

Inter and Intramolecular *N*-Conjugate Addition Reactions Using Cinchona Derived Primary Amines

By Anthony Ball, MChem



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School of Chemistry

University of Nottingham

University Park

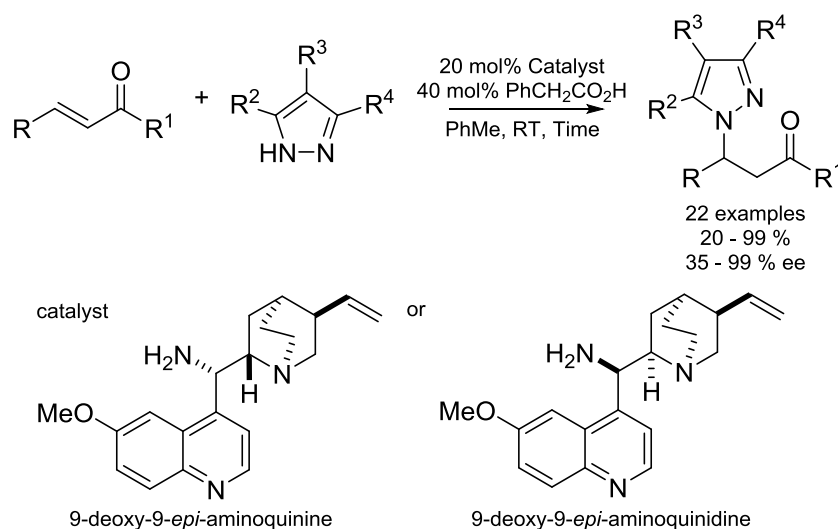
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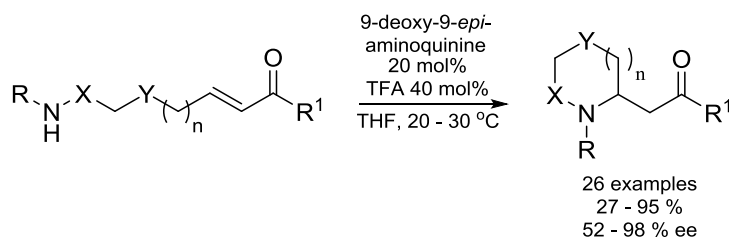
Abstract

This thesis describes the conjugate addition of nitrogen nucleophiles to α,β -unsaturated enones using cinchona derived amines. Two separate projects are outlined within, intermolecular and intramolecular *N*-conjugate addition reactions.

The first project involves the investigation of a range of nitrogen nucleophiles in their intermolecular additions to α,β -unsaturated ketones. The reactions were performed using either 9-deoxy-9-*epi*-aminoquinine or 9-deoxy-9-*epi*-aminoquinidine as the catalyst with phenylacetic acid as a co-catalyst. These catalysts were found to promote conjugate addition of a range of nitrogen heterocycles to acyclic α,β -unsaturated ketones. In particular, the addition of pyrazoles was found to proceed in high yield and enantioselectivity. In contrast, addition of these nucleophiles to cyclic ketones gave low enantioselectivity.



The second project involves the investigation of intramolecular *N*-conjugate addition processes. In this case, the reactions were performed using 9-deoxy-9-*epi*-aminoquinine and trifluoroacetic acid as the catalyst system. Several different groups on nitrogen were investigated and the reaction conditions optimised for each group. The ring size and substitution around the ring system formed were also investigated with high yields and enantioselectivities obtained.



Acknowledgements

I wish to thank Prof. Barry Lygo for his combined support, enthusiasm and ideas for this project. I would also like to thank the members of the Lygo group past and present Dr Bhaven Patel, Dr Claude-Eric Roy, Dr Graham Moore, Dr Tim Evans, Chris Davison, Oliver Bridgewood, Kevan Grant, Lee Eccleshare, Andrew Rawlings, James Quinn, Tom Worboys, Chris Clarke and Lucy Robson for useful discussions and experimental assistance. Special thanks are extended to Dr Tim Evans for his work on the conjugate additions of pyrazoles, and Kevan Grant for his work on the intramolecular conjugate addition reactions. I also wish to thank Mr. Kevin Butler, Mr. Shaz Aslam (NMR), Mr. Graham Coxhill, Mr. Lloyd Hollingworth and Dr Mick Cooper (mass spectrometry), and Mr Dane Toplis for their technical assistance. Funding from the EPSRC is gratefully acknowledged.

I would like to thank my family for their unwavering belief and support during my time as a PhD student.

Abbreviations

Ac	Acetyl
Bn	Benzyl
Boc	<i>tert</i> -Butoxycarbonyl
Bu	Butyl
Bz	Benzoyl
Cbz	Carboxybenzyl
d	Days
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
de	Diastereomeric Excess
DIAD	Diisopropyl Azodicarboxylate
DIBAL-H	Diisobutylaluminium Hydride
DMAP	4-Dimethylaminopyridine
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethylsulfoxide
DPPA	Diphenylphosphoryl Azide
ee	Enantiomeric Excess
eq	Equivalent
Et	Ethyl
Fmoc	Fluorenylmethyloxycarbonyl
h	Hours
Hep	Heptyl
Hex	Hexyl
H-G II	Hoveyda Grubbs 2 nd Generation Catalyst
HPLC	High Performance Liquid Chromatography
IPA	Isopropyl Alcohol
IR	Infra Red
LUMO	Lowest Unoccupied Molecular Orbital
Me	Methyl

Min	Minutes
Ms	Mesyl
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
Ns	4-Nitrobenzenesulfonyl
Pent	Pentyl
Ph	Phenyl
pK_a	Acid Dissociation Constant (logarithmic scale)
ppm	Parts Per Million
Pr	Propyl
<i>p</i> -TSA	<i>p</i> -Toluenesulfonic Acid
RT	Room Temperature
S_NAr	Nucleophilic Aromatic Substitution
TBS	<i>tert</i> -Butyldimethylsilyl
Temp	Temperature
TFA	Trifluoroacetic Acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
Ts	Tosyl

Contents Page

Abstract	i
Acknowledgements	ii
Abbreviations	iii
<u>Chapter 1: Intermolecular <i>N</i>-Conjugate Additions</u>	1
1.1 C-N Bond Formation	1
1.2 Organocatalysis	1
1.3 <i>N</i> -Conjugate Addition Reactions to Substituted Enals	2
1.4 Differences between Enals and Enones	6
1.5 <i>N</i> -Conjugate Addition Reactions to Substituted Enones	7
1.6 Bifunctional Catalysis	16
1.7 Project Aims	17
1.8 Synthesis of Potential Catalysts Starting from Cinchona Alkaloids	19
1.9 Pyrazole Conjugate Additions	22
1.9.1 Initial Studies	23
1.9.2 Investigating the Pyrazole Scope	25
1.9.3 Determining the Absolute Stereochemistry of the Addition Products	29
1.9.4 Investigating the Regiochemistry of the Pyrazole Addition	30
1.9.5 Investigating the Enone Scope	32
1.9.5.1 Acyclic Enones	32
1.9.5.2 Cyclic Enones	35
1.9.6 Investigation of 9-deoxy-9- <i>epi</i> -aminoquinidine as a catalyst	37
1.10 Conjugate Addition of 1,2,4-Dithiazolidine-3,5-dione	39
1.10.1 Synthesis of 1,2,4-Dithiazolidine-3,5-dione	40
1.10.2 Conjugate Addition to Substituted Enones	41
1.11 Amide and Carbamate Conjugate Additions	43

1.12 Conclusions	45
<u>Chapter 2: Intramolecular <i>N</i>-Conjugate Additions</u>	47
2.1 Intramolecular <i>N</i> -Conjugate Addition Reactions to Enals	47
2.2 Intramolecular <i>N</i> -Conjugate Addition Reactions to Enones	49
2.3 Project Aims	58
2.4 Intramolecular Pyrazole Substrate	58
2.5 Amide Substrates	64
2.5.1 External Amide Substrates	64
2.5.1.1 Synthesis of Cyclization Precursors	64
2.5.1.2 Optimisation of Cyclization Conditions	69
2.5.1.3 Investigation of Substrate Scope	71
2.5.2 Lactam Substrates	75
2.5.2.1 Synthesis of δ -Lactam Cyclization Precursor	75
2.5.2.2 Optimisation of Cyclization Conditions	76
2.5.2.3 Investigation of Substrate Scope	77
2.6 Sulfonamide Substrates	79
2.6.1 Synthesis of Cyclization Precursors	79
2.6.2 Optimisation of Cyclization Conditions	80
2.6.3 Investigation of Substrate Scope	82
2.6.4 Determination of Absolute Stereochemistry	85
2.7 Substitution of Heteroatoms into Substrates	86
2.7.1 1,2-Oxazinane Substrates	86
2.7.1.1 Synthesis of Cyclization Precursor	86
2.7.1.2 Optimisation of Cyclization Conditions	88
2.7.1.3 Investigation of Substrate Scope	89
2.7.2 Morpholine Substrates	96

2.7.2.1 Synthesis of Cyclization Precursor	96
2.7.2.2 Optimisation of Cyclization Conditions	97
2.7.2.3 Investigation of Substrate Scope	98
2.7.3 Piperazine Substrate	100
2.8 Conclusions	101
<u>Chapter 3: Experimental</u>	103
3.1 General Experimental	103
3.2 General Procedures	103
3.3 Experimental Data	107
<u>Chapter 4: References</u>	199
<u>Chapter 5: X-Ray Crystallography Data</u>	206

Chapter 1: Intermolecular N-Conjugate Additions

1.1 Carbon-Nitrogen Bond

The C-N bond is one of the most common in organic chemistry. In the pharmaceutical industry this type of bond is found in nearly all of the top 200 selling drugs in America in 2010.^[1] In 2007 amongst the list of aspirational reactions identified by an industrial review was an efficient process for C-N bond formation.^[2] The pharmaceutical industry also aims to be as environmentally friendly as possible in chemical synthesis. The conjugate addition of nitrogen nucleophiles to α,β -unsaturated aldehydes and ketones would fit these requirements: it is atom-efficient, the reaction is amenable to asymmetric catalysis and the carbonyl moiety enables further functionalisation.

1.2 Organocatalysis

Organocatalysis has been a fast growing field in chemistry over the last fifteen years since the first highly enantioselective Diels Alder example published by MacMillan in 2000.^[3] This field is very attractive as an alternative to metal catalysis due to the fact they very rarely require inert reaction conditions and are often less expensive than some of the rare metals commonly used. Also in some cases the catalyst can be recovered and re-used making it a very efficient process.

One of the ways of activating α,β -unsaturated aldehydes and ketones to nucleophilic attack is by amine catalysis (*Figure 1*). By forming the iminium species **3** by the condensation of carbonyl species **2** and amine catalyst **1** (*Figure 1*), the LUMO of the α,β -unsaturated system is lowered, making the double bond more susceptible to nucleophilic attack. A nitrogen nucleophile **4** can then attack the double bond and after proton transfer lead to iminium species **6**. This compound can be hydrolysed back to the carbonyl, yielding product **7** and regenerating amine catalyst **1**. It is essential to choose the right amine catalyst **1** so that it forms the iminium species and not perform the conjugate addition reaction. The nitrogen nucleophile **4** is also more nucleophilic to make sure it performs the conjugate addition.

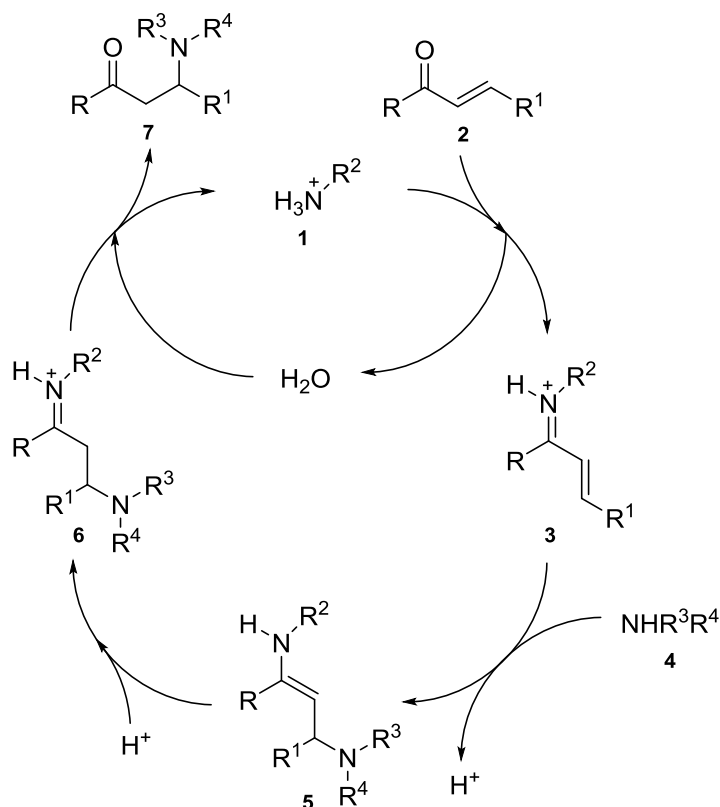
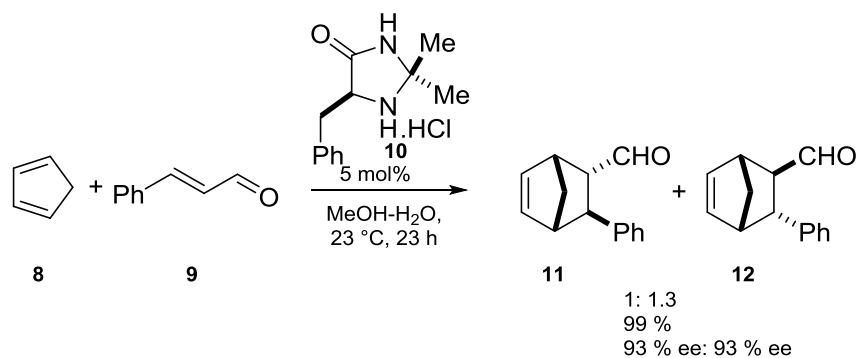


Figure 1

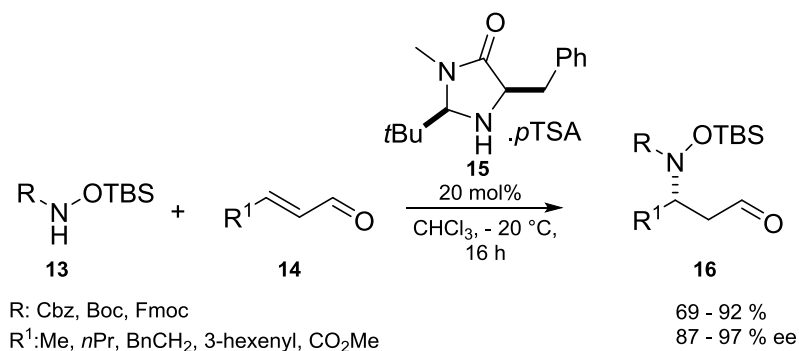
1.3 N-Conjugate Addition Reactions to Substituted Enals

The use of chiral organic molecules as catalysts for asymmetric transformations had been reported since the 1970s but in low enantioselectivities.^[4-7] It was not until MacMillan and co-workers published the first highly enantioselective organocatalytic reaction that interest in organocatalysis really started to grow. The formation of an iminium species from a secondary amine and an enal was known to increase their reactivity in the Diels-Alder reaction.^[8] MacMillan used chiral imidazolidinone salt **10** as a catalyst in the Diels-Alder reaction of aldehyde **9** with cyclopentadiene **8** yielding substituted bicycles **11** and **12** in high enantioselectivity (*Scheme 1*).^[3] The absolute stereochemistry of the products was confirmed by comparison of the optical rotation of compound **11** with the previously reported literature value.^[9]



Scheme 1

It was not until six years later in 2006 that the first secondary amine-catalysed intermolecular asymmetric nitrogen conjugate addition was reported, again by MacMillan and co-workers.^[10] Using *N*-silyloxycarbamates **13** as the nitrogen nucleophile, and various enals **14** with imidazolidinone **15** as the chiral catalyst the reaction was shown to work in good yields with high enantioselectivities (*Scheme 2*).^[10] The absolute stereochemistry was confirmed by conversion of a derivative to β -amino acid **17** and comparison of literature optical rotation data showing it to be the opposite enantiomer to that previously reported (*Figure 2*).^[11]



Scheme 2

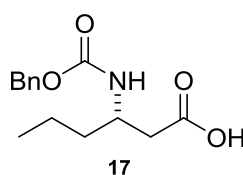
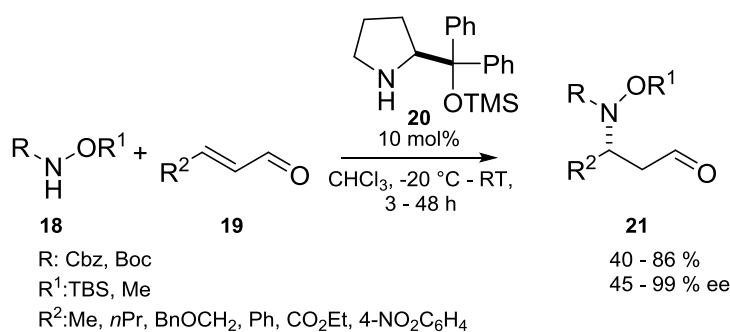


Figure 2

A year later the first example of a nitrogen conjugate addition performed with a diphenylprolinol TMS ether catalyst **20** was reported.^[12] *N*-Silyloxycarbamates **18** were added to enals **19** using catalyst **21** in good yields and enantioselectivities (*Scheme 3*).^[12] The absolute stereochemistry was again determined by conversion to β -amino acid **22** and comparison of literature optical rotation data showing it to be the opposite enantiomer to that previously reported (*Figure 3*).^[13]



Scheme 3

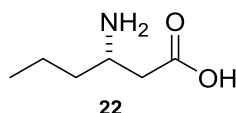
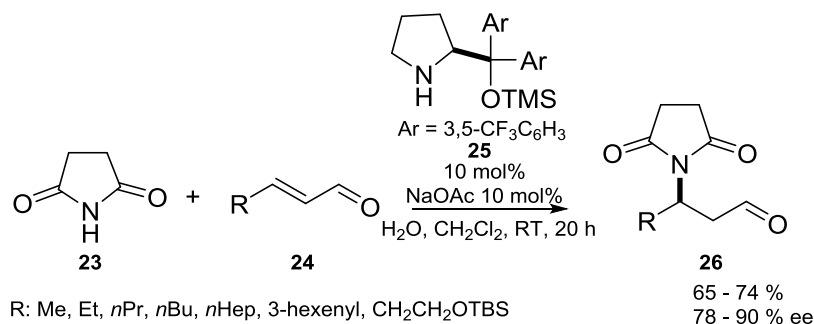


Figure 3

The first example of a non-hydroxylamine derived nitrogen nucleophile performing a conjugate addition to an enal with organocatalysis was reported by Jørgenson and co-workers in the same year. It was reported that succinimide **23** could be added to a range of enals **24** in good yields and high enantioselectivities with the use of sodium acetate as a co-catalyst (Scheme 4).^[14] The absolute stereochemistry was determined by conversion to compound **27** and comparison with the literature optical rotation data showing it to be the same enantiomer to that previously reported (Figure 4).^[15]



Scheme 4

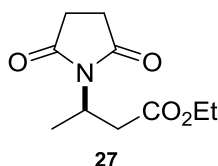
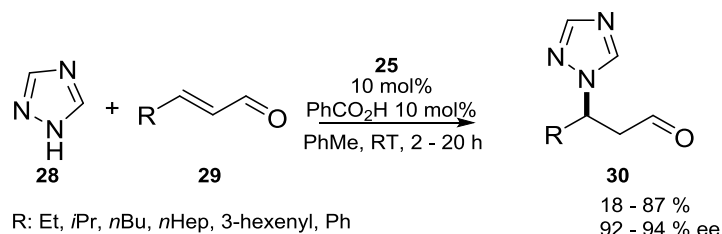


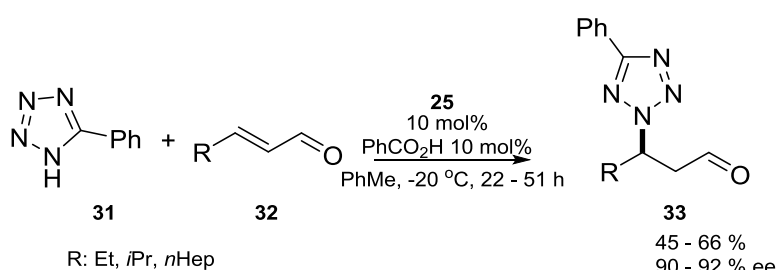
Figure 4

Jørgensen and co-workers then reported the first example of a nitrogen heterocycle as a nucleophile. Using 1,2,4-triazole **28** they obtained good yields with only one regioisomer observed and high enantioselectivities with the same catalyst system they had reported

previously (Scheme 5).^[16] They also reported the addition of 5-phenyl tetrazole **31** to substituted enals **32** using the same catalyst system (Scheme 6). The absolute stereochemistry was determined by conversion of an enriched tetrazole addition to a benzoate ester and X-ray analysis of crystalline product **34** (Figure 5).



Scheme 5



Scheme 6

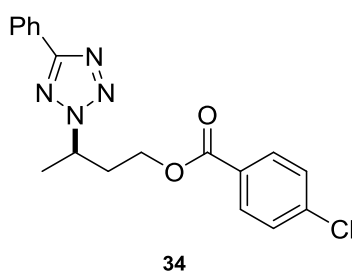
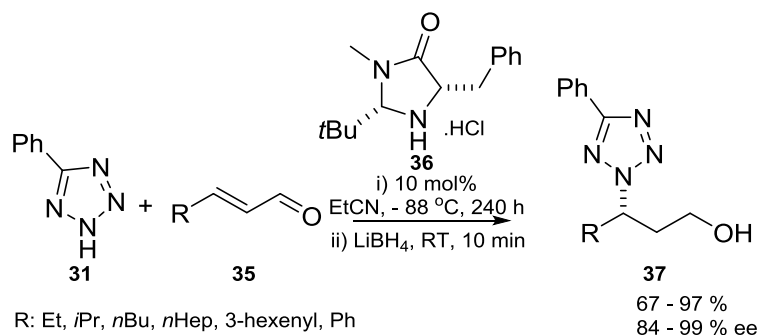


Figure 5

Following on from this work Vicario and co-workers reported 5-phenyltetrazole **31** adding to a range of enals using the enantiomer of catalyst **15** as the hydrochloride salt. The reaction had to be performed at lower temperatures than used with previous nucleophiles, with the resulting aldehydes reduced to the primary alcohols **37** in good yields and high enantioselectivities (Scheme 7).^[17] The absolute stereochemistry was determined by comparison of compound **38** with the literature optical rotation data previously reported by Jørgensen showing it to be the opposite enantiomer (Figure 6).^[12] Interestingly catalyst **36** yields the same absolute stereochemistry as its enantiomer catalyst **15** did in the conjugate addition of N-silyloxycarbamates **13** but this was not studied in any more detail.



Scheme 7

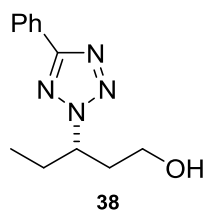


Figure 6

1.4 Differences between Enals and Enones

Despite all these examples of conjugate addition of nitrogen nucleophiles to enals, there had still been no reported *N*-conjugate additions to enones using iminium catalysis. This was possibly due to the lower reactivity of amines towards ketones when compared to that of aldehydes. In addition, the geometry around the iminium species formed would be more difficult to control with the enone than with an enal (*Figure 7*). There is very little difference between R² and the α-carbon in *trans* iminium species **40**, in terms of steric clash so the molecule can react as either conformation. This will lead to a mixture of isomers formed even when R² is as small as a methyl group.

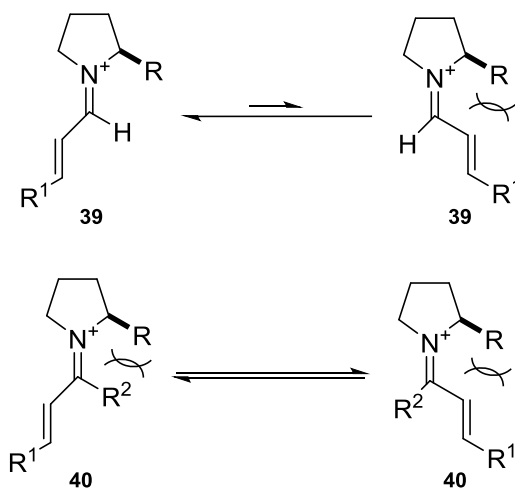


Figure 7

A possible solution to this problem would be activation of a ketone with a primary amine catalyst rather than a secondary amine catalyst (*Figure 8*). In order to reduce the steric clash between R and R², the molecule **41** should sit in the *s-trans* arrangement preferentially around the iminium leading to the formation of one product selectively.

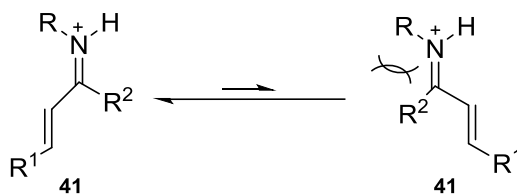
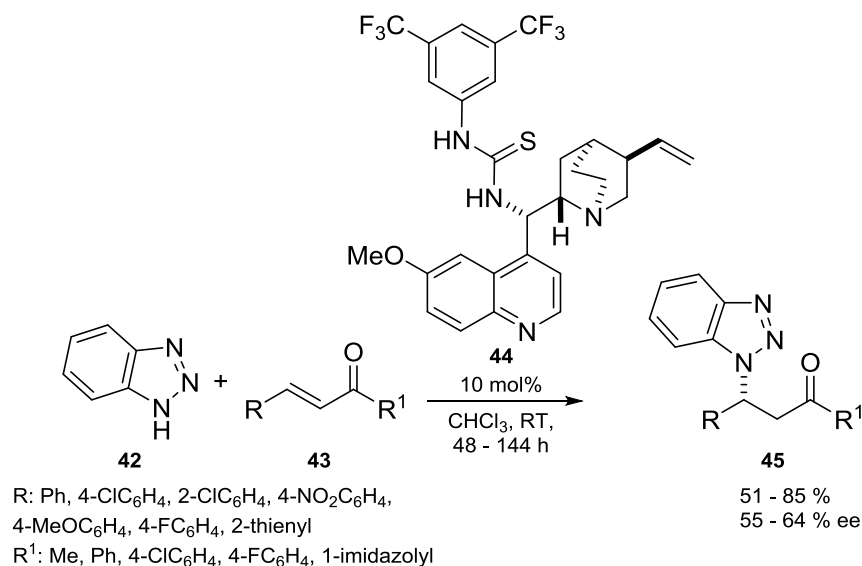


Figure 8

1.5 N-Conjugate Addition Reactions to Substituted Enones

The first reported asymmetric conjugate addition of a nitrogen nucleophile to an enone using an organocatalyst was not one involving an iminium formation but focused on hydrogen bonding interactions. Wang reported that thiourea derived quinine catalyst **44** promoted addition of benzotriazole **42** to chalcones **43** gave good yields but could only yield modest enantioselectivities (*Scheme 8*).^[18] The absolute stereochemistry was determined by X-ray diffraction of a single crystal of compound **46** (*Figure 9*).



Scheme 8

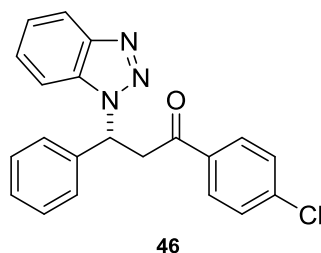
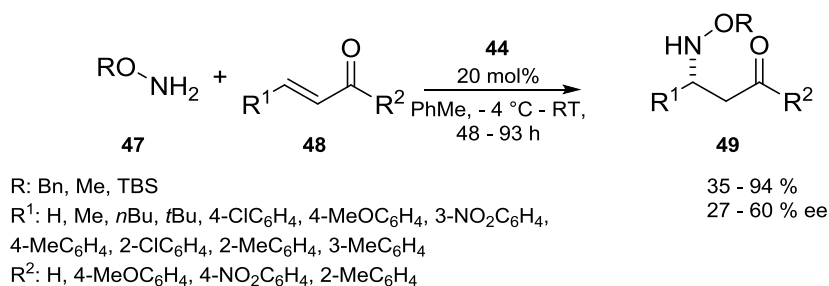


Figure 9

The same catalyst was later reported to promote addition of *O*-benzylhydroxylamines **47** to chalcones **48** in good yields but again with modest enantioselectivities (*Scheme 9*).^[19] The absolute stereochemistry was determined by comparison of compound **50** with literature chiral HPLC and optical rotation data proving it to be the opposite enantiomer (*Figure 10*).^[20] They proposed that the thiourea group hydrogen bonded to the carbonyl and the quinuclidine nitrogen hydrogen bonded to the hydroxylamine to give the stereochemistry observed (*Figure 11*).^[19]



Scheme 9

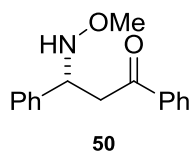


Figure 10

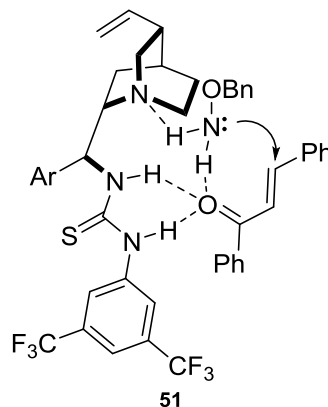
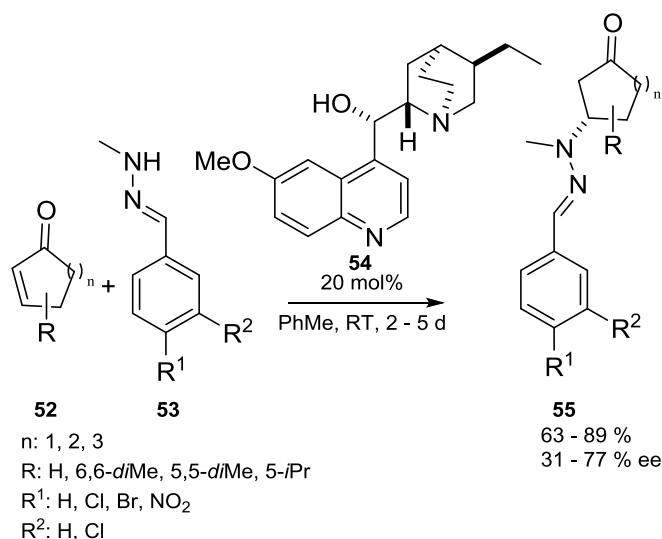


Figure 11

The next milestone in this area was the first addition of hydrazones **53** to cyclic enones **52** reported by Jørgensen and co-workers (*Scheme 10*).^[21] This reaction was performed with catalyst **54**, derived from quinine, showing cinchona alkaloids to be the catalyst of choice for these types of addition. The absolute stereochemistry was assigned by X-ray diffraction of a single crystal of derivative **56** (*Figure 12*). This agreed with their proposed transition state with the hydroxyl group of catalyst **54** hydrogen bonding with the carbonyl and the quinuclidine hydrogen bonding to the hydrazone (*Figure 13*).^[21]



Scheme 10

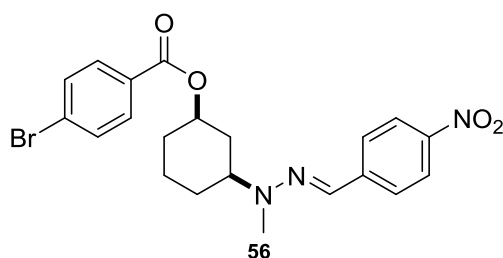


Figure 12

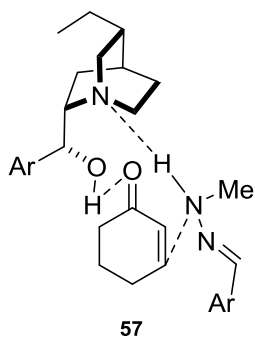
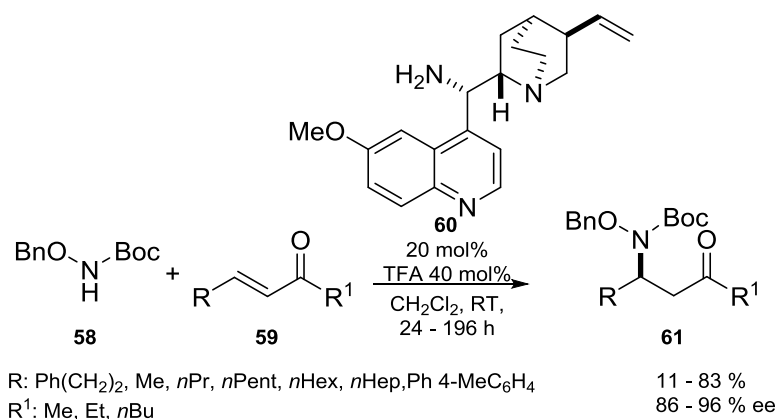


Figure 13

The following year, Deng and co-workers reported that 9-deoxy-9-*epi*-aminoquinine **60** was an effective catalyst for the addition of hydroxylamine derivatives **58** to acyclic enones **59** (Scheme 11).^[22] Trifluoroacetic acid was required as an additive presumably to promote the formation of the iminium ion intermediate between the catalyst and enone. The absolute stereochemistry was determined by conversion to compound **62** and comparison with literature optical rotation data confirming it to be the same enantiomer (Figure 14).^[23]



Scheme 11

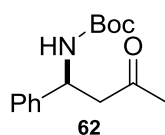
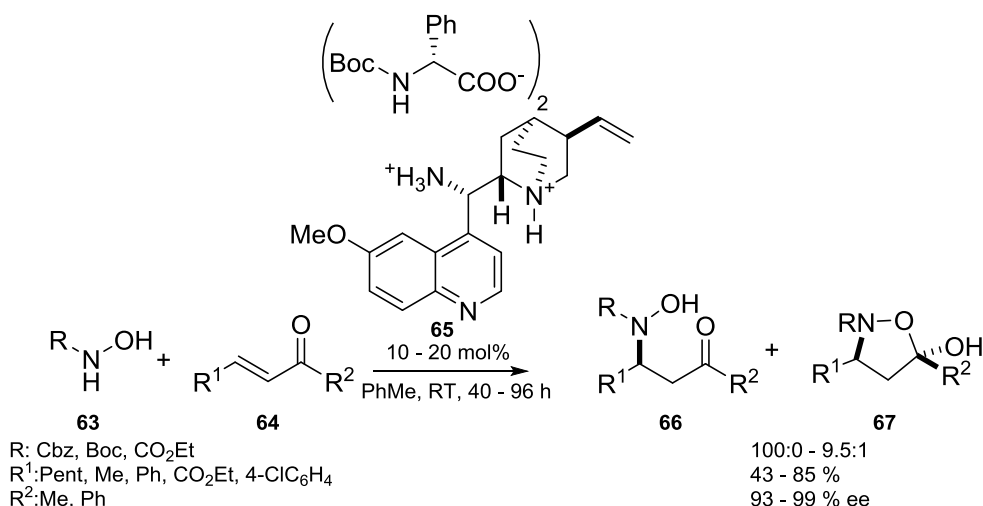
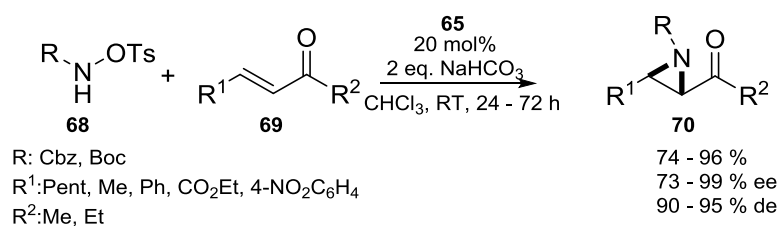


Figure 14

Soon afterwards, Melchiorre and co-workers reported that if you premixed an aminoquinine derivative and two equivalents of a chiral acid, D-*N*-Boc-phenylglycine, the resulting bis-salt **65** could be isolated. This was shown to promote addition of *N*-substituted hydroxylamines **63** to acyclic enones **64** with high enantioselectivity.^[24] However the reaction yielded a mixture of linear **55** and cyclised product **56** (Scheme 12).^[24] It was also shown that aziridines could be formed if O-tosyl hydroxylamines **68** were used as the nucleophile and base was added (Scheme 13).^[24] The absolute stereochemistry of the aziridine products was assigned by Electronic Circular Dichroism (ECD) spectra.

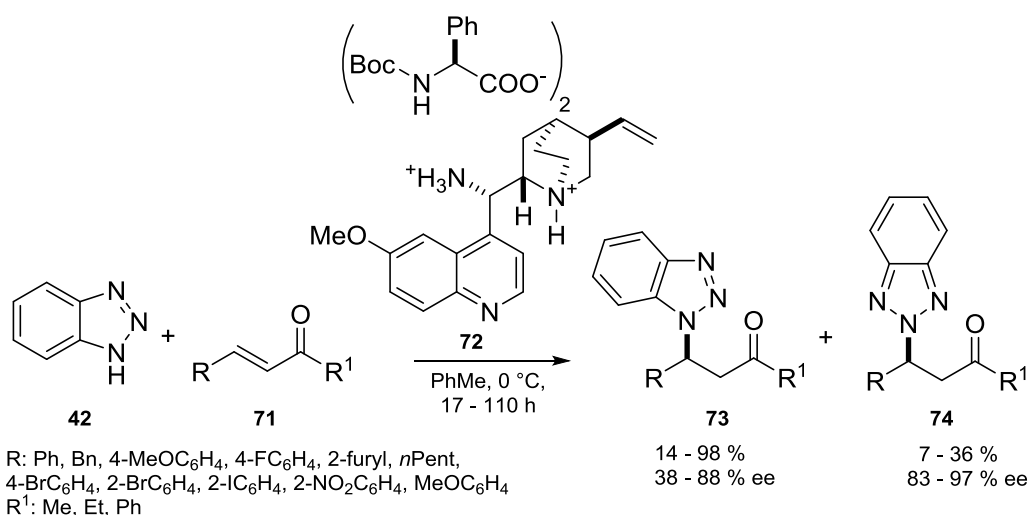


Scheme 12



Scheme 13

The diastereomeric bis-salt **72** was then shown to promote addition of benzotriazole **42** to acyclic enones **71**. Interestingly salt **72** gave the same major enantiomer to that of salt **65** suggesting the chiral acid isn't involved in determining the enantioselectivity of the reaction. This resulted in modest to high enantioselectivity and a mixture of regioisomers (Scheme 14).^[25] The absolute stereochemistry was determined by comparison of compounds **75** and **76** with literature optical rotation data (Figure 15).^[18,26]



Scheme 14

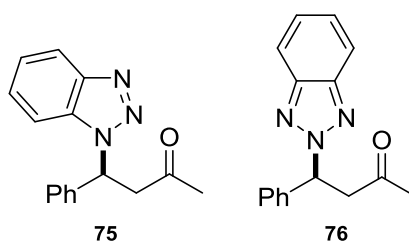
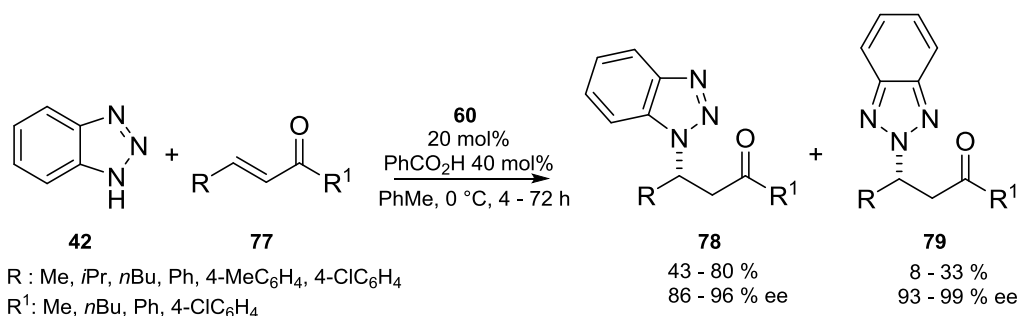


Figure 15

Later Wang and co-workers investigated the process in more detail and found that enone stoichiometry and concentration affected the enantioselectivity of the reaction.^[27] An excess of enone and increased reaction concentrations were found to be optimal (Scheme 15).^[207] Benzoic acid was used as the co-catalyst in this example. Compound **60** gave a different enantiomer in this case to that previously reported with the diastereomeric salts **65** and **72**. The absolute stereochemistry was determined by comparison with their previous optical rotation data.^[25] They proposed that the

quinuclidine nitrogen hydrogen bonded to the benzotriazole to perform an attack on the iminium species to give the stereochemistry observed (Figure 16).^[27]



Scheme 15

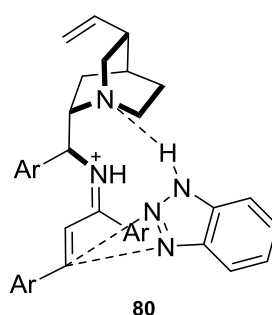
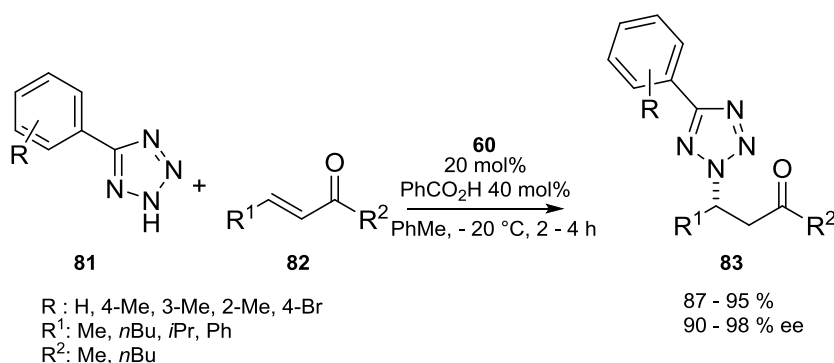


Figure 16

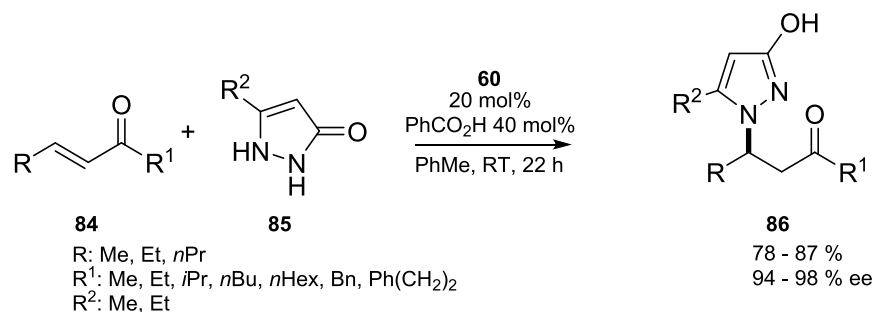
They also reported that this reaction could be extended to allow addition of tetrazoles **81** to enones **82**. In this case only a single regioisomer was observed (Scheme 16).^[27] The absolute stereochemistry was assigned by analogy with the previously reported benzotriazole additions.



