Synthesis of Nitrogen-Containing Heterocycles using Conjugate Addition Approaches

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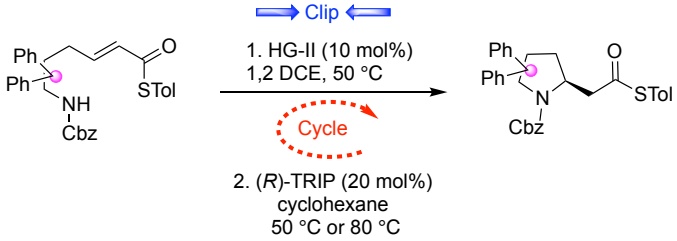
Abstract

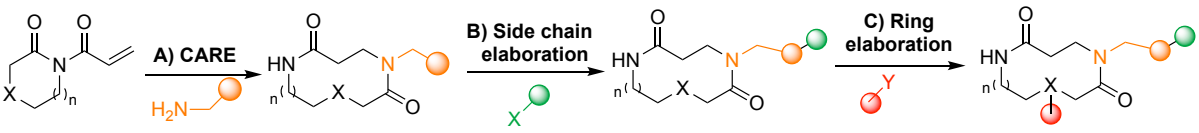
This thesis describes the development of novel methods for the synthesis of nitrogen-containing heterocycles that make use of nitrogen conjugate addition reactions. New methods including asymmetric synthesis, kinetic resolution, and ring expansion have all been developed, inspired by the relevance of pyrrolidines and macrocyclic lactams in bioactive molecules.

The first part of the thesis details an enantioselective synthesis of 2- and 3- phenyl pyrrolidines via Brønsted acid-catalysed cyclisation. A kinetic resolution of a racemic 3-substituted precursor using (*R*)-TRIP afforded a 3-pyrrolidine product with high enantioselectivity, good diastereocontrol. Relative and absolute stereochemistry was assigned for the 2-phenyl pyrrolidine through comparison with literature compounds, while derivatization attempts were undertaken to assign the stereochemistry of the 3-phenyl pyrrolidine.



The second part is focused on the synthesis of medium-sized ring lactams via a cross-metathesis/intramolecular rearrangement sequence. While precursor synthesis was achieved, the key metathesis step proved challenging, yielding the desired product in only 2%, indicating a need for further optimisation.

The final part of the thesis introduces a modular and scalable 'Nitrogen Conjugate Addition/Ring Expansion' (*N*-CARE) strategy for the synthesis of 10- to 13-membered macrocyclic lactams from acryloyl imides. A three-step sequence enabled broad functional group tolerance and downstream derivatisation, with **67** novel lactams synthesised in total. Although biological screening against bacterial strains showed no activity, the synthetic platform offers a valuable foundation for future medicinal chemistry efforts.



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I would also like to give a huge thank to my little 'squirrel', my niece Masal, for being such a wonderful playmate.

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To my mum and dad, Sevdagul and Nurbay

Whilst writing this thesis,
I often found myself back in the car with you
driving by the sea, songs playing softly,
and your voices keeping me company.

Declaration

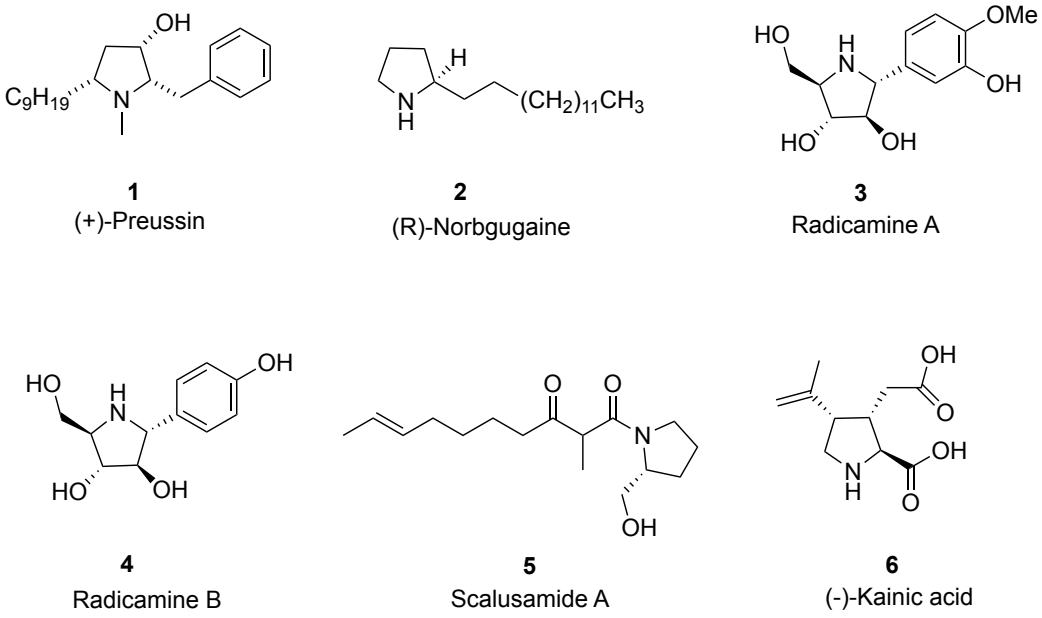
I hereby declare that the substance of this thesis has not been submitted, nor is currently being submitted, in candidature for any other degree.

I also declare that the work embodied in this thesis is the result of my own investigations and in the event the work of others has been used this has been fully acknowledged in the text.

1-Introduction-Asymmetric Synthesis and Kinetic Resolutions of Substituted Pyrrolidines

1.1 Pyrrolidines in natural products

Pyrrolidines − saturated 5-membered rings containing a single nitrogen atom − are found in numerous natural products[1-8] that exhibit a wide range of biological activities (Scheme 1). For example, the pyrrolidine alkaloid named (+)-preussin **1**, isolated from the fermentation of *Aspergillus ochceus*, is an antifungal agent. (*R*)-Norbgugaine **2** is a naturally occurring pyrrolidine alkaloid derived from the plant *Arisarum vulgare*, which shows antibacterial activity against the bacterium *Pseudomonas aeruginosa.* Radicomine A **3** and B **4** can be used for the treatment of Alzheimer's disease, Parkinson's disease, and other neurodegenerative disorders. Scalusamide A **5** was extracted from the fungus Penicillium citrinum, which was obtained from the gastrointestinal tract of a marine fish. (−)-Kainic **6** acid is naturally occurring neurotoxic compound that plays an important role in experimental neurobiology, as a tool for studying neurodegenerative diseases, epilepsy, and excitotoxicity.

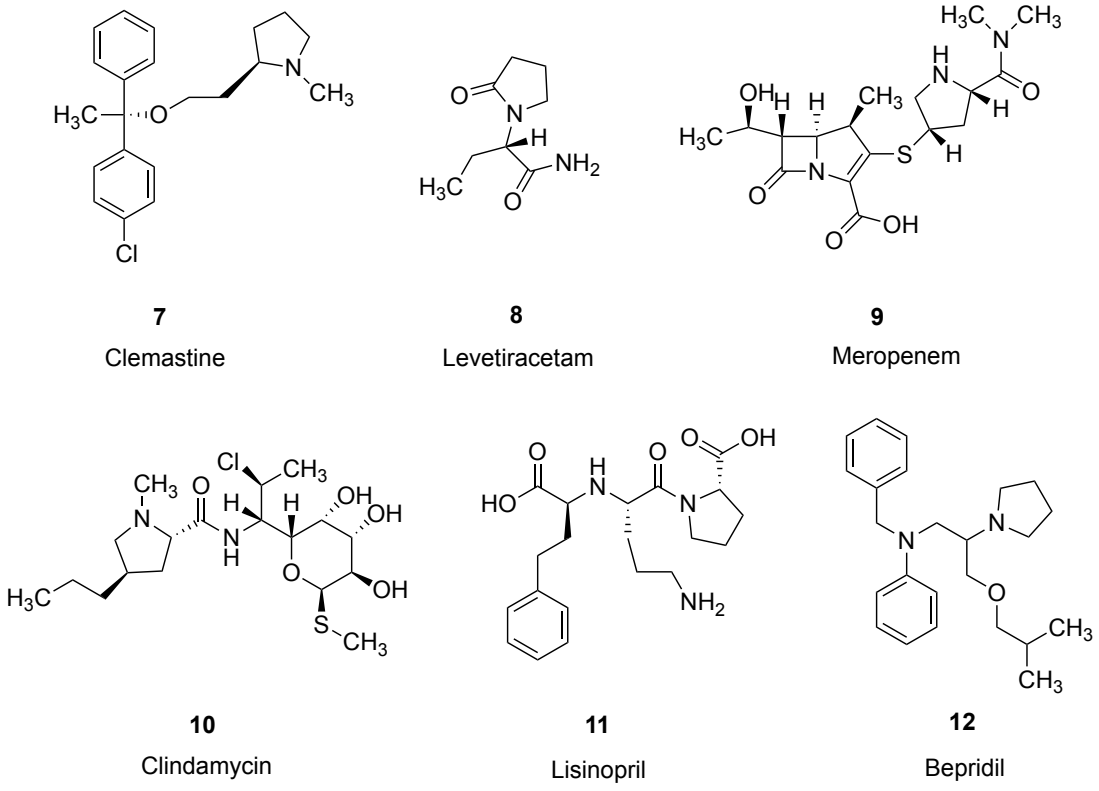


Scheme 1: Structures of pyrrolidine-containing natural products

1.2 Pyrrolidines in pharmaceuticals

Pyrrolidine derivatives have a significant presence in the field of pharmaceuticals due to their diverse biological activities and ability to serve as scaffolds in the design of bioactive compounds (Scheme 2). The incorporation of various substituents at different positions on

the pyrrolidine ring, along with the potential for up to four stereogenic centres, makes pyrrolidines an attractive scaffold for drug development. Clemastine **7** is an antihistamine used to treat allergic conditions such as rhinitis and works by blocking the effects of histamine.[9] Levetiracetam **8**, an anticonvulsant, is widely prescribed for epilepsy and is based on a pyrrolidine structure that modulates neurotransmitter release to prevent seizures.[10] Meropenem **9**, a broad-spectrum carbapenem antibiotic, is effective against a wide range of bacterial infections, particularly those caused by Gram-negative organisms.[11] Clindamycin **10** is an antibiotic used to treat various bacterial infections, including those caused by anaerobic bacteria.[12] Lisinopril **11** is an antihypertensive agent that works by inhibiting the enzyme angiotensin-converting enzyme (ACE), helping to lower blood pressure and manage heart failure.[13] Bepridil **12** is a calcium channel blocker used for arrhythmias and helps regulate the heart's electrical activity.[14] These examples highlight the versatility of pyrrolidine derivatives in treating a broad spectrum of medical conditions, including infections, cardiovascular diseases, neurological disorders and allergies.

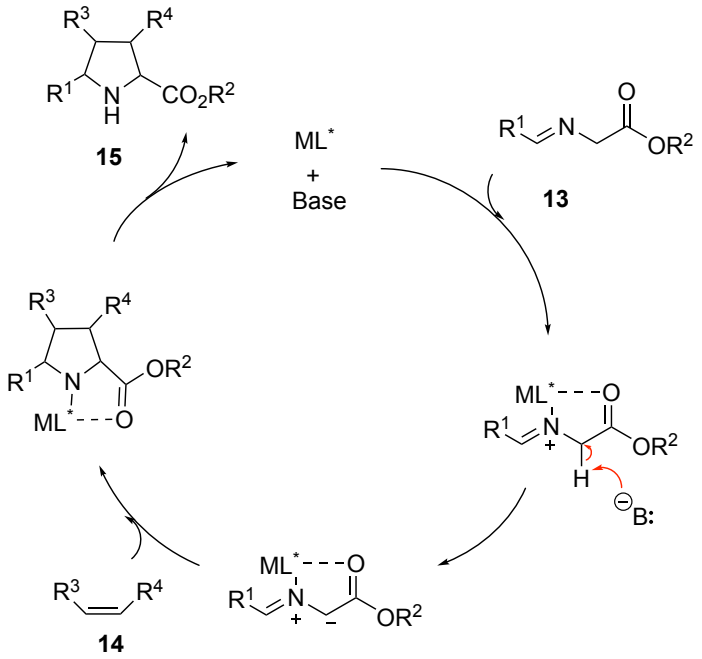


Scheme 2: Structures of pyrrolidines in pharmaceuticals

1.3 General Approaches for Asymmetric Synthesis of Pyrrolidines

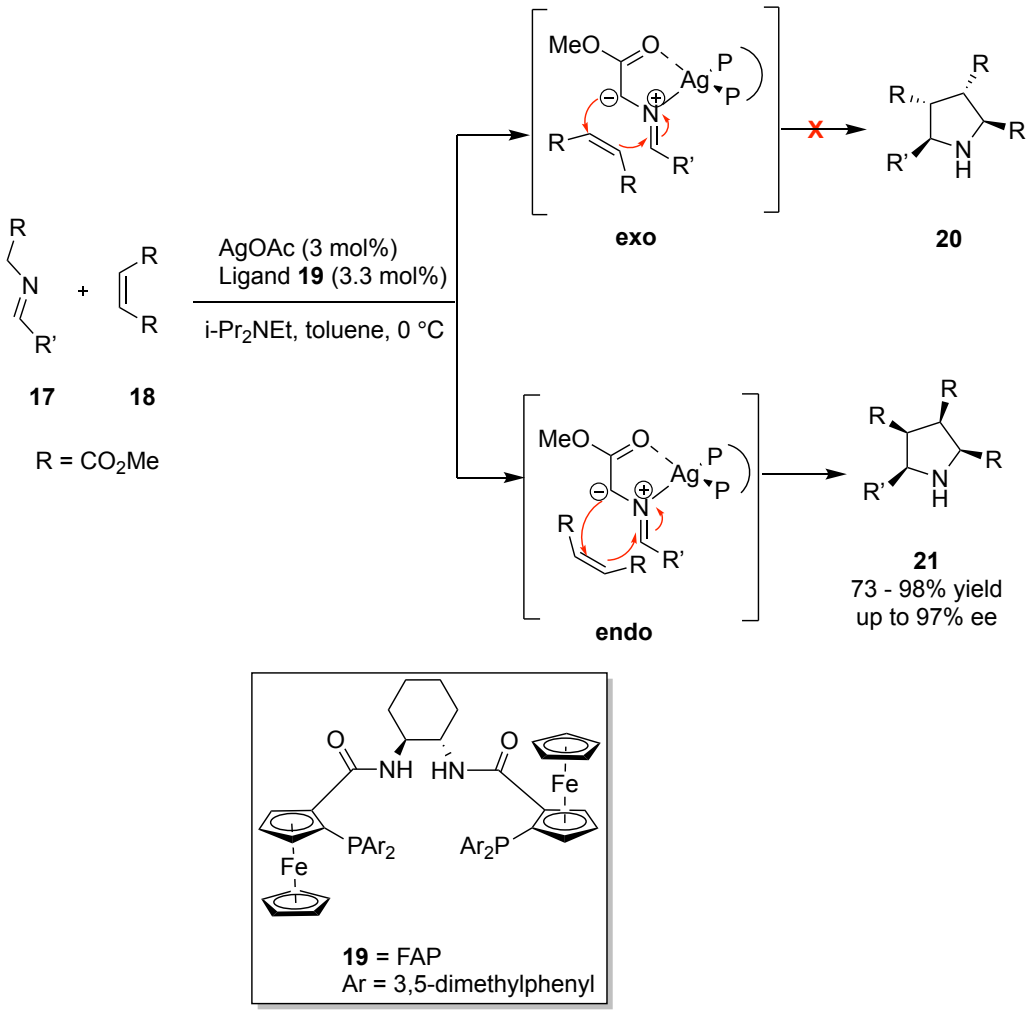
1.3.1 Synthesis of Pyrrolidines via Cycloaddition Reactions

Cycloaddition reactions offer a versatile means of synthesizing pyrrolidines, whereby two or more components combine to form the cyclic structure. The formation of pyrrolidine rings by [3+2] cycloadditions is a particularly important method, where the cycloaddition can be induced using metal-catalysts, organocatalysts, or other catalytic systems. Asymmetric cycloadditions can also be performed and often rely on chiral catalysts to direct the enantioselective formation of specific pyrrolidine stereoisomers. Cycloaddition reactions are particularly beneficial for generating complex structures, as they allow for the incorporation of multiple functional groups in a single step, enabling efficient and atom-economical syntheses. Recent advances in catalytic methods have expanded the scope of cycloaddition reactions, providing access to a wide range of pyrrolidine derivatives with diverse functionalisation patterns. Among these methods, azomethine dipolar cycloaddition stands out as a particularly effective strategy. This pericyclic reaction involves the interaction between azomethine ylides **13** and alkenes **14**, leading to the formation of highly functionalized pyrrolidines **15** (Scheme 3). Notably, asymmetric azomethine ylide cycloaddition reactions have been extensively explored, especially in the context of metal-catalysed enantioselective transformations. Chiral catalysts, including Lewis acids and organocatalysts, have been employed to activate both the dipole and the dipolarophile, thereby controlling the stereochemistry of the resulting products. Azomethine cycloaddition reactions allow for the creation of enantioenriched pyrrolidines, which are prevalent in numerous natural products and biologically active molecules.[15-22]

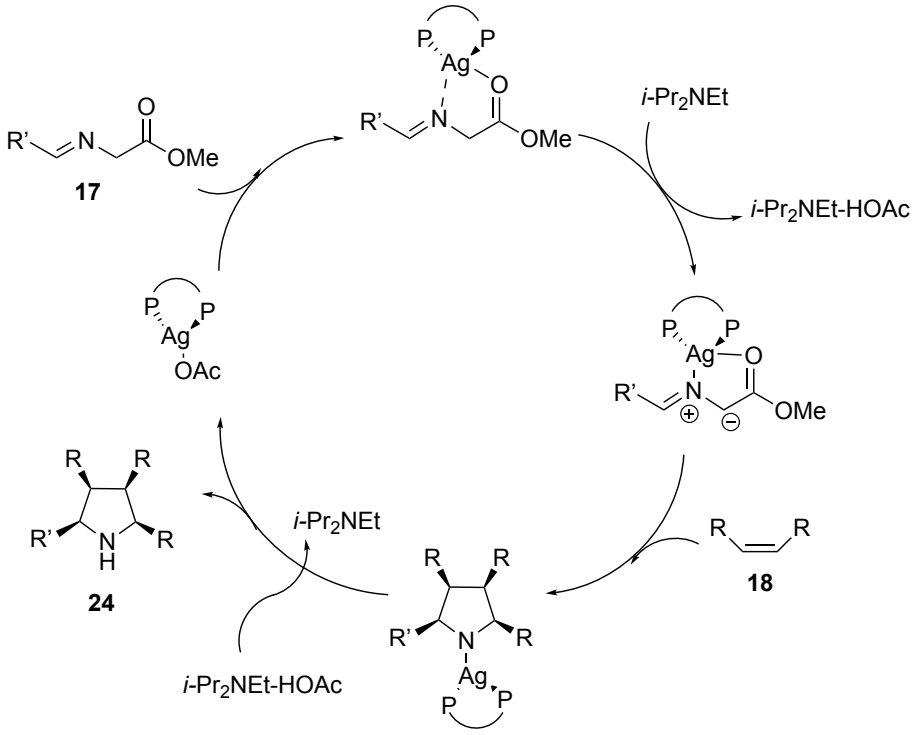


Scheme 3: General concerted 1,3-dipolar cycloaddition; this Scheme depicts a stepwise formal cycloaddition process, with concerted pericyclic variants also known, and featured in later Schemes.

Zhang and co-workers reported the cycloaddition of azomethine ylides using a complex of AgOAc as the catalytic precursor and *bis*-ferrocenyl amide phosphine (FAP) **19** as the ligand (Scheme 4).[23] In the reaction mechanism, the chiral Ag(I) catalyst first coordinates with the α-iminoester **17**, and subsequent deprotonation with *i*-Pr_2NEt generates a metalated azomethine ylide. The presence of 3,5-dimethyl phenyl groups on the diphosphine ligand contribute to blocking one of the enantiotopic faces of the azomethine ylide. This directs the reaction pathway, leading to the highly enantioselective formation of endo pyrrolidine products **21** (Scheme 5).

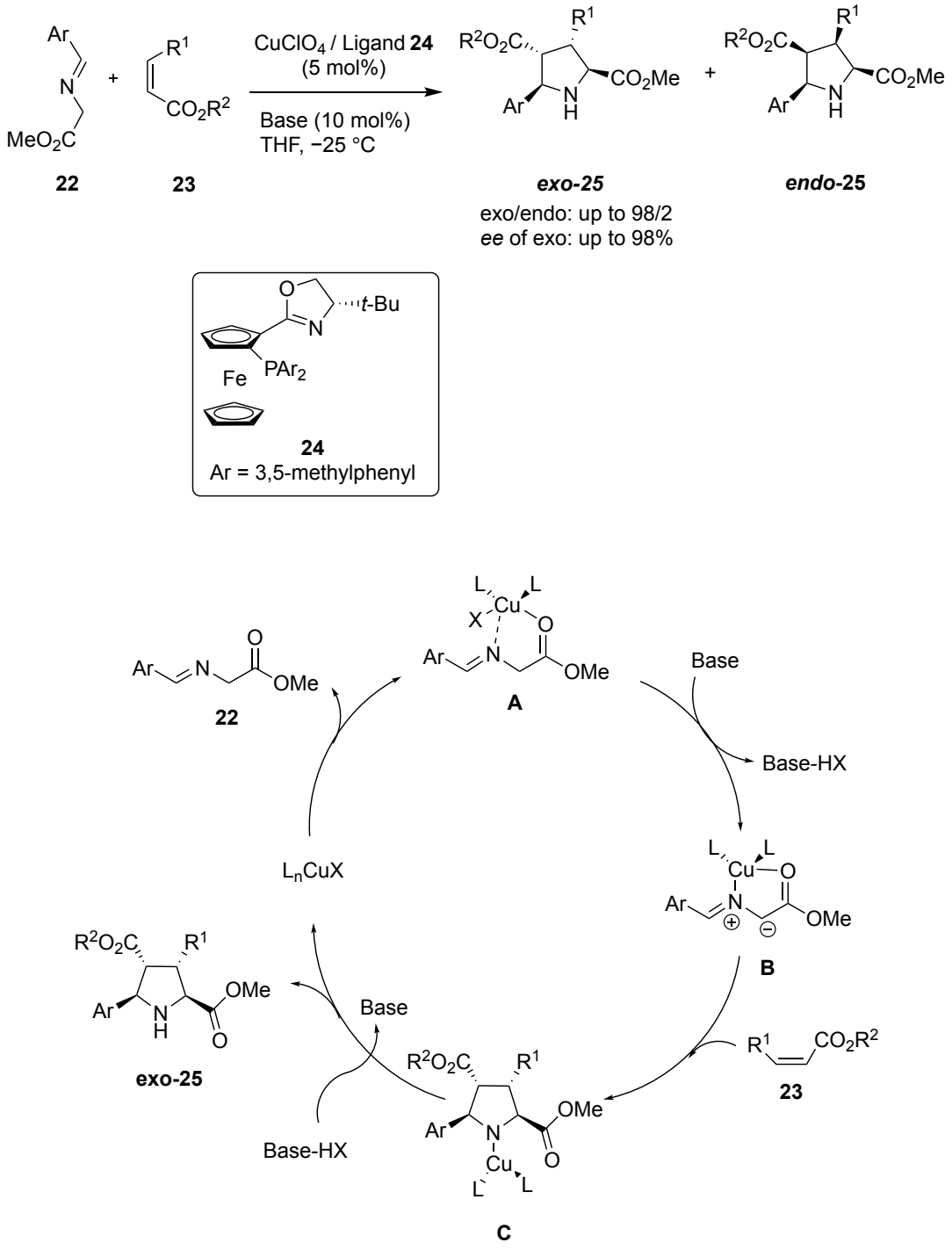


*Scheme 4: Azomethine cycloaddition using a complex of AgOAc and FAP **19***



*Scheme 5: Proposed mechanism for the formation of **21***

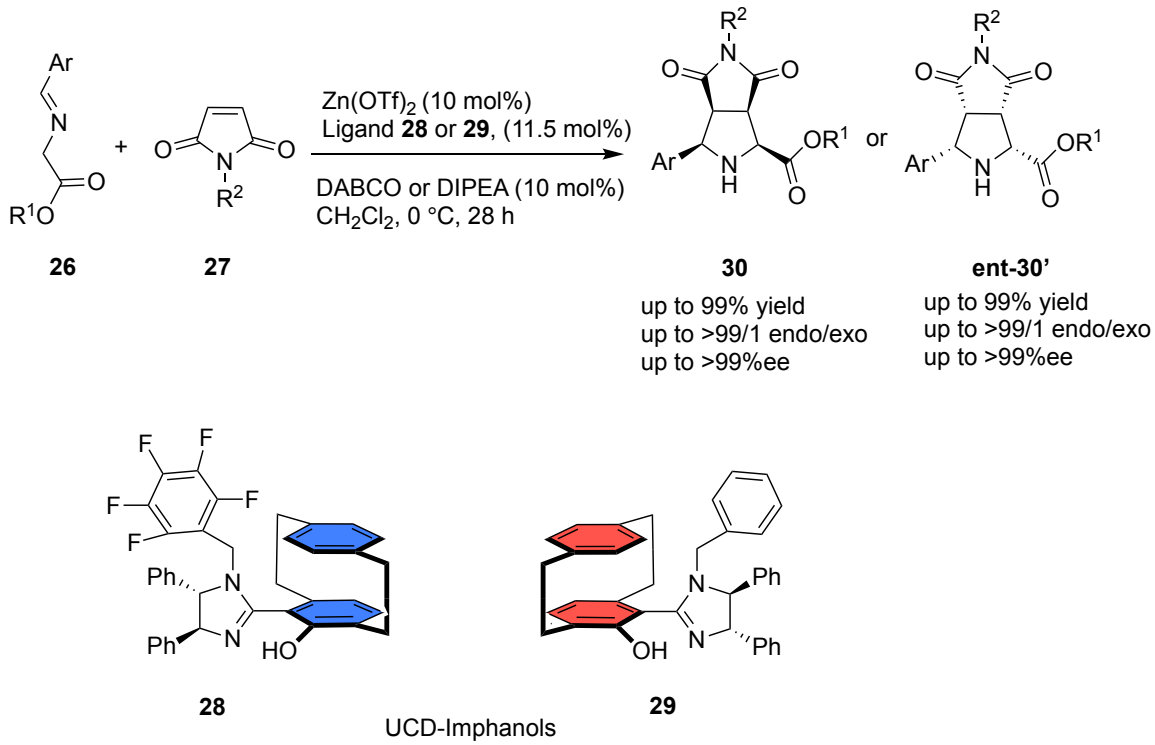
While the Ag(I)-catalysed azomethine ylide cycloaddition system demonstrates excellent synthetic versatility and utility in forming a wide variety of endo pyrrolidine cycloadducts, it does not provide access to *exo* isomers **20**. In the following year, Zhang and co-workers developed a novel Cu(I)/P,N-ligand cycloaddition approach, which achieved exceptionally high *exo*-selectivity (up to 98%) and an enantiomeric excess (*ee*) of up to 98% (Scheme 6).[24] The process begins with the formation of complex **A**, where the imine **22** coordinates with the Cu(I) catalyst. This leads to the generation of the reactive azomethine ylide-Cu(I) complex **B**, formed when the amine base abstracts a proton. Complex **B** then interacts with various dipolarophiles **23**, leading to the formation of intermediate **C**. Protodemetallation then releases the desired cycloaddition product ***exo*-25**, while simultaneously regenerating both the active catalyst and the base. Complex **B** is an 18-electron complex with a tetrahedral ligand arrangement around the copper centre.



Scheme 6: Catalytic asymmetric 1,3-dipolar cycloaddition using a complex of $CuClO_4$ and PHOX

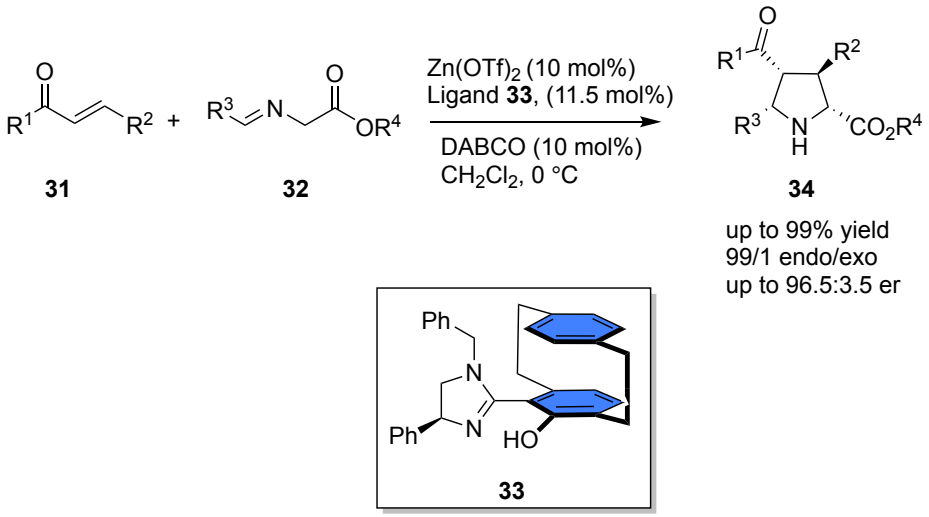
These studies demonstrate how a change in the metal catalyst (Cu vs. Ag) leads to completely opposite diastereoselectivity, without requiring additional protecting groups or additives. The findings underscore the power of asymmetric catalysis in precisely dictating stereochemical outcomes through fine-tuned catalyst-ligand interactions and transition state control.

In recent years, newly developed chiral Zn-catalyst combination systems have emerged as a significant alternative to Ag- or Cu-based catalysis, owing to their unique advantages, including non-toxicity, eco-friendliness, abundance, and cost-effectiveness. Guiry and Kumar recently introduced a new class of imidazoline *N,O*-ligands derived from [2,2]paracyclophane (UCD-IMPHANOL) and demonstrated their applications in zinc-catalysed [3+2] cycloaddition of azomethine ylide with maleimides to form enantioenriched pyrrolidines.[25] The ligand screening analysis demonstrated that the diastereomeric ligand pair functioned as pseudo-enantiomeric ligands, with planar chirality identified as the key factor contributing to the exceptionally high levels of asymmetric induction observed. Several maleimides and imino esters were compatible under these conditions, yielding the corresponding products **30** in good yields and with high enantioselectivities when $Zn(OTf)_2$ was paired with ligand **28**. Similarly, the use of ligand **29** in the presence of diisopropyl ethylamine (DIPEA) as the base led to the formation of cycloadducts **30'** with comparable yields and enantioselectivities (Scheme 7). It was shown that planar chirality plays a crucial role in controlling asymmetric induction, as evidenced by the excellent enantiomeric excess values (up to > 99% *ee*) and the facile synthesis of both enantiomerically pure cycloadducts.

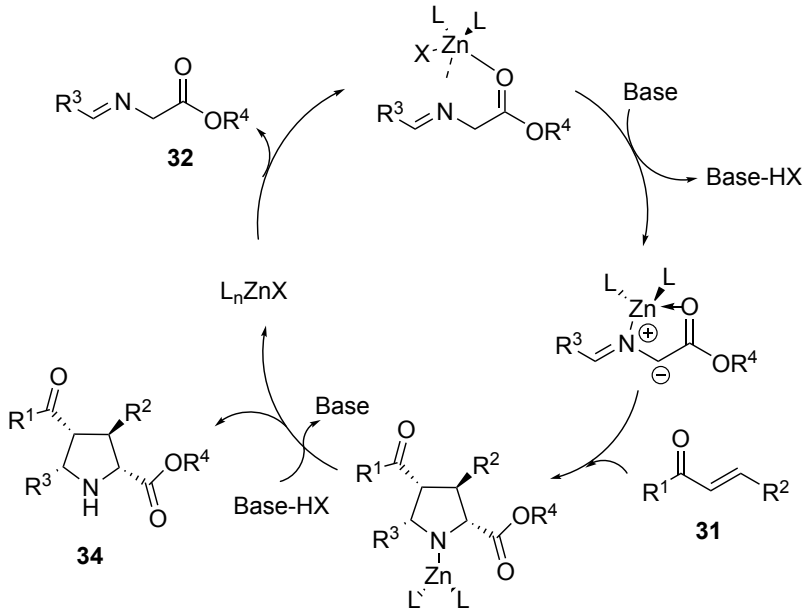


Scheme 7: Zn/Ligand catalytic asymmetric cycloaddition of maleimides with imino esters

By using Zn(II)/UCD-Imphanol catalysis in 2024, a similar approach was expanded to include cycloaddition of acyclic enones **31** with azomethine ylides **32**, providing a straightforward approach to highly functionalized pyrrolidine derivatives **34**.[26] This method exhibits a broad substrate scope, delivering products in excellent yields (up to 95%) with outstanding regio-, diastereo-, and enantioselectivities (up to >99% ee) (Scheme 8). Mechanistic investigations suggest a stepwise cycloaddition pathway. The Zn(II) center coordinates with both the carbonyl group of the enone and the nitrogen atom of the azomethine ylide precursor, facilitating ylide generation through imine deprotonation. This dual coordination not only stabilises the transition state but also induces facial selectivity, thereby controlling the stereochemical outcome. The rate-determining step is proposed to involve nucleophilic attack of the ylide onto the β-position of the enone, followed by cyclisation to form the pyrrolidine core (Scheme 9).



Scheme 8: Zn/Ligand catalytic asymmetric formal 1,3-dipolar cycloaddition of acyclic enones with azomethine ylides



Scheme 9: Mechanism of Zn(II)-catalysed formal 1,3-dipolar cycloaddition

1.3.2 Synthesis of Pyrrolidines via Asymmetric Cyclisation Reactions

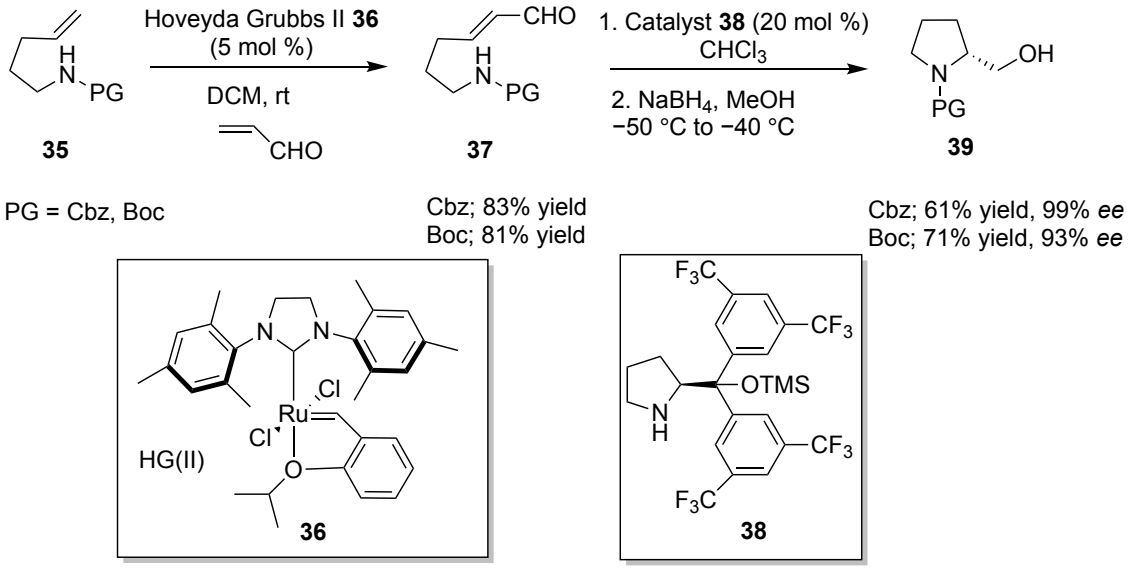
Asymmetric cyclisation reactions are a core strategy in the enantioselective synthesis of pyrrolidines, wherein an intramolecular nucleophilic attack leads to ring closure, resulting in the formation of the pyrrolidine ring. These reactions are often facilitated by the use of chiral catalysts or reagents, which provide control over the stereochemistry of the final product. Cyclisation reactions can occur through a variety mechanism, including nucleophilic substitution, addition to electrophilic centres, and radical-induced ring closure. Among the

most prominent approaches are intramolecular aza-Michael additions and organocatalytic cyclisation. These methods allow the direct formation of the five-membered pyrrolidine ring while inducing stereogenic centres in a controlled manner.

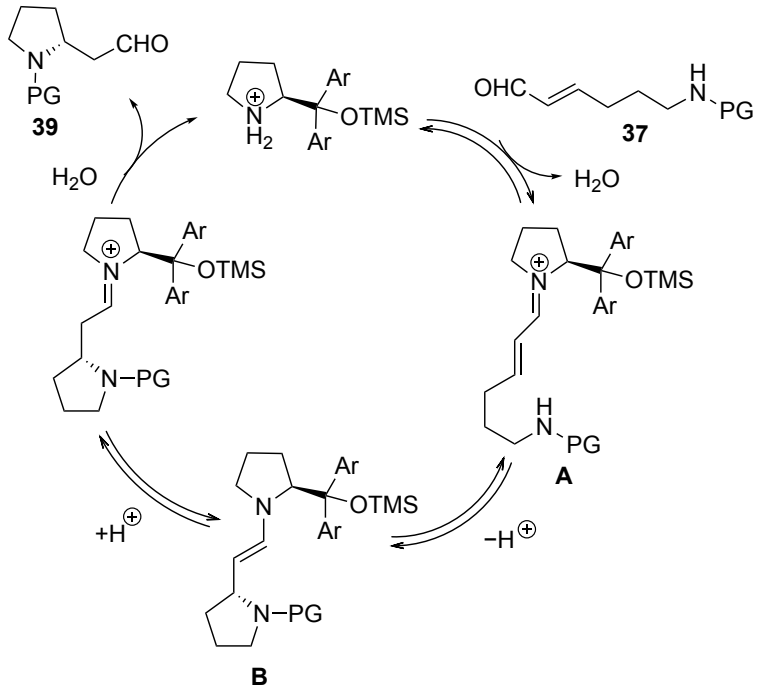
1.3.2.1 The Intramolecular Aza-Michael Addition in Pyrrolidine Synthesis

The aza-Michael reaction is a specific nucleophilic addition process in which a nitrogen-containing nucleophile, such as an amine, adds to an activated alkene, typically an α,β-unsaturated carbonyl compound. This reaction can occur both intramolecularly, where the nucleophile and the Michael acceptor are part of the same molecule, or intermolecularly, where the two components are separate. The intramolecular aza-Michael addition has gained significant attention in the synthesis of pyrrolidines due to its ability to efficiently form cyclic structures. In asymmetric synthesis, the aza-Michael addition can be tailored to selectively produce enantioenriched pyrrolidines with control over the stereochemistry of the newly formed stereogenic centres. This can be achieved through the use of catalysts, chiral auxiliary or reagents, which direct the addition process to provide the desired stereoisomers.[27-30]

Fustero *et. al.* reported a tandem enantioselective organocatalytic reaction that begins with a conjugate addition, followed by an intramolecular aza-Michael cyclisation to construct enantioenriched pyrrolidine frameworks.[31] The reaction involves carbamates containing remote α,β-unsaturated aldehydes **37** as Michael acceptors, and various catalytic conditions were explored to optimize efficiency and selectivity. When the Jørgensen catalyst **38** was employed, this reaction yielded the desired products **39** with good efficiency (61−71% yield) and exceptional enantiomeric excess (93−99% *ee*, Scheme 10). In the proposed mechanism, the process starts with the organocatalytic conjugate addition of a nitrogen nucleophile to the α,β-unsaturated aldehyde **37**, generating an iminium salt **A**. Of the two possible iminium conformations, the *Re* face of the *E*-isomer is sterically hindrance by the bulky group of the catalyst, forcing nucleophilic attack at the β-carbon from the *Si* face, leading to the formation of an enamine intermediate **B**. This intermediate then undergoes a structural rearrangement, triggering an intramolecular aza-Michael reaction, followed by hydrolysis which completes the formation of the pyrrolidine ring **39** (Scheme 11).



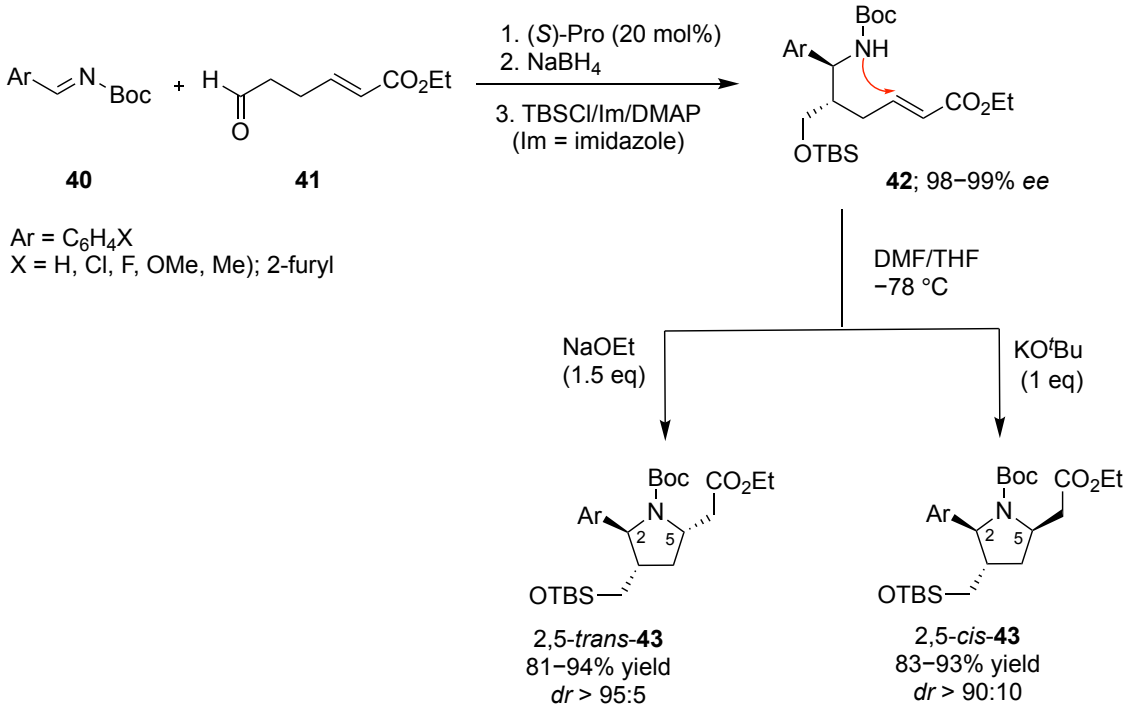
Scheme 10: Asymmetric synthesis of pyrrolidines 39 through cross metathesis followed by intramolecular aza-Michael reaction



*Scheme 11: Proposed mechanism for the formation of **39***

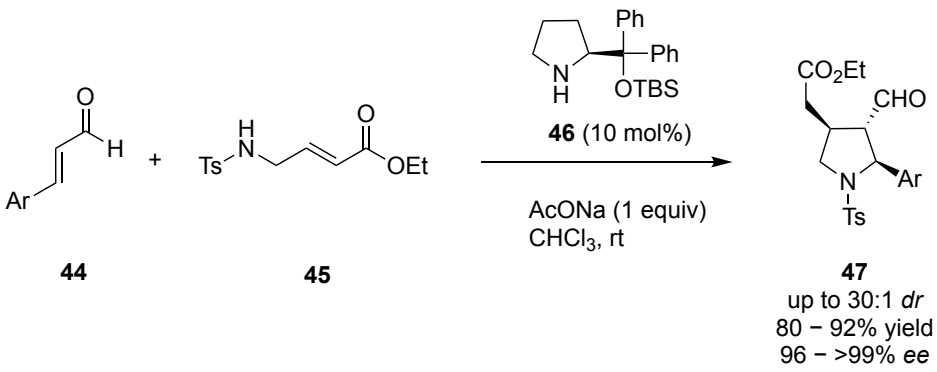
Enkisch and Schneider developed a stereodivergent strategy for synthesising 2,3,5-trisubstituted pyrrolidines **43** through a base-promoted, diastereoselective intramolecular aza-Michael reaction of diastereo- and enantiopure *O,N*-protected ε-amino hexenoates.[32] These precursors were efficiently accessed via a proline-catalysed Mannich reaction between *N*-protected aldimines **40** and α,β-unsaturated aldehyde esters **41**. The stereochemical outcome at the C-5 position of the pyrrolidine ring in compounds **43** was found to be highly

dependent on the choice of base. Specifically, NaOEt promoted the selective formation of 2,5-*trans*-isomers of **43** with excellent diastereoselectivity (*dr* > 95:5), while the use of the stronger, sterically hindered KO^{t}Bu led predominantly to 2,5-*cis*-configured pyrrolidines (Scheme 12). This divergence in product distribution can be attributed to a switch between kinetic and thermodynamic control. Using the weaker base (NaOEt) the kinetic *trans*-pyrrolidine formed, while the stronger base (KO^{t}Bu) renders the reaction reversible, and allows epimerisation, leading predominantly to the *trans* isomer. This stereodivergent approach highlights the crucial role of base selection in dictating the stereochemical outcome of aza-Michael reactions, offering a powerful synthetic strategy for the construction of highly substituted pyrrolidines.



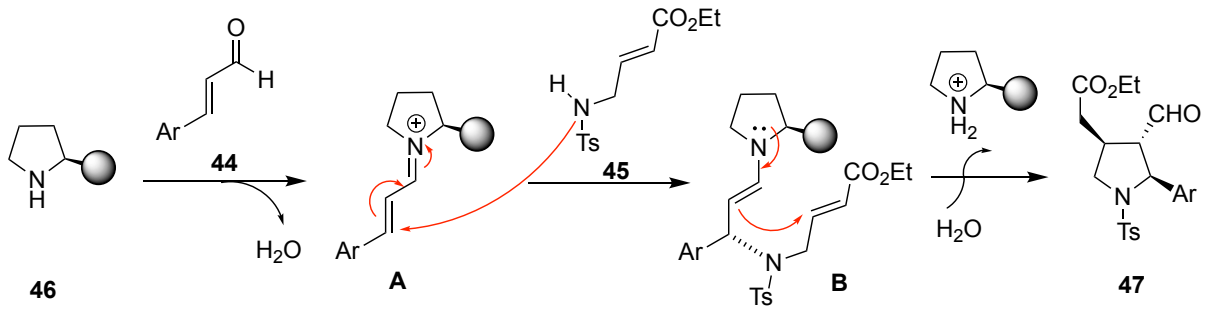
*Scheme 12: Synthesis of 2,3,5-trisubstituted pyrrolidines **43** via base-promoted intramolecular aza-Michael reaction*

In 2008, Wang *et. al.* introduced a highly enantio- and diastereoselective organocatalytic cascade aza-Michael-Michael reaction as a direct and efficient method for the synthesis of trisubstituted chiral pyrrolidines **47** from α,β-unsaturated aldehydes **44** and *N*-tosylated acrylate **45** (Scheme 13).[33] This reaction employs a chiral diphenylprolinol TMS ether catalyst **46** in combination with a base (AcONa) to promote a sequential aza-Michael addition followed by a Michael reaction.



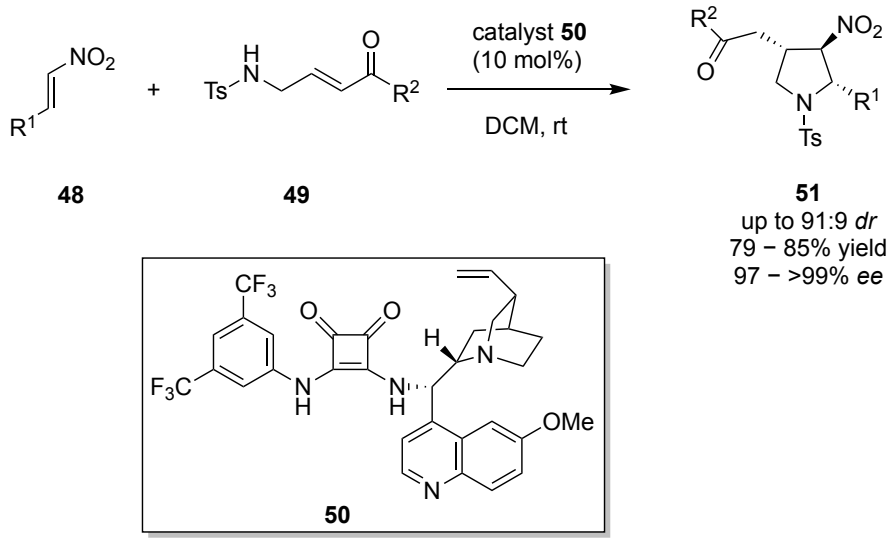
*Scheme 13: Organocatalytic cascade aza-Michael-Michael reaction for the synthesis of chiral pyrrolidines **47***

The mechanism involves the initial activation of the α,β-unsaturated aldehyde **44** by the catalyst **46**, forming an iminium intermediate **A**. This intermediate undergoes an aza-Michael addition with an *N*-tosylated acrylate **45**, leading to the formation of a chiral enamine intermediate **B**. The presence of the Ts (tosyl) protecting group is crucial for the efficiency of the reaction. The strong electron-withdrawing effect of the Ts increases the acidity of the NH group, which in turn facilitates the formation of a more nucleophilic nitrogen anion under basic conditions. This enhanced nucleophilicity is essential for the cascade process, as no reaction occurs with other protecting groups such as Ac, Boc and Cbz under the proposed conditions. The electronic nature and position of substituents on the enal component **44** do not significantly affect the reaction rate or selectivity, making this approach broadly applicable. Following the aza-Michael addition, an intramolecular Michael reaction takes place, and after hydrolysis leads to formation of the trisubstituted chiral pyrrolidines **47** with good yield (80 – 92%) and excellent enantiomeric excess (96 – >99% *ee*, Scheme 14).

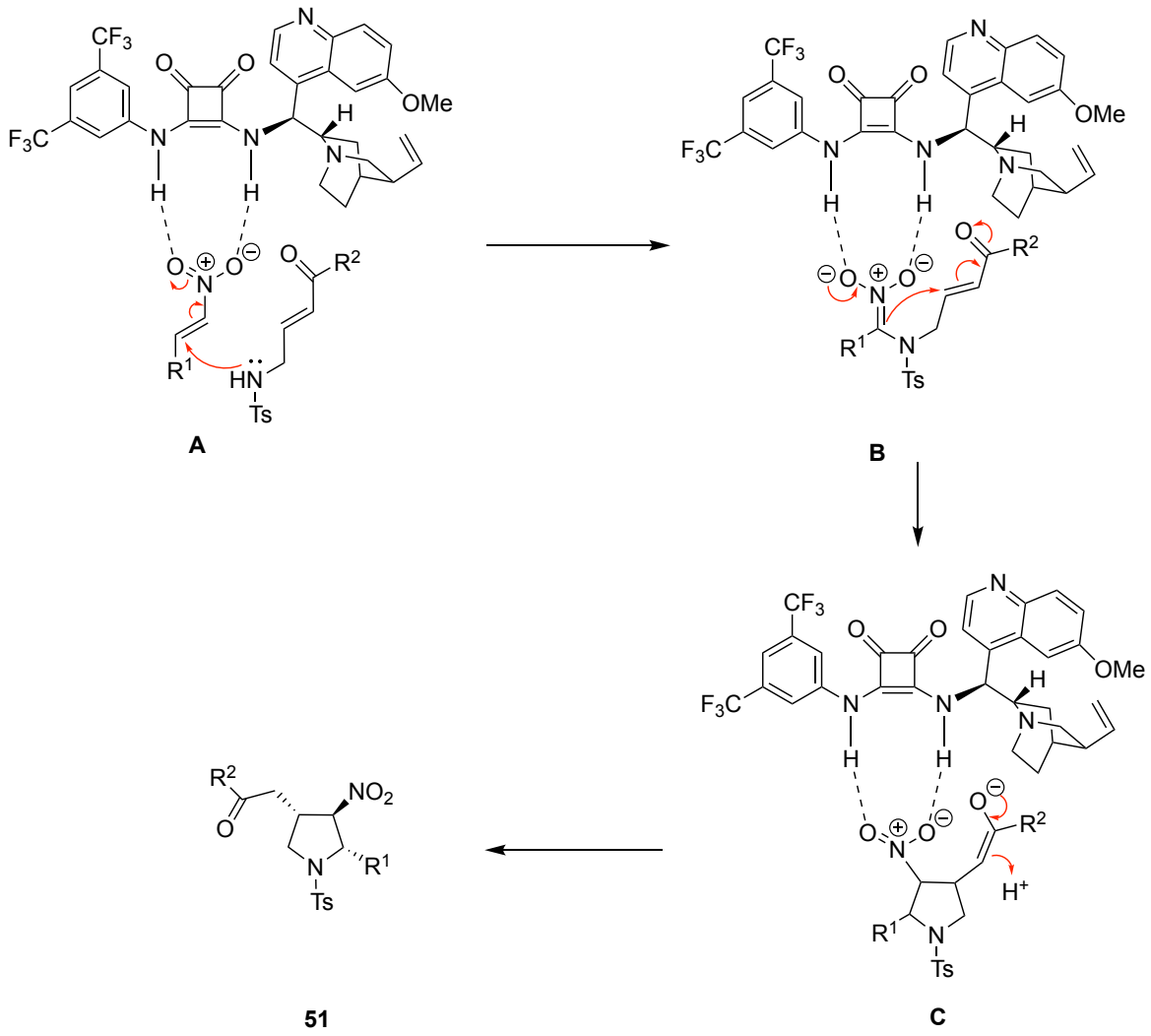


*Scheme 14: Proposed mechanism for the formation of **47***

In the following year, Du and co-workers expanded the scope of the organocatalytic aza-Michael-Michael cascade reaction by utilizing nitroolefins **48** as the key electrophilic component, instead of the α,β-unsaturated aldehydes **44** to synthesise chiral trisubstituted pyrrolidines **51** (Scheme 15).[34] Nitroolefins are highly stabilized by resonance due to the electron-withdrawing nature of the nitro group, which increases the polarization of the double bond and makes the carbonyl carbon more susceptible to nucleophilic attack. This effect enables better stereochemical control, resulting in higher enantioselectivity in the final product. By using nitroolefins in combination with the squaramide catalyst **50**, which activates both the electrophilic nitroolefin and the nucleophile through hydrogen bonding, the reaction becomes more efficient and selective (Scheme 16). As a result, the reaction produces superior stereochemical outcomes, with enantioselectivities exceeding 99% and diastereoselectivities up to 91:9 *dr*.



*Scheme 15: Synthesis of trisubstituted pyrrolidines **51***



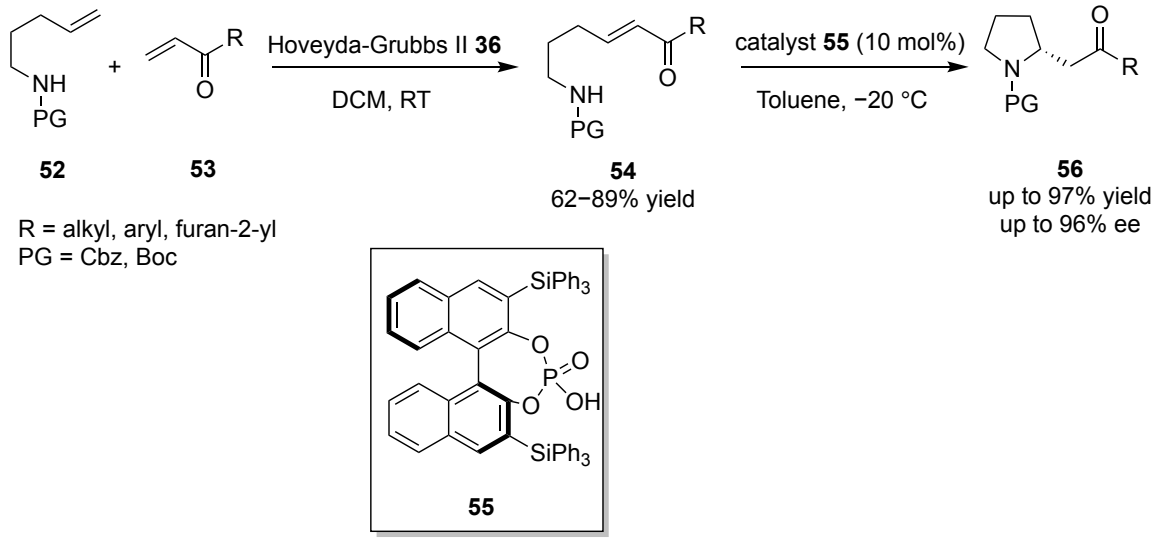
Scheme 16: Possible mechanism of the reaction

1.3.2.2 Brønsted Acid Catalysed Asymmetric Cyclisation in Pyrrolidine Synthesis

Brønsted acid catalysis has become an essential tool in the asymmetric synthesis of pyrrolidines, particularly through cyclisation strategies that provide high stereoselectivity under mild conditions.[35-37] Unlike Lewis acids, which function by coordinating to electron-rich centres, Brønsted acids activate substrates via protonation or hydrogen bonding, enhancing their electrophilicity and facilitating nucleophilic attack. This unique activation mode makes Brønsted acids highly effective for enantioselective cyclisation reactions, where precise stereocontrol is required. A particular powerful approach involves chiral Brønsted acids, such as BINOL-derived phosphoric acids, which create a defined chiral environment around the reactive centre. These catalysts have been extensively utilised in asymmetric cyclisation, including the intramolecular aza-Michael addition a key strategy in pyrrolidine synthesis. In

this reaction, a nucleophilic amine attacks an electrophilic Michael acceptor, forming a five-membered ring with high enantioselectivity. The catalytic system not only accelerates the reaction but also dictates the absolute configuration of the product, making it a valuable method for constructing complex pyrrolidine-containing natural products and pharmaceuticals.

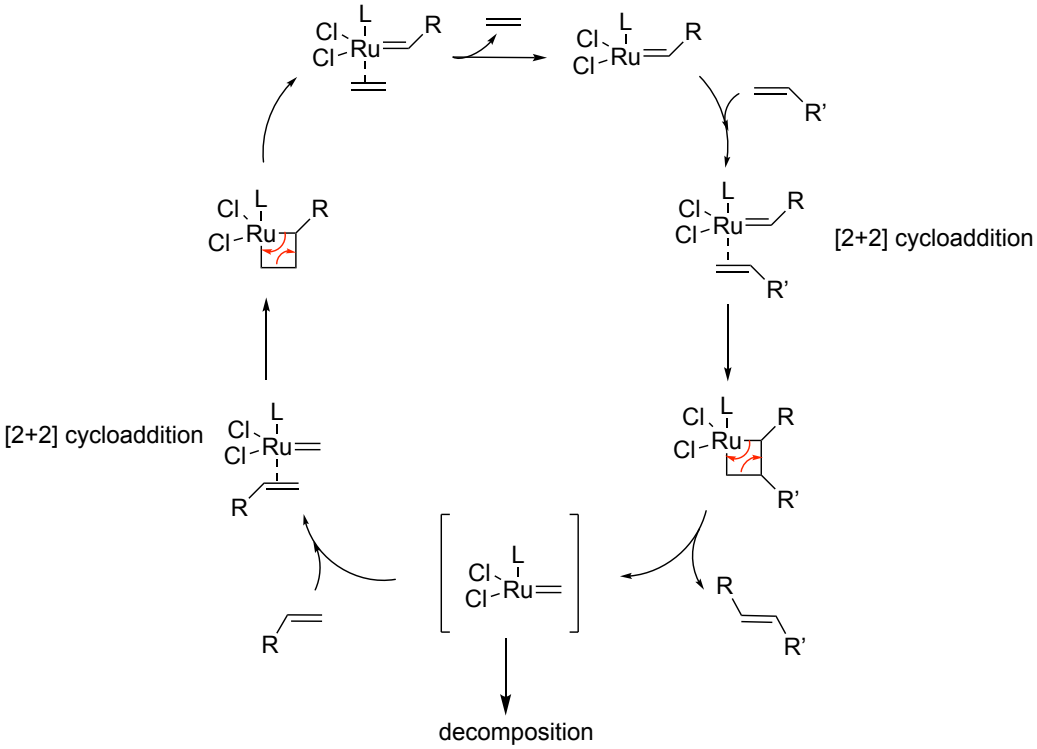
In this context, in 2012, Yu *et. al.* introduced a highly enantioselective method for synthesising 2-substituted pyrrolidines **56** through a domino cross metathesis followed by an intramolecular aza-Michael addition.[38] The process begins with a cross metathesis between an enone carbamate **52** and an olefin **53**, forming an intermediate **54** that undergoes an intramolecular aza-Michael addition catalysed by BINOL-derived chiral phosphoric acid **55**, yielding a series of 2-substituted pyrrolidines **56** in good yields (84–97%) and high enantioselectivity (82−96% ee) (Scheme 17). The authors highlight that Cbz-protected carbamates were more suitable than their Boc-protected counterparts. This preference is attributed to the fact that Cbz-protected substrates facilitated the desired intramolecular aza-Michael addition more effectively, leading to higher yields and enantioselectivities.



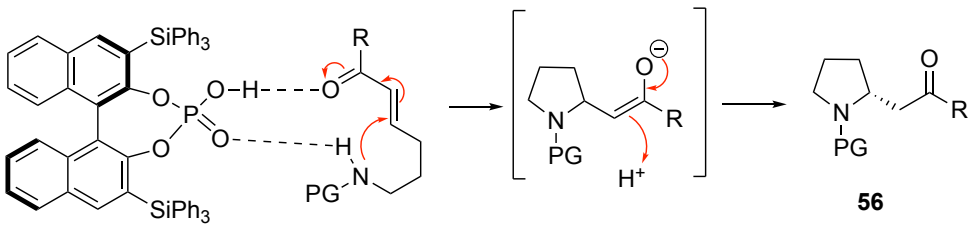
*Scheme 17: Asymmetric synthesis of 2-substituted pyrrolidines **56***

The accepted reaction mechanism for the cross-metathesis step follows a [2+2] cycloaddition and retro-[2+2]-cycloaddition pathway, beginning with the coordination of the alkene to the metal-carbene complex and formation of a four-membered metallacyclobutane intermediate. This intermediate undergoes cyclo-reversion, generating a new metal-carbene

and an exchanged alkene. The process repeats with the second alkene, ultimately yielding the cross-metathesized product while regenerating the catalyst **36** (Scheme 18). Subsequently, the BINOL-derived chiral phosphoric acid **55**, acting as a Brønsted acid catalyst, facilitates an intramolecular transformation by increasing the electrophilicity of the imine substrate through hydrogen bonding with the phosphoric acid moiety. This allows the protected amine to attack the conjugated α,β-unsaturated electrophile in an intramolecular reaction, forming a carbon-nitrogen bond and closing the ring to form a pyrrolidine structure **56** (Scheme 19).



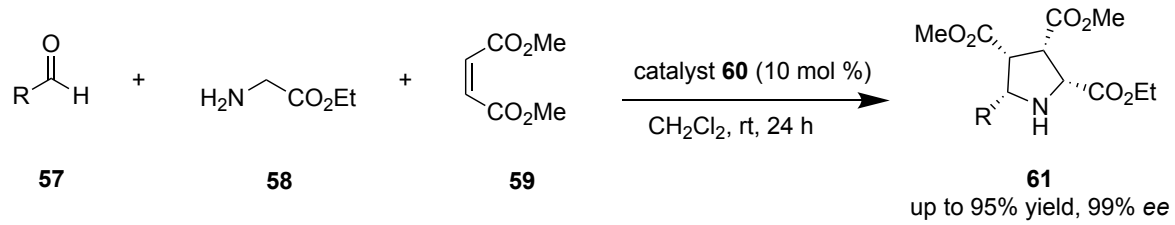
Scheme 18: Mechanism of the cross-metathesis reaction



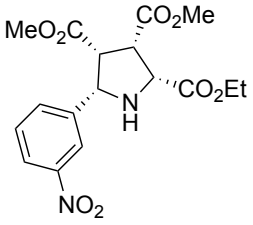
*Scheme 19: Proposed mechanism for the formation of **56***

Gong *et al.* reported a one-pot asymmetric organocatalytic three-component 1,3-dipolar cycloaddition of aldehydes **57**, amino esters **58**, and dimethyl fumarate **59**, enabling the efficient synthesis of multisubstituted pyrrolidines **61** (Scheme 20).[39] This reaction employs a

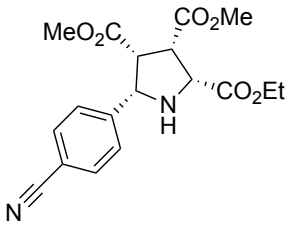
chiral Brønsted acid **60**, specifically a bisphosphoric acid derived from BINOL, to catalyse the formation of azomethine ylides **A** or **B** from aldehydes **57** and amino esters **58**. The reaction begins with the activation of aldehyde **57** and amino ester **58** to generate an azomethine ylide intermediate **A** or **B**. The activated azomethine ylide then undergoes a 1,3-dipolar cycloaddition with the electron-deficient dimethyl fumarate **59**, acting as a dipolarophile. The chiral environment provided by the catalyst effectively controls the stereochemistry during the cycloaddition, leading to the formation of highly enantioenriched pyrrolidines **61**. (Scheme 21).



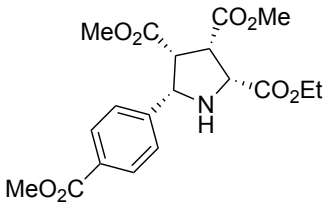
57 **58** **59** **61**
up to 95% yield, 99% *ee*



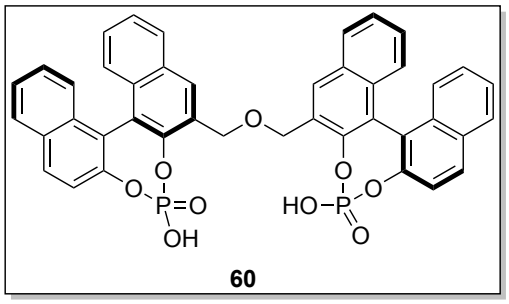
61a
95% yield, 99% *ee*



61b
94% yield, 95% *ee*

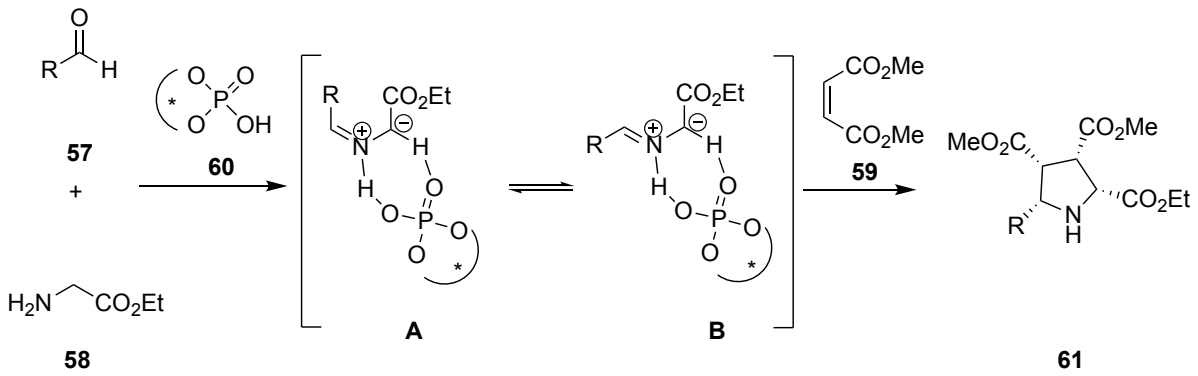


61c
88% yield, 98% *ee*



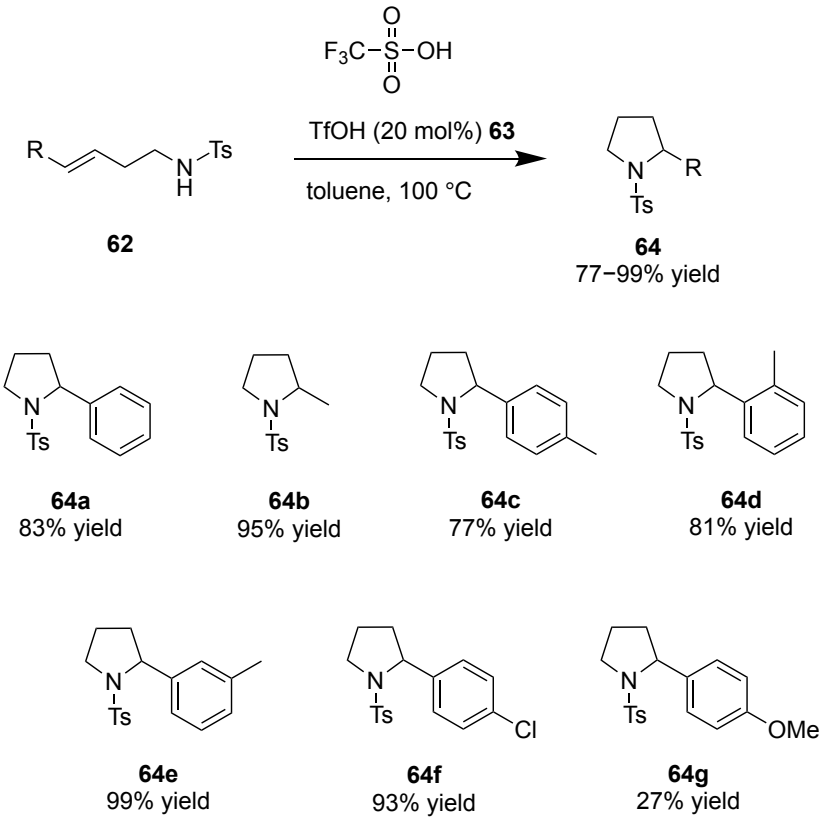
60

*Scheme 20: Three-component 1,3-dipolar cycloaddition catalysed by **61** and the proposed model for BINOL coordination to the azomethine ylide*

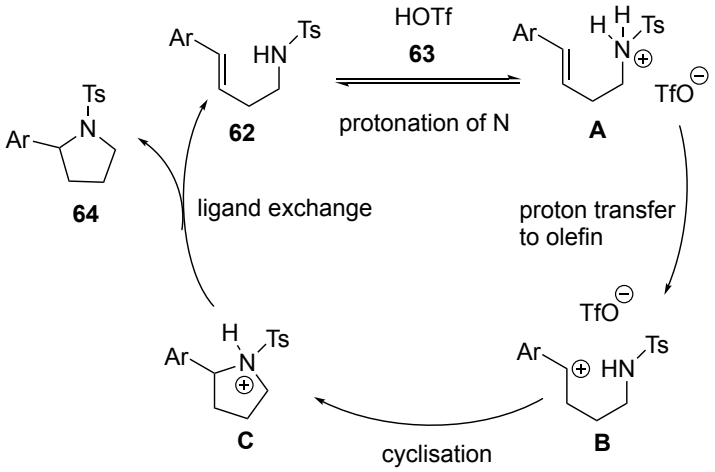


*Scheme 21: Using Brønsted acid catalyst **60** to form trisubstituted pyrrolidines **61***

Hartwig and Schlummer developed an alternative method the synthesising pyrrolidines **64** via a Brønsted acid-catalysed intramolecular hydroamination of protected alkenylamines **62** (Scheme 22).[40] The reaction proceeds through a protonation-initiated cyclisation mechanism, in which triflic acid (TfOH) **63** protonates the alkene, increasing its electrophilicity and facilitating intramolecular nucleophilic attack by the protected amine. This step leads to C–N bond formation and subsequent ring closure, yielding intermediate **C**. Finally, deprotonation restores neutrality and regenerates the Brønsted acid catalyst (Scheme 23). The method proved effective for pyrrolidine synthesis, achieving good yields (77 – 99%) for most substrates. An exception was the *N*-tosyl-2-(methoxyphenyl)pyrrolidine, which gave a significantly lower yield of only 27%.



*Scheme 22: Synthesis of pyrrolidines **64** via intramolecular hydroamination reaction*

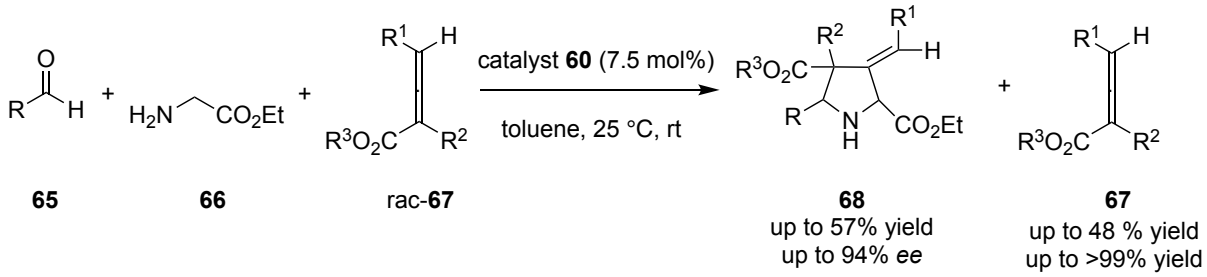


*Scheme 23: Proposed reaction mechanism for the synthesis of **64***

1.3.3 Kinetic Resolution

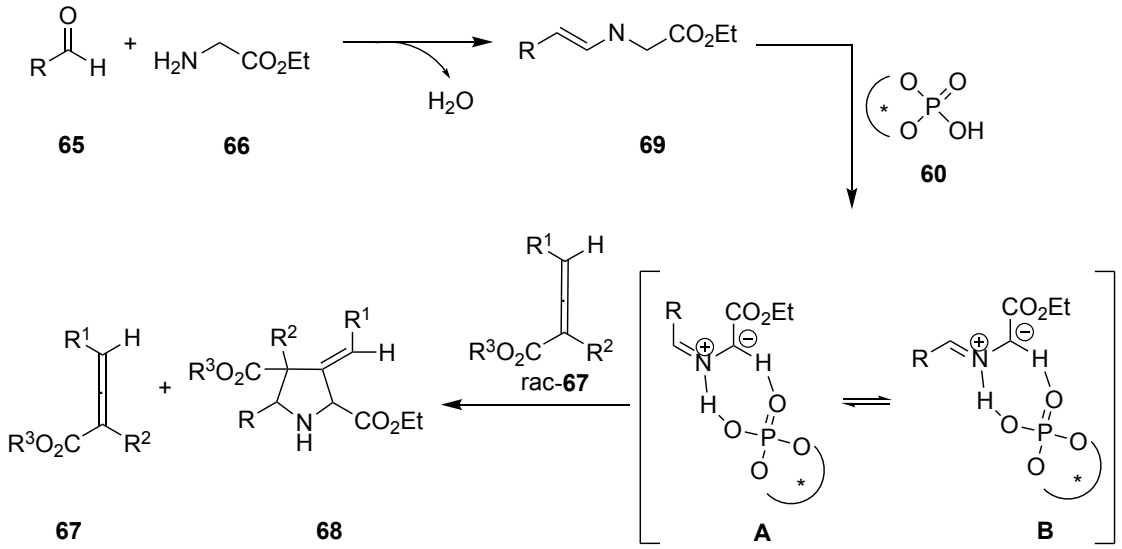
Kinetic resolution is a widely employed strategy in asymmetric synthesis for the formation of enantiomerically enriched products, and/or enantiomerically enriched recovered starting materials, from racemic mixtures based on the differing reaction rates of the starting material enantiomers with a chiral reagent or catalyst. This approach offers a powerful means of obtaining enantiomerically enriched compounds, which are of significant interest in pharmaceutical and natural product synthesis. By selectively transforming one enantiomer over the other, kinetic resolution can provide access to valuable chiral building blocks such as pyrrolidines with high enantiopurity. Various enzymatic and non-enzymatic methods have been developed to achieve efficient kinetic resolution, often involving transition metal catalysts or organocatalysts. The effectiveness of a kinetic resolution process is commonly evaluated in terms of conversion and selectivity factor (s factor), which reflects the discrimination between the enantiomers.

Building upon their previous work on asymmetric organocatalytic three-component 1,3-dipolar cycloaddition using a chiral Brønsted acid (discussed under the section Brønsted Acid Catalysed Asymmetric Cyclisation in Pyrrolidine Synthesis),[39] Gong *et al.* extended their research to a kinetic resolution approach. They demonstrated the efficient resolution of racemic 2,3-allenoates rac-**67** by organocatalytic asymmetric 1,3-dipolar cycloaddition (Scheme 24).[41] In this approach, azomethine ylides **69**, generated in situ from aldehydes **65** and α-amino esters **66**, undergo [3+2] cycloaddition with racemic 2,3-allenoates rac-**67** in the presence of a chiral Brønsted acid catalyst **60**, previously optimized in their earlier work (Scheme 25). The reaction proceeds under mild conditions, affording chiral pyrrolidine derivatives **68** in yields of up to 57% with enantiomeric excess (*ee*) up to 94%, while the unreacted allenoate **67** is recovered with up to 99% *ee*. The reaction exhibits excellent selectivity (s-factor > 50 in some cases) and broad substrate applicability, though steric effects influenced efficiency in certain cases. This work highlights the versatility of 1,3-dipolar cycloaddition chemistry in the kinetic resolution of allene-based dipolarophiles and further extends the synthetic utility of 2,3-allenoates rac-**67** as valuable enantioenriched intermediates in asymmetric synthesis.



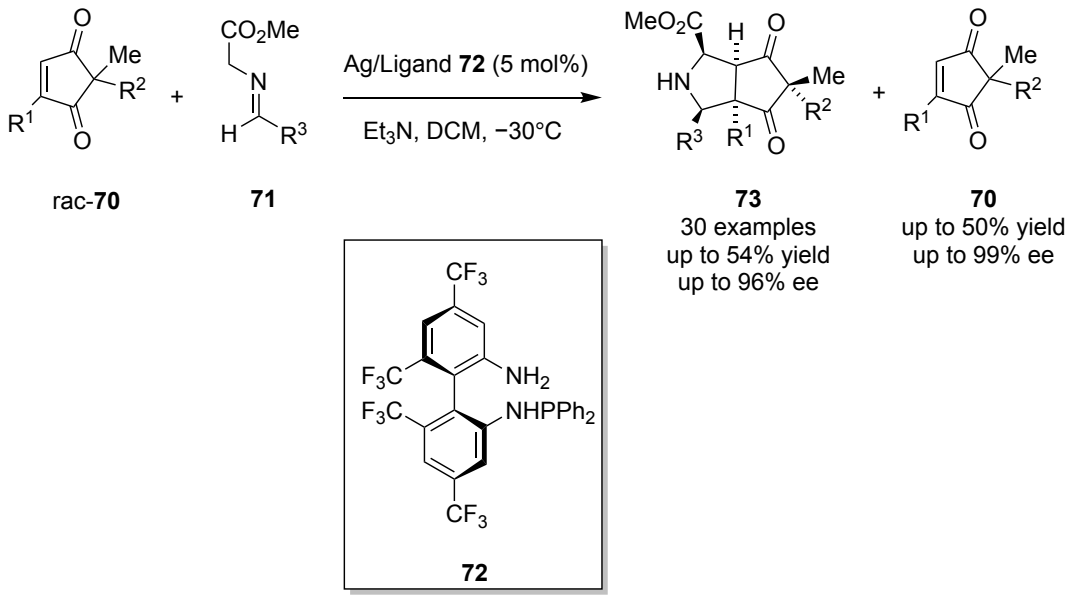
R = 4-BrC_6H_4
R^1= Et, $Cl(CH_2)_2$, $PhCH_2$
R^2 = Bn, Me, Allyl, H, CH_2CO_2Bn, 4-$BrC_6H_4CH_2$
R^3 = (9-anthracenyl)methyl

*Scheme 24: Kinetic resolution of racemic 2,3 allenoates **67** via asymmetric 1,3-dipolar cycloaddition*



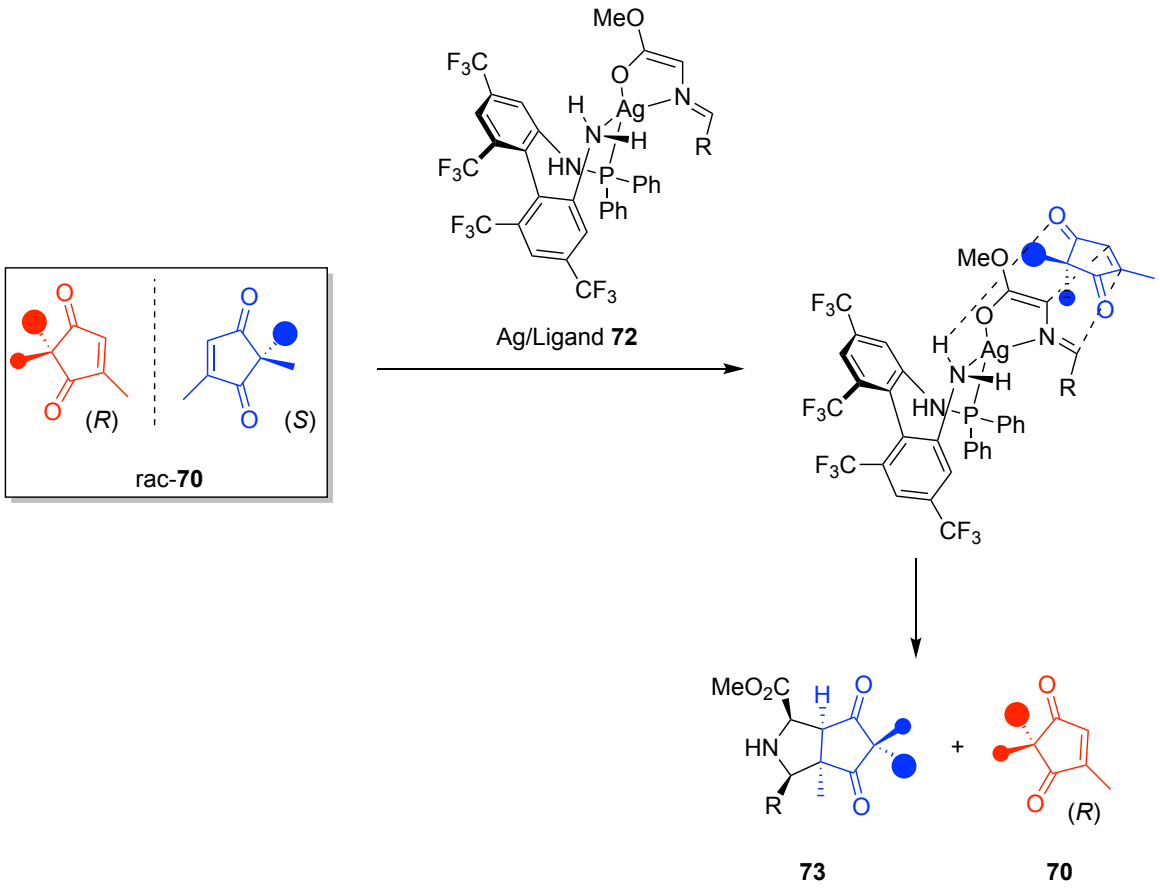
*Scheme 25: Proposed model for kinetic resolution of racemic 2,3 allenoates **65***

A related reaction by Wang *et al.* demonstrates a similar 1,3-dipolar cycloaddition of racemic cyclopentene-1,3-diones rac-**70**, catalysed by Ag(I), with various azomethine ylides **71**, aimed at synthesising bicyclic pyrrolidine derivatives **73** (Scheme 26).[42] Under modified reaction conditions for the kinetic resolution of different cyclopentenediones rac-**70**, excellent enantioselectivities were obtained, with up to 99% *ee* for the recovered starting cyclopentenediones **70** and up to 96% *ee* for the resulting polycyclic products **73**.



*Scheme 26: Kinetic resolution of racemic cyclopentene-1,3-diones rac-**70** via asymmetric 1,3-dipolar cycloaddition*

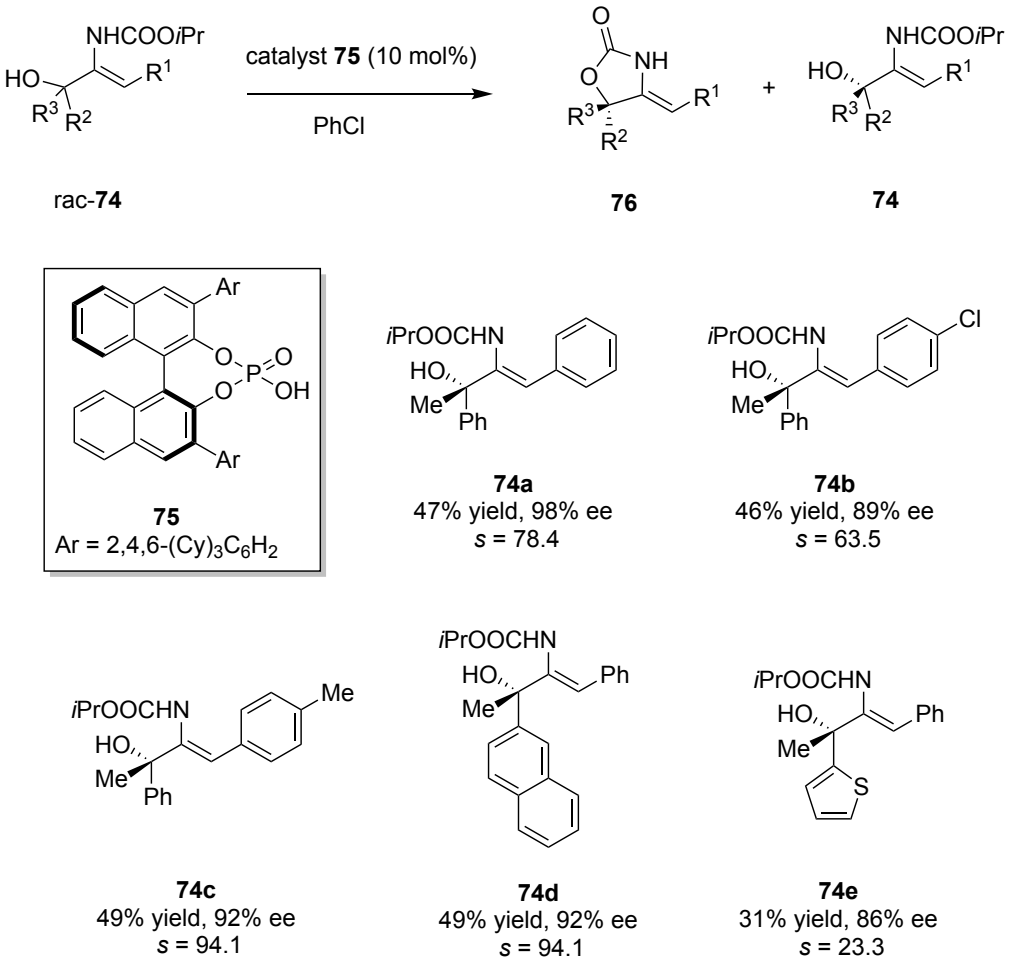
The proposed transition state in this mechanism involves the Ag(I) centre coordinated to the chiral ligand **72**, forming a complex that coordinates with the substrate. This coordination activates the cyclopentene-1,3-dione towards nucleophilic attack while inducing stereocontrol. The diastereoselectivity of the reaction is determined by the facial difference created by the chiral ligand **72**, which preferentially orients the substrate in a way that favours the formation of one enantiomer over the other. Meanwhile, regioselectivity is governed by the steric hindrance of the trisubstituted alkene, directing the nucleophile to the less hindered position and ensuring selective reactivity (Scheme 27). Notably, the authors also demonstrated the synthetic utility of this method through a one-pot sequential transformation strategy. In this approach, the enantioenriched products and unreacted starting materials could be directly reacted to undergo further derivatisation in the same reaction vessel, enabling efficient access to structurally diverse chiral compounds without intermediate purification.



Scheme 27: Proposed transition state of the reaction

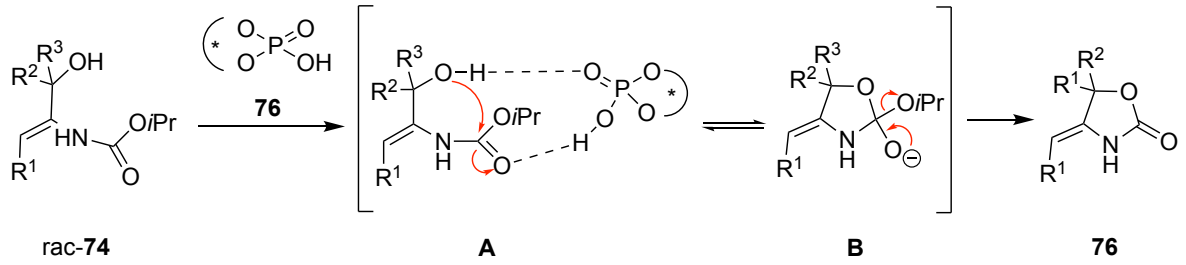
Kinetic resolution represents a pivotal strategy for accessing enantiomerically enriched secondary alcohols; however, the application of this methodology to racemic tertiary alcohols remains relatively underexplored. A significant advancement in this area was reported by the Yang research group in 2019, who developed an efficient kinetic resolution protocol for racemic tertiary alcohols rac-**74** using a chiral phosphoric acid catalyst **75**.[43] In their study, racemic alcohol rac-**74** was employed as a model substrate, and a series of chiral phosphoric acids were systematically screened to identify optimal catalytic conditions. The highest enantioselectivity was achieved using catalyst **75** in chlorobenzene as the solvent (Scheme 28). Following this optimization, the substrate scope was expanded to evaluate the general applicability of the method. Although this study does not constitute an example of kinetic resolution for pyrrolidine, it has been included in this thesis because it represents an intriguing and noteworthy advancement in the broader field. The results demonstrated that substrates bearing various substituted aryl groups yielded excellent enantioselectivity and

selectivity. Importantly, the method also proved effective for tertiary alcohols containing methyl or primary alkyl substituents, further highlighting its versatility.



