New Strategies for the Synthesis of Constrained Peptides

Wenzheng Gao

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy

The University of Sheffield
Department of Chemistry

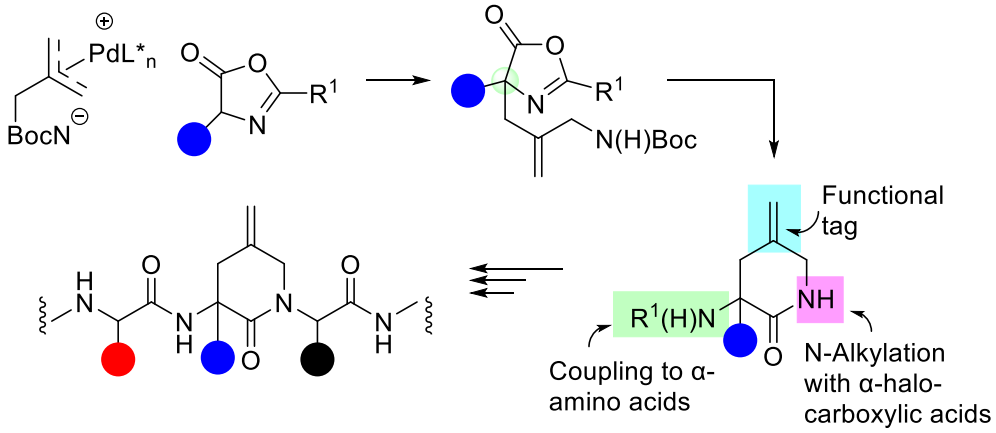
July 2023

Abstract

This thesis documents the synthesis of α-amino acid building blocks using a readily available carbamate as starting material via a Pd-catalyzed asymmetric allylation reaction.

This method produces lactams bearing a range of polar and hydrophobic side chains, and can be used to synthesize di-peptidomimetic containing Freidinger lactams directly. In addition, a mild hydrolysis protocol via a phthalimide intermediate allows the transformation of azlactones into the corresponding free amine containing constrained amino acid building blocks through a simple three step sequence, generating the products in good yield and enantiocontrol.

Further studies demonstrated that tri-peptidomimetics based on MIF-1 and RGD can be synthesized with these Freidinger lactams, and the former analogue had a stable βII-turn structure. Finally, the olefin on the Freidinger lactam building blocks can be modified into other functional groups showing the synthetic tractability of the method.



Acknowledgements

"Long, long is my road, and far, far is the journey; high and low, up and down, I'll search with will."

路漫漫其修远兮，吾将上下而求索

Joe - You are the most responsible and patient professor I have ever met. Your erudition and passion for your work have had a profound impact on me and motivate me to keep going. I remember I had just attended a question group meeting. I feeled very strenuous and even a little tired of learning these chemical mechanisms, but your patient guidance inspired me to keep learning and reading chemistry books, and gradually enjoying it. I was so thankful that you were always available in the office when I had problems and that you always gave me lots of helpful advice to overcome my challenges. You always patiently helped me revise sentence by sentence, and gave me a lot of writing suggestions so that I can concentrate on doing experiments without the pain of writing. I'm really really really grateful to you and really really really lucky to have you as my supervisor. There is an old Chinese saying: "A teacher for one day, a father for life." You are not only my supervisor I respect, but also an elder I respect and love.

Mum and Dad - 谢谢你们为我所付出的一切。我记得当你们送我出国时，你们的眼里噙满了泪水。真的很抱歉让你们担心我。你们一直在背后默默支持我，给予我最大的尊重和自由去追求和拥抱我的梦想。我很幸运也很自豪有你们这样的父母。记得在一本书上写道：“所谓父女母子一场，只不过意味着，你和他的缘分就是今生今世不断地在目送他的背影渐行渐远。”回首这么多年，我只是一意孤行没有考虑过你们的感受，直到看见你们的皱纹，我才意识到今生似乎无以为报。 希望我成为了你们心中值得自豪的孩子。 我爱你们，我的父亲母亲。Thank you for everything you do for me. I remember the tears were in your eyes when you sent me abroad. I'm really sorry for making you worry about me. You have been silently supporting me behind the scenes, giving me the utmost respect and freedom to pursue and embrace my dreams. I am lucky and proud to have parents like you. I remember writing in a book: " The so-called parents-children relationship just means that the fate between you and them is that you are constantly watching their back gradually drifting away in this life." Looking back on so many years, I just insisted on walking my own path without considering your feelings into. It wasn't until I saw your grey hair that I realized I have been unable to make any recompense. Only hope I have become the child you can be proud of. I love you, my mum and dad.

Jiaxin - You are an incredibly strong and hardworking girl. Over the years, we have supported each other through many ups and downs. I remember when we started

our project, we were so unfamiliar with everything, and even smattering about the use of experimental instruments. However, we always firmly believe that there was no challenge we can't overcome as long as the two of us were together. Because of you, my abroad study life is full of warmth and beauty. Because of you, I understand what responsibility is. Thank you for always being by my side and facing the world with me.

Fernando - You are my role model. You are an unbelievable hard-working man. I remember when I first came here, your appearance of working day and night left a deep impression on me and I used this as a standard to demand myself. At the beginning of my project, you always patiently helped me solve the problems I encountered. Your sophisticated experimental skills can always inspire and help me a lot in my experiments. Your scheduling of lab items makes me can focus on my experiments. Your rich chemical knowledge reserve inspires me to keep learning. In all, you are my mentor.

Larry - You are such a gentle and helpful man. You even came to the lab specifically to help us to address experimental problem. You're always joking with us to ease the seriousness of the lab. When I first came, I rarely communicated with team members because everything was unfamiliar, but you always chatted with me. I remember once when I was purifying the product, you called me Mr Column because you saw that I always used flash column chromatography. Anyway, you made me feel very relaxed and ease. Although you ended your work in the laboratory very early, but you left a deep impression on me.

Sophie - Thank you for starting this project. You did a lot of preliminary experiments and left precious experimental data. These data provided great help to my experiments and saved me from many detours.

Dan - As the only postdoc of our lab, you assumed responsibility for the safety of the entire laboratory. Thank you so much for everything you did for this lab. Your rich experimental experience helped me solve many problems and I always got something every time when I discussed chemistry with you.

Dr. Craig - I am very very grateful for your help with the recrystallization. I kept seeking your help because of the recrystallization failure, and you always answered my questions patiently and gently. You are a very responsible academic. In order to help me get more accurate x-ray data, you even send my sample to the National Facility by yourself. You always have a smile on your face, so I feel relaxed and happy every time I meet you. Anyway, thank you so much for all you did.

Dr. Khalid - Thank you for your help with nmr analysis. Every time you met me in the nmr room, you always asked me whether I had any problems. You always gave me the thumbs up when I said no problem, which makes me feel interesting and warm. I remembered once I complained to you that many nmr samples were waiting to be analysed. You seem to see that I need nmr data urgently. Although you didn't say

anything, I got my results 5 minutes after I got back to the lab. I am very, very lucky to be able to conduct research under the help of an academic like you.

Jingyi Wang, Xinyu Zhao– My beeeesssssst friend !!!! We've been friends since high school. Meeting you is the greatest luck in my life. Even the matter of going abroad was decided by me after you jerked me around. I remember that Zhao jerked me to say IELTS was easy to pass and Wang also agreed with Zhao. It wasn't until I started preparing that I realized they were also hearsay. As a person with no language talent, it was a difficult time! ! ! It can be said that you two friends changed my life. Although there was a time difference between us, whenever I met troubles, you always putted down your work and listen to my complaints. Thank you for being by my side for so many years.

Robbie - Thank you for your help with HPLC. I was very touched when I used the wrong solvent and the instrument was temporarily unusable, and you didn't complain, but accompanied me to solve the problem. Finally, he accompanied me to purify the sample. In short, thank you for your help, let me finish the project perfectly.

All team member - Thank you for all you did for the lab. With your help, I can concentrate on my experiment and not be disturbed by other trivial matters.

All technician - Thank you for the maintenance and repair of the experimental equipment. With your help, my experiment was able to proceed smoothly.

Everyone I met in my life - The staff who bought my tube tickets for me when I first came to the UK, the strangers who helped me pay for my transport (lost my wallet on the way home), the waiter who picked up my lost bag and returned it to me and Passers-by who smile at me when I walk on the road, you made me believe that the world is full of beautiful and kind. I believe in these wonderful qualities and will spend the rest of my life putting **them** into action.

Myself - The process of learning is actually a process of enduring loneliness and resisting temptation. Thanks for my persistence and hard work over the years. **“**The most precious thing for people is life, and life is only once for people. A person's life should be spent in this way: when he looks back on the past, he will not regret for being mediocre and wasting his time, nor will he feel guilty for being a despicable person and living a vulgar life.” I will spend my life taking these words and putting them into action.

Abbreviations

Ac	Acetyl
ACN	Acetonitrile
Ar	Aryl
aq	Aqueous
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
^{i}Bu	isobutyl
^{t}Bu	*tert*-Butyl
Cbz	Carboxybenzyl
DAAA	Decarboxylative Asymmetric Allylic Alkylation
Dba	dibenzylideneacetone
DCM	Dichloromethane
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DIPEA	*N*,*N*-Diisopropylethylamine
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide.HCl
ee	Enantiomeric excess
eq.	Equivalents
EWG	Electron-Withdrawing Group

h	Hour(s)
HRMS	High Resolution Mass Spectrometry
RGD	Arginylglycylaspartic acid
L	Ligand
LCMS	Liquid Chromatography Mass Spectrometry
m.p.	Melting point
MIF	Melanocyte-inhibiting factor
Ms	Methanesulfonyl
NMR	Nuclear magnetic resonance
Nu	Nucleophile
Pbf	pentamethyldihydrobenzofuran-5-sulfonyl
R	Generic carbon-containing group
RT	Room Temperature
SN1	Nucleophilic Substitution, First Order
SN2	Nucleophilic Substitution, Second Order
TFA	2,2,2-Trifluoroacetic acid
THF	Tetrahydrofuran
TMS	Trimethylsilyl

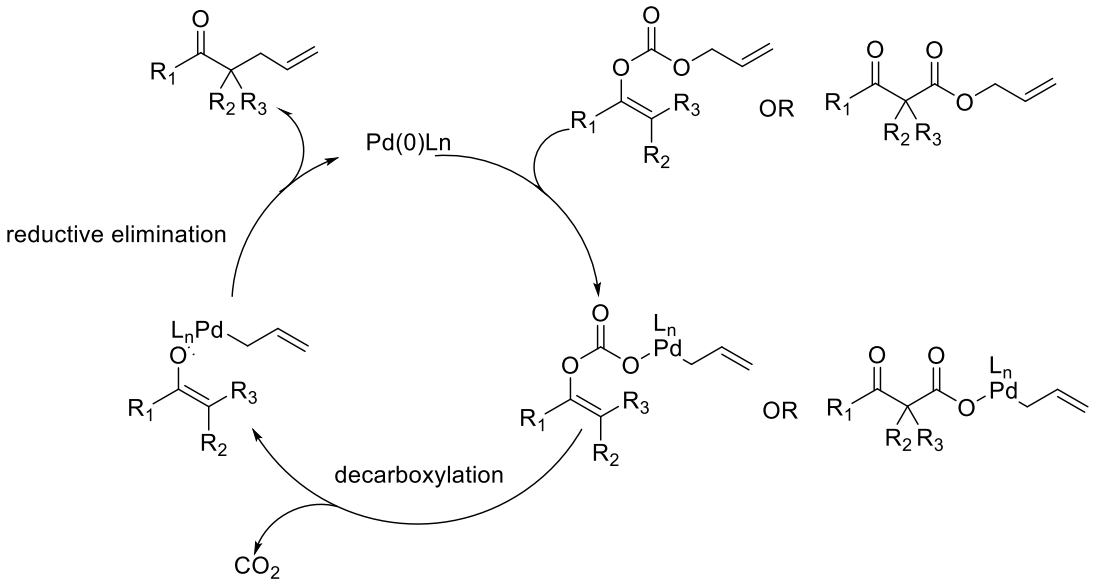
Table of Contents

1. Introduction

1.1. Palladium-Catalysed Decarboxylative Asymmetric Allylic Alkylation (DAAA)

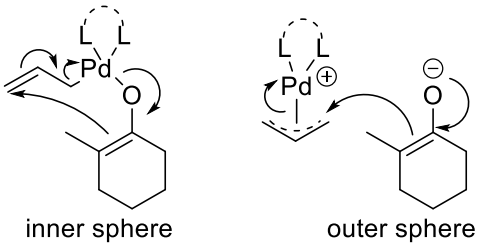
In 1980, Tsuji et al. first reported that allyl acetoacetate can rearrange in THF under $Pd(OAc)_2$ and PPh_3 catalysis to produce γ,δ-unsaturated methyl ketones.[1] In the following years, although the Tsuji group and others extended the reaction scope and demonstrated that the reaction offered excellent regioselectivities, the enantioselectivity of such reactions has only begun to be studied in the past 20 years.

The accepted DAAA mechanism consists of three steps (**Scheme 1.1**). The first step is the process of oxidative addition. In this step, the Pd(0) complex coordinates with the allyl fragment and ionization of the allylic carbonate takes place. Decarboxylation is the second step. In this step, a Pd(II) enolate is formed by releasing CO_2. In the last step, the intermediate allyl Pd(II) enolate undergoes reductive elimination to form the final product and the Pd(0) complex can be regenerated at the same time. In this process, the specific mechanism and enantioselectivity will be influenced by the type of ligand and other factors (such as solvents, additives, temperature, and so on). [2]



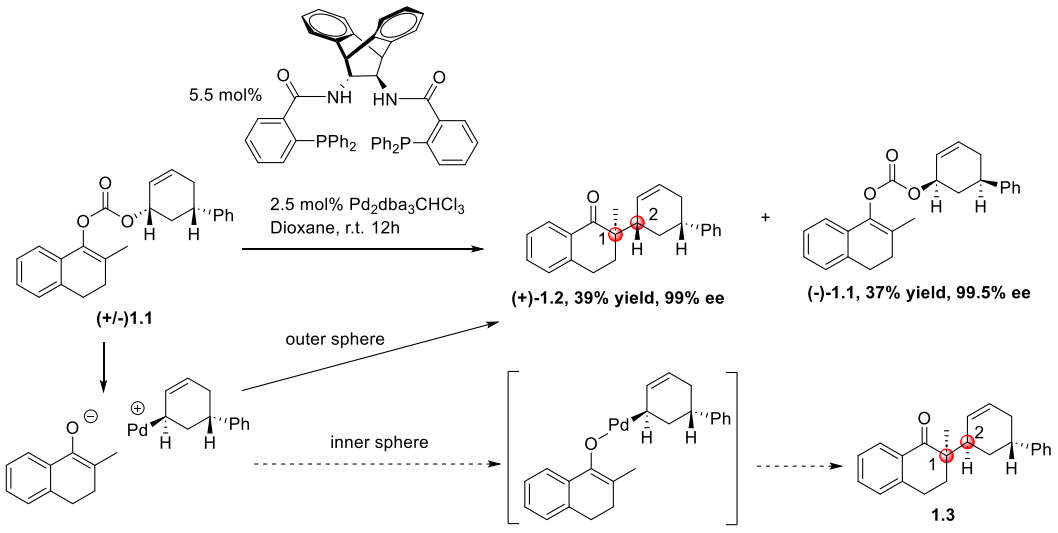
Scheme 1.1

The controversial part of DAAA mechanism is whether the reductive elimination occurs via an inner sphere or outer sphere mechanism (**Scheme 1.2**). Although there is general acceptance that pro-nucleophiles with pKa<25 participate in outer sphere alkylation, the picture is quite complex and the precise mechanism depends on many factors.[3]



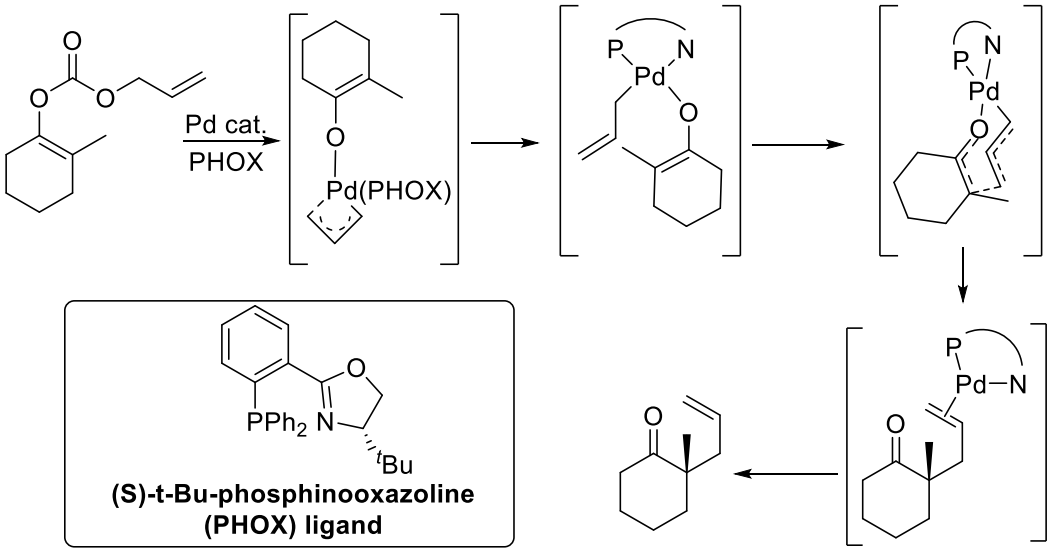
Scheme 1.2

In 2009, the Trost group studied the reductive elimination step of the DAAA by using stereochemical probes and they reported that a nearly perfect kinetic resolution was observed which supports the outer sphere mechanism (**Scheme 1.3**).[4] The study showed that one enantiomer of **(+/-)-1.1** was converted to the allylation product **(+)-1.2** but the other enantiomer did not react. They further discovered that the relative stereochemistry of the C1-methyl group and C2-H of **(+)-1.2** derived from an outer sphere elimination because if elimination reaction occurred via inner sphere, the C1-methyl group and C2-H could be on the same side, as drawn (**product 1.3)**.



Scheme 1.3

Computational studies performed by the Stoltz group demonstrated that the DAAA reaction between hard prochiral enolate nucleophiles and non-prochiral allyl groups using (*S*)-*t*-Bu-phosphinooxazoline (PHOX) ligand occurred via an inner sphere pathway, which was different from outer sphere DAAA reaction between soft enolate nucleophiles and prochiral allyl fragments (**Scheme 1.4**).[5] They also proposed a seven-membered intermediate that operated during the reductive elimination step, highlighting the possibility of inner-sphere reductive elimination.

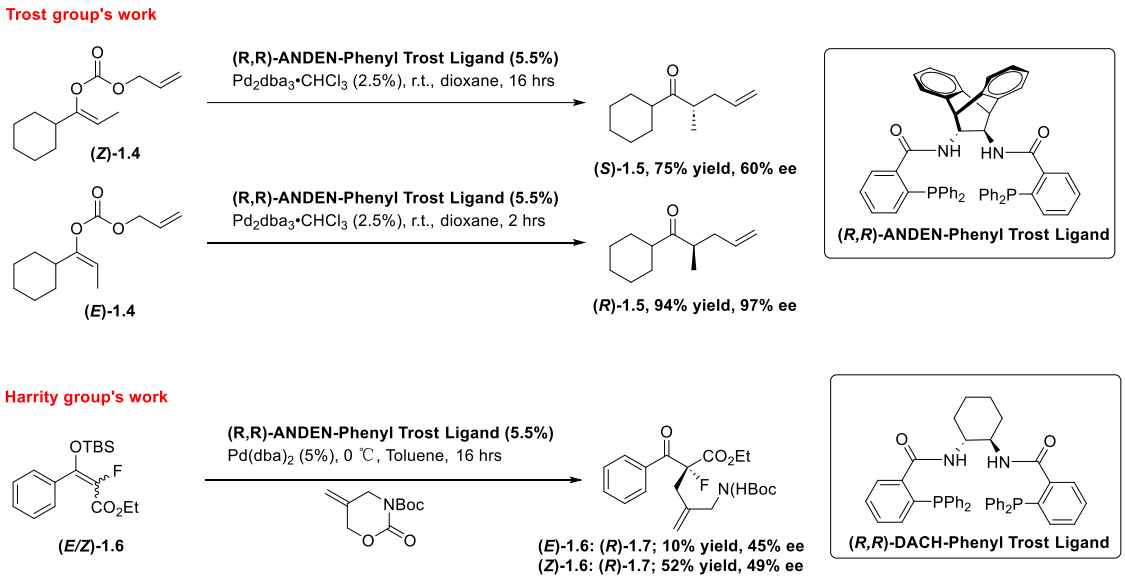


Scheme 1.4

In general, although opinions differ on the nature of the reductive elimination step, the general mechanism of DAAA reaction is almost always the same. However, further studies of the DAAA mechanism will continue to help us understand the structure of key intermediates which can help in the optimisation of enantioselective conditions.

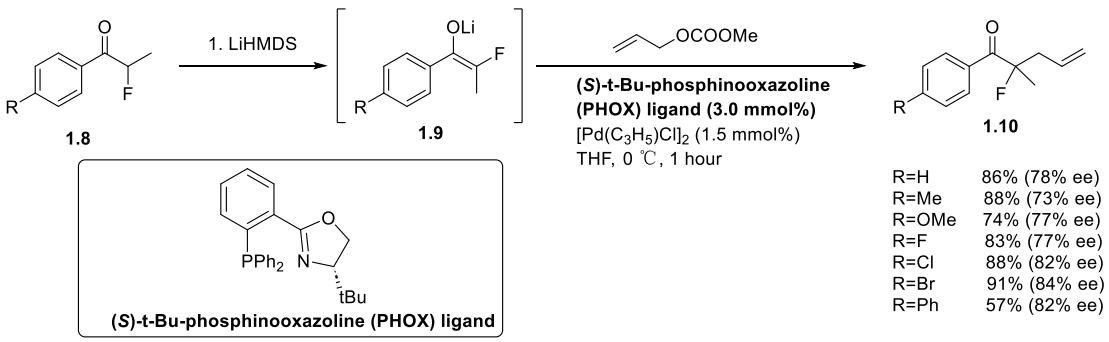
The Trost group discovered that the cis-trans isomerism of enolate carbonates played a vital role in the DAAA reaction (**Scheme 1.5**).[6] In this case, two enol carbonate isomers showed different stereochemical outcomes under the same enantioselective conditions. The reaction of **(*E*)-1.4** afforded one enantiomer product **(*R*)-1.5** with high yield and high ee but **(*Z*)-1.4** afford the other enantiomer product **(*S*)-1.5** with a lower yield and selectivity. The Harrity group also observed the similar situation

when they used **(*E/Z*)-1.6** as substrates.[7] Although the cis-trans isomerism did not influence the enantioselectivity, the yield decreased from 52% to 10%. Overall, these results suggest that single enol isomers should be used when carrying out enantioselective DAAA reactions.



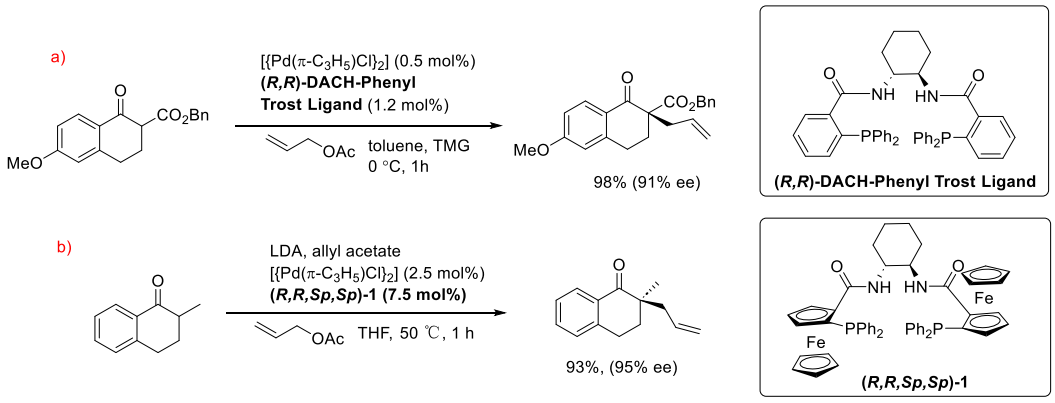
Scheme 1.5

α-Disubstituted ketones have been used in the DAAA reaction to generate the corresponding α-quaternary substituted allylation products. The Wang group used the 2-fluoropropiophenone **1.8** as a substrate to afford α-carbonyl tertiary alkyl fluorides **1.10** with useful yield and ee values (**Scheme 1.6**).[8] It was worth noting that they pre-formed the enolate intermediate **1.9** using LiHMDS, and that this enolate intermediate participate in the DAAA reaction as a single *Z*-isomer.



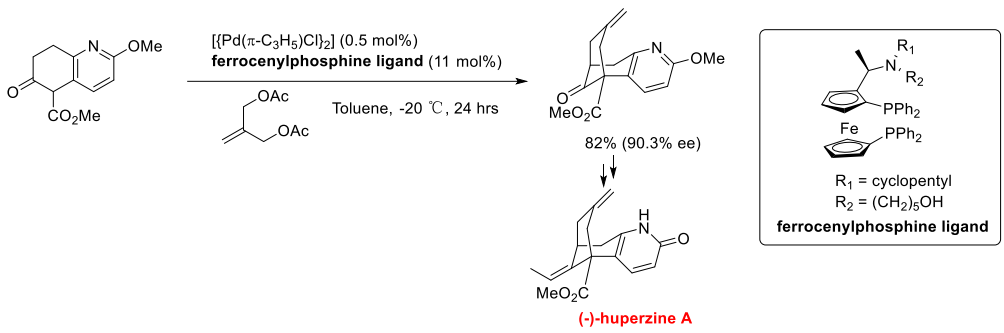
Scheme 1.6

Cyclic ketoesters have also been widely employed in the DAAA reaction. In 1997, the Trost group reported that the enantioselectivity could be significantly enhanced by adding *N*,*N*,*N*',*N*'-tetramethylguanidinium (TMG) as an basic additive in the allylation of α-tetralones, but the enantioselectivity was only between -16 and 70 by using other basic additives (NaH, *n*-C_4H_9Li, Na_2CO_3), which can suggest that optimising enantioselectivity is not limited to solvent, ligands and reaction temperature (**Scheme 1.7 a**).[9] Although β-keto esters are excellent substrates for decarboxylative asymmetric allylic alkylation with the standard Trost ligand, ketone enolates are not ideal. In 2001, You et al. published a more efficient ligand (**(*R,R,Sp,Sp*)-1**) which can afford allylation products with high ee values (up to 95% ee, **Scheme 1.7 b**).[10]



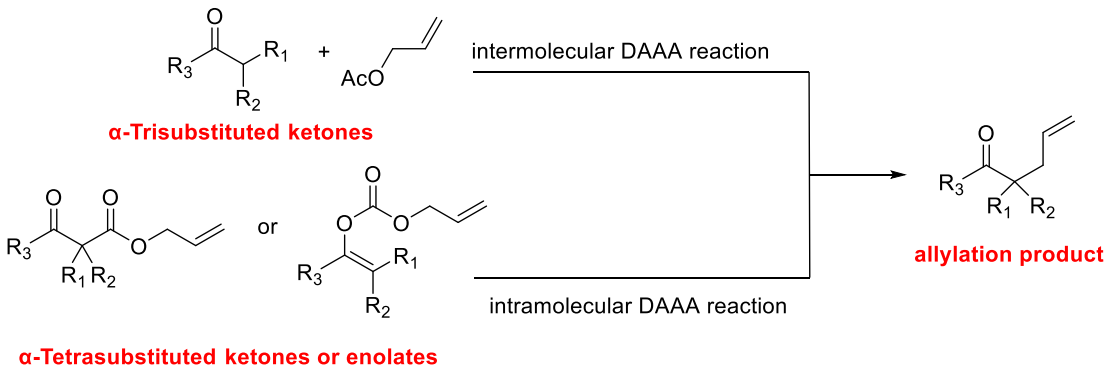
Scheme 1.7

Interestingly, He and Wang et al. reported the synthesis of a double allylation product, a crucial intermediate in the total synthesis of (-)-huperzine A, with high enantioselectivity and yield (**Scheme 1.8**).[11]



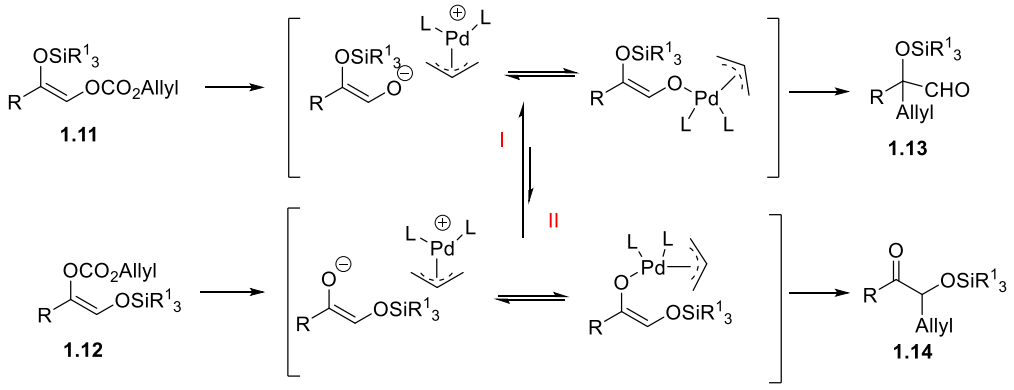
Scheme 1.8

α-Trisubstituted ketones or their enolates can also be used in the DAAA reaction. These are distinguished from α-tetrasubstituted ketones or enolates by the difference between an intermolecular reaction and a formal intramolecular reaction (**Scheme 1.9**). Carbonate as a functional group replaces the H on the α-C of disubstituted ketones to form a trisubstituted substrate or the corresponding enolate. Intramolecular reactions usually occur rapidly and the ratio of nucleophilic fragments to electrophilic fragments is strictly 1:1, which can suppress side reactions caused by excess substrate.



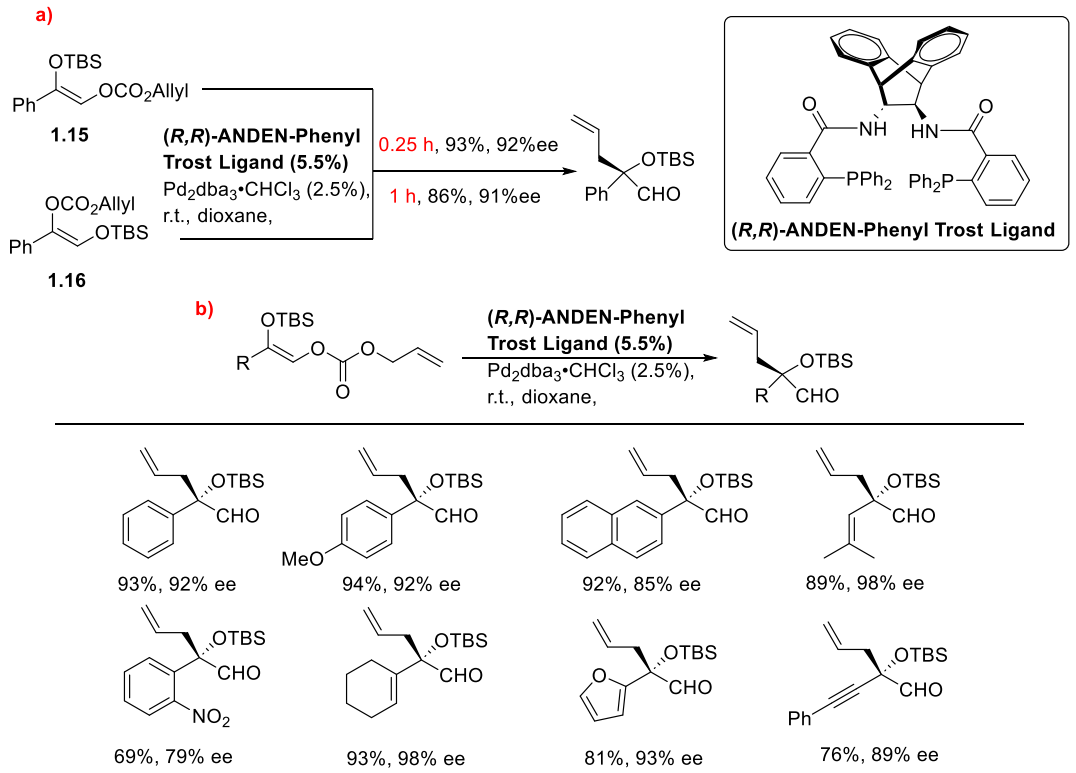
Scheme 1.9

An interesting example of this chemistry was reported by the Trost group who investigated the regioselectivity of allylation of α-hydroxycarbonyl derivatives (**Scheme 1.10**).[12]In this case, **1.11** and **1.12** can be converted into isomeric enolates that lead to products **1.13** or **1.14**. The Trost group speculated that there was an equilibrium between intermediates I and II. Considering that the stability of I was higher than II, the product **1.13** should be the thermodynamic product which required the rate of allylation to be slower than the rate of equilibration. They speculated that the rate difference of allylation versus equilibration could be influenced by the ligand and the size of the silyl group.



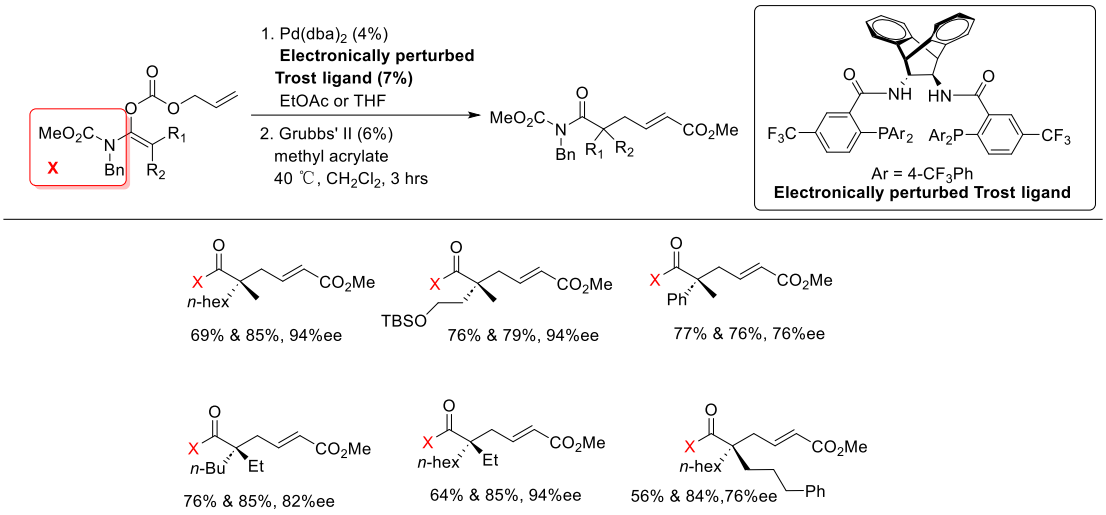
Scheme 1.10

In practice, the two enol carbonates gave the same product, although the reaction rates were quite different. As shown as **Scheme 1.11 a)**, the reaction rate of **1.15** is faster than that of **1.16** although the yield and enantioselectivity were not significantly different. This was reasonable, considering that **1.16** needed to undergo a silyl transfer step to form the allylation product. The scope of this process was broad, and afforded a series of products with high yield and enantioselectivities (**Scheme 1.11 b**).



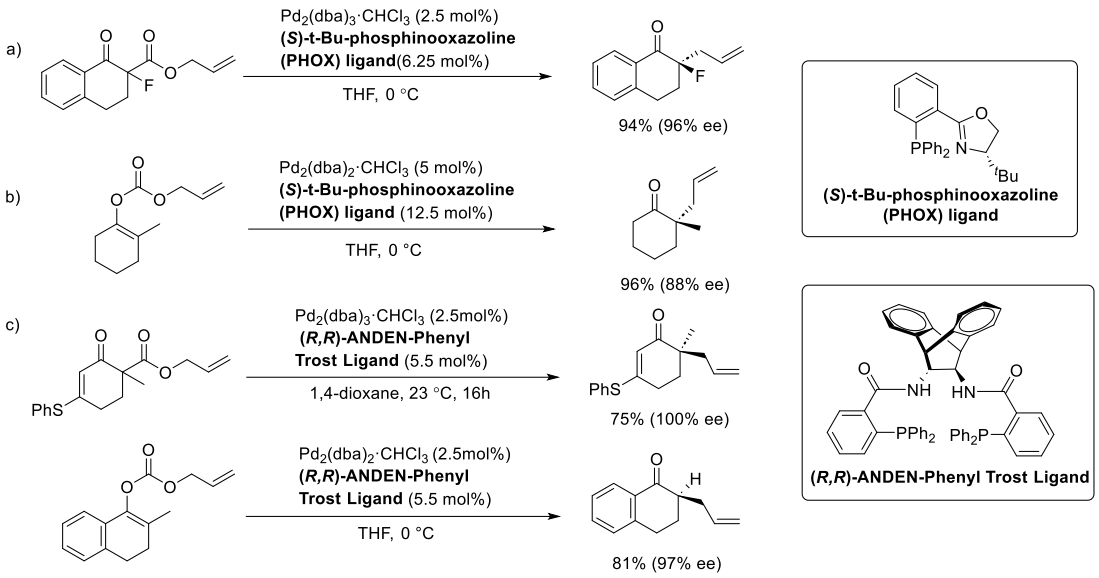
Scheme 1.11

Stoltz reported a new class of amide enolates and applied them in the DAAA reaction to generate a new carbon backbone with quaternary carbon stereocenter (**Scheme 1.12**).[13] This methodology afforded highly enantioselective products by using a novel electronically perturbed Trost ligand.



Scheme 1.12

As with α-substituted cyclic ketones, α-substituted cyclic keto esters and enol carbonates are also prevalent in asymmetric allylation reactions. The Nakamura group reported that α-fluoro-β-keto esters can be allylated to afford α-fluoro-β-allyl ketones with high enantioselectivity (**Scheme 1.13 a**).[14] The Behenna group demonstrated that 1-cyclohexenyl allyl carbonates can undergo the DAAA reaction to provide the corresponding allylation products with high ee (**Scheme 1.13 b**).[15] Similar reactions with very high enantioselectivities were published by the Trost group (**Scheme 1.13 c**).[16]

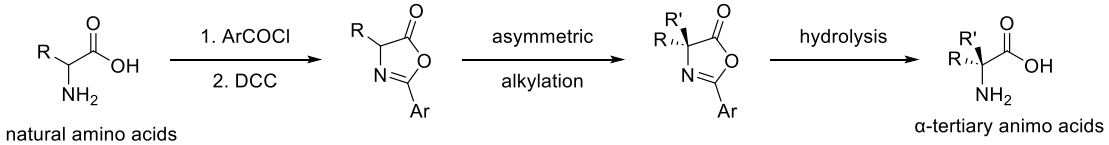


Scheme 1.13

In summary, a large number of studies have demonstrated that the DAAA reaction is a powerful method to generate chiral quaternary stereocenters on carbon backbones. This makes the synthesis of many natural products and small molecule drug scaffolds possible.

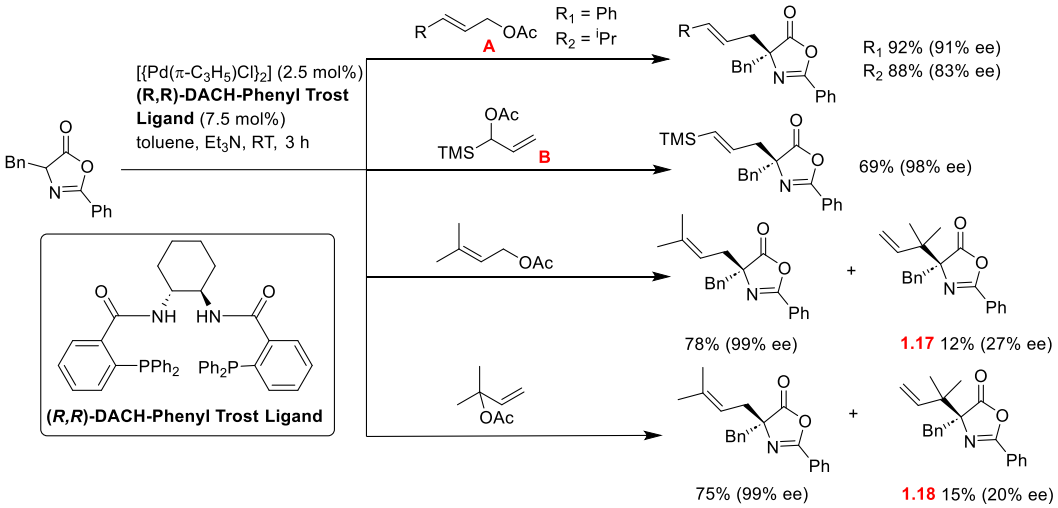
1.2 The application of azlactones in DAAA reaction

Azlactones have proven to be a powerful class of substrates for the synthesis of unnatural amino acids bearing quaternary *C*-stereocenters (**Scheme 1.14**).[3] Although the azlactones can be readily synthesised from commercial natural amino acids, they racemize in this process. Thus, the enantioselective DAAA reaction offers an effective method to address this problem.



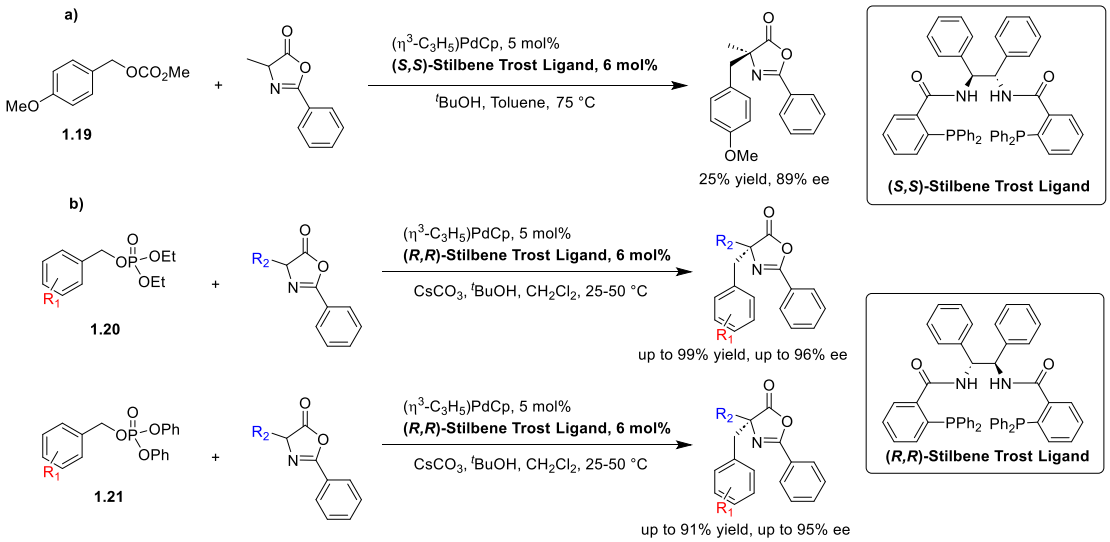
Scheme 1.14

The Trost group reported using β-benzyl azlactones as substrates in the DAAA reaction (**Scheme 15**).[17] Compared with linear allylic acetates **A**, the reactions with branched substituted allylic acetates **B** had higher ee values. They also discovered that the nucleophilic fragment (azlactones) could attack the more substituted carbon of the allyl group, this results in the generation of the di-tertiary products **1.17, 1.18** albeit in minor amounts which were recovered in low yield with poor enantioselectivity.



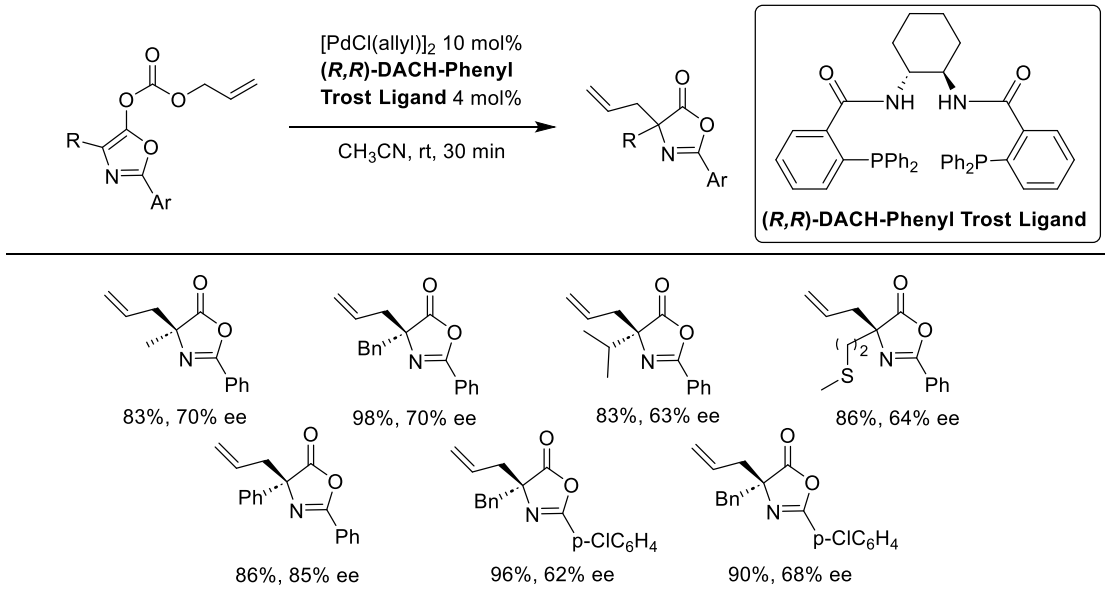
Scheme 1.15

Phosphates were introduced as replacements for carbonate by the Trost group in 2012.[18] When *p*-methoxybenzyl methyl carbonate **1.19** was used for allylating azlactones, the yield was low although the enantioselectivity was high (**Scheme 1.16 a**). When using phosphates **1.20**, **1.21** that exhibit higher reactivity, adding Cs_2CO_3 and ^tBuOH can significantly improve the yield and enantioselectivity of the reaction (**Scheme 1.16 b**).



Scheme 1.16

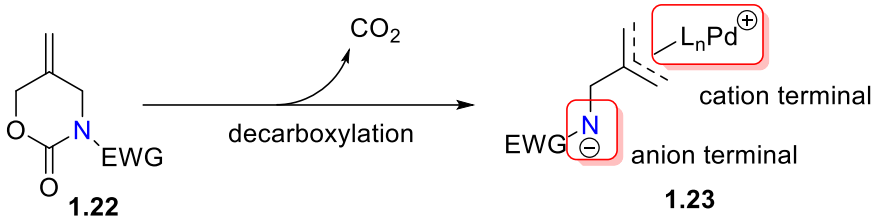
It is worth mentioning that Serra et al. reported that azlactone enol carbonates can also be converted into the corresponding allylation product with useful yield and enantioselectivity (**Scheme 1.17**).[19]



Scheme 1.17

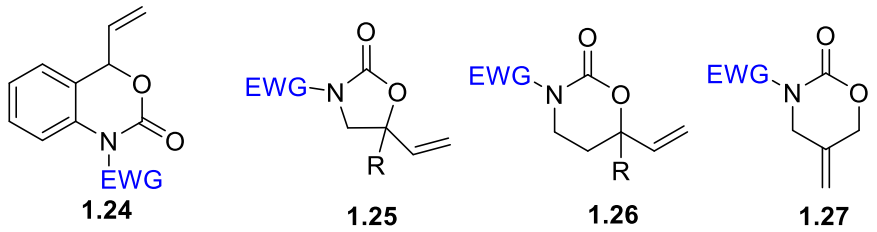
1.3 The application of zwitterionic intermediates in the DAAA reaction

Due to their excellent cyclization reactivity, cyclic carbamates **1.22** have been widely applied in the DAAA reaction (**Scheme 1.18**). Zwitterionic π-allylpalladium intermediate **1.23** can be formed after decarboxylation of these precursors. The cation-terminal of **1.23** can be attacked by the nucleophilic fragment and the anion-terminal can be used in the synthesis of functionalized nitrogen heterocycles by intramolecular reaction.



Scheme 1.18

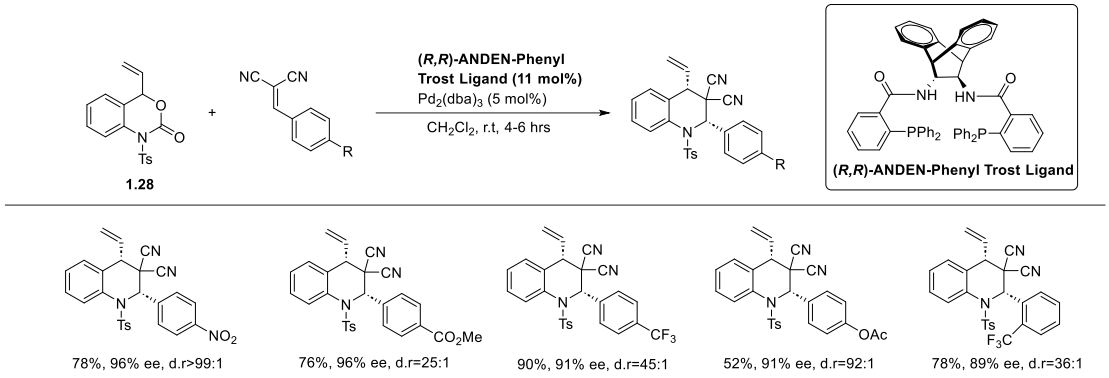
Thus, the design of zwitterionic precursors is crucial for the DAAA-cycloaddition reaction. Diverse lactones and cyclic carbamates have been applied in the DAAA-cycloaddition reaction to realize the synthesis of various cyclic compounds with the potential to generate chiral quaternary stereocenters.[20] This section of the thesis mainly introduces the application of carbamates in this reaction (**Scheme 1.19**).



Scheme 1.19

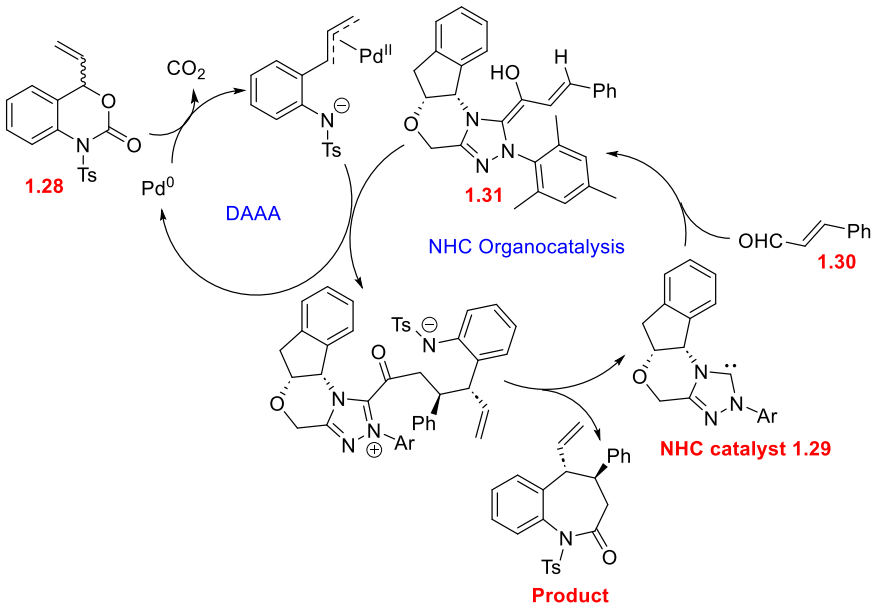
Carbamate **1.28** has been commonly applied in decarboxylative [4+2] cycloaddition reactions for synthesis of aromatic nitrogen heterocycles. The Tunge group reported a new [4+2] cycloaddition reaction to synthesise hydroquinolines by using carbamate

1.28 as a precursor (**Scheme 1.20**) in 2008.[21] The hydroquinolines afforded by this protocol were generated with excellent yields, enantioselectivities and diastereoselectivities.

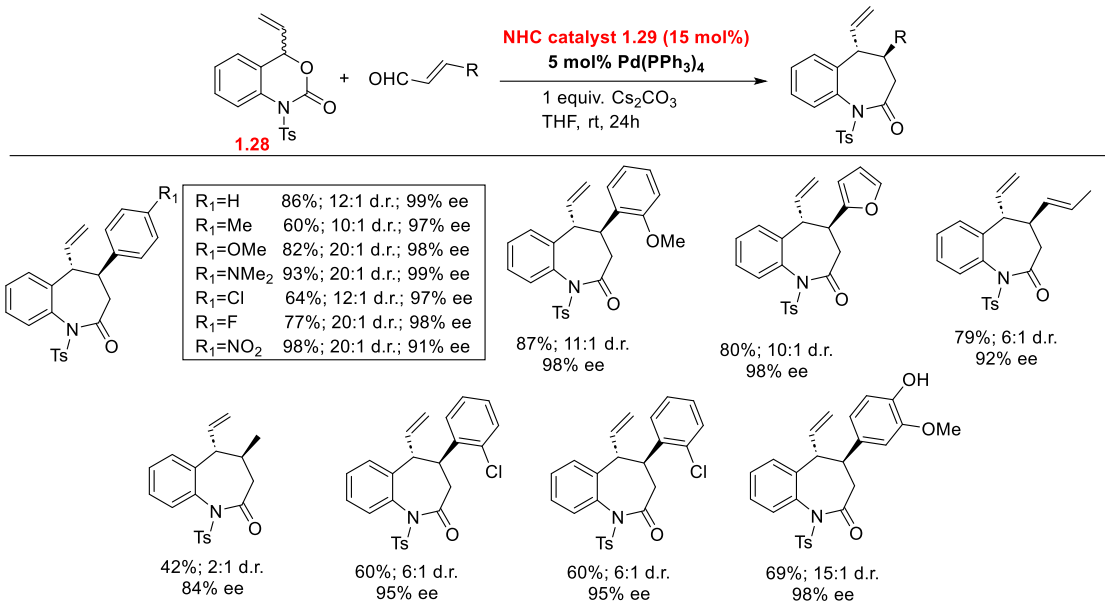


Scheme 1.20

Enantioenriched benzazepines have been synthesized by the Glorius group by using carbamate **1.28** in a DAAA-NHC organocatalysed synergistic reaction.[22] NHC catalyst **1.29** cannot only convert the enal **1.30** to NHC-homoenolate **1.31** but also work as chiral auxiliary to control the enantioselectivity of the reaction (**Scheme 1.21**). Glorius screened a variety of enals to afford diverse benzazepines with excellent enantioselectivities (**Scheme 1.22**).

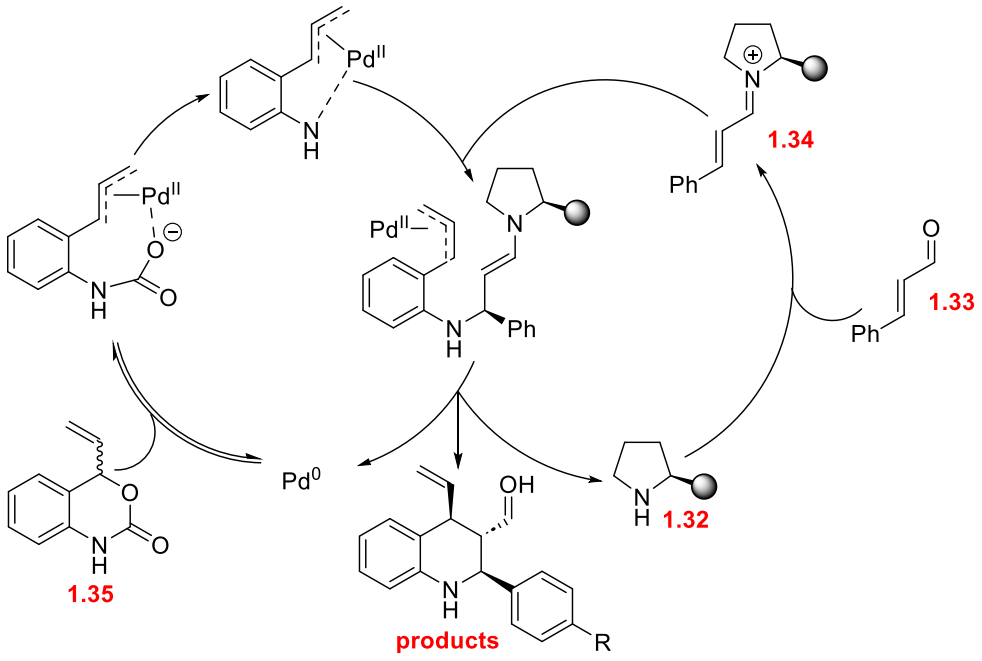


Scheme 1.21



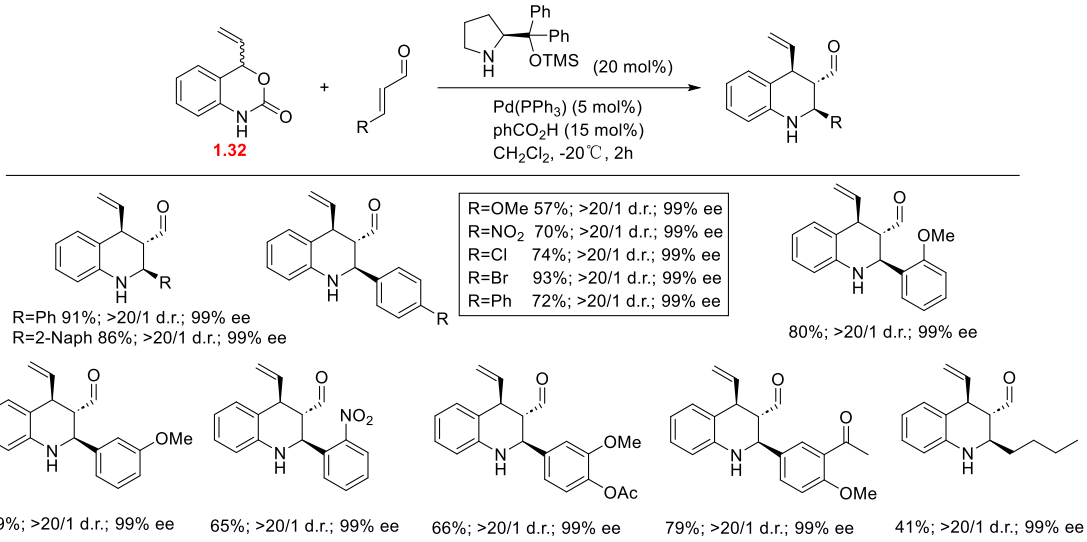
Scheme 1.22

In 2016, the Jørgensen group first reported the synthesis of tetrahydroquinolines with high enantioselectivities and diastereoselectivities by introducing chiral organocatalyst **1.32** on the α,β-unsaturated aldehyde **1.33** instead of using a chiral ligand. [23] Iminium-ion intermediate **1.34** underwent DAAA-cycloaddition reaction with carbamate **1.35** to form corresponding tetrahydroquinoline (**Scheme 1.23**).



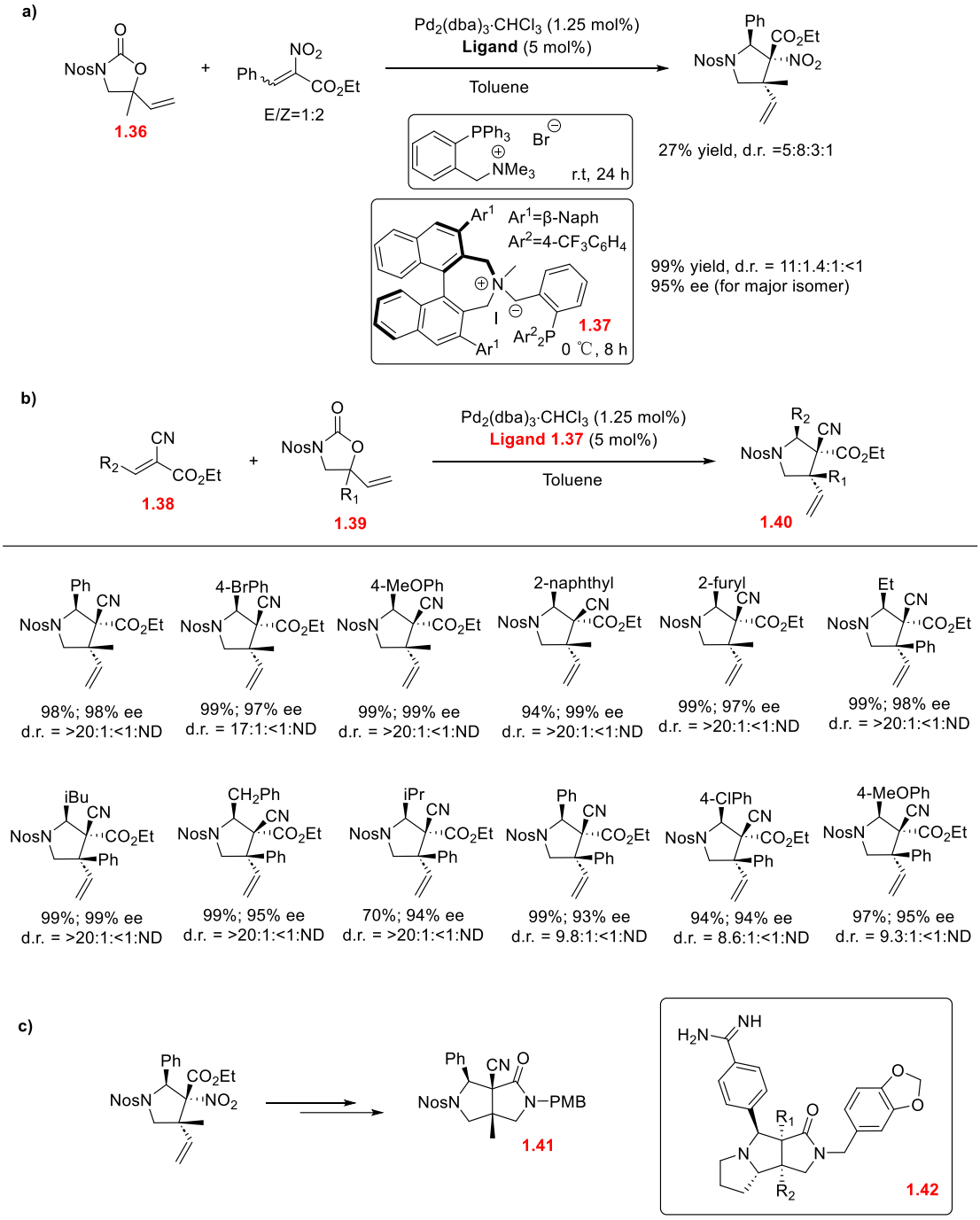
Scheme 1.23

Jørgensen screened aldehydes with diverse aromatic groups and alkyl groups to afford various tetrahydroquinolines with excellent enantioselectivity and diastereoselectivity (**Scheme 1.234**).



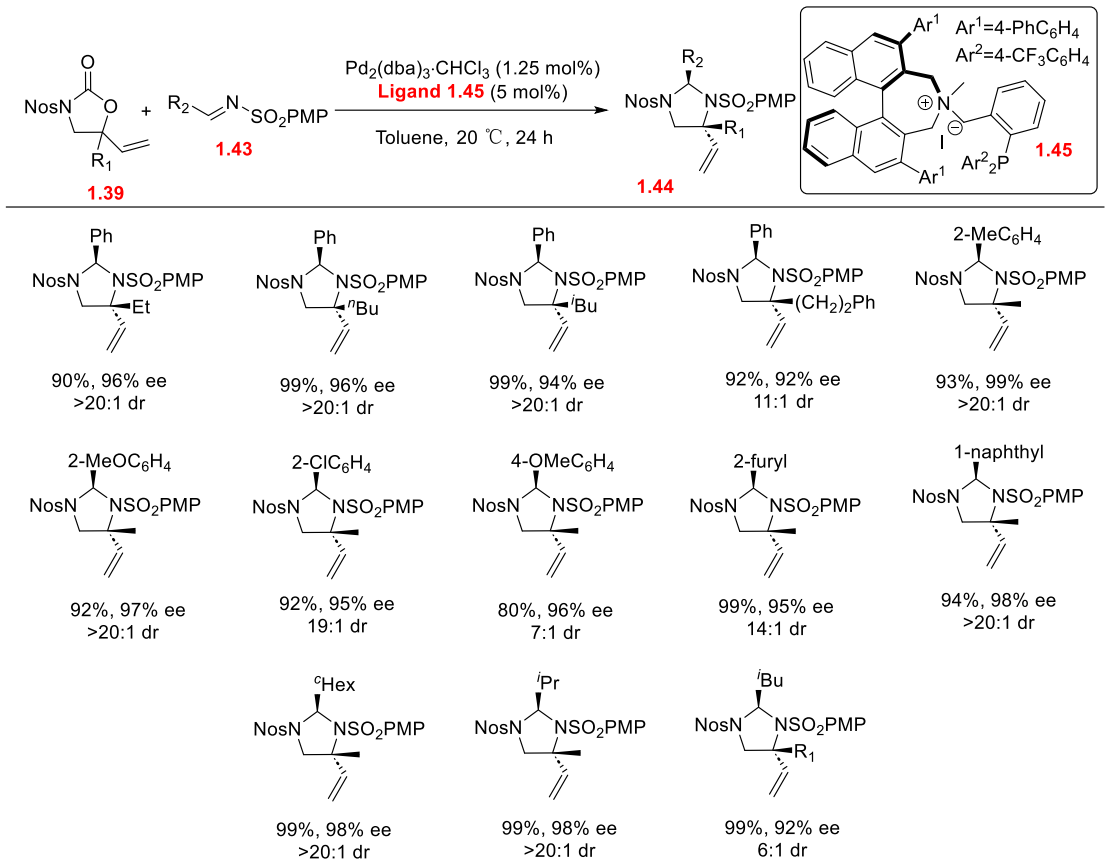
Scheme 1.24

5-Vinyloxazolidinones **1.36** and trisubstituted alkenes can be combined to synthesize pyrrolidine with control of multiple stereocentres by a [3+2] metal catalysed cycloaddition in the presence of a new chiral onium–phosphine hybrid ligand **1.37**.[24] In this study, chiral ligand **1.37** played a vital role in construction of three contiguous stereocentres (**Scheme 1.25 a**). The Ooi group screened different trisubstituted alkenes **1.38** and carbamates **1.39** to build various pyrrolidines **1.40** with excellent enantioselectivity and diastereoselectivity (**Scheme 1.25 b**). These intermediates could be converted into the bicyclic lactams **1.41** which is the scaffold of thrombin inhibitor analogues **1.42** (**Scheme 1.25 c)**.