Scheme 16

Zhao and co-workers then reported the first example of 2-pyrazolin-5-ones **85** as nitrogen nucleophiles for conjugate addition to enones using 9-deoxy-9-*epi*-aminoquinine **60**. Benzoic acid was again reported to be the best acid additive giving high enantioselectivities (Scheme 17).^[28] The absolute stereochemistry was assigned by X-ray diffraction of a single crystal of compound **87** (Figure 17). They proposed that the quinuclidine nitrogen deprotonates the 2-pyrazolin-5-one forming a tight ionic interaction

and then reacts through the nitrogen with the iminium species to give the stereochemistry observed (*Figure 18*).^[28]



Scheme 17

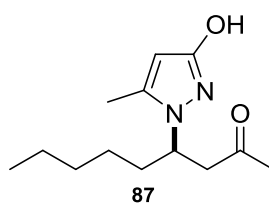


Figure 17

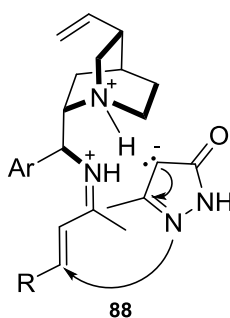
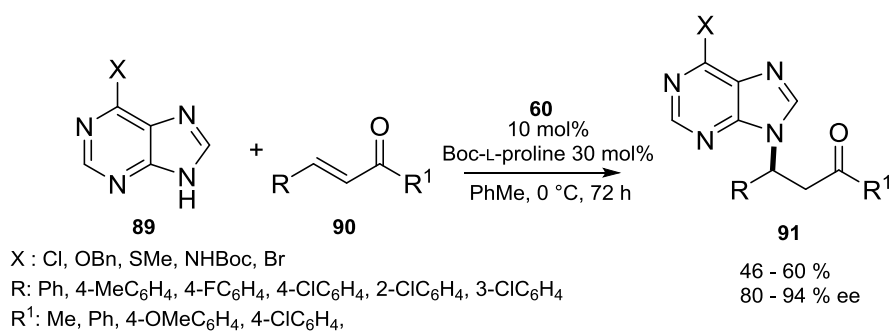


Figure 18

Wang and co-workers then reported the first example of purine bases **89** in conjugate addition to chalcones **90** using 9-deoxy-9-*epi*-aminoquinine **60**. This time Boc-L-proline was reported to be the best acid additive yielding very high enantioselectivities with only one regioisomer formed (*Scheme 18*).^[29] The absolute stereochemistry was determined by comparison of compound **92** with literature optical rotation data (*Figure 19*).^[30] They proposed that the quinuclidine nitrogen hydrogen bonded to the purine, this can then attack the iminium species to give the stereochemistry observed (*Figure 20*).^[29]



Scheme 18

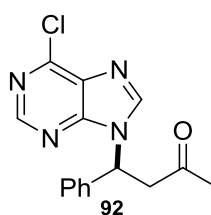


Figure 19

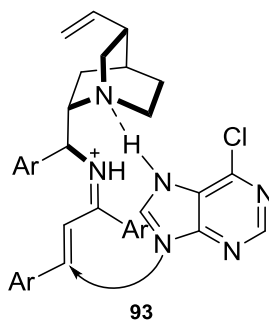
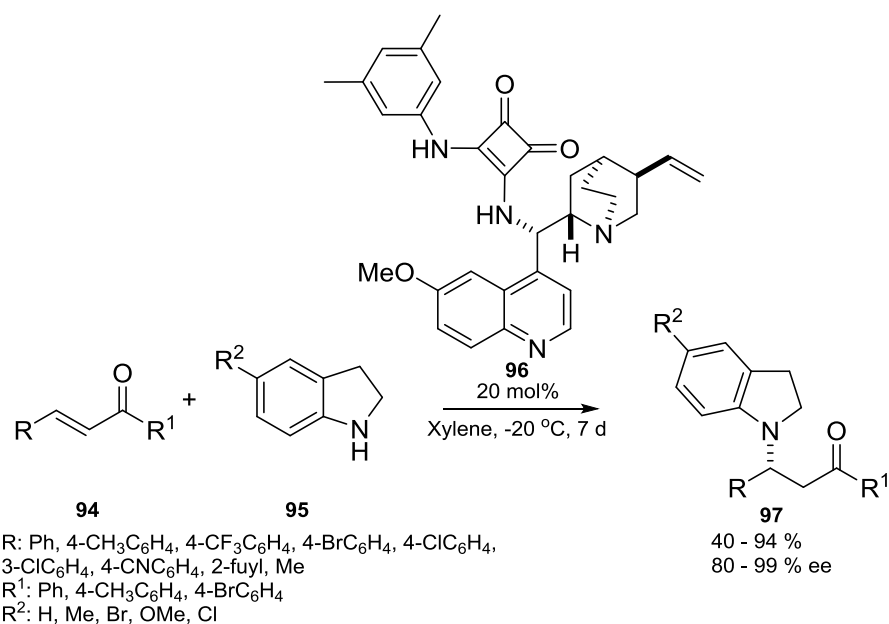


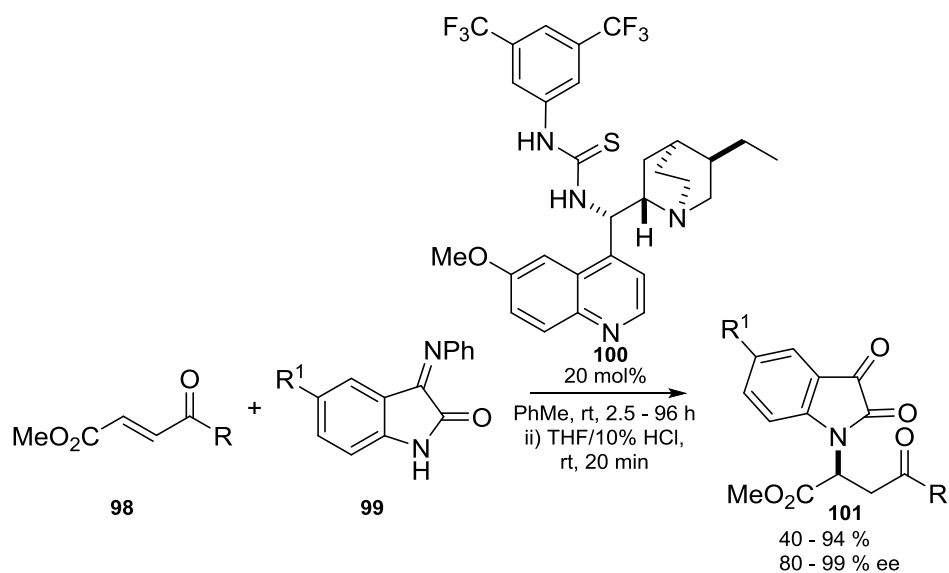
Figure 20

Ghosh then reported the first example of indolines **95** as nitrogen nucleophiles for conjugate addition to substituted enones using quinine derived squaramide catalyst **96** (Scheme 19).^[31] Low reaction temperatures were required to obtain good enantioselectivities. The absolute stereochemistry was tentatively assigned by comparing to previous 1,4-conjugate additions using catalyst **96**.^[32]



Scheme 19

Kanger and co-workers then reported the conjugate addition of 3-phenylimine isatin derivatives **99** to unsaturated 1,4-ketoesters **98** using thiourea catalyst **100**. The resulting compound was then converted *in situ* to substituted isatin products **101** by acid hydrolysis (Scheme 20).^[33] The absolute stereochemistry was assigned by X-ray diffraction of a single crystal of compound **102** (Figure 21).



Scheme 20

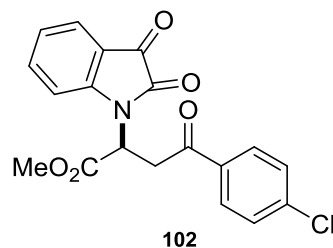
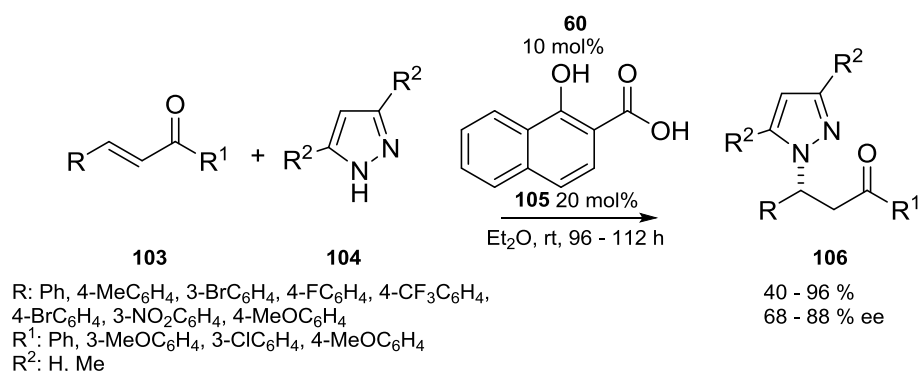


Figure 21

Wang and co-workers then reported the first example of pyrazoles **104** as nitrogen nucleophiles for conjugate addition to substituted chalcones **103** using 9-deoxy-9-*epi*-aminoquinine **60**. In this case 1-hydroxy-2-naphthoic acid **105** was found to be the best acid additive giving good yields and high enantioselectivities (*Scheme 21*).^[34] The absolute stereochemistry was tentatively assigned based on previous nitrogen heterocycle additions using the same catalyst.^[27]



Scheme 21

1.6 Bifunctional catalysis

Quinine **107** and 9-deoxy-9-*epi*-aminoquinine **60** are examples of organocatalysts that can act as bifunctional catalysts. This is because they contain functionality that can activate both reactants, allowing the reaction to proceed faster than when only one of them is activated. For example, quinine **107** can activate an electrophile via H-bonding to the secondary hydroxyl group and the quinuclidine nitrogen can act as a Lewis base. Similarly 9-deoxy-9-*epi*-aminoquinine **60** can activate a carbonyl-containing electrophile via iminium ion formation involving the 9-amino group, and the quinuclidine nitrogen can again activate a nucleophile by acting as a Lewis base (*Figure 22*).

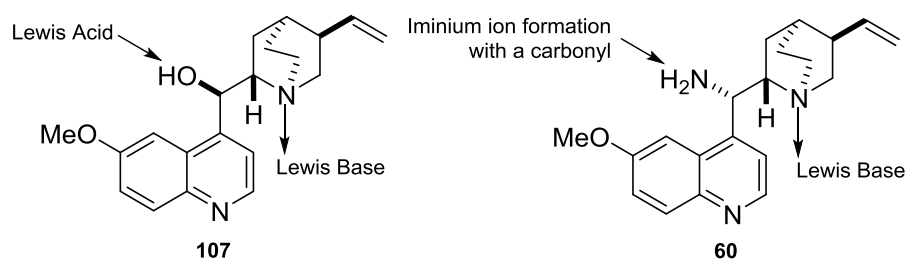


Figure 22

9-Deoxy-9-*epi*-aminoquinine **60** is an excellent example of this type of catalyst, as shown by its use in the *N*-conjugate addition reactions discussed earlier. The chiral primary amine can form the iminium species under acidic conditions, thus lowering the LUMO of the C-C double bond and making it more susceptible to attack. The quinuclidine nitrogen can then deprotonate the NH of the nucleophile, the acidity of the NH being critical in this respect. This arrangement selectively delivers the nucleophile to one face of the double bond (*Figure 23*).

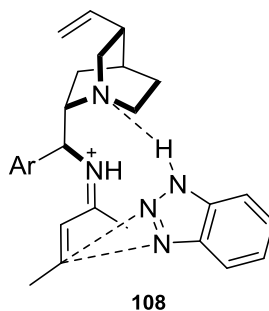
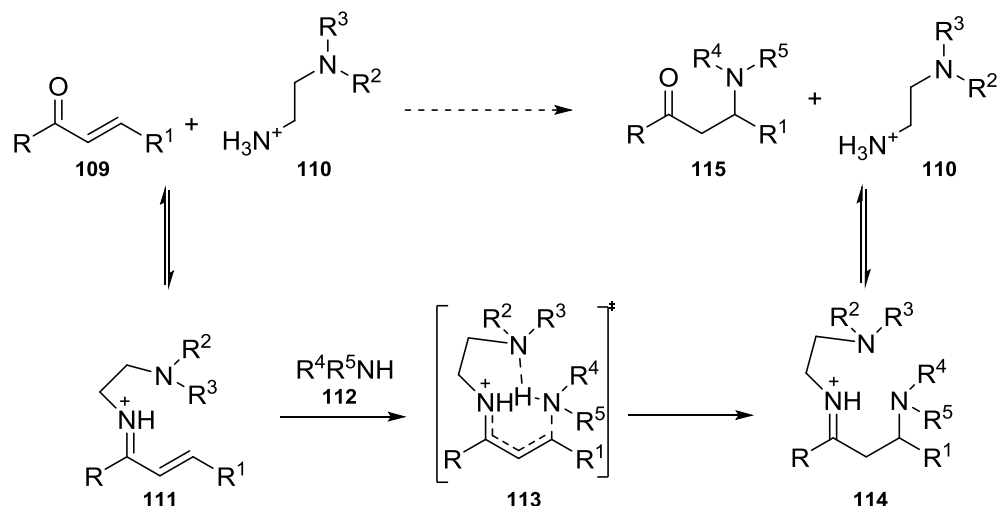


Figure 23

1.7 Project aims

The aim of the project was to develop and optimise new amine catalysed carbon-nitrogen bond forming processes that proceed via conjugate addition of a nitrogen nucleophile to an enone. A general scheme for the processes of interest is shown below (*Scheme 22*).



Scheme 22

The nitrogen nucleophiles that have been reported for this type of catalysis when the project was started are shown below with their pK_a values (Figure 24).

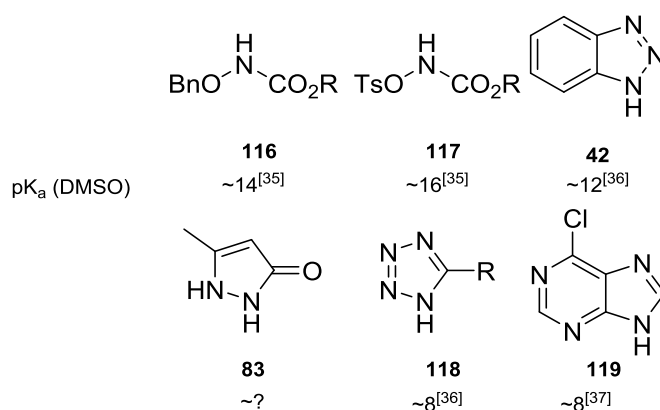


Figure 24

We selected the following nitrogen nucleophiles for investigation in the conjugate addition reaction (Figure 25). We choose pyrazole **120** and imidazole **121** as they had a much higher pK_a value than previous nitrogen heterocycles reported. Imides **122** and **123** were chosen as they could be converted to the primary amine after addition. Compounds **124**, **125** and **126** had not been previously reported and could undergo further chemical transformations after conjugate addition.

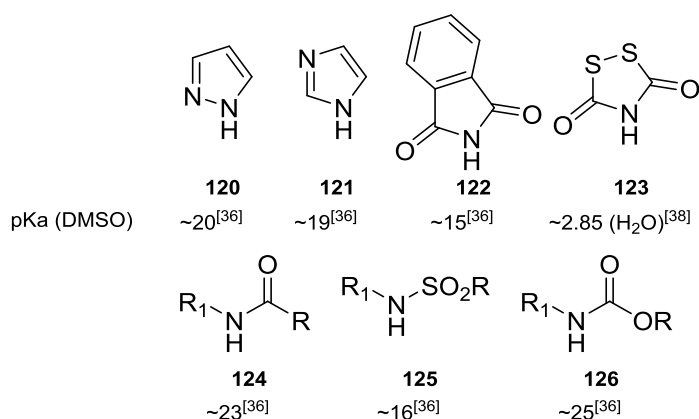
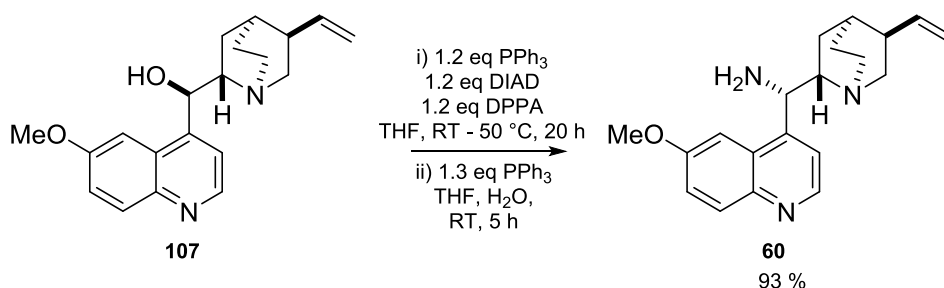


Figure 25

As 9-deoxy-9-*epi*-aminoquinine **60** has so far proved to be the most effective catalyst for conjugate additions of this type, we decided to start by investigating use of 9-amino derivatives of cinchona alkaloids.

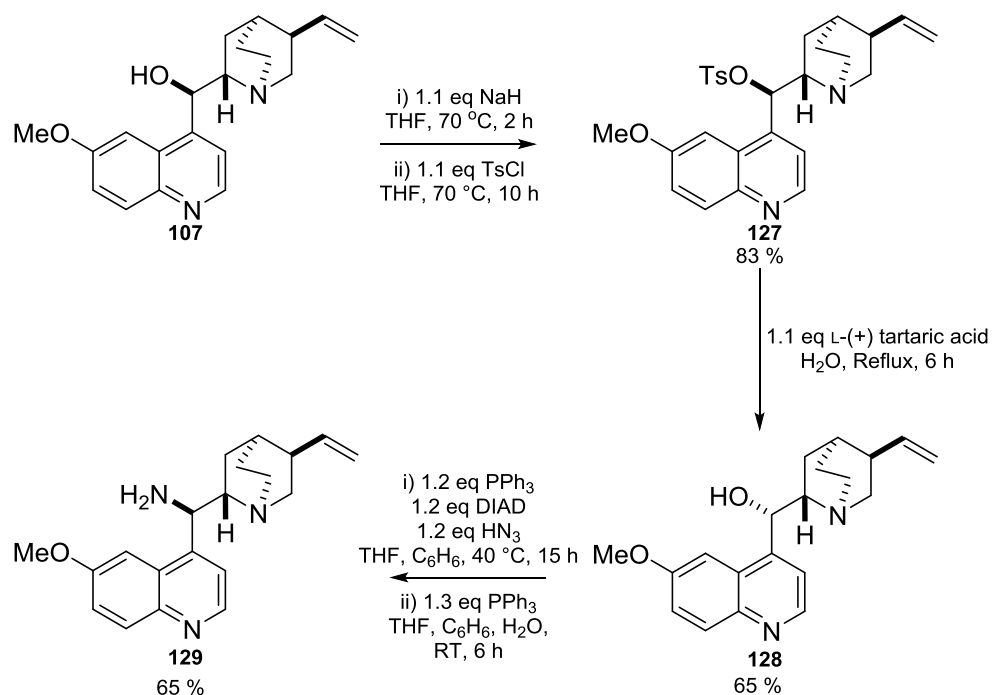
1.8 Synthesis of Potential Catalysts Starting from Cinchona Alkaloids

Oliva and co-workers have reported a one-pot process for the preparation of 9-deoxy-9-*epi*-aminoquinine **60** from quinine **107**.^[39] The first step of this being a Mitsunobu displacement of the 9-hydroxy group with diphenylphosphoryl azide. The resulting azide is then reduced *in situ* using a Staudinger reaction to yield amine **60** in high yield (Scheme 22).^[39]



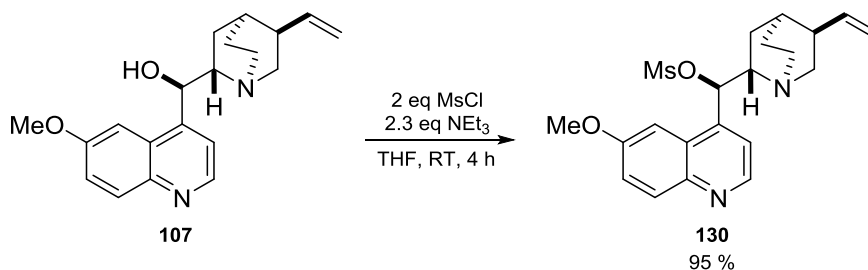
Scheme 23

The synthesis worked as described giving a high yield of product and the reaction could be repeated on a larger scale to obtain enough material for further study. For comparison, we were also interested in accessing and studying 9-deoxy-9-aminoquinine **129**. The compound has previously been synthesised from quinine **107** by converting the alcohol in the 9 position to sulfonamide **127** and epimerisation to **128** with water. This is converted to the azide using a Mitsunobu reaction followed by reduction to the desired amine **129** (Scheme 24).^[28]



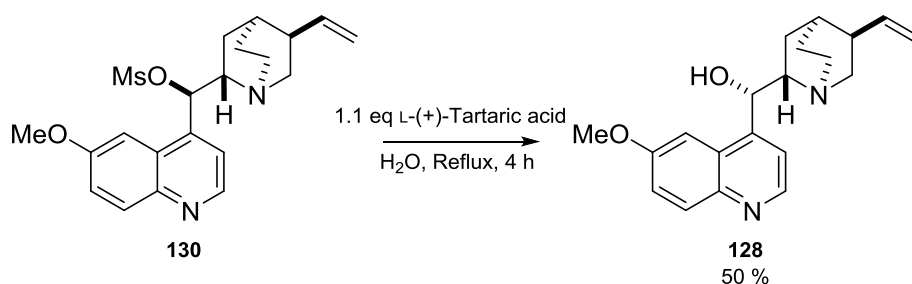
Scheme 24

We wanted to take a similar approach to this without the use of hydrazoic acid due to its high toxicity and explosive properties.^[41,42] First quinine **107** was functionalised using mesyl chloride and triethylamine as previously reported (Scheme 25).^[43] Mesyl compound **130** was isolated in high yield and used directly in the next step.



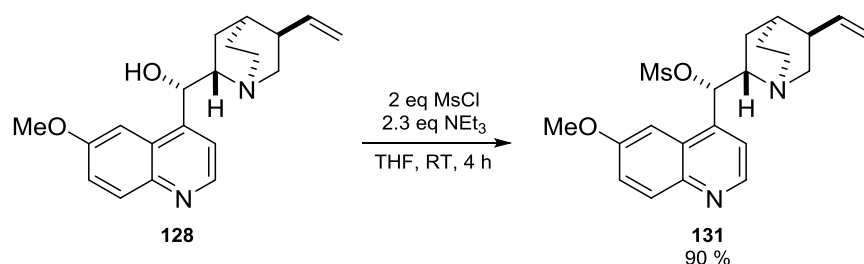
Scheme 25

The next step was epimerisation of the 9 position using L-(+)-tartaric acid and water according to literature conditions (Scheme 26).^[43] The tartaric acid was found to prevent side reactions by protonating the quinuclidene nitrogen. Heating mesylate **130** under reflux in distilled water gave alcohol **128** in 11 % yield after extraction with diethyl ether and purification by silica gel chromatography.^[43] Further product **128**, 39 %, could be isolated with by extracting the aqueous solution with dichloromethane and required no further purification.



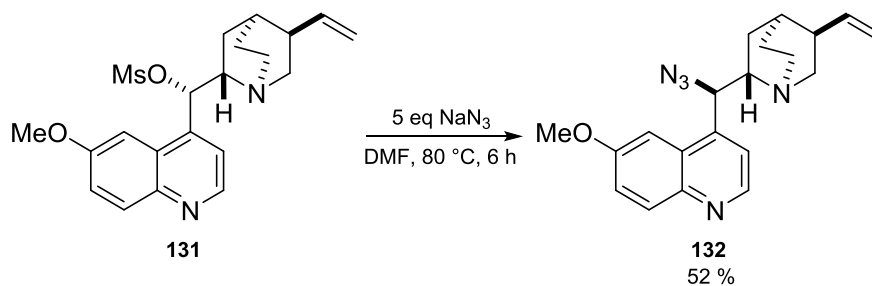
Scheme 26

9-*epi*-Quinine **128** was converted to the corresponding mesylate **131** (Scheme 27).^[43] The reaction proceeded as before with no need for purification.



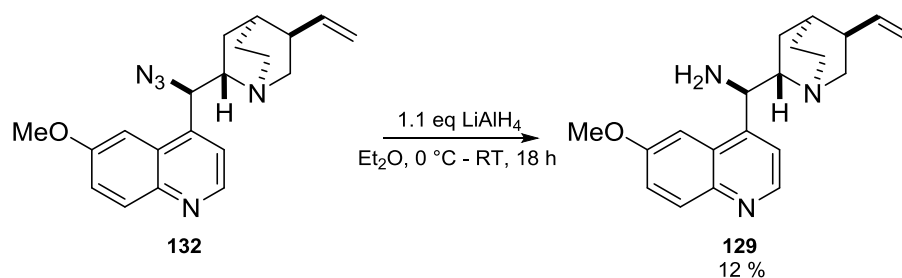
Scheme 27

Conversion of the mesylate **131** into azide **132** proved to be troublesome. After some experimentation it was found that displacement with sodium azide proceeded in modest yield with the remaining reaction mass being starting material as shown by ¹H NMR analysis of the crude reaction mixture (Scheme 28).^[44] The material isolated from extraction as before proved pure enough to use in the final step.



Scheme 28

The final step of this synthesis was the reduction of azide **132** to amine **129**. This was performed with lithium aluminium hydride after the Standinger reaction used previously had failed (Scheme 29).^[44] The crude reaction mixture showed multiple spots by TLC with the desired product **129** and starting material **132** running close together. This resulted in a low isolated yield, but the amount of material obtained was suitable for our subsequent investigations.



Scheme 29

With sufficient quantities of 9-deoxy-9-aminoquinine **129** along with 9-deoxy-9-*epi*-aminoquinine **60** available we moved on to investigate their use in *N*-conjugate addition reactions.

1.9 Pyrazole Conjugate Additions

In section 1.7 we outlined a series of nitrogen nucleophiles that were of interest. Of these, pyrazoles were of particular interest as they are generally straightforward to prepare and can exhibit a wide range of pK_a values for the NH-group.

Pyrazoles are also found in a number of multiple pharmaceutical drugs, such as Celebrex^[45] **133**, Sulphaphenazole^[46] **134**, and Crizotinib^[47] **135**, as well as pesticide Topramezone^[48] **136** (Figure 26).

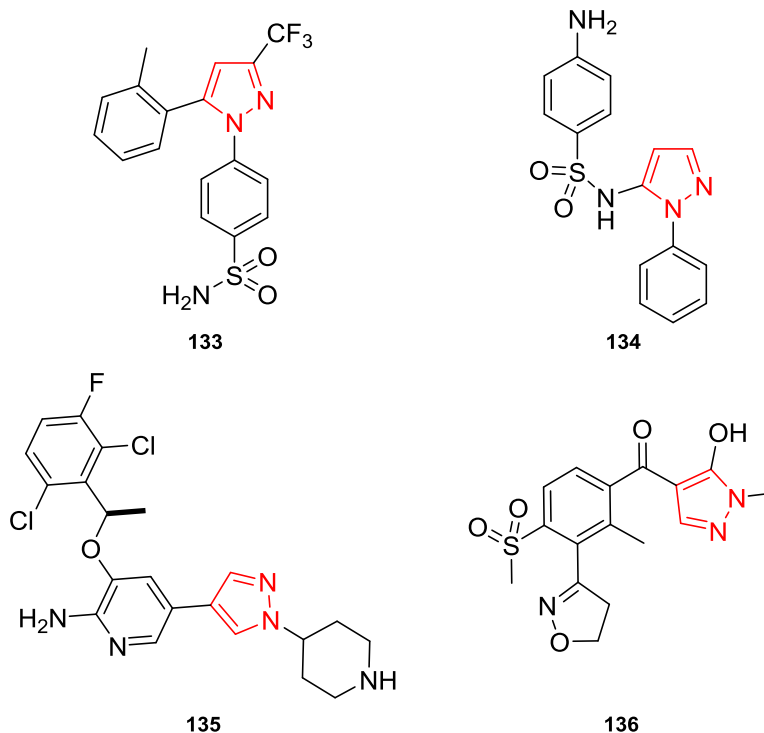
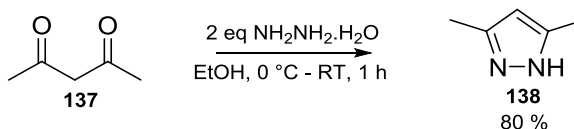


Figure 26

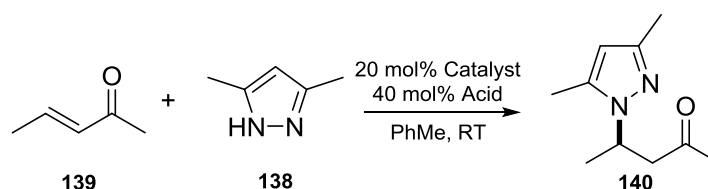
1.9.1 Initial Studies

We started with 3,5-dimethylpyrazole **138** as our potential nucleophile. This was chosen as we would not have to worry about the regioselectivity of the reaction as it is symmetrically substituted. It is also readily synthesised by condensing acetylacetone **137** with hydrazine hydrate (Scheme 30).^[49] The resulting pyrazole **138** is isolated by filtration and obtained in a good yield, allowing large quantities to be prepared.



Scheme 30

3-Penten-2-one **139** was selected as our initial enone as it is commercially available and sufficiently volatile so as to allow easy removal from the reaction mixture. With these substrates in hand, we started our study by investigating whether compounds **60**, **129** and **107** were capable of promoting their enantioselective coupling. Preliminary results of this investigation are shown below (Table 1). Pleasingly the pyrazole performed the conjugate addition through nitrogen as substituted pyrazoles had previously been reported to perform conjugate addition reactions through carbon using organocatalysis.^[50,51] This type of addition will not be further discussed in this thesis.



Entry	Catalyst	Acid	Time (h)	Yield (%)	E.e. (%) ¹
1	-	-	84	0	-
2	-	PhCO ₂ H	18	15	0
3	60	-	84	0	-
4	60	PhCO ₂ H	18	74	68
5	129	PhCO ₂ H	84	4	-4
6	107	PhCO ₂ H	84	0	-
7	141	TFA	18	67	0

¹ Determined by chiral HPLC

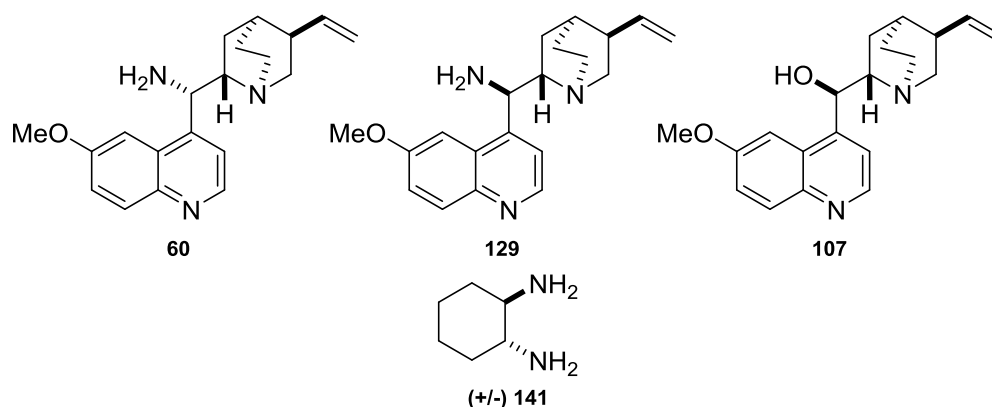
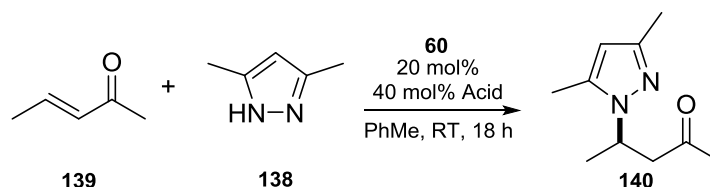


Table 1

First the addition was investigated with no catalyst or acid (*Entry 1*) and this gave no conversion over a prolonged time. The most commonly used acid additive in the literature, benzoic acid was added and after 18 hours gave a low yield of racemic product (*Entry 2*). Amine **60** without an acid additive gave no conversion over a prolonged time but when mixed with benzoic acid pleasingly gave a good yield and modest enantioselectivity of the desired product **140** (*Entries 3 and 4*). Due to this result all further screening of catalysts were performed with this acid. The next compound investigated was amine **129** with the opposite stereochemistry in the 9-position to that of amine **60**. After prolonged reaction time enough conversion was observed with amine **129** to allow isolation of the product **110** in poor yield and negligible enantioselectivity. Quinine **107** gave no conversion to product (*Entries 5 and 6*). These results suggest that an amine and acid additive are needed for this reaction so it may proceed through iminium catalysis. Also it appears a *trans* relationship was needed between the two nitrogens to obtain high enantioselectivity and good yields. Also investigated was racemic *trans*-diamine **141** which led to the formation of racemic product so an assay could be developed (*Entry 7*). The best catalyst, amine **60**, was taken forward to investigate the effect of the acid additive (*Table 2*).



Entry	Acid	pK _a (H ₂ O)	pK _a (DMSO)	Yield (%)	E.e. (%) ¹
1	TFA	-0.3	3.5	82	12
2	4-CH ₃ C ₆ H ₄ SO ₃ H	2.1	-	22	34
3	3-NO ₂ C ₆ H ₄ CO ₂ H	2.5	9.1	75	86
4	3-ClC ₆ H ₄ CO ₂ H	3.8	-	80	94
5	PhCO ₂ H	4.2	11.1	74	68
6	4-CH ₃ C ₆ H ₄ CO ₂ H	4.2	-	38	94
7	PhCH ₂ CO ₂ H	4.3	-	80	96
8	CH ₃ CO ₂ H	4.8	12.6	26	86
9	(CH ₃) ₃ CO ₂ H	5.0	-	25	92
10	Phthalic Acid ²	3.0, 5.4	-	20	56
11	Isophthalic Acid ²	3.5, 4.5	-	20	82
12	Terephthalic Acid ²	3.5, 4.8	-	24	60
13	Adipic Acid ²	4.4, 5.4	-	48	18

¹ Determined by chiral HPLC ² 20 mol% acid added

Table 2

The acid investigation was carried out using amine **60** with the same reaction conditions as previously used for 18 hours. Decreasing the pK_a of the acid led to varying yields and much poorer enantioselectivities (*Entries 1 and 2*). A range of di-carboxylic acids were also investigated but gave poor yields and enantioselectivities (*Entries 10 - 13*). The best enantioselectivities found were with 3-chlorobenzoic acid (*Entry 4*) and phenylacetic acid (*Entry 7*). Phenylacetic acid showed a higher enantioselectivity so it was chosen for future conjugate additions. With the optimised conditions found, it was decided to investigate the scope of the reaction for the nitrogen nucleophile.

1.9.2 Investigating the Pyrazole Scope

Seven pyrazoles and indazole **148**, a related heterocycle, were chosen to investigate the scope of the nucleophile. This includes unsubstituted pyrazole **120** and bis-trifluoromethylpyrazole **142**. Other examples that are substituted in the 4-position include electron donating (OMe) or electron withdrawing groups (NO₂ and CO₂Et) present to probe the effect on the pK_a of the nitrogen (*Figure 27*). We also investigated the 4-Br substituted compound as it would allow further chemical transformations to be performed in later steps.

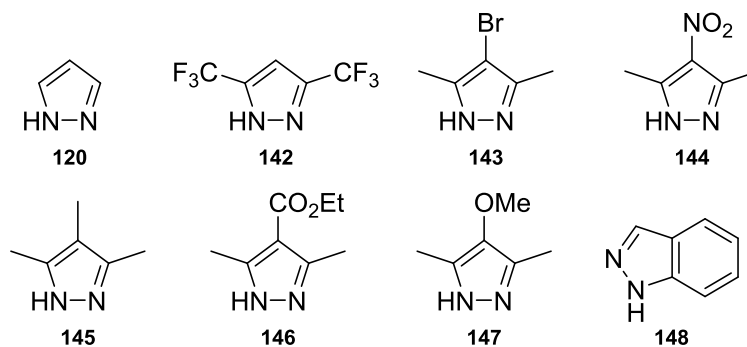
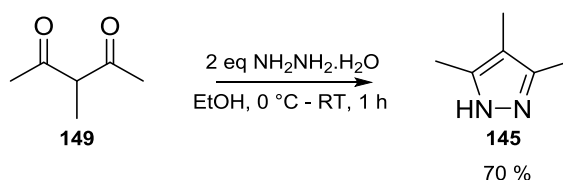


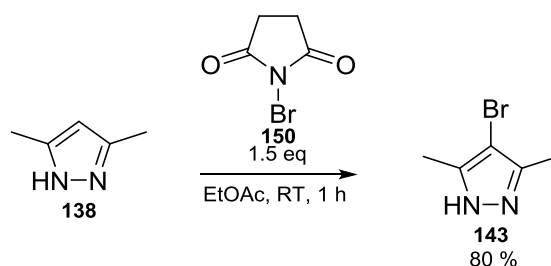
Figure 27

Compounds **120**, **142** and **148** were commercially available. Pyrazole **145** was synthesised from 3-methylpentan-2,4-dione **149** following the procedure used to make 3,5-dimethylpyrazole **138**. The reaction gave pyrazole **145** in good yield (*Scheme 31*).



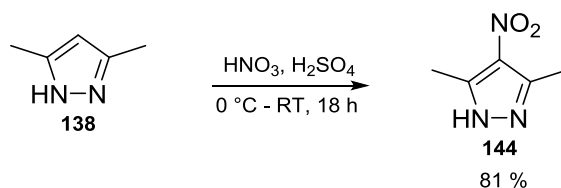
Scheme 31

4-Bromo-3,5-dimethylpyrazole **143** was synthesised from 3,5-dimethylpyrazole **138** using an excess of *N*-bromosuccinimide **150** following literature conditions.^[52] A simple aqueous wash yielded pyrazole **143** in good yield (*Scheme 32*).



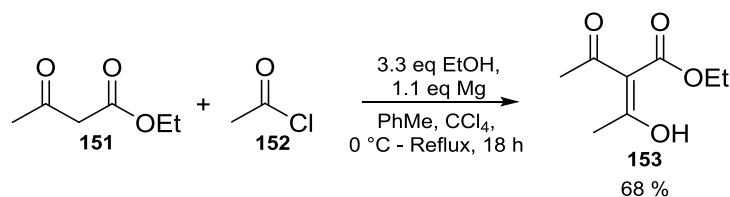
Scheme 32

4-Nitro-3,5-dimethylpyrazole **144** was synthesised from 3,5-dimethylpyrazole **138** in one step using the standard nitration conditions of concentrated nitric acid and sulfuric acid (*Scheme 33*).^[53]



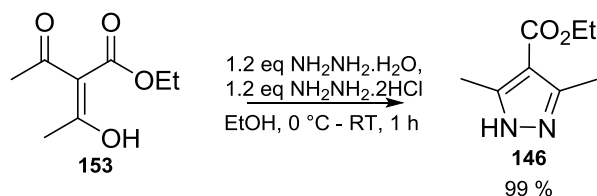
Scheme 33

Pyrazole **146** was prepared in two steps from ethyl acetoacetate **151**.^[53] First, C-acylation with acetyl chloride **152** gave intermediate **153** in good yield (Scheme 34).



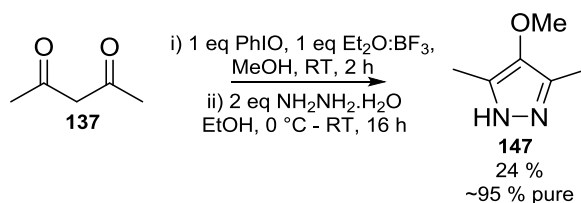
Scheme 34

This was then reacted with hydrazine to yield target pyrazole **146** (Scheme 35). The hydrazine used in the literature was the monohydrochloride salt, but this was no longer commercially available.^[53] Because of this, the desired salt was generated *in situ* using a 1: 1 mixture of hydrazine hydrate and the bis-hydrochloride salt. The reaction proceeded in quantitative yield with no need for further purification.



Scheme 35

The final pyrazole 4-methoxy-3,5-dimethylpyrazole **147** was synthesised via oxidation of acetylacetone **136** followed by reaction with hydrazine.^[54] Attempts to isolate the initial oxidation product failed, so the crude oxidation material was reacted with hydrazine directly (Scheme 36). After purification by silica gel chromatography, desired pyrazole **133** was isolated in low yield, and contaminated with ~5% impurities as judged by ^1H NMR analysis. As this was the best we could achieve it was used in subsequent investigations.