*Scheme 28: Kinetic resolution of racemic tertiary alcohols rac-**74***

The mechanism begins with the activation of the ester carbonyl group through hydrogen bonding with the chiral phosphoric acid catalyst. This non-covalent interaction increases the electrophilicity of the carbonyl carbon and orients the substrates within a chiral environment, facilitating enantioselective induction. The hydroxyl group of the allylic alcohol engages in an intramolecular nucleophilic attack on the activated carbonyl carbon, forming a tetrahedral intermediate **B**. This intermediate undergoes rearrangement, facilitating the elimination of the leaving group and resulted in the formation of the cyclic product **76** (Scheme 29).



Scheme 29: Proposed mechanism for the intramolecular transesterification by chiral Brønsted acid

Although various efficient methods have previously been developed for the asymmetric synthesis of pyrrolidines from achiral starting materials, such strategies are still relatively limited in terms of the structural diversity and complexity of the resulting compounds.

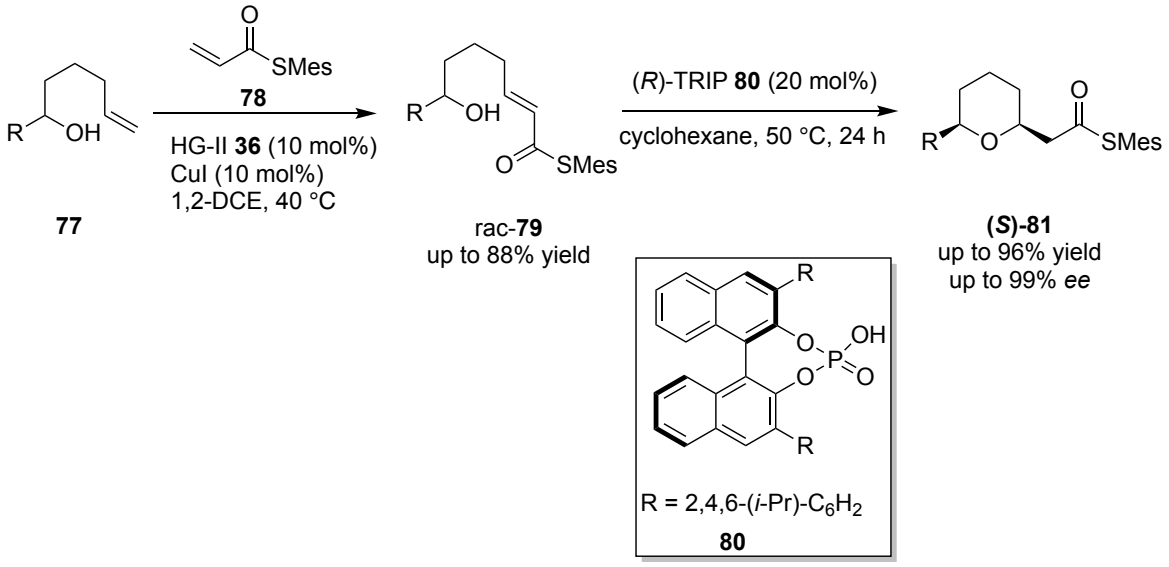
The following Chapter 2 aim to address this limitation by introducing a novel, general approach for chiral cyclic amine derivatives, called 'Clip-Cycle' methodology. This methodology enables the synthesis of various cyclic amines, including 2,5- and 3,5-disubstituted pyrrolidines (the focus of Chapter 2), which remain largely unexplored in the current literature and hold significant potential for further applications in medicinal and synthetic chemistry.

2- Results and Discussion

2.1 Background Work in the Clarke Group

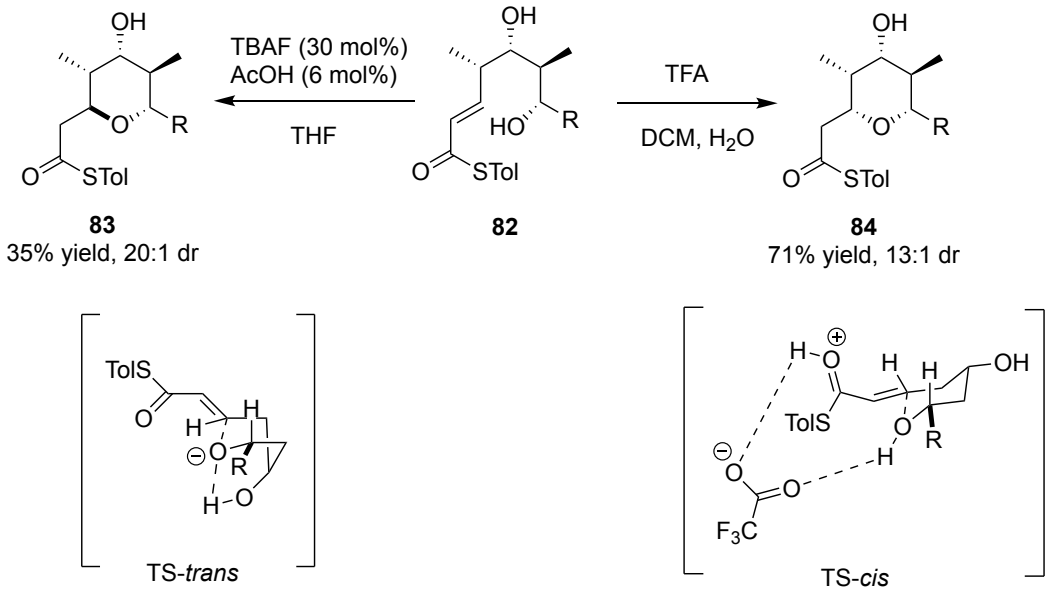
The Clarke group has for many years focused on the stereoselective synthesis of heterocycles, recognizing their fundamental role in the construction of natural products and bioactive molecules. Given the widespread occurrence of chiral heterocycles in both natural products and pharmaceuticals, the group actively pursued innovative strategies to enable their efficient and asymmetric synthesis.[44–47] These efforts not only contributed to advancement in synthetic methodology but also supported broader applications in total synthesis and drug development.

The Clarke group has developed a modular and enantioselective strategy for the synthesis of tetrahydropyrans (THPs) via a tandem ring-closing metathesis and oxa-Michael cyclisation, using an approach they have named 'clip-cycle' methodology.[48] In this approach, alkene-tethered nucleophiles (*e.g.* alcohols **77**) are reacted with thioacrylate **78** in a cross-metathesis reaction to generate racemic Michael acceptors (*e.g.* rac-**79**). This is the 'clip' step of the approach. Then, subsequent intramolecular oxa-Michael addition, catalysed by a chiral phosphoric acid (CPA) **80**, furnishes the desired heterocycle (in this example, THP derivatives **(*S*)-81**) in the 'cycle' step (Scheme 30).



*Scheme 30: Asymmetric 'clip-cycle' synthesis of tetrahydropyrans (S)-**81**. The stereochemical assignment (S) refers to the stereogenic centre formed in the 'cycle' step.*

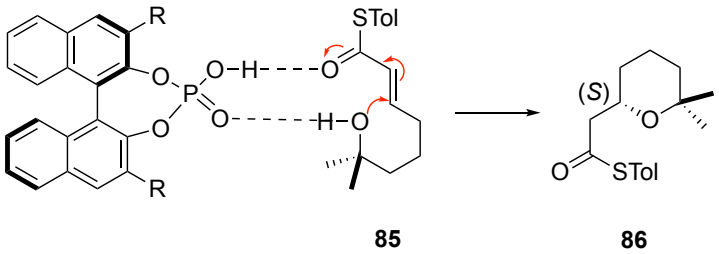
To explain the selection of thioesters as the Michael acceptors in this sequence, earlier mechanistic studies by the Clarke group can be considered.[49] These studies demonstrated that α,β-unsaturated thioesters undergo highly stereodivergent oxa-Michael cyclisation depending on the reaction conditions. Under basic conditions (TBAF), 2,6-*trans*-tetrahydropyran products **83** were formed with up to 20:1 diastereoselectivity, whereas switching to trifluoroacetic acid (TFA) led to the preferential formation of 2,6-*cis*-tetrahydropyran isomers **84** (up to 13:1 dr, Scheme 31). Computational studies revealed that under the TFA conditions, the acid acts as a proton shuttle, simultaneously protonating the thioester carbonyl and deprotonating the hydroxyl nucleophile. This dual role facilitates a chair-like transition state that favours formation of the *cis*-product **84**. In contrast, under TBAF conditions, the 4-hydroxyl group plays a key role as a hydrogen-bond donor, stabilising a distinct transition state that led to the *trans*-isomer **83**.



Scheme 31: Stereodivergent oxa-Michael reactions

To explain the selectivity of the asymmetric variant of the reaction using chiral phosphoric acid (CPA) the computationally derived model below indicates that when using CPA, both diastereomers are preferentially formed with (*S*)-configuration **86**, findings that are consistent with the experimental results (Scheme 32).[49] The use of a thioesters Michael acceptor proved to be particularly important in the asymmetric variant. When more electron withdrawing groups (*e.g.* an aldehyde or ketone) were used, cyclisation took place too easily,

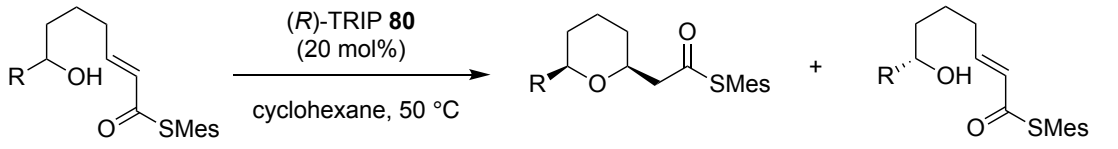
without needing the CPA catalyst, and hence led to the formation of racemic products. Less electron withdrawing groups (*e.g.* esters) were not reactive enough to cyclise. Thus, the thioester provided the ideal balance; it was reactive enough to cyclise, but only with assistance from the CPA catalyst.



85 **86**

Scheme 32: Preliminary computational study of the CPA catalysed oxa-Michael cyclisation

Another important aspect investigated in previous Clarke group work was the kinetic resolution of racemic alcohol substrates, leading to the formation of enantioenriched tetrahydropyran products. When racemic alcohols were employed as substrates, the oxa-Michael step catalysed by the chiral phosphoric acid can proceed with high enantioselectivity, with one of the starting material enantiomers reacting in preference to the other, allowing for the isolation of enantioenriched tetrahydropyran products (*S*)-**81** and enantioenriched alcohol (*S*)-**79** (Scheme 33). This outcome highlights the versality of the 'clip-cycle' methodology, demonstrating its utility not only in the enantioselective synthesis of THPs but also in the resolution of racemic secondary alcohols under mild, metal-free conditions.



rac-**79**

a, R = Ph
b, R = *i*Pr

(*S*)-81

Conversion: 58% at 8 h; **a**, 68% *ee*
Conversion: 52% at 6 h; **b**, 92% *ee*

(*S*)-79

a, R = Ph, 97% *ee*
b, R = *i*Pr 85% *ee*

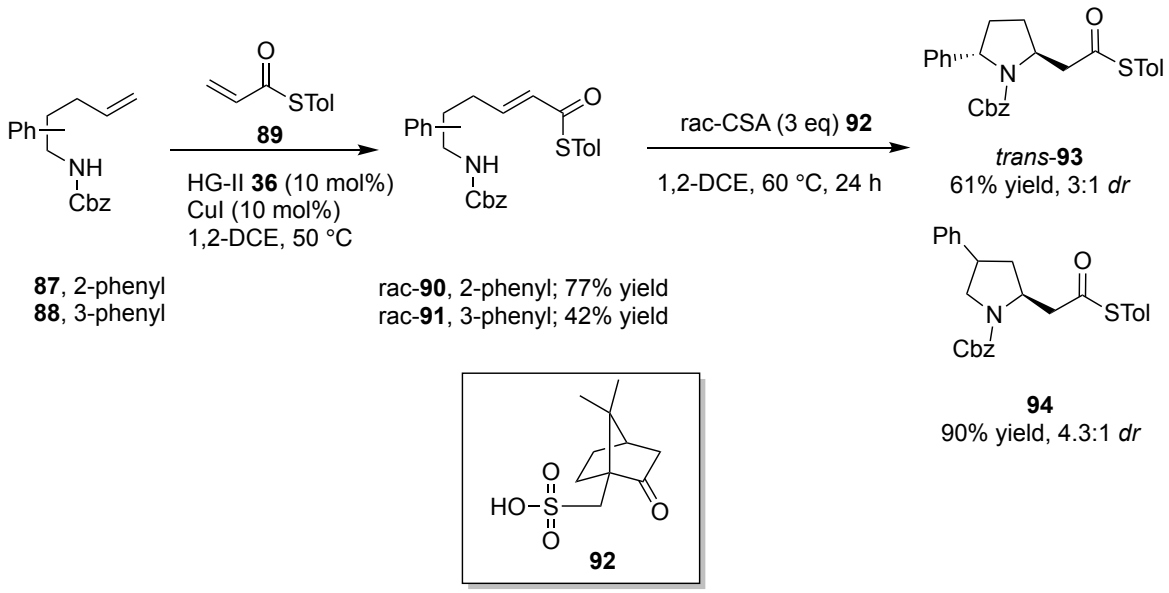
*Scheme 33: Kinetic resolution of alcohols rac-**79** via the 'clip-cycle' methodology*

	% *ee*	% conversion	

R	(*S*)-81	(S)-79	(*S*)-81	(*S*)-79	conversion time (hours)
Ph	68	97	58	42	8
*i*Pr	92	85	52	48	6

*Table 1: Kinetic resolution of alcohols rac-**79***

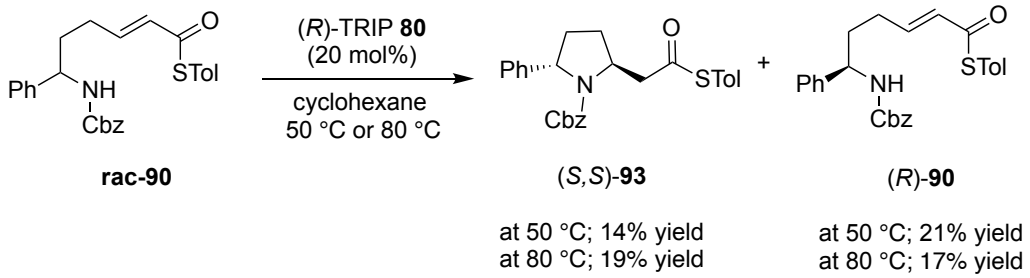
Building upon the successful application of the 'clip-cycle' methodology to oxygen-containing heterocycles, the Clarke group extended this approach to the synthesis of nitrogen-based systems, specifically 2- and 3-substituted pyrrolidines.[50] In this work, Cbz-protected amines **87** and **88** were subjected to cross-metathesis with α,β-unsaturated thioester **89** using the Hoveyda-Grubbs II catalyst **36** in the presence of CuI to generate cyclisation precursors rac-**90** and rac-**91**. Subsequent treatment with racemic camphorsulfonic acid (rac-CSA) **92** facilitated aza-Michael cyclisation to afford racemic pyrrolidine products *trans*-**93** and **94**, which enabled chromatographic resolution and HPLC analysis (Scheme 34).



*Scheme 34: Asymmetric Michael reaction for the synthesis of pyrrolidines trans-**93** and **94***

Following the synthesis of racemic pyrrolidines, efforts focused on the kinetic resolution of the 2-substituted systems (rac-**90**). This was tested using (*R*)-TRIP **80** as a catalyst in cyclohexane at 50 °C and 80 °C for 24 hours. For the resolution of rac-**90**, 52% conversion into

2,5-pyrrolidine (*S,S*)-**93** was observed after 9 hours at 50 °C by chiral HPLC analysis. The reaction was stopped at this time point. The enantiomeric excess of (*S,S*)-**93** was found to be 69%, with the remaining 48% of the reaction mixture consisting of unreacted starting material, which was enriched to 79% *ee* as the (*R*)-enantiomer (*R*)-**90**. When the reaction temperature was increased to 80 °C, 50% conversion was achieved within 3.5 hours, yielding pyrrolidine (*S,S*)-**93** with a modest enantiomeric excess of 51% *ee*, while the precursor was obtained with 90% *ee* (Scheme 35). Isolated yields for all products are given in the Scheme below.



*Scheme 35: Kinetic resolution of 2-substituted pyrrolidine precursor rac-**90***

Temperature	% *ee*		% conversion		conversion time (hours)
	(*S,S*)-**93**	(*R*)-**90**	(*S,S*)-**93**	(*R*)-**90**	
50 °C	69	79	52	48	3.5
80 °C	90	51	50	49	9

*Table 2: Kinetic resolution of 2-substituted pyrrolidine precursor rac-**90***

To summarise the previous studies, the Clarke group successfully applied the 'clip-cycle' methodology to the enantioselective synthesis of THPs, as described above. They also completed some work on the enantioselective synthesis of 2-substituted pyrrolidines, although examples based on kinetic resolution were limited. Restrictions imposed by the COVID-19 pandemic at the time this work was done meant that laboratory access was limited, and experiments aimed at studying the resolution of 2-substituted pyrrolidines were incomplete. Furthermore, work to study the resolution of 3-substituted pyrrolidine was also not completed, and the stereochemical assignments of the products in both the 2- and 3-substituted pyrrolidine series remained inconclusive. Of particular note, while the kinetic resolutions in Scheme 34 and 35 show the stereochemistry of the major enantiomer formed,

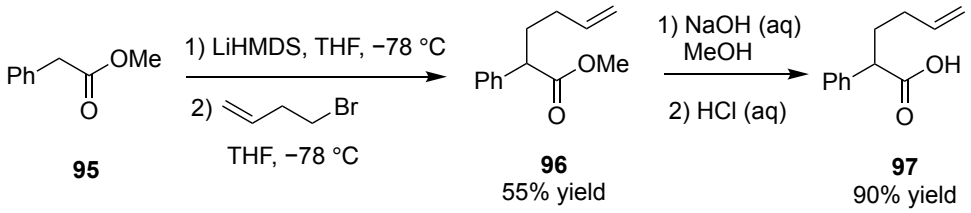
these assignments were not known at the time; the assignments were made retrospectively, based on the results that follow in this Chapter.

Therefore, the aim of my work described in this Chapter was to address these gaps and unambiguously determining the absolute stereochemistry of these pyrrolidines. We also focused on improving the kinetic resolution of 3-substituted pyrrolidine, which was only very briefly explored before this PhD.

2.2 2-Substituted Pyrrolidine

2.2.1 Synthesis of Cyclisation Precursor

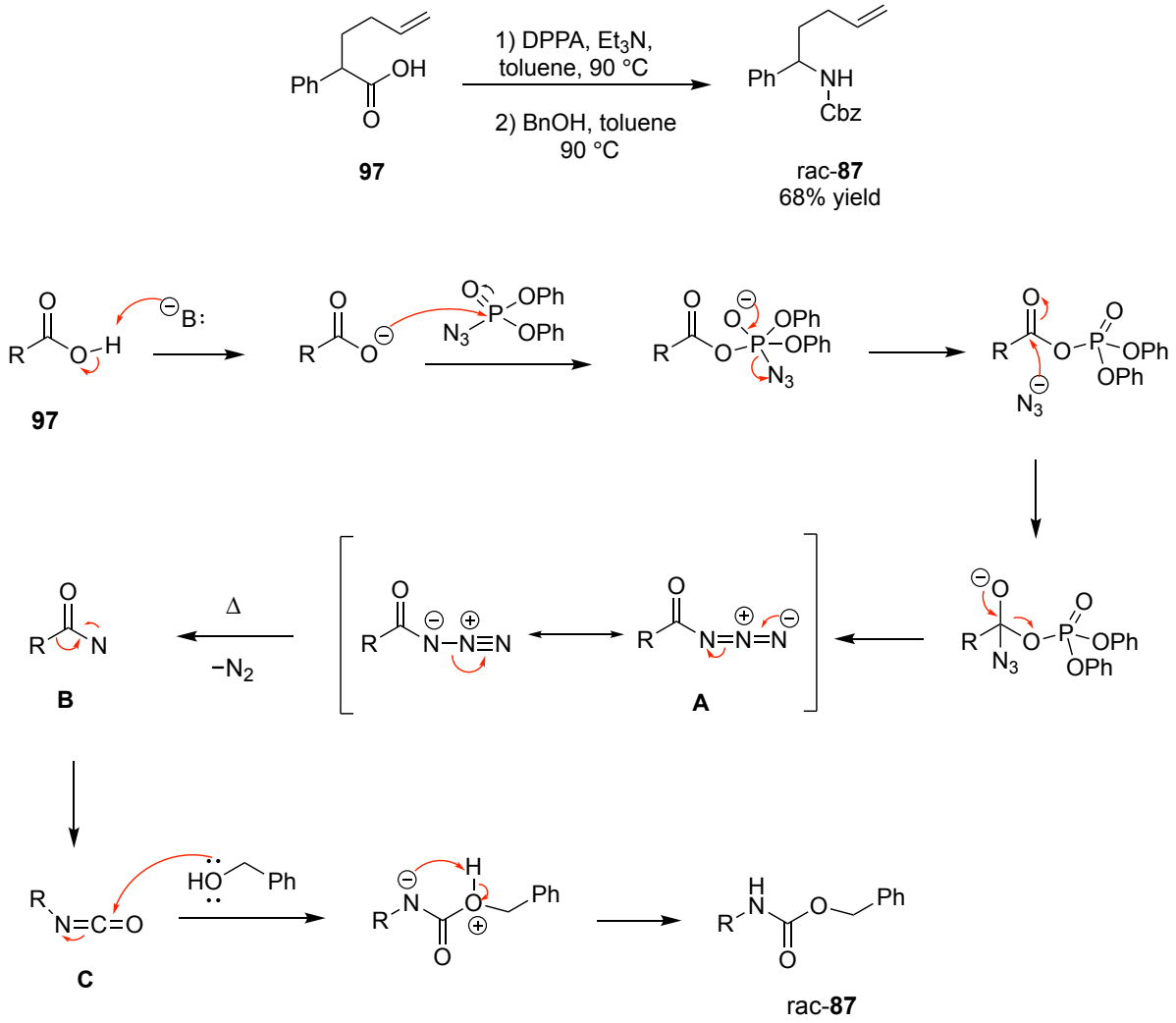
Building on previous work in the Clarke group, the initial stage of this project focused on establishing the absolute stereochemistry of the 2-phenyl pyrrolidine product that we now know to be (*S,S*)-**93**. This required the preparation of racemic amine rac-**87** as a cyclisation precursor, which would undergo subsequent aza-Michael cyclisation. The process began with the deprotonation of methyl phenylacetate **95** in the presence of LiHMDS, followed by alkylation with 4-bromobutene to afford alkenyl ester **96** in 55% yield. The ester **96** was then hydrolysed under basic conditions to give the corresponding carboxylic acid **97** in 90% yield (Scheme 36).



*Scheme 36: Synthesis of carboxylic acid **97***

The carboxylic acid **97** was then subjected to a Curtius rearrangement, starting by using diphenylphosphoryl azide (DPPA) and triethylamine (Et_3N) to form the acyl azide intermediate **A**. This step proceeds via nucleophilic attack of the anion on the electrophilic phosphorus centre of DPPA, followed by elimination to generate the acyl azide **A**. Upon gentle heating, intermediate **A** underwent thermal decomposition, releasing molecular nitrogen (N_2) and forming a nitrene **B**. A subsequent 1,2-migration of the R group from the carbonyl carbon to the nitrogen atom results in the formation isocyanate intermediate **C**. Usually at this point of

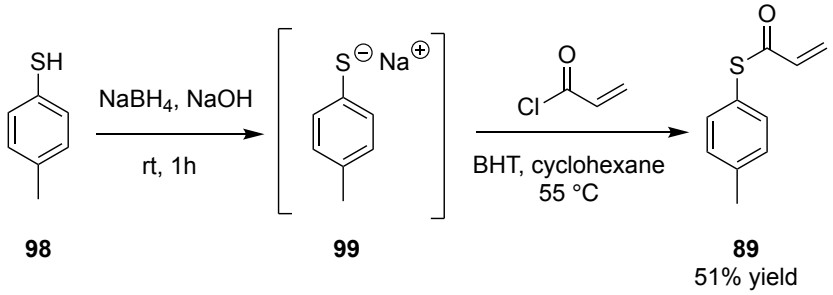
the reaction, the isocyanate is hydrolysed under reflux to produce a free amine. However, we opted to avoid the isolation of the free amine, and instead benzyl alcohol was added directly to the reaction mixture after isocyanate formation. This allowed for nucleophilic attack on the electrophilic carbon of the isocyanate intermediate **C**, leading to the formation of the amine rac-**87** with a Cbz protecting group in situ (Scheme 37).



*Scheme 37: The Curtius rearrangement for the synthesis of rac-**87***

Having successfully synthesised amine rac-**87**, the next step involved forming the α,β-unsaturated thioester **89**, which would function as the aza-Michael acceptor. The synthesis began with deprotonation of thiol **98** using aqueous NaOH/$NaBH_4$, generating the corresponding thiolate anion **99**, which acts as a hard nucleophile while limiting undesired attack at the β-position of acryloyl chloride. The thiolate **99** was then reacted with acryloyl chloride, dissolved in cyclohexane and stabilized with butylated hydroxytoluene (BHT),

yielding the desired product via nucleophilic substitution. The inclusion of $NaBH_4$ prevented disulfide formation in the starting material, and BHT inhibited radical polymerization of both the acryloyl chloride and the product. The resulting thioester **89** was isolated by column chromatography in 51% yield (Scheme 38).

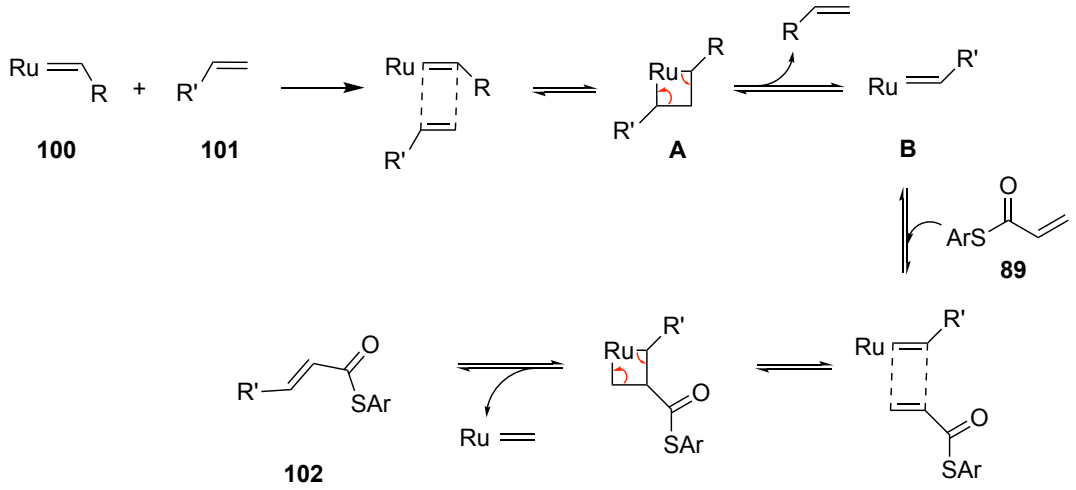


*Scheme 38: Synthesis of thioester **89***

With the amine rac-**87** and thioester **89** available, the synthesis proceeds with a cross-metathesis reaction to produce the precursor for the aza-Michael cyclization. Cross-metathesis is a type of olefin metathesis reaction in which two different alkenes exchange fragments to form new alkenes. As a guide for researchers designing such reactions, Grubbs and coworkers systematically classified olefins for cross-metathesis based on their propensity for homodimerisation: Type-I olefins, such as the simple mono-substituted alkene in our Cbz-protected amine-tethered alkene, which undergo rapid homodimerisation, and Type-II olefins, like arylates, which homodimerize more slowly.[51] The study emphasizes how the rapid homodimerisation of Type-I olefins can lead to unwanted side products, while Type-II olefins often exhibit more predictable reactivity, improving selectivity in cross metathesis reactions when coupling Type-I and Type-II alkenes together. The authors also highlight the value of using the second-generation Grubbs catalyst, which enhances reaction efficiency and minimises side reactions.

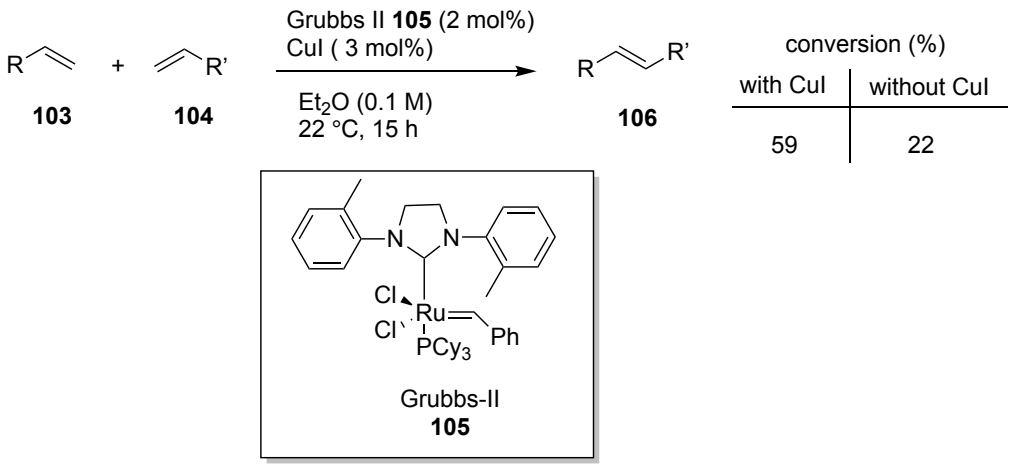
When cross metathesis is catalysed by the Hoveyda-Grubbs 2nd generation (HG-II) **36**, a ruthenium-based complex featuring a chelating benzylidene ligand, the reaction proceeds through a well-defined mechanism. Initially, the Ru-carbene complex interacts with the alkene **100** to form a metallacyclobutane intermediate **A** via a [2+2] cycloaddition. This intermediate then undergoes a cycloreversion step, releasing a new alkene and generating a

new Ru-carbene **B** species. This newly formed species can then react with the second alkene **89**, repeating the cycle and ultimately producing the cross-metathesis product **102** (Scheme 39).



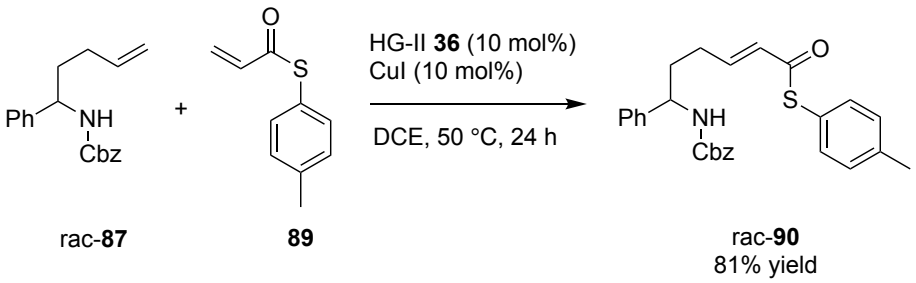
*Scheme 39: Simplified mechanism of cross metathesis reaction via Hoveyda Grubbs II **36***

Previous studies conducted by the Clarke group confirmed that the use of 10 mol% of the HG-II **36** catalyst in the presence of copper(I) iodide (CuI) as a co-catalyst resulted in high to excellent yields of the cross-metathesis product.[45,52] This finding builds on earlier research by Lipshutz, who demonstrated that the addition of CuI improves reaction rates and overall efficiency by stabilising the catalyst through iodide coordination and by removing excess phosphines that could otherwise deactivate the catalyst when using the standard Grubbs 2nd generation (Grubbs-II) catalyst **105** (Scheme 40).[53]



Scheme 40: Cross metathesis in the presence of CuI

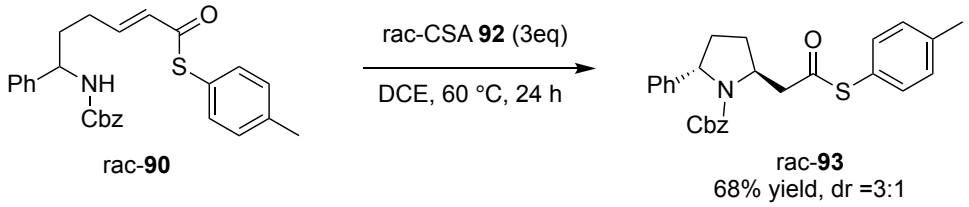
While this explanation does not apply to our reaction, as the (HG-II) **36** catalyst does not contain a phosphine ligand, we decided to retain the use of CuI as this additive was included as standard in previous cross metathesis reactions in the Clarke group and worked well. In this regard, a cross-metathesis reaction was performed between thioester **89** and amine rac-**87** under optimized conditions in DCE at 50 °C resulted in 81% yield (Scheme 41). The effect of included CuI in a related cross metathesis using (HG-II) **36** catalyst is discussed later in this Thesis in a different context (see section 4, pages 104 − 106).



*Scheme 41: Cross metathesis reaction for the cyclization precursor rac-**90***

2.2.2 Brønsted Acid Catalysed Cyclization

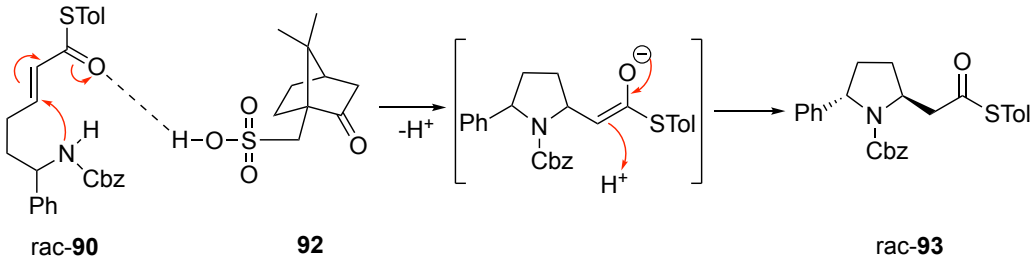
Following the synthesis of the pyrrolidine precursor rac-**90**, its conversion into racemic pyrrolidine rac-**93** was performed, to support the *ee* determinations described earlier (see Table 2). To do this, a cyclisation reaction was first carried out using an excess of racemic (±)-camphorsulfonic acid (rac-CSA) **92** under the conditions previously optimised (Scheme 42).[50]



*Scheme 42: Racemic cyclization of 2-phenyl pyrrolidine (S,S)-**93***

The Brønsted acid-catalysed cyclisation using rac-CSA **92** follows a protonation-based mechanism that facilitates intramolecular nucleophilic attack. CSA **92** acts as a catalyst by protonating the substrate, which increases the electrophilicity of the Michael acceptor and makes it more susceptible to nucleophilic attack. The use of racemic CSA leads to the generation of racemic product, as a 3:1 mixture of diastereoisomers. This allowed us to

establish conditions for the separation of the enantiomers of each diastereoisomer via chiral HPLC, which was essential for the *ee* determination (see above, Table 2). Upon protonation, the substrate undergoes ring closure, forming a cyclic intermediate. This intermediate undergoes further proton transfers to yield the final product. (Scheme 43).



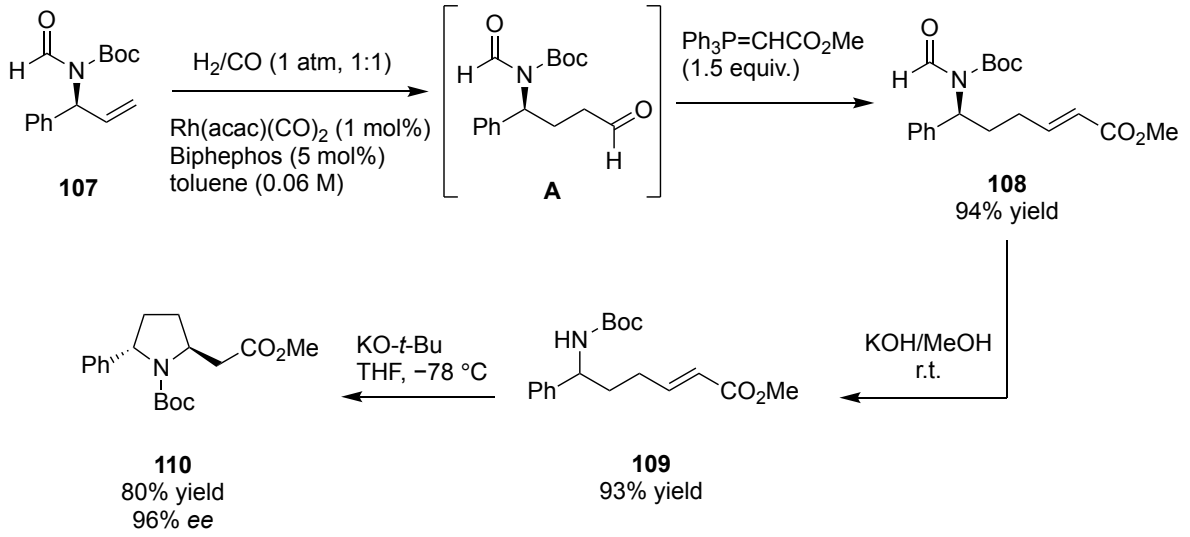
rac-**90** **92** rac-**93**

*Scheme 43: Proposed mechanism of cyclization through rac-CSA **92***

2.2.3 Confirmation of Absolute Stereochemistry

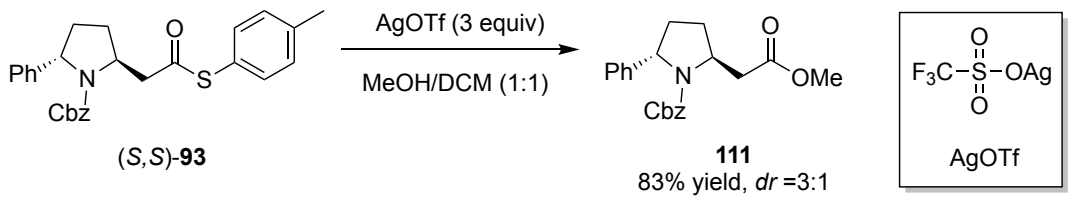
It was expected that the both relative and absolute stereochemistry of the major 2-phenyl pyrrolidine product formed in the kinetic resolution discussed above (see Scheme 35) could be assigned by a ^{1}H NMR comparison with a known literature compound.[54] Farwick and Helmchen developed a highly efficient and stereoselective synthetic route to pyrrolidine derivatives via hydroformylation of allylamines, followed by a Witting olefination and a subsequent intramolecular aza-Michael addition. As shown in Scheme 44, the reaction sequence began with rhodium-catalysed hydroformylation of an allylamine under atmospheric pressure of synthesis gas (H_2:CO 1:1). The double bond in allylamine **107** underwent insertion of a formyl group via a rhodium hydride intermediate, favouring the formation of the linear aldehyde **A**. This selectivity is largely governed by the electronic and steric influence of the adjacent amino group, which can weakly coordinate to the metal centre and stabilise the transition state leading to the linear product. Without isolation, the resulting aldehyde is subjected to a Witting olefination using a stabilized phosphonium ylide ($Ph_3P{=}CHCO_2Me$), yielding an α,β-unsaturated ester **108** in 94% yield. Following olefination, the N-formyl protecting group is removed under basic conditions using KOH in methanol to release the free secondary amine **109**. The aza-Michael reaction is then carried out with KO-*t*-Bu as base, affording the Boc-protected pyrrolidine product **110** with high stereoselectivity. This sequence provides a reliable basis for assigning both the relative and absolute stereochemistry of our product (*S,S*)-**93**, based comparison of our spectroscopic data with

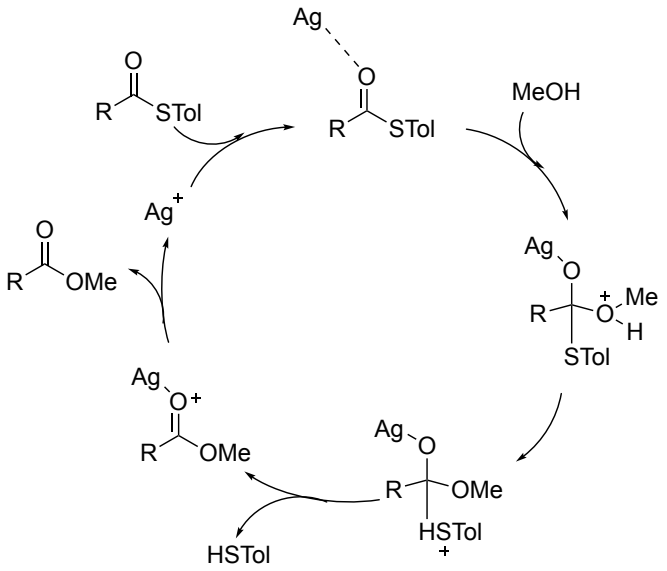
those of the reported compound, provided we could generate the same pyrrolidine via a 'clip-cycle' pathway.



*Scheme 44: Synthesis of Boc-protected pyrrolidine **110***

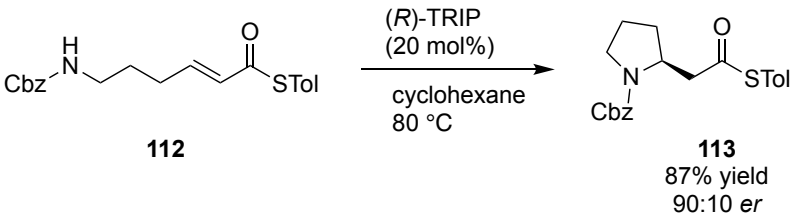
After having made 2-phenyl pyrrolidine (*S,S*)-**93** via 'clip-cycle', it was decided to begin by converting the thioester group into a methyl ester under standard conditions, to generate the same product **110** produced in Farwick and Helmchen's work to compare their data.[55] Thus, to a solution of pyrrolidine (*S,S*)-**93** in MeOH/DCM were added 3 equiv. of AgOTf were added and the reaction was stirred for 3 hours in room temperature, followed by purification by column chromatography. Using this method, the pyrrolidine (*S,S*)-**93** was converted into the methyl ester **111** in 83% yield and with no change in diastereomeric ratio (Scheme 45). Thus compound **111** very similar to Farwick and Helmchen's **110** was successfully prepared, the only difference being it having a Cbz rather than Boc protecting group.





Scheme 45: Transesterification reaction using silver triflate and methanol

At this stage, it is worth noting that based on the results obtained with similar methodology for the asymmetric synthesis of pyrrolidines with 2-substituents, the absolute stereochemistry of the cyclisation of the 2-substituted precursor was expected to be (*S*)-configuration for the major enantiomer (Scheme 46).[56] In a publication by Maddocks in the Clarke group, it was reported that the pyrrolidine product **113** was synthesised from the precursor **112** cyclised by the (*R*)-TRIP (20% mol) with an enantiomeric ratio of 90:10. We can see that the cyclisation product (*S*)-**113** reported by Maddocks matches the structure of the product **110** of the reported compound. Thus, the main focus of the subsequent reactions, was to establish the relative stereochemistry of 2-substituted pyrrolidine analogues.



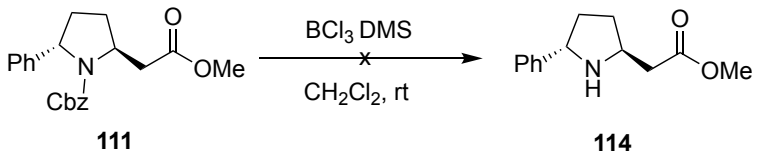
112

113
87% yield
90:10 *er*

*Scheme 46: Cyclization of the unsubstituted precursor (S)-**113** using (R)-TRIP*

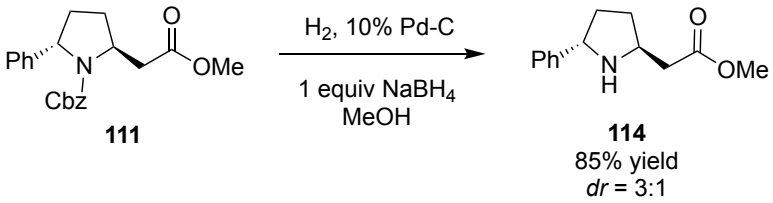
To confirm the relative stereochemistry, a Cbz- to Boc-protecting group switch was needed. The initial deprotection method tested was based on a procedure previously used in the Clarke group, employing a boron trichloride-dimethyl sulfide complex for the removal of the Cbz group.[57] However, when this method was applied to the cyclised pyrrolidine **111**, only

decomposition products were observed by ^{1}H NMR, with none of the desired product or starting material recovered (Scheme 47). Cbz is preferred to Boc for the Clip-Cycle method, because of its stability under acidic conditions, which is important given that the cyclisation procedures are carried out using acid catalyst. However, the stability of Cbz protecting group presents more challenges in its removal.



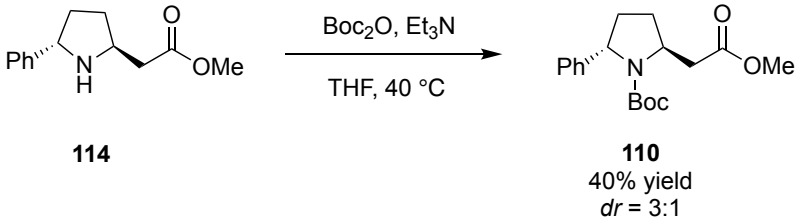
Scheme 47: Cbz deprotection using BCl_3.DMS

An alternative approach for the cleavage of Cbz via the combination of 10% Pd-C/$NaBH_4$ in a MeOH under an atmosphere of hydrogen.[58] To test this strategy, *N*-Cbz pyrrolidine was treated with 10 wt % Pd-C used as a catalyst and 1 equiv of $NaBH_4$ in MeOH. Pleasingly, complete hydrogenolysis of the benzyl ester occurred to give the free amine **114** in 85% yield (Scheme 48). The 3:1 *dr* of the product mirrored that obtained during the 'clip-cycle' reaction, suggesting that no unwanted epimerisation took place.



*Scheme 48: Hydrogenation for the removal of the Cbz protecting group **114***

With the free amine successfully formed, we could proceed with the protection which would generate the Boc-protected pyrrolidine **110**. In a control experiment, the protection of free amine pyrrolidine **114** was carried out with Boc_2O at 40 °C for 3 hours (Scheme 49).



*Scheme 49: Boc protection of pyrrolidine **114***

Again, as expected, the 3:1 diastereomeric ratio from compound (*S,S*)-**93** was reflected in the *dr* of **110** (also 3:1), confirming that the stereochemical integrity of the product was maintained on converting **114** into **110**. The two diastereoisomers can be identified clearly by looking at the ^{1}H NMR spectra. For instance, the diagnostic methine proton (H-4), adjacent to both the nitrogen and ester side chain, appeared as two distinct doublets at δ 4.99 ppm (*J* = 8.2 Hz) and δ 4.85 ppm (*J* = 8.2 Hz) corresponding to the minor and major diastereoisomer, respectively. Similarly, H-7 (major) appeared as multiplet from δ 4.57 – 4.51 ppm and the H-7 (minor) appeared as multiplet from δ 4.45 – 4.40 ppm. The methyl ester group also gave rise to two singlets at δ 3.71 ppm (major) and δ 3.69 ppm (minor), corresponding to the OCH_3 protons of the respective diastereoisomers. H-3 (major) giving a doublet at δ 3.11 ppm (*J* = 15.0, 3.5 Hz) for 1 proton, and H-3 (minor) giving a doublet at δ 2.98 ppm (15.1, 2.5 Hz) for 1 proton. One H-6 proton overlapped with the other H-3' proton as the multiplet at δ 2.43 – 2.31 ppm. The H-5 (both diastereoisomers) protons were assigned as the multiplet at δ 1.78 – 1.69 ppm. Notably, the *tert*-butyl (Boc) protecting group resonated as distinct singlets at δ 1.46 ppm (minor) and δ 1.13 ppm (major) for 9 protons, corresponding to the H-14 methyl protons in each diastereomer (Figure 1).

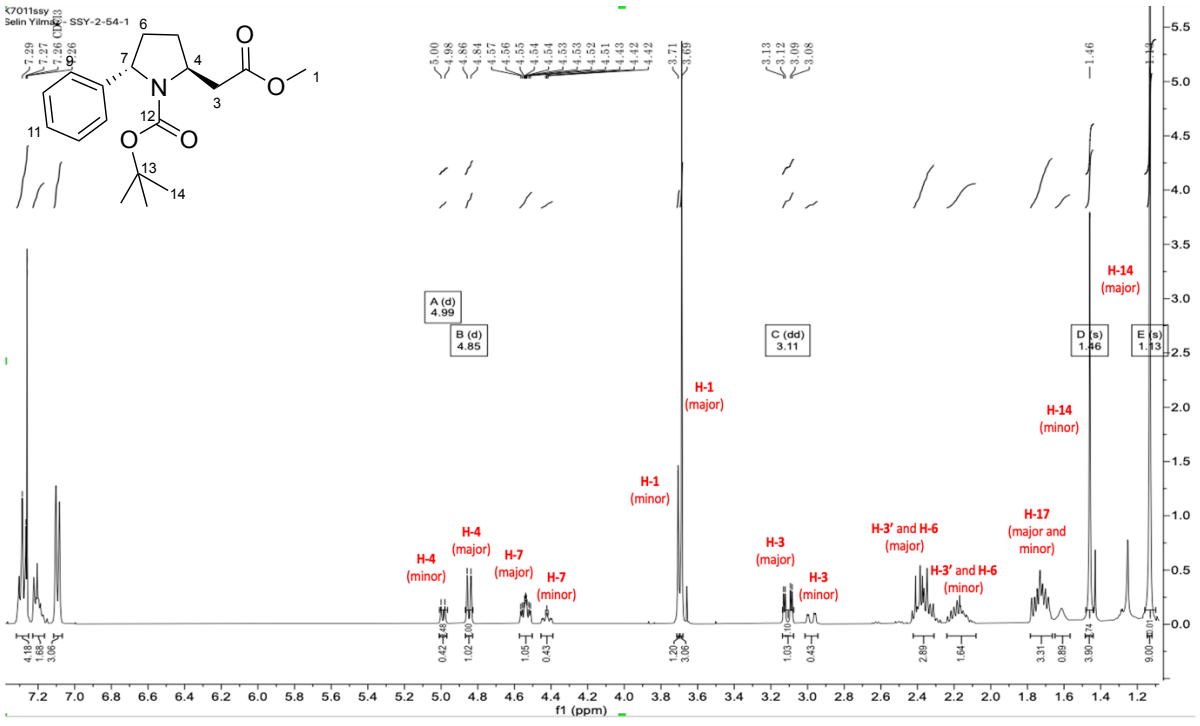


*Figure 1: 1H NMR spectrum for pyrrolidine **110***

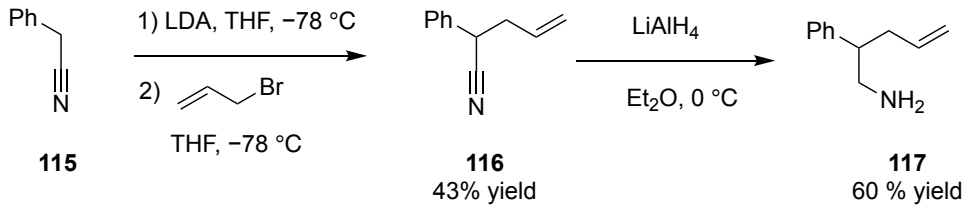
In the procedure described in the literature, the compound **110** was analysed by NMR (^{1}H, ^{13}C) at 300 MHz at 90 °C using toluene-d_8 as the solvent. To compare with literature Boc-protected pyrrolidine **110** analysed by NMR at 400 MHz at room temperature *via* toluene-d_8. The signal that represents the 9H observed as a singlet at δ 1.16 ppm. A dd with an integration of 1H was observed at δ 2.19 ppm (*J* = 15.3, 10.1 Hz), alongside a singlet peak at δ 3.35 ppm which integrated to 3H. The signal at δ 4.60 – 4.62 ppm which corresponds to 1H showed a multiplet. These assignments all matched those reported in the literature data, thus clearly indicating that the major diastereomer of **110** (and by analogy (*S,S*)-**93**) is the *trans*-configuration. Similarly, diastereoselectivity would likely be observed for other 2,5-disubstituted pyrrolidines also.

In summary, the relative stereochemistry of the major stereoisomer was confirmed as being *trans* by direct comparison to literature data, and the absolute stereochemistry assigned based on the established Clarke group model.[56]

2.3 3-Substituted Pyrrolidine

2.3.1 Synthesis of Cyclisation Precursor

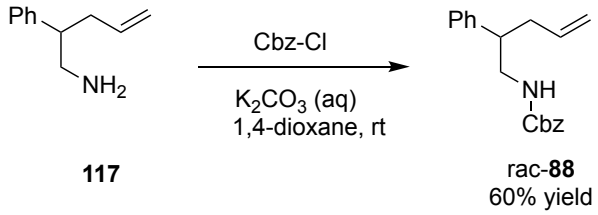
To extend the range of substrates beyond the 2-substituted pyrrolidine, a precursor designed to lead to a 3-substituted pyrrolidine was next prepared from commercially available nitrile **115**. The initial step in synthesizing the precursor was to deprotonate the nitrile **115** with LDA and then alkylate with allyl bromide to afford the nitrile **116** in 43% yield. Subsequent reduction of the nitrile **116** using lithium aluminium hydride ($LiAlH_4$) produced the free amine **117** (Scheme 50).



115 **116** 43% yield **117** 60 % yield

*Scheme 50: Synthesis of free amine **117***

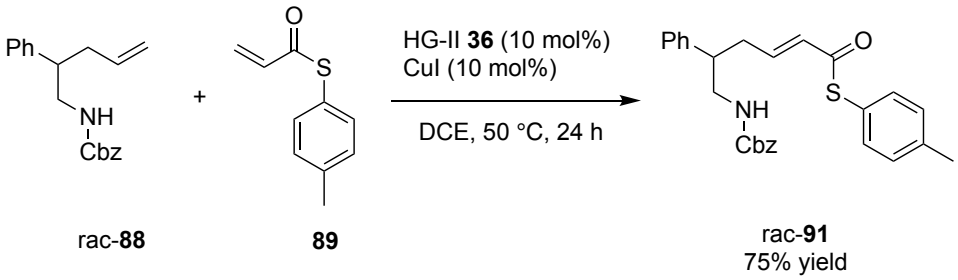
Amine **117** was then protected with benzyl chloroformate to form the Cbz-protected amine **118** in 60% yield (Scheme 51).



117 rac-**88** 60% yield

*Scheme 51: Synthesis of Cbz-protected amine rac-**88***

The resultant Cbz-protected amine rac-**88** was then 'clipped' with the thioester **89** via cross metathesis, using one equivalent of CuI alongside HG-II catalyst, leading to the formation of the desired intermediate rac-**91** in 75% yield, as a single geometrical isomer. This step proceeded smoothly under mild conditions (Scheme 52).

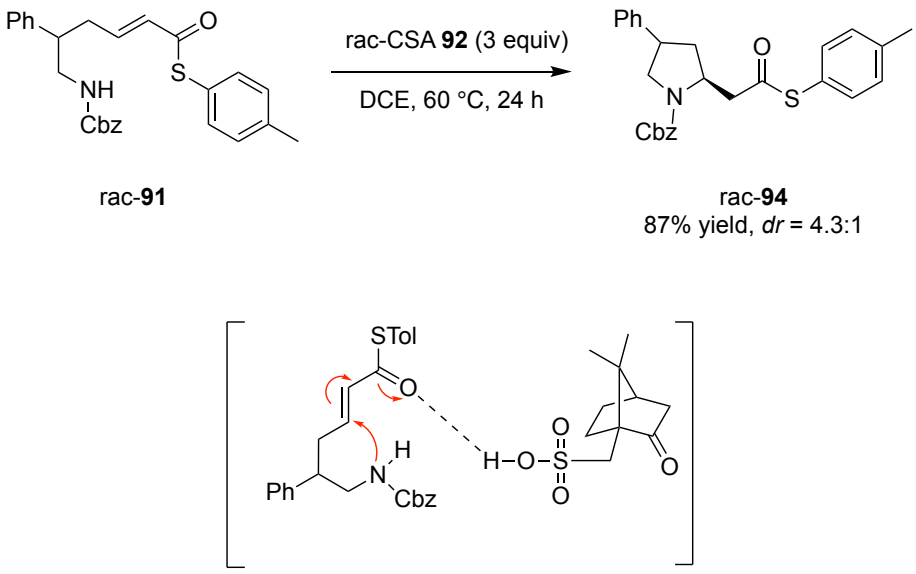


rac-**88** **89** rac-**91** 75% yield

*Scheme 52: Cross metathesis rection for the cyclisation precursor rac-**91***

2.3.2 Brønsted Acid Catalysed Cyclisation

Before studying the planned asymmetric cyclization reactions, a racemic variant was performed. This was done to obtain a racemic sample for analysis, including chiral HPLC, and verify the viability of the cyclisation in our hands. The formation of the pyrrolidine ring (*S*)-**94** was duly achieved through a Brønsted acid promoted cyclisation an excess of rac-CSA **92** in DCE at 60 °C, enabling the successful synthesis of precursor (*S*)-**94** in 87% yield, and formed as a 4.3:1 mixture of diastereoisomers. Having a method to observe all four stereoisomers (two enantiomers of two diastereoisomers) and determine the enantiomeric ratio, via HPLC was important for the later asymmetric work, with the resolution of these peaks discussed subsequently (Scheme 53).



rac-**91**

rac-**94**
87% yield, *dr* = 4.3:1

*Scheme 53: Racemic cyclisation of 3-substituted precursor (S)-**94***

To confirm the formation of cyclisation product, the ^{1}H NMR spectrum of compound (*S*)-**94** is presented in Figure 2. The aromatic protons from the Cbz group and thioester appear as a multiplet in the range of δ 7.42 – 7.28 ppm, while the benzylic protons are observed as a multiplet at δ 7.23 – 7.21 ppm. The H-8 proton, formed after cyclisation, appears as a multiplet at δ 4.34 – 4.27 ppm, with a corresponding carbon signal at δ 55.5 ppm, as confirmed by the HMQC spectrum (Figure 3). The two protons attached to C-7 (δ 47.2 ppm) appear as two broad multiplets at δ 3.61 – 3.40 ppm and δ 3.03 – 2.83 ppm, respectively, also supported by the HMQC spectrum. These assignments are further corroborated by the COSY spectrum in Figure 4, which shows H-H coupling of the H-7 and H-7', as well as with H-8. Finally, the methyl protons (H-1) from the thioester group are identified as a singlet at δ 2.38 ppm.

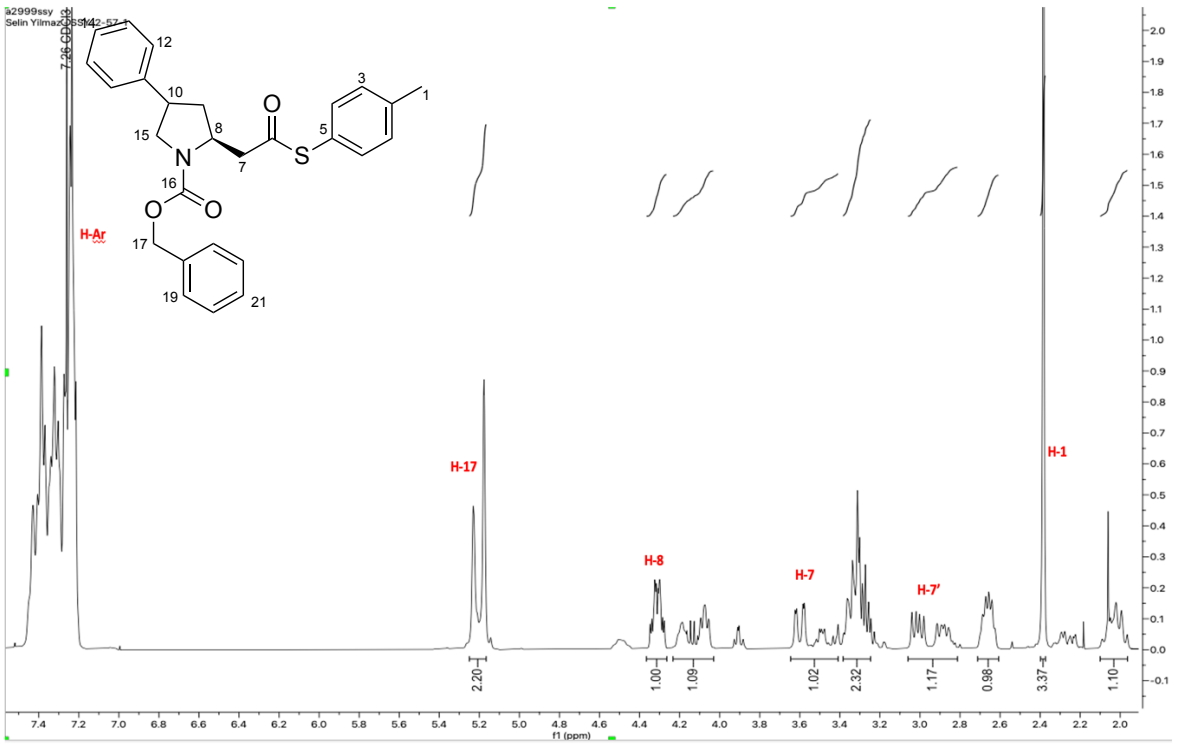


*Figure 2: 1H NMR of (S)-**94***

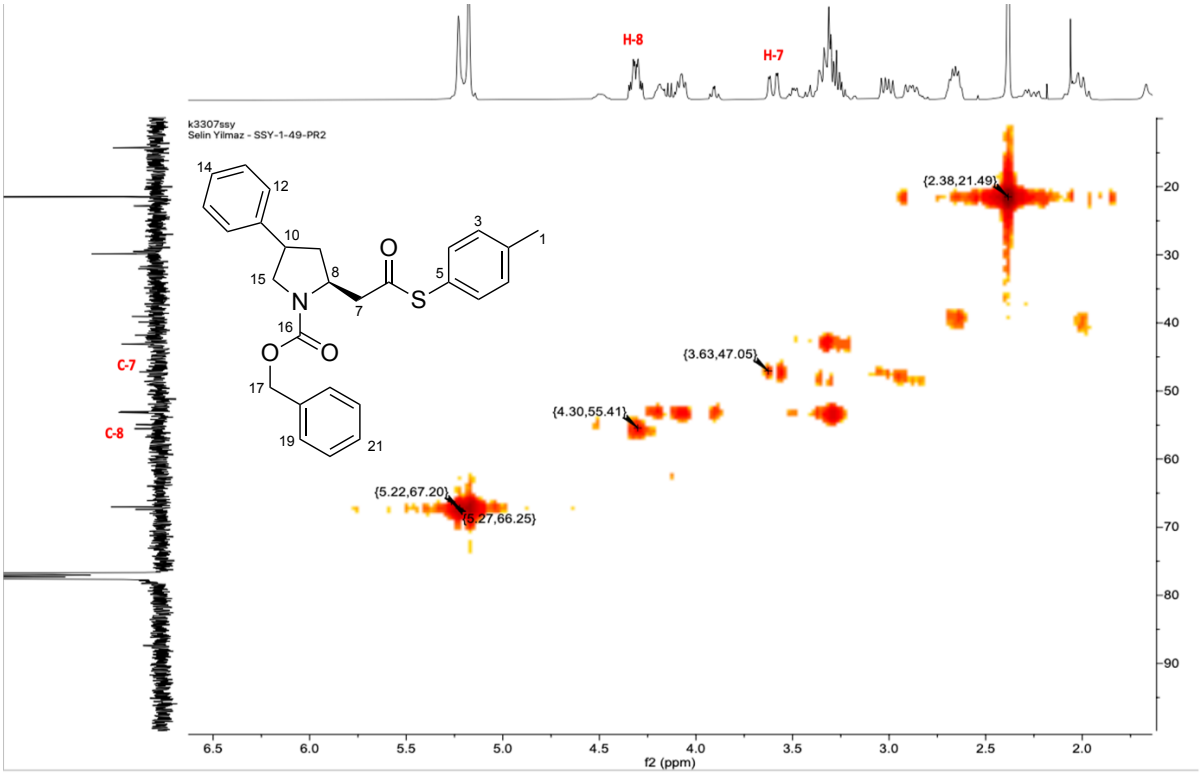


*Figure 3: HMQC spectrum showing C-1, C-7 and C-8 with respective protons in (S)-**94***

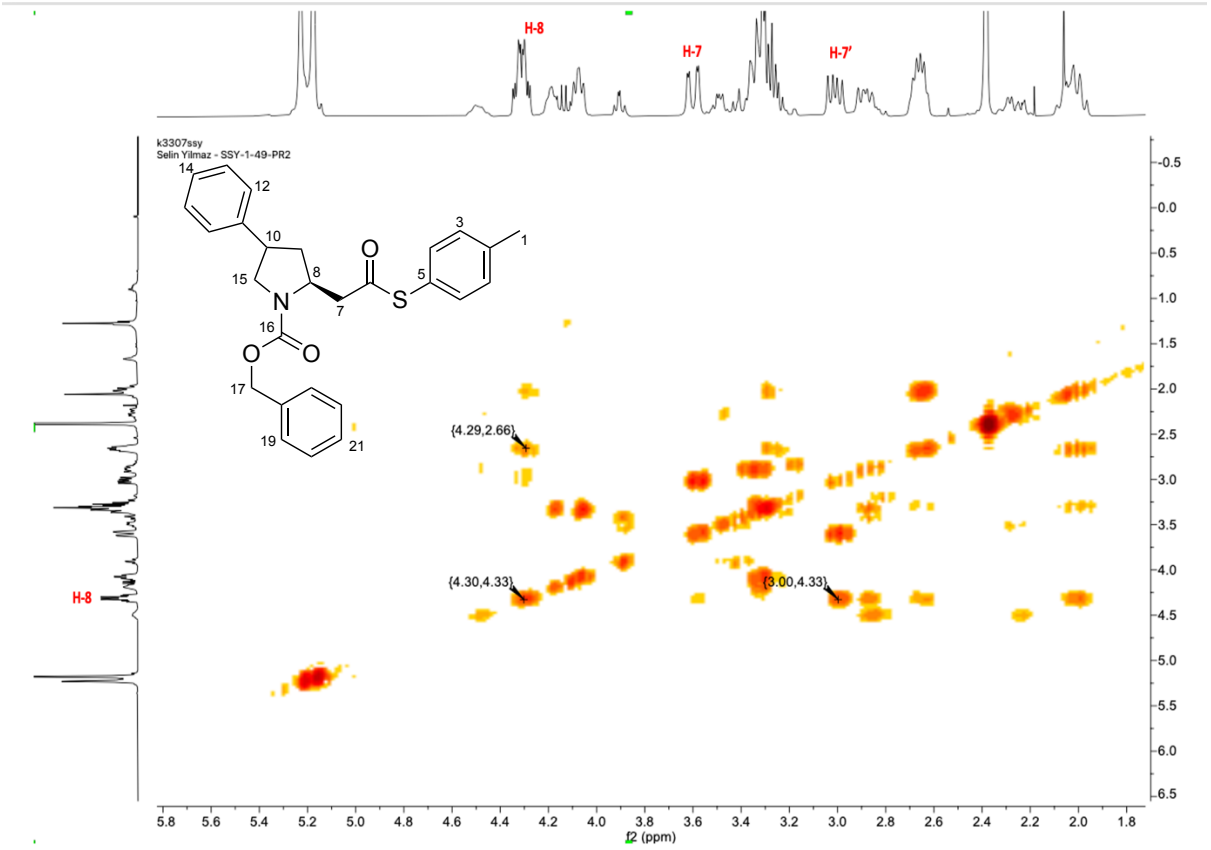
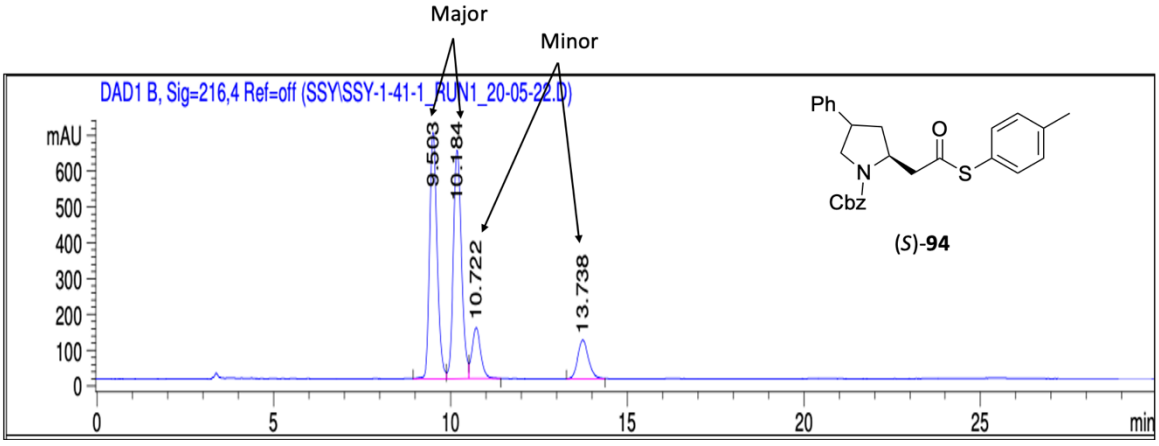


*Figure 4: COSY spectrum showing correlation between C-7 and C-8 in (S)-**94***

Once the racemic product (*S*)-**94** was synthesized and characterised, the two diastereoisomers, and the two enantiomers of each, were resolved using chiral HPLC. Chiral HPLC allows the separation of the enantiomers depending on their interaction with the chiral stationary phase of the column. After evaluation of various HPLC conditions, good separation of four stereoisomers was observed using an IA column, eluting with 80:20 of hexane:IPA at a flow rate of 1.0 mL/min at 40 °C. As expected, the two diastereomers were each observed as a 1:1 pair of the two enantiomers given that they are racemic; the major diastereoisomer appear as two sharp equal intensity peaks with retention times at 9.5 and 10 minutes, while the minor diastereoisomer appeared as two smaller peaks at 10.7 and 13.7 minutes respectively (Table 3). Taking the ratio between the area under the peaks, the diastereomeric ratio was determined as 4.3:1, based on analysis of the HPLC chromatogram recorded at 216 nm.



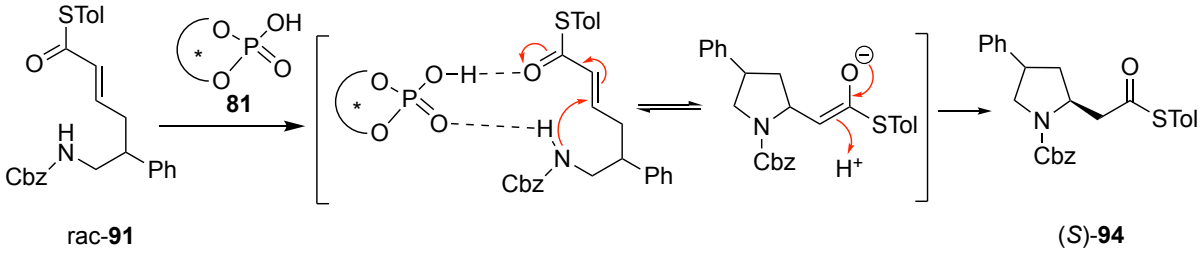
Racemic Substrate	Hexane :IPA	Major isomer (Time / min)	Area (%)	Minor isomer (Time / min)	Area (%)	Flow rate (mL / min)
rac-**91**	80:20	9.503	40.6	10.722	9.7	1
		10.184	40.7	13.738	9.0	

*Table 3: HPLC chromatogram for cyclisation of (S)-**94** with rac-CSA **92***

2.3.3 Kinetic Resolution of 3-Substituted Pyrrolidine Precursor

Kinetic resolution is a strategy often employed to separate enantiomers by exploiting differences in their reaction rates with a chiral catalyst or reagent. In the context of this study, it was hypothesised that using an enantiomerically pure Brønsted acid catalyst ((*R*)-TRIP) could selectively accelerate the cyclisation of one enantiomer of the racemic starting material, leading to enantioenrichment of the desired product, similarly to the strategy used on the 2-substituted precursor described earlier. With suitable HPLC conditions established to allow us to track all four possible stereoisomers (see above) the asymmetric cyclisation of a 3-substituted precursor **rac-91** was thus attempted using (*R*)-TRIP as the catalyst in cyclohexane, at two different reaction temperatures (50 °C and 80 °C). The aim was to achieve approximately 50% conversion and analyse for enantiomeric enrichment in both the cyclised and linear products.

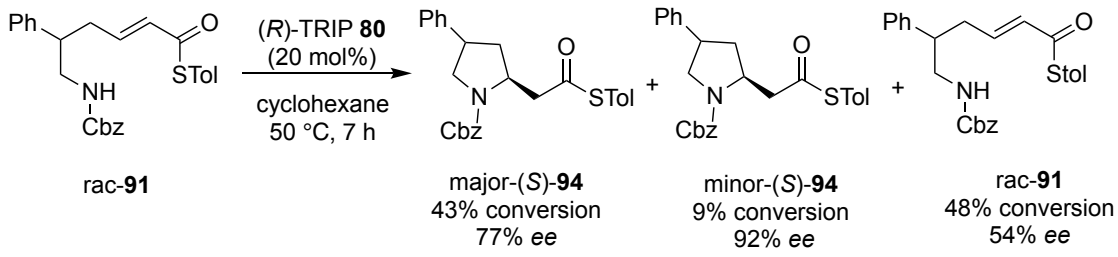
The cyclisation mediated by (*R*)-TRIP is thought to proceed via a chiral Brønsted acid catalysed mechanism, wherein the enantiopure phosphoric acid catalyst engages in hydrogen bonding interactions with the substrate to activate the electrophilic centre while simultaneously directing the nucleophile in a stereocontrolled manner. The chiral environment created by the bulky BINOL backbone and the sterically demanding 3,3'-aryl substituents of the catalyst potentially allows for differential stabilization of transition states associated with the cyclisation of each enantiomer of the substrate, thereby promoting the formation of one enantiomerically enriched product over time (Scheme 54).



Scheme 54: Proposed mechanism for the cyclization by (R)-TRIP

The reaction was initially carried out at 50 °C. Small aliquots were taken at 1-hour intervals and analysed by chiral HPLC. The results are summarized in Table 1. From the same chromatograms, the percentage of starting material and the relative amounts of the major and minor diastereoisomers were determined by comparing the integrals of the enantiomeric pairs for each diastereoisomer. The same experimental procedure was followed for each reaction: aliquots (0.2 mL) were taken at various time points, quenched with triethylamine (0.1 mL), and filtered through a pipette column prior to HPLC analysis. Since a kinetic resolution was targeted, each reaction was stopped after exceeding 50% conversion of the starting material. The mixture was quenched with triethylamine, and the enantioenriched product (*S*)-**94** and remaining starting material rac-**91** were separated by flash column chromatography. In the asymmetric reaction of starting material rac-**91** at 50 °C, the amount of major product (*S*)-**94** increased steadily, reaching 43% over a 7-hour period. Enantiomeric enrichment of the product (*S*)-**94** was already evident after 1 hour (70% ee), while the enantiomeric excess of the recovered starting material rac-**91** gradually increased to 54%

after 7 hours. After quenching with triethylamine, the reaction mixture was purified via column chromatography. The starting material rac-**91** and the product (*S*)-**94** were isolated in 21% and 23% yields, respectively, and analysed by HPLC, giving enantiomeric excesses of 62% and 72%, respectively and these values were between experimental error (Table 4). The difference between the observed conversion and the isolated yields is attributed to challenges in compound separation (Scheme 55).



*Scheme 55: Kinetic resolution of 3-substituted precursor rac-**91** at 50 °C*

	% Conversion			% *ee*		
Time (h)	**%Product (Major)**	**%Product (Minor)**	**%SM**	**Product (Major)**	**Product (Minor)**	**SM**
0	0	0	100	0	0	0
1	8.270	1.095	90.528	70.316	83.289	4.087
2	18.729	4.177	77.093	69.643	79.353	14.905
3	25.149	4.362	70.488	77.841	92.438	23.203
4	27.383	6.271	66.346	85.154	62.270	31.739
5	36.439	6.679	56.881	78.772	91.849	38.521
6	39.677	7.969	52.354	78.565	85.569	47.105
7	42.611	9.116	48.273	76.539	92.058	53.523

*Table 4: Conversion and ee % of starting material rac-**91** and product (S)-**94** at 50 °C*

The data in Table 2 are represented graphically below. Figure 5a depicts a steady decline in starting material from 100% to 48%, accompanied by a rise in formation both the major product and minor diastereoisomers of the cyclised product, reaching 43% and 9%, respectively, by 7 hours. The reaction progress suggests a relatively diastereoselective transformation favouring the major diastereoisomer by around 5:1. Meanwhile, the Figure 5b demonstrates high enantioselectivity for both diastereoisomers, with the major product maintaining 70−85 % *ee* and the minor product achieving 62−92% *ee* throughout the reaction. Notably, the *ee* of the major product peaks at 85% at 4 hours, while the minor product shows fluctuations, possibly due to errors accurately analysing the amount of this minor product.

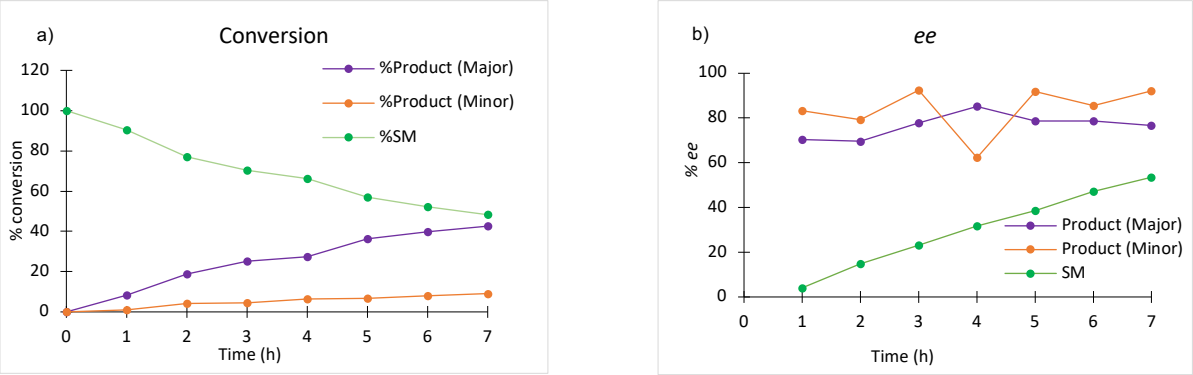
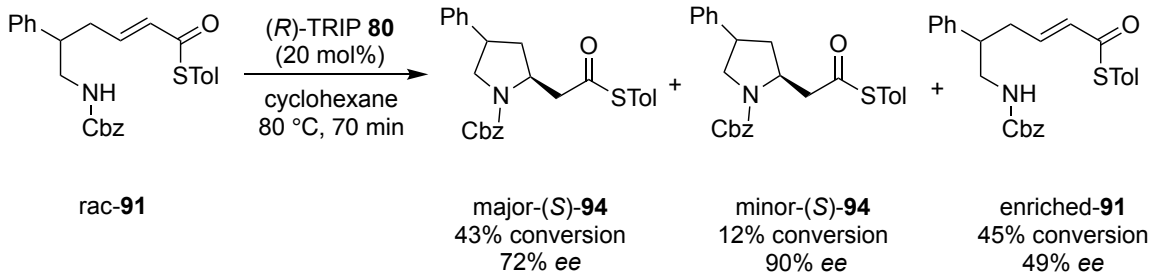


Figure 5: a) Conversion of major and minor vs SM; b) ee of major and minor vs SM at 50°C

At 80 °C, reaction aliquots were taken every 10 minutes and analysed by HPLC (Table 4). After 70 minutes, the conversion of the starting material reached 55%, with 45% of the starting material remaining. At this point, the reaction was quenched with triethylamine and purified using a pipette column. The enantioselectivity of the major product was initially high, measured at 82% *ee* after 10 minutes, but decreased to 72% as the reaction approached 50% conversion. The quenched reaction mixture was subsequently purified by column chromatography, affording the starting material enriched-**91** in 31% yield and the product (*S*)-**94** in 23% yield.

As shown in Figure 6a and Table 5, the starting material undergoes steady conversion, decreasing from 100% to approximately 45% over 70 minutes. In parallel, the major diastereoisomer of product accumulates progressively, reaching 43% conversion by the end of the reaction. The formation of the minor product is significantly slower, reaching only 12%

conversion, indicating reasonable diastereoselectivity. Figure 6b displays the evolution of enantiomeric excess for the reaction components. The major product initially exhibits high enantioselectivity (82% *ee* at 10 minutes), which gradually decreases to 73% at 43% conversion. The minor product retains a consistently high *ee* throughout the reaction. In contrast, the enantiomeric excess of the recovered starting material increases steadily from 7% to 49%, indicating the preferential reaction of one enantiomer and the progressive enrichment of the unreacted enantiomer.



rac-**91**

major-(*S*)-**94**
43% conversion
72% *ee*

minor-(*S*)-**94**
12% conversion
90% *ee*

enriched-**91**
45% conversion
49% *ee*

*Scheme 56: Kinetic resolution of 3-substituted precursor rac-**91** at 80 °C*

	% Conversion			% ee		
Time (minute)	**%Product (Major)**	**%Product (Minor)**	**%SM**	**Product (Major)**	**Product (Minor)**	**SM**
0	0	0	100	0	0	0
10	11.197	1.938	86.865	82.416	83.154	7.318
20	17.332	3.429	79.239	75.495	91.419	12.828
30	24.521	5.473	70.006	74.467	85.657	20.366
40	31.596	7.495	60.910	75.296	86.478	27.653
50	38.299	9.907	51.794	73.662	87.929	35.336
60	38.643	10.126	51.231	73.376	89.019	41.523
70	43.172	12.022	44.806	72.470	90.440	48.866

*Table 5: Conversion and ee % of starting material rac-**91** and product (S)-**94** at 80 °C*

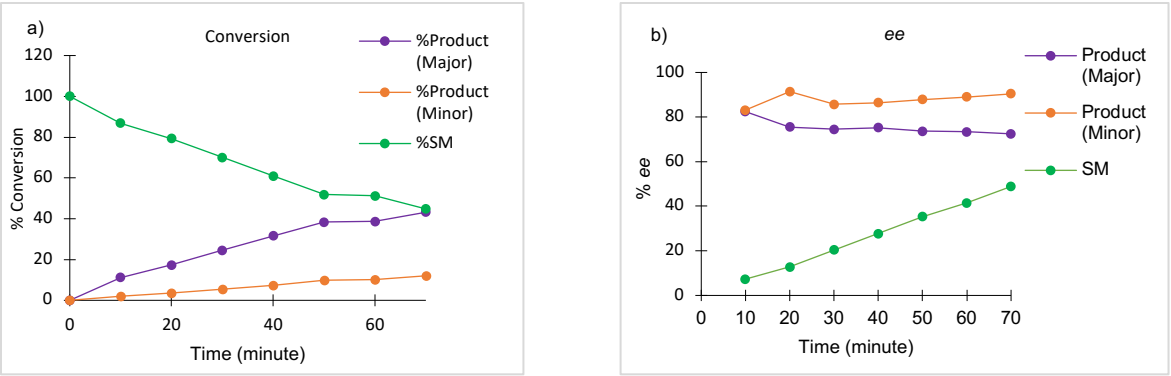


Figure 6: a) Conversion of major and minor vs SM; b) ee of major and minor vs SM at 80°C

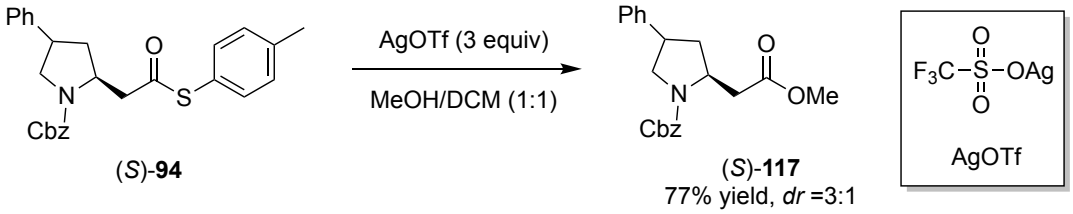
Temperature	%ee		%conversion			Yield of (*S*)-94 (%)	Conversion Time
	Major	Minor	Major	Minor	SM		
50 °C	76	92	43	9	48	23	7 hours
80 °C	72	90	43	12	45	69	70 minutes

Table 6: Conditions screen for 3-substituted pyrrolidine

Surprisingly, increasing the reaction temperature had minimal impact on the enantioselectivity of the kinetic resolution of 3-substituted compounds, with both the major and minor enantiomers maintaining remarkably stable enantiomeric excess across the two temperatures. This stability suggests that the stereochemical integrity of the transition state is largely independent of temperature. The result highlights the robustness of the enantioselectivity mechanism, which might be due to the inherently ordered nature of the catalyst and its interactions with the substrate. However, the increase in temperature significantly affected both the yield and conversion time. At 80 °C, the reaction reached nearly identical conversion levels (55%) in just 70 minutes, whereas at 50 °C, the same conversion level required 7 hours. This dramatic reduction in reaction time at higher temperatures is consistent with the expected influence of thermal energy in increasing molecular collisions, accelerating reaction kinetics, and promoting faster catalyst turnover. Additionally, the yield of the desired product was substantially enhanced at the elevated temperature, with the proportion of unreacted SM decreasing from 23% at 50 °C to 69% at 80 °C.

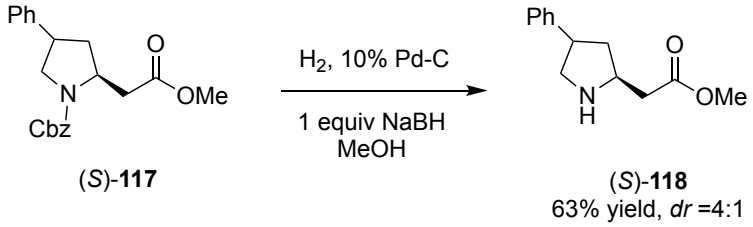
2.3.4 Confirmation of Absolute Stereochemistry

With the kinetic resolution of 3-substituted pyrrolidine (*S*)-**94** also achieved, we considered how we might be able to determine the stereochemical assignment of this pyrrolidine product. The initial plan was to follow a procedure similar to that used for to assign the 2-substituted pyrrolidine. To begin with the conversion of the thioester group to the methyl ester, transesterification method was employed using AgOTf to form methyl ester pyrrolidine (*S*)-**117**. Gratifyingly, the transformation proceeded smoothly, delivering the desired product in 77% yield (Scheme 57).



Scheme 57: Transesterification reaction using silver triflate and methanol

Next, the Cbz-protected pyrrolidine (*S*)-**117** was then be subjected to the hydrogenolysis method, as had been done for 2-substituted pyrrolidine **110**, which yielded the free amine pyrrolidine (*S*)-**118** (Scheme 58).



Scheme 58: Hydrogenation for the removal of the Cbz protecting group

Unfortunately, a known literature compound is not available in this substitution series for comparison. As a result, while we know the reaction gives a *dr* of 4:1, it has not yet been determined whether the major diastereoisomer of pyrrolidine has a *trans* or *cis* configuration. Pyrrolidine (*S*)-**118** has been fully characterised as a mixture, but the separation of the isomers was not possible. Therefore, the relative stereochemical assignment remains unresolved at this stage.

2.4 Conclusion

This project has advanced the synthetic methodology for substituted pyrrolidines, building upon the previous work of the Clarke group. The enantioselective synthesis of 2-substituted pyrrolidines had already been achieved using the 'clip-cycle' approach; however, further investigations into 3-substituted analogues were halted due to restrictions during the COVID-19 pandemic.

