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Investigations into a Palladium-Catalysed Heterocyclisation-Allylation Reaction and Studies Towards the Validation of DPY-31 as a Novel Target for the Treatment of Parasitic Nematode Infections

Lewis Williams (MSci)

A thesis submitted in part fulfilment of the requirements of the degree of Doctor of Philosophy

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Abstract

The opening chapter details investigations undertaken into heteroallylation methodology developed within the France group. The first section gives an overview of the existing strategies for palladium-catalysed alkene difunctionalisation reactions which construct a new nitrogen-containing heterocycle. Particular attention is devoted to the construction of new carbon–carbon bonds and the relative lack of methods to construct new $sp^3–sp^3$ C–C bonds.

The second section details the results of a mechanistic investigation into the previously developed oxyallylation methodology. The investigation successfully provided evidence that an isohypsic-palladium(II) catalysed mechanism was operative.

The third section discusses attempts towards the extension of the heteroallylation methodology to include the construction of nitrogen-containing heterocycles. Initial attempts focussed on the aminoallylation of tosylamides, from which four new heterocycles were synthesised. Further investigations with hydroxamates allowed the synthesis of three further heterocycles, but the results demonstrate the potential for a greater substrate scope in the future.

The fourth section details experimental procedures and compound data.
The second chapter details research undertaken towards the validation of a novel therapeutic target for the treatment of parasitic nematode infections. The first section details the current treatments and the growing levels of resistance to these treatments. Furthermore, previously published data concerning nematode astacins, the proposed new target, is presented, providing information which was utilised for the design of the new inhibitors.

The second section discusses the design and synthesis of proposed nematode astacin inhibitors, and details the biological testing results gathered by our collaborators. Two compounds, in particular, were demonstrated to be the most potent known compounds against the new therapeutic target. Taken together, the results demonstrate a start point towards to goal of a new class of nematode-infection therapeutics.

![Chemical structures](image)

\( \text{IC}_{50} \): *B. Malayi* = 76 \( \mu \)M

* T. Circumcineta = 26 \( \mu \)M

\( \text{IC}_{50} \): *B. Malayi* = 28 \( \mu \)M

* T. Circumcineta = 34 \( \mu \)M

The third section details experimental procedures and compound data.
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To Helmi, my muse and shining light, my Hufflepuff, my great emu, I have only this to say: Mina olen amblikmees, sina oled puksutaja.

I must also acknowledge King Pyrrhus and Sisyphus, without whom I would have no convenient metaphors to attach to my PhD research; Veronica Mars, for teaching me that stubbornness is a gift; and, finally, Pink Floyd, whose wisdom has been truly enlightening.

“How can you have any pudding, if you don’t eat your meat?”
Author’s Declaration

This thesis represents the original work of Lewis Williams unless otherwise explicitly stated in the text. The research was carried out at the University of Glasgow in the Raphael and Henderson Laboratories under the supervision of Dr. David France during the period of October 2011 to March 2015. Portions of the work described herein have been published elsewhere, as below:

# Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Å</td>
<td>angstrom(s)</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>acac</td>
<td>acetylacetonate</td>
</tr>
<tr>
<td>aq.</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>BAIB</td>
<td>(Bis(acetoxy)iodo)benzene</td>
</tr>
<tr>
<td>BINAP</td>
<td>(2,2'-(Bis(diphenylphosphino)-1,1'-binaphthyl)</td>
</tr>
<tr>
<td>bipy</td>
<td>2,2-bipyridine</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butyloxycarbonyl</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>°C</td>
<td>degrees Celsius</td>
</tr>
<tr>
<td>cat.</td>
<td>catalytic</td>
</tr>
<tr>
<td>CDI</td>
<td>carbonyl diimidazole</td>
</tr>
<tr>
<td>CI</td>
<td>chemical ionisation</td>
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<tr>
<td>conc.</td>
<td>concentration</td>
</tr>
<tr>
<td>COSY</td>
<td>correlation spectroscopy</td>
</tr>
<tr>
<td>Cy</td>
<td>cyclohexyl</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylideneacetone</td>
</tr>
<tr>
<td>DCC</td>
<td>dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DIPEA</td>
<td>diisopropylethyl amine</td>
</tr>
<tr>
<td>dppf</td>
<td>diphenylphosphorylferrocene</td>
</tr>
<tr>
<td>DME</td>
<td>dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>DPE-Phos</td>
<td>bis[(2-diphenylphosphino)phenyl] ether</td>
</tr>
<tr>
<td>EDC</td>
<td>1-Ethyl-3-(3-dimethyl)aminopropyl</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>EI</td>
<td>electron ionisation</td>
</tr>
<tr>
<td>equiv.</td>
<td>equivalents</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionisation</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>Fmoc</td>
<td>Fluorenylmethyloxycarbonyl</td>
</tr>
<tr>
<td>g</td>
<td>gram(s)</td>
</tr>
</tbody>
</table>
q          quartet
quant.     Quantitative
Rf         retention factor
RT         room temperature
s          singlet
sat.       saturated
SPhos      2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
SSRI       selective serotonin reuptake inhibitor
t          triplet
T3P        Propylphosphonic anhydride
TBACl      tetrabutylammonium chloride
Temp       temperature
TFA        trifluoroacetic acid
THF        tetrahydrofuran
TIPS       triisopropylsilyl
TIPS-EBX   triisopropylsilyl ethynylbenziodoxolone
TLC        thin layer chromatography
Tf         trifluoromethanesulfonyl
Ts         4-toluenesulfonyl
μL         microlitre(s)
μw         microwave
% wt.      percentage by weight
Chapter 1: Investigations into a Palladium-Catalysed heterocyclisation-allylation process: Mechanistic insights and expansion of reaction scope

1.1: Palladium-Catalysed alkene difunctionalisation: Synthesis of Nitrogen-Containing Heterocycles

1.1.1: Background

Nitrogen-containing heterocycles are prevalent in natural products, and have been subject to significant chemical research due to their pharmacological and biological activities.[1] In particular, pyrrolidines and piperidines[2] are common architectures in alkaloid natural products, including tropane alkaloids (e.g. atropine),[3] and opioid alkaloids (e.g. codeine). Molecules containing aminocyclic functionality are known to exhibit a diverse range of pharmacological activities and many alkaloids are considered vital medicines (Figure 1.1).[1,4]

![Figure 1.1: Representative alkaloid natural products](image)

Synthetic alkaloids have also been demonstrated to exhibit powerful pharmacological activity. Aripiprazole, an antipsychotic drug marketed for the treatment of schizophrenia, is currently one of the world’s highest grossing drugs, with sales of ca. $6.5 billion in 2013 (Figure 1.2).[5]

![Figure 1.2: Structure of aripiprazole](image)

The construction of nitrogen-containing heterocycles is consequently of great importance and novel efficient methods are highly sought after. Reports on synthetic protocols towards the formation of nitrogen-containing heterocycles are extensive and wide-ranging. Current strategies for the construction of aminocycles via C–N bond formation include, but are not limited to, halolactamisation,[6,7] hetero-Diels–Alder reactions,[8] and alkene functionalisation reactions
catalysed by a range of transition metals.[9] Recent efforts have allowed significant growth in the field of enantioselective C–N bond formation,[10] adding key reactions to the chemists’ toolbox.

Palladium-catalysed alkene functionalisation is the most common method for the construction of nitrogen-containing heterocycles via transition metal catalysis.[9,11,12] This report will describe the wide range of multiple-bond forming reactions which have been coupled with palladium-catalysed aminocyclisation.

**Aza-Wacker Reaction**

Over the past 100 years, the field of transition-metal catalysis has been subject to much research and palladium-catalysed transformations have been among the most heavily investigated. Since the 1970s, huge advances have been made and the importance of palladium catalysis was highlighted by the award of the 2010 Nobel Prize in Chemistry to Richard Heck, Akira Suzuki and Ei-Ichi Negishi for their contributions to palladium catalysed cross-coupling reactions (Scheme 1.1).

![Scheme 1.1: General Cross-Coupling Mechanism](image)

The reactivity of palladium cross-couplings relies on the oxidative addition of palladium into a carbon–halogen bond, yielding an organopalladium(II) intermediate. However, for the application of palladium catalysis to alkene difunctionalisation it was necessary to utilise different reactivity: the coordination of the alkene by a Lewis acidic palladium salt. The traditional nucleophilic nature of the alkene is reversed, increasing electrophilicity and activating to nucleophilic attack.

The genesis of the aza-Wacker reaction occurred in the late 19th century, with the discovery of the Wacker reaction. The Wacker reaction is the addition of water across an alkene, catalysed by a palladium salt. The process was commercialised in the 1950s after the procedure was made more efficient through the use of an oxidant (Scheme 1.2).[13] Coordination of the palladium catalyst across ethylene gives rise to complex 1.1 which facilitates the nucleophilic addition of water, leading to
alkylpalladium(II) intermediate 1.2. β-Hydride elimination from alkylpalladium (II) intermediate 1.2 yields palladium(0) and enol 1.3, the latter of which will rapidly tautomerise to produce acetaldehyde 1.4. The resulting Pd(0) was reoxidised to Pd(II) using a copper salt, thus completing the catalytic cycle. There is still, however, much debate regarding the mechanism of the Wacker process, primarily over the mechanism of the oxypalladation.[14]

![Scheme 1.2: Mechanism of the Wacker process](image)

Further research showed that palladium(II) salts could facilitate the nucleophilic attack of a wide range of nucleophiles onto activated alkenes (Scheme 1.3). Early research from Hosokawa and co-workers was centred on the utilisation of oxygen nucleophiles.[15]

![Scheme 1.3: Nucleophilic addition onto activated alkenes](image)

In 1974 Hegedus and co-workers provided evidence for addition of nitrogen nucleophiles across a palladium-activated alkene. Addition of diethylamine to activated ethylene, followed by hydrogenation of the resultant diethylethyleneamine, produced triethylamine in high yields (Eq. 1.1).[16]
While not a viable commercial synthesis of triethylamine, the report provided proof of concept for the aza-Wacker process, which would be rapidly expanded upon. Further work from Hegedus et al. utilised tethered nucleophiles, demonstrating the first example of palladium-catalysed aminocyclisation (Eq. 1.2). The reaction represents an efficient synthesis of indoles under tolerant reaction conditions, albeit with stoichiometric palladium.

\[ \text{Scheme 1.4: Mechanism for 2-methylindole synthesis} \]

In 1978, Hegedus et al. introduced an oxidant to the above reaction, allowing it to proceed catalytically in palladium (Eq. 1.3). The mechanism proceeds via the same pathway as described above.

Since this work was undertaken, there have been many reports of oxidative and non-oxidative aminocyclisation reactions facilitated by palladium(II) salts. The reactions generally have broad scope and are air- and moisture-tolerant.

**1.1.2: Multiple-bond forming strategies**

It was recognised that alkylpalladium(II) intermediate 1.8, formed by aminopalladation of alkene 1.7 during the aza-Wacker reaction, could be utilised for further transformations, rather than allowing it
to terminate via β-hydride elimination (Scheme 1.5). The proposed strategy would allow more rapid and efficient building of molecular complexity.

Scheme 1.5: Potential for further transformation

Alkylpalladium(II) intermediates (e.g. 1.8) have been demonstrated to participate in a large number of transformations. The known examples of aminocyclisation-difunctionalisation reactions catalysed by palladium(II) salts are summarised below (Scheme 1.6). In each case, a new nitrogen-containing heterocycle is formed by C–N bond formation, and a second bond is formed to an sp³ hybridised carbon centre. Extensive research has been undertaken towards the formation of a second carbon–carbon bond. Examples include formation of new sp³–sp³ C–C bonds (Products 1.11 and 1.12), as well as new sp³–sp bonds (product 1.13). The formation of new carbon–oxygen, carbon–halogen (product 1.14) and of a second new carbon–nitrogen bond (product 1.15) have also been achieved under a wide range of methodologies.[20]

Scheme 1.6: Summary of Pd(II)-catalysed aminocyclisation-difunctionalisation reactions

Mechanistic considerations
Each of the reactions discussed in the following sections share a common first step: intramolecular aminopalladation. Aminopalladation is known to occur via one of two mechanisms: cis- or trans-aminopalladation (Scheme 1.7). Cis-aminopalladation, in which nucleophilic attack occurs via a pre-coordinated amine, leads to syn-alkylpalladium intermediates (1.17). Trans-aminopalladation occurs from direct alkene coordination to palladium, followed by nucleophilic attack of the amine, leading
to *anti*-alkylpalladium intermediates (1.18). The specific mechanism will control the stereochemical outcome of aminopalladation and will consequently have important implications on attempts to develop enantio- or diastereo-selective oxidative amination reactions.

The mechanism of aminopalladation has been investigated thoroughly in several systems and a number of sophisticated mechanistic experiments have been utilised. It has been demonstrated that even small changes in substrate or in reaction conditions can have a profound effect on the mechanism of aminopalladation.

A further consideration when proposing a second bond-forming event is the relative rate of β-hydride elimination (See Scheme 1.5). β-Hydride elimination is an intramolecular process and can rapidly terminate the reactivity of alkylpalladium(II) intermediates (e.g. 1.8). There are, however, strategies to circumvent β-hydride elimination (Scheme 1.8). Strategy 1 utilises geminally-disubstituted alkenes (e.g. 1.19). Alkylpalladium(II) intermediate 1.20, arising from aminopalladation of alkene 1.19 does not contain a β-hydrogen atom and, consequently, cannot undergo β-hydride elimination. Strategy 2 involves stabilisation of alkylpalladium(II) intermediate 1.21, thus slowing the relative rate of β-hydride elimination. Strategy 3 involves a rapid transformation of alkylpalladium(II) intermediate 1.21, such as oxidation to alkylpalladium(IV) intermediate 1.23, and thus inhibiting β-hydride elimination.
The following sections will contain a detailed discussion into a number of aminopalladation processes, leading to the formation of a new nitrogen-containing heterocycle and a range of new carbon–carbon and carbon–heteroatom bonds.

1.1.3: Carboamination

Carboamination reactions are processes which introduce a new carbon–nitrogen bond and a new carbon–carbon bond across an olefin (Eq. 1.4). Through the use of tethered nucleophiles, it is possible to synthesise a new nitrogen-containing heterocycle. The second new bond is formed between an sp³-hydridised carbon and a sp³, sp²- or sp³-hybridised carbon. In the following sections, the range of transformations will be discussed in terms of the hybridisation of the second carbon.

sp³–sp² bond formation

In the vast majority of aminocyclisation reactions followed by C–C bond formation the second bond is formed between an sp³-hydridised carbon and an sp²-hydridised carbon, such as pyrrolidone 1.26 (Scheme 1.9). There is a large extent of potential transformations, for example, alkene-carbopalladation (1.26, where Y = C) or carbonylation (1.26, where Y = O). A representative range of these transformations will be discussed in the following sections.

Scheme 1.9: General sp³–sp² C–C bond forming carboamination

Carbopalladation

As has been discussed previously with regards to aminopalladation, alkenes can be activated by palladium(II) salts towards insertion of a nucleophile. Alkylpalladium(II) intermediates (e.g. 1.8, Scheme 1.10) have been demonstrated to undergo a similar process with alkenes (Scheme 1.11). This process, known as carbopalladation, is often terminated by β-hydride elimination to yield alkene products, such as 1.27.
Early examples demonstrated that enones and acrylate esters were particularly suitable for carbopalladation with alkylpalladium(II) intermediates. In 1980, Hegedus and co-workers demonstrated the carboamination of o-allyl anilines (Scheme 1.1).[22] Treatment of methylallylaniline 1.28 with a palladium(II) salt in the presence of methylvinylketone efficiently yielded desired indoline 1.32. The reaction was proposed to proceed via alkylpalladium(II) intermediate 1.30. It was necessary to utilise gem-disubstituted alkenes because alkylpalladium(II) intermediate 1.31, the product of aminopalladation of allylaniline 1.29, rapidly underwent β-hydride elimination to afford indole 1.34.

Hegedus and co-workers demonstrated, through the introduction of a second tethered alkene, that intramolecular carboamination is an efficient method for the synthesis of fused heterocycles (Scheme 1.12).[22] Treatment of acrylamide 1.35 with Pd(II) formed alkylpalladium(II) intermediate 1.36, which selectively underwent 5-exo-trig intramolecular carbopalladation to yield pyrrolizine 1.37 (mixture of two alkene isomers). There was no observed formation of indolizine 1.38, a product of 6-endo carbopalladation from alkylpalladium(II) intermediate 1.36.
Scheme 1.12: Carboamination via intramolecular carbopalladation

In 2006, Yang et al. reported the first example of an enantioselective palladium(II)-catalysed carboamination, utilising the carbopalladation onto a tethered alkene (Scheme 1.13). The use of sparteine as a ligand for palladium allowed aminopalladation of anilide 1.39 to proceed enantioselectively, affording alkylpalladium(II) intermediate 1.40. Alkylpalladium(II) intermediate 1.40 was trapped via intramolecular carbopalladation with the enone moiety. Subsequent β-hydride elimination delivered desired aminocyclic pyrrolizine 1.41 with high optical purity.

Scheme 1.13: Sparteine-mediated enantioselective carboamination

**Aminocarbonylation**

CO migratory-insertion is the addition of carbon monoxide into carbon–metal bonds, forming a metallo-acyl complex, eventually leading to new carbonyl units. This phenomenon has been observed for a wide range of transition metals, and the utilisation of migratory-insertion in palladium catalysis has been particularly well investigated. In 1974 Heck et al. demonstrated the palladium-catalysed esterification and amidation of aryl, benzyl and vinyl halides (Scheme 1.14). The reactions demonstrated the trapping of acylpalladium(II) intermediate 1.42 by oxygen and nitrogen nucleophiles, providing proof of concept for multiple-bond forming strategies utilising palladium-carbon monoxide migratory insertion strategies.
The seminal example of aminocyclisation–carbonylation was reported by Yoshida et al. in 1988. The methodology demonstrated that alkylpalladium(II) intermediate 1.44, the product of aminopalladation of urea 1.43, could be rapidly trapped by carbon monoxide, preventing β-hydride elimination and furnishing a new carbonyl unit, eventually yielding cyclic urea 1.45 (Scheme 1.15).\(^\text{[27]}\) The reaction successfully furnishes a new nitrogen-containing heterocycle, and a new sp\(^2\)–sp\(^3\) C–C bond in a single step.

The proposed mechanism for the reaction is shown below (Scheme 1.16). Aminopalladation of urea 1.43 furnishes alkylpalladium(II) intermediate 1.44. Intermediate 1.44 rapidly undergoes migratory insertion with carbon monoxide, preventing β-hydride elimination and affording acylpalladium(II) intermediate 1.46. De-insertion by nucleophilic attack of methanol produces the desired product 1.45 and Pd(0), the latter of which was reoxidised to complete the catalytic cycle.
As was demonstrated by Heck (Scheme 1.14), it is possible to employ a range of nucleophiles to trap the acylpalladium(II) intermediate, giving access to a range of amide and ester products. Further investigations by Yoshida et al. exhibited the potential for using a tethered nucleophile, allowing the synthesis of two new heterocycles in a single step (Eq. 1.5).\textsuperscript{27} When urea 1.47 was subjected to aminocarbonylation, bicyclic urea 1.48 was observed as a single product.

The proposed mechanism for the formation of pyrimidone 1.48 is discussed below (Scheme 1.17). 5-exo-trig aminopalladation of urea 1.47 yields alkylpalladium(II) pyrrolidine intermediate 1.50. Migratory insertion of carbon monoxide yields acylpalladium(II) intermediate 1.51 which undergoes nucleophilic displacement with the tethered methylamide moiety to yield the desired bicycle 1.48. This example is especially efficient as it installs two C–N bonds, both forming new heterocycles, and a new sp\textsuperscript{3}–sp\textsuperscript{2} C–C bond.
A second report by Yoshida et al. demonstrated the use of tethered allylic alcohols to synthesise lactone containing bicyclic systems (Eq. 1.6). Treatment of allylic alcohol 1.52 with a Pd(II) salt and carbon monoxide afforded lactone 1.53. Like the above reaction, two new fused heterocycles are synthesised in a single, high-yielding reaction. The work demonstrates efficient methodology for the synthesis of multiple heterocycles in a single step. The formation of 1.53 proceeds via the same mechanism as above (Scheme 1.17), instead trapping the acylpalladium(II) intermediate with the tethered allylic alcohol.

**Aminoarylation**

Wolfe et al. published a report describing an arylation-aminocyclisation protocol (Eq. 1.7). Treatment of napthyl bromide 1.55 with a palladium(0) catalyst and alkenylamine 1.54 afforded 2-substituted pyrrolidine 1.56. The methodology allows for the synthesis of a range of substituted pyrrolidines under mild conditions, with an efficient catalyst system. The methodology has also been demonstrated to allow the synthesis of substituted indolines.
The full proposed mechanism is shown below (Scheme 1.18). Oxidative addition of Pd(0) with aryl bromide 1.57 yields arylpalladium(II) intermediate 1.58. Subsequent coordination to alkenylamine 1.59 of the palladium(II) induces aminopalladation, which results in aryl-alkylpalladium(II) intermediate 1.60. Carbon–carbon bond forming reductive elimination from intermediate 1.60 results in desired pyrrolidine 1.61. The reaction was successfully able to avoid β-hydride elimination from alkylpalladium(II) intermediate 1.60 because the competing reductive elimination was more rapid.

Scheme 1.18: Mechanism of Wolfe aminoarylation

It was further noted that intramolecular delivery of the alkenylamine moiety would allow the synthesis of a second heterocycle/carbocycle, as well as the new aminocycle. This would demonstrate a more concise and efficient method towards vicinal-carbo/heterocycles (Scheme 1.19).[31] Treatment of arylbromide 1.60 with a palladium(0) catalyst yielded a mixture of pyrrolidines 1.61 and 1.62, the products of cis-aminopalladation and trans-aminopalladation respectively. It was discovered that the ligand had a significant effect on the mechanism of aminopalladation, and thus the stereoselectivity of the reaction. Utilising racemic BINAP resulted in no selectivity between cis- and trans-aminopalladation processes, and thus an equal mixture of two diastereomers. Tricyclohexylphosphine provided the highest selectivity for cis-aminopalladation and thus allowed the development of diastereoselective aminoarylation reaction conditions.
Furthermore, Wolfe and co-workers successfully demonstrated enantioselective arylamination reaction conditions, allowing the construction of 2-substituted pyrrolidine with high optical purity (Eq. 1.8).\cite{32} The protocol allowed for synthesis of 2-(arylmethyl)pyrrolidines (e.g. 1.64) with high enantioselective induction by utilising (R)-Siphos-PE and demonstrated a range of aryl and vinyl coupling partners. The reaction proceeds via the same mechanism as shown above (Scheme 1.18).

**Scheme 1.19: Diastereoselective intramolecular aminoarylation**

*sp*-\textsuperscript{3}--\textsuperscript{sp} C--C bond formation

In 2010, Waser et al. published a report on the oxyalkynylation of alkenes with tethered alcohol and carboxylic acid nucleophiles, leading to the synthesis of new oxygen-containing heterocycles (Scheme 1.20).\cite{33} Within this paper there was a single example of a nitrogen nucleophile. When treated with a palladium(II) salt and TIPS-EBX, O-benzyl hydroxamate 1.65 underwent aminoalkynylation to yield lactone 1.66. The reaction, however, suffered from lack of chemoselectivity between amino- and oxyalkynylation, resulting in a substantial yield of imidate 1.67.
In 2011, the same group reported a general procedure for the palladium-catalysed aminoalkynylation of alkenes. Tosylamide 1.68 successfully underwent aminoalkynylation, producing pyrrolidone 1.69 in high yield (Eq. 1.9).\cite{34} By utilising tosylamides, rather than benzylhydroxamates, excellent chemoselectivity for aminocyclisation was observed and a range of nitrogen-containing heterocycles were constructed.

The role of the hypervalent iodide species remains consistent between the oxyalkynylation and aminoalkynylation reactions: a strong oxidant to allow the oxidation of alkylpalladium(II) intermediates to alkylpalladium(IV). The full mechanism is described below (Scheme 1.21). Aminopalladation of tosylamide 1.68 by a palladium(II) salt will produce alkylpalladium(II) intermediate 1.70. Oxidative addition into the iodo-alkynyl bond of the hypervalent iodide species yields alkylpalladium(IV) intermediate 1.71, which undergoes reductive elimination to afford pyrrolidone 1.69 and recycle the palladium(II) salt.
The methodology was limited to the aminocyclisation of sulfonyl-protected amides, carbamates and ureas, although the group has demonstrated the reduction of pyrrolidone 1.73 to the respective pyrrolidine. The methodology has been applied towards the synthesis of alkaloid (±)-trachelanthamidine, demonstrating the potential for reduction to the pyrrolidine, as well as efficient N-sulfonyl group deprotection (Scheme 1.22).

Scheme 1.22: Synthesis of (±)-trachelanthamidine

Towards the goal of direct pyrrolidine synthesis from the aminooalkynylation of amines, Waser and co-workers developed a palladium(0)-catalysed system (Eq. 1.10).[35] Treatment of alkenyl carbamate 1.74 with palladium(0) and an alkynyl bromide allowed the construction of a range of 2-alkynyl pyrrolidines 1.75.
While pyrrolidine 1.75 was structurally similar to the products formed by the previously discussed aminoalkynylation methodology (Eq. 1.9), the process is mechanistically distinct (Scheme 1.23). The mechanism was reminiscent of Wolfe and co-workers aminoarylation reaction (Scheme 1.18). Oxidative addition into the alkynyl-bromide bond yields alkynylpalladium(II) intermediate 1.76, which then catalyses the aminopalladation process with alkenylcarbamate 1.74 to yield alkylpalladium(II) intermediate 1.77. Subsequent reductive elimination from alkylpalladium(II) intermediate 1.77, producing 2-alkenyl pyrrolidine 1.75.

![Scheme 1.23: Mechanism for Pd(0)-catalysed aminoalkynylation](image)

While the initial account was limited to the introduction of silyl-protected acetylenes, a further report demonstrated increased scope of alkynylation using alkyl-bromoacetylenes, allowing the synthesis of linear and branched alkyl-alkynyl pyrrolidines (Scheme 1.24).[^36] The methodology was particularly important because it represent the first aminoalkynylation reaction using aliphatic bromoacetylenes.

![Scheme 1.24: Scope of dialkyl-alkyne synthesis](image)

[^36]: The report also discussed a one-pot aminoalkynylation-hydrogenation procedure, allowing the indirect synthesis of a new sp^3–sp^3 C–C bond (Eq. 1.11). The reaction was efficient in synthesising...
2-alkyl substituted pyrrolidines, but as a method for sp³–sp³ C–C bond formation, it has a significant lack of functional group tolerance due to the utilisation of hydrogenation reaction conditions.

Conventional approaches to aminopalladation, and all of those described previously in this report, utilise a nucleophilic nitrogen species in conjunction with an oxidising species for carbon–carbon bond formation. In 2015, Bower and co-workers demonstrated an umpolung approach towards aminopalladation, utilising an electrophilic amine species (Eq. 1.12)\textsuperscript{[37]} Treatment of O-pentafluorobenzyloxime 1.80 with a Pd(0) catalyst and an alkynylboronic acid resulted in 2-substituted dihydropyrrole 1.82. This approach allowed the utilisation of the vast range of commercially available metalloid-coupling reagents. O-Pentafluorobenzyloximes have previously demonstrated strong reactivity towards oxidative addition with palladium(0) catalysts, yielding alkylidene amino-palladium species, which have, in turn, shown strong reactivity to insertion into tethered alkenes in amino-Heck processes.\textsuperscript{[38]}

Like the reports by Waser and co-workers above, the reaction creates a new nitrogen-containing heterocycle and a new sp³–sp C–C bond, however, in this case it occurs via a mechanistically distinct approach (Scheme 1.25). Oxidative addition of the palladium(0) catalyst into the oxime N–O bond leads to iminopalladium(II) intermediate 1.84. Iminopalladation onto the tethered alkene will yield alkylpalladium(II) intermediate 1.85. In the case of the alkynylation work, R³ = methyl, so β-hydride elimination from this intermediate was not possible. Transmetallation with an alkynyl-boronic ester will yield alkynylpalladium(II) intermediate 1.86 and subsequent reductive elimination afforded desired pyrrole 1.87.
What is particularly striking is that the methodology provides the first “unified strategy” for a wide-range of carboaminations. Simply by varying the nucleophile, it has been demonstrated that the methodology can also achieve amino-acylation, carboxylation, arylation and vinylation (Scheme 1.26). Trapping alkylpalladium(II) intermediate 1.85 with aryl- or vinylboronic esters allows the synthesis of product types 1.88 and 1.89, creating a new $sp^3$–$sp^2$ C–C bond. The previously discussed strategy of CO migratory insertion, followed by nucleophilic displacement was demonstrated here, allowing the synthesis of a range of esters (1.90). CO migratory insertion and subsequent trapping with aryl-boronates was also successful, allowing the synthesis of aryl ketones (1.91). In order to circumvent $\beta$-hydride elimination, most examples utilise geminally-disubstituted alkenes ($R^1 = \text{methyl}$). There are, however, several examples in which $R^1 = \text{H}$, showing that the intermolecular trapping of alkylpalladium(II) intermediate 1.85 via transmetallation can be as rapid as $\beta$-hydride elimination.
This methodology demonstrates an important step in the advancement of palladium-catalysed carboamination processes. Previously, as has been established in this report, it has been necessary to employ distinct methodologies to achieve small changes in product functionality. Although the group has demonstrated the reductive transformation of the imines to the respective pyrrolidines, further development of other electrophilic nitrogen-sources would allow for a wide-ranging scope of aminocycles.

**sp**$^3$–**sp**$^3$ C–C bond formation

For many years, the synthesis of preclinical drug candidates was biased towards achiral, aromatic molecules. High-throughput drug discovery practices tended towards compounds with higher synthetic tractability, or those for which analogues are more easily constructed, which often led to high-aromatic ring count. However, these practices have been demonstrated to have a detrimental effect on clinical success rate.$^{[39]}$

There is a demonstrated correlation between an increase in Fsp$^3$ (defined as number of sp$^3$-hybrised carbon atoms/total number of carbon atoms) and higher clinical trial success rate, suggesting that compounds with greater levels of saturation are more likely to succeed in clinical testing. (Figure 1.3).$^{[40]}$ There is also a similar trend when comparing the number of drug-candidates with at least one stereocentre at each stage of development.

![Figure 1.3: Mean Fsp$^3$ change as development proceeds](image)

At the start of this work, there was no report in the literature of a palladium-catalysed carboamination reaction of alkenes directly resulting in a new sp$^3$–sp$^3$ carbon–carbon bond. The one-pot aminoalkynylation-hydrogenation procedure described by Waser et al. (Eq. 1.11) demonstrates an indirect formation of a new sp$^3$–sp$^3$ bond,$^{[36]}$ but suffers from low functional group tolerance due to the hydrogenation protocol.
An early example of palladium-catalysed sp$^3$–sp$^3$ carbon–carbon bond formation was demonstrated in 1986 by Canty and co-workers (Scheme 1.27). Treatment of dimethylpalladium(II)-bipy complex 1.92 with methyl iodide was found to produce ethane. It was proposed that the reaction proceeded via oxidative addition of methyl iodide into Pd(II) complex 1.92 yielding palladium(IV) intermediate 1.93. Subsequent reductive elimination resulting in palladium(II) iodide complex 1.94 and released ethane. Importantly, this represented the first example of an sp$^3$–sp$^3$ carbon–carbon bond forming reductive elimination from a palladium(IV) intermediate.

Scheme 1.27: Oxidative addition of Pd(II) to Pd(IV)

This proposal was confirmed by concentration of the reaction mixture which yielded x-ray quality crystals. $^1$H NMR spectroscopic and crystallographic analysis of the crystals allowed the full characterisation of complex 1.93. The crystal structure is shown below (Figure 1.4). While mechanisms proceeding via organopalladium(IV) intermediates had been proposed previously,$^{42,43,44}$ the isolation of this palladium(IV) complex represented the first fully characterised example.

Figure 1.4: X-ray crystal structure of Pd(IV) complex 1.93

Previous work within the France group has developed conditions for the difunctionalisation of unactivated alkenes with tethered nucleophiles and external electrophiles. The reaction facilitates the formation of a new oxygen-containing heterocycle and a new sp$^3$–sp$^3$ C–C bond (Eq. 1.13).$^{45}$
The reaction demonstrated a significant advance because, typically, the new C–C bond is to a sp- or sp\(^2\)-hydrided carbon. As discussed above, the synthesis of a new sp\(^3\)–sp\(^3\) C–C bond was also of particular importance because increasing sp\(^3\)-C content has been identified as a major goal of the pharmaceutical industry.

The optimised methodology allowed the construction of 21 oxycyclic products, with a number of different oxygen-containing heterocycles. The reaction also exhibits high functional group tolerance. A representative range of the synthesised oxycycles is displayed below (Figure 1.5). Benzofurans (1.94 and 1.95), isobenzofurans (1.96 and 1.97) and benzoxyran (1.98) have been efficiently constructed, as well as aliphatic furans 1.99 and 1.100. Bulky alkenes are tolerated by the reaction conditions, as demonstrated by the synthesis of tert-butyl furan 1.97. The synthesis of bromobenzofuran 1.95 exhibits tolerance of aryl bromides, which is an important handle for further transformations. Spirocyclic piperidine 1.100 demonstrates the applicability of the reaction to a protected-nitrogen species. That the reaction proceeds in high yield was particularly gratifying because nitrogen-ligands have been demonstrated to significantly retard reaction rate. Finally, the construction of a range of lactones (e.g. 1.101) demonstrated the applicability of carboxylic acid nucleophiles.

Furthermore, the applicability of the methodology was demonstrated by the synthesis of citalopram, a widely prescribed selective serotonin reuptake inhibitor (SSRI) for the treatment of depression (Scheme 1.28). Oxyallylation precursor 1.103 was synthesised in two steps from commercially available cyanophthalide 1.102. Oxyallylation of 1.103 proceeding in good yield to afford isobenzofuran 1.104. A dihydroxylation/oxidative cleavage protocol, followed by reductive amination yielded citalopram in 5 steps.
Scheme 1.28: Synthesis of Citalopram

1.1.4: C–X bond formation

Aminocycle-forming alkene difunctionalisation reactions are not limited to the formation of a new carbon–carbon bond, and there are a number of established protocols for the introduction of new carbon–halogen, carbon–oxygen or a second carbon–nitrogen bond.

**Haloamination**

Palladium-catalysed haloamination reactions are an efficient method for introducing a new carbon-halogen bonds, a moiety with large range of potential functional transformations. Vicinally halogenated nitrogen-containing heterocycles can represent important synthetic intermediates, and in some cases are included in medicinal agents.[46]

In the first instance, products of a palladium-catalysed haloamination process were observed as undesired side-products when utilising copper halide salts as reoxidants.[27,28] The first protocol optimised towards palladium-catalysed intramolecular aminobromination and aminochlorination, utilising copper halide salts, was described in 2004 by Chemler and co-workers (Eq. 1.14).[47] The reaction allowed the transformation of tosyl-protected amines **1.105** into aminohalogenation products in high yields. A major concern, however, was the poor regioselectivity between endo-aminopalladation and exo-aminopalladation, in this case giving a mixture of pyrrolidine **1.106** and piperidine **1.107** respectively.
In the same year, Lu and co-workers reported their own haloamination protocol (Scheme 1.29).\textsuperscript{[48]} The transformation of allylic alcohol with tosyl isocyanate yields carbamate intermediate $\text{1.108}$. Subsequent treatment with a palladium(II) catalyst, a copper(II) halide and lithium halide allowed efficient synthesis of chlorinated/brominated oxazolidones $\text{1.109/1.110}$. The methodology also allows the synthesis of halogenated-piperidones through the utilisation of homo-allylic alcohols. In contrast to the previous haloamination protocol by Chemler and co-workers, this reaction does not suffer from poor endo- vs exo regioselectivity.

![Scheme 1.29: One pot synthesis of halo-pyrrolidones $\text{1.109}$ and $\text{1.110}$](image)

The proposed mechanism is shown below (Scheme 1.30). Alkene coordination and subsequent trans-aminopalladation gave rise to alkylpalladium(II) intermediate $\text{1.112}$. Oxidative cleavage of the carbon–palladium bond with copper(II) bromide yields brominated pyrrolidone $\text{1.110}$. An important factor in this mechanism was the relative rate of oxidative cleavage compared to that of $\beta$-hydride elimination. Alkene $\text{1.13}$ was not observed, and the reaction was highly chemoselective for the halogenation process. It has been previously demonstrated that excess halide ions in solution can inhibit the $\beta$-hydride elimination process.\textsuperscript{[49]}

![Scheme 1.30: Lu haloamination mechanism](image)

Vicinal aminofluorine functionality is an extensively utilised building block in biologically active molecules.\textsuperscript{[50]} Several groups have reported selective fluorination of aromatic C–H bonds.\textsuperscript{[51,52]} In 2009, Liu and co-workers applied the concepts to aminocyclisation (Eq. 1.15).\textsuperscript{[53]} The aminofluorination of sulfonamide $\text{1.114}$ allows the efficient construction of fluorine-bearing compounds.

\[\text{Scheme 1.29: One pot synthesis of halo-pyrrolidones $\text{1.109}$ and $\text{1.110}$}\]

\[\text{Scheme 1.30: Lu haloamination mechanism}\]
piperidine 1.115. It is important to note that, unlike the majority of aminocyclisation reactions discussed in this document, this reaction proceeds via a 6-endo-trig aminopalladation.

\[
\begin{align*}
\text{NHTs} & \quad \text{Pd(OAc)}_2 (10 \text{ mol. %}) & \quad \text{PhII(DCDO)Bu}_2 (2 \text{ equiv.}) & \quad \text{AgF, MgSO}_4, \text{MeCN, RT} & \quad 84\% \\
\text{F} & \quad \text{NHTs} & \quad \text{1.115}
\end{align*}
\]

Aminoacetoxylation
Palladium-catalysed aminoacetoxylation, the introduction of a new carbon–nitrogen and a new carbon–oxygen bond across an olefin, allows for the synthesis of protected vicinal aminoalcohols. 1,2-Aminoalcohols represent an important functionality in biologically active and pharmaceutical molecules, for example, sphingoid bases.[54,55]

The seminal acyclic example of aminoacetoxylation was reported by Bäckvall and co-workers in 1980 (Scheme 1.3). Treatment of \textit{trans}-butene 1.116 with a palladium(II) salt, dimethylamine and lead(IV) acetate yielded syn-vicinal acetoxyamine 1.117, which was subsequently reduced \textit{in situ} to yield syn 1,2-aminoalcohol 1.118. It was also demonstrated that aminoacetoxylation of \textit{trans}-butene 1.119 allowed access to anti-1,2-aminoalcohol 1.121.

\[
\begin{align*}
\text{1.116} & \quad \text{PdCl}_2(\text{MeCN})_2\text{Me}_2\text{NH} & \quad \| & \quad \text{Pb(OAc)}_2\cdot\text{HAc} & \quad \text{OA} & \quad \text{NMe}_2 & \quad \text{OH} & \quad \text{NM} & \quad \text{OH} \\
\text{1.116} & \quad \text{ii}) & \quad \text{ii}) & \quad \text{LiAlH}_4 & \quad \text{58\% over 2 steps} & \quad \text{1.118} \\
\text{1.118} & \quad \text{NR}_2 & \quad \text{1.117} & \quad \text{ii}) & \quad \text{LiAlH}_4 & \quad \text{29\% over 2 steps} & \quad \text{1.120} & \quad \text{NR}_2 & \quad \text{1.121} \\
\text{1.119} & \quad \text{PdCl}_2(\text{MeCN})_2\text{Me}_2\text{NH} & \quad \| & \quad \text{Pb(OAc)}_2\cdot\text{HAc} & \quad \text{OA} & \quad \text{NMe}_2 & \quad \text{OH} & \quad \text{NM} & \quad \text{OH} \\
\text{1.119} & \quad \text{ii}) & \quad \text{ii}) & \quad \text{LiAlH}_4 & \quad \text{58\% over 2 steps} & \quad \text{1.118} \\
\text{1.118} & \quad \text{NR}_2 & \quad \text{1.117} & \quad \ii) & \quad \text{LiAlH}_4 & \quad \text{29\% over 2 steps} & \quad \text{1.120} & \quad \text{NR}_2 & \quad \text{1.121}
\end{align*}
\]

Scheme 1.3: Bäckvall oxyamination

In 2005, Sorenson \textit{et al.} reported a palladium-catalysed aminoacetoxylation of tethered alkenes, giving access to nitrogen-containing heterocycles bearing vicinal-protected alcohol functionality (Eq. 1.16).[57] Treatment of carbamate 1.108 with a palladium(II) salt and bis-acetoxyiodobenzene (BAIB) allowed the construction of oxazolidone 1.122.

\[
\begin{align*}
\text{NTs} & \quad \text{NH} & \quad \text{PdCl}_2(\text{PhCN})_2 (6 \text{ mol. %}) & \quad \text{PhII(OAc)}_2 (2 \text{ equiv.}) & \quad \text{CH}_3\text{CO}_2, \text{RT} & \quad 66\% \\
\text{1.108} & \quad \text{OA} & \quad \text{NTs} & \quad \text{1.122}
\end{align*}
\]
This aminoacetoxylation was demonstrated to be diastereoselective in a similar manner to the Bäckvall oxyamination described above (Scheme 1.31). Aminoacetoxylation of cis-alkene 1.23 yielded syn-aminoacetoxy oxazolidone 1.24 and aminoacetoxylation of trans-alkene 1.25 yielded anti-aminoacetoxy oxazolidone 1.26 (Scheme 1.32). Both reactions are indicative of an anti-aminopalladation process.

\[
\text{Scheme 1.32: Mechanistic investigation into aminoacetoxylation reaction}
\]

The full mechanism is shown below (Scheme 1.33). The reaction is initiated by trans-aminopalladation of carbamate 1.25 to give anti-alkylpalladium(II) intermediate 1.27 in high diastereoselectivity. Oxidative addition with BAIB results in palladium(IV) intermediate 1.28. Carbon–oxygen bond-forming reductive elimination yields desired oxazolidone 1.26 and recycles the palladium(II) catalyst.

\[
\text{Scheme 1.33: Mechanism for Aminoacetoxylation}
\]

**Alkene Diamination**

The 1,2-diamino moiety is recognised as valuable functionality, and is exhibited in many natural and pharmaceutically active molecules and, as a consequence, the synthesis of 1,2-diamines has been
subject to significant research. Early attempts towards palladium-catalysed dianimation of alkenes were performed by Bäckvall and co-workers, in a similar manner to the oxidative-aminoacetoxylation reactions discussed above (Scheme 1.31). Treatment of *trans*-butene with a palladium(II) salt, dimethylamine and *m*CPBA yielded syn-diamine 1.131 (Scheme 1.34). The reaction proceeds via alkene-coordination of the palladium, followed by selective *anti*-aminopalladation, yielding alkylpalladium(II) intermediate 1.129. Oxidation by *m*CPBA yields organopalladium(IV) intermediate 1.130. In contrast to the aminoacetoxylation examples described above, where the intramolecular delivery of the nucleophile results in retention of stereochemistry, *S*<sub>N</sub>2-type reductive cleavage of the Pd–C bond yields diamine 1.131 with an inversion of stereochemistry.