Scheme 36

With the desired pyrazoles now available we moved on to study their effect in the conjugate addition to 3-penten-2-one **139** (Table 3).

Entry	Pyrazole	R	R ¹	Product	Time (h)	Yield (%)	E.e. (%) ¹
1	120	H	H	154	18	77	88
2	142	CF ₃	H	155	18	76	40
3	142	CF ₃	H	155	18	66	93 ²
4	143	Me	Br	156	18	99	94
5	144	Me	NO ₂	157	120	53	92 ³
6	145	Me	Me	158	18	72	81
7	146	Me	CO ₂ Et	159	18	53	42
8	146	Me	CO ₂ Et	159	18	20	82 ⁴
9	147	Me	OMe	160	18	75	88
10	148	Indazole		161	71	90	89

¹ Determined by chiral HPLC ² Run at 0 °C ³ 2 eq pyrazole used ⁴ 20 mol% Isophthalic acid used

Table 3

Unsubstituted pyrazole **120** (Entry 1) gave comparable yield with a slightly lower enantioselectivity to that obtained when 3,5-dimethylpyrazole **138** was used (80 %, 96 % ee). Bis-trifluoromethylpyrazole **142** gave a much lower enantioselectivity at room temperature but lowering the temperature to 0 °C gave high enantioselectivity (93 % ee) (Entries 2 and 3).

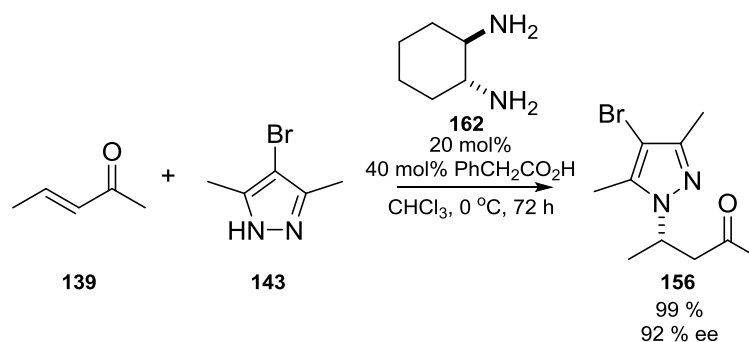
Substitution in the 4 position of the pyrazole lead to varied results. The ethyl ester substituted pyrazole **146** giving a much lower enantioselectivity (42 % ee) compared to the nitro substituted pyrazole **144** (92 % ee) (Entries 5 and 7). Both these reactions also gave much lower conversions, stalling at around 60 % conversion by ¹H NMR spectroscopy, and a second equivalent of nitropyrazole **144** was needed to achieve a reasonable reaction time. The lower conversions may be due to the lower nucleophilicity of the nitrogen or their ability to act as a good leaving group (ie reversible reaction). After brief investigation, it was found using isophthalic acid as the acid additive in the ethyl

ester pyrazole **146** addition gave a much higher enantioselectivity (82 % ee) but a much lower isolated yield (*Entry 8*).

The electron rich pyrazole **147** gave a good yield and high enantioselectivity in the same reaction time as dimethylpyrazole **138** (*Entry 9*). The other two pyrazoles (**143** and **145**) also gave good yields in the same reaction time, but trimethylpyrazole **145** gave lower enantioselectivity (*Entry 6*). Indazole **148** underwent the conjugate addition in a slightly longer reaction time with high yield and enantioselectivity (*Entry 10*).

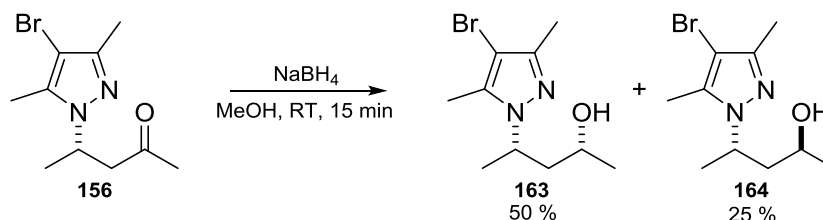
1.9.3 Determining the Absolute Stereochemistry of the Addition Products

Unfortunately, the products of the conjugate addition reactions were all found to be oils. In order to prove the stereochemistry of the products we needed an X-ray structure of a derivative of one of these products. Another group member, Tim Evans, performed the conjugate addition of pyrazole **143** to 3-penten-2-one **139** using (*R,R'*)-1,2-diaminocyclohexane **162** (*Scheme 37*).^[56]



Scheme 37

The resulting addition product **156** was then reduced with sodium borohydride to give a mixture of diastereoisomers **163** and **164** (*Scheme 38*). Compound **164** was found to be a crystalline solid and an X-ray crystal structure was obtained (*Figure 28*).^[56]



Scheme 38

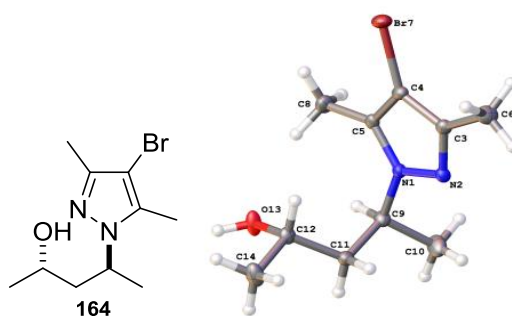


Figure 28

This confirms the stereocentre formed in the conjugate addition is (S) for this catalyst. When we compare the optical rotation of compound **156** with diamine catalyst **162**, +16.2 (c 0.7, CHCl₃, 92 % ee)^[56] and catalyst 9-deoxy-9-*epi*-aminoquinine **60**, -23.6 (c 0.7, CHCl₃, 94 % ee) we can see that they are opposite so the stereocentre formed with catalyst **60** is (R). This is confirmed by having different major enantiomers by chiral HPLC.

1.9.4 Investigating the Regiochemistry of the Pyrazole Addition

After investigating the reaction scope for symmetrically substituted pyrazoles we moved on to investigate the regiochemistry of the reaction using unsymmetrically substituted pyrazoles. Four pyrazoles **165** – **168** were chosen (*Figure 29*). Pyrazoles **165** – **167** were chosen to allow study of the effect of steric bulk on the regioisomer ratio. Pyrazole **168** had substitution in both the 3 and 5 positions so it would be interesting to see how the differing substituents would affect the ratio of regioisomers. Unsymmetrical pyrazoles such as pyrazole **168** have been shown to a mixture of tautomers in solution so mono-substituted pyrazoles will be drawn with the substituent in the 3 position.^[57]

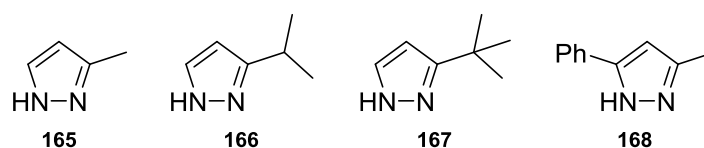
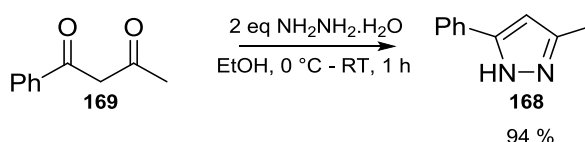


Figure 29

Pyrazole **168** was synthesised in one step via reaction of hydrazine with commercially available 1-phenyl-1,3-butadione **169**. The reaction proceeded in high yield using conditions previously described (*Scheme 39*).^[58]



Scheme 39

Pyrazole **165** was commercially available and pyrazoles **166** and **167** were synthesised by Tim Evans^[56] using conditions previously reported.^[59] With all pyrazoles available they could be investigated in their addition to 3-penten-2-one **139** under the conditions previously used (*Table 4*).



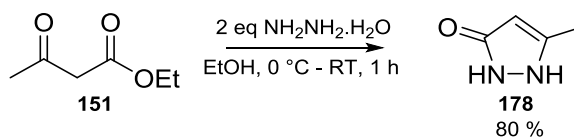
Entry	Pyrazole	R	R ¹	Time (h)	Products	Ratio ¹	Yield (%)	E.e. (%) ³
1	165	H	Me	18	170:171	70:30	96 ²	88:94
2	166	H	<i>i</i> Pr	42	172:173	70:30	62:18	79:95
3	167	H	<i>t</i> Bu	42	174:175	>95:5	75:0	84:-
4	168	Me	Ph	68	176:177	50:50	30:20	73:86

¹ Determined by ¹H NMR ² Regisomers could not be separated ³ Determined by chiral HPLC

Table 4

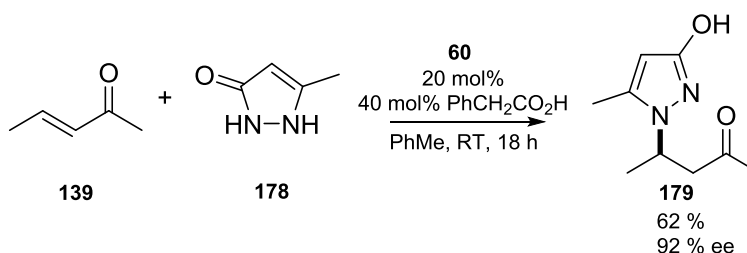
Unfortunately the two regioisomers formed from 3-methylpyrazole **165** addition could not be separated by silica gel chromatography. Fortunately we were able to separate all four stereoisomers by chiral HPLC so the enantioselectivity of these products could still be determined (*Entry 1*). The identity of these regioisomers were determined by another group member, Tim Evans, who successfully isolated each compound and analysed them using nOe spectroscopy.^[56] The *iso*-propyl group substituted pyrazole **166** gave a similar regioisomer ratio, but when the bulkier *tert*-butyl substituted pyrazole **167** was used, only one regioisomer was obtained (*Entries 2 and 3*). These results show that regiocontrol is possible, and that larger substituents lead to an increase in the regioselectivity. The 5-phenyl-3-methylpyrazole **168** gave a 1:1 mixture of regioisomers (*Entry 4*). It is interesting to note that when two regioisomers were obtained, the regioisomer with the more bulky substituent next to the enone fragment always had the higher enantiomeric excess.

To complete this part of the study, we also wanted to investigate the reaction using 3-methylpyrazol-5-one **178**. This pyrazalone had previously been reported in the literature using similar conditions (*Scheme 17*).^[28] The 3-methylpyrazol-5-one **178** was prepared following the literature procedure in good yield (*Scheme 40*).^[49]



Scheme 40

Compound **178** was found to be this tautomer with the ^1H NMR showing a single CH, as opposed to a CH_2 , and the IR spectra showing a stretch of 1644 cm^{-1} suggesting a α,β -unsaturated carbonyl. The conjugate addition reaction was then investigated with only regioisomer **179** being isolated with a lower yield and enantioselectivity than that previously reported by Zhao and co-workers (85 %, 96 % ee) (Scheme 41).^[28]



Scheme 41

We have shown that a range of pyrazole nucleophiles can be added to 3-penten-2-one **139** using 9-deoxy-9-*epi*-aminoquinine **60**. The pyrazole tolerates substitution in all positions with electron deficient pyrazoles undergoing slower addition with lower isolated yields possibly due to retro addition. We have also shown we have some regiocontrol with unsymmetrically substituted pyrazoles with larger groups in the 3-position.

1.9.5 Investigating the Enone Scope

1.9.5.1 Acyclic Enones

We next moved on to investigate the effect of different substituents in the enone moiety. For the purposes of this study we selected seven enones (**180** - **186**) for investigation (Figure 30). This series was chosen to probe the effect of changing the nature of the substituent at either end of the enone, and also in the case of enones **185** and **186**, to investigate the regioselectivity of addition when two electrophilic sites were present. Enones **181** and **182** were commercially available.

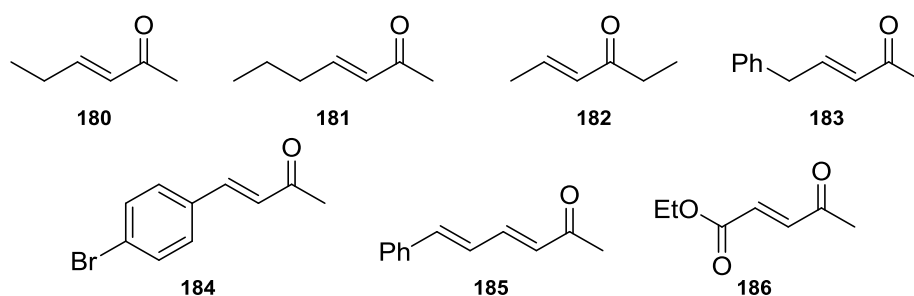


Figure 30

Enones **180**, **183**, **185** and **186** were synthesised by Wittig reaction between aldehydes, **187** - **190**, and (acetylmethylene)triphenylphosphorane **191** (Table 5). Enone **184** was synthesised by the same method previously in the laboratory by another group member.^[56]

$ \begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{C}-\text{H} \end{array} + \begin{array}{c} \text{O} \\ \parallel \\ \text{Ph}_3\text{P}=\text{C}-\text{CH}_3 \end{array} \xrightarrow{\text{Solvent, RT, 18 h}} \begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{CH}=\text{CH}-\text{C}-\text{CH}_3 \end{array} $					
	187 - 190	191			
Entry	Aldehyde	R	Solvent	Enone	Yield (%)
1	187	Et	CH ₂ Cl ₂	180	80
2	188	PhCH ₂	CH ₂ Cl ₂	183	25
3	189	(<i>E</i>)PhCH=CH	THF	185	52 ¹
4	190	CO ₂ Et	PhMe	186	21

¹ Heated at reflux

Table 5

Enones **180** and **183** were prepared as previously reported in the literature with a slightly lower yield obtained for enone **183**, due to difficulty in separating it by silica gel chromatography from unreacted starting material (*Entries 1 and 2*).^[60,61] The reaction using *trans*-cinnamaldehyde **189** required heating at reflux in tetrahydrofuran (*Entry 3*). Ethyl glyoxalate **190** was only available as a 50 % solution (w/w) in toluene, so this reaction was performed in toluene. A low yield was obtained due to difficulties separating unreacted ylide **191** from the product (*Entry 4*).

With the enones **180** - **186** available we moved on to investigate their effect in the conjugate addition reactions. For this part of the study we chose to use pyrazole **143**. This pyrazole was selected for three reasons:

- It was most likely to give crystalline adducts which would potentially aid purification of the products and possibly allow for determination of absolute stereochemistry via X-ray crystallography.
- The bromo-substituent potentially provides a handle for introduction of other substituents. Hence the products could allow access to a range of other pyrazole products.

iii. It was easily prepared in large quantities.

The previously used conditions involving 9-deoxy-9-*epi*-aminoquinine **60** and phenylacetic acid in toluene were used for this study (Table 6).

$\text{R}-\text{CH}=\text{CH}-\text{C}(=\text{O})-\text{R}^1$ + $\text{Br}-\text{indazole}$ $\xrightarrow[\text{PhMe, RT, Time}]{\text{60 (20 mol\%), 40 mol\% PhCH}_2\text{CO}_2\text{H}}$ Product

180 - 186 **143** **192 - 198**

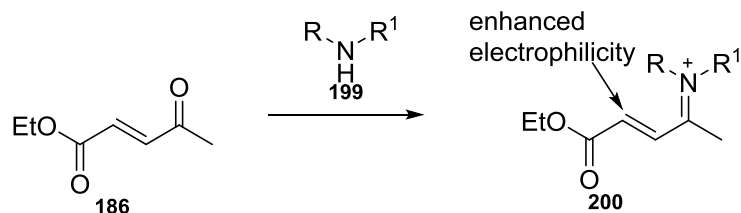
Entry	Enone	R	R ¹	Product	Time (h)	Yield (%)	E.e. (%) ¹
1	180	<i>n</i> Pr	Me	192	18	92	97
2	181	Et	Me	193	18	80	95
3	182	Me	Et	194	18	75	93
4	183	PhCH ₂	Me	195	66	60	97
5	184	<i>p</i> -BrC ₆ H ₄	Me	196	118	80	94
6	185	(<i>E</i>)PhCH=CH	Me	197	120	23	74
7	186	CO ₂ Et	Me	198	168	20	81

¹ Determined by chiral HPLC

Table 6

Reaction involving enones **180** - **182** gave good yields and comparable enantioselectivities to that obtained with 3-penten-2-one **156** (94 % ee) (Entries 1 - 3). Enone **183** required a significantly longer reaction time and did not reach completion leading to a lower isolated yield, but the product **195** still had high enantiomeric excess (Entry 4). This suggests that increasing the size of the substituent adjacent to the point of addition is possible, but can significantly slow the reaction. When this substituent was changed to an aromatic group (Entry 5), the reaction slowed further, but again high enantiomeric excess was obtained.

The addition to dienone **185** gave complete regioselectivity in the β -position, shown by the diastereotopic protons being doublet of doublets in the ¹H NMR, albeit in poor yield and reduced enantioselectivity (Entry 6). Finally only one regioisomer was isolated in the addition to enone **186** (Entry 7). The regiochemistry was assigned by comparing the chemical shifts in the ¹H NMR of the diastereotopic protons for this addition with literature values of analogous compounds.^[62,63] The chemical shift suggests that the nitrogen is next to the ester group and not the ketone. This regioselectivity is as would be expected if an iminium ion intermediate is involved as this could only form with the ket-group in enone **186** (Scheme 42).



Scheme 42

Overall these results show that variation in the substituents at either end of the enone can be tolerated. However as the size of these groups increase, the rate of reaction slows. This is not too surprising as the ketone needs to be accessible in order to form an iminium ion intermediate, and the β -position of the enone needs to be accessible in order for the nucleophile to add. The results obtained with enones **185** and **186** suggest that more electron deficient alkenes are less reactive. At first glance this appears to be counter-intuitive, but this could simply be that these alkenes are more stable because of the increased level of conjugation or that the reaction is rendered reversible and the conversions observed are the equilibrium point.

1.9.5.2 Cyclic Enones

At this point we were interested to see if the reaction could be extended to cyclic enones such as cyclohexenone. This represents a significant change because cyclohexenone is fixed in an *s-trans* conformation (Figure 31).

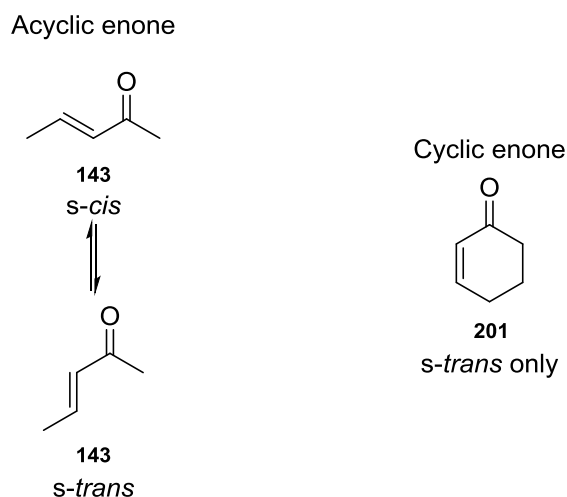
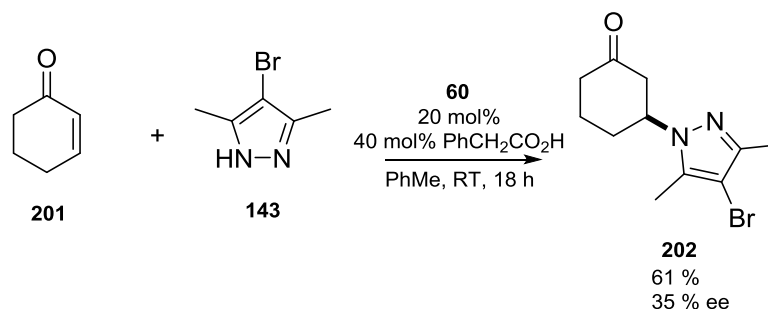


Figure 31

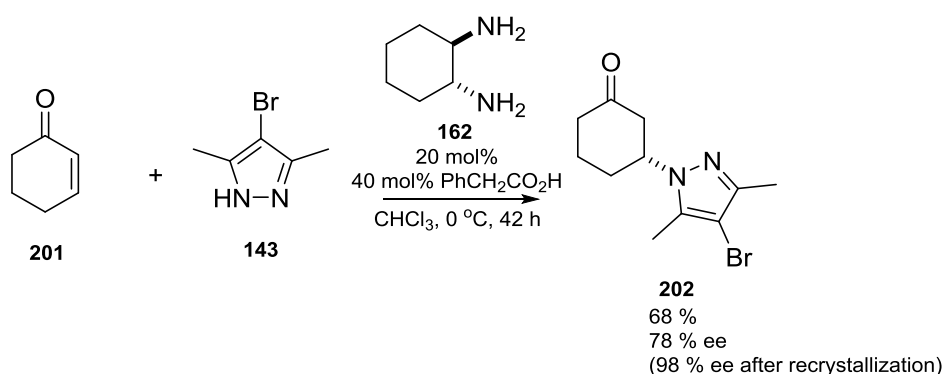
If the acyclic enones were to react via a *s-trans* conformation, we would expect cyclic enones to behave similarly and hence give good yields and enantioselectivity. However, if the acyclic enone were reacting via a *s-cis* conformation the cyclic enones would be expected to give quite different results and could potentially give the opposite enantiomer of product relative to their acyclic counterpart.

Interestingly most studies involving 9-deoxy-9-*epi*-aminoquinine catalyzed conjugate additions to enones only report results for acyclic ketones. However, there are a few studies which also report addition to cyclic enones, and they generally claim similar results for both types of enone.^[24,27] For the purposes of our study we examined the addition of pyrazole **143** to cyclohexenone **201** (Scheme 43).



Scheme 43

The reaction gave the desired product **202** in good yield, but with poor enantioselectivity. The absolute stereochemistry of the product was established by X-ray crystallography of the enantiomer which was formed using *R,R'*-1,2-diaminocyclohexane **162** as the catalyst (Scheme 44). This catalyst had been shown by another member of the group to give the opposite enantiomer of product compared to 9-deoxy-9-*epi*-aminoquinine **60**.^[56] this was also confirmed by comparison of optical rotation and HPLC traces. The product obtained using diamine **162** had a higher initial enantiomeric excess (78 % ee) allowing it to be enriched to 98 % ee by recrystallization. This enabled us to obtain an X-ray of a single enantiomer (the X-ray crystal was re-assessed by HPLC to confirm that it was the major enantiomer) (Figure 32).



Scheme 44

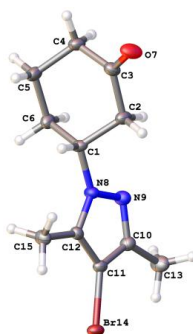


Figure 32

The fact that the (*S*)-enantiomer of product is obtained when 9-deoxy-9-*epi*-aminoquinine **60** is used for the addition to cyclohexenone **201** is interesting. This is the opposite enantiomer from that formed when the same catalyst is used with acyclic enones (*Table 6*). This strongly suggests that the acyclic enones react via a different mechanism to cyclic enones, and could be explained by the former reacting preferentially via a *s-cis* conformation (*Figure 33*).

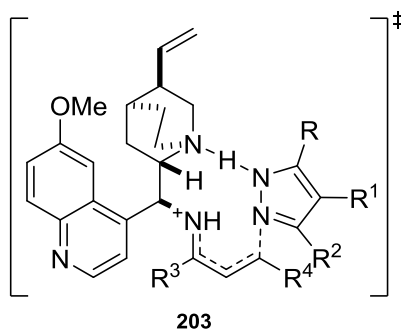


Figure 33

1.9.6 Investigation of 9-deoxy-9-*epi*-aminoquinidine as a catalyst

With 9-deoxy-9-*epi*-aminoquinine **60** proving to be a good catalyst for the conjugate addition of pyrazoles to enones we were interested in finding out what would happen if stereochemistry at C-8 and C-9 of the catalyst was inverted. If this lead to the opposite enantiomer of product, it would provide some support to the transition state proposed in *Figure 33*.

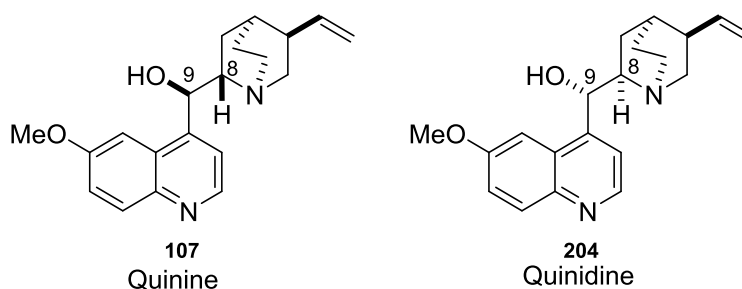
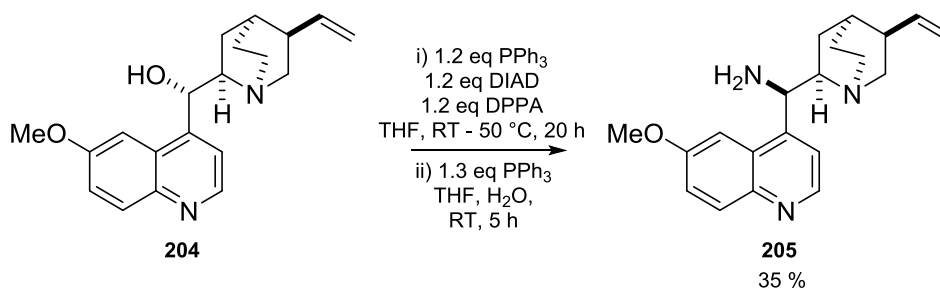


Figure 34

Quinidine **204** is a natural product found in the cinchona bark along with quinine **107** and is epimeric at the C-8 and C-9 positions (*Figure 34*). Amine **205** was prepared from quinidine **204** using the methodology used previously for quinine (*Scheme 45*). However, in this case a low yield of the desired product **205** was obtained along with a mixture of starting material, and the elimination product **206** (*Figure 35*). After purification by silica gel chromatography, 9-deoxy-9-*epi*-aminoquinidine **205** was isolated in 35 % yield. Although this was not ideal, it did allow sufficient quantities of **205** to be prepared.



Scheme 45

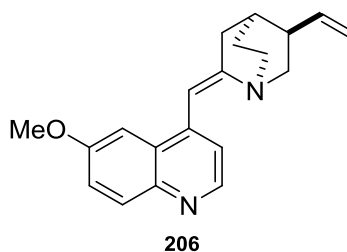
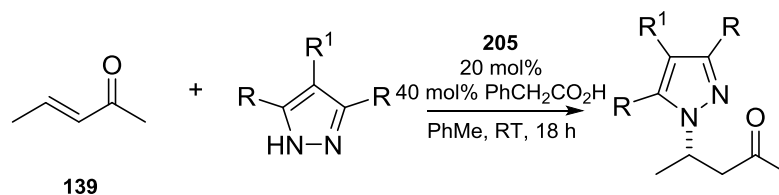


Figure 35

Amine **205** was then tested in a series of pyrazole additions. Three different pyrazoles with increasing number of substituents were used, along with indazole, to test if a similar nitrogen nucleophile would react (*Table 7*).

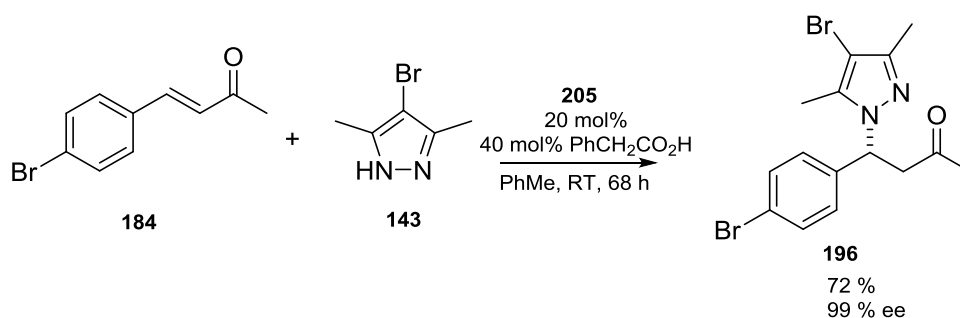


Entry	Pyrazole	R	R ¹	Product	Yield (%)	E.e. (%) ¹
1	120	H	H	154	90	88
2	138	Me	H	140	80	94
3	143	Me	Br	156	81	93
4	148	Indazole		161	92	85

¹ Determined by chiral HPLC

Table 7

In all cases the results obtained were comparable to those obtained using 9-deoxy-9-*epi*-aminoquinine **60**. Both yields and enantioselectivities were high and the opposite enantiomer was produced as hypothesised. The least reactive enone previously investigated, conjugated enone **184** was also tested to probe the scope of catalyst **205** (Scheme 46). This reaction also proceeded well with a shorter reaction time and a higher enantioselectivity than was obtained using 9-deoxy-9-*epi*-aminoquinine **60**.



Scheme 46

Overall these results show that the C-8 and C-9 positions are key to obtaining high enantioselectivity. The other stereocentres in catalysts **60** and **205** appear to have little effect on the stereochemical course of the reactions. Taken together their data provides support for the addition proceeding via the transition state depicted in Figure 33.

1.10 Conjugate Addition of 1,2,4-Dithiazolidine-3,5-dione

The results obtained so far show that *N*-heterocycles with a range of pK_a values are capable of undergoing enantioselective conjugate addition to enones using 9-deoxy-9-*epi*-aminoquinine **60** as the catalyst. Based on this we were keen to try alternative NH-nucleophiles and became interested in 1,2,4-dithiazolidine-3,5-dione **123** (Figure 36). This group is most commonly used for protecting amine groups in protein synthesis.^[64-66]

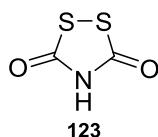
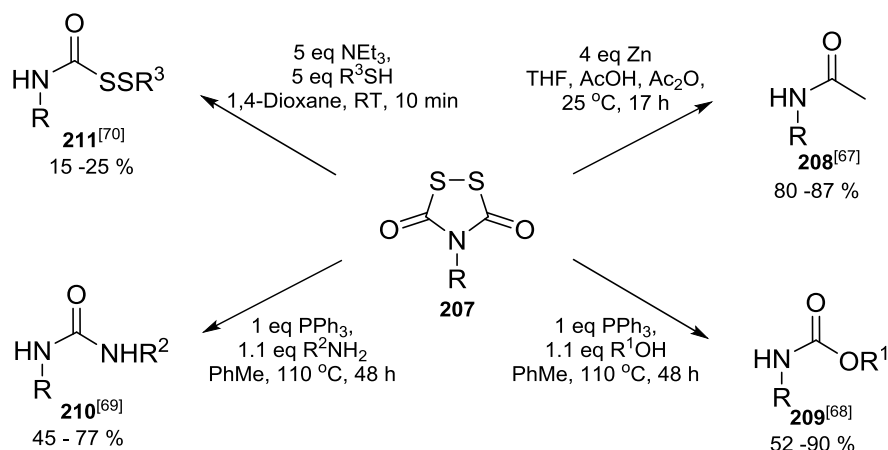


Figure 36

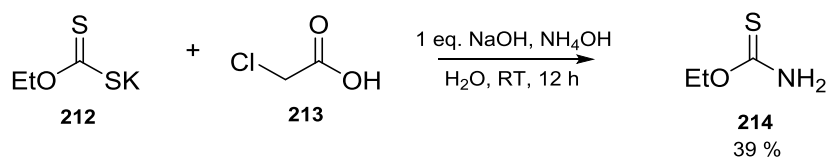
It is also of interest because the dithiazolodinedione fragment has been reported to be a direct precursor to a range of amine derivatives (*Scheme 47*).^[67-70]



Scheme 47

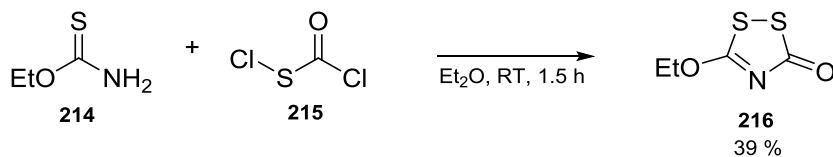
1.10.1. Synthesis of 1,2,4-Dithiazolidine-3,5-dione

1,2,4-Dithiazolidine-3,5-dione **123** was synthesised in three steps using conditions previously reported.^[71] First step was generation of *O*-ethyl thiocarbamate **214** from chloroacetic acid **213** and potassium salt **212** (*Scheme 48*).



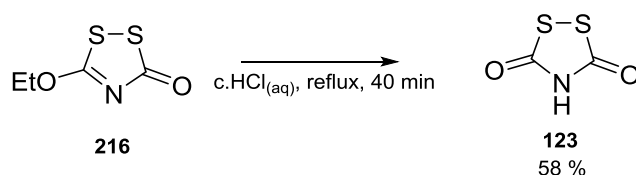
Scheme 48

Compound **214** was then reacted with chlorocarbonylsulfonyl chloride **215** (*Scheme 45*).^[71] The product was purified by recrystallization.



Scheme 49

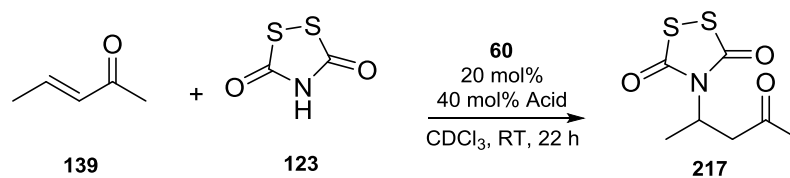
Finally compound **216** was hydrolysed to give 1,2,4-dithiazole-3,5-dione **123** using concentrated hydrochloric acid. Filtration and subsequent recrystallization from toluene gave the desired product in 58 % yield (*Scheme 50*).^[71]



Scheme 50

1.10.2. Conjugate Addition to Substituted Enones

We next examined conjugate addition of **123** to 3-penten-2-one **139**. First the background reaction and the effect of catalyst **60** in combination with several different acids was examined (*Table 8*). These reactions were all performed in CDCl_3 to allow the reaction progress to be monitored by ^1H NMR.



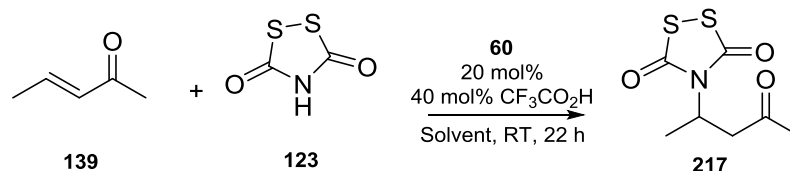
Entry	Acid	Yield (%)	E.e. (%) ¹
1	None	0 ^{2,3}	ND
2	None	94	10
3	PhCO ₂ H	69	2
4	CF ₃ CO ₂ H	82	29
5	CF ₃ CO ₂ H	80	6 ⁴
6	CF ₃ SO ₃ H	82	21

¹ Determined by chiral HPLC ² No catalyst added

³ Less than 10% conversion by ^1H NMR ⁴ 20 mol% acid used

Table 8

Without catalyst **60**, no reaction was observed by ^1H NMR (*Entry 1*). Addition of catalyst **60** led to product formation even in the absence of an acid additive, but enantioselectivity was low (10 % ee) (*Entry 2*). Of the acids investigated trifluoroacetic acid gave the best result (*Entries 3, 4 and 5*). Lowering the amount of trifluoroacetic acid to 20 mol% gave a similar yield but lower enantioselectivity (6 % ee) (*Entry 5*). In an effort to improve the enantioselectivity we next investigated the effect of changing the solvent (*Table 9*).

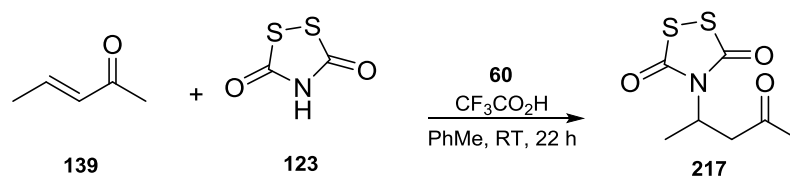


Entry	Solvent	Yield (%)	E.e. (%) ¹
1	CH_2Cl_2	59	14
2	MeCN	90	2
3	THF	90	0
4	MeOH	48	8
5	Et_2O	63	1
6	PhMe	80	32

¹ Determined by chiral HPLC

Table 9

Of the six solvents investigated toluene was the only one that gave higher enantioselectivity (*Entry 6*). The effect of changing the catalyst loading was next investigated (*Table 10*).

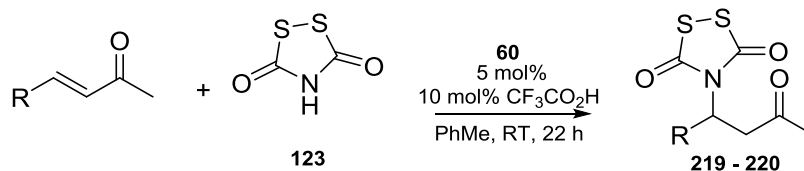


Entry	Cat (mol%)	Acid (mol%)	Yield (%)	E.e. (%) ¹
1	10	20	78	55
2	5	10	63	65
3	2.5	5	57	66
4	5	10	10	57 ²

¹ Determined by chiral HPLC ² Run at -30 °C with 1 drop MeOH

Table 10

It was found that decreasing the amount of catalyst and acid resulted in an increase in enantioselectivity but a decrease in the yield (*Entries 1 - 3*). The best overall conditions, 5 mol% cat and 10 mol% acid (*Entry 2*), were repeated at -30 °C, but this resulted in poor conversion. This was probably because the nucleophile **123** was completely insoluble at this temperature. In an attempt to improve the solubility, one drop of methanol was added, and after 70 hours a low yield of product was obtained with similar enantioselectivity (*Entry 4*). We next investigated the effect of altering the enone structure (*Table 11*).



Entry	Enone	R	Time (h)	Product	Yield (%)	E.e. (%) ¹
1	174	<i>n</i> Pr	48	219	67	67
2	218	Ph	101	220	17	3
3	218	Ph	101	220	13	39 ²

¹ Determined by chiral HPLC ² Reaction performed with 2.5 mol% **60** and 5 mol% TFA

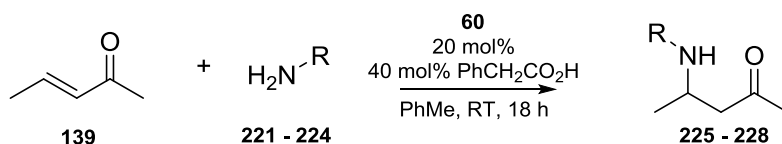
Table 11

The aliphatic enone **174** gave a similar yield and enantioselectivity (67 % ee) to that seen with 3-penten-2-one **139** (Entry 1). 4-Phenyl-3-buten-2-one **218** gave poor conversion over a longer reaction time and almost racemic product (Entry 2). Interestingly decreasing the catalyst and acid loading to 2.5 mol% and 5 mol% respectively resulted in improved enantioselectivity for this product (Entry 3). Given the modest enantioselectivities, we decided to suspend this study and look at alternative N-nucleophiles.

1.11 Amide and Carbamate Conjugate Additions

Given that the main aim of our studies using dithiazolidindione was to access amine and common amine derivatives (e.g. carbamates or amides), we decided to investigate if carbamates and amides could be added directly. This was anticipated to be far more challenging as the *pK_a* of such nucleophiles was higher (Figure 12), and beyond the range of nucleophiles that have been used in this type of chemistry to date (Figure 11).

A small series of commercial primary amide and carbamate nucleophiles were briefly investigated using the same conditions as before (Table 12).



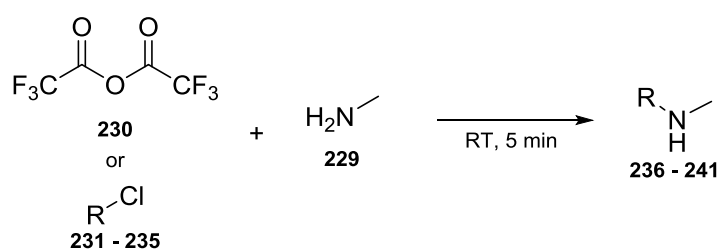
Entry	Substrate	R	Product	Conversion (%) ¹
1	221	CO ₂ Me	225	<10
2	222	Boc	226	<10
3	223	Cbz	227	<10
4	224	Bz	228	<10

¹ Determined by ¹H NMR analysis

Table 12

In all cases no conversion to the desired product was observed by ^1H NMR analysis after concentration of the reaction mixture. This suggests that these nucleophiles are not sufficiently nucleophilic or acidic enough to participate.

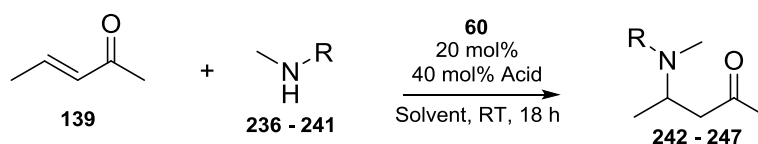
In an attempt to increase the nucleophilicity of these types of nucleophiles we next investigated carbamates and amides possessing an N-methyl substituent. The N-methyl group is known to significantly increase the nucleophilicity of a nitrogen.^[72] We also expanded the range of amides to increase their NH acidity and included a sulfonamide in the study. The nucleophiles for this study were prepared as outlined below (Table 13).