The studies described in this Chapter detail the successful racemic synthesis of both 2- and 3-substituted pyrrolidines via Brønsted acid-catalysed cyclisation using rac-CSA. The racemic pyrrolidine precursor and the corresponding cyclisation product of the 3-substituted compound were subsequently analysed by chiral HPLC to investigate the conditions required for kinetic resolution studies. The kinetic resolution of the 3-substituted pyrrolidine precursor using (*R*)-TRIP as a chiral Brønsted acid catalyst was successfully demonstrated, with selective conversion observed at both 50 °C and 80 °C. At 50 °C, the reaction proceeded steadily, yielding enantiomerically enriched product and recovered starting material with enantiomeric excesses of up to 72% and 62%, respectively. Higher temperature (80 °C) significantly accelerated the reaction while maintaining excellent enantioselectivity, achieving comparable conversions in a much shorter time frame. The enantioselectivity remained stable across both temperatures, suggesting a robust, temperature-independent stereoselective mechanism. Notably, the minor diastereoisomer consistently exhibited high enantiomeric excess, hinting at a distinct and highly selective formation pathway.

The relative stereochemistry of the 2-substituted pyrrolidine product was determined by NMR comparison with structurally analogous compounds reported in the literature. Following conversion of the thioester into a methyl ester and subsequent Cbz to Boc deprotection and reprotection sequence, the final Boc-protected pyrrolidine exhibited ^{1}H and ^{13}C NMR data in agreement with the literature compound previously assigned as having a trans-configuration. These findings, supported by spectral correlation and stereochemical precedent from related asymmetric cyclisation, confirm the major product has the (*S*)-*trans* configuration.

In an effort to extend the stereochemical analysis to the 3-substituted pyrrolidine scaffold, the major product of the kinetic resolution was subjected to derivatization following the approach previously applied to the 2-substituted series. The thioester functionality was successfully converted into a methyl ester using AgOTf, yielding the corresponding ester in 77% yield. Subsequent deprotection afforded the free amine derivative; however, unlike the 2-substituted system, no suitable literature compound exists for direct spectral comparison. Consequently, while the pyrrolidine product was fully characterised, our inability to isolate individual diastereoisomers has prevented assignment of the relative or absolute stereochemistry.

2.5 Future Work

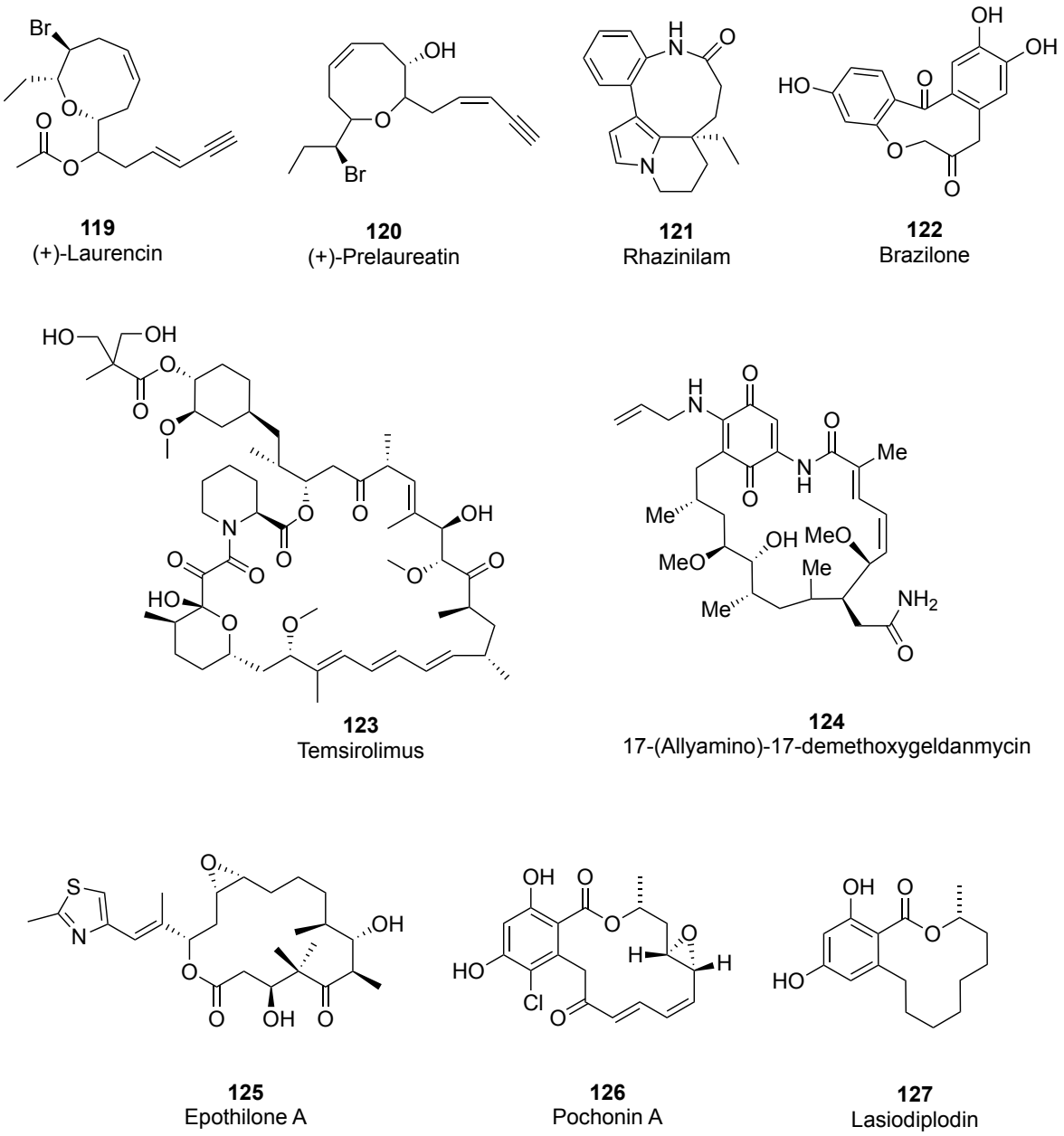
To further enhance the enantioselectivity observed during the kinetic resolution of 3-substituted pyrrolidines, future research should focus on optimising reaction conditions by exploring a broader range of solvents, chiral catalysts, protecting groups, and temperatures. In parallel, the confirming the absolute and relative stereochemical assignment of these 3-substituted pyrrolidines remains a crucial objective, which requires the successful isolation of pure diastereoisomers, a goal that has not yet been achieved. Once isolated, these diastereoisomers could be subjected to chiral derivatisation techniques and X-ray crystallography in order to determine their absolute configurations. Furthermore, expanding the substrate scope to include other substituted pyrrolidines, particularly 3,4- and 2,3-disubstituted derivatives, would be valuable for evaluating the generality and robustness of the cyclisation and resolution methodology. Finally, mechanistic investigations, including kinetic experiments and computational studies, are expected to provide critical insights into the transition states involved in both the cyclisation and resolution process, thereby guiding the rational design of improved catalysts and enhancing the overall reaction selectivity.

3-Introduction

3.1 Medium-sized rings and macrocycles in natural products

Natural products have long served as a valuable source of structurally diverse and biologically active molecules. Among these, compounds containing medium-sized rings (8−11 membered) and macrocycles (12-membered or larger) are frequently found at the core of many clinically relevant natural products and have emerged as key scaffolds in drug discovery and chemical biology (Scheme 59).[59–67]

Medium-sized rings present unique synthetic and biological challenges. From a synthetic perspective, these rings often exhibit increased ring strain and transannular interactions, which make their construction more complex than that of smaller or larger rings. However, nature assembles such frameworks efficiently through biosynthetic strategies involving cyclisation, oxidative coupling, or enzyme-mediated ring expansion. Notable examples include (+)-laurencin **119** and (+)-prelaureatin **120**, which contain eight-membered cyclic ethers derived from marine algae and exhibit antimicrobial and cytotoxic properties. Rhazinilam **121**, an indole alkaloid with a fused medium-sized carbocyclic ring, disrupts microtubule dynamics and is of interest for its potential anticancer activity. Similarly, brazilone **122**, a pigment found in *Caesalpinia* species, contains an oxygen-containing medium-sized ring and demonstrates antioxidant and anti-inflammatory effects. Macrocyclic natural products, with their large and often highly functionalized ring systems, are equally significant in nature and medicine. Compounds such as temsirolimus **123**, a macrocyclic lactone, functions as an mTOR inhibitor and is used clinically in cancer treatment. 17-(Allylamino)-17-demethoxygeldanmycin (17-AAG) **124**, a derive of geldanamycin, has undergone clinical investigation as an antitumor agent. Epothilone B **125**, isolated from *Sorangium cellulosum,* stabilises microtubules and has inspired the development of clinically approved analogues for cancer therapy. Pochonin A **126**, a resorcyclic acid lactone with a 14-membered macrocyclic structure, exhibits antifungal and antiproliferative activity. Lasiodiplodin **127**, a 12-membered lactone isolated from *Lasiodiplodia* species, displays cytotoxic and antimicrobial properties.



Scheme 59: Medium ring and macrocycle containing natural products

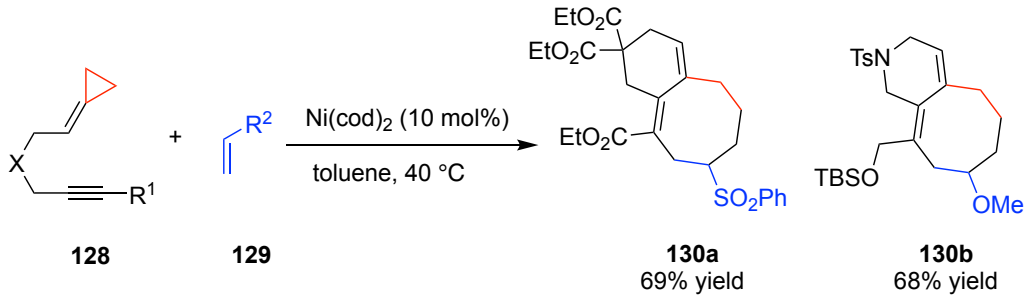
3.2 End-to-end Cyclisation

3.2.1 Transition Metal Catalysis

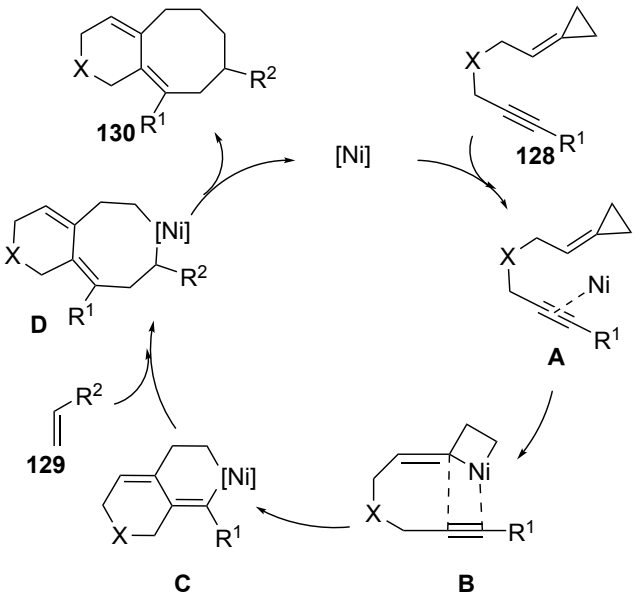
Transition metal catalysis plays a critical role in enhancing the efficiency and selectivity of end-to-end cyclisation reactions. Transition metal complexes containing metals such as palladium and copper are commonly employed to activate functional groups, to enable coupling. In addition, by coordinating to the reactive functional groups at bonds ends of the molecule, some metal complexes can help align the reacting species, thereby promoting ring

closure. This catalytic approach significantly enhances the rate of cyclisation and, in many cases, allows reactions to proceed under milder conditions, thereby minimising side reactions and improving product selectivity.

Mascarenãs *et al.* developed a nickel-catalysed [3+2+2] cycloaddition of alkynylidenecyclopropanes (ACPs) **128** with activated alkenes **129** to generate 6,7-bicyclic systems **130a-b** (Scheme 60).[68] The reaction proceeds via a ring expansion mechanism initiated by oxidative insertion of nickel into the proximal C−C bond of the cyclopropane, forming a nickelacyclobutane intermediate **C**. This species undergoes intramolecular alkyne insertion to generate a nickelcyclohexene **B**. The intermediate **B** engages an external alkene, incorporating it into the growing ring system and yielding the final cycloadduct **130** (Scheme 61).

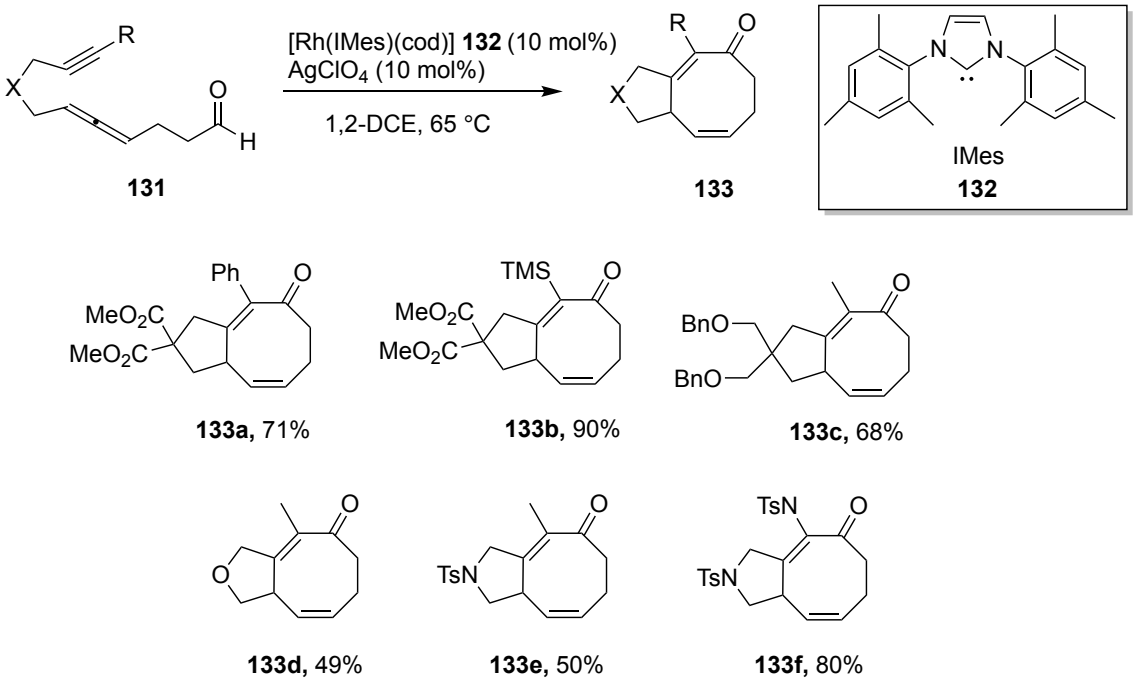


Scheme 60: Ni-catalysed [3+2+2] cycloadditions of alkylidenecyclopropanes and alkenes

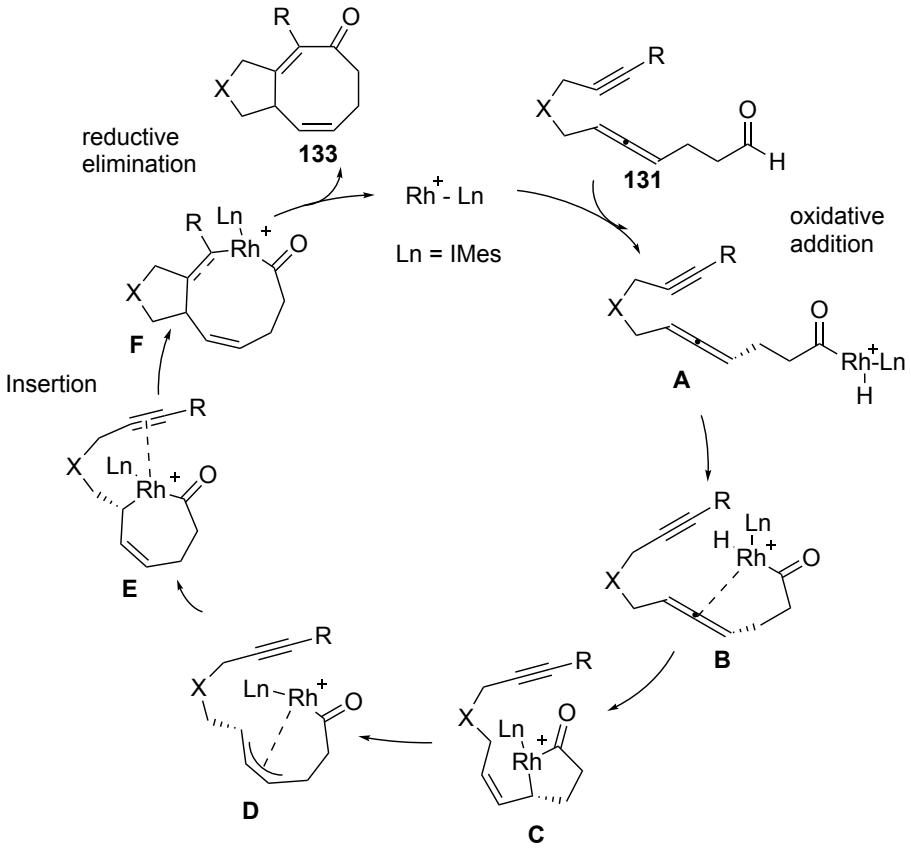


Scheme 61: Proposed Mechanism of the reaction

Sato *et al.* describe a novel strategy for the synthesis of fused bicyclic ketones **133** through a Rh(I)-catalysed formal [6+2] cycloaddition reaction.[69] The reaction involves 4-allenals, which contain both an allenic moiety and a reactive aldehyde group, in combination with alkynes or alkenes tethered to an appropriate functional group (Scheme 62). The catalytic cycle is initiated by oxidative addition of the Rh(I) catalyst into the formyl C−H bond of substrate **131**, followed by coordination and insertion of the C＝C bond of the allene to form an oxo-rhodacyclic intermediate **A**. This is then engaged in a second migratory insertion involving the alkyne or alkene moiety, and the sequence concludes with reductive elimination to afford the bicyclic ketone product **133** (Scheme 63).

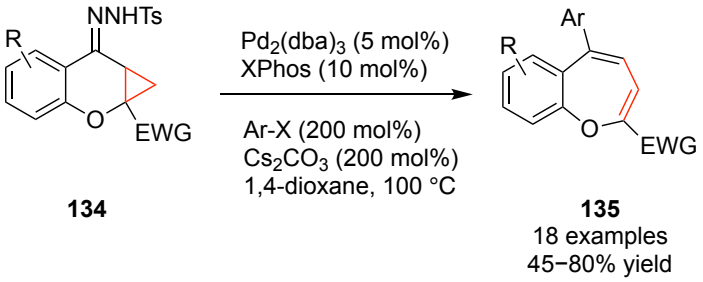


Scheme 62: Ru(I) catalysed [6+2] cycloaddition to perform bicyclic ketones

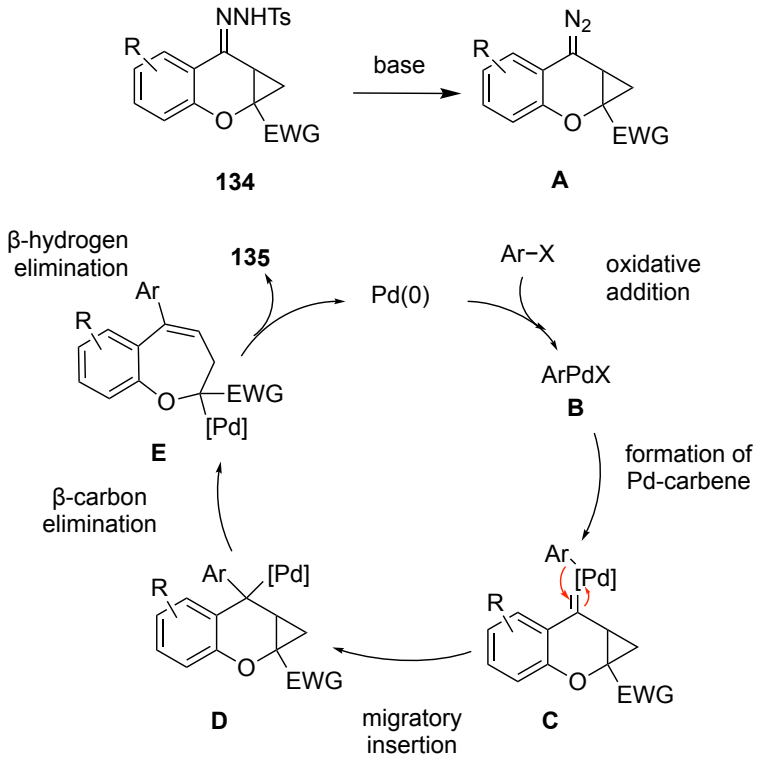


Scheme 63: Possible mechanism for Ru(I) catalysed [6+2] cycloaddition reaction

In a significant advancement of ring-expansion strategies, Zhou *et al.* reported a Pd-catalysed method for the regiospecific synthesis of benzoxepines **135** via the cross-coupling of aryl halides with oxabicyclo[4.1.0]heptyl *N*-tosylhydrazones **134**, proceeding through cyclopropyl carbinyl carbene migratory insertion and C−C bond activation (Scheme 64).[70] This transformation employs a diazo compound **A** as a carbene precursor, which reacts with a Pd(0) to form a Pd-carbene intermediate **C**. The mechanism initiates with the oxidative addition of the active Pd(0) complex into the carbon halogen bond of an aryl halide (Ar−X), generating a Pd(II) complex. The Pd(II) intermediate then reacts with diazo compound **A** to form a Pd-carbene species **C**, which then undergoes migratory insertion into Pd−C bond, yielding the bicyclic cyclopropyl carbinyl palladium species **D**. Regioselective cleavage of the C−C bond through β-carbon elimination results in the formation of intermediate **E**, which subsequently undergoes β-hydrogen elimination to produce the seven-membered benzoxepine **135**, while also regenerating the palladium catalyst to complete the catalytic cycle (Scheme 65).



Scheme 64: Pd-catalysed cross-coupling of N-tosylhydrazones 135 with aryl halides

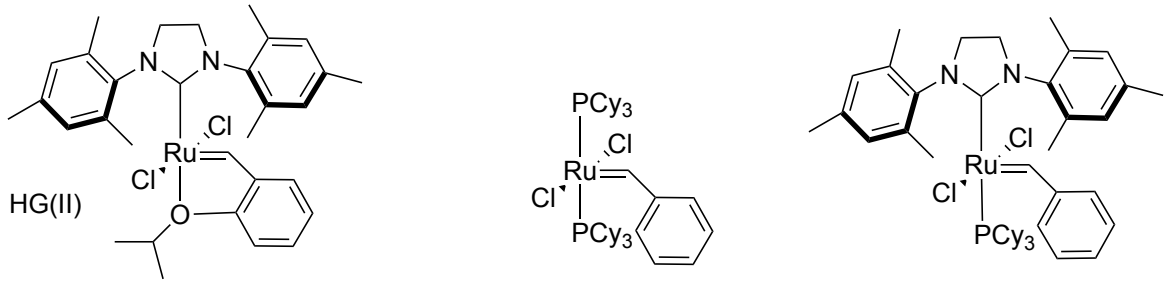


Scheme 65: Proposed reaction mechanism

Transition metal-catalysed cyclization is often advantageous for reactions that would otherwise require harsher conditions. It can also allow for greater control over the formation of specific ring sizes. However, the use of these catalysts is not without drawbacks. Transition metals can be expensive, toxic, and difficult to handle, especially on a large scale. Additionally, issues such as catalyst deactivation, metal leaching, and environmental concerns related to metal waste are significant challenges that need to be addressed in practical applications.

3.2.2 Ring-Closing Metathesis

Ring-closing metathesis (RCM) is a widely used reaction in organic synthesis that transforms linear dienes into cyclic alkenes through the use of a metal-carbene catalyst, typically based on ruthenium carbenoid catalysts (see Figure 7). This method can be particularly effective for constructing medium-sized and macrocyclic rings, compared to other cyclisation modes, offering high efficiency, functional group tolerance, and broad applicability across various substrates.



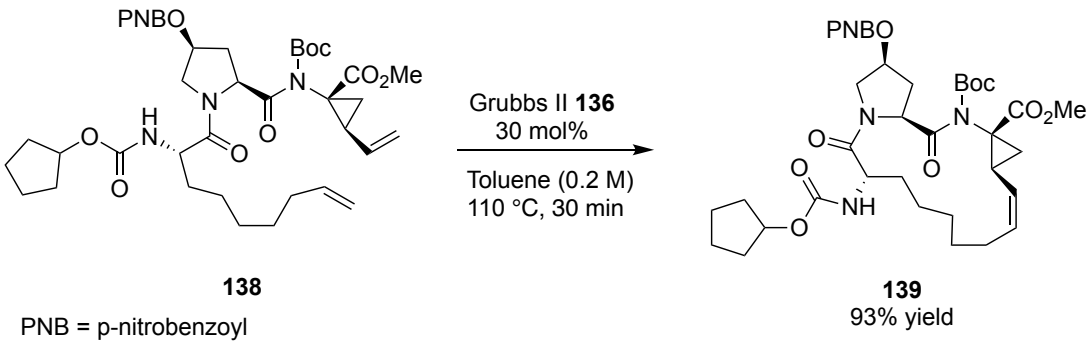
36
Hoveyda-Grubbs
2nd generation (HG-II)

136
Grubbs 1st generation
Grubbs-I

137
Grubbs 2nd generation
Grubbs-II

Figure 7: Typical catalyst employed in ring-closing metathesis

Shu *et al.* developed an highly efficient and environmentally friendly ring-closing metathesis reaction using Grubbs second generation catalyst **137** in the synthesis of the hepatitis C virus (HCV) protease inhibitor BILN 2061 **139** (Scheme 66).[71] Mechanistically, the RCM proceeds via a [2+2] cycloaddition between the Ru-carbene complex **140** and an alkene **141** to form a metallacyclobutane intermediate **A**, which then undergoes cycloreversion to establish a new C＝C bond while regenerating forming a new tethered Ru(II) carbenoid. A second [2+2] cycloaddition, this time intramolecular, followed by cycloreversion then completes the catalystic to form the cyclic product **142** (Scheme 67).

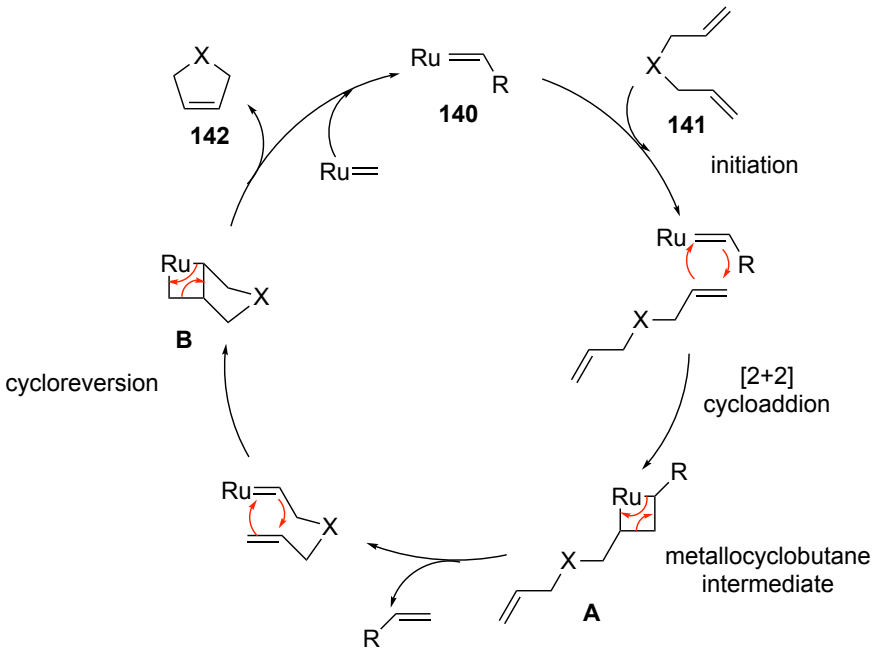


138

PNB = p-nitrobenzoyl

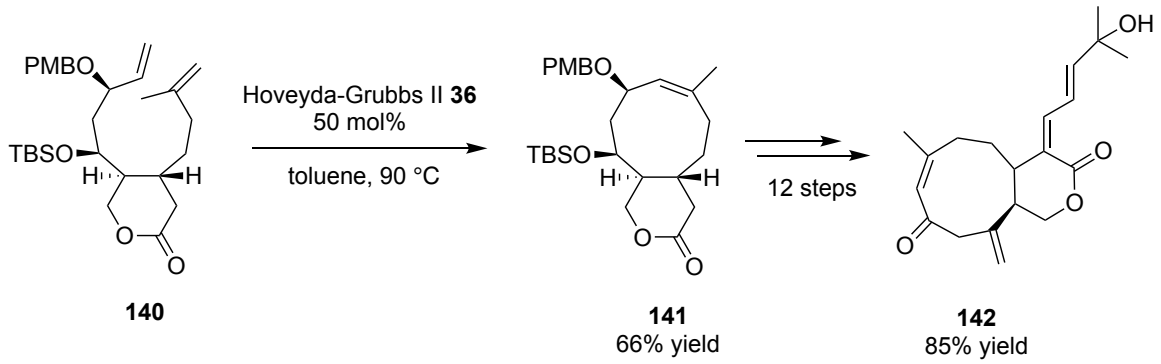
139
93% yield

*Scheme 66: RCM reaction via Grubbs (II) catalyst for the synthesis of **139***



*Scheme 67: Mechanism of RCM via Grubbs II **136***

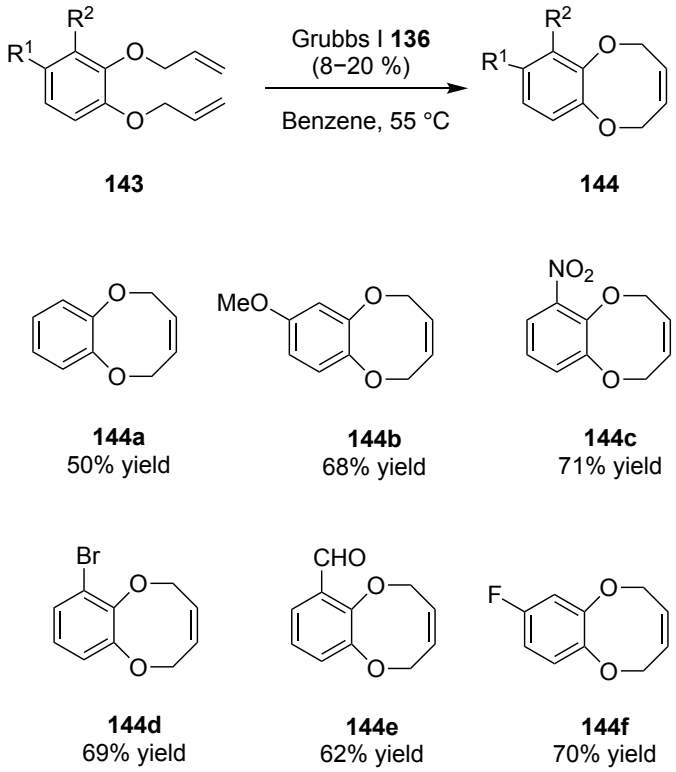
In 2008, Altmann *et al.* reported the first total synthesis of the *Xenia* diterpenoid blumiolide C, a cytotoxic marine natural product featuring a *trans*-fused oxabicyclic core.[72] A key transformation in this route was the formation of the nine-membered ring containing *Z*-configured double bond via RCM. Under optimized conditions, treatment of intermediate **141** with the Hoveyda-Grubbs second generation catalyst **36** (50 mol%) in toluene at 90 °C furnished the nine-membered ring **142** in 66% yield (Scheme 68). The high steric hindrance around the alkene moieties necessitated an unusually high catalyst loading, which was essential to obtain the product **142** in sufficient yields, reflecting a common challenge in medium-sized ring synthesis via RCM.



140 **141** 66% yield **142** 85% yield

Scheme 68: Total synthesis of blumiolide C 142 via ring-closing metathesis

R. Mamouni *et al.* reported the synthesis oxygen-containing medium ring systems via ring closing metathesis reaction (Scheme 69).[73] The diene **143** underwent cyclisation in the presence of Grubbs-I **136** catalyst affording the eight-membered benzodioacycles **144** in good yields.



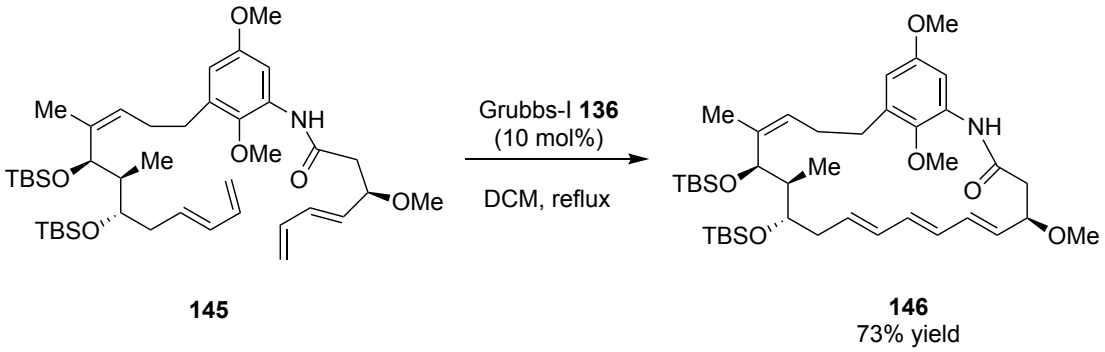
143 **144**

144a 50% yield **144b** 68% yield **144c** 71% yield

144d 69% yield **144e** 62% yield **144f** 70% yield

Scheme 69: RCM forming eight-membered benzodiooxacycles

Evano *et al.* demonstrated the synthesis of the macrocyclic core of cytotrienins, employing ring-closing metathesis as the key step for the efficient macrocyclisation (Scheme 70).[74] The 16-membered macrocycle **146** was formed from a highly functionalised diene **145** using Grubbs-I **136** catalyst, yielding the product **146** in 73% yield.



145 **146**
73% yield

Scheme 70: RCM for the synthesis of the 16-membered macrocyclic core of cytotrienins

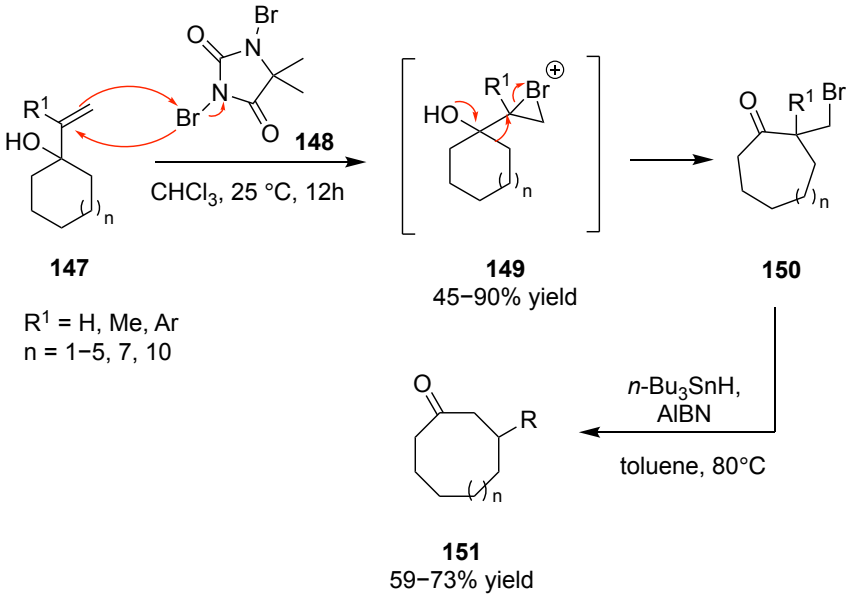
3.3 Ring Expansion Reactions

Ring expansion reactions involve the transformations of a smaller ring system into a larger one via a rearrangement reaction. As discussed previously, medium-sized rings and macrocycles are challenging to construct via direct end-to-end cyclisation reactions due to unfavourable entropic and enthalpic factors, including transannular strain, poor preorganisation of the precursors, and competitive side reactions.[75,76] Ring expansion overcomes many of these limitations by starting from smaller, conformationally constrained systems and modifying them through bond reorganisation, rearrangement, or fragmentations processes that increase ring size, whilst avoid unfavourable end-to-end macrocyclisation.

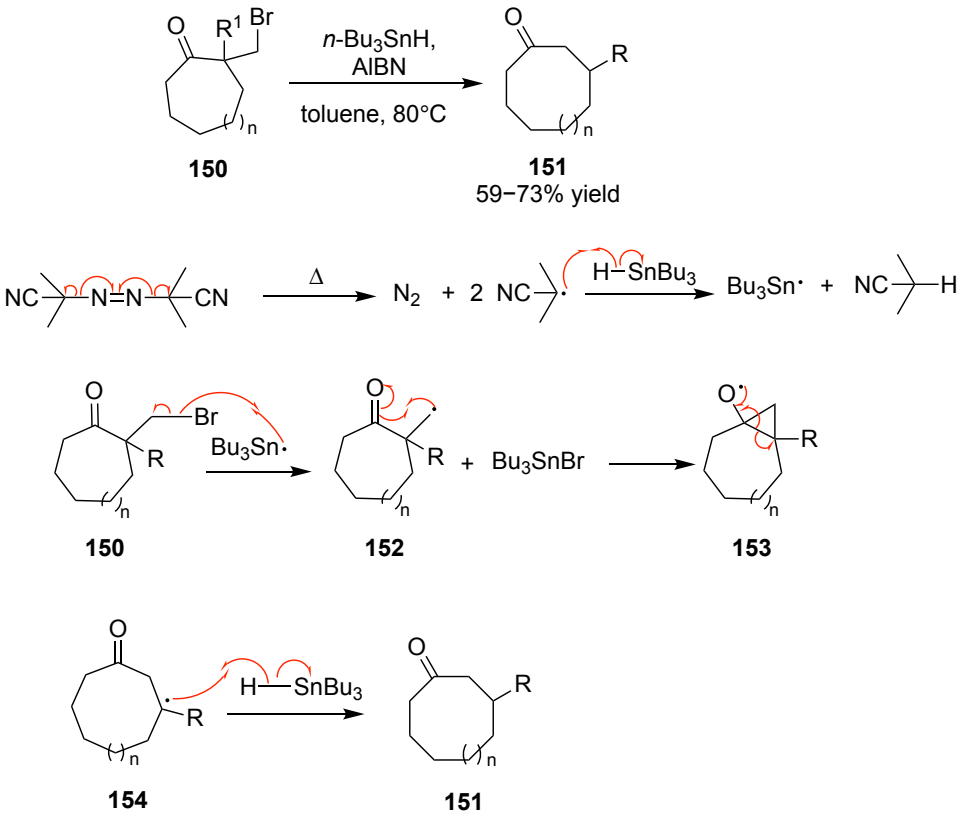
3.3.1 Radical Ring Expansion Reactions

High-energy radical intermediates have been employed in ring expansion reactions for the synthesis of medium and macrocyclic ring systems. A classic example of such transformations is the Dowd-Beckwith rearrangement, which involves the formation of a carbon-centred radical adjacent to a cyclic ketone, followed by a radical-mediated transannular 1,2-shift that leads to ring expansion. Building on this strategy, Liu and Yeung report an efficient, catalyst-free strategy for the synthesis of macrocyclic ketones, also including a semi-pinacol rearrangement, and demonstrating its utility through the total synthesis of (±)-muscone, a

valuable macrocyclic musk compound.[77] In this reaction, a series of 1-vinylcycloalkan-1-ol derivatives **147** were treated with 1,3-dibromo-5,5-dimethylhydantoin (DBH) **148**, enabling activation of the olefin moiety by bromonium ion formation. This electrophilic process resulted in the formation of one-carbon homologated β-bromo ketones **150** (Scheme 71). These intermediates then engaged in a Dowd-Beckwith rearrangement, in which homolytic cleavage of the C−Br bond generated a carbon−centred radical adjacent to the carbonyl. This radical cyclized intramolecularly onto the carbonyl group to form a cyclopropanol radical intermediate **153**, which subsequently fragmented via β-scission to furnish the ring-expanded ketone products **151**, as depicted in Scheme 72.

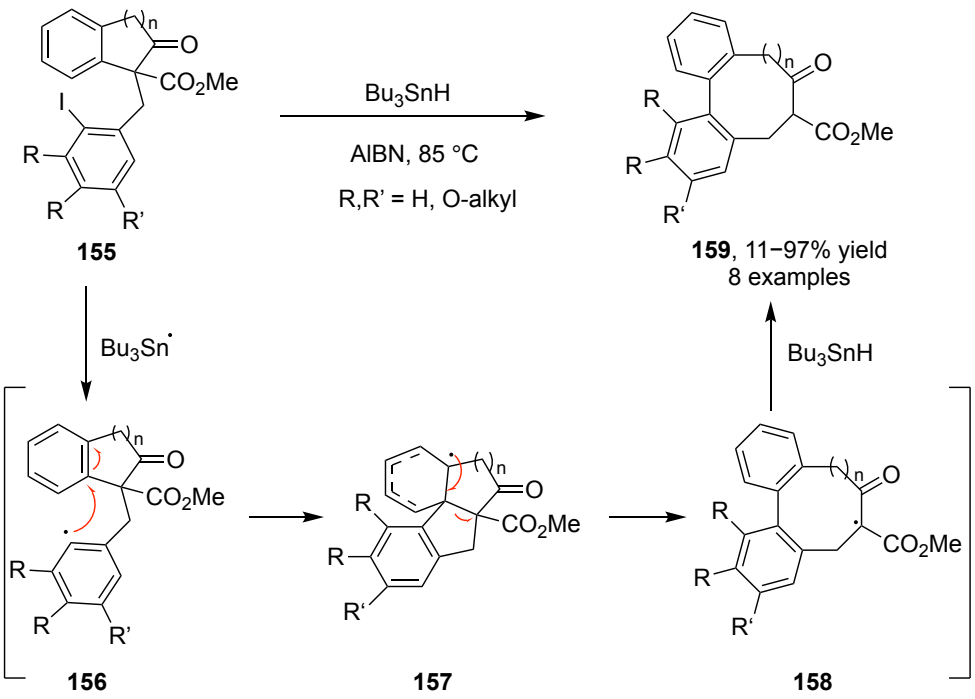


Scheme 71: Ring expansion by semi-pinacol rearrangement and subsequent Dowd-Beckwith reaction



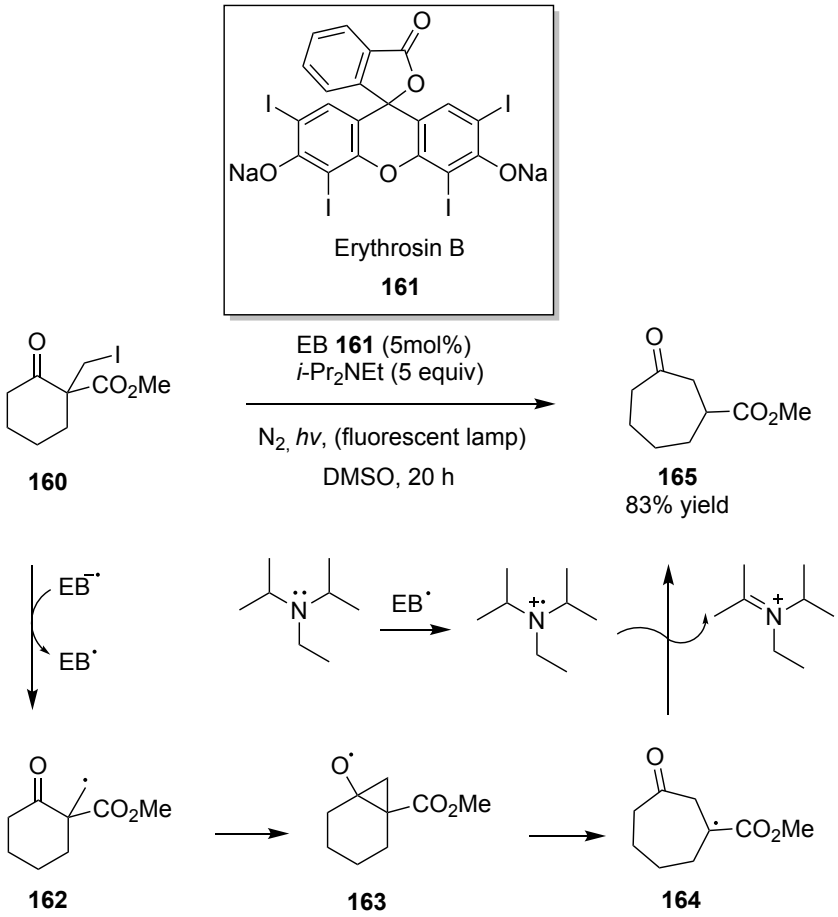
Scheme 72: Mechanism for the Dowd-Beckwith reaction

Harrowven *et al.* developed a method for the synthesis of eight- and nine-membered β-keto esters **159** via radical *ipso*-substitution, employing carbon-centred radicals to achieve ring expansion.[78] In this strategy, aryl radicals **155** are generated through *ipso*-substitution at the C3 position of an aromatic system, followed by a 5-*exo*-trig cyclisation that leads to a delocalised radical intermediate **157**. This intermediate **157** undergoes radical-induced rearomatisation via fragmentation, resulting in a ring-expanded tertiary radical **158** that is further stabilised by an adjacent ester group (Scheme 73). Such a mechanism effectively combines cyclisation and fragmentation steps to achieve medium ring formation with high efficiency.



Scheme 73: Medium ring synthesis via aryl ipso-substitution

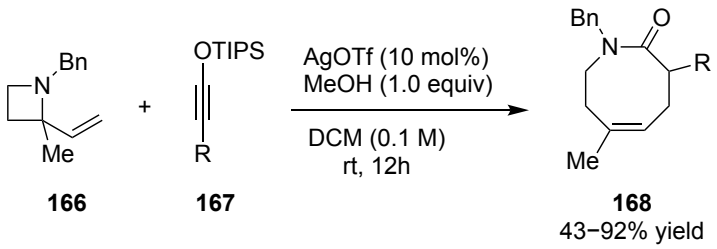
Itoh *et al.* introduced a radical ring expansion method catalysed by erythrosine B (EB) under fluorescent light irradiation.[79] This approach enables the synthesis of medium-sized rings via a Dowd-Beckwith rearrangement, initiated by photoinduced single electron transfer (SET) from the excited dye to a halogenated β-keto ester substrate. The resulting carbon-centred radical undergoes intramolecular cyclization followed by fragmentation, resulting in ring expansion (Scheme 74). The method proceeds under mild conditions, exhibits a broad substrate scope, and affords moderate to good yields, offering an environmentally friendly alternative to traditional radical-mediated ring expansion strategies.



Scheme 74: Dowd-Beckwith radical ring expansion reaction via photocatalyst

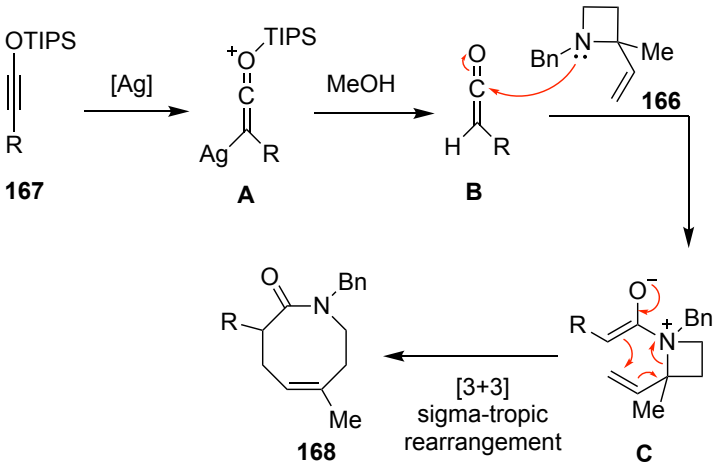
3.3.2 Pericyclic Reactions

Pericyclic reactions are concerted process that proceed through cyclic transition states and are governed by orbital symmetry considerations. This class of reactions includes electrocyclic reactions, cycloadditions, and sigmatropic rearrangements, each facilitating the formation or reorganization of chemical bonds in a stereospecific and predictable pathway. Williams *et al.* introduced a method for synthesising eight-membered lactams **168** via a formal [6+2] cyclization between siloxy alkynes **167** and vinylazetidines **166**, catalysed by silver triflate (AgOTf) (Scheme 75).[80] The work directly addresses long-standing difficulties in synthesising medium-sized rings, particularly ring strain, transannular interactions, and entropic disfavour, which often lead to low yields, poor selectivity, or competing side reactions in traditional cyclization approaches. By employing vinylazetidines **166** and siloxy alkynes **167** as reactants, the authors overcame these challenges using AgOTf as a Lewis acid catalyst to activate the siloxy alkyne toward nucleophilic attack.



Scheme 75: Synthesis of eight-membered lactams via a formal [6+2] cyclization

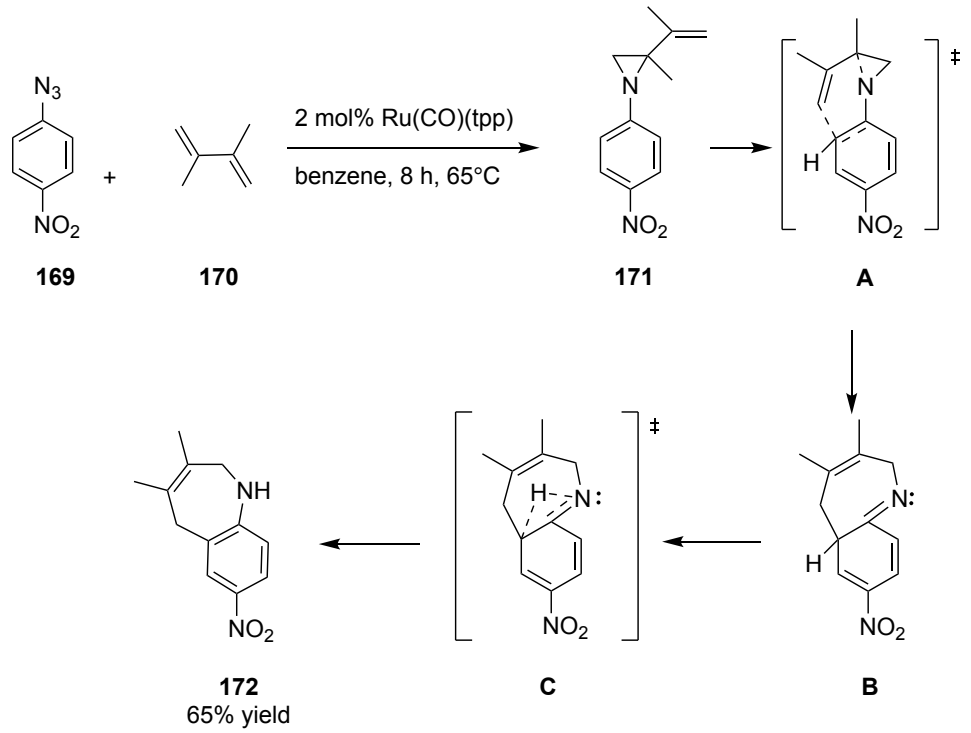
In the proposed mechanism, the silver catalyst coordinates to the siloxy alkyne **167**, increasing its electrophilicity and enabling a regioselective cycloaddition with the strained four-membered vinylazetidine **166**. This step generates a reactive ketene intermediate **C**, which then undergoes a 3,3-sigmatropic rearrangement to yield the eight-membered lactam. Notably, the reaction avoids the need for high temperatures or harsh reagents, proceeding under mild conditions and producing the lactams **168** in yields ranging from 43% to 92%, depending on the substrate (Scheme 76).



Scheme 76: Proposed reaction mechanism

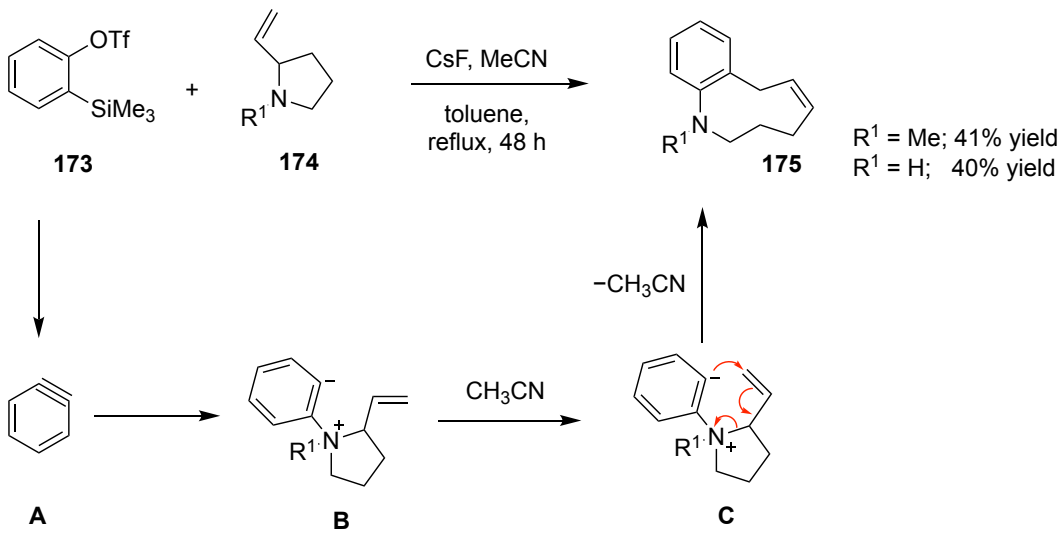
Gallo *et al.* demonstrated that *N*-aryl-2-vinylaziridines **169** can undergo [3,3]-Claisen rearrangement in the presence of a ruthenium catalyst to afford 2,5-dihydro-1*H*-benzo[b]azepines **172**.[81] These rearrangements are proposed to proceed via a concerted mechanism involving cleavage of the aziridine ring and migration of the vinyl group, resulting in ring expansion (Scheme 77). The proposed mechanism is initiated by a nucleophilic attack of the vinyl group to the aryl ring, accompanied by cleavage of the aziridine C−N bond. This concerted rearrangement leads to the formation of an imine-containing intermediate **B**,

which subsequently aromatizes. The aromatization step involves a proton shift from the aryl ring to the nitrogen atom, along with migration of the imine double bond into conjugation with the aromatic system, furnishing the benzoazepine product **172**.



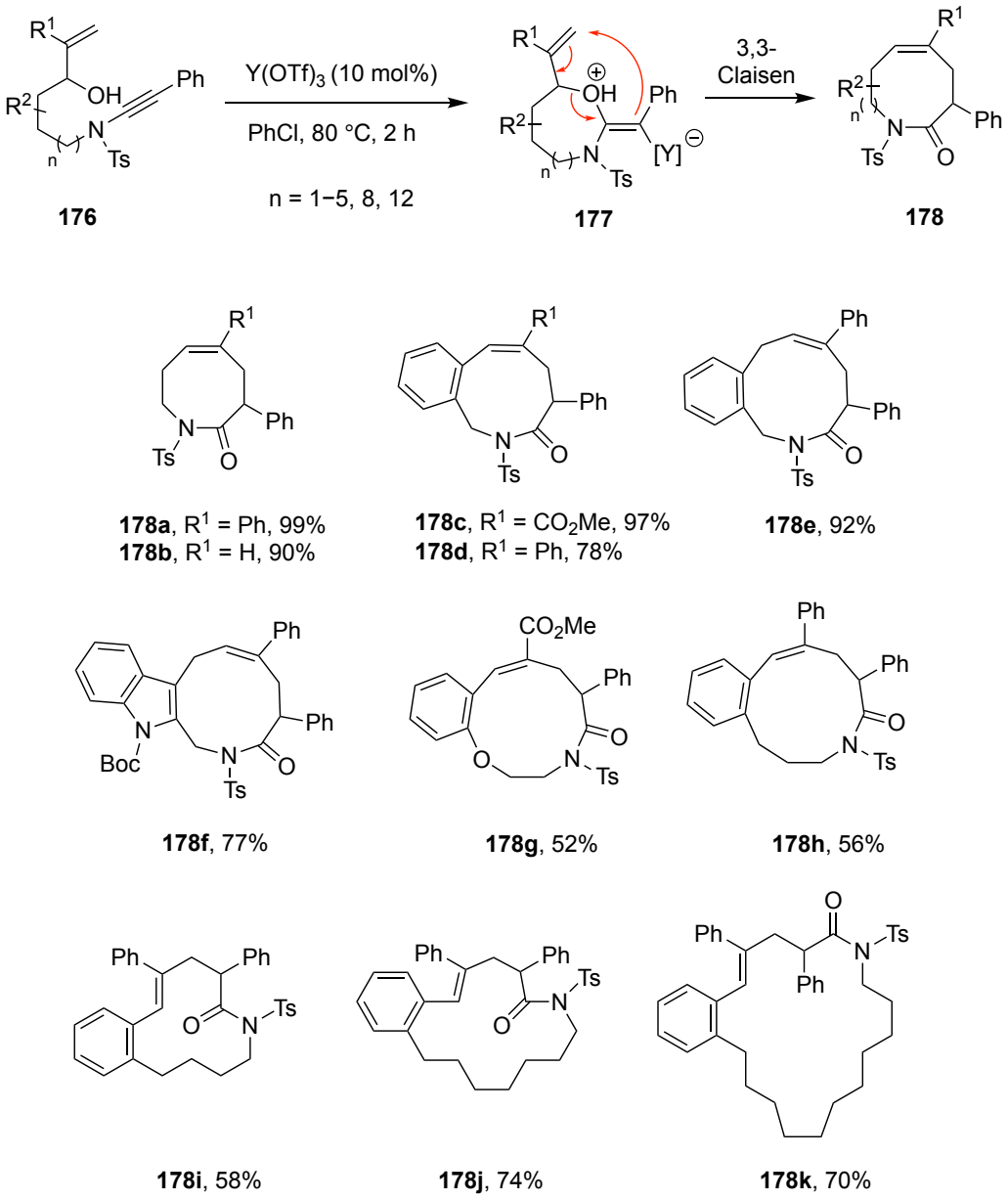
Scheme 77: Ruthenium catalysed aza-Claisen rearrangement

Aza-Claisen-type reactions involve a 3,3-sigmatropic rearrangement in which bond reorganisation occurs in a concerted pathway, typically within nitrogen-containing allyl systems. In this context, Greaney *et al.* demonstrated this approach in a reaction involving the in-situ generation of electrophilic benzyne from a silyl triflate precursor in the presence of CsF at elevated temperature (110 °C), which rapidly reacts with a tertiary allylamine nucleophile.[82] This addition produces a zwitterionic **B**, which is protonated in solution to afford **C**. The resulting intermediate **C** undergoes an intramolecular 3,3-aza-Claisen rearrangement, followed by rearomatisation to form nine-membered ring systems (Scheme 78).



Scheme 78: The aza-Claisen rearrangement forming nine-membered benzannulated amines

Yu *et al.* developed an efficient yttrium(III)-catalysed tandem intramolecular hydroalkoxylation/Claisen rearrangement sequence for the synthesis of medium-sized and macrocyclic lactams **178**.[83] In this methodology, sulfonyl-protected ynamides **176** undergo activation by yttrium triflate [$Y(OTf)_3$], promoting intramolecular nucleophilic attack by the hydroxyl group. This leads to the formation of cyclic vinyl esters **177**, which then undergoes [3,3]-sigmatropic Claisen rearrangement to afford the medium to large ring lactams **178** in moderate to excellent yields (Scheme 79).

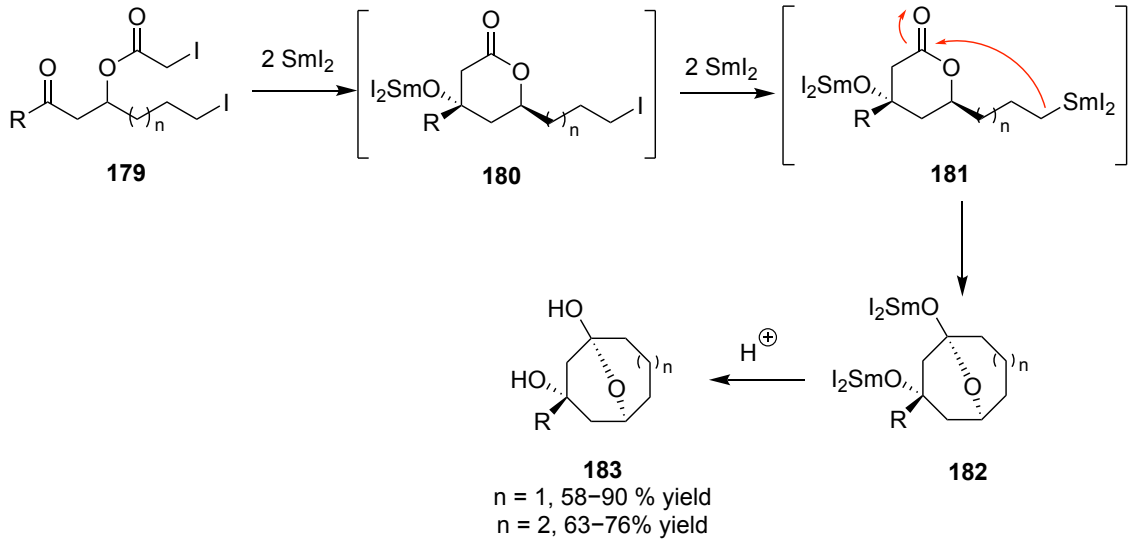


Scheme 79: Lactams synthesis via hydroalkoxylation/Claisen rearrangement

3.3.3 Fragmentation-Based Ring Expansion

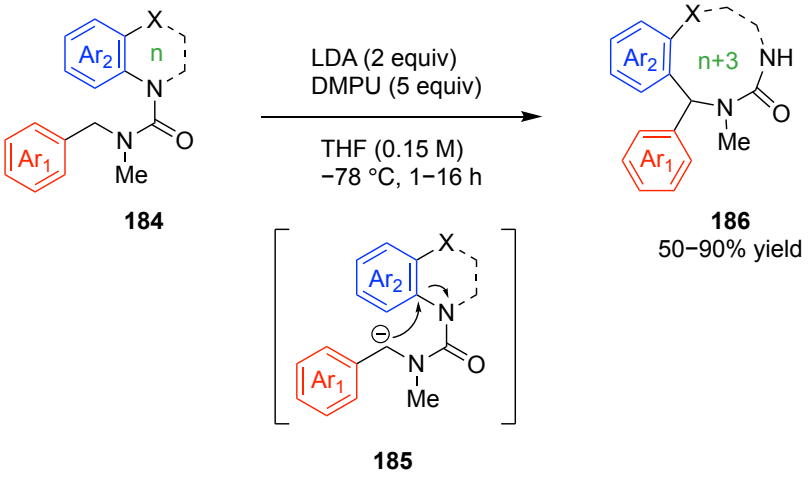
The fragmentation reaction is a strategic synthetic method involving the controlled cleavage of cyclic or acyclic precursors to generate reactive intermediates such as carbocations, radicals, or carbenes, which then undergo ring expansion. This transformation provides efficient access to medium and large ring systems, which are often difficult synthesize due to entropic and enthalpic barriers. This methodology plays an important role in the synthesis of complex molecules, including natural products, pharmaceuticals, and macrocyclic scaffolds.

Molander *et al.* demonstrated a sequential intramolecular Reformatsky/nucleophilic acyl substitution reaction mediated by samarium (II) iodide (SmI_2) for the stereoselective synthesis of medium-sized carbocycles.[84] Treatment of substrate **179** with SmI_2 initiates a Reformatsky reaction, forming β-hydroxy lactone **180**. The resulting alkoxide intermediate **181** then undergoes an intramolecular nucleophilic acyl substitution, displacing the lactone carbonyl to afford a stereodefined eight- and nine-membered carbocycle **183** (Scheme 80).



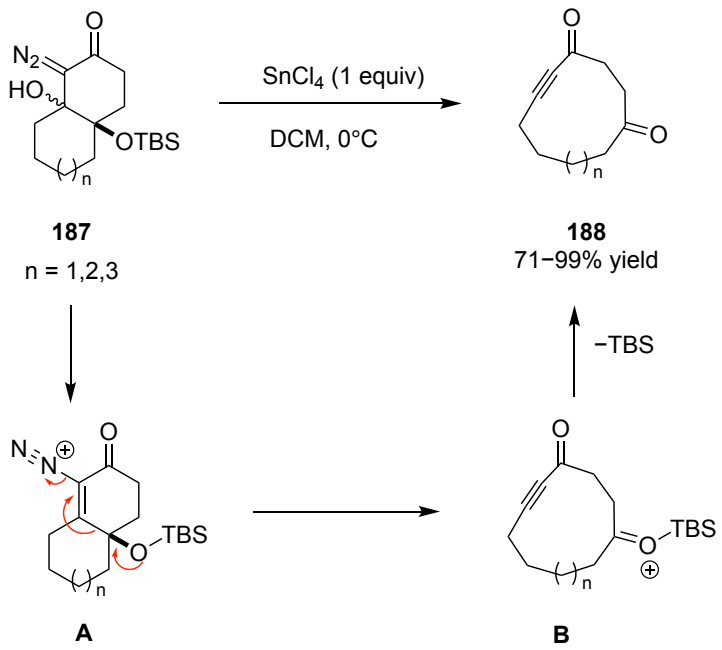
Scheme 80: The Reformatsky/nucleophilic acyl substitution reaction promoted by samarium (II) iodide

Clayden *et al.* developed a strategy for the synthesis of medium-sized (8 to 12-membered) nitrogen-containing heterocycles via a migratory ring expansion mechanism.[85] The process begin with the deprotonation of *N*-alkyl ureas **184** using LDA in the presence of DMPU, generating a lithiated urea anion **185**. This reactive intermediate **185** undergoes an aryl migration from a neighbouring carbon atom onto the nitrogen atom, accompanied by cleavage of a C−N bond, resulting in ring expansion **186** (Scheme 81).



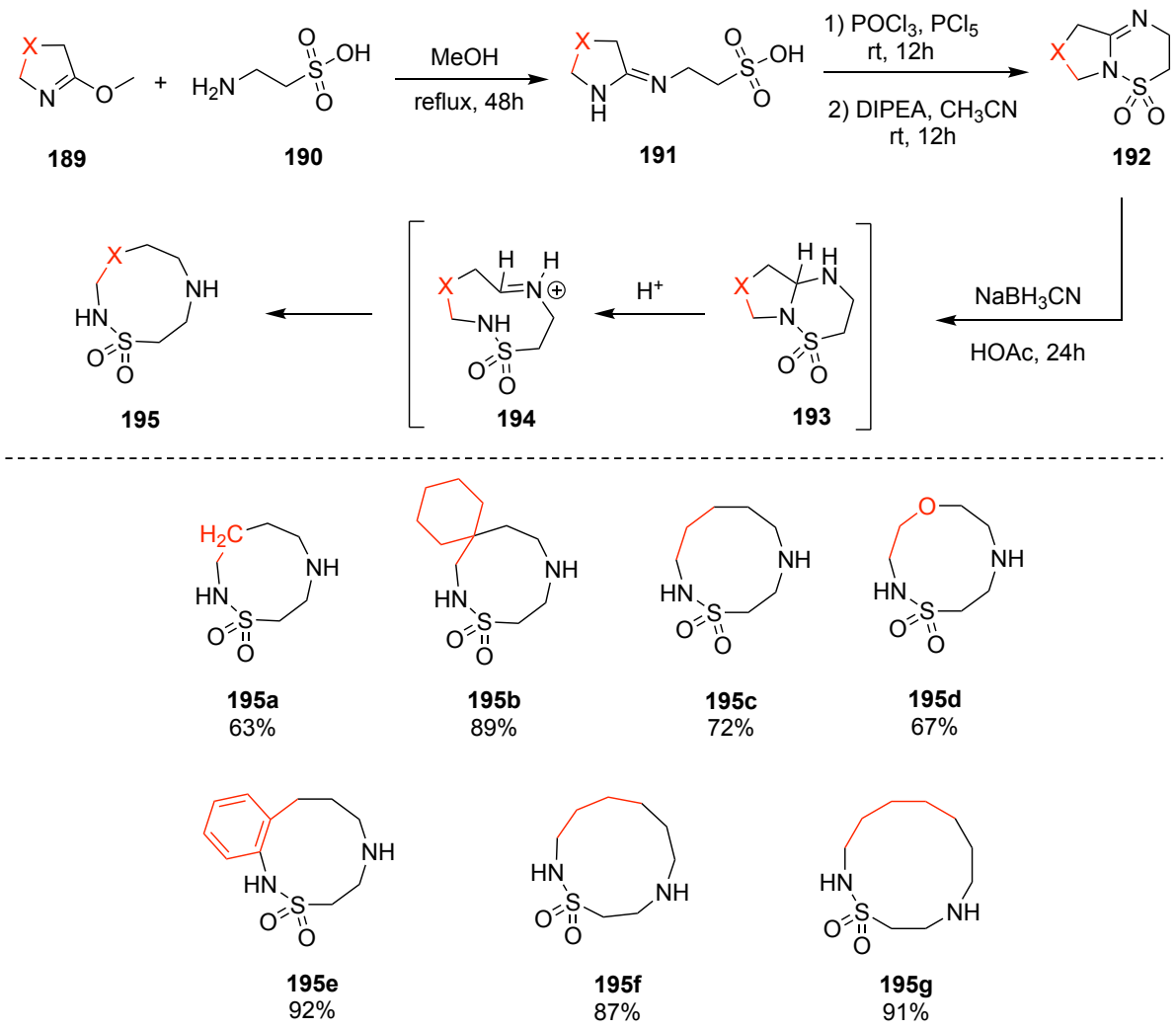
Scheme 81: Based-promoted ring expansion by LDA/DMPU

Brewer *et al.* reported a method for the synthesis of 10−12−membered rings **188** via a fragmentation-based strategy.[86] This method involves the preparation of bicyclic *γ*-silyloxy-β-hydroxy-α-diazoketones, which underwent Lewis acid-promoted fragmentation in the presence of tin(IV) chloride ($SnCl_4$). As illustrated in Scheme 82, the mechanism begins with the elimination of the β-hydroxyl group under acidic conditions, leading to the formation of a vinyl diazonium intermediate **A**. This intermediate **A** undergoes β-fragmentation, resulting in the release of nitrogen gas (N_2). Finally, desilylation removes the *tert*-butyldimethylsilyl (TBS) protecting group, affords the medium-sized cyclic 2-alkynones **188**.



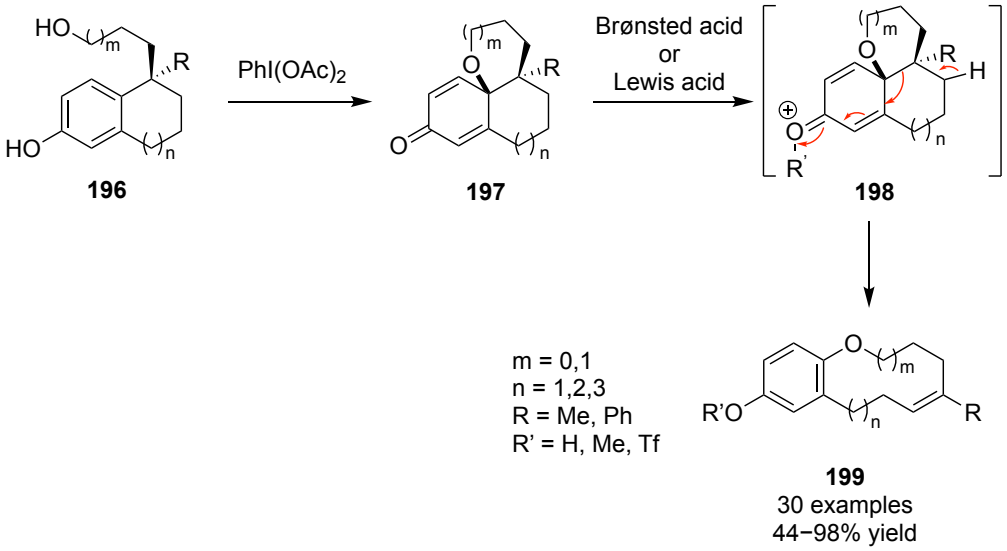
*Scheme 82: Fragmentation-based ring expansion for the synthesis of 10-, 11-, and 12-membered rings **188***

Kostyuk *et al.* introduced an efficient method for the synthesis of medium-sized ring azasultams **195** through the reductive cleavage of annulated 5,6-dihydro-2*H*-1,2,4-thiadiazine-1,1-dixides **189**.[87] The synthesis begins with the preparation of these thiadiazine derivatives **191** by reacting cyclic imidates **189** with taurine **190**, followed by treatment with phosphorus oxychloride ($POCl_3$) in the presence of *N*,*N*-diisopropylethylamine (DIPEA). Subsequent reduction using sodium cyanoborohydride ($NaBH_3CN$) cleaves the thiadiazine ring, yielding 9−12 membered azasultams **195** (Scheme 83).



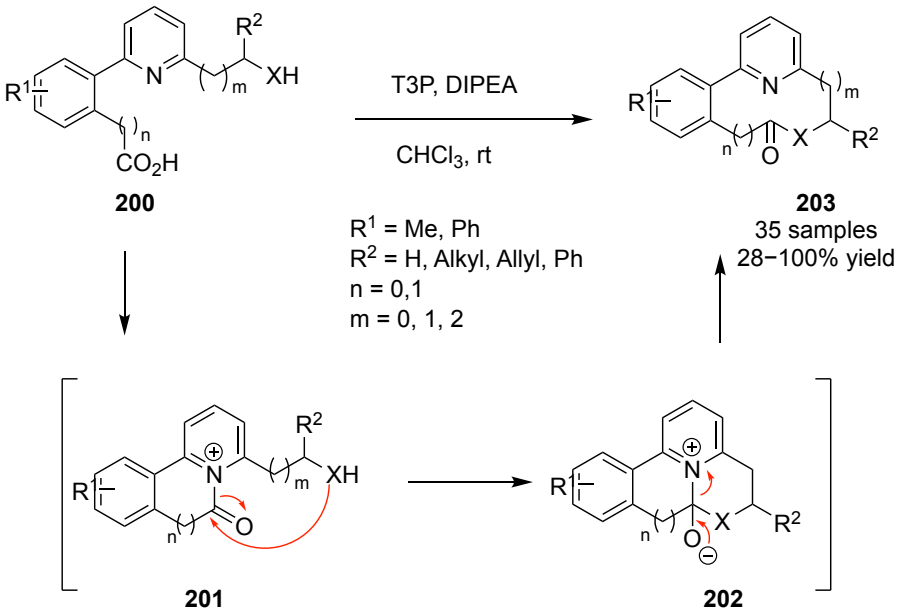
*Scheme 83: Reductive cleavage of thiadiazine dioxides 189 to form medium-sized azasultams **195***

An alternative route for the synthesis of benzannulated medium rings **199** using oxidative dearomatisation-ring expanding rearomatization (ODRE) was reported by Tan *et al.*[88] In this two-step method, bicyclic phenol derivatives **196** undergo oxidative dearomatisation to form polycyclic cyclohexadienone intermediates **197**. These intermediates **197** are then subjected to Lewis or Brønsted acid-promoted ring expansion, accompanied by rearomatisation, yielding 8- to 11-membered medium-sized rings **199** (Scheme 84).



Scheme 84: Synthesis of medium-sized rings xx via oxidative dearomatisation-ring expanding rearomatization

An original strategy developed by the Unsworth group involves an intramolecular cyclisation/ring expansion cascade for the synthesis of medium-sized lactones and lactams.[89] This method employs a linear precursor containing a strategically positioned internal amine, which acts as a nucleophilic catalyst. Upon activation of a carboxylic acid **200**, the internal amine attacks the electrophilic centre, forming an acyl ammonium ion intermediate **201**. This intermediate **201** then undergoes a spontaneous ring expansion, affording the medium-sized product **203** (Scheme 85).



Scheme 85: Cyclisation/ring expansion reaction for the synthesis of lactones and lactams

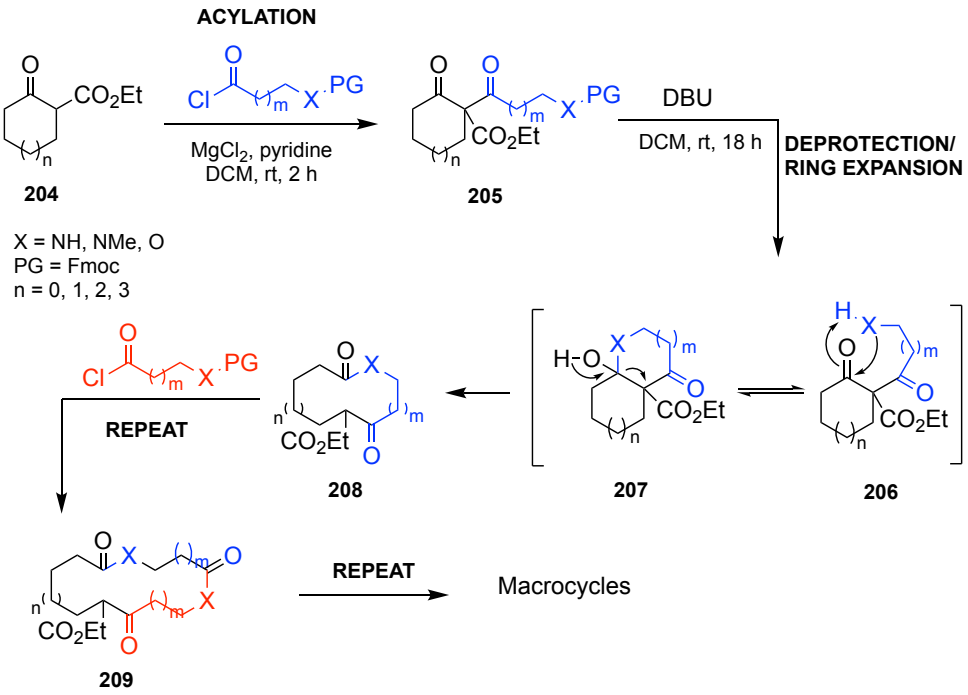
Significant progress has been achieved in ring expansion methodologies for the synthesis of medium-sized and macrocyclic compounds; however, limitations in substrate scope, selectivity, and functional group compatibility remain. Although recent developments have addressed some of these challenges through improved reactivity and broader applicability, several key issues still exist, particularly in achieving consistently efficient transformations and in extending these methods to more structurally complex systems.

4- A Combined Cross Metathesis-Ring Expansion Approach

4.1 Ring Expansion Strategies Inspired by the Methodology of the Unsworth Group

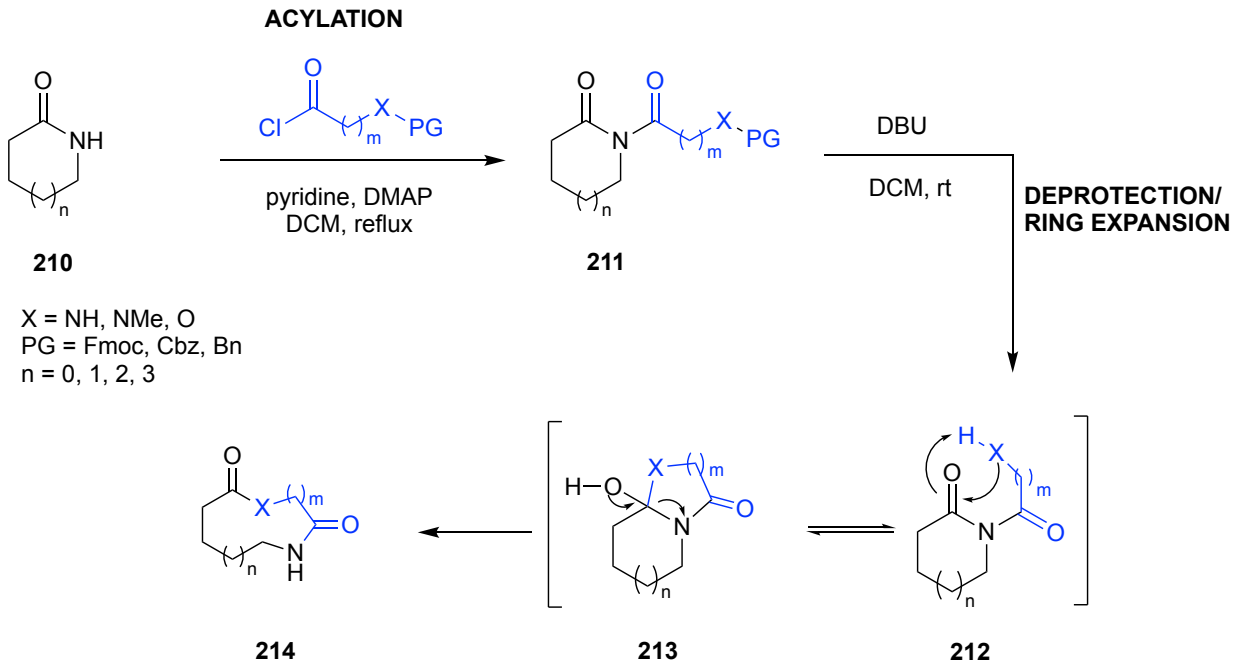
Building upon the foundational principles developed by the Unsworth Group, significant progress has been made in application of ring expansion methodologies for the synthesis of structurally diverse medium-sized and macrocyclic compounds. The group has pioneered innovative strategies, including the Successive Ring Expansion (SuRE) approach and cascade cyclisation/ring expansion sequences mediated by internal nucleophilic catalysts. These methodologies effectively address the longstanding synthetic challenges associated with medium-ring and macrocycle formation, offering notable advantages such as modularity, functional group tolerance, and high efficiency. In the following section, selected representative examples relevant to the research results in this chapter are summarised, and their applications are presented and discussed.

In 2015, Unsworth *et al.* introduced a versatile and modular strategy for macrocycle synthesis based on the SuRE approach, which proceeds through a two-step sequence.[90] Initially, the α-carbon of the β-keto ester **204** is acylated using an acid chloride derived from an amino or hydroxy acid. Following acylation, the protecting group (Fmoc) is removed under basic conditions using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Deprotection reveals the nucleophile that undergoes a spontaneous intramolecular attack, resulting in ring expansion via a bicyclic intermediate. This transformation increases the ring size by three or four atoms, depending on the structure of the amino or hydroxy acid employed. Notably, the product retains the same reactive functional group as the starting material, thus enabling further iterative ring expansion steps (Scheme 86).



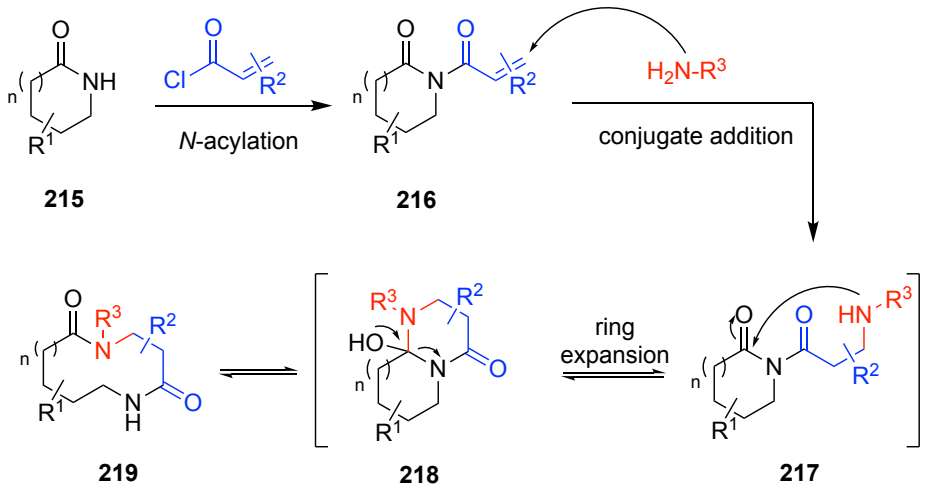
Scheme 86: SuRE reactions of cyclic β-keto esters

In another variation of SuRE, the amide nitrogen of a lactam was used as the nucleophile in the ring expansion process.[91] In this approach, the lactam **210** undergoes acylation with an acid chloride. After protected group removal, the exposed amine nitrogen initiates an intramolecular attack, leading to ring expansion. The strategy preserves the modular nature of the SuRE method while broadening its applicability to lactam-based starting materials (Scheme 87).



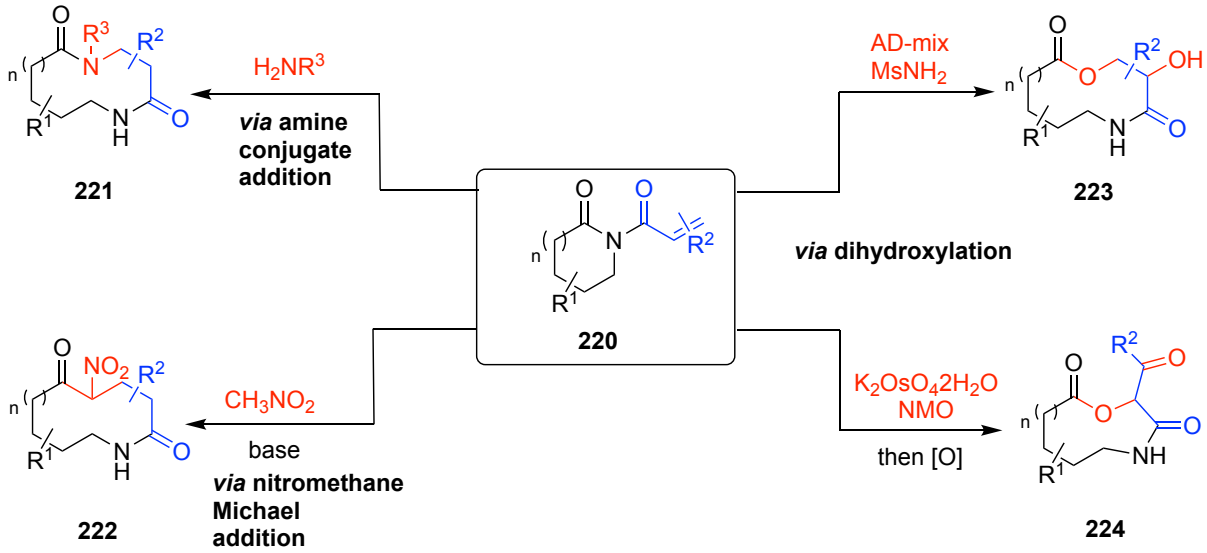
Scheme 87: SuRE reactions of lactams

An additional innovative strategy developed by Unsworth group involves a cascade reaction sequence known as the Conjugate Addition/Ring Expansion (CARE) process.[92] The sequence begins with the *N*-acylation of a lactam **215** using an α,β-unsaturated acid chloride. Next, the imide **216** performs conjugation addition with primary amine, forming a new C−N bond and generating an intermediate amine **217**. This intermediate **217** then undergoes intramolecular ring expansion through nucleophilic attack on a carbonyl group, resulting in the formation of a larger nitrogen containing ring **219** (Scheme 88).



Scheme 88: Conjugate addition/ring expansion with primary amines

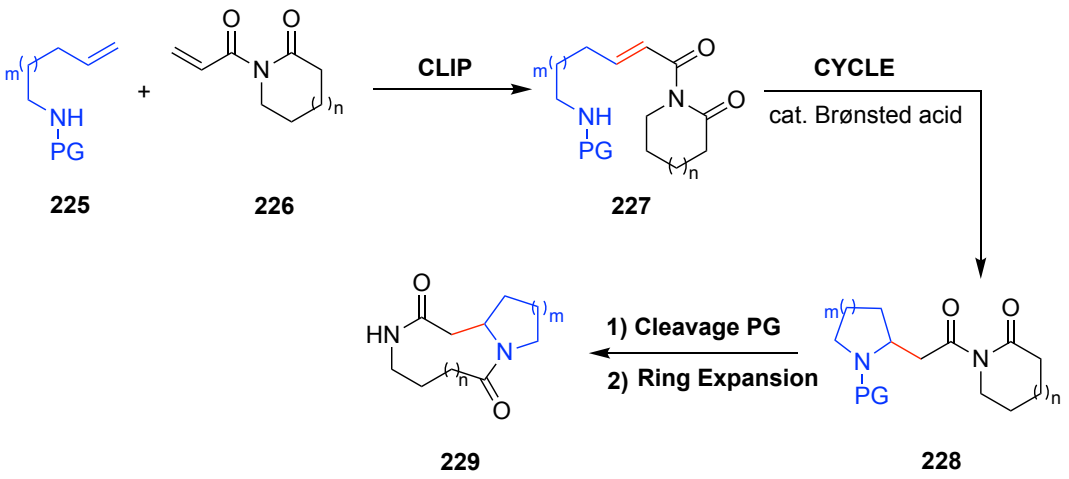
Following the initial development of the CARE strategy, further work in our group extended this approach through the investigation of acryloyl imides versatile intermediates for ring expansion reactions.[93] Unlike the original CARE protocol, this study introduced three distinct reaction pathways: amine conjugation addition/ring expansion, nitromethane Michael addition/ring expansion, and dihydroxylation/ring expansion. Each transformation begins functionalisation of the alkene of the acryloyl moiety, which is then followed by an intramolecular nucleophilic attack that drives ring expansion (Scheme 89). These new approaches preserve the protecting group-free and step-efficient nature of the CARE strategy, while significantly broadening its functional group tolerance and the structural diversity of products that can be made.