![Scheme 1.34: Bäckvall deamination reaction](image)

In 2005, Muñiz and co-workers demonstrated the applicability of tethered amine-nucleophiles to the dianimation process (Eq. 1.17). Alkenyl urea 1.132, when treated with palladium acetate and BAIB, undergoes a dianimation process to yield imidazolidinone 1.133. The methodology efficiently allows for the construction of two new fused nitrogen-containing heterocycles in a single step.

![Scheme 1.34: Bäckvall deamination reaction](image)

The full reaction mechanism is displayed below (Scheme 1.35). Coordination of the palladium(II) salt to alkene 1.132 and subsequent selective *anti*-aminopalladation yields alkylpalladium(II) pyrrolidine intermediate 1.134. Oxidation to organopalladium(IV) intermediate 1.135 was achieved using BAIB. Palladium(IV) subsequently underwent nucleophilic displacement with the second ureic nucleophile to yield imidazolidinone 1.133 and regenerate the palladium(II) salt. Pyrrole 1.136, the product of β-hydride elimination from either alkylpalladium(II) intermediate 1.134 or alkylpalladium(IV) intermediate 1.135, was not observed, demonstrating that the relative rate of oxidation was faster than that of β-hydride elimination.
A similar, but mechanistically distinct approach was published by Lloyd-Jones and co-workers in 2005 (Eq. 1.18). Treatment of dienes 1.137 with \(N,N'\)-diethylurea and a palladium(II) salt allowed the synthesis of a range of alkenyl-imidazolidinones 1.138. The reaction creates two new C–N bonds in a single step.

The full reaction mechanism is discussed below (Scheme 1.36). Intermolecular aminopalladation of \(N,N'\)-diethylurea onto diene 1.139, catalysed by a palladium(II) salt, yields alkylpalladium(II) intermediate 1.140, which will rapidly isomerise into \(\pi\)-allyl palladium(II) intermediate 1.141. Formation of the \(\pi\)-allyl palladium(II) intermediate 1.141 inhibits \(\beta\)-hydride elimination and increases electrophilicity, activating the intermediate towards nucleophilic displacement, affording imidazolidinone 1.142. Reoxidation of the resultant Pd(0) species completes the catalytic cycle.
Scheme 1.36: Diene-diamination mechanism

1.1.5 Summary
Palladium-catalysed alkene difunctionalisation-aminocyclisation is a rich area of chemistry, allowing the formation of new nitrogen-containing heterocycles and the formation of a second new bond in a single step. This second bond formation has been demonstrated to include carbon–carbon (sp$^3$–sp$^2$ and sp$^3$–sp), carbon–heteroatom and carbon–halogen bond formation. The remaining challenge is the design of methodology to allow the formation of a nitrogen-containing heterocycle and a sp$^3$–sp$^3$ carbon–carbon bond in a single step.
1.2: Insights into oxyallylation reaction mechanism

1.2.1: Introduction and Aims

Investigations into alkene-difunctionalisation reactions were undertaken within the France group, leading to the discovery of a palladium-catalysed oxyallylation of unactivated alkenes (Eq. 1.19).[45] The methodology constructs an oxygen-containing heterocycle via C–O bond formation and a new sp$^3$–sp$^3$ carbon–carbon bond in a single step.

\[
\text{R}^{1}\text{OH} \quad \xrightarrow{\text{Pd}([\text{tfa}]_2, \text{cat.})} \quad \text{NaHCO}_3, \text{PhMe}, 50 \degree \text{C} \quad \text{R}^{2}\text{X} \quad \xrightarrow{\text{R}^{1}\text{O}} \quad \text{R}^{1}\text{R}^{2}\text{O} \quad \text{R}^{2}\text{X} \quad \text{R}^{2}\text{O} \quad \text{R}^{1}\text{R}^{2}\text{O}
\]

The reaction can be considered to proceed in two distinct processes: a) oxypalladation of an unactivated alkene 1.143 to yield oxacyclic alkylpalladium(II) intermediate 1.145 and b) subsequent trapping of alkylpalladium(II) intermediate 1.145 to yield allylated product 1.144 (Scheme 1.37). The first process is well established methodology for carbo- or heterocycle synthesis, and will not be discussed here (for a detailed discussion on this process in relation to aminocycle synthesis, see section 1.1).

\[
\text{R}^{1}\text{OH} \quad \xrightarrow{\text{Pd}X_2} \quad \text{R}^{1}\text{O} \quad \text{X} \quad \text{R}^{2}\text{X} \quad \text{R}^{2}\text{O} \quad \text{R}^{2}\text{O} \quad \text{R}^{1}\text{R}^{2}\text{O}
\]

Scheme 1.37: Oxyallylation process

While the mechanism by which alkylpalladium intermediate 1.145 is trapped by an allylic electrophile (process b) is not fully elucidated, the importance of the allylic halide has been demonstrated. A study into the scope of allyl-X was undertaken by a previous group member (Table 1.1).[64] Utilisation of either allyl chloride or bromide (entries 1, 2) furnished desired benzofuran 1.147 with complete consumption of phenol 1.146. The use of allyl iodide (entry 3), however, resulted in substantially lower conversion of phenol 1.146. Using either allyl acetate or benzoate (entries 4, 5) completely shut down the oxyallylation reactivity. Furthermore, no desired oxycyclisation product was observed when alkyl halides were utilised (not shown).[64]
The primary goal of the investigation was to elucidate a mechanism for the trapping of alkylpalladium(II) intermediate 1.145 by allylic halides, and, in particular, one which would provide an explanation for the limitation to allylic halides. It is proposed that comprehension of the operative reaction mechanism will allow for the extension of substrate scope and the suppression of undesired side-products.

1.2.2: Mechanistic Proposals

It is possible to propose several different mechanisms for the oxyallylation transformation. One possible mechanism is proposed to proceed via an allylpalladium(IV) intermediate (Scheme 1.38). The allylpalladium(IV) intermediate has potential to exist as either an η-1 intermediate, or as a π-allylpalladium(IV) intermediate. Initial oxypalladation of hydroxyalkene 1.148 would yield alkylpalladium(II) intermediate 1.149. This alkylpalladium(II) intermediate would undergo oxidative addition with the allyl electrophile to afford η-1 palladium(IV) intermediate 1.150 which may rapidly undergo isomerisation to π-allylpalladium(IV) intermediate 1.151. Reductive elimination from either η-1 palladium(IV) intermediate 1.150 (mechanism A) or from π-allylpalladium(IV) intermediate 1.151 (mechanism B) will yield the desired isobenzofuran 1.152 and regenerate the Pd(II) salt.
The mechanistic proposals can be justified by previous organopalladium(IV) chemistry. A report by Waser et al. on the oxyalkynylation of hydroxyalkenes utilises a similar substrate scope to this oxyallylation reaction (Eq. 1.20). The oxyalkynylation reaction utilises hypervalent iodide reagent TIPS-EBX to facilitate oxidation to Pd(IV) and, consequently, furnish a new sp$^3$–sp C–C bond (for further information, see section 1.1.3).

The formation of organopalladium(IV) intermediates via the oxidative addition of alkyl halides into alkylpalladium(II) intermediates was demonstrated by Canty and co-workers and is discussed in detail in Section 1.1.3.

A second mechanistic proposal accounts for the similarities which have been recognised between the oxyallylation work undertaken within the France group and the extensive studies into palladium-catalysed carboetherification undertaken by Wolfe and co-workers (Scheme 1.40). In both cases, treatment of hydroxyalkenes with a palladium catalyst and an aryl/allyl halide allows the construction of 2-substituted tetrahydrofurans bearing a new aryl/allyl-methyl group.

To this end, Pd(0) catalysed mechanism C was proposed (Scheme 1.41). The mechanism bears significant similarities to the previously discussed heterocyclisation-arylation research by Wolfe and
co-workers (Section 1.1.3). Oxidative addition of a Pd(0) catalyst to an allylic halide is proposed to form allylpalladium(II)-halide dimer $1.154$. Complexation and oxypalladation of benzylic alcohol $1.148$ will give alkylpalladium(II) intermediate $1.155$. Subsequent reductive elimination will form desired isobenzofuran $1.152$ and Pd(0) to complete the catalytic cycle.

![Scheme 1.41: Proposed Pd(0)-catalysed mechanism](image)

Evidence against this mechanism has previously been gathered within the group.$^{[64]}$ In order to probe the proposed palladium(0)-catalysed mechanism, a palladium(0) catalyst was utilised under the optimised conditions (Eq. 1.21). The reaction did not proceed to the desired benzofuran $1.147$, giving indication that the reaction is unlikely to proceed via a palladium(0) catalysed mechanism. However, without an exhaustive ligand screen, the mechanism cannot be ruled out based on this experiment alone, due to the importance of ligand environment in the optimised reaction.$^{[64]}

![Reaction Equation 1.21](image)

During the extension of substrate scope for the oxyallylation reaction, aryl bromide-containing phenol $1.156$ successfully underwent oxyallylation to yield bromobenzofuran $1.157$ (Eq. 1.22). In the presence of palladium(0), there is a plausible side-reaction proceeding via oxidative addition into the aryl bromide moiety, potentially leading to allylation/proto-dehalogenation of starting material/product (products $1.158$ and $1.159$). None of these potential products were observed, thus giving further credence to the proposal that the reaction does not proceed via a palladium(0) intermediate.
Another possible mechanism is one in which the alkene reactivity is essential, potentially accounting for the lack of reactivity of non-alkenyl halides (Scheme 1.42). Initial oxypalladation of benzylic alcohol 1.148 yields alkylpalladium(II) intermediate 1.149. This intermediate will undergo carbopalladation with the allyl halide to give a second alkylpalladium(II) intermediate 1.160. The reaction is terminated by β-halide elimination, affording isobenzofuran 1.152. The mechanism is devoid of change in palladium oxidation state change, a process known as “isohypsic”.\[69\]

**Scheme 1.42: Proposed isohypsic oxypalladation-carbopalladation mechanism**

Although there are far fewer examples of β-halide elimination in the chemical literature compared to β-hydride elimination, it is a phenomenon which was first observed by Heck in 1968,\[70\] and has since been proposed in numerous systems.\[71\] The allylation protocol described by Heck demonstrated selectivity for β-halide elimination over four potential β-hydride eliminations (Scheme 1.43).

**Scheme 1.43: Palladium-catalysed allylation**
It should also be recognised that the proposed β-halide elimination from alkylpalladium(II) intermediate 1.160 is in competition with four potential β-hydride eliminations. Alkylpalladium(II) intermediate 1.163, which bears significant similarity to alkylpalladium(II) intermediate 1.160, selectively undergoes β-halide elimination to yield allylbenzene 1.164. Furthermore, Lu and co-workers undertook an investigation into the relative rate of β-eliminations, demonstrating that, in their system, β-halide elimination was significantly quicker than β-hydride elimination.\[72\]

1.2.3: Elucidating the mechanism

In order to decipher between the different mechanistic proposals, a mechanistic experiment was proposed. Treatment of benzylic alcohol 1.148 with Pd(II) and selectively deuterated allyl bromide 1.165 was proposed to form either isobenzofuran 1.166 or 1.167 (or a mixture of both). The experiment was designed so that the observed ratio of deuterated isomers 1.166 and 1.167 will be different depending on the operative mechanism (Table 1.2). If there reaction is proceeding via mechanism A, isobenzofuran 1.166 will be observed as a single product. Conversely, if process D is the operative oxyallylation mechanism isobenzofuran 1.167 will be observed as a single product. In the case of mechanisms B or C, both of which are proposed to proceed via a π-allyl palladium intermediate, it is immediately clear that the position of deuteration will be scrambled upon reductive elimination, resulting in an equal ratio of deuterated isomers 1.166 and 1.167.

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>1.166 : 1.167 ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (η-1 allylpalladium(IV) intermediate)</td>
<td>1:0</td>
</tr>
<tr>
<td>B (π-allylpalladium(IV) intermediate)</td>
<td>1:1</td>
</tr>
<tr>
<td>C (π-allylpalladium(II) intermediate)</td>
<td>1:1</td>
</tr>
<tr>
<td>D (Alkylpalladium(II) intermediate)</td>
<td>0:1</td>
</tr>
</tbody>
</table>

A more detailed explanation of the selectivity in mechanisms A and D is shown below (Scheme 1.44). In mechanism A, oxidative addition of alkylpalladium(II) intermediate 1.149 into the carbon–bromine bond of allyl bromide 1.165 results in the deuterated methylene carbon directly bonded to the palladium in allylpalladium(IV) intermediate 1.168. Reductive elimination from this intermediate results in isobenzofuran 1.166, which is deuterated in the allylic position. Contrasted to this, mechanism D demonstrates how carbo palladation of allyl bromide 1.165 results in alkylpalladium(II) intermediate 1.169, which is deuterated in the palladium β-position. β-Halide elimination from alkylpalladium(II) intermediate 1.169 will yield dideuterolekene 1.167.
In order to run the experiment, the substrates were synthesised. 3,3-$d^2$-Allyl bromide was synthesised in two steps from acryloyl chloride by a previously reported procedure (Scheme 1.45). Acryloyl chloride was reduced to allyl alcohol 1.170 using lithium aluminium deuteride. Subsequent $S_N2$ bromination yielded dideutero-allyl bromide 1.165. Importantly, isomeric dideutero-allyl bromide 1.171, the product of $S_N2'$ bromination, was not observed.

**Scheme 1.45: Synthesis of labelled allyl bromide**

Benzylic alcohol 1.148 was synthesised in three steps, following the protocol previously utilised within the France group (Scheme 1.46). Wittig methylenation of benzaldehyde 1.172 and subsequent carboxylation of the resultant aryl bromide 1.173 generated benzoic acid 1.174. Reduction of acid 1.174 completed the synthesis of benzylic alcohol 1.148.

**Scheme 1.46: Synthesis of benzylic alcohol 1.148**
With the required materials in hand, the mechanistic experiment was performed (Eq. 1.23). Treatment of benzylic alcohol 1.148 with Pd(II) and dideutero-allyl bromide 1.165 resulted in the chemoselective transformation to isobenzofuran 1.167, providing evidence that mechanism D is the operative oxyallylation reaction mechanism. This proposal was particularly gratifying as it explains the lack of reactivity of non-alkenyl halides. That isomeric dideutero-isobenzofuran 1.166 was not observed is strong evidence against the formation of a π-allylpalladium intermediate at any stage of the transformation.

Further experiments were undertaken utilising methyl-allyl halides to expand the scope of the reaction and provide supporting mechanistic evidence. While methyl-labelling studies are non-ideal because the increased electron-richness and sterics can have a significant effect on reactivity, they are useful to back-up previous work. Treatment of benzylic alcohol 1.148 with Pd(II) and 3-chloro-1-pentene 1.175 resulted in the transformation to isobenzofuran 1.176 (Eq. 1.24). The new sp³–sp³ C–C bond of isobenzofuran 1.176 was formed to C-1, the terminal methylene carbon of the allylic chloride. This result was in agreement with the previous mechanistic experiments.

The experiment was repeated with phenol 1.146 (Eq. 1.25). In accordance with the results obtained from oxyallylation of benzyl alcohol 1.148, the reaction of phenol 1.146 yielded benzofuran 1.178, the product with a new sp³–sp³ C–C bond to the terminal methylene carbon of the allylic chloride. This was in agreement with a carbopalladation–β-halide elimination mechanism.

Further investigations were undertaken with disubstituted alkenes (Scheme 1.47). Treatment of benzylic alcohol 1.148 with 1,2-disubstituted allyl chloride 1.180 under the oxyallylation conditions yielded isobenzofuran 1.176 as the major product. Isobenzofuran 1.177, the predicted product based
on previous mechanistic evidence was observed as a minor component of the crude reaction mixture. It is probable that, rather than proceeding via a different mechanism, 1,2-disubstituted alkene 1.180 was undergoing a palladium-catalysed isomerisation to mono-substituted alkene 1.175, via π-allylpalladium(II) intermediate 1.181.\[74\] Monosubstituted alkene 1.175 will subsequently undergo carbopalladation, reflecting the reactivity shown above (Eq. 1.24). That the reaction is highly chemoselective for isobenzofuran 1.176 suggests that carbopalladation with 1,2-disubstituted alkene 1.180 is a significantly slower process than isomerisation to, and carbopalladation of monosubstituted alkene 1.175. That the substitution of the alkene has such a large effect on the reaction rate was indicative of a carbopalladation process, providing further evidence for mechanism D.

Scheme 1.47: Oxyallylation utilising 1,2-disubstituted allylic halide

Comprehension of the operative oxyallylation reaction mechanism allowed for the expansion of scope with respect to the allyl electrophile. It was proposed, for example, that utilisation of dibromopropene 1.182 would allow selective construction of vinyl bromide 1.183 (Eq. 1.26). Vinyl bromides are a useful functionality which can be utilised in further transformations, especially palladium-catalysed cross-coupling reactions. Treatment of benzylic alcohol 1.148 with dibromopropene 1.182 under oxyallylation conditions afforded vinyl bromide-isobenzofuran 1.183 in high yield.

The mechanism for the 1,2-disubstituted vinyl bromide is discussed below (Scheme 1.48). The reaction is proposed to proceed via oxypalladation and carbopalladation as discussed previously to yield dibromo-alkylpalladium(II) intermediate 1.184. The palladium can only undergo β-elimination with the terminal bromide, thus the secondary bromine atom remains intact.
1.2.4: Conclusions

These investigations have given evidence for the operative mechanism proceeding via carbopalladation followed by β-halide elimination (Scheme 1.49). The mechanism is consistent with the results obtained within the scope of this project and previously published work.\[64\]
1.3: Expansion of heteroallylation scope – synthesis of aminocycles

1.3.1: Introduction and aims

As discussed previously (section 1.1.1), nitrogen-containing heterocycles are crucial intermediates in organic synthesis and are a common structural motif in natural products and pharmaceutically active compounds (See Figures 1.1 & 1.2). As a consequence, new methodologies for aminocyclisation are constantly being sought after.

The aim of this project was to extend the scope of the previously optimised oxyallylation methodology to include the construction of aminocycles (Scheme 1.50). The reaction utilises palladium-catalysed heterocyclisation of tethered amines onto unactivated alkenes, followed by allylation using an allylic halide.

The proposed reaction would construct a new nitrogen-containing heterocycle and furnish a new sp$^3$–sp$^3$ C–C bond in a single step. This would represent a significant advance as it would demonstrate the first example of an sp$^3$–sp$^3$ C–C bond forming palladium-catalysed carboamination reaction. All previous palladium-catalysed carboamination strategies, discussed in detail in chapter 1.1, yield products with a new sp$^3$–sp$^2$ or sp$^3$–sp bond, most commonly via aminoarylation$^{[29]}$ and aminocarbonylation$^{[27]}$. Increased Fsp$^3$ content in drug candidates has been directly correlated to the chance of the candidate’s success and is, consequently, a major goal of the pharmaceutical industry (Figure 1.3, Section 1.1.3).

The reaction mechanism for the oxyallylation process was investigated in section 1.2, and it was postulated that the desired aminoaallylation methodology would proceed via a similar reaction mechanism (Scheme 1.51). Palladium(II)-catalysed aminopalladation of alkenylamine 1.185 will lead to alkylpalladium(II) intermediate 1.186. Carbopalladation of intermediate 1.186 with an allylic halide will afford alkylpalladium(II) intermediate 1.187. β-Halide elimination will yield desired aminocyclic product 1.188 and recycle the palladium(II) catalyst.
1.3.2: Aminoallylation reaction development

The utilisation of sulfonyl-protected nitrogen species towards aminopalladative processes are well preceded and, in the first instance, was utilised to attenuate amine complexation to palladium.\textsuperscript{[75]} Above all, N-tosyl protected amines/amides have gained significant popularity, and have been utilised in a wide-range of reactions.\textsuperscript{[61,76,77]}

In particular, the aminolkyynylation protocol reported by Waser and co-workers in 2011 demonstrated efficacious reactivity when utilising tosylamides, and bears similarity to the desired aminoallylation methodology (Scheme 1.52). Alkylpalladium(II) intermediate 1.190 is a common intermediate in each process. Waser and co-workers demonstrated the trapping of alkylpalladium(II) intermediate 1.190 with hypervalent alkynyl reagent TIPS-EBX to yield alkynylpiperidone 1.191, but this work will attempt to trap the alkylpalladium(II) intermediate with an allyl halide, in the manner of the previously discussed oxyallylation methodology, to yield piperidine 1.192. Importantly, pyridone 1.193, the product of β-hydride elimination from alkylpalladium(II) intermediate 1.190, was not observed. A mechanistic study undertaken by Poli and co-workers demonstrated that β-hydride elimination from alkylpalladium(II) intermediates arising from reversible aminopalladation of tosylamides (e.g. 1.190) is impeded by palladium-sulfonyl coordination and, as a consequence, intermediates 1.190 either collapse to alkenyl-tosylamide or must undergo an alternative reaction.\textsuperscript{[78]}

\textbf{Scheme 1.51:} Proposed catalytic cycle
Scheme 1.52: Common reactivity between this work and Waser alkynylation

As a consequence, N-tosyl amides (1.189) were selected as ideal substrates for development of aminoaallylation reaction conditions, and were proposed to allow construction of a range of pyrrolidones and piperidones. Tosylamides can be efficiently constructed from the corresponding carboxylic acid using the commercially available tosyl isocyanate (Eq. 1.27).\(^{[79]}\)

\[
\text{R-OH} + \text{OSO}_2\text{Cl} \rightarrow \text{R-CONHN} = \text{SO}_2\text{H} \quad (1.27)
\]

Tosylamide 1.189 was synthesised in three steps, following a protocol published by Waser and co-workers (Scheme 1.53).\(^{[34]}\) Allylation of commercially available iodide 1.194 yielded alkenyl ester 1.195. Subsequent ester hydrolysis and isocyanate mediated tosylamide synthesis yielded desired substrate tosylamide 1.189 in a 79% yield over three steps.

Scheme 1.53: Synthesis of tosylamide 1.189

Tosylamide 1.189 was subjected to the reaction conditions previously optimised for the oxyallylation methodology (Eq. 1.28). The reaction did not produce the desired isoquinolone product 1.192, instead yielding N-allyl tosylamide 1.196 as a single product. This was likely due to the increased acidity of the tosylamide proton (pK\(_a\) ca. 3-5) compared to that of phenols (pK\(_a\) ca. 10).\(^{[80]}\) The
mechanism for the formation of $N$-allyl tosylamide 1.196 was postulated to proceed via formal deprotonation of the amide followed by substitution with allyl bromide (in absence of palladium, $N$-allyl amide 1.196 was still produced).

In order to prevent the formation of $N$-allyl amide 1.196, the reaction was attempted in the absence of base (Eq. 1.29). Base-free reaction conditions successfully prevented the formation of $N$-allyl amide 1.196 and the desired aminoallylation reaction proceeded, affording desired piperidone 1.192 in high yield. The desired isoquinolone product, however, was contaminated with pyridone 1.193, a by-product which proved to be inseparable. At this stage, simultaneous investigations were undertaken to a) find a suitable base for the reaction and; b) investigate conditions which prevent $\beta$-hydride elimination.

The aminopalladation process produces a stoichiometric amount of HX. In order to allow the aminoallylation of acid-sensitive substrates a base must be introduced into the reaction mixture. A base screen was undertaken in an attempt to find an appropriate base (Table 1.3). As discussed previously, no base (entry 1) prevented formation of $N$-allyl tosylamide 1.196, and sodium bicarbonate (entry 2) results in complete conversion to $N$-allyl tosylamide 1.196. Sodium acetate (entry 3) also gave $N$-allyl tosylamide 1.196 as a single product. In an attempt to make the conditions homogeneous, two organic nitrogen bases were tested. Pyridine (entry 4) prevented any reactivity, most likely through ligation to palladium, but 2,6-di-tert-butylypyridine (entry 5), where bulky tert-buty substituents may prevent metal ligation, successfully formed desired isoquinolone 1.192 and pyridone side-product 1.193, but suffered from reduced reaction rate. Monobasic potassium phosphate (entry 6) resulted in complete conversion to lactams 1.192 and 1.193, and allowed the reaction to proceed at a good rate. Dibasic and tribasic potassium phosphate (entries 7 and 8) resulted in complete $N$-allylation of tosylamide 1.189, affording amide 1.196. Monobasic potassium phosphate was, consequently, selected as the optimal based for the aminoallylation process.
Table 1.3: Base Screen

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>1.189 : 1.192 : 1.193 : 1.196</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>0 : 10 : 1 : 0</td>
</tr>
<tr>
<td>2</td>
<td>NaHCO₃</td>
<td>0 : 0 : 0 : 1</td>
</tr>
<tr>
<td>3</td>
<td>NaOAc</td>
<td>0 : 0 : 0 : 1</td>
</tr>
<tr>
<td>4</td>
<td>pyridine</td>
<td>1 : 0 : 0 : 0</td>
</tr>
<tr>
<td>5</td>
<td>2,6-((tBu)₂C₅H₃N</td>
<td>1 : 9 : 1 : 0</td>
</tr>
<tr>
<td>6</td>
<td>KH₂PO₄</td>
<td>0 : 9 : 1 : 0</td>
</tr>
<tr>
<td>7</td>
<td>K₂HPO₄</td>
<td>0 : 0 : 0 : 1</td>
</tr>
<tr>
<td>8</td>
<td>K₃PO₄</td>
<td>0 : 0 : 0 : 1</td>
</tr>
</tbody>
</table>

In order to prevent formation of pyridone side-product 1.193, and consequently allow isolation of piperidine 1.192, it is important to understand how, mechanistically, pyridone 1.193 was formed (Scheme 1.54). Alkylpalladium(II) intermediate 1.190, the product of aminopalladation of amide 1.189, can undergo two competing processes: carbopalladation, where subsequent β-halide elimination yields the desired piperidine 1.192 and; β-hydride elimination to exo-cyclic alkene 1.197. Rapid isomerisation yields pyridone 1.193.

A brief solvent screen was undertaken to test the effect of solvent polarity on the rate of β-hydride elimination (Table 1.4). Using dichloromethane as a solvent demonstrated slightly poorer yield and product ratio than that of toluene (entries 1 and 2). Ethanol, previously utilised by Waser and Co-workers for aminooalkynylation,[34] completely shut down aminooalkynylation reactivity.
Table 1.4: Aminoallylation solvent screen

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield (1.192 : 1.193)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhMe</td>
<td>84% (10 : 1)</td>
</tr>
<tr>
<td>2</td>
<td>CH2Cl2</td>
<td>73% (8 : 1)</td>
</tr>
<tr>
<td>3</td>
<td>EtOH</td>
<td>-</td>
</tr>
</tbody>
</table>

In order to prevent β-hydride elimination, attempts were made to increase the relative rate of the competing process: carbopalladation (Table 1.5). Results 1–3 show the effect of varying the concentration of allyl bromide. As expected, fewer equivalents of allyl bromide (entries 1 and 2) resulted in poorer chemoselectivity for piperidone 1.192. Aminoallylation reactions utilising dichloromethane as a solvent displayed a similar trend when varying allyl bromide equivalents (entries 4–6), albeit with lower selectivity for piperidone 1.192. It was expected that increasing the equivalents further would yield further improvements in the ratio, but in attempts to avoid waste it was decided that other solutions would be sought. Allyl chloride (entry 4) was utilised, and proved to have a pronounced effect on chemoselectivity, as undesired pyridone 1.193 was not observed under these conditions (see Table 1.10 for information).

Table 1.5: allyl electrophile optimisation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Y (equiv.)</th>
<th>X</th>
<th>Yield (1.192 : 1.193)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhMe</td>
<td>2</td>
<td>Br</td>
<td>71% (5 : 1)</td>
</tr>
<tr>
<td>2</td>
<td>PhMe</td>
<td>3</td>
<td>Br</td>
<td>68% (5 : 1)</td>
</tr>
<tr>
<td>3</td>
<td>PhMe</td>
<td>5</td>
<td>Br</td>
<td>84% (10 : 1)</td>
</tr>
<tr>
<td>4</td>
<td>CH2Cl2</td>
<td>2</td>
<td>Br</td>
<td>48% (3 : 1)</td>
</tr>
<tr>
<td>5</td>
<td>CH2Cl2</td>
<td>3</td>
<td>Br</td>
<td>59% (5 : 1)</td>
</tr>
<tr>
<td>6</td>
<td>CH2Cl2</td>
<td>5</td>
<td>Br</td>
<td>73% (8 : 1)</td>
</tr>
<tr>
<td>7</td>
<td>PhMe</td>
<td>5</td>
<td>Cl</td>
<td>76% (&gt;20 : 1)</td>
</tr>
</tbody>
</table>

With optimisation conditions for base and allyl electrophile in hand, it was chosen to investigate the effect of palladium ligand. Initial investigations had utilised Pd(hfacac)2 because previous oxyallylation work has been optimised with this catalyst, but there are many cheaper commercially available palladium(II) salts (Table 1.6). Utilisation of either palladium trifluoroacetate or palladium chloride (entries 2 and 3) resulted in a retarded rate of aminoallylation. Palladium acetate allowed
complete conversion of tosylamide 1.189, but with a reduced yield of isolated piperidone 1.192. Bidentate phosphine ligand diphenylphosphinoferrocene (dppf) completely shut down aminoaallylation reactivity. The previously optimal conditions, utilising a hexafluoroacetylacetanoate ligand (entry 1), proved to be ideal for the aminoaallylation of amide 1.189.

**Table 1.6: Ligand screen**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand (X)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>hfacac</td>
<td>100% conversion of SM (76% yield)</td>
</tr>
<tr>
<td>2</td>
<td>TFA</td>
<td>80% conversion of SM</td>
</tr>
<tr>
<td>3</td>
<td>Cl</td>
<td>Low conversion of SM</td>
</tr>
<tr>
<td>4</td>
<td>OAc</td>
<td>100% conversion of SM (63% yield)</td>
</tr>
<tr>
<td>5</td>
<td>dppf</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

Lithium chloride has been previously demonstrated to increase the relative rate of β-halide elimination processes.\(^7\) When utilised in the aminoaallylation process (Table 1.7, entry 1) lithium chloride demonstrated precisely no effect, most likely due to low solubility in toluene. The reaction proceeded to complete conversion, and the isolated yield of 76% was identical to same conditions without lithium chloride (Table 1.5, entry 1). In an attempt to increase the solubility of lithium chloride, a 1:1 mixture of water and toluene was utilised (entry 2), but no effect was demonstrated. These results, however, did demonstrate the tolerance of water in the developed aminoaallylation reaction conditions. Utilisation of lithium chloride in ethanol (entry 3), as per Waser’s aminoalkynylation protocol,\(^3\) resulted in the inhibition of aminoaallylation reactivity.
Table 1.7: Addition of lithium chloride

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>1.189: 1.192</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>0 : 1 (76%)</td>
</tr>
<tr>
<td>2</td>
<td>Toluene/H₂O (1:1)</td>
<td>0 : 1 (73%)</td>
</tr>
<tr>
<td>3</td>
<td>EtOH</td>
<td>1 : 0</td>
</tr>
</tbody>
</table>

(isolated yield of 1.192)

In the course of optimisation, significant precipitation was observed on the sides of the reaction vessel. This precipitate was proposed to be an insoluble sodium salt of tosylamide 1.189. In comparison to the previously optimised conditions (Table 1.6, entry 1), an attempt under aqueous biphasic conditions allowed complete dissolution and, as a consequence, the isolated yield of isoquinolone 1.192 was further improved to 95% (Table 1.8, entry 2). In comparison to the previously attempted biphasic conditions with lithium chloride (Table 1.7, entry 3), this reaction was significantly higher yielding. Finally, it was found that the reaction conditions were still efficient and high-yielding when utilising a lower catalytic loading (entry 3). The optimal conditions are mild and high-yielding, and do not require an inert atmosphere. These conditions are similar to the oxyallylation reaction conditions previously discussed, with only the base (KH₂PO₄ rather than NaHCO₃) and solvent (toluene/H₂O rather than toluene) being altered.¹⁴⁵

Table 1.8: Final optimisation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>X (mol. %)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>10</td>
<td>76%</td>
</tr>
<tr>
<td>2</td>
<td>Toluene/H₂O (1:1, v/v)</td>
<td>10</td>
<td>95%</td>
</tr>
<tr>
<td>3</td>
<td>Toluene/H₂O (1:1, v/v)</td>
<td>5</td>
<td>84%</td>
</tr>
</tbody>
</table>

The aminocyclisation process creates a new stereocentre, adjacent to the nitrogen atom. Chiral amines are important synthetic intermediates and are common structural motifs in pharmaceutically active molecules.¹⁰ As a consequence, the development of enantioselective reaction conditions was a key objective. Attempts towards the control of stereochemistry using chiral ligands are detailed below (Table 1.9). In 2012, Zhang and co-workers demonstrated an asymmetric aza-Wacker protocol utilising a pyrox (pyridyl-oxazoline) ligand.¹⁸¹ Pyrox (entry 1) and iPr-Quinox (entry 2) resulted in
complete shutdown of aminoallylation reactivity. Bisoxazoline 1.198 (entry 3) demonstrated the same effect. Pyridine was previously demonstrated to have a negative effect on reactivity, so the results were expected. In 2010, Wolfe and co-workers demonstrated that a range of arylphosphines can control the stereochemistry in aminoarylation reactions.[32] T-Binap (entry 4) prevented the aminoallylation from proceeding. Furthermore, triphenylphosphine was discovered to have the same effect (entry 5). The results demonstrate that two major classes of asymmetric palladium ligands inhibit aminoallylation reactivity. As a consequence, no further chiral ligands were utilised.

Table 1.9: Utilisation of chiral ligands

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>1.189 : 1.192</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pyrox</td>
<td>1 : 0</td>
</tr>
<tr>
<td>2</td>
<td>iPr-Quinox</td>
<td>1 : 0</td>
</tr>
<tr>
<td>3</td>
<td>Bisoxazalone</td>
<td>1.198</td>
</tr>
<tr>
<td>4</td>
<td>(S)-T-Binap</td>
<td>1 : 0</td>
</tr>
<tr>
<td>5</td>
<td>PPh₃</td>
<td>1 : 0</td>
</tr>
</tbody>
</table>

Mechanistic Considerations

As discussed previously (Section 1.2.1), utilising different allylic halides can have a profound effect on the reactivity. One possible explanation is that this was due to the palladium halide species formed by β-halide elimination. In an attempt to further understand the effect, the aminoallylation reaction conversion was compared for a variety of halides (Table 1.10). In 1 h, aminoallylation with allyl chloride (entry 1) proceeded to 66% conversion of amide 1.189 to piperidone 1.192. Aminoallylation with allyl bromide (entry 2) proceeded to 25% conversion, but with allyl iodide (entry 3) formation of the desired piperidone was not observed. Addition of lithium chloride (entries 4 and 5) had no significant effect on reactivity, although this was proposed to be due to low solubility of lithium chloride in toluene. Addition of soluble chloride salt tetrabutylammonium chloride (entries 6 and 7) resulted in no conversion of tosylamide 1.189. The investigation demonstrated that the reaction rate when utilising allyl chloride is faster for tosylamide 1.192. Previous work has demonstrated that, in many cases, utilisation of allyl bromide results in more efficient heteroallylation. There is, as yet, no
demonstrable trend to which substrates react more efficiently with either allyl bromide or allyl chloride.

Table 1.10: Halide investigation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Allyl-X</th>
<th>Additive</th>
<th>1.189 : 1.192</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Chloride</td>
<td>-</td>
<td>1 : 2</td>
</tr>
<tr>
<td>2</td>
<td>Bromide</td>
<td>-</td>
<td>3 : 1</td>
</tr>
<tr>
<td>3</td>
<td>Iodide</td>
<td>-</td>
<td>1 : 0</td>
</tr>
<tr>
<td>4</td>
<td>Bromide</td>
<td>Lithium Chloride (2 equiv.)</td>
<td>4 : 1</td>
</tr>
<tr>
<td>5</td>
<td>Iodide</td>
<td>Lithium Chloride (2 equiv.)</td>
<td>1 : 0</td>
</tr>
<tr>
<td>6</td>
<td>Bromide</td>
<td>TBACl (2 equiv.)</td>
<td>1 : 0</td>
</tr>
<tr>
<td>7</td>
<td>Iodide</td>
<td>TBACl (2 equiv.)</td>
<td>1 : 0</td>
</tr>
</tbody>
</table>

As discussed in section 1.2.3, alkene substitution of the allylic halide will have a significant effect on the rate of carbopalladation, if the reaction is proceeding via the proposed aminopalladation–carbopalladation mechanism. Gem-disubstituted allyl chloride was utilised in the aminoallylation of tosylamide 1.189 (Scheme 1.55). While desired isoquinolone 1.199 was observed, the reaction resulted in significant conversion to pyridone 1.193, the product of β-hydride elimination from alkylpalladium(II) intermediate 1.190. Pyridone 1.193 was not observed when utilising allyl chloride under the same reaction conditions (Table 1.4).

Scheme 1.55: Utilisation of gem-disubstituted allyl halide

That the alkene substitution has a major effect on the carbon–carbon bond forming event supports the proposal of carbopalladation–β-halide elimination. In order to increase the relative rate of the intermolecular carbopalladation process, the reaction concentration was increased (Eq. 1.30). When tosylamide 1.189 was treated with methylallyl chloride under aminoallylation reaction conditions at a concentration of 0.5 M (as opposed to 0.25 M in Scheme 1.55) pyridone by-product 1.193 was only
observed as 10% of the crude material. Desired isoquinolone product 1.199 was isolated in a 71% yield.

1.3.3: Substrate scope – Tosyl-protected Amides

With optimised conditions having been discovered for tosylamide 1.189, the next goal was increase the substrate scope, and to test the limitations of the methodology. It was proposed that pyrrole-containing tosylamides (e.g. 1.202) would allow access to piperazine derivatives, a common motif in biologically active compounds. Pyrrole 1.202 was synthesised in three steps from methyl pyrrole-2-carboxylate following a known protocol (Scheme 1.56). Pyrrole 1.200 was subjected to base-promoted allylation conditions to yield N-allyl pyrrole 1.201. The substrate synthesis was completed by ester hydrolysis and formation of tosylamide 1.202 using tosyl isocyanate.

Scheme 1.56: Synthesis of pyrrole 1.202

N-Tosyl pyrrole 1.202 was subjected to the previously optimised conditions (Scheme 1.57). Although desired piperazine 1.204 was observed, the reaction rate was slow and the overall conversion of tosylamide 1.202 was less than 10%. Pyrazine 1.205, the product of β-hydride elimination from alkylpalladium(II) intermediate 1.203 followed by isomerisation, was not observed. Consequently, it was proposed that the slow reaction rate was due to a retarded rate of aminopalladation.

Scheme 1.57: Synthesis of piperazine 1.204
In order to increase the conversion of tosylamide 1.202, increasing the rate of aminopalladation was targeted (Table 1.11). When subjected to the previously optimised conditions (entry 1), the reaction was slow and the conversion of tosylamide 1.202 low (<10%). Increased concentration (entry 2) led to an increase in the conversion of tosylamide 1.202 to 50%. It was found that there was no further catalyst turnover at 50% conversion, so an increase of catalyst loading (entry 3) demonstrated an expected improvement in conversion to 66%, although the isolated yield of piperazine 1.204 was low (30%). Increasing the reaction temperature to 80 °C (entry 4), further increase in the conversion of pyrrole 1.202 was demonstrated (90%), and allowed isolation of piperazine 1.204 in a 61% yield.

**Table 1.11: aminoallylation of pyrrole 1.202**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Solvent</th>
<th>Concentration (M)</th>
<th>X (mol. %)</th>
<th>1.202 : 1.204 (isolated yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>PhMe</td>
<td>0.25 M</td>
<td>5</td>
<td>&gt; 10 : 1</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>PhMe</td>
<td>0.50 M</td>
<td>5</td>
<td>1 : 1</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>PhMe/H₂O</td>
<td>0.50 M</td>
<td>10</td>
<td>1 : 2 (30%)</td>
</tr>
<tr>
<td>4</td>
<td>80</td>
<td>PhMe/H₂O</td>
<td>0.50 M</td>
<td>10</td>
<td>1 : 9 (61%)</td>
</tr>
</tbody>
</table>

Indole tosyl amides (e.g. 1.208) were proposed to give access to indolo-piperazines, a motif which has been incorporated in pharmaceutically-active compounds.[84,85] Tosylamide 1.208 was synthesised via the same protocol as described for pyrrole 1.202 (Scheme 1.58). Allylation of indole 1.206, followed by ester hydrolysis and tosyl-amide formation yielded desired indole 1.208 in 52% yield over three steps.

**Scheme 1.58: Synthesis of indole 1.208**

Indole 1.208 was subjected to the aminoallylation conditions found optimal for pyrrole 1.202 (table 1.12, entry 1). Desired piperazine 1.209 was observed, but the conversation of the starting tosylamide was poorer than for pyrrole 1.202 (50% vs 90%). A significant volume of precipitate was observed, which was previously resolved through the use of aqueous reaction conditions. In this case, addition of water (entry 2) allowed an increase of conversion to 75%, although precipitation was still observed. Increasing solvent volume (entry 3) allowed complete dissolution and allowed 90%
conversion of indole 1.209, with a 54% isolated yield of piperazine 1.209. Entry 4 demonstrates reproducibility and scalability of the reaction conditions.

**Table 1.12: Indole optimisation**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Concentration (M)</th>
<th>Scale (mmol)</th>
<th>1.208 : 1.209 (isolated yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhMe</td>
<td>0.50</td>
<td>0.16</td>
<td>1 : 1</td>
</tr>
<tr>
<td>2</td>
<td>PhMe/H₂O</td>
<td>0.50</td>
<td>0.16</td>
<td>1 : 3</td>
</tr>
<tr>
<td>3</td>
<td>PhMe/H₂O</td>
<td>0.25</td>
<td>0.06</td>
<td>1 : 9 (54%)</td>
</tr>
<tr>
<td>4</td>
<td>PhMe/H₂O</td>
<td>0.25</td>
<td>0.42</td>
<td>1 : 9 (60%)</td>
</tr>
</tbody>
</table>

Having demonstrated the synthesis of piperidones and piperazines, subsequent efforts focussed on the synthesis of pyrrolidones. Tosylamide 1.212, a vinyl analogue of allyl tosylamide 1.189 used previously, was chosen for initial trials, and was synthesised in two steps (Scheme 1.59). Wittig methlenation of aldehyde 1.210 yielded 2-vinyl benzoic acid 1.211. Subsequent tosyl amide formation yielded amide 1.212.

