. No information could be garnered about the facial selectivity of the methyl iodide quench with the O-crotyl and O-cinnamyl tethers additions, there is eight different diastereomers, which could be formed during the reaction. Unlike dearomatised **317** the diastereomers at H4a were not separable by column chromatography and therefore **318b** and **318d** were both isolated as mixtures. Attempts were also made to cyclise the prenyl ether **314c**, but no dearomatised products were isolated from the reaction mixtures.

3.1.3 Functionalisation of dearomatised products

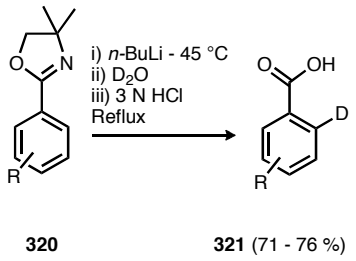
In order to establish how these dearomatised products could be further functionalised we carried out some preliminary studies. Initial functionalisation

attempts looked at the reactivity of the unsaturated bonds in the dearomatised molecule. We focused on key double bond transformations; epoxidation, bromination and hydrogenation. However all these reactions did not proceed cleanly, and showed no preference as to which unsaturated bond reacted and led to complicated mixtures of unidentified products.



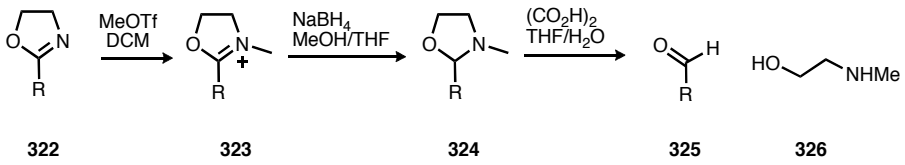
Scheme 3.7 Functionalisation reactions carried out on 317

Due to the unselective functionalisation reactions we wanted to investigate whether the oxazoline functionality could be removed. From the literature the most common way to deprotect a geminal dimethyl oxazoline is high temperature acid catalysed hydrolysis in both ethereal and alcoholic solvents, which should furnish the acid or the ester.[106] This has been utilized by Meyers for the removal of 4,4-dimethyl oxazoline to form benzoic acids of the type **320** (Scheme 3.8).[107]



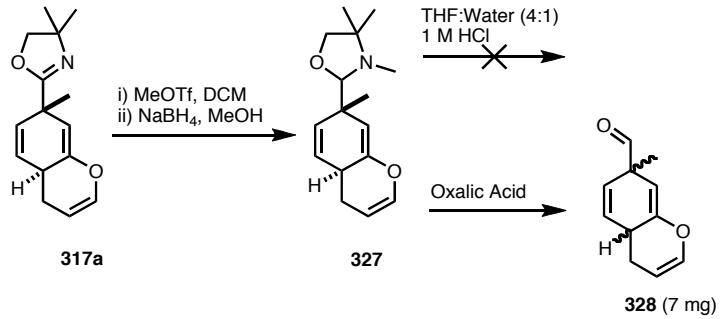
Scheme 3.8 Meyers acid hydrolysis of gem-dimethyl oxazolines

Due to the instability of the dearomatised products, **317a** was subjected to the milder *N*-quaternisation-reduction reaction conditions as described by Meyers (Scheme 3.9).[25] After the alkylation to form the oxazolinonium salt **323** using MeOTf, the salt is reduced using sodium borohydride to form the oxazolidine **324**. This process is usually carried out in one pot. Oxazolidine **324** can then be hydrolysed using oxalic acid to yield the aldehyde **325** and 2-(methylamino)ethanol **(326)**.



Scheme 3.9 General scheme for the alkylation-reduction method

Applying this method to 40 mg of **317a**, after the one-pot alkylation and reduction to the oxazolidine **327** the crude ^{1}H NMR spectrum showed the presence of the additional methyl group. This material was then split to trial the hydrolysis to the aldehyde using both the HCl and the oxalic acid methods. From the HCl reaction aldehydes were present in the ^{1}H NMR spectrum but changes were also present in the double bond region. Attempts were made to purify the products but were unsuccessful due to the instability of the products formed. The oxalic acid method gave after work up 7 mg of material, which from the crude ^{1}H NMR spectrum has signals, which may relate to **328**, there is the presence of an aldehyde signal at 9.21 ppm and loss of the signal for the CH_2 of the oxazoline. However attempts to purify this material for further analysis failed.



Scheme 3.10 Attempts to remove the 4,4-dimethyloxazoline

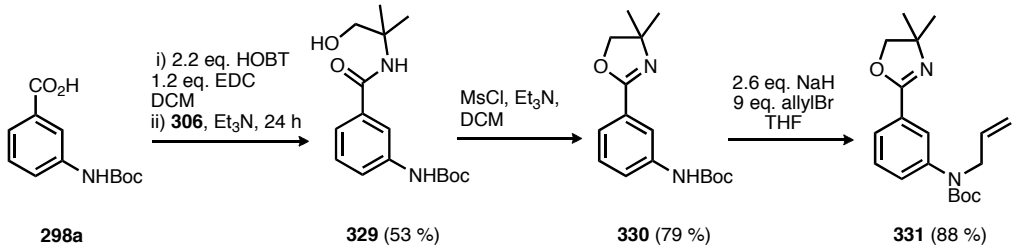
Due to time constraints and the instability of **317a** we were unable to scale up the hydrolysis reaction.

3.2 *N*-Allylic organolithium tethers

Due to the successful cyclisation of the O-allylic tethers we wanted to also investigate N-allylic tethers allowing us to vary the heteroatom in the newly formed ring. As the lithiated *N*-(Boc)-allyl cyclised in the chiral system (Scheme 2.38) we used the same protection method as the starting point for the achiral system.

3.2.1 *N*-Boc protected N-allylic organolithium tethers - construction and lithiation

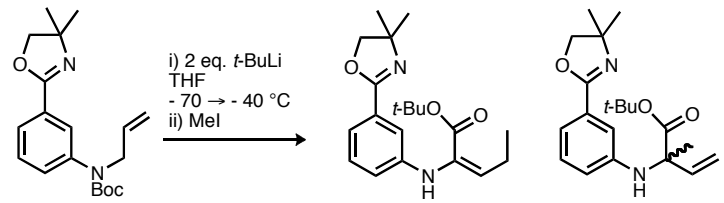
We had already synthesized the Boc protected 3-(amino)-benzoic acid **298a** for the synthesis of the *N*-Boc tethered allyl with the chiral oxazoline (Scheme 2.36). The Boc protecting group was shown to be labile under the conditions of the one-pot oxazoline synthesis method (Scheme 2.35), therefore we used EDC and HOBT to couple the carboxylic acid and 2-amino-2-ethylpropan-1-ol (**306**) to give the amide **329** in 53 % yield. To prevent deprotection of the Boc group during the cyclisation, we did not treat **329** with thionyl chloride as we did for the previous formation of the 4,4-dimethyloxazoline (Scheme 3.2). Instead methanesulphonyl chloride was used to give the desired oxazoline **330**. Finally the allyl group was installed by alkylation to give the lithiation precursor **331**.



298a **329** (53 %) **330** (79 %) **331** (88 %)

Scheme 3.11 Construction of the 4,4-dimethyloxazoline activated *N*-Boc protected *N*-allyl tether

With the precursor in hand we attempted lithiation using the conditions used to cyclise the (4*R*,5*R*)-4,5-diphenyloxazoline activated *N*-(Boc)-*N*-(phenyl)allylamine substrate (Scheme 2.38), but in this case no dearomatised products were formed. Instead a mixture of the products formed by the migration of the Boc group **332a** and **332b** was isolated in a 2.5:1 ratio that was inseparable by flash column chromatography (Scheme 3.12).

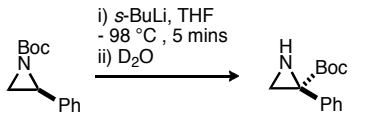


331 **332a : 332b** (2.5:1)

Scheme 3.12 Boc migration products formed by the lithiation of the *N*-Boc protected *N*-allyl tether

The mixture was characterised by the presence of signals relating to an ethyl group for **332a** (q at 2.18 ppm and t at 1.05 ppm). Where as for **332b** there is a methyl group with no coupling at 3.06 ppm and a CH and a CH_2 group which only couple to each other using correlation spectroscopy.

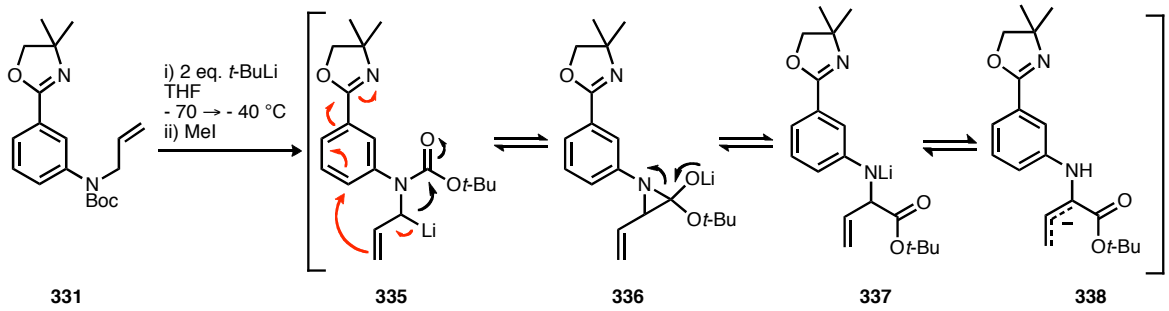
This type of [1,2] migration has been reported by Florio.[108] Whilst investigating the use of aziridines as *ortho*-lithiation directing groups, it was observed that the lithiations of *N*-Boc-phenylaziridine **333** resulted in the formation of 2-phenyl-2-Boc-aziridine **334** in 90 % yield (Scheme 3.13). The migration for **333** is proposed to occur via a [1,2] aza-Wittig rearrangement.



333 **334** (90 %)

Scheme 3.13 Boc migration observed from the lithiation of *N*-Boc-phenylaziridines

A possible mechanism for the formation of **332a** and **332b** is shown in Scheme 3.14. After α-lithiation of **331**, the new organolithium **335**, instead of attacking the *para* position of the aromatic ring to form the dearomatised intermediate (shown in red arrows in Scheme 3.14), attacks the carbonyl forming a 3-membered ring intermediate **336**. The Boc group then migrates from nitrogen to the α carbon to form the next intermediate with the lithium stabilised on nitrogen **337**. In order to form the isolated intermediates, the α carbon must be secondly deprotonated, as **337** is a lithium amide this process may occur via deprotonation by a second molecule of **337**. The dearomatised allylic system **338** formed from this deprotonation can now be alkylated either at the α-position to give **332b** or at the γ-position of the extended delocalized system to afford **332a**.



Scheme 3.14 Possible mechanism for the formation of the Boc migration products

For the chiral substrate **302b** (Scheme 2.38) the dearomatising cyclisation must be the faster process as no products of Boc migration were isolated. With the Boc group migration taking place in preference to cyclisation for the achiral substrate **331** no further lithiation attempts were tried on this substrate and other nitrogen protecting groups were investigated.

3.2.2 *Tert*-butyl sulfinamide protected N-allyl tether - construction and lithiation

The stability of Bus (*tert*-butyl sulfonamide) protecting group to organolithium such as *n*-BuLi, *t*-BuLi and *sec*-BuLi has been reported.[109-111] We aimed to construct Bus protected lithiation precursor **339** forming the *t*-butyl sulfinamide protected substrate **340** and then oxidizing to the sulfonamide. The sulfinamide **340** could itself be accessed by coupling the free allyl amine **341** with *t*-butylsulfinyl chloride. The simplest way to the free allyl amine is by deprotection of the *N*-Boc protected allyl amine **331**.

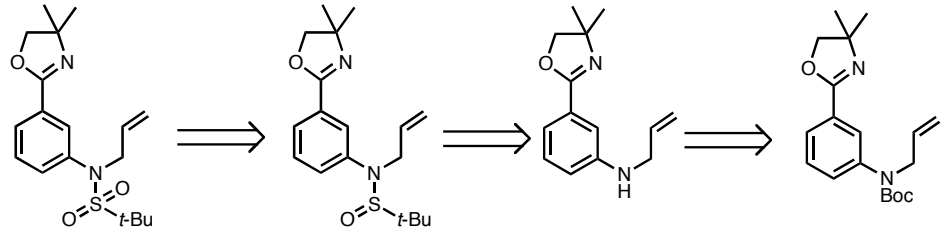
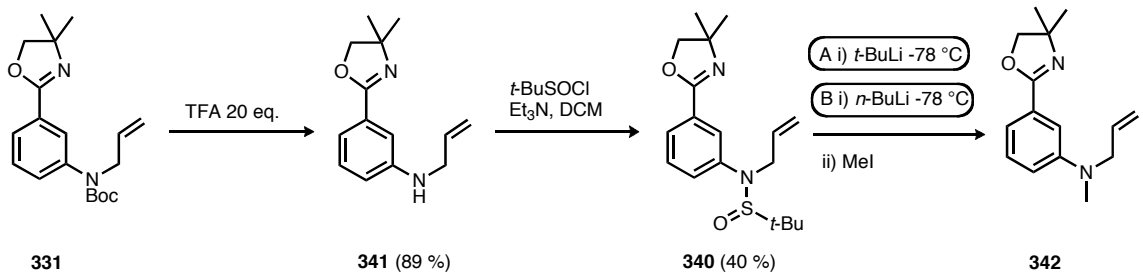


Figure 3.1 Retrosynthesis for the construction of the *N*-Bus protected allyl

The deprotection of **331** could be effected by TFA to give the free amine **341** in 89 % yield. The yield for the reprotection was low, yielding 40 % of **340**. Due to time constraints we did not attempt the oxidation of **340** to give the Bus protected tether, but a lithiation of **340** was attempted.



331 **341** (89 %) **340** (40 %) **342**

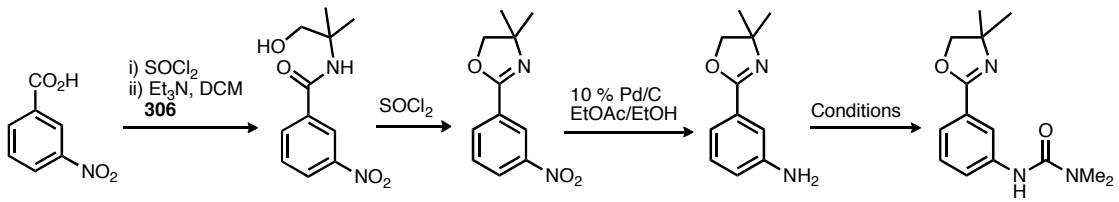
Scheme 3.15 Construction and lithiation of the *N*-*t*-Bu sulphinamide protected allyl

Unfortunately the lithiation of **340** was unsuccessful using *t*-BuLi or *n*-BuLi; under the lithiation conditions the protecting group was labile. After quenching the reaction with methyl iodide *N*-methylated derivative **342** was isolated, characterised by the loss of the $C(CH_3)_3$ group in the crude ^1H NMR spectrum and the presence of a CH_3 singlet at 2.97 ppm.

3.2.3 3,3-Dimethylurea protected *N*-allylic organolithium tether – construction and lithiation

We wanted to explore whether a dimethyl urea group could be used as an effective protecting group of an allyl amine tether. The N-C rearrangement observed in the 1-benzyl-3,3-dimethylurea tethered systems (Scheme 2.23) should not be a reaction pathway for this 3,3-dimethylurea protected N-allylic system as both the site of lithiation and the aryl ring are attached to the same nitrogen.

To construct the 3,3-dimethylurea protected allylic amines we installed the oxazoline first to give us access to different allylic amines by late stage alkylation. The oxazoline installation was achieved by the usual method to give the required nitro substrate **344** in 93 % over the three steps. The nitro functionality could then be reduced using Pd/C hydrogenation to give the free amine **345** quantitatively. The installation of the 3,3-dimethyl urea was problematic as the reaction was initially very sluggish. The optimization of this reaction is shown in Table 3.4.



246 **343** (94 %) **344** (93 %) **345** (quant.) **346** 84 %

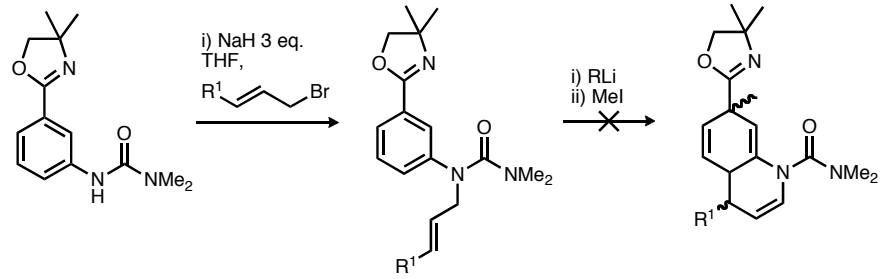
Scheme 3.16 Construction of the dimethyl urea tether

Entry	Carbomyl chloride eq.	Base eq.	Additive	Solvent	Temp	Time	Ratio [a]345:346
1	1 + 1 after 12 h	Et_3N (2)	10 % DMAP after 12 h	DCM	RT	36 h	33:66
2	2	Et_3N (3)	10 % DMAP	DCM	50 °C	36 h	33:66
3	2	*n*-BuLi(1)	-	THF	-78 °C - RT	18 h	66:33
4	2	Pyridine(5)	10 % DMAP	DCM	RT	34 h	0:100

[a] Ratio determined by ^{1}H NMR spectrum of the crude reaction mixture

Table 3.4 Conditions used for the formation of the dimethyl urea tether

By using pyridine and 10 % DMAP the dimethylurea **346** could be isolated in 84 % yield after 34 h (Entry 4). With the protected amine in hand alkylations were carried out to give the allyl **347a**, crotyl **347b** and cinnamyl **347c** lithiation precursors. The yield for the cinnamyl precursor was reduced by difficult removal of residual cinnamyl bromide due to co-elution by column chromatography.



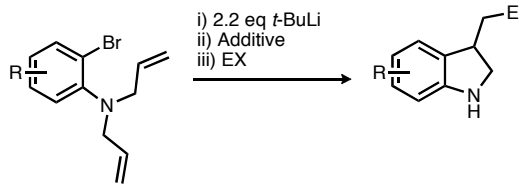
346 **347a** R^1 = H = 93 % **347b** = Me = 87 % **347c** = Ph = 10 % **348**

Scheme 3.17 Alkylation of the dimethyl urea protected amine

The lithiation of the dimethyl urea tethers **347a**, **347b**, and **347c** was attempted using *t*-BuLi, *n*-BuLi and LDA at -78 °C and with warming to 0 °C. However no dearomatised products were present in the crude reaction mixtures by ^{1}H NMR spectrum, which would be characterised by the loss of the aromatic protons. Instead there were complex mixtures of uncharacterised products thought to be due to unselective methylation of the allylic system and possible urea migration.

3.2.4 *N,N*-Diallyl organolithium tether - construction and lithiation

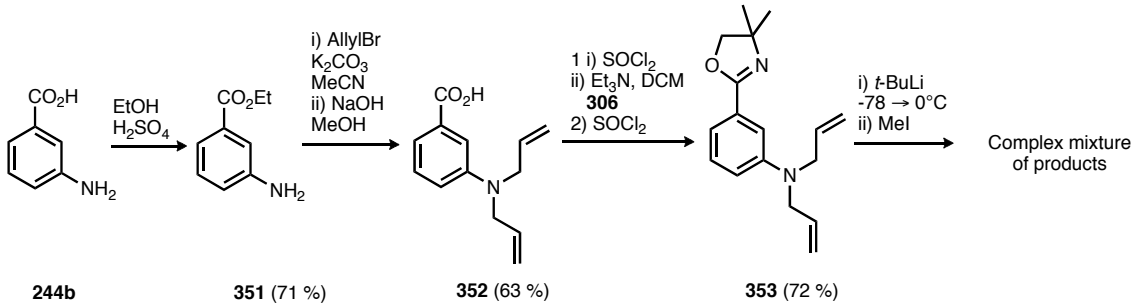
As the presence of a protecting group on nitrogen was causing undesired side products, we hoped that the *N,N*-diallyl tether would be more successful as it gives two possible sites for lithiation and the remaining allyl group may be removed using palladium.[112] Anionic cyclisation of an aryllithium onto allyl amines has been reported.[113, 114] When there is a bromine *ortho* to the diallylamine (**349)** lithium-halogen exchange gives a phenyl lithium which cyclises onto the allyl in the presence of an additive such as *t*-BuOMe[113] or TMEDA[114] to form indolines of the type **350**.



349 **350**

Scheme 3.18 Formation of indolines from an anionic cyclisation of a aryllithium onto an *N,N*-diallyl amine

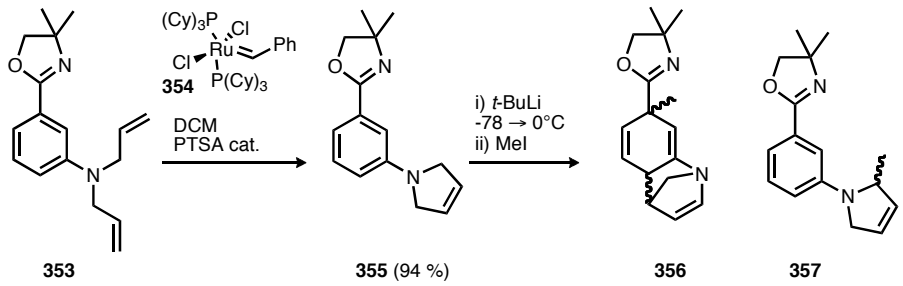
To construct the required tether we first esterified 3-aminobenzoic acid **244b** to give ethyl 3-aminobenzoate **351** in 71 % yield. Ester **351** was then alkylated by heating with allyl bromide using K_2CO_3 as the base. This ester could then be saponified to give the carboxylic acid **352**, which was subjected to the same oxazoline formation conditions used to form the 4,4-dimethyloxazoline activated O-allylic substrates. These conditions furnished the required lithiation precursor **353** in 72 % yield over the three steps. Unfortunately treatment of **353** with *t*-BuLi created a complex mixture of products, none of which appeared to be dearomatised from the crude ^{1}H NMR spectrum.



244b **351** (71 %) **352** (63 %) **353** (72 %)

Scheme 3.19 Construction of the diallyl tether 353

As no dearomatised products could be isolated from the lithiation of **353** we utilised it in a ring closing metathesis reaction to form a dihydropyrrole ring **355**. As **355** still has an allylic system so it was hoped that it would lithiate in a similar way to the other allylic systems, attacking the aromatic ring forming a tricyclic fused ring system such as **356**.

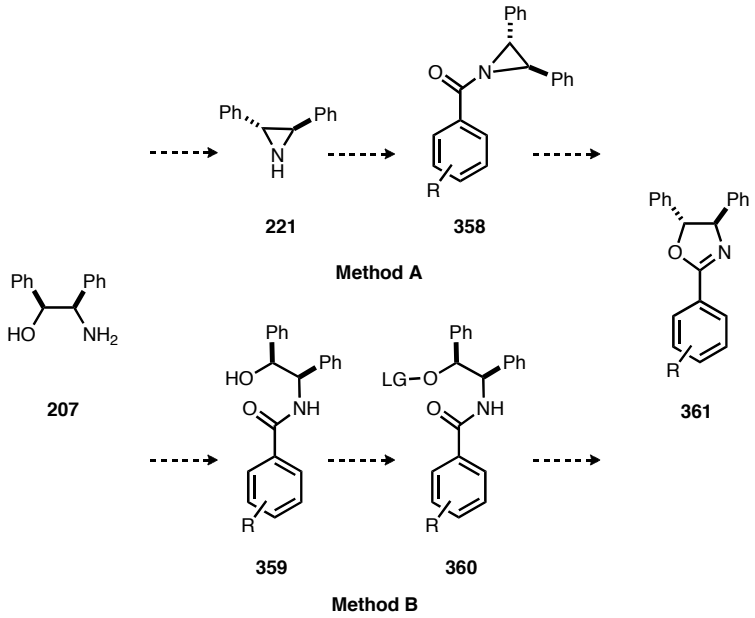


Scheme 3.20 Ring closing metathesis and lithiation of the 2,5-dihydropyrrole product

The ring closing metathesis was achieved using Grubb's 1st generation catalyst (**354**) to give the expected 2,5-dihydropyrrole **355** in 94 % yield. This substrate however was not stable and degraded on standing. Some lithiation conditions were however attempted. Lithiation of **355** with 2 eq. *t*-BuLi at -78 → 0 °C gave methylated starting material (25 mg, 80 %) meaning that the required deprotonation was occurring, but we were unable to find conditions that effected cyclisation. Due to the unstability of **355** we were unable to further investigate the lithiation of **359**.

4 Synthesis of (4*R*,5*R*)-4,5-diphenyloxazolines

Within this work three different *trans* oxazoline synthesis routes have been utilised to form the (4*R*,5*R*)-4,5-diphenyl oxazoline withdrawing group. These methods all use the (1*S*,2*R*)-2-amino-1,2-diphenyl ethanol **207** as the starting point. The required stereochemistry is introduced by an inversion of the alcoholic centre during the synthetic route (Scheme 4.1).



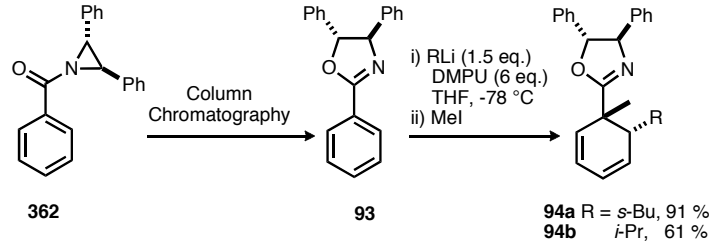
Scheme 4.1 Retrosynthesis of the two routes used to synthesise (4*R*,5*R*)-4,5-diphenyl oxazolines

For Method A the inversion of stereochemistry takes place during the Mitsunobu reaction used to form the (2*R*,3*R*)-2,3-diphenylaziridine (**221**), which later undergoes a stereospecific rearrangement to give the required oxazoline. In Method B, the required stereochemistry is achieved in the last step during the ring closing displacement of the activated β-hydroxyl group of **360**.

The development of these two routes is outlined in this chapter.

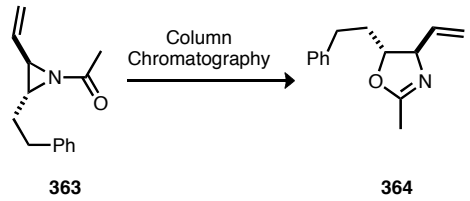
4.1 Benzoyl aziridine rearrangement

There are many different reported methods for the rearrangement of benzoyl and acyl aziridines to form oxazolines including the use of nucleophiles such as iodide and Lewis acids.[115-119] Work by Purewal on the dearomatising cyclisation of **362**,[47] was shown by Parris and Cabedo to be the dearomatising addition of organolithiums to the (4*R*,5*R*)-4,5-diphenyl oxazoline **93**, as acyl aziridine **362** had undergone a silica promoted stereospecific rearrangement during purification by column chromatography. This work led to the development of the intermolecular dearomatisation discussed in Section 1.3.2.4.[48, 49, 120]



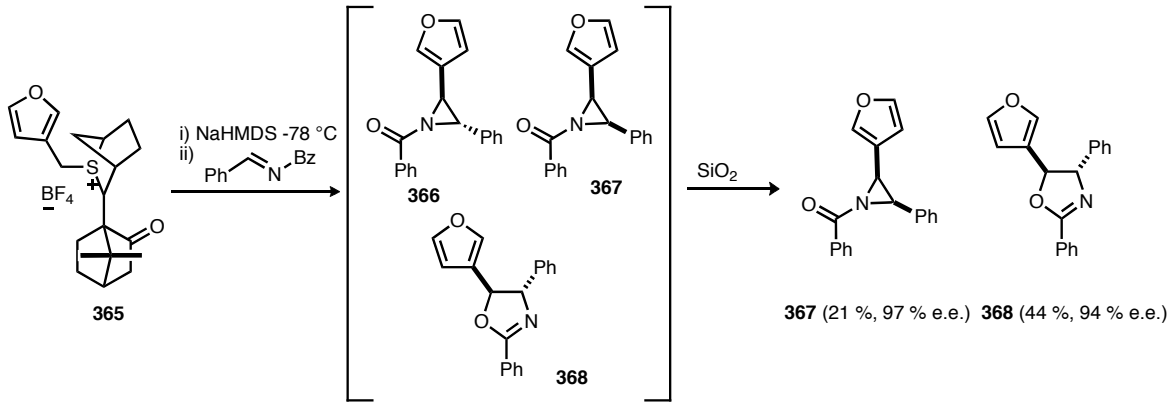
Scheme 4.2 Rearrangement of benzyoyl (2*R*,3*R*)-2,3-diphenylaziridine

There has only been two other cases of silica promoted rearrangement of benzoyl aziridines reported in the literature. Somfai observed the rearrangement of *N*-acyl aziridine **363** upon purification to give the undesired oxazoline **364**.[121]



Scheme 4.3 Rearrangement of N-acyl aziridine upon purification

Aggarwal[122] reported a synthesis of benzoyl aziridines via the coupling of sulfonium salt **365** with (E)-N-benzylidenebenzamide to give a mixture of *trans* and *cis* benzoyl aziridines **366** and **367** and the *trans* oxazoline **368** (Scheme 4.4). Purification of the mixture by column chromatography promoted further rearrangement of the *trans* benzoyl aziridine to yield only the *cis* benzoyl aziridine and the *trans* oxazoline.



Scheme 4.4 Synthesis of benzoyl aziridines via sulfonium salt couplings

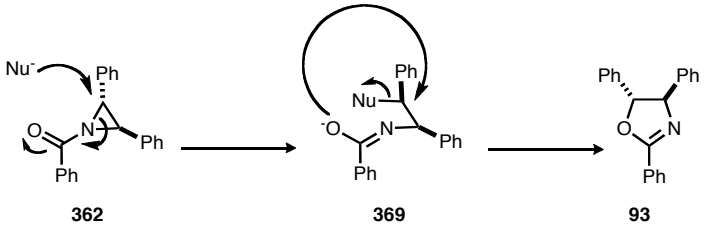
A small reduction in the enantiomeric excess of the *trans*-oxazoline was observed. This is believed to be due to partial isomerisation of the *cis* benzoyl aziridine into the *ent-trans* oxazoline.

Three methods have been proposed for the rearrangement of *trans*-acyl and benzoyl aziridines;[123]

1. Addition-elimination mechanism (S_N2-S_N2)
2. Carbocation mechanism (S_N1)
3. Front sided direct attack mechanism (S_Ni)

All three of these mechanisms give the retention of configuration as observed in the rearrangement of the (4*R*,5*R*)-4,5-diphenyl benzoylaziridine. Most *cis*-benzoyl aziridines undergo a non-stereospecific rearrangement to give mixtures of *trans* and *cis* oxazolines,[122, 124, 125] although stereoselective rearrangements have been reported.[126]

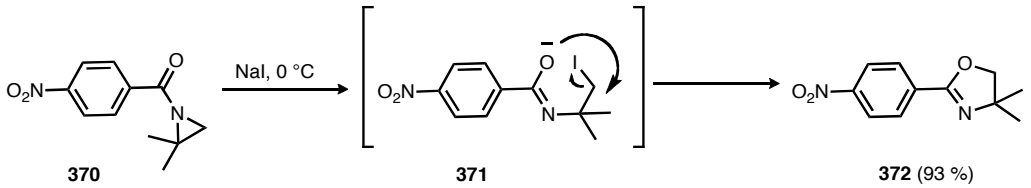
4.1.1 Addition-elimination mechanism



Scheme 4.5 Addition-elimination mechanism

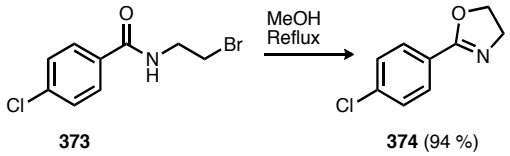
When using a nucleophile to promote the rearrangement the addition-elimination mechanism proposed by Heine is the most probable mechanistic pathway.[117] Here nucleophilic attack opens the aziridine ring with inversion at the C1 position, to give a linear product. Attack of the amide oxygen displaces the nucleophile by way of a second S_N2 displacement giving net retention of configuration at the C1 position. Heine

proposed this mechanism for the rearrangement of *para*-nitro benzoyl aziridine **370** using sodium iodide as the nucleophile (Scheme 4.6).



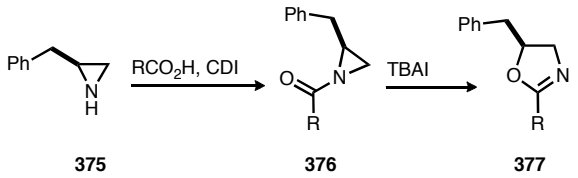
Scheme 4.6 Sodium Iodide promoted benzoyl aziridine rearrangement

This mechanism was further supported by his work on *N*-(2-bromoethyl)benzamide **373**, which on heating in methanol gave the phenyl oxazoline **374** in 94 % yield.[127]



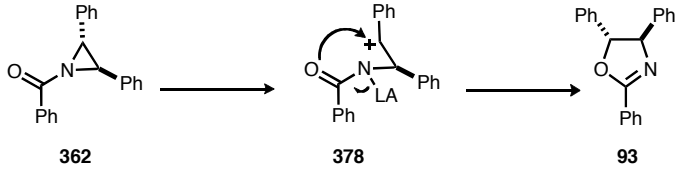
Scheme 4.7 Cyclisation of N-(2-bromoethyl)benzamides

Similarly, tetrabutylammonium iodide (TBAI) was used by Bates to perform the rearrangement in his one-pot coupling and rearrangement. Here carbonyldiiimidazole (CDI) was used to couple the aziridine **375** with the carboxylic acid, before the addition of the TBAI.[128]



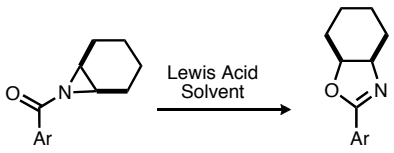
Scheme 4.8 TBAI promoted benzoyl aziridine rearrangement

4.1.2 Carbocation mechanism



Scheme 4.9 Carbocation mechanism

The carbocation mechanism has been proposed by Lectka for the Lewis acid rearrangement of benzoyl aziridines such as **379** (Scheme 4.10).[115] He proposed that the reaction occurs by co-ordination of the Lewis acid to the aziridine nitrogen, allowing the cleavage of the C-N bond to give a carbocation at the C1 position. Attack by the amide oxygen closes the ring forming the oxazoline.



379 380

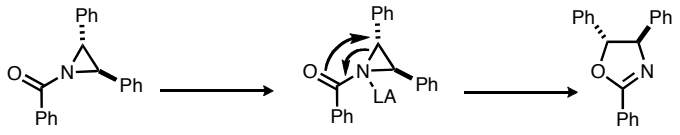
Scheme 4.10 Lewis acid promoted rearrangement of benzoyl aziridines

Entry	Solvent	Lewis Acid	Time	Yield
1	DCM	10 % $Cu(OTf)_2$	48 h	80 %
2	DCM	10 % $Sn(OTf)_2$	48 h	80 %
3	THF:DME (20:1)	10 % $Cu(OTf)_2$	7 h	84 %
4	THF:DME (20:1)	10 % $Sn(OTf)_2$	12 h	87 %

Table 4.1 Effect of solvent on Lewis acid promoted rearrangement of benzoyl aziridines

Lectka also showed that cation-coordinating solvents such as THF and DME accelerated the reaction rates. Stereoselectivity may only be achieved by this mechanism when the carbocation is solvated from the backside preventing epimerisation by blocking the back face from attack. Without some form of stabilization the cation could easily epimerise. The conditions used for the rearrangement of our (4*R*,5*R*)-4,5-diphenyl benzoylaziridine substrates use dichloromethane as the reaction solvent. Dichloromethane is a poor cation solvating solvent and we observe only one diastereoisomer of the product.[a] Therefore this mechanism does not fully explain our observed stereoselectivity.

4.1.3 Front sided direct attack mechanism

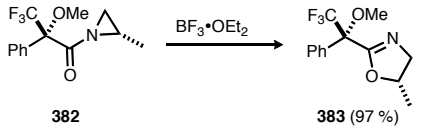


362 381 93

Scheme 4.11 Mechanism of the front sided direct attack mechanism

The most investigated S_Ni mechanisms are the chlorination of alcohols using thionyl chloride[129] and the decomposition of alkyl chloroformates and chloro sulfites.[106, 130] Hori proposed the front sided direct attack mechanism to account for the selectivity observed in the boron trifluoride promoted acyl aziridine rearrangement. In this mechanism when the C-N bond breaks the C-O bond reforms on the same side as the broken C-N bond.

[a] Only one set of oxazoline peaks are seen in the crude ^{1}H NMR spectrum.



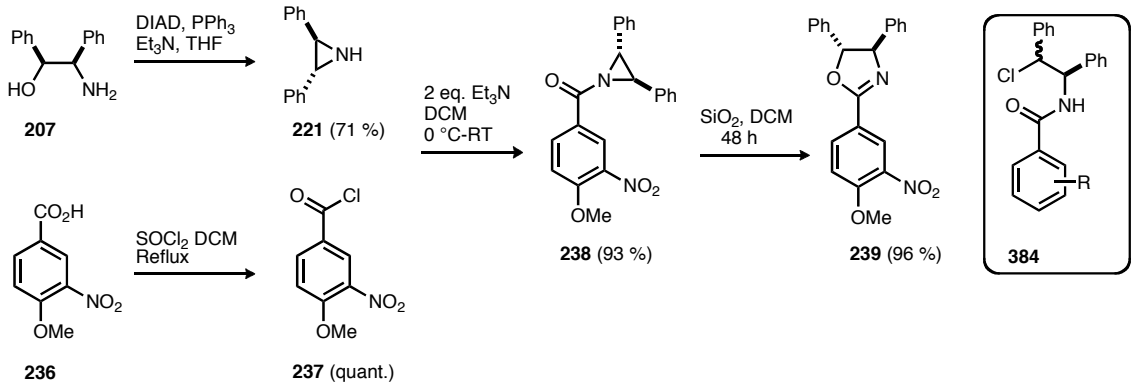
382 **383** (97 %)

Scheme 4.12 $BF_3 \cdot OEt_2$ promoted rearrangement of acyl aziridines

This mechanism explains the lack of epimerisation observed in our (4*R*,5*R*)-4,5-diphenyl benzoylaziridine substrates. However S_Ni mechanisms are often difficult to prove, as they are hard to distinguish from S_N1 tight ion pair mechanisms. The *ab initio* calculations of the polar transition state of the front sided direct attack mechanism calculated the activation energy (E_a) of the S_Ni mechanism of the above reaction (Scheme 4.12) without a Lewis acid to be 49.2 kcal mol^{-1}. After the addition of a Lewis acid the E_a of the O-protonated intermediate is 48.2 kcal mol^{-1} where as the E_a of the N-protonated 38.9 kcal mol^{-1} making the N-stabilised mechanism as shown in Scheme 4.11 more favorable. Hori attempted to model the tight ion pair mechanism of the type shown in Scheme 4.9 where the nitrogen is complexed to the Lewis acid and the three membered ring is broken for substrate **382**, but they failed to optimise this intermediate suggesting that there is no tight ion pair with a broken three membered ring in this mechanism.[123]

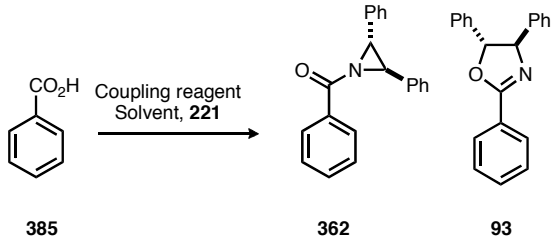
4.1.4 Development of a one-pot silica promoted benzoyl aziridine rearrangement

In the rearrangement described by Parris the benzoyl aziridine was formed by the coupling of (2*R*,3*R*)-2,3-diphenylaziridine (**221**) with a benzoyl chloride (Scheme 1.26). This route could be utilised very successfully for the synthesis of (4*R*,5R)-2-(4'-methoxy-3'-nitrophenyl)-4,5-diphenyloxazoline **239**. Here the (2*R*,3*R*)-2,3-diphenyl aziridine is first formed by treating (1*S*,2*R*)-2-amino-1,2-diphenyl ethanol **207** with diisopropyl azodicarboxylate (DIAD) to perform an intramolecular Mitsunobu reaction. The aziridine **221** could then be coupled with the preformed benzoyl chloride. The crude benzoyl aziridine **238** was then stirred in a SiO_2/dichloromethane slurry for 48 hours to give the oxazoline **239** in 96 % yield (Scheme 4.13).