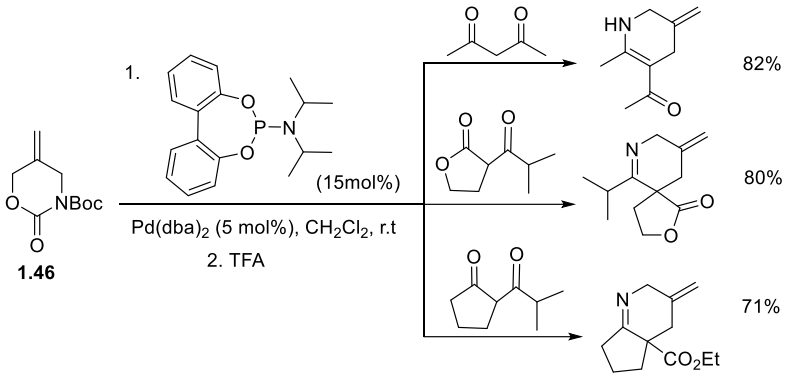
Scheme 1.25

In the same year, the Ooi group also published the synthesis of various imidazolidines **1.44** with high enantioselectivity and diastereoselectivity by the metal-catalysed cycloaddition reaction between the carbamates **1.39** and *N*-sulfonyl imines **1.43** in the presence of the chiral onium–phosphine hybrid ligand **1.45** (**Scheme 1.26**).[25]



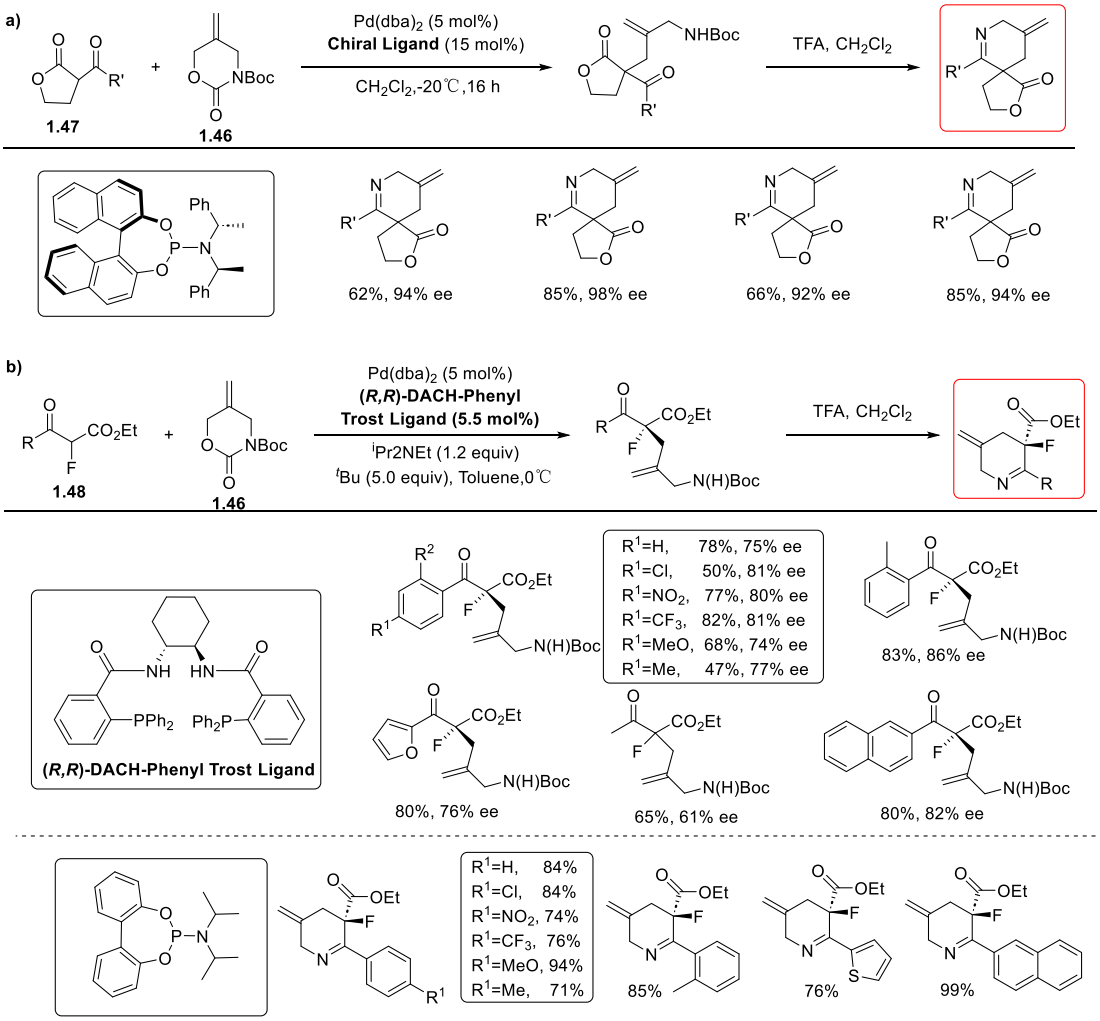
Scheme 1.26

The Harrity group reported that diverse piperidine analogues can be afforded by a simple and versatile Pd-catalyzed cycloaddition strategy between carbamate **1.46** and diones and keto lactones (**Scheme 1.27**).[26]



Scheme 1.27

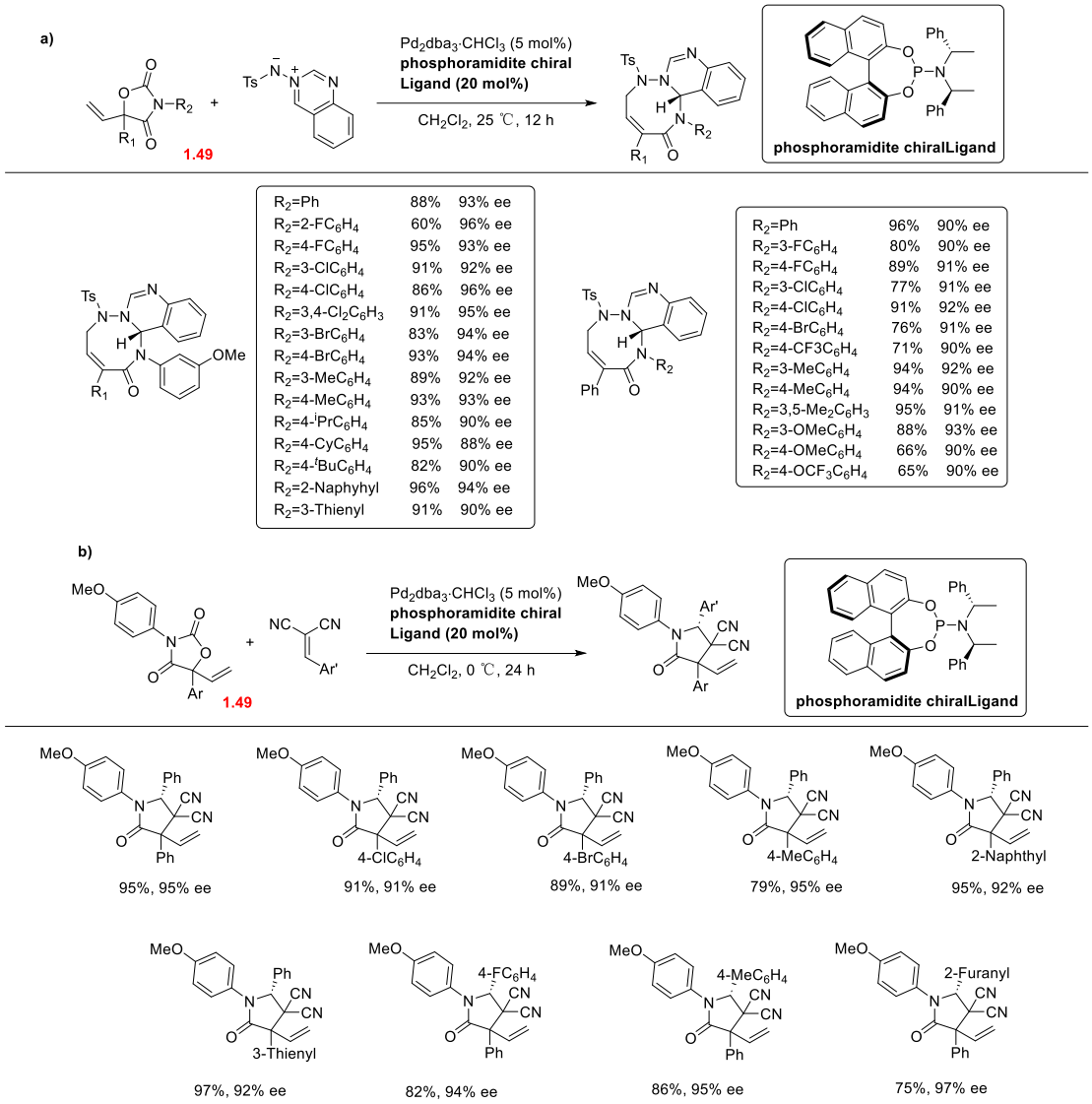
On this basis, Harrity's group designed a range of DAAA-cycloaddition reactions between different substrates and carbamates **1.46** to provide different piperidine products with high enantioselectivity and yield in the presence of different chiral ligands. Spiropiperidines can be provided by the reaction between carbamate **1.46** and keto ester substrates **1.47** (**Scheme 1.28 a**).[26] 3-Fluoropiperidines can be delivered by the reaction between carbamate **1.46** and α-fluoro-β-ketoester substrates **1.48** (**Scheme 1.28 b**).[7, 27]



Scheme 1.28

New carbamates are being designed to be suitable not only for the synthesis of target heterocyclic compounds, but also to address limitations associated with charge stabilising groups. For example, Guo designed new carbamate **1.49** where the electron-withdrawing group at the N atom forms a part of the target heterocycle.[28]

The Guo group screened diverse carbamates and nucleophilic substrates to afford various eight-membered heterocycle products (**Scheme 1.29 a**) and γ-lactams with excellent enantioselectivity and yield (**Scheme 1.29 b**).

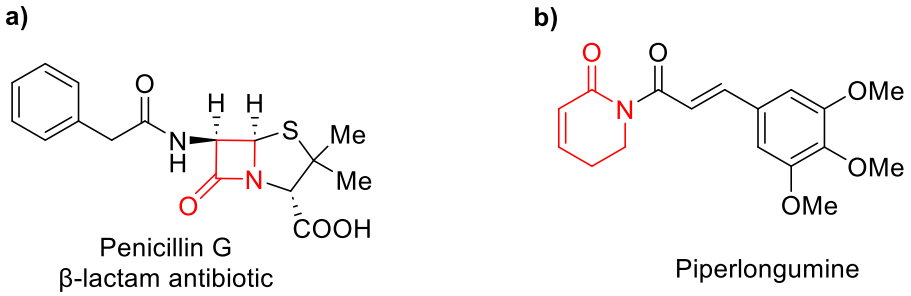


Scheme 1.29

In conclusion, carbamates are a powerful zwitterionic precursors that build diverse heterocycle compounds which can be used as the scaffold of many target compounds. New carbamates and cycloaddition protocols will continue to be designed to deliver more diverse heterocyclic compounds.

1.4 The development of Freidinger lactams

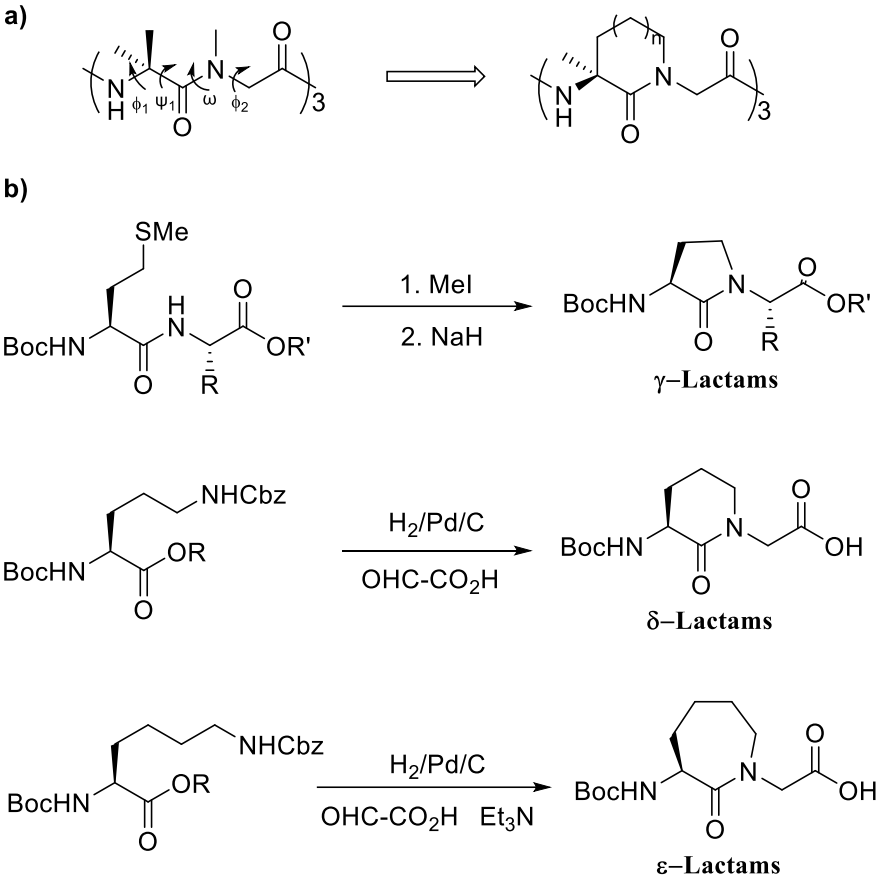
About 60% of FDA-approved drugs contain a nitrogen heterocycle.[29] The lactam as a drug scaffold is widely present in traditional drugs and natural products. For example, penicillin G is a β-lactam antibiotic (**Scheme 1.30 a**). Piperlongumine used as an Asian traditional medicine for millennia shows antitumour activity (**Scheme 1.30 b**)[30]. Therefore, the design and application of the lactam scaffold is of great significance for the development of drugs.



Scheme 1.30

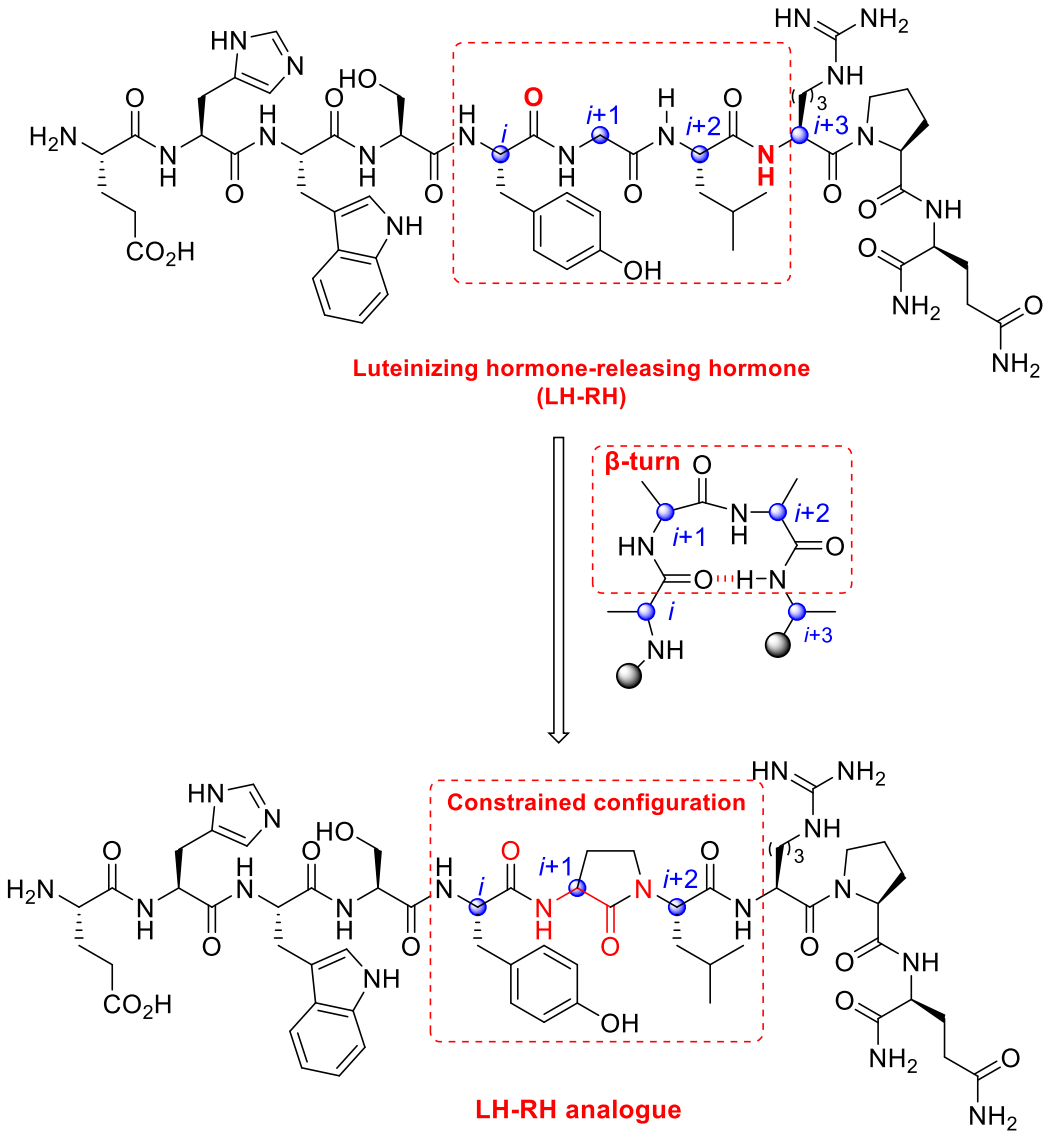
Researchers have for many years been committed to the synthesis and study of amino acid analogues. Among the many approaches taken, the use of peptide bond surrogates and novel peptide chain backbones have been employed to generate compounds with improved pharmacokinetic profiles, better drug properties and higher market value.

Freidinger et al. found that the introduction of dipeptide lactams into a polypeptide chain is an effective method of limiting the conformation of the peptide (**Scheme 1.31 a**).[31] The resulting lactam can enforce the trans conformation of the amido bond in the peptide chain (ω) along with controlling the dihedral angles of the main chain ψ_1. The lactam ring can also impact conformational flexibility of the dihedral angles ϕ_1 and ϕ_2. Although several strategies exist for the synthesis of Freidinger lactams, they generally provide motifs that lack functionality that limits their further elaboration downstream (**Scheme 1.31 b**).[30]



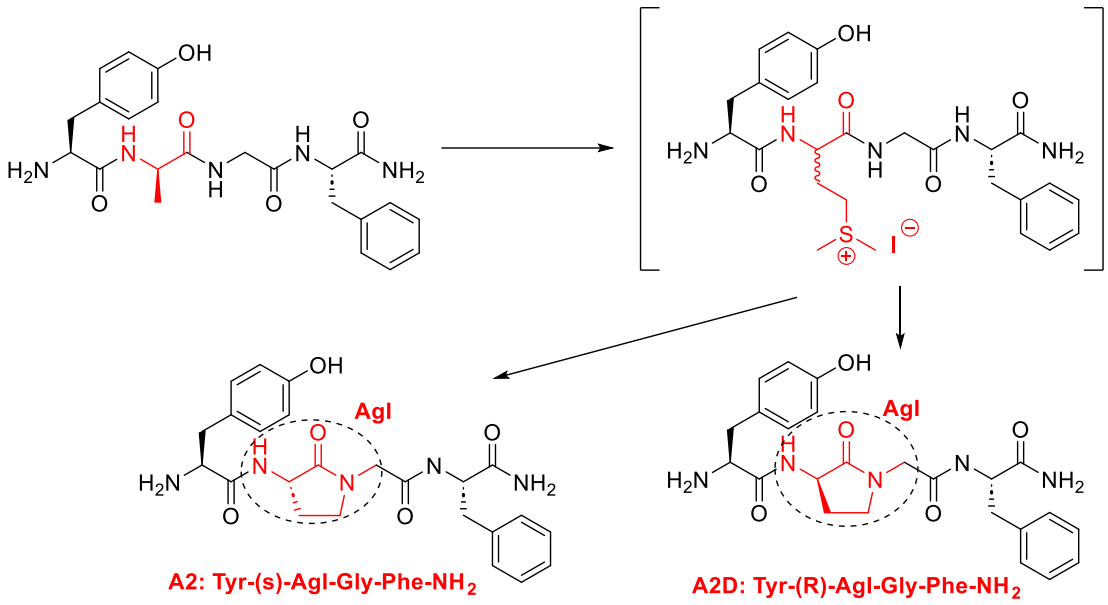
Scheme 1.31

The introduction of Freidinger lactams has been shown to improve the potency of peptide drugs. For example, the luteinizing hormone-releasing hormone (LH-RH) has a β-turn that is stabilised by the formation of the H-bond between carbonyl-O of the (*i*)-tyrosine residue and amide-H of the (*i*+3)-leucine residue (**Scheme 1.32**). The β-turn played a vital role in the bioactivity of LH-RH. The Freidinger group showed that a constrained configuration can be built into the LH-RH by using γ-lactam as surrogate for the (*i*+1)-glycine residue (Scheme 1.26).[32] This constrained peptide fragment can stabilise the β-turn structure to enhance the potency of the LH-RH which was demonstrated both in vivo and in vitro.



Scheme 1.32

The Stefanucci group reported that [D-Ala2, des-Leu5] enkephalin amide (DAPEA) analogue A2D, which was generated by introducing (*R*)-α-amino-γ-lactam (Agl) in DAPEA, has high selectivity and potency at the MOR receptor (a class of opioid receptors) (**Scheme 1.33**).[33] By using docking studies, they identified the conformation of A2D which led to the proposal that a β-turn played an important role in binding at the MOR receptor. Interestingly, A2, a diastereomer of A2D, did not show the β-turn feature.



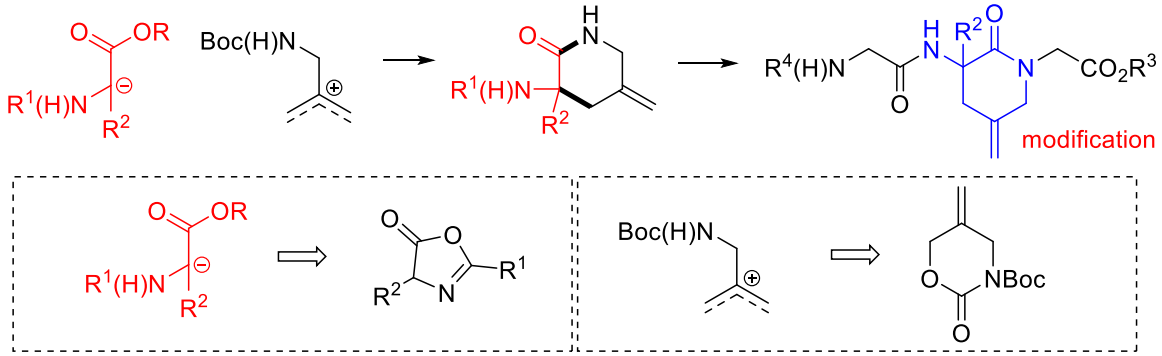
Scheme 1.33

In summary, the introduction of Freidinger lactams in peptide drugs is a strong and effective strategy to improve their therapeutic potential.

2. Previous work

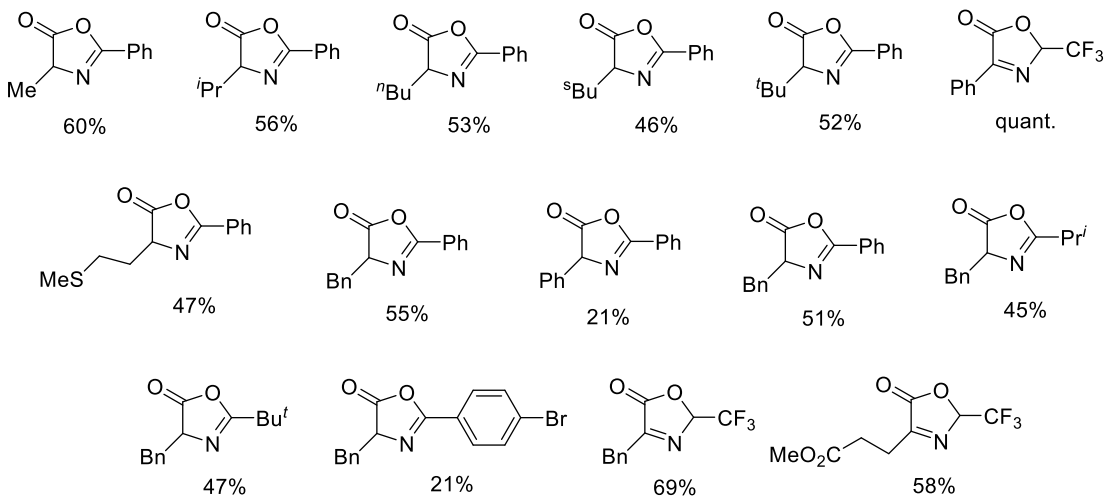
Current approaches to Freidinger lactams rely almost exclusively on the stereospecific elaboration of available α-amino acids, and *de novo* asymmetric routes to functionalizable constrained amino acid building blocks are almost unknown. In addition, in many of these cases, the building of Freidinger lactams relies on the α-amino acids with special side groups (such as methionine, lysine and so on) that are involved in the ring forming process. This means that Freidinger lactams cannot be introduced at all sites in a peptidomimetic. At the same time, this approach is limited by the fact that the side groups are sacrificed in the ring forming process.

We envisaged that functionalized Freidinger lactams could be made available through the condensation reaction of a 2-aminomethyl π-allyl intermediate and an α-amino acid anion equivalent (**Scheme 2.1**). We identified azlactones as synthetic equivalent of the amino acid anion, and the cyclic carbamate as the electrophilic component.



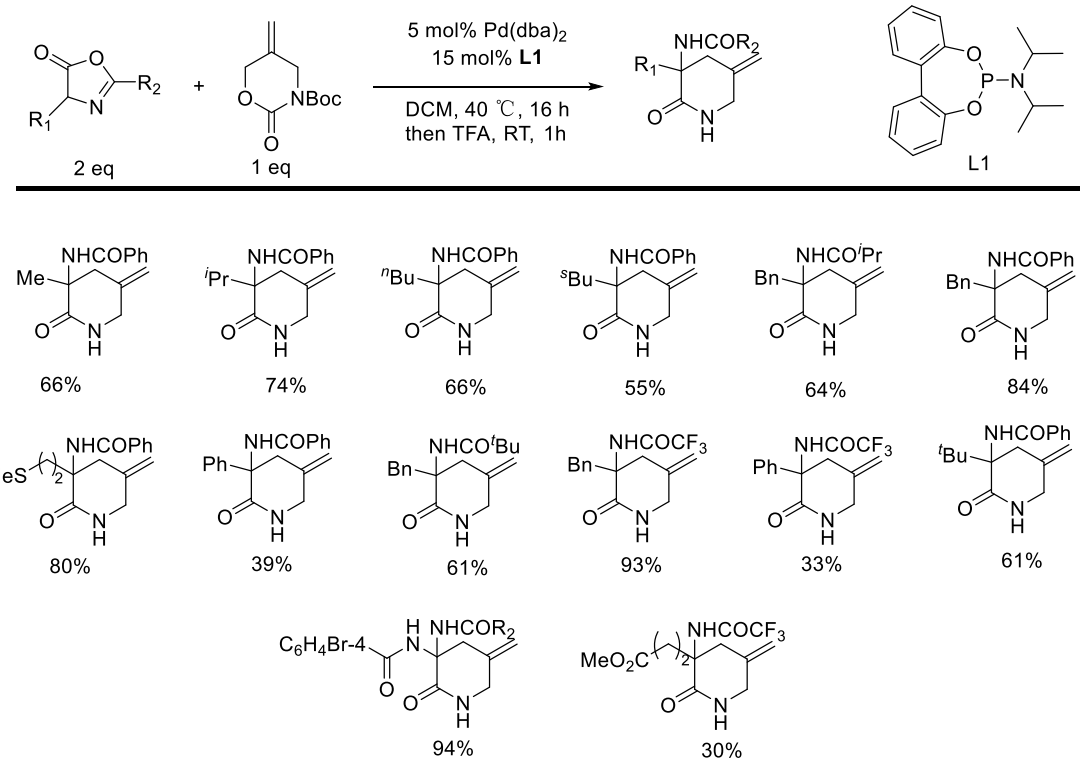
Scheme 2.1. Strategy of this project to synthesize Freidinger lactams.

The synthesis of a series azlactones was performed within the group before commencing the project (**Scheme 2.2**) and these were convenient for use as substrates in the lactam forming reaction.[34]



Scheme 2.2. Azlactones synthesized previously in the group.

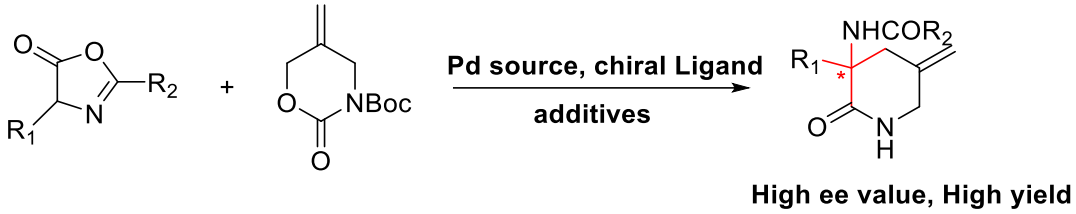
Previous work also presented feasible experimental conditions for the synthesis of δ-lactams via allylation/cyclization of azlactones (**Scheme 2.3**). Under these conditions, a series of different δ-lactams were synthesized in useful yields. However, at this point, the method was restricted to the synthesis of racemic δ-lactams, which limits their application in biology and medicine.



Scheme 2.3. δ-Lactams synthesized previously in the group

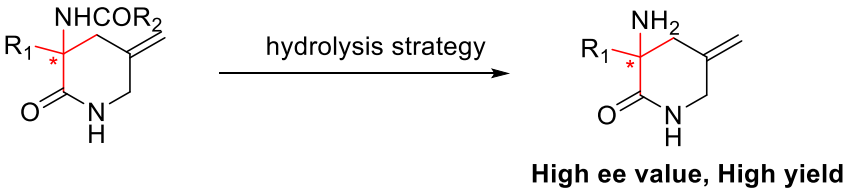
3. Aims

This project will focus on the development of a facile and enantioselective route to lactam motifs that could be integrated into peptidomimetics (**Scheme 3.1**). At the same time, this strategy needs to ensure the high reactivity and versatility in order to be used in gram scale experiments.



Scheme 3.1. Enantioselective synthesis strategy for Freidinger lactams.

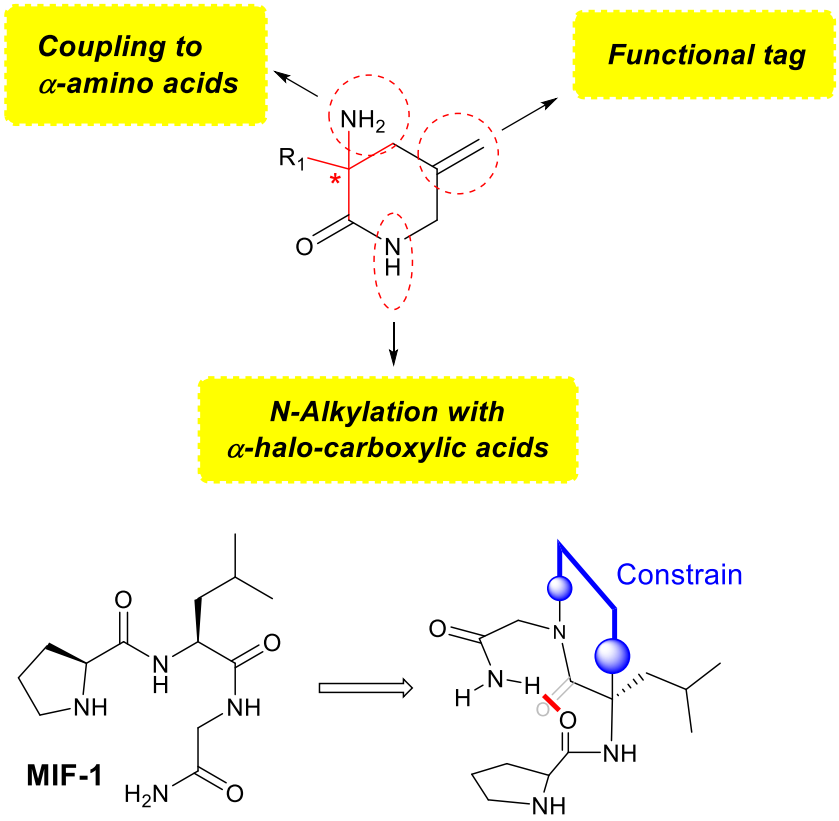
After identifying optimal conditions for the asymmetric synthesis of the key lactam motifs, a suitable hydrolysis strategy for the removal of the amide group needs to be developed for forming single Freidinger lactam blocks with a free amine group (**Scheme 3.2**). These Freidinger lactam monomers can be used to synthesize constrained oligopeptide fragments bearing an olefin that offers the potential for late-stage functionalisation.



Scheme 3.2. Hydrolysis strategy

Finally, targets will be developed that incorporate these Freidinger lactam building blocks, with the work mainly divided into two directions (**Scheme 3.3**). One is modification of the olefin so that it can be tagged with functional molecules such as a

fluorescent organic dye. Another goal is the synthesis of constrained peptidomimetics by using these lactams.

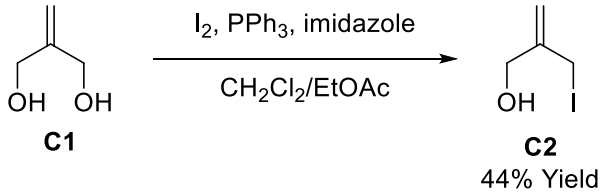


Scheme 3.3. Modification and application of Freidinger lactam blocks.

4. Synthesis of Substrates and Ligands

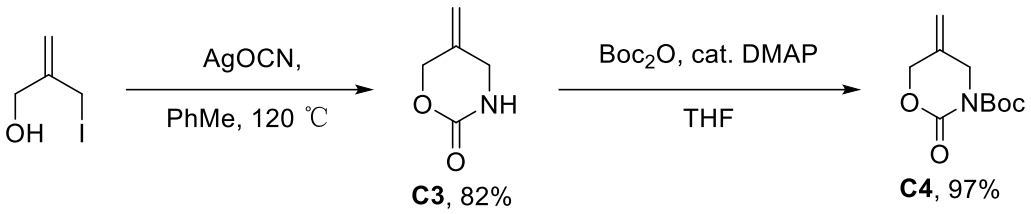
4.1. Synthesis of carbamate

Carbamate (**C4**) is the precursor to our key dipolar intermediate for the lactam synthesis, and is made in a three-step sequence. The first step involves treating the commercial diol (**C1**) with I_2 and PPh_3 in DCM/EtOAc (1:1) with imidazole to form 3-iodo-propan-1-ol (**C2**) (**Scheme 4.1**). There are two things to note about this reaction. The first point is that the reaction is performed in the dark because light will not only accelerate the decomposition of iodine but it also decomposes the product. The second point is that the reaction is highly exothermic upon addition of iodine. Thus, it is necessary to keep the mixture (diol, imidazole, PPh_3 in DCM/EtOAc) at 0 ℃ and to add the iodine slowly to the mixture.



Scheme 4.1. Method to synthesize **C2**.

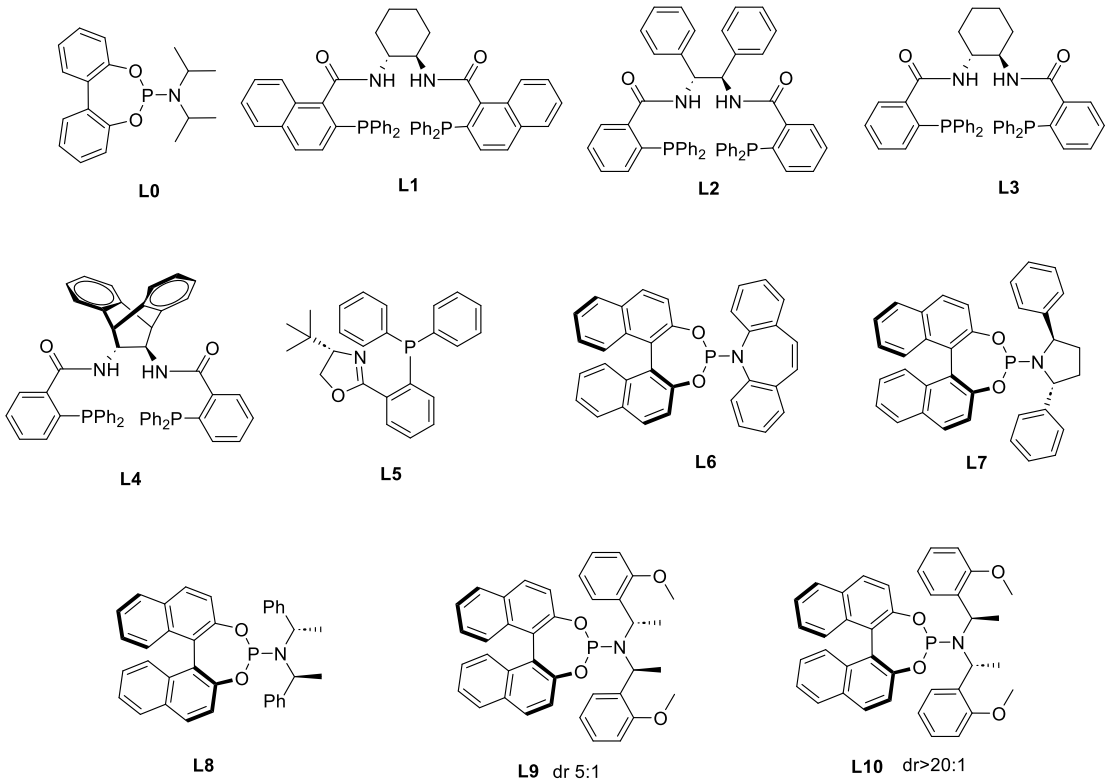
In the subsequent step, AgOCN in refluxing toluene was used to convert **C2** to the cyclic carbamate **C3** (**Scheme 4.2**). This reaction was also carried out in the absence of light. Finally, the cyclic carbamate intermediate (**C3**) was protected by Boc using DMAP as catalyst. The final product carbamate (**C4**) was generally isolated as a colorless oil after purification by flash column chromatography. However, it slowly transformed to a white solid after storing in the freezer for about one week.



Scheme 4.2. Method to synthesize carbamate.

4.2. Synthesis of Ligands

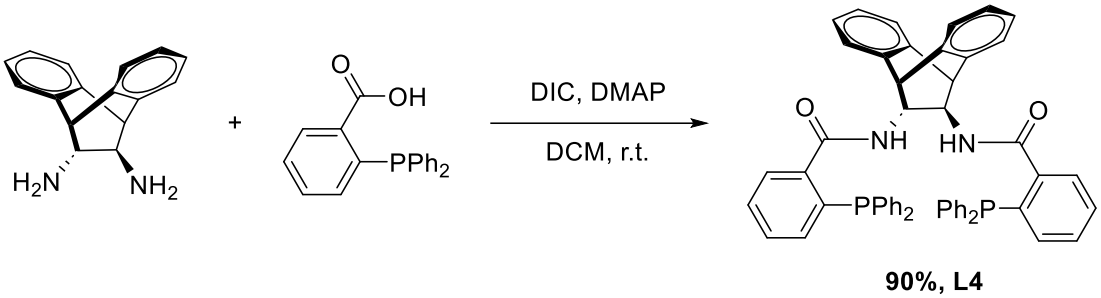
The chiral ligands used to develop the asymmetric allylation step in this project were all purchased or provided by the laboratory (synthesized by previous team members, **Scheme 4.3**).



Scheme 4.3. The list of ligands used in this project.

Ligand **L4** ((*R*,*R*)-ANDEN-phenyl Trost ligand) was particularly expensive, so we had to prepare this to have reasonable quantities for screening/optimization studies (**Scheme 4.4**). The ligand was synthesized by the coupling reaction of chiral diamine

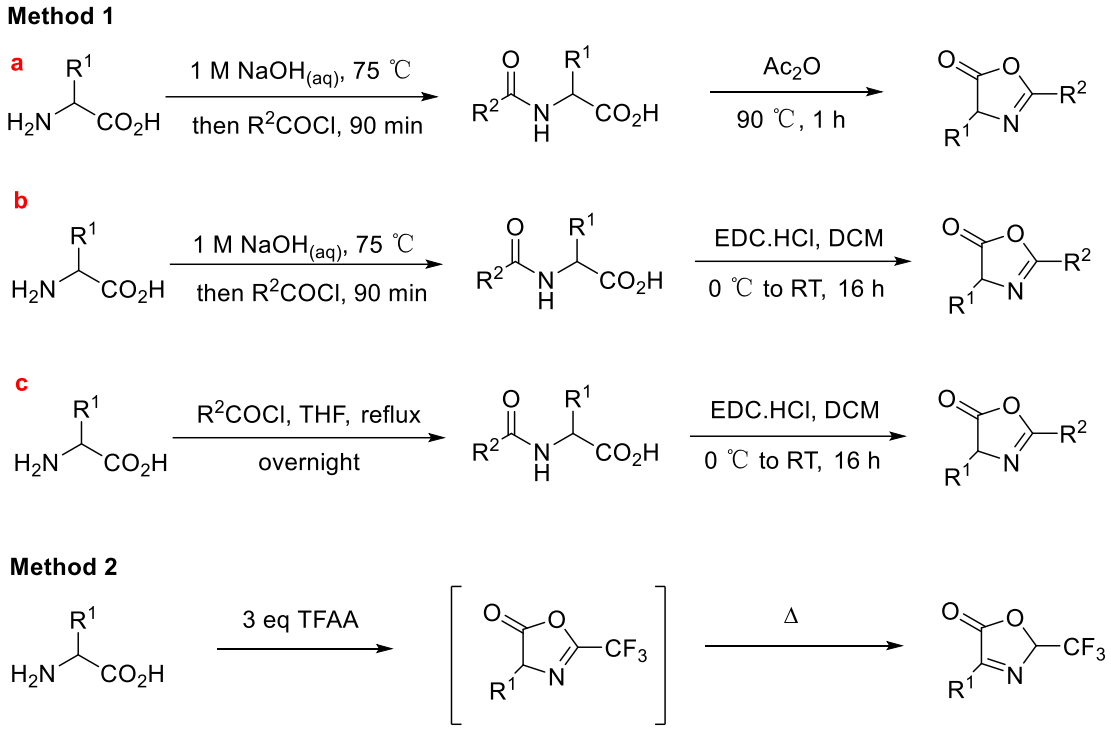
and benzoic acid. Usually DIC, DCC and EDC.HCl were used as the coupling reagents to promote such reactions. However, after many experiments, it was found that DIC was more suitable for this reaction. Use of EDC.HCl resulted in a decrease in yield, while DCC raised problems as the by-product DCU was difficult to remove by flash column chromatography due to co-elution with the product (**L4**). In contrast, the by-product of DIC can be easily removed by flash column chromatography.



Scheme 4.4. Method to synthesize **L4**.

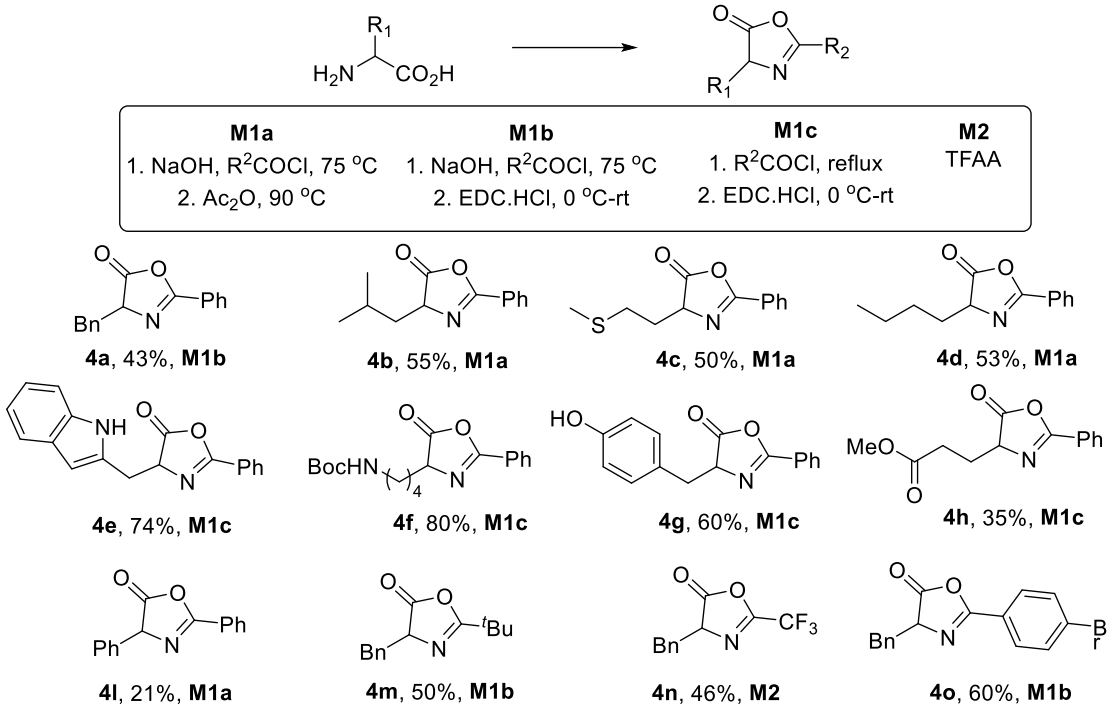
4.3. Synthesis of azlactones

Although a number of azlactones were available when the project started (c.f. **Scheme 2.4**), additional examples were required as the project progressed and their synthesis will be discussed here. Generally speaking, synthetic approaches to azlactones can be divided into two methods (**Scheme 4.5**). The first method is to first synthesize the amide intermediate in an alkaline aqueous solution or THF, and then use a dehydrating agent (Ac_2O or EDC.HCl) to cyclize the amide intermediate to obtain an azlactone. In a modification of this route that is used in cases where R^1 groups are easily hydrolysed when heated in a strong alkaline aqueous solution (such as ester groups), an acid chloride is employed to form the amide intermediate. The second method is to use TFAA directly. In this approach, TFAA not only generates the corresponding amide intermediate, but also acts as a dehydrating agent to cyclize the amide to the corresponding azlactone. In this case, the azlactone has a specific R^2 group ($-CF_3$).



Scheme 4.5. Strategies for synthesizing azlactones

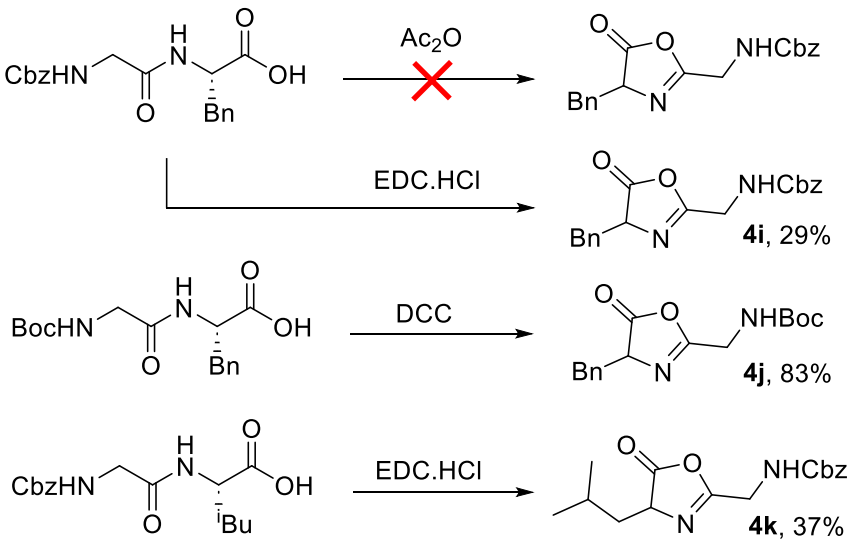
Although routes to a range of azlactones were developed within the group, many azlactones with important amino acid residues (such as tryptophan, glutamic acid, and lysine and so on) were missing. Accordingly, we synthesized azlactones with neutral side chains (eg. **4a, 4b**), acidic side chains (ester protected, **4h**) and basic side chains (Boc protected, **4f**) by the above method (**Scheme 4.6**). Overall, the azlactones prepared allowed us to access many different types of analogues of natural amino acids.



Scheme 4.6. Using different strategies to synthesize corresponding azlactones.

In the process of synthesizing azlactones, we found many things worth exploring. First of all, for the choice of Ac_2O versus EDC.HCl, the latter was preferable even though it had little effect on the yield. The post-treatment of EDC.HCl is simpler which greatly reduces the product loss during post-treatment and purification. Moreover, the conditions used with EDC.HCl are milder, and it is more suitable as a dehydrating agent for the synthesis of azlactones with readily hydrolysable groups. Secondly, the properties of azlactone (**4o**) are quite special. Although the polarity of this substance is very low, its solubility in DCM is also very low. Therefore, a large amount of white solid appeared after the reaction, and this was collected by filtration to obtain the product with a yield of 60%. The reason for this property has not been identified, but it could be closely related to the influence of bromine atom because Br is polarisable and can undergo halogen-bonding. A final note is that all azlactones need to be kept in the refrigerator. Some azlactones are readily hydrolyzed even when stored in the refrigerator, and such azlactones need to be used immediately after synthesis.

We also synthesized some special azlactones using dipeptides (**Scheme 4.7**). The reasons for studying these systems are twofold. On the one hand, dipeptide-like Freidinger lactam building blocks can be finally obtained using such azlactones as starting materials. On the other hand, the influence of the R^2 group on the reaction efficiency and stereoselectivity can be studied and compared to the corresponding aryl groups. A summary of our routes to these azlactones is shown in **Scheme 4.7**.

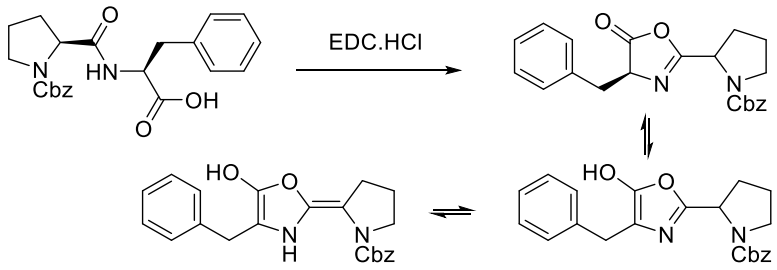


Scheme 4.7. Using dipeptides to synthesize corresponding azlactones.

From the analysis of the results, we found that EDC.HCl is the most suitable dehydrating agent when Cbz is used as the *N*-protected group. Although the yield of azlactone is only 20%-30%, when other dehydrating agents (Ac_2O or DCC) were used the reaction did not proceed at all. For the Boc *N*-protected group, DCC is the most suitable dehydrating agent and the yield of azlactone was up to 83% in this case.

We also synthesized the corresponding azlactones using Z-Pro-Phe as the starting material (**Scheme 4.8**). The lactam obtained from this azlactone would allow the direct incorporation of proline, a naturally occurring constrained amino acid. Unfortunately, the synthesis of this azlactone was not successful. The NMR spectrum of the purified compound was very complex and could not be conclusively analyzed. The mass spectrum showed that there were two products; respectively, the molecular weight of the target product (M) and the molecular weight of the target

product plus 18 (M+18). Since the specific reason for the failure of the reaction is unclear, we propose that a combination of proline racemization and Cbz rotamers may lead to a complex NMR spectrum, and the hydrolysis of the azlactone may cause product (M+18) to appear in the mass spectrum. Regardless, our inability to easily work with this compound led to the approach being abandoned.



Scheme 4.8. Possible racemization of azlactone from Z-Pro-Phe.

5. Selected Optimization Experiments

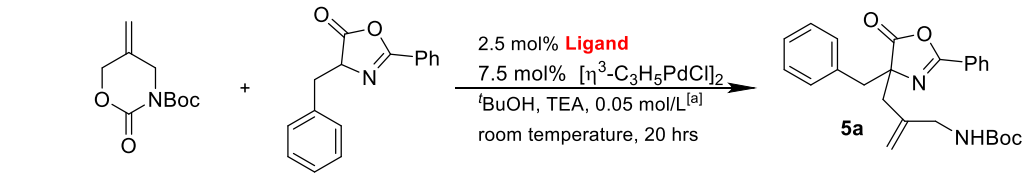
5.1. First Selected Optimization Experiments

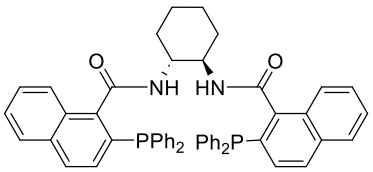
This part of the research project took place during the pandemic, and so many of the required reagents could not be delivered in time. Accordingly, we used a single variable method to screen the best experimental conditions. That is, only one of the conditions was changed in adjacent experiments, and the best conditions were selected for the next experiment.

5.1.1. Ligand screening

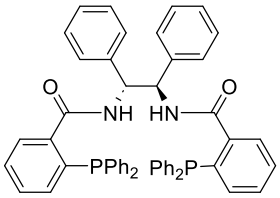
Ligand identification is critical for establishing efficient asymmetric transformations. It was our view that the fine tuning of other factors should be built on the best ligand candidate, and so we decided to screen all the ligands first under the same conditions and then choose the best ligand to go on to the next optimization process. We first selected one ligand from each of the three different types of ligands (Phox Ligand, BINAP Ligand, and Trost Ligands) for comparison (**Table 1, Entries 1, 2, 3**). We found the Trost ligand family more suitable for our experiments than the other two. According to the comparison (**Table 1, Entries 4, 5, 6, 7**), we found **L4** to be our best Trost Ligand, providing product with an ee value of up to 81%.

Table 1. Ligand screening

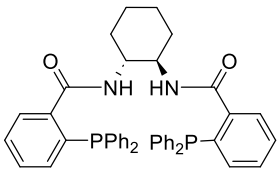




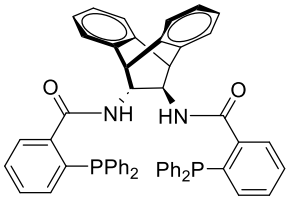
L1



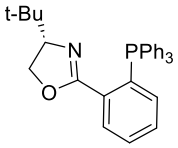
L2



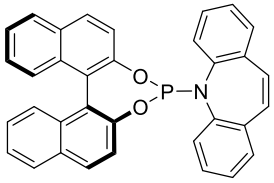
L3



L4



L5



L6

Entry	solvent	Ligand (L)	Yield (%) [b]	ee (%) [c]
1	DCM	**L5**	98	14
2	DCM	**L6**	95	8
3	DCM	**L1**	93	25
4	Dioxane	**L1**	96	53
5	Dioxane	**L2**	98	49
6	Dioxane	**L3**	85	63
7	Dioxane	**L4**	30	81

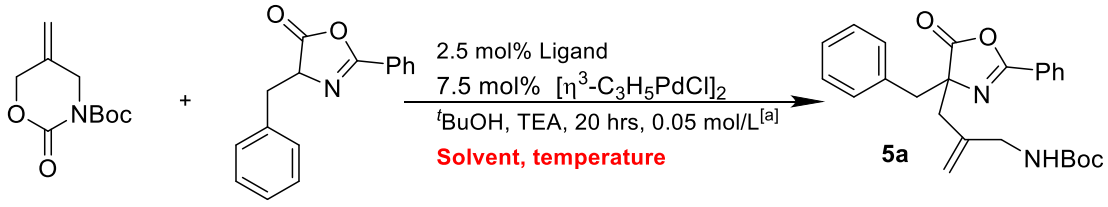
[a] Concentration with respect to cyclic carbamate. [b] Yield after chromatography. [c] Determined by chiral HPLC with a constant flow rate of 1 mL/min using hexane/isopropyl alcohol 95:5 as the mobile phase.

5.1.2. The optimisation of solvent and temperature

In our selected optimization experiments, the type of solvent also plays a vital role. According to the comparison of **entry 1**, **entry 2**, and **entry 6** (**Table 2**) enantioselectivities improved in the order: 1,4-dioxane > DCM > acetonitrile, and

comparing **entries 8**, **entry 9**, and **entry 10**, dioxane proved to be the superior ether based solvent. Toluene as the least polar solvent also gave a relatively high ee value but the yield was very poor in this case.

Table 2. Solvent and temperature screening.



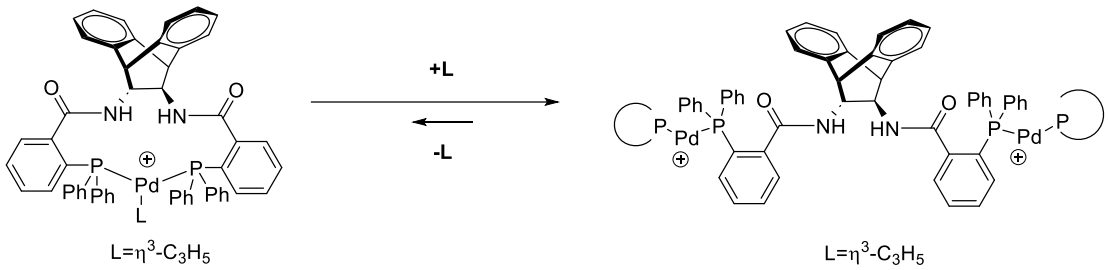
Entry	solvent	Temp	Ligand (L)	Yield (%) [a]	ee (%) [b]
1	Acetonitrile	rt	**L1**	95	10
2	DCM	rt	**L1**	93	25
3	DCM	0	**L1**	93	35
4	DCM	-20	**L1**	83	25
5	Toluene	0	**L1**	10	50
6	Dioxane	rt	**L1**	96	53
7	Dioxane	rt	**L2**	98	49
8	Dioxane	rt	**L3**	85	63
9	DME	rt	**L3**	98	16
10	THF	rt	**L3**	71	46
11	Dioxane	rt	**L4**	40	81

[a] Concentration with respect to cyclic carbamate. [b] Yield after chromatography. [c] Determined by chiral HPLC with a constant flow rate of 1 mL/min using hexane/isopropyl alcohol 95:5 as the mobile phase.

The reaction temperature can also influence the ee value. According to **entry 2**, **entry 3**, and **entry 4** (**Table 2**), we found the relationship between reaction temperature and ee value is non-linear. With the decrease in temperature, the ee value increased at first and then fell. Although a reaction temperature of 0 ℃ appeared to be best in DCM, unfortunately the freezing point of 1,4-dioxane is 10 ℃, and so we conducted reactions in this solvent at room temperature for convenience.

5.1.3. Summary of other factors explored

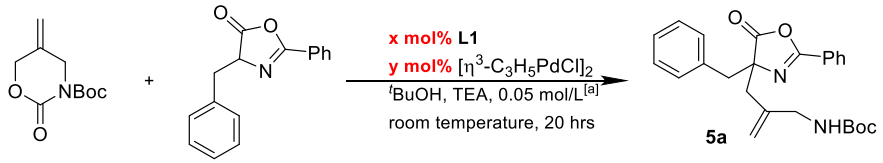
In general, the most common Pd/ligand ratios are between 1:1.1 and 1:3. If the ratio of the ligand is too high, oligomeric Pd-complexes rather than monomeric Pd-complexes predominate, which typically leads to a reduction in the enantioselectivity of the ensuing allylation reaction (**Scheme 5.1**).[35]



Scheme 5.1. Oligomerisation of Trost ligand based catalysts.

We therefore compared the influence of two different Pd/ligand ratios on the enantioselectivity (**Table 3**). According to the result, we found a small increase in ligand ratio does not significantly affect yield and enantioselectivity. Thus, we decided to maintain a 2:3 Pd/ligand ratio in order to produce an efficient reaction while minimising waste of the chiral ligand.

Table 3. Pd/ligand ratio screening



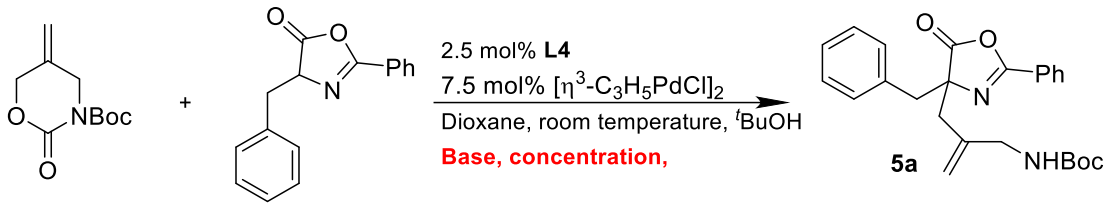
Entry	solvent	Pd loading (x mol%)	Ligand loading (y mol%)	Pd: Ligand	Yield (%) [b]	ee (%) [c]
1	DCM	2.5	7.5	2:3	93	35
2	DCM	2.5	15	1:3	94	35

[a] Concentration with respect to cyclic carbamate. [b] Yield after chromatography. [c] Determined by chiral HPLC with a constant flow rate of 1 mL/min using hexane/isopropyl alcohol 95:5 as the mobile phase.

A surprising observation was that the reaction did not proceed in the absence of base (**Table 4, Entries 8 and 9**), and using a stronger base than triethylamine can increase the yield, but has no influence on enantioselectivity (**Entries 1 and 2**). When we used DBU as base we found that some white precipitate formed and TLC analysis showed there was no azlactone remaining in the reaction mixture after 20 hours, although some carbamate still remained. We thought it was possible that azlactone was hydrolysed by a strong base. Thus, we wanted to improve the yield by decreasing the concentration of the reaction to prevent the formation of by-products. Fortunately, with the decrease in concentration, not only the yield but also the ee value increased, although the latter change was relatively insignificant (**Table 4, Entries 3, 4, 5, 6**). Finally, we found when the concentration was 0.0167 mol/L, the yield and ee values arrived at 85% when using DBU as a base.

According to **Table 4, Entry 7**, we found the main function of ^{t}BuOH was to increase the yield of the reaction. ^{t}BuOH can promote the enol structure of azlactones by analogy to studies reported by Trost's group.[36]

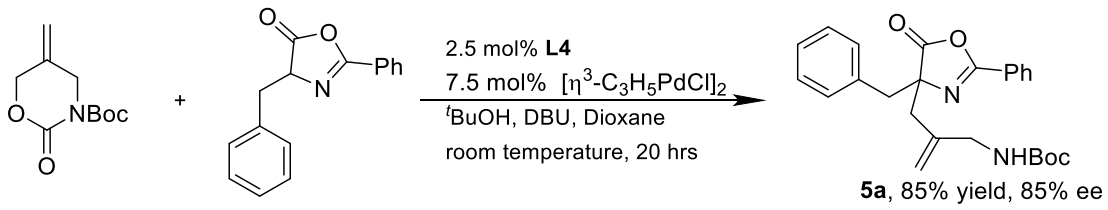
Table 4. Concentration and base screening.



Entry	Conc.[a] (mol/L)	Base	Yield (%) [b]	ee (%) [c]
1	0.05	TEA	30	81
2	0.05	DBU	50	81
3	0.025	DBU	67	82
4	0.0167	DBU	85	85
5	0.0125	DBU	78	84
6	0.01	DBU	64	82
7[d]	0.0167	DBU	50	83
8[e]	0.0167	-	No reaction	-
9[f]	0.0167	-	No reaction	-

[a] Concentration with respect to cyclic carbamate. [b] Yield after chromatography. [c] Determined by chiral HPLC with a constant flow rate of 1 mL/min using hexane/isopropyl alcohol 95:5 as the mobile phase. [d] Reaction without ^{t}BuOH. [e] Reaction without DBU. [f] Reaction without DBU and ^{t}BuOH. The palladium source is $\{\eta^3\text{-}C_3H_5PdCl\}_2$.

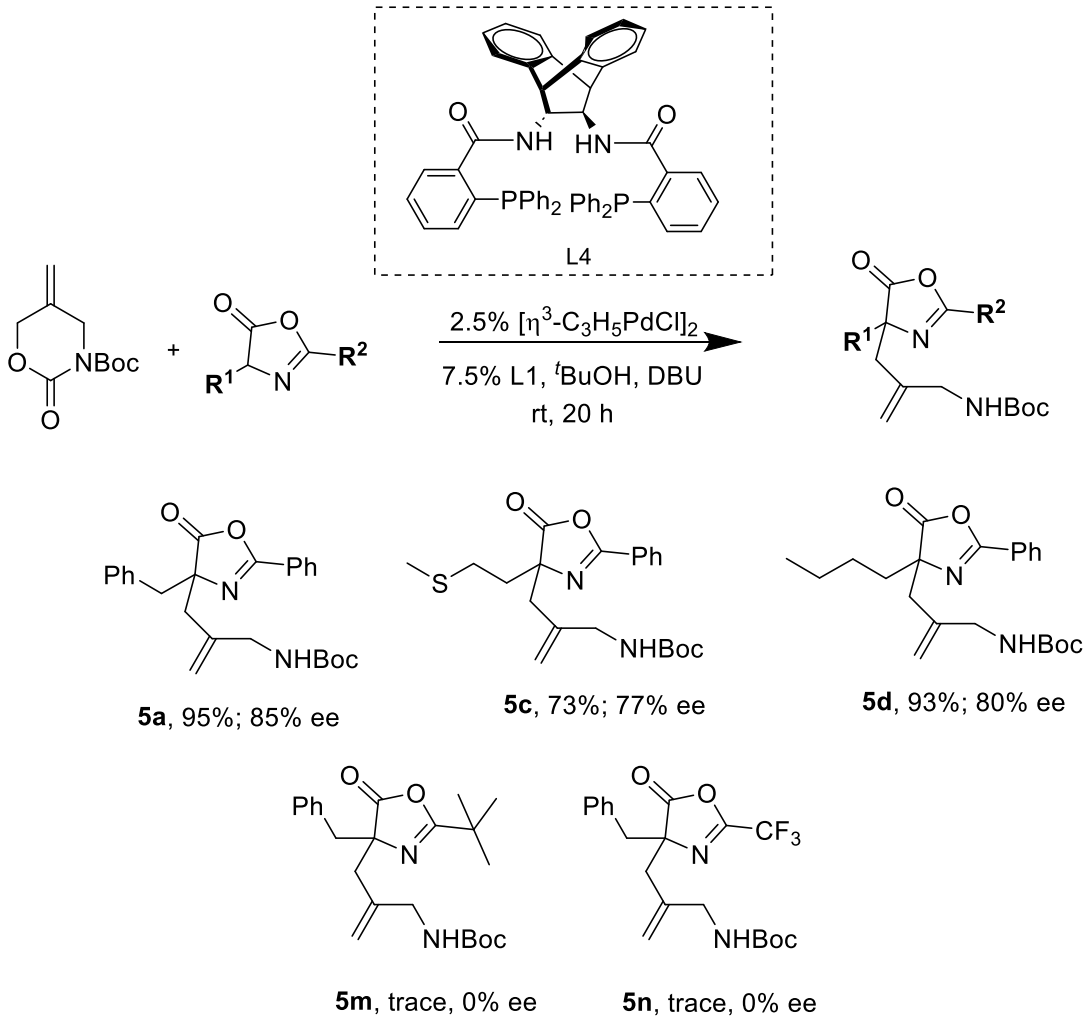
Ultimately, the optimum yield and enantioselectivity at the first selected optimization experiments were found to be the conditions shown in **Scheme 5.2**, which provided the intermediate compound with 85% ee and 85% yield by using **L4** as a chiral ligand and dioxane as solvent at room temperature.