**Scheme 1.59: Synthesis of vinyl-benzamide 1.212**

Tosylamide 1.212 was subjected to the aminoallylation conditions (Scheme 1.60). Rather than yielding desired aminoallylation product isoindolinone 1.214, which was not observed in the crude material, the attempted aminoallylation of tosylamide 1.212 instead produced a high yield of exo-cyclic methylene pyrrolidone 1.215. Pyrrolidone 1.215 was formed as a result of β-hydride elimination from alkylpalladium(II) intermediate 1.213 (vide infra). It was also demonstrated that an increase in reaction concentration had no effect on reactivity.
Scheme 1.60: Aminoaallylation of tosylamide 1.212

The reaction demonstrates a catalytic aza-Wacker reaction without a traditional stoichiometric reoxidant (Scheme 1.61). β-Hydride elimination from alkylpalladium(II) intermediate 1.213 would result in pyrrolidone 1.215 and palladium(0), which would ordinarily be reoxidised by oxygen or a copper salt. The reaction was run in atmospheric conditions, so oxygen was a potential reoxidant, but it is also possible that the high concentration of allyl chloride was facilitating reoxidation via oxidative addition to an allylpalladium chloride species.

Scheme 1.61: Proposed mechanism for catalytic aza-Wacker cyclisation of tosylamide 2.212

In an attempt to suppress β-hydride elimination, diphenylphosphinoferrocene(dppf)-palladium chloride was utilised. It was demonstrated by Hartwig and co-workers that larger ligands on arylpalladium(II) intermediates accelerated the relative rate of reductive elimination over β-hydride elimination.\(^8\) It was further demonstrated that dppf favoured reductive elimination over β-hydride elimination due to chelation and a large bite angle.\(^7\) Upon utilisation of PdCl\(_2\)(dppf) in the aminoaallylation reaction (Eq. 1.31), there was no conversion of tosylamide 1.212 and no product of aminoaallylation was observed. It has been previously demonstrated that phosphine ligands have a detrimental effect on aminoaallylation reactivity (Table 1.9).
Previous reports have demonstrated that an increase in halide ion concentration, especially chloride ion concentration, can decrease the relative rate of β-hydride elimination.\cite{88,89} The aminoalkynylation report by Waser and co-workers demonstrated the utilisation of lithium chloride to inhibit the formation of β-hydride elimination products.\cite{34} In the case of the aminoallylation of tosylamide 1.212, addition of lithium chloride had no effect on reactivity and desired isoindolinone 1.214 was not observed (Eq. 1.32).

The addition of acetic acid has previously been demonstrated to attenuate β-hydride elimination from alkylpalladium(II) intermediates in certain systems.\cite{78} This approach was not viable for the aminoallylation protocol, however, because treatment of tosylamide 1.212 with acetic acid under the aminoallylation reaction conditions proved to prevent conversion of tosylamide 1.212. Neither pyrrolidone 1.214 or 1.215 were observed (Eq. 1.33).

Clearly, in the case of tosylamide 1.212, the aminoallylation reaction conditions are highly chemoselective for β-hydride elimination product 1.215 (Scheme 1.62). This was in contrast to the reactivity of tosylamide 1.189, which successfully underwent aminoallylation to yield isoquinolone 1.192 with high chemoselectivity. Alkylpalladium(II) intermediates 1.213 and 1.190 are functionally similar, but undergo different termination processes. It is probable that the rate of carboxypalladation with allyl chloride is not significantly different in either case. It was thus proposed that β-hydride elimination from alkylpalladium(II) intermediate 1.213 was significantly faster. Three possible explanations for this are: a) increased rate of β-hydride elimination of a benzylic hydrogen atom; b)
alignment of the palladium atom and the β-hydrogen are more closely coplanar in alkylpalladium intermediate 1.213; or c) the external C–C bond angle of isoindoline intermediate 1.213 destabilises palladium-sulfonyl coordination. To the author’s best knowledge this difference in reactivity has not been previously remarked upon.

Scheme 1.62: Contrasting alkylpalladium(II) intermediates 1.213 and 1.190

Having concluded that tosylamide 1.212 is highly chemoselective for the β-hydride elimination, it was decided to investigate whether the increased rate of β-hydride elimination was accelerated by the presence of a benzylic hydride. Towards this goal, tosylamide 1.218 was synthesised via a 2 step protocol (Scheme 1.63). Suzuki-coupling of arylbromide 1.216 with a vinylboronate proceeded in excellent yield. Subsequent tosylamide formation gave tosylamide 1.218 in a 54% yield.

Scheme 1.63: Synthesis of tosylamide 1.218

When treated with Pd(II) under aminopalladation conditions, tosylamide 1.218 was found to be completely unreactive. Neither desired piperidone 1.219 nor piperidone 1.220, the product of β-hydride elimination, were observed. That the aminopalladation did not occur does not provide any conclusive results about the reactivity of conjugated alkenes to aminopalladation. Attempts to force conversion of tosylamide 1.218 through increased temperature, increased concentration and increased catalyst loading were all unsuccessful.
In an attempt to increase the substrate scope, it was decided to move away from aromatic-ring containing tosylamides, which is important from the perspective of increasing Fsp$^3$. Tosylamide 1.68 was synthesised in a single step from commercially available pentenoic acid 1.221 (Eq. 1.35). Tosylamide formation proceeded efficiently under the previously used isocyanate-mediated protocol.

Tosylamide 1.68 was synthesised in a single step from commercially available pentenoic acid 1.221 (Eq. 1.35).

Treatment of tosylamide 1.68 with Pd(II) and allyl chloride under the aminoallylation protocol did not yield either desired pyrrolidone 1.222 or pyrrolidone 1.223 – the product of β-hydride elimination and isomerisation.

Attempts to increase the rate of aminopalladation are summarised below (Table 1.13). The optimal aminoallylation conditions utilised above (Eq. 1.36) are shown in entry 1. Increasing the reaction temperature (entry 2), increasing the reaction concentration (entry 3) and use of allyl bromide (entry 4) all had no effect on the reactivity. Pyrrolidones 1.222 and 1.223 were not observed under any conditions.

Table 1.13: Aminoallylation attempts towards pyrrolidone 1.222

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Concentration (M)</th>
<th>Allyl-X</th>
<th>1.68 : 1.222 : 1.223</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>0.25</td>
<td>Cl</td>
<td>1 : 0 : 0</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>0.25</td>
<td>Cl</td>
<td>1 : 0 : 0</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>0.50</td>
<td>Cl</td>
<td>1 : 0 : 0</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>0.25</td>
<td>Br</td>
<td>1 : 0 : 0</td>
</tr>
</tbody>
</table>

Concurrently, the analogous hexenamide substrate 1.225 was synthesised from commercially available hexenoic acid 1.224 in a single step using the previously discussed isocyanate-mediated protocol (Scheme 1.64). With the substrate in hand, it was subjected to the optimal aminoallylation
conditions. As with pentenamide 1.68 above, there was no conversion of tosylamide 1.225 and desired piperidone 1.226 was not observed. Piperidone 1.227, the product of β-hydride elimination, was also not observed.

**Scheme 1.64:** Synthesis and attempted aminoallylation of tosylamide 1.225

In the case of tosylamides 1.68 and 1.225, no product of an aminopalladative process was observed. The lack of products arising from β-hydride elimination, which has been demonstrated to be a rapid process, suggests that neither tosylamide is undergoing aminopalladation. This was in contradiction to Waser’s aminoalkynylation report however, which demonstrated that both tosylamides 1.68 and 1.225 successfully undergo aminopalladation (Eq. 1.37). As a consequence, the reason for a lack of aminoallylation of either 1.68 or 1.225 is currently unknown.

It was proposed that taking advantage of the gem-disubstituent effect would allow the aminoallylation reaction to proceed, either by lowering the energy of the aminopalladation reactive rotamer or through stabilisation of the resultant alkylpalladium(II) intermediate. By introducing gem-dimethyl functionality to the α-amide position, the rotamer population will be shifted in favour of the reactive rotamer, potentially increasing the rate of aminopalladation. Tosylamide 1.230 was proposed to test this theory (Scheme 1.65). Double deprotonation of isobutyric acid 1.228, followed by allylation of the resultant dianion yielded dimethylpentenoic acid 1.229. Tosylamide formation under the tosylisocyanate-mediated conditions yielded tosylamide 1.230.

**Scheme 1.65:** Synthesis of tosylamide 1.230
With the tosylamide 1.230 in hand, the substrate was subjected to the aminoaallylation reaction conditions (Scheme 1.66). The substrate successfully underwent aminopalladation, but desired pyrrolidone 1.232 was not observed. Pyrrolidone 1.233, a product of β-hydride elimination from alkylpalladium(II) intermediate 1.231, was observed as a single product.

![Scheme 1.66: Attempted cyclisation of gem-dimethyl tosylamide 1.230](image)

Attempts made towards increasing the rate of carbopalladation are summarised below (Table 1.14). The previously optimal conditions are detailed in entry 1. Change of palladium ligand to acetate, which previously allowed rapid aminoaallylation (Table 1.6), did not result in the synthesis of pyrrolidone 1.232. Attempts to prevent β-hydride elimination by utilising the diphenylphosphinoferrocene ligand (entry 3) completely prevented aminopalladation, corroborating the previously demonstrated non-reactivity with phosphine ligands. Increase in concentration (entry 4) did not increase the relative rate of carbopalladation enough to overcome β-hydride elimination. Utilisation of allyl bromide (entry 5) had a profoundly negative effect on aminopalladation, and the only observed reactivity was alkene isomerisation, yielding alkene 1.234.

![Table 1.14: Attempts towards the synthesis of pyrrolidone 1.232](image)
Concurrently, cyclohexyl-tosylamide 1.237 was proposed in an attempt to increase the population of the reactive rotamer, similarly to gem-dimethyl tosylamide 1.230. Tosylamide 1.237 was synthesised in 2 steps, starting from cyclohexylcarboxylic acid 1.235, via the same protocol as gem-dimethyl substrate 2.30 (Scheme 1.67).

![Scheme 1.67: Synthesis of cyclohexyl-tosylamide 1.237](image)

Cyclohexyl-tosylamide 1.237 was subjected to the optimal aminoallylation conditions (Scheme 1.68). In a similar manner to tosylamide 1.230, desired pyrrolidone 1.239 was not observed. Pyrrolidone 1.240 was observed as a single product, which would indicate that cyclohexyl-tosylamide 1.237 successfully undergoes aminopalladation to yield alkylpalladium(II) intermediate 1.238, but subsequently undergoes β-hydride elimination and isomerisation.

![Scheme 1.68: Attempted aminoallylation of cyclohexyl-tosylamide 1.237](image)

Similar attempts towards the synthesis of cyclohexyl-pyrrolidone 1.237 were made to those shown for gem-dimethyl tosylamide 1.230 (Table 1.15). Changing the catalyst from Pd(hfacac)₂ (entry 1) to palladium acetate (entry 2) or palladium acetylacetanone (entry 3) demonstrated no change in reactivity. Addition of lithium chloride (entry 4) completely inhibited aminopalladation of tosylamide 1.237.
Table 1.15: Attempts towards aminomallylation of cyclohexylamide 1.237

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd(X)$_2$</th>
<th>Additive</th>
<th>1.237 : 1.239 : 1.240</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(hfacac)$_2$</td>
<td>-</td>
<td>0 : 0 : 1</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)$_2$</td>
<td>-</td>
<td>0 : 0 : 1</td>
</tr>
<tr>
<td>3</td>
<td>Pd(acac)$_2$</td>
<td>-</td>
<td>0 : 0 : 1</td>
</tr>
<tr>
<td>4</td>
<td>Pd(hfacac)$_2$</td>
<td>LiCl (3 equiv.)</td>
<td>1 : 0 : 0</td>
</tr>
</tbody>
</table>

While attempts towards pyrrolidone synthesis have been, thus far, unsuccessful, previous attempts towards the synthesis of piperidones have shown chemoselectivity for allylation over β-hydride elimination (Scheme 1.60). *Gem*-dimethyl tosylamide 1.242 was designed to give access to saturated piperidones. The substrate was synthesised by a similar protocol to tosylamide 1.230 above (Scheme 1.69). C-Alkylation of isobutyric acid with homoallylic bromide yielded dimethylhexenoic acid 1.241, in a 58% yield. Formation of the tosylamide proceeded in good yield to garner tosylamide 1.242.

Scheme 1.69: Synthesis of tosylamide 1.242

Tosylamide 1.242 was subjected to the optimal aminomallylation reaction conditions (Eq. 1.38). Piperidone 1.243 was not observed. Furthermore, no other product of an aminopalladative process was observed. Tosylamide 1.242 was recovered.

In order to increase the rate of aminopalladation, the catalyst loading was increased. After 48 h, the only observed reaction of tosylamide 1.242 was N-allylation to N-allyl tosylamide 1.244 (Eq. 1.39). No further attempts were made towards the synthesis of piperidine 1.243.
Previous straight-chained tosylamides suffered either from $\beta$-hydride elimination or from a lack of aminopalladation. Malonamide 1.248 was prepared in an attempt to combat the latter by increasing the number of potential reactive rotamers (Scheme 1.70). It may also, if successful, assess whether the reaction can tolerate an amide which is not involved in the cyclisation. Dimethylmalonate 1.245 was allylated under basic conditions to yield 2-allyl-dimethylmalonate 1.246. Subsequent ester hydrolysis furnished allyl malonic acid 1.247. Isocyanate mediated amide formation yielded the desired tosylmalonamide 1.248.

The substrate was subjected to the optimal aminopalladation reaction conditions (Eq. 1.40). Desired product 1.249 was not observed in the crude material and malonamide 1.248 was recovered. Despite having two possible reactive-rotamers, malonamide 1.248 did not undergo aminopalladation (neither desired pyrrolidone 1.249 nor pyrrolidone 1.250, the product of $\beta$-hydride elimination and isomerisation were observed), highlighting the slow rate of aminopalladation in aliphatic tosylamides.

In their 2011 aminoalkynylation report, Waser and co-workers demonstrated the applicability of the aminoalkynylation reaction conditions to a range of carbamates and ureas. Carbamate 1.253 was proposed to test the applicability of carbamates to the aminoallylation methodology (Scheme 1.71). Benzaldehyde underwent Grignard addition with allylmagnesium bromide to yield benzylic alcohol 1.252. Subsequent carbamate formation yielded the desired tosylcarbamate 1.253.
Carbamate 1.253 was submitted to the optimal aminoallylation conditions, but there was no reactivity (Eq. 1.41). That oxazinone 1.254, nor any product of β-hydride elimination, was observed, suggests that tosylcarbamate 1.253 was not undergoing aminopalladation.

Attempts to increase the rate of aminopalladation by increasing reaction temperature only resulted in N-allylation (Eq. 1.42). That the substrate preferentially yields N-allyl carbamate 1.255, rather than undergoing aminoallylation demonstrates that the current aminoallylation conditions are not suitable for the synthesis of aminocycle 1.254.

1.3.4: Overcoming β-hydride elimination

A significant number of the attempted aminoallylation reactions attempted thus far have suffered from β-hydride elimination, rather than undergoing allylation. As previously discussed in section 1.1.3, many carboamination protocols relied on rapid trapping of the alkylpalladium(II) intermediate to prevent β-hydride elimination. In attempts towards aminoallylation, it has been demonstrated that, for many substrates, the rate of carbopalladation with allyl halides is slower than the rate of β-hydride elimination. Towards the goal of generalised aminoallylation conditions which would allow the synthesis of a range of nitrogen-containing heterocycles, a method to reliably prevent β-hydride elimination was sought.

The oxyallylation methodology demonstrated that heteropalladation onto a disubstituted alkene was an efficient way to prevent β-hydride elimination (Scheme 1.72). Initial oxypalladation of alkene 1.148 resulted in alkylpalladium(II) intermediate 1.149. β-Hydride elimination from this
intermediate is impossible, and thus must either collapse back to starting material 1.148, or undergo carbopalladation to the isobenzofuran 1.152. For the application to aminoallylation, disubstituted alkene 1.256 was proposed.

![Scheme 1.72: Oxyallylation intermediate](image)

The proposed contrast in reactivity between disubstituted alkene 1.256 and mono-substituted alkene 1.212 is summarised in Scheme 1.73. Aminopalladation onto a mono-substituted alkene 1.212 results in alkylpalladium(II) intermediate 1.213. Rapid β-hydride elimination yields isoindolinone 1.215. Carbopalladation to isoindolinone 1.214 was not observed. Aminopalladation onto a gem-disubstituted alkene 1.256 is proposed to yield alkylpalladium(II) intermediate 1.257. β-Hydride elimination is not possible from this intermediate. Alkylpalladium(II) intermediate must, therefore, either collapse back to the starting material 1.256, undergo carbopalladation to isoindolinone 1.258 or undergo another, undesired, termination process.

![Scheme 1.73: Proposed aminoallylation reactivity of disubstituted alkenes](image)

Previous examples of aminopalladation by protected-amides onto gem-disubstituted alkenes are relatively uncommon. The previously discussed report on aminoalkynylation from Waser and co-
workers reported a single example of a gem-disubstituted alkene (Eq. 1.43). Aminoalkynylation of the disubstituted alkene proceeded in good yield when compared to the mono-substituted, albeit under slightly altered conditions and an extended reaction time. Further examples have been demonstrated by Zhang and Yoshida.

Model disubstituted alkene substrate 1.256 was synthesised in a single step from previously utilised 2-isopropenyl benzoic acid 1.174 using the isocyanate-mediated tosylamide formation protocol (Eq. 1.44).

Tosylamide 1.256 was subjected to the optimised aminoallylation conditions (Scheme 1.74). However, no conversion to pyrrolidone 1.257 was observed, and the starting material was recovered. At this stage, it was unknown whether the lack of reactivity was due to a slow rate of aminopalladation leading to alkylpalladium(II) intermediate 1.257, or a slow rate of carbopalladation of intermediate 1.257 with allyl chloride.

Attempts made at increasing the rate of both processes are summarised in Table 1.16. Increased reaction temperature (entries 1, 2 and 3) did not allow conversion of 1.256 to pyrrolidone 1.258. An increase in reaction concentration (entries 4 and 5) also failed to yield pyrrolidone 1.258.
Table 1.16: Variation of concentration and temperature

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Concentration (M)</th>
<th>1.256 : 1.258</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>0.25</td>
<td>1 : 0</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>0.25</td>
<td>1 : 0</td>
</tr>
<tr>
<td>3</td>
<td>110</td>
<td>0.25</td>
<td>1 : 0</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>0.50</td>
<td>1 : 0</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>1.0</td>
<td>1 : 0</td>
</tr>
</tbody>
</table>

It was next proposed that the bulky bidentate hexafluoroacetyl acetate ligand was preventing aminopalladation onto the bulkier gem-disubstituted alkene. The results of the catalyst screen are summarised in (Table 1.17). Palladium acetate, which previously showed good conversion in mono-substituted alkenes (Table 1.6), showed no improvement, either at 0.25 M (entry 1) or at the increased concentration of 0.5 M (entry 2). Palladium chloride (entry 3), a significantly smaller ligand than hfacac, also showed no improvement in reactivity.

Table 1.17: Catalyst screen

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Concentration (M)</th>
<th>1.256 : 1.258</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)$_2$</td>
<td>0.25</td>
<td>1 : 0</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)$_2$</td>
<td>0.50</td>
<td>1 : 0</td>
</tr>
<tr>
<td>3</td>
<td>PdCl$_2$</td>
<td>0.25</td>
<td>1 : 0</td>
</tr>
</tbody>
</table>

Attempts towards aminoallylation of geminally-disubstituted alkenes were also, concurrently, undertaken on tosylamide 1.260, the disubstituted alkene analogue of model substrate 1.189. The substrate was synthesised in 3-steps following a modification to the procedure used for the synthesis of tosylamide 1.189 (Scheme 1.75). Allylation of aryl iodide 1.194 with 2-methylallyl chloride yielded methallylbenzyl ester 1.259. Subsequent ester hydrolysis and tosylamide-formation yielded tosylamide 1.260 in 3 steps.
Initial attempts towards the aminoallylation of tosylamide 1.260 were made using the then optimal aminoallylation reaction conditions (Scheme 1.76). Desired isoquinolone product 1.262 was observed as part of the crude material, but the conversion of tosylamide 1.260 was low.

It is unknown if slow aminopalladation to alkylpalladium(II) intermediate 1.261 or slow carbopalladation of intermediate 1.261 with allyl chloride was the cause of low reactivity. Both processes are palladium catalysed, so the catalytic loading of palladium was increased (Eq. 1.45). The increased catalytic loading allowed for increased conversion of tosylamide 1.260 and desired isoquinolone 1.262 was isolated in a 33% yield.

Attempts to increase the rate of aminoallylation are summarised in Table 1.18. Increased temperature to 80 °C (entry 2) resulted in lower conversion of alkene 1.260 due to rapid catalyst deactivation. Further increase of temperature to 110 °C (entry 3) prevented aminoallylation altogether, and the only reactivity was isomerisation of alkene 1.260 to tri-substituted alkene 1.263. Increased concentration (entry 4) also resulted in rapid catalyst deactivation.
**Table 1.18:** Attempts towards high-yielding reaction conditions for the aminoallylation of tosylamide 1.260

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Concentration (M)</th>
<th>1.260 : 1.262 : 1.263</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>0.5</td>
<td>2 : 1 (33%) : 0</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>0.5</td>
<td>9 : 1 : 0</td>
</tr>
<tr>
<td>3</td>
<td>110</td>
<td>0.5</td>
<td>1 : 0 : 1</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>1.0</td>
<td>9 : 1 : 0</td>
</tr>
</tbody>
</table>

In the case of Waser and co-workers’ aminoalkynylation, the single example of a gem-disubstituted alkene required different conditions, including the use of 4-chlorosalicylic acid. Addition of 4-chlorosalicylic acid (Table 1.19, entry 2) completely inhibited aminoallylation reactivity. This was potentially caused by the viscosity of the reaction mixture due to the low solubility of 4-chlorosalicylic acid. Increased solvent volume (entry 3) allowed dissolution, but aminoallylation did not proceed. It is unknown whether this was due to the significantly lowered concentration or the 4-chlorosalicylic acid. Utilisation of dichloromethane (entry 4), the solvent utilised by Waser *et al.* had no improvement on reactivity. Addition of lithium chloride and utilisation of ethanol as the solvent (entry 5), the conditions utilised by Waser *et al.* for mono-substituted alkenes, resulted in gem-dimethyl piperidone product 1.264. Piperidone 1.264 is proposed to be either a product of protodepalladation from alkylpalladium(II) intermediate 1.261 or of direct hydroamination of alkene 1.260 with HCl, an acidic by-product of the desired aminoallylation process. In order to prevent this process, mono potassium phosphate was added (entry 6), which successfully prevented formation of piperidone 1.264 but also prevented formation of desired isoquinolone 1.262. Utilisation of lithium chloride with the previously optimised conditions also failed to demonstrate conversion of alkene 1.260.
Table 1.19: Utilisation of Waser’s conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Additive (2 equiv.)</th>
<th>Concentration (M)</th>
<th>1.260 : 1.262 : 1.264</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhMe</td>
<td>-</td>
<td>0.50</td>
<td>2 : 1 (33%) : 0</td>
</tr>
<tr>
<td>2</td>
<td>PhMe</td>
<td>4-Chlorosalicylic acid</td>
<td>0.50</td>
<td>1 : 0 : 0</td>
</tr>
<tr>
<td>3</td>
<td>PhMe</td>
<td>4-Chlorosalicylic acid</td>
<td>0.05</td>
<td>1 : 0 : 0</td>
</tr>
<tr>
<td>4</td>
<td>CH₂Cl₂</td>
<td>4-Chlorosalicylic acid</td>
<td>0.05</td>
<td>1 : 0 : 0</td>
</tr>
<tr>
<td>5</td>
<td>EtOH</td>
<td>LiCl</td>
<td>0.50</td>
<td>0 : 0 : 1</td>
</tr>
<tr>
<td>6</td>
<td>EtOH</td>
<td>LiCl + KH₂PO₄</td>
<td>0.50</td>
<td>1 : 0 : 0</td>
</tr>
<tr>
<td>7</td>
<td>PhMe</td>
<td>LiCl + KH₂PO₄</td>
<td>0.50</td>
<td>1 : 0 : 0</td>
</tr>
</tbody>
</table>

Waser also gave a single example of the aminoalkynylation of a disubstituted alkene in his 2010 oxyalkynylation report.[33] The optimised conditions were tested with the addition of allyl chloride, but no conversion of alkene 1.260 to either desired piperidone 1.262 or piperidone by-product 1.264 was observed (Eq. 1.45).

1.3.5: Substrate Scope – Boc-protected amides

It was proposed that tuning the reactivity of the nitrogen through variation of the protecting group would have a significant effect on aminoaallylation, and hence allow the expansion of substrate scope. tert-Butyl carbamate groups (Boc-amines) are a common nitrogen protecting group used regularly in palladium-catalysed aminocyclisation, but there are currently no examples of aminopalladation reactions with Boc-protected amides in the chemical literature, though they have been utilised for other aminocyclisation strategies.[7] The model Boc-amide substrate 1.265 was synthesised in a single step from previously synthesised benzoic acid 1.174, by treatment with tert-butyl carbamate and phenylsilane (Eq. 1.47).
The model substrate was subjected to the previously optimised conditions aminoallylation conditions (Scheme 1.77). There was no observed conversion to desired isoindolinone 1.267, and Boc-amide 1.265 was recovered.

Scheme 1.77: Attempted aminoallylation of amide 1.267

It was proposed that aminoallylation reactivity was inhibited by either a slow rate of aminopalladation of Boc-amide 1.265 or a slow rate of carbopalladation of alkylpalladium(II) intermediate 1.266 with allyl chloride. Attempts to increase the rate of both processes are detailed below (Table 1.20). Increased concentration (entry 2) had no effect. Change of catalyst to palladium acetate (entry 3), a less bulky ligand than hexafluoroacetylacetanate, also had no effect. An increase in temperature to 80 °C demonstrated no conversion of Boc-amide 1.265. Further increase of temperature to 110 °C demonstrated complete conversion of the starting material, but did not yield desired isoindolinone 1.267 (see Scheme 1.78).

Table 1.20: Attempted cyclisation of 1.265

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Pd(X)₂</th>
<th>Concentration (M)</th>
<th>1.265 : 1.267</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>Pd(hfacac)₂</td>
<td>0.25</td>
<td>1 : 0</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>Pd(hfacac)₂</td>
<td>0.50</td>
<td>1 : 0</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>Pd(OAc)₂</td>
<td>0.50</td>
<td>1 : 0</td>
</tr>
<tr>
<td>4</td>
<td>80</td>
<td>Pd(OAc)₂</td>
<td>0.50</td>
<td>1 : 0</td>
</tr>
<tr>
<td>5</td>
<td>110</td>
<td>Pd(OAc)₂</td>
<td>0.50</td>
<td>0 : 0</td>
</tr>
</tbody>
</table>
At 110 °C, full conversion of Boc-amide 1.265 was observed, but rather than forming desired pyrrolidone 1.267, the reaction proceeded to form lactone 1.268 (Scheme 1.78). The formation of lactone 1.268 is proposed to proceed via initial carbamate hydrolysis of Boc-amide 1.265 by adventitious water to yield isopropenyl benzoic acid 1.174. The acid subsequently undergoes efficient oxyallylation to yield lactone 1.268.[45]

![Scheme 1.78: Proposed mechanism for formation of lactone 1.268](image)

The optimised aminoallylation protocol allows the reaction to proceed under non-inert conditions. In this case however, it was predicted that water-free reaction conditions would inhibit the hydrolysis of Boc-amide 1.265 and, consequently, the formation of lactone 1.268 (Eq. 1.48). The reaction successfully prevented formation of lactone 1.268, but there was also no observed aminoallylation to pyrrolidone 1.268 and Boc-amide 1.265 was recovered.

![Scheme 1.78: Proposed mechanism for formation of lactone 1.268](image)

As a consequence, it was proposed that di-substituted alkenyl Boc-amides are not suitable aminoallylation substrates under the current optimal reaction conditions. Mono-substituted alkenyl Boc-amide 1.270 was utilised to test the applicability of Boc-amides to the aminoallylation of mono-substituted alkenes (Eq. 1.49). Boc-amide 1.270 was synthesised in a single step from allyl benzoic acid 1.269 via the same protocol as for Boc-amide 1.265 (Eq. 1.47).

![Scheme 1.78: Proposed mechanism for formation of lactone 1.268](image)
Aminoallylation of monosubstituted alkene 1.270 was attempted under the conditions optimised for the tosylamide 1.189 (Eq. 1.50). Piperidone 1.271 (R = Boc) was not observed, and Boc-amide 1.270 was recovered. In comparison to the aminoallylation of tosylamide 1.189, which yields desired piperidone 1.192 in high yield, this result suggests that Boc-amide substrates are not suitable for aminoallylation. It is possible that the lack of reactivity was a result on the increased bulk of the tert-butyl moiety slowing the rate of aminopalladation. Another possible explanation is that the lack of a sulfonyl-moiety prevents the formation of a stable alkylpalladium(II) intermediate.\[\text{78}\]

1.3.6: Mesyl-protected amides

The only nitrogen species to have thus far successfully undergone aminoallylation is the tosylamide. It was proposed that the toluene-sulfonyl moiety was too bulky to allow aminoallylation onto gem-disubstituted alkenes, so attempts were made towards a less bulky sulfonyl-protected amide. Mesylamides have not been previously utilised for palladium-catalysed aminocyclisations, but there are examples of mesyl-protected amines successfully undergoing aminopalladative processes.\[\text{91}\]

Mesylisocyanate is not commercially available and requires a multi-step synthesis,\[\text{92}\] so it was decided to seek a different protocol than the one utilised for tosylamides. Chemler and co-workers demonstrated the synthesis of sulfonylamides from the respective carboxylic acids and a sulfonamide under peptide-coupling conditions.\[\text{47}\] The protocol utilised coupling reagent EDC to promote the coupling with toluenesulfonamide to yield a range of tosylamides (Eq. 1.51). In 2011, Waser and co-workers demonstrated the applicability of the EDC protocol to aromatic carboxylic acids.\[\text{34}\]

Mesylamide 1.272 was proposed as the model substrate for the investigations into the aminoallylation of methanesulfonyl amides. Attempts to synthesise it from benzoic acid 1.174 are detailed below (Table 1.21). Utilisation of the Chemler protocol detailed above (entry 1) demonstrated no conversion of benzoic acid 1.174. Utilising CDI (entry 2) as the amide coupling reagent also provided no conversion.\[\text{93}\] Attempted synthesis of mesylamide 1.272 via the acyl chloride resulted in degradation of the material (entry 3).
Table 1.21: Attempted methylsulfonamide couplings

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.273, EDC, DMAP, CH₂Cl₂, 0 °C to RT, 24 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>1.273, CDI, DMAP, CH₂Cl₂, RT, 24 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>1) (COCl)₂, DMF, Et₂O, 0 °C 18 h, 2) 1.273, NEt₃, Et₂O 0 °C to 40 °C, 3 h</td>
<td>Degradation</td>
</tr>
</tbody>
</table>

Attempts to synthesise mesylamide 1.272 then centred on sulfonyl-protection of amide 1.274, which was synthesised in a single step from 2-isopropenyl benzoic acid 1.174 (Scheme 1.79). The protocol for the formation of benzamide 1.274 was low yielding. Substitution of benzamide with mesyl chloride successful allowed the synthesis of mesylamide 1.272 in a 25% yield over two steps.

Scheme 1.79: Synthesis of mesylamide 1.272

With mesylamide 1.272 in hand, it was subjected to the optimised aminooallylation reaction conditions (Eq. 1.52). Gratifyingly, desired isoindolinone 1.275 was observed as part of the crude material. The major observed product was pyridone 1.276.

The proposed mechanism for the formation of piperidone 1.276 is detailed below (Scheme 1.80). 6-endo aminopalladation yields alkylpalladium(II) intermediate 1.278. Subsequent β-hydride elimination will yield exo-cyclic methylene piperidone 1.279, which rapidly isomerises to yield vinylic-amide 1.276. This pathway is in competition with 5-exo aminopalladation to alkylpalladium(II) intermediate 1.277, from which subsequent carbopalladation and β-halide elimination yield desired isoquinolone 1.275.
Attempts to increase the yield of desired isoindolinone $1.275$ were aimed at increasing the relative rate of carbopalladation of alkylpalladium(II) intermediate $1.277$ with the allyl electrophile (Table 1.22). Utilisation of allyl bromide (entry 2) increased the ratio of desired isoindolinone $1.275$ over piperidone $1.276$, but with significantly lower conversion. Increase of temperature (entry 3) allowed improved conversion, and the desired aminocycle was observed as 60% of the crude material. The most promising conditions, however, were observed by cooling the aminoallylation reaction with allyl chloride to room temperature (entry 4), which resulted in complete conversion with no observed 6-endo product $1.272$, however there was a significant yield of an side-product $1.280$.

The side product of the aminoallylation conditions discussed above (Table 1.22, entry 4) is proposed to be pseudo-dimeric pyrrolidone $1.280$ (Scheme 1.81). The formation of product $1.280$ is proposed to arise from carbopalladation of alkylpalladium(II) intermediate $1.277$ with desired product $1.275$. A similar side-product was encountered during the optimisation of the oxyallylation reaction.$^{[64]}$ It was predicted that increased concentration of allyl electrophile would decrease the yield of pseudo-dimeric aminocycle $1.280$. Subsequent research utilising mesylamides demonstrated difficulty in

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Temperature ($^\circ$C)</th>
<th>Time (h)</th>
<th>Cat. Loading (mol. %)</th>
<th>$1.272 : 1.275 : 1.276$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cl</td>
<td>50</td>
<td>24</td>
<td>5</td>
<td>0 : 1 : 1.2</td>
</tr>
<tr>
<td>2</td>
<td>Br</td>
<td>50</td>
<td>72</td>
<td>5</td>
<td>1.2 : 1 : 0.3</td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td>80</td>
<td>20</td>
<td>10</td>
<td>0.2 : 1 : 0.2</td>
</tr>
<tr>
<td>4</td>
<td>Cl</td>
<td>RT</td>
<td>80</td>
<td>10</td>
<td>0 : &gt;20 : 0</td>
</tr>
</tbody>
</table>

Table 1.22: Optimisation of isoquinolone $1.275$ synthesis

---

Scheme 1.80: Competitive pathways for the synthesis of $1.275$ and $1.276$
substrate synthesis (see below) and as a consequence, no further work was attempted with mesylamide 1.272, despite the promising results obtained.

**Scheme 1.81: Proposed formation of pseudo-dimeric pyrrolidone 1.280**

Previous investigations with non-substituted aliphatic tosylamides demonstrated a total lack of aminopalladation. It was proposed that the less bulky mesylamide may lower the energy of the reactive rotamer and transition state of aminopalladation (Scheme 1.82). Mesylamide 1.282 was synthesised from hexenoic acid 1.224 via amide 1.281.

**Scheme 1.82: Synthesis of mesylamide 1.224**

When subjected to the aminoaallylation conditions, mesylamide 1.282 failed to undergo aminopalladation, and neither desired piperidone 1.283 nor dihydropyridone 1.284, were observed (Eq. 1.53). Attempts at increasing the rate of aminoaallylation through increased temperature also demonstrated a lack of aminopalladation.

**N-Mesyl allylbenzamides 1.288 and 1.289** were proposed because the tosyl analogues had previously successfully undergone aminoaallylation. First attempts focussed on the synthesis of intermediate benzamides 1.286 and 1.287, following the same protocol utilised for the synthesis of mesylamide 1.272. Mono- and di-substituted alkenyl benzoic acids 1.269 and 1.285 were subjected to the conditions previously used for non-protected benzamide synthesis (entries 1 and 2), but no
conversion of the starting material was observed. Attempts to synthesise the amides \textit{via} acyl chlorides (entries 3 and 4) resulted in degradation of reaction material.

\begin{table}[h]
\centering
\caption{Attempted allylbenzamide synthesis}
\begin{tabular}{llc}
\hline
Entry & R & Conditions & Result (1.286 : 1.287) \\
\hline
1 & H & CDI, DMF, 60 °C, 2 h then NH₄Cl, RT, 2 h & 1 : 0 \\
2 & Me & CDI, DMF, 60 °C, 2 h then NH₄Cl, RT, 2 h & 1 : 0 \\
3 & H & SOCl₂, CH₂Cl₂, 50 °C then NH₄Cl, 0 °C, 2 h & degradation \\
4 & Me & SOCl₂, CH₂Cl₂, 50 °C then NH₄Cl, 0 °C, 2 h & degradation \\
\hline
\end{tabular}
\end{table}

The synthesis of \textit{N}-mesyl allylbenzamides 1.288 and 1.289 was then attempted using the direct amide-coupling protocol previously used by Chemler and co-workers (Table 1.24, entries 1 and 2).\cite{47}

The conditions failed to yield either desired product and the starting material was recovered. When attempting the coupling \textit{via} the acyl chloride (entries 3 and 4), the reaction material degraded.

\begin{table}[h]
\centering
\caption{Attempts towards the synthesis \textit{N}-mesyl allylbenzamides 1.288 and 1.289}
\begin{tabular}{llc}
\hline
Entry & R & Conditions & Result (1.288 : 1.289) \\
\hline
1 & H & 1.273, EDC, DMAP, CH₂Cl₂, 0 °C to RT, 24 h & 1 : 0 \\
2 & Me & 1.273, EDC, DMAP, CH₂Cl₂, 0 °C to RT, 24 h & 1 : 0 \\
3 & H & 1) (COCl₂), DMF, Et₂O, 0 °C 18 h & Degradation \\
& & 2) 1.273, NEt₃, Et₂O, 0 °C to 40 °C, 3 h & \\
4 & Me & 1) (COCl₂), DMF, Et₂O, 0 °C 18 h & Degradation \\
& & 2) 1.273, NEt₃, Et₂O, 0 °C to 40 °C, 3 h & \\
\hline
\end{tabular}
\end{table}

The preliminary results into the utilisation of mesylamides were encouraging, despite difficulties in synthesising certain substrates. These attempts were by no means exhaustive, and further experimentation could conceivably allow for a wider scope of mesylamides. More promising results
were, however, obtained from other research directions. Consequently, the research into aminoaallylation of mesylamides was discontinued.

1.3.7: Substrate Scope – Hydroxamates

Attempted aminocyclisations of geminally-disubstituted alkenes thus far have utilised strongly electron-withdrawing nitrogen protecting groups. O-Functionalised hydroxamic acids have demonstrated the potential to undergo efficient aminopalladation, but have thus far been underutilised. It is proposed that the hydroxamates will exhibit increased nucleophilicity as a result of the alpha effect,[95] potentially increasing the rate of aminopalladation.

For example, a single instance in the oxyalkynylation report by Waser and co-workers utilised benzyloxyamide 1.65 (Eq. 1.54). The gem-disubstituted alkene successfully underwent aminoalkynylation but suffered from poor N vs O heterocyclisation chemoselectivity, yielding a mixture of lactam 1.66 and imidate 1.67.[33]

In 2012, Zhang et al. reported an enantioselective palladium-catalysed aza-Wacker cyclisation of trisubstituted alkenes with tethered hydroxamate functionality (Eq. 1.55).[81] The methodology demonstrated high chemoselectivity for aminopalladation (no oxypalladation products were observed) with either benzyloxy- or methoxy amides.

Methoxyamide 1.292 was chosen as a model substrate for reaction optimisation, and was synthesised in a single step by treating previously synthesised benzoic acid 1.174 with O-methylhydroxylamine hydrochloride under peptide coupling conditions (Eq. 1.56).
With methoxyamide 1.292 in hand, it was subjected to the reaction conditions previously optimised for oxyallylation (Table 1.25). Gratifyingly, the desired product of aminallylation, pyrrolidone 1.293, was observed when utilising either allyl bromide or chloride. There was, however, two significant side-products: Pseudo-dimeric product 1.295 and brominated product 1.296. In the case of allyl chloride, there was no observed chlorination, but there was significant isomerisation of the product alkene (1.294).

**Table 1.25: Aminoallylation of methoxyamide 1.292**

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>1.292 : 1.293 : 1.294 : 1.295 : 1.296</th>
<th>Isolated yield of 1.293</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cl</td>
<td>0 : 1.0 : &gt; 1.0 : 0.8 : 0</td>
<td>18%</td>
</tr>
<tr>
<td>2</td>
<td>Br</td>
<td>0 : 1.0 : 0 : 0.5 : 0.7</td>
<td>-</td>
</tr>
</tbody>
</table>

**Mechanistic considerations:**
In order to design conditions which limit the formation of undesired side-products 1.295 and 1.196, it is important to understand the mechanisms for their formation. Desired product pyrrolidone 1.293 was formed via the aminocyclisation–carbopalladation–β-halide elimination sequence discussed in the previous chapters (Scheme 1.83). Intramolecular aminopalladation of methoxyamide 1.292 proceeds to garner alkylpalladium(II) intermediate 1.297. Carbopalladation with allyl chloride/bromide produces alkylpalladium(II) intermediate 1.298. Subsequent β-halide elimination yields the desired pyrrolidone 1.293 and releases the active palladium(II) salt.
Pseudo-dimeric isoindolinone 1.295 is proposed to be formed by an aminopalladation–β-hydride elimination sequence (Scheme 1.84). Aminopalladation of alkene 1.292 with a palladium(II) salt yields alkylpalladium(II) intermediate 1.297. Carbopalladation with a second molecule of alkene 1.292, as opposed to the allylic halide, leads to alkylpalladium(II) intermediate 1.298, which will rapidly undergo β-hydride elimination, yielding 1.299. Alkene 1.299 will then undergo aminopalladation with the now-tethered methoxyamide to yield alkylpalladium(II) intermediate 1.300. β-Hydride elimination will yield the pseudo-dimerised product 1.295.

One criticism for the mechanism is the proposal that alkylpalladium(II) intermediate 1.297 will undergo carbopalladation more rapidly with disubstituted alkene 1.292 than with the mono-
substituted allylic halide, despite the concentration of the allylic halide considerably higher. Previous evidence in this thesis highlighted that the carbopalladation of gem-disubstituted alkene in the aminoaallylation reaction has a significant retarding effect on the reaction rate (Scheme 1.85). As a consequence, it was expected that carbopalladation with allyl chloride would be significantly more rapid than with hydroxamate 1.292.