Scheme 4.13 Synthesis of (4*R*,5R)-2-(4'methoxy-3'-nitrophenyl)-4,5-diphenyloxazoline

This result however was not general to other carboxylic acids, as some of the benzoyl aziridine substrates formed underwent a ring opening at the C1 position by chloride, to form products of the type **384**. This is due in part to the low energy barrier of the first S_N2 displacement. For his studies on the rearrangement of **382 (**Scheme 4.12) Hori calculated the barrier to be 14 kcal mol^{-1} when using Cl^- to model the double inversion mechanism. The second S_N2 displacement was shown to have a much higher activation barrier of 45.4 kcal mol^{-1}, this high barrier presumably allows us to isolate the ring opened intermediate **384**.[123] Presumably the E_a for such rearrangements is linked to the aromatic substitution, which may explain why the ring-opened products are not seen for all substrates. To try and avoid this side product and with a view to establishing a one-pot coupling and rearrangement, screens were carried out to try and utilize amide coupling reagents (Table 4.2, Scheme 4.14).



Scheme 4.14 Amide coupling reagent screen

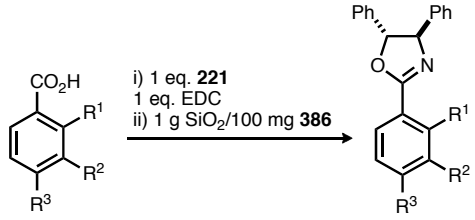
Entry	Coupling Reagent	Time	DMF [a]	Time	DCM[a]	Time	THF[a]
1	EDC	12 h	68:32:00	12 h	90:10:00	12 h	66:34:00
2	DIC and HOBT	12 h	16:17:67	12 h	100:00:00	12 h	100:00:00
3	HBTU	12 h	64:23:07	12 h	14:39:29	12 h	96:04:00
4	DCC	12 h	-	12 h	44:56:00	12 h	69:31:00

[a] Results determined by ratio in ^{1}H NMR spectrum **362**:**385**:**93**

Table 4.2 Amide coupling reagent screen

Diisopropylcarbodiimide/N-hydroxybenzotriazole (DIC/HOBt) in DCM was found to be the most successful coupling reagent for the model substrate **385**. However when applied to the intended substrates only small amounts of coupling was observed.

Further studies were therefore carried out using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) with commercially available benzoic acids to investigate the tolerance of substitution on the aromatic ring. The free base of EDC was used to stop the formation of the ring-opened products that were observed when using the HCl salt.



386 **387**

Scheme 4.15 Substrate tolerance of the one-pot coupling and silica mediated benzoyl aziridine rearrangement

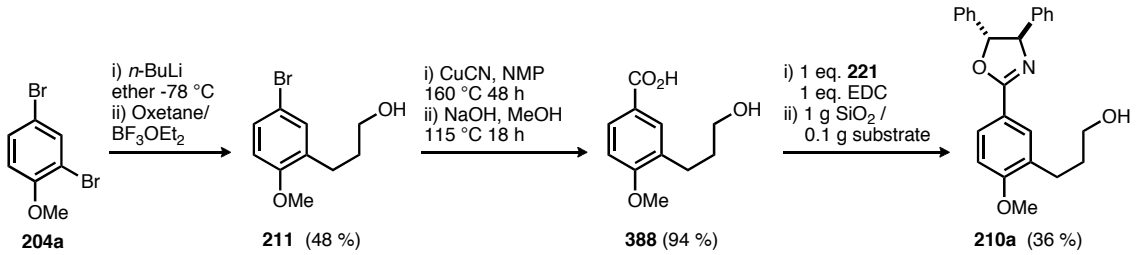
Entry	R^1	R^2	R^3	Days[a]	Yield (%)
1	H	H	H	1	27 [b]
2[c,d]	NO_2	H	H	14	70
3[c,d]	H	NO_2	H	7	43
4[c]	H	H	NO_2	4	97
5[c]	H	CN	H	13	3
6[c]	H	H	CN	14	23
7[c]	H	Br	H	4	6
8	H	H	F	5	28 [b]
9[c]	H	OMe	H	8	100
10[c]	H	H	Ph	4	100

[a] number of days stirred in DCM with SiO_2 [b] Yield [c] Yield determined by ^1H NMR spectrum [d] 100 mg SiO_2 per 2 g of **383** [e] For entries 1-10 experiments were carried out by Nuffield bursary student Ailsa Bennet

Table 4.3 Substrate tolerance of the one-pot coupling and silica mediated benzoyl aziridine rearrangement

The results of this screen show that the reaction is general with most of the benzoyl aziridines formed undergoing the rearrangement. However extended reaction times were often needed and when the products were isolated (Entries 1 and 8) the yields were found to be poor. This was thought to be due to the low solubility of the final products.

We submitted substrate **388**, which is an intermediate for forming the hydrocarbon tether **203**, to the one pot coupling/benzoyl aziridine rearrangement conditions. The substrate had been formed by installation of the tether using the lithiation followed by oxetane/$BF_3.Et_2O$ quench as before. The carboxylic acid was then introduced by S_NAr displacement of bromine with cyanide, followed by hydrolysis to give the carboxylic acid **388** in good yield.

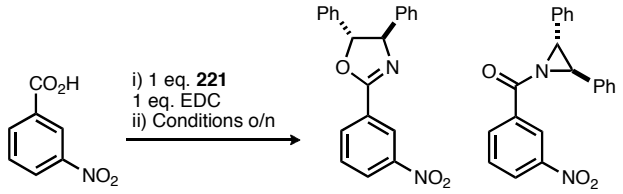


204a **211** (48 %) **388** (94 %) **210a** (36 %)

Scheme 4.16 Synthesis of 210a via the one pot coupling/benzoyl aziridine rearrangement method

As with the examples in Table 4.3 although the reaction went to completion according to the crude ^{1}H NMR spectrum the yield of **210a** was low.

These results prompted us to investigate other literature conditions which have been shown to promote the benzoyl aziridine rearrangement. Work by Parris attempted to use iodine as a nucleophile, this however this was unsuccessful with no oxazoline forming after stirring ((2*R*,3*R*)-2,3-diphenylaziridin-1-yl)(4-methoxyphenyl)methanone ten days with sodium iodide in acetone.[48] Investigations into other conditions are shown in Table 4.4. 3-Nitrobenzoic acid was chosen as the substrate as it gave a low yield over an extended length of reaction under the initial SiO_2 screen (Table 4.3, Entry 3).



246 **247** **389**

Scheme 4.17 Attempts to optimise the rearrangement of ((2*R*,3*R*)-2,3-diphenylaziridine)(3-nitrophenyl)methanone

Entry	Conditions	Observations
1	Normal SiO_2	**389**
2	Dried (120 °C o/n) SiO_2	**389**
3	SiO_2/H_2O	**389**
4[a]	SiO_2/H_2SO_4	**389**:**247** (7:3)
5	Amberlyst	**289**
6[a]	Dried Amberlyst (120 °C o/n)	**389**:**247** (9:2)
7	RT Amberlyst	**389**
8[a,b]	40 °C Amberlyst	**389**:**247** (1:3)
9	10 % $Sc(OTf)_2$	**389**

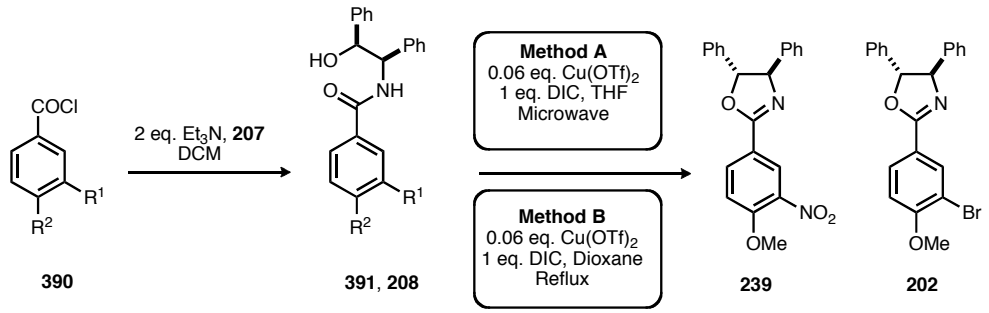
[a] Ratio determined by ^{1}H NMR spectrum [b] After 8 days

Table 4.4 Attempts to optimise the rearrangement of ((2*R*,3*R*)-2,3-diphenylaziridine)(3-nitrophenyl)methanone

Unfortunately none of these conditions were an improvement on the original SiO_2 method and due to the narrow scope of the rearrangement another route to the (4*R*,5*R*)-4,5-diphenyloxazolines was investigated.

4.2 Hydroxyl activation

In Method B (Scheme 4.1) the alcohol moiety of the β-hydroxyamide is activated to allow S_N2 displacement by the amide oxygen. Due to this inversion, amino alcohol (**207**) with the opposite stereochemistry to that required at C4 is used. Within the Clayden group the original method for the oxazoline formation was developed from that of Linclau.[82] The required amide is formed by amide coupling of the amino alcohol (**207**) with a benzoyl chloride. A copper promoted cyclisation follows activation of the alcohol with diisopropylcarbodiimide. This can be carried out either by microwave irradiation in THF, or by refluxing in 1,4-dioxane. The results of which are shown in Table 4.5.



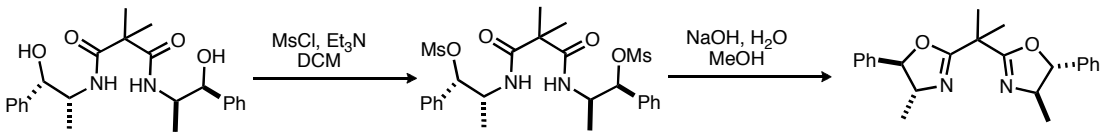
Scheme 4.18 Comparison of the different methods of cyclising the activated β-hydroxyl

Entry	R^1	R^2	Method	Yield (%)	Yield (%)
1	NO_2	OMe	140 °C 30 mins (A)	**391a** (69)	**239** (31)
2	NO_2	OMe	80 °C 7 hours (B)	**391a** (69)	**239** (35)
3	Br	OMe	140 °C 30 mins (A)	**208** (92)	**202** (37)
4	Br	OMe	110 °C 18 hours (B)	**208** (92)	**202** (85)

Table 4.5 Comparison of the different methods of cyclising the activated β-hydroxyl

Although good yields are observed for 3-bromo-*N*-((1'*R*,2'*S*)-2'-hydroxy-(1'-diphenyl ethyl)-4-methoxy benzamide **391b** (Entry 4), for other substrates this method gave only moderate yields.

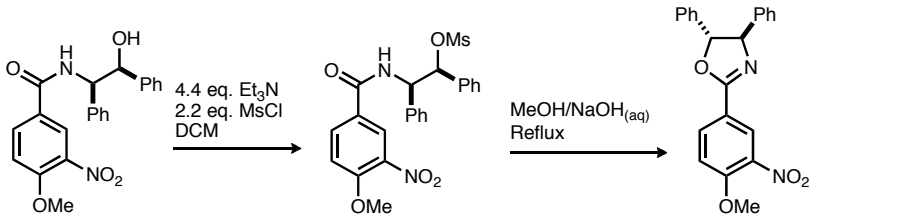
There are other methods of activating the hydroxyl group towards displacement. For the preparation of 4,5-disubstituted bisoxazolines such as **394**, Desmoni used methanesulfonyl chloride to form the mesylate **393**. Heating **393** in a sodium $hydroxide_{(aq)}$/methanol mixture effected cyclisation to the corresponding bisoxazoline in 72 % yield.[131]



392 **393** **394** (27 %)

Scheme 4.19 Desmoni's synthesis of bis-oxazolines

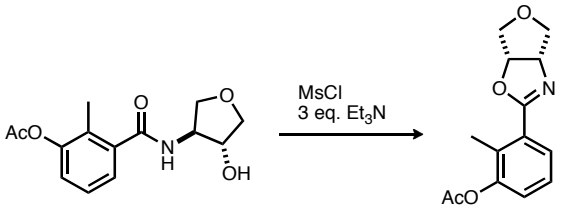
We applied these conditions to *N*-((1*R*,2*R*)-2-hydroxy-1,2-diphenylethyl)-4-methoxy-3-nitrobenzamide **391a**, which had shown poor yields of oxazoline under the previous hydroxyl activating conditions (Entry 1 and 2, Table 4.5). The intermediate mesylate **395** was not characterized and was carried through crude to give the oxazoline **239** in 93 % but with a d.r of 90:10 (Scheme 4.20).



391a **395** **239** (93 %, d.r 90:10)

Scheme 4.20 Oxazoline formation via mesylation

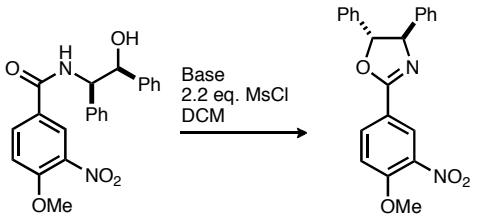
Within the Clayden group it was observed that with some substrates, oxazoline was present when characterizing the mesylated intermediate.[50, 53] This has also been observed by Borer and workers,[132] who obtained the fused oxazoline **397** when treating amide **396** with methanesulfonyl chloride and excess triethylamine (Scheme 4.21).



396 **397**

Scheme 4.21 Oxazoline formation by mesylate displacement, using mesylation conditions

In order to ascertain the optimum base to promote cyclisation, a screen of bases was carried out (Table 4.6).



391a **239**

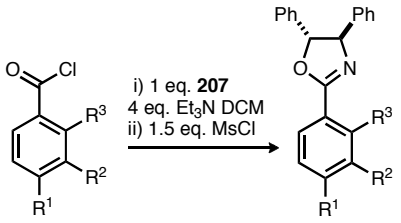
Scheme 4.22 Base screen for promoting the cyclisation of the mesylate under mesylation conditions

Entry	Base	Eq.	Ratio in ^{1}H NMR spectrum after 24 h (**391a**:**239**)
1	Pyridine	2	100:0
2	Pyridine	4	46:54
3	*i*-Pr_2NEt	2	66:44
4	Et_3N	2	60:40
5	Et_3N	4	36:64

Table 4.6 Base screen for promoting the cyclisation of the mesylate under mesylation conditions

For amide **391a** it appeared that 4 eq. of triethylamine was the most effective for promoting the cyclisation and it was selective yielding only the desired *trans*-diphenyloxazoline **239**.

These conditions have shown to be the most general for the Clayden group, with good results for both commercially available benzoyl chlorides (Entries 1-6, Table 4.7) and carboxylic acids. The carboxylic acids were first transformed to the benzoyl chloride first using $SOCl_2$ before reacting with the amino alcohol **207** (Entries 7-13).[133] In all cases both the amide coupling and the cyclisation steps were monitored by TLC with the amide coupling being allowed to stir over night before the addition of the methanesulphonyl chloride.



398 **399**

Scheme 4.23 Optimised one-pot coupling, mesylation and cyclisation conditions

Entry	R^1	R^2	R^3	Product	Yield (%)
1[b,c]	H	H	H	**399a**	71
2[b,c]	OMe	H	H	**399b**	80
3[c]	F	H	H	**399c**	90
4[c]	H	OMe	H	**399d**	88
5[c]	H	F	H	**399e**	80
6[c]	H	H	F	**399f**	46
7[a]	OMe	$CH_2CH_2CH_2OSi(iPr)_3$	H	**214**	88
8[a]	OMe	$CH_2OSi(iPr)_3$	H	**225**	67
9[a]	OMe	CH_2Cl	H	**399g**	67
10[a]	OMe	$CH_2CH_2CH_2OC(O)N(iPr)_2$	H	**233**	90
11[a]	OMe	$N(CH_3)C(O)N(CH_3)CH_2Ph$	H	**242**	67
12[a,b]	H	OCH_2CHCH_2	H	**275**	66
13[a,b]	OMe	OCH_2CHCH_2	H	**275a**	20
14[a]	H	OC(O)Ph	H	**290**	69
15[a]	H	NO_2	H	**247**	58

[a] The benzoyl chloride had to be preformed first [b] Reactions performed by O Karlubikova[50] [c] Reactions performed by J Clayton[53]

Table 4.7 Optimised one-pot coupling, mesylation and cyclisation conditions

This method is an uncomplicated stereoselective one-pot synthesis of 2-aryl oxazolines, which is applicable to a range of substituted products as shown in Table 4.7. The presence of electron-withdrawing and electron-donating groups was well tolerated, and yields were generally good to excellent. Unfortunately lower yields of 2-oxazolines were observed when electron-withdrawing substituents were present in the *ortho*-position. This is presumed to be due to the inductive decrease in the nucleophilicity of the amide C=O bond, which reduces the rate of cyclisation. The method has also been scaled, the synthesis of **399b** (Entry 2) was successfully carried out on a 10 g scale.

5 Conclusions and Future Work

- That (4*R*,5*R*)-4,5-diphenyloxazolines and 4,4-dimethyloxazolines are able to activate benzene rings towards a novel regio-selective dearomatising cyclisation of lithiated O-allylic tethers to give novel fused ring products.

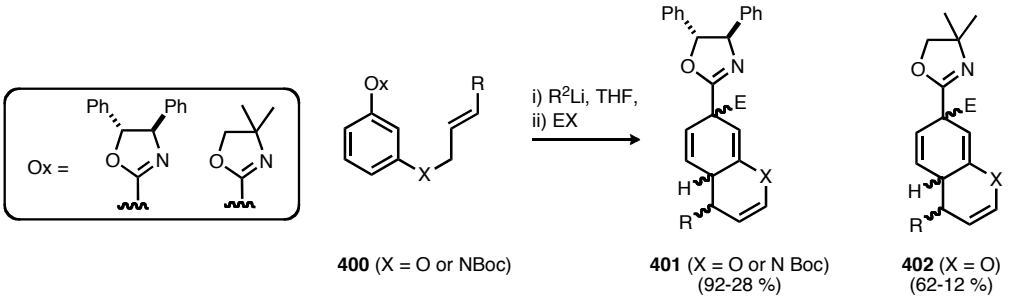


Figure 5.1 Summary of the novel regio-selective dearomatising cyclisation

However these products have limited stability further and work would need to establish ways to reduce the reactivity of these dearomatised products. For example use of flow hydrogenation to reduce the crude reaction mixtures before degradation can occur.

- Investigations have shown that the one-pot amide coupling, mesylation and cyclisation is a general method for (4*R*,5*R*)-4,5-diphenyloxazoline synthesis for a range of substituted aromatic rings.

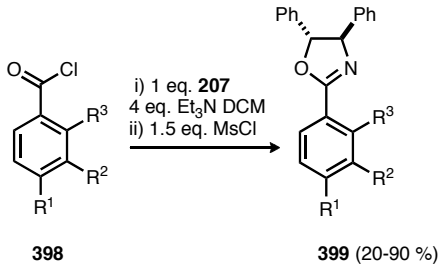


Figure 5.2 Summary of the one-pot amide coupling, mesylation and cyclisation method

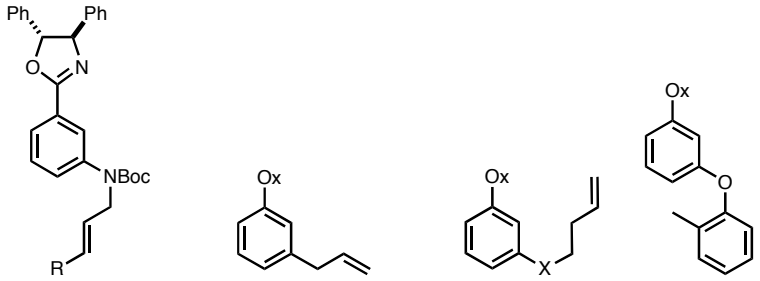
Any future work in this area would need to address the poor stereoselectivity observed for the dearomatising cyclisation.

- By improvement of the lithiating conditions, for example the use of chiral lithium amides that may improve the facial selectivity of the attack.
- Investigations into other electrophillic quenches used (bulkier electrophiles maybe more selective).

In order for this methodology to be useful, more in-depth investigations into the functionalisation of the dearomatised products needs to be carried out.

- To establish the reactivity of the unsaturated double bonds in the products.
- To optimise the conditions for the removal of the oxazoline moiety. Hopefully removal of the oxazoline would also allow the determination of the absolute stereochemistry of the dearomatised products as the alcohol products or their derivatives maybe more crystalline.

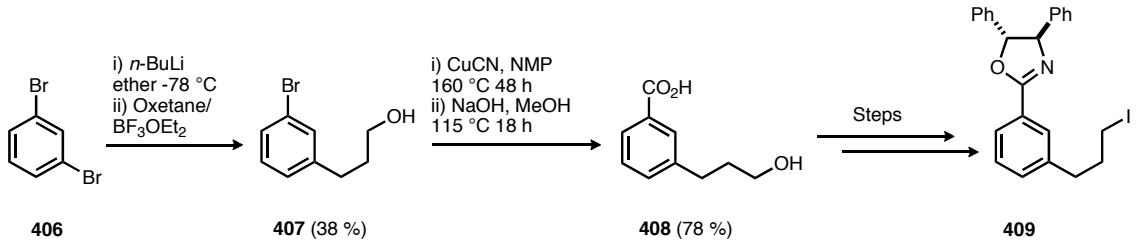
Further work could be carried out on the *N*-Boc protected allyl tether **402** to include establishing the selectivity of other quenches and different allylic tethers. Future work would also include the investigation of new tethers that would allow the creation of new ring systems, which hopefully may be formed more selectively. These could include other tethers that include unsaturated functionality e.g. **403** and **404**. Biaryl ether **405** could be laterally lithiated to form a stable organolithium which may be capable of undergoing dearomatising additions to oxazoline activated benzenoids.



402 **403** **404** **405**

Scheme 5.1 Other tethers which could be investigated

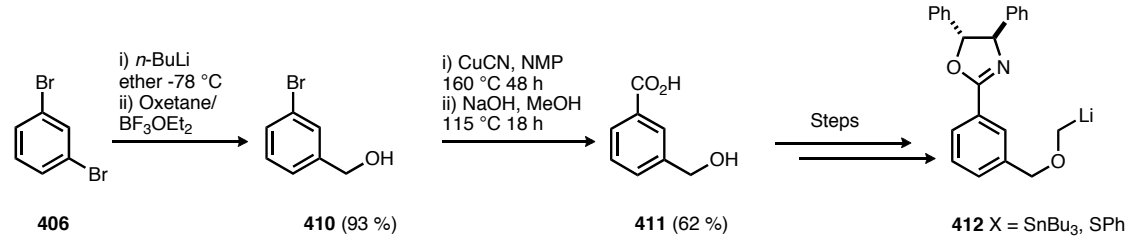
Now that it has been established that the dearomatising cyclisation of the allylic tethers occurs selectively at the *para*-position, other non-allylic tethers could be investigated using both the chiral and the achiral oxazolines. The synthesis of the hydrocarbon tether **409** has been shown to be viable, via the lithiation of 2,4-dibromo benzene **406**.



406 **407** (38 %) **408** (78 %) **409**

Scheme 5.2 Possible starting point for the synthesis of a *des*-OMe hydrocarbon tether

By quenching the lithiation of 2,4-dibromobenzene with DMF followed by reduction affords the benzyl alcohol **410**. Which after conversion to the acid could be used to synthesise an ether tethered organolithium **412** by either tin-lithium exchange, or reductive lithiation of a phenyl sulfide.



406 **410** (93 %) **411** (62 %) **412** X = $SnBu_3$, SPh

Scheme 5.3 Possible starting point for the synthesis of an ether tethered substrate

6 Experimental

6.1 General

^{1}H, ^{13}C, DEPT, HMQC, NOESY and COSY NMR spectra were recorded on a Varian XL 300 or Bruker Ultrashield 200, 300, 400 or 500 spectrometers. The chemical shifts (δ) are reported in ppm downfield of trimethylsilane and coupling constants (J) reported in hertz and rounded to 0.1 Hz. Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (qn), mulitiplet (m), broad (br), or a combination of these. Solvents were used as internal standard when assigning NMR spectra (δ_H: $CDCl_3$ 7.26 ppm; δ_C: $CDCl_3$ 77.0 ppm; δ_H: DMSO-d_6 2.50 ppm; δ_C: DMSO-d_6 39.4 ppm). J values were calculated using Mestre-C 4.4.8 software or ACDLabs 9.0 1D NMR processor software.

Low resolution mass spectra (EI, CI) were recorded on a Fisons VG Trio 2000. High resolution mass spectra (accurate mass measurement) were recorded on a Kratos Concept-IS mass spectrometer, and are accurate to ± 0.001 Daltons. Infrared spectra were recorded on a Ati Matson Genesis Series FTIR spectrometer and only absorption maxima (ν_{max}) of interest are reported and quoted as wavenumbers (cm^{-1}) all absorbances are sharp unless stated as broad (br). Microanalysis were carried out using Carlo-Erba automatic analyser by members of staff of the University of Manchester. Melting points (mpt) were determined on a GallenKamp apparatus and are uncorrected. Thin layer chromatography was performed using commercially available pre-coated plates (Macherey-Nagel alugram. Sil $G/_{UV254}$) and Flash Chromatography was carried out using Fluorochem Davilsil 40-63µ 60Å.

All reactions were conducted in dried glassware with magnetic stirring under a nitrogen atmosphere, unless otherwise stated. Tetrahydrofuran and diethylether were distilled from sodium and benzophenone under nitrogen. Methylene chloride and toluene were obtained by distillation from calcium hydride under nitrogen. Anhydrous dimethylformamide and was obtained by distillation from molecular sieves. Petrol refers to the fraction of light petroleum ether boiling between 40-65 °C. All other solvents and commercially obtained reagents were used as received or purified using

standard procedures. *n*-Butyllithium was obtained as a solution in cyclohexane which was titrated prior to use against a cooled solution of diphenylacetic acid. *t*-Butyllithium was obtained as a solution in cyclohexane and titrated against a solution of *N*–benzylbenzamide in tetrahydrofuran at - 40 °C.

6.2 General procedures

General Procedure 1: *Amide synthesis*

Carboxylic acid (1.0 eq.) in methylenechloride (5 mL/mmol) and thionyl chloride (5 mL/mmol) were stirred at reflux for 5 h. The solvent and thionyl chloride was removed under reduced pressure to afford the benzoyl chloride. The crude benzoyl chloride (1.0 eq.) in methylene chloride (3 mL/mmol) was then added drop-wise to a stirred solution of the amine (1.0 eq.) in methylene chloride (5 mL/mmol) and Et_3N (2 eq.) at 0 °C. The amide formed as a white precipitate in the solution, this was collected by vacuum filtration and washed with water (2 x reaction volume), acetone (2 x reaction volume), ethyl acetate (1 x reaction volume). The filtrate was concentrated under recduced pressure, transferred to a seperating funnel, acidified (1M HCl) and then washed with ethyl acetate (2 x reaction volume). The combined organic layers were then dried and the solvent was removed under reduced pressure to afford additional amide, which was then combined with the amide collected by filtration.

General Procedure 2a: *Carboxylic acid synthesis*

Aryl bromide (1.0 eq.) and copper cyanide (1.15 eq.) were stirred together in *N*-methylpyrrolidinone (2.5 mL/mmol) at 160 °C for 48 h. The reaction mixture was then partitioned between ethyl acetate (3 x (4 x reaction volume)) and saturated copper sulfate solution (1 x (4 x reaction volume)). The combined organic layers were then dried ($MgSO_4$) and the solvent was removed under reduced pressure. The aryl cyanide was then dissolved in methanol (1 mL/mmol) and 5M NaOH (4 mL/mmol). The reaction mixture was stirred at 115 °C for 18 h then acidified using 3M HCl. The reaction mixture was extracted into ethyl acetate (3 x 25 mL). The combined organic layers were then washed water (2 x 10 mL) and brine (2 x 10 mL). The organic layer was then dried ($MgSO_4$) and the solvent was removed under reduced pressure to give the carboxylic acid.

General Procedure 2b: *Carboxylic acid synthesis*

n-Buli was added dropwise to a solution of the aryl bromide (1.0 eq.) in tetrahydrofuran (17 mL/mmol) at -78 °C. The reaction mixture was then stirred for 20 mins. Carbon dioxide was bubbled through the reaction mixture for 1.5 h. The reaction was quenched with methanol then acidified with 3M HCl. The reaction mixture was then concentrated, partioned with water (50 mL) and ethyl acetate (50 mL) and then washed with further portions of ethyl acetate (2 x 50 mL). The combined organic layers were then dried ($NaSO_4$) and the solvent was removed under reduced pressure to give the carboxylic acid.

General Procedure 3 a: *Oxazoline synthesis. Rearrangement of benzoyl aziridines.*

A solution of the carboxylic acid (1 eq.), (2*S*,3*R*)-2,3-diphenylaziridine (**229**) (1eq.) and amide coupling reagent (1 eq.) in methylene chloride (10 mL/mmol) was stirred for 16 h. SiO_2 (2 g/mmol) was then added and the reaction was left to stir until complete conversion to oxazoline was observed by ^{1}HNMR. The reaction mixture was then filtered washing with methylene chloride (4 x reaction volume) and ethyl acetate (14 x reaction volume). The filtrate was then concentrated under reduced pressure to give the crude oxazoline.

General Procedure 3b: *Oxazoline synthesis. 1 pot amide coupling, mesylation and cyclisation*

Carboxylic acid (1 eq.) was stirred in a solution of thionyl chloride:methylene chloride (1 mL:1 mL/ 3 mmol) until complete by IR. The solvent and thionyl chloride was removed under reduced pressure to afford the benzoyl chloride. The crude benzoyl chloride (1.0 eq.) in methylene chloride (2 mL/mmol) was then added drop-wise to a stirred solution of the (1*S*,2*R*)-2-amino-1,2-diphenylethanol (1.0 eq.) in methylene chloride (15 mL/mmol) and Et_3N (4 eq.) at 0 °C. The reaction mixture was warmed to RT then stirred until complete by thin layer chromatography. Methanesulfonyl chloride was then added (1.5 eq.) then stirred until no amide remains by thin layer chromatography. The reaction mixture was then quenched with $NH_4Cl_{(aq)}$ (0.25 x reaction volume). The organic layer was seperated and the aqueous layer was further washed with methylene chloride (3 x (0.25 x reaction volume). The combined organic

layers were then dried ($NaSO_4$) and the solvent was then removed under reduced pressure to give the crude oxazoline.

General Procedure 4: *Triisopropylsilyl Protection*

To a stirred solution of the alcohol (1 eq.) in methylene chloride (1 mL/0.1 mmol) was added imidazole (2 eq.) and triisopropylsilylchloride (1.1 eq.). The reaction mixture was then stirred for 15 h. Brine (0.5 x reaction volume) was added, the organic layer was separated and washed with further portions of brine (2 x (0.5 x reaction volume)). The combined aqueous layers were then washed with methylene chloride (reaction volume). The combined organic layers were dried (Na_2SO_4) and the solvent was then removed under reduced pressure to give the crude protected alcohol.

General Procedure 5: *Triisopropylsilyl Deprotection*

To a stirred solution of the protected alcohol (1 eq.) in tetrahydrofuran (27 mL/mmol) at 0 °C was added tetrabutylammoniumfluoride (1M in tetrahydrofuran) (1.75 eq.). The reaction mixture was stirred until complete by TLC. The reaction was quenched with NH_4Cl (reaction volume/ 2.5) and partitioned with ethyl acetate (1.5 x reaction volume). The organics were then washed sequentially with $CuSO_{4(aq)}$ (reaction volume/1.6), $NaHCO_{3(aq.)}$ (reaction volume/1.6) and brine (reaction volume/1.6) and dried (Whatman 1PS Filter Tube). The solvent was removed under reduced pressure to give the crude alcohol.

General Procedure 6a: Nucleophilic Addition to Aryl Oxazolines

The organolithium was added drop-wise to a stirred solution of oxazoline in the stated dry solvent (0.05 mmol/mL) and co-solvent at – 78 °C under a nitrogen atmosphere. After the stated time, the electrophile was added and the reaction mixture allowed to warm to ambient temperature before addition of excess Methanol. The reaction mixture was reduced under vacuum and passed through a silica plug (1:1 EtOAc: petrol) and solvent removed before purification by flash chromatography.

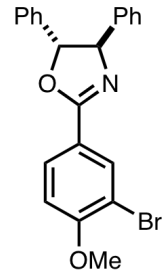
General Procedure 6b: Nucleophilic Addition to Aryl Oxazolines

The organolithium was added drop-wise to a stirred solution of the allylic ether in THF at -78 °C. After stirring the green solution for 5 min, the reaction mixture was warmed

to 0 °C for a further 25 min. The reaction was then quenched by drop-wise addition of excess electrophile. The reaction was then warmed to room temperature and an excess of methanol was added. The reaction mixture was then partitioned between water (5 mL) and diethyl ether (10 mL). The organic phase was separated and the aqueous layer was washed with further portions of diethyl ether (5 mL x 2). The combined organic layers were dried (Na_2SO_4) and evaporated to give the crude product which was purified using flash chromatography.

6.3 Experimental details for Chapter 2

***(4R,5R)-2-(3-bromo-4-methoxyphenyl)-4,5-diphenyloxazoline,* 202**

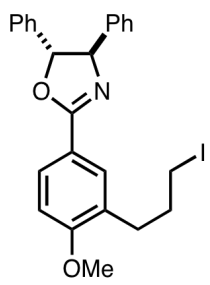


Method A - Diisopropylcarbodiimide (0.19 mL, 1.8 mmol) was added to a solution of **208** (0.78 g, 1.8 mmol) and $Cu(OTf)_2$ (0.040 g, 0.11 mmol) in 10 mL tetrahydrofuran. The reaction mixture was heated under microwave irradiation in a closed vial at 140 ºC for 0.5 h. A precipitate formed, this was washed with ethyl acetate (2 x 10 mL) and the filtrate was then concentrated under reduced pressure to give the crude product. Purification by flash column chromatography, eluting with 2:1 petrol:ethyl acetate afforded oxazoline **202** (0.28 g, 37%) as clear colourless oil.

Method B - Diisopropylcarbodiimide (0.12 mL, 0.775 mmol) was added to a solution of **208** (0.5 g, 1.18 mmol) and $Cu(OTf)_2$ (0.026 g, 0.071 mmol) in 6 mL anhydrous dioxane. The reaction mixture was heated to 110 ºC for 18 h. A precipitate formed which was collected by vaccum filtration, this was then washed with ethyl acetate (2 x 10 mL) and the filtrate was then concentrated under reduced pressure. This was then portioned between methylene chloride (25 mL) and water (25 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure to give the crude product. Purification by flash column chromatography, eluting with 2:1 petrol:ethyl acetate, afforded oxazoline **202** (0.27 g, 85 %) as a clear colourless oil.

R_f: 0.69 (2:1 Pet:EtOAc); **$[\alpha]_D^{24}$**: - 4.3 (c. 0.7, methylene chloride); **MS *m/z* (CI^+)**: 410 (100 %, M(^{81}Br)H^+); (ES^+) (Found: 408.0600, M(^{79}Br)H^+. $C_{22}H_{19}O_2N_1Br$ requires M(^{79}Br)H^+, 408.0594); **IR ν_{max}(CH_2Cl_2)/cm^{-1}**: 1630 (C=N), 1528; **^{1}H (MeOD, 500 MHz):** δ 8.14 (d, 1H, *J* 1.5, Ar*H*), 7.94 (dd, 1H, *J* 1.5 and 8.5, Ar*H*), 7.34-7.29 (m, 5H, Ph*H*), 7.25-7.23 (m, 3H, Ph*H*), 7.19-7.18 (m, 2H, Ph*H*), 7.08 (d, 1H, *J* 8.5, Ar*H*), 5.37 (d, 1H, *J* 8.0, PhC*H*O), 5.06 (d, 1H, *J* 8.0, PhC*H*N), 3.87 (s, 3H, OCH_3); **^{13}C (DMSO, 125 MHz)**: δ 165.2, 142.7, 141.1 (2C), 130.3 (2C), 130.22, 130.1 (2C), 129.3, 128.0, 126.9, 121.6, 112.7 (2C), 74.1, 69.9, 55.1;

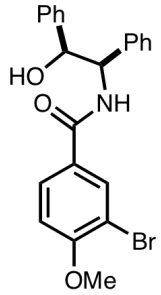
***(4R,5R)-1-[2'(3"-Iodo-propyl)-4'-methoxy-phenyl-4,5-diphenyl-oxazoline,* 203**



To a solution of **210** (0.050 g, 0.13 mmol) in tetrahydrofuran (1 mL) and acetonitrile (4 mL) at 0 °C, was added triphenylphosphine (0.068 g, 0.26 mmol) and imidazole (0.036 g, 0.52 mmol). The reaction mixture was stirred for 15 mins. Iodine (0.065 g, 0.52 mmol) was added and the solution was warmed to RT then stirred for 1h. The reaction was quenched with 10 % $Na_2S_2O_3$ solution in water (5 mL) then extracted with diethylether (3 x 5 mL). The combined organic layers were washed with brine (10 mL) then dried (Na_2SO_4). The solvent was then removed under reduced pressure to give the crude iodide. Purification by flash column chromatography, eluting with 4:1 petrol:ethyl acetate, afforded iodide **203** (0.041 g, 64 %) as a yellow gum.

R_f: 0.86 (2:1 Pet:EtOAc); **$[\alpha]_D^{19.5}$**: - 33 (c = 1.05, methylene chloride); **MS *m/z (ES$^+$)***: 498.0 (40 %, MH^+); 520.0 (100 %, MNa^+) (Found: 498.0938, MH^+. $C_{25}H_{25}O_2NI$ requires MH^+, 498.0924); **IR υ_{max}(film)/cm^{-1}**: 1643 (C=N), 1499 (=C-O-C), 1253 (OMe); **^{1}H (CDCl$_3$, 400 MHz)**: δ 7.99 (dd, 1H, *J* 8.0 and 2.0, Ar*H*), 7.96 (d, *J* 2.0, Ar*H*), 7.44-7.28 (m, 10H, Ar*H*), 6.92 (d, *J* 8.0, Ar*H*), 5.39 (d, *J* 7.5, PhC*H*O), 5.2 (d, *J* 7.5, PhC*H*N), 3.90 (s, 3H, OMe), 3.21 (t, 2H, *J* 7.0, ArCH_2), 2.83-2.70 (m, 2H, $CH_2CH_2CH_2$), 2.16 (m, 2H, CH_2I); **^{13}C (CDCl$_3$, 100 MHz)**: δ 164.0, 160.4, 142.2, 140.6, 130.5, 129.2, 128.9 (2C), 128.6, 128.4, 127.8, 126.8, 125.7, 119.6, 110.0, 88.9, 79.0, 55.5, 33.5, 31.3, 6.4;

***3-Bromo-N-((1R,2S)-2-hydroxy-1,2-diphenylethyl)-4-methoxybenzamide,* 208**

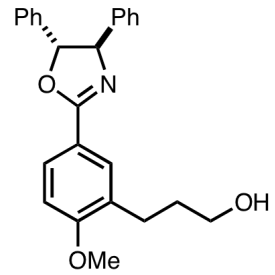


General procedure 1 was applied to 3-bromo-4-methoxy benzoic acid (1.0 g, 4.3 mmol) and thionyl chloride (21.5 mL) in methylene chloride (21.5 mL) to afford the benzoyl chloride as a white amorphous solid. The crude 3-bromo-4-methoxybenzoyl chloride (1.06 g, 4.3 mmol) was then mixed with (1*S*,2*R*)-2-amino-1,2-diphenylethanol (0.92 g, 4.3 mmol) and Et_3N (1.5 mL) to afford amide **208** (1.45 g, 92 %) as a white amorphous solid. Further purification was not required.