Scheme 5.2. General mechanism of DAAA

5.2. Preliminary study of the scope of the allylation reaction

We screened the allylation reaction of a small selection of different azlactones using the optimal reaction conditions. Unfortunately, although the yields were acceptable, the ee values were just around 80% (**Scheme 5.3**), which was not useful enough for the next stage of the research program. Thus, it was necessary to find a better set of conditions that would provide higher ee values. We also explored the effect of various substituents at the azlactone *C*-2 position. We found that when the R_2 group is too big (**5m**, -$C(CH_3)_3$) or small (**5n**, -CF_3) the enantioselectivity was lost. This latter result was particularly disappointing because -CF_3 was significant for later hydrolysis strategies, as the corresponding lactams are generated as trifluoroacetamides.

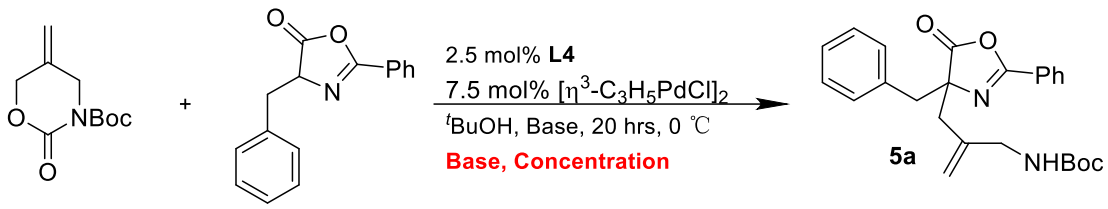


Scheme 5.3. Initial scope of allylation intermediates.

5.3. Second Selected Optimization Experiments

In order to improve the reaction further, we returned to the idea of modulating the reaction temperature. As we discussed in **5.2.2**, we continued to use room temperature rather than 0 ℃ because the freezing point of dioxane is 10 ℃. Thus, we wondered if the process of mixing dioxane with other solvents could lower the freezing point of the medium. Toluene was chosen as the solvent additive because, according to **Table 2, Entries 5,6**, the reaction proceeds with low conversion but the ee value of the product is basically the same as that in dioxane. We tried different toluene/dioxane ratios and found the solvent did not freeze when the ratio of these solvents was 2:8. Pleasingly, as shown in **Table 5, Entry 1**, the ee value increased to 91% although the yield decreased to 20%. Finally, we increased the yield of the reaction from 20% to 90% by changing the reaction concentration and using Hünig's base (**Table 6, Entry 4**).

Table 6. Second Selected Optimization Experiments



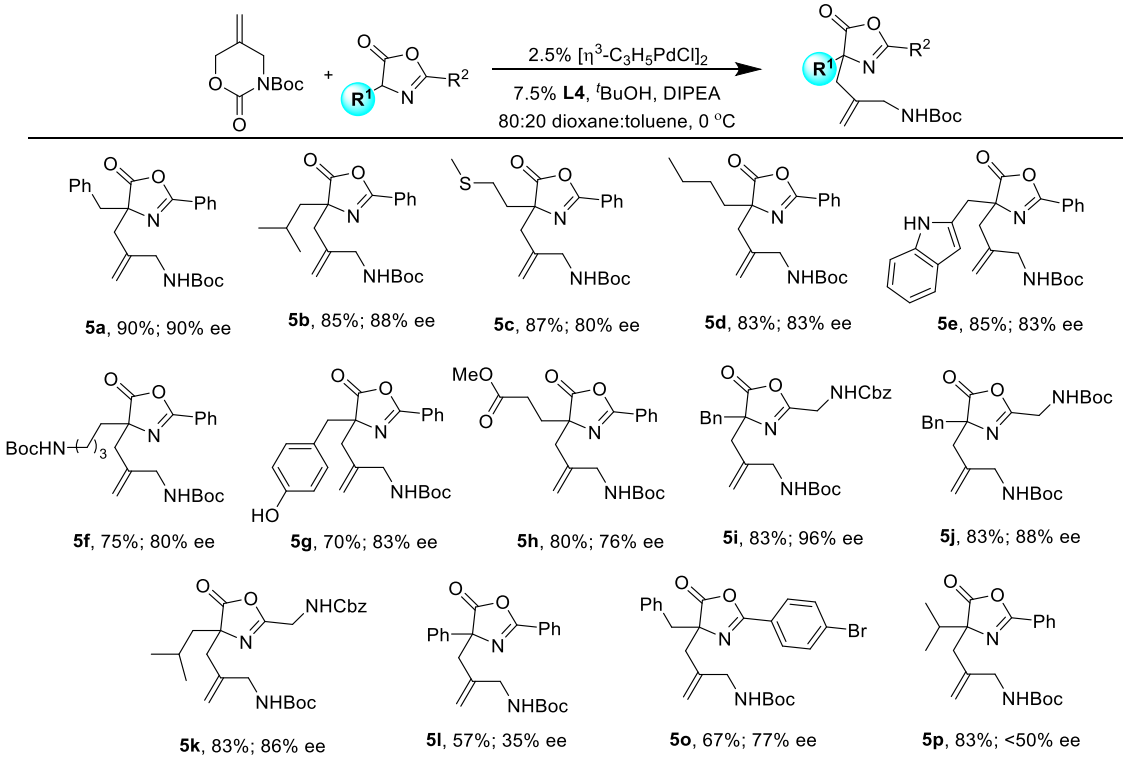
Entry	solvent	Conc.[a] (mol/L)	Base	Yield (%) [b]	ee (%) [c]
1	20% toluene in dioxane	0.0167	DBU	20	91
2	20% toluene in dioxane	0.05	TEA	20	91
3	20% toluene in dioxane	0.05	DIPEA	70	91
4	20% toluene in dioxane	0.1	DIPEA	90	90

[a] Concentration with respect to cyclic carbamate. [b] Yield after chromatography. [c] Determined by chiral HPLC with a constant flow rate of 1 mL/min using hexane/isopropyl alcohol 95:5 as the mobile phase.

5.4. Further study of the scope of the allylation reaction

We continued to screen the allylation reaction of different azlactones using the new optimal conditions. Pleasingly, as shown in **Scheme 5.4**, the ee values of target allylation intermediates (**5a**-**5h**) were found to be between 80-90%. When we used azlactones derived from dipeptides, the ee value of the allylation intermediates (**5i**-**5k**) was found to increase, with the example bearing a Cbz protecting group delivering the product with up to 96% ee.

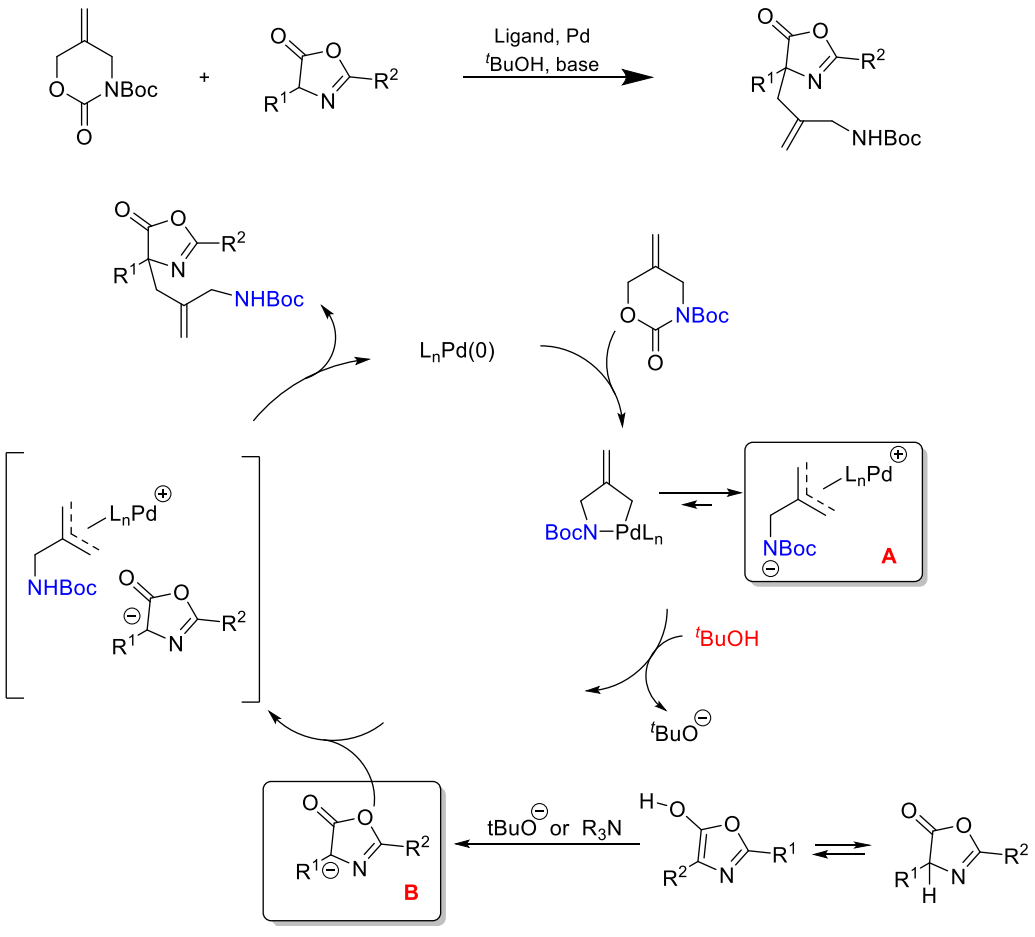
Regarding the scope of R^1, we generally focused on natural amino acid side chains. However, we found when R^1 was a phenyl group, not only the ee value but also the yield of **5l** was lower as compared to other products. In addition, when R^1 was an isopropyl group, although two enantiomers were not fully separated by chiral HPLC, the ee value was lower than 50%. These results suggests that branched substituents at R^1 can result in reduced enantioselectivity.



Scheme 5.4. Scope of enantioselectivity in allylation products.

5.5. Mechanism of the allylation reaction

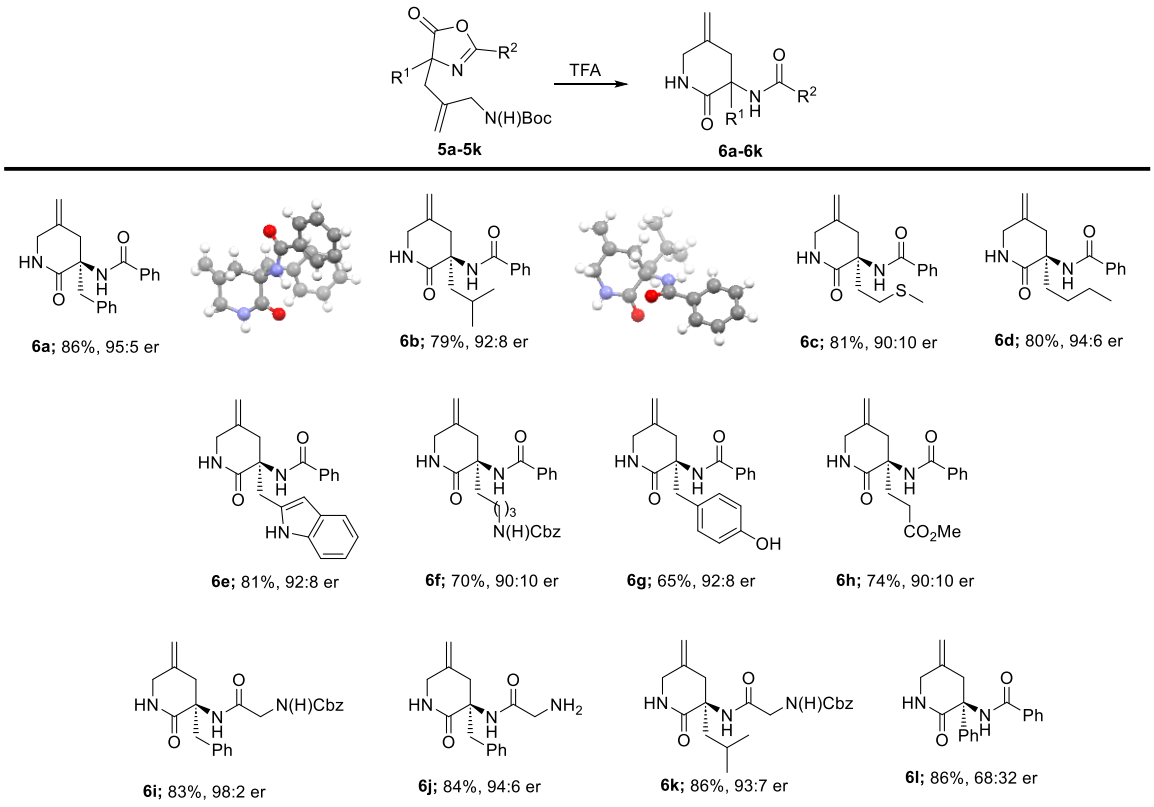
A plausible catalytic cycle based on the data from our experiments is depicted in **Scheme 5.5**. We found that when we used an achiral ligand the reaction proceeded in the absence of base although the yield was just 40%. However, the reaction did not proceed when we used Trost Ligands without a base. It is possible that when we used an achiral ligand, the Pd complex **A** played the role of base. However, when we used Trost ligands, because of the large steric hindrance, the Pd complex **A** was not able to function in this way. Therefore, the base additive converted the azlactone to the corresponding enolate **B**, while ^{t}BuOH prevented Pd complex **A** from transforming to the unreactive a five-membered metallocycle. What is less clear is why both ^{t}BuOH and the base additive are required, and so there may be an added role played by the H-bond donor properties of ^{t}BuOH.



Scheme 5.5. Mechanism of our DAAA reaction.

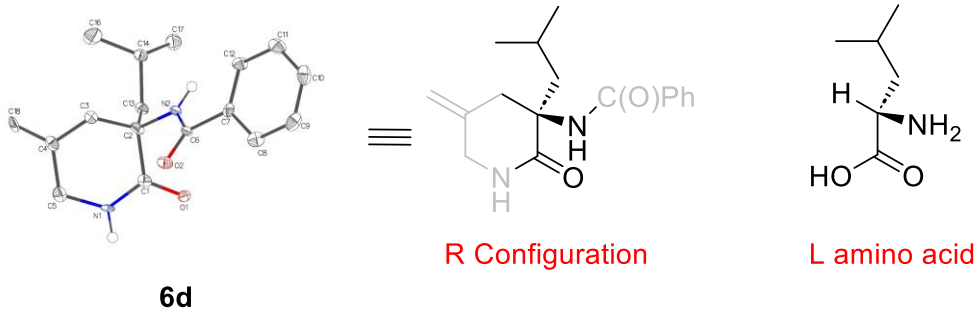
6. The Synthesis of Freidinger Lactams

The allylation intermediates (**5a-5l**) could be smoothly transformed to the corresponding lactams (**6a-6l**) after removal of the Boc-group with TFA. The methodology showed good generality, delivering lactam mimics bearing both polar and hydrophobic side-chains. Moreover, we were able to crystallize lactams **6a,b** and both showed the (*R*)-configuration at the newly generated stereogenic center. The stereochemistry of the remaining compounds was assigned by inference. Pleasingly, the subjection of azlactones **5i-k** to our optimized conditions generated FL_{Phe}-Gly dipeptides with or without a Cbz-protecting group, and Cbz-protected FL_{Leu}-Gly, both with high enantiomeric ratios. It is worth noting that indole can be decomposed by highly concentrated TFA solution (75 mmol TFA in 10 mL DCM). Thus, when we synthesized FL_{Trp} (**6e**), we used a relatively low-concentration TFA solution (8 mmol TFA in 10 mL DCM) and monitored the reaction carefully by TLC analysis.



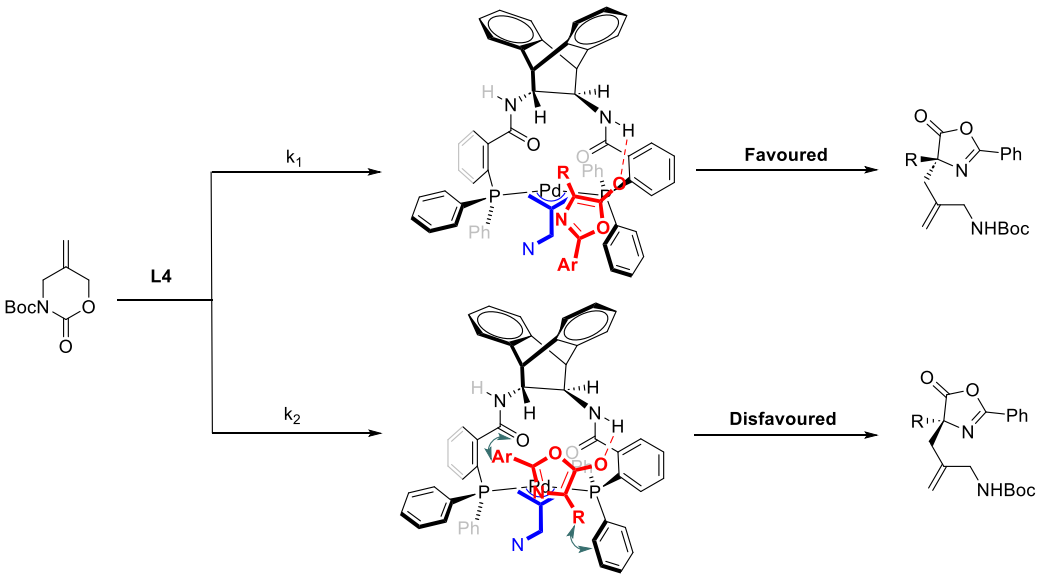
Scheme 6.1. Scope of enantioselective Freidinger lactam syntheses.

Fortunately, according to the 3D structures of **6a,b**, the configuration of the newly generated stereogenic center is the same as the natural amino acids (exemplified specifically with L-leucine in **Scheme 6.2**). It means we can synthesize constrained L-amino acid building blocks with synthetically useful enantiomeric ratios with good efficiency.



Scheme 6.2. Comparison between structure of 6b and natural L-leucine.

We have developed a model to explain the trends observed in our asymmetric allylation process. As shown in **Scheme 6.3**, pathway k_1 proceeds via a H-bond interaction with the catalyst N-H group according to the Lloyd-Jones Norrby model[36]. The alternative approach k_2 is less favorable as the *C*-4 substituent Ph points towards the catalyst 'roof' leading to destabilizing steric interactions.

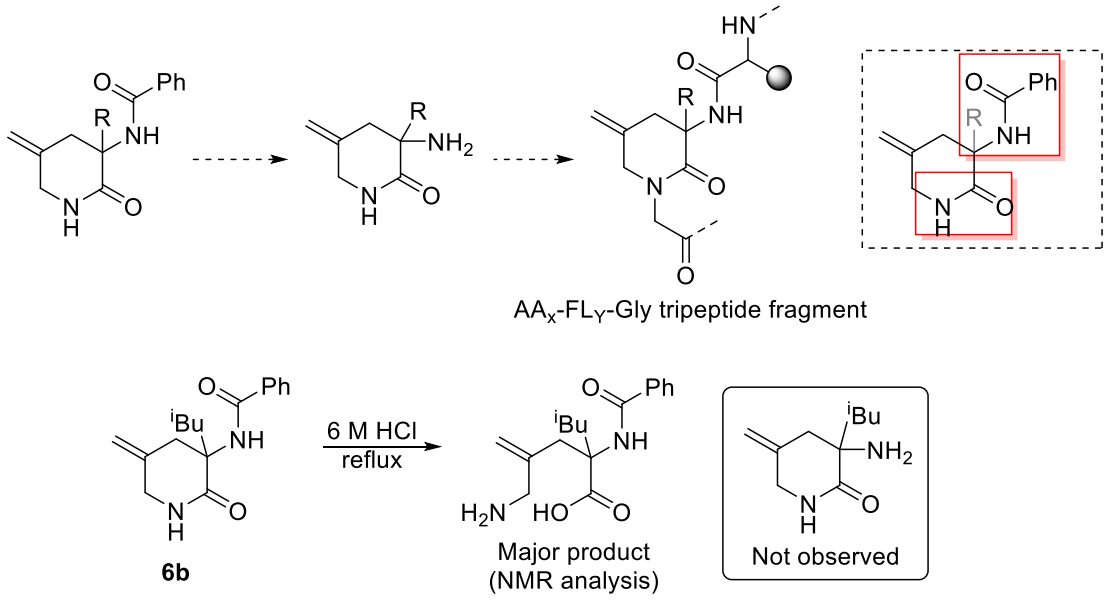


Scheme 6.3. Influence on enantioselectivity

7. Synthesis of Freidinger Lactam building blocks bearing a free amine group

7.1. The design of a new hydrolysis strategy

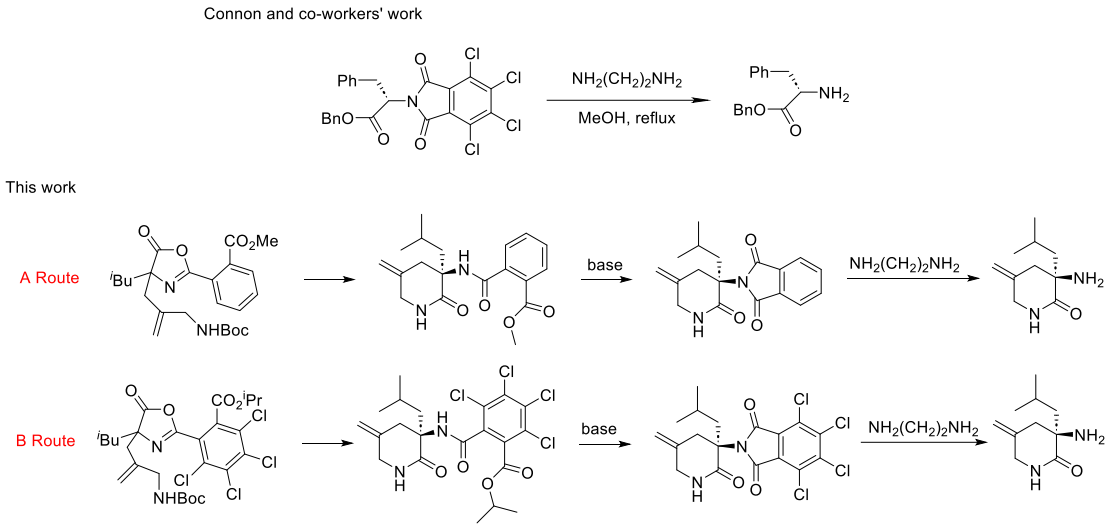
Originally, we planned to synthesize the Freidinger lactam building blocks with a free amine group by hydrolysing the benzamide group generated in our initial studies. However, we were aware of the potential problem that the lactams can also be hydrolysed during this process. Indeed, after attempting to hydrolyse the amide of **6b** using 6 M HCl at reflux, by analyzing the crude ^{1}H NMR spectrum, we found that the diagnostic AB spin peaks on the lactam ring disappeared, and a large number of new peaks appeared between 1-2 ppm (**Scheme 7.1**).



Scheme 7.1. Hydrolysis studies of **6b**

In this context, Connon and co-workers designed a family of azlactones that offer mild hydrolysis protocols via formation of phthalimide intermediates, and so we set out to investigate whether this chemistry could offer a useful solution to this

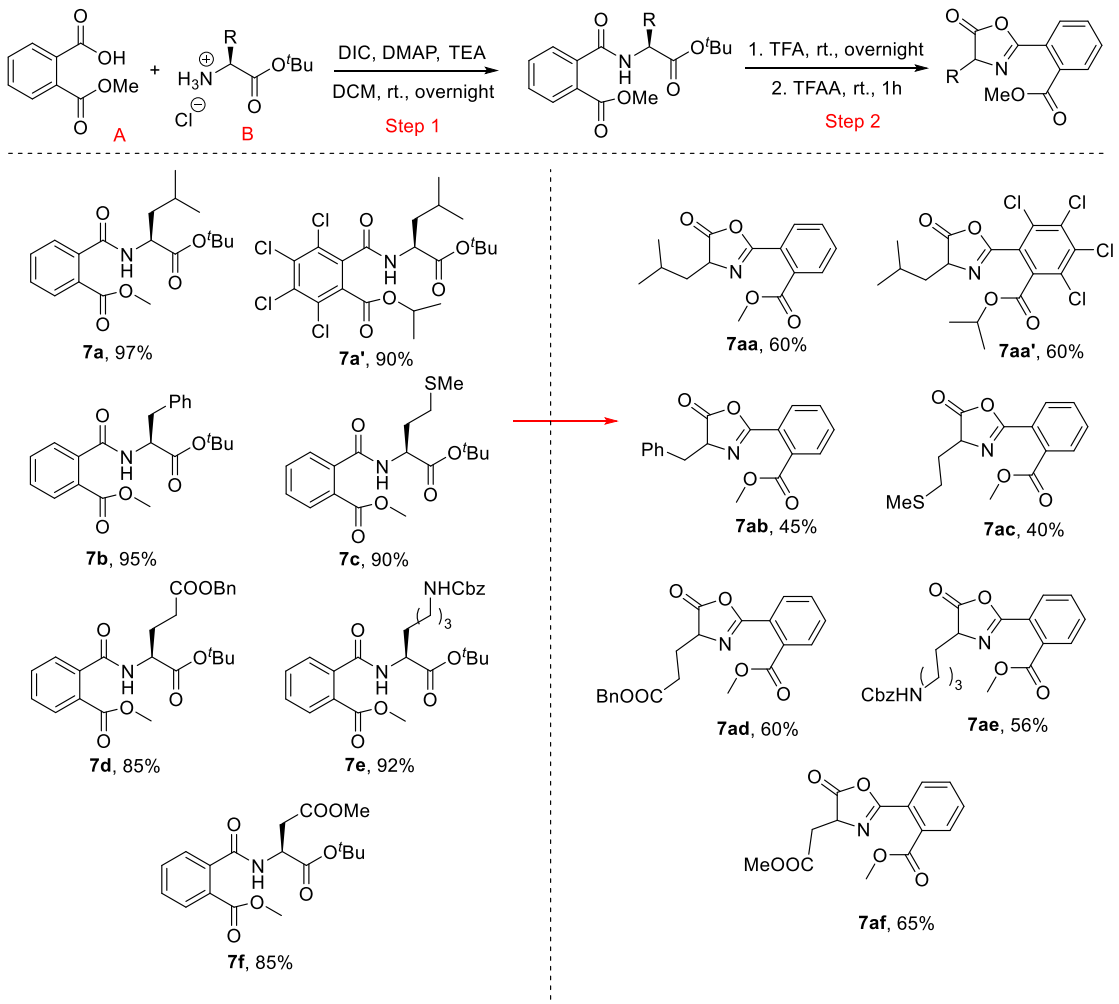
problem (**Scheme 7.2**).[37] We designed two routes to synthesise the relevant phthalimide intermediates and we chose route B as our preferred procedure. The reasons for this choice will be discussed in **7.3.**



Scheme 7.2. Designing a new hydrolysis strategy

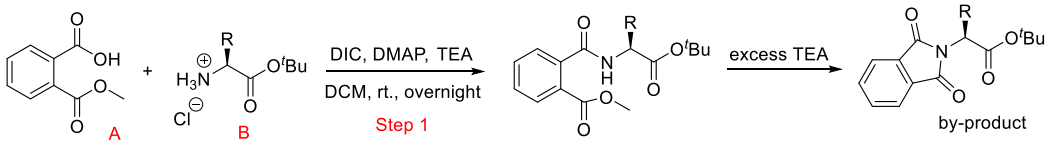
7.2 Synthesis of new azlactones

Pleasingly, we were able to synthesize the required azlactones containing an *ortho*-benzoate moiety using established chemistry. Thus, we could access analogues with neutral side chains (eg. **7a, 7b, 7c**), acidic side chains (ester protected, **7d, 7f**) and basic side chains (Cbz protected, **7e**) (**Scheme 7.3**) successfully.



Scheme 7.3. Scope of new azlactones

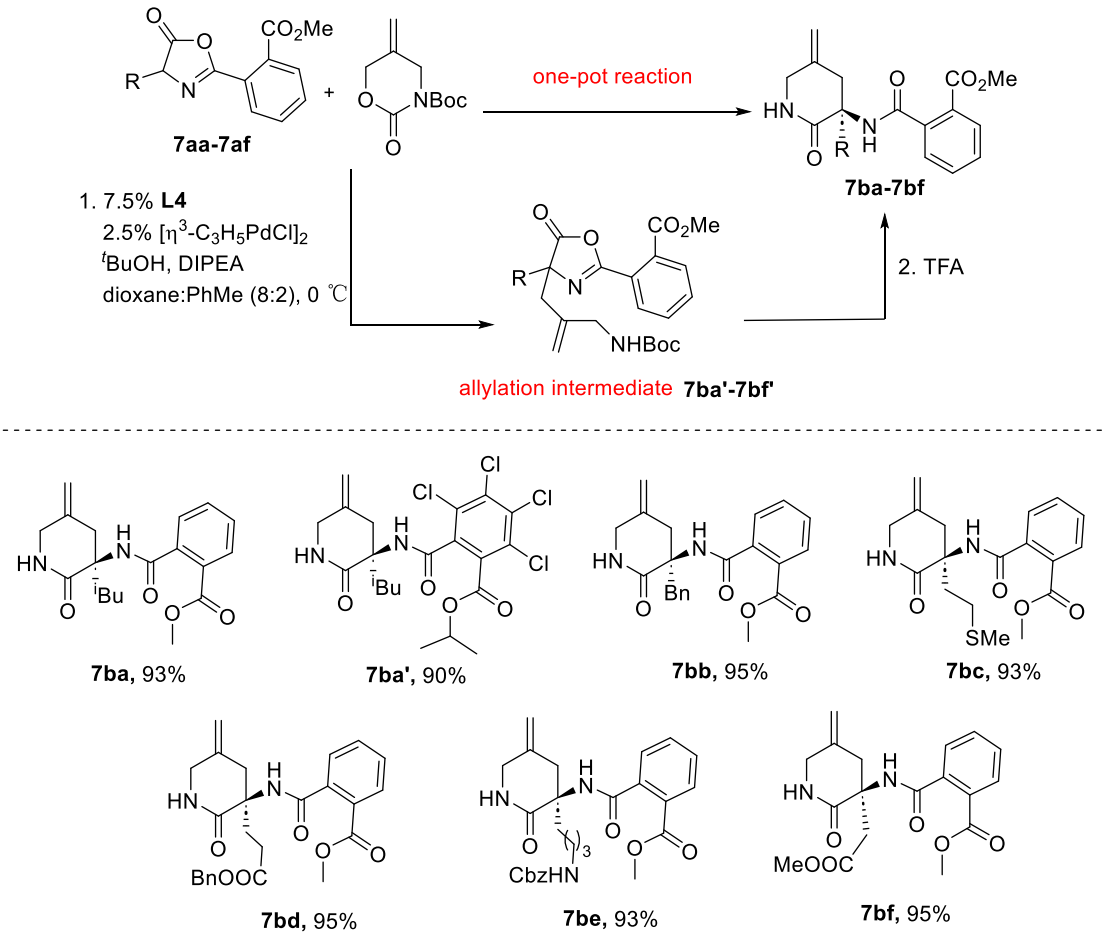
It should be noted that the purpose of adding triethylamine (TEA) in the first step is to neutralize hydrochloric acid to release the free amino group for reaction. However, triethylamine also could promote phthalimide formation as a side product which was isolated and analysed by nmr (**Scheme 7.4**). Therefore, TEA should not be added in excess; the protonated amine (B) should be stirred with 1 equivalent of TEA before adding the remaining reagents (monomethyl phthalate A, DMAP, and DIC, stirring for 30 mins, **Scheme 7.4)**.



Scheme 7.4. The side-reaction of step 1

7.3 Synthesis of new Freidinger lactams

With regard to the key allylation-cyclisation step, we used a one-pot reaction to synthesize Freidinger lactams directly because we found the allylation intermediates were difficult to resolve by chiral HPLC. The crude allylation intermediates (**7ba'-7bf'**) could be smoothly transformed to the corresponding lactams (**7ba-7bf**) after removal of the Boc-group with TFA (Scheme 7.5). The product ee was not assessed at this stage due to the propensity for cyclisation to the imide.

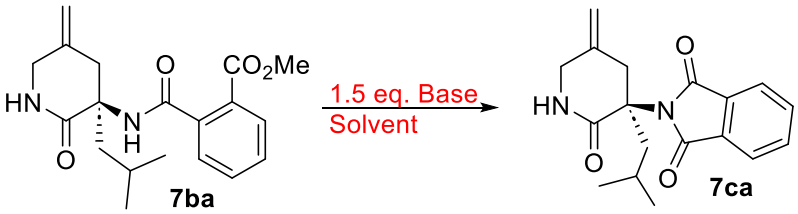


Scheme 7.5. The scope of new Freidinger lactam syntheses

7.4 Synthesis of phthalimide intermediates

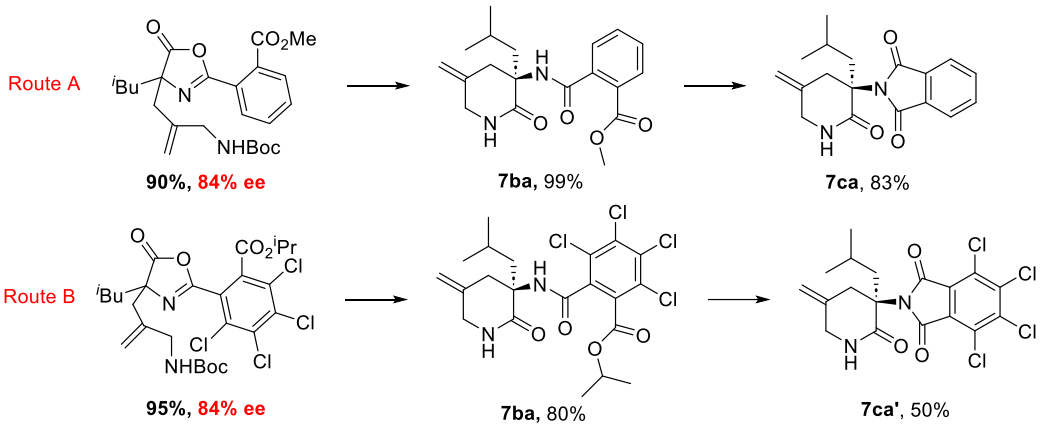
The next step in this sequence was the formation of the phthalimide unit. For this step, base appears to play a vital role in ensuring a high conversion in the cyclisation step. According to **Table 7.1, Entries 1, 2, and 3**, with the pKa of base increasing, the conversion increases from 0% to 80%. Finally, heating the reaction at 80 °C in THF delivered the optimal conditions.

Table 7.1. Base, solvent and temperature screening



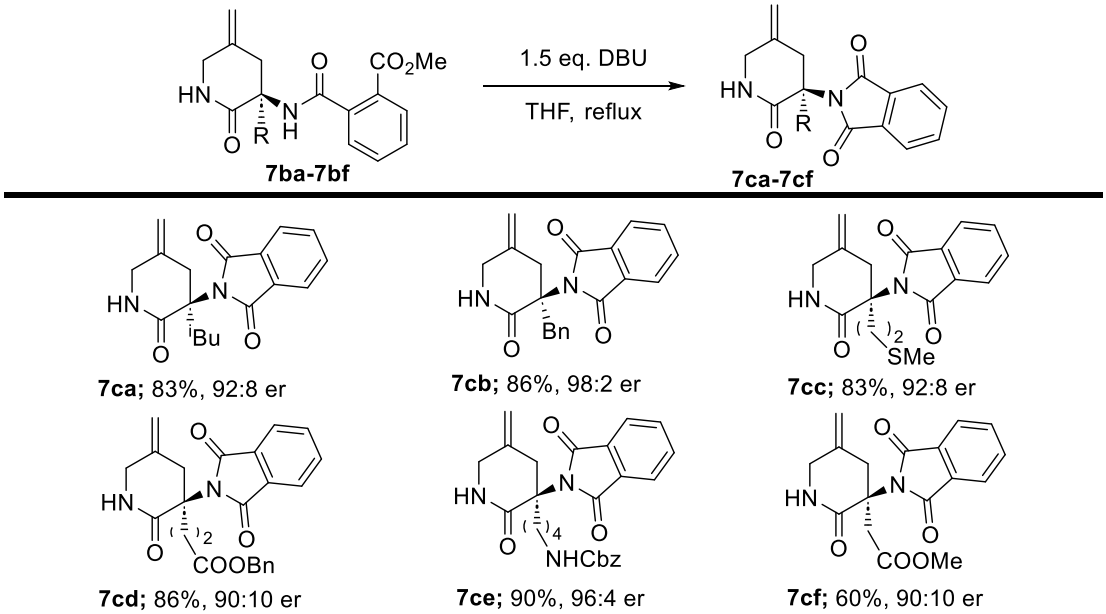
Entry	Base	Solvent	Temperature	Conversion
1	TEA	$CHCl_3$	40 ℃	0
2	DIPEA	$CHCl_3$	40 ℃	30%
3	DBU	$CHCl_3$	40 ℃	80%
4	DBU	THF	80 ℃	100%

As was discussed in **Scheme 7.2**, we decided to synthesise two phthalimide intermediates (**7ca** and **7ca'**) according to Connon's work[37] and to investigate their suitability for the synthesis of free amine products (**Scheme 7.6**). In the event, we found route A to be more effective for two reasons. Firstly, we found that the polarity of **7ca'** and **7ba'** were very similar, which meant that it was difficult to monitor the reaction by TLC analysis, and purify the product by flash column chromatography. Secondly, although the ee value of the product **7ca** was as same as the compound **7ca'** generated by route B, the yield of **7ca** was high than **7ca'**. Thus, we chose the route A as our synthetic strategy.



Scheme 7.6. Comparative routes to two phthalimide intermediates.

Finally, the Freidinger lactams (**7ba - 7bf**) could be smoothly transformed to the corresponding phthalimide intermediates (**7ca - 7cf**) (**Scheme 7.7**). Interestingly we observed that racemic **7cb** and **7cf** were poorly soluble in common organic solvents. Additionally, **7cf** showed particularly weak UV absorption which made it difficult to analyse by chiral HPLC. Thus, we based the ee value on the allylation product (**7bf**) in this particular case as these should be the same as the lactam product. During the synthesis of enantiomer **7cf** the extremely low solubility resulted in difficulties when purifying via flash chromatography thereby giving lower yields relative to the other analogues.

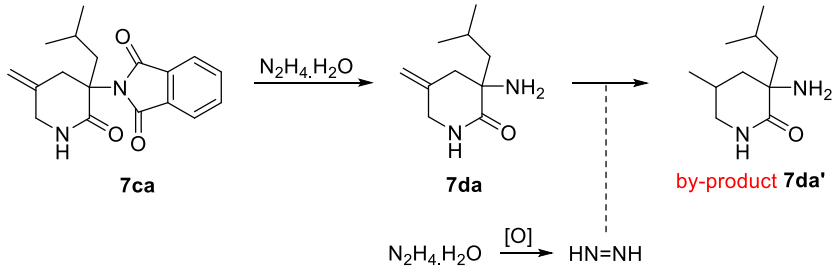


Scheme 7.7 The scope of phthalimide intermediate syntheses

7.5 Synthesis of the Freidinger lactam building blocks containing a free amine group.

The final step involved the hydrolysis of the phthalimide group. Initial studies using hydrazine in THF (1 M) showed poor reactivity. In contrast, hydrazine monohydrate led to complete conversion and the product **7da** was clearly observable. Surprisingly however, some reduced by-product **7da'** was formed at the same time. Finally, we realized that hydrazine could react with oxygen to form diimide, a strong reducing agent. Thus, we conducted the reaction under a nitrogen atmosphere, and we were pleased to find that the formation of by-products was greatly suppressed.

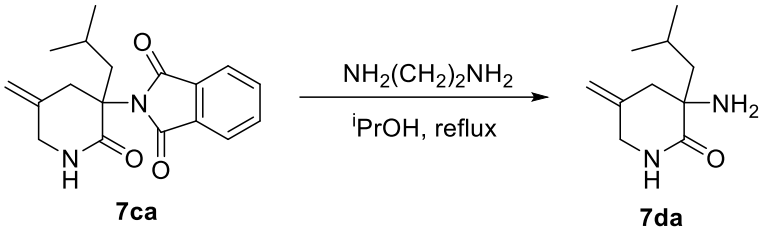
Table 7.2. hydrolysis optimisation



Atm.	Solvent	Temp.	hydrazine monohydrate (eq)	Reaction time	Conversion	Product : By-product
Air	EtOH	75	6	16 h	100%	1 : 1
Air	EtOH	75	6	6 hours	60%	2 : 1
Air	^{i}PrOH	75	6	16 h	100%	1 : 1
Air	^{i}PrOH	65	3	16 h	60%	1 : 0.1
N_2	^{i}PrOH	75	6	16 h	95%	>98:2

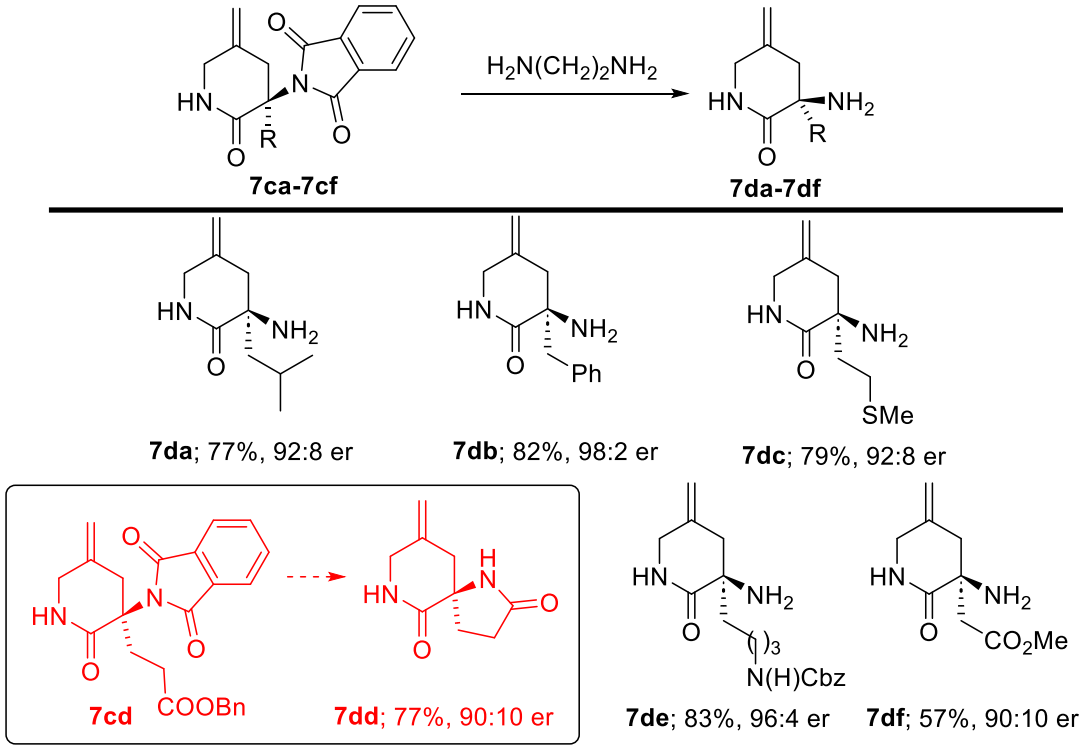
We continued to optimize our experimental conditions (**Table 7.3**). Finally, we found ethylenediamine to be superior to hydrazine for phthalimide hydrolysis; conversion was at 100% with no reduced by-product observed.

Table 7.3. hydrolysis condition optimizing



$NH_2(CH_2)_2NH_2$ (eq)	Conc. (M)	Reaction time (h)	Conversion
4.5	0.1	16	80%
4.5	0.1	24	90%
9	0.2	24	100%

We were able to transform **7ca**-**7cf** into the corresponding free amine building blocks **7da-7df** through a simple protocol, generating the products in good yield and enantiocontrol. Interestingly, the product derived from glutamic acid based **7cd** underwent further cyclization when subjected to this sequence, generating functionalized spiro lactam **7dd**.

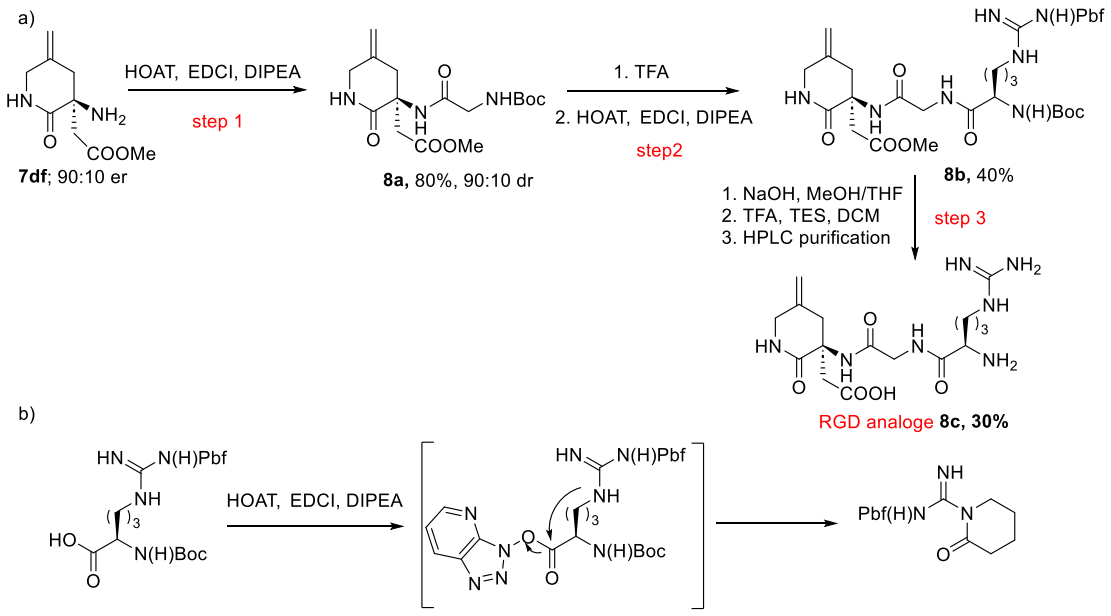


Scheme 7.7 The scope of phthalimide intermediate syntheses

8. Application in Tripeptide Synthesis

8.1. Synthesis of RGD analogue

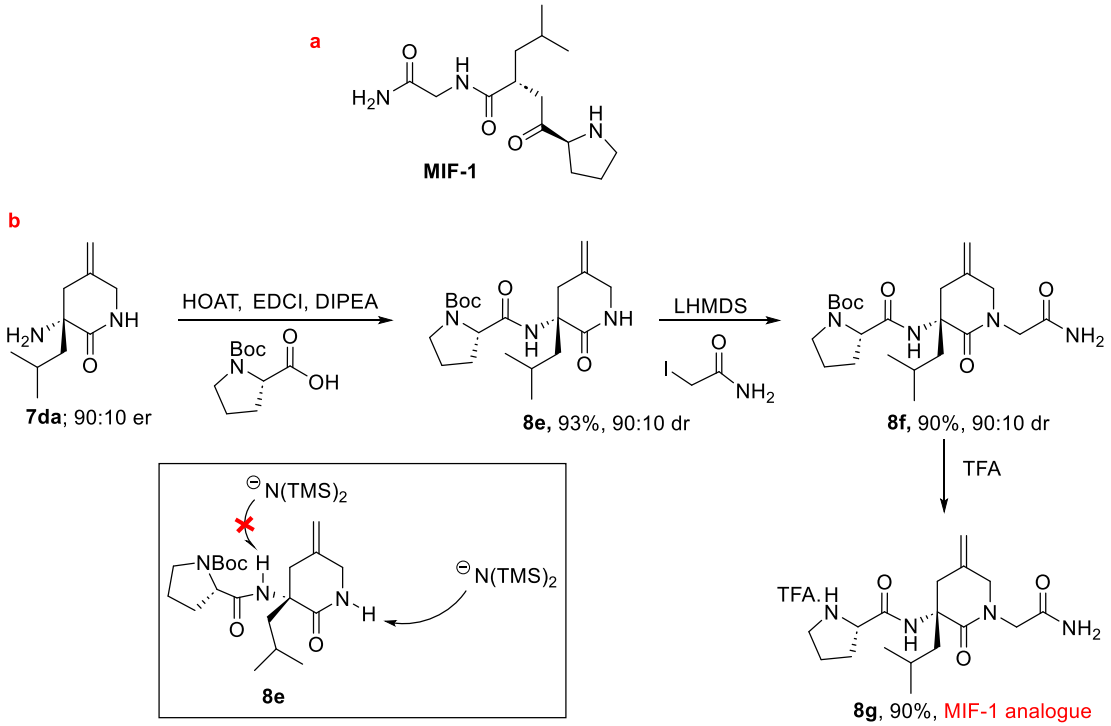
RGD is a recognition motif for integrin receptors and the incorporation of this tripeptide into cyclic pentapeptides has led to the successful identification of selective ligands for integrin receptor sub-types, with Cilengitide being a prominent exemplar.[38] We targeted a constrained RGD analogue using **7df** as the starting amino acid in order to establish the potential of this chemistry for peptidomimetic synthesis (**Scheme 8.1 a**). Initially, we were concerned that the free amino group of **7df** was not going to be reactive enough towards amide formation because of steric hindrance. However, the yield of step 1 turned out to be excellent by using HOAt and EDCI as coupling reagents. Disappointingly, the yield of the step 2 was not high (40%), which may be due to the intramolecular condensation of arginine itself (**Scheme 8.1 b**). Finally, the deprotection reaction was successful as expected. Notably, purification of **8b** allowed its isolation as a single diastereoisomer, and the final analogue **8c** was purified by preparative HPLC.



Scheme 8.1. The procedure of RGD analogue syntheses

8.2. Synthesis of MIF-1 analogue

MIF-1 (**Scheme 8.2a**) is a hypothalamic neuropeptide derived endogenously by cleavage of the hormone oxytocin.[39] It displays a range of bioactivities and has been studied for the treatment of Parkinson's disease, as well as for its antidepressant and nootropic activities. Pleasingly, we were able to successfully synthesize MIF-1 analogue **8g** within a short synthetic sequence (**Scheme 8.2b**). In step 2, we used LHMDS as base directly in order to exploit the large steric hindrance of this base to select the less sterically hindered lactam proton rather than the amide.



Scheme 8.2. MIF-1 analogue synthesis

To demonstrate the effect of the Freidinger lactam building blocks on the peptide structure, we needed to perform X-ray analysis on the MIF-1 analogues. Although the MIF-1 analogue **8g** was a yellow oil, fortunately, **8f** was a colourless solid. Thus, we grew suitable crystals of **8f** for X-ray crystallographic analysis. We used different solvents in a ratio of 1:9 (high polarity solvent: low polarity solvent) to dissolve **8f**. With the high polarity solvent evaporating, crystals would grow in the low polarity

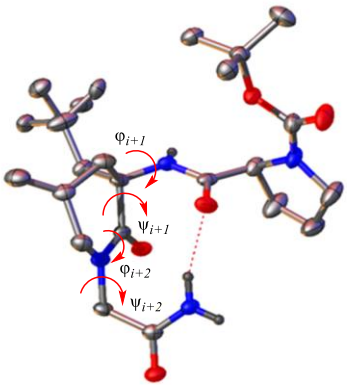
solvent (**Table 8.1**). Finally, after trying different solvent mixtures we obtained crystals suitable for X-ray diffraction using acetone/hexane as a solvent mixture.

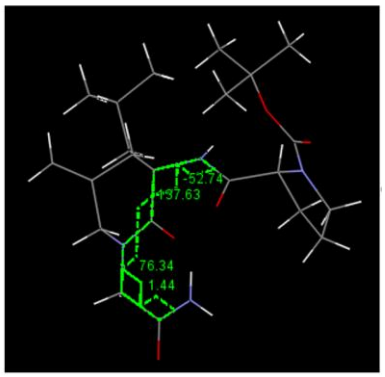
Table 8.1 Mixture solvents screening for crystal growing.

Entry	High polarity solvent	low polarity solvent
1	DCM	Toluene/Hexane/Petrol
2	Et_2O	Toluene/Hexane/Petrol
3	EtOAc	Toluene/Hexane/Petrol
4	Acetone	Toluene/Hexane/Petrol

We were able to grow suitable crystals of **8f** for X-ray crystallographic analysis and as shown in **Table 8.2** this compound showed the 10-membered glycinamide-proline hydrogen bond and dihedral angles that are consistent with βII-type turns. Notably, the H-bond interaction between the *C*-terminal glycinamide hydrogen and the prolyl carbonyl oxygen has been observed in natural MIF-1, both in solution and in the solid state,[40] highlighting that these lactam mimics can deliver peptides that maintain key secondary structural features.

Table 8.2 X-ray crystallographic analysis of **8f**





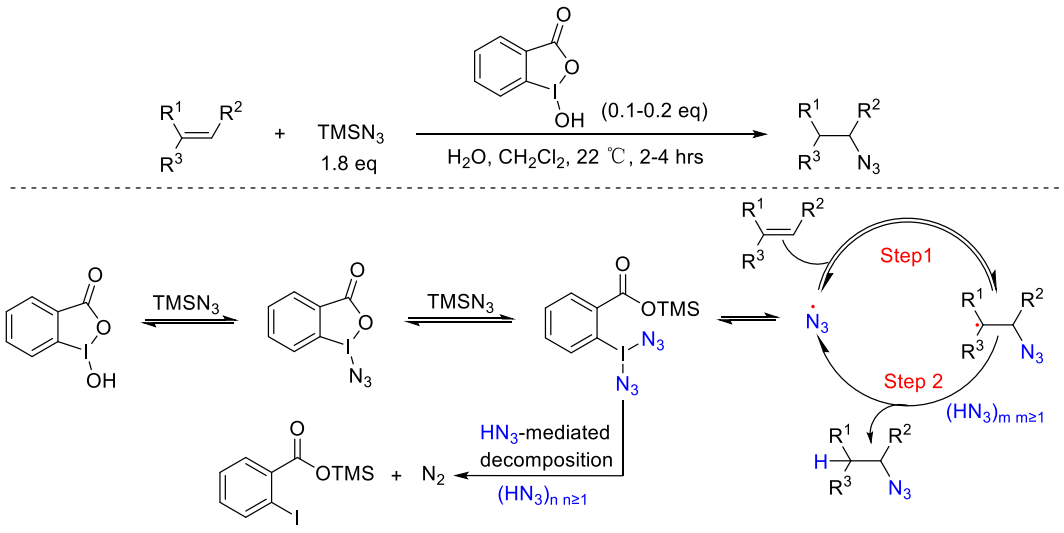
	ϕ_{i+1}	ψ_{i+1}	ϕ_{i+2}	ψ_{i+2}
type II	-60	120	80	0
type II'	60	-120	-80	0
MIF-1 analogue	-52.74	137.63	76.34	1.44

9. Modification of the olefin

In planning experiments for the modification of the olefin, we had anticipated that this objective should be relatively straightforward. However, by comparison to similar reactions described in the literature, we found that the alkene functionalisation of our lactams raised a number of challenges. This chapter discusses these reactions one by one and discusses the possible reasons for the problems that arose.

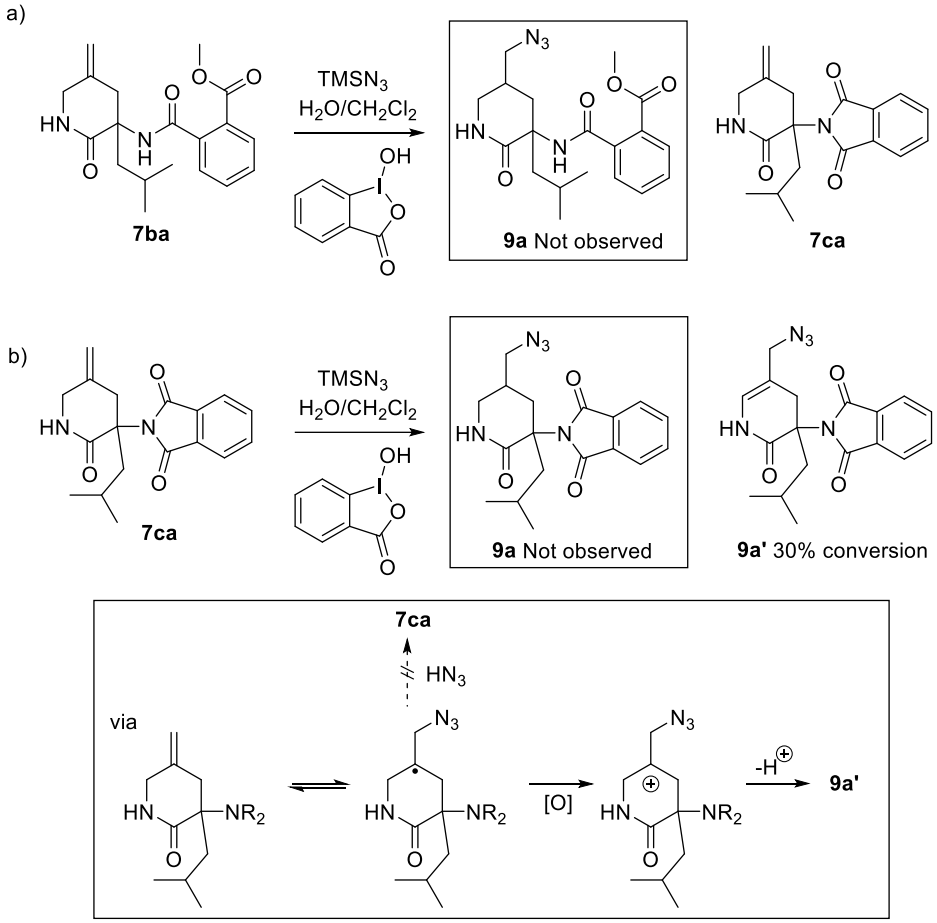
9.1 Hydroazidation of the olefin

As Freidinger lactam building blocks were designed for the synthesis of peptidomimetics, we first thought of addition of hydrazoic acid across an alkene. This would introduce the azide that could be exploited in click chemistry. Xu's work provided a feasible plan (**Scheme 9.1**).[41] They proposed that an azide radical, generated by the reaction between $TMSN_3$ and benziodoxole, would add to an alkene. Then HN_3 which was formed through the reaction between azide radical and H_2O, would convert the carbon radical to a C-H bond thus reforming the azide radical for propagation.



Scheme 9.1

We performed this reaction using **7ba** as starting material. However, the product **9a** was not formed as expected, but instead phthalimide intermediate **7ca** was generated (**Scheme 9.2a**). We speculated that phthalimide formation could be consuming the reagents and so we used intermediate **7ca** directly. Unfortunately, the target product **9a** was still not formed (**Scheme 9.2b**), although the by-product **9a'** was isolated, albeit after only 30% conversion. We believe that **9a'** arises after the formation of the carbon radical intermediate which does not react with HN_3 as hoped, but instead is further oxidised to form an enamide. This approach was abandoned at this stage.

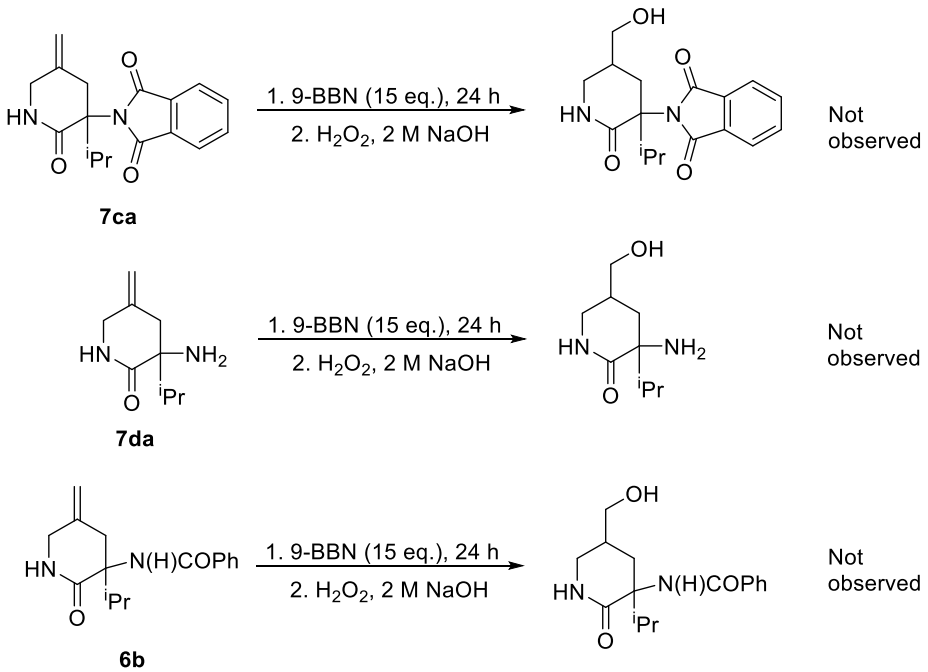


Scheme 9.2

9.2 Hydroboration–oxidation of the olefin

After failed attempts to introduce the azide group directly on the alkene, we decided to convert the alkene to hydroxyl group by a hydroboration-oxidation reaction. Although quite rare, hydroboration in the presence of amides is known which provided some reassurance that we could complete this transformation chemoselectively.[42] We initially used phthalimide intermediate **7ca** as the starting material for this purpose (**Scheme 9.3**). However, we did not get the corresponding alcohol product. It is possible that the phthalimide carbonyl may compete for reaction with 9-BBN. Thus, we used **7da** with 9-BBN in large excess (15 eq). Unfortunately, we still did not observe the target product. Finally, we used **6b** as the starting material for a final attempt. Once again, the target product was not generated.

By analyzing the crude ^{1}H NMR spectrum of these three reactions, we found that the diagnostic AB spin peaks on the amide ring disappeared, and a large number of new peaks appeared between 1-2 ppm. It is likely then that the hydroboration cannot compete with lactam reduction in our system.



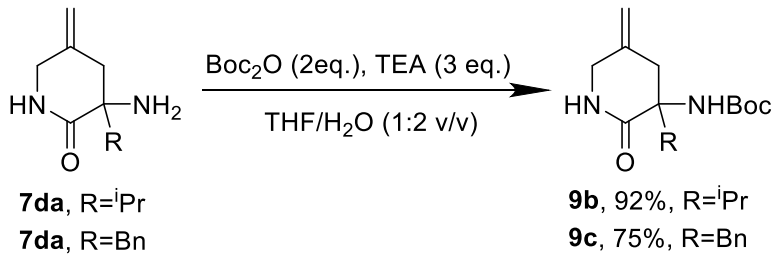
Scheme 9.3

9.3. Oxidative cleavage strategies

We decided to persist with alcohol forming reactions as the hydroxyl group provides a convenient point from which to attach other useful functionality (e.g. alkyne, azide). Therefore, we next tried to convert the olefin to a hydroxyl group via the corresponding ketone.

9.3.1 Oxidative cleavage of the olefin to ketone.

Before converting the olefin into a carbonyl group, we decided to protect the free amino group as a tert-butyl carbamate. After some optimisation we found that the use of THF/water (1:2 v/v) mixed solvent gave excellent yields in the protection step of 75-92% (**Scheme 9.4**).

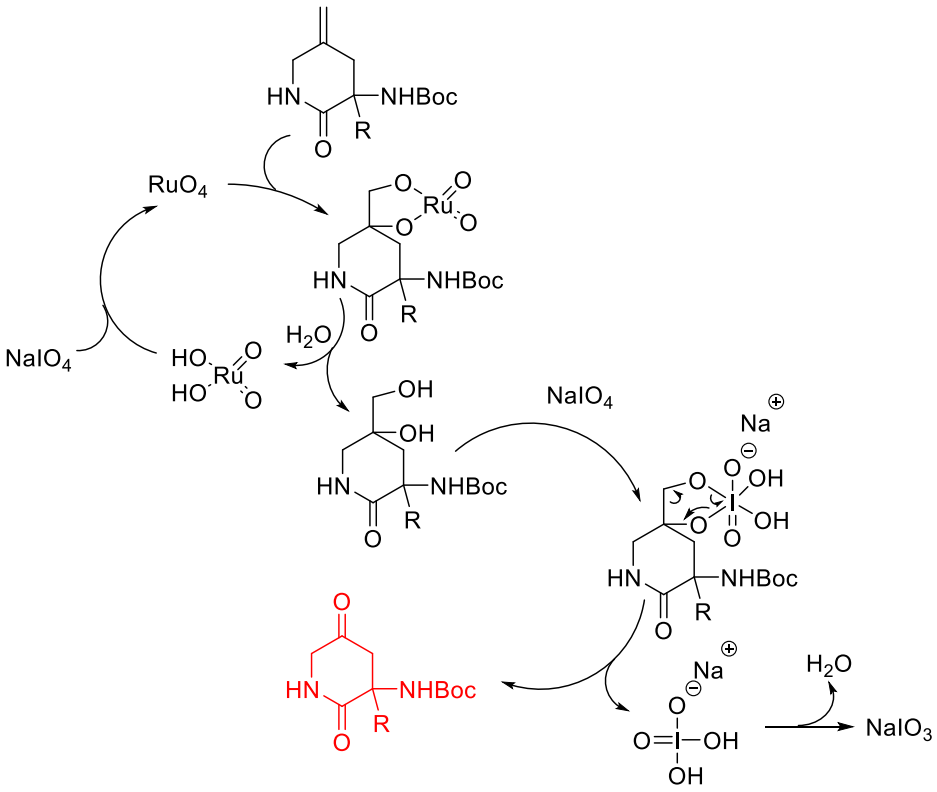


7da, R=^{i}Pr
7da, R=Bn

9b, 92%, R=^{i}Pr
9c, 75%, R=Bn

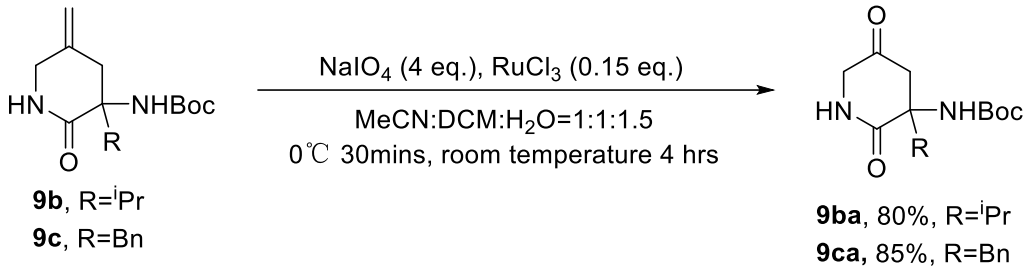
Scheme 9.4

We then converted the olefin to a carbonyl using $RuCl_3$ and $NaIO_4$. Compared with the oxidation of an olefin with O_3, the advantages of this method are that the reactants were more readily available and safer, the reaction conditions are milder and the work-up is simpler. From a mechanistic viewpoint, $RuCl_3$ and $NaIO_4$ first form RuO_4, which can oxidize the olefin to a 1,2-diol. Then the excess of $NaIO_4$ can oxidize the diol to two carbonyls by breaking the C-C bond. Sub-stoichiometric amounts of $RuCl_3$ can be used because the Ru^{VI} formed in the reaction can be oxidized by $NaIO_4$ to reform RuO_4 (**Scheme 9.5**).