Entry	Substrate	R	Product	Yield (%)
1	230	COCF_3	236	13
2	231	CO_2Me	237	32
3	232	Bz	238	94
4	233	$p\text{-NO}_2\text{C}_6\text{H}_4\text{CO}$	239	44
5	234	Cbz	240	90
6	235	$p\text{-MeC}_6\text{H}_4\text{SO}_2$	241	80

Table 13

With these six compounds, **236 - 241** available their addition to 3-penten-2-one **139** was next investigated (Table 14).^[73]

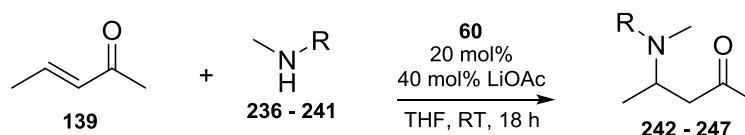


Entry	Substrate	R	Acid	Solvent	Product	Conversion (%) ¹
1	236	COCF_3	$\text{PhCH}_2\text{CO}_2\text{H}$	PhMe	242	<10
2	236	COCF_3	TFA	THF	242	<10
3	237	CO_2Me	$\text{PhCH}_2\text{CO}_2\text{H}$	PhMe	243	<10
4	237	CO_2Me	TFA	THF	243	<10
5	238	Bz	$\text{PhCH}_2\text{CO}_2\text{H}$	PhMe	244	<10
6	238	Bz	TFA	THF	244	<10
7	239	$p\text{-NO}_2\text{C}_6\text{H}_4\text{CO}$	$\text{PhCH}_2\text{CO}_2\text{H}$	PhMe	245	<10
8	239	$p\text{-NO}_2\text{C}_6\text{H}_4\text{CO}$	TFA	THF	245	<10
9	240	Cbz	$\text{PhCH}_2\text{CO}_2\text{H}$	PhMe	246	<10
10	240	Cbz	TFA	THF	246	<10
11	241	$p\text{-MeC}_6\text{H}_4\text{SO}_2$	$\text{PhCH}_2\text{CO}_2\text{H}$	PhMe	247	<10
12	241	$p\text{-MeC}_6\text{H}_4\text{SO}_2$	TFA	THF	247	<10

¹ Determined by ^1H NMR analysis

Table 14

In all cases no conversion was observed by ^1H NMR analysis of the crude reaction mixture. These results show that simple carbamates and amides will not add under the conditions employed. In a final effort to get these reactions to work we considered the use of 9-deoxy-9-*epi*-aminoquinine **60** in combination with a base. Although this combination seems odd, similar conditions have been shown to be effective in promoting the addition of succinimide to enals (Scheme 4).^[14] The six substrates **236** - **241** were tested with lithium acetate as a co-catalyst with 9-deoxy-9-*epi*-aminoquinine **60** (Table 15).



Entry	Substrate	R	Product	Conversion (%) ¹
1	236	COCF_3	242	<10
2	237	CO_2Me	243	<10
3	238	Bz	244	<10
4	239	$p\text{-NO}_2\text{C}_6\text{H}_4\text{CO}$	245	<10
5	240	Cbz	246	<10
6	241	$p\text{-MeC}_6\text{H}_4\text{SO}_2$	247	<10

¹ Determined by ^1H NMR analysis

Table 15

Again no conversion was observed by ^1H NMR. At this point we decided to move on to investigate intramolecular reactions which were hoped would be more facile.

1.12 Conclusions

We have shown that 9-deoxy-9-*epi*-aminoquinine **60** and 9-deoxy-9-*epi*-aminoquininidine **205** are effective catalysts for the *N*-conjugate addition of pyrazoles to acyclic enones. Phenylacetic acid was found to be an important additive. A range of pyrazoles and indazole were shown to participate in this chemistry, with the electron deficient pyrazoles giving lower conversions and isolated yields, possibly due to a retro addition process. For the unsymmetrically substituted pyrazoles, the less hindered N-atom preferentially underwent addition, and the regioselectivity was dependent on the degree of steric hindrance.

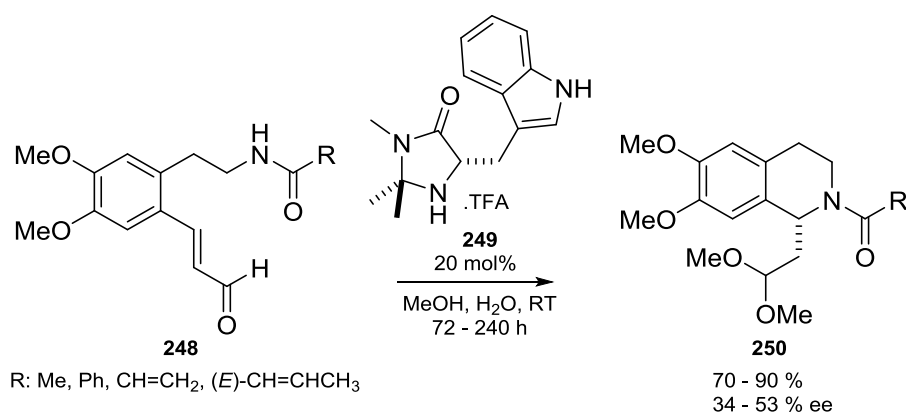
We have also shown that the reaction can tolerate substitution at either end of the enone, although additional conjugating groups appear to slow the reaction and reduce enantioselectivity. Unfortunately cyclic enones (cyclohexenone) do not appear to be good substrates for this reaction, giving significantly lower enantioselectivities and the opposite enantiomer of product. Based on the results obtained we have proposed that these additions proceed via an iminium ion intermediate in an *s-cis* conformation.

Attempts to expand the range of nucleophiles beyond pyrazoles has met with limited success. 1,2,4-Diathiazolidine-3,5-dione **123** was found to add, but enantioselectivities were significantly lower (39 - 67 % ee). Simple amide, carbamate and sulphonamides did not add at all.

Chapter 2: Intramolecular *N*-Conjugate Addition

2.1 Intramolecular *N*-Conjugate Addition Reactions to Enals

The first example of an organocatalytic intramolecular nitrogen conjugate addition reaction involving the use of a chiral imidazolidinone was published in 2003 by Ihara and co-workers. Amides **248** were cyclised using imidazolidinone **249** to yield tetrahydroisoquinolines **250**, as the more stable dimethyl acetate, in high yield but with modest enantioselectivities (Scheme 51).^[74] The absolute stereochemistry was determined by conversion to compound **251** and agreement with literature optical rotation data (Figure 37).^[75] Further work was needed as only four substrates were shown to work with prolonged reaction times required.



Scheme 51

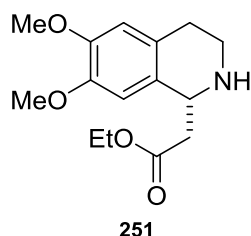
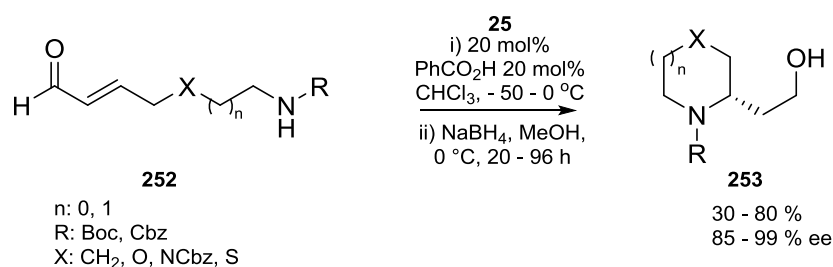


Figure 37

Later, Fustero and co-workers reported that an intramolecular enal conjugate addition was possible using proline derived catalyst **25** first reported by Jørgenson.^[76] The aldehyde formed from the conjugate addition reaction is reduced *in situ* to the more stable alcohol product with good yields and high enantioselectivities (Scheme 52).^[76] The absolute stereochemistry was determined by comparison of compound **254** with literature optical rotation data (Figure 38).^[77] The reaction was also proven to tolerate heteroatom substitution in the ring formed.



Scheme 52

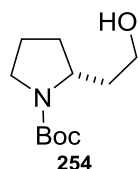
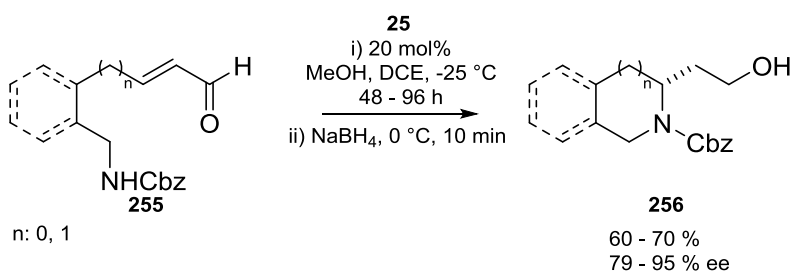


Figure 38

Carter and co-workers reported that the acid additive was not essential to obtain good enantioselectivities using catalyst **25** (Scheme 53).^[78] The aldehyde formed was reduced *in situ* to the alcohol to form a range of pyrrolidine, piperidine and indoline derivatives **256**. The absolute stereochemistry was determined by conversion to a natural product, homopipelicolic Acid **257** and comparison with literature optical rotation data (Figure 39).^[79]



Scheme 53

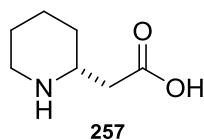
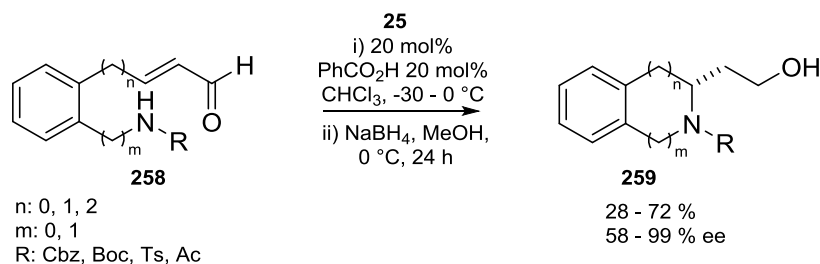


Figure 39

Fustero and co-workers later showed that their reported conditions could be expanded to include the use of substituted aromatic and aniline derived compounds **258** without diminishing yield and enantioselectivities (Scheme 54).^[80] The absolute stereochemistry was determined by conversion to a natural product, angustureine **260** and comparison with literature optical rotation data (Figure 40).^[81] This also showed the only example of a

sulfonamide being used in an intramolecular conjugate addition to enals with good yield and high enantioselectivities.



Scheme 54

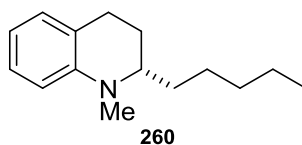
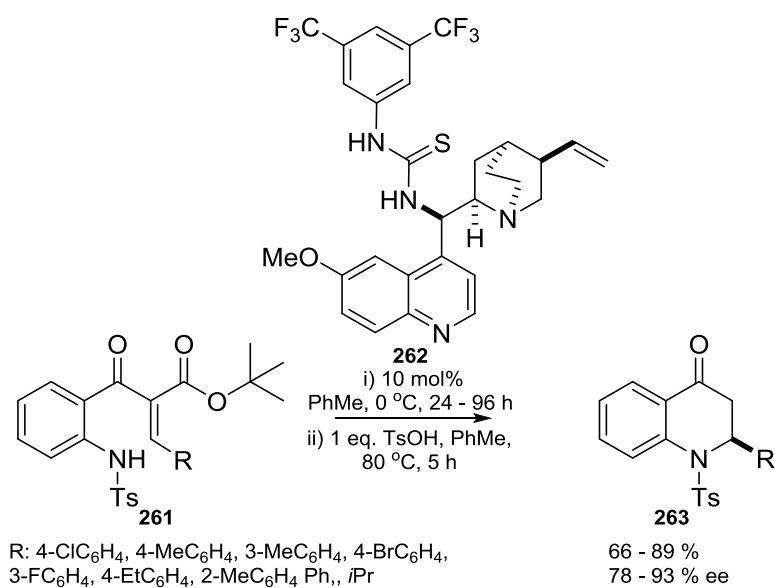


Figure 40

2.2 Intramolecular N-Conjugate Addition Reaction of Enones

The organocatalytic intramolecular enone conjugate addition was not reported until two years later in 2010 when Lu and co-workers reported the addition of sulfonamides to β -ketoesters using a quinidine derived thiourea catalyst **262**. The reaction could be performed in good yield, with a one pot process to remove the ester moiety, with high enantioselectivities (*Scheme 55*).^[82] The absolute stereochemistry was determined by comparison of compound **264** with literature HPLC data (*Figure 41*).^[83] They proposed that the thiourea hydrogen bonds to the dicarbonyl and the quinuclidine nitrogen deprotonates the sulfonamide which attacks the enone to give the stereochemistry observed (*Figure 42*).^[82]



Scheme 55

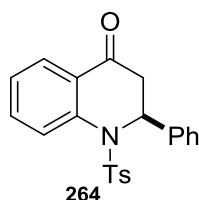


Figure 41

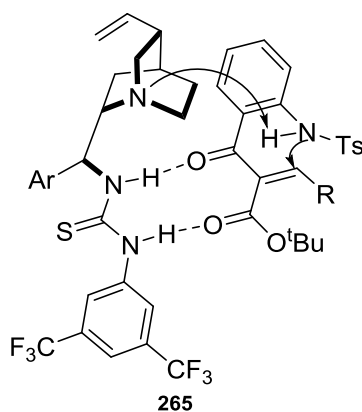
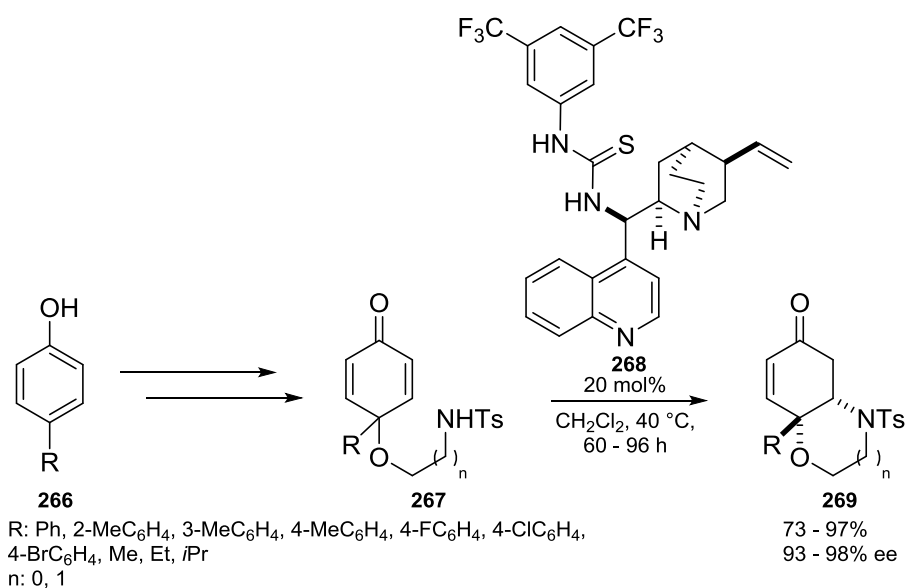


Figure 42

You and co-workers then reported the intramolecular nitrogen conjugate addition of sulfonamides to cyclohexadienones using cinchonine derived thiourea **268**.^[84] First the corresponding phenol was oxidised and then the crude enone was cyclized in good yield and high enantioselectivities (Scheme 56).^[84] The absolute stereochemistry was confirmed by X-ray diffraction of a single crystal of compound **270** (Figure 43).



Scheme 56

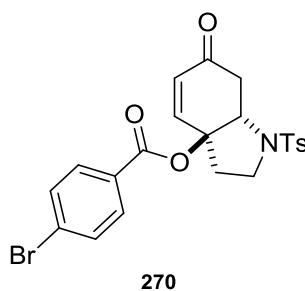
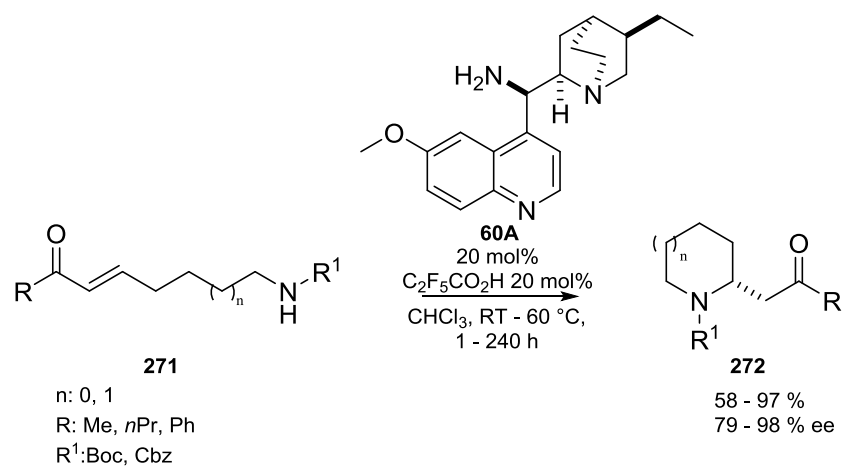


Figure 43

Fustero and co-workers reported the first example of an intramolecular nitrogen conjugate addition involving iminium activation using dihydro-9-deoxy-9-*epi*-aminoquinine derivative **60A** as the catalyst.^[85] The paper reports the optimisation of the formation of 2-substituted piperidines and pyrrolidines **272** with excellent enantioselectivity (*Scheme 57*).^[85] The absolute stereochemistry was determined by comparison of compound **273** with literature optical rotation data (*Figure 44*).^[86] They proposed that an iminium species is formed between the carbonyl and the primary amine and the protonated quinuclidine nitrogen hydrogen bonds to the carbamate carbonyl which then reacts to give the stereochemistry observed (*Figure 45*).^[85]



Scheme 57

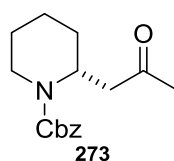


Figure 44

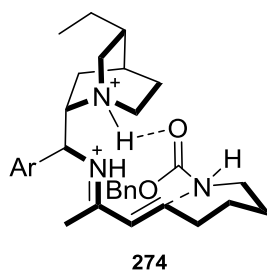


Figure 45

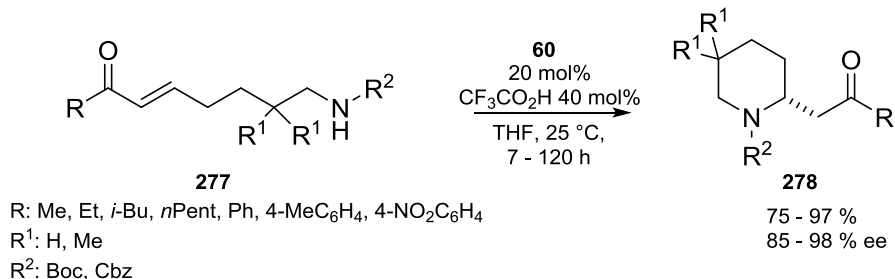
Also reported was the intramolecular conjugate addition of substituted aromatic enones and anilines in good yield and enantioselectivity (*Scheme 58*).^[85] These were the first reported enantioselective example of carbamates acting as an intramolecular nitrogen nucleophile using an organocatalyst.



Scheme 58

Fan and co-workers then investigated the effect of enone substitution on the formation and enantioselectivity of substituted piperidine products **278**. The reaction was performed using trifluoroacetic acid and tetrahydrofuran as the solvent (*Scheme 59*).^[73]

The absolute stereochemistry was determined by comparison of compound **273** with literature optical rotation data.^[86] They proposed a similar mechanism but with the enone reacting in a (*E*)-*s-trans* conformation to give the stereochemistry observed (*Figure 46*).^[73]



Scheme 59

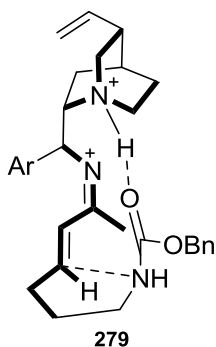
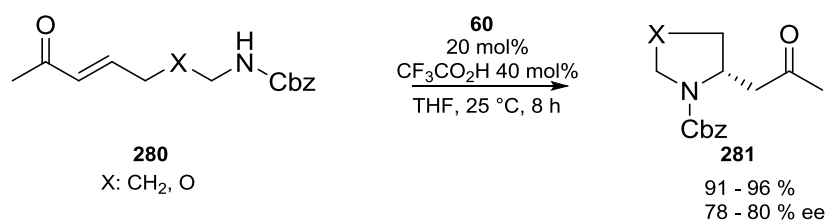


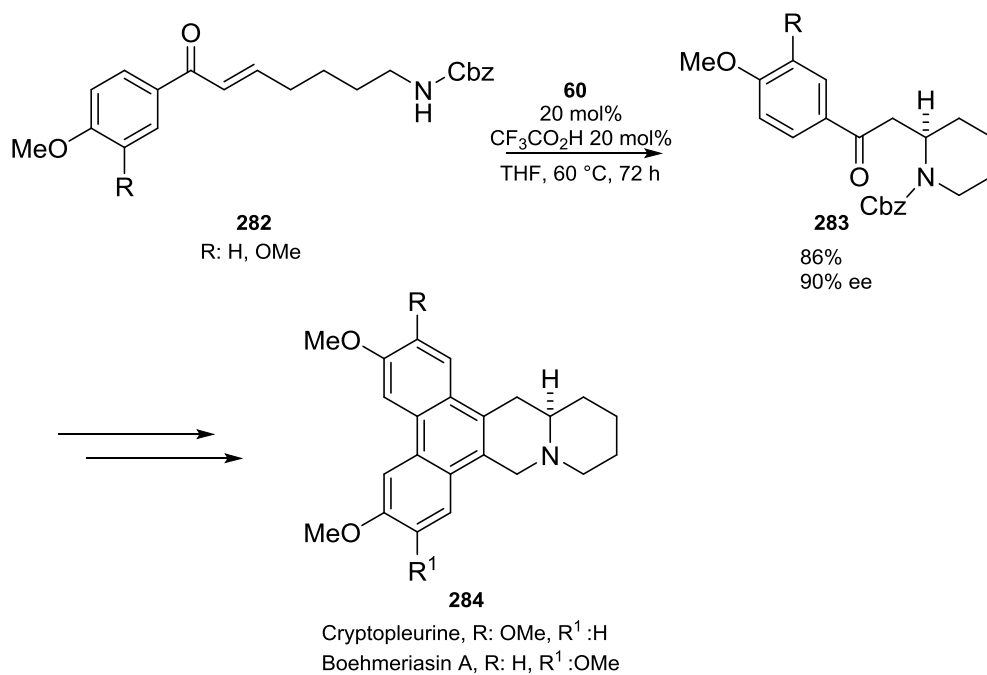
Figure 46

Also reported was an example of heteroatom incorporation into the ring formed using the same reaction conditions in good yield and enantioselectivity (*Scheme 60*).^[73]



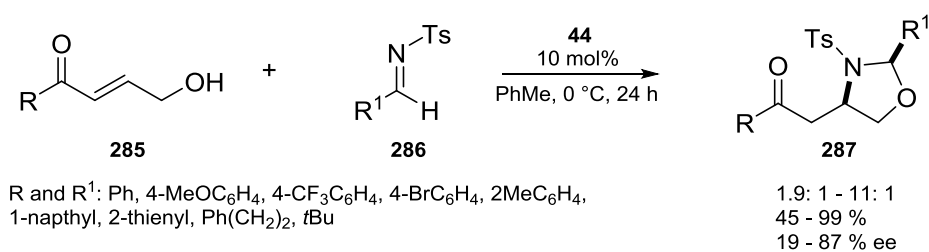
Scheme 60

This methodology was then applied to the total synthesis of boehmeriasin A^[87] and cryptopleurine,^[88] with an intramolecular nitrogen conjugate addition step used to form the key stereocentre.^[89] Enones **282** required heating for several days giving desired products **283** in high enantioselectivity which in subsequent steps was converted to the two desired natural products (*Scheme 61*).^[89]



Scheme 61

Asano and co-workers reported chiral 1,3-oxazolidines **287** could be synthesised from hydroxyenones **285** and imines **286** using an intramolecular nitrogen conjugate addition catalyzed by quinine derived thiourea **44** (Scheme 62);^[90] the reaction yielded enantioselectivities and diastereoselectivities ranging from poor to good. The absolute stereochemistry was determined by X-ray analysis of a single crystal of major diastereoisomer **288** (Figure 47).



Scheme 62

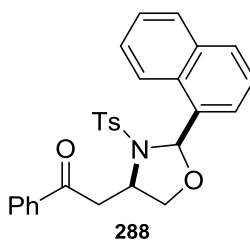
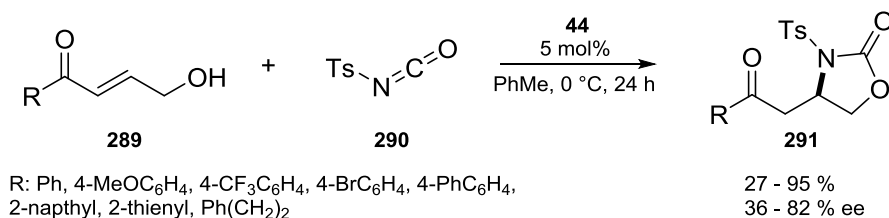


Figure 47

Later that year Asano reported a similar protocol for the synthesis of 2-oxazolidinones **291** using tosyl isocyanate **290** with a catalyst loading of only 5 mol% of thiourea **44** (Scheme 63).^[91] However the enantioselectivities again showed large variations. The absolute stereochemistry was determined by conversion to compound **292** and comparison with literature optical rotation data (Figure 48).^[92]



Scheme 63

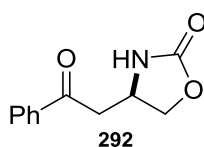
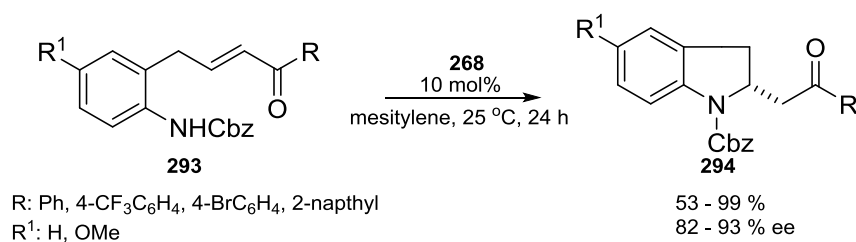


Figure 48

More recently Asano and co-workers reported the synthesis of indolines **294** from the corresponding anilines **293** using quinidine based thiourea **268**. A range of ketones **293** were investigated and gave good yields and high enantioselectivities (Scheme 64).^[93] The absolute stereochemistry was assigned by X-ray diffraction of a single crystal of compound **295** (Figure 49).



Scheme 64

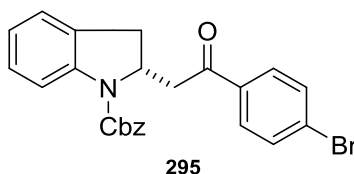
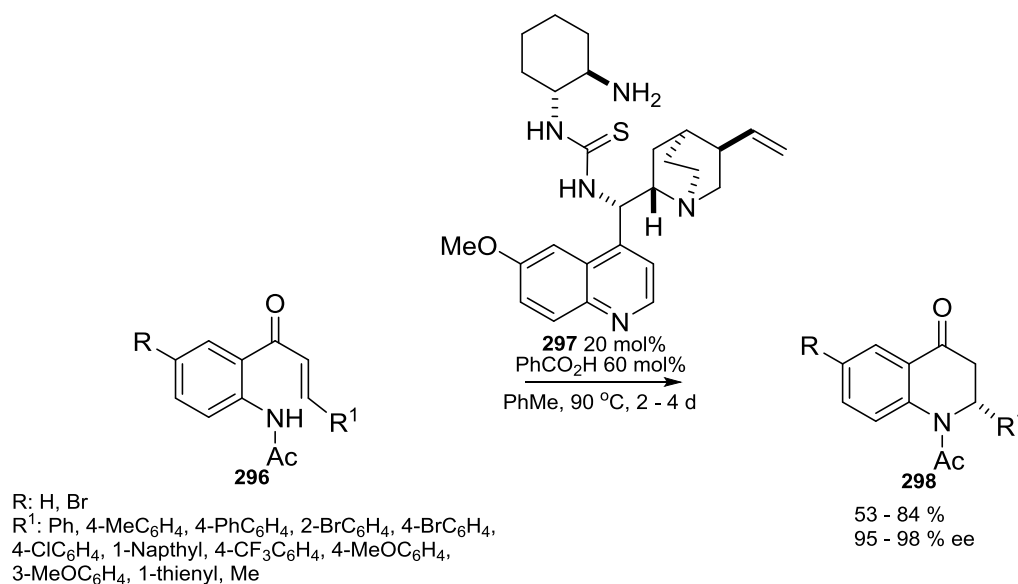


Figure 49

Yu and co-workers then reported the first example of acetyl amides **296** performing an intramolecular cyclization to generate 2-substituted azaflavones **298**. The reaction was performed with quinine derived primary amine catalyst **297** with benzoic acid, its first reported use in this type of cyclization (Scheme 65).^[94] The absolute stereochemistry was confirmed by comparison of compound **299** with literature optical rotation data (Figure 50).^[83] They proposed a similar mechanism as discussed previously with the primary amine forming an iminium species with the enone and the quinuclidine nitrogen deprotonating the amide which then attacks the iminium species (Figure 51).



Scheme 65

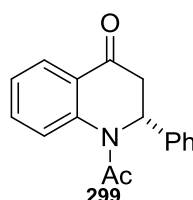


Figure 50

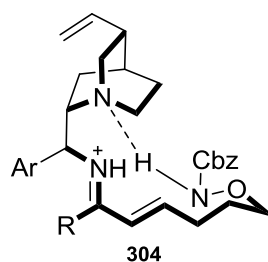


Figure 53

2.3 Project Aims

When this project was started only three intramolecular process of this type using iminium catalysis have been reported ^[73,85,89] so this needed be studied in more detail after a suitable catalyst system has been optimised (*Figure 54*). Functionalisation on the nitrogen has been limited to two carbamates, *tert*-butyl and benzyl, so this can be investigated to test if other groups are suitable for this mode of catalysis and their effect on yield and enantioselectivity.

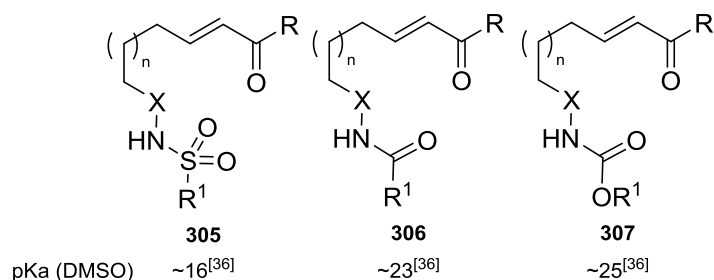
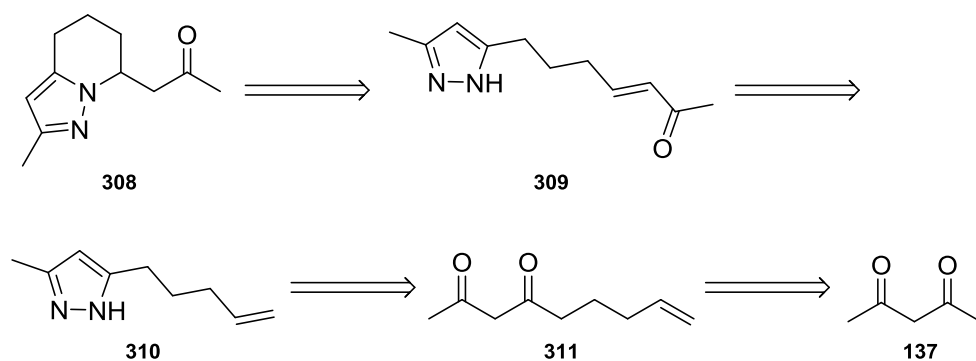


Figure 54

We also wanted to investigate if the chemistry we have observed in the intermolecular reaction could be transferred to an intramolecular addition. In order to do this we would need to tether a pyrazole and a suitable enone together with enough carbons to allow reaction.

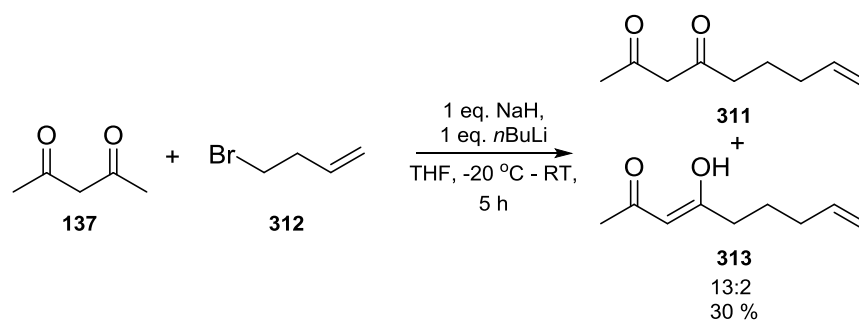
2.4 Intramolecular Pyrazole Substrate

The most reported ring size formed by this type of catalysis is six, so it was decided to design the molecule to form a six membered ring when cyclized giving a five-six fused ring system. The retrosynthetic analysis of the desired compound **308** is shown below in four steps (*Scheme 67*).



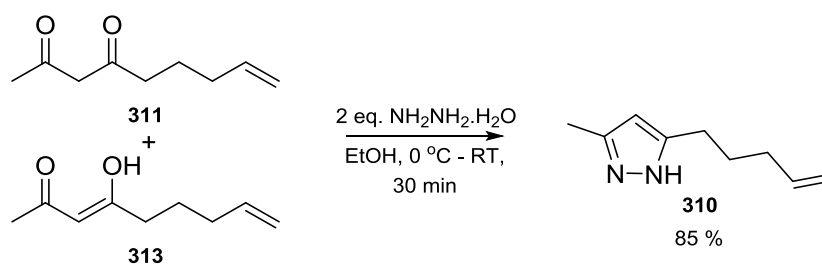
Scheme 67

The first step of the synthesis was the alkylation of acetylacetone **137** with 4-bromobut-1-ene **312** following literature conditions (Scheme 68).^[96] The desired product **311** was isolated with tautomer **313** in low yield and this was taken directly onto the next step.



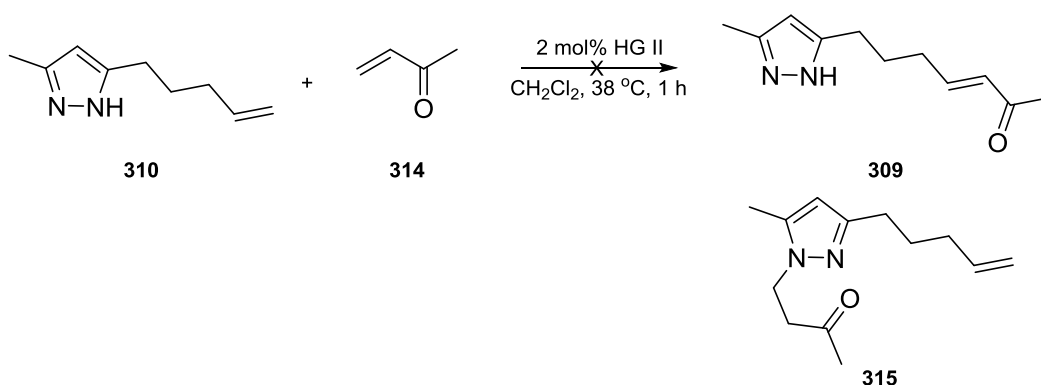
Scheme 68

The mixture of tautomers was then converted to pyrazole **310** using conditions previously described (Scheme 69) in excellent yield.



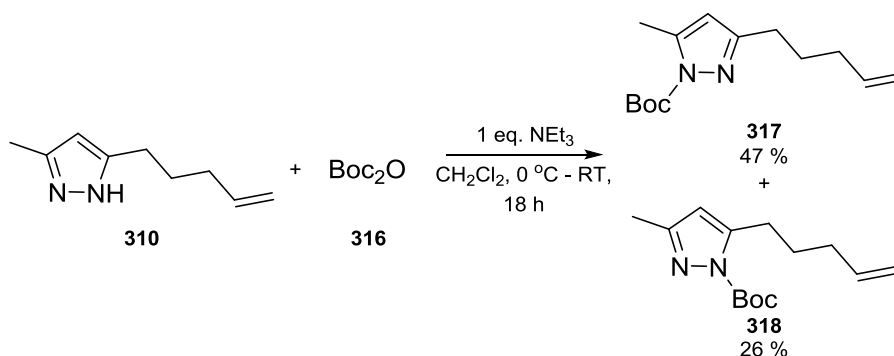
Scheme 69

Pyrazole **310** was then reacted with methyl vinyl ketone **314** using cross metathesis conditions previously described in the literature (Scheme 70).^[73] However no desired product was observed by ¹H NMR analysis with most of the material being by-product **315**. This compound was not isolated so its regiochemistry is unknown.



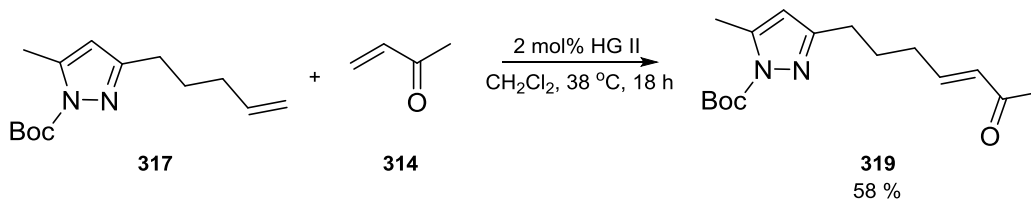
Scheme 70

In order to prevent this conjugate addition we would need to protect the nitrogen group, *tert*-butoxycarbonyl (Boc) was chosen as it would be easy to remove after the cross metathesis reaction. Pyrazole **310** was reacted with di-*tert*-butyl dicarbonate **316** using conditions previously described in the literature.^[97] This yielded a 2: 1 mixture of regioisomers **317** and **318**, which were tentatively assigned with the major product **317** reducing the steric hindrance between the alkyl chain and the Boc group (*Scheme 71*). Both regioisomers were taken forward to make sure they reacted in the same manner.



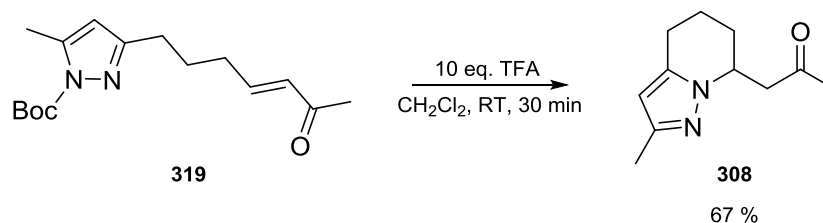
Scheme 71

Major pyrazole regioisomer **317** was then reacted with methyl vinyl ketone **314** using the conditions previously described to yield desired enone **319** in modest yield (*Scheme 72*). The yield was lower than expected with unreacted starting material **317** recovered for further reactions (25 %).



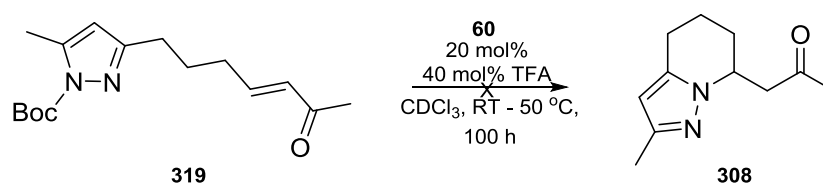
Scheme 72

The next step was removal of the Boc group using TFA with careful reaction monitoring to attempt to prevent cyclization of the product (Scheme 73).^[98] After 30 minutes TLC showed disappearance of starting material **319** and appearance of a single reaction product which, after isolation was found to be cyclized product **308**.



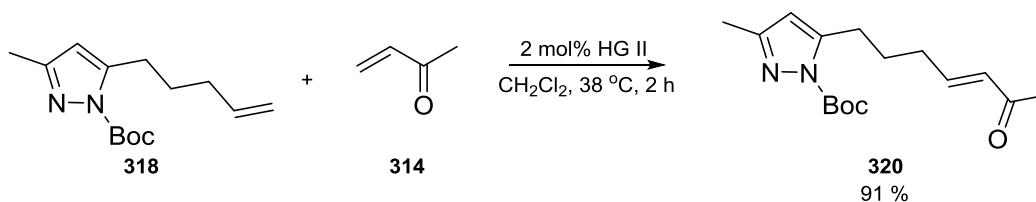
Scheme 73

It was thought that isolation of pyrazole **309** would prove difficult so direct conversion to desired cyclized product **308** was attempted. Pyrazole **319** was then subjected to cyclization conditions found in the literature for these types of process using 9-deoxy-9-*epi*-aminoquinine **60** and TFA using deuterated chloroform as the reaction solvent to allow monitoring by ^1H NMR (Scheme 74).^[73] However even after heating, no conversion to the desired product **308** was observed, with only unreacted starting material **319** observed.



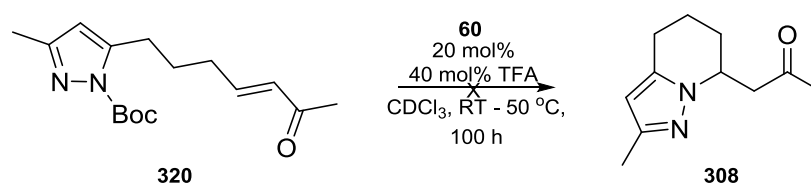
Scheme 74

We wanted to investigate if the other pyrazole regioisomer **318** would cyclize under these reaction conditions. First enone **320** was synthesised using the conditions discussed previously (Scheme 75). This regioisomer gave a much higher yield in a much shorter reaction time.