R_f: 0.27 (2:1 Pet:EtOAc); **Mpt**: 212-216 °C (EtOAc); **$[\alpha]_D^{24}$**: + 0.5 (c. 1, DMSO); **MS *m/z* (CI$^+$)**: 426 (40 %, M(^{79}Br)H^+), 428 (40 %, M(^{81}Br)H^+); (ES^+) (Found: 426.0698, M(^{79}Br)H^+. $C_{22}H_{21}O_3N_1Br$ requires M(^{79}Br)H^+, 426.0699); **IR υ_{max}(film)/cm^{-1}**: 3333 (OH), 1630 (C=O), 1528; **^{1}H (DMSO, 500 MHz)**: δ 8.72 (d, 1H, *J* 8.0, Ar*H*), 7.94 (s,

1H, Ar*H*), 7.79 (d, 1H, *J* 8.0, Ar*H*), 7.52 (m, 4H, Ph*H*), 7.39-7.33 (m, 4H, Ph*H*), 7.31-7.26 (m, 2H, Ph*H*), 7.20 (d, 1H, *J* 4.5, N*H*) 5.54 (d, 1H, *J* 4.5, O*H*), 5.19 (m, 1H, C*H*NH), 4.98 (m, 1H, C*H*OH), 3.94 (s, 3H OCH_3); **^{13}C (DMSO, 125 MHz)**: δ 163.3, 157.4, 143.6, 141.3, 131.7, 128.5, 127.9 (2C), 127.6 (2C), 127.0, 126.8, 126.7, 111.9, 110.0, 74.5, 59.0, 56.5;

***3-[5'-((4"R,5"R)-4,5-Diphenyl-oxazoline)-2'-methoxy-phenyl]-propan-1-ol,* 210**

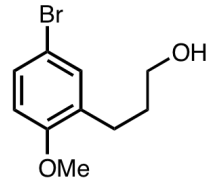


Method A - General procedure 5 was applied to **214** (0.50 g, 1 mmol) to give the crude alcohol. Purification by flash column chromatography, eluting with 4:1 petrol:ethyl acetate gave alcohol **210** (0.28 g, 79 %) as a white foam.

Method B - General procedure 3a was applied to **407** (0.20 g, 0.95 mmol) using 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide as the coupling reagent. The reaction mixture was stirred with silica for 7 days. Purification by flash column chromatography, eluting with 4:1 petrol:ethyl acetate, afforded alcohol **210** (0.10 g, 33 %) as a white foam.

R_f: 0.24 (2:1 Pet:EtOAc); **$[\alpha]_D^{19.5}$**: - 37.5 (c = 1.04, methylene chloride); **MS *m/z (ES$^+$)***: 388.0 (70 %, MH^+); (Found: 388.1892, MH^+. $C_{25}H_{26}O_3N$ requires MH^+, 388.1907); **IR υ_{max}(film)/cm^{-1}:** 3317 (OH), 1643 (C=N), 1258 (=C-O-C), 1027 (OMe); **^{1}H ($CDCl_3$, 500 MHz)**: δ 7.98-7.93 (m, 2H, Ar*H*), 7.44-7.27 (m, 10H, Ar*H*), 6.92 (d, 1H, *J* 8.0, Ar*H*), 5.38 (d, 1H, *J* 7.0, PhC*H*O), 5.19 (d, 1H, *J* 7.0, PhC*H*N), 3.89 (s, 3H, OCH_3), 3.61 (t, 2H, *J* 6.0, CH_2OH), 2.81-2.69 (m, 2H, ArCH_2), 1.94 (brs, 1H, O*H*), 1.91-1.84 (m, 2H, $CH_2CH_2CH_2$); **^{13}C ($CDCl_3$, 125 MHz)**: δ 164.1, 160.3, 142.2, 140.6, 130.6, 130.4, 128.9, 128.9, 128.4, 128.3, 127.8, 126.8, 125.7, 119.7, 109.9, 88.9, 79.0, 61.9, 55.6, 32.7, 26.0;

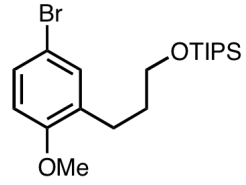
***3-(5'-Bromo-2'-methoxy-phenyl)propan-1-ol,* 211**



n-Butyllithium (7.61 mL, 2.47 M solution) was added dropwise to a stirred solution of 2,4-dibromoanisole (5.0 g, 18.8 mmol) in tetrahydrofuran (50 mL) at –78 °C. After 0.3 h trimethyleneoxide (2.45 mL, 37.6 mmol) was added followed directly by dropwise addition of BF_3OEt_2 (2.39 mL, 18.8 mmol) and the mixture stirred at –78 °C for a further 1 h. A saturated aqueous solution of $NaHCO_3$ (7 mL). The reaction mixture was extracted with water (3 x 25 mL). The combined aqueous layers were then washed with diethylether (25 mL). The organic layers were then combined and was dried ($NaSO_4$). The solvent was removed under reduced pressure to give the crude product. Purification by flash column chromatography, eluting with 4:1 petrol:ethyl acetate, afforded alcohol **211** (2.13 g, 46 %) as a clear colourless oil.

R_f: 0.33 (2:1 Pet:EtOAc); **MS *m/z (CI$^+$)***: 262 (100 %, M(^{79}Br)NH_4^+), 264 (100 %, M(^{81}Br)NH_4^+); (ES^+) (Found: 262.0436, M(^{79}Br)NH_4^+. $C_{10}H_{17}BrNO_2$ requires M(^{79}Br)NH_4^+, 262.0437); **IR υ_{max}(film)/cm^{-1}**: 3345 (OH), 1031 (CBr); **^{1}H ($CDCl_3$, 500 MHz)**: δ 7.21 (d, 1H, *J* 2.5, Ar*H*), 7.18 (dd, 1H, *J* 7.0 and 2.5, Ar*H*), 6.65 (d, 1H, 7.0, Ar*H*), 3.74 (s, 3H, OCH_3), 3.53 (t, 2H, *J* 6.0, CH_2OH), 2.61 (t, 2H, *J* 7.0, ArCH_2), 1.77-1.73 (m, 2H, $CH_2CH_2CH_2$), 1.72 (s, 1H, O*H*); **^{13}C ($CDCl_3$, 125 MHz)**: δ 156.5, 132.7, 132.4, 129.8, 112.8, 112.0, 61.8, 55.6, 32.6, 25.8;

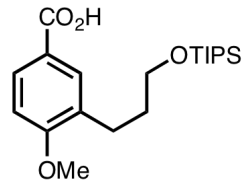
***(3-(5'-Bromo-2'-methoxy-phenyl)propoxy)triisopropylsilane,* 212**



General procedure 4 was applied to **211** (3.50 g, 14.3 mmol) to give the protected alcohol **212** (5.70 g, 100 %) as a colourless oil.

R_f: 0.52 (4:1 Pet:EtOAc); **IR υ_{max}(film)/cm^{-1}**: 2941 (CH), 1489 (OSi), 1234 (OCH_3); **^{1}H ($CDCl_3$ 300 MHz)**: δ 7.22-7.12 (m, 2H, Ar*H*), 6.62 (d, 1H, *J* 9.0 Ar*H*), 3.71 (s, 3H, OCH_3), 3.63 (t, 2H, *J* 6.0, OCH_2), 2.64-2.52 (m, 2H, ArCH_2), 1.79-1.65 (m, 2H, $CH_2CH_2CH_2$), 1.09-0.88 (m, 21H, Si(C*H*(CH_3)$_2$)$_3$; **^{13}C ($CDCl_3$, 75 MHz)**: δ 156.7, 133.1, 132.6, 129.4, 112.5, 111.8, 62.8, 55.4, 32.7, 26.5, 18.1, 12.3; Compound not detectable by m/s

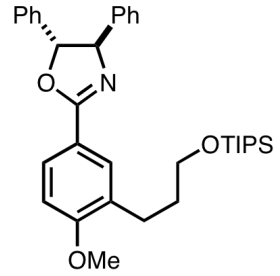
***(3-Propyloxy-4-methoxy benzoic acid)triisopropylsilane,* 213**



General procedure 2b was applied to **212** (5.80 g, 14.4 mmol) using *n*-Buli (1.1 eq., 2.6 M) to give the crude carboxylic acid. Purification by crystallisation from minimal ethyl acetate:petrol, afforded carboxylic acid **213** (3.60 g, 68 %) as a white crystalline solid.

R_f: 0.69 (2:1 Pet:EtOAc); **Mpt**: 140-144 °C (Pet:EtOAc); **MS *m/z* (ES^+)**: 389.1 (70 %, MNa^+); (Found: 389.2133, MNa^+. $C_{20}H_{34}O_4NaSi$ requires MNa^+, 389.2119); **IR υ_{max}(film)/cm^{-1}**: 2941 (CH), 2500 (OH), 1672 (C=O); **^{1}H ($CDCl_3$ 500 MHz)**: δ 7.97 (dd, 1H, *J* 8.0 and 2.0, Ar*H*), 7.91 (d, 1H, *J* 2.0, Ar*H*), 6.88 (d, 1H, *J* 8.0, Ar*H*), 3.89 (s, 3H, OCH_3), 3.73 (t, 2H, *J* 6.0, OCH_2), 2.76-2.68 (m, 2H, ArCH_2), 1.89-1.80 (m, 2H, $CH_2CH_2CH_2$), 1.16-1.01 (m, 21H, OSi(C*H*(CH_3)$_2$)$_3$); **^{13}C ($CDCl_3$ 100 MHz)**: δ 171.5, 162.0, 132.0, 130.9, 130.3, 121.1, 109.6, 62.9, 55.5, 32.7, 26.5, 18.0, 12.0;

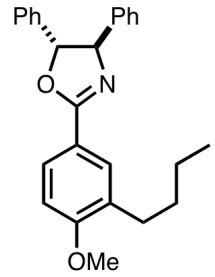
***(4R,5R)-2-(-4'-Methoxy-3'-propyloxy)triisopropylsilane-4,5-diphenyl-oxazoline,* 214**



General procedure 3b was applied to **213** (0.54 g, 1.5 mmol) to give the crude oxazoline. Purification by flash column chromatography, eluting with 4:1 petrol:ethyl acetate, afforded oxazoline **214** (0.64 g, 88 %) as a clear colourless oil.

R_f: 0.43 (4:1 Pet:EtOAc); **$[\alpha]_D^{19.5}$:** - 27.6 (c = 1, methylene chloride); **MS *m/z* (ES^+)**: 544 (50 %, MH^+), 567.6 (100 %, MNa^+); (Found: 544.3247, $C_{36}H_{46}O_3NSi$ requires MH^+, 544.3241); **IR υ_{max}(film)/cm^{-1}**: 2940 (CH), 2863 (OSi(*i*Pr)$_3$), 1647 (C=N), 1499 (=C-O-C), 1252 (OMe); **^{1}H ($CDCl_3$, 400 MHz)**: δ 8.00-7.94 (m, 2H, Ar*H*), 7.44-7.27 (m, 10H, Ar*H*), 6.91 (d, 1H, *J* 8.0, Ar*H*), 5.38 (d, 1H, *J* 7.5, PhC*H*O), 5.20 (d, 1H, *J* 7.5, PhC*H*N), 3.89 (s, 3H, OMe), 3.72 (t, 2H, *J* 6.0, OCH_2), 2.78-2.70 (m, 2H, ArCH_2), 1.92-1.83 (m, 2H, $CH_2CH_2CH_2$), 1.14-1.03 (m, 21H, OSi(C*H*(CH_3)$_2$)$_3$); **^{13}C ($CDCl_3$, 100 MHz)**: δ 164.2, 160.5, 142.3, 140.7, 131.1, 130.4, 128.9, 128.8, 128.4, 128.1, 127.7, 126.8, 125.7, 119.4, 109.8, 88.9, 79.0, 63.2, 55.4, 32.9, 26.7, 18.1, 12.0;

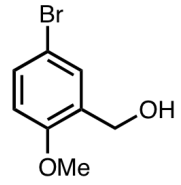
***(4R,5R)-2-(4-methoxy-3-pentylphenyl)-4,5-diphenyloxazoline,* 218**



General procedure 6a was used employing oxazoline **203** (20 mg, 0.04 mmol), *t*-BuLi (0.062 mL, 0.08 mmol), DMPU (0.024 mL, 0.2 mmol) in THF at -75 °C, reaction stirred for 5 mins at -78 °C then warmed to - 40 °C for 30 mins then quenched with MeI (0.5 mL). The reaction was stirred for a further hour at -40 °C then water was added. After usual work up afforded methylated product **218** (16 mg, 65 %) as a clear colourless oil.

R_f: 0.86 (2:1 Pet:EtOAc); **MS**: *m/z (ES$^+$)* 386 (50 %, MH$^+$); **^{1}H (CDCl$_3$, 400MHz)**: δ 7.90-7.81 (m, 2H, Ar*H*), 7.43-7.39 (m, 2H, Ph*H*), 7.32-7.21 (m, 8 H, Ph*H*), 6.82 (d, 1H, *J* 7.5, Ar*H*), 5.32 (d, 1H, *J* 7.5, PhC*H*O), 5.11 (d, 1H, *J* 7.5, PhC*H*N), 3.80 (s, 3H, OCH_3), 2.60-2.50 (m, 2H, ArCH_2), 1.92-1.84 (m, 2H, ArCH$_2$CH_2), 1.62-1.53 (m, 2H, CH_2CH$_3$) 1.87 (t, 3H, *J* 6, CH$_2$CH_3);

***(5-bromo-2-methoxy-phenyl)methanol,* 219**

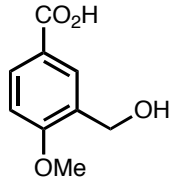


n-Butyllithium (8.01 ml of a 2.3 M) was added dropwise to a stirred solution of 2,4 dibromoanisole (5 g, 18.8 mmol) in dry diethylether (50 ml) at –78 °C. After 0.3 h dry DMF (1.56 ml, 22.6 mmol) was added and the mixture was stirred for 5 mins at –78 °C. The reaction mixture was allowed to warm up to room temperature over 1 h. A saturated solution of NH_4Cl (5 ml) was added. The ether layer was washed with water (3 x 25 ml), dried ($MgSO_4$) and then reduced under vacuum to give the crude aldehyde. The aldehyde was then taken up in MeOH (65 ml) and cooled to 0 °C. $NaBH_4$ (1.07 g, 28.2 mmol) was added and the reaction mixture was stirred for 18 h. The reaction was quenched with saturated NH_4Cl (5 ml). The solvent was removed under vacuum then dissolved in diethylether (25 ml) and washed with water (3 x 25 ml). The combined aqueous was washed with diethylether (2 x 25 ml). The combined organic was then dried ($NaSO_4$) and solvent was removed under vacuum to give crude product. Purification by flash column chromatography, eluting with 4:1 petrol:ethyl acetate, afforded alcohol **219** (3.62 g, 84 %) as a white amorphous solid.

R_f: 0.4 (2:1 Pet:EtOAc); **Mpt**: 74-77 °C (EtOAc); **MS *m/z (EI$^+$)***: *216* (100 %, MH$^+$); (Found: 215.9782, MH$^+$. $C_8H_9O_2Br_1$ requires MH$^+$, 215.9780); **IR ν_{max}(film)/cm^{-1}**: 3410 (s, OH), 2919 (CO_2H), 1035 (CBr); **^{1}H (CDCl$_3$, 500MHz)**: *δ* 7.41 (d, 1H, *J* 2.5,

ArH), 7.34 (dd, 1H, *J* 8.5 and 2.5, ArH), 6.73 (d, 1H, *J* 8.5, ArH), 4.63 (s, 2H, ArC*H*$_2$OH), 3.83 (s, 3H, OCH_3), 2.35 (s, 1H, OH); **^{13}C (CDCl$_3$, 125 MHz)**: 156.4, 131.3, 131.2 (2C), 112.9, 111.9, 61.3, 55.6;

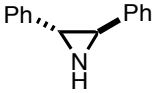
***3-(hydroxymethyl)-4-methoxy-benzoic acid,* 220**



General procedure 2a was applied to **219** (3.0 g, 13 mmol) to give the carboxylic acid **220** (1.91g, 80 %) as a beige amorphous solid.

R$_f$: 0.09 (EtOAc); **Mpt**: 218-220 °C (EtOAc); **MS *m/z* (ES$^-$)**: 181.2 (100 %, M-H); (Found: 181.0504, M-H. $C_9H_{10}O_4$ requires M-H, 181.0506); **IR ν_{max}(film)/cm^{-1}**: 3421 (s, OH), 1643 (CO); **^{1}H (DMSO, 500MHz)**: δ 13.00-12.50 (brs, 1H, COOH), 8.00 (s, 1H, ArH), 7.84 (d, 1H, *J* 8.5, ArH), 7.27 (d, 1H, *J* 8.5 ArH) 4.50 (s, 2H, ArC*H*$_2$OH), 3.84 (s, 3H, OCH_3); **^{13}C (DMSO, 125MHz)**: δ 167.3, 159.4, 130.3, 129.7, 128.0, 122.5, 109.7, 57.5, 55.5;

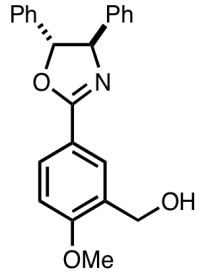
***(2R,3R)-2,3-diphenyl aziridine,* 221**



To a solution of (1*S*,2*R*)-(+)-amino-1,2-diphenylethanol (2.0 g, 9.38 mmol) in tetrahydrofuran (40 mL) was added triphenylphosphine (2.95 g, 11.2 mmol), Et_3N (2.61 mL, 18.7 mmol) and diisopropylazodicarboxylate (2.21 mL, 11.2 mmol) then stirred at room temperature for 18 h. The solvent was removed under reduced pressure to give the crude aziridine. Purification by flash column chromatography, eluting with 10:1 petrol:ethyl acetate, afforded aziridine **221** (1.29 g, 71 %) as white needles.

R$_f$: 0.16 (9:1 Pet:EtOAc); **Mpt**: 44-46 ºC (Pet:EtOAc) (lit.45-46 ºC)[118]; **[α]$_D^{20}$**: + 350 (c. 0.4, EtOH)[134]; **MS *m/z* (CI$^+$)**: 196 (100 %, MH$^+$); (Found: 194.0959, MH$^+$. $C_{14}H_8N$ requires MH$^+$, 194.0964); **IR υ_{max}(film)/cm^{-1}**: 3030 (NH_2), 1602, 1496; **^{1}H (CDCl$_3$, 500 MHz)**: δ 7.45-7.22 (m, 10H, Ar*H*), 3.18 (*s*, 2H, C*H*Ph), 1.50 (brs, 1H, N*H*); **^{13}C (CDCl$_3$, 125 MHz)**: δ 139.9, 128.9, 127.6, 125.8, 44.0;

***[5-((4'R,5'R)-4',5'-Diphenyl-oxazoline)-2-methoxy-phenyl]methanol*, 222**

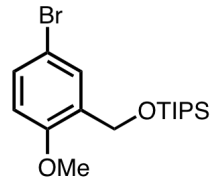


Method A - General procedure 3a was applied to **220** (0.20 g) using 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide as the coupling reagent, stirred with silica for 7 days. Purification by flash column chromatography, eluting with 4:1 petrol:ethyl acetate, afforded alcohol **222** (0.13 g, 32 %) as a colourless gum.

Method B - General procedure 5 was applied to **225** (0.426 g, 0.82 mmol) to give the crude alcohol. Purification by flash column chromatography, eluting with 2:1 petrol:ethyl acetate, afforded alcohol **222** (0.25 g, 83 %) as a colourless gum.

R_f: 0.16 (2:1 Petrol:EtOAc); **$[\alpha]_D^{19.5}$**: 39.8 (c = 1.095, DCM); **MS *m/z* *(ES$^+$)***: 382.1 (100 %, MNa^+); (Found: 382.1426, MNa^+. $C_{23}H_{21}O_3NNa$ requires MNa^+, 382.1414); **IR ν_{max}(film)/cm^{-1}**: 3265 (OH), 1643 (C=N), 1496 (=C-O-C), 1261 (OMe); **^{1}H ($CDCl_3$, 400MHz)**: δ 8.03 (d, 1H, *J* 2.0, Ar*H*) 7.98 (dd, 1H, *J* 8.0 and 2.0, Ar*H*) 7.35-7.16 (m, 10H, Ar*H*), 6.86 (d, 1H, *J* 8.0, Ar*H*), 5.30 (d, 1H, *J* 7.0, PhC*H*O), 5.10 (d, 1H, *J* 7.0, PhC*H*N), 4.62 (s, 2H, ArCH_2), 3.84 (s, 3H, OCH_3), 2.54 (br, 1H, O*H*); **^{13}C ($CDCl_3$ 100 MHz)**: δ 163.9, 160.1, 142.1, 140.5, 129.8, 129.5, 129.1, 128.9, 128.8, 128.4, 127.7, 126.8, 125.7, 120.0, 110.0, 89.0, 61.4, 57.5, 55.6;

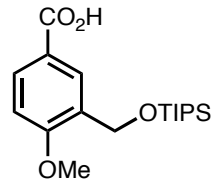
***(5-bromo-2-methoxy-benzyloxy)triisopropylsilane*, 223**



General procedure 4 was applied to **219** (5.70 g, 26.0 mmol) to give the protected alcohol **223** (10.0 g, quant) as a colourless oil.

R_f: 0.47 (4:1 Pet:EtOAc); **IR ν_{max}(film)/cm^{-1}**: 2942, 2866 (OSi), 1487 1463 (SiC), 1240 (OMe); **^{1}H ($CDCl_3$, 300MHz)**: δ 7.65 (d, 1H, *J* 2, Ar*H*), 7.30 (dd, 1H, *J* 8.0 and 2.0, Ar*H*), 6.68 (d, 1H, *J* 8.0, Ar*H*), 4.80 (s, 2H, ArCH_2), 3.78 (s, 3H, OCH_3), 1.29-0.92 (m, 21H, Si(*i*Pr)$_3$); **^{13}C ($CDCl_3$, 75MHz)**: δ 154.8, 132.5, 129.8, 129.3, 113.1, 111.1, 59.8, 55.3, 18.1, 12.1; Compound not detectable by MS

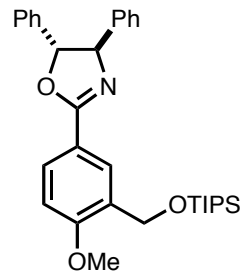
***(3-benzyoxy-4-methoxy-benzoic acid)triisopropylsilane*, 224**



General procedure 2b was applied to **223** (10.12 g, 27 mmol) using *n*-Buli (1.1 eq) to give the crude carboxylic acid. Re-crystalisation from ethyl acetate:petrol gave carboxylic acid **224** (6.10 g, 66 %) as a white crystalline solid.

R_f: 0.4 (4:1 Pet:EtOAc); **Mpt**: 170-173 ^oC (Pet:EtOAc); **MS *m/z (ES$^-$)***: 337.2 (100 %, M-H); (Found: 337.1833, M-H. $C_{18}H_{29}O_4Si$ requires M-H, 337.1841); **IR**: ν_{max}(film)/cm^{-1} 2942 (OSi), 2800 (OH), 1676 (C=O), 1256 (OMe); **^{1}H ($CDCl_3$, 300MHz)**: δ 8.33 (d, 1H, *J* 2.0, Ar*H*), 8.03 (dd, 1H, *J* 8.0 and 2.0, Ar*H*), 6.87 (d, 1H, *J* 8.0, Ar*H*), 4.84 (s, 2H, ArCH_2), 3.89 (s, 3H, OCH_3), 1.29-1.02 (m, 21H, Si(*i*Pr)$_3$; **^{13}C ($CDCl_3$, 75MHz)**: δ 171.6, 160.2, 130.7, 130.4, 128.9, 121.5, 109.1, 60.0, 55.4, 18.1, 12.1;

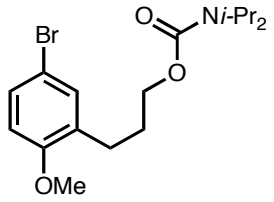
***(4R,5R)-2-(-2'-methoxybenzyloxy)triisopropylsilane-4,5-diphenyloxazoline*, 225**



General procedure 3b was applied to **224** (0.45 g, 1.3 mmol) to give the crude oxazoline. Purification by flash column chromatography, eluting with 4:1 petrol:ethyl acetate, afforded oxazoline **225** (0.49 g, 67%) as a yellow gum.

R_f: 0.73 (2:1 Petrol:EtOAc); **$[\alpha]_D^{19.5}$: -**48.2 (c = 1.025, $CDCl_3$); **MS *m/z (ES$^+$)***: 516.3 (100%, MH$^+$); (Found: 516.2931, MH$^+$. $C_{32}H_{42}O_3NSi$ requires MH$^+$, 516.2928); **IR ν_{max}(film)/cm^{-1}**: 2945, 2865 (OSi), 1647 (C=N), 1497 (=C-O-C), 1259 (OMe); **^{1}H ($CDCl_3$, 500MHz)**: δ 8.25 (s, 1H, Ar*H*), 7.96 (d, 1H, *J* 9.0, Ar*H*), 7.31-7.17 (m, 10H, Ph*H*), 6.79 (d, 1H, *J* 9.0, Ar*H*), 5.31 (d, 1H, *J* 7.0, PhC*H*O), 5.10 (d, 1H, *J* 7.0, PhC*H*N), 4.78 (s, 2H, ArCH_2), 3.76 (s, 3H, OCH_3), 1.07 (m, 21H, Si(*i*Pr)$_3$); **^{13}C ($CDCl_3$, 75MHz)**: δ 163.3, 157.8, 141.5, 139.9, 129.2, 127.8, 127.7, 127.1 (2C), 126.6, 126.5, 125.8, 124.4, 118.8, 108.4, 87.5, 77.9, 59.2, 54.4, 17.0, 11.0;

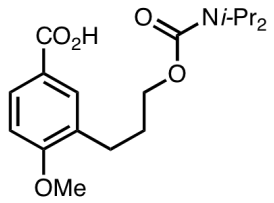
***3-(5'-Bromo-2'-methoxyphenyl)propyl diisopropylcarbamate,* 231**



To a solution of **211** (2.0 g, 8.1 mmol) in pyridine (anhydrous) (1.0 mL, 12.2 mmol) was added *N,N*-diisopropylcarbomyl chloride (1.30 g, 8.1 mmol) at room temperature. Reaction was refluxed for 24 h then poured into ice and conc. HCl. The mixture was extracted with diethylether (3 x 50 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure to give the crude carbamate. Purification by flash column chromatography, eluting with 4:1 petrol:ethyl acetate, afforded carbamate **231** (2.50 g, 83 %) as a colourless oil.

R_f: 0.66 (2:1 Pet:EtOAc); **MS *m/z (ES$^+$)***: 394.0 (100 %, M(^{79}Br)Na^+); 396.0 (100 %, M(^{81}Br)Na^+); (ES^+) (Found: 394.0976, M(^{79}Br)Na^+. $C_{17}H_{26}O_3NBrNa$ requires M(^{79}Br)Na^+, 394.0988); **IR υ_{max}(film)/cm^{-1}**: 1684 (C=O), 1290 (OMe); **^{1}H ($CDCl_3$, 400 MHz)**: δ 7.22-7.15 (dd, 1H, *J* 8.5 and 2.5, Ar*H*), 7.19 (d, 1H, *J* 2.5, Ar*H*), 6.79 (d, 1H, *J* 8.5, Ar*H*), 4.03 (t, 2H, *J* 6.5, CH_2O), 3.73 (s, 3H, OCH_3), 4.16-3.68 (m, 2H, N(CH(CH_3)$_2$)$_2$, 2.69-2.66 (m, 2H, ArCH_2), 1.88-1.80 (m, 2H, $CH_2CH_2CH_2$), 1.24 (m, 12H, N(CH(CH_3)$_2$)$_2$; **^{13}C ($CDCl_3$, 75 MHz)**: δ 156.6, 156.5, 132.5, 132.4, 129.8, 112.6, 111.9, 64.3, 55.5, 46.0, 29.2, 27.0, 21.0;

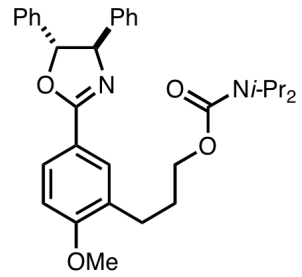
***3-(3'-(Diisopropylcarbamoyl)-propyl)-4-methoxy-benzoic acid,* 232**



General procedure 2b was applied to **231** (3.60 g, 9.5 mmol) using *n*-BuLi (0.98 eq., 2.6 M) to give the crude carboxylic acid. Purification by crystallisation from minimal ethyl acetate:petrol, afforded carboxylic acid **232** (1.4 g, 44 %) as a white crystalline solid.

R_f: 0.34 (2:1 Pet:EtOAc); **Mpt**: 116-119 °C; **MS *m/z (ES$^+$)***: 360.1 (100 %, MNa^+); (Found: 360.1793, MNa^+. $C_{18}H_{27}O_5NNa$ requires MNa^+, 360.1781); **IR υ_{max}(film)/cm^{-1}**: 2968 (OH), 1684 (C=O), 1606 (C=O), 1258 (OMe); **^{1}H ($CDCl_3$, 500 MHz)**: δ 12.00-10.50 (brs, 1H, CO_2H), 7.97 (dd, 1H, *J* 8.0 and 2.0, Ar*H*), 7.89 (d, 1H, *J* 2.0, Ar*H*), 6.89 (d, 1H, *J* 8.0, Ar*H*), 4.12 (t, 2H, *J* 6.0, CH_2O), 3.89 (s, 3H, OCH_3), 4.30-3.59 (m, 2H, N(CH(CH_3)$_2$)$_2$, 2.80-2.68 (m, 2H, ArCH_2), 2.01-1.90 (m, 2H, $CH_2CH_2CH_2$), 1.29-1.17 (m, 12H, N(CH(CH_3)$_2$)$_2$; **^{13}C ($CDCl_3$, 75 MHz)**: δ 171.6, 162.0, 155.9, 132.0, 130.5, 130.2, 121.4, 110.0, 64.4, 55.5, 45.7, 29.2, 27.1, 21.0; **Elem. Anal.** For $C_{18}H_{27}O_5N$: calcd % (found %): C, 64.07 (64.15); H, 8.07 (8.19); N, 4.15 (4.14).

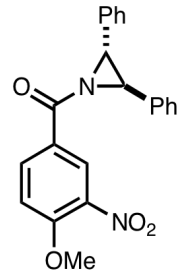
***Di-isopropyl-carbamic acid-3-[5'-((4''R,5''R)-4,5-diphenyl-oxazoline)-2'-methoxy-phenyl]-propylester,* 235**



General procedure 3b was applied to **232** (0.50 g, 1.9 mmol) to give the crude oxazoline. Purification by flash column chromatography, eluting with 4:1 petrol:ethyl acetate, afforded oxazoline **235** (0.61 g, 90 %) as a colourless gum.

R_f: 0.4 (4:1 Pet:EtOAc); **$[\alpha]_D^{19.5}$:** -37 (c = 1.2, methylene chloride); **MS *m/z (ES$^+$)***: 515.1 (100 %, MH^+); (Found: 515.2898, MH^+. $C_{32}H_{39}O_4N_2$ requires MH^+, 515.2904); **IR υ_{max}(film)/cm^{-1}**: 1690 (C=N), 1646 (C=O), 1500 (=C-O-C), 1289 (OMe); **^{1}H (CDCl$_3$, 300 MHz)**: δ 8.00 (d, 1H, *J* 8.5 and 2.0, Ar*H*), 7.96 (d, 1H, *J* 2.0, Ar*H*), 7.44-7.27 (m, 10H, Ph*H*) 6.92 (d, 1H, *J* 8.5, Ar*H*), 5.40 (d, 1H, *J* 7.5, PhC*H*O), 5.20 (d, *J* 7.5, PhC*H*N), 4.12 (m, 2H, OCH_2), 4.10-3.59 (m, 2H, N(C*H*(CH$_3$)$_2$)$_2$, 3.80 (s, 3H, OMe), 2.83-2.68 (m, 2H, ArCH_2), 1.92-1.83 (m, 2H, CH$_2$CH_2CH$_2$), 1.21 (m, 12H, N(CH(CH_3)$_2$)$_2$; **^{13}C (CDCl$_3$, 100 MHz):** δ 164.1, 160.4, 155.9, 142.1, 140.6, 130.4, 130.3, 128.9 (2C), 128.8, 128.4, 127.7, 126.8, 125.7, 119.4, 109.9, 88.9, 79.0, 64.5, 55.5, 43.7, 29.3, 27.1, 21.4;

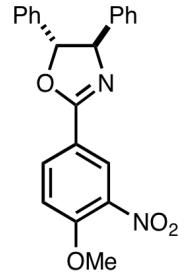
***((2R,3R)-2,3-Diphenyl-aziridin-1-yl)-4'-methoxy-3'-nitro-phenyl)-methanone,* 238**



General procedure 1 was applied to 4-methoxy-3-nitrobenzoic acid (1.0 g, 5.07 mmol) to afford the benzoyl chloride as a pale beige amorphous solid. The crude 4-methoxy-3-nitrobenzoyl chloride (1.10 g, 5.07 mmol) was then mixed with (2*R*,3*R*)-2,3-diphenyl-aziridine **221** (0.99 g, 5.07 mmol) and Et_3N (0.74 mL, 5.31 mmol) to afford acyl aziridine **238** (1.76 g, 93 %) as a yellow amorphous solid. Further purification was not required.

R_f: 0.21 (2:1 Pet:EtOAc); **Mpt**: 60-64 °C (methylene chloride); **$[\alpha]_D^{24}$**: - 1.7 (c. 1, methylene chloride); **MS *m/z* (CI$^+$)**: 375 (100 %, MH^+); (Found: 375.1333, MH^+. $C_{22}H_{19}O_4N_2$ requires MH^+, 375.1339); **IR υ_{max}(film)/cm^{-1}**: 2930 (CH_3), 1616 (C=N), 1532 (C-O), 1354 (C-NO_2); **^{1}H (CDCl$_3$, 500 MHz)**: δ 8.39 (d, 1H, *J* 2.0, Ar*H*), 8.03 (dd, 1H, *J* 8.5 and 2.0, Ar*H*) 7.27-7.22 (m, 10H, Ph), 6.93 (d, 1H, *J* 8.5, Ar*H*), 4.02 (s, 2H, PhC*H*C*H*N), 3.91 (s, 3H, OCH_3); **^{13}C (CDCl$_3$, 125 MHz)**: δ 173.5, 155.7, 138.8, 135.2, 134.6, 128.8 (2C), 128.6, 128.5, 128.4, 126.8, 126.5 (2C), 126.1, 112.9, 56.8, 49.1 (2C);

***(4R,5R)- 2-(4'-Methoxy-3'-nitro-phenyl)-4,5-diphenyloxazoline,* 239**



Method A - A solution of **238** (1.0 g, 2.7 mmol) and SiO_2 (15.0 g) in methylene chloride (27 mL) was stirred for 48 h. The SiO_2 was removed via filtration. The filtrate was then concentrated under reduced pressure to give the oxazoline **239** (0.96 g, 96 %) as a pale yellow amorphous solid.

Method B - Diisopropylcarbodiimide (0.13 mL, 0.84 mmol) was added to a solution of **391a** (0.50 g, 1.28 mmol) and $Cu(OTf)_2$ (0.028 g, 0.078 mmol) in 10 mL tetrahydrofuran under N_2. The reaction mixture was heated by microwave irradiation in a closed vial at 140 °C for 0.5 h. A precipitate formed, this was washed with ethyl acetate 2 x 10 mL and the filtrate was then concentrated under reduced pressure to give the crude product. Purification by flash column chromatography, eluting with 2:1 petrol:ethyl acetate, afforded oxazoline **239** (0.099 g, 31 %) as a pale yellow amorphous solid.

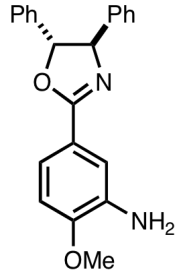
Method C - Diisopropylcarbodiimide (0.13 mL, 0.84 mmol) was added to a solution of **391a** (0.50 g, 1.28 mmol) and $Cu(OTf)_2$ (0.028 g, 0.078 mmol) in 4 mL dry dioxane under N_2. Reaction mixture was heated to 80 °C for 16 h, then for a further 7 h at 110 °C. A precipitate formed, this was washed with ethyl acetate 2 x 10 mL and the filtrate was then reduced under reduced pressure. The residue was then partitioned between methylene chloride (25 mL) and water (25 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure to give crude product. Purification by flash column chromatography, eluting with 2:1 petrol:ethyl acetate, afforded oxazoline **239** (0.11 g, 35 %) as a pale yellow amorphous solid.

Method D - General procedure 3a was applied to 4-methoxy-3-nitrobenzoic acid (1.01 g, 5 mmol) using diisopropylcarbodiimide (1.1 eq.) and N-hydroxybenzotriazole (1.1 eq.) as the coupling reagents. The final reaction mixture was stirred for 48 h. The crude oxazoline was purified by flash column chromatography, eluting with 2:1 petrol:ethyl acetate, afforded oxazoline **239** (0.52 g, 27 %) as a pale yellow amorphous solid.

R_f: 0.3 (2:1 Pet:EtOAc); **Mpt**: 62-66 °C (methylene chloride); **$[\alpha]_D^{24}$:** -3.4 (c. 1, methylene chloride); **MS *m/z* (CI^+)**: 375 (100 %, MH^+); (ES^+) (Found: 375.1345, MH^+. $C_{22}H_{19}O_4N_2$ requires MH^+, 375.1339); **IR υ_{max}(film)/cm^{-1}**: 1650 (C=N), 1349 (C-NO_2); **^{1}H ($CDCl_3$, 500 MHz)**: δ 8.60 (d, 1H, *J* 2.0, Ar*H*), 8.33 (dd, 1H, *J* 8.5 and 2.0, Ar*H*), 7.44-7.3 (m, 10H, Ph*H*), 7.19 (d, 1H *J* 8.5, Ar*H*), 5.45 (d, 1H, *J* 7.5, PhC*H*O), 5.26 (d,

1H, *J* 7.5, PhC*H*N), 4.05 (s, 1H, OCH_3); **^{13}C (DMSO, 125 MHz)**: δ 161.9, 155.2, 141.5, 139.9, 139.5, 134.2, 129.0 (2C), 128.7, 128.0, 126.7, 126.1, 125.8, 120.1, 113.4, 89.5, 79.0, 56.9;

***(4R,5R)- 2-(3'-Amino-4'-methoxy-phenyl)-4,5-diphenyloxazoline,* 240**

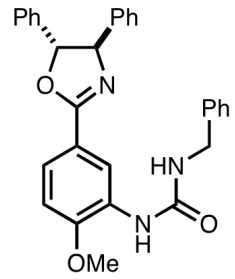


Method A - A solution of **239** (0.45 g, 1.21 mmol) in ethyl acetate (16 mL) and EtOH (8 mL), was passed through the H-Cube twice using 30 mm 5 % Pd/$CaCO_3$(Pb) CatCart® at 0.5 mL min^{-1}, 20 °C and 50 bar. The solvent was removed under reduced pressure to give amine **240** (0.37 g, 88 %) as a light yellow amorphous solid. Further purification was not required.