Scheme 9.5

After several small-scale tests, we found that using 4 eq. $NaIO_4$ and 0.15 eq. of $RuCl_3$ resulted in a smooth reaction with the olefin at room temperature (**Scheme 9.6**).



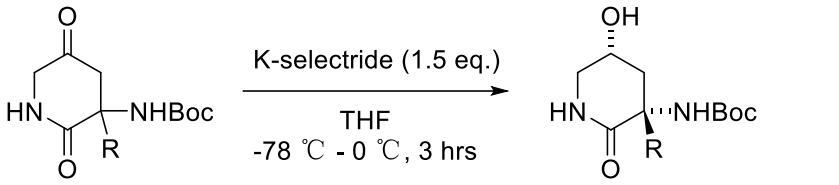
9b, R=^{i}Pr
9c, R=Bn

9ba, 80%, R=^{i}Pr
9ca, 85%, R=Bn

Scheme 9.6

9.3.2 Reduction of carbonyl to hydroxyl

As expected, the carbonyl group was successfully reduced by K-Selectride to the hydroxyl group. However, as shown as **Scheme 9.7**, different R groups had a significant influence on the reduction diastereoselectivity. The d.r. value was only 2:1 when the R was Bn group but the d.r. value could be up to 10:1 when R was an ^{i}Bu group. The major diastereomer of **9bb** was assigned as the 1,3-*cis* amino alcohol, and the assignment is discussed later.



9ba, R=^{i}Bu
9ca, R=Bn

9bb, R=^{i}Bu, 88% yield, d.r.=10:1
9cb, R=Bn, 85% yield, d.r.=2:1

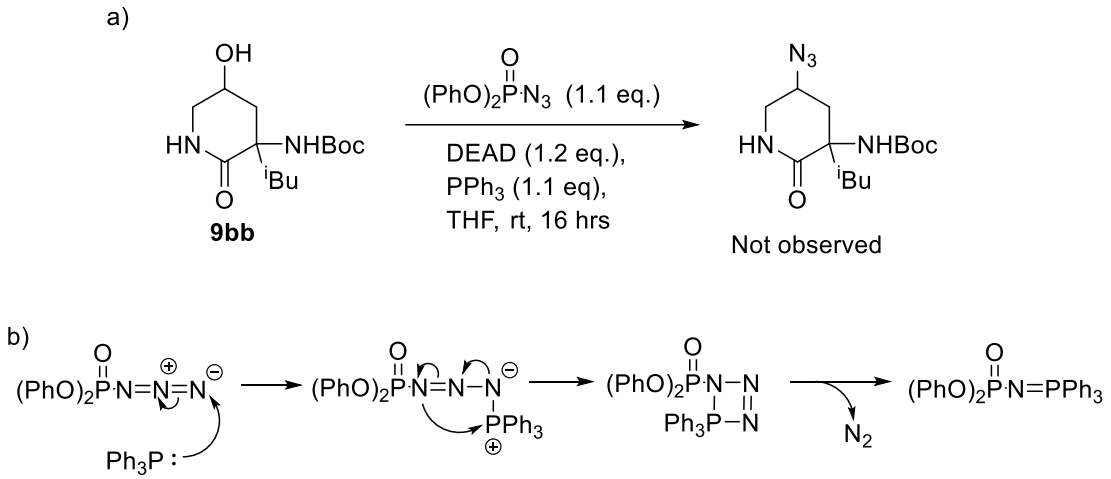
Scheme 9.7

9.4. Modification of the hydroxyl group.

We wanted to use the hydroxyl to append an azide group or alkyne by a Mitsunobu reaction or a substitution reaction. Thus, we designed two experimental protocols to achieve this goal.

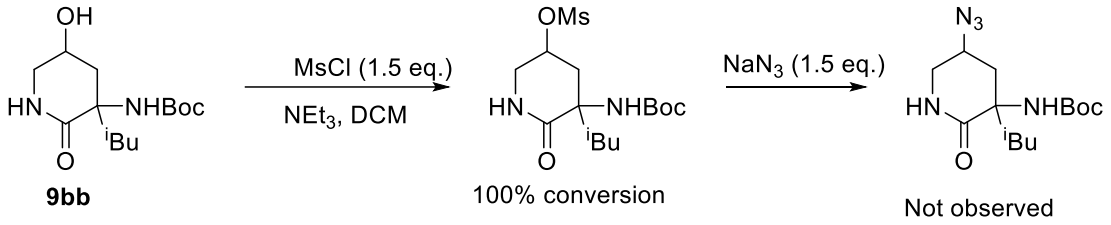
9.4.1 Conversion of the hydroxyl to the azide group

At first, we wanted to convert the hydroxyl group to the azide group by a Mitsunobu reaction (**Scheme 9.8 a**). Notably, it is necessary to stir the mixture of **9bb**, DEAD and PPh_3 for half an hour and then slowly to add diphenyl phosphoryl azide to prevent triphenylphosphine undergoing a Staudinger reaction (**Scheme 9.8 b**). Unfortunately, the product did not form after repeated experiments.



Scheme 9.8

We next tried to convert the hydroxyl to a better leaving group which could be replaced by an azide anion. Thus, we converted the hydroxyl to the corresponding mesylate group which proceeded in 100% conversion. Unfortunately, the azide substitution reaction was found to be unsuccessful even in the presence of a number of different bases (TEA, DIPEA, DBU) (**Scheme 9.9**).

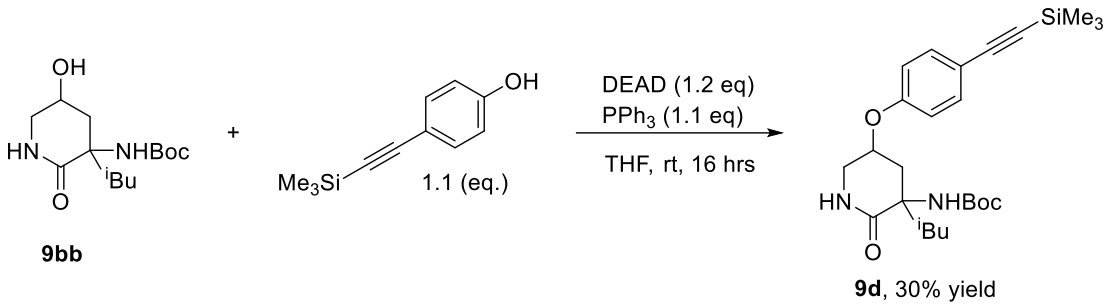


Scheme 9.9

9.4.2 Conversion of the hydroxyl to an alkyne.

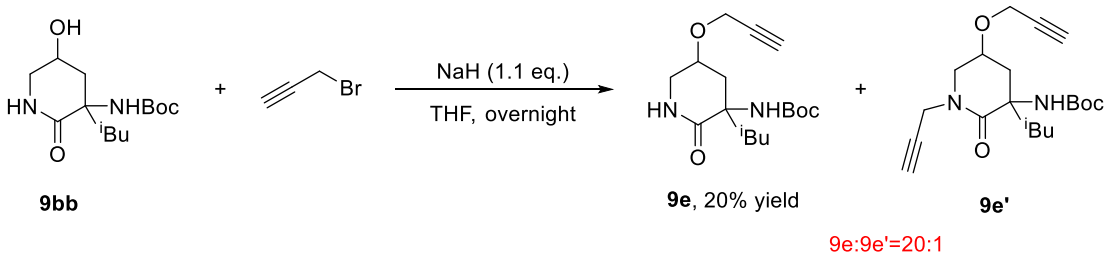
As we were unable to incorporate an azide, we decided to install an alkyne as an alternative way of enabling downstream 'click' chemistry. At first, we tried the Mitsunobu reaction to connect the alkyne onto the hydroxyl (**Scheme 9.10**). However, the yield of the reaction was quite poor. We tried to increase the yield by heating,

prolonging the reaction time, increasing the concentration of the reaction substrate etc. but the results were not satisfactory.



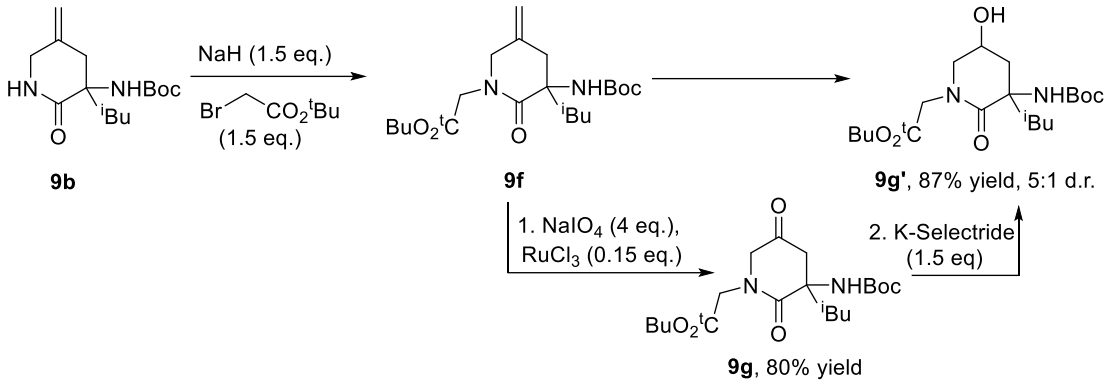
Scheme 9.10

We then decided to explore a base promoted alkylation of **9bb** with propargyl bromide to connect an alkyne. However, we recognised the potential for the base to simultaneously deprotonate the lactam N-H, leading to the formation of by-products. Thus, we did a small-scale test to establish which group was more reactive (**Scheme 9.11**).



Scheme 9.11

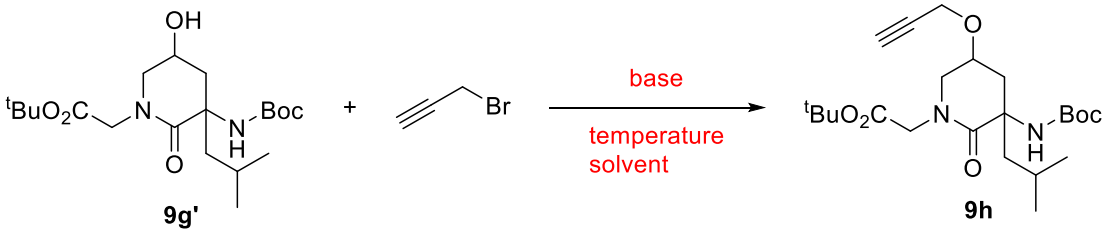
As shown as **Scheme 9.11**, it appears that the hydroxyl group was far more reactive than the lactam. However, the yield was far lower than we had expected (only 20%). Thus, we decided to protect the lactam first to avoid the problem of non-selective alkylation (**Scheme 9.12**). Then we used 4 eq. $NaIO_4$ and 0.15 eq. of $RuCl_3$ resulted in a smooth reaction to convert the olefin to a carbonyl followed by using K-Selectride to reduce the ketone to give primary alcohol product **9g'**.



Scheme 9.12

With substrate **9g'** in hand, we re-examined the alkylation step. As shown in the **Table 9.1**, we found that the use of excess strong base (**Entry 5**) or elevated temperatures (**Entries 3**), led to hydrolysis of the starting material **9g'**. When we used fewer equivalents of base at room temperature, the conversion of the reaction was only 10%. Finally, we found that using NaOH as base and acetone as solvent, the reaction yield could be improved to 30% when the reaction was heated at reflux. However, this result was still not satisfactory.

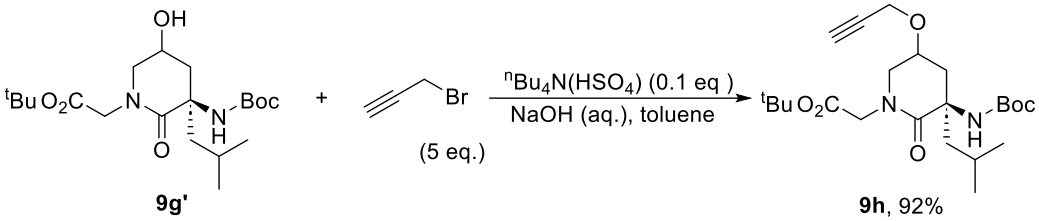
Table 9.1



Entry	Base	Equivalent	Solvent	Temperature	Yield
1	Li^{n}Bu	1.5eq	THF	r.t.	10% conversion
2	LHMDS	1.5eq	THF	r.t.	10% conversion
3	LHMDS	1.5eq	THF	reflux	Hydrolysis[a]
4	NaH	1.5eq	THF	r.t.	10% conversion
5	NaH	3eq	THF	r.t.	hydrolysis
7	NaOH	4eq	Acetone	r.t.	10% conversion
8	NaOH	4eq	Acetone	reflux	30%

a) Neither products **9h** nor starting materials **9g'** could be detected by ^{1}H NMR spectroscopy.

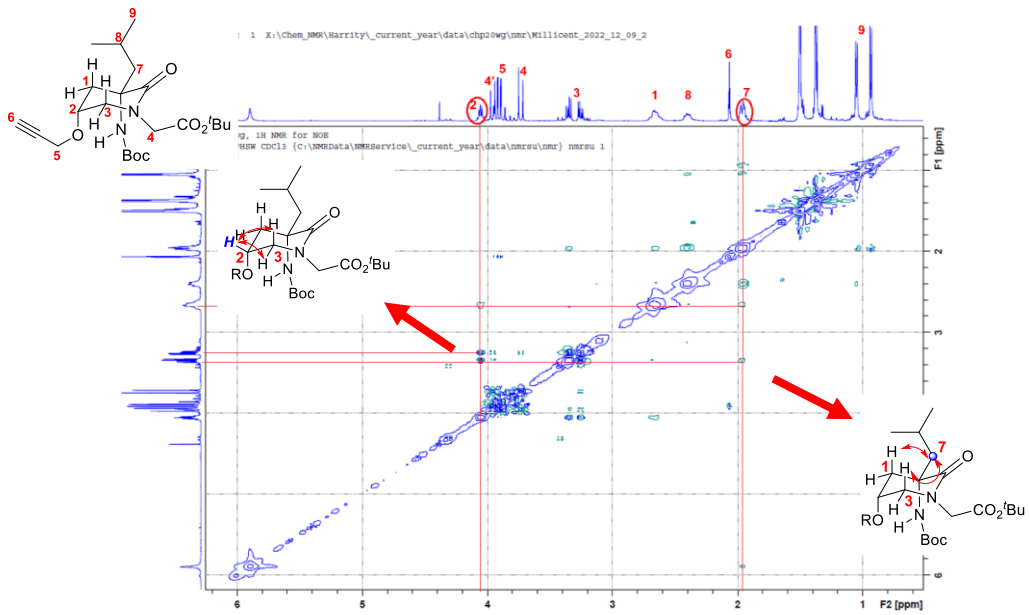
Finally, we used NaOH as base, toluene/water (1:1 v/v) as the solvent, and tetrabutylammonium hydrogensulfate as phase-transfer catalyst for the reaction (**Scheme 9.13**). Pleasingly, the reaction yield was significantly improved up to 92%.



Scheme 9.13

9.4.3 nOe Analysis of compound 9h

Examination of compound **9h** by nOe nmr spectroscopy indicated that both H atoms of C7 show a through space correlation signal with only the axial H atoms of C3 and C1. Additionally, there is also a through space correlation signal between the equatorial H atom of C2 and both the axial and equatorial H atoms of C3. If the the H atom of C2 was axial, there would be no through space correlation signal with the axial H atom of C3, therefore C2 is (*R*) rather than (*S*).

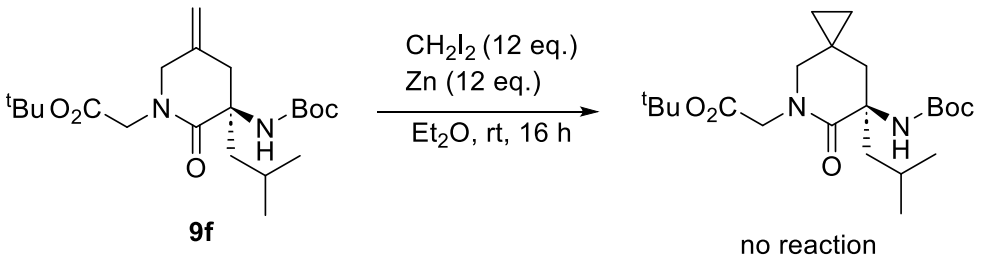


Scheme 9.14

9.5. Other modifications of the olefin

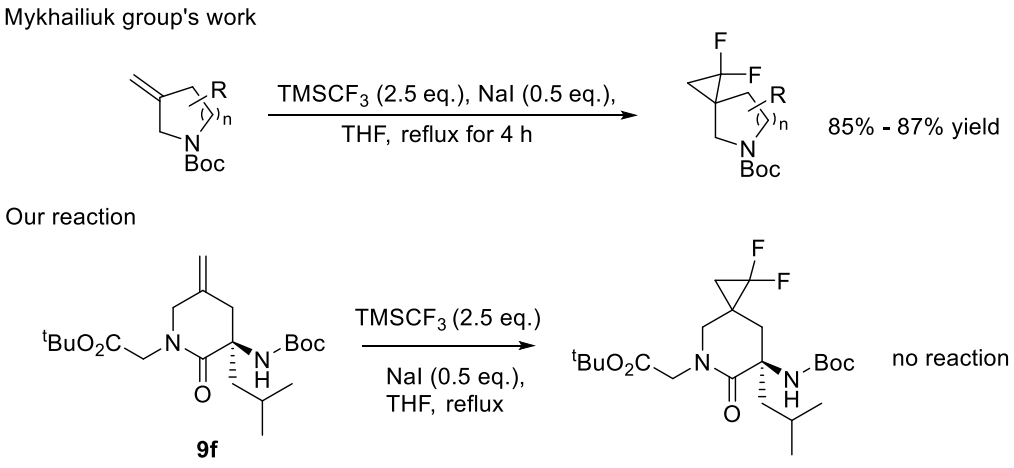
9.5.1 Cyclopropanation of the olefin

We chose to try to 'cap' the olefin as an inert hydrocarbon by performing a Simmons-Smith reaction. Thus, we used **9f** as starting material to carry out this reaction (**Scheme 9.15**). Disappointingly, cyclopropanation of the olefin was not successful, neither heating the reaction mixture nor adding excess Zn and CH_2I_2 improved matters.



Scheme 9.15

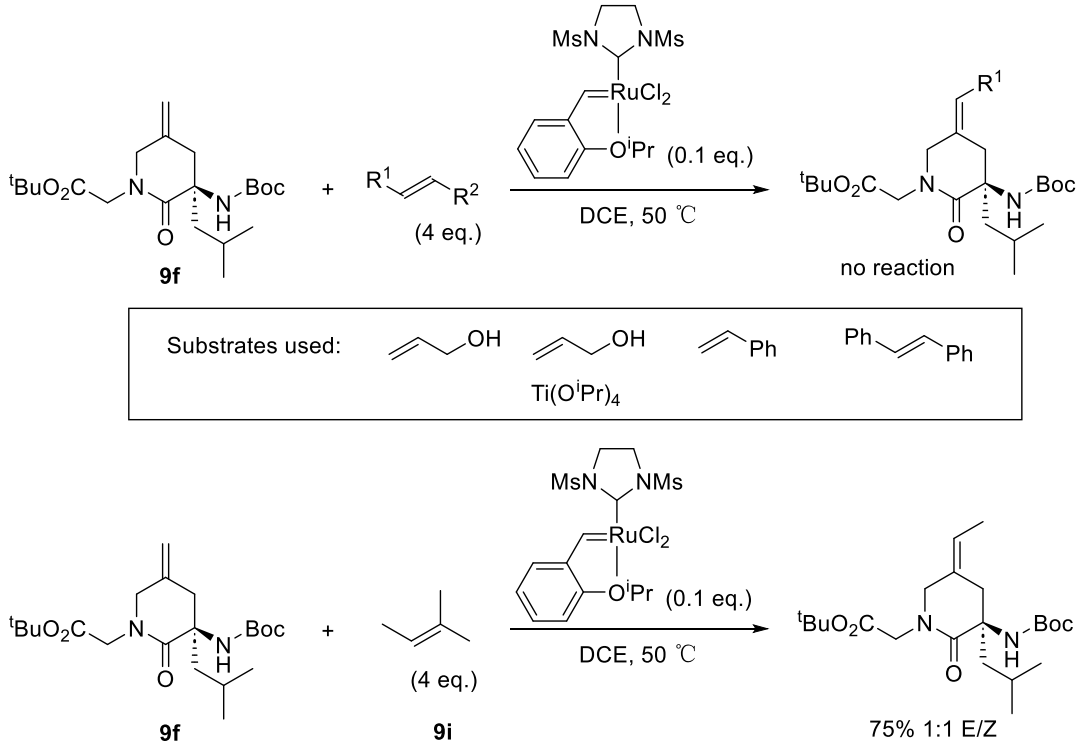
Mykhailiuk group reported a useful approach to convert olefins to difluorinated cyclopropanes (**Scheme 9.16**).[44] Unfortunately, this protocol did not work on our reaction.



Scheme 9.16

9.5.2 Olefin metathesis

We tried a series of metathesis reactions but the results were not satisfactory (**Scheme 9.17**). At first, we used allyl alcohol as the metathesis partner but the reaction was not successful. We added $Ti(O^iPr)_4$ in an attempt to sequester the primary alcohol. However, the reaction still did not proceed. While neither styrene nor stilbene participated in the reaction, we found that when alkene **9i** was used as a substrate, the reaction was successful and complete conversion of our alkene was observed. Interestingly, we found that the reaction was selective for formation of the monomethyl- instead of dimethylolefin, albeit with no E/Z selectivity.

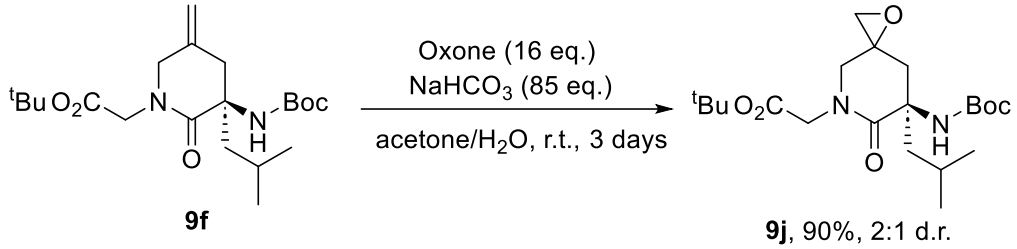


Scheme 9.17

9.5.3 Olefin Epoxidation

We next explored olefin epoxidation as a means to introducing an alternative functional group that could enable the lactam to be further derivatized. We used the

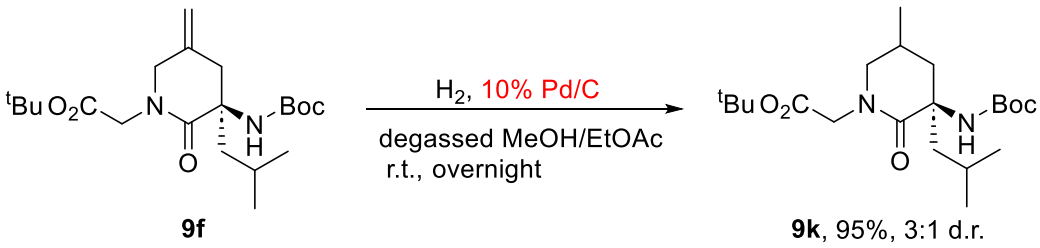
relatively mild conditions of oxone and acetone in the presence of $NaHCO_3$ (**Scheme 9.18**). The reaction rate unexpectedly slow, and took three days to reach completion, however, the product was isolated in excellent yield.



Scheme 9.18

9.5.3 Olefin reduction

Finally, as the cyclopropanation reaction had failed to 'cap' the olefin, we decided to explore the hydrogenation of **9f**. The reaction proceeded smoothly and in high yield, although compound **9j** was generated with modest diastereoselectivity (3:1 d.r., **Scheme 9.19**).

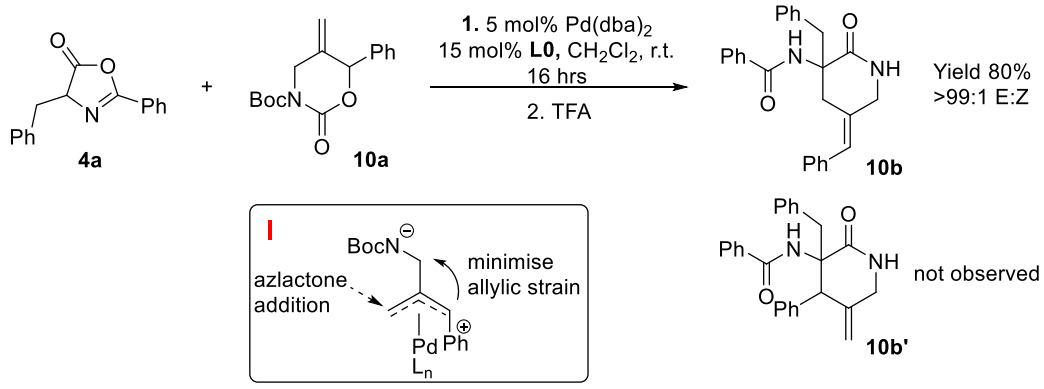


Scheme 9.19

10. Opportunities for Further Study

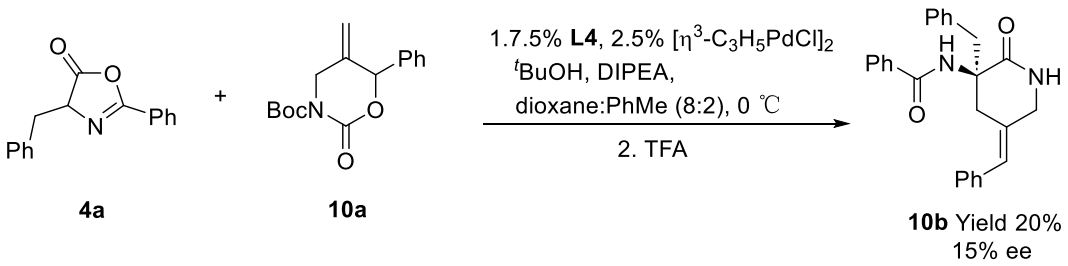
10.1 Reaction of pre-functionalised carbamates

We have undertaken preliminary studies of the use of more heavily substituted carbamate derivative **10a** (provided by a group member) in the lactam forming reaction (**Scheme 10.1**). Pleasingly, **10a** was transformed into lactam **10b** in high yield, and with excellent regiocontrol and E/Z selectivity. We attribute the high selectivity to a combination of minimization of steric effects and allylic strain as highlighted in I.



Scheme 10.1

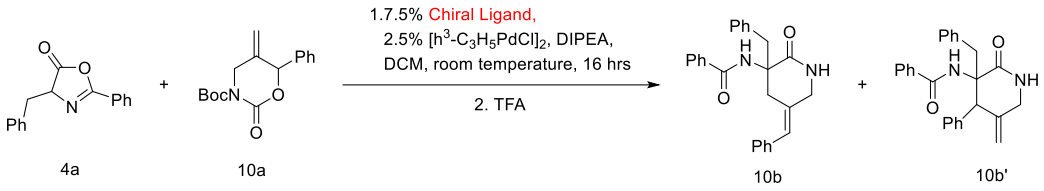
We used our enantioselective conditions to develop the asymmetric allylation step for this reaction (**Scheme 10.2**). Unfortunately, not only was the yield very low, but also both the E/Z selectivity and the enantioselectivity were poor.

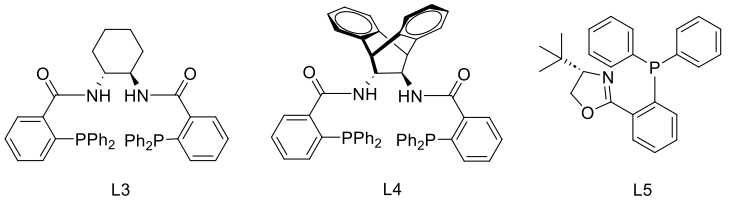


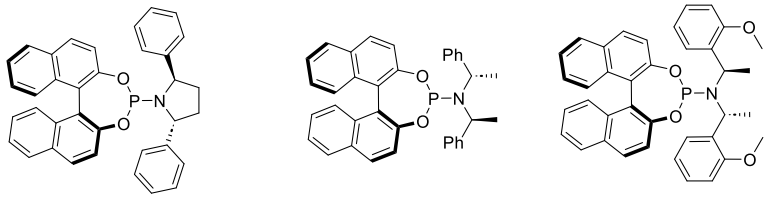
Scheme 10.2

Finally, we were unable to generate **10b** with useful levels of enantiocontrol despite screening a range of chiral ligands and efforts to address this limitation could be a useful avenue of further study (**Table 10.1**).

Table 10.1.



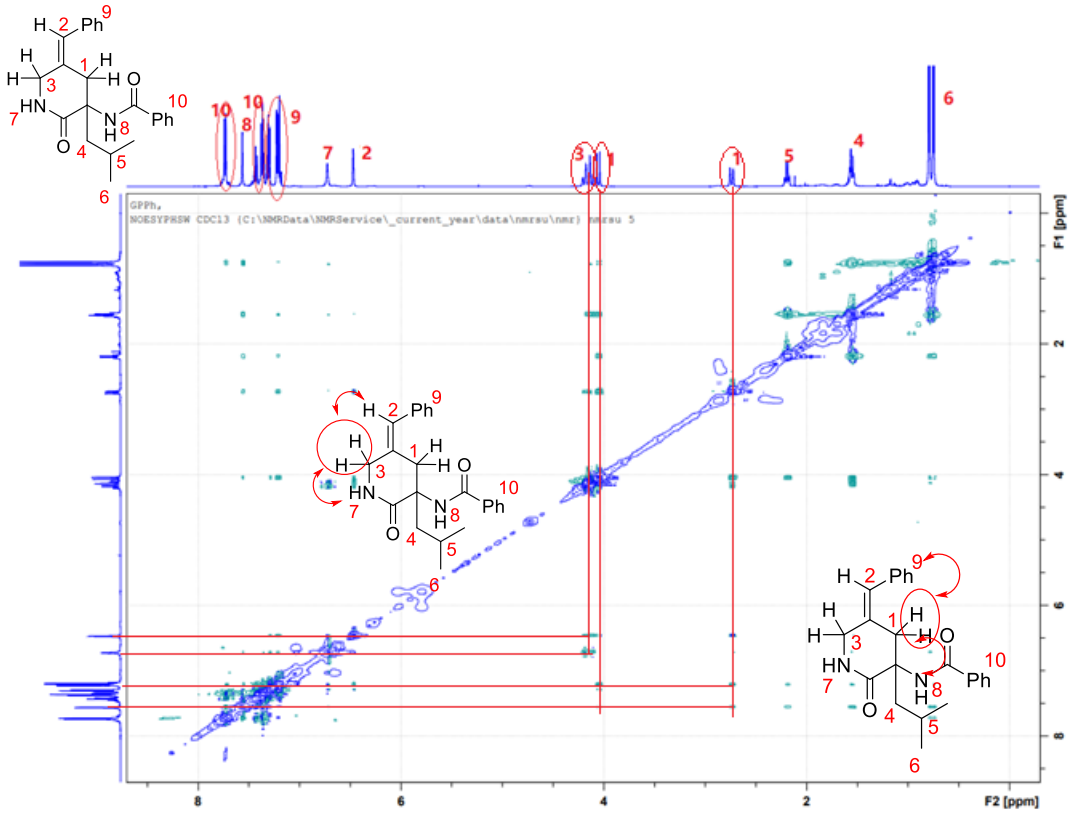




	Ligand	Yield of **10b**	Yield of **10b'**	ee value of **10b**
1	**L5**	10%	10%	5%
2	**L4**	20%	10%	14%
3	**L3**	10%	30%	15%
4	**L7**	90%	-	20%
5	**L8**	80%	-	15%
6	**L9**	85%	-	20%

10.2 nOe Analysis of compound 10b

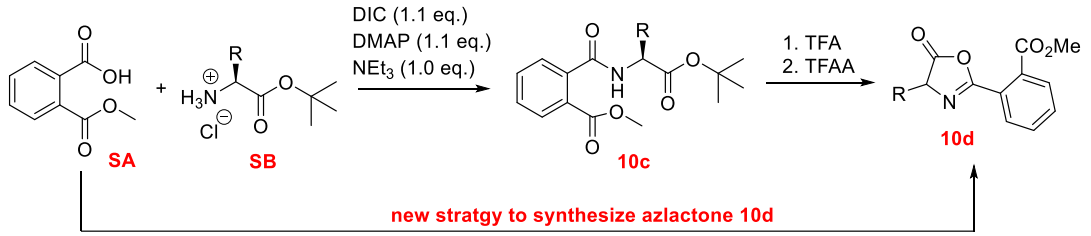
Examination of compound **10b** by nOe nmr spectroscopy indicated that the H atoms of C3 show a through space correlation signal with the H atoms of C2 and N7. Additionally, there is also a through space correlation signal between the H atoms of C1 and aromatic H of phenyl C9 but the H atoms of C3 show no space correlation signal with any aromatic H. Therefore **10b** is (E) rather than (Z).



Scheme 10.3

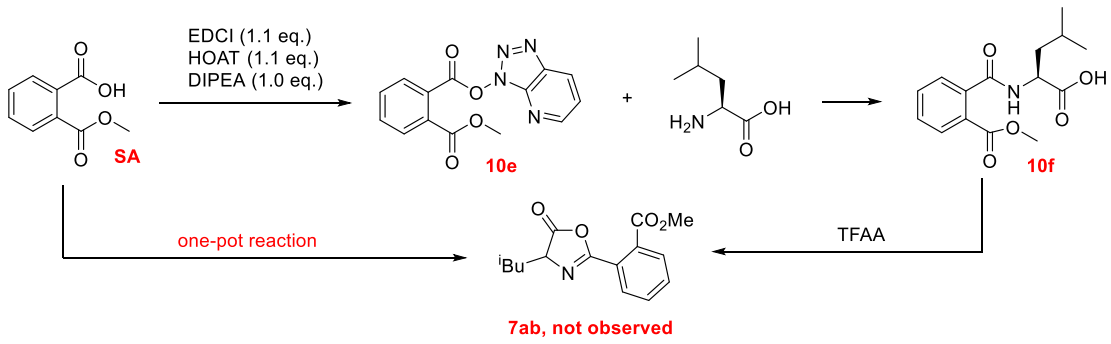
10.3 Development of a new strategy to synthesise azlactones

The synthesis of azlactones **10d** was limited by the availability of the starting material **SB**. Unfortunately, they are limited commercially with respect to available amino acid side chains.



Scheme 10.4

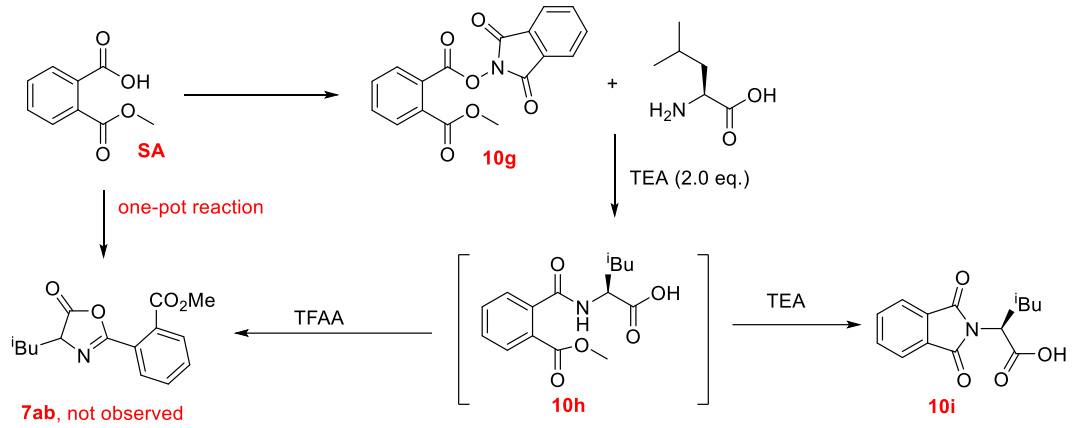
An alternative was to try to use the parent amino acid but the challenge was to couple with **SA** without homocoupling of the amino acid substrate. Originally, we wanted to address this problem by amide coupling reaction (**Scheme 10.5**). According to the assumption, **SA** would be activated by EDCI-HOAt to form intermediate **10e** followed by adding L-leucine to form intermediate **10f**. Finally, TFAA was added to convert **10f** to product **7ab.** Unfortunately, the strategy was not successful.



Scheme 10.5

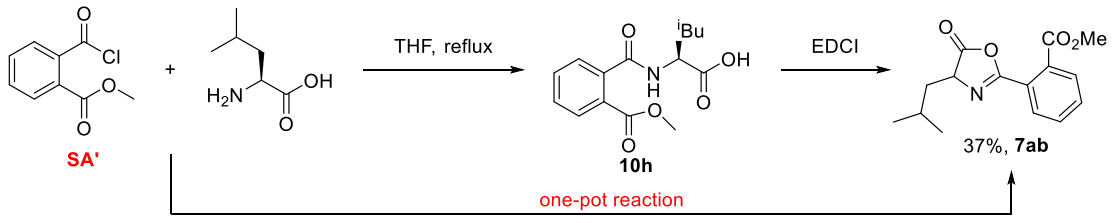
We wanted to clarify the reason why the strategy failed. Thus, a new experimental protocol was designed. We used *N*-hydroxyphthalimide to activate **SA** and separated

pure activated product **10g** successfully followed by coupling reaction with L-leucine with TEA as catalyst to form intermediate **10h**. Unfortunately, product **7ab** was not generated after adding TFAA. According to the crude NMR, it appears that TEA promoted phthalimide **10i** formation as discussed in **Scheme 7.4**.



Scheme 10.6

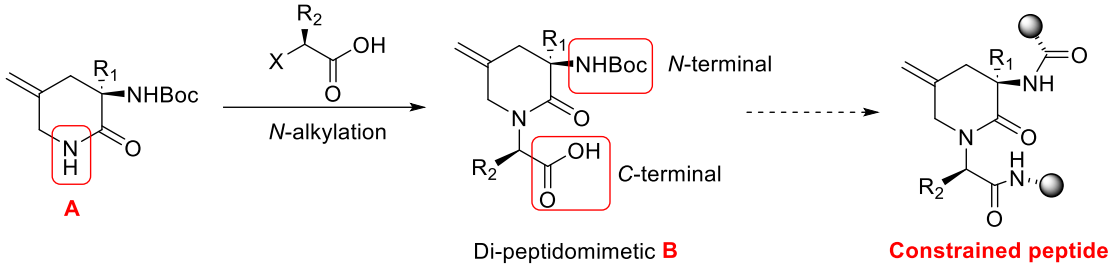
Thus, we wanted to synthesize intermediate **10h** without base catalyst. According to the method for the synthesis of **4g** (**Scheme 4.6**), we used benzoic acid **SA'** as starting material to couple with leucine under refluxing tetrahydrofuran (**Scheme 10.7**) followed by addition of EDCI to synthesise **7ab**. Pleasingly, this reaction occurred successfully, although the yield (37%) was not high enough, but this new synthetic route of azlactone synthesis addresses the limitation of lack of commercial carboxyl-protected amino acids.



Scheme 10.7

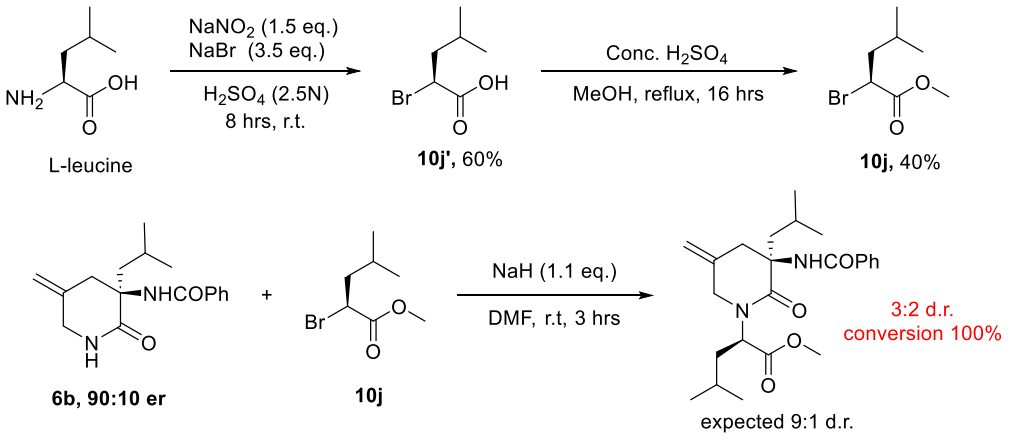
10.4 *N*-Alkylation with Substituted α-Halo Carboxylic Acids

The development of *N*-alkylation with substituted α-halo carboxylic acids would allow us to incorporate amino acid mimics into our lactams beyond glycine. This would represent a very important step in our goal to make this methodology suitable for the synthesis of a range of constrained peptides.



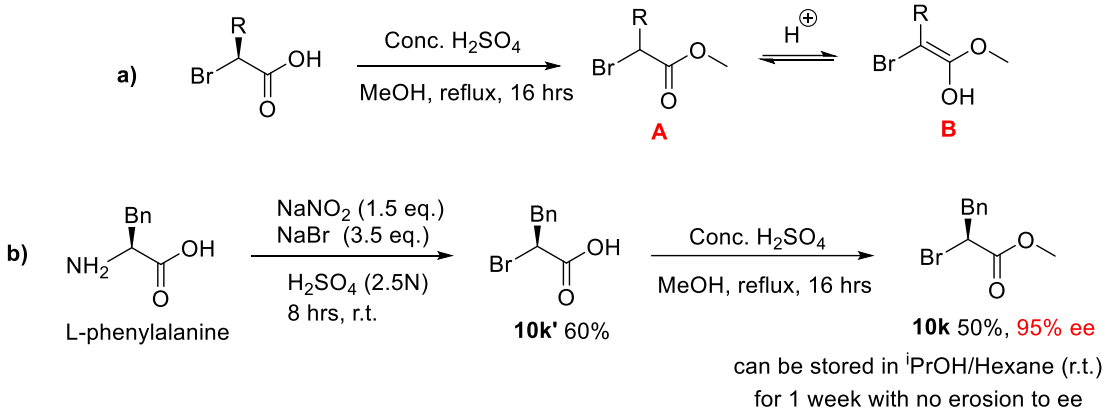
Scheme 10.8

In an attempt to achieve this, we investigated the conversion of α-amino acids to the corresponding α-halo derivatives. We used $NaNO_2$ and NaBr to convert L-leucine to Br-carboxylic acid **10j'** under an acidic aqueous solution (**Scheme 10.9**). In order to facilitate subsequent analysis, we esterified the carboxyl group of **10j'** to generate the product **10j**. The Freidinger lactam **6b** (80% ee) was used to investigate the ensuing *N*-alkylation step. Unfortunately, although the conversion was high, the d.r (3:2) was far lower than expected (9:1).



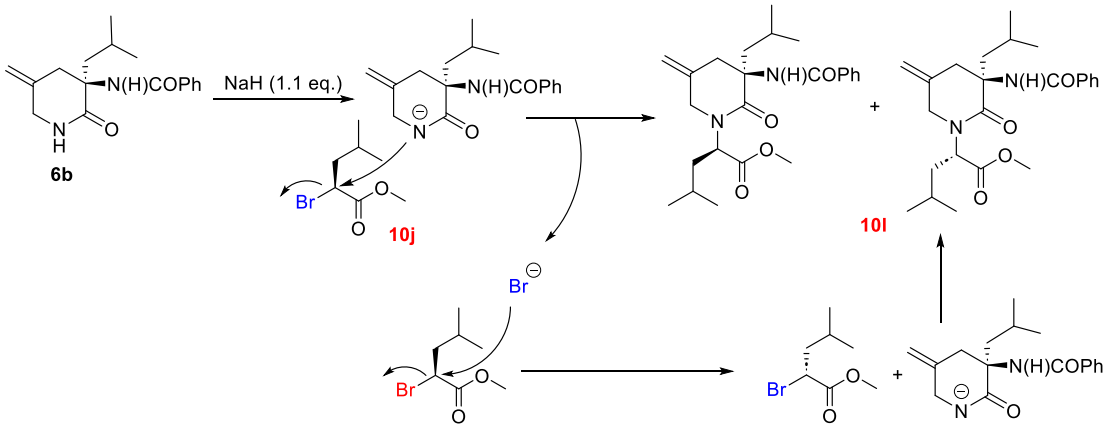
Scheme 10.9

Initially, we thought that the esterification of the Br-carboxylic acid could have resulted in racemization (**Scheme 10.9 a**). Thus, L-phenylalanine was used in the synthesis of **10k** and the enantiopurity of **10k** was measured and found to be up to 95% ee (**Scheme 10.9b**). Notably, no change of enantiopurity was detected after keeping in ^{i}PrOH/hexane solution for one week at room temperature.



Scheme 10.9

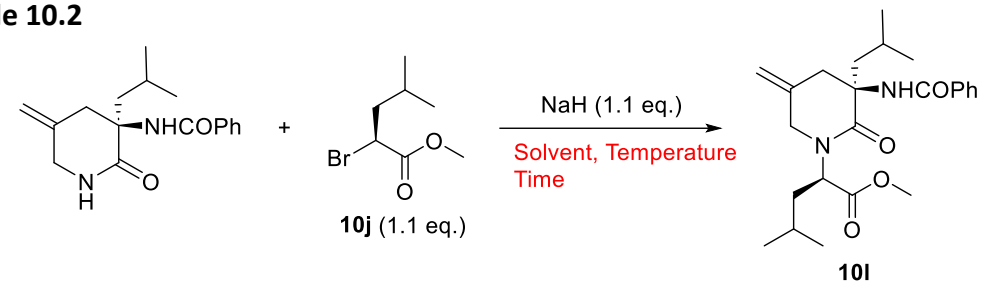
Thus, it meant that the racemization of **10j** should occur during the *N*-alkylation step (**Scheme 10.10**). Because NaBr was soluble in the reaction solvent (DMF), it's possible that the free Br anion, generated in the *N*-alkylation step, could attack the substrate **10j** resulting in configuration inversion. Thus, we tried to use acetonitrile to replace DMF because NaBr is known to be insoluble in acetonitrile.



Scheme 10.10

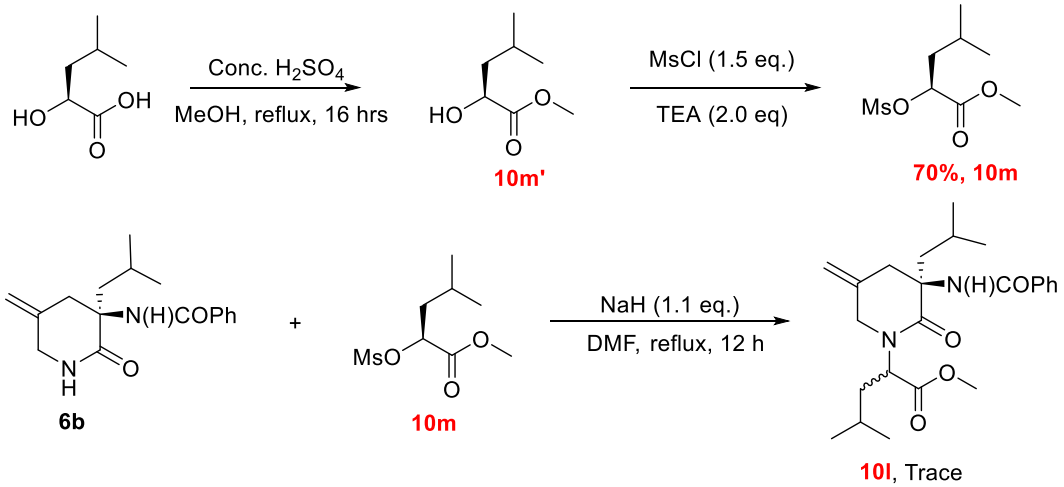
After using acetonitrile as solvent, the d.r value of **10l** did not increase significantly but the conversion decreased from 100% to 50% (**Table 10.2, Entry 2**). Then we used THF as the solvent to confirm the relationship between the polarity of the solvent and the diastereoselectivity of this reaction (polarity: DMF > ACN > THF). However, the polarity of the solvent only had an impact on the conversion and had no significant effect on the d.r. value.

Table 10.2



Entry	solvent	Time (h)	temperature	conversion	d.r.
1	DMF	3	r.t.	100%	3:2
2	ACN	3	r.t.	50%	2:1
3	THF	12	r.t.	-	-
4	THF	12	reflux	20%	2:1

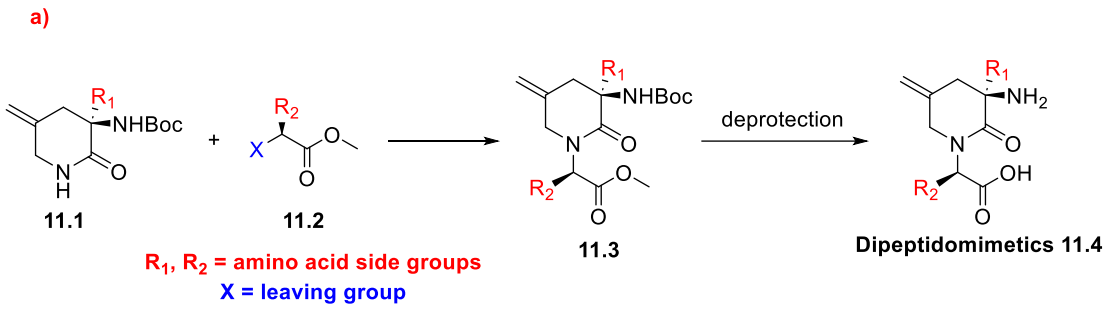
We next decided to explore an alternative leaving group (**Scheme 10.11**). Thus, we designed substrate **10l** for the alkylation. Unfortunately, the subsequent alkylation reaction did not occur as expected, and only a trace product peak of **10d** appeared according to mass spectrometric analysis.



Scheme 10.11

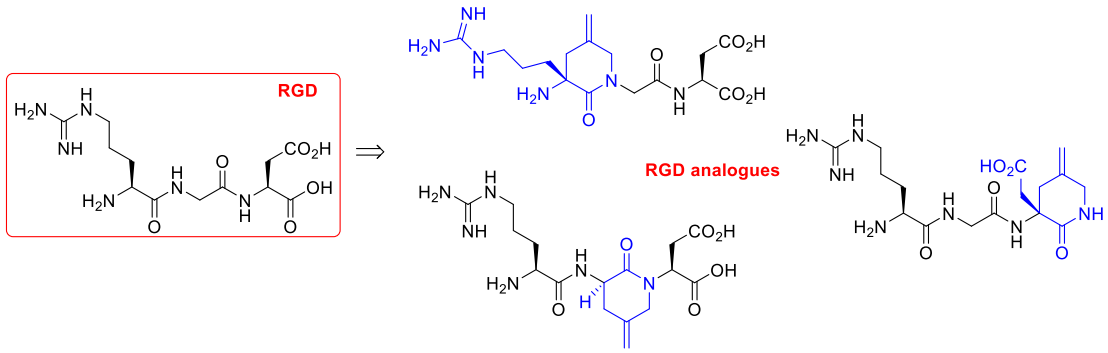
11. Future work

A key future goal is to continue to design new experimental protocols to afford the single diastereomer **11.3** directly (**Scheme 11.1 a**). Dipeptidomimetics **11.4** generated by the deprotection of **11.3** can be applied in downstream peptide synthesis.



Scheme 11.1

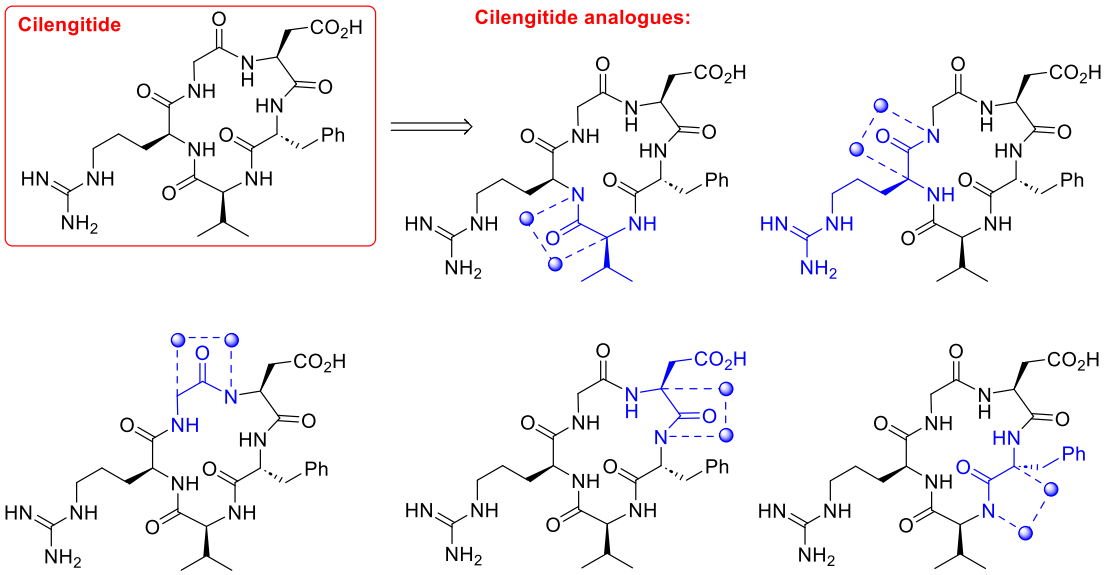
Having demonstrated that this chemistry can deliver RGD mimics, we can use the corresponding Freidinger lactams to systematically change the three amino acid residues of RGD to generate three RGD analogs and we will test the biological activity of these three analogues (**Scheme 11.2**).



Scheme 11.2

Cilengitide, designed and synthesized at the Technical University Munich in collaboration with Merck KGaA in Darmstadt, is under investigation to treat

glioblastoma. It is possible to replace each amino acid residue with corresponding Freidinger lactams to synthesize five Cilengitide analogues and test the biological activity of these five analogues.



Scheme 11.3

12. Experimental Section

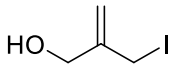
All reactions were carried out in flame-dried glassware under high vacuum, unless stated otherwise. For reactions carried out under an inert atmosphere, solvents were purified using a PureSolv MD purification system and transferred under nitrogen. Infrared (IR) spectra were recorded on a Perkin Elmer Paragon FTIR spectrometer (ν_{max}/cm^{-1}). Samples were recorded neat as thin films. ^{1}H NMR spectra were recorded on a Bruker AVIII HD 400 (400 MHz), Bruker AVI 400 (400 MHz) or Bruker AMX400 (400 MHz). Chemical shifts are reported in parts per million (ppm) from tetramethylsilane, using the residual protic solvent resonance as the internal reference: ($CHCl_3$: δ 7.26 ppm, MeOH: δ 3.31 ppm) unless otherwise stated. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constant (Hz), integration). ^{13}C NMR spectra were recorded on a Bruker AVIII HD 400 (101 MHz), Bruker AVI 400 (101 MHz) or Bruker AMX-400 (101 MHz) with broadband proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal reference ($CDCl_3$: δ 77.16 ppm, CD_3OD: δ 49.00 ppm). ^{19}F NMR spectra were recorded on a Bruker AVIII HD 400 (128 MHz). High-resolution mass spectra (HRMS) recorded for accurate mass analysis, were performed on a Micromass LCT operating in electrospray mode (TOF, ESI+, ESI–). Thin layer chromatography (TLC) was performed on aluminium-backed plates pre-coated with silica (0.2 mm, Merck 60 F254) which were developed using standard visualizing agents: UV light or potassium permanganate. Flash chromatography was performed on silica gel (Merck 40-63 μm) or Florisil® (60-100 mesh). Melting points were recorded on Gallenkamp melting point apparatus and are uncorrected.

Carbamate **10a** was prepared according to procedures previously described[43].

Optical rotations were recorded for enantioenriched compounds of 95:5 er or better.

12.1 The synthesis of starting material

2-(Iodomethyl)prop-2-en-1-ol (C2)[34]

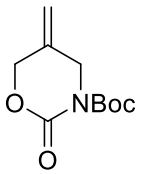


To a solution of 2-methylene-1,3-propanediol (**C1**) (2.0 g, 185 mmol), triphenylphosphine (6.55 g, 24.97 mmol) and imidazole (1.70 g, 24.97 mmol) in a mixture of DCM (25.73 mL) and EtOAc (25.73 mL) at 0 °C under nitrogen was added iodine (5.76 g, 22.70 mmol) portion-wise and the resulting mixture stirred at room temperature in the dark for 24 h

ours. **Workup:** Dilute the reaction mixture with EtOAc (35 mL) followed by washing with water (70 mL). The aqueous layer was extracted with EtOAc (3 × 15 mL) and the organic layers was combined, dried ($MgSO_4$) and concentrated to yield crude material. **Purification:** The solvent was then removed under vacuum (CAUTION: alkylating agents) and the residue purified by Flash column chromatography (FCC) (gradient from 10-30% EtOAc in petroleum ether) to afford 2- (iodomethyl)prop-2-en-1-ol (**C2**) as a yellow oil (2.00 g, 44%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38 (s, 1H, C=CH), 5.23 (s, 1H, C=CH), 4.34 (s, 2H, CH_2), 4.00 (s, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 145.8, 114.2, 63.9, 5.8. Data is consistent with literature.

***tert*-Butyl 5-methylene-2-oxo-1,3-oxazinane-3-carboxylate (C4)** [34]

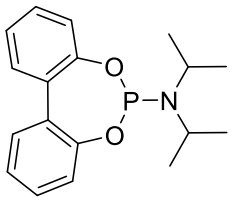


To a suspension of silver cyanate (7.2 g, 47.99 mmol) in toluene (84.6 mL) under nitrogen was added 2-(iodomethyl)prop-2-en-1-ol (**C2**) (6.35 g, 31.99 mmol) in toluene (3 mL) and the resulting mixture heated at 120 °C for 24 hours. After cooling

to room temperature, the mixture was filtered through celite, the filter pad washed with Et_2O (3 x 40 mL) and the combined filtrates concentrated under vacuum. The crude solid and 4-dimethylaminopyridine (0.82 g, 6.4 mmol) were then dissolved in DCM (48.36 mL) under nitrogen and the resulting mixture cooled to 0 °C. Di-*tert*-butyl dicarbonate (13.96 g, 63.98 mmol) was then added slowly and the resulting mixture heated at 25 °C for 24 hours. Removal of the solvent under vacuum and purification by FCC (gradient from 20-25% EtOAc in 40-60 petroleum ether) afforded tert-butyl 5-methylene-2-oxo-1,3-oxazinane-3-carboxylate (**C4**) as a colourless oil which converted to a white solid upon standing in the freezer (2.154 g, 32%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.18 (br, 2H, C=CH_2), 4.64 (s, 2H, CH_2), 4.29 (s, 2H, CH_2), 1.52 (s, 9H, $C(CH_3)_3$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ152.0, 150.9, 134.7, 113.0, 83.9, 69.9, 48.7, 28.0. Data is consistent with literature.

N,N-Diisoproyldibenzo[d,f][1,3,2]dioxaphosphenpin-6-amine [34]



PCl_3 (0.87 mL, 1.4 eq, 10 mmol) was dissolved in THF (40 mL) under an inert atmosphere and cooled to 0 °C. Et3N (7.0 mL, 6.8 eq, 50 mmol) was added dropwise and the mixture was stirred for 10 minutes. Then, $NHPr^i_2$ (1.4 mL, 1.4 eq, 10 mmol) was added dropwise and stirred at room temperature for 6 hours. The mixture was cooled to 0 °C and 2,2'-biphenol (1.364 g, 1.0 eq, 7.3 mmol) was added. The 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. Purification of the crude residue by flash column chromatography 150 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, $CDCl_3$) δ 7.52-7.44 (m, 2H, CH_{Ar}), 7.40-7.32 (m, 2H, CH_{Ar}), 7.24-7.16 (m, 4H, CH_{Ar}), 3.51 (dhept., J = 10.5 Hz, 7.0 Hz, 2H, 2xCH), 1.25 (d, J = 7.0 Hz,

12H, 4xCH_3); **^{31}P-NMR (162 MHz, $CDCl_3$)** 152.0 (t, J = 10.5 Hz). Data is consistent with literature.

General Procedure 1

The amino acid (1 eq) was dissolved in 1 M NaOH (aq) and to this solution was added the acid chloride (1.2 eq) in 1,4-dioxane slowly over a period of 5 min. The reaction mixture was allowed to stir at 75 °C for 30 min, then acidified to pH~2 using conc. HCl and extracted using EtOAc. The solvent was removed under reduced pressure to give the *N*-acylated amino acid which was used directly in the next step as crude material.

General Procedure 2

The amino acid (1 eq) was dissolved in THF and the acid chloride (1.2 eq) was added dropwise. The reaction mixture was stirred at 80 °C overnight then cooled to room temperature. This mixture was extracted with EtOAc and the solvent removed under reduced pressure to give the *N*-acylated amino acid which was used directly in the next step as crude material.

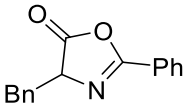
General Procedure 3

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 mixture was 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 4

The *N*-acylated amino acid was dissolved in Ac_2O (10 mL) under nitrogen atmosphere and stirred at 90 °C for 30 minutes. After cooling to room temperature, the reaction mixture was quenched with sat. aq. $NaHCO_3$ and the product 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.

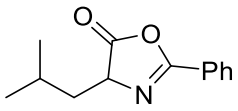
2-Phenyl-4-benzyl-2-oxazolin-5-one, 4a[45]



Phenylalanine (1.07 g, 6.5 mmol) in 1 M NaOH (aq) (8 mL) and PhCOCl (0.77 mL, 6.6 mmol) were subjected to general procedure 1. The crude *N*-acylated amino acid and EDC.HCl (1.42 g, 7.4 mmol) in dry DCM (20 mL), were subjected to general procedure 3 and the crude residue was purified by flash column chromatography eluting with 2% EtOAc in petrol to give the azlactone 2-phenyl-4-benzyl-2-oxazolin-5-one (**4a**) (696 mg, 43%) as a white amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98-7.91 (m, 2H, CH_{Ar}), 7.63-7.53 (m, 1H, CH_{Ar}), 7.52-7.44 (m, 2H, CH_{Ar}), 7.34-7.19 (m, 5H, CH_{Ar}), 3.72 (dd, J = 6.5, 5.0 Hz, 1H, CH), 3.40 (dd, J = 14.0, 5.0 Hz, 1H, CH), 3.22 (dd, J = 14.0, 6.5 Hz, 1H, CH); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 177.6, 161.7, 135.3, 132.7, 129.6, 128.7, 128.4, 127.9, 127.2, 125.8, 66.6, 37.3. Data is consistent with literature.

2-Phenyl-4-isobutyl-2-oxazolin-5-one, 4b[46]

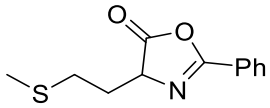


Leucine (2.0 g, 15.25 mmol) in 1 M NaOH (aq) (20 mL) and PhCOCl (2.1 mL, 18.3 mmol) were subjected to general procedure 1. The crude *N*-acylamino acid was dissolved in Ac_2O (28 mL, 0.23 mol) and subjected to general procedure 4 and the crude residue was purified by flash column chromatography eluting with 6% Et_2O in petrol to give the azlactone 2-phenyl-4-isobutyl-2-oxazolin-5-one (**4b**) (1.8 g, 55%) as an amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05-7.98 (m, 2H, CH_{Ar}), 7.62-7.56 (m, 1H, CH_{Ar}), 7.54-7.47 (m, 2H, CH_{Ar}), 4.43 (dd, 1H, J = 9.0, 6.0 Hz, CH), 2.15-2.02 (m, 1H, CH), 1.86 (ddd, J = 13.5, 8.0, 6.0 Hz, 1H, CH), 1.70 (ddd, J = 13.5, 9.0, 6.0 Hz, 1H, CH), 1.06 (d, *J* = 6.5 Hz, 3H, CH_3), 1.03 (d, *J* = 6.5 Hz, 1H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 179.0, 161.4,

132.7, 128.8, 127.9, 126.1, 64.0, 40.8, 25.2, 22.8, 22.1. Data is consistent with literature.