Scheme 89: Divergent reaction pathways in the ring expansion of acryloyl imides

The Unsworth group has pioneered innovative ring expansion strategies to address the synthetic challenges associated with medium-sized and macrocyclic systems. The Successive Ring Expansion (SuRE) approach enables sequential ring enlargement via bicyclic intermediates, while the Conjugate Addition/Ring Expansion (CARE) cascade offers distinct advantages, including improved overall efficiency, shorter reaction times, and a more streamlined process by reducing the number of synthetic steps and reagents required. In this context and building upon the synthetic experience gained in our previous work on 'Clip-Cycle' reactions, described in Chapter 2, we decided to try to develop an approach that combines these methods. Particularly, the use of cross metathesis reactions for the

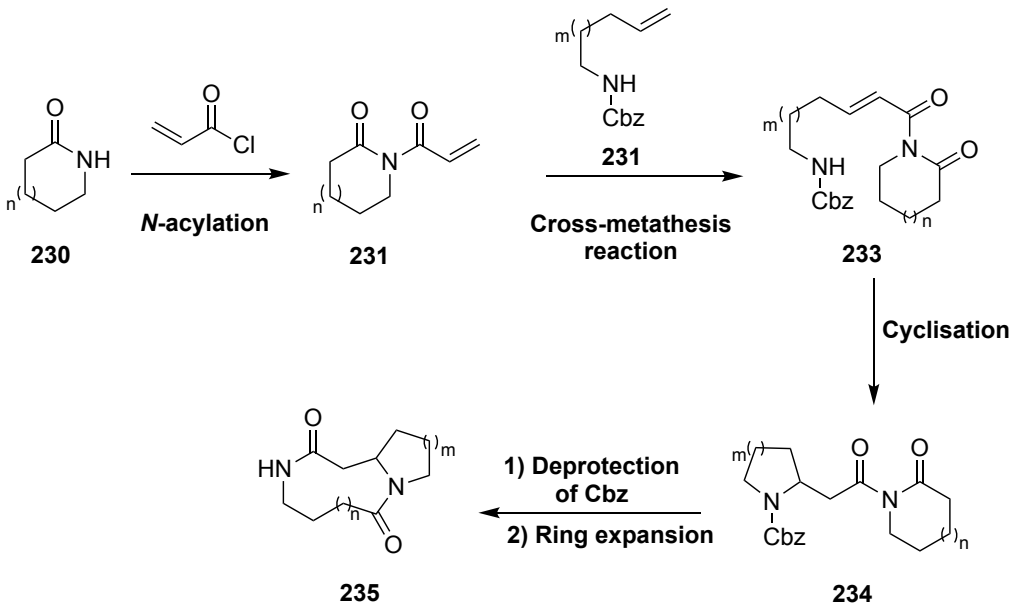
preparation of key intermediates primed to undergo ring expansion was a key goal, thus combining the methods of the Clarke and Unsworth groups. We hypothesised that cross metathesis could serve as a synthetically versatile method for installing unsaturated side chains, which may then undergo conjugate addition and subsequent ring expansion to generate structurally diverse medium-sized lactams (Scheme 90).



Scheme 90: Proposed reaction pathway

4.2 Cross metathesis/ Ring Expansion Approach

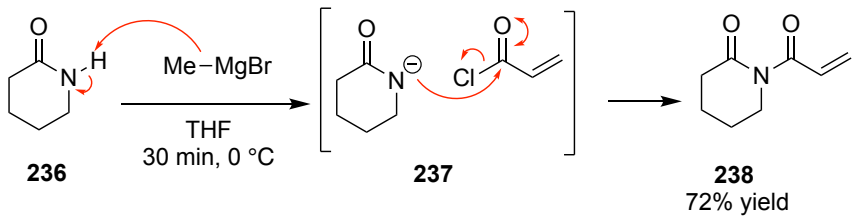
To expand the synthetic utility of ring expansion strategies, this project proposes a novel sequence involving cross-metathesis followed by intramolecular rearrangement for the synthesis of medium-sized lactams. As illustrated in Scheme 91, the proposed approach relies on a cross-metathesis reaction between a Cbz-protected amine **232** and a functionalised acryloyl imide substrate **231**. This reaction is expected to yield a tethered imide-amine intermediate **233**, which could then be subjected to an enantioselective cyclisation catalysed by R-TRIP to form **234**. Following removal of the Cbz protecting group, the resulting free amine was then expected to undergo spontaneous ring expansion (**234** → **235**), via a rearrangement mechanism similar to that proposed by the Unsworth group during the development of their SuRE and CARE methods.



Scheme 91: A general scheme for cross-metathesis/ring expansion that are planned

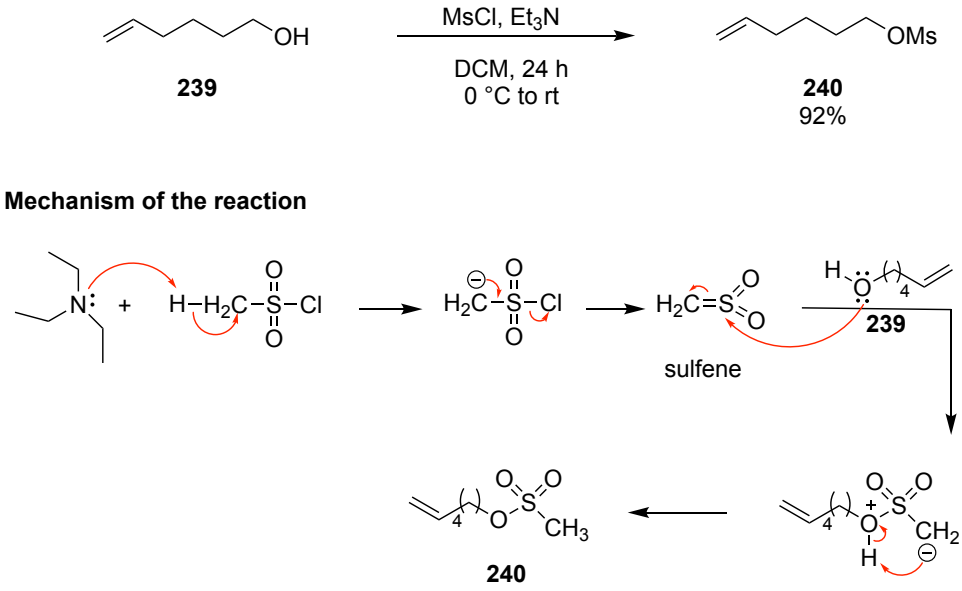
4.2.1 Synthesis of Conjugation Addition Precursors

The project began with the synthesis of acryloyl imide **238**. In this approach, the corresponding imide **238** was formed via *N*-acylation of 6-membered lactam **236** with the α,β-unsaturated acid chloride, a well-established procedure within the Unsworth group (Scheme 92).[76] In the proposed mechanism, the nitrogen atom of the imide acts as a nucleophile and attacks the electrophilic carbonyl carbon of acryloyl chloride. Deprotonation of the lactam **236** with a Grignard reagent was necessary, in order to increase the nucleophilicity of the amide nitrogen. This nucleophilic acyl substitution leads to the formation of a tetrahedral intermediate **237**, which subsequently undergoes elimination of a chloride ion to yield the *N*-acryloyl imide **238** in 72% yield.



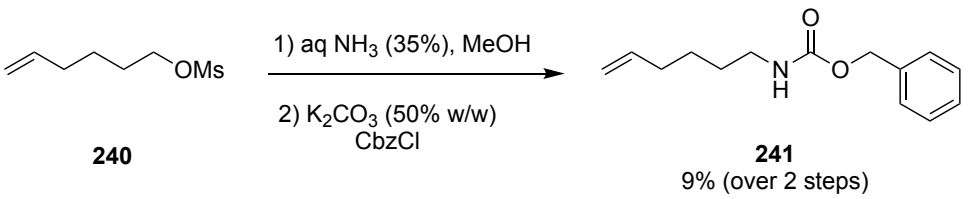
*Scheme 92: Acylation reaction of the lactam **236***

After isolating the desired product **238**, the focus next turned to the synthesis of the Cbz-protected amine **241**. This reaction was carried out via a two-step sequence starting from 5-hexen-1-ol **239**. Initially, 5-hexen-1-ol **239** was converted into the corresponding mesylate **240** by reaction with methanesulfonyl chloride (Scheme 93).

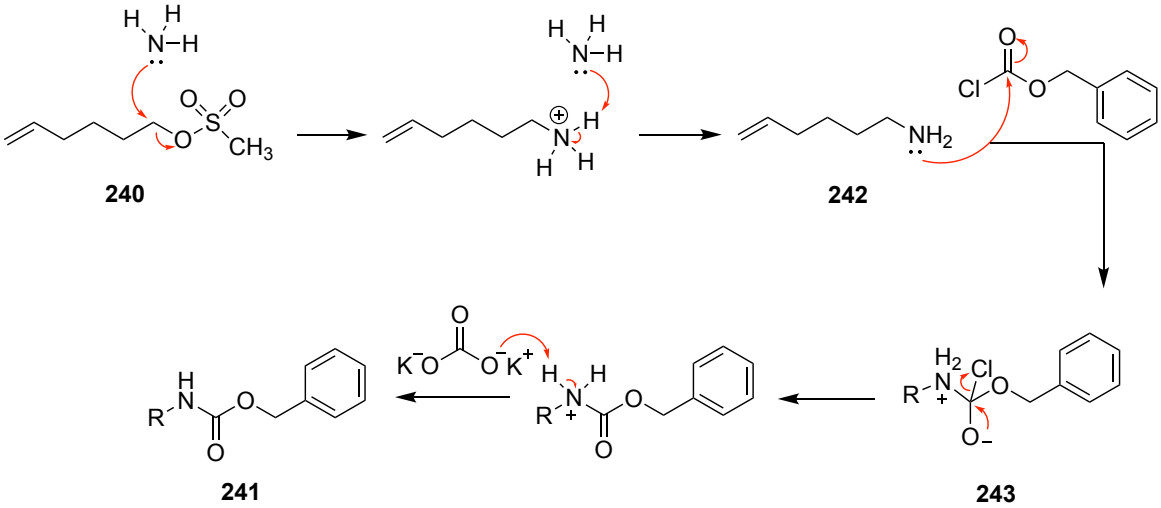


*Scheme 93: Formation of mesylate 240 starting from alcohol **239***

The intermediate **240** was subjected to nucleophilic substitution with aqueous ammonia in methanol, resulting in the formation of the primary amine **242** via an S_N2 mechanism. Subsequently, the amine **242** was reacted with benzyloxycarbonyl chloride (CbzCl) in the presence of potassium carbonate (K_2CO_3) as a base. In this sequence, the amine nitrogen attacks the electrophilic carbonyl carbon of CbzCl, generating a tetrahedral intermediate **243** that collapses to eliminate chloride and form the Cbz-protected amine **241**. This two-step sequence afforded the protected product in a relatively low yield of 9% (Scheme 94).

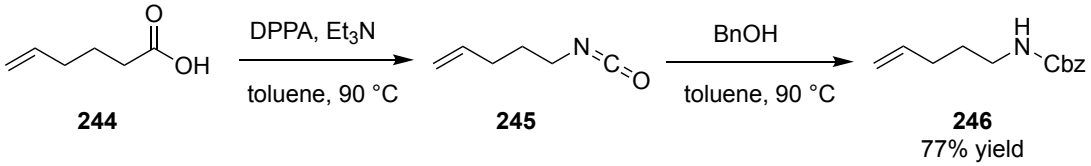


Mechanism of the reaction:



*Scheme 94: Two-step synthesis of Cbz-protected amine **241** from mesylate **240***

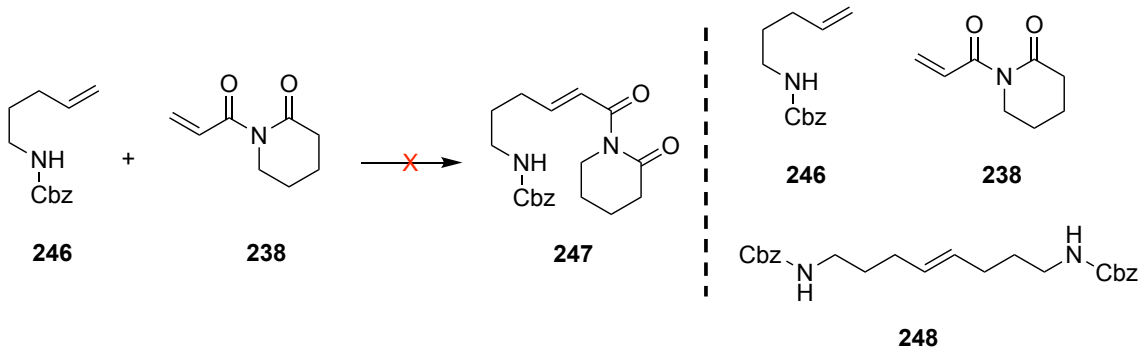
Given the low yield obtained, an alternative route was investigated involving the Curtius rearrangement, which was expected to provide a more efficient synthesis of the Cbz-protected amine **246**. The first reaction conditions tested were based on a previously established protocol used for the synthesis of the amine rac-**88**, employing DPPA in the presence of Et_3N, followed by trapping of the isocyanate **245** with benzyl alcohol (Scheme 95). Under these conditions, the desired Cbz-protected amine **246** was obtained in significantly improved 77% yield, confirming the efficiency of this strategy compared to the previous two-step mesylation-amination process.



*Scheme 95: Curtius rearrangement reaction for synthesis of Cbz-amine **246***

4.2.2 Cross-Metathesis Reaction

With the precursors in hand, efforts were directed toward the development of a cross-metathesis reaction between the Cbz-protected amine **246** and imide **238**. The initial reaction was performed under conditions previously reported for similar substrates (Chapter 2, Scheme 41), using the Hoveyda-Grubbs 2nd generation (HG-II) catalyst (**36**,10 mol%) in 1,2-dichloromethane (1,2-DCE) at 50 °C in the presence of CuI as an additive. However, none of the desired product **247** could be isolated under these conditions, and analysis by TLC and ^{1}H NMR primarily revealed only the presence of both unreacted starting materials, with some evidence of additional product formation, likely the homodimerised product **248**. To further probe the reaction scope, a series of conditions were attempted in 1,2-DCE at 50 °C (and 80 °C in one case), varying the equivalents of amine **246** and lactam **238**, catalyst loading (5−10 mol%), reaction time (24−48 hours), and the presence or absence of CuI. The results are summarised in Table 7, which shows that despite extensive variation of conditions, no significant conversion to the desired product **247** was achieved. In most cases (Entries 1,2, and 5−10), only the unreacted starting materials (amine and lactam) were recovered cleanly, with no evidence of product **247** formation by TLC and ^{1}H NMR. Additional signals likely indicative of the formation of homodimer **248** were also observed in the crude ^{1}H NMR spectra, although this product could was not isolated cleanly. These findings either suggest that the lactam substrate **238** is inherently unreactive under the metathesis conditions, or that certain reaction parameters led to catalyst deactivation or undesired side reactions. The presence or absence of CuI had no noticeable effect on the reaction outcome, and increasing the temperature (Entry 11) similarly failed to promote product formation.

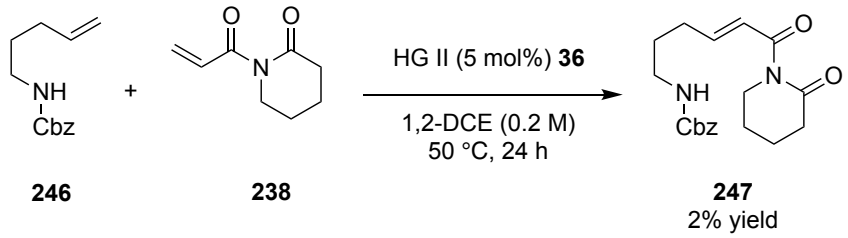


*Scheme 96: Unsuccessful cross metathesis reaction between Cbz-protected amine **246** and imide **238***

Entry	Equivalent of amine	Equivalent of lactam	catalyst	t / hrs	T / °C	Additive	result
1	1	3	10 mol% Hoveyda Grubbs II	24	50 °C	CuI	unreacted starting materials
2	1	3	10 mol% Hoveyda Grubbs II	48	50 °C	-	unreacted starting materials
3	3	1	10 mol% Hoveyda Grubbs II	24	50 °C	-	unreacted starting materials and homodimer of the amine
4	3	1	10 mol% Hoveyda Grubbs II	48	50 °C	-	unreacted starting materials and homodimer of the amine
5	1	1	5 mol% Grubbs II	24	50 °C	-	unreacted starting materials
6	1	2	5 mol% Grubbs II	24	50 °C	-	unreacted starting materials
7	1	3	5 mol% Grubbs II	24	50 °C	-	unreacted starting materials
8	1	3	10 mol% Grubbs II	24	50 °C	-	unreacted starting materials
9	1	3	10 mol% Grubbs II	24	50 °C	CuI	unreacted starting materials
10	1	3	10 mol% Grubbs II	24	80 °C	-	unreacted starting materials

Table 7: Conditions screen for Cbz-protected β-amino imide

One of the conditions tested did lead to the formation of the expected product, albeit in low yield. Under conditions summarised below in Scheme 97, employing HG-II catalyst (**36**, 5 mol%) at 50 °C in 1,2-DCE for 24 hours, with 1 equivalent of amine **246** and 2 equivalent of lactam **238**, the desired product **247** was obtained in only 2% yield. However, a large part of lactam and amine, alongside suspected homodimer **248**, also remained unreacted following the reaction. This reaction was monitored by TLC and ^{1}H NMR, both of which confirmed low conversion of the starting materials.



*Scheme 97: Curtius rearrangement reaction for synthesis of Cbz-amine **247***

Despite the low yield, the successful synthesis of **247** was confirmed by its NMR data. Inspection of the ^{13}C NMR spectrum confirmed the presence of the expected number of carbon resonances. The observed signal count and chemical shifts were consistent with the proposed structure, with no indication of rotamer splitting. The ^{1}H NMR spectrum was analysed, and proton signals were assigned based on their expected chemical shift ranges. The aromatic protons from the Cbz group appeared as a multiplet between δ 7.35 – 7.29 ppm. The newly formed H-8 and H-7 protons, resulting from the conjugation, appeared as multiplet at δ 6.91-6.84 ppm and a doublet at δ 6.73 ppm, respectively. The coupling constant for H-7 (J = 15.4 Hz) confirmed the *E*-geometry of the newly formed alkene. Their corresponding carbon resonances, observed at δ 146.0 ppm and δ 126.0 ppm, were confirmed through the HMQC spectrum. A broad singlet at δ 4.91 ppm was attributed to the N-H proton. The remaining proton assignment were determined using 2D NMR spectra.

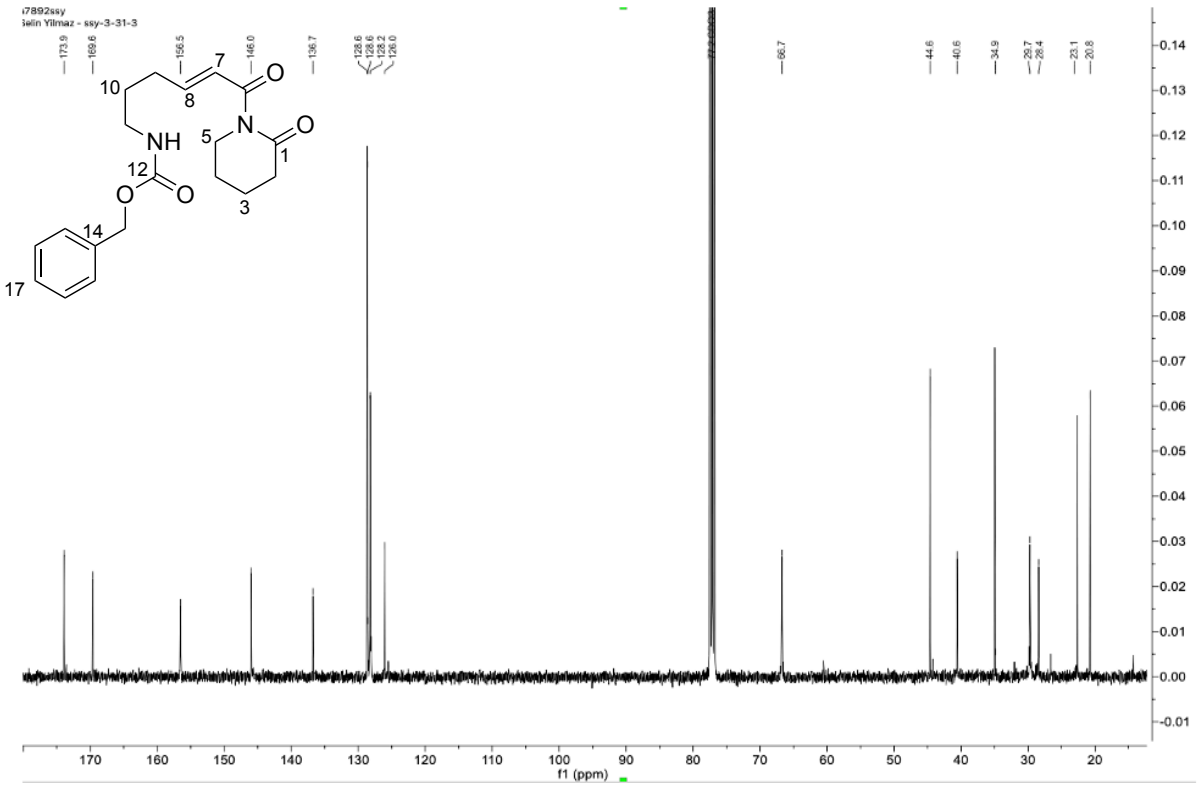


*Figure 8: 13C NMR of **247***

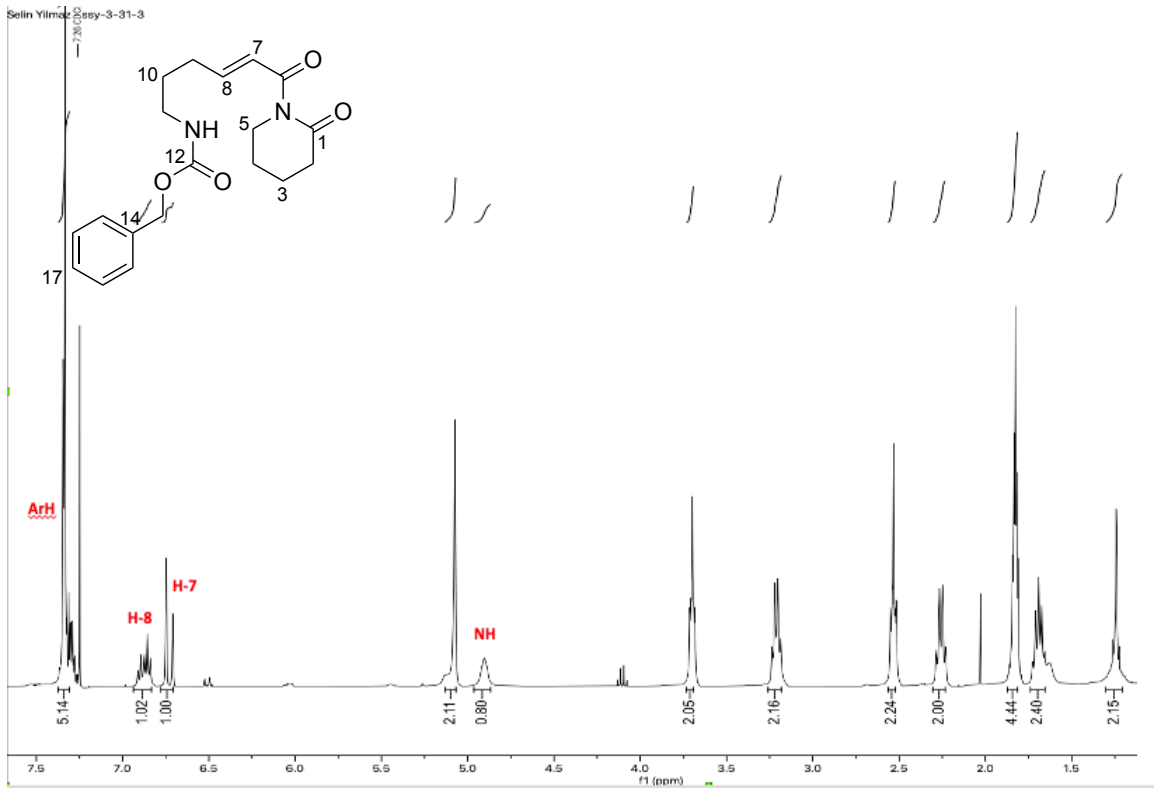


*Figure 9: 1H NMR of **247***

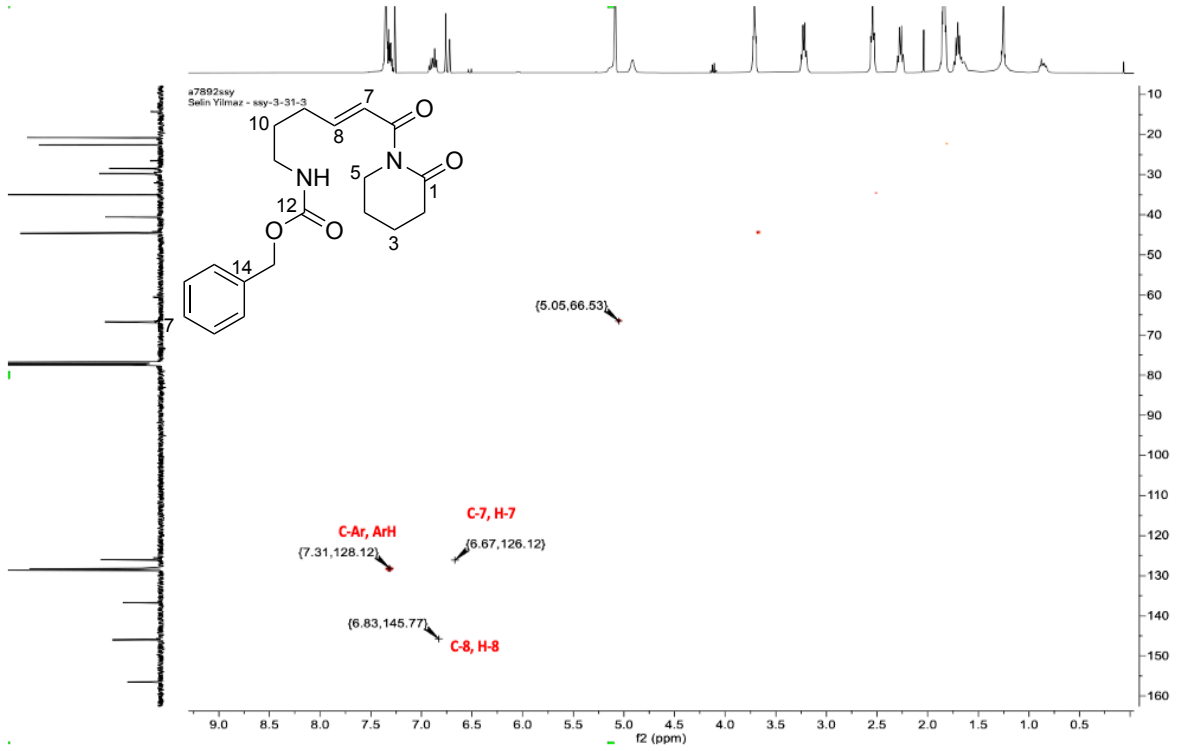
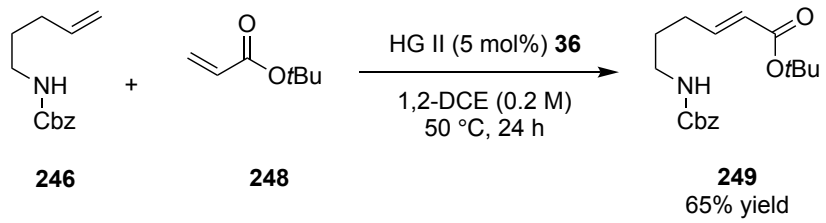


*Figure 10: HMQC spectrum showing C-7 and C-8 with respective protons in **247***

To assess whether amine **246** is reactive under similar cross metathesis conditions, a control reaction with *tert*-butyl acrylate **248** was performed under the same conditions described in Chapter 2 for the cross-metathesis of α,β-unsaturated thioester **89** with Cbz-protected amines rac-**87** and rac-**88**. The reaction proceeded efficiently, affording the cross-metathesis product in 65% isolated yield (Scheme 98). This result clearly demonstrates that amine **246** is reactive under the metathesis conditions, and that the problems with the lie in the low reactivity of acryloyl imide **238**.



*Scheme 98: Cross metathesis reaction with tert-butyl acrylate **248** and amine **249***

Thus, these experiments indicates that the cross-metathesis between **246** and **238** proceeds with extremely low efficiency under ruthenium-catalysed conditions. With the exception of a single reaction yielding the desired product **247** in just 2% yield, the reactions predominantly resulted in the recovery of unreacted starting materials and homodimerization of the more reactive alkene **246**, to form **247**. Given these limitations, it was decided to discontinue efforts to attempt the cross-metathesis reaction between the protected amine **246** and the imide **238**.

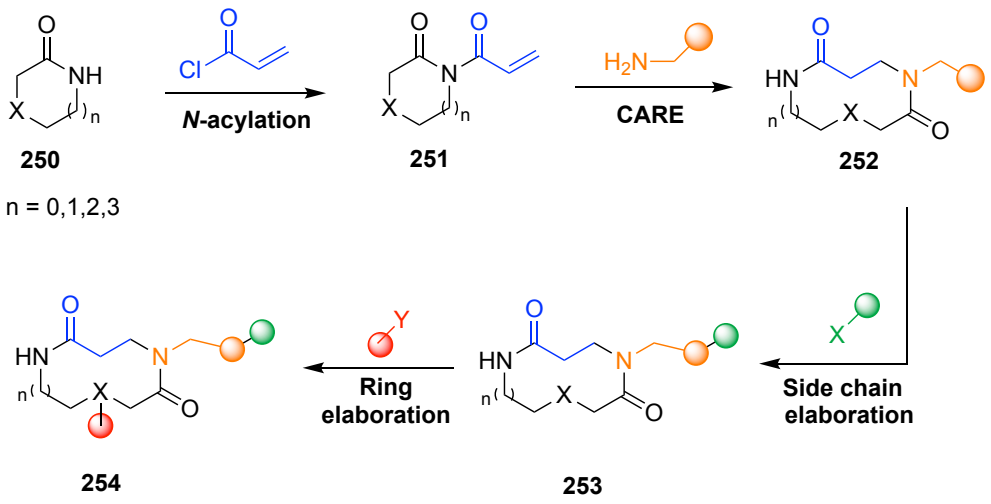
4.3 Summary of Chapter

This short chapter presents attempts to develop a ring-expansion strategy aim at synthesising medium-sized lactam rings through a cross-metathesis/intramolecular rearrangement sequence. The methodology integrated synthetic approaches developed independently within the Clarke and Unsworth groups, involving the preparation of a Cbz-protected amine and a functionalised imide as key intermediates. Precursor synthesis was successfully achieved, particularly through the use of the Curtius rearrangement for the amine. However, the subsequent cross-metathesis step proved highly challenging. Despite extensive optimisation of reaction parameters, the desired product was obtained in only 2% yield. Further work could explore alternative catalyst systems for cross metathesis or modified protecting group or substrate designs that reduce steric congestion. Alternatively, alkene forming methods that do rely on metathesis could also be explored, although as unifying the Clarke and Unsworth group methods was a significant driver in this project, this was not attempted. While ultimately unsuccessful, the reaction design featured in this chapter still has the potential to deliver interesting new approach for the construction of medium-sized lactams, if the limitations with the cross-metathesis step can be overcome.

5- Cascade Ring Expansion Reactions

5.1 Conjugate Addition – Ring Expansion

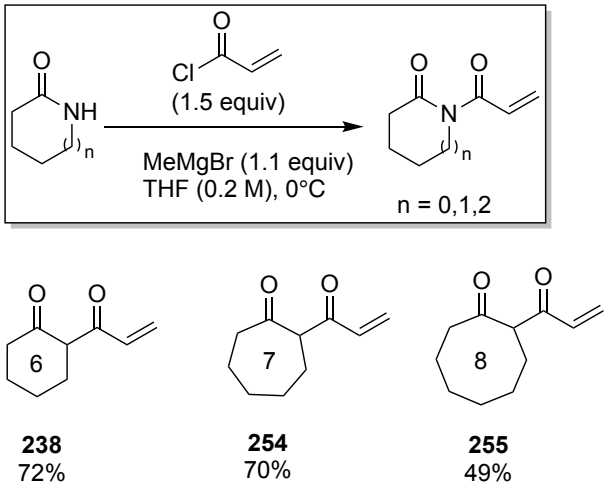
Previous work within the Unsworth group, as discussed in Chapter 4, demonstrated the efficiency of the conjugate addition/ring expansion (CARE) strategy for the synthesis of medium-sized lactams.[76] In the group's published study, the methodology was successfully applied to 6-membered lactams using a range of primary amines, resulting in the formation of 10-membered ring-expanded products (Scheme 88). These findings highlighted the potential of the CARE approach for generating larger and more complex nitrogen-containing ring systems in a modular and efficient manner. Building upon these initial results, the work described in this chapter aimed to developed new variants of the CARE strategy for the synthesis of more diverse libraries of novel medium-sized rings and macrocycles for biological evaluation. The investigation includes further studies on 6-membered lactams and was extensions to other lactam ring sizes, including 7-, 8- and 9- membered systems. Additionally, a broader selection of primary amines was examined to assess the generality of the approach and identify potential limitations (Scheme 99). Finally, strategies to elaborate the ring expanded products via the inclusion of reactive functional handles are also described.



Scheme 99: Synthesis of the macrocyclic and medium-sized ring lactams

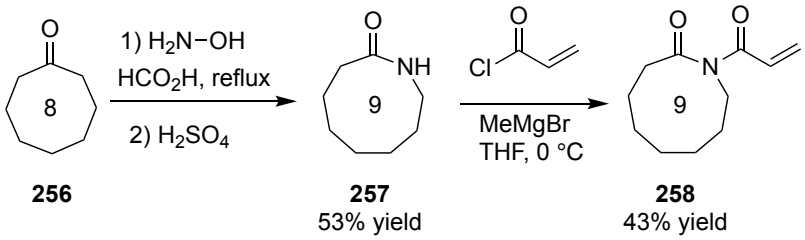
5.1.1 Synthesis of Acryloyl Imides

The synthesis of the various acryloyl imides needed for this study was achieved via a straightforward *N*-acylation of lactam derivatives with acryloyl chloride, a well-practiced procedure within the Unsworth group. This method has proven to be a reliable approach for introducing an α,β-unsaturated moiety onto nitrogen-containing heterocycles. In a typical procedure, the corresponding lactam was treated with acryloyl chloride in the presence of methylmagnesium bromide (MeMgBr) as a base, in anhydrous THF at 0 °C (Scheme 100). The products were obtained in good yields (49–72%) after purification by column chromatography.



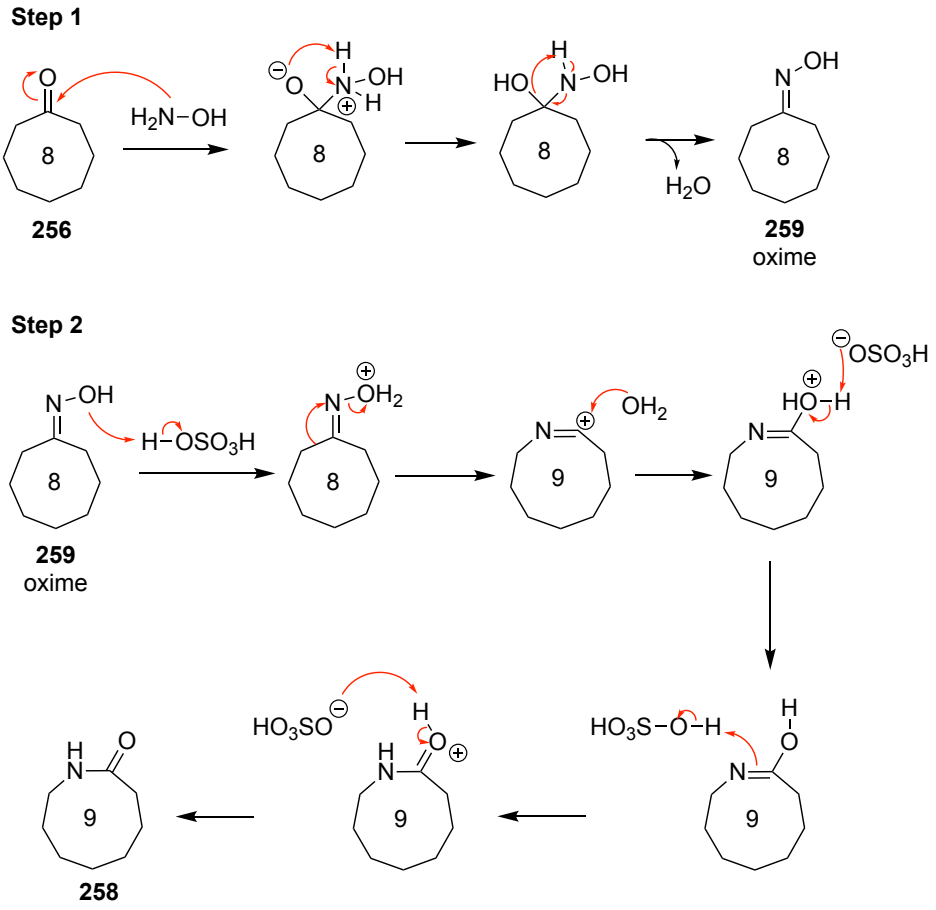
Scheme 100: Acylation reaction of the lactam

While 6-, 7-, and 8-membered lactams starting materials used above were easily available commercially, the homologous the 9-membered lactam **258** could not be purchased, and hence its synthesis was needed. Thus, the synthesis of the 9-membered imide **258** was done using a Beckmann rearrangement strategy, initiated from cyclooctenone, which was first converted to azonan-2-one **257** ring via a two-step conversion involving formic acid and hydroxylamine-*O*-sulphonic acid. *N*-Acylation with acryloyl chloride using the method described above then enabled the formation of the desired 9-membered imide **258** (Scheme 101).



*Scheme 101: Synthesis of 9-membered lactam **258** starting from cyclooctenone **256***

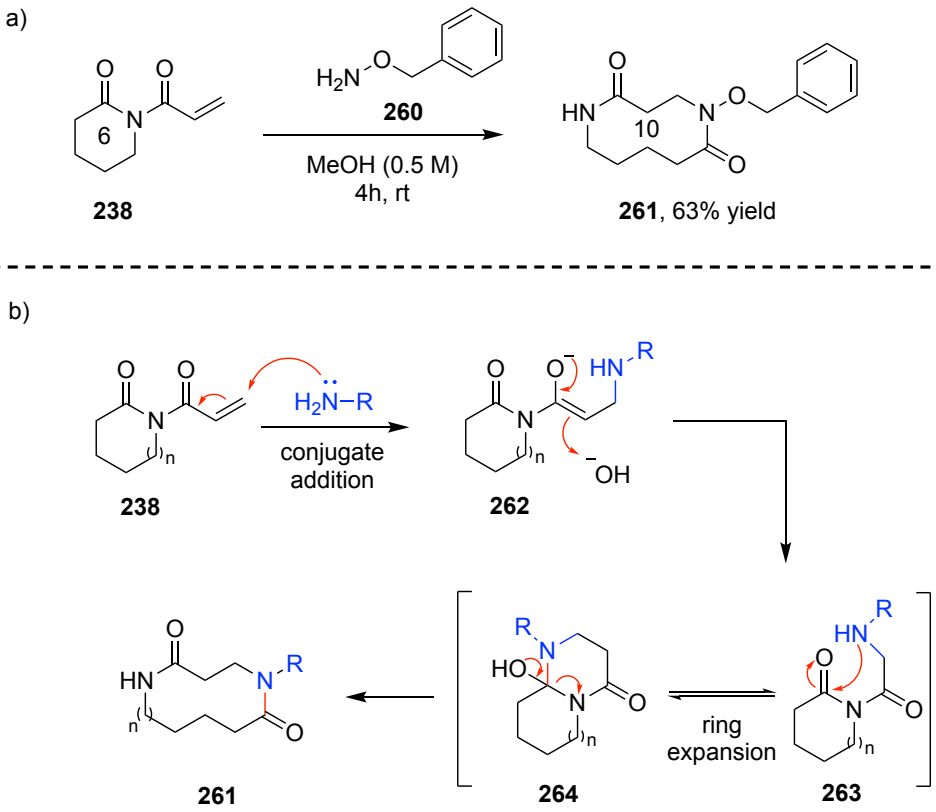
A proposed mechanism of the synthesis of **258** from cyclooctenone **256** is provided in Scheme 102. The ketone is first converted to the oxime **259** via a condensation reaction with hydroxylamine in formic acid. This intermediate **259** then undergoes an acid-promoted Beckmann rearrangement as shown, resulting in one-atom ring expansion and formation of azonan-2-one **258**.



*Scheme 102: Proposed mechanism for the formation of **258** via oxime formation and Beckmann rearrangement*

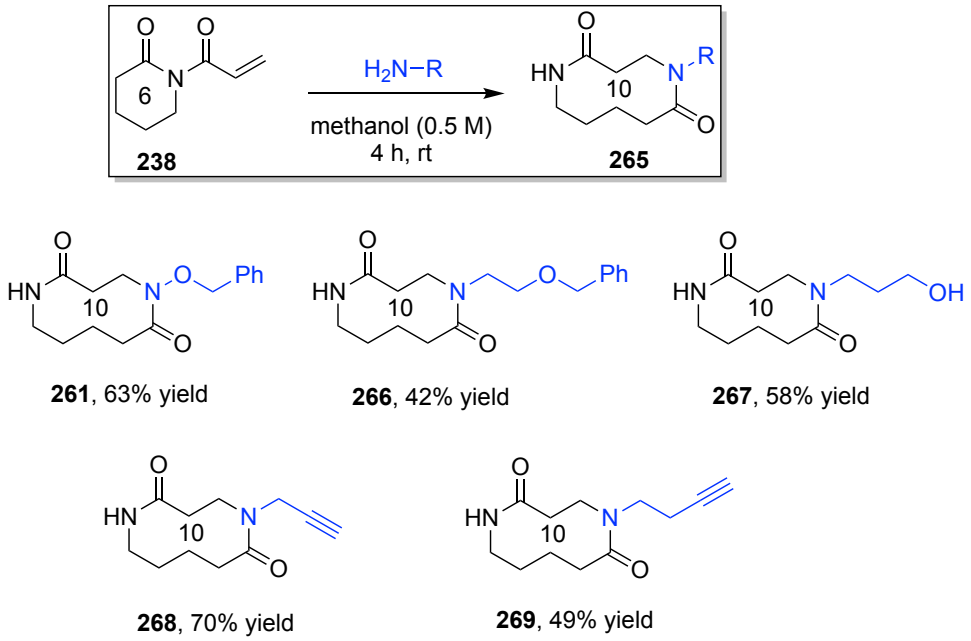
5.1.2 Nitrogen CARE

Having successfully isolated a series of acryloyl imides, the next step focused on exploring their CARE reactions. The initial objective was to perform a conjugate addition/ring expansion of the 6-membered acryloyl imide **238** with a selection of primary amines to afford a 10-membered ring product. When selecting a model amine to test, benzyl-o-hydroxylamine **260** was envisioned as a good choice, as this was predicted to be a reactive nucleophile, but had not been explored in the group's earlier work on CARE reactions. The reaction was carried out in methanol (0.5 M) at room temperature, under conditions previously shown to be effective in similar systems.[76] Following purification by column chromatography, the product **261** was obtained in 63% yield (Scheme 103a). The proposed mechanism for this reaction is indicated in Scheme 103b. In the first step, the primary amine **260** performs a conjugate addition to the β-position of the α,β-unsaturated imide **238**, generating an intermediate **262**. This is followed by intramolecular ring-opening and rearrangement of the imide moiety, resulting in a ring expansion.



*Scheme 103: a) Nitrogen CARE reaction of 6-membered lactam **238** and benzyl-o-hydroxylamine **260***

To expand the scope of the nitrogen CARE reaction, a series of other primary amines was reacted with the 6-membered lactam **238** under the standard conditions. It was demonstrated that 6-membered lactam **238** can undergo ring expansion to form 10-membered lactams, with yields ranging from 42−70% (Scheme 104). As shown in Scheme 101, the reaction was tolerant of diverse nucleophilic partners. Benzyl-*O*-hydroxylamine and its ether analogs efficiently delivered the corresponding products in good yields, highlighting the compatibility of oxygen-containing side chains. In addition, amines functionalised with nitrile and alkene groups also successfully underwent the ring expansion, demonstrating the functional tolerance of the method. Notably, 3-aminopropanol gave the desired ring-expanded product **267** smoothly, showing that the presence of a free hydroxyl group did not negatively affect the reaction outcome.

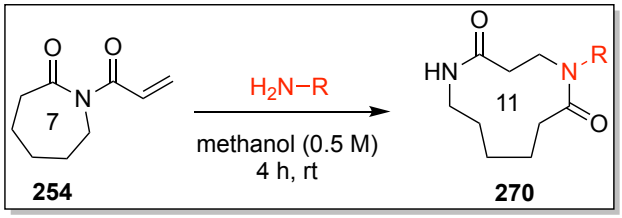


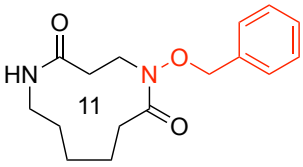
Scheme 104: Nitrogen CARE reaction with various primary amines

5.1.2.1 Scope of Ring Size in Nitrogen CARE

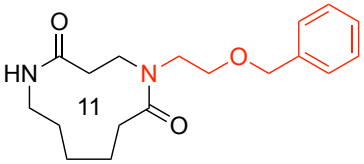
To evaluate the influence of lactam ring size on the efficiency and outcome of the nitrogen CARE reaction, it was decided to investigate the reaction on lactams from 7–9 membered rings, that had been far less well explored in the Unsworth group previously. This strategy was chosen as it offers a convenient method to access medium-sized and macrocyclic lactam ring systems (11–13 membered). Initially, 7- and 8- membered lactams were subjected to the

CARE reaction using a series of primary amines under the same reaction conditions previously optimized for the 6-membered systems. Subsequently, attention turned to expanding the methodology to 9-membered lactams. As shown in Scheme 105, a wide a range of primary amines were successfully employed in the nitrogen CARE reaction, with the exception of aniline, which failed to afford the desired product **312**. In this case, the lower nucleophilicity of the aniline amine likely explains this outcome, as a result of amine resonance delocalization into the benzene ring.

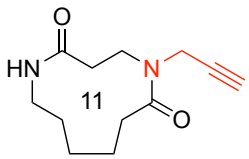




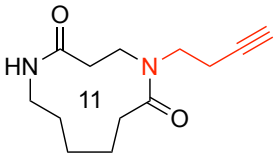
271, 65% yield



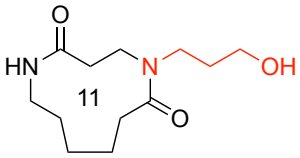
272, 55% yield



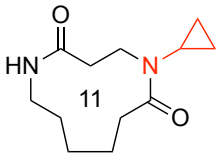
273, 71% yield



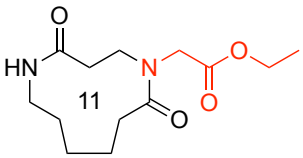
274, 78% yield



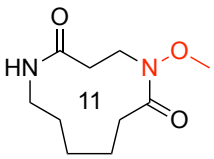
275, 56% yield



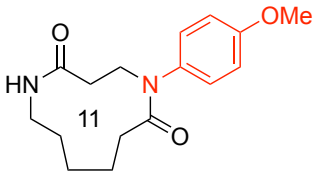
276, 37% yield



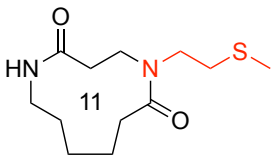
277, 76% yield



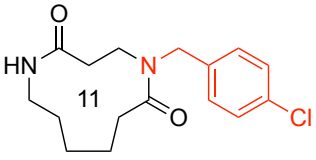
278, 52% yield



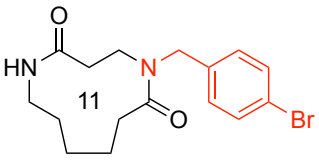
279, 0% yield



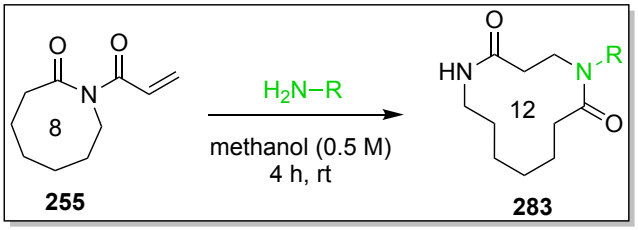
280, 52% yield

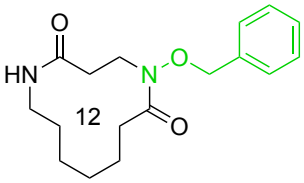


281, 48% yield

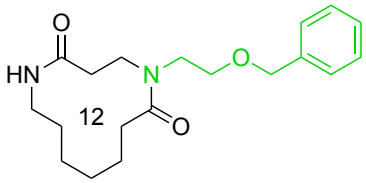


282, 64% yield

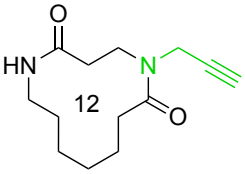




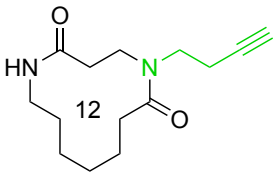
284, 61% yield



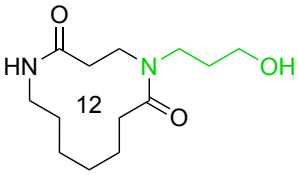
285, 59% yield



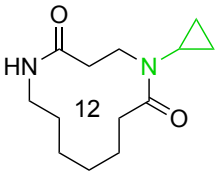
286, 71% yield



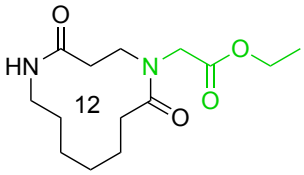
287, 64% yield



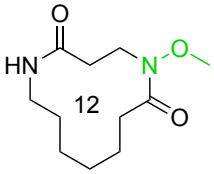
288, 65% yield



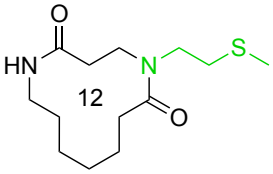
289, 42% yield



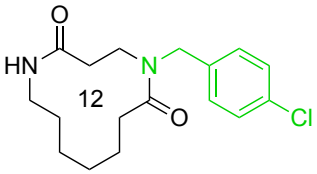
290, 44% yield



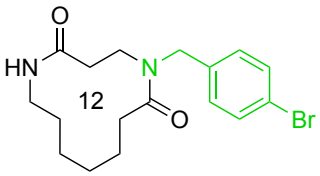
291, 46% yield



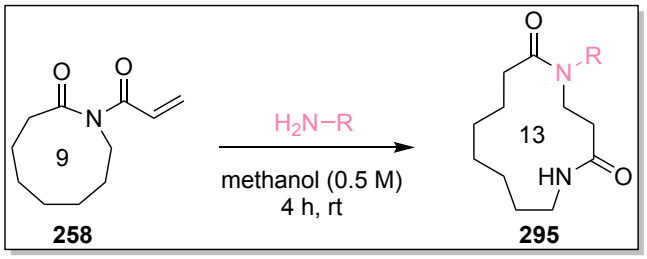
292, 65% yield

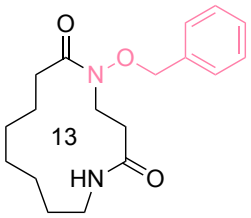


293, 29% yield

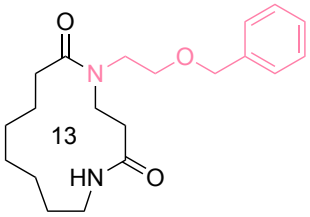


294, 22% yield

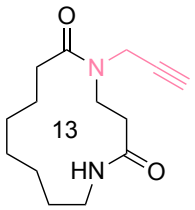




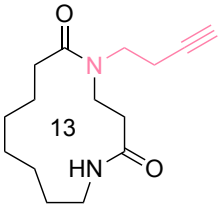
296, 54% yield



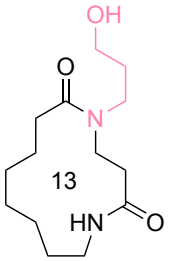
297, 54% yield



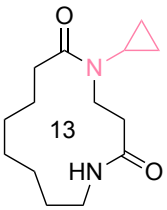
298, 63% yield



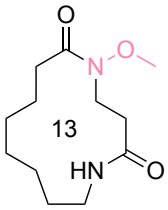
299, 55% yield



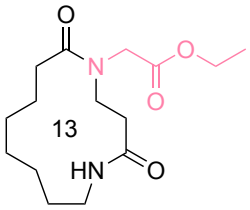
300, 55% yield



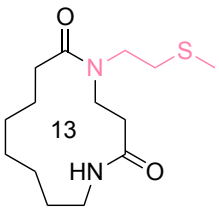
301, 45% yield



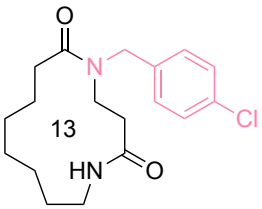
302, 41% yield



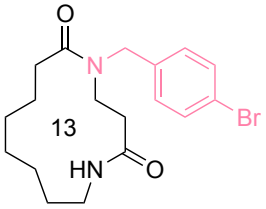
303, 46% yield



304, 54% yield



305, 76% yield



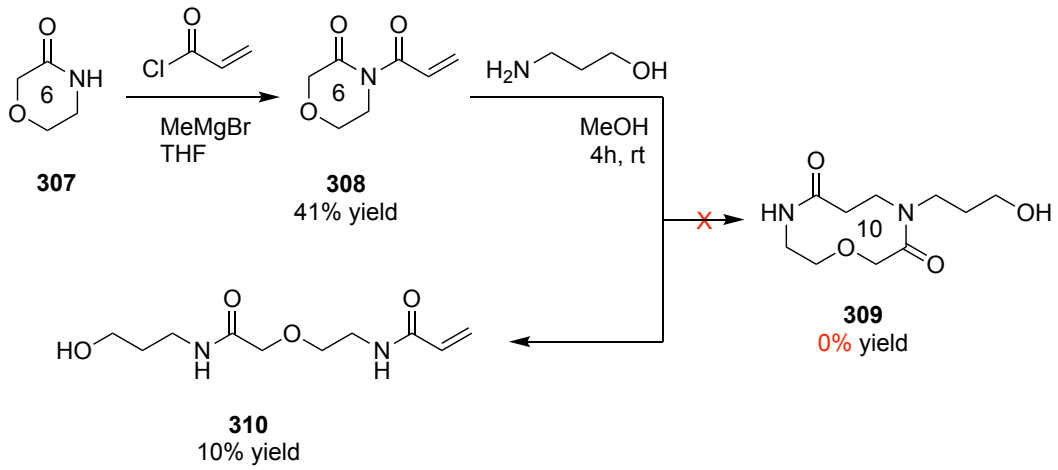
306, 53% yield

Scheme 105: Scope of the Nitrogen CARE reaction with various primary amines

Overall, the CARE method has been shown to work well for the synthesis of a diverse library of 10- to 13- membered lactams. The methodology allows the use of a broad range of functionalized primary amines and has been successfully applied to lactam ring sizes from 6- to- 9- members. In total, 39 novel medium-sized and macrocyclic lactams were generated in this way, and all were fully characterised. These results collectively highlight the broad scope and utility of the CARE strategy in medium-sized and macrocyclic nitrogen-containing ring system.

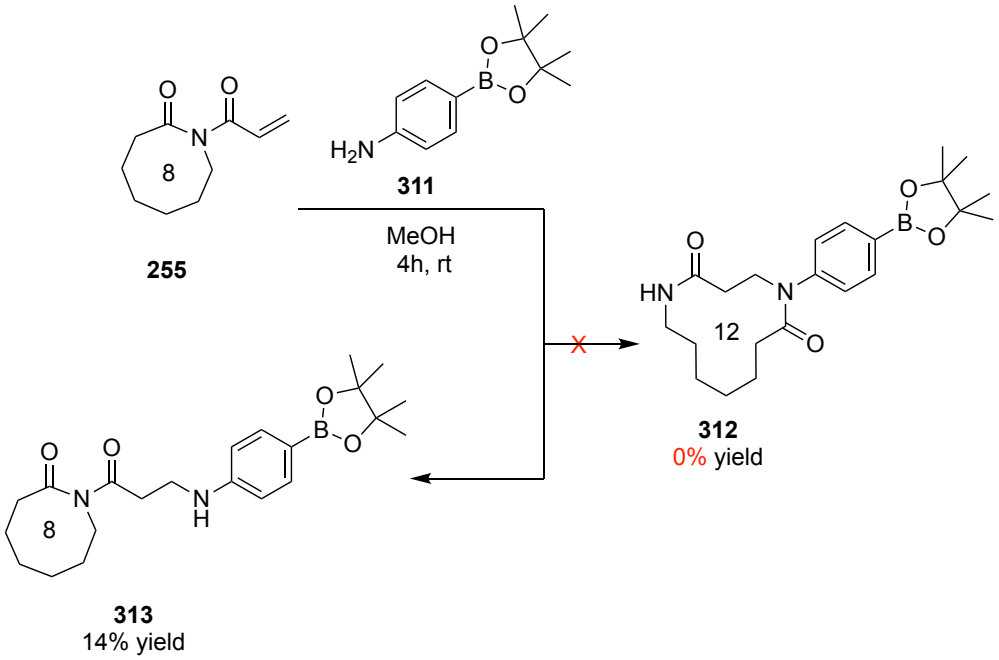
5.1.2.2 Lactam Scope in Nitrogen CARE

In order to further expand the scope of ring expansion, efforts turned to investigating the CARE reaction with more functionalised lactam starting materials. When a morpholine-derived amide **307** was subjected to the standard reaction conditions, no evidence of the desired ring-expanded product **309** was detected (Scheme 106). In this case, nucleophilic attack by methanol or amine at the β-lactam carbonyl appears to have resulted in the formation of the ring-opened side product **310**. The presence of the ether oxygen atom likely increases the electrophilicity of the internal carbonyl group, which may account for the observed change in chemoselectivity for this imide.



*Scheme 106: Attempted CARE reaction of a Morpholine-derived imide **307** resulting in ring-opened product **310***

In another example, the CARE reaction was attempted using the 8-membered imide **255** and Bpin-substituted aniline **311** as the nucleophile. Under the standard conditions, no evidence of the desired ring-expanded product **312** was observed. Instead, the reaction yielded the conjugate addition product **313**, as confirmed by NMR spectroscopy (Scheme 107). This outcome is likely due to the reduced nucleophilicity of the aniline nitrogen, arising from delocalisation of its lone pair into the aromatic ring, in contrast to the aliphatic amines typically used in CARE reactions.



*Scheme 107: Attempted CARE reaction using Bpin-substituted aniline **311***

The formation of the conjugate addition product **313** was confirmed by detailed analysis of the NMR spectra. The ^{1}H NMR spectrum exhibits characteristic resonances for a linear side chain bearing a secondary amine, supporting nucleophilic addition to the α,β-unsaturated system without subsequent ring expansion. Notably, H-9 and H-10 protons adjacent to the nitrogen atom appear as a triplets at δ 3.52 ppm and δ 3.16 ppm, respectively. In the HMQC spectrum, these protons direct correlations to carbon signals at δ 39.3 and δ 38.9 ppm, confirming the presence of a conjugated side chain (−CH_2−CH_2−NH−). The NH proton appears as a broad singlet at δ 4.38 ppm and does not exhibit COSY correlations with vinylic protons, consistent with the absence of a double bond. Further support comes from the HMBC spectrum, where long-range correlations are observed between C-1 at δ 178.6 ppm and adjacent aliphatic C-2 and C-7, but not with the NH proton. Additionally, the aliphatic region displays a series of overlapping multiplets between δ 2.64 ppm and δ 1.40 ppm, attributable to the CH_2 protons of the eight-membered lactam ring.

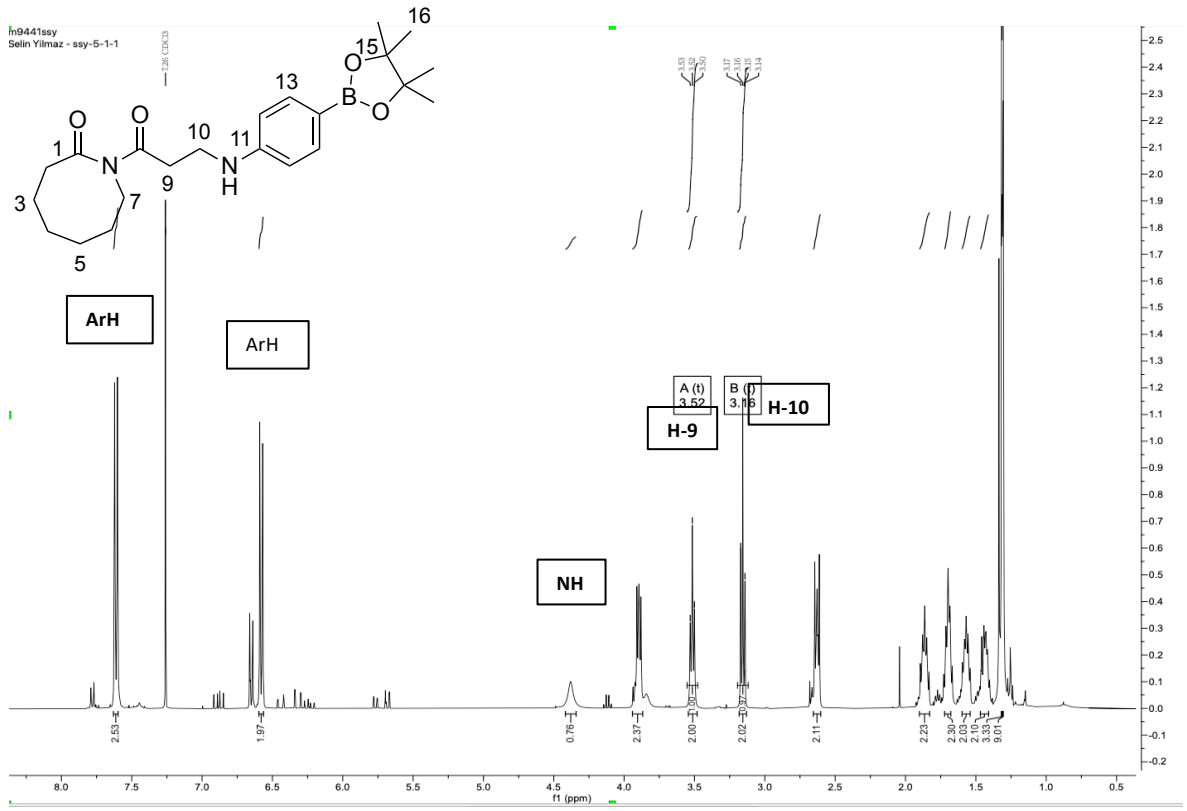


*Figure 11: 1H NMR of **313***

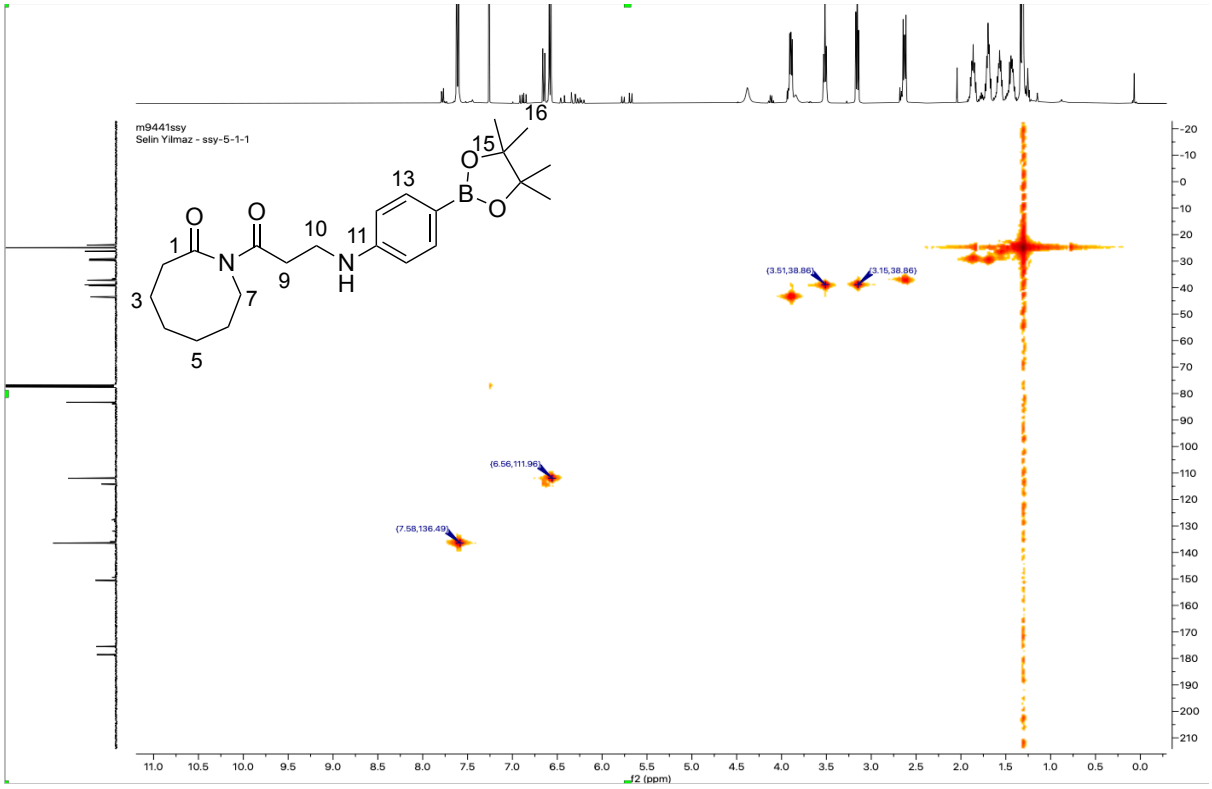


*Figure 12: HMQC of **313***

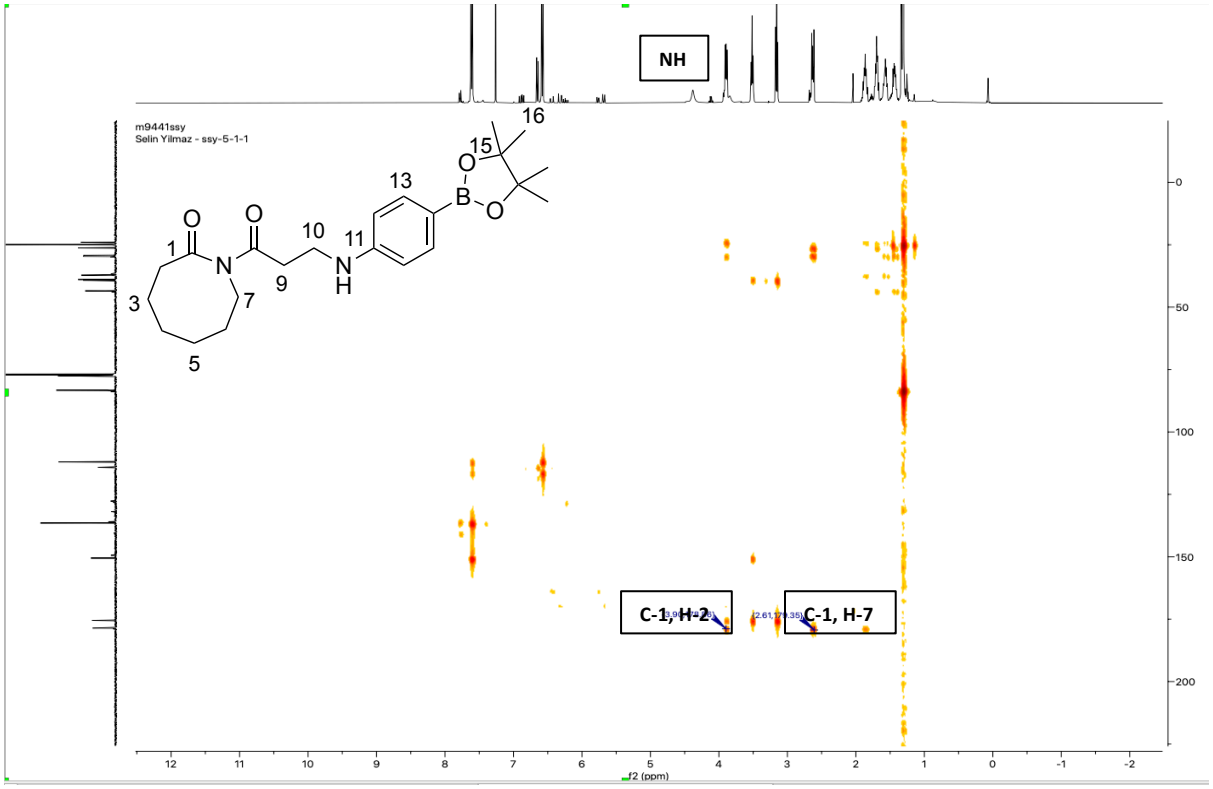


*Figure 13: HMBC of **313***

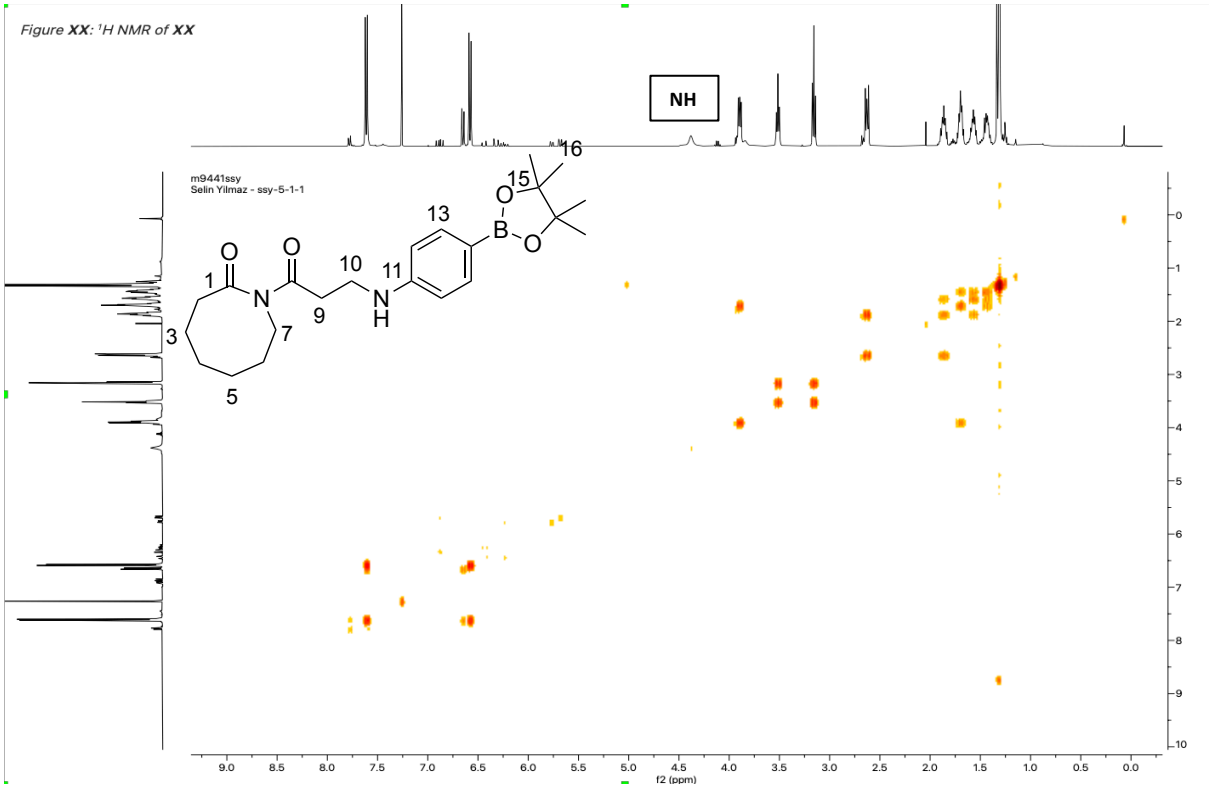
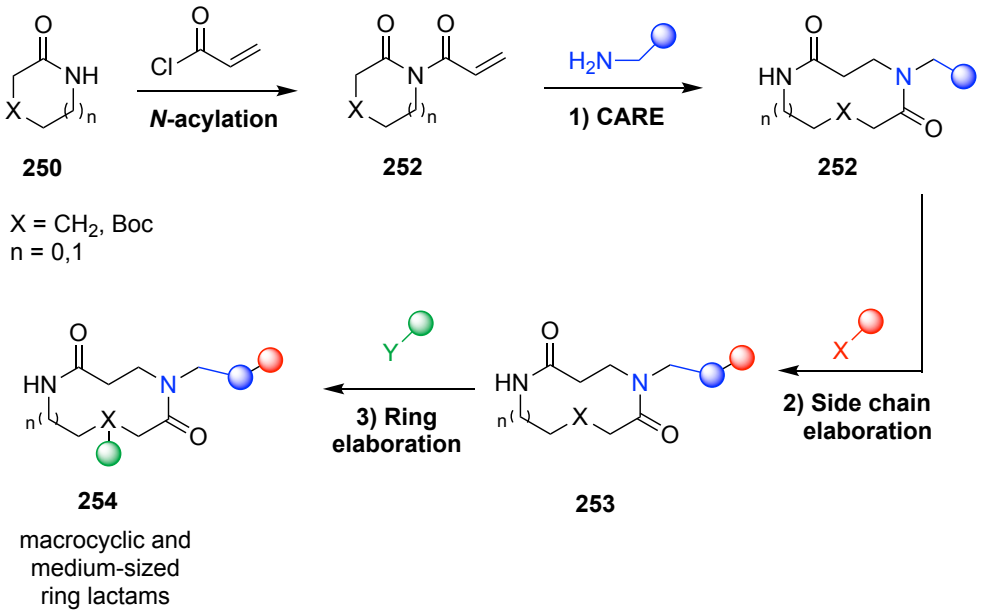


*Figure 14: COSY of **313***

5.2 Expanding the Cascade Ring Expansion Methodology

Having demonstrated the versatility of the CARE strategy across a diverse array of lactams, we next attempted to extend the approach to more complex and medicinally relevant macrocyclic and medium-sized ring lactams through a modular three-step sequence. In this approach, the ring expanded lactams are first prepared via CARE, and them elaborated by further reactions, using synthetic handles built into the starting materials (Scheme 108). For example, starting from a functionalised lactam **250**, formation of imide **252** is followed by the CARE (step 1) to generate the ring expanded scaffold **252**. If this done using starting materials containing reactive groups in the ring and on the amines, these handles can then enable further diversification via side-chain elaboration (step 2) and ring functionalization (step 3); for example, by employing cross-coupling, amination, or alcohol derivatisation reactions.

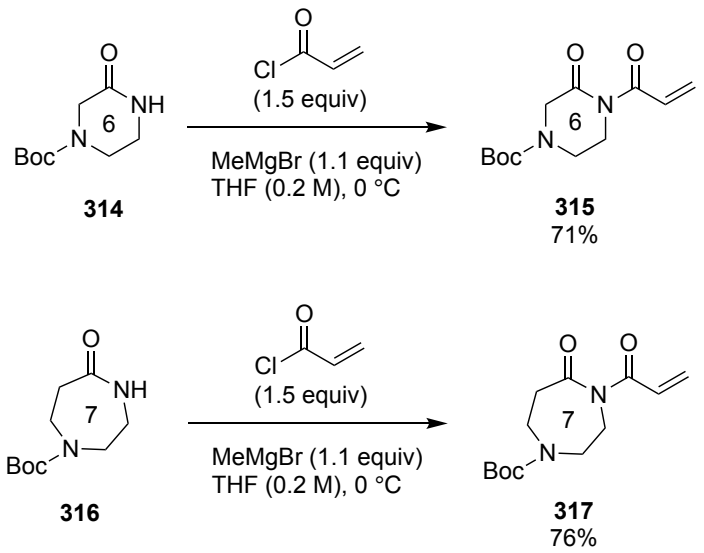


Scheme 108: Synthesis of macrocyclic and medium-sized lactams using cascade ring expansion reaction

5.2.1 Synthesis of Building Blocks via CARE

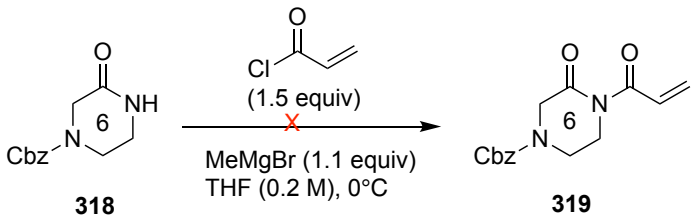
5.2.1.1 Synthesis of N-Boc Protected Imides

Acylation of 6- and 7-membered lactams containing an additional *N*-Boc group (**314** and **316**) was done using the standard conditions and afforded the corresponding imides (**315** and **317**, respectively) in good yields (Scheme 109).



*Scheme 109: Synthesis of N-Boc protected imides **315** and **317***

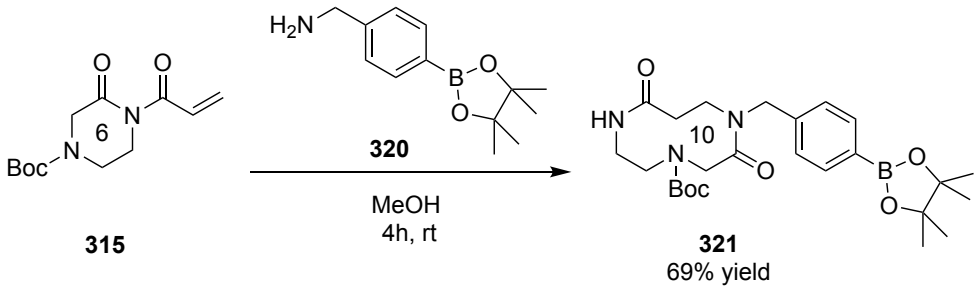
An attempt at the *N*-acylation reaction to form an acryloyl imide was also carried starting from the analogues Cbz protected substrate **318** (Scheme 110). In this case, the crude reaction mixture was analysed by mass spectrometry, and this analysis confirmed the presence of a peak consistent with the expected molecular ion of the Cbz-protected imide **319**. However, the product could not be purified, as it was found to be very poorly soluble in common organic solvents. Therefore, standard purification techniques such as column chromatography or recrystallization could not be applied successfully. One possible explanation for the poor solubility may lie in the structural properties of the Cbz group. Unlike the Boc group, which is aliphatic and relatively flexible, the Cbz group contains a rigid aromatic moiety that may promote π–π stacking interactions and reduce solubility by increasing molecular aggregation. While full characterization was not possible, the mass spectrometric evidence strongly suggests successful product formation, and failure to make this product can plausibly be attributed to poor solubility of product complicating its purification. Subsequent studies therefore focused on using the Boc-protected imides **315** and **317** instead.



*Scheme 110: Attempted synthesis of N-Cbz protected imide **319***

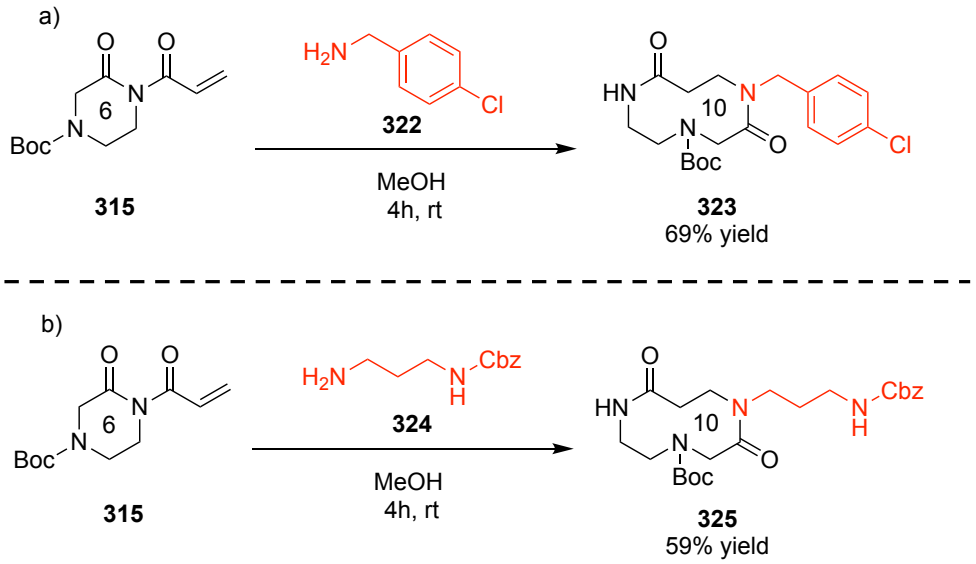
5.2.1.2 CARE Reaction with 6-Membered Imide 315

Given the limited success observed with more constrained or less nucleophilic amine partners (Section 5.1.2.2), we next examined the reactivity of a 6-membered *N*-Boc protected imide **315** toward a more reactive amine nucleophile. To do this, Bpin-substituted aniline **311** was replaced with Bpin-phenyl methanamine **320**, which was expected to exhibit improved nucleophilicity due to the insertion of a methylene between the aromatic ring and the amine group. This modification removes the delocalisation of the nitrogen lone pair into the aromatic system, thereby increasing the nucleophilic character of the amine and facilitating the conjugate addition step. Pleasingly, as expected, upon applying this modified amine to the CARE reaction with the N-Boc protected imide **315**, the ring expansion proceeded efficiently to furnish the 10-membered lactam in 69% yield (Scheme 111).



*Scheme 111: CARE reaction using Bpin-phenyl methanamine **320***

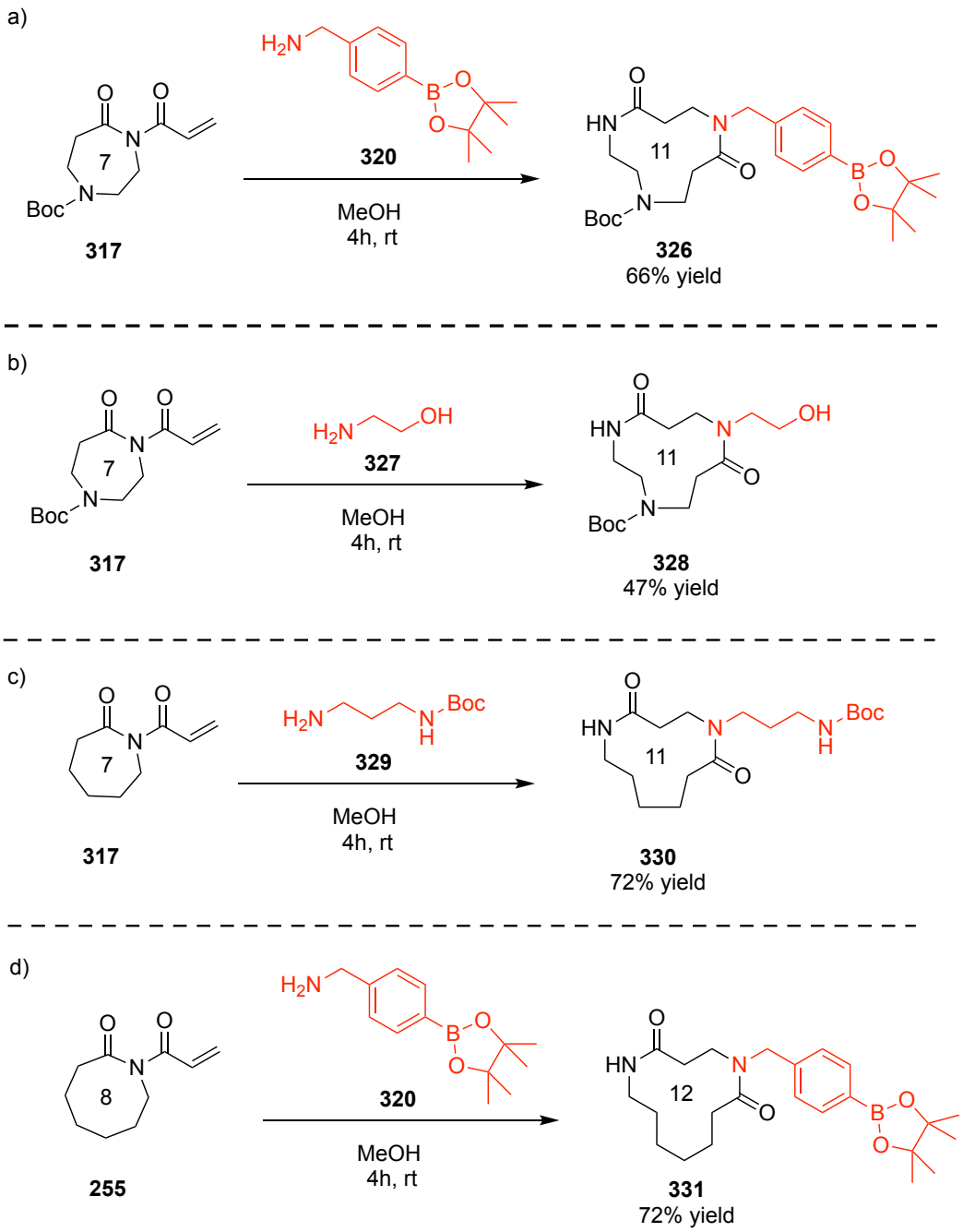
Similarly, Scheme 112 depicts other succesful synthesis of 10-membered lactams, using imides and amine substrates containing reactive handles. Pleasingly, all examples led to formation of the corresponding 10-membered ring-expanded products **323** and **325** in good yields.



*Scheme 112: Synthesis of 10-membered ring expanded products **323** and **325** using various amines*

5.2.1.3 Extension to Larger Ring Imides

Building on these promising results, a similar methodology was applied to larger ring systems. The previously synthesised 7- and 8- membered acryloyl imides **317** and **255** were each subjected to the CARE reaction using functionalised amines containing synthetically valuable groups, including a boronic ester, aryl halide, protected amine and free alcohol functionalities. This approach provided access to a range of 11- and 12- membered lactams, each incorporating a versatile synthetic handle suitable for further elaboration (Scheme 113). All ring expanded products were formed clearly, with no detection of side products or isomeric impurities. Notably, the lower yield observed for the free alcohol derivative is assumed to result from the high polarity of the alcohol moiety, which makes the product more difficult to purify.



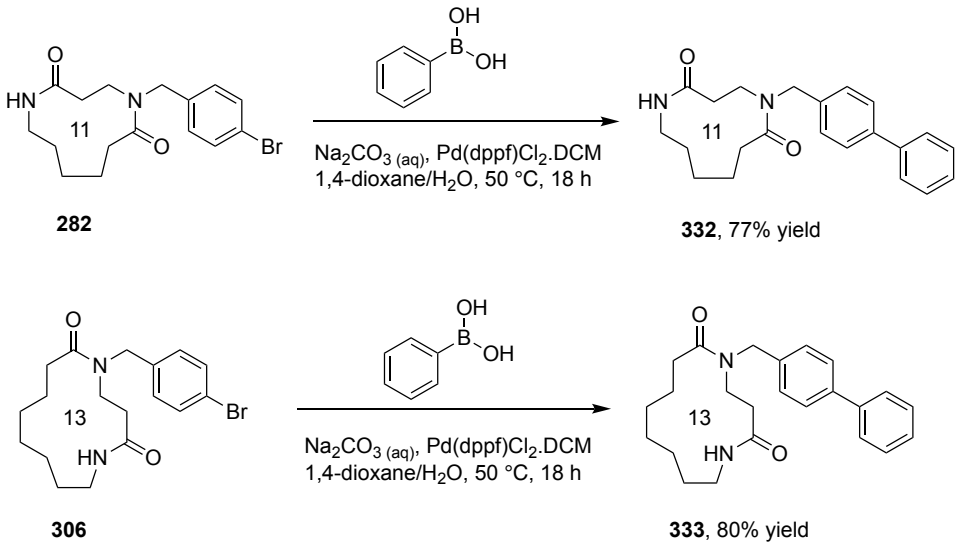
Scheme 113: Synthesis of 11- and 12- membered ring expanded products using various amines

5.2.2 Side Chain Elaboration – Monofunctionalisation

Having successfully synthesised a series of ring-expanded lactams, subsequent efforts focused on the functionalization of the CARE-derived products via side chain elaboration. A range of monofunctionalisation strategies were explored, including Suzuki-Miyaura cross coupling, *N*-functionalisation, and *O*-alkylation.