Method B - To a solution of **239** (2.0 g, 5.30 mmol) in ethyl acetate (120 mL) and EtOH (60 mL), was added Lindlar catalyst (5 % Pd, 0.56 g). The reaction mixture was stirred under H_2 for 8 days, then filtered through Celite™. The solvent was removed under reduced pressure to give amine **240** (1.95 g, quantative) as a light yellow amorphous solid. Further purification was not required.

R_f: 0.58 (1:1 Pet:EtOAc); **Mpt**: 62-63 °C (EtOAc); **$[\alpha]_D^{24}$**: **-** 4.4 (c. 1, methylene chloride); **MS *m/z* (CI$^+$)**: 345 (100 %, MH$^+$); (Found: MH$^+$, 345.1604. $C_{22}H_{20}N_2O_2$ requires MH$^+$, 345.1598); **IR υ_{max}(film)/cm^{-1}**: 3376 (NH), 1610 (C=N); **^{1}H ($CDCl_3$, 500 MHz)**: δ 7.45 (dd, 1H, *J* 8.5 and 2.0, *ArH),* 7,43 (d, 1H, *J* 2.0, Ar*H*), 7.33-7.21 (m, 10H, Ph*H*), 6.76 (d, 1H, *J* 8.5, Ar*H*), 5.29 (d, 1H, *J* 7.5, PhCH_2O), 5.09 (d, 1H, *J* 7.5 PhCH_2N), 3.84 (s, 3H, OCH_3); **^{13}C ($CDCl_3$, 125MHz)**: δ 164.3, 150.1, 142.3, 140.7, 136.1, 128.9, 128.8, 128.4, 127.7, 126.8, 125.7, 120.1, 119.7, 114.7, 109.7, 88.8, 79.0, 55.6;

***1-Benzyl-3-(5'-((4"R,5"R)-4",5"-diphenyloxazoline)-2'-methoxy-phenyl)urea,* 242**

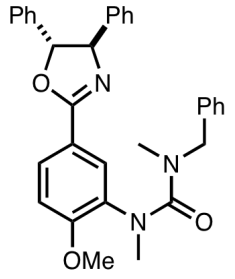


Method A - Benzyl isocyanate (0.18 mL, 1.45 mmol) was added dropwise to a solution of **240** (0.50 g, 1.45 mmol) in methylene chloride (15 mL) at 0 °C. The reaction mixture was warmed to room temperature and allowed to stir for 12 h. The solvent was removed under reduced pressure to give the crude urea. Purification by flash column chromatography, eluting with 1:1 petrol:ethyl acetate, afforded urea **242** (0.39 g, 57 %) as a biege amorphous solid.

Method B - General procedure 3b was applied to **245** (0.40 g, 1.2 mmol) to give the crude oxazoline. Purification by flash chromatography, eluting with 4:1 petrol:ethyl acetate, afforded oxazoline **242** (0.39 g, 67 %) as a pale yellow amorphous solid.

R_f: 0.7 (1:1 Pet:EtOAc); **Mpt**: 81-84 °C (EtOAc); **$[\alpha]_D^{24}$: -** 3.4 (c. 1, methylene chloride); **MS *m/z* (ES$^+$)**: 478.4 (100 %, MH^+); (Found: MNa^+, 500.1936. $C_{30}H_{27}N_3O_3Na$ requires MNa^+, 500.1845); **IR υ_{max}(film)/cm^{-1}**: 3350 (NH), 1644 (C=N), 1555 (C=N); **^{1}H (CDCl$_3$, 500 MHz)**: δ 8.71, (d, 1H, *J* 2.0, *ArH*), 7.69 (dd, 1H, *J* 8.5 and 2.0, Ar*H*), 7.28-7.09 (m, 15H, Ph), 6.74 (d, 1H, *J* 8.5, Ar*H*), 5.64 (m, 1H, N*H*), 5.26 (d, 1H, *J* 7.5, PhC*H*O), 5.06 (d, 1H, *J* 7.5, PhC*H*N) 5.04 (s, 1H, N*H*), 4.31-4.18 (m, 2H, CH_2Ph), 3.67 (s, 3H, OCH_3); **^{13}C (CDCl$_3$, 125 MHz)**: δ 164.3, 158.3, 155.2, 150.7, 142.1, 140.5, 139.2, 139.0, 128.8, 128.5, 128.3, 127.7, 127.4, 127.3, 126.8, 125.8, 123.6, 120.3, 119.7, 109.8, 89.0, 78.9, 55.8, 44.4;

***1-Benzyl-3-(5'-((4"R,5"R)-4",5"-diphenyloxazoline)-2'-methoxy-phenyl)-1,3-dimethylurea,* 243**

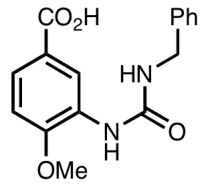


Sodium hydride (60 % in mineral oil) (0.42 g, 10.5 mmol) was added portionwise to a stirred solution of **242** (1.0 g, 2.1 mmol) in DMF (20 mL) at 0 °C. The reaction mixture was stirred for 1 h, then methyl iodide (0.39 mL, 6.27 mmol) was added and reaction mixture was left to stir for a further 12 h at room temperature. The reaction mixture was partitioned between ethyl acetate (30 mL) and water (30 mL). The water layer was extracted with ethyl acetate (3 x 30 mL) and the combined organic layers were washed with water (6 x 30 mL). The organic layer was then dried ($MgSO_4$) and the solvent was removed under reduced pressure to give the

crude product. Purification by flash column chromatography, eluting with 4:1 petrol:ethyl acetate, afforded dimethylurea **243** (0.71 g, 67 %) as a yellow amorphous solid.

R_f: 0.15 (1:2 Pet:EtOAc); **$[\alpha]_D^{24}$: -** 1.5 (c. 1, methylene chloride); **MS *m/z* (ES^+)**: 506.3 (50 %, MH^+), 528.3 (100 %, MNa^+); (Found: 506.2438, MH^+. $C_{32}H_{32}O_3N_3$ requires MH^+, 506.2438); **IR υ_{max}(film)/cm^{-1}**: 1646 (C=O), 1605 (C=N), ; **^{1}H ($CDCl_3$, 500 MHz)**: δ 7.92 (m, 2H, Ar*H*), 7.43-7.29 (m, 10H, Ph*H*), 7.21-7.14 (m, 5H, Ph*H*), 6.95 (d, 1H, *J* 8.5, Ar*H*), 5.40 (d, 1H, *J* 7.5, PhC*H*O), 5.21 (d, 1H, *J* 7.5, PhC*H*N), 4.33 (A of AB quartet, 1H, *J* 15.5, PhCH_2), 4.28 (B of AB quartet, 1H, *J* 15.5, PhCH_2), 3.91 (s, 3H, OCH_3), 3.15 (s, 3H, ArNCH_3), 2.46 (s, 3H, NC$H_3$$CH_2$Ph); **^{13}C (DMSO, 125 MHz)**: δ 163.2, 162.7, 156.9, 142.0, 140.4, 137.9, 135.0, 129.0, 128.9, 128.5, 128.3, 128.1, 128.1, 127.8, 127.8, 126.9, 126.8, 125.8, 120.6, 111.6, 89.1, 79.0, 60.4, 53.7, 38.6, 36.0;

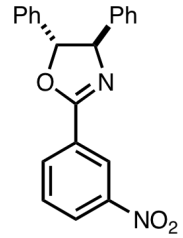
***3-(3-Benzylureido)-4-methoxybenzoic acid,* 245**



Benzyl isocyanate (0.85 mL, 6 mmol) was added dropwise to a stirred solution of 3-amino-4-methoxybenzoic acid (1.0 g, 6 mmol) in methylene chloride (30 mL) at 0 °C. The reaction mixture was warmed to room temperature and allowed to stir for 12 h. The solvent was removed under reduced pressure to give crude urea. Purfication by crystallisation from minimal methylene chloride afforded urea **245** (1.52 g, 85 %) as a white solid.

R_f: 0.1 (EtOAc); **Mpt**: 272-276 °C (methylene chloride); **MS *m/z* (ES^+)**: 301 (100 %, MH^+), 323.1 (80 %, MNa^+); (Found: 323.1007, MNa^+. $C_{16}H_{16}O_4N_2Na$ requires MNa^+, 323.1002); **IR υ_{max}(film)/cm^{-1}**: 3317 (s, NH), 2909 (COOH), 2847 (CH), 1610 (C=O); **^{1}H (DMSO, 500 MHz)**: δ 12.54 (s, 1H, CO_2H), 8.76 (s, 1H, ArN*H*), 8.16 (s, 1H, Ar*H*), 7.55 (d, 1H, *J* 8.5, Ar*H*), 7.39-7.23 (m, 5H, Ph*H*), 7.06 (d, 1H, *J* 8.5, Ar*H*), 4.31 (d, 2H, *J* 5.5, PhCH_2), 3.91 (s, 3H, OCH_3); **^{13}C (DMSO, 100 MHz)**: δ 167.4, 155.0, 150.6, 140.9, 129.0, 128.3, 127.2, 126.9, 126.7, 123.2, 118.9, 109.9, 55.9, 42.7;

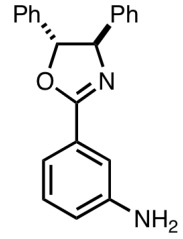
***(4R,5R)-2-(3-nitrophenyl)-4,5-diphenyloxazoline,* 247**



General procedure 3b was applied to 3-nitro benzoic acid (3.33 g, 19.94 mmol) to give the crude oxazoline. Purification by flash column chromatography, eluting with 4:1 petrol:ethyl acetate, afforded oxazoline **247** (3.96 g, 58 %) as a clear yellow oil.

R_f: 0.7 (2:1 Pet:EtOAc); **$[\alpha]_D^{28}$**: -9.6 (c. 1, $CDCl_3$); **MS**: *m/z (ES$^+$)* 367 (100 %, MNa^+); (Found: 345.1231, MH^+. $C_{21}H_{17}O_3N_2$ requires MH^+, 345.1234); **IR ν_{max}(film)/cm^{-1}**: 2920 (CH), 1650 (C=N), 1529 (C-O), 1347 (NO_2); **^{1}H ($CDCl_3$, 500 MHz)**: δ 8.97 (d, 1H, *J* 2.0, Ar*H*), 8.47 (dd, 1H, *J* 8.0 and 2.0, Ar*H*), 8.41 (d, 1H, *J* 8.0, Ar*H*), 7.69 (t, 1H, *J* 8.0, Ar*H*), 7.46 – 7.29 (m, 10H, Ph*H*), 5.51 (d, 1H, *J* 8.0, PhC*H*O), 5.31 (d, 1H, *J* 8.0, PhC*H*N); **^{13}C ($CDCl_3$, 500 MHz)**: δ 162.3, 148.4, 141.2, 139.7, 134.3, 129.7, 129.3, 129.1, 129.0, 128.8, 128.1, 126.7, 126.2, 125.8, 123.7, 89.7, 79.0;

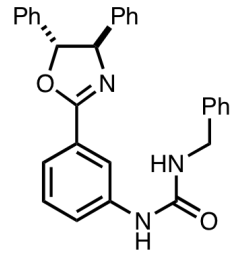
***3-((4R,5R)-4,5-Diphenyloxazoline)aniline,* 248**



To a solution of **247** (4.0 g, 11.61 mmol) in ethyl acetate (240 mL) and ethanol (160 mL) was added Lindlar catalyst (5 % Pd, 1.12 g). The reaction mixture was stirred under atmospheric H_2 until starting material was consumed. The catalyst was removed by filtration through Celite^{TM}. The filtrate was concentrated under reduced pressure to give the crude amine. Purification by flash chromatography, eluting with 4:1 petrol:ethyl acetate, afforded amine **248** (2.78 g, 76 %) as a lime green amorphous solid.

R_f: 0.37 (2:1 Pet:EtOAc); **Mpt**: 127-129 °C (Pet:EtOAc); **$[\alpha]_D^{28}$**: -28.9 (c. 1, $CDCl_3$); **MS**: *m/z (ES$^+$)* 314 (30 %, MH^+), 337 (100 %, MNa; (Found: 315.1494, MH^+. $C_{21}H_{19}ON_2$ requires MH^+, 315.1492); **IR ν_{max}(film)/cm^{-1}**: 3377 (NH_2), 3026 (CH), 1644 (C=N), 1619 (C-O); **^{1}H ($CDCl_3$, 400 MHz)**: δ 7.44 (dd, 1H, *J* 8.0 and 1.5, Ar*H*), 7.39 (d, 1H, *J* 1.5, Ar*H*), 7.34 – 7.16 (m, 11H, Ar*H* and Ph*H*), 6.78 (m, 1H, Ar*H*), 5.31 (d, 1H, *J* 7.5, PhC*H*O), 5.12 (d, 1H, *J* 7.5, PhC*H*N), 3.21 (bs, 2H, ArNH_2); **^{13}C ($CDCl_3$, 100 MHz)**: δ 164.3, 146.5, 142.0, 140.6, 129.5, 128.9 (2C), 128.4, 128.4, 127.8, 126.8, 125.7, 118.8, 118.3, 114.9, 88.9, 79.0;

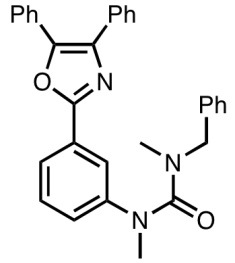
***1-Benzyl-3-(3-((4R,5R)-4,5-diphenyloxazoline)phenyl)urea,* 249**



Benzyl isocyanate (0.24 mL, 1.91 mmol) was added dropwise to a solution of **248** (0.60 g, 1.91 mmol) in methylene chloride (15 mL) at 0 °C. The reaction mixture was warmed to room temperature and left to stir for 12 h. Reaction mixture was then partitioned with water (10 mL). The organic layer was separated and the aqueous layer was washed with further portions of methylene chloride (2 x 10 mL). The combined organic layers were dried (Na_2SO_4) and the solvent removed by reduced pressure to afford the benzyl urea **249** (0.85 g, 99 %) as a cream amorphous solid. Further purification was not required.

R_f: 0.28 (2:1 Pet:EtOAc); **Mpt**: 203-204 °C (methylene chloride); **$[\alpha]_D^{28}$**: -4.9 (c. 1, $CDCl_3$); **MS *m/z (ES$^+$)***: 470.4 (100 %, MNa^+); (Found: 470.1828, MNa^+. $C_{29}H_{25}O_2N_3Na_1$ requires MNa^+, 470.1839); **IR ν_{max}(film)/cm^{-1}**: 3302 (NH), 3027 (CH), 1637 (C=N), 1570 (C-O); **^{1}H ($CDCl_3$, 500 MHz)**: δ 7.84 (s, 1H, Ar*H*), 7.68 (d, 1H, *J* 8.0, Ar*H*), 7.59 (d, 1H, *J* 8.0, Ar*H*) 7.34-7.14 (m, 16H, Ph*H* and Ar*H*), 6.78 (s, 1H, ArN*H*), 5.19 (d, 1H, *J* 8.0, PhC*H*O), 5.29 (brs, 1H, CH_2N*H*), 5.00 (d, 1H, *J* 8.0, PhC*H*N), 4.21 (d, 2H, *J* 6.0, CH_2); **^{13}C ($CDCl_3$, 300 MHz)**: δ 164.1, 155.5, 141.7, 140.2, 139.2, 138.8, 129.4, 128.9 (2C), 128.7, 128.5, 127.9, 127.5 (2C), 127.4, 126.8, 125.7, 123.7, 123.4, 119.9, 89.1, 78.8, 44.2;

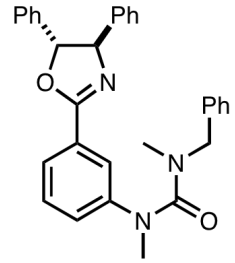
***1-benzyl-3-(3-(4,5-diphenyloxazol-2-yl)phenyl)-1,3-dimethylurea*, 250**



Sodium hydride (60 % in mineral oil) (0.35 g, 8.9 mmol) was added portion-wise to a stirred solution of **249** (1.0 g, 2.2 mmol) in dimethylformamide (10 mL) at 0 °C. The reaction mixture was stirred for 1 h, methyl iodide (0.4 mL, 6.6 mmol) was added and the reaction mixture was left to stir for a further 12 h. The reaction mixture was then partitioned between ethyl acetate (30 mL) and water (30 mL). The aqueous layer was then extracted with further portions of ethyl acetate (3 x 30 mL). The combined organic layers were washed with water (6 x 30 mL), then dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude methylated urea. Purification by flash column chromatography, eluting with 4:1 petrol:ethyl acetate, afforded oxazole **250** (0.97 g, 92 %) as a yellow gum.

R_f: 0.4 (4:1 Pet:EtOAc); **^{1}H (CDCl$_3$, 500MHz)**: δ 7.60 (s, 1H, Ar*H*), 7.51 (d, 1H, *J* 7.5, Ar*H*), 7.45-7.41 (m, 2H, Ph*H*), 7.33 (m, 1H, Ar*H*), 7.29-7.06 (m, 11H, Ph*H*), 7.03-6.96 (m, 2H, Ph*H*), 6.90-6.86 (d, 1H, *J* 7.5, Ar*H*), 4.22 (m, 2H, PhCH_2), 3.10 (s, 3H, NCH_3), 2.40 (s, 3H, NCH_3);

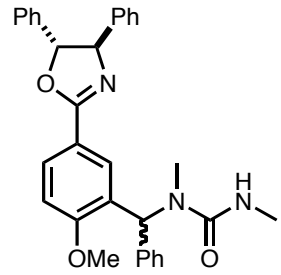
***1-Benzyl-3-(3-((4R,5R)-4,5-diphenyloxazoline)phenyl)-1,3-dimethylurea,* 251**



Sodium hydride (60 % in mineral oil) (0.35 g, 8.9 mmol) was added portion-wise to a stirred solution of **249** (1.00 g, 2.2 mmol) in tetrahydrofuran (10 mL) at 0 °C. The reaction mixture was stirred for 1 h, methyl iodide (0.4 mL, 6.6 mmol) was added and the reaction mixture was left to stir for a further 12 h at RT. The reaction mixture was then partitioned between ethyl acetate (30 mL) and water (30 mL). The aqueous layer was then extracted with further portions of ethyl acetate (3 x 30 mL). The combined organic layers were washed with water (6 x 30 mL), then dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude methylated urea. Purification by flash column chromatography, eluting with 2:1 petrol:ethyl acetate, afforded dimethylurea **251** (0.97 g, 92 %) as a yellow gum.

R_f: 0.31 (2:1 Pet:EtOAc); **$[\alpha]_D^{28}$**: - 1.4 (c. 1, $CDCl_3$); **MS *m/z (ES$^+$)***: 498 (100 %, MH^+); (Found: 498.2148, MNa^+. $C_{31}H_{29}O_2N_3Na$ requires MNa^+, 498.2152); **IR ν_{max}(film)/cm^{-1}**: 3028 (CH), 1644 (C=N), 1599 (C-O); **^{1}H (CDCl$_3$, 500 MHz)**: δ 7.91 (s, 1H, Ar*H*), 7.89 (d, 1H, *J* 8.0, Ar*H*), 7.47-7.24 (m, 17H, Ar*H* and Ph*H*), 5.47 (d, 1H, *J* 8.0, PhC*H*O), 5.28 (d, 1H, *J* 8.0, PhC*H*N), 4.49 (A of AB quartet, 1H, *J* 15.0, NMeCH_2Ph), 4.42 (B of AB quartet, 1H, *J* 15.0, NCH_2Ph), 3.34 (s, 3H, ArNCH_3), 2.59 (s, 3H, N(CH_3)CH$_2$); **^{13}C (CDCl$_3$, 125 MHz)**: 163.6, 161.8, 155.2, 147.1, 141.7, 140.2, 137.4, 129.6, 129.0, 128.9, 128.8, 128.6, 128.5, 128.1, 127.9, 127.3, 126.8, 125.8, 124.5, 123.5, 89.3, 78.9, 53.6, 40.0, 36.2;

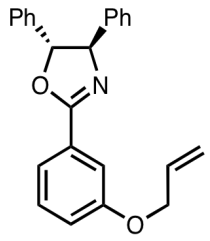
***1-((5-(4,5-diphenyloxazoline)-2-methoxyphenyl)(phenyl)methyl)-1,3-dimethylurea,* 256**



General procedure 6a was used employing oxazoline **251** (20 mg, 0.03 mmol), *n*-BuLi (0.19 mmol), DMPU (0.024 mL, 1.05 mmol) in THF at -75 °C, and $NH_4Cl_{(aq)}$ (0.5 mL) quench after 5 min. Purification by flash column chromatography, eluting with 4:1 petrol:ethyl acetate, afforded cyclised product **256** (13 mg, 65 %), in a 7:1 ratio with the starting material, as a clear colourless oil.

R_f: 0.35 (2:1 Pet:EtOAc); ignoring the peaks related to **251** **^{1}H ($CDCl_3$, 400MHz)**: δ 8.09 (m, 1H, Ar*H*), 7.75 (s, 1H, Ar*H*), 7.33-7.15 (m, 13H, Ar'*H* and Ph*H*), 7.15 (m, 2H, Ar'*H*), 6.90 (d, 1H, *J* 8.0, Ar*H*), 6.74 (s, 0.5 H, C*H*a), 6.72 (s, 0.5 H, C*H*a), 5.26 (d, 1H, *J* 7.5, PhC*H*O), 5.07 (d, 1H, *J* 7.5, PhC*H*N), 4.45 (brs, 1H, NH), 3.74 (s, 3H, OCH_3), 2.75 (s, 3H, NCH_3), 2.64 (s, 3H, NCH_3); **^{13}C ($CDCl_3$, 125MHz)**: δ 163.8, 161.0, 159.3, 140.6, 139.5, 129.9, 129.0 (2C), 128.9, 128.8, 128.4, 128.2, 127.7, 127.3, 127.2, 126.8, 125.8, 125.6, 119.8, 110.4, 88.9, 79.1, 57.2, 55.9, 31.8, 27.9;

***(4R,5R)-2-(3-(Allyloxy)phenyl)-4,5-diphenyloxazoline,* 275**

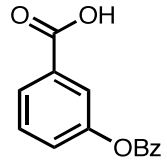


Sodium hydride (60 % in mineral oil) (0.076 g, 1.9 mmol) was added portion-wise to a solution of **291** (0.30 g, 0.95 mmol) and allyl bromide (0.41 mL, 4.74 mmol) in tetrahydrofuran (10 mL) at 0 °C. The reaction was stirred for a further 30 mins then warmed to room temperature and stirred for a further 48 h. The reaction was quenched with NH_4Cl (5 mL). The mixture was washed with methylene chloride (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure to give the crude allyl ether. Purification by flash column chromatography, eluting with 9:1 petrol:ethyl acetate, afforded **275** (0.15 g, 44 %) as a clear, colourless oil.

R_f: 0.57 (2:1 Pet:EtOAc); **$[\alpha]_D^{25}$**: - 12.0 (c. 1, DCM); **MS**: *m/z (ES$^+$)* 378 (100 %, MNa^+); (Found: 356.1643, MH^+. $C_{24}H_{22}O_2N_1$ requires MH^+, *356.1645*); **IR ν_{max}(film)/cm^{-1}**: 3028 (CH), 1646 (C=N), 1582 (C-O); **^{1}H ($CDCl_3$ 500, MHz)**: δ 7.75 (d, 1H, *J* 7.5, Ar*H*), 7.70 (s, 1H, Ar*H*), 7.40-7.39 (m, 11H, Ar*H* and Ph*H*), 7.14 (d, 7.5, Ar*H*), 6.08 (ddt, 1H, *J* 17.0, 10.5, and 5.0, CH_2CHCH_2), 5.45 (dd, 1H, *J* 17.0 and 1.5, $CH_2CHCH_{(trans)}$), 5.44 (d, 1H, *J* 7.5, PhC*H*O), 5.31 (dd, 1H, *J* 10.5 and 1.5,

$CH_2CHCH_{(cis)}$), 5.25 (d, 1H, *J* 7.5, PhC*H*N), 4.62 (dt, 2H, *J* 5.0, CH_2CHCH_2); **^{13}C (CDCl$_3$, 75 MHz)**: δ 164.2, 158.7, 141.8, 140.4, 133.0, 129.6 (2C), 129.0, 128.5, 127.9, 126.8 (2C), 125.7, 121.3, 119.3, 117.8, 114.0, 89.1, 78.9, 69.0;

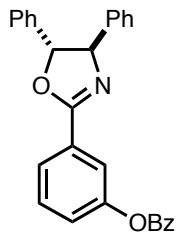
3-(phenylcarbonyloxy)benzoic acid, **289**



Benzoyl chloride (8.40 mL, 72.4 mmol) was added drop-wise with vigorous stirring to a solution of 3-hydroxy benzoic acid (10.0 g, 72.4 mmol) and potassium carbonate (25.0 g, 0.18 mol) in water (286 mL) and *iso*-propanol (110 mL) at 0 °C. The reaction mixture was stirred for 12 h then neutralised with HCl (6M). A white precipitate formed which was collected by vacuum filtration, washing with water. The isolated precipitate was dried under reduced pressure until a consistent weight was achieved to afford carboxylic acid **289** (16.55 g, 94 %) as a white amorphous solid. Used without further purification.

R$_f$: 0.11 (2:1 Pet:EtOAc); **Mpt**: 154-155 °C (Water); **MS** *m/z (ES$^-$)*: 227 (100 %, M-H); (Found: 227.0717, M-H. $C_{14}H_{11}O_3$ requires M-H*, 227.0713*); **IR ν$_{max}$(film)/cm^{-1}**: 3003 (OH), 2881 (CH), 1730 (C=O), 1681 (C=O); **^{1}H (CDCl$_3$, 400 MHz)**: δ 11.00-9.47 (brs, 1H. CO_2H), 8.23 (d, 2H, *J* 7.0, Ar*H*2' and Ar*H*6'), 8.05 (d, 1H, *J* 7.5, Ar*H*6), 7.99 (s, 1H, Ar*H*2), 7.67 (t, *J* 7.5, Ar*H*5), 7.59-7.50 (m, 4H, Ar*H*3',4',5' and Ar*H*4); **^{13}C (CDCl$_3$, MHz)**: δ 171.2, 165.0, 151.0, 133.9, 130.9, 130.3, 129.7, 129.1, 128.7, 127.7, 127.4, 123.6;

***3-((4R,5R)-4,5-Diphenyloxazoline)phenyl benzoate,* 290**

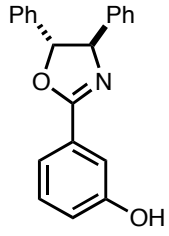


3-(Phenylcarbonyloxy)benzoic acid **289** (7.0 g, 28.9 mmol) was refluxed with thionyl chloride (23 mL) and toluene (50 mL) in order to give the crude benzoyl chloride. General procedure 3b was then followed to give the crude oxazoline. Purification by flash chromatography, eluting with 2:1 petrol:ethyl acetate, afforded oxazoline **290** (8.40 g, 69 %) as a cream gum.

R$_f$: 0.82 (2:1 Pet:EtOAc); **[α]$_D^{28}$**: -3.2 (c. 1, DCM); **MS *m/z (ES$^+$)***: 442 (100 %, MNa$^+$); (Found: 420.1598, MH$^+$. $C_{28}H_{22}O_3N$ requires MH$^+$*, 420.1594*); **IR ν$_{max}$(film)/cm^{-1}**: 3030 (CH), 1737 (C=O), 1650 (C=N), 1585 (C-O);**^{1}H (CDCl$_3$, 300 MHz)**: δ 8.21 (d, 2H, *J* 7.0, Ar*H*2',6'), 8.06 (d, 1H, *J* 8.0, Ar*H*), 8.01 (s, 1H, Ar*H*), 7.69-7.63 (m, 1H, Ar*H*) 7.59-7.50 (m, 3H, Ar*H*), 7.46-7.29 (m, 11H, Ar*H* and Ph*H*), 5.43 (d, 1H, *J* 7.5,

PhC*H*O), 5.24 (d, 1H, *J* 7.5, PhC*H*N); **^{13}C (CDCl$_3$, 100 MHz)**: δ 166.0, 165.1, 151.0, 141.7, 140.2, 133.8, 130.2, 129.7, 129.2, 129.0, 128.9, 128.7, 128.6, 127.9, 127.6, 126.8, 126.2, 125.8, 125.3, 122.1, 89.3, 78.9;

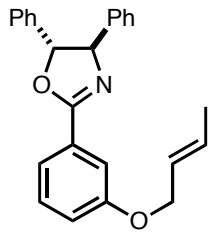
***3-((4R,5R)-4,5-Diphenyloxazoline)phenol,* 291**



A solution of **290** (1.50 g, 3.58 mmol) in 2M $NaOH_{aq}$ (5 mL) and ethanol (12 mL) was heated at reflux for 2 hours. The reaction mixture was then cooled and partitioned with methylene chloride (50 mL). The organic layer was separated and the aqueous layer was washed with methylene chloride (2 x 10 mL). The combined organic layers were dried (Na_2SO_4) and the solvent removed by reduced pressure to afford the crude phenol. Purification by column chromatography, eluting with 4:1 petol:ethyl acetate, afforded the phenol **291** (1.1 g, 97 %) as a white amorphous solid.

R_f: 0.64 (2:1 Pet:EtOAc); **Mpt**: 73-75 °C (Pet:EtOAc); **$[\alpha]_D^{28}$**: - 8.8 (c. 1, DCM); **MS**: *m/z (ES$^+$)* 316 (70 %, MH^+), 338 (100 %, MNa^+); (Found: 338.1165, MNa^+. $C_{21}H_{17}O_2N_1Na$ requires MH^+, *338.1152*); **IR ν_{max}(film)/cm^{-1}**: 3029 (CH), 2930 (OH), 1636 (C=N), 1581 (C-O); **^{1}H (CDCl$_3$, 400 MHz)**: δ 7.65 (d, 1H, 8.0, Ar*H*), 7.62 (s, 1H, Ar*H*), 7.44-7.28 (m, 11H, Ar*H* and Ph*H*), 6.99 (d, 1H, *J* 8.0, Ar*H*), 5.43 (d, 1H, *J* 7.5, OC*H*Ph), 5.24 (d, 1H, *J* 7.5, NC*H*Ph); **^{13}C (CDCl$_3$, 125 MHz)**: δ 164.6, 156.3, 141.9, 140.4, 130.1, 129.2, 129.1, 128.8 (2C), 128.1, 127.0, 125.9, 121.1, 119.6, 115.7, 89.3, 78.8;

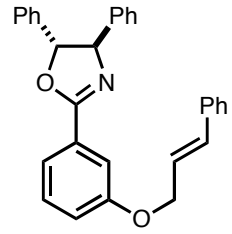
***(4R,5R)-2-(3-((E)-but-2-enyloxy)phenyl)-4,5-diphenyloxazoline,* 292a**



Sodium hydride (60 % in mineral oil) (0.076 g, 1.9 mmol) was added portion-wise to a solution of **291** (0.30 g, 0.95 mmol) and crotyl bromide (0.48 mL, 4.66 mmol) in tetrahydrofuran (10 mL) at 0 °C. The reaction was stirred for 30 mins then warmed to room temperature and stirred for a further 48 h. The reaction was quenched with $NH_4Cl_{(aq)}$ (5 mL). The mixture was washed with methylene chloride (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure to give the crude allylic ether. Purification by flash column chromatography, eluting with 9:1 petrol:ethyl acetate afforded oxazoline **292a** (0.20 g, 51 %) as a clear, colourless oil.

R_f: 0.5 (4:1 Pet:EtOAc); **$[\alpha]_D^{20}$**: - 6.8 (c. 1, DCM); **MS**: *m/z (ES$^+$)* 392 (100 %, MNa^+); (Found: 370.1809, MH^+. $C_{25}H_{24}O_2N$ requires MH^+, *370.1802*); **IR ν_{max}(film)/cm^{-1}**: 3027 (CH), 1646 (C=N), 1581 (C-O); **^{1}H (CDCl$_3$, 300 MHz)**: δ 7.78-7.69 (m, 2H, Ar*H*), 7.44-7.28 (m, 11H, Ar*H* and Ph*H*), 7.16-7.09 (m, 1H, Ar*H*), 5.96-5.68 (m, 2H, $CH_2CHCHCH_3$), 5.44 (d, 1H, *J* 7.5, PhC*H*O), 5.25 (d, 1H, *J* 7.5, PhC*H*N), 4.68 (dd, 1H, *J* 4.5 and 1.0, C*H*CHCHCH$_3$), 4.54 (dd, 1H, *J* 5.8 and 1.0, C*H*CHCHCH$_3$), 1.78 (m, 3H, CHC*H*$_3$); **^{13}C (CDCl$_3$, 75 MHz)**: δ 164.2, 158.8, 141.9, 140.4, 130.8, 129.6, 129.0, 128.9, 127.9, 126.8, 125.8, 125.7, 125.3, 121.2, 119.4, 113.9, 113.7, 89.1, 78.9, 69.0, 17.9;

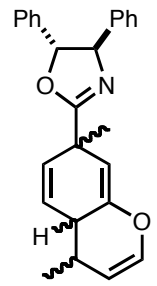
***(4R,5R)-2-(3-(cinnamyloxy)phenyl)-4,5-diphenyloxazoline,* 292b**



Sodium hydride (60 % in mineral oil) (0.076 g, 1.9 mmol) was added portion-wise to a solution of phenol **291** (0.30 g, 0.95 mmol) and cinnamyl bromide (0.48 mL, 4.66 mmol) in tetrahydrofuran (10 mL) at 0 °C. The reaction was stirred for a further 30 mins then warmed to room temperature and stirred for a further 48 h. The reaction was quenched with NH_4Cl (5 mL). The mixture was washed with methylene chloride (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed by reduced pressure to give the crude allylic ether. Purification by flash column chromatography, eluting with 9:1 petrol:ethyl acetate, afforded oxazoline **292b** (0.34 g, 44 %) as a yellow oily solid.

R_f: 0.6 (2:1 Pet:EtOAc); **$[\alpha]_D$**: - 12.4 (c. 1, DCM) ; **MS**: *m/z (ES$^+$)* 454 (100 %, MNa^+); (Found: 432.1955, MH^+. $C_{30}H_{26}O_2N_1$ requires MH^+, *432.1958*); **IR ν_{max}(film)/cm^{-1}**: 3027 (CH), 1646 (C=N), 1581 (C-O); **^{1}H (CDCl$_3$, 300 MHz)**: δ 7.69-7.63 (m, 2H, Ar*H*), 7.36-7.13 (m, 16H, Ar*H* and Ph*H*), 7.08-7.04 (m, 1H, Ar*H*), 6.67 (d, 1H, *J* 16.0, CHC*H*Ph), 6.34 (dt, 1H, *J* 16.0 and 6.0, C*H*CHPh), 5.34 (d, 1H, *J* 7.5, PhC*H*O), 5.16 (d, 1H, *J* 7.5, PhC*H*N), 4.69 (d, 2H, *J* 6.0, CH_2CH); **^{13}C (CDCl$_3$, 75MHz)**: δ 164.1, 158.7, 141.9, 140.4, 136.5, 133.3, 129.7, 129.0, 128.9, 128.7, 128.6, 128.5, 127.9, 127.7, 126.8, 126.5, 125.7, 124.1, 121.4, 119.3, 114.0, 89.1, 78.9, 68.8;

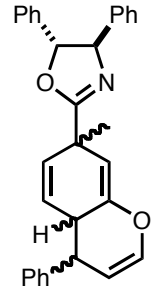
***(4R,5R)-2-(4,7-Dimethyl-4a,7-dihydro-4H-chromen-7-yl)-4,5-diphenyloxazoline,* 293a**



General procedure 6a was used employing oxazoline **292a** (65 mg, 0.18 mmol), *t*-BuLi (0.35 mmol in pentane), DMPU (0.13 mL, 1.05 mmol) in THF, and MeI (0.025 mL, 0.40 mmol) quench after 10 min. Purification by flash column chromatography, eluting with 4:1 petrol:ethyl acetate, afforded cyclised product **293a** (25 mg, 37 %), as a clear colourless oil.

R_f: 0.6 (2:1 Pet:EtOAc); **MS**: *m/z (ES$^+$)* 384 (100 %, MH$^+$); (Found:, 384.1949, MH$^+$. $C_{26}H_{26}O_2N_1$ requires MH$^+$, *384.1958*); **IR ν_{max}(film)/cm^{-1}**: 2965 (CH), 1739, 1649 (C=N), 1582 (C-O); Mixture of two diastereoisomers can be observed at H4a in 1:1 ratio (A and B) **^{1}H ($CDCl_3$, 400MHz)**: δ 7.34-7.11 (m, 8 H, Ph*H*), 6.85-6.93 (m, 2H, Ph*H*), 6.28-6.25 (m, 1H, H2), 5.97-5.88 (2H, m, H5 and H6), 5.45-5.67 (m, 1H, H8), 5.15 (d, 1H, *J* 7.0, PhC*H*O), 4.91 (d, 1H, *J* 7.1, PhC*H*N), 4.59 (ddd, 1H, *J* 9.0, 6.0 and 1.5, H3), 2.69-2.65 (m, 0.5 H, isomer A H4a), 2.62-2.58 (m, 0.5 H, isomer B H4a), 2.17-2.05 (m, 1H, H4), 1.50 (s, 3H, C(CH_3)), 1.09-1.05 (m, 3H, CH(CH_3)); Mixture of diastereoisomers **^{13}C ($CDCl_3$, 100 MHz)**: δ 172.8, 171.3, 157.6, 142.1, 140.8, 140.5, 129.8, 129.6, 128.9, 128.8, 128.3, 127.7, 127.4, 126.7, 126.6, 126.4, 125.7, 125.4, 108.3, 93.5, 88.9, 88.4, 78.8, 78.5, 42.6, 40.4, 38.8, 38.1, 32.5, 32.4, 28.19, 28.16, 19.0, 17.9;

***(4R,5R)-2-(7-Methyl-4-phenyl-4a,7-dihydro-4H-chromen-7-yl)-4,5-diphenyloxazoline*, 293b**

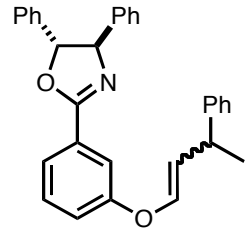


General procedure 6a was used employing oxazoline **292b** (134 mg, 0.31 mmol), *t*-BuLi (0.57 mL, 0.62 mmol in pentane), DMPU (0.22 mL, 1.86 mmol) in THF, the reaction was stirred for 5 mins at – 78 then the reaction was warmed to - 40 °C. MeI (0.038 mL, 0.62 mmol) quench after 10 min. Purification by flash column chromatography, eluting with 9:1 petrol:ethylacetate, afforded cyclised product **293b** (38 mg, 28 %) as a clear colourless oil as mixture of diastereoisomers in a ratio of 1:0.6 (A:B) as an unseparable mixture.