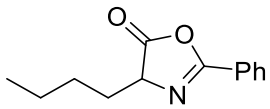
2-Phenyl-4-[2-(methylthio)ethyl)]-2-oxazolin-5-one, 4c[47]



Methionine (1.05 g, 7.0 mmol) in 1 M NaOH (aq) (10 mL) and PhCOCl (1 mL, 8.6 mmol) were subjected to general procedure 1. The crude *N*-acylamino acid in Ac_2O (10 mL, 0.11 mmol) was subjected to general procedure 4 and the crude residue was purified by flash column chromatography eluting with 5% EtOAc in petrol to give the azlactone 2-phenyl-4-[2-(methylthio)ethyl)]-2-oxazolin-5-one (**4c**) (836 mg, 50%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04-7.96 (m, 2H, CH_{Ar}), 7.65-7.53 (m, 1H, CH_{Ar}), 7.48 (t, J = 7.5 Hz, 2H, CH_{Ar}), 4.61 (dd, J = 7.0, 6.0 Hz, 1H, CH), 2.73 (t, J = 7.0 Hz, 2H, SCH_2), 2.41-2.25 (m, 1H, CH), 2.24-2.06 (m, 1H, CH), 2.11 (s, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 175.7, 162.3, 128.9, 128.0, 127.2, 125.8, 63.7, 30.4, 30.0, 15.1. Data is consistent with literature.

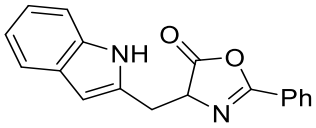
2-Phenyl-4-butyl-2-oxazolin-5-one, 4d[48]



Norleucine (922 mg, 7.0 mmol) in 1 M NaOH (aq) (10 mL) then PhCOCl (0.96 mL, 1.2 eq, 8.2 mmol) were subjected to general procedure 1. The crude *N*-acylamino acid was dissolved in Ac_2O (10 mL, 15 eq, 0.11 mol) and subjected to general procedure 4 and the crude residue was purified by flash column chromatography eluting with 5% EtOAc in petrol to give the azlactone 2-phenyl-4-butyl-2-oxazolin-5-one (**4d**) (802 mg, 53%) as a white amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, J = 7.0, 1.5 Hz, 2H, CH_{Ar}), 7.65-7.56 (m, 1H, CH_{Ar}), 7.55-7.46 (m, 2H CH_{Ar}), 4.47-4.37 (m, 1H, CH), 2.16-1.97 (m, 1H, CH), 1.97-1.77 (m, 1H, CH), 1.58- 1.34 (m, 4H, 4xCH), 0.94 (t, J = 7.0 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 176.2, 167.7, 133.6, 132.9, 132.0, 128.9, 65.3, 31.3, 27.2, 22.3, 13.8. Data is consistent with literature.

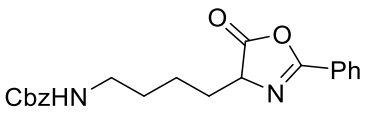
2-Phenyl-4-((1H-indol-2-yl)methyl)-2-oxazolin-5-one, 4e[47]



Tryptophan (2.5 g, 12.0 mmol) in 1 M NaOH (aq) (20 mL) then PhCOCl (1.67 mL, 14.4 mmol) were subjected to general procedure 2. The crude *N*-acylamino acid was dissolved in Ac_2O (23 mL, 0.18 mol) and subjected to general procedure 4 and the crude residue was purified by flash column chromatography eluting with 20% EtOAc in petrol to give the azlactone 2-phenyl-4-((1H-indol-2-yl)methyl)-2-oxazolin-5-one (**4e**) (2.6 g, 74%) as a yellow amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H, NH), 7.95-7.87 (m, 2H, CH_{Ar}), 7.78-7.79 (m, 1H, CH_{Ar}), 7.54 (t, J = 7.5 Hz, 1H, CH_{Ar}), 7.44 (t, J = 7.5 Hz, 2H, CH_{Ar}), 7.34-7.26 (m, 1H, CH_{Ar}), 7.21-7.10 (m, 3H, CH_{Ar}), 4.78 (dd, J = 6.0, 5.0 Hz, 1H, CH), 3.56 (dd, J = 15.0, 5.0 Hz, 1H, CH), 3.43 (dd, J = 15.0, 6.0 Hz, 1H, CH); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 178.0, 161.9, 136.0, 132.7, 128.7, 127.9, 127.4, 125.8, 123.5, 122.1, 119.6, 119.2, 111.1, 109.6, 66.6, 27.3. Data is consistent with literature.

Benzyl (4-(5-oxo-2-phenyl-4,5-dihydrooxazol-4-yl)butyl)carbamate, 4f

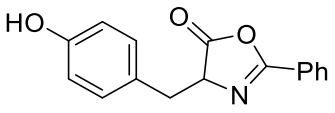


H-Lys(Z)-OH (2.8 g, 10 mmol) in THF (10 mL) then PhCOCl (1.4 mL, 12 mmol) were subjected to general procedure 2. The crude *N*-acylamino acid and EDC.HCl (2.3 g, 12 mmol) in dry DCM (40 mL) were subjected to general procedure 3. The crude residue

was purified by flash column chromatography eluting with 30% EtOAc in petrol to give the azlactone benzyl (4-(5-oxo-2-phenyl-4,5-dihydrooxazol-4-yl)butyl)carbamate (**4f**) (3.0 g, 80%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3334, 3062, 1821, 1702, 1652; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.05-7.99 (m, 2H, CH_{Ar}), 7.60 (t, J = 7.5 Hz, 1H, CH_{Ar}), 7.51 (t, J = 7.5 Hz, 2H, CH_{Ar}), 7.41-7.29 (m, 5H, CH_{Ar}), 5.11 (s, 2H, CH_2), 4.86 (s, 1H, NH), 4.42 (t, 1H, J = 6.5 Hz, CH), 3.31-3.09 (m, 2H, CH_2), 2.17-1.97 (m, 1H, CH_2), 1.96-1.77 (m, 1H, CH), 1.71-1.42 (m, 4H, 4xCH); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 178.3, 161.7, 156.5, 136.7, 132.8, 128.8, 128.5, 128.1 (×2 C), 127.9, 125.9, 66.6, 66.2, 40.7, 31.2, 29.5, 22.6. **MS (ESI^+)** 367 (100%, $M+H^+$); **HRMS (ESI^+)** $C_{21}H_{22}N_2O_4$ requires $M+H^+$ 367.1652, found 367.1659.

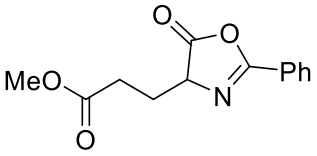
2-Phenyl-4-(4-hydroxybenzyl)-2-oxazolin-5-one, 4g[47]



Tyrosine (1.8 g, 10 mmol) in THF (10 mL) then PhCOCl (1.4 mL, 12 mmol) were subjected to general procedure 2. The crude *N*-acylamino acid and EDC.HCl (2.3 g, 12 mmol) in dry DCM (40 mL) were subjected to general procedure 3. The crude residue was purified by flash column chromatography eluting with 40% EtOAc in petrol to give the azlactone 2-phenyl-4-(4-hydroxybenzyl)-2-oxazolin-5-one (**4g**) (1.6 g, 60%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97-7.90 (m, 2H, CH_{Ar}), 7.62-7.53 (m, 1H, CH_{Ar}), 7.50-7.41 (m, 2H, CH_{Ar}), 7.15-7.07 (m, 2H, CH_{Ar}), 6.75-6.65 (m, 2H, CH_{Ar}), 5.77 (s, 1H, OH), 4.69 (dd, J = 6.5, 5.0 Hz, 1H, CH), 3.33 (dd, J = 14.0, 5.0 Hz, 1H, CH), 3.14 (dd, J = 14.0, 6.5 Hz, 1H, CH); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 177.5, 162.1, 155.0, 132.9, 130.8, 128.8, 128.0, 126.9, 125.6, 115.4, 66.7, 36.5. Data is consistent with literature.

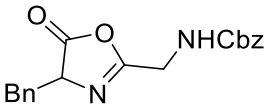
2-Phenyl-4-methyl propanoate-2-oxazolin-5-one, 4h[49]



H-Glu(OMe)-OH (1.6 g, 10 mmol) in THF (10 mL) then PhCOCl (1.4 mL, 12 mmol) were subjected to general procedure 2. The crude *N*-acylamino acid and EDC.HCl (2.3 g, 1.2 eq, 12 mmol) in dry DCM (40 mL) were subjected to general procedure 3. The crude residue was purified by flash column chromatography eluting with 30% EtOAc in petrol to give the azlactone 2-phenyl-4-methyl propanoate-2-oxazolin-5-one (**4h**) (870 mg, 35%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05-7.98 (m, 2H, CH_{Ar}), 7.65-7.56 (m, 1H, CH_{Ar}), 7.55-7.47 (m, 2H, CH_{Ar}), 4.53 (dd, J= 8.0, 6.0 Hz, 1H, CH), 3.70 (s, 3H, CH_3), 2.62 (t, J = 7.5 Hz, 2H, CH_2), 2.46-2.33 (m, 1H, CH), 2.17 (dq, J = 15.0, 7.5 Hz, 1H, CH); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 177.9, 172.7, 162.1, 132.9, 128.8, 128.0, 125.7, 64.2, 51.8, 29.8, 26.7. Data is consistent with literature.

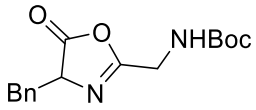
Benzyl (4-benzyl-5-oxo-4,5-dihydro-oxazol-2-ylmethyl)-carbamic acid, 4i[52]



Z-Gly-Phe-OH (500 mg, 1.4 mmol) and EDC.HCl (351 mg, 1.8 mmol) in dry DCM (20 mL) were subjected to general procedure 3. The crude residue was purified by flash column chromatography eluting with a gradient of 20-40% EtOAc in petrol to give the azlactone benzyl (4-benzyl-5-oxo-4,5-dihydro-oxazol-2-ylmethyl)-carbamic acid (**4i**) (139 mg, 29%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.22 (m, 10H, CH_{Ar}), 5.97 (s, 1H, NH), 5.16-5.05 (m, 2H, CH_2), 4.95 (t, J = 5.5 Hz, 1H, CH), 3.99-3.87 (m, 2H, CH_2), 3.83- 3.68 (m, 1H, CH) 3.68-3.47 (m, 1H, $PhCH_2CH$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 164.9, 164.3, 156.1, 136.1, 133.7, 129.3, 128.9, 128.6, 128.3, 128.2, 127.5, 98.0, 67.2, 43.2, 34.3. Data is consistent with literature.

***tert*-Butyl (4-benzyl-5-oxo-4,5-dihydro-oxazol-2-ylmethyl)-carbamic acid, 4j**[53]

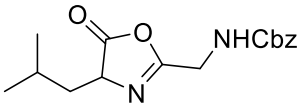


Glycylphenylalanine (1.04 g, 4.7 mmol) and $NaHCO_3$ (1.18 g, 14 mmol) were dissolved in water (14 mL) and THF (14 mL). To this solution, Boc_2O (1.20 g, 5.5 mmol) was added and the mixture was stirred at room temperature overnight. The reaction mixture was washed with Et_2O (20 mL), then acidified to pH~2 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 crude Boc-glycylphenylalanine (600 mg, 57%).

Boc-Glycylphenylalanine (207 mg, 0.64 mmol) in dry DCM (10 mL) under a nitrogen atmosphere was cooled to 0 °C, and DCC (146 mg, 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 re-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 *tert*-butyl (4-benzyl-5-oxo-4,5-dihydro-oxazol-2-ylmethyl)-carbamic acid (**4j**) (161 mg, 83%) as a white cloudy oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.17 (m, 5H, CH_{Ar}), 5.05 (s, 1H, NH), 4.48 (m, 1H, CH), 4.02 (d, J = 3.5 Hz, 2H, CH_2), 3.27 (dd, J = 14.0, 5.0 Hz, 1H, CH), 3.09 (dd, J = 14.0, 6.5 Hz, 1H, CH), 1.47 (s, 9H, $C(CH_3)_3$); **^{13}C-NMR (101 MHz, $CDCl_3$)** 176.9, 162.9, 155.4, 134.8, 129.5, 128.5, 127.4, 80.4, 65.5, 38.3, 36.8, 28.3. Data is consistent with literature.

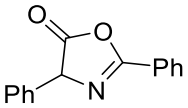
Benzyl (4-isobutyl-5-oxo-4,5-dihydro-oxazol-2-ylmethyl)-carbamic acid, 4k[52]



Z-Gly-Lys-OH (3.22 g, 10 mmol) and EDC.HCl (2.30 g, 12 mmol) in dry DCM (20 mL) were subjected to general procedure 3. The crude residue was purified by flash column chromatography eluting with a gradient of 70% Et_2O in petrol to give the azlactone benzyl (4-isobutyl-5-oxo-4,5-dihydro-oxazol-2-ylmethyl)-carbamic acid (**4k**) (1.10 g, 37%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.29 (m, 5H, CH_{Ar}), 5.96 (s, 1H, NH), 5.23-4.97 (m, 3H, CH_2 & CH), 3.81-3.68 (m, 1H, CH), 3.69-3.57 (m, 1H, CH), 2.49-2.47 (m, 2H, CH_2), 2.19-2.16 (m, 1H, CH), 0.98 (d, J = 6.5 Hz, 6H, 2×CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.5, 165.2, 156.2, 136.1, 128.6, 128.3, 128.2, 98.0, 67.3, 43.3, 36.6, 26.1, 22.4. Data is consistent with literature.

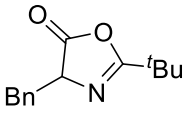
2-Phenyl-4-phenyl-2-oxazolin-5-one, 4l[47]



Phenylglycine (2.06 g, 14 mmol) in 1 M NaOH(aq) (15 mL) and PhCOCl (1.7 mL, 15 mmol) in 1,4-dioxane (15 mL) were subjected to general procedure 1. The crude N-acylated amino acid and EDC.HCl (2.81 g, 15 mmol) in dry DCM (40 mL) were subjected to general procedure 3 and the crude residue was purified by flash column chromatography eluting with a gradient of 2-5% EtOAc in petrol to give the 2-Phenyl-4-phenyl-2-oxazolin-5-one (**4l**) (679 mg, 21%) as a yellow amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13-8.08 (2H, m, CH_{Ar}), 7.68-7.36 (8H, m, CH_{Ar}), 5.83 (1H, m, CH); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 176.3, 162.6, 133.5, 133.1, 129.2, 129.1, 128.9, 128.2, 127.4, 125.7, 68.2. Data is consistent with literature.

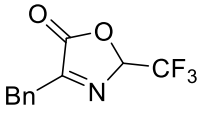
2-(1,1-dimethylethyl)-4-benzyl-2-oxazolin-5-one, 4m[50]



Phenylalanine (5.06 g, 31 mmol) in 1 M NaOH(aq) (40 mL) and ^{t}BuCOCl (4.1 mL, 33 mmol) in 1,4-dioxane (40 mL) were subjected to general procedure 1. The crude N-acylamino acid and EDC.HCl (6.35 g, 33 mmol) in dry DCM (100 mL) were subjected to procedure 3. The crude residue was purified by flash column chromatography eluting with a gradient of 10-20% EtOAc in petrol to give the azlactone 2-(1,1-dimethylethyl)-4-benzyl-2-oxazolin-5-one (**4m**) (3.02 g, 43%) as a white amorphous solid.

^{1}H NMR (400 MHz, CDCl3) δ 7.30-7.20 (3H, m, CH_{Ar}), 7.17 (2H, d, J = 7.5 Hz, CH_{Ar}), 4.47 (1H, t, J = 5.0 Hz, CH), 3.27 (1H, dd, J = 13.5 & 5.0 Hz, CH), 3.18 (1H, dd, J = 13.5 & 5.0 Hz, CH), 1.06 (9H, s, $C(CH_3)_3$); **^{13}C NMR (101 MHz, CDCl3)** δ 179.1, 175.1, 135.6, 129.4, 128.7, 127.3, 53.1, 38.7, 37.1, 27.3. Data is consistent with literature.

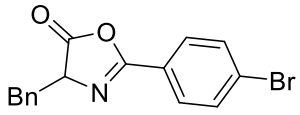
4-Benzyl-2-(trifluoromethyl)- 3-oxazolin-5-one, 4n[51]



Phenylalanine (5.04 g, 31 mmol) dissolved in TFAA (17 mL, 0.12 mol) was 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 eluting with 20% EtOAc in petrol to give the the 4-Benzyl-2-(trifluoromethyl)- 3-oxazolin-5-one (**4n**) (5.63 g, 76%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.30 (5H, m, CH_{Ar}), 6.16-6.07 (1H, m, $CHCF_3$), 4.12 - 4.00 (2H, m, CH_2); **^{13}C NMR (101 MHz, CDCl3)** δ 167.3, 163.4, 132.5, 129.4, 129.1, 127.9, 120.2 (q, J = 281.5 Hz, CF_3), 93.1 (q, J = 35.0 Hz, $CHCF_3$), 34.5; **^{19}F NMR (376 MHz, CDCl3)** δ -78.7 (d, J = 4.0 Hz, CF3). Data is consistent with literature.

2-(4-bromophenyl)-4-benzyl-2-oxazolin-5-one, 4o[50]

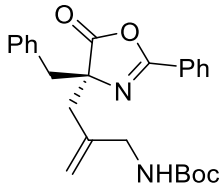


Phenylalanine (500 mg, 3.0 mmol) in 1M NaOH(aq) (20 mL) and 4-BrC_6H_4COCl (496 mg, 2.3 mmol) in 1,4- dioxane (20 mL) were subjected to general procedure 1. The crude N-acylamino acid and EDC.HCl (649 mg, 4.0 mmol) in dry DCM (40 mL) were subjected to general procedure 3. The crude residue was purified by flash column chromatography eluting with a gradient of 2-10% EtOAc in petrol to give 2-(4-bromophenyl)-4-benzyl-2-oxazolin-5-one (**4o**) (206 mg, 28%) as a white amorphous solid.

^{1}H NMR (400 MHz, CDCl3) δ 7.80 (d, J = 8.5 Hz, 2H, CH_{Ar}), 7.61 (d, J = 8.5 Hz, 2H, CH_{Ar}), 7.36-7.10 (m, 5H, CH_{Ar}), 4.70 (dd, J = 6.5 & 5.0 Hz, 1H, CH), 3.40 (dd, J = 14.0 & 5.0 Hz, 1H, CH), 3.21 (dd, J = 14.0 & 6.5 Hz, 1H, CH); **^{13}C NMR (101 MHz, CDCl3)** δ 177.3, 161.0, 135.1, 121.1, 129.6, 129.3, 128.5, 127.7, 127.3, 124.7, 66.6, 37.3. Data is consistent with literature.

12.2 the scope of the allylation intermediates

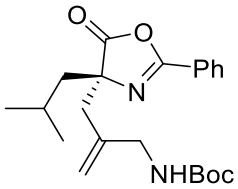
tert-butyl (*R*)-(2-((4-benzyl-5-oxo-2-phenyl-4,5-dihydrooxazol-4-yl)methyl)allyl)carbamate, 5a



N-Boc-5-methylenecyclohexacarbamate (**C4**) (21 mg, 0.1 mmol), (*R,R*)-ANDEN-phenyl Trost ligand (6 mg, 0.075), $\{\eta^3\text{-}C_3H_5PdCl\}_2$ (1 mg, 0.025 mmol), ^{t}BuOH (0.045 ml, 0.5 mmol) and DIPEA (0.025 ml, 0.2 mmol) were dissolved in dry 20% toluene in dioxane (1 mL) at 0 °C for 20 mins. Then 2-phenyl-4-benzyl-2-oxazolin-5-one (**4a**) (75 mg, 0.3 mmol) was added. The mixture was stirred at 0 °C overnight. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 20% EtOAc in petrol to give *tert*-butyl (*R*)-(2-((4-benzyl-5-oxo-2-phenyl-4,5-dihydrooxazol-4-yl)methyl)allyl)carbamate **(5a**) (38 mg, 90%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3381, 2978, 2928, 1816, 1712, 1651; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.82-7.83 (m, 2H, CH_{Ar}), 7.51-7.54 (m, 1H, CH_{Ar}), 7.40-7.43 (m, 2H, CH_{Ar}), 7.12-7.16 (m, 5H, CH_{Ar}), 5.12 (s, 1H, NH), 5.07 (s, 1H, C=CH), 5.03 (s, 1H, C=CH), 3.72 (br, 2H, CH), 3.26 (d, J = 12.0 Hz, 1H, CH), 3.17 (d, J = 12.0 Hz, 1H, CH), 2.75 (s, 2H, CH), 1.43 (s, 9H, $C(CH_3)_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 179.3, 160.1, 155.8, 140.6, 134.1, 132.7, 130.2, 128.7, 128.2, 127.8, 127.3, 125.5, 116.3, 79.3, 75.3, 46.2, 43.5, 41.0, 28.4; **MS (ESI$^+$)** 421 (100%, M+H$^+$); **HRMS (ESI$^+$)** $C_{25}H_{28}N_2O_4$ requires M+H$^+$ 421.2122, found 421.2134; **HPLC** (Cellulose-2, hexane:^{i}PrOH 95:5, flow rate 1.0 mL/min, λ = 254 nm, 22 °C) t_R(major) = 9.090, t_R(minor) = 10.323, er = 95:5. $[\alpha]_D^{22} = -10$ (*c* 1.0, $CHCl_3$).

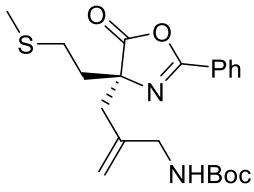
***tert*-butyl-(*R*)-(2-((4-isobutyl-5-oxo-2-phenyl-4,5-dihydrooxazol-4-yl)methyl)allyl)-carbamate, 5b**



N-Boc-5-methylenecyclohexacarbamate (**C4**) (21 mg, 0.1 mmol), (*R*,*R*)-ANDEN-phenyl Trost ligand (6 mg, 0.075), $\{\eta^3\text{-}C_3H_5PdCl\}_2$ (1 mg, 0.025 mmol), ^{t}BuOH (0.045 ml, 0.5 mmol) and DIPEA (0.025 ml, 0.2 mmol) were dissolved in dry 20% toluene in dioxane (1 mL) at 0 °C for 20 mins. Then 2-phenyl-4-isobutyl-2-oxazolin-5-one (**4b**) (65 mg, 0.3 mmol) was added. The mixture was stirred at 0 °C overnight. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 20% EtOAc in petrol to give *tert*-butyl *tert*-butyl-(*R*)-(2-((4-isobutyl-5-oxo-2-phenyl-4,5-dihydrooxazol-4-yl)methyl)allyl)-carbamate (**5b**) (32 mg, 83%) as a white solid.

FTIR ν_{max} (thin film/cm^{-1}) 3346, 2960, 1815, 1713, 1651; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.02 (d, *J* = 7.5 Hz, 2H, CH_{Ar}), 7.64 – 7.57 (m, 1H, CH_{Ar}), 7.51 (t, J = 7.5 Hz, 2H, CH_{Ar}), 5.04 (s, 1H, C=CH), 4.98 (br, 2H, NH, C=CH), 3.67 (br, 2H, CH_2), 2.70 – 2.55 (m, 2H, CH_2), 1.97 (dd, J = 14.0, 5.5 Hz, 1H, CH), 1.83 (dd, J = 14.0, 7.0 Hz, 1H, CH), 1.67 – 1.55 (m, 1H, CH), 1.43 (s, 9H, $C(CH_3)_3$), 0.90 (d, J = 6.5 Hz, 3H, CH_3), 0.88 (d, J = 6.5 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 180.6, 159.9, 156.8, 140.4, 132.8, 128.9, 127.9, 125.7, 116.0, 79.2, 73.9, 46.2, 46.1, 42.3, 28.4, 24.9, 24.1, 23.2; **MS (ESI$^+$)** 387 (100%, M+H$^+$); **HRMS (ESI$^+$)** $C_{22}H_{30}N_2O_4$ requires M+H$^+$ 387.2278, found 387.2276; **HPLC** (Cellulose-1, hexane:^{i}PrOH 99:1, flow rate 1.0 mL/min, λ = 254 nm, 22 °C) t_R(major) = 12.643, t_R(minor) = 10.993, er = 8.5:91.5.

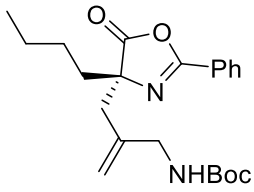
***tert*-butyl-(*S*)-(2-((4-(2-(methylthio)ethyl)-5-oxo-2-phenyl-4,5-dihydrooxazol-4-yl)methyl)allyl)carbamate, 5c**



N-Boc-5-methylenecyclohexacarbamate (**C4**) (21 mg, 0.1 mmol), (*R,R*)-ANDEN-phenyl Trost ligand (6 mg, 0.075), $\{\eta^3\text{-}C_3H_5PdCl\}_2$ (1 mg, 0.025 mmol), ^{t}BuOH (0.045 ml, 0.5 mmol) and DIPEA (0.025 ml, 0.2 mmol) were dissolved in dry 20% toluene in dioxane (1 mL) at 0 °C for 20 mins. Then 2-phenyl-4-[2-(methylthio)ethyl)]-2-oxazolin-5-one (**4c**) (71 mg, 0.3 mmol) was added. The mixture was stirred at 0 °C overnight. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 15% EtOAc in petrol to give *tert*-butyl-(*S*)-(2-((4-(2-(methylthio)ethyl)-5-oxo-2-phenyl-4,5-dihydrooxazol-4-yl)methyl)allyl)carbamate (**5c**) (35 mg, 87%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3355, 2976, 2920, 1815, 1713, 1650; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.00 (d, 2H, J = 7.5 Hz, CH_{Ar}), 7.58 (t, 1H, J = 7.5 Hz, CH_{Ar}), 7.49 (t, 2H, J = 7.5 Hz, CH_{Ar}), 5.05 (s, 1H, C=CH), 5.01 (s, 1H, NH), 4.99 (s, 1H, C=CH), 3.67 (br, 2H, CH_2), 2.65 (d, J = 14.0 Hz, 1H), 2.60 (d, J = 14.0 Hz, 1H), 2.50-2.40 (m, 1H, CH), 2.39-2.29 (m, 1H, CH), 2.27-2.17 (m, 2H, CH_2), 2.04 (s, 3H, CH_3), 1.41 (s, 9H, $C(CH_3)_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ. 179.8, 160.8, 156.8, 140.3, 133.0, 128.9, 128.0, 125.5, 116.3, 79.3, 73.2, 46.1, 41.4, 36.2, 28.6, 28.4, 15.2; **MS (ESI$^+$)** 404 (100%, M+H$^+$); **HRMS (ESI$^+$)** $C_{21}H_{28}N_2O_4S$ requires M+H$^+$ 404.1848, found 405.1843; **HPLC** (Cellulose-2, hexane:^{i}PrOH 97.5:2.5, flow rate 1.0 mL/min, λ = 254 nm, 22 °C) t_R(major) = 18.903, t_R(minor) = 11.037, er = 90:10.

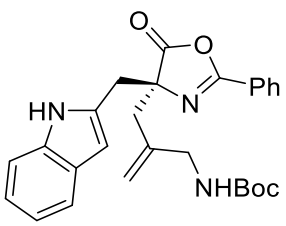
***tert*-butyl-(*R*)-(2-((4-butyl-5-oxo-2-phenyl-4,5-dihydrooxazol-4-yl)methyl)allyl)carbamate, 5d**



N-Boc-5-methylenecyclohexacarbamate (**C4**) (21 mg, 0.1 mmol), (*R*,*R*)-ANDEN-phenyl Trost ligand (6 mg, 0.075), $\{\eta^3\text{-}C_3H_5PdCl\}_2$ (1 mg, 0.025 mmol), ^{t}BuOH (0.045 ml, 0.5 mmol) and DIPEA (0.025 ml, 0.2 mmol) were dissolved in dry 20% toluene in dioxane (1 mL) at 0 °C for 20 mins. Then 2-phenyl-4-butyl-2-oxazolin-5-one (**4d**) (65 mg, 0.3 mmol) was added. The mixture was stirred at 0 °C overnight. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 10% EtOAc in petrol to give *tert*-butyl-(*R*)-(2-((4-butyl-5-oxo-2-phenyl-4,5-dihydrooxazol-4-yl)methyl)allyl)carbamate (**5d**) (33 mg, 85%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3346, 2960, 2930, 1817, 1717, 1654; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.01 (d, J = 7.5 Hz, 2H, CH_{Ar}), 7.59 (t, J = 7.5 Hz, 1H, CH_{Ar}), 7.50 (t, J = 7.5 Hz, 2H, CH_{Ar}), 5.04 (br, 2H, C=CH, NH), 4.99 (s, 1H, C=CH), 3.69 (br, 2H, CH_2), 2.64 (s, 2H, CH_2), 1.97 – 1.84 (m, 2H, CH_2), 1.97 – 1.84 (m, 9H, $C(CH_3)_3$), 1.35 – 1.06 (m, 4H, 4xCH), 0.86 (t, J = 7.0 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 180.1, 160.2, 155.8, 140.7, 132.8, 128.9, 128.0, 125.6, 115.8, 79.2, 74.3, 46.2, 41.1, 37.2, 28.4, 25.8, 22.5, 13.8; **MS (ESI$^+$)** 387 (100%, M+H$^+$); **HRMS (ESI$^+$)** $C_{22}H_{30}N_2O_4$ requires M+H$^+$ 387.2278, found 387.2297; **HPLC** (Cellulose-1, hexane:^{i}PrOH 99:1, flow rate 1.0 mL/min, λ = 254 nm, 22 °C) t_R(major) = 13.663, t_R(minor) = 11.960, er = 6:94.

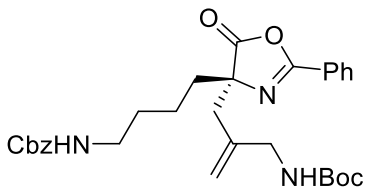
***tert*-butyl (*S*)-(2-((4-((1*H*-indol-2-yl)methyl)-5-oxo-2-phenyl-4,5-dihydrooxazol-4-yl)methyl)allyl)carbamate, 5e**



N-Boc-5-methylenecyclohexacarbamate (**C4**) (21 mg, 0.1 mmol), (*R*,*R*)-ANDEN-phenyl Trost ligand (6 mg, 0.075), {η^3-C_3H_5PdCl}$_2$ (1 mg, 0.025 mmol), ^{t}BuOH (0.045 ml, 0.5 mmol) and DIPEA (0.025 ml, 0.2 mmol) were dissolved in dry 20% toluene in dioxane (1 mL) at 0 °C for 20 mins. Then 2-phenyl-4-((1*H*-indol-2-yl)methyl)-2-oxazolin-5-one (**4e**) (87 mg, 0.3 mmol) was added. The mixture was stirred at 0 °C overnight. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 20% EtOAc in petrol to give *tert*-butyl (*S*)-(2-((4-((1*H*-indol-2-yl)methyl)-5-oxo-2-phenyl-4,5-dihydrooxazol-4-yl)methyl)allyl)carbamate (**5e**) (39 mg, 85%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3319, 2978, 2921, 1814, 1693, 1653; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.11 (br, 1H, PhNH), 7.84 – 7.76 (m, 2H, CH_{Ar}), 7.74 – 7.67 (m, 1H, CH_{Ar}), 7.53 – 7.46 (m, 1H, CH_{Ar}), 7.38 (t, *J* = 7.5 Hz, 2H, CH_{Ar}), 7.26 – 7.20 (m, 1H, CH_{Ar}), 7.13 – 7.04 (m, 2H, CH_{Ar}), 7.02 (d, *J* = 2.5 Hz, 1H, CH_{Ar}), 5.24 (br, 1H, NH), 5.09 (s, 1H, C=CH), 5.07 (s, 1H, C=CH), 3.84 – 3.66 (m, 2H, CH_2), 3.42 (d, J = 14.0 Hz, 1H, CH), 3.37 (d, J = 14.0 Hz, 1H, CH), 2.90 – 2.77 (m, 2H, CH_2), 1.47 (s, 9H, $C(CH_3)_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 179.8, 160.3, 155.9, 140.8, 135.7, 132.5, 128.6, 127.9, 127.6, 125.5, 123.8, 121.9, 119.6, 119.5, 116.1, 110.9, 108.6, 79.3, 75.8, 46.3, 40.8, 33.4, 28.4; **MS (ESI$^+$)** 460 (100%, M+H$^+$); **HRMS (ESI$^+$)** $C_{27}H_{29}N_3O_4$ requires M+H$^+$ 460.2231, found 460.2238; **HPLC** (Cellulose-2, hexane:^{i}PrOH 90:10, flow rate 1.0 mL/min, λ = 254 nm, 22 °C) t_R(major) = 15.463, t_R(minor) = 23.853, er = 91.5:8.5.

***tert*-butyl (*R*)-(2-((4-(4-(((benzyloxy)carbonyl)amino)butyl)-5-oxo-2-phenyl-4,5-dihydrooxazol-4-yl)methyl)allyl)carbamate, 5f**

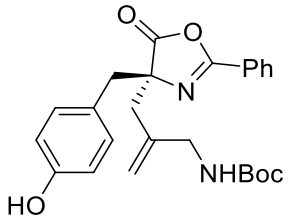


N-Boc-5-methylenecyclohexacarbamate (**C4**) (21 mg, 0.1 mmol), (*R*,*R*)-ANDEN-phenyl Trost ligand (6 mg, 0.075), {η^3-C_3H_5PdCl}$_2$ (1 mg, 0.025 mmol), ^{t}BuOH (0.045 ml, 0.5 mmol) and DIPEA (0.025 ml, 2 eq, 0.2 mmol) were dissolved in dry 20% toluene in

dioxane (1 mL) at 0 °C for 20 mins. Then benzyl (4-(5-oxo-2-phenyl-4,5-dihydrooxazol-4-yl)butyl)carbamate (**4f**) (110 mg, 0.3 mmol) was added. The mixture was stirred at 0 °C overnight. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 20% EtOAc in petrol to give *tert*-butyl (*R*)-(2-((4-(4-(((benzyloxy)carbonyl)amino)butyl)-5-oxo-2-phenyl-4,5-dihydrooxazol-4-yl)methyl)allyl)-carbamate (**5f**) (40 mg, 75%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3334, 2929, 1816, 1695, 1654; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.01 (d, J = 7.5 Hz, 2H, CH_{Ar}), 7.61 (t, J = 7.5 Hz, 1H, CH_{Ar}), 7.51 (t, J = 7.5 Hz, 2H, CH_{Ar}), 7.40 – 7.29 (m, 5H, CH_{Ar}), 5.07 (s, 2H, C=CH_2, NH), 5.05 (s, 1H, C=CH), 4.99 (br, 2H, CH_2), 4.81 (br, 1H, NH), 3.80 – 3.59 (m, 2H, CH_2), 3.17 (d, J = 7.0 Hz, 1H, CH), 3.13 (d, J = 7.0 Hz, 1H, CH), 2.67 – 2.57 (m, 2H, CH_2), 1.99 – 1.87 (m, 2H, CH_2), 1.62 – 1.47 (m, 2H, CH_2), 1.44 (s, 9H, $C(CH_3)_3$), 1.36 – 1.11 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 179.9, 160.4, 156.3, 155.8, 140.5, 136.5, 132.9, 128.9, 128.5, 128.1, 128.0, 127.2, 125.5, 115.8, 79.3, 74.1, 66.6, 46.2, 41.1, 40.6, 36.8, 29.6, 28.4, 21.0; **MS (ESI$^+$)** 536 (100%, M+H$^+$); **HRMS (ESI$^+$)** $C_{30}H_{37}N_3O_6$ requires M+H$^+$ 536.2755, found 536.2768; **HPLC** (Cellulose-2, hexane:^{i}PrOH 80:20, flow rate 1.0 mL/min, λ = 254 nm, 22 °C) t_R(major) = 18.570, t_R(minor) = 14.300, er = 10:90.

tert-butyl (_R_)-(2-((4-(4-hydroxybenzyl)-5-oxo-2-phenyl-4,5-dihydrooxazol-4-yl)methyl)-allyl)carbamate, 5g

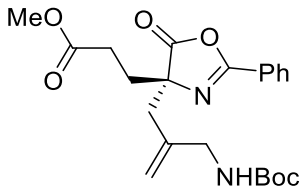


N-Boc-5-methylenecyclohexacarbamate (**C4**) (21 mg, 0.1 mmol), (*R*,*R*)-ANDEN-phenyl Trost ligand (6 mg, 0.075), {η^3-C_3H_5PdCl}$_2$ (1 mg, 0.025 eq, 0.025 mmol), ^{t}BuOH (0.045 ml, 0.5 mmol) and DIPEA (0.025 ml, 0.2 mmol) were dissolved in dry 20% toluene in dioxane (1 mL) at 0 °C for 20 mins. Then 2-phenyl-4-(4-hydroxybenzyl)-2-oxazolin-5-one (**4g**) (80 mg, 0.3 mmol) was added. The mixture was stirred at 0 °C overnight.

The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 20% EtOAc in petrol to give *tert*-butyl (*R*)-(2-((4-(4-hydroxybenzyl)-5-oxo-2-phenyl-4,5-dihydrooxazol-4-yl)methyl)-allyl)carbamate (**5g**) (31 mg, 70%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3332, 2978, 1816, 1689, 1653; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.92 – 7.79 (m, 2H, CH_{Ar}), 7.58 – 7.49 (m, 1H, CH_{Ar}), 7.46 – 7.38 (m, 2H, CH_{Ar}), 7.00 (d, J = 8.5 Hz, 2H, CH_{Ar}), 6.64 (d, J = 8.5 Hz, 2H, CH_{Ar}), 6.17 (s, 1H, OH), 5.17 (s, 1H, NH), 5.05 (s, 1H, C=CH), 5.02 (s, 1H, C=CH), 3.84 – 3.56 (m, 2H, CH_2), 3.16 (d, J = 13.5 Hz, 1H, CH), 3.07 (d, J = 13.5 Hz, 1H, CH), 2.73 (s, 2H, CH_2), 1.44 (s, 9H, $C(CH_3)_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 179.4, 160.2, 156.1, 155.3, 140.4, 132.7, 131.3, 128.8, 127.9, 125.6, 125.4, 116.3, 115.2, 79.1, 75.5, 46.2, 42.7, 40.8, 28.4; **MS (ESI$^+$)** 437 (100%, M+H$^+$); **HRMS (ESI$^+$)** $C_{25}H_{28}N_2O_5$ requires M+H$^+$ 437.2071, found 437.2088; **HPLC** (Cellulose-2, hexane:^{i}PrOH 95:5, flow rate 1.0 mL/min, λ = 254 nm, 22 °C) t_R(major) = 49.013, t_R(minor) = 44.447, er = 8.5:91.5.

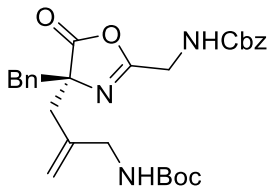
Methyl (*R*)-3-(4-(2-(((*tert*-butoxycarbonyl)amino)methyl)allyl)-5-oxo-2-phenyl-4,5-dihydrooxazol-4-yl)propanoate, 5h



N-Boc-5-methylenecyclohexacarbamate (**C4**) (21 mg, 0.1 mmol), (*R*,*R*)-ANDEN-phenyl Trost ligand (6 mg, 0.075), {η^3-C_3H_5PdCl}$_2$ (1 mg, 0.025 mmol), ^{t}BuOH (0.045 ml, 0.5 mmol) and DIPEA (0.025 ml, 0.2 mmol) were dissolved in dry 20% toluene in dioxane (1 mL) at 0 °C for 20 mins. Then 2-phenyl-4-methyl propanoate-2-oxazolin-5-one (**4h**) (74 mg, 0.3 mmol) was added. The mixture was stirred at 0 °C overnight. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 20% EtOAc in petrol to give methyl (*R*)-3-(4-(2-(((*tert*-butoxycarbonyl)amino)-methyl)allyl)-5-oxo-2-phenyl-4,5-dihydrooxazol-4-yl)propanoate (**5h**) (33 mg, 80%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3384, 2977, 1817, 1738, 1714, 1654; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.03 – 7.96 (m, 2H, CH_{Ar}), 7.64 – 7.56 (m, 1H, CH_{Ar}), 7.56 – 7.45 (m, 2H, CH_{Ar}), 5.07 (s, 1H, C=CH), 5.01 (s, 1H, C=CH), 4.96 (s, 1H, NH), 3.74 – 3.65 (m, 2H, CH_2), 3.62 (s, 3H, CH_3), 2.66 (s, 2H CH_2), 2.38 – 2.20 (m, 4H, 4xCH), 1.43 (s, 9H, $C(CH_3)_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 179.4, 172.4, 160.7, 156.8, 140.3, 133.1, 128.9, 128.0, 125.3, 116.1, 79.3, 73.2, 51.8, 46.1, 40.8, 32.1, 28.8, 28.4; **MS (ESI^+)** 417 (100%, $M+H^+$); **HRMS (ESI^+)** $C_{22}H_{28}N_2O_6$ requires $M+H^+$ 417.2026, found 417.2024; **HPLC** (Cellulose-1, hexane:^{i}PrOH 90:10, flow rate 1.0 mL/min, λ = 254 nm, 22 °C) t_R(major) = 16.587, t_R(minor) = 14.743, er = 12:88.

***tert*-butyl (*R*)-(2-((4-benzyl-2-((((benzyloxy)carbonyl)amino)methyl)-5-oxo-4,5-dihydrooxazol-4-yl)methyl)allyl)carbamate, 5i**

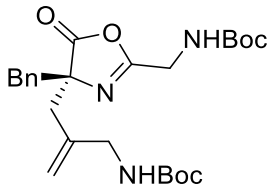


N-Boc-5-methylenecyclohexacarbamate (**C4**) (21 mg, 0.1 mmol), (*R*,*R*)-ANDEN-phenyl Trost ligand (6 mg, 0.075), $\{\eta^3\text{-}C_3H_5PdCl\}_2$ (1 mg, 0.025 mmol), ^{t}BuOH (0.045 ml, 0.5 mmol) and DIPEA (0.025 ml, 0.2 mmol) were dissolved in dry 20% toluene in dioxane (1 mL) at 0 °C for 20 mins. Then benzyl (4-benzyl-5-oxo-4,5-dihydro-oxazol-2-ylmethyl)-carbamic acid (**4i**) (102 mg, 3 eq, 0.3 mmol) was added. The mixture was stirred at 0 °C overnight. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 30% EtOAc in petrol to give *tert*-butyl (*R*)-(2-((4-benzyl-2-((((benzyloxy)carbonyl)amino)methyl)-5-oxo-4,5-dihydrooxazol-4-yl)methyl)allyl)-carbamate (**5i**) (45 mg, 90%) as a colorless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3332, 2978, 1821, 1693, 1516; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.44 – 7.30 (m, 5H, CH_{Ar}), 7.30 – 7.21 (m, 3H, CH_{Ar}), 7.17 – 7.07 (m, 2H, CH_{Ar}), 6.30 (s, 1H, NH), 5.24 – 5.09 (m, 2H, CH_2), 5.09 – 4.98 (m, 1H, NH), 4.94 (s, 1H, C=CH), 4.93 (s, 1H, C=CH), 4.08 – 3.86 (m, 3H, 3xCH), 3.34 (dd, J = 17.5 & 4.0 Hz, 1H, CH), 2.79 (d, J = 13.5 Hz, 1H, CH), 3.10 (s, 2H, CH_2), 2.43 (d, J = 13.5 Hz, 1H, CH), 1.39 (s, 9H, $C(CH_3)_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 178.7, 161.5, 156.6, 155.9, 140.9, 136.5, 133.7, 130.2, 128.4, 128.3, 128.13, 128.08, 127.5, 112.7, 79.7, 75.3, 67.0, 45.6, 43.1, 40.3, 38.7, 28.3; **MS (ESI$^+$)** 508 (100%, M+H$^+$); **HRMS (ESI$^+$)** $C_{28}H_{33}N_3O_6$ requires M+Na$^+$ 530.2262, found 530.2284; **HPLC** (Cellulose-1, hexane:^{i}PrOH 90:10, flow rate 1.0 mL/min, λ = 254 nm, 22 °C) t_R(major) = 15.243, t_R(minor) = 17.807, er = 98.5:1.5; $[\alpha]_D^{22} = -10$ (*c* 1.0, $CHCl_3$).

tert-butyl (_R_)-(2-((4-benzyl-2-(((tert-butoxycarbonyl)amino)methyl)-5-oxo-4,5-dihydrooxazol-4-yl)methyl)allyl)carbamate, 5j

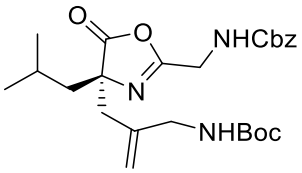


N-Boc-5-methylenecyclohexacarbamate (**C4**) (21 mg, 0.1 mmol), (*R*,*R*)-ANDEN-phenyl Trost ligand (6 mg, 0.075), {η^3-C_3H_5PdCl}$_2$ (1 mg, 0.025 mmol), ^{t}BuOH (0.045 ml, 0.5 mmol) and DIPEA (0.025 ml, 0.2 mmol) were dissolved in dry 20% toluene in dioxane (1 mL) at 0 °C for 20 mins. Then *tert*-butyl (4-benzyl-5-oxo-4,5-dihydro-oxazol-2-ylmethyl)-carbamic acid (**4j**) (91 mg, 0.3 mmol) was added. The mixture was stirred at 0 °C overnight. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 60% Et_2O in petrol to give *tert*-butyl (*R*)-(2-((4-benzyl-2-(((*tert*-butoxycarbonyl)amino)methyl)-5-oxo-4,5-dihydrooxazol-4-yl)methyl)allyl)-carbamate (**5j**) (44 mg, 93%) as a colorless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3347, 2978, 2928, 1823, 1693, 1516; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.29 – 7.19 (m, 3H, CH_{Ar}), 7.17 – 7.08 (m, 2H, CH_{Ar}), 5.73 (s, 1H, NH), 5.21 (s, 1H, NH), 4.96 (s, 1H, C=CH), 4.92 (s, 1H, C=CH), 4.08 – 3.86 (m, 3H, 3xCH), 3.50 – 3.37 (m, 1H, CH), 3.09 (s, 2H, CH_2), 2.77 (d, J = 13.5 Hz, 1H, CH), 2.44 (d, J = 13.5 Hz, 1H, CH), 1.46 (s, 9H, $C(CH_3)_3$), 1.44 (s, 9H, $C(CH_3)_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 178.8, 161.6, 156.0, 155.9, 141.0, 133.8, 130.1, 128.2, 127.4, 112.9, 80.0, 79.4, 75.4, 45.5, 43.2, 40.3, 38.4, 28.4, 28.4; **MS (ESI$^+$)** 474 (100%, M+H$^+$); **HRMS (ESI$^+$)** $C_{25}H_{35}N_3O_6$ requires M+H$^+$ 474.2604, found 474.2590; **HPLC** (Cellulose-1, hexane:^{i}PrOH 97.5:2.5,

flow rate 1.0 mL/min, λ = 254 nm, 22 °C) t_R(major) = 18.007, t_R(minor) = 27.023, er = 94:6.

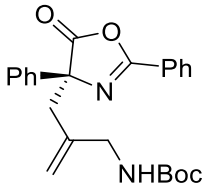
Benzyl-(*R*)-((4-(2-(((*tert*-butoxycarbonyl)amino)methyl)allyl)-4-isobutyl-5-oxo-4,5-dihydrooxazol-2-yl)methyl)carbamate, 5k



N-Boc-5-methylenecyclohexacarbamate (**C4**) (21 mg, 0.1 mmol), (*R*,*R*)-ANDEN-phenyl Trost ligand (6 mg, 0.075), $\{\eta^3\text{-}C_3H_5PdCl\}_2$ (1 mg, 0.025 mmol), ^{t}BuOH (0.045 ml, 0.5 mmol) and DIPEA (0.025 ml, 0.2 mmol) were dissolved in dry 20% toluene in dioxane (1 mL) at 0 °C for 20 mins. Then benzyl (4-isobutyl-5-oxo-4,5-dihydro-oxazol-2-ylmethyl)-carbamic acid (**4k**) (91 mg, 0.3 mmol) was added. The mixture was stirred at 0 °C overnight. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 50% Et_2O in petrol to give benzyl-(*R*)-((4-(2-(((*tert*-butoxycarbonyl)amino)methyl)allyl)-4-isobutyl-5-oxo-4,5-dihydrooxazol-2-yl)methyl)-carbamate (**5k**) (43 mg, 90%) as a colorless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3356, 2960, 1825, 1692, 1513; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.41 – 7.27 (m, 5H, CH_{Ar}), 6.50 (t, *J* = 6.0 Hz, 1H, NH), 5.14 (s, 2H, CH_2), 5.07 – 4.99 (m, 1H, NH), 4.91 (s, 1H, C=CH), 4.86 (s, 1H, C=CH), 4.32 – 4.15 (m, 2H, CH_2), 3.96 (dd, J = 18.0, 8.0 Hz, 1H, CH), 3.26 (dd, J = 18.0, 5.0 Hz, 1H, CH), 2.61 (d, J = 13.5 Hz, 1H, CH), 2.29 (d, J = 13.5 Hz, 1H, CH), 1.83 (dd, J = 14.0, 5.5 Hz, 1H, CH), 1.74 (dd, J = 14.0, 7.0 Hz, 1H, CH), 1.55 (dp, J = 13.5, 6.5 Hz, 1H, CH), 1.39 (s, 9H, $C(CH_3)_3$), 0.89 (d, J = 6.5 Hz, 3H, CH_3), 0.85 (d, J = 6.5 Hz, 3H, CH_3) ; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 180.2, 161.4, 156.8, 156.0, 140.7, 136.5, 128.4, 128.1, 128.0, 112.5, 79.7, 73.9, 67.0, 45.9, 45.8, 41.6, 40.0, 28.3, 24.7, 24.1, 23.1; **MS (ESI^+)** 474 (100%, $M+H^+$); **HRMS (ESI^+)** $C_{25}H_{35}N_3O_6$ requires $M+H^+$ 474.2604, found 474.2587; **HPLC** (Cellulose-1, hexane:^{i}PrOH 97.5:2.5, flow rate 1.0 mL/min, λ = 254 nm, 22 °C) t_R(major) = 40.313, t_R(minor) = 50.510, er = 93:7.

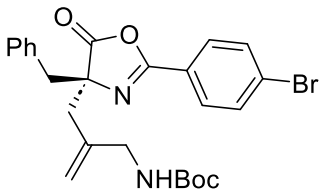
tert-butyl (*S*)-(2-((5-oxo-2,4-diphenyl-4,5-dihydrooxazol-4-yl)methyl)allyl)-carbamate, 5l



N-Boc-5-methylenecyclohexacarbamate (**C4**) (21 mg, 0.1 mmol), (*R*,*R*)-ANDEN-phenyl Trost ligand (6 mg, 0.075), $\{\eta^3\text{-}C_3H_5PdCl\}_2$ (1 mg, 0.025 mmol), ^{t}BuOH (0.045 ml, 0.5 mmol) and DIPEA (0.025 ml, 0.2 mmol) were dissolved in dry 20% toluene in dioxane (1 mL) at 0 °C for 20 mins. Then 2-Phenyl-4-phenyl-2-oxazolin-5-one (**4l**) (72 mg, 0.3 mmol) was added. The mixture was stirred at 0 °C overnight. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 20% EtOAc in petrol to give tert-butyl (*S*)-(2-((5-oxo-2,4-diphenyl-4,5-dihydrooxazol-4-yl)methyl)allyl)-carbamate (**5l**) (16 mg, 40%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3350, 2971, 1816, 1717, 1654; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.15 – 8.07 (m, 2H, CH_{Ar}), 7.77 – 7.66 (m, 2H, CH_{Ar}), 7.66 – 7.59 (m, 1H, CH_{Ar}), 7.59 – 7.49 (m, 2H, CH_{Ar}), 7.47 – 7.32 (m, 3H, CH_{Ar}), 5.05 (br, 2H, C=CH, NH), 5.00 – 4.96 (s, 1H, C=CH), 3.72 (br, 2H, CH_2), 3.09 – 2.98 (d, J = 14.0Hz, 1H, CH), 2.98 – 2.89 (d, J = 14.0 Hz, 1H, CH), 1.51 – 1.36 (s, 9H, $C(CH_3)_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 178.3, 160.5, 155.8, 140.3, 137.8, 133.1, 128.9, 128.7, 128.4, 128.1, 125.7, 125.6, 116.3, 79.3, 75.0, 46.3, 44.3, 28.4; **MS (ESI$^+$)** 407 (100%, M+H$^+$); **HRMS (ESI$^+$)** $C_{22}H_{28}N_2O_6$ requires M+H$^+$ 407.1965, found 407.1983; **HPLC** (Cellulose-2, hexane:^{i}PrOH 99:1, flow rate 1.0 mL/min, λ = 254 nm, 22 °C) t_R(major) = 28.593, t_R(minor) = 32.263, er = 68:32.

5o

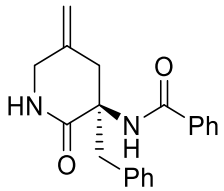


N-Boc-5-methylenecyclohexacarbamate (**C4**) (21.32 mg, 0.1 mmol), (*R,R*)-ANDEN-Phenyl Trost Ligand (6 mg, 0.075), $\{\eta^3\text{-}C_3H_5PdCl\}_2$ (1 mg, 0.025 mmol), ^{t}BuOH (0.045 ml, 0.5 mmol) and DIPEA (0.025 ml, 0.2 mmol) were dissolved in dry 20% toluene in dioxane (1 mL) at 0 °C for 20 mins. Then 2-(4-bromophenyl)-4-benzyl-2-oxazolin-5-one (**4o**) (99.05 mg, 0.3 mmol) was added. The mixture was stirred at 0 °C overnight. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 20% EtOAc in petrol to give (**5o**) (33 mg, 67%) as a white solid.

FTIR ν_{max} (thin film/cm^{-1}) 3335, 2972, 2926, 1817, 1702, 1651; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.71 (2H, d, *J* = 8.5 Hz, CH_{Ar}), 7.61 – 7.55 (2H, m, CH_{Ar}), 7.22 – 7.10 (m, 5H, CH_{Ar}), 5.09 (s, 1H, C=CH), 5.04 (s, 1H, C=CH), 3.70 (br, 2H, CH_2), 3.25 (d, J = 13.5 Hz, 1H, CH), 3.16 (d, J = 13.5 Hz, 1H, CH), 2.85 – 2.68 (m, 2H, CH_2), 1.45 (s, 9H, $C(CH_3)_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 178.9, 159.5, 156.8, 140.5, 133.9, 132.1, 130.1, 129.3, 128.2, 127.7, 127.4, 124.3, 116.2, 79.4, 75.4, 46.1, 43.5, 40.9, 28.4; **MS (ESI$^+$)** 501 (100%, M+H$^+$); **HRMS (ESI$^+$)** $C_{25}H_{27}BrN_2O_4$ requires M+H$^+$ 499.1227 & 501,121, found 499.125 & 501.1234; **HPLC** (Cellulose-1, hexane:^{i}PrOH 95:5, flow rate 1.0 mL/min, λ = 254 nm, 22 °C) t_R(major) = 9.403, t_R(minor) = 10.637, er = 88.6:11.4.

12.3 the scope of Freidinger lactams

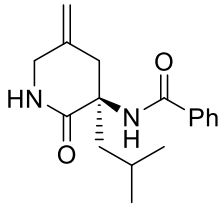
(*R*)-*N*-(3-Benzyl-5-methylene-2-oxopiperidin-3-yl)benzamide, 6a



To a solution of *tert*-butyl (*R*)-(2-((4-benzyl-5-oxo-2-phenyl-4,5-dihydrooxazol-4-yl)methyl)-allyl)carbamate (**5a**) (84 mg, 0.2 mmol) dissolved in dry DCM (2 mL) was added TFA (1.2 mL, 15 mmol) and the mixture stirred at room temperature. After 1 hour, EtOAc was added and the mixture was quenched with sat. aq. $NaHCO_3$. The layers were separated, and the aqueous layer was further extracted with EtOAc. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 60% EtOAc in petrol to give (*R*)-*N*-(3-benzyl-5-methylene-2-oxopiperidin-3-yl)benzamide **(6a)** (61 mg, 95%) as a white solid.

m.p.: 63.4 – 64.0 ℃ (After recrystallisation from DCM and hexane); **FTIR** ν_{max} (thin film/cm^{-1}) 3279, 2927, 1667, 1629; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.75 – 7.65 (m, 2H, CH_{Ar}), 7.57 – 7.45 (m, 1H, CH_{Ar}), 7.45 – 7.35 (m, 2H, CH_{Ar}), 7.29 – 7.21 (m, 4H, CH_{Ar}, NH), 7.20 – 7.10 (m, 2H, CH_{Ar}), 6.17 (s, 1H, NH), 5.25 (s, 1H, C=CH), 5.18 (s, 1H, C=CH), 4.23 (d, J = 15.0 Hz, 1H, CH), 4.12 (d, J = 15.0 Hz, 1H, CH), 3.75 (d, J = 14.0 Hz, 1H, CH), 3.66 (d, J = 14.0 Hz, 1H, CH), 3.07 (d, J = 14.0 Hz, 1H, CH), 2.92 (d, J = 14.0 Hz, 1H, CH); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.5, 166.9, 136.5, 135.7, 134.9, 131.5, 130.2, 128.5, 128.3, 127.1, 126.9, 114.1, 59.5, 47.2, 40.0, 39.2; **MS (ESI$^+$)** 321 (100%, M+H$^+$); **HRMS (ESI$^+$)** $C_{20}H_{20}N_2O_2$ requires M+H$^+$ 321.1603, found 321.1598. **HPLC** (Cellulose-2, hexane:^{i}PrOH 90:10, flow rate 1.0 mL/min, λ = 254 nm, 22 °C) t_R(major) = 29.823, t_R(minor) = 27.390, er = 95:5. $[\alpha]_D^{22} = +30$ (*c* 1.0, $CHCl_3$).

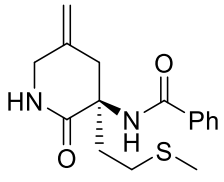
(*R*)-*N*-(3-Isobutyl-5-methylene-2-oxopiperidin-3-yl)benzamide, 6b



To a solution of *tert*-butyl-(*R*)-(2-((4-isobutyl-5-oxo-2-phenyl-4,5-dihydrooxazol-4-yl)methyl)-allyl)carbamate (**5b**) (77 mg, 0.2 mmol) dissolved in dry DCM (2 mL) was added TFA (1.2 mL, 15 mmol) and the mixture stirred at room temperature. After 1 hour, EtOAc was added and the mixture was quenched with sat. aq. $NaHCO_3$. The layers were separated, and the aqueous layer was further extracted with EtOAc. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 60% EtOAc in petrol to give (*R*)-*N*-(3-isobutyl-5-methylene-2-oxopiperidin-3-yl)benzamide (**6b**) (53 mg, 95%) as a white solid.

m.p.: 163.7 – 166.4 ℃ (After recrystallisation from toluene); **FTIR** ν_{max} (thin film/cm^{-1}) 3229, 2971, 1739, 1649; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.88 – 7.79 (m, 2H, CH_{Ar}), 7.64 (s, 1H, NH), 7.55 – 7.49 (m, 1H, CH_{Ar}), 7.50 – 7.41 (m, 2H, CH_{Ar}), 6.14 (s, 1H, NH), 5.15 (s, 1H, C=CH), 5.07 (s, 1H, C=CH), 4.16 (d, *J* = 15.5 Hz, 1H, CH), 4.05 (d, J = 15.5 Hz, 1H, CH), 3.69 (dd, J = 14.0, 3.5 Hz, 1H, CH), 2.78 (d, J = 14.0 Hz, 1H, CH), 2.38 (ddd, J = 14.5, 5.5, 1.5 Hz, 1H, CH_2), 1.89 – 1.75 (m, 1H, CH), 1.64 (dd, J = 14.5, 6.5 Hz, 1H, CH_2), 0.94 (d, J = 6.5 Hz, 3H, CH_3), 0.92 (d, J = 6.5 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 173.9, 166.3, 136.7, 135.0, 131.4, 128.5, 126.9, 113.4, 58.9, 46.7, 42.3, 40.0, 24.23, 24.20, 23.8; **MS (ESI^+)** 287 (100%, $M+H^+$); **HRMS (ESI^+)** $C_{17}H_{22}N_2O_2$ requires $M+H^+$ 287.1754, found 287.1752. **HPLC** (Cellulose-2, hexane:^{i}PrOH 80:20, flow rate 1.0 mL/min, λ = 254 nm, 22 °C) t_R(major) = 10.203, t_R(minor) = 11.650, er = 90:10.

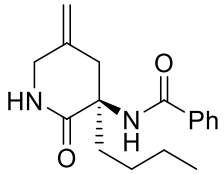
(*S*)-*N*-(5-Methylene-3-(2-(methylthio)ethyl)-2-oxopiperidin-3-yl)benzamide, 6c



To a solution of *tert*-butyl-(*S*)-(2-((4-(2-(methylthio)ethyl)-5-oxo-2-phenyl-4,5-dihydrooxazol-4-yl)methyl)allyl)carbamate (**5c**) (80 mg, 0.2 mmol) dissolved in dry DCM (2 mL) was added TFA (1.2 mL, 15 mmol) and the mixture stirred at room temperature. After 1 hour, EtOAc was added and the mixture was quenched with sat. aq. $NaHCO_3$. The layers were separated, and the aqueous layer was further extracted with EtOAc. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 60% EtOAc in petrol to give (*S*)-*N*-(5-methylene-3-(2-(methylthio)ethyl)-2-oxopiperidin-3-yl)benzamide (**6c**) (56 mg, 93%) as a white solid.

FTIR ν_{max} (thin film/cm^{-1}) 3257, 2966, 1662, 1652; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.89 – 7.79 (m, 2H, CH_{Ar}), 7.72 (s, 1H, NH), 7.56 – 7.50 (m, 1H, CH_{Ar}), 7.48 – 7.44 (m, 2H, CH_{Ar}), 6.15 (s, 1H, NH), 5.17 (s, 1H, C=CH), 5.11 (s, 1H, C=CH), 4.18 (d, J = 15.0 Hz, 1H, CH), 4.00 (d, J = 15.0 Hz, 1H, CH), 3.57 (d, J = 14.0 Hz, 1H, CH), 2.92 (d, J = 14.0 Hz, 1H, CH), 2.73 – 2.46 (m, 3H, 3xCH), 2.10 (s, 3H, CH_3), 2.08 – 1.96 (m, 1H, CH); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.7, 166.6, 136.1, 134.5, 131.7, 128.6, 127.0, 114.1, 59.0, 47.2, 39.5, 34.3, 28.5, 15.7; **MS (ESI^+)** 305 (100%, $M+H^+$); **HRMS (ESI^+)** $C_{21}H_{28}N_2O_4S$ requires $M+H^+$ 305.1328, found 321.1318.

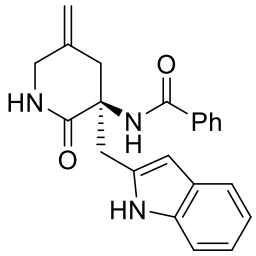
(*R*)-*N*-(3-butyl-5-methylene-2-oxopiperidin-3-yl)benzamide, 6d



To a solution of *tert*-butyl-(*R*)-(2-((4-butyl-5-oxo-2-phenyl-4,5-dihydrooxazol-4-yl)methyl)-allyl)carbamate (**5d**) (77 mg, 0.2 mmol) dissolved in dry DCM (2 mL) was added TFA (1.2 mL, 15 mmol) and the mixture stirred at room temperature. After 1 hour, EtOAc was added and the mixture was quenched with sat. aq. $NaHCO_3$. The layers were separated, and the aqueous layer was further extracted with EtOAc. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 80% EtOAc in petrol to give (*R*)-*N*-(3-butyl-5-methylene-2-oxopiperidin-3-yl)benzamide (**6d**) (52 mg, 94%) as a white solid.

FTIR ν_{max} (thin film/cm^{-1}) 3275, 2961, 1659, 1629; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.85 – 7.79 (m, 2H, CH_{Ar}), 7.54 – 7.46 (m, 1H, CH_{Ar}), 7.47 – 7.39 (m, 3H, CH_{Ar}, NH), 6.52 (s, 1H, NH), 5.12 (s, 1H, C=CH), 5.05 (s, 1H, C=CH), 4.12 (d, J = 15.0 Hz, 1H, CH), 3.95 (d, J = 15.0 Hz, 1H, CH), 3.50 (d, J = 14.0Hz, 1H, CH), 2.90 (d, J = 14.0 Hz, 1H, CH), 2.29 – 2.21 (m, 1H, CH), 1.76 – 1.64 (m, 1H, CH), 1.42 – 1.21 (m, 4H, 4xCH), 0.86 (t, J = 7.0 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 173.8, 166.8, 136.5, 134.7, 131.5, 128.5, 127.0, 113.5, 58.9, 46.9, 39.1, 34.6, 25.7, 22.7, 13.9; **MS (ESI^+)** 287 (100%, $M+H^+$); **HRMS (ESI^+)** $C_{17}H_{22}N_2O_2$ requires $M+H^+$ 287.1765, found 287.1754.

(*S*)-*N*-(3-((1*H*-Indol-2-yl)methyl)-5-methylene-2-oxopiperidin-3-yl)benzamide, 6e

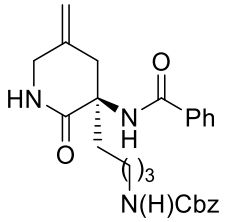


To a solution of *tert*-butyl (*S*)-(2-((4-((1*H*-indol-2-yl)methyl)-5-oxo-2-phenyl-4,5-dihydrooxazol-4-yl)methyl)allyl)carbamate (**5e**) (92 mg, 0.2 mmol) dissolved in dry DCM (4 mL) was added TFA (0.13 mL, 1.6 mmol) and the mixture stirred at room temperature. After 2 hours, EtOAc was added and the mixture was quenched with sat. aq. $NaHCO_3$. The layers were separated, and the aqueous layer was further extracted with EtOAc. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 80% EtOAc in petrol to give (*S*)-*N*-(3-((1*H*-indol-2-yl)methyl)-5-methylene-2-oxopiperidin-3-yl)benzamide (**6e**) (68 mg, 95%) as a white solid.

FTIR ν_{max} (thin film/cm^{-1}) 3288, 2923, 1653; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 10.97 (s, 1H, NH), 7.82 (s, 1H, NH), 7.78 – 7.62 (m, 3H, CH_{Ar}), 7.62 – 7.48 (m, 2H, CH_{Ar}), 7.35-7.41 (m, 2H, CH_{Ar}), 7.35 (d, J = 8.0 Hz, 1H, CH_{Ar}), 7.20 (s, 1H, NH), 7.06 (t, J = 7.5 Hz, 1H, CH_{Ar}), 6.97 (t, J = 7.4 Hz, 1H, CH_{Ar}), 5.01 (s, 1H, C=CH), 4.91 (s, 1H, C=CH), 4.01 (d, J = 15.0 Hz, 1H, CH), 3.88 (d, J = 15.0 Hz, 1H, CH), 3.41 (d, J = 14.0 Hz, 1H, CH), 3.24 (d, J = 14.0 Hz, 1H, CH), 3.04 (d, J = 14.0 Hz, 1H, CH), 2.98 (d, J = 14.0 Hz, 1H, CH);**^{13}C NMR**

(101 MHz, $CDCl_3$) δ 171.8, 166.3, 138.8, 136.3, 135.2, 131.8, 128.8, 128.7, 127.4, 125.3, 121.3, 118.9, 118.7, 112.5, 111.9, 108.5, 59.5, 46.7, 38.7, 31.1; **MS (ESI^+)** 360 (100%, $M+H^+$); **HRMS (ESI^+)** $C_{22}H_{21}N_3O_2$ requires $M+H^+$ 360.1712, found 360.1716.