![Scheme 1.85: Comparison in carbopalladation of mono- and di-substituted allylic chlorides in the aminoaallylation of tosylamide 1.189](image)

One possible explanation for the formation of pseudo-dimer 1.295 is the metal-chelation exhibited by hydroxamic acids. Hydroxamic acids have previously demonstrated strong chelation with a range of metals[96] and, in particular, have been demonstrated to form labile complexes with palladium(II) species[97]. It was proposed that chelation of alkylpalladium(II) intermediate 1.297 by hydroxamate 1.292 will act to accelerate carbopalladation onto gem-disubstituted alkene 1.292 (Figure 1.6). Tosylamide 1.189 lacks the ability to ligate palladium in the same manner and, as a consequence, no dimeric products were observed.

![Figure 1.6: Proposed complexation of alkylpalladium(II) intermediate 1.297 with hydroxamate 1.292](image)

Brominated isoindolinone 1.296 was observed from aminoaallylation reactions utilising allyl bromide. Two potential mechanisms for formation of brominated isoindolinone 1.296 are shown below (Scheme 1.86). Proposal 1 is a palladium-catalysed mechanism wherein alkylpalladium(II) intermediate 1.297 will undergo a carbon–bromine bond forming reductive elimination. Proposal 2 is non-palladium catalysed and involves an electrophilic bromine source. Attempts were made towards preventing the formation of a bromonium species by removing potential oxidants (e.g. O2) from the reaction mixture, thus preventing formation of benzylic cation 1.301. These attempts,
however, had no effect on the reaction. As a consequence, efforts were focussed on the palladium-catalysed proposal.

![Scheme 1.86: Potential mechanisms for bromo-isoindolinone 1.296 formation](image)

The full mechanism for proposal 1 is shown below (Scheme 1.87). Aminopalladation of hydroxamate 1.292 leads to alkylpalladium(II) intermediate 1.297. Where X = Br, alkylpalladium(II) intermediate 1.297 may undergo C–Br bond-forming reductive elimination to yield brominated pyrrolidone 1.296. Although this is not possible on the first catalyst turnover (where X = hfacac), β-halide elimination from alkylpalladium(II) intermediate 1.302 will yield a palladium(II) bromide salt. Lautens and co-workers have demonstrated that carbon–halogen bond-forming reductive elimination from a palladium(II) intermediate can allow the formation of new sp3 carbon–iodine bonds,[98] but the analogous carbon–bromine and carbon–chlorine bond forming reactions are highly inefficient.[99]

![Scheme 1.87: Proposed palladium(II) catalysed formation of bromo-isoindolinone 1.296](image)

Alternatively, there are a number of reports of palladium-catalysed carbon–bromine bond forming processes in which reductive elimination from a palladium(IV) intermediate is implicated.[47,48] It was proposed that alkylpalladium(II) intermediate 1.297 can undergo an oxidation event to yield alkylpalladium(IV) intermediate, from which reductive elimination will yield pyrrolidone 1.296.
(Scheme 1.88). As above, the catalytic cycle which forms pyrrolidone 1.296 is not possible on the first catalytic turnover.

![Scheme 1.88: Proposed palladium(IV) catalysed formation of bromo-isoindolinone 1.296](image)

Previous mechanistic experiments demonstrated that the desired heteroallylation process does not proceed via a palladium(IV) intermediate and no oxidative addition of alkylpalladium(II) intermediates with allyl halides was observed (section 1.2.3). There are, however, examples of alkylhalide mediated oxidation of organopalladium(II) intermediates. The aminoallylation reactions are run under atmospheric conditions, so another possible mechanism for the formation of proposed alkylpalladium(IV) intermediate 1.303 is oxidation by atmospheric oxygen. In order to probe the potential for oxidation, non-ambient reaction conditions were utilised (Table 1.26).

Treatment of hydroxamate 1.292 under air-free aminoallylation conditions (entry 2) had little effect on the ratio of desired pyrrolidone 1.293 to brominated pyrrolidone 1.296 compared to ambient reaction (entry 1). Undertaking the aminoallylation reaction in the absence of air and water (entry 3) also results in a similar proportional formation of brominated pyrrolidone 1.296. The results confirm that atmospheric oxygen was not involved in the formation of brominated isoindolinone 1.296.

**Table 1.26: Probing palladium oxidation**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Probe</th>
<th>1.293 : 1.295 : 1.296</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ambient</td>
<td>1.0 : 0.3 : 0.9</td>
</tr>
<tr>
<td>2</td>
<td>Air-free</td>
<td>1.0 : 0.2 : 1.5</td>
</tr>
<tr>
<td>3</td>
<td>Air and water-free</td>
<td>1.0 : 0.2 : 0.7</td>
</tr>
</tbody>
</table>
Furthermore, it can be proposed that brominated product 1.296 is a reactive intermediate towards desired pyrrolidone 1.293 and pseudo-dimerised product 1.295 (Scheme 1.89). Oxidative addition of a palladium(0) species into the carbon–bromine bond would produce alkylpalladium(II) intermediate 1.297.

![Scheme 1.89: Proposed transformation from brominated isoindolinone 1.296 to desired isoindolinone 1.293 and by-product 1.295](image)

In order to probe the possibility that brominated isoindolinone 1.296 is an intermediate towards the synthesis of desired isoindolinone 1.293, the isolated brominated product 1.296 was resubmitted to the reaction conditions (Eq. 1.57). Under these conditions, neither desired pyrrolidone 1.293 nor pseudo-dimerised product 1.295 were observed and bromo-pyrrolidone 1.296 was recovered.

There is potential that the active catalytic species for the carbopalladation process was generated by aminopalladation of amide 1.292. In order to probe this, a spiking experiment, in which 5 mol. % of amide 1.292 was added to the reaction mixture, was performed (Eq. 1.58). The experiment failed to yield either pyrrolidone 1.293 or pseudo-dimerised product 1.295. Consequently, it is proposed that brominated aminocycle 1.296 is not an intermediate towards products 1.293 and 1.295, and is simply an undesired by-product.
**Reaction optimisation:**

Based on the mechanistic proposals above, a direct comparison can be drawn between the pathways towards the three major products (Scheme 1.90). Alkylpalladium(II) intermediate 1.297 is the common intermediate in pathways 1, 2 and 3. Pathway 1, the desired pathway, relies on an intermolecular carbopalladation of alkylpalladium(II) intermediate 1.297 with allyl bromide. Pathway 2 involves intermolecular carbopalladation of alkylpalladium(II) intermediate 1.297 with hydroxamate 1.292. Pathway 3 is proposed to involve a C–Br bond forming elimination event from alkylpalladium(II) intermediate 1.297.

![Scheme 1.90: Common intermediate towards desired isoindolinone 1.296 and by-products 1.295 and 1.296](image)

Consequently, it was hypothesised that increased relative concentration of allyl bromide would increase the relative yield of desired pyrrolidone 1.293 (Table 1.27). In the case of both allyl chloride (entries 1 & 2) and allyl bromide (entries 3 & 4), increased equivalents of the allylic halide improved the relative ratio of desired product 1.293 to side products 1.295 and 1.296. In the case of allyl chloride, there was no observed chlorinated product, but there was significant isomerisation of the desired alkene 1.293. As a result of the isomerisation of the desired product, it was decided that further investigations would utilise allyl bromide.
Table 1.27: Variation of allylic halide

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Y (Equiv.)</th>
<th>1.293 : 1.295 : 1.296</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cl</td>
<td>5</td>
<td>1.0 : 0.8 : 0</td>
</tr>
<tr>
<td>2</td>
<td>Cl</td>
<td>10</td>
<td>1.0 : 0.5 : 0</td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td>5</td>
<td>1.0 : 0.5 : 0.7</td>
</tr>
<tr>
<td>4</td>
<td>Br</td>
<td>10</td>
<td>1.0 : 0.3 : 0.4</td>
</tr>
</tbody>
</table>

One factor that has a major effect on the fate of alkylpalladium(II) intermediate 1.297 was the identity of the X ligand on palladium (Scheme 1.90). To probe this, a range of palladium(II) salts were tested (Table 1.28). The previous results using Pd(hfacac)₂ are shown in entry 1. Pd(acac)₂ (entry 2) and PdCl₂(dpff) (entry 3) gave zero or very poor conversion of the starting material. Bis(benzonitrile)palladium chloride (entry 4) allowed complete conversion of the starting material, but with a poorer ratio of desired pyrrolidone 1.293 to pseudo-dimer 1.295 in comparison to Pd(hfacac)₂, while palladium chloride (entry 5) gave similarly efficient conversion, but an even poorer ratio of 1.293 and 1.295. Utilising palladium acetate and palladium trifluoroacetate salts gave the best ratio, both allowing complete conversion of starting material.

Table 1.28: Screen of palladium catalysts

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd(X)₂</th>
<th>1.292 : 1.293 : 1.295</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(hfacac)₂</td>
<td>0 : 1.0 : 0.4</td>
</tr>
<tr>
<td>2</td>
<td>Pd(acac)₂</td>
<td>1.0 : 0 : 0.2</td>
</tr>
<tr>
<td>3</td>
<td>Pd(dpff)(Cl)₂</td>
<td>1.0 : 0 : 0</td>
</tr>
<tr>
<td>4</td>
<td>Pd(C₆H₅CN)₂Cl₂</td>
<td>0 : 1.0 : 0.5</td>
</tr>
<tr>
<td>5</td>
<td>Pd(Cl)₂</td>
<td>0 : 1.0 : 0.8</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OCCOF₃)₂</td>
<td>0 : 1.0 : 0.2</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OCOCl)₂</td>
<td>0 : 1.0 : 0.2</td>
</tr>
</tbody>
</table>

An investigation into the effect of reaction temperature was undertaken in toluene (Table 1.29). At room temperature (entry 1), aminoallylation did not proceed and hydroxamate 1.292 was recovered.
At 80 °C (entry 3), there was an improvement in desired pyrrolidone 1,293 to side products 1,295 and 1,296 ratio compared to 50 °C (entry 2).

Table 1.29: Temperature Screen

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>1,292 : 1,293 : 1,295 : 1,296</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RT</td>
<td>1 : 0 : 0 : 0</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>0 : 1.0 : 0.3 : 0.7</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>0 : 1.0 : 0.1 : 0.8</td>
</tr>
</tbody>
</table>

It has been hypothesised that the formation of brominated side-product 1,296 may involve a halide salt. Hence, solvent polarity can have a major effect on the solubility of a potential intermediate. Solvent polarity will also have an effect on nitrogen-nucleophilicity due to the alpha effect. Toluene (Table 1.30, entry 1) gave a roughly 1:1 ratio of desired product 1,293 to undesired side-products 1,295 and 1,296, with full conversion of starting material 1,292. Utilisation of a 1:1 biphasic mixture of toluene and water prevented aminoallylation reactivity. A study of increasingly polar solvents demonstrated that dichloromethane (entry 3) gave near-identical results to toluene, but ethereal solvents THF, diethyl ether and 2-methyl-THF prevented aminoallylation. Acetonitrile, known to be a weakly coordinating ligand for palladium, and thus proposed to potentially break-up hydroxamate chelation, resulted in poor conversion of amide 1,292. Finally DME, previously utilised for palladium-catalysed carboallylation reactions in the France group, demonstrated excellent conversion and a reduced relative yield of pseudo-dimerised side-product 1,295. DME, however, demonstrated increased conversion to brominated product 1,296. It was decided to continue optimisation with DME and PhMe, because each solvent had its relative merits.
It was proposed that, because the desired carbopalladation is an intermolecular process, increased reaction concentration will increase the relative rate of carbopalladation compared to any intramolecular process (Table 1.31). Decreased reaction concentration of either 0.1 M (entry 1) or 0.25 M (entry 2) demonstrate a reduced relative yield of desired pyrrolidone 1.293 compared to previously utilised conditions (0.5 M, entry 3). Increased concentration to 0.8 M (entry 4) and 1.0 M (entry 5) show similar results to 0.5 M (entry 3), but the high concentration also resulted in significant precipitation. Increased reaction concentration in toluene from 0.25 M (entry 6) to 0.5 M (entry 7) showed a similar trend, as the relative ratio of both side-products 1.295 and 1.296 decreased.

Table 1.31: Variation in concentration in an attempt to prevent bromination

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Concentration (M)</th>
<th>1.293 : 1.295 : 1.296</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DME</td>
<td>0.10</td>
<td>1.0 : 0.3 : 1.8</td>
</tr>
<tr>
<td>2</td>
<td>DME</td>
<td>0.25</td>
<td>1.0 : 0.2 : 1.6</td>
</tr>
<tr>
<td>3</td>
<td>DME</td>
<td>0.50</td>
<td>1.0 : 0.1 : 1.0</td>
</tr>
<tr>
<td>4</td>
<td>DME</td>
<td>0.80</td>
<td>1.0 : 0.2 : 1.1</td>
</tr>
<tr>
<td>5</td>
<td>DME</td>
<td>1.0</td>
<td>1.0 : 0.2 : 0.7</td>
</tr>
<tr>
<td>6</td>
<td>PhMe</td>
<td>0.25</td>
<td>1.0 : 0.3 : 0.7</td>
</tr>
<tr>
<td>7</td>
<td>PhMe</td>
<td>0.50</td>
<td>1.0 : 0.2 : 0.6</td>
</tr>
</tbody>
</table>
In order to further optimise the aminoallylation reaction, the range of bases tolerated by the reaction conditions was investigated. Initially, the reaction was attempted in the absence of base (Eq. 1.59), but only yielded dimethyl isoindolinone 1.304. Isoindolinone 1.304 was proposed to be a product of hydroamination, catalysed by excess HX in solution. A similar product (1.264) was seen for the aminoallylation of tosylamide 1.260 (Eq. 1.46).

With the necessity of base addition demonstrated, a range of bases were tested in the aminoallylation reaction (Table 1.32). Mono potassium phosphate (entry 2) demonstrated poorer conversion than sodium bicarbonate (entry 1), although pseudo-dimer 1.295 was not observed. As has been demonstrated previously, weak amine bases have a detrimental effect on aminoallylation reactivity. No conversion of hydroxamate 1.292 was observed when utilising pyridine (entry 3) or DBU (entry 4). Employment of potassium acetate (entry 5), a stronger heterogeneous base than sodium bicarbonate, resulted in no observed aminoallylation. There was also no observed conversion to N-allylated products.

**Table 1.32: Base Screen**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>1.292 : 1.293 : 1.295 : 1.296</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaHCO₃</td>
<td>0 : 1.0 : 0.1 : 1.0</td>
</tr>
<tr>
<td>2</td>
<td>KH₂PO₄</td>
<td>0.4 : 1.0 : 0 : 0.9</td>
</tr>
<tr>
<td>3</td>
<td>Pyridine</td>
<td>1.0 : 0 : 0 : 0</td>
</tr>
<tr>
<td>4</td>
<td>DBU</td>
<td>1.0 : 0 : 0 : 0</td>
</tr>
<tr>
<td>5</td>
<td>KOAc</td>
<td>1.0 : 0 : 0 : 0</td>
</tr>
</tbody>
</table>

Further attempts to inhibit the formation of brominated aminocycle 1.296 are summarised below (Table 1.33). Addition of silver salts (entries 2–4), commonly used to sequester halide ions, resulted in a number of products arising from N-allylation of amide 1.292 (the products of N-allylation were not isolated). This was most likely a consequence of increased electrophilicity of allyl bromide. Potassium hexafluorophosphate (entry 5), a potassium salt with a soluble counter-ion, was added in an attempt to precipitate potassium bromide and thus, decrease conversion to brominated...
isoindolinone 1.1296. The additive, however, proved to have no observed effect on the reaction. Aminoallylation reactions with halide salts lithium chloride (entry 6) and sodium iodide (entry 7) were attempted to see if either chlorinated/iodinated analogue of 1.296 was observed, which would potentially give mechanistic insight. Aminoallylation did not proceed in either case.

### Table 1.33: Additives to limit bromination

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>1.292 : 1.293 : 1.295 : 1.296</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>0 : 1.0 : 0.2 : 0.6</td>
</tr>
<tr>
<td>2</td>
<td>AgTFA</td>
<td>N-allylation</td>
</tr>
<tr>
<td>3</td>
<td>AgOAc</td>
<td>N-allylation</td>
</tr>
<tr>
<td>4</td>
<td>Ag₂CO₃</td>
<td>N-allylation</td>
</tr>
<tr>
<td>5</td>
<td>KPF₆</td>
<td>0 : 1.0 : 0.1 : 0.7</td>
</tr>
<tr>
<td>6</td>
<td>LiCl</td>
<td>1.0 : 0 : 0 : 0</td>
</tr>
<tr>
<td>7</td>
<td>NaI</td>
<td>1.0 : 0 : 0 : 0</td>
</tr>
</tbody>
</table>

It was proposed that, if brominated product 1.296 is formed by alkylpalladium(II) halide reductive elimination (Scheme 1.87), introduction of an electron rich phosphine ligand may inhibit the elimination process (Table 1.34). Previous utilisation of phosphate ligands in heteroallylation research in the France group has demonstrated complete inhibition of reactivity (Table 1.9) but addition of triphenylphosphine (entry 2) in the aminoallylation of hydroxamate 1.292 decreased the yield of brominated product 1.296 while retaining complete conversion of starting material. XPhos (entry 3) and BrettPhos (entry 4) demonstrated similar reactivity. SPhos (entry 5) gave the most impressive product ratio thus far, in which the crude material was relatively pure isoindolinone 1.293, although it was only isolated in a 40% yield. Utilising SPhos in the reaction with DME (entry 6) produced a significant amount of brominated pyrrolidone 1.296, thus ending attempts towards aminoallylation in DME. Attempts towards an enantioselective aminoallylation were undertaken with (S)-Binap (entry 7), but no aminoallylation reactivity was observed under these conditions.
Table 1.34: Phosphine ligand trials

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>PR$_3$</th>
<th>1.292 : 1.293 : 1.295 : 1.296</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhMe</td>
<td>-</td>
<td>0 : 1.0 : 0.1 : 1.0</td>
</tr>
<tr>
<td>2</td>
<td>PhMe</td>
<td>PPh$_3$</td>
<td>0 : 1.0 : 0.2 : &lt;0.2</td>
</tr>
<tr>
<td>3</td>
<td>PhMe</td>
<td>XPhos</td>
<td>0 : 1.0 : 0.1 : &lt;0.2</td>
</tr>
<tr>
<td>4</td>
<td>PhMe</td>
<td>BrettPhos</td>
<td>0 : 1.0 : 0.3 : &lt;0.2</td>
</tr>
<tr>
<td>5</td>
<td>PhMe</td>
<td>SPhos</td>
<td>0 : 1.0 (40%) : 0.1 : &lt;0.2</td>
</tr>
<tr>
<td>6</td>
<td>DME</td>
<td>SPhos</td>
<td>0 : 1.0 : 0.2 : 0.8</td>
</tr>
<tr>
<td>7</td>
<td>PhMe</td>
<td>(S)-Binap</td>
<td>1 : 0 : 0 : 0</td>
</tr>
</tbody>
</table>

The current optimal conditions for the aminoallylation of $O$-substituted hydroxamates is shown below (Eq. 1.60). The low yield is due, in part, to instability of isoindolinone 1.293 to silica chromatography, with a 20% mass loss observed on repeated subjection to purification. Reproducibility of the reaction has been demonstrated with near-identical isolated yield.

The remainder of the reaction mass balance is, as yet, unaccounted for. Analysis of the crude material shows trace amounts of several alkene products which have been tentatively assigned to alkenes 1.305 and 1.306, different elimination products of the pseudo-dimerisation pathway (Figure 1.7).

Due to the instability of $N$-methoxyisoindolone 1.293 to column chromatography, utilisation of a different hydroxamate was proposed. Benzzyloxyamides, for example 1.65, were previously utilised for aminoalkynylation by Waser and co-workers.$^{[33]}$ The substrate was synthesised in a single step.
under amide coupling conditions from previously utilised benzoic acid 1.174 and O-benzyl hydroxylamine (Eq. 1.61).

![Chemical structure and reaction](image)

Benzyloxyamides and methoxyamides allow access to different functionality after deprotection protocols (Scheme 1.91). Treatment of methoxyamides with samarium diiodide results in demethoxylation to yield the respective amide. Hydrogenation of benzyloxyamides yields the respective hydroxamic acid. Aminoallylation reaction conditions which can tolerate the application of either methoxy- or benzyloxy-amides is desirable for synthetic applicability.

![Scheme 1.91: Altered deprotection strategies for O-methyl and O-benzyl hydroxamates](image)

Benzyloxyamide 1.65 was subjected to the optimal hydroxamate-aminoallylation reaction conditions (Eq. 1.62). The reaction proceeded to full conversion of benzyloxyamide 1.65 and successfully allowed isolation of the desired isoindolinone 1.307 in a 41% yield. There was no observed bromination or pseudo-dimerisation products under the reaction conditions. The reaction also produced protocyclised product 1.308 in a low (<2%) yield.

Towards the synthesis of isoquinolones, methoxyamide 1.309 was proposed. It was synthesised in a single step from previously utilised benzoic acid 1.285 in a single step using amide-coupling reagent propylphosphonic anhydride (T3P) and O-methyl hydroxylamine (Eq. 1.63).
N-Methoxyamide 1.285 was subjected to the optimal hydroxamate-aminallylation conditions (Eq. 1.64). The reaction allowed complete conversion of amide 1.309 and the desired isoquinolone product 1.310 was isolated in a 33% yield. No products of bromination or pseudo-dimerisation were observed under these conditions.

Furthermore, attempts were made towards the synthesis of saturated heterocycles. Gem-dimethyl amide 1.312 was synthesised in a single step from the respective carboxylic acid 1.311 in a single step (Eq. 1.65).

N-Methoxyamide 1.312 was subsequently submitted to the optimal hydroxamate-aminallylation reaction conditions (Eq. 1.66). Amide 1.312, however, did not undergo aminallylation and pyrrolidone 1.313 was not observed. That no products of bromination or pseudo-dimerisation were observed implies that the lack of reactivity was due to slow aminopalladation.

In conclusion, O-methyl, and O-benzyl hydroxamates have been observed to undergo aminallylation onto gem-disubstituted alkenes. The applicability to gem-disubstituted alkenes is tantamount to the goal of generalised aminallylation reaction conditions which reliably avoid β-hydride elimination. The yields, however, are currently sub-optimal.

1.3.8: Substrate Scope – Amines and Anilines

The aminallylation using N-sulfonylamines was proposed as a method for further increasing substrate scope. It was envisaged to have the potential to synthesise a series of piperidine/pyrrolidine containing alkaloids, for example, tropane alkaloids (Scheme 1.92).
Benzylc amine 1.316 was synthesised by a known protocol (Scheme 1.93). Allylation of bromobenzonitrile 1.314 yielded allylbenzonitrile 1.315 in a 56% yield. Subsequent nitrile reduction yielded benzylamine 1.316.

While the eventual goal was to tune the reactivity through amine protection, unprotected benzylamine 1.316 was subjected to the aminoallylation conditions (Eq. 1.67). The desired isoquinoline product 1.317 was not observed and the starting material was recovered. Furthermore, no product of amine allylation/diallylation was observed in the crude reaction material.

Due to the significantly different pKa of benzylc amines compared to tosylamides (ca. 35 vs 4), it was decided to test the effect of varying the base (Table 1.35). Utilisation of sodium bicarbonate (entry 1), Hünig’s base (entry 2), dimethylaniline (entry 3) and di-tert-butyl pyridine (entry 4) did not allow for the aminoallylation of amine 1.316. Neither desired isoquinoline 1.317 nor isoquinoline 1.318, the product of β-hydride elimination and alkene isomerisation, were observed under any conditions. One explanation is that unprotected amine 1.316 was not undergoing aminopalladation, due to strong ligation to palladium.
**Table 1.35: Base screen for aminoallylation of benzylic amine 1.316**

![Image of Table 1.35]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>1.316 : 1.317 : 1.318</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaHCO₃</td>
<td>1 : 0 : 0</td>
</tr>
<tr>
<td>2</td>
<td>EtN(iPr)₂</td>
<td>1 : 0 : 0</td>
</tr>
<tr>
<td>3</td>
<td>PhN(CH₃)₂</td>
<td>1 : 0 : 0</td>
</tr>
<tr>
<td>4</td>
<td>2,6-(Bu)C₆H₄N</td>
<td>1 : 0 : 0</td>
</tr>
</tbody>
</table>

Sulfonamides have been utilised in a number of aminopalladative processes to tune amine reactivity, primarily due to weaker ligation to palladium. Tosyl-protection of benzylic amine 1.316 successfully allowed the synthesis of sulfonamide 1.319.

Sulfonamide 1.319 was submitted to the optimised aminoallylation conditions at 50 ºC and 80 ºC but desired isoquinolone 1.321 was not observed and isoquinoline 1.322 was yielded as a single product (Scheme 1.94). Isoquinoline 1.322 was a product of β-hydride elimination from alkylpalladium(II) intermediate 1.320, which confirms that tosylamine 1.319 does undergo aminopalladation. Under the previously optimised conditions, however, the reaction was highly chemoselective for β-hydride elimination.

![Image of Scheme 1.94]

**Scheme 1.94: Attempted aminoallylation of sulfonamide 1.319**

In an attempt to tailor the reaction conditions towards allylation, amine ligands were utilised (Table 1.36). In 2005, Lu demonstrated that the use of pyridine and 2,2-bipyridine (bipy) can effectively inhibit β-hydride elimination in favour of other processes. Treatment of sulfonamide 1.319 under aminoallylation reaction conditions with pyridine (entry 1) and bipy (entry 2) as ligands results in complete inhibition of aminopalladation. The use of pyridine as a base (entry 3) had the same result.
In the absence of amine ligands, the reaction was so highly chemoselective for isoquinoline 1.322 that further attempts towards aminocycle 1.321 were not made.

Table 1.36: Ligand screen for aminallylation of sulfonamide 1.319

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Ligand</th>
<th>1.319 : 1.321 : 1.322</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaHCO₃</td>
<td>Pyridine (20 mol. %)</td>
<td>1 : 0 : 0</td>
</tr>
<tr>
<td>2</td>
<td>NaHCO₃</td>
<td>Bipy (20 mol. %)</td>
<td>1 : 0 : 0</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>Pyridine (2 equiv.)</td>
<td>1 : 0 : 0</td>
</tr>
</tbody>
</table>

In an attempt to differently tune the reactivity, amine 1.316 was protected as a carbamate. Boc-protected amines have been previously demonstrated to undergo aminopalladation.\[^{101}\] Carbamate 1.323 was synthesised in a single step from amine 1.316 in an 86% yield (Eq. 1.68).

With carbamate 1.323 in-hand, it was subjected to aminallylation conditions (Scheme 1.95). As with sulfonamide 1.319, carbamate 1.323 selectively underwent aminopalladation to alkylpalladium(II) intermediate 1.324 and subsequently terminated via β-hydride elimination and isomerisation to yield isoquinoline 1.326. Desired isoquinoline 1.325 was not observed under the reaction conditions.

Previous investigations into heteroallylation processes have demonstrated that the allyl halide has a large effect on reaction rate.\[^{45}\] In an attempt to increase the relative rate of allylation, allyl bromide was utilised (Eq. 1.69). The aminallylation of carbamate 1.323 with allyl bromide proceeded as before and desired isoquinoline 1.325 was not observed in the crude material.
In an effort to improve the rate of carbopalladation, allylpalladium chloride dimer was utilised as a catalyst. It was proposed that, by intra-molecularly delivering the alkene via ligation to palladium, the rate of carbopalladation could be increased (Scheme 1.96). The aminopalladation of carbamate 1.323 with allylpalladium chloride dimer was proposed to result in alkylpalladium(II) intermediate 1.327, thus allowing intramolecular delivery of the allyl moiety. The reaction, however, was unsuccessful, and neither isoquinoline 1.325 nor 1.326 was observed.

Scheme 1.96: Proposal aminoallylation of Boc-amine 1.323

In an attempt to prevent β-hydride elimination, utilisation of a gem-disubstituted alkene was proposed. Carbamates and sulfonamides have both been demonstrated to undergo efficient aminopalladation onto gem-disubstituted alkenes, and the examples are more wide-ranging than for protected-amide species. Disubstituted alkene 1.329 was proposed as a model substrate for the study (Scheme 1.97). The same protocol was followed as for the monosubstituted alkene (Scheme 1.93), but utilised methylallyl bromide in the allylation reaction. Both allylation and reduction proceeded in high yields to afford benzylic amine 1.329.

Scheme 1.97: Synthesis of disubstituted-alkene 1.329

Previous investigations demonstrated aminopalladation of the non-protected amine was unsuccessful (Eq. 1.67). As a consequence, no attempts were made towards the aminoallylation of benzylic amine 1.329, which was instead protected as a sulfonamide (1.330) and a carbamate (1.331) (Scheme 1.98).
Scheme 1.98: Amine-protection of disubstituted alkene 1.329

Methyl-sulfonamide 1.330 and carbamate 1.331 were subjected to the optimised aminoallylation reaction conditions (Eq. 1.70). Neither amine demonstrated conversion to the desired isoquinoline product.

Changing the base to either sodium acetate or sodium bicarbonate had no effect on reactivity and methyl sulfonamide 1.330 was recovered (Eq. 1.71).

Subsequent investigations were undertaken to test the effect of varying the palladium salt (table 1.37). Neither palladium chloride (entry 2) nor palladium acetate (entry 3) successfully catalysed the aminoallylation of sulfonamide 1.330. Palladium trifluoroacetate (entry 4), previously utilised in aza-Wacker cyclisations of tosylamides,[21] also demonstrated no conversion. Finally, aminoallylation with palladium acetylacetonate failed to provide isoquinoline 1.332.
Table 1.37: Catalyst screen for aminoallylation of mesylamine 1.330

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>1.330 : 1.332</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>hfacac</td>
<td>1 : 0</td>
</tr>
<tr>
<td>2</td>
<td>Cl</td>
<td>1 : 0</td>
</tr>
<tr>
<td>3</td>
<td>OAc</td>
<td>1 : 0</td>
</tr>
<tr>
<td>4</td>
<td>TFA</td>
<td>1 : 0</td>
</tr>
<tr>
<td>5</td>
<td>acac</td>
<td>1 : 0</td>
</tr>
</tbody>
</table>

Anilines have been used extensively for aminocyclisation reactions in the past. For example, allylaniline 1.333 was utilised in the seminal aminocyclisation research of Hegedus and co-workers in the 1970s (Eq. 1.72).\(^{17}\) It was proposed that the utilisation of aniline substrates will give access to a range of 2-substituted indoles.

\[
\text{Aniline 1.333 was subjected to the aminoallylation reaction conditions with a range of bases (Table 1.38). The use of sodium bicarbonate (entry 1), as per the optimised conditions for oxyallylation, did not yield desired indole 1.336. The crude reaction mixture contained only aniline 1.333. This non-reactivity was matched by the use of homogenous nitrogen-bases (entries 2–4). That 2-methylindole 1.334, the product of β-hydride elimination and isomerisation, was not observed led to the conclusion that allylaniline 1.333 was not undergoing aminopalladation under the aminoallylation reaction conditions.} \]

Aniline 1.333 was subjected to the aminoallylation reaction conditions with a range of bases (Table 1.38). The use of sodium bicarbonate (entry 1), as per the optimised conditions for oxyallylation, did not yield desired indole 1.336. The crude reaction mixture contained only aniline 1.333. This non-reactivity was matched by the use of homogenous nitrogen-bases (entries 2–4). That 2-methylindole 1.334, the product of β-hydride elimination and isomerisation, was not observed led to the conclusion that allylaniline 1.333 was not undergoing aminopalladation under the aminoallylation reaction conditions.
Table 1.38: Variation of base in aniline aminoallylation reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>1.333 : 1.336 : 1.334</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaHCO$_3$</td>
<td>1 : 0 : 0</td>
</tr>
<tr>
<td>2</td>
<td>EtN(iPr)$_2$</td>
<td>1 : 0 : 0</td>
</tr>
<tr>
<td>3</td>
<td>PhN(CH$_3$)$_2$</td>
<td>1 : 0 : 0</td>
</tr>
<tr>
<td>4</td>
<td>(t-Bu)$_2$C$_6$H$_3$N</td>
<td>1 : 0 : 0</td>
</tr>
</tbody>
</table>

Previously, efforts towards the palladium-catalysed aminocyclisation of aniline-substrates have demonstrated the applicability of carbamates.$^{[103]}$ Carbamate protection was achieved using di-tert-butyl-dicarbonate under basic conditions, successfully affording carbamate 1.337.

Carbamate 1.337 was subjected to the conditions optimised for tosylamide aminoallylation (Scheme 1.99). Desired indole 1.339 was not observed under the aminoallylation conditions, with only methylindole 1.340 being produced. 2-methylindole is a result of β-hydride elimination from alkylpalladium(II) intermediate 1.338, followed by isomerisation. This result suggest that, unlike the non-protected aniline substrate 1.333, the carbamate-protected aniline was undergoing aminopalladation. However, the reaction is highly chemoselective for β-hydride elimination that no efforts were made towards conditions to chemically favour allylation.

Scheme 1.99: Attempted aminoallylation of aniline 1.337
1.3.9: Conclusions and Future Work

Over the course of this research, methodology has been developed to synthesise nitrogen-containing heterocycles substituted in the 2-position, constructing a new C–N and C–C sp<sup>3</sup>–sp<sup>3</sup> bond in a single step from aromatic tosylamides. Four new isoquinolones were synthesised in yields of 33–84% (Scheme 1.100).

\[
\text{Scheme 1.100: Summary of tosylamide aminoallylation}
\]

The reactions are operationally simple. Technical grade solvents were utilised, and the reactions were carried out under air. Other than the change of base from sodium bicarbonate to monopotassium phosphate, necessitated by the lower pKa of the tosylamides, the conditions are in-line with those utilised for the previously optimised oxyallylation reaction.

The current conditions, however, have significant limitations (Figure 1.8). It is clear that the developed aminoallylation reaction is sensitive to nitrogen pKa (successful examples have a pK<sub>a</sub> of approximately 4). Attempts towards pyrroles, pyrrolidines, piperidines, aliphatic piperidones, and any Boc-functionalised aminocycles were unsuccessful.

\[
\text{Figure 1.8: Summary of substrates which did not undergo aminoallylation}
\]
The most recent results utilising methyl substituted hydroxamates have demonstrated the potential for efficient aminoaallylation of geminally-disubstituted alkenes. Utilisation of gem-disubstituted alkenes is a common method for avoiding β-hydride elimination (Scheme 1.101).

![Scheme 1.101: Optimal conditions for the aminoaallylation of hydroxamates](image)

While examples of isoquinolone-containing alkaloid natural products are known,\textsuperscript{[104]} they are less common than other nitrogen heterocycles. Consequently, aminoaallylation conditions which are broadly applicable to the construction of a range of aminocycles are still being sought.
1.4: Supporting Information

1.4.1: General Methods

Reactions involving air-sensitive agents and dry solvents were performed in glassware that had been dried in an oven (150 °C) or flame-dried prior to use. These reactions were carried out with the exclusion of air using an argon atmosphere. All microwave reactions were carried out using a Biotage Initiator system. NMR spectra were recorded on a Bruker DPX-400 spectrometer (1H NMR at 400 MHz and 13C NMR at 100 MHz) or a Bruker DPX-500 spectrometer (1H NMR at 500 MHz and 13C NMR at 125 MHz). Chemical shifts are reported in ppm. 1H NMR spectra were recorded with CDCl₃, using residual CHCl₃ (δ = 7.26) as internal standard, and for 13C NMR spectra the chemical shifts are reported relative to the central resonance of CDCl₃ (δ = 77.16) and with d₆-DMSO, using the central resonance of residual DMSO (δ = 2.50) as internal standard, and for 13C NMR spectra the chemical shifts are reported relative to the central resonance of d₆-DMSO (δ = 39.51). Signals in NMR spectra are described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), septet (sept), multiplet (m), broad (br) or combination of these, which refers to the spin–spin coupling pattern observed. Spin–spin coupling constants reported are uncorrected. Two-dimensional (COSY, HSQC, HMBC, NOESY) NMR spectroscopy was used where appropriate to assist the assignment of signals in the 1H and 13C NMR spectra. IR spectra were obtained employing a Shimadzu FTIR-8400 instrument with a Golden Gate™ attachment that uses a type Ila diamond as a single reflection element so that the IR spectrum of the compound (solid or liquid) could be detected directly (thin layer). High resolution mass spectra were recorded under FAB, ESI and CI conditions by the analytical services at the University of Glasgow. Flash column chromatography was performed using forced flow of the indicated solvent system on EMD Geduran® Silica Gel 60 as solid support and HPLC graded solvents as eluent. Reactions were monitored by thin layer chromatography (TLC) on Merck silica gel 60 covered aluminium sheets. TLC plates were developed under UV-light and/or with an acidic ethanolic anisaldehyde solution or a KMnO₄ solution. Liquid reagents were distilled prior to use where stated. All reagents were purchased from commercial suppliers and used without further purification unless otherwise stated.
1.4.2: Mechanistic experiments

2-isopropenylbromobenzene 1.173

To a stirred suspension of methyl triphenylphosphonium bromide (7.2 g, 20 mmol) in THF (51 mL) was added a solution of potassium tert-butoxide (2.3 g, 20 mmol) in THF (21 mL). The resulting bright yellow suspension was stirred at room temperature for 15 minutes then a solution of o-bromoacetophenone 1.172 (3.4 g, 17 mmol) in THF (34 mL) added dropwise. The resulting suspension was stirred at room temperature for 3 h then quenched with sat. aq. NH₄Cl (100 mL). The mixture was extracted with Et₂O (3 x 50 mL) and the combined organic extracts dried (MgSO₄), filtered and concentrated in vacuo. Purification by flash chromatography (petroleum ether) afforded title compound 1.173 as a colourless oil (2.6 g, 77%). Analytical data observed were in accordance with literature values.[105]

2-isopropenylbenzoic acid 1.174

To a cooled (0 °C) solution of 1-bromo-2-(prop-1-en-2-yl) benzene 1.173 (2.6 g, 13 mmol) in Et₂O (26 mL) was added dropwise a solution of n-butyllithium (1.7 M in hexanes, 7.8 mL, 13 mmol). The resulting yellow suspension was stirred for 15 minutes, before CO₂ was bubbled through. The mixture was allowed to warm to room temperature over 2 h then quenched with sat. aq. NaHCO₃ (100 mL). The mixture was extracted with Et₂O (2 x 50 mL) and the aqueous phase adjusted to pH 1 with 1 M aq. HCl. The aqueous phase was then extracted with Et₂O (3 x 100 mL) and the combined organic extracts dried (Na₂SO₄), filtered and concentrated in vacuo to title compound 1.174 as a sticky white solid (1.7 g, 99%). Analytical data observed were in accordance with literature values.[33]

2-(2-isopropenylphenyl)methanol 1.148

To a stirred suspension of lithium aluminium hydride (0.49 g, 13 mmol) in Et₂O (25 mL) was added a solution of 2-isopropenylbenzoic acid 1.174 (0.80 g, 4.9 mmol) in Et₂O (5 mL) at 0 °C. The solution was stirred for 20 h, before quenching by addition of sat. aq. potassium sodium tartrate (30 mL). After a further 4 h of stirring, the organic phase was extracted with Et₂O (3 x 30 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated in vacuo to yield title compound 1.148 as a colourless oil (0.63 g, 87%). No further
puriﬁcation was required. Analytical data observed were in accordance with those previously observed within the group.  

1-(4′,4″-d5-buty-3′-enyl)-1,3-dihydro-1-methylisobenzofuran 1.167

A 4 mL glass screw-top vial was charged with (2-(prop-1-en-2-yl)phenyl) methanol 1.148 (51 mg, 0.34 mmol), freshly prepared deuterated allyl bromide 1.165 (0.21 mg, 1.7 mmol), toluene (1.3 mL), NaHCO3 (37 mg, 0.68 mmol) and Pd(hfacac)2 (8.5 mg, 0.017 mmol). The mixture was heated at 50 °C for 4 h then additional Pd(hfacac)2 (8.5 mg, 0.017 mmol) added. Heating was continued for a further 2 h, then the mixture was allowed to cool to room temperature and subjected directly to flash chromatography (petroleum ether:EtOAc, 9:1) to afford title compound 1.167 as a yellow oil (53 mg, 82%). 1H NMR (400 MHz, CDCl3) δ 7.28 – 7.07 (4H, m, Ar-H), 5.38 – 5.30 (2H, m, 3′-CH & 4′-CH), 5.12 – 5.04 (2H, m, 3-CH2), 2.03 – 2.02 (1H, m, 2′-CH), 1.91 – 1.71 (3H, m, 1′-CH2 & 2′-CH), 1.59 – 1.47 (6H, m, C1-CH3 & C4′-CH3); 13C NMR (125 MHz, CDCl3) δ 145.3 (C), 139.2 (C), 138.6 (CH), 127.5 (CH), 127.4 (CH), 121.1 (CH), 121.0 (CH), 113.6 (J (C-D) = 24.0 Hz, CD2), 88.3 (C), 71.8 (CH3), 41.0 (CH2), 28.5 (CH2), 27.6 (CH3); IR (thin ﬁlm) 1765, 1451, 1358, 1030; HRMS (CI/Iso-butane) exact mass calculated for C13H15D2O [M+H]+ m/z 191.1405, found m/z 191.1413.