R_f: 0.59 (4:1 Pet:EtOAc); **MS**: *m/z (ES$^+$)* 468 (100 %, MNa$^+$); (Found: 446.2115, MH$^+$. $C_{31}H_{28}O_2N_1$ requires MH$^+$, *446.2115*); **IR ν_{max}(film)/cm^{-1}**: 2962 (C-H), 1649 (C=N), 1582 (C-O); **^{1}H ($CDCl_3$, 500 MHz)**: δ 7.52-6.90 (m, 15 H, A and B Ph*H*), 6.43-6.41

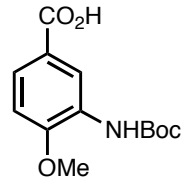
(m, 1H, A and B H2), 5.88-5.84 (m, 0.6 H, A H6), 5.80-5.77 (m, 0.4 H, B H6), 5.52 (d, 0.6 H, *J* 18.3, A H5), 5.47-5.43 (m, 0.6 H, A H8), 4.48-5.43 (m, 0.8 H, B H5 and H8), 5.17 (d, 0.6 H, *J* 7.0, A PhC*H*O), 5.12 (d, 0.4 H, *J* 7.0, B PhC*H*O), 4.93 (d, 0.6 H, *J* 7.0, A PhC*H*N), 4.87 (d, 0.4 H, *J* 7.0, B PhC*H*N), 4.76 (d, 0.6 H, *J* 6.5, A H3), 4.78 (d, 0.4 H, B *J* 6.5, H3), 3.26-3.23 (m, 0.6 H, A H4), 3.20-3.17 (m, 0.4 H, B H4), 2.96 (d, 0.6 H, *J* 11, A H4a), 3.06-3.03 (m, 0.4 H, B H4a), 1.47 (s, 1.8 H, A C(CH_3)$_3$) 1.53 (s, 1.2 H, B C(CH_3)$_3$; **^{13}C (CDCl$_3$, 75 MHz)**: δ 171.2, 157.8, 149.6, 149.5, 149.4, 142.2, 141.6, 129.3, 128.9, 128.8, 128.6, 128.5, 128.5, 128.4, 128.2, 127.9, 127.8, 127.4, 127.1, 126.9, 126.3, 126.1, 124.5, 106.6, 106.5, 88.9, 78.4, 44.6, 44.4, 38.7, 38.5, 28.6, 28.1, 21.9;

***(4R,5R)-4,5-Diphenyl-2-{3-((E0-3-phenyl-but-1-enyloxy)-phenyl]oxazoline,* 294**



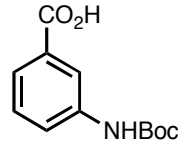
General procedure 6a was used employing oxazoline **292b** (88 mg, 0.20 mmol), *t*-BuLi (0.4 mmol in pentane), DMPU (0.14 mL, 1.2 mmol) in THF, and MeI (0.025 mL, 0.40 mmol) quench after 10 min. Purification by flash column chromatography, eluting with 4:1 petrol:ethylacetate, afforded product **294** (66 mg, 37 %), as a clear yellow oil. **R$_f$**: 0.7 (2:1 Pet:EtOAc); **MS**: *m/z (ES$^+$)* 468 (100 %, MNa$^+$); (Found: 446.2107, MH$^+$. $C_{31}H_{28}O_2N$ requires MH$^+$, *446.2115*); **IR ν$_{max}$(film)/cm^{-1}**: 2963 (C-H), 1649 (C=N), 1582 (C-O); **^{1}H (CDCl$_3$, 400 MHz)**: δ 7.80-7.75 (m, 2H, Ar*H*), 7.42-7.23 (m, 15H, Ar*H* and Ph*H*), 7.20-7.13 (m, 2H, Ph*H*), 6.41 (d, 1H, *J* 6.0, OC*H*CH), 5.38 (d, 1H, *J* 7.5, PhC*H*O), 5.19 (d, 1H, *J* 7.5, PhC*H*N), 5.00 (m, 1H, OCHC*H*), 4.11 (m, 1H, C*H*(CH$_3$)), 1.38 (m, 3H, CH(CH_3)); **^{13}C (CDCl$_3$, 100 MHz)**: δ 163.7, 162.8, 157.5, 156.3, 146.2, 141.9, 140.4, 129.9, 129.0, 128.5 (2C), 126.9, 126.8, 126.8, 126.5, 126.1, 125.8, 122.9, 120.0, 118.8, 116.0, 89.2, 79.1, 34.6, 21.9;

***3-((Tert-butyloxycarbonyl)amino)-4-methoxybenzoic acid,* 298a**



Using the method of Cushman.[102] To a solution of 3-amino-4-methoxybenzoic acid (1.0 g, 5.98 mmol) in 1,4 dioxane:water (15.3 mL: 7.6 mL) was added triethylamine (1.25 mL, 8.97 mmol) and di-*tert*-butyl dicarbonate (2.0 g, 8.97 mmol). The reaction mixture was stirred at room temperature for 24 h. The solvent was removed by reduced pressure. The residue was then treated with 3M HCl to form a white precipitate. The precipitate was then filtered washing with water. The solid was then dried in an oven until a consistent weight was achieved, to give the acid **298b** (1.56 g, 98 %) as a white amorphous solid. **Mpt**: 198-200 °C (water) (lit.[135] 193-194 °C (hexane)); **IR υ_{max}(film)/cm^{-1}**: 3351 (NH), 2965 (brs, COOH), 1710 (C=O), 1606 (C=O); **^{1}H (CDCl$_3$, 500 MHz)**: δ 13.63-9.37 (brs, 1H, CO_2H), 8.80 (brs, 1H, ArN*H*), 7.80 (d, 1H, *J* 8.5, Ar*H*), 7.09 (s, 1H, Ar*H*), 6.90 (d, 1H, *J* 8.5, Ar*H*), 3.95 (s, 3H, OCH_3), 1.56 (s, 9H, $C(CH_3)_3$); **^{13}C (CDCl$_3$, 75 MHz)**: δ 171.6, 152.6, 151.7, 128.0, 125.6, 122.2, 119.8, 109.3, 80.8, 55.9, 28.3;

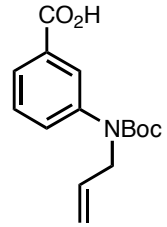
***3-(Tert-butoxycarbonylamino)benzoic acid*, 298b**



Using the method of Cushman.[102] To a solution of 3-amino benzoic acid (6.0 g, 43.8 mmol) in 1,4 dioxane (100 mL) and water (50 mL) was added Et_3N (9.14 mL, 65.7 mmol) and di-*tert*-butyl dicarbonate (14.3 g, 65.7 mmol). The reaction mixture was stirred at room temperature for 24 h. The solvent was removed by reduced pressure. The residue was then treated with 3M HCl to form a white precipitate. The precipitate was collected by vacuum filtration and washed with water. The precipitate was then dried in an oven until a consistent weight was achieved, to afford the acid **298b** (10.06 g, 97 %) as a white amorphous solid. Further purification was not required. Data consistent with published data.[102]

R$_f$: 0.11 (2:1 Pet:EtOAc); **Mpt**: 176-178 °C (water) (lit. 189-190 °C); **IR υ_{max}(film)/cm^{-1}**: 3736 (brs, OH), 3349 (NH), 1693 (C=O); **^{1}H (DMSO, 300 MHz)**: δ 12.90 (brs, 1H, CO_2H), 9.56 (s, 1H, ArN*H*), 8.14 (s, 1H, Ar*H*), 7.63-7.59 (m, 1H, Ar*H*), 7.52 (d, 1H, *J* 8.0, Ar*H*), 7.35 (t, 1H, *J* 8.0, Ar*H*), 1.47 (s, 9H, $C(CH_3)_3$); **Elem. Anal.** For $C_{12}H_{15}NO_3$: calcd % (found %): C, 60.75 (60.25); H, 6.37 (6.29); N, 5.90 (5.84).

***3-(Allyl(tert-butoxycarbonyl)amino)benzoic acid,* 300b**

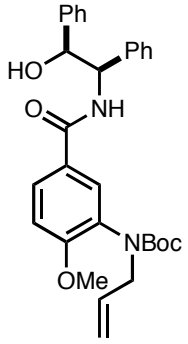


Sodium hydride (60 % in mineral oil) (0.046 g, 1 mmol) was added portion-wise to a stirred solution of **298b** (0.088 g, 0.37 mmol), allyl bromide (0.33 mL, 3.7 mmol) in anhydrous dimethylformamide (2 mL) at 0 °C. The reaction mixture was stirred for 10 mins at 0 °C then warmed to room temperature and stirred for a further 12 hours. NH_4Cl (4 mL) was added and the biphasic mixture was extracted with diethyl ether (5 x 5 mL). The combined organic layers were washed with brine (10 mL) then dried (Na_2SO_4) then the solvent was removed under reduced pressure to give the crude allylated product. Purification by flash column chromatography, eluting with 4:1 petrol:ethyl acetate, afforded *tert*-butyl-3-((allyloxy)carbonyl)phenylallylcarbamate (0.078 g, 66 %) as a clear oil.

Sodium hydroxide (0.297 g, 6.25 mmol) was added to a stirred solution of *tert*-butyl-3-((allyloxy)carbonyl)phenylallylcarbamate (1.0 g, 2.87 mmol) in tetrahydrofuran:water (125 ml:125 ml). The resulting solution was refluxed for 48 h, the solvent was removed under reduced pressure. 10% Citric acid (50 mL) was added to the residue, then the mixture was extracted with methylene chloride (3 x 50 mL). The combined organics layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure to afford carboxylic acid **300b** (0.85 g, 96 %) as a pale orange solid. Further purification was not required.

R_f: 0.28 (2:1 Pet:EtOAc); **Mpt**: 82-84 °C (methylene chloride); **MS *m/z (ES+)***: 276 (100 %, M-H); (Found: 276.1231, M-H. $C_{15}H_{18}NO_4$ requires M-H, *276.1241*); **IR υ_{max}(film)/cm^{-1}**: 3002 (brs, COOH), 1696 (C=O); **^{1}H (CDCl$_3$, 500 MHz)**: δ 13.05-9.54 (brs, 1H, CO_2H), 8.00 (s, 1H, Ar*H*), 7.93 (d, 1H, *J* 7.5, Ar*H*), 7.52 (d, 1H, *J* 7.5, Ar*H*), 7.43 (t, 1H, *J* 7.5, Ar*H*), 5.93 (ddt, 1H, *J* 17.0, 10.0 and 6.0, NCH_2CHCH_2), 5.21-5.16 (m, 2H, NCH_2CHCH_2), 4.28 (d, 2H, *J* 6.0, NCH_2CHCH_2), 1.47 (s, 9H, $C(CH_3)_3$); **^{13}C (CDCl$_3$, 75 MHz)**: δ 171.4, 154.2, 143.1, 133.9, 131.7, 129.9, 128.7, 127.8, 127.4, 116.9, 81.0, 52.7, 28.3;

***Tert-butyl-5-((1R,2S)-2-hydroxy-1,2-diphenylethylcarbamoyl)-2-methoxyphenylallylcarbamate,* 301a**



Sodium hydride (60 % in mineral oil) (0.46 g, 11.5 mmol) was added portion-wise to a stirred solution of **298a** (1.0 g, 3.7 mmol) and allyl bromide (3.23 mL, 37.0 mmol) in anhydrous DMF (20 mL) at 0 °C. Reaction mixture was stirred for 10 mins at 0 °C the warmed to RT and stirred for a further 12 hours. NH_4Cl (4 mL) was added and the biphasic mixture was extracted with diethylether (5 x 5 mL). The combined organics were washed with brine (10 mL) then dried (Na_2SO_4) then the solvent was removed under vacuum to give the crude allylated product. Purification by flash column chromatography, eluting with 4:1 petrol:ethyl acetate, afforded 3-(allyl(*tert*-butoxycarbonyl)amino)-4-methoxy-benzoic acid allyl ester (1.34 g, quantitative) as a yellow clear oil.

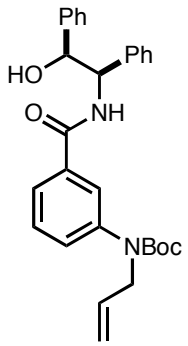
Sodium hydroxide (0.25 g, 6.25 mmol) was added to a stirred solution of 3-(allyl(*tert*-butoxycarbonyl)amino)-4-methoxy-benzoic acid allyl ester (1.0 g, 2.87 mmol) in tetrahydrofuran:water (125 mL: 125 mL). The resulting solution was heated at reflux for 48 h, then the solvent was removed under vacuum. 10 % Citric acid (50 mL) was added, then the mixture was extracted with methylene chloride (3 x 50 mL). The combined organics were dried (Na_2SO_4) then the solvent was removed under vacuum to give 3-(allyl(tert-butoxycarbonyl)amino)-4-methoxy-benzoic acid **300a** (0.85 g, 96 %) as a white amorphous solid. Further purification was not necessary.

N-Hydroxybenzotriazole (0.048 g, 0.36 mmol) and *N,N′*-dicyclohexylcarbodiimide (0.074 g, 0.36 mmol) were added at 0 °C with vigourous stirring to a solution of 3-(allyl(tert-butoxycarbonyl)amino)-4-methoxy-benzoic acid (**300a**) (0.10 g, 0.32 mmol) in anhydrous methylene chloride (10 mL). The reaction was stirred for 1 hour then (1*S*,2*R*)-2-amino-1,2-diphenylethanol (**207**) (0.069 g, 0.32 mmol) and triethylamine (0.045 mL, 0.32 mmol) were added and the mixture was stirred for 1 day at RT. The reaction mixture was filtered and the filtrate was concentrated under vacuum. The resulting oil was dissolved in ethyl acetate (10 mL) and washed with $NaHCO_3$ (aq) (3 x 5 mL) followed by brine (3 x 5mL). The organic layer was dried (Na_2SO_4) then the solvent was removed under reduced pressure to give the crude amide. Purification by

flash column chromatography, eluting with 4:1 petrol:ethyl acetate, afforded amide **301a** (0.16 g, 98 %) as a white amorphous solid.

R_f: 0.2 (2:1 Pet:EtOAc); **Mpt**: 88-90 °C (Pet:EtOAc); **$[\alpha]_D^{28}$**: + 70.4 (c. 1, $CDCl_3$); **MS *m/z* (ES^+)**: 503.3 (40 %, MH^+), 525.1 (100 %, MNa^+); (Found: 503.2529, MH^+. $C_{30}H_{35}O_5N_2$ requires MH^+, 503.2540); **IR ν_{max}(film)/cm^{-1}**: 3321 (OH), 2927 (CH), 1697 (C=O), 1637 (C=O); A mixture of two Boc-rotamers (A and B) **^{1}H ($CDCl_3$, 500 MHz)**: δ 7.68 (d, 1H, *J* 7.0, Ar*H*), 7.57 (s, 1H, Ar*H*), 7.26-6.93 (m, 11H, Ph*H* and N*H*), 6.90 (d, 1H, *J* 7.0, Ar*H*), 5.86 (ddt, 1H, *J* 17.0, 10.5 and 6.5, NCH_2CHCH_2), 5.45 (brs, 1H, PhC*H*O), 5.17 (brs, 1H, PhC*H*N), 5.08-5.03 (m, 2H, NCH_2CHCH_2), 4.27 (brs, 1H, $NCHCHCH_2$), 4.03 (brs, 1H, $NCHCHCH_2$), 3.86 (s, 3H, OCH_3), 1.51 (brs, 3H, rotamer A - $C(CH_3)_3$), 1.33 (brs, 6H, rotamer B - $C(CH_3)_3$); **^{13}C ($CDCl_3$, 125 MHz)**: δ 166.5, 158.1, 154.8, 139.9 (2C), 137.4, 134.2, 131.2, 128.2, 128.1 (2C), 128.0 (2C), 127.8, 127.6, 126.6 (2C), 116.9, 80.0, 59.8, 55.4, 49.2, 33.9, 28.6;

***Tert-butyl-3-((1R,2S)-2-hydroxy-1,2-diphenylethylcarbamoyl)phenylallylcarbamate,* 301b**

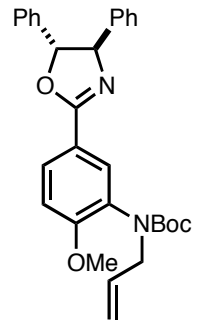


N-Hydroxybenzotriazole (0.27 g, 2.0 mmol) and *N*,*N*'-dicyclohexylcarbodiimide (0.41 g, 2.0 mmol) were added at 0 ºC with vigorous stirring to a solution of **300b** (0.50 g, 1.8 mmol) in methylene chloride (50 mL). The reaction mixture was stirred for 1 hour then (1*S*,2*R*)-2-amino-1,2-diphenylethanol (**207)** (0.38 g, 1.8 mmol) and triethylamine (0.25 mL, 1.8 mmol) were added and the mixture was stirred for a further 24 hours at room temperature. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The resulting oil was dissolved in ethyl acetate (10 mL) and washed with $NaHCO_3$ (aq) (3 x 5 mL) followed by brine (3 x 5mL). The organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure to give the crude amide. Purification by flash column chromatography, eluting with 4:1 petrol:ethyl acetate, afforded amide **301b** (0.60 g, 70 %) as a pale cream amorphous solid.

R_f: 0.4 (2:1 Pet:EtOAc); **Mpt**: 116-118 °C (petrol:ethyl acetate); **$[\alpha]_D^{28}$**: + 70.4 (c. 1, $CDCl_3$); **MS *m/z* (ES^+)**: 495.3 (100 %, MNa^+); (Found: 495.2248, MNa^+.

$C_{29}H_{32}O_4N_2Na_1$ requires MNa^+, 495.2254); **IR υ_{max}(film)/cm^{-1}**: 3321 (OH), 2978 (CH), 1698 (C=O), 1634 (C=O); **^{1}H (CDCl$_3$, 300 MHz)**: 7.60-7.59 (m, 1H, Ar*H*), 7.40 (dt, 1H, *J* 7.5 and 1.5, Ar*H*), 7.30-6.92 (m, 12H, Ar*H*, PhCHN*H* and Ph*H*), 5.82 (ddt, 1H, *J* 17.5, 10.0 and 5.5, NCH_2CHCH_2), 5.46-5.32 (m, 1H, NCH_2CHCH_2), 5.20-5.13 (m, 3H, NCH_2CHCH_2, PhC*H*OH and PhC*H*NH), 4.25 (d, 2H, *J* 5.5, NCH_2CHCH_2), 3.45 (brs, 1H, CHO*H*), 1.49 (s, 9H, $C(CH_3)_3$); **^{13}C (CDCl$_3$, 75 MHz)**: δ 166.9, 154.3, 143.2, 139.9, 137.2, 135.1, 134.0, 129.6, 128.8, 128.1 (2C), 128.0, 127.8, 127.7 (2C), 125.0, 124.0, 116.8, 81.0, 59.7, 52.8, 33.9, 28.3;

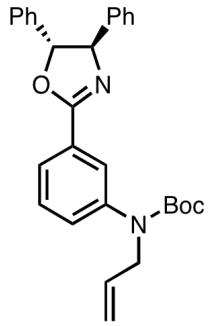
***Tert-butyl allyl-5-((4R,5R)-4,5-diphenyloxazoline)-2-methoxyphenylcarbamate,* 302a**



Methanesulfonyl chloride (0.12 mL, 1.6 mmol) was added drop-wise to a solution of **301a** (0.50 g, 1.0 mmol) and triethylamine (0.42 mL, 3.0 mmol) in methylene chloride (20 ml) at 0 °C. The reaction mixture was stirred at room temperature for 24 hours then quenched with $NH_4Cl_{(aq)}$ (50 mL). The phases were separated and the aqueous layer was further extracted with methylene chloride (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure to give the crude amide. Purification by flash column chromatography, eluting with 4:1 petrol:ethyl acetate, afforded oxazoline **302a** (0.41 g, 84 %) as a cream amorphous solid.

R$_f$: 0.62 (2:1 Pet:EtOAc); **Mpt**: 102-104 °C (petrol:ethyl acetate); **[α]$_D^{28}$**: - 28.2 (c. 1, $CDCl_3$); **MS *m/z (ES$^+$)***: 485.4 (100 %, MH^+); (Found: 485.2450, MH^+. $C_{30}H_{33}O_4N_2$ requires MH^+, 485.2435); **IR ν_{max}(film)/cm^{-1}**: 2974 (CH), 1699 (C=O), 1646 (C=N), 1506 (C-O); A mixture of two Boc-rotamers A and B. **^{1}H (CDCl$_3$, 500 MHz)**: δ 8.03 (d, 1H, *J* 8.0, Ar*H*), 7.97 (brs, 0.25 H, rotamer A, Ar*H*), 7.88 (brs, 0.75 H, rotamer B, Ar*H*), 7.43-7.30 (m, 10 H, Ph*H*), 6.97 (d, 1H, *J* 7.9, Ar*H*), 5.89 (ddt, 1H, *J* 16.0, 10.0, 6.0, NCH_2CHCH_2), 5.40 (d, 1H, *J* 6.5, PhC*H*O), 5.21 (d, 1H, *J* 6.5, PhC*H*N), 5.11 (d, 1H, *J* 16.0, CHC*H*) 5.06 (d, 1H, *J* 10.0, CHC*H*), 4.27 (brs, 1H, $NCHCHCH_2$), 4.12 (brs, 1H, $NCHCHCH_2$), 3.91 (s, 3H, OCH_3), 1.51 (bs, 3H, rotamer A, $C(CH_3)_3$) 1.36 (bs, 6H, rotamer B, $C(CH_3)_3$); **^{13}C (CDCl$_3$, 125 MHz)**: δ 163.5, 158.1, 154.9, 142.1, 140.5, 134.2, 131.3, 130.6, 129.6, 128.9, 128.9, 128.5, 127.8, 126.8, 125.8, 120.0, 119.8, 116.9, 116.5, 111.7, 111.0, 89.1, 80.3, 79.8, 79.1, 55.9, 55.6, 53.1, 52.2, 28.3;

***Tert-butyl allyl-3-((4R,5R) -4,5-diphenyloxazoline)phenylcarbamate,* 302b**

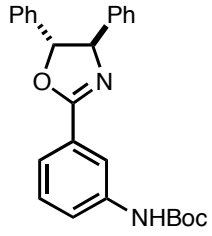


Method A - Methanesulphonyl chloride (0.12 mL, 1.6 mmol) was added drop-wise to a solution of **301b** (0.50 g, 1.0 mmol) and triethylamine (0.44 mL, 3.1 mmol) in methylene chloride (20 mL) at 0 °C. The reaction mixture was stirred at room temperature for 24 hours then quenched with $NH_4Cl_{(aq)}$ (50 mL). The phases were separated and the aqueous layer was further extracted with methylene chloride (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure to give the crude amide. Purification by flash column chromatography, eluting with 4:1 petrol:ethyl acetate, afforded **302b** (0.43 g, 89 %) as a lemon yellow oil which solidified on standing.

Method B – To a solution of **303** (0.5 g, 1.2 mmol) and allyl bromide (0.52 mL, 6.0 mmol) at 0 °C was added NaH (60 % dispersion in mineral oil) (0.096 g, 2.4 mmol). The reaction mixture was warmed to RT and stirred overnight. The reaction was quenched with NH_4Cl (5 mL) and the mixture was washed with methylene chloride (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed by reduced pressure to give the crude allylic amine. Purification by flash column chromatography, eluting with 4:1 petrol:ethyl acetate, afforded oxazoline **302b** (0.51 g, 94 %) as a lemon oil which solidified on standing.

R_f: 0.86 (2:1 Pet:EtOAc); **Mpt**: 90-92 °C (Pet:EtOAc); **$[\alpha]_D^{29}$**: - 19 ($CDCl_3$); **MS *m/z* *(ES$^+$)***: 455.3 (100 %, MH^+); (Found: 455.2320, MH^+. $C_{29}H_{31}O_3N_2$ requires MH^+, 455.2329); **IR ν_{max}(film)/cm^{-1}**: 2922 (s, CH), 1702 (s, C=O), 1650 (C=N); **^{1}H ($CDCl_3$, 300 MHz)**: δ 7.99 (s, 1H, Ar*H*), 7.94-7.90 (m, 1H, Ar*H*), 7.39-7.24 9 (m, 12H, Ar*H* and Ph*H*), 5.88 (ddt, 1H, *J* 17.0, 10.0 and 6.0, NCH_2CHCH_2), 5.37 (d, 1H, *J* 7.5, PhC*H*O), 5.19 (d, 1H, *J* 7.5, PhC*H*N), 5.17-5.09 (m, 2H, NCH_2CHCH_2), 4.24 (d, 2H, *J* 6.0, NCH_2CHCH_2), 1.43 (s, 9H, $C(CH_3)_3$); **^{13}C ($CDCl_3$, 75 MHz)**: δ 162.6, 153.3, 142.0, 140.9, 139.4, 133.0, 128.9, 127.9, 127.8, 127.7, 127.4, 127.1, 126.8, 125.7, 125.4, 124.9, 124.7, 115.7, 88.1, 79.7, 78.0, 51.7, 27.3;

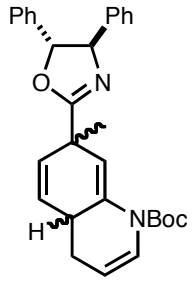
***Tert-butyl 3-((4R,5R)-4,5-diphenyloxazoline)phenylcarbamate,* 303**



To a solution of **248** (1.0 g, 3.1 mmol) and Et_3N (0.66 mL, 4.7 mmol) in 1,4-dioxane:water (8mL:4mL) was added di-*tert*-butyl dicarbonate (1.04 g, 4.7 mmol). The reaction mixture was left to stir overnight. The reaction mixture was then diluted with methylene chloride and washed with brine. The phases were separated and the aqueous layer was further washed with methylene chloride (2 x 20 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure to give the crude amine. Purification by flash column chromatography, eluting with 2:1 petrol:ethyl acetate, afforded **303** (1.28 g, 97 %) as a pale yellow foam.

R_f: 0.7 (2:1 Pet:EtOAc); **^{1}H ($CDCl_3$, 500 MHz)**: δ 7.92 (s, 1H, Ar*H*), 7.74 (d, 7.5, Ar*H*), 7.60 (m, 1H, Ar*H*), 7.37-7.18 (m, 11H, Ar*H* and Ph*H*), 6.46 (s, 1H, N*H*), 5.35 (d, 1H, *J* 7.5, PhC*H*O), 5.11 (d, 1H, *J*, 7.5, PhC*H*N), 1.45 (s, 9H, C(CH_3)$_3$);

***7-((4R,5R)-4,5-Diphenyl-oxazoline)-7-methyl-4a,7-dihydro-4H-quinoline-1-carboxylic acid tert-butyl ester*, 304**

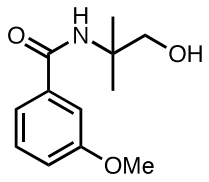


General procedure 6a was used employing oxazoline **302b** (100 mg, 0.22 mmol), *t*-BuLi (0.47 mL, 0.44 mmol in pentane), DMPU (0.16 mL, 1.32 mmol) in THF, the reaction was stirred for 5 mins at –78 °C then the reaction was warmed to -40 °C. MeI (0.027 mL, 0.44 mmol) quench after 10 min. Purification by flash column chromatography, eluting with 9:1 Petrol: EtOAc, afforded cyclised product **304** (38 mg, 39 %), as a clear colourless oil.

R_f: 0.38 (4:1 Pet:EtOAc); **MS**: *m/z (ES$^+$)* 491 (100 %, MNa^+); (Found: 469.2498, MH^+. $C_{30}H_{33}O_3N_2$ requires *MH^+*,469.2486); **IRν$_{max}$(film)/cm^{-1}**: 2973 (C-H), 1704 (C=O), 1649 (C=N); **^{1}H (C_6D_8, 400 MHz 90 °C)**: δ 7.31-7.00 (m, 11H, Ph*H* and H2), 6.47-6.38 (m, 1H, H8), 6.02-5.96 (m, 1H, H6), 5.65-5.57 (m, 1H, H5), 5.20-5.00 (m, 2H, PhC*H*O and PhC*H*N), 4.75-4.68 (m, 1H, H3), 2.76 (m, 1H, H4a), 2.15-2.00 (m, 2H, H4), 1.81-1.74 (m, 3H, CH_3), 1.43-1.41 (m, 9H, C(CH_3)$_3$); **^{13}C (C_6D_8, 400 MHz 90 °C)**, δ 170.7, 162.5, 151.4, 143.4, 141.8, 129.0, 128.8, 127.4, 127.0, 126.9, 126.0, 125.7, 124.1, 119.5, 119.0, 104.0, 89.1, 80.9, 79.2, 41.3, 33.5, 31.8, 30.1, 28.1;

6.4 Experimental details for Chapter 3

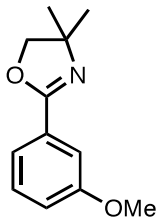
***N-(1-Hydroxy-2-methylpropan-2-yl)-3-methoxybenzamide,* 307**



A solution of 2-amino-2-dimethyl-1-propanol (13.60 mL, 142.29 mmol) in methylene chloride (30 mL) was added drop-wise to a stirred solution of 3-methoxy benzoyl chloride (5 mL, 35.58 mmol) in methylene chloride (30 mL). The reaction mixture was stirred for 96 hours. Water (50 mL) was added. The organic phase was separated and the aqueous phase was further washed with methylene chloride (30 mL x 2). The combined organics were dried (Na_2SO_4) then the solvent was removed under reduced pressure to give the crude amide. Purification by flash column chromatography, eluting with 4:1 petrol:ethyl acetate, afforded **307** (7.61 g, 94 %) as colourless needles.

R_f: 0.15 (2:1 Pet:EtOAc); **Mpt**: 84-86 °C (petrol:ethyl acetate); **MS *m/z (ES$^+$)***: 224.2 (3 %, MH^+), 246.2 (100 %, MNa^+); (Found: 224.1282, MH^+. $C_{12}H_{18}O_3N_1$ requires MH^+, 224.1281); **IR υ_{max}(film)/cm^{-1}**: 3315 (brs, OH), 2933 (CH), 1637 (C=O); **^{1}H (CDCl$_3$, 300 MHz)**: δ 7.36-7.31 (m, 2H, Ar*H*), 7.23 (dt, 1H, *J* 8.0 and 1.0, Ar*H*), 7.05 (dd, 1H, *J* 8.0 and 1.0, Ar*H*), 6.20 (brs, 1H, CN*H*), 4.72 (m, 1H, CH_2O*H*), 3.86 (s, 3H, OCH_3), 3.70 (d, 2H, *J* 6.0, CH_2OH), 1.42 (s, 6H, $C(CH_3)_2$); **^{13}C (CDCl$_3$, 75 MHz)**: δ 168.2, 159.9, 136.3, 129.6, 118.6, 117.8, 112.4, 70.7, 56.5, 55.5, 24.8;

***4,5- 3-methoxyphenyl)-4,4-dimethyloxazoline,* 308**

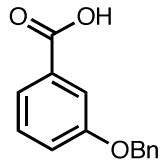


Thionyl chloride (2.06 mL, 28.46 mmol) was added drop-wise with stirring to **307** (1.0 g, 4.48 mmol). The reaction mixture was stirred for 10 min. Diethyl ether (30 mL) and 2M NaOH (30 mL) was added and reaction mixture was stirred for a further 25 min. The organic layer was separated and the aqueous layer was further washed with diethyl ether (30 mL x 2). The combined organic layers were dried (Na_2SO_4) then the solvent was removed under reduced pressure to afford **308** (0.77 g, 84 %) as a clear colourless oil. Further purification was not required.

R_f: 0.55 (2:1 Pet:EtOAc); **MS *m/z (ES$^+$)***: 206.2 (100 %, MH^+); (Found: 206.1178, MH^+. $C_{12}H_{16}O_2N_1$ requires MH^+, 206.1176); **IR ν_{max}(film)/cm^{-1}**: 2963 (CH), 1646

(C=N), 1584 (C-O); **^{1}H (CDCl$_3$, 400 MHz)**: δ 7.54 (dt, 1H, *J* 8.0 and 1.5, Ar*H*), 7.47 (dd, 1H, *J* 2.5 and 1.5, Ar*H*), 7.31 (t, 1H, *J* 8.0, Ar*H*), 7.02 (dd, 1H, *J* 8.0 and 2.5, Ar*H*), 4.12 (s, 2H, OC*H*$_2$C(CH$_3$)$_2$), 3.85 (s, 3H, OC*H*$_3$), 1.40 (s, 6H, OCH$_2$C(C*H*$_3$)$_2$); **^{13}C (CDCl$_3$, 75 MHz)**: δ 166.6, 159.5, 129.4, 120.8 (2C), 118.1, 112.6, 79.2, 67.6, 55.5, 28.4;

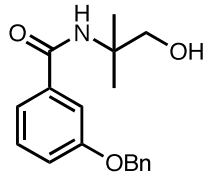
***3-(Benzyloxy)benzoic acid,* 311**



To a solution of 3-hydroxy benzoic acid (20.0 g, 0.14 mol) in a solution of 2M KOH (350 mL, 0.7 mol) was added benzyl bromide (17.6 mL, 0.15 mol). Reaction mixture was stirred for 16 hours at 120 °C. The reaction mixture was cooled and the acidified with 3M HCl. A precipitate formed that was removed by filtration and washed with excess water. The isolated precipitate was dried under reduced pressure until a consistent weight was achieved to afford acid **311** (17.50 g, 53 %) as a white amorphous solid.

R$_f$: 0.53 (2:1 Pet:EtOAc); **Mpt**: 133-135 °C (Water) (lit. 133-137 °C)[136] ; **MS *m/z (ES$^-$)***: 227 (100 %, M-H); (Found: 227.0717, M-H. $C_{14}H_{11}O_3$ requires M-H, 227.0713); **IR ν$_{max}$(film)/cm^{-1}**: 2894 (brs, COOH), 1677 (s, C=O); **^{1}H (CDCl$_3$, 500 MHz)**: δ 8.52-8.01 (brs, 1H, CO$_2$*H*), 7.71 (d, 1H, *J* 7.5, Ar*H*), 7.70 (s, 1H, Ar*H*), 7.45-7.33 (m, 6H, Ar*H*), 7.19 (d, 1H, *J* 7.5, Ar*H*), 5.09 (s, 2H, OC*H*$_2$Ph); **^{13}C (CDCl$_3$, 125 MHz)**: δ 172.0, 158.7, 136.5, 131.1, 129.6, 128.7, 128.1, 127.6, 122.9, 121.0, 115.4, 70.2;

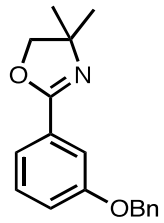
***3-(Benzyloxy)-N-(1-hydroxy-2-methylpropan-2-yl)benzamide,* 312**



Thionyl chloride (10 mL, 0.138 mol) was added to a stirred solution of **311** (1.0 g, 4.38 mmol) in methylene chloride (10 mL) at room temperature. The reaction mixture was stirred for 48 h, and then the solvent was removed by reduced pressure. The crude benzoyl chloride was then dissolved in methylene chloride (50 mL) and added drop-wise to a solution of 2-amino-2-methyl-1-propanol (1.67 mL, 17.50 mmol) in methylene chloride (20 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature then stirred overnight. Water (20 mL) was added and the organic layer was separated. The aqueous layer was then washed with methylene chloride (3 x 20 mL). The combined organic layers were dried (Na$_2$SO$_4$) then the solvent was removed by reduced pressure to give the crude β-hydroxyamide. Purification by flash column chromatography, eluting 2:1

petrol:ethyl acetate, afforded amide **312** (1.08 g, 82 %) as a pale peach amorphous solid. **R_f**: 0.2 (2:1 Pet:EtOAc); **Mpt**: 87-91 °C (petrol:ethyl acetate); **MS *m/z* (ES^+)**: 300.2 (95 %, MH^+); (Found: 300.1598, MH^+. $C_{18}H_{22}O_3N_1$ requires MH^+, 300.1594); **IR ν_{max}(film)/cm^{-1}**: 3327 (NH), 3275 (brs, OH), 2926 (CH), 1627 (s, C=O); **^{1}H ($CDCl_3$, 400 MHz)**: δ 7.40-7.18 (m, 9H, Ar*H* and NH), 7.03 (dd, 1H, *J* 8.0 and 2.5, Ar*H*), 6.17 (brs, 1H, O*H*), 5.01 (s, 2H, OCH_2Ph), 3.60 (s, 2H, CH_2OH), 1.32 (s, 6H, C(CH_3)$_2$); **^{13}C ($CDCl_3$, 125 MHz)**: δ 168.2, 159.0, 136.5, 136.3, 129.7, 128.7, 128.2, 127.6, 119.0, 118.4, 113.4, 70.7, 70.2, 56.5, 24.8;

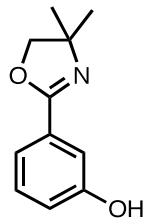
***2-(3-(Benzyloxy)phenyl)-4,4-dimethyloxazoline,* 313**



Thionyl chloride (0.18 mL, 2.48 mmol) was added drop-wise with stirring to **312** (0.10 g, 0.33 mmol). The reaction mixture was stirred for 20 min. Diethyl ether (5 mL) was added and the solution was basified using 20 % NaOH. The organic layer was separated and the aqueous layer was further washed with diethyl ether (10 mL x 3). The combined organic layers were dried (Na_2SO_4) then the solvent was removed under reduced pressure to afford oxazoline **313** (0.063 g, 67 %) as a pale yellow amorphous solid. Further purification was not required.

R_f: 0.66 (2:1 Pet:EtOAc); **Mpt**: 56-58 °C (diethyl ether); **MS *m/z* (ES^+)**: 282.1 (100 %, MH^+); (Found: 282.1501, MH^+. $C_{18}H_{20}O_2N_1$ requires MH^+, 282.1489); **IR ν_{max}(film)/cm^{-1}**: 2922 (CH), 1642 (C=N), 1578 (C-O); **^{1}H ($CDCl_3$, 300 MHz)**: δ 7.62-7.45 (m, 2H, Ar*H*), 7.37-7.20 (m, 6H, Ar*H* and Ph*H*), 7.00 (dd, 1H, *J* 8.0 and 1.0, Ar*H*), 5.01 (s, 2H, OCH_2Ph), 4.02 (s, 2H, OCH_2C(CH_3)$_2$), 1.31 (s, 6H, C(CH_3)$_2$); **^{13}C ($CDCl_3$, 75 MHz)**: δ 160.9, 157.6, 135.7, 128.4, 127.6 (2C), 127.0, 126.5, 120.0, 117.6, 112.7, 78.1, 69.1, 66.6, 27.4;

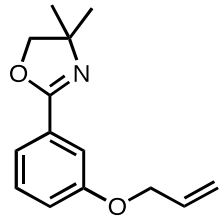
***3-(4,4-dimethyloxazoline)phenol,* 314**



A solution of **313** (0.66 g, 2.3 mmol) in methanol (46 mL), was passed twice through the H-Cube twice using 30mm 10 % Pd/C CatCart® at 1 $mLmin^{-1}$, 50 °C and full H_2. The solvent was removed under reduced pressure to afford oxazoline **314** (0.40 g, 91 %) as a brown crystaline solid.