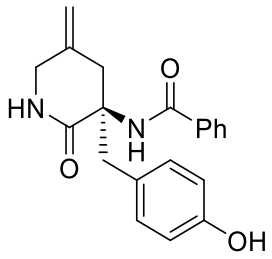
Benzyl (*S*)-(2-(3-benzamido-5-methylene-2-oxopiperidin-3-yl)ethyl)carbamate, 6f



To a solution of *tert*-butyl (*R*)-(2-((4-(4-(((benzyloxy)carbonyl)amino)butyl)-5-oxo-2-phenyl-4,5-dihydrooxazol-4-yl)methyl)allyl)-carbamate (**5f**) (107 mg, 0.2 mmol) dissolved in dry DCM (2 mL) was added TFA (1.2 mL, 15 mmol) and the mixture stirred at room temperature. After 1 hour, EtOAc was added and the mixture was quenched with sat. aq. $NaHCO_3$. The layers were separated, and the aqueous layer was further extracted with EtOAc. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 90% EtOAc in petrol to give benzyl (*S*)-(2-(3-benzamido-5-methylene-2-oxopiperidin-3-yl)ethyl)carbamate (**6f**) (80 mg, 92%) as a white solid.

FTIR ν_{max} (thin film/cm^{-1}) 3318, 2950, 1670, 1645; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.83 – 7.79 (m, 2H, CH_{Ar}), 7.62 (s, 1H, NH), 7.44 (t, J = 7.5 Hz, 1H, CH_{Ar}), 7.40 – 7.17 (m, 7H, CH_{Ar}), 7.06 (s, 1H, NH), 5.31 (s, 1H, NH), 5.14 – 4.82 (m, 4H, 4xCH), 4.03 (d, J = 15.0 Hz, 1H, CH), 3.82 (d, J = 15.0 Hz, 1H, CH), 3.37 – 3.04 (m, 3H, 3xCH), 2.97 (d, J = 14.0 Hz, 1H, CH), 2.16 – 2.09 (m, 1H, CH), 1.85 – 1.56 (m, 1H, CH), 1.53 – 1.14 (m, 4H, 4xCH);**^{13}C NMR (101 MHz, $CDCl_3$)** δ 173.8, 167.4, 156.9, 136.7, 136.6, 134.5, 131.5, 128.5, 128.4, 128.0, 128.0, 127.2, 113.3, 66.5, 58.7, 46.9, 40.0, 38.7, 34.4, 29.6, 20.1; **MS (ESI^+)** 436 (100%, $M+H^+$); **HRMS (ESI^+)** $C_{23}H_{25}N_3O_4$ requires $M+H^+$ 436.2236, found 436.2239.

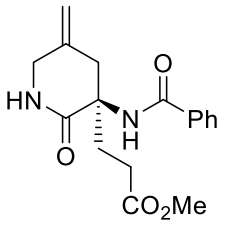
(*R*)-*N*-(3-(4-Hydroxybenzyl)-5-methylene-2-oxopiperidin-3-yl)benzamide, 6g



To a solution of *tert*-butyl (*R*)-(2-((4-(4-hydroxybenzyl)-5-oxo-2-phenyl-4,5-dihydrooxazol-4-yl)methyl)-allyl)carbamate (**5g**) (87 mg, 0.2 mmol) dissolved in dry DCM (2 mL) was added TFA (1.2 mL, 15 mmol) and the mixture stirred at room temperature. After 1 hour, EtOAc was added and the mixture was quenched with sat. aq. $NaHCO_3$. The layers were separated, and the aqueous layer was further extracted with EtOAc. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with EtOAc to give (*R*)-*N*-(3-(4-hydroxybenzyl)-5-methylene-2-oxopiperidin-3-yl)benzamide (**6g**) (63 mg, 93%) as a white solid.

FTIR ν_{max} (thin film/cm^{-1}) 3296, 2942, 2831, 1645; **^{1}H NMR (400 MHz, MeOD)** δ 7.78 – 7.66 (m, 2H, CH_{Ar}), 7.59 – 7.48 (m, 1H, CH_{Ar}), 7.51 – 7.37 (m, 2H, CH_{Ar}), 7.12 – 6.97 (m, 2H, CH_{Ar}), 6.78 – 6.63 (m, 2H, CH_{Ar}), 5.08 (s, 1H, C=CH), 5.04 (s, 1H, C=CH), 4.14 (d, J = 15.0 Hz, 1H, CH), 3.92 (d, J = 15.0 Hz, 1H, CH), 3.33 (d, J = 13.5 Hz, 1H, CH), 3.15 (d, J = 14.0 Hz, 1H, CH), 3.07 (d, J = 13.5 Hz, 1H, CH), 3.02 (d, J = 14.0 Hz, 1H, CH);**^{13}C NMR (101 MHz, MeOD)** δ 172.9, 168.0, 156.4, 137.2, 134.5, 131.5, 131.2, 128.3, 126.7, 125.8, 114.7, 112.2, 59.3, 46.4, 40.1, 38.3; **MS (ESI$^+$)** 337 (100%, $M+H^+$); **HRMS (ESI$^+$)** $C_{20}H_{20}N_2O_3$ requires $M+H^+$ 337.1552, found 337.1557.

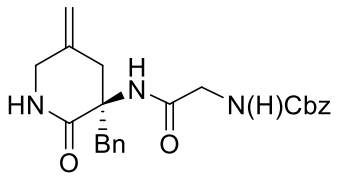
Methyl (*R*)-3-(3-benzamido-5-methylene-2-oxopiperidin-3-yl)propanoate, 6h



To a solution of methyl (*R*)-3-(4-(2-(((*tert*-butoxycarbonyl)amino)-methyl)allyl)-5-oxo-2-phenyl-4,5-dihydrooxazol-4-yl)propanoate (**5h**) (107 mg, 0.2 mmol) dissolved in dry DCM (2 mL) was added TFA (1.2 mL, 15 mmol) and the mixture stirred at room temperature. After 1 hour, EtOAc was added and the mixture was quenched with sat. aq. $NaHCO_3$. The layers were separated, and the aqueous layer was further extracted with EtOAc. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 90% EtOAc in petrol to give methyl (*R*)-3-(3-benzamido-5-methylene-2-oxopiperidin-3-yl)propanoate (**6h**) (80 mg, 92%) as a white solid.

FTIR ν_{max} (thin film/cm^{-1}) 3363, 2958, 1667, 1643; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.05 (s, 1H, NH), 7.81 (d, J = 7.5 Hz, 2H, CH_{Ar}), 7.51 – 7.42 (m, 1H, CH_{Ar}), 7.42 – 7.32 (m, 2H, CH_{Ar}), 7.12 (s, 1H, NH), 5.05 (s, 1H, C=CH), 5.07 (s, 1H, C=CH), 4.09 (d, J = 15.0 Hz, 1H, CH), 3.82 (d, J = 15.0 Hz, 1H, CH), 3.63 (s, 3H, CH_3), 3.19 (br, 1H, CH), 2.98 (br, 1H, CH), 2.61 (br, 1H, CH), 2.51 – 2.20 (m, 2H, CH_2), 2.21 – 1.96 (m, 1H, CH);**^{13}C NMR (101 MHz, $CDCl_3$)** δ 178.5, 176.3, 172.3, 141.5, 138.2, 135.4, 132.1, 130.9, 116.4, 62.0, 54.9, 50.8, 43.1, 34.7, 31.9.; **MS (ESI$^+$)** 317 (100%, M+H$^+$); **HRMS (ESI$^+$)** $C_{17}H_{20}N_2O_4$ requires M+H$^+$ 317.1501, found 317.1500.

Benzyl-(*R*)-(2-((3-benzyl-5-methylene-2-oxopiperidin-3-yl)amino)-2-oxoethyl)-carbamate, 6i

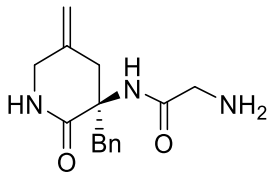


To a solution of *tert*-butyl (*R*)-(2-((4-benzyl-2-((((benzyloxy)carbonyl)amino)methyl)-5-oxo-4,5-dihydrooxazol-4-yl)methyl)allyl)-carbamate (**5i**) (102 mg, 0.2 mmol) dissolved in dry DCM (2 mL) was added TFA (1.2 mL, 15 mmol) and the mixture stirred at room temperature. After 1 hour, EtOAc was added and the mixture was quenched with sat. aq. $NaHCO_3$. The layers were separated, and the aqueous layer was further extracted with EtOAc. The solvent was removed under reduced pressure

and residue purified by flash column chromatography eluting with 90% EtOAc in petrol to give benzyl-(*R*)-(2-((3-benzyl-5-methylene-2-oxopiperidin-3-yl)amino)-2-oxoethyl)-carbamate (**6i**) (75 mg, 92%) as a white solid.

FTIR ν_{max} (thin film/cm^{-1}) 3315, 2952, 1723, 1667; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.49 – 7.19 (m, 8H, CH_{Ar}), 7.18 – 7.00 (m, 4H, $CH_{Ar,}$ NH), 6.13 (s, 1H, NH), 5.09 (s, 4H, 4xCH), 4.07 (d, J = 15.0 Hz, 1H, CH), 3.97 – 3.80 (m, 2H, CH_2), 3.71 (d, J = 13.0 Hz, 1H, CH), 3.25 (d, J = 13.5 Hz, 1H, CH), 3.13 – 2.78 (m, 3H, 3xCH);**^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.8, 169.4, 156.6, 136.4, 136.3, 134.9, 130.4, 128.5 (×2C), 128.2, 128.1, 127.3, 114.1, 67.0, 58.9, 47.2, 44.7, 40.6, 37.9; **MS (ESI$^+$)** 408 (100%, M+H$^+$); **HRMS (ESI$^+$)** $C_{23}H_{25}N_3O_4$ requires M+H$^+$ 408.1936, found 408.1918. $[\alpha]_D^{22} = +40$ (*c* 1.0, $CHCl_3$).

(*R*)-2-Amino-*N*-(3-benzyl-5-methylene-2-oxopiperidin-3-yl)acetamide, 6j

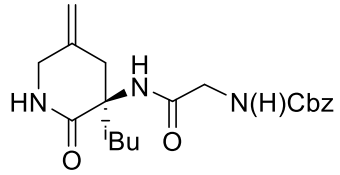


To a solution of *tert*-butyl (*R*)-(2-((4-benzyl-2-(((tert-butoxycarbonyl)amino)methyl)-5-oxo-4,5-dihydrooxazol-4-yl)methyl)allyl)-carbamate (**5j**) (95 mg, 0.2 mmol) dissolved in dry DCM (2 mL) was added TFA (1.2 mL, 15 mmol) and the mixture stirred at room temperature. After 1 hour, EtOAc was added and the mixture was quenched with sat. aq. $NaHCO_3$. The layers were separated, and the aqueous layer was further extracted with EtOAc. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 90% EtOAc in petrol to give (*R*)-2-amino-*N*-(3-benzyl-5-methylene-2-oxopiperidin-3-yl)acetamide (**6j**) (50 mg, 90%) as a colorless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3298, 2986, 1672; **^{1}H NMR (400 MHz, MeOD)** δ 7.36 – 7.11 (m, 5H, CH_{Ar}), 4.99 (s, 1H, C=CH), 4.92 (s, 1H, C=CH), 4.06 (d, J = 15.0 Hz, 1H, CH), 3.81 (d, J = 15.0 Hz, 1H, CH), 3.77 – 3.57 (m, 2H, CH_2), 3.26 (d, J = 13.5 Hz, 1H, CH), 3.11 – 2.99 (m, 2H, CH_2), 2.92 (d, J = 14.0 Hz, 1H, CH);**^{13}C NMR (101 MHz, MeOD)** δ 172.6,

166.0, 136.8, 135.1, 130.4, 127.8, 126.8, 112.3, 59.4, 46.3, 41.4, 40.6, 38.5; **MS (ESI$^+$)** 274 (100%, M+H$^+$); **HRMS (ESI$^+$)** $C_{15}H_{19}N_3O_2$ requires M+H$^+$ 274.1563, found 274.1556.

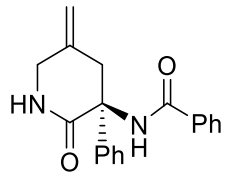
Benzyl-(*R*)-(2-((3-isobutyl-5-methylene-2-oxopiperidin-3-yl)amino)-2-oxoethyl)-carbamate, 6k



To a solution of benzyl-(*R*)-((4-(2-(((*tert*-butoxycarbonyl)amino)methyl)allyl)-4-isobutyl-5-oxo-4,5-dihydrooxazol-2-yl)methyl)-carbamate (**5k**) (95 mg, 0.2 mmol) dissolved in dry DCM (2 mL) was added TFA (1.2 mL, 15 mmol) and the mixture stirred at room temperature. After 1 hour, EtOAc was added and the mixture was quenched with sat. aq. $NaHCO_3$. The layers were separated, and the aqueous layer was further extracted with EtOAc. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 5% methanol in DCM to give benzyl-(*R*)-(2-((3-isobutyl-5-methylene-2-oxopiperidin-3-yl)amino)-2-oxoethyl)-carbamate (**6k**) (71 mg, 95%) as a colorless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3287, 2956, 1708, 1651; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.38 – 7.26 (m, 6H, CH_{Ar}, NH), 6.62 (s, 1H, NH), 5.89 (s, 1H, NH), 5.12 (s, 2H, CH_2), 5.05 (s, 1H, C=CH), 5.01 (s, 1H, C=CH), 4.05 (d, J = 15.0 Hz, 1H, CH), 3.98 – 3.77 (m, 3H, 3xCH), 3.25 (d, J = 14.0 Hz, 1H, CH), 2.82 (d, J = 14.0 Hz, 1H, CH), 2.05 (dd, J = 14.5, 5.0 Hz, 1H, CH), 1.81 – 1.69 (m, 1H, CH), 1.55 (dd, J = 14.5, 5.0 Hz, 1H, CH), 0.90 (d, J = 6.5 Hz, 3H, CH_3), 0.87 (d, J = 6.5 Hz, 3H, CH_3);**^{13}C NMR (101 MHz, $CDCl_3$)** δ 173.4, 168.6, 156.6, 136.7, 136.3, 128.5, 128.2, 128.1, 113.3, 67.0, 58.8, 46.7, 44.8, 42.8, 39.4, 24.2, 24.0, 23.7; **MS (ESI$^+$)** 374 (100%, M+H$^+$); **HRMS (ESI$^+$)** $C_{20}H_{27}N_3O_4$ requires M+H$^+$ 374.2080, found 374.2084.

(*S*)-N-(5-methylene-2-oxo-3-phenylpiperidin-3-yl)benzamide, 6l

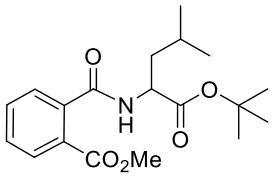


To a solution of tert-butyl (S)-(2-((5-oxo-2,4-diphenyl-4,5-dihydrooxazol-4-yl)methyl)allyl)-carbamate (**5l**) (41 mg, 0.1 mmol) dissolved in dry DCM (1 mL) was added TFA (0.6 mL, 7.5 mmol) and the mixture stirred at room temperature. After 1 hour, EtOAc was added and the mixture was quenched with sat. aq. $NaHCO_3$. The layers were separated, and the aqueous layer was further extracted with EtOAc. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 90% EtOAc in petrol to give (*S*)-N-(5-methylene-2-oxo-3-phenylpiperidin-3-yl)benzamide (**6l**) (29 mg, 95%) as a white solid.

FTIR ν_{max} (thin film/cm^{-1}) 3251, 3062, 1685, 1650; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.18 – 8.06 (s, 1H, NH), 7.87 – 7.76 (m, 2H, CH_{Ar}), 7.68 – 7.58 (m, 2H, CH_{Ar}), 7.56 – 7.45 (m, 1H, CH_{Ar}), 7.47 – 7.38 (m, 2H, CH_{Ar}), 7.39 – 7.26 (m, 3H, CH_{Ar}), 6.85 – 6.65 (s, 1H, NH), 5.17 – 5.00 (s, 1H, C=CH), 5.00 – 4.87 (s, 1H, C=CH), 4.38 – 4.19 (d, J = 16.0 Hz, 1H, CH), 4.08 – 3.87 (d, J = 15.5 Hz, 1H, CH), 3.76 – 3.54 (d, J = 15.5 Hz, 1H, CH), 3.36 – 3.06 (d, J = 16.0 Hz, 1H, CH);**^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.5, 166.1, 138.0, 137.2, 134.5, 131.6, 128.6, 128.5, 128.2, 127.4, 127.1, 112.2, 61.1, 45.9, 37.8; **MS (ESI^+)** 307 (100%, $M+H^+$); **HRMS (ESI^+)** $C_{19}H_{19}N_2O_2$ requires $M+H^+$ 307.1447, found 307.1452.

12.4 Synthesis of new azlactones

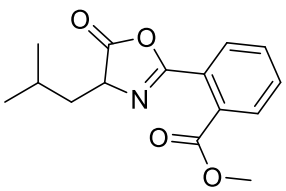
Methyl 2-((1-(*tert*-butoxy)-4-methyl-1-oxopentan-2-yl)carbamoyl)benzoate, 7a



Monomethyl phthalate (1.80 g, 10.0 mmol), N,N'-Diisopropylcarbodiimide (1.40 g, 10 mmol), 4-Dimethylaminopyridine (122 mg, 1 mmol) were dissolved in dry DCM (100 ml). The mixture was stirred at room temperature for 30 minutes. Then H-Leu-OtBu.HCl (2.30 g, 10.0 mmol) and NEt_3 (1.4 mL, 10 mmol) were added in the mixture. The mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 20% EtOAc in petrol to give methyl 2-((1-(*tert*-butoxy)-4-methyl-1-oxopentan-2-yl)carbamoyl)benzoate (**7a**) (3.40 g, 97%) as a white solid.

FTIR ν_{max} (thin film/cm^{-1}) 3319, 2957, 1727, 1651; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.88 (dd, J = 8.0, 1.5 Hz, 1H, CH_{Ar}), 7.61 – 7.42 (m, 3H, CH_{Ar}), 6.28 (d, J = 8.5 Hz, 1H, NH), 4.74 (dt, J = 8.5, 5.5 Hz, 1H, CH), 3.87 (s, 3H, CH_3), 1.88 – 1.59 (m, 3H, 3xCH), 1.51 (s, 9H, $C(CH_3)_3$), 1.04 (d, J = 6.5 Hz, 3H, CH_3), 1.01 (d, J = 6.5 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.1, 168.6, 167.2, 137.8, 131.8, 130.1, 129.8, 129.6, 127.6, 82.0, 52.5, 51.8, 42.0, 28.0, 25.0, 22.8, 22.2; **MS (ESI^+)** 372 (100%, $M+Na^+$); **HRMS (ESI^+)** $C_{19}H_{27}NO_5$ requires $M+Na^+$ 372.1787, found 372.1787.

Methyl 2-(4-isobutyl-5-oxo-4,5-dihydrooxazol-2-yl)benzoate, 7aa

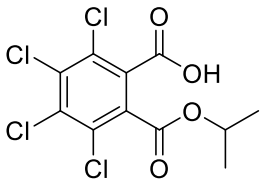


To a solution of methyl 2-((1-(*tert*-butoxy)-4-methyl-1-oxopentan-2-yl)carbamoyl)benzoate (**7a**) (3.4 g, 10 mmol) dissolved in dry DCM (20 mL) was

added TFA (20 mL) and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure. The residue and TFAA (4.5 mL, 13 mmol) were dissolved in dry DCM (30 mL) and the mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure and purified by flash column chromatography eluting with 20% Et_2O in petrol to give methyl 2-(4-isobutyl-5-oxo-4,5-dihydrooxazol-2-yl)benzoate (**7aa**) (1.6 g, 60%) as a yellow oil.

FTIR ν_{max} (thin film/cm^{-1}) 2957, 2872, 1824, 1731, 1657; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.88 – 7.73 (m, 2H, CH_{Ar}), 7.66 – 7.57 (m, 2H, CH_{Ar}), 4.42 (dd, J = 9.5, 5.5 Hz, 1H, CH), 3.91 (s, 3H, OCH_3), 2.13-2.02 (m, 1H, CH), 1.86 (ddd, J = 13.5, 8.0, 5.5 Hz, 1H, CH), 1.72 (ddd, J = 13.5, 9.5, 6.0 Hz, 1H, CH), 1.06 (d, J = 6.5 Hz, 3H, CH_3), 1.04 (d, J = 6.5 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 178.6, 167.3, 161.7, 131.9, 131.7, 131.5, 129.8, 129.5, 129.4, 64.0, 52.7, 40.5, 25.3, 22.8, 21.9; **MS (ESI^+)** 276 (100%, $M+H^+$); **HRMS (ESI^+)** $C_{15}H_{17}NO_4$ requires $M+H^+$ 276.1158, found 276.1321.

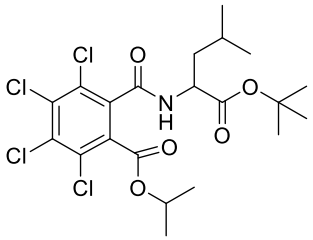
2,3,4,5-Tetrachloro-6-(isopropoxycarbonyl)benzoic acid



3,4,5,6-tetrachlorophthalic anhydride (2.86 g, 10.0 mmol) was dissolved in IPA (20 mL) and NEt_3 (1.4 mL, 10.0 mmol) and the mixture was stirred at room temperature overnight. The mixture was acidified to PH=2 with 2 M HCl(aq). The acidified crude mixture was extracted with Et_2O (3x20 mL), the organic phases were combined and dried with $MgSO_4$, then filtered and the solvent removed under reduced pressure to give 2,3,4,5-tetrachloro-6-(isopropoxycarbonyl)benzoic acid (3.40 g, 99%) as a white solid.

^{1}H NMR (400 MHz, CDCl3) δ 8.45 (s, 1H, COOH), 5.31 (hept, J = 6.5 Hz, 1H, CH), 1.39 (d, J = 6.5 Hz, 6H, $2CH_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 168.3, 163.2, 136.7, 135.9, 132.8, 130.60, 130.59, 130.53, 71.6, 21.4. Data is consistent with literature.

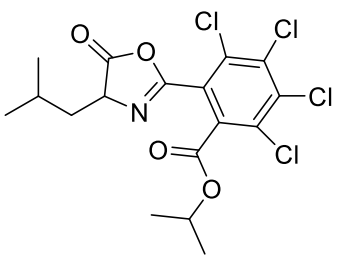
Isopropyl 2-((1-(tert-butoxy)-4-methyl-1-oxopentan-2-yl)carbamoyl)-3,4,5,6-tetrachlorobenzoate, 7a'



2,3,4,5-Tetrachloro-6-(isopropoxycarbonyl)benzoic acid (**7a'**) (3.40 g, 10.0 mmol), H-Leu-OtBu.HCl (2.30 g, 10.0 mmol), N, N'-Diisopropylcarbodiimide (1.40 g, 10 mmol) and NEt_3 (1.4 mL, 10 mmol) were dissolved in dry DCM. The mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 10% Et_2O in petrol to give isopropyl 2-((1-(tert-butoxy)-4-methyl-1-oxopentan-2-yl)carbamoyl)-3,4,5,6-tetrachlorobenzoate (**7a'**) (2.17 g, 42%) as a white solid.

FTIR ν_{max} (thin film/cm^{-1}) 3317, 2980, 2872, 1732, 1660; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 6.50 (d, J = 8.5 Hz, 1H, NH), 5.21 (hept, J = 6.5 Hz, 1H, CH), 4.70 – 4.60 (m, 1H, CH), 1.86 – 1.72 (m, 1H, CH), 1.72 – 1.55 (m, 2H, CH_2), 1.47 (s, 9H, $C(CH_3)_3$), 1.34 (d, J = 1.5 Hz, 3H, CH_3), 1.33 (d, J = 1.5 Hz, 3H, CH_3), 0.98 (d, J = 6.5 Hz, 6H, $2CH_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.0, 163.3, 162.4, 134.9, 134.8, 134.3, 132.9, 130.0, 129.8, 82.3, 71.2, 52.0, 42.1, 28.0, 24.8, 22.7, 22.2, 21.5, 21.4; **MS (ESI^+)** 538 (100%, $M+Na^+$); **HRMS (ESI^+)** $C_{21}H_{27}Cl_4NO_5$ requires $M+Na^+$ 536.0541 and 538.0512, found 536.0557 and 538.0536.

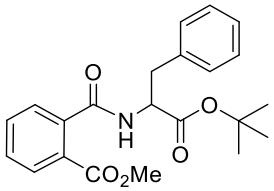
Isopropyl 2,3,4,5-tetrachloro-6-(4-isobutyl-5-oxo-4,5-dihydrooxazol-2-yl)benzoate, 7aa'



To a solution of isopropyl 2-((1-(tert-butoxy)-4-methyl-1-oxopentan-2-yl)carbamoyl)-3,4,5,6-tetrachlorobenzoate (**7a'**) (2.17 g, 4.2 mmol) was dissolved in dry DCM (10 mL) was added TFA (10 mL) and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure. The residue and TFAA (0.8 mL, 5.5 mmol) was dissolved in dry DCM (15 mL) and the mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure and purified by flash column chromatography eluting with 5% Et_2O in petrol to give isopropyl 2,3,4,5-tetrachloro-6-(4-isobutyl-5-oxo-4,5-dihydrooxazol-2-yl)benzoate (**7aa'**) (1.2 g, 64%) as a colorless oil.

FTIR ν_{max} (thin film/cm^{-1}) 2960, 2872, 1833, 1728, 1668 ; **^{1}H NMR (400 MHz, $CDCl_3$)** ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 – 5.16 (m, 1H, CH), 4.38 (dd, J = 9.5, 5.5 Hz, 1H, CH), 2.13 – 1.95 (m, 1H, CH), 1.91 – 1.78 (m, 1H, CH), 1.75 – 1.61 (m, 1H, CH), 1.39 (d, J = 2.6 Hz, 3H, CH_3), 1.37 (d, J = 2.6 Hz, 3H, CH_3), 1.04 (d, J = 6.0 Hz, 6H, $2CH_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 177.3, 163.1, 158.0, 137.1, 135.6, 134.8, 132.5, 130.5, 125.7, 71.4, 63.8, 40.1, 25.2, 22.7, 21.8, 21.59, 21.56; **MS (ESI^+)** 442 (100%, $M+H^+$); **HRMS (ESI^+)** $C_{17}H_{17}Cl_4NO_4$ requires $M+H^+$ 439.9990 and 441.9960, found 440.0011 and 441.9986.

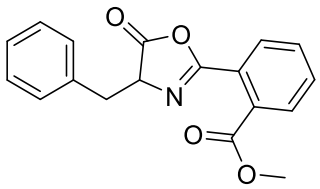
Methyl 2-((1-(*tert*-butoxy)-1-oxo-3-phenylpropan-2-yl)carbamoyl)benzoate, 7b



Monomethyl phthalate (1.80 g, 10.0 mmol), N,N'-Diisopropylcarbodiimide (1.40 g, 10 mmol), 4-Dimethylaminopyridine (122 mg, 1 mmol) were dissolved in dry DCM (100 ml). The mixture was stirred at room temperature for 30 minutes. Then H-Phe-OtBu.HCl (3.60 g, 10.0 mmol) and NEt_3 (1.4 mL, 10 mmol) were added in the mixture. The mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 20% EtOAc in petrol to give methyl 2-((1-(*tert*-butoxy)-1-oxo-3-phenylpropan-2-yl)carbamoyl)benzoate (**7b**) (3.60 g, 95%) as a yellow oil.

FTIR ν_{max} (thin film/cm^{-1}) 3317, 2978, 1724, 1651; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.92 – 7.80 (m, 1H, CH_{Ar}), 7.54 – 7.43 (m, 2H, CH_{Ar}), 7.45 – 7.34 (m, 1H, CH_{Ar}), 7.34 – 7.19 (m, 5H, CH_{Ar}), 6.47 (d, J = 7.5 Hz, 1H, NH), 4.98 (dt, J = 7.5, 6.0 Hz, 1H, CH), 3.84 (s, 3H, CH_3), 3.29 – 3.18 (m, 2H, CH_2), 1.42 (s, 9H, $C(CH_3)_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 170.5, 168.4, 167.1, 137.6, 136.3, 131.8, 130.1, 129.8, 129.7, 129.6, 128.4, 127.5, 126.9, 82.5, 54.0, 52.5, 38.0, 28.0; **MS (ESI^+)** 406 (100%, $M+Na^+$); **HRMS (ESI^+)** $C_{22}H_{25}NO_5$ requires $M+Na^+$ 406.1630, found 406.1624.

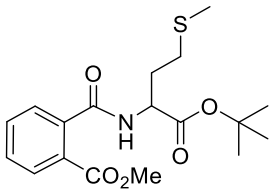
Methyl 2-(4-benzyl-5-oxo-4,5-dihydrooxazol-2-yl)benzoate, 7ab



To a solution of methyl 2-((1-(*tert*-butoxy)-1-oxo-3-phenylpropan-2-yl)carbamoyl)benzoate (**7b**) (3.6 g, 10 mmol) dissolved in dry DCM (20 mL) was added TFA (20 mL) and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure. The residue and TFAA (4.5 mL, 13 mmol) was dissolved in dry DCM (30 mL) and the mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure and purified by flash column chromatography eluting with 40% Et_2O in petrol to give methyl 2-(4-benzyl-5-oxo-4,5-dihydrooxazol-2-yl)benzoate (**7ab**) (1.4 g, 45%) as a yellow oil.

FTIR ν_{max} (thin film/cm^{-1}) 3031, 2952, 1817, 1726, 1655; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.84 – 7.74 (m, 1H, CH_{Ar}), 7.61 – 7.49 (m, 3H, CH_{Ar}), 7.36 – 7.21 (m, 5H, CH_{Ar}), 4.70 (dd, J = 7.0, 5.0 Hz, 1H, CH), 3.80 (s, 3H, CH_3), 3.40 (dd, J = 14.0, 5.0 Hz, 1H, CH), 3.21 (dd, J = 14.0, 7.0 Hz, 1H, CH); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 177.3, 167.1, 162.0, 135.5 (×2C), 131.7, 131.5, 129.9, 129.7, 129.5, 128.5, 127.2, 126.4, 66.5, 52.7, 37.0; **MS (ESI^+)** 310 (100%, $M+H^+$); **HRMS (ESI^+)** $C_{18}H_{15}NO_4$ requires $M+H^+$ 310.1079, found 310.1080.

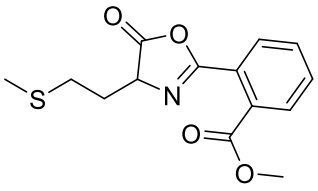
Methyl 2-((1-(*tert*-butoxy)-4-(methylthio)-1-oxobutan-2-yl)carbamoyl)benzoate, 7c



Monomethyl phthalate (1.80 g, 10.0 mmol), N,N'-Diisopropylcarbodiimide (1.40 g, 10 mmol), 4-Dimethylaminopyridine (122 mg, 1 mmol) were dissolved in dry DCM (100 ml). The mixture was stirred at room temperature for 30 minutes. Then H-Met-OtBu.HCl (2.40 g, 10.0 mmol) and NEt_3 (1.4 mL, 10 mmol) were added in the mixture. The mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 20% EtOAc in petrol to give methyl 2-((1-(*tert*-butoxy)-4-(methylthio)-1-oxobutan-2-yl)carbamoyl)benzoate (**7c**) (3.30 g, 90%) as a yellow oil.

FTIR ν_{max} (thin film/cm^{-1}) 3300, 2976, 1725, 1650; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.87 – 7.80 (m, 1H, CH_{Ar}), 7.55 – 7.40 (m, 3H, CH_{Ar}), 6.63 (d, J = 7.5 Hz, 1H, NH), 4.78-4.73 (m, 1H, CH), 3.83 (s, 3H, CH_3), 2.68 – 2.51 (m, 2H, CH_2), 2.31 – 2.18 (m, 1H, CH), 2.10 (s, 3H, CH_3), 2.14 – 1.96 (m, 1H, CH), 1.47 (s, 9H, $C(CH_3)_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 170.9, 168.7, 166.9, 137.7, 131.9, 130.1, 129.8, 129.3, 127.5, 82.5, 52.6, 52.5, 32.1, 29.8, 28.0, 15.4; **MS (ESI$^+$)** 368 (100%, $M+H^+$); **HRMS (ESI$^+$)** $C_{18}H_{25}NO_5S$ requires $M+H^+$ 368.1532, found 368.1534.

Methyl 2-(4-(2-(methylthio)ethyl)-5-oxo-4,5-dihydrooxazol-2-yl)benzoate, 7ac

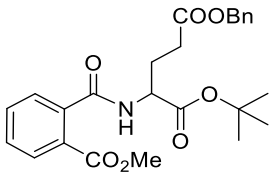


To a solution of 2-((1-(*tert*-butoxy)-4-(methylthio)-1-oxobutan-2-yl)carbamoyl)-benzoate (**7c**) (3.4 g, 9 mmol) dissolved in dry DCM (20 mL) was added TFA (20 mL) and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure. The residue and TFAA (4.5 mL, 13 mmol) were

dissolved in dry DCM (30 mL) and the mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure and purified by flash column chromatography eluting with 40% Et_2O in petrol to give methyl 2-(4-(2-(methylthio)ethyl)-5-oxo-4,5-dihydrooxazol-2-yl)benzoate (**7ac**) (1.1 g, 40%) as a yellow oil.

FTIR ν_{max} (thin film/cm^{-1}) 3264, 2924, 1719, 1649; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.89 – 7.81 (m, 1H, CH_{Ar}), 7.83 – 7.76 (m, 1H, CH_{Ar}), 7.69 – 7.57 (m, 2H, CH_{Ar}), 4.64 (dd, J = 7.5, 6.0 Hz, 1H, CH), 3.92 (s, 3H, CH_3), 2.77 (t, J = 7.0 Hz, 2H, CH_2), 2.42 – 2.26 (m, 1H, CH), 2.24 – 2.13 (m, 4H, 4xCH); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 178.0, 162.5, 132.8, 131.8, 131.6, 129.8, 129.6, 126.4, 63.8, 52.8, 52.7, 30.3, 30.1, 15.2; **MS (ESI^+)** 294 (100%, $M+H^+$); **HRMS (ESI^+)** $C_{14}H_{15}NO_4S$ requires $M+H^+$ 294.0800, found 294.0806.

5-benzyl 1-(tert-butyl) (2-(methoxycarbonyl)benzoyl)glutamate, 7d

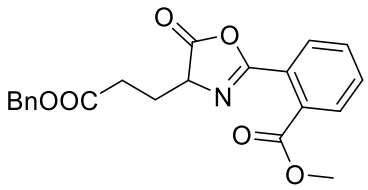


Monomethyl phthalate (1.80 g, 10.0 mmol), N,N'-Diisopropylcarbodiimide (1.40 g, 10 mmol), 4-Dimethylaminopyridine (122 mg, 1 mmol) were dissolved in dry DCM (100 ml). The mixture was stirred at room temperature for 30 minutes. Then H-Glu(OBn)-OtBu.HCl (4 g, 12.0 mmol) and NEt_3 (1.4 mL, 10 mmol) were added in the mixture. The mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 20% EtOAc in petrol to give methyl 5-benzyl 1-(tert-butyl) (2-(methoxycarbonyl)benzoyl)glutamate (**7d**) (4.0 g, 85%) as a colorless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3345, 2977, 1725, 1651; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.94 – 7.84 (m, 1H, CH_{Ar}), 7.60 – 7.45 (m, 3H, CH_{Ar}), 7.41 – 7.31 (m, 5H, CH_{Ar}), 6.54 (d, J = 8.0 Hz, 1H, NH), 5.18 – 5.06 (s, 2H, CH_2), 4.81 – 4.67 (m, 1H, CH), 3.86 – 3.77 (s, 3H, CH_3), 2.70 – 2.48 (m, 2H, CH_2), 2.46 – 2.29 (m, 1H, CH), 2.18 – 2.01 (m, 1H, CH), 1.57 – 1.46 (s, 9H, $C(CH_3)_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.8, 170.9, 168.9, 167.0, 137.6,

135.8, 131.9, 130.1, 129.9, 129.4, 128.6, 128.3, 128.2, 127.5, 82.7, 66.5, 52.5, 52.5, 30.3, 28.0, 27.8; **MS (ESI$^+$)** 456 (100%, M+H$^+$); **HRMS (ESI$^+$)** $C_{25}H_{30}NO_7$ requires M+H$^+$ 456.2022, found 456.2020.

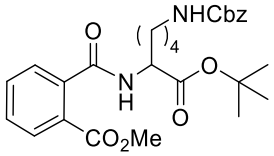
Methyl 2-(4-(3-(benzyloxy)-3-oxopropyl)-5-oxo-4,5-dihydrooxazol-2-yl)benzoate, 7ad



To a solution of 5-benzyl 1-(tert-butyl) (2-(methoxycarbonyl)benzoyl)glutamate (**7d**) (3.6 g, 8 mmol) dissolved in dry DCM (20 mL) was added TFA (20 mL) and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure. The residue and TFAA (4.5 mL, 13 mmol) were dissolved in dry DCM (30 mL) and the mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure and purified by flash column chromatography eluting with 30% EtOAc in petrol to give methyl 2-(4-(3-(benzyloxy)-3-oxopropyl)-5-oxo-4,5-dihydrooxazol-2-yl)benzoate (**7ad**) (1.8 g, 60%) as a yellow oil.

FTIR ν_{max} (thin film/cm^{-1}) 3036, 2952, 1821, 1726, 1657; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.91 – 7.81 (m, 1H, CH_{Ar}), 7.81 – 7.74 (m, 1H, CH_{Ar}), 7.69 – 7.57 (m, 2H, CH_{Ar}), 7.46 – 7.29 (m, 5H, CH_{Ar}), 5.24 – 5.10 (s, 2H, CH_2), 4.57 (d, J = 6.0 Hz, 0.5H, CH), 4.53 – 4.45 (m, 1H, CH), 3.97 – 3.81 (s, 3H, CH_3), 2.79 – 2.59 (m, 2H, CH_2), 2.50 – 2.35 (m, 1H, CH_2), 2.30 – 2.06 (m, 1H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 177.5, 172.1, 167.1, 162.4, 135.7, 131.9, 131.8, 131.6, 129.8, 129.6, 128.6, 128.3, 128.3, 126.3, 66.6, 64.3, 52.7, 29.9, 26.4.; **MS (ESI$^+$)** 382 (100%, M+H$^+$); **HRMS (ESI$^+$)** $C_{21}H_{19}NO_6$ requires M+H$^+$ 382.1291, found 382.1298.

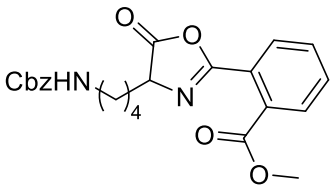
Methyl 2-((6-(((benzyloxy)carbonyl)amino)-1-(tert-butoxy)-1-oxohexan-2-yl)-carbamoyl)benzoate, 7e



Monomethyl phthalate (1.80 g, 10.0 mmol), N,N'-Diisopropylcarbodiimide (1.40 g, 10 mmol), 4-Dimethylaminopyridine (122 mg, 1 mmol) were dissolved in dry DCM (100 ml). The mixture was stirred at room temperature for 30 minutes. Then H-Lys(Z)-OtBu.HCl (3.8 g, 10.0 mmol) and NEt_3 (1.4 mL, 10 mmol) were added in the mixture. The mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 40% EtOAc in petrol to give methyl 2-((6-(((benzyloxy)carbonyl)amino)-1-(tert-butoxy)-1-oxohexan-2-yl)-carbamoyl)-benzoate (**7e**) (4.6 g, 92%) as a colorless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3318, 2949, 1722, 1650; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.88 - 7.86 (m, 1H, CH_{Ar}), 7.57 – 7.42 (m, 3H, CH_{Ar}), 7.39 – 7.28 (m, 5H, CH_{Ar}), 6.53 (d, J = 8.0 Hz, 1H, NH), 5.28 – 5.23 (br, 1H, NH), 5.05 (d, J = 12.0 Hz, 1H, CH), 4.99 (d, J = 12.0 Hz, 1H, CH), 4.75 – 4.66 (m, 1H, CH), 3.83 – 3.78 (s, 3H, CH_3), 3.32 – 3.14 (m, 2H, CH_2), 2.09 – 1.96 (m, 1H, CH), 1.83 – 1.73 (m, 1H, CH), 1.68 – 1.52 (m, 3H, 3xCH), 1.50 – 1.39 (m, 10H, CH, $C(CH_3)_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.5, 168.8, 167.0, 156.6, 138.1, 136.7, 132.0, 130.1, 129.7, 129.2, 128.5, 128.1, 128.0, 127.7, 82.3, 66.5, 52.9, 52.5, 40.5, 32.0, 29.3, 28.0, 22.0; **MS (ESI^+)** 499 (100%, $M+H^+$); **HRMS (ESI^+)** $C_{27}H_{34}N_2O_7$ requires $M+H^+$ 499.2444, found 499.2449.

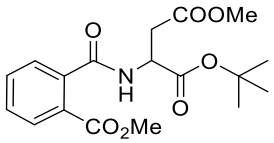
Methyl 2-(4-(4-(((benzyloxy)carbonyl)amino)butyl)-5-oxo-4,5-dihydrooxazol-2-yl)benzoate, 7ae



To a solution of methyl 2-((6-(((benzyloxy)carbonyl)amino)-1-(tert-butoxy)-1-oxohexan-2-yl)-carbamoyl)-benzoate (**7e**) (4.5 g, 9 mmol) dissolved in dry DCM (25 mL) was added TFA (25 mL) and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure. The residue and TFAA (4.5 mL, 13 mmol) were dissolved in dry DCM (30 mL) and the mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure and purified by flash column chromatography eluting with 30% EtOAc in petrol to give methyl 2-(4-(4-(((benzyloxy)carbonyl)amino)butyl)-5-oxo-4,5-dihydrooxazol-2-yl)benzoate (**7ae**) (2.2 g, 56%) as a yellow oil.

FTIR ν_{max} (thin film/cm^{-1}) 3331, 2952, 1709, 1661; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.88 – 7.81 (m, 1H, CH_{Ar}), 7.81 – 7.72 (m, 1H, CH_{Ar}), 7.66 – 7.57 (m, 2H, CH_{Ar}), 7.43 – 7.27 (m, 5H, CH_{Ar}), 5.09 – 4.96 (m, 3H, CH_2, NH), 4.44 – 4.36 (m, 1H, CH), 3.87 (s, 3H, CH_3), 3.26 – 3.20 (m, 2H, CH_2), 2.10 – 2.02 (m, 1H, CH), 1.97 – 1.81 (m, 1H, CH), 1.67 – 1.45 (m, 4H, 4xCH); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 178.0, 167.1, 162.2, 156.5, 136.6, 136.5, 131.8, 131.6, 129.9, 129.6, 128.5, 128.1, 128.1, 126.5, 66.6, 65.3, 52.8, 40.7, 30.9, 29.5, 22.7; **MS (ESI$^+$)** 425 (100%, $M+H^+$); **HRMS (ESI$^+$)** $C23H24N_2O_6$ requires $M+H^+$ 425.1713, found 425.1714.

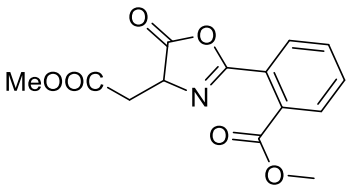
1-(tert-butyl) 4-methyl (2-(methoxycarbonyl)benzoyl)aspartate, 7f



Monomethyl phthalate (1.80 g, 10.0 mmol), N,N'-Diisopropylcarbodiimide (1.40 g, 10 mmol), 4-Dimethylaminopyridine (122 mg, 1 mmol) were dissolved in dry DCM (100 ml). The mixture was stirred at room temperature for 30 minutes. Then (S)-1-tert-Butyl 4-methyl 2-aminosuccinate hydrochloride (2.4 g, 10.0 mmol) and NEt_3 (1.4 mL, 10 mmol) were added in the mixture. The mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 40% EtOAc in petrol to give 1-(tert-butyl) 4-methyl (2-(methoxycarbonyl)benzoyl)-aspartate (**7f**) (3.1 g, 85%) as a colorless oil.

FTIR ν_{max} (thin film/cm^{-1})3346, 2981, 1725, 1655; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.82 – 7.78 (m, 1H, CH_{Ar}), 7.49 – 7.39 (m, 3H, CH_{Ar}), 6.82 (d, J = 8.0 Hz, 1H, NH), 4.87- 4.82 (m, 1H, CH), 3.78 (s, 3H, CH_3), 3.63(s, 3H, CH_3), 3.05 - 2.95 (m, 2H, CH_2), 1.41 (s, 9H, $C(CH_3)_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.4, 169.4, 168.7, 166.7, 137.7, 132.0, 130.0, 129.7, 129.1, 127.5, 82.6, 52.3, 51.7, 49.5, 36.0, 27.8; **MS (ESI^+)** 366 (100%, $M+H^+$); **HRMS (ESI^+)** $C_{18}H_{23}NO_7$ requires $M+H^+$ 366.1552, found 366.1552.

Methyl 2-(4-(2-methoxy-2-oxoethyl)-5-oxo-4,5-dihydrooxazol-2-yl)benzoate, 7af

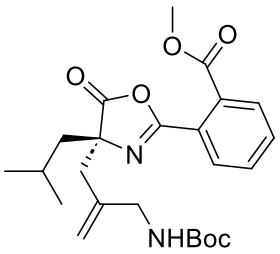


To a solution of 1-(tert-butyl) 4-methyl (2-(methoxycarbonyl)benzoyl)aspartate (**7f**) (2.9 g, 8 mmol) dissolved in dry DCM (20 mL) was added TFA (20 mL) and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure. The residue and TFAA (4.5 mL, 13 mmol) were dissolved in dry DCM (30 mL) and the mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure and purified by flash column chromatography eluting with 20% EtOAc in petrol to give methyl methyl 2-(4-(2-methoxy-2-oxoethyl)-5-oxo-4,5-dihydrooxazol-2-yl)benzoate (**7af**) (1.5 g, 65%) as a yellow oil.

FTIR ν_{max} (thin film/cm^{-1}) 3004, 2954, 1822, 1727, 1653; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.87 – 7.73 (m, 2H, CH_{Ar}), 7.63 – 7.54 (m, 2H, CH_{Ar}), 4.64 (d, J = 5.0 Hz, 0.5H, CH), 4.63 (d, J = 5.0 Hz, 0.5H, CH), 3.87 (s, 3H, CH_3), 3.70 (s, 3H, CH_3), 3.12 (dd, J = 17.0, 5.0 Hz, 1H, CH), 3.02 (dd, *J* = 17.0, 5.0 Hz, 1H, CH); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 177.1, 169.7, 167.3, 163.2, 131.9, 131.8, 131.5, 129.9, 129.5, 126.3, 61.8, 52.7, 52.3, 34.8; **MS (ESI^+)** 292 (100%, $M+H^+$); **HRMS (ESI^+)** $C_{14}H_{13}NO_6$ requires $M+H^+$ 292.0821, found 292.0815.

12.5 The synthesis of new Freidinger lactams

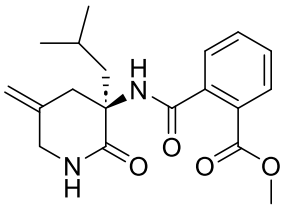
Methyl-(*R*)-2-(4-(2-(((tert-butoxycarbonyl)amino)methyl)allyl)-4-isobutyl-5-oxo-4,5-dihydrooxazol-2-yl)benzoate



Carbamate **C4** (21.32 mg, 0.1 mmol), (R, R)-ANDEN-Phenyl Trost Ligand (6 mg, 0.075), $\{\eta^3\text{-}C_3H_5PdCl\}_2$ (1 mg, 0.025 mmol), ^{t}BuOH (0.045 ml, 0.5 mmol) and DIPEA (0.025 ml, 0.2 mmol) were dissolved in dry 20% toluene in dioxane (1 mL) at 0 °C for 20 mins. Then methyl 2-(4-isobutyl-5-oxo-4,5-dihydrooxazol-2-yl)benzoate (**7aa**) (82.59 mg, 0.3 mmol) was added. The mixture was stirred at 0 °C overnight. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 20% EtOAc in petrol to give methyl-(*R*)-2-(4-(2-(((tert-butoxycarbonyl)-amino)-methyl)allyl)-4-isobutyl-5-oxo-4,5-dihydrooxazol-2-yl)benzoate (40 mg, 90%) as a colorless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3397, 2958, 1815, 1714, 1649; **^{1}H NMR (400 MHz, $CDCl_3$)** δ7.89 – 7.81 (m, 1H, CH_{Ar}), 7.82 – 7.76 (m, 1H, CH_{Ar}), 7.69 – 7.54 (m, 2H, CH_{Ar}), 5.12 (s, 2H, C=CH & HN), 5.02 (s, 1H, C=CH), 3.92 (s, 3H, CH_3), 3.71 (d, J = 6.0 Hz, 2H, CH_2), 2.62 (d, J = 2.5 Hz, 2H, CH_2), 1.98 (dd, J = 14.0 & 5.5 Hz, 1H, CH), 1.81 (dd, J = 14.0 & 7.0 Hz, 1H, CH), 1.75-1.64 (m, 1H, CH), 0.95 (d, J = 6.5 Hz, 3H, CH_3), 0.91 (d, *J* = 6.5 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 180.2, 167.5, 160.2, 155.9, 140.45, 131.8, 131.5, 130.1, 129.4, 126.0, 115.7, 79.1, 73.7, 52.8, 45.9, 45.7, 42.0, 28.4, 24.8, 24.2, 23.2; **MS (ESI$^+$)** 445 (100%, M+H$^+$); **HRMS (ESI$^+$)** $C_{24}H_{32}N_2O_6$ requires M+H$^+$ 445.2260, found 445.2357; **HRMS (ESI$^+$)** $C_{24}H_{32}N_2O_6$ requires M+Na$^+$ 467.2158, found 417.2182; **HPLC** (Cellulose-1, hexane:^{i}PrOH 97.5:2.5, flow rate 0.25 mL/min, λ = 254 nm, 22 °C) t_R(major) = 54.413, t_R(minor) = 50.350, er = 7.5:92.5.

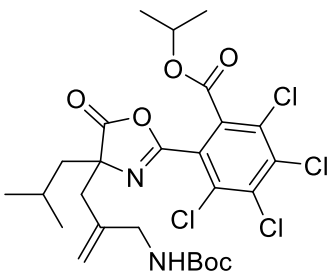
Methyl-(*R*)-2-((3-isobutyl-5-methylene-2-oxopiperidin-3-yl)carbamoyl)benzoate, 7ba



To a solution of methyl 2-(4-(2-(((tert-butoxycarbonyl)-amino)-methyl)allyl)-4-isobutyl-5-oxo-4,5-dihydrooxazol-2-yl)benzoate (89 mg, 0.2 mmol) was dissolved in dry DCM (2 mL) was added TFA (1.2 mL, 15 mmol) and the mixture stirred at room temperature. After 1 hour, EtOAc was added and the mixture was quenched with sat. aq. NaHCO3. The layers were separated and the aqueous layer was further extracted with EtOAc. The solvent was then removed under reduced pressure to give methyl-(*R*)-2-((3-isobutyl-5-methylene-2-oxopiperidin-3-yl)carbamoyl)benzoate (**7ba**) (68 mg, 99%) as a white solid.

FTIR ν_{max} (thin film/cm^{-1}) 3262, 2953, 1727, 1650; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.85 (dd, J = 7.5 & 1.5 Hz, 1H, CH_{Ar}), 7.61 – 7.38 (m, 3H, CH_{Ar}), 7.16 (s, 1H, NH), 6.51 (s, 1H, NH), 5.13 (s, 1H, C=CH), 5.05 (s, 1H, C=CH), 4.12 (d, J = 15.0 Hz, 1H, CH), 4.00 (d, J = 15.0 Hz, 1H, CH), 3.88 (s, 3H, CH_3), 3.66 (d, J = 14.5 Hz, 1H, CH), 2.89 (d, J = 14.5 Hz, 1H, CH), 2.34 (dd, J = 14.5 and 5.5 Hz, 1H, CH), 1.93-1.82 (m, 1H, CH), 1.62 (dd, J = 14.5 and 5.5 Hz, 1H, CH), 1.01 (d, J = 6.5 Hz, 3H, CH_3), 0.90 (d, J = 6.5 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 173.7, 168.0, 167.2, 138.6, 136.8, 131.8, 130.0, 129.6, 129.4, 127.4, 113.3, 59.2, 52.4, 46.6, 42.7, 39.3, 24.4, 24.2, 23.6; **MS (ESI^+)** 345 (100%, $M+H^+$); **HRMS (ESI^+)** $C_{19}H_{24}N_2O_4$ requires $M+H^+$ 345.1814, found 345.1831.

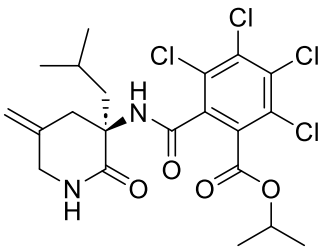
Isopropyl-(*R*)-2-(4-(2-(((tert-butoxycarbonyl)amino)methyl)allyl)-4-isobutyl-5-oxo-4,5-dihydrooxazol-2-yl)-3,4,5,6-tetrachlorobenzoate



Carbamate **C4** (21.32 mg, 0.1 mmol), (R, R)-ANDEN-Phenyl Trost Ligand (6 mg, 0.075), $\{\eta^3\text{-}C_3H_5PdCl\}_2$ (1 mg, 0.025 mmol), ^{t}BuOH (0.045 ml, 0.5 mmol) and DIPEA (0.025 ml, 2 eq, 0.2 mmol) were dissolved in dry 20% toluene in dioxane (1 mL) at 0 °C for 20 mins. Then isopropyl 2,3,4,5-tetrachloro-6-(4-isobutyl-5-oxo-4,5-dihydrooxazol-2-yl)benzoate (**7aa'**) (132.3 mg, 0.3 mmol) was added. The mixture was stirred at 0 °C overnight. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 15% Et_2O in petrol to give isopropyl-(*R*)-2-(4-(2-(((tert-butoxycarbonyl)amino)methyl)allyl)-4-isobutyl-5-oxo-4,5-dihydrooxazol-2-yl)-3,4,5,6-tetrachlorobenzoate (58 mg, 95%) as a colorless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3423, 2979, 1830, 1720, 1665; **^{1}H NMR (400 MHz, $CDCl_3$)** 5.26 (hept, J = 6.5 Hz, 1H, OCH), 5.16 (s, 2H, NH and C=CH), 5.04 (s, 1H, C=CH), 3.74 (dd, J = 17.5 & 6.0 Hz, 1H, CH), 3.63 (dd, J = 17.5 & 6.0 Hz, 1H, CH), 2.60 (s, 2H, CH_2), 2.05 – 1.99 (m, 1H, CH), 1.84 – 1.68 (m, 2H, 2xCH), 1.45 (s, 9H, $C(CH_3)_3$), 1.45 (d, J = 6.5 Hz, 3H, CH_3), 1.37 (d, J = 6.5 Hz, 3H, CH_3), 0.97 (d, J = 6.5 Hz, 3H, CH_3), 0.86 (d, J = 6.5 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 179.0, 163.3, 155.9, 155.7, 140.0, 137.1, 135.9, 134.8, 132.6, 130.3, 124.7, 116.2, 79.1, 74.0, 71.8, 45.6, 45.5, 41.7, 28.4, 24.6, 24.4, 22.9, 21.54, 21.51; **MS (ESI$^+$)** 633 (100%, M+Na$^+$); **HRMS (ESI$^+$)** $C_{26}H_{32}Cl_4N_2O_6$ requires M+Na$^+$ 633.0833 and 631.0912, found 633.0929 and 631. 1008; **HPLC** (Cellulose-1, hexane:^{i}PrOH 99:1, flow rate 1 mL/min, λ = 254 nm, 22 °C) t_R(major) = 10.577, t_R(minor) = 9.187, er = 7.3:92.7.

Isopropyl-(*R*)-2,3,4,5-tetrachloro-6-((3-isobutyl-5-methylene-2-oxopiperidin-3-yl)carbamoyl)benzoate, 7ba'

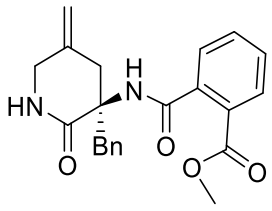


To a solution of isopropyl 2-(4-(2-(((tert-butoxycarbonyl)amino)methyl)allyl)-4-isobutyl-5-oxo-4,5-dihydrooxazol-2-yl)-3,4,5,6-tetrachlorobenzoate (77 mg, 1.0 eq, 0.2 mmol) was dissolved in dry DCM (2 mL) was added TFA (1.2 mL, 75eq, 15 mmol)

and the mixture stirred at room temperature. After 1 hour, EtOAc was added and the mixture was quenched with sat. aq. NaHCO3. The layers were separated and the aqueous layer was further extracted with EtOAc. The solvent was then removed under reduced pressure to give GP-9f (56 mg, 99%) as a white solid. Recrystallisation by cooling hot saturated solution of isopropyl-(*R*)-2,3,4,5-tetrachloro-6-((3-isobutyl-5-methylene-2-oxopiperidin-3-yl)carbamoyl)benzoate (**7ba'**) in toluene afforded the product as a white solid (43 mg, 80%).

FTIR ν_{max} (thin film/cm^{-1}) 3342, 2957, 1730, 1663; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.36 (s, 1H, NH), 6.79 (s, 1H, NH), 5.24 (hept, J = 6.5 Hz, 1H, OCH), 5.13 (s, 1H, C=CH), 5.06 (s, 1H, C=CH), 4.10 (d, J = 16.0 Hz, 1H, CH), 4.02 (d, J = 16.0 Hz, 1H, CH) 3.62 (d, J = 14.5 Hz, 1H, CH), 2.69 (d, J = 14.5 Hz, 1H, CH), 2.34 (dd, J = 14.5 & 3.5 Hz, 1H, CH), 2.01 – 1.82 (m, 1H, CCH), 1.58 (dd, J = 14.5 & 8.0 Hz, 1H, CH), 1.43 (d, J = 6.5Hz, 3H, CH_3), 1.35 (d, J = 6.5 Hz, 3H, CH_3), 0.96 (d, J = 6.5 Hz, 3H, CH_3), 0.85 (d, J = 6.5 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 173.2, 163.7, 161.8, 136.3, 135.0, 134.7, 134.7, 133.0, 129.9, 113.6, 71.21, 59.6, 46.2, 42.8, 39.2, 24.8, 23.7, 223.0, 21.6; **MS (ESI$^+$)** 511 (100%, M+H$^+$); **HRMS (ESI$^+$)** $C_{21}H_{24}Cl_4N_2O_4$ requires M+H$^+$ 511.0539 and 509.0568, found 511.0570, 509.0577.

Methyl-(*R*)-2-((3-benzyl-5-methylene-2-oxopiperidin-3-yl)carbamoyl)benzoate, 7bb

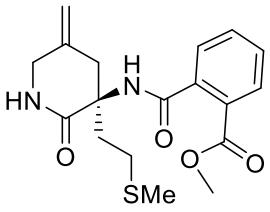


N-Boc-5-Methylenecyclohexacarbamate (**C4**) (42 mg, 0.2 mmol), (*R*,*R*)-ANDEN-phenyl Trost ligand (12 mg, 0.015 mmol), {η^3-C_3H_5PdCl}$_2$ (2 mg, 0.005 mmol), ^{t}BuOH (0.09 ml, 1.0 mmol) and DIPEA (0.03 ml, 0.4 mmol) were dissolved in dry 20% toluene in dioxane (2 mL) at 0 °C for 20 mins. Then methyl 2-(4-benzyl-5-oxo-4,5-dihydrooxazol-2-yl)benzoate (**7ab**) (186 mg, 0.6 mmol) was added. The mixture was stirred at 0 °C overnight. The solvent was removed under reduced pressure give the crude product which was dissolved in dry DCM (2 mL). TFA (1.2 mL, 15 mmol) was added and the

mixture stirred at room temperature. After 1 hour, EtOAc was added and the mixture was quenched with sat. aq. $NaHCO_3$. The layers were separated, and the aqueous layer was further extracted with 60% EtOAc. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with EtOAc to give methyl-(*R*)-2-((3-benzyl-5-methylene-2-oxopiperidin-3-yl)carbamoyl)benzoate (**7bb**) (72 mg, 95%) as a colorless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3264, 2951, 1726, 1650; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.93 – 7.74 (m, 1H, CH_{Ar}), 7.55 – 7.38 (m, 2H, CH_{Ar}), 7.37 – 7.12 (m, 6H, CH_{Ar}), 6.95 (s, 1H, NH), 6.92 (s, 1H, NH), 5.20 (s, 1H, C=CH), 5.11 (s, 1H, C=CH), 4.12 (d, J = 14.0 Hz, 1H, CH), 4.01 (d, J = 14.0 Hz, 1H, CH), 3.85 (s, 3H, CH_3), 3.72 (d, J = 14.0 Hz, 1H, CH), 3.61 (d, J = 13.0 Hz, 1H, CH), 3.07 (d, J = 13.0 Hz, 1H, CH), 2.99 (d, J = 14.0 Hz, 1H, CH); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 168.8, 168.3, 167.3, 138.1, 136.5, 135.9, 131.8, 130.4, 129.9, 129.7, 129.6, 128.2, 127.3, 127.0, 113.8, 59.8, 52.4, 46.8, 40.4, 38.4; **MS (ESI^+)** 379 (100%, $M+H^+$); **HRMS (ESI^+)** $C_{22}H_{22}N_2O_4$ requires $M+H^+$ 379.1658, found 379.1656.

Methyl-(*S*)-2-((5-methylene-3-(2-(methylthio)ethyl)-2-oxopiperidin-3yl)carbamoyl)-benzoate, 7bc

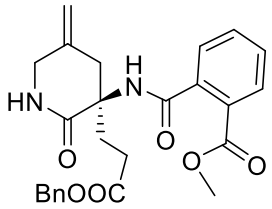


N-Boc-5-Methylenecyclohexacarbamate (**C4**) (42 mg, 0.2 mmol), (*R*,*R*)-ANDEN-phenyl Trost ligand (12 mg, 0.015 mmol), $\{\eta^3\text{-}C_3H_5PdCl\}_2$ (2 mg, 0.005 mmol), ^{t}BuOH (0.09 ml, 1.0 mmol) and DIPEA (0.03 ml, 0.4 mmol) were dissolved in dry 20% toluene in dioxane (2 mL) at 0 °C for 20 mins. Then methyl 2-(4-(2-(methylthio)ethyl)-5-oxo-4,5-dihydrooxazol-2-yl)benzoate (**7ac**) (176 mg, 0.6 mmol) was added. The mixture was stirred at 0 °C overnight. The solvent was removed under reduced pressure give the crude product which was dissolved in dry DCM (2 mL). TFA (1.2 mL, 15 mmol) was added and the mixture stirred at room temperature. After 1 hour, EtOAc was added and the mixture was quenched with sat. aq. $NaHCO_3$. The layers were separated, and

the aqueous layer was further extracted with EtOAc. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with EtOAc to give methyl-(*S*)-2-((5-methylene-3-(2-(methylthio)ethyl)-2-oxopiperidin-3-yl)carbamoyl)-benzoate (**7bc**) (67 mg, 93%) as a colorless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3279, 2950, 1726, 1652; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.93 – 7.77 (m, 1H, CH_{Ar}), 7.59 – 7.36 (m, 3H, CH_{Ar}), 7.23 (s, 1H, NH), 6.68 (s, 1H, NH), 5.15 (s, 1H, C=CH), 5.08 (s, 1H, C=CH), 4.11 (d, J = 15.0 Hz, 1H, CH), 3.93 (d, J = 15.0 Hz, 1H, CH), 3.89 (s, 3H, CH_3), 3.58 (d, J = 14.0 Hz, 1H, CH), 2.97 (d, J = 14.0 Hz, 1H, CH), 2.73 (td, J = 12.0, 5.0 Hz, 1H, CH), 2.67 – 2.55 (m, 1H, CH), 2.48 (td, J = 12.0, 5.0 Hz, 1H, CH), 2.11 (s, 3H, CH_3), 2.04 – 1.90 (m, 1H, CH); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.7, 168.6, 167.1, 138.3, 136.0, 131.9, 130.0, 129.7, 129.2, 127.6, 114.1, 59.2, 52.5, 47.0, 38.8, 34.7, 28.3, 15.5; **MS (ESI^+)** 363 (100%, $M+H^+$); **HRMS (ESI^+)** $C_{18}H_{22}N_2O_4S$ requires $M+H^+$ 363.1379, found 363.1382.