(E/Z)-1-methyl-1-(pent-3′-enyl)-1,3-dihydroisobenzofuran 1.176

A 4 mL glass screw-top vial was charged with (2-(prop-1-en-2-yl)phenyl) methanol 1.148 (51 mg, 0.34 mmol), 3-chloro-1-butene 1.175 (0.17 mL, 1.7 mmol), toluene (1.3 mL), NaHCO3 (57 mg, 0.68 mmol) and Pd(hfacac)2 (8.5 mg, 0.017 mmol). The mixture was heated at 50 °C for 6 h. The mixture was allowed to cool to room temperature and subjected directly to flash chromatography (petroleum ether:EtOAc, 9:1) to afford title compound 1.176 as a yellow oil (53 mg, 82%, E/Z = 3:1). 1H NMR (500 MHz, CDCl3) δ 7.28 – 7.07 (4H, m, Ar-H), 5.38 – 5.30 (2H, m, 3′-CH & 4′-CH), 5.12 – 5.04 (2H, m, 3-CH2), 2.03 – 2.02 (1H, m, 2′-CH), 1.91 – 1.71 (3H, m, 1′-CH2 & 2′-CH), 1.59 – 1.47 (6H, m, C1-CH3 & C4′-CH3); 13C NMR (125 MHz, CDCl3) δ 145.4 (C), 139.2 (C), 130.4/131.2 (major/minor isomer) (CH), 127.40 (CH), 127.35 (CH), 123.9/124.5 (CH), 121.0 (CH), 120.9 (CH), 88.4 (C), 71.8 (CH2), 41.6 (CH2), 27.6 (CH2), 21.9 (CH3), 12.7/18.1 (CH3); IR (thin ﬁlm) 1767, 1452, 1358, 1030; HRMS (CI/Iso-butane) exact mass calculated for C14H16O [M+H]+ m/z 203.1436, found m/z 203.1451.
(E/Z)-2-methyl-2-(pent-3'-en-1'-yl)-2,3-dihydrobenzofuran 1.178

A 4 mL glass screw-top vial was charged with 2-(2-methyl)allylphenol 1.146 (51 mg, 0.34 mmol), 3-chloro-1-butene 1.175 (0.17 mmol, 1.7 mmol), toluene (1.3 mL), NaHCO$_3$ (37 mg, 0.68 mmol) and Pd(hfacac)$_2$ (8.5 mg, 0.017 mmol). The mixture was heated at 50 °C for 36 h then additional Pd(hfacac)$_2$ (8.5 mg, 0.017 mmol) added. Heating was continued for a further 36 h, then the mixture was allowed to cool to room temperature and subjected directly to flash chromatography (petroleum ether:EtOAc, 9:1) to afford title compound 1.178 as a yellow oil (51 mg, 74%, E/Z = 3:1).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.15 – 7.08 (2H, m, Ar-H), 6.83 – 6.72 (2H, m, Ar-H), 5.48 – 5.35 (2H, m, 3'-CH & 4'-CH), 3.13 – 2.90 (2H, m, 3-CH$_2$), 2.19 – 2.08 (2H, m, 2'-CH$_2$), 1.80 – 1.75 (2H, m, 1'-CH$_2$), 1.64 – 1.55 (3H, m, C4'-CH), 1.45 – 1.42 (3H, m, C2-CH$_3$);

$^{13}$C NMR (125 MHz, CDCl$_3$) δ: 159.1 (C), 130.0 (CH), 128.08/128.05 (major/minor isomer) (CH), 127.0 (C), 125.20/125.17 (CH), 124.3 (CH), 120.0 (CH), 109.5 (CH), 88.6 (C), 41.28/41.27 (CH$_2$), 41.03/41.16 (CH$_2$), 26.5/26.6 (CH$_3$), 21.8 (CH$_2$), 12.8 (CH$_3$); IR (thin film) 1699, 1439, 1346, 1084; LRMS (CI/Isobutane) mass calculated for C$_{14}$H$_{19}$O [M+H]$^+$ m/z 203.1, found m/z 203.2.

1-(3'-bromobut-3'-en-1'-yl)-1-methyl-1,3-dihydroisobenzofuran 1.183

A 4 mL glass screw-top vial was charged with (2-(prop-1-en-2-yl)phenyl)methanol 1.148 (51 mg, 0.34 mmol), 2,3-dibromopropene 1.182 (0.18 mL, 1.7 mmol), toluene (1.3 mL), NaHCO$_3$ (57 mg, 0.68 mmol) and Pd(hfacac)$_2$ (8.5 mg, 0.017 mmol). The mixture was heated at 50 °C for 16 h. The mixture was allowed to cool to room temperature and subjected directly to flash chromatography (petroleum ether:EtOAc, 9:1) to afford title compound 1.183 as a yellow oil (69 mg, 74%).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.31 – 7.25 (2H, m, Ar-H), 7.22 – 7.18 (1H, m, Ar-H), 7.14 – 7.09 (1H, m, Ar-H), 5.50 – 5.48 (1H, m, 4’-CH), 5.32 (1H, d, J = 1.6 Hz, 4’-CH), 5.08 (2H, dd, J = 20.7, 12.4 Hz, 3-CH$_2$), 2.58 – 2.46 (1H, m, 2’-CH), 2.19 – 2.01 (3H, m, 2’-CH & 1’-CH$_2$), 1.49 (3H, s, C1-CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) 144.8 (C), 139.1 (C), 134.8 (C), 127.7 (2 x CH), 121.1 (CH), 121.0 (CH), 116.2 (CH$_2$), 87.7 (C), 71.8 (CH$_2$), 40.3 (CH$_2$), 36.6 (CH$_3$), 27.7 (CH$_3$); IR (thin film); HRMS (ESI positive) exact mass calculated for C$_{13}$H$_{15}$OBrNa [M+Na]$^+$ m/z 289.0198, found m/z 289.0199.
Methyl-2-allyl benzoate 1.195

Following a modification of a reported procedure,[34] to a suspension of magnesium turnings (2.0 g, 67 mmol) and a crystal of iodine in THF (30 mL) was added dropwise 1-bromo-n-butane (7.2 mL, 67 mmol). The mixture was stirred for 15 minutes then cooled to –40 °C before dropwise addition of methyl-2-iodobenzoate 1.196 (5.0 mL, 34 mmol). The mixture was stirred at –40 °C for 1.5 h. A freshly prepared solution of LiCl (3.4 g, 80 mmol) and CuCN (3.4 g, 40 mmol) in THF (60 mL) was added and the mixture was stirred for a further 15 min, followed by the addition of allyl bromide (12 mL, 140 mmol). The mixture was stirred at –40 °C for a further 10 min, then warmed to room temperature. The mixture was diluted with EtOAc (200 mL) and filtered over Celite®. The filtrate was washed with 25% aq. NH₄OH (200 mL). The aqueous layer was further extracted with EtOAc (2 x 200 mL), and the combined organic extracts washed with brine (200 mL), dried (Na₂SO₄), filtered and concentrated in vacuo. Purification by flash chromatography (petroleum ether:EtOAc, 9:1), afforded title compound 1.195 as a colourless oil (5.3 g, 90%). Analytical data observed were in accordance with literature values.[107]

2-allyl benzoic acid 1.269

Methyl-2-allyl benzoate 1.195 (2.7 g, 17 mmol) was dissolved in EtOH (250 mL), and 2 M aq. NaOH (200 mL) added. The mixture was stirred for at room temperature for 4 h then EtOH was removed in vacuo. The residue was extracted with Et₂O (2 x 150 mL), acidified to pH 3 with 2 M aq. HCl and extracted with EtOAc (3 x 150 mL). The combined organics were dried (Na₂SO₄), filtered and concentrated in vacuo to afford title compound 1.269 as a colourless solid (2.7 g, quant.), which was used directly without further purification.

2-allyl-N-tosylbenzamide 1.189

To a solution of 2-allyl benzoic acid 1.269 (2.7 g, 17 mmol) in THF (50 mL) was added p-tosyl isocyanate (3.3 g, 17 mmol). The resulting solution was stirred for 10 min then triethylamine (2.3 mL, 17 mmol) added dropwise. Gas evolution was observed on addition. After 1 h, the mixture was diluted with EtOAc (50 mL) and washed with 2 M aq. HCl (50 mL) and brine (50 mL). The organic extracts were dried (Na₂SO₄), filtered and concentrated in vacuo. The crude product was purified by column chromatography.
(CH₂Cl₂) to afford title compound 1.189 as a colourless solid (4.6 g, 88%). Analytical data observed were in accordance with literature values.[34]

Methyl-1-allyl-pyrrole-2-carboxylate 1.201

Following a modification of a reported procedure,[34] to a cooled (0 °C) suspension of NaH (60% dispersion in mineral oil, 0.48 g, 12 mmol) in DMF (10 mL) was added a solution of methyl-2-pyrrole-carboxylate 1.200 (1.0 g, 8.0 mmol) in DMF (2.0 mL). The resulting mixture was stirred for 20 min at 0 °C, then allyl bromide (1.2 mL, 14 mmol) added dropwise. The mixture was allowed to warm to room temperature, and stirred for 2 h, then quenched by pouring onto ice (30 g). The mixture was extracted with Et₂O (3 x 15 mL) and the combined organic extracts were washed with water (4 x 15 mL), brine (1 x 15 mL), dried (Na₂SO₄), filtered and concentrated in vacuo to afford title compound 1.201 as a colourless oil (1.3 g, 95%). Analytical data observed were in accordance with literature values.[108]

1-allyl-pyrrole-2-carboxylic acid 1.341

To a solution of methyl-1-allyl-pyrrole-2-carboxylate 1.201 (1.3 g, 7.6 mmol) in EtOH (18 mL) was added 1 M aq. NaOH (21 mL). The mixture was refluxed for 1.5 h, then EtOH was removed in vacuo. The aqueous phase was washed with EtOAc (3 x 25 mL) then acidified to pH 2 with 4 M aq. HCl and extracted with EtOAc (3 x 25 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated in vacuo to afford title compound 1.341 as a colourless solid (1.0 g, 89%) which was used directly without further purification.

1-allyl-N-tosyl-pyrrole-2-carboxamide 1.202

To a flask charged with 1-allyl-pyrrole-2-carboxylic acid 1.341 (0.50 g, 3.3 mmol) in THF (10 mL) was added p-tosyl isocyanate (0.77 g, 6.6 mmol). The resulting solution was stirred for 10 min then triethylamine (0.50 mL, 3.6 mmol) added dropwise. Gas evolution was observed on addition. After 1 h, the mixture was diluted with EtOAc (50 mL) and washed with 2 M aq. HCl (50 mL) and brine (50 mL). The organic extracts were dried (Na₂SO₄), filtered and concentrated in vacuo. The crude product was purified by column chromatography (CH₂Cl₂) to afford title compound 1.202 as a colourless solid (0.71 g, 61%). Analytical data observed were in accordance with literature values.[34]
**Ethyl-1-allyl-indole-2-carboxylate 1.207**

Following a reported procedure,[34] to a cooled (0 °C) suspension of NaH (60% dispersion in mineral oil, 0.32 g, 8.0 mmol) in DMF (10 mL) was added a solution of methyl-2-indole-carboxylate 1.206 (1.0 g, 5.3 mmol) in DMF (4.0 mL). The resulting mixture was stirred for 20 min at 0 °C, then allyl bromide (0.78 mL, 9.0 mmol) added dropwise. The mixture was heated at 100 °C for 2 h, then cooled and quenched by pouring onto ice (30 g). The mixture was extracted with Et₂O (3 x 15 mL) and the combined organic extracts were washed with water (4 x 15 mL), brine (1 x 15 mL), dried (Na₂SO₄), filtered and concentrated in vacuo to afford title compound 1.207 as a colourless oil. Material was used directly without further purification.

**1-allyl-indole-2-carboxylic acid 1.342**

To a solution of methyl-1-allyl-indole-2-carboxylate 1.207 (1.3 g, 5.8 mmol) in EtOH (15 mL) was added 1 M aq. NaOH (18 mL). The mixture was refluxed for 1.5 h, then EtOH was removed in vacuo. The aqueous phase was washed with EtOAc (3 x 25 mL) then acidified to pH 2 with 4 M aq. HCl and extracted with EtOAc (3 x 25 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated in vacuo, to title compound 1.342 as a colourless solid (0.73 g, 68% over 2 steps) which was used directly without further purification.

**1-allyl-N-tosyl-1H-indole-2-carboxamide 1.208**

To a flask charged with 1-allyl-indole-2-carboxylic acid 1.342 (0.20 g, 1.0 mmol) in THF (4.0 mL) was added p-tosyl isocyanate (0.16 mL, 1.0 mmol). The resulting solution was stirred for 10 min then triethylamine (0.14 mL, 1.0 mmol) added dropwise. Gas evolution was observed on addition. After 1 h, the mixture was diluted with EtOAc (20 mL) and washed with 2 M aq. HCl (20 mL) and brine (20 mL). The organic extracts were dried (Na₂SO₄), filtered and concentrated in vacuo. The crude product was purified by flash chromatography (CH₂Cl₂) to afford title compound 1.208 as a colourless solid (0.28 g, 78%). Analytical data observed were in accordance with literature values.[34]
2-vinyl benzoic acid 1.211

To a stirred suspension of methyltriphenylphosphonium bromide (19 g, 53 mmol) in THF (80 mL) was added dropwise a solution of potassium tert-butoxide (8.8 g, 79 mmol) in THF (40 mL). The resultant yellow solution was stirred for 1.5 h, before the addition of a solution of 2-carboxybenzaldehyde 1.210 (5.0 g, 33 mmol) in THF (20 mL). The solution was warmed to 60 °C and stirred overnight, before cooling and the addition of acetic acid (5.0 mL) and the solution was filtered over Celite®. The filtrate was concentrated in vacuo, before being washed with sat. aq. NaHCO₃ (3 x 50 mL). The combined aqueous extracts were acidified to pH 1 with 1 M aq. HCl, and the aqueous phase was extracted with Et₂O (3 x 50 mL). The organic extracts were dried (Na₂SO₄), filtered and concentrated in vacuo to afford title compound 1.211 (3.7 g, 74%). No further purification was required. Analytical data observed were in accordance with literature values.[109]

N-tosyl-2-vinyl benzamide 1.212

To a solution of 2-vinyl benzoic acid 1.211 (1.6 g, 11 mmol) and p-tosyl isocyanate (3.4 mL, 22 mmol) in THF (25 mL) was added triethylamine (3.0 mL, 22 mmol) at room temperature, with the release of gas. The solution was stirred for 4 h, before the reaction was diluted with EtOAc (20 mL). The organic phase was washed with 1 M aq. HCl (40 mL), and the aqueous extracted with EtOAc (3 x 20 mL). The organic extracts were dried (Na₂SO₄), filtered and concentrated in vacuo. The crude product was purified by column chromatography (CH₂Cl₂) to yield the title compound 1.212 (0.93 g, 28%). ¹H NMR (400 MHz, CDCl₃) δ 8.47 (1H, brs, NH), 8.02 (2H, d, J = 8.3 Hz, Ts-H), 7.52–7.27 (6H, m, Ar-H & Ts-H), 6.87 (1H, dd, J = 17.4, 11.0 Hz, ArCH₂H₂), 5.64 (1H, d, J = 17.4 Hz, CH₂-H₃), 5.36 (1H, d, J = 11.0 Hz, CH₂-H₅), 2.45 (3H, s, Ts-CH₃); ¹³C NMR (125 MHz, CDCl₃) δ 165.8 (C), 145.5 (C), 137.2 (C), 135.5 (C), 134.0 (CH), 132.2 (CH), 131.4 (C), 129.8 (CH), 128.12 (CH), 128.09 (CH), 127.5 (CH), 119.0 (CH₂), 21.9 (CH₃); IR (thin film); 3217, 1724, 1342; HRMS (EI⁺) exact mass calculated for C₁₆H₁₅NO₃S [M]⁺ m/z 301.0773; found m/z 301.0769.

2-(2-vinylphenyl)acetic acid 1.217

To a 2.0 mL microwave vial, equipped with stirrer, was added 2-(2-bromophenyl)acetic acid 1.216 (0.050 g, 0.23 mmol), potassium vinyldifluoroborates (0.027 g, 0.23 mmol), isopropanol (0.90 mL) triethylamine (0.11 mL, 0.81 mmol) and
Pd(dppf)Cl$_2$ (9.0 mg, 0.011 mmol). The vial was sealed and the reaction was stirred at room temperature until homogeneous. The reaction mixture was subsequently heated to 130 °C for 5 minutes. The resultant mixture was diluted with H$_2$O (1.0 mL) and Et$_2$O (1.0 mL). The organic phase was extracted with Et$_2$O (3 x 1.0 mL). The aqueous phase was acidified to pH 1 with 1 M aq. HCl, followed by extraction of the organic phase by Et$_2$O (3 x 2.0 mL). The combined organic extracts were dried (Na$_2$SO$_4$), filtered and concentrated in vacuo to afford title compound 1.217. The crude material was used directly in the following step.

$N$-tosyl-2-(2-vinylphenyl)acetamide 1.218

To a solution of 2-(2-vinylphenyl)acetic acid 1.217 (0.050 g, 0.31 mmol) in THF (3.0 mL) was added $p$-tosyl isocyanate (0.063 mL, 0.34 mmol). The resultant solution was stirred at room temperature for 10 min, before the addition of triethylamine (0.050 mL, 0.34 mmol), with the release of gas. The solution was stirred for 4 h, before quenching with 2 M aq. HCl (5.0 mL). The aqueous mixture was extracted with EtOAc (3 x 5.0 mL). The combined organic extracts were dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. The crude product was purified by flash chromatography (CH$_2$Cl$_2$) to afford title compound 1.218 as a colourless oil (0.058 g, 56%). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.22 (1H, brs, NH), 7.92 – 7.80 (3H, m, Ts-H & Ar-H), 7.49 (1H, d, $J$ = 7.6 Hz, Ar-H), 7.33 – 7.22 (3H, m, Ts-H & Ar-H), 7.11 (1H, d, $J$ = 7.6 Hz, Ar-H), 6.63 (1H, dd, $J$ = 17.2, 11.0 Hz, CH=CH$_2$), 5.58 (1H, dd, $J$ = 17.2, 1.2 Hz, CH=CH$_2$), 5.21 (1H, dd, $J$ = 11.0, 1.2 Hz, CH=CH$_2$), 3.64 (2H, s, ArCH$_2$), 2.43 (3H, s, Ts-CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 168.4 (C), 145.3 (C), 137.8 (C), 135.3 (C), 133.4 (CH), 131.0 (CH), 129.8 (C), 129.6 (CH), 128.9 (CH), 128.8 (CH), 127.0 (CH), 126.6 (CH), 118.1 (CH$_2$), 41.9 (CH$_2$), 21.8 (CH$_3$); IR (thin film) 1703, 1439, 1169; HRMS (EI+) exact mass calculated for C$_{17}$H$_{17}$NO$_3$S [M]$^+$ m/z 315.0929; found m/z 315.0931.

$N$-tosyl-pent-4-enamide 1.68

Following a reported procedure,[34] to a solution of 4-pentenoic acid 1.221 (0.20 mL, 2.1 mmol) and $p$-tosyl isocyanate (0.31 mL, 2.1 mmol) in THF (6.0 mL) was added dropwise triethylamine (0.29 mL, 2.1 mmol), with the release of gas. After 1 h, the mixture was diluted with EtOAc (10 mL) and washed with 2 M aq. HCl (10 mL) and brine (10 mL), dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. The crude product was dissolved in Et$_2$O to obtain a saturated solution and petroleum ether was added to precipitate the title product 1.68 (0.36 g, 70%) as a colourless crystalline solid. Analytical data observed were in accordance with literature values.[34]
**N-tosyl-hex-5-enamide 1.225**

Following a reported procedure,\(^{[34]}\) to a solution of 5-hexenoic acid **1.224** (0.11 mL, 1.0 mmol) and \(p\)-tosyl isocyanate (0.25 mL, 1.0 mmol) in THF (5.0 mL) was added dropwise triethylamine (0.074 mL, 1.0 mmol), with the release of gas. After 1 h, the mixture was diluted with EtOAc (10 mL) and washed with 2 M aq. HCl (5 mL) and brine (5 mL), dried (Na\(_2\)SO\(_4\)), filtered and concentrated \textit{in vacuo}. The crude product was dissolved in Et\(_2\)O to obtain a saturated solution and petroleum ether was added to precipitate title compound **1.225** (89 mg, 35%) as a colourless crystalline solid. Analytical data observed were in accordance with literature values.\(^{[34]}\)

**2,2-dimethylpent-4-enoic acid 1.229**

Following a reported procedure,\(^{[34]}\) to a suspension of NaH (0.15 g, 6.2 mmol) and diisopropylamine (0.93 mL, 6.6 mmol) in THF (10 mL) was added dropwise isobutyric acid **1.228** (0.50 mL, 5.5 mmol) The resulting suspension was heated at reflux for 1 h, then cooled to 0 °C, followed by dropwise addition \textit{n}-butyllithium (2.2 M solution in hexanes, 2.8 mL, 6.1 mmol). The resulting solution was stirred at 0 °C for 15 min, and at room temperature for 1 h, before being re-cooled to 0 °C and allyl bromide (0.48 mL, 5.5 mmol) was added dropwise to give an off-white suspension which was stirred at 0 °C for 1 h and at room temperature overnight. The suspension was quenched with water (20 mL) at 0 °C and the organic layer washed with 1 M aq. NaOH (3 x 20 mL). The combined aqueous extracts were acidified to pH 1 with 1 M aq. HCl and extracted with Et\(_2\)O (3 x 20 mL). The organic extracts were dried (Na\(_2\)SO\(_4\)), filtered and concentrated \textit{in vacuo}. The crude product was purified by flash chromatography (petroleum ether/EtOAc/AcOH 95:5:0.5) to afford title compound **1.229** (0.33 g, 47 %) as a colourless oil. Material was used directly in the following step.

**2,2-dimethyl-N-tosylpent-4-enamide 1.230**

To a solution of 2,2-dimethylpent-4-enoic acid **1.229** (0.33 g, 2.6 mmol) and \(p\)-tosyl isocyanate (0.81 mL, 5.2 mmol) in THF (6.0 mL) was added dropwise triethylamine (0.40 mL, 2.9 mmol) with the release of gas. The mixture was stirred at room temperature for 4 hours, before dilution with EtOAc (20 mL). The organic phase was washed with 2 M aq. HCl (20 mL) and brine (20 mL), dried (Na\(_2\)SO\(_4\)), filtered and concentrated \textit{in vacuo}. The crude product was purified by flash chromatography (CH\(_2\)Cl\(_2\)/AcOH 100:0.5) to afford
title compound 1.230 (0.19 g, 27%) as a colourless solid. Analytical data observed were in accordance with literature values.\[^{34}\]

### 1-allylcyclohexanecarboxylic acid 1.236

Following a reported procedure,\[^{34}\] to a solution of diisopropylamine (1.4 mL, 9.8 mmol) in THF (6.0 mL) was added dropwise a solution of \( n \)-butyllithium in hexanes (2.2 M, 4.5 mL, 9.8 mmol) at \(-78\ ^\circ\mathrm{C} \). The mixture was warmed to 0 \( ^\circ\mathrm{C} \) and stirred for 10 min, before the dropwise addition of a solution of cyclohexanecarboxylic acid 1.235 (0.50 g, 3.9 mmol) in THF (4.0 mL). The resulting mixture was stirred at room temperature for 40 min, warmed to reflux for 50 min, before cooling to 0 \( ^\circ\mathrm{C} \) and dropwise addition of allyl bromide (0.84 mL, 9.8 mmol). The resulting pale yellow solution was stirred overnight at room temperature. The reaction was quenched by addition of sat. aq. NH\(_4\)Cl (30 mL). The aqueous layer was separated, acidified to pH 1 with 2 M aq. HCl and extracted with Et\(_2\)O (3 x 20 mL). The organic extracts were dried (Na\(_2\)SO\(_4\)), filtered and concentrated in vacuo. The crude product was purified by flash chromatography (CH\(_2\)Cl\(_2\)/EtOAc/AcOH 95:4.5:0.5 to 90:9.5:0.5) to afford title compound 1.236 (0.19 g, 30%) as a colourless oil.

### 1-allyl-N-tosylcyclohexanecarboxamide 1.237

To a solution of 1-allylcyclohexanecarboxylic acid 1.236 (0.19 g, 1.2 mmol) and \( p \)-tosyl isocyanate (0.35 mL, 2.3 mmol) in THF (2.5 mL) was added dropwise triethylamine (0.18 mL, 1.3 mmol) with the release of gas. The mixture was stirred at room temperature for 4 hours, before dilution with EtOAc (10 mL). The organic phase was washed with 2 M aq. HCl (10 mL) and brine (10 mL), dried (Na\(_2\)SO\(_4\)), filtered and concentrated in vacuo. The crude product was purified by flash chromatography (CH\(_2\)Cl\(_2\)/EtOAc/AcOH 99:0.5:0.5 to 95:4.5:0.5) to afford title compound 1.237 (0.27 g, 72%) as a colourless solid. Analytical data observed were in accordance with literature values.\[^{34}\]

### 2,2-dimethylhex-5-enoic acid 1.241

To a suspension of NaH (0.15 g, 6.2 mmol) and diisopropylamine (0.93 mL, 6.6 mmol) in THF (10 mL) was added dropwise isobutyric acid 1.228 (0.50 mL, 5.5 mmol). The resulting suspension was heated at reflux for 1 h, then cooled to 0 \( ^\circ\mathrm{C} \), followed by dropwise addition of a solution of \( n \)-butyllithium in hexanes (2.3 M, 2.6 mL, 6.1 mmol). The resulting
solution was stirred at 0 °C for 15 min, and at room temperature for 1 h, before being re-cooled to 0 °C and homoallyl bromide (0.56 mL, 5.5 mmol) was added dropwise to give an off-white suspension which was stirred at 0 °C for 1 h and at room temperature overnight. The suspension was quenched with water (20 mL) at 0 °C and the organic layer washed with 1 M aq. NaOH (3 x 20 mL). The combined aqueous extracts were acidified to pH 1 with 1 M aq. HCl and extracted with Et2O (3 x 20 mL). The organic extracts were dried (Na2SO4), filtered and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc/AcOH 95:4.5:0.5) to afford title compound 1.241 (0.45 g, 58%) as a colourless oil. Analytical data observed were in accordance with literature values.\[\text{\cite{110}}\]

2,2-dimethyl-N-tosyl-5-enamide 1.242

To a solution of 2,2-dimethylhex-5-enoic acid 1.241 (0.12 g, 0.86 mmol) and p-tosyl isocyanate (0.15 mL, 0.95 mmol) in THF (4.0 mL) was added dropwise triethylamine (0.13 mL, 0.95 mmol) with the release of gas. The mixture was stirred at room temperature for 4 h, before dilution with EtOAc (10 mL) and sat. aq. NH4Cl (10 mL). The aqueous phase was extracted with EtOAc (2 x 10 mL), and the combined organics were basified with sat. aq. K2CO3 (30 mL). The aqueous was extracted with EtOAc (2 x 10 mL), and acidified to pH 1 with 1 M aq. HCl. The aqueous phase was extracted with EtOAc (3 x 10 mL), and the organic extracts were dried (Na2SO4), filtered and concentrated in vacuo to afford title compound 1.242 (0.18 g, 71%) as a colourless solid.

1H NMR (500 MHz, CDCl3) δ 8.77 (1H, brs, NH), 7.94 (2H, d, J = 8.3 Hz, Ts-H), 7.34 (2H, d, J = 8.1 Hz, Ts-H), 5.63 (1H, ddt, J = 17.0, 10.2, 6.5 Hz, 5-CH), 4.90 – 4.84 (2H, m, 6-CH2), 2.44 (3H, s, Ts-CH3), 1.80 – 1.77 (2H, m, 4-CH2), 1.55 – 1.51 (2H, m, 3-CH2), 1.13 (6H, s, (CH3)2); 13C NMR (125 MHz, CDCl3) δ 175.5 (C), 145.2 (C), 137.7 (C), 135.6 (C), 129.7 (CH), 128.5 (CH), 115.0 (CH2), 43.4 (C), 39.8 (CH2), 28.9 (CH2), 24.7 (CH3), 21.8 (CH3); IR (thin film) 3263, 1717, 1410; HRMS (CI/Isobutane) exact mass calculated for C15H22NO3S [M+H]+ m/z 296.1320; found m/z 296.1316.

2-allyl-dimethylmalonate 1.246

To a suspension of sodium hydride (60% dispersion in mineral oil, 0.26 g, 6.5 mmol) in THF (70 mL) was added dropwise dimethylmalonate 1.245 (1.0 mL, 8.7 mmol) at 0 °C. Once effervescence had ceased, allyl chloride (0.40 mL, 4.8 mmol) was added dropwise. The mixture was warmed to room temperature and stirred for 2 h, before warming to reflux for 18 h. The reaction mixture was subsequently cooled to room temperature and
quenched by the addition of H₂O (50 mL). The mixture was extracted with Et₂O (3 x 50 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated in vacuo. The crude material was used directly in the following step.

2-allyl-dimethylmalonic acid 1.247

To a solution of 2-allyldimethylmalonate 1.246 (4.8 mmol) in ethanol (15 mL) was added 1 M aq. NaOH (15 mL). The mixture was stirred at room temperature for 24 h. The ethanol was subsequently removed in vacuo, and the resultant aqueous solution was extracted with Et₂O (3 x 15 mL). The aqueous solution was subsequently acidified to pH 1 with 1 M aq. HCl and was extracted with Et₂O (3 x 15 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated in vacuo to yield the title compound 1.247 as a white powdered solid (0.17 g, 25% over 2 steps). Analytical data observed were in accordance with literature values.[111]

2-allyl-N,N'-di-tosyl-malonamide 1.248

To a solution of 2-allyl malonic acid 1.247 (0.17 g, 1.1 mmol) in THF (10 mL) was added p-tosyl isocyanate (0.38 mL, 2.5 mmol). The resultant solution was stirred at room temperature for 10 min, before the addition of triethylamine (0.35 mL, 2.5 mmol), with the release of gas. The solution was stirred for 16 h, before quenching with 2 M aq. HCl (10 mL). The aqueous mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether:EtOAc, 4:1) to yield title compound 1.248 as a colourless oil (0.35 g, 70%). ¹H NMR (400 MHz, CDCl₃) δ 7.87 (4H, d, J = 8.3 Hz, Ts-H), 7.28 (4H, d, J = 8.2 Hz, Ts-H), 5.40 (1H, ddt, J = 17.1, 10.0, 7.1 Hz, 3'-CH₂), 4.78 (1H, d, J = 10.1 Hz, 3'-CH), 4.73 (1H, d, J = 17.1 Hz, 3'-CH₂), 3.26 (1H, t, J = 7.0 Hz, 2'-CH), 2.45-2.40 (8H, m, Ts-CH₃ & 1'-CH₂); ¹³C NMR (100 MHz, CDCl₃) δ 167.9 (C), 145.5 (C), 135.2 (C), 131.7 (CH), 129.8 (CH), 128.6 (CH), 119.6 (CH₂), 53.7 (CH), 35.7 (CH₂), 21.8 (CH₃); IR (thin film) 1713, 1437, 1155; HRMS (ESI positive) exact mass calculated for C₂₀H₂₂N₂O₆S₂Na [M+Na]+ m/z 473.0811; found m/z 473.0810.

1-phenyl-3-butenol 1.252

To a stirred solution of benzaldehyde 1.251 (1.0 mL, 9.8 mmol) in Et₂O (10 mL) at 0 °C was added allyl magnesium bromide (1.0 M solution in hexanes, 15 mL, 15 mmol). The reaction was warmed to room temperature over 1 h, and subsequently stirred at room temperature for 20 h. The reaction mixture was quenched by the addition of 2% aq.
NH₄Cl (60 mL). The mixture was extracted with Et₂O (3 x 50 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated \textit{in vacuo}. The crude material was purified by column chromatography (petroleum ether:EtOAc, 19:1) to afford title compound 1.252 as a colourless oil (1.2 g, 85%). Analytical data observed were in accordance with literature values.\[112\]

\textbf{1-phenyl-3-butenyltosylcarbamate 1.253}

To a solution of 1-phenyl-3-butenol 1.252 (0.50 g, 3.4 mmol) in CH₂Cl₂ (7.0 mL) was added dropwise \textit{p}-tosyl isocyanate (0.53 mL, 3.4 mmol) at 0 °C. The reaction mixture was warmed to room temperature, and stirred for 1.5 h. The reaction mixture was concentrated \textit{in vacuo}, and the subsequent oil was diluted with EtOAc (20 mL) and H₂O (20 mL). The organic phase was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated \textit{in vacuo}. The crude material was purified by column chromatography (petroleum ether:EtOAc, 19:1) to afford title compound 1.253 as a colourless oil (0.54 g, 46%). Analytical data observed were in accordance with literature values.\[113\]

\textbf{2-isopropenyl-N-tosyl benzamide 1.256}

To a solution of 2-isopropenylbenzoic acid 1.174 (0.50 g, 4.1 mmol) in THF (13 mL) was added \textit{p}-tosyl isocyanate (0.63 mL, 4.1 mmol). The solution was stirred at room temperature for 10 min, before the dropwise addition of triethylamine (0.57 mL, 4.1 mmol), with the release of gas. The resulting solution was stirred at room temperature for 2 h, and quenched with 1 M aq. HCl (15 mL). The aqueous phase was extracted with EtOAc (3 x 15 mL) and the combined organic extracts dried (Na₂SO₄), filtered and concentrated \textit{in vacuo}. The crude material was purified by flash chromatography (petroleum ether/CH₂Cl₂ 1:1) to afford title compound 1.256 (0.66 g, 51%) as a white amorphous solid. \textit{1H} NMR (500 MHz, CDCl₃) δ 8.79 (1H, brs, NH), 8.02 (2H, d, \textit{J} = 8.3 Hz, Ts-H), 7.70 (1H, d, \textit{J} = 7.7 Hz, Ar-H), 7.46 (1H, td, \textit{J} = 7.5, 1.3 Hz, Ar-H), 7.37 – 7.32 (3H, m, Ar-H), 7.21 (1H, dd, \textit{J} = 7.6, 0.8 Hz, Ar-H), 5.32 (1H, s, ArCCH₂-H), 5.08 (1H, s, ArCCH₂-H), 2.45 (3H, s, Ts-CH₃), 1.97 (3H, s, ArCCH₃); \textit{13C} NMR (125 MHz, CDCl₃) δ 166.2 (C), 146.0 (C), 145.0 (C), 142.7 (C), 136.1 (C), 132.1 (CH), 129.6 (C), 129.5 (CH), 129.2 (CH), 128.78 (CH), 128.76 (CH), 127.9 (CH), 117.4 (CH₂), 24.6 (CH₃), 21.7 (CH₃); IR (thin film) 3217, 1722, 1342; HRMS (Cl/Isobutane) exact mass calculated for C₁₇H₁₇NO₃S [M]+ \textit{m/z} 315.0929; found \textit{m/z} 315.0930.
Methyl-2-(2-methylallyl) Benzoate 1.259

Following a modification of a reported procedure,[34] to a mixture of magnesium turnings (0.22 g, 9.2 mmol) and a crystal of iodine in THF (15 mL) was added dropwise 1-bromo-\(n\)-butane (0.82 mL, 7.6 mmol). The mixture was stirred for 15 minutes then cooled to \(-40\) °C before dropwise addition of a solution of methyl-2-iodobenzoate 1.194 (1.0 g, 3.8 mmol) in THF (30 mL). The mixture was stirred at \(-40\) °C for 1.5 h. A freshly prepared solution of LiCl (0.39 g, 9.1 mmol) and CuCN (0.39 g, 4.5 mmol) in THF (20 mL) was added and the mixture was stirred for a further 15 min, followed by the addition of 3-chloro-2-methyl-1-propene (1.5 mL, 15 mmol). The mixture was stirrer at \(-40\) °C for a further 10 min, then warmed to room temperature. The mixture was diluted with EtOAc (20 mL) and filtered over Celite®. The filtrate was washed with 25% aq. NH\(_4\)OH (20 mL). The aqueous layer was further extracted with Et\(_2\)O (2 x 20 mL), acidified to pH 3 with 2M aq. HCl and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried (Na\(_2\)SO\(_4\)), filtered and concentrated \textit{in vacuo}. Purification by flash chromatography (petroleum ether/EtOAc, 9:1), afforded title compound 1.259 as a colourless oil (0.65 g, 89%). Material was used directly in the subsequent step.

2-(2-methylallyl) benzoic acid 1.285

Methyl-2-(2-methylallyl) benzoate 1.259 (0.65 g, 3.4 mmol) was dissolved in EtOH (7.5 mL), and 2 M aq. NaOH (5.0 mL) added. The mixture was heated to reflux for 4 h, cooled to room temperature, and EtOH was removed \textit{in vacuo}. The residue was extracted with Et\(_2\)O (2 x 20 mL), acidified to pH 3 with 2M aq. HCl and extracted with EtOAc (3 x 20 mL). The combined organics were dried (Na\(_2\)SO\(_4\)), filtered and concentrated \textit{in vacuo} to afford title compound 1.285 as a colourless solid (0.48 g, 80%), which was used directly without further purification.

2-(2-methylallyl)-N-tosyl-benzamide 1.260

To a solution of 2-(2-methylallyl)-benzoic acid 1.285 (0.48 g, 2.7 mmol) in THF (30 mL) was added \(p\)-tosyl isocyanate (0.96 mL, 6.3 mmol). The resulting solution was stirred for 10 min then triethylamine (0.81 mL, 6.3 mmol) added dropwise. Gas evolution was observed on addition. After 4 h, the mixture was diluted with EtOAc (30 mL) and washed with 2 M aq. HCl (30 mL) and brine (30 mL). The organic extracts were dried (Na\(_2\)SO\(_4\)), filtered and concentrated \textit{in vacuo}. The crude product was purified by column
chromatography (CH$_2$Cl$_2$) to afford title compound 1.260 as a colourless solid (0.83 g, 93%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.54 (1H, brs, NH), 8.00 (2H, d, $J$ = 8.3 Hz, Ts-H), 7.49–7.48 (1H, m, Ar-H), 7.44–7.41 (1H, m, Ar-H), 7.36 (2H, d, $J$ = 8.3 Hz, Ts-H), 7.30–7.27 (1H, m, Ar-H), 7.20–7.19 (1H, m, Ar-H), 4.80 (1H, s, 4-CH), 4.28 (1H, s, 4-CH), 3.39 (2H, s, 1-CH$_2$), 2.46 (3H, s, Ts-CH$_3$), 1.72 (3H, s, 3-CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 166.2 (C), 146.5 (C), 145.3 (C), 137.9 (C), 135.6 (C), 133.4 (C), 131.92 (CH), 131.90 (CH), 129.7 (CH), 128.8 (CH), 128.6 (CH), 127.1 (CH), 112.9 (CH$_2$), 41.4 (CH$_2$), 23.1 (CH$_3$), 21.8 (CH$_3$); IR (thin film) 3217, 2922, 1724, 1595; HRMS (CI/Isobutane) exact mass calculated for C$_{18}$H$_{20}$NO$_3$S [M+H]$^+$ m/z 330.1164; found m/z 330.1158.

$N$-Boc-2-isopropenylbenzamide 1.265

To a solution of 2-isopropenyl benzoic acid 1.174 (0.20 g, 1.2 mmol) and tert-butylcarbamate (0.15 g, 1.2 mmol) in DMF (10 mL) was added dropwise phenylsilane (0.72 mL, 3.7 mmol). The solution was stirred for 5 h, and quenched with water and diluted with EtOAc (15 mL). The organic phase was washed with water (4 x 10 mL) and brine (10 mL), dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. The crude product was purified by flash chromatography (CH$_2$Cl$_2$) to yield title compound 1.265 (0.23 g, 71%) as a colourless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.94 (1H, dd, $J$ = 7.8, 1.1 Hz, Ar-H), 7.49 (1H, td, $J$ = 7.6, 1.4 Hz, Ar-H), 7.35 (1H, td, $J$ = 7.7, 1.4 Hz, Ar-H), 7.26 (1H, dd, $J$ = 7.6, 1.2 Hz, Ar-H) 5.13 (1H, s, C=CH), 4.90 (1H, s, C=CH), 4.77 (1H, brs, NH), 2.12 (3H, s, CH$_3$), 1.46 (9H, s, Boc-(CH$_3$)$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 172.7 (C), 157.8 (C), 146.8 (C), 146.2 (C), 132.5 (CH), 130.8 (CH), 129.8 (CH), 128.5 (C), 127.1 (CH), 114.0 (CH$_2$), 80.4 (C), 28.4 (CH$_3$), 24.4 (CH$_3$); IR (thin film) 3219, 1722, 1595; HRMS (ESI positive) exact mass calculated for C$_{10}$H$_{10}$O$_2$Na (hydrolysis product) [M(hydrolysis) + Na]$^+$ m/z 185.0578; found m/z 185.0582

2-allyl-$N$-Boc-benzamide 1.270

To a solution of 2-allyl benzoic acid 1.269 (0.20 g, 1.2 mmol) and tert-butyl carbamate (0.15 g, 1.2 mmol) in DMF (10 mL) was added dropwise phenylsilane (0.46 mL, 3.7 mmol). The mixture was stirred at room temperature for 5 h, before addition of water (20 mL) and EtOAc (30 mL). The organic phase was extracted with water (4 x 20 mL) and brine (1 x 20 mL), dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. The crude product
was purified by column chromatography (CH$_2$Cl$_2$) to afford title compound 1.270 as a colourless oil (0.27 g, 83%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 11.46 (1H, brs, NH), 8.06 – 8.03 (1H, m, Ar-H), 7.48 (1H, td, $J$ = 7.5 Hz, 1.5 Hz, Ar-H), 7.32 – 7.28 (2H, m, Ar-H), 6.06 (1H, ddt, $J$ = 17.7, 9.4, 6.5 Hz, ArCH$_2$CHCH$_2$), 5.08 – 5.03 (2H, m, ArCH$_2$CHCH$_2$), 5.84 (2H, d, $J$ = 6.5 Hz, ArCH$_2$CHCH$_2$), 1.48 (9H, s, Boc-(CH$_3$)$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.3 (C), 158.0 (C), 142.5 (C), 137.5 (CH), 132.7 (CH), 131.5 (CH), 131.1 (CH), 129.2 (C), 126.3 (CH), 115.7 (CH$_2$), 80.4 (C), 38.5 (CH$_2$), 28.4 (CH$_3$); IR (thin film) 2926, 1695, 1394; LRMS (EI$^+$) mass calculated for C$_{10}$H$_{12}$NO [$M$ – C$_5$H$_8$O$_2$]$^+$ $^{[114]}$ m/z 161.1; found m/z 161.1.

2-isopropenylbenzamide 1.274

To a solution of isopropenylbenzoic acid 1.174 (0.10 g, 0.62 mmol) in DMF (2.0 mL) was added CDI (0.11 g, 0.68 mmol) at room temperature. The mixture was heated to 60 °C and stirred for 2 h, before addition to a stirred solution of sat. aq. NH$_4$Cl (2.0 mL). The resultant mixture was stirred for a further 30 mins, before dilution with CHCl$_3$ (5 mL). The reaction mixture was washed with water (5 x 2 mL) and brine (2 mL). The organic phase was dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. The crude mixture was purified by column chromatography (CH$_2$Cl$_2$) to afford title compound 1.270 as a colourless oil (0.27 g, 83%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 11.46 (1H, brs, NH), 8.06 – 8.03 (1H, m, Ar-H), 7.48 (1H, td, $J$ = 7.5 Hz, 1.5 Hz, Ar-H), 7.32 – 7.28 (2H, m, Ar-H), 6.06 (1H, ddt, $J$ = 17.7, 9.4, 6.5 Hz, ArCH$_2$CHCH$_2$), 5.08 – 5.03 (2H, m, ArCH$_2$CHCH$_2$), 5.84 (2H, d, $J$ = 6.5 Hz, ArCH$_2$CHCH$_2$), 1.48 (9H, s, Boc-(CH$_3$)$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.3 (C), 158.0 (C), 142.5 (C), 137.5 (CH), 132.7 (CH), 131.5 (CH), 131.1 (CH), 129.2 (C), 126.3 (CH), 115.7 (CH$_2$), 80.4 (C), 38.5 (CH$_2$), 28.4 (CH$_3$); IR (thin film) 2926, 1695, 1394; LRMS (EI$^+$) mass calculated for C$_{10}$H$_{12}$NO [$M$ + H]$^+$ $^{[114]}$ m/z 161.1; found m/z 161.1.