5.2.2.1 Suzuki-Miyaura Cross Coupling

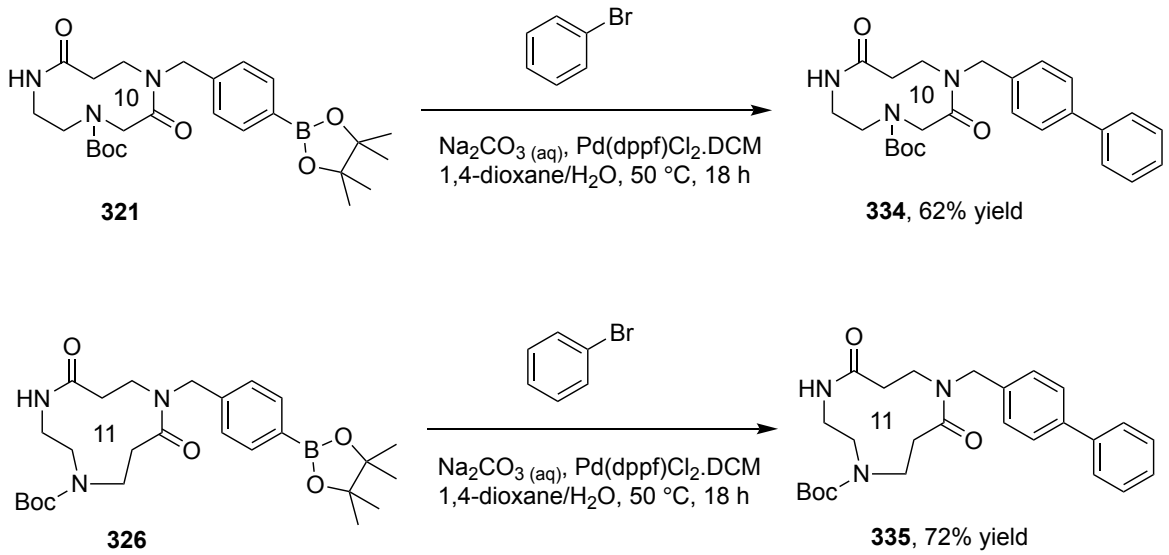
As an initial approach, Suzuki-Miyaura cross coupling (SMCC) reactions were performed on CARE products of two different rings sizes. Specifically, 11- and 13- membered lactams containing aryl bromide (**282** and **306**), synthesised using the method described earlier in section 5.1.2.1, were subjected to SMCC using phenyl boronic acid as the coupling partner in the presence of a catalytic amount of the palladium complex $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ and saturated Na_2CO_3 solution at 50 °C under an inert atmosphere. The reaction protocol was based on conditions previously developed and successfully applied in our research group.[77] Pleasingly, this step proceeded as planned, affording the desired products in 77−80% yields respectively (Scheme 114).



Scheme 114: SMCC reactions of 11- and 13- lactams using phenyl boronic ester

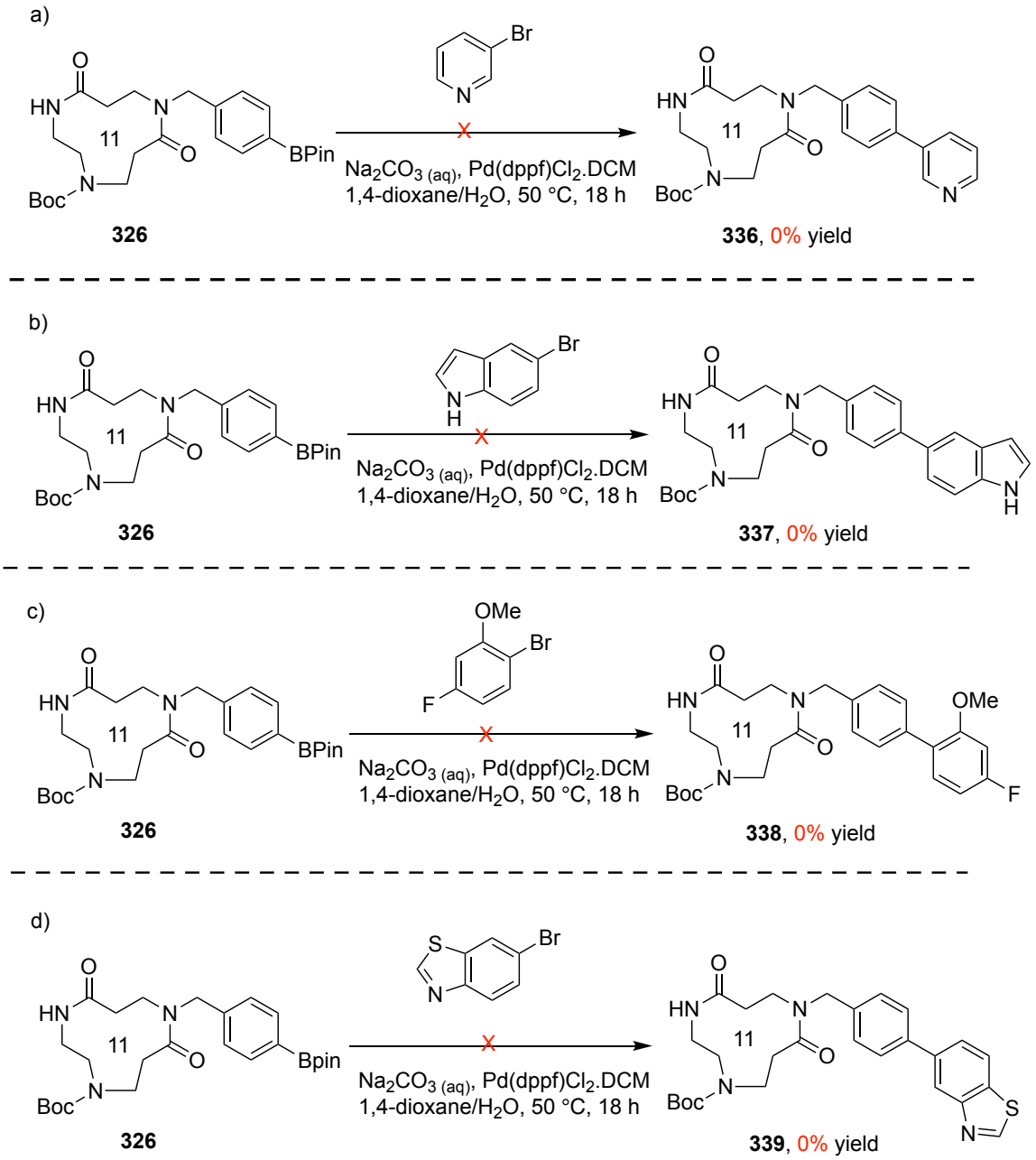
With a reliable procedure developed for the cross-coupling reaction of 11- and 13- membered lactams with phenylboronic acid, the next step was to explore the scope of this reaction on *N*-Boc protected derivatives. *N*-Boc protected 6- and 7- membered ring-expanded lactams, **321** and **326**, containing boronic ester (Bpin) functionalities were subjected to the same SMCC protocol, this time employing using phenyl bromide as the coupling partner (Scheme 115). The desired products, **334** and **335**, were successfully isolated in 62% and 72% yield respectively. Although these yields were lower compared to those obtained for their simpler hydrocarbon analogues, the consistent outcome across both ring sizes indicates that the presence of the *N*-Boc group does not cause a meaningful obstruction or difficulty in the cross-coupling process. Furthermore, applying identical catalytic conditions to more compact

lactam systems provided an opportunity to assess the reactivity of these substrates and to evaluate the influence of the *N*-Boc protection on reaction efficiency.



Scheme 115: SMCC reactions of N-Boc protected 6- and 7- lactams using phenyl bromide

In light of the results above, we decided to investigate alternative boronic acid coupling partners to further expand the utility of the cross-coupling methodology. To this end, *N*-Boc protected lactam **326** was treated with a series of electronically and sterically varied aryl bromides under the previously optimised SMCC conditions (Scheme 116). Unfortunately, none of the desired products **336**–**339** were obtained in any of the reaction attempts. In most cases, ^{1}H NMR analysis of the crude reaction revealed complex mixtures, with no remaining starting material detectable. Although multiple spots were observed by TLC and the expected mass peak was detected by mass spectrometry, attempts at purification by column chromatography were unsuccessful, as partial co-elution of the spots prevented separation and made identification of the desired product challenging.



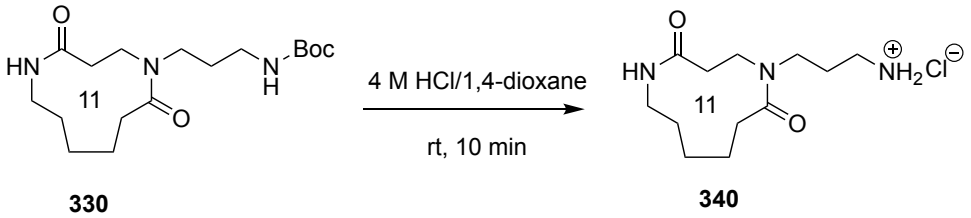
*Scheme 116: N-Boc protected lactam **326** which failed to undergo SMCC reaction*

In summary, the application of SMCC reactions demonstrated the utility of selective side-chain elaboration, yielding products in good yields across both macrocyclic and *N*-Boc protected systems. While the methodology proved robust under standard conditions, attempts to expand the reaction scope with a broader range of boronic acids were unsuccessful, highlighting the strengths and limitations of the current approach. But notably, optimisation of the SMCC for these additional substrates was not performed. Given the vast array of published SMCC procedures, it is reasonable that such optimisation could provide

solutions and improved SMCC for other substrates, and this should be a priority in future work on this system.

5.2.2.2 N-Functionalisation of Ring Expanded Lactam

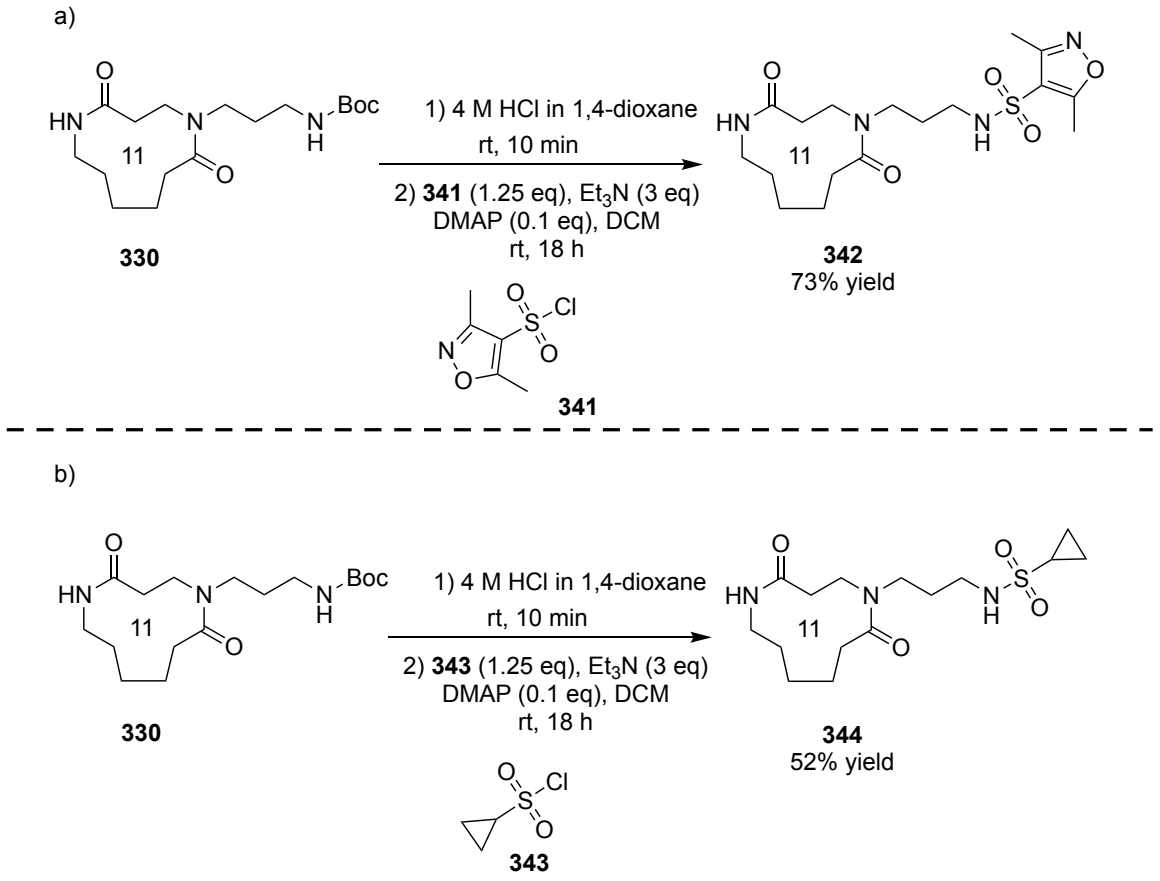
Following successful side-chain derivatization via SMCC, attention *N*-functionalisation reactions. To start, a representative Boc-protected amine derivative **330** was selected for further diversification through a series of *N*-functionalisation strategies. Before undertaking each reaction, the Boc protecting group was removed under acidic conditions. The compound **330** was treated with 4 M HCl in 1,4-dioxane and stirred at room temperature for 10 minutes to promote Boc cleavage. The reaction mixture was then concentrated under reduced pressure to afford the corresponding hydrochloride salt **340**, which was used directly in the subsequent *N*-functionalisation steps without further purification (Scheme 117).



330 **340**

Scheme 117: Boc deprotection process

The first *N*-functionalization strategy explored was sulfonylation. As noted above, the Boc protecting group was first removed using 4 M HCl in 1,4-dioxane to afford the corresponding hydrochloride salt **340**. Without purification, the crude salt was then reacted with 3,5-dimethylisoxazole-4-sulfonyl chloride **341** in the presence of triethylamine and a catalytic amount of DMAP in DCM. The reaction was initially carried out at room temperature for 18 hours (Scheme 118a). An excess of triethylamine was used to free-base the hydrochloride salt in situ, thereby enabling direct conversion to the sulfonamide without requiring isolation and purification of the free amine. Following this initial success, a second sulfonylation was performed using cyclopronesulfonyl chloride **343** under the same reaction method (Scheme 118b). Both reactions demonstrated the feasibility of sulfonamide formation as a robust *N*-functionalisation strategy on this scaffold.

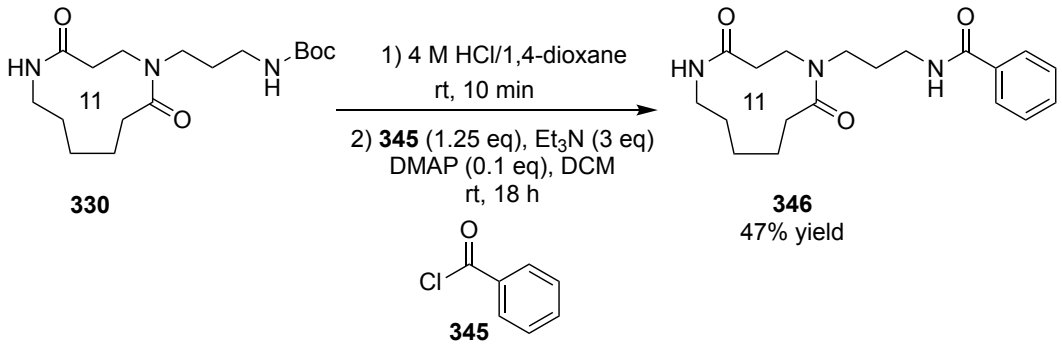


Scheme 118: Sulfonylation reactions for the synthesis of sulfonamides

The sulfonylation reactions proceeded with moderate to good yields, depending on the sulfonyl chloride employed. Specifically, the use of 3,5-dimethylisoxazole-4-sulfonyl chloride **341** afforded the corresponding sulfonamide **342** in 73% yield, whereas cyclopronesulfonyl chloride **343** gave a lower yield of 52%. This difference is likely due to the contrasting electronic and steric properties of the sulfonylating agents. 3,5-Dimethylisoxazole-4-sulfonyl group contains an electron-withdrawing heteroaromatic ring, which enhances the electrophilicity of the sulfur atom, thereby facilitating nucleophilic attack by the amine. In contrast, the cyclopronesulfonyl group is weakly electron-donating, likely making the sulfur centre less electrophilic in comparison. Additionally, differences in solubility and purification characteristics may have contributed to the lower isolated yield of the cyclopropyl derivative.

Building on the successful sulfonylation step, *N*-acylation applied to the deprotected amine salt derived from compound **330**. Following Boc removal, the resulting hydrochloride salt **340** was treated with benzoyl chloride in the presence of triethylamine and a catalytic amount of DMAP in DCM at room temperature for 18 hours. After work-up and purification by column

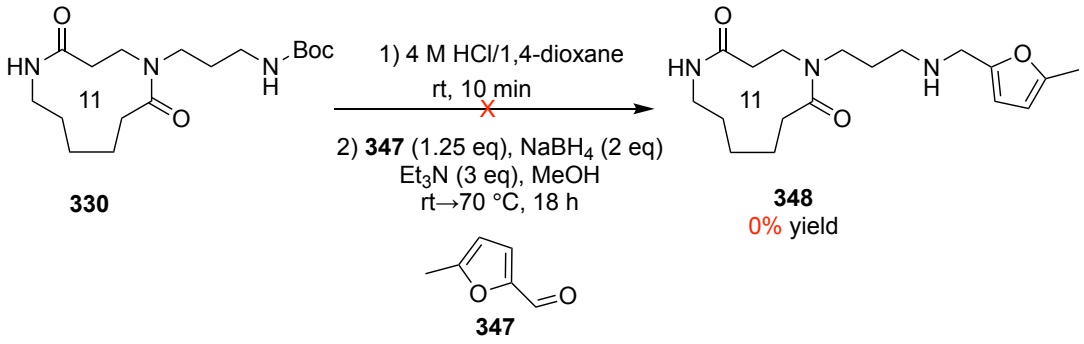
chromatography, the desired *N*-benzoyl imide **346** was successfully isolated in 47% yield (Scheme 119). The proposed mechanism involves the nucleophilic attack of the free amine of **340**, generated upon Boc deprotection, on the carbonyl carbon of benzoyl chloride. Triethylamine acts as a base to neutralize the released HCl, while DMAP facilitates the reaction by acting as a nucleophilic catalyst. The reaction proceeds through a typical nucleophilic acyl substitution pathway, resulting in the formation of the *N*-benzoyl imide **346** under mild conditions.



*Scheme 119: N-acylation with benzoyl chloride for the synthesis of N-benzoyl imide **346***

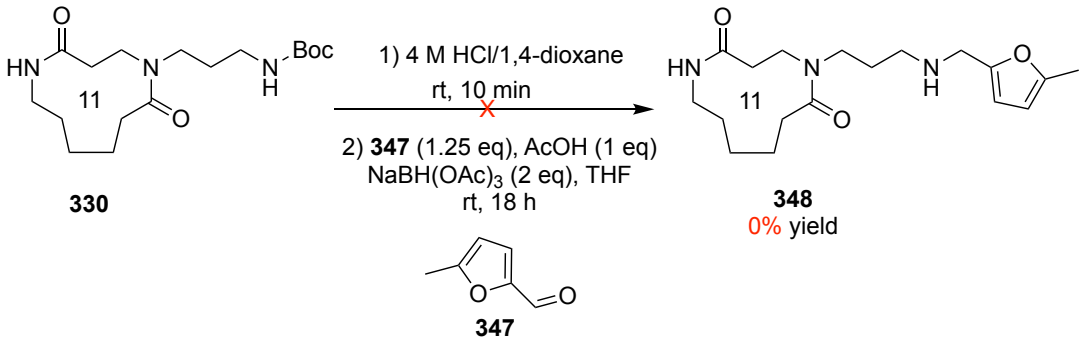
5.2.2.3 Unsuccessful Efforts in *N*-Functionalisation Diversification

As part of continued efforts to expand the scope of *N*-functionalisation, a reductive amination approach was explored using the Boc-protected lactam **330**. After removal of the Boc group under the standard acidic conditions, the resulting hydrochloride salt **340** was neutralized with triethylamine and subsequently treated with 5-methylfuran-2-carbaldehyde **347** in methanol. The reaction mixture was stirred at room temperature for 4 hours to allow imine formation, after which $NaBH(OAc)_3$ was added as the reducing agent. The reaction was then heated to 70 °C and stirred for 18 hours (Scheme 120). Mass spectrometric analysis of the crude mixture revealed a peak consisted with the expected molecular weight of the reductively aminated product, suggesting that the desired transformation may have occurred. However, purification by column chromatography failed to yield a pure product; instead, a mixture of unidentified compounds was isolated.



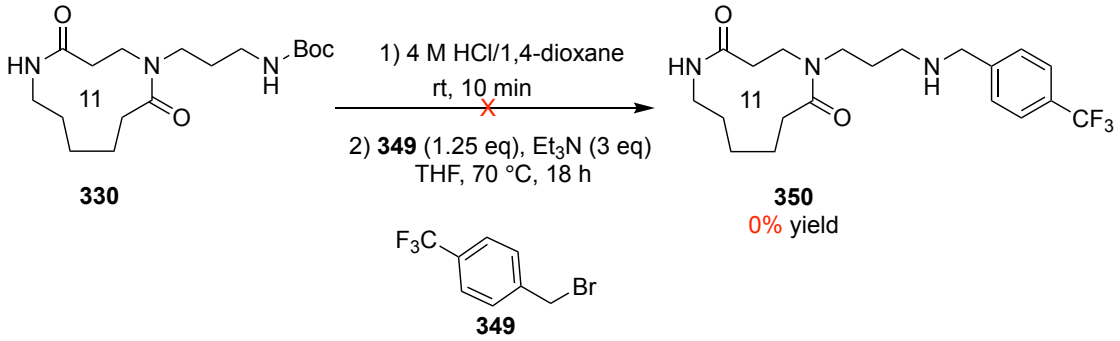
Scheme 120: First attempt at reductive amination using methanol as solvent and thermal activation

In an attempt to improve the reaction outcome, the reductive amination was repeated under modified conditions. The hydrochloride salt **340** was treated with 5-methylfuran-2-carbaldehyde **347**, one equivalent of acetic acid, and two equivalents of $NaBH(OAc)_3$ in THF at room temperature for 18 hours (Scheme 121). Following work-up and purification, analysis again resulted in the isolation of a complex mixture of compounds, none of which could be confidently assigned as the desired product **348**. These observations suggest that the reductive amination pathway, under both sets of conditions, may be hindered by the instability of reactive intermediates or competing side reactions. Mass spectrometry evidence was obtained indicating the presence of a product with the expected molecular weight, but the failure to isolate a pure compound by column chromatography also points to challenges during purification, in addition to side product formation. These difficulties may arise from the formation of closely related by-products with similar polarity, complicating chromatographic separation, or from decomposition of the target compound on silica gel. Furthermore, strong adsorption of the polar amine product to the stationary phase may have further impeded its elution.



Scheme 121: Second attempt at reductive amination using THF and acetic acid under mild conditions

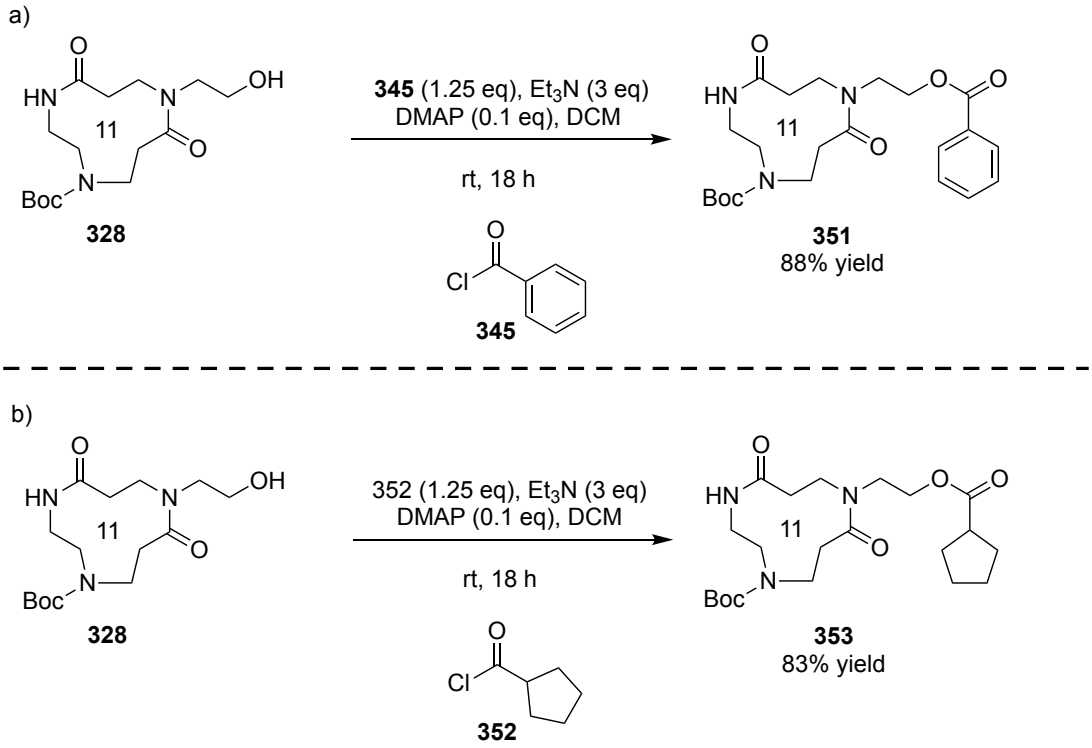
To further explore *N*-functionalisation of the ring expanded lactam **330**, an S_N2 *N*-alkylation was attempted using a trifluoromethyl-substituted bromomethylbenzene **349** as the alkylating agent. The hydrochloride salt **340** was treated with trifluoromethyl-substituted bromomethylbenzene **349** in the presence of triethylamine in THF at 70 °C for 18 hours (Scheme 122). However, analysis of the crude mixture by ^{1}H NMR revealed incomplete conversion of the starting material, along with the formation of unidentified side products. The expected product mass was not observed when analysed by mass spectrometry, therefore efforts complete this functionalisation were abandoned.



*Scheme 122: Attempted S_N2 N-alkylation of ring expanded lactam **330** with trifluoromethyl-substituted bromomethylbenzene **349***

5.2.2.4 *O*-Functionalisation of Ring Expanded Lactams

In addition to *N*-functionalisation, attention was also directed toward the functionalization of oxygen-containing moieties within the ring-expanded lactam. In particular, *O*-acylation of hydroxy functionalities present in the scaffold to form esters was investigated. These transformations aimed to explore the chemical versality of the ring system and to introduce additional points of structural diversification. In contrast to *N*-functionalisation, *O*-acylation is accomplished by the nucleophilic attack of an oxygen atom on an acyl electrophile, typically under basic conditions. To achieve this, alcohol substituted CARE product **328** was treated with benzoyl chloride **345** in the presence of triethylamine and a catalytic amount of DMAP in DCM at room temperature for 18 hours. After work-up and purification by column chromatography, the corresponding benzoate ester **352** was isolated in excellent yield (88%). Encouraged by this result, a second *O*-acylation was performed under identical conditions using cyclopentanecarbonyl chloride **352** as the acylating agent, affording ester **353** in 83% yield (Scheme 123).



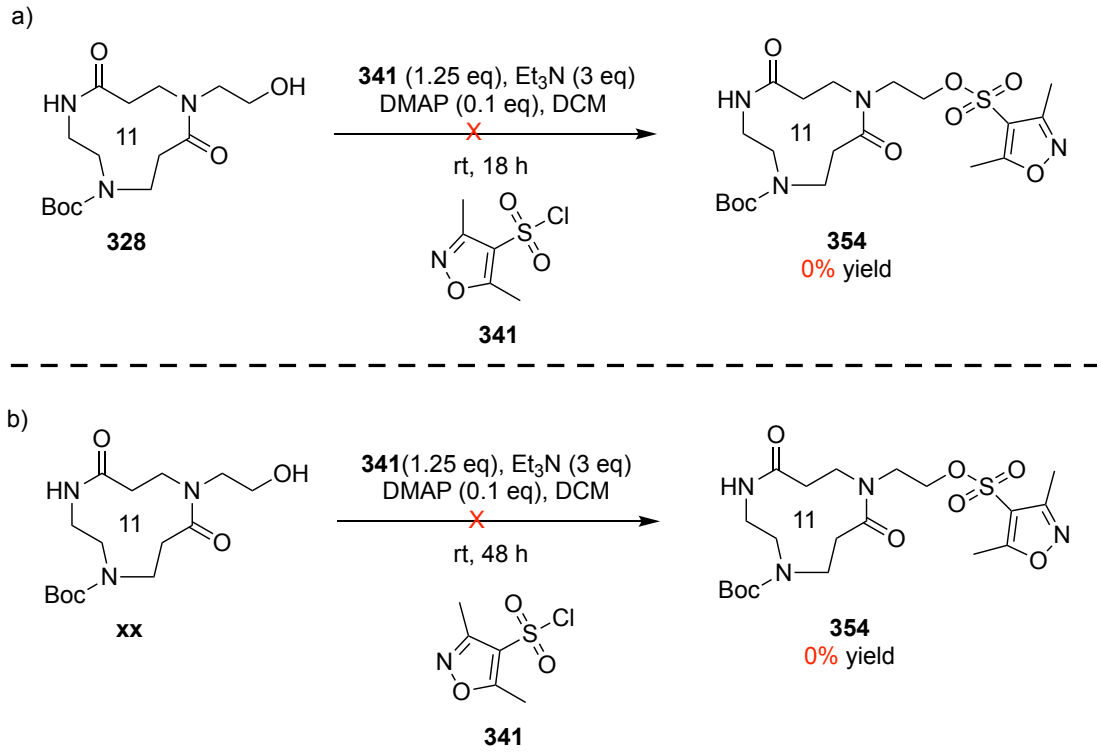
*Scheme 123: a) O-acylation with benzoyl chloride **345** b) O-acylation with cyclopentanecarbonyl chloride **352***

The high efficiency and selectivity of these reactions highlight the synthetic potential of *O*-functionalization on this scaffold. Unlike the previously described *N*-acylation reaction, these transformations did not require prior Boc deprotection, which simplified the reaction sequence and minimized purification challenges. The consistently high yields observed in both cases suggest that the hydroxyl group is sufficiently reactive under the employed conditions, and that steric or electronic interference from the neighbouring lactam does not significantly hinder acylation.

5.2.2.5 Unsuccessful Attempts in *O*-Functionalisation

Unfortunately, further efforts to diversify the hydroxyl-containing lactam **328** via *O*-sulfonylation and *O*-alkylation were unsuccessful. Under all tested conditions, no formation of the expected product **354** was observed, as confirmed by ^{1}H NMR and mass spectrometric analysis. In the case of *O*-sulfonylation, compound **328** was treated with 3,5-dimethylisoxazole-4-sulfonyl chloride **341** under conditions previously optimised for *N*-sulfonylation (3 equivalents of triethylamine and a catalytic amount of DMAP in DCM at room temperature for 18 hours). However, ^{1}H NMR analysis of the crude reaction mixture revealed

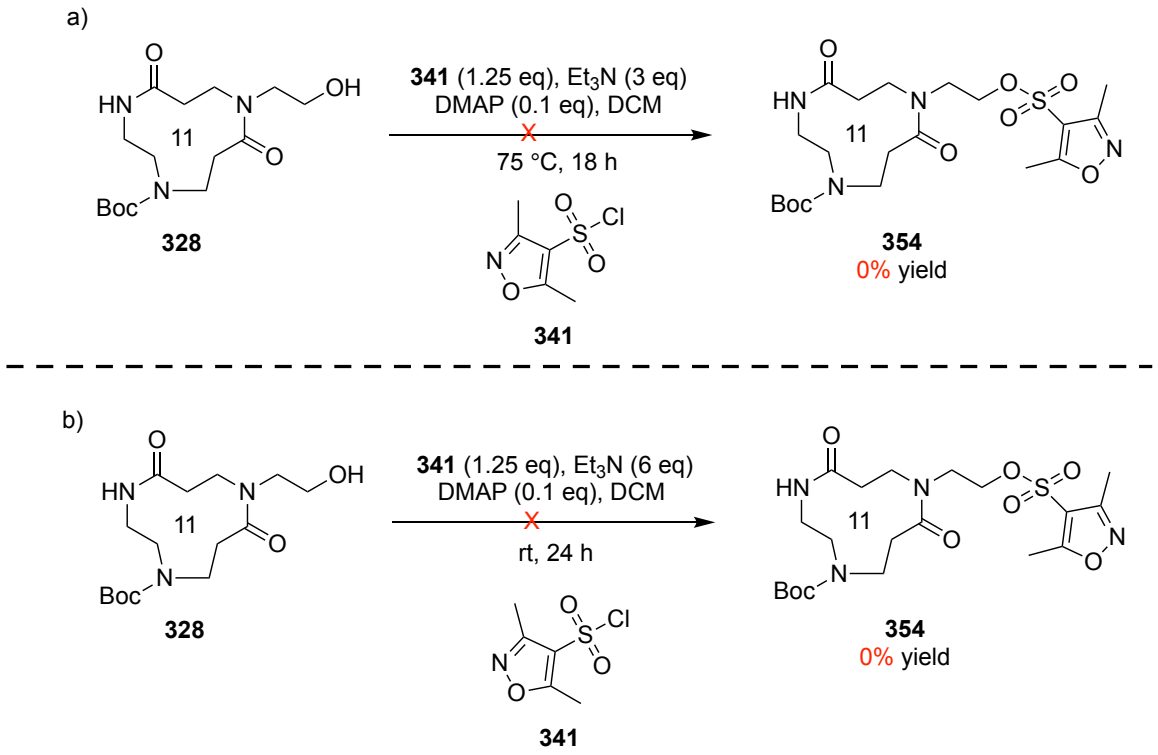
predominantly unreacted starting material, with only trace amounts of unidentified side products. In an attempt to the reaction to improve conversion, the reaction time was extended to 48 hours to allow the remaining starting material to react, but this resulted in no significant product formation; the starting material was still present as the major component. (Scheme 124).



*Scheme 124: Failed attempted O-sulfonylation using 3,5-dimethylisoxazole-4-sulfonyl chloride **328***

Performing the reaction under reflux led to a similar outcome, with no observable product formation and additional signs of isomerisation. In a final attempt to improve reactivity, the amount of triethylamine was increased from 3 to 6 equivalents (Scheme 125). This adjustment was intended to more effectively neutralise the HCl that may be generated during the reaction and to help maintain a more strongly basic environment, which could potentially enhance the nucleophilicity of the hydroxyl group. It was also expected to suppress acid-catalysed side reactions or decomposition pathways. Nonetheless, crude ^{1}H NMR once again showed mostly starting material, indicating that no effective transformation had occurred. These collective observations suggest that the hydroxyl group may be insufficiently nucleophilic within the sterically and electronically constrained lactam framework, or that

competing decomposition or rearrangement pathways inhibit productive *O*-sulfonylation under the tested conditions.



Scheme 125: a) Failed attempted O-sulfonylation under reflux conditions; b) Failed attempted O-sulfonylation with increased triethylamine loading

5.2.3 Ring Elaboration – Difunctionalisation

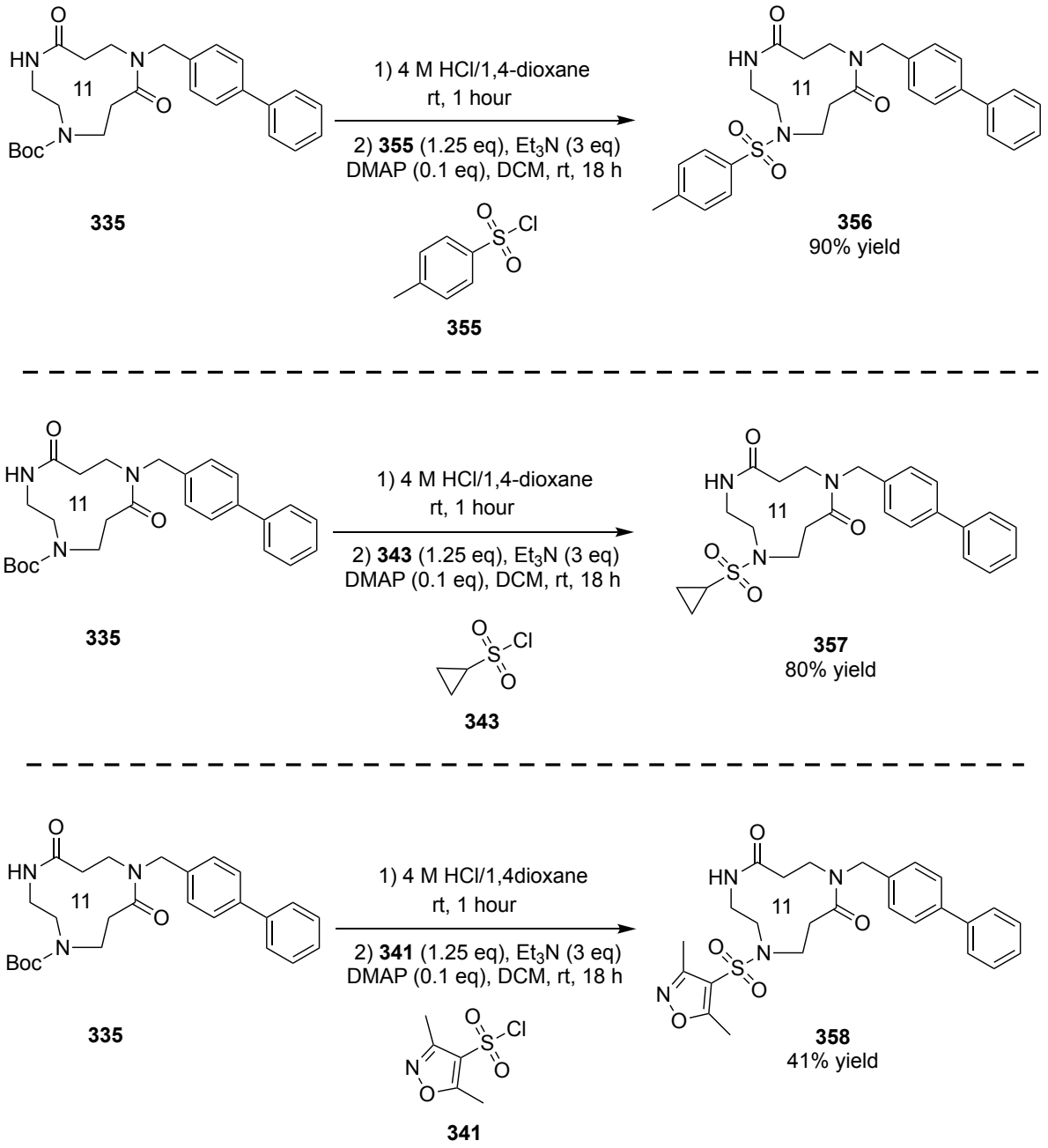
Having explored a variety of monofunctionalisation strategies on the ring-expanded lactam scaffolds, attention was next directed toward the generation of difunctionalisation derivatives via ring elaboration. This approach involved a second derivatisation step applied to the side chain-modified intermediates previously described in section 5.2.2 (Side Chain Elaboration). Importantly, it was found that the CARE product lactams could tolerate the acidic conditions required for Boc deprotection, allowing further transformations to be carried out efficiently. The focus of this study was on the elaboration of intermediates (**335**, **351** and **353**), all of which contain a Boc-protected amine within their medium-sized or macrocyclic rings. In each case, Boc group removal was directly followed by *N*-functionalisation, without isolation of the intermediate free amine, leading to the formation of difunctionalised products through a concise two-step sequence.

5.2.3.1 *N*-Sulfonylation with SO_2Cl

N-Sulfonylation reactions were performed on Boc-protected ring-expanded lactams derived from both Suzuki coupling and *O*-alkylation of hydroxyl-containing intermediates. The general reaction conditions involved treating the substrates with 3 equivalents of triethylamine and a catalytic amount of DMAP in DCM at room temperature for 18 hours. These mild conditions were chosen based on prior successful sulfonylation reactions on similar scaffolds.

a) *N*-Sulfonylation of Suzuki-derived lactam 335

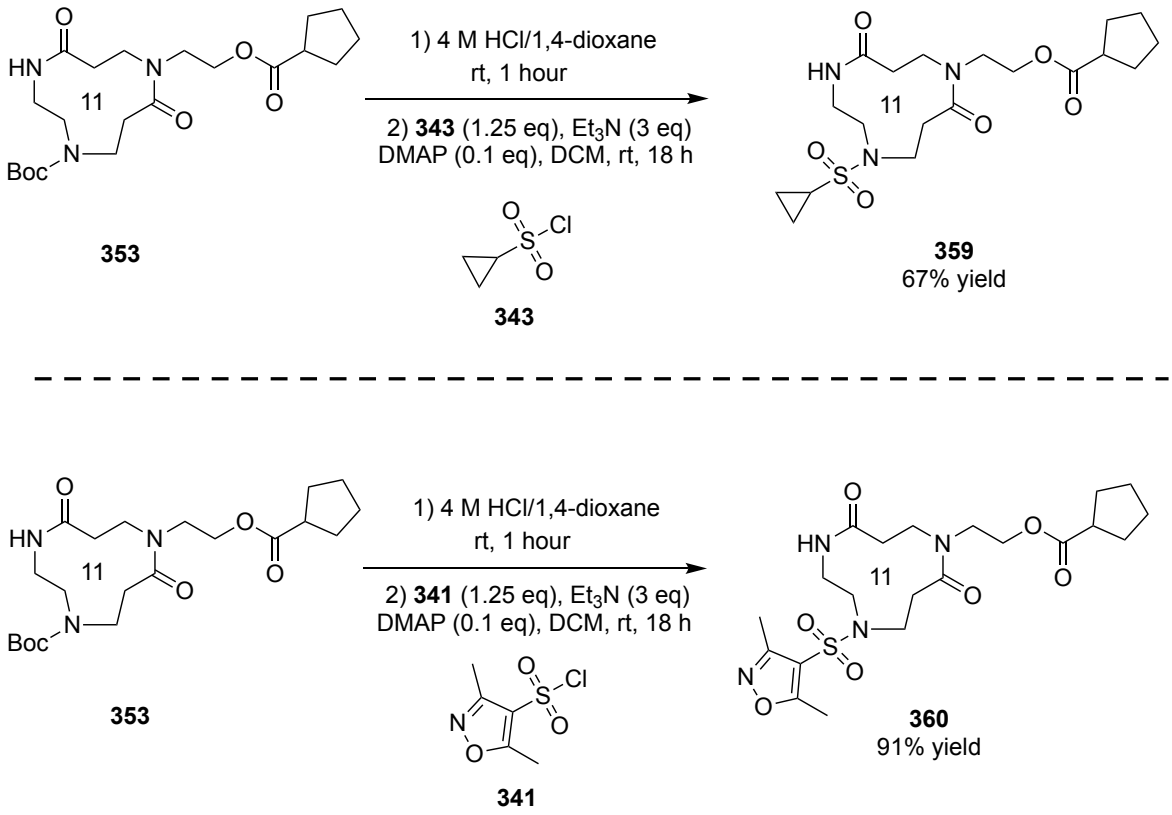
The suzuki derived lactams, following Boc deprotection to yield the corresponding hydrochloride salt, were subjected to *N*-sulfonylation using a range of sulfonyl chlorides under the general conditions. The reaction proceeded efficiently with *p*-toluenesulfonyl chloride **355**, affording the *N*-tosylated product **356** in 90% yield. Cyclopropanesulfonyl chloride **343** was also well tolerated, giving the desired sulfonamide **357** in 80% yield (Scheme 126). In contrast, use of the more sterically and electronically complex 3,5-dimethylisoxazole-4-sulfonyl chloride **341** resulted in a significantly lower yield of 41%, possibly due to reduced electrophilicity or steric hindrance.



*Scheme 126: N-Sulfonylation of Suzuki derived lactam **335***

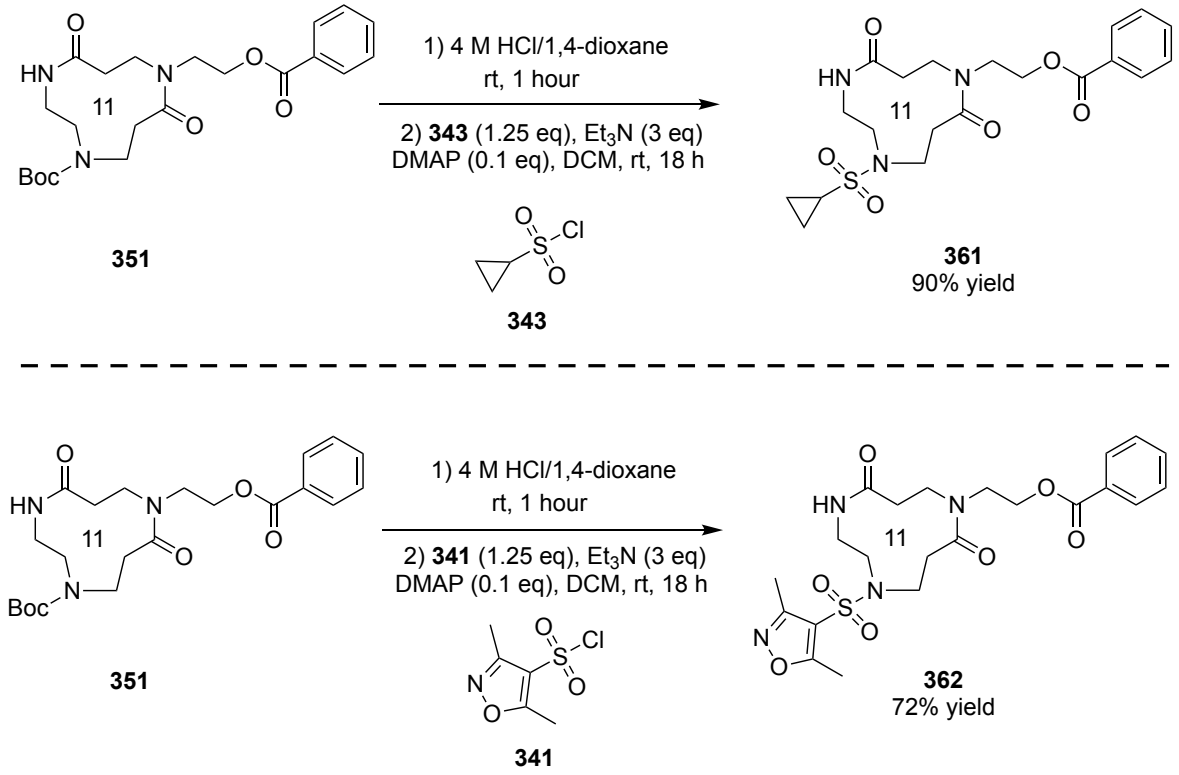
b) *N*-Sulfonylation of *O*-alkylated lactams 351 and 353

Following successful *O*-alkyaltion of ring expanded lactams, the resulting *N*-Boc-protected compounds **351** and **353** were subjected to Boc deprotection to yield the corresponding hydrochloride salt, which were then evaluated in *N*-sulfonylation reactions. In the case of cyclopentyl-substituted lactam **353**, *N*-sulfonylation with cyclopanesulfonyl chloride **343** provided the desired product **359** in 67% yield, whereas the use of 3,5-dimethylisoxazole-4-sulfonyl chloride **341** afforded the sulfonamide **360** in an 91% yield (Scheme 127).



*Scheme 127: N-Sulfonylation of cyclopentyl-substituted lactam **353***

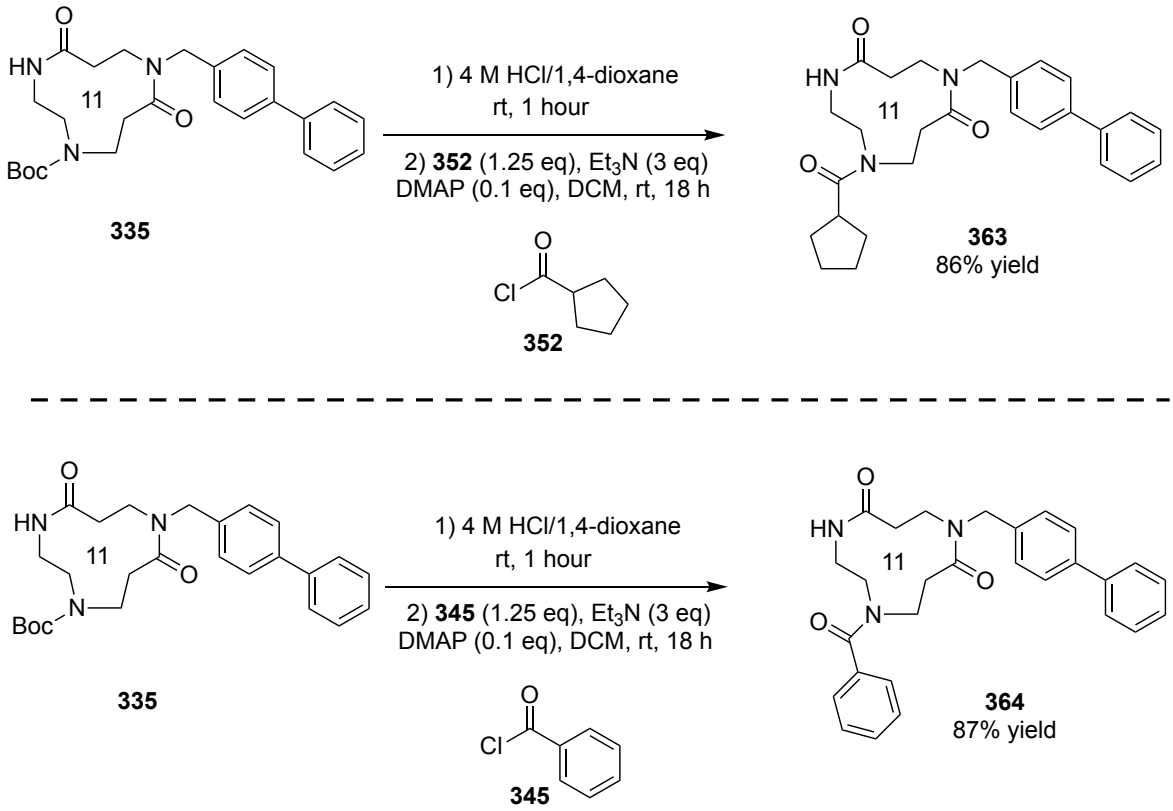
For the benzyl-substituted analogue **351**, sulfonylation with cyclopanesulfonyl chloride **343** gave a 90% yield, while reaction with 3,5-dimethylisoxazole-4-sulfonyl chloride **341** resulted in a 72% yield (Scheme 128).



*Scheme 128: N-Sulfonylation of benzyl-substituted lactam **351***

5.2.3.2 *N*-Acylation with COCl

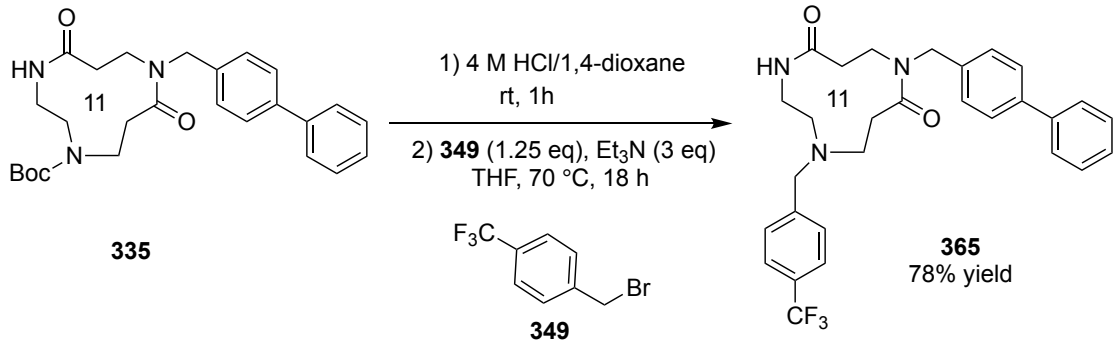
Building on the previous functionalisation efforts, *N*-acylation reactions were next explored as a means of introducing additional structural diversity. The study employed lactam **335**, which was first subjected to acidic Boc deprotection, followed by direct acylation using the corresponding acid chlorides **345 and 352** under standard conditions. Two representative examples were investigated. *N*-acylation of the deprotected lactam with cyclopentylcarbonyl chloride **352** afforded the desired product **363** in 86% yield, while reaction with benzoyl chloride **345** proceed smoothly to give the corresponding *N*-benzoylated product **364** in 87% yield. Both reactions demonstrated high efficiency and produced the desired products in high purity following purification by column chromatography (Scheme 129).



*Scheme 129: N-Acylation of Suzuki-derived lactam **335***

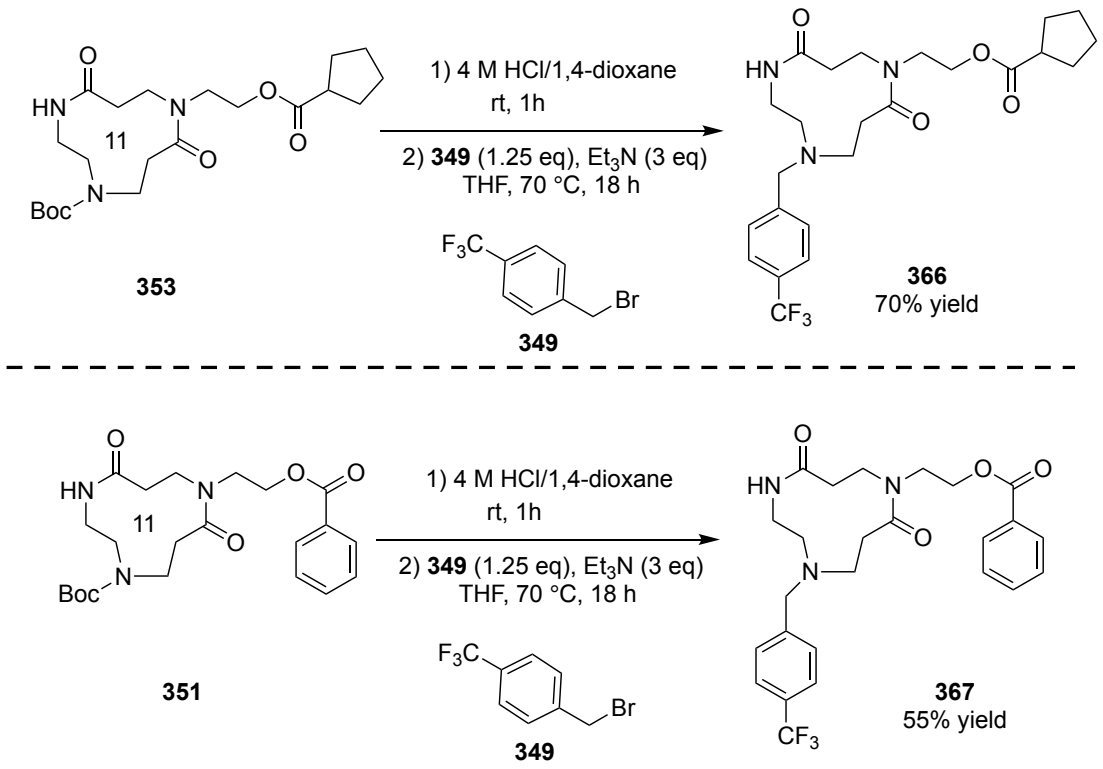
5.2.3.3 *N*-Alkylation with $ArCH_2Br$

To further expand the scope of *N*-functionalisation and access increasingly complex ring-expanded products, *N*-alkylation reactions were next explored. The initial study focused on the Suzuki-derived lactam **335**. Following acid-mediated removal of the Boc protecting group, the resulting hydrochloride salt was subjected to *N*-alkylation with bromomethylbenzene in the presence of triethylamine in THF at 70 °C for 18 hours. After purification, the desired *N*-benzylated product **365** was obtained in 78% yield (Scheme 130).



*Scheme 130: N-Alkylation of Suzuki-derived lactam **335***

Encouraged by this outcome, structurally related analogues featuring cyclopentyl and benzyl substituents on the ring (**353** and **351**) were also investigated under the same conditions as above. The corresponding *N*-alkylated products **366** and **367** were successfully isolated in 70% and 55% yields, respectively (Scheme 131). In both cases, ^{1}H NMR analysis revealed the products were found to exist as a mixture of two rotamers, with no evidence of side products.

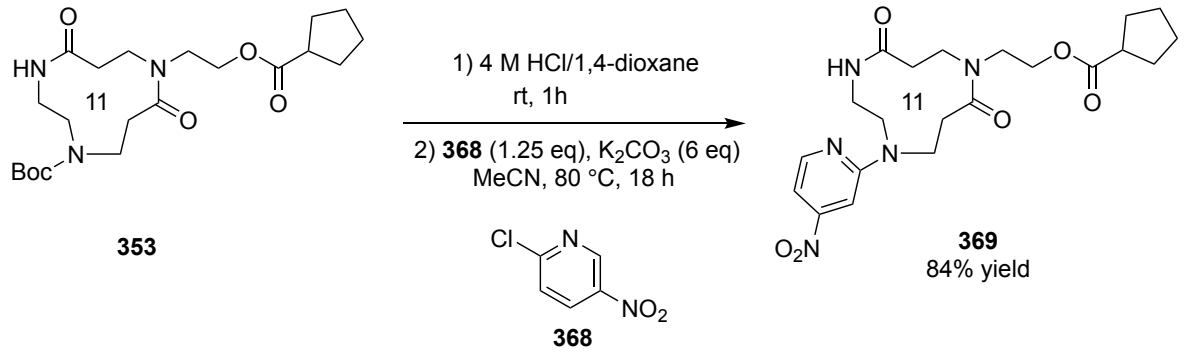


*Scheme 131: N-Alkylation of cyclopentyl- and benzyl-substituted lactams (**351** and **353**)*

5.2.3.4 *N*-Arylation via S_NAr with ArCl

As an additional strategy to diversify via *N*-functionalisation, a nucleophilic aromatic substitution (S_NAr) approach was investigated. In this study, the cyclopentyl-substituted lactam **353** bearing a Boc-protected amine was subjected to Boc deprotection, and the resulting hydrochloride salt was reacted with 2-chloro-5-nitropyridine **368** in the presence of 3 equivalents of K_2CO_3 in acetonitrile at 80 °C for 18 hours. However, ^{1}H NMR analysis of the reaction mixture revealed a complex distribution of products, and none of the desired compound **369** could be isolated after column chromatography. Subsequently, the amount of K_2CO_3 was increased from 3 to 6 equivalents. This adjustment led to a significantly cleaner reaction mixture, as evidence by ^{1}H NMR and mass spectrometry analysis, which showed a

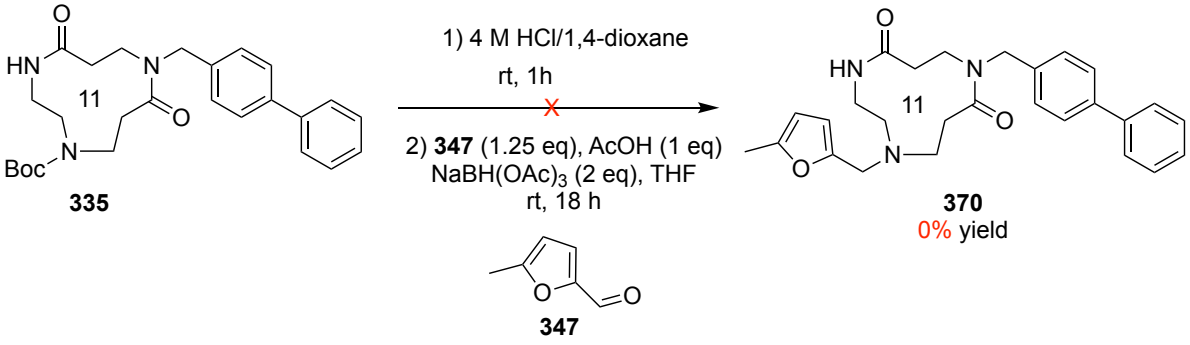
major product peak consistent with the expected structure. After purification, the desired product **369** was isolated in 84% yield (Scheme 132).

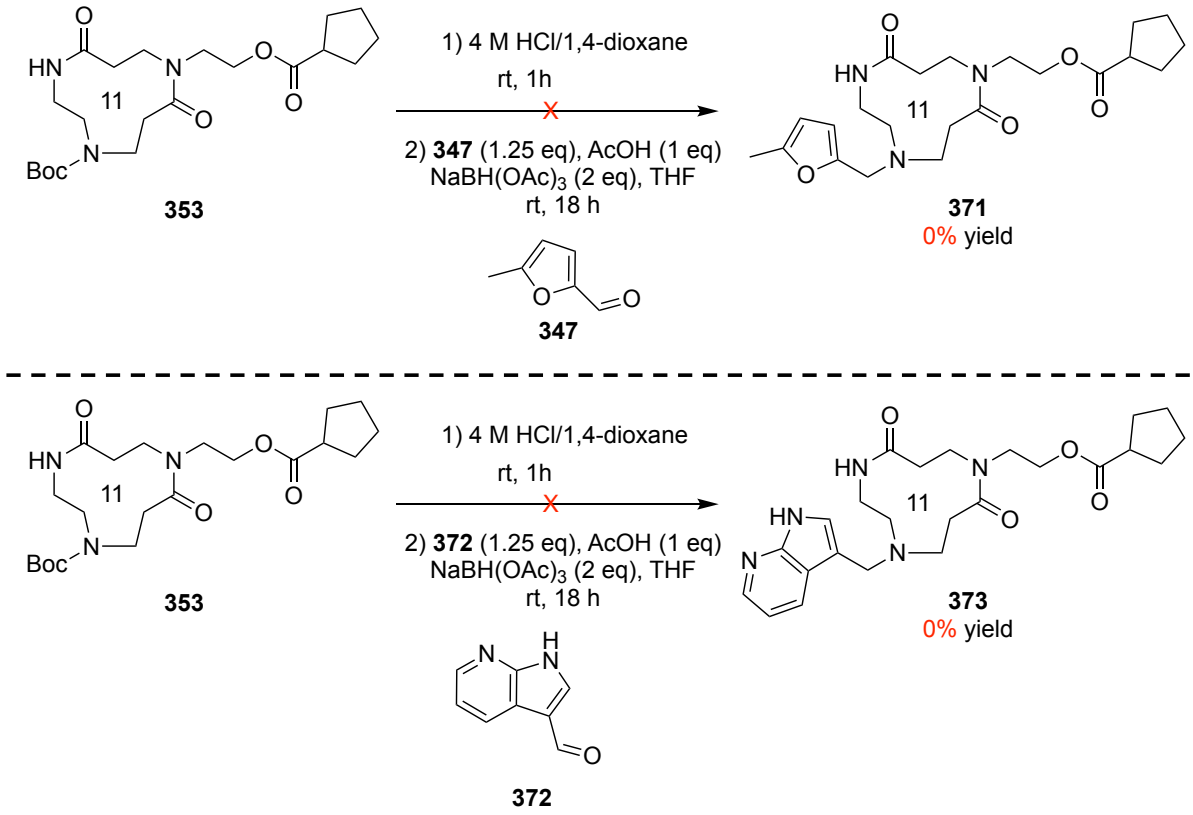


*Scheme 132: S_NAr N-Alkylation of cyclopentyl-substituted lactam **353***

5.2.3.5 Unsuccessful Attempts in Ring Elaboration

Several attempts were made to expand the ring system via reductive amination, using various aldehyde coupling partners with both Suzuki-derived and cyclopentyl-substituted lactams (**335** and **353**). The initial approach involved the reaction of the Suzuki-derived lactam **335** with 5-methylfuran-2-carbaldehyde **347**; however, none of the desired product was obtained. Subsequently, efforts were redirected toward the cyclopentyl-substituted lactam **353**, first employing the same aldehyde and then pyrrolopyridine-carbaldehyde **372** as alternative electrophilic partners. Despite these variations, all attempts under standard reductive amination conditions failed to yield isolable products. These unproductive outcomes, which may reflect either steric hindrance, low nucleophilicity of the amine, or incompatibility of the reaction conditions, are summarised in Scheme 133.





Scheme 133: Unsuccessful reductive amination attempts with selected lactams

5.3 Biological Evaluation of Synthesis of Synthesized Lactams

Macrocyclic and medium-sized lactams represent underexplored chemical space in medicinal chemistry, especially when compared to the more commonly investigated 5−7-membered ring scaffolds. A key motivation behind this work was to establish a robust synthetic platform capable of rapidly generating diverse libraries of such lactams suitable for biological screening.

To assess the biological potential of the synthesized lactams, a subset of 60 representative novel lactams made this project was selected for antibacterial activity testing against two model organisms: the Gram-positive *Staphylococcus aureus* and the Gram-negative *Escherichia coli*. The compounds were diluted in Mueller-Hinton (MH) medium as final concentration 100 µM. Unfortunately, none of the tested compounds exhibited significant bacterial growth inhibition under the conditions employed. Note that these bioassays were conducted in collaboration with colleagues within the Chemistry department in York, Dr

Angelo Frei and Çağrı Özsan. I performed the sample preparations myself, while Çağrı Özsan did the antibacterial activity testing. The results are summarised below.

Single Dose Response Antibacterial Activity

A single colony of *Staphylococcus aureus* (CCUG 19434) was cultured overnight in Tryptic Soy Broth (TSB), while *Escherichia coli* (NCTC 13476) was grown under similar conditions in Luria-Bertani (LB) medium, both at 37 °C. Test compounds were initially dissolved in DMSO to yield 10 µM stock solutions, which were subsequently diluted to 5 mM to obtain a final assay concentration of 100 µM in Mueller-Hinton (MH) medium. The bacterial cultures were diluted in their respective growth media and incubated until the optical density at 600 nm (OD600) reached a range of 0.6−1.0, after which they were further diluted to an OD600 of 0.022 in MH medium. Then, 10 µL of the diluted bacterial solution was used to inoculate 300 µL of the sample solutions. The plates were then incubated at 37 °C for 16 hours. Each experimental setup included standard controls: a control of broth only and a growth control of broth with bacterial inoculum without antibiotics were included in two columns of the plate. As positive controls, polymyxin B and vancomycin were employed at 20 µg/mL for *E. coli* and *S. aureus*. The growth was measured by analysing the absorbance of the bacterial suspension at 600 nm, and each experiment was repeated in triplicate.

Compound	*S.aureus*	*E. coli*	Compound	*S.aureus*	*E. coli*
7a	103.1 ± 7.0	99.6 ± 6.9	**10d**	87.5 ± 2.1	103.2 ± 3.4
7b	97.8 ± 6.8	95.3 ± 8.7	**10e**	89.8 ± 2.5	104.4 ± 2.4
7c	99.0 ± 8.9	91.8 ± 10.9	**10g**	92.2 ± 3.3	103.0 ± 1.9
7d	96.9 ± 9.3	92.4 ± 10.3	**10f**	95.0 ± 5.1	102.6 ± 2.1
7e	95.8 ± 9.3	95.4 ± 7.2	**10h**	96.4 ± 3.9	99.9 ± 3.3
8a	96.7 ± 10.3	98.0 ± 5.5	**10i**	103.9 ± 10.3	102.7 ± 3.6
8b	99.3 ± 12.8	97.2 ± 7.6	**10j**	97.9 ± 3.7	103.6 ± 6.0
8c	100.1 ± 11.9	95.9 ± 5.9	**10k**	93.6 ± 3.6	101.7 ± 6.0
8d	103.0 ± 13.0	94.0 ± 4.9	**13a**	95.8 ± 4.1	101.5 ± 6.6
8e	102.8 ± 11.8	97.6 ± 6.2	**13b**	92.4 ± 4.1	104.4 ± 4.6
8f	106.6 ± 13.7	99.8 ± 4.7	**41**	84.1 ± 4.0	101.8 ± 5.8
8g	107.9 ± 14.9	102.7 ± 3.8	**14m**	73.1 ± 7.1	128.0 ± 4.4

8h	99.1 ± 5.0	106.2 ± 5.8	**14a**	92.0 ± 2.7	104.4 ± 2.6
8i	92.6 ± 3.9	102.0 ± 5.7	**14e**	93.5 ± 1.9	104.6 ± 2.7
8j	93.8 ± 4.8	99.5 ± 7.1	**14d**	92.5 ± 5.0	104.4 ± 3.1
8k	91.9 ± 4.5	99.3 ± 7.3	**14b**	95.8 ± 4.1	103.7 ± 2.1
9a	90.1 ± 5.1	100.4 ± 4.9	**14f**	88.9 ± 9.8	126.6 ± 12.9
9b	89.2 ± 3.6	100.9 ± 5.9	**14j**	99.8 ± 5.7	99.5 ± 3.5
9c	91.3 ± 4.2	100.7 ± 5.3	**14i**	98.2 ± 3.6	99.5 ± 6.0
9d	91.1 ± 5.0	100.6 ± 5.0	**13i**	93.0 ± 4.7	102.4 ± 5.9
9e	95.1 ± 4.9	99.7 ± 3.3	**13h**	92.3 ± 4.3	103.6 ± 5.2
9g	97.5 ± 6.3	100.9 ± 3.1	**13j**	90.5 ± 3.5	103.5 ± 4.6
9f	98.8 ± 5.3	101.2 ± 5.3	**12l**	87.6 ± 4.4	104.1 ± 3.9
9h	105.8 ± 13.0	102.1 ± 4.0	**11j**	94.8 ± 4.9	105.1 ± 5.1
9i	96.5 ± 5.0	104.5 ± 5.7	**7l**	86.8 ± 5.6	107.1 ± 2.7
9j	95.5 ± 4.1	102.8 ± 3.1	**13d**	92.1 ± 7.1	107.7 ± 4.7
9k	94.0 ± 6.1	101.6 ± 4.9	**13c**	94.6 ± 7.8	107.9 ± 3.1
10a	89.3 ± 4.0	102.1 ± 6.5	**14k**	98.4 ± 2.7	101.3 ± 5.6
10b	89.0 ± 4.1	101.1 ± 6.6	**14h**	96.1 ± 3.2	102.6 ± 5.9
10c	88.4 ± 2.7	101.3 ± 6.5	**14l**	92.2 ± 3.1	102.7 ± 5.4

Table 8: Viability of S. aureus and E. coli after treatment with 100 µM of the corresponding

5.4 Conclusions

The primary objective of the work described in this chapter was to develop a novel and modular ring expansion strategy for the synthesis of valuable macrocyclic lactams via the Nucleophilic Conjugate Addition/Ring Expansion (*N*-CARE) approach. This goal was successfully achieved through the use of α,β-unsaturated γ-lactams as key precursors, enabling efficient access to a diverse range of 10- to 13-membered macrocycles in moderate to good yields under mild reaction conditions. A significant innovation of this study lies in the development of a scalable and flexible three-step sequence ring-expansion, side-chain diversification, and cross-coupling, which allowed for precise structural modulation and facilitated the construction of more elaborate macrocyclic frameworks. In total **67** novel medium-sized ring and macrocyclic lactams synthesised in this project.

One of the core strengths of the methodology is its capacity to tolerate various functional groups and to incorporate *N*-Boc protected imides as stable and versatile intermediates. These intermediates were successfully subjected to Suzuki-Miyaura cross-coupling reactions and *N*-functionalisation steps, further expanding the synthetic scope of the platform. Moreover, the strategic incorporation of orthogonal functional groups, including aryl halides, boronates, sulfonamides, and alcohols, not only enabled downstream derivatization but also created opportunities for modifications at advanced synthetic stages, enhancing the overall modularity and utility of the method. All key products and intermediates were isolated and fully characterised by ^{1}H NMR, ^{13}C NMR, and HRMS, confirming the successful formation of the desired macrocyclic structures.

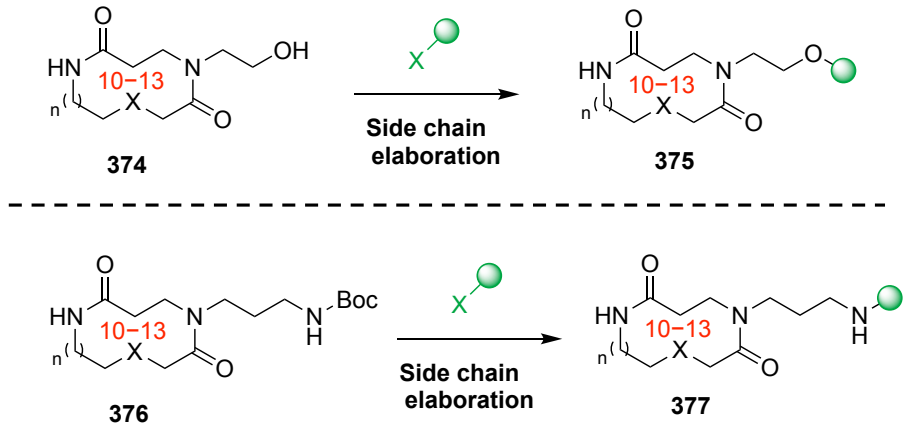
To assess the potential biological relevance of the synthesized scaffolds, selected macrocyclic compounds were subjected to antibacterial screening against Gram-positive *Staphylococcus aureus* and Gram-negative *Escherichia coli*. bacterial strains. Unfortunately, none of the tested compounds exhibited significant antibacterial activity. These preliminary bioassays suggest that further optimisation, such as the incorporation of polar or charged groups, increasing conformational rigidity, or targeting other bioactive motifs, may be necessary to enhance biological activity.

In summary, this work presents a robust and modular synthetic platform that significantly advances ring expansion chemistry. The developed approach offers high functional group tolerance, structural flexibility, and broad applicability, making it a valuable tool not only for the synthesis of complex macrocycles but also for their subsequent functional derivatization. These findings provide a strong foundation for further exploration of *N*-CARE based methodologies in both complex molecule synthesis and early-stage medicinal chemistry.

5.5 Future Work

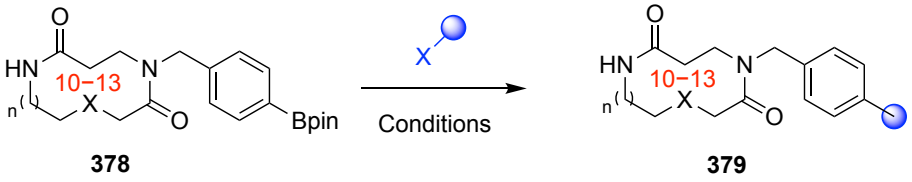
While the development of the CARE methodology has enabled the efficient synthesis of diverse macrocyclic and medium-sized lactams, several strategic avenues remain open for further exploration. One potential direction for future work is the further optimisation of *N*-

and *O*-functionalisation, which could expand the chemical diversity of the generated scaffolds (Scheme 134).



Scheme 134: Possible N-functionalization and O-functionalization

In addition, the failure of the Suzuki cross-coupling attempts with Bpin-substituted CARE-derived lactams highlights the need to further explore both the reaction conditions and substrate scope. Expanding the range of Suzuki coupling partners, such as using different aryl or heteroaryl halides, or modifying the lactam scaffold to enhance its reactivity, may improve the efficiency and applicability of this transformation (Scheme 135).



Scheme 135: Alternative cross-coupling strategies for CARE-derived lactams

Biological evaluation of the synthesized compounds revealed limited antibacterial activity at the tested concentration. Future studies may involve broadening the screening panel to include alternative bacterial strains, or non-bacterial assays.

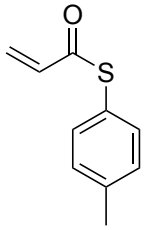
6. EXPERIMENTAL

6.1 General Experimental

Unless otherwise noted all compounds were bought from commercial suppliers and used without further purification. Where a solvent is described as ''dry'' it was purified by PureSolv alumina columns from Innovative Technologies. Melting points were determined using a Stuart SMP3 apparatus. Infra-red spectra were acquired on a ThermoNicolet Avatar 370 FT-IR spectrometer. Nuclear magnetic resonance spectra were recorded on a Jeol ECS-400 at ambient temperature. Coupling constants (*J*) are quoted in Hertz. Mass spectrometry was performed by the University of York mass spectrometry service using electron spray ionisation (ESI) technique. Thin layer chromatography was performed on aluminium sheets coated with Merck Silica gel F_{254}. The plates were developed using ultraviolet light, acidic aqueous ceric ammonium molybdate or basic aqueous potassium permanganate. Liquid chromatography was performed using forced flow (flash column) with the solvent systems indicated. The stationary phase was silica gel 60 (220−240 mesh) supplied by Fluorochem or silica gel Merck TLC grade 11695 supplied by Sigma-Aldrich. NMR assignments were made using 2D NMR including COSY, HMBC, HMQC techniques. All numbering on the structures below is for the benefit of characterisation and does not necessarily conform to IUPAC rules.

6.2 Characterization Data and Procedures

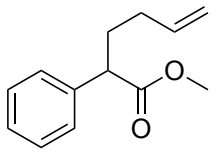
Thioacrylic acid S-*p*-tolyl ester (89)



To a solution of NaOH (15% w/w aq., 20 mL) was added $NaBH_4$ (40 mg, 0.97 mmol) and *p*-thiocresol (4.00 g, 32.0 mmol) which was then stirred at RT for 3 hours. In another flask, a solution of butylated hydroxytoluene (BHT, 0.11 g, 0.48 mmol) and acryloyl chloride (3.9 mL, 48 mmol) in cyclohexane (30 mL) was cooled to 0 °C. The aqueous solution of *p*-thiocresol was added dropwise to the acyrolyol chloride solution and the reaction warmed to RT. The

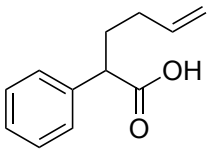
reaction was then heated to 55 °C for 35 min. After this time the reaction mixture was cooled to RT and extracted with Et_2O (80 mL). The combined organics were washed with brine solution (100 mL), then dried over $MgSO_4$. The crude was purified by column chromatography (1:49 Et_2O:hexane) to afford the title compound as a pale-yellow oil (2.90 g, 51% yield). **IR** (ATR): ν_{max}/cm^{-1} 3023, 2921, 1682, 1612, 1493, 1394, 1160, 1018, 986, 940, 806, 721, 528, 470; δ_H (400 MHz, $CDCl_3$) 7.35 – 7.32 (2H, m, Ar**H**), 7.25 – 7.23 (2H, m, Ar**H**), 6.46 (1H, dd, *J* = 17.2, 9.6 Hz, C**H**), 6.38 (1H, dd, *J* = 17.2, 1.6 Hz, C**H**H'), 5.76 (1H, dd, *J* = 9.6, 1.6 Hz, CH**H'**), 2.39 (3H, s, C$\mathbf{H}_3$); δ_C (100 MHz, $CDCl_3$) 189.1 (**C**O), 139.4 (**C**Ar), 134.7 (Ar**C**H), 134.5 (**C**H), 130.2 (Ar**C**H), 127.4 (**C**HH'), 123.7 (**C**Ar), 21.5 (**C**H_3). **HRMS (ESI)**: calcd. for $C_{10}H_{11}OS$, 179.0526. Found: $[MH]^+$, 179.0525 (−0.7 ppm error).

Methyl 2-phenylhex-5-enoate (96)



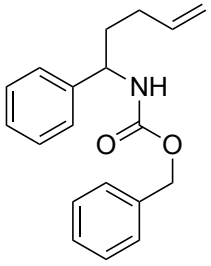
To a solution of LiHMDS (11 mL, 11.0 mmol) in dry THF (5.0 mL) at −78 °C under N_2 was added methyl 2-phenylacetate (1.4 mL, 10.0 mmol) in dry THF (5.0 mL) over 3 min and stirred at −78 °C for 45 min. 4-Bromo-1-butene (2.0 mL, 20.0 mmol) was added dropwise over 2 min at −78 °C and the reaction warmed to RT and stirred for 20 hours. The reaction was quenched with 1 M a.q. HCl (10 mL) and extracted with Et_2O (3 x 30 mL). The combined organics were washed with saturated brine solution (30 mL) and dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (1:49 ethyl acetate:hexane → 1:19 ethyl acetate:hexane) to afford the title compound as a colourless oil (1.10 g, 55% yield); R_f 0.54 (1:19 ethyl acetate:hexane). **IR** (ATR): ν_{max}/cm^{-1} 2951, 1734, 1161, 913, 734, 698, 512; δ_H (400 MHz, $CDCl_3$) 7.29 − 7.18 (5H, m, Ar**H**), 5.73 (1H, ddt, *J* = 16.9, 10.3, 6.5 Hz, C**H**), 4.99 – 4.93 (2H, m, C**HH'**), 3.61 (3H, s, C$\mathbf{H}_3$), 3.57 – 3.52 (1H, m, C**H**CAr), 2.19 – 2.10 (1H, m, C$\mathbf{H}_2$), 2.00 – 1.93 (2H, m, C$\mathbf{H}_2$), 1.87 – 1.79 (1H, m, C$\mathbf{H}_2$); δ_C (100 MHz, $CDCl_3$) 174.5 (**C**O), 139.0 (**C**Ar), 137.7 (**C**H), 128.8 (Ar**C**H), 128.1 (Ar**C**H), 127.4 (Ar**C**H), 115.5 (**C**HH'), 52.1 (**C**H_3), 50.8 (**C**HCAr), 32.6 (**C**H_2), 31.6 (**C**H_2). **HRMS (ESI)**: calcd. for $C_{13}H_{16}NaO_2$, 227.1049. Found: $[MNa]^+$, 227.1043 (−2.7 ppm error).

2-Phenyhex-5-enoic acid (97)



To a solution of methyl 2-phenylhex-5-enoate **96** (381.5 mg, 1.9 mmol) in MeOH (26 mL) was added NaOH (20% w/w, 6.5 mL) and the reaction heated to reflux while stirring overnight. Reaction was cooled to RT and diluted with H_2O (25 mL) and extracted with Et_2O (2 x 30 mL). The aqueous layer was acidified to pH 1 with 2M aq. HCl and then extracted with Et_2O (3 x 30 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the title compound as a colourless oil (318.4 mg, 90% yield); R_f 0.73 (1:9 ethyl acetate:hexane). **IR** (ATR): ν_{max}/cm^{-1} 2951, 1698, 910, 726, 696; δ_H (400 MHz, $CDCl_3$) 7.33 - 7.27 (5H, m, Ar**H**), 5.83 – 5.72 (1H, m, C**H**), 5.03 – 4.98 (2H, m, C**HH'**), 3.61 − 3.56 (1H, m, C**H**CAr), 2.23 – 2.14 (1H, m, C$\mathbf{H}_2$), 2.05 – 2.00 (2H, m, C$\mathbf{H}_2$), 1.93 – 1.84 (1H, m, C$\mathbf{H}_2$); δ_C (100 MHz, $CDCl_3$) 180.3 (**C**O), 138.3 (**C**Ar), 137.5 (**C**H), 128.8 (Ar**C**H), 128.3 (Ar**C**H), 127.6 (Ar**C**H), 115.7 (**C**HH'), 50.8 (**C**HCAr), 32.1 (**C**H_2), 31.5 (**C**H_2). **HRMS (ESI)**: calcd. for $C_{12}H_{14}NaO_2$, 213.0884. Found: $[MNa]^+$, 213.0886 (0.7 ppm error).

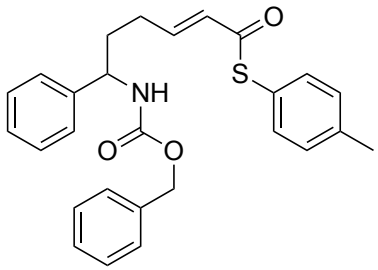
Benzyl (1-phenylpent-4-en-1-yl)carbamate (87)



To a solution of 2-phenyhex-5-enoic acid **97** (598 mg, 3.14 mmol) in dry toluene (10.5 mL) under N_2 was added DPPA (740 µL, 3.45 mmol) and Et_3N (530 µL, 3.77 mmol) and the reaction was stirred at 90 °C. After 2 hours, benzyl alcohol (490 µL, 4.71 mmol) was added and the reaction was stirred at 90 °C for 48 hours. The reaction was then quenched with H_2O (20 mL) and extracted with EtOAc (3 x 30 mL). The combined organics were washed with saturated brine solution (30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude was purified by column chromatography (1:9 ethyl acetate:hexane) to afford the title compound

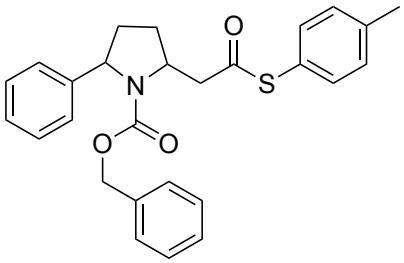
as a colourless oil (630 mg, 68% yield); R_f 0.21 (1:9 ethyl acetate:hexane). **IR** (ATR): υ_{max}/cm^{-1} 3321, 3064, 3031, 2938, 1692, 1530, 1454, 1243, 1044, 911, 748, 697; δ_H (400 MHz, $CDCl_3$) 7.36 – 7.27 (10H, m, Ar**H**), 5.85 – 5.75 (1H, m, C**H**), 5.10 (1H, d, *J* = 12.2 Hz, N**H**), 5.06 – 4.97 (4H, m, 2 x C**H**$_2$), 4.73 – 4.69 (1H, m, C**H**CAr), 2.11 – 1.98 (2H, m, C**H**$_2$), 1.95 – 1.80 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 155.8 (**C**O), 142.4 (**C**Ar), 137.6 (**C**H), 136.6 (**C**Ar), 128.8 (Ar**C**H), 128.7 (Ar**C**H), 128.3 (2 x Ar**C**H, overlapping), 127.6 (Ar**C**H), 126.5 (Ar**C**H), 115.5 (**C**HH'), 66.9 (O**C**H$_2$), 55.2 (**C**HCAr), 35.9 (**C**H$_2$), 30.4 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{19}H_{21}NNaO_2$, 318.1468. Found: $[MNa]^+$, 318.1464 (−1.2 ppm error).

_S_-(_p_-tolyl) (_E_)-6-(((benzyloxy)carbonyl)amino)-6-phenylhex-2-enethioate (90)



A solution of thioacrylic acid S-p-tolyl ester **89** (3.7 mg, 2.07 mmol) in 1,2-DCE (10 mL) was added under N_2 to a dry flask containing Hoveyda-Grubbs Catalyst™ 2nd generation (43.9 mg, 0.07 mmol) and copper iodide (131.8 mg, 0.69 mmol) while stirring. A solution of benzyl (1-phenylpent-4-en-1-yl) rac-**87** (203 mg, 0.69 mmol) in 1,2-DCE (10 mL) was added and the reaction mixture was stirred at 50 °C for 24 hours. The reaction was cooled to RT and then concentrated *in vacuo*. The crude was purified by column chromatography (1:9 ethyl acetate:hexane) to afford the title compound (249.5 mg, 81% yield) as a pale-yellow oil; R_f 0.07 (1:9 ethyl acetate:hexane). **IR** (ATR): υ_{max}/cm^{-1} 3331, 3030, 2946, 1690, 1631, 1526, 1454, 1242, 1044, 808, 699; δ_H (400 MHz, $CDCl_3$) 7.34 - 7.21 (14H, m, Ar**H**), 6.95 – 6.88 (1H, m, C**H**), 6.15 (1H, d, *J* = 15.5 Hz, C**H**), 5.12 (1H, d, *J* = 12.2 Hz, N**H**), 5.07 – 5.04 (2H, m, OC**H**$_2$), 4.74 – 4.65 (1H, m, C**H**), 2.30 – 2.13 (2H, m, C**H**$_2$), 2.05 (3H, s, C**H**$_3$), 2.03 – 1.79 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 188.5 (**C**O), 155.8 (**C**O), 144.9 (**C**H), 141.6 (**C**Ar), 139.8 (**C**Ar), 136.4 (**C**Ar), 134.7 (**C**H), 130.1 (Ar**C**H), 129.0 (Ar**C**H), 128.7 (Ar**C**H), 128.4 (Ar**C**H), 128.3 (2 x Ar**C**H, overlapping), 127.9 (Ar**C**H), 126.5 (Ar**C**H), 124.1 (**C**Ar), 67.0 (**C**H$_2$), 55.3 (**C**H), 34.9 (**C**H$_2$), 29.2 (**C**H$_2$), 21.4 (**C**H$_3$). **HRMS (ESI)**: calcd. for $C_{27}H_{27}NNaO_3S$, 468.1617. Found: $[MNa]^+$, 468.1604 (−2.9 ppm error).