Methyl-(*R*)-2-((3-(3-(benzyloxy)-3-oxopropyl)-5-methylene-2-oxopiperidin-3-yl)carbamoyl)- benzoate, 7bd

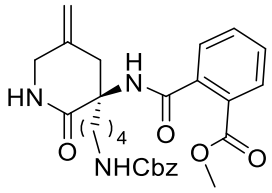


N-Boc-5-Methylenecyclohexacarbamate (**C4**) (42 mg, 0.2 mmol), (*R*,*R*)-ANDEN-phenyl Trost ligand (12 mg, 0.015 mmol), $\{\eta^3\text{-}C_3H_5PdCl\}_2$ (2 mg, 0.005 mmol), ^{t}BuOH (0.09 ml, 1.0 mmol) and DIPEA (0.03 ml, 0.4 mmol) were dissolved in dry 20% toluene in dioxane (2 mL) at 0 °C for 20 mins. Then methyl 2-(4-(3-(benzyloxy)-3-oxopropyl)-5-oxo-4,5-dihydrooxazol-2-yl)benzoate (**7ad**) (229 mg, 0.6 mmol) was added. The mixture was stirred at 0 °C overnight. The solvent was removed under reduced pressure give the crude product which was dissolved in dry DCM (2 mL). TFA (1.2 mL, 15 mmol) was added and the mixture stirred at room temperature. After 1 hour, EtOAc was added and the mixture was quenched with sat. aq. $NaHCO_3$. The layers were separated, and the aqueous layer was further extracted with EtOAc. The

solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with EtOAc to give methyl-(*R*)-2-((3-(3-(benzyloxy)-3-oxopropyl)-5-methylene-2-oxopiperidin-3-yl)carbamoyl)- benzoate (**7bd**) (86 mg, 95%) as a colorless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3315, 2952, 1727, 1651; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.88 – 7.86 (m, 1H, CH_{Ar}), 7.64 – 7.43 (m, 3H, CH_{Ar}), 7.39 – 7.32 (m, 5H, CH_{Ar}), 7.23 (s, 1H, NH), 6.29 (s, 1H, NH), 5.19 – 5.07 (m, 4H, 4xCH), 4.12 (d, J = 15.0 Hz, 1H, CH), 3.96 (d, J = 15.0 Hz, 1H, CH), 3.84 (s, 3H, CH_3), 3.61 (d, J = 14.0 Hz, 1H, CH), 3.01 (d, J = 14.0 Hz, 1H, CH), 2.75 – 2.58 (m, 2H, CH_2), 2.57 – 2.47 (m, 1H, CH), 2.24 – 2.12 (m, 1H, CH); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 173.3, 172.4, 168.6, 167.1, 138.3, 136.1, 135.9, 131.9, 130.1, 129.7, 129.3, 128.5, 128.3(x2C), 127.5, 114.1, 66.4, 58.5, 52.4, 46.9, 39.1, 29.6, 28.9; **MS (ESI$^+$)** 451 (100%, M+H$^+$); **HRMS (ESI$^+$)** $C_{25}H_{26}N_2O_6$ requires M+H$^+$ 451.1869, found 451.1973.

Methyl (*R*)-2-((3-(4-(((benzyloxy)carbonyl)amino)butyl)-5-methylene-2-oxopiperidin-3-yl)carbamoyl)benzoate, 7be

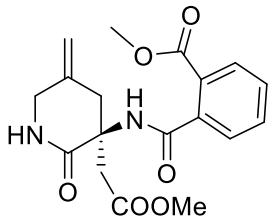


N-Boc-5-Methylenecyclohexacarbamate (**C4**) (42 mg, 0.2 mmol), (*R*,*R*)-ANDEN-phenyl Trost ligand (12 mg, 0.015 mmol), {η^3-C_3H_5PdCl}$_2$ (2 mg, 0.005 mmol), ^{t}BuOH (0.09 ml, 1.0 mmol) and DIPEA (0.03 ml, 0.4 mmol) were dissolved in dry 20% toluene in dioxane (2 mL) at 0 °C for 20 mins. Then methyl 2-(4-(4-(((benzyloxy)carbonyl)amino)butyl)-5-oxo-4,5-dihydrooxazol-2-yl)benzoate (**7ae**) (255 mg, 0.6 mmol) was added. The mixture was stirred at 0 °C overnight. The solvent was removed under reduced pressure give the crude product which was dissolved in dry DCM (2 mL). TFA (1.2 mL, 15 mmol) was added and the mixture stirred at room temperature. After 1 hour, EtOAc was added and the mixture was quenched with sat. aq. $NaHCO_3$. The layers were separated, and the aqueous layer was further extracted

with EtOAc. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with EtOAc to give methyl (*R*)-2-((3-(4-(((benzyloxy)-carbonyl)amino)butyl)-5-methylene-2-oxopiperidin-3-yl)carbamoyl)benzoate (**7be**) (92 mg, 93%) as a colorless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3322, 2953, 1710, 1652; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.86 – 7.84 (m, 1H, CH_{Ar}), 7.59 – 7.40 (m, 3H, CH_{Ar}), 7.40 – 7.26 (m, 5H, CH_{Ar}), 7.19 (s, 1H, NH), 6.19 (s, 1H, NH), 5.30 (s, 1H, NH), 5.13 (s, 1H, C=CH), 5.06 (s, 1H, C=CH), 4.98 (s, 2H, CH_2), 4.12 (d, J = 15.0 Hz, 1H, CH), 3.95 (d, J = 15.0 Hz, 1H, CH), 3.83 (s, 3H, CH_3), 3.58 (d, J = 14.0 Hz, 1H, CH), 3.32 – 3.10 (m, 2H, CH_2), 2.98 (d, J = 14.0 Hz, 1H, CH), 2.44 – 2.26 (m, 1H, CH), 1.78 – 1.61 (m, 2H, CH_2), 1.62 – 1.42 (m, 2H, CH_2), 1.40 – 1.16 (m, 1H, CH); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 173.0, 168.6, 167.1, 156.7, 138.7, 136.7, 136.5, 131.9, 130.0, 129.5, 129.1, 128.5, 128.1, 128.0, 127.7, 113.7, 66.5, 59.2, 52.5, 47.0, 40.2, 39.0, 34.0, 29.6, 20.4; **MS (ESI$^+$)** 494 (100%, M+H$^+$); **HRMS (ESI$^+$)** $C_{27}H_{31}N_3O_6$ requires M+H$^+$ 494.2291, found 494.2300.

Methyl-(*S*)-2-((3-(2-methoxy-2-oxoethyl)-5-methylene-2-oxopiperidin-3-yl)carbamoyl)-benzoate, 7bf



N-Boc-5-Methylenecyclohexacarbamate (**C4**) (42 mg, 0.2 mmol), (*R*,*R*)-ANDEN-phenyl Trost ligand (12 mg, 0.015 mmol), {η^3-C_3H_5PdCl}$_2$ (2 mg, 0.005 mmol), ^{t}BuOH (0.09 ml, 1.0 mmol) and DIPEA (0.03 ml, 0.4 mmol) were dissolved in dry 20% toluene in dioxane (2 mL) at 0 °C for 20 mins. Then methyl 2-(4-(2-methoxy-2-oxoethyl)-5-oxo-4,5-dihydrooxazol-2-yl)benzoate (**7af**) (175 mg, 0.6 mmol) was added. The mixture was stirred at 0 °C overnight. The solvent was removed under reduced pressure give the crude product which was dissolved in dry DCM (2 mL). TFA (1.2 mL, 15 mmol) was added and the mixture stirred at room temperature. After 1 hour, EtOAc was added and the mixture was quenched with sat. aq. $NaHCO_3$. The layers were

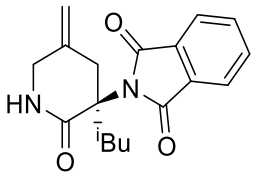
separated, and the aqueous layer was further extracted with EtOAc. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with EtOAc to give methyl-(*S*)-2-((3-(2-methoxy-2-oxoethyl)-5-methylene-2-oxopiperidin-3-yl)carbamoyl)-benzoate (**7bf**) (65 mg, 90%) as a colorless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3265, 2952, 1723, 1651; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.88 – 7.86 (m, 1H, CH_{Ar}), 7.61 – 7.51 (m, 2H, CH_{Ar}), 7.51 – 7.42 (m, 1H, CH_{Ar}), 7.32 (s, 1H, NH), 6.71 (s, 1H, NH), 5.10 (s, 2H, CH_2), 4.15 (d, J = 14.5 Hz, 1H, CH), 3.88 (s, 4H, 4xCH), 3.69 (s, 3H, CH_3), 3.28 (d, J = 14.0 Hz, 1H, CH), 3.17 (d, J = 14.0 Hz, 1H, CH), 3.10 (d, J = 14.5 Hz, 1H, CH), 2.83 (d, J = 14.5 Hz, 1H, CH); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 170.9, 170.8, 168.7, 167.0, 138.1, 136.3, 132.0, 130.0, 129.7, 129.0, 127.7, 114.5, 57.8, 52.4, 52.1, 47.4, 39.2, 38.5; **MS (ESI^+)** 361 (100%, $M+H^+$); **HRMS (ESI^+)** $C_{18}H_{20}N_2O_6$ requires $M+H^+$ 361.1400, found 361.1408. ; **HPLC** (SA, hexane:^{i}PrOH 60:40, flow rate 1.0 mL/min, λ = 210 nm, 25 °C) t_R(major) = 6.963, t_R(minor) = 9.727, er = 90:10

.

12.6 The synthesis of phthalimide intermediates

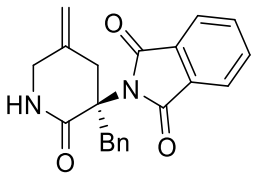
(*R*)-2-(3-Isobutyl-5-methylene-2-oxopiperidin-3-yl)isoindoline-1,3-dione, 7ca



To a solution of methyl (*R*)-2-((3-isobutyl-5-methylene-2-oxopiperidin-3-yl)carbamoyl)-benzoate (**7ba**) (62 mg, 0.2 mmol) dissolved in dry THF (2 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.03 mL, 0.2 mmol) and the mixture heated at 70 ℃ for 24 hours. The solvent was removed under reduced pressure and the residue purified by flash column chromatography eluting with 60% EtOAc in petrol to give (*R*)-2-(3-isobutyl-5-methylene-2-oxopiperidin-3-yl)isoindoline-1,3-dione (**7ca**) (56 mg, 90%) as a white solid.

FTIR ν_{max} (thin film/cm^{-1}) 3223, 2956, 1708, 1677; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.81 (dd, J = 5.5, 3.0 Hz, 2H, CH_{Ar}), 7.75 – 7.65 (m, 2H, CH_{Ar}), 5.83 (s, 1H, NH), 5.00 (s, 1H, C=CH), 4.98 (s, 1H, C=CH), 4.11 (d, J = 15.0 Hz, 1H, CH), 3.99 (d, J = 15.0 Hz, 1H, CH), 3.36 (d, J = 14.0 Hz, 1H, CH), 2.66 (d, J = 14.0 Hz, 1H, CH), 2.54 (dd, J = 14.5, 4.0 Hz, 1H, CH), 2.14 (dd, J = 14.5, 6.0 Hz, 1H), 1.95 – 1.81 (m, 1H, CH), 0.97 (d, J = 6.5 Hz, 6H, 2xCH_3) **^{13}C NMR (101 MHz, $CDCl_3$)** δ 170.4, 168.4, 137.0, 134.0, 131.6, 123.1, 113.1, 63.0, 47.1, 42.3, 40.0, 24.7, 24.4, 24.1; **MS (ESI^+)** 313 (100%, $M+H^+$); **HRMS (ESI^+)** $C_{18}H_{20}N_2O_3$ requires $M+H^+$ 313.1552, found 313.1557. **HPLC** (Cellulose-2, hexane:^{i}PrOH 80:20, flow rate 1.0 mL/min, λ = 254 nm, 22 °C) t_R(major) = 18.923, t_R(minor) = 24.240, er = 92:8.

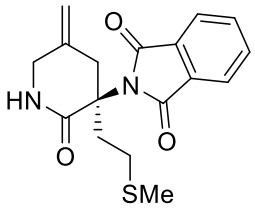
(*R*)-2-(3-Benzyl-5-methylene-2-oxopiperidin-3-yl)isoindoline-1,3-dione, 7cb



To a solution of methyl (*R*)-2-((3-benzyl-5-methylene-2-oxopiperidin-3-yl)carbamoyl)-benzoate (**7bb**) (76 mg, 0.2 mmol) dissolved in dry THF (2 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.03 mL, 0.2 mmol) and the mixture heated at 70 ℃ for 24 hours. The solvent was removed under reduced pressure and the residue purified by flash column chromatography eluting with 40% EtOAc in petrol to give (*R*)-2-(3-benzyl-5-methylene-2-oxopiperidin-3-yl)isoindoline-1,3-dione (**7cb**) (64 mg, 92%) as a white solid.

FTIR ν_{max} (thin film/cm^{-1}) 3227, 2933, 1709, 1680; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.85 – 7.75 (m, 2H, CH_{Ar}), 7.75 – 7.64 (m, 2H, CH_{Ar}), 7.47 – 7.36 (m, 2H, CH_{Ar}), 7.28 – 7.12 (m, 3H, CH_{Ar}), 6.49 (s, 1H, NH), 4.85 (br, 2H, C=CH_2), 3.96 – 3.90 (m, 2H, CH_2), 3.83 (d, J = 15.0 Hz, 1H, CH), 3.76 (d, J = 13.0 Hz, 1H, CH), 3.42 (d, J = 14.5 Hz, 1H, CH), 2.58 (d, J = 14.5 Hz, 1H, CH); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 169.7, 168.2, 136.8, 136.0, 134.2, 131.5, 131.4, 128.1, 126.9, 123.2, 112.8, 63.9, 46.7, 39.4, 37.8; **MS (ESI$^+$)** 347 (100%, M+H$^+$); **HRMS (ESI$^+$)** $C_{21}H_{18}N_2O_3$ requires M+H$^+$ 347.1396, found 347.1392. **HPLC** (Cellulose-1, hexane:^{i}PrOH 70:30, flow rate 1.0 mL/min, λ = 254 nm, 22 °C) t_R(major) = 11.120, t_R(minor) = 21.303, er = 98:2; $[\alpha]_D^{22} = -40$ (*c* 1.0, $CHCl_3$).

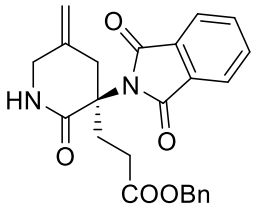
(*S*)-2-(5-Methylene-3-(2-(methylthio)ethyl)-2-oxopiperidin-3-yl)isoindoline-1,3-dione, 7cc



To a solution of methyl (*S*)-2-((5-methylene-3-(2-(methylthio)ethyl)-2-oxopiperidin-3-yl)carbamoyl)-benzoate (**7bc**) (73 mg, 0.2 mmol) dissolved in dry THF (2 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.03 mL, 0.2 mmol) and the mixture heated at 70 ℃ for 24 hours. The solvent was removed under reduced pressure and the residue purified by flash column chromatography eluting with 60% EtOAc in petrol to give (*S*)-2-(5-methylene-3-(2-(methylthio)ethyl)-2-oxopiperidin-3-yl)isoindoline-1,3-dione (**7cc**) (58 mg, 88%) as a white solid.

FTIR ν_{max} (thin film/cm^{-1}) 3235, 2919, 1712, 1678; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.89 – 7.77 (m, 2H, CH_{Ar}), 7.78 – 7.62 (m, 2H, CH_{Ar}), 6.23 (s, 1H, NH), 5.07 (s, 1H, C=CH), 5.04 (s, 1H, C=CH), 4.16 (d, J = 14.5 Hz, 1H, CH), 3.94 (d, J = 14.5 Hz, 1H, CH), 3.30 (d, J = 13.5 Hz, 1H, CH), 3.03 – 2.83 (m, 1H, CH), 2.80 – 2.58 (m, 3H, 3xCH), 2.52 – 2.35 (m, 1H, CH), 2.17 (s, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.9, 168.4, 136.0, 134.2, 131.6, 123.2, 114.2, 62.4, 47.4, 40.6, 35.0, 29.3, 15.3; **MS (ESI^+)** 331 (100%, $M+H^+$); **HRMS (ESI^+)** $C_{17}H_{18}N_2O_3S$ requires $M+H^+$ 331.1116, found 331.1113. **HPLC** (Cellulose-1, hexane:^{i}PrOH 70:30, flow rate 1.0 mL/min, λ = 254 nm, 22 °C) t_R(major) = 13.273, t_R(minor) = 33.117, er = 92:8.

Benzyl-(*R*)-3-(3-(1,3-dioxoisoindolin-2-yl)-5-methylene-2-oxopiperidin-3-yl)propanoate, 7cd

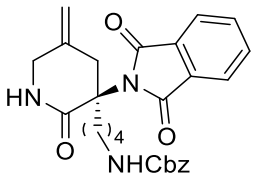


To a solution of methyl-(R)-2-((3-(3-(benzyloxy)-3-oxopropyl)-5-methylene-2-oxopiperidin-3-yl)carbamoyl)benzoate (**7bd**) (90 mg, 0.2 mmol) dissolved in dry THF (2 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.03 mL, 0.2 mmol) and the mixture heated at 70 ℃ for 24 hours. The solvent was removed under reduced pressure and the residue purified by flash column chromatography eluting with 60% EtOAc in petrol to give benzyl-(*R*)-3-(3-(1,3-dioxoisoindolin-2-yl)-5-methylene-2-oxopiperidin-3-yl)propanoate (**7cd**) (72 mg, 86%) as a colorless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3229, 2927, 1712, 1678; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.85 – 7.77 (m, 2H, CH_{Ar}), 7.77 – 7.69 (m, 2H, CH_{Ar}), 7.43 – 7.25 (m, 5H, CH_{Ar}), 6.00 (s, 1H, NH), 5.11 (s, 2H, CH_2), 5.07 (s, 1H, C=CH), 5.05 (s, 1H, C=CH), 4.16 (d, J = 14.5 Hz, 1H, CH), 3.93 (d, J = 14.5 Hz, 1H, CH), 3.31 (d, J = 13.5 Hz, 1H, CH), 3.13 – 2.93 (m, 1H, CH), 2.90 – 2.72 (m, 1H, CH), 2.72 – 2.46 (m, 3H, 3xCH); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 173.0, 169.8, 168.4, 136.1, 135.9, 134.2, 131.6, 128.5, 128.1, 128.1, 123.2, 114.2, 66.2, 61.8, 47.4, 40.9, 30.0, 29.5; **MS (ESI^+)** 419 (100%, $M+H^+$); **HRMS (ESI^+)**

$C_{24}H_{22}N_2O_5$ requires M+H$^+$ 419.1607, found 419.1612. **HPLC** (Cellulose-1, hexane:^{i}PrOH 60:40, flow rate 1.0 mL/min, λ = 254 nm, 22 °C) t_R(major) = 21.053, t_R(minor) = 38.207, er = 90:10.

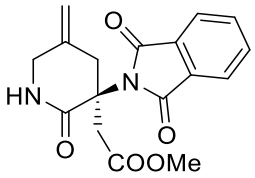
Benzyl-(*R*)-(4-(3-(1,3-dioxoisoindolin-2-yl)-5-methylene-2-oxopiperidin-3-yl)butyl)-carbamate, 7ce



To a solution of methyl (R)-2-((3-(4-(((benzyloxy)carbonyl)amino)butyl)-5-methylene-2-oxopiperidin-3-yl)carbamoyl)benzoate (**7be**) (100 mg, 0.2 mmol) dissolved in dry THF (2 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.03 mL, 0.2 mmol) and the mixture heated at 70 ℃ for 24 hours. The solvent was removed under reduced pressure and the residue purified by flash column chromatography eluting with 80% EtOAc in petrol to give benzyl-(*R*)-(4-(3-(1,3-dioxoisoindolin-2-yl)-5-methylene-2-oxopiperidin-3-yl)butyl)-carbamate (**7ce**) (83 mg, 90%) as a colorless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3320, 2925, 1708, 1677; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.82 – 7.75 (m, 2H, CH_{Ar}), 7.74 – 7.66 (m, 2H, CH_{Ar}), 7.38 – 7.26 (m, 5H, CH_{Ar}), 6.41 (s, 1H, NH), 5.19 (s, 1H, NH), 5.09 (s, 2H, CH_2), 5.00 (s, 1H, C=CH), 4.98 (s, 1H, C=CH), 4.11 (d, J = 14.5 Hz, 1H, CH), 3.89 (d, J = 14.5 Hz, 1H, CH), 3.32 – 3.11 (m, 3H, 3xCH), 2.65 (d, J = 13.5 Hz, 1H, CH), 2.56 – 2.47 (m, 1H, CH), 2.29 – 2.17 (m, 1H, CH), 1.64 – 1.40 (m, 4H, 4xCH); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 170.4, 168.6, 156.4, 136.8, 136.5, 134.1, 131.7, 128.5, 128.0, 128.0, 123.2, 113.6, 66.4, 62.8, 47.3, 40.4, 40.1, 33.9, 29.5, 21.9; **MS (ESI$^+$)** 462 (100%, M+H$^+$); **HRMS (ESI$^+$)** $C_{26}H_{27}N_3O_5$ requires M+H$^+$ 462.2029, found 462.2031. **HPLC** (Cellulose-1, hexane:^{i}PrOH 80:20, flow rate 1.0 mL/min, λ = 254 nm, 22 °C) t_R(major) = 54.863, t_R(minor) = 97.607, er = 96:4; $[\alpha]_D^{22} = -50$ (*c* 1.0, $CHCl_3$).

Methyl-(*S*)-2-(3-(1,3-dioxoisoindolin-2-yl)-5-methylene-2-oxopiperidin-3-yl)acetate, 7cf

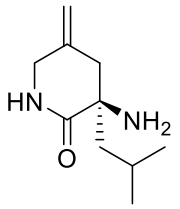


To a solution of methyl-(S)-2-((3-(2-methoxy-2-oxoethyl)-5-methylene-2-oxopiperidin-3-yl)carbamoyl)-benzoate (**7bf**) (73 mg, 0.2 mmol) dissolved in dry THF (2 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.03 mL, 0.2 mmol) and the mixture heated at 70 ℃ for 24 hours. The solvent was removed under reduced pressure and the white solid was filtered. Then, the residue purified by flash column chromatography eluting with 60% EtOAc in petrol to give methyl-(*S*)-2-(3-(1,3-dioxoisoindolin-2-yl)-5-methylene-2-oxopiperidin-3-yl)acetate (**7cf**) (40 mg, 60%) as a colorless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3357, 2951, 1708, 1677; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.90 – 7.76 (m, 2H, CH_{Ar}), 7.75 – 7.57 (m, 2H, CH_{Ar}), 6.48 (s, 1H, NH), 4.98 (s, 1H, C=CH), 4.96 (s, 1H, C=CH), 4.07 (d, J = 15.0 Hz, 1H, CH), 4.01 (d, J = 15.0 Hz, 1H, CH), 3.68 (s, 3H, CH_3), 3.42 (d, J = 14.0 Hz, 1H, CH), 3.36 (d, J = 16.5 Hz, 1H, CH), 3.25 (d, J = 16.5 Hz, 1H, CH), 3.22 (d, J = 14.0 Hz, 1H, CH); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 170.7, 169.7, 168.2, 136.1, 134.2, 131.5, 123.3, 113.9, 60.9, 51.7, 47.0, 37.9, 37.4; **MS (ESI^+)** 329 (100%, $M+H^+$); **HRMS (ESI^+)** $C_{17}H_{16}N_2O_5$ requires $M+H^+$ 329.1137, found 329.1130.

12.7 The synthesis of the Freidinger lactams containing a free amine group.

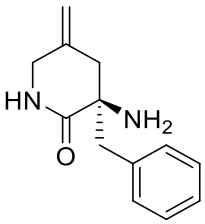
(*R*)-3-Amino-3-isobutyl-5-methylenepiperidin-2-one, 7da



To a solution of (*R*)-2-(3-isobutyl-5-methylene-2-oxopiperidin-3-yl)isoindoline-1,3-dione (**7ca**) (66 mg, 0.2 mmol) dissolved in dry ^{i}PrOH (1 mL) was added ethylenediamine (0.1 mL, 1.6 mmol) and the mixture heated at 80 ℃ for 24 hours. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 10% MeOH in DCM to give (*R*)-3-amino-3-isobutyl-5-methylenepiperidin-2-one (**7da**) (34 mg, 93%) as a colorless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3227, 2953, 1658; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 6.19 (s, 1H, NH), 5.08 (s, 1H, C=CH_2), 5.06 (s, 1H, C=CH_2), 3.94 (s, 2H, CH_2), 2.60 (d, J = 13.5 Hz, 1H, CH), 2.38 (d, J = 13.5 Hz, 1H, CH), 2.05 (s, 2H, NH_2), 1.86-1.76 (m, 1H, CH), 1.56 (dd, J = 14.0, 6.0 Hz, 1H, CH), 1.48 (dd, J = 14.0, 6.0 Hz, 1H, CH), 0.93 (d, J = 4.5 Hz, 3H, CH_3), 0.91 (d, J = 4.5 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 177.5, 137.5, 113.0, 56.1, 47.6, 46.8, 41.9, 24.6, 24.5, 23.7; **MS (ESI$^+$)** 183 (100%, M+H$^+$); **HRMS (ESI$^+$)** $C_{10}H_{18}N_2O$ requires M+H$^+$ 183.1492, found 183.1499.

(*R*)-3-Amino-3-benzyl-5-methylenepiperidin-2-one, 7db

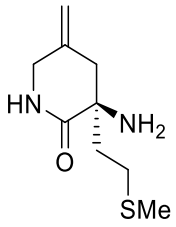


To a solution of (*R*)-2-(3-benzyl-5-methylene-2-oxopiperidin-3-yl)isoindoline-1,3-dione (**7cb**) (69 mg, 0.2 mmol) dissolved in dry ^{i}PrOH (1 mL) was added

ethylenediamine (0.1 mL, 1.6 mmol) and the mixture heated at 80 ℃ for 24 hours. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 5% MeOH in DCM to give (*R*)-3-amino-3-benzyl-5-methylenepiperidin-2-one (**7db**) (41 mg, 95%) as a colorless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3220, 2920, 1657; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.39 – 7.19 (m, 5H, CH_{Ar}), 6.44 (br, 1H, NH), 5.12 (s, 1H, C=CH), 5.05 (s, 1H, C=CH), 4.03 – 3.97 (m, 1H, CH), 3.98 – 3.89 (m, 1H, CH), 3.06 (d, J = 13.5 Hz, 1H, CH), 2.84 (d, J = 13.5 Hz, 1H, CH), 2.54 (d, J = 13.5 Hz, 1H, CH), 2.33 (d, J = 13.5 Hz, 1H, CH), 1.80 (br, 2H, NH_2); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 176.5, 137.1, 136.2, 130.9, 128.1, 126.8, 113.6, 56.7, 47.9, 44.3, 40.6; **MS (ESI$^+$)** 217 (100%, M+H$^+$); **HRMS (ESI$^+$)** $C_{13}H_{16}N_2O$ requires M+H$^+$ 217.1341, found 217.1343. $[\alpha]_D^{22} = -40$ (*c* 1.0, $CHCl_3$).

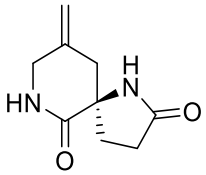
(*S*)-3-Amino-5-methylene-3-(2-(methylthio)ethyl)piperidin-2-one, 7dc



To a solution of (*S*)-2-(5-methylene-3-(2-(methylthio)ethyl)-2-oxopiperidin-3-yl)isoindoline-1,3-dione (**7cc**) (69 mg, 0.2 mmol) dissolved in dry ^{i}PrOH (1 mL) was added ethylenediamine (0.1 mL, 1.6 mmol) and the mixture heated at 80 ℃ for 24 hours. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 5% MeOH in DCM to give (*S*)-3-amino-5-methylene-3-(2-(methylthio)ethyl)piperidin-2-one (**7dc**) (41 mg, 95%) as a colorless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3207, 2916, 1661; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 6.19 (s, 1H, NH), 5.08 (s, 1H, C=CH), 5.06 (s, 1H, C=CH), 4.02 (d, J = 14.5 Hz, 1H, CH), 3.96 (d, J = 14.5 Hz, 1H, CH), 2.67 – 2.49 (m, 3H, 3xCH), 2.42 (d, J = 13.5 Hz, 1H, CH), 2.11 (s, 3H, CH_3), 1.95 – 1.84 (m, 2H, CH_2), 1.82 (s, 2H, NH_2); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 176.6, 136.7, 113.6, 55.8, 47.8, 41.4, 38.3, 28.0, 15.6; **MS (ESI$^+$)** 201 (100%, M+H$^+$); **HRMS (ESI$^+$)** $C_9H_{16}N_2OS$ requires M+H$^+$ 201.1062, found 201.1063.

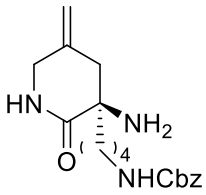
(*R*)-9-methylene-1,7-diazaspiro[4.5]decane-2,6-dione, 7dd



To a solution of benzyl-(R)-3-(3-(1,3-dioxoisoindolin-2-yl)-5-methylene-2-oxopiperidin-3-yl)propanoate (**7cd**) (84 mg, 0.2 mmol) dissolved in dry ^{i}PrOH (1 mL) was added ethylenediamine (0.1 mL, 1.6 mmol) and the mixture heated at 80 ℃ for 24 hours. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 10% MeOH in DCM to give (*R*)-9-methylene-1,7-diazaspiro[4.5]decane-2,6-dione (**7dd**) (33mg, 90%) as a colorless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3238, 2924, 1678; **^{1}H NMR (400 MHz, MeOD)** δ 5.15 (s, 1H, C=CH), 5.12 (s, 1H, C=CH), 4.02 (d, J = 14.5 Hz, 1H, CH), 3.90 (d, J = 14.5 Hz, 1H, CH), 2.82 (d, J = 13.0 Hz, 1H, CH), 2.59 (d, J = 13.0 Hz, 1H, CH), 2.55 – 2.31 (m, 2H, CH_2), 2.30 – 2.15 (m, 1H, CH), 2.12 – 1.95 (m, 1H, CH); **^{13}C NMR (101 MHz, MeOD)** δ 179.6, 136.4, 112.9, 61.7, 46.9, 41.6, 31.7, 29.4; **MS (ESI^{+})** 181 (100%, M+H^{+}); **HRMS (ESI^{+})** $C_9H_{16}N_2OS$ requires M+H^{+} 181.0977, found 181.0977.

(*R*)-9-methylene-1,7-diazaspiro[4.5]decane-2,6-dione, 7de

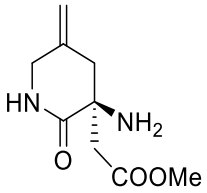


To a solution of benzyl-(R)-(4-(3-(1,3-dioxoisoindolin-2-yl)-5-methylene-2-oxopiperidin-3-yl)butyl)-carbamate (**7ce**) (95 mg, 0.2 mmol) dissolved in dry ^{i}PrOH (1 mL) was added ethylenediamine (0.1 mL, 1.6 mmol) and the mixture heated at 80 ℃ for 24 hours. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 10% MeOH in DCM to give (*R*)-9-methylene-1,7-diazaspiro[4.5]decane-2,6-dione (**7de**) (61mg, 92%) as a colorless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3287, 2939, 1703, 1650; **^{1}H NMR (400 MHz, CDCl3)** δ 7.46 – 7.25 (m, 5H, CH_{Ar}), 6.37 (s, 1H, NH), 5.09 (s, 2H, CH_2), 5.03 (s, 1H, C=CH), 5.00 (s, 1H,

C=CH), 3.92 (s, 2H, CH_2), 3.32 – 3.09 (m, 2H, CH_2), 2.55 (d, J = 13.5 Hz, 1H, CH), 2.36 (d, J = 13.5 Hz, 1H, CH), 1.88 (s, 2H, NH_2), 1.65 – 1.53 (m, 2H, CH_2), 1.52 – 1.44 (m, 2H, CH_2), 1.45 – 1.31 (m, 2H, CH_2); **^{13}C NMR (101 MHz, CDCl3)** δ 177.1, 156.4, 137.1, 136.7, 128.5, 128.13, 128.07, 113.2, 66.5, 55.8, 47.7, 41.3, 40.7, 38.1, 30.0, 20.2; **MS (ESI$^+$)** 332 (100%, M+H$^+$); **HRMS (ESI$^+$)** $C_{18}H_{25}N_3O_3$ requires M+H$^+$ 332.1974, found 332.1977. $[\alpha]_D^{22} = -50$ (*c* 1.0, $CHCl_3$).

Methyl-(*S*)-2-(3-amino-5-methylene-2-oxopiperidin-3-yl)acetate, 7df

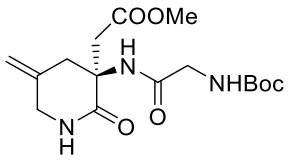


To a solution of methyl-(S)-2-(3-(1,3-dioxoisoindolin-2-yl)-5-methylene-2-oxopiperidin-3-yl)acetate (**7cf**) (66 mg, 0.2 mmol) dissolved in dry ^{i}PrOH (1 mL) was added ethylenediamine (0.1 mL, 1.6 mmol) and the mixture heated at 80 ℃ for 24 hours. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 10% MeOH in DCM to give methyl-(S)-2-(3-amino-5-methylene-2-oxopiperidin-3-yl)acetate (**7df**) (30 mg, 75%) as a colorless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3353, 2954, 1723, 1643; **^{1}H NMR (400 MHz, CDCl3)** δ 6.68 (s, 1H, NH), 5.09 (s, 1H, C=CH), 5.04 (s, 1H, C=CH), 4.00 (d, J = 14.0 Hz, 1H, CH), 3.91 (d, J = 14.0 Hz, 1H, CH), 3.67 (s, 3H, CH_3), 2.91 (d, J = 13.5 Hz, 1H, CH), 2.80 (d, J = 15.5 Hz, 1H, CH), 2.54 (d, J = 15.5 Hz, 1H, CH), 2.41 (d, J = 13.5 Hz, 1H, CH), 2.02 (s, 2H, NH_2); **^{13}C NMR (101 MHz, CDCl3)** δ 175.4, 171.4, 136.6, 114.1, 54.8, 51.6, 48.0, 42.5, 41.1; **MS (ESI$^+$)** 199 (100%, M+H$^+$); **HRMS (ESI$^+$)** $C_9H_{14}N_2O_3$ requires M+H$^+$ 199.1083, found 199.1085.

12.8 The synthesis of RGD analogue and MIF-1 analogue

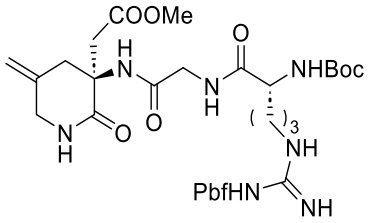
Methyl (*S*)-2-(3-(2-((tert-butoxycarbonyl)amino)acetamido)-5-methylene-2-oxopiperidin-3-yl)acetate, 8a



L-Glycine-Boc (95mg, 0.54 mmol), HOAT (75 mg, 0.54 mmol), DIPEA (0.15 mL, 0.9 mmol), EDC.HCl (104 mg, 0.54 mmol) were dissolved in dry DCM (2 mL) at room temperature for 20 mins. Then methyl-(S)-2-(3-amino-5-methylene-2-oxopiperidin-3-yl)acetate (**7df**) (90mg, 0.45 mmol) was added and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 3% MeOH in EtOAc to give methyl (S)-2-(3-(2-((tert-butoxycarbonyl)amino)acetamido)-5-methylene-2-oxopiperidin-3-yl)acetate (**8a**) (122 mg, 80%) as a white solid.

FTIR ν_{max} (thin film/cm^{-1}) 3318, 2978, 1710, 1657; **^{1}H NMR (400 MHz, $CDCl_3$)** δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H, NH), 6.97 (s, 1H, NH), 5.60 (s, 1H, NH), 5.04 (s, 1H, C=CH), 4.99 (s, 1H, C=CH), 4.06 (d, J = 14.0 Hz, 1H, CH), 3.93 – 3.69 (m, 3H , 3xCH), 3.65 (s, 3H, CH_3), 3.11 (d, J = 13.0 Hz, 1H, CH), 2.94 – 2.59 (m, 3H, 3xCH), 1.42 (s, 9H, $C(CH_3)_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.0, 170.6, 169.7, 156.0, 136.2, 114.3, 79.8, 57.2, 52.0, 47.5, 44.3, 39.3, 38.6, 28.3; **MS (ESI^+)** (100%, $M+H^+$) 356; **HRMS (ESI^+)** $C_{16}H_{26}N_3O_4$ requires $M+H^+$ 356.1822, found 356.1818

Methyl 2-((*S*)-3-(2-((*R*)-2-((tert-butoxycarbonyl)amino)-5-(3-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)guanidino)pentanamido)-acetamido)-5-methylene-2-oxopiperidin-3-yl)acetate, 8b

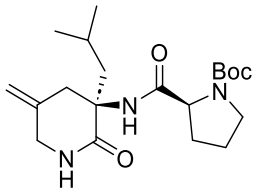


To a solution of methyl (S)-2-(3-(2-((tert-butoxycarbonyl)amino)acetamido)-5-methylene-2-oxopiperidin-3-yl)acetate (**8a**) (122 mg, 0.35 mmol) dissolved in dry DCM (2 mL) was added TFA (1.2 mL, 27 mmol) and the mixture stirred at room temperature. After one hour, TFA was removed followed by adding DIPEA (1.5 mL) and dry DCM (1.5 mL) to make cocktail A. L-Arg(Pbf)-Boc (276mg, 0.53 mmol), HOAT (71 mg, 0.53 mmol), DIPEA (0.15 mL, 0.9 mmol), EDC.HCl (101 mg, 0.53 mmol) were dissolved in dry DCM (1.5 mL) at room temperature for 20 mins. Then cocktail A was added, and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 5% MeOH in DCM to give methyl 2-((*S*)-3-(2-((*R*)-2-((tert-butoxycarbonyl)amino)-5-(3-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)-guanidino)pentanamido)acetamido)-5-methylene-2-oxopiperidin-3-yl)acetate (**8b**) (107 mg, 40%) as a white solid.

FTIR ν_{max} (thin film/cm^{-1}) 3329, 2926, 2853, 2249, 1660; **^{1}H NMR (400 MHz, $CDCl_3$)** δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H, NH), 7.62 (s, 1H, NH), 7.56 (s, 1H, NH), 6.37 (br, 3H, NH), 5.66 (s, 1H, NH), 5.07 (s, 1H, C=CH), 5.01 (s, 1H, C=CH), 4.36 – 4.16 (m, 1H, CH), 4.09 – 4.01 (m, 2H, CH_2), 3.87 (d, J = 14.0 Hz, 1H, CH), 3.77 (d, J = 14.0 Hz, 1H, CH), 3.68 (s, 3H, CH_3), 3.20 (br, 2H, CH_2), 3.09 (d, J = 13.5 Hz, 1H, CH), 2.95 (s, 2H, CH_2), 2.84 (d, J = 14.5 Hz, 1H, CH), 2.73 – 2.67 (m, 2H, CH_2), 2.57 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 1.89 (br, 1H, CH), 1.69 (br, 1H, CH), 1.57 (br, 2H, 2xCH), 1.46 (s, 6H, 2xCH_3), 1.41 (s, 9H, $C(CH_3)_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 173.4, 171.2, 170.6, 169.4, 158.6, 156.5, 155.8, 138.3, 135.9, 133.1, 132.3, 124.5, 117.4, 114.6, 86.3, 79.8, 57.3, 53.7, 53.5, 52.2, 47.4, 43.2, 43.0, 39.4, 38.7, 30.0, 28.6, 28.4, 24.7, 19.3, 17.9,

12.5; **MS (ESI$^+$)** 764 (100%, M+H$^+$) ; **HRMS (ESI$^+$)** $C_{35}H_{53}N_7O_{10}S$ requires M+H$^+$ 764.3653, found 764.3650.

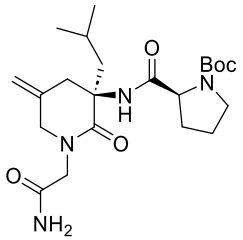
tert-butyl (_S_)-2-(((_R_)-3-isobutyl-5-methylene-2-oxopiperidin-3-yl)carbamoyl)-pyrrolidine-1-carboxylate, 8e



L-Proline-Boc (431 mg, 2.0 mmol), HOAT (272 mg, 2.0 mmol), DIPEA (0.57 mL, 3.3 mmol), EDC.HCl (383 mg, 2.0 mmol) were dissolved in dry DCM (20 mL) at room temperature for 20 mins. Then (*R*)-3-amino-3-isobutyl-5-methylenepiperidin-2-one (**7da**) (300 mg, 1.64 mmol) was added, and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 50% EtOAc in petrol to give *tert*-butyl (*S*)-2-(((*R*)-3-isobutyl-5-methylene-2-oxopiperidin-3-yl)carbamoyl)-pyrrolidine-1-carboxylate (**8e**) (592 mg, 95%, 90:10 dr) as a colourless oil and a mixture of rotamers (1:1).

FTIR ν_{max} (thin film/cm^{-1}) 3285, 2956, 1661; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.75 (br, 0.5H, NH), 7.28 (br, 0.5H, NH), 6.79 (br, 0.5H, NH), 6.46 (br, 0.5H, NH), 5.03 (br, 1H, C=CH), 5.00 (s, 1H, C=CH), 4.38 – 4.12 (m, 1H, CH), 4.07 (d, J = 15.5 Hz, 1H, CH), 3.94 (br, 1H, CH), 3.56 – 3.21 (m, 3H, 3xCH), 2.81 – 2.54 (m, 1H, CH), 2.32 – 2.00 (m, 3H, 3xCH), 1.93 – 1.82 (m, 2H, 2xCH), 1.72 (br, 1H, CH) 1.56 – 1.37 (m, 10H, CH, $C(CH_3)_3$), 0.89 (d, J = 6.5 Hz, 3H, CH_3), 0.84 (d, J = 6.5 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 173.5, 171.6, 171.3, 137.2, 112.9, 80.1, 61.5, 60.4, 58.3, 46.9, 46.6, 46.3, 42.8, 42.5, 39.6, 28.4, 24.3, 23.9, 23.7, 23.4; **MS (ESI$^+$)** 380 (100%, M+H$^+$); **HRMS (ESI$^+$)** $C_{20}H_{33}N_3O_4$ requires M+H$^+$ 380.2549, found 380.2555.

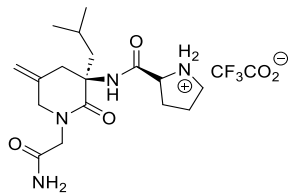
***tert*-butyl (*S*)-2-(((*R*)-1-(2-amino-2-oxoethyl)-3-isobutyl-5-methylene-2-oxopiperidin-3-yl)carbamoyl)pyrrolidine-1-carboxylate, 8f**



A mixture of (*S*)-2-(((*R*)-3-isobutyl-5-methylene-2-oxopiperidin-3-yl)carbamoyl)-pyrrolidine-1-carboxylate (**8e**) (543 mg, 1.43 mmol) and lithium bis(trimethylsilyl)amide (1.0 M in hexanes) (2 mL, 2.0 mmol) was dissolved in dry THF at -78 ℃ for 30 mins. Then -iodoacetamide (370 mg, 2.0 mmol) was added. The mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 90% EtOAc in petrol to give *tert*-butyl (*S*)-2-(((*R*)-1-(2-amino-2-oxoethyl)-3-isobutyl-5-methylene-2-oxopiperidin-3-yl)carbamoyl)-pyrrolidine-1-carboxylate (**8f**) (592 mg, 95%, 90:10 dr) as a white solid and a mixture of rotamers (1:1).

m.p.: 206 – 209 ℃ (After recrystallisation from acetone and hexane). **FTIR** ν_{max} (thin film/cm^{-1}) 3375, 2957, 1643; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.72 (s, 0.5H, NH), 7.44 (s, 1H, NH), 6.78 (s, 0.5H, NH), 5.74 (s, 1H, NH), 5.28 (s, 1H, CH), 5.04 (s, 1H, C=CH), 4.97 (s, 1H, C=CH), 4.83 (d, J = 16.5 Hz, 1H, CH), 4.25-4.14 (m, 2H, 2xCH), 3.74 (d, J = 13.5 Hz, 1H, CH), 3.37 (br, 2H, CH_2), 3.25 (d, J = 16.5 Hz, 1H, CH), 3.11 (d, J = 12.5 Hz, 1H, CH), 2.57 (br, 1H, CH), 1.96 – 1.75 (m, 4H, 4xCH), 1.71 – 1.52 (m, 2H, 2xCH), 1.45 (s, 9H, $C(CH_3)_3$), 0.95-0.91 (m, 6H, $2CH_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.2, 171.0, 170.7, 136.4, 113.8, 80.6, 59.6, 59.0, 54.6, 54.5, 53.5, 51.5, 47.1, 44.8, 39.2, 28.3, 24.6, 24.2, 24.1, 23.7; **MS (ESI^+)** 437 (100%, $M+H^+$); **HRMS (ESI^+)** $C_{22}H_{36}N_4O_5$ requires $M+H^+$ 437.2764, found 437.2765.

(*R*)-2-(((*R*)-1-(2-Amino-2-oxoethyl)-3-isobutyl-5-methylene-2-oxopiperidin-3-yl)carbamoyl)-pyrrolidin-1-ium, 8g

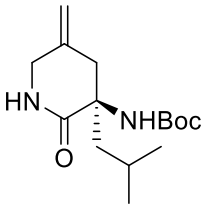


The *tert*-butyl (S)-2-(((R)-1-(2-amino-2-oxoethyl)-3-isobutyl-5-methylene-2-oxopiperidin-3-yl)carbamoyl)pyrrolidine-1-carboxylate (**8f**) was dissolved in TFA (8 mL, 105 mmol) and the mixture was stirred at room temperature for 1 hour. TFA was removed under reduced pressure to furnish (*R*)-2-(((*R*)-1-(2-amino-2-oxoethyl)-3-isobutyl-5-methylene-2-oxopiperidin-3-yl)carbamoyl) pyrrolidin-1-ium (**8g**) (610 mg, 100%, 90:10 dr) as a yellow oil.

FTIR ν_{max} (thin film/cm^{-1}) 3285, 2960, 1666, 1637; **^{1}H NMR (400 MHz, $CDCl_3$)** 9.71 (br, 1H,NH), 7.87 (br, 1H, NH), 7.52 (br, 1H, NH), 7.44 (br, 1H, NH), 7.11 (br, 1H, NH), 5.13 (s, 1H, C=CH), 5.07 (s, 1H, C=CH), 4.79 (d, J = 16.5 Hz, 1H, CH), 4.63 (br, 1H, CH), 4.25 (d, J = 14.0 Hz, 1H, CH), 3.84 (d, J = 14.0 Hz, 1H, CH), 3.44 – 3.34 (m, 3H, 3xCH), 3.18 (d, J = 13.5 Hz, 1H, CH), 2.55 (d, J = 13.5 Hz, 1H, CH), 2.45 (br, 1H, CH), 2.25 – 1.92 (m, 3H, 3xCH), 1.90 – 1.55 (m, 3H, 3xCH), 0.96 (d, J = 6.5 Hz, 3H, CH_3), 0.88 (d, J = 6.5 Hz, 3H, 3xCH); **^{13}C NMR (101 MHz, $CDCl_3$)** 172.4, 170.1, 168.7, 161.17 (q, J = 47.0 Hz), 135.3, 115.8 (q, J = 290.0 Hz), 114.7, 59.8, 59.8, 54.8, 51.1, 46.7, 45.1, 40.0, 29.8, 24.1, 24.0, 23.8, 23.5; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -76.9; **MS (ESI^+)** 337 (100%, $M+H^+$); **HRMS (ESI^+)** $C_{17}H_{28}N_4O_3$ requires $M+H^+$ 337.2225, found 337.2222.

12.9 Synthesis of Alkyne Tagged Lactam

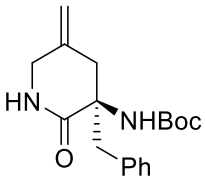
tert-butyl (*R*)-(3-isobutyl-5-methylene-2-oxopiperidin-3-yl)carbamate, 9b



To a solution of 3-amino-3-isobutyl-5-methylenepiperidin-2-one (**7da**) (183 mg, 1.0 mmol) dissolved in THF/H_2O (1:2 v/v, 30 mL) was added Boc_2O (426 mg, 2.0 mmol) and TEA (0.42 mL, 3.0 mmol). The mixture was stirred at 0 °C for 2 hours then stirred at room temperature for 4 hours. This mixture was extracted with EtOAc and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography eluting with 30% EtOAc in petrol to give *tert*-butyl (*R*) (3-isobutyl-5-methylene-2-oxopiperidin-3-yl)carbamate (**9b**) (259mg, 92%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3229, 2957, 1717, 1672; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 6.80 (s, 1H, NH), 5.80 (s, 1H, NH), 5.01 (s, 1H, C=CH), 4.97 (s, 1H, C=CH), 4.06 (d, J=15.0, 1H, CH), 3.92 (d, J = 15.0 Hz, 1H, CH), 3.24 (d, J = 14.0 Hz, 1H, CH), 2.76 (d, J = 14.0 Hz, 1H, CH), 2.03-1.98 (m, 1H, CH), 1.80-1.72 (m, 1H, CH), 1.50-1.42 (m, 10H, CH, $C(CH_3)_3$), 0.92 (d, J = 6.5 Hz, 3H, CH_3), 0.86 (d, J = 6.5 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 174.0, 154.5, 137.2, 112.8, 79.1, 57.7, 46.7, 42.8, 40.3, 28.4, 24.2, 24.0, 23.7; **MS (ESI^+)** 283 (100%, $M+H^+$); **HRMS (ESI^+)** $C_{15}H_{26}N_2O_3$ requires $M+H^+$ 283.2022, found 283.2027.

tert-Butyl (*R*)-(3-benzyl-5-methylene-2-oxopiperidin-3-yl)carbamate, 9c

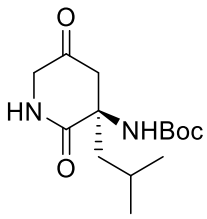


To a solution of (*R*)-3-amino-3-benzyl-5-methylenepiperidin-2-one (**7db**) (216 mg, 1.0 mmol) dissolved in THF/H_2O (1:2 v/v, 30 mL) was added Boc_2O (426 mg, 2.0 mmol)

and TEA (0.42 mL, 3.0 mmol). The mixture was stirred at 0 °C for 2 hours then stirred at room temperature for 4 hours. This mixture was extracted with EtOAc and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography eluting with 30% EtOAc in petrol to give *tert*-butyl (*R*)-(3-benzyl-5-methylene-2-oxopiperidin-3-yl)carbamate (**9c**) (259mg, 92%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3291, 2977, 1714, 1674; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.46 – 7.23 (m, 3H, CH_{Ar}), 7.21 – 7.03 (m, 2H, CH_{Ar}), 6.61 (s, 1H, NH), 5.56 (s, 1H, NH), 5.15 (s, 1H, C=CH), 5.11 (s, 1H, C=CH), 4.13 (d, J = 15.0 Hz, 1H, CH), 4.00 (d, J = 15.0 Hz, 1H, CH), 3.37 (d, J = 14.0 Hz, 1H, CH), 2.94 (d, J = 14.0 Hz, 1H, CH), 2.86 (d, J = 14.0 Hz, 1H, CH), 1.47 (s, 9H, $C(CH_3)_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.8, 154.6, 136.9, 135.8, 130.3, 128.2, 127.0, 113.6, 79.4, 58.6, 47.1, 40.5, 39.4, 28.4; **MS (ESI^+)** 283 (100%, $M+H^+$); **HRMS (ESI^+)** $C_{18}H_{24}N_2O_3$ requires $M+H^+$ 317.1865, found 317.1869.

***tert*-Butyl (*R*)-(3-isobutyl-2,5-dioxopiperidin-3-yl)carbamate, 9ba**

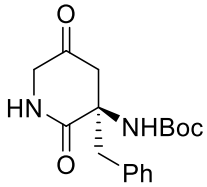


To a solution of *tert*-butyl (3-isobutyl-5-methylene-2-oxopiperidin-3-yl)carbamate (**9b**) (140 mg, 0.5 mmol) dissolved in MeCN/DCM/H_2O (1:1:2 v/v/v, 10 mL) was added $RuCl_3$ (16 mg, 0.15 mmol) and the mixture was stirred at 0 °C for 30 mins. Then $NaIO_4$ (852 mg, 4 mmol) was added and the mixture was stirred at room temperate. After 4 hours, DCM was added. The layers were separated, and the aqueous layer was further extracted with DCM. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 40% Et_2O in petrol to give *tert*-butyl (*R*)-(3-isobutyl-2,5-dioxopiperidin-3-yl)carbamate (**9ba**) (113 mg, 80%) as a colorless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3312, 2959, 1721, 1678; **^{1}H NMR (400 MHz, $CDCl_3$)** 6.93 (s, 1H, NH), 5.72 (s, 1H, NH), 3.98 (s, 2H, CH_2), 3.43 (d, J = 16.5 Hz, 1H, CH), 3.12 (d, J =

16.5 Hz, 1H, CH), 2.27 – 2.00 (m, 1H, CH), 1.88 – 1.72 (m, 1H, CH), 1.45 (s, 10H, CH, $C(CH_3)_3$), 0.97 (d, J = 6.5 Hz, 3H, CH_3), 0.92 (d, J = 6.5 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 202.4, 172.5, 154.3, 79.9, 56.8, 51.4, 47.6, 42.9, 28.4, 24.0, 23.8; **MS (ESI$^+$)** 307 (100%, M+Na^+); **HRMS (ESI$^+$)** $C_{14}H_{24}N_2O_4$ requires M+Na^+ 307.1634, found 307.1621.

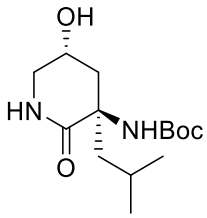
***tert*-butyl (*R*)-(3-benzyl-2,5-dioxopiperidin-3-yl)carbamate, 9ca**



To a solution of *tert*-butyl (R)-(3-benzyl-5-methylene-2-oxopiperidin-3-yl)carbamate (**9c**) (160 mg, 0.5 mmol) dissolved in MeCN/DCM/H_2O (1:1:2 v/v/v, 10 mL) was added $RuCl_3$ (16 mg, 0.15 mmol) and the mixture was stirred at 0 °C for 30 mins. Then $NaIO_4$ (852 mg, 4 mmol) was added and the mixture was stirred at room temperate. After 4 hours, DCM was added. The layers were separated, and the aqueous layer was further extracted with DCM. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 40% Et_2O in petrol to give tert-butyl (*R*)-(3-benzyl-2,5-dioxopiperidin-3-yl)carbamate (**9ba**) (135 mg, 85%) as a colorless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3301, 2978, 1715, 1674; **^{1}H NMR (400 MHz, $CDCl_3$)** 7.37 – 7.24 (m, 3H, CH_{Ar}), 7.24 – 7.10 (m, 2H, CH_{Ar}), 5.51 (s, 1H, NH), 3.82 (d, J = 16.5 Hz, 1H, CH), 3.51 – 3.16 (m, 4H, 4xCH), 2.96 (d, J = 13.5 Hz, 1H, CH), 1.47 (s, 9H, $C(CH_3)_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 202.1, 171.8, 154.6, 133.6, 130.6, 128.6, 127.8, 80.2, 58.0, 51.4, 46.8, 42.1, 28.4; **MS (ESI$^+$)** 341 (100%, M+Na^+); **HRMS (ESI$^+$)** $C_{17}H_{22}N_2O_4$ requires M+Na^+ 341.1477, found 341.1480.

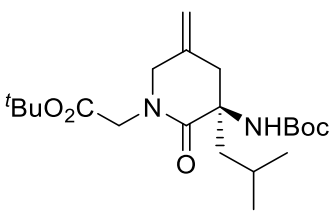
***tert*-Butyl ((3*R*,5*R*)-5-hydroxy-3-isobutyl-2-oxopiperidin-3-yl)carbamate, 9bb**



To a solution of *tert*-butyl (*R*)-(3-isobutyl-2,5-dioxopiperidin-3-yl)carbamate (**9ba**) (71 mg, 0.25 mmol) dissolved in dry THF (2.5 mL) was added K-selectride (1.0 M in THF) (0.5 mL, 0.5 mmol) at -78 °C. Then the mixture was stirred at room temperature. After 30 mins, DCM was added and the mixture was quenched with brine. The layers were separated, and the aqueous layer was further extracted with DCM. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 20% EtOAc in petrol to give *tert*-butyl ((3*R*,5*R*)-5-hydroxy-3-isobutyl-2-oxopiperidin-3-yl)carbamate (**9bb**) (63 mg, 88%, 10:1 dr) as a colorless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3310, 2970, 1715, 1660; **^{1}H NMR (400 MHz, $CDCl_3$)** 6.25 (s, 1H, NH), 5.34 (s, 1H, NH), 4.41 – 4.31 (m, 1H, CH), 3.65 – 3.55 (m, 1H, CH), 3.30 – 3.20 (m, 1H, CH), 2.57 (dd, J = 14.5, 5.0 Hz, 1H, CH), 2.26 (dd, J = 14.5, 7.0 Hz, 1H, CH), 2.03 (dd, J = 14.0, 5.5 Hz, 1H, CH), 1.92 – 1.78 (m, 1H, CH), 1.77 (dd, J = 14.0, 6.0 Hz, 1H, CH), 1.45 (s, 9H, $C(CH_3)_3$), 0.98 (d, J = 1.5 Hz, 3H, CH_3), 0.96 (d, J = 1.5 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 174.3, 154.9, 79.7, 63.5, 57.5, 48.0, 46.6, 39.7, 28.4, 24.3, 24.13, 24.11; **MS (ESI$^+$)** 309 (100%, M+Na$^+$); **HRMS (ESI$^+$)** $C_{14}H_{26}N_2O_4$ requires M+Na$^+$ 309.1790, found 309.1797.

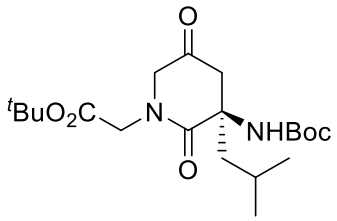
***tert*-butyl (*R*)-2-(3-((*tert*-butoxycarbonyl)amino)-3-isobutyl-5-methylene-2-oxopiperidin-1-yl)acetate, 9f**



A mixture of (3-isobutyl-5-methylene-2-oxopiperidin-3-yl)carbamate (**9b**) (200 mg, 0.7 mmol) and lithium bis(trimethylsilyl)amide (1.0 M in hexanes) (1.4 mL, 1.4 mmol) was dissolved in dry THF at -78 ℃for 30 mins. Then *tert*-butyl bromoacetate (273 mg, 1.4 mmol) was added. The mixture was stirred at room temperature 2 hours. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 20% Et_2O in petrol to give *tert*-butyl (*R*)-2-(3-((*tert*-butoxycarbonyl)amino)-3-isobutyl-5-methylene-2-oxopiperidin-1-yl)acetate (**9f**) (231 mg, 83%) as a colorless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3408, 2978 1741, 1715, 1650; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.91 (s, 1H, NH), 5.02 (s, 1H, C=CH), 4.98 (s, 1H, C=CH), 4.14 – 3.96 (m, 3H, 3xCH), 3.88 (d, J = 17.0 Hz, 1H, CH), 3.36 (d, J = 14.0 Hz, 1H, CH), 2.76 (d, J = 14.0 Hz, 1H, CH), 2.13 – 1.95 (m, 1H, CH), 1.79 – 1.65 (m, 1H, CH), 1.55 – 1.48 (m, 1H, CH), 1.46 (s, 9H, $C(CH_3)_3$), 1.42 (s, 9H, $C(CH_3)_3$), 0.92 (d, J = 6.5 Hz, 3H, CH_3), 0.82 (d, J = 6.5 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.0, 167.6, 154.4, 136.7, 112.6, 82.0, 79.0, 57.9, 53.5, 49.5, 42.8, 40.4, 28.4, 28.1, 24.1, 24.0, 23.7; **MS (ESI^+)** 397 (100%, $M+H^+$); **HRMS (ESI^+)** $C_{21}H_{36}N_2O_5$ requires $M+H^+$ 397.2702, found 397.2704.

***tert*-butyl (*R*)-2-(3-((tert-butoxycarbonyl)amino)-3-isobutyl-2,5-dioxopiperidin-1-yl)acetate, 9g**

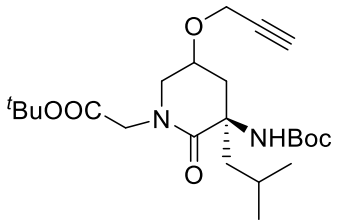


To a solution of *tert*-butyl 2-(3-((*tert*-butoxycarbonyl)amino)-3-isobutyl-5-methylene-2-oxopiperidin-1-yl)acetate (**9f**) (198 mg, 0.5 mmol) dissolved in MeCN/DCM/H_2O (1:1:2 v/v/v, 10 mL) was added $RuCl_3$ (16 mg, 0.15 mmol) and the mixture was stirred at 0 °C for 30 mins. Then $NaIO_4$ (852 mg, 4 mmol) was added and the mixture was stirred at room temperate. After 4 hours, DCM was added. The layers were separated, and the aqueous layer was further extracted with DCM. The solvent was removed under reduced pressure and residue purified by flash column chromatography

eluting with 40% Et_2O in petrol to give *tert*-butyl (*R*)-2-(3-((*tert*-butoxycarbonyl)amino)-3-isobutyl-2,5-dioxopiperidin-1-yl)acetate (**9g**) (150 mg, 75%) as a colorless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3404, 2978, 1738, 1721, 1667; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.78 (s, 1H, NH), 4.32 – 4.05 (m, 2H, 2xCH), 3.85-3.80 (m, 2H, 2xCH), 3.49 (d, J = 16.0 Hz, 1H, CH), 3.12 (d, J = 16.0 Hz, 1H, CH), 2.24 – 2.06 (m, 1H, CH), 1.82 – 1.66 (m, 1H, CH), 1.45 (s, 10H, CH, $C(CH_3)_3$), 1.42 (s, 9H, $C(CH_3)_3$), 0.93 (d, J = 6.5 Hz, 3H, CH_3), 0.86 (d, J = 6.5 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 201.5, 170.9, 167.2, 154.2, 82.6, 79.7, 57.5, 49.1, 47.5, 42.7, 42.1, 28.3, 28.0, 24.0, 23.9, 23.8; **MS (ESI^+)** 421 (100%, $M+Na^+$); **HRMS (ESI^+)** $C_{20}H_{34}N_2O_6$ requires $M+Na^+$ 421.2315, found 421.2316.

***tert*-butyl 2-((3*R*)-((*tert*-butoxycarbonyl)amino)-3-isobutyl-2-oxo-(5*R*)-(prop-2-yn-1-yloxy) pi peridin-1-yl)acetate, 9h**

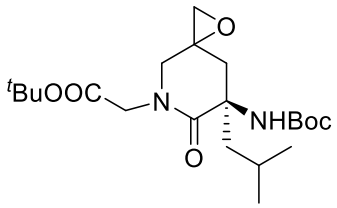


To a solution of *tert*-butyl 2-(3-((tert-butoxycarbonyl)amino)-3-isobutyl-2,5-dioxopiperidin-1-yl)acetate (**9g**) (100 mg, 0.25 mmol) dissolved in dry THF (2.5 mL) was added K-selectride (1.0 M in THF) (0.5 mL, 0.5 mmol) at -78 °C. Then the mixture was stirred at room temperature. After 30 mins, DCM was added and the mixture was quenched with brine. The layers were separated, and the aqueous layer was further extracted with DCM. The solvent was removed under reduced pressure to give the crude product. The crude product and propargyl bromide (150 mg, 1.25 mmol) were dissolved in toluene (2.5 mL). Tetrabutylammonium bisulfate (8.5 mg, 0.025 mmol) was dissolved in 50% NaOH solution (0.8 mL). The two solutions were combined and stirred at room temperature overnight. The layers were separated, and the aqueous layer was further extracted with DCM. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 20% EtOAc in petrol to give *tert*-butyl 2-((3*R*)-((*tert*-

butoxycarbonyl)amino)-3-isobutyl-2-oxo-(5*R*)-(prop-2-yn-1-yloxy) piperidin-1-yl)acetate (**9h**) (100 mg, 92%, 5:1 dr) as a colorless oil.

Major diastereomer: **FTIR** ν_{max} (thin film/cm^{-1}) 3407, 3301, 2977, 1739, 1713, 1652; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.50 (s, 1H, NH), 4.31 – 4.16 (m, 3H, 3xCH), 4.05 (d, J = 17.0 Hz, 1H, CH), 3.96 (d, J = 17.0 Hz, 1H, CH), 3.61 (dd, J = 12.0, 6.0 Hz, 1H, CH), 3.51 (dd, J = 12.0, 6.0 Hz, 1H, CH), 2.74 – 2.57 (m, 1H, CH), 2.51 – 2.34 (m, 2H, 2xCH), 2.14 – 1.98 (m, 1H, CH), 1.88 – 1.70 (m, 2H, 2xCH), 1.48 (s, 9H, $C(CH_3)_3$), 1.44 (s, 9H, $C(CH_3)_3$), 0.96 – 0.87 (m, 6H, $2CH_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.0, 167.8, 154.5, 82.0, 79.5, 79.2, 74.6, 69.4, 58.1, 56.0, 52.3, 50.3, 45.4, 36.4, 28.4, 28.0, 24.3, 24.2, 23.9; **MS (ESI^+)** 429 (100%, $M+H^+$); **HRMS (ESI^+)** $C_{23}H_{38}N_2O_6$ requires $M+H^+$ 439.2808, found 439.2809.

***tert*-butyl 2-((7*R*)-7-((tert-butoxycarbonyl)amino)-7-isobutyl-6-oxo-1-oxa-5-azaspiro[2.5]-octan-5-yl)acetate, 9j**

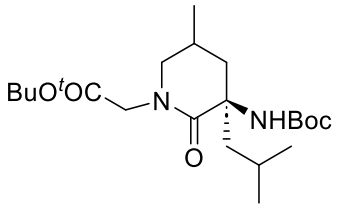


Oxone (1.07 g, 3.5 mmol) and $NaHCO_3$ (1.57 g, 18.7 mmol) were dissolved in water (3 mL) and stirred for 10 mins. To this solution, *tert*-butyl 2-(3-((*tert*-butoxycarbonyl)amino)-3-isobutyl-5-methylene-2-oxopiperidin-1-yl)acetate (**9f**) (85 mg, 0.22 mmol) in acetone (3 mL) was added and the mixture was left to stir at room temperature 3 days. The mixture was diluted with water and extracted with EtOAc. Purification by flash column chromatography eluting with a gradient of 40% Et_2O in petrol to give *tert*-butyl 2-((7*R*)-7-((tert-butoxycarbonyl)amino)-7-isobutyl-6-oxo-1-oxa-5-azaspiro[2.5]-octan-5-yl)acetate (**9j**) the major diastereomer (73 mg, 61%) as a colourless oil and the minor diastereomer (37 mg, 31%) as a colourless oil.

Major diastereomer: **FTIR** ν_{max} (thin film/cm^{-1}) 3408, 2977, 1740, 1716, 1656; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.94 (s, 1H,NH), 4.22 (d, J = 17.0 Hz, 1H, CH), 3.76 (d, J = 17.0 Hz, 1H, CH), 3.59 – 3.42 (m, 2H, 2xCH), 2.88 (s, 2H, 2xCH), 2.63 (d, J = 13.5 Hz,

1H, CH), 2.52 (d, J = 13.5 Hz, 1H, CH), 2.29 – 2.19 (m, 1H, CH), 1.82 – 1.67 (m, 2H, 2xCH), 1.47 (s, 9H, $C(CH_3)_3$), 1.42 (s, 9H, $C(CH_3)_3$), 0.95 (d, J = 6.5 Hz, 3H, CH_3), 0.87 (d, J = 6.5 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.5, 167.5, 154.3, 82.3, 65.8, 58.0, 55.9, 53.3, 52.8, 49.7, 43.1, 38.8, 28.4, 28.0, 24.1, 24.1, 23.9; **MS (ESI$^+$)** 413 (100%, M+H$^+$); **HRMS (ESI$^+$)** $C_{21}H_{36}N_2O_6$ requires M+H$^+$ 413.2652, found 413.2659.