2-isopropenyl-N-mesylbenzamide 1.272

To a solution of 2-isopropenylbenzamide 1.274 (0.20 g, 1.2 mmol) in THF (15 mL) was added LiHMDS (1.0 M in THF, 3.7 mL, 3.7 mmol). The mixture was stirred at room temperature for 15 min before the addition of mesyl chloride (0.20 mL, 2.5 mmol) The resultant mixture was stirred at room temperature for 3 h, before quenching by addition of H$_2$O (15 mL). The aqueous mixture was acidified to pH 3 with 1 M aq. HCl, and extracted with Et$_2$O (3 x 15 mL). The combined organic extracts were dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. The crude mixture was purified by flash chromatography (CH$_2$Cl$_2$ + 0.5% AcOH) to yield title compound 1.272 as a colourless oil (0.22 g, 72%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.69 (1H, brs, NH) 7.82 (1H, dd, $J$ = 7.5, 1.0 Hz, Ar-H), 7.52 (1H, td, $J$ = 7.5, 1.0 Hz, Ar-H), 7.41 (1H, td, 7.5, 1.0 Hz, Ar-H), 7.28 – 7.26 (1H, m, Ar-H), 5.42 (1H, s, Ar-C(CH$_3$)CH$_2$), 5.28 (1H, s, Ar-C(CH$_3$)CH$_2$), 3.38 (3H, s, Ms-CH$_3$), 2.16 (3H, s, Ar-C(CH$_3$)CH$_2$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 166.7 (C), 146.2 (C), 142.9 (C), 132.8 (CH), 130.0 (C), 129.8 (CH), 129.5 (CH), 128.2 (CH), 118.0 (CH$_2$), 41.8 (CH$_3$), 25.0 (CH$_3$); IR (thin film) 3192, 2539, 1695, 1340; HRMS (EI$^+$) exact mass calculated for C$_{11}$H$_{14}$NO$_3$S [M+H]$^+$ m/z 240.0694; found m/z 240.0693.
5-hexenamide 1.281

To a solution of 5-hexenoic acid 1.224 (1.0 mL, 8.4 mmol) in CHCl₃ (20 mL) was added thionyl chloride (0.73 mL, 10 mmol). The reaction mixture was heated to reflux for 2 h, before quenching by addition to a stirred solution of sat. aq. NH₄Cl (20 mL) at 0 °C. The organic phase was extracted with CH₂Cl₂ (3 x 20 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated in vacuo to yield title compound 1.281 as a colourless oil. The crude material was used directly in the following step.

N-mesyI-hex-5-enamide 1.282

5-hexenamide 1.281 (0.26 g, 2.3 mmol) was dissolved in THF (30 mL) and a LiHMDS (1.0 M solution in THF, 6.9 mL, 6.9 mmol) was added dropwise. The solution was stirred for 15 min, before the addition of mesyl chloride (0.36 mL, 4.6 mmol). The solution was stirred at room temperature for 5 h, before quenching with water (20 mL). The aqueous phase was acidified to pH 3 with 1 M aq. HCl, and extracted with Et₂O (3 x 30 mL). The organic extracts were dried (Na₂SO₄), filtered and concentrated in vacuo. The crude product was purified by column chromatography (CH₂Cl₂:Acetic acid 99/1) to afford title compound 1.282 (90 mg, 16%) as a white powdered solid. ¹H NMR (500 MHz, CDCl₃) δ 8.14 (1H, brs, NH), 5.76 (1H, ddt, J = 17.1, 10.2, 6.8 Hz, 5-CH), 5.07 – 5.01 (2H, m, 6-CH₂), 3.31 (3H, s, Ms-CH₃), 2.34 (2H, t, J = 7.4 Hz, 2-CH₂), 2.12 (2H, td, J = 14.4, 6.9 Hz, 4-CH₂), 1.78 (2H, tt, J = 14.7, 7.4 Hz, 3-CH₂); ¹³C NMR (125 MHz, CDCl₃) δ 171.7 (C), 137.3 (CH), 116.2 (CH₂), 41.8 (CH₃), 35.7 (CH₂), 32.8 (CH₂), 23.4 (CH₂); IR (thin film) 3218, 1716, 1442; HRMS (EI+) exact mass calculated for C₁₇H₁₃NO₅S [M]+ m/z 191.0616; found m/z 191.0616.

2-isopropenyl-N-methoxybenzamide 1.292

To a solution of 2-isopropenylbenzoic acid 1.174 (0.20 g, 1.2 mmol) in THF (5.0 mL) was added HOBT (0.20 g, 1.5 mmol), EDC (0.29 g, 1.5 mmol), and O-methylhydroxylamine hydrochloride (0.13 g, 1.5 mmol). The reaction was stirred at room temperature for 5 min, before addition of iPr₂NEt (0.26 mL, 1.5 mmol). The reaction was stirred at room temperature for 16 h. The resultant mixture was diluted with H₂O (10 mL), and the aqueous mixture was extracted with Et₂O (3 x 10 mL). The combined organic extracts
were dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. The crude mixture was purified by flash chromatography (Petroleum ether/EtOAc, 1:1) to afford title compound 1.292 as an amorphous solid (0.22 g, 92%). ¹H NMR (500 MHz, CDCl$_3$, δ 8.71 (1H, s, NH), 7.60 (1H, d, $J = 7.6$ Hz, Ar-H), 7.41 (1H, td, $J = 7.6$, 1.4 Hz, Ar-H), 7.32 (1H, td, $J = 7.6$, 1.3 Hz, Ar-H), 7.23 (1H, d, $J = 7.6$ Hz, Ar-H), 5.25 (1H, s, C=CH), 5.09 (1H, s, C=CH), 3.85 (3H, s, NOCH$_3$), 2.10 (3H, s, CCH$_3$); ¹³C NMR (125 MHz, CDCl$_3$, δ 167.6 (C), 145.8 (C), 142.1 (C), 131.0 (CH & C), 129.0 (CH), 128.8 (CH), 127.7 (CH), 116.7 (CH$_2$), 64.4 (CH$_3$), 24.4 (CH$_3$); IR (thin film) 1640, 1508, 1300; HRMS (ESI positive) exact mass calculated for C$_{11}$H$_{13}$NO$_2$Na [M+Na]$^+$ m/z 214.0838; found m/z 214.0848.

**N-(benzyloxy)-2-isopropenyl benzoic acid 1.65**

To a solution of 2-isopropenyl benzoic acid 1.174 (0.16 g, 1.0 mmol) and O-benzyl hydroxylamine hydrochloride (0.16 g, 1.0 mmol) in CH$_2$Cl$_2$ (5.0 mL) was added triethylamine (0.15 mL, 1.1 mmol) and DCC (0.25 g, 1.2 mmol). The mixture was stirred at room temperature for 16 h, before concentration in vacuo. The filtrate was washed with sat. aq. NH$_4$Cl (10 mL), and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined organic extracts were dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. The crude material was purified by flash chromatography (Petroleum ether/EtOAc, 3:2) to afford title compound 1.65 as an amorphous solid (0.083 g, 30%). ¹H NMR (500 MHz, CDCl$_3$, δ 8.63 (1H, brs, NH), 7.55 (1H, d, $J = 7.3$ Hz, Ar-H), 7.42 – 7.28 (7H, m, Ar-H), 7.19 (1H, d, $J = 7.5$ Hz, Ar-H), 5.12 (1H, s, C=CH$_2$), 5.02 (2H, s, OCH$_3$Ph), 4.99 (1H, s, C=CH$_3$), 2.01 (3H, s, CCH$_3$); ¹³C NMR (125 MHz, CDCl$_3$, δ 167.3 (C), 145.6 (C), 142.2 (C), 135.5 (C), 131.1 (C), 130.9 (CH), 129.1 (CH), 128.9 (CH), 128.8 (CH), 128.6 (2 x CH), 127.5 (CH), 116.5 (CH$_2$), 78.2 (CH$_2$), 24.3 (CH$_3$); IR (thin film) 3221, 1646, 1497; HRMS (ESI positive) exact mass calculated for C$_{17}$H$_{17}$NO$_2$Na [M+Na]$^+$ m/z 290.1151; found m/z 290.1159. Analytical data observed were in accordance with literature values. [33]

**2-(2-methylallyl)-N-methoxy-benzamide 1.309**

To a solution of 2-(2-methylallyl) benzoic acid 1.285 (0.65 g, 3.7 mmol) in CH$_2$Cl$_2$ (10 mL) was added T3P (50% w/v in EtOAc, 6.6 mL, 11 mmol). The mixture was stirred at room temperature for 1 h, before the addition of O-methylhydroxylamine hydrochloride (0.50 g, 7.4 mmol) and iPr$_2$NEt (1.3 mL, 7.4 mmol). The mixture was
stirred at room temperature for 24 h, before being concentrated in vacuo. The crude product was purified by flash chromatography (Petroleum Ether:EtOAc 7:3) to afford title compound 1.309 as a white powdered solid (0.51 g, 67%). 1H NMR (500 MHz, CDCl3) δ 8.82 (1H, brs, NH), 7.38 – 7.34 (2H, m, Ar-H), 7.23 – 7.20 (2H, m, Ar-H), 4.84 (1H, s, C=CHa), 4.49 (1H, s, C=CHb), 3.81 (3H, s, NOCH3), 3.46 (2H, s, ArCH2), 1.73 (3H, s, CCH2); 13C NMR (125 MHz, CDCl3) δ 167.8 (C), 145.8 (C), 137.9 (C), 133.2 (C), 131.1 (CH), 130.7 (CH), 128.1 (CH), 126.5 (CH), 112.5 (CH2), 64.5 (CH3), 41.2 (CH2), 22.9 (CH3); IR (thin film) 2363, 1637, 1040; HRMS (ESI positive) exact mass calculated for C12H15NO2Na [M+Na]+ m/z 228.0995; found m/z 228.1002.

N-methoxy-4-methyl-2,2-dimethylpent-4-enamide 1.312

To a solution of 2,2-dimethyl-4-methyl-hexenoic acid 1.311[115] (0.12 g, 0.84 mmol) and O-methyl hydroxylamine hydrochloride (0.060 g, 0.84 mmol) in CH2Cl2 (5.0 mL) was added triethylamine (0.14 mL, 1.0 mmol), HOBT (0.14 g, 1.0 mmol) and DCC (0.21 g, 1.0 mmol). The mixture was stirred at room temperature for 16 h, before concentration in vacuo. The filtrate was washed with sat. aq. NH4Cl (10 mL), and the aqueous layer was extracted with CH2Cl2 (3 x 10 mL). The combined organic extracts were dried (Na2SO4), filtered and concentrated in vacuo. The crude material was purified by flash chromatography (Petroleum ether:EtOAc, 3:2) to afford title compound 1.312 as an amorphous solid (0.069 g, 49%). 1H NMR (400 MHz, CDCl3) δ 8.94 (1H, brs, NH), 4.79 (1H, s, 5-CH), 4.65 (1H, s, 5-CH), 3.70 (3H, s, NOCH3), 2.27 (2H, s, 3-CH2), 1.67 (3H, s, 4-CCH3), 1.15 (6H, s, (CH3)2); 13C NMR (100 MHz, CDCl3) δ 175.5 (C), 142.4 (C), 114.6 (CH2), 64.0 (CH3), 48.4 (CH2), 41.2 (C), 25.4 (CH3), 23.9 (CH3); IR (thin film) 1643, 1473, 1054; HRMS (ESI positive) exact mass calculated for C9H17NO2Na [M+Na]+ m/z 194.1151; found m/z 194.1155.

2-allylbenzonitrile 1.315

Following a modification of a literature procedure,[100] to a mixture of magnesium turnings (20 mg, 0.80 mmol) and a crystal of iodine in THF (0.50 mL) was added dropwise 1-bromo-n-butane (0.059 mL, 0.55 mmol). To the resulting mixture was added a solution of n-butyllithium (1.8 M in hexanes, 0.60 mL, 1.1 mmol) at 0 °C. The solution was stirred for 10 min, before addition of a solution of 2-bromobenzo nitrile 1.314 (0.20 g, 1.1 mmol) in THF (2.0 mL) at −40 °C and stirring for 30 min, followed by addition of a solution of copper (I) cyanide (28 mg, 0.33 mmol) and lithium chloride (28 mg, 0.66 mmol) in THF (0.20 mL), then addition of allyl bromide (0.36 mL, 4.1 mmol). After 20 min, the reaction was quenched with sat. aq.
NH$_4$Cl (10 mL), and diluted with EtOAc (10 mL). The aqueous layer was extracted with EtOAc (2 x 10 mL), and the organic extracts washed with brine, dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc 9:1) to afford title compound 1.315 (89 mg, 56 %) as a colourless oil. Material was used directly in the following step.

2-allylbenzylamine 1.316

To a suspension of LiAlH$_4$ (0.13 g, 4.5 mmol) in Et$_2$O (10 mL) was added dropwise a solution of 2-allylbenzonitrile 1.315 (0.20 g, 1.4 mmol) in Et$_2$O (2.0 mL) at 0 °C. After being stirred for 2 h, the mixture was re-cooled to 0 °C and sat. aq. potassium sodium tartrate (15 mL) added slowly. The biphasic mixture was allowed to stir at room temperature for 16 h then extracted with Et$_2$O (2 x 20 mL). The organic extracts were washed with water (50 mL), dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. The crude material was purified by flash chromatography (EtOAc:NEt$_3$ 98:2) to yield title compound 1.316 (0.13 g, 63%) as a colourless oil. Analytical data observed were in accordance with literature values.$^{[100]}$

2-allyl-N-tosylbenzylamine 1.317

To a solution of (2-allylphenyl)methanamine 1.316 (1.3 g, 8.8 mmol) and tosyl chloride (1.7 g, 8.8 mmol) in CH$_2$Cl$_2$ (15 mL) was added triethylamine (1.9 mL, 14 mmol) at room temperature and stirred for 1 h. The reaction mixture was washed with water (15 mL) and the organic phase dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. Crude product was recrystallised with Et$_2$O to afford title compound 1.317 (2.1 g, 79%) as a colourless crystalline solid. Analytical data observed were in accordance with literature values.$^{[116]}$

2-allyl-N-Boc-benzylamine 1.323

To a solution of (2-allylphenyl)methanamine 1.316 (74 mg, 0.50 mmol) in 1:1 THF/H$_2$O (3.0 mL) was added a solution of NaHCO$_3$ (0.13 g, 1.5 mmol) and di-tert-butyl-dicarbonate (0.13 g, 0.60 mmol) in 1:1 THF/H$_2$O (7.0 mL) at 0 °C. The solution was warmed to room temperature and stirred overnight, before being diluted with Et$_2$O (10 mL). The aqueous phase was extracted with Et$_2$O (2 x 10 mL) and the organic extracts were dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. The crude product was purified by flash chromatography (CH$_2$Cl$_2$/petroleum ether 1:1) to afford title compound 1.323 (0.11 g, 86%) as an amorphous crystalline solid. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.30 – 7.18 (4H, m, Ar-H), 5.98 (1H,
ddt, J = 17.1, 10.1, 6.2 Hz, ArCH2CHCH2, 5.09 (1H, dd, J = 10.1, 1.5 Hz, CH-H2), 5.00 (1H, dd, J = 17.1, 1.6 Hz, CH-H5), 4.76 (1H, brs, NH), 4.34 (2H, d, J = 5.5 Hz, ArCH2NHBoc), 3.44 (2H, d, J = 6.2 Hz, ArCH2CHCH2), 1.47 (9H, s, Boc-(CH3)3); 13C NMR (125 MHz, CDCl3) δ 155.8 (C), 138.0 (CH), 137.1 (C), 136.6 (CH), 130.1 (C), 128.7 (CH), 127.8 (CH), 126.8 (CH), 116.1 (CH2), 79.5 (C), 42.3 (CH2), 37.0 (CH2), 28.5 (CH3); IR (thin film) 3356, 2972, 1682; HRMS (CI/Isobutane) exact mass calculated for C15H22NO2 [M+H]+ m/z 248.1651; found m/z 248.1648.

2-(2-methylallyl)benzonitrile 1.328

Following a modification of a literature procedure,[100] to a mixture of magnesium turnings (0.076 g, 3.3 mmol) and a crystal of iodine in THF (5.0 mL) was added dropwise bromobutane (0.30 mL, 2.8 mmol). To the resulting solution was added a solution of n-butyllithium (2.1 M in hexanes, 2.6 mL, 5.5 mmol) at 0 °C. The solution was stirred for 10 min, before addition of a solution of 2-bromobenzonitrile 1.314 (1.0 g, 5.5 mmol) in THF (10 mL) at −40 °C and stirring for 30 min, followed by addition of a solution of copper (I) cyanide (0.14 g, 1.7 mmol) and lithium chloride (0.14 g, 3.3 mmol) in THF (10 mL), then addition of 3-chloro-2-methylpropene (2.0 mL, 19 mmol). After 20 min, the reaction was quenched with sat. aq. NH4Cl (25 mL), and diluted with EtOAc (25 mL). The aqueous layer was extracted with EtOAc (2 x 100 mL). The organic extracts were washed with brine, dried (Na2SO4), filtered and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether:EtOAc 9:1) to afford title compound 1.328 (0.74 g, 85%) as a colourless oil. Material was used directly in the following step.

2-(2-methylallyl)-benzylamine 1.329

To a suspension of LiAlH4 (1.6 g, 43 mmol) in Et2O (90 mL) was added dropwise a solution of 2-(2-methylallyl)benzonitrile 1.328 (2.1 g, 13 mmol) at 0 °C. After being stirred for 4 h, the mixture was re-cooled to 0 °C and sat. aq. potassium sodium tartrate (100 mL) added slowly. The biphasic mixture was allowed to stir at room temperature for 16 h then extracted with Et2O (2 x 100 mL). The organic extracts were washed with water (50 mL), dried (Na2SO4), filtered and concentrated in vacuo. The crude material was purified by flash chromatography (EtOAc:NEt3 98:2) to afford title compound 1.329 (1.7 g, 79%) as a colourless oil.

1H NMR (500 MHz, CDCl3) δ 7.21 – 7.12 (4H, m, Ar-H), 4.80 (1H, s, C=CH), 4.50 (1H, s, C=CH), 3.82 (2H, s, ArCH2NH2), 3.35 (2H, s, ArCH2C), 1.73 (3H, s, CH3), 1.42 (2H, brs, NH2); 13C NMR (125 MHz, CDCl3) δ 145.1 (C), 141.8 (C), 137.0 (C), 130.6 (CH), 127.8 (CH), 126.9 (CH), 126.8 (CH), 111.9 (CH2), 43.8 (CH2), 41.1 (CH2), 22.8 (CH3); IR (thin film) 2932, 1647; HRMS (CI/Isobutane) exact mass calculated for C11H16N [M+H]+ m/z 162.1283; found m/z 162.1280.
2-(2′-methylallyl)-N-mesyl-benzylamine 1.333

To a solution of 2-(2-methylallyl)-benzylamine 1.329 (0.50 g, 3.1 mmol) and triethylamine (0.47 mL, 3.4 mmol) in CH₂Cl₂ (5.0 mL) was added mesyl chloride (0.24 mL, 3.1 mmol) at 0 °C. The mixture was stirred for 1 h, before being quenched by addition of brine (10 mL). The aqueous phase was extracted by CH₂Cl₂ (3 x 10 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated in vacuo. The crude product was purified by flash chromatography (CH₂Cl₂/AcOH 99.5:0.5) to afford title compound 1.333 as a colourless oil (0.59 g, 80%).

1H NMR (400 MHz, CDCl₃) δ 7.37 – 7.18 (4H, m, Ar-H), 4.85 (1H, s, 4'-CH), 4.66 (1H, brs, NH), 4.48 (1H, s, 4'-CH), 4.29 (2H, d, J ′= 6.4 Hz, ArCH₂NHMs), 3.40 (2H, s, 1'-CH₂), 2.85 (3H, s, Ms-CH₃), 1.76 (3H, s); 13C NMR (125 MHz, CDCl₃) δ 145.3 (C), 138.0 (C), 134.9 (C), 131.2 (CH), 129.5 (CH), 128.5 (CH), 127.2 (CH), 112.3 (CH₂), 45.0 (CH₂), 41.2 (CH₂), 40.9 (CH₃), 22.9 (CH₃); IR (thin film) 3215, 1595, 1159; HRMS (ESI negative) exact mass calculated for C₁₂H₁₆NO₂S [M–H]⁻ m/z 238.0907; found m/z 238.0905.

2-(2-methylallyl)-N-tosylbenzylamine 1.331

To a solution of (2-(2-methyl)-allylphenyl)methanamine 1.324 (0.41 g, 2.5 mmol) in 1:1 THF/H₂O (25 mL) was added a solution of NaHCO₃ (0.63 g, 7.5 mmol) and di-tert-butyl-dicarbonate (0.67 g, 3.0 mmol) in 1/1 THF:H₂O (25 mL) at 0 °C. The solution was warmed to room temperature and stirred overnight, before being diluted with Et₂O (30 mL). The aqueous phase was extracted with Et₂O (2 x 30 mL) and the organic extracts were dried (Na₂SO₄), filtered and concentrated in vacuo. The crude product was purified by flash chromatography (CH₂Cl₂) to afford title compound 1.331 (0.52 g, 80%) as a colourless oil. 1H NMR (500 MHz, CDCl₃) δ 7.30 – 7.15 (4H, m, Ar-H), 4.82 (1H, s, C=CH), 4.70 (1H, brs, NH), 4.49 (1H, s, C=CH), 4.31 (2H, d, J ′= 5.5 Hz, ArCH₂NH), 3.35 (2H, s, ArCH₂C), 1.74 (3H, s, CH₃), 1.45 (9H, s, Boc-(CH₃)₃); 13C NMR (125 MHz, CDCl₃) δ 155.8 (C), 146.9 (C), 144.9 (C), 137.1 (C), 130.7 (CH), 128.7 (CH), 127.6 (CH), 126.9 (CH), 112.1 (CH₂), 85.3 (C), 42.4 (CH₂), 41.2 (CH₂), 28.6 (CH₃), 22.9 (CH₃); IR (thin film) 2970, 1718; LRMS (ESI positive) exact mass calculated for C₁₆H₁₄NO₂Na [M+Na]⁺ m/z 284.2; found m/z 284.2.
2-allylaniline 1.333

Following a literature procedure,[117] to a solution of \( \text{N-allylaniline 1.335} \) (1.0 g, 7.5 mmol) in toluene (15 mL) in a microwave vial, was added dropwise \( \text{BF}_3\cdot\text{OEt}_2 \) (1.1 mL, 9.0 mmol) at \(-78{\,}^\circ\text{C}\). The mixture was allowed to warm to room temperature, before warming by microwave irradiation at 180 \({\,}^\circ\text{C}\) for 2 h. The mixture was quenched by addition \( \text{NaHCO}_3 \) (10 mL), and the aqueous phase was extracted with \( \text{EtOAc} \) (3 x 15 mL). The organic extracts were dried (\( \text{Na}_2\text{SO}_4 \)), filtered and concentrated \( \text{in vacuo} \). The crude material was purified by column chromatography (petroleum ether/EtOAc 19:1) to afford title compound 1.333 (0.75 g, 75%) as a yellow oil. Analytical data observed were in accordance with literature values.[117]

N-Boc-2-allylaniline 1.337

To a stirred solution of \( \text{di-tert-butyl-dicarbonate} \) (0.39 g, 1.8 mmol) and sodium bicarbonate (0.37 g, 4.4 mmol) in 1:1 THF/H\(_2\)O (30 mL) was added a solution of \( \text{2-allylaniline 1.333} \) (0.20 g, 1.5 mmol) in THF (1.0 mL) at 0 \({\,}^\circ\text{C}\). The mixture was stirred for 1 h, before warming to room temperature and stirring overnight. The aqueous phase was extracted with \( \text{Et}_2\text{O} \) (3 x 30 mL) and the organic extracts were washed with brine (30 mL), dried (\( \text{Na}_2\text{SO}_4 \)), filtered and concentrated \( \text{in vacuo} \). The crude product was purified by column chromatography (CH\(_2\)Cl\(_2\)/petroleum ether 1:1) to afford title compound 1.337 (0.29 g, 83%) as a white powdered solid. Analytical data observed were in accordance with literature values.[103]

1.4.4: Aminoallylation Reactions

3-(but-3’-en-1’-yl)-2-tosyl-3,4-dihydroisoquinolin-1-one 1.192

A 4 mL screw-top glass vial was charged with 2-allyl-\( \text{N-tosyl-benzamide 1.189} \) (50 mg, 0.16 mmol), toluene (0.64 mL), \( \text{H}_2\text{O} \) (0.64 mL), \( \text{KH}_2\text{PO}_4 \) (44 mg, 0.32 mmol), allyl chloride (0.067 mL, 0.79 mmol) and \( \text{Pd(hfacac)}_2 \) (4.2 mg, 0.0082 mmol). The vial was sealed under ambient atmosphere and the mixture was heated by immersion of the entire vial into a pre-heated aluminium block at 50 \({\,}^\circ\text{C}\) for 21 h. The mixture was cooled to room temperature, and subjected directly to flash chromatography (petroleum ether/EtOAc, 9:1) to afford title compound 1.192 as an amorphous solid (47 mg, 84%). \(^1\text{H NMR} \) (500 MHz, CDCl\(_3\)) \( \delta \) 8.03 – 7.95 (3H, m, Ar-H) 7.50 – 7.46 (1H, m, Ar-H), 7.34 – 7.19 (4H, m, Ar-H), 5.76 (1H, ddt, \( J = 16.9 \) Hz, 10.3 Hz, 6.5 Hz, 3’-CH), 5.06 – 4.95 (3H, m, 4’-CH\(_2\) & 3-CH), 3.35 (1H, dd, \( J = 16.2 \) Hz, 5.5 Hz, CH-4), 2.97 (1H, dd, \( J = 16.3 \) Hz, 1.8 Hz, CH-4), 2.41 (3H, s, Ts-CH\(_3\)), 2.09 (3H, s, Ts-CH\(_3\)), 2.06 (3H, s, Ts-CH\(_3\)).
2.17 – 2.10 (2H, m, CH₂-2’), 1.91 – 1.80 (1H, m, CH-1’), 1.68 – 1.49 (1H, m, CH-1’); ¹³C NMR (125 MHz, CDCl₃) δ 163.0 (C), 144.8 (C), 137.0 (C), 136.9 (CH), 136.9 (C), 133.8 (CH), 129.5 (CH), 129.1 (CH), 129.1 (CH), 128.3 (C), 128.3 (CH), 127.6 (CH), 115.8 (CH₂), 55.5 (CH), 32.8 (CH₂), 32.4 (CH₂), 30.7 (CH₂), 21.8 (CH₃); IR (thin film) 2924, 1684; HRMS (CI/Isobutane) exact mass calculated for C₂₀H₂₂NO₃S [M+H⁺] m/z 356.1320; found m/z 356.1319.

3-(3'-methylbut-3'-en-1'-yl)-2-tosyl-3,4-dihydroisoquinolin-1-one 1.199

A 4 mL screw-top glass vial was charged with 2-allyl-N-tosyl-benzamide 1.189 (50 mg, 0.16 mmol), toluene (0.32 mL), H₂O (0.32 mL), KH₂PO₄ (44 mg, 0.32 mmol), (2-methyl)allyl chloride (0.088 mL, 0.79 mmol) and Pd(hfacac)₂ (8.4 mg, 0.016 mmol). The vial was sealed under ambient atmosphere and the mixture was heated by immersion of the entire vial into a pre-heated aluminium block at 50 °C for 21 h. The mixture was cooled to room temperature, and subjected directly to flash chromatography (petroleum ether/EtOAc, 9:1) to afford title compound 1.199 as an amorphous solid (42 mg, 71%).¹H NMR (400 MHz, CDCl₃) δ 8.01 – 7.95 (3H, m, Ar-H & Ts-H), 7.48 (1H, dt, J = 7.5, 1.3 Hz, Ar-H), 7.39 – 7.29 (3H, m, Ar-H & Ts-H), 7.20 (1H, d, J = 7.6 Hz, Ar-H), 4.97 – 4.91 (1H, m, 3'-CH), 4.73 (1H, s, 4'-CH₃), 4.67 (1H, s, 4'-CH₃), 3.34 (1H, dd, J = 16.2, 5.5 Hz, 4'-CH₃), 2.99 (1H, dd, J = 16.3, 1.8 Hz, 4'-CH₃), 2.41 (3H, s, Ts-CH₃), 2.13 – 2.04 (2H, m, 2'-CH₂), 1.96 – 1.84 (1H, m, 1'-CH₃), 1.70 – 1.63 (4H, m, 3'-CH₃ & 1'-CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 163.0 (C), 144.8 (C), 144.2 (C), 136.93 (C), 136.86 (C), 133.8 (CH), 129.5 (2 x CH), 129.08 (CH), 129.05 (CH), 128.3 (CH), 127.6 (CH), 111.0 (CH₂), 55.6 (CH), 34.6 (CH₂), 32.2 (CH₂), 31.2 (CH₂), 22.4 (CH₃), 21.8 (CH₃); IR (thin film) 1684, 1342, 1169; HRMS (EI+) exact mass calculated for C₂₁H₂₃NO₃S [M+H⁺] m/z 369.1399; found m/z 369.1402.

3-(but-3'-en-1'-yl)-2-tosyl-3,4-dihydropyrrolo[1,2-e]pyrazin-1-one 1.204

A 4 mL glass screw-top vial was charged with 1-allyl-N-tosyl-pyrrole-2-carboxamide 1.202 (48 mg, 0.16 mmol), toluene (0.64 mL), H₂O (0.64 mL), KH₂PO₄ (44 mg, 0.32 mmol), allyl chloride (0.067 mL, 0.79 mmol) and Pd(hfacac)₂ (8.4 mg, 0.016 mmol). The vial was sealed under ambient atmosphere and the mixture was heated by immersion of the entire vial into a pre-heated aluminium block at 80 °C for 19 h. The mixture was cooled to room temperature, and subjected directly to column chromatography (petroleum ether/EtOAc, 90:10) to afford title compound 1.204 as an
amorphous solid (33 mg, 61%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.99 (2H, d, $J = 8.4$ Hz, Ts-H), 7.31 (2H, d, $J = 8.1$ Hz, Ts-H), 6.97 (1H, dd, $J = 4.0$ Hz, 1.5 Hz, Ar-H), 6.76 (1H, dd, 2.2, 1.7 Hz, Ar-H), 6.23 (1H, dd, $J = 4.0$ Hz, 2.5 Hz, Ar-H), 5.80 (1H, ddt, $J = 10.3$, 6.5, 3.5 Hz, 3'-CH), 5.09 – 5.03 (2H, m, 4'-CH$_2$), 4.98 – 4.93 (1H, m, 3-CH), 4.29 (1H, dd, $J = 13.2$, 3.9 Hz, 4-CH), 4.15 (1H, dd, 13.2, 1.5 Hz, 4-CH), 2.42 (3H, s, Ts-CH$_3$), 2.17 (2H, m, 2'-CH$_2$), 1.84 (1H, m, 1'-CH), 1.68 (1H, m, 1'-CH);

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 156.1 (C), 144.8 (C), 136.6 (C), 136.5 (CH), 129.4 (CH), 129.0 (CH), 125.1 (CH), 116.8 (CH), 116.2 (CH$_2$), 111.0 (CH), 55.6 (CH), 47.0 (CH$_2$), 31.5 (CH$_2$), 30.2 (CH$_2$), 21.7 (CH$_3$); IR (thin film) 2359, 1670, 1161; HRMS (EI) exact mass calculated for C$_{18}$H$_{20}$N$_2$O$_3$S [M]$^+$ m/z 344.1195; found m/z 344.1197.

3-(but-3'-en-1'-yl)-2-tosyl-3,4-dihydropyrazino[5,6-a]indol-1-one 1.209

A 4 mL glass screw-top vial was charged with 1-allyl-N-tosyl-indole-2-carboxamide 1.208 (20 mg, 0.060 mmol), toluene (0.20 mL), H$_2$O (0.20 mL), KH$_2$PO$_4$ (16 mg, 0.12 mmol), allyl chloride (0.025 mL, 0.30 mmol) and Pd(hfacac)$_2$ (3.8 mg, 0.0060 mmol). The vial was sealed under ambient atmosphere and the mixture was heated by immersion of the entire vial into a pre-heated aluminium block at 80 °C for 48 h. The mixture was cooled to room temperature, and subjected directly to column chromatography (petroleum ether/CH$_2$Cl$_2$, 1:1) to afford title compound 1.209 as an amorphous solid (12 mg, 54%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.03 (2H, d, $J = 8.4$ Hz, Ts-H), 7.67 (1H, d, $J = 8.2$ Hz, Ar-H), 7.39 – 7.29 (5H, m, Ar-H), 7.19 – 7.15 (1H, m, Ar-H), 5.74 (1H, ddt, $J = 17.2$, 10.3, 5.7 Hz, 3'-H), 5.12 – 5.02 (3H, m, 3-H & 4'-CH$_2$), 4.48 (1H, dd, $J = 12.9$, 1.6 Hz, 4-H), 4.27 (1H, dd, $J = 12.9$, 3.9 Hz, 4-H), 2.43 (3H, s, Ts-CH$_3$), 2.21 – 2.15 (2H, m, 2'-CH$_2$), 1.93 – 1.84 (1H, m, 1'-CH), 1.73 – 1.64 (1H, m, 1'-CH); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 157.4 (C), 145.2 (C), 137.1 (C), 136.5 (CH), 136.4 (C), 129.6 (CH), 129.2 (CH), 128.6 (C), 127.0 (C), 126.2 (CH), 123.3 (CH), 121.4 (CH), 116.4 (CH$_2$), 109.8 (CH), 109.4 (CH), 56.0 (CH), 43.5 (CH$_2$), 32.1 (CH$_2$), 30.5 (CH$_2$), 21.8 (CH$_3$); IR (thin film) 2926, 1684, 1346; HRMS (EI) exact mass calculated for C$_{22}$H$_{22}$N$_2$O$_3$S [M]$^+$ m/z 394.1351; found m/z 394.1353.
3-(but-3'-en-1'-yl)-3-methyl-2-tosyl-3,4-dihydroisoquinolin-1-one 1.262

A 4 mL screw-top glass vial was charged with 2-(2-methyl)-allyl-N-tosyl-benzamide 1.260 (52 mg, 0.16 mmol), toluene (0.64 mL), H2O (0.64 mL), KH2PO4 (44 mg, 0.32 mmol), allyl chloride (0.067 mL, 0.79 mmol) and Pd(hfacac)2 (8.0 mg, 0.016 mmol). The vial was sealed under ambient atmosphere and the mixture was heated by immersion of the entire vial into a pre-heated aluminium block at 50 °C for 48 h. The mixture was cooled to room temperature, and subjected directly to flash chromatography (CH2Cl2) to afford title compound 1.262 as an amorphous solid (17 mg, 33%). 1H NMR (500 MHz, CDCl3) δ 7.95 (2H, d, J = 8.4 Hz, Ts-H), 7.80 (1H, d, J = 7.8 Hz, Ar-H), 7.48 – 7.45 (1H, td, J = 7.5, 1.0 Hz, Ar-H), 7.31 – 7.22 (3H, m, Ts-H & Ar-H) 7.14 (1H, d, J = 7.8 Hz, Ar-H), 5.74 (1H, ddt, J = 17.0, 10.3, 6.4 Hz, CH-3'), 5.00 (1H, dd, J = 17.1, 1.7 Hz, CHa), 4.95 (1H, dd, J = 10.1, 1.6 Hz, CHb), 3.07 (2H, s, CH2-4), 2.42 (3H, s, Ts-CH3), 2.23 – 2.10 (4H, m, (CH2)2-1'&2'), 1.93 (3H, s, C3-CH3); 13C NMR (125 MHz, CDCl3) δ 165.1 (C), 144.1 (C), 138.8 (C), 137.7 (CH), 136.3 (C), 133.6 (CH), 129.2 (C), 128.7 (2 x CH), 127.6 (CH), 127.0 (CH), 115.3 (CH2), 66.9 (C), 42.1 (CH2), 38.8 (CH2), 29.6 (CH2), 27.9 (CH3), 21.8 (CH3); IR (thin film) 3394, 1683, 1348; HRMS (CI/Isobutane) exact mass calculated for C21H24NO3S [M]+ 370.1477; found 370.1475.

3-(but-3'-en-1'-yl)-N-methoxy-3-methylisoindolin-1-one 1.293

A 4 mL glass screw-top vial was charged with Pd(OAc)2 (2.3 mg, 0.010 mmol), SPhos (8.2 mg, 0.020 mmol) and toluene (0.40 mL). This mixture was stirred at room temperature for 10 min, before the addition of N-methoxy-2-isopropenylbenzamide 1.292 (38 mg, 0.20 mmol), NaHCO3 (34 mg, 0.40 mmol) and allyl bromide (0.090 mL, 1.0 mmol). The vial was sealed under ambient atmosphere and the mixture was heated by immersion of the entire vial into a pre-heated aluminium block at 80 °C for 24 h. The mixture was cooled to room temperature, and subjected directly to column chromatography (petroleum ether/EtOAc, 4:1) to afford title compound 1.293 as a pale yellow oil (18 mg, 40%). 1H NMR (400 MHz, CDCl3) 7.83 (1H, d, J = 7.5 Hz, Ar-H), 7.57 (1H, td, J = 7.5, 1.1 Hz, Ar-H), 7.44 (1H, td, J = 7.5, 1.0 Hz, Ar-H), 7.31 (1H, d, J = 7.6 Hz, Ar-H), 5.62 (1H, ddt, J = 17.8, 9.4, 6.5 Hz, 3'-CH), 4.89 – 4.83 (2H, m, 4'-CH2), 4.05 (3H, s, NOCH3), 2.20 – 2.13 (1H, m, 2'-CH3), 1.98 – 1.90 (1H, m, 2'-CH3), 1.80 – 1.73 (1H, m, 1'-CH2), 1.59 (3H, s, C3-CH3), 1.40 – 1.30 (1H, m, 1'-CH2); 13C NMR (125 MHz, CDCl3) δ 165.1 (C), 145.0 (C), 132.6 (CH), 132.4 (C), 129.6 (CH), 129.2 (CH), 128.3
(CH), 124.0 (CH), 121.1 (CH2), 65.6 (C), 65.4 (CH3), 36.6 (CH2), 29.8 (CH2), 22.1 (CH3); IR (thin film) 2361, 1705, 1467; HRMS (EI+) exact mass calculated for C14H17NO2 [M]+ m/z 231.1259; found m/z 231.1263.

N-(benzyloxy)-3-(but-3'-en-1'-yl)-3-methyloisodolin-1-one 1.307

A 4 mL glass screw-top vial was charged with Pd(OAc)2 (2.3 mg, 0.010 mmol), SPhos (8.2 mg, 0.020 mmol) and toluene (0.40 mL). This mixture was stirred at room temperature for 10 min, before the addition of N-benzyloxy-2-isopropenylbenzamide 1.65 (53 mg, 0.20 mmol), NaHCO3 (34 mg, 0.40 mmol) and allyl bromide (0.090 mL, 1.0 mmol). The vial was sealed under ambient atmosphere and the mixture was heated by immersion of the entire vial into a pre-heated aluminium block at 80 °C for 24 h. The mixture was cooled to room temperature, and subjected directly to column chromatography (petroleum ether:EtOAc, 4:1) to yield the title compound 1.307 as a yellow oil (25 mg, 41%). 1H NMR (400 MHz, CDCl3) 7.85 (1H, d, J = 7.4 Hz, Ar-H), 7.61 – 7.24 (8H, m, Ar-H), 5.59 (1H, ddt, J = 17.7, 9.7, 6.4 Hz, 3'-CH), 5.30 (1H, d, J = 10.2 Hz, OCHaPh), 5.20 (1H, d, J = 10.2 Hz, OCHbPh), 4.86 – 4.82 (2H, m, C4'-CH2), 2.16 – 2.09 (1H, m, C2'-CH), 1.93 – 1.86 (1H, m, C2'-CH), 1.84 – 1.74 (1H, m, C1'-CH), 1.43 (3H, s, C3'-CH3), 1.39 – 1.29 (1H, m, C1'-CH); 13C NMR (100 MHz, CDCl3) δ 165.5 (C), 146.9 (C), 137.4 (CH), 135.6 (C), 132.4 (CH), 129.7 (CH), 129.8 (C), 129.6 (C), 129.0 (CH), 128.6 (CH), 128.4 (CH), 123.8 (CH), 121.1 (CH), 114.9 (CH2), 79.0 (CH2), 66.4 (C), 36.6 (CH2), 27.9 (CH2), 24.7 (CH3); IR (thin film) 2361, 1707, 1454; HRMS (EI+) exact mass calculated for C20H21NO2 [M]+ m/z 307.1572; found m/z 307.1569.

3-(but-3'-en-1'-yl)-2-methoxy-3-methyl-3,4-dihydroisoquinolin-1-one 1.310

A 4 mL glass screw-top vial was charged with Pd(OAc)2 (2.3 mg, 0.010 mmol), SPhos (8.2 mg, 0.020 mmol) and toluene (0.40 mL). This mixture was stirred at room temperature for 10 min, before the addition of N-methoxy-2-(2-methylallyl)benzamide 1.309 (41 mg, 0.20 mmol), NaHCO3 (34 mg, 0.4 mmol) and allyl bromide (0.090 mL, 1.0 mmol). The vial was sealed under ambient atmosphere and the mixture was heated by immersion of the entire vial into a pre-heated aluminium block at 80 °C for 48 h. The mixture was cooled to room temperature, and subjected directly to column
chromatography (petroleum ether/EtOAc, 4:1) to afford title compound 1.310 as a colourless oil (16 mg, 33%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.12 (1H, td, $J = 7.8, 1.1$ Hz, Ar-H), 7.45 (1H, td, $J = 7.5, 1.4$ Hz, Ar-H), 7.34 (1H, t, $J = 7.5$ Hz, Ar-H), 7.14 (1H, d, $J = 7.5$ Hz, Ar-H), 5.72 (1H, ddt, $J = 17.0, 10.2, 6.4$ Hz, 3'-CH), 4.97 (1H, dd, $J = 17.1, 1.7$ Hz, 4'-H$_b$), 4.92 (1H, dd, $J = 10.2, 1.7$ Hz, 4'-H$_a$), 3.94 (3H, s, NO$_2$H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 164.8 (C), 138.0 (CH), 136.0 (C), 132.6 (CH), 128.4 (C), 128.3 (CH), 127.6 (CH), 115.0 (CH$_2$), 64.7 (C), 64.5 (CH$_3$), 40.9 (CH$_2$), 36.7 (CH$_2$), 29.1 (CH$_2$), 23.4 (CH$_3$); IR (thin film) 2934, 1670, 1327; HRMS (ESI positive) exact mass calculated for C$_{15}$H$_{19}$NO$_2$Na [M+Na]$^+$ m/z 268.1308; found m/z 268.1306.