R_f: 0.26 (2:1 Pet:EtOAc); **Mpt**: 161-163 °C (methanol); **MS *m/z* (ES^+)**: 192 (100 %, MH^+); (Found: 192.1015, MH^+. $C_{11}H_{14}O_2N_1$ requires MH^+,192.1019); **IR ν_{max}(film)/cm^{-1}**: 2966 (OH), 1637 (C=N), 1582 (C-O); **^{1}H ($CDCl_3$, 300 MHz)**: δ 7.40 (d, 1H, *J* 2.0, Ar*H*), 7.34 (d, 1H, *J* 8.0, Ar*H*), 7.17 (t, 1H, *J* 8.0, Ar*H*), 6.96 (dd, 1H, *J* 8.0 and 2.0, Ar*H*), 4.12 (s, 2H, $OCH_2C(CH_3)_2$), 1.38 (s, 6H, $C(CH_3)_2$); **^{13}C ($CDCl_3$, 75 MHz)**: δ 163.4, 156.9, 129.6, 128.2, 119.8, 119.6, 115.4, 79.3, 67.3, 28.2;

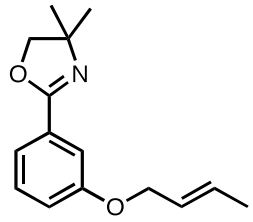
***2-(3-(Allyloxy)phenyl)-4,4-dimethyloxazoline,* 314a**



NaH (60 % in mineral oil) (0.16 g, 4.0 mmol) was added to a solution of **309** (0.30 g, 1.57 mmol), allyl bromide (1.16 mL, 13.40 mmol) in tetrahydrofuran (10 mL) at 0 °C. The reaction mixture was stirred for 10 min then warmed to RT for 4 days. NH_4Cl (30 mL) was added and then extracted with diethyl ether (20 mL x 5). The combined organic layers were dried (Na_2SO_4) then the solvent was removed under reduced pressure to give the crude allyl ether. Purification by flash column chromatography, eluting with 2:1 petrol:ethyl acetate, afforded oxazoline **314a** (0.32 g, 89 %) as a colourless oil.

R_f: 0.36 (4:1 Pet:EtOAc); **MS *m/z* (ES^+)**: 254 (100 %, MNa^+); (Found: 232.1333, MH^+. $C_{14}H_{18}O_2N_1$ requires MH^+, 232.1332); **IR ν_{max}(film)/cm^{-1}**: 2967 (CH), 1637 (C=N), 1583 (C=O); **^{1}H ($CDCl_3$, 400 MHz)**: δ 7.53 (dd, 1H, *J* 8.0 and 1.0, Ar*H*), 7.48 (d, 1H, *J* 1.0, Ar*H*), 7.30 (t, 1H, *J* 8.0 Ar*H*), 7.03 (dd, 1H, *J* 8.0 and 1.0, Ar*H*), 6.05 (ddt, 1H, *J* 17.0, 10.5 and 5.3, CH_2CHCH_2), 5.42 (dd, 1H, *J* 17.0 and 1.5, CH_2CHCH), 5.29 (dd, 1H, *J* 10.5 and 1.5, CH_2CHCH), 4.57 (dt, 2H, *J* 5.0 CH_2CHCH_2), 4.11 (s, 2H, $CH_2C(CH_3)_2$), 1.39 (s, 6H, $C(CH_3)_2$); **^{13}C ($CDCl_3$, 100 MHz)**: δ 162.0, 158.4, 132.9, 129.3, 129.2, 120.8, 118.5, 117.7, 113.5, 79.09, 68.8, 67.5, 28.4;

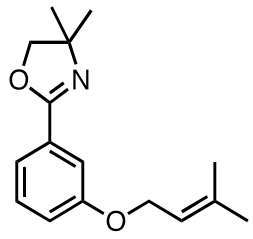
***2-(3-((E)-But-2-enyloxy)phenyl)-4,4-dimethyloxazoline,* 314b**



NaH (60 % in mineral oil) (0.63 g, 15.66 mmol) was added to a solution of **309** (1.0 g, 5.23 mmol), crotyl bromide (2.69 mL, 26.15 mmol) in tetrahydrofuran (30 mL) at 0 °C. The reaction was stirred for 30 min then warmed to room temperature and stirred for a further for 4 days. Aqueous NH_4Cl (60 mL) was added and then extracted with diethyl ether (20 mL x 5). The combined organic layers were dried (Na_2SO_4), then the solvent was removed under reduced pressure to give the allylic ether. Purification by flash column chromatography, eluting with 2:1 petrol:ethyl acetate, afforded oxazoline **314b** (1.12 g, 87 %) as a yellow clear oil.

R_f: 0.73 (2:1 Pet:EtOAc); **MS *m/z (ES$^+$)***: 246.0 (100 %, MH^+); (Found: 246.1487, MH^+. $C_{15}H_{20}O_2N_1$ requires MH^+, 246.1489); **IR ν_{max}(film)/cm^{-1}**: 2965 (CH), 1646 (C=N), 1581 (C-O); **^{1}H (CDCl$_3$, 500 MHz)**: δ 7.53 (d, 1H, *J* 7.0, Ar*H*), 7.47 (s, 1H, Ar*H*), 7.20 (t, 1H, *J* 7.0, Ar*H*), 6.94 (d, 1H, *J* 7.0, Ar*H*), 5.91-5.72 (m, 2H, $OCH_2CHCHCH_3$), 4.50 (d, 2H, *J* 5.5, $OCH_2CHCHCH_3$), 4.10 (s, 2H, $OCH_2C(CH_3)_2$), 1.77 (d, 3H, *J* 6.3, $OCH_2CHCHCH_3$), 1.39 (s, 6H, $C(CH_3)_2$); **^{13}C (CDCl$_3$, 125 MHz)**: δ 162.0, 158.6, 130.7, 129.3, 128.9, 125.8, 120.8, 118.7, 113.4, 79.1, 68.9, 67.6, 28.4, 17.9;

***2-(3-((E)-4-Methylpent-2-enyloxy)phenyl)-4,4-dimethyloxazoline,* 314c**

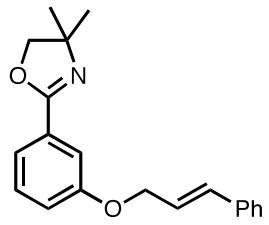


NaH (60 % in mineral oil) (0.63 g, 15.66 mmol) was added to a solution of **309** (1.0 g, 5.23 mmol), prenyl bromide (3.02 mL, 26.15 mmol) in tetrahydrofuran (30 mL) at 0 °C. The reaction mixture was stirred for 30 min then warmed to room temperature and stirred for a further 4 days. $NH_4Cl_{(aq)}$ (60 mL) was added and then extracted with diethyl ether (20 mL x 5). The combined organic layers were dried (Na_2SO_4), then the solvent was removed under reduced pressure to give the crude allylic ether. Purification by flash column chromatography, eluting with 2:1 petrol:ethyl acetate, afforded oxazoline **314c** (1.21 g, 89 %) as a orange clear oil.

R_f: 0.73 (2:1 Pet:EtOAc); **MS *m/z (ES$^+$)***: 260 (80 %, MH^+), 282 (100 %, MNa^+); (Found: 206.1653, MH^+. $C_{16}H_{22}O_2N_1$ requires MH^+, 260.1645); **IR ν_{max}(film)/cm^{-1}**: 2967 (CH), 1646 (C=N), 1581 (C-O); **^{1}H (CDCl$_3$ 500 MHz)**: δ 7.53 (d, 1H, *J* 8.0, Ar*H*), 7.48 (s, 1H, Ar*H*), 7.30 (t, 1H, *J* 8.0, Ar*H*), 7.03 (d, 1H, *J* 8.0, Ar*H*), 5.50 (t, 1H, *J* 7.0,

$OCH_2CHC(CH_3)_2$), 4.55 (d, 2H, *J* 7.0, $OCH_2CHC(CH_3)_2$), 4.11 (s, 2H, $OCH_2C(CH_3)_2$), 1.81 (s, 3H, $OCH_2CHC(CH_3)_2$), 1.75 (s, 3H, $OCH_2CHC(CH_3)_2$), 1.39 (s, 6H, $C(CH_3)_2$); **^{13}C ($CDCl_3$ 125 MHz)**: δ 162.0, 158.8, 138.5, 129.3 (2C), 120.7, 119.4, 118.8, 113.2, 79.1, 67.6, 65.0, 28.4, 25.9, 18.3;

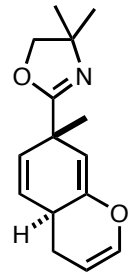
2-(3-(Cinnamyloxy)phenyl)-4,4-dimethyloxazoline, **314d**



NaH (60 % in mineral oil) (0.63 g, 15.66 mmol) was added to a solution of **309** (1.0 g, 5.23 mmol), cinnamyl bromide (3.87 mL, 26.15 mmol) in tetrahydrofuran (30 mL) at 0 °C. The reaction mixture was stirred for 30 min then warmed to room temperature for a further 4 days. $NH_4Cl_{(aq)}$ (60 mL) was added and then extracted with diethyl ether (20 mL x 5). The combined organic layers were dried (Na_2SO_4) then the solvent was removed under reduced pressure to give the crude allylic ether. Purification by flash column chromatography, eluting with 2:1 petrol:ethyl acetate, afforded oxazoline **314d** (0.41 g, 25 %) as a light yellow amorphous solid.

R_f: 0.6 (2:1 Pet:EtOAc); **Mp**: 62-64 °C (petrol:ethyl acetate); **MS *m/z* (*ES*$^+$)**: 308 (90 %, MH^+); (Found: 308.1636, MH^+. $C_{20}H_{22}O_2N_1$ requires MH^+, 308.1645); **IR ν_{max}(film)/cm^{-1}**: 2971 (CH), 1647 (C=N), 1576 (C-O); **^{1}H ($CDCl_3$, 400 MHz)**: δ 7.47 (d, 1H, *J* 8.0, Ar*H*), 7.46 (s, 1H, Ar*H*), 7.33 (d, 2H, *J* 7.5, Ph*H*), 7.27-7.22 (m, 4H, Ar*H* and Ph*H*), 6.99 (d, 1H, *J* 8.0, Ar*H*), 6.66 (d, 1H, *J* 16.0, $OCH_2CHCHPh$), 6.33 (dt, 1H, *J* 16.0 and 5.5, $OCH_2CHCHPh$), 4.66 (d, 2H, *J* 5.5, OCH_2CH), 4.02 (s, 2H, $OCH_2C(CH_3)_2$), 1.31 (s, 6H, $C(CH_3)_2$); **^{13}C ($CDCl_3$, 100 MHz)**: δ 162.0, 158.5, 136.5, 133.1, 129.4, 129.3, 128.6, 127.9, 126.6, 124.2, 121.0, 118.6, 113.6, 79.2, 68.8, 67.6, 28.4;

2-((4aS,7S)-4a,7-dihydro-7-methyl-4H-chromen-7-yl)-4,4-dimethyloxazoline **317a**

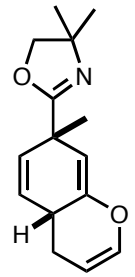


General procedure 6b was followed employing *t*-BuLi (0.51 mL, 1.39 M), **314a** (0.10 g, 0.43 mmol), tetrahydrofuran (6 mL), excess methyl iodide (0.5 mL). Purification by flash chromatography, eluting with 1:9 ethyl acetate:petrol, gave the oxazoline **317a** (26 mg, 25 %) as a clear yellow oil.

R_f: 0.48 (2:1 Pet:EtOAc); **MS *m/z* (*ES*$^+$)**: 246.0 (100 %, MH^+); (Found: 246.1486, MH^+. $C_{15}H_{20}O_2N_1$ requires MH^+, 146.1489); **IR ν_{max}(film)/cm^{-1}**: 2961 (CH), 1653 (C=N); **^{1}H ($CDCl_3$, 400 MHz)**: δ 6.36-6.33 (m, 1H, H2), 5.81-5.68

(m, 2H, H5 and H6), 5.29-5.23 (m, 1H, H8), 4.86 (apparent dq, 1H, *J* 6.0 and 2.0, H3), 3.90-3.89 (m, 2H, CH_2C(CH_3)$_2$), 3.09-2.97 (m, 1H, H4a), 2.28-2.19 (m, 1H, H4), 2.00-1.86 (m, 1H, H4), 1.38 (s, 3H, C(CH_3)), 1.25 (s, 6H, CH_2C(CH_3)$_2$); **^{13}C ($CDCl_3$, 100 MHz)**: δ 168.9, 141.8, 129.2, 126.5, 126.0, 105.4, 101.0, 79.1, 66.9, 40.2, 30.8, 28.2, 28.1, 27.0;

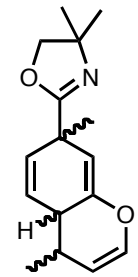
2-((4aR,7S)-4a,7-dihydro-7-methyl-4H-chromen-7-yl)-4,4-dimethyloxazoline **317b**



Also isolated **317b** (2 mg, 2 %) as a clear yellow oil.

R_f: 0.37 (2:1 Pet:EtOAc); **MS *m/z (ES$^+$)***: 246.0 (100 %, MH^+); (Found: 246.1486, MH^+. $C_{15}H_{20}O_2N_1$ requires MH^+, 146.1489); **IR ν_{max}(film)/cm^{-1}**: 2961 (CH), 1653 (C=N); **^{1}H ($CDCl_3$, 400 MHz)**: δ 6.37 (ddd, 1H, *J* 6.0, 2.0 and 1.0, H2), 5.86 (dd, 1H, *J* 9.5 and 6.0, H6), 5.45 (d, 1H, *J* 9.5, H8), 5.42 (d, 1H, *J* 6.0, H5), 4.92 (dt, 1H, *J* 6.0 and 2.0, H3), 3.94 (s, 2H, CH_2C(CH_3)$_2$), 2.75-2.70 (m, 1H, H4a), 2.07-1.95 (m, 2H, H4), 1.40 (s, 3H, C(CH_3)), 1.29-1.28 (m, 6H, C(CH_3)$_2$); **^{13}C ($CDCl_3$, 100 MHz)**: δ 167.6, 152.7, 141.5, 124.7, 121.8, 102.5, 99.8, 79.1, 66.9, 41.6, 40.6, 28.5, 21.8, 19.1;

2-(4-7-dimethyl-4a,7-dihydro-4H-chromen-7-yl)-4,4-dimethyloxazoline**, 318b**



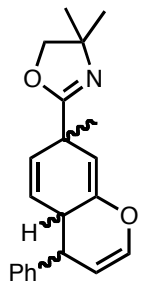
General procedure 6b was followed employing *t*-BuLi (0.72 mL, 0.82 mmol), **314b** (0.10 g, 0.41 mmol), tetrahydrofuran (6 mL), excess methyl iodide (0.5 mL). Purification by flash chromatography, eluting with 1:9 ethyl acetate:petrol, gave the oxazoline **318b** (35.4 mg, 35 %) as a clear colourless oil as a misture of diastereoisomers in a ratio of 1:0.4.

R_f: 0.52 (2:1 Pet:EtOAc); **MS *m/z (ES$^+$)***: 282.1 (100 %, MNa^+); (Found: 282.1457, MNa^+. $C_{16}H_{21}O_2N_1Na_1$ requires MNa^+, *282.1465*); **IR ν_{max}(film)/cm^{-1}**: 2963 (CH), 1652 (C=N); **^{1}H ($CDCl_3$, 400 MHz)**: δ 6.29 (dd, 0.7H, *J* 5.0 and 2.5, A H2), 6.31 (dd, 0.3H, *J* 6.0 and 2.5, B H2), 5.88 (d, 0.7H, *J* 3.0, A H6), 5.90 (d, 0.3H, *J* 3.0, B H6), 5.83 (t, 0.7H, *J* 3.0, A H5), 5.81 (t, 0.3H, *J* 3.0, B H5), 5.32-5.28 (m, 0.7H, A H8), 5.26-5.23 (m, 0.3H, B H8), 4.62 (dd, 0.7H, *J* 6.0 and 1.5, A H3), 4.63 (dd, 0.3H, *J* 6.0 and 1.5, B H3), 3.89 (s, 1.4H, A CH_2C(CH_3)$_2$), 3.88 (s, 0.6H, B CH_2C(CH_3)$_2$), 2.53-2.49 (m, 0.7H, A H4a), 2.61-2.56 (m, 0.3H, B H4a), 2.20-2.06 (m, 0.7H, A H4), 2.20-2.06 (m, 0.3H, B H4), 1.39 (s, 2.1H, A C(CH_3), 1.36 (s, 0.9H, B C(CH_3)), 1.25 (s, 4.2H, A

$CH_2C(CH_3)_2$), 1.25 (s, 1.8H, B $CH_2C(CH_3)_2$), 1.10 (d, 2.1H, *J* 7.0, A $CH(CH_3)$, 1.11 (d, 0.9H, *J* 7.0, $CH(CH_3)$);

^{13}C (CDCl$_3$, 100 MHz) peaks for major isomer only: δ 168.8, 149.3, 140.4, 129.9, 124.0, 108.2, 105.9, 79.2, 68.9, 39.9, 32.4, 28.4 (2C), 28.0, 18.9;

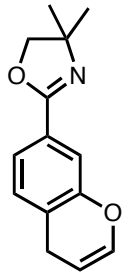
***4,4-Dimethyl-2-(7-methyl-4-phenyl-4a-7-dihydro-4H-chromen-7-yl)oxazoline*, 318d**



General procedure 2b was followed employing *t*-BuLi (0.58 mL, 0.66 mmol), **314d** (0.10 g, 0.33 mmol), tetrahydrofuran (6 mL), excess methyl iodide (0.5 mL). Purification by flash chromatography, eluting with 1:10 ethyl acetate:petrol, gave the oxazoline **318d** (12.2 mg, 10 %) as a clear colourless oil as a mixture of diastereoisomers in a ratio of 1:0.6.

R$_f$: 0.37 (2:1 Pet:EtOAc); **MS *m/z (ES$^+$)***: 322.1 (100 %, MH^+), 344.2 (100 %, MNa^+); (Found: 344.1625, MNa^+. $C_{21}H_{23}O_2N_1Na$ requires MNa^+, 344.1621); **IR ν_{max}(film)/cm^{-1}**: 2964 (CH), 1645 (C=N); Mixture of steroisomers in a 1:0.6 ratio (A:B) **^{1}H (CDCl$_3$, 400 MHz)**: δ 7.37-7.22 (m, 5H, A and B Ph*H*), 6.48 (dd, 0.6H, *J* 6.0 and 2.0, A H2), 6.49 (dd, 0.4H, *J* 6.0 and 2.0, B H2), 5.77 (dt, 0.6H, *J* 10.0 and 2.0, A H6), 5.68 (dt, 0.4H, *J* 10.0 and 2.0, B H6), 5.45 (dd, 0.6H, *J* 10.0 and 2.5, A H5), 5.46 (dd, 0.4H, *J* 10.0 and 2.5, B H5), 5.42 (d, 0.6H, *J* 2.0, A H8), 5.34 (d, 0.4H, *J* 2.0, B H8), 4.83 (m, 1H, H3), 3.93 (s, 1.2H, A $CH_2(CH_3)_2$), 3.88 (s, 0.8H, B $CH_2(CH_3)_2$), 3.31-3.20 (m, 1H, H4), 3.10-3.04 (m, 0.4H, B H4a), 3.02-2.96 (m, 0.6H, A H4a), 1.36 (s, 1.8H, $C(CH_3)$), 1.43 (s, 1.2H, B $C(CH_3)$), 1.29 (s, 3.6H, A $CH_2(CH_3)_2$), 1.24 (s, 2.4H, B $CH_2(CH_3)_2$); **^{13}C (CDCl$_3$, 100 MHz)**: δ 168.8, 167.5, 149.0 (2C), 142.4, 141.5, 129.8, 129.7, 128.7, 128.6 (2C), 128.3 (2C), 128.2 (2C), 127.1, 127.0, 124.4, 124.0, 106.7 (2C), 79.2 (2C), 66.9 (2C), 53.4 (2C), 44.5, 44.2, 40.2 (2C), 38.5, 38.3, 28.2; 28.0;

***2-(4H-Chromen-7-yl)-4,4-dimethyl-oxazoline*, 319a**



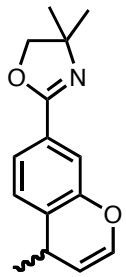
Method A - General procedure 6b was followed employing *t*-BuLi (0.51 mL, 0.86 mmol), **314a** (0.10 g, 0.43 mmol), tetrahydrofuran (6 mL), with excess NH_4Cl (0.5 mL) for the quench. Purification by flash chromatography, eluting with 1:9 ethyl acetate:petrol, afforded the oxazoline **319a** (18 mg, 18 %) as a clear colourless oil.

Method B - General procedure 6b was followed employing *t*-BuLi (0.765 mL, 0.86 mmol), **314a** (0.10 g, 0.43 mmol) in tetrahydrofuran (6 mL). After the stated

time the nitrogen line was replaced with a drying tube and the reaction mixture was allowed to warm to RT overnight. Purification by flash chromatography, eluting with 1:9 ethyl acetate:petrol, afforded the oxazoline **319a** (7 mg, 7 %) as a clear colourless oil.

R_f: 0.39 (2:1 Pet:EtOAc); **MS *m/z* (ES^+)**: 230.0 (100 %, MH^+); (Found: 230.1173, MH^+. $C_{14}H_{16}O_2N$ requires MH^+, *230.1176*); **IR ν_{max}(film)/cm^{-1}**: 2967 (CH), 1649 (C=N), 1574 (C-O), **^{1}H ($CDCl_3$, 300 MHz)**: δ 7.55 (dd, 1H, *J* 8.0 and 2.0, H6), 7.40 (d, 1H, *J* 2.0, H8), 7.02 (d, 1H, *J* 8.0, H5), 6.48 (d, 1H, *J* 6.0, H2), 4.92 (dt, 1H, *J* 6.0 and 3.5, H3), 4.09 (s, 2H, C*H*$_2$C(CH_3)$_2$), 3.42-3.40 (m, 2H, H4), 1.38 (s, 6H, CH_2 C(C*H*$_3$)$_2$); **^{13}C ($CDCl_3$, 75 MHz)**: δ 161.7, 151.4, 140.8, 129.5, 129.3, 127.5, 122.3, 116.4, 100.1, 79.2, 67.6, 28.4, 23.1;

***4,4-Dimethyl-2-(4-methyl-4H-chromen-7-yl)oxazoline*, 319b**

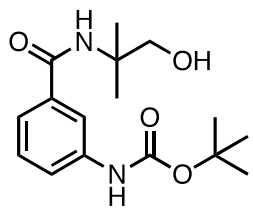


Method A - General procedure 6b was followed employing *t*-BuLi (0.72 mL, 0.82 mmol), **314b** (0.10 g, 0.41 mmol), tetrahydrofuran (6 mL), with excess NH_4Cl (0.5 mL) for the quench. Purification by flash chromatography, eluting with 1:9 ethyl acetate:petrol, gave the oxazoline **319b** (5.9 mg, 6 %) as a clear colourless oil.

Method B - General procedure 6b was followed employing *t*-BuLi (0.72 mL, 0.82 mmol), **314b** (0.10 g, 0.41 mmol), tetrahydrofuran (6 mL). After the stated time the nitrogen line was replaced with a drying tube and the reaction mixture was allowed to warm to RT overnight. Purification by flash chromatography, eluting with 1:9 ethyl acetate:petrol, gave the oxazoline **319b** (22 mg, 22 %) as a clear colourless oil.

R_f: 0.58 (2:1 Pet:EtOAc); **^{1}H ($CDCl_3$, 500 MHz)**: δ 7.60 (dd, 1H, *J* 8.0 and 1.5, H6), 7.42 (d, 1H, *J* 1.5, H8), 7.14 (d, 1H, *J* 8.0, H5), 6.48 (d, 1H, *J* 6.0, H2), 4.90 (dd, 1H, *J* 6.3 and 4.0, H3), 4.10 (s, 2H, C*H*$_2$C(CH_3)$_1$), 3.55-3.50 (m, 1H, H4), 1.38 (s, 6H, CH_2C(C*H*$_3$)$_1$), 1.34 (d, 3H, *J* 7.0, (CH(C*H*$_3$)); **^{13}C ($CDCl_3$, 100 MHz)**: δ 161.2, 158.0, 150.6, 139.4, 128.6, 123.1, 116.3, 106.4, 100.0, 79.1, 67.6, 28.4, 27.8, 25.6;

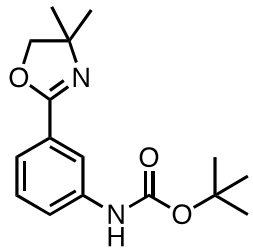
***Tert-butyl 3-(1-hydroxy-2-methylpropan-2-ylcarbamoyl)phenylcarbamate,* 329**



To a solution of **298a** (2.0 g, 8.43 mmol) in methylene chloride (80 mL) was added *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (1.78 mL, 10.0 mmol) and 1-hydroxybenzotriazole (2.61 g, 19.30 mmol). After 1 hour of stirring at RT, triethylamine (1.16 mL, 8.43 mmol) and 2-amino-2-methyl-1-propanol (0.8 mL, 8.43 mmol) were added. The reaction mixture was then left to stir overnight. A white precipitate formed which was collected by vacuum filtration and washed with portions of dichloromethane (20 mL x 3) and water (20 mL x 3). The isolated precipitate was dried under reduced pressure until a consistent weight was achieved to afford amide **329** (1.34 g, 53 %) as a white amorphous solid. Further purification was not required.

R_f: 0.06 (2:1 Pet:EtOAc); **Mpt**: 174-176 °C (methylene chloride:Water); **MS *m/z* (ES^+)**: 309 (95 %, MH^+); (Found: 309.1804, MH^+. $C_{16}H_{25}O_4N_2$ requires MH^+, 309.1809); **IR ν_{max}(film)/cm^{-1}**: 3251 (OH), 2980 (CH), 1715 (C=O), 1567 (C=O); **^{1}H (MeOD, 300 MHz)**: δ 7.70 (s, 1H, Ar*H*), 7.43 (d, 1H, *J* 7.5, Ar*H*), 7.21 (d, 1H, *J* 7.5, Ar*H*), 7.19 (t, 1H, *J* 7.5, Ar*H*), 3.61 (s, 2H, OHCH_2C$(CH_3)_2$), 1.42 (s, 9H, C$(CH_3)_3$), 1.33 (s, 6H, OHCH_2C$(CH_3)_2$); **^{13}C (CDCl$_3$, 400 MHz)**: δ 168.1, 152.6, 138.8, 135.6, 129.3, 121.5, 121.3, 116.9, 80.2 70.8, 56.6, 28.3, 24.8;

***Tert-butyl 3-(4,4-dimethyloxazoline)phenylcarbamate,* 330**

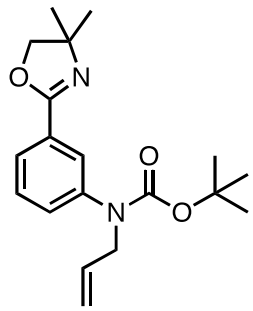


Method A - To a stirred solution of **329** (1.20 g, 3.81 mmol) and triethylamine (1.63 mL, 11.43 mmol) in methylene chloride (50 mL) at 0 °C, was added methanesulphonyl chloride (0.30 mL, 3.81 mmol). The reaction mixture was stirred at room temperature for 24 hours then quenched with $NH_4Cl_{(aq)}$ (50 mL). The phases were separated and the aqueous layer was further extracted with methylene chloride (20 mL x 3). The combined organic layers were dried (Na_2SO_4) then the solvent was removed under reduced pressure to give the crude oxazoline. Purification by flash column chromatography, eluting with 2:1 petrol:ethyl acetate, afforded **330** (0.87 g, 79 %) as colourless needles.

Method B - To a stirred solution of **345** (1 g, 5.25 mmol) in 1,4 dioxane (13.4 mL) and water (6.7 mL) was added triethylamine (1.1 mL, 7.89 mmol) followed by di-*tert*-butyl di-carbonate (1.72 g, 7.88 mmol). The reaction mixture was stirred overnight then concentrated under reduced pressure. The residue was taken up with methylene chloride (20 mL) and washed with brine (20 mL). The organic layer was seperated and the aqueous layer was further washed with methylene chloride (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) then the solvent was removed by reduced pressure to afford the amine **330** (1.36 g, 89 %). Further purification was not required

R_f: 0.5 (2:1 Pet:EtOAc); **Mpt**: 132-134 °C (methylene chloride); **MS *m/z (ES$^+$)***: 291 (60 %, MH^+), 313 (100 %, MNa^+; (Found: 291.1692, MH^+. $C_{16}H_{23}O_3N_2$ requires MH^+, 291.1703); **IR ν_{max}(film)/cm^{-1}**: 3313 (NH), 2970 (CH), 2358 (CH), 1723 (C=N), 1646 (C=O), 1590 (C-O); **^{1}H ($CDCl_3$, 300 MHz)**: δ 7.85 (s, 1H, Ar*H*), 7.55-7.45 (m, 2H, Ar*H*), 7.32 (m, 1H, Ar*H*), 6.61 (brs, 1H, ArN*H*), 4.09 (s, 2H, OCH_2), 1.51 (s, 9H, C(CH_3)$_3$), 1.37 (s, 6H, OC(CH_3)$_2$); **^{13}C ($CDCl_3$, 75 MHz)**: δ 161.8, 152.7, 138.5, 129.1, 128.8, 122.8, 121.2, 118.2, 80.7, 79.2, 67.6, 28.4, 28.3;

***Tert-butyl allyl-3-(4,4-dimethyloxazoline)phenylcarbamate*, 331**

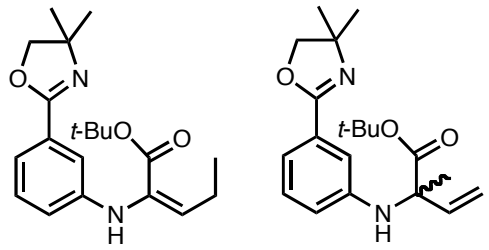


NaH (60 % dispersion in mineral oil) (0.090 g, 2.25 mmol) was added portion-wise to a solution of **330** (0.25 g, 0.86 mmol) and allyl bromide (0.65 mL, 7.50 mmol) in tetrahydrofuran (10 mL) at 0 °C. The reaction mixture was stirred for a further 20 mins at 0 °C then at room temperature for a further 4 hours. $NH_4Cl_{(aq)}$ (30 mL) was added and the aqueous layer was washed with diethyl ether (20 mL x 5). The combined organics were dried (Na_2SO_4) and the solvent was removed under reduced pressure to give the crude allyl amine. Purification by flash column chromatography, eluting with 4:1 petrol:ethyl acetate, afforded **331** (0.25 g, 88 %) as a colourless gum.

R_f: 0.62 (2:1 Pet:EtOAc); **MS *m/z (ES$^+$)***: 331.1 (90 %, MH^+); (Found: 331.2026, MH^+. $C_{19}H_{27}O_3N_2$ requires MH^+, 331.2016); **IR ν_{max}(film)/cm^{-1}**: 2971 (CH), 1700 (C=O), 1649 (C=N), 1585 (C-O); **^{1}H ($CDCl_3$, 300 MHz)**: δ 7.80-7.75 (m, 2H, Ar*H*), 7.38-7.33 (m, 2H, Ar*H*), 5.90 (ddt, 1H, *J* 17.0, 10.6 and 5.5, NCH_2CHCH_2), 5.18-5.12 (m, 2H, NCH_2CHCH_2), 4.24 (d, 2H, *J* 5.7, NCH_2CHCH_2), 4.10 (s, 2H, $OCH_2C(CH_3)_2$), 1.44 (s,

9H, C(C*H*$_3$)$_3$), 1.38 (s, 6H, OCH$_2$C(C*H*$_3$)$_2$); **^{13}C (CDCl$_3$, 75 MHz)**: δ 161.6, 154.3, 142.8, 134.0, 129.5, 128.8, 128.5, 126.2, 125.7, 116.7, 80.6, 79.2, 67.7, 52.8, 28.4, 28.3;

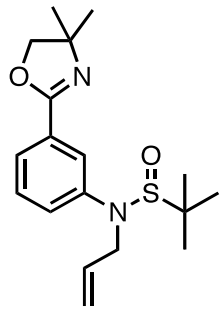
***Tert-butyl 2-(3-(4,4-dimethyloxazoline)phenylamino)pent-2-enoate,* 322a *and Tert-butyl 2-(3-(4,4-dimethyloxazoline)phenylamino)-2-methylbut-3-enoate,* 322b**



332a : 332b (2.5:1)

General procedure 6a was used employing oxazoline **331**(30 mg, 0.09 mmol), *t*-BuLi (0.10 mL, 0.18 mmol), in THF at -78 °C, reaction stirred for 5 mins at -78 °C then warmed to - 40 °C for 30 mins then quenched with MeI (0.5 mL). The reaction was stirred for a further hour at -40 °C then methanol was added. After usual work up afforded a 2.5:1 mixture of **322a** and **322b** (16.7 mg, 54 %) as a clear colourless oil. **^{1}H (CDCl$_3$, 500MHz)**: δ 7.34-7.25 (m, 2H, Ar*H*), 7.15-7.07 (m, 2H, Ar*H*), 6.83 (d, 0.3H, *J* 8.0, B N*H*), 6.68 (t, 1H, *J* 7.5, A CC*H*CH$_2$), 6.61 (d, 0.7H, *J* 7.5, A N*H*), 6.28 (dd, 1H, *J* 17.0 and 10.0, B CC*H*), 5.18 (d, 1H, *J* 17.0, B CCHC*H*), 5.15 (d, 1H, *J* 10.0, B CCHC*H*), 4.08 (s, 2H, A and B OC*H*$_2$), 3.06 (s, 0.9H, B CC*H*$_3$), 2.18 (apparent qn, 1.4H, *J* 7.5, A CHC*H*$_2$), 1.37 (s, 6H, A and B C(C*H*$_3$)$_2$), 1.32 (s, 9H, A and B C(CH$_3$)$_3$), 1.05 (t, 2.1H, *J* 7.5, A CH$_2$CH$_3$);

***N-Allyl-N-(3-(4,4-dimethyloxazoline)phenyl)-2-methylpropane-2-sulfinamide,* 340**

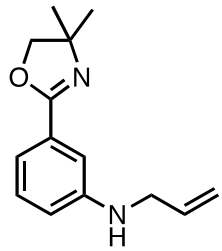


Tert-butyl sulfinyl chloride (0.54 mL, 4.2 mmol) was added drop-wise to a solution of **341** (0.50 g, 2.1 mmol), triethylamine (3.03 mL, 20.10 mmol) in methylene chloride (25 mL) at 0 °C. The reaction was stirred for 12 h at room temperature. Saturated aqueous NaHCO$_3$ solution (20 mL) was added. The organic phase was separated and the aqueous layer was washed with methylene chloride (2 x 20 mL). The combined organic layers were dried (Na$_s$SO$_4$) and the solvent removed by reduced pressure to give the crude sulfinamide. Purification by flash column chromatography, eluting with 2:1 petrol:ethyl acetate, afforded **340** (0.20 g, 40 %) as yellow oil.

R$_f$: 0.23 (2:1 Pet:EtOAc); **MS *m/z (ES$^+$)***: 357.1 (100 %, MNa$^+$); (Found: 357.1620, MNa$^+$. C$_{18}$H$_{26}$O$_2$N$_2$Na$_1$S$_1$ requires MNa$^+$, 357.1607); **IR ν$_{max}$(film)/cm^{-1}**: 2966 (CH),

2360 (CH), 1648 (C=N), 1581 (C-O); **^{1}H (CDCl$_3$, 400 MHz)**: δ 7.69-7.65 (m, 2H, Ar*H*), 7.33-7.27 (m, 2H, Ar*H*), 5.62 (ddt, 1H, *J* 17.0, 10.3 and 5.3, CH_2CHCH), 5.17-5.12 (m, 2H, CH_2CHCH_2), 4.29-4.22 (m, 1H, NC*H*CH), 4.09 (s, 2H, OCH_2C), 4.14-4.06 (m, 1H, NC*H*CH), 1.37 (s, 6H, $OCH_2C(CH_3)_2$), 1.24 (s, 9H, $C(CH_3)_3$); **^{13}C (CDCl$_3$, 125 MHz)**: δ 161.6, 145.2, 133.7, 129.0, 129.0, 124.8, 123.6, 121.4, 118.2, 79.2, 67.7, 60.4, 46.2, 28.4, 23.5;

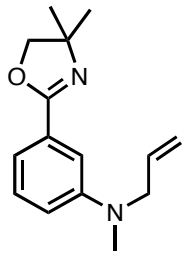
***N-Allyl-3-(4,4-dimethyloxazoline)benzenamine,* 341**



Trifluoroacetic acid (4.64 mL, 60.6 mmol) was added dropwise to **331** (1.0 g, 3.03 mmol) cooled to 0 °C, the reaction was stirred for 1 hour. The reaction mixture was then neutralised with saturated $NaHCO_3$ solution (40 mL). The aqueous mixture was then washed with methylene chloride (3 x 50 mL). The combined organic layers were dried (Na_2SO_4) then the solvent was removed under reduced pressure to afford the amine **341** (0.62 g, 89 %) as a brown oil. Further purification was not required.

R$_f$: 0.46 (2:1 Pet:EtOAc); **MS *m/z (ES$^+$)***: 231.0 (100 %, MH^+); (Found: 231.1488, MH^+. $C_{14}H_{19}O_1N_2$ requires MH^+, 231.1492); **IR ν_{max}(film)/cm^{-1}**: 3285 (brs, NH), 2964 (CH), 2358 (CH), 1643 (C=N), 1584 (C-O); **^{1}H (CDCl$_3$, 400 MHz)**: δ 7.48 (s, 1H, Ar*H*), 7.15-7.29 (m, 2 H, Ar*H*), 6.81 (d, 1H, *J* 8.0, Ar*H*), 5.82 (ddt, 1H, *J* 17.0, 10.0 and 5.0, NCH_2CHCH_2), 5.21 (dd, 1H, *J* 17.0 and 1.5, NCH_2CHCH), 5.14 (dd, 1H, *J* 10.0 and 1.5, NCH_2CHCH), 4.49 (s, 2H, OCH_2), 3.90 (dt, 2H, *J* 5.0 and 1.5, NCH_2CHCH_2), 1.47 (s, 6H, $C(CH_3)_2$); **^{13}C (CDCl$_3$, 100 MHz)**: δ 162.5, 147.9, 135.1, 129.2, 128.8, 117.4, 116.3, 115.7, 112.5, 79.1, 67.4, 46.4, 28.4;

***N-allyl-3-(4,4-dimethyloxazoline)-N-methylaniline,* 342**

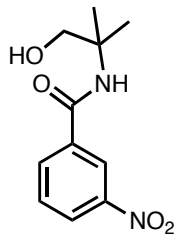


General procedure 6a was used employing oxazoline **340** (20 mg, 0.06 mmol), *n*-BuLi (0.029 mL, 0.07 mmol), in THF at -78 °C, reaction stirred for 5 mins at -78 °C then warmed to 0 °C for 30 mins then quenched with MeI (0.2 mL). The reaction was warmed to RT then methanol was added. After usual work up afforded a **342** (14 mg, 100 %) as a clear colourless oil.

^{1}H (CDCl$_3$, 500MHz): δ 7.29-7.27 (m, 2H, Ar*H*), 7.23 (t, 1H, *J* 8.0, Ar*H*), 6.81 (d, 1H, *J* 8.0, Ar*H*), 5.83 (ddt, 1H, 17.5, 10.0 and 5.0, $CHCH_2$), 5.17-5.13 (m, 2H, CH_2CHCH_2),

4.08 (s, 2H, OCH_2), 3.96-3.95 (m, 2H, NCH_2), 2.97 (s, 3H, NCH_3), 1.38 (s, 6H, C(CH_3)$_2$); **^{13}C (CDCl$_3$, 100MHz)**: δ 162.7, 149.3, 133.4, 129.0, 128.8, 116.4, 116.3, 115.2, 111.8, 79.0, 67.5, 55.1, 38.1, 28.4;

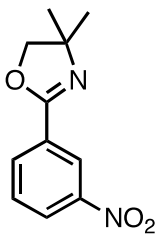
***N-(1-Hydroxy-2-methylpropan-2-yl)-3-nitrobenzamide,* 343**



A solution of 3-nitrobenzoic acid (10.0 g, 59.84 mmol) and thionyl chloride (20 mL, 0.28 mol) was stirred at 70 °C for 12 h. The thionyl chloride was removed by vaccum distillation. The crude benzoyl chloride was then dissolved in methylene chloride (40 mL) and added drop-wise to a solution of 2-amino-2-methyl-1-propanol (22.84 mL, 0.24 mol) in methylene chloride (100 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature then stirred for 8 h. Water (100 mL) was added and the organic layer separated. The aqueous layer was then washed with methylene chloride (3 x 50 mL). The combined organic layers were dried (Na_2SO_4) then the solvent was removed by reduced pressure to afford **343** (13.39 g, 94 %) as white needles. Further purification was not needed.

R_f: 0.08 (1:1 Pet:EtOAc); **Mpt**: 119-120 °C (methylene chloride); **MS *m/z (ES$^-$)***: 237 (100 %, M-H); (Found: 237.0871, M-H. $C_{11}H_{13}N_2O_4$ requires M-H, 237.0880); **IR ν_{max}(film)/cm^{-1}**: 3269 (NH), 3083 (brs, OH), 2915 (CH), 1632 (C=O), 1344 (NO_2); **^{1}H (CDCl$_3$, 400 MHz)**: δ 8.53 (d, 1H, *J* 2.0, Ar*H*), 8.29 (dd, 1H, *J* 8.0 and 2.0, Ar*H*), 8.09 (d, 1H, *J* 8.0, Ar*H*), 7.60 (t, 1H, *J* 8.0, Ar*H*), 6.67 (brs, 1H, CN*H*), 3.67 (s, 2H, OCH_2C(CH_3)$_2$), 1.43 (s, 6H, OCH_2C(CH_3)$_2$); **^{13}C (CDCl$_3$, 100 MHz)**: δ 165.7, 148.1, 136.7, 133.2, 129.8, 126.0, 121.9, 70.0, 56.6, 24.2;

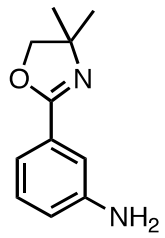
***4,4-dimethyl-2-(3-nitrophenyl)oxazoline,* 344**



Thionyl chloride (30 mL, 0.41 mol) was added to **343** (13.39 g, 56.16 mmol) with vigourous stirring at 0 °C. The reaction mixture was stirred for 30 min then 10 mL of diethyl ether was added. The mixture was basified with 5 M NaOH solution, and the organic layer was separated. The aqueous layer was further extracted with diethyl ether (3 x 50 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed by reduced pressure to give the **344** (11.51 g, 93 %) as light yellow plates. Further purification was not required.

R_f: 0.4 (1:1 Pet:EtOAc); **Mpt**: 81-83 °C (diethyl ether); **MS *m/z* (ES^+)**: 221 (40 %, MH^+); (Found: 221.0922, MH^+. $C_{11}H_{13}N_2O_3$ requires MH^+, *221.092*); **IR ν_{max}(film)/cm^{-1}**: 2961 (CH), 1646 (C=N), 1587 (C-O), 1537 (NO_2), 1435 (NO_2); **^{1}H ($CDCl_3$, 400 MHz)**: δ 8.79 (t, 1H, *J* 2.0, Ar*H*), 8.33 (dd, 1H, 8.0 and 2.0, Ar*H*), 8.28 (dd, 1H, *J* 8.0 and 2.0, Ar*H*), 7.61 (t, 1H, *J* 8.0, Ar*H*), 4.18 (s, 2H, $OCH_2C(CH_3)_2$), 1.42 (s, 6H, $OCH_2C(CH_3)_2$); **^{13}C ($CDCl_3$, 125 MHz)**: δ 160.1, 148.5, 134.0, 129.9, 129.4, 125.7, 123.3, 79.6, 68.1, 28.4; **Elem. Anal.** For $C_{11}H_{12}N_2O_3$: calcd % (found %): C, 59.99 (59.69); H, 5.49 (5.29); N, 12.72 (12.55).

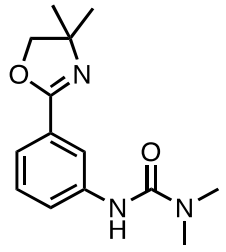
***3-(4,4-dimethyloxazoline)aniline,* 345**



To a solution of **344** (10.0 g, 45.41 mmol) in ethyl acetate (226 mL) and ethanol (133 mL), Pd/C (10 % Pd, 0.50 g) was added under nitrogen. The reaction mixture was stirred under H_2 for 24 h, then filtered through Celite^{TM}. The solvent was removed under reduced pressure to give amine **345** (8.82 g, quant.) as a peach amorphous solid. Further purification was not required.

R_f: 0.13 (2:1 Pet:EtOAc); **Mpt**: 85-88 °C (EtOH:EtOAc); **MS *m/z* (ES^+)**: 213 (100 %, MNa^+); (Found: 213.1009, MNa^+. $C_{11}H_{14}ON_2Na$ requires MNa^+, 213.0998); **IR ν_{max}(film)/cm^{-1}**: 2942 (brs, NH_2), 1723 (C=N), 1653 (C-O); **^{1}H ($CDCl_3$, 500 MHz)**: δ 7.30-7.26 (m, 2H, Ar*H*), 7.13 (t, 1H, *J* 8.0, Ar*H*), 6.76 (d, 1H, *J* 8.0, Ar*H*), 4.07 (s, 2H, $OCH_2C(CH_3)_2$), 3.72 (brs, 2H, $ArNH_2$), 1.36 (s, 6H, $OCH_2C(CH_3)_2$); **^{13}C ($CDCl_3$, 125 MHz)**: δ 161.3, 145.4, 128.2, 127.8, 117.3, 116.8, 113.5, 78.1, 66.4, 27.4.

***3-(3-(4,4-Dimethyloxazoline)phenyl)-1,1-dimethylurea,* 346**

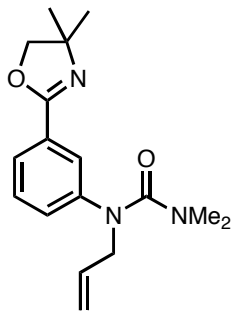


To a solution of **345** (5.0 g, 26.28 mmol) and pyridine (10.6 mL, 0.131 mol) in methylene chloride (100 mL) was added dimethylcarbamoyl chloride (4.80 mL, 52.13 mmol) and 4-dimethylaminopyridine (0.30 g, 2.46 mmol). The reaction mixture was stirred for 34 h. Saturated aqueous solution of NH_4Cl (100 mL) was added and the organic separated. The aqueous layer was washed further with methylene chloride (2 x 50 mL). The combined organics were dried (Na_2SO_4) and the solvent removed under reduced pressure to give the crude urea. Purification by flash

column chromatography, eluting with 4:1 petrol:ethyl acetate, afforded **346** (5.74 g, 84 %) as a white amorphous solid.

R_f: 0.06 (2:1 Pet:EtOAc); **Mpt**: 163-166 °C (Pet:EtOAc); **MS *m/z (ES$^+$)***: 284 (100 %, MNa^+); (Found: 284.1372, MNa^+. $C_{14}H_{19}O_2N_3Na$ requires MNa^+,284.1369); **IR ν_{max}(film)/cm^{-1}**: 3248 (NH), 2970 (CH), 1716, (C=N), 1583 (C-O), 1568 (C=O); **^{1}H (CDCl$_3$, 500 MHz)**: δ 7.87 (d, 1H, *J* 8.0, Ar*H*), 7.70 (s, 1H, Ar*H*), 7.57 (d, 1H, *J* 8.0, Ar*H*), 7.35 (t, 1H, *J* 8.0, Ar*H*), 6.31 (s, 1H ArN*H*), 4.11 (s, 2H, $OCH_2C(CH_3)_2$), 3.03 (s, 6H, $N(CH_3)_2$), 1.38 (s, 6H, $OCH_2C(CH_3)_2$); **^{13}C (CDCl$_3$, 100 MHz)**: δ 162.0, 155.4, 129.1, 128.4, 122.5, 118.9, 113.7, 109.4, 79.2, 67.5, 36.4, 28.5; **Elem. Anal.** For $C_{14}H_{19}N_3O_2$: calcd % (found %): C, 64.35 (64.11); H, 7.33 (7.28); N, 16.08 (15.49);

***1-Allyl-1-(3-(4,4-dimethyloxazoline)phenyl)-3,3-dimethylurea,* 347a**

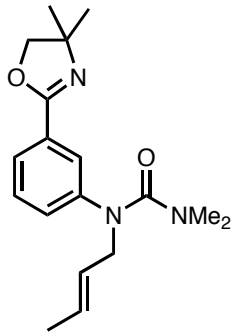


Sodium hydride (60 % in mineral oil) (0.46 g, 11.48 mmol) was added portion-wise to a solution of **346** (1.0 g, 3.82 mmol) and allyl bromide (3.31 mL, 38.25 mmol) in tetrahydrofuran (30 mL) at 0 °C. The reaction mixture was stirred for 1h at 0 °C then warmed to room temperature for a further 12 h. The reaction was quenched with saturated aqueous NH_4Cl solution (15 mL) and partitioned with methylene chloride (30 mL). The organic layer was separated and the aqueous layer was washed with further portions of methylene chloride (2 x 30 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure to give the crude allyl amine. Purification by column chromatography, eluting with 2:1 petrol:ethyl acetate, afforded **347a** (1.15 g, 93 %) as a pale yellow clear gum.

R_f: 0.1 (2:1 Pet:EtOAc); **MS *m/z (ES$^+$)***: 324.2 (100 %, MNa^+); (Found: 324.1676, MNa^+. $C_{17}H_{23}O_2N_3Na_1$ requires MNa^+, 324.1682); **IR ν_{max}(film)/cm^{-1}**: 2964 (CH), 1649 (C=N), 1598 (C=O); **^{1}H (CDCl$_3$, 300 MHz)**: δ 7.69 (d, 1H, *J* 8.0, Ar*H*), 7.62 (s, 1H, Ar*H*), 7.33 (t, 1H, *J* 8.0, Ar*H*), 7.10 (d, 1H, *J* 8.0, Ar*H*), 5.95 (ddt, 1H, *J* 17.0, 10.5 and 5.5, NCH_2CHCH_2), 5.16-5.06 (m, 2H, NCH_2CHCH_2), 4.28-4.25 (m, 2H, NCH_2CHCH_2), 4.11 (s, 2H, $OCH_2C(CH_3)_2$), 2.70 (s, 6H, $N(CH_3)_2$), 1.39 (s, 6H, $OCH_2C(CH_3)_2$); **^{13}C (CDCl$_3$, 100 MHz)**: δ 161.5, 160.9, 145.8, 135.0, 129.5, 129.2, 126.7, 124.2, 123.4, 116.7, 79.2, 67.7, 54.3, 38.0, 28.4;

(

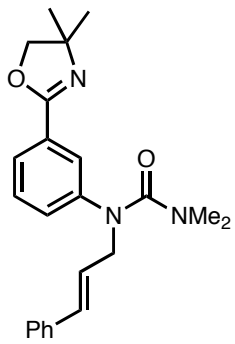
***(E)-1-(But-2-enyl)-1-(3-(4,4-dimethyloxazoline)phenyl)-3,3-dimethylurea,* 347b**



Sodium hydride (60 % in mineral oil) (0.46 g, 11.48 mmol) was added portion-wise to a solution of **346** (1.0 g, 3.82 mmol) and crotyl bromide (1.97 mL, 19.13 mmol) in tetrahydrofuran (30 mL) at 0 °C. The reaction mixture was stirred for 1h at 0 °C then warmed up to room temperature for a further 12 h. The reaction was quenched with saturated aqueous NH_4Cl solution (15 mL) and partitioned with methylene chloride (30 mL). The organic layer was separated and the aqueous layer was washed with further portions of methylene chloride (2 x 30 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure to give the crude crotyl amine. Purification by column chromatography, eluting with 2:1 petrol:ethyl acetate, afforded **347b** (1.06 g, 87 %) as an oil which crystallised on standing to give colourless plates.

R_f: 0.16 (2:1 Pet:EtOAc); **Mpt**: 59-61 °C (Pet:EtOAc); **MS *m/z* (*ES*$^+$)**: 338 (100 %, MNa^+); (Found: 338.1840, MNa^+. $C_{18}H_{25}O_2N_3Na$ requires MNa^+, 338.1839); **IR ν_{max}(film)/cm^{-1}**: 2963 (CH), 1646 (C=O), 1601 (C=N), 1597 (C-O); **^{1}H (CDCl$_3$, 400 MHz)**: δ 7.69-7.62 (m, 2H, Ar*H*), 7.32 (t, 1H, *J* 8.0, Ar*H*), 7.13-7.08 (m, 1H, Ar*H*), 5.63-5.48 (m, 2H, $NCH_2CHCHCH_3$), 4.30-4.18 (m, 2H, $NCH_2CHCHCH_3$), 4.11 (s, 2H, OCH_2C), 2.69 (s, 6H, $N(CH_3)_2$), 1.63 (d, 3H, *J* 5.5, $NCH_2CHCHCH_3$), 1.40 (s, 6H, $C(CH_3)_2$); **^{13}C (CDCl$_3$, 75 MHz)**: δ 161.6, 161.0, 145.8, 145.7, 129.1, 128.1, 127.6, 126.9, 124.1, 123.6, 79.2, 67.7, 53.7, 37.9, 28.4, 17.7;

***1-Cinnamyl-1-(3-(4,4-dimethyloxazoline)phenyl)-3,3-dimethylurea,* 347c**

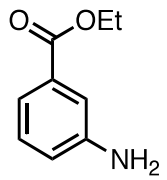


Sodium hydride (60 % in mineral oil) (0.46 g, 11.48 mmol) was added portion-wise to a solution of **346** (1.0 g, 3.82 mmol) and cinnamyl bromide (2.83 mL, 19.13 mmol) in tetrahydrofuran (30 mL) at 0 °C. The reaction mixture was stirred for 1h at 0 °C the nwarmed up to room temperature for a further 12 h. The reaction was quenched with saturated aqueous NH_4Cl solution (15 mL) and partitioned with methylene chloride (30 mL). The organic layer was separated and the aqueous layer was washed with further portions of methylene chloride (2 x 30 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was

removed under reduced pressure to give the crude cinnamyl amine. Purification by column chromatography, eluting with 2:1 petrol:ethyl acetate, afforded **347c** (0.14 g, 10 %) as a brown amorphous solid.

R_f: 0.06 (2:1 Pet:EtOAc); **Mpt**: 68-70 °C (Pet:EtOAc); **IR ν_{max}(film)/cm^{-1}**: 2975 (CH), 1720 (C=O), 1614 (C=N), 1598 (C-O); **^{1}H (CDCl$_3$, 400 MHz)**: δ 8.02 (d, 1H, *J* 7.5, Ar*H*), 7.85 (s, 1H, Ar*H*), 7.36-7.13 (m, 7H, Ar*H* and Ph*H*), 6.43-6.29 (m, 2H, CH_2CHCHPh), 4.42 (d, 2H, *J* 4.0, CH_2CHCH), 4.34 (s, 2H, $CH_2C(CH_3)_2$), 2.69 (s, 6H, $N(CH_3)_2$), 1.46 (s, 6H, $CH_2C(CH_3)_2$); **^{13}C (CDCl$_3$, 100 MHz)**: δ 165.4, 161.1, 145.6, 136.7, 132.3, 130.2, 129.6, 129.0, 128.5 (2C), 127.5, 126.4, 126.3, 125.2, 69.0, 54.9, 53.8, 38.2, 23.1;

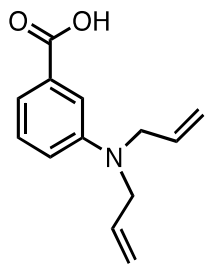
***Ethyl 3-aminobenzoate,* 351**



Following the procedure of Bergbreiter.[137] To a solution of 3-aminobenzoic acid (10.0 g, 72.91 mmol) in ethanol (200 mL) was added 98 % H_2SO_4 (14 mL). The reaction mixture was stirred for 12 h at 70 °C, then cooled and diluted with water (200 mL). The mixture was then taken to pH 10 by slow addition of 4N NaOH solution. The ethanol was then removed under reduced pressure and the remaining aqueous residue was extracted with methylene chloride (2 x 50 mL) and ethyl acetate (2 x 50 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure to give the crude ester **351** (8.45 g, 71 %) as an orange oil. Further purification not required. NMR data consistent with literature.[138]

MS *m/z (ES$^+$)*: 165.9 (100 %, MH^+); (Found:166.0853, MH^+. $C_9H_{12}O_2N_1$ requires *MH^+, 166.0863*); **IR ν_{max}(film)/cm^{-1}**: 3116 (NH_2), 2971 (CH), 1651 (C=O); **^{1}H (CDCl$_3$, 400 MHz)**: δ 7.44 (dd, 1H, *J* 1.0 and 8.0, Ar*H*-6), 7.36 (d, 1H, *J* 1.0, Ar*H*-2), 7.22 (t, 1H, *J* 8.0, Ar*H*-5), 6.86 (ddd, 1H, *J* 1.0 and 8.0, Ar*H*-4), 4.36 (q, 2H, *J* 7.0, OCH_2CH_3), 3.79 (brs, 2H, NH_2), 1.39 (t, 3H, *J* 7.0, OCH_2CH_3); **^{13}C (CDCl$_3$, 100 MHz)**: δ 166.8, 146.4, 131.5, 129.2, 119.7, 119.3, 115.7, 60.9, 14.3;

***3-(Diallylamino)benzoic acid,* 352**



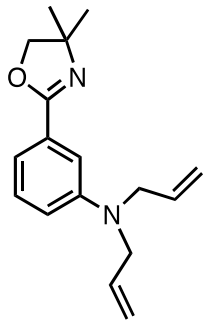
Following the procedure of Chan.[139] A solution of **351** (8.65 g, 52.34 mmol), allyl bromide (26.30 mL, 0.30 mol) and K_2CO_3 (14.47 g, 0.12 mol) in acetonitrile (26 mL) was heated to 80 °C. The reaction mixture was stirred until all the starting material was consumed, then cooled and filtered through Celite^{TM} washing with ethyl acetate. The solvent was removed by reduced pressure to afford ethyl 3-(diallylamino)benzoate (13.24 g, quant.) as an orange oil. Further purification was not required.

R_f: 0.86 (2:1 Pet:EtOAc); **MS *m/z (ES$^+$)***: 268.1 (60 %, MNa^+); (Found: 268.1298, MNa^+. $C_{15}H_{19}O_2N_1Na_1$ requires MNa^+, 268.1308); **IR ν_{max}(film)/cm^{-1}**: 2979 (CH), 1712 (C=O); **^{1}H (CDCl$_3$, 300 MHz)**: δ 7.40 (m, 2H, Ar*H*), 7.36 (t, 1H, *J* 8.0, Ar*H*), 6.86 (d, 1H, *J* 8.0, Ar*H*), 5.87 (ddt, 2H, *J* 17.5, 10.0 and 5.0, NCH_2CHCH_2), 5.22-5.16 (m, 4H, CH_2CHCH_2), 4.36 (q, 2H, *J* 7.0, OCH_2CH_3), 3.99-3.94 (m, 4H, NCH_2CH), 1.38 (t, 3H, *J* 7.0, OCH_2CH_3); **^{13}C (CDCl$_3$, 75 MHz)**: δ 167.3, 148.6, 133.5, 131.2, 129.0, 117.4, 116.6, 116.3, 113.2, 60.8, 52.8, 14.4;

A solution of ethyl 3-(diallylamino)benzoate (12.34 g, 50.30 mmol) and NaOH (13.28 g, 0.33 mol) in methanol (200 mL) was refluxed for 1.5 h. The reaction was cooled to room temperature then the solvent was removed under reduced pressure. The residue was dissolved in water (500 mL) and neutralised with conc. HCl. A precipitated formed which was collected by vacuum filtration. The isolated precipitate was dried under reduced pressure until a consistent weight was achieved to afford **352** (6.79 g, 62 %) as a beige amorphous solid. Further purification was not required.

R_f: 0.1 (EtOAc); **Mpt**: 86-88 °C (water); **MS *m/z (ES$^+$)***: 218.0 (100 %, MH^+); (Found: 218.1189, MH^+. $C_{13}H_{16}O_2N_1$ requires MH^+, 218.1176); **IR ν_{max}(film)/cm^{-1}**: 3315 (OH), 2977 (CH), 1639 (C=O); **^{1}H (CDCl$_3$, 500 MHz)**: δ 13.67-11.01 (brs, 1H, CO_2H), 7.44 (s, 1H, Ar*H*), 7.43 (d, 1H, *J* 7.5, Ar*H*), 7.28 (t, 1H, *J* 7.5, Ar*H*), 6.92 (d, 1H, *J* 7.5, Ar*H*), 5.87 (ddt, 2H, *J* 17.5, 10.0 and 4.5, NCH_2CHCH_2), 5.20 (m, 4H, NCH_2CHCH_2), 3.98 (d, 4H, *J* 4.5, NCH_2CHCH_2); **^{13}C (CDCl$_3$, 125 MHz)**: δ 172.6, 148.6, 133.3, 129.9, 129.2, 118.0, 117.4, 116.3, 113.5, 52.8;

***N,N-Diallyl-3-(4,4-dimethyloxazoline)benzenamine,* 353**



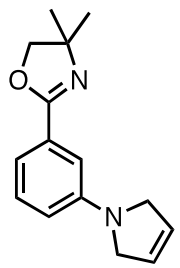
Thionyl chloride (15 mL, 0.207 mol) was added to **352** (3.0 g, 13.81 mmol) with vigorous stirring at room temperature. The reaction mixture was stirred for 48 h, then the excess thionyl chloride was removed by vacuum distillation. The crude benzoyl chloride was then dissolved in methylene chloride (12 mL) and added drop-wise to a solution of 2-amino-2-methyl-1-propanol (5.27 mL, 55.22 mmol) in methylene chloride (30 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature then stirred for 8 h. Water (100 mL) was added and the organic layer was separated. The aqueous layer was then washed with methylene chloride (3 x 50 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed by reduced pressure to give the crude β-hydroxyamide. Purification by flash column chromatography, eluting 2:1 petrol:ethyl acetate, afforded 3-(diallylamino)-N-(1-hydroxy-2-methylpropan-2-yl)benzamide (4.09 g, quant.) as an orange oil.

R_f: 0.26 (2:1 petrol: Pet:EtOAc); **MS *m/z* *(ES$^+$)***: 311.1 (100 %, MNa^+); (Found: 311.1732, MNa^+. $C_{17}H_{24}O_2N_2Na_1$ requires MNa^+, 311.1730); **IR ν_{max}(film)/cm^{-1}**: 3318 (OH), 3078 (NH), 2975 (CH), 1639 (C=O); **^{1}H ($CDCl_3$, 500 MHz)**: δ 7.17 (t, 1H, *J* 8.0, Ar*H*), 7.12 (s, 1H, Ar*H*), 6.88 (d, 1H, *J* 8.0, Ar*H*), 6.77 (d, 1H, *J* 8.0, Ar*H*), 6.31 (brs, 1H, CN*H*), 5.75 (ddt, 2H, *J* 16.0, 11.0 and 4.5, CH_2CHCH_2), 5.16-5.10 (m, 4H, CH_2CHCH_2), 5.10 (brs, 1H, $OHCH_2$), 3.94 (d, 4H, *J* 4.5, CH_2CHCH_2), 3.63, (d, 2H, *J* 5.0, $OCH_2C(CH_3)_2$), 1.37 (s, 6H, $OHCH_2C(CH_3)_2$); **^{13}C ($CDCl_3$, 125 MHz)**: δ 169.3, 149.0, 135.8, 133.5, 129.3, 116.2, 115.2, 113.8, 111.2, 70.8, 56.4, 52.8, 24.9;

Thionyl chloride (7.65 mL, 0.10 mol) was added drop-wise to 3-(diallylamino)-N-(1-hydroxy-2-methylpropan-2-yl)benzamide (4.09 g, 14.2 mmol) with vigorous stirring at 0 ˚C. Reaction mixture was stirred for 1 h then 200 mL of diethyl ether was added. The mixture was basified with 20 % NaOH solution, and then the organic layer was separated. The aqueous layer was further extracted with diethyl ether (3 x 50 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed by reduced pressure to give the crude oxazoline. Purification by flash column chromatography, eluting with 9:1 petrol:ethyl acetate, afforded **353** (2.67 g, 72 %) as an orange glassy solid.

R_f: 0.63 (2:1 Pet:EtOAc); **Mpt**: 32-34 °C (Pet:EtOAc); **MS *m/z (ES$^+$)***: 271.1 (55 %, MH^+), 293.1 (100 %, MNa^+); (Found: 271.1817, MH^+. $C_{17}H_{23}O_1N_2$ requires *MH*$^+$, 271.1805); **IR ν_{max}(film)/cm^{-1}**: 2965 (CH), 1644 (C=N), 1595 (C-O); **^{1}H (CDCl$_3$, 500 MHz)**: δ 7.28 (dd, 1H, *J* 8.0 and 1.0, Ar*H*), 7.25 (d, 1H, *J* 1.0, Ar*H*), 7.21 (t, 1H, *J* 8.0, Ar*H*), 6.79 (d, 1H, *J* 8.0, Ar*H*), 5.86 (ddt, 2H, *J* 16.5, 10.7 and 5.0, NCH_2CHCH_2), 5.20-5.15 (m, 4H, NCH_2CHCH_2), 4.08 (s, 2H, $OCH_2C(CH_3)_2$), 3.96 (dt, 4H, *J* 5.0 and 1.5, NCH_2CHCH_2), 1.38 (s, 6H, $OCH_2C(CH_3)_2$); **^{13}C (CDCl$_3$, 100 MHz)**: δ 162.6, 148.5, 133.6, 129.0, 128.8, 116.4, 116.2, 115.1, 111.7, 79.0, 67.5, 52.5, 28.4;

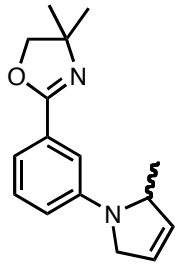
***2-(3-(2,5-Dihydro-1H-pyrrol-1-yl)phenyl)-4,4-dimethyloxazoline,* 355**



Following the procedure described by Majumdar.[140] To a solution of **353** (0.5 g, 1.8 mmol) in methylene chloride (25 mL) was added Grubbs 1st generation catalyst (purchased from Fluka ≤97% (0.074 g, 0.09 mmol) and a catalytic amount of *para*-toluenesulphonic acid. The reaction mixture was stirred for 1 h. The solvent was then removed under reduced pressure to give the crude 2,5-dihydro-pyrrol. Purification by flash column chromatography, eluting with 2:1 petrol:ethyl acetate, afforded **355** (0.41 g, 94 %) as a green crystalline solid.

R_f: 0.46 (2:1 Pet:EtOAc); **Mpt**: 66-68 °C (Pet:EtOAc); **MS *m/z (ES$^+$)***: 243 (60 %, MH^+) 265 (100 %, MNa^+); (Found: 243.1503, MH^+. $C_{15}H_{19}ON_2$ requires MH^+, 243.1492); **IR ν_{max}(film)/cm^{-1}**: 2965 (CH), 1658 (C=N); **^{1}H (CDCl$_3$, 400 MHz)**: δ 7.19-7.17 (m, 2H, ArH), 6.99 (s, 1H, Ar*H*), 6.55-6.50 (m, 1H, Ar*H*), 5.85 (s, 2H, CH_2CH), 4.05 (s, 4H, CH_2CH), 4.00 (s, 2H, $OCH_2C(CH_3)_2$), 1.30 (s, 6H, $OCH_2C(CH_3)_2$); **^{13}C (CDCl$_3$, MHz)**: δ 162.8, 146.9, 129.2, 126.3, 120.0, 115.6, 114.0, 110.6, 79.0, 67.5, 54.6, 28.5;

***4,4-dimethyl-2-(3-(2-methyl-2,5-dihydro-1H-pyrrol-1-yl)phenyl)oxazoline*, 357**

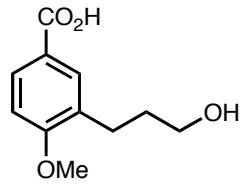


General procedure 6a was used employing oxazoline **355** (30 mg, 0.12 mmol), *t*-BuLi (0.219 mL, 0.24 mmol), in THF at -78 °C, reaction stirred for 5 mins at -78 °C then warmed to 0 °C for 25 mins then quenched with MeI (0.5 mL). The reaction was warmed to RT then methanol was added and the reaction mixture was worked up as usual to give the crude product. Purification by flash column chromatography, eluting with 9:1 petrol:ethyl acetate afforded cyclised product **357** (25 mg, 80 %), as a clear colourless oil.

R_f: 0.4 (9:1 Pet:EtOAc); **^{1}H (CDCl$_3$, 400MHz)**: δ 7.02 (t, 1H, *J* 8.0, Ar*H*), 6.79 (d, 1H, *J* 8.0, Ar*H*), 6.70 (s, 1H, Ar*H*), 6.33 (d, 1H, *J* 8.0, Ar*H*), 5.89-5.87 (m, 2H, C*H*C*H*CH$_2$NAr), 4.09 (s, 2H, OC*H*$_2$C(CH$_3$)$_2$), 4.10-4.00 (m, 1H, C*H*CH$_3$), 3.45-3.36 (m, 2H, CHCHC*H*$_2$N), 1.19-1-15 (m, 3H, C*H*$_3$CH), 0.89 (s, 6H, C(C*H*$_3$)$_2$);

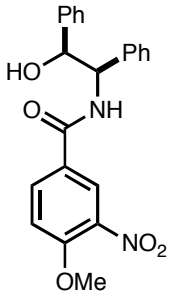
6.5 Experimental details for Chapter 4

***3-(3-Hydroxypropyl)-4-methoxybenzoic acid,* 388**



General procedure 2a was applied to **211** (1.0 g, 4 mmol) to give carboxylic acid **388** (0.81 g, 94 %) as a peach amorphous solid. **R_f**: 0.1 (1:1 Pet:EtOAc); **Mpt**: 144-149 °C (EtOAc); **MS *m/z (ES$^-$)***: 209.3 (100 %, M-H); (Found: 209.0814, M-H. $C_{11}H_{13}O_4$ requires M-H, 209.0819); **IR υ_{max}(film)/cm^{-1}**: 3433 (OH), 1643 (C=O); **^{1}H (DMSO, 500 MHz)**: δ 12.56 (brs, 1H, CO_2H), 7.86 (dd, 1H, *J* 8.5 and 2.0, Ar*H*), 7.78 (d, 1H, *J* 2.0, Ar*H*), 7.09 (d, 1H, 8.5, Ar*H*), 4.53 (s, 1H, O*H*), 3.91 (s, 3H, OCH_3), 3.46 (t, 2H, *J* 6.0, OCH_2), 2.66 (t, 2H, *J* 6.0, ArCH_2), 1.75-1.70 (m, 2H, $CH_2CH_2CH_2$); **^{13}C (DMSO, 125 MHz)**: δ 167.2, 160.7, 130.6, 129.9, 129.2, 122.4,110.2, 60.3, 55.6, 32.3, 26.0;

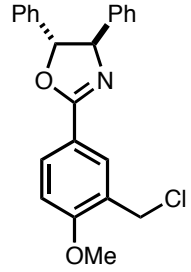
***N-((1R,2S)-2-Hydroxy-1,2-diphenylethyl)-4-methoxy-3-nitrobenzamide,* 391a**



General procedure 1 was applied to 4-methoxy-3-nitrobenzoic acid (2 g, 10.1 mmol) to afford the benzoyl chloride as a pale beige amorphous solid. The crude 4-methoxy-3-nitrobenzoyl chloride (2.15 g, 10.1 mmol) was then mixed with (1*S*,2*R*)-2-amino-1,2-diphenylethanol (2.16 g, 10.1 mmol) and Et_3N (1.48 mL, 10.62 mmol) to afford amide **391a** (2.60 g, 69 %) as a cream amorphous solid.

R_f: 0.69 (2:1 Pet:EtOAc); **Mpt**: 198-200 °C (methylene chloride); **$[\alpha]_D^{24}$**: + 0.5 (c. 1, DMSO); **MS *m/z* (ES$^+$)**: 415.1 (100 %, MNa^+); (Found: 415.1262, MNa^+. $C_{22}H_{20}O_5N_2Na$ requires MNa^+, 415.1264); **IR υ_{max}(film)/cm^{-1}**: 3317 (OH), 1625 (C=O), 1345 (C-NO_2); **^{1}H (DMSO, 500MHz)**: δ 8.82 (d, 1H, *J* 9.0, ArH), 8.22 (s, 1H, Ar*H)*, 7.87 (d, 1H, *J* 9.0, Ar*H*), 7.46-7.38 (m, 5H, Ph*H*), 7.31-7.23 (m, 5H, Ph*H*), 5.51 (d, 1H, *J* 5.0, N*H*), 5.14 (t, 1H, *J* 9.0, PhC*H*OH), 4.93 (dd, 1H, *J* 5.0 and 9.0, PhC*H*NH), 3.95 (s, 3H, OCH_3); **^{13}C (DMSO, 125 MHz)**: δ 162.8, 154.0, 143.5, 141.0, 138.4, 133.4, 128.4, 127.6 (2C), 127.0, 126.8 (2C), 126.3, 124.0, 114.1, 74.5, 59.1, 57.0;

***(4R,5R)-2-(3'-Chloromethyl-4'-methoxy-phenyl)-4,5-diphenyl-oxazoline,* 399g**

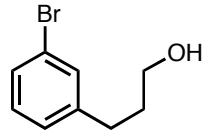


General procedure 3b was applied to 3-(chloromethyl)-4-methoxybenzoic acid (0.50 g, 2.50 mmol) to give the crude oxazoline. Purification by flash column chromatography, eluting with 4:1 petrol:ethyl acetate, afforded oxazoline **399g** (0.64 g, 67%) as a white amorphous solid.

R_f: 0.79 (2:1 Pet:EtOAc); **Mpt**: 108-110 ^oC; **$[\alpha]_D^{19.5}$: -40** (c = 1.115, DCM); **MS *m/z* *(ES$^+$)***: 400.0 (100 %, MNa^+); (Found: 400.1088, MNa^+. $C_{23}H_{20}O_2NClNa$ requires MNa^+, 400.1075); **IR**: ν_{max}(film)/cm^{-1}: 1648 (C=N), 1504 (=C-O-C); **^{1}H (CDCl$_3$, 400MHz)**: 8.22 (d, 1H, *J* 2.0, Ar*H*), 8.15 (dd, 1H, *J* 8.5 and 2.0, Ar*H*), 7.47-7.31 (m, 10H, Ph*H*), 6.99 (d, 1H, *J* 8.5, Ar*H*), 5.44 (d, 1H, *J* 7.5, PhC*H*O), 5.26 (d, 1H, *J* 7.5, PhC*H*N), 4.70 (m, 2H, CH_2), 3.94 (s, 3H, OMe); **^{13}C (CDCl$_3$, 75MHz)**: 163.3, 160.0, 141.9, 140.3, 131.0, 130.7, 128.8, 128.7, 128.3, 127.6, 126.6, 126.0, 125.6, 119.8, 110.5, 88.9, 78.8, 55.7, 41.0;

6.6 Experimental details for Chapter 5

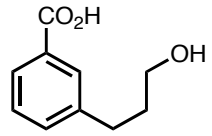
***3-(3-bromophenyl)propan-1-ol,* 407**



n-Butyllithium (8.17 mL of a 2.47 M solution in hexane) was added dropwise to a stirred solution of 2,4 dibromobenzene (2.5 mL, 20.6 mmol) in dry THF (50 ml) at –78 °C. After 0.3 h trimethyloxide (2.68 mL, 41.2 mmol) was added followed directly by dropwise addition of BF_3OEt_2 (2.61 mL, 20.6 mmol) and the mixture stirred at –78 °C for a further 1 h. A saturated solution of $NaHCO_3$ (7 mL) was added. The mixture was washed with water (3 x 25 mL). The combined aqueous was then extracted with diethylether (25 mL). The combined organic was then dried ($NaSO_4$) and solvent was removed under vacuum to give the crude alcohol. Purification by flash column chromatography, eluting with 4:1 petrol:ethyl acetate, afforded alcohol **407** (1.68 g, 38 %) as a brown oil.

R_f: 0.33 (2:1 Pet:EtOAc); **MS *m/z* (EI$^+$)**: 247.1 (100%, MH+$[SH_2]^+$); **IR ν_{max}(CH_2Cl_2)/cm^{-1}**: 3433 (s, OH), 1070 (CBr); **^{1}H (CDCl$_3$, 500MHz)**: δ 7.36 (s, 1H, ArH), 7.32 (d, 1H, *J* 7.5, Ar*H*), 7.17-7.131 (m, 2H, Ar*H*), 3.67 (t, 2H, *J* 6.0, OCH_2), 2.69 (t, 2H, *J* 7.5, ArCH_2), 1.88 (m, 2H, $CH_2CH_2CH_2$); **^{13}C (CDCl$_3$, 125MHz)**: δ 144.2, 131.5, 130.0, 129.0, 127.1, 122.5, 62.0, 33.9, 31.7;

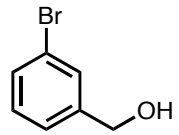
***3-(3-hydroxypropyl)benzoic acid,* 408**



General procedure 2a was applied to **407** (1.40 g, 6.5 mmol) to give carboxylic acid **408** (0.92 g, 78 %) as a brown oil.

R_f: 0.1 (2:1 Pet:EtOAc); **MS *m/z* (ES^-)**: 179.2 (100 %, M-H); **IR $\nu_{max}(CH_2Cl_2)/cm^{-1}$**: 3406 (s, OH), 2936 (COOH), 1700 (C=O); **^1H ($CDCl_3$, 300MHz)**: δ 7.95-7.93 (m, 2H, ArH), 7.48-7.36 (m, 2H, ArH), 3.71 (t, 2H, *J* 5.5, OCH_2), 2.79 (t, 2H, *J* 8.0, ArCH_2), 1.98 (m, 2H, $CH_2CH_2CH_2$); **^{13}C ($CDCl_3$, 125MHz)**: δ 177.3, 171.8, 142.3, 134.0, 130.1, 129.5, 128.6, 61.1, 33.9, 31.8;

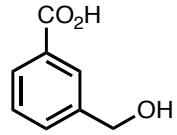
***(3-bromophenyl)methanol,* 410**



n-Butyllithium (8.81 mL of a 2.3 M solution in hexane) was added dropwise to a stirred solution of 2,4 dibromobenzene (2.50 mL, 20.6 mmol) in dry THF (50 mL) at –78 °C. After 0.3 h DMF (anhy.) (1.91 mL, 24.7 mmol) was added and the mixture was stirred for 5 mins at –78 °C. The reaction mixture was allowed to warm up to room temperature over 1 h. A saturated solution of NH_4Cl (5 mL) was added. The ether layer was washed with water (3 x 25 mL), dried ($MgSO_4$) and then reduced under vacuum to give the crude aldehyde. The aldehyde was then taken up in MeOH (65 mL) and cooled to 0 ºC. $NaBH_4$ (1.17 g, 30.9 mmol) was added and the reaction mixture was stirred for 18 h. The reaction was quenched with saturated NH_4Cl solution (5 mL). The solvent was removed under vacuum then dissolved in diethylether (25 mL) and washed with water (3 x 25 mL). The combined aqueous was washed with diethylether (2 x 25 mL). The combined organic was then dried ($NaSO_4$) and solvent was removed under vacuum to give crude product to give the alcohol **410** (3.60 g, 93 %) as a clear colourless oil.