Benzyl 2-(2-oxo-2-(*p*-tolylthio)ethyl)-5-phenylpyrrolidine-1-carboxylate (93)



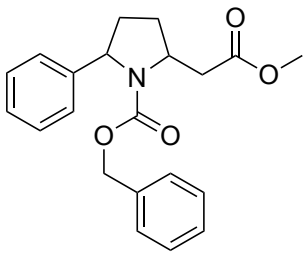
Racemic

A solution of *s*-(*p*-tolyl) (*E*)-6-(((benzyloxy)carbonyl)amino)-6-phenylhex-2-enethioate **90** (163 mg, 0.37 mmol) in 1,2-DCE (38 mL) was added to rac-CSA (255.2 mg, 1.10 mmol) under N_2 and the reaction heated to 60 °C for 24 hours. The reaction was quenched with saturated $NaHCO_3$ solution (35 mL) and extracted with DCM (3 x 35 mL). The combined organics were washed with saturated brine solution (35 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (1:9 ethyl acetate:hexane) to afford the title compound as a colourless oil (122.91 mg, 0.28 mmol, 75% yield); R_f 0.31 (1:9 ethyl acetate:hexane). **IR** (ATR): ν_{max}/cm^{-1} 3338, 3031, 2923, 2856, 1689, 1630, 1494, 1453, 1240, 1043, 996, 807, 754, 698. In solution in $CDCl_3$, the product exists as a roughly 1:2 mixture of diastereoisomers; δ_H (400 MHz, $CDCl_3$) 7.31 – 7.26 (6H, m, Ar**H**, both diastereoisomers), 7.24 – 7.22 (3H, m, Ar**H**, both diastereoisomers), 7.12 – 7.08 (3H, m, Ar**H**, both diastereoisomers), 6.81 – 6.79 (2H, m, Ar**H**, both diastereoisomers), 5.22 (1H, d, *J* = 12.4 Hz, C**H**H', minor diastereoisomer), 5.13 (1H, d, *J* = 12.4 Hz, CH**H**', minor diastereoisomer), 5.05 – 5.00 (2H, m, C**H** and C**H**H', both diastereoisomers), 4.90 (1H, d, *J* = 12.6 Hz, CH**H**', major diastereoisomer), 4.66 − 4.56 (1H, m, C**H**, both diastereoisomers), 3.47 (1H, dd, *J* = 14.8, 3.1 Hz, C$\mathbf{H}_2$, major diastereoisomer), 3.22 (1H, dd, *J* = 14.8, 2.7 Hz, C$\mathbf{H}_2$, minor diastereoisomer), 2.82 (1H, dd, *J* = 14.8, 9.7 Hz, C$\mathbf{H}_2$, major diastereoisomer), 2.73 (1H, dd, *J* = 14.8, 10.0 Hz, C$\mathbf{H}_2$, minor diastereoisomer), 2.39 – 2.38 (4H, m, C**H**H' and C$\mathbf{H}_3$, major diastereoisomer), 2.23 – 2.12 (1H, m, C$\mathbf{H}_2$, both diastereoisomers), 1.89 – 1.84 (1H, m, C$\mathbf{H}_2$, both diastereoisomers), 1.82 – 1.75 (1H, m, CH**H**', major diastereoiosomer). ^{13}C NMR data for the major diastereoisomer only; δ_C (100 MHz, $CDCl_3$) 196.1 (**C**O), 154.5 (**C**O), 144.2 (**C**Ar), 139.9 (**C**Ar), 136.6 (**C**Ar), 134.6 (Ar**C**H), 130.2 (Ar**C**H), 128.6 (Ar**C**H), 128.3 (Ar**C**H), 127.6 (Ar**C**H), 127.4 (Ar**C**H), 126.9 (Ar**C**H), 125.3 (Ar**C**H), 124.2 (**C**Ar), 66.7 (**C**H_2), 61.7 (**C**H), 56.1 (**C**H), 46.2 (**C**H_2), 32.7 (**C**H_2), 26.8 (**C**H_2), 21.5

(**C**H_3). **HRMS (ESI)**: calcd. for $C_{27}H_{27}NNaO_3S$, 468.1610. Found: $[MNa]^+$, 468.1604 (−1.3 ppm error).

Characteristic ^{13}C NMR data for the minor diastereoisomer can be found at; δ_C (100 MHz, $CDCl_3$) 195.9 (**C**O), 154.0 (**C**O), 143.1 (**C**Ar), 140.1 (**C**Ar), 136.7 (**C**Ar), 134.5 (Ar**C**H), 130.2 (Ar**C**H), 128.7 (Ar**C**H), 128.3 (Ar**C**H), 127.0 (Ar**C**H), 124.0 (**C**Ar), 67.2 (**C**H_2), 61.8 (**C**H), 55.4 (**C**H), 47.5 (**C**H_2), 31.7 (**C**H_2), 27.7 (**C**H_2) 21.5 (**C**H_3).

Benzyl 2-(2-methoxy-2-oxoethyl)-5-phenylpyrrolidine-1-carboxylate (111)

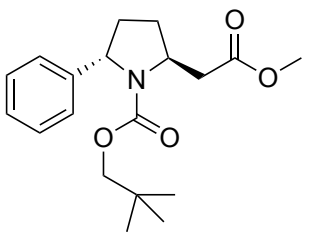


To a solution of pyrrolidine benzyl 2-(2-oxo-2-(*p*-tolylthio)ethyl)-5-phenylpyrolidine-1-carboxylate **93** (22.4 mg, 0.05 mmol) in dry MeOH:DCM (1:1, 0.8 mL) was added AgOTf (38.8 mg, 0.15 mmol) and the reaction was stirred for 3 hours at RT. The reaction was quenched with Et_2O (3 mL) and filtered through a silica plug followed by Et_2O. The combined filtrate was concentrated *in vacuo* and the crude was purified by column chromatography (1:4 ethylacetate:hexane) to afford the title compound as a pale-yellow oil (14.82 mg, 83% yield); R_f 0.18 (1:4 ethyl acetate:hexane). **IR** (ATR): ν_{max}/cm^{-1} 3030, 2951, 2925, 2853, 1735, 1698, 1405, 1348, 1307, 1164, 1114, 750, 699. In solution in $CDCl_3$, the product exists as a roughly 1:2 mixture of diastereoisomers; δ_H (400 MHz, $CDCl_3$) 7.31 – 7.23 (4H, m, Ar**H**, both diastereoisomers), 7.13 – 7.08 (4H, m, Ar**H**, both diastereoisomers), 6.79 (2H, d, *J* = 6.9 Hz, Ar**H**, both diastereoisomers), 5.19 – 5.12 (2H, m, C**H**$_2$, minor diastereoisomer), 5.06 – 5.00 (2H, m, C**H** and C**H**H', both diastereoisomers), 4.88 (1H, d, *J* = 12.7 Hz, CH**H'**, major diastereoisomer), 4.62 – 4.53 (1H, m, C**H**, both diastereoisomers), 3.70 (3H, s, C**H**$_3$, major diastereoisomer), 3.67 (3H, s, C**H**$_3$, minor diastereoisomer), 3.17 (1H, dd, *J* = 15.3, 3.4 Hz, C**H**$_2$, major diastereoisomer), 2.95 (1H, dd, *J* = 15.3, 2.9 Hz, C**H**$_2$, minor diastereoisomer), 2.46 – 2.31 (2H, m, C**H**$_2$, both diastereoisomers), 2.25 – 2.15 (1H, m, C**H**$_2$, both diastereoisomers), 1.81 – 1.72 (2H, m, C**H**$_2$, both diastereoisomers). ^{13}C NMR data for the major diastereoisomer

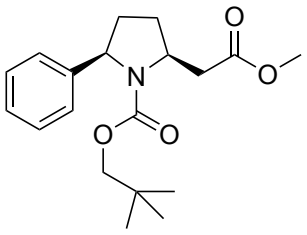
only; δ_C (100 MHz, $CDCl_3$) 172.0 (**C**O), 154.5 (**C**O), 144.3 (**C**Ar), 136.6 (**C**Ar), 128.6 (Ar**C**H), 128.2 (Ar**C**H), 127.6 (Ar**C**H), 127.4 (Ar**C**H), 126.9 (Ar**C**H), 125.3 (Ar**C**H), 66.7 (**C**H_2), 61.6 (**C**H), 55.6 (**C**H), 51.8 (**C**H_3), 37.7 (**C**H_2), 32.6 (**C**H_2), 27.2 (**C**H_2); **HRMS (ESI)**: calcd. for $C_{21}H_{23}NNaO_4$, 376.1521. Found: $[MNa]^+$, 376.1519 (−0.3 ppm error).

Characteristic ^{13}C NMR data for the minor diastereoisomer can be found at; δ_C (100 MHz, $CDCl_3$) 171.8 (**C**O), 154.1 (**C**O), 143.2 (**C**Ar), 136.8 (**C**Ar), 128.6 (Ar**C**H), 128.61 (Ar**C**H), 127.0 (Ar**C**H), 125.3 (Ar**C**H), 67.1 (**C**H_2), 61.8 (**C**H), 55.0 (**C**H), 51.8 (**C**H_3), 38.9 (**C**H_2), 31.7 (**C**H_2), 28.1 (**C**H_2).

***tert*-Butyl 2-(2-methoxy-2-oxoethyl)-5-phenylpyrrolidine-1-carboxylate (110)**



major diastereoisomer



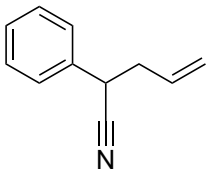
minor diastereoisomer

To a solution of benzyl 2-(2-methoxy-2-oxoethyl)-5-phenylpyrrolidine-1-carboxylate **111** (103.0 mg, 0.29 mmol) and 10 % Pd/C (106.40 mg) in MeOH (8.0 mL) was added $NaBH_4$ (11.0 mg, 0.29 mmol). The reaction was completed with 5−10 min (monitored by TLC) and filtered by EtOAc. Then the reaction was neutralised with 2 M aq. HCl, followed by saturated $NaHCO_3$ solution and extracted with EtOAc. The combined organics were washed with saturated brine solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude (the free amine) was used in the next step without purification. A solution of free amine (27.9 mg, 0.079 mmol) and Boc_2O (20.7 mg, 0.095 mmol) were dissolved in THF (0.5 mL). Et_3N (0.03 mL) in THF (0.2 mL) was then added at 0 °C over 1 min. The reaction allowed to warm to RT before being heated at 40 °C for 3 hours. The reaction was cooled to RT, quenched with H_2O (1.0 mL) and extracted with Et_2O (3 x 5 mL). The combined organics were washed with saturated brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (1:9 ethylacetate:hexane) to afford the title compound as a colourless oil (10.14 mg, 40% yield). **IR** (ATR): υ_{max}/cm^{-1} 2974, 1736, 1689, 1452, 1385,

1366, 1308, 1254, 1164, 1119, 1060, 910, 701. In solution in $CDCl_3$, the product exists as a roughly 1:2 mixture of diastereoisomers. NMR data for the major diastereoisomer only; δ_H (400 MHz, $CDCl_3$) 7.31 – 7.27 (3H, m, Ar**H**), 7.10 – 7.08 (2H, m, Ar**H**), 4.85 (1H, d, *J* = 8.2 Hz, C**H**), 4.57 – 4 .51 (1H, m, C**H**), 3.69 (3H, s, C**H**$_3$), 3.11 (1H, dd, *J* = 15.0, 3.5 Hz, C**H**$_2$), 2.43 – 2.28 (3H, m, C**H**$_2$), 2.24 – 2.10 (1H, m, C**H**$_2$), 1.78 – 1.69 (3H, m, C**H**$_2$), 1.13 (9H, s, 3 x C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 172.2 (**C**O), 154.0 (**C**O), 145.1 (**C**Ar), 128.3 (Ar**C**H), 126.7 (Ar**C**H), 125.3 (Ar**C**H), 79.6 (**C**CH$_3$), 61.9 (**C**H), 55.1 (**C**H), 51.8 (**C**H$_3$), 38.1 (**C**H$_2$), 32.5 (**C**H$_2$), 28.6 (**C**H$_2$), 28.2 (**C**H$_3$), 27.3 (**C**H$_2$); **HRMS (ESI)**: calcd. for $C_{18}H_{25}NNaO_4$, 342.1676. Found: $[MNa]^+$, 342.1676 (−0.0 ppm error).

Characteristic NMR data for the minor diastereoisomer can be found at; δ_H (400 MHz, $CDCl_3$) 7.22 – 7.15 (5H, m, Ar**H**), 4.99 (1H, d, *J* = 8.2 Hz, C**H**), 4.45 – 4.40 (1H, m, C**H**), 3.71 (3H, s, C**H**$_3$), 2.98 (1H, dd, *J* = 15.2 2.6 Hz, C**H**$_2$), 2.24 – 2.09 (4H, m, 2 x C**H**$_2$), 1.46 (9H, s, 3 x C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 172.1 (**C**O), 153.6 (**C**O), 143.7 (**C**Ar), 128.5 (Ar**C**H), 126.8 (Ar**C**H), 125.1 (Ar**C**H), 80.1 (**C**CH$_3$), 61.2 (**C**H), 55.1 (**C**H), 51.8 (**C**H$_3$), 38.9 (**C**H$_2$), 31.8 (**C**H$_2$), 29.8 (**C**H$_2$), 28.6 (**C**H$_3$), 27.9 (**C**H$_2$).

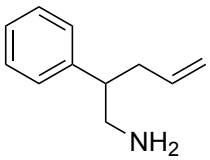
2-Phenylpent-4-enenitrile (116)



To a solution of diisopropylamine (1.3 mL, 8.54 mmol) in dry THF (5.0 mL) at −78 °C under N_2 was added n-BuLi (2.08 M in hexane, 9.39 mmol) and the solution stirred for 45 min. A solution of phenylacetonitrile (1.0 mL, 8.54 mmol) in dry THF (3.5 mL) was added over 3 min at −78 °C and the reaction stirred for 45 min. Allyl bromide (0.7 mL, 8.54 mmol) was added over 2 min at −78 °C and the reaction warmed to RT. The reaction was stirred overnight and quenched with 1 M HCl (10 mL) and extracted with Et_2O (3 x 15 mL). The combined organics were washed with saturated brine solution (15 mL) and dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (1:49 ethyl acetate:hexane) to afford the title compound as a colourless oil (574 mg, 43% yield); R_f 0.33

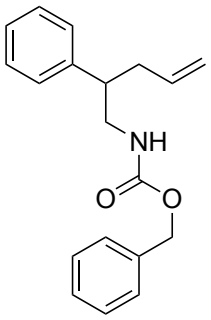
(1:49 ethyl acetate:hexane). **IR** (ATR): ν_{max}/cm^{-1} 3072, 2913, 2241, 1643, 1495, 994, 925, 754, 698, 622, 511; δ_H (400 MHz, $CDCl_3$) 7.41 – 7.31 (5H, m, Ar**H**), 5.86 – 5.75 (1H, m, C**H**), 5.22 – 5.17 (2H, m, C**HH'**), 3.86 (1H, dd, *J* = 7.9, 6.6 Hz, CC**H**), 2.67 – 2.62 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 135.3 (**C**Ar), 132.7 (**C**H), 129.2 (Ar**C**H), 128.3 (Ar**C**H), 127.5 (Ar**C**H), 120.4 (**C**N), 119.5 (**C**HH'), 40.0 (**C**H_2), 37.6 (C**C**H). **HRMS (APCI)**: calcd. for $C_{11}H_{12}N$, 158.095694. Found: $[MH]^+$, 158.096426 (4.6 ppm error).

2-Phenylpent-4-en-1-amine (117)



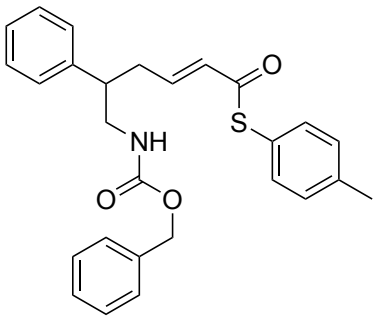
To a solution of 2-phenylpent-4-enenitrile **116** (570 mg, 3.63 mmol) in dry diethyl ether (10 mL) at 0 °C under N_2 was added $LiAlH_4$ (210 mg, 5.53 mmol) in dry diethyl ether (10 mL) over 5 min and the solution stirred at 0 °C for 30 min. The reaction was then warmed to RT and stirred overnight. The reaction was cooled to 0 °C and quenched with H_2O (0.2 mL), followed by NaOH solution (15% w/w aq, 0.2 mL), followed by H_2O (0.6 mL). The solution was filtered through a pad of Celite and concentrated *in vacuo* to afford the title compound as a colourless oil (574 mg, 94% yield); R_f 0.18 (1:19 ethyl acetate:hexane). **IR** (ATR): ν_{max}/cm^{-1} 3063, 3027, 2920, 2241, 1639, 1493, 1452, 994, 991, 759, 699, 648, 543; δ_H (400 MHz, $CDCl_3$) 7.34 – 7.17 (5H, m, Ar**H**), 5.74 – 5.64 (1H, m, C**H**), 5.02 – 4.92 (2H, m, C**HH'**), 2.96 (1H, dd, *J* = 12.7, 5.2 Hz, C**H**$_2$), 2.85 (1H, dd, *J* = 12.7, 8.7 Hz, C**H**$_2$), 2.72 – 2.64 (1H, m, C**H**), 2.45 – 2.32 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 143.1 (**C**Ar), 136.7 (**C**H), 128.6 (Ar**C**H), 128.1 (Ar**C**H), 126.6 (Ar**C**H), 116.2 (**C**HH'), 49.5 (C**C**H), 47.5 (**C**H_2), 38.4 (**C**H_2). **HRMS (APCI)**: calcd. for $C_{11}H_{16}N$, 162.1279. Found: $[MH]^+$, 162.1277 (−0.8 ppm error).

Benzyl (2-phenylpent-4-en-1-yl)carbamate (88)



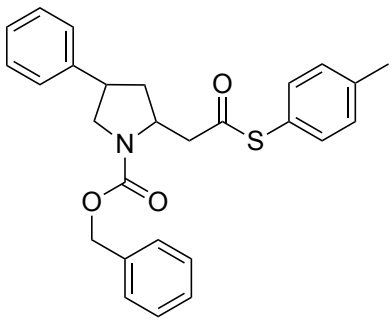
A solution 2-phenylpent-4-en-1-amine **117** (510 mg, 3.16 mmol) in 1,4-dioxane (15 mL) was treated with K_2CO_3 solution (520 mg, 3.79 mmol), followed by benzyl chloroformate (650 mg, 3.79 mmol) and the reaction was stirred for 3 hours at RT. The reaction was then quenched with H_2O (20 mL) and extracted with DCM (3 x 20 mL). The combined organics were washed with saturated brine solution (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude was purified by column chromatography (1:19 ethyl acetate:hexane) to afford the title compound as a yellow oil (560 mg, 60% yield); R_f 0.30 (1:4 ethyl acetate:hexane). **IR** (ATR): υ_{max}/cm^{-1} 3336, 3030, 2927, 1702, 1516, 1453, 1294, 1140, 997, 914, 755, 699; δ_H (400 MHz, $CDCl_3$) 7.38 – 7.15 (10H, m, Ar**H**), 5.73 – 5.63 (1H, m, C**H**), 5.01 – 4.95 (4H, m, 2 x C**H**$_2$), 4.60 (1H, s, N**H**), 3.67 – 3.53 (1H, m, C**H**$_2$), 3.25 (1H, ddd, *J* = 13.7, 9.1, 4.6 Hz, C**H**), 2.91 – 2.77 (1H, m, C**H**$_2$), 2.45 – 2.33 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 156.4 (**C**O), 142.1 (**C**Ar), 136.6 (**C**H), 135.9 (**C**Ar), 128.8 (Ar**C**H), 128.6 (Ar**C**H), 128.2 (2 x Ar**C**H, overlapping), 127.9 (Ar**C**H), 127.0 (Ar**C**H), 116.8 (**C**HH'), 66.7 (O**C**H$_2$), 46.1 (**C**H$_2$), 45.8 (**C**H), 38.2 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{19}H_{21}NNaO_2$, 318.1469. Found: $[MNa]^+$, 318.1464 (−1.3 ppm error).

***S*-(*p*-Tolyl) (*E*)-6-(((benzyloxy)carbonyl)amino)-5-phenylhex-2-enethioate (91)**



A solution of thioacrylic acid s-tolyl ester **89** (781.6 mg, 4.39 mmol) in 1,2-DCE (10 mL) was added under N_2 to a dry flask containing Hoveyda-Grubbs Catalyst^{TM} 2nd generation (91.6 mg, 0.15 mmol) and copper iodide (278.4 mg, 1.46 mmol) while stirring. A solution of benzyl (2-phenylpent-4-en-1-yl)carbamate **88** (431.7 mg, 1.46 mmol) in 1,2-DCE (10 mL) was added and the reaction was stirred at 50 °C for 24 hours. The reaction was cooled to RT and then concentrated *in vacuo*. The crude was purified by column chromatography (1:9 ethyl acetate:hexane) to afford the title compound (490.5 mg, 75% yield) as a pale-yellow oil; R_f 0.07 (1:9 ethyl acetate:hexane). **IR** (ATR): υ_{max}/cm^{-1} 3030, 2252, 1712, 1514, 1494, 1243, 1017, 904, 808, 726, 648; δ_H (400 MHz, $CDCl_3$) 7.35 – 7.14 (14H, m, Ar**H**), 6.82 – 6.75 (1H, m, C**H**), 6.12 (1H, d, *J* = 15.5, Hz, C**H**), 5.14 – 5.04 (2H, m, C**H**$_2$), 4.63 – 4.58 (1H, m, N**H**), 3.65 – 3.53 (1H, m, C**H**H'), 3.30 (1H, ddd, *J* = 13.6, 7.9, 5.0 Hz, CH**H**'), 3.02 – 2.91 (1H, m, C**H**), 2.63 – 2.49 (2H, m, C**H**$_2$), 2.37 (3H, s, C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 188.4 (**C**O), 156.4 (**C**O), 143.2 (**C**H), 140.9 (**C**Ar), 139.7 (**C**Ar), 136.9 (**C**Ar), 135.4 (**C**H), 130.1 (Ar**C**H), 129.5 (Ar**C**H), 129.1 (Ar**C**H), 128.7 (Ar**C**H), 128.3 (Ar**C**H), 128.2 (Ar**C**H), 127.8 (Ar**C**H) 127.4 (Ar**C**H), 124.0 (**C**Ar), 66.9 (**C**H$_2$), 46.2 (**C**H$_2$), 45.3 (**C**H), 36.5 (**C**H$_2$), 21.4 (**C**H$_3$). **HRMS (ESI)**: calcd. for $C_{27}H_{27}NNaO_3S$, 468.1610. Found: $[MNa]^+$, 468.1604 (−1.3 ppm error).

Benzyl 2-(2-oxo-2-(*p*-tolylthio)ethyl)-4-phenylpyrrolidine-1-carboxylate (94)



Racemic-CSA

The title compound **94** was synthesis using same procedure as benzyl 2-(2-oxo-2-(*p*-tolylthio)ethyl)-5-phenylpyrrolidine-1-carboxylate **93** with s-(*p*-toly) (*E*)-6-(((benzyloxy)carbonyl)amino)-6-phenylex-2-enethioate **90** (87.7 mg, 0.20 mmol) and rac-CSA (137.2 mg, 0.59 mmol) in 1,2-DCE (21 mL) and the reaction was heated to 60 °C for 24 hours. The crude was purified by column chromatography (1:9 ethyl acetate:hexane) to afford the title compound as a colourless oil (76.04 mg, 87% yield).

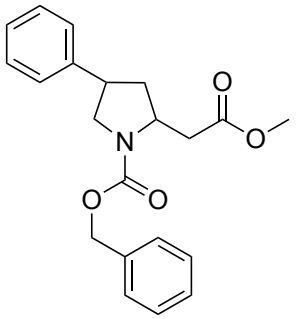
Asymmetric – (R)-TRIP, 50°C

The title compound **94** was synthesis using same procedure as benzyl 2-(2-oxo-2-(*p*-tolylthio)ethyl)-5-phenylpyrrolidine-1-carboxylate **93** with s-(*p*-toly) (*E*)-6-(((benzyloxy)carbonyl)amino)-6-phenylex-2-enethioate **90** (25.7 mg, 0.06 mmol,) and (R)-TRIP (8.04 mg, 0.01 mmol) in cyclohexane (0.02M) and the reaction was heated to 50 °C for 24 hours. The crude was purified by column chromatography (1:9 ethyl acetate:hexane) to afford the title compound as a colourless oil (17.04 mg, 68% yield).

Asymmetric – (R)-TRIP, 80°C

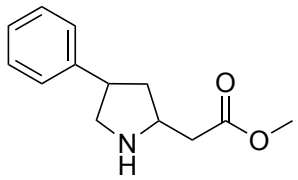
The title compound **94** was synthesised using the same procedure as the (R)-TRIP conditions with s-(*p*-toly) (*E*)-6-(((benzyloxy)carbonyl)amino)-6-phenylex-2-enethioate **90** (25.96 mg, 0.06 mmol) and (R)-TRIP (8.04 mg, 0.01 mmol) in cyclohexane (0.02M) and the reaction was heated to 80 °C for 24 hours. The crude was purified by column chromatography (1:9 ethyl acetate:hexane) to afford the title compound as a colourless oil (23.19 mg, 93% yield). R_f 0.40 (1:4 ethyl acetate:hexane). **IR** (ATR): ν_{max}/cm^{-1} 3030, 2922, 2854, 1702, 1454, 1413, 1355, 1108, 989, 807, 756, 698; δ_H (400 MHz, $CDCl_3$) 7.43 – 7.27 (9H, m, Ar**H**), 7.24 – 7.21 (5H, m, Ar**H**), 5.23 – 5.18 (2H, m, C**H**$_2$), 4.35 – 4.28 (1H, m, C**H**), 4.19 – 4.06 (1H, m, C**H**H'), 3.62 – 3.41 (1H, m, C**H**$_2$), 3.36 – 3.25 (2H, m, CH**H'** and C**H**), 3.04 – 2.83 (1H, m, C**H**$_2$), 2.69 – 2.63 (1H, m, C**H**$_2$), 2.38 (3H, s, C**H**$_3$), 2.09 – 1.97 (1H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 196.1 (**C**O), 154.9 (**C**O), 140.1 (**C**Ar), 139.9 (**C**Ar), 136.8 (**C**Ar), 134.6 (**C**Ar), 134.58 (Ar**C**H), 130.2 (Ar**C**H), 128.8 (Ar**C**H), 128.7 (Ar**C**H), 128.1 (Ar**C**H), 127.3 (Ar**C**H), 127.2 (Ar**C**H), 127.1 (Ar**C**H), 67.0 (**C**H$_2$), 55.7 (**C**H), 53.2 (**C**H$_2$), 47.2 (**C**H$_2$), 43.1 (**C**H), 39.1 (**C**H$_2$), 21.5 (**C**H$_3$). **HRMS (ESI)**: calcd. for $C_{27}H_{27}NNaO_3S$, 468.1613. Found: $[MNa]^+$, 468.1604 (−1.9 ppm error).

Benzyl 2-(2-methoxy-2-oxoethyl)-4-phenylpyrrolidine-1-carboxylate (117)



To a solution of benzyl 2-(2-oxo-2-(*p*-tolylthio)ethyl)-4-phenylpyrrolidine-1-carboxylate **94** (96.5 mg, 0.22 mmol) in dry MeOH:DCM (1:1, 3.5 mL) was added AgOTf (166.9 mg, 0.65 mmol) and the reaction was stirred for 3 hours at RT. The reaction was quenched with Et_2O (5 mL) and filtered through a silica plug followed by Et_2O. The combined filtrate was concentrated *in vacuo* and the crude was purified by column chromatography (1:4 ethylacetate:hexane) to afford the title compound as a pale-yellow oil (58.95 mg, 78% yield). R_f 0.32 (1:4 ethyl acetate:hexane). **IR** (ATR): ν_{max}/cm^{-1} 3031, 2951, 2920, 1734, 1696, 1411, 1355, 1197, 1153, 1100, 756, 734, 697, 604; δ_H (400 MHz, $CDCl_3$) 7.37 – 7.30 (8H, m, Ar**H**), 7.25 – 7.23 (2H, m, Ar**H**), 5.18 – 5.14 (2H, m, C**H**$_2$), 4.30 – 4.23 (1H, m, C**H**), 4.18 – 4.05 (1H, m, C**H**$_2$), 3.68 – 3.64 (3H, m, C**H**$_3$), 3.37 – 3.22 (2H, m, C**H**H' and C**H**), 2.69 – 2.48 (2H, m, CH**H'** and C**H**$_2$), 1.99 – 1.87 (1H, m, C**H**$_2$), 1.29 – 1.25 (1H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 172.0 (**C**O), 154.8 (**C**O), 140.2 (**C**Ar), 136.8 (**C**Ar), 128.7 (Ar**C**H), 128.6 (Ar**C**H), 128.1 (Ar**C**H), 128.0 (Ar**C**H), 127.3 (Ar**C**H), 127.1 (Ar**C**H), 66.6 (**C**H$_2$), 55.1 (**C**H), 53.2 (**C**H$_2$), 51.7 (**C**H$_3$), 43.1 (**C**H), 38.6 (**C**H$_2$), 29.8 (**C**H$_2$); **HRMS (ESI)**: calcd. for $C_{21}H_{23}NNaO_4$, 376.1524. Found: $[MNa]^+$, 376.1519 (−1.2 ppm error).

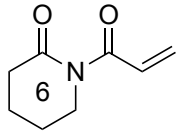
Methyl 2-(4-phenylpyrrolidin-2-yl)acetate (118)



To a solution of benzyl 2-(2-methoxy-2-oxoethyl)-4-phenylpyrrolidine-1-carboxylate **xx** (103.0 mg, 0.29 mmol) and 10 % Pd/C (106.4 mg) in MeOH (8.0 mL) was added $NaBH_4$ (11.0 mg, 0.29 mmol). The reaction was completed with 5−10 min (monitored by TLC) and filtered by EtOAc. Then the reaction mixture was neutralized with 2 M aq. HCl, followed by saturated $NaHCO_3$ solution and extracted with EtOAc. The combined organics were washed with saturated brine solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. R_f 0.40 (1:4 ethyl acetate:hexane). **IR** (ATR): ν_{max}/cm^{-1} 3031, 2951, 2920, 1734, 1696, 1411, 1355, 1153, 1100, 807, 756; δ_H (400 MHz, $CDCl_3$) 7.31 – 7.23 (5H, m, Ar**H**), 5.31 – 5.24 (1H, m, N**H**), 3.87 – 3.80 (1H, m, C**H**), 3.69 (3H, s, C**H**$_3$), 3.56 – 3.49 (1H, m, C**H**$_2$), 3.43 – 3.34 (1H, m, C**H**), 3.15 – 3.09 (1H, m, C**H**$_2$), 2.85 – 2.63 (2H, m, C**H**$_2$), 2.52 – 2.43 (1H, m, C**H**$_2$), 1.74 – 1.65 (1H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 172.2 (**C**O), 141.8 (**C**Ar), 128.8 (Ar**C**H), 127.3 (Ar**C**H), 126.9 (Ar**C**H), 55.9 (**C**H),

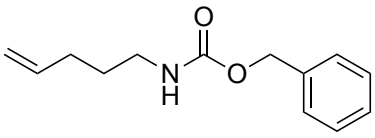
52.8 (**C**H_2), 52.0 (**C**H_3), 45.0 (**C**H), 40.2 (**C**H_2), 39.3 (**C**H_2); **HRMS (ESI)**: calcd. for $C_{13}H_{18}NO_2$, 220.1332. Found: $[MH]^+$, 220.1332 (−0.1 ppm error).

1-Acryloyl -piperidin-2-one (238)



A solution of δ-valerolactam (1.02 mg, 10.3 mmol) in dry THF (36.5 mL) was cooled to 0 °C and a solution of MeMgBr (3M in diethyl ether, 3.65 mL, 11.0 mmol) was added using a syringe pump over 15 min. The reaction was stirred for 10 min at 0 °C, then acryloyl chloride (1.3 mL, 15.5 mmol) was added and the reaction was stirred 30 min at 0 °C. The reaction was quenched with saturated aq. NH_4Cl solution (30 mL) and extracted with Et_2O (3 x 35 mL). The combined organics were washed with saturated $NaHCO_3$ solution (2 x 30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (1:1 diethyl ether:hexane) to afford the title compound as a pale-yellow liquid (1.2 g, 72% yield); R_f 0.40 (1:1 diethyl ether:hexane). **IR** (ATR): ν_{max}/cm^{-1} 2953, 1678, 1403, 1384, 1289, 1209, 1155, 1003, 796, 607; δ_H (400 MHz, $CDCl_3$) 6.96 (1H, dd, *J* = 16.9, 10.4 Hz, COC**H**), 6.33 – 6.29 (1H, m, C**H**H'), 5.70 – 5.66 (1H, m, CH**H'**), 3.74 – 3.71 (2H, m, C**H**$_2$), 2.57 – 2.53 (2H, m, C**H**$_2$), 1.86 – 1.83 (4H, m, 2 x C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 173.8 (**C**O), 169.7 (**C**OCH), 132.0 (CO**C**H), 128.0 (**C**HH'), 44.7 (**C**H_2), 34.9 (**C**H_2), 22.6 (**C**H_2), 20.8 (**C**H_2); **HRMS (ESI)**: calcd. for $C_8H_{11}NNaO_2$, 176.0682. Found: $[MNa]^+$, 176.0682 (−0.1 ppm error).

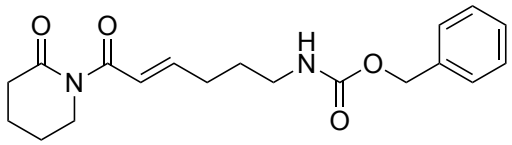
Benzyl pent-4-en-1-ylcarbamate (246)



To a solution of 5-hexenoic acid (716 mg, 6.27 mmol) in dry toluene (21 mL) under N_2 was added DPPA (1.49 mL, 6.90 mmol) and Et_3N (1.0 mL, 7.52 mmol) and the reaction was stirred at 90 °C. After 2 hours, benzyl alcohol (0.97 mL, 9.41 mmol) was added, and the reaction was stirred at 90 °C for 48 hours. The reaction was then quenched with H_2O (50 mL) and extracted

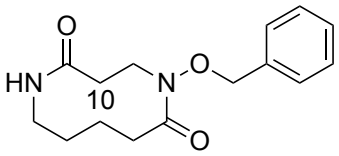
with EtOAc (3 x 40 mL). The combined organics were washed with saturated brine solution (50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo.* The crude was purified by flash column chromatography (1:9 ethyl acetate:hexane) to afford the title compound as a colourless oil (1.06 g, 77% yield); R_f 0.21 (1:9 ethyl acetate:hexane). **IR** (ATR): ν_{max}/cm^{-1} 3331, 3067, 3034, 2935, 1696, 1528, 1454, 1415, 1252, 1136, 1041, 995, 735, 696; δ_H (400 MHz, $CDCl_3$) 7.37 – 7.29 (5H, m, Ar**H**), 5.85 – 5.74 (1H, m, C**H**), 5.15 – 5.10 (2H, m, C**H**$_2$), 5.06 – 4.97 (2H, m, C**HH'**), 4.77 (1H, s, N**H**), 3.24 – 3.19 (2H, m, C**H**$_2$), 2.11 – 2.06 (2H, m, C**H**$_2$), 1.64 – 1.57 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 156.5 (**C**O), 137.8 (**C**H), 136.8 (**C**Ar), 128.7 (Ar**C**H), 128.3 (Ar**C**H), 128.2 (Ar**C**H), 115.4 (**C**HH'), 66.8 (**C**H$_2$), 40.7 (**C**H$_2$), 31.0 (**C**H$_2$), 29.2 (**C**H$_2$); **HRMS (ESI)**: calcd. for $C_{13}H_{17}NNaO_2$, 242.1151. Found: $[MNa]^+$, 242.1151 (0.0 ppm error).

Benzyl (E)-(6-oxo-6-(2-oxopiperidin-1-yl)hex-4-en-1-yl)carbamate



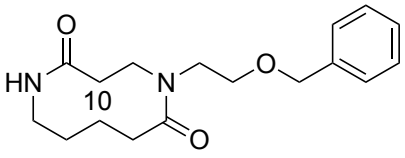
A solution of benzyl pent-4-en-1-yl carbamate **246** (350.9 mg, 1.6 mmol) in 1,2-DCE (4.0 mL) was added under N_2 to a dry flask containing Hoveyda-Grubbs Catalyst™ 2nd generation (50.1 mg, 0.08 mmol) while stirring. A solution of 1-acryloyl -piperidin-2-one **238** (490 mg, 3.2 mmol) in 1,2-DCE (4.0 mL) was added and the reaction was stirred at 50 °C for 24 hours. The reaction was cooled to RT and then concentrated *in vacuo*. The crude was purified by column chromatography (1:4 ethyl acetate:hexane → 1:1 ethyl acetate:hexane) to afford the title compound (12.9 mg, 2% yield). **IR** (ATR): ν_{max}/cm^{-1} 3346, 2925, 1694, 1674, 1527, 1454, 1385, 1342, 1330, 1289, 1245, 1207, 1152, 1024, 973, 698; δ_H (400 MHz, $CDCl_3$) 7.35 – 7.29 (5H, m, Ar**H**), 6.91 – 6.84 (1H, m, C**H**), 6.73 (1H, d, *J* = 15.4 Hz, C**H**), 5.13 - 5.07 (2H, m, C**H**$_2$), 4.91 (1H, s, N**H**), 3.72 – 3.69 (2H, m, C**H**$_2$), 3.24 – 3.20 (2H, m, C**H**$_2$), 2.56 – 2.52 (2H, m, C**H**$_2$), 2.30 – 2.24 (2H, m, C**H**$_2$), 1.87 – 1.82 (4H, m, 2 x C**H**$_2$), 1.73 – 1.66 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 173.9 (**C**O), 169.6 (**C**O), 156.5 (**C**O), 146.0 (**C**H), 136.7 (**C**Ar), 128.6 (Ar**C**H), 128.2 (2 x Ar**C**H, overlapping), 126.0 (**C**H), 66.7 (**C**H$_2$), 44.6 (**C**H$_2$), 40.6 (**C**H$_2$), 34.9 (**C**H$_2$), 29.7 (**C**H$_2$), 28.4 (**C**H$_2$), 22.6 (**C**H$_2$), 20.8 (**C**H$_2$); **HRMS (ESI)**: calcd. for $C_{19}H_{24}N_2NaO_4$, 367.1624. Found: $[MNa]^+$, 367.1624 (1.1 ppm error).

5-(Benzyloxy)-1,5-diazecane-2,6-dione (261)



To a solution of 1-acryloyl-piperidin-2-one **238** (153 mg, 1.00 mmol) in dry methanol (2.0 mL) was added benzyl-o-hydroxylamine (130 µL, 1.1 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate) to afford the title compound as a white solid (175 mg, 63% yield). In solution in $CDCl_3$, some evidence of rotameric broadening in the ^{1}H NMR data, with trace (<10%) signals for a minor rotamer; m.p. 115–117 °C; R_f 0.48 (1:9 methanol:ethyl acetate); **IR** (ATR): υ_{max}/ cm^{-1} 3313, 2930, 2871, 2240, 1650, 1531, 1441, 1379, 1312, 1175, 992, 909, 728, 699, 509; δ_H (400 MHz, $CDCl_3$) 7.38 – 7.36 (5H, m, Ar**H**), 5.55 (1H, d, *J* = 6.6 Hz, N**H**), 4.83 (2H, s, C**H**$_2$), 4.73 – 4.65 (1H , m, C**H**$_2$), 3.53 – 3.46 (1H, m, C**H**$_2$), 3.20 – 3.16 (1H, m, C**H**$_2$), 2.98 – 2.95 (1H, m, C**H**$_2$), 2.90 – 2.84 (1H, m, C**H**$_2$), 2.58 (1H, app td, *J* = 12.6, 5.5 Hz, C**H**$_2$), 2.20 – 2.16 (1H, m, C**H**$_2$), 2.07 – 1.89 (2H, m, C**H**$_2$), 1.85 – 1.72 (2H, m, C**H**$_2$), 1.44 – 1.35 (1H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 178.8 (**C**O), 170.1 (**C**O), 134.4 (**C**Ar), 129.7 (Ar**C**H), 129.3 (Ar**C**H), 128.9 (Ar**C**H), 77.4 (**C**H$_2$), 45.3 (**C**H$_2$), 39.9 (**C**H$_2$), 34.5 (**C**H$_2$), 31.6 (**C**H$_2$), 27.8 (**C**H$_2$), 23.5 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{15}H_{20}N_2NaO_3$ 299.1365. Found [MNa]$^+$ 299.1366 (0.3 ppm error).

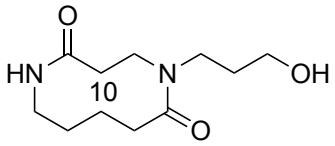
5-(2-(Benzyloxy)ethyl)-1,5-diazecane-2,6-dione (266)



To a solution of 1-acryloyl-piperidin-2-one **238** (153 mg, 1.00 mmol) in dry methanol (2.0 mL) was added 2-(benzyloxy)-1-ethanamine (100 µL, 1.10 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate) to afford the title compound as a white solid (127 mg, 42% yield); m.p. 108−110 °C; R_f 0.26 (1:19 methanol:ethyl acetate). **IR** (ATR): υ_{max}/cm^{-1} 3301, 2929, 2859, 1616, 1556, 1454, 1353, 1208, 1162, 1096,

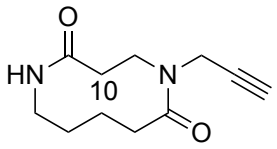
1082, 1014, 734, 698; δ_H (400 MHz, $CDCl_3$) 7.35 – 7.27 (5H, m, Ar**H**), 6.37 (1H, d, *J* = 10.2 Hz, N**H**), 4.57 – 4.50 (2H, m, C**H**$_2$), 4.25 – 4.12 (2H , m, C**H**$_2$), 3.98 – 3.91 (1H, m, C**H**$_2$), 3.69 – 3.60 (1H , m, C**H**$_2$), 3.56 – 3.51 (1H, m, C**H**$_2$), 3.20 – 3.14 (1H, m, C**H**$_2$), 3.01 – 2.94 (1H, m, C**H**$_2$), 2.53 – 2.50 (1H, m, C**H**$_2$), 2.49 – 2.45 (2H, m, C**H**$_2$), 2.15 – 2.11 (1H, m, C**H**$_2$), 2.09 – 1.97 (2H, m, C**H**$_2$), 1.57 – 1.48 (2H, m, C**H**$_2$), 1.23 – 1.12 (1H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 174.5 (**C**O), 171.0 (**C**O), 136.8 (**C**Ar), 128.8 (Ar**C**H), 128.5 (2 x Ar**C**H, overlapping), 73.8 (**C**H_2), 67.0 (**C**H_2), 49.4 (**C**H_2), 48.3 (**C**H_2), 38.6 (**C**H_2), 37.5 (**C**H_2), 28.7 (**C**H_2), 26.2 (**C**H_2), 24.7 (**C**H_2). **HRMS (ESI)**: calcd. for $C_{17}H_{24}N_2NaO_3$, 327.1678. Found: $[MNa]^+$, 327.1679 (0.3 ppm error).

5-(3-Hydroxypropyl)-1,5-diazecane-2,6-dione (267)



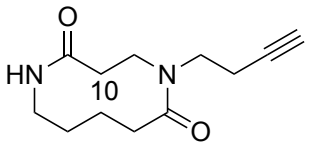
To a solution of 1-acryloyl-piperidin-2-one **238** (77 mg, 0.50 mmol) in dry methanol (1.0 mL) was added 3-aminopropan-1-ol (50 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a white solid (66 mg, 58% yield); m.p. 117−120 °C; R_f 0.46 (2:3 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3286, 2930, 2860, 2236, 1609, 1176, 1060, 1040, 921, 813, 729. δ_H (400 MHz, $CDCl_3$) 5.81 (1H, d, *J* = 9.5 Hz, N**H**), 4.03 – 3.90 (2H, m, C**H**$_2$), 3.87 – 3.78 (1H, m, C**H**$_2$), 3.63 – 3.47 (2H , m, C**H**$_2$), 3.31 – 3.25 (1H , m, C**H**$_2$), 3.15 – 3.09 (1H, m, C**H**$_2$), 2.93 – 2.89 (1H, m, C**H**$_2$), 2.69 – 2.61 (1H, m, C**H**$_2$), 2.36 – 2.31 (2H , m, C**H**$_2$), 2.15 – 2.05 (2H, m, C**H**$_2$), 1.84 – 1.58 (4H, m, 2 x C**H**$_2$), 1.48 – 1.39 (1H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 175.7 (**C**O), 170.9 (**C**O), 59.0 (**C**H_2), 45.6 (**C**H_2), 43.0 (**C**H_2), 39.3 (**C**H_2), 38.1 (**C**H_2), 30.5 (**C**H_2), 28.4 (**C**H_2), 25.9 (**C**H_2), 23.7 (**C**H_2). **HRMS (ESI)**: calcd. for $C_{11}H_{20}N_2NaO_3$, 251.1364. Found: $[MNa]^+$, 251.1366 (0.7 ppm error).

5-(Prop-2-yn-1-yl)-1,5-diazecane-2,6-dione (268)



To a solution of 1-acryloyl-piperidin-2-one **238** (77 mg, 0.50 mmol) in dry methanol (1.0 mL) was added propargylamine (40 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a colourless oil (73 mg, 70% yield); R_f 0.45 (1:9 methanol:ethyl acetate); **IR** (ATR): υ_{max}/cm^{-1} 3290, 3096, 2932, 2857, 2242, 1621, 1558, 1442, 1456, 1350, 1205, 1178, 1110, 729; δ_H (400 MHz, $CDCl_3$) 5.65 – 5.63 (1H, m, N**H**), 4.68 (1H, d, *J* = 17.1 Hz, C**H**$_2$), 4.10 – 4.03 (1H, m, C**H**$_2$), 3.90 – 3.79 (2H, m, C**H**$_2$), 3.51 – 3.47 (1H, m, C**H**$_2$), 2.92 – 2.89 (1H, m, C**H**$_2$), 2.75 – 2.59 (2H, m, C**H**$_2$), 2.35 – 2.29 (2H, m, C**H** and C**H**H'), 2.16 – 2.09 (2H, m, C**H**$_2$), 1.73 – 1.60 (2H, m, C**H**$_2$), 1.55 – 1.45 (1H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 173.8 (**C**O), 171.0 (**C**O), 80.9 (**C**CH), 72.4 (**C**H), 47.4 (**C**H$_2$), 39.4 (**C**H$_2$), 37.8 (**C**H$_2$), 36.7 (**C**H$_2$), 28.3 (**C**H$_2$), 25.7 (**C**H$_2$), 24.0 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{11}H_{16}N_2NaO_2$, 231.1109. Found $[MNa]^+$ 231.1104 (−2.1 ppm error).

5-(But-3-yn-1-yl)-1,5-diazecane-2,6-dione (269)

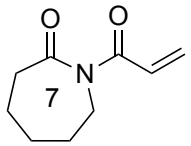


To a solution of 1-acryloyl-piperidin-2-one **238** (77 mg, 0.50 mmol) in dry methanol (1.00 mL) was added but-3-yn-1-amine (50 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a white solid (54 mg, 49% yield); m.p. 148 – 150 °C; R_f 0.42 (1:9 methanol:ethyl acetate); **IR** (ATR): υ_{max}/cm^{-1} 3301, 3094, 2931, 2241, 1615, 1556, 1458, 1423, 1349, 1201, 1176, 727, 645. In solution in $CDCl_3$, the product exists as a 10:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 6.01 (1H, s, N**H**), 4.01 – 3.94 (1H, m, C**H**$_2$), 3.82 – 3.69 (1H, m, C**H**$_2$), 3.52 – 3.49 (2H, m, C**H**$_2$), 3.36 – 3.32 (1H, m, C**H**$_2$), 2.91 – 2.87 (1H, m, C**H**$_2$), 2.74 – 2.70 (1H, m, C**H**$_2$), 2.63 – 2.55 (1H, m, C**H**$_2$), 2.47 – 2.42 (2H, m, C**H**$_2$), 2.29 – 2.26 (1H, m, C**H**$_2$), 2.07 – 1.99

(3H, m, C**H** and C**H**$_2$), 1.74 – 1.54 (2H, m, C**H**$_2$), 1.45 – 1.36 (1H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 174.4 (**C**O), 171.0 (**C**O), 83.3 (**C**CH), 70.6 (**C**H), 47.3 (**C**H$_2$), 47.1 (**C**H$_2$), 39.2 (**C**H$_2$), 38.3 (**C**H$_2$), 28.6 (**C**H$_2$), 26.1 (**C**H$_2$), 24.1 (**C**H$_2$), 17.9 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{12}H_{18}N_2O_2$, 245.1257. Found $[MNa]^+$ 245.1260 (1.2 ppm error).

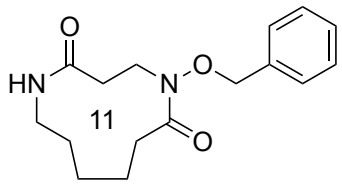
Characteristic NMR data for the minor rotamer can be found at: δ_H (400 MHz, $CDCl_3$) 5.89 – 5.85 (1H, m, N**H**).

1-Acryloyl-azepan-2-one (254)



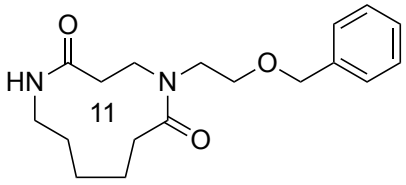
A solution of caprolactam (1.13 g, 10.00 mmol) in dry THF (36.5 mL) was cooled to 0 °C and a solution of MeMgBr (3M in diethyl ether, 3.7 mL, 11 mmol) was added dropwise using a syringe pump over 15 min. The reaction was stirred for 10 min at 0 °C, then acryloyl chloride (1.2 mL, 15.00 mmol) was added and the reaction was stirred 30 min at 0 °C. The reaction was quenched with saturated aq. NH_4Cl solution (40 mL) and extracted with Et_2O (40 mL). The combined organics were washed with saturated aq. $NaHCO_3$ solution (2 x 40 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (1:1 diethyl ether:hexane) to afford the title compound as a colourless liquid (1.17 g, 70% yield); R_f 0.40 (1:1 diethyl ether:hexane). **IR** (ATR): ν_{max}/cm^{-1} 2953, 1678, 1403, 1384, 1289, 1209, 1155, 1003, 796, 607; δ_H (400 MHz, $CDCl_3$) 6.93 (1H, dd, *J* = 16.9, 10.1 Hz, C**H**CHH'), 6.33 – 6.29 (1H, m, CHC**H**H'), 5.70 – 5.67 (1H, m, CHCH**H'**), 3.92 – 3.90 (2H, m, C**H**$_2$), 2.72 – 2.70 (2H, m, C**H**$_2$), 1.78 – 1.70 (6H, m, 3 x C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 178.1 (**C**O), 169.0 (**C**O), 132.0 (**C**HCHH'), 128.1 (CH**C**HH'), 43.8 (**C**H$_2$), 39.5 (**C**H$_2$), 29.4 (**C**H$_2$), 28.7 (**C**H$_2$), 23.8 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_9H_{13}NNaO_2$, 190.0838. Found $[MNa]^+$, 190.0838 (−0.3 ppm error).

5-(Benzyloxyl)-1,5-diazacycloundecane-2,6-dione (271)



To a solution of 1-acryloyl-azepan-2-one **254** (170 mg, 1.00 mmol) in dry methanol (2.0 mL) was added benzyl-o-hydroxylamine (130 µL, 1.10 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate) to afford the title compound as a white solid (189 mg, 65% yield). In solution in $CDCl_3$, some evidence of rotameric broadening in the ^1H NMR data, with trace (<10%) signals for a minor rotamer; R_f 0.49 (1:9 methanol:ethyl acetate). **IR** (ATR): υ_{max}/ cm^{-1} 3301, 2933, 2871, 2234, 1645, 1539, 1441, 1405, 1350, 1226, 1190, 1169, 984, 912, 730, 699, 645, 523; δ_H (400 MHz, $CDCl_3$) 7.40 – 7.38 (5H, m, Ar**H**), 5.80 – 5.61 (1H, m, N**H**), 4.98 – 4.75 (3H, m, NOC$\mathbf{H}_2$ and C**H**H'), 3.71 – 3.63 (1H , m, C$\mathbf{H}_2$), 3.21 – 3.18 (1H, m, CH**H'**), 2.92 – 2.86 (1H, m, C$\mathbf{H}_2$), 2.79 – 2.78 (1H, m, C$\mathbf{H}_2$), 2.65 – 2.57 (1H, m, C$\mathbf{H}_2$), 2.25 – 2.22 (1H, m, C$\mathbf{H}_2$), 1.98 – 1.84 (2H, m, C$\mathbf{H}_2$), 1.68 – 1.64 (1H, m, C$\mathbf{H}_2$), 1.58 – 1.51 (2H, m, C$\mathbf{H}_2$), 1.37 – 1.24 (2H, m, C$\mathbf{H}_2$); δ_C (100 MHz, $CDCl_3$) 175.9 (**C**O), 170.3 (**C**O), 134.2 (**C**Ar), 129.7 (Ar**C**H), 129.4 (Ar**C**H), 129.0 (Ar**C**H), 77.4 (NO**C**H_2), 42.2 (**C**H_2), 39.7 (**C**H_2), 34.5 (**C**H_2), 30.9 (**C**H_2), 27.0 (**C**H_2), 24.5 (**C**H_2), 24.1 (**C**H_2). **HRMS (ESI)**: calcd. for $C_{16}H_{22}N_2NaO_3$, 313.1520. Found $[MNa]^+$ 313.1523 (0.8 ppm error).

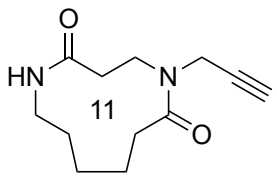
5-(2-(Benzyloxyl)ethyl-1,5-diazacycloundecane-2,6-dione (272)



To a solution of 1-acryloyl-azepan-2-one **254** (167 mg, 1.00 mmol) in dry methanol (2.0 mL) was added 2-(benzyloxy)-1-ethanamine (160 µL, 1.10 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate) to afford the title compound as a white solid (175 mg, 55% yield); m.p. 129−130 °C; R_f 0.36 (1:9 methanol:ethyl

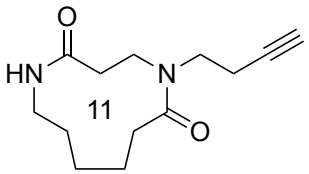
acetate). **IR** (ATR): υ_{max}/cm^{-1} 3312, 2931, 2864, 2239, 1623, 1549, 1351, 1167, 1093, 1028, 906, 728, 698; δ_H (400 MHz, $CDCl_3$) 7.35 – 7.27 (5H, m, Ar**H**), 6.90 (1H, s, N**H**), 4.59 – 4.49 (2H, m, C**H**$_2$), 4.29 – 4.23 (1H, m, C**H**$_2$), 4.12 – 4.06 (1H, m, C**H**$_2$), 4.03 – 3.96 (1H, m, C**H**$_2$), 3.54 – 3.48 (1H, m, C**H**$_2$), 3.43 – 3.33 (1H, m, C**H**$_2$), 3.18 – 3.10 (1H, m, C**H**$_2$), 3.02 – 2.93 (1H, m, C**H**$_2$), 2.62 – 2.57 (1H, m, C**H**$_2$), 2.38 – 2.32 (1H, m, C**H**$_2$), 2.15 – 2.12 (2H, m, C**H**$_2$), 1.97 – 1.93 (2H, m, C**H**$_2$), 1.73 – 1.62 (1H, m, C**H**$_2$), 1.49 – 1.48 (2H, m, C**H**$_2$), 1.24 – 1.17 (1H, m, C**H**$_2$), 0.76 – 0.60 (1H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 174.1 (**C**O), 171.4 (**C**O), 136.9 (**C**Ar), 128.8 (Ar**C**H), 128.5 (Ar**C**H), 128.3 (Ar**C**H), 73.8 (**C**H$_2$), 67.5 (**C**H$_2$), 49.1 (**C**H$_2$), 48.1 (**C**H$_2$), 40.9 (**C**H$_2$), 37.1 (**C**H$_2$), 29.1 (**C**H$_2$), 25.9 (**C**H$_2$), 24.3 (**C**H$_2$), 22.6 (**C**H$_2$); **HRMS (ESI)**: calcd. for $C_{18}H_{26}N_2NaO_3$, 341.1832. Found [MNa]$^+$ 341.1836 (1.2 ppm error).

5-(Prop-2-yn-1-yl)-1,5-diazacycloundecane-2,6-dione (273)



To a solution of 1-acryloyl-azepan-2-one **254** (84 mg, 0.50 mmol) in dry methanol (1.0 mL) was added propargylamine (40 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a white solid (78.5 mg, 71% yield); m.p. 152−155 °C; R_f 0.46 (1:9 methanol:ethyl acetate); **IR** (ATR): υ_{max}/cm^{-1} 3297, 3092, 2934, 2867, 2240, 1624, 1556, 1450, 1352, 1289, 1228, 730. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data (the same sample) is more useful for determining the identity and purity of the product. δ_H (400 MHz, $CDCl_3$) 6.30 (1H, s, N**H**), 4.76 – 4.38 (1H, m, C**H**$_2$), 4.13 – 3.42 (4H, m, 2 x C**H**$_2$), 2.66 – 1.99 (7H, m, 3 x C**H**$_2$ and CC**H**), 1.75 – 1.60 (3H, m, C**H**$_2$), 1.35 – 0.79 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 173.0 (**C**O), 171.4 (**C**O), 80.9 (**C**CH), 72.0 (C**C**H), 46.7 (**C**H$_2$), 41.9 (**C**H$_2$), 37.0 (**C**H$_2$), 35.9 (**C**H$_2$), 28.4 (**C**H$_2$), 25.3 (**C**H$_2$), 24.4 (**C**H$_2$), 22.9 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{12}H_{18}N_2NaO_2$, 245.1262. Found [MNa]$^+$ 245.1260 (−0.5 ppm error).

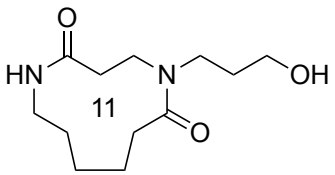
5-(But-3-yn-1-yl)-1,5-diazacycloundecane-2,6-dione (274)



To a solution of 1-acryloyl-azepan-2-one **254** (84 mg, 0.50 mmol) in dry methanol (1.0 mL) was added but-3-yn-1-amine (50 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a white solid (91.6 mg, 78% yield); m.p. 125 – 127 °C; R_f 0.49 (1:9 methanol:ethyl acetate); **IR** (ATR): υ_{max}/cm^{-1} 3300, 3090, 2933, 2866, 2239, 1620, 1555, 1454, 1422, 1368, 1231, 1182, 1024, 922, 729. The ^{1}H NMR spectrum is complicated by rotameric broadening; ^{13}C NMR data is more useful for determining the identity and purity of the product. In solution in $CDCl_3$, the product exists as a 13:1:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 6.45 (1H, s, N**H**), 4.18 – 3.79 (1H, m, C**H**$_2$), 3.77 – 3.56 (1H, m, C**H**$_2$), 3.50 – 3.47 (2H, m, C**H**$_2$), 3.41 – 3.18 (1H, m, C**H**$_2$), 2.77 – 2.29 (6H, m, 3 x C**H**$_2$), 2.18 – 1.99 (3H, m, C**H**$_2$ and CC**H**), 1.68 – 1.57 (3H, m, C**H**$_2$), 1.36 – 1.17 (1H, m, C**H**$_2$), 1.01 – 0.68 (1H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 174.0 (**C**O), 171.5 (**C**O), 83.5 (**C**CH), 70.3 (C**C**H), 47.0 (**C**H$_2$), 46.8 (**C**H$_2$), 41.5 (**C**H$_2$), 37.8 (**C**H$_2$), 28.8 (**C**H$_2$), 25.4 (**C**H$_2$), 24.4 (**C**H$_2$), 22.6 (**C**H$_2$), 17.7 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{13}H_{20}N_2NaO_2$, 259.1418. Found $[MNa]^+$ 259.1417 (−0.5 ppm error).

Characteristic NMR data for the NH peaks of the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 6.19 – 6.10 (1H, m, N**H**), 5.76 – 5.72 (1H, m, N**H**).

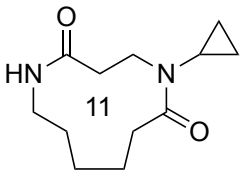
5-(3-Hydroxypropyl)-1,5-diazacycloundecane-2,6-dione (275)



To a solution of 1-acryloyl-azepan-2-one **254** (84 mg, 0.50 mmol) in dry methanol (1.0 mL) was added 3-aminopropan-1-ol (50 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100%

ethyl acetate → 1:19 methanol:ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a white solid (67.5 mg, 56% yield); m.p. 119−121 °C; R_f 0.40 (2:3 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3285, 2933, 2868, 2239, 1614, 1455, 1426, 1350, 1182, 1042, 905, 727. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. δ_H (400 MHz, $CDCl_3$) 6.41 (1H, s, N**H**), 4.08 – 3.82 (2H, m, C**H**$_2$), 3.69 – 3.07 (5H , m, 2 x C**H**$_2$ and C**H**H'), 2.77 – 1.93 (6H , m, 3 x C**H**$_2$), 1.83 – 1.55 (5H , m, 2 x C**H**$_2$ and CH**H'**), 1.38 – 0.79 (2H , m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 174.9 (**C**O), 171.4 (**C**O), 58.9 (**C**H$_2$), 45.0 (**C**H$_2$), 42.2 (**C**H$_2$), 41.7 (**C**H$_2$), 37.3 (**C**H$_2$), 30.4 (**C**H$_2$), 28.5 (**C**H$_2$), 25.1 (**C**H$_2$), 24.4 (**C**H$_2$), 22.7 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{12}H_{22}N_2NaO_3$, 265.1528. Found: $[MNa]^+$, 265.1523 (−1.9 ppm error).

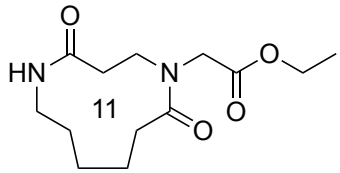
5-Cyclopropyl-1,5-diazacycloundecane-2,6-dione (276)



To a solution of 1-acryloyl-azepan-2-one **254** (84 mg, 0.50 mmol) in dry methanol (1.0 mL) was added cyclopropylamine (40 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a colourless oil (41.2 mg, 37% yield); R_f 0.22 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3288, 3088, 2932, 2869, 2236, 1631, 1547, 1441, 1409, 1260, 1227, 1153, 1032, 906, 727. In solution in $CDCl_3$, the product exists as a 6:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 6.07 – 6.06 (1H, m, N**H**), 4.38 (1H, ddd, *J* = 14.2, 8.5, 5.7 Hz, C**H**$_2$), 3.68 – 3.60 (1H , m, C**H**$_2$), 3.10 – 2.97 (2H , m, C**H**$_2$), 2.87 – 2.82 (1H, m, C**H**$_2$), 2.81 – 2.76 (1H, m, C**H**), 2.73 – 2.67 (1H, m, C**H**$_2$), 2.58 – 2.51 (1H, m, C**H**$_2$), 2.10 – 2.04 (1H, m, C**H**$_2$), 1.83 – 1.73 (1H, m, C**H**$_2$), 1.64 – 1.54 (4H , m, 2 x C**H**$_2$), 1.41 – 1.34 (1H, m, C**H**$_2$), 1.00 – 0.94 (1H, m, cyclopropyl C**H**$_2$), 0.85 – 0.78 (1H, m, cyclopropyl C**H**$_2$), 0.72 – 0.59 (2H, m, cyclopropyl C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 177.7 (**C**O), 171.0 (**C**O), 42.8 (**C**H$_2$), 39.0 (**C**H$_2$), 35.3 (**C**H$_2$), 33.8 (**C**H$_2$), 30.3 (**C**H), 26.8 (**C**H$_2$), 24.2 (**C**H$_2$), 23.7 (**C**H$_2$), 12.0 (cyclopropyl **C**H$_2$), 7.3 (cyclopropyl **C**H$_2$). **HRMS (ESI)**: calcd. for $C_{12}H_{20}N_2NaO_2$, 247.1416. Found: $[MNa]^+$, 247.1417 (0.4 ppm error).

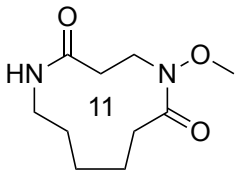
Characteristic NMR data for the minor rotamer can be found at: δ_H (400 MHz, $CDCl_3$) 6.26 – 6.20 (1H, m, N**H**).

Ethyl 2-(4,11-dioxo-1,5-diazacycloundecan-1-yl)acetate (277)



To a solution of 1-acryloyl-azepan-2-one **254** (84 mg, 0.50 mmol) in dry methanol (1.1 mL) was added glycine ethyl ester (86.5 mg, 0.62 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a white solid (102.5 mg, 76% yield); m.p. 133 – 135 °C; R_f 0.40 (1:9 methanol:ethyl acetate). **IR** (ATR): υ_{max}/cm^{-1} 3337, 3088, 2934, 2869, 2243, 1728, 1639, 1551, 1448, 1206, 1157, 1028, 728; δ_H (400 MHz, $CDCl_3$) 8.09 (1H, s, N**H**), 4.72 (1H, d, *J* = 17.1 Hz, C**H**H'COO), 4.26 – 4.20 (2H, m, C**H**$_2$), 4.18 – 4.07 (1H, m, C**H**$_2$), 3.72 – 3.67 (1H, m, C**H**$_2$), 3.32 (1H, d, *J* = 17.1 Hz, CH**H'**COO), 3.24 – 3.20 (1H, m, C**H**$_2$), 2.61 – 2.48 (2H, m, C**H**$_2$), 2.46 – 2.42 (1H, m, C**H**$_2$), 2.26 – 2.22 (1H, m, C**H**$_2$), 2.14 – 2.01 (2H , m, C**H**$_2$), 1.76 – 1.70 (1H, m, C**H**$_2$), 1.62 – 1.55 (2H, m, C**H**$_2$), 1.30 (3H, t, *J* = 7.2 Hz, C**H**$_3$), 1.24 – 1.17 (1H, m, C**H**$_2$), 0.93 – 0.82 (1H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 173.6 (**C**O), 172.2 (**C**O), 171.2 (**C**O), 62.2 (**C**H$_2$), 50.8 (**C**H$_2$), 48.3 (**C**H$_2$), 41.6 (**C**H$_2$), 37.1 (**C**H$_2$), 28.0 (**C**H$_2$), 25.2 (**C**H$_2$), 24.5 (**C**H$_2$), 22.7 (**C**H$_2$), 14.2 (**C**H$_3$). **HRMS (ESI)**: calcd. for $C_{13}H_{22}N_2NaO_4$, 293.1472. Found: $[MNa]^+$, 293.1472 (−0.0 ppm error).

5-Methoxy-1,5-diazacycloundecane-2,6-dione (278)

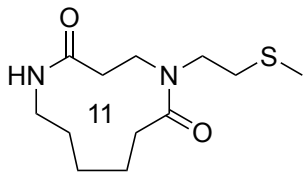


To a solution of 1-acryloyl-azepan-2-one **254** (84 mg, 0.50 mmol) in dry methanol (1.6 mL) was added methoxyamine (63 mg, 0.75 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a yellow oil (55.8 mg,

52% yield); R_f 0.27 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3301, 3088, 2933, 2238, 1643, 1544, 1442, 1406, 1190, 1017, 922, 800, 728. In solution in $CDCl_3$, the product exists as a 5:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 5.77 – 5.76 (1H, m, N**H**), 4.79 – 4.71 (1H, m, C**H**$_2$), 3.69 (3H, s, C**H**$_3$), 3.66 – 3.59 (1H , m, C**H**$_2$), 3.33 – 3.29 (1H , m, C**H**$_2$), 2.91 – 2.80 (2H, m, C**H**$_2$), 2.62 – 2.54 (1H, m, C**H**$_2$), 2.28 – 2.25 (1H, m, C**H**$_2$), 2.10 – 2.05 (1H, m, C**H**$_2$), 1.90 – 1.83 (1H, m, C**H**$_2$), 1.68 – 1.65 (1H , m, C**H**$_2$), 1.56 – 1.53 (2H, m, C**H**$_2$), 1.41 – 1.30 (2H , m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 175.3 (**C**O), 170.3 (**C**O), 61.9 (**C**H$_3$), 41.0 (**C**H$_2$), 39.7 (**C**H$_2$), 34.3 (**C**H$_2$), 31.0 (**C**H$_2$), 27.0 (**C**H$_2$), 24.5 (**C**H$_2$), 24.2 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{10}H_{18}N_2NaO_3$, 237.1209. Found: $[MNa]^+$, 237.1210 (0.1 ppm error).

Characteristic NMR data for the minor rotamer can be found at: δ_H (400 MHz, $CDCl_3$) 6.49 – 6.35 (1H, m, N**H**).

5-(2-(Methylthio)ethyl)-1,5-diazacycloundecane-2,6-dione (280)

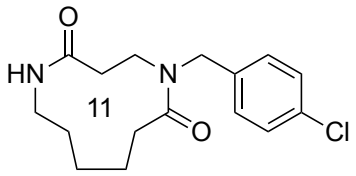


To a solution of 1-acryloyl-azepan-2-one **254** (84 mg, 0.50 mmol) in dry methanol (1.1 mL) was added 2-(methylthio)ethylamine (50 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate) to afford the title compound as a pale-yellow oil (66.9 mg, 52% yield); R_f 0.44 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3288, 2928, 1620, 1555, 1424, 1351, 1301, 1229, 1179, 921, 728. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. In solution in $CDCl_3$, the product exists as a roughly 2:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 6.77 (1H, s, N**H**), 4.22 – 3.90 (1H, m, C**H**$_2$), 3.78 – 3.41 (3H, m, C**H**$_2$ and C**H**H'), 3.23 – 3.19 (1H, m, CH**H'**), 3.10 – 2.85 (1H, m, C**H**$_2$), 2.74 – 2.56 (1H, m, C**H**$_2$), 2.51 – 2.45 (1H, m, C**H**$_2$), 2.41 – 2.33 (2H, m, C**H**$_2$), 2.18 (3H, s, C**H**$_3$), 2.12 – 2.00 (1H, m, C**H**$_2$), 1.77 – 1.63 (6H, m, 3 x C**H**$_2$), 1.34 – 1.16 (1H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 173.9 (**C**O), 171.4 (**C**O), 46.5 (**C**H$_2$), 46.2 (**C**H$_2$), 41.4 (**C**H$_2$),

37.6 (**C**H_2), 32.0 (**C**H_2), 28.7 (**C**H_2), 25.3 (**C**H_2), 24.3 (**C**H_2), 22.5 (**C**H_2), 15.5 (**C**H_3). **HRMS (ESI)**: calcd. for $C_{12}H_{22}N_2NaO_2S$, 281.1297. Found: $[MNa]^+$, 281.1294 (−0.8 ppm error).

Characteristic NMR data for the minor rotamer can be found at: δ_H (400 MHz, $CDCl_3$) 5.96 – 5.83 (1H, m, N**H**); δ_C (100 MHz, $CDCl_3$) 179.1 (**C**O), 42.8 (**C**H_2), 36.7 (**C**H_2), 30.6 (**C**H_2), 29.8 (**C**H_2), 23.5 (**C**H_2), 14.2 (**C**H_3).

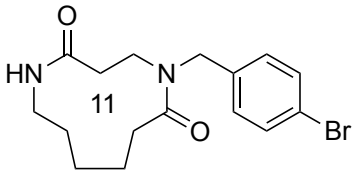
5-(4-Chlorobenzyl)-1,5-diazacycloundecane-2,6-dione (281)



To a solution of 1-acryloyl-azepan-2-one **254** (84 mg, 0.50 mmol) in dry methanol (2.0 mL) was added 4-chlorobenzylamine (70 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a white solid (73.6 mg, 48% yield); m.p. 158 – 160 °C; R_f 0.56 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3293, 2932, 1636, 1617, 1561, 1488, 1450, 1421, 1437, 1225, 1177, 1090, 905, 841, 798, 727, 563. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. In solution in $CDCl_3$, the product exists as a 7:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 7.28 – 7.18 (4H, m, Ar**H**), 6.07 (1H, s, N**H**), 5.26 – 4.68 (1H, m, C**H**$_2$), 4.42 – 3.82 (2H, m, C**H**$_2$), 3.76 – 3.13 (2H, m, C**H**$_2$), 2.63 – 2.02 (6H, m, 3 x C**H**$_2$), 1.79 – 1.49 (4H, m, 2 x C**H**$_2$), 1.36 – 0.83 (1H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 173.6 (**C**O), 171.4 (**C**O), 136.5 (**C**Ar), 133.6 (**C**Ar), 129.6 (Ar**C**H), 129.1 (Ar**C**H), 48.1 (**C**H_2), 44.8 (**C**H_2), 41.7 (**C**H_2), 36.9 (**C**H_2), 28.5 (**C**H_2), 25.2 (**C**H_2), 24.4 (**C**H_2), 22.8 (**C**H_2). **HRMS (ESI)**: calcd. for $C_{16}H_{21}ClN_2NaO_2$, 331.1185. Found: $[MNa]^+$, 331.1184 (−0.4 ppm error).

Characteristic NMR data for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 5.89 – 5.85 (1H, m, N**H**); δ_C (100 MHz, $CDCl_3$) 175.3 (**C**O), 171.0 (**C**O), 135.5 (**C**Ar), 133.6 (**C**Ar), 129.1 (Ar**C**H), 128.0 (Ar**C**H), 53.5 (**C**H_2), 43.0 (**C**H_2), 37.4 (**C**H_2), 34.6 (**C**H_2), 33.8 (**C**H_2), 25.9 (**C**H_2), 23.4 (**C**H_2), 22.3 (**C**H_2).

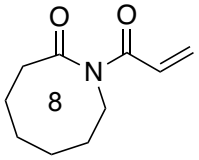
5-(4-Bromobenzyl)-1,5-diazacycloundecane-2,6-dione (282)



To a solution of 1-acryloyl-azepan-2-one **254** (84 mg, 0.50 mmol) in dry methanol (2.0 mL) was added 4-bromobenzylamine (70 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:99 methanol:ethyl acetate) to afford the title compound as a white solid (112.9 mg, 64% yield); m.p. 180 – 183 °C; R_f 0.54 (1:9 methanol:ethyl acetate). **IR** (ATR): υ_{max}/cm^{-1} 3296, 3089, 2933, 2239, 1625, 1556, 1487, 1452, 1404, 1351, 1182, 1070, 1011, 908, 795, 730. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. In solution in $CDCl_3$, the product exists as a 7:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 7.50 – 7.40 (2H, m, Ar**H**), 7.22 – 7.11 (2H, m, Ar**H**), 5.79 (1H, s, N**H**), 5.19 – 4.71 (1H, m, C**H**$_2$), 4.41 – 3.85 (2H, m, C**H**$_2$), 3.80 – 3.16 (2H, m, C**H**$_2$), 2.66 – 2.03 (6H, m, 3 x C**H**$_2$), 1.92 – 1.47 (4H, m, 2 x C**H**$_2$), 1.45 – 1.14 (1H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 173.6 (**C**O), 171.3 (**C**O), 137.2 (**C**Ar), 132.1 (**C**Ar), 130.0 (Ar**C**H), 121.8 (Ar**C**H), 48.3 (**C**H$_2$), 44.9 (**C**H$_2$), 41.8 (**C**H$_2$), 37.1 (**C**H$_2$), 28.6 (**C**H$_2$), 25.2 (**C**H$_2$), 24.4 (**C**H$_2$), 22.8 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{16}H_{21}{}^{79}BrN_2NaO_2$, 375.0686. Found: $[MNa]^+$, 377.0679 (−2.0 ppm error).

Characteristic NMR data for the minor rotamer can be found at: δ_C (100 MHz, $CDCl_3$) 175.4 (**C**O), 171.0 (**C**O), 136.1 (**C**Ar), 132.1 (**C**Ar), 128.4 (Ar**C**H), 121.7 (Ar**C**H), 53.7 (**C**H$_2$), 43.2 (**C**H$_2$), 37.4 (**C**H$_2$), 34.7 (**C**H$_2$), 33.8 (**C**H$_2$), 25.9 (**C**H$_2$), 23.3 (**C**H$_2$), 22.2 (**C**H$_2$).

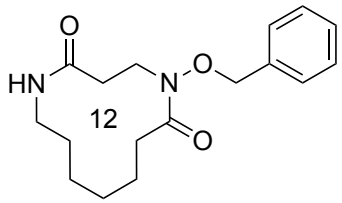
1-Acryloyl-azocan-2-one (255)



A solution of 1-aza-2-cyclooctanone (510 mg, 4.00 mmol) in dry THF (14 mL) was cooled to 0 °C and a solution of MeMgBr (3M in diethyl ether, 1.4 mL) was added *via* dropwise using a

syringe pump over 15 min. The reaction was stirred for 10 min at 0 °C, then acryloyl chloride (0.5 mL, 6.00 mmol) was added and the reaction was stirred 30 min at 0 °C. The reaction was quenched with saturated aq. NH_4Cl solution (15 mL) and extracted with Et_2O (25 mL). The combined organics were washed with saturated $NaHCO_3$ solution (2 x 15 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified with flash column chromatography (1:1 diethyl ether:hexane) to afford the title compound as a colourless oil (358 mg, 49% yield); R_f 0.43 (1:1 diethyl ether:hexane). **IR** (ATR): υ_{max}/cm^{-1} 2927, 2359, 1679, 1445, 1402, 1378, 1304, 1248, 1203, 1175, 1127, 1093, 973, 797, 589 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.87 (1H, dd, *J* = 16.8, 10.5 Hz, C**H**CHH'), 6.31 (1H, dd, *J* = 16.8, 1.7 Hz, CHC**H**H'), 5.67 (1H, dd, *J* = 10.5, 1.7 Hz, CHCH**H**'), 3.93 – 3.90 (2H, m, NC**H**$_2$), 2.67 – 2.64 (2H, m, C**H**$_2$), 1.92 – 1.85 (2H, m, C**H**$_2$), 1.79 – 1.73 (2H, m, C**H**$_2$), 1.63 – 1.57 (2H, m, C**H**$_2$), 1.49 – 1.44 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 178.7 (**C**O), 169.2 (**C**O), 131.8 (**C**HCHH'), 127.5 (CH**C**HH'), 43.7 (**C**H$_2$), 36.6 (**C**H$_2$), 29.8 (**C**H$_2$), 29.2 (**C**H$_2$), 26.1 (**C**H$_2$), 23.8 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{10}H_{15}NNaO_2$, 204.0994. Found: $[MNa]^+$, 204.0995 (0.4 ppm error).

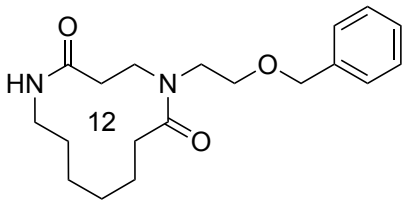
5-(Benzyloxy)-1,5-diazacyclododecane-2,6-dione (283)



To a solution of 1-acryloyl-azocan-2-one **255** (113 mg, 0.60 mmol) in dry methanol (1.3 mL) was added benzyl-o-hydroxylamine (80 µL, 0.7 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude product was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a white solid (117 mg, 61% yield); m.p. 125-127 °C; R_f 0.18 (1:19 methanol:ethyl acetate. **IR** (ATR): υ_{max}/cm^{-1} 3300, 2928, 2862, 2239, 1650, 1548, 1454, 1411, 1220, 1196, 978, 906, 728, 699, 645; δ_H (400 MHz, $CDCl_3$) 7.41 – 7.35 (5H, m, Ar**H**), 5.78 (1H, s, N**H**), 4.85 – 4.77 (3H, m, NOC**H**$_2$ and C**H**H'), 3.36 – 3.29 (1H , m, C**H**$_2$), 3.27 – 3.19 (1H, m, CH**H'**), 2.87 – 2.81 (1H, m, C**H**$_2$), 2.73 – 2.65 (1H, m, C**H**$_2$), 2.44 – 2.40 (1H, m, C**H**$_2$), 2.04 – 1.99 (1H, m, C**H**$_2$), 1.95 – 1.92 (1H, m, C**H**$_2$), 1.62 – 1.53 (2H, m, C**H**$_2$), 1.51 – 1.44 (2H, m, C**H**$_2$), 1.35 – 1.21 (4H, m, 2 x C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 174.7 (**C**O), 169.9 (**C**O), 134.1 (**C**Ar),

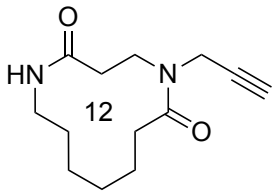
129.6 (Ar**C**H), 129.4 (Ar**C**H), 129.0 (Ar**C**H), 76.7 (NO**C**H_2), 40.0 (**C**H_2), 37.7 (**C**H_2), 34.4 (**C**H_2), 29.3 (**C**H_2), 25.7 (**C**H_2), 25.4 (**C**H_2), 22.3 (**C**H_2), 22.0 (**C**H_2). **HRMS (ESI)**: calcd. for $C_{17}H_{24}N_2NaO_3$, 327.1675. Found: $[MNa]^+$, 327.1679 (1.3 ppm error).

5-(2-(Benzyloxy)ethyl)-1,5-diazacyclododecane-2,6-dione (285)



To a solution of 1-acryloyl-azocan-2-one **255** (91 mg, 0.50 mmol) in dry methanol (1.0 mL) was added 2-(benzyloxy)-1-ethanamine (80 µL, 1.1 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude product was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate) to afford the title compound as a white solid (98 mg, 59% yield); m.p. 83 – 86 °C; R_f 0.48 (1:9 methanol:ethyl acetate. **IR** (ATR): ν_{max}/cm^{-1} 3289, 3087, 2925, 2859, 2234, 1640, 1620, 1550, 1453, 1208, 1099, 923, 732, 698. In solution $CDCl_3$, this compound exists as a roughly 1:1 mixture of rotamers. δ_H (400 MHz, $CDCl_3$) 7.36 − 7.33 (5H, m, Ar**H**), 7.32 − 7.28 (5H, m, Ar**H**), 6.44 (1H, d, *J* = 8.5 Hz, N**H**), 6.18 – 6.17 (1H, m, N**H**), 4.59 – 4.49 (6H, m, 3 x C**H**$_2$), 3.78 – 3.71 (2H , m, C**H**$_2$), 3.63 – 3.53 (4H, m, 2 x C**H**$_2$), 3.48 – 3.43 (1H, m, C**H**$_2$), 2.97 – 2.90 (1H, m, C**H**$_2$), 2.89 – 2.83 (1H, m, C**H**$_2$), 2.75 – 2.68 (1H, m, C**H**$_2$), 2.57 – 2.47 (3H, m, C**H**$_2$), 2.16 – 2.00 (5H, m, C**H**$_2$), 1.83 – 1.70 (2H, m, C**H**$_2$), 1.62 – 1.53 (3H, m, C**H**$_2$), 1.49 – 1.40 (4H, m, C**H**$_2$), 1.39 – 1.24 (8H, m, C**H**$_2$), 1.18 (2H, s, C**H**$_2$), 1.07 – 0.98 (1H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 175.9 (**C**O), 175.5 (**C**O), 171.3 (**C**O), 170.3 (**C**O), 137.7 (**C**Ar), 137.0 (**C**Ar), 128.9 (Ar**C**H), 128.6 (Ar**C**H), 128.5 (Ar**C**H), 128.1 (Ar**C**H), 128.0 (Ar**C**H), 127.7 (Ar**C**H), 73.7 (**C**H_2), 73.5 (**C**H_2), 68.2 (**C**H_2), 68.1 (**C**H_2), 49.5 (**C**H_2), 48.4 (**C**H_2), 48.3 (**C**H_2), 41.4 (**C**H_2), 39.0 (**C**H_2), 37.2 (**C**H_2), 36.3 (**C**H_2), 35.6 (**C**H_2), 32.1 (2 x **C**H_2, overlapping), 27.4 (**C**H_2), 26.8 (**C**H_2), 26.4 (**C**H_2), 25.6 (**C**H_2), 24.0 (**C**H_2), 23.6 (**C**H_2), 22.5 (**C**H_2), 22.0 (**C**H_2). **HRMS (ESI)**: calcd. for $C_{19}H_{28}N_2NaO_3$, 355.1993. Found: $[MNa]^+$, 355.1992 (−0.2 ppm error).

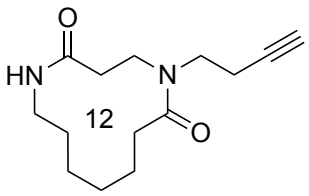
5-(Prop-2-yn-1-yl)-1,5-diazacyclododecane-2,6-dione (286)



To a solution of 1-acryloyl -azocan-2-one **255** (91 mg, 0.50 mmol) in dry methanol (1.0 mL) was added propargylamine (40 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a white solid (78.5 mg, 71% yield); m.p. 142 – 144 °C; R_f 0.5 (1:9 methanol:ethyl acetate); **IR** (ATR): ν_{max}/cm^{-1} 3302, 3088, 2929, 2862, 2243, 1628, 1552, 1453, 1418, 1355, 1227, 1206, 907, 727, 646. In solution in $CDCl_3$, the product exists as a 2:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 6.39 – 6.38 (1H, m, N**H**), 4.65 (1H, dt, *J* = 15.6, 8.0 Hz, C**H**$_2$), 4.13 – 4.12 (1H, m, C**H**$_2$), 3.62 – 3.53 (1H, m, C**H**$_2$), 3.00 – 2.94 (1H, m, C**H**$_2$), 2.93 – 2.88 (1H, m, C**H**$_2$), 2.68 – 2.64 (2H, m, C**H**$_2$), 2.52- 2.45 (2H, m, C**H**), 2.35- 2.34 (1H, m, C**H**$_2$), 2.16 – 2.05 (1H, m, C**H**$_2$), 1.63 – 1.55 (1H, m, C**H**$_2$), 1.49 – 1.39 (4H, m, 2 x C**H**$_2$), 1.35 – 1.29 (2H, m, C**H**$_2$), 1.14 – 1.02 (1H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 175.1 (**C**O), 170.0 (**C**O), 78.4 (C**C**H), 73.5 (**C**CH), 41.8 (**C**H$_2$), 38.9 (**C**H$_2$), 38.4 (**C**H$_2$), 35.6 (**C**H$_2$), 32.0 (**C**H$_2$), 27.3 (**C**H$_2$), 25.6 (**C**H$_2$), 23.0 (**C**H$_2$), 21.7 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{13}H_{20}N_2NaO_2$, 259.1414. Found $[MNa]^+$ 259.1417 (1.3 ppm error).

Characteristic NMR data for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 5.86 (1H, s, N**H**), 2.28 – 2.27 (1H, m, C**H**), 2.26 – 2.19 (2H, m, C**H**$_2$), 1.79 (2H, s, C**H**$_2$), 1.26 – 1.21 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 174.2 (**C**O), 170.8 (**C**O), 80.9 (C**C**H), 71.6 (**C**CH), 46.7 (**C**H$_2$), 36.9 (**C**H$_2$), 36.7 (**C**H$_2$), 35.5 (**C**H$_2$), 31.2 (**C**H$_2$), 26.6 (**C**H$_2$), 23.9 (**C**H$_2$), 22.5 (**C**H$_2$).

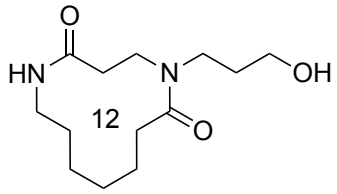
5-(But-3-yn-1-yl)-1,5-diazacyclododecane-2,6-dione (287)



To a solution of 1-acryloyl-azocan-2-one **255** (91 mg, 0.50 mmol) in dry methanol (1.0 mL) was added but-3-yn-1-amine (50 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a white solid (80 mg, 64% yield); m.p. 100 – 104 °C; R_f 0.49 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3302, 2928, 2860, 2239, 1620, 1554, 1455, 1421, 1354, 1244, 1200, 1100, 1025, 905, 727, 646. In solution in $CDCl_3$, the product exists as a 4:2:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 6.34 (1H, d, *J* = 8.4, N**H**), 4.50 – 4.43 (1H, m, C**H**$_2$), 3.78 – 3.64 (2H, m, C**H**$_2$), 3.45 – 3.38 (1H, m, C**H**$_2$), 3.00 (1H, dt, *J* = 14.7, 5.7 Hz, C**H**$_2$), 2.86 – 2.76 (2H, m, C**H**$_2$), 2.56 – 2.49 (2H, m, C**H**$_2$), 2.46 – 2.41 (3H, m, C**H**$_2$), 2.05 – 1.97 (2H, m, C**H** and C**H**H'), 1.63 – 1.54 (2H, m, CH**H'** and C**H**$_2$), 1.49 – 1.40 (4H, m, 2 x C**H**$_2$), 1.28 – 1.14 (1H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 175.5 (**C**O), 170.2 (**C**O), 80.3 (C**C**H), 71.2 (**C**CH), 47.2 (**C**H$_2$), 41.2 (**C**H$_2$), 39.2 (**C**H$_2$), 35.4 (**C**H$_2$), 32.4 (**C**H$_2$), 27.3 (**C**H$_2$), 25.6 (**C**H$_2$), 24.0 (**C**H$_2$), 22.3 (**C**H$_2$), 19.0 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{14}H_{22}N_2NaO_2$, 273.1576. Found: $[MNa]^+$, 273.1573 (−0.9 ppm error).