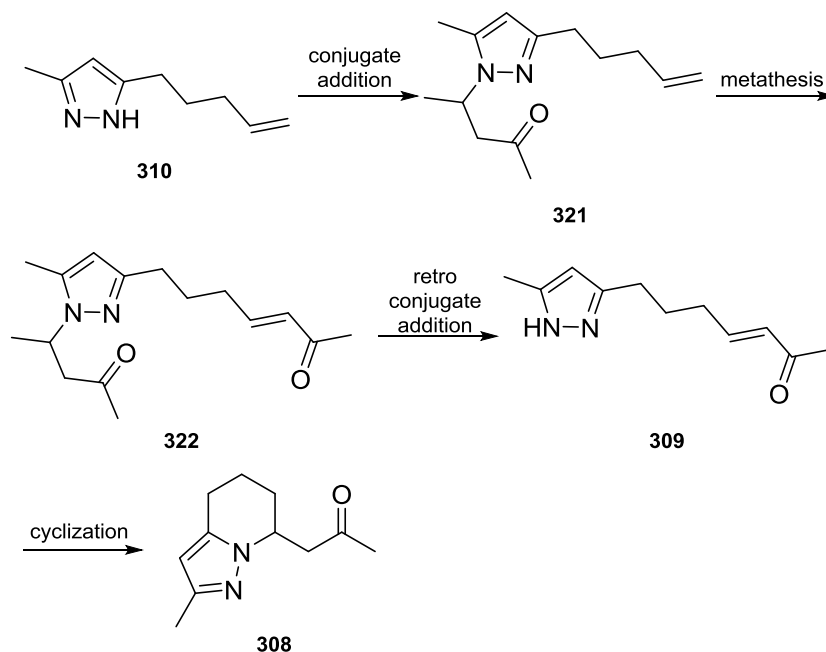
Scheme 75

Enone **320** was then reacted with the conditions discussed previously (Scheme 76). No conversion to desired product **308** was observed for this compound either with only starting material observed with ^1H NMR analysis.



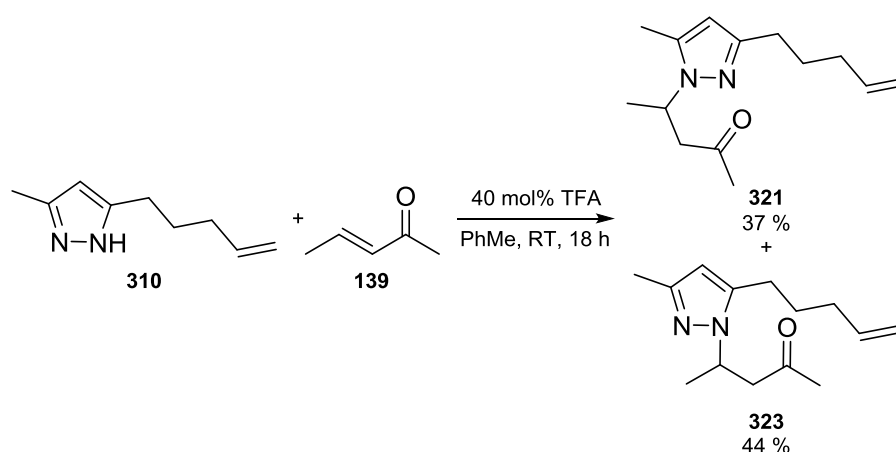
Scheme 76

Instead of using a protecting group on the nitrogen it was proposed to use a molecule that could eliminate under the cyclization reaction conditions. 3-Penten-2-one **139** has proven to undergo conjugate addition with pyrazoles previously. Reaction of pyrazole **310** and enone **139** would generate pyrazole **321**. This can then be converted to enone **322** by cross metathesis with methyl vinyl ketone **314**. This could be cyclized with reaction conditions previously discussed to yield desired product **308** (Scheme 77). Pyrazole **322** would first perform the retro conjugate addition reaction to generate pyrazole **309** *in situ* which would cyclize under the reaction conditions.



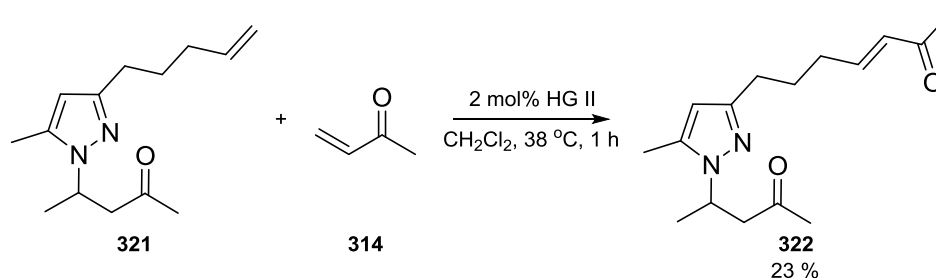
Scheme 77

First pyrazole **310** was added to 3-penten-2-one **139** using trifluoroacetic acid as a catalyst (Scheme 78). The reaction gave a 1: 1 mixture of regioisomers which were separated by silica gel chromatography and regioisomer **321** was taken forward with the tentative assignment of regiochemistry by NOESY spectroscopy.



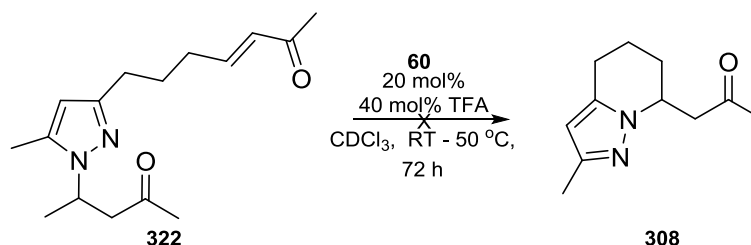
Scheme 78

Pyrazole **321** was then reacted with the conditions discussed previously to generate enone **322** (Scheme 79). The isolated yield was low with only 25 % conversion observed by ^1H NMR analysis, with the majority of starting material **321** recovered (66%).



Scheme 79

Enone **322** was then reacted with the cyclization conditions discussed previously with deuterated chloroform to allow monitoring of conversion to desired product **308** (Scheme 80).^[73] However no conversion to product was observed at room temperature or after increasing the temperature to 50 °C by ^1H NMR analysis.



Scheme 80

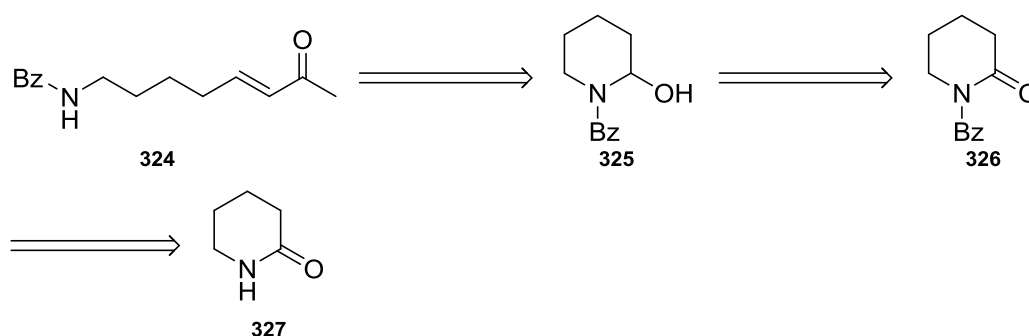
Given the problems isolating pyrazole **308**, we decided to suspend this study and instead to investigate different groups on nitrogen for intramolecular cyclizations.

2.5 Amide Substrates

2.5.1. External Amides

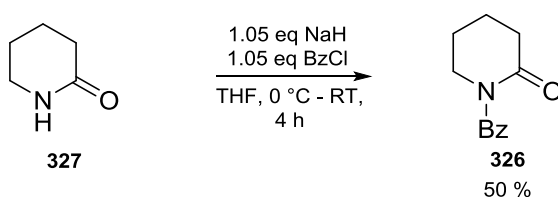
2.5.1.1 Synthesis of External Amide Cyclization Precursors

It was decided to synthesise a range of substituted amides to investigate the effect of different amide groups on the rate and enantioselectivity of cyclizations. The best amide group found could then be optimized and ring sizes could be investigated. A retrosynthetic analysis of desired benzamide enone **324** was performed (*Scheme 81*).



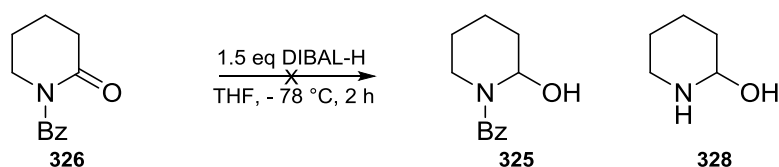
Scheme 81

Enone **324** can be synthesised by Wittig reaction of cyclic hemi-aminal **325**, with ylide **191**, which can be made by reduction of lactam **326**. This compound can be made by the reaction of commercially available δ -valerolactam **327** with benzoyl chloride. The first transformation of this three step reaction sequence was the functionalisation of the nitrogen with benzoyl chloride (*Scheme 82*).^[99] The reaction proceeded in moderate yield with material lost due to difficulty in separation from starting materials.



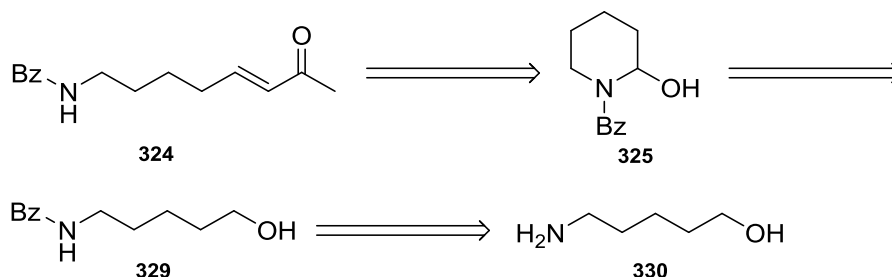
Scheme 82

The next step was the reduction of amide **326** to cyclic hemi-aminal **325** using conditions previously described in the literature (*Scheme 83*).^[89] After two hours starting material **326** had been consumed by TLC and after purification by silica chromatography a complex mixture was recovered. The target compound **325** was found to be inseparable from benzaldehyde and an unknown compound thought to be reduced δ -valerolactam **328**.



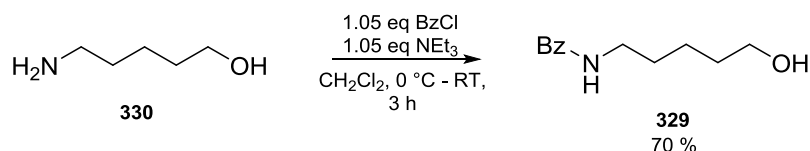
Scheme 83

Selectivity between the two carbonyls was thought to be problematic and a new retrosynthetic analysis was performed (*Scheme 84*).



Scheme 84

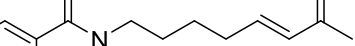
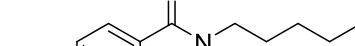
Hemi-aminal **325** could be synthesised by oxidation of alcohol **329** via the aldehyde, this could be prepared from commercially available 5-aminopentan-1-ol **330**. The first step was functionalisation of the nitrogen with benzoyl chloride using conditions previously described in the literature (*Scheme 85*).^[100]



Scheme 85

The reaction gave a mixture of products with substitution on both heteroatoms, which were easily separated by silica chromatography, lowering the isolated yield. The next step was the oxidation of alcohol **329** to aldehyde **325**. Investigation of the literature revealed a one-pot oxidative Wittig process, optimised by Taylor and co workers, meaning the possibly unstable aldehyde **325** did not need to be isolated.^[101-103] Methyl enones were shown to be isolated, however there were no reported examples of nitrogen atom incorporation into the products. Alcohol **329** was heated with manganese dioxide and corresponding ylide **191** for 20 hours (*Scheme 86*).




331

332


333

334

Figure 55

$$\text{H}_2\text{N}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{OH} \xrightarrow[\text{CH}_2\text{Cl}_2, 0^\circ\text{C} - \text{RT}, 3\text{ h}]{1.05\text{ eq Reagent}, 1.05\text{ eq NEt}_3} \text{R}-\text{C}(=\text{O})-\text{NH}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{OH}$$

330 **337 - 340**

Table 16

66

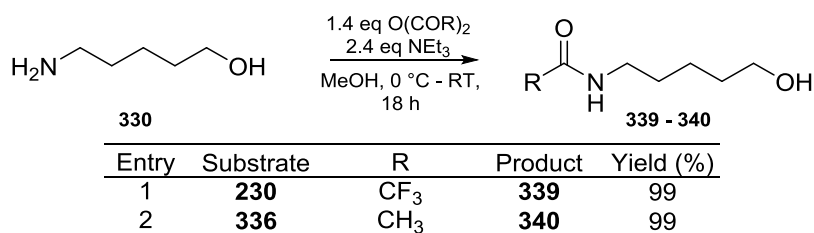


Table 17

Both reactions gave quantitative yield of the desired amides. Alcohols **337** - **340** were then reacted with ylide **191** using the conditions previously described (*Table 18*).

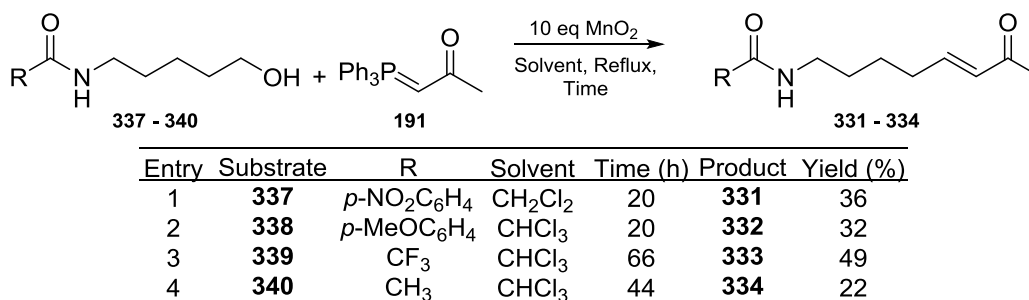


Table 18

Chloroform was found to be a better reaction solvent for alcohols **338** - **339** enabling increased reaction temperatures to improve isolated yields (*Entries 2* - *4*). Three further amides **331** - **333** were desired for investigation but were unsuitable for synthesis via this route (*Figure 56*). This included a cyanamide **343**, a group that had not been previously investigated in these types of conjugate addition.

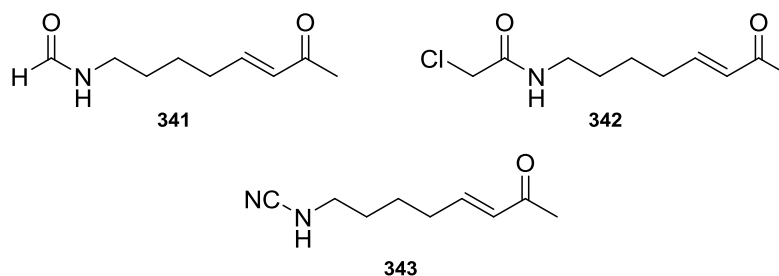
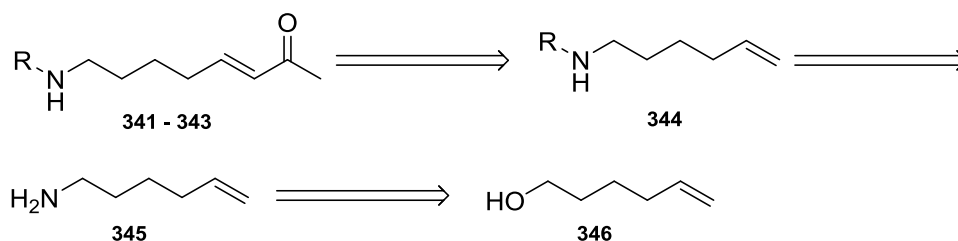


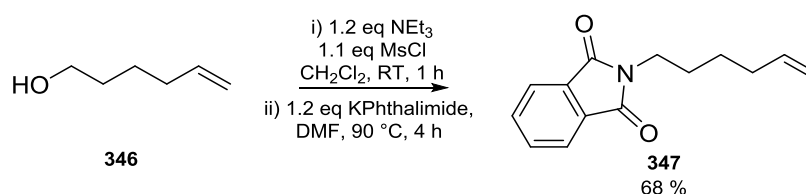
Figure 56

A new retrosynthetic analysis was performed (*Scheme 87*). Enones **341** - **343** could be synthesised by cross metathesis from terminal alkene **344**. This can be synthesised from hex-5-en-1-amine **345** by *N*-functionalisation. However, this amine is not commercially available so would need to be synthesised from hex-5-en-1-ol **346**.



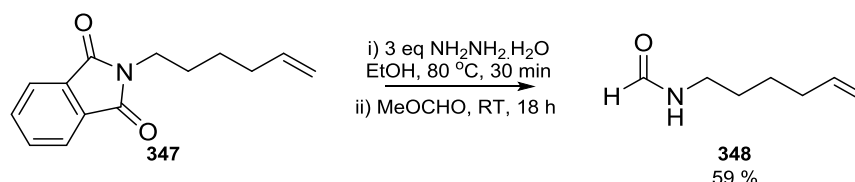
Scheme 87

The literature showed difficulties in isolating amine **345** due to its high volatility so would be best used *in situ* for the acylation step. Hex-5-en-1-ol **346** was first converted to the mesylate and then displaced with potassium phthalimide to generate functionalised phthalimide **347** in good yield using conditions previously described in the literature (Scheme 88).^[105]



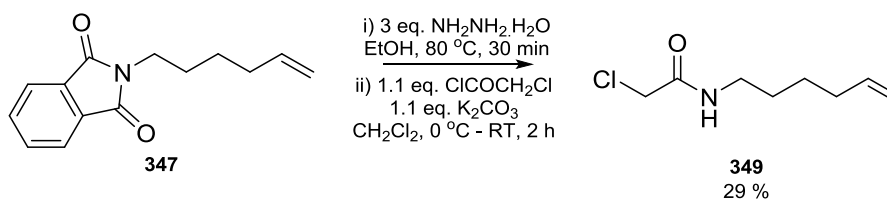
Scheme 88

Alkene **347** was then deprotected according to conditions previously described in the literature and the crude amine isolated after extraction with dichloromethane.^[105] The crude amine, dissolved in dichloromethane, was then mixed directly with methyl formate and stirred overnight to yield formamide **348** in good yield (Scheme 89).



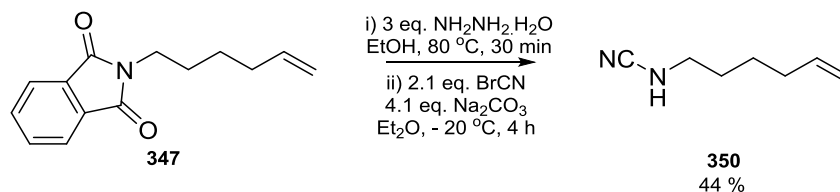
Scheme 89

Alkene **347** was then converted to amide **349** by removal of the phthalimide group by the conditions previously described, followed by alkylation using conditions previously described in the literature (Scheme 90).^[106]



Scheme 90

Finally cyanamide **350** was synthesised. Alkene **347** was deprotected and the crude amine reacted with cyanogen bromide using conditions previously described in the literature (Scheme 91).^[107] The reaction temperature had to be controlled very carefully, with any increase leading to unwanted formation of byproduct **351** (Figure 57).



Scheme 91

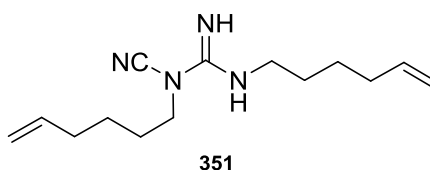
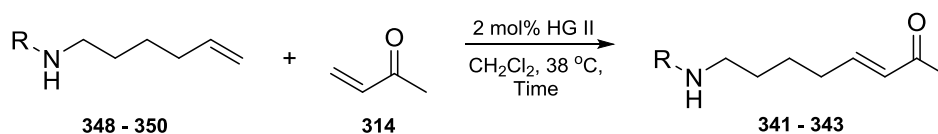


Figure 57

Terminal alkenes **348** - **350** were then converted to the corresponding enones by cross metathesis with methyl vinyl ketone **314** as previously discussed (Table 19). Enones **341** and **342** were isolated in excellent yield, but enone **343** was isolated in poor yield with majority of starting material recovered (60 %). After several repeats this was the highest isolated yield, but the recovered starting material could be used in the cross metathesis reaction meaning enough material could be isolated to investigate in the cyclization step.

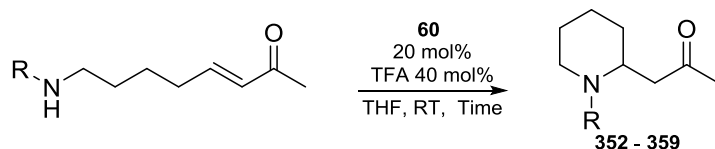


Entry	Substrate	R	Time (h)	Product	Yield (%)
1	348	CHO	2	341	81
2	349	COCH_2Cl	1	342	72
3	350	CN	1	343	28

Table 19

2.5.1.2 Optimisation of Cyclization Conditions

All eight amides were now available and their cyclizations could be investigated (Table 20). The previously reported literature conditions for this type of cyclization were used.^[73]

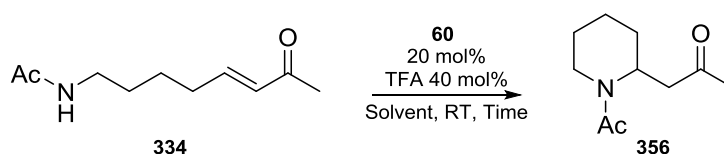


Entry	Substrate	R	Time (h)	Product	Yield (%)	E.e. (%) ¹
1	324	PhCO	120	352	0	-
2	331	<i>p</i> -NO ₂ C ₆ H ₄ CO	120	353	0	-
3	332	<i>p</i> -OMeC ₆ H ₄ CO	120	354	0	-
4	333	CF ₃ CO	120	355	0	-
5	334	Ac	18	356	50	86
6	341	CHO	144	357	81	78
7	342	COCH ₂ Cl	120	358	0	-
8	343	CN	18	359	89	64

¹ Determined by Chiral HPLC

Table 20

Amides **324**, **331** and **332** showed no product formation by ¹H NMR analysis after prolonged reaction times (*Entries 1 - 3*). This may be due to reduced nucleophilicity of the nitrogen caused by the conjugation between the amide and aromatic group. Amides **333** and **342** did not cyclize possibly due to the deactivation of the nitrogen by the adjacent electron-withdrawing group on the amide (*Entries 4 and 7*). Acetyl **334** and formyl **341** amides cyclized with a large difference in reaction times due to the reduced nucleophilicity of the formamide group (*Entries 5 and 6*). Cyanamide **343** cyclized in high yield but with modest enantioselectivity (*Entry 8*). Acetyl **334** was taken forward for solvent screening as it had the fastest reaction time and highest enantioselectivity. Acetyl **287** was cyclized with the same catalyst system in ten different solvents (*Table 21*).



Entry	Solvent	Time (h)	Conversion (%) ¹	E.e. (%) ²
1	CHCl ₃	24	>95	88
2	CH ₂ Cl ₂	24	>95	80
3	EtOAc	46	>95	82
4	IPA	144	82	21
5	MeCN	96	>95	10 ³
6	MeOH	144	<10	-
7	PhMe	96	>95	66
8	THF	24	>95	86
9	CO(OEt) ₂	46	>95	89
10	2-MeTHF	46	>95	90

¹ Measured by ¹H NMR ² Determined by Chiral HPLC ³ Opposite enantiomer

Table 21

Methanol gave no conversion to product after a prolonged reaction time (*Entry 6*). The other alcohol investigated, 2-propanol, gave poor enantioselectivity (21 % ee) and slow

reaction rate (*Entry 4*). Acetonitrile was the only solvent to yield the opposite enantiomer in very poor enantioselectivity (*Entry 5*). This suggests that the solvent may be able to influence the reaction to proceed via a different reaction pathway to yield the opposite enantiomer. Toluene gave a much lower enantioselectivity than expected for this type of reaction (*Entry 7*). All other solvents investigated gave high enantioselectivity with the highest being 2-MeTHF (*Entry 10*). This result was taken forward to investigate the effect of temperature on the reaction (*Table 22*).

Entry	Temp (°C)	Time (h)	Conversion (%) ¹	E.e. (%) ²
1	10	336	>95	86
2	20	48	>95	90
3	30	27	>95	89

¹ Measured by ¹H NMR ² Determined by Chiral HPLC

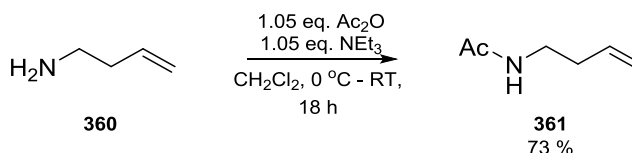
Table 22

The highest enantioselectivity was achieved at 20 °C, increasing or decreasing temperature from this was detrimental to enantioselectivity. With the optimized conditions found we wished to investigate the scope of the reaction with respect to ring size and substitution on the enone.

2.5.1.3. Investigation of Substrate Scope

First we investigated ring size as there has been few reported examples of these in the literature.^[73,90,91] The ring sizes we chose to investigate were four, five and seven membered rings.

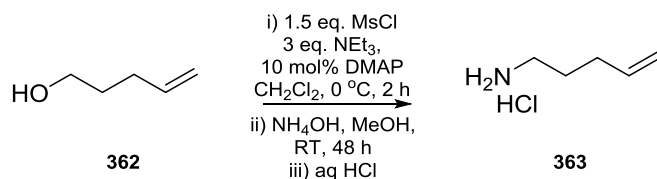
The four and five membered cyclization enone precursors were synthesised from the corresponding amines. For the four membered precursor, 3-but-1-enamine **360** was acylated with acetic anhydride (*Scheme 92*).



Scheme 92

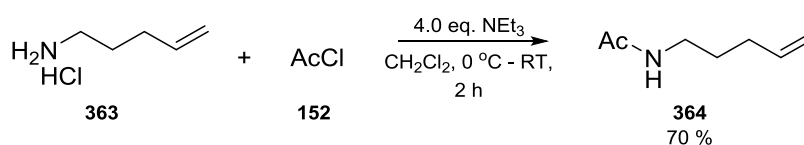
Unfortunately 4-penten-1-amine was not commercially available and too volatile to use with the previous method used for 5-hexen-1-amine **345**. Instead hydrochloride salt **363** was synthesised using conditions previously described in the literature. Salt **363** was synthesised by displacement of the corresponding mesylate with concentrated aqueous

ammonia solution and concentration of the crude reaction mixture from aqueous hydrochloric acid (Scheme 93).^[108]



Scheme 93

After concentration, salt **363** was isolated crude and not purified further. Crude salt **363** was used in excess with acetyl chloride **152** to yield amide **364** (Scheme 88).



Scheme 94

With functionalised terminal alkenes **361** and **364** available, enones **365** and **366** could be synthesised by cross metathesis with methyl vinyl ketone **314** (Table 23).

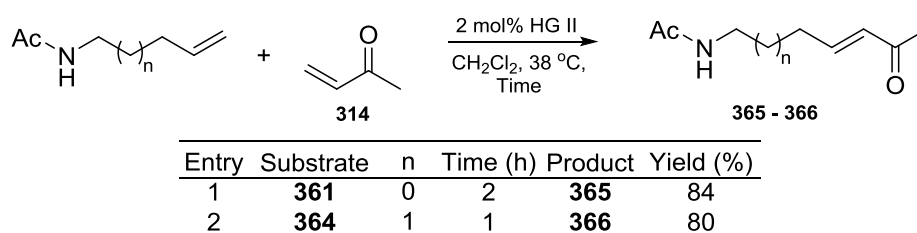
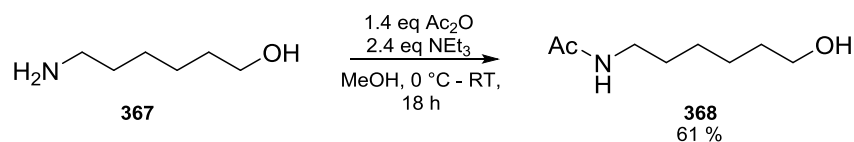


Table 23

The seven membered ring precursor was synthesised by the route previously discussed for the six membered compound, with the first step being *N*-functionalisation of the aminoalcohol **367** (Scheme 95).



Scheme 95

Alcohol **368** was then converted to enone **369** using conditions previously described (Scheme 96).


$$\text{Ac-NH-CH}_2\text{-(CH}_2\text{)}_n\text{-CH}_2\text{-CH=CH-C(=O)CH}_3 \xrightarrow[\text{2-MeTHF, 20 } ^\circ\text{C, Time}]{\begin{array}{c} \text{60} \\ \text{20 mol\%} \\ \text{TFA 40 mol\%} \end{array}} \text{Ac-N(CH}_2\text{)}_n\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-C(=O)CH}_3$$
¹ Determined by Chiral HPLC ² Performed with 20 mol% TFA

Table 24

With the ring size studied, the substitution on the enone was studied next. The six membered ring was chosen for study as the most optimisation had been carried out on this compound. Two enones were chosen for investigation, ethyl and phenyl (*Figure 58*). The ethyl group was chosen to study how the chain extension would affect the rate and enantioselectivity of the cyclization reaction. The phenyl group was chosen to see the effect of a bulkier group and if the extended conjugation would affect the cyclization.

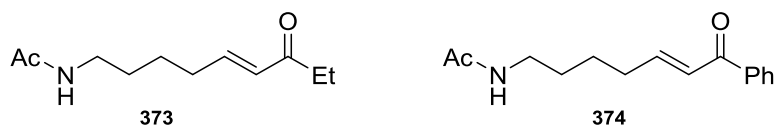
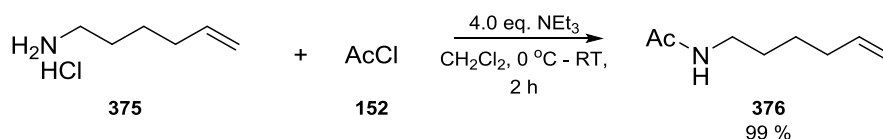


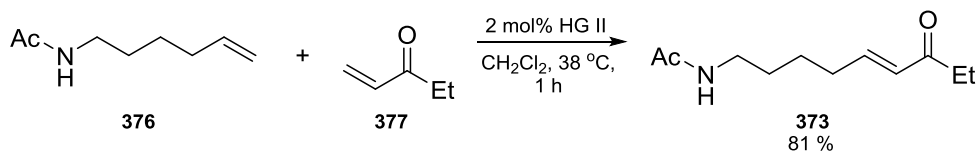
Figure 58

The corresponding Wittig reagent was not available to synthesise enone **373** by the Wittig route previously discussed, so it was decided to synthesise it by the metathesis route previously used for the five membered compounds. Salt **375** had been synthesised previously by another group member, using the same route used previously, and was acylated with acetyl chloride **152** to give alkene **376** in quantitative yield (*Scheme 97*).



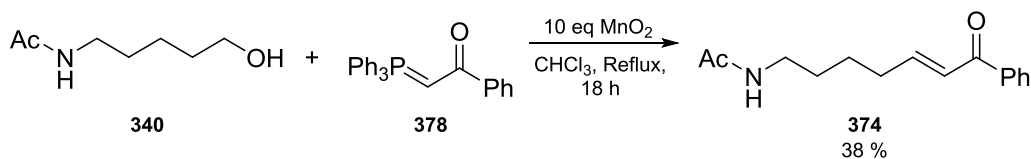
Scheme 97

Enone **329** was converted to ethyl enone **326** with ethyl vinyl ketone **330** using conditions previously described in high yield (*Scheme 92*).



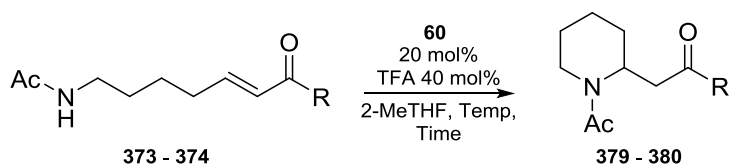
Scheme 98

Enone **327** was synthesised from alcohol **293** using the conditions previously discussed with ylide **331** (*Scheme 99*).



Scheme 99

With enones **373** and **374** available they could be investigated under the optimized cyclization conditions (*Table 25*).



Entry	Substrate	R	Time (h)	Temp (°C)	Product	Yield (%)	E.e. (%) ¹
1	373	Et	120	20	379	75	93
2	374	Ph	72	50	380	78	78

¹ Determined by Chiral HPLC

Table 25

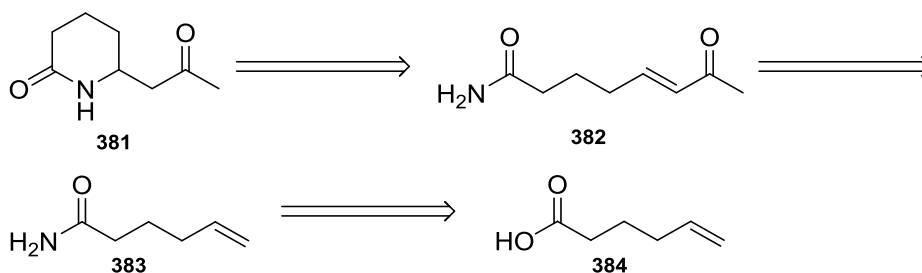
Enones **373** and **374** cyclized at a much slower rate than the methyl enone (48 h), this may be due to a bad steric interaction with the catalyst slowing the rate of reaction. In spite of the decreased yield and rate of reaction enone **373** achieved a higher enantioselectivity than the methyl derivative (90 % ee) (*Entry 1*). Enone **374** was heated at 50 °C to increase the rate of reaction due to the unreactive nature of the conjugated enone in forming an iminium species, it cyclized with decreased enantioselectivity (*Entry 2*).

With the scope of the acetyl group investigated it was envisioned that making the amide part of the ring may be possible. This would yield a secondary amide that can be functionalised in further steps.

2.5.2 Lactam Substrates

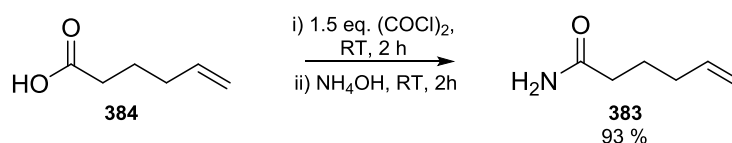
2.5.2.1 Synthesis of δ -Lactam Cyclization Precursor

We decided to investigate the six membered ring as it had given the highest enantioselectivity. Desired δ -lactam **381** could be synthesised in three steps from commercially available **384** (*Scheme 100*).



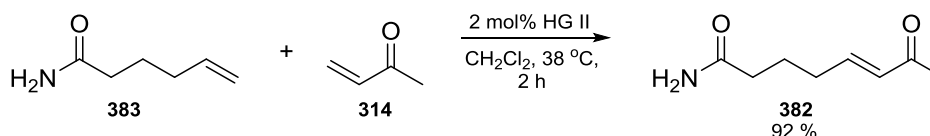
Scheme 100

The first step was generation of primary amide **383** from acid **384**. This was achieved by conversion to the acid chloride using conditions previously described in the literature and reacted with concentrated aqueous ammonia to give desired amide **383** in excellent yield (*Scheme 101*).^[109]



Scheme 101

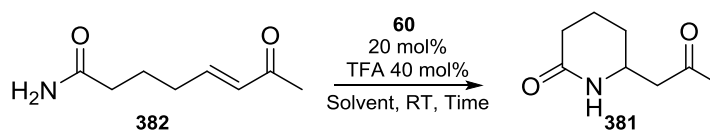
Amide **383** was reacted with methyl vinyl ketone **314** using conditions previously described to generate enone **382** in excellent yield (*Scheme 102*).



Scheme 102

2.5.2.2. Optimisation of Cyclization Conditions

With enone **382** available the cyclization conditions could be investigated, first was the screening of the reaction solvent (*Table 26*).

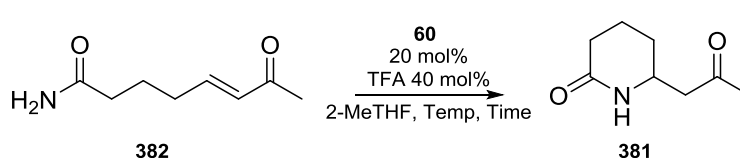


Entry	Solvent	Time (h)	Conversion (%) ¹	E.e. (%) ²
1	CHCl ₃	22	>95	95
2	CH ₂ Cl ₂	19	>95	95
3	EtOAc	19	>95	93
4	IPA	96	>95	72
5	MeCN	96	>95	72
6	MeOH	144	<10	-
7	PhMe	19	>95	87
8	THF	22	>95	96
9	CO(OEt) ₂	144	91	94
10	2-MeTHF	22	>95	95

¹ Measured by ¹H NMR ² Determined by Chiral HPLC

Table 26

The reaction worked in all solvents with the exception of methanol which gave no conversion to product after prolonged reaction time (*Entry 6*). Diethyl carbonate required a prolonged reaction time to get almost complete conversion but still gave a high enantioselectivity (*Entry 9*). 2-Propanol and acetonitrile gave lower enantioselectivities after prolonged reaction times (*Entries 4 and 5*). All other solvents gave complete conversion with similar reaction times with THF yielding the highest enantioselectivity (*Entry 8*). The reaction temperature was then investigated with THF as the solvent (*Table 27*).



Entry	Temp (°C)	Time (h)	Conversion (%) ¹	E.e. (%) ²
1	10	120	>95	92
2	20	22	>95	95
3	30	22	>95	93

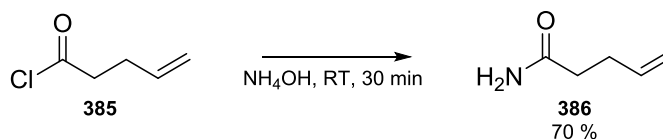
¹ Measured by ¹H NMR ² Determined by Chiral HPLC

Table 27

The highest enantioselectivity found was at 20 °C with changes in temperature found only to diminish enantioselectivity. With the optimized conditions found we wished to investigate the scope of the reaction with respect to ring size and substitution on the enone.

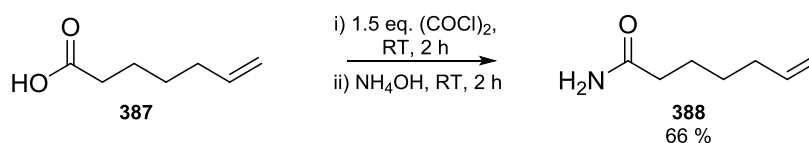
2.5.2.3. Investigation of Substrate Scope

First we investigated the five and seven membered rings. For the five membered ring, acid chloride **385** was converted to primary amide **386** using concentrated aqueous ammonia solution (*Scheme 103*).



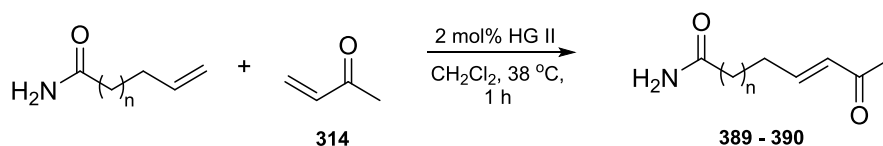
Scheme 103

For the seven membered synthesis, acid **387** was converted to primary amide **388** using conditions previously discussed for the six membered compound (*Scheme 104*).



Scheme 104

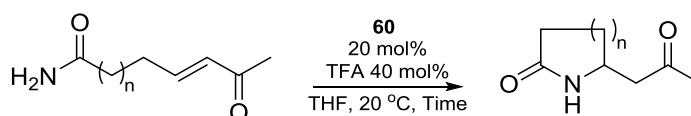
Alkenes **386** and **388** were reacted with methyl vinyl ketone **314** using the conditions previously used to yield enones **389** and **390** (*Table 28*).



Entry	Substrate	n	Product	Yield (%)
1	386	1	389	63
2	388	3	390	90

Table 28

With both enones available they were investigated with the optimised reaction conditions along with enone **334** for comparison (*Table 29*).

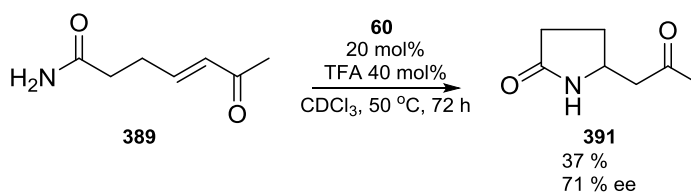


Entry	Substrate	n	Time (h)	Product	Yield (%)	E.e. (%) ¹
1	389	1	120	391	0	-
2	382	2	22	381	90	95
3	390	3	120	392	0	-

¹ Determined by Chiral HPLC

Table 29

Unfortunately enones **389** and **390** did not cyclize after prolonged reaction times (*Entries 1 and 3*). However enone **389** did cyclize in deuterated chloroform with an elevated reaction temperature of 50 °C, the isolated yield was low with only 40 % conversion observed by ¹H NMR analysis (*Scheme 99*).



Scheme 105

With the ring size studied, the enone substitution was studied next. The two enone substitutions previously investigated were chosen, ethyl and phenyl (*Figure 59*).

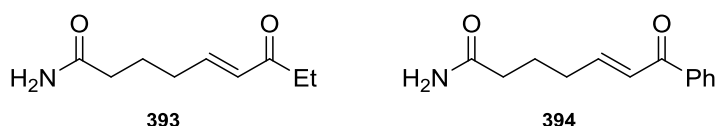


Figure 59

Enones **393** and **394** were synthesised from terminal alkene **383** using conditions previously described (Table 30).

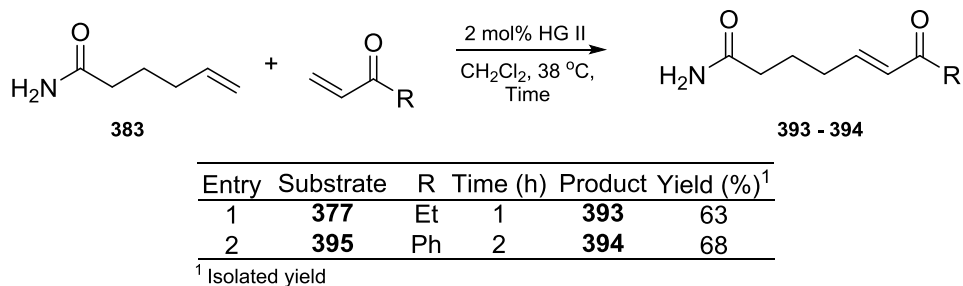


Table 30

Enones **393** and **394** were obtained in modest yield and were subjected to the optimized reaction conditions (Table 31).