1.4.5: Undesired side products

$N,2$-diallyl-$N$-tosylbenzamide 1.196

A 4 mL screw-top glass vial was charged with 2-allyl-$N$-tosyl-benzamide 1.189 (50 mg, 0.16 mmol), toluene (0.64 mL), H$_2$O (0.64 mL), NaHCO$_3$ (27 mg, 0.32 mmol), allyl chloride (0.067 mL, 0.79 mmol) and Pd(hfacac)$_2$ (8.4 mg, 0.016 mmol). The vial was sealed under ambient atmosphere and the mixture was heated by immersion of the entire vial into a pre-heated aluminium block at 50 °C for 4 h. The mixture was cooled to room temperature, and subjected directly to flash chromatography (CH$_2$Cl$_2$) to afford title compound 1.196 (55 mg, 98%) as a colourless oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.78 (2H, d, $J = 8.4$ Hz, Ts-H), 7.33 (1H, td, $J = 7.5, 1.3$ Hz, Ar-H), 7.28 (2H, d, $J = 8.1$ Hz, Ts-H), 7.20 – 7.07 (3H, m, Ar-H), 5.86 (1H, ddt, $J = 17.2, 10.3, 5.9$ Hz, CH-2”), 5.77 (1H, ddt, $J = 17.1, 10.0, 6.7$ Hz, CH-2”), 5.21 – 5.14 (2H, m, CH$_2$-3”), 5.01 – 4.91 (2H, m, CH$_2$-3”), 4.36 (2H, d, $J = 5.8$ Hz, CH$_2$-1”), 3.16 (2H, d, $J = 6.8$ Hz, CH$_2$-1”), 2.43 (3H, s, TS-Ch$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 170.6 (c), 144.9 (C), 137.6 (C), 136.6 (C), 136.0 (CH), 134.8 (C), 133.0 (CH), 130.3 (CH), 129.7 (CH), 129.4 (CH), 128.9 (CH), 126.8 (CH), 125.8 (CH), 118.9 (CH$_2$), 116.8 (CH$_2$), 50.0 (CH$_2$), 37.1 (CH$_2$), 21.7 (CH$_3$); IR (thin film) 3063, 1686, 1354; HRMS (EI) exact mass calculated for C$_{20}$H$_{22}$NO$_3$S [M+H]$^+$ m/z 356.1320; found m/z 356.1317.

3-methyl-2-tosylisoquinolin-1-one 1.193

A 4 mL screw-top glass vial was charged with $N$-tosyl-2-allylbenzamide 1.189 (44 mg, 0.16 mmol), toluene (0.64 mL), H$_2$O (0.64 mL), KH$_2$PO$_4$ (44 mg, 0.32 mmol), allyl bromide (0.065 mL, 0.79 mmol) and Pd(hfacac)$_2$ (8.4 mg, 0.016 mmol). The vial was sealed under ambient atmosphere and the mixture was heated by immersion of the entire vial into a pre-heated aluminium block at 50 °C for 20 h. The mixture was cooled to room temperature, and subjected directly to flash chromatography (petroleum ether/CH$_2$Cl$_2$ 1:1) to yield the title compound 1.193 (3.9 mg, 8%) as a white powdered solid. Analytical data observed were in accordance with literature values.\textsuperscript{[75]}
3-methylene-2-tosylisoindolin-1-one 1.215

A 4 mL screw-top glass vial was charged with 2-vinyl-N-tosyl-benzamide 1.212 (48 mg, 0.16 mmol), toluene (0.64 mL), H₂O (0.64 mL), KH₂PO₄ (44 mg, 0.32 mmol), allyl chloride (0.067 mL, 0.79 mmol) and Pd(hfacac)₂ (8.4 mg, 0.016 mmol). The vial was sealed under ambient atmosphere and the mixture was heated by immersion of the entire vial into a pre-heated aluminium block at 50 °C for 20 h. The mixture was cooled to room temperature, and subjected directly to flash chromatography (CH₂Cl₂) to afford title compound 1.215 (38 mg, 80%) as a white powdered solid. ¹H NMR (500 MHz, CDCl₃) δ 8.00 (2H, d, J = 8.4 Hz, Ts-H), 7.79 (1H, d, J = 7.7 Hz, Ar-H), 7.70–7.65 (2H, m, Ar-H), 7.49 (1H, t, J = 7.1 Hz, Ar-H), 7.32 (2H, d, J = 8.1 Hz, Ts-H), 6.20 (1H, d, J = 2.1 Hz, C-CH₂), 5.54 (1H, d, J = 2.1 Hz, C-CH₂), 2.41 (3H, s, Ts-H); ¹³C NMR (125 MHz, CDCl₃) δ 165.1 (C), 145.5 (C), 138.1 (C), 137.6 (C), 136.0 (C), 134.3 (CH), 130.2 (CH), 129.9 (CH), 128.3 (C), 128.3 (CH), 124.5 (CH), 120.2 (CH), 96.8 (CH₂), 21.8 (CH₃); IR (thin film) 1750, 1172; LRMS (CI/Isobutane) mass calculated for C₁₆H₁₄NO₃S [M+H]+ m/z 300.1; found m/z 300.1.

3,3,5-trimethyl-1-tosyl-pyrrolo-2-one 1.233

A 4 mL screw-top glass vial was charged with 2,2-dimethyl-N-tosyl-pent-4-enamide 1.230 (44 mg, 0.16 mmol), toluene (0.64 mL), H₂O (0.64 mL), KH₂PO₄ (44 mg, 0.32 mmol), allyl chloride (0.067 mL, 0.79 mmol) and Pd(hfacac)₂ (8.4 mg, 0.016 mmol). The vial was sealed under ambient atmosphere and the mixture was heated by immersion of the entire vial into a pre-heated aluminium block at 50 °C for 20 h. The mixture was cooled to room temperature, and subjected directly to flash chromatography (petroleum ether/CH₂Cl₂ 1:1) to afford title compound 1.233 (37 mg, 83%) as a colourless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.88 (2H, d, J = 8.4 Hz), 7.32 (2H, d, J = 8.1 Hz), 5.07 (1H, d, J = 1.4 Hz), 2.43 (3H, s), 2.27 (3H, d, J = 1.4 Hz), 1.08 (6H, s); ¹³C NMR (125 MHz, CDCl₃) δ 165.1 (C), 145.5 (C), 138.1 (C), 137.6 (C), 136.0 (C), 134.3 (CH), 130.2 (CH), 129.9 (CH), 128.6 (C), 128.3 (CH), 124.5 (CH), 120.2 (CH), 96.8 (CH₂), 21.8 (CH₃); IR (thin film) 1755, 1172; HRMS (CI/Isobutane) exact mass calculated for C₁₄H₁₈NO₃S [M+H]+ m/z 280.1007; found m/z 280.1006.

3-methyl-2-tosyl-2-azaspiro[4,5]dec-3-en-1-one 1.240

A 4 mL screw-top glass vial was charged with 1-allyl-N-tosyl-cyclohexanecarboxamide 1.232 (51 mg, 0.16 mmol), toluene (0.64 mL), H₂O (0.64 mL), KH₂PO₄ (44 mg, 0.32 mmol), allyl chloride (0.067 mL, 0.79 mmol) and Pd(hfacac)₂ (8.4 mg, 0.016 mmol). The vial was sealed under ambient atmosphere and the mixture was heated by immersion of the entire vial into a pre-heated aluminium block at 50 °C for 20 h. The mixture was cooled to room temperature, and subjected directly to flash chromatography (petroleum ether/CH₂Cl₂ 1:1) to yield the title compound 1.240 (37 mg, 73%) as a colourless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.87 (2H,
3,3-dimethyl-2-tosyl-3,4-dihydroisoquinolin-1-one 1.264

A 4 mL screw-top glass vial was charged with 2-(2-methyl)-allyl-N-tosyl-benzamide 1.260 (52 mg, 0.16 mmol), toluene (0.64 mL), H2O (0.64 mL), allyl chloride (0.067 mL, 0.79 mmol) and Pd(hfacac)2 (8.4 mg, 0.0080 mmol). The vial was sealed under ambient atmosphere and the mixture was heated by immersion of the entire vial into a pre-heated aluminium block at 50 °C for 48 h. The mixture was cooled to room temperature, and subjected directly to flash chromatography (CH2Cl2) to afford title compound 1.264 as a colourless oil (42 mg, 80%). 1H NMR (500 MHz, CDCl3) δ 8.20 (1H, dd, J = 7.9, 0.8 Hz, Ar-H), 7.93 (2H, d, J = 8.3 Hz, Ts-H), 7.51 (1H, td, J = 7.5, 1.3 Hz, Ar-H), 7.35 – 7.28 (3H, m, Ts-H & Ar-H), 7.10 (1H, d, J = 7.5 Hz, Ar-H), 2.95 (2H, s, ArCH2), 2.42 (3H, s, Ts-CH3), 1.28 (6H, s, (CH3)2); 13C NMR (100 MHz, CDCl3) δ 162.6 (C), 143.0 (C), 139.5 (C), 136.8 (C), 134.5 (CH), 130.1 (CH), 129.0 (CH), 128.4 (CH), 128.0 (CH), 127.8 (CH), 124.5 (C), 83.4 (C), 38.9 (CH2), 26.7 (CH3), 21.7 (CH3); IR (thin film) 1684, 1549, 1310, 1163; HRMS (EI) exact mass calculated for C18H16NO3S [M+H]+ m/z 329.1086; found m/z 329.1319.

3-(But-3-enyl)-3-methylisobenzofuran-1-one 1.268

A 4 mL screw-top glass vial was charged with N-Boc-2-isopropenylbenzamide 1.265 (0.16 g, 0.63 mmol), toluene (1.3 mL), KH2PO4 (0.17 mg, 1.3 mmol), allyl chloride (0.26 mL, 3.2 mmol) and Pd(OAc)2 (14 mg, 0.06 mmol). The vial was sealed under ambient atmosphere and the mixture was heated by immersion of the entire vial into a pre-heated aluminium block at 110 °C for 48 h. The mixture was cooled to room temperature, and subjected directly to flash chromatography (petroleum ether/CH2Cl2 1:1) to afford title compound 1.268 as a white powdered solid (87 mg, 73%). 1H NMR (500 MHz, CDCl3) δ 7.87 (1H, dd, J = 7.6, 0.9 Hz, Ar-H), 7.66 (1H, td, J = 7.5, 1.1 Hz, Ar-H), 7.50 (1H, td, J = 7.5, 0.8 Hz, Ar-H), 7.36 (1H, d, J = 7.7 Hz, Ar-H), 5.74 – 5.66 (1H, m, 3-CH), 4.94 – 4.89 (2H, m, 4-CH2), 2.15 (1H, ddd, J = 13.6, 11.2, 4.8 Hz, 1-CH), 2.10 – 2.02 (1H, m, 2-CH), 1.96 (1H, ddd, J = 13.7, 11.0, 4.6 Hz, 1-CH), 1.80 – 1.73 (1H, m, 2-CH), 1.65 (3H, s, CH3); 13C NMR (125 MHz, CDCl3) δ 169.9 (C), 153.9 (C), 137.3 (CH), 134.2 (CH), 129.1 (CH), 126.5 (C), 126.0 (CH), 121.0 (CH), 115.2 (CH2), 87.3 (C), 39.3 (CH2), 28.0 (CH2), 26.3 (CH3); IR (thin film) 1751, 1285, 1030; HRMS (EI) exact mass calculated for C13H15O2 [M]+ m/z 202.0994, found m/z 202.0991.
3,3’-(ethene-1,2-diyl)bis(2-methoxy-3-methylisoindolin-1-one) 1.295

A 4 mL glass screw-top vial was charged with Pd(OAc)$_2$ (2.3 mg, 0.010 mmol), SPhos (8.2 mg, 0.020 mmol) and toluene (0.40 mL). This mixture was stirred at room temperature for 10 min, before the addition of N-methoxy-2-isopropenylbenzamide 1.292 (38 mg, 0.20 mmol), NaHCO$_3$ (34 mg, 0.40 mmol) and allyl bromide (0.090 mL, 1.0 mmol). The vial was sealed under ambient atmosphere and the mixture was heated by immersion of the entire vial into a pre-heated aluminium block at 80 °C for 24 h. The mixture was cooled to room temperature, and subjected directly to column chromatography (petroleum ether:EtOAc, 1:1) to afford title compound 1.295 as a pale yellow oil (5.0 mg, 6%). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.96 (2H, m, Ar-$H$), 7.17 – 7.10 (2H, m, Ar-$H$), 7.08 – 7.01 (2H, m, Ar-$H$), 6.93 – 6.78 (2H, ddt, $J$ = 13.4, 7.5, 1.0 Hz, Ar-$H$), 5.75 – 5.72 (2H, m, C=CH), 3.85 – 3.82 (6H, m, NO$_2$CH$_3$), 1.29 – 1.25 (6H, m, C-$CH_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 164.5/164.4 (major/minor diastereomer) (C), 146.64/146.59 (C), 133.0 (CH), 132.83/132.79 (CH), 128.9 (CH), 128.73/128.66 (C), 124.30/124.27 (CH), 128.81/121.7 (CH), 66.2/66.1 (C), 65.5/65.4 (CH$_3$), 21.91/21.85 (CH$_3$); IR (thin film) 2936, 1705, 1614, 1468; HRMS (ESI positive) exact mass calculated for C$_{22}$H$_{22}$N$_2$O$_4$Na [M]$^+$ m/z 410.1477; found m/z 401.1464.

3-(bromomethyl)-2-methoxy-3-methylisoindolin-1-one 1.296

A 4 mL glass screw-top vial was charged N-methoxy-2-isopropenylbenzamide 1.292 (38 mg, 0.20 mmol), NaHCO$_3$ (34 mg, 0.40 mmol), DME (0.40 mL), allyl bromide (0.090 mL, 1.0 mmol) and Pd(OAc)$_2$ (2.3 mg, 0.010 mmol). The vial was sealed under ambient atmosphere and the mixture was heated by immersion of the entire vial into a pre-heated aluminium block at 50 °C for 24 h. The mixture was cooled to room temperature, and subjected directly to column chromatography (petroleum ether:EtOAc, 4:1) to afford title compound 1.296 as a colourless oil (11 mg, 20%). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.86 (1H, d, $J$ = 7.6 Hz, Ar-$H$), 7.61 (1H, td, $J$ = 7.5, 1.0 Hz, Ar-$H$), 7.51 (1H, td, $J$ = 7.5, 1.0 Hz, Ar-$H$), 7.40 (1H, d, $J$ = 7.6 Hz, Ar-$H$), 4.12 (3H, s, NOCH$_3$), 3.82 (1H, d, $J$ = 10.8 Hz, CHBr), 3.76 (1H, d, $J$ = 10.8 Hz, CHBr), 1.73 (3H, s, C-$CH_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 165.1 (C), 145.0 (C), 132.6 (CH), 129.6 (C), 129.2 (CH), 124.0 (CH), 121.1 (CH), 65.6 (C), 65.4 (CH$_3$), 36.7 (CH$_2$), 22.2 (CH$_3$); IR (thin film) 2930, 1699, 1659, 1317; HRMS (EI+) exact mass calculated for C$_{11}$H$_{12}$NO$_2$Br [M]$^+$ m/z 269.0051; found m/z 269.0050.

2-methoxy-3,3-dimethylisoindolin-1-one 1.304

A 4 mL glass screw-top vial was charged with Pd(OAc)$_2$ (2.3 mg, 0.010 mmol), SPhos (8.2 mg, 0.020 mmol) and toluene (0.40 mL). This mixture was stirred at room temperature for 10 min, before the addition of N-methoxy-2-isopropenylbenzamide 1.292 (38 mg, 0.20 mmol), NaHCO$_3$ (34 mg, 0.40 mmol) and allyl chloride (0.081 mL, 1.0 mmol).
The vial was sealed under ambient atmosphere and the mixture was heated by immersion of the entire vial into a pre-heated aluminium block at 50 °C for 24 h. The mixture was cooled to room temperature, and subjected directly to column chromatography (petroleum ether:EtOAc, 4:1) to afford title compound 1.304 as an amorphous solid (8 mg, 21%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.83 (1H, d, \(J = 7.6\) Hz, Ar-H), 7.56 (1H, td, \(J = 7.6, 1.1\) Hz, Ar-H), 7.44 (1H, td, \(J = 7.5, 1.0\) Hz, Ar-H), 7.35 (1H, d, \(J = 7.6\), Ar-H), 4.06 (3H, s, NO\(-\)CH\(_3\)), 1.56 (6H, s, (CH\(_3\))\(_2\)); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 164.1 (C), 148.9 (C), 132.3 (CH), 128.6 (C), 128.3 (CH), 124.0 (CH), 120.8 (CH), 65.4 (CH\(_3\)), 63.6 (C), 25.2 (CH\(_3\)); IR (thin film) 2931, 1705, 1287; HRMS (ESI positive) exact mass calculated for C\(_{11}\)H\(_{13}\)NO\(_2\)Na \([\text{M}+\text{Na}]^+\) m/z 214.0838; found m/z 214.0835.

\(\text{N-benzyloxy-3,3-dimethylisoindolin-1-one 1.308}\)

A 4 mL glass screw-top vial was charged with Pd(OAc)\(_2\) (2.3 mg, 0.010 mmol), SPhos (8.2 mg, 0.020 mmol) and toluene (0.40 mL). This mixture was stirred at room temperature for 10 min, before the addition of \(\text{N-benzyloxy-2-isopropenylbenzamide 1.65}\) (53 mg, 0.20 mmol) and allyl chloride (0.081 mL, 1.0 mmol). The vial was sealed under ambient atmosphere and the mixture was heated by immersion of the entire vial into a pre-heated aluminium block at 80 °C for 24 h. The mixture was cooled to room temperature, and subjected directly to column chromatography (petroleum ether:EtOAc, 4:1) to afford title compound 1.308 as a colourless oil (15 mg, 28%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.85 (1H, d, \(J = 7.6\) Hz, Ar-H), 7.58–7.32 (8H, m, Ar-H), 5.26 (2H, s, OCH\(_2\)Ph), 1.44 (6H, s, (CH\(_3\))\(_2\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 164.7 (C), 149.2 (C), 135.6 (C), 132.3 (CH), 129.8 (CH), 129.0 (CH), 128.6 (CH), 128.3 (CH & C), 123.9 (CH), 120.9 (CH), 79.2 (CH\(_2\)), 63.6 (C), 25.1 (CH\(_3\)); IR (thin film) 2336, 1705, 1616; HRMS (ESI positive) exact mass calculated for C\(_{17}\)H\(_{17}\)NO\(_2\)Na \([\text{M}]^+\) m/z 290.1151; found m/z 290.1151.

\(\text{3-methyl-2-tosyl-1,2-dihydroisoquinoline 1.322}\)

A 4 mL screw-top glass vial was charged with \(\text{N-(2-allylbenzyl)-4-methylbenzenesulfonamide 1.319}\) (44 mg, 0.16 mmol), toluene (0.64 mL), H\(_2\)O (0.64 mL), KH\(_2\)PO\(_4\) (44 mg, 0.32 mmol), allyl chloride (0.067 mL, 0.79 mmol) and Pd(hfacac)\(_2\) (8.4 mg, 0.016 mmol). The vial was sealed under ambient atmosphere and the mixture was heated by immersion of the entire vial into a pre-heated aluminium block at 50 °C for 20 h. The mixture was cooled to room temperature, and subjected directly to flash chromatography (petroleum ether/CH\(_2\)Cl\(_2\) 1:1) to afford title compound 1.322 (30 mg, 64%) as a white powdered solid. Analytical data observed were in accordance with literature values\(^{[75]}\).

\(\text{N-Boc-3-methyl-1,2-dihydroisoquinoline 1.326}\)

A 4 mL screw-top glass vial was charged with 2-allyl-N-Boc-benzylamine 1.323 (44 mg, 0.16 mmol), toluene (0.64 mL), H\(_2\)O (0.64 mL), KH\(_2\)PO\(_4\) (44 mg, 0.32 mmol), allyl chloride (0.067 mL, 0.79 mmol) and Pd(hfacac)\(_2\) (8.0 mg, 0.02 mmol). The vial
was sealed under ambient atmosphere and the mixture was heated by immersion of the entire vial into a pre-heated aluminium block at 50 °C for 20 h. The mixture was cooled to room temperature, and subjected directly to flash chromatography (petroleum ether/CH₂Cl₂ 1:1) to afford title compound 1.326 (27 mg, 69%) as a colourless oil. Analytical data observed were in accordance with literature values.[118]

2-methylindole 1.334

A 4 mL screw-top glass vial was charged with 2-allylaniline 1.333 (37 mg, 0.16 mmol), toluene (0.32 mL), H₂O (0.32 mL), KH₂PO₄ (44 mg, 0.32 mmol), allyl chloride (0.067 mL, 0.79 mmol) and Pd(hfacac)₂ (8.0 mg, 0.02 mmol). The vial was sealed under ambient atmosphere and the mixture was heated by immersion of the entire vial into a pre-heated aluminium block at 50 °C for 48 h. The mixture was cooled to room temperature, and subjected directly to flash chromatography (CH₂Cl₂) to yield the title compound 1.334 (18 mg, 88%) as a colourless oil. Analytical data observed matched analysis of commercially available compound.

N-Boc-2-methylindole 1.340

A 4 mL screw-top glass vial was charged with 2-allyl-N-Boc-aniline 1.337 (44 mg, 0.16 mmol), toluene (0.64 mL), H₂O (0.64 mL), KH₂PO₄ (44 mg, 0.32 mmol), allyl chloride (0.067 mL, 0.79 mmol) and Pd(hfacac)₂ (8.0 mg, 0.02 mmol). The vial was sealed under ambient atmosphere and the mixture was heated by immersion of the entire vial into a pre-heated aluminium block at 50 °C for 20 h. The mixture was cooled to room temperature, and subjected directly to flash chromatography (petroleum ether/CH₂Cl₂ 1:1) to afford title compound 1.340 (21 mg, 57%) as a colourless oil. Analytical data observed were in accordance with literature values.[119]
Chapter 2: Identification and Activity of Inhibitors of the Essential Nematode-Specific Metalloprotease DPY-31.

2.1: Introduction

2.1.1: Background
Parasitic nematodes are known to infect humans and livestock worldwide, leading to chronic, debilitating and potentially lethal infections. Over 1 billion humans globally, particularly in the developing regions in Asia, Latin America and sub-Saharan Africa, suffer from nematode infections resulting in substantial mortality and morbidity.\textsuperscript{[120,121]}

Despite these vast nematode-infected populations, relatively little research funding is directed to nematode treatments compared to HIV/AIDS, malaria and tuberculosis. Several nematode-induced diseases were included on a recent World Health Organisation list of neglected tropical diseases aimed at increased funding.\textsuperscript{[122]}

The socio-economic impact on the agricultural industry due to costs of treatments and livestock loss is significant, with the annual cost of sheep and cattle infections in Australia alone estimated at $1 billion.\textsuperscript{[123]} There are also major losses in plant-based food production, estimated at $80 billion annually, due to nematode infections in important crops.\textsuperscript{[124]}

Parasitic nematodes (also known as roundworms), one of the two major phyla of Helminth, include intestinal parasites and filarial worms. Diseases caused by parasitic nematode infections are diverse. \textit{Ascariasis lumbricoides}, an intestinal parasite and the most prevalent nematode worldwide, causes Ascariasis infection which in most cases present no symptoms whatsoever, whereas \textit{Brugia malayi}, a filarial nematode, causes lymphatic filariasis, more commonly known as elephantiasis, which is a horribly debilitating disease. A comprehensive review of Helminth infections has been undertaken by Hotez and co-workers.\textsuperscript{[125]}

GI-tract nematode infections in mammals usually occur \textit{via} ingestion of contaminated water or food. Infections to the food supply add an additional risk for humans eating contaminated livestock. Filarial infections are transmitted by blood-feeding insects, most commonly mosquitoes. The site of development of filarial nematodes varies between species, and human filarial infections are known to occupy subcutaneous fat, the lymphatic system and the thoracic muscle.\textsuperscript{[126]}

Parasitic nematode infections are currently treated through preventative chemotherapy through mass anthelmintic drug administration. Conventional anthelmintic drugs were initially developed for treatment of veterinary parasites and were subsequently applied to human parasites. Huge advances
in the field of veterinary anthelmintics were made between 1960 and 1980, and effective doses are now in the micromolar range, a small fraction compared to the gram doses necessary for the treatments used 20 years previously.\[127,128,129\]

The most commonly used anthelmintic drugs fall into two categories: Avermectins and benzimidazoles, although there is a significant number of other treatments which do not fall into these categories.\[127\] Avermectins are macrocyclic lactone containing drugs, used as a broad spectrum treatment for parasitic nematode infections. The most commonly used avermectin, and indeed the most widely used anthelmintic, for nematode infections is Ivermectin, a mixture of Avermectin B\(_{1a}\) and B\(_{1b}\) (Figure 2.1). The global significance of Ivermectin is highlighted by the inclusion on the World Health Organisation’s model list of essential medicines.\[4\]

![Figure 2.1: Structure of Ivermectin](image)

Ivermectin has a broad therapeutic range of nematode targets, and is commonly used to medicate lymphatic filariasis, Onchocerciasis (caused by nematode \textit{Onchocerca volvulus}) as well as several intestinal roundworms, and non-nematode helminths. Avermectins are known to cause paralysis of nematode mobility, eventually leading to expulsion. The exact mode of action is unknown, but studies have identified several different effects exhibited by Ivermectin.\[130,131,132,133\]

The other major class of anthelmintics are benzimidazoles, which are a large group of drugs for the treatment of nematode infections of general structure shown (Figure 2.2). The group can be further classified into thiazoles (e.g. thiabendazole) and carbamates (e.g. albendazole). Benzimidazoles are generally used for the treatment of GI-tract nematodes in a broad range of species. The therapeutic action of benzimidazoles is through direct binding to nematode \(\beta\)-tubulin, and consequently inhibits the formation of microtubulin. Lack of microtubulin formation eventually leads to cell lysis.\[134\]

![Figure 2.2: Benzimidazoles](image)
The chemotherapeutic strategy of mass administration, however, is one which will be progressively selective for drug resistance in nematode populations. GI parasites in livestock have demonstrated multiple drug resistance to current anthelmintic treatments\cite{135,136,137,138} and there are already examples of selective drug resistances developing in human filarial nematode populations.\cite{121,139} As a consequence, there is significant concern that multidrug resistance will develop in human nematode populations. There have been only a limited number of novel treatment methods discovered in recent years,\cite{140} thus limiting the prospects for effective control in either human or veterinary parasites.

Attempts to increase the efficacy of current anthelmintic drugs have been thoroughly researched. For example, resistance to benzimidazoles has been associated with reduced affinity to nematode β-tubulin.\cite{141} Attempts to combat the resistance has centred on increasing the exposure time of the therapeutic to β-tubulin, primarily through modifications to drug metabolism. A combination of two benzimidazoles, oxfendazole and parbendazole (Figure 2.3), has demonstrated slowed metabolism, however they have not reached market for commercial reasons.\cite{142,143} Another novel strategy targeted sensitising nematodes to current treatments through interruption of detoxification pathways.\cite{124} Attempts have been made towards the development of a vaccine, although no product has yet reached the market.\cite{144,145}

![Figure 2.3: Structures of Oxfendazole and Pardendazole](image)

The success of the strategies, however, has been limited. Furthermore, very few drugs with novel modes of action have become available in recent years, consequently limiting the ability to control nematode populations in livestock. As a result, the identification of new targets is at a critical stage and new drug candidates are urgently required.

### 2.1.2: Nematode Astacin Metalloproteases

Recently, the nematode cuticle has been identified as a potential target for chemotherapeutic intervention.\cite{146} All nematodes are encased by a protective cuticle exoskeleton, primarily comprised of collagen proteins, which surrounds the nematode, protecting it from the external environment during development. The lifecycle of parasitic nematodes requires a moulting process at several stages during maturation.\cite{147} The moulting process involves the biosynthesis of a new cuticle and simultaneous exsheathment of the old. The cuticle biogenesis process is a complex, multi-enzyme process.\cite{148}
Free-living nematode *Caenorhabditis elegans* (*C. elegans*) is a non-parasitic nematode which has been subject to significant research as a model organism.\(^{[147]}\) *C. elegans* expresses cuticle sequence homology throughout the nematode phyla, for example, in *Teladorsagia circumcincta* and *Haemonchus contortus*,\(^{[149,150]}\) two major causes of veterinary infections. Furthermore, many of the cuticle synthesising enzymes and proteases crucial to *C. elegans* cuticle biosynthesis are also present in parasitic counterparts.\(^{[146]}\)

Astacin metalloprotease enzymes have demonstrated key functionality in cuticle biosynthesis in *C. elegans*.\(^{[148]}\) Astacin metalloproteases contain a penta-coordinated zinc ion in the N-terminal active site.\(^{[151]}\) DPY-31 (also known as NAS-35), a nematode-specific astacin, is a zinc endopeptidase which has demonstrated essential functionality the cuticle biosynthesis. DPY-31 has been established to cleave at the short C-terminal domain of essential cuticle collagen SQT-3.\(^{[152]}\)

Suppression of the gene encoding DPY-31 causes failure in the processing of procollagens, such as SQT-3, and consequently results in severe morphological defects (Figure 2.4). Compared to wildtype *C. elegans* (A), DPY-31 suppressed mutants (B) appear shorter and fatter. This non-viable phenotype is known as “dumpy” (DPY).

**Figure 2.4:** *C. elegans* demonstrating lethal morphology defect caused by suppression of DPY-31 gene

Although the crystal structure of DPY-31, or indeed any nematode-specific astacin metalloprotease, is yet to be ascertained, the crystal structure of astacin metalloprotease enzyme from *Astacus astacus*, a freshwater crayfish, has been determined.\(^{[151]}\) Furthermore, the enzyme has also been crystallised with a phosphinate inhibitor bound in the catalytic site, revealing important information about substrate-inhibitor interactions.\(^{[153]}\) The crayfish astacin metalloprotease has 76% amino-acid sequence homology with DPY-31, and is thus proposed to be an effective model for nematode astacin metalloproteases.\(^{[154,155]}\) The functionality of crayfish astacin has been subject to significant research, and the findings may be directly employable towards the development of DPY-31 inhibitors. It has also been established that DPY-31 retains significant structural homology between different nematode species.\(^{[156]}\)
2.1.3: Hydroxamates as Zinc metalloprotease inhibitors

Hydroxamic acids have long been known to exhibit strong binding to, and consequently inhibition of, zinc metalloprotease enzymes.\textsuperscript{157,158} Hydroxamate functionality provides a strong bidentate chelation of the catalytic Zn\textsuperscript{2+} ion, through binding with each oxygen of the hydroxamate functionality (Figure 2.5). Furthermore, it has been demonstrated that the hydroxamate nitrogen is protonated during binding, and may function as a hydrogen bond donor.\textsuperscript{159} Due to this bidentate interaction, hydroxamate containing compounds exhibit superior binding to Zn\textsuperscript{2+} than other metalloprotease inhibitors, including the widely utilised phosphinic acid group.\textsuperscript{160}

![Figure 2.5: Hydroxamate interaction with catalytic zinc in metalloprotease matrilysin](image)

In 1990, Wolz and co-workers established the applicability of amino acid hydroxamates to inhibition of crayfish astacin metalloprotease (Figure 2.6).\textsuperscript{161} The most potent inhibitors were demonstrated to be those with aromatic side-chains, and tyrosine-hydroxamate (IC\textsubscript{50} = 175 µM) represented the then-most potent reversible inhibitor of crayfish astacin metalloprotease. The report demonstrated the significant effect that the N-1 amino acid residue imparts on inhibitor binding.

![Figure 2.6: Hydroxamate inhibitors of crayfish astacin metalloprotease](image)

Various reports have shown that hydroxamate-based compounds also exhibit efficacious inhibition of Bone morphogenetic protein-1 (BMP-1). BMP-1 is a vertebrate procollagen C-proteinase (PCP), also a member of the astacin metalloprotease family,\textsuperscript{155} which is known to play a crucial role in bone/cartilage formation by breakdown of procollagen to allow formation of collagen in humans. In 2000, Ovens and co-workers demonstrated several potent hydroxamic acids inhibitors of PCP (Figure 2.7).\textsuperscript{162} Hydroxamate dipeptide \textbf{2.1} was demonstrated to be a powerful inhibitor of PCP, preventing
the cleavage of procollagen. The importance of the non-zinc binding hydroxamate-NH was demonstrated by the lack of inhibition exhibited by N-methylated analogue 2.2.

![Figure 2.7: Hydroxamate inhibitor of PCP](image)

Two further reports from Pfizer in 2007 and 2008 reported oxadiazole PCP inhibitors with improved potency, from which compounds 2.3 and 2.4 were selected as drug candidates (Figure 2.8).[163,164]

![Figure 2.8: Pfizer PCP-inhibitor drug candidates](image)

As was discussed previously, DPY-31 is a homologue of BMP-1, so it was hypothesised that these hydroxamate compounds may also exhibit inhibition of DPY-31, and thus affect the morphology, potentially lethally, of the nematode. Page and co-workers tested a range of hydroxamic acid drug candidates against *T. circumcincta* DPY-31 (Table 2.1).[165] Actinonin and oxadizoles 2.3–2.6 have previously been shown to exhibit efficacious and reversible inhibition of Pro-collagen peptidases. When screened against nematode DPY-31, actinonin and pyridyl-oxadizole 2.5 proved effective inhibitors, albeit at a high concentration. Furthermore, phenotypic testing against *C. elegans* demonstrated that compounds 2.3 – 2.6 all caused morphological defects, leading to the “dumpy” phenotype.
Table 2.1: Hydroxamate inhibitors of DPY-31

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC$_{50}$ rDPY-31 (T. circumcincta)</th>
<th>Phenotypic effect against C. Elegans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actinonin</td>
<td>50 µM</td>
<td>“Dumpy”, immobility</td>
</tr>
<tr>
<td>2.3</td>
<td>N/A</td>
<td>“Dumpy”, immobility</td>
</tr>
<tr>
<td>2.4</td>
<td>N/A</td>
<td>“Dumpy”, immobility</td>
</tr>
<tr>
<td>2.5</td>
<td>40 µM</td>
<td>“Dumpy”, immobility</td>
</tr>
<tr>
<td>2.6</td>
<td>&lt;100 µM</td>
<td>“Dumpy”, immobility</td>
</tr>
</tbody>
</table>
2.2: Results and Discussion

2.2.1: Introduction and aim

The increased resistance of parasitic nematodes towards current anthelmintic drug treatments, coupled with the limited number of drugs candidates in recent years, has left the field of nematode infection treatment at a critical point: novel drug targets are urgently required.\textsuperscript{\[165\]} Inhibition of cuticle exsheathment (ICE), through targeted binding to zinc metalloprotease DPY-31, is proposed as a novel method for the treatment. Previous work has shown that nematode astacin enzyme DPY-31 plays a significant role in the moulting process of the nematode collagen exoskeleton.\textsuperscript{\[152\]} Non-expression of DPY-31 causes severe morphological defects and results in the lethal phenotype “dumpy”.\textsuperscript{\[165\]} There are currently no drugs on the market for the treatment of nematode infections which act via the DPY-31 therapeutic target.

The aim of this project was the design and synthesis of new metalloprotease inhibitors to allow the validation of ICE as a potential strategy for the treatment of parasitic nematode infections. The project represents the first step towards the development a totally novel mechanism for drug intervention.

Compounds containing hydroxamic acid functionality have previously demonstrated inhibition of zinc metalloproteases and, more specifically, have demonstrated inhibition of astacin metalloprotease enzymes Pro-collagen C proteinase BMP-1 and in crayfish Astacus astacus. Collaborators tested a range of known hydroxamic acid drug candidates against T. circumcincta DPY-31 (section 2.1.3, table 2.1), demonstrating the potential for treatment of nematode infections via inhibition of cuticle exsheathment, but with low potency.\textsuperscript{\[165\]} While phosphinate compounds have also been proved to exhibit zinc metalloprotease inhibition,\textsuperscript{\[166,167,168\]} hydroxamates form stronger bonds to the active-site zinc and at a faster rate.\textsuperscript{\[161,169\]} Thus, phosphinic acid inhibitors were not targeted.

Several different compound design approaches were undertaken in an attempt to discover potent inhibitors of nematode DPY-31: 1) mimics of the known DPY-31 cleavage site in C. elegans; 2) using SAR data published for well-researched metalloproteases, such as Astacus astacus (crayfish) astacin and Pro-collagen C proteinase BMP-1 which are known to exhibit high structural homology to nematode astacin DPY-31 inhibitors and; 3) Known metalloprotease inhibitor marimastat was synthesised for in vivo testing as a treatment for inhibition of parasitic nematode DPY-31 and to allow for the synthesis of analogues.
2.2.2: Hydroxamic acid SQT-3 cleavage site mimics

Design

A mutant suppressor screen in *C. elegans* identified the target of astacin metalloprotease DPY-31 to be essential cuticle collagen SQT-3, and highlighted the specific peptide sequence at which DPY-31 cleaves the collagen in the C-terminal domain (Figure 2.9).[152,170] Although the overall sequence homology of each member of the SQT-3 sub-family (SQT-3, RAM-4, DPY-13 and DPY-4) is ca. 60%, the C-terminal putative cleavage site of SQT-3 is highly conserved, with near identical sequence of amino acid residues.

![Figure 2.9: Analysis of DPY-31 cleavage site on C-terminus of collagens of the SQT-3 subfamily](image)

At the DPY-31 cleavage site in the SQT-3 collagens, there is a common alanine-leucine/isoleucine motif at the binding site of DPY-31. It was proposed that by mimicking this amino acid sequence, effective binding to DPY-31 can be achieved. Towards this goal, dipeptide hydroxamates 2.7 and 2.8 were targeted for synthesis (Figure 2.10).

![Figure 2.10: Proposed SQT-3 mimics.](image)

Compound synthesis

Alanine-Leucine dipeptide was synthesised in three steps from commercially available amino acids (Scheme 2.1). Peptide coupling of leucine-methyl ester 2.9 and Boc-protected alanine under DCC coupling conditions, followed by ester hydrolysis yielded dipeptide 2.11 in an 80% yield over 2 steps. Subsequent conversion to the hydroxamate under amide-coupling conditions afforded hydroxamic acid 2.7.
In order to comprehend the effect of the amine-protection, the non-protected dipeptides of acid 2.11 and hydroxamic acid 2.7 were also synthesised (Scheme 2.2). Trifluoroacetic acid-mediated carbamate hydrolysis, followed by anion exchange, yielded hydrochloride salts 2.12 and 2.13 in good yields.

The same protocol was utilised for the synthesis of alanine-isoleucine hydroxamic acid 2.8 (Scheme 2.3). The DCC-mediated coupling between Boc-protected alanine and isoleucine-methyl ester, followed by ester hydrolysis yielded dipeptide amino acid 2.15 in a 76% yield over two steps. Subsequent transformation to hydroxamic acid 2.8 proceeded smoothly to yield dipeptide 2.8.

As discussed previously, the non-protected amines were required for testing (Scheme 2.4). Carbamate hydrolysis proceeded efficiently to garner alanine-isoleucine amino acid 2.16 and alanine-isoleucine hydroxamate 2.17 in good yield.
Biological screening

An astacin assay screen was performed on the synthesised alanine-leucine dipeptides to determine the inhibitory activity against recombinant DPY-31 from *T. circumcincta* and *B. malayi*. The screens were undertaken by researchers at Institute of Biodiversity at the University of Glasgow. The results of the absorbance assay undertaken against *T. circumcincta* DPY-31 is displayed below (Figure 2.11). As expected, dipeptides 2.11 and 2.12 exhibited no inhibitory activity. Boc-protected hydroxamic acid 2.7 exhibited inhibition of DPY-31 at high concentrations. Non-protected hydroxamic acid dipeptide 2.13 demonstrated no inhibition of DPY-31.

In contrast to the assay screen against *T. circumcincta*, screening against recombinant DPY-31 from human filarial nematode *T. malayi* did not identify any compound exhibiting inhibition (Figure 2.12). As expected, amino acids 2.11 and 2.12 did not demonstrate activity. Hydroxamic acids 2.7 and 2.13 also failed to demonstrate any significant inhibition.
A more detailed analysis of Boc-protected hydroxamate 2.7 allowed confirmation that it acts as a weak inhibitor of *T. circumcincta* DPY-31 but displays little effect against *B. malayi* DPY-31, with both trends extending at higher concentrations (Figure 2.13).

Absorbance assay screening of alanine-isoleucine dipeptides recombinant DPY-31 from *T. circumcincta*, *H. contortus* and *B. malayi* demonstrated similar results to the alanine-leucine dipeptides discussed above. Amino acids 2.15 and 2.16 failed to exhibit inhibition of either *T.
circumcineta or B. malayi DPY-31 (Figure 2.14). This result reaffirms the lack of activity of carboxylic acids against parasitic nematode DPY-31.

![Graph showing absorbance tests](image)

**Figure 2.14:** Assay testing of compounds 2.15 to 2.16 against *T. circumcineta*

Hydroxamic acid alanine-leucine dipeptides 2.8 and 2.17 were subsequently subjected to absorbance assay testing (Figure 2.15). As was demonstrated for hydroxamic acid 2.13, non-protected hydroxamic acid 2.17 demonstrated no inhibition of *T. circumcineta* DPY-31. Boc-protected analogue 2.8, however, demonstrated weak inhibition of *T. circumcineta* DPY-31 and *H. contortus* DPY-31.
Phenotypic screening of the dipeptide hydroxamic acid 2.8 resulted in morphological defects in parasitic nematodes *T. circumcincta* and *H. contortus*, resulting in either cuticle blistering, or retention of an old cuticle by a new larval stage. Promisingly, phenotypic testing against non-parasitic *C. elegans* displayed the “dumpy” phenotype – a severe morphological defect.