Characteristic NMR data for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 6.03 (1H, s, N**H**), 5.88- 5.77 (1H, m, N**H**); δ_C (100 MHz, $CDCl_3$) 175.3 (**C**O), 171.1 (**C**O), 84.4 (C**C**H), 70.0 (**C**CH), 46.8 (**C**H$_2$), 42.0 (**C**H$_2$), 37.7 (**C**H$_2$), 36.7 (**C**H$_2$), 32.2 (**C**H$_2$), 31.4 (**C**H$_2$), 28.2 (**C**H$_2$), 26.8 (**C**H$_2$), 25.9 (**C**H$_2$), 24.5 (**C**H$_2$), 23.6 (**C**H$_2$), 17.4 (**C**H$_2$).

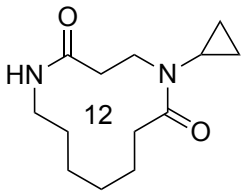
5-(3-Hydroxypropyl)-1,5-diazacyclododecane-2,6-dione (288)



To a solution of 1-acryloyl -azocan-2-one **255** (91 mg, 0.50 mmol) in dry methanol (1.0 mL) was added 3-aminopropan-1-ol (50 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a colourless oil (83.1 mg, 65% yield); R_f 0.49 (2:3 methanol:ethyl acetate). **IR** (ATR): υ_{max}/cm^{-1} 3288, 3093, 2928, 2863, 2237, 1642, 1614, 1556, 1456, 1440, 1424, 1354, 1199, 1053, 908, 728, 645. In solution in $CDCl_3$, the product exists as a 2:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 6.60 (1H, s, N**H**), 4.54 (1H, ddd, *J* = 14.7, 10.3, 5.0 Hz, C**H**$_2$), 3.68 – 3.59 (4H, m, 2 x C**H**$_2$), 3.40 – 3.32 (1H , m, C**H**$_2$), 2.94 – 2.83 (2H, m, C**H**$_2$), 2.74 – 2.68 (1H, m, C**H**$_2$), 2.59 – 2.47 (2H, m, C**H**$_2$), 2.16 – 2.00 (2H, m, C**H**$_2$), 1.82 – 1.70 (3H, m, C**H**$_2$), 1.60 – 1.53 (1H , m, C**H**$_2$), 1.48 – 1.41 (3H , m, C**H**$_2$), 1.39 – 1.32 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 175.7 (**C**O), 170.5 (**C**O), 59.3 (**C**H$_2$), 45.4 (**C**H$_2$), 40.8 (**C**H$_2$), 39.0 (**C**H$_2$), 35.5 (**C**H$_2$), 31.9 (**C**H$_2$), 31.8 (**C**H$_2$), 27.4 (**C**H$_2$), 25.5 (**C**H$_2$), 23.5 (**C**H$_2$), 22.0 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{13}H_{24}N_2NaO_3$, 279.1678. Found: $[MNa]^+$, 279.1679 (0.3 ppm error).

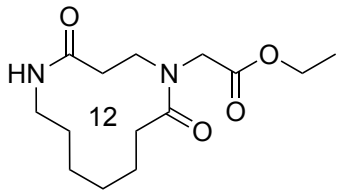
Characteristic NMR data for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 6.36 – 6.33 (1H, m, N**H**), 3.49 – 3.46 (1H , m, C**H**$_2$), 2.41 – 2.38 (1H , m, C**H**$_2$), 1.25 – 1.20 (1H , m, C**H**$_2$), 1.07 – 0.97 (1H , m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 176.2 (**C**O), 171.0 (**C**O), 58.5 (**C**H$_2$), 44.4 (**C**H$_2$), 41.3 (**C**H$_2$), 37.0 (**C**H$_2$), 36.7 (**C**H$_2$), 30.7 (**C**H$_2$), 29.9 (**C**H$_2$), 26.8 (**C**H$_2$), 23.3 (**C**H$_2$), 22.5 (**C**H$_2$).

5-Cyclopropyl-1,5-diazacycloundodecane-2,6-dione (289)



To a solution of 1-acryloyl-azocan-2-one **255** (91 mg, 0.50 mmol) in dry methanol (1.0 mL) was added cyclopropylamine (40 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a white solid (49.7 mg, 42% yield); m.p. 145 – 147 °C; R_f 0.29 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3286, 3087, 2928, 2862, 2234, 1642, 1549, 1448, 1407, 1375, 1263, 1156, 1069, 1030, 921, 727, 644; δ_H (400 MHz, $CDCl_3$) 6.36 (1H, d, *J* = 7.4 Hz, N**H**), 4.71 – 4.62 (1H, m, C**H**$_2$), 3.73 – 3.64 (1H, m, C**H**), 2.91 – 2.72 (4H , m, 2 x C**H**$_2$), 2.71 – 2.68 (1H , m, C**H**), 2.65 – 2.58 (1H , m, C**H**$_2$), 2.21 – 2.11 (2H, m, C**H**$_2$), 1.64 – 1.56 (1H, m, C**H**$_2$), 1.53 – 1.33 (5H, m, C**H**$_2$), 1.07 – 1.00 (1H, m, cyclopropyl C**H**$_2$), 0.99 – 0.91 (1H, m, C**H**$_2$), 0.90 – 0.83 (1H, m, cyclopropyl C**H**$_2$), 0.77 – 0.66 (2H, m, cyclopropyl C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 177.5 (**C**O), 170.3 (**C**O), 39.9 (**C**H$_2$), 38.6 (**C**H$_2$), 35.5 (**C**H$_2$), 33.0 (**C**H$_2$), 28.7 (**C**H), 27.7 (**C**H$_2$), 25.8 (**C**H$_2$), 22.5 (**C**H$_2$), 21.1 (**C**H$_2$), 11.9 (cyclopropyl **C**H$_2$), 6.8 (cyclopropyl **C**H$_2$). **HRMS (ESI)**: calcd. for $C_{13}H_{22}N_2NaO_2$, 261.1575. Found: $[MNa]^+$, 261.1573 (−0.6 ppm error).

Ethyl 2-(4,12-dioxo-1,5-diazacyclododecan-1-yl)acetate (290)

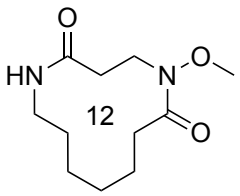


To a solution of 1-acryloyl-azocan-2-one **255** (102 mg, 0.56 mmol) in dry methanol (1.1 mL) was added glycine ethyl ester (86.5 mg, 0.62 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a white solid (101 mg, 63% yield); m.p. 115 – 117 °C; R_f 0.45 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-}

[1] 3300, 3087, 2928, 2861, 1738, 163, 1548, 1448, 1353, 1197, 1159, 1027, 728. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. In solution in $CDCl_3$, the product exists largely as a single rotamer, along with 2 minor rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 7.18 (1H, s, N**H**), 4.23 – 4.12 (4H, m, 2 x C**H**$_2$), 3.33 – 3.28 (1H, m, C**H**$_2$), 2.43 – 2.36 (4H, m, 2 x C**H**$_2$), 1.56 – 1.55 (4H, m, 2 x C**H**$_2$), 1.32 – 1.24 (10H, m, C**H**$_3$ and C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 174.6 (**C**O), 171.8 (**C**O), 171.1 (**C**O), 61.9 (**C**H$_2$), 50.2 (**C**H$_2$COO), 48.3 (**C**H$_2$), 37.4 (**C**H$_2$), 37.2 (**C**H$_2$), 31.5 (**C**H$_2$), 26.3 (**C**H$_2$), 25.7 (**C**H$_2$), 23.1 (**C**H$_2$), 22.8 (**C**H$_2$), 14.2 (**C**H$_3$). **HRMS (ESI)**: calcd. for $C_{14}H_{24}N_2NaO_4$, 307.1625. Found: $[MNa]^+$, 307.1628 (0.9 ppm error).

Characteristic NMR data for the minor rotamers can be found at; δ_H (400 MHz, $CDCl_3$) 6.53 – 6.52 (1H, m, C**H**$_2$), 5.70 – 5.57 (1H, m, C**H**$_2$), 4.76 – 4.68 (1H, m, C**H**$_2$), 3.49 – 3.40 (2H, m, C**H**$_2$), 3.34 – 3.29 (2H, m, C**H**$_2$), 3.10 – 3.03 (1H, m, C**H**$_2$), 2.95 – 2.92 (1H, m, C**H**$_2$), 2.82 – 2.77 (1H, m, C**H**$_2$), 2.65 – 2.59 (1H, m, C**H**$_2$). δ_C (100 MHz, $CDCl_3$) 175.2 (**C**O), 170.4 (**C**O), 62.1 (**C**H$_2$), 51.0 (**C**H$_2$), 43.7 (**C**H$_2$), 42.0 (**C**H$_2$), 38.8 (**C**H$_2$), 35.8 (**C**H$_2$), 32.4 (**C**H$_2$), 32.2 (**C**H$_2$), 31.8 (**C**H$_2$), 28.2 (**C**H$_2$), 27.0 (**C**H$_2$), 25.8 (**C**H$_2$), 23.1 (**C**H$_2$), 21.7 (**C**H$_2$), 14.3 (**C**H$_3$).

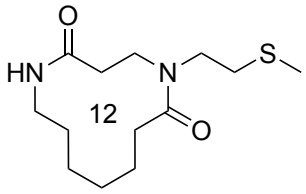
5-Methoxy-1,5-diazacycloundecane-2,6-dione (291)



To a solution of 1-acryloyl-azocan-2-one **255** (91 mg, 0.50 mmol) in dry methanol (1.6 mL) was added methoxyamine (63 mg, 0.75 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a white solid (52.7 mg, 46% yield); m.p. 103 – 105 °C; R_f 0.24 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3300, 3088, 2930, 2863, 2239, 1644, 1549, 1443, 1413, 1199, 1065, 995, 906, 727, 645; δ_H (400 MHz, $CDCl_3$) 5.81 (1H, s, N**H**), 4.78 – 4.70 (1H, m, C**H**$_2$), 3.68 (3H, s, C**H**$_3$), 3.34 – 3.24 (3H , m, C**H**$_2$), 2.88 – 2.81 (1H, m, C**H**$_2$), 2.69 – 2.61 (1H, m, C**H**$_2$), 2.47 – 2.43 (1H, m, C**H**$_2$), 2.12 – 2.02 (2H,

m, C**H**$_2$), 1.59 – 1.54 (1H, m, C**H**$_2$), 1.52 – 1.45 (2H , m, C**H**$_2$), 1.40 – 1.21 (4H, m, 2 x C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 174.2 (**C**O), 169.8 (**C**O), 61.6 (**C**H$_3$), 39.0 (**C**H$_2$), 37.8 (**C**H$_2$), 34.3 (**C**H$_2$), 29.1 (**C**H$_2$), 25.7 (**C**H$_2$), 25.6 (**C**H$_2$), 22.4 (**C**H$_2$), 21.9 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{11}H_{20}N_2NaO_3$, 251.1363. Found: $[MNa]^+$, 251.1366 (1.1 ppm error).

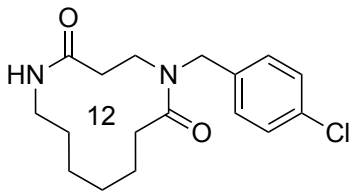
5-(2-(Methylthio)ethyl)-1,5-diazacylododecane-2,6-dione (292)



To a solution of 1-acryloyl-azocan-2-one **255** (91 mg, 0.50 mmol) in dry methanol (1.0 mL) was added 2-(methylthio)ethylamine (50 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate) to afford the title compound as a pale-yellow liquid (88.2 mg, 65% yield); R_f 0.5 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3288, 2924, 2236, 1639, 1553, 1454, 1359, 1300, 1100, 906, 726. In solution in $CDCl_3$, the product exists as a roughly 3:1 mixture of rotamers. NMR data for both rotamers; δ_H (400 MHz, $CDCl_3$) 6.56 – 6.54 (1H, m, N**H**), 4.44 – 4.37 (1H, m, C**H**$_2$), 3.70 – 3.56 (2H, m, C**H**$_2$), 3.47 – 3.43 (1H, m, C**H**$_2$), 3.29 – 3.25 (1H, m, C**H**$_2$), 2.96 – 2.90 (1H, m, C**H**$_2$), 2.83 – 2.73 (3H, m, C**H**$_2$), 2.63 – 2.57 (2H, m, C**H**$_2$), 2.48 – 2.42 (1H, m, C**H**$_2$), 2.40 – 2.34 (2H, m, C**H**$_2$), 2.09 – 2.08 (3H, m, C**H**$_3$), 1.74 – 1.71 (1H, m, C**H**$_2$), 1.56 – 1.52 (4H, m, 2 x C**H**$_2$), 1.43 – 1.40 (3H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 175.2 (**C**O), 170.1 (**C**O), 48.4 (**C**H$_2$), 41.5 (**C**H$_2$), 39.0 (**C**H$_2$), 35.3 (**C**H$_2$), 32.9 (**C**H$_2$), 32.3 (**C**H$_2$), 27.2 (**C**H$_2$), 25.5 (**C**H$_2$), 24.0 (**C**H$_2$), 22.3 (**C**H$_2$), 15.9 (**C**H$_3$). **HRMS (ESI)**: calcd. for $C_{13}H_{24}N_2NaO_2S$, 295.1447. Found: $[MNa]^+$, 295.1451 (1.2 ppm error).

Characteristic NMR data for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 6.27 – 6.11 (1H, m, N**H**), 4.44 – 4.37 (2H, m, C**H**$_2$), 2.96 – 2.90 (2H, m, C**H**$_2$), 2.31 – 2.20 (1H, m, C**H**$_2$), 2.00 – 1.91 (2H, m, C**H**$_2$), 1.20 – 1.16 (1H, m, C**H**$_2$), 1.08 – 0.99 (1H, m, C**H**$_2$). δ_C (100 MHz, $CDCl_3$) 177.8 (**C**O), 171.0 (**C**O), 41.8 (**C**H$_2$), 32.3 (**C**H$_2$), 32.1 (**C**H$_2$), 28.1 (**C**H$_2$), 25.7 (**C**H$_2$), 24.5 (**C**H$_2$), 15.5 (**C**H$_3$).

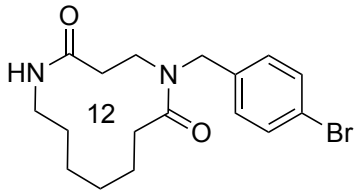
5-(4-Chlorobenzyl)-1,5-diazacyclododecane-2,6-dione (293)



To a solution of 1-acryloyl-azocan-2-one **255** (97 mg, 0.54 mmol) in dry methanol (2.0 mL) was added 4-chlorobenzylamine (70 µL, 0.59 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a yellow oil (51.3 mg, 29% yield); m.p. 138 – 140 °C; R_f 0.59 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3295, 2931, 2241, 1629, 1617, 1553, 1491, 1454, 1353, 1092, 906, 727. In solution in $CDCl_3$, the product exists as a 6:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 7.28 – 7.25 (2H, m, Ar**H**), 7.04 (2H, m, Ar**H**), 6.39 (1H, d, *J* = 8.8 Hz, N**H**), 4.81 (1H, d, *J* = 16.9 Hz, C**H**H'Ph), 4.46 – 4.39 (1H, m, C**H**$_2$), 4.35 (1H, d, *J* = 16.9 Hz, CH**H**'Ph), 3.75 – 3.66 (1H, m, C**H**$_2$), 2.86 – 2.73 (3H, m, C**H**$_2$), 2.54 – 2.40 (2H, m, C**H**$_2$), 2.12 – 1.95 (2H, m, C**H**$_2$), 1.58 – 1.52 (1H, m, C**H**$_2$), 1.49 – 1.39 (5H, m, C**H**$_2$), 1.15 – 1.07 (1H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 175.7 (**C**O), 170.2 (**C**O), 135.2 (**C**Ar), 133.7 (**C**Ar), 129.2 (Ar**C**H), 127.9 (Ar**C**H), 51.6 (**C**H$_2$), 41.3 (**C**H$_2$), 39.3 (**C**H$_2$), 35.1 (**C**H$_2$), 32.6 (**C**H$_2$), 27.3 (**C**H$_2$), 25.7 (**C**H$_2$), 24.2 (**C**H$_2$), 22.4 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{17}H_{23}ClN_2NaO_2$, 345.1330. Found: $[MNa]^+$, 345.1340 (2.9 ppm error).

Characteristic NMR data for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 5.46 – 5.40 (1H, m, N**H**), 4.62 – 4.57 (2H, m, C**H**$_2$), 1.77 – 1.76 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 175.0 (**C**O), 170.8 (**C**O), 137.5 (**C**Ar), 136.8 (**C**Ar), 129.9 (Ar**C**H), 128.9 (Ar**C**H), 48.2 (**C**H$_2$), 44.9 (**C**H$_2$), 36.8 (**C**H$_2$), 30.8 (**C**H$_2$), 26.8 (**C**H$_2$), 26.7 (**C**H$_2$), 23.5 (**C**H$_2$), 22.5 (**C**H$_2$).

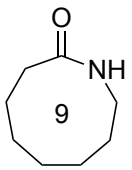
5-(4-Bromobenzyl)-1,5-diazacyclododecane-2,6-dilone (294)



To a solution of 1-acryloyl-azocan-2-one **255** (91.0 mg, 0.5 mmol) in dry methanol (1.0 mL) was added 4-bromobenzylamine (700 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:99 methanol:ethyl acetate) to afford the title compound as a white solid (40.4 mg, 22% yield); m.p. 150 – 152 °C; R_f 0.59 (1:9 methanol:ethyl acetate). **IR** (ATR): υ_{max}/cm^{-1} 3293, 3086, 2928, 2861, 2238, 2239, 1627, 1553, 1487, 1453, 1404, 1352, 1207, 1070, 1010, 908, 795, 727. In solution in $CDCl_3$, the product exists as a 5:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 7.45 (2H, d, *J* = 8.2 Hz, Ar**H**), 7.02 (2H, d, *J* = 8.2 Hz, Ar**H**), 6.40 (1H, s, N**H**), 4.82 (1H, d, *J* = 17.0 Hz, C**H**H'Ph), 4.48 – 4.43 (1H, m, C**H**$_2$), 4.37 (1H, d, *J* = 17.0 Hz, CH**H'**Ph), 3.77 – 3.70 (1H, m, C**H**$_2$), 2.89 – 2.77 (3H, m, C**H**$_2$), 2.57 – 2.42 (2H, m, C**H**$_2$), 2.14 – 1.96 (2H, m, C**H**$_2$), 1.61 – 1.54 (1H, m, C**H**$_2$), 1.51 – 1.42 (5H, m, C**H**$_2$), 1.18 – 1.10 (1H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 175.8 (**C**O), 170.3 (**C**O), 135.7 (**C**Ar), 132.2 (Ar**C**H), 128.2 (Ar**C**H), 121.7 (**C**Ar), 51.7 (**C**H$_2$), 41.3 (**C**H$_2$), 39.3 (**C**H$_2$), 35.1 (**C**H$_2$), 32.6 (**C**H$_2$), 27.3 (**C**H$_2$), 25.7 (**C**H$_2$), 24.2 (**C**H$_2$), 22.4 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{17}H_{23}{}^{79}BrN_2NaO_2$, 389.0830. Found: $[MNa]^+$, 389.0835 (1.2 ppm error).

Characteristic NMR data for the minor rotamer can be found at: δ_H (400 MHz, $CDCl_3$) 5.50 – 5.40 (1H, m, N**H**); δ_C (100 MHz, $CDCl_3$) 175.0 (**C**O), 170.8 (**C**O), 137.3 (**C**Ar), 131.9 (Ar**C**H), 130.2 (Ar**C**H), 121.6 (**C**Ar), 48.3 (**C**H$_2$), 44.9 (**C**H$_2$), 36.8 (**C**H$_2$), 30.8 (**C**H$_2$), 26.8 (**C**H$_2$), 26.7 (**C**H$_2$), 23.5 (**C**H$_2$), 22.5 (**C**H$_2$).

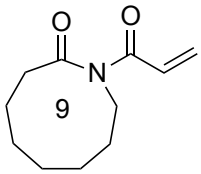
Azonan-2-one (257)



To a solution of cyclooctenone **256** (1.27 g, 10.0 mmol) in formic acid (10 mL) was added hydroxyl-amine-o-sulphonic acid (1.70 g, 15.00 mmol) in formic acid (5 mL) *via* dropwise using a syringe pump over 30 min. The reaction was heated to reflux and stirred for 18 hours. The reaction was quenched with ice-cold water (20 mL), neutralised with 2M NaOH (200 mL) and then extracted with $CHCl_3$ (3 x 60 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified with flash column chromatography (1:1 hexane:ethyl acetate → 100% ethyl acetate → 1:19 methanol:ethyl acetate) to afford the title compound as a colouless liquid (768.5 mg, 54% yield); R_f 0.50 (1:19 methanol: ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3300, 2926, 2867, 1647, 1458, 1452, 1285, 1153, 1031, 979, 785, 710, 570. In solution in $CDCl_3$, the product exists as a 1:4 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 6.18 (1H, s, NH), 3.35 – 3.31 (2H, m, C**H**$_2$), 2.42 – 2.39 (2H, m, C**H**$_2$), 1.83 – 1.77 (2H, m, C**H**$_2$), 1.60 – 1.56 (6H, m, 3 x C**H**$_2$), 1.53 – 1.49 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 178.1 (**C**O), 43.4 (**C**H$_2$), 33.1 (**C**H$_2$), 30.1 (**C**H$_2$), 27.9 (**C**H$_2$), 25.5 (**C**H$_2$), 24.6 (**C**H$_2$), 23.1 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_8H_{15}NNaO$, 164.1049. Found $[MNa]^+$, 164.1046 (−1.8 ppm error).

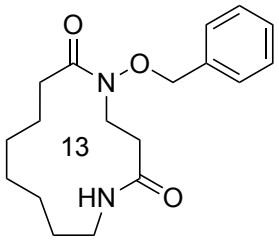
Characteristic NMR data for the minor rotamer can be found at: δ_H (400 MHz, $CDCl_3$) 5.45 – 5.43 (1H, m, N**H**); δ_C (100 MHz, $CDCl_3$) 176.7 (**C**O), 40.4 (**C**H$_2$), 38.8 (**C**H$_2$), 29.4 (**C**H$_2$), 29.3 (**C**H$_2$), 25.9 (**C**H$_2$), 25.5 (**C**H$_2$), 23.8 (**C**H$_2$).

1-Acryloylazonan-2-one (3d)



A solution of azonan-2-one **257** (830.6 mg, 5.88 mmol) in dry THF (33 mL) was cooled to 0 °C and a solution of MeMgBr (3M in diethyl ether, 2.2 mL, 6.67 mmol) was added *via* dropwise using a syringe pump over 30 min. The reaction was stirred for 10 min at 0 °C, then acryloyl chloride (0.7 mL, 8.80 mmol) was added and the reaction was stirred 30 min at 0 °C. The reaction was quenched with saturated aq. NH_4Cl solution (20 mL) and extracted with Et_2O (20 mL). The combined organics were washed with saturated $NaHCO_3$ solution (2 x 20 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified with flash column chromatography (1:1 diethyl ether:hexane) to afford the title compound as a colourless liquid (487.6 mg, 43% yield); R_f 0.60 (1:1 diethyl ether:hexane). **IR** (ATR): ν_{max}/cm^{-1} ν_{max} 2927, 2868, 1676, 1619, 1445, 1402, 1378, 1227, 1164, 1020, 975, 905, 793, 720, 570; δ_H (400 MHz, $CDCl_3$) 6.73 (1H, dd, *J* = 16.9, 10.5 Hz, C**H**CHH'), 6.32 (1H, dd, *J* = 16.9, 1.8 Hz, CHC**H**H'), 5.67 (1H, dd, *J* = 10.5, 1.8 Hz, CHCH**H**'), 3.8 – 3.84 (2H, m, NC**H**$_2$), 2.68 – 2.65 (2H, m, C**H**$_2$), 1.90 – 1.85 (2H, m, C**H**$_2$), 1.82 – 1.75 (2H, m, C**H**$_2$), 1.67 – 1.61 (2H, m, C**H**$_2$), 1.51 – 1.45 (2H, m, C**H**$_2$), 1.42 – 1.36 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 180.4 (**C**O), 168.6 (**C**O), 131.1 (**C**HCHH'), 128.0 (CH**C**HH'), 45.0 (**C**H$_2$), 38.8 (**C**H$_2$), 28.5 (**C**H$_2$), 28.1 (**C**H$_2$), 26.0 (**C**H$_2$), 25.5 (**C**H$_2$), 21.3 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{11}H_{17}NNaO_2$, 218.1152. Found $[MNa]^+$, 218.1151 (−0.3 ppm error).

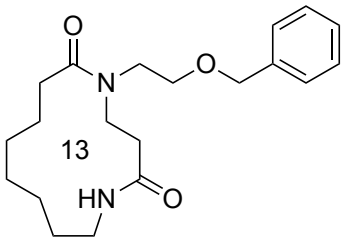
5-(Benzyloxy)-1,5-diazacyclotridecane-2,6-dione (296)



To a solution of 1-acryloylazonan-2-one **258** (155 mg, 0.80 mmol) in dry methanol (1.6 mL) was added benzyl-o-hydroxylamine (100 µL, 0.9 mmol). The reaction was stirred for 4 hours

at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate) to afford the title compound as a white solid (137 mg, 54% yield); m.p. 102 – 105 °C; R_f 0.40 (1:19 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3302, 2927, 2860, 2239, 1644, 1548, 1439, 1416, 1359, 1199, 974, 729, 69. δ_H (400 MHz, $CDCl_3$) 7.40 – 7.38 (5H, m, Ar**H**), 6.38 (1H, s, N**H**), 4.83 (2H, s, **C**H$_2$), 3.37 – 3.09 (2H, m, **C**H$_2$), 2.66 – 1.89 (5H, m, **C**H$_2$), 1.76 – 1.59 (2H, m, **C**H$_2$), 1.55 – 1.49 (2H, m, **C**H$_2$), 1.38 – 1.13 (7H, m, **C**H$_2$); δ_C (100 MHz, $CDCl_3$) 175.8 (**C**O), 170.2 (**C**O), 134.2 (**C**Ar), 129.3 (Ar**C**H), 129.2 (Ar**C**H), 128.9 (Ar**C**H), 76.3 (**C**H$_2$), 42.0 (**C**H$_2$), 39.8 (**C**H$_2$), 34.6 (**C**H$_2$), 31.6 (**C**H$_2$), 27.6 (**C**H$_2$), 26.6 (**C**H$_2$), 26.9 (**C**H$_2$), 25.4 (**C**H$_2$), 22.5 (**C**H$_2$); **HRMS (ESI)**: calcd. for $C_{18}H_{26}N_2NaO_3$, 341.1838. Found $[MNa]^+$ 341.1836 (−0.8 ppm error).

5-(2-(Benzyloxy)ethyl)-1,5-diazacyclotridecane-2,6-dione (297)

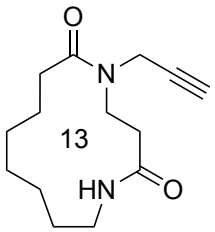


To a solution of 1-acryloylazonan-2-one **258** (98 mg, 0.50 mmol) in dry methanol (1.0 mL) was added 2-(benzyloxy)-1-ethanamine (80 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate) to afford the title compound as a white solid (94 mg, 54% yield); m.p. 117 − 119 °C; R_f 0.50 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3300, 3087, 2927, 2858, 2239, 1622, 1552, 1454, 1359, 1100, 1028, 908, 733, 698, 600. In solution in $CDCl_3$, the product exists as a roughly 2:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 7.37 – 7.31 (5H, m, Ar**H**), 6.68 (1H, s, N**H**), 4.49 (2H, s, **C**H$_2$), 3.60 – 3.59 (1H, m, **C**H$_2$), 3.57 – 3.54 (2H, m, **C**H$_2$), 3.52 – 3.50 (1H, m, **C**H$_2$), 2.63 (2H, m, **C**H$_2$), 2.40 – 2.37 (2H, m, **C**H$_2$), 1.73 – 1.67 (2H, m, **C**H$_2$), 1.54 – 1.51 (2H, m, **C**H$_2$), 1.38 – 1.30 (6H, m, 3 x **C**H$_2$), 1.26 – 1.20 (4H, m, 2 x **C**H$_2$); δ_C (100 MHz, $CDCl_3$) 176.0 (**C**O), 170.6 (**C**O), 137.9 (**C**Ar), 128.6 (Ar**C**H), 128.0 (Ar**C**H), 127.6 (Ar**C**H), 73.4 (NO**C**HH'), 68.0 (**C**H$_2$), 49.0 (**C**H$_2$), 42.5 (**C**H$_2$), 39.7 (**C**H$_2$), 35.2 (**C**H$_2$), 32.7 (**C**H$_2$), 27.9 (**C**H$_2$), 27.1 (**C**H$_2$), 26.9 (**C**H$_2$),

25.7 (**C**H_2), 23.8 (**C**H_2); **HRMS (ESI)**: calcd. for $C_{20}H_{30}N_2NaO_3$, 369.2144. Found $[MNa]^+$ 369.2149 (1.2 ppm error).

NMR data for the minor rotamer can be found at; δ_H (400 MHz, $CDCl_3$) 7.29 – 7.26 (5H, m, Ar**H**), 6.33 – 6.32 (1H, m, N**H**), 4.52 (2H, s, **C**H_2), 3.84 – 3.82 (2H, m, **C**H_2), 3.60 – 3.59 (2H, m, **C**H_2), 2.94 – 2.93 (2H, m, **C**H_2), 2.31 – 2.28 (2H, m, **C**H_2); δ_C (100 MHz, $CDCl_3$) 174.2 (**C**O), 171.3 (**C**O), 137.2 (**C**Ar), 128.8 (Ar**C**H), 128.4 (Ar**C**H), 127.9 (Ar**C**H), 73.7 (NO**C**HH'), 68.9 (**C**H_2), 47.5 (**C**H_2), 38.2 (**C**H_2), 37.0 (**C**H_2), 30.3 (**C**H_2), 26.7 (**C**H_2), 26.5 (**C**H_2), 25.0 (**C**H_2), 24.8 (**C**H_2), 23.3 (**C**H_2).

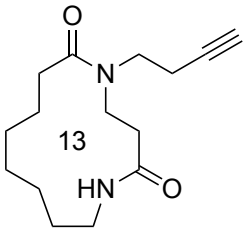
5-(Prop-2-yn-1-yl)-1,5-diazacyclotridecane-2,6-dione (298)



To a solution of 1-acryloylazonan-2-one **258** (123 mg, 0.63 mmol) in dry methanol (1.3 mL) was added 2-propylamine (50 µL, 0.69 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a white solid (99 mg, 63% yield); m.p. 125-128 °C; R_f 0.54 (2:3 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3304, 2929, 2860, 2243, 1631, 1552, 1441, 1418, 1372, 1359, 1287, 1229, 906, 728, 647. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. In solution in $CDCl_3$, the product exists as a 4:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 6.73 (1H, s, N**H**), 4.22 – 4.13 (3H, m, C**H**$_2$), 2.66 – 2.63 (2H , m, C**H**$_2$), 2.42 – 2.41 (2H, m, C**H**$_2$), 2.33 – 2.29 (1H, m, C**H**), 1.78 – 1.67 (3H, m, C**H**$_2$), 1.60 – 1.49 (4H, m, 2 x C**H**$_2$), 1.42 (2H, s, C**H**$_2$), 1.29 – 1.24 (4H, m, 2 x C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 175.4 (**C**O), 170.3 (**C**O), 78.4 (**C**CH), 73.0 (C**C**H), 42.4 (**C**H_2), 39.6 (**C**H_2), 38.8 (**C**H_2), 35.1 (**C**H_2), 32.9 (**C**H_2), 27.8 (**C**H_2), 27.1 (**C**H_2), 27.0 (**C**H_2), 25.5 (**C**H_2), 23.6 (**C**H_2). **HRMS (ESI)**: calcd. for $C_{14}H_{22}N_2NaO_2$, 273.1567. Found: $[MNa]^+$, 273.1573 (2.4 ppm error).

Characteristic NMR data for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 6.05 (1H, s, N**H**); δ_C (100 MHz, $CDCl_3$) 173.1 (**C**O), 171.1 (**C**O), 80.7 (**C**CH), 71.7 (C**C**H), 45.2 (**C**H_2), 38.5 (**C**H_2), 36.7 (**C**H_2), 29.9 (**C**H_2), 26.8 (**C**H_2), 25.7 (**C**H_2), 25.0 (**C**H_2), 24.8 (**C**H_2), 22.9 (**C**H_2).

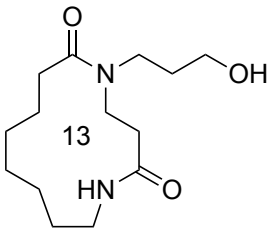
5-(But-3-yn-1-yl)-1,5-diazacyclotridecane-2,6-dione (299)



To a solution of 1-acryloylazonan-2-one **258** (98 mg, 0.50 mmol) in dry methanol (1.0 mL) was added but-3-yn-1-amine (50 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a white solid (72.3 mg, 55% yield); m.p. 115 – 118 °C; R_f 0.60 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3303, 3089, 2928, 2859, 2239, 1623, 1552, 1455, 1422, 1360, 1252, 1021, 1063, 1021, 921, 729, 644. In solution in $CDCl_3$, the product exists as a 7:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 6.54 (1H, s, N**H**), 3.60 (2H, s, C**H**$_2$), 2.78 – 2.65 (2H, m, C**H**$_2$), 2.44 – 2.31 (5H, m, C**H**$_2$), 2.00 – 1.99 (1H, m, C**H**), 1.76 – 1.70 (2H, m, C**H**$_2$), 1.61 − 1.52 (3H, m, C**H**$_2$), 1.37 – 1.22 (8H, m, 4 x C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 175.5 (**C**O), 170.6 (**C**O), 80.4 (**C**CH), 71.1 (C**C**H), 48.1 (**C**H_2), 42.7 (**C**H_2), 39.7 (**C**H_2), 35.0 (**C**H_2), 32.7 (**C**H_2), 27.9 (**C**H_2), 27.2 (**C**H_2), 27.0 (**C**H_2), 25.9 (**C**H_2), 24.2 (**C**H_2), 18.8 (**C**H_2). **HRMS (ESI)**: calcd. for $C_{15}H_{24}N_2NaO_2$, 287.1723. Found: $[MNa]^+$, 287.1730 (2.5 ppm error).

Characteristic ^{13}C NMR data for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 6.09 (1H, s, N**H**), 3.74 – 3.71 (2H, m, C**H**$_2$), 3.44 – 3.41 (2H, m, C**H**$_2$), 3.39 – 3.36 (2H, m, C**H**$_2$), 2.57 – 2.53 (2H, m, C**H**$_2$), 1.69 – 1.64 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 174.0 (**C**O), 171.3 (**C**O), 83.8 (**C**CH), 69.9 (C**C**H), 46.3 (**C**H_2), 45.9 (**C**H_2), 38.1 (**C**H_2), 37.3 (**C**H_2), 29.8 (**C**H_2), 26.7 (**C**H_2), 25.4 (**C**H_2), 24.9 (**C**H_2), 24.4 (**C**H_2), 22.8 (**C**H_2), 17.7 (**C**H_2).

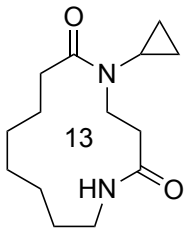
5-(3-Hydroxypropyl)-1,5-diazacyclotridecane-2,6-dione (300)



To a solution of 1-acryloylazonan-2-one **258** (98 mg, 0.50 mmol) in dry methanol (1.0 mL) was added 3-aminopropan-1-ol (40 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a white solid (73.9 mg, 55% yield); m.p. 100 – 105 °C; R_f 0.55 (2:3 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3290, 2928, 2861, 1619, 1557, 1435, 1360, 1300, 1193, 1056, 701. In solution in $CDCl_3$, the product exists as a 4:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 6.94 – 6.92 (1H, m, N**H**), 3.65 – 3.62 (2H, m, C**H**$_2$), 3.50 – 3.45 (3H, m, C**H**$_2$), 2.63 (2H, s, C**H**$_2$), 2.39 – 2.31 (3H, m, C**H**$_2$), 1.81 – 1.63 (5H, m, C**H**$_2$), 1.53 – 1.50 (2H, m, C**H**$_2$), 1.38 – 1.37 (2H, m, C**H**$_2$), 1.34 – 1.28 (3H, m, C**H**$_2$), 1.25 – 1.21 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 175.7 (**C**O), 170.8 (**C**O), 59.4 (**C**H$_2$), 46.3 (**C**H$_2$), 42.2 (**C**H$_2$), 39.8 (**C**H$_2$), 35.1 (**C**H$_2$), 32.5 (**C**H$_2$), 31.7 (**C**H$_2$), 27.9 (**C**H$_2$), 27.1 (**C**H$_2$), 26.8 (**C**H$_2$), 25.7 (**C**H$_2$), 23.9 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{14}H_{26}N_2NaO_3$, 293.1839. Found: $[MNa]^+$, 293.1836 (−1.2 ppm error).

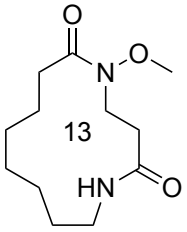
Characteristic NMR data for the minor rotamer can be found at: δ_H (400 MHz, $CDCl_3$) 6.37 – 6.34 (1H, m, N**H**), 3.68 – 3.66 (2H, m, C**H**$_2$), 3.40 – 3.36 (2H, m, C**H**$_2$), 1.68 – 1.63 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 175.1 (**C**O), 171.3 (**C**O), 58.5 (**C**H$_2$), 43.9 (**C**H$_2$), 41.9 (**C**H$_2$), 38.1 (**C**H$_2$), 36.6 (**C**H$_2$), 30.0 (**C**H$_2$), 29.8 (**C**H$_2$), 26.6 (**C**H$_2$), 25.1 (**C**H$_2$), 24.8 (**C**H$_2$), 24.5 (**C**H$_2$), 22.6 (**C**H$_2$).

5-Cyclopropyl-1,5-diazacyclotridecane-2,6-dione (301)



To a solution of 1-acryloylazonan-2-one **258** (98 mg, 0.50 mmol) in dry methanol (1.0 mL) was added cyclopropylamine (40 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a white solid (57.1 mg, 45% yield); m.p. 125 – 130 °C; R_f 0.50 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3300, 3088, 2926, 2857, 2235, 1632, 1549, 1444, 1410, 1364, 1267, 1157, 1060, 1031, 922, 729, 644. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product; δ_H (400 MHz, $CDCl_3$) 6.52 (1H, s, N**H**), 3.49 – 3.13 (2H , m, C**H**$_2$), 2.75 – 2.70 (1H, m, C**H**), 2.69 – 2.66 (2H , m, C**H**$_2$), 1.95 – 1.70 (2H, m, C**H**$_2$), 1.64 – 1.62 (2H, m, C**H**$_2$), 1.59 – 1.53 (2H, m, C**H**$_2$), 1.40 – 1.19 (8H, m, 4 x C**H**$_2$), 0.97 – 0.94 (2H, m, CHC**H**$_2$), 0.77 – 0.76 (2H, m, cyclopropyl C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 177.3 (**C**O), 170.7 (**C**O), 42.0 (**C**H$_2$), 39.7 (**C**H$_2$), 35.2 (**C**H$_2$), 33.4 (**C**H$_2$), 30.3 (**C**H), 28.1 (**C**H$_2$), 26.8 (**C**H$_2$), 26.9 (**C**H$_2$), 26.0 (**C**H$_2$), 22.9 (**C**H$_2$), 6.7 (cyclopropyl **C**H$_2$). **HRMS (ESI)**: calcd. for $C_{14}H_{24}N_2NaO_2$, 275.1730. Found: $[MNa]^+$, 275.1730 (0.1 ppm error).

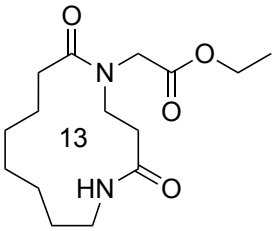
5-Methoxy-1,5-diazacyclotridecane-2,6-dione (302)



To a solution of 1-acryloylazonan-2-one **258** (98 mg, 0.50 mmol) in dry methanol (1.6 mL) was added methoxyamine (63 mg, 0.75 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a white solid (49.1 mg,

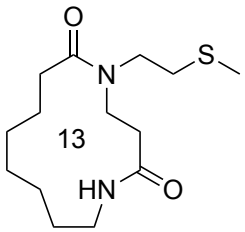
41% yield); m.p. 99 – 101 °C; R_f 0.29 (1:9 methanol:ethyl acetate). **IR** (ATR): υ_{max}/cm^{-1} 3302, 3088, 2929, 2860, 2241, 1643, 1548, 1437, 1416, 1359, 1202, 1055, 999, 905, 728. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product; δ_H (400 MHz, $CDCl_3$) 6.39 – 6.38 (1H, m, N**H**), 4.31- 3.00 (7H, m, C**H**$_3$ and 2 x C**H**$_2$), 2.67 – 2.20 (4H, m, 2 x C**H**$_2$), 1.90 – 1.63 (2H, m, C**H**$_2$), 1.55 – 1.49 (2H, m, C**H**$_2$), 1.41 (2H, s, C**H**$_2$), 1.35 – 1.30 (2H, m, C**H**$_2$), 1.28 – 1.23 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 175.4 (**C**O), 170.2 (**C**O), 61.4 (**C**H$_3$), 39.8 (**C**H$_2$), 34.6 (**C**H$_2$), 31.4 (**C**H$_2$), 27.6 (**C**H$_2$), 26.74 (**C**H$_2$), 26.7 (**C**H$_2$), 25.4 (**C**H$_2$), 22.5 (**C**H$_2$), 21.9 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{12}H_{22}N_2NaO_3$, 265.1522. Found: $[MNa]^+$, 265.1523 (0.4 ppm error).

Ethyl 2-(4,13-dioxo-1,5-diazacyclotridecan-1-yl)acetate (303)



To a solution of 1-acryloylazonan-2-one **258** (98 mg, 0.50 mmol) in dry methanol (1.0 mL) was added glycine ethyl ester (77 mg, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a pale yellow solid (68.9 mg, 46% yield); m.p. 104 – 107 °C; R_f 0.48 (1:9 methanol:ethyl acetate). **IR** (ATR): υ_{max}/cm^{-1} 3314, 3087, 2930, 2861, 2240, 1739, 1635, 1548, 1440, 1206, 1319, 1211, 1171, 1099, 921, 729; δ_H (400 MHz, $CDCl_3$) 7.13 (1H, s, N**H**), 3.98 – 3.95 (1H, m, CH_2), 3.91 – 3.85 (1H, m, C**H**$_2$), 3.76 (2H, s, C**H**$_2$), 3.58 – 3.52 (1H, m, C**H**$_2$), 3.47 – 3.40 (1H, m, C**H**$_2$), 3.20 – 3.13 (1H, m, C**H**$_2$), 2.42 – 2.33 (3H, m, C**H**$_2$), 2.32 – 2.28 (1H, m, C**H**$_2$), 1.85 – 1.77 (1H, m, C**H**$_2$), 1.61 – 1.50 (4H, m, 2 x C**H**$_2$), 1.47 – 1.46 (3H, m, C**H**$_3$), 1.41 – 1.37 (2H, m, C**H**$_2$), 1.33 – 1.30 (4H, m, 2 x C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 173.5 (**C**O), 172.8 (**C**O), 171.0 (**C**O), 55.4 (**C**H$_2$), 52.8 (**C**H$_2$COO), 44.0 (**C**H$_2$), 39.1 (**C**H$_2$), 37.2 (**C**H$_2$), 30.1 (**C**H$_2$), 26.2 (**C**H$_2$), 26.1 (**C**H$_2$), 25.0 (**C**H$_2$), 24.4 (**C**H$_2$), 22.5 (**C**H$_2$), 13.9 (**C**H$_3$). **HRMS (ESI)**: calcd. for $C_{15}H_{26}N_2NaO_4$, 321.1786. Found: $[MNa]^+$, 321.1785 (−0.5 ppm error).

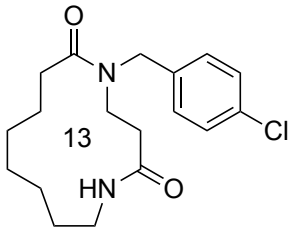
5-(2-(Methylthio)ethyl)-1,5-diazacyclotridecane-2,6-dione (304)



To a solution of 1-acryloylazonan-2-one **258** (98 mg, 0.50 mmol) in dry methanol (1.0 mL) was added 2-(methylthio)ethylamine (50 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate) to afford the title compound as a white solid (77.9 mg, 54% yield); m.p. 101 – 105 °C; R_f 0.54 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3299, 2922, 2859, 1623, 1552, 1428, 1359, 1299, 1231, 729. In solution in $CDCl_3$, the product exists as a 6:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 6.51 (1H, s, N**H**), 3.69 – 3.37 (4H, m, 2 x C**H**$_2$), 2.66 – 2.61 (4H, m, 2 x C**H**$_2$), 2.34 – 2.30 (2H, m, C**H**$_2$), 2.13 (3H, s, C**H**$_3$), 1.78 – 1.71 (2H, m, C**H**$_2$), 1.55 – 1.52 (2H, m, C**H**$_2$), 1.38 – 1.22 (8H, m, 4 x C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 175.3 (**C**O), 174.0 (**C**O), 49.2 (**C**H$_2$), 42.9 (**C**H$_2$), 39.7 (**C**H$_2$), 35.2 (**C**H$_2$), 32.8 (**C**H$_2$), 32.5 (**C**H$_2$), 28.0 (**C**H$_2$), 27.2 (**C**H$_2$), 26.9 (**C**H$_2$), 25.9 (**C**H$_2$), 24.1 (**C**H$_2$), 16.0 (**C**H$_3$). **HRMS (ESI)**: calcd. for $C_{14}H_{26}N_2NaO_2S$, 309.1607. Found: $[MNa]^+$, 309.1607 (0.0 ppm error).

Characteristic NMR data for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 6.21 – 6.20 (1H, m, N**H**); δ_C (100 MHz, $CDCl_3$) 170.5 (**C**O), 171.3 (**C**O), 46.4 (**C**H$_2$), 45.8 (**C**H$_2$), 38.1 (**C**H$_2$), 37.3 (**C**H$_2$), 32.0 (**C**H$_2$), 29.8 (**C**H$_2$), 26.7 (**C**H$_2$), 25.5 (**C**H$_2$), 24.9 (**C**H$_2$), 24.4 (**C**H$_2$), 22.9 (**C**H$_2$), 15.6 (**C**H$_3$).

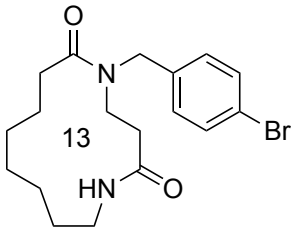
5-(4-Chlorobenzyl)-1,5-diazacyclotridecane-2,6-dione (305)



To a solution of 1-acryloylazonan-2-one **258** (98 mg, 0.50 mmol) in dry methanol (1.0 mL) was added 4-chlorobenzylamine (70 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a white solid (128.6 mg, 76% yield); m.p. 149 – 152 °C; R_f 0.66 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3299, 2929, 2859, 2238, 1628, 1553, 1491, 1443, 1407, 1359, 1091, 1014, 915, 729. In solution in $CDCl_3$, the product exists as a 8:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 7.33 – 7.29 (2H, m, Ar**H**), 7.09 – 7.06 (2H, m, Ar**H**), 6.59 (1H, s, N**H**), 4.65 – 4.57 (2H, m, C**HH'**Ph), 3.69 – 3.20 (3H, m, C**H**$_2$), 2.88 – 2.72 (3H, m, C**H**$_2$), 2.54 – 2.40 (2H, m, C**H**$_2$), 2.67 (2H, s, C**H**$_2$), 2.31 – 2.24 (2H, m, C**H**$_2$), 1.78 – 1.71 (2H, m, C**H**$_2$), 1.58 – 1.53 (2H, m, C**H**$_2$), 1.43 – 1.29 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 175.9 (**C**O), 170.6 (**C**O), 135.3 (**C**Ar), 133.6 (**C**Ar), 129.2 (Ar**C**H), 127.8 (Ar**C**H), 52.4 (**C**H$_2$), 42.8 (**C**H$_2$), 39.7 (**C**H$_2$), 35.0 (**C**H$_2$), 32.8 (**C**H$_2$), 27.9 (**C**H$_2$), 27.3 (**C**H$_2$), 27.1 (**C**H$_2$), 25.9 (**C**H$_2$), 24.2 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{18}H_{25}ClN_2NaO_2$, 359.1492. Found: $[MNa]^+$, 359.1497 (1.2 ppm error).

Characteristic NMR data for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 5.45 – 5.43 (1H, m, N**H**); δ_C (100 MHz, $CDCl_3$) 173.9 (**C**O), 171.0 (**C**O), 137.0 (**C**Ar), 133.5 (**C**Ar), 129.8 (Ar**C**H), 128.9 (Ar**C**H), 48.6 (**C**H$_2$), 44.4 (**C**H$_2$), 38.3 (**C**H$_2$), 36.7 (**C**H$_2$), 29.9 (**C**H$_2$), 26.8 (**C**H$_2$), 25.4 (**C**H$_2$), 25.2 (**C**H$_2$), 24.7 (**C**H$_2$), 22.9 (**C**H$_2$).

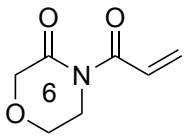
5-(4-Bromobenzyl)-1,5-diazacyclotridecane-2,6-dione (306)



To a solution of 1-acryloylazonan-2-one **258** (98 mg, 0.50 mmol) in dry methanol (1.0 mL) was added 4-bromobenzylamine (700 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate → 1:19 methanol:ethyl acetate) to afford the title compound as a white solid (101.7 mg, 53% yield); m.p. 159 – 162 °C; R_f 0.66 (1:9 methanol:ethyl acetate). **IR** (ATR): υ_{max}/cm^{-1} 3300, 3088, 2929, 2860, 1633, 1554, 1488, 1446, 1359, 1230, 1071, 1011, 919, 797, 731. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. In solution in $CDCl_3$, the product exists as a 8:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 7.45 – 7.39 (2H, m, Ar**H**), 6.70 (2H, d, *J* = 8.4 Hz, Ar**H**), 6.76 – 6.74 (1H, m, N**H**), 4.63 – 4.53 (2H, m, C**H**$_2$), 4.00 – 2.97 (4H, m, 2 x C**H**$_2$), 2.84 – 2.49 (2H, m, C**H**$_2$), 2.28 – 2.25 (2H, m, C**H**$_2$), 1.75 – 1.69 (2H, m, C**H**$_2$), 1.61 – 1.51 (2H, m, C**H**$_2$), 1.39 – 1.28 (6H, m, 3 x C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 175.8 (**C**O), 170.6 (**C**O), 135.9 (**C**Ar), 132.1 (Ar**C**H), 128.1 (Ar**C**H), 121.5 (**C**Ar), 52.6 (**C**H$_2$), 43.0 (**C**H$_2$), 39.6 (**C**H$_2$), 34.8 (**C**H$_2$), 32.8 (**C**H$_2$), 27.9 (**C**H$_2$), 27.2 (**C**H$_2$), 27.1 (**C**H$_2$), 25.9 (**C**H$_2$), 24.3 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{18}H_{25}{}^{79}BrN_2NaO_2$, 403.0993. Found: $[MNa]^+$, 403.0992 (−0.3 ppm error).

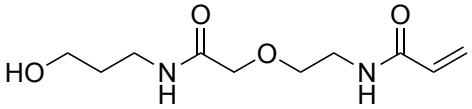
Characteristic NMR data for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 5.79 – 5.76 (1H, m, N**H**); δ_C (100 MHz, $CDCl_3$) 173.8 (**C**O), 171.1 (**C**O), 137.3 (**C**Ar), 131.8 (Ar**C**H), 130.1 (Ar**C**H), 121.4 (**C**Ar), 48.4 (**C**H$_2$), 44.2 (**C**H$_2$), 38.2 (**C**H$_2$), 36.5 (**C**H$_2$), 29.9 (**C**H$_2$), 26.7 (**C**H$_2$), 25.3 (**C**H$_2$), 25.2 (**C**H$_2$), 24.7 (**C**H$_2$), 22.8 (**C**H$_2$).

4-Acryloylmorpholin -3-one (308)



A solution of morpholin-3-one (1.00 g, 10.00 mmol) in dry THF (36) was cooled to 0 °C and a solution of MeMgBr (3M in diethyl ether, 3.6 mL, 11.00 mmol) was added *via* dropwise using a syringe pump over 30 min. The reaction was stirred for 10 min at 0 °C, then acryloyl chloride (1.2 mL, 15.00 mmol) was added and the reaction was stirred 30 min at 0 °C. The reaction was quenched with saturated aq. NH_4Cl solution (50 mL) and extracted with Et_2O (50 mL). The combined organics were washed with saturated aq. $NaHCO_3$ solution (2 x 40 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified with flash column chromatography (1:1 diethyl ether:hexane) to afford the title compound as a white solid (634.0 mg, 41% yield); m.p. 60 − 62 °C; R_f 0.43 (1:1 diethyl ether:hexane). **IR** (ATR): ν_{max}/cm^{-1} 2953, 1678, 1403, 1384, 1289, 1209, 1155, 1003, 796, 607; δ_H (400 MHz, $CDCl_3$) 7.20 (1H, dd, *J* = 16.9, 10.4 Hz, NCOC**H**CHH'), 6.41 (1H, dd, *J* = 16.9, 1.8 Hz, NCOCHC**H**H'), 5.80 (1H, dd, *J* = 10.4, 1.7 Hz, NCOCHCH**H**'), 4.27 (2H, s, NC$\mathbf{H}_2$), 3.94 – 3.91 (2H, m, C$\mathbf{H}_2$CON), 3.82 – 3.80 (2H, m, $CH_2OC\mathbf{H}_2$); δ_C (100 MHz, $CDCl_3$) 169.7 (**C**O), 168.2 (**C**O), 131.3 (NCO**C**HCHH'), 130.2 (NCOCH**C**HH'), 69.0 (N**C**H_2), 64.1 (**C**H_2CON), 43.7 (**C**H_2); **HRMS (ESI)**: calcd. for $C_7H_9NNaO_3$, 178.0475. Found $[MNa]^+$ 178.0475 (0.0 ppm error).

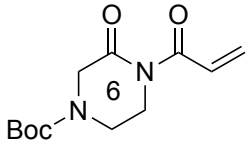
***N*-(2-(2-((3-Hydroxypropyl)amino)-2-oxoethoxy)ethyl)acrlamide (310)**



To a solution of 4-acryloylmorpholin-3-one **308** (83 mg, 0.54 mmol) in dry methanol (1.1 mL) was added 3-aminopropan-1-ol (50 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated in *vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a colourless oil (12.2 mg, 10% yield); R_f 0.44 (2:3 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3300, 2936, 1657, 1627, 1540, 1397, 1312, 1204, 1113, 1068, 981, 728, 566; δ_H (400 MHz, $CDCl_3$) 7.30 – 7.29 (1H, m, N**H**), 6.41 (1H, s, N**H**), 6.31 (1H, dd, *J* = 17.0, 1.4 Hz,

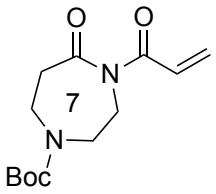
NCOC**H**CHH'), 6.14 (1H , dd, *J* = 17.0, 10.2 Hz, NCOCHC**H**H'), 5.67 (1H, dd, *J* = 10.2, 1.4 Hz, NCOCHCH**H'**), 3.97 (2H, s, C$\mathbf{H}_2$), 3.70 (2H, m, C$\mathbf{H}_2$), 3.64 – 3.61 (2H, m, C$\mathbf{H}_2$), 3.58 – 3.54 (2H, m, C$\mathbf{H}_2$), 3.47 – 3.43 (2H , m, C$\mathbf{H}_2$), 1.75 – 1.70 (2H, m, C$\mathbf{H}_2$); δ_C (100 MHz, $CDCl_3$) 170.3 (**C**O), 166.2 (**C**O), 130.7 (**C**H), 127.2 (**C**HH'), 70.7 (**C**H_2), 70.5 (**C**H_2), 60.3 (**C**H_2), 39.5 (**C**H_2), 36.6 (**C**H_2), 31.7 (**C**H_2). **HRMS (ESI)**: calcd. for $C_{10}H_{18}N_2NaO_4$, 253.1159. Found: $[MNa]^+$, 253.1157 (−0.9 ppm error).

***tert*-Butyl 4-acryloyl-3-oxopiperazine-1-carboxylate (315)**



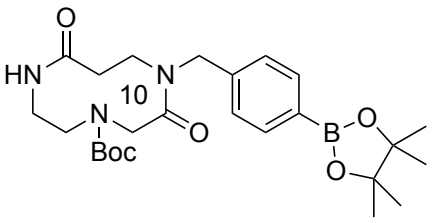
To a stirring solution of *tert*-butyl 3-oxopiperazine-1-carboxylate **314** (1.00 g, 5.00 mmol) in dry THF (18 mL) cooled to 0 °C was added a solution of MeMgBr (3M in diethyl ether, 1.8 mL, 5.5 mmol) *via* dropwise using a syringe pump over 30 min. The reaction was stirred for 10 min at 0 °C, then acryloyl chloride (0.6 mL, 7.5 mmol) was added and the reaction was stirred 30 min at 0 °C. The reaction was quenched with saturated aq. NH_4Cl solution (35 mL) and extracted with Et_2O (35 mL). The combined organics were washed with saturated aq. $NaHCO_3$ solution (2 x 35 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified with flash column chromatography (1:1 diethyl ether:hexane) to afford the title compound as a colourless oil (905 mg, 71% yield); R_f 0.51 (1:1 diethyl ether:hexane). **IR** (ATR): υ_{max} /cm^{-1} 2977, 2934, 1686, 1477, 1407, 1390, 1305, 1366, 1243, 1163, 1133, 1022, 919, 864, 796, 769 609; δ_H (400 MHz, $CDCl_3$) 7.14 (1H, dd, *J* = 16.9, 10.4 Hz, NCOC**H**CHH'), 6.42 (1H, dd, *J* = 16.9, 1.5 Hz, NCOCHC**H**H'), 5.81 (1H, dd, *J* = 10.4, 1.5 Hz, CHCH**H**'), 4.23 (2H, s, C$\mathbf{H}_2$), 3.90 – 3.87 (2H, m, C$\mathbf{H}_2$), 3.64 – 3.62 (2H, m, C$\mathbf{H}_2$), 1.47 (9H, s, 3 x CH_3); δ_C (100 MHz, $CDCl_3$) 168.8 (**C**O), 168.1 (**C**O), 153.7 (*t*-BuO-**C**O), 131.1 (**C**HCHH'), 130.3 (CH**C**HH'), 81.3 (COO**C**), 49.2 (**C**H_2), 42.3 (**C**H_2), 40.8 (**C**H_2), 28.4 (**C**H_3). **HRMS (ESI)**: calcd. for $C_{12}H_{18}N_2NaO_4$, 277.1159. Found: $[MNa]^+$, 277.1159 (0.1 ppm error).

***tert*-Butyl 4-acryloyl-5-oxo-1,4-diazepane-1-carboxylate (317)**



A solution of *tert*-butyl 5-oxo-1,4-diazepane-1-carboxylate **316** (2.0 g, 9.3 mmol) in dry THF (34 mL) was cooled to 0 °C and a solution of MeMgBr (3M in diethyl ether, 3.4 mL, 10.3 mmol) was added *via* dropwise using a syringe pump over 30 min. The reaction was stirred for 10 min at 0 °C, then acryloyl chloride (1.2 mL, 14.0 mmol) was added and the reaction was stirred 30 min at 0 °C. The reaction was quenched with saturated aq. NH_4Cl solution (30 mL) and extracted with Et_2O (30 mL). The combined organics were washed with saturated $NaHCO_3$ solution (2 x 30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified with flash column chromatography (1:1 diethyl ether:hexane → 2:1 diethyl ether:hexane) to afford the title compound as a white solid (1.9 gram, 76% yield); m.p. 70 – 74 °C; R_f 0.36 (2:1 diethyl ether:hexane). **IR** (ATR): ν_{max} /cm^{-1} 3357, 2977, 2933, 1682, 1561, 1420, 1405, 1366, 1329, 1242, 1161, 1116, 1042, 957, 864, 795, 770, 585; δ_H (400 MHz, $CDCl_3$) 6.93 (1H, dd, *J* = 16.8, 10.3 Hz, C**H**CHH'), 6.40 (1H, dd, *J* = 16.8, 1.5 Hz, CHC**H**H'), 5.73 (1H, dd, *J* = 10.3, 1.5 Hz, CHCH**H**'), 4.00 – 3.98 (2H, m, C**H**$_2$), 3.67 – 3.59 (4H, m, 2 x C**H**$_2$), 2.84 – 2.81 (2H, m, C**H**$_2$), 1.45 (9H, s, 3 x CH_3); δ_C (100 MHz, $CDCl_3$) 176.0 (**C**O), 168.5 (**C**O), 154.6 (*t*-BuO-**C**O), 131.3 (**C**HCHH'), 129.1 (CH**C**HH'), 80.9 (**C**CH_3), 47.5 (**C**H_2), 44.1 (**C**H_2), 41.4 (2 x **C**H_2, overlapping), 28.4 (**C**H_3). **HRMS (ESI)**: calcd. for $C_{13}H_{20}N_2NaO_4$, 291.1310. Found: $[MNa]^+$, 291.1315 (1.7 ppm error).

***tert*-Butyl 2,8-dioxo-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1,4-7-triazecane-4-carboxylate (321)**

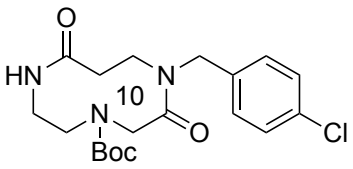


To a solution of *tert*-butyl 4-acryloyl-3-oxopiperazine-1-carboxylayte **315** (127 mg, 0.50 mmol) in dry methanol (1.0 mL) was added benzyl(3-aminopropyl)carbamate (156 mg, 0.75 mmol).

The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (1:99 methanol: ethyl acetate) to afford the title compound as a white solid (167.8 mg, 69% yield). In solution in $CDCl_3$, this compound exists as a 1:3 mixture of rotamers; m.p. 77 – 80 °C; R_f 0.66 (1:9 methanol:ethyl acetate). **IR** (ATR): υ_{max}/cm^{-1} 3300, 3085, 2978, 2934, 2247, 1657, 1547, 1488, 1456, 1400, 1359, 1246, 1162, 1143, 1088, 962, 911, 859, 729, 657; NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 7.73 – 7.71 (2H, m Ar**H**), 7.16 – 7.14 (2H, m, Ar**H**), 5.84 (1H, s, N**H**), 5.15 – 4.97 (2H, m, C**H**$_2$), 4.30 – 4.04 (3H, m, C**H**$_2$), 3.69 – 3.65 (1H, m, C**H**$_2$), 3.27 – 3.24 (1H, m, C**H**$_2$), 3.07 – 2.98 (1H, m, C**H**$_2$), 2.93 – 2.82 (2H, m, C**H**$_2$), 2.70 – 2.69 (1H, m, C**H**$_2$), 2.43 – 2.41 (1H, m, C**H**$_2$), 1.47 – 1.42 (9H, m, 3 x C**H**$_3$), 1.28 (12H, s, 4 x C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 172.6 (**C**O), 170.8 (**C**O), 155.1 (*t*-BuO-**C**O), 140.0 (**C**Ar), 135.4 (Ar**C**H), 135.3 (**C**Ar), 126.5 (Ar**C**H), 83.8 (**C**CH$_3$), 81.2 (COO**C**), 52.0 (**C**H$_2$), 51.5 (**C**H$_2$), 49.1 (**C**H$_2$), 41.6 (**C**H$_2$), 38.7 (**C**H$_2$), 35.0 (**C**H$_2$), 28.3 (3 x **C**H$_3$), 24.9 (4 x **C**H$_3$). **HRMS (ESI)**: calcd. for $C_{25}H_{38}BN_3NaO_6$, 510.2760. Found: $[MNa]^+$, 510.2746 (−2.0 ppm error).

Characteristic NMR data for the minor rotamers can be found at: δ_C (100 MHz, $CDCl_3$) 171.8 (**C**O), 154.1 (**C**O), 139.5 (**C**Ar), 83.9 (**C**CH$_3$), 81.3 (COO**C**), 52.3 (**C**H$_2$), 42.2 (**C**H$_2$), 41.0 (**C**H$_2$), 38.4 (**C**H$_2$), 34.8 (**C**H$_2$), 28.3 (**C**H$_3$).

***tert*-Butyl 1-(4-chlorobenzyl)-2,8-dioxo-1,4,7-triazecane-4-carboxylate (323)**

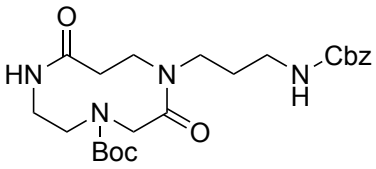


To a solution of *tert*-butyl 4-acryloyl-3-oxopiperazine-1-carboxylayte **315** (127 mg, 0.50 mmol) in dry methanol (1.0 mL) was added 4-chlorobenzylamine (78 mg, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (1:99 methanol: ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a white solid (167.8 mg, 69% yield); m.p. 77 – 80 °C; R_f 0.60 (1:9 methanol:ethyl acetate). **IR** (ATR): υ_{max}/cm^{-1} 3300, 3086, 2977, 2246, 1653, 1547, 1406, 1366, 1245, 1160, 1128, 1091, 726, 646. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of

the product. The ratio could not be determined due to the presence of a complex mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 7.26 – 7.24 (2H, m Ar**H**), 7.10 – 7.08 (2H, m, Ar**H**), 5.85 – 5.83 (1H, m, N**H**), 5.08 (1H, d, *J* = 16.5 Hz, C**H**H'), 4.99 – 4.95 (1H, m, C$\mathbf{H}_2$), 4.22 – 4.16 (2H, m, C$\mathbf{H}_2$), 4.10 – 4.06 (1H, m, CH**H**'), 3.72 – 3.68 (1H, m, C$\mathbf{H}_2$), 3.25 – 3.21 (1H, m, C$\mathbf{H}_2$), 3.02 – 2.99 (1H, m, C$\mathbf{H}_2$), 2.96 – 2.91 (1H, m, C$\mathbf{H}_2$), 2.84 – 2.80 (1H, m, C$\mathbf{H}_2$), 2.76 – 2.69 (1H, m, C$\mathbf{H}_2$), 2.47 – 2.40 (1H, m, C$\mathbf{H}_2$), 1.47 (9H, s, 3 x C$\mathbf{H}_3$); δ_C (100 MHz, $CDCl_3$) 172.6 (**C**O), 170.7 (**C**O), 155.1 (*t*-BuO-**C**O), 135.5 (**C**Ar), 133.4 (**C**Ar), 129.0 (Ar**C**H), 128.5 (Ar**C**H), 81.4 (**C**CH_3), 52.3 (**C**H_2), 51.6 (**C**H_2), 49.2 (**C**H_2), 41.7 (**C**H_2), 38.8 (**C**H_2), 35.1 (**C**H_2), 28.3 (3 x **C**H_3). **HRMS (ESI)**: calcd. for $C_{19}H_{26}ClN_3NaO_4$, 418.1496. Found: $[MNa]^+$, 418.1504 (1.9 ppm error).

Characteristic NMR data for the minor rotamers can be found at: δ_C (100 MHz, $CDCl_3$) 171.8 (**C**O), 154.0 (**C**O), 153.9 (**C**O), 134.9 (**C**Ar), 133.8 (**C**Ar), 129.6 (Ar**C**H), 129.2 (Ar**C**H), 129.1 (Ar**C**H), 128.0 (Ar**C**H), 80.9 (**C**CH_3), 52.4 (**C**H_2), 42.2 (**C**H_2), 41.1 (**C**H_2), 38.5 (**C**H_2), 34.8 (**C**H_2), 28.3 (**C**H_3).

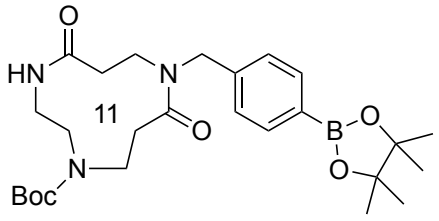
tert-Butyl1-(3-(((benzyloxy)carbonyl)aminopropyl)-2,8-dioxo-1,4,7-triazecane-4-carboxylate (323)



To a solution of *tert*-butyl 4-acryloyl-3-oxopiperazine-1-carboxylayte **315** (127 mg, 0.50 mmol) in dry methanol (1.0 mL) was added (4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl) methanamine (128 mg, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate) to afford the title compound as a colourless oil (135.4 mg, 59% yield); R_f 0.40 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3316, 2975, 2935, 2246, 1659, 1536, 1454, 1433, 1405, 1366, 1244, 1157, 911, 728, 697; δ_H (400 MHz, $CDCl_3$) 7.33 – 7.32 (5H, m Ar**H**), 5.63 (1H, s, N**H**), 5.61 (1H, s, N**H**), 5.09 – 5.07 (2H, m, C$\mathbf{H}_2$), 4.90 (1H, d, *J* = 14.2 Hz, C**H**H'), 4.27 – 4.24 (1H, m, C$\mathbf{H}_2$), 4.05 – 4.02 (1H, m, C$\mathbf{H}_2$), 3.77 – 3.69 (2H, m,

C**H**$_2$), 3.32 – 3.25 (2H, m, C**H**$_2$), 3.22 – 3.18 (1H, d, *J* = 14.2 Hz, CH**H'**), 3.06 – 3.00 (2H, m, C**H**$_2$), 2.98 – 2.94 (1H, m, C**H**$_2$), 2.86 – 2.82 (1H, m, C**H**$_2$), 2.77 – 2.70 (1H, m, C**H**$_2$), 2.47 – 2.40 (1H, m, C**H**$_2$), 1.80 – 1.75 (1H, m, C**H**$_2$), 1.71 – 1.65 (1H, m, C**H**$_2$), 1.45 (9H, s, C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 172.1 (**C**O), 170.8 (**C**O), 156.7 (**C**O), 155.4 (**C**O), 136.8 (**C**Ar), 128.6 (Ar**C**H), 128.5 (**C**Ar), 128.1 (Ar**C**H), 81.7 (**C**CH$_3$), 66.6 (**C**H$_2$), 51.8 (**C**H$_2$), 49.1 (**C**H$_2$), 47.0 (**C**H$_2$), 42.1 (**C**H$_2$), 38.9 (**C**H$_2$), 38.5 (**C**H$_2$), 35.2 (**C**H$_2$), 29.2 (**C**H$_2$), 28.3 (**C**H$_3$). **HRMS (ESI)**: calcd. for $C_{23}H_{34}N_4NaO_6$, 485.2377. Found: $[MNa]^+$, 485.2371 (−1.4 ppm error).

tert-Butyl 5,9-dioxo-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1,4-8-triazacycloundecane-1-carboxylate (326)

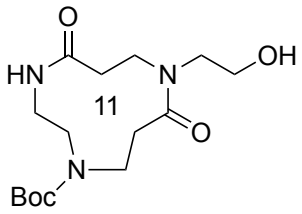


To a solution of *tert*-butyl 4-acryloyl-5-oxo-1,4-diazepane-1-carboxylayte **317** (134 mg, 0.50 mmol) in dry methanol (1.00 mL) was added (4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanamine (128 mg, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated in *vacuo*. The crude was purified by column chromatography (1:99 methanol: ethyl acetate) to give the title compound as a white solid (180.5 mg, 72% yield); m.p. 54 – 60 °C; R_f 0.66 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3318, 2979, 2933, 2249, 1646, 1548, 1478, 1405, 1359, 1247, 1166, 1142, 906, 858, 726, 648. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. In solution in $CDCl_3$, the product exists as a 5:3:2 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 7.71 – 7.69 (2H, m, Ar**H**), 7.28 – 7.24 (2H, m, Ar**H**), 6.10 – 6.08 (1H, m, N**H**), 4.90 – 4.74 (1H, m, C**H**$_2$), 4.64 (1H, s, C**H**$_2$), 4.28 – 4.16 (2H, m, C**H**$_2$), 3.59 – 3.51 (2H, m, C**H**$_2$), 3.25 – 3.21 (3H, m, C**H**$_2$), 2.94 – 2.75 (3H, m, C**H**$_2$), 2.15 – 2.07 (2H, m, C**H**$_2$), 1.27 (22H, s, C**H**$_2$ and C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 174.6 (**C**O), 170.4 (**C**O), 156.4 (*t*-BuO-**C**O), 139.8 (**C**Ar), 135.4 (Ar**C**H), 135.3 (**C**Ar), 125.8 (Ar**C**H), 83.9 (**C**CH$_3$), 79.8 (OO**C**CH$_3$), 53.1 (**C**H$_2$), 53.0 (**C**H$_2$), 51.5 (**C**H$_2$), 42.6 (**C**H$_2$),

38.9 (**C**H_2), 35.2 (**C**H_2), 32.6 (**C**H_2), 28.3 (**C**H_3), 24.8 (**C**H_3). **HRMS (ESI)**: calcd. for $C_{26}H_{40}BN_3NaO_6$, 524.2902. Found: $[MNa]^+$, 524.2916 (−1.7 ppm error).

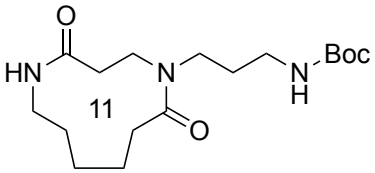
Characteristic NMR data for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 5.94 – 5.92 (1H, m, N**H**), 5.80 (1H, m, N**H**); δ_C (100 MHz, $CDCl_3$) 173.7 (**C**O), 171.5 (**C**O), 156.0 (**C**O), 155.8 (**C**O), 141.7 (**C**Ar), 141.2 (**C**Ar), 139.5 (Ar**C**H), 135.1 (**C**Ar), 127.4 (Ar**C**H), 125.7 (Ar**C**H), 83.8 (**C**CH_3), 80.6 (OO**C**CH_3), 80.4 (OO**C**CH_3), 52.4 (**C**H_2), 50.7 (**C**H_2), 49.7 (**C**H_2), 49.2 (**C**H_2), 48.3 (**C**H_2), 46.8 (**C**H_2), 45.5 (**C**H_2), 45.0 (**C**H_2), 42.2 (**C**H_2), 38.8 (**C**H_2), 36.8 (**C**H_2), 33.7 (**C**H_2), 31.4 (**C**H_2), 28.4 (**C**H_3).

***tert*-Butyl 8-(2-hydroxyethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate (328)**



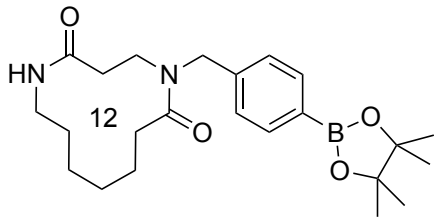
To a solution of *tert*-butyl 4-acryloyl-5-oxo-1,4-diazepane-1-carboxylate **317** (268 mg, 1.00 mmol) in dry methanol (2.0 mL) was added ethanolamine (70 µL, 1.1 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (1:19 methanol:ethyl acetate → 1:9 methanol:ethyl acetate → 1:4 methanol:ethyl acetate) to afford the title compound as a yellow oil (155.3 mg, 47% yield). R_f 0.47 (1:4 methanol:ethyl acetate). **IR** (ATR): υ_{max}/cm^{-1} 3299, 2978, 2933, 2864, 2248, 1642, 1476, 1408, 1351, 1247, 1163, 1067, 906, 725, 646; The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. δ_H (400 MHz, $CDCl_3$) 7.56 (1H, s, N**H**), 4.42 – 4.04 (2H, m, C**H**$_2$), 3.91 – 3.45 (5H , m, C**H**$_2$), 3.38 – 3.23 (3H , m, C**H**$_2$), 3.11 – 2.91 (2H, m, C**H**$_2$), 2.79 – 2.41 (2H, m, C**H**$_2$), 2.33 – 1.98 (2H, m, C**H**$_2$), 1.46 (9H, s, 3 x C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 174.2 (**C**O), 172.0 (**C**O), 156.5 (**C**O), 80.0 (**C**CH_3), 61.4 (**C**H_2), 60.5 (**C**H_2), 53.1 (**C**H_2), 52.7 (**C**H_2), 44.2 (**C**H_2), 39.0 (**C**H_2), 36.8 (**C**H_2), 31.9 (**C**H_2), 28.5 (**C**H_3). **HRMS (ESI)**: calcd. for $C_{15}H_{27}N_3NaO_5$, 352.1828. Found: $[MNa]^+$, 352.1843 (4.3 ppm error).

***tert*-Butyl (3-(4,11-dioxo-1,5-diazacycloundecan-1-yl)propyl)carbamate (330)**



To a solution of 1-acryloylazepan-2-one **317** (1.47 g, 8.8 mmol) in dry methanol (17.5 mL) was added *N*-Boc-1,3-diaminopropane (1.68 g, 9.7 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (1:19 methanol:ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a off-white solid (2.50 g, 83% yield); m.p. 108 – 111 °C; R_f 0.60 (1:4 methanol:ethyl acetate). **IR** (ATR): υ_{max}/cm^{-1} 3305, 2934, 1690, 1623, 1454, 1365, 1250, 1169. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product; δ_H (400 MHz, $CDCl_3$) 6.92 – 6.90 (1H, m, N**H**), 5.27 (1H, s, N**H**), 3.72 – 3.42 (2H, m, C**H**$_2$), 3.33 – 2.90 (5H, m, C**H**$_2$), 2.60 – 2.32 (4H, m, 2 x C**H**$_2$), 2.09 – 1.95 (1H, m, C**H**$_2$), 1.73 – 1.62 (6H, m, 3 x C**H**$_2$), 1.38 (11H, m, C**H**$_2$ and 3 x C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 174.1 (**C**O), 171.7 (**C**O), 156.4 (**C**O), 79.3 (**C**CH$_3$), 45.7 (**C**H$_2$), 43.5 (**C**H$_2$), 41.4 (**C**H$_2$), 37.9 (overlapping, 2 x **C**H$_2$), 29.0 (**C**H$_2$), 28.5 (overlapping **C**H$_2$ and **C**H$_3$), 25.3 (**C**H$_2$), 24.3 (**C**H$_2$), 22.5 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{17}H_{31}N_3NaO_4$, 364.2204. Found: [MNa]$^+$, 364.2207 (0.8 ppm error).

5-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1,5-diazacyclododecane-2,6-dione (331)

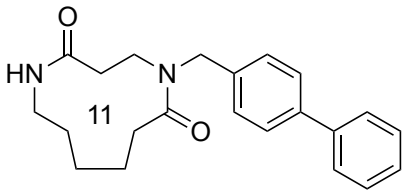


To a solution of 1-acryloylazonan-2-one **255** (98 mg, 0.50 mmol) in dry methanol (1.0 mL) was added (4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanamine (128 mg, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate) to afford the title

compound as a white solid (120.1 mg, 58% yield). In solution in $CDCl_3$, this compound exists as a 6:1 mixture of 2 rotamers; m.p. 77 – 80 °C; R_f 0.61 (1:9 methanol:ethyl acetate). **IR** (ATR): υ_{max}/cm^{-1} 3300, 3085, 2978, 2931, 1645, 1614, 1556, 1456, 1406, 1361, 1273, 1214, 1144, 1089, 1021, 963, 859, 657; NMR data for the major rotamer only: δ_H (400 MHz, $CDCl_3$) 7.78 (2H, d, *J* = 7.9 Hz, Ar**H**), 7.14 (2H, d, *J* = 7.9 Hz, Ar**H**), 6.44 – 6.42 (1H, m, N**H**), 4.90 (1H, d, *J* = 17.1 Hz, C**H**H'Ph), 4.53 (1H, ddd, *J* = 14.2, 9.3, 5.1 Hz, C**H**$_2$), 4.42 (1H, d, *J* = 17.1 Hz, CH**H'**Ph), 3.79 – 3.70 (1H, m, C**H**$_2$), 2.89 – 2.83 (2H, m, C**H**$_2$), 2.80 – 2.74 (1H, m, C**H**$_2$), 2.60 – 2.53 (1H, m, C**H**$_2$), 2.49 – 2.43 (1H, m, C**H**$_2$), 2.14 – 2.03 (2H, m, C**H**$_2$), 1.61 – 1.41 (6H, m, 3 x C**H**$_2$), 1.33 (12H, s, 4 x C**H**$_3$), 1.17 – 1.12 (1H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 176.1 (**C**O), 170.3 (**C**O), 139.7 (**C**Ar), 135.5 (**C**Ar), 128.0 (Ar**C**H), 125.8 (Ar**C**H), 84.0 (**C**CH$_3$), 52.0 (**C**HH'Ph), 41.1 (**C**H$_2$), 39.2 (**C**H$_2$), 35.2 (**C**H$_2$), 32.5 (**C**H$_2$), 27.4 (**C**H$_2$), 25.8 (**C**H$_2$), 25.0 (**C**H$_3$), 23.9 (**C**H$_2$), 22.2 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{23}H_{35}BN_2NaO_4$, 437.2592. Found: $[MNa]^+$, 437.2582 (−1.2 ppm error).

Characteristic NMR data for the minor rotamers can be found at: δ_C (100 MHz, $CDCl_3$) 175.0 (**C**O), 170.9 (**C**O), 141.9 (**C**Ar), 135.3 (**C**Ar), 127.2 (Ar**C**H), 49.6 (**C**H$_2$), 45.6 (**C**H$_2$), 37.1 (**C**H$_2$), 36.8 (**C**H$_2$), 31.0 (**C**H$_2$), 26.8 (**C**H$_2$), 24.7 (**C**H$_3$), 23.6 (**C**H$_2$), 22.6 (**C**H$_2$).

5-([1,1'-Biphenyl]-4-ylmethyl)-1,5-diazacycloundecane-2,6-dione (332)

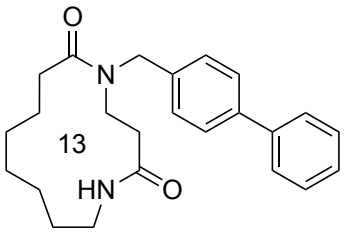


5-(4-Bromobenzyl)azacycloundecane-2,6-dione **282** (71.0 mg, 0.2 mmol) and phenylboronic acid (37.0 mg, 0.3 mmol) were dissolved in 1,4-dioxane (2.0 mL) then Na_2CO_3 (64.0 mg, 0.6 mmol) was dissolved in water (1.0 mL), was added while stirring subsequently. Pd(dppf)Cl_2(CH_2Cl_2) (8.0 mg, 0.05 mmol) was added, and the reaction was heated to 50 °C and stirred for 18 hours. The reaction was then cooled to RT and quenched with H_2O (15 mL) and extracted with DCM (3 x 15 mL). The combined organics dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a white solid (54.1 mg, 77% yield); m.p. 180 –184 °C; R_f 0.45 (1:49 methanol:ethyl acetate). **IR** (ATR): υ_{max}/cm^{-1}

3300, 3087, 2933, 2866, 1624, 1560, 1488, 1453, 1293, 1229, 1183, 1152, 758, 699. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. In solution in $CDCl_3$, the product exists as a 7:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 7.56 – 7.54 (4H, m, Ar**H**), 7.44 – 7.41 (2H, m, Ar**H**), 7.37 – 7.33 (3H, m, Ar**H**), 6.06 – 6.05 (1H, m, N**H**), 5.21 – 4.83 (1H, m, C**H**$_2$), 4.50 – 4.21 (1H, m, C**H**$_2$), 4.13 – 3.19 (3H, m, C**H**$_2$), 2.69 – 2.40 (2H, m, C**H**$_2$), 2.27 – 2.06 (4H, m, 2 x C**H**$_2$), 1.70 – 1.64 (3H, m, C**H**$_2$), 1.39 – 0.95 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 173.6 (**C**O), 171.5 (**C**O), 140.8 (**C**Ar), 140.5 (**C**Ar), 137.2 (**C**Ar), 129.0 (Ar**C**H), 128.7 (Ar**C**H), 127.6 (Ar**C**H), 127.5 (Ar**C**H), 127.1 (Ar**C**H), 48.6 (N**C**H$_2$), 45.0 (**C**H$_2$), 41.7 (**C**H$_2$), 37.0 (**C**H$_2$), 28.5 (**C**H$_2$), 25.3 (**C**H$_2$), 24.4 (**C**H$_2$), 22.8 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{22}H_{26}N_2NaO_2$, 373.1883. Found: $[MH]^+$, 373.1886 (1.0 ppm error).

Characteristic NMR data for the minor rotamer can be found at: δ_H (400 MHz, $CDCl_3$) 5.95 – 5.93 (1H, s, N**H**), δ_C (100 MHz, $CDCl_3$) 175.4 (**C**O), 171.1 (**C**O), 140.8 (**C**Ar), 136.0 (**C**Ar), 53.8 (**C**H$_2$), 43.0 (**C**H$_2$), 37.5 (**C**H$_2$), 34.7 (**C**H$_2$), 33.8 (**C**H$_2$), 26.0 (**C**H$_2$), 23.5 (**C**H$_2$), 22.4 (**C**H$_2$).

3-([1,1'-Biphenyl]-4-ylmethyl)-1,3-diazacyclotridecane-2,6-dione (333)

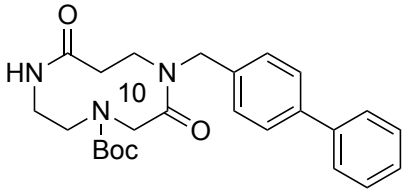


To a solution of 5-(4-bromobenzyl)-1,5-diazacyclotridecane-2,6-dione **306** (60 mg, 0.16 mmol) and phenylboronic acid (29.0 mg, 0.24 mmol) were dissolved in 1,4-dioxane (2.0 mL) then Na_2CO_3 (64 mg, 0.6 mmol) was dissolved in water (1.0 mL) and the solution added while stirring. Pd(dppf)Cl_2(CH_2Cl_2) (6.5 mg, 0.008 mmol) was added, and the reaction mixture was heated to 50 °C and stirred for 18 hours. The reaction mixture was cooled to RT and quenched with H_2O (10 mL) and extracted with DCM (3 x 10 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a yellow solid (48.3 mg, 80% yield); m.p. 127 – 131 °C; R_f 0.56 (1:49 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3289, 2977, 2931, 1612, 1561, 1404, 1359, 1271,

1143, 1088, 962, 859, 732, 658; The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. In solution in $CDCl_3$, this compound exists as a 9:1:1 mixture of 3 rotamers. NMR data for the major rotamer: δ_H (400 MHz, $CDCl_3$) 7.58 – 7.54 (4H, m, Ar**H**), 7.47 – 7.32 (4H, m, Ar**H**), 7.21 (2H, d, *J* = 8.1 Hz, Ar**H**), 6.84 (1H, s, N**H**), 4.88 – 4.58 (2H, m, C**H**$_2$), 4.03 – 2.91 (4H, m, 2 x C**H**$_2$), 2.85 – 2.53 (2H, m, C**H**$_2$), 2.45 – 2.32 (2H, m, C**H**$_2$), 1.79 – 1.77 (2H, m, C**H**$_2$), 1.59 (2H, s, C**H**$_2$), 1.45 (2H, s, C**H**$_2$), 1.41 – 1.36 (2H, m, C**H**$_2$), 1.33 – 1.32 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 176.1 (**C**O), 170.7 (**C**O), 140.7 (**C**Ar), 140.5 (**C**Ar), 135.6 (**C**Ar), 128.9 (Ar**C**H), 127.7 (Ar**C**H), 127.5 (Ar**C**H), 127.1 (Ar**C**H), 126.8 (Ar**C**H), 52.4 (**C**H$_2$), 42.5 (**C**H$_2$), 39.7 (**C**H$_2$), 35.0 (**C**H$_2$), 33.0 (**C**H$_2$), 27.9 (**C**H$_2$), 27.2 (**C**H$_2$), 27.0 (**C**H$_2$), 25.7 (**C**H$_2$), 24.1 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{24}H_{30}N_2NaO_2$, 401.2201. Found: $[MNa]^+$, 401.2199 (−0.3 ppm error).