R_f: 0.46 (2:1 Pet:EtOAc); **IR $\nu_{max}(CH_2Cl_2)/cm^{-1}$**: 3339 (s, OH), 1069 (CBr); **^1H ($CDCl_3$, 500MHz)**: δ 7.43 (s, 1H, ArH), 7.33 (d, 1H, *J* 7.5, ArH), 7.18 (d, 1H, 7.5, ArH), 7.15 (t, *J* 7.5, ArH), 4.57 (s, 2H, CH_2OH); **^{13}C ($CDCl_3$, 125MHz)**: δ 143.1, 130.6, 130.1, 129.9, 126.3,122.6, 64.4;

***3-(hydroxymethyl)benzoic acid,* 411**



General procedure 2a was applied to **410** (2.0 g, 20.6 mmol) to give the carboxylic acid **411** (1.0 g, 62 %) as a beige amorphous solid.

R_f: 0.46 (2:1 Pet:EtOAc); **Mpt**: 109-111 °C (EtOAc); **MS *m/z* (ES^-)**: 151.2 (100 %, M-H); **IR $\nu_{max}(CH_2Cl_2)/cm^{-1}$**: 3339 (s, OH); **$^1H$ (DMSO, 500MHz)** δ 13.00-12.80 (brs, 1H, CO_2H), 7.95 (s, 1H, ArH), 7.83 (d, 1H, *J* 13.0, ArH), 7.57 (d, 1H, 13.0, ArH), 7.47 (t, *J* 13.0, ArH), 5.35 (s, 1H, OH), 4.58 (s, 2H, C*H*$_2$OH);

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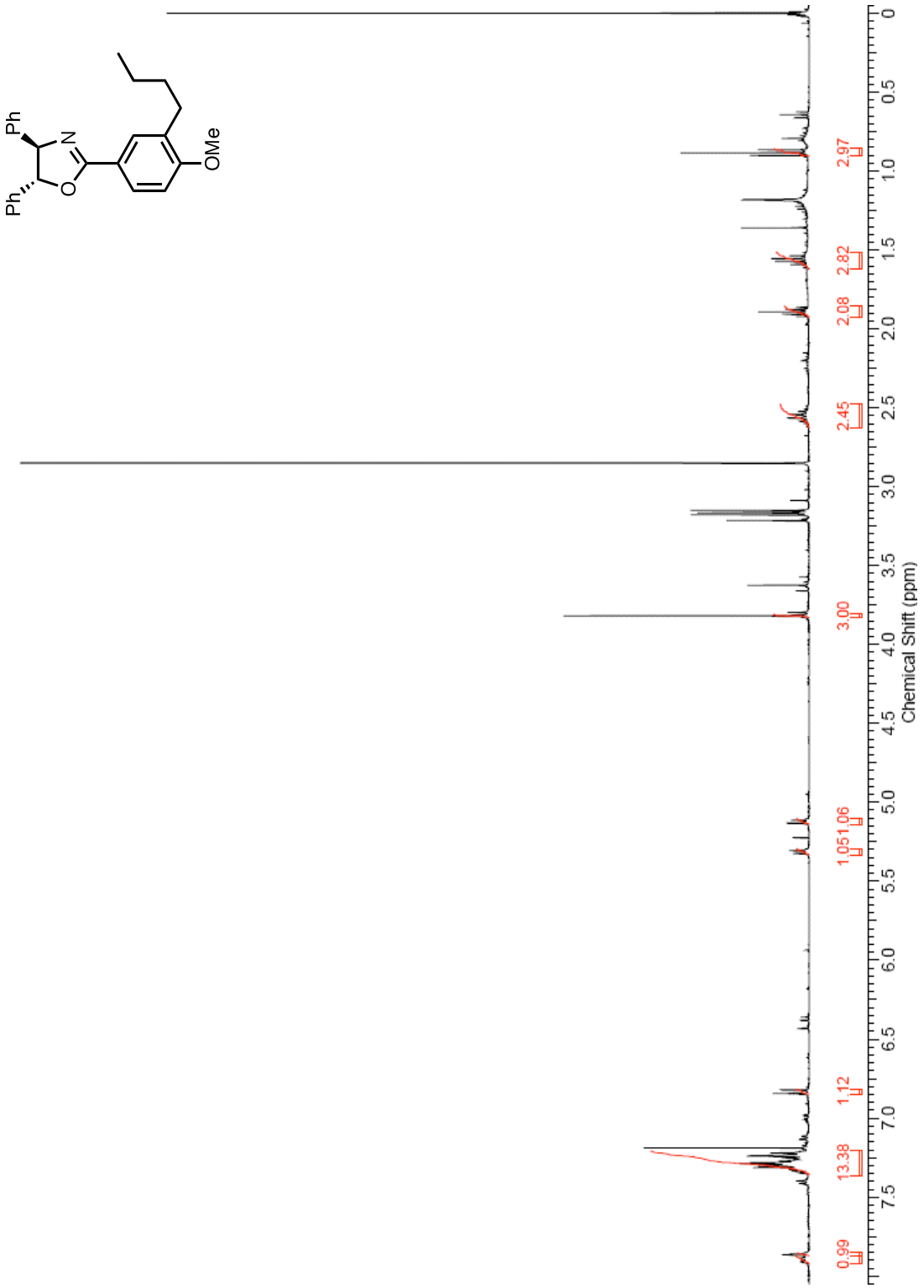
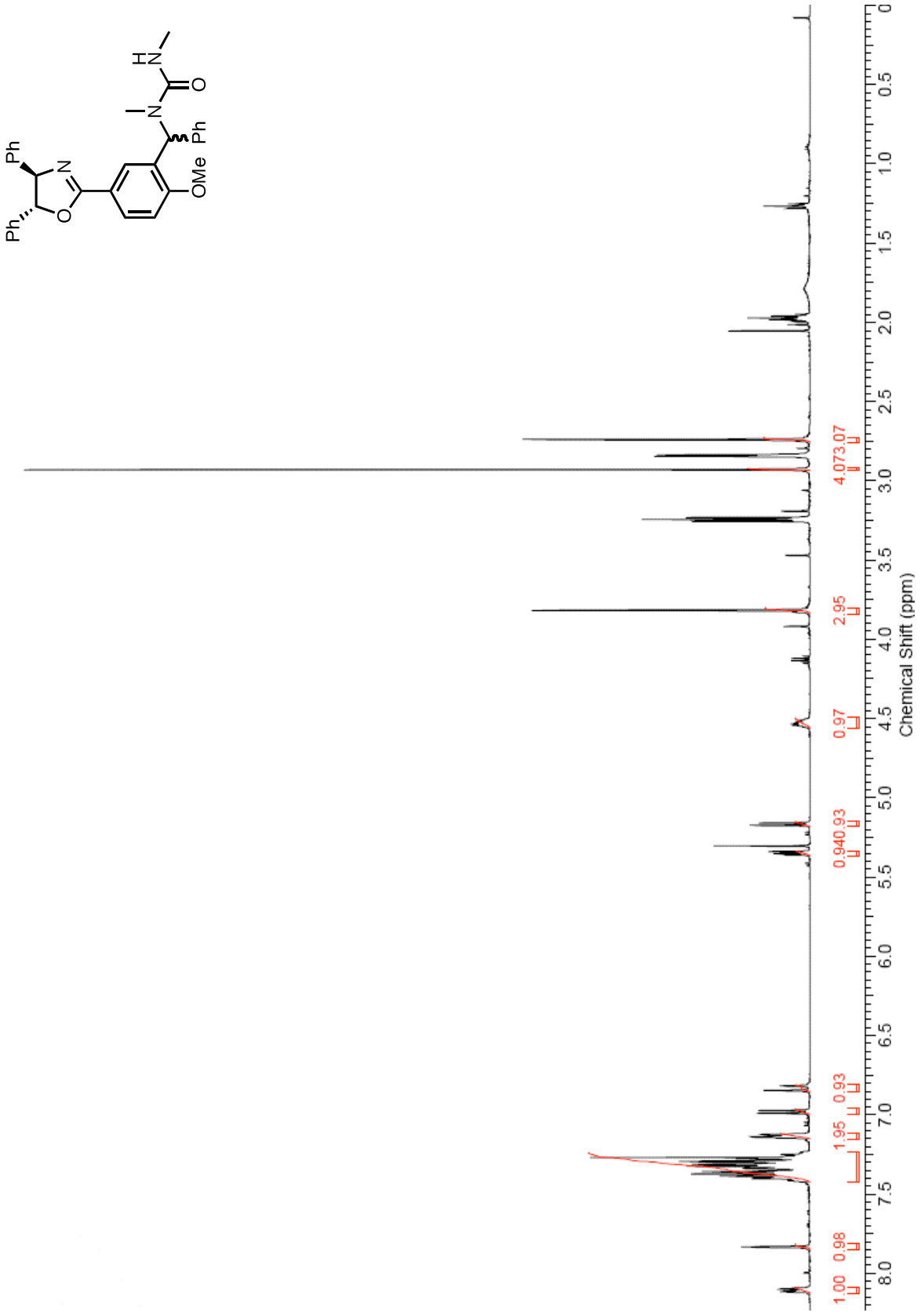
8 Appendix

8.1 Selected HNMR spectra

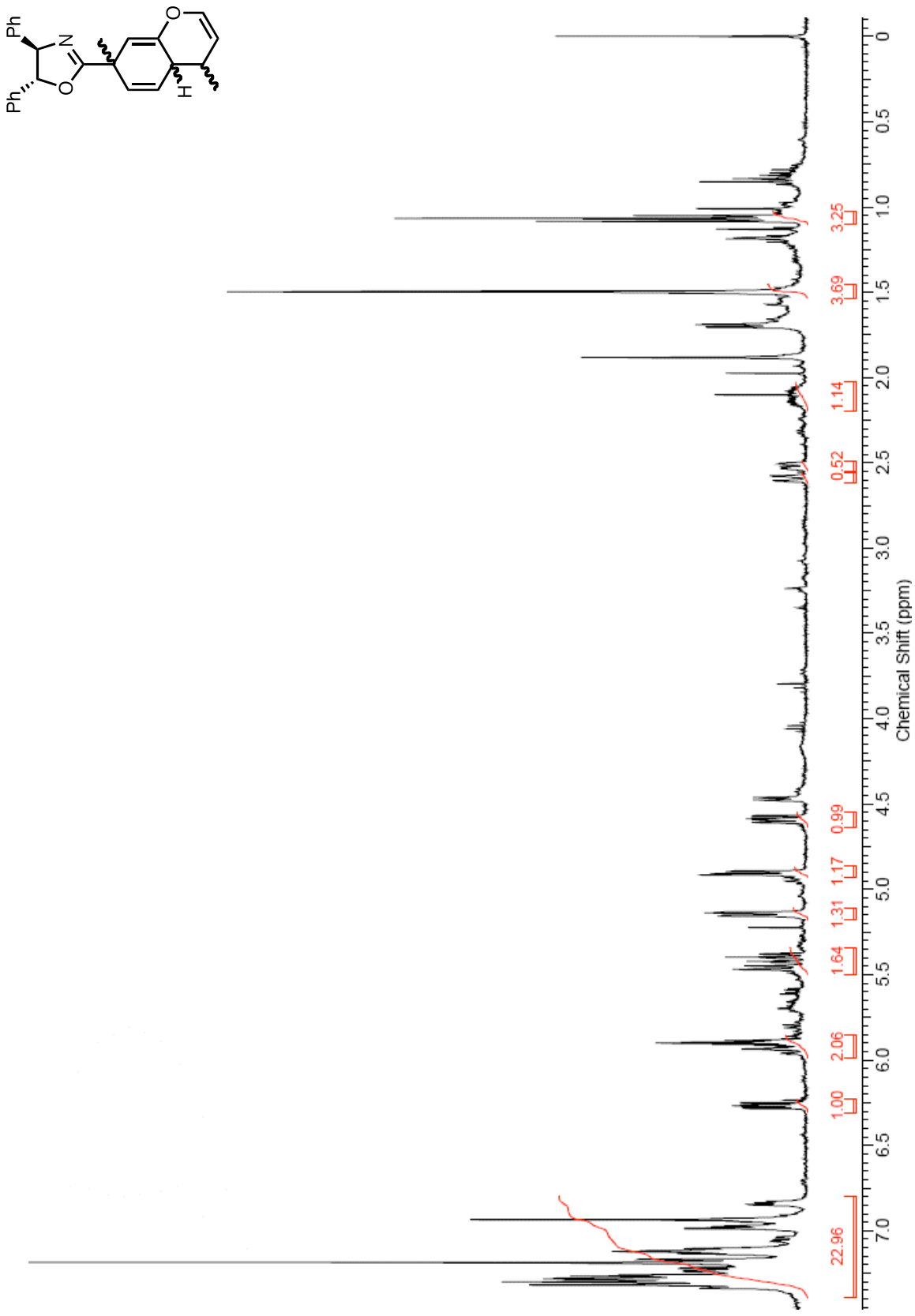
8.1.1 ^{1}H NMR spectra of 218



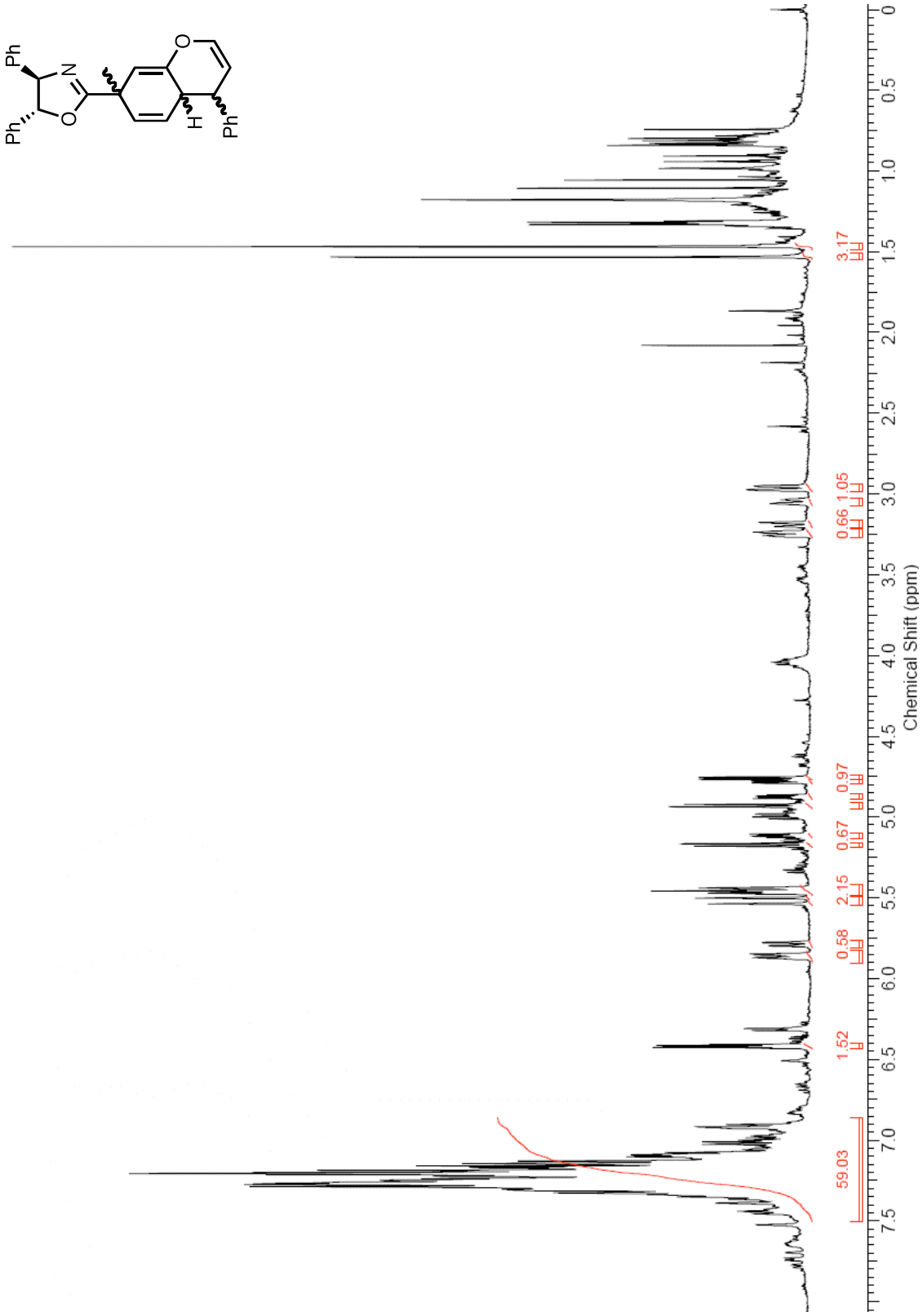
8.1.2 ^{1}H NMR spectra of 256



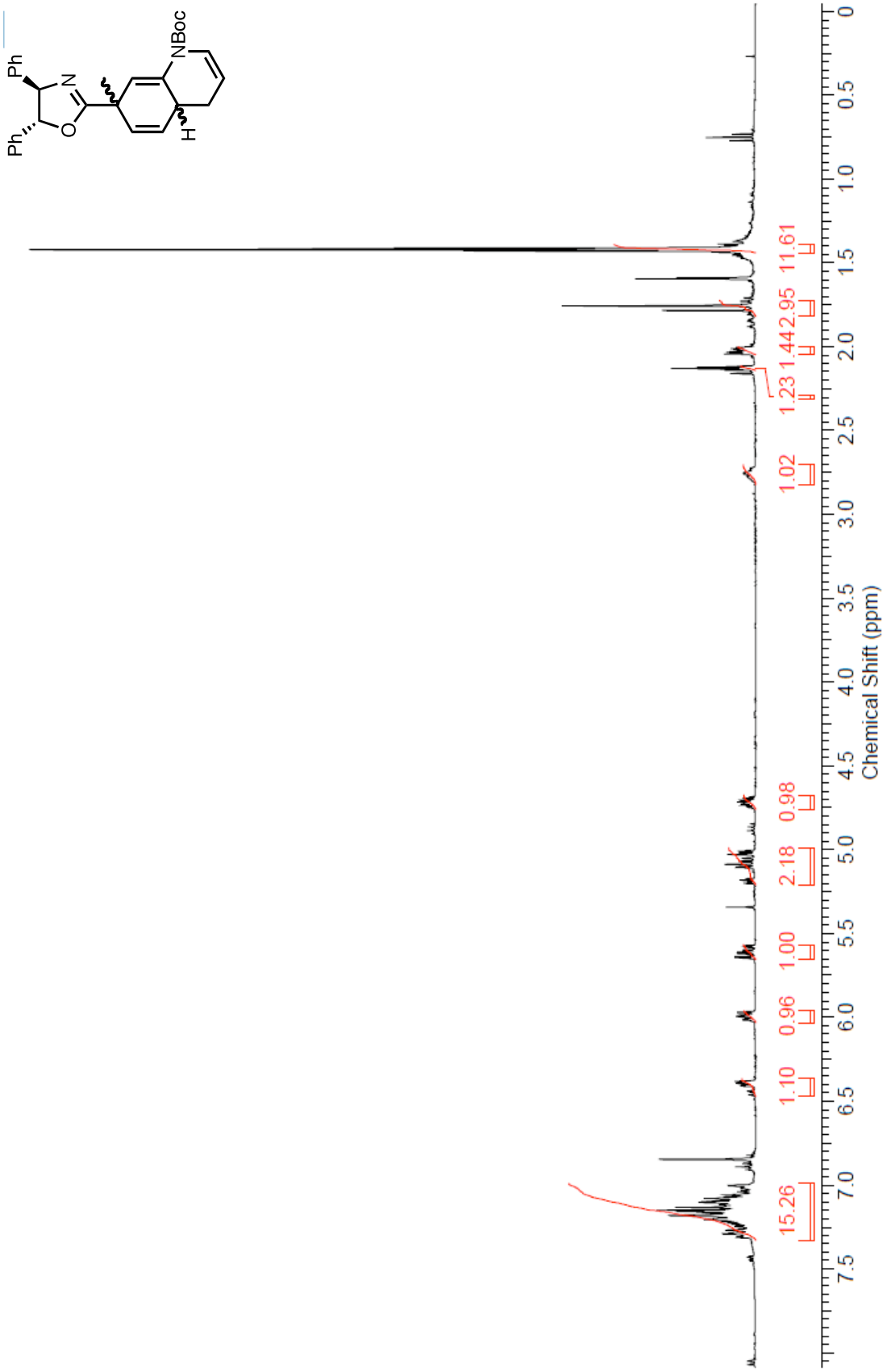
8.1.3 ^{1}H NMR of 293a



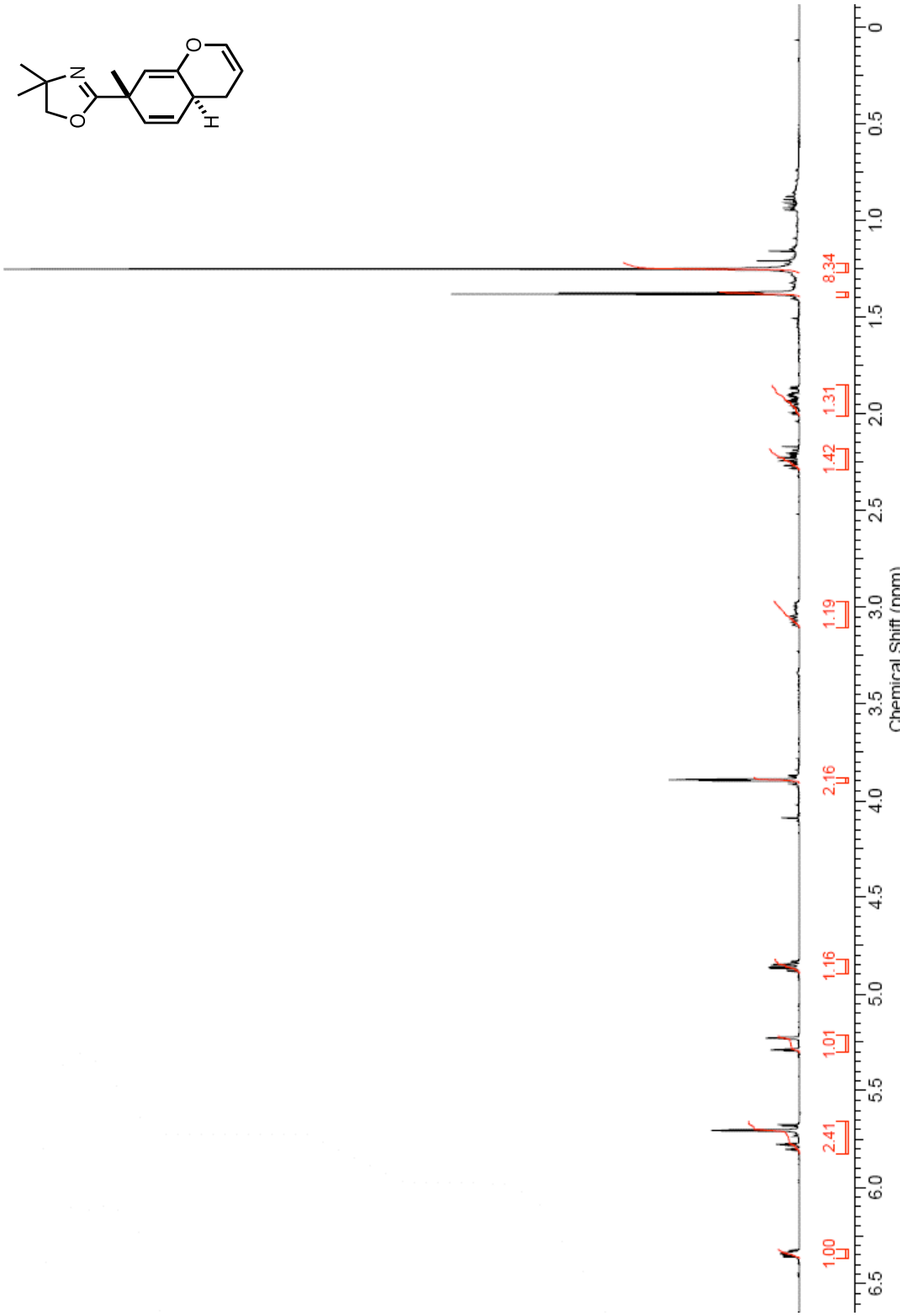
8.1.4 ^{1}HNMR of 293b



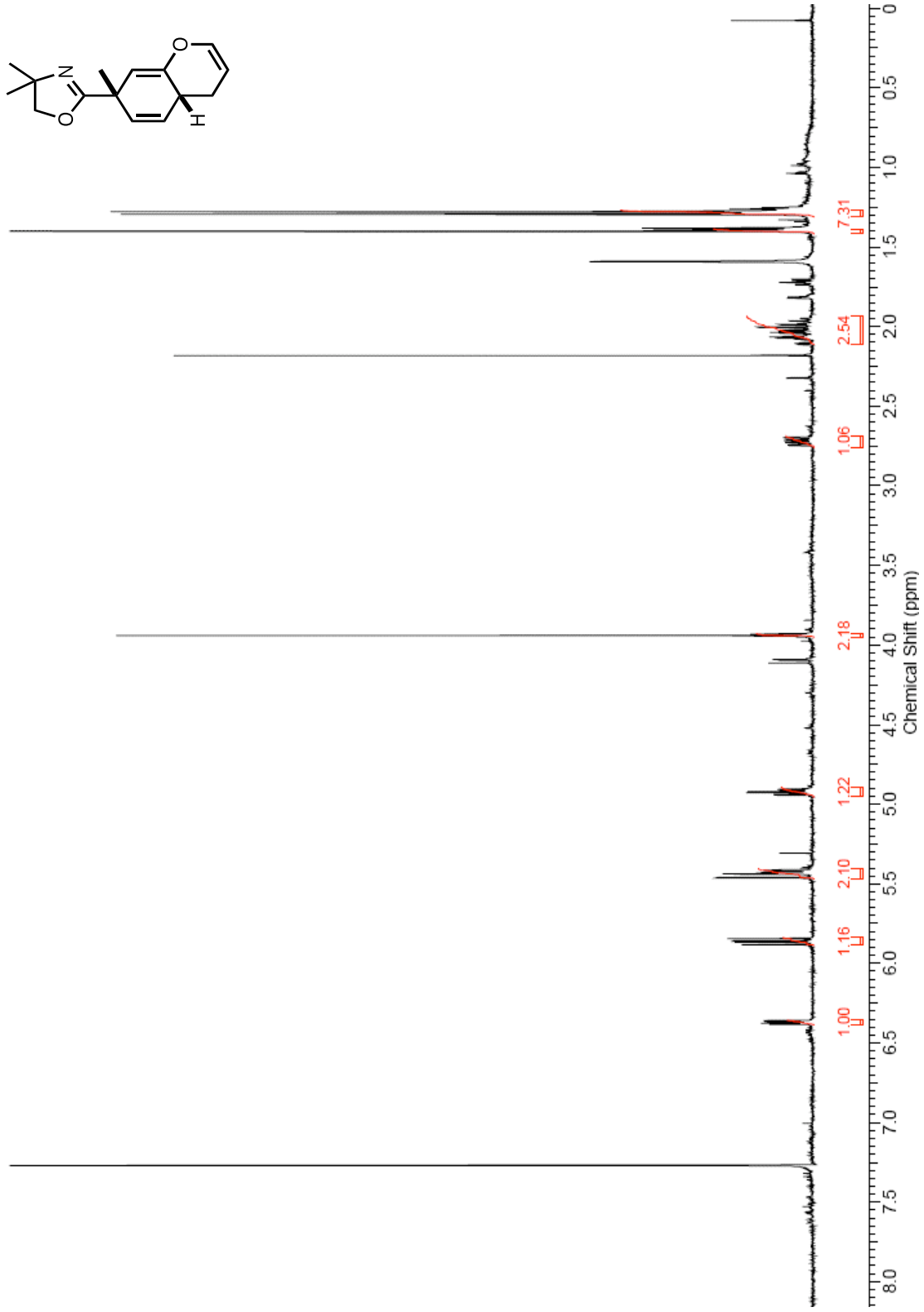
8.1.5 ^{1}H NMR of 304



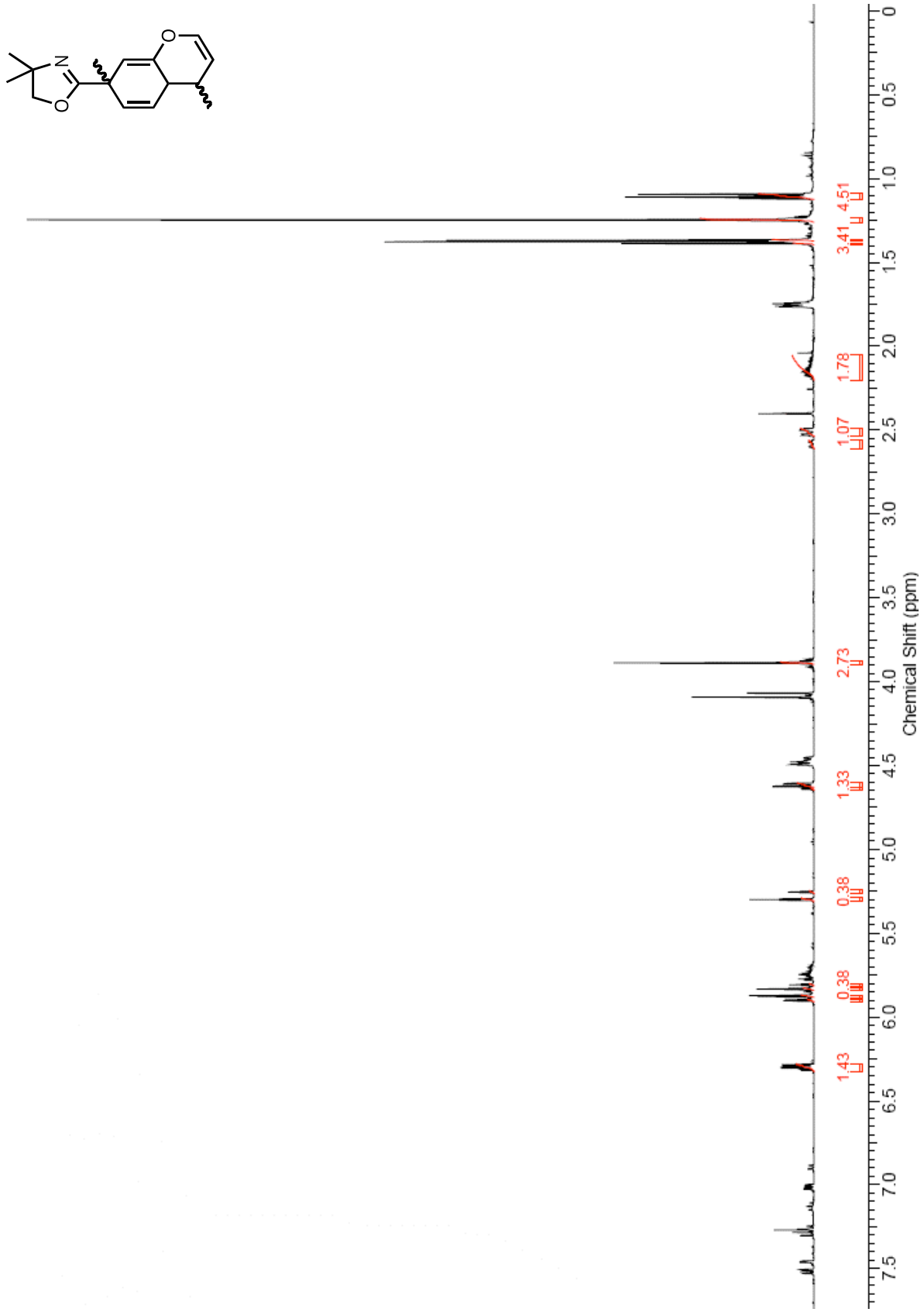
8.1.6 ^{1}H NMR spectra of 317a



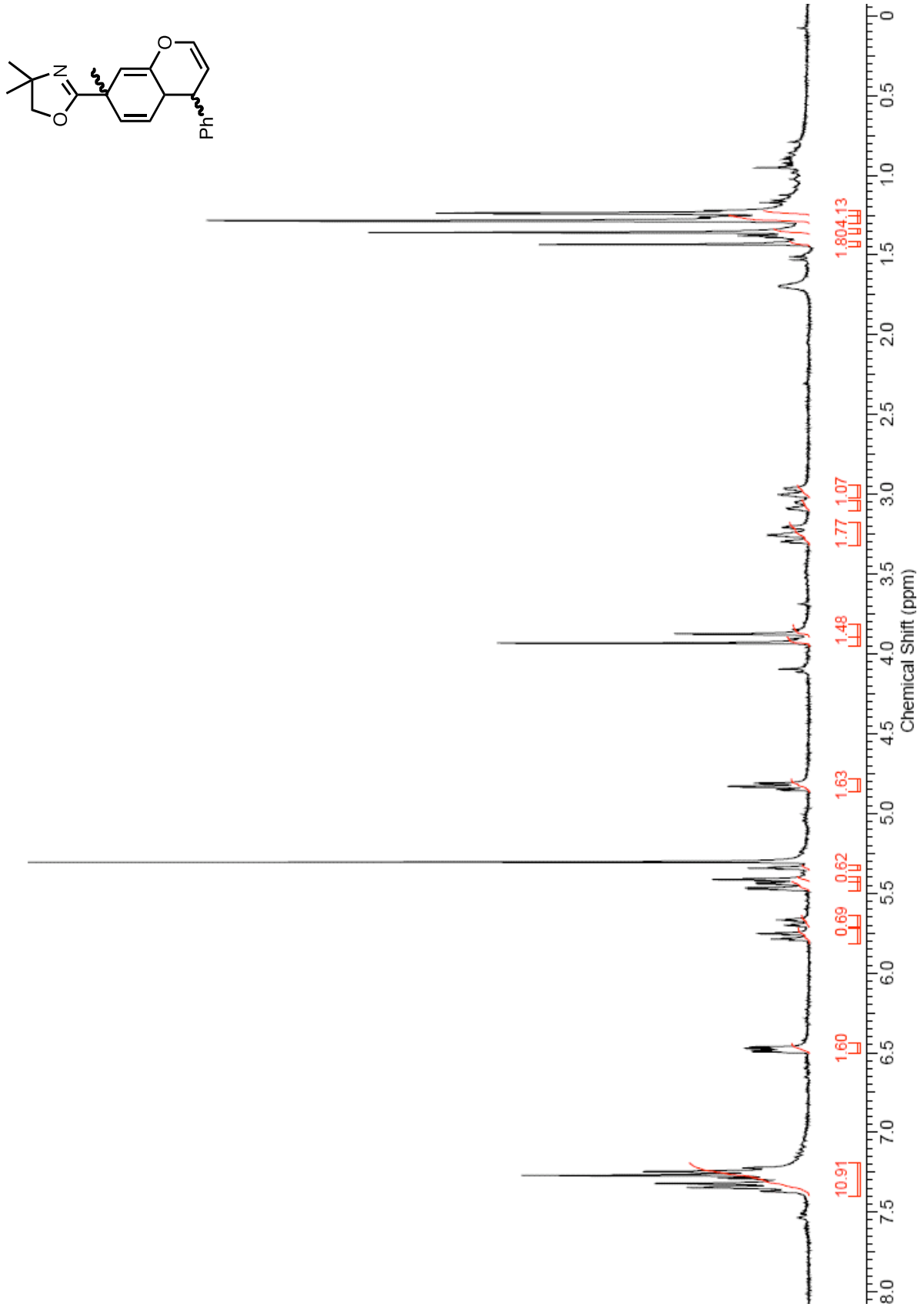
8.1.7 ^{1}H NMR spectra of 317b



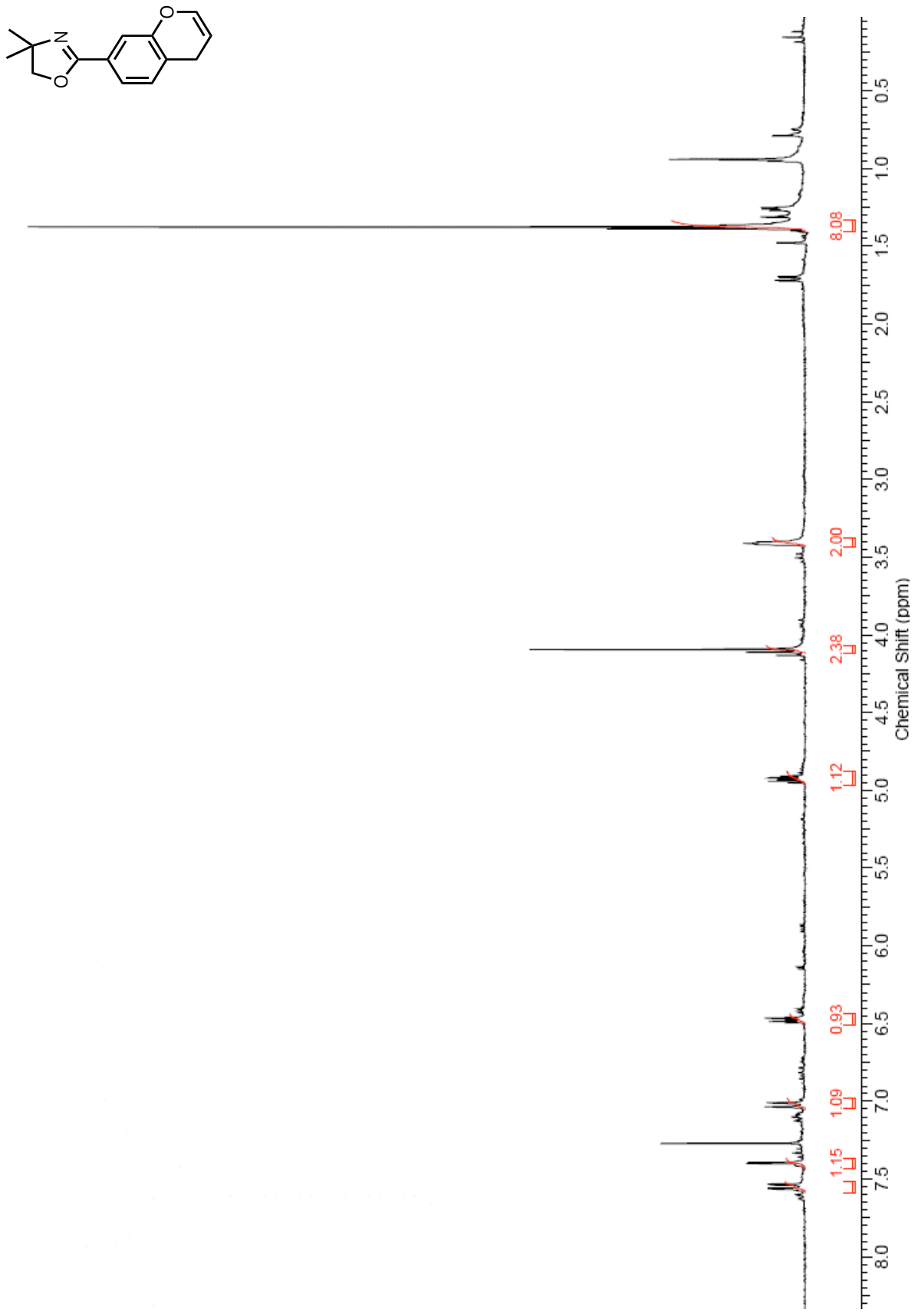
8.1.8 ^{1}H NMR spectra of 318b



8.1.9 ^{1}H NMR spectra of 318d



8.1.10 ^{1}H NMR spectra of 319a



8.1.11 ^{1}H NMR spectra of 319b