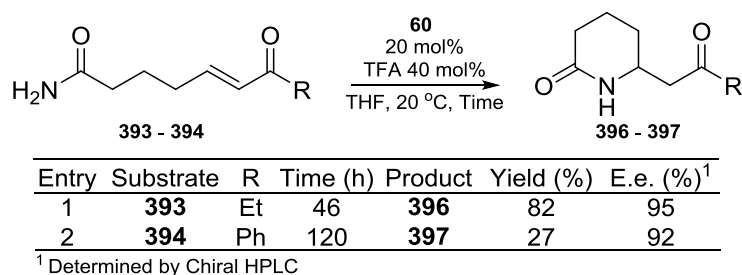


Table 31

Enones **393** and **394** required prolonged reaction times, with enone **394** only giving a 35 % conversion by ¹H NMR analysis. The enantioselectivities for both enones were comparable to that of the methyl enone (95 % ee).

We have found that amides perform the cyclization with iminium catalysis using 9-deoxy-9-*epi*-aminoquinine **60** for both five and six membered rings in high enantioselectivities (71 - 95 % ee). We have also discovered we can have the amide group on the outside of the ring formed or inside to form 6-substituted δ -lactams. Unfortunately four and seven membered rings do not perform the addition in any case possibly due to ring strain and entropic penalties. With the reaction scope of the amide now investigated it was decided to study if sulfonamides would cyclize under similar reaction conditions.

2.6 Sulfonamide Substrates

2.6.1 Synthesis of Sulfonamide Cyclization Precursors

It was decided to investigate three different sulfonamides and how they affect the reaction with the most studied ring size and enone substitution (Figure 60).

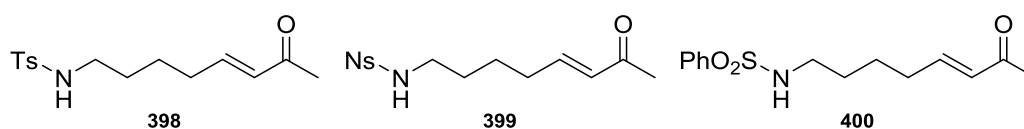
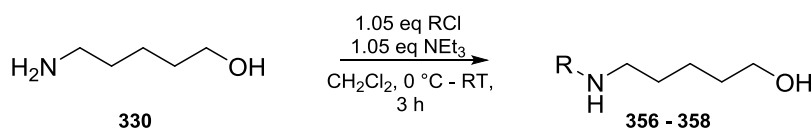


Figure 60

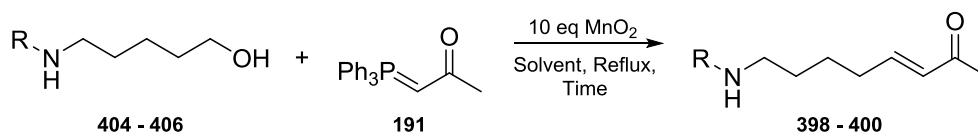
Enones **398** - **400** were synthesised in two steps from 5-aminopentan-1-ol **330**, first the nitrogen was functionalised using the corresponding sulfonyl chloride (*Table 32*). The yields were lower than expected due to di-substitution on the nitrogen.



Entry	Substrate	R	Product	Yield (%)
1	401	Ts	404	78
2	402	Ns	405	63
3	403	PhSO ₂	406	75

Table 32

Alcohols **404** - **406** were converted to the desired enones using conditions previously described (*Table 33*). Phenyl sulfonamide **406** required higher reaction temperature and prolonged heating in chloroform (*Entry 3*).

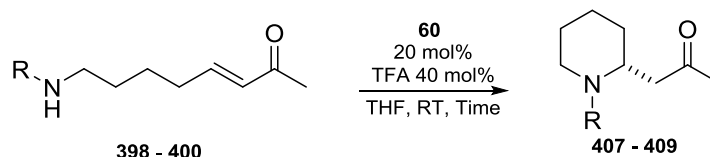


Entry	Substrate	R	Solvent	Time (h)	Product	Yield (%)
1	404	Ts	CH ₂ Cl ₂	20	398	38
2	405	Ns	CH ₂ Cl ₂	20	399	41
3	406	PhSO ₂	CHCl ₃	44	400	45

Table 33

2.6.2 Optimisation of Cyclization Conditions

With the three sulfonamides available the cyclization could now be investigated using the previously used reaction conditions (*Table 34*).

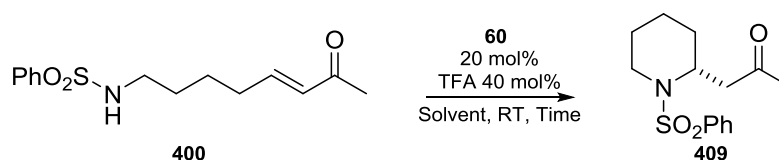


Entry	Substrate	R	Time (h)	Product	Yield (%)	E.e. (%) ¹
1	398	Ts	22	407	90	88
2	399	Ns	46	408	92	89
3	400	PhSO ₂	22	409	90	92

¹ Isolated yield ² Determined by Chiral HPLC

Table 34

All three sulfonamides **398** - **400** cyclized under the reaction conditions. Nosyl substrate **399** cyclized at a slower rate than the other two enones, possibly due to the reduced nucleophilicity of the nitrogen because of the electron-withdrawing nitro group (*Entry 2*). The best result found, phenyl sulfonamide **400**, was taken forward for solvent investigation (*Table 35*).

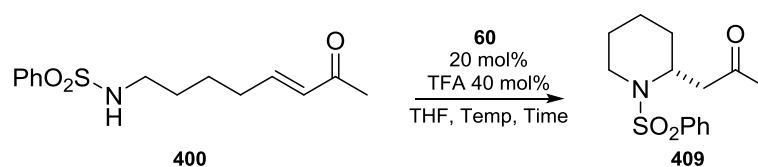


Entry	Solvent	Time (h)	Conversion (%) ¹	E.e. (%) ²
1	CHCl ₃	19	>95	84
2	CH ₂ Cl ₂	19	>95	91
3	EtOAc	29	>95	89
4	IPA	29	>95	64
5	MeCN	96	>95	29
6	MeOH	120	52	38 ³
7	PhMe	29	>95	86
8	THF	19	>95	92
9	CO(OEt) ₂	29	>95	89
10	2-MeTHF	29	>95	87

¹ Measured by ¹H NMR ² Determined by Chiral HPLC ³ Opposite enantiomer

Table 35

Sulfonamide **400** cyclized in all solvents with methanol yielding the opposite enantiomer with a prolonged reaction time and poor enantioselectivity (*Entry 6*). Acetonitrile and 2-propanol gave much poorer enantioselectivities than other solvents investigated (*Entries 4 and 5*). The best enantioselectivity found was THF in one of the quickest reaction times and this was used in further reactions. The temperature of the reaction was now investigated (*Table 36*).



Entry	Temp (°C)	Time (h)	Conversion (%) ¹	E.e. (%) ²
1	10	120	>95	88
2	20	22	>95	93
3	30	8	>95	95

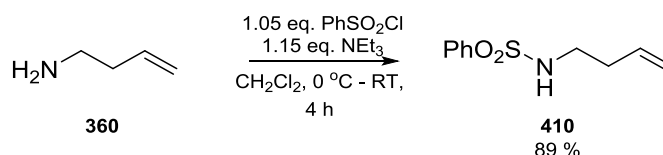
¹ Measured by ¹H NMR ² Determined by Chiral HPLC

Table 36

It was found increasing the reaction temperature increased both the rate and enantioselectivity with the best result being 30 °C (*Entry 3*). With the optimized conditions found we wanted to investigate the scope of the reaction with respect to ring size and substitution on the enone.

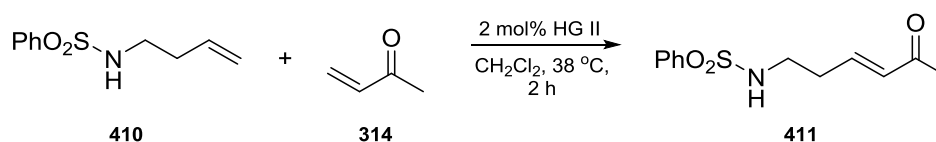
2.6.3 Investigation of Substrate Scope

First we investigated the four, five and seven membered rings. The five membered cyclization precursor had been synthesised previously by another member of the group using methodology previously described so was available. The four membered cyclization precursor was synthesised in two steps. The first step was reaction of 3-buten-1-amine **360** with benzenesulfonyl chloride in high yield (*Scheme 106*).



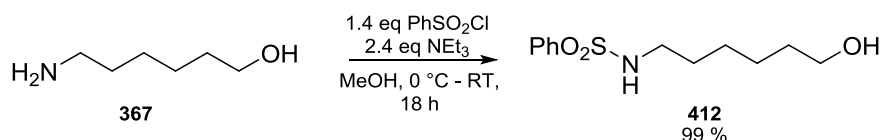
Scheme 106

Alkene **410** was then converted to enone **411** using the conditions previously described with methyl vinyl ketone **314** (*Scheme 101*).



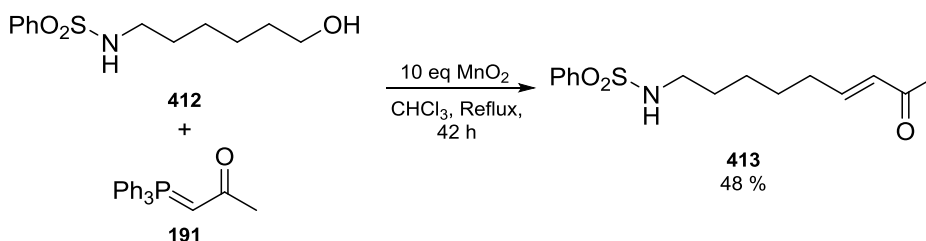
Scheme 107

The seven membered ring was synthesised using the same methodology used for the acetyl compound with the first step being *N*-functionalisation of aminoalcohol **367** with benzenesulfonyl chloride (*Scheme 108*).



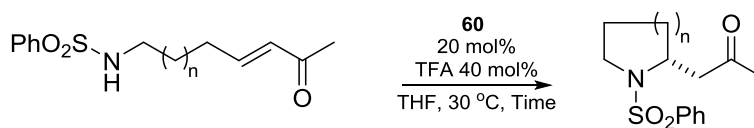
Scheme 108

Alcohol **412** was then converted to enone **413** using conditions previously described (Scheme 109).



Scheme 109

The enones could then be investigated in the optimized reaction conditions. Enone **400** was repeated to obtain an isolated yield and for comparison to the other cyclizations (Table 37).



Entry	Substrate	n	Time (h)	Product	Yield (%)	E.e. (%) ¹
1	411	0	48	415	0	-
2	414	1	5	416	96	86
3	414	1	8	416	92	94 ²
4	400	2	8	409	93	95
5	413	3	48	417	0	-

¹ Determined by Chiral HPLC ² Performed with 20 mol% TFA

Table 37

The four and seven membered enone precursors **411** and **413** showed no sign of cyclization, like the acetyl compounds previously studied, after 48 hours by ¹H NMR analysis (Entries 1 and 5). Five membered enone precursor **414** cyclized very rapidly but in a decreased enantioselectivity to that of six membered enone **400** (Entries 2 and 4). Lowering the acid additive to 20 mol% gave cyclised product **416** in a similar enantioselectivity to that of the six membered ring (Entry 3).

With the ring size studied, the enone substitution was studied next. The six membered ring was again chosen for study as most optimisation had been carried out on this compound. The previously investigated enone substitutions were chosen, ethyl and phenyl (Figure 61).

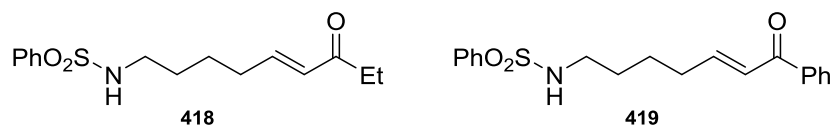
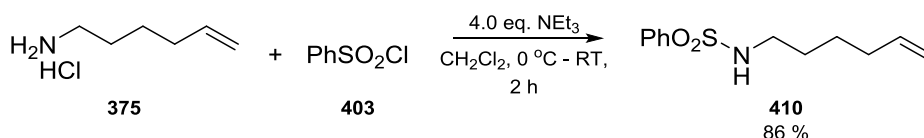


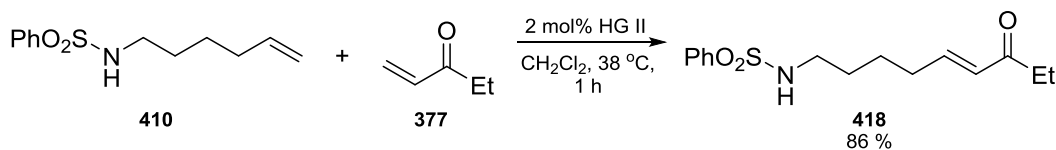
Figure 61

Enones **418** and **419** using the methodology previously discussed with the acetyl derived compounds. First salt **375** was reacted with benzenesulfonyl chloride **403** to give desired alkene **410** in high yield (*Scheme 110*).



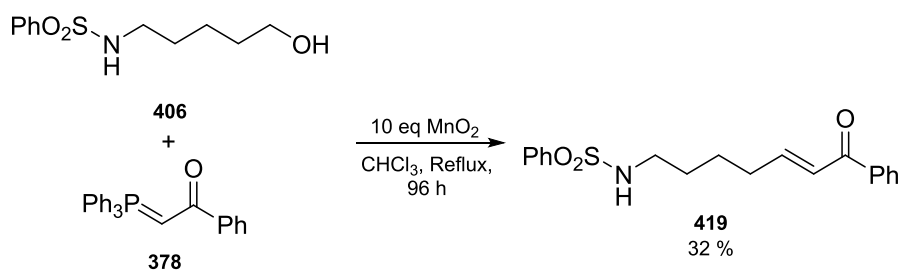
Scheme 110

Enone **410** was subjected to the cross metathesis conditions used previously, using ethyl vinyl ketone **377** to generate ethyl enone **418** in good yield (*Scheme 111*).



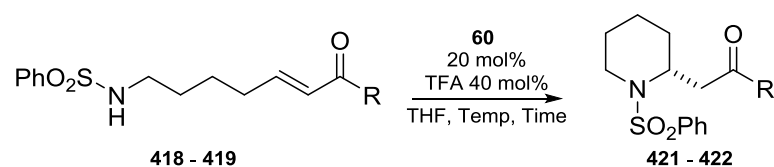
Scheme 111

Enone **419** was synthesised from alcohol **406** with ylide **378** using conditions previously described (*Scheme 112*). This required a longer reaction time than other examples and the product proved difficult to separate from other compounds, requiring two purifications by silica chromatography.



Scheme 112

Enones **331** and **332** were now investigated under the cyclization conditions used previously (*Table 38*).



Entry	Substrate	R	Time (h)	Temp (°C)	Product	Yield (%)	E.e. (%) ¹
1	418	Et	8	30	421	85	97
2	419	Ph	72	50	422	58	92

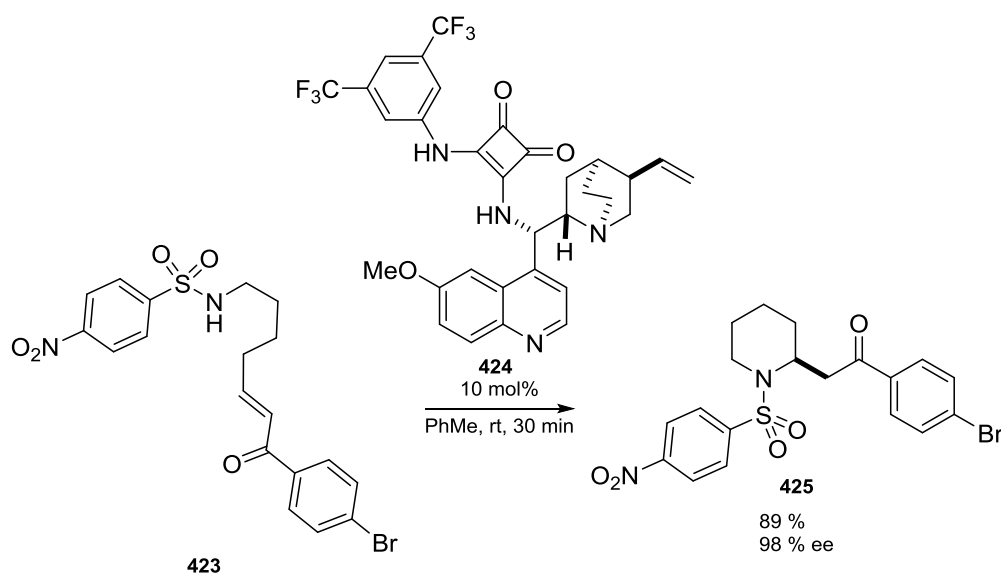
¹ Determined by Chiral HPLC

Table 38

Enone **418** cyclized at the same rate as that of the methyl enone with a reduced yield but higher enantioselectivity (*Entry 1*). Enone **419** was heated at 50 °C, as with acetyl compound **374**, and cyclized with similar enantioselectivity (90 % ee) (*Entry 2*). There was a reduced isolated yield with only ~65 % conversion observed by ¹H NMR analysis even after prolonged reaction time. These results showed that the sulfonamide group was better than the acetyl group when changing the substitution on the enone maintaining high enantioselectivities in both cases. Again the four and seven membered rings did not cyclize.

2.6.4 Determination of Absolute Stereochemistry

Unfortunately, the cyclised products were found to be oils. In order to prove the stereochemistry of the product we again needed an X-ray structure of a derivative. Another group member, Chris Davison, performed the intramolecular cyclization of enone **423** using quinine derived squaramide catalyst **424** to yield compound **425** (*Scheme 113*).^[110] This compound was found to be a crystalline solid and an X-ray crystal structure confirmed the (S)-stereocentre formed (*Figure 62*).^[110]



Scheme 113

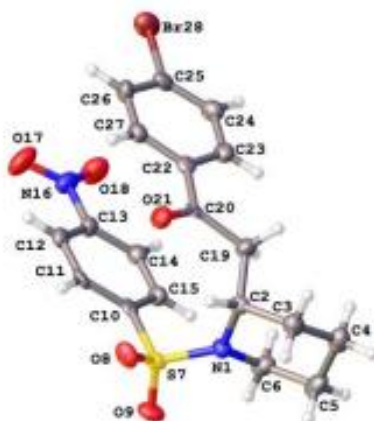


Figure 62

Also synthesised by this method was cyclized compound **422** which we can compare the optical rotation data to. For cyclization with squaramide catalyst **424** the optical rotation is -37.0 (c 0.8, CHCl_3 , 99 % ee)^[90] and for 9-deoxy-9-*epi*-aminoquinine **60** is $+27.6$ (c 0.9, CHCl_3 , 92 % ee). We can see that they are opposite and so the stereocentre formed with catalyst **60** is (R). This is confirmed by having different major enantiomers by chiral HPLC. With the functional group on nitrogen investigated, it was thought to study heteroatom substitution in the ring with the view to making the molecules more drug-like compounds.

2.7 Substitution of Heteroatoms into Substrates

2.7.1 1,2-Oxazinanane Substrates

2.7.1.1. Synthesis of Cyclization Precursor

The easiest positions to substitute for synthesis were the two and four positions of the piperidine ring. The first compound chosen for investigation was enone **426** which would lead to 3-substituted 1,2-oxazinanane **427** (Figure 63). The highest enantioselectivity reported for iminium catalyzed six membered piperidine ring formations was when the *tert*-butoxy group (Boc) was used on nitrogen so this group was chosen for this study.^[73,85]

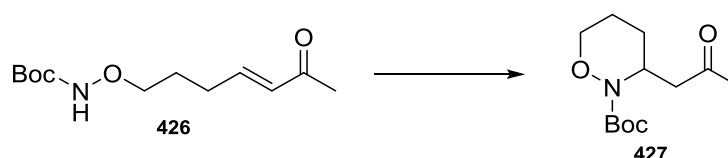
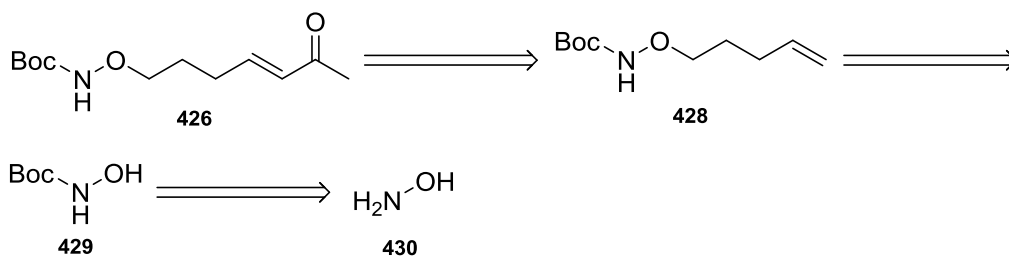


Figure 63

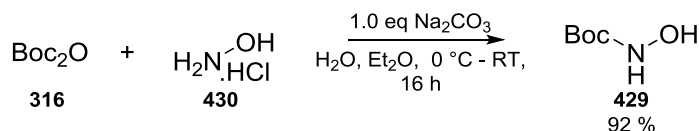
The retrosynthetic analysis for enone **426** was carried out and could be synthesised in three steps from commercially available materials (Scheme 114). Hydroxylamine **430**

can be selectively protected on the nitrogen with di-*tert*-butyl dicarbonate. The resulting product **429** can then be alkylated with 5-bromopent-1-ene. Alkene **428** can then undergo cross metathesis with methyl vinyl ketone to generate desired enone **426**.



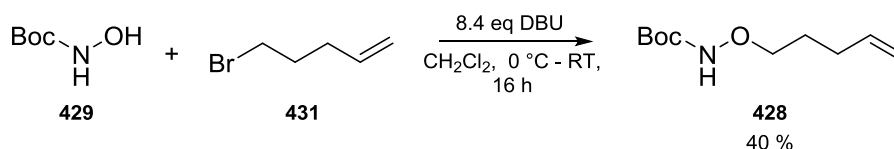
Scheme 114

First hydroxylamine **430** was reacted with di-*tert*-butyl dicarbonate **316** using conditions previously reported in the literature to give the *N*-substituted compound exclusively in high yield (Scheme 115).^[111]



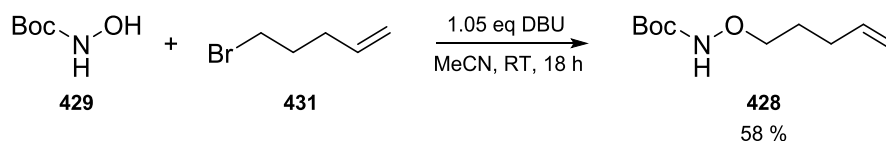
Scheme 115

Compound **429** was then alkylated with 5-bromopent-1-ene **431** using conditions previously reported in the literature (Scheme 116).^[112] The reaction gave a complex mixture and after purification by silica chromatography, alkene **428** was obtained in a lower yield than reported (60 %).



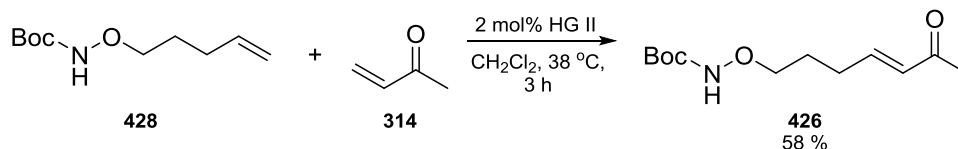
Scheme 116

However this chemistry did not perform well on larger scale giving mixed yields and various impurities, the reaction was changed to using a much lower ratio of reagents (Scheme 117). This chemistry proved to be more reproducible on a larger scale giving higher isolated yields.



Scheme 117

Alkene **428** was then reacted with methyl vinyl ketone **314** using the conditions previously described to give enone **426** (Scheme 118).

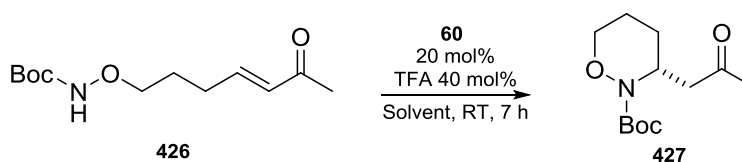


Scheme 118

Enone **426** was now available in large enough quantity for the cyclization conditions to be investigated.

2.7.1.2. Optimisation of Cyclization Conditions

Enone **426** was cyclized using the conditions previously discussed, first the reaction solvent was investigated (Table 39). The stereochemistry was confirmed by comparison with of the optical rotation with literature data.^[95]



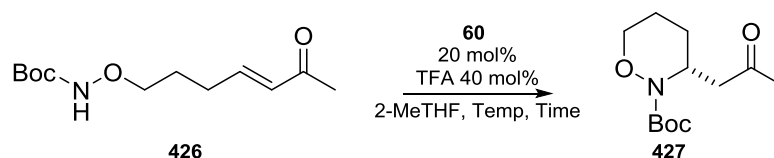
Entry	Solvent	Conversion (%) ¹	E.e. (%) ²
1	CHCl ₃	>95	86
2	CH ₂ Cl ₂	>95	94
3	EtOAc	>95	93
4	IPA	90	51
5	MeCN	80	58
6	MeOH	>95	16 ³
7	PhMe	>95	96
8	THF	87	96
9	CO(OEt) ₂	92	94
10	2-MeTHF	>95	96

¹ Measured by ¹H NMR ² Determined by Chiral HPLC

³ Opposite enantiomer

Table 39

Enone **426** cyclized to desired compound **427** in all solvents investigated and was stirred for seven hours to allow direct comparison of the reaction rate. Four solvents showed a slower rate 2-propanol, acetonitrile, tetrahydrofuran and diethyl carbonate (*Entries 4, 5, 8 and 9*). Methanol gave the lowest enantioselectivity with the opposite enantiomer isolated (*Entry 6*). All other solvents gave high enantioselectivities and 2-methyltetrahydrofuran was chosen as the reaction solvent due to its use in industry as a green solvent (*Entry 10*).^[113] With the best solvent found, the temperature of the reaction was investigated (*Table 40*).



Entry	Temp (°C)	Time (h)	Conversion (%) ¹	E.e. (%) ²
1	10	42	>95	93
2	20	9	>95	97
3	30	5	>95	95

¹ Measured by ¹H NMR ² Determined by Chiral HPLC

Table 40

The best temperature found was 20 °C with changes in this temperature found only to lower enantioselectivity. With the optimized conditions found we wished to investigate the scope of the reaction with respect to the functional group on the nitrogen, ring size and substitution on the enone.

2.7.1.3 Investigation of Substrate Scope

First we decided to study the group on the nitrogen, we chose three groups that had previously been reported and investigated Cbz, Ac and PhSO₂ (Figure 64).^[73,85] We wanted to investigate whether these groups would make a difference to the rate and enantioselectivity of the reaction.

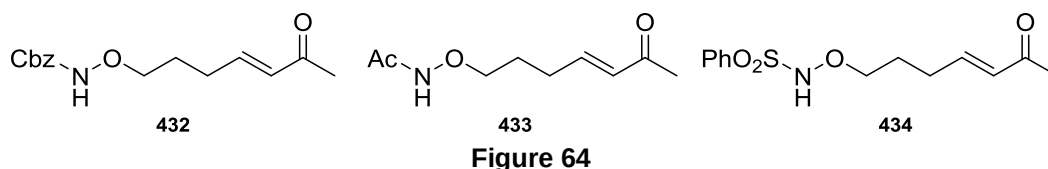
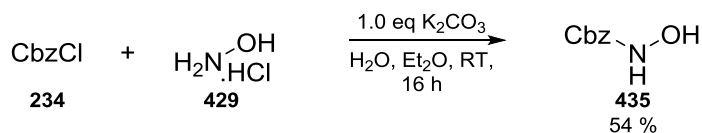


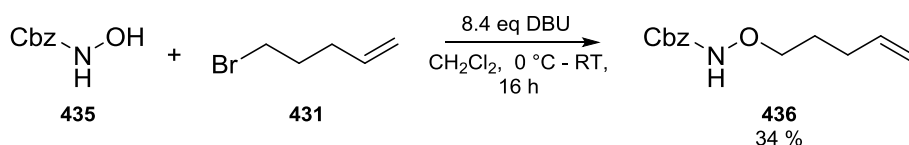
Figure 64

Enones **432** and **433** could be synthesised using the methodology previously discussed, starting with different substitution on hydroxylamine. First hydroxylamine hydrochloride **429** was reacted with benzyl chloroformate **234** using conditions previously described in the literature to yield *N*-Cbz-hydroxylamine **435** as a colourless solid (Scheme 119).^[114]



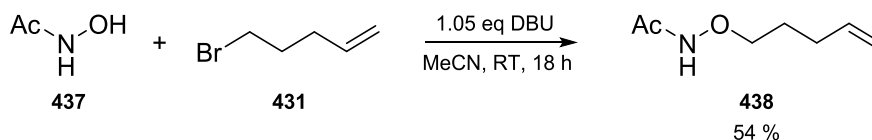
Scheme 119

This was then reacted with 5-bromopent-1-ene **431** using the first set of conditions previously discussed with *N*-Boc-hydroxylamine **429** (Scheme 120).



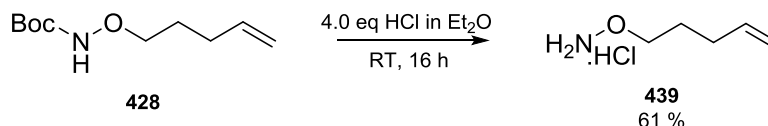
Scheme 120

Acetohydroxyamic acid **437** was commercially available and was reacted with 5-bromopent-1-ene **431** according to conditions previously described with *N*-Boc-hydroxylamine **429** (Scheme 121).



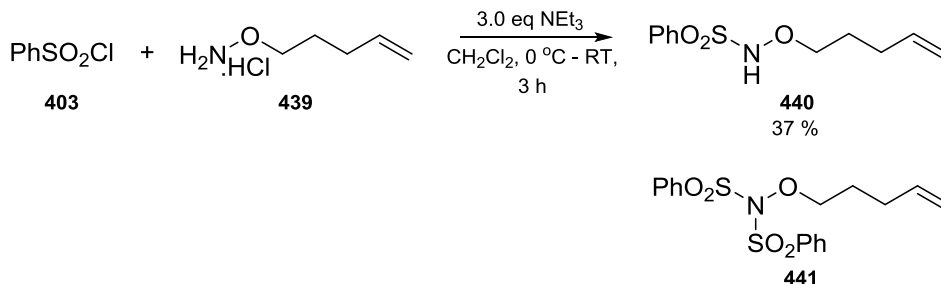
Scheme 121

The corresponding *N*-phenylsulfonamidehydroxylamine was reported in the literature but had proven difficult to isolate and purify.^[115] It was instead decided to deprotect alkene **428** and isolate the amine as the hydrochloride salt, this could then be reacted with benzenesulfonyl chloride **403** to give the desired sulfonamide. The Boc group on alkene **428** was removed with hydrochloric acid in diethyl ether, with salt **439** precipitating out of solution (Scheme 122).



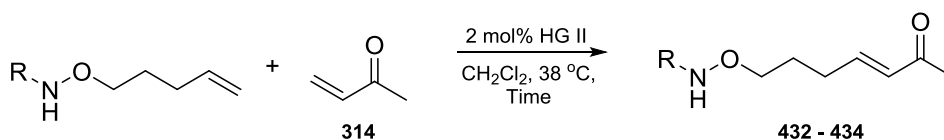
Scheme 122

Salt **439** was reacted with benzenesulfonyl chloride **403** with a low isolated yield due to problems isolating it from the byproduct, the di-substituted sulfonamide **441** (Scheme 123).



Scheme 123

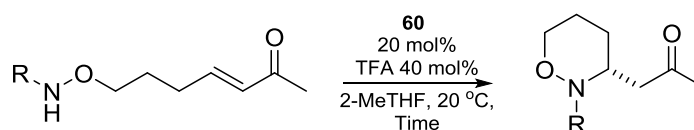
Enones **432** - **434** were then synthesised from the corresponding alkenes with methyl vinyl ketone **314** using conditions previously discussed in good yield (Table 41).



Entry	Substrate	R	Time (h)	Product	Yield (%)
1	436	Cbz	1	432	77
2	438	Ac	2	433	71
3	440	PhSO ₂	2	434	86

Table 41

With the enones now available they could be investigated with the optimised reaction conditions. Enone **426** was repeated to obtain an isolated yield and compare the rate and enantioselectivity with the other groups (*Table 42*). The stereochemistry of the products was assigned by comparison to the literature and analogy for the Ac and PhSO₂ groups.^[95]



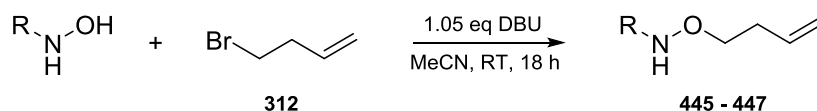
Entry	Substrate	R	Time (h)	Product	Yield (%)	E.e. (%) ¹
1	426	Boc	7	427	90	97
2	432	Cbz	22	442	90	96
3	433	Ac	22	443	92	52
4	434	PhSO ₂	22	444	92	98

¹ Determined by Chiral HPLC

Table 42

All the enones investigated cyclized under the reaction conditions with the enone **426** cyclizing at a much faster rate than the other enones (*Entry 1*). Enone **433** cyclized with a much lower enantioselectivity than the other groups investigated (*Entry 3*). This may be due to the background cyclization being much quicker than the other enones, as shown by difficulties in obtaining ¹³C NMR data without cyclized compound **433** present.

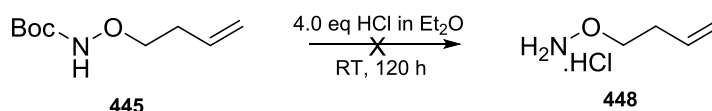
It was next decided to investigate how the ring size affects the rate and enantioselectivity with all the *N*-substituted compounds studied. First the five membered ring size was studied. The enone precursors could be synthesised using the methodology previously discussed, using 4-bromobut-1-ene **312** to give one carbon less in the enone chains. First the Boc, Cbz and acetyl substituted alkenes were synthesised using the previously discussed conditions (*Table 43*).



Entry	Substrate	R	Product	Yield (%)
1	429	Boc	445	41
2	435	Cbz	446	37
3	437	Ac	447	40

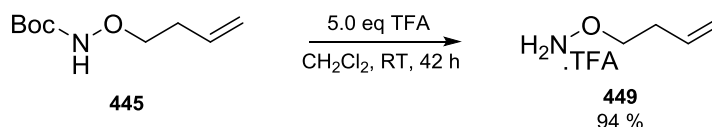
Table 43

The phenylsulfonamide was synthesised using the route previously discussed with the first step being removal of the Boc group of alkene **445** (Scheme 124). However the conditions used previously failed to give any conversion to product possibly due to a bad batch of hydrochloric acid in ether.



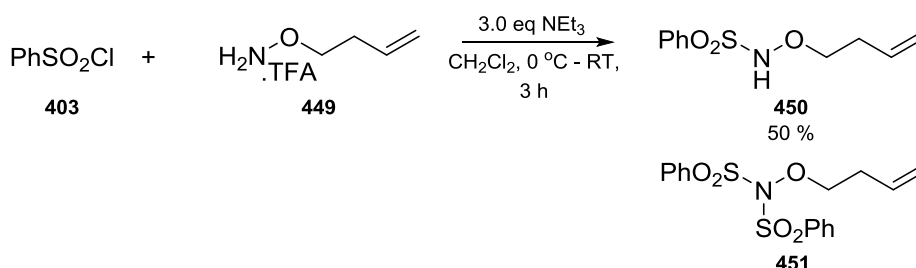
Scheme 124

Alkene **445** was recovered in high yield (90 %) and reacted with trifluoroacetic acid to yield salt **449** with small amounts of impurities and was used crude directly in the next step (Scheme 125).^[116]



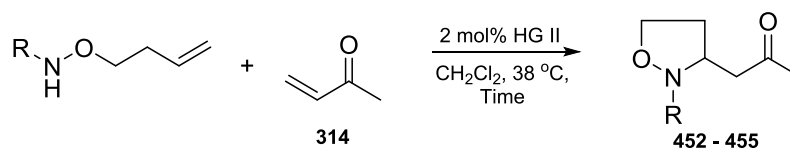
Scheme 125

Salt **449** was reacted with benzenesulfonyl chloride **403** using the conditions previously described to yield sulfonamide **450** (Scheme 126). A modest yield was isolated again due to difficulties separating the desired product from the di-substituted sulfonamide byproduct **451**.



Scheme 126

With the terminal alkenes now available they could be reacted with methyl vinyl ketone **314** using the conditions previously described in an attempt to generate the desired enones (*Table 44*).

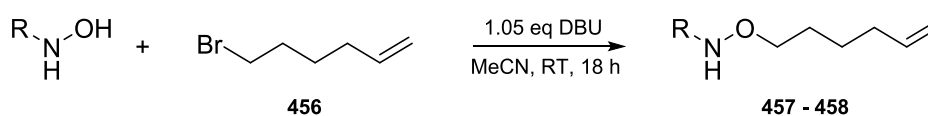


Entry	Substrate	R	Time (h)	Product	Yield (%)
1	445	Boc	2	452	37
2	446	Cbz	2	453	57
3	447	Ac	2	454	0
4	450	PhSO ₂	1	455	70

Table 44

However in all cases the enone could not be isolated with all attempts leading to isolation of the corresponding isoxazolidine **452** – **455**. Alkene **445** gave a crude 1: 1: 1 mixture of starting material, desired enone and isoxazolidine **452** by ¹H NMR analysis. When isolation by silica chromatography was attempted the enone cyclized and only isoxazolidine **452** was isolated (*Entry 1*). For alkenes **446**, **447** and **450** the desired enone was not observed by ¹H NMR analysis and the corresponding isoxazolidine was observed. However, isoxazolidine **454** could not be isolated cleanly from remaining starting material **447** (*Entry 3*).

Since the five membered enone precursors could not be isolated it was decided to synthesise the seven membered enone precursors instead. It was hoped that the oxygen would activate the nitrogen sufficiently to give possibly the first example of an enantioenriched seven membered cyclization under iminium catalysis. It was decided to synthesise all the *N*-functionalised groups investigated before using the appropriate chemistry. First the carbamates were synthesised by reaction of the corresponding hydroxylamines with 6-bromohex-1-ene **456** using the conditions previously described (*Table 45*).

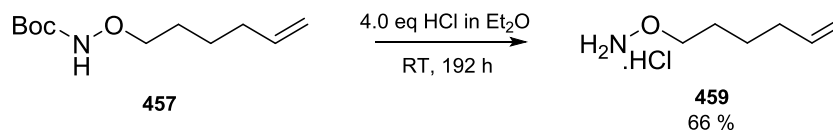


Entry	Substrate	R	Product	Yield (%)
1	429	Boc	457	42
2	435	Cbz	458	49

Table 45

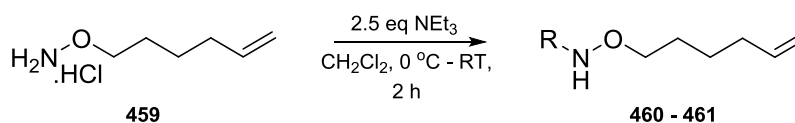
There was no acetohydroxyamic acid **437** left after previous reactions so it was decided to make the acetyl substituted compound from amine salt **459** and acetic anhydride. The

Boc group of amine **457** was removed with hydrochloric acid in diethyl ether with salt **459** precipitating out of solution (*Scheme 127*).



Scheme 127

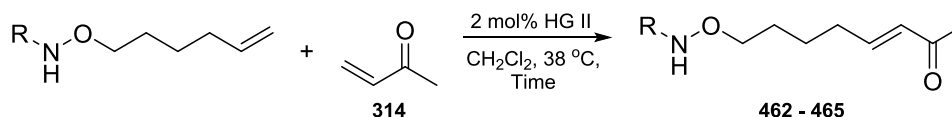
Salt **459** was then reacted with acetic anhydride and benzenesulfonyl chloride to give the corresponding *N*-substituted compounds (*Table 46*).



Entry	Substrate	R	Product	Yield (%)
1	Ac ₂ O	Ac	460	85
2	PhSO ₂ Cl	PhSO ₂	461	53

Table 46

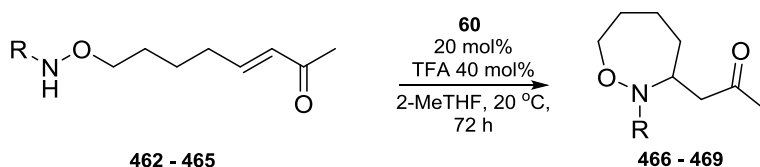
With the alkenes available the cross metathesis reactions could be investigated. The alkenes were reacted with methyl vinyl ketone **314** under the previously discussed reaction conditions (*Table 47*).



Entry	Substrate	R	Time (h)	Product	Yield (%)
1	457	Boc	2	462	81
2	458	Cbz	1	463	91
3	460	Ac	1	464	61
4	461	PhSO ₂	1	465	87

Table 47

Enones **462 - 465** were successfully isolated by silica chromatography with no sign of cyclization by ¹H NMR analysis. Alkene **457** required longer heating to obtain complete conversion of starting material (*Entry 1*). Enones **462 - 465** were then subjected to the previously optimised conditions (*Table 48*).



Entry	Substrate	R	Product	Yield (%)	E.e. (%) ¹
1	462	Boc	466	0	-
2	463	Cbz	467	0	-
3	464	Ac	468	50	67
4	465	PhSO ₂	469	0	-

¹ Determined by Chiral HPLC

Table 48

Enone **464** was the only compound to undergo cyclization with modest enantioselectivity (*Entry 3*). The isolated yield was also modest with the conversion stalling at ~60 % by ¹H NMR analysis, but this was possibly the first example of a seven membered ring being formed under these reaction conditions. The other three enones investigated did not cyclize after prolonged reaction times with no conversion to product observed by ¹H NMR analysis.

With the ring size now studied, the substitution on the enone was studied next. The six membered *N*-Boc substituted compound was chosen as it been optimised. The two previously investigated substitutions ethyl and phenyl were chosen for investigation (*Figure 64*).

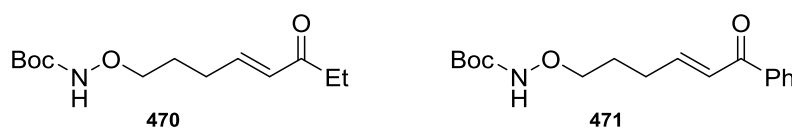


Figure 64

Enones **424** and **425** were synthesised as previously described by cross metathesis with the corresponding vinyl ketone and terminal alkene **380** (*Table 49*).



Entry	Substrate	R	Time (h)	Product	Yield (%)
1	377	Et	1	470	93
2	395	Ph	2	471	65

Table 49

Enone **471** required longer heating with only 75 % conversion observed by ¹H NMR analysis (*Entry 2*). Enones **470** and **471** were then subjected to the previously optimized

cyclization conditions (*Table 50*). The stereochemistry was assigned by analogy with previously reported results.^[95]

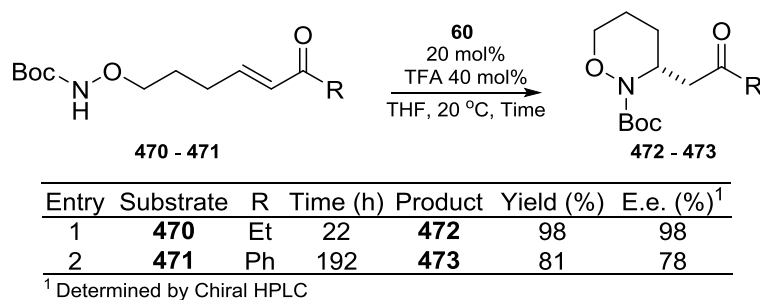


Table 50

Both enones cyclized under the reaction conditions but were slower than the methyl ketone (9 h). Enone **472** gave a similar yield and enantioselectivity to that of the methyl ketone (*Entry 1*). Enone **473** required a prolonged reaction time, as previously observed with other phenyl enones, possibly due to difficulties in forming an iminium species and gave a lower enantioselectivity (*Entry 2*).

We have found that substitution of oxygen in the 2-position of the piperidine is possible with all groups on nitrogen investigated cyclising. The acetyl group gave a modest enantioselectivity for the 6 membered ring and was the only group that allowed 7 membered cyclization to occur. Attempts to synthesise the 5 membered ring precursors proved unsuccessful for all N-functionalisation with the enone cyclising under the metathesis conditions. With the 2-position now studied we moved on to the design of a 4-substituted compound.

2.7.2. Morpholine Substrates

2.7.2.1 Synthesis of Cyclization Precursor

The *tert*-butoxy (Boc) substitution on nitrogen and the oxygen heteroatom were studied in the most detail previously so these were again chosen. This lead to enone **474** and when cyclized would generate 2-substituted morpholine compound **475** (*Figure 65*).

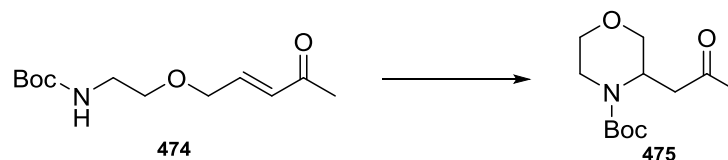
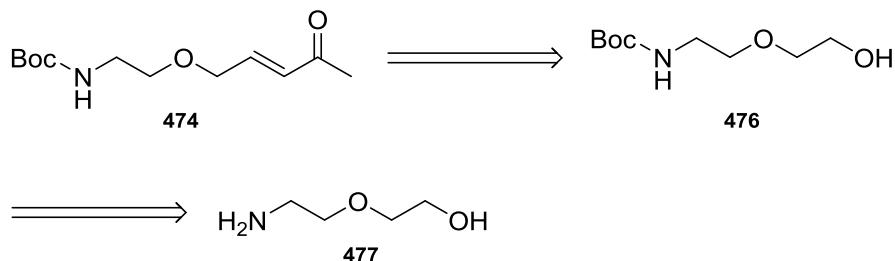


Figure 65

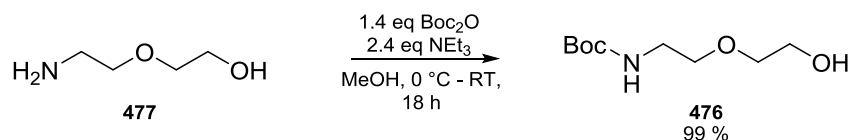
The retrosynthetic analysis for this molecule was carried out and could be synthesised in two steps from commercially available materials (*Scheme 128*). Enone **474** could be synthesised from alcohol **476** using previously discussed chemistry. Alcohol **476** could

be synthesised from commercially available 2-(aminoethoxy)ethanol **477** by selective *N*-functionalisation with di-*tert*-butyl dicarbonate.



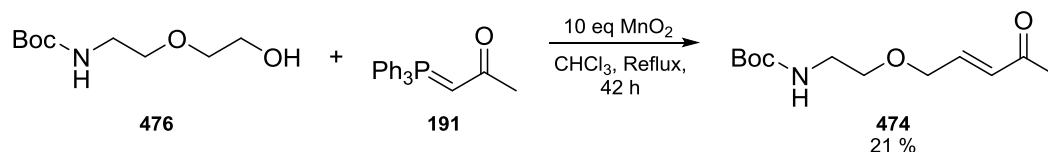
Scheme 128

First 2-(aminoethoxy)ethanol **477** was reacted with di-*tert*-butyl dicarbonate using conditions previously discussed to yield alcohol **476** in quantitative yield (*Scheme 129*).



Scheme 129

Alcohol **476** was then reacted with ylide **191** using the conditions previously described (*Scheme 130*). The isolated yield of the reaction was lower than for previous examples with more impurities observed by ^1H NMR analysis possibly due to the heteroatom in the chain.

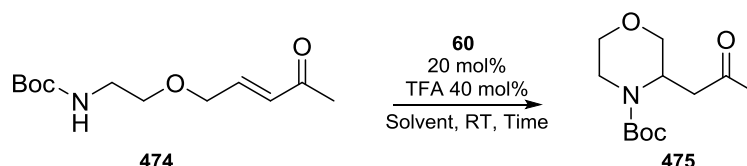


Scheme 130

Enone **474** was now available in large enough quantity for the cyclization conditions to be investigated.

2.7.2.2 Optimisation of Cyclization Conditions

Enone **474** was cyclized using the conditions previously discussed, first the reaction solvent was investigated (*Table 51*).

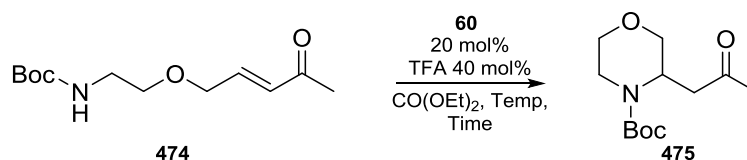


Entry	Solvent	Time (h)	Conversion (%) ¹	E.e. (%) ²
1	CHCl ₃	22	>95	94
2	CH ₂ Cl ₂	22	>95	95
3	EtOAc	22	>95	96
4	IPA	22	>95	29
5	MeCN	48	>95	13
6	MeOH	70	>95	54 ³
7	PhMe	22	>95	90
8	THF	22	>95	94
9	CO(OEt) ₂	22	>95	98
10	2-MeTHF	22	>95	95

¹ Measured by ¹H NMR ² Determined by Chiral HPLC ³ Opposite enantiomer

Table 51

Enone **474** cyclized in all solvents investigated, with acetonitrile and methanol requiring prolonged reaction times to give complete conversion (*Entries 5 and 6*). Acetonitrile and 2-propanol gave the lowest enantioselectivities and methanol yielded the opposite enantiomer in modest enantioselectivity. All other solvents gave high enantioselectivities in the same reaction time, with diethyl carbonate giving the highest and this was used in further reactions. With the best solvent found, the temperature of the reaction was investigated (*Table 52*).



Entry	Temp (°C)	Time (h)	Conversion (%) ¹	E.e. (%) ²
1	10	120	>95	94
2	20	22	>95	98
3	30	8	>95	93

¹ Measured by ¹H NMR ² Determined by Chiral HPLC

Table 52

The best temperature found was 20 °C with changes in this temperature found only to lower enantioselectivity. With the optimized conditions found we wished to investigate the scope of the reaction with respect to functional group on the nitrogen and the heteroatom substitution.

2.7.2.3 Investigation of Substrate Scope

First we decided to study the group on the nitrogen, we chose three groups that had previously been investigated Cbz, Ac and PhSO₂ (*Figure 66*). We wanted to investigate

whether these groups would make a difference to the rate and enantioselectivity of this reaction.

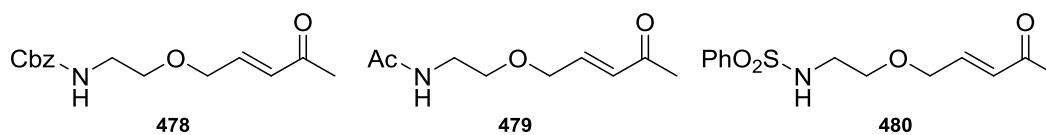
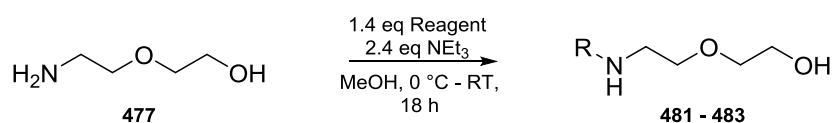


Figure 66

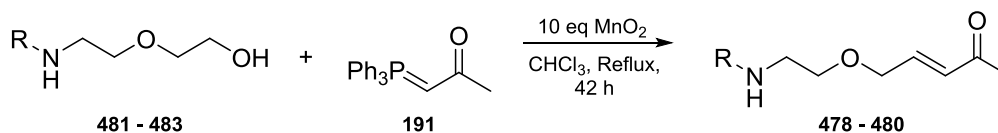
Enones **478** - **480** could be synthesised using the route previously described for the *N*-Boc substituted compound. First, 2-(aminoethoxy)ethanol **477** was reacted with the corresponding reagent, using the previously used conditions to generate desired alcohols **481** - **483** in quantitative yields (*Table 53*).



Entry	Reagent	R	Product	Yield (%)
1	CbzCl	Cbz	481	99
2	Ac ₂ O	Ac	482	99
3	PhSO ₂ Cl	PhSO ₂	483	99

Table 53

Alcohols **481** - **483** were reacted with ylide **191** using the conditions previously discussed (*Table 54*). The isolated yields were low due to difficulties separating the desired enone product from several unidentified impurities. Alcohol **481** required prolonged heating to obtain complete consumption of starting material (*Entry 1*).



Entry	Substrate	R	Time (h)	Product	Yield (%)
1	481	Cbz	96	478	20
2	482	Ac	42	479	21
3	483	PhSO ₂	42	480	16

Table 54

With enones **478** - **480** available they could be investigated with the optimised reaction conditions. Enone **474** was cyclized to obtain an isolated yield and compare the rate and enantioselectivity with the other groups (*Table 55*).

Entry	Substrate	R	Time (h)	Product	Yield (%)	E.e. (%) ¹
1	474	Boc	22	475	96	98
2	478	Cbz	22	484	91	96
3	479	Ac	72	485	0	-
4	480	PhSO ₂	22	486	88	96

¹ Determined by Chiral HPLC

Table 55

All enones cyclised under the optimized reaction conditions but enone **479** only gave a 25 % conversion after prolonged reaction time, and could not be isolated from remaining starting material (*Entry 3*). The other enones investigated cyclized at the same rate in similar yields and enantioselectivities as the N-Boc substituted enone. With the scope of the functional group on the nitrogen now studied we wanted to investigate if we could replace the oxygen heteroatom with a nitrogen heteroatom.

2.7.3. Piperazine Substrate

Enone **487** was designed with the nitrogen in the 4 position of the chain protected by a Boc group to prevent side reactions occurring (*Figure 67*).

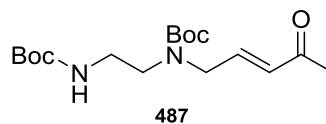
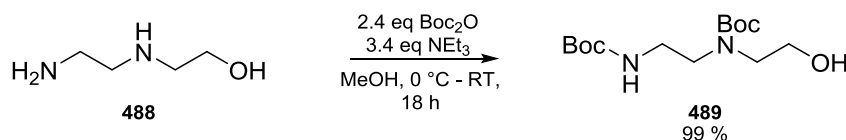


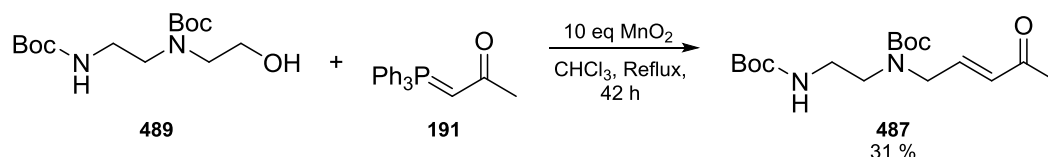
Figure 67

Enone **487** could be synthesised in two steps using the chemistry previously discussed. First *N*-(2-hydroxyethyl)ethylenediamine **488** was reacted with di-*tert*-butyl dicarbonate giving alcohol **489** in quantitative yield (*Scheme 131*).



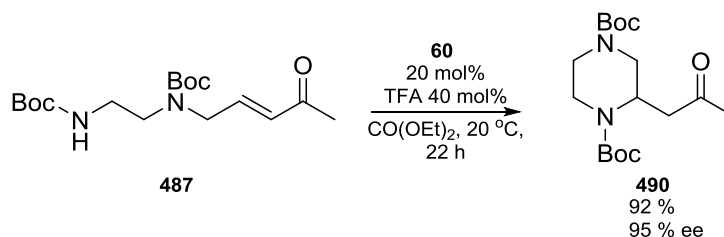
Scheme 131

Alcohol **489** was reacted with ylide **191** using the conditions previously discussed to yield enone **487** (*Scheme 132*).



Scheme 132

Enone **487** was then subjected to the optimised cyclization conditions to yield piperazine **490** in high yield and enantioselectivity (*Scheme 133*).



Scheme 133

2.8 Conclusion

Attempted synthesis of intermolecular pyrazole enone **309** proved unsuccessful by two routes and use of 3-penten-2-one **139** as a masking group for the cyclization also proved unsuccessful. Initial attempts at the synthesis of benzamide enone **324** using previous literature proved unsuccessful and a new route was developed using an oxidative Wittig reaction to give the target compound. This chemistry proved successful for several different types of nitrogen substitution with no reported examples of nitrogen atoms being present in this type of reaction previously. Conjugated and electron deficient amides proved unsuitable for the intramolecular cyclization but acetyl, formyl and cyanoamides performed the addition with varied enantioselectivities.

The internal amide derivative **382** cyclized under the reaction conditions to give 6-substituted δ -valerolactam **381** in high yield and enantioselectivity. Sulfonamides performed the cyclizations with high enantioselectivities using the conditions used previously. We found methanol to give no conversion or the opposite enantiomer for these cyclizations to other solvents suggesting a potential different mode of catalysis in this solvent. Acetonitrile and 2-propanol were found to be unsuitable solvents for this method of catalysis giving much lower enantioselectivities than other solvents.

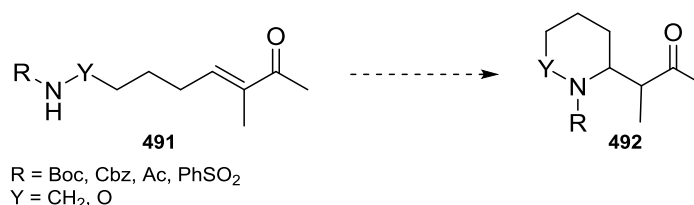
The phenyl sulfonamide and acetyl groups were found to perform the cyclizations of five membered rings with slightly modified conditions in comparable enantioselectivities for the sulfonamide and amide. No groups allowed the cyclization of four and seven membered rings with no conversion observed by ¹H NMR analysis possibly due to ring strain and entropic penalties. Ethyl enones reacted to yield similar enantioselectivities but with increased reaction times in all cases. The longer reaction times for these reactions may be due to increased steric bulk leading to potential steric clashes with the catalyst.

Phenyl enones required longer reaction times with some cases requiring increased temperature. Acetyl substituted compound **374** gave a much lower enantioselectivity than other examples.

Heteroatom incorporation into the piperidine ring system proved successful in the 2 and 4 positions giving high enantioselectivities and yields. However the acetyl group gave poor results with a modest enantioselectivity for the 1,2-oxazinane **443**. The five membered enone derivatives were unstable and could not be isolated, cyclizing to the corresponding isoxazolidine due to the increased nucleophilicity of the nitrogen when compared to no heteroatom substitution in the 2-position. Pleasingly the increased nucleophilicity of the nitrogen allowed possibly the first example of a seven membered ring cyclizing under iminium catalysis with the acetyl group yielding a modest enantioselectivity. The phenyl and ethyl enone derivatives reacted as previously found.

The morpholine derived compounds reacted in similar yields and enantioselectivities to that of the 1,2-oxazinanes with the acetyl group giving too low a conversion to isolate the desired morpholine **485** from remaining starting material. It was also found that di-Boc substituted piperidine **490** could be synthesised using this methodology in high yield and enantioselectivity.

Further work could be carried out into substitution on the 2-position of the enone with no examples currently published and would require further investigation with the optimised groups and conditions (*Scheme 134*).



Scheme 134

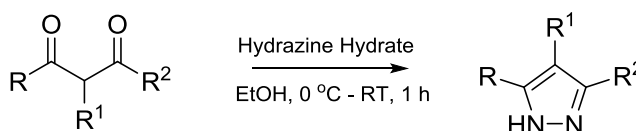
Chapter 3: Experimental

3.1 General Experimental

All solvents and reagents were used as supplied from commercial sources or where specified purified by standard techniques.^[117,118] Melting points (m.p.) were determined using a Stuart SMP3 electrothermal apparatus and are uncorrected. Specific rotations ($[\alpha]_D$) were measured on a Bellingham and Stanley ADP440 polarimeter at wavelength 589 nm, corresponding to the sodium line D, at the temperature indicated and are given in units of $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$. Infrared (IR) spectra were recorded using a Perkin-Elmer 1600 FT-IR or a Nicolet Avatar 360 FT-IR spectrometer in the range $4000 - 600 \text{ cm}^{-1}$. Spectra were recorded as neat samples or as chloroform solutions as indicated. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on Bruker spectrometers (AV400, AV(III)400, DPX400, DPX500) at 18°C . All chemical shifts (δ) were referenced to the residual peak of the indicated solvent and are reported in parts per million (ppm). All multiplicities are designated by the following abbreviations: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad, or any combination of those. All coupling constants J are reported, to the nearest 0.5, in Hertz. All ^{13}C NMR spectra were acquired using broadband decoupled mode and assignments were aided by using DEPT135 and DEPT90 sequences. Mass spectra were obtained on a Bruker microTOF (electrospray ionisation ES) machine. High performance liquid chromatography (HPLC) was performed using a Varian ProStar chromatograph with chiral analytical $4.6 \times 250 \text{ mm}$ Chiralcel and Chiralpak column (AD-H, OD-H, OJ-H or AS) with a SiO_2 guard column attached using conditions outlined in the relevant experimental procedures. Flash chromatography was carried out using Kieselgel 60 (230-400 mesh) using the solvent systems specified. Analytical thin layer chromatography (TLC) was performed using pre-coated glass backed plates (Kieselgel 60 with F254 UV indicator). Plates were visualised using short-wave UV followed by staining with ninhydrin or potassium permanganate. Petrol refers to light petroleum ether $40-60^\circ\text{C}$. Racemic intermolecular adducts were prepared using racemic *trans*-1,2-diaminocyclohexane.

3.2 General Procedures

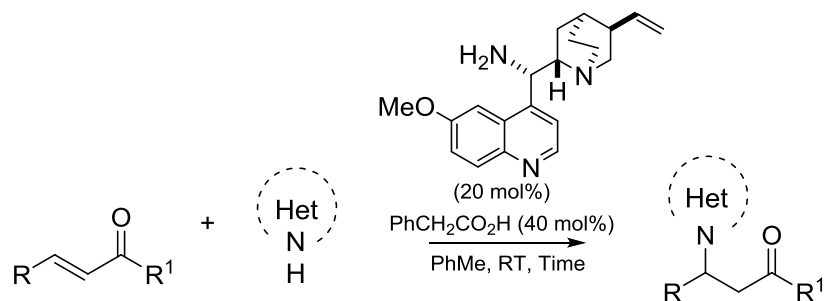
General procedure 1



The dicarbonyl species (7.70 mmol) was cooled to 0°C and a solution of hydrazine hydrate (15.4 mmol) in ethanol (1.08 ml) was added dropwise. The reaction mixture was allowed to warm to room temperature then stirred for 1 hour. The reaction mixture was

then cooled to 0 °C and the resulting precipitate filtered and washed with ice-cold ethanol to yield the product.

General procedure 2



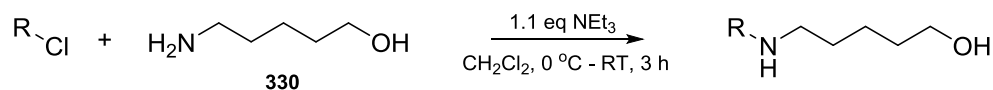
Enone (500 μmol) was added to a solution of 9-deoxy-9-*epi*-aminoquinine **60** (100 μmol) in toluene (3 ml). Phenylacetic acid (200 μmol) was added and the reaction was stirred at room temperature for 20 min. *N*-Heterocycle (500 μmol) was added and the reaction mixture was stirred for the time stated. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography on silica gel to yield the product.

General Procedure 3



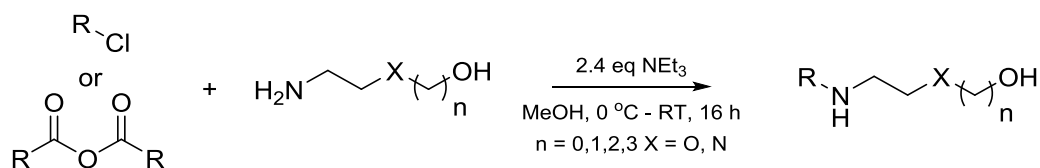
Acid chloride or sulfonyl chloride (5.30 mmol) was added dropwise to a solution of methylamine in water (40 % w/w, 5 ml) and shaken for 5 minutes. The resulting solution was then extracted with dichloromethane (3 x 3 ml). The combined organic layers were dried (magnesium sulfate) and concentrated under reduced pressure to yield the product.

General procedure 4a



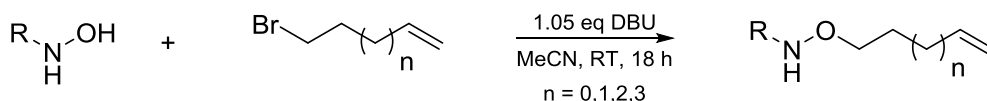
A solution of acid chloride or sulfonyl chloride (5.00 mmol) and triethylamine (5.00 mmol) dissolved in dichloromethane (5 ml) was added to a solution of 5-aminopentanol **330** (4.90 mmol) in dichloromethane (20 ml) dropwise at 0 °C. The mixture was allowed to warm to room temperature and stirred for 3 hours. Water (25 ml) was added and the resulting layers separated. The aqueous layer was re-extracted with dichloromethane (15 ml) and the combined organics were dried (magnesium sulfate) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to yield the product.

General procedure 4b



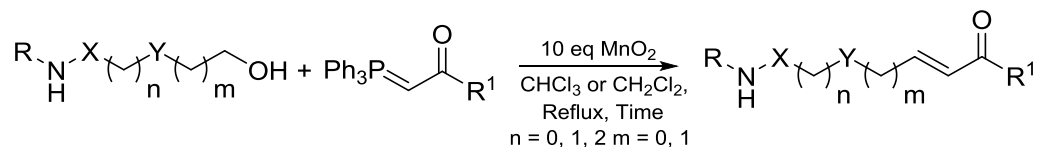
Triethylamine (11.8 mmol) was added to a solution of aminoalcohol (4.90 mmol) in methanol (4 ml) at 0 °C. The acid chloride, sulfonyl chloride or anhydride (6.70 mmol) was added dropwise over 10 minutes and the mixture allowed to warm to room temperature then stirred for 16 hours. The reaction mixture was concentrated under reduced pressure and the residue purified by flash chromatography on silica gel to yield the product.

General procedure 5



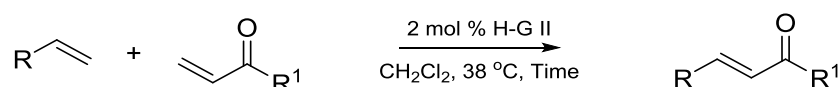
DBU was added (7.80 mmol) dropwise to a solution of *N*-substituted hydroxylamine (7.40 mmol) and bromoalkene (8.50 mmol) in acetonitrile (18.5 ml) and the reaction mixture stirred at room temperature for 18 hours. The reaction mixture was concentrated under reduced pressure and the residue portioned between 0.1 M hydrochloric acid (50 ml) and ethyl acetate (50 ml). The aqueous layer was further extracted with ethyl acetate (25 ml). The combined organics were dried (magnesium sulfate) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to yield the product.

General procedure 6



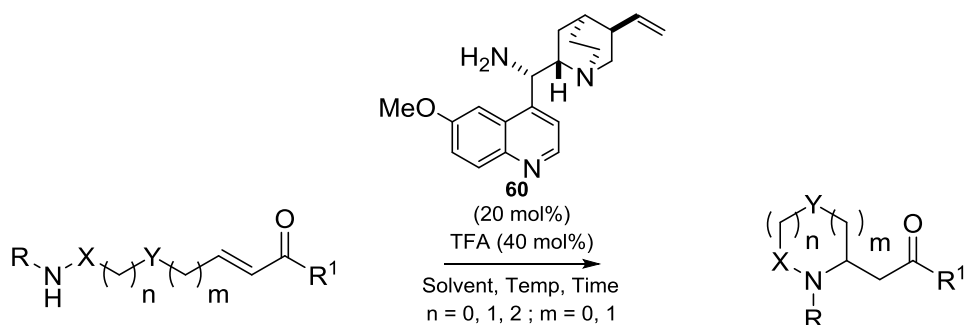
The alcohol (1.60 mmol) was dissolved in dichloromethane or chloroform (14 ml) and the appropriate ylide (2.60 mmol) was added. Manganese dioxide (16.0 mmol) was added and the reaction mixture stirred at reflux for the time stated. The mixture was allowed to cool to room temperature and Celite was added. The mixture was then filtered, washed with chloroform (100 ml). The resulting solution was then concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel to yield the product.

General procedure 7



The terminal alkene (1.00 mmol) was dissolved in dichloromethane (15 ml) and Hoveyda-Grubbs 2nd generation catalyst (20.0 μ mol) was added. Vinylketone (2.00 mmol or 5.00 mmol as specified) was added and the mixture heated at reflux for the time stated. The mixture was allowed to cool to room temperature and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to yield the product.

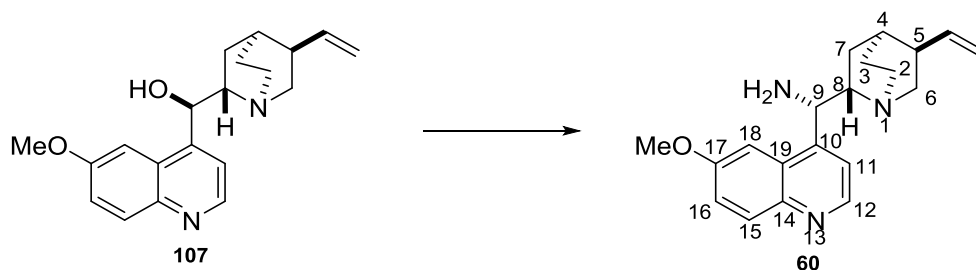
General procedure 8



Trifluoroacetic acid (40.0 μ mol) dissolved in the appropriate solvent (0.2 ml) was added to a solution of 9-deoxy-9-*epi*-aminoquinine **60** (20.0 μ mol) in the same solvent (0.4 ml). After 5 minutes a solution of enone (100 μ mol) dissolved in the same solvent (0.4 ml) was added. The resulting mixture was stirred at the appropriate temperature for the time stated. The reaction mixture was then passed through a plug of silica, then concentrated under reduced pressure to yield the product.

3.3 Experimental Data

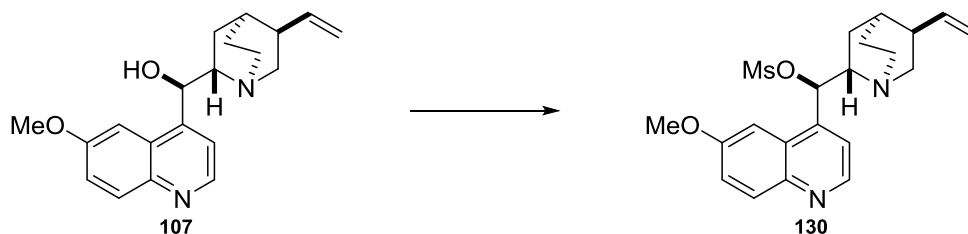
9-Deoxy-9-*epi*-aminoquinine **60**^[39]



To a solution of quinine **107** (3.75 g, 11.6 mmol) and triphenylphosphine (3.64 g, 13.9 mmol) in anhydrous tetrahydrofuran (56 ml) cooled to 0 °C was added diisopropyl azodicarboxylate (2.73 ml, 13.9 mmol). A solution of diphenylphosphoryl azide (3.00 ml, 13.9 mmol) in tetrahydrofuran (26 ml) was then added dropwise and the reaction mixture was allowed to warm to room temperature, then stirred for 18 hours. The solution was then heated to 50 °C and stirred for a further 2 hours. Triphenylphosphine (3.94 g, 15.0 mmol) was then added and the mixture stirred at 50 °C for a further 1 hour until gas evolution had ceased. The solution was then cooled to room temperature, water (1.3 ml) was added and the resulting solution was stirred for 4 hours. The volatiles were then removed under reduced pressure and the residue portioned between dichloromethane (50 ml) and 2M hydrochloric acid (50 ml). The aqueous phase was washed with dichloromethane (3 x 50 ml) and was then adjusted to pH 9 with an excess of concentrated aqueous ammonia solution. The aqueous was then extracted with dichloromethane (3 x 50 ml). The combined organic layers of the later extracts were dried (magnesium sulfate) and concentrated under reduced pressure to yield **60** (3.50 g, 93 %) as a yellow oil; R_f 0.5 (9 : 1 chloroform: methanol); $[\alpha]_D^{25} +75.0$ (c 0.8, CHCl_3); $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 3377, 3080, 2948, 1622, 1509, 1260, 1242; δ_{H} (400 MHz, CDCl_3) 8.70 (1H, d, J 7.5, C_{12}H), 8.00 (1H, d, J 2.0, C_{18}H), 7.63 (1H, br m, C_{15}H), 7.42 (1H, d, J 7.5, C_{11}H), 7.35 (1H, dd, J 9.5, 2.0, C_{16}H), 5.77 (1H, ddd, J 17.5, 10.0, 7.5, $\text{CH}=\text{CH}_2$), 4.97 - 4.94 (2H, m, $\text{CH}=\text{CH}_2$), 4.56 (1H, d, J 9.5, C_9H), 3.93 (3H, s, OCH_3), 3.24 (1H, dd, J 14.0, 10.0, C_2H), 3.21 - 2.97 (2H, m, $\text{C}_6\text{H} + \text{C}_8\text{H}$), 2.83 - 2.71 (2H, m, $\text{C}_6\text{H} + \text{C}_2\text{H}$), 2.30 - 2.20 (1H, m, C_5H), 2.15 - 1.89 (2H, m, NH_2), 1.62 - 1.57 (1H, m, C_4H), 1.56 - 1.46 (2H, m, C_3H_2), 1.40 (1H, dd, J 11.0, 11.0, C_7H), 0.74 (1H, dddd, J 13.5, 7.5, 2.0, 2.0, C_7H); δ_{C} (100 MHz, CDCl_3) 157.6 (C_{17}), 147.9 (C_{12}H), 147.0 (C), 144.8 (C), 141.8 ($\text{CH}=\text{CH}_2$), 131.8 (C_{15}H), 128.8 (C_{19}), 121.2 (C_{16}H), 120.0 (C_{11}H), 114.3 ($\text{CH}=\text{CH}_2$), 102.0 (C_{18}H), 61.9 (C_8H), 60.1 (C_9H), 56.4 (C_2H_2), 55.5 (OCH_3), 41.0 (C_3H_2), 39.9 (C_5H), 28.2 (C_6H_2), 27.6 (C_4H), 26.1 (C_7H_2); m/z (ES) 324 ($[\text{M}+\text{H}]^+$, 100 %); m/z (ES) Found 324.2053.

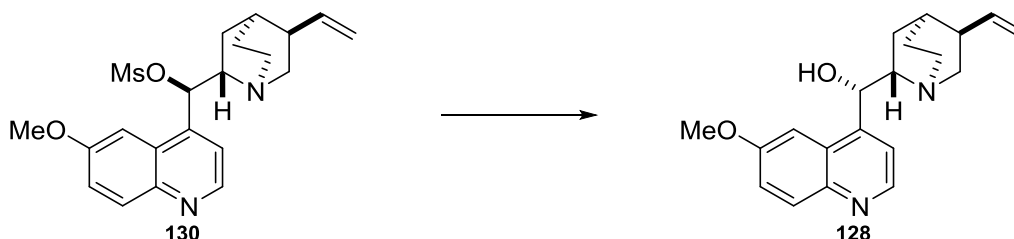
$C_{20}H_{26}N_3O^+$ requires 324.2070. The ^1H and ^{13}C NMR data are in agreement with those previously reported.^[39]

9-Mesyloxyquinine **130**^[43]



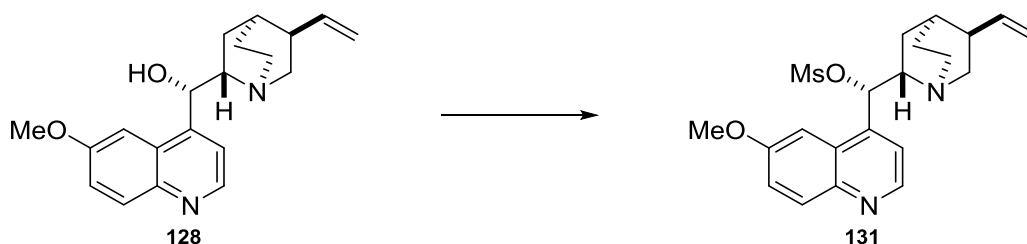
Quinine **107** (10.0 g, 31.0 mmol) was dissolved in tetrahydrofuran (180 ml) and triethylamine (9.90 ml, 72.0 mmol) and methanesulfonyl chloride (4.82 ml, 62.0 mmol) were added. The reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was quenched with saturated aqueous sodium hydrogen carbonate. The mixture was then extracted with dichloromethane (40 ml) and chloroform (50 ml), the combined organics were dried (sodium sulfate) and concentrated under reduced pressure to yield **130** (13.0 g, 95 %) as a clear oil. R_f : 0.5 (Ethyl acetate); $[\alpha]_D^{22}$ -40.0 (c 0.8 in $CHCl_3$); (Lit. $[\alpha]_D^{25}$ -71.9 (c 1.0 in $CHCl_3$))^[99]; ν_{max} (neat)/ cm^{-1} 2954, 2870, 1361, 1242, 1175; δ_H (400 MHz, $CDCl_3$) 8.81 (1H, d, J 4.5, $C_{12}H$), 8.06 (1H, d, J 2.0, $C_{18}H$), 7.51 - 7.34 (3H, m, $C_{15}H + C_{11}H + C_{16}H$), 6.17 (1H, br s, C_9H), 5.84 (1H, ddd, J 17.5, 10.0, 7.5, $CH=CH_2$), 5.06 - 4.99 (2H, m, $CH=CH_2$), 3.97 (3H, s, OCH_3), 3.54 - 3.32 (1H, m, C_2H), 3.19 - 3.06 (1H, m, C_6H), 2.99 (1H, dd, J 13.5, 10.5, C_8H), 2.70 - 2.57 (5H, m, $C_6H + C_2H + SCH_3$), 2.28 (1H, br s, C_5H), 2.08 (1H, br s, C_4H), 1.96 - 1.87 (1H, m, C_3H), 1.82 - 1.72 (1H, m, C_3H), 1.71 - 1.62 (1H, m, C_7H), 1.61 - 1.51 (1H, m, C_7H); δ_C (100 MHz, $CDCl_3$) 158.4 (C_{17}), 147.5 ($C_{12}H$), 145.0 (C), 141.5 ($CH=CH_2$), 132.2 ($C_{15}H$), 126.5 (C_{19}), 122.2 ($C_{16}H + C_{11}H$), 119.2 (C), 114.6 ($CH=CH_2$), 100.9 ($C_{18}H$), 59.9 (C_9H), 56.5 (C_2H_2), 55.7 (CH_3), 42.2 (C_6H_2), 39.5 (OCH_3), 39.2 (C_3H_2), 27.6 ($C_5H + C_8H$), 27.3 (C_4H), 25.1 (C_7H_2); m/z (ES) 403 ($[M+H]^+$, 100 %); m/z (ES) found $[M+H]^+$ 403.1687. $C_{21}H_{27}N_2O_4S$ requires 403.1686. The ^1H and ^{13}C NMR data are in agreement with those previously reported.^[119]

9-*epi*-Quinine **128**^[119]



9-Mesyloxyquinine **130** (13.0 g, 30.2 mmol) was suspended in distilled water (200 ml) and L-tartaric acid (4.80 g, 33.2 mmol) was added. The resulting mixture was heated at reflux for 4 hours, then cooled to room temperature. The solution was then adjusted to pH 7 with solid sodium hydrogen carbonate, then extracted with ether (3 x 50 ml). The combined organics were dried (magnesium sulfate) and concentrated under reduced pressure to yield a 4: 1 mixture of starting material **130** and product **128**. The product was purified by flash chromatography on silica gel (ethyl acetate) to yield **128** (1.05 g, 11 %). The aqueous was re-extracted with dichloromethane (3 x 50 ml), dried (magnesium sulfate) and concentrated under reduced pressure to yield additional **128** (3.70 g, 39 %) as an off white solid. M.p. 176 - 178 °C; Lit. m.p. 172 - 173 °C^[100]; R_f : 0.4 (ethyl acetate). $[\alpha]_D^{24} +36.0$ (c 0.1 in CHCl₃); (Lit. $[\alpha]_D^{25} +39.5$ (c 0.9 in CHCl₃))^[99]; $\nu_{\max}$ (CHCl₃)/cm⁻¹ 3365, 2954, 1622, 1510, 1242; δ_H (400 MHz, CDCl₃) 8.72 (1H, d, J 7.5, C₁₂H), 8.02 (1H, d, J 2.0, C₁₈H), 7.64 (1H, d, J 7.5, C₁₅H), 7.39 (1H, d, J 7.5, C₁₁H), 7.36 (1H, dd, J 7.5, 2.0, C₁₆H), 5.73 (1H, ddd, J 17.5, 10.0, 7.5, CH=CH₂), 5.04 - 4.91 (3H, m, C₉H + CH=CH₂), 3.92 (3H, s, OCH₃), 3.25 (1H, dd, J 14.0, 10.0, C₂H), 3.21 - 3.14 (1H, m, C₆H), 3.10 (1H, dd, J 9.5, 9.5, C₈H), 2.82 - 2.72 (2H, m, C₆H + C₂H), 2.35 - 2.25 (1H, br s, C₅H), 1.74 - 1.67 (1H, m, C₄H), 1.64 - 1.55 (2H, m, C₃H₂), 1.50 - 1.40 (1H, m, C₇H), 0.95 (1H, dddd, J 13.5, 8.0, 1.5, 1.5, C₇H); δ_C (100 MHz, CDCl₃) 157.4 (C₁₇), 147.5 (C₁₂H), 144.8 (C), 144.3 (C), 141.3 (CHCH₂), 131.5 (C₁₅H), 128.1 (C₁₉), 121.2 (C₁₆H), 120.0 (C₁₁H), 114.6 (CH=CH₂), 102.5 (C₁₈H) 71.3 (C₉H), 61.4 (C₈H), 55.8 (C₂H₂), 55.4 (OCH₃), 40.7 (C₃H₂), 39.8 (C₅H), 27.9 (C₆H₂), 27.2 (C₄H), 25.1 (C₇H₂); m/z (ES) 325 ([M+H]⁺, 100 %); m/z (ES) found [M+H]⁺ 325.1909. C₂₀H₂₅N₂O₂ requires 325.1911. The ¹H and ¹³C NMR data are in agreement with those previously reported.^[119]

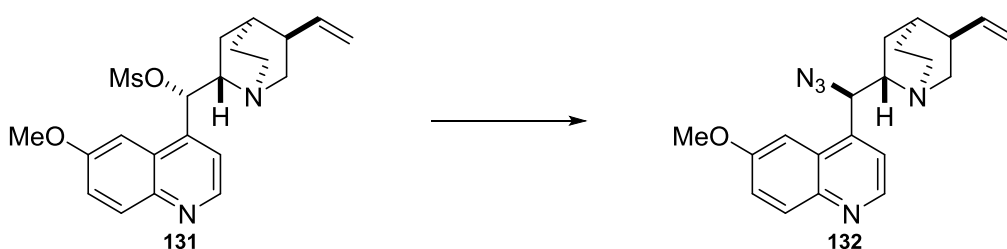
9-*epi*-Mesyloxyquinine **131**^[119]



9-*epi*-Quinine **128** (3.70 g, 11.4 mmol) was dissolved in tetrahydrofuran (70 ml) and triethylamine (3.67 ml, 26.0 mmol) and methanesulfonyl chloride (1.76 ml, 22.8 mmol) were added. The reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was quenched with saturated aqueous sodium hydrogen carbonate. The mixture was extracted with dichloromethane (40 ml) and chloroform (50 ml), dried (sodium sulfate) and concentrated under reduced pressure to yield **131** (4.20 g, 90 %) as a colourless solid. M.p. 142 - 144 °C (decomp.); R_f : 0.5 (ethyl acetate); $[\alpha]_D^{23} +40.1$ (c 0.8 in CHCl₃); $\nu_{\max}$ (CHCl₃)/cm⁻¹ 2951, 1622, 1359, 1242, 1172; δ_H (400 MHz, CDCl₃)

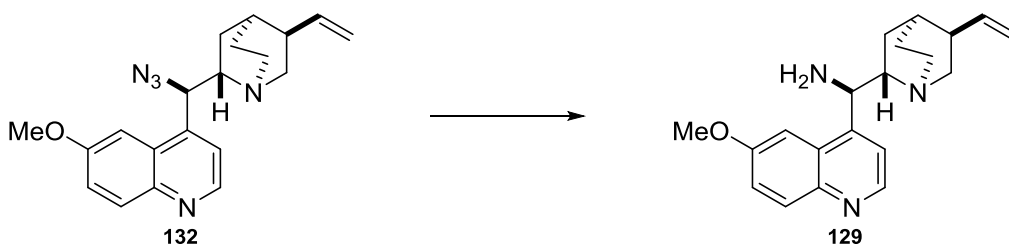
8.81 (1H, d, J 7.5, C₁₂H), 8.07 (1H, d, J 2.0, C₁₈H), 7.57 - 7.37 (3H, m, C₁₅H + C₁₁H + C₁₆H), 6.34 (1H, br s, C₉H), 5.80 (1H, br s, CH=CH₂), 5.10 - 4.94 (2H, m, CH=CH₂), 3.99 (3H, s, OCH₃), 3.56 - 3.20 (3H, m, C₂H + C₆H + C₈H), 3.08 - 2.92 (3H, br s, SCH₃), 2.90 - 2.80 (2H, m, C₆H + C₂H), 2.32 (1H, br s, C₅H), 1.73 - 1.66 (1H, m, C₄H), 1.64 - 1.53 (2H, m, C₃H₂), 1.52 - 1.30 (1H, m, C₇H), 0.74 (1H, dddd, J 14.0, 8.0, 2.0, 2.0, C₇H); δ_C (100 MHz, CDCl₃) 158.5 (C₁₇), 147.5 (C₁₂H), 141.3 (CH=CH₂), 139.7 (C), 132.1 (C₁₅H), 132.0 (C), 127.4 (C₁₉), 122.2 (C₁₆H), 119.8 (C₁₁H), 114.7 (CH=CH₂), 100.5 (C₁₈H), 59.7 (C₉H), 55.7 (C₂H₂), 55.7 (C₈H), 55.7 (CH₃), 41.1 (C₃H₂), 39.3 (C₅H), 39.2 (OCH₃), 27.8 (C₆H₂), 27.3 (C₄H), 25.0 (C₇H₂); m/z (ES) 403 ([M+H]⁺, 100 %); m/z (ES) found [M+H]⁺ 403.1685. C₂₁H₂₇N₂O₄S requires 403.1686.

9-Deoxy-9-azidoquinine **132**^[44]



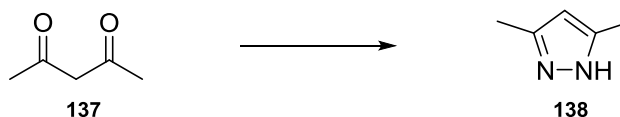
Sodium azide (3.22 g, 49.5 mmol) was added to a solution of 9-*epi*-mesyloxyquinine **131** (4.16 g, 9.90 mmol) in *N,N*-dimethylformamide (35 ml). The resulting mixture was heated to 80 °C for 6 hours. This was then cooled to room temperature and quenched with saturated aqueous sodium hydrogen carbonate. The reaction mixture was extracted with chloroform (30 ml). The organic layer was washed with water (3 x 30 ml) and brine (10 ml), then dried (magnesium sulfate) and concentrated under reduced pressure to yield **132** (1.80 g, 52 %) as a yellow oil. R_f : 0.6 (ethyl acetate); $[\alpha]_D^{24}$ -24.1 (c 0.7 in CHCl₃); (Lit. $[\alpha]_D^{22}$ -28.2 (c 1.0 in CHCl₃))^[121]; $\nu_{\max}$ (neat)/cm⁻¹ 2949, 2105, 1622, 1509, 1242; δ_H (400 MHz, CDCl₃) 8.79 (1H, d, J 7.5, C₁₂H), 8.06 (1H, d, J 2.0, C₁₈H), 7.43 - 7.38 (2H, m, C₁₁H + C₁₅H), 7.31 (1H, dd, J 7.5, 2.0, C₁₆H), 5.83 (1H, ddd, J 17.5, 10.0, 7.5, CH=CH₂), 5.16 - 5.02 (2H, m, CH=CH₂), 4.99 (1H, ddd, J 3.5, 1.5, 1.5, C₉H), 3.96 (3H, s, OCH₃), 3.27 (1H, ddd, J 8.0, 8.0, 8.0, C₂H), 3.19 - 3.01 (2H, m, C₆H + C₈H), 2.70 - 2.59 (2H, m, C₆H + C₂H), 2.32 - 2.23 (1H, m, C₅H), 1.97 - 1.84 (2H, m, C₃H₂), 1.76 - 1.65 (1H, m, C₄H), 1.61 - 1.48 (2H, m, C₇H); δ_C (100 MHz, CDCl₃) 158.1 (C₁₇), 147.6 (C₁₂H), 144.9 (C), 141.9 (C), 141.6 (CH=CH₂), 132.1 (C₁₅H), 127.1 (C₁₉), 121.7 (C₁₆H), 119.5 (C₁₁H), 114.5 (CH=CH₂), 101.1 (C₁₈H), 65.4 (C₉H), 58.5 (C₈H), 56.6 (C₂H₂), 55.6 (OCH₃), 42.0 (C₃H₂), 39.6 (C₅H), 27.7 (C₆H₂), 27.6 (C₄H), 25.1 (C₇H₂); m/z (ES) 350 ([M+H]⁺, 100 %); m/z (ES) found [M+H]⁺ 350.1979. C₂₀H₂₄N₅O requires 350.1975. The ¹H and ¹³C NMR data are in agreement with those previously reported.^[121]

9-Deoxy-9-aminoquinine **129**^[44]



9-Deoxy-9-azidoquinine **132** (1.80 g, 5.20 mmol) was dissolved in diethyl ether (60 ml) and the solution was cooled to 0 °C. 1M Lithium aluminium hydride in diethyl ether (5.70 ml, 5.70 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature and stirred for 18 hours. The mixture was quenched with water (6 ml). Diethyl ether (30 ml) and water (30 ml) were then added. The organic layer was washed with brine (30 ml) then dried over magnesium sulphate, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (dichloromethane: methanol; 4: 1) to yield **129** (201 mg, 12 %) as an orange oil. R_f : 0.2 (dichloromethane: methanol; 4: 1); $[\alpha]_D^{23}$ -34.4 (c 0.08 in CHCl_3); (Lit. $[\alpha]_D^{24}$ -53.6 (c 0.8 in CHCl_3))^[93] ν_{max} (neat)/ cm^{-1} 3379, 3080, 2948, 1622, 1509, 1242; δ_{H} (400 MHz, CDCl_3) 8.74 (1H, d, J 7.5, C_{12}H), 8.01 (1H, d, J 2.0, C_{18}H), 7.42 (1H, d, J 7.5, C_{15}H), 7.38 - 7.32 (2H, m, $\text{C}_{11}\text{H} + \text{C}_{16}\text{H}$), 5.94 (1H, ddd, J 17.5, 10.0, 7.5, $\text{CH}=\text{CH}_2$), 5.06 - 5.03 (2H, m, $\text{CH}=\text{CH}_2$), 4.57 (1H, d, J 9.5, C_9H), 3.94 (3H, s, OCH_3), 3.19 (1H, ddd, J 8.5, 8.5, 8.5, C_2H), 3.02 (1H, dd, J 14.0, 10.0, C_8H), 2.98 - 2.89 (1H, m, C_6H), 2.68 - 2.61 (1H, m, C_6H), 2.58 - 2.48 (1H, m, C_2H), 2.30 - 2.21 (1H, m, C_5H), 2.20 - 2.11 (1H, m, C_4H), 1.91 - 1.85 (1H, m, C_3H), 1.70 - 1.40 (5H, m, $\text{C}_3\text{H} + \text{C}_7\text{H}_2 + \text{NH}_2$); δ_{C} (100 MHz, CDCl_3) 157.8 (C_{17}), 149.3 (C), 148.0 (C_{12}H), 144.8 (C), 142.0 ($\text{CH}=\text{CH}_2$), 132.0 (C_{15}H), 127.7 (C_{19}) 129.0 (C_{16}H), 118.3 (C_{11}H), 114.3 ($\text{CH}=\text{CHf}_2$), 101.2 (C_{18}H), 60.6 (C_9H), 56.3 (C_2H_2), 55.5 (OCH_3), 53.9 (C_8H), 41.9 (C_3H_2), 39.8 (C_5H), 27.9 (C_6H_2), 27.8 (C_4H), 26.7 (C_7H_2); m/z (ES) 324 ($[\text{M}+\text{H}]^+$, 100 %); m/z (ES) found $[\text{M}+\text{H}]^+$ 324.2065. $\text{C}_{20}\text{H}_{26}\text{N}_3\text{O}$ requires 324.2070. The ^1H and ^{13}C NMR data are in agreement with those previously reported.^[93]

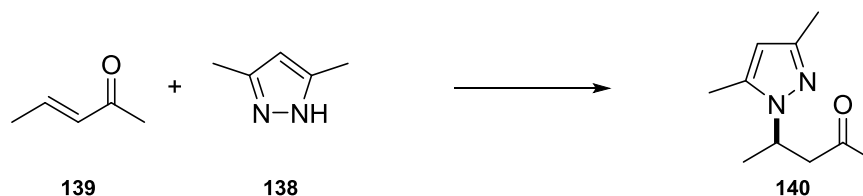
3,5-Dimethylpyrazole **138**



Following general procedure 1, acetylacetone **137** (860 μl , 7.70 mmol) was condensed with hydrazine hydrate (750 μl , 15.4 mmol) to yield **138** (590 mg, 80 %) as a colourless solid. M.p. 107 – 109 °C; Lit. m.p. 108 °C^[122]; ν_{max} / cm^{-1} (CHCl_3) 2942, 2877, 1595, 1484; δ_{H} (400 MHz, CDCl_3) 8.27 (1H, s, NH), 5.83 (1H, s, ArH), 2.27 (6H, s, 2CH_3); δ_{C} (100 MHz, CDCl_3) 104.1 (CH), 12.2 (CH_3); m/z (ES) 119 ($\text{M}+\text{Na}^+$, 100 %); m/z (ES) $[\text{M}+\text{Na}]^+$

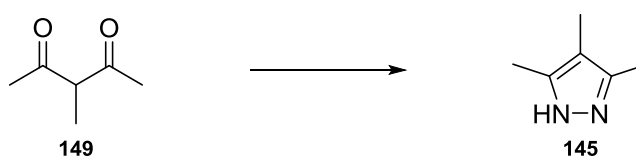
119.0584. $C_5H_8N_2Na$ requires 119.0580. The ^1H and ^{13}C NMR data are in agreement with those previously reported.^[122]

(4*R*)-4-(3',5'-Dimethylpyrazol-1'-yl)-pentan-2-one 140



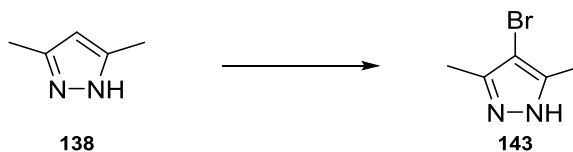
Following general procedure 2, 3,5-dimethylpyrazole **138** (48.0 mg, 500 μ mol) was reacted with 3-penten-2-one **139** (72.0 μ l, 500 μ mol) for 19 hours to give the crude product. Purification by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 1: 3) yielded **140** (85.0 mg, 80 %) as a colourless oil. R_f : 0.5 (light petroleum ether: ethyl acetate; 1: 3); $[\alpha]_D^{25}$ -33.2 (c 0.7 in $CHCl_3$); ν_{max} / cm^{-1} (neat) 2944, 1708, 1552; δ_H (400 MHz, $CDCl_3$) 5.72 (1H, s, ArH), 4.74 - 4.64 (1H, m, CHN), 3.37 (1H, dd, J 16.0, 8.0, CH_AH_B), 2.82 (1H, dd, J 16.0, 8.0, CH_AH_B), 2.27 (3H, s, CH_3), 2.22 (3H, s, CH_3), 2.08 (3H, s, $COCH_3$), 1.41 (3H, d, J 4.0, $CHCH_3$); δ_C (100 MHz, $CDCl_3$) 206.7 (C), 147.4 (C), 138.5 (C), 104.5 (CH), 49.3 (CH_2), 48.6 (CH), 30.7 (CH_3), 21.3 (CH_3), 13.6 (CH_3), 10.9 (CH_3); m/z (ES) 181 ($M+H^+$, 100 %). m/z (ES) $[M+H]^+$ 181.1344. $C_{10}H_{17}N_2O$ requires 181.1335. R_t HPLC: Chiralpak AD-H; mobile phase, hexane: 2-propanol (49: 1 v/v); flow rate, 1 ml/min; 6.2 min (2.2 %), 7.2 min (97.8 %) 96 % e.e.

3,4,5-Trimethylpyrazole 145



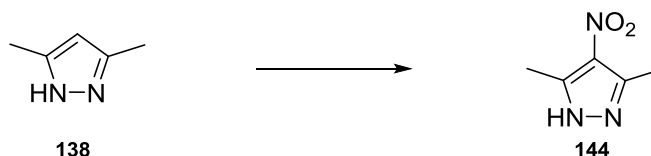
Following general procedure 1, 3-methylpentan-2,4-dione **149** (500 mg, 5.10 mmol) was condensed with hydrazine hydrate (905 μ l, 10.2 mmol) to yield **145** (400 mg, 70 %) as a colourless solid. M.p. 141 - 143 $^{\circ}C$; Lit m.p. 137 - 139 $^{\circ}C$ ^[123], ν_{max} / cm^{-1} ($CHCl_3$) 2920, 1597, 1524, 1476, 1418, 1298; δ_H (400 MHz, $CDCl_3$) 7.87 (1H, bs, NH), 2.19 (6H, s, 2 CH_3), 1.91 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 141.9 (C), 110.5 (C), 10.8 (CH_3), 7.5 (CH_3). m/z (ES) 111 ($M+H^+$, 100 %); m/z (ES) $[M+H]^+$ 111.0864. $C_6H_{11}N_2$ requires 111.0844. The ^1H and ^{13}C NMR data are in agreement with those previously reported.^[123]

4-Bromo-3,5-dimethylpyrazole **143**^[52]

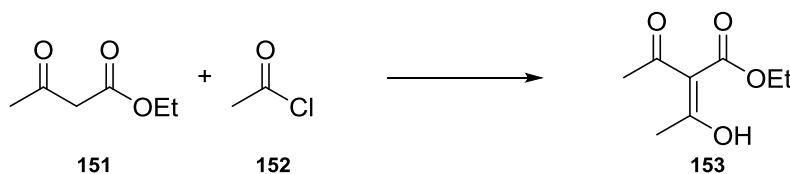


3,5-Dimethylpyrazole **138** (1.00 g, 10.4 mmol) was dissolved in ethyl acetate (50 ml) and *N*-bromosuccinimide (2.78 g, 15.6 mmol) was added in one portion. The resulting solution was stirred at room temperature for 1 hour. The solution was washed with saturated aqueous sodium thiosulfate (3 x 50 ml), the organic layer dried (magnesium sulfate) and concentrated to yield **143** (1.40 g, 80 %) as a colourless solid. M.p. 120 - 122 °C; lit. m.p. 124 - 125 °C^[52]; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3382, 1633, 1220; δ_{H} (400 MHz, CDCl₃) 10.34 (1H, bs, NH), 2.27 (6H, s, 2CH₃); δ_{C} (100 MHz, CDCl₃) 142.8 (C), 94.2 (C), 11.3 (CH₃); m/z (ES) 175 (M⁷⁹Br+H⁺, 100 %), 177 (M⁸¹Br+H⁺, 99). m/z (ES) [M+H]⁺ 174.9869. C₅H₈⁷⁹BrN₂ requires 174.9866. The ¹H and ¹³C NMR data are in agreement with those previously reported.^[52]

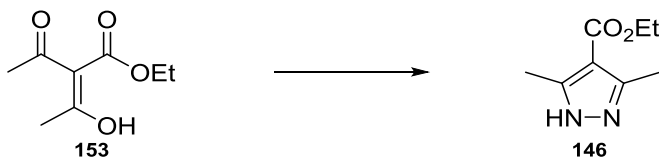
4-Nitro-3,5-dimethylpyrazole **144**



3,5-Dimethylpyrazole **138** (1.00 g, 10.4 mmol) was dissolved in concentrated sulphuric acid (2 ml) and the solution cooled to 0 °C. Concentrated nitric acid (1.2 ml) was added dropwise and the reaction was stirred at 0 °C for 1 hour. Concentrated sulphuric acid (1.2 ml) was added dropwise and the solution was warmed to room temperature then stirred for 18 hours. The reaction mixture was poured onto ice and adjusted to pH 8 with aqueous potassium hydroxide solution. The aqueous was extracted with dichloromethane (3 x 20 ml). The combined organics were dried (magnesium sulfate) and concentrated under reduced pressure to yield **144** (1.20 g, 81 %) as an off white solid. M.p. 128 - 130 °C; Lit m.p. 124 - 126 °C^[124]; $\nu_{\max}/\text{cm}^{-1}$ (CHCl₃) 2992, 1592, 1507, 1440, 1415, 1362; δ_{H} (400 MHz, CDCl₃) 8.76 (1H, bs, NH), 2.62 (6H, s, 2CH₃); δ_{C} (100 MHz, CDCl₃) 144.6 (C), 131.1 (C), 13.2 (CH₃); m/z (ES) 142 (M+H⁺, 100 %), 164 (M+Na⁺, 23). m/z (ES) [M+H]⁺ 142.0597. C₅H₈N₃O₂ requires 142.0572. The ¹H and ¹³C NMR data are in agreement with those previously reported.^[125]

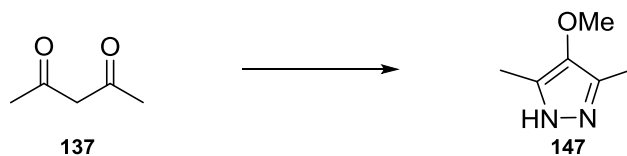
Ethyl 2-acetyl-3-hydroxy-2-butenate **153**^[53]

Ethyl acetoacetate **151** (1.50 ml, 12.0 mmol) was added to a mixture of ethanol (2.30 ml, 40.0 mmol), carbon tetrachloride (300 μ l) and magnesium (294 mg, 12.1 mmol) in toluene (30 ml) under an argon atmosphere. This was stirred for 30 minutes at room temperature and then heated to reflux and stirred for 1 hour. The mixture was cooled to 0 °C and acetyl chloride **152** (860 μ l, 12.1 mmol) was added dropwise over 8 minutes. After 20 minutes stirring a white gum formed. This mixture was washed with 2 M hydrochloric acid (25 ml), saturated aqueous sodium bicarbonate (25 ml) and brine (25 ml). The organic layer was dried (magnesium sulfate) and concentrated under reduced pressure to yield **153** (1.41 g, 68 %) as a colourless oil. R_f : 0.4 (light petroleum ether: ethyl acetate; 9: 1); $\nu_{\max}$ / cm^{-1} (neat) 3649, 2984, 1712, 1557, 1446, 1418; δ_{H} (400 MHz, CDCl_3) 11.65 (1H, s, OH), 4.27 (2H, q, J 8.0, CH_2CH_3), 2.38 (6H, s, 2 CH_3), 1.35 (3H, t, J 8.0, CH_2CH_3); δ_{C} (100 MHz, CDCl_3) 196.5 (C), 167.1 (C), 108.7 (C), 60.7 (CH_2), 25.9 (CH_3), 14.2 (CH_3); m/z (ES) 195 ($\text{M}+\text{H}^+$, 100 %), 181 (37). m/z (ES) $[\text{M}+\text{H}]^+$ 195.0638. $\text{C}_8\text{H}_{13}\text{O}_4$ requires 195.0628. The ^1H and ^{13}C NMR data are in agreement with those previously reported.^[53]

Ethyl 3,5-dimethylpyrazole-4-carboxylate **146**^[53]

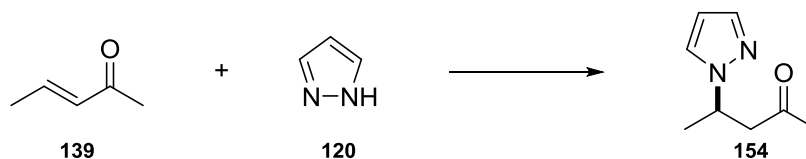
Dione **153** (1.41 g, 8.10 mmol) was dissolved in ethanol (16 ml) cooled to 0 °C and hydrazine dihydrochloride (980 mg, 9.80 mmol) and hydrazine hydrate (35%, 870 μ l, 9.80 mmol) were added. This was allowed to warm to room temperature then stirred for 3 hours. The reaction mixture was concentrated and diethyl ether (15 ml) was added and the resulting solid filtered to yield **146** (1.40 g, 99 %) as a colourless solid. M.p. 206 - 208 °C; $\nu_{\max}$ / cm^{-1} (solid) 3244, 2923, 1683, 1462, 1130; δ_{H} (400 MHz, d_6 -DMSO) 4.17 (2H, q, J 7.0, CH_2CH_3), 2.34 (6H, s, 2 CH_3), 1.27 (3H, t, J 7.0, CH_2CH_3); δ_{C} (100 MHz, d_6 -DMSO) 163.0 (C), 147.6 (C), 109.5 (C), 60.2 (CH_2), 14.5 (CH_3), 12.3 (CH_3); m/z (ES) 169 ($\text{M}+\text{H}^+$, 100 %), 107 (56). m/z (ES) $[\text{M}+\text{H}]^+$ 169.0972. $\text{C}_8\text{H}_{13}\text{N}_2\text{O}_2$ requires 169.0932. The ^1H and ^{13}C NMR data are in agreement with those previously reported.^[53]

4-Methoxy-3,5-dimethylpyrazole **147**



Iodosobenzene (2.43 g, 10.0 mmol) was suspended in methanol (40 ml) and boron trifluoride etherate (1.27 ml, 10.0 mmol) was added with stirring followed by 2,4-pentadione **137** (1.00 ml, 10.0 mmol) dropwise. This mixture was stirred at room temperature for 2 hours and concentrated under reduced pressure and the resulting solution poured into saturated sodium bicarbonate (40 ml) and the aqueous layer extracted with dichloromethane (3 x 40 ml). The combined organics were dried (magnesium sulfate) and concentrated under reduced pressure. The residue was dissolved in ethanol (10 ml) and hydrazine hydrate (35 %, 1.77 ml, 20 mmol) was added dropwise at 0 °C and stirred at room temperature for 16 hours. The solution was concentrated and the residue partitioned between water (30 ml) and dichloromethane (30 ml). The aqueous layer was extracted with dichloromethane (2 x 30 ml). The combined organics were dried (magnesium sulfate) and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (ethyl acetate) to yield **147** (305 mg, 24 %) as an off white solid. M.p. 160 - 161 °C; R_f : 0.3 (ethyl acetate); $\nu_{\max}$ /cm⁻¹ (neat) 3218, 2931, 1600, 1525, 1452, 1235; δ_H (400 MHz, CDCl₃) 9.81 (1H, bs, NH), 3.72 (3H, s, OCH₃), 2.23 (6H, s, 2CH₃); δ_C (100 MHz, CDCl₃) 140.3 (C), 134.4 (C), 62.0 (CH₃), 9.7 (CH₃); m/z (ES) 127 (M+H⁺, 100 %). m/z (ES) [M+H]⁺ 127.0835, C₅H₁₁N₂O requires 127.0866.

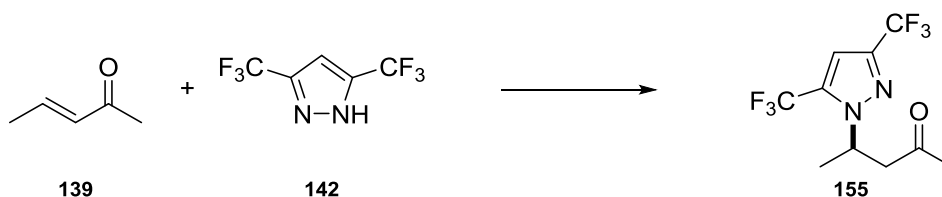
(4R)-4-(Pyrazol-1'-yl)-pentan-2-one **154**



Following general procedure 2, pyrazole **120** (34.0 mg, 500 μ mol) was reacted with 3-penten-2-one **139** (72.0 μ l, 500 μ mol) for 19 hours to give the crude product. Purification by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 1: 3) yielded **154** (58.0 mg, 77 %) as a colourless oil. R_f : 0.6 (light petroleum ether: ethyl acetate; 1: 3); $[\alpha]_D^{26}$ -37.3 (c 0.7 in CHCl₃); $\nu_{\max}$ /cm⁻¹ (neat) 2982, 1717, 1509, 1399, 1367, 1286; δ_H (400 MHz, CDCl₃) 7.51 (1H, d, J 4.0, ArH), 7.43 (1H, d, J 4.0, ArH), 6.20 (1H, t, J 4.0, ArH), 4.84 (1H, m, CHN), 3.25 (1H, dd, J 20.0, 8.0, CH_AH_B), 2.81 (1H, dd, J 20.0, 8.0, CH_AH_B), 2.08 (3H, s, COCH₃), 1.53 (3H, d, J 8.0, CHCH₃); δ_C (100 MHz, CDCl₃) 206.0 (C), 139.3 (CH), 128.5 (CH), 104.8 (CH), 53.3 (CH), 49.8 (CH₂), 30.5 (CH₃), 21.2 (CH₃); m/z (ES) 153 (M+H⁺, 100 %). m/z (ES) [M+H]⁺ 153.0842. C₈H₁₃N₂O requires 153.1022;

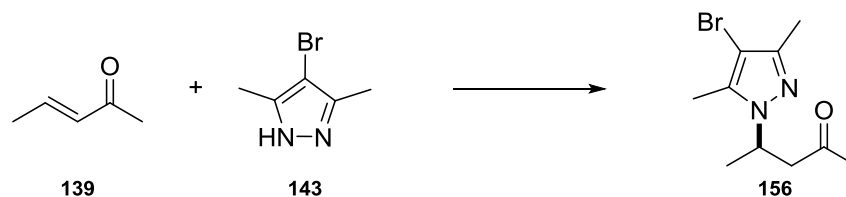
R_t HPLC: Chiralpak AS-H; mobile phase, hexane: 2-propanol (19: 1 v/v); flow rate, 0.8 ml/min; 14.3 min (5.7 %), 22.9 min (94.3 %) 88 % e.e.

(4*R*)-4-(3',5'-Bistrifluoromethylpyrazol-1'-yl)pentan-2-one 155



Following general procedure 2, 3,5-bistrifluoromethylpyrazole **142** (102 mg, 500 μ mol) was reacted with 3-penten-2-one **139** (72.0 μ l, 500 μ mol) for 18 hours to give the crude product. Purification by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 1: 1) yielded **155** (96.0 mg, 66 %) as a colourless oil. R_f : 0.5 (light petroleum ether: ethyl acetate; 1: 1); [α]_D²³ -7.7 (c 1.0, CHCl₃); $\nu_{\max}$ / cm⁻¹ (neat) 2944, 1724, 1564, 1499, 1458, 1410; δ_{H} (400 MHz, CDCl₃) 6.82 (1H, s, ArH), 5.09 - 4.99 (1H, m, CHN), 3.40 (1H, dd, *J* 16.0, 8.0, CH_AH_B), 2.97 (1H, dd, *J* 16.0, 8.0, CH_AH_B), 2.15 (3H, s, COCH₃), 1.50 (3H, d, *J* 8.0, CHCH₃); δ_{C} (100 MHz, CDCl₃) 204.7 (C), 141.7 (C, q, *J* 39.0), 132.9 (C, q, *J* 39.0), 120.4 (C, q, *J* 267), 119.2 (C, q, *J* 268), 105.7 (CH), 104.3 (C), 53.5 (CH), 48.5 (CH₂), 30.2 (CH₃), 21.4 (CH₃); *m/z* (ES) 311 (M+Na⁺, 100%), 227 (50). *m/z* (ES) [M+Na]⁺ 311.0585. C₁₀H₁₀F₆N₂NaO requires 311.0590; R_t HPLC: Chiralcel OJ-H; mobile phase, hexane: 2-propanol (9: 1 v/v); flow rate, 1.0 ml/min; 4.8 min (97.8 %), 5.6 min (2.2 %) 96 % e.e.

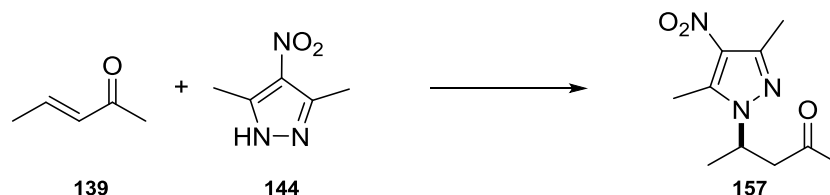
(4*R*)-4-(4'-Bromo-3',5'-dimethylpyrazol-1'-yl)-pentan-2-one 156



Following general procedure 2, 4-bromo-3,5-dimethylpyrazole **143** (88.0 mg, 500 μ mol) was reacted with 3-penten-2-one **139** (72.0 μ l, 500 μ mol) for 18 hours to give the crude product. Purification by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 2: 1) yielded **156** (129 mg, 99 %) as a colourless oil. R_f : (light petroleum ether: ethyl acetate; 2: 1); [α]_D²⁶ -23.6 (c 0.7, CHCl₃); $\nu_{\max}$ / cm⁻¹ (neat) 2932, 1717, 1546, 1474, 1425; δ_{H} (400 MHz, CDCl₃) 4.78 - 4.66 (1H, m, CHN), 3.34 (1H, dd, *J* 16.0, 8.0, CH_AH_B), 2.77 (1H, dd, *J* 16.0, 4.0, CH_AH_B), 2.27 (3H, s, CH₃), 2.18 (3H, s, CH₃), 2.08 (3H, s, COCH₃), 1.37 (3H, d, *J* 8.0, CHCH₃); δ_{C} (100 MHz, CDCl₃) 206.1 (C), 145.9 (C), 136.8 (C), 93.5 (C), 49.8 (CH), 48.9 (CH₂), 30.6 (CH₃), 21.2 (CH₃), 12.4 (CH₃), 10.1 (CH₃); *m/z* (ES) 261 (M+H⁺, 100 %), 259 (48), 176 (21), 174 (23). *m/z* (ES) [M+H]⁺ 261.0417.

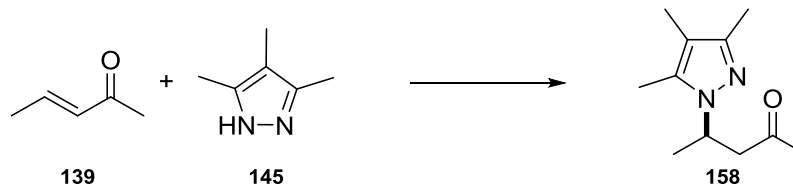
$C_{10}H_{16}^{81}BrN_2O$ requires 261.0421; R_t HPLC: Chiralpak AD-H; mobile phase, hexane: 2-propanol (99 : 1 v/v); flow rate, 1 ml/min; 7.4 min (3.1 %), 8.2 min (96.9 %) 94 % e.e.

(4R)-4-(4'-Nitro-3',5'-dimethylpyrazol-1'-yl)-pentan-2-one **157**



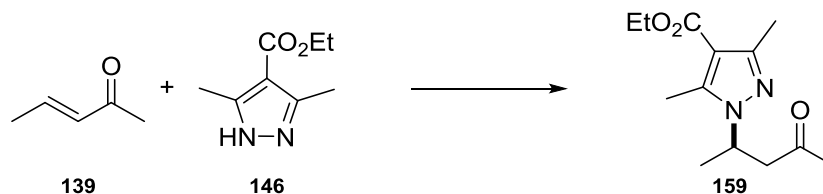
Following general procedure 2, 4-nitro-3,5-dimethylpyrazole **144** (140 mg, 1.00 mmol) was reacted with 3-penten-2-one **139** (72.0 μ l, 500 μ mol) for 120 hours to give the crude product. Purification by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 3: 2) yielded **157** (60.0 mg, 53 %) as a colourless oil. R_f : 0.5 (light petroleum ether: ethyl acetate; 3: 2); $[\alpha]_D^{24}$ -18.7 (c 0.7, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2982, 1717, 1562, 1492, 1419; δ_H (400 MHz, $CDCl_3$) 4.87 - 4.74 (1H, m, CHN), 3.43 (1H, dd, J 20.0, 12.0, CH_AH_B), 2.79 (1H, dd, J 20.0, 4.0, CH_AH_B), 2.69 (3H, s, CH_3), 2.47 (3H, s, CH_3), 2.11 (3H, s, COCH₃), 1.41 (3H, d, J 8.0, CHCH₃); δ_C (100 MHz, $CDCl_3$) 205.4 (C), 146.2 (C), 140.1 (C), 49.5 (CH), 48.3 (CH₂), 30.3 (CH₃), 20.8 (CH₃), 14.3 (CH₃), 11.2 (CH₃); m/z (ES) 248 ($M+Na^+$, 100%), 226 ($M+H^+$, 23). m/z (ES) [$M+Na$]⁺ 248.1006. $C_{10}H_{16}N_3O_3Na$ requires 248.1006; R_t HPLC: Chiralpak AD-H; mobile phase, hexane: 2-propanol (9: 1 v/v); flow rate, 1 ml/min; 7.3 min (3.9 %), 8.7 (96.1 %) 92 % e.e.

(4R)-4-(3',4',5'-Trimethylpyrazol-1'-yl)-pentan-2-one **158**



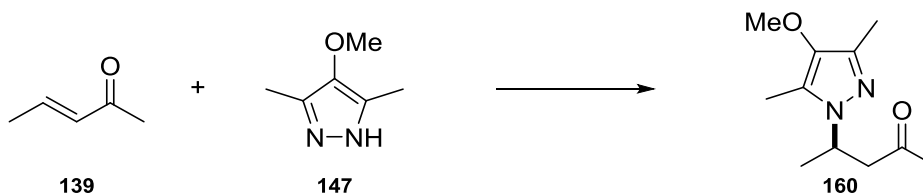
Following general procedure 2, 3,4,5-trimethylpyrazole **145** (56.0 mg, 500 μ mol) was reacted with 3-penten-2-one **139** (72.0 μ l, 500 μ mol) for 18 hours to give the crude product. Purification by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 2: 1) yielded **158** (70.0 mg, 72 %) as a colourless oil, R_f : 0.5 (light petroleum ether: ethyl acetate; 2: 1); $[\alpha]_D^{26}$ -21.4 (c 0.7, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2979, 1716, 1577, 1495; δ_H (400 MHz, $CDCl_3$) 4.74 - 4.61 (1H, m, CHN), 3.32 (1H, dd, J 16.0, 4.0, CH_AH_B), 2.79 (1H, dd, J 16.0, 4.0, CH_AH_B), 2.16 (3H, s, CH_3), 2.14 (3H, s, CH_3), 2.07 (3H, s, COCH₃), 1.87 (3H, s, CH_3), 1.38 (3H, d, J 8.0, CHCH₃); δ_C (100 MHz, $CDCl_3$) 206.8 (C), 146.1 (C), 135.4 (C), 110.6 (C), 49.3 (CH₂), 48.7 (CH), 30.7 (CH₃), 21.4 (CH₃), 11.9 (CH₃), 9.4 (CH₃), 8.0 (CH₃); m/z (ES) 195 ($M+H^+$, 100 %). m/z (ES) [$M+H$]⁺ 195.01497. $C_{11}H_{19}N_2O$ requires 195.1492; R_t HPLC: Chiralpak AD-H; mobile phase, hexane: 2-propanol (99: 1 v/v); flow rate, 1 ml/min; 9.1 min (9.4 %), 11.7 min (90.6 %) 81 % e.e.

Ethyl (R)-3,5-dimethyl-1-(4'-oxopentan-2'-yl)-pyrazole-4-carboxylate **159**



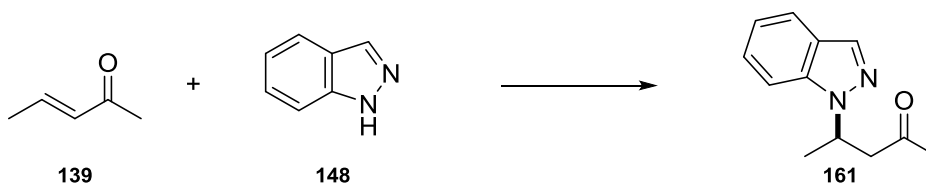
Following general procedure 2, ethyl 3,5-dimethylpyrazole-4-carboxylate **146** (84.0 mg, 500 μ mol) was reacted with 3-penten-2-one **139** (72.0 μ l, 500 μ mol) and isophthalic acid (33.0 mg, 100 μ mol) for 18 hours to give the crude product. Purification by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 1: 1) yielded **159** (25.0 mg, 20 %) as a colourless oil. R_f : 0.5 (light petroleum ether: ethyl acetate; 1: 1); $[\alpha]_D^{26}$ -9.3 (c 1.0 in CHCl_3); ν_{max} / cm^{-1} (neat) 2981, 1700, 1549, 1488, 1432; δ_{H} (400 MHz, CDCl_3) 4.84 - 4.72 (1H, m, CHN), 4.27 (2H, q, J 8.0, CH_2CH_3), 3.39 (1H, dd, J 16.0, 8.0, $\text{CH}_\text{A}\text{H}_\text{B}$), 2.81 (1H, dd, J 16.0, 8.0, $\text{CH}_\text{A}\text{H}_\text{B}$), 2.57 (3H, s, CH_3), 2.40 (3H, s, CH_3), 2.10 (3H, s, COCH_3), 1.40 (3H, d, J 8.0, CHCH_3), 1.35 (3H, d, J 8.0, CH_2CH_3); δ_{C} (100 MHz, CDCl_3) 206.0 (C), 164.7 (C), 150.5 (C), 143.6 (C), 109.1 (C), 59.5 (CH_2), 48.8 (CH), 48.7 (CH_2), 30.5 (CH_3), 21.0 (CH_3), 14.4 (CH_3), 10.9 (CH_3); m/z (ES) 275 ($\text{M}+\text{Na}^+$, 100 %), 253 ($\text{M}+\text{H}^+$, 84). m/z (ES) $[\text{M}+\text{Na}]^+$ 275.1360. $\text{C}_{13}\text{H}_{21}\text{N}_2\text{O}_3\text{Na}$ requires 275.1366; R_t HPLC: Chiralpak AD-H; mobile phase, hexane: 2-propanol (9: 1 v/v); flow rate, 1 ml/min; 5.6 min (9.1 %), 6.3 (90.9 %) 82 % e.e.

(4R)-(4'-Methoxy-3',5'-dimethylpyrazol-1'-yl)pentan-2-one **160**



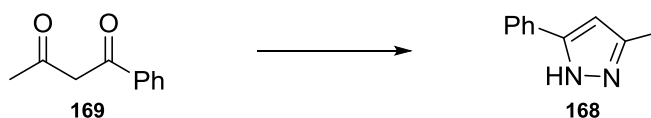
Following general procedure 2, 4-methoxy-3,5-dimethylpyrazole **147** (63.0 mg, 500 μ mol) was reacted with 3-penten-2-one **139** (72.0 μ l, 500 μ mol) for 18 hours to give the crude product. Purification by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 1: 1) yielded **160** (75.0 mg, 75 %) as a colourless oil. R_f : 0.4 (light petroleum ether: ethyl acetate; 1: 1); $[\alpha]_D^{23}$ -18.6 (c 0.9 in CHCl_3); ν_{max} / cm^{-1} (neat) 2930, 1717, 1579, 1508, 1448, 1367; δ_{H} (400 MHz, CDCl_3) 4.67 - 4.57 (1H, m, CHN), 3.66 (3H, s, OCH_3), 3.29 (1H, dd, J 16.0, 8.0, $\text{CH}_\text{A}\text{H}_\text{B}$), 2.76 (1H, dd, J 16.0, 4.0, $\text{CH}_\text{A}\text{H}_\text{B}$), 2.17 (6H, s, 2CH_3), 2.06 (3H, s, COCH_3), 1.36 (3H, d, J 8.0, CHCH_3); δ_{C} (100 MHz, CDCl_3) 206.5 (C), 139.9 (C), 138.6 (C), 128.3 (C), 62.3 (CH_3), 49.0 (CH), 48.9 (CH_2), 30.7 (CH_3), 21.2 (CH_3), 10.9 (CH_3), 8.2 (CH_3); m/z (ES) 211 ($\text{M}+\text{H}^+$, 100 %). m/z (ES) $[\text{M}+\text{H}]^+$ 211.1440. $\text{C}_{11}\text{H}_{19}\text{N}_2\text{O}_2$ requires 211.1441; R_t HPLC: Chiralpak AD-H; mobile phase, hexane: 2-propanol (19: 1 v/v); flow rate, 1.0 ml/min; 7.1 min (6.4 %), 7.6 min (93.6 %) 88 % e.e.

(4*R*)-4-(1'-Indazol-1'-yl)-pