The University Of Sheffield.

Transition Metal-Catalysed Approaches towards Novel Amide-Containing Heterocyclic Scaffolds

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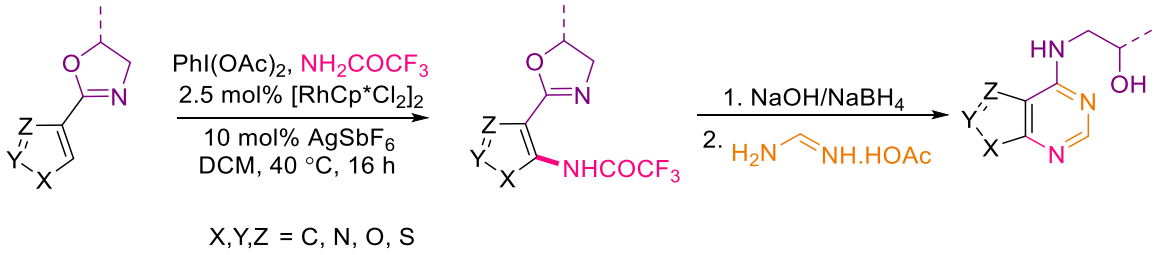
Foreword

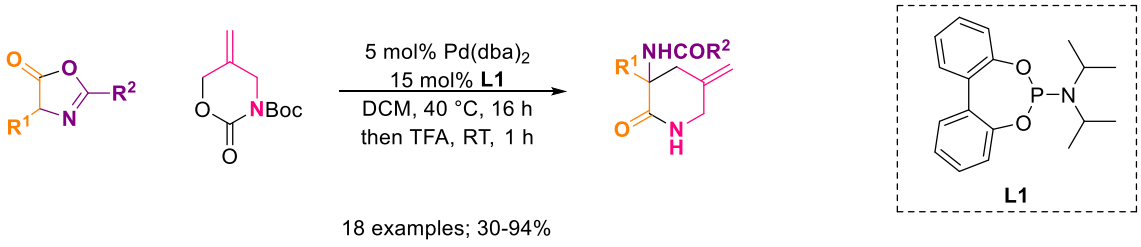
This thesis documents the synthesis of novel heterocyclic scaffolds using transition metal catalysis.

Firstly, azolopyrimidines were targeted via a rhodium-catalysed oxazoline-directed C-H amidation of azoles (*Scheme 1*). Ultimately, only thienopyrimidines were accessible, as other azoles proved too electron-rich to undergo nitrene insertion. Incorporation of electron-withdrawing groups did not significantly improve these results, even under highly forcing conditions. 1,2,4-Substituted arenes were also subjected to the C-H amidation conditions, however steric congestion at the reactive site lead to no reaction occurring.



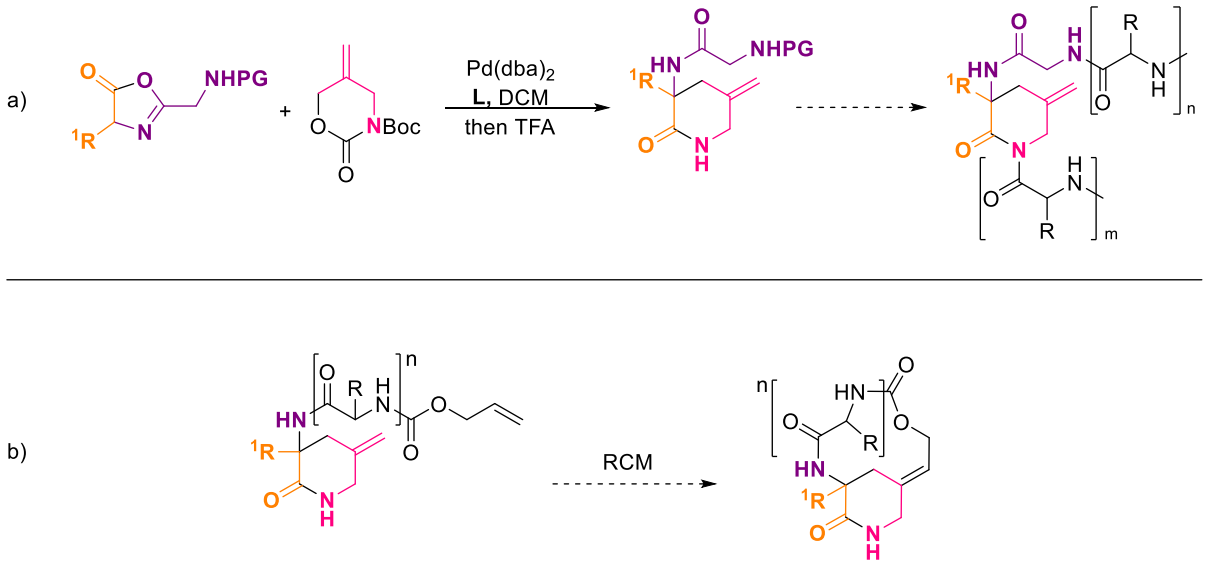
Scheme 1 *–C-H amidation reactions of oxazolinyl azoles towards azolopyrimidines.*

Secondly, the two-step one-pot allylations/cyclisation of azlactones was undertaken, with a cyclic carbamate provided the allylic component with a pendant nitrogen (*Scheme 2*). A wide scope of azlactones were successfully subjected to these conditions, giving their corresponding lactams in good yields. The lactams contain three synthetic handles which could be selectively targeted. Unfortunately, asymmetric synthesis of these lactams using chiral phosphoramidite ligands was not successful.



Scheme 2 *- allylation/cyclisation of azlactones using a cyclic carbamate, Pd(dba)₂ and* ***L1****.*

Freidinger lactams are utilised as conformation-restraining motifs in polypeptide chains in order to produce peptidomimetic bioactive compounds such as β-turn mimics. The allylation/cyclisation methodology could be applied to dipeptide-derived azlactones, giving dipeptidic Freidinger lactams, which could undergo peptide chain expansion at both the lactam and amine sites to form tri- and tetrapeptide surrogates (*Scheme 3b*). In theory, the incorporation of an Alloc-protecting group would allow these peptidic mimics to undergo ring-closing metathesis (*Scheme 3b*), in the hopes that polypeptidic macrocycles could be accessed. Unfortunately, RCM was not successful on these substrates, likely due to the unfavourable formation of a trisubstituted alkene and an 11-membered ring. It is hoped that an alternative route to these macrocycles will be possible by expansion of the exocyclic alkene to a monosubstituted alkene.



Scheme 3 *– Synthesis of peptidomimetic scaffolds by allylation/cyclisation of polypeptide derived azlactones and subsequent functionalisations.*

Acknowledgements

"You can design a new molecule that no-one's ever made – or even thought of – before. You can come up with a route to make it, you can go and make it, and you can prove you've made it. You have control over all of the atoms in that molecule."

Professor Joe Harrity – October 2015

Joe – you've pushed me hard over the past 4 years to get the most out of this experience. It's been tough at times, especially when reactions just don't want to work, but we got some yields that are more than 0%, and learnt some stuff along the way! I've heard you say that quote many times over the years; a fresh-faced Sophie wrote it down in a project and it perfectly sums up how interesting organic chemistry can be (when it works)!

Steve and Hartmut – vielen Dank für Ihren Beitrag über die Jahre! It was so useful to get the opinion of people outside of the academic world. I was very disappointed that a pandemic prevented my placement, I was really looking forward to the experience, and as you can see, I'd even learnt some German!

Harrity Group – Olivier, Matt, Nick, Dan, Chris, Marie, Larry, Kenji, Dave, Su, Fernando, Robbie, Wenzheng, Jiaxin and Ningqi (I could list all the Masters' students too but we'd be here even longer)! A stupid pandemic has got in the way of us socialising, or even working with each other. I haven't had the chance to get to know the newbies as much as would have happened in normal times, but I wish you the best of luck with your projects! P.S. Christmas meals need organising in October before all the restaurants get fully booked!

Anthony – Thank you for always lighting up the corridor with your laughter. Your proof-reading skills have been invaluable over the last 5 years and I've definitely appreciated having another office to run away to when things got a bit too much! Good luck, and wherever you end up, they'll be lucky to have you!

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Charlotte – Mrs Wild/Almost-Dr Kiker, what can I say?! I don't think I would have survived without having a buddy that would get coffee with me on such short notice. CHIP is possibly one of your greatest inventions, who doesn't want to knit for 2 hours on Wednesday afternoon?! You've always been a friendly face in the department but hating our PhDs has definitely brought us closer together. Good luck with wherever the future takes you, you deserve nothing but good things!

Flat C Girls – You have been a constant in my life since I started in Sheffield. Even though we all live in different cities now, I know I can always rely on you to cheer me up and remind me that I am a strong independent woman. It's been 8 years almost to the day since we were thrown together under one roof, and I am grateful that we ended up in each other's lives. I'm proud of everything you have all achieved since then, and I'm sure I'll be writing something else soppy about you all in another 8 years!

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Ja Spade – You got me through Lockdown 1. I think I might have gone (more) insane without you all there to keep me company. Even though most of your bosses managed to keep you busy for the whole 4 months, you all made sure I had someone to keep me entertained after I'd written up every result I had in less than 6 weeks. Even though we no longer live together, it still feels like we're family and I'll be ever thankful that I chose 12 Brandreth!

Annabelle – Somehow you make dong a PhD look easy. A part of me secretly hopes you start to hate it, but the much larger, nice part of me really wants you to continue having a good run of it! It's strange you not being in the room next to me, with all our late night chats on the landing in our granny PJs.

Mum and Dad – you've always been supportive even if your knowledge of what I do is "makes plant drugs" and "something about hands…?" You've encouraged me to work hard, and always helped me wherever you could – buying me food shops, paying vet bills when the pigs got ill, and using your annual leave to help me move house who knows how many times. When I finished my Masters', you told anyone who would listen that your daughter got a First Class Degree in Chemistry, and now you can brag that your little girl is a Doctor! Thank you so much for all your love and support – may I never have to move back (and maybe one day you'll get rid of Adam too)!

Nan and Grandad – At my graduation, you morbidly said that the doctors are keeping you alive until I get my next graduation. I certainly hope that they keep you alive a lot longer than that, as Graduation 2.0 is nearly upon us! Ever since I was little, you've always been there for me, spoiling me rotten and giving me sound life advice. I don't think you've ever understood a word that I've said when you've asked me about my PhD, and yet you've always supported and encouraged me to keep at it even when I was having a rough time. I love you both, and in future if you will need address my birthday cards to "Dr Senior Princess"!

サムさん – It's so rare to find someone who you click with as much as I have with you. Not having had any other PhD people outside of the department, I'm glad I found someone who understands how getting a doctorate can be. A global pandemic may have got in the way of us doing normal couple-y things, but now we sit at our dining table on a Wednesday evening with a nice cup of tea and play the board game. Maybe we're old… You've worked so hard for your doctorate, and soon you'll be Dr Jenkins! Now you just need to get over your imposter syndrome and realise you're good at what you do (neutrinos or something?). Thank you for looking after me when I'm sad and for letting me get more guinea pigs. You're a wonderful partner and PigDad, I love you.

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"Research is what I'm doing when I don't know what I'm doing." – Wernher von Braun

Abbreviations

Ac	Acetyl
Ar	Aryl
aq	Aqueous
ATR	Attenuated total reflectance
BINOL	1,1'-Bi-2-naphthol
bipy	2,2-Bipyridyl
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
^{i}Bu	*iso*-Butyl
^{s}Bu	*sec*-Butyl
^{t}Bu	*tert*-Butyl
cat.	Catalytic
Cbz	Carboxybenzyl
CDI	Carbonyldiimidazole
cod	1,5-Cyclooctadiene
coe	Cyclooctene
COSY	^{1}H-^{1}H Correlation Spectroscopy
Cp*	Pentamethylcyclopentadienyl
Δ	Heat/Reflux
DCB	1,2-Dichlorobenzene
DCC	*N,N'*-Dicyclohexycarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
dcype	1,2-Bis(dicyclohexylphosphino)ethane
DG	Directing Group
DMAP	4-Dimethylaminopyridine

DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
dr	Diastereomer ratio
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	Enantiomeric excess
eq.	Equivalents
ESI	Electrospray Ionisation
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EWG	Electron-Withdrawing Group
FG	Functional group
h	Hour(s)
HRMS	High Resolution Mass Spectrometry
HMBC	Heteronuclear multiple bond coherence
HSQC	Heteronuclear single quantum correlation
L	Ligand
LCMS	Liquid Chromatography Mass Spectrometry
m.p.	Melting point
Me	Methyl
MeO	Methoxy
min	Minute(s)
NFSI	*N*-Fluorobenzenesulfonimide
NMM	*N*-Methyl Morpholine
NMR	Nuclear magnetic resonance
Nu	Nucleophile
Ph	Phenyl
Pin	Pinacolato

PivOH	Pivalic Acid
^{i}Pr	*iso*-Propyl
PMP	*para*-Methoxylphenyl
R	Generic carbon-containing group
RCM	Ring Closing Metathesis
RSM	Recovered Starting Material
RT	Room Temperature
T	Temperature
t	Time
Tf	Triflate, Trifluoromethanesulfonate
TFA	2,2,2-Trifluoroacetic acid
TFE	2,2,2-Trifluoroethanol
THF	Tetrahydrofuran
TM	Transition Metal
TMS	Trimethylsilyl
Tol	Toluene
Ts	Tosyl (4-methylbenzene-1-sulfonyl)
TS	Transition State

Contents

Chapter I

Regioselective C-H Amidation of Azoles towards Functionalised Heterocyclic Scaffolds

1.1 Abstract

A variety of aryl oxazolines were synthesised from their commercially available parent aldehydes and carboxylic acids, and studied in the rhodium-catalysed C-H amidation process developed by Maiden. C-H amidation reactions proved successful for the thienyl oxazolines prepared, giving the trifluoroacetamide products in moderate to good yields under mild conditions. Hydrolysis/reduction of the intermediate amide followed by cyclisation with formamidine acetate gave the corresponding thienopyrimidines in excellent yields.

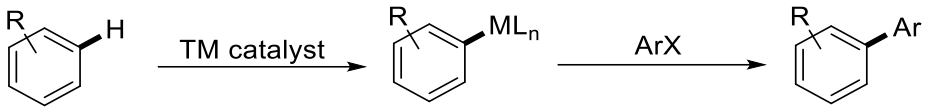
While thiophenes have been successful, more electron-deficient azoles have proven to be a much more difficult class of substrate to manipulate. C-H amidation of the pyrazoles was unsuccessful even under forcing conditions. Deuteration experiments were carried out, which suggested that C-H activation was successful, while nitrene insertion was problematic. Introducing electron-withdrawing groups marginally improved the results; however a lack of promising data lead us to conclude that continuing this project would not be fruitful. Use of other literature methods on both the pyrazoles and thiophenes showed that the methodology developed by Maiden gave superior results.

Attempts to simplify oxazoline synthesis by forming oxazoline coupling reagents – that would allow Suzuki cross-couplings to aryl halides – were unsuccessful, with oxazolinyl lithium not reacting with ^{i}PrOBPin to give the oxazolinyl boronic ester.

In order to conclude the work undertaken by Maiden, 1,2,3,4-tetrasubstituted arenes were targeted via the oxazoline-directed rhodium-catalysed methodology, however these substrates proved too sterically hindered to undergo nitrene insertion, although deuterium studies showed that C-H activation was taking place.

1.2 Introduction

C-H activation processes typically comprise of a cross-coupling reaction utilising the formation of an organometallic complex *via* insertion of a transition metal catalyst by oxidative addition into a carbon-hydrogen bond (*Scheme 4*).[1] The resulting organometallic species can then undergo coupling reactions with aryl halides, alkenes (e.g. Heck) and amines (e.g. Buchwald-Hartwig).[2]

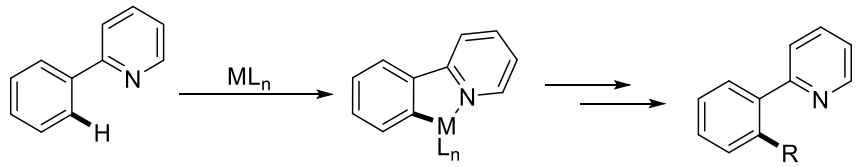


Scheme 4 *– a general example of C-H activation cross-coupling with an aryl halide.*

C-H activation is more difficult than traditional cross-coupling reactions (e.g. Suzuki-Miyaura, Negishi, Stille) due to the unreactive nature of the C-H bond. In cross-couplings such as the Kumada reaction, the organomagnesium species readily undergoes a transmetallation with $L_nPd^{II}ArI$. During the Heck and Buchwald-Hartwig reactions, an aryl halide undergoes oxidative addition to the Pd^0 species, followed by reaction with alkenes and amines respectively. Both of these steps rely on a very polar and reactive bond; organomagnesium species (Grignard reagents) are highly nucleophilic and can attack electrophilic groups such as carbonyls or alkyl halides. A C-H activation substrate can replace either the nucleophilic organometallic species or the electrophilic aryl halide, and sometimes it can replace both in a double C-H activation process. Generally, harsher conditions are needed to allow C-H activation to occur, and often a directing group is necessary to make the species more activated (by coordinating to the catalyst) and to control regioselectivity.

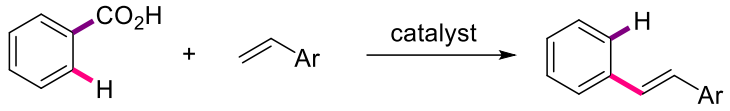
1.2.1 Directing groups

C-H activation is usually assisted by the presence of a directing group: a heteroatom-containing group that coordinates to the metal, providing a chelation-assisted route to the organometallic complex (*Scheme 5*).



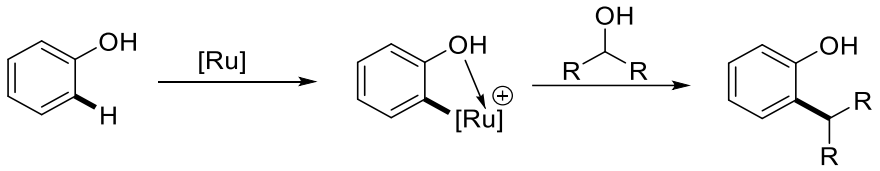
Scheme 5 *– a general example of directing group/chelation-assisted C-H activation.*

There are many examples of oxygen-based directing groups, for example, carboxylic acids can be used as traceless directing groups (*Scheme 6*),[3] with carbon dioxide being released in a metal-catalysed decarboxylative mechanism.



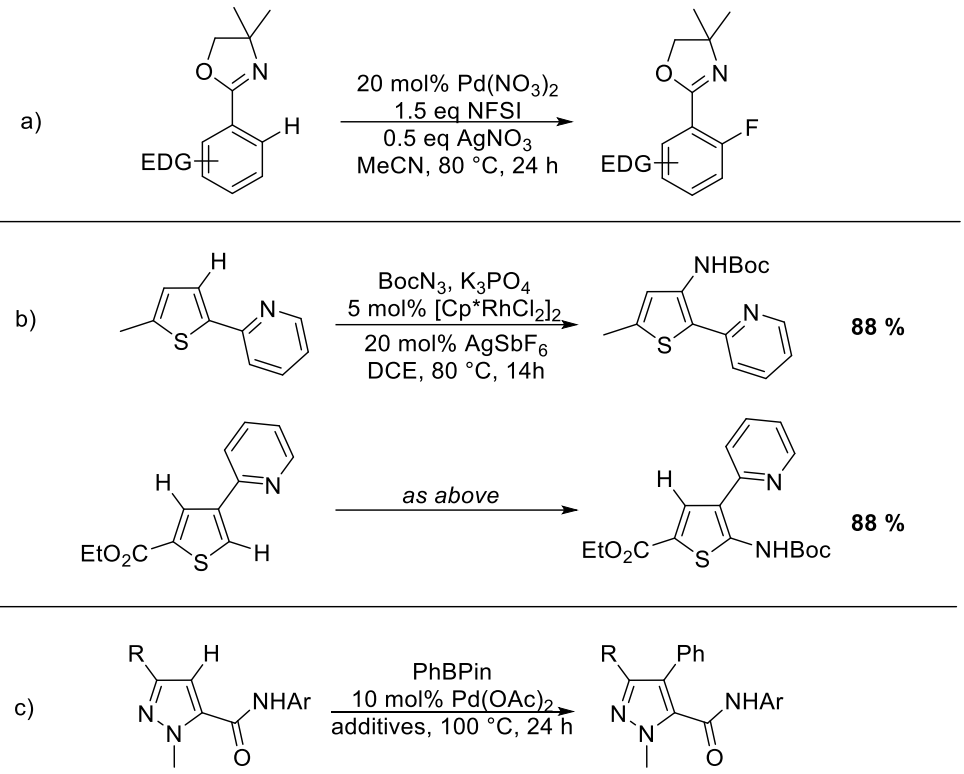
Scheme 6 *– an example of decarboxylative C-H activation.*[3]

The hydroxyl group of phenol has been shown to direct ortho-alkylation using alcohols as the coupling partner in a dehydrative C-H activation process (*Scheme 7*).[4]



Scheme 7 *– an example of decarboxylative C-H activation.*[4]

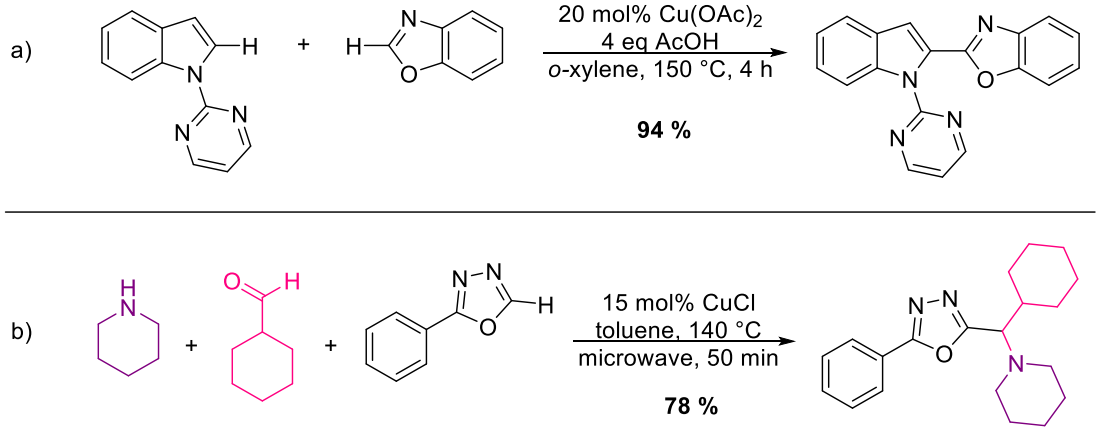
Nitrogen-coordinating directing groups are more common; oxazoline-based directing groups have been used in palladium nitrate catalysed ortho-fluorination *via* C-H activation (*Scheme 8a*).[5] Fluorination worked well in the presence of electron donating groups, however the presence of electron withdrawing groups was found to lower the yield drastically as the ability of the oxazoline to coordinate to palladium was reduced. Further examples from Bach highlight regioselective C-H amidations of thiophenes. In this case a pyridine directing group was employed (*Scheme 8b*) In addition, the C-H amidation of benzene using an oxazoline directing group took place in a 96% yield.[6] The intrinsic directing group properties of pyrazoles can be overcome using a weakly coordinating amine directing group,[7] allowing them to arylate at the 4-position on a 1,3,5-substituted pyrazoles with moderate success (46% yield, *Scheme 8c*).



Scheme 8 *– C-H amidations utilising nitrogen-coordinating directing groups.* [5,6,7]

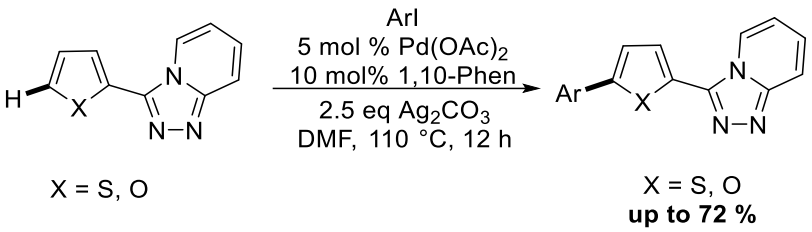
1.2.2 C-H Activation of Azoles

Most of the literature examples of C-H activation on 5-membered heterocycles involve coupling to carbon and do not utilise any directing groups. In 2012, $Cu(OAc)_2$ was used to couple indoles and benzoxazoles *via* a double C-H activation mechanism at C2 on both molecules (*Scheme 9a*).[8] Copper(I) chloride has also been used to C-H activate the C2 position on 5-substituted oxadiazoles,[9] forming a nucleophilic cuprate that reacts with imines (*Scheme 9b*).



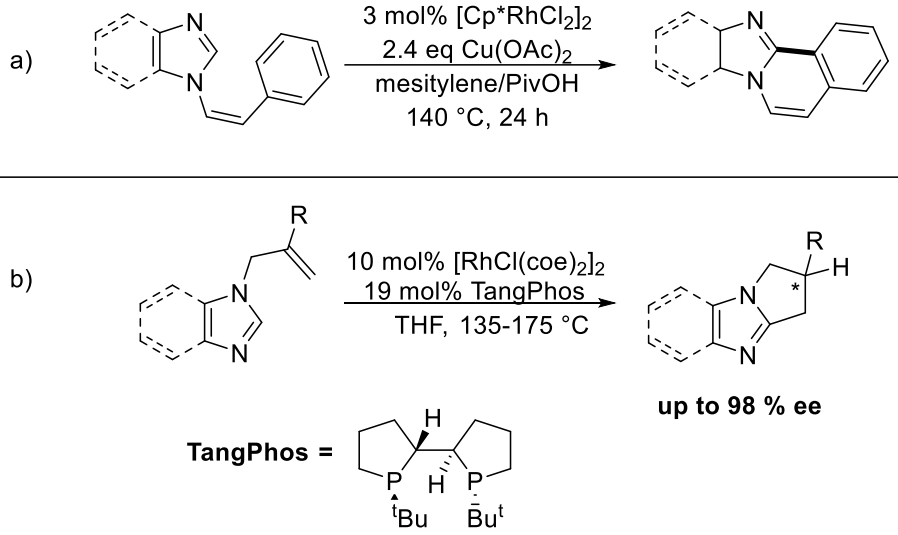
Scheme 9 *– Copper-catalysed C-H activation on azoles.* [8,9]

Palladium catalysis has also been used in the C-H activation of 5-membered heterocycles, with Zhou arylating and alkylating the 2-position of benzoxazoles[10] and Nagarajan arylating the 5-position of 2-substituted thiophenes and furans (*Scheme 10*).[11]



Scheme 10 *– Arylation of thiophenes and furans via C-H activation using $Pd(OAc)_2$.*[11]

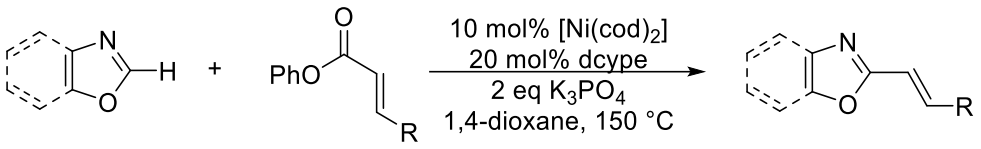
$[Cp^*RhCl_2]_2$ has been used to catalyse the intramolecular coupling of phenyl groups to imidazoles and benzimidazoles at the 2-position (*Scheme 11a*),[12] while a rhodium catalyst in conjunction with the TangPhos ligand has been used to promote to C-H activation of benzimidazoles at the 2-position and alkylate with an intramolecular *N*-allyl enantioselectively (*Scheme 11b*).[13]



Scheme 11 *– Rhodium-catalysed intramolecular C-H activations.*

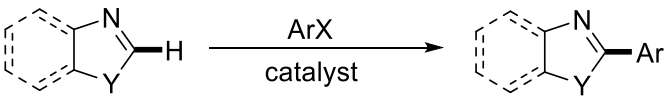
C-H activation reactions of benzoxazoles and benzimidazoles have been developed using nickel catalysts. Styrene enols and cinnamate esters have been used to alkenylate benzoxazoles and 4,5-disubstituted oxazoles (*Scheme 12*).[14] Arylation and alkenylation at

the 2-position of benzimidazoles, imidazole, oxazoles and thiazoles has also been carried out using aryl and alkenyl carbamates.[15]



Scheme 12 *– Nickel-catalysed arylation and alkenylation of benzazoles.*

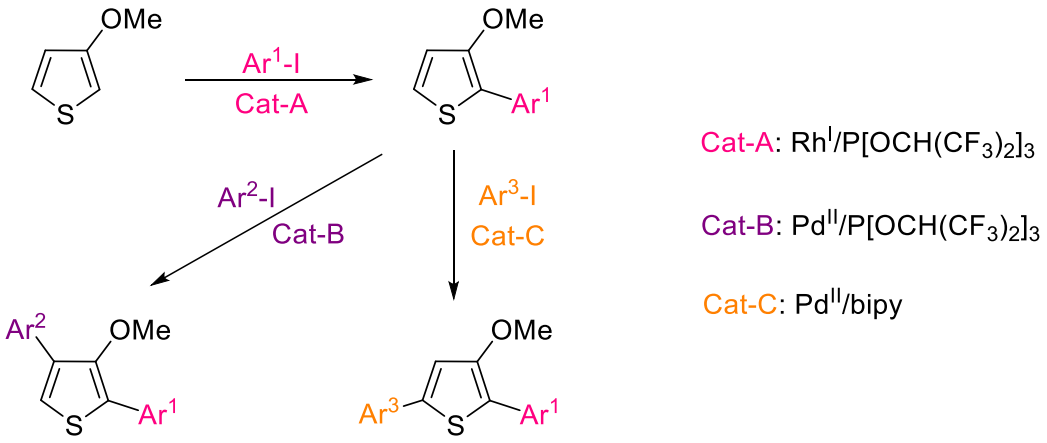
While these methods show that C-H activation of diazoles is possible, even without a directing group, a limitation is that only the most acidic site is activated (C2 for azoles and 1,3-diazoles, C5 for 1,2-diazoles; *Scheme 13*). Indeed, these are also the sites at which lithiation occurs. The challenge is therefore to activate the other C-H bonds on these heterocycles to allow access to a more diverse array of substituted 5-membered heterocycles.



Scheme 13 *– the C-H activation and arylation of 1,3-diazoles at the most acidic site.*[16]

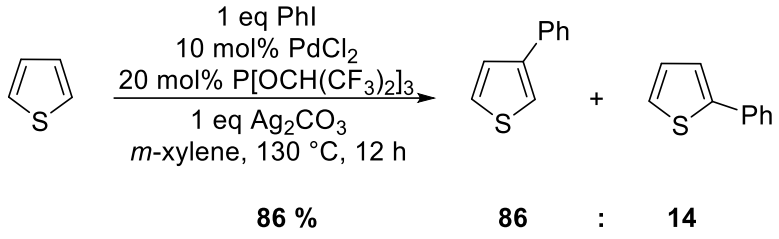
The regioselective arylation of heteroaromatic systems was reported by Itami *et. al.* in 2006. They studied the selective arylation of 3-methoxythiophene, and found it to take place at the 2-position when using [RhCO(P(OCH(CF_3)$_2$)$_3$)Cl] as a catalyst.[17] Interestingly, when 1-phenylpyrrole was used in place of 3-methoxythiophene, C-H activation occurred at the 3-position, possibly due to the sterically bulky phenyl group on the nitrogen. When 1-methylindole was used, a mixture of C2 (minor) and C3 (major) substituted products were isolated. It was found that a strongly π-accepting ligand was essential for high yields and good selectivities in these reactions. Subsequent studies successfully expanded this work to achieve the selective arylation of 2,3-disubstituted thiophenes in either the 4- or 5-position using palladium catalysts.[18]

In contrast to the rhodium catalyst previously used, when $PdCl_2$ was combined with the $P(OCH(CF_3)_2)_3$ ligand, there was a high selectivity for C-H activation at the 4-position. However, when $PdCl_2$ was combined with BIPY, the reaction took place at the expected 5-position (*Scheme 14*).



Scheme 14 *– Regioselective C-H activation of 2,3-disubstituted thiophenes.*[17,18]

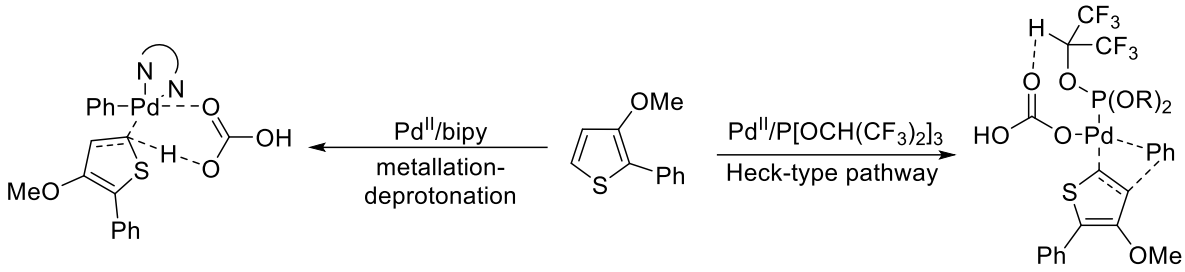
This powerful approach allows all sites on the thiophene to be sequentially and selectively activated, and the methoxy substituent provides an anchor for further functionalisation. Further development of this methodology resulted in the use of the Pd-catalyst system to selectively undertake C-H activation and arylation at C4 of monosubstituted thiophenes.[19] The same system can be used to arylate unsubstituted thiophenes with a good C3/C2 selectivity of 86:14 (*Scheme 15*).



Scheme 15 *– Regioselective C-H arylation of thiophenes.*

Regarding the mechanism, a S_EAr mechanism was postulated; the thiophene C2 undergoes electrophilic attack by the arylpalladium species followed by migration of the aryl group from palladium onto C3. However, a later computational mechanistic study[20] on these systems showed that the use of BIPY ligands promotes a metalation-deprotonation pathway and leads to the C5 substituted product, while the use of the

$P(OCH(CF_3)_2)_3$ ligand makes a Heck-type mechanism more energetically favourable and leads to the C4 substituted product (*Scheme 16*).



Scheme 16 *– Key transition states involved in the regioselective C-H activation of thiophenes.*[20]

It was discovered that the phosphine ligand has the ability to hydrogen bond to bicarbonate in the catalyst system which is crucial to the stabilisation of the transition state in the Heck-type pathway.

The lack of evidence for C-H aminations suggests it is a more challenging transformation than the corresponding carbon-carbon bond forming process used in traditional C-H activation methods. Using aromatic amides as directing groups, with $[RuCl_2(p\text{-Cymene})]_2$ and K_2CO_3 as a co-catalyst, a variety of morpholine-substituted azoles were accessible. Thiophenes could be aminated selectively in the 2- and 3-positions, furan in the 3-position and 1,3,5-substituted pyrazole in the 4 position (*Figure 1*).[21]

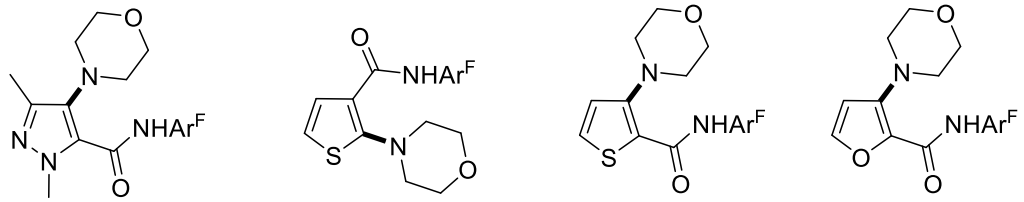


Figure 1 *– C-H amination of azoles with amide directing groups.*

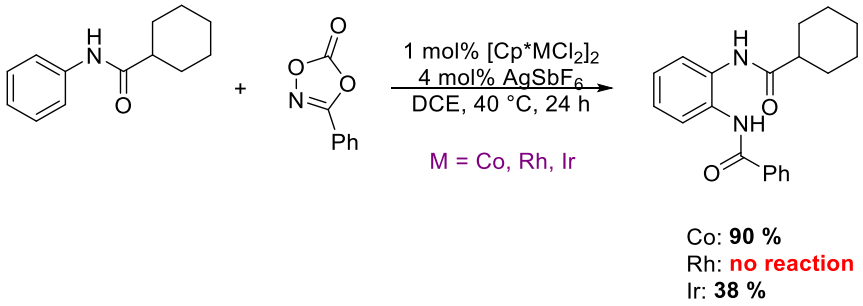
Some of these methods have been optimised specifically for their substrates, however there is not yet a general process under which azoles can be regioselectively amidated via metal catalysed C-H activation, and developments in this area are still ongoing.

1.2.3 C-H Amidation

1.2.3.1 First Row Transition Metals

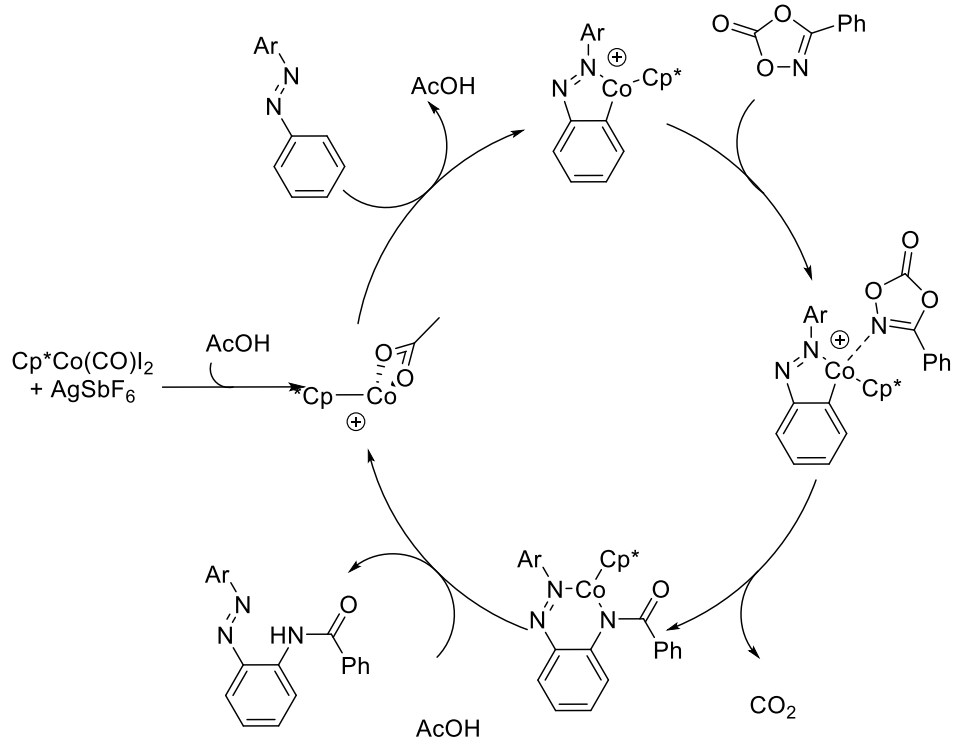
First row transition metal catalysed C-H activation reactions have mostly utilised cobalt and nickel catalysts. Cp* cobalt complexes are often used; Jiao demonstrated the amidation of benzene rings can be performed using 5 mol% $[Cp^*Co(MeCN)_3][SbF_6]_2$ and employing purines as directing groups.[22] Chang employed a combination of 1 mol% $[Cp^*CoCl_2]_2$ and pyridines as well as both *N*-coordinating and *O*-coordinating amides as directing groups, to amidate benzene rings with up to 95% yield.[23]

It was also found that under the same conditions, transition metals from the same group did not perform as well. Rhodium catalysts did not promote the reaction while iridium catalysts only gave low yields of the desired product (*Scheme 17*). 6-Methylated pyridine proved to be an ineffective directing group, with the reaction not proceeding. This suggested that the steric hindrance prevents coordination to the catalyst due to the bulky Cp* ligand.



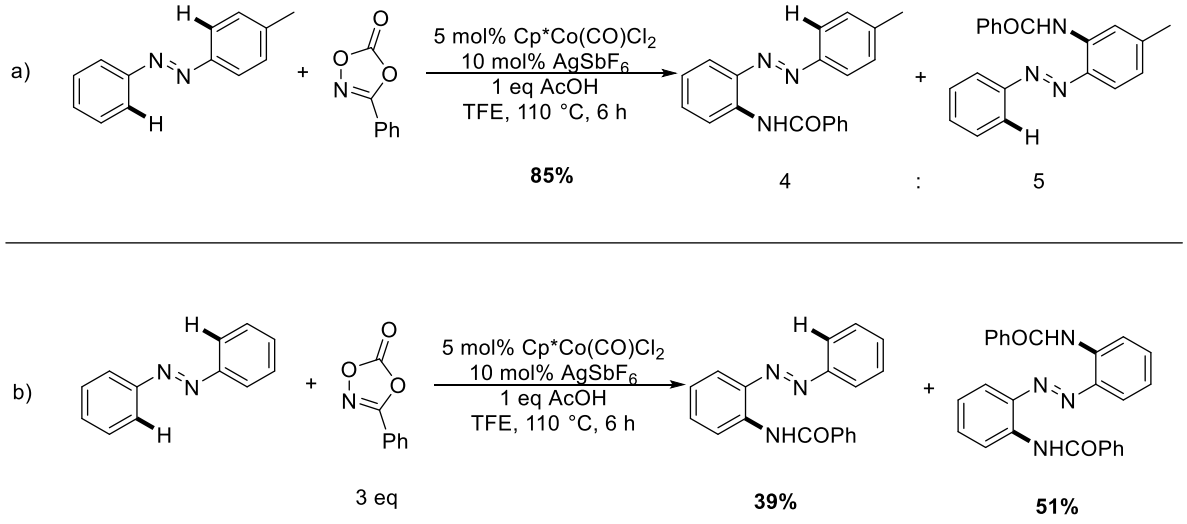
Scheme 17 *– the effect of changing the group X metal in [Cp*MCl₂] on C-H amidations.*[23]

C-H amidation of azobenzenes can be performed using $[Cp^*Co(CO)I_2]$,[24] utilising the internal directing power of the azo group (*Scheme 18*).



Scheme 18 *– the C-H amidation mechanism of azobenzenes with dioxazolones.*

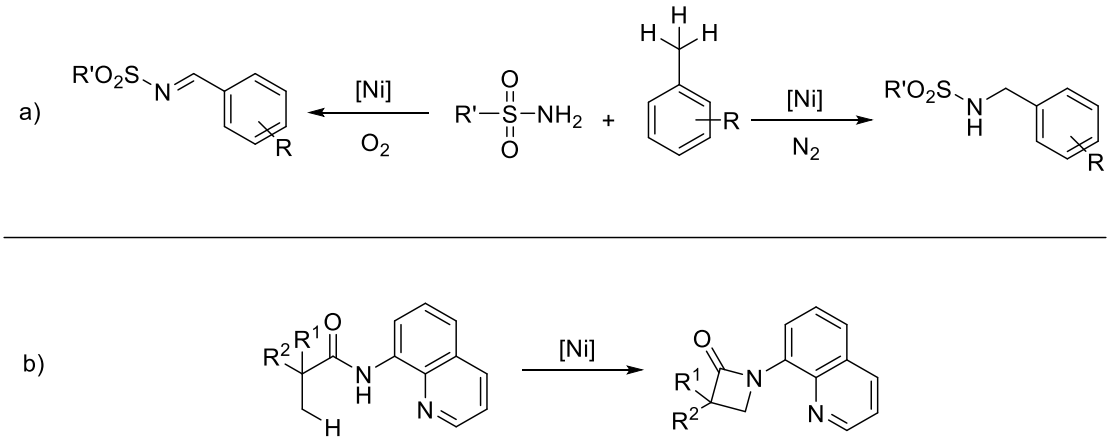
Asymmetric azobenzenes gave a mixture of substitution at the unsubstituted benzene ring versus the substituted ring (*Scheme 19a*), which was likely due to the substituted ring being more electron-rich. Only monosubstituted product was observed under the standard conditions. However, when an excess of dioxazolone was used (3 eq), a mixture of mono- (39%) and disubstituted (51%) products was observed (*Scheme 19b*).



Scheme 19 *– the effects of substitution and equivalents of dioxazolone on the C-H amidation reactions of azobenzenes.*

In all of these examples, a dioxazolone was used as the amidating agent, which releases carbon dioxide during the course of the reaction, providing an entropic driving force.

Nickel catalysed C-H amidation reactions are usually performed on sp^3 carbon-hydrogen bonds. Nickel(II) acetate is utilised to activate the benzylic C-H groups of toluenes to generate sulphonamides.[25] Under a nitrogen atmosphere, the sulfonamide product is synthesised, whereas under an oxygen atmosphere, the sulfonimine is formed (*Scheme 20a*). $[Ni(dme)_2I_2]$ was used to activate the β-sp^3 C-H and amidate with the intramolecular amide to form the β-lactam (*Scheme 20b*).[26]

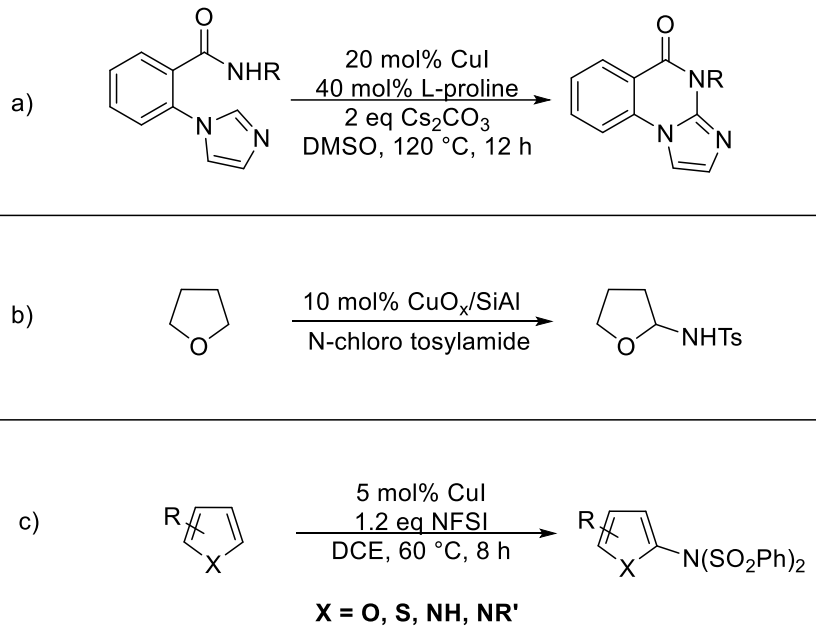


Scheme 20 *– Nickel-catalysed C-H amidations.*

While the results for first row transition metal based catalysts are promising, the conditions used are quite harsh, requiring high temperatures (80-150 °C) and halogenated solvents. In addition, cobalt and nickel complexes are highly toxic. There is a strong incentive to use copper- or iron-catalysed processes over cobalt and nickel. Their complexes are a lot less toxic and conditions can be a lot milder, if, for example, copper catalysts are used.

However, while there are several examples of copper-catalysed C-H amidation reactions, there are no examples in the literature of C-H amidation using an iron catalyst. Many iron catalysts are very air- and moisture-sensitive, requiring complex procedures to handle them and are therefore rarely used. The development of an iron-catalysed process using a bench-stable iron source would be highly beneficial in providing much less expensive route to C-H amidation products, but this has yet to be achieved.

Examples of copper-catalysed C-H amidation include the intramolecular C-H amidation on the C2 position of imidazoles using a copper(I) iodide catalyst (*Scheme 21a*), with a proline ligand under a nitrogen atmosphere.[27] Complementary to this, a heterogeneous process has been developed in order to promote C-H amidations of sp^3 C-H bonds in substrates such as THF and dioxane (*Scheme 21b*), using CuO_x/SiAl as the solid-phase catalyst.[28]



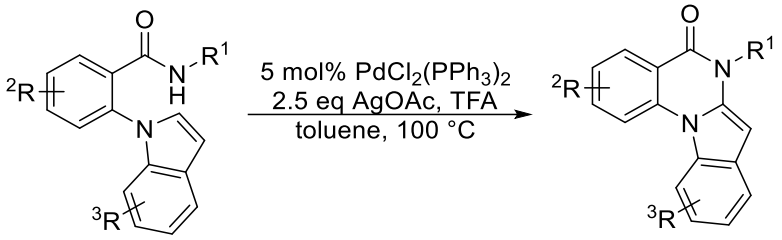
Scheme 21 *– Copper-catalysed C-H amidations.*

Pan *et al*. successfully introduced sulfonimides onto 5-membered heterocycles and azoles in the 2-position using copper iodide as the catalyst and sulfonimides as the amidating agent (*Scheme 21c*).[29] The reaction can be performed at lower temperatures than many other C-H activations, at just 60 °C in DCE. Electron-withdrawing and –donating groups are tolerated on various positions of the thiophenes, furans and pyrazoles. Of the 25 substrates included in the scope, only 5-methoxyfuran and 5-formylthiophene were not tolerated in the reaction and therefore deemed unsuitable substrates for this process.

While there is good scope in copper-catalysed C-H amidation and some of the reactions take place under much milder conditions as compared to those of cobalt and nickel complexes, there is a lack of regioselectivity. Only the most activated sites (e.g. the most acidic site or positions activated towards aromatic substitution) are activated by copper, limiting the products accessible by these methods.

1.2.3.2 Second Row Transition Metals

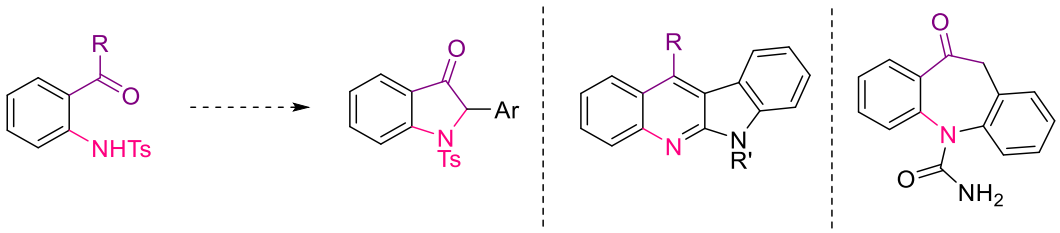
Cross-couplings and C-H activation reactions catalysed by palladium are well established, with some examples of C-H amidations using palladium(II) catalysts. Lithium carboxylates have been used to direct amidation of carbamates to benzene rings using palladium(II) acetate.[30] Good yields were maintained in the presence of both electron-donating and -withdrawing groups. Intramolecular cross-coupling reactions of amides to the 2-position of heterocycles such as indoles using $PdCl_2(PPh_3)_2$ to activate the C-H bond provides access to a range of substituted tetracyclic quinazolinones (*Scheme 22*).[31]



Scheme 22 *– Synthesising tetracyclic quinazolinones.[31]*

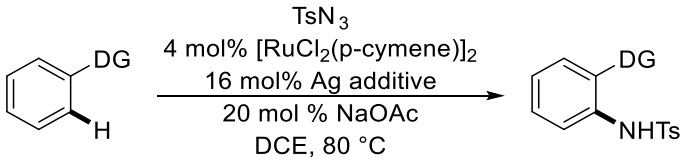
Ruthenium-catalysed C-H amidation reactions use sulfonazides as amidating agents, releasing nitrogen gas as an entropic driving force for the reaction. In this case, weakly coordinating ketone directing groups can be used along with a catalyst system consisting of 5 mol% $[Ru(p\text{-Cymene})Cl_2]_2$, 20 mol% $AgSbF_6$ and 50 mol% $Cu(OAc)_2$.[32] The chemistry has been exemplified on benzene analogues containing electron-donating and -withdrawing groups, although the latter usually gives lower yields.

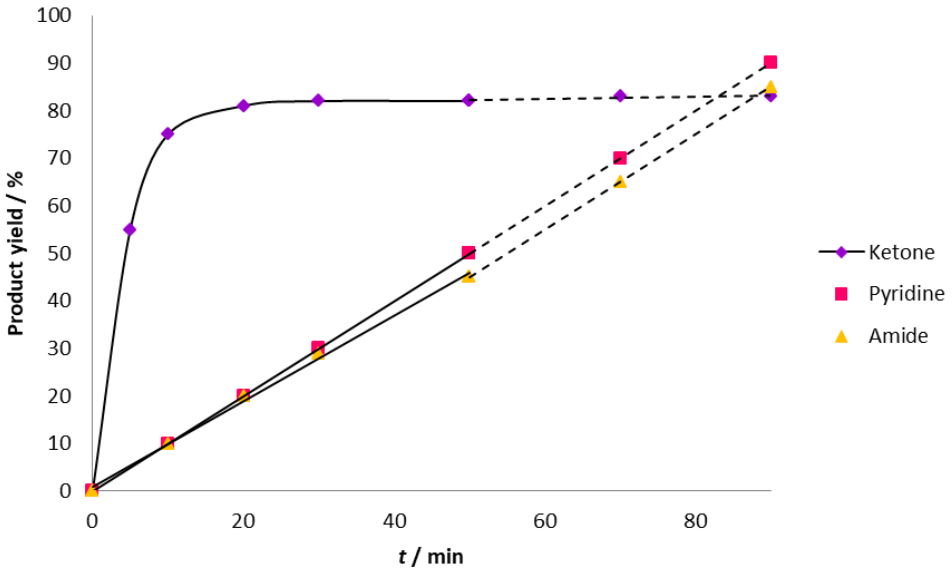
Subsequent studies by Jiao optimised the reaction conditions for this process.[33] Under argon, the catalyst loading could be reduced to 2.5 mol% $[Ru(p\text{-Cymene})Cl_2]_2$ 10 mol% for $AgSbF_6$ and 30 mol% $Cu(OAc)_2$ and the temperature could be lowered from 100 °C to 80 °C. Cyclisation of these products utilises both the directing group and the sulfonamide nitrogen in the final product giving high atom economy (*Scheme 23*). Using the ruthenium catalyst and sulfonamide substrates, aliphatic amide directing groups can assist in the C-H amidation reactions of benzene analogues in the ortho position, with excellent yields in the absence of a copper(II) acetate co-catalyst when $AgNTf_2$ is used as the co-catalyst in place of $AgSbF_6$.[34]



Scheme 23 *– Some cyclisation products of amidated benzenes; the ketone directing group (purple) and amide (pink) are retained in the products.*[33]

Other directing groups were trialled, and it was found that ketones give better conversion with time initially, however nitrogen coordinating groups were found to give similar yields at longer reaction times (*Scheme 24*). C-H amidation under the same conditions using an *N*-keto directing group leads to amidation on 7-position of indolines,[35] where electron-donating and -withdrawing groups, and aliphatic and aromatic ketones are tolerated.



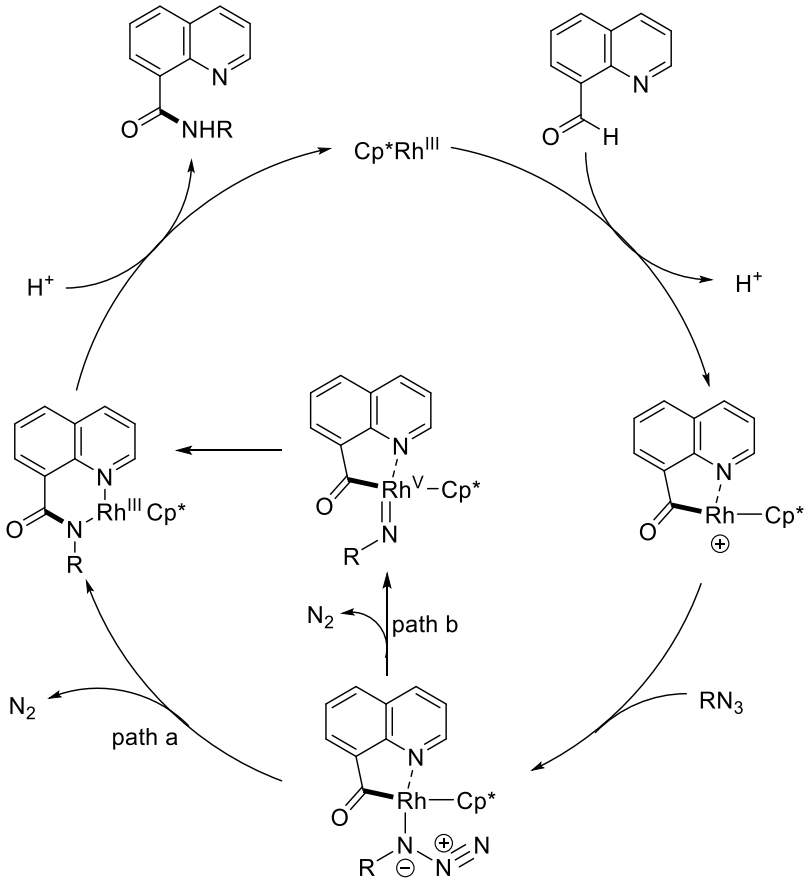


Scheme 24 *– difference in rate of reaction with different directing groups (dashed = extrapolation).*[34]

Again, there are issues with ruthenium- and palladium-catalysed C-H amidation processes, such as modest yields and limited substrate scopes. Both metal catalysts are

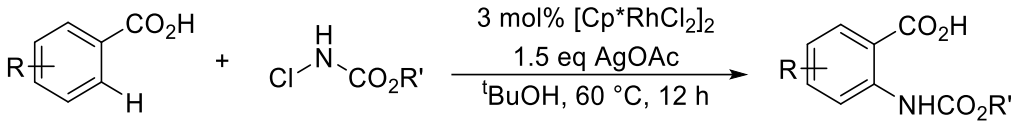
also highly toxic as well as expensive, and the C-H amidation reactions are undertaken in halogenated solvents at temperatures of 80-100 °C.

Rhodium catalysts are well documented in the field of C-H amidations; they are reactive to C-H insertion of many substrates, including benzenes, thiophenes and aldehydes.[36] For example, $[Cp^*Rh(MeCN)_3][SbF_6]_2$ is able to insert into the C-H bond of aldehydes on the C9 position of quinolines using the quinoline nitrogen as a directing group, thereby converting the aldehyde into an amide (*Scheme 25*). A wide range of amides can be introduced, including sulphonamides and aliphatic and aromatic amides, all in excellent yields. Thioanisoles are also suitable substrates for aldehyde C-H activation, giving excellent yields of aromatic amides.



Scheme 25 *–Proposed mechanisms for the C-H amidation of aldehydes.*

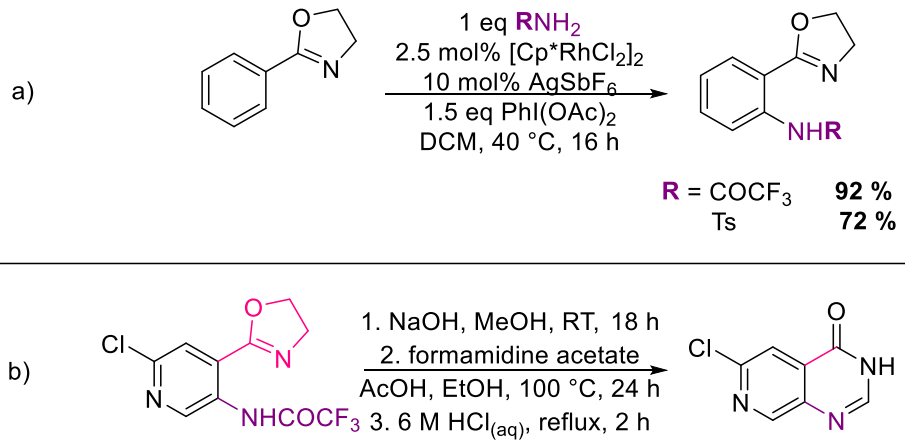
Both carboxylic acids and pyridine have been used as directing groups to facilitate C-H activations and amidations, giving carbamic products. $[Cp^*RhCl_2]_2$ has been used in a carboxylic acid directed C-H amidation using *N*-chlorocarbamates (*Scheme 26*).[37]



Scheme 26 *– Carboxylic acids directing Rh-catalysed C-H amidations with N-chlorocarbamates.*

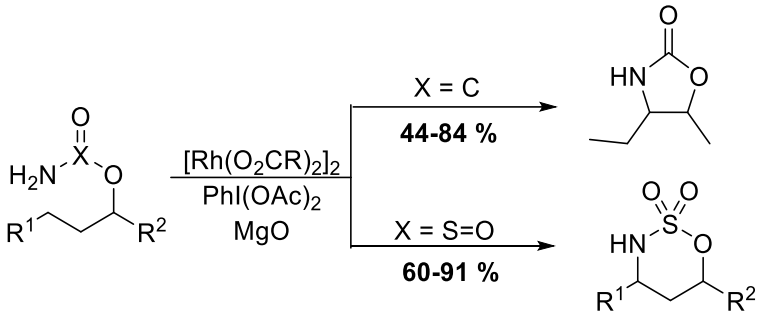
C-H amidation reactions using this method were also successful on thiophene-2-carboxylic acids; the same catalyst has been used to regioselectively introduce NHBoc groups to thiophenes,[37] using pyridine to direct the C-H activation to the adjacent position on the thiophene ring (*Scheme 8b*).

C-H amidation of 6-membered heterocycles using trifluoroacetamide as the amidating agent has been well documented, with several examples of $[Cp^*RhCl_2]_2$ catalysing the oxazoline-directed amidation of benzenes[38] and pyridines[39] (*Scheme 27a*). A wide variety of functional groups were found to be tolerated under the amidating conditions, including halides. Sulfonamides were also found to be suitable amidating agents,[40] however the reactions were found to proceed at a slower rate and required higher temperatures to achieve similar yields. The resulting trifluoroacetamide-coupled aromatics could be further functionalised; cyclisation with amidines gave an array of quinazolines. These products can be hydrolysed to their corresponding quinazolinones (*Scheme 27b*), a scaffold found in bioactive molecules such as the pharmaceuticals halofuginone and febrifugine.[41]



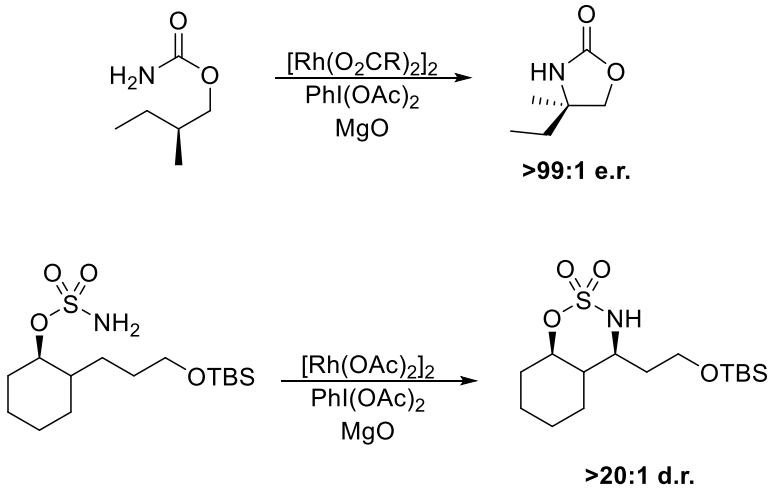
Scheme 27 *– C-H amidations of 6-membered heteroaromatics.*[39,40]

Saturated heterocycles have been accessed *via* C(sp^3)-H activation reactions using rhodium catalysts followed by the cyclisation of an intramolecular amide (*Scheme 28*). When the intramolecular amide is a carbamate,[42] the β C-H bond is activated towards metal insertion and a 5-membered ring is formed. When the amide is a sulfamate,[43] the resulting heterocycle is 6-membered due to the activation of the γ C-H bond.



Scheme 28 *– sp^3 C-H activation and cyclisation with intramolecular carbamates and sulfamates.*

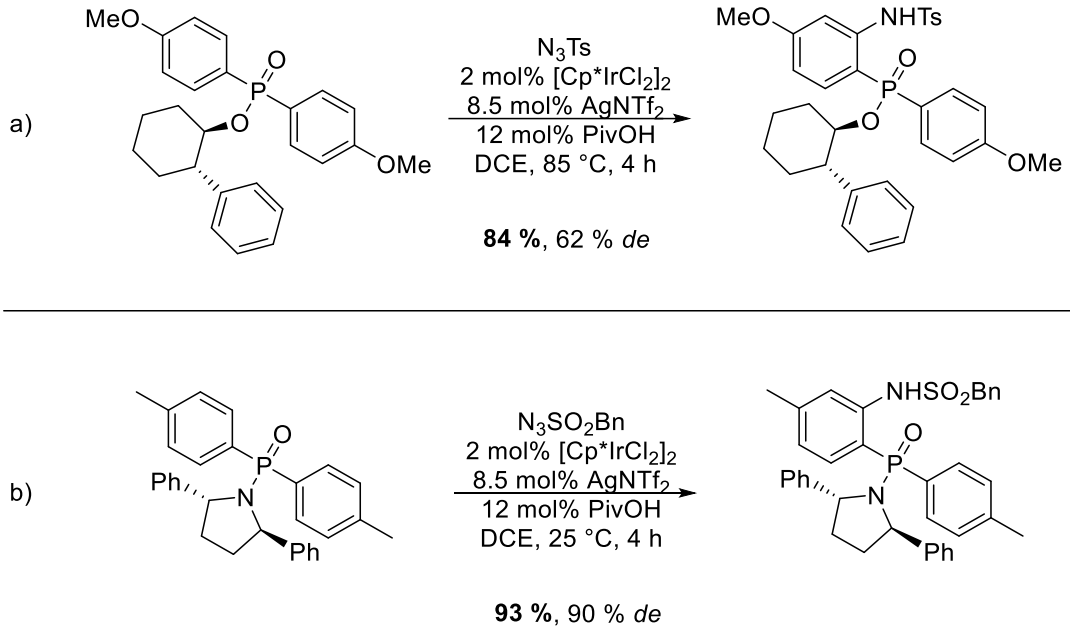
The reactivities suggest that this type of reaction proceeds *via* a rhodium nitrene, where the nitrene is formed first followed by the C-H activation step. This hypothesis also accounts for the difference in regioselectivity between carbamates and sulfamates. Sulfur is much larger than carbon, and S-O and S-N bonds are much longer than their carbon counterparts, leading to a preference of activating the δ C-H over the β C-H and therefore a 6-membered ring. This methodology also has applications in the asymmetric synthesis. There are stereospecific and diastereoselective examples using both carbamates and sulfamates (*Scheme 29*).



Scheme 29 *– Stereoselective sp^3 C-H activation and cyclisation with intramolecular carbamates and sulfamates.*

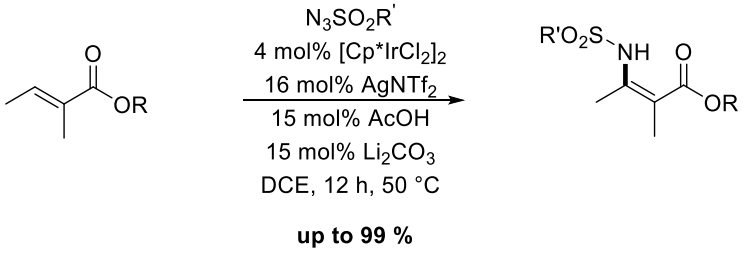
1.2.3.3 Third Row Transition Metals

An interesting desymmetrisation reaction of arylphosphoryl compounds has been devised using iridium-catalysed C-H amidations by exploiting a chiral auxiliary.[44] The amidation produces a P-stereogenic centre with good diastereocontrol, and is facilitated by the directing power of the P=O bond (*Scheme 30a*). Diastereomeric excesses of up to 62% were achieved when reacted with a chiral sulfonazide, and up to 90% when one of the substituents on phosphorus is a C_2-symmetric chiral pyrrolidine auxiliary (*Scheme 30b*).



Scheme 30 *– Regioselective C-H amidation of arylphosphoryls to give P-stereogenic centres.*[44]

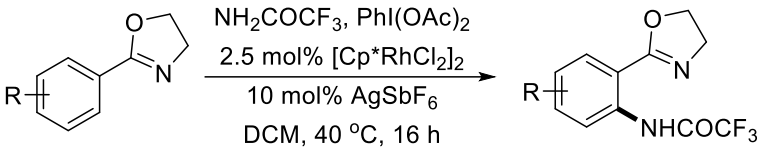
Esters have also been found to be effective directing groups in reactions catalysed by $[Cp^*IrCl_2]_2$ (*Scheme 31*),[45] allowing C-H amidation reactions on a wide variety of substrates to be undertaken, including benzene analogues and both cyclic and acyclic alkenes.



Scheme 31 *– Esters as directing groups in iridium-catalysed C-H amidations.*

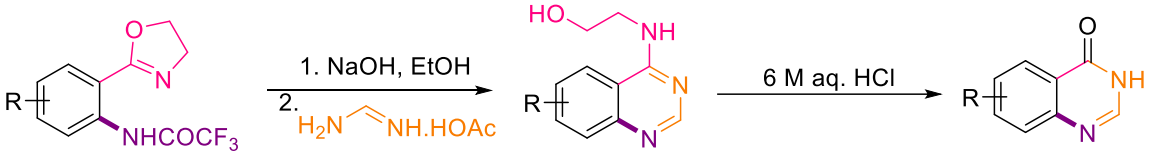
1.3 Previous Work

Previously, Maiden has synthesised a wide variety of quinazolines and quinazolinones.[39,40,41,46] Oxazolinyl benzene and pyridine analogues were subjected to oxazoline-directed rhodium-catalysed C-H amidation reaction conditions (*Scheme 25*), in order to insert an amide in the *ortho*-position to provide an anchor for the quinazoline cyclisation (*Scheme 32*). Optimised conditions for the C-H amidation reactions of these substrates include using trifluoroacetamide as the limiting reagent (1.2 eq. oxazoline) with 2.5 mol% of $[Cp^*RhCl_2]_2$, 10 mol% $AgSbF_6$ and 1.5 equivalents of $PhI(OAc)_2$.



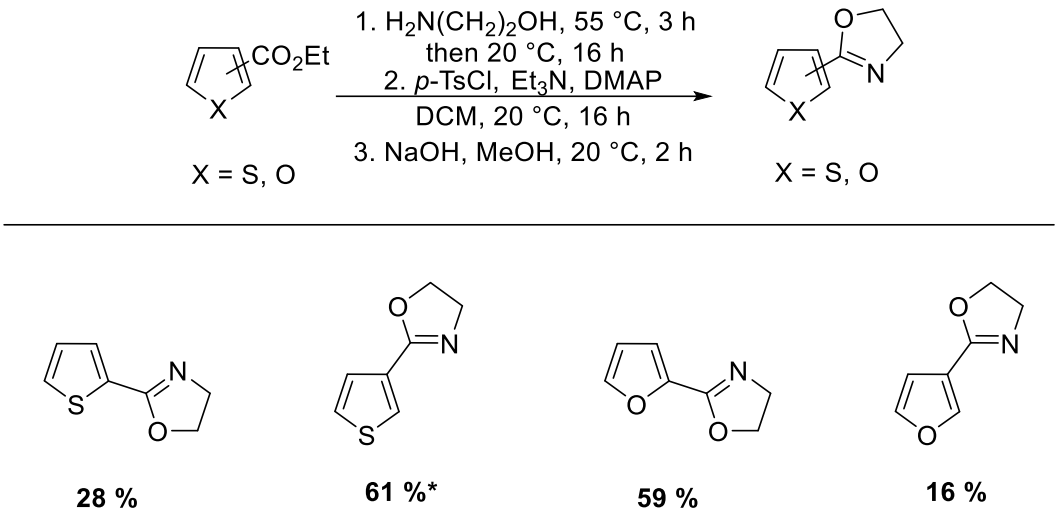
Scheme 32 *– C-H amidation reactions of benzene analogues.*

The amide products were then cyclised to their quinazolines and quinazolinones *via* the amine, incorporating both the directing group and the amine into the bicyclic scaffold (*Scheme 33*).



Scheme 33 *– Cyclisation of C-H amidation reaction products to form the quinazolines and quinazolinones.*

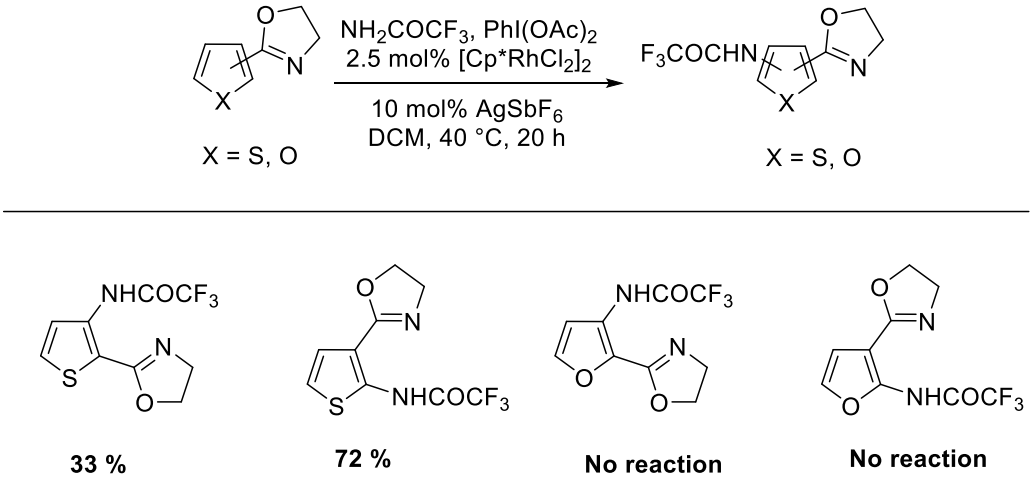
Maiden also applied the C-H amidation methodology to thiophenes and furans with varying degrees of success. The oxazolinyl azoles were synthesised from the ethyl esters or carboxylic acids and gave moderate to good yields over 3 or 4 steps (*Scheme 34*).



Scheme 34 *– Maiden's synthesis of oxazolinyl azoles.*

**made from the carboxylic acid using $(COCl)_2$ and cat. DMF then ethanolamine and Et_3N, followed by the tosylation and cyclisation steps.*

These oxazolinyl azoles were then subjected to the C-H amidation conditions (*Scheme 35*), and trifluoroacetamides were successfully coupled to the thiophenes with 33% and 72% yields for the 2-oxazolinyl and 3-oxazolinyl thiophenes respectively. Unfortunately, the furans did not react under these conditions.



Scheme 35 *– the C-H amidation reactions of thiophenes and furans.*

1.4 Azolopyrimidine Scaffolds

Bicyclic pyrimidines and pyrimidinones are key structures present in many bioactive molecules, both in the pharmaceutical industry and in nature. Their bioactive capabilities stem from their high number of H-bonding sites and their similarity to the purine DNA bases (*Figure 2*). Adenine is an imidazopyrimidine, while guanine is an imidazopyrimidinone.

Figure 2 *– Azolo-pyrimidines and –pyrimidinones feature in DNA bases.*

Examples of bioactive thionopyrimidines include Pictilisib,[47] a P13K inhibitor with anti-cancer properties, and MCI-225 – a 5-HT3 antagonist with possible uses in treating depression and irritable bowel syndrome (*Figure 3*).[48]

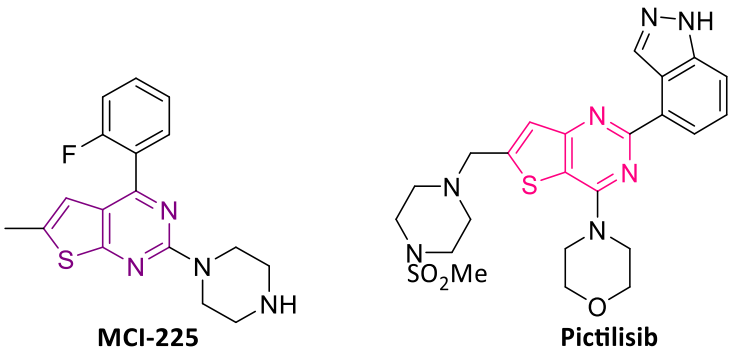
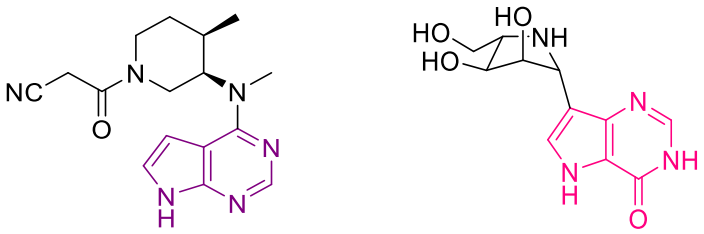


Figure 3 *– Bioactive thionopyrimidines.*[47,48]

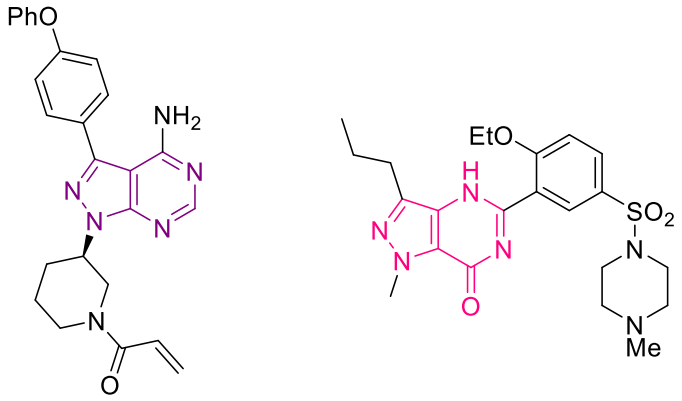
Tofacitinib is a commercially available pyrrolopyrimidine.[49] It is used in the treatment of rheumatoid arthritis as it is a janus kinase inhibitor (*Figure 4*). Forodesine is a pyrrolopyrimidinone which works as a transition state analogue inhibitor of purine nucleoside phosphorylase approved in Japan for the treatment of T-cell leukemia.[50]



Tofacitinib **Forodesine**

Figure 4 *– pyrrolopyrimidines and pyrimidinones in pharmaceuticals.*[49,50]

Anti-cancer drug and pyrazolopyrimidine, Ibrutinib inhibits Bruton's tyrosine kinase, and is an effective treatment for B-cell cancers such as mantle cell lymphoma.[51] Sildenafil is a pyrazolopyrimidinone, as well as potent and selective cGMP phosphodiesterase type-5 inhibitor (*Figure 5*).[52] It was initially developed as a treatment for angina and hypertension, but is now marketed under the brand name Viagra for the treatment of erectile dysfunction.

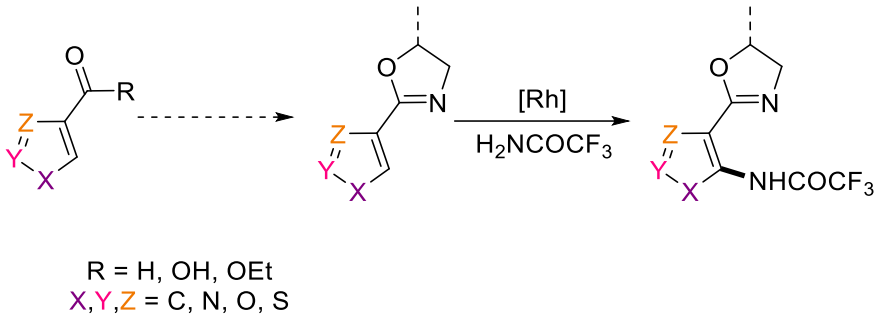


Ibrutinib **Sildenafil**

Figure 5 *– Commerically available pyrazolopyrimidines and pyrimidinones.*[51,52]

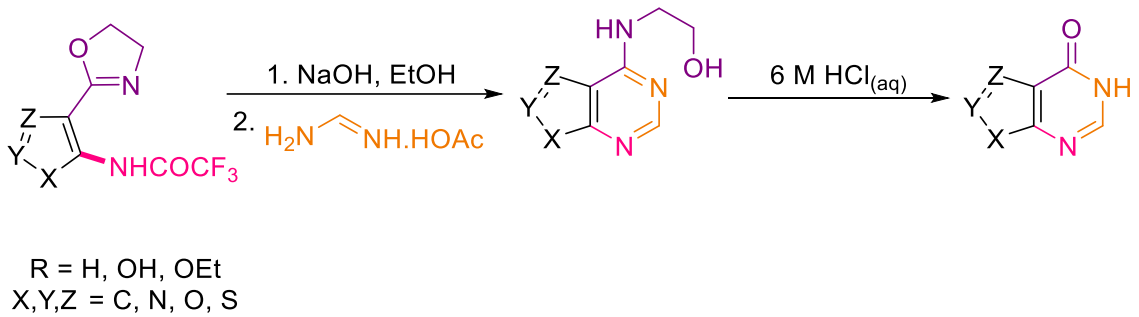
1.5 Aims

Azolopyrimidines are interesting scaffolds from a pharmaceutical and agrochemical point of view due to their similarities to biological molecules such as DNA bases. A range of azolopyrimidines and pyrimidinones will be synthesised from their carboxylic acids or aldehydes using the C-H amidation chemistry described by Maiden. First, the oxazolines will be synthesised, followed by the oxazoline-directed rhodium-catalysed regioselective C-H amidation reaction (*Scheme 36*).



Scheme 36 *– Synthesis and C-H amidation reactions of azoles.*

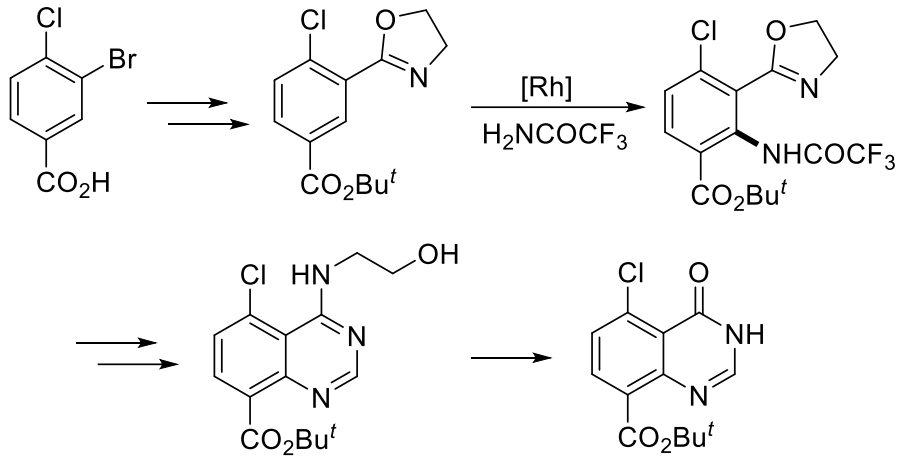
Hydrolysis of the amide to the amine followed by cyclisation will afford the azolopyrimidines, incorporating the amine and directing group into product and giving a high atom economy (*Scheme 37*). Hydrolysis of the pyrimidine to the pyrimidinone using aqueous hydrochloric acid will give a variety of azolopyrimidinones.



Scheme 37 *– Synthesis of pyrimidines and pyrimidinones with high atom economy.*

To expand on the work carried out by Maiden, the synthesis 1,2,3,4-tetrasubstituted benzenes via C-H amidation will be attempted, followed by their subsequent cyclisation and hydrolysis to give 5,8-disubstituted quinazolinones (*Scheme 38*). Groups of

orthogonal functionality (e.g. -Cl and -CO_2Bu^t) will be included at the 1- and 4-positions (later the 5- and 8-positions), to give handles for late-stage functionalisation.



Scheme 38 *– Synthesising 5,8-disubstituted quinazolines and quinazolinones.*

1.6 Results and Discussion

1.6.1 A General Route to Oxazolines

The synthesis of oxazoline substrates required for this study can take up to 5 steps. We were therefore inspired to devise more convergent methods for the introduction of directing groups into aromatic substrates. In this regard, Sadow reported the synthesis of a tris(4,4-dimethyl-2-oxazoliny)borate species (*Figure 6a*),[53] *via* an oxazoline-lithium intermediate (*Figure 6b*).

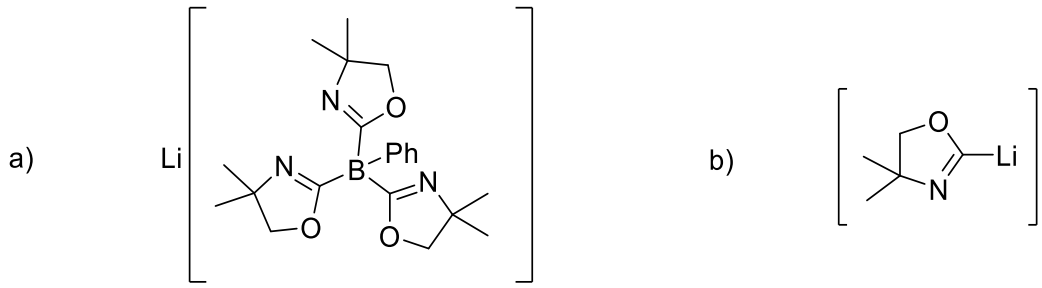
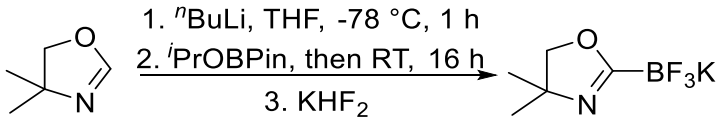


Figure 6 *– Sadow's oxazoline species.*[53]

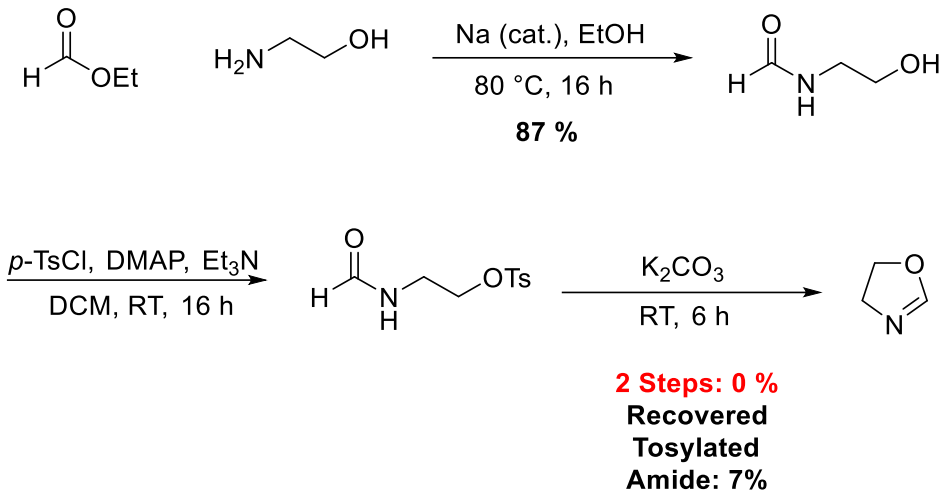
Trifluoroborates are bench-stable Suzuki cross-coupling reagents, which slowly release the boronic acid under the reaction conditions. They are easily synthesised from lithiated species, using ^{i}PrOBpin as an electrophile and converting to the trifluoroborate using KHF_2 (*Scheme 39*). As Sadow has shown that oxazolines can be lithiated at the 2-position, we envisaged that their corresponding trifluoroborates should be accessible. This would then open up the possibility of incorporating this fragment by cross-coupling chemistry.



Scheme 39 *– the attempted synthesis of oxazoline trifluoroborates.*

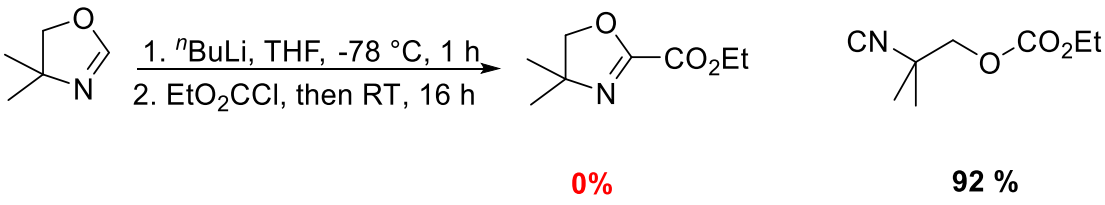
We began these studies by attempting to synthesise the parent oxazoline by cyclisation of an amide intermediate. Unfortunately, the cyclisation of the tosylated formamide (*Scheme 40*) did not give any product, returning the starting material with a low mass balance. It is likely that oxazoline was formed, but as it is very polar, it stayed in the

aqueous layer during workup and extraction. Attempts to undertake chromatographic purification directly on the crude material were also unsuccessful. This may have been due to problems with visualising the product on TLC by UV or staining with potassium permanganate or vanillin.



Scheme 40 *– the synthesis of oxazoline.*

As the parent oxazoline proved difficult to access, we turned our attention to 4,4-dimethyl-2-oxazoline as this is available commercially. The oxazoline was lithiated and ^{i}PrOBpin was added followed by KHF_2. Unfortunately, no trifluoroborate was obtained and the crude reaction mixture showed no signs of oxazoline by NMR or LCMS analysis. To deduce whether the lithiation step had been successful, the oxazoline was again mixed with ^{n}BuLi and ethyl chloroformate was added as the electrophile (*Scheme 41*). However, instead of accessing the oxazoline product, the addition of ^{n}BuLi caused ring opening to form an isocyanide which was then trapped by ethyl chloroformate, as documented by Lindhorst *et al*.[54]

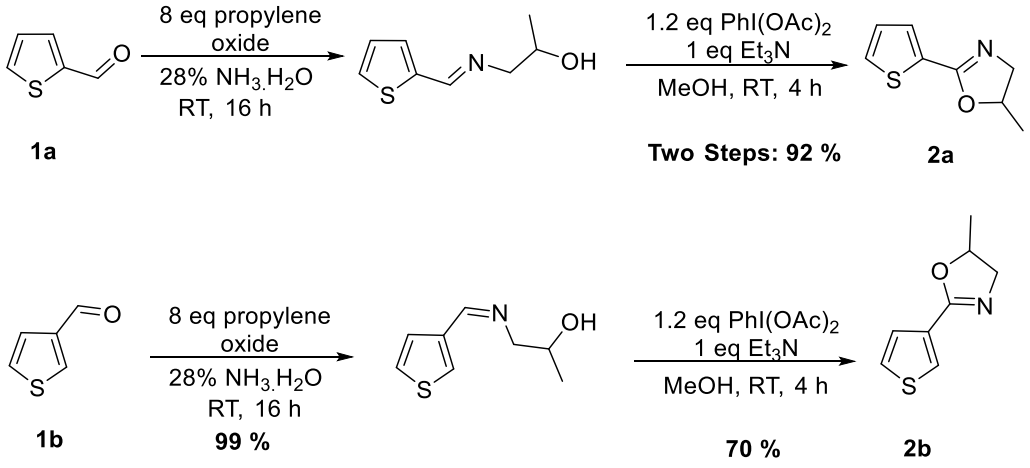


Scheme 41 *– the lithiation of oxazolines induces ring opening to the hydroxyisocyanide.*[54]

This rearrangement makes clear why so little material was observed after the initial attempt to make the oxazoline trifluoroborate; the lithium intermediate is less likely to react with iPrOBPin and after work up, the isocyanide will have solubilised in the aqueous phase. As it is known that lithiation causes this rearrangement in oxazolines, it was therefore unlikely that the oxazoline coupling partners could be accessed using traditional borylation methods and this chemistry was discontinued.

1.6.2 Thiophenes

Maiden's oxazolinyl-thiophene syntheses proceeded *via* an acid chloride which employed oxalyl chloride and chlorinated solvents, both of which are unattractive from an environmental and economical point of view. Moreover, this route required three or more steps to access the substrate from the commercial material. In contrast, the route employed in this work delivered both oxazolinyl thiophene substrates in just two steps under milder conditions. Compounds **2a** and **2b** were generated from commercial aldehydes in good to excellent yields (*Scheme 42*).

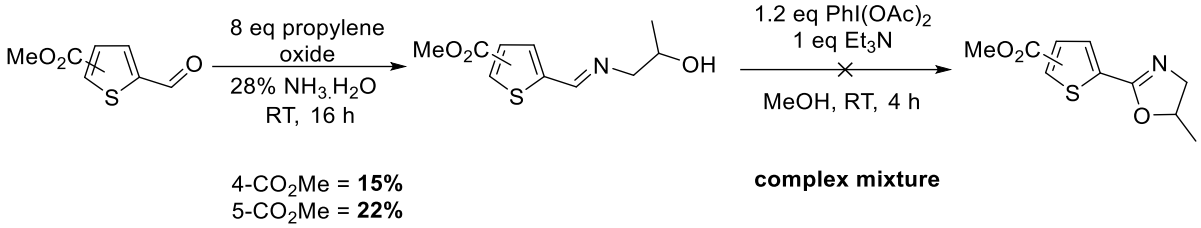


Scheme 42 *– the synthesis of oxazolinyl thiophenes from their aldehydes.*

The use of aqueous ammonia to form the imine provides a greener route to making oxazolines, and the following cyclisation using (diacetoxy)iodobenzene in a non-halogenated solvent is both greener and requires less steps than the Maiden method.

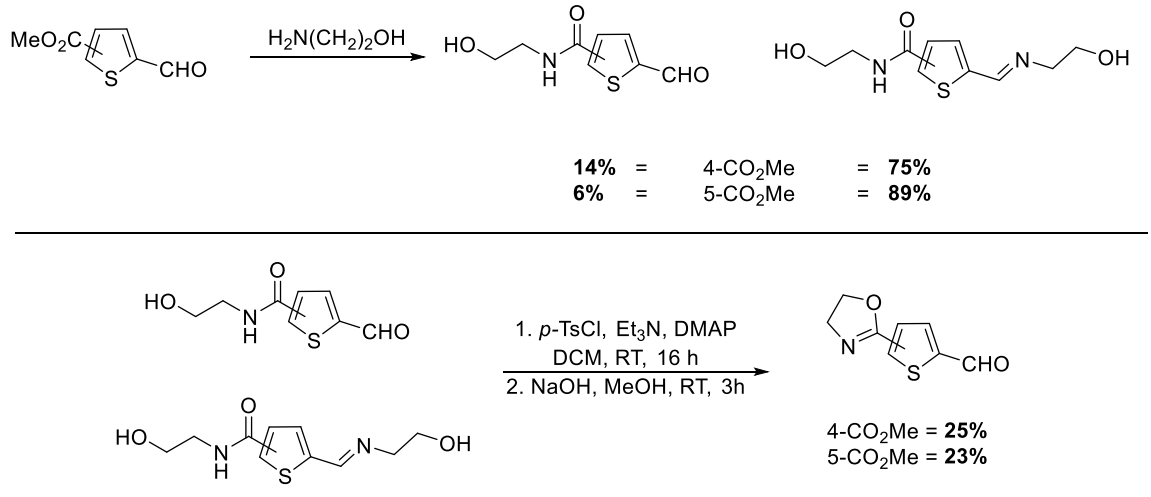
Access to electron-deficient thiophenes proved more complex. The aforementioned route applied to ester-substituted oxazolinyl thiophenes did not give the desired product due to the intermediate imine not being pure (*Scheme 43*), containing significant

amounts of the amino alcohol by-products from the reactions of ammonium hydroxide with propylene oxide. These contaminants could have an inhibitory effect on the cyclisation step, and while more equivalents of (diacetoxy)iodobenzene and triethylamine could be added, this would negate the use of this more environmentally friendly synthesis.



Scheme 43 *– ester-substituted oxazolinyl thiophene synthesis via imine formation.*

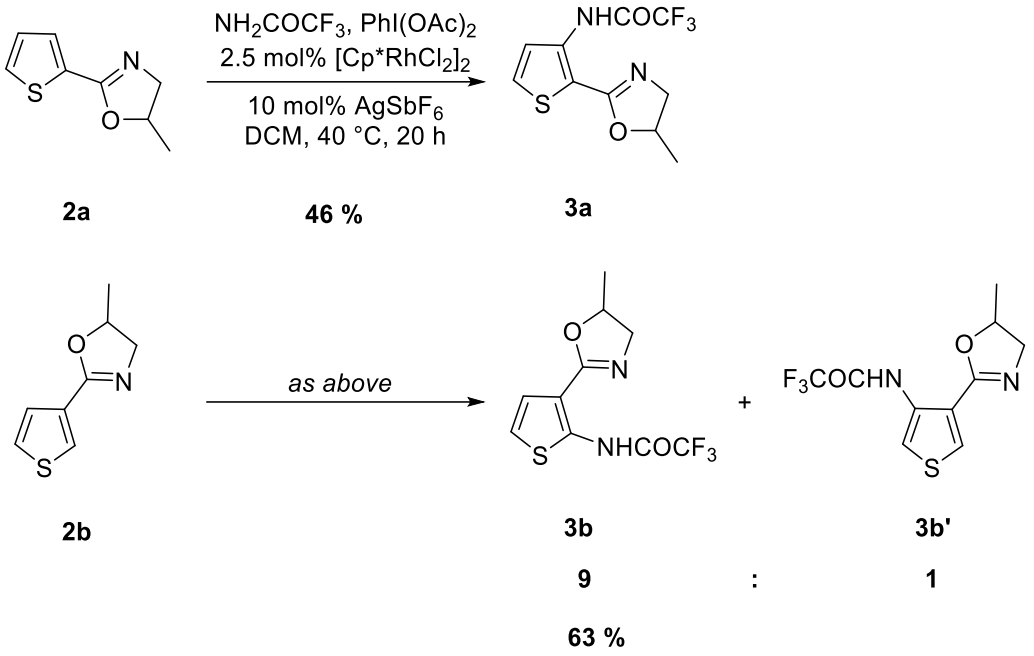
Accessing 2-aldehyde-substituted oxazolinyl thiophenes *via* amidation of the ester the was possible, however the yields across the process were low (*Scheme 44*) due to the formation of the imine, and it was not possible to separate the aldehyde and imine amides at this stage.



Scheme 44 *– Synthesis of aldehyde-substituted oxazolinyl thiophenes via amide formation.*

Subjecting these mixtures to the tosylation-cyclisation gave low yields. Approximately 20 mg of each oxazoline was synthesised from 200 mg of the methyl ester, which was proved inadequate to test C-H amidation. Due to the financially prohibitive nature of the starting materials, more of these substrates were not synthesised.

Building upon Maiden's work with CH amidations and thiophenes, the CH amidations of **2a** and **2b** were successfully undertaken (*Scheme 45*), giving 46% and 63% yields respectively.

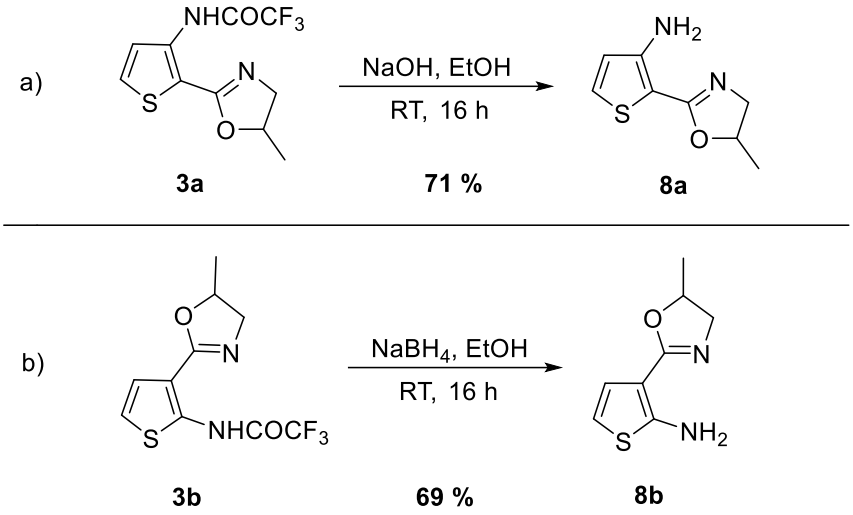


Scheme 45 *– C-H amidation of thiophenes.*

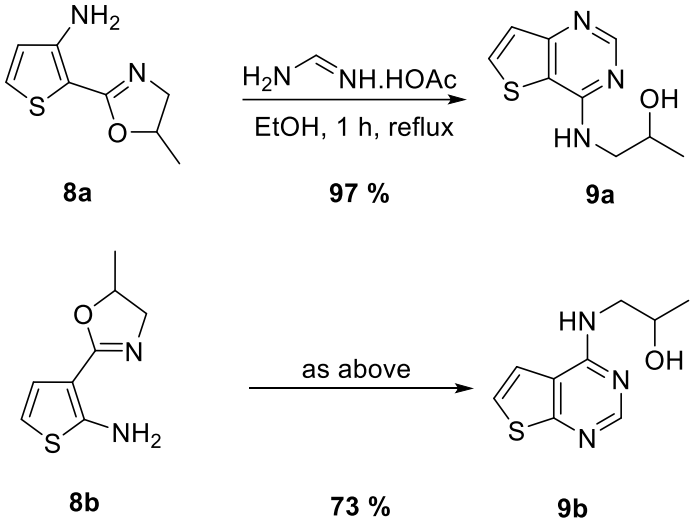
These yields compared favourably to Maiden's 33% and 72% yields for similar reactions where the unsubstituted oxazoline was used. Interestingly, the CH amidation of **2b** displayed high selectivity; the crude NMR spectrum showed a ratio of 9:1 for amidation in the 2 and 3 positions respectively.

In order to cyclise to the azolopyrimidine, the trifluoroacetamide must first be hydrolysed or reduced to afford the amine, then cyclised with formamidine acetate. The pyrimidine can then be converted to the pyrimidinone using 6 M $HCl_{(aq)}$ at reflux. Using Maiden's methodology, **3a** and **3b** were stirred with NaOH in ethanol at room temperature for 6 hours. Compound **3a** showed some conversion to the aniline under these conditions, and increasing the reaction time to 16 hours lead to a much better yield of 71% for **8a** (*Scheme 46a*). However, **3b** was not as easily hydrolysed, and increasing the reaction time to 24 hours resulted in the 3-oxazolinyl thiophene amide **8b** being produced in just a 7% yield. Heating the reaction to 40 °C failed to return product. Instead, sodium borohydride was used to reduce the amide **3b** (*Scheme 46b*), with the reaction proceeding overnight at room temperature to give **8b** with a 69% yield. While

sodium borohydride is not usually able to reduce amides, the highly electron-withdrawing CF_3 group makes the amide reactive enough to be reduced with ease using $NaBH_4$.



Scheme 46 *– the conversion of the amide to the amine.*

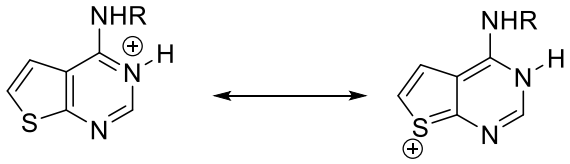


Scheme 47 *– the synthesis of thienopyrimidines.*

Subsequently, **8a** and **8b** were stirred with formamidine acetate in order to synthesise the thienopyrimidines **9a** and **9b** in 97% and 73% yields respectively (*Scheme 47*). Pleasingly, thiophene aldehydes can be taken through to their respective pyrimidines in just 5 steps efficiently and regioselectively.

Unfortunately, hydrolyses of **9a** and **9b** with 6 M $HCl_{(aq)}$ to the thienopyrimidinones were unsuccessful, with the reactions returning the thienopyrimidines, **9a-b**. It is possible that

these substrates are not undergoing hydrolysis due to the stabilisation of the protonated pyrimidine *via* resonance (*Scheme 48*).

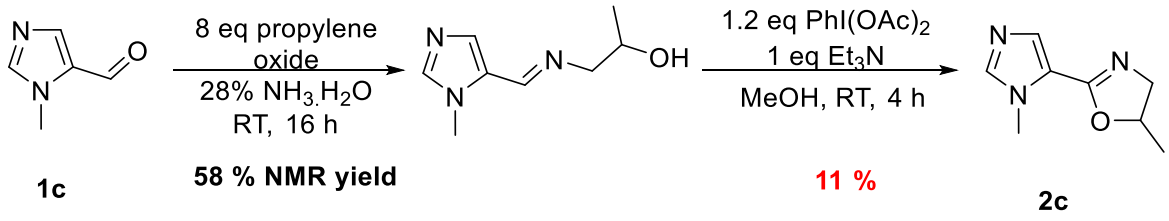


Scheme 48 *– resonance stabilisation of* ***9b*** *under acidic conditions.*

It is documented that purines can be hydrolysed to their xanthine derivatives by the addition of nitric oxide or sodium nitrite under acidic conditions.[55] These alternative methods would likely allow the thienopyrimidinones to be accessed in the future, although it was not tested at this time.

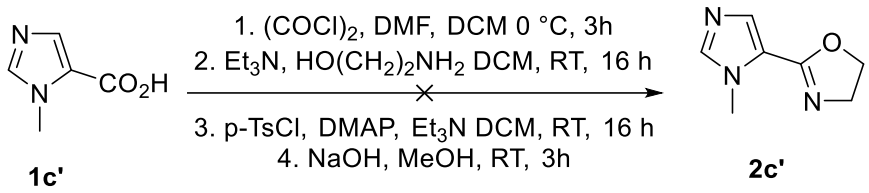
1.6.3 Imidazoles

Unfortunately, the procedure used to make the oxazolinyl thiophenes proved to be unsuitable for the synthesis of **2c**, owing to its high water solubility. There were issues extracting the imidazole imine out of the aqueous ammonia; the solution had to be saturated with NaCl and extracted using 10% MeOH in DCM to achieve a reasonable mass balance. In addition, these imines were not stable to silica gel, meaning that purification by column chromatography was not viable. Furthermore, these exhaustive extraction conditions also transferred large amounts of the amino alcohol by-products into the organic phase, and this could have had an inhibitory effect on the cyclisation step, giving a product yield of just 11% yield (*Scheme 49*). More equivalents of (diacetoxy)iodobenzene and triethylamine could be used, however the benefits of this route would then be lost.



Scheme 49 *– the synthesis of oxazolinyl imidazole using the ammonia methodology.*

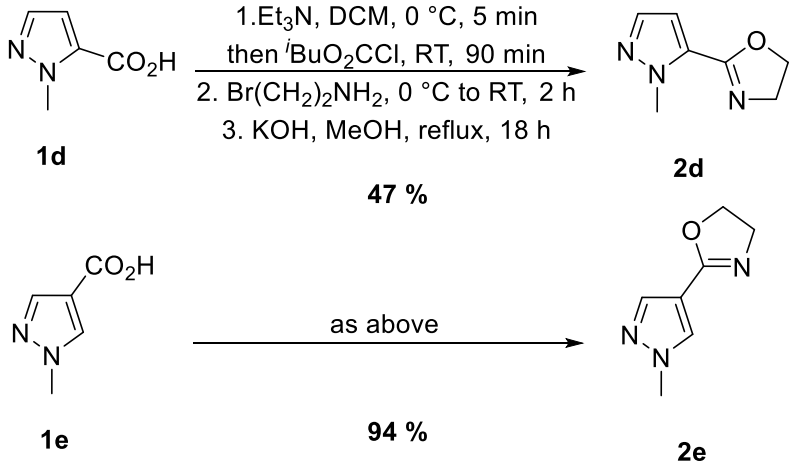
As the green synthesis of **2c** proved fruitless, the synthesis of oxazolinyl pyrazoles was attempted from the carboxylic acids rather than the aldehydes, using methods described by Maiden (*Scheme 50*). These syntheses also proved to be challenging; the Appel methodology used by Maiden was unsuccessful, and tosylation of the oxygen followed by treatment with base to facilitate the cyclisation step also proved unsuccessful. ^{1}H NMR spectra of the crude reaction mixtures in between steps suggested that the amide formation was likely to have been the problematic step in these cases.



Scheme 50 *– attempted synthesis of oxazolinyl* N*-Me imidazole from the carboxylic acid.*

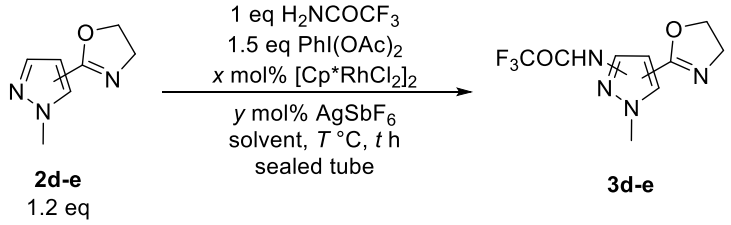
1.6.4 Pyrazoles

A patent by Luo *et al*.[56] described the synthesis of 1-methyl-4-oxazolinylpyrazole, and this method appeared to be quite appealing. In the event, the three step one-pot method was applied to synthesise 1-methyl-4-oxazolinylpyrazole and its isomer, 2-methyl-3-oxazolinylpyrazole, with yields of 47% and 94% yields respectively (*Scheme 51*). The cyclisation step using this method is more efficient than in the Appel methodology; a bromide is already in place as a leaving group, as opposed to having to convert the alcohol to the halide in a subsequent step.



Scheme 51 *– the synthesis of oxazolinyl pyrazoles.*

Upon treating the pyrazole substrates with the standard CH amidation conditions optimised by Maiden, complex mixtures and starting materials were returned, and the amidated products were not observed (*Table 1, entries 1 & 7*). Increasing the temperatures and catalyst loading also failed to generate the desired products (*Scheme 52, Table 1, entries 2-3 & 8-9*).



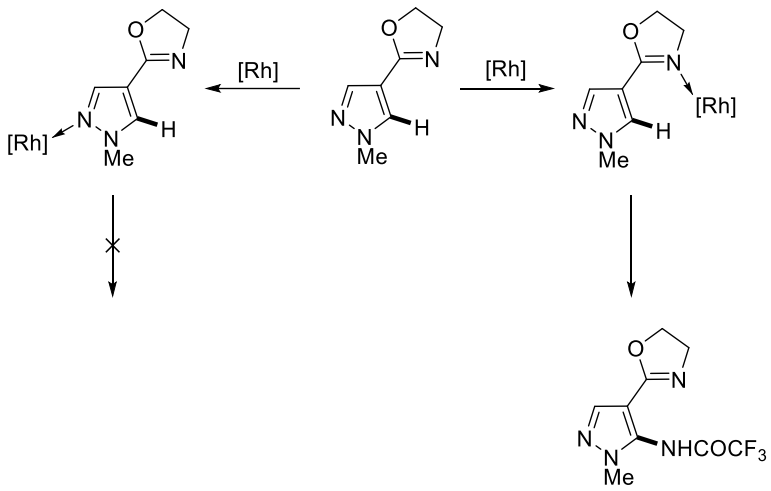
Scheme 52 *– The C-H amidation reactions of pyrazoles.*

Table 1 – the optimisation of pyrazole C-H amidations.

Entry	Substrate	Solvent	*t* / h	*T* / °C	Catalyst Loading /mol% (x/y)*	Yield /%
1*	***2d***	DCM	16	40	2.5/10	0
2	***2d***	DCM	16	40	2.5/10	0
3	***2d***	DCM	16	40	5/20	0
4	***2d***	4:1 DCE/CD_3OD	16	80	2.5/10	0
5	***2d***	DCE	24	100	2.5/10	5
6	***2d***	DCE	24	100	5/10	5
7*	***2e***	DCM	16	40	2.5/10	0
8	***2e***	DCM	16	40	5/20	0
9	***2e***	DCM	16	40	12.5/50	0
10	***2e***	4:1 DCE/CD_3OD	16	80	2.5/20	5
11	***2e***	DCE	24	100	5/10	0

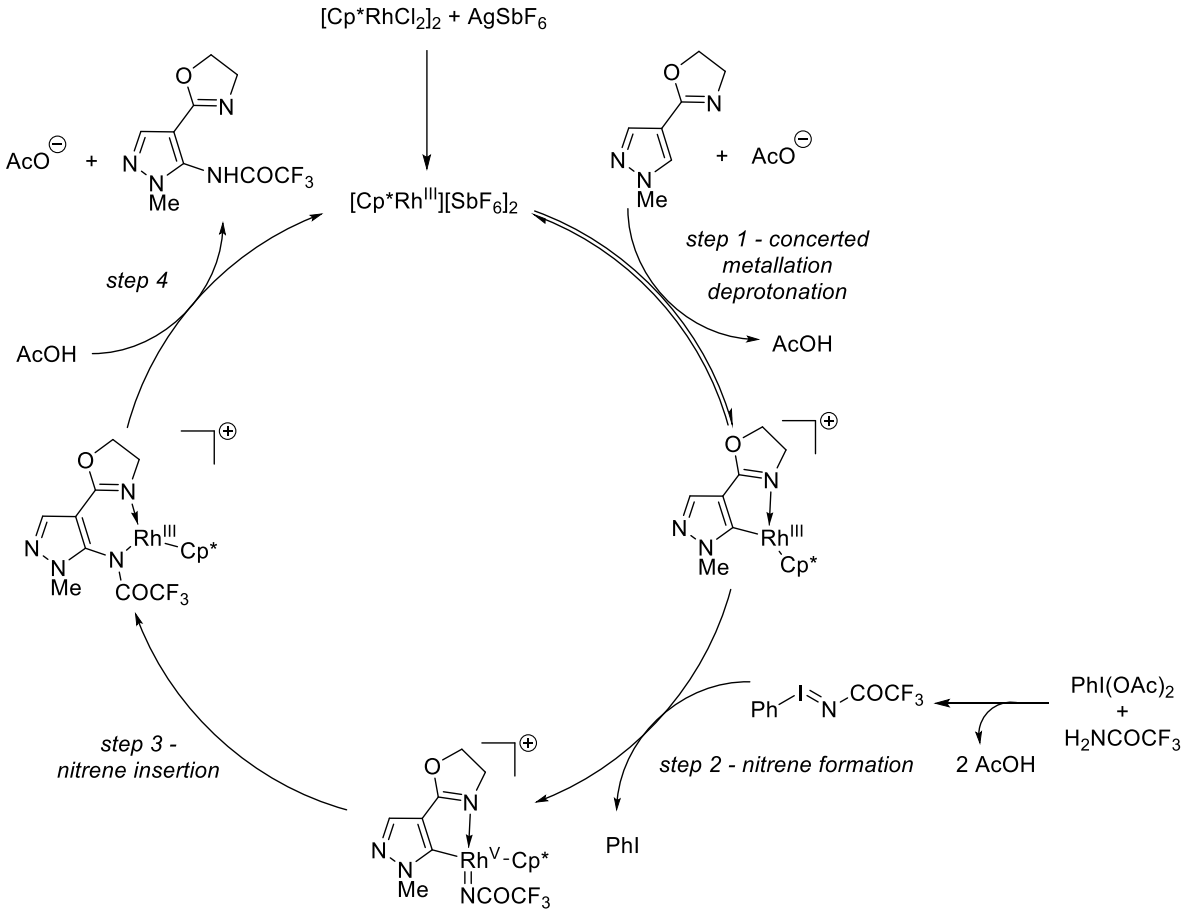
**Reaction performed in round-bottom flask with reflux apparatus.*

It is possible that the pyrazole nitrogen was coordinating to rhodium instead of the oxazoline nitrogen, thereby preventing the C-H activation necessary to insert the amide (*Scheme 53*).



Scheme 53 *– The coordination modes of oxazolinyl pyrazoles to rhodium.*

The reactions were repeated in a mixture of deuterated protic solvent (*Table 1, entries 4 & 10*) and DCE – to avoid the need for sealed reactions. If the rhodium is inserting into the C-H bond (*Scheme 54, step 1*), the excess of deuterated protic solvent will result in deuterium incorporation into any recovered starting material.

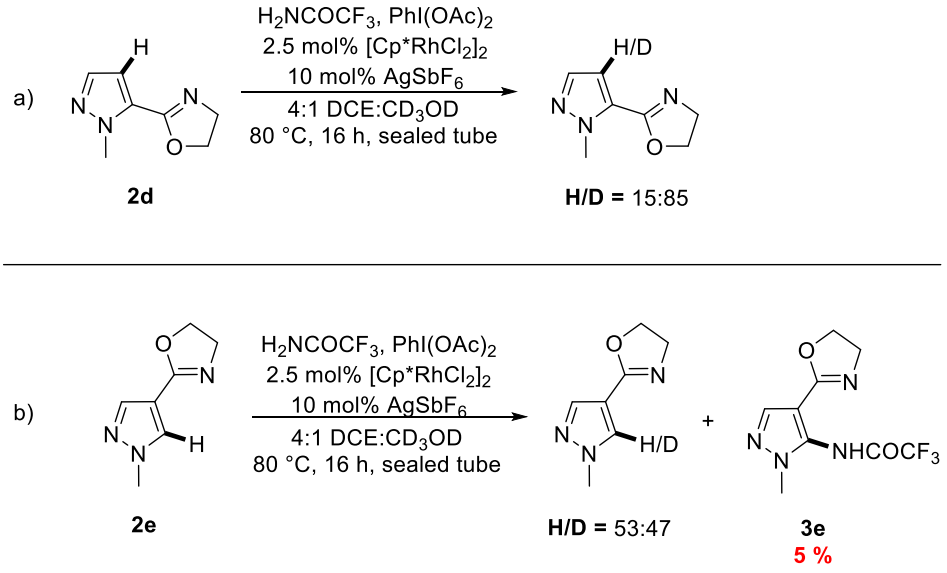


Scheme 54*- Rhodium-catalysed C-H amidation reaction mechanism.*

If deuterium was being incorporated in an acceptable percentage, but no product was formed, then it is likely that the problematic step is later in the catalytic cycle. This could be the formation of the nitrene or insertion into the carbon-rhodium bond (*Scheme 54, steps 2 & 3*), and could be attributed to a poor reactivity of one of the organorhodium complexes or the slow reaction rate of one of these steps. The imidoiodinane adduct could be decomposing before it is able to react with the organorhodium complex, although this is the most unlikely scenario, as this class of adduct is well documented and known to be stable.

In the event, **2d** returned starting material that was 85% deuterated (*Scheme 55a*), and **2e** returned 47% deuterated starting material (*Scheme 55b*) which co-eluted with some product. This suggests that the rhodium insertion step is occurring, although it is slower for **2e** than it is for **2d**. It can therefore be deduced that in this case, nitrene formation or insertion is problematic, with the latter being more likely. Nonetheless, the trace amount of **3e** observed suggests that nitrene formation/insertion is viable in the case of **2e**.

The fact that only a trace of product was seen when increasing the equivalents of the imidoiodinane, the catalyst and increasing the temperature to up to 100 °C suggests that this reaction is not going to suddenly proceed at high yield with the methods and equipment we have access to.

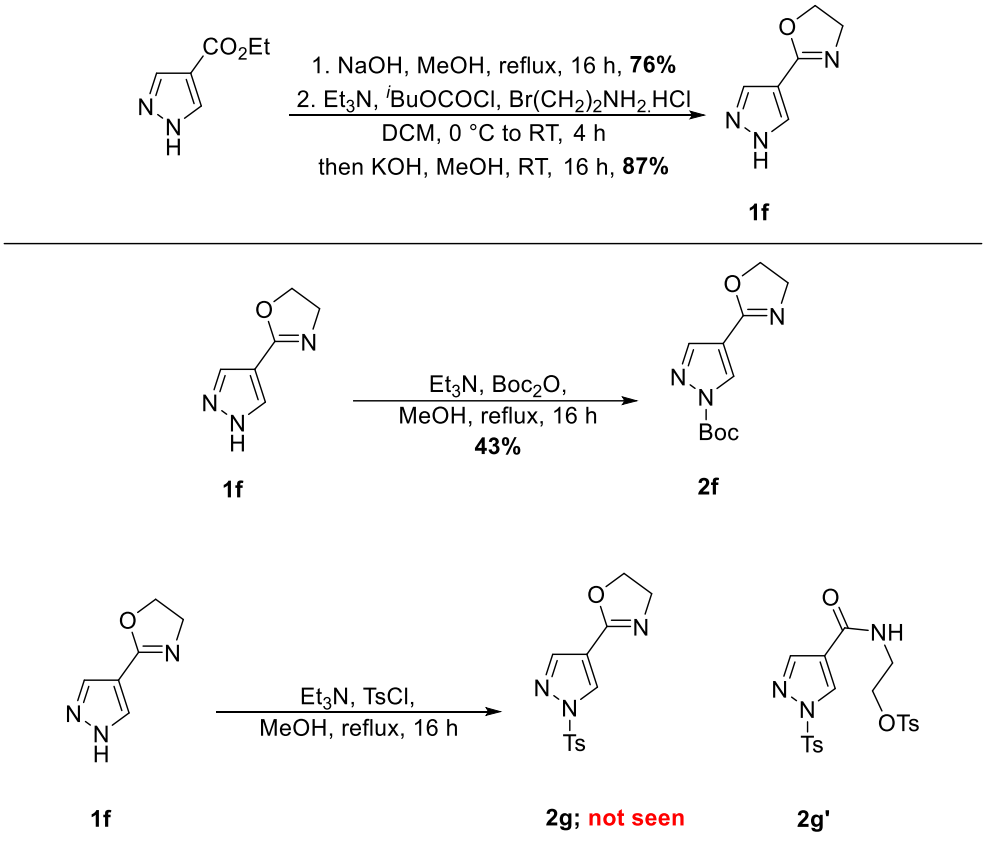


Scheme 55 *– The hydrogen-deuterium exchange in C-H amidation reactions of oxazolinyl pyrazoles.*

1.6.4.1 Electron-deficient Pyrazoles

Previous results on the pyrazole substrates suggest that the nitrene insertion step is not occurring, and this is most likely due to their inherently electron-rich properties. It may be possible to overcome this issue by introducing an electron-withdrawing group to counteract this property. Obviously, the easiest way to introduce such a group to a pyrazole is *via* *N*-substitution, and a removable protecting group would be most desirable from a general method point of view.

Therefore, we decided to synthesise and test *N*-Boc and *N*-Ts pyrazoles in our reaction conditions. Unfortunately, accessing the *N*-Ts pyrazole substrate proved difficult, and the yield of the *N*-Boc substrate left much to be desired (*Scheme 56*).

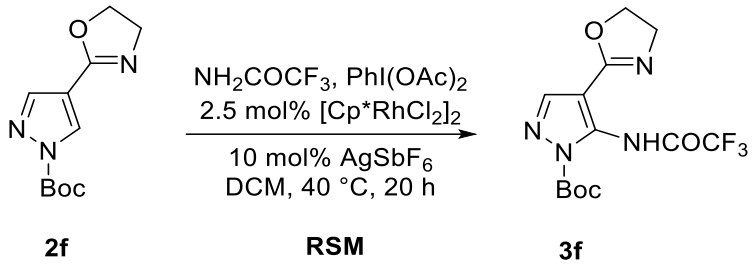


Scheme 56 *– The synthesis of* N*-EWG pyrazoles.*

It was hoped that the addition of TsCl to **1f** would produce **2g**, however a product consistent with ditosylation was produced as part of a mixture of unknowns. **2g'** has

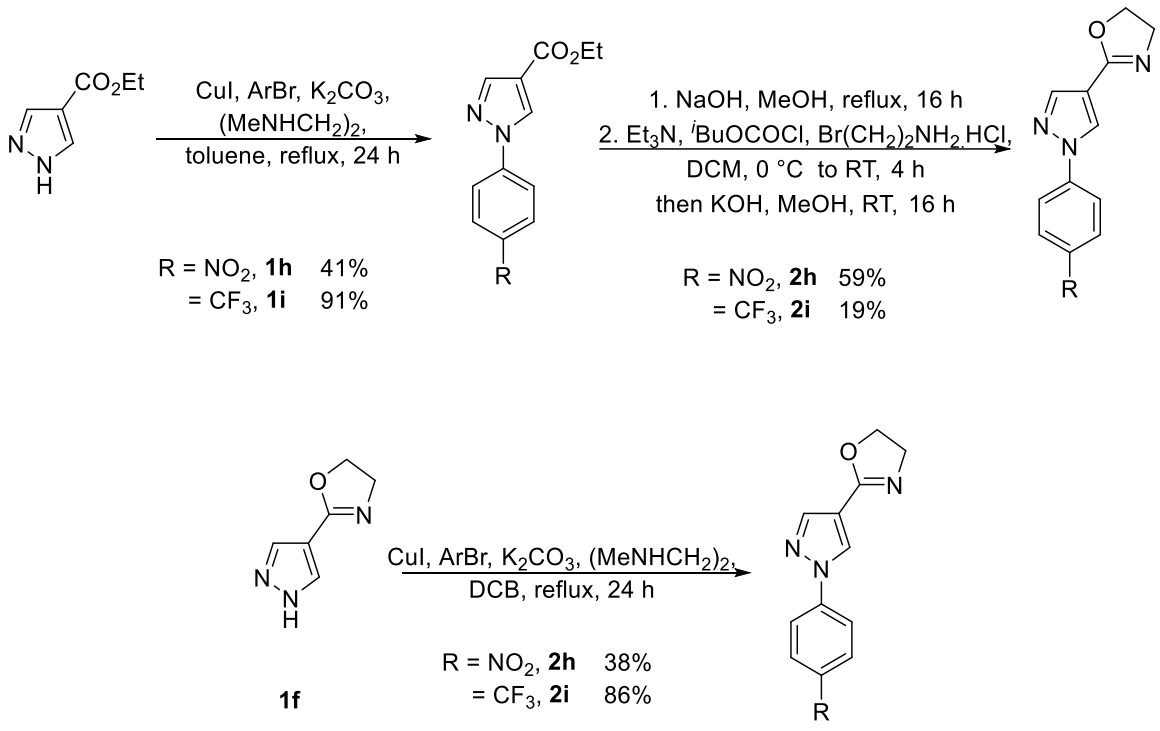
been postulated as the most likely structure of this by-product, whereby the reaction conditions caused a ring-opening of the oxazoline, although the mechanism is unclear.

Upon subjecting the *N*-Boc pyrazole to the C-H amidation conditions, only starting material was returned, suggesting that either this group is not compatible with the reaction conditions, or that it does not affect the electronic properties of the pyrazole ring enough (*Scheme 57*).



Scheme 57 *– C-H amidation of N-Boc oxazolinyl pyrazole* ***2f****.*

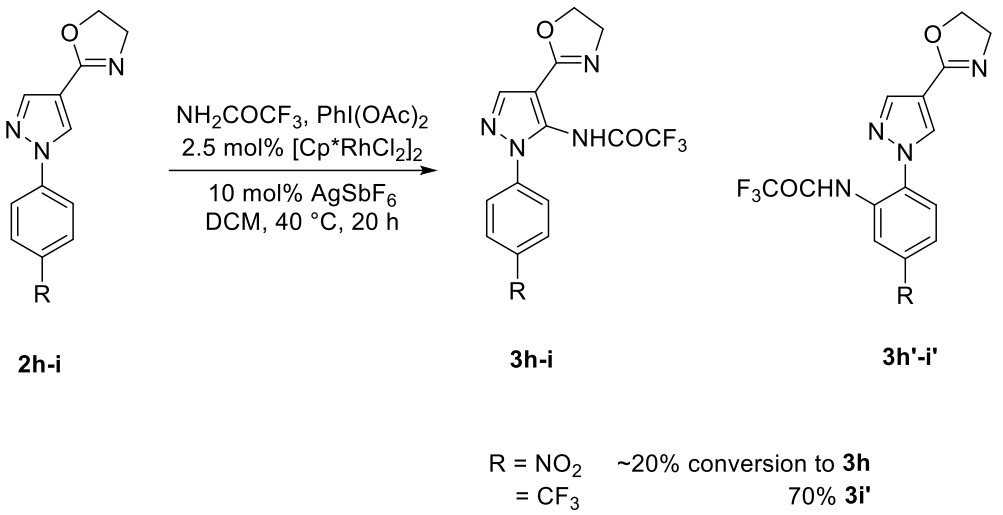
Our next thought was to substitute electron-deficient aryl groups onto the nitrogen of the pyrazole in the hopes that these might provide more fruitful results:



Scheme 58 *– synthesis of electron-deficient N-aryl oxazolinyl pyrazoles.*

The synthesis of these pyrazole substrates was straightforward (*Scheme 58*), using the pyrazole ester or oxazoline (**1f**) or as a common precursor and using copper iodide and aryl bromides. Comparable yields for both procedures were achieved for **2h**, however it was found that **2i** had a significantly better overall yield when working from **1f**.

Subjecting these substrates to the C-H amidation conditions gave some interesting results, however they did not give us hope for the future of this project.



Scheme 59 *– C-H amidation of N-aryl oxazolinyl pyrazoles.*

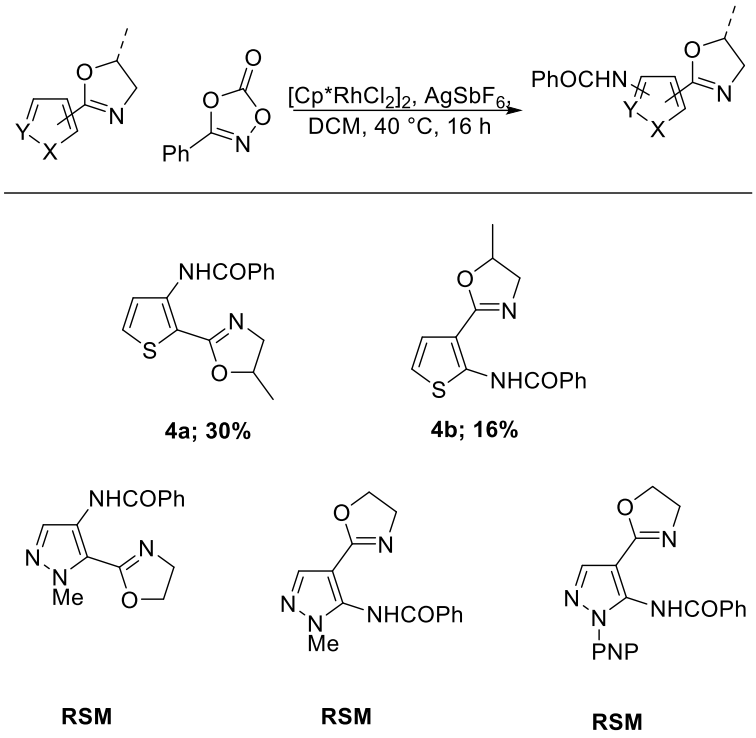
While **2h** gave some of the desired product at a low conversion (*Scheme 59*), this could not be isolated, and nor could the reaction be optimised to proceed at a higher conversion by increasing the temperature, catalyst loading, or equivalents of amidating agent. The conversion was determined by integration of the 1H-NMR spectrum, where the C-H peak that is amidated diminishes while other peaks maintain their integration ratio.

Unfortunately, the less electron-withdrawing *p*-CF_3 substrate, **2i**, provided only the product of C-H amidation on the aryl ring, which is consistent with previous examples in the literature where pyrazoles can be used as an effective directing group for C-H activation of aryl rings.

1.6.4.2 Alternative Amide Sources and Directing Groups

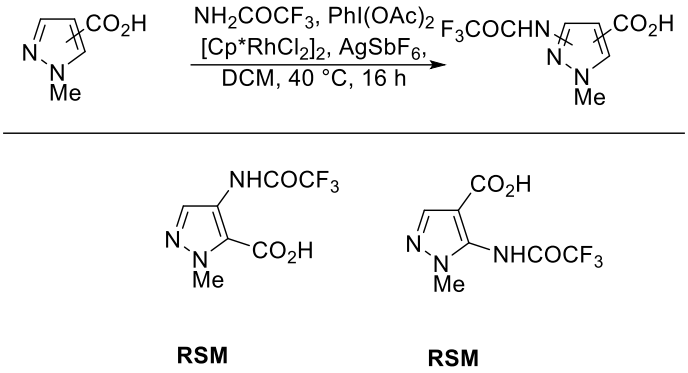
In order to test whether this procedure was the best method for these substrates, we decided to use alternative amide sources and vary the directing group based on those used on arenes in the literature.

Chang's dioxazolone was synthesised *via* the literature method with a comparable yield of 80%.[23] However, it was found that none of our pyrazoles were susceptible to this amidating agent (*Scheme 60*). Trials of this amidating agent on our thiophene substrates gave lower yields than we had achieved with our methodology. Therefore, it can be said that the combination of trifluoroacetamide/$PhI(OAc)_2$ is a more powerful amidating reagent than the widely-used dioxazolones.



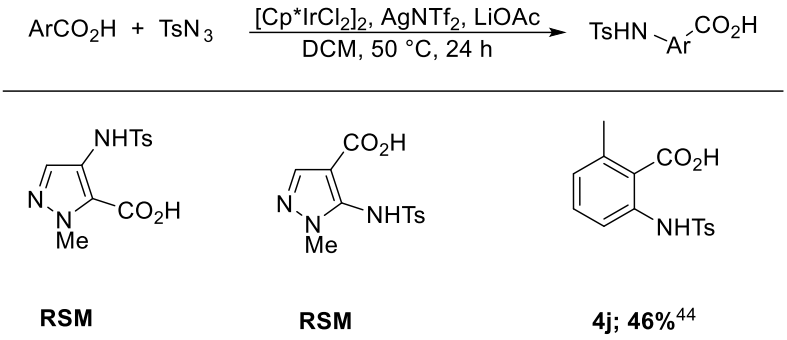
Scheme 60 *– C-H amidation of azoles using Chang's dioxazolone amidating reagent.*

The use of carboxylic acids as a directing group (the starting material for our *N*-Me pyrazole oxazolines) also proved ineffective in conjunction with our reaction conditions, with starting material returned (*Scheme 61*).

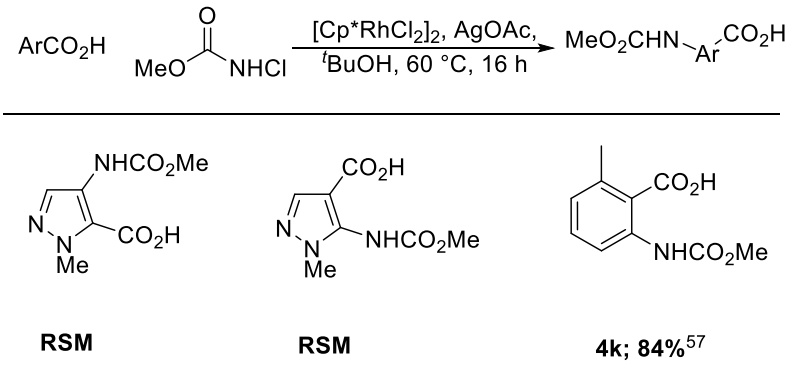


Scheme 61 *– C-H amidation of N-Me pyrazole carboxylic acids.*

Alternative conditions in the literature using TsN_3 (*Scheme 62*)[44] or methyl *N*-chlorocarbamate (*Scheme 63*)[57] were used on the *N*-Me pyrazole carboxylic acids, again returning starting material.



Scheme 62 *– C-H amidation of (hetero)aryl carboxylic acids using Tosyl azide.*[44]

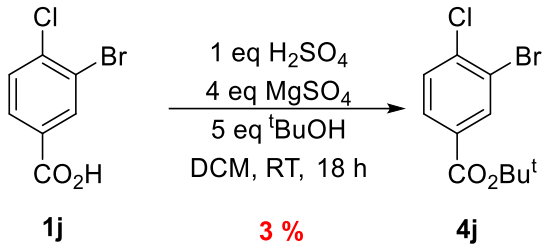


Scheme 63 *– C-H amidation of (hetero)aryl carboxylic acids using methyl N-chlorocarbamate.*[57]

An aryl substrate from these papers was also subjected to these conditions as a control, giving comparable yields to those in the literature. Again, this shows that the pyrazole moiety is the issue with C-H amidation reactions.

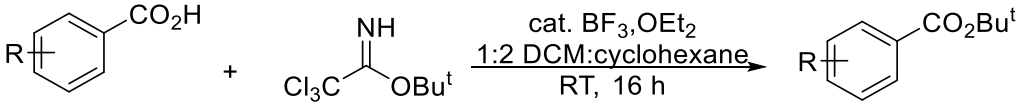
1.6.5 1,4-Substituted Arenes

Finally, we turned our attention to the functionalised arene substrates. The synthesis route required the protection of the carboxylic acid as an ester. We envisaged that ^{t}butyl 3-bromo-4-chlorobenzoate (**4j**) would be readily accessible from 3-bromo-4-chlorobenzoic acid (**1j**), however this step proved to be rather challenging. A common method of synthesising benzoic ^{t}Bu esters using concentrated sulfuric acid and magnesium sulfate proved unfruitful, [58] giving only a 3% yield (*Scheme 64*).



Scheme 64 *– a common method for the synthesis of benzoic ^{t}Bu esters.[58]*

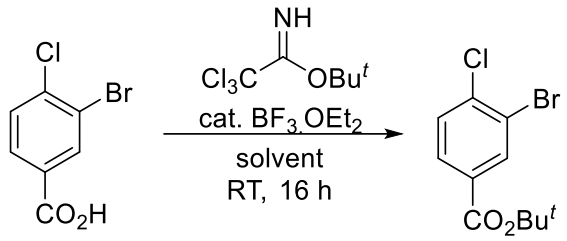
Jackson and co-workers[59] used a ^{t}Bu 2,2,2-trichloroacetimidate to synthesise aromatic ^{t}Bu esters and ethers from their corresponding carboxylic acids and alcohols (*Scheme 65*). A sub-stoichiometric amount of $BF_3.OEt_2$ was added to provide the catalytic amount of HF necessary to activate the acetimidate. Application of this method to **1j** showed promising results, giving a 30% yield, with room for improvement upon optimisation.



Scheme 65 *– the literature method described by Jackson and co-wokers.[59]*

The equivalents of acetimidate, the solvent mediums and their stoichiometries were varied in order to optimise this step (*Scheme 66, Table 2*). It was found that cyclohexane generally provided an improvement (*Table 2, entries 1 and 2*), albeit the overall yields were still rather low. It was speculated that poor yields when using DCM were likely due to the extremely low solubility of the carboxylic acid in the solvent. Indeed, a 1:1 mixture of DCM and cyclohexane and 2 eq. of acetimidate (*Table 2, entry 3*) proved more successful, achieving a moderate yield of 53%. However, it was noticeable that **1j** still did not fully dissolve under these conditions. Subsequently, ^{t}BuOH was chosen as the polar solvent (*Table 2, entry 4*), but it was found that this failed to promote dissolution of the

carboxylic acid and only a 22% yield of product was obtained. By changing the solvent system to 1:2 acetonitrile:cyclohexane, the reaction mixture became much less cloudy upon the addition of $BF_3.OEt_2$, with the majority of the carboxylic acid dissolving. Optimisation of the number of equivalents of acetimidate (*Table 2, entries 5-8*) showed that 1.5 equivalents of this reagent was optimal, with a yield of 61% (*Table 2, entry 6*).



1j **4j**

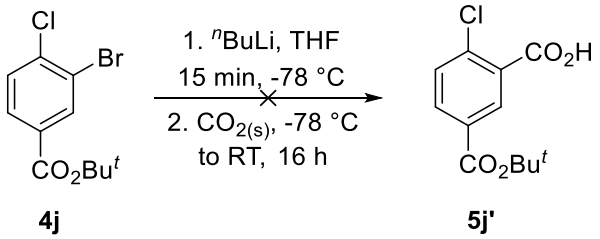
Scheme 66 *– ^{t}Butyl esterification of 3-bromo-4-chlorobenzoic acid.*

Table 2 – Optimisation of ^{t}butyl esterification.

Entry	Eq. Acetimidate	Solvent	Yield / %
1	1	1:2 DCM:cyclohexane	30
2	2	DCM	28
3	2	1:1 DCM:cyclohexane	53
4	2	1:2 tBuOH:cyclohexane	22
5	1	1:2 MeCN:cyclohexane	16
6	**1.5**	**1:2 MeCN:cyclohexane**	**61**
7	2	1:2 MeCN:cyclohexane	16
8	3	1:2 MeCN:cyclohexane	9

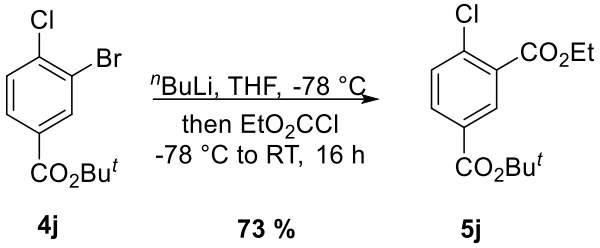
The above reactions were undertaken in the winter months when the room temperature was below 20 °C. Repeats of this procedure by a Masters' student in the summer months gave drastically reduced yields when performed at room temperature (≈25 °C). In order to achieve comparable yields, the reaction mixture was cooled to -20 °C for 8 hours before leaving the mixture to warm to room temperature overnight. These unusual results are due to the formation of a ^{t}Bu cation in solution, which at increased temperatures can undergo elimination to irreversibly form gaseous isobutylene.

Once the acid had been protected as a ^{t}Bu ester, the conversion of the bromide to the oxazoline directing group could begin. The literature route for the conversion of the bromide to the carboxylic acid *via* lithium-halogen exchange and use of dry ice as the electrophile proved to be unsuccessful, with only the debrominated arene seen in the crude mixture (*Scheme 67*).[60]



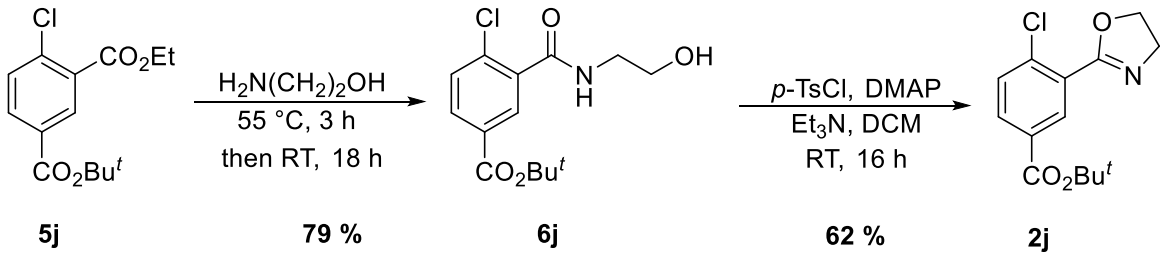
Scheme 67 *– Synthesising carboxylic acids from aryl bromides.*[60]

From Maiden's work, it was known that the conversion of an ester to the oxazoline is much easier than from the carboxylic acid. Therefore, ethyl chloroformate could be used to obtain the ethyl ester. Addition of the chloroformate immediately after ^{n}BuLi limited the potential formation of benzyne intermediates (due to *o*-elimination), and **5j** was obtained in 73% yield (*Scheme 68*).



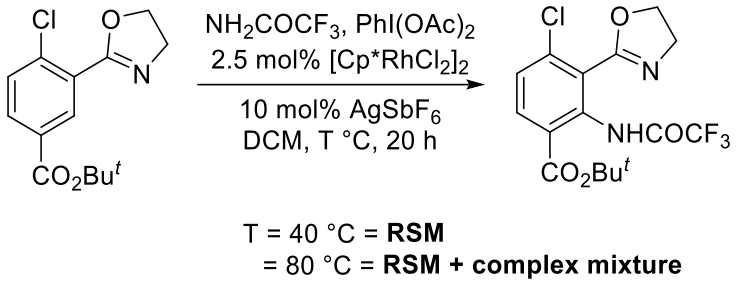
Scheme 68 *– Converting the bromide to the ethyl ester.*

This ester could then be converted easily to the oxazoline *via* a conversion to the amide and subsequent tosylation of the alcohol and cyclisation with base (*Scheme 69*). Amide **6j** was obtained in 79% yield by stirring the ester in neat ethanolamine. The cyclisation to the oxazoline *via* tosylation was successful, giving **2j** in 62% yield in just one step.



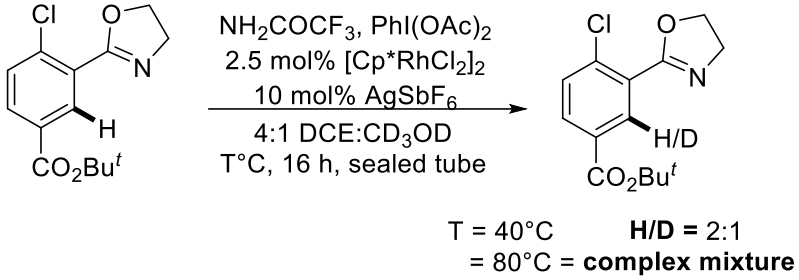
Scheme 69 *– Synthesising the oxazoline from the ethyl ester.*

Unfortunately, subjecting this substrate to the C-H amidation conditions returned only starting material (*Scheme 70*). This was not completely unexpected owing to the steric crowding at the C-H amidation site – in previous work, only a fluorine adjacent to the C-H amidation site was tolerated, which greatly contrasts in size to a ^{t}Bu ester. Increasing the temperature of the reaction lead to a complex mixture, of which a small amount of starting material was detected by LCMS, but no desired product was observed.



Scheme 70 *– C-H amidation of 2-oxazolinyl-1,4-substituted arenes.*

A deuterium labelling study on this substrate was undertaken to determine whether C-H activation was occurring in the case of this substrate.



Scheme 71 *– deuterium labelling study of 2-oxazolinyl-1,4-substituted arene C-H amidation.*

The deuterium labelling study of this substrate shows that C-H activation is occurring (*Scheme 71*), while again it is the nitrene insertion step that is proving problematic. It is likely that the combination of bulky catalyst, nitrene and sterically hindered substrate limits the substrate's ability to undergo C-H amidation.

1.7 Conclusions

Unfortunately, the C-H amidation reaction of azoles is an area of research that shows little promise with methodology currently available due to their inherent electron-rich properties. Currently only thiophenyl substrates are able to undergo C-H amidation *via* this procedure, which is in-line with other results in the literature, although results using this methodology give consistently better yields than those using other available literature methods

Commercially available thiophene aldehydes were successfully converted to thiophene oxazolines using a green ammonia-based method with excellent yields. These substrates were then successfully subjected to Maiden's C-H amidation conditions to give trifluoroacetamide products in good yields. Synthesis of *N*-methyl imidazole oxazoline amides using the aforementioned method proved unsuitable, and attempts at accessing the oxazoline from the carboxylic acid were also unsuccessful.

N-Methyl pyrazole oxazolines were synthesised from their commercially available carboxylic acids with moderate to good yields. Subjecting these substrates to Maiden's C-H amidation conditions proved unsuccessful, although upon increasing the temperature to 100 °C, trace amounts of the amide products were observed. Deuterium studies suggest C-H activation is occurring; however nitrene formation or insertion is problematic. It is likely that the high electron density of the ring is to blame, and therefore a variety of electron-withdrawing groups were incorporated. Boc-protection also afforded no product, while *p*-nitrophenyl gave some, albeit low, conversion. Unfortunately, this result could not be improved upon, and the use of other electron-withdrawing aromatics gave C-H amidation on the benzene ring. This was not that surprising as pyrazoles are known directing groups for C-H activation.

Concluding studies on Maiden's arene substrates were undertaken. The oxazoline substrate was successfully synthesised from the commercially available 3-chloro-4-bromobenzoic acid. C-H amidation of this substrate was unfortunately unsuccessful, likely due to the steric hindrance surrounding the C-H amidation site.

Chapter II

Palladium-Catalysed Allylations towards Peptidomimetic δ-Lactam Scaffolds

2.1 Abstract

A variety of δ-Lactams derived from acylated amino acids have been synthesised in good yield from azlactones via a two-step one-pot allylation/cyclisation. A cyclic carbamate previously developed by the group was used as the source of the π-allyl palladium, incorporating a pendant nitrogen group, which had previously not been documented in the literature. Attempts at accessing these lactams enantioselectively using chiral phosphoramidite ligands gave some promising but mixed results, and it is possible that a different class of chiral ligands may perform better.

Late-stage functionalisations of the lactams allowed us to access a variety of new functional groups, and the endo- and exocyclic amides were able to be selectively targeted by utilising both the difference in steric and electronic properties.

A range of peptidomimetic lactams were synthesised, using azlactones derived from di- and tri-peptides. The Cbz-protected dipeptide proved excessively difficult to synthesise, even using methods from the literature, however swapping to the Boc-protected dipeptide gave very good results. It was hoped that Alloc-protection of these lactams would allow us to access the Ring Closing Metathesis products, however the exocyclic alkene proved too unreactive and only the dimer at the allyl site was seen.

2.2 Introduction

2.2.1 δ-Lactams

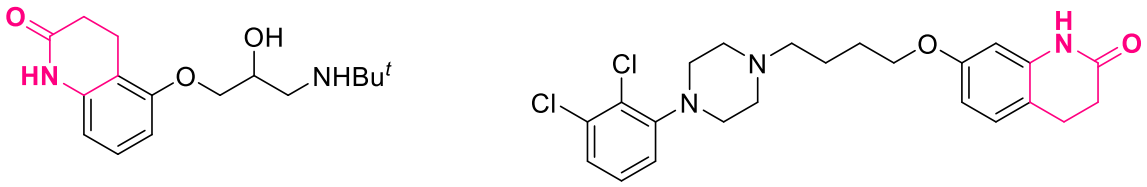
Approximately 60% of FDA-approved drugs contain a nitrogen heterocycle.[61] The δ-lactam ring is found in many biologically active molecules, including natural products and pharmaceuticals (*Figures 7 and 8*).

Brevianamide A
Secondary Metablotile
of *Penicillium*

Piperlongumine
Traditional Medicine

Figure 7 *– Natural products containing δ-lactams.*

Brevianamides are a natural product produced as a secondary metabolite by fungi of the genera *Penicillium* and *Aspergillus*.[62] While they have been shown to have some insecticidal properties, they have been found to induce cytotoxicity in mammalian pulmonary cells,[63] meaning that they would not be suitable as pesticides for many crops. Piperlongumine (also known also piplartine) is an alkaloid found in the *Piper longum* plant.[64] Long peppers have been used in Asian traditional medicine for millennia, and piperlongumine has been shown to have antitumour activity, with ongoing studies into its possible applications.



Carteolol
Beta Blocker

Aripiprazole
Antipsychotic

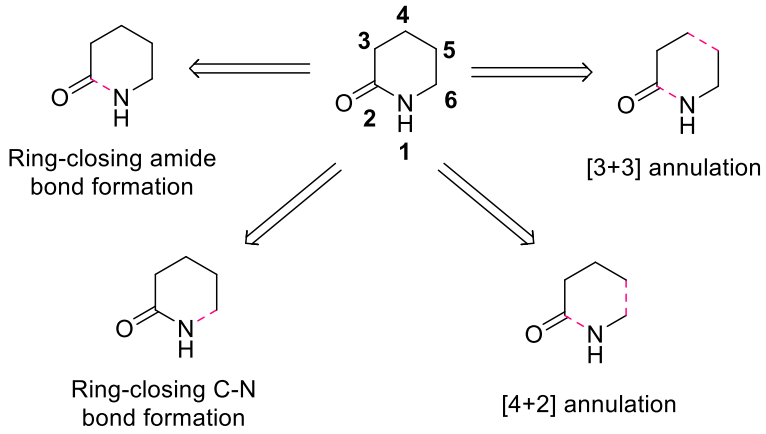
Figure 8 *– FDA-approved pharmaceuticals containing δ-lactam rings*

There are several FDA-approved therapeutics containing δ-lactams; Carteolol (*Ocupress*, among other brand names) is a beta blocker that is administered as an eye drop to control the increased pressure within the eye as a result of glaucoma. Aripiprazole is an

antipsychotic, sold under the brand name *Abilify*, used in the treatment of schizophrenia and bipolar disorder.

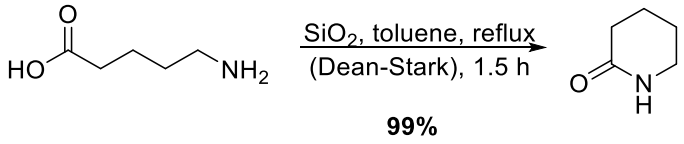
2.2.1.1 Synthetic routes

There are a number of routes towards δ-lactams that can be retrosynthetically identified (*Scheme 72*).



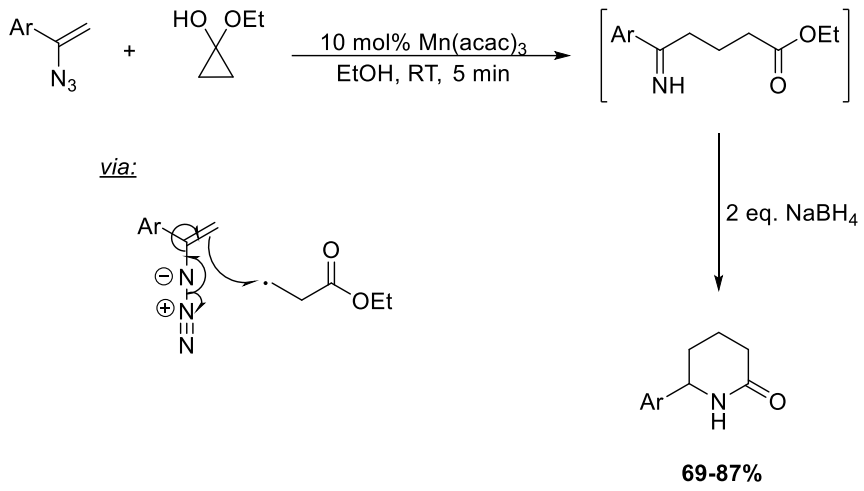
Scheme 72 *– Retrosynthetic routes towards δ-lactams.*

Traditionally, valerolactam and its simple derivatives are made by dehydrative cyclisation under Lewis acidic conditions to form the amide bond from 5-aminovaleric acid (*Scheme 73*).[65]



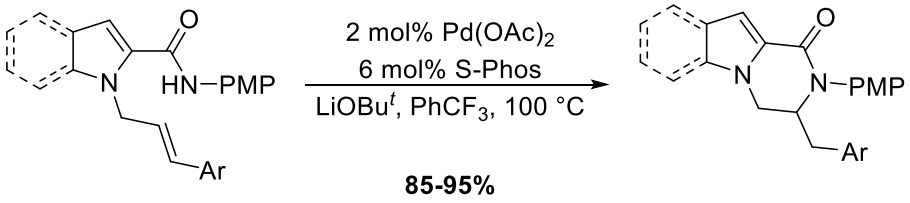
Scheme 73 *– Synthesis of Valerolactam.*[65]

While this route is highly effective, it only gives access to simple valerolactams, and therefore more complex lactams have been synthesised by more exotic routes. After synthesising aryl-subsitituted pyridines *via* a Mn(III)-mediated [3+3] annulation, Chiba found that use of an ethoxy group on the cyclopropane substrate gave rise to the keto ester after an aqueous work up of the imine (*Scheme 74*).[66] Treatment of the crude imine with $NaBH_4$ gave access to a variety of 2-aryl lactams in good yields.



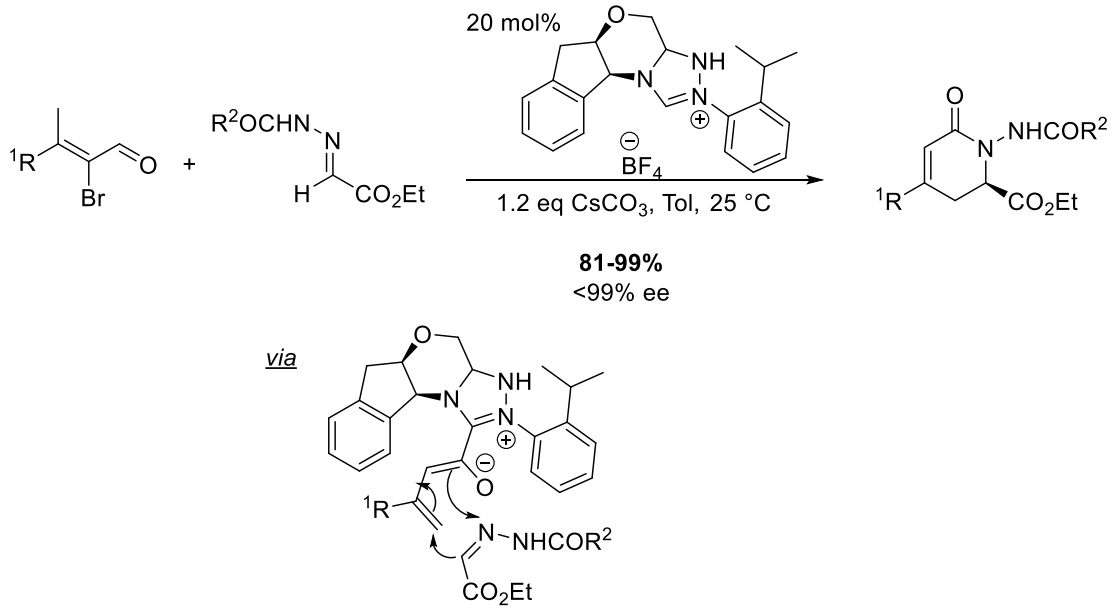
Scheme 74 *– synthesis of 6-aryl-δ-lactams via the δ-imino ester.*

Wolfe was able to synthesis lactams from substituted pyrroles and indoles *via* a palladium cross-coupling (*Scheme 75*).[67] They were also able to remove the PMP protecting group to afford the unprotected amides in high yields.



Scheme 75 *– Pd-catalysed carboamination to form δ-lactams.*[67]

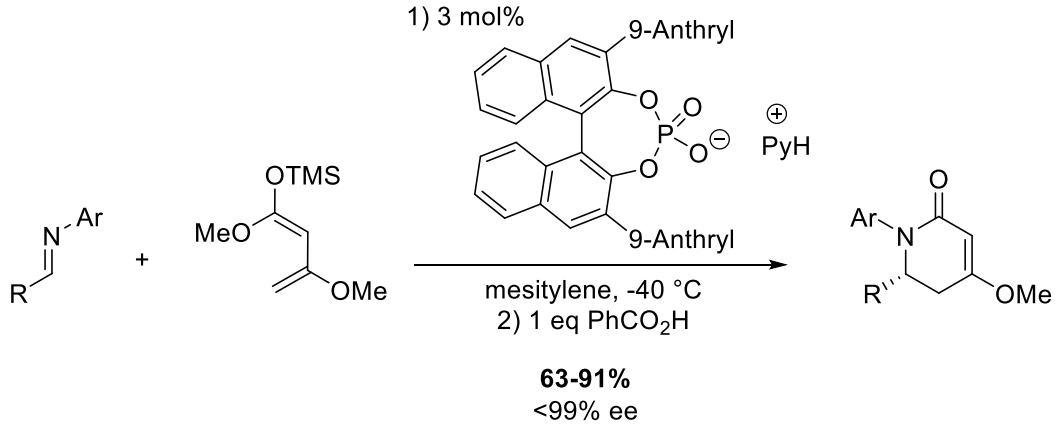
Another route to these scaffolds is *via* [4+2] annulations. A paper by Gao *et al.* described a NHC-catalysed route to lactams with high enantioselectivities (*Scheme 76*).[68]



Scheme 76 *– Enantioselective NHC-catalysed [4+2] cycloaddition towards lactams.*[68]

Condensation of the catalyst with the aldehyde followed by loss of HBr gives the extended enolate with which the cycloaddition occurs. Both aryl and methyl groups were tolerated on the α,β-unsaturated aldehyde moiety, however incorporation of an ^{i}Pr group only gave trace amounts of the lactam. Routes using organocatalysis have garnered significant attention in recent years due to the high cost and often high toxicity of transition metal catalysts.[69]

Aza-Diels-Alder reactions also fall under the [4+2] annulation category. Diels-Alder reactions to form heterocycles have been well developed, and Akiyama and co-workers outline a method to make lactams enantioselectively (*Scheme 77*).[70]



Scheme 77 *– Enantioselective aza-Diels-Alder using a chiral Brønsted acid organocatalyst.*[70]

Akiyama proposes that the extremely bulky organocatalyst coordinates *via* H-bonding with the imine to induce the high enantioselectivities observed in the products. In order for this coordination to occur, a H-bond donor (such as a hydroxy group) is necessary to be in the *o*-position of the aromatic ring, somewhat reducing the generality of this procedure.

2.2.2 Freidinger Lactams and Peptidomimicry

The ability to mimic β-turns to produce therapeutics is a very interesting and lucrative field, with many companies investing in peptidomimetic therapeutics. Turns are often seen on the outside of proteins, and therefore are likely to be involved in binding. Being able to target these structures allows new drugs to come to the market. Peptide-based therapeutics are highly desirable as they often use readily-available amino acids as

building blocks, and are less likely to have toxic side effects. An unfortunate downside of this class of molecule is that they can be unstable to biological conditions and easily metabolised. Williams *et al.* were able to synthesise a mimic of an antibody β-turn by conformationally restricting a polypeptide.[71] Instead of H-bonds holding the turn in place, a fully covalent ring was introduced to reduce the flexibility of the chain (*Figure 9*).

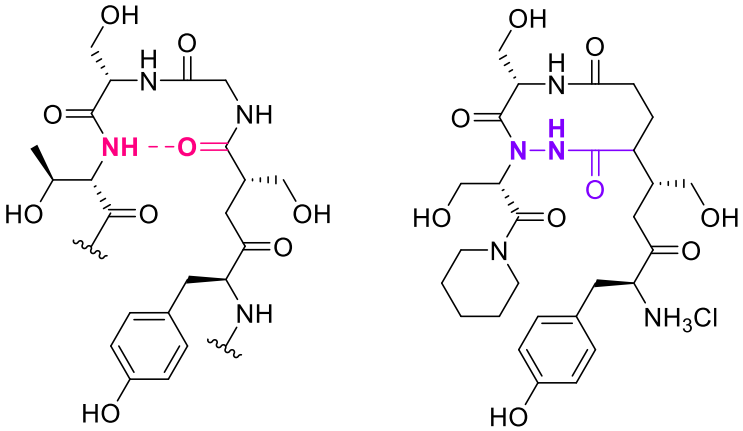


Figure 9 *– A low-molecular weight mimic of an antibody β-turn.*[71]

Freidinger lactams were developed in 1980 as a conformationally restricted peptide mimic,[72] where they can be incorporated into a peptide chain in place of a natural amino acid to create peptidomimetics (*Figure 10*).

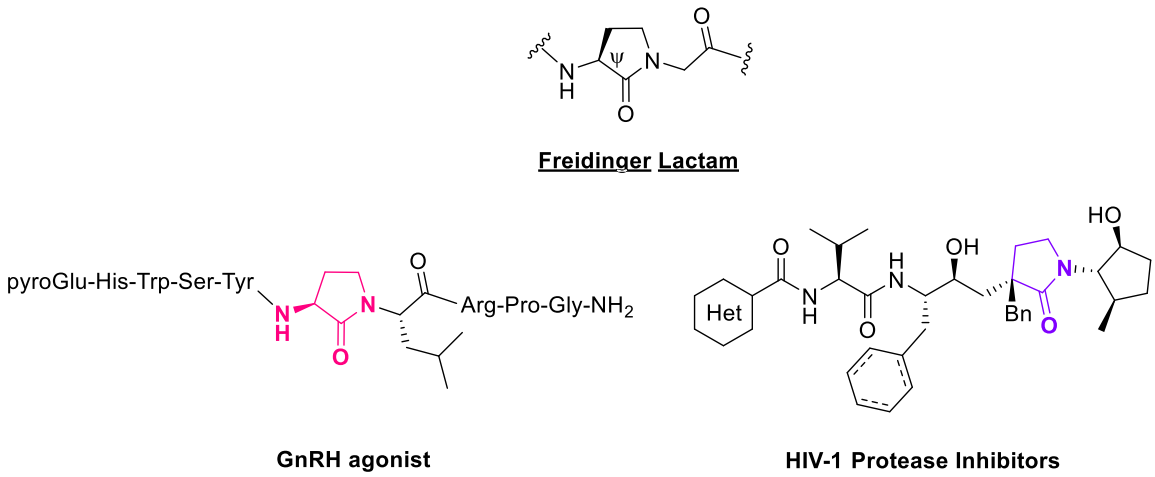


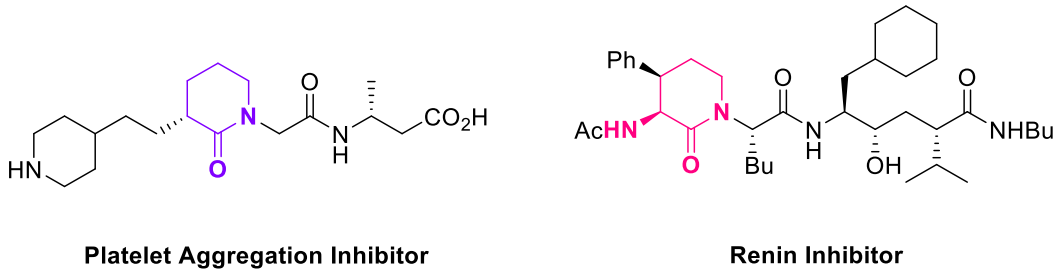
Figure 10 *– Freidinger lactams and biologically active examples of peptide mimics containing γ-lactams.*[72,73]

An agonist and β-turn mimic of Gonadotropin-releasing hormone (GnRH, *Figure 10, left*) has been developed. GnRH is a hormone which signals the release of the more well-

known Luteinising hormone (LH) and Follicle-stimulating hormone (FSH). Hungate and co-workers found that their class of structures (*Figure 10, right*) showed promising activity against HIV-1 protease.[73] In this case, the lactam is not a true Freidinger lactam, however it serves the purpose of a conformationally restricted terminal peptide that is more resistant to metabolism than a natural amino acids.

Over the years, the scope has been increased to include larger rings. It has been shown that larger rings are often more biologically active. [74] While 7+ membered rings are more active, they are harder to make, usually requiring the ring to be pre-installed then functionalised. [75]

The ease of synthesis of 6-membered lactams compared to larger rings means more biologically active molecules of this class have been documented and brought to clinical trial (*Figure 11*).



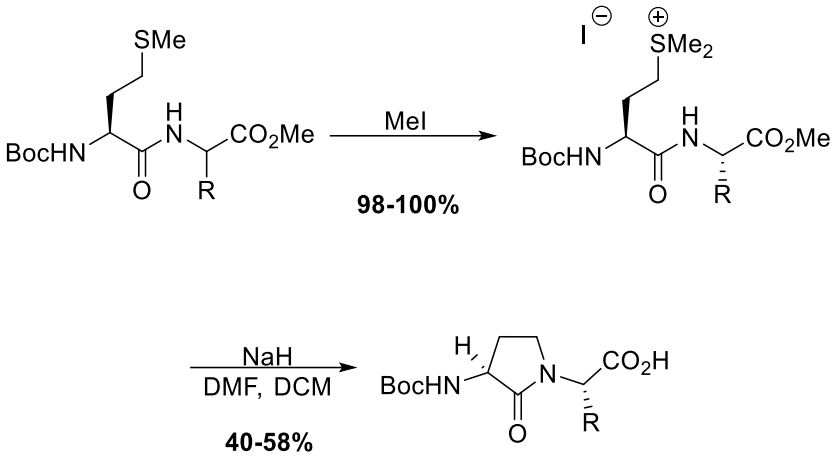
Platelet Aggregation Inhibitor **Renin Inhibitor**

Figure 11 *– Biologically active peptidomimetics containing 6-membered lactams.*[76,77]

Duggan and co-workers developed a highly potent fibrinogen receptor antagonist (*Figure 11, left*), which results in reduced platelet aggregation.[76] It was found that this compound was stable to oral administration, an impressive feat considering the highly acidic nature of the stomach which is often the downfall of many peptides. The above-right compound (*Figure 11*) was synthesised by de Laszlo in an attempt to make conformationally restricted isosteres of a known polypeptidic Renin inhibitor.[77] Whilst de Laszlo showed that this compound exhibited selective bioactivity against the target, it was 25 times less potent than the control. It was, however, less susceptible to metabolism than the control, which was one of the reasons for making these peptidomimetics.

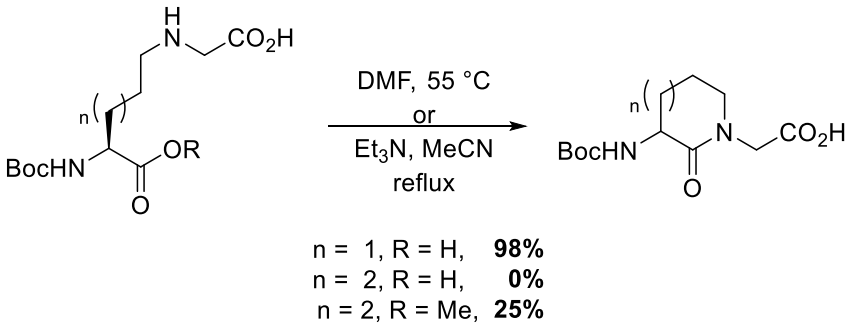
2.2.2.1 Synthetic Routes

The first examples of Freidinger lactams were synthesised by methylation of a methionine residue, which could then be substituted by the amide nitrogen from the neighbouring amino acid residue (*Scheme 78*).[78]



Scheme 78 *– Freidinger's synthesis of γ-lactams using methionine residues.*[78]

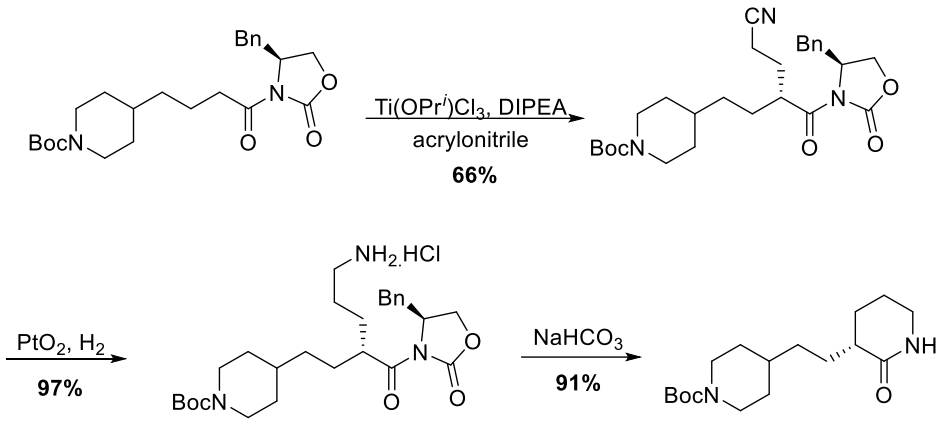
As analogues of methionine with longer alkyl chains are not available, Freidinger utilised the nucleophilic properties of ornithine and lysine to synthesise δ- and ε-lactams respectively (*Scheme 79*).[79] Yields were significantly reduced in the synthesis of the ε-lactam due to the forming of thermodynamically unfavourable 7-membered rings.



Scheme 79 *– Freidinger's synthesis of δ- and ε –lactams from ornithine and lysine residues.*[79]

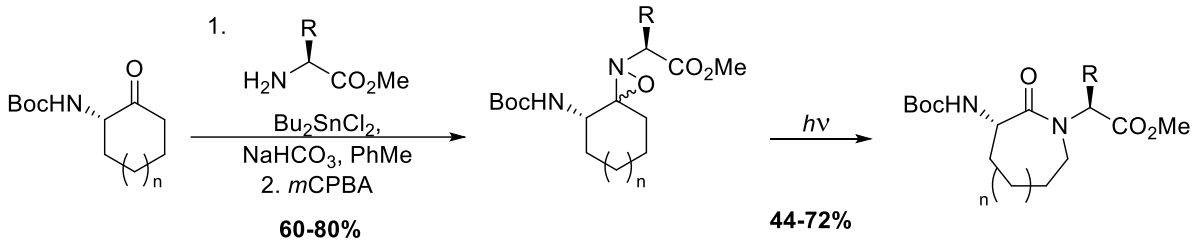
This type of cyclisation of an amine onto a carboxylic acid equivalent has continued to be the most common route to making Freidinger lactams of all sizes.

Duggan *et al.* used Evans' chiral auxiliary to alkylate in the α-position using acrylonitrile as the electrophile.[76] Reduction of the nitrile to the amine hydrochloride using PtO_2 and hydrogen gas, followed by treatment with base, gave the lactam (*Scheme 80*).



Scheme 80 *– Synthesis of Duggan's platelet aggregation inhibitor using Evans' chiral auxiliary.[76]*

Larger ring sizes have been accessed *via* expansion of smaller, more readily available α-amino cyclic ketones (*Scheme 81*).[79]



Scheme 81 *– Synthesis of ε- and ζ-lactams by oxaziridine formation and subsequent microwave-induced rearrangement.[79]*

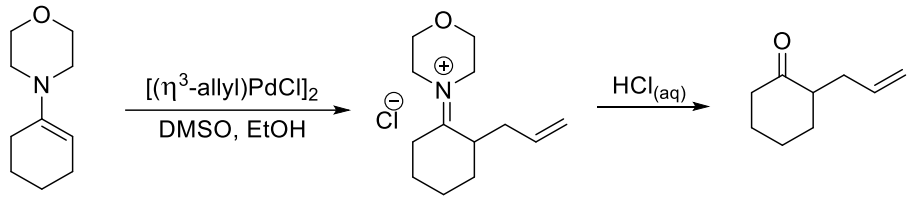
Aubé was able to synthesise usually difficult-to-access Freidinger lactams by rearrangement of a spirocyclic oxaziridine using microwave irradiation. The stereoselectivities of the oxaziridine formation were mixed, with more sterically hindered amino acids such as phenylalanine and valine achieving high dr's (>95:5) compared to the 1:1 dr observed with β-methyl aspartate.

In all of these cases, functionality on the ring has rarely been seen, with late-stage functionalisations mainly focussing on extending the peptide chains. This leaves a huge

gap in possible structural motifs that have yet to be accessed, and may require more inventive routes in their syntheses.

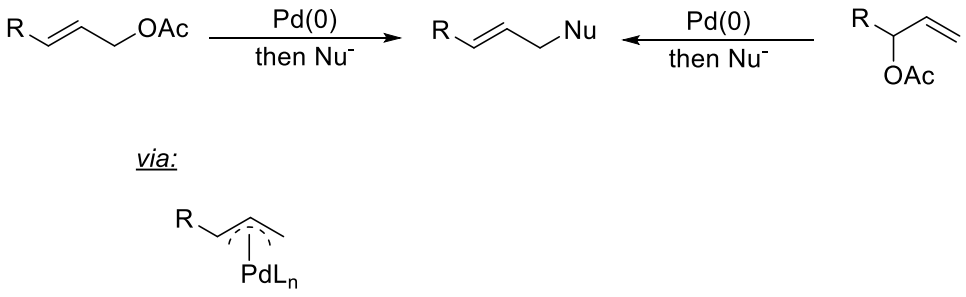
2.2.3 Tsuji-Trost Allylations

In 1965, Tsuji documented the allylation of β-diesters and enamines using π-allylpalladium chloride (*Scheme 82*).[80]



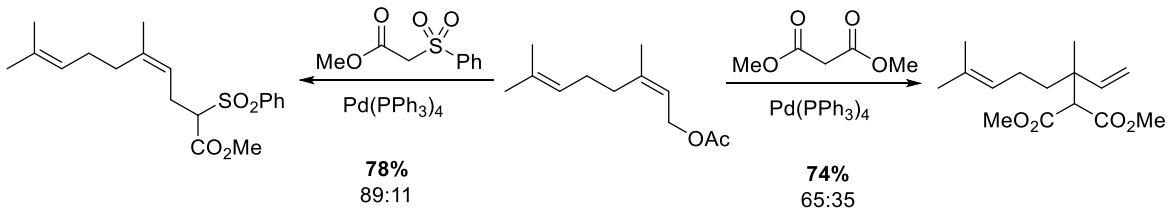
Scheme 82 *– Tsuji's allylation of 1-morpholinocyclohexene.*[80]

Subsequently, Trost continued this initial work, employing triphenylphosphine as a ligand.[81] His initial work showed that this addition caused the reactions to proceed instantaneously at room temperature, and he was able to expand the scope of the allylic groups. Use of Pd(0) in the form of palladium tetrakis allowed the reactions to become catalytic in palladium,[82] where the previous work had used stoichiometric Pd(II). The site of nucleophilic attack on the π-allylpalladium species is usually determined by the steric hindrance on the π-allylpalladium species.[83] Due to the η^3-coordination in the allylpalladium complex, the position of the leaving group has no effect on the final product (*Scheme 81*), with the regioselectivity of the nucleophilic attack determined by sterics. Generally, the reaction proceeds *via* nucleophilic attack on the least sterically hindered terminus of the π-allylpalladium (*Scheme 83*).



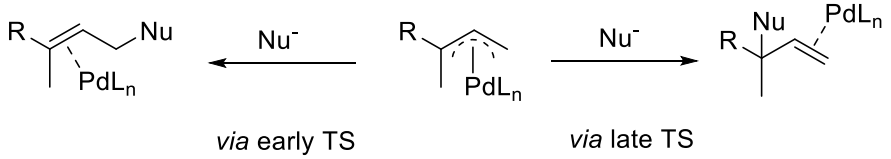
Scheme 83 *– the regioselectivity of Tsuji-Trost allylations.*

However, this is an oversimplification. Regioselectivity can also depend on the nucleophile: a bulkier nucleophile often gives a major product whereby nucleophilic attack has occurred at the less sterically hindered allyl terminus. On the other hand, less sterically bulky nucleophiles tend to provide the product from attack at the more hindered terminus (*Scheme 84*).[84]



Scheme 84 *– Nucleophile-depended differences in the regioselectivity of Tsuji-Trost allylations.*[85]

This difference in regioselectivity is explained not only by sterics, but also by the relative stability of the products and transition states (*Scheme 85*).

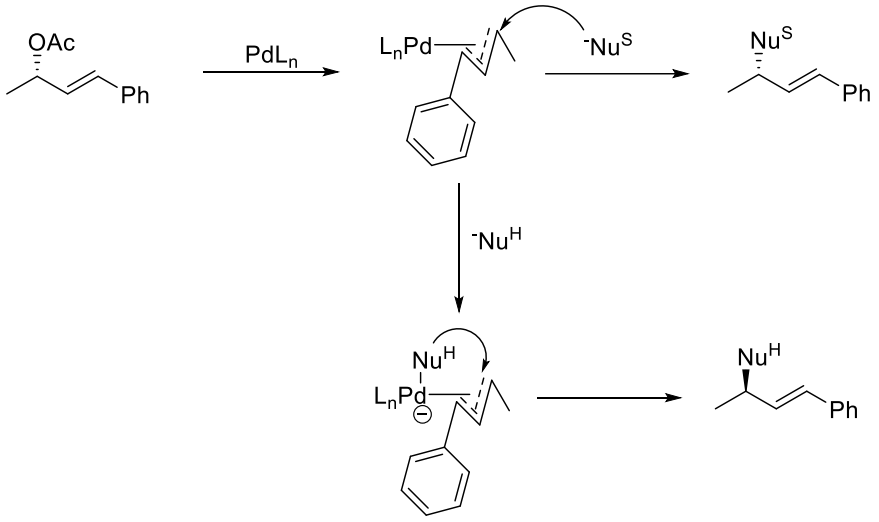


Scheme 85 *– the alkene complexes formed by nucleophilic attack of a allylpalladium species via early and late transition states.*[84]

Less sterically bulky nucleophiles are more likely to go through a late transition state to form the more stable above-right alkene complex. This is because the LUMO of the alkene is decreased, leading to a greater degree of back bonding from the Pd(0) centre. Bulky nucleophiles are more likely to go through an early transition state (above-left) where attack occurs at the least hindered site due to the combined steric interference of both the π-allylpalladium and the nucleophile. Use of bulkier phosphine ligands can give a higher regioselectivity for nucleophilic attack at the least hindered terminus.

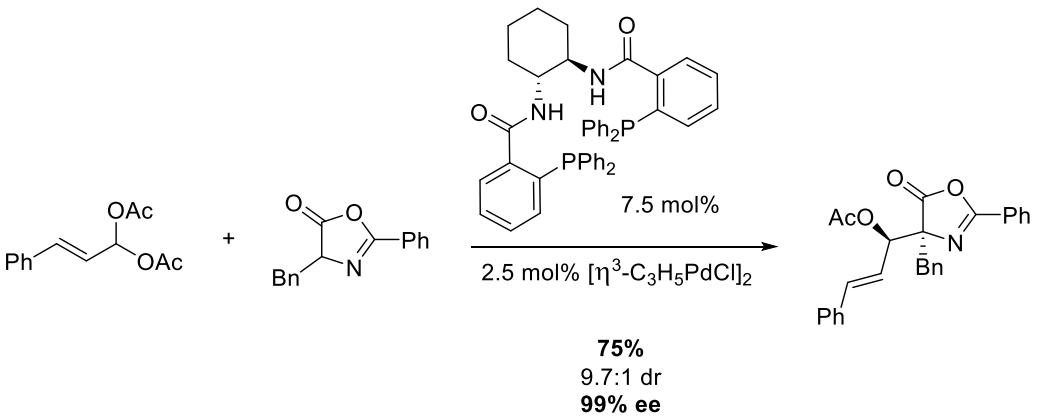
For this class of reaction to proceed, the nucleophiles must be relatively soft. Malonates and their related compounds (β-ketoesters, α-sulfonyl esters etc.) have all be found to be good pro-nucleophiles. However, ketones tend to give poor results and require "softening" with the addition of groups such as thioethers,[85] or by converting them into

stannyl or silyl enol ethers.[86] Hard nucleophiles are, however, also compatible with π-allylpalladium chemistry. These nucleophiles are known to attack the metal centre and give the corresponding product *via* reductive elimination. This difference in mechanism leads to distinct differences in stereoselectivity, thereby influencing the developments of asymmetric allylation.[87] With soft nucleophiles, the stereochemistry of the substrate is retained as all reactivity occurs on the face that is not coordinated to the palladium centre. On the other hand, when hard nucleophiles are used, the nucleophile approaches from the same face of the metal, leading to an inversion of stereochemistry (*Scheme 86*).



Scheme 86 *– the difference in stereoselectivity of hard and soft nucleophiles in Tsuji-Tros allylations.[88]*

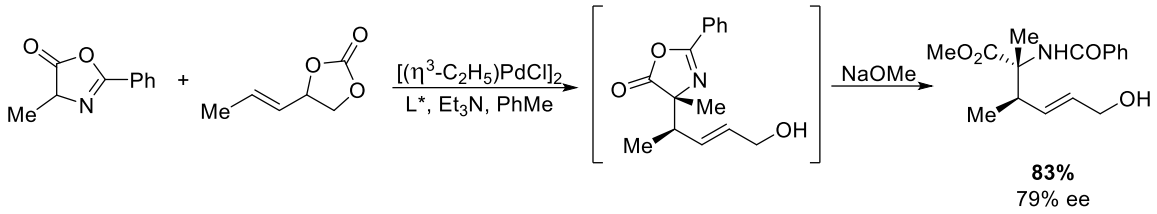
In the late 1990's, Azlactones were employed by Trost as prochiral pro-nucleophiles in the synthesis of unnatural allylated amino acids (*Scheme 87*).[88]



Scheme 87 *– Asymmetric allylation of a phenylalanine-derived azlactone with a moderate dr and a high enantioselectivity.[88]*

Chiral bridged diphosphine ligands were utilised, giving excellent enantioselectivities of up to 99% ee. Although the diastereomers produced were separable in most cases, the diastereoselectivities were moderate, with dr's of between 2:1 and 9.7:1 being obtained. To exemplify their utility, a selection of the azlactone products were ring opened to their corresponding amino acid derivatives.

Zhang was able to allylate azlactones with high yields (Scheme 88), diastereoselectivities and enantioselectivities using an allylic cyclic carbonate and chiral phosphoramidite ligands.[89]

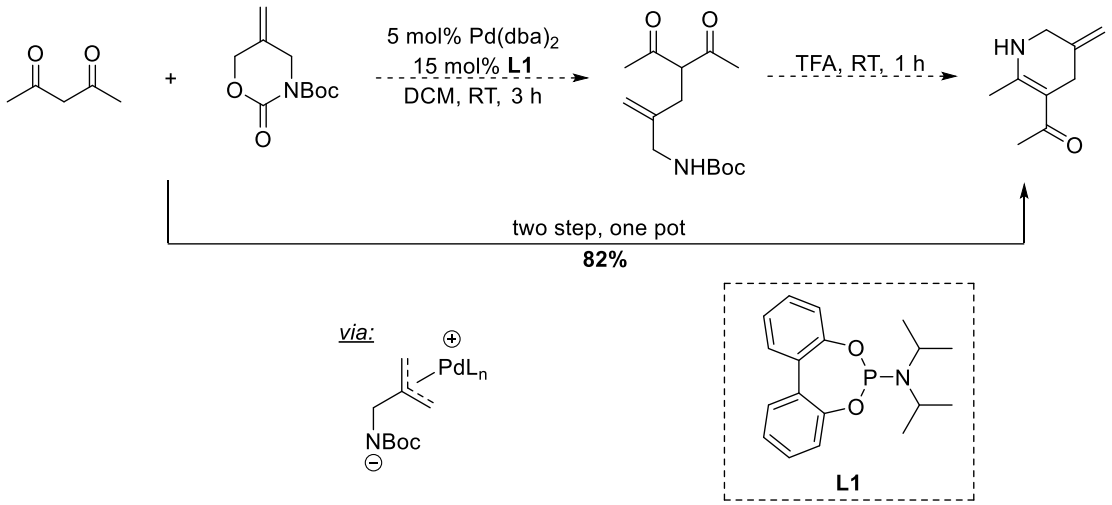


Scheme 88 *– The enantioselective allylation of an azlactone using a carbonic allylating agent to give the allylic alcohol, followed by ring opening of the azlactone using sodium methoxide.*[89]

This transformation is particularly interesting as the reaction not only proceeds in the presence of an unprotected alcohol, but it is thought that hydrogen bonding of the alcohol contributes to the high enantioselectivities measured.

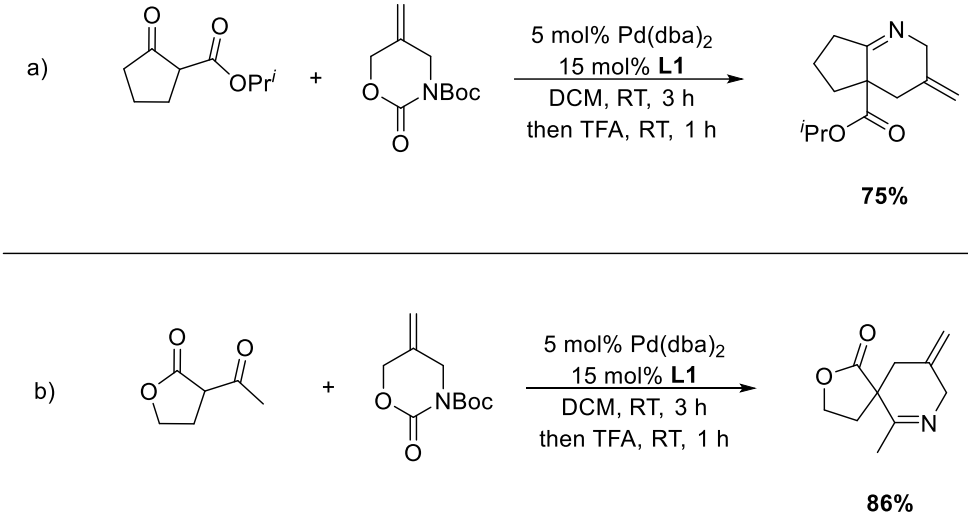
2.3 Previous Work

Published work in the by Harrity and co-workers has demonstrated the utility of a cyclic carbamate in the allylation of diketones and other similar compounds.[90,91] The allyl palladium complex formed exhibits a pendant *N*-Boc amine (*Scheme 89*).



Scheme 89 *– the two-step, one-pot allylation/cyclisation of a diketone using a cyclic carbamate.*[90]

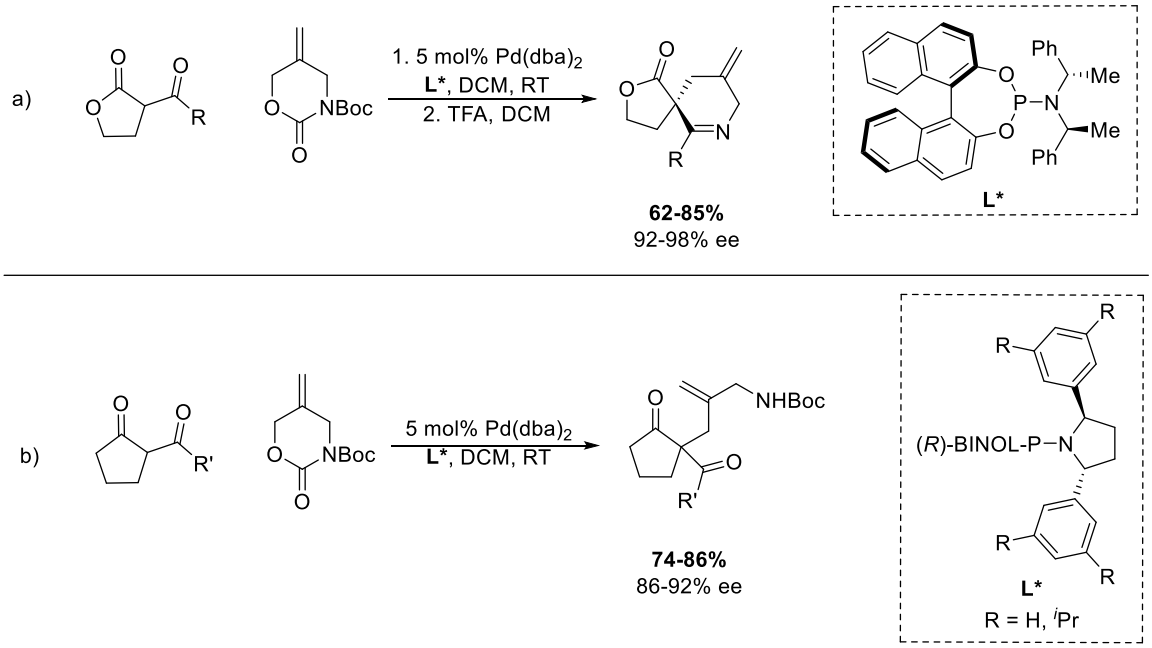
In situ deprotection of the amine on the allylated diketone with TFA resulted in the cyclisation of the amine onto the ketone to form a cyclic enamine. Use of cyclic β-ketoesters gave bicyclic products (*Scheme 90*).



Scheme 90 *– the allylation/cyclisation of cyclic ketoesters to form bicyclic products.*[90]

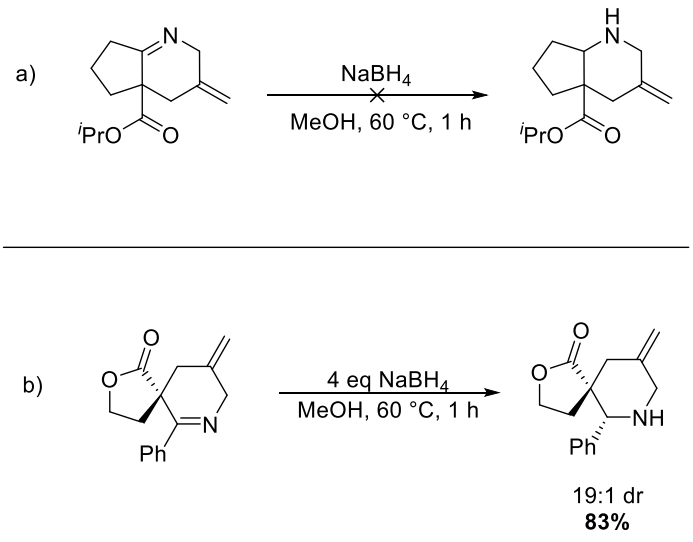
In both cases, cyclisation occurred onto the more reactive ketone as opposed to the ester. This gave access to both fused (*Scheme 90a*) and spirocyclic (*Scheme 90b*)

products. Chiral phosphoramidite ligands were shown to give good to excellent enantioselectivities in both β-ketoesters (*Scheme 91a*) and β-diketones (*Scheme 91b*).[90]



Scheme 91 *– enantioselective allylation of β-ketoesters and β-diketones using chiral phosphoramidite ligands.[90]*

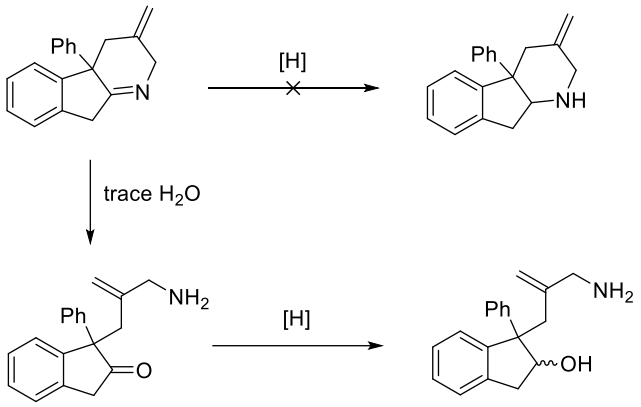
Attempt to reduce the imines to the piperidines gave mixed results (*Scheme 92*).



Scheme 92 *– Reduction of the bicyclic imines with $NaBH_4$.*

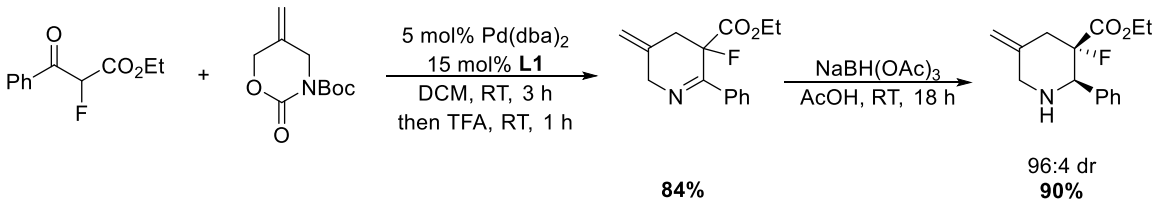
Reduction of the spirocyclic imines proceeded well (*Scheme 90b*), however the 5,6-fused ring systems did not undergo reduction when treated with $NaBH_4$ (*Scheme 90a*).

Indanones and tetralones were also subjected to the allylation/cyclisation conditions, with tetralones giving excellent results in both the allylation/cyclisation, and the subsequent imine reduction.[91] Unfortunately, the indanone derivatives proved difficult to access, and reduction of the imine was not possible due to the ring-strain imposed on a 5,6-ring system by the sp^2-hybridised bridgehead carbon (*Scheme 93*).[91,92] Instead, trace amounts of water caused hydrolysis of the imine and the resulting alcohol was observed as a result of the reduction of the indanone.



Scheme 93 *– reduction of the indanone-derived imine could not be reduced to the piperidine, instead ring opening due to trace water occurred and the resulting indanone was reduced.*

This work was then expanded to include α-fluoro-β-ketoesters (*Scheme 94*).[92,93]

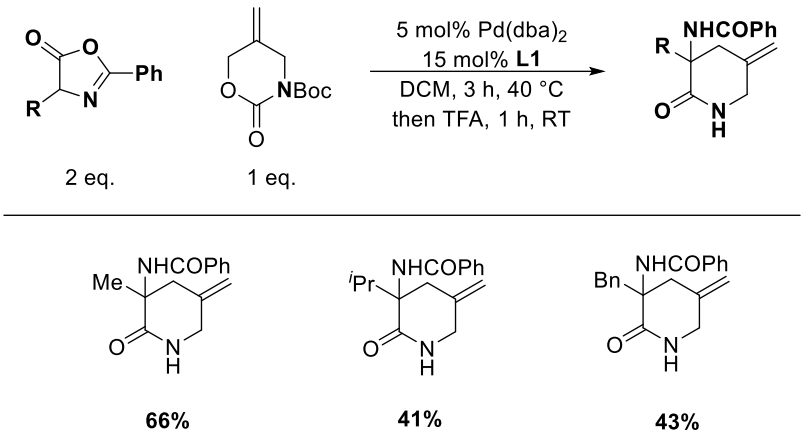


Scheme 94 *– the allylation/cyclisation of α-fluoro-β-ketoesters followed by the highly diastereoselective reduction to the fluorinated piperidine.*[93]

A wide scope of aryl and alkyl fluoropiperidine imines were accessed in excellent yields (49-99%). Unfortunately, attempts at developing an asymmetric method were unsuccessful. The chiral phosphoramidites which gave Allen good results, gave poor enantioselectivities in the case of α-fluoro-β-ketoesters.

Cyclisation of the allylated products onto a carbon with oxidation level 3 had not yet been seen as a more reactive ketone had always been present, however the potential to

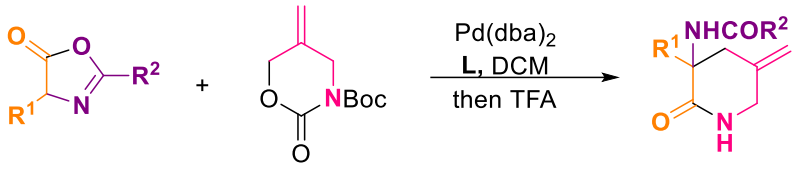
synthesise Freidinger lactams through this route is possible if a different dicarbonyl surrogate were to be used. Azlactones are a β-diester surrogate, and they have been shown to be effective targets for allylation.[86,87,88] A small scope of azlactones have previously been subjected to the allylation/cyclisation conditions with promising results (*Scheme 95*).[94]



Scheme 95 *– initial attempts at the allylation/cyclisation of azlactones using the cyclic carbamate.*[94]

2.4 Aims

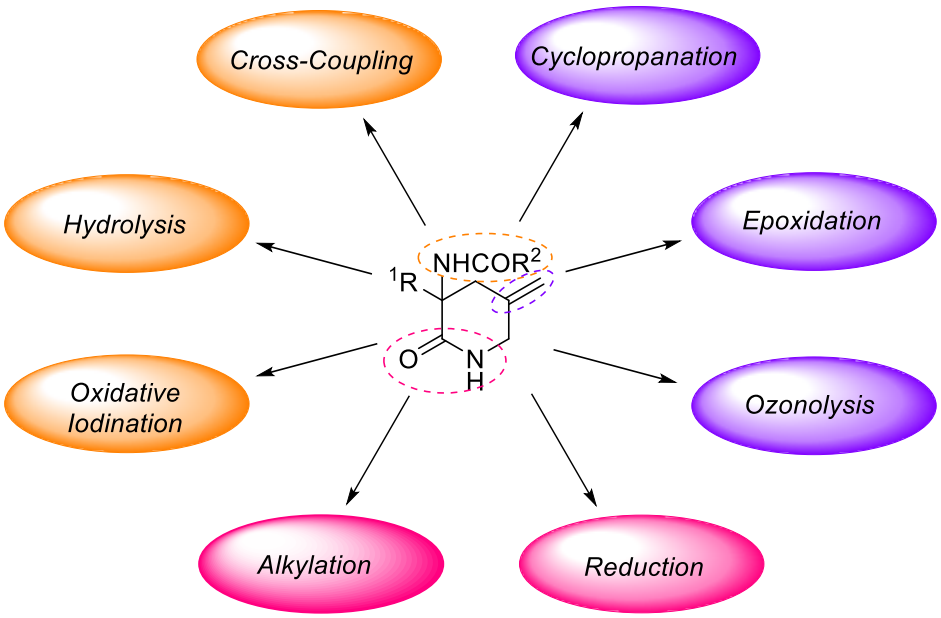
The main aim of this project has been to improve on the initial results from the allylation/cyclisation of azlactones with the cyclic allylic carbamate, and to create a scope of this class of molecule (*Scheme 96*).



***Scheme 96** – allylation/cyclisation of azlactones. Colours highlight where the starting materials are incorporated into the δ-lactam products.*

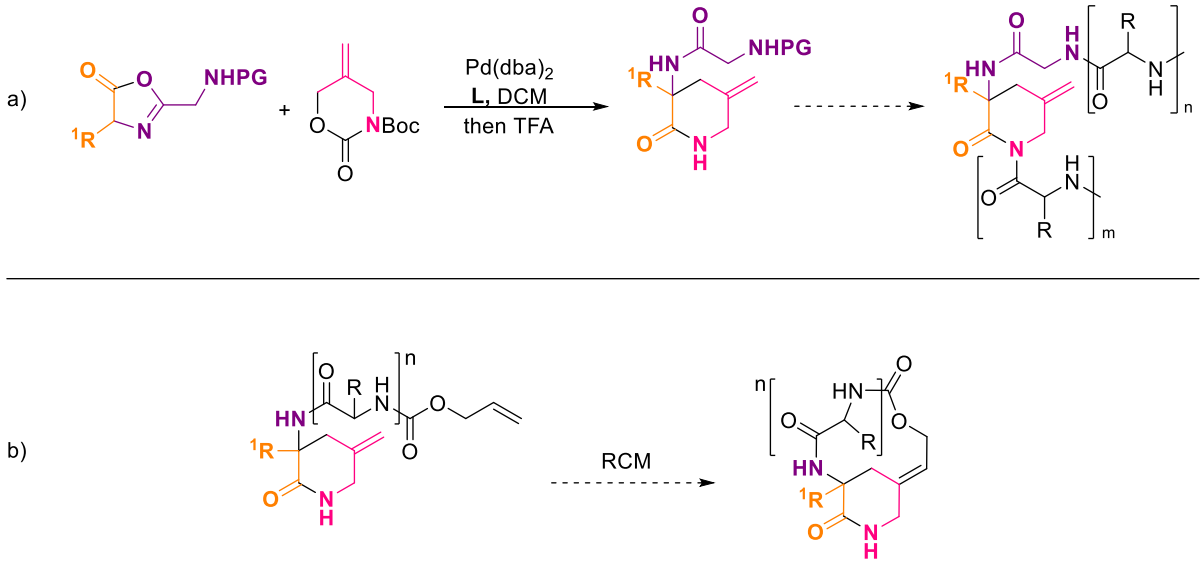
Attempts to undertake these reactions asymmetrically will be made using chiral phosphoramidite ligands, in the hopes that the resulting peptide-derived lactams can be synthesised with high enantioselectivities.

Late-stage functionalisations will be undertaken to highlight the utility of these scaffolds, as well as the selectivity of each of the functional handles present (*Scheme 97*).



***Scheme 97** – Possible late-stage functionalisations of the δ-lactams at each synthetic handle.*

The final aim of this project was to develop these substrates into peptidomimetic Freidinger lactams. It was hoped that they could be incorporated into polypeptide chains (*Scheme 98a*), and possibly even into cyclic peptides (*Scheme 98b*), in order to develop a new class of β-turn mimics.

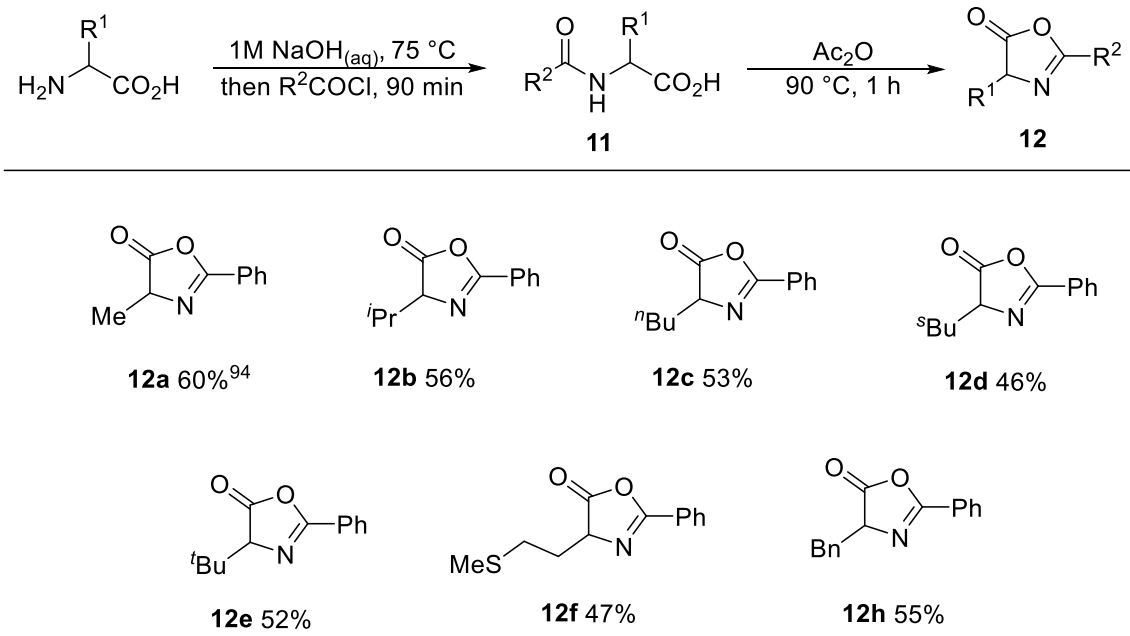


Scheme 98 *– Synthesis of peptidomimetic scaffolds by allylation/cyclisation of polypeptide derived azlactones and subsequent functionalisation. Colours highlight how the starting materials are incorporated into the products.*

2.5 Results and Discussion

2.5.1 Azlactone Synthesis

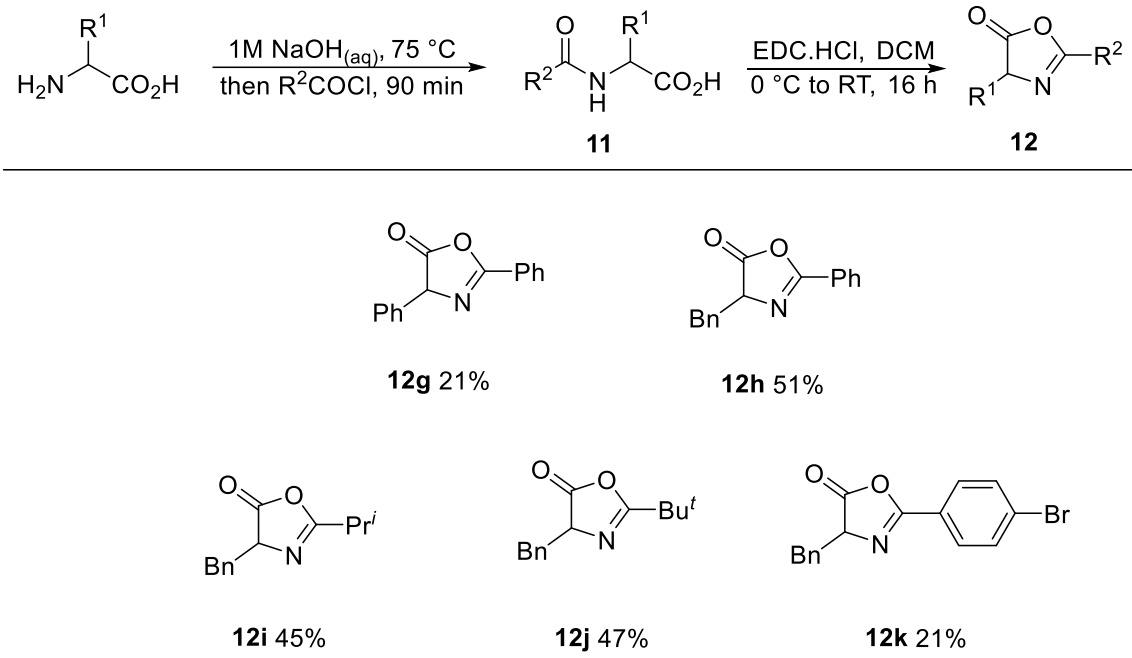
Azlactones are facile to produce via the dehydrative cyclisation of *N*-acylated amino acids. There are many well-documented routes towards these scaffolds, with inexpensive commercially available starting materials. The most common route involves acylation of the amino acid using sodium hydroxide and the appropriate acid chloride, followed by heating of the intermediate amide in acetic anhydride to give the azlactone (*Scheme 99*).



***Scheme 99**– the synthesis of azlactones **12a-12f** and **12h** using NaOH, RCOCl and Ac_2O.*

Acylation of these common amino acids gave the acylated intermediate in excellent yields (93-100%), however the yields for the dehydrative cyclisation were lower. Azlactone **12a** was particularly unstable, and must be used immediately, as it degraded even when stored at -18 °C under an inert atmosphere. Substrates **12b**-**12f** and **12h** were significantly more stable and resisted degradation when stored in the freezer for up to a month. Only azlactones bearing non-basic or acidic side chains were explored, as it was anticipated that these could interfere in subsequent transition metal catalysed allylation steps. Conducting the cyclisation in Ac_2O often led to a complex crude mixture,

which in turn made purification quite difficult, resulting in lower yields. Therefore, alternative cyclisation conditions were explored (*Scheme 100*).



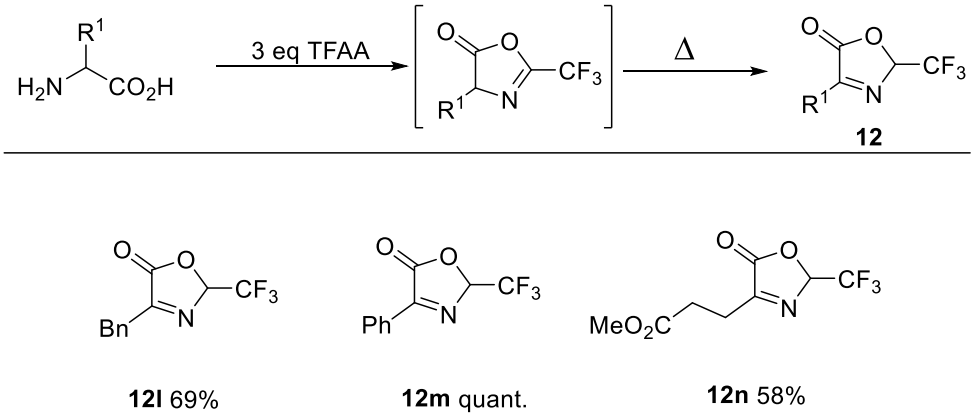
Scheme 100 *– the synthesis of azlactones* ***12g-12l*** *using EDC.HCl to cyclise the acylated amino acids.*

In the event, EDC hydrochloride as the dehydration agent gave comparable isolated yields to those achieved using Ac_2O (*Scheme 98*). However, EDC gave a much less complex crude mixture than using Ac_2O, with the entirety of the product being isolated using column chromatography.

Substrate **12g** suffered from being significantly unstable to hydrolysis; the cyclisation reaction was complete almost instantly upon the addition of EDC, indicated by the reaction mixture turning bright yellow. However, exposure to elevated temperatures resulted in hydrolysis to the starting material, requiring rotary evaporation to be conducted using an ice-cold bath. It was also found to degrade very quickly on silica, fluorosil and alumina. Therefore, it has been challenging to obtain a clean sample for characterisation even when prepared on a large scale.

Substrate **12k** was synthesised to include a handle for late-stage functionalisations such as Pd-cross couplings. Whilst the yield was low, the optimisation of this reaction was not undertaken due to the prohibitive cost of the required acid chloride.

Azlactones where R^2=CF_3 group (*Scheme 101*) were targeted next, as this would lead to the allylated lactam products containing a trifluoroacetamide group. This group was desirable as it can be easily cleaved using $NaOH_{(aq)}$ or $NaBH_4$, and thus would give simple access to the free amine. This type of azlactone has been previously documented; however they tend to be formed as the tautomer with the acidic proton next to the CF_3 group.[92] The tautomers can be easily distinguished from each other using NMR spectroscopy, as the resonance of the acidic proton occurs as at approximately δ 6.1 ppm when adjacent to the CF_3 group, compared to approximately δ 4.7 ppm when adjacent to the carbonyl.



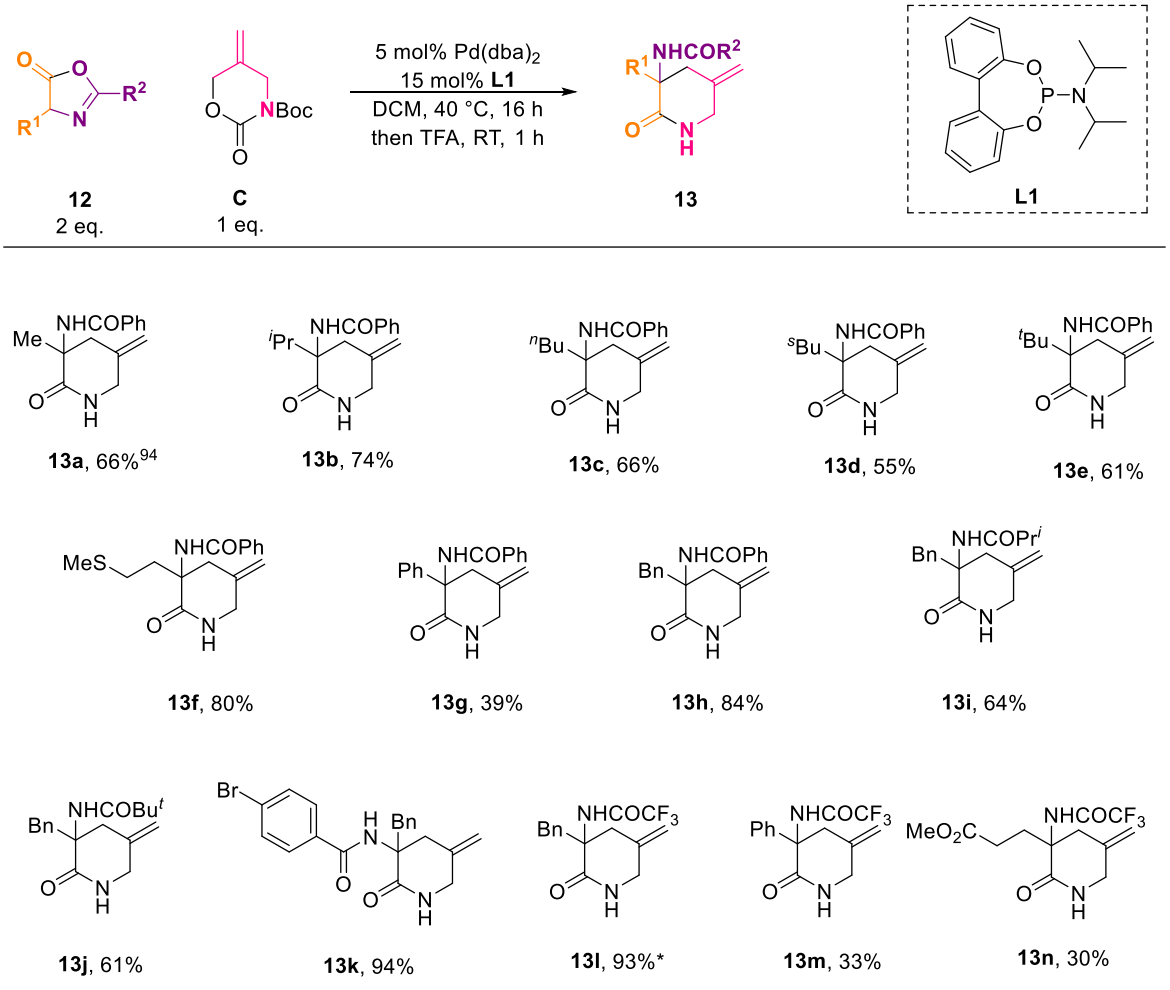
Scheme 101 *– the synthesis of -CF_3 azlactones* ***12l-12n*** *in one step from the amino acids using TFAA.*

Treating phenylalanine with TFAA and stirring overnight at room temperature led to a mixture of tautomers being formed. Whilst both tautomers should be active in our allylation reaction, they had significantly different R_f values. In order to simplify the purification, it was therefore decided to push the azlactone to the more thermodynamically favourable tautomer by heating the reaction to 40 °C. In the case of the azlactone derived from phenylglycine (**12m**), quantitative conversion was achieved without need for column chromatography. However, as with **12g**, it was unstable and underwent hydrolysis even when stored at -18 °C. Azlactone **12n** was synthesised in order to introduce a synthetic handle on R^1 for further functionalisations, and a good yield of this substrate was achieved.

2.5.2 Allylation/Cyclisation to form δ-Lactams

Previously performed unpublished research has shown that the allylation and subsequent cyclisation via Boc-deprotection using TFA can be done as a 2-step 1-pot reaction. The allylations reactions were heated for 3 hours, giving the desired products in moderate yields (41-66%).[94]

By heating the allylation reactions overnight, the yields of these previously studied transformations were improved (66-84%), and this allowed for a general method to be established (*Scheme 102*). It should be noted that attempts using fewer equivalents of the azlactone led to a reduced yield, as did adjusting the mol% of **L1**.



Scheme 102 *– allylation/cyclisation of azlactones using cyclic carbamate* ***C****, Pd(dba)₂ and* ***L1****.*

As it was possible that the Boc-deprotected nitrogen may attack either the C=O or the C=N of the azlactones – which would lead to different products – a crystal structure of compound **13h** was obtained (*Figure 12*). This confirmed that the lactam product had been obtained.

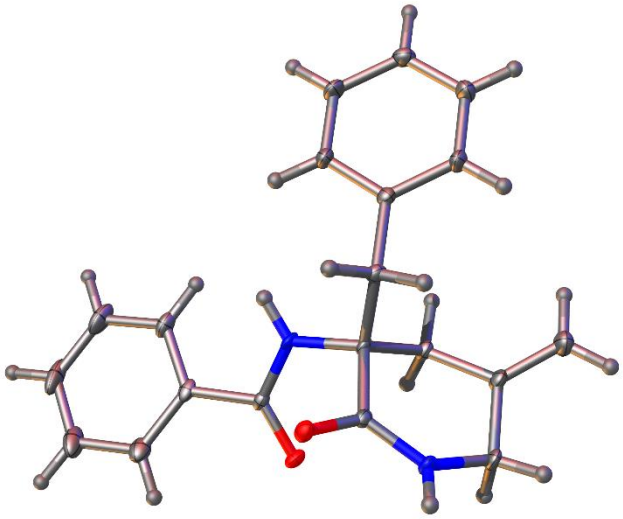
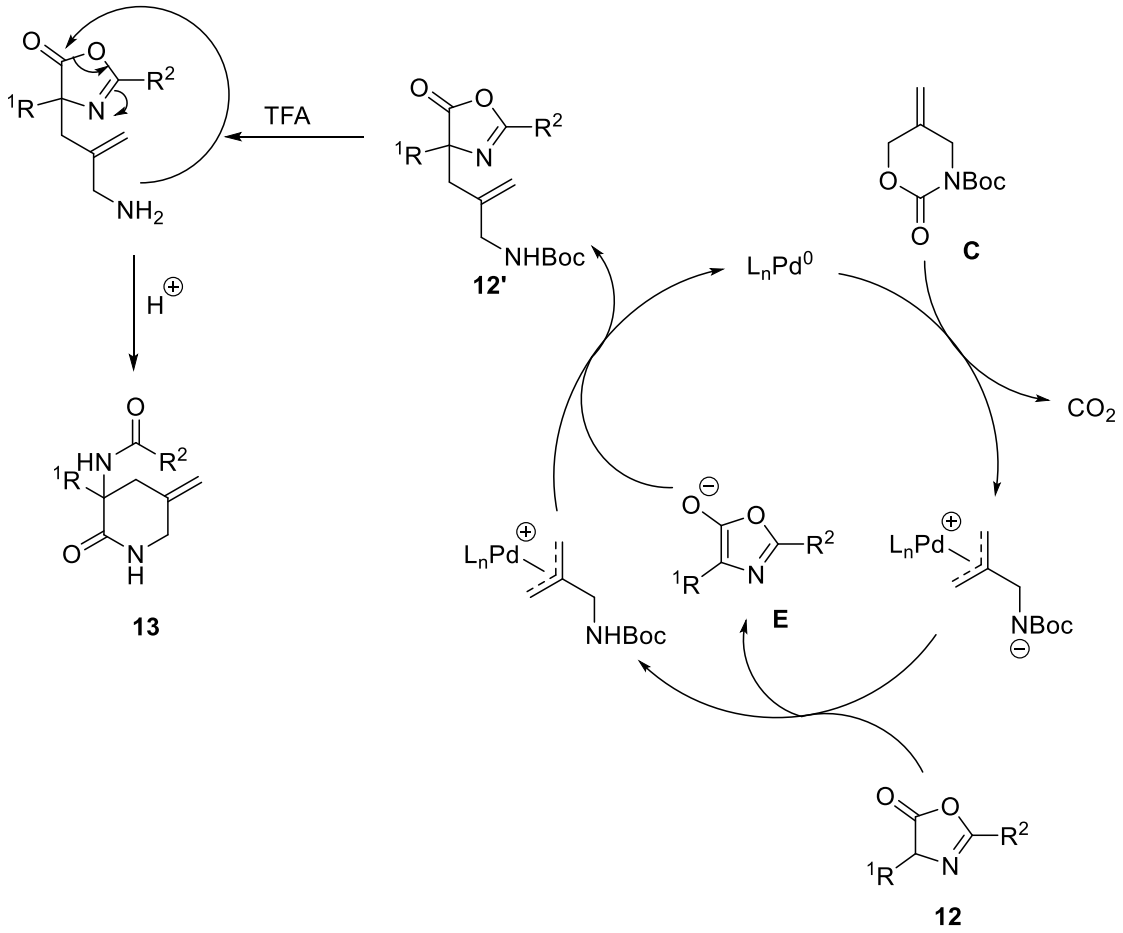


Figure 12 *– The x-ray crystal structure of* ***13h****.*

Most azlactones gave lactams in good to excellent yields (55-94%), with the notable exceptions of **13g**, **13m** and **13n**. It was possible that the steric hindrance on azlactones **12g** and **12m** due to the bulky phenyl group led to these significantly reduced yields compared to the phenylalanine derivatives (**13h** and **13l**).

An alternative explanation was that the enolate (*Scheme 103, **E***) was very stable due to the extended conjugated system formed, and therefore did not act as a nucleophile.



Scheme 103 *– Proposed mechanism for the Pd-catalysed allylation followed by TFA-induced cyclisation.*

It was less clear why the yield of **13n** was so much lower than that of **13f**, as both contain heteroatoms as part of their R^1 groups. It was possible that due to the ester, there was competition between the deprotonation of the adjacent carbon versus that of the azlactone. It was possible that the competition of these species greatly reduced the rate of formation of the desired product due to the presence of these non-reactive species outside the catalytic cycle.

It is possible that the scope of products could be expanded to include more polar side chains, provided that the side chains were sufficiently protected in order to reduce their interactions with the catalyst and potentially stall the reaction.

2.5.3 Asymmetric Synthesis of Lactams

Previously published work has shown promising results in the asymmetrical allylation step using chiral phosphoramidite ligands (*Figure 13*) to generate the corresponding products with high enantioselectivity.[89]

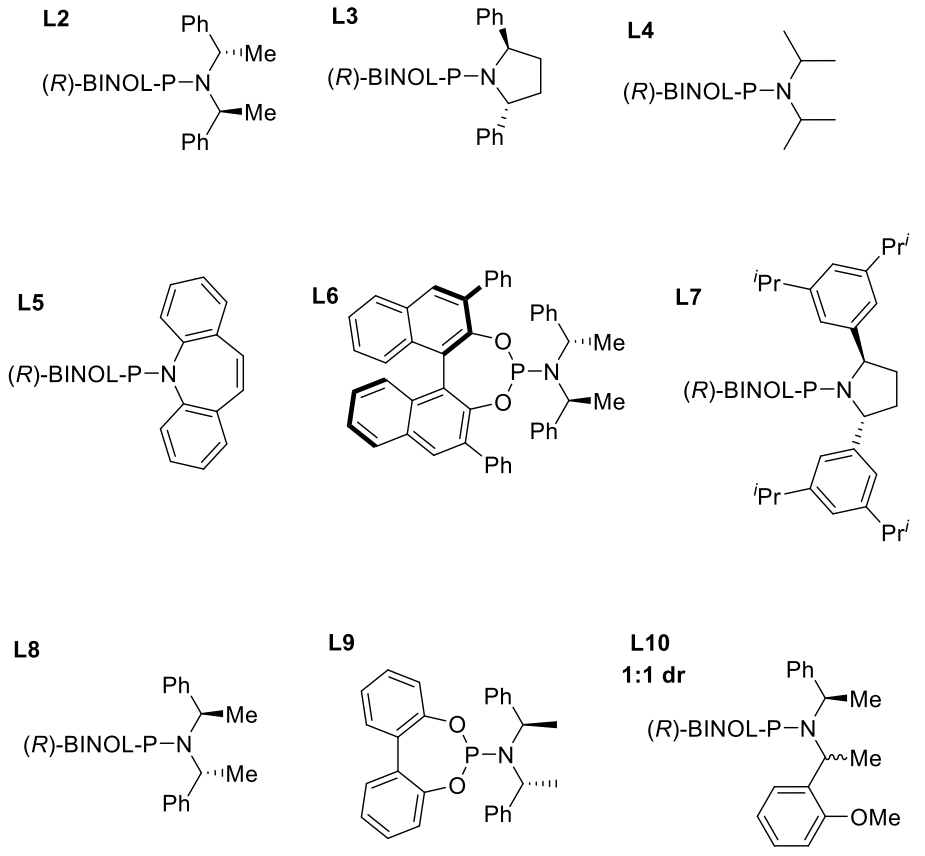
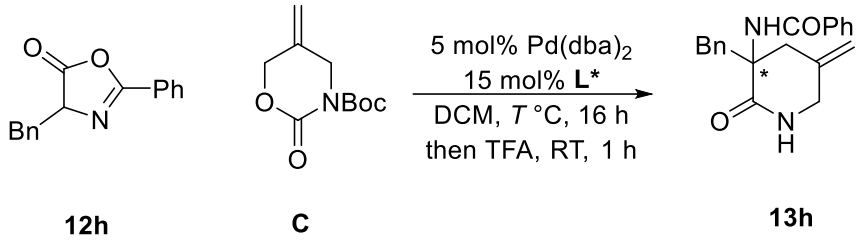


Figure 13 *– Chiral phosphoramidite ligands available in the laboratory.*

A range of chiral phosphoramidite ligands (**L2-10**) were available in the laboratory and a screen of these ligands in the lactam synthesis was undertaken (*Scheme 104, Table 3*).



Scheme 104 *– Asymmetric synthesis of* ***13h.***

Table 3 – Screen of chiral phosphoramidite ligands in the allylation of **12h**.

Positive and negative ee values were assigned based on the major peak in the chiral HPLC trace, and are not necessarily indicative of the (+) or (-) enantiomers. Negative values were assigned when the peak with the shorter retention time was the minor peak, and conversely positive value were assigned when the peak with a short retention time was the major peak.

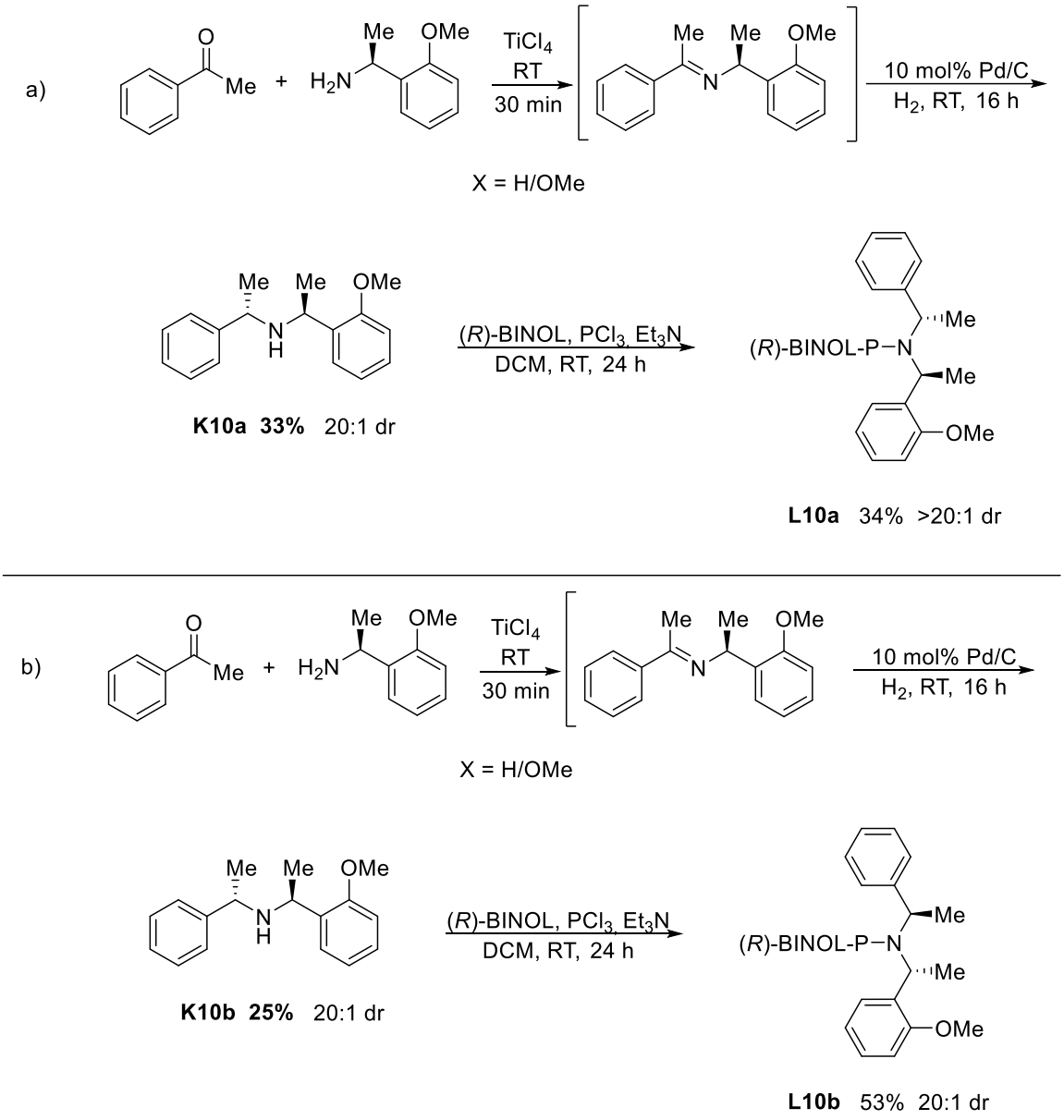
Entry	Ligand	T/ °C	Yield / %	ee / %
1	L2	40	64	+36
2	L3	40	62	+32
3	L4	40	75	+2
4	L5	40	90	-8
5	L6	40	86	+20
6	L7	40	0	-
7	L8	40	45	-24
8	L9	40	66	-26
9	L10	40	97	+51
10	L10	RT	53	+59
11	L10	-20 to 10	0	-
12	L10	RT (Toluene)	0	-

Reactions which utilised **L2** and **L3** initially showed some promising results (*Table 3, entries 1 and 2*), with low-moderate ee's. The use of **L4** and **L5** gave almost-racemic product (*Table 3, entries 3 and 4*), which suggested that it was imperative to have a

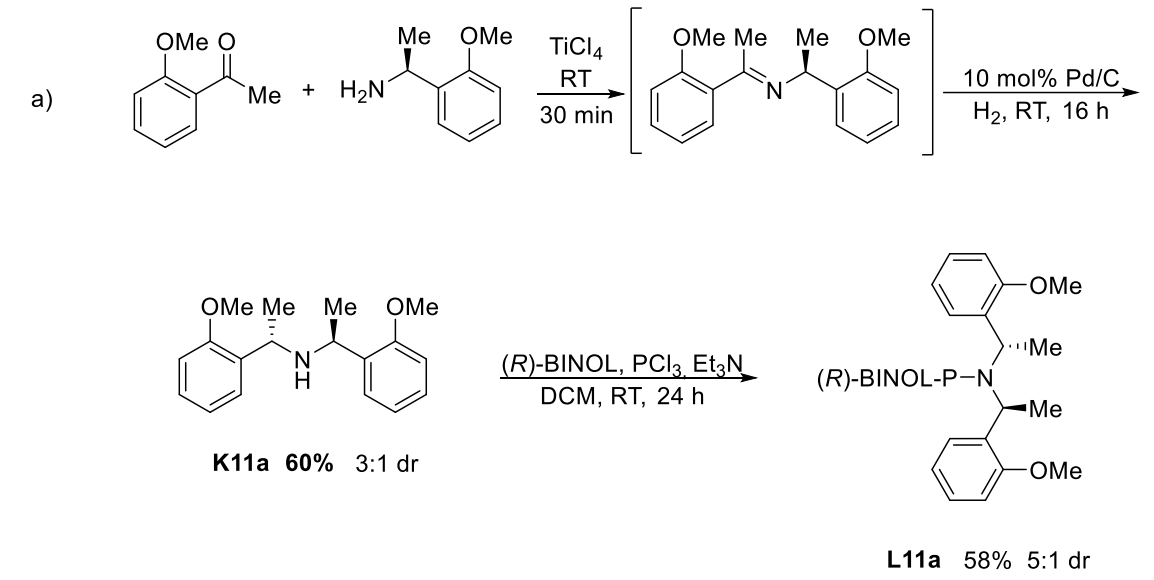
chiral diamine in the ligand structure. **L6** gave a lower ee than **L2** (*Table 3, entry 5*), suggesting that the addition of the extra steric bulk on the aromatic diol portion of the ligand was unfavourable in this system. Increasing the steric bulk on the diamine side of the ligand was also unfavourable, as no reaction occurred with **L7** (*Table 3, entry 6*). Ligand **L8** incorporated the opposite enantiomer of the chiral amine moiety compared to **L2**, and gave a comparable ee to that of **L2**, albeit of the opposite enantiomer of product (*Table 3, entry 7*). In **L9**, the aromatic diol is not chiral, and yet a similar ee value to **L8** was achieved (*Table 3, entry 8*). This suggested that the aromatic diol played a minor role in controlling the enantioselectivity of this reaction.

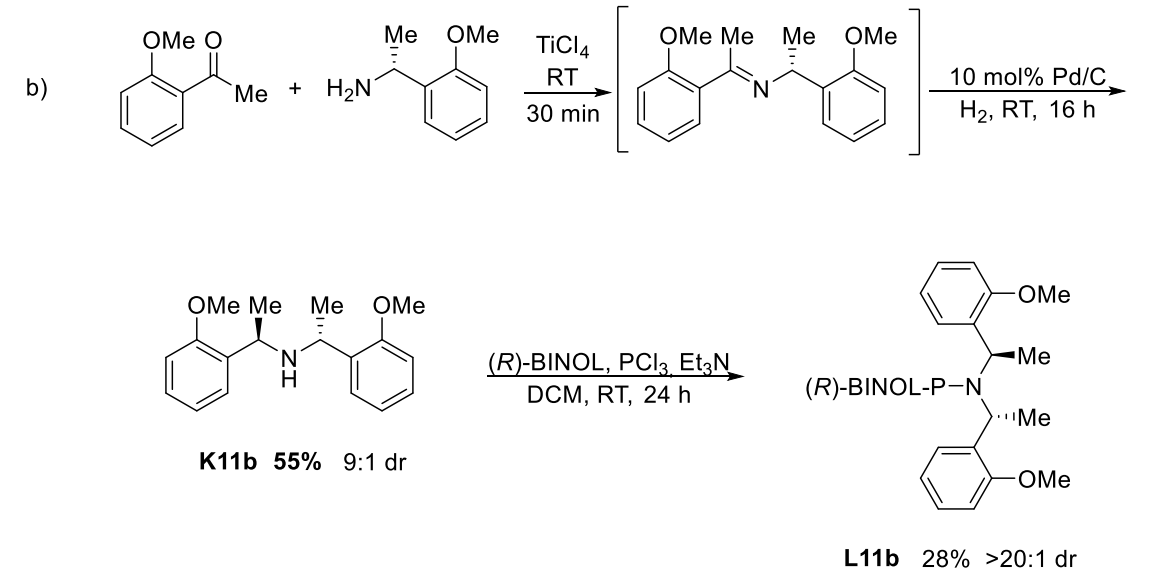
Most peculiarly, **L10** (a 1:1 mixture of diastereomers) gave the most promising result of +51% ee with a 97% yield under the standard conditions (*Table 3, entry 9*). A decrease in temperature – which often leads to better enantioselectivity – gave a slightly higher ee of +59%, although the yield dropped significantly to 53% (*Table 3, entry 10*). Upon further lowering of the temperature, no reaction occurred. Changing the solvent to toluene (to lower solvent effects on the catalytic system) also showed no conversion, with starting material recovered (*Table 3, entries 11 and 12*).

Due to the success of **L10** (*Table 3, entries 9 and 10*), a variety of methoxyphenyl-containing ligands (**L10a-11b**) were synthesised (*Schemes 105 and 106*).



Scheme 105 *– Synthesis of* ***L10a-b*** *via diastereoselective chiral imine reduction.*



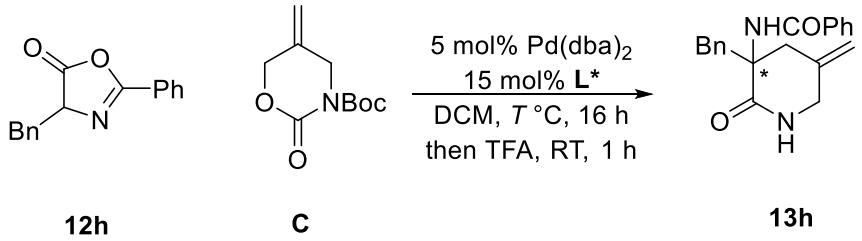


Scheme 106 *– Synthesis of* ***L11a-b*** *via diastereoselective chiral imine reduction.*

A mixture of the acetophenone with chiral amine in neat $TiCl_4$ gave the imine *in situ*, which was then diastereoselectively reduced by adding Pd/C and H_2 to give the *anti*-diamine product in moderate yields (25-60%). Both **K10a** and **K10b** offered excellent diastereomer ratios, while the dr's of **K11a** and **K11b** were modest. These amines were progressed to the corresponding phosphoramidites with (*R*)-BINOL and PCl_3, to give the ligands in moderate yields (28-58%), with excellent diastereomers ratios for **L10a**, **L10b** and **L11b**, and acceptable dr in the case of **L11a-b**. The relative stereochemistry of each secondary amine was determined by comparison with the literature NMR data, and the

absolute stereochemistry of the final ligands was determined by optical rotation and comparison with the literature values.

These chiral phosphoramidite ligands were then inserted into the allylation reaction of **12h** (*Scheme 107, Table 4*).



12h **C** **13h**

Scheme 107 – *Asymmetric synthesis of* ***13h.***

Table 4 – Screen of methoxy chiral phosphoramidite ligands in the allylation of **12h**.

Entry	Ligand	T/ °C	Yield / %	ee / %
1	**L10a**	40	61	+29
2	**L10b**	40	97	+26
3	**L10b**	RT	87	+30
4	**L11a**	40	74	+50
5	**L11b**	40	64	+26

L10b is one of the diastereomers present in **L10** (synthesised at 20:1 dr), and this led to an allylation product ee of +26% under standard conditions, with a slight increase to +30% ee when undertaken at room temperature (*Table 4, entries 2 and 3*). On the first reaction of **L10b**, an ee of 57% was obtained, although inexplicably every subsequent attempt gave ee values of +20 to +26%. The origin of this anomalous result remains unclear. As **L2** gave a higher ee than **L8**, **L10a** was also synthesised in the hopes that an increase in the enantioselectivity would be observed. Unexpectedly, while the enantioselectivity was comparable to that of **L10b** (*Table 4, entry 1*), a change in the enantiomer was not observed in this case. This result suggests that the asymmetric catalytic system was more complicated with this type of ligand than initially thought.

In order to try to establish the role of the methoxy group on these ligands, **L11a-b** were explored to examine the effects of an additional methoxy group. In this case, **L11b** gave a similar result to **L10b** (*Table 4, entry 5*). Again, a change in enantiomer of product was not observed, however **L11a** gave the highest enantioselectivity of this ligand family (*Table 4, entry 4*). The fact that ligands with higher proportions of the *syn*-amine diastereomer (**L10** used a 1:1 ratio and **L11a** was 5:1) gave the best results suggests that perhaps it was the *syn*-diamine derivative that was the more selective ligand in this system. Unfortunately, selectively synthesising the *syn*-diamine was not possible, as inseparable mixtures of diastereomers were obtained even when using other routes.

The ligands which gave the most promising enantioselectivities from the screening were then tested with other azlactones to see whether the results were consistent or could even be improved upon.

Table 5 – Asymmetric allylations of azlactones.

Entry	Substrate	Ligand	Yield / %	ee / %
1	**12b**	**L10b**	61	+13
2	**12c**	**L10b**	78	+13
3	**12f**	**L10**	58	+55
4	**12j**	**L2**	87	+26
5		**L3**	0	-
6		**L5**	20	+5
7		**L6**	24	+6
8		**L9**	92	+26
9	**12l**	**L2**	78	-9

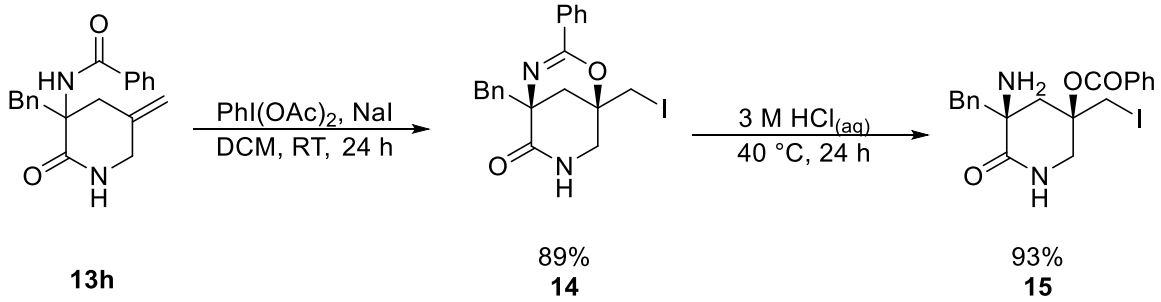
The use of **L10** in the allylation/cyclisation with **12f** gave a similar ee to the reaction with **12h** (*Table 5, entry 3*). Attempts as synthesising another batch of **L10** did not give the 1:1 mixture of diastereomers necessary to give directly comparible results, therefore the single enantiomer **L10b** was used on substrates **12b-c**. The enantioselectivities in these cases were much lower than the results from **12h** (*Table 5, entries 1-2*), likely due to less

sterically bulky enolates being formed. Substrate **12j**, with its bulky ^{t}Bu amide, was chosen for another smaller screen to determine whether comparible, if not better, enantioselectivities could be obtained. **L2** produced an almost identical result (*Table 5, entry 4*), while unexpectedly no reaction occurred with the use of **L3** (*Table 5, entry 5*). Similarly to **12h**, **L5** gave a low enantioselectivity (*Table 5, entry 6*), although the yield was much lower. **L6** also gave a low yield and a poor ee (*Table 5, entry 7*), which was quite different from the reaction with **12h**. Interestingly, **L9** did not lead to the change in enantiomer of product that was seen previously, although a similar level of enantioselectivity was seen with a higher yield (*Table 5, entry 8*). Substrate **12l** combined with **L2** gave a lower enantioselectivity (*Table 5, entry 9*), which is to be expected as the CF_3 group is much less bulky than a phenyl or ^{t}butyl.

2.5.4 Further Functionalisation Reactions

2.5.4.1 Exocyclic Amide Functionalisation

First, the exocyclic amide was targeted for further elaboration and an oxidative iodination allowed the transfer of functionality across the ring (*Scheme 108*).



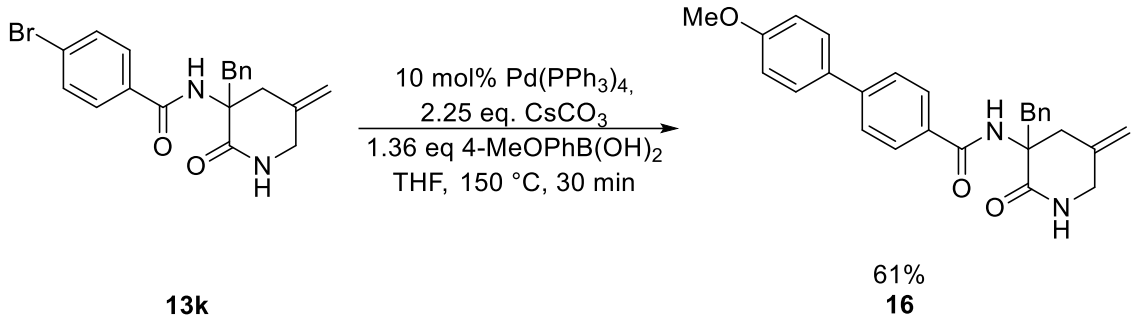
13h **14** **15**

Scheme 108 *– the oxidative iodination of* ***13h*** *followed by acid-catalysed hydrolysis of the ring (stereochemistry is relative).*

The iodonium-promoted cyclisation worked well and hydrolysis of the newly formed ring in 3 M $HCl_{(aq)}$ afforded an excellent yield of the lactam (93%) bearing an ester and a free amine – both of which were potentially exploitable synthetically. This reaction proceeded with complete diastereocontrol as the amide can only reach one face of the alkene in the first step. The possibility of formation of the amide/alcohol product was ruled out using spectroscopic data. The IR spectrum of **15** exhibited the characteristic

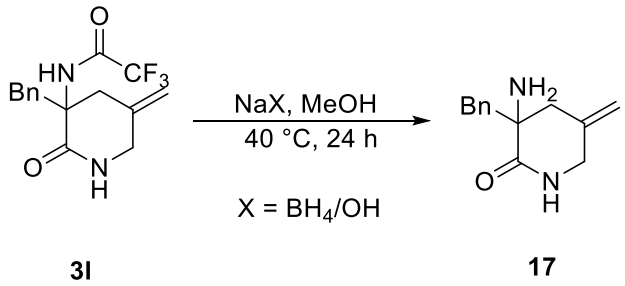
dual stretches of a primary at 3320 and 3276 cm^{-1}, while the carbonyl resonance in the ^{13}C NMR spectrum was significantly different from that of the amide in **13h**, and more consistent with that of an ester.

By introducing an aromatic bromide onto the amide, substrate **13k** was synthesised as a coupling partner for a Suzuki reaction. The cross-coupling of **13k** proceeded with a good yield (61%), showing that the lactam motif was compatible with cross-coupling conditions (*Scheme 109*).



Scheme 109 *– Suzuki cross-coupling of* ***13k*** *with p-methoxyphenylboronic acid.*

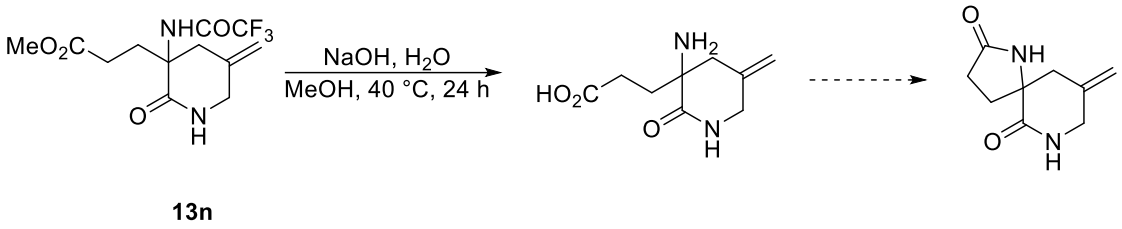
Lactams **13l**-**n** were developed specifically to allow us to cleave the exocyclic amide selectively, as they are known to be more prone to hydrolysis and can even be cleaved using $NaBH_4$ (*Scheme 110*).



Scheme 110 *– cleavage of the exocyclic amide on* ***13l*** *to give* ***17****.*

Treatment of **3l** using 5 eq. $NaBH_4$ gave a low conversion to the amine of 30%; no attempt to optimise this reaction was made due to the possibility that $NaBH_4$ may also react with the lactam. In comparison, the use of NaOH in H_2O and MeOH gave excellent conversion of up to 100%. Sodium hydroxide did not always give consistent results which were difficult to reproduce with variable levels the conversion of starting material (>80%). Nonetheless, it was easy to separate the product and starting material in the lower-conversion cases by formation of the HCl salt.

It was hoped that the simultaneous cleavage of the ester and exocyclic amide in **13n** would allow us to access the spirocyclic [5,6]-dilactam (*Scheme 111*).



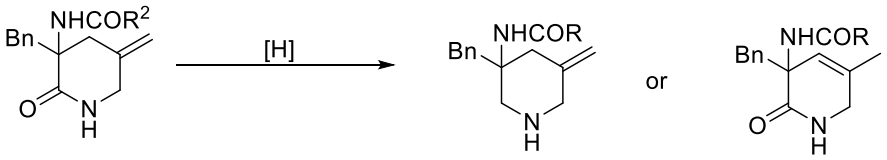
13n

Scheme 111 *– Base-catalysed hydrolysis of* ***13n****.*

Using the conditions that gave **17**, **13n** was treated with NaOH in water and MeOH. It was possible that the amino acid was formed, as the crude ^{1}H NMR spectrum indicated the loss of the methoxy group, however attempts to isolate this species via salt formation were unsuccessful.

2.5.4.2 Lactam Functionalisation

It is documented that lactams can be reduced to their corresponding piperidines by treatment with BH_3.[95] This work presented the challenge of the presence of two competing sites (amide and alkene). In the event, subjecting **13j** and **13l** to a variety of reducing conditions gave mixed results (*Scheme 112, Table 5*).



R = Bu^t **13j**
= CF_3 **13l**

F **G**

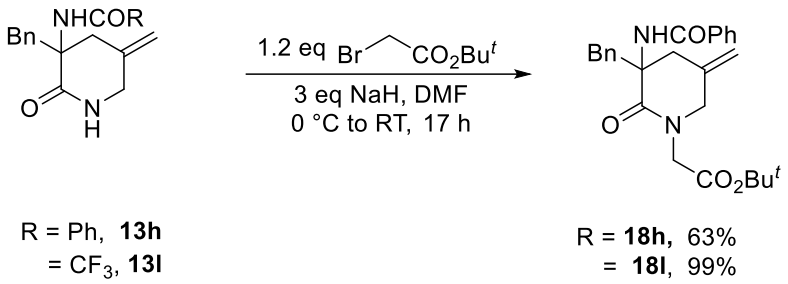
Scheme 112 *– attempts to reduce lactams* ***13j*** *and* ***13l*** *to the piperidine (****F****), and the hydroboration/ isomerisation by-product (****G****).*

Table 6 – Conditions used to attempt the lactam reduction

Entry	Substrate	[H] (eq)	Conditions	Conversion / %
1	**13j**	BH_3.THF (1.5)	THF, RT, 16 h	20 (**G**)
2	**13l**	$BH_3.SMe_2$ (1.5)	THF, RT, 16 h	Complex mixture
3	**13j**	$BH_3.SMe_2$ (1.5)	THF, RT, 16 h	Complex mixture
4	**13l**	TMDS (4)	$Ru_3(CO)_{12}$, toluene, 50 °C, 16 h	Complex mixture
5	**13j**	$LiAlH_4$ (1.1)	THF, 0 °C to RT,16 h	Complex mixture

Interestingly, ^{1}H NMR and LCMS analysis of the crude mixture showed that the use of BH_3.THF on substrate **13j** gave some isomerisation to the endocyclic alkene (*Table 6, entry 1*). This suggested that hydroboration was occurring at the exocyclic alkene, with the alkylborane forming at the tertiary carbon. Either this hydroboration was reversible or the work up of hydroborated substrate reforms the alkene at the more thermodynamically favourable endocyclic position. Unfortunately, all other attempts to reduce the lactam to the piperidine were unsuccessful, with complex mixtures being obtained in the use of $BH_3.SMe_3$ (*Table 6, entries 2 &3*), TMDS/$Ru_3(CO)_{12}$ (*Table 6, entry 4*) and $LiAlH_4$ (*Table 6, entry 5*), and therefore this functionalisation approach was discontinued.

It was possible that the lactam amide could be selectively alkylated as it was less sterically hindered than the exocyclic amide. The exocyclic amide also exhibits a more stabilised anion in the case of **13h** and **13l** due to the electron-withdrawing effects of the phenyl or trifluoromethyl groups. ^{t}Butyl bromoacetate was chosen as the alkylating agent as this transforms the lactam into a protected glycine residue (*Scheme 113*), and it would give yet another synthetic handle.



Scheme 113 *– Alkylation of* ***13h*** *and* ***13l*** *with* ^{t}*butyl bromoacetate using NaH.*

The alkylation reactions proceeded with good to excellent yields (63-99%).

NMR analysis was used to determine the regiochemistry of the products. In the case of **18h**, the resonance of the lactam carbonyl peak in the ^{13}C NMR spectrum had moved further up-field, from δ 172 ppm to δ 171 ppm which suggested the glycyl group was in close proximity to this carbonyl. In the reaction of **13l**, both carbonyl resonances had new shifts, with the lactam moving up-field by 2 ppm and the trifluoroacetamide moving down-field by 3 ppm. Therefore, 2D NMR was employed to confirm the regiochemistry

of **18l** to be the same as that in **18h**. It would be expected that the CH_2 resonances of glycyl group would be correlated to the α-CH_2 carbon of the lactam. The HMBC of **18l** shows that this correlation is present (*Figure 14*), with the glycyl proton at δ 3.85 ppm correlating to the carbon at δ 53.4 ppm.

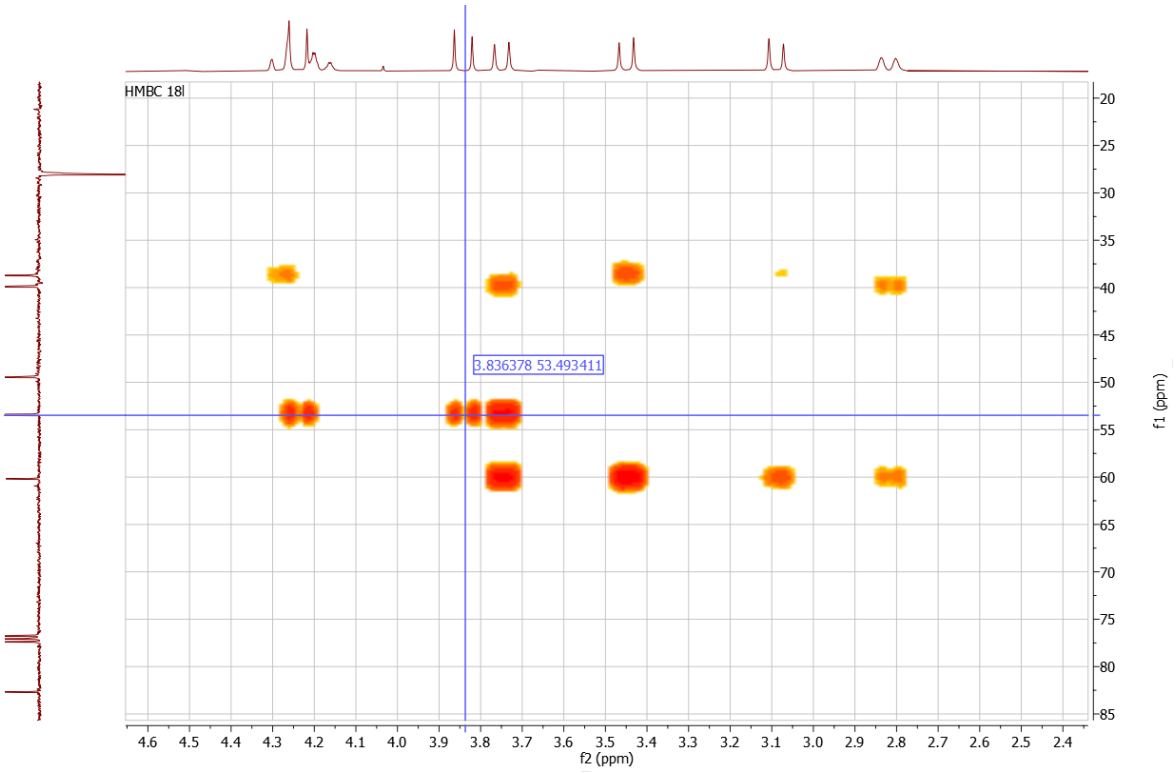


Figure 14 *– HMBC correlation of glycyl CH_2 protons with α-CH_2 carbon of the lactam.*

Furthermore, coupling can be seen between the aforementioned glycl CH_2 protons and the carbonyl of the lactam, with no coupling to the trifluoroacetamide carbonyl (**Figure 15**). This confirms that the alkylation has occurred on the lactam nitrogen as opposed to the exocyclic amide.

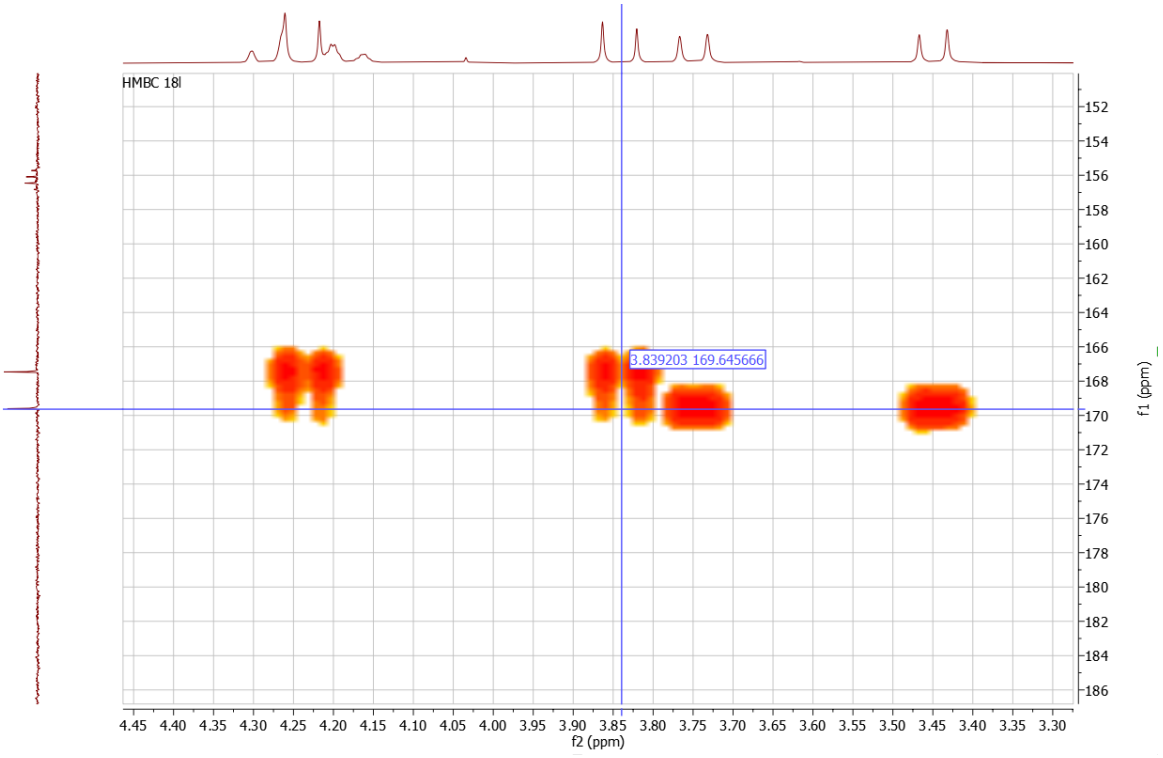
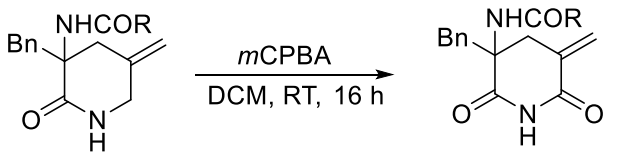


Figure 15 *– HMBC correlation of glycyl CH_2 protons with the lactam carbonyl.*

2.5.4.3 Alkene Functionalisation

The alkene moiety in the lactam provides another synthetic handle which can be selectively targeted. A classic example of alkene functionalisation is epoxidation. Traditionally, epoxidations are undertaken using *m*CPBA (*Scheme 114)*.



R = ^{t}Bu, **13j**
= CF_3, **13l**

R = ^{t}Bu, **19j** 35%
= CF_3, **19l** 19%

Scheme 114 *– the attempted epoxidation of **13j** and **13l** using* m*CPBA.*

Surprisingly, when **13j** and **13l** were subjected to *m*CPBA, the expected epoxides were not observed. Instead, only the glutarimides (**19**) and recovered starting material were observed. The ^{1}H NMR spectrum showed a significant change in environment of alkenyl protons, while a set of CH_2 protons were no longer observable. Analysis of the HMBC

NMR spectrum of **19j** shows all the retained CH_2 protons correlate with the quaternary carbon at the 3-position of the ring (*Figure 16*), confirming that the glutarimide had been formed.

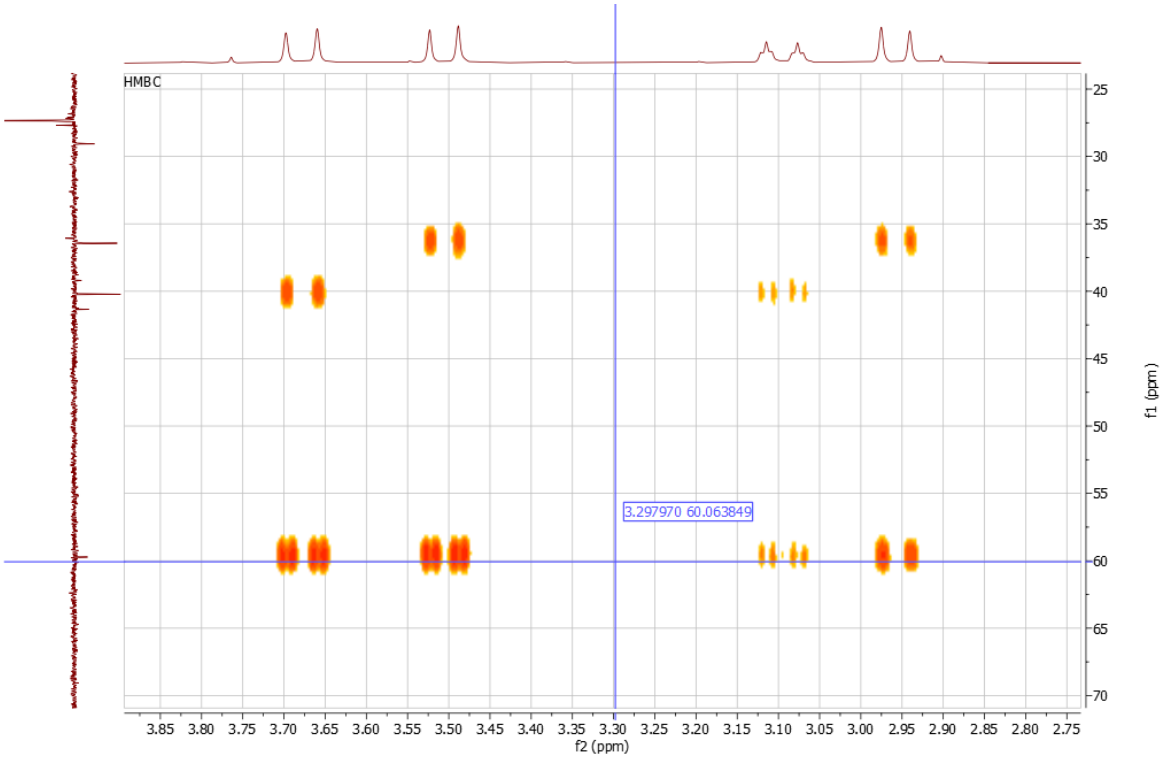
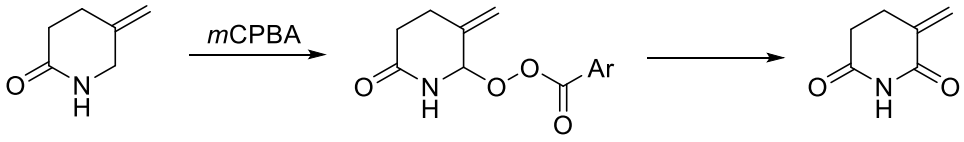


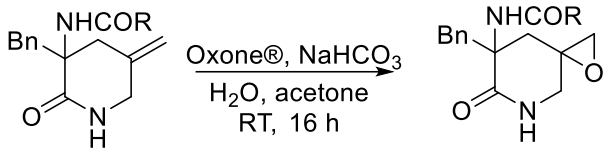
Figure 16 *– HMBC correlation of the CH_2 protons with the quaternary 3-position carbon.*

This process has been documented in the literature,[95,96,97] with several examples describing the oxidation of amides to imides using peroxides in the presence of a catalyst (*Scheme 115a*). The exact mechanism for this is unknown,[nature paper] but is thought to involve metal-catalysed formation of the peroxide radical, followed by hydrogen atom abstraction of either the C-H or N-H. This then recombines with the peroxide radical (*Scheme 115*), which then undergoes another hydrogen atom extraction to form the imide.



Scheme 115 *– oxidation of amides to imides using peroxides*.

In order to access the epoxides, an alternative epoxidising agent, Oxone®, was used. Pleasingly, this reagent was successful and formed the epoxides in good to excellent yields (*Scheme 116*), albeit with poor diastereocontrol.



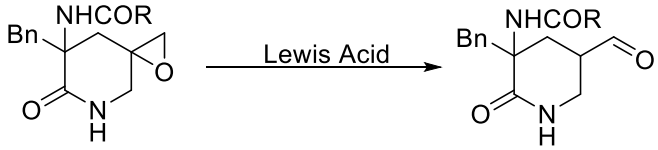
R = Ph, **13h**
= ^{t}Bu, **13j**
= CF_3, **13l**

R = Ph, **20h** 59% dr 2:1
= ^{t}Bu, **20j** 98% dr 2:1
= CF_3, **20l** 51% dr 2:1

Scheme 116 *– the epoxidations of* ***13h, 13j*** *and* ***13l*** *with oxone®.*

Conversion of the epoxide to an aldehyde would allow access an even wider variety of substrates, as these can be converted to carboxylic acid derivatives or undergo Wittig reactions.

Typically, epoxides can be easily opened by treatment with a Lewis acid (*Scheme 117*). Attempts at promoting this transformation are summarised in Table 7.



R = Ph, **20h**
= ^{t}Bu, **20j**
= CF_3, **20l**

H

Scheme 117 *– unsuccessful attempts at Lewis acid induced ring opening of epoxides.*

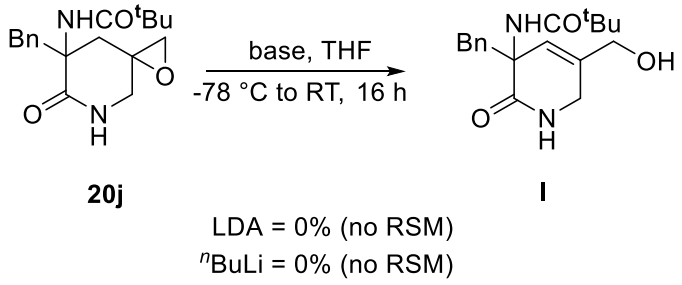
Table 7 – Treatment of lactam epoxides with Lewis acids.

Entry	Epoxide	Lewis Acid	Eq.	Solvent	t / h	T / °C	Yield / %
1	**20j**	$BF_3.OEt_2$ (bottle)	1.1	Toleune	1	RT	0
2	**20l**	$BF_3.OEt_2$ (bottle)	1.1	Toluene	1	RT	0
3	**20j**	$BF_3.OEt_2$ (distilled)	1.1	THF	16	RT	0
4	**20l**	$BF_3.OEt_2$ (distilled)	1.1	THF	16	RT	0
5	**20h**	$BF_3.OEt_2$ (bottle)	2+1	$CHCl_3$	0.5	RT	0
6	**20l**	$BF_3.OEt_2$ (bottle)	5+5	$CHCl_3$	24	RT	0
7	**20j**	$MgBr_2$	5	Toluene	72	110	0
8	**20l**	$MgBr_2$	5	Toluene	72	110	0

Initial attempts using $BF_3.OEt_2$ proved unsuccessful, with only starting material being observed. When commercial grade $BF_3.OEt_2$ failed to give any conversion to the desired product (*Table 7, entries 1 and 2*), freshly distilled $BF_3.OEt_2$ was used to ensure that the Lewis acid was free from degradation products that may hinder its effectiveness (*Table 7, entries 3 and 4*). As this was also unsuccessful, it was speculated that the BF_3 was coordinating to the amides, and so an excess of Lewis acid was used to ensure that the oxygen of the epoxide could be activated. Increasing the number of equivalents of $BF_3.OEt_2$ used did not give any desired product either (*Table 7, entries 5 and 6*). Upon addition of the Lewis acid, the reaction mixture turned slightly cloudy and TLC analysis showed the starting material was no longer present. Although after work-up, TLC analysis showed the starting material were again present, along with a bright spot on the baseline. The crude residue was markedly less soluble in a variety of solvents, with d^4-MeOD needed to obtain a crude NMR spectrum. Unfortunately, the crude ^1H NMR did not show a characteristic aldehyde resonance. The resonance for an α,β-unsaturated alcohol was also not present, which is a possible product if elimination to give the endocyclic alkene had occurred.

An alternative Lewis acid was also explored (*Table 6, entries 7 and 8*) as it has also been shown to induce the ring opening of epoxides.[98] Unfortunately, even 5 eq. of $MgBr_2$ in refluxing toluene returned only starting material after 3 days.

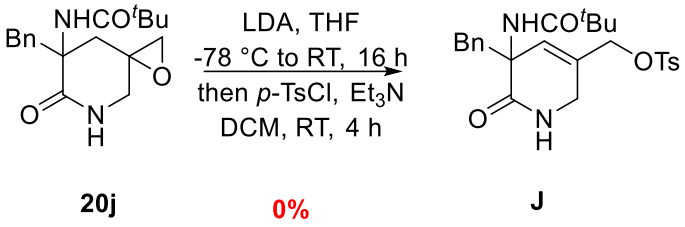
Epoxides can also be ring opened with the use of base, which would give the unsaturated alcohol, **I**, as the product (*Scheme 118*).



Scheme 118 *– Base-induced epoxide ring opening of* ***20j****.*

The use of both ^{n}BuLi and LDA gave very poor mass balance after flash column chromatography, and no starting material was recovered. This suggested that whatever product had been formed was extremely polar and failed to elute from the column. In

order to determine whether this could be the alcohol, the crude mixture was treated with tosylation conditions in the hopes that any polar groups would be transformed into something that could be more easily purified (*Scheme 119*).

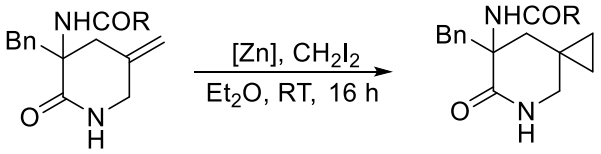


20j 0% **J**

Scheme 119 *– Base-induced epoxide ring opening of* ***20j*** *followed by tosylation*.

Unfortunately, subjecting the base-treated epoxide to tosylation conditions did not improve on this result, and nothing of interest eluted from the column. It was therefore likely that the alcohol is not one of the products formed.

As the alkene is reactive towards epoxidation, we hoped to be able to also make the spirocyclic cyclopropane by use of Simmons-Smith conditions (*Scheme 120, Table 8*). Cyclopropanes are a desirable component in many pharmaceuticals, so inclusion of this ring would give a highly desirable substrate.



R = ^{t}Bu, **13j**
= CF_3, **13l**

M

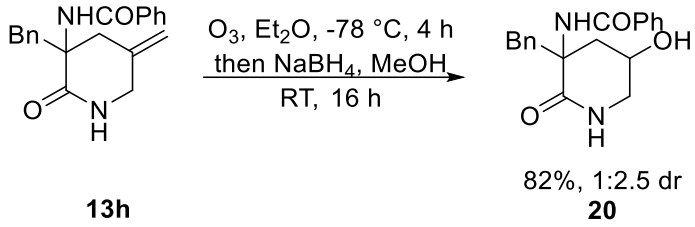
Scheme 120 *– Simmons-Smith cyclopropanation of* ***13j*** *and* ***13l****.*

Table 8 – Simmons-Smith conditions used on **13j** and **13l**.

Entry	Substrate	Zn Source	Conversion / %
1	**13j**	Zn, CuCl	0
2	**13l**	Zn, CuCl	0
3	**13j**	$ZnEt_2$	0
4	**13l**	$ZnEt_2$	0

Traditional Simmons-Smith conditions (Zn and CuCl) failed to give the cyclopropane (*Table 8, entries 1 and 2*), so modified conditions ($ZnEt_2$) were tested (*Table 8, entries 3 and 4*). Again, no cyclopropanated product was observed, with only starting material seen by TLC and NMR analysis after 16 h.

Another classical transformation of an alkene is that of ozonolysis. Depending on the work up, alcohols, carbonyls and carboxylic acids can all be accessed. In this case, a reductive ozonolysis was undertaken. After forming the ozonide intermediate under standard conditions, methanol and sodium borohydride were added and the alcohol **20** was isolated as a 1:2.5 mixture of diastereomers in an excellent yield, albeit with poor diastereocontrol (*Scheme 121*).



13h **20**

Scheme 121 *– Reductive ozonolysis of* ***13h*** *to give the alcohol* ***20*** *as a mixture of diastereomers.*

This class of lactam has been selectively functionalised at the amide, alkene and lactam sites, with most reactions proceeding without problem. The diastereoselectivities of these funationalisations were poor, and the reduction of the lactam to the corresponding piperdine, as well as cyclopropanation, did not give positive results. the use of mCPBA gave the glutarimides instead of the epoxides, however switching to Oxone® gave the desired epoxide products.

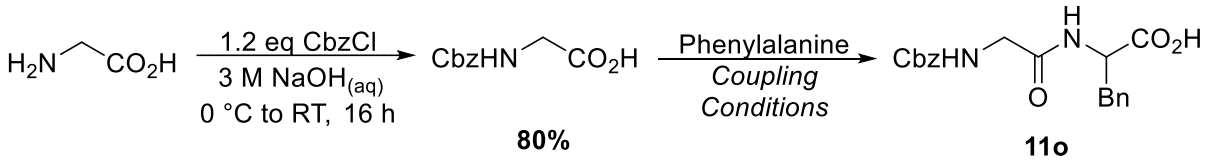
2.5.5 Dipeptide Surrogates

2.5.5.1 Cbz-Protected Motifs

Examples of azlactones derived from *N*-protected dipeptides are seen in the literature,[99] and therefore it stands to reason that these substrates would also undergo allylation and subsequent cyclisation under our conditions to give the dipeptide-like lactams. It was decided that initially we would use the azlactone derived from Cbz-Gly-Phe, as the

Cbz group can be relatively easily removed by hydrogenation. This would give access to the free amine for further functionalisation or coupling to a longer peptide chain. The first challenge was to synthesise this azlactone.

Attempts to synthesise Cbz-Gly-Phe (**11o**) from the individual amino acids were undertaken (*Scheme 122, Table 9*), with the Cbz-protection of glycine using benzyl chloroformate in aqueous NaOH proceeding with an excellent yield of 80%.

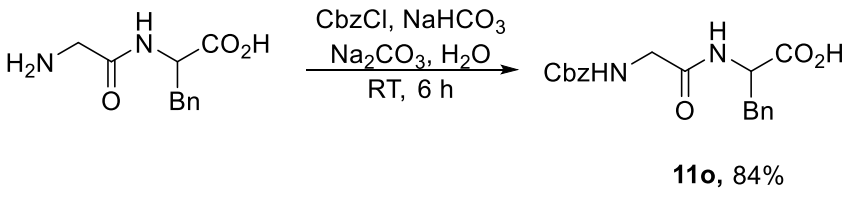


Scheme 122 *– Cbz protection of glycine followed by the coupling with phenylalanine to give Cbz-Gly-Phe.*

Table 9 – Coupling of Cbz-Gly and Phenylalanine

Entry	Conditions	Yield/ %
1	EtOCOCl, Et_3N, THF, H_2O, 0 °C, 1 h	trace
2	^{i}BuOCOCl, Et_3N, THF, 0 °C to RT, 16 h	trace
3	HATU, NMM, DMF, 50 °C, 16 h	0

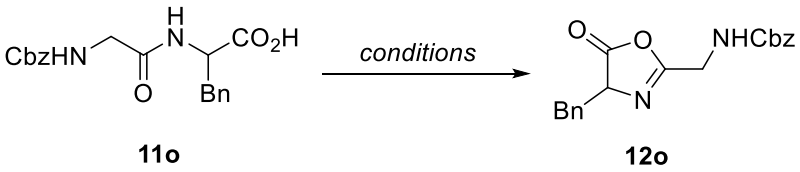
However, attempts to couple this to phenylalanine using traditional peptide coupling reagents such as chloroformates and HATU proved unsuccessful (*Table 9*). Both EtOCOCl and ^{i}BuOCOCl appeared to give some conversion to the dipeptide (*Table 9, entries 1 and 2*), however it was impossible to separate this from the starting materials and the Phe-Phe dipeptide produced as a by-product. HATU resulted in no conversion to the dipeptide (*Table 9, entry 3*), and as we knew purification would be difficult, we decided to use a different route that avoids this issue. It was found that the Cbz-protection of the (more expensive) commercially available dipeptide was much simpler way to access the desired substrate (*Scheme 123*).



Scheme 123 *– Cbz protection of Glycyl-Phenylalanine to give Cbz-Gly-Phe.*

Cbz-protection was achieved using a mixture of $NaHCO_3$ and Na_2CO_3 in water, as the method used on the monopeptide gave yields of less than 50% on this substrate.

With the Cbz-protected dipeptide in hand, cyclodehydration to the azlactone was attempted (*Scheme 124, Table 10*).



11o **12o**

Scheme 124 *– Dehydrative Cyclisation of Cbz-Gly-Phe to give the dipeptidic azlactone.*

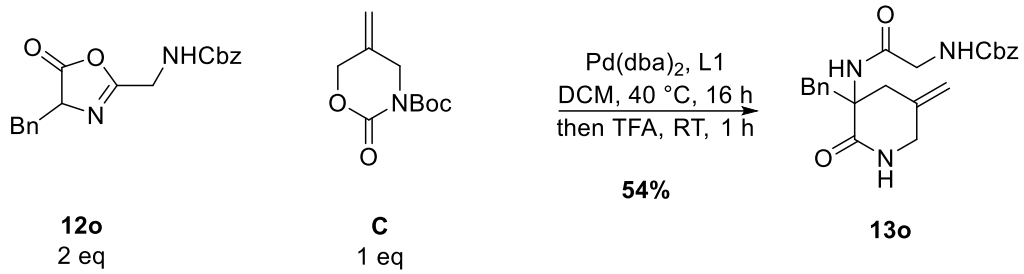
Table 10 – The optimisation of the dehydrative cyclisation of Cbz-Gly-Phe.

Entry	Dehydrating Agent (eq)	T / °C	t / h	Conversion / %	Yield / %
1	DCC (1.2)	0	4	0	-
2	Ac_2O (excess)	90	0.5	Complex mixture	-
3	Ac_2O (excess) + pyridine (1)	RT	1	Complex mixture	-
4	EDC.HCl (1.05)ref	0 to RT	1	0	-
5	EDC.HCl (1.1)	0	1	10	-
6	EDC.HCl (1.2)	0 to RT	16	25	19
7	EDC.HCl (1.5)	0 to RT	16	35	25
8	EDC.HCl (2)	0 to RT	16	27	5
9	EDC.HCl (2.2)	0 to RT	16	26	16
10	EDC.HCl (3)	0 to RT	16	28	19
11	EDC.HCl (2+1)	0 to RT	9+16	60	11
12	EDC.HCl (1+1+2)	0 to RT	3+6+16	35	26
13	EDC.HCl (1+1+1+1+1)	0 to RT	1+1+1+1+1	8	0
14	EDC.HCl (10)	0 to RT	16	35	-

Unfortunately, it proved exceedingly difficult to access this azlactone, despite attempts using several literature procedures. The use of DCC resulted in no conversion (*Table 10, entry 1*), whilst the use of Ac_2O gave a complex mixture from which the product could not be isolated (*Table 10, entries 2 and 3*). Methods that had worked in the literature

and previously with the acylated amino acids (*Table 10, entries 4-7*) gave very poor conversion. Using more forcing conditions (*Table 10, entries 8-14*), higher conversions were achieved in some cases, but upon attempts to purify the mixture by flash column chromatography, the samples simply degraded or hydrolysed on silica, giving very poor isolated yields.

Despite these setbacks, a sample large enough to undergo further reactions was obtained and was subjected to the Pd-catalysed allylation-cyclisation conditions (*Scheme 125*).



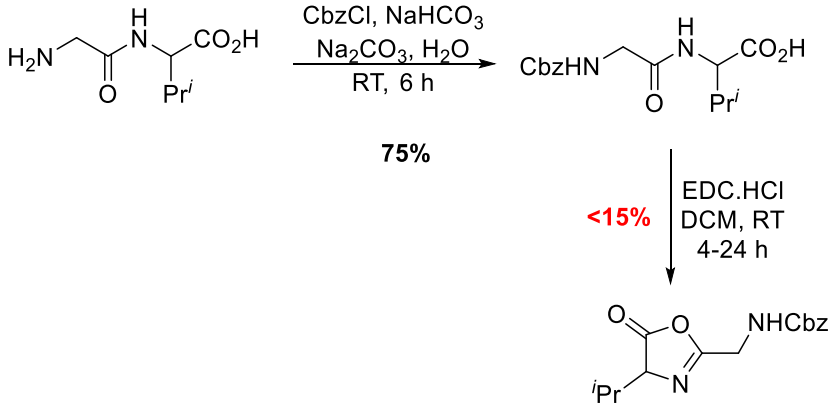
12o
2 eq

C
1 eq

13o

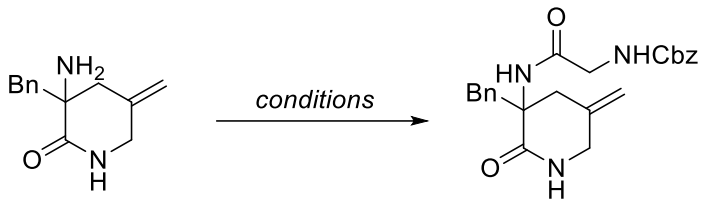
Scheme 125 *– The allylation/cyclisation of the dipeptidic azlactone to the dipeptide Freidinger lactam.*

The allylation-cyclisation proceeded with a good yield of 54%, showing that dipeptide-derived azlactones are compatible with the reaction conditions of our key step. Attempts to investigate different dipeptides were unfortunately hampered by the same issues when using glycylvaline (*Scheme 126*).



Scheme 126 *– Cbz protection of glycylvaline followed by the dehydrative cyclisation to give the dipeptidic azlactone.*

With the difficulties in making this type of azlactone, it was decided that a different route to the lactam would be worthwhile. The easily cleaved trifluoroacetamide group was employed by simply treating **13l** with NaOH in water and methanol to give the amine **17**, which could then be coupled to Cbz-protected glycine (*Scheme 127, Table 11*).



17 **13o**

Scheme 127 *– The coupling of lactam **17** with Cbz-Glycine to give the dipeptidic lactam*.

Table 11 – The optimisation of the coupling of **17** with Cbz-Glycine

Entry	Conditions	Conversion/ %
1	^{i}BuOCOCl, Et_3N, THF, 0 °C to RT, 17 h	0
2	EtOCOCl, Et_3N, THF, 0 °C to RT, 17 h	0
3	1-Hydroxy-7-azabenzotriazole, EDC.HCl, DIPEA, DCM, 0 °C to RT 16 h	100

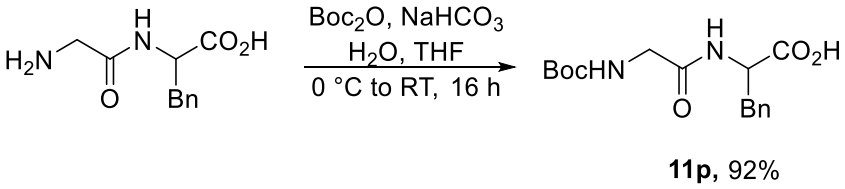
The use of ^{i}BuOCOCl and EtOCOCl both gave no conversion (*Table 11, entries 1 and 2*), which was not surprising due to the bulky nature of the amine. Coupling agent 1-hydroxy-7-azabenzotriazole, however, has been shown to give good results with tertiary amines. This reagent gave us good conversion (*Table 11, entry 3*). Unfortunately, we found that as a MeOH/EtOAc was needed to purify the product via silica gel column chromatography, by-products that are also formed in the reaction were also eluting at the same time, giving an unclean sample with an indeterminate yield.

2.5.5.2 Boc-Protected Motifs

While initially accessing the Cbz-protected dipeptide lactam was a priority, it was possible that a different protecting group could work better. Boc-protected dipeptide azlactones have also been documented in the literature.[100] At first, they were not considered as an option as there would likely be problems in the cyclisation reaction,

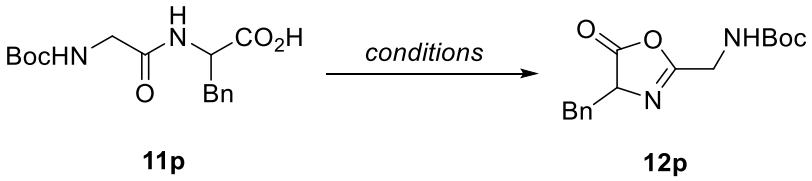
where the use of TFA could also remove this Boc group. This would provide a free primary amine - which are notoriously difficult to purify – as part of a messy crude mixture. However, as the Cbz-protected substrate was proving difficult, it was decided that it would be worth attempting to use the Boc-protected azlactone and instead return to forming the lactam in as two steps rather than as a telescoped procedure. Purification or even semi-purification of the allylated intermediary azlactone in order to remove all the undesired species would give a much cleaner crude mixture after the TFA step, which in turn would allow the formation of a salt which would hopefully precipitate cleanly.

A simple Boc-protection using a literature procedure gave the Boc-dipeptide in a good yield of 92% (*Scheme 128*).[100]



Scheme 128 *– The Boc-protection of Glycl-Phenylalanine to give Boc-Gly-Phe.*

Cyclisation of **11p** proceeded to give the azlactone **12p** (*Scheme 129, Table 12*).



11p **12p**

Scheme 129 *– The dehydrative cyclisation of Boc-Gly-Phe to give the Boc-azlactone.*

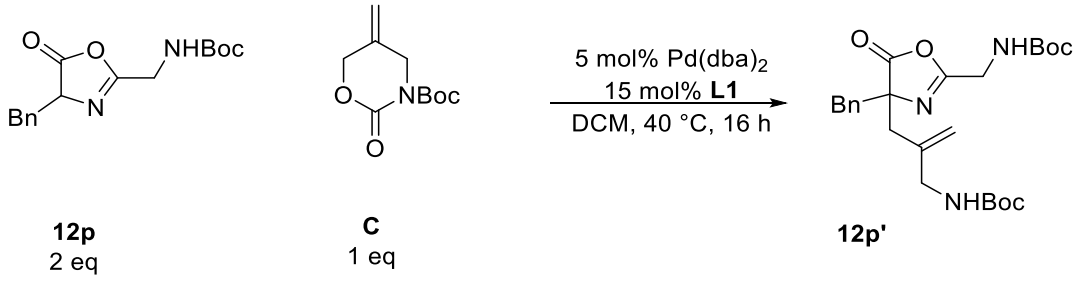
Table 12 - The optimisation of the dehydrative cyclisation of Boc-Gly-Phe.

Entry	Dehydrating Agent (eq)	T / °C	t / h	Yield / %
1	EDC.HCl (1.5)	RT	16	26
2	DCC (1.1)	0	4	83
3	**DCC (1.2)**	**0**	**6**	**93**

Treating the Boc-protected dipeptide with the standard EDC conditions used to make earlier azlactones gave a lower yield than previous azlactones (*Table 12, entry 1*), however results were comparable to the conversion for the Cbz-protected azlactone. In contrast to the Cbz-protected azlactone, however, the Boc-protected azlactone did not seem to degrade on the silica and therefore the Boc-protected azlactone was easily isolated.

Literature procedures have used DCC to cyclise Boc-protected dipeptides into their azlactones, and following this procedure, we obtained the azlactone in a good yield with no need for chromatography (*Table 12, entry 2*). After filtration of the urea by-product, it was observed that some starting materials remained in the mixture when analysed by NMR spectroscopy. These could be simply washed out with a saturated solution of $NaHCO_3$. In order to improve on this initial result, a slight increase in the equivalents of DCC was employed and the reaction mixture was left for longer to ensure the reaction went to completion (*Table 12, entry 3*). This gave an improvement to the yield from 83% to 93%.

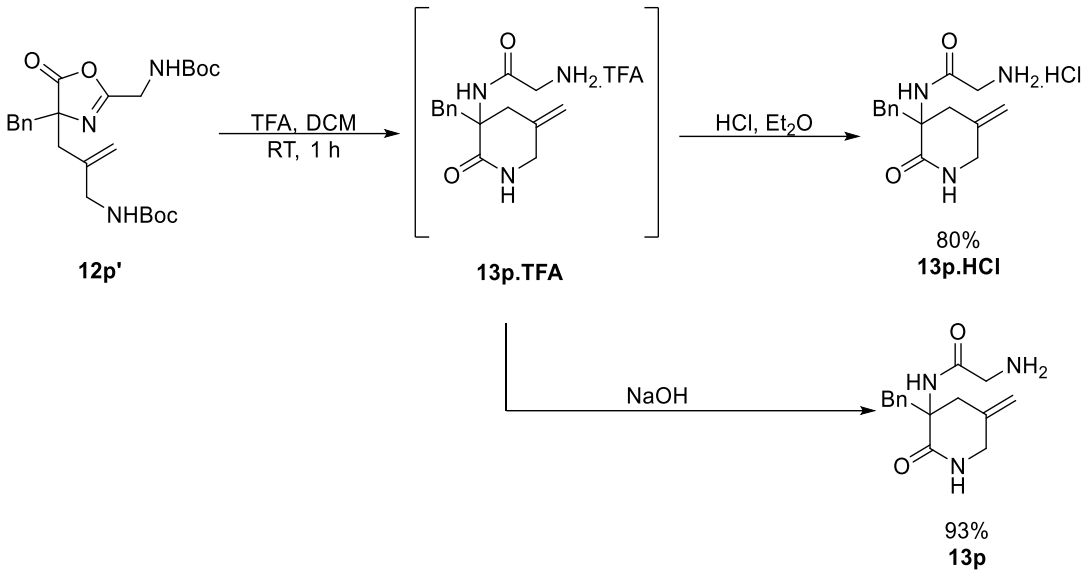
Subjecting the Boc-protected azlactone to the allylation reaction conditions gave good conversion to the allylated intermediate (*Scheme 130*).



Scheme 130 *– The allylation of the Boc-protected azlactone* ***12p****.*

This was semi-purified by chromatography; the starting azlactone was eluted by flushing with 10% EtOAc in petrol, then all fractions containing product were collected, giving the intermediate as a crude mixture.

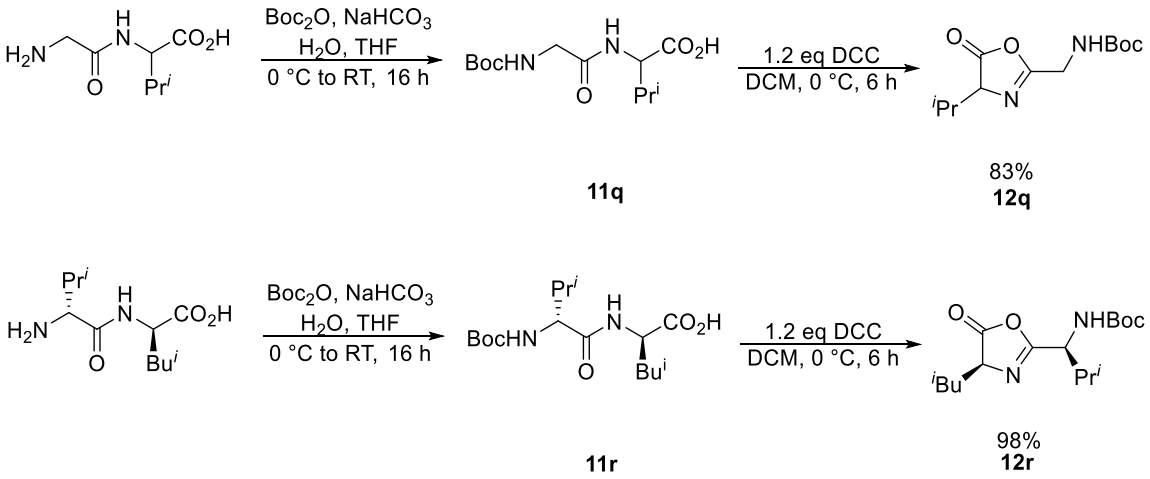
Treatment of the allylated intermediate with TFA followed by evaporation of the excess TFA and solvent gave the TFA salt of the lactam (*Scheme 131*).



Scheme 131 *– The cyclisation of the allylated azlactone to give the lactam, followed by salt exchange to give the HCl salt as a precipitate, or basification with NaOH to give the free amine.*

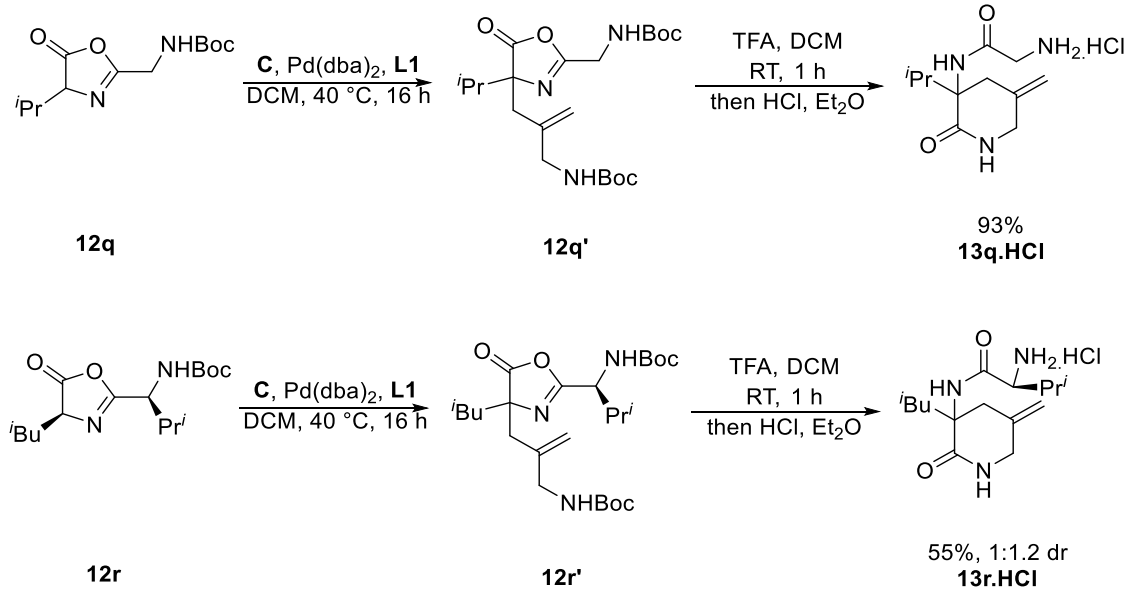
However, this lactam salt appeared to be quite soluble in a variety of solvents, so we decided to exchange the TFA anion and form the HCl salt. This was done by adding HCl in Et_2O until no more precipitate formed, as the HCl salt was very insoluble in Et_2O, and 1**3p.HCl** was obtained in a good yield of 80%. The free amine (**13p**) can also be accessed by quenching of the TFA with aqueous NaOH, with a yield of 93%.

At this point, the scope of dipeptides was expanded. The Boc-protected azlactones were made in excellent yields from dipeptide Gly-Val and Val-Leu via Boc-protection and subsequent cyclisation using DCC (*Scheme 132*). Compound **12r** was isolated as a single diastereomer.



Scheme 132 *– Synthesis of* ***12q*** *and* ***12r*** *from Boc-protected dipeptides.*

Subjecting these azlactones to the allylation conditions, semi-purification and then the deprotection cyclisation conditions gave **13q.HCl** in an excellent yield, and **13r.HCl** in a good yield as an inseparable 1:1.2 mixture of diastereomers (*Scheme 133*).



Scheme 133 *– Allylation and subsequent cyclisation and salt exchange of* ***12q*** *and* ***12r*** *to make the hydrochloride salts of* ***13q*** *and* ***13r.***

Despite the difficulties in synthesising **12o** and **13o**, the ease of access of **12p** has allowed a scope of dipeptidic surrogate lactams hydrochloride salts to be accessed in good yields. This class of lactam is made in two steps, with the intermediate allylated azlactone semi-purified by chromatography. The resulting salts can be neutralised to give the amines by washing with 1 M $NaOH_{(aq)}$.

2.5.5.3 Macrocycle Formation

There are many examples of polypeptide macrocycles being utilised as β-turn mimics.[101] A conformation-restraining motif is often present in cyclic polypeptides; in many cases, this is done using proline, D-amino acids or an aromatic linker (*Figure 17*).

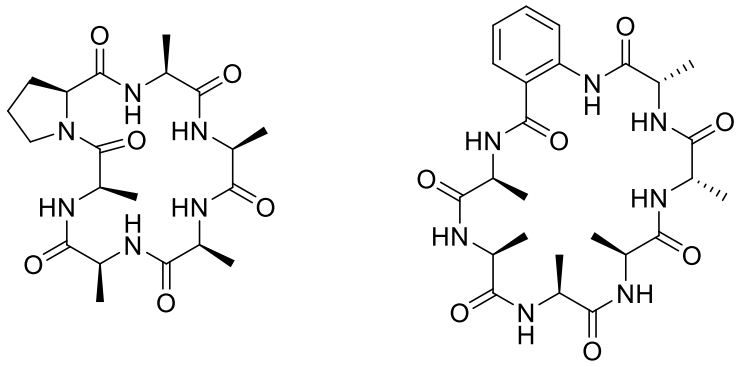
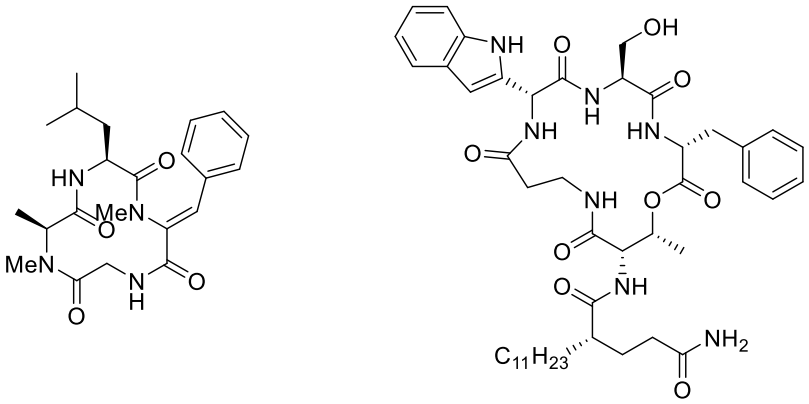


Figure 17 *– examples of conformation-restraining moieties in cyclic polypeptides using proline (left) and an aromatic linker (right).*

Colisporifungin, isolated from *Colispora cavincola*, is an antifungal lipopeptide.[102] It shows potency against *Aspergillus fumigatus* and *Candida albicans*, the most common causes of invasive fungal infections (*Figure 18*).



Tentoxin **Colisporifungin**

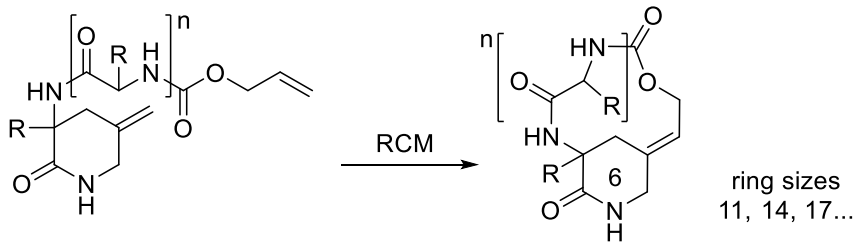
Figure 18 *– Natural cyclic polypeptides with potent biological activities.*

Tentoxin is a cyclic tetrapeptide produced by the *Alternaria alternata* fungus and has been shown to selectively induce chlorosis in a variety of plants.[103,104] It has been shown to be effective against the weeds of many crop plants, such as corn, cruciferous

vegetables[105] and mung bean,[106] while the crop itself is unaffected, and therefore is a good herbicide candidate.

Typically, these compounds are isolated directly from the fungus after fermentation, but the low yields have prevented any large-scale use. Initial attempts at the synthesis of Tentoxin gave low yields of 25% over several steps,[104] which was not deemed viable, especially when broad-spectrum herbicides such as glyphosate (Round Up®) are far more economical. More recently, herbicide-resistance in weeds has brought this class of natural herbicide to the forefront of agrichemical research.[107] Tentoxin has since been synthesised with a 60% yield from Boc-Leu-Gly.[108]

It was envisaged that the Freidinger lactam could be utilised as a conformation-stabilising motif in a polypeptidic macrocycle, by installation of an Alloc protecting group followed by RCM (*Scheme 134*). It has been shown that Freidinger lactams stabilise peptidomimetics to metabolism, so it was hoped that the inclusion of this motif will also slow down degradation affects in an agrochemical setting,[74] whilst maintaining high biological activity.



Scheme 134 *– cyclic polypeptide mimics containing the δ-lactam motif.*

Protection of the dipeptidic lactam hydrochloride salt (**13p.HCl**) gave a low yield (*Scheme 135, Table 13, entry 1*), however this was increased by using the free amine **13p** (*Table 13, entry 2*).

13p **13s**

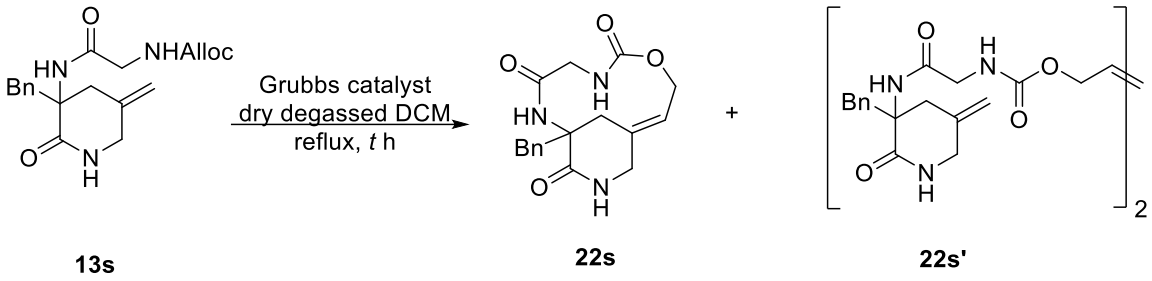
Scheme 135 *– Alloc-protection of the dipeptidic lactam.*

Table 13 – Optimisation of the Alloc-protection.

Entry	Amine	Base (eq)	Eq. AllocCl	Yield / %
1	**13p.HCl**	Et_3N (10)	1.5	34
2	**13p**	Et_3N (5)	1.2	46
3	**13p**	**Et_3N (5)**	**2**	**69**
4	**13p**	Et_3N (5)	3	55
5	**13p**	Et_3N (10)	2	71
6	**13p**	DIPEA (5)	2	74
7	**13p**	Et_3N (5) DMAP (0.2)	2	53

Increasing the equivalents of AllocCl to 2 eq. gave a better yield (*Table 13, entry 3*), whilst 3 eq. saw this improvement reversed (*Table 13, entry 4*). Increasing the equivalent of base (*Table 13, entry 5*) and changing the base (*Table 13, entry 6*) gave no obvious improvement to the yield of the Alloc-protected product, and adding a catalytic amount of DMAP reduced the yield significantly (*Table 13, entry 7*).

Attempts to induce ring closing metathesis on the Alloc-protected motif gave varied results (*Scheme 136, Table 14*). It is important to note that both trisubstituted alkenes and 11-membered rings are notoriously difficult to make via RCM.[109] To increase the chances of RCM vs intermolecular cross-metathesis, high dilutions were used.



13s **22s** **22s'**

Scheme 136 *– Ring Closing Metathesis of the Alloc-protected dipeptidic lactam to give an 11-membered macrocycle, and the dimer of intermolecular metathesis at the Alloc group.*

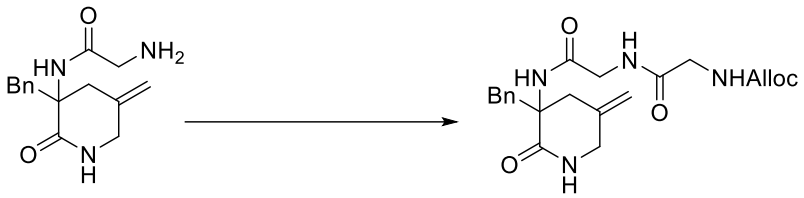
Table 14 – Optimisation of RCM.

Entry	Catalyst	Concentration / M	t / h	RSM / %	Yield A / %	Yield B / %
1	G-I	0.01	16	54	-	20
2	G-II	0.01	16	37	-	23
3	HG-II	0.01	16	59	-	-
4	G-II	0.005	48	40	-	16
5	HG-II	0.01	48	32	-	25

Both Grubbs I and Grubbs II catalysts gave a significant portion of recovered starting material after 16 hours (*Table 14, entries 1 and 2*), with the only product being the dimer formed by cross-metathesis. Hoveyda-Grubbs II also gave a significant amount of recovered starting material (*Table 14, entry 3*), although no dimer was seen and neither was the desired product. In order to favour formation the RCM product, the reaction was done under more dilute condition for a longer period of time using Grubbs II – which, has been shown to be most active at making trisubstituted alkenes.[110] Unfortunately, this also gave only recovered starting material and the intermolecular dimer product (*Table 14, entry 4*). As no conversion of starting material was observed using HG-II, the reaction was repeated with an extended reaction time of 48 hours. This

time, conversion to the dimer was observed, with no trace of the desired RCM product (*Table 14, entry 5*).

Given the challenges associated with generating medium-sized macrocycles, larger ring sizes were targeted. Therefore, the free amine was coupled to Alloc-protected glycine in order to increase the chain length which would lead to a 14-membered ring after RCM (*Scheme 137*).



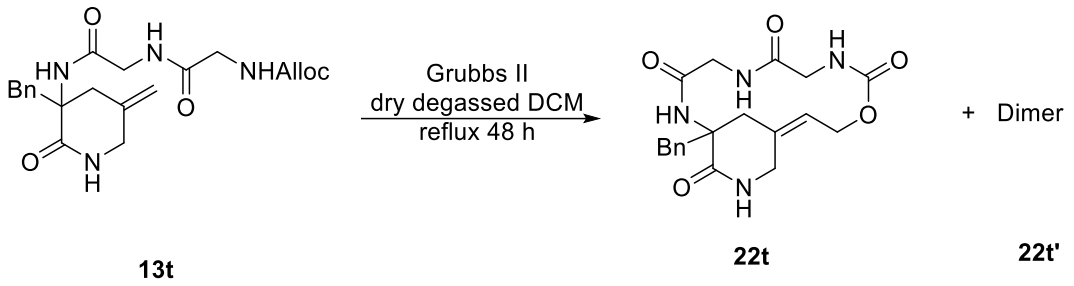
Scheme 137 *– Coupling the dipeptidic lactam with Alloc-Glycine to extend the peptide chain.*

Table 15 – Optimisation of the coupling of the dipeptidic lactam and Alloc-Glycine.

Entry	Conditions	Yield / %
1	1-hydroxy-7-azabenzotriazole, DCC, DMF, 0 °C to RT, 16 h	31
2	1-hydroxy-7-azabenzotriazole, EDC, DIPEA, DCM, 0 °C to RT, 16 h	46
3	**^{i}BuOCOCl, Et_3N, THF, 0 °C to RT, 16 h**	**100**

Coupling of the dipeptidic lactam to Alloc-glycine gave low-moderate yields when using 1-hydroxy-7-azabenzotriazole with either DCC in DMF (*Table 15, entry 1*), or EDC and DIPEA in DCM (*Table 15, entry 2*). In contrast, using isobutyl chloroformate as the coupling reagent gave full conversion to a quantitative yield of the extended peptidic motif (*Table 15, entry 3*).

This tripeptidic lactam was then subjected to ring closing metathesis conditions (*Scheme 138*). Grubbs-II was chosen as the catalyst due to there being more literature precedence for RCM to occur on disubstituted alkenes (forming trisubstituted alkenes).[110]

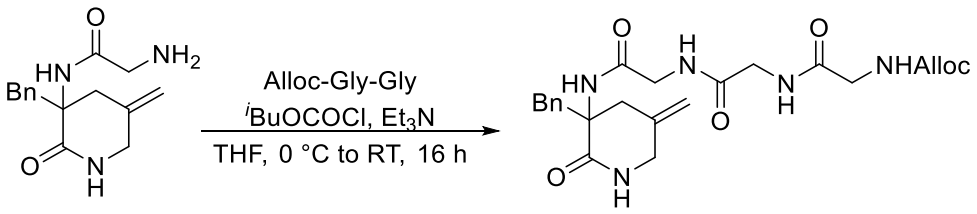


13t **22t** **22t'**

Scheme 138 *– Ring Closing Metathesis of* ***13t****.*

Unfortunately, the test reaction with Grubbs-II catalyst gave a conversion of approximately 60% to the dimer, with no trace of the RCM product seen.

Given that neither 11- or 14-membered rings could be accessed using RCM, attempts were made to increase the ring size by one more amino acid residue in the hopes that the 17-membered ring could be accessed. Using the method optimised for coupling lactam **13p** and Alloc-Glycine, lactam **13p** was also coupled to Alloc-Glycyl-Glycine (*Scheme 139*).

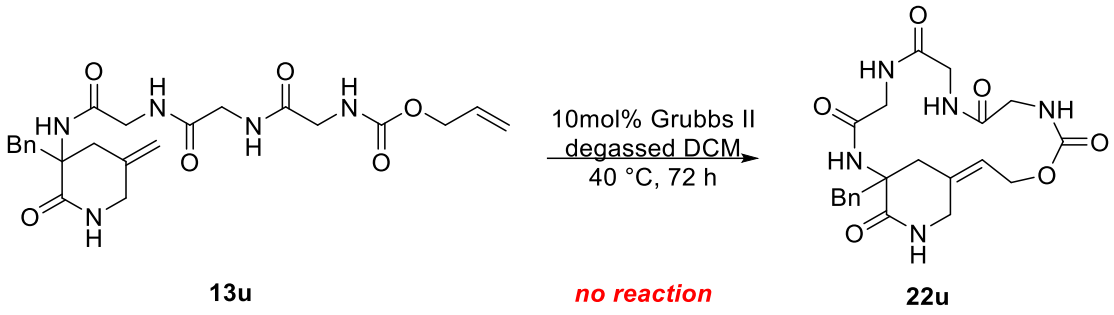


13p **13u**

Scheme 139 *– Coupling of the dipeptidic lactam to Alloc-Gly-Gly.*

Upon the addition of isobutyl chloroformate and triethylamine to Alloc-Glycyl-Glycine, the reaction mixture turned deep red. This is characteristic of the formation of a cyclic dipeptide. Subsequent addition of **13p** gave a very poor yield of the desired product **13u**. The yield was slightly improved to 13% by adding ^{i}BuOCOCl and Et$_3$N to a solution of **13p** and Alloc-Gly-Gly, thereby allowing the amine to compete with cyclisation. Polypeptide

surrogate **13u** was subsequently subjected to RCM using Grubbs-II catalyst (*Scheme 140*).



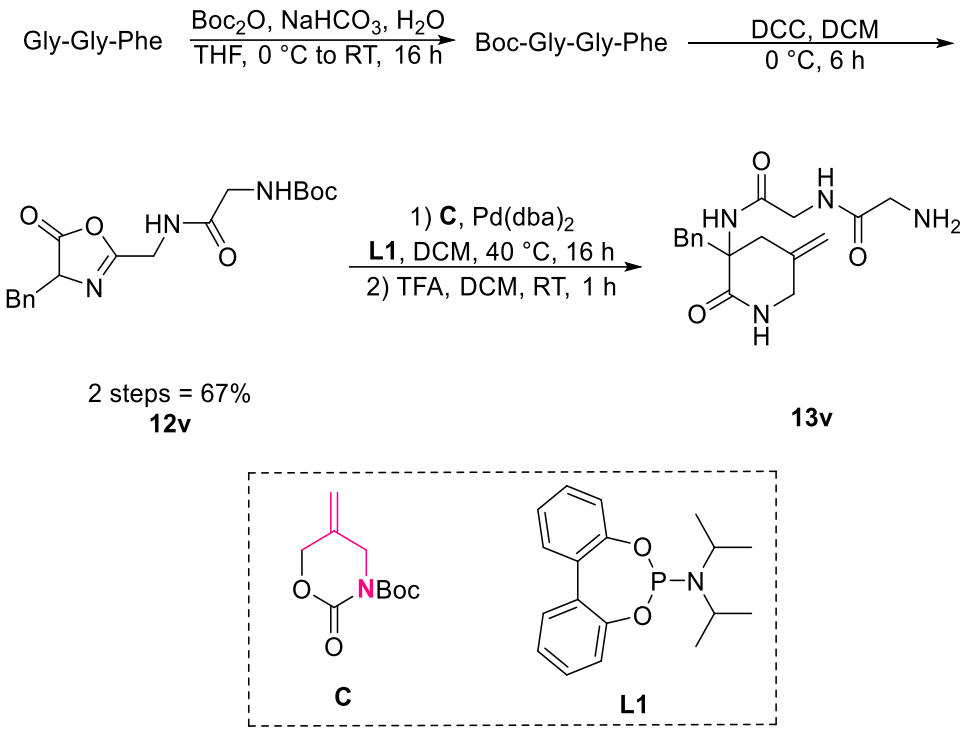
Scheme 140 *– the Ring Closing Metathesis of* ***13u****.*

Unfortunately, after 72 hours of monitoring by TLC, a large amount of starting material remained. Analysis by LCMS showed that neither the dimer nor the macrocycle were formed, and all other species were derivatives of the catalyst.

Disappointingly, all attempts at ring closing metathesis were unsuccessful. Increasing the ring size to ones more favourable for RCM did not improve reactivity at the 1,1-disubstituted alkene. These disappointing results were most likely due to the inactivity of the 1,1-disubstituted alkene, a notoriously difficult olefin for even cross-metathesis.

2.5.5.5 Extending the Peptide Chain

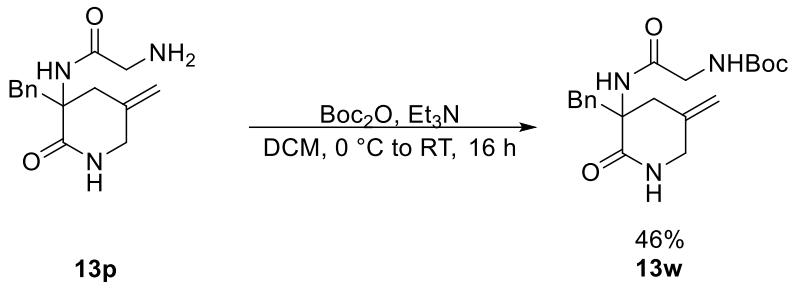
Freidinger lactams are often incorporated into peptide chains to provide modified proteins. Therefore, the lactams were incorporated into longer peptide chains in order to show that this type of peptidomimetic can be accessed. Previously when working towards RCM, it was shown that Alloc-Glycine can be coupled to the dipeptidic lactam scaffold. Direct synthesise of this structure was undertaken from the tripeptide via the azlactone and allylation/cyclisation (*Scheme 141*).



Scheme 141 *– Synthesis of the tripeptidic lactam from the tripeptide via the azlactone.*

The tripeptidic azlactone was made with a good yield of 67% over 2 steps from the tripeptide. Upon treating this with the allylation conditions, the conversion to the allylated intermediate was observed after semi-purification to be low. This was not completely unexpected, as similarly to substrate **12n**, a highly coordinating group (an amide in this case) can compete with the reactive site (the azlactone). Subjecting the allylated intermediate to the cyclisation conditions gave only trace amounts of the lactam **13v**.

Lactam **13p** was subjected to Boc-protection to provide an easily removable protecting group and prevent the amine interfering with functionalisation reactions elsewhere on the motif (*Scheme 142*).

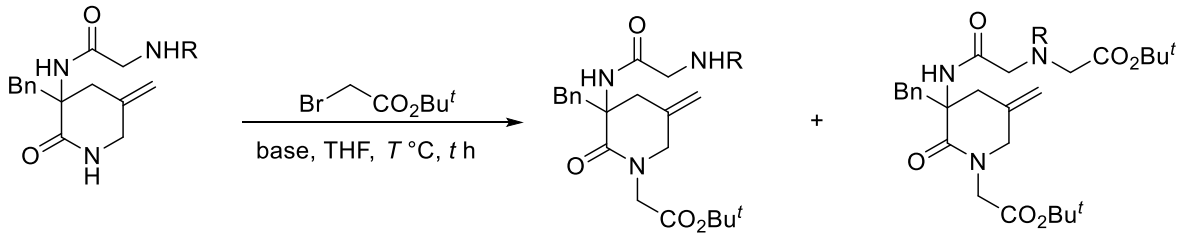


13p **13w**

Scheme 142 *– the Boc-protection of* ***13p****.*

The reaction proceeded to give **13w** in with a moderate yield of 46%, which is open to future optimisation.

Insertion of this Freidinger lactam motif into the middle of a peptide chain sequence, and not just at the terminus, was highly desirable. In order to do this, ^{t}butyl bromoacetate and base were used to alkylate the lactam nitrogen and convert it into a glycine mimic (*Scheme 143*).



R = Cbz, **13o**
= Alloc, **13s**
= Boc, **13w**

R = Cbz, **18o**
= Alloc, **18s**
= Boc, **18w**

R = Cbz, **18o'**
= Alloc, **18s'**
= Boc, **18w'**

Scheme 143 *– Alkylation of the lactam on dipeptide surrogates* ***3o****,* ***3s*** *and* ***3t****.*

The first attempt at this reaction using the conditions previously used in the synthesis of 18h and 18l gave only product 18o' (*Table 16, entry 1*). As it was likely that this disubstitution product had occurred due to excess base, 1 equivalent of NaH was instead used (*Table 16, entry 2*). Unfortunately, this led to an approximately 1:1 mixture of

mono- and di-substituted products (**18s** and **18s'**). As NaH has no steric bulk, this likely led to the lack of selectivity in this reaction, therefore the reaction was optimised by varying the base (*Table 16*).

Table 16 – Optimisation of the alkylation using *t*-butyl bromoacetate.

Entry	Lactam	Base (eq)	Conditions	Yield 18/ %	Yield 18'/ %
1	**13o**	NaH (3)	DMF, 0 to 20 °C, 17 h	-	64
2	**13s**	NaH (1)	DMF, 0 to 20 °C, 17 h	39	39
3	**13o**	K_2CO_3 (1.5)	DMF, 0 to 20 °C, 17 h	-	-
4	**13s**	LDA (1)	THF, -78 to 20 °C, 17 h	46	-
5	**13s**	**LDA (1.4)**	**THF, -78 to 20 °C, 17 h**	**69**	**-**
6	**13w**	**LDA (1.4)**	**THF, -78 to 20 °C, 17 h**	**72**	**-**

K_2CO_3 was chosen as a slightly weaker base, in the hopes that it would only be able to deprotonate the most acidic proton, and therefore only **18** would be formed. Unfortunately this base did not lead any alkylation (*Table 16, entry 3*), suggesting this base was not strong enough to deprotonate any of the nitrogen centres in this molecule.

It was postulated that a nitrogen-centred base may be more appropriate for this system, and the use of bulky LDA would hopefully allow for selective deprotonation at the least hindered site (the lactam). Subjecting **13s** to 1 eq. of LDA gave a 46% yield of **18s** (*Table 16, entry 4*) notably without any evidence of **18s'**. Increasing the number of equivalents of LDA from 1 to 1.4 significantly increased the yield (*Table 16, entry 5*). The disubstituted product was not observed despite the excess of LDA present. Use of these conditions on **13w** gave a comparable yield of 72% for **18w** (*Table 16, entry 6*), without observation of any disubstitution.

By reacting the lactam nitrogen to form a glycine mimic, this handle would allow this motif to be inserted into longer peptide sequences, and allow analysis of any secondary structures that may be influenced by the δ-lactam.

2.6 Conclusions

A variety of azlactones have undergone allylation using a palladium catalyst and a cyclic carbamate as the allylic precursor. Subsequent Boc-deprotection using TFA resulted in the cyclisation of the amine, opening of the azlactone and gave novel Freidinger lactams containing an exocyclic methylene group. Unfortunately, use of chiral phosphoramidite ligands did not give the exceptionally high enantioselectivities seen with previous dicarbonyl substrates. It is hoped that an alternative class of ligands will promote a highly enantioselective synthesis of this class of lactam.

The lactams produced contained three potential synthetic handles. The lactam, amide and alkene in the products could be selectively functionalised using a variety of techniques: lactam alkylation, hydrolysis of TFA amides, and epoxidation of the alkene to form a spirocycle. Suzuki couplings, ozonolysis and oxidative iodinations all proceeded in high yields. Poor disastereoselectivities were observed in reactions at the exocyclic alkene, with diastereomer ratios of 2:1 in most cases. Attempts at reduction of the lactam, epoxide ring-opening, cyclopropanation were unsuccessful, with complex mixtures being obtained in the former reactions, whilst no reaction occurred in the latter.

Peptidomimetic motifs containing the lactam scaffold were developed. The azlactones derived from Cbz-protected dipeptides proved exceedingly difficult to synthesise, however this setback was overcome by the use of Boc-protected dipeptides. The allylated intermediates were semi-purified before being subjected to TFA, as the primary amine product would otherwise have been difficult to isolate from the crude reaction mixture. These dipeptide surrogates could be protected with a variety of amine protecting groups, and subsequent alkylation could be undertaken using 1.1-1.4 eq. LDA to access a tripeptidic sequence.

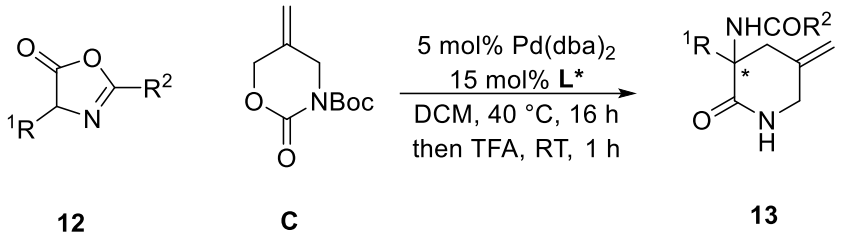
Protection of the dipeptidic surrogates using AllocCl allowed attempts at ring-closing metathesis to be undertaken. Unfortunately, subjecting these substrates to Grubbs catalysts were not successful, with tri-substituted alkenes and 11-membered macrocycle being infamously difficult to synthesise. Removing the barrier of the ring size by

increasing the number of glycine residues in the peptide surrogate also yielded no macrocycle. In all cases, only starting material and the cross-metathesis dimer were observed.

It is hoped that in the future, an alternative route to these medium-sized macrocycles will be established, perhaps by extending the exocyclic alkene to a mono-substituted alkene, which is more compatible with ring-closing metathesis.

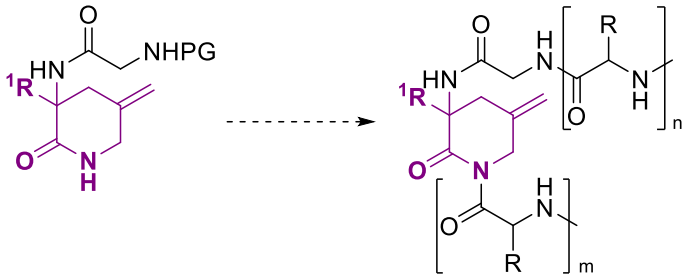
2.7 Future Work

A key area of interesting in the progression of this work is the development of an asymmetric variant (*Scheme 144*). It is hoped that by the use of a different class of ligands, for example those used by Trost,[88] the lactams can be accessed with high enantioselectivies. Further studies into the *syn*-diastereomers of ligands **L10**-**L11** could also give high selectivities.



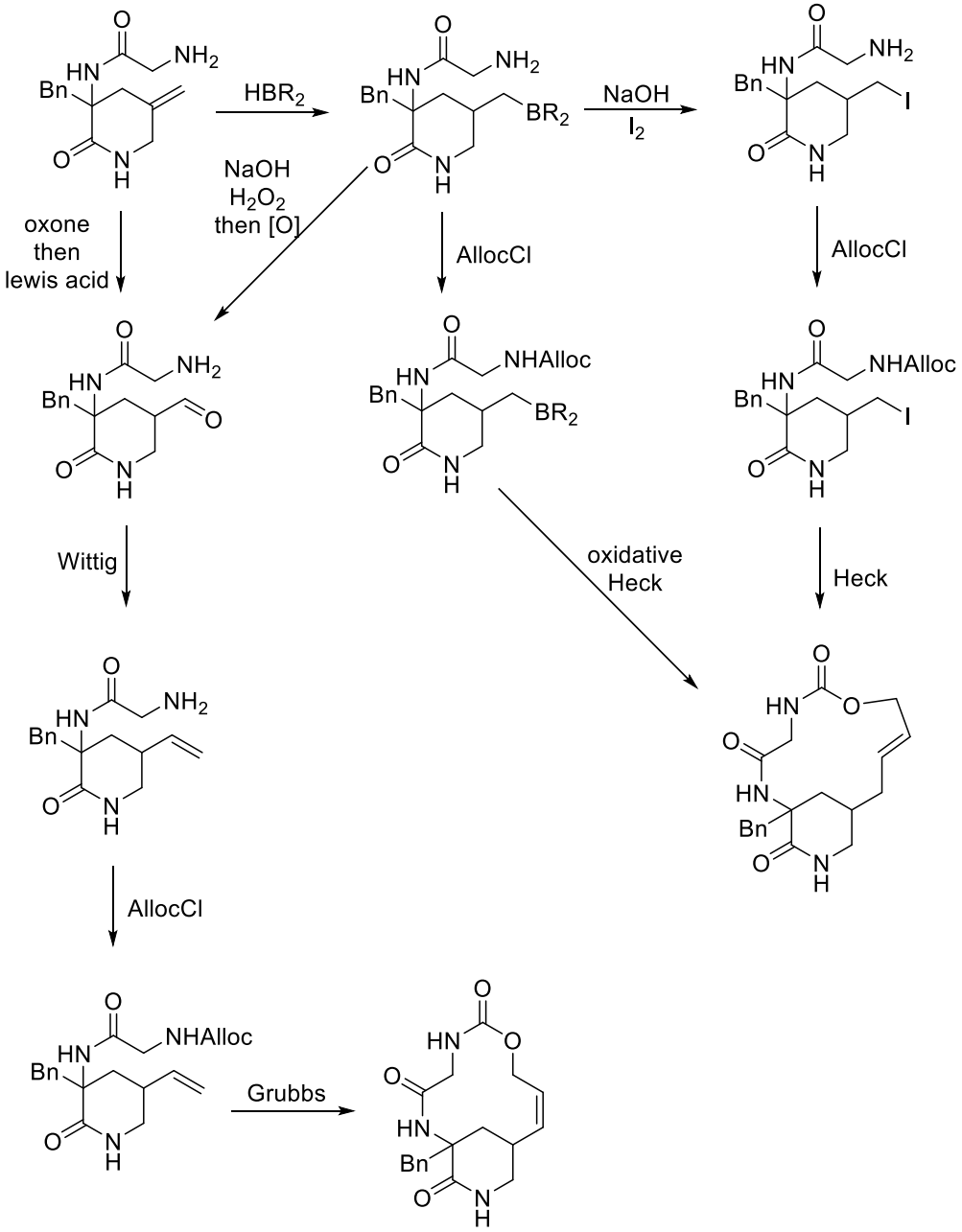
Scheme 144 *– Enantioselective synthesis of δ-lactams.*

Insertion of the Freidinger δ-lactams into more complex polypeptide sequences is also an area of interest (*Scheme 145*). This could allow for the development of a peptidomimetic from a known bioactive polypeptide with therapeutic or agrichemical properties.



Scheme 145 *– Incorporation of the Freidinger δ-lactam into complex polypeptides.*

The synthesis of macrocyclic peptidomimetics containing the Freidinger lactam motif is also an area of investigation currently underway. It is possible that by extending the exocyclic alkene, we may be able to access peptidic macrocycles via a number of different routes (*Scheme 146*).



Scheme 146 *– possible routes to achieving unsaturated peptidic macrocycles.*

Chapter III

Data

3.1 Experimental

3.1.1 General Considerations

All non-aqueous reactions were conducted in flame-dried glassware under an inert atmosphere of dry nitrogen unless stated otherwise. Diethyl ether, DMF, THF and toluene were dried before use over an alumina column. DCM was distilled from calcium hydride. Commercially available materials were acquired from Acros, Aldrich, Alfa Aesar, Fluorochem, Fluka, Manchester Organics, Lancaster and Sigma and were used as supplied.

Flash column chromatography was carried out using silica gel 60 Å (0.040-0.063 mm) (Fischer or Sigma) using head pressure by means of a compressed air line. Thin layer chromatography was performed on commercially available pre-coated aluminium-backed plates (Merck silica Kieselgel 60 F254). Spots were made visible either by the quenching of UV fluorescence or by staining with a potassium permanganate solution.

^{1}H-NMR spectra were recorded on Bruker AVIII HD 400 (400 MHz), Bruker AVI 400 (400 MHz), Bruker AMX-400 (400 MHz) or DPX-400 (400 MHz) supported by an Aspect 3000 data system and referenced to the residual solvent peak ($CDCl_3$: δ 7.26 ppm). Signal positions were recorded in δ ppm with the abbreviations *s*, *d*, *t*, *q*, *sept*, *br* and *m* denoting singlet, doublet, triplet, quartet, septet, broad and multiplet respectively and combinations of these were used to denote higher order multiplicities. ^{13}C-NMR spectra were recorded on a Bruker AVIIIHD-400 (101 MHz) or a Bruker AV1-400 (100 MHz) and were referenced to the residual solvent peak ($CDCl_3$: δ 77.16 ppm). Signal positions were recorded in δ ppm. All signals were recorded as singlets unless otherwise stated. ^{19}F-NMR spectra were recorded on the Bruker AVIIIHD-400 (377 MHz) and are uncorrected. ^{31}P-NMR spectra were recorded on the Bruker AVIIIHD-400 (162 MHz) and are uncorrected. All NMR chemical shifts are reported in ppm and all coupling constants, *J*, are quoted in Hz.

Infrared spectra were recorded on a Perkin-Elmer Paragon 100 FTIR spectrometer. Spectra were analysed as thin films on an ATR surface or as thin films between KBr

plates. The most intense peaks and structurally important peaks are quoted. Absorption maxima (ν_{max}) are recorded in wavenumbers (cm^{-1}).

High-resolution mass spectra (HRMS) recorded for accurate mass analysis, were performed on either a MicroMass LCT operating in Electrospray mode (TOF ES+) or a MicroMass Prospec operating in FAB (FAB+), EI (EI+) or CI (CI+) mode.

Melting points were obtained using a Gallenkamp melting apparatus and areuncorrected.

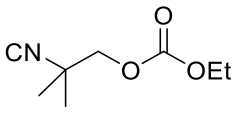
“Petrol” refers to the fraction of petroleum ether boiling in the range 40-60 °C unless otherwise stated.

Enantioselectivities were determined by high performance liquid chromatography (HPLC) analysis employing a Gilson HPLC chain with an ABI Analytical Spectroflow 738 UV or SPD-10 Shimadzu UV-vis detector (λ 210 or 256 nm), using a mixture of hexane and propan-2-ol as the mobile phase and Phenomenex Lux 3µ Cellulose-1 or 110 Phenomenex Lux 3µ Cellulose-2 as the stationary phase. Mobile phase flow rate, unless otherwise stated, was 1.0 mL/min.

3.1.2 Chapter I Experimental

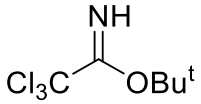
3.1.2.1 Reagent Synthesis

Ethyl 4,4-dimethyl-5H-1,3-oxazole-2-carboxylate[54]



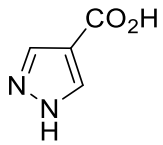
4,4-dimethyloxazoline (0.21 mL, 1.0 eq, 2.0 mmol) was dissolved in dry THF (8 mL) and cooled to -78 °C under argon. To this solution, ^{n}BuLi (0.84 mL, 1.05 eq, 2.5 M in hexane, 2.1 mmol) was added and the reaction was stirred for 15 minutes. Ethyl chloroformate (0.78 mL, 4.1 eq, 8.2 mmol) was then added and the reaction was allowed to warm to room temperature overnight. The reaction was quenched with methanol and the solvent removed under reduced pressure. The crude mixture was purified by column chromatography, eluting with 20% EtOAc in petrol to give the product (320 mg, 94%) as a pale yellow oil. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 4.23 (2H, *q*, *J* = 7.0 Hz, CH_2CH_3), 4.08 (2H, *s*, CH_2), 1.46 (6H, *s*, $(CH_3)_2$), 1.32 (3H, *t, J* = 7.0 Hz, CH_3); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 155.8 (C), 154.7 (C), 72.4 (CH_2), 68.1 (C), 64.6 (CH_2), 25.8 (CH_3) 14.2 (CH_3). Data is consistent with literature.

***tert*-Butyl 2,2,2-trichloroethanimidate[59]**



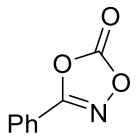
A solution of sodium *tert*-butoxide (622 mg, 0.1 eq, 6.5 mmol) in *tert*-butanol (12 mL, 2.1 eq, 125 mmol) and dry diethyl ether (12 mL) was added slowly over 15 minutes to an ice-cooled solution of trichloroacetonitrile (6 mL, 1.0 eq, 60 mmol) in dry diethyl ether (12 mL). The reaction was allowed to warm to room temperature over 1 hour, and then heated at reflux for 1 hour. The solvent was removed under reduced pressure, and the residue was dissolved in petrol (12 mL) and filtered. Removing the solvent under reduced pressure gave the acetimidate (11.11 g, 86%) as an orange oil. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 8.24 (1H, s, NH), 1.59 (9H, s, $C(CH_3)_3$); ν_{max}/cm^{-1} (ATR) 2982 (C-H), 1657 (C=N), 1323 (C-O). Data is consistent with literature.

Pyrazole-4-carboxylic acid[111]



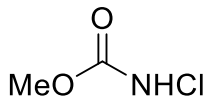
Ethyl pyrazole-4-carboxylate (5.02 g, 1.0 eq, 36 mmol) and NaOH (10.12 g, 7.0 eq, 0.25 mol) were dissolved in water (60 mL) and stirred at reflux for 3 hours. The crude mixture was acidified to pH4 with 1M $HCl_{(aq)}$ and extracted with EtOAc (2x100 mL). the organic layers were combined, dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure to give the carboxylic acid (3.53 mg, 88%) as a white amorphous solid. ^{1}H-NMR δ/ppm (400 MHz, d^6-DMSO) 8.04 (2H, *s,* CH_{Ar}); ^{13}C-NMR δ/ppm (100 MHz, DMSO) 164.7 (C=O), 138.2 ($C_{Ar}H$), 114.9 (C_{Ar}). Data is consistent with literature.

3-Phenyl-1,4,2-dioxazol-5-one[24]



N-Hydroxybenzamide (585 mg, 1.0 eq, 4.3 mmol) was dissolved in DCM (50 mL) and CDI (828 mg, 1.2 eq, 5.1 mmol) was added. The reaction mixture was stirred for 30 minutes at room temperature, the quenched with 1 M $HCl_{(aq)}$ and extracted with DCM (2x50 mL).The solvent was removed under reduced pressure to give the dioxazolone (516 mg, 74%) as an amorphous white solid. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 7.90-7.85 (2H, m, CH_{Ar}), 7.68 (1H, *tt, J* = 7.5 & 1.0 Hz, CH_{Ar}), 7.62-7.52 (2H, m, CH_{Ar}); ^{13}C-NMR δ/ppm (100 MHz, $CDCl_3$) 163.8 (C=N), 154.0 (C=O), 133.8 (C), 129.6 (CH), 126.8 (CH), 120.2 (CH). Data is consistent with literature.

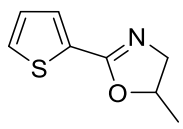
Methyl *N*-chlorocarbamate[57]



Methyl carbamate (2.07 g, 1.0 eq, 28 mmol) and trichloroisocyanuric acid (2.22 g, 0.34 eq, 9.6 mmol) were dissolved in MeOH (130 mL) and stirred at room temperature for 1 hour. The reaction mixture was filtered and the solvent removed under reduced pressure to give the *N*-chlorocarbamate (2.60 g, 86%) as a colourless oil. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 5.28 (1H, *s*, NH), 3.74 (3H, *s*, CH_3); ^{13}C-NMR δ/ppm (100 MHz, $CDCl_3$) 157.7 (C=O), 54.0 (CH_3). Data is consistent with literature.

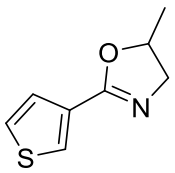
3.1.2.2 Oxazoline Synthesis

5-Methyl-2-(thiophen-2-yl)-4,5-dihydro-1,3-oxazole, 2a



Under an inert atmosphere, the thiophene carboxaldehyde **1a** (0.84 mL, 1.0 eq, 9.0 mmol) was dissolved in aqueous ammonia (28%, 9 mL) and propylene oxide (5.0 mL, 7.8 eq, 71 mmol) was added. The reaction mixture was stirred at room temperature overnight and then extracted using Et_2O (3x10 mL). The solvent was removed under reduced pressure and the residue was dissolved in methanol (16 mL), after which (diacetoxyiodo)benzene (3.47 g, 1.2 eq, 11 mmol) and trimethylamine (1.2 mL, 1.0 eq, 9.0 mmol) was added. The reaction mixture was stirred at room temperature overnight, then the solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica, eluting first with petrol then with 30% ethyl acetate in petrol to obtain the oxazoline **2a** (1.45 g, 97%) as a pale yellow oil. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 7.63 (1H, *d*, *J* = 3.5 Hz, CH_{Ar}), 7.46 (1H, *d*, *J* = 5.0 Hz, CH_{Ar}), 7.07 (1H, *dd*, *J* = 5.0 & 3.5 Hz, CH_{Ar}), 4.98-4.78 (1H, *m*, CH), 4.14 (1H, *dd*, *J* = 14.5 & 9.5 Hz, CH_2), 3.61 (1H, *dd*, *J* = 14.5 & 7.5 Hz, CH_2), 1.43 (3H, *d*, *J* = 6.0 Hz, CH_3); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 160.0 (O-C=N), 130.4 ($C_{Ar}H$), 130.2 (C_{Ar}), 129.9 ($C_{Ar}H$), 127.6 ($C_{Ar}H$), 77.1 (CH), 61.0 (CH_2), 20.9 (CH_3); ν_{max}/cm^{-1} (ATR) 2869 (C-H), 1640 (C=N), 1252 (C-O); HRMS (ES) found MH^+ 168.0472, $C_8H_{10}NOS$, requires MH^+, 168.0478.

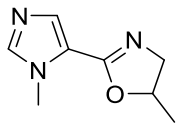
5-Methyl-2-(thiophen-3-yl)-4,5-dihydro-1,3-oxazole, 2b



Under an inert atmosphere, the thiophene carboxaldehyde **1b** (0.83 mL, 1.0 eq, 9.5 mmol) was dissolved in aqueous ammonia (28%, 10 mL) and propylene oxide (5.0 mL, 7.5 eq, 71 mmol) was added. The reaction was stirred at room temperature overnight and then extracted using Et_2O (3x10 mL). The solvent was removed under reduced pressure and the residue was dissolved in methanol (17 mL) after which (diacetoxyiodo)benzene (3.27 g, 1.1 eq, 10 mmol) and triethylamine (1.2 mL, 0.95 eq, 9.0 mmol) was added. The reaction was stirred at room temperature overnight then the solvent was removed under reduced

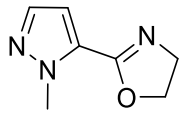
pressure and the crude product was purified by column chromatography on silica, eluting a gradient of 0-40% EtOAc in petrol to obtain the oxazoline **2b** (975 mg, 66%) as a yellow oil. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 7.88 (1H, *d*, *J* = 1.5 Hz, CH_{Ar}), 7.52 (1H, *dd*, *J* = 5.0 & 1.5 Hz, CH_{Ar}) 7.33-7.31 (1H, *m*, CH_{Ar}), 4.87-4.78 (1H, *m*, CH), 4.12 (1H, *dd*, *J* = 14.5 & 9.5 Hz, CH_2) 3.59 (1H, *dd*, *J* = 14.5 & 7.5 Hz, CH_2) 1.42 (3H, *d*, *J* = 6.0 Hz, CH_3); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 160.4 (O-C=N), 130.3 (C_{Ar}), 128.5 ($C_{Ar}H$), 127.2 (CH), 126.1 ($C_{Ar}H$), 76.1 (CH), 61.3 (CH_2), 21.1 (CH_3); ν_{max}/cm^{-1} (ATR) 2872 (C-H), 1644 (C=N), 1255 (C-O); HRMS (ES) found MH^+ 168.0475, $C_8H_{10}NOS$, requires MH^+, 167.0478.

5-Methyl-2-(3-methylimidazol-4-yl)-4,5-dihydro-1,3-oxazole, 1c



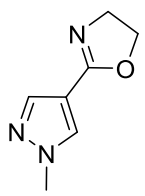
Under an inert atmosphere, **1c** (99 mg, 1.0 eq, 0.90 mmol) was dissolved in aqueous ammonia (28%, 0.92 mL) and propylene oxide (0.26 mL, 4.1 eq, 3.7 mmol) was added. The reaction mixture was stirred at room temperature overnight and then extracted by saturating the aqueous layer with solid NaCl and using 10% methanol in DCM (3x5 mL) as the extraction solvent. The solvent was removed under reduced pressure and the crude imine alcohol was redissolved in methanol (1.3 mL) with (diacetoxyiodo)benzene (356 mg, 1.2 eq, 1.1 mmol) and trimethylamine (0.13 mL, 1.0 eq, 0.93 mmol) was added. The reaction mixture was lightly stoppered and stirred at room temperature overnight. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica, eluting a gradient of 0-10% methanol in ethyl acetate to obtain, the oxazoline **2c** (17 mg, 12%) as a pale yellow oil. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 7.55 (1H, *s*, CH_{Ar}), 7.53 (1H, *s*, CH_{Ar}), 4.81-4.73 (1H, *m*, CH), 4.13 (1H, *dd*, *J* = 14.5 & 9.5 Hz, CH_2), 3.93 (3H, *s*, NCH_3), 3.59 (1H, *dd*, *J* = 14.5 & 7.5 Hz, CH_2), 1.42 (3H, *d*, *J* = 6.0 MHz, CH_3); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$); 156.9 (O-C=N), 141.5 ($C_{Ar}H$), 134.6 (C_{Ar}), 134.3 ($C_{Ar}H$), 75.3 (CH), 61.6 (CH_2), 34.2 (N-CH_3), 20.9 (CH_3); ν_{max}/cm^{-1} (ATR) 3126 (C-H), 2947 (C-H), 2880 (C-H) 1657 (C=N), 1251 (C-O); HRMS (ES) found MH^+, 166.0976, $C_8H_{12}N_3O$, requires MH^+, 166.0975.

2-(2-Methylpyrazol-3-yl)-4,5-dihydro-1,3-oxazole, 2d



2-Methylpyrazole-3-carboxylic acid **1d** (1.02 g, 1.0 eq, 8.1 mmol) was dissolved in DCM (60 mL) under argon and the reaction mixture cooled to 0 °C. To this solution, triethylamine (6.1 mL, 5.5 eq, 44 mmol) was added and the mixture was stirred for 5 minutes. ^{i}BuOCOCl (2.4 mL, 2.3 eq, 19 mmol) was then added dropwise over 10 minutes and the reaction mixture was allowed to warm to room temperature and allowed to stir for 1.5 hours. The reaction mixture was cooled to 0 °C, 2-bromoethylamine hydrochloride (3.73 g, 2.2 eq, 18.2 mmol) was added in one portion and the mixture was stirred at room temperature for a further 2 hours. The solvent was removed under reduced pressure, and the residue was redissolved in methanol (60 mL) with potassium hydroxide (3.64 g, 8.0 eq, 65 mmol). The reaction mixture was stirred at reflux under argon for 18 hours, and then cooled to room temperature before the solvent was removed under reduced pressure. The crude product was then purified by column chromatography eluting ethyl acetate to give **2d** (1.15 g, 94%) as a white amorphous solid. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 7.47 (1H, *d*, *J* = 2.0 Hz, CH_{Ar}), 6.71 (1H, *d*, *J* = 2.0 Hz, CH_{Ar}), 4.38 (2H, *t*, *J* = 9.5 Hz, CH_2), 4.21 (3H, *s*, CH_3), 4.09 (2H, *t*, *J* = 9.5 Hz, CH_2); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 157.1 (O-C=N), 138.0 ($C_{Ar}H$), 130.6 (C_{Ar}), 109.4 ($C_{Ar}H$), 66.9 (CH_2), 55.2 (CH_2), 39.5 (CH_3); ν_{max}/cm^{-1} (ATR) 3129 (C-H), 2949 (C-H), 2881 (C-H) 1663 (C=N), 1234 (C-O); HRMS (ES) found MH^+, 152.0816, $C_7H_{10}N_3O$, requires MH^+, 152.0818.

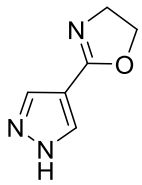
2-(1-Methylpyrazol-4-yl)-4,5-dihydro-1,3-oxazole, 2e



1-Methylpyrazole-4-carboxylic acid **1e** (1.00 g, 1.0 eq, 7.9 mmol) was dissolved in DCM (60 mL) under argon and the reaction mixture cooled to 0 °C. To this solution, triethylamine (6.1 mL, 5.5 eq, 44 mmol) was added and the mixture was stirred for 5 minutes. ^{i}BuOCOCl (2.4 mL, 2.3 eq, 19 mmol) was then added dropwise over 10 minutes and the reaction mixture was allowed to warm to room temperature and allowed to stir for 1.5 hours. The reaction mixture was cooled to 0 °C, 2-bromoethylamine hydrochloride (3.71 g, 2.3 eq, 18 mmol) was added in one portion and the mixture was stirred at room temperature for a further

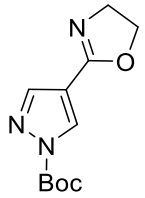
2 hours. The solvent was removed under reduced pressure, the residue redissolved in methanol (60 mL) with potassium hydroxide (3.65 g, 8.0 eq, 65 mmol). The reaction mixture was stirred at reflux under argon for 18 hours, and then cooled to room temperature before the solvent was removed under reduced pressure. The crude product was then purified by column chromatography eluting 0-10% methanol in EtOAc to give the **2e** (567 mg, 47%) as a pale yellow oil. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 7.86 (1H, s, CH_{Ar}), 7.78 (1H, s, CH_{Ar}), 4.34 (2H, *t*, *J* = 9.5 Hz, CH_2), 3.97 (2H, *t*, *J* = 9.5 Hz, CH_2), 3.92 (3H, *s*, CH_3); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 159.8 (O-C=N), 139.6 ($C_{Ar}H$), 131.2 ($C_{Ar}H$), 111.2 (C_{Ar}), 67.1 (CH_2), 54.4 (CH_2), 39.2 (CH_3); ν_{max}/cm^{-1} (ATR) 3379 (C-H), 2949 (C-H), 1662 (C=N), 1216 (C-O); HRMS (ES) found MH^+, 152.0813, $C_7H_{10}N_3O$, requires MH^+, 152.0818.

2-Pyrazole-4,5-dihydro-1,3-oxazole, 1f



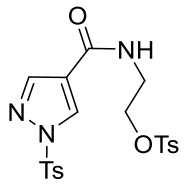
Pyrazole-4-carboxylic acid (103 mg, 1.0 eq, 0.92 mmol) was dissolved in DCM (7 mL) under nitrogen and cooled to 0 °C. Et_3N (0.69 mL, 5.3 eq, 4.9 mmol) was then added and stirred for 5 minutes, followed by ^{i}BuOCOCl (0.27 mL, 2.3 eq, 2.1 mmol). The reaction mixture was then stirred for a further 10 minutes at 0 °C, then 90 minutes at room temperature. The mixture was cooled to 0 °C and 1-bromoethylamine hydrobromide (423 mg, 2.2 eq, 2.1 mmol) was added before stirring for 2 hours at room temperature. The solvent was exchanged for MeOH (7 mL) and KOH (218 mg, 4.2 eq, 3.9 mmol) was added, then stirred at room temperature overnight. The solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography eluting with a gradient of 5-10% MeOH in EtOAc to give **1f** (110 mg, 87%) as an amorphous white solid. ^{1}H-NMR δ/ppm (400 MHz, d^4-MeOD) 8.05 (2H, *s*, CH_{Ar}), 4.48 (2H, *t, J* = 9.5 Hz, CH_2), 3.99 (2H, *t, J* = 9.5 Hz , CH_2); ^{13}C-NMR δ/ppm (101 MHz, d^4-MeOD) 161.7 (O-C=N), 139.5 ($C_{Ar}H$), 131.2 ($C_{Ar}H$), 111.0 (C_{Ar}), 67.2 (CH_2), 54.6 (CH_2); ν_{max}/cm^{-1} (ATR) 2991 (C-H), 1728 (C=N), 1257 (C-O); HRMS (ES) found MH^+ 138.0667, $C_6H_8N_3O$, requires MH^+, 138.0666.

2-(1-Boc-pyrazol-4-yl)-4,5-dihydro-1,3-oxazole, 2f



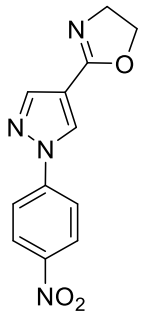
1f (95 mg, 1.0 eq, 0.69 mmol) and Boc_2O (379 mg, 2.5 eq, 1.7 mmol) were dissolved in MeOH (2 mL) under an inert atmosphere. Et_3N (0.2 mL, 2.1 eq, 1.4 mmol) was added and the mixture was stirred at reflux overnight. After cooling, the solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography eluting with a gradient of 0-10% MeOH in EtOAc to give **2f** (70 mg, 43%) as a colourless oil. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 8.50 (1H, *s*, CH_{Ar}), 8.09 (1H, *s*, CH_{Ar}), 4.45 (2H, *t, J* = 9.5 Hz, CH_2), 4.05 (2H, *t, J* = 9.5 Hz, CH_2), 1.67 (9H, *s*, $C(CH_3)_3$); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 153.6 (O–C=N), 146.9 (C=O), 143.1 ($C_{Ar}H$), 131.4 ($C_{Ar}H$), 113.9 (C_{Ar}), 86.4($C(CH_3)_3$), 67.4 (CH_2), 54.7 (CH_2), 27.8 ($C(CH_3)_3$); ν_{max}/cm^{-1} (ATR) 2981 (C-H), 1753 (C=O), 1670 (C=N), 1251 (C-O), 1145 (C-O); HRMS (ES) found MH^+ 238.1192, $C_{11}H_{16}N_3O_3$, requires MH^+, 238.1192.

1-Tosyl-3(*O*-tosylethyl-2'-ol)amidopyrazole, 2g'



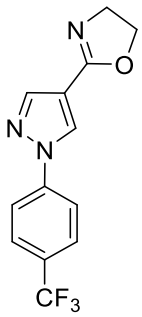
1f (209 mg, 1.0 eq, 1.5 mmol) and p-TsCl (350 mg, 1.2 eq, 1.8 mmol) were dissolved in MeOH (5 mL) under an inert atmosphere. Et_3N (1.0 mL, 4.7 eq, 7.1 mmol) was added and the mixture was stirred at reflux overnight. After cooling, the solvent was removed under reduced pressure and semi-purified by filtration through a silica plug, first eluting with petrol then EtOAc to give a mixture in which **2g'** was identified as the main component. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 8.34 (2H, *s*, NH & CH_{Ar}), 8.10 (1H, *s*, CH_{Ar}), 7.72 (4H, *d, J* = 8.0 Hz, CH_{Ar}), 7.26 (4H, *d, J* = 8.0 Hz, CH_{Ar}), 4.89 (2H, *t, J* = 9.0 Hz, CH_2), 4.15 (2H, *t, J* = 9.0 Hz, CH_2), 2.39 (6H, *s*, CH_3).

2-(1-(4-Nitrophenyl)pyrazol-4-yl)-4,5-dihydro-1,3-oxazole, 2h



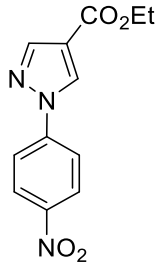
1f (199 mg, 1.0 eq, 1.5 mmol), 4-bromonitrobenzene (453 mg, 1.5 eq, 2.2 mmol), K_2CO_3 (431 mg, 2.1 eq, 3.1 mmol), CuI (22 mg, 8 mol%, 0.12 mmol) and *N,N*-dimethylethan-1,2-diamine (0.02 mL, 15 mol%, 0.18 mmol) were dissolved in toluene (1.5 mL) under an inert atmosphere and stirred at reflux for 24 hours. After cooling, the solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography eluting with a gradient of 0-20% MeOH in EtOAc to give **2h** (106 mg, 38%) as a yellow oil. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 8.47 (1H, *s*, CH_{Ar}), 8.39 (2H, *d, J =* 9.0 Hz, CH_{Ar}), 8.17 (1H, *s*, CH_{Ar}), 7.93 (2H, *d, J =* 9.0 Hz, CH_{Ar}), 4.44 (2H, *t, J =* 9.5 Hz, CH_2), 4.07 (2H, *t, J =* 9.5 Hz, CH_2); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 162.3 (C=O), 146.3 (C_{Ar}), 143.6 (C_{Ar}), 143.4 (CArH), 130.3 ($C_{Ar}H$), 127.4 (C_{Ar}), 125.5 ($C_{Ar}H$), 119.3 ($C_{Ar}H$), 60.8 (CH_2), 53.4 (CH_2); ν_{max}/cm^{-1} (ATR) 2964 (C-H), 1720 (C=N), 1528 (NO_2), 1184 (C-O); HRMS (ES) found MH^+ 259.0831, $C_{12}H_{11}N_4O_3$, requires MH^+, 259.0833.

2-(1-(4-Trifluoromethylphenyl)pyrazol-4-yl)-4,5-dihydro-1,3-oxazole, 2i



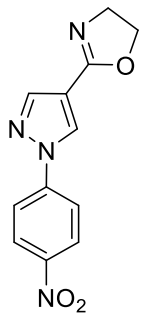
1f (44 mg, 1.0 eq, 0.32 mmol), 4-bromotrifluoromethylbenzene (0.06 mL, 1.3 eq, 0.43 mmol), K_2CO_3 (124 mg, 2.8 eq, 0.90 mmol), CuI (6 mg, 10 mol%, 0.032 mmol) and *N,N*-dimethylethan-1,2-diamine (0.01 mL, 29 mol%, 0.093 mmol) were dissolved in *o*-DCB (2 mL) under an inert atmosphere and stirred at 110 °C for 24 hours. After cooling, the solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography eluting with petrol, then a gradient of 0-10% MeOH in EtOAc to give **2i** (77 mg, 86%) as a yellow oil. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 8.42 (1H, *s*, CH_{Ar}), 8.14 (1H, *s*, CH_{Ar}), 7.87 (2H, *d, J =* 8.5Hz, CH_{Ar}), 7.76 (2H, *d, J =* 8.5 Hz, CH_{Ar}), 4.43 (2H, *t, J =* 9.5 Hz, CH_2), 4.06 (2H, *t, J =* 9.5 Hz, CH_2); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 159.2 (C=N), 141.7 ($C_{Ar}H$), 134.8 (*q, J =* 35.5 Hz, CCF_3), 128.0 ($C_{Ar}H$), 127.0 ($C_{Ar}H$), 123.8 (*q, J =* 272.0 Hz, CF_3), 119.1 ($C_{Ar}H$), 67.5 (CH_2), 54.5 (CH_2); ν_{max}/cm^{-1} (ATR) 2995 (C-H), 1707 (C=N), 1122 (C–O); HRMS (ES) found MH^+ 282.0854, $C_{13}H_{11}F_3N_3O$, requires MH^+, 282.0861.

Ethyl 1-(4-nitrophenyl)pyrazoles-3-carboxylate, 1h



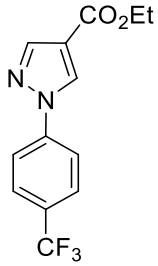
Ethyl pyrazole-4-carboxylate (508 mg, 1.0 eq, 3.6 mmol), 4-bromonitrobenzene (905 mg, 1.2 eq, 4.5 mmol), K_2CO_3 (1.12 g, 2.3 eq, 8.1 mmol), CuI (39 mg, 6 mol%, 0.20 mmol) and *N,N*-dimethylethane-1,2-diamine (0.10 mL, 26 mol%, 0.93 mmol) were dissolved in toluene (7 mL) under an inert atmosphere and stirred at reflux for 24 hours. After cooling, the solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography eluting with a gradient of 25-75% EtOAc in petrol to give **1h** (386 mg, 41%) as a yellow oil. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 8.55 (1H, *s*, CH_{Ar}), 8.43-8.36 (2H, *m*, CH_{Ar}), 8.18 (1H, *s*, CH_{Ar}), 7.98-7.91 (2H, *m*, CH_{Ar}), 4.38 (2H, *q, J* = 7.0 Hz, CH_2), 1.41 (3H, *t, J* = 7.1 Hz, CH_3); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 162.3 (C=O), 146.3 (CNO_2), 143.6 (C_{Ar}), 143.4 ($C_{Ar}H$), 130.3 ($C_{Ar}H$), 125.5 ($C_{Ar}H$), 119.3 ($C_{Ar}H$), 115.7 (C_{Ar}), 60.8 (CH_2), 14.4 (CH_3); ν_{max}/cm^{-1} (ATR) 3125 (C-H), 1716 (C=O), 1518 (NO_2), 1275 (C-O); HRMS (ES) found MH^+ 262.0828, $C_{12}H_{12}N_3O_4$, requires MH^+, 262.0822.

2-(1-(4-Nitrophenyl)pyrazol-4-yl)-4,5-dihydro-1,3-oxazole, 2h



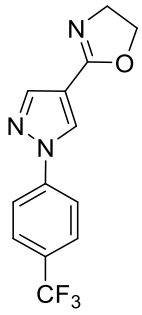
1h (99 mg, 1.0 eq, 0.38 mmol) and NaOH (202 mg, 13 eq, 5.1 mmol) were dissolved in water (2 mL) and stirred at reflux for 3 hours. The mixture was then cooled and acidified to pH4 with 1 M $HCl_{(aq)}$, then filtered to give the carboxylic acid as a white powder (72 mg). This was then redissolved in DCM (10 mL) under an inert atmosphere and cooled to 0 °C. Et_3N (0.24 mL, 4.5 eq, 1.7 mmol) was then added and stirred for 5 minutes, followed by ^{i}BuOCOCl (0.1 mL, 2.0 eq, 0.77 mmol). The reaction mixture was then stirred for a further 10 minutes at 0 °C, then 90 minutes at room temperature. The mixture was cooled to 0 °C and 2-bromoethylamine hydrobromide (161 mg, 2.1 eq, 0.79 mmol) was added before stirring for 2 hours at room temperature. The solvent was exchanged for MeOH (10 mL) and KOH (103 mg, 4.7 eq, 1.8 mmol) was added, then stirred at room temperature overnight. The solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography eluting with a gradient of 0-20% MeOH in EtOAc to give **2h** (58 mg, 72%) as a yellow oil.

Ethyl 1-(4-trifluromethylphenyl)pyrazoles-3-carboxylate, 1i



Ethyl pyrazole-4-carboxylate (203 mg, 1.0 eq, 1.5 mmol), 4-bromotrifluoromethylbenzene (0.24 mL, 1.1 eq, 1.7 mmol), K_2CO_3 (415 mg, 2.0 eq, 3.0 mmol), CuI (30 mg, 10 mol%, 0.16 mmol) and *N,N*-dimethylethane-1,2-diamine (0.06 mL, 37 mol%, 0.56 mmol) were dissolved in toluene (2 mL) under an inert atmosphere and stirred at reflux for 24 hours. After cooling, the solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography eluting with a gradient of 25-75% EtOAc in petrol to give **1i** (376 mg, 91%) as a yellow oil. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 8.50 (1H, *s*, CH_{Ar}), 8.15 (1H, *s*, CH_{Ar}), 7.88 (2H, *d, J* = 8.5 Hz, CH_{Ar}), 7.78 (2H, *d, J* = 8.5 Hz, CH_{Ar}), 4.38 (2H, *q, J* = 7.0 Hz, CH_2), 1.41 (3H, *t, J* = 7.0 Hz, CH_3); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 162.1 (C=O), 142.8 ($C_{Ar}H$), 130.1 ($C_{Ar}H$), 129.2 (*q, J* = 5.0 Hz, $C_{Ar}CF_3$), 127.0 ($C_{Ar}H$), 119.4 ($C_{Ar}H$), 115.1 (*q, J* = 33.5 Hz, CF_3). 117.8 (C_{Ar}), 60.7 (CH_2), 14.4 (CH_3); ^{19}F-NMR δ/ppm (377 MHz, $CDCl_3$) -62.5 (CF_3); ν_{max}/cm^{-1} (ATR) 3137 (C-H), 2995 (C-H), 1708 (C=O), 1261 (C-O), 1109 (C-F); HRMS (ES) found MH^+ 285.0851, $C_{13}H_{12}F_3N_2O_2$, requires MH^+, 285.0849.

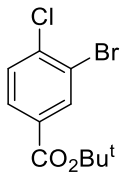
2-(1-(4-Trifluoromethylphenyl)pyrazol-4-yl)-4,5-dihydro-1,3-oxazole, 2i



1i (907 mg, 1.0 eq, 3.2 mmol) and NaOH (1.172 g, 9.2 eq, 29 mmol) were dissolved in water (10 mL) and stirred at reflux for 3 hours. The mixture was then cooled and acidified to pH4 with 1 M $HCl_{(aq)}$, then filtered to give the carboxylic acid as a white powder (759 mg). This was then redissolved in DCM (25 mL) under an inert atmosphere and cooled to 0 °C. Et_3N (2.0 mL, 4.4 eq, 14 mmol) was then added and stirred for 5 minutes, followed by ^{i}BuOCOCl (0.8 mL, 1.9 eq, 6.2 mmol). The reaction mixture was then stirred for a further 10 minutes at 0 °C, then 90 minutes at room temperature. The mixture was cooled to 0 °C and 1-bromoethylamine hydrobromide (1.34 g, 2.0 eq, 6.6 mmol) was added before stirring for 2 hours at room temperature. The solvent was exchanged for MeOH (25 mL) and KOH (1.52 g, 8.5 eq, 27 mmol) was added, then stirred at room temperature overnight. The solvent was removed under reduced pressure and the crude residue was

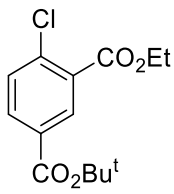
purified by flash column chromatography eluting with a gradient of 50-100% EtOAc in petrol to give **2i** (157 mg, 17%) as a yellow oil.

<u>*tert*-Butyl 3-bromo-4-chlorobenzoate, 4j</u>



Benzoic acid **1j** (509 mg, 1.0 eq, 2.2 mmol) was dissolved in acetonitrile (2 mL) and cyclohexane (4 mL) under nitrogen. To this solution, *t*-butyl 2,2,2-trichloroacetimidate (0.57 mL, 1.5 eq, 3.2 mmol) was added, followed by a catalytic amount of trifluoroboron etherate (43 µl, 0.16 eq, 0.35 mmol), and the mixture was stirred room temperature overnight. The solvent was removed under reduced pressure and the crude product was extracted from sat.aq. $NaHCO_3$ (10 mL) using ethyl acetate (2x10 mL). The solvent was removed under reduced pressure and the residue redissolved in petrol, before being purified by filtering through a silica gel plug and flushing with petrol. The solvent was removed under reduced pressure to give **4j** (391 mg, 62%) as a white amorphous solid. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 8.23 (1H, *d*, *J* = 2.0 Hz, CH_{Ar}), 7.87 (1H, *dd*, *J* = 8.5 & 2.0 Hz, CH_{Ar}), 7.51 (1H, *d*, *J* = 8.5 Hz, CH_{Ar}), 1.61 (9H, *s*, $C(CH_3)_3$); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 163.7 (C=O), 138.9 (C_{Ar}), 134.7 ($C_{Ar}H$), 131.9 (C_{Ar}), 130.2 ($C_{Ar}H$), 129.3 ($C_{Ar}H$), 122.4 (C_{Ar}), 82.1 (C), 28.1(CH_3); ν_{max}/cm^{-1} (ATR) 2980 (C-H), 1711 (C=O), 1293 (C-O); HRMS (ES) found M^+ 289.9709, $C_{11}H_{12}{}^{79}Br^{35}ClO_2$, requires M^+, 289.9709; HRMS (ES) found M^+, 291.9689 & 291.9680, $C_{11}H_{12}{}^{81}Br^{35}ClO_2$ & $C_{11}H_{12}{}^{79}Br^{37}ClO_2$, requires M^+, 291.9690; HRMS (ES) found M^+ 293.9659, $C_{11}H_{12}{}^{81}Br^{37}ClO_2$, , requires M^+, 293.9661.

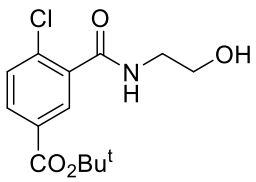
<u>1-*tert*-Butyl 3-ethyl 4-chlorobenzene-1,3-dicarboxylate, 5j</u>



Aryl bromide **4j** (643 mg, 1.0 eq, 2.2 mmol) was dissolved in dry tetrahydrofuran (16 mL) and cooled to -78 °C under argon. To this solution, *n*-butyllithium (0.90 mL, 2.5 M in hexane, 1.05 eq, 2.3 mmol) was added, followed immediately by ethyl chloroformate (0.66 mL, 3.1 eq, 6.9 mmol). The reaction mixture was stirred overnight while warming to room temperature, then quenched with methanol (1 mL). The solvent was removed under

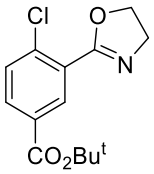
reduced pressure and the crude residue was purified by column chromatography eluting with 2% Et_2O in petrol to give **5j** (457 mg, 73%) as a colourless oil. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 8.39 (1H, *d*, *J* = 2.0 Hz, CH_{Ar}), 7.99 (1H, *dd*, *J* = 8.5, 2.0 Hz, CH_{Ar}), 7.48 (1H, *d*, *J* = 8.5 Hz, CH_{Ar}), 4.41 (2H, *q*, *J* = 7.0 Hz, CH_2), 1.59 (9H, *s*, $C(CH_3)_3$), 1.41 (3H, *t*, *J* = 7.0 Hz, CH_3); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 165.1 (C=O), 164.1 (C=O), 137.8 ($C_{Ar}Cl$), 132.9 ($C_{Ar}H$), 132.3 ($C_{Ar}H$), 131.0 ($C_{Ar}H$), 130.6 (C_{Ar}), 130.5 (C_{Ar}), 82.0 ($C(CH_3)_3$), 61.8 (CH_2), 28.1 ($C(CH_3)_3$), 14.2 (CH_3); ν_{max}/cm^{-1} (ATR) 2979 (C-H), 1717 (C=O) 1241 (C-O); HRMS (ES) found MH^+, 285.0887, $C_{14}H_{18}{}^{35}ClO_4$, requires MH^+, 285.0888; HRMS (ES) found MH^+, 309.0684, $C_{14}H_{17}{}^{37}ClO_4Na$, requires MNa^+, 309.0683.

<u>*tert*-Butyl 4-chloro-3-[(2-hydroxyethyl)carbamoyl]benzoate, 6j</u>



Diester **5j** (210 mg, 1.0 eq, 0.74 mmol) was heated to 55 °C under an inert atmosphere and ethanolamine (0.1 mL, 2.2 eq, 1.7 mmol) was added dropwise. The reaction mixture was stirred at 55 °C for 3 hours, then at room temperature for 18 hours. The crude mixture was then purified by column chromatography eluting with 25% petrol in EtOAc to give **6j** (174 mg, 79%) as a pale yellow oil. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 8.15 (1H, *d, J* = 2.0 Hz, CH_{Ar}), 7.92 (1H, *dd, J* = 8.5, 2.0 Hz, CH_{Ar}), 7.42 (1H, *d*, *J* = 8.5 Hz, CH_{Ar}), 6.86 (1H, *s*, NH), 3.94-3.71 (2H, *m*, CH_2) 3.68-3.57 (2H, *m*, CH_2), 1.58 (9H, *s*, $C(CH_3)_3$); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 164.0 (C=O), 161.3 (C=O), 132.2 (C_{Ar}) 132.2 (C_{Ar}), 129.0 ($C_{Ar}H$), 128.1(C_{Ar}), 127.7 ($C_{Ar}H$), 127.3 ($C_{Ar}H$), 79.2 ($C(CH_3)_3$), 58.8 (CH_2), 39.8 (CH_2), 25.2 ($C(CH_3)_3$); ν_{max}/cm^{-1} (ATR) 3287 (O-H), 3094 (N-H), 2978 (C-H) 1714 (C=O), 1642 (C=O), 1288 (C-O), 1249 (C-O); HRMS (ES) found MH^+, 300.1001, $C_{14}H_{19}{}^{35}ClNO_4$, requires MH^+, 300.0997; HRMS (ES) found MH^+, 302.0973, $C_{14}H_{19}{}^{37}ClNO_4$, requires MH^+, 302.0976.

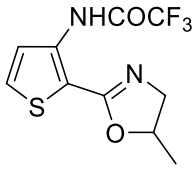
***tert*-Butyl 4-chloro-3-(4,5-dihydro-1,3-oxazol-2-yl)benzoate, 2j**



Amide **6j** (97 mg, 1.0 eq, 0.32 mmol), DMAP (14 mg, 0.3 eq, 0.11 mmol) and *p*-TsCl (117 mg, 1.9 eq, 0.61 mmol) were dissolved in dry DCM (1 mL) under an inert atmosphere and Et_3N (0.1 mL, 2.2 eq, 0.72 mmol) was added. The reaction mixture was stirred at room temperature overnight, then diluted with DCM and washed with water. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 25% EtOAc in petrol to give **2j** (57 mg, 62%) as an off-white amorphous solid. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 8.38 (1H, *d, J* = 2.0 Hz, CH_{Ar}), 7.99 (1H, *dd, J* = 8.5 & 2.0 Hz, CH_{Ar}), 7.52 (1H, *d, J* = 8.5 Hz, CH_{Ar}), 4.48 (2H, *t, J* = 9.5 Hz, CH_2) 4.17 (2H, *t, J* = 9.5 Hz, CH_2), 1.61 (9H, *s*, $C(CH_3)_3$); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 164.2 (C=N), 162.5 (C=O), 132.4 (C_{Ar}), 132.3 ($C_{Ar}H$), 132.2 ($C_{Ar}H$), 130.8 (C_{Ar}), 127.4 (C_{Ar}), 81.9 ($C(CH_3)_3$), 67.6 (CH_2), 55.5 (CH_2), 28.2 ($C(CH_3)_3$); ν_{max}/cm^{-1} (ATR) 2977 (C-H), 1716 (C=O) 1639 (C=N), 1255 (C-O), 1163 (C-O); HRMS (ES) found MH^+, 282.0895, $C_{14}H_{17}{}^{35}ClNO_3$, requires MH^+, 282.0891; HRMS (ES) found MH^+, 284.0867, $C_{14}H_{17}{}^{37}ClNO_3$, requires MH^+, 284.0879.

3.1.2.3 C-H Amidation

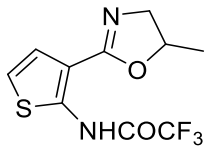
2,2,2-Trifluoro-N-[2-(5-methyl-4,5-dihydro-1,3-oxazol-2-yl)thiophen-3-yl]acetamide, 3a



Oxazoline **2a** (438 mg, 1.2 eq, 2.62 mmol), trifluoroacetamide (249 mg, 1.0 eq, 2.20 mmol), (diacetoxyiodo)benzene (1.06 g, 1.5eq, 3.28 mmol), silver hexafluoroantimonate(V) (76 mg, 10 mol%, 0.22 mmol), and pentamethylcyclopentadienylrhodium(III) chloride dimer (34 mg, 2.5 mol%, 0.05 mmol) were dissolved in dry DCM (15 mL) under an inert atmosphere and stirred at reflux overnight. The solvent was removed under reduced pressure and the crude mixture was purified using column chromatography on silica, eluting with petrol followed by DCM to give **3a** (283 mg, 46%) as a white amorphous solid. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 12.31 (1H, s, NH), 8.09 (1H, *d*, *J* = 5.5 Hz, ArH), 7.46 (1H, *d*, *J* = 5.5 Hz, ArH), 4.92-4.83 (1H, *m*, CH), 4.22 (1H, *dd*, *J* = 14.5 & 9.5 Hz, CH_2), 3.69 (1H, *dd*, *J* = 14.5 & 7.5 Hz, CH_2), 1.47 (3H, *d*, *J* = 6.0 Hz, CH_3); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 160.4

(O-C=N), 154.4 (*q*, *J* = 38.0 Hz, C=O), 138.6 (C_{Ar}), 128.6 ($C_{Ar}H$), 122.0 ($C_{Ar}H$), 115.9 (*q*, *J* = 288.0 Hz, CF_3), 111.6 (C_{Ar}), 76.6 (CH), 60.9 (CH_2), 20.8 (CH_3); ^{19}F-NMR δ/ppm (377 MHz, $CDCl_3$) -75.8 (CF_3); ν_{max}/cm^{-1} (ATR) 3100 (C-H), 2881 (C-H), 1715 (C=O), 1626 (C=N) 1244 (C-O); HRMS (ES) found MH^+ 279.0412, $C_{10}H_{10}F_3N_2O_2S$, requires MH^+, 279.0410.

2,2,2-Trifluoro-N-[3-(5-methyl-4,5-dihydro-1,3-oxazol-2-yl)thiophen-2-yl]acetamide, 7b

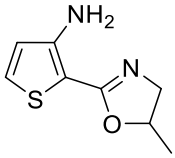


Oxazoline **2b** (491 mg, 1.2 eq, 2.9 mmol), trifluoroacetamide (278 mg, 1.0 eq, 2.5 mmol), (diacetoxy)iodobenzene (1.1872 g, 1.5 eq, 3.7 mmol), silver hexafluoroantimonate(V) (88 mg, 10mol%, 0.25 mmol) and pentamethylcyclopentadienyl rhodium(III) dichloride dimer (40 mg, 2.5 mol%, 0.064 mmol) were dissolved in DCM (15 mL) under an inert atmosphere and stirred overnight at reflux. The solvent was then removed under reduced pressure and a 9:1 mixture of regioisomers **7b** and **7b'** were observed by ^{1}H NMR in the crude residue. The crude mixture was purified by flash column chromatography, eluting with petrol then DCM to give the amidated thiophene **7b** (429 mg, 63%) as a pale brown amorphous solid. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 7.21 (1H, *d*, *J* = 5.5 Hz, CH_{Ar}),6.96 (1H, *d*, *J* = 5.5 Hz, CH_{Ar}), 4.95-4.86 (1H, *m*, CH), 4.20 (1H, *dd*, *J* = 14.0 & 9.5 Hz, CH_2), 3.67 (1H, *dd*, *J* = 14.0 & 7.5 Hz, CH_2), 1.48 (3H, *d*, *J* = 6.0 Hz, CH_3); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 162.2 (C=N), 142.5 (*q*, *J* = 46.5 Hz, C=O), 123.2 ($C_{Ar}H$), 119.1 ($C_{Ar}H$), 118.3 (C_{Ar}), 113.6 (*q*, *J* = 150.0 Hz, CF_3) 112.7 (C_{Ar}), 76.6 (CH), 59.6 (CH_2), 20.9 (CH_3); ^{19}F-NMR δ/ppm (377 MHz, $CDCl_3$) -75.3 (CF_3); ν_{max}/cm^{-1} (ATR) 3093 (C-H), 2991 (C-H), 1636 (C=O), 1594 (C=N) 1231 (C-O); HRMS (ES) found MH^+ 279.0404, $C_{10}H_{10}F_3N_2O_2S$, requires MH^+, 279.0410.

7b': ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 8.09 (1H, *d*, *J* = 3.5 Hz, CH_{Ar}), 7.84 (1H, *d*, *J* = 3.5 Hz, CH_{Ar}), 4.91-4.82 (1H, *m*, CH), 4.18 (1H, *dd*, *J* = 14.5 & 9.5 Hz, CH_2), 3.65 (1H, *dd*, *J*= 14.5 & 7.5 Hz, CH_2), 1.47 (3H, *d*, *J* = 6.0 Hz, CH_3); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 160.5 (C=N), 154.8 (*q*, *J* = 38.5 Hz, C=O) 133.1 (C_{Ar}), 128.0 ($C_{Ar}H$), 119.7 (C_{Ar}), 115.9 (*q*, *J* = 287.5 Hz, CF_3), 113.1 ($C_{Ar}H$), 76.1 (CH), 60.4 (CH_2), 20.9 (CH_3); ^{19}F-NMR δ/ppm (377 MHz, $CDCl_3$) -75.9 (CF_3); ν_{max}/cm^{-1} (ATR) 3147 (C-H), 3116 (C-H) 2983 (C-H), 1707 (C=O), 1641 (C=N), 1235 (C-O); HRMS (ES) found MH^+ 279.0417, $C_{10}H_{10}F_3N_2O_2S$, requires MH^+, 279.0410.

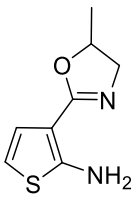
3.1.2.4 Azolopyrimidine Synthesis

2-(5-Methyl-4,5-dihydro-1,3-oxazol-2-yl)thiophen-3-amine, 8a



A solution of **7a** (74 mg, 1.0 eq, 0.41 mmol) and sodium hydroxide (211 mg, 33 eq, 14 mmol) in ethanol (12 mL) was stirred at room temperature overnight. The solvent was then removed under reduced pressure and the residue was redissolved in water (10 mL). The crude product was then extracted using ethyl acetate (3x10 mL) and washed with water (10 mL) and brine (10 mL). The organic layers were combined and dried using magnesium sulfate, then filtered and the solvent removed under reduced pressure to give the amine **8a** (63 mg, 73%) as a yellow oil. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 7.21 (1H, *d*, *J* = 5.5 Hz, CH_{Ar}), 6.60 (1H, *d*, *J* = 5.5 Hz, CH_{Ar}), 5.49 (2H, *s*, NH), 4.81-4.73 (1H, *m*, CH), 4.16 (1H, *dd*, *J* = 14.0 & 9.0 Hz, CH_2), 3.62 (1H, *dd*, *J* = 14.0 & 7.5 Hz, CH_2), 1.43 (3H, *d*, *J* = 6.0 Hz, CH_3); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 161.1 (C=N), 150.4 (C-NH_2), 128.3 ($C_{Ar}H$), 127.3 (C_{Ar}), 120.0 ($C_{Ar}H$), 75.6 (CH), 61.4 (CH_2), 20.9 (CH_3); ν_{max}/cm^{-1} (ATR) 3312 (N-H), 3105 (N-H), 2972 (C-H), 2928 (C-H), 2868 (C-H), 1613 (C=N), 1258 (C-O); HRMS (ES) found MH^+ 183.0582, $C_8H_{11}N_2OS$, requires MH^+, 183.0587.

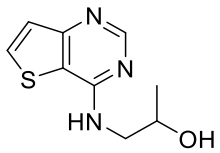
3-(5-Methyl-4,5-dihydro-1,3-oxazol-2-yl)thiophen-2-amine, 8b



A solution of **7b** (188 mg, 1.0 eq, 0.68 mmol) and sodium borohydride (136 mg, 5.3 eq, 3.6 mmol) in dry ethanol (12 mL) was stirred overnight at room temperature. The solvent was then removed under reduced pressure and the residue was redissolved in water (10 mL). The crude product was extracted using ethyl acetate (3x10 mL). The organic layers were combined and dried using magnesium sulfate, then filtered and the solvent removed under reduced pressure to give **8b** (85 mg, 69%) as a brown oil. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 6.94 (1H, *d*, *J* = 5.5 Hz, CH_{Ar}), 6.26 (1H, *d*, *J* = 5.5 Hz, CH_{Ar}), 4.79-4.71 (1H, *m*, CH), 4.12 (1H, *dd*, *J* = 13.5 & 9.0 Hz, CH_2), 3.58 (1H, *d*, *J* = 13.5, 7.5 Hz, CH_2), 1.42 (3H, *d*, *J* = 6.0 Hz, CH_3); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 162.1 (C=N), 125.2 ($C_{Ar}H$) 114.3 (C_{Ar}), 107.4 ($C_{Ar}H$), 103.6 (C_{Ar}),

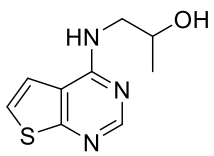
75.1 (CH), 60.7 (CH_2), 21.0 (CH_3); ν_{max}/cm^{-1} (ATR) 3436 (N-H), 1635 (C=N), 1375 (C-O); HRMS (ES) found MH^+ 183.0584, $C_8H_{11}N_2OS$, requires MH^+, 183.0587.

1-{Thieno[3,2-d]pyrimidin-4-ylamino}propan-2-ol, 9a



A solution of **8a** (608 mg, 1.0 eq, 3.3 mmol) and formamidine acetate (690 mg, 2.0 eq, 6.6 mmol) in ethanol (20 mL) was stirred for 1 hour at reflux. The reaction mixture was then cooled and the solvent removed under reduced pressure. The crude mixture was purified using column chromatography, eluting a gradient of 0-10% methanol in DCM to give **9a** (680 mg, 97%) as a white amorphous solid. ^{1}H-NMR δ/ppm (400 MHz, d^4-MeOD) 8.44 (1H, *s*, N=CH-N), 8.01 (1H, *d*, *J* = 5.5 Hz, CH_{Ar}), 7.36 (1H, d, J = 5.5 Hz, CH_{Ar}), 4.15-3.99 (1H, *m*, CH), 3.66 (1H, *dd*, *J* = 13.5 & 4.5 Hz, CH_2), 3.55 (1H, *dd*, *J* = 13.5 & 7.5 Hz, CH_2). 1.24 (3H, *d*, *J* = 6.5 Hz, CH_3); ^{13}C-NMR δ/ppm (101 MHz, d_6-DMSO) 159.7 (N=C-NH), 157.5 (C-N), 154.9 (N=CH-N), 133.3 ($C_{Ar}H$), 124.8 ($C_{Ar}H$), 115.1 (C_{Ar}), 65.2 (CH), 48.5 (CH_2), 21.7 (CH_3); ν_{max}/cm^{-1} (ATR) 3291 (N-H), 3061, 2969 (C-H), 1594 (C=N), 1052 (C-O); HRMS (ES) found MH^+ 210.0687, $C_9H_{12}N_3OS$, requires MH^+, 210.0696.

1-{Thieno[2,3-d]pyrimidin-4-ylamino}propan-2-ol, 9b



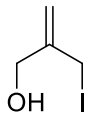
A solution of **8b** (74 mg, 1.0 eq, 0.41 mmol) and formamidine acetate (211 mg, 4.9 eq, 2.0 mmol) in ethanol (12 mL) was stirred for 1 hour at reflux. The reaction mixture was then cooled and the solvent removed under reduced pressure. The crude mixture was purified by column chromatography, eluting a gradient of 0-10% MeOH in DCM to give **9b** (63 mg, 73%) as a pale brown amorphous solid. ^{1}H-NMR δ/ppm (400 MHz, d^4-MeOD) 8.33 (1H, *s*, N-CH=N), 7.52-7.46 (2H, *m*, CH_{Ar}), 4.11-4.04 (1H, *m*, CH), 3.64 (1H, *dd*, *J* = 13.5 & 4.5 Hz, CH_2), 3.51 (1H, *dd*, *J* = 13.5 & 7.5 Hz, CH_2), 1.24 (3H, *d*, *J* = 6.5 Hz, CH_3); ^{13}C-NMR δ/ppm (101 MHz, d^4-MeOD) 157.6 (N=C-NH), 153.1 (N-CH=N), 142.8 (S-C-N), 122.5 ($C_{Ar}H$), 117.2 ($C_{Ar}H$), 116.7 (C_{Ar}), 70.3 (CH), 66.0 (CH_2), 19.6 (CH_3); ν_{max}/cm^{-1} (ATR) 3313 (N-H), 3059 (C-H), 2924 (C-H),

1569 (C=N) 1317 (C-O); HRMS (ES) found MH^+ 210.0692, $C_9H_{12}N_3OS$, requires MH^+, 210.0696.

3.1.3 Chapter II Experimental

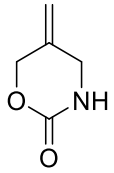
3.1.3.1 Carbamate Synthesis

3-iodo-2-methylenepropan-1-ol, A[90]



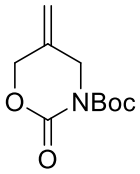
2-methylenepropan-1,3-diol (9.26 mL, 1.0 eq, 0.11 mol), PPh_3 (32.9 g, 1.1 eq, 0.13 mol) and imidazole (8.5 g, 1.1 eq, 0.12 mol) were dissolved in DCM (150 mL) and EtOAc (150 mL) under an inert atmosphere in the dark and cooled to 0 °C. I_2 (29.0 g, 1 eq, 0.11 mol) was added portionwise and the reaction was stirred at room temperature for 24 hours. The mixture was diluted with EtOAc (300 mL) and washed with water (500 mL). The organic phase was dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. The resulting residue was purified by flash column chromatography eluting with 20% EtOAc in petrol to give iodide **A** (9.7 g, 43%) as a pale yellow oil. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 5.37 (1H, *dd, J* = 1.5 & 1.0 Hz, C=CH_2), 5.22 (1H, *dd, J* = 2.5 & 1.5 Hz, C=CH_2), 4.33 (2H, *d, J* = 6.0 Hz, CH_2OH), 4.15 (1H, *s*, OH), 4.00 (2H, *s*, CH_2I); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 145.7 (*C*=CH_2), 114.1 (C=*C*H_2), 64.6 (CH_2OH), 5.6 (CH_2I). Data is consistent with literature.

5-methylenecyclohexacarbamate, B[90]



Iodide A (9.71 g, 1.0 eq, 49 mmol) was dissolved in toluene (150 mL) under an inert atmosphere in the dark. AgOCN (11.0 g, 1.5 eq, 74 mmol) was added and the reaction mixture was stirred at reflux for 22 hours. The mixture was cooled to room temperature and filtered through celite, washing with EtOAc (150 mL). The solvent was removed under reduced pressure to give carbamate **B** (4.42 g, 79%) as a colourless oil. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 5.25 (2H, *s*, C=CH_2), 4.69 (2H, *s*, CH_2O), 3.99 (2H, *s*, CH_2N); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 155.0 (C=O), 133.2 (*C*=CH_2), 113.9 (C=*C*H_2), 70.0 (CH_2NH), 45.3 (CH_2O). Data is consistent with literature.

***N*-Boc-5-methylenecyclohexacarbamate, C[90]**



Carbamate **B** (4.42 g, 1.0 eq, 39 mmol) and DMAP (0.967 g, 0.2 eq, 7.9 mmol) were dissolved in DCM (120 mL) under an inert atmosphere. Boc_2O (17.0 g, 2.0 eq, 78 mmol) was added and the mixture was stirred at room temperature for 24 hours. The reaction mixture was then washed with water (100 mL), dried with $MgSO_4$, and filtered. The solvent was removed under reduced pressure and the resulting residue was purified by flash column chromatography eluting with 20% EtOAc in petrol to give carbamate **C** (4.9 g, 58%) as an off-white amorphous solid. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 5.23 (1H, *s*, C=CH_2), 5.21 (1H, *s*, C=CH_2), 4.67 (2H, *s*, CH_2O), 4.33 (2H, *s*, CH_2N), 1.55 (9H, *s*, $C(CH_3)_3$); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 152.0 (C=O), 150.9 (C=O), 134.6 (*C*=CH_2), 112.9 (C=*C*H_2), 83.9 (*C*$(CH_3)_3$), 69.8 (CH_2N), 48.6 (CH_2O), 30.0 (C(*C*$H_3)_3$). Data is consistent with literature.

3.1.3.2 Ligand Synthesis

General Procedure K

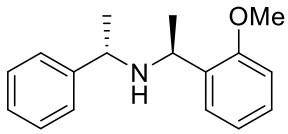
Chiral amine (1 eq) and aryl methylketone (1 eq) were dissolved in Ti(OPr^i)$_4$ under an inert atmosphere and stirred at room temperature for 30 minutes. 10% Pd on activated charcoal (2 mol%) was added and the atmosphere was exchanged for hydrogen using a balloon. The reaction mixture was stirred at room temperature overnight, then 1 M $NaOH_{(aq)}$ and EtOAc were added. The mixture was filtered through celite, flushing with EtOAc and the organic layer was separated. The solvent was removed under reduced pressure then redissolved in Et_2O and acidified to pH4 with 2 M HCl in Et_2O. The solvent was removed by reduced pressure and the hydrochloride salt was recrystallized by evaporation from 3:1 Et_2O:MeOH. The resulting crystals were free-based using 1 M $NaOH_{(aq)}$ and extracted with DCM to give amine **K**.

General Procedure L

PCl_3 (1 eq) was dissolved in THF under an inert atmosphere and cooled to 0 °C. Et_3N (10 eq) was added dropwise and the mixture was stirred for 10 minutes. The amine was

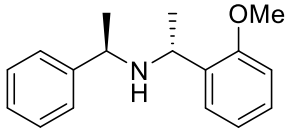
added dropwise and stirred at room temperature for 6 hours. The mixture was cooled to 0 °C and the aromatic diol (1 eq) was added. The reaction mixture was stirred at room temperature overnight and then filtered, washing with DCM. The solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography to give ligand **L**.

<u>*N*-(*R*)-Methylphenyl-*N*-(*R*)-methyl-*o*-methoxyphenylamine, K10a[112]</u>



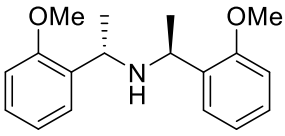
(-)-Phenylethylamine (2.0 mL, 1.0 eq, 16 mmol), 2-acetylanisole (2.2 mL, 1.0 eq, 16 mmol) and 10% Pd/C (324 mg, 2 mol%, 0.30 mmol) in $Ti(OPr^i)_4$ (14 mL) were subjected to general procedure *K*. After purification by flash column chromatography eluting with 10% EtOAc in petrol, **K10a** (1.32 g, 33%) was obtained as a colourless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) 7.46-7.17 (6H, *m*, CH_{Ar}), 7.05-7.88 (3H, *m*, CH_{Ar}), 3.82 (3H, *s*, OCH_3), 3.80 (1H, *q, J*= 6.5 Hz, CH), 3.61 (1H, *q, J* = 6.5 Hz, CH), 1.36 (3H, *d, J* = 6.5 Hz, CH_3), 1.36 (3H, *d, J* = 6.5 Hz, CH_3); HRMS (ESI) found MH^+ $C_{17}H_{22}NO$, requires MH^+ 256.1701, found 256.1698. Data is consistent with literature.

<u>*N*-(*S*)-Methylphenyl-*N*-(*S*)-methyl-*o*-methyloxyphenylamine, K10b[113]</u>



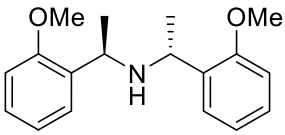
(+)-Phenylethylamine (2.0 mL, 1.0 eq, 16 mmol), 2-acetylanisole (2.2 mL, 1.0 eq, 16 mmol) and 10% Pd/C (326 mg, 2 mol%, 0.31 mmol) in $Ti(OPr^i)_4$ (14 mL) were subjected to general procedure *K*. After purification by flash column chromatography eluting with 10% EtOAc in petrol, the single diastereomer **K10b** (2.34 g, 58%) was obtained as a colourless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) 7.39-7.14 (H, *m*, CH_{Ar}), 6.97 (1H, *td, J* = 7.5 & 0.5 Hz, CH_{Ar}), 6.91 (1H, *d, J* = 8.0 Hz, CH_{Ar}), 3.80 (3H, *s*, OCH_3), 3.78 (1H, *q, J* = 7.0 Hz, CH), 3.56 (1H, *q, J* = 6.5 Hz, CH), 1.34 (3H, *d, J* = 7.0 Hz, CH_3), 1.31 (3H, *d, J* = 6.5 Hz, CH_3); HRMS (ESI) found MH^+ $C_{17}H_{22}NO$, requires MH^+ 256.1701, found 256.1696. Data is consistent with literature.

***N,N*-Di{(*R*)-methyl-o-methyloxyphenyl]amine, K11a[102]**



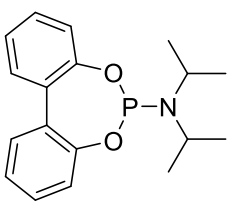
(-)-1-(2-Methoxyphenyl)ethanamine (1.0 mL, 1.02 eq, 6.6 mmol), 2-acetylanisole (0.9 mL, 1.0 eq, 6.5 mmol) and 10% Pd/C (130 mg, 2 mol%, 0.12 mmol) in $Ti(OPr^i)_4$ (6 mL) were subjected to general procedure K to give **K11a** (1.13 g, 60%) as a colourless oil with a d.r. of 3:1. ^{1}H-NMR (400 MHz, $CDCl_3$) 7.37-7.34 (2H, *m*, CH_{Ar}), 7.25-7.19 (2H, *m*, CH_{Ar}), 6.99-6.93 (2H, *m*, CH_{Ar}), 6.88-6.83 (2H, *m*, CH_{Ar}), 4.16 (0.5H, *q, J* = 6.5 Hz, CH), 3.90 (1.5H, *q, J* = 6.5 Hz, CH), 3.78 (1.5H, *s*, OCH_3), 3.75 (4.5H, *s*, OCH_3), 1.36 (1.5H, *d, J* = 6.5 Hz, CH_3), 1.31 (4.5H, *d, J* = 6.5 Hz, CH_3); HRMS (ESI) found MH^+ $C_{18}H_{24}NO_2$, requires MH^+ 286.1807, found 286.1821. Data is consistent with literature.

***N,N*-Di[(*S*)-methyl-o-methyloxyphenyl]amine, K11b[114]**



(+)-1-(2-Methoxyphenyl)ethanamine (1.0 mL, 1.02 eq, 6.6 mmol), 2-acetylanisole (0.9 mL, 1.0 eq, 6.5 mmol) and 10% Pd/C (133 mg, 2 mol%, 0.12 mmol) in $Ti(OPr^i)_4$ (6 mL) were subjected to general procedure K. After flushing through a silica plug washing with 20% EtOAc in petrol, **K11b** (1.03 g, 55%) was obtained as a colourless oil with a d.r. of 9:1. ^{1}H-NMR (400 MHz, $CDCl_3$) 7.39-7.33 (2H, *m*, CH_{Ar}), 7.28-7.19 (2H, *m*, CH_{Ar}), 7.06-6.94 (2H, *m*, CH_{Ar}), 6.86-6.81 (2H, *m*, CH_{Ar}), 4.15 (0.2H, *q, J* = 6.5 Hz, CH), 3.89 (1.8H, *q, J* = 6.5 Hz, CH), 3.78 (0.6H, *s*, OCH_3), 3.74 (5.4H, *s*, OCH_3), 1.36 (0.6H, *d, J* = 6.5 Hz, CH_3), 1.30 (5.4H, *d, J* = 6.5 Hz, CH_3); HRMS (ESI) found MH^+ $C_{18}H_{24}NO_2$, requires MH^+ 286.1807, found 286.1813. Data is consistent with literature.

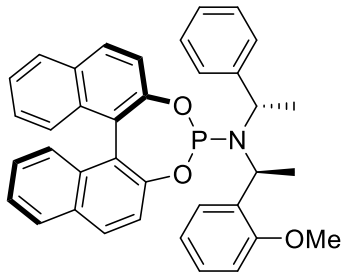
***N,N*-Diisoproyldibenzo[*d,f*][1,3,2]dioxaphosphenpin-6-amine, L1[90]**



PCl_3 (0.87 mL, 1.4 eq, 10 mmol), Et_3N (7.0 mL, 6.8 eq, 50 mmol), $NHPr^i_2$ (1.4 mL, 1.4 eq, 10 mmol) and 2,2'-biphenol (1.364 g, 1.0 eq, 7.3 mmol) in THF (40 mL) were subjected to general procedure L. Purification of the crude residue by flash column chromatography

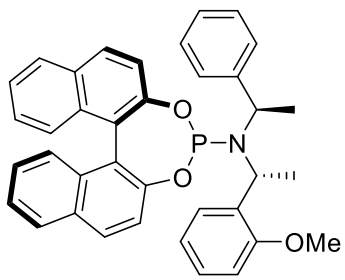
eluting with a gradient of 10-30% DCM in petrol gave **L1** (2.03 g, 88%) as a white amorphous solid. ^{1}H-NMR (400 MHz, $CDCl_3$) 7.48 (2H, *dd, J* = 7.5 & 1.5 Hz, CH_{Ar}), 7.36 (2H, *td, J* = 8.0 & 1.5 Hz, CH_{Ar}), 7.25 (4H, *d, J* = 7.5 Hz, CH_{Ar}), 7.21 (2H, *d, J* = 8.0 Hz, CH_{Ar}), 3.75-3.34 (2H, *m*, CH), 1.25 (12H, *d, J* = 7.0 Hz, CH_3); ^{31}P-NMR (162 MHz, $CDCl_3$) 152.0 (*t, J* = 10.5 Hz). Data is consistent with literature.

(11b*R*)-*N*-(*R*)-Methylphenyl-*N*-(*R*)-methyl-*o*-methyloxyphenyldinaphtho[2,1-*d*:1'2'-*f*][1,3,2]dioxaphosphenpin-4-amine, L10a[112]



PCl_3 (0.52 mL, 1.2 eq, 6.0 mmol), Et_3N (5.4 mL, 7.5 eq, 38 mmol), amine **K10a** (1.31 g, 1.0 eq, 5.1 mmol), and (*R*)-BINOL (1.78 g, 1.2 eq, 6.2 mmol) in DCM (40 mL), were subjected to general procedure *L*. Flash column chromatography eluting with 20% DCM in petrol gave the single diastereomer **L10a** (987 mg, 34%) as a white amorphous solid. ^{1}H-NMR (400 MHz, $CDCl_3$) 8.04 (1H, *d, J* = 9.0 Hz, CH_{Ar}), 8.02-7.74 (4H, *m*, CH_{Ar}), 7.66 (1H, *d, J* = 8.5 Hz, CH_{Ar}), 7.60 (1H, *d, J* = 9.0 Hz, CH_{Ar}), 7.56-7.36 (4H, *m*, CH_{Ar}), 7.35-7.18 (3H, *m*, CH_{Ar}), 7.15-7.10 (2H, *m*, CH_{Ar}), 7.03 (1H, *td, J* = 8.0 & 1.5 Hz, CH_{Ar}), 6.94-6.86 (2H, *m*, CH_{Ar}), 6.83 (1H, *td, J* = 7.5 & 0.5 Hz, CH_{Ar}), 6.52 (1H, *dd, J* = 19.0 & 8.5 Hz, CH_{Ar}), 4.96 (1H, *dq, J* = 15.0 & 7.5 Hz, CH), 4.65 (1H, *qd, J* = 7.0 & 4.0 Hz, CH) 3.53 (3H, *s,* OCH_3), 1.71 (3H, *dd, J* = 7.5 & 1.0 Hz, CH_3), 1.61 (3H, *d, J* = 7.0 Hz, CH_3); ^{31}P-NMR (162 MHz, $CDCl_3$) 144.6. Data is consistent with literature.

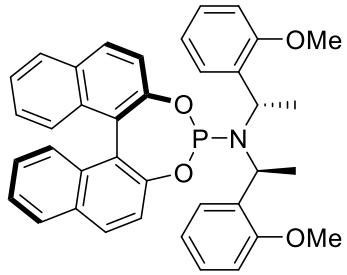
(11bR)-*N*-(*S*)-Methylphenyl-*N*-(*S*)-methyl-*o*-methyloxyphenyldinaphtho[2,1-*d*:1'2'-*f*][1,3,2]dioxaphosphenpin-4-amine, L10b[115]



PCl_3 (0.93 mL, 1.2 eq, 10.7 mmol), Et_3N (9.6 mL, 7.5 eq, 68 mmol), amine **K10b** (2.34 g, 1.0 eq, 9.1 mmol), and (*R*)-BINOL (3.19 g, 1.2 eq, 11.1 mmol) in DCM (65 mL), were subjected to general procedure *L*. Flash column chromatography eluting with 20% DCM in petrol gave **L10b**

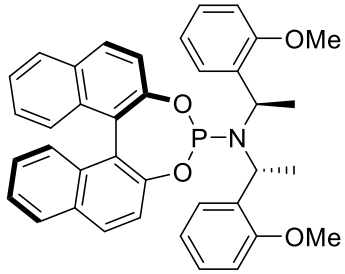
(2.74 g, 53%) as a white amorphous solid with a d.r. of 20:1. $[\alpha]_D^{21}$ = -55.1 (1.0 , $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) 8.03 (1H, *d, J* = 9.0 Hz, CH_{Ar}), 7.96 (1H, *d, J* = 9.0 Hz, CH_{Ar}), 7.83 (1H, *d, J* = 8.0 Hz, CH_{Ar}), 7.77 (1H, *d, J* = 7.5 Hz, CH_{Ar}), 7.73 (1H, *d, J* = 9.0 Hz, CH_{AR}), 7.61 (1H, *d, J* = 8.5 Hz, CH_{Ar}), 7.50-6.98 (H, *m*, CH_{Ar}), 6.95 (1H, *td, J* = 7.5 & 0.5 Hz, CH_{Ar}) 6.56 (1H, *d, J* = 8.0 Hz, CH_{Ar}), 4.78 (1H, *dq, J* = 14.5 & 7.5 Hz, CH), 4.67-4.49 (1H, *m*, CH), 3.46 (3H, *s*, OCH_3), 1.67 (2H, *dd, J* = 7.5 & 1.5 Hz, CH_3), 1.59 (3H, *d, J* = 6.5 Hz, CH_3); ^{31}P-NMR (162 MHz, $CDCl_3$) 151.1 (*d, J* = 13.5 Hz, *major*), 147.2 (*d, J* = 13.0 Hz, *minor*). Data is consistent with literature.

(11bR)-*N,N*-Di((*R*)-methyl-*o*-methyloxyphenyl)dinaphtho[2,1-*d*:1'2'-*f*][1,3,2]dioxaphosphenpin-4-amine, L11a[112]



PCl_3 (0.40 mL, 1.1 eq, 4.6 mmol), Et_3N (4.16 mL, 7.4 eq, 30 mmol), amine **K11a** (1.13 g, 1.0 eq, 4.0 mmol), and (*R*)-BINOL (1.385 g, 1.2 eq, 4.8 mmol) in DCM (31 mL), were subjected to general procedure *L*. Flash column chromatography eluting with a gradient of 20-30% DCM in petrol gave **L11a** (1.38 g, 58%) as a white amorphous solid with a d.r. of 5:1. $[\alpha]_D^{21}$ = +12.7 (1.0 , $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) 8.03-7.91 (3H, *m*, CH_{Ar}), 7.85 (0.33H, *d, J* = 8.0 Hz, CH_{Ar}), 7.72 (0.33H, *d, J* = 7.5 Hz, CH_{Ar}), 7.62-7.53 (2.33H, *m*, CH_{Ar}), 7.47-7.32 (6H, *m*, CH_{Ar}), 7.32-7.14 (2H, *m*, CH_{Ar}), 7.05 (0.33H, *t, J* = 7.5 Hz, CH_{Ar}), 6.95 (1.66H, *m,* CH_{Ar}), 6.82 (0.33H, *d, J* = 8.0 Hz, CH_{Ar}), 6.72-6.62 (2H, *m*, CH_{Ar}) 6.43 (1.66H, *d, J* = 8.0 Hz, CH_{Ar}), 5.17 (0.17H, *q, J* = 7.0 Hz, CH), 5.14 (0.17H, *q, J* = 7.0 Hz, CH), 5.05 (0.83H, *q, J* = 7.5 Hz, CH), 5.03 (0.83H, *q, J* = 7.5 Hz, CH) 3.52 (5H, *s*, OCH_3), 3.48 (1H, *s*, OCH_3), 1.59 (1H, *s*, CH_3), 1.58 (5H, *s*, CH_3); ^{31}P-NMR (162 MHz, $CDCl_3$) 151.4 (*t, J* = 8.5 Hz, *major*), 149.3 (*br. s*, *minor*). Data is consistent with literature.

(11bR)-*N,N*-Di-(*S*)-methyl-*o*-methyloxyphenyldinaphtho[2,1-*d*:1'2'-*f*][1,3,2]dioxaphosphenpin-4-amine, L11b[116]



PCl_3 (0.36 mL, 1.1 eq, 4.1 mmol), Et_3N (3.8 mL, 7.5 eq, 27 mmol), amine **K11b** (1.03 g, 1.0 eq, 3.6 mmol), and (*R*)-BINOL (1.27 g, 1.2 eq, 4.4 mmol) in DCM (29 mL), were subjected to general procedure *L*. Flash column chromatography eluting with a gradient of 20-30% DCM in petrol gave the single diastereomer **L11b** (604 mg, 28%) as a white amorphous solid. ^{1}H-NMR (400 MHz, $CDCl_3$) 8.01 (1H, *d, J* = 9.0 Hz, CH_{Ar}), 7.94 (1H, *d, J* = 8.0 Hz, CH_{Ar}), 7.82 (1H, *d, J* = 8.5 Hz, CH_{Ar}), 7.62 (1H, *d, J* = 9.0 Hz, CH_{Ar}), 7.59 (1H, *d, J* = 9.0 Hz, CH_{Ar}), 7.56 (1H, *d, J* = 7.5 Hz, CH_{Ar}), 7.48-7.15 (8H, *m*, CH_{Ar}), 7.08 (2H, *td, J* = 8.1 & 1.5 Hz, CH_{Ar}), 6.83 (2H, *t, J* = 7.5 Hz, CH_{Ar}), 6.51 (2H, *d, J* = 8.0 Hz, CH_{Ar}), 4.98 (1H, *q*, J = 7.0 Hz, CH), 4.96 (1H, *q*, J = 7.0 Hz, CH), 3.56 (6H, *s*, OCH_3), 1.53 (6H, *d, J* = 7.0 Hz, CH_3); ^{31}P-NMR (162 MHz, $CDCl_3$) 154.5 (*t, J* = 8.5 Hz). Data is consistent with literature.

3.1.3.3 Azlactone Synthesis

General Procedure A1

The amino acid (1 eq) was dissolved in 6% w/v $NaOH_{(aq)}$ and the acid chloride (1.2 eq) was added dropwise. The reaction mixture was stirred at 75 °C for 30 minutes then cooled to room temperature and acidified to pH4 using conc. HCl. This mixture was extracted with EtOAc and the solvent removed under reduced pressure to give the *N*-acylated amino acid which was taken through to the next step as crude material.

General Procedure A2

The amino acid (1 eq) was dissolved in 1 M $NaOH_{(aq)}$ and to this solution, a solution of the acid chloride (1.2 eq) in 1,4-dioxane was added slowly. The reaction mixture was allowed to stir at room temperature overnight, then was acidified to pH2 using conc. HCl and extracted using EtOAc. The solvent was removed under reduced pressure to give the *N*-acylated amino acid which was taken through to the next step as crude material.

General Procedure B

The amino acid (1 eq) was dissolved in MeOH and to this solution, the acid anhydride (2 eq) was added slowly. The reaction mixture was stirred at reflux for 6 hours, and after cooling to room temperature, EtOAc was added. The resulting precipitate was collected *via* filtration to give the *N*-acylated amino acid which was taken through to the next step as crude material.

General Procedure C

The *N*-acylated amino acid was dissolved in Ac_2O (10 mL) under an inert atmosphere and stirred at 90 °C for 30 minutes. After cooling to room temperature, the reaction mixture was quenched with sat. aq. $NaHCO_3$, then extracted with Et_2O. The solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography to give the azlactone.

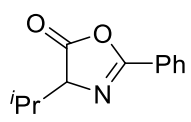
General Procedure D

The *N*-acylated amino acid (1 eq) was dissolved in dry DCM under an inert atmosphere and cooled to 0 °C. To this solution, EDC.HCl (1.2 eq) was added in one portion. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was then quenched with sat. aq. $NaHCO_3$ and extracted with DCM, and the solvent removed under reduced pressure. The resulting residue was then purified by flash column chromatography to give the azlactone.

General Procedure E

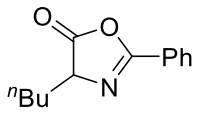
The amino acid (1 eq) was dissolved in TFAA (3 eq) under an inert atmosphere and stirred at reflux overnight. The reaction mixture was then quenched with sat. aq. $NaHCO_3$, then extracted with DCM, and the resulting crude was purified by flash column chromatography to give the azlactone.

2-Phenyl-4-(1-methylethyl)-2-oxazolin-5-one, 12b[117]



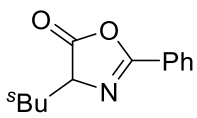
Valine (5.04 g, 1.0 eq, 43 mmol) in 6% w/v $NaOH_{(aq)}$ (60 mL) and PhCOCl (5.35 mL, 1.2 eq, 47 mmol) were subjected to general procedure *A1*. The crude *N*-acylamino acid was dissolved in Ac_2O (34 mL, 10 eq, 0.43 mol) and subjected to general procedure *C* and the crude residue was purified by flash column chromatography eluting with 5% EtOAc in petrol to give the azlactone **12b** (1.58 g, 18%) as a colourless oil. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 8.02 (2H, *d, J* = 7.5 Hz, CH_{Ar}), 7.58 (1H, *t, J* = 7.5 Hz, CH_{Ar}), 7.50 (2H, *t, J* = 7.5 Hz, CH_{Ar}), 4.31 (1H, *d, J* = 5.0 Hz, C=OCH), 2.40 (1H, *hd, J* = 7.0 & 5.0 Hz, C*H*$(CH_3)_2$), 1.16 (3H, *d, J* = 7.0 Hz, CH_3), 1.03 (3H, *d, J* = 7.0 Hz, CH_3); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 177.8 (C=N), 161.7 (C=O), 132.7 (C_{Ar}), 128.8(C_{Ar}H), 127.9 (C_{Ar}H), 125.9 (C_{Ar}H), 70.1 (CH), 31.3 (C*H*$(CH_3)_2$), 18.8 (CH_3), 17.6 (CH_3). Data is consistent with literature.

2-Phenyl-4-butyl-2-oxazolin-5-one, 12c[118]



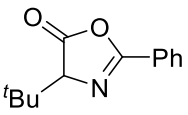
Norleucine (922 mg, 1.0 eq, 7.0 mmol) in 6% w/v $NaOH_{(aq)}$ (10 mL) then PhCOCl (0.96 mL, 1.2 eq, 8.2 mmol) were subjected to general procedure *A1*. The crude *N*-acylamino acid was dissolved in Ac_2O (10 mL, 15 eq, 0.11 mol) and subjected to general procedure *C* and the crude residue was purified by flash column chromatography eluting with 5% EtOAc in petrol to give the azlactone **12c** (802 mg, 53%) as a white amorphous solid. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 8.02 (2H, *dd*, *J* = 7.0 & 1.5 Hz, CH_{Ar}), 7.65-7.56 (1H, *m*, CH_{Ar}), 7.55-7.46 (2H, *m*, CH_{Ar}), 4.47-4.37 (1H, *m*, CH), 2.16-1.97 (1H, *m* , CH_2CH), 1.97-1.77 (1H, *m*, CH_2CH), 1.58-1.34 (4H, *m*, CH_2), 0.94 (3H, *td*, *J* = 7.0 & 2.0 Hz, CH_3); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 176.2 (C=N), 167.7 (C=O), 133.6 (C_{Ar}), 132.9 (C_{Ar}H), 132.0 (C_{Ar}H), 128.9 (C_{Ar}H), 65.3 (CH), 31.3 (CH_2), 27.2 (CH_2), 22.3 (CH_2), 13.8 (CH_3). Data is consistent with literature.

2-Phenyl-4- (1-methylpropyl)-2-oxazolin-5-one, 12d[119]



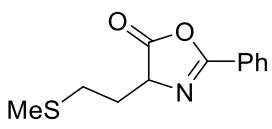
Isoleucine (1.03 g, 1.0 eq, 7.9 mmol) in 6% w/v $NaOH_{(aq)}$ (10 mL) and PhCOCl (0.96 mL, 1.1 eq, 8.3 mmol) were subjected to general procedure *A1*. The crude *N*-acylamino in Ac_2O (10 mL) was subjected to general procedure *C* and the crude residue was purified by flash column chromatography eluting with 5% EtOAc in petrol to give the azlactone **12d** (823 mg, 46%, d.r. 1:1.1) as a white amorphous solid. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 8.05-7.98 (2H, *m*, CH_{Ar}), 7.62-7.44 (3H, *m*, CH_{Ar}), 4.43 (0.5H, *d*, *J* = 4.0 Hz, CH), 4.37 (0.5H, *d*, *J* = 4.5 Hz, CH), 2.21-2.08 (2H, *m*, CH_2), 1.76-1.64 (0.5H, *m*, CH), 1.67-1.52 (0.5H, *m*, CH), 1.52-1.33 (1H, *m*, CH_2), 1.08 (1.5H, *d*, *J* = 7.0 Hz, CHCH_3), 1.03 (1.5H, *t*, *J* = 7.5 Hz, CH_2CH_3), 0.98 (1.5H, *t*, *J* = 7.5 Hz, CH_2CH_3), 0.92 (1.5H, *d*, *J* = 7.0 Hz, CHCH_3); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 178.5 (C=N), 177.7 (C=N), 161.7 (C=O), 161.6 (C=O), 132.7 ($C_{Ar}H$), 130.6 ($C_{Ar}H$), 128.9 ($C_{Ar}H$), 128.8 ($C_{Ar}H$), 127.89 ($C_{Ar}H$), 127.86 ($C_{Ar}H$), 125.96 (C_{Ar}), 125.95 (C_{Ar}), 69.7 (CH), 69.1 (CH), 38.1 (CH), 37.7 (CH), 26.2 (CH_2), 25.0 (CH_2), 15.4 (CH_3), 14.5 (CH_3), 11.8 (CH_3), 11.7 (CH_3). Data is consistent with literature.

2-Phenyl-4-(1,1-demethylethyl)-2-oxazolin-5-one, 12e[120]



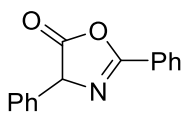
tert-Leucine (479 mg, 1.0 eq, 3.6 mmol) in 6% w/v $NaOH_{(aq)}$ (5 mL) and PhCOCl (0.46 mL, 1.1 eq, 4.0 mmol) were subjected to general procedure *A1*. The crude *N*-acylamino acid in Ac_2O (3.3 mL, 9.7 eq, 35 mmol) was subjected to general procedure *C* and the crude residue was purified by flash column chromatography eluting with 5% EtOAc in petrol to give the azlactone **12e** (409 mg, 52%) as a white amorphous solid. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 8.03 (2H, *dd*, *J* = 5.0 & 3.5 Hz, CH_{Ar}), 7.62-7.55 (1H, *m*, CH_{Ar}), 7.55-7.46 (2H, *m*, CH_{Ar}), 4.11 (1H, *s*, CH), 1.16 (9H, *s*, $C(CH_3)_3$); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 177.1 (C=N), 161.3 (C=O), 132.6 ($C_{Ar}H$), 128.8 ($C_{Ar}H$), 127.9 ($C_{Ar}H$), 126.0 (C_{Ar}), 74.1 (CH), 36.0 ($C(CH_3)_3$), 26.2 ($C(CH_3)_3$). Data is consistent with literature.

2-Phenyl-4-[2-(methylthio)ethyl)]-2-oxazolin-5-one 12f[117]



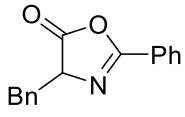
Methionine (1.05 g, 1.0 eq, 7.0 mmol), 6% w/v $NaOH_{(aq)}$ (10 mL) and PhCOCl (1 mL, 1.2 eq, 8.6 mmol) were subjected to general procedure *A1*. The crude *N*-acylamino acid in Ac_2O (10 mL, 15 eq, 0.11 mmol) was subjected to general procedure *C* and the crude residue was purified by flash column chromatography eluting with 5% EtOAc in petrol to give the azlactone **12f** (836 mg, 50%) as a white amorphous solid. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 8.04-7.96 (2H, *m*, CH_{Ar}), 7.65-7.53 (1H, *m*, CH_{Ar}), 7.48 (2H, *t*, *J* = 7.5 Hz, CH_{Ar}), 4.61 (1H, *dd*, *J* = 7.0 & 6.0 Hz, CH), 2.73 (2H, *t*, J = 7.0 Hz, SCH_2), 2.41-2.25 (1H, *m*, C*H*$_2$CH), 2.24-2.06 (1H, *m*, C*H*$_2$CH), 2.11 (3H, *s*, CH_3); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 175.7 (C=N), 162.3 (C=O), 128.9 ($C_{Ar}H$), 128.0 ($C_{Ar}H$), 127.2 ($C_{Ar}H$), 125.8 (C_{Ar}), 63.7 (CH), 30.4 (CH_2), 30.0 (CH_2), 15.1 (CH_3). Data is consistent with literature.

2-Phenyl-4-phenyl-2-oxazolin-5-one, 12g[117]



Phenylglycine (2.06 g, 1.0 eq, 14 mmol) in 1 M $NaOH_{(aq)}$ (15 mL) and PhCOCl (1.7 mL, 1.1 eq, 15 mmol) in 1,4-dioxane (15 mL) were subjected to general procedure *A2*. The crude *N*-acylated amino acid and EDC.HCl (2.81 g, 1.1 eq, 15 mmol) in dry DCM (40 mL) were subjected to general procedure *D* and the crude residue was purified by flash column chromatography eluting with a gradient of 2-5% EtOAc in petrol to give the azlactone **12g** (679 mg, 21%) as a yellow amorphous solid. ^{1}H NMR δ/ppm (400 MHz, $CDCl_3$) 8.13-8.08 (2H, *m*, CH_{Ar}), 7.68-7.36 (8H, *m*, CH_{Ar}), 5.83 (1H, *m*, CH); ^{13}C NMR δ/ppm (101 MHz, $CDCl_3$) 176.3 (C=N), 162.6 (C=O), 133.5 (C_{Ar}), 133.1 ($C_{Ar}H$), 129.2 ($C_{Ar}H$), 129.1 ($C_{Ar}H$), 128.9 ($C_{Ar}H$), 128.2 ($C_{Ar}H$), 127.4 ($C_{Ar}H$), 125.7 (C_{Ar}), 68.2 (CH). Data is consistent with literature.

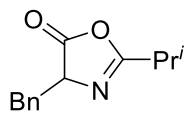
2-Phenyl-4-benzyl-2-oxazolin-5-one, 12h[117]



Phenylalanine (1.07 g, 1.0 eq, 6.5 mmol), 6% w/v $NaOH_{(aq)}$ (8 mL) and PhCOCl (0.77 mL, 1.0 eq, 6.6 mmol) were subjected to general

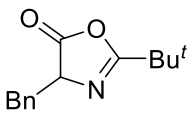
procedure *A1*. The crude *N*-acylated amino acid and EDC.HCl (1.42 g, 1.1 eq, 7.4 mmol) in dry DCM (20 mL), were subjected to general procedure *D* and the crude residue was purified by flash column chromatography eluting with 2% EtOAc in petrol to give the azlactone **12h** (696 mg, 43%) as a white amorphous solid. ^{1}H NMR δ/ppm (400 MHz, $CDCl_3$); 7.98-7.91 (2H, *m*, CH_{Ar}), 7.62-7.53 (1H, *m*, CH_{Ar}), 7.52-7.44 (2H, *m*, CH_{Ar}), 7.34-7.19 (5H, *m*, CH_{Ar}), 4.72 (1H, *dd, J* = 6.5 & 5.0 Hz, CH), 3.40 (1H, *dd, J* = 14.0 & 5.0 Hz, CH_2), 3.22 (1H, *dd, J* = 14.0 & 6.5 Hz, CH_2); ^{13}C NMR δ/ppm (101 MHz, & $CDCl_3$) 177.6 (C=N), 161.7 (C=O), 135.3 (C_{Ar}), 132.7 ($C_{Ar}H$), 129.6 ($C_{Ar}H$), 128.7 ($C_{Ar}H$), 128.4 ($C_{Ar}H$), 127.9 ($C_{Ar}H$), 127.2 ($C_{Ar}H$), 125.8 (C_{Ar}), 66.6 (CH), 37.3 (CH_2). Data is consistent with literature.

2-(1-methylethyl)-4-benzyl-2-oxazolin-5-one, 12i[121]



Phenylalanine (514 mg, 1.0 eq, 3.1 mmol) in 1 M $NaOH_{(aq)}$ (20 mL) and ^{i}PrCOCl (0.35 mL, 1.1 eq, 3.3 mmol) in 1,4-dioxane (20 mL) were subjected to general procedure *A2*. The crude *N*-acylamino acid and EDC.HCl (699 mg, 1.2 eq, 3.6 mmol) in dry DCM (20 mL) were subjected to general procedure *D*. The crude residue was purified by flash column chromatography eluting with a gradient of 5-15% EtOAc in petrol to give the azlactone **12i** (241 mg, 36%) as a colourless oil. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 7.34-7.16 (5H, *m*, CH_{Ar}), 4.49 (1H, *td, J* = 5.0 & 1.5 Hz, CH), 3.29 (1H, *dd, J* = 14.0 & 5.0 Hz, CH_2), 3.18 (1H, *dd, J* = 14.0 & 5.0 Hz, CH_2), 2.58 (1H, *hd, J* = 7.0 & 1.5 Hz, C*H*$(CH_3)_2$), 1.11 (3H, *d, J* = 7.0 Hz, CH_3), 1.05 (3H, d, J = 7.0 Hz, CH_3); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 178.00 (C=N), 170.1 (C=O), 134.6 (C_{Ar}), 129.8 ($C_{Ar}H$), 128.3 ($C_{Ar}H$), 127.3 ($C_{Ar}H$), 65.4 (CH), 36.8 (CH_2), 29.0 (*C*H$(CH_3)_2$), 18.4 (CH_3), 18.3 (CH_3). Data is consistent with literature.

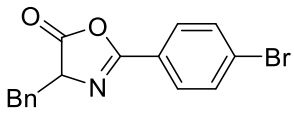
2-(1,1-dimethylethyl)-4-benzyl-2-oxazolin-5-one, 12j[122]



Phenylalanine (5.06 g, 1.0 eq, 31 mmol) in 1 M $NaOH_{(aq)}$ (40 mL) and ^{t}BuCOCl (4.1 mL, 1.1 eq, 33 mmol) in 1,4-dioxane (40 mL) were subjected to general procedure *A2*. The crude *N*-acylamino acid and

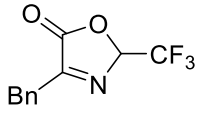
EDC.HCl (6.35 g, 1.1 eq, 33 mmol) in dry DCM (100 mL) were subjected to general procedure *D*. The crude residue was purified by flash column chromatography eluting with a gradient of 10-20% EtOAc in petrol to give the azlactone **12j** (3.02 g, 43%) as an off-white amorphous solid. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 7.30-7.20 (3H, *m*, CH_{Ar}), 7.17 (2H, *d, J =* 7.5 Hz, CH_{Ar}), 4.47 (1H, t_{app}*, J =* 5.0 Hz, CH), 3.27 (1H, *dd, J =* 13.5 & 5.0 Hz, CH_2), 3.18 (1H, *dd, J =* 13.5 & 5.0 Hz, CH_2), 1.06 (9H, *s*, $C(CH_3)_3$); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 179.1 (C=N), 175.1 (C=O), 135.6 (C_{Ar}), 129.4 ($C_{Ar}H$), 128.7 ($C_{Ar}H$), 127.3 ($C_{Ar}H$), 53.1 (CH), 38.7 ($C(CH_3)_3$), 37.1 (CH_2), 27.3 ($C(CH_3)_3$). Data is consistent with literature.

2-(4-bromophenyl)-4-benzyl-2-oxazolin-5-one, 12k[122]



Phenylalanine (500 mg, 1.3 eq, 3.0 mmol) in 1M $NaOH_{(aq)}$ (20 mL) and 4-BrC_6H_4COCl (496 mg, 1.0 eq, 2.3 mmol) in 1,4-dioxane (20 mL) were subjected to general procedure *A2*. The crude *N*-acylamino acid and EDC.HCl (649 mg, 1.7 eq, 4.0 mmol) in dry DCM (40 mL) were subjected to general procedure *D*. The crude residue was purified by flash column chromatography eluting with a gradient of 2-10% EtOAc in petrol to give the azlactone **12k** (206 mg, 28%) as a white amorphous solid. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 7.80 (2H, *d, J =* 8.5 Hz, CH_{Ar}), 7.61 (2H, *d, J =* 8.5 Hz, CH_{Ar}), 7.36-7.10 (5H, *m*, CH_{Ar}), 4.70 (1H, *dd, J =* 6.5 & 5.0 Hz, CH), 3.40 (1H, *dd, J =* 14.0 & 5.0 Hz, CH_2), 3.21 (1H, *dd, J =* 14.0 & 6.5 Hz, CH_2); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 177.3 (C=N), 161.0 (C=O), 135.1 (C_{Ar}), 121.1 ($C_{Ar}H$), 129.6 ($C_{Ar}H$), 129.3 ($C_{Ar}H$) 128.5 ($C_{Ar}H$), 127.7 (C_{Ar}), 127.3 ($C_{Ar}H$), 124.7 (C_{Ar}), 66.6 (CH), 37.3 (CH_2). Data is consistent with literature.

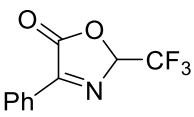
4-Benzyl-2-(trifluoromethyl)- 3-oxazolin-5-one, 12l[92]



Phenylalanine (5.04 g, 1.0 eq, 31 mmol) in TFAA (17 mL, 4.0 eq, 0.12 mol) was subjected to general procedure *E* and the crude mixture was purified by flash column chromatography eluting with 20% EtOAc in petrol to give the azlactone **12l** (5.63 g, 76%) as a yellow oil. ^{1}H NMR δ/ppm (400 MHz,

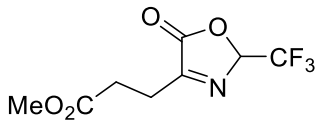
$CDCl_3$) 7.45-7.30 (5H, m, CH_{Ar}), 6.16-6.07 (1H, *m*, $CHCF_3$), 4.12-4.00 (2H, m, $PhCH_2$); ^{13}C NMR δ/ppm (101 MHz, $CDCl_3$) 167.3 (C=N), 163.4 (C=O), 132.5 (C_{Ar}), 129.4 ($C_{Ar}H$), 129.1 ($C_{Ar}H$), 127.9 ($C_{Ar}H$), 120.2 (*q*, *J* = 281.5 Hz, CF_3), 93.1 (*q*, *J* = 35.0 Hz, *C*HCF_3), 34.5 (CH_2); ^{19}F NMR δ/ppm (376 MHz, $CDCl_3$) -78.7 (*d, J* = 4.0 Hz, CF_3). Data is consistent with literature.

4-Phenyl-2-(trifluoromethyl)- 3-oxazolin-5-one, 12m[92]



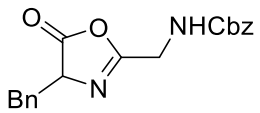
Phenylglycine (5.03 g, 1.0 eq, 33 mmol) in TFAA (14 mL, 3.0 eq, 0.10 mol) was subjected to general procedure *E* to give the azlactone **12m** (6.96 g, 91%) as a yellow amorphous solid. ^1H NMR δ/ppm (400 MHz, $CDCl_3$) 8.47 (2H, *dt*, *J* = 8.5 & 1.5 Hz, CH_{Ar}), 7.68 (2H, *m*, CH_{Ar}), 7.63-7.52 (1H, m, CH_{Ar}), 6.29 (1H, *q*, *J* = 4.0 Hz, $CHCF_3$); ^{13}C NMR δ/ppm (101 MHz, $CDCl_3$) 162.7 (C=N), 160.6 (C=O), 134.0 ($C_{Ar}H$), 129.14 ($C_{Ar}H$), 129.06 ($C_{Ar}H$), 127.3 (C_{Ar}), 120.4 (*q*, *J* = 282.0 Hz, CF_3), 92.3 (*q*, *J* = 35.5 Hz, *C*HCF_3); ^{19}F NMR δ/ppm (376 MHz, $CDCl_3$) -78.6 (*d*, *J* = 4.0 Hz, CF_3). Data is consistent with literature.

Methyl (2-(trifluoromethyl)-5-oxo-2,3-dihyrdo-oxazol-4-yl)propanoate, 12n



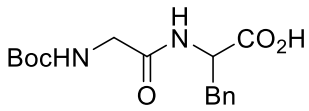
Glutamic acid methyl ester (1.01 g, 1.0 eq, 6.2 mmol) in TFAA (2.6 mL, 3.1 eq, 19 mmol) was subjected to general procedure *E* and the crude residue was purified by flash column chromatography eluting with a gradient of 10-20% EtOAc in petrol to give the azlactone **12n** (1.09 g, 73%) as a colourless oil. ^1H-NMR δ/ppm (400 MHz, $CDCl_3$) 6.18-6.07 (1H, *m*, $CHCF_3$), 3.68 (3H, *s*, CH_3), 3.05-2.94 (2H, *m*, CH_2), 2.90-2.81 (2H, *m*, CH_2); ^{13}C-NMR δ /ppm (101 MHz, $CDCl_3$) 171.9 (*C*O_2Me), 168.0 (C=O), 163.2 (C=N), 120.1 (*q*, *J* = 281.5 Hz, CF_3), 93.2 (*q*, *J* = 35.5 Hz, *C*HCF_3), 52.0 (CH_3), 29.1 (CH_2), 23.5 (CH_2); ^{19}F-NMR δ /ppm (377 MHz, CDCl3) -79.0 (*d*, *J* = 4.0 Hz, CF_3), ν_{max}/cm^{-1} (thin film) 2961 (C–H), 2856 (C–H), 1801 (C=O), 1729 (C=N), 1654 (C=O); HRMS (ESI) found MH^+ 240.0478, $C_8H_8F_3NO_4$, requires MH^+, 240.0490.

Benzyl (4-Benzyl-5-oxo-4,5-dihydro-oxazol-2-ylmethyl)-carbamic acid, 12o[99]



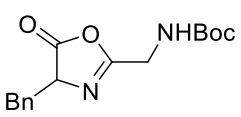
Z-Gly-Phe-OH (500 mg, 1.0 eq, 1.4 mmol) and EDC.HCl (351 mg, 1.3 eq, 1.8 mmol) in dry DCM (20 mL) were subjected to general procedure *D*. The crude residue was purified by flash column chromatography eluting with a gradient of 20-40% EtOAc in petrol to give the azlactone **12o** (139 mg, 29%) as a colourless oil. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 7.45-7.22 (10H, *m*, CH_{Ar}), 5.97 (1H, *s*, NH), 5.16-5.05 (2H, *m*, CH_2), 4.95 (1H, *t, J* = 5.5 Hz, CH_2), 3.99-3.87 (2H, *m*, CH_2), 3.83-3.68 (1H, *m,* PhC*H*$_2$CH) 3.68-3.47 (1H, *m*, PhC*H*$_2$CH); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 164.9 (C=N), 164.3 (C=O), 156.1 (C=O), 136.1 (C_{Ar}), 133.7 (C_{Ar}), 129.3 ($2C_{Ar}H$), 128.9 ($2C_{Ar}H$), 128.6 ($2C_{Ar}H$), 128.3 ($C_{Ar}H$), 128.2 ($2C_{Ar}H$), 127.5 ($C_{Ar}H$), 98.0 (CH), 67.2 (CH_2), 43.2 (CH_2), 34.3 (CH_2). Data is consistent with literature.

***N*-Boc Glycylphenylalanine, 11p[100]**



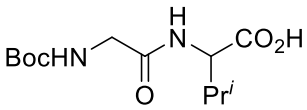
Glycylphenylalanine (1.04 g, 1.0 eq, 4.7 mmol) and $NaHCO_3$ (1.18 g, 3.0 eq, 14 mmol) were dissolved in water (14 mL) and THF (14 mL). To this solution, Boc_2O (1.20 g, 1.2 eq, 5.5 mmol) was added and the reaction was stirred at room temperature overnight. The reaction mixture was washed with Et_2O (20 mL), then acidified to <pH4 with 1 M $HCl_{(aq)}$. The acidified crude mixture was extracted with EtOAc (2x20 mL), the organic phases were combined and dried with $MgSO_4$, then filtered and the solvent removed under reduced pressure to give **11p** (1.387 g, 92%) as a white amorphous solid. ^{1}H-NMR δ/ppm (400 MHz, d^4-MeOD) 7.36-7.10 (5H, *m*, CH_{Ar}), 4.70 (1H, *dd, J* = 7.5 & 5.0 Hz, CH), 3.74 (1H, *d, J* = 17.0 Hz, CH_2), 3.67 (1H, *d, J* = 17.0 Hz, CH_2), 3.21 (1H, *dd, J* = 14.0 & 5.0 Hz, CH_2), 3.04 (1H, *d, J* = 14.0 & 7.5 Hz, CH_2), 1.45 (9H, *s*, $C(CH_3)_3$); ^{13}C-NMR δ/ppm (101 MHz, d^4-MeOD) 172.9 (C=O), 170.8 (C=O), 136.7 (C_{Ar}), 129.0 ($C_{Ar}H$), 128.1 ($C_{Ar}H$), 126.5 ($C_{Ar}H$), 79.3 ($C(CH_3)_3$), 53.5 (CH), 43.1 (CH_2), 37.0 (CH_2), 27.3 ($C(CH_3)_3$). Data is consistent with literature.

***tert*-Butyl (4-Benzyl-5-oxo-4,5-dihydro-oxazol-2-ylmethyl)-carbamic acid, 12p[100]**



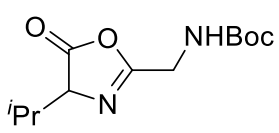
11p (207 mg, 1.0 eq, 0.64 mmol) in dry DCM (10 mL) under an inert atmosphere was cooled to 0 °C, and DCC (146 mg, 1.1 eq, 0.71 mmol) was added. The mixture was stirred for 4 hours, then filtered to remove the urea by-product. The crude residue was concentrated and a minimal amount of DCM was added to dissolve the residue. This was then stored in the freezer overnight to precipitate the remaining starting materials, and filtered once more. The solvent was removed to give the azlactone **12p** (161 mg, 83%) as a white cloudy oil. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 7.35-7.17 (5H, *m*, CH_{Ar}), 5.05 (1H, *s*, NH), 4.48 (1H, *m,* CH), 4.02 (2H, *d*, J = 3.5 Hz, CH_2), 3.27 (1H, *dd, J* = 14.0 & 5.0 Hz*,* PhCH_2) 3.09 (1H, *dd, J* = 14.0 & 6.5 Hz, PhCH_2CH), 1.47 (9H, s, $C(CH_3)_3$); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 176.9 (HNC=O), 162.9 (C=N), 155.4 (C=O), 134.8 (C_{Ar}), 129.5 ($C_{Ar}H$), 128.5 ($C_{Ar}H$), 127.4 ($C_{Ar}H$), 80.4 ($C(CH_3)_3$), 65.5 (CH), 38.3 (CH_2), 36.8 (CH_2), 28.3 ($C(CH_3)_3$). Data is consistent with literature.

***N*-Boc Glycylphenylalanine, 11q[124]**



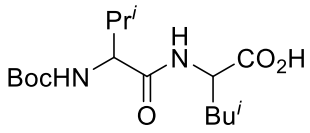
Glycylvaline (2.94 g, 1.0 eq, 14 mmol) and $NaHCO_3$ (4.26 g, 3.6 eq, 51 mmol) were dissolved in water (50 mL) and THF (50 mL). To this solution, Boc_2O (4.49 g, 1.5 eq, 21 mmol) was added and the reaction was stirred at room temperature overnight. The reaction mixture was washed with Et_2O (50 mL), then acidified to <pH4 with 1 M $HCl_{(aq)}$. The acidified crude mixture was extracted with EtOAc (2x50 mL), the organic phases were combined and dried with $MgSO_4$, then filtered and the solvent removed under reduced pressure to give **11q** (1.74 g, 38%) as a white amorphous solid. ^{1}H-NMR δ/ppm (400 MHz, d^4-MeOD) 4.39 (1H, *d, J* = 5.5 Hz, CH), 4.14 (1H, *d, J* = 7.0 Hz, CH_2), 4.10 (1H, *d, J* = 7.0 Hz, CH_2), 2.30-2.11 (1H, *m*, $CH(CH_3)_2$), 0.98 (6H, t_{app}*, J* = 7.0 Hz, CH_3); ^{13}C-NMR δ/ppm (101 MHz, d^4-MeOD) 173.1 (C=O), 171.1 (C=O), 79.4 ($C(CH_3)_3$), 57.3 (CH), 43.2 (CH_2), 30.6 (CH), 27.3 ($C(CH_3)_3$), 19.5 (CH_3), 13.1 (CH_3). Data is consistent with literature.

***tert*-Butyl (4-*iso*-Propyl-5-oxo-4,5-dihydro-oxazol-2-ylmethyl)-carbamic acid, 12q[99]**



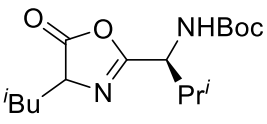
11q (1.74 g, 1.0 eq, 6.3 mmol) in dry DCM (100 mL) under an inert atmosphere was cooled to 0 °C, and DCC (1.58 mg, 1.2 eq, 0.77 mmol) was added. The mixture was stirred for 4 hours, then filtered to remove the urea by-product. The crude residue was concentrated and a minimal amount of DCM was added to dissolve the residue. This was then stored in the freezer overnight to precipitate the remaining starting materials, and filtered once more. The solvent was removed to give the azlactone **12q** (1.61 g, 99%) as an off-white cloudy oil. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 5.22 (1H, *s*, NH), 4.18-4.11 (2H, m, CH_2), 4.06 (1H, *dt, J =* 4.5 & 2.5 Hz, CH), 2.27 (1H, *dsept, J =* 7.0 & 2.5 Hz, C*H*$(CH_3)_2$), 1.45 (9H, *s*, $C(CH_3)_3$), 1.07 (3H, *d*, J = 7.0 Hz, CHC*H*$_3$), 0.94 (3H, *d, J =* 7.0 Hz, CHC*H*$_3$) ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 177.1 (HNC=O), 162.7 (C=N), 155.5 (C=O), 80.3 (*C*$(CH_3)_3$), 69.7 (CH), 34.9 (CH_2), 30.69, 28.3 (C(*C*$H_3)_3$), 18.6 (CH*C*H_3), 17.29 (CH*C*H_3). Data is consistent with literature.

***N*-Boc Valylleucine, 11r[124]**



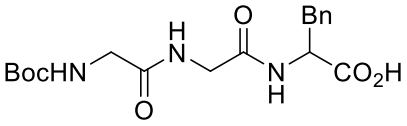
Valylleucine (467 mg, 1.0 eq, 2.0 mmol) and $NaHCO_3$ (518 mg, 3.1 eq, 6.2 mmol) were dissolved in water (30 mL) and THF (30 mL). To this solution, Boc_2O (568 mg, 1.3 eq, 2.7 mmol) was added and the reaction was stirred at room temperature overnight. The reaction mixture was washed with Et_2O (30 mL), then acidified to <pH4 with 1 M $HCl_{(aq)}$. The acidified crude mixture was extracted with EtOAc (2x30 mL), the organic phases were combined and dried with $MgSO_4$, then filtered and the solvent removed under reduced pressure to give **11r** (613 mg, 92%) as a white amorphous solid. ^{1}H-NMR δ/ppm (400 MHz, d^4-MeOD) 4.52-4.43 (1H, *m*, CHBu^i), 3.88 (1H, *d, J =* 7.5 Hz, CHPr^i), 2.10-1.97 (1H, *m*, CH), 1.75 (1H, *dt, J =* 19.5 & 6.5 Hz, CH), 1.70-1.59 (2H, *m*, CH_2), 1.46 (9H, *s*, $C(CH_3)_3$), 1.07-0.87 (12H, *m*, CH_3); ^{13}C-NMR δ/ppm (101 MHz, d^4-MeOD) 174.3 (C=O), 171.8 (C=O), 81.4 (*C*$(CH_3)_3$), 60.1 (CH), 50.5 (CH), 40.3 (CH_2), 30.6 (CH), 27.3 (C(*C*$H_3)_3$), 24.5 (CH), 22.0 (CH_3), 20.4 (CH_3), 18.4 (CH_3), 17.1 (CH_3). Data is consistent with literature.

***tert*-Butyl (4-*iso*-Butyl-5-oxo-4,5-dihydro-oxazol-2-yl-1-(L)-*iso*-propylmethyl)-carbamic acid, 12r**



11r (607 mg, 1.0 eq, 1.8 mmol) in dry DCM (10 mL) under an inert atmosphere was cooled to 0 °C, and DCC (467 mg, 1.3 eq, 2.3 mmol) was added. The mixture was stirred for 4 hours, then filtered to remove the urea by-product. The crude residue was concentrated and a minimal amount of DCM was added to dissolve the residue. This was then stored in the freezer overnight to precipitate the remaining starting materials, and filtered once more. The solvent was removed to give the azlactone **12r** (571 mg, 98%) as a white cloudy oil. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 5.00 (1H, *d, J* = 9.0 Hz, NH), 4.44 (1H, *dd, J* = 8.5 & 5.5 Hz, CH), 4.21 (1H, *dd, J* = 9.0 & 5.5 Hz, CHPr^i), 2.19-2.11 (1H, *m,* C*H*$(CH_3)_2$) 2.01-1.90 (1H, *m*, C*H*CH_2), 1.46 (9H, *s*, C$(CH_3)_3$, 1.37-1.26 (2H, *m,* CH_2), 1.02 (3H, *d, J* = 7.0 Hz, CH_3), 0.99 (3H, *d, J* = 8.5 Hz, CH_3), 0.97 (3H, *d, J* = 7.0 Hz, CH_3), 0.97 (3H, *d, J* = 6.5 Hz, CH_3); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 178.6 (NHC=O), 164.6 (C=N), 155.5 (C=O) 80.2 (*C*$(CH_3)_3$), 63.0 (CH), 54.7 (CHPr^i), 53.1 (CHPr^i) 30.6 (CH_2C*H*), 28.3 (C(*C*$H_3)_3$), 24.7 (CH_2), 22.7 (CH_3), 22.0 (CH_3), 19.0 (CH_2CH*C*H_3), 17.5 (*C*H_3); ν_{max}/cm^{-1} (ATR) 2998 (C–H), 1722 (C=O), 1280 (C–O); HRMS (ESI) found MH$^+$ 313.2127, $C_{14}H_{16}N_2O_2$, requires MH$^+$, 313.2133.

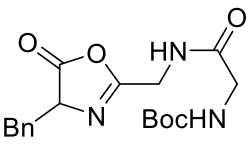
***N*-Boc Glycylglycylphenyalanine, 11v[125]**



Glycylglycylphenylalanine (494 mg, 1.0 eq, 1.7 mmol) and $NaHCO_3$ (539 mg, 3.6 eq, 6.1 mmol) were dissolved in water (25 mL) and THF (25 mL). To this solution, Boc_2O (509 mg, 1.5 eq, 2.5 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was washed with Et_2O (30 mL), then acidified to <pH4 with 1 M $HCl_{(aq)}$. The acidified crude mixture was extracted with EtOAc (2x30 mL), the organic phases were combined and dried with $MgSO_4$, then filtered and the solvent removed under reduced pressure to give **11r** (384 mg, 57%) as a white amorphous solid. ^{1}H-NMR δ/ppm (400 MHz, d^4-MeOD) 7.34-7.05 (5H, *m*, CH_{Ar}), 4.67 (1H, *dd, J* = 8.5 & 5.0 Hz, CH), 3.92 (1H, *d, J* = 17.0 Hz, CH_2), 3.81 (1H, *d, J* = 17.0 Hz, CH_2), 3.74 (2H, *s*, CH_2), 3.22 (1H, *dd, J* = 14.0 & 5.0 Hz, CH_2), 3.03 (1H, *dd, J* = 14.0 & 8.5 Hz, CH_2),

1.48 (9H, *s*, $C(CH_3)_3$); ^{13}C-NMR δ/ppm (101 MHz, d^4-MeOD) 173.6 (C=O), 171.0 (C=O), 168.3 (C=O), 156 (C=O), 129.9 (C_{Ar}), 129.0 ($C_{Ar}H$), 128.1 ($C_{Ar}H$), 126.4 ($C_{Ar}H$), 80.4 ($C(CH_3)_3$), 53.9 (CH), 43.4 (CH_2), 41.7 (CH_2), 36.9 (CH_2) 27.3 ($C(CH_3)_3$). Data is consistent with literature.

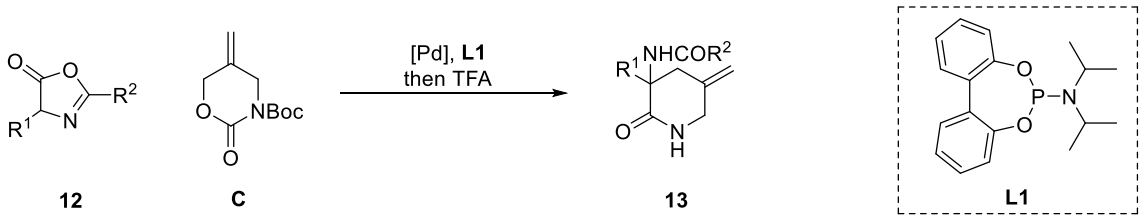
<u>*tert*-Butyl (4-*iso*-Propyl-5-oxo-4,5-dihydro-oxazol-2-ylmethyl)-carbamic acid, 12v</u>



11s (379 mg, 1.0 eq, 1.0 mmol) in dry DCM (10 mL) under an inert atmosphere was cooled to 0 °C, and DCC (311 mg, 1.3 eq, 1.5 mmol) was added. The mixture was stirred for 4 hours, then filtered to remove the urea by-product. The crude residue was concentrated and a minimal amount of DCM was added to dissolve the residue. This was then stored in the freezer overnight to precipitate the remaining starting materials, and filtered once more. The solvent was removed to give the azlactone **12s** (328 mg, 87%) as a white gum. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 7.32-7.10 (5H, m, CH_{Ar}), 4.45 (1H, *dd, J* = 7.0 & 5.0 Hz, CH), 4.19-4.02 (2H, m, CH_2), 3.79 (2H, s, CH_2) 3.21 (1H, dd, J = 14.0 & 5.0 Hz, CH_2), 3.02 (1H, dd, J = 14.0 & 7.0 Hz, CH_2), 1.43 (9H, s, $C(CH_3)_3$); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 176.7 (C=O), 166.8 (C=O), 163.0 (C=N), 155.1 (C=O), 134.2 (C_{Ar}), 129.9 ($C_{Ar}H$), 128.6 ($C_{Ar}H$), 127.4 ($C_{Ar}H$), 80.1 ($C(CH_3)_3$), 65.3 (CH), 38.4 (CH_2), 36.9 (CH_2), 34.3 (CH_2), 28.2 ($C(CH_3)_3$). ν_{max}/cm^{-1} (ATR) 2933 (C–H), 1642 (C=O), 1215(C–O); HRMS (ESI) found MH^+ 362.1716, $C_{18}H_{24}N_3O_5$, requires MH^+, 362.1726.

3.1.3.4 Lactam Synthesis

General Procedure



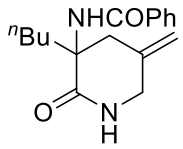
Azlactone **12** (2 eq), carbamate **C** (1 eq), $Pd(dba)_2$ (5 mol%) and ligand **L1** (15 mol%) were dissolved in dry DCM under an inert atmosphere and stirred at reflux for 16 hours. The mixture was then cooled to room temperature and TFA was added. After 1 hour, EtOAc was added and the reaction was quenched with sat. aq. $NaHCO_3$. The layers were separated and the aqueous layer was further extracted with EtOAc. The solvent was then removed under reduced pressure and the crude residue was purified by flash column chromatography eluting with petrol and EtOAc to give the lactam **13**.

3-(1-Methylethyl)-3-benzamido-5-methylene-2-piperidinone, 13b

Azlactone **12b** (107 mg, 2.3 eq, 0.53 mmol), carbamate **C** (49 mg, 1.0 eq, 0.23 mmol), $Pd(dba)_2$ (8 mg, 6 mol%, 0.014 mmol) and **L1** (12 mg, 17 mol%, 0.038 mmol) dissolved in dry DCM (4 mL) were reacted according to the general procedure. The crude mixture was purified by flash column chromatography eluting with 50-100% EtOAc in petrol to give the lactam **13b** (46 mg, 74%) as a white amorphous solid. m.p. 148-150 °C; ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 7.86-7.77 (2H, *m,* CH_{Ar}), 7.55-7.40 (3H, m, CH_{Ar}), 7.30 (1H, *s*, NH), 6.61 (1H, *d, J* = 3.0 Hz, NH), 5.12 (1H, *s*, C=CH_2), 5.03 (1H, *s*, C=CH_2), 4.18 (1H, *d, J* = 15.0 Hz, CH_2), 3.96 (1H, *d, J* = 15.0 Hz, CH_2), 3.67 (1H, *dd, J* = 14.5 & 3.0 Hz, CH_2), 2.97 (1H, *d, J* = 14.5 Hz, CH_2), 2.19 (1H, *sept, J* = 7.0 Hz, CH), 1.10 (3H, *d, J* = 7.0 Hz, CH_3), 1.03 (3H, *d, J* = 7.0 Hz, CH_3); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 173.2 (C=O), 167.0 (C=O), 137.1 (C), 135.2 (C), 131.5 ($C_{Ar}H$), 128.6 ($C_{Ar}H$), 127.0 ($C_{Ar}H$), 113.0 (C=*C*H_2), 61.7 (C), 47.1 (CH_2), 36.3 (CH_2), 34.4 (CH), 17.5 (CH_3), 17.4 (CH_3); ν_{max}/cm^{-1} (thin film) 3259 (N–H), 3059 (C–H), 2969 (C–H),

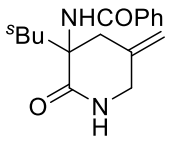
1654 (C=O), 1602 (C=O); HRMS (ESI) found MH^+ 273.1598, $C_{16}H_{20}N_2O_2$, requires MH^+, 273.1600.

3-Butyl-3-benzamido-5-methylene-2-piperidinone, 13c



Azlactone **12c** (146 mg, 2.1 eq, 0.67 mmol), carbamate **C** (68 mg, 1.0 eq, 0.32 mmol), $Pd(dba)_2$ (10 mg, 5 mol%, 0.018 mmol) and **L1** (14 mg, 13 mol%, 0.043 mmol) dissolved in dry DCM (4 mL) were reacted according to the general procedure. The crude mixture was purified by flash column chromatography eluting with a gradient of 25-50% EtOAc in petrol to give the lactam **13c** (61 mg, 66%) as a white amorphous solid. m.p. 122-126 °C; ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 7.88-7.79 (2H, *m*, CHAr), 7.60-7.39 (4H, *m*, CH_{Ar} & NH), 6.20 (1H, *s*, NH), 5.15 (1H, *s*, C=CH_2), 5.08 (1H, *s*, C=CH_2), 4.17 (1H, *d, J* = 15.0 Hz, CH_2), 4.01 (1H, *d*, *J* = 15.0 Hz, CH_2), 3.62 (1H, *d*, *J* = 14.0 Hz, CH_2), 2.86 (1H, *d*, *J* = 14.0 Hz, CH_2), 2.40-2.26 (1H, *m*, CH_2), 1.79-1.62 (1H, *m*, CH_2), 1.42-1.20 (4H, *m*, CH_2), 0.87 (3H, *t*, *J* = 7.0 Hz, CH_3); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 173.6 (C=O), 166.5 (C=O), 136.6 (C), 134.8 (C), 121.5 ($C_{Ar}H$), 128.5 ($C_{Ar}H$), 127.0 ($C_{Ar}H$), 113.5 (C=*C*H_2), 59.0 (C), 47.0 (CH_2), 39.3 (CH_2), 34.5 (CH_2), 25.8 (CH_2), 22.7 (CH_2), 14.0 (CH_3); ν_{max}/cm^{-1} (ATR) 3333 (N–H), 3275 (N–H), 3070 (C–H), 2961 (C–H), 1659 (C=O), 1629 (C=O); HRMS (ESI) found MH^+ 287.1754, $C_{17}H_{23}N_2O_2$, requires MH^+, 287.1765.

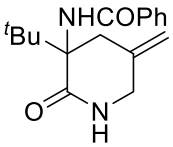
3-(1-Methylpropyl)-3-benzamido-5-methylene-2-piperidinone, 13d



Azlactone **12d** (109 mg, 2.1 eq, 0.50 mmol), carbamate **C** (51 mg, 1.0 eq, 0.24 mmol), $Pd(dba)_2$ (8 mg, 5 mol%, 0.013 mmol) and **L1** (14 mg, 19 mol%, 0.045 mmol) dissolved in dry DCM (4 mL) were reacted according to the general procedure. The crude mixture was purified by flash column chromatography eluting with a gradient of 25-50% EtOAc in petrol to give the lactam **13d** (38 mg, 55%, d.r. 1:1.2) as a white amorphous solid. ^{1}H-MR δ/ppm (400 MHz, $CDCl_3$) 7.80 (2H, *d, J* = 7.0 Hz, CH_{Ar}), 7.51-7.41 (3H, *m*, CH_{Ar} & NH), 7.32-7.24 (1H, *m*, CH_{Ar}), 6.37 (1H, *s*, NH), 5.11 (1H, *s*, C=CH_2), 5.04 (1H, *s*, C=CH_2), 4.20 (1H, *d*, *J* = 14.5 Hz, CH_2), 3.99

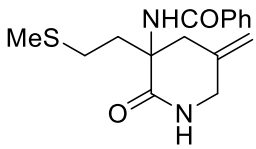
(1H, *d*, *J* = 14.5 Hz, CH_2), 3.71 (0.5H, *d*, *J* = 14.5 Hz, CH_2), 3.63 (0.5H, *d, J* = 14.5 Hz, CH_2), 3.01 (0.5H, *d*, *J* = 16.5 Hz, CH_2), 3.00 (0.5H, *d*, *J* = 16.5 Hz, CH_2), 1.99-1.81 (1.5H, *m*, C*H*$_2$CH & CH_2C*H*), 1.78-1.64 (0.5H, *m*, CH_2C*H*), 1.25-1.15 (1H, *m*, C*H*$_2$CH), 1.11 (1.5H, *d*, *J* = 7.0 Hz, C*H*$_3$CH), 1.02 (1.5H, *d*, *J* = 7.0 Hz, C*H*$_3$CH), 0.94 (1.5H, *t*, *J* = 7.5 Hz, C*H*$_3$$CH_2$), 0.90 (1.5H, *t*, *J* = 7.5 Hz, C*H*$_3$$CH_2$); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 173.9 (C=O), 173.4 (C=O), 167.0 (C=O), 166.9 (C=O), 137.3 (C), 135.1 (C), 131.5 (C_{Ar}H), 128.5 (C_{Ar}H), 127.0 (C_{Ar}H), 112.9 (C=CH_2), 112.8 (C=CH_2), 62.1 (C), 53.5 (C), 47.0 (CH_2), 41.5 (CH), 41.2 (CH), 36.2 (CH_2), 35.9 (CH_2), 23.8 (CH_2), 23.7 (CH_2), 13.5 (CH_3), 13.3 (CH_3), 12.6 (CH_3), 12.4 (CH_3); ν_{max}/cm^{-1} (ATR) 3239 (N–H), 2969 (C–H), 1661 (C=O), 1650 (C=O); HRMS (ESI) found MH^+ 287.1754, $C_{17}H_{23}N_2O_2$, requires MH^+, 287.1765.

3-(1,1-Dimethylethyl)-3-benzamido-5-methylene-2-piperidinone, 13e



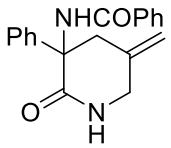
Azlactone **12e** (107 mg, 2.0 eq, 0.49 mmol), carbamate **C** (54 mg, 1.0 eq, 0.25 mmol), $Pd(dba)_2$ (8 mg, 6 mol%, 0.014mmol) and **L1** (12 mg, 15 mol%, 0.038mmol) dissolved in dry DCM (4 mL) were reacted according to the general procedure. The crude mixture was purified by flash column chromatography eluting with a gradient of 25-50% EtOAc in petrol to give the lactam **13e** (44 mg, 61 %) as a white amorphous solid. m.p. 93-99 °C; ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 7.85-7.75 (2H, *m*, CH_{Ar}), 7.57-7.37 (3H, *m*, CH_{Ar}), 7.21 (1H, *s*, NH), 6.59 (1H, *s*, NH), 5.13 (1H, *s*, C=CH_2), 4.99 (1H, *s*, C=CH_2), 4.22 (1H, *d*, *J* = 15.0 Hz, CH_2), 3.97 (1H, *d*, *J* = 15.0 Hz, CH_2), 3.70 (1H, *d*, *J* = 15.0 Hz, CH_2), 3.11 (1H, *dd*, *J* = 15.0 Hz, CH_2), 1.20 (9H, *s*, C(CH_3)$_3$); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 172.1 (C=O), 166.4 (C=O), 138.3 (C), 135.3 (C), 131.4 (C_{Ar}H), 128.6 (C_{Ar}H), 126.9 (C_{Ar}H), 112.0 (C=*C*H_2), 63.7 (C), 47.3 (CH_2), 39.9 (*C*(CH_3)$_3$), 36.6 (CH_2), 27.3 (C(*C*H_3)$_3$); ν_{max}/cm^{-1} (ATR) 3282 (N–H), 2961 (C–H), 1645 (C=O); HRMS (ESI) found MH^+ 287.1754, $C_{17}H_{23}N_2O_2$, requires MH^+, 287.1767.

3-[2-(methylthio)ethyl)]-3-benzamido-5-methylene-2-piperidinone, 13f



Azlactone **12f** (117 mg, 1.9 eq, 0.49 mmol), carbamate **C** (56 mg, 1.0 eq, 0.26 mmol), $Pd(dba)_2$ (10 mg, 7 mol%, 0.017mmol) and **L1** (17 mg, 20 mol%, 0.053mmol) dissolved in dry DCM (4 mL) were reacted according to the general procedure. The crude mixture was purified by flash column chromatography eluting with a gradient of 25-50% EtOAc in petrol to give the lactam **13f** (64 mg, 81%) as an off-white amorphous solid. m.p. 107-110 °C; ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 7.83 (2H, *d*, *J* = 7.5 Hz, CH_{Ar}), 7.76 (1H, *s*, NH), 7.51 (1H, *t*, *J* = 7.5 Hz, CH_{Ar}), 7.44 (2H, *t*, *J* = 7.5 Hz, CH_{Ar}), 6.81 (1H, *s*, NH), 5.13 (1H, *s*, C=CH_2), 5.08 (1H, *s*, C=CH_2), 4.15 (1H, *d*, *J* = 15.0 Hz, CH_2), 3.95 (1H, *d*, *J* = 15.0 Hz, CH_2), 3.47 (1H, *d*, *J* = 14.0 Hz, CH_2), 2.92 (1H, *d*, *J* = 14.0 Hz, CH_2), 2.65-2.46 (3H, *m*, CH_2), 2.08 (3H, SCH_3), 2.02 (1H, *ddd*, *J* = 14.5, 7.0 & 5.0 Hz, CH_2); ^{13}C-NMR δ /ppm (101 MHz, $CDCl_3$) 172.9 (C=O), 166.7 (C=O), 136.0 (*C*=CH_2), 134.4 (C_{Ar}), 131.7 ($C_{Ar}H$), 128.6 ($C_{Ar}H$), 127.0 ($C_{Ar}H$), 114.1 (C=*C*H_2), 58.9 (C), 47.1 (CH_2), 39.3 (CH_2), 34.6 (CH_2), 28.5 (CH_2), 15.7 (CH_3); ν_{max}/cm^{-1} (ATR) 3257 (N–H), 2966 (C–H), 1662 (C=O), 1652 (C=O); HRMS (ESI) found MH^+ 305.1318, $C_{16}H_{21}N_2O_2S$, requires MH^+, 305.1328.

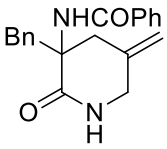
3-Phenyl-3-benzamido-5-methylene-2-piperidinone, 13g



Azlactone **12g** (118 mg, 1.6 eq, 0.50 mmol), carbamate C (66 mg, 1.0 eq, 0.31 mmol), $Pd(dba)_2$ (11 mg, 6 mol%, 0.019 mmol) and **L1** (11 mg, 11 mol%, 0.035 mmol) dissolved in dry DCM (4 mL) were reacted according to the general procedure. The crude mixture was purified by flash column chromatography eluting with a gradient of 25-75% EtOAc in petrol to give the lactam **13g** (40 mg, 42%) as an off-white gum. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 8.12 (1H, *s*, NH), 7.80 (2H, *d, J* = 7.5 Hz, CH_{Ar}), 7.61 (2H, *d, J* = 7.0 Hz, CH_{Ar}), 7.48 (1H, *t, J* = 7.5 Hz, CH_{Ar}), 7.41 (2H, *t, J* = 7.5 Hz, CH_{Ar}), 7.38-7.26 (3H, *m*, CH_{Ar}), 6.90 (1H, *s*, NH), 5.04 (1H, *s*, C=CH_2), 4.93 (1H, *s*, C=CH_2), 4.24 (1H, *d, J* = 15.5 Hz, CH_2), 3.94 (1H, *d, J* = 15.0 Hz, CH_2), 3.63 (1H, *d, J* = 15.5 Hz, CH_2), 3.16 (1H, *d, J* = 15.0 Hz, CH_2); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 172.6 (C=O), 166.1 (C=O), 138.0 (C), 137.2 (C), 134.5 (C), 131.6 ($C_{Ar}H$), 128.5 ($4C_{Ar}H$), 128.2 ($C_{Ar}H$), 127.08 ($2C_{Ar}H$), 127.05 ($2C_{Ar}H$), 112.2 (C=*C*H_2), 60.4 (C), 45.8 (CH_2),

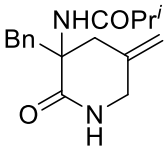
37.8 (CH_2); ν_{max}/cm^{-1} (ATR) 3224 (N–H), 2986 (C–H), 1680 (C=O), 1659 (C=O); HRMS (ESI) found MH^+ 307.1441, $C_{19}H_{19}N_2O_2$, requires MH^+, 307.1443.

3-Benzyl-3-benzamido-5-methylene-2-piperidinone, 13h



Azlactone **12h** (120 mg, 2.0 eq, 0.46 mmol), carbamate **C** (52 mg, 1.0 eq, 0.24 mmol), $Pd(dba)_2$ (7 mg, 5 mol%, 0.013mmol) and **L1** (13 mg, 18 mol%, 0.042 mmol) dissolved in dry DCM (4 mL) were reacted according to the general procedure. The crude mixture was purified by column chromatography eluting with 25-50% EtOAc in petrol to give the lactam **13h** (66 mg, 85%) as a white amorphous solid. m.p. 163-167 °C; ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$), 7.70 (2H, *d*, *J* = 7.0 Hz, CH_{Ar}), 7.49 (1H, t_{app}, *J* = 7.5 Hz, CH_{Ar}), 7.41 (2H, *t*, *J* = 7.5 Hz, CH_{Ar}), 7.28-7.25 (3H, *m*, CH_{Ar}), 7.17-7.15 (2H, *m*, CH_{Ar}), 6.79 (1H, *s*, NH), 5.22 (1H, *s*, C=CH_2), 5.15 (1H, *s*, C=CH_2), 4.20-4.05 (2H, *m*, NCH_2), 3.77 (1H, *d*, *J* = 14.0 Hz, CH_2), 3.64 (1H, *d*, *J* = 14.0 Hz, CH_2), 3.06 (1H, *d*, *J* = 14.0 Hz, CH_2), 2.91 (1H, *d*, *J* = 14.0 Hz, CH_2); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 172.7 (C=O), 167.0 (C=O), 136.5 (C), 135.7 (C), 134.9 (C), 131.5 ($C_{Ar}H$), 130.2 ($C_{Ar}H$), 128.5 ($C_{Ar}H$), 128.3 ($C_{Ar}H$), 127.1 ($C_{Ar}H$), 126.9 ($C_{Ar}H$), 114.2 (C=*C*H_2), 59.7 (C), 47.1 (CH_2), 40.0 (CH_2), 39.0 (CH_2); ν_{max}/cm^{-1} (thin film) 3364 (N-H), 3279 (N-H), 3032 (C-H), 2927 (C-H), 1667 (C=O), 1629 (C=O), 1265 (C-N); HRMS (ESI) found MH^+ 321.1598, $C_{20}H_{20}N_2O_2$, requires MH^+, 321.1603.

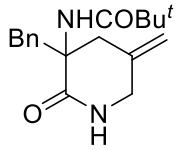
3-Benzyl-3-(1-methylpropanamido)-5-methylene-2-piperidinone, 13i



Azlactone **12i** (72 mg, 2.0 eq, 0.33 mmol), carbamate **C** (37 mg, 1.0 eq, 0.17 mmol), $Pd(dba)_2$ (6 mg, 6 mol%, 0.011 mmol) and **L1** (10 mg, 19 mol%, 0.032 mmol) dissolved in dry DCM (3 mL) were reacted according to the general procedure. The crude mixture was purified by flash column chromatography eluting with a gradient of 50-75% EtOAc in petrol to give the lactam **13i** (32 mg, 64%) as an off-white glassy solid. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 7.64-7.22 (3H, *m*, CH_{Ar}), 7.17-7.05 (2H, *m*, CH_{Ar}), 6.55 (1H, *s*, NH), 6.51 (1H, *s*, NH), 5.16 (1H, *s*, C=CH_2), 5.11 (1H, *s*, C=CH_2), 4.15 (1H, *d, J* = 15.5 Hz, CH_2), 4.03 (1H, *d, J* = 15.5 Hz, CH_2),

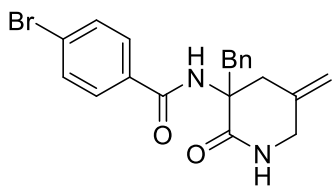
3.57 (1H, *d, J* = 14.0 Hz, CH_2), 3.49 (1H, *d, J* = 13.5 Hz, CH_2), 2.96 (1H, *d, J* = 13.5 Hz, CH_2), 2.78 (1H, *d, J* = 14.0 Hz, CH_2), 2.37-2.23 (1H, *sept, J* = 6.5 Hz, CH), 1.11 (3H, *d, J* = 6.5 Hz, CH_3), 1.10 (3H, *d, J* = 6.5 Hz, CH_3); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 176.7 (C=O), 172.8 (C=O), 136.4 (C), 135.7 (C), 130.3 ($C_{Ar}H$), 128.1 ($C_{Ar}H$), 127.1 ($C_{Ar}H$), 113.9 (C=*C*H_2), 59.0 (C), 47.1 (CH_2), 40.1 (CH_2), 39.2 (CH_2), 36.0 (CH), 19.5 (CH_3); ν_{max}/cm^{-1} (ATR) 3281 (N–H), 2967 (C–H), 1683 (C=O), 1634 (C=O); HRMS (ESI) found MH^+ 287.1754, $C_{17}H_{23}N_2O_2$, requires MH^+, 287.1767.

3-Benzyl-3-(1,1-dimethylpropanamido)-5-methylene-2-piperidinone, 13j



Azlactone **12j** (1.00 g, 2.0 eq, 4.3 mmol), carbamate **C** (449 mg, 1.0 eq, 2.1 mmol), $Pd(dba)_2$ (65 mg, 5 mol%, 0.11 mmol) and **L1** (123 mg, 18 mol%, 0.38 mmol) dissolved in dry DCM (40 mL) were reacted according to the general procedure. The crude mixture was purified by flash column chromatography eluting with a gradient of 20-30% EtOAc in petrol to give the lactam **13j** (384 mg, 61%) as an off-white gum. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 7.33-7.23 (3H, *m*, CH_{Ar}), 7.13 (2H, *dd*, *J* = 7.5 & 1.5 Hz, CH_{Ar}), 6.66 (1H, *s*, NH), 6.32 (1H, *s*, NH), 5.16 (1H, *s*, C=CH_2), 5.12 (1H, *s*, C=CH_2), 4.17 (1H, *dt*, *J* = 15.0 & 1.5 Hz, CH_2), 4.03 (1H, *d*, *J* = 15.0 Hz, CH_2), 3.50 (1H, *d*, *J* = 14.0 Hz, CH_2), 3.45 (1H, *d*, *J* = 13.5 Hz, CH_2), 2.97 (1H, *d*, *J* = 13.5 Hz, CH_2), 2.79 (1H, *d*, J = 14.0 Hz, CH_2), 1.13 (9H, *s*, $C(CH_3)_3$); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 178.1 (C=O), 172.9 (C=O), 136.7 (C), 135.7 (C), 130.3 ($C_{Ar}H$), 128.2 ($C_{Ar}H$), 127.1 ($C_{Ar}H$), 113.8 (C=*C*H_2), 58.7 (C), 47.2 (CH_2), 40.2 (CH_2), 39.1 (*C*$(CH_3)_3$), 39.0 (CH_2), 27.5 (C(*C*$H_3)_3$); ν_{max}/cm^{-1} (ATR) 3262 (N–H), 2961 (C–H), 2870 (C–H), 1644 (C=O), 1496 (C=O); HRMS (ESI) found MH^+ 301.1911, $C_{18}H_{25}N_2O_2$, requires MH^+, 301.1925.

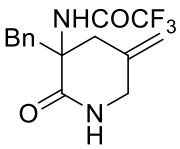
3-Benzyl-3-(4-bromobenzamido)-5-methylene-2-piperidinone, 13k



Azlactone **12k** (159 mg, 1.9 eq, 0.48 mmol), carbamate **C** (54 mg, 1.0 eq, 0.25 mmol), $Pd(dba)_2$ (11 mg, 8 mol%, 0.019 mmol) and **L1** (19 mg, 23 mol%, 0.059 mmol) dissolved in dry DCM (4 mL) were reacted according to the general

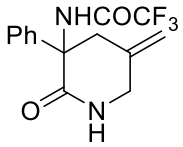
procedure. The crude mixture was purified by flash column chromatography eluting with a gradient of 25-50% EtOAc in petrol to give the lactam **13k** (95 mg, 94%) as a white amorphous solid. m.p. 121-125 °C; ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 7.54 (4H, *s*, CH_{Ar}), 7.28-7.22 (3H, *m*, CH_{Ar}), 7.20 (1H, *s*, NH), 7.13-7.10 (2H, *m*, CH_{Ar}), 6.26 (1H, *s*, NH), 5.25 (1H, *s*, C=CH_2), 5.18 (1H, *s*, C=CH_2), 4.22 (1H, *d*, J = 15.0 Hz, CH_2), 4.12 (1H, *d*, *J* = 15.0 Hz, CH_2), 3.74 (1H, *d*, *J* = 14.0 Hz, CH_2), 3.63 (1H, *d, J* = 14.0 Hz, CH_2), 3.05 (1H, *d, J* = 14.0 Hz, CH_2), 2.90 (1H, *d, J* = 14.0 Hz, CH_2); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 172.5 (C=O), 166.0 (C=O), 136.2 (C), 135.6 (C), 133.7 (C), 131.8 ($C_{Ar}H$), 130.1 ($C_{Ar}H$), 128.6 ($C_{Ar}H$), 128.3 ($C_{Ar}H$), 127.2 ($C_{Ar}H$), 126.2 (C_{Ar}), 114.3 (C=*C*H_2), 59.8 (C), 47.1 (CH_2), 39.9 (CH_2), 39.1 (CH_2); ν_{max}/cm^{-1} (ATR) 3301 (N–H), 2928 (C–H), 2854 (C–H), 1717 (C=O), 1662 (C=O); HRMS (ESI) found MH^+ 399.0703, $C_{20}H_{20}{}^{79}BrN_2O_2$, requires MH^+, found 399.0707; HRMS (ESI) found MH^+ 401.0688, $C_{20}H_{20}{}^{81}BrN_2O_2$, requires MH^+, 401.0691.

3-Benzyl-3-trifluoroacetamido-5-methylene-2-piperidinone, 13l



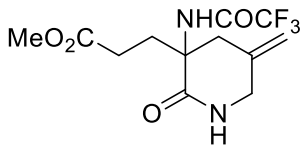
Azlactone **12l** (119 mg, 1.9 eq, 0.49 mmol), carbamate **C** (55 mg, 1.0 eq, 0.26 mmol), $Pd(dba)_2$ (10 mg, 7 mol%, 0.002 mmol) and **L1** (16 mg, 19 mol%, 0.05 mmol) dissolved in dry DCM (4 mL) were reacted according to the general procedure. The crude mixture was purified by flash column chromatography eluting with a gradient of 20-30% EtOAc in petrol to give the lactam **13l** (53 mg, 66%) as a yellow oil. ^{1}H NMR δ/ppm (400 MHz, $CDCl_3$) 7.49 (1H, *s*, NH), 7.31-7.27 (3H, *m*, $C_{Ar}H$), 7.10-7.04 (2H, *m*, $C_{Ar}H$), 6.58 (1H, *s*, NH), 5.26 (1H, *s*, C=CH_2), 5.20 (1H, *s*, C=CH_2), 4.21-4.07 (2H, *m,* CH_2), 3.67 (1H, *d*, *J* = 14.0 Hz, CH_2), 3.47 (1H, *d*, *J* = 14.0 Hz, CH_2), 3.05 (1H, *d*, *J* = 14.0 Hz, CH_2), 2.76 (1H, *dt*, *J* = 14.0 & 2.0 Hz, CH_2) ; ^{13}C NMR δ/ppm (101 MHz, $CDCl_3$) 171.4 (C=O), 156.3 (*q, J* = 37.0 Hz, F_3CC=O), 135.1 (C), 134.5 (C), 129.9 ($C_{Ar}H$), 128.4 ($C_{Ar}H$), 127.5 ($C_{Ar}H$), 115.5 (*q, J* = 289.0 Hz, CF_3), 114.9 (C=*C*H_2), 60.0 (C), 46.8 (CH_2) 39.7 (CH_2), 38.6 (CH_2); ^{19}F NMR δ/ppm (376 MHz, $CDCl_3$) -76.1 (*s*, CF_3); ν_{max}/cm^{-1} (ATR) 3349 (N–H), 2938 (C–H), 1727 (C=O), 1652 (C=O); HRMS (ESI) found MH^+ 313.1158, $C_{15}H_{16}F_3N_2O_2$, requires MH^+, 313.1166.

3-Phenyl-3-trifluoroacetamido-5-methylene-2-piperidinone, 13m



Azlactone **12m** (107 mg, 1.9 eq, 0.46 mmol), carbamate **C** (53 mg, 1.0 eq, 0.25 mmol), $Pd(dba)_2$ (9 mg, 6 mol%, 0.16 mmol) and **L1** (15 mg, 19 mol%, 0.046 mmol) dissolved in dry DCM (4 mL) were reacted according to the general procedure. The crude mixture was purified by flash column chromatography eluting with a gradient of 20-75% EtOAc in petrol to give the lactam **13m** (10 mg, 14%) as a pale yellow oil. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 8.34 (1H, s, NH), 7.55 (2H, *dd, J* = 7.5 & 1.5 Hz, CH_{Ar}), 7.43-7.31 (3H, *m*, CH_{Ar}), 6.42 (1H, *s*, NH), 5.13 (1H, *s*, C=CH_2), 4.99 (1H, *s*, C=CH_2), 4.30 (1H, *d, J* = 16.0 Hz, CH_2), 3.97-3.89 (1H, *m,* CH_2), 3.61 (1H, *d, J* = 16.0 Hz, CH_2), 2.94 (1H, *d, J* = 16.0 Hz, CH_2); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 171.1 (C=O), 155.6 (*q, J* = 37.5 Hz, *C*OCF_3), 135.9 (C), 135.7 (C), 128.9 ($C_{Ar}H$), 128.8 ($C_{Ar}H$), 127.0 ($C_{Ar}H$), 115.5 (*q, J* = 289.0 Hz, CF_3), 113.0 (C=*C*H_2), 60.9 (C), 45.4 (CH_2), 36.3 (CH_2); ^{19}F-NMR δ/ppm (376 MHz, $CDCl_3$) -76.1 (*s*, CF_3); ν_{max}/cm^{-1} (ATR) 3212 (N–H), 2996 (C–H), 1725 (C=O), 1670 (C=O); HRMS (ESI) found MH^+ 299.1002, $C_{14}H_{14}F_3N_2O_2$, requires MH^+, 299.1017.

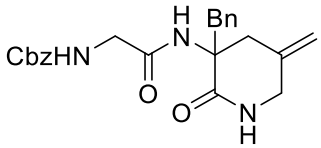
Methyl (2-(trifluoromethyl)-5-oxo-2,3-dihyrdo-oxazol-4-yl)propanoate, 13n



Azlactone **12n** (342 mg, 1.9 eq, 1.4 mmol), carbamate **C** (156 mg, 1.0 eq, 0.73 mmol), $Pd(dba)_2$ (23 mg, 6 mol%, 0.041 mmol) and **L1** (34 mg, 15 mol%, 0.11 mmol) dissolved in dry DCM (12 mL) were reacted according to the general procedure. The crude mixture was purified by flash column chromatography eluting with a gradient of 25-60% EtOAc in petrol to give the lactam **13n** (92 mg, 30%) as a colourless oil. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 8.14 (1H, *s*, NH), 6.31 (1H, *s*, NH), 5.17 (1H, *s*, C=CH_2), 5.14 (1H, *s*, C=CH_2), 4.15 (1H, *d*, *J* = 15.0 Hz, CH_2), 3.99 (1H, *d*, *J* = 15.0 Hz, CH_2), 3.69 (3H, *s*, CH_3), 3.28 (1H, *d*, *J* = 14.0 Hz, CH_2), 2.92 (1H, *d*, *J* = 14.0 Hz, CH_2), 2.59-2.34 (3H, *m*, CH_2), 2.22-2.09 (1H, *m*, CH_2) ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 174.0 (*C*O_2Me), 170.8 (C=O), 156.4 (*q*, *J* = 37.5 MHz, *C*OCF_3), 135.0 (*C*=CH_2), 115.5 (*q*, *J* = 288.5 MHz, CF_3), 115.0 (C=*C*H_2), 58.6 (C), 52.1 (CH_3), 47.0 (CH_2), 38.8 (CH_2), 29.2 (CH_2), 28.3 (CH_2) ; ^{19}F-NMR δ/ppm (377 MHz, $CDCl_3$) -

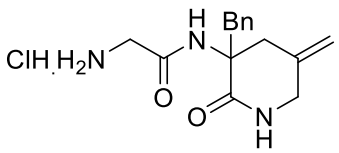
76.0 (*s*, CF_3); ν_{max}/cm^{-1} 2993 (C–H), 1643 (C=O), 1638 (C=O), 1236 (C–O); HRMS (ESI) found MH^+ 309.1057, $C_{12}H_{16}N_2O_4$, requires MH^+, 309.1065.

Benzyl [1-(3-Benzyl-5-methylene-2-piperidinon-3-yl)acetomidyl]-carbamic acid, 13o



Azlactone **12o** (211 mg, 1.9 eq, 0.62 mmol), carbamate **C** (70 mg, 1.0 eq, 0.33 mmol), $Pd(dba)_2$ (14 mg, 7 mol%, 0.024 mmol) and **L1** (16 mg, 15 mol%, 0.050 mmol) dissolved in dry DCM (5 mL) were reacted according to the general procedure. The crude mixture was purified by flash column chromatography on silica eluting with a gradient of 30-40% EtOAc in petrol to give the lactam **13o** (71 mg, 54%) as a white foamy gum. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 7.44-7.19 (8H, *m*, CH_{Ar}), 7.14-7.12 (2H, *m*, CH_{Ar}), 7.00 (1H, *s*, NH), 6.69 (1H, *s*, NH), 5.85 (1H, *s*, NH), 5.13 (1H, *s*, $C=CH_2$), 5.11 (3H, *s*, $C=CH_2$ + CH_2), 4.09 (1H, *d, J* = 16.0 Hz, CH_2), 3.97-3.78 (2H, *m*, CH_2), 3.73 (1H, *dd, J* = 16.5 & 5.0 Hz, CH_2), 3.35 (1H, *d, J* = 13.5 Hz, CH_2), 3.26 (1H, *d, J* = 14.0 Hz, CH_2), 2.96 (1H, *d, J* = 13.5 Hz, CH_2), 2.90 (1H, *d, J* = 14.0 Hz, CH_2);^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 172.3 (C=O), 168.7 (C=O), 156.4 (C=O), 138.0 (*C*=CH_2), 136.2 (C_{Ar}), 135.1 (C_{Ar}), 130.2 ($C_{Ar}H$), 128.6 ($C_{Ar}H$), 128.5 ($C_{Ar}H$), 128.2 ($C_{Ar}H$), 128.1 ($C_{Ar}H$), 127.2 ($C_{Ar}H$), 114.3 (C=*C*H_2), 67.1 (CH_2), 59.2 (C), 47.2 (CH_2), 44.7 (CH_2), 40.4 (CH_2), 38.5 (CH_2); ν_{max}/cm^{-1} (ATR) 3315 (N–H), 3031 (C–H), 2952 (C–H), 1723 (C=O), 1667 (C=O), 1520 (C=O); HRMS (ESI) found MH^+ 408.1918, $C_{23}H_{26}N_3O_4$ requires MH^+, 408.1936.

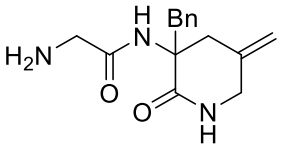
3-Benzyl-3-glycylamido-5-methylene-2-piperidinone hydrochloride, 13p.HCl



Azlactone **12p** (1.21 g, 2.0 eq, 4.0 mmol), carbamate **C** (427 mg, 1.0 eq, 2.0 mol), $Pd(dba)_2$ (64 mg, 5 mol%, 0.1 mmol) and **L1** (99 mg, 15 mol%, 0.3 mmol) dissolved in dry DCM (35 mL) were reacted under an inert atmosphere at reflux overnight. The crude mixture concentrated and purified by flash column chromatography on silica eluting with 10% then 20% EtOAc in petrol to give the intermediate allylated azlactone as a non-pure mixture. A portion of this azlactone mixture (240 mg, 1.0 eq, 0.5 mmol) was

dissolved in DCM (10 mL) under an inert atmosphere. TFA (2 mL) was added and the mixture was stirred for 1 hour at room temperature, before the solvent was then removed. The crude residue was dissolved in a minimal amount of DCM and 2M HCl in Et_2O (2 mL) was added. The solvent was then removed under reduced pressure and the resulting solid was washed with Et_2O to remove the impurities and give **13p.HCl** (125 mg, 80%) as a pale orange solid. m.p. 122-125 °C; ^{1}H-NMR δ/ppm (400 MHz, d^6-DMSO) 8.13 (1H, s, NH), 8.10-7.92 (3H, m, NH_3), 7.91 (1H, s, NH), 7.44-7.07 (5H, *m*, CH_{Ar}), 5.01 (1H, *s*, C=CH_2), 4.92 (1H, *s*, C=CH_2), 3.93 (1H, *d, J* = 15.5 Hz, CH_2), 3.85 (1H, *d, J* = 15.5 Hz, CH_2), 3.59-3.47 (2H, *m*, C*H*$_2$$NH_3$), 3.23 (1H, *d, J* = 13.5 Hz, CH_2), 3.01 (1H, *d, J* = 14.0 Hz, CH_2), 2.93 (1H, *d*, *J* = 13.5 Hz, CH_2), 2.73 (1H, *d, J* = 14.0 Hz, CH_2); ^{13}C-NMR δ/ppm (101 MHz, d^6-DMSO) 170.4 (C=O), 166.3 (C=O), 138.1 (*C*=CH_2), 136.4 (C_{Ar}), 130.9 (CH_{Ar}), 128.3 (CH_{Ar}), 127.1 (CH_{Ar}), 112.8 (C=*C*H_2), 59.9 (C), 46.2 (CH_2), 44.1 (CH_2), 40.3 (CH_2), 35.4 (CH_2); ν_{max}/cm^{-1} (ATR) 3336 (N–H), 2984 (C–H), 1643 (C=O); HRMS (ESI) found MH$^+$ 274.1556, $C_{15}H_{20}N_3O_2$, requires MH$^+$, 274.1568.

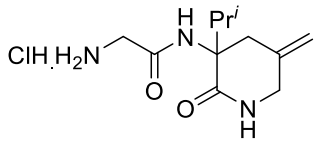
3-Benzyl-3-glycylamido-5-methylene-2-piperidinone, 13p



Azlactone **12p** (2.32 g, 2.0 eq, 7.6 mmol), carbamate **C** (813 mg, 1.0 eq, 3.8 mol), $Pd(dba)_2$ (120 mg, 5.5 mol%, 0.21 mmol) and **L1** (189 mg, 16 mol%, 0.6 mmol) dissolved in dry DCM (65 mL) were reacted under an inert atmosphere at reflux overnight. The crude mixture concentrated and purified by flash column chromatography on silica eluting with 10% then 20% EtOAc in petrol to give the intermediate allylated azlactone as a non-pure mixture. This was then dissolved in DCM (65 mL) under an inert atmosphere. TFA (16 mL) was added and the mixture was stirred for 1 hour at room temperature. The crude mixture was basified with 1 M $NaOH_{(aq)}$ and extracted with DCM (100 mL). The organic layers were combined and dried using $MgSO_4$, then filtered and the solvent removed under reduced pressure to give **13p** (971 mg, 93%) as an orange foamy gum. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 7.89 (1H, *s*, NH), 7.39-7.23 (3H, *m*, CH_{Ar}), 7.19 (2H, *dd, J* = 7.5 & 1.5 Hz, CH_{Ar}), 6.05 (1H, *s*, NH), 5.16 (1H, *d, J* = 2.5 Hz, C=CH_2), 5.15 (1H, *d, J* = 2.0 Hz, C=CH_2), 4.75 (2H, *s*, NH_2), 4.20 (1H, *d, J* = 14.5 Hz, CH_2), 4.00 (1H, *d, J* = 14.5 Hz, CH_2), 3.36 (1H, *d, J* = 14.0 Hz, CH_2), 3.29

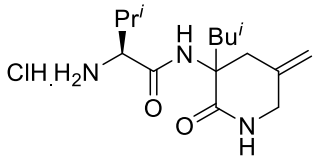
(1H, *d, J* = 7.5 Hz, CH_2), 3.23 (1H, *d, J* = 14.0 Hz, CH_2), 3.02 (1H, *d, J* = 13.5 Hz, CH_2), 2.97 (1H, *d, J* = 13.5 Hz, CH_2); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 170.2 (C=O), 166.1 (C=O), 138.3 (*C*=CH_2), 136.5 (C_{Ar}), 131.0 (CH_{Ar}), 128.3 (CH_{Ar}), 127.2 (CH_{Ar}), 112.8 (C=*C*H_2), 59.9 (C), 46.2 (CH_2), 41.8 (CH_2), 40.3 (CH_2), 35.4 (CH_2); ν_{max}/cm^{-1} (ATR) 3298 (N–H), 2986 (C–H), 1672 (C=O); HRMS (ESI) found MH^+ 274.1556, $C_{15}H_{20}N_3O_2$, requires MH^+, 274.1563.

3-iso-Propyl-3-glycylamido-5-methylene-2-piperidinone hydrochloride, 13q.HCl



Azlactone **12q** (244 mg, 1.9 eq, 0.95 mmol), carbamate **C** (108 mg, 1.0 eq, 0.51 mol), $Pd(dba)_2$ (15 mg, 5 mol%, 0.03 mmol) and **L1** (27 mg, 17 mol%, 0.09 mmol) dissolved in dry DCM (8 mL) were reacted under an inert atmosphere at reflux overnight. The crude mixture concentrated and purified by flash column chromatography on silica eluting with 10% then 20% EtOAc in petrol to give the intermediate allylated azlactone as a non-pure mixture. A portion of this azlactone (202 mg) was dissolved in DCM (10 mL) under an inert atmosphere. TFA (2 mL) was added and the mixture was stirred for 1 hour at room temperature, before the solvent was then removed. The crude residue was dissolved in a minimal amount of DCM and 2M HCl in Et_2O (5 mL) was added. The solvent was then removed under reduced pressure and the resulting solid was washed with Et_2O to remove the impurities and give **13q.HCl** (92 mg, 93%) as an off-white solid. m.p. 137-139 °C; ^{1}H-NMR δ/ppm (400 MHz, d^4-MeOD) 5.06 (2H, *s*, C=CH_2), 4.17-4.08 (1H, *m,* CH_2), 3.90 (1H, *d, J* = 15.0 Hz, CH_2), 3.73 (2H, *d, J* = 4.0 Hz, CH_2), 2.75 (1H, *d, J* = 14.0 Hz), 2.19-2.10 (1H, m, CH_2), 2.11 (1H, *sept, J* = 7.0 Hz, CH), 1.07 (3H, d, *J* = 7.0 Hz CH_3), 1.05 (3H, d, *J* = 7.0 Hz CH_3); ^{13}C-NMR δ/ppm (101 MHz, d^4-MeOD) 172.9 (C=O), 165.8 (C=O), 138.1 (*C*=CH_2), 111.3 (C=*C*H_2), 61.4 (C), 46.6 (CH_2), 40.3 (CH_2), 35.4 (CH_2), 33.3 (CH), 15.7 (CH_3), 15.6 (CH_3); ν_{max}/cm^{-1} (ATR) 3281 (N–H), 2971 (C–H), 1667 (C=O); HRMS (ESI) found MH^+ 226.1556, $C_{11}H_{20}N_3O_2$ requires MH^+, 226.1558.

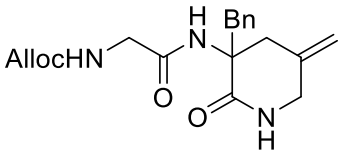
3-iso-Butyl-3-(L)-valylamido-5-methylene-2-piperidinone hydrochloride, 13r.HCl



Azlactone **12r** (300 mg, 2.0 eq, 0.96 mmol), carbamate **C** (102 mg, 1.0 eq, 0.48 mol), $Pd(dba)_2$ (14 mg, 5 mol%, 0.024 mmol) and **L1** (22 mg, 15 mol%, 0.07 mmol) dissolved in dry DCM (8 mL) were reacted under an inert atmosphere at reflux overnight. The crude mixture concentrated and purified by flash column chromatography on silica eluting with 10% then 20% EtOAc in petrol to give the intermediate allylated azlactone as a non-pure mixture. This was re-dissolved in DCM (10 mL) under an inert atmosphere. TFA (3 mL) was added and the mixture was stirred for 1 hour at room temperature, before the solvent was then removed. The crude residue was dissolved in a minimal amount of DCM and 2M HCl in Et_2O (5 mL) was added. The solvent was then removed under reduced pressure and the resulting solid was washed with Et_2O to remove the impurities and give **13r.HCl** (167 mg, 55%) as an off-white amorphous solid with a d.r. of 1:1.2. ^{1}H-NMR δ/ppm (400 MHz, d^4-MeOD) 5.13 (0.55H, s, C=CH_2), 5.11 (0.45H, s, C=CH_2), 5.06 (0.55H, s, C=CH_2), 5.04 (0.45H, s, C=CH_2), 4.11 (1H, *dt, J =* 15.0 & 2.0 Hz, CH_2), 3.92 (0.55H, *d, J =* 5.5 Hz, CH2), 3.88 (0.45H, *d, J =* 5.0 Hz, CH_2), 3.79 (0.45H, *d, J =* 5.5 Hz, CH_2), 3.75 (0.55H, *d, J =* 6.5 Hz, CH_2), 3.25 (1H, *d, J =* 13.5 Hz, CH), 2.64 (0.55H, *d, J =* 5.0 Hz, CH_2), 2.61 (0.45H, *d, J =* 5.0 Hz, CH_2), 2.30-2.12 (**1.26H**, *m*, CH), 2.03-1.83 (**1.30** Hz, *m*, CH), 1.82-1.64 (**2.72**H, *m*, CH2), 1.14 (1.65H, *d, J =* 7.0 Hz, CH_3), 1.12-1.03 (**5.86**H, *m*, CH_3), 1.02-0.93 (**5.89**H, *m*, CH_3), 0.91 (1.35H, *d, J =* 6.5 Hz, CH_3). ; ^{13}C-NMR δ/ppm (101 MHz, d^4-MeOD) 173.0 (C=O), 171.8 (C=O), 167.9 (C=O), 167.4 (C=O), 138.0 (*C*=CH_2), 137.4 (*C*=CH_2) 112.4 (C=*C*H_2), 112.2 (C=*C*H_2), 58.2 (C), 58.1 (C), 45.2 (CH_2), 46.6 (CH_2), 45.0 (CH_2), 40.1 (CH_2), 38.6 (CH_2), 30.3 (CH), 30.1 (CH), 23.5 (CH_3), 23.3 (CH_3), 23.2 (CH_3), 23.0 (CH_3), 22.5 (CH), 17.6 (CH_3), 17.5 (CH_3), 16.7 (CH_3), 16.4 (CH_3); ν_{max}/cm^{-1} (ATR) 3341 (N–H), 2972 (C–H), 1683 (C=O); HRMS (ESI) found MH^+ 282.2182, $C_{15}H_{28}N_3O_2$, requires MH^+, 282.2176.

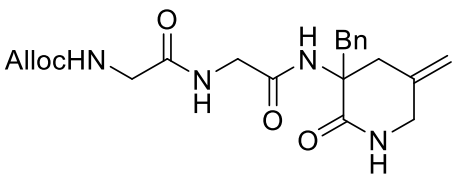
3.1.3.5 Further Functionalisation Reactions

Allyl [1-(3-Benzyl-5-methylene-2-piperidinon-3-yl)acetomidyl]-carbamic acid, 13s



Lactam **13p** (287 mg, 1.0 eq, 1.0 mmol) was dissolved in dry THF (15 mL) under an inert atmosphere and cooled to 0 °C. Et_3N (0.71 mL, 5.0 eq, 5.1 mmol) was added, followed by AllocCl (0.22 mL, 2.0 eq, 2.1 mmol) and the reaction mixture was stirred overnight warming to room temperature. To the crude mixture, EtOAc (20 mL) was added and the mixture was washed with water (20 mL) and saturated $NaHCO_{3(aq)}$ (20 mL). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography eluting with a gradient of 0-7% MeOH in EtOAc to give **13s** (260 mg, 69%) as an off-white foamy gum. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 7.33-7.20 (3H, *m*, CH_{Ar}), 7.14 (2H, *d, J* = 7.0 Hz, CH_{Ar}), 7.03 (1H, *s*, NH), 6.82 (1H, *s*, NH), 6.07-5.80 (1H, m, C*H*=CH_2), 5.85 (1H, *t, J* = 5.5 Hz, NH) 5.32 (1H, *d, J* = 15.0 Hz, CH=C*H*$_2$), 5.22 (1H, *d, J* = 10.5 Hz, CH=C*H*$_2$), 5.13 (1H, *s*, C=C*H*$_2$), 5.11 (1H, *s*, C=C*H*$_2$), 4.56 (2H, *d, J* = 5.0 Hz, CH_2), 4.12 (1H, *d, J* = 14.5 Hz, CH_2), 3.95 (1H, d, J = 14.5 Hz, CH_2), 3.85 (1H, *dd, J* = 17.0 & 5.5 Hz, CH_2), 3.73 (1H, *dd, J* = 17.0 & 5.5 Hz, CH_2), 3.35 (1H, *d, J* = 14.0 Hz, CH_2), 3.25 (1H, *d, J* = 14.0 Hz, CH_2), 2.97 (1H, *d, J* = 14.0 Hz, CH_2), 2.92 (1H, *d, J* = 14.0 Hz, CH_2); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 172.5 (C=O), 168.9 (C=O), 156.4 (OC=O), 136.5 (*C*=CH_2), 135.2 (C_{Ar}), 132.7 (*C*H=CH_2), 130.3 (C_{Ar}H), 128.4 (C_{Ar}H), 127.2 (C_{Ar}H), 117.8 (CH=*C*H_2), 114.0 (C=*C*H_2), 65.9 (CH_2), 59.2 (C), 47.2 (CH_2), 44.7 (CH_2), 40.5 (CH_2), 39.4 (CH_2); ν_{max}/cm^{-1} (ATR) 2879 (C–H), 1723 (C=O), 1641 (C=O), 1231 (C–O); HRMS (ESI) found MH^+ 358.1767, $C_{19}H_{24}N_3O_4$, requires MH^+, 358.1763.

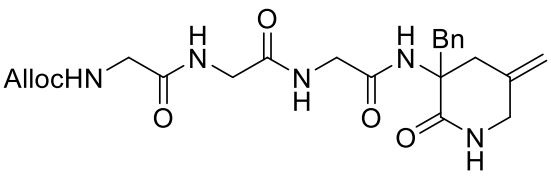
Allyl [1-(3-Benzyl-5-methylene-2-piperidinon-3-yl)glycylglycyl]-carbamic acid, 13t



Alloc-Glycine (33 mg, 1.0 eq, 0.21 mmol) was dissolved in dry THF (5 mL) under an inert atmosphere and cooled to 0 °C. ^{i}BuOCOCl (0.04 mL, 1.5 eq, 0.31 mmol) followed by Et_3N (0.13 mL, 5.0 eq, 0.92 mmol) were added and the mixture was stirred for 1 hour. Lactam **13p**

(52 mg, 0.9 eq, 0.19 mmol) in dry THF (5 mL) was added and the reaction mixture was stirred overnight warming to room temperature. To the crude mixture, EtOAc (20 mL) was added and the mixture was washed with water (20 mL) and saturated $NaHCO_{3(aq)}$ (20 mL). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography eluting with a gradient of 0-10% MeOH in EtOAc to give **13t** (73 mg, 92%) as an off-white foamy gum. ^{1}H-NMR δ/ppm (400 MHz, d^4-MeOD) 7.35-7.13 (5H, *m*, CH_{Ar}), 6.01-5.90 (1H, *m,* C*H*=CH_2), 5.35 (1H, *dd, J =* 17.0 & 1.0 Hz, CH=C*H*$_2$), 5.21 (1H, *dd, J =* 10.5 & 1.0 Hz, CH=C*H*$_2$), 5.01 (1H,*s*, C=CH_2), 4.95 (1H, *s*, C=CH_2), 4.59 (2H, *dt, J =* 5.5 & 1.4 Hz, CH_2), 4.07 (1H, *d, J =* 15.0 Hz, CH_2), 3.91 (1H, *d, J =* 17.0 Hz, CH_2), 3.88-3.79 (4H, *m*, CH_2), 3.28 (1H, *d, J =* 13.5 Hz, CH_2), 3.04-2.96 (3H, *m*, CH_2); ^{13}C-NMR δ/ppm (101 MHz, d^4-MeOD) 172.4 (C=O), 171.4 (C=O), 169.4 (C=O), 157.5 (C=O), 137.1 (*C*=CH_2), 135.2 (C_{Ar}), 132.9 (*C*H=CH_2), 130.3 (C_{Ar}H), 127.9 (C_{Ar}H), 126.8 (C_{Ar}H), 116.4 (CH=*C*H_2), 112.3 (C=*C*H_2), 65.5 (CH_2), 59.0 (C), 46.3 (CH_2), 43.7 (CH_2), 42.5 (CH_2), 41.1 (CH_2), 38.3 (CH_2); ν_{max}/cm^{-1} (ATR) 2940 (C–H), 1724 (C=O), 1661 (C=O) 1260 (C–O); HRMS (ESI) found MNa$^+$ 437.1801, $C_{21}H_{26}N_4NaO_5$, requires MNa$^+$, 437.1783.

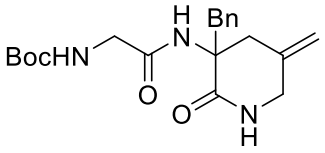
Allyl [1-(3-Benzyl-5-methylene-2-piperidinon-3-yl)glycylglycylglycyl]-carbamic acid, 13u



Lactam **13p** (102 mg, 1.0 eq, 0.37 mmol) and Alloc-Glycyl-Glycine (131 mg, 1.0 eq, 0.37 mmol) were dissolved in dry THF (10 mL) under an inert atmosphere and cooled to 0 °C. ^{i}BuOCOCl (0.08 mL, 1.5 eq, 0.62 mmol) was added and the mixture stirred for 10 minutes. Et_3N (0.26 mL, 5.0 eq, 1.8 mmol) was added dropwise and the reaction mixture was stirred overnight warming to room temperature. To the mixture, DCM (50 mL) was added and the mixture was washed with water (20 mL), saturated $NaHCO_{3(aq)}$ (20 mL) and brine (20 mL). The organic phase was dried with $MgSO_4$, filtered and then the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography eluting with a gradient of 0-20% MeOH in EtOAc to give **13u** (23 mg, 13%) as an off-white foamy gum. ^{1}H-NMR δ/ppm (400 MHz, d^4-MeOD) 7.36-7.13 (5H, *m*, CH_{Ar}), 5.93 (1H, *ddd, J =* 16.5, 13.5 & 8.0 Hz, C*H*=CH_2), 5.31 (1H, *dd, J =* 16.5

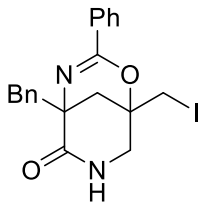
& 1.5 Hz, CH=CH_2), 5.18 (1H, *dd, J* = 10.5 & 1.5 Hz, CH=CH_2), 4.98 (1H, *s*, C=CH_2), 4.93 (1H, *s*, C=CH_2), 4.55 (2H, *d, J*= 5.5 Hz, CH_2), 3.81 (2H, *d, J* = 10.5 Hz, CH_2), 3.53 (2H, *d, J* = 10.5 Hz, CH_2), 3.27 (1H, *d, J* = 13.5 Hz, CH_2), 3.00 (1H, *d, J* = 8.0 Hz, CH_2), 2.95 (2H, *s*, CH_2), 2.89 (2H, *s*, CH_2); ^{13}C-NMR δ/ppm (101 MHz, d^4-MeOD) 172.6 (C=O), 171..0 (C=O), 168.4 (C=O), 166.8 (C=O), 158.9 (C=O), 137.1 (*C*=CH$_2$), 133.7 (C$_{Ar}$), 132.9 (*C*H=CH$_2$), 130.3 (C$_{Ar}$H), 127.9 (C$_{Ar}$H), 126.8 (C$_{Ar}$H), 116.2 (CH=*C*H$_2$), 112.3 (C=*C*H$_2$), 73.2 (CH$_2$), 65.3 (C), 46.5 (CH$_2$), 46.4 (CH$_2$), 46.0 (CH$_2$), 42.6 (CH$_2$), 41.1 (CH$_2$), 40.3, 38.4 (CH$_2$); ν_{max}/cm^{-1} (ATR) 2914 (C–H), 1729 (C=O), 1641 (C=O), 1221 (C–O); HRMS (ESI) found MH$^+$ 472.2196, $C_{23}H_{30}N_5O_6$, requires MH$^+$, 472.2191.

tert-Butyl [1-(3-Benzyl-5-methylene-2-piperidinon-3-yl)acetomidyl]-carbamic acid, 13w



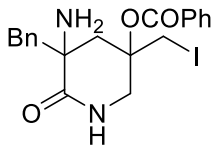
Lactam **13p** (203 mg, 1.0 eq, mmol) was dissolved in dry THF (10 mL) under an inert atmosphere and cooled to 0 °C. Et_3N (0.51 mL, 5.0 eq, mmol) was added, followed by Boc_2O (0.34 mL, 2.0 eq, mmol) and the reaction mixture was stirred overnight warming to room temperature. To the mixture, EtOAc (20 mL) was added and the mixture was washed with water (20 mL) and saturated $NaHCO_{3(aq)}$ (20 mL). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography eluting with a gradient of 0-5% MeOH in EtOAc to give **13w** (128 mg, 46%) as a white foamy gum. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 7.36-7.20 (3H, *m*, CH$_{Ar}$), 7.14 (2H, *d, J* = 7.0 Hz, CH$_{Ar}$), 6.99 (1H, *s*, NH), 6.68 (1H, *s*, NH), 5.64 (1H, *s*, NH), 5.12 (2H, *s*, C=CH_2), 4.19-4.04 (2H, *m*, CH_2), 3.94 (1H, *d, J* = 15.0 Hz, CH_2), 3.80 (1H, *d, J* = 17.0 Hz, CH_2), 3.63 (1H, *d, J* = 16.0 Hz, CH_2), 3.30 (1H, *dd, J* = 13.5 & 7.5 Hz, CH_2), 3.21-3.05 (1H, *m*, CH_2), 2.94 (1H, *m,* CH_2) 1.42 (9H, *s*, C(CH_3)$_3$); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 172.6 (C=O), 169.5 (C=O), 156.0 (C=O), 136.4 (*C*=CH$_2$), 135.1 (C$_{Ar}$), 130.3 (C$_{Ar}$H), 128.5 (C$_{Ar}$H), 127.2(C$_{Ar}$H), 114.1 (C=*C*H$_2$), 80.0 (*C*(CH$_3$)$_3$), 59.0 (C), 47.1 (CH2), 44.3 (CH$_2$), 40.5 (CH$_2$), 38.2 (CH$_2$), 28.3 (C(*C*H$_3$)$_3$); ν_{max}/cm^{-1} (ATR) 2950 (C–H), 1720 (C=O), 1651 (C=O), 1203 (C–O); HRMS (ESI) found MH$^+$ 374.2080, $C_{20}H_{28}N_3O_4$, requires MH$^+$, 374.2074.

1-(1-Iodomethyl)-3-phenyl-5-benzyl-2-oxa-4,7-diazabicyclo[3.3.1]non-3-en-6-one, 14



Lactam **13h** (250 mg, 1.0 eq, 0.78 mmol), $PhI(OAc)_2$ (306 mg, 1.2 eq, 0.97 mmol) and NaI (159 mg, 1.4 eq, 1.1 mmol) were dissolved in dry DCM (8 mL) under an inert atmosphere and stirred at room temperature for 24 hours. The reaction mixture was diluted with DCM (10 mL) and washed with saturated $Na_2S_2O_{3(aq)}$. The solvent was removed under reduced pressure and the resulting residue was purified by recrystallization from MeOH to give the oxazine **14** (310 mg, 89%) as a white amorphous solid. m.p. 187-189 °C; ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 8.15-8.04 (2H, *m*, CH_{Ar}), 7.54-7.18 (8H, *m*, CH_{Ar}), 5.87 (1H, *s*, NH), 3.70 (1H, *dt*, *J* = 13.0 & 2.5 *Hz*, CH_2), 3.58 (1H, *d*, *J* = 13.5 *Hz*, CH_2), 3.47 (1H, *d*, *J* = 13.0 *Hz*, CH_2), 3.42 (1H, *d*, *J* = 11.0 *Hz*, CH_2), 3.39 (1H, *d, J* = 11.0 Hz, CH_2), 3.32 (1H, *d*, *J* = 13.5 *Hz*, CH_2), 2.10 (1H, *d*, *J* = 13.0 *Hz*, CH_2I), 1.71 (1H, *dd*, *J* = 13.0 & 2.5 *Hz*, CH_2I); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 170.5 (C=N), 156.4 (C=O), 136.8 (C_{Ar}), 132.2 (C_{Ar}), 131.2 ($C_{Ar}H$), 130.8 ($C_{Ar}H$), 128.2 ($C_{Ar}H$), 128.1 ($C_{Ar}H$), 127.7 ($C_{Ar}H$), 126.6 ($C_{Ar}H$), 58.1 (C), 53.1 (C), 42.7 (CH_2), 33.5 (CH_2), 31.0 (CH_2), 11.2 (CH_2I); ν_{max}/cm^{-1} (thin film) 3189 (N–H), 3065 (C–H), 2918 (C–H), 1660 (C=O), 1645 (C=O); HRMS (ESI) found MH+ 447.0564, $C_{20}H_{20}IN_2O_2$, requires MH^+, 447.0563.

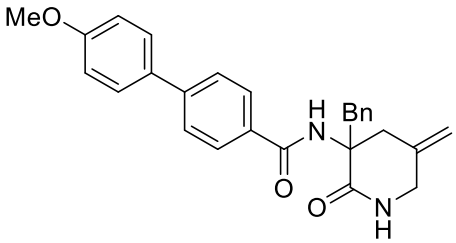
3-Benzyl-3-amino-5-(1-iodomethyl)-5-benzoyloxy-2-piperidinone, 15



Oxazine **14** (97 mg, 1.0 eq, 0.22 mmol) was dissolved in 3M HCl (10 mL) and stirred at 40°C for 24 hours. The reaction mixture was cooled to room temperature and basified with 1M $NaOH_{(aq)}$. The crude product was extracted using EtOAc and the solvent was removed under reduced pressure. The crude mixture was purified by trituration from Et_2O using 4 M HCl in Et_2O to give the product as a HCl salt. The crude salt was neutralised by washing with 1 M $NaOH_{(aq)}$ and extracting with EtOAc. Removal of the solvent under reduced pressure gave the product **15** (94 mg, 93%) as a white amorphous solid. m.p. 155-159 °C; ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 8.02-7.94 (2H, *m*, CH_{Ar}), 7.66-7.55 (1H, *m*, CH_{Ar}), 7.52-7.41 (2H, *m*, CH_{Ar}), 7.39-7.21 (5H, *m*, CH_{Ar}), 5.64 (1H, *d*, *J* = 5.5 *Hz*, NH), 4.10 (1H, *ddd, J* = 13.0, 5.5 & 3.5 *Hz*, CH_2), 3.80 (1H, *d*, *J* = 11.0 *Hz*, CH_2), 3.74 (1H, *d, J* = 11.0 Hz, CH_2), 3.26 (1H, *d*, J =

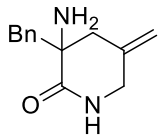
13.0 *Hz*, CH_2), 2.85 (1H, *d*, *J* = 13.0 Hz, CH_2I) 2.72 (1H, *d*, *J* = 13.0 *Hz*, CH_2), 2.71 (1H, *dd*, *J* = 13.0 & 3.5 *Hz*, CH_2) 2.16 (1H, *d*, *J* = 13.0 *Hz*, CH_2I) ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 175.9 (C=O), 165.9 (C=O), 135.9 (C_{Ar}), 133.5 ($C_{Ar}H$), 130.5 ($C_{Ar}H$), 130.2 (C_{Ar}), 129.7 ($C_{Ar}H$), 128.7 ($C_{Ar}H$), 128.5 ($C_{Ar}H$), 127.1 ($C_{Ar}H$), 56.5 (C), 48.1 (CH_2), 47.9 (CH_2), 40.9 (CH_2), 31.0, (C), 9.0 (CH_2I); ν_{max}/cm^{-1} (thin film) 3320 (N–H), 3276 (N–H), 3061 (C–H), 1717 (C=O), 1660 (C=O), 1265 (C–O); HRMS (ESI) found MH^+ 365.0670, $C_{20}H_{22}IN_2O_3$ requires MH^+, 365.0667.

3-Benzyl-3-[4-(4-methoxyphenyl)benzamido]-5-methylene-2-piperidinone, 16



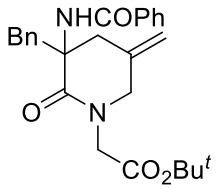
Lactam **13k** (70 mg, 1.0 eq, 0.18 mmol), 4-methoxyphenylboronic acid (27 mg, 1.0 eq, 0.18 mmol), Cs_2CO_3 (134 mg, 2.4 eq, 0.41 mmol), and $Pd(PPh_3)_4$ (16 mg, 8 mol%, 0.014 mmol) were dissolved in dry THF (1 mL) and stirred at 150 °C for 30 mins. The mixture was then diluted with EtOAc (10 mL) and washed with 1M $NaOH_{(aq)}$ (10 mL). The solvent was removed under reduced pressure and the crude residue was purified by column chromatography eluting with a gradient of 25-75% EtOAc in petrol to give the product **16** (46 mg, 61%) as a colourless oil. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$,) 7.75 (2H, *d*, *J* = 8.5 Hz, CH_{Ar}), 7.59 (2H, *d*, *J* = 8.5 Hz, CH_{Ar}), 7.56 (2H, *d, J* = 8.5 Hz, CH_{Ar}), 7.33-7.23 (3H, *m*, CH_{Ar}), 7.18-7.16 (2H, *m*, CH_{Ar}), 7.00 (2H, *d, J* = 9.0 Hz, CH_{Ar}), 6.46 (1H, *s*, NH), 5.24 (1H, *s*, C=CH_2), 5.17 (1H, *s*, C=CH_2), 4.22 (1H, *d, J* = 15.0 Hz, CH_2), 4.11 (1H, *d, J* = 15.0 Hz, CH_2), 3.87 (3H, *s*, OCH_3), 3.74 (1H, *d, J* = 14.0 Hz, CH_2), 3.67 (1H, *d, J* = 14.0 Hz, CH_2), 3.08 (1H, *d, J* = 14.0 Hz, CH_2), 2.93 (1H, *d, J* = 14.0 Hz, CH_2); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 172.6 (C=O), 166.7 (C=O), 159.7 (C_{Ar}OMe), 143.9 (C=CH_2), 136.5 (C_{Ar}), 135.8 (C_{Ar}), 132.9 (C_{Ar}), 132.5 (C_{Ar}), 132.2 ($C_{Ar}H$), 132.1 ($C_{Ar}H$), 131.98 ($C_{Ar}H$), 131.95 ($C_{Ar}H$), 130.2 ($C_{Ar}H$), 128.6 ($C_{Ar}H$), 128.5 ($C_{Ar}H$), 128.3 ($2C_{Ar}H$), 127.5 ($C_{Ar}H$), 127.1 ($C_{Ar}H$), 126.6 ($C_{Ar}H$), 114.4 ($C_{Ar}H$), 114.0 (C=CH_2), 59.7 (C), 55.4 (CH_3), 47.1 (CH_2), 40.0 (CH_2), 39.2 (CH_2); ν_{max}/cm^{-1} (ATR) 2963 (C–H), 1623 (C=O), 1172 (C–O); HRMS (ESI) found MH^+ 427.2016, $C_{27}H_{27}N_2O_3$, requires MH^+, 427.2016.

3-Benzyl-3-amino-5-methylene-2-piperidinone, 17



Lactam **13l** (481 mg, 1.0 eq, 1.5 mmol) and NaOH (559 mg, 9.3 eq, 14 mmol) were dissolved in MeOH (24 mL) and water (24 mL) and stirred at 40 °C for 24 hours. The mixture was cooled to room temperature and neutralised with 1 M $HCl_{(aq)}$, then extracted with EtOAc (50 mL). The organic phase was dried with $MgSO_4$, filtered and the solvent was removed to give **17** (273 mg, 78%) as a yellow oil. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 7.73 (2H, *s*, NH_2), 7.50 (1H, *s*, NH), 7.3-7.26 (3H, *m*, CH_{Ar}), 7.09-7.07 (2H, *m*, CH_{Ar}), 5.22 (1H, *s*, C=CH_2), 5.17 (1H, *s*, C=CH_2), 4.13 (1H, *d, J* = 16. 0Hz, CH_2), 4.05 (1H, *d, J* = 16.0 Hz, CH_2), 3.54 (1H, *d, J = 1*4.0 Hz, CH_2), 3.43 (1H, *d, J* = 14.0 Hz, CH_2), 3.03 (1H, *d, J* = 14.0 Hz, CH_2), 2.80 (1H, *d, J* = 14.0 Hz, CH_2); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 171.3 (C=O), 136.9 (*C*=CH_2), 135.9 (C_{Ar}), 130.9 (C_{Ar}H), 128.2 (C_{Ar}H), 126.9 (C_{Ar}H), 133.8 (C=*C*H_2), 59.9 (C), 47.7 (CH_2), 43.9 (CH_2), 40.4 (CH_2); ν_{max}/cm^{-1} (ATR) 3333 (N-H), 2934 (C–H), 1673 (C=O); HRMS (ESI) found MH^+ 217.1341, $C_{13}H_{17}N_2O$, requires MH^+, 217.1350.

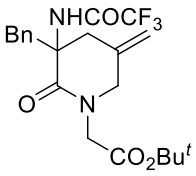
1,1-Dimethylethyl (3-Benzyl-3-benzamido-5-methylene-2-piperidinon-1-yl)acetate, 18h



Lactam **13h** (52 mg, 1.0 eq, 0.16 mmol) was dissolved in dry DMF (5 mL) under nitrogen and cooled to 0°C. To this solution, NaH (18 mg, 60% w/w dispersion in mineral oil, 2.8 eq, 0.45 mmol) was added and the mixture was stirred for 30 mins. ^{t}Butylbromoacetate (0.03 mL, 1.1 eq, 0.018 mmol) was added and the reaction mixture was left to stir at room temperature overnight. The mixture was diluted with EtOAc (20 mL) and washed twice with brine. The organic phase was then concentrated under reduced pressure and the crude residue was purified by flash column chromatography eluting with a gradient of 10-20% EtOAc in petrol to give lactam **18h** (46 mg, 63%) as a colourless oil. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 7.68-7.62 (2H, *m*, CH_{Ar}), 7.48 (1H, *t, J* = 7.5 Hz, CH_{Ar}), 7.39 (2H, *t, J* = 7.5 Hz, CH_{Ar}), 7.31 (1H, *s*, NH), 7.19 (3H, *m*, CH_{Ar}), 7.11 (2H, *dd, J* = 6.5 & 3.0 Hz, CH_{Ar}). 5.26 (1H, *s*, C=CH_2), 5.18 (1H, *s*, C=CH_2), 4.30 (1H, *d, J* = 17.0 Hz, CH_2), 4.26 (2H, *m,* CH_2), 3.92 (1H, *d, J* = 14.0 Hz, CH_2), 3.83 (1H, *d, J* = 17.0 Hz, CH_2), 3.67 (1H, *d, J* = 13.5 Hz, CH_2), 3.37 (1H, *d, J* = 17.0 Hz, CH_2), 3.10 (1H, *d, J* = 13.5 Hz, CH_2), 2.93 (1H, *d, J* = 14.0 Hz, CH_2),

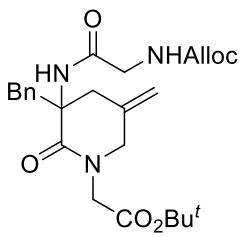
1.52 (9H, *s*, $C(CH_3)_3$); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 171.0 (C=O), 167.8 (CO_2Bu^t), 167.0 (C=O), 136.0 (C=CH_2), 135.8 (C_{Ar}), 135.1 (C_{Ar}), 131.4 ($C_{Ar}H$), 130.4 ($C_{Ar}H$), 128.5 ($C_{Ar}H$), 128.0 ($C_{Ar}H$), 126.9 ($C_{Ar}H$), 113.8 (C=CH$_2$), 82.4 ($C(CH_3)_3$), 60.0 (C), 53.6 ($CH_2CO_2Bu^t$), 49.4 (CH_2), 40.0 (CH_2), 39.5 (CH_2), 28.1 (C(CH_3)$_3$); ν_{max}/cm^{-1} (thin film), 3406 (N-H), 1686 (C=O), 1654 (C=O), 1636 (C=O); HRMS (ESI) found MH^+ 435.2278, $C_{26}H_{31}N_2O_4$, requires MH^+, 435.2293.

1,1-Dimethylethyl (3-Benzyl-3-trifluoroacetamido-5-methylene-2-piperidinon-1-yl)acetate, 18l



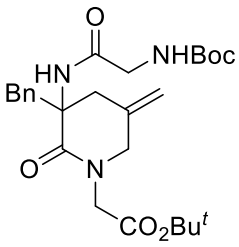
Lactam **13l** (105 mg, 1.0 eq, 0.34 mmol) was dissolved in dry DMF (10 mL) under nitrogen and cooled to 0°C. To this solution, NaH (23 mg, 60% dispersion in mineral oil, 1.6 eq, 0.57 mmol) was added and the mixture was stirred for 30 mins. ^{t}Butylbromoacetate (0.05 mL, 1.0 eq, 0.34 mmol) was added and the reaction mixture was left to stir at room temperature overnight. The mixture was diluted with EtOAc (40 mL) and washed twice with brine. The organic phase was then concentrated under reduced pressure and the crude residue was purified by flash column chromatography eluting with a gradient of 10-20% EtOAc in petrol to give lactam **18l** (145 mg, 99%) as a colourless oil. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 7.53 (1H, s, NH), 7.30-7.18 (3H, *m*, CH_{Ar}), 7.04 (2H, *dd, J* = 6.0 & 3.5 Hz, CH_{Ar}), 5.25 (1H, *s*, C=CH_2), 5.19 (1H, *s*, C=CH_2), 4.29 (1H, *d, J* = 16.0 Hz, CH_2), 4.23 (1H, *d*, *J* = 17.0 Hz, CH_2), 4.22-4.13 (1H, m, CH2), 3.83 (1H, *d, J* = 17.0 Hz, CH_2), 3.75 (1H, *d*, *J* = 14.0 Hz, CH_2), 3.44 (1H, *d, J* = 14.0 Hz, CH_2), 3.08 (1H, *d, J* = 14.0 Hz, CH_2), 2.81 (1H, *d, J* = 14.0 Hz, CH_2), 1.51 (9H, *s*, $C(CH_3)_3$); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 169.5 (C=O), 167.5 (C=O), 156.3 (*q*, *J* = 40.0 Hz, F_3CC=O), 134.8 (C=CH_2), 134.5 (C_{Ar}), 130.1 ($C_{Ar}H$), 128.1 ($C_{Ar}H$), 127.3 ($C_{Ar}H$), 115.4 (*q*, *J* = 289.0 Hz, CF_3), 114.6 (C=CH$_2$), 82.7 ($C(CH_3)_3$), 60.4 (C), 53.4 ($CH_2CO_2Bu^t$), 49.4 (CH_2), 39.9 (CH_2), 38.7 (CH_2), 28.1 (C(CH_3)$_3$); ^{19}F-NMR δ/ppm (376 MHz, $CDCl_3$) -76.2 (*s*, CF_3); ν_{max}/cm^{-1} (thin film), 3406 (N-H), 1686 (C=O), 1654 (C=O), 1636 (C=O); HRMS (ESI) found MH^+ 435.2278, $C_{26}H_{31}N_2O_4$, requires MH^+, 435.2293.

1',1'-Dimethylethyl {Allyl [1-(3-Benzyl-5-methylene-2-piperidinon-3-yl)acetomidyl]-carbamic acid}acetate, 18u



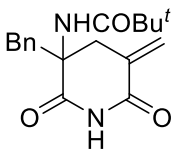
Lactam **13u** (117 mg, 1.0 eq, 0.33 mmol) was dissolved in dry THF (10 mL) under argon and cooled to -78 °C. To this solution LDA (6.1 mL, 0.075 M in THF, 1.4 eq, 0.45 mmol) was added dropwise and the mixture was stirred for 1 hour. ^{t}Butylbromoacetate (0.06 mL, 1.2 eq, 0.41 mmol) was added and the reaction mixture was left to stir overnight warming to room temperature. The mixture was diluted with EtOAc (20 mL) and washed with water (20 mL) then saturated $NaHCO_{3(aq)}$ (20 mL) followed by brine (20 mL). The organic phase was then dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography eluting with 85% EtOAc in petrol to give lactam **18u** (107 mg, 69%) as a white foamy gum. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 7.29-7.16 (3H, *m*, CH_{Ar}), 7.08 (2H, *dd, J* = 7.0 & 2.0 Hz, CH_{Ar}), 6.83 (1H, *s,* NH), 5.96-5.87 (1H, *m*, C*H*=CH_2), 5.42 (1H, *s*, NH), 5.3 (1H, *d, J* = 17.0 Hz, CH=C*H*$_2$), 5.22 (1H, *d, J* = 10.5 Hz, CH=C*H*$_2$), 5.18 (1H, *s,* C=CH_2), 5.14 (1H, *s*, C=CH_2), 4.57 (2H, *d, J* = 5.5 Hz, CH_2), 4.29 (1H, *d, J* = 17.0 Hz, CH_2), 4.20-4.15 (2H, *m*, CH_2), 3.77 (2H, *t, J* = 4.0 Hz, CH_2), 3.74 (1H, *d, J* = 6.5 Hz, CH_2), 3.57 (1H, *d, J* = 14.0 Hz, CH_2), 3.41 (*d, J* = 14.0 Hz, CH_2), 3.01 (1H, *d, J* = 14.0 Hz, CH_2), 2.89 (1H, *d, J* = 14.0 Hz, CH_2), 1.50 (9H, *s*, C(CH_3)$_3$); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 172.5 (C=O), 168.9 (C=O), 167.9 (C=O), 156.4 (C=O), 136.5 (*C*=CH_2), 135.2 (C_{Ar}), 132.7 (*C*H=CH_2), 130.3 (C_{Ar}H), 128.4 (C_{Ar}H), 127.2 (C_{Ar}H), 117.8 (CH=*C*H$_2$), 114.0 (C=*C*H$_2$), 80.1 (*C*(CH_3)$_3$), 65.9 (CH_2), 59.2 (C), 52.8 (CH_2), 47.2 (CH_2), 44.7 (CH_2), 40.5 (CH_2), 39.4 (CH_2) 28.1 (C(*C*H$_3$)$_3$); ν_{max}/cm^{-1} (ATR) 2981 (C–H), 1725 (C=O), 1648 (C=O), 1228 (C–O); HRMS (ESI) found MH$^+$ 472.2448, $C_{25}H_{34}N_2O_6$, requires MH$^+$, 472.2453.

1',1'-Dimethylethyl {tert-Butyl [1-(3-Benzyl-5-methylene-2-piperidinon-3-yl)acetomidyl]-carbamic acid}acetate, 18w



Lactam **13w** (97 mg, 1.0 eq, 0.26 mmol) was dissolved in dry THF (10 mL) under argon and cooled to -78 °C. To this solution, LDA (5.1 mL, 0.075 M in THF, 1.4 eq, 0.38 mmol) was added dropwise and the mixture was stirred for 1 hour. ^{t}Butylbromoacetate (0.05 mL, 1.2 eq, 0.34 mmol) was added and the reaction mixture was left to stir overnight warming to room temperature. The mixture was diluted with EtOAc (20 mL) and washed with water (20 mL) then saturated $NaHCO_{3(aq)}$ (20 mL) followed by brine (20 mL). The organic phase was then dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography eluting with 50% EtOAc in petrol to give lactam **18w** (91 mg, 72%) as a white foamy gum. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 7.29-7.17 (3H, m, CH_{Ar}), 7.08 (2H, *dd, J =* 7.5 & 2.0 Hz, CH_{Ar}), 6.86 (1H, *s*, NH), 5.18 (1H, *s*, C=CH_2), 5.13 (1H, *s*, C=CH_2), 5.08 (1H, *s*, NH), 4.27 (1H, *d, J =* 17.0 Hz, CH_2), 4.17 (2H, *s*, CH_2), 3.76 (1H, *d, J =* 17.0 Hz, CH_2), 3.70 (2H, *s*, CH_2), 3.58 (1H, *d, J =* 14.0 Hz, CH_2), 3.42 (1H, *d, J =* 14.0 Hz, CH_2), 3.00 (1H, *d, J =* 14.0 Hz, CH_2), 2.88 (1H, *d, J =* 14.0 Hz, CH_2), 1.50 (9H, *s*, $C(CH_3)_3$), 1.43 (9H, *s*, $C(CH_3)_3$); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 170.6 (C=O), 168.8 (C=O), 167.7 (C=O), 155.7 (C=O), 135.9 (*C*=CH_2), 1355 (C_{Ar}), 130.3 ($C_{Ar}H$), 128.1 ($C_{Ar}H$), 127.0 ($C_{Ar}H$), 113.8 (C=*C*H_2), 82.3 (*C*$(CH_3)_3$), 79.9 (*C*$(CH_3)_3$), 59.6 (C), 53.6 (CH_2), 49.4 (CH_2), 44.5 (CH_2), 40.3 (CH_2), 39.2 (CH_2), 28.3 (C(*C*$H_3)_3$), 28.1 (C(*C*$H_3)_3$); ν_{max}/cm^{-1} (ATR) 2983 (C–H), 1721 (C=O), 1628 (C=O), 1211 (C–O); HRMS (ESI) found MH^+ 488.2761, $C_{26}H_{38}N_2O_6$, requires MH^+, 488.2764.

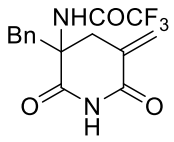
3-Benzyl-3-(1,1-dimethylpropanamido)-5-methyleneglutarimide, 19j



Lactam **13j** (104 mg, 1.0 eq, 0.35 mmol) was dissolved in dry DCM (17 mL) under an inert atmosphere and to this mixture was added *m*CPBA (85 mg, 1.1 eq, 0.38 mmol). The reaction mixture was stirred at room temperature overnight before another portion of *m*CPBA (78 mg, 1.0 eq, 0.35 mmol) was added, and the reaction mixture was left to stir for 6 hours. The reaction was quenched with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The solvent

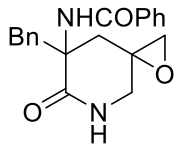
was removed under reduced pressure and the crude residue was purified by flash column chromatography eluting with a gradient of 25-75% EtOAc in petrol to give glutarimide **19j** (39 mg, 35%) as a mixture with *meta*-chlorobenzoic acid. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 8.67 (1H, *s*, NH), 7.36-7.30 (3H, *m*, CH_{Ar}), 7.08 (2H, *dd*, *J* = 7.0 & 2.5 Hz, CH_{Ar}), 6.55 (1H, *d*, *J* = 1.5 Hz, C=CH_2), 6.49 (1H, *s*, NH), 5.86 (1H, *d*, *J* = 1.5 Hz, C=CH_2), 3.68 (1H, *d*, *J* = 15.0 Hz, CH_2), 3.51 (1H, *d*, *J* = 14.0 Hz, CH_2Ph), 3.10 (1H, *dt*, *J* = 15.0 & 2.0 Hz, CH_2), 2.96 (1H, *d*, *J* = 14.0 Hz, CH_2Ph), 1.16 (9H, *s*, C(CH_3)$_3$); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 178.6 (^{t}Bu*C*=O), 173.1 (C=O), 164.6 (C=C–*C*=O), 134.0 (C_{Ar}), 133.1 (*C*=CH_2), 129.8 (C_{Ar}H), 128.6 (C=*C*H_2), 128.3 (C_{Ar}H), 127.8 (C_{Ar}H), 59.7 (C), 41.3 (*C*(CH_3)$_3$), 40.2 (CH_2), 36.4 (CH_2Ph), 17.4 (C(*C*H_3)$_3$); ν_{max}/cm^{-1} 2923 (C-H), 1678 (C=O), 1548 (C=O), 1276 (C-O); HRMS (ESI) found MH^+ 315.1703, $C_{18}H_{23}N_2O_3$, requires MH^+, 315.1716.

3-Benzyl-3-trifluoroacetamido-5-methyleneglutarimide, 19l



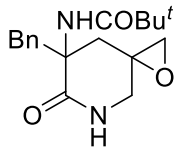
Lactam **13l** (125 mg, 1.0 eq, 0.40 mmol) was dissolved in dry DCM (20 mL) under an inert atmosphere and to this mixture was added *m*CPBA (93 mg, 1.0 eq, 0.42 mmol). The reaction mixture was stirred at room temperature overnight before another portion of *m*CPBA (102 mg, 1.1 eq, 0.45 mmol) was added and left to stir for 6 hours. The reaction was quenched with saturated $NaHCO_{3(aq)}$ and extracted with DCM. The solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography eluting with a gradient of 20-30% EtOAc in petrol to give glutarimide **19l** (24 mg, 19%) as a mixture with *meta*-chlorobenzoic acid. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 8.51 (1H, *s*, NH), 7.37-7.29 (3H, *m,* CH_{Ar}), 7.21 (1H, *s*, NH), 7.05-6.37 (2H, *m*, CH_{Ar}), 6.64 (1H, *dd, J* = 2.5 & 0.5 Hz, C=CH_2), 5.99-5.93 (1H, *m,* C=CH_2), 3.90 (1H, *d, J* = 15.0 Hz, CH_2), 3.57 (1H, *d, J* = 14.0 Hz, CH_2), 3.04 (1H, *dd, J* = 15.0 & 2.5 Hz, CH_2), 3.03 (1H, *d, J* = 14.0 Hz, CH_2); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 177.7 (C=O), 171.2 (C=O), 169.3 (*q, J* = 37.5 Hz, F_3C*C*=O), 132.8 (*C*=CH_2), 132.3 (*q, J* = 288 Hz, CF_3), 131.8(C_{Ar}), 129.6 (C_{Ar}H), 128.9 (C_{Ar}H), 128.2 (C_{Ar}H), 114.5 (C=*C*H_2), 56.8 (C), 39.9 (CH_2), 36.1 (CH_2); ^{19}F-NMR δ/ppm (377 MHz, $CDCl_3$) -76.1 (*s*, CF_3); ν_{max}/cm^{-1} (ATR) 3228 (C-H), 1701 (C=O), 1208 (C-O), 1165 (C-F); HRMS (ESI) found MH^+ 327.0951, $C_{15}H_{14}F_3N_2O_3$, requires MH^+, 327.0964.

Spiro(3-benzyl-3-benzamido-5-oxiranyl-2-piperidinone), 20h



Oxone (1.48 g, 15 eq, 4.8 mmol) and $NaHCO_3$ (1.95g, 75 eq, 23 mmol) were dissolved in water (5.5 mL) and stirred for 10 mins. To this solution, lactam **13h** (103 mg, 1.0 eq, 0.32 mmol) in acetone (4.4 mL) was added and the reaction was left to stir at room temperature overnight. The mixture was diluted with water and extracted with EtOAc to give the crude product as a 2:1 mixture of diastereomers. Purification by flash column chromatography eluting with a gradient of 50-100% EtOAc in petrol to give **20h** as the major diastereomers (40 mg, 34%) as a colourless oil and a 1:1 mixture of diastereomers (27 mg, 25%) as a colourless oil ^{1}H-NMR δ/ppm (major diastereomer, 400 MHz, $CDCl_3$) 7.76 (2H, *m*, CH_{Ar}), 7.50 (1H, *t, J =* 7.0 Hz, CH_{Ar}), 7.42 (2H, *t, J =* 7.5 Hz, CH_{Ar}), 7.31-7.19 (4H, *m*, CH_{Ar} & NH), 7.20-7.05 (2H, *m*, CH_{Ar}), 6.64 (1H, *s*, NH), 3.74 (1H, *d, J =* 13.5 Hz, CH_2), 3.53 (1H, *dd, J =* 13.0 & 3.0 Hz, CH_2), 3.45 (1H, *dd, J =* 13.0 & 1.5 Hz, CH_2), 3.32 (1H, *d, J =* 13.5 Hz, CH_2), 2.96 (1H, *d, J =* 14.5 Hz, CH_2), 2.92 (1H, *d, J =* 4.5 Hz, CH_2), 2.87 (1H, *d, J =* 4.5 Hz, CH_2), 2.60 (1H, *d, J =* 14.5 Hz, CH_2); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 172.2 (C=O), 167.0 (C=O), 135.2 (C_{Ar}), 134.5 (C_{Ar}), 131.7 ($C_{Ar}H$), 130.2 ($2C_{Ar}H$), 128.6 ($2C_{Ar}H$), 128.4 ($2C_{Ar}H$), 127.4 ($C_{Ar}H$), 127.0 ($2C_{Ar}H$), 59.6 (C), 54.7 (CH_2O), 53.5 (C–O), 47.1 (CH_2), 41.1 (CH_2), 38.2 (CH_2); ν_{max}/cm^{-1} (ATR) 2942 (C–H), 1638 (C=O), 1281 (C–O); HRMS (ESI) found MH^+ 337.1547, $C_{20}H_{21}N_2O_3$, requires MH^+, 337.1562.

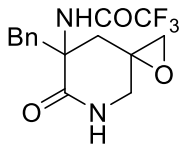
Spiro[3-benzyl-3-(1,1-dimethylpropanamido)-5-oxiranyl-2-pieridinone], 20j



Oxone (1.55 g, 16 eq, 5.1 mmol) and $NaHCO_3$ (2.28 g, 85 eq, 27 mmol) were dissolved in water (5.5 mL) and stirred for 10 mins. To this solution, lactam **13j** (95 mg, 1.0 eq, 0.32 mmol) in acetone (5 mL) was added and the reaction was left to stir at room temperature overnight. The mixture was diluted with water and extracted with EtOAc to give an inseparable 2:1 mixture of diastereomers of the epoxide **20j** (98 mg, 98%) as a colourless oil. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 7.39-7.23 (3H, *m*, CH_{Ar}), 7.14-7.10 (2H, *m*, CH_{Ar}), 6.94 (0.7H, *s*, NH), 6.71 (0.3H, *s*, NH) 6.69 (0.7H, *s*, NH), 6.64 (0.3H, *s*, NH), 4.09 (0.3H, *dd, J =* 13.5 & 1.0 Hz, CH_2), 3.59-3.44 (1.7H, *m,* CH_2), 3.36 (1H, *dd, J =* 13.0 & 2.0 Hz, CH_2), 3.19 (1H, *d, J =*

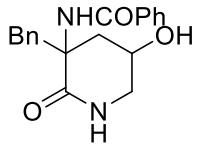
13.5 Hz, CH_2), 3.18 (0.3H, *d, J* = 13.5 Hz, CH_2), 3.01 (0.3H, *dt, J* = 13.0 & 2.5 Hz, CH_2), 2.86-2.78 (1.7H, *m*, CH_2), 2.75 (0.7H, *d, J* = 14.0 Hz, CH_2), 2.43 (0.7H, *d, J* = 14.0 Hz, CH_2), 2.00 (0.3H, *dd, J* = 14.5 & 2.0 Hz, CH_2), 1.12 (6H, *s*, $C(CH_3)_3$), 1.10 (3H, *s*, $C(CH_3)_3$); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 178.10 (C=O), 178.07 (C=O), 172.8 (C=O), 172.6 (C=O), 135.3 (C_{Ar}), 135.1 (C_{Ar}), 130.8 ($C_{Ar}H$), 130.3 ($C_{Ar}H$), 128.6 ($C_{Ar}H$), 128.2 ($C_{Ar}H$), 127.4 ($C_{Ar}H$), 127.3 ($C_{Ar}H$), 58.6 (C–O), 57.6 (C–O), 54.6 (CH_2), 53.9 (C), 53.5 (C), 49.4 (CH_2), 48.4 (CH_2), 46.9 (CH_2), 41.4 (CH_2), 41.0 (CH_2), 39.0 ($C(CH_3)_3$), 38.8 ($C(CH_3)_3$), 38.1 (CH_2), 34.8 (CH_2), 27.4 ($C(CH_3)_3$), 27.3 ($C(CH_3)_3$); ν_{max}/cm^{-1} (ATR) 2935 (C–H), 1633 (C=O), 1277 (C–O); HRMS (ESI) found MH^+ 317.1860, $C_{18}H_{25}N_2O_3$, requires MH^+, 317.1863.

Spiro(3-benzyl-3-trifluoroacetamido-5-oxiranyl-2-piperidinone), 20l



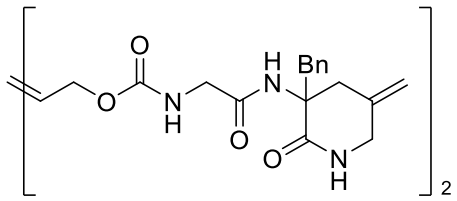
Oxone (1.49 g, 15 eq, 4.8 mmol) and $NaHCO_3$ (2.11 g, 75 eq, 25 mmol) were dissolved in water (5 mL) and stirred for 10 minutes. To this solution, lactam **13l** (102 mg, 1.0 eq, 0.33 mmol) in acetone (4 mL) was added and the reaction was left to stir at room temperature overnight. The mixture was diluted with water and extracted with EtOAc and the solvent evaporated. The crude residue was purified by flash column chromatography eluting with a gradient of 25-50% EtOAc in petrol to give an inseparable 2:1 mixture of diastereomers of the epoxide **20l** (55 mg, 51%) as a colourless oil. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 7.52 (0.7H, *s*, NH), 7.39-7.26 (3.2H, *m*, CH_{Ar} & NH), 7.24-7.16 (0.7H, m, CH_{Ar}), 7.13-7.08 (1.4H, *m*, CH_{Ar}), 6.90 (0.7H, *s*, NH), 6.77 (0.3H, *s*, NH), 4.03 (0.3H, *dd, J* = 13.5 & 1.5 Hz, CH_2), 3.67-3.46 (1.7H, *m,* CH_2), 3.38 (0.7H, *dd, J* = 13.5 & 4.0 Hz, CH_2), 3.31 (0.3H, *d, J* = 14.0 Hz, CH_2), 3.29 (0.7H, *d, J* = 13.5 Hz, CH_2), 3.19 (0.3H, *d, J* = 13.5 Hz, CH_2), 2.98-2.81 (2.7H, *m*, CH_2), 2.71 (0.3H, *d, J* = 14.5 Hz, CH_2), 2.47 (1H, *d, J* = 14.5 Hz, CH_2); ^{13}C-NMR δ/ppm (101 MHz, $CDCl_3$) 171.1 (C=O), 170.7 (C=O), 156.3 (*q, J* = 37.5 Hz, F_3CC=O), 134.1 (C_{Ar}), 134.0 (C_{Ar}), 130.4 ($C_{Ar}H$), 130.0 ($C_{Ar}H$), 128.7 ($C_{Ar}H$), 128.5 ($C_{Ar}H$), 127.8 ($C_{Ar}H$), 127.7 ($C_{Ar}H$), 115.4 (*q, J* = 288.0 Hz, CF_3) 59.8 (C–O), 59.4 (C–O), 54.2 (CH_2O), 53.1 (C) 52.8 (C), 49.6 (CH_2O), 48.2 (CH_2), 46.9 (CH_2), 40.9 (CH_2), 40.5 (CH_2), 37.4 (CH_2) 35.5 (CH_2); ^{19}F-NMR δ/ppm (377 MHz, $CDCl_3$) -76.1 (*s*, CF_3); ν_{max}/cm^{-1} (ATR) 2937 (C–H), 1647 (C=O), 1275 (C–O); HRMS (ESI) found MH^+ 329.1108, $C_{15}H_{16}F_3N_2O_3$, requires MH^+, 329.1111.

3-Benzyl-3-benzamido-5-hydroxy-2-piperidinone, 21



Lactam **13h** (105 mg, 1.0 eq, 0.33 mmol) was dissolved in Et_2O (5 mL) and MeOH (1 mL) and cooled to -78°C. Ozone was bubbled through the solution for 4 hours before warming to room temperature and diluting with MeOH (3 mL). $NaBH_4$ (147 mg, 12 eq, 3.9 mmol) was added in one portion and the reaction was stirred at room temperature overnight. The reaction was quenched with water (10 mL) and extracted with EtOAc (3 x 20 mL). The organic layers were combined and dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography eluting with a gradient of 50-100% EtOAc in petrol to give the alcohol **21** (87 mg, 82%) as a white amorphous solid of 1:2.5 mixture of diastereomers. ^{1}H-NMR δ/ppm ($CDCl_3$ + d^4-MeOD, 400 MHz) 7.74 (0.7H, d, J = 7.5 Hz, CH_{Ar}), 7.66 (1.3H, *d, J* = 7.5 Hz, CH_{Ar}), 7.53-7.20 (9.3H, *m*, CH_{Ar} & NH), 7.03 (0.7H, s, NH), 4.32-4.22 (0.7H, *m*, C*H*OH), 3.88-3.78 (0.3H, *m*, C*H*OH), 3.64-3.51 (1.4H, *m*, CH_2), 3.35 (0.3H, *d, J* = 13.0 Hz, CH_2), 3.24 (0.7H, *d, J* = 13.5 Hz, CH_2), 3.18 (0.3H, *dd, J* = 11.5 & 6.0 Hz, CH_2), 3.10 (0.7H, dd, J = 12.5 & 5.5 Hz, CH_2), 3.02 (0.3H, *d, J* = 13.0 Hz, CH_2), 2.76 (0.7H, *dd*, *J* = 12.5 & 3.5 Hz, CH_2), 2.66 (0.3H, *dd, J* = 12.5 & 3.5 Hz, CH_2), 2.41 (1H, *d*, *J* = 5.5 Hz, CH_2) 2.31 (0.3 H, dd, J = 14.5 & 6.0 Hz, CH_2); ^{13}C-NMR δ/ppm (d^4-MeOD, 101 MHz) 173.2 (C=O), 168.0 (C=O), 135.1 (C_{Ar}), 133.9 (C_{Ar}), 132.6 (C_{Ar}), 131.83 ($C_{Ar}H$), 131.78 ($C_{Ar}H$), 131.1 (C_{Ar}), 130.8 ($C_{Ar}H$), 130.4 ($C_{Ar}H$), 128.5 ($C_{Ar}H$), 128.4 ($C_{Ar}H$), 127.6 ($C_{Ar}H$), 127.3 ($C_{Ar}H$), 127.1 ($C_{Ar}H$), 126.8 ($C_{Ar}H$), 63.0 (CHOH), 61.8 (CHOH), 58.0 (C), 579 (C), 47.8 (CH_2), 47.5 (CH_2), 44.3 (CH_2), 43.1 (CH_2) 40.2 (CH_2), 37.5 (CH_2); ν_{max}/cm^{-1} (ATR) 3356 (N–H), 3275 (N–H), 3176 (O–H), 2946 (C–H), 1669 (C=O), 1642 (C=O); HRMS (ESI) found MH^+ 325.1547, $C_{19}H_{21}N_2O_3$, requires MH^+, 325.1554.

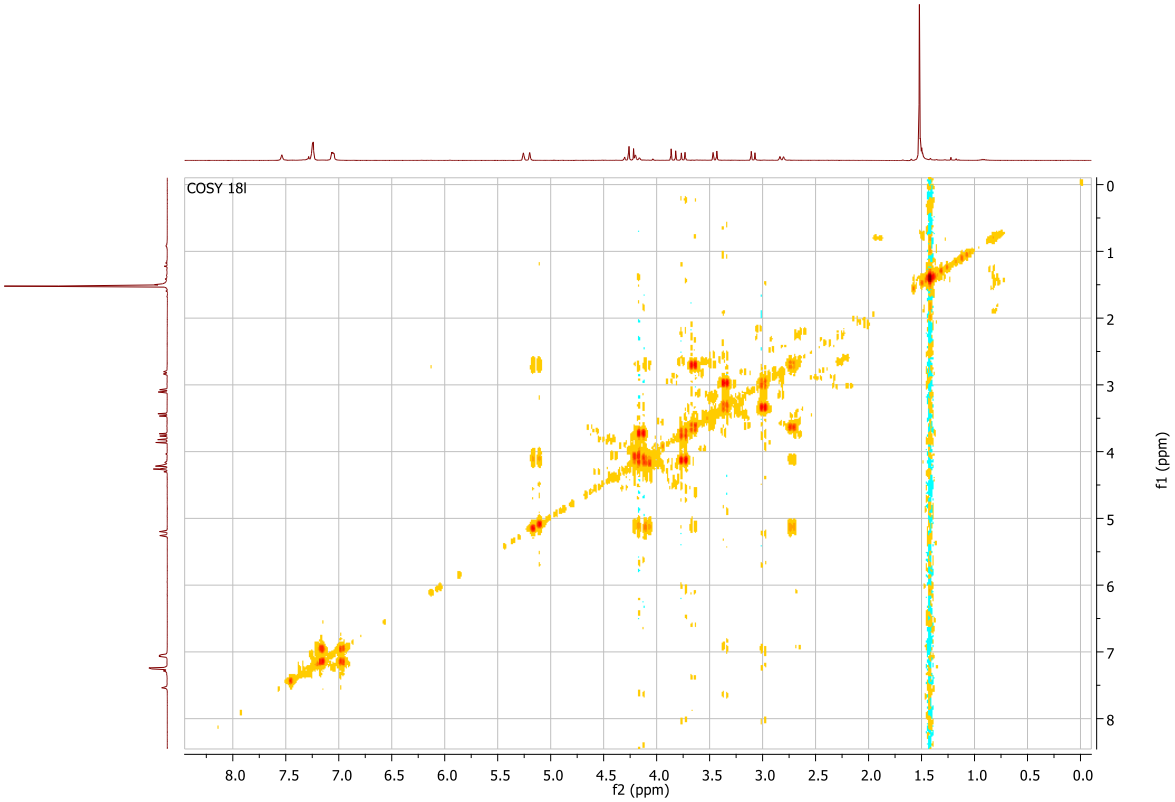
Allyl [1-(3-Benzyl-5-methylene-2-piperidinon-3-yl)acetomidyl]-carbamic acid dimer, 22u'

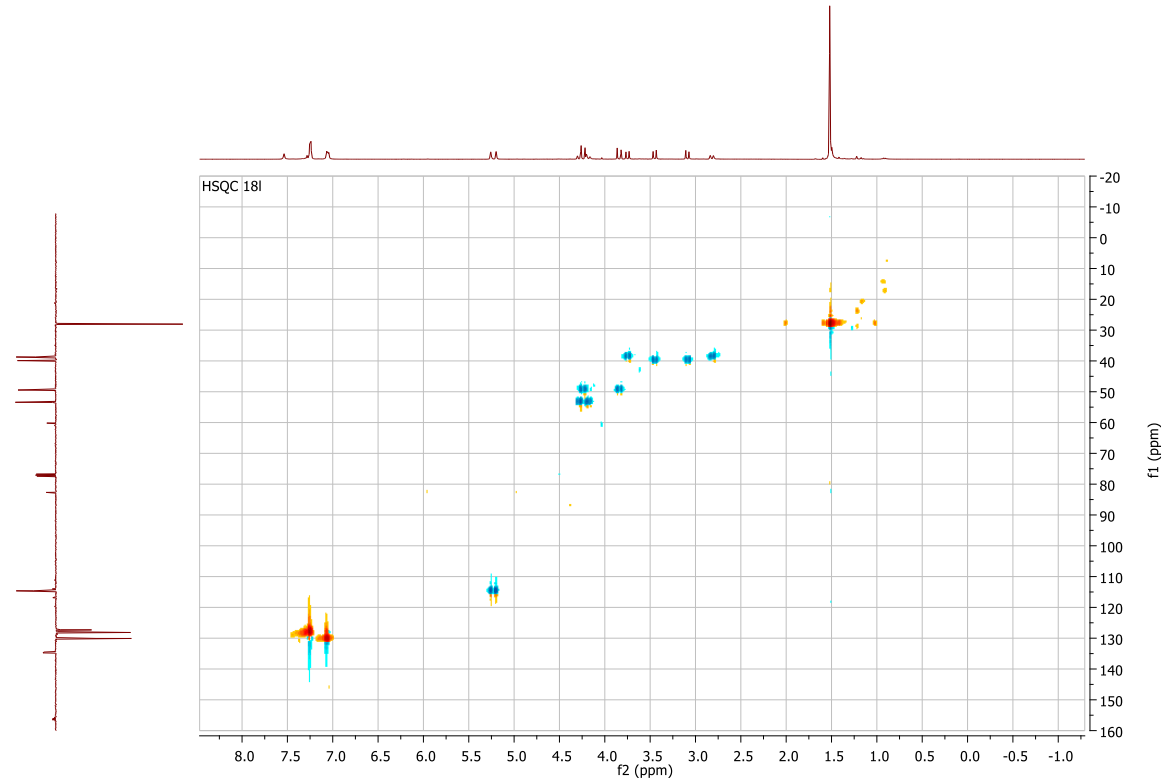


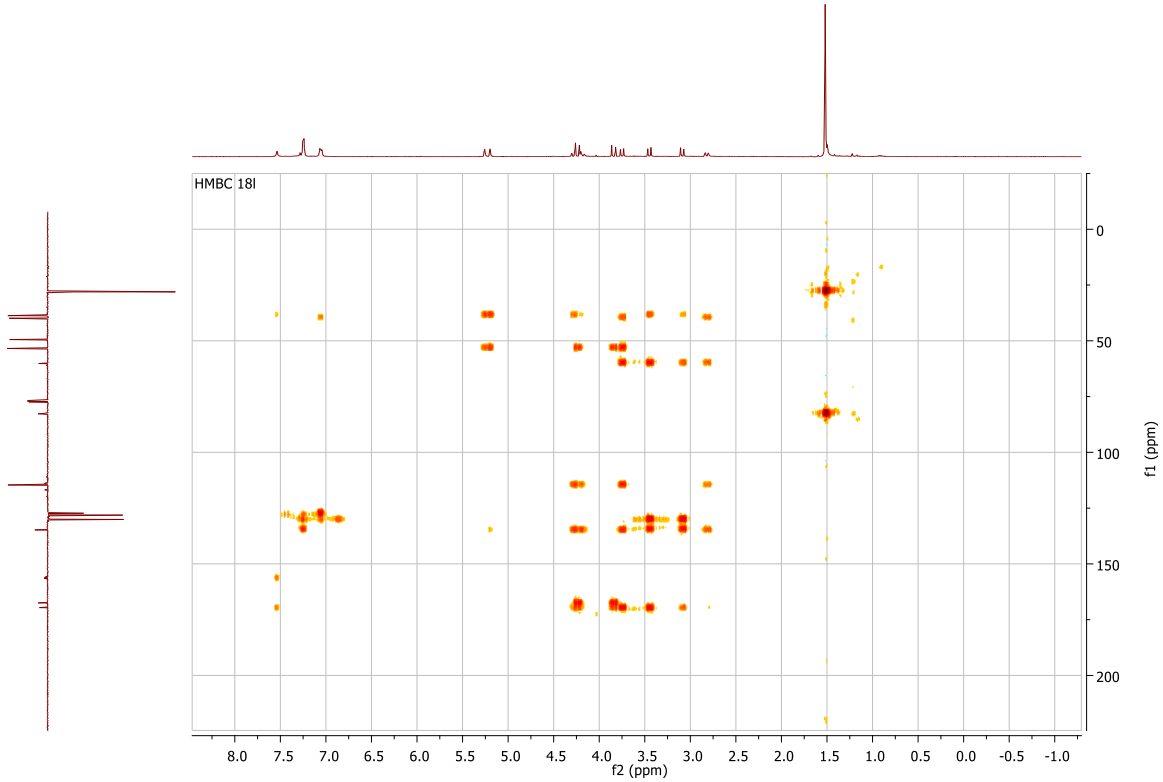
Lactam **13u** (50 mg, 1.0 eq, mmol) was dissolved in dry, degassed DCM (14 mL) under an inert atmosphere and heated to reflux. Grubbs II (12 mg, 10 mol%, mmol) in dry, degassed DCM (1.4 mL) was added and the mixture was stirred at reflux overnight. The mixture was concentrated under reduced pressure and purified by flash column chromatography eluting with a gradient of 0-10% MeOH in EtOAc to give dimer **22u'** (22 mg, 48%) as a yellow oil. ^{1}H-NMR δ/ppm (400 MHz, $CDCl_3$) 7.36-7.15 (10H, *m*, CH_{Ar}), 5.88 (2H, *s_{app},* C=CH), 5.09 (2H, *s*, C=CH_2), 5.05 (2H, *s*, C=CH_2), 4.70-4.42 (4H, *m*, CH_2), 4.09 (2H, *d, J =* 14.5 Hz, CH_2), 3.92 (2H, *d, J =* 14.0 Hz, CH_2), 3.73 (4H, *s*, CH_2), 3.29 (2H, *d, J =* 13.5 Hz, CH_2), 3.05 (2H, *d, J =* 14.0 Hz, CH_2), 2.98 (2H, *d, J =* 13.5 Hz, CH_2), 2.94 (2H, *d, J =* 14.5 Hz, CH_2); ^{13}C-NMR δ/ppm (101 MHz, d^4-MeOD) 172.5 (C=O), 168.9 (C=O), 156.4 (OC=O), 137.2 (*C*=CH_2), 135.1 (C_{Ar}), 130.2 (C_{Ar}H), 128.1 (C_{Ar}H), 127.7 (*C*H=CH_2), 126.8 (C_{Ar}H), 112.6 (C=*C*H_2), 64.3 (CH_2), 58.8 (C), 46.3 (CH_2), 44.1 (CH_2), 40.5 (CH_2), 38.0 (CH_2); ν_{max}/cm^{-1} (ATR) 2982 (C–H), 1721 (C=O), 1644 (C=O), 1231 (C–O); HRMS (ESI) found MH^+ 686.3064, $C_{36}H_{42}N_6O_8$, requires MH^+, 686.3060.

3.2 Appendices

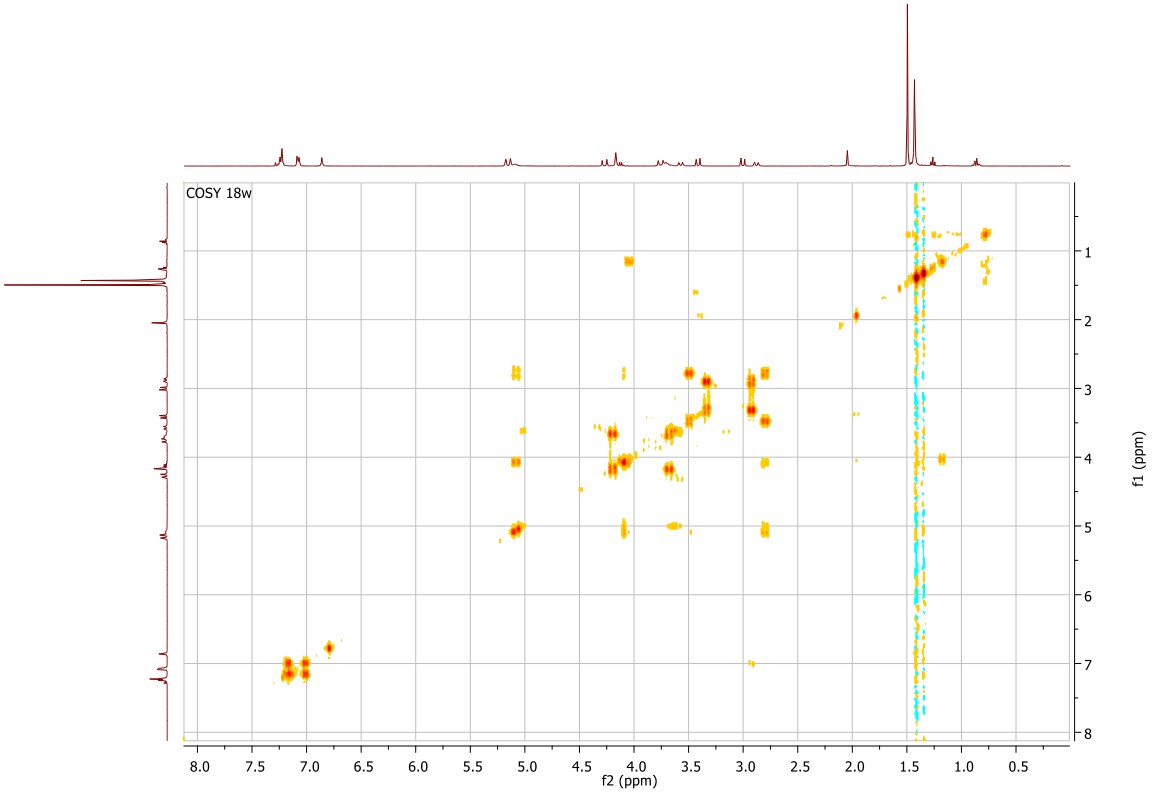
3.2.1 2D NMR Spectra of 18l

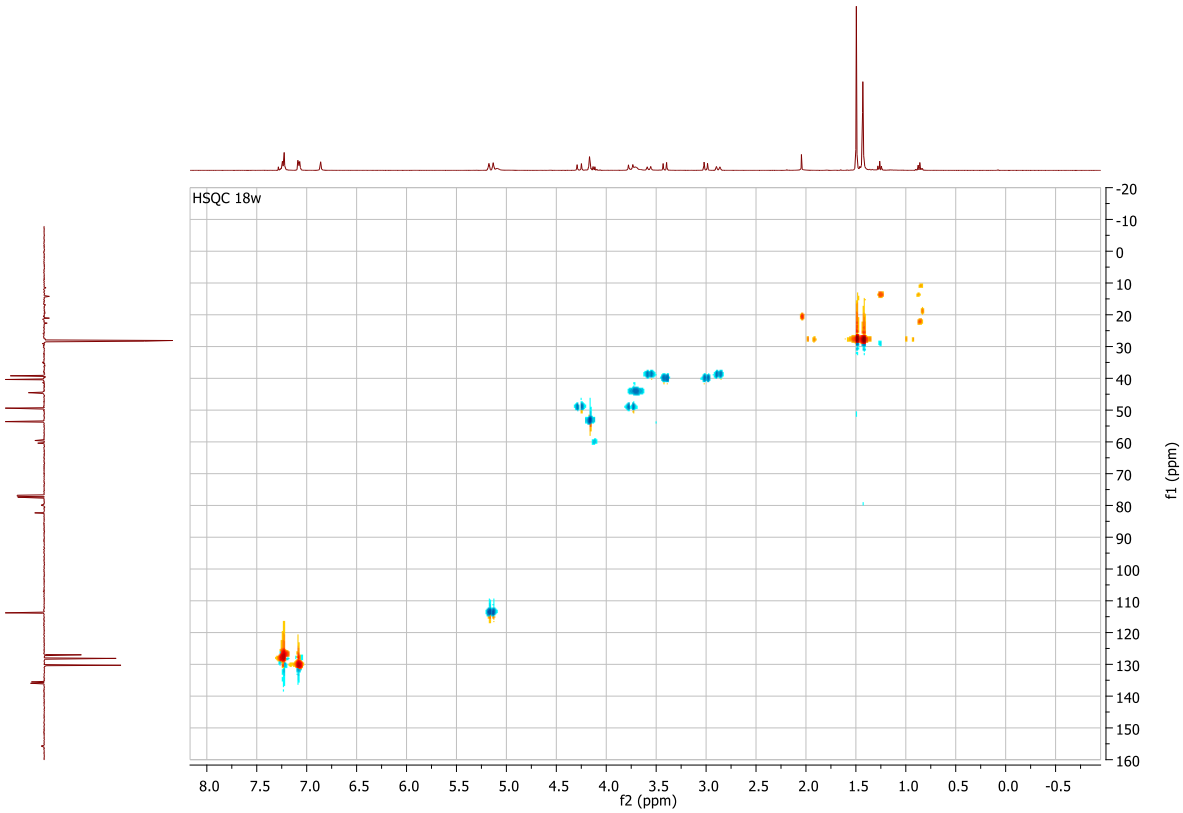


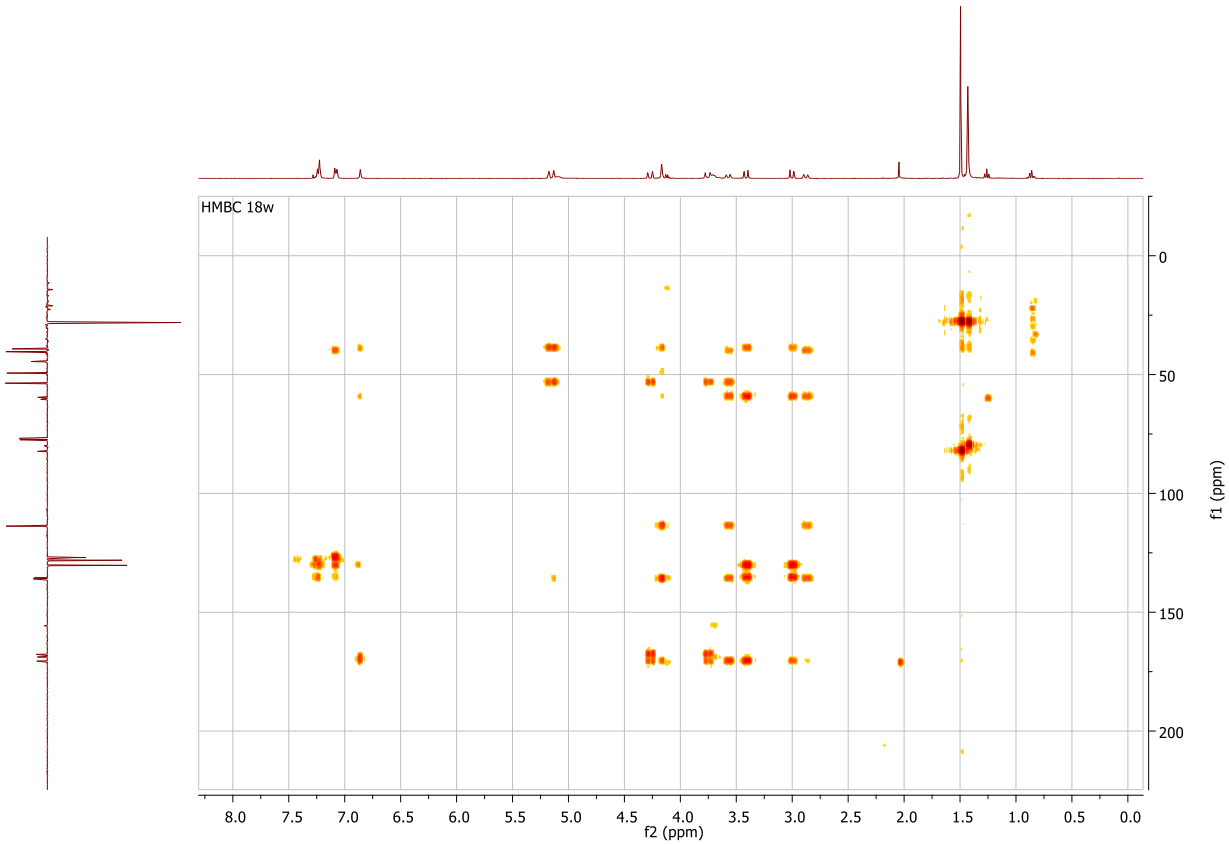




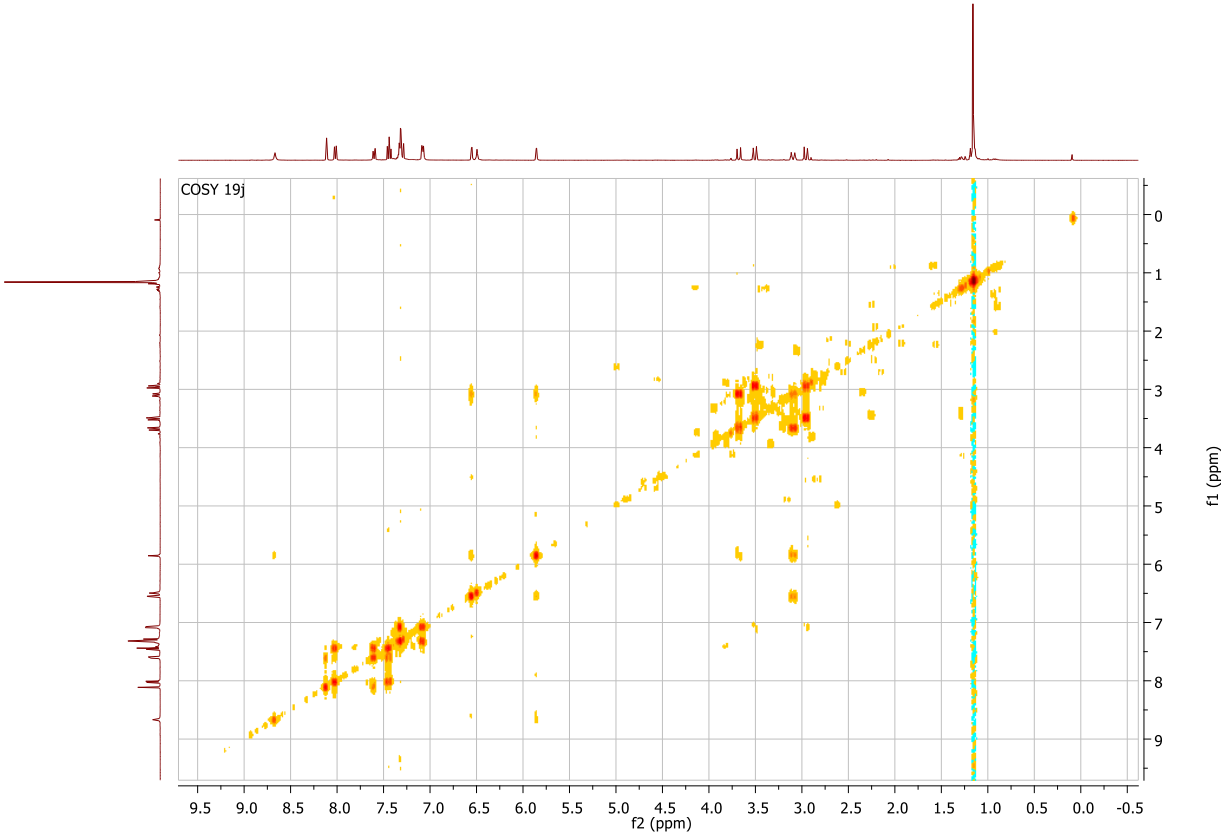
3.2.2 2D NMR Spectra of 18w

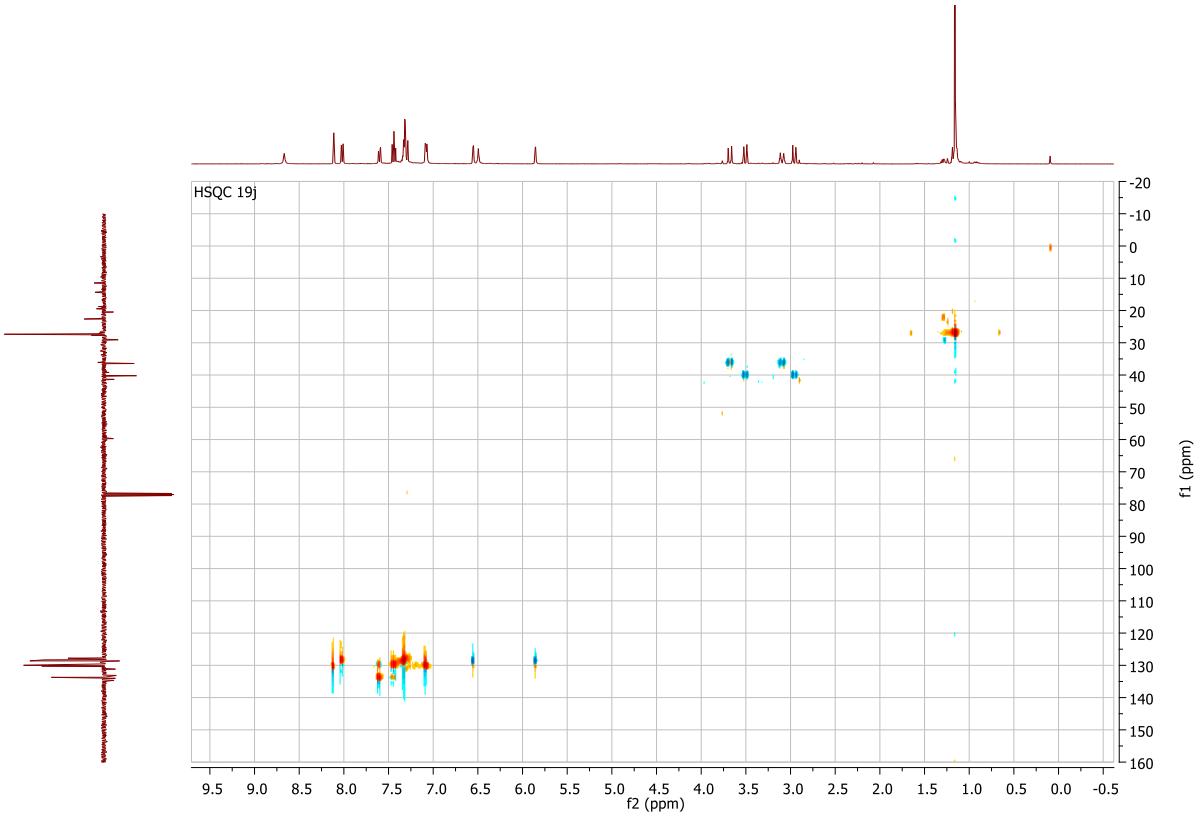


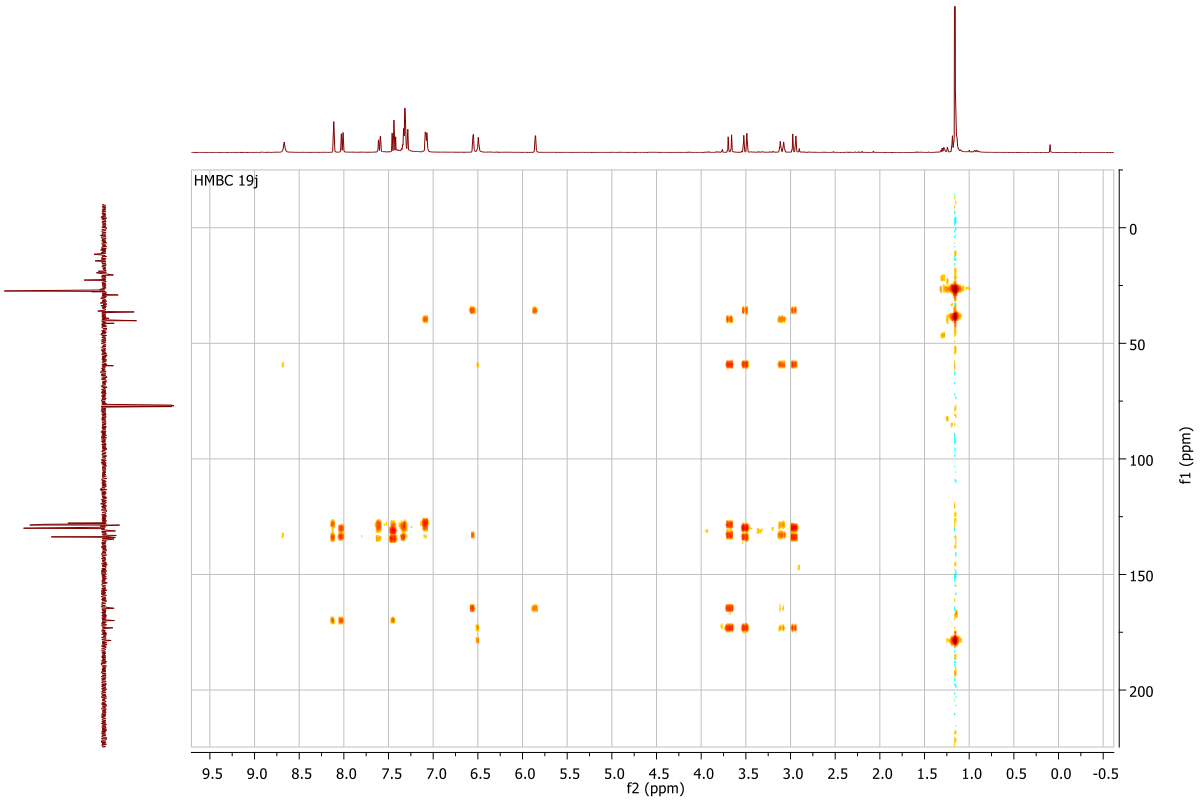

HSQC 18w
f2 (ppm)
f1 (ppm)


HMBC 18w
f2 (ppm)
f1 (ppm)

3.2.3 2D NMR Spectra of 19j







3.2.4. X-Ray Crystallography data for 12h

Table 1 Crystal data and structure refinement for OHJ384_0m.

Identification code	OHJ384_0m
Empirical formula	$C_{20}H_{20}N_2O_2$
Formula weight	320.38
Temperature/K	100.02
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	8.9871(2)
b/Å	17.7991(4)
c/Å	11.3169(3)
α/°	90
β/°	112.3860(10)
γ/°	90
Volume/Å^3	1673.85(7)
Z	4
ρ_{calc}g/cm^3	1.271
μ/mm^{-1}	0.661
F(000)	680.0
Crystal size/mm^3	0.54 × 0.19 × 0.1
Radiation	CuKα (λ = 1.54178)

2Θ range for data collection/°	9.804 to 144.458
Index ranges	-11 ≤ h ≤ 10, -21 ≤ k ≤ 21, -13 ≤ l ≤ 13
Reflections collected	26533
Independent reflections	3284 [R_{int} = 0.0708, R_{sigma} = 0.0420]
Data/restraints/parameters	3284/0/217
Goodness-of-fit on F^2	1.113
Final R indexes [I>=2σ (I)]	R_1 = 0.0617, wR_2 = 0.1535
Final R indexes [all data]	R_1 = 0.0657, wR_2 = 0.1572
Largest diff. peak/hole / e $Å^{-3}$	0.66/-0.48

Table 2 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters ($Å^2$×10^3) for OHJ384_0m. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
O1	3219.6(14)	5358.1(6)	5616.5(11)	14.1(3)
O2	954.1(14)	4381.2(7)	3281.0(11)	14.8(3)
N1	1571.5(17)	4728.5(8)	6338.1(14)	14.0(3)
N2	3583.1(16)	4075.6(8)	4348.8(13)	11.8(3)
C1	3404.2(19)	4006.1(9)	5579.8(15)	10.8(3)
C2	2683.6(19)	4754.3(9)	5829.2(15)	11.4(3)
C3	749(2)	4055.9(10)	6540.2(18)	17.3(4)
C4	1758(2)	3370.9(9)	6637.8(17)	14.9(4)
C5	2370(2)	3314.1(9)	5575.7(16)	13.6(4)
C6	2023(2)	2870.3(11)	7564.6(19)	23.4(4)
C7	2314(2)	4287.8(9)	3288.3(16)	11.8(3)
C8	2666(2)	4402.4(10)	2107.5(16)	14.6(4)
C9	1850(2)	4966.0(11)	1258.4(18)	21.8(4)
C10	2147(3)	5082.3(14)	152.2(19)	30.7(5)
C11	3225(3)	4628.6(15)	-115.9(19)	32.8(5)
C12	4040(3)	4063.5(13)	722(2)	29.3(5)
C13	3780(2)	3957.8(11)	1843.0(18)	20.0(4)
C14	5099(2)	3963.6(9)	6667.6(16)	13.0(3)
C15	6076(2)	3254.2(9)	6774.8(16)	13.1(4)
C16	6282(2)	2740.2(11)	7752.0(18)	19.6(4)
C17	7260(2)	2108.5(11)	7901.2(19)	21.7(4)
C18	8043(2)	1981.6(10)	7081.6(18)	18.2(4)
C19	7853(2)	2491.3(11)	6108.9(19)	21.1(4)
C20	6882(2)	3121.2(11)	5960.5(18)	18.9(4)

Table 3 Anisotropic Displacement Parameters ($Å^2×10^3$) for OHJ384_0m. The Anisotropic displacement factor exponent takes the form: $-2π^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+…]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	14.5(6)	11.6(6)	19.4(6)	0.4(4)	10.0(5)	-0.9(4)
O2	11.0(6)	18.2(6)	17.8(6)	-1.1(5)	8.4(5)	0.4(4)
N1	15.4(7)	13.9(7)	18.0(7)	1.5(5)	12.1(6)	2.9(5)
N2	9.1(7)	16.4(7)	13.5(7)	-0.5(5)	8.3(5)	1.1(5)
C1	10.1(8)	12.5(8)	13.4(8)	0.0(6)	8.5(6)	0.5(6)
C2	10.8(8)	13.8(8)	10.4(7)	0.2(6)	4.9(6)	0.8(6)
C3	16.4(9)	18.7(9)	23.8(9)	5.0(7)	15.4(7)	1.9(7)
C4	13.7(8)	15.2(8)	20.0(9)	1.2(6)	11.1(7)	-0.7(6)
C5	13.5(8)	12.9(8)	17.7(8)	-0.4(6)	9.7(6)	-1.4(6)
C6	26.4(10)	22.2(9)	28.0(10)	8.0(7)	17.5(8)	3.7(7)
C7	13.2(8)	9.9(7)	15.4(8)	-2.0(6)	8.9(6)	-1.9(6)
C8	11.4(8)	20.1(8)	13.4(8)	-3.3(6)	5.8(6)	-6.4(6)
C9	14.9(9)	31.0(10)	18.3(9)	2.7(7)	5.1(7)	-3.2(7)
C10	22.2(10)	49.5(13)	17.7(10)	11.1(9)	4.6(8)	-6.8(9)
C11	23.6(10)	62.0(15)	15.8(9)	0.3(9)	10.8(8)	-15.1(10)
C12	26.7(11)	44.6(13)	24.9(10)	-7.7(9)	19.1(9)	-6.4(9)
C13	20.2(9)	25.1(9)	20.2(9)	-3.3(7)	13.9(7)	-3.8(7)
C14	11.4(8)	14.2(8)	14.3(8)	-0.4(6)	6.0(6)	1.8(6)
C15	9.9(8)	14.4(8)	15.6(8)	1.0(6)	5.4(6)	-0.3(6)
C16	21.0(9)	23.7(9)	19.7(9)	6.9(7)	14.2(7)	6.4(7)
C17	23.2(10)	21.9(9)	24.1(10)	10.3(7)	13.6(8)	7.1(7)
C18	15.4(8)	16.2(8)	23.6(9)	2.2(7)	8.3(7)	4.2(6)
C19	19.8(9)	25.6(10)	24.2(9)	3.8(7)	15.4(7)	6.8(7)
C20	16.7(9)	22.2(9)	22.9(9)	7.6(7)	13.1(7)	4.7(7)

Table 4 Bond Lengths for OHJ384_0m.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O1	C2	1.238(2)	C8	C9	1.389(3)
O2	C7	1.230(2)	C8	C13	1.396(3)
N1	C2	1.331(2)	C9	C10	1.391(3)
N1	C3	1.470(2)	C10	C11	1.381(3)
N2	C1	1.467(2)	C11	C12	1.385(3)
N2	C7	1.357(2)	C12	C13	1.387(3)
C1	C2	1.553(2)	C14	C15	1.516(2)
C1	C5	1.542(2)	C15	C16	1.392(2)
C1	C14	1.553(2)	C15	C20	1.393(2)

C3	C4	1.498(2)	C16	C17	1.397(3)
C4	C5	1.504(2)	C17	C18	1.380(3)
C4	C6	1.327(3)	C18	C19	1.386(3)
C7	C8	1.500(2)	C19	C20	1.391(3)

Table 5 Bond Angles for OHJ384_0m.

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
C2	N1	C3	126.90(14)	N2	C7	C8	115.74(14)
C7	N2	C1	120.26(13)	C9	C8	C7	118.66(16)
N2	C1	C2	107.72(12)	C9	C8	C13	119.59(17)
N2	C1	C5	110.39(13)	C13	C8	C7	121.74(16)
N2	C1	C14	109.13(13)	C8	C9	C10	119.88(19)
C2	C1	C14	104.39(13)	C11	C10	C9	120.1(2)
C5	C1	C2	113.14(13)	C10	C11	C12	120.43(18)
C5	C1	C14	111.80(13)	C11	C12	C13	119.7(2)
O1	C2	N1	121.73(15)	C12	C13	C8	120.24(19)
O1	C2	C1	119.27(14)	C15	C14	C1	117.84(13)
N1	C2	C1	118.88(14)	C16	C15	C14	120.60(15)
N1	C3	C4	110.37(13)	C16	C15	C20	117.92(16)
C3	C4	C5	113.03(14)	C20	C15	C14	121.34(15)
C6	C4	C3	121.74(16)	C15	C16	C17	120.83(17)
C6	C4	C5	125.21(16)	C18	C17	C16	120.58(17)
C4	C5	C1	110.32(13)	C17	C18	C19	119.13(17)
O2	C7	N2	122.82(15)	C18	C19	C20	120.34(17)
O2	C7	C8	121.45(15)	C19	C20	C15	121.19(17)

Table 6 Hydrogen Bonds for OHJ384_0m.

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
N1	H1	O2[1]	0.88	2.24	2.9315(18)	134.7

[1]-X,1-Y,1-Z

Table 7 Torsion Angles for OHJ384_0m.

A	B	C	D	Angle/˚	A	B	C	D	Angle/˚
O2	C7	C8	C9	35.0(2)	C6	C4	C5	C1	-122.12(19)
O2	C7	C8	C13	-144.82(17)	C7	N2	C1	C2	-52.60(18)
N1	C3	C4	C5	-49.1(2)	C7	N2	C1	C5	71.38(18)
N1	C3	C4	C6	132.38(18)	C7	N2	C1	C14	-165.37(14)

N2	C1	C2	O1	-43.97(19)	C7	C8	C9	C10	-179.68(17)
N2	C1	C2	N1	139.98(15)	C7	C8	C13	C12	177.97(17)
N2	C1	C5	C4	-162.45(13)	C8	C9	C10	C11	1.4(3)
N2	C1	C14	C15	-70.69(17)	C9	C8	C13	C12	-1.8(3)
N2	C7	C8	C9	-145.16(16)	C9	C10	C11	C12	-1.1(3)
N2	C7	C8	C13	35.1(2)	C10	C11	C12	C13	-0.6(3)
C1	N2	C7	O2	-5.0(2)	C11	C12	C13	C8	2.0(3)
C1	N2	C7	C8	175.13(13)	C13	C8	C9	C10	0.1(3)
C1	C14	C15	C16	-106.62(19)	C14	C1	C2	O1	71.95(18)
C1	C14	C15	C20	77.9(2)	C14	C1	C2	N1	-104.10(16)
C2	N1	C3	C4	24.5(2)	C14	C1	C5	C4	75.87(17)
C2	C1	C5	C4	-41.65(18)	C14	C15	C16	C17	-176.12(17)
C2	C1	C14	C15	174.38(13)	C14	C15	C20	C19	176.20(17)
C3	N1	C2	O1	174.70(15)	C15	C16	C17	C18	0.0(3)
C3	N1	C2	C1	-9.4(2)	C16	C15	C20	C19	0.6(3)
C3	C4	C5	C1	59.46(19)	C16	C17	C18	C19	0.3(3)
C5	C1	C2	O1	-166.27(15)	C17	C18	C19	C20	-0.2(3)
C5	C1	C2	N1	17.7(2)	C18	C19	C20	C15	-0.3(3)
C5	C1	C14	C15	51.72(19)	C20	C15	C16	C17	-0.5(3)

Table 8 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for OHJ384_0m.

Atom	*x*	*y*	*z*	U(eq)
H1	1299.69	5159.87	6579.25	17
H2	4517.24	3979.26	4297.84	14
H3A	-300.36	3997.41	5819.08	21
H3B	543.57	4113.99	7334.82	21
H5A	1449.21	3281	4744.77	16
H5B	3023.23	2852.21	5685.57	16
H6A	1567.9	2941.35	8188.8	28
H6B	2668.01	2440.83	7604.02	28
H9	1090.66	5271.36	1432.79	26
H10	1607.08	5474.52	-419.67	37
H11	3408.67	4704.62	-880.12	39
H12	4772.86	3749.65	530.12	35
H13	4363.23	3581.37	2432.73	24
H14A	5739.02	4392.48	6562.25	16
H14B	4967.26	4036.39	7489.65	16
H16	5751.68	2819.91	8324.49	23
H17	7386.69	1763.31	8572.99	26
H18	8703.37	1550.56	7182.72	22

H19	8389.1	2410.08	5540.62	25
H20	6766.78	3466.74	5291.54	23

1.

Crystal structure determination of OHJ384_0m

Crystal Data for $C_{20}H_{20}N_2O_2$ (*M* =320.38 g/mol): monoclinic, space group $P2_1/c$ (no. 14), *a* = 8.9871(2) Å, *b* = 17.7991(4) Å, *c* = 11.3169(3) Å, *β* = 112.3860(10)°, *V* = 1673.85(7) $Å^3$, *Z* = 4, *T* = 100.02 K, μ(CuKα) = 0.661 mm^{-1}, *Dcalc* = 1.271 g/cm^3, 26533 reflections measured (9.804° ≤ 2Θ ≤ 144.458°), 3284 unique (R_{int} = 0.0708, R_{sigma} = 0.0420) which were used in all calculations. The final R_1 was 0.0617 (I > 2σ(I)) and wR_2 was 0.1572 (all data).

Refinement model description

Number of restraints - 0, number of constraints - unknown.

3.3 References

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