### 2.2.3: Hydroxamic acid analogues of potent phosphinic pseudopeptide

#### Compound design and synthesis

The crystal structure for crayfish (*Astacus astacus*) astacin has been determined and has subsequently been subject to significant research (Section 2.1.3). The structural homology between crayfish and nematode astacin is high (ca. 76%).\[^{154}\] It was consequently proposed that information gathered regarding the inhibition of crayfish astacin metalloproteases can be directly applicable to the inhibition of nematode astacin DPY-31. Phosphinic acid pseudopeptide 2.18 has demonstrated nanomolar range inhibitory activity against crayfish astacin (Figure 2.16).\[^{171}\] The crystallisation of a similar phosphinic acid in the Crayfish astacin binding pocket demonstrated important inhibitor-substrate binding between each amino-acid residue.\[^{153}\] Hydroxamic acids have demonstrated stronger and faster binding than phosphinic acid counterparts,\[^{161,169}\] and consequently, hydroxamic acid 2.19 was proposed to be a highly potent nematode astacin inhibitor.
In order to fully grasp any change in potency provided through change in amino acid residue, modifications relative to hydroxamic acids 2.7 and 2.8 were introduced stepwise. Hydroxamic acid dipeptide 2.20 (Figure 2.17) was designed to probe the inclusion of an aromatic amino acid residue at the P1 position, as exhibited by phosphinic acid 2.18. The inclusion of an aromatic amino acid residue at the P1 position has previously been demonstrated to exhibit stronger inhibitor–enzyme binding of hydroxamic acids to astacin metalloproteases.[161]

Hydroxamate 2.20 was synthesised via the same protocol described for leucine and isoleucine analogues (Scheme 2.5). Dipeptide 2.21 was synthesised from phenylalanine-methyl ester and Boc-alanine fragments using peptide coupling conditions. Ester hydrolysis and subsequent hydroxamic acid formation afforded desired dipeptide 2.20. The unprotected hydroxamic acid was not sought, because previous results demonstrated inactivity of the amine to DPY-31.
A 1995 report discussed inhibitors with significantly improved inhibition of astacin metalloprotease activity by inclusion of a proline residue at P3 position of a phosphinic acid inhibitors.\textsuperscript{[171]} The same report established that the crayfish astacin binding pocket is long, and an increased number of amino acid residues produced greater substrate binding, and consequently, greater potency. Boc- and Fmoc-protected proline containing hydroxamic acids 2.23 and 2.24 were proposed to improve the inhibition of nematode DPY-31 (Figure 2.18).

Previously synthesised dipeptide 2.21 was deprotected to yield the amine 2.25, which was subsequently coupling with a Boc-protected proline residue, yielding tripeptide 2.26 (Scheme 2.6). Ester hydrolysis, followed by hydroxamic acid formation yielded the desired substrate 2.23.
Fmoc-protected tripeptide 2.24 was synthesised via the same protocol as above (Scheme 2.7). Unprotected-dipeptide 2.25 was coupled with Fmoc-protected proline to yield tripeptide 2.28. Ester hydrolysis, followed by hydroxamic acid formation yielded desired substrate 2.24.

Scheme 2.7: Synthesis of tripeptide 2.24

**Testing results:**

Hydroxamic acids 2.20, 2.23 and 2.24 were submitted to absorbance assay testing\(^\text{[165]}\) to determine inhibitory activity of recombinant DPY-31 from three parasitic nematodes: *T. circumcincta*, *H. contortus* and *B. malayi*. Alanine–phenylalanine dipeptide 2.20 demonstrated inhibition of *T. circumcincta* at similar concentrations to non-aromatic dipeptides 2.7 and 2.8. Tripeptides 2.23 and 2.24, however, exhibited significantly improved potency, with Fmoc protected hydroxamic acid 2.24 exhibiting the greatest potency (Figure 2.19).
**Figure 2.19:** Absorbance assay results for the inhibition of recombinant *T. circumcincta* DPY-31 by hydroxamic acids 2.20, 2.23 and 2.24

Similar results were demonstrated for the inhibition of recombinant *H. contortus* DPY-31 (Figure 2.20). Alanine–phenylalanine dipeptide hydroxamic acid 2.20 demonstrated comparable activity to alanine–isoleucine dipeptide 2.7. Tripeptide hydroxamic acids 2.23 and 2.24 exhibited significantly greater potency.

**Figure 2.20:** Absorbance assay results for the inhibition of recombinant *H. contortus* DPY-31 by hydroxamic acid analogues of phosphinic acid pseudo-peptide

Tripeptides 2.23 and 2.24 were then tested for inhibition against DPY-31 from human parasite *Brugia malayi* (Figure 2.21). No compound previously synthesised as part of this project has demonstrated inhibition against *B. malayi* DPY-31. Encouragingly, both Boc- and Fmoc protected tripeptides 2.23 and 2.24 were demonstrated to be effective inhibitors.
Figure 2.21: Absorbance assay results for the inhibition of recombinant *B. malayi* DPY-31 by tripeptide hydroxamic acids 2.23 and 2.24

The IC\textsubscript{50} values calculated for tripeptides 2.23 and 2.24 and are displayed below (Table 2.2). Both of the tripeptide hydroxamic acids synthesised as part of this project (2.23 and 2.24) exhibited low µM range inhibition against rDPY-31 from veterinary parasite *T. circumcincta*. Promisingly, Fmoc-protected tripeptide 2.24 also exhibits low µM range inhibition against rDPY-31 from human filarial parasite *B. malayi*. These results are consistent with the proposed homology between DPY-31 enzymes across nematode species.\textsuperscript{[156]} At this time, Fmoc-protected tripeptide 2.24 exemplifies the most potent inhibitor of nematode DPY-31 currently known.

The results compare favourably to previously the values calculated for oxadiazole 2.5 and marimastat which were measured under the same absorbance assay conditions. Oxadiazole 2.5 exhibited similar activity to Fmoc-protected hydroxamic acid 2.24 against both *T. circumcincta* and *B. malayi*, but marimastat was a significantly poorer inhibitor of nematode DPY-31. Interestingly, phosphinic acid 2.30, which contains an identical *N*-terminal amino-acid sequence to phosphinic acid 2.30, was inactive in this assay.
Table 2.2: IC<sub>50</sub> values recorded for tripeptides 2.23 and 2.24 and comparison to values recorded for known hydroxamic acids 2.5 and marimastat and phosphinic acid 2.30

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; rDPY-31(µM)</th>
<th>B. malayi</th>
<th>T. circumcincta</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.23</td>
<td></td>
<td>76</td>
<td>26</td>
</tr>
<tr>
<td>2.24</td>
<td></td>
<td>26</td>
<td>34</td>
</tr>
<tr>
<td>2.5</td>
<td></td>
<td>22</td>
<td>40</td>
</tr>
<tr>
<td>Marimastat</td>
<td></td>
<td>181</td>
<td>71</td>
</tr>
<tr>
<td>2.30</td>
<td></td>
<td>&gt; 500</td>
<td>&gt; 500</td>
</tr>
</tbody>
</table>

Phenotypic screening of tripeptides 2.23 and 2.24 was undertaken to assess any morphological defects caused. Wild-type free-living nematode *C. elegans* (A) is displayed below (Figure 2.22). Treatment with 50 µM of Boc-protected tripeptide 2.23 (B) resulted in the shorter, fatter morphology called “dumpy”. This phenotype is consistent with the loss of function of DPY-31.<sup>[152]</sup>

![Figure 2.22: Phenotypic screen of wild-type *C. elegans*](A. B.)

Similar results were observed upon treatment of TP224 (C) – a *T. circumcincta* DPY-31 transgenically-rescued *C. elegans* DPY-31 mutant (Figure 2.23). Treatment with 100 µM of Boc-protected tripeptide 2.23 (D) also demonstrated the “dumpy” phenotype.
Furthermore, veterinary parasite *T. circumcincta* (E) was treated with 500 µM of Fmoc-protected tripeptide 2.24 (Figure 2.24). A higher concentration was required, but the “dumpy” phenotype was observed, confirming the DPY-31 inhibitory effect.

**Figure 2.24:** Phenotypic screen of parasitic nematode *T. circumcincta*

### 2.2.4: Marimastat:

Marimastat is a hydroxamic acid which has demonstrated pharmaceutical activity, initially designed as a broad spectrum zinc metalloprotease inhibitor for the treatment of cancer and has demonstrated promising pharmacokinetic properties in mice (Figure 2.25). It has previously exhibited metalloprotease inhibition, but was less effective against parasitic nematode DPY-31 than compounds previously synthesised in this project (Table 2.2). The combination of the known pharmacokinetic properties of marimastat and activity against recombinant DPY-31 motivated a study into the in vivo efficacy for the treatment of nematode infections in mice which was undertaken in collaboration with a group at the University of Edinburgh. It was proposed that synthesising the compound, rather than purchasing, would afford the opportunity to efficiently construct analogues.

**Figure 2.25:** Marimastat structure
In 2000, Davenport et al. reported an improved synthesis of marimastat. The key step of the reaction sequence was the construction of the central amide bond by coupling carboxylic acid fragment 2.31 with amine fragment 2.32. Fragments 2.31 and 2.32 are made from commercially available starting materials, L-(-)-malic acid and Boc-tert-leucine respectively (Scheme 2.8). Importantly, the late stage fragment coupling is conducive to rapid synthesis of analogues.

![Scheme 2.8: Retrosynthetic analysis of Marimastat](image)

The synthesis of acid fragment 2.31 began with Fischer esterification of L-(-)-malic acid to yield (S)-diisopropylmalate. The allylation of (S)-diisopropylmalate to yield 2.33 was successful using LDA and methallyl iodide (Scheme 2.9).

![Scheme 2.9: Esterification and allylation of Malic acid](image)

Attempts towards the allylation were undertaken with the freshly prepared methyl iodide, as well as methallyl chloride and bromide due to their ready availability (Table 2.3). Methallyl chloride (entry 1) did not result in desired product 2.33. Methallyl bromide (entry 2) gave a 7:1 diastereomeric ratio of separable diastereomers 2.33 to 2.34, and an isolated yield of 32%. Methallyl iodide (entry 3) gave an improved diastereomeric ratio of 9:1 in the crude product, with a slightly improved yield.
Table 2.3: Optimisation of allylation

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>2.33;2.34</th>
<th>Yield of 2.33</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cl</td>
<td>-</td>
<td>Not observed</td>
</tr>
<tr>
<td>2</td>
<td>Br</td>
<td>7 : 1</td>
<td>32%</td>
</tr>
<tr>
<td>3</td>
<td>I</td>
<td>9 : 1</td>
<td>35%</td>
</tr>
</tbody>
</table>

The diastereoselectivity of the allylation reaction is proposed to arise from cyclic intermediate 2.35 (Scheme 2.10).\(^{[174]}\) Chelation between the lithium enolate and the alkoxide of the malate dianion hinders approach of the electrophile on the bottom face, giving rise to diastereoselectivity of up to 10:1 in favour of anti-product 2.33.

Scheme 2.10: Explanation of diastereoselectivity

Acid fragment 2.31 was prepared from 2.33 following a known procedure (Scheme 2.11).\(^{[172]}\) Hydrogenation of olefin 2.33 proceeded with excellent yield to yield diester 2.36, which was subsequently hydrolysed under basic conditions. Lactonisation of dicarboxylic acid 2.37 produced the acetonide and completed the synthesis of Acid fragment 2.31 in 5 steps.

Scheme 2.11: Synthesis of carboxylic acid fragment 2.31
Amine fragment 2.32 was synthesised in two steps from Boc-tert-Leucine (Scheme 2.12). Methylamide formation proceeded smoothly to yield Boc-protected amine 2.38. Deprotection using trifluoroacetic acid gave fragment 2.32 as the trifluoroacetate salt in a 70% yield over 2 steps.

Scheme 2.12: Synthesis of amine fragment 2.32

With both fragments in hand, attempts were made towards the coupling of fragments 2.31 and 2.32 (Table 2.4). The protocol previously utilised by Davenport and co-workers were tested, but the coupling to the bulky tert-leucine fragment proved to be unsuccessful under these conditions.\(^{[173]}\) Use of CDI (entry 2) proved to have no improvement. In both cases, activation of the carboxylic acid (fragment 2.31) was observed, but the subsequent amide bond formation with fragment 2.32 was unsuccessful. Addition of nucleophilic catalyst DMAP (entry 3) successfully allowed the coupling of fragment 2.32 to the activated species derived from fragment 2.31, and desired peptide 2.39 was obtained in a 69% yield.

Table 2.4: Attempted coupling of fragments 2.31 and 2.32

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result (isolated yield of 2.39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EDC, NEt(_3), CH(_2)Cl(_2), RT, 40 h</td>
<td>No conversion of B</td>
</tr>
<tr>
<td>2</td>
<td>CDI, NEt(_3), THF, RT, 40 h</td>
<td>No conversion of B</td>
</tr>
<tr>
<td>3</td>
<td>EDC, DMAP, DMF, 0 °C, 24 h</td>
<td>Full conversion (69%)</td>
</tr>
</tbody>
</table>

With acetonide 2.39 in hand, the synthesis of marimastat was completed by direct acetonide attack from hydroxylamine (Eq. 2.2). Repeated crystallisation provided highly pure marimastat which was suitable for \textit{in vivo} trials.
**Testing results:**

*In situ* biological testing was undertaken by researchers at the Institute of Structural and Molecular Biology at the University of Edinburgh. Mice infected by *Heligmosomoides polygyrus* (common rodent intestinal nematode parasite) were treated with marimastat, injected by gavage (an oral administration method). Treatment with marimastat showed a reduction in faecal egg count compared to gavage injection of water (Figure 2.26). Mice with no gavage however, demonstrated significantly lower faecal egg counts, suggesting that gavage injection has a negative effect on the immune response of the mouse.

![Figure 2.26: Faecal egg count after 14 days of marimastat treatment](image)

Although the egg count after treatment with marimastat was 50% lower, there was no reduction in the total worm count (Figure 2.27). This would suggest that marimastat was having a negative effect on the health of the nematode, but does not reliably eliminate the worm.

![Figure 2.27: Worm count after 14 days of marimastat treatment](image)

### 2.2.5: Conclusions

Boc-protected hydroxamic acid dipeptides 2.7 and 2.8 demonstrated weak inhibition against DPY-31 in recombinant *T. circumcincta* and *H. contortus* (Figure 2.28). Alanine–leucine dipeptide 2.7 has also been demonstrated to cause morphological defects in parasitic nematodes. The results also provided evidence that amino-acids and non-protected hydroxamic acids are not effective
metalloprotease inhibitors. It is also important to consider that no major improvement in activity was demonstrated by introducing an aromatic P1 amino acid residue (dipeptide 2.20), as opposed to the apolar aliphatic residues utilised in compounds 2.7 and 2.8. This is contrary to the proposal that the aromatic moiety would allow stronger substrate–inhibitor binding,[161] although is in agreement with the alternate proposal that the P1 position plays only a minor role in substrate binding.[175]

![Figure 2.28: Dipeptide hydroxamic acids exhibiting nematode DPY-31 inhibition](image)

More promising results were obtained from tripeptide hydroxamic acids 2.23 and 2.24 (Figure 2.29). Both the Boc- and Fmoc-protected analogues have demonstrated inhibition of DPY-31 in recombinant *B. malayi* (human filarial nematode) and *T. circumcincta* (sheep GI parasite) assay testing. Furthermore, phenotypic screening against several nematode strains displayed significant occurrence of the DPY phenotype, a non-viable body morphology associated with the inhibition of DPY-31, supporting the findings. Fmoc-protected tripeptide 2.24 is currently the most potent known inhibitor of nematode DPY-31.

![Figure 2.29: Hydroxamic acids 2.23 and 2.24](image)

Taken together, these results represent a start point in developing new metalloprotease inhibitors for the treatment of nematode infections through inhibition of DPY-31, a totally novel chemotherapeutic target.

### 2.2.6: Future work

Towards the long-term goal of the discovery of viable drug candidates for the inhibition of DPY-31, significantly more potent compounds must be discovered. Additionally, there is currently no data on pharmacokinetic of ADMET properties of the synthesised hydroxamic acids and, consequently, it is unknown if the tripeptide compounds are suitable drug candidates.
The results obtained, however, are particularly promising because tripeptide 2.19, the lysine analogue of 2.24, the current most potent inhibitor of DPY-31 (Figure 2.30) may provide improved substrate–inhibitor binding, increased drug potency.\textsuperscript{171}

![Figure 2.30: Target hydroxamic acid 2.19](image)

Due to time constraints, the desired analogues of marimastat were not synthesised. It is proposed, however, that coupling carboxylic acid fragment 2.31 with different, longer chain, amino acid sequences would allow for improved inhibition of DPY-31 (Figure 2.31). Proposed analogue 2.40 was designed using the C-terminus of potent pseudo-phosphinic acid 2.18.

![Figure 2.31: Proposed analogue of marimastat](image)
2.3 Supporting Information

2.3.1 General Methods

General methods are as described in Section 1.4.1.

2.3.2 General Procedures

General Procedure A: Amide bond formation

![Reaction scheme for amide bond formation]

To a stirred solution of amino acid-methyl ester.HX (1.1 equiv.) in CH$_2$Cl$_2$ (0.50 M) at 0 °C was added carbamate protected amino acid (1.0 equiv.). The resulting suspension was stirred for 10 mins, before addition of a solution of dicyclohexylcarbodiimide (1.2 equiv.) and triethylamine (1.1 equiv.). The solution was warmed to room temperature and allowed to stir for 4 h, before cooling to 0 °C and filtering. The filtrate was washed with sat. aq. NaHCO$_3$, and the resultant mixture was extracted with CH$_2$Cl$_2$ (x 3). The combined organics were dried (Na$_2$SO$_4$), filtered and concentrated in vacuo.

General Procedure B: Methyl ester hydrolysis

![Reaction scheme for methyl ester hydrolysis]

Methyl ester (1.0 equiv.) was stirred in 3:2 ethanol:1.0 M aq. NaOH (0.10 M) at room temperature for 1 h. Upon reaction completion, ethanol was removed in vacuo, and the aqueous solution was washed with EtOAc. The aqueous layer was acidified to pH 1 with 0.10 M aq. HCl and extracted with EtOAc (x 3). The combined organic extracts were dried (Na$_2$SO$_4$), filtered and concentrated in vacuo.

General Procedure C: Hydroxamic acid synthesis

![Reaction scheme for hydroxamic acid synthesis]

To a solution of N-protected amino acid (1.0 equiv.) in THF (0.050 M) was added carbonyl diimidazole (1.2 equiv.). The solution was stirred at room temperature for 1 h, before the addition of O-trimethylsilyl hydroxylamine (3.2 equiv.). The resultant mixture was stirred for 16 h at room temperature, before the quenching with MeOH. The solution was stirred for 1 h, and concentrated in vacuo.
**General Procedure D: Removal of Boc protecting group**

To a stirred solution of Boc-protected amino acid (1.0 equiv.) in CH$_2$Cl$_2$ (0.50 M) was added trifluoroacetic acid (1:2 v/v w.r.t. CH$_2$Cl$_2$) at room temperature. The solution was stirred at room temperature for 1 h, before concentrating *in vacuo*. The resultant solution was taken up in water, washed with EtOAc (x 3) and concentrated *in vacuo* to yield the trifluoroacetate salt.

**2.3.3: Compound Synthesis**

**SQT-3 Cleavage site mimics:**

Following general procedure A, Boc-Ala-OH (1.9 g, 10 mmol) and leucine methyl ester hydrochloride 2.9 (2.0 g, 11 mmol) were coupled. The crude material was used directly in the following step.

**Boc-Ala-Leu-OMe 2.10**

Following general procedure B, Boc-Ala-Leu-OMe (10 mmol) was hydrolysed to afford title compound 2.11 (2.6 g, 87% over 2 steps). No further purification was required. Observed analytical data was in accordance with literature values.$^{[176]}$

**Boc-Ala-Leu-NHOH 2.7**

Following general procedure C, Boc-Ala-Leu-OH 2.11 (0.50 g, 1.7 mmol) was transformed into the corresponding hydroxamate. The crude product was taken up in H$_2$O (10 mL) and washed with Et$_2$O (3 x 10 mL). The aqueous phase was then extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried (Na$_2$SO$_4$), filtered and concentrated to afford title compound (0.14 g, 27%) as a
white powdered solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.63 (1H, s, NH$OH$), 8.84 (1H, s, NH$OH$), 7.73 (1H, m, NH-Leu), 6.93 (1H, $d = 7.6$ Hz, NH-Ala), 4.24 – 4.18 (1H, m, Ala-$\alpha$CH), 3.96 (1H, $t$, $J = 7.3$ Hz, Leu-$\alpha$CH), 1.59 – 1.51 (1H, m, Leu-CH(CH$_3$)$_2$), 1.49 – 1.31 (11H, m, Boc-(CH$_3$)$_3$) & Leu-CH$_2$), 1.13 (3H, $d = 7.0$ Hz, Ala-CH$_3$), 0.88 – 0.81 (6H, m, Leu-(CH$_3$)$_2$); $^{13}$C NMR (125 MHz, DMSO) δ 172.2 (C), 168.4 (C), 155.1 (C), 78.1 (C), 49.7 (CH), 48.5 (CH), 41.4 (CH$_2$), 28.2 (CH$_3$), 24.0 (CH$_3$), 22.8 (CH), 21.9 (CH$_3$), 18.0 (CH$_3$); IR (thin film) 1670, 1640, 1528; HRMS (ESI negative) exact mass calculated for C$_{14}$H$_{26}$N$_3$O$_5$ [M–H]$^–$ m/z 316.1878; found m/z 316.1867.

H-Ala-Leu-NHOH.HCl 2.13

Following general procedure D, Boc-Ala-Leu-NHOH 2.7 (0.30 g, 0.95 mmol) was deprotected to yield the trifluoroacetate salt. The salt was taken up in 0.1M aq. HCl and concentrated in vacuo to afford title compound 2.13 (0.13 g, 54%) as a powdered solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.79 (1H, s, NH$OH$), 8.93 (1H, s, NH$OH$), 8.32 – 7.88 (3H, m, NH$_3$), 4.31 – 4.21 (1H, m, Ala-$\alpha$CH), 3.87 (1H, m, Leu-$\alpha$CH), 1.69 – 1.39 (3H, m, Leu-CH$_2$ & Leu-CH(CH$_3$)$_2$), 1.36 – 1.29 (3H, m, Ala-CH$_3$), 0.92 – 0.82 (6H, m, Leu-(CH$_3$)$_2$); $^{13}$C NMR (125 MHz, DMSO) δ 173.4 (C), 169.6 (C), 50.5 (CH), 47.9 (CH$_2$), 24.2 (CH), 22.9 ((CH$_3$)$_2$), 21.2 (CH), 17.1 (CH$_3$); IR (thin film) 1659, 1547, 1184; HRMS (ESI positive) exact mass calculated for C$_9$H$_{20}$N$_3$O$_3$ [M+H]$^+$ m/z 218.1499; found m/z 218.1495.

H-Ala-Leu-OH.HCl 2.12

Following general procedure D, Boc-Ala-Leu-OH 2.11 (0.40 g, 1.3 mmol) was deprotected to yield the trifluoroacetate salt. The salt was taken up in 0.1 M aq. HCl and concentrated in vacuo to afford title compound 2.12 (0.31 g, 99%) as an amorphous solid. No further purification was required. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.83 (1H, $d = 7.5$ Hz, NH), 8.25 (3H, s, NH$_3$), 4.42 – 4.21 (1H, m, Ala-$\alpha$CH), 3.87 (1H, m, Leu-$\alpha$CH), 1.79 – 1.44 (3H, m, Leu-CH(CH$_3$)$_2$ and CH$_2$), 1.42 – 1.31 (3H, m, Leu-CH(CH$_3$)$_2$ and CH$_2$), 0.90 – 0.86 (6H, m, Leu-(CH$_3$)$_2$); $^{13}$C NMR (125 MHz, DMSO) δ 173.6 (C), 169.6 (C), 50.6 (CH$_2$), 48.0 (CH$_2$), 24.2 (CH), 22.9 (CH$_3$), 21.2 (CH), 17.1 (CH$_3$); IR (thin film) 1702, 1661, 1184, 1138; HRMS (ESI positive) exact mass calculated for C$_9$H$_{19}$N$_2$O$_3$ [M]$^+$ m/z 203.1390; found m/z 203.1381.
Boc-Ala-Ile-OMe 2.14

Following general procedure A, Boc-Ala-OH (2.0 g, 11 mmol) and isoleucine methyl ester hydrochloride (1.9 g, 10 mmol) were coupled. The crude material was used directly in the following step.

Boc-Ala-Ile-OH 2.15

Following general procedure B, Boc-Ala-Ile-OMe 2.14 (10 mmol) was hydrolysed to afford title compound 2.15 (2.3 g, 76% over 2 steps). No further purification was required. Observed analytic data is in accordance with literature values.\[177\]

Boc-Ala-Ile-NHOH (2.8)

Following a modification to general procedure C, where the reaction mixture was heated to 60 °C for 48 h, Boc-Ala-Ile-OH 2.15 (0.60 g, 2.0 mmol) was transformed into the corresponding hydroxamate. The crude product was taken up in CH₂Cl₂ (10 mL) and extracted with H₂O (3 x 10 mL). The combined aqueous extracts were acidified to pH 3 using 0.1 M aq. HCl and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic extracts were washed with sat. aq. NaHCO₃ (10 mL), dried (Na₂SO₄), filtered and concentrated in vacuo to afford title compound 2.17 (0.31 g, 49%) as an amorphous solid. \[H NMR (400 MHz, DMSO-d₆) δ 10.59 (1H, s, NH-OH), 8.86 (1H, s, NH-OH), 7.67 (1H, d, J = 9.4 Hz, Ile-NH), 6.99 (1H, d, J = 7.4 Hz, Ala-NH), 4.15 (1H, dd, J = 9.3, 6.5 Hz, Ile-αCH), 4.01 (1H, m, Ala-αCH), 1.74 – 1.64 (1H, m, Ile-CH), 1.37 (9H, s, Boc-(CH₃)₃), 1.31 – 1.09 (5H, m, Ala-CH₃ and Ile-CH₂), 0.89 – 0.74 (6H, m, 2 x Ile-CH₃); 13C NMR (100 MHz, DMSO) δ 172.6 (C), 167.6 (C), 155.0 (C), 78.1 (C), 54.9 (CH), 53.4 (CH), 49.4 (CH), 37.1 (CH₂), 28.1 (CH₂), 25.5 (CH₃), 18.2 (CH₃), 14.5 (CH₃); IR (thin film) 1647, 1522, 1165; HRMS (ESI negative) exact mass calculated for C₁₄H₂₆N₃O₅ [M–H]⁻ m/z 316.1862; found m/z 316.1862.\]

H-Ala-Ile-NHOH.HCl 2.17

Following general procedure D, Boc-Ala-Ile-NHOH 2.8 (0.21 g, 0.66 mmol) was deprotected to yield the trifluoroacetate salt. The salt was taken up in 0.1 M aq. HCl and concentrated in vacuo to afford title compound 2.17 as a white amorphous solid (0.11 g, 66%). No further purification was required. \[H NMR
Following general procedure D, Boc-Ala-Ile-OH 2.15 (0.50 g, 1.7 mmol) was deprotected to yield the trifluoroacetate salt. The salt was taken up in 0.1 M aq. HCl and concentrated in vacuo to afford title compound 2.16 (0.39 g, 96%) as a powdered solid. No further purification was required. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.54 (1H, d, $J = 8.3$ Hz, Ile-$\alpha$CH), 8.22 (3H, s, NH$_3$), 4.29 – 4.16 (1H, m, Ile-$\alpha$CH), 3.94 (1H, s, Ala-$\alpha$CH), 1.88 – 1.77 (1H, m, Ile-$\gamma$CH), 1.35 (3H, d, $J = 7.0$ Hz, Ala-$\gamma$CH), 1.22 (1H, m, H$_a$), 0.93 – 0.81 (6H, m, 2 x Ile-$\gamma$CH); $^{13}$C NMR (125 MHz, DMSO) δ 172.4 (C), 169.7 (C), 56.5 (CH), 47.8 (CH), 36.3 (CH), 24.6 (CH$_2$), 17.2 (CH$_3$), 15.6 (CH$_3$), 11.3 (CH$_3$); IR (thin film) 1709, 1663, 1186, 1138; HRMS (ESI positive) exact mass calculated for C$_9$H$_{19}$N$_2$O$_3$ [M]$^+$ m/z 203.1390; found m/z 203.1387.

**Hydroxamate analogues of phosphinic acid pseudopeptide:**

Following general procedure A, Phenylalanine methyl ester hydrochloride (1.2 g, 5.5 mmol) was coupled with Boc-Ala-OH (0.95 g, 5.0 mmol). The crude mixture was purified by column chromatography (Petroleum Ether:EtOAc, 7:3) to afford title compound 2.21 (1.4 g, 80%) as a white powdered solid. Analytical data observed were in accordance with literature values.$^{[178]}$
Boc-Ala-Phe-OH 2.22

Following general procedure B, Boc-Ala-Phe-OMe (0.35 g, 1.0 mmol) was hydrolysed to afford title compound 2.22 (0.31 g, 89%). No further purification was required. Analytical data observed were in accordance with literature values.[178]

Boc-Ala-Phe-NHOH 2.20

Following general procedure C, Boc-Ala-Ile-OH (0.34 g, 1.0 mmol) was transformed into the corresponding hydroxamate. The crude product was taken up in CH₂Cl₂ (10 mL) and extracted with H₂O (3 x 10 mL). The combined aqueous extracts were acidified to pH 3 using 0.1 M aq. HCl and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic extracts were washed with sat. aq. NaHCO₃ (10 mL), dried (Na₂SO₄), filtered and concentrated in vacuo to afford title compound as a white powdered solid (0.13 g, 37%). ¹H NMR (400 MHz, DMSO-d₆) δ 10.60 (1H, s, NHOH), 8.89 (1H, s, NH), 7.97 – 7.74 (1H, m, Phe-NH), 7.40 – 7.04 (5H, m, 5 x Phe-CH), 6.97 – 6.80 (1H, m, Ala-NH), 4.41 – 4.35 (1H, m, Phe-αCH), 3.95 – 3.88 (1H, m, Ala-αCH), 3.14 – 2.70 (2H, m, Phe-CH₂), 1.51 – 1.15 (9H, m, Boc-(CH₃)₃), 1.18 – 0.99 (3H, m, Ala-CH₃); ¹³C NMR (100 MHz, DMSO) δ 171.8 (C), 167.2 (C), 159.7 (C), 137.2 (C), 128.9 (CH), 127.7 (CH), 125.9 (CH), 78.0 (C), 51.2 (CH), 50.0 (CH), 33.1 (CH₂), 28.0 (CH₃), 17.8 (CH₃); IR (thin film); 1695, 1660, 1445; HRMS (ESI positive) exact mass calculated for C₁₇H₂₅N₃O₅Na [M+Na]⁺ m/z 374.1669; found m/z 374.1686.

H-Ala-Phe-OMe.TFA 2.25

Following general procedure D, Boc-Ala-Phe methyl ester (0.50 g, 1.4 mmol) was deprotected to yield title compound 2.25 (0.48 g, 92%) as a white powdered solid. The material was used directly in following steps.
**Boc-Pro-Ala-Phe-OMe 2.26**

Following general procedure A, H-Ala-Phe methyl ester trifluoroacetate 2.25 (0.60 g, 1.7 mmol) was coupled with Boc-Pro-OH (0.32 g, 1.5 mmol). The crude mixture was purified by column chromatography (Petroleum ether:EtOAc, 2:3) to afford title compound 2.26 (0.45 g, 60%) as a colourless oil.

**Boc-Pro-Ala-Phe-OMe 2.27**

Following general procedure B, Boc-Pro-Ala-Phe-OMe 2.26 (0.7 g, 2.0 mmol) was hydrolysed to yield the title compound 2.27. The crude material subjected directly to the following transformation.

**Boc-Pro-Ala-Phe-NHOH 2.23**

Boc-Pro-Ala-Phe-OH 2.27 (0.43 g, 1.0 mmol) was subjected to general procedure C. The crude mixture was diluted with water and acidified to pH 3 with 0.1 M aq. HCl. The mixture was extracted with CH₂Cl₂ (3 x 15 mL) and the combined organics were washed with sat. aq. NaHCO₃ (3 x 15 mL), dried (Na₂SO₄), filtered and concentrated to afford title compound 2.23 (0.15 g, 33%) as an amorphous solid. ¹H NMR (500 MHz, DMSO-d₆) δ 10.60 (1H, m, NHOH), 8.90 (1H, s, NH), 8.01 – 7.88 (2H, m, 2 x NH), 7.26 – 7.17 (5H, m, 5 x Ar-H), 4.37 – 4.06 (3H, m, 3 x α-CH), 3.27 – 3.16 (2H, m, Pro-CH₂), 2.93 – 2.77 (2H, m, Ph-CH₂), 2.08 – 2.00 (1H, m, Pro-CH₃), 1.79 – 1.71 (3H, m, Pro-CH₂CH₂ & Pro-CH₃), 1.37 – 1.29 (9H, m, Boc-(CH₃)₃), 1.18 – 1.13 (3H, m, Ala-CH₃); ¹³C NMR (125 MHz, DMSO) δ 172.0 (C), 171.6 (C), 167.3 (C), 153.2 (C), 137.4 (C), 129.1 (CH), 128.0 (CH), 126.3 (CH), 78.3 (C), 59.2 (CH), 51.5 (CH), 47.9 (CH), 46.5 (CH₂), 37.9 (CH₂), 30.8 (CH₂), 28.0 (CH₃), 23.1 (CH₂), 18.3 (CH₃); IR (thin film) 1686, 1661, 1634, 1537, 1416; HRMS (ESI positive) exact mass calculated for C₂₂H₃₂N₄O₆Na [M+Na]+ m/z 471.2209; found m/z 471.2214.
Fmoc-Pro-Ala-Phe-OMe 2.28

Following general procedure A, H-Ala-Phe methyl ester trifluoroacetate 2.25 (0.20 g, 0.55 mmol) was coupled with Fmoc-Pro-OH (0.17 g, 0.50 mmol). The crude material was subjected directly to the following transformation.

Fmoc-Pro-Ala-Phe-OH 2.29

To a solution of Fmoc-Pro-Ala-Phe methyl ester 2.28 (0.10 g, 0.18 mmol) in isopropanol (7.0 mL) was added a calcium chloride (0.80 M aq. solution, 3.0 mL) and sodium hydroxide (8.5 mg, 0.21 mmol). The mixture was stirred at room temperature for 2 h, before quenching with AcOH (20 mg), and concentrating in vacuo. The crude material subjected directly to the following transformation.

Fmoc-Pro-Ala-Phe-NHOH 2.24

Fmoc-Pro-Ala-Phe-OMe 2.29 (0.40 g, 0.75 mmol) was subjected to general procedure C. The crude mixture was diluted with water and acidified to pH 3 with 0.1 M aq. HCl. The mixture was extracted with CH$_2$Cl$_2$ (3 x 10 mL) and the combined organics were washed with sat. aq. NaHCO$_3$ (3 x 10 mL), dried (Na$_2$SO$_4$), filtered and concentrated to afford Fmoc-Pro-Ala-Phe hydroxamate (0.12 g, 28%) as a white amorphous solid. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 10.63 – 10.55 (1H, m, NHOH), 9.55 (1H, s, NHOH), 8.27 – 7.82 (4H, m, 2 x Fmoc Ar-CH & 2 x NH), 7.71 – 7.58 (2H, m, 2 x Fmoc Ar-H), 7.48 – 7.13 (9H, m, 5 x Ar-H & 4 x Fmoc Ar-H), 4.44 – 4.07 (6H, m, 3 x $\alpha$-CH & Fmoc-CH$_2$ & Fmoc-CHCH$_2$), 3.49 – 3.40 (2H, m, Pro-NCH$_3$C$_4$H$_2$), 3.09 – 3.01 (1H, m, H$_6$), 2.96 – 2.86 (1H, m, H$_6$), 2.25 – 2.01 (1H, m, H$_6$), 1.96 – 1.57 (3H, m, Pro-NCH$_2$CH$_2$ & H$_6$), 1.20 – 1.09 (3H, m, Ala-CH$_3$); $^{13}$C NMR (125 MHz, DMSO) $\delta$ 171.9 (C), 171.7 (C), 171.4 (C), 154.0 (C), 140.7 (C), 140.6 (C), 137.3 (C), 129.2 (CH), 128.9 (CH), 128.2 (CH), 128.0 (CH), 127.6 (CH), 127.1 (CH), 125.3 (CH), 67.0 (CH$_2$), 66.5 (CH), 59.0 (CH), 54.9 (CH), 48.2 (CH), 46.7 (CH$_2$), 36.7 (CH$_2$), 31.3 (CH$_2$), 21.0 (CH$_2$), 18.2 (CH$_3$); IR (thin film) 1732, 1697, 1668, 1649, 1433; HRMS (ESI positive) exact mass calculated for C$_{32}$H$_{34}$N$_4$O$_6$Na [M+Na]$^+$ m/z 593.2366; found m/z 593.2371.
Marimastat:

To a solution of L-(−)-Malic acid (20 g, 150 mmol) in isopropyl alcohol (60 mL) was added conc. sulfuric acid (0.4 mL, 1 mol. %). The mixture was warmed at reflux for 72 h. The mixture was allowed to cool to room temperature before the addition of sat. aq. NaHCO₃ (100 mL). The mixture was extracted with Et₂O (3 x 50 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated in vacuo to afford (2S)-diisopropylmalate (43 g, 66 %) as a colourless oil. No further purification was necessary.

(2S,3R)-diisopropyl-3-(2'-methylallyl)malate 2.33

To a stirred solution of diisopropylamine (14 mL, 100 mmol) in THF (50 mL) was added dropwise a solution of n-butyllithium (2.1 M in hexanes, 47 mL, 99 mmol) at −78 °C. The solution was warmed to 0 °C and stirred for 15 mins before cooling to −78 °C. A solution of (2S)-diisopropylmalate (9.8 g, 45 mmol) in THF (150 mL) was added dropwise. The solution was allowed to warm to −20 °C, whereupon it was stirred for 2 h, before the addition of methallyl iodide (8.2 g, 45 mmol). The solution was warmed to room temperature and stirred for 16 h. The reaction mixture was quenched with sat. aq. NH₄Cl (150 mL) and the aqueous extracted with Et₂O (3 x 150 mL). The combined organic extracts were washed with brine (100 mL), dried (Na₂SO₄), filtered and concentrated in vacuo. The crude product was purified by flash chromatography (15% EtOAc/Petroleum ether) to afford title compound 2.33 (4.3 g, 35%) as a colourless oil. Observed analytic data is in accordance with literature values.[172]
(2S,3R)-diisopropyl-3-isobutylmalate 2.36
To a stirred suspension of palladium on carbon (0.43 g, 10% w/w r.t. 2.33) in EtOH (35 mL) held under an inert atmosphere was added a solution of (2S,3R)-diisopropyl-3-(2'-methylallyl)malate 2.33 (4.3 g, 16 mmol) in EtOH (35 mL). The reaction mixture was flushed with hydrogen, and stirred for 24 h at room temperature. The crude reaction mixture was flushed with argon, and filtered through Celite®. The filtrate was concentrated in vacuo to afford title compound 2.36 (4.1 g, 16 mmol, 98%). No further purification was necessary. Observed analytic data is in accordance with literature values.[172]

(2S,3R)-3-isobutylmalic acid 2.37
To a solution of (2S,3R)-diisopropyl-3-isobutylmalate 2.36 (4.1 g, 16 mmol) in Dioxane/H2O (1:1 v/v, 30 mL) was added 3.5 M aq. KOH (13.5 mL, 48 mmol). The mixture was warmed to 90 °C for 24 h. The aqueous mixture was extracted with Et2O (3 x 30 mL), and acidified to pH 2 with 1 M aq. HCl. The acidified aqueous mixture was extracted with Et2O (3 x 30 mL), and the combined organic extracts were dried (Na2SO4), filtered and concentrated in vacuo to afford title compound 2.37 as a white powdered solid (3.0 g, quant.). No further purification was required. Observed analytic data is in accordance with literature values.[172]

(R)-2-((S)-2,2-dimethyl-5-oxo-1,3-dioxolan-4-yl)-4-methylpentanoic acid 2.31
To a solution of (2S,3R)-3-isobutylmalic acid 2.37 (3.0 g, 16 mmol) in 2,2-dimethoxypropane (200 mL) was added p-toluenesulfonic acid (0.30 g, 1.6 mmol). The mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated in vacuo. The crude mixture was purified by flash chromatography (4:1 EtOAc/Petroleum ether) to afford 2.31 (1.8 g, 50%) as a colourless oil. Observed analytic data is in accordance with literature values.[172]

(R)-N-((S)-3,3-dimethyl-1-(methylamino)-1-oxobutan-2-yl)-2-((S)-2,2-dimethyl-5-oxo-1,3-dioxolan-4-yl)-4-methylpentanamide 2.39
To a solution of carboxylic acid 2.31 (1.1 g, 4.8 mmol) in DMF (15 mL) was added HOBT (0.78 g, 5.8 mmol), and EDC (1.1 g, 5.8 mmol) at 0 °C. After 15 min, a solution of tert-leucine methylamide.TFA 2.32 (1.4 g, 5.8 mmol) and DMAP (0.12 g, 1.0 mmol) in DMF (5 mL) was added, followed by iPr2NEt (1.0 mL, 5.8 mmol). The mixture was stirred at room temperature for 16 h, before the addition of H2O (20 mL). The aqueous mixture was extracted with Et2O (2 x 30 mL), and the combined organic extracts were washed with H2O (5 x 20 mL), brine (20 mL), dried (Na2SO4), filtered and concentrated in vacuo. The crude mixture was purified by flash chromatography (1:1 EtOAc/Petroleum ether) to afford title compound 2.39 (0.95 g, 56%) as a colourless oil.
Marimastat

To a solution of 2.39 (0.95 g, 2.7 mmol) in THF (2 mL) was added 50% w/v aq. hydroxylamine (0.95 mL). The mixture was heated to reflux for 3 h. The reaction mixture was concentrated in vacuo and the crude product was washed with water, resulting in a white precipitate. The precipitate was collected by filtration to afford marimastat (0.58 g, 65%) as a white crystalline solid. Observed analytic data is in accordance with literature values. $^\text{(172)}$ $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 10.54 (1H, s), 8.86 (1H, s), 7.85 (1H, q, $J = 4.5$ Hz), 7.47 (1H, d, $J = 9.5$ Hz), 5.35 (1H, d, $J = 8.0$ Hz), 4.17 (1H, d, $J = 9.5$ Hz), 3.71 (1H, t, $J = 8.1$ Hz), 2.72 – 2.66 (1H, m), 2.56 (3H, d, $J = 4.5$ Hz), 1.49–1.31 (2H, m), 0.96 – 0.91 (1H, m), 0.89 (9H, s), 0.82 – 0.76 (6H, m); $^{13}$C NMR (125 MHz, DMSO) $\delta$ 172.2, 170.5, 168.8, 71.3, 59.8, 47.8, 37.4, 34.1, 26.6, 25.3, 25.2, 23.4, 21.8; Anal. Calc. for C$_{15}$H$_{29}$N$_3$O$_5$: C, 54.38; H, 8.76; N, 12.69; Found: C, 54.21; H, 8.87; N, 12.55.
References


[172] Dickens, J. P.; Crimmen, M. J.; Beckett, P. R. WO 9402447 A1 19940203, **1995**