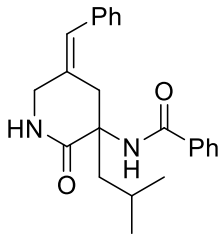
***tert*-butyl 2-((3*R*)-3-((tert-butoxycarbonyl)amino)-3-isobutyl-5-methyl-2-oxopiperidin-1-yl)acetate, 9k**



To a solution of *tert*-butyl 2-(3-((tert-butoxycarbonyl)amino)-3-isobutyl-5-methylene-2-oxopiperidin-1-yl)acetate (**9f**) (80 mg, 0.2 mmol) dissolved in degas MeOH/EtOAc (3:1, 2 mL) was added Pd/C (10 wt%, 25 mg, 2 mmol) and the mixture heated at room temperature for overnight. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with 20% Et_2O in petrol to give *tert*-butyl 2-((3*R*)-3-((tert-butoxycarbonyl)amino)-3-isobutyl-5-methyl-2-oxopiperidin-1-yl)-acetate (**9k**) the major diastereomer (59 mg, 74%) as a colourless oil and the minor diastereomer (20 mg, 25%) as a colourless oil.

Major diastereomer: **FTIR** ν_{max} (thin film/cm^{-1}) 2961, 2253, 1708, 1646; **^{1}H NMR (400 MHz, $CDCl_3$)** δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47 (br, 1H, NH), 4.14 (d, J = 17.0 Hz, 1H, CH), 3.71 (d, J = 17.0 Hz, 1H, CH), 3.36 – 3.20 (m, 1H, CH), 3.17 – 2.95 (m, 1H, CH), 2.57 – 2.37 (m, 1H, CH), 2.32 – 2.19 (m, 1H, CH), 2.09 – 1.97(m, 2H, 2xCH), 1.91 – 1.78 (m, 1H, CH), 1.62 (dd, J = 14.5, 6.0 Hz, 1H, CH), 1.46 (s, 9H, $C(CH_3)_3$), 1.42 (s, 9H, $C(CH_3)_3$), 0.99 (d, J = 6.5 Hz, 3H, CH_3), 0.95 (d, J = 6.5 Hz, 3H, CH_3), 0.90 (d, J = 6.5 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.6, 168.1, 154.8, 81.7, 79.1, 58.3, 56.2, 49.9, 45.4, 39.6, 28.4, 28.1, 25.3, 24.5, 24.3, 23.7, 19.0; **MS (ESI$^+$)** 399 (100%, M+H$^+$); **HRMS (ESI$^+$)** $C_{21}H_{38}N_2O_5$ requires M+H$^+$ 399.2859, found 399.2857.

(*E*)-*N*-(5-benzylidene-3-isobutyl-2-oxopiperidin-3-yl)benzamide, 4b



Tert-butyl 5-methylene-2-oxo-6-phenyl-1,3-oxazinane-3-carboxylate (**10a**) (62 mg, 0.2 mmol), ligand **L1** (5 mg, 0.015 mmol), $\{\eta^3\text{-}C_3H_5PdCl\}_2$ (2 mg, 0.005 mmol), ^{t}BuOH (0.09 ml, 1.0 mmol) and DIPEA (0.03 ml, 0.4 mmol) were dissolved in dry 20% toluene in dioxane (2 mL) at 0 °C for 20 mins. Then methyl 2-(4-benzyl-5-oxo-4,5-dihydrooxazol-2-yl)benzoate (**1b**) (130 mg, 0.6 mmol) was added. The mixture was stirred at 0 °C overnight. The solvent was removed under reduced pressure give the crude product which was dissolved in dry DCM (2 mL). TFA (1.2 mL, 15 mmol) was added and the mixture stirred at room temperature. After 1 hour, EtOAc was added and the mixture was quenched with sat. aq. $NaHCO_3$. The layers were separated, and the aqueous layer was further extracted with 50% EtOAc. The solvent was removed under reduced pressure and residue purified by flash column chromatography eluting with EtOAc to give (*E*)-*N*-(5-benzylidene-3-isobutyl-2-oxopiperidin-3-yl)benzamide (**4b**) (60 mg, 83%, >99:1 E/Z) as a white solid.

FTIR ν_{max} (thin film/cm^{-1}) 3265, 2956, 1643, 1602; **^{1}H NMR (400 MHz, $CDCl_3$)** δ ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 – 7.71 (m, 2H, CH_{Ar}), 7.56 (s, 1H, NH), 7.47 – 7.40 (m, 1H, CH_{Ar}), 7.40 – 7.33 (m, 2H, CH_{Ar}), 7.34 – 7.27 (m, 2H, CH_{Ar}), 7.26 – 7.17 (m, 3H, CH_{Ar}), 6.73 (s, 1H, C=CH), 6.47 (s, 1H, NH), 4.19 (d, J = 15.5 Hz, 1H, CH), 4.12 (d, J = 15.5 Hz, 1H, CH), 4.05 (d, J = 15.5 Hz, 1H, CH), 2.74 (d, J = 15.5 Hz, 1H, CH), 2.25 – 2.15 (m, 1H, CH), 1.64 – 1.47 (m, 2H, 2xCH), 0.79 (d, J = 6.0 Hz, 3H, CH_3), 0.75 (d, J = 6.0 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 174.0, 166.4, 136.0, 134.9, 131.5, 129.7, 128.8, 128.6, 128.5, 127.5, 127.2, 127.0, 59.2, 48.0, 42.1, 35.3, 24.4, 24.0, 23.8; **MS (ESI^+)** 363 (100%, $M+H^+$); **HRMS (ESI^+)** $C_{23}H_{27}N_2O_2$ requires $M+H^+$ 363.2073, found 363.2077.

X-ray crystallographic analysis for compound 6a (OJH420v_0m)

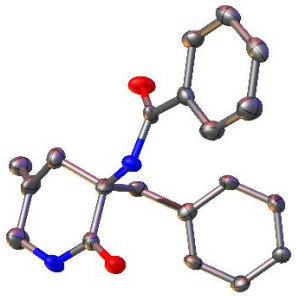


Table 1 Crystal data and structure refinement for 6a.

Identification code	OJH420v_0m
Empirical formula	$C_{20.25}H_{20.5}Cl_{0.5}N_2O_2$
Formula weight	341.61
Temperature/K	99.99
Crystal system	monoclinic
Space group	C2
a/Å	13.6360(5)
b/Å	13.6561(5)
c/Å	20.1817(8)
α/°	90
β/°	94.189(2)
γ/°	90
Volume/Å^3	3748.1(2)
Z	8
ρ_{calc}g/cm^3	1.211
μ/mm^{-1}	1.261
F(000)	1444.0
Crystal size/mm^3	0.5 × 0.098 × 0.06
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	4.39 to 133.618
Index ranges	$-14 \leq h \leq 16$, $-16 \leq k \leq 14$, $-24 \leq l \leq 23$
Reflections collected	27279
Independent reflections	6456 [R_{int} = 0.0436, R_{sigma} = 0.0360]
Data/restraints/parameters	6456/3/463
Goodness-of-fit on F^2	1.165
Final R indexes [I>=2σ (I)]	R_1 = 0.0671, wR_2 = 0.1742
Final R indexes [all data]	R_1 = 0.0682, wR_2 = 0.1750
Largest diff. peak/hole / e Å^{-3}	0.49/-0.31
Flack parameter	0.095(14)

Table 2 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for 6a. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
O1	7828(3)	5499(3)	5854(2)	30.8(9)
O2	8884(3)	2187(3)	5514(2)	36.3(11)
N1	6990(4)	5428(4)	4857(3)	35.3(13)
N2	8663(3)	3792(3)	5751(2)	23.8(10)
C1	7552(4)	5034(4)	5359(3)	26.8(13)
C2	7792(4)	3937(4)	5296(3)	26.2(13)
C3	7997(5)	3714(5)	4571(3)	31.5(14)
C4	7106(5)	3975(5)	4125(3)	36.9(15)
C5	6790(6)	5034(5)	4181(3)	43.8(18)
C6	9117(4)	2917(4)	5849(3)	23.5(12)
C7	9928(4)	2865(4)	6390(3)	23.9(12)
C8	10569(4)	2066(4)	6360(3)	27.2(13)
C9	11329(4)	1955(4)	6848(3)	32.0(14)
C10	11460(4)	2617(5)	7364(3)	31.4(14)
C11	10829(5)	3397(5)	7393(3)	38.6(15)
C12	10069(5)	3535(5)	6896(3)	33.3(14)
C13	6914(4)	3323(4)	5495(3)	27.7(13)
C14	6677(4)	3412(4)	6216(3)	26.0(12)
C15	6094(4)	4163(4)	6421(3)	28.7(13)
C16	5853(4)	4225(4)	7081(3)	27.6(13)
C17	6217(4)	3551(4)	7539(3)	25.0(12)
C18	6806(5)	2788(5)	7340(3)	30.8(13)
C19	7035(5)	2721(4)	6683(3)	32.7(14)
C20	6652(5)	3359(5)	3713(3)	41.7(16)
O3	7179(3)	7856(3)	9224(2)	25.6(9)
O4	6214(3)	4471(3)	9331(2)	26.1(9)
N3	8116(4)	7654(4)	10185(3)	26.3(11)
N4	6402(3)	6110(3)	9234(2)	19.3(9)
C21	7518(4)	7326(4)	9676(3)	20.3(11)
C22	7303(4)	6217(4)	9663(3)	20.5(11)
C23	7183(4)	5858(4)	10379(3)	21.0(11)
C24	8098(4)	6110(5)	10806(3)	26.2(12)
C25	8343(5)	7174(5)	10826(3)	33.7(14)
C26	5928(4)	5266(4)	9096(3)	19.2(11)
C27	5031(4)	5311(4)	8625(3)	18.4(10)
C28	4399(4)	4512(4)	8611(3)	22.1(11)
C29	3557(4)	4504(5)	8180(3)	31.0(14)
C30	3344(4)	5278(5)	7753(3)	29.9(13)
C31	3969(4)	6082(5)	7768(3)	31.9(14)

Table 2 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for 6a. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
C32	4800(4)	6101(4)	8204(3)	23.1(11)
C33	8178(4)	5665(4)	9392(3)	20.7(11)
C34	8362(4)	5846(4)	8675(3)	20.2(11)
C35	8896(4)	6677(4)	8490(3)	23.9(12)
C36	9097(4)	6808(4)	7834(3)	27.6(13)
C37	8777(4)	6134(5)	7353(3)	28.1(13)
C38	8241(4)	5326(5)	7530(3)	26.5(12)
C39	8051(4)	5192(4)	8189(3)	22.6(11)
C40	8640(5)	5437(5)	11147(3)	33.4(14)
Cl1	4490.6(12)	8097.2(12)	9333.6(9)	41.2(4)
C41	5000	8768(8)	10000	73(5)

Table 3 Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for 6a. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	42(2)	24(2)	26(2)	-4.0(17)	-1.9(18)	5.7(18)
O2	38(2)	25(2)	43(3)	-15(2)	-10(2)	4.0(19)
N1	58(4)	22(3)	25(3)	0(2)	-6(2)	11(2)
N2	28(2)	17(2)	26(2)	-2.0(18)	-2(2)	2.0(18)
C1	34(3)	25(3)	22(3)	3(2)	3(2)	3(2)
C2	24(3)	31(3)	23(3)	0(2)	1(2)	9(2)
C3	33(3)	38(4)	23(3)	-1(2)	1(2)	1(3)
C4	47(4)	44(4)	19(3)	-10(3)	-1(3)	8(3)
C5	62(5)	39(4)	28(3)	-4(3)	-11(3)	11(3)
C6	39(3)	16(3)	15(3)	-1(2)	-3(2)	0(2)
C7	25(3)	23(3)	24(3)	5(2)	2(2)	1(2)
C8	31(3)	19(3)	32(3)	-5(2)	5(2)	0(2)
C9	28(3)	24(3)	44(4)	7(3)	3(3)	2(2)
C10	25(3)	32(3)	37(4)	12(3)	-1(3)	-2(2)
C11	45(4)	36(4)	34(3)	-9(3)	-4(3)	4(3)
C12	36(3)	27(3)	36(3)	-6(3)	0(3)	7(3)
C13	38(3)	19(3)	26(3)	-9(2)	-5(2)	3(2)
C14	22(3)	29(3)	27(3)	-7(2)	0(2)	-3(2)
C15	36(3)	18(3)	31(3)	1(2)	-4(2)	8(2)
C16	27(3)	25(3)	32(3)	-1(2)	9(2)	3(2)
C17	31(3)	18(3)	26(3)	-4(2)	2(2)	-2(2)
C18	37(3)	27(3)	28(3)	5(2)	1(3)	6(2)
C19	44(4)	21(3)	32(3)	-1(2)	0(3)	13(3)
C20	51(4)	40(4)	33(3)	-8(3)	-6(3)	12(3)
O3	26(2)	16(2)	34(2)	4.4(16)	-0.2(17)	-1.1(15)

Table 3 Anisotropic Displacement Parameters ($Å^2×10^3$) for 6a. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O4	28(2)	8.4(18)	40(2)	2.2(16)	-9.2(17)	-1.3(15)
N3	33(3)	13(3)	32(3)	-7(2)	-2(2)	-4(2)
N4	22(2)	9(2)	26(2)	-2.5(17)	-1.9(18)	0.9(17)
C21	19(3)	12(3)	30(3)	-3(2)	2(2)	0(2)
C22	27(3)	11(3)	23(3)	1(2)	-3(2)	3(2)
C23	25(3)	14(3)	25(3)	-3(2)	2(2)	-1(2)
C24	32(3)	29(3)	18(3)	-2(2)	0(2)	-2(2)
C25	36(3)	35(4)	30(3)	-12(3)	-4(3)	-7(3)
C26	21(3)	12(3)	25(3)	1(2)	4(2)	4(2)
C27	17(2)	18(3)	20(2)	-4(2)	3(2)	3(2)
C28	22(3)	9(2)	36(3)	1(2)	4(2)	0(2)
C29	21(3)	33(3)	39(3)	-10(3)	3(2)	-3(2)
C30	23(3)	39(4)	28(3)	-5(3)	-1(2)	1(3)
C31	27(3)	37(3)	32(3)	13(3)	3(2)	8(3)
C32	24(3)	23(3)	22(3)	-6(2)	4(2)	2(2)
C33	19(3)	14(3)	29(3)	-1(2)	-3(2)	-0.1(19)
C34	19(3)	19(3)	22(3)	0(2)	-1(2)	8(2)
C35	15(2)	19(3)	38(3)	-3(2)	1(2)	-2(2)
C36	25(3)	24(3)	35(3)	7(2)	8(2)	0(2)
C37	23(3)	35(3)	26(3)	6(2)	3(2)	8(2)
C38	25(3)	33(3)	21(3)	-3(2)	-1(2)	3(2)
C39	23(3)	19(3)	26(3)	2(2)	0(2)	1(2)
C40	32(3)	37(4)	30(3)	7(3)	-7(3)	-9(3)
Cl1	36.0(8)	36.3(9)	50.9(9)	-10.4(7)	1.6(7)	-0.6(7)
C41	152(14)	20(5)	39(6)	0	-44(7)	0

Table 4 Bond Lengths for 6a.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O1	C1	1.220(7)	O4	C26	1.236(7)
O2	C6	1.233(7)	N3	C21	1.340(8)
N1	C1	1.338(8)	N3	C25	1.463(9)
N1	C5	1.473(8)	N4	C22	1.457(7)
N2	C2	1.460(7)	N4	C26	1.341(7)
N2	C6	1.353(7)	C21	C22	1.542(7)
C1	C2	1.541(8)	C22	C23	1.547(7)
C2	C3	1.540(8)	C22	C33	1.545(7)
C2	C13	1.538(9)	C23	C24	1.503(8)
C3	C4	1.502(9)	C24	C25	1.490(9)
C4	C5	1.515(10)	C24	C40	1.339(9)
C4	C20	1.306(10)	C26	C27	1.495(7)

Table 4 Bond Lengths for 6a.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
C6	C7	1.498(7)	C27	C28	1.389(7)
C7	C8	1.402(8)	C27	C32	1.394(8)
C7	C12	1.376(8)	C28	C29	1.390(8)
C8	C9	1.386(9)	C29	C30	1.382(9)
C9	C10	1.380(10)	C30	C31	1.389(9)
C10	C11	1.373(9)	C31	C32	1.383(8)
C11	C12	1.400(9)	C33	C34	1.508(8)
C13	C14	1.518(8)	C34	C35	1.413(8)
C14	C15	1.379(8)	C34	C39	1.371(8)
C14	C19	1.396(8)	C35	C36	1.384(9)
C15	C16	1.397(8)	C36	C37	1.385(9)
C16	C17	1.372(8)	C37	C38	1.385(9)
C17	C18	1.392(8)	C38	C39	1.386(8)
C18	C19	1.389(9)	Cl1	C41	1.730(6)
O3	C21	1.228(7)			

Table 5 Bond Angles for 6a.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C1	N1	C5	127.6(6)	C26	N4	C22	125.6(4)
C6	N2	C2	123.6(5)	O3	C21	N3	123.2(5)
O1	C1	N1	122.4(6)	O3	C21	C22	120.3(5)
O1	C1	C2	121.3(5)	N3	C21	C22	116.5(5)
N1	C1	C2	116.3(5)	N4	C22	C21	105.1(4)
N2	C2	C1	104.3(5)	N4	C22	C23	112.4(4)
N2	C2	C3	112.0(5)	N4	C22	C33	112.4(4)
N2	C2	C13	112.1(5)	C21	C22	C23	109.1(4)
C3	C2	C1	108.9(5)	C21	C22	C33	109.5(4)
C13	C2	C1	109.5(5)	C33	C22	C23	108.2(4)
C13	C2	C3	109.8(5)	C24	C23	C22	108.8(4)
C4	C3	C2	109.2(5)	C25	C24	C23	114.4(5)
C3	C4	C5	113.8(6)	C40	C24	C23	122.8(6)
C20	C4	C3	123.7(6)	C40	C24	C25	122.8(5)
C20	C4	C5	122.6(6)	N3	C25	C24	112.3(5)
N1	C5	C4	112.6(5)	O4	C26	N4	122.8(5)
O2	C6	N2	122.5(5)	O4	C26	C27	120.1(5)
O2	C6	C7	120.5(5)	N4	C26	C27	117.1(4)
N2	C6	C7	117.0(5)	C28	C27	C26	117.2(5)
C8	C7	C6	115.8(5)	C28	C27	C32	118.9(5)
C12	C7	C6	124.5(5)	C32	C27	C26	123.9(5)
C12	C7	C8	119.7(5)	C27	C28	C29	120.1(5)
C9	C8	C7	119.4(6)	C30	C29	C28	120.7(6)

Table 5 Bond Angles for 6a.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C10	C9	C8	120.9(6)	C29	C30	C31	119.4(5)
C11	C10	C9	119.5(6)	C32	C31	C30	120.0(6)
C10	C11	C12	120.5(6)	C31	C32	C27	120.8(5)
C7	C12	C11	119.9(6)	C34	C33	C22	116.5(4)
C14	C13	C2	115.5(5)	C35	C34	C33	120.7(5)
C15	C14	C13	121.0(5)	C39	C34	C33	121.0(5)
C15	C14	C19	118.6(5)	C39	C34	C35	118.3(5)
C19	C14	C13	120.3(5)	C36	C35	C34	119.9(5)
C14	C15	C16	120.9(6)	C35	C36	C37	120.6(5)
C17	C16	C15	120.1(5)	C38	C37	C36	119.6(5)
C16	C17	C18	119.8(5)	C37	C38	C39	119.6(6)
C19	C18	C17	119.9(5)	C34	C39	C38	122.0(5)
C18	C19	C14	120.6(5)	Cl1[1]	C41	Cl1	116.1(6)
C21	N3	C25	127.2(5)				

[1]1-X,+Y,2-Z

Table 6 Hydrogen Bonds for 6a.

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
N1	H1	O2[1]	0.81(7)	2.07(7)	2.760(7)	142(6)
N3	H3	O4[2]	0.85(9)	2.04(8)	2.796(6)	148(7)

[1]3/2-X,1/2+Y,1-Z; [2]3/2-X,1/2+Y,2-Z

Table 7 Torsion Angles for 6a.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
O1	C1	C2	N2	-23.3(7)	O3	C21	C22	N4	-22.8(7)
O1	C1	C2	C3	-143.1(6)	O3	C21	C22	C23	-143.6(5)
O1	C1	C2	C13	96.8(7)	O3	C21	C22	C33	98.1(6)
O2	C6	C7	C8	18.0(8)	O4	C26	C27	C28	17.6(7)
O2	C6	C7	C12	-161.8(6)	O4	C26	C27	C32	-162.2(5)
N1	C1	C2	N2	159.8(5)	N3	C21	C22	N4	159.9(5)
N1	C1	C2	C3	40.0(7)	N3	C21	C22	C23	39.1(6)
N1	C1	C2	C13	-80.1(7)	N3	C21	C22	C33	-79.2(6)
N2	C2	C3	C4	-174.3(5)	N4	C22	C23	C24	-173.0(4)
N2	C2	C13	C14	50.4(7)	N4	C22	C33	C34	50.0(6)
N2	C6	C7	C8	-162.0(5)	N4	C26	C27	C28	-163.7(5)
N2	C6	C7	C12	18.2(8)	N4	C26	C27	C32	16.5(7)
C1	N1	C5	C4	13.2(11)	C21	N3	C25	C24	18.4(9)
C1	C2	C3	C4	-59.4(7)	C21	C22	C23	C24	-56.8(6)

Table 7 Torsion Angles for 6a.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
C1	C2	C13	C14	-64.9(6)	C21	C22	C33	C34	-66.4(6)
C2	N2	C6	O2	7.0(9)	C22	N4	C26	O4	0.6(8)
C2	N2	C6	C7	-173.0(5)	C22	N4	C26	C27	-178.1(5)
C2	C3	C4	C5	57.6(8)	C22	C23	C24	C25	58.1(6)
C2	C3	C4	C20	-123.9(7)	C22	C23	C24	C40	-122.9(6)
C2	C13	C14	C15	84.7(7)	C22	C33	C34	C35	82.6(6)
C2	C13	C14	C19	-96.3(7)	C22	C33	C34	C39	-100.0(6)
C3	C2	C13	C14	175.6(5)	C23	C22	C33	C34	174.7(4)
C3	C4	C5	N1	-32.8(9)	C23	C24	C25	N3	-36.9(7)
C5	N1	C1	O1	165.2(7)	C25	N3	C21	O3	162.0(6)
C5	N1	C1	C2	-17.9(10)	C25	N3	C21	C22	-20.8(8)
C6	N2	C2	C1	179.7(5)	C26	N4	C22	C21	-178.0(5)
C6	N2	C2	C3	-62.6(7)	C26	N4	C22	C23	-59.4(7)
C6	N2	C2	C13	61.3(7)	C26	N4	C22	C33	63.0(7)
C6	C7	C8	C9	-178.9(5)	C26	C27	C28	C29	-179.4(5)
C6	C7	C12	C11	177.5(6)	C26	C27	C32	C31	178.2(5)
C7	C8	C9	C10	0.3(9)	C27	C28	C29	C30	1.1(9)
C8	C7	C12	C11	-2.3(9)	C28	C27	C32	C31	-1.6(8)
C8	C9	C10	C11	-0.2(10)	C28	C29	C30	C31	-1.5(9)
C9	C10	C11	C12	-1.2(10)	C29	C30	C31	C32	0.3(9)
C10	C11	C12	C7	2.5(10)	C30	C31	C32	C27	1.2(9)
C12	C7	C8	C9	0.9(9)	C32	C27	C28	C29	0.4(8)
C13	C2	C3	C4	60.5(7)	C33	C22	C23	C24	62.3(6)
C13	C14	C15	C16	178.0(5)	C33	C34	C35	C36	177.0(5)
C13	C14	C19	C18	-178.9(6)	C33	C34	C39	C38	-177.7(5)
C14	C15	C16	C17	1.8(9)	C34	C35	C36	C37	0.2(8)
C15	C14	C19	C18	0.2(9)	C35	C34	C39	C38	-0.3(8)
C15	C16	C17	C18	-1.8(9)	C35	C36	C37	C38	0.7(8)
C16	C17	C18	C19	1.0(9)	C36	C37	C38	C39	-1.4(8)
C17	C18	C19	C14	-0.2(10)	C37	C38	C39	C34	1.2(8)
C19	C14	C15	C16	-1.0(9)	C39	C34	C35	C36	-0.5(8)
C20	C4	C5	N1	148.7(7)	C40	C24	C25	N3	144.2(6)

Table 8 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for 6a.

Atom	*x*	*y*	*z*	U(eq)
H1	6850(50)	5990(60)	4920(30)	26(18)
H2	8850(30)	4370(20)	6030(20)	0(11)
H3A	8569.51	4099.83	4445.48	38
H3B	8151.26	3010.65	4522.75	38
H5A	7142.32	5435.17	3865.85	53

Table 8 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for 6a.

Atom	*x*	*y*	*z*	U(eq)
H5B	6077.35	5085.27	4053.2	53
H8	10483.34	1605.3	6008.16	33
H9	11766.9	1416.32	6827.9	38
H10	11981.92	2532.84	7697.66	38
H11	10908.53	3846.81	7751.78	46
H12	9651.83	4090.91	6909.57	40
H13A	6325.4	3518.69	5209.29	33
H13B	7047.9	2626.58	5400.43	33
H15	5854.61	4643.58	6110.38	34
H16	5435.25	4735.75	7212.16	33
H17	6067.02	3604.25	7989.69	30
H18	7051.26	2313.94	7654.72	37
H19	7438.61	2201.06	6549.25	39
H20A	6882.71	2705.29	3684.71	50
H20B	6090.27	3564.96	3442.6	50
H3	8140(50)	8270(70)	10220(40)	40(20)
H4	6140(40)	6710(30)	9010(30)	19(15)
H23A	6605.59	6176.78	10557.47	25
H23B	7076.95	5140.78	10380.14	25
H25A	7967.69	7496.73	11166.8	40
H25B	9051.57	7254.39	10958.5	40
H28	4543.94	3970.23	8897.12	27
H29	3122.44	3959.47	8179.1	37
H30	2774.95	5260.93	7452.23	36
H31	3826.78	6619.34	7477.33	38
H32	5217.52	6658.1	8217.31	28
H33A	8781.4	5844.22	9668.86	25
H33B	8071.61	4954.52	9451	25
H35	9116.43	7144.58	8816.18	29
H36	9458.84	7366.89	7712.14	33
H37	8924.57	6225.16	6904.24	34
H38	8005.8	4867.24	7202.6	32
H39	7693.71	4628.78	8308.03	27
H40A	9207.51	5630.06	11417.22	40
H40B	8458	4765.75	11120.2	40
H41A	5517.18	9197.45	9838.95	87
H41B	4482.8	9197.43	10161.06	87

Table 9 Atomic Occupancy for 6a

Atom	*Occupancy*	Atom	*Occupancy*	Atom	*Occupancy*

Table 9 Atomic Occupancy for 6a

Atom	*Occupancy*	Atom	*Occupancy*	Atom	*Occupancy*
H41A	0.5	H41B	0.5		

Table 10 Solvent masks information for 6a.

Number	X	Y	Z	Volume	Electron count	Content
1	0.000	0.012	0.500	15.1	0.0	
2	0.000	0.605	0.500	151.9	54.1	1 hexane
3	0.000	0.694	0.000	7.2	0.0	
4	0.500	0.105	0.500	151.9	54.0	1 hexane
5	0.500	0.194	0.000	7.2	0.0	
6	0.500	0.512	0.500	15.1	0.0	

Crystal structure determination of 3

Crystal Data for $C_{20.25}H_{20.5}Cl_{0.5}N_2O_2$ (*M* =341.61 g/mol): monoclinic, space group C2 (no. 5), *a* = 13.6360(5) Å, *b* = 13.6561(5) Å, *c* = 20.1817(8) Å, *β* = 94.189(2)°, *V* = 3748.1(2) Å^3, *Z* = 8, *T* = 99.99 K, μ(CuKα) = 1.261 mm^{-1}, *Dcalc* = 1.211 g/cm^3, 27279 reflections measured (4.39° ≤ 2Θ ≤ 133.618°), 6456 unique (R_{int} = 0.0436, R_{sigma} = 0.0360) which were used in all calculations. The final R_1 was 0.0671 (I > 2σ(I)) and wR_2 was 0.1750 (all data).

X-ray crystallographic analysis for compound 6b (2022ncs0016z)

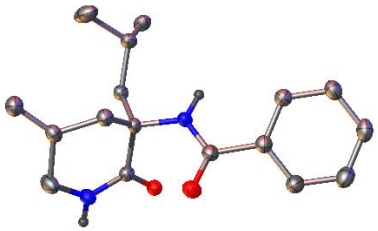


Table 1 Crystal data and structure refinement for 6b.

Identification code	2022ncs0016z
Empirical formula	$C_{17}H_{22}N_2O_2$
Formula weight	286.36
Temperature/K	100(2)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	8.04670(10)
b/Å	11.0689(2)
c/Å	17.3352(4)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1544.01(5)
Z	4
ρ_{calc}g/cm^3	1.232
μ/mm^{-1}	0.647
F(000)	616.0
Crystal size/mm^3	0.21 × 0.02 × 0.01
Radiation	Cu Kα (λ = 1.54178)
2Θ range for data collection/°	9.48 to 153.196
Index ranges	$-6 \le h \le 9$, $-13 \le k \le 13$, $-21 \le l \le 21$
Reflections collected	22416
Independent reflections	3130 [R_{int} = 0.0514, R_{sigma} = 0.0263]
Data/restraints/parameters	3130/0/192
Goodness-of-fit on F^2	1.077
Final R indexes [I>=2σ (I)]	R_1 = 0.0407, wR_2 = 0.0960
Final R indexes [all data]	R_1 = 0.0471, wR_2 = 0.1009
Largest diff. peak/hole / e Å^{-3}	0.25/-0.24
Flack parameter	0.21(11)

Table 2 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for 6b. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
O1	5347(2)	7635.3(15)	5011.0(12)	26.4(4)
O2	4763(2)	8089.0(17)	6742.9(11)	30.9(4)
N1	7249(3)	6401(2)	5544.7(13)	27.9(5)
N2	2977(3)	6903.7(19)	6062.9(13)	25.1(5)
C1	5696(3)	6777(2)	5450.3(16)	25.0(5)
C2	4277(3)	6055(2)	5826.0(15)	23.6(5)
C3	4880(3)	5326(2)	6526.9(16)	27.5(6)
C4	6435(3)	4643(2)	6335.6(16)	26.7(6)
C5	7812(3)	5419(3)	6046.7(19)	36.8(7)
C6	3357(3)	7888(2)	6496.4(16)	25.6(5)
C7	1927(3)	8722(2)	6661.4(15)	26.4(5)
C8	2253(4)	9953(2)	6753.0(16)	30.9(6)
C9	968(4)	10739(3)	6931.1(18)	34.9(6)
C10	-635(4)	10312(3)	7034.2(17)	34.6(7)
C11	-968(4)	9084(3)	6947.6(17)	31.8(6)
C12	317(3)	8306(2)	6757.8(16)	28.4(6)
C13	3596(3)	5260(2)	5165.9(16)	25.7(6)
C14	2028(3)	4497(2)	5326.7(17)	28.6(6)
C15	2424(4)	3201(3)	5580(2)	47.6(8)
C16	964(4)	4448(2)	4601.5(19)	35.6(7)
C17	6646(4)	3468(2)	6446.3(18)	33.4(6)

Table 3 Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for 6b. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	22.3(9)	22.8(8)	34.1(10)	2.9(7)	0.1(8)	0.4(7)
O2	23.4(10)	32.0(9)	37.4(11)	-3.9(8)	-0.5(8)	-2.2(8)
N1	18.9(11)	27.2(11)	37.5(13)	5.7(10)	1.6(9)	-0.6(9)
N2	17.5(10)	21.5(10)	36.4(12)	-2.3(9)	0.6(9)	-0.5(8)
C1	22.6(13)	20.9(11)	31.4(14)	-1.0(11)	-0.7(11)	-0.4(10)
C2	17.3(12)	20.5(11)	33.0(15)	-0.2(10)	1.2(10)	2.2(10)
C3	23.6(13)	25.5(12)	33.5(15)	1.3(11)	1.2(11)	1.6(11)
C4	19.8(12)	29.4(13)	30.8(14)	0.7(11)	-2.0(10)	1.4(11)
C5	22.6(13)	38.2(15)	49.7(18)	14.2(14)	-3.1(12)	1.5(12)
C6	22.1(13)	24.0(12)	30.6(14)	1.8(11)	2.4(11)	-0.8(10)
C7	25.4(13)	24.9(12)	28.9(13)	0.3(10)	1.4(11)	1.3(11)
C8	29.9(14)	26.7(13)	36.0(15)	-2.3(11)	4.1(12)	-1.6(11)
C9	42.5(16)	24.8(13)	37.4(16)	-0.1(12)	5.2(13)	3.0(12)

Table 3 Anisotropic Displacement Parameters ($Å^2×10^3$) for 6b. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C10	35.1(16)	31.0(14)	37.6(16)	-0.8(12)	2.3(12)	11.7(13)
C11	24.4(14)	34.1(14)	37.1(16)	-2.5(12)	2.2(12)	3.8(12)
C12	26.3(13)	25.5(12)	33.5(15)	-0.9(11)	1.4(11)	-0.1(11)
C13	20.3(12)	24.2(12)	32.6(14)	-0.5(11)	0.1(10)	0.8(10)
C14	22.5(13)	24.5(13)	38.7(15)	-2.4(11)	0.7(11)	-2.6(11)
C15	45.2(19)	31.7(15)	66(2)	11.9(15)	-17.3(17)	-12.1(14)
C16	30.5(14)	24.3(13)	52.0(18)	-0.5(13)	-7.2(13)	-3.0(11)
C17	29.5(14)	29.8(14)	41.0(16)	1.5(12)	-1.2(13)	4.2(12)

Table 4 Bond Lengths for 6b.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O1	C1	1.250(3)	C4	C17	1.326(4)
O2	C6	1.230(3)	C6	C7	1.503(4)
N1	C1	1.327(3)	C7	C8	1.397(4)
N1	C5	1.464(3)	C7	C12	1.385(4)
N2	C2	1.464(3)	C8	C9	1.386(4)
N2	C6	1.358(3)	C9	C10	1.385(4)
C1	C2	1.538(3)	C10	C11	1.394(4)
C2	C3	1.537(4)	C11	C12	1.385(4)
C2	C13	1.545(4)	C13	C14	1.543(3)
C3	C4	1.499(4)	C14	C15	1.533(4)
C4	C5	1.488(4)	C14	C16	1.522(4)

Table 5 Bond Angles for 6b.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C1	N1	C5	126.7(2)	O2	C6	N2	123.0(2)
C6	N2	C2	120.6(2)	O2	C6	C7	121.8(2)
O1	C1	N1	121.7(2)	N2	C6	C7	115.2(2)
O1	C1	C2	119.1(2)	C8	C7	C6	118.5(2)
N1	C1	C2	118.9(2)	C12	C7	C6	122.3(2)
N2	C2	C1	108.43(19)	C12	C7	C8	119.1(3)
N2	C2	C3	109.9(2)	C9	C8	C7	119.8(3)
N2	C2	C13	108.7(2)	C10	C9	C8	120.6(3)
C1	C2	C13	104.2(2)	C9	C10	C11	119.9(3)
C3	C2	C1	111.9(2)	C12	C11	C10	119.2(3)
C3	C2	C13	113.5(2)	C7	C12	C11	121.3(2)
C4	C3	C2	110.7(2)	C14	C13	C2	117.9(2)
C5	C4	C3	113.9(2)	C15	C14	C13	113.2(2)
C17	C4	C3	124.7(3)	C16	C14	C13	109.3(2)

Table 5 Bond Angles for 6b.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C17	C4	C5	121.3(3)	C16	C14	C15	108.7(2)
N1	C5	C4	113.5(2)				

Table 6 Hydrogen Bonds for 6b.

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
N1	H1	O1[1]	0.88	2.04	2.878(3)	157.7
N2	H2	O1[2]	0.88	2.17	2.864(3)	135.9

[1]1/2+X,3/2-Y,1-Z; [2]-1/2+X,3/2-Y,1-Z

Table 7 Torsion Angles for 6b.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
O1	C1	C2	N2	-40.5(3)	C2	C13	C14	C15	-94.5(3)
O1	C1	C2	C3	-161.8(2)	C2	C13	C14	C16	144.3(2)
O1	C1	C2	C13	75.2(3)	C3	C2	C13	C14	63.8(3)
O2	C6	C7	C8	30.9(4)	C3	C4	C5	N1	-37.9(3)
O2	C6	C7	C12	-146.2(3)	C5	N1	C1	O1	179.3(3)
N1	C1	C2	N2	145.7(2)	C5	N1	C1	C2	-7.1(4)
N1	C1	C2	C3	24.4(3)	C6	N2	C2	C1	-51.4(3)
N1	C1	C2	C13	-98.7(3)	C6	N2	C2	C3	71.2(3)
N2	C2	C3	C4	-168.3(2)	C6	N2	C2	C13	-164.1(2)
N2	C2	C13	C14	-58.8(3)	C6	C7	C8	C9	-177.8(3)
N2	C6	C7	C8	-149.4(3)	C6	C7	C12	C11	176.7(3)
N2	C6	C7	C12	33.4(4)	C7	C8	C9	C10	1.3(4)
C1	N1	C5	C4	13.3(4)	C8	C7	C12	C11	-0.4(4)
C1	C2	C3	C4	-47.8(3)	C8	C9	C10	C11	-0.9(5)
C1	C2	C13	C14	-174.3(2)	C9	C10	C11	C12	-0.1(5)
C2	N2	C6	O2	-3.7(4)	C10	C11	C12	C7	0.7(4)
C2	N2	C6	C7	176.6(2)	C12	C7	C8	C9	-0.6(4)
C2	C3	C4	C5	56.1(3)	C13	C2	C3	C4	69.8(3)
C2	C3	C4	C17	-127.5(3)	C17	C4	C5	N1	145.6(3)

Table 8 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for 6b.

Atom	*x*	*y*	*z*	U(eq)
H1	8019.59	6780.16	5278.07	33
H2	1940.77	6774.81	5923.15	30
H3A	5098.7	5881.52	6963.04	33

Table 8 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for 6b.

Atom	*x*	*y*	*z*	U(eq)
H3B	4002.91	4752.18	6687.46	33
H5A	8407.72	5770.04	6493.34	44
H5B	8609.69	4909.28	5758.53	44
H8	3353	10251.16	6693.46	37
H9	1188.27	11578.13	6982.92	42
H10	-1505.14	10855.37	7163.8	42
H11	-2063.98	8784.02	7017.8	38
H12	89.41	7470.03	6692.42	34
H13A	3353.73	5793.07	4721.47	31
H13B	4492.74	4702.2	5004.31	31
H14	1374.07	4898.58	5744.74	34
H15A	3101.64	2805.71	5183.39	71
H15B	1386.33	2751.59	5649.32	71
H15C	3038.67	3218.84	6067.59	71
H16A	613.16	5267.13	4461.73	53
H16B	-18.7	3947.1	4697.92	53
H16C	1611.6	4098.31	4178.08	53
H17A	7691.73	3105.36	6340.81	40
H17B	5751.51	2988.64	6631.16	40

Crystal structure determination of 6b

Crystal Data for $C_{17}H_{22}N_2O_2$ (*M* =286.36 g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), *a* = 8.04670(10) Å, *b* = 11.0689(2) Å, *c* = 17.3352(4) Å, *V* = 1544.01(5) Å^3, *Z* = 4, *T* = 100(2) K, μ(Cu Kα) = 0.647 mm^{-1}, *Dcalc* = 1.232 g/cm^3, 22416 reflections measured (9.48° ≤ 2Θ ≤ 153.196°), 3130 unique (R_{int} = 0.0514, R_{sigma} = 0.0263) which were used in all calculations. The final R_1 was 0.0407 (I > 2σ(I)) and wR_2 was 0.1009 (all data).

X-ray crystallographic analysis for compound 8g (ojh419ncs_2022ncs0294_1a)

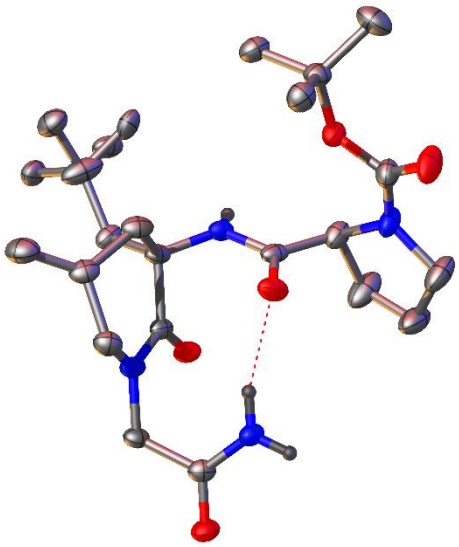


Table 1 Crystal data and structure refinement for 8g.

Identification code	ojh419ncs_2022ncs0294_1a
Empirical formula	$C_{22}H_{36}N_4O_5$
Formula weight	436.55
Temperature/K	100.00(10)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	10.3188(3)
b/Å	14.5578(5)
c/Å	16.1464(4)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2425.50(12)
Z	4
ρ_{calc}g/cm^3	1.195
μ/mm^{-1}	0.695
F(000)	944.0
Crystal size/mm^3	0.19 × 0.025 × 0.02
Radiation	Cu Kα (λ = 1.54178)
2Θ range for data collection/°	8.178 to 136.476
Index ranges	$-12 \le h \le 12$, $-11 \le k \le 17$, $-18 \le l \le 19$
Reflections collected	18854
Independent reflections	4443 [R_{int} = 0.0292, R_{sigma} = 0.0252]
Data/restraints/parameters	4443/7/318
Goodness-of-fit on F^2	1.022
Final R indexes [I>=2σ (I)]	R_1 = 0.0442, wR_2 = 0.1086
Final R indexes [all data]	R_1 = 0.0474, wR_2 = 0.1110

Largest diff. peak/hole / e Å^{-3}	0.52/-0.51
Flack parameter	0.11(6)

Table 2 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for 8g. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
O1	3269(2)	6966.3(16)	4973.2(12)	28.1(5)
O2	131(2)	6112.9(17)	6294.7(13)	32.8(5)
O3	1410(2)	7154.4(17)	3396.2(13)	33.7(5)
O4	3(2)	8500.9(19)	1359.8(15)	45.4(7)
O5	2114(2)	8064.1(16)	1552.7(12)	28.4(5)
N1	2450(2)	5573.5(19)	4673.4(14)	24.4(5)
N2	170(2)	6578.3(19)	4956.0(16)	25.9(6)
N3	3593(2)	7312.3(19)	3310.3(15)	25.1(5)
N4	1111(3)	8822(2)	2542.1(17)	33.2(7)
C1	3132(3)	6331(2)	4472.5(17)	23.8(6)
C2	3824(3)	6386(2)	3621.1(17)	24.6(6)
C3	3325(3)	5671(2)	2986.1(18)	29.6(7)
C4	3042(3)	4774(2)	3399.4(18)	28.2(7)
C5	2061(3)	4866(2)	4075.7(19)	29.0(7)
C6	1852(3)	5552(2)	5489.9(17)	26.3(6)
C7	631(3)	6120(2)	5600.0(18)	25.3(6)
C8	2368(3)	7640(2)	3268.2(17)	27.7(7)
C9	2232(3)	8656(2)	3076.2(19)	31.9(7)
C10	1893(4)	9218(3)	3852(3)	54.9(12)
C11	482(4)	9354(4)	3827(2)	50.8(11)
C12	23(4)	9258(3)	2967(2)	49.1(10)
C13	980(3)	8458(2)	1780(2)	32.3(7)
C14	2226(3)	7595(2)	753.8(19)	28.9(7)
C15	1265(3)	6801(2)	715(2)	32.8(7)
C16	3610(3)	7239(2)	781(2)	33.1(7)
C17	2059(4)	8272(3)	45(2)	43.7(9)
C18	5276(3)	6235(2)	3834.3(19)	28.8(7)
C19	6266(4)	6065(3)	3164(2)	52.4(11)
C20A	7587(4)	5851(3)	3586(3)	37.2(12)
C20B	6608(17)	5578(11)	2529(9)	41(4)
C21A	6371(4)	6795(3)	2582(3)	35.6(12)
C21B	7324(13)	6982(11)	3216(9)	38(4)
C22	3576(4)	3985(3)	3197(2)	39.7(8)

Table 3 Anisotropic Displacement Parameters (Å^2×10^3) for 8g. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	27.6(11)	36.4(12)	20.3(10)	-4.3(10)	1.2(8)	-2.4(9)
O2	31.2(12)	44.4(13)	22.7(11)	-0.2(10)	5.0(9)	4.1(10)
O3	20.4(11)	55.2(15)	25.5(11)	8.5(10)	-2.6(9)	-2.3(10)
O4	38.5(14)	57.4(16)	40.3(14)	-13.4(12)	-19.6(12)	22.1(12)
O5	27.9(11)	35.1(11)	22.2(10)	-2.8(9)	-4.6(8)	7.0(9)
N1	21.1(12)	35.1(14)	16.9(11)	-0.4(10)	-0.5(10)	0.7(11)
N2	20.5(13)	35.4(14)	21.9(13)	-1.3(11)	0.9(11)	2.9(11)
N3	18.6(12)	36.9(15)	19.9(12)	1.8(11)	0.1(10)	-1.5(11)
N4	27.4(14)	39.6(16)	32.5(14)	-8.4(12)	-6.2(12)	14.4(12)
C1	17.6(13)	35.2(17)	18.5(13)	1.7(13)	-2.4(11)	2.7(12)
C2	21.8(14)	35.3(17)	16.9(13)	0.4(12)	-1.0(11)	-1.6(12)
C3	26.8(15)	44.6(19)	17.4(14)	-3.5(14)	-2.4(12)	-6.7(14)
C4	27.1(15)	38.4(18)	19.3(14)	-7.1(13)	-2.8(12)	-4.3(13)
C5	27.5(16)	34.4(17)	25.1(15)	0.9(13)	-0.8(12)	-4.4(14)
C6	25.6(15)	35.3(17)	17.9(14)	3.4(13)	0.2(12)	-1.3(13)
C7	22.1(14)	32.0(16)	21.9(14)	-2.0(13)	-0.6(12)	-5.5(13)
C8	20.6(14)	47.7(19)	14.9(13)	-0.4(13)	-0.7(11)	1.5(14)
C9	26.1(16)	41.1(19)	28.7(16)	-11.0(14)	-6.6(13)	6.5(14)
C10	41(2)	76(3)	48(2)	-33(2)	-10.4(19)	16(2)
C11	41(2)	80(3)	31.7(19)	-6(2)	2.9(16)	18(2)
C12	34.7(19)	63(3)	50(2)	-25(2)	-5.2(18)	18.7(19)
C13	33.7(17)	32.4(17)	30.8(17)	-2.9(14)	-4.8(14)	10.2(14)
C14	31.0(16)	34.8(17)	20.8(15)	-1.9(13)	-0.4(12)	0.4(14)
C15	29.0(16)	36.3(18)	33.2(17)	-3.2(14)	-1.8(13)	0.3(14)
C16	27.8(16)	41.7(19)	29.7(17)	-7.2(14)	3.4(13)	-0.1(15)
C17	57(2)	45(2)	28.5(17)	8.1(16)	-5.5(17)	-7.2(18)
C18	22.0(15)	39.5(18)	24.9(15)	-9.0(14)	-3.3(12)	3.5(13)
C19	31.1(19)	90(3)	36(2)	-24(2)	3.5(16)	-4(2)
C20A	28(2)	48(3)	36(2)	3(2)	1.8(19)	11.7(19)
C20B	43(9)	37(9)	43(9)	-11(7)	9(7)	0(7)
C21A	24(2)	37(3)	46(3)	-8(2)	-1.7(19)	9.4(19)
C21B	22(7)	63(11)	31(7)	3(7)	4(6)	1(7)
C22	49(2)	43(2)	27.0(17)	-5.3(15)	6.2(15)	-4.5(17)

Table 4 Bond Lengths for 8g.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O1	C1	1.237(4)	C2	C18	1.553(4)
O2	C7	1.235(4)	C3	C4	1.495(5)
O3	C8	1.232(4)	C4	C5	1.495(4)
O4	C13	1.217(4)	C4	C22	1.316(5)
O5	C13	1.353(4)	C6	C7	1.517(4)
O5	C14	1.464(4)	C8	C9	1.518(5)

Table 4 Bond Lengths for 8g.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
N1	C1	1.348(4)	C9	C10	1.536(5)
N1	C5	1.468(4)	C10	C11	1.470(6)
N1	C6	1.456(4)	C11	C12	1.473(5)
N2	C7	1.324(4)	C14	C15	1.525(5)
N3	C2	1.458(4)	C14	C16	1.519(5)
N3	C8	1.353(4)	C14	C17	1.519(5)
N4	C9	1.463(4)	C18	C19	1.509(5)
N4	C12	1.462(4)	C19	C20A	1.555(6)
N4	C13	1.347(4)	C19	C20B	1.296(13)
C1	C2	1.551(4)	C19	C21A	1.422(6)
C2	C3	1.549(4)	C19	C21B	1.727(14)

Table 5 Bond Angles for 8g.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C13	O5	C14	120.3(2)	O3	C8	N3	122.6(3)
C1	N1	C5	124.0(2)	O3	C8	C9	121.3(3)
C1	N1	C6	117.2(3)	N3	C8	C9	116.1(3)
C6	N1	C5	117.7(2)	N4	C9	C8	110.7(3)
C8	N3	C2	119.7(3)	N4	C9	C10	102.3(3)
C12	N4	C9	113.7(3)	C8	C9	C10	111.9(3)
C13	N4	C9	123.6(3)	C11	C10	C9	106.0(3)
C13	N4	C12	121.5(3)	C10	C11	C12	109.4(3)
O1	C1	N1	120.9(3)	N4	C12	C11	103.7(3)
O1	C1	C2	119.2(3)	O4	C13	O5	125.9(3)
N1	C1	C2	119.8(3)	O4	C13	N4	124.9(3)
N3	C2	C1	106.1(2)	N4	C13	O5	109.1(3)
N3	C2	C3	109.8(2)	O5	C14	C15	109.8(3)
N3	C2	C18	111.4(3)	O5	C14	C16	102.0(2)
C1	C2	C18	103.9(2)	O5	C14	C17	110.6(3)
C3	C2	C1	113.5(3)	C16	C14	C15	110.7(3)
C3	C2	C18	111.9(3)	C17	C14	C15	112.8(3)
C4	C3	C2	110.9(2)	C17	C14	C16	110.4(3)
C5	C4	C3	112.3(3)	C19	C18	C2	121.1(3)
C22	C4	C3	124.8(3)	C18	C19	C20A	108.2(3)
C22	C4	C5	122.9(3)	C18	C19	C21B	105.4(6)
N1	C5	C4	111.0(3)	C20B	C19	C18	147.3(8)
N1	C6	C7	116.5(2)	C20B	C19	C21B	106.8(9)
O2	C7	N2	124.6(3)	C21A	C19	C18	113.7(4)
O2	C7	C6	116.7(3)	C21A	C19	C20A	111.8(4)
N2	C7	C6	118.7(3)				

Table 6 Hydrogen Bonds for 8g.

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
N2	H2A	O1[1]	0.85(3)	2.07(3)	2.890(4)	162(4)
N3	H3	O2[2]	0.87(4)	2.04(4)	2.860(4)	157(4)

[1]-1/2+X,3/2-Y,1-Z; [2]1/2+X,3/2-Y,1-Z

Table 7 Torsion Angles for 8g.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
O1	C1	C2	N3	-45.9(3)	C5	N1	C1	O1	169.3(3)
O1	C1	C2	C3	-166.6(3)	C5	N1	C1	C2	-14.3(4)
O1	C1	C2	C18	71.7(3)	C5	N1	C6	C7	-91.8(3)
O3	C8	C9	N4	-38.6(4)	C6	N1	C1	O1	1.9(4)
O3	C8	C9	C10	74.8(4)	C6	N1	C1	C2	178.4(3)
N1	C1	C2	N3	137.6(3)	C6	N1	C5	C4	-160.7(3)
N1	C1	C2	C3	16.9(4)	C8	N3	C2	C1	-52.8(3)
N1	C1	C2	C18	-104.8(3)	C8	N3	C2	C3	70.3(3)
N1	C6	C7	O2	-179.1(3)	C8	N3	C2	C18	-165.2(3)
N1	C6	C7	N2	1.4(4)	C8	C9	C10	C11	-98.1(4)
N3	C2	C3	C4	-156.9(3)	C9	N4	C12	C11	-1.2(5)
N3	C2	C18	C19	-77.5(4)	C9	N4	C13	O4	171.6(4)
N3	C8	C9	N4	143.0(3)	C9	N4	C13	O5	-10.2(5)
N3	C8	C9	C10	-103.6(3)	C9	C10	C11	C12	-22.8(6)
N4	C9	C10	C11	20.5(5)	C10	C11	C12	N4	15.1(5)
C1	N1	C5	C4	32.0(4)	C12	N4	C9	C8	107.4(3)
C1	N1	C6	C7	76.4(3)	C12	N4	C9	C10	-12.0(4)
C1	C2	C3	C4	-38.3(4)	C12	N4	C13	O4	4.6(6)
C1	C2	C18	C19	168.7(3)	C12	N4	C13	O5	-177.2(3)
C2	N3	C8	O3	-8.2(4)	C13	O5	C14	C15	-60.4(4)
C2	N3	C8	C9	170.1(2)	C13	O5	C14	C16	-177.9(3)
C2	C3	C4	C5	58.3(3)	C13	O5	C14	C17	64.6(4)
C2	C3	C4	C22	-122.2(4)	C13	N4	C9	C8	-60.5(4)
C2	C18	C19	C20A	-174.7(3)	C13	N4	C9	C10	-179.9(4)
C2	C18	C19	C20B	-54.1(18)	C13	N4	C12	C11	167.0(4)
C2	C18	C19	C21A	60.4(5)	C14	O5	C13	O4	-3.3(5)
C2	C18	C19	C21B	116.9(6)	C14	O5	C13	N4	178.5(3)
C3	C2	C18	C19	45.9(4)	C18	C2	C3	C4	78.9(3)
C3	C4	C5	N1	-53.9(3)	C22	C4	C5	N1	126.7(3)

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

Atom	*x*	*y*	*z*	U(eq)
H2A	-500(30)	6910(30)	5020(20)	34(10)
H2B	550(40)	6590(30)	4480(20)	33(10)
H3	4200(40)	7730(30)	3320(30)	45(12)
H3A	2543.59	5901	2724.3	36
H3B	3973.06	5580.56	2558.6	36
H5A	1227.93	5026.53	3838.27	35
H5B	1967.81	4281.66	4358.6	35
H6A	2486.91	5761.01	5890.97	32
H6B	1647.78	4918.55	5622.09	32
H9	3024.74	8891.3	2817.67	38
H10A	2140.81	8888.04	4349.02	66
H10B	2338.52	9804.47	3844.47	66
H11A	267.88	9960.25	4034.59	61
H11B	58.81	8902.22	4175.88	61
H12A	-746.61	8876.34	2941.03	59
H12B	-171.2	9853.35	2727.06	59
H15A	1383.3	6410.91	1188.47	49
H15B	1409.8	6453.02	218.45	49
H15C	397.4	7038.61	713.72	49
H16A	4195.18	7744.35	856.23	50
H16B	3806.32	6931.54	269.83	50
H16C	3701.11	6815.59	1232.75	50
H17A	1203.57	8529.38	64.75	66
H17B	2180.3	7958.68	-472.16	66
H17C	2688.6	8753.93	96.2	66
H18A	5561.55	6770.64	4141.58	35
H18B	5318.39	5717.92	4212.14	35
H19	5998.19	5513.81	2860.1	63
H19A	6805.81	5697.3	3537.27	63
H20A	7491.14	5331.31	3945.97	56
H20B	7861.32	6374.58	3901.94	56
H20C	8222.54	5716.36	3169.01	56
H20D	7360.93	5221.64	2666.23	61
H20E	6804.16	5976.87	2072.6	61
H20F	5912.01	5173.51	2377.49	61
H21A	7014.96	6643.7	2175.23	53
H21B	6617.76	7348.09	2864.36	53
H21C	5550.38	6885.22	2313.73	53
H21D	7930.07	6884.63	3658.09	58
H21E	6845.42	7536.77	3316.83	58
H21F	7784.12	7035.87	2701.34	58
H22A	3346.12	3451.98	3478.54	48

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

Atom	*x*	*y*	*z*	U(eq)
H22B	4182.43	3959.48	2771.27	48

Table 9 Atomic Occupancy for 8g.

Atom	*Occupancy*	Atom	*Occupancy*	Atom	*Occupancy*
H19	0.772(7)	H19A	0.228(7)	C20A	0.772(7)
H20A	0.772(7)	H20B	0.772(7)	H20C	0.772(7)
C20B	0.228(7)	H20D	0.228(7)	H20E	0.228(7)
H20F	0.228(7)	C21A	0.772(7)	H21A	0.772(7)
H21B	0.772(7)	H21C	0.772(7)	C21B	0.228(7)
H21D	0.228(7)	H21E	0.228(7)	H21F	0.228(7)

Crystal structure determination of 8g

Crystal Data for $C_{22}H_{36}N_4O_5$ (*M* =436.55 g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), *a* = 10.3188(3) Å, *b* = 14.5578(5) Å, *c* = 16.1464(4) Å, *V* = 2425.50(12) Å^3, *Z* = 4, *T* = 100.00(10) K, μ(Cu Kα) = 0.695 mm^{-1}, *Dcalc* = 1.195 g/cm^3, 18854 reflections measured (8.178° ≤ 2Θ ≤ 136.476°), 4443 unique (R_{int} = 0.0292, R_{sigma} = 0.0252) which were used in all calculations. The final R_1 was 0.0442 (I > 2σ(I)) and wR_2 was 0.1110 (all data).

Reference

1. I. Shimizu, T. Yamada and J. Tsuji, *Tetrahedron Letters*, 1980, **21**, 3199–3202.
2. J. James, M. Jackson and P. J. Guiry, *Adv. Synth. Catal.*, 2019, 361, 3016–3049.
3. B. Trost and J. Schultz, *Synthesis*, 2019, **51**, 1–30.
4. B. M. Trost, J. Xu and T. Schmidt, *J. Am. Chem. Soc.*, 2009, **131**, 18343–18357.
5. J. A. Keith, D. C. Behenna, J. T. Mohr, S. Ma, S. C. Marinescu, J. Oxgaard, B. M. Stoltz and W. A. Goddard, *J. Am. Chem. Soc.*, 2007, **129**, 11876–11877.
6. B. M. Trost, J. Xu and T. Schmidt, *J. Am. Chem. Soc.*, 2009, **131**, 18343–18357.
7. J. Han, L. Hoteite and J. P. A. Harrity, *Chemistry A European J*, , DOI:10.1002/chem.202201595.
8. W. Wang, H. Shen, X.-L. Wan, Q.-Y. Chen and Y. Guo, *J. Org. Chem.*, 2014, **79**, 6347–6353.
9. B. M. Trost, R. Radinov and E. M. Grenzer, *J. Am. Chem. Soc.*, 1997, **119**, 7879–7880.
10. S.-L. You, X.-L. Hou, L.-X. Dai and X.-Z. Zhu, *Org. Lett.*, 2001, **3**, 149–151.
11. X.-C. He, B. Wang, G. Yu and D. Bai, *Tetrahedron: Asymmetry*, 2001, **12**, 3213–3216.
12. B. M. Trost, J. Xu and M. Reichle, *J. Am. Chem. Soc.*, 2007, **129**, 282–283.
13. P. Starkov, J. T. Moore, D. C. Duquette, B. M. Stoltz and I. Marek, *J. Am. Chem. Soc.*, 2017, **139**, 9615–9620.
14. X.-X. Yan, C.-G. Liang, Y. Zhang, W. Hong, B.-X. Cao, L.-X. Dai and X.-L. Hou, *Angew. Chem. Int. Ed.*, 2005, **44**, 6544–6546.
15. D. C. Behenna and B. M. Stoltz, *J. Am. Chem. Soc.*, 2004, **126**, 15044–15045.
16. B. M. Trost, R. N. Bream and J. Xu, *Angew. Chem. Int. Ed.*, 2006, **45**, 3109–3112.

17. B. M. Trost and X. Ariza, *J. Am. Chem. Soc.*, 1999, **121**, 10727–10737.

18. B. M. Trost and L. C. Czabaniuk, *J. Am. Chem. Soc.*, 2012, **134**, 5778–5781.

19. M. Serra, E. Bernardi, G. Marrubini, E. De Lorenzi and L. Colombo, *Eur. J. Org. Chem.*, 2019, **2019**, 732–741.

20. K. Li, S. Zhen, W. Wang, J. Du, S. Yu, Y. Wu and H. Guo, *Chem. Sci.*, 2023, **14**, 3024–3029.

21. C. Wang and J. A. Tunge, *J. Am. Chem. Soc.*, 2008, **130**, 8118–8119.

22. C. Guo, D. Janssen-Müller, M. Fleige, A. Lerchen, C. G. Daniliuc and F. Glorius, *J. Am. Chem. Soc.*, 2017, 139, 4443–4451.

23. L. A. Leth, F. Glaus, M. Meazza, L. Fu, M. K. Thøgersen, E. A. Bitsch and K. A. Jørgensen, *Angew. Chem. Int. Ed.*, 2016, 55, 15272–15276.

24. K. Ohmatsu, N. Imagawa and T. Ooi, *Nature Chem*., 2014, 6, 47–51.

25. K. Ohmatsu, S. Kawai, N. Imagawa and T. Ooi, *ACS Catal.*, 2014, 4, 4304–4306.

26. B. D. W. Allen, M. J. Connolly and J. P. A. Harrity, *Chem. Eur. J.*, 2016, **22**, 13000–13003.

27. V. García-Vázquez, L. Hoteite, C. P. Lakeland, D. W. Watson and J. P. A. Harrity, *Org. Lett.*, 2021, **23**, 2811–2815.

28. K. Li, S. Zhen, W. Wang, J. Du, S. Yu, Y. Wu and H. Guo, *Chem. Sci.*, 2023, 14, 3024–3029.

29. E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257–10274

30. D. P. Bezerra, C. Pessoa, M. O. De Moraes, N. Saker-Neto, E. R. Silveira and L. V. Costa-Lotufo, *European Journal of Pharmaceutical Sciences*, 2013, **48**, 453–463.

31. R. M. Freidinger, *J. Med. Chem.*, 2003, **46**, 5553–5566.

32. R. M. Freidinger, D. F. Veber, D. S. Perlow, J. R. Brooks and R. Saperstein, *Science*, 1980, **210**, 656-658.

33. A. Della Valle, A. Stefanucci, G. Scioli, E. Szűcs, S. Benyhe, S. Pieretti, P. Minosi, C. Sturaro, G. Calò, G. Zengin and A. Mollica, *Bioorganic Chemistry*, 2021, **115**, 105219.

34. S. Greaves, PhD Thesis, The University of Sheffield, DATE.

35. C. P. Butts, E. Filali, G. C. Lloyd-Jones, P.-O. Norrby, D. A. Sale and Y. Schramm, *J. Am. Chem. Soc.*, 2009, **131**, 9945–9957

36. B. M. Trost and M. U. Frederiksen, *Angew. Chem. Int. Ed.*, 2005, 44, 308–310.

37. S. Tallon, F. Manoni and S. J. Connon, *Angew. Chem. Int. Ed.*, 2015, **54**, 813–817.

38. C. Mas-Moruno, F. Rechenmacher and H. Kessler, *ACAMC*, 2010, **10**, 753–768.

39. W. Pan, A. J. Kastin, *Peptides* **2007**, *28*, 2411-2434

40. H. Li, S.-J. Shen, C.-L. Zhu and H. Xu, *J. Am. Chem. Soc.*, 2019, **141**, 9415–9421.

41. (a) R. Walter, I. Bernal, L. F. Johnson, "Chemistry and Biology of Peptides," Ann Arbor Science Publishers, Ann Arbor, 1972, pp 131-135; (b) L. L. Reed, P. L. Johnson, *J. Am. Chem. Soc*., 1973, **95**, 7523-7524.

42. W. G. Beyersbergen Van Henegouwen, R. M. Fieseler, F. P. J. T. Rutjes and H. Hiemstra, *Angew. Chem. Int. Ed.*, 1999, **38**, 2214–2217.

43. R. M. Bychek, V. V. Levterov, I. V. Sadkova, A. A. Tolmachev and P. K. Mykhailiuk, *Chem. Eur. J.*, 2018, **24**, 12291–12297.

44. B. D. W. Allen, PhD Thesis, The University of Sheffield, DATE.

45. Melhado, A. D.; Luparia, M.; Toste, F. D. *J. Am. Chem. Soc.* **2007,** *129*, 12638-12639.

46. Badiola, E.; Fiser, B.; Gomez-Bengoa, E.; Mielgo, A.; Olaizola, I.; Urruzuno, I.; Garcia, J. M.; Odriozola, J. M.; Razkin, J.; Oiarbide, M. *J. Am. Chem. Soc.* **2014,** *136*, 17869-17881.

47. Zhang, H.; Yang, Z.; Zhao, B. N.; Li, G. *J. Org. Chem.* **2018,** *83*, 644-655.

48. He, S.; Gu, H.; He, Y.-P.; Yang, X. *Org. Lett.* **2020,** *22*, 5633-5639.

49. Peddibhotla, S.; Tepe, J. *Synthesis* **2003**, 1433-1440.

50. Z. Li, J. Peng, C. He, J. Xu and H. Ren, J. Org. Chem. 2020, 85, 3894-3901.

51. V. Garcia-Vasquez, L. Hoteite, C. P. Lakeland, D. W. Watson and J. P. A. Harrity, Org. Lett., 2021, 23, 2811–2815.

52. Chen, F. M.; Benoiton, N. L. *Int. J. Peptide and Protein Res.* **1987,** *30*, 683-688.

53. Uraguchi, D.; Asai, Y.; Ooi, T. *Angew. Chem. Int. Ed.* **2009,** *48*, 733-737.