Characteristic NMR data for the minor rotamers can be found at: δ_C (100 MHz, $CDCl_3$) 175.8 (**C**O), 173.8 (**C**O), 171.1 (**C**O), 137.6 (**C**Ar), 135.9 (**C**Ar), 132.1 (**C**Ar), 128.1 (Ar**C**H), 127.5 (Ar**C**H), 52.5 (**C**H$_2$), 48.9 (**C**H$_2$), 44.7 (**C**H$_2$), 42.9 (**C**H$_2$), 38.4 (**C**H$_2$), 36.7 (**C**H$_2$), 32.8 (**C**H$_2$), 30.0 (**C**H$_2$), 29.8 (**C**H$_2$), 26.8 (**C**H$_2$), 25.9 (**C**H$_2$), 25.3 (**C**H$_2$), 24.8 (**C**H$_2$), 24.3 (**C**H$_2$), 23.0 (**C**H$_2$).

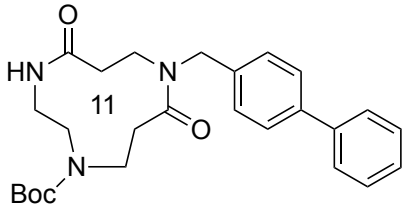
***tert*-Butyl 1-([1,1'-biphenyl]-4-ylmethyl)-2,8-dioxo-1,4,7-triazecane-4-carboxylate (334)**



tert-Butyl 2,8-dioxo-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1,4-7-triazecane-4-carboxylate **321** (209 mg, 0.43 mmol) and bromobenzene (0.07 mL, 0.64 mmol) were dissolved in 1,4-dioxane (4.0 mL). Then Na_2CO_3 (136.7 mg, 1.29 mmol) was dissolved in water (2.0 mL), and was added while stirring. $Pd(dppf)Cl_2(CH_2Cl_2)$ (17.4 mg, 0.02 mmol) was added, and the reaction mixture was heated to 50 °C and stirred for 18 hours. The reaction mixture was cooled to RT and quenched with H_2O (15 mL) and extracted with DCM (3 x 15 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a white solid (116 mg, 62% yield); R_f = 0.25 (3:1

dichloromethane : acetone); m.p. 145–149 °C; ν_{max}/cm^{-1} (thin film) 3314, 2975, 1648, 1554, 1455, 1435, 1408, 1366, 1247, 1162, 1129, 1071, 950, 759, 698; In solution in $CDCl_3$, this compound exists predominantly as a single rotamer, but with 2 minor rotamers also evident in the NMR spectra; δ_H (400 MHz, $CDCl_3$) 7.60 – 7.51 (4H, m, 4 x Ar**H**, both rotamers), 7.42 (2H, m, 2 x Ar**H**, both rotamers), 7.33 (1H, m, Ar**H**, both rotamers), 7.29 – 7.21 (2H, m,2 x Ar**H**, both rotamers), 5.79 (1H, d, J = 8.5 Hz, N**H**, major rotamer), 5.19 (1H, d, *J* = 16.5 Hz, C**H₂**, major rotamer), 5.07 (1H, d, *J* = 14.0 Hz, C**H₂**, major rotamer), 4.35 – 4.23 (1H, m, C**H₂**, both rotamers), 4.19 (1H, d, *J* = 16.5 Hz, C**H₂**, major rotamer), 3.73 (1H, dt, *J* = 14.0, 2.5 Hz, C**H₂**, major rotamer), 3.43 – 3.34 (1H, m, C**H₂**, major rotamer), 3.31 (1H, d, *J* = 14.0 Hz, C**H₂**, major rotamer), 3.16 – 2.97 (2H, m, C**H₂**, major rotamer), 2.88 (1H, d, *J* = 14.0 Hz, C**H₂**, major rotamer), 2.78 (1H, ddd, *J* = 13.0, 8.5, 6.0 Hz, C**H₂**, major rotamer), 2.50 (1H, ddd, *J* = 13.0, 8.5, 4.5 Hz, C**H₂**, major rotamer), 1.52 (9H, s, 3 x C**H₃**, major rotamer), 1.49 (9H, s, 3 x C**H₃**, minor rotamer), 1.46 (9H, s, 3 x C**H₃**, minor rotamer), 1.40 (9H, s, 3 x C**H₃**, minor rotamer); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 172.7 (**C**O), 170.9 (**C**O), 155.2 (**C**O), 140.7 (Ar**C**), 136.0 (Ar**C**), 128.9 (Ar**C**), 128.8 (Ar**C**H), 127.6 (Ar**C**H), 127.6 (Ar**C**H), 127.4 (Ar**C**H), 127.1 (Ar**C**), 80.2 (O**C**$(CH_3)_3$), 52.6 (**C**H_2), 51.6 (**C**H_2), 49.1 (**C**H_2), 41.7 (**C**H_2), 38.8 (**C**H_2), 35.2 (**C**H_2), 28.3 (3 x **C**H_3); HRMS (ESI) calcd. for $C_{25}H_{31}N_3NaO_4^+$, 460.2207. Found: $[MH]^+$ 460.2214 (−1.6 ppm error).

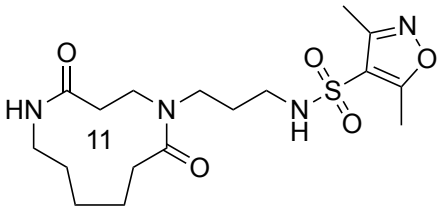
***tert*-Butyl 8-([1,1'-biphenyl]-4-ylmethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate (335)**



tert-Butyl-5,9-dioxo-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1,4-8-triazacycloundecane-1-carboxylate **326** (648.4 mg, 1.29 mmol) and bromobenzene (0.2 mL, 1.94 mmol) were dissolved in 1,4-dioxane (10 mL). Then Na_2CO_3 (410.2 mg, 3.87 mmol) was dissolved in water (5 mL), was added while stirring. $Pd(dppf)Cl_2(CH_2Cl_2)$ (52.3 mg, 0.07 mmol) was added, and the reaction mixture was heated to 50 °C and stirred overnight. The reaction

mixture was then cooled to room temperature and quenched with H_2O (50 mL) and extracted with DCM (3 x 50 mL). The organic fractions were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate → 1:9 methanol:ethyl acetate) to give the title compound as a solid (416.5 mg, 72% yield); R_f 0.64 (1:9 methanol:ethyl acetate). **IR** (ATR): υ_{max}/cm^{-1} 3308, 2975, 2931, 1649, 1551, 1479, 1408, 1366, 1247, 1167, 759, 731, 699. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) δ_H (400 MHz, $CDCl_3$) 7.56 – 7.53 (6H, m, Ar**H**), 7.44 – 7.40 (3H, m, Ar**H**), 6.10 – 6.07 (1H, m, N**H**), 4.94 – 4.87 (1H, m, C**H**$_2$), 4.77 – 4.64 (1H, m, C**H**$_2$), 4.35 – 4.26 (2H, m, C**H**$_2$), 3.66 – 3.52 (2H, m, C**H**$_2$), 3.35 – 3.28 (2H, m, C**H**$_2$), 2.96 – 2.86 (2H, m, C**H**$_2$), 2.23 – 2.16 (3H, m, C**H**$_2$), 1.57 – 1.46 (11H, m, C**H**$_2$ and C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 174.8 (**C**O), 170.6 (**C**O), 156.5 (*t*-BuO-**C**O), 140.9 (**C**Ar), 140.6 (**C**Ar), 135.8 (**C**Ar), 128.9 (Ar**C**H), 127.7 (Ar**C**H), 127.6 (Ar**C**H), 127.5 (Ar**C**H), 127.1 (Ar**C**H), 80.8 (COO**C**), 53.1 (**C**H$_2$), 52.9 (**C**H$_2$), 51.7 (**C**H$_2$), 42.8 (**C**H$_2$), 39.1 (**C**H$_2$), 35.3 (**C**H$_2$), 32.8 (**C**H$_2$), 28.4 (**C**H$_3$). **HRMS (ESI)**: calcd. for $C_{26}H_{33}N_3NaO_4$, 474.2359. Found: $[MNa]^+$, 474.2363 (0.9 ppm error).

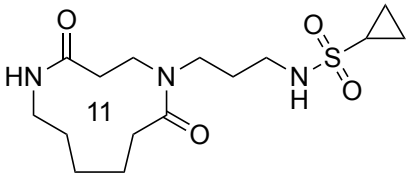
_N_-(3-(4,11-dioxo-1,5-diazacycloundecan-1-yl)propyl)-3,5-dimethylisoxazole-4-sulfonamide (342)



tert-Butyl (3-(4,11-dioxo-1,5-diazacycloundecan-1-yl)propyl)carbamate **330** (171 mg, 0.5 mmol) was dissolved in 4 M HCl in 1,4-dioxane (3.0 mL). The solution was stirred at RT for 1 hours, after which the solution was concentrated *in vacuo* to yield the salt product. The salt product was then dissolved in dry DCM (10 mL), was cooled to 0 °C and dry triethylamine (0.20 mL, 1.5 mmol) was added dropwise. Next, 3,5-dimethylisoxazole-4-sulfonyl chloride (123.2 mg, 0.63 mmol) and DMAP (6 mg, 0.05 mmol) were added and the reaction mixture was allowed to warm to RT while being stirred for 18 hours. The reaction mixture was diluted with ethyl acetate (15 mL) washed with saturated brine solution (15 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (1:9

methanol:ethyl acetate → 1:4 methanol:ethyl acetate) to afford the title compound as a yellow oil (145.8 mg, 73% yield); R_f 0.50 (1:9 methanol:ethyl acetate). **IR** (ATR): υ_{max}/cm^{-1} 3286, 2936, 2249, 1619, 1455, 1332, 1261, 1178, 1124, 906, 725, 646, 573. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data (the same sample) is more useful for determining the identity and purity of the product; δ_H (400 MHz, $CDCl_3$) 7.34 – 7.33 (1H, m, N**H**), 7.07 – 7.04 (1H, m, N**H**), 4.29 – 3.85 (2H, m, C**H**$_2$), 3.63 – 2.76 (8H, m, 4 x C**H**$_2$), 2.60 – 2.56 (3H, m, C**H**$_3$), 2.40 – 2.36 (3H, m, C**H**$_3$), 2.04 – 1.98 (2H, m, C**H**$_2$), 1.71 – 1.57 (8H, m, 4 x C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 174.1 (CH_3**C**O), 172.6 (**C**O), 171.7 (**C**O), 157.7 (CH_3**C**N), 116.0 (OOS**C**), 44.8 (**C**H$_2$), 43.0 (**C**H$_2$), 41.1 (**C**H$_2$), 40.1 (**C**H$_2$), 36.6 (**C**H$_2$), 28.2 (**C**H$_2$), 26.2 (**C**H$_2$), 25.2 (**C**H$_2$), 24.2 (**C**H$_2$), 22.2 (**C**H$_2$), 12.6 (**C**H$_3$), 10.6 (**C**H$_3$). **HRMS (ESI)**: calcd. for $C_{17}H_{28}N_4NaO_5S$, 423.1670. Found: $[MNa]^+$, 423.1673 (0.6 ppm error).

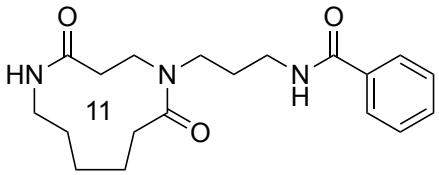
***N*-(3-(4,11-Dioxo-1,5-diazacycloundecan-1-yl)propyl)cyclopropanesulfonamide (344)**



tert-Butyl (3-(4,11-dioxo-1,5-diazacycloundecan-1-yl)propyl)carbamate **330** (146 mg, 0.43 mmol) was dissolved in 4 M HCl in 1,4-dioxane (4.0 mL). The solution was stirred at RT for 1 hours, after which the solution was concentrated *in vacuo* to yield the salt product. The salt product was then dissolved in dry DCM (12 mL), was cooled to 0 °C and dry triethylamine (0.18 mL, 1.29 mmol) was added dropwise. Next, cyclopronesulfonyl chloride (0.05 mL, 0.54 mmol) and DMAP (5.3 mg, 0.043 mmol) were added and the reaction mixture was allowed to warm to RT while being stirred for 18 hours. The reaction mixture was diluted with ethyl acetate (20 mL) washed with saturated brine solution (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a white solid (76.9 mg, 52% yield); m.p. 86 – 90 °C; R_f 0.24 (1:9 methanol:ethyl acetate). **IR** (ATR): υ_{max}/cm^{-1} 3281, 2934, 1616, 1553, 1437, 1323, 1299, 1142, 1041, 892, 727, 645; The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR

data is more useful for determining the identity and purity of the product; δ_H (400 MHz, $CDCl_3$) 7.28 (1H, s, N**H**), 6.29 – 6.26 (1H, m, N**H**), 4.31 – 3.71 (2H, m, C**H**$_2$), 3.65 – 2.67 (6H, m, 3 x C**H**$_2$), 2.63 – 2.17 (5H, m, C**H** and 2 x C**H**$_2$), 2.06 – 1.58 (8H, m, 4 x C**H**$_2$), 1.07 (2H, s, cyclopropyl C**H**$_2$), 0.93 – 0.92 (2H, m, cyclopropyl C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 174.0 (**C**O), 171.9 (**C**O), 44.9 (**C**H$_2$), 43.1 (**C**H$_2$), 41.1 (**C**H$_2$), 40.8 (**C**H$_2$), 36.8 (**C**H$_2$), 29.7 (**C**H), 28.3 (**C**H$_2$), 27.1 (**C**H$_2$), 25.2 (**C**H$_2$), 24.3 (**C**H$_2$), 22.3 (**C**H$_2$), 5.2 (cyclopropyl **C**H$_2$). **HRMS (ESI)**: calcd. for $C_{15}H_{27}N_3NaO_4S$, 368.1623. Found: $[MNa]^+$, 368.1614 (−2.2 ppm error).

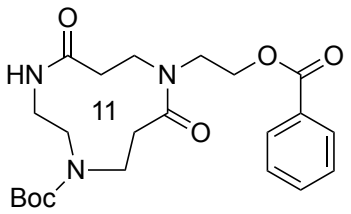
***N*-(3-(4,11-Dioxo-1,5-diazacycloundecan-1-yl)propyl)benzamide (346)**



tert-Butyl (3-(4,11-dioxo-1,5-diazacycloundecan-1-yl)propyl)carbamate **330** (171 mg, 0.5 mmol) was dissolved in 4 M HCl in 1,4-dioxane (4.0 mL). The solution was stirred at RT for 1 hours, after which the solution was concentrated *in vacuo* to yield the salt product. The salt product was then dissolved in dry DCM (11 mL), was cooled to 0 °C and dry triethylamine (0.4 mL, 3.0 mmol) was added dropwise. Next, benzoyl chloride (70 µL, 0.63 mmol) and DMAP (6 mg, 0.05 mmol) were added and the reaction mixture was allowed to warm to RT while being stirred for 18 hours. The reaction mixture was diluted with ethyl acetate (15 mL) washed with saturated brine solution (15 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate → 1:9 methanol:ethyl acetate → 1:4 methanol:ethyl acetate) to afford the title compound as a white solid (80.6 mg, 47% yield); m.p. 171 – 175 °C; R_f 0.53 (1:4 methanol:ethyl acetate). **IR** (ATR): υ_{max}/cm^{-1} 3296, 2934, 1631, 1545, 1453, 1304, 703. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product; δ_H (400 MHz, $CDCl_3$) 7.84 (2H, d, *J* = 7.6 Hz, Ar**H**), 7.53 – 7.49 (1H, m, Ar**H**), 7.47 – 7.40 (2H, m, Ar**H**), 6.87 – 6.86 (1H, m, N**H**), 4.20 – 2.86 (8H, m, 4 x C**H**$_2$), 2.70 – 2.28 (4H, m, 2 x C**H**$_2$), 2.21 – 1.95 (2H, m, C**H**$_2$), 1.79 (2H, s, C**H**$_2$), 1.66 (2H, s, C**H**$_2$), 1.42 – 1.04 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 174.5 (**C**O), 171.7 (**C**O), 167.6 (**C**O), 134.4 (**C**Ar), 131.6 (Ar**C**H), 128.7 (Ar**C**H), 127.2 (Ar**C**H), 45.5 (**C**H$_2$), 43.1 (**C**H$_2$), 41.5 (**C**H$_2$), 37.8 (**C**H$_2$), 37.0

(**C**H_2), 28.6 (**C**H_2), 28.2 (**C**H_2), 25.3 (**C**H_2), 24.3 (**C**H_2), 22.7 (**C**H_2). **HRMS (ESI)**: calcd. for $C_{19}H_{27}N_3NaO_3$, 368.1957. Found: $[MNa]^+$, 368.1945 (−3.5 ppm error).

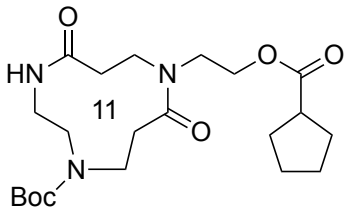
***tert*-Butyl 8-(2-(benzoyloxy)ethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate (351)**



To a solution of *tert*-butyl 8-(2-hydroxyethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate **328** (213.8 mg, 0.65 mmol) was dissolved in dry DCM (14 mL), was cooled to 0 °C and dry triethylamine (0.27 mL, 1.95 mmol) was added dropwise. Next, benzyl chloride (90 µL, 0.81 mmol) and DMAP (7.9 mg, 0.065 mmol) were added and the reaction mixture was allowed to warm to RT while being stirred for 18 hours. The reaction mixture was diluted with ethyl acetate (15 mL) washed with saturated brine solution (15 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (1:19 methanol:ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a colourless oil (247.1 mg, 88% yield); R_f 0.50 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3315, 2975, 1644, 1547, 1365, 1161, 1114, 1026, 857, 710. The ^{1}H NMR spectrum is complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. In solution in $CDCl_3$, the product exists as a 2.5:1.2:1 mixture of rotamers; δ_H (400 MHz, $CDCl_3$) 7.89 – 7.86 (2H, m, Ar**H**, major rotamer), 7.49 – 7.43 (1H , m, Ar**H**, major roatmer), 7.37 – 7.31 (2H , m, Ar**H**, major rotamer), 6.53 (1H, s, N**H**, major rotamer), 4.44 – 4.37 (3H, m, C**H**$_2$, major rotamer), 4.21 – 4.09 (3H, m, C**H**$_2$, major rotamer), 3.54 – 3.46 (3H, m, C**H**$_2$, major rotamer), 3.19 – 3.07 (4H, m, C**H**$_2$, major rotamer), 2.85 – 2.71 (3H, m, C**H**$_2$, major rotamer), 1.40 – 1.39 (20H, m, C**H**$_3$, major and minor rotamers); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 174.3 (**C**O), 170.4 (**C**O), 166.3 (**C**O), 166.0 (**C**O), 156.4 (**C**Ar), 133.3 (Ar**C**H), 129.4 (Ar**C**H), 128.5 (Ar**C**H), 80.5 (**C**CH_3), 62.1 (**C**H_2), 52.9 (**C**H_2), 51.5 (**C**H_2), 48.4 (**C**H_2), 43.1 (**C**H_2), 38.8 (**C**H_2), 34.9 (**C**H_2), 32.3 (**C**H_2), 28.1 (**C**H_3). **HRMS (ESI)**: calcd. for $C_{22}H_{31}N_3NaO_6$, 456.2108. Found: $[MNa]^+$, 456.2105 (−0.6 ppm error).

Diagnostic NMR data for minor rotamer can be found at; δ_H (400 MHz, $CDCl_3$) 7.98 – 7.96 (2H, m, Ar**H**), 6.28 – 6.26 (1H, m, N**H**), 6.22 – 6.19 (1H, m, N**H**), 4.05 – 3.98 (1H, m, C**H**$_2$), 3.72 – 3.69 (1H, m, C**H**$_2$), 3.39 – 3.33 (1H, m, C**H**$_2$), 2.40 – 2.34 (1H, m, C**H**$_2$), 2.27 (1H, s, C**H**$_2$), 2.04 – 2.00 (1H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 79.7 (**C**CH_3), 62.8 (**C**H_2), 60.2 (**C**H_2), 53.4 (**C**H_2), 50.6 (**C**H_2), 28.3 (**C**H_3).

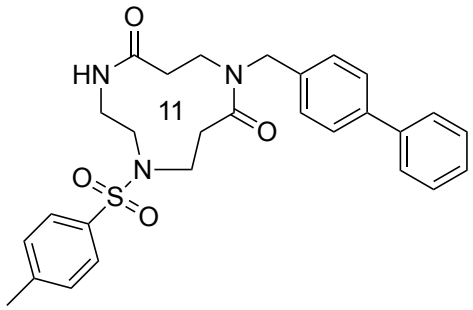
tert-butyl 8-(2-((Cyclopentanecarbonyl)oxy)ethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate (353)



To a solution of *tert*-butyl 8-(2-hydroxyethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate **328** (224 mg, 0.68 mmol) was dissolved in dry DCM (15 mL), was cooled to 0 °C and dry triethylamine (0.3 mL, 3.00 mmol) was added dropwise. Next, cyclopentane carbonyl chloride (0.1 mL, 0.85 mmol) and DMAP (8.3 mg, 0.068 mmol) were added and the reaction mixture was allowed to warm to RT while being stirred for 18 hours. The reaction mixture was diluted with ethyl acetate (20 mL) washed with saturated brine solution (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (1:19 methanol:ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a colourless oil (239.2 mg, 83% yield); R_f 0.50 (1:9 methanol:ethyl acetate). In solution in $CDCl_3$, the product exists as a 4:1.1:1 mixture of 3 rotamers based on NH peaks. All ^1H and ^{13}C signals are broadened due to rotamer interconversion; δ_H (400 MHz, $CDCl_3$) 6.66 (1H, s, N**H**, minor rotamer), 6.60 (1H, s, N**H**, minor rotamer), 6.23 – 6.21 (1H, m, N**H**, major rotamer), 4.12 – 3.71 (8H, m, C**H**$_2$), 3.64 – 3.60 (1H, m, C**H**$_2$), 3.53 – 3.50 (1H, m, C**H**$_2$), 3.46 – 3.42 (2H, m, C**H**$_2$), 3.33 – 3.02 (8H, m, 2 x C**H** and 3 x C**H**$_2$), 2.98 – 2.81 (3H, m, C**H**$_2$), 2.75 – 2.63 (2H, m, C**H**$_2$), 2.56 – 2.49 (2H, m, C**H**$_2$), 2.30 – 2.23 (3H, m, C**H**$_2$), 1.97 – 1.91 (1H, m, C**H**$_2$), 1.89 – 1.86 (1H, m, C**H**$_2$), 1.72 – 1.68 (4H, m, C**H**$_2$), 1.61 – 1.50 (9H, m, C**H**$_2$), 1.43 – 1.39 (4H, m, C**H**$_2$), 1.32 (7H, m, C**H**$_3$), 1.30 (9H, m, C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 179.2 (**C**O), 177.1 (**C**O), 176.2 (**C**O), 176.1 (**C**O), 174.1

(**C**O), 173.6 (**C**O), 170.3 (**C**O), 156.2 (**C**O), 80.3 (**C**CH_3), 80.2 (**C**CH_3), 79.5 (**C**CH_3), 61.9 (**C**H_2), 61.5 (**C**H_2), 52.7 (**C**H_2), 51.2 (**C**H_2), 48.0 (**C**H_2), 45.3 (**C**H), 43.5 (**C**H), 43.4 (**C**H), 42.8 (**C**H_2), 38.7 (**C**H_2), 36.7 (**C**H_2), 34.9 (**C**H_2), 32.3 (**C**H_2), 31.4 (**C**H_2), 30.3 (**C**H_2), 29.8 (**C**H_2), 29.7 (**C**H_2), 28.1 (**C**H_3), 28.0 (**C**H_3), 25.5 (**C**H_2). **HRMS (ESI)**: calcd. for $C_{21}H_{35}N_3NaO_6$, 448.2429. Found: $[MNa]^+$, 448.2418 (−2.4 ppm error).

8-([1,1'-Biphenyl]-4-ylmethyl)-1-tosyl-1,4,8-triazacycloundecane-5,9-dione (356)

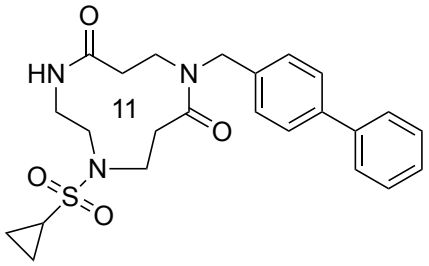


tert-Butyl 8-([1,1'-biphenyl]-4-ylmethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate **335** (100 mg, 0.22 mmol) was dissolved in 4 M HCl in dioxane (4.0 mL). The solution was stirred at RT for 10 min, after which the solution was concentrated *in vacuo* to yield the salt product. The salt product was then dissolved in dry DCM (6.0 mL), was cooled to 0 °C and dry triethylamine (0.09 mL, 0.66 mmol) was added dropwise. Next, 4-methylbenzenesulfonyl chloride (53.4 mg, 0.28 mmol) and DMAP (2.7 mg, 0.022 mmol) were added and the reaction mixture was allowed to warm to RT while being stirred for 18 hours. The reaction mixture was diluted with ethyl acetate (20 mL) washed with saturated brine solution (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a white solid (100.5 mg, 90% yield over 2 steps); m.p. 92 – 95 °C; R_f 0.64 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3295, 2929, 2247, 1640, 1547, 1360, 1337, 1196, 1159, 986, 907, 864, 815, 726, 694, 644, 548. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. In solution in $CDCl_3$, the product exists as a 4:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 7.70 (2H, d, *J* = 8.3 Hz, Ar**H**), 7.52 – 7.49 (3H, m, Ar**H**), 7.41 – 7.30 (8H, m, Ar**H**), 7.21 – 7.18 (1H, m, N**H**), 5.33 – 5.06 (1H, m, C**H**$_2$), 4.55 – 4.38 (1H, m, C**H**$_2$), 4.31 – 4.07

(1H, m, C**H**$_2$), 4.03 – 3.77 (1H, m, C**H**$_2$), 3.70 – 3.22 (5H, m, C**H**$_2$), 3.09 – 3.05 (2H, m, C**H**$_2$), 2.56 – 2.50 (1H, m, C**H**$_2$), 2.44 – 2.36 (5H, m, C**H**$_3$ and C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 172.3 (**C**O), 170.3 (**C**O), 143.7 (**C**Ar), 140.6 (**C**Ar), 140.4 (**C**Ar), 137.0 (**C**Ar), 133.6 (Ar**C**H), 129.8 (Ar**C**H), 128.8 (Ar**C**H), 128.7 (Ar**C**H), 127.8 (Ar**C**H), 127.4 (Ar**C**H), 127.0 (Ar**C**H), 48.5 (**C**H$_2$), 47.5 (**C**H$_2$), 46.5 (**C**H$_2$), 44.6 (**C**H$_2$), 41.5 (**C**H$_2$), 36.4 (**C**H$_2$), 30.1 (**C**H$_2$), 21.5 (**C**H$_3$). **HRMS (ESI)**: calcd. for $C_{28}H_{31}N_3NaO_4S$, 528.1944. Found: $[MNa]^+$, 528.1927 (−3.1 ppm error).

Characteristic NMR data for the minor rotamer can be found at: δ_H (400 MHz, $CDCl_3$) 6.41 – 6.39 (1H, m, N**H**); δ_C (100 MHz, $CDCl_3$) 172.6 (**C**O), 171.1 (**C**O), 144.2 (**C**Ar), 140.7 (**C**Ar), 140.4 (**C**Ar), 136.1 (**C**Ar), 133.3 (Ar**C**H), 130.0 (Ar**C**H), 128.8 (Ar**C**H), 127.7 (Ar**C**H), 127.5 (Ar**C**H), 127.3 (Ar**C**H), 127.2 (Ar**C**H), 52.9 (**C**H$_2$), 51.3 (**C**H$_2$), 51.0 (**C**H$_2$), 43.4 (**C**H$_2$), 39.7 (**C**H$_2$), 35.9 (**C**H$_2$), 35.0 (**C**H$_2$), 21.6 (**C**H$_3$).

8-([1,1'-Biphenyl]-4-ylmethyl)-1-(cyclopropylsulfonyl)-1,4,8-triazacycloundecane-5,9-dione (357)

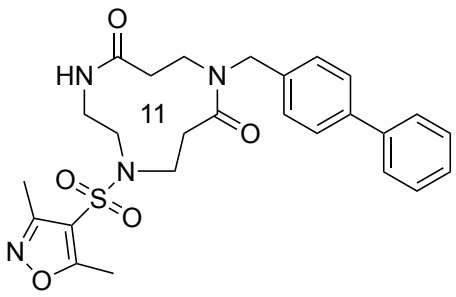


tert-Butyl 8-([1,1'-biphenyl]-4-ylmethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate (100 mg, 0.22 mmol) **335** was dissolved in 4 M HCl in dioxane (4.0 mL). The solution was stirred at RT for 10 min, after which the solution was concentrated *in vacuo* to yield the salt product. The salt product was then dissolved in dry DCM (6.0 mL), was cooled to 0 °C and dry triethylamine (0.09 mL, 0.66 mmol) was added dropwise. Next, cyclopronesulfonyl chloride (0.03 mL, 0.28 mmol) and DMAP (2.7 mg, 0.022 mmol) were added and the reaction mixture was allowed to warm to RT while being stirred for 18 hours. The reaction mixture was diluted with ethyl acetate (20 mL) washed with saturated brine solution (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title

compound as a brown solid (80.2 mg, 80% yield over 2 steps); m.p. 85 – 89 °C; R_f 0.48 (1:9 methanol:ethyl acetate). **IR** (ATR): υ_{max}/cm^{-1} 3299, 2931, 2250, 1641, 1547, 1334, 1193, 1149, 1074, 1041, 986, 723, 647, 540. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. In solution in $CDCl_3$, the product exists as a 3:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 7.53 – 7.50 (4H, m Ar**H**), 7.41 – 7.38 (2H, m, Ar**H**), 7.34 – 7.31 (3H, m, Ar**H**), 6.86 (1H, s, N**H**), 3.63 – 3.49 (2H, m, C**H**$_2$), 3.43 – 3.14 (6H, m, 3 x C**H**$_2$), 2.52 – 2.25 (5H, m, 2 x C**H**$_2$ and C**H**), 1.19 (2H, s, cyclopropyl C**H**$_2$), 1.02 (2H, s, cyclopropyl C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 172.2 (**C**O), 170.5 (**C**O), 140.6 (**C**Ar), 140.5 (**C**Ar), 136.9 (**C**Ar), 128.8 (Ar**C**H), 128.6 (Ar**C**H), 127.5 (Ar**C**H), 127.4 (Ar**C**H), 127.0 (Ar**C**H), 48.6 (**C**H$_2$), 47.1 (**C**H$_2$), 46.2 (**C**H$_2$), 44.7 (**C**H$_2$), 41.3 (**C**H$_2$), 36.5 (**C**H$_2$), 30.4 (**C**H$_2$), 26.5 (**C**H), 5.0 (cyclopropyl **C**H$_2$). **HRMS (ESI)**: calcd. for $C_{24}H_{29}N_3NaO_4S$, 478.1773. Found: $[MNa]^+$, 478.1771 (−0.4 ppm error).

Characteristic NMR data for the minor rotamer can be found at: δ_H (400 MHz, $CDCl_3$) 6.21 (1H, s, N**H**), 5.03 (1H, d, *J* = 16.6 Hz, C**H**H'), 4.48 (1H, d, *J* = 16.6 Hz, CH**H'**), 3.74 – 3.71 (2H, m, C**H**$_2$), 2.18 – 2.15 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$)) 172.6 (**C**O), 171.0 (**C**O), 140.8 (**C**Ar), 140.3 (**C**Ar), 135.9 (**C**Ar), 128.8 (Ar**C**H), 127.7 (Ar**C**H), 127.2 (Ar**C**H), 52.6 (**C**H$_2$), 51.4 (**C**H$_2$), 50.9 (**C**H$_2$), 43.3 (**C**H$_2$), 39.4 (**C**H$_2$), 35.9 (**C**H$_2$), 34.9 (**C**H$_2$), 25.6 (**C**H), 4.84 (cyclopropyl **C**H$_2$).

8-([1,1'-Biphenyl]-4-ylmethyl)-1-((3,5-dimethylisoxazol-4-yl)sulfonyl)-1,4,8-triazacycloundecane-5,9-dione (358)

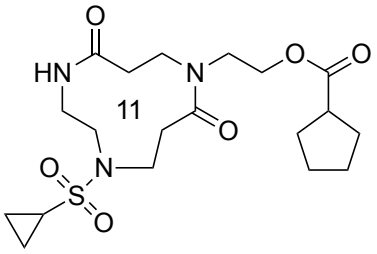


tert-Butyl 8-([1,1'-biphenyl]-4-ylmethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate **335** (100 mg, 0.22 mmol) was dissolved in 4 M HCl in dioxane (4.0 mL). The solution was stirred at RT for 10 min, after which the solution was concentrated *in vacuo* to yield the salt product. The salt product was then dissolved in dry DCM (6.0 mL), was cooled to 0 °C and dry triethylamine (0.18 mL, 1.32 mmol) was added dropwise. Next, 3,5-dimethylisoxazole-4-

sulfonyl chloride (54 mg, 0.28 mmol) and DMAP (2.7 mg, 0.022 mmol) were added and the reaction mixture was allowed to warm to RT while being stirred for 18 hours. The reaction mixture was diluted with ethyl acetate (20 mL) washed with saturated brine solution (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate → 1:19 methanol:ethyl acetate) to afford the title compound as a white solid (45.5 mg, 41% yield over 2 steps); m.p. 85 – 90 °C; R_f 0.84 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3295, 2930, 1643, 1586, 1454, 1408, 1263, 1121, 985, 922, 863, 760, 706, 623, 572. The ^1H NMR spectrum is complicated by rotameric broadening; ^{13}C NMR data is most useful for determining the identity and purity of the product. In solution in $CDCl_3$, this compound exists as a 3:1 mixture of rotamers. Data for the major rotamer; δ_H (400 MHz, $CDCl_3$) 7.57 – 7.55 (4H, m Ar**H**), 7.45 – 7.35 (5H, m, Ar**H**), 6.63 – 6.56 (1H, m, N**H**), 5.21 – 5.00 (1H, m, C**H**$_2$), 4.59 – 4.27 (2H, m, C**H**$_2$), 3.69 – 3.61 (1H, m, C**H**$_2$), 3.52 – 3.42 (2H, m, C**H**$_2$), 3.38 – 3.15 (5H, m, C**H**$_2$), 2.69 – 2.68 (3H, m, C**H**$_3$), 2.46 (3H, s, C**H**$_3$), 1.43 – 1.39 (1H, m, C**H**$_2$), 1.29 – 1.25 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 174.1 (CH_3**C**O), 172.2 (**C**O), 170.2 (**C**O), 157.9 (CH_3**C**N), 141.0 (**C**Ar), 140.6 (**C**Ar), 136.8 (**C**Ar), 128.9 (Ar**C**H), 128.9 (Ar**C**H), 127.7 (Ar**C**H), 127.6 (Ar**C**H), 127.2 (Ar**C**H), 114.1 (OOS**C**), 49.0 (**C**H$_2$), 47.1 (**C**H$_2$), 45.8 (**C**H$_2$), 45.0 (**C**H$_2$), 41.1 (**C**H$_2$), 36.7 (**C**H$_2$), 30.2 (**C**H$_2$), 13.4 (**C**H$_3$), 11.8 (**C**H$_3$). **HRMS (ESI)**: calcd. for $C_{26}H_{30}N_4NaO_5S$, 533.1836. Found: $[MNa]^+$, 533.1829 (−1.2 ppm error).

Characteristic NMR data for the minor rotamers can be found at: δ_C (100 MHz, $CDCl_3$) 135.6 (**C**Ar), 49.4 (**C**H$_2$), 43.2 (**C**H$_2$), 38.6 (**C**H$_2$), 29.8 (**C**H$_2$), 13.1 (**C**H$_3$), 11.3 (**C**H$_3$).

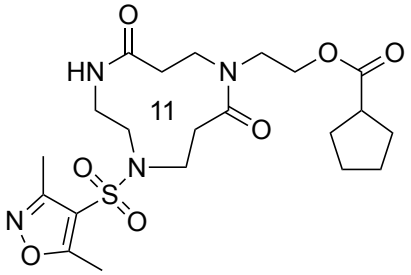
2-(1-(Cyclopropylsulfonyl)-5,9-dioxo-1,4,8-triazacycloundecan-8-yl)ethyl cyclopentanecarboxylate (359)



tert-Butyl 8-(2-((cyclopentanecarbonyl)oxy)ethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate **353** (245.7 mg, 0.58 mmol) was dissolved in 4 M HCl in 1,4-dioxane (2.0 mL). The solution was stirred at RT for 1 hours, after which the solution was concentrated *in vacuo* to yield the salt product. The salt product was then dissolved in dry DCM (17 mL), was cooled to 0 °C and dry triethylamine (0.24 mL, 1.73 mmol) was added dropwise. Next, cyclopronesulfonyl chloride (70 µL, 0.72 mmol) and DMAP (7.1 mg, 0.058 mmol) were added and the reaction mixture was allowed to warm to RT while being stirred for 18 hours. The reaction mixture was diluted with ethyl acetate (20 mL) washed with saturated brine solution (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (1:19 methanol:ethyl acetate → 1:9 methanol:ethyl acetate → 1:4 methanol:ethyl acetate) to afford the title compound as a yellow oil (166 mg, 67% yield); R_f 0.49 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3315, 2952, 1726, 1636, 1549, 1454, 1332, 1147, 889, 725, 541. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. In solution in $CDCl_3$, the product exists as a 4:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 6.78 (1H, s, N**H**), 4.31 (2H, s, C**H**$_2$), 3.74 – 3.12 (10H, m, 5 x C**H**$_2$), 2.72 – 2.67 (1H, m, C**H**), 2.53 – 2.49 (1H, m, C**H**), 2.47 – 2.29 (3H, m, C**H**$_2$), 1.89 – 1.84 (2H, m, C**H**$_2$), 1.77 – 1.65 (5H, m, C**H**$_2$), 1.59 – 1.54 (2H, m, C**H**$_2$), 1.24 – 1.18 (2H, m, cyclopropyl C**H**$_2$), 1.04 – 0.95 (2H, m, cyclopropyl C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 176.7 (**C**O), 172.1 (**C**O), 170.9 (**C**O), 62.3 (**C**H$_2$), 47.0 (**C**H$_2$), 46.9 (**C**H$_2$), 46.8 (**C**H$_2$), 46.0 (**C**H$_2$), 43.8 (**C**H), 41.3 (**C**H$_2$), 37.2 (**C**H$_2$), 30.6 (**C**H$_2$), 30.2 (**C**H$_2$), 27.1 (**C**H), 25.9 (**C**H$_2$), 5.2 (cyclopropyl **C**H$_2$). **HRMS (ESI)**: calcd. for $C_{19}H_{31}N_3NaO_6S$, 452.1828. Found: $[MNa]^+$, 452.1826 (−0.4 ppm error).

Diagnostic NMR data for the minor rotamer can be found at: δ_H (400 MHz, $CDCl_3$) 6.11 – 6.08 (1H, m, N**H**); δ_C (100 MHz, $CDCl_3$) 176.6 (**C**O), 172.6 (**C**O), 170.9 (**C**O), 62.1 (**C**H_2), 52.8 (**C**H_2), 51.0 (**C**H_2), 47.0 (**C**H_2), 43.7 (**C**H_2), 43.2 (**C**H), 39.5 (**C**H_2), 36.0 (**C**H_2), 34.8 (**C**H_2), 30.1 (**C**H_2), 25.7 (**C**H_2), 4.9 (cyclopropyl **C**H_2).

2-(1-((3,5-Dimethylisoxazol-4-yl)sulfonyl-5,9-dioxo-1,4,8-triazacycloundecan-8-yl)ethyl cyclopentanecarboxylate (360)

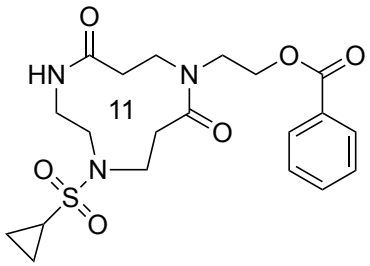


tert-Butyl 8-(2-((cyclopentanecarbonyl)oxy)ethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate **353** (70 mg, 0.16 mmol) was dissolved in 4 M HCl in 1,4-dioxane (1.0 mL). The solution was stirred at RT for 1 hours, after which the solution was concentrated *in vacuo* to yield the salt product. The salt product was then dissolved in dry DCM (5 mL), was cooled to 0 °C and dry triethylamine (70 µL, 0.48 mmol) was added dropwise. Next, cyclopronesulfonyl chloride (39 mg, 0.20 mmol) and DMAP (2 mg, 0.016 mmol) were added and the reaction mixture was allowed to warm to RT while being stirred for 18 hours. The reaction mixture was diluted with ethyl acetate (10 mL) washed with saturated brine solution (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (1:9 methanol:ethyl acetate) to afford the title compound as a white solid (70.4 mg, 91% yield); m.p. 85 – 90 °C; R_f 0.23 (1:9 methanol:ethyl acetate). **IR** (ATR): υ_{max}/cm^{-1} 3300, 2955, 2871, 2247, 1728, 1641, 1262, 1174, 1120, 985, 915, 727, 704, 621, 571. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. In solution in $CDCl_3$, the compoud exists predominantly as a single rotamer, with trace amount of a minor rotamer evident in the ^{13}C NMR spectrum. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 6.93 (1H, s, N**H**), 4.48 – 3.23 (10H, m, 5 x C**H**$_2$), 3.15 (2H, s, C**H**$_2$), 2.72 – 2.66 (1H, m, C**H**), 1.89 – 1.81 (2H, m,

C**H**$_2$), 1.77 – 1.69 (2H, m, C**H**$_2$), 1.68 – 1.62 (2H, m, C**H**$_2$), 1.60 – 1.50 (2H, m, C**H**$_2$), 2.64 (3H, s, C**H**$_3$), 2.38 (3H, s, C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 176.6 (CH_3**C**O), 174.0 (**C**O), 172.2 (**C**O), 170.1 (**C**O), 157.8 (CH_3**C**N), 114.1 (OOS**C**), 62.2 (**C**H_2), 46.8 (**C**H_2), 46.7 (**C**H_2), 45.6 (**C**H_2), 43.8 (**C**H), 41.1 (**C**H_2), 37.2 (**C**H_2), 30.2 (**C**H_2), 30.1 (**C**H_2), 13.2 (**C**H_3), 11.6 (**C**H_3). **HRMS (ESI)**: calcd. for $C_{21}H_{32}N_4NaO_7S$, 507.1874. Found: $[MNa]^+$, 507.1884 (2.0 ppm error).

Diagnostic NMR data for minor rotamer can be found at; δ_H (400 MHz, $CDCl_3$) 6.29 – 6.18 (1H, m, N**H**), 4.72 – 4.64 (1H, m, C**H$_2$**).

2-(1-(Cyclopropylsulfonyl)-5,9-dioxo-1,4,8-triazacycloundecan-8-yl)ethyl benzoate (361)

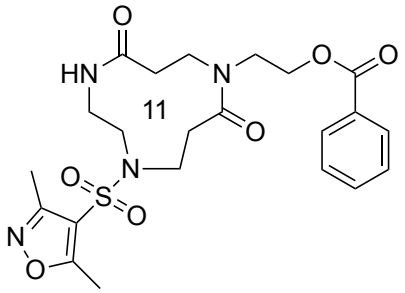


tert-Butyl 8-(2-(benzoyloxy)ethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate **351** (88 mg, 0.20 mmol) was dissolved in 4 M HCl in 1,4-dioxane (1.0 mL). The solution was stirred at RT for 1 hours, after which the solution was concentrated *in vacuo* to yield the salt product. The salt product was then dissolved in dry DCM (6 mL), was cooled to 0 °C and dry triethylamine (80 µL, 0.60 mmol) was added dropwise. Next, cyclopronesulfonyl chloride (30 µL, 0.25 mmol) and DMAP (2.4 mg, 0.02 mmol) were added and the reaction mixture was allowed to warm to RT while being stirred for 18 hours. The reaction mixture was diluted with ethyl acetate (10 mL) washed with saturated brine solution (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (1:9 methanol:ethyl acetate → 1:4 methanol:ethyl acetate) to afford the title compound as a white solid (78.5 mg, 90% yield); m.p. 85 – 90 °C; R_f 0.24 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3287, 2932, 2247, 1716, 1638, 1544, 1451, 1332, 1271, 1147, 1112, 1026, 987, 915, 711, 540. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. In solution in $CDCl_3$, the product exists as a 4:1 mixture of rotamers. NMR data for the major rotamer; δ_H

(400 MHz, $CDCl_3$) 7.96 – 7.94 (2H, m, Ar**H**), 7.56 – 7.52 (1H , m, Ar**H**), 7.43 – 7.39 (2H , m, Ar**H**), 6.99 – 6.98 (1H, m, N**H**), 4.52 – 4.50 (2H, m, C$\mathbf{H}_2$), 4.26 – 3.80 (3H, m, C$\mathbf{H}_2$), 3.62 – 3.08 (8H, m, 4 x C$\mathbf{H}_2$), 2.48 – 2.36 (3H, m, C**H** and C$\mathbf{H}_2$), 1.23 – 1.14 (3H, m, C$\mathbf{H}_2$), 1.00 – 0.91 (2H, m, C$\mathbf{H}_2$); δ_C (100 MHz, $CDCl_3$) 172.0 (**C**O), 170.7 (**C**O), 166.6 (**C**O), 133.4 (Ar**C**H), 129.7 (**C**Ar), 129.6 (Ar**C**H), 128.6 (Ar**C**H), 63.0 (**C**H_2), 46.7 (**C**H_2), 46.5 (**C**H_2), 46.3 (**C**H_2), 46.0 (**C**H_2), 41.2 (**C**H_2), 37.2 (**C**H_2), 30.4 (**C**H_2), 26.8 (**C**H), 13.2 (cyclopropyl **C**H_2). **HRMS (ESI)**: calcd. for $C_{20}H_{27}N_3NaO_6S$, 460.1526. Found: $[MNa]^+$, 460.1513 (−3.0 ppm error).

Diagnostic NMR data for the minor rotamer can be found at: δ_H (400 MHz, $CDCl_3$) 6.27 (1H, s, N**H**); δ_C (100 MHz, $CDCl_3$) 166.3 (**C**O), 133.4 (Ar**C**H), 129.4 (**C**Ar), 62.7 (**C**H_2), 52.6 (**C**H_2), 50.8 (**C**H_2), 43.0 (**C**H_2), 43.2 (**C**H), 39.6 (**C**H_2), 35.8 (**C**H_2), 34.6 (**C**H_2), 25.6 (**C**H_2).

2-(1-((3,5-Dimethylisoxazol-4-yl)sulfonyl)-5,9-dioxo-1,4,8-triazacycloundecan-8-yl)ethyl benzoate (362)

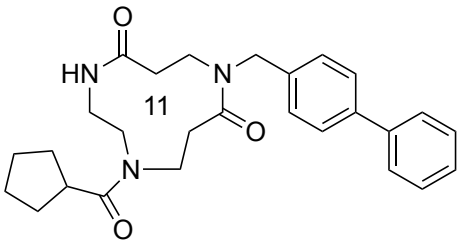


tert-Butyl 8-(2-(benzoyloxy)ethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate **351** (209 mg, 0.48 mmol) was dissolved in 4 M HCl in 1,4-dioxane (2.0 mL). The solution was stirred at RT for 1 hours, after which the solution was concentrated *in vacuo* to yield the salt product. The salt product was then dissolved in dry DCM (10 mL), was cooled to 0 °C and dry triethylamine (0.2 mL, 1.44 mmol) was added dropwise. Next, cyclopronesulfonyl chloride (118 mg, 0.60 mmol) and DMAP (6 mg, 0.048 mmol) were added and the reaction mixture was allowed to warm to RT while being stirred for 18 hours. The reaction mixture was diluted with ethyl acetate (15 mL) washed with saturated brine solution (15 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (1:19 methanol:ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a white

solid (170.4 mg, 72% yield); m.p. 182 – 185 °C; R_f 0.36 (1:9 methanol:ethyl acetate). **IR** (ATR): υ_{max}/cm^{-1} 3378, 2938, 1715, 1627, 1540, 1405, 1269, 1172, 1025, 983, 917, 859, 706, 621, 570; The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. In solution in $CDCl_3$, the compoud exists as a 2:1 mixture of rotamers. NMR data for the major rotamer; δ_H (400 MHz, $CDCl_3$) 7.89 (2H, d, *J* = 7.5 Hz, Ar**H**), 7.49 – 7.45 (1H , m, Ar**H**), 7.36 – 7.32 (2H , m, Ar**H**), 6.70 – 6.56 (1H, m, N**H**), 4.45 – 4.42 (2H, m, C**H**$_2$), 4.20 – 3.72 (3H, m, C**H**$_2$), 3.65 – 2.98 (7H, m, C**H**$_2$), 2.72 – 2.16 (10H, m, 2 x C**H**$_3$ and 2 x C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 174.9 (CH_3**C**O), 173.9 (**C**O), 172.5 (**C**O), 170.5 (**C**O), 166.5 (**C**Ar), 157.8 (CH_3**C**N), 133.3 (Ar**C**H), 129.5 (Ar**C**H), 128.5 (Ar**C**H), 114.0 (OOS**C**), 62.8 (**C**H$_2$), 46.4 (**C**H$_2$), 46.37 (**C**H$_2$), 46.0 (**C**H$_2$), 45.6 (**C**H$_2$), 41.0 (**C**H$_2$), 36.9 (**C**H$_2$), 30.0 (**C**H$_2$), 13.2 (**C**H$_3$), 11.6 (**C**H$_3$). **HRMS (ESI)**: calcd. for $C_{22}H_{28}N_4NaO_7S$, 515.1589. Found: $[MNa]^+$, 515.1571 (−3.5 ppm error).

Diagnostic NMR data for minor rotamer can be found at; δ_H (400 MHz, $CDCl_3$) 7.01 – 6.88 (1H, m, N**H**); δ_C (100 MHz, $CDCl_3$) 174.0 (**C**O), 172.4 (**C**O), 157.5 (CH_3**C**N), 133.5 (Ar**C**H), 129.6 (Ar**C**H), 128.6 (Ar**C**H), 114.3 (OOS**C**), 62.7 (**C**H$_2$), 13.3 (**C**H$_3$), 11.7 (**C**H$_3$).

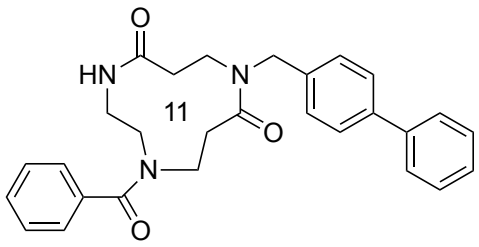
5-([1,1'-Biphenyl]-4-ylmethyl)-9-(cyclopentanecarbonyl)-1,5-diazacycloundecane-2,6-dione (363)



tert-Butyl 8-([1,1'-biphenyl]-4-ylmethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate **335** (100 mg, 0.22 mmol) was dissolved in 4 M HCl in dioxane (4.0 mL). The solution was stirred at RT for 10 min, after which the solution was concentrated *in vacuo* to yield the salt product. The salt product was then dissolved in dry DCM (6 mL), was cooled to 0 °C and dry triethylamine (0.18 mL, 1.32 mmol) was added dropwise. Next, cyclopentane carbonyl chloride (0.04 mL, 0.28 mmol) and DMAP (2.7 mg, 0.022 mmol) were added and the reaction zmixture was allowed to warm to RT while being stirred for 18 hours. The reaction mixture

was diluted with ethyl acetate (10 mL) washed with saturated brine solution (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:99 methanol:ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a white solid (84.6 mg, 86% yield over 2 steps); m.p. 89 – 93 °C; R_f 0.58 (1:9 methanol:ethyl acetate). **IR** (ATR): υ_{max}/cm^{-1} 3294, 2944, 2868, 2244, 1628, 1554, 1457, 1412, 1356, 1212, 1149, 1075, 1007, 908, 728, 698, 646. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data (the same sample) is more useful for determining the identity and purity of the product. δ_H (400 MHz, $CDCl_3$) 7.54 – 7.52 (4H, m Ar**H**), 7.43 – 7.39 (2H, m, Ar**H**), 7.34 – 7.27 (3H, m, Ar**H**), 6.07 – 6.05 (1H, m, N**H**), 4.94 – 4.91 (1H, m, C**H**$_2$), 4.54 (1H, s, C**H**$_2$), 4.35 (1H, s, C**H**$_2$), 3.96 – 3.95 (1H, m, C**H**$_2$), 3.72 – 3.62 (2H, m, C**H** and CH**H**'), 3.50 (2H, s, C**H**$_2$), 3.33 – 3.11 (2H, m, C**H**$_2$), 2.99 – 2.80 (2H, m, CH**H'** and C**H**$_2$), 2.26 – 2.23 (3H, m, C**H**$_2$), 2.05 – 1.60 (8H, m, 4 x C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 178.9 (**C**O), 171.8 (**C**O), 171.4 (**C**O), 140.9 (**C**Ar), 140.4 (**C**Ar), 136.7 (**C**Ar), 128.9 (Ar**C**H), 128.4 (Ar**C**H), 127.7 (Ar**C**H), 127.5 (Ar**C**H), 127.1 (Ar**C**H), 49.0 (**C**H$_2$), 46.2 (**C**H$_2$), 45.6 (**C**H$_2$), 45.2 (**C**H$_2$), 41.1 (**C**H), 38.7 (**C**H$_2$), 36.7 (**C**H$_2$), 31.4 (**C**H$_2$), 29.6 (**C**H$_2$), 26.3 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{27}H_{33}N_3NaO_3$, 470.2422. Found: $[MNa]^+$, 470.2414 (−1.7 ppm error).

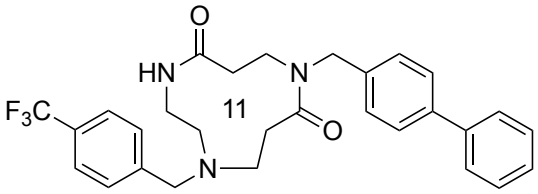
8-([1,1'-Biphenyl]-4-ylmethyl)-1-benzoyl-1,4,8-triazacycloundecane-5,9-dione (364)



tert-Butyl 8-([1,1'-biphenyl]-4-ylmethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate **335** (100 mg, 0.22 mmol) was dissolved in 4 M HCl in dioxane (4.0 mL). The solution was stirred at RT for 10 min, after which the solution was concentrated *in vacuo* to yield the salt product. The salt product was then dissolved in dry DCM (5.0 mL), was cooled to 0 °C and dry triethylamine (0.18 mL, 1.32 mmol) was added dropwise. Next, benzyl chloride (0.03 mL, 0.28 mmol) and DMAP (2.7 mg, 0.022 mmol) were added and the reaction mixture was allowed to warm to RT while being stirred for 18 hours. The reaction mixture was diluted with ethyl acetate (10 mL) washed with saturated brine solution (10 mL) and extracted with ethyl

acetate (3 x 10 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate) to afford the title compound as a white solid (87 mg, 87% yield over 2 steps); m.p. 93 – 97 °C; R_f 0.53 (1:9 methanol:ethyl acetate). **IR** (ATR): υ_{max}/cm^{-1} 3296, 3004, 1624, 1551, 1411, 1355, 1272, 1216, 1146, 1075, 1007, 908, 750, 703, 666. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product; δ_H (400 MHz, $CDCl_3$) 7.53 – 7.50 (7H, m Ar**H**), 7.41 – 7.37 (5H, m, Ar**H**), 7.27 – 7.24 (2H, m, Ar**H**), 6.74 (1H, s, N**H**), 4.26 – 4.13 (1H, m, C**H**$_2$), 3.94 – 2.89 (10H, m, 5 x C**H**$_2$), 2.38 – 2.09 (3H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 173.7 (**C**O), 171.9 (**C**O), 171.1 (**C**O), 140.7 (**C**Ar), 140.4 (**C**Ar), 137.0 (**C**Ar), 136.6 (**C**Ar), 129.3 (Ar**C**H), 128.8 (Ar**C**H), 128.5 (Ar**C**H), 128.3 (Ar**C**H), 127.5 (Ar**C**H), 127.45 (Ar**C**H), 127.0 (Ar**C**H), 126.7 (Ar**C**H), 48.2 (**C**H$_2$), 47.5 (**C**H$_2$), 47.1 (**C**H$_2$), 44.3 (**C**H$_2$), 38.6 (**C**H$_2$), 36.3 (**C**H$_2$), 31.5 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{28}H_{29}N_3NaO_3$, 478.2111. Found: $[MNa]^+$, 478.2101 (−2.1 ppm error).

8-([1,1'-Biphenyl]-4-ylmethyl)-1-(4-(trifluoromethyl)benzyl)-1,4,8-triazacycloundecane-5,9-dione (365)

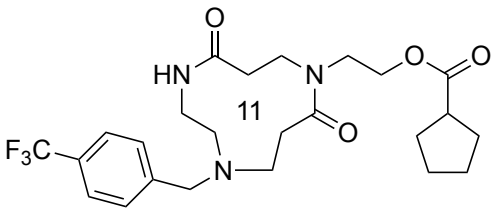


tert-Butyl 8-([1,1'-biphenyl]-4-ylmethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate **335** (100 mg, 0.22 mmol) was dissolved in 4 M HCl in dioxane (4.0 mL). The solution was stirred at RT for 10 minutes, after which the solution was concentrated *in vacuo* to yield the salt product. The salt product was dissolved in dry THF to which was added 1-(bromomethyl)-4-(trifluoromethyl) benzene (65.7 mg, 0.28 mmol) followed by dry Et_3N (0.09 mL, 0.66 mmol) and the reaction stirred at 70 °C for 18 hours. The reaction mixture was allowed to cool to RT, and then concentrated *in vacuo*. The crude was purified by column chromatography (1:19 methanol:ethyl acetate) to afford the title compound as a liquid (87.2 mg, 78% yield over 2 steps); R_f 0.60 (1:9 methanol:ethyl acetate). **IR** (ATR): υ_{max}/cm^{-1} 3312, 2930, 2830, 2243, 1632,

1324, 1160, 1107, 1120, 1065, 1018, 907, 822,728, 698, 646. In solution in $CDCl_3$, the product exists as a 3:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 7.60 – 7.55 (7H, m Ar**H**), 7.47 – 7.42 (6H, m, Ar**H**), 5.70 (1H, s, N**H**), 4.93 – 4.90 (1H, m, C**H**$_2$), 4.64 – 4.61 (1H, m, C**H**$_2$), 4.08 – 4.01 (1H, m, C**H**$_2$), 3.96 – 3.90 (1H, m, C**H**$_2$), 3.75 – 3.71 (1H, m, C**H**$_2$), 3.47 – 3.44 (1H, m, C**H**$_2$), 3.37 – 3.34 (2H, m, C**H**$_2$), 2.93 – 2.87 (1H, m, C**H**$_2$), 2.69 – 2.64 (1H, m, C**H**$_2$), 2.60 – 2.54 (1H, m, C**H**$_2$), 2.46 – 2.41 (1H, m, C**H**$_2$), 2.30 – 2.23 (2H, m, C**H**$_2$), 2.09 – 2.02 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 172.6 (**C**O), 171.5 (**C**O), 140.8 (**C**Ar), 140.4 (**C**Ar), 137.4 (**C**Ar), 129.7 (Ar**C**H), 129.5 (Ar**C**H), 128.9 (Ar**C**H), 128.8 (Ar**C**H), 127.6 (Ar**C**H), 127.1 (Ar**C**H), 126.9 (Ar**C**H), 125.3 (Ar**C**H, q, $J_{F\text{-}C}$ = 3.7 Hz), 62.3 (**C**H$_2$), 53.7 (**C**H$_2$), 51.4 (**C**H$_2$), 49.3 (**C**H$_2$), 45.6 (**C**H$_2$), 40.3 (**C**H$_2$), 36.9 (**C**H$_2$), 31.4 (**C**H$_2$). The two ^{13}C NMR signals closest to the fluorine groups were not observed. **HRMS (ESI)**: calcd. for $C_{29}H_{31}F_3N_3O_2$, 510.2374. Found: $[MH]^+$, 510.2363 (−2.1 ppm error).

Characteristic NMR data for the minor rotamer can be found at: δ_H (400 MHz, $CDCl_3$) 7.37 – 7.33 (1H, m, Ar**H**), 7.18 (1H, d, *J* = 8.0 Hz, Ar**H**), 6.18 – 6.17 (1H, m, N**H**), 4.72 (1H, d, *J* = 16.7 Hz, C**H**$_2$), 4.41 – 4.34 (2H, m, C**H**$_2$), 3.96 – 3.93 (1H, m, C**H**$_2$), 3.56 – 3.53 (1H, m, C**H**$_2$), 3.04 – 2.96 (2H, m, C**H**$_2$), 2.76 – 2.70 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 173.7 (**C**O), 171.8 (**C**O), 143.9 (**C**Ar), 143.2 (**C**Ar), 140.8 (**C**Ar), 135.7 (**C**Ar), 58.4 (**C**H$_2$), 53.0 (**C**H$_2$), 52.8 (**C**H$_2$), 50.9 (**C**H$_2$), 43.1 (**C**H$_2$), 37.7 (**C**H$_2$), 34.8 (**C**H$_2$), 34.0 (**C**H$_2$).

2-(5,9-Dioxo-1-(4-(trifluoromethyl)benzyl)-1,4,8-triazacycloundecan-8-yl)ethyl cyclopentanecarboxylate (366)

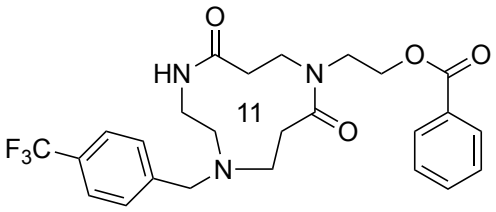


tert-Butyl 8-(2-((cyclopentanecarbonyl)oxy)ethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate **353** (73 mg, 0.17 mmol) was dissolved in 4 M HCl in 1,4-dioxane (2.0 mL). The solution was stirred at RT for 1 hours, after which the solution was concentrated *in vacuo* to yield the salt product. The salt product was dissolved in dry THF to which was added 1-(bromomethyl)-4-(trifluoromethyl) benzene (51.3 mg, 0.21 mmol) followed by dry Et_3N (0.07

mL, 0.51 mmol) and the reaction stirred at 70 °C for 18 hours. The reaction mixture was allowed to cool to RT, and then concentrated *in vacuo*. The crude was purified by column chromatography (1:19 methanol:ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a yellow oil (57.8 mg, 70% yield); R_f 0.51 (1:9 methanol:ethyl acetate). **IR** (ATR): υ_{max}/cm^{-1} 3314, 2958, 1729, 1640, 1543, 1454, 1323, 1158, 1119, 1065, 1017, 852, 822, 732. In solution in $CDCl_3$, the product exists as a roughly 5:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 7.52 (2H, d, *J* = 7.9 Hz, Ar**H**), 7.34 (2H, d, *J* = 7.9 Hz, Ar**H**), 6.29 (1H, s, N**H**), 4.47 – 4.44 (2H, m, C**H**$_2$), 4.24 – 4.15 (1H, m, C**H**$_2$), 4.03 – 3.98 (1H, m, C**H**$_2$), 3.82 – 3.79 (1H, m, C**H**$_2$), 3.64 – 3.61 (1H, m, C**H**$_2$), 3.39 – 3.32 (2H, m, C**H**$_2$), 3.28 – 3.22 (1H, m, C**H**$_2$), 2.92 – 2.79 (2H, m, C**H**$_2$), 2.66 – 2.58 (2H, m, C**H** and C**H**H'), 2.51 – 2.48 (2H, m, C**H**$_2$), 2.44 – 2.38 (1H, m, CH**H'**), 2.30 – 2.27 (1H, m, C**H**$_2$), 2.01 (2H, m, C**H**$_2$), 1.87 – 1.81 (2H, m, C**H**$_2$), 1.72 – 1.66 (4H, m, 2 x C**H**$_2$), 1.55 – 1.53 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 176.6 (**C**O), 173.2 (**C**O), 171.6 (**C**O), 143.9 (**C**Ar), 129.3 (Ar**C**H), 125.3 (Ar**C**H, q, $J_{F\text{-}C}$ = 3.7 Hz), 62.6 (**C**H$_2$), 62.4 (**C**H$_2$), 53.8 (**C**H$_2$), 52.0 (**C**H$_2$), 48.0 (**C**H$_2$), 47.5 (**C**H$_2$), 43.7 (**C**H), 40.2 (**C**H$_2$), 37.1 (**C**H$_2$), 31.6 (**C**H$_2$), 30.2 (**C**H$_2$), 25.9 (**C**H$_2$). The two ^{13}C NMR signals closest to the fluorine groups were not observed. **HRMS (ESI)**: calcd. for $C_{24}H_{32}F_3N_3NaO_4$, 506.2240. Found: $[MNa]^+$, 506.2237 (−0.6 ppm error).

Characteristic NMR data for the minor rotamer can be found at; δ_H (400 MHz, $CDCl_3$) 7.37 – 7.33 (1H, m, Ar**H**), 7.18 (1H, d, *J* = 8.0 Hz, Ar**H**), 6.18 – 6.17 (1H, m, N**H**), 4.72 (1H, d, *J* = 16.7 Hz, C**H**$_2$), 4.41 – 4.34 (2H, m, C**H**$_2$), 3.96 – 3.93 (1H, m, C**H**$_2$), 3.56 – 3.53 (1H, m, C**H**$_2$), 3.04 – 2.96 (2H, m, C**H**$_2$), 2.76 – 2.70 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 173.7 (**C**O), 171.8 (**C**O), 135.7 (**C**Ar), 133.4 (**C**Ar), 125.3 (Ar**C**H), 58.4 (**C**H$_2$), 53.0 (**C**H$_2$), 52.8 (**C**H$_2$), 50.9 (**C**H$_2$), 43.1 (**C**H$_2$), 37.7 (**C**H$_2$), 34.8 (**C**H$_2$), 34.0 (**C**H$_2$).

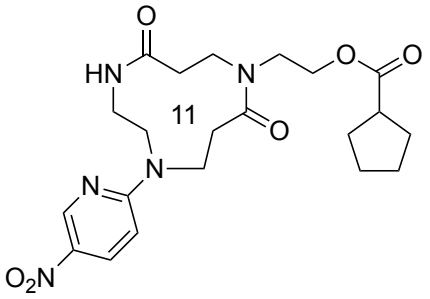
2-(5,9-Dioxo-1-(4-(trifluoromethyl)benzyl)-1,4,8-triazacycloundecan-8-yl)ethyl benzoate (367)



tert-Butyl 8-(2-(benzoyloxy)ethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate **351** (52.5 mg, 0.12 mmol) was dissolved in 4 M HCl in 1,4-dioxane (1.0 mL). The solution was stirred at RT for 1 hours, after which the solution was concentrated *in vacuo* to yield the salt product. The salt product was dissolved in dry THF to which was added 1-(bromomethyl)-4-(trifluoromethyl) benzene (36.0 mg, 0.15 mmol) followed by dry Et_3N (0.05 mL, 0.36 mmol) and the reaction stirred at 70 °C for 18 hours. The reaction mixture was allowed to cool to RT, and then concentrated *in vacuo*. The crude was purified by column chromatography (1:9 methanol:ethyl acetate → 1:4 methanol:ethyl acetate to afford the title compound as a yellow oil (32.6 mg, 55% yield); R_f 0.5 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3315, 3072, 2928, 2847, 2236, 1718, 1640, 1553, 1323, 1271, 1159, 1115, 1065, 999, 852, 823, 712. In solution in $CDCl_3$, the product exists as a roughly 2:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 7.99 – 7.97 (2H, m, Ar**H**), 7.57 – 7.55 (3H, m, Ar**H**), 7.45 – 7.39 (4H, m, Ar**H**), 6.13 – 6.12 (1H, m, N**H**), 4.75 – 4.60 (2H, m, C**H**$_2$), 3.81 – 3.61 (4H, m, 2 x C**H**$_2$), 3.36 – 3.34 (2H, m, C**H**$_2$), 2.90 – 2.83 (2H, m, C**H**$_2$), 2.60 – 2.25 (6H, m, 3 x C**H**$_2$), 2.12 – 1.87 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 173.1 (**C**O), 171.3 (**C**O), 166.8 (**C**O), 143.5 (**C**Ar), 133.6 (Ar**C**H), 129.7 (**C**Ar), 129.6 (Ar**C**H), 129.5 (Ar**C**H), 128.7 (Ar**C**H), 128.6 (Ar**C**H), 125.4 (Ar**C**H, q, $J_{F\text{-}C}$ = 3.7 Hz), 63.4 (**C**H$_2$), 62.4 (**C**H$_2$), 53.7 (**C**H$_2$), 51.8 (**C**H$_2$), 47.6 (**C**H$_2$), 47.4 (**C**H$_2$), 43.5 (**C**H$_2$), 40.0 (**C**H$_2$), 37.5 (**C**H$_2$), 31.6 (**C**H$_2$). The two ^{13}C NMR signals closest to the fluorine groups were not observed. **HRMS (ESI)**: calcd. for $C_{25}H_{28}F_3N_3NaO_4$, 514.1920. Found: $[MNa]^+$, 514.1924 (0.8 ppm error).

Characteristic NMR data for the minor rotamer can be found at: δ_H (400 MHz, $CDCl_3$) 6.05 – 6.04 (1H, m, N**H**), 4.14 – 4.02 (2H, m, C**H**$_2$), 3.57 – 3.47 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 166.4 (**C**O), 62.2 (**C**H$_2$), 61.1 (**C**H$_2$), 59.1 (**C**H$_2$), 43.5 (**C**H$_2$), 31.5 (**C**H$_2$).

2-(1-(5-Nitropyridin-2-yl)-5,9-dioxo-1,4,8-triazacycloundecan-8-yl)ethyl cyclopentanecarboxylate (369)



tert-Butyl 8-(2-((cyclopentanecarbonyl)oxy)ethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate **353** (81.4 mg, 0.19 mmol) was dissolved in 4 M HCl in 1,4-dioxane (2.0 mL). The solution was stirred at RT for 1 hours, after which the solution was concentrated *in vacuo* to yield the salt product. The salt product was dissolved in dry MeCN to which was added -2-chloro-5-nitropyridine (37.2 mg, 0.23 mmol) followed by K_2CO_3 (158 mg, 1.14 mmol) and the reaction stirred at 80 °C for 18 hours. The reaction mixture was allowed to cool to RT, and then concentrated *in vacuo*. The crude was purified by column chromatography (1:9 methanol:ethyl acetate) to afford the title compound as a yellow solid (71.6 mg, 84% yield); m.p. 102 – 105 °C; R_f 0.49 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3301, 2954, 1730, 1642, 1515, 1333, 1293, 1164, 1119, 1001; The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. δ_H (400 MHz, DMSO-*d*$_6$) 8.95 (1H, d, *J* = 2.8 Hz, Ar**H**), 8.21 (1H, dd, *J* = 9.6, 2.8 Hz, Ar**H**), 8.09 – 8.06 (1H, m, Ar**H**), 7.25 – 7.23 (1H, m, N**H**), 4.12 – 4.09 (2H, m, C**H**$_2$), 3.36 (12H, m, 6 x C**H**$_2$), 2.74 – 2.66 (1H, m, C**H**), 1.85 – 1.76 (2H, m, C**H**$_2$), 1.70 – 1.49 (8H, m, 4 x C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 175.6 (**C**O), 171.2 (**C**O), 171.0 (**C**O), 161.0 (**C**Ar), 145.3 (Ar**C**H), 134.4 (Ar**C**H), 131.8 (Ar**C**H), 108.1 (**C**Ar), 61.3 (**C**H$_2$), 54.9 (**C**H$_2$), 47.8 (**C**H$_2$), 45.1 (**C**H$_2$), 44.0 (**C**H$_2$), 43.0 (**C**H), 36.6 (**C**H$_2$), 35.9 (**C**H$_2$), 30.1 (**C**H$_2$), 29.4 (**C**H$_2$), 25.3 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{21}H_{29}N_5NaO_6$, 470.2016. Found: $[MNa]^+$, 470.2010 (−1.4 ppm error).

7. Abbreviations

(*R*)-TIPSY	(*R*)-3,3'-Bis(triphenylsilyl)-1-1'-binaphthyl-2-2'-diyl hydrogenphosphate
(*R*)-TRIP	(*R*)-3,3'-Bis(2,4,6-triisopropylphenyl)-1-1'-binaphthyl-2-2'-diyl hydrogenphosphate
1,2-DCE	1,2-dichloroethane
α	alpha
Ac	acetyl
AIBN	azobisisobutyronitrile
aq	aqueous
Ar	aryl
β	beta
BHT	butylated hydroxy toluene (2,6-di-*tert*-butyl-4-methylphenol)
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Boc	tert-butyloxycarbonyl
bp	boiling point
Bpin	boronic Pinacol Ester
Bu	butyl
°C	degrees Celsius
cat.	catalyst
Cbz	carboxybenzyl
COSY	correlated spectroscopy
CPA	chiral phosphoric acid
CSA	camphorsulfonic acid
d	doublet
dd	doublet of doublet
ddt	doublet of triplet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DEPT	distortionless enhancement by polarisation transfer

DIPEA	*N*,*N*-diisopropylethylamine
DMAP	*N,N*-dimethylaminopyridin-4-amine
DMF	dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethysulfoxide
DPPA	diphenylphosphoryl azide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
ee	enantiomeric excess
equiv	equivalent
er	enantiomeric ratio
ESI	electrospray ionisation
Et	ethyl
Fmoc	fluorenylmethyloxycarbonyl
HIV	human immunodeficiency virus
HG-II	Hoveyda Grubbs 2nd generation
HMBC	heteronuclear multiple bond coherence
HMQC	heteronuclear multiple quantum coherence
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
h	hour(s)
IC_{50}	half maximal inhibitory concentration
i-Pr	isopropyl
IPA	isopropyl alcohol
IR	infrared spectroscopy
J	coupling constant (Hz)
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
m	multiplet
Me	methyl
Mes	mesityl (1,3,5-trimethylbenzene)
min	minute

mp	melting point
M	molar
MIC	minimum inhibitory concentration
min	minutes
Ms	mesyl
NaHMDS	sodium bis(trimethylsilyl)amide
NMR	nuclear magnetic resonance spectroscopy
Pd	palladium
PG	protecting group
Ph	phenyl
ppm	part(s) per million
Pyr	pyridine
q	quartet
rac-	racemic
rac-CSA	racemic camphorsulfonic acid
R_f	retention factor (in chromatography)
rt	room temperature
s	singlet
sat	saturated
SM	starting material
S_NAr	nucleophilic aromatic substitution reaction
SMCC	Suzuki-Miyaura cross-coupling
t	triplet
t-Bu	tert-butyl
TBAF	tetra-*n*-butylammonium fluoride
TBS	*t*-butyldimethylsilyl
Tf	trifluoromethanesulfonate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSE	trimethylsilyl ester

Ts	*p*-toluenesulfonyl
μ	micro
XRD	X-ray diffraction

8. References

1 C. S. Pak and G. H. Lee, *J. Org. Chem.*, 1991, **56**, 1128−1133.

2 M. S. Majik, D. Naik, C. Bhat, S. Tilve, S. Tilvi, L. DeSouza, *Bioorg. Med.Chem. Lett.*, 2013, **23**, 5514−5518.

3 Y. X. Li, R. Iwaki, A. Kato, Y. M. Jia, G. W. J. Fleet, X. Zhao, M. Xiao, and C. Y. Yu, *Eur. J. Org. Chem.*, 2016, 1429−1438.

4 M. Tsuda, M. Sasaki, T. Mugishima, K. Komatsu, T. Sone, M. Tanaka, Y. Mikami, and J. Kobayashi, *J. Nat. Prod.*, 2005, **68**, 273−276.

5 M. Lévesque and M. Avoli, *Neurosci. Biobehav. Rev.*, 2013, **37**, 2887−2899.

6 W. J. Olivier, J. A Smith and A. C. Bissember, *Chem. Rec.*, 2022, e202100277.

7 J. W. Daly, T. F. Spande and H. M. Garraffo, *J. Nat. Prod.*, 2005, **68**, 1556−1575.

8 D. O'Hagan, *Nat. Prod. Rep.*, 2000, **17**, 435−446.

9 S. Poyraz, H. A. Döndaş, N. Y. Döndaş and J. M. Sansano, *Front. Pharmacol.*, 2023, **14**, 1239658.

10 F. Gualtieri, D. Manetti, M. N. Romanelli and C. Ghelardini, *Curr. Pharm. Des.*, 2002, **8**, 125−138.

11 M. Hurst and H. M. Lamb, *Drugs,* 2000, **59**, 653−680.

12 V. K. Dhawan and H. Thadepalli, *Rev. Infect. Dis.,* 1982, **4**, 1133−1153.

13 J. E. Heeg, P. E. de Jong, G. K. van der Hem, D. de Zeeuw, *Kidney Int.*, 1989, **36**, 272−279.

14 L. M. Hollingshead, D. Faulds and A. Fitton, *Drugs*, 1992, **44**, 835−857.

15 I. Arrastia, A. Arrieta and F. P. Cossio, *Eur. J. Org. Chem.*, 2018, 4101−4117.

16 P. Betschmann, S. Sahil, F. Diederich, U. Obst, *Helv. Chim. Acta.*, 2002, **85**, 1210−1228.

17 P. R. Sebahar and R. M. Williams, *J. Am. Chem. Soc.*, 2000, **122**, 5666−5667.

18 H. Pellissier, *Tetrahedron*, 2007, **63**, 3235−3285.

19 I. Riaño, E. Diaz, U. Uria, E. Reyes, L. Carrillo and J. L. Vicario, *Chem. Commun.*, 2016, **52**, 2330−2333.

20 L. M. Stanley and M. P. Sibi, *Chem. Rev.*, 2008, **108**, 2887−2902.

21 J. Adrio and J. C. Carretero, *Chem. Commun.*, 2014, **50**, 12434−12446.

22 S. Kanemasa, *Synlett*, 2002, **9**, 1371−1387.

23 J. M. Longmire, B. Wang and X. Zhang, *J. Am. Chem. Soc.*, 2002, **124**, 13400−13401.

24 W. Gao, X. Zhang and M. Raghunath, *Org. Lett.*, 2005, **7**, 4241−4244.

25 S. V. Kumar and P. J. Guiry, *Angew. Chem. Int. Ed.*, 2022, **61**, e202205516.

26 S. V. Kumar, J. Olusegun and P. J. Guiry, *Org. Biomol. Chem.* 2024, **22**, 7148−7153.

27 M. S. Rosello, J. L. Aceña, A. S. Fuentes and C. del Pozo, *Chem. Soc. Rev.*, 2014, **43**, 7430−7453.

28 F. Yin, A. Garifullina and F. Tanaka, *Org. Biomol. Chem.*, 2017, **15**, 6089−6092.

29 P. R. Krishna, A. Sreeshailam and R. Srinivas, *Tetrahedron*, 2009, **65**, 9657−9672.

30 M. G. Vinogradov, O. V. Turova and S. G. Zlotin, *Org. Biomol. Chem.*, 2019, **17**, 3670−3708.

31 S. Fustero, D. Jiménez, J. Moscardó, S. Catalán and C. del Pozo, *Org. Lett.*, 2007, **9**, 5283−5286.

32 C. Enkisch and C. Schneider, *Eur. J. Org. Chem.*, 2009, 5549−5564.

33 H. Li, L. Zu, H. Xie, J. Wang and W. Wang, *Chem. Commun.*, 2008, 5636−5638.

34 B. L. Zhao, Y. Lin, H. H. Yan and D. M. Du, *Org. Biomol. Chem.*, 2015, **13**, 11351−11361.

35 A. Garg, D. Rendina, H. Bendale, T. Akiyama and I. Ojima, *Front Chem.*, 2024, **12**, 1398397.

36 J. S. Lin, P. Yu, L. Huang, P. Zhang, B. Tan and X. Y. Liu, *Angew. Chem.*, 2015, **127**, 7958−7962.

37 J. Yu, F. Shi and L. Z. Gong, *Acc. Chem. Res.*, 2011, **44**, 1156−1171.

38 H. Liu, C. Zeng, J. Guo, M. Zhang and S. Yu, *RSC Adv.*, 2013, **3**, 1666−1668.

39 X. H. Chen, W. Q. Zhang and L. Z. Gong, *J. Am. Chem. Soc.*, 2008, **130**, 5652−5653.

40 B. Schlummer and J. F. Hartwih, *Org. Lett.*, 2002, **4**, 1471−1474.

41 J. Yu, W. J. Chen and L. Z. Gong, *Org. Lett.*, 2010, **12**, 4050−4053.

42 H. C. Liu, L. Wei, R. Huang, H. Y. Tao, H. Cong and C. J. Wang, *Org. Lett.*, 2018, **20**, 3482−3486.

43 S. Rajkumar, S. He and X. Yang, *Angew. Chem. Int. Ed.*, 2019, **58**, 10315−10319.

44 P. A. Clarke, S. Santo, N. Mistry, L. Burroughs and A. C. Humphries, *Org. Lett.*, 2011, **13**, 624−627.

45 P. A. Clarke and K. Ermanis, *Org. Lett.*, 2012, **14**, 5550–5553.

46 N. M. Nasir, K. Ermanis and P. A. Clarke, *Org. Biomol. Chem.*, 2014, **12**, 3323–3335.

47 P. A. Clarke, N. M. Nasir, P.B. Sellars, A. M. Peter, C. A. Lawson and J. L. Burroughs, *Org. Biomol. Chem.*, 2016, **14**, 6840–6852.

48 K. Alomari, N. S. P. Chakravarthy, B. Duchadeau, K. Ermanis and P. A. Clarke, *Org. Biomol. Chem.*, 2022, **20**, 1181−1185.

49 K. Ermanis, Y. T. Hsiao, U. Kaya, A. Jeuken and P. A. Clarke, *Chem. Sci.*, 2017, **8**, 482–490.

50 A. Agora, MSc Thesis, University of York, 2020.

51 A. K. Chatterjee, T.-L. Choi, D. P. Sanders and R. H. Grubbs, *J. Am. Chem. Soc.*, 2003, **125**, 11360–11370.

52 K. Ermanis, Y. T. Hsiao, U. Kaya, A. Jeuken and P. A. Clarke, *Chem. Sci.*, 2016, **8**, 482–490.

53 K. Voigtritter, S. Ghorai and B. H. Lipshutz, *J. Org. Chem.*, 2011, **76**, 4697–4702.

54 A. Farwick, G. Helmchen, *Adv. Synth. Catal*, 2010, **352**, 1023-1032.

55 S. Hanessian, A. Tehim and P. Chen, *J. Org. Chem.*, 1993, **58**, 7768–7781.

56 C.J. Maddock, K. Ermanis and P.A. Clarke, *Org. Lett*, 2020, **22**, 8116-8121.

57 C.J. Maddock, PhD thesis, University of York, 2020.

58 P.R. Sultane, T.B. Mete, R.G. Bhat, *Tetrahedron Lett.*, 2015, **56**, 2067-2070.

59 A. Hussain, S. K. Yousuf, D. Mukherjee, *RSC Adv.,* 2014, **4**, 43241−43257.

60 J. Mallinson and I. Collins, *Future Med. Chem.*, 2012, **4**, 1409−1438.

61 M. T. Crimmins and E. A. Tabet, *J. Am. Chem. Soc.,* 2000, **122**, 5473−5476.

62 E. Moulin, S. Barluenga, N. Winssinger, *Org. Lett.*, 2005, **7**, 5539−5747.

63 D. J. Abraham and R. D. Rosenstein, *Tetrahedron Lett.,* 1972, **10**, 909−912.

64 A. Shemet and E. M. Carreira, *Org. Lett.*, 2017, **19**, 5529−5532.

65 T. P. Majhi, B. Achari and P. Chattopadhyay, *Heterocycles*, 2007, **71**, 1011−1052.

66 O. Darlami, R. Pun, S. H. Ahn, S. H. Kim, D. Shin, *Eur. J. Med. Chem.*, 2024, **272**, 116501.

67 M. Dow, F. Marchetti, K. A. Abrahams, L. Vaz, G. S. Besra, S. Warriner, A. Nelson, *Chem. Eur. J.*, 2017, **23**, 7207−7211.

68 L. Saya, G. Bhargava, M. A. Navarro,M. Gulias, F. López, I. Fernández, L. Castedo, J. L. Mascareñas, *Angew. Chem.*, 2010, **122**, 10082−10086.

69 Y. Oonishi, A. Hosotani, Y. Sato, *J. Am. Chem. Soc.*, 2011, **133**, 10386−10389.

70 Y. Xie, P. Zhang, L. Zhou, *J. Org. Chem.,* 2016, **81**, 2128−2134.

71 C. Shu, X. Zeng, M. Hao, X. Wei, N. K. Yee, C. A. Busacca, Z. Han, V. Farina, C. H. Senanayake, *Org. Lett.*, 2008, **10**, 1039−1323.

72 C. Hamel, E. V. Prusov, J. Gertsch, W. B. Schweizer, K. H. Altmann, *Angew. Chem. Int. Ed.*, 2008, **47**, 10081−10085.

73 R. Mamouni, M. Soukri, S. Lazar, M. Akssira, G. Guillaumet, *Tetrahedron Lett.*, 2004, **45**, 2631−2633.

74 G. Evano, J. V. Schaus, J. S. Panek, *Org. Lett.*, 2004, **6**, 525−528.

75 G. Mehta and V. Singh, *Chem. Rev.*, 1999, **99**, 881−930.

76 J. R. Donald and W. P. Unsworth, *Chem. Eur. J.*, 2017, **23**, 8780−8799.

77 Y. Liu and Y. Yeung, *Org. Lett.*, 2017, **19**, 1422−1425.

78 D. C. Harrowven, N. L'Helias, J. D. Moseley, N. J. Blumire, S. R. Flanagan, *Chem. Commun.*, 2003, **21**, 2658−2659.

79 M. Deguchi, A. Fujiya, E. Yamaguchi, N. Tada, B. Uno, A. Itoh, *RSC. Adv.*, 2018, **8**, 15825−15830.

80 A. Wu, Q. Feng, H. H. Y. Sung, I. D. Williams, J. Sun, *Angew. Chem. Int. Ed.,* 2019, **58**, 6776−6780.

81 S. Fantauzzi, E. Gallo, A. Caselli, C. Piangiolino, F. Ragaini, N. Re, S. Cenini, *Chem. Eur. J.,* 2009, **15**, 1241−1251.

82 A. A. Cant, G. H. V. Bertrand, J. L. Henderson, L. Roberts, M. F. Greaney, *Angew. Chem. Int. Ed.,* 2009, **48**, 5199−5202.

83 B. Zhoui L. Li, X. Zhu, J. Yan, Y. Guo, L. Ye, *Angew. Chem. Int. Ed.,* 2017, **56**, 4015−4019.

84 G. A. Molander, G. A. Brown, I. S. Gracia, *J. Org. Chem.,* 2002, **67**, 3459−3463.

85 J. Hall, J. Matlock, J. Ward, K. V. Gray, J. Clayden, *Angew. Chem. Int. Ed.,* 2016, **55**, 11153−11157.

86 N. P. Tsvetkov, A. Bayir, S. Schneider, M. Brewer, *Org. Lett.,* 2012, **14**, 264−267.

87 V. Lysenko, K. Nazarenko, S. Shishkina, A. Kostyuk, *Chem. Commun.,* 2023, **59**, 9396−9399.

88 R. A. Bauter, T. A. Wenderski, D. S. Tan, *Nat. Chem. Biol.,* 2013, **9**, 21−29.

89 A. Lawer, J. A. Rossi-Ashton, T. C. Stephens, B. J. Challis, R. G. Epton, J. M. Lynam, W. P. Unsworth, *Angew. Chem. Ed.,* 2019, **58**, 13942−13947.

90 C. Kitsiou, J. J. Hindes, P. I'Anson, P. Jackson, T. C. Wilson, E. K. Daly, H. R. Felstead, P. Hearnshaw, W. P. Unsworth, *Angew. Chem. Int., Ed.,* 2015, **54**, 15794−15798.

91 T. C. Stephens, M. Lodi, A. M. Steer, Y. Lin, M. T. Gill, W. P. Unsworth, *Chem. Eur. J.,* 2017, **23**, 13314−13318.

92 K. Y. Palate, Z. Yang, A. C. Whitwood, W. P. Unsworth, *RSC Chem. Biol.*, 2022, **3**, 334−340.

93 W. E. Orukotan, K. Y. Palate, B. Pogrányi, P. Bobinski, R. G. Epton, L. Duff, A. C. Whitwood, G. Grogan, J. M. Lynam, W. P. Unsworth, *Chem. Eur. J.*, 2024, **30**, e202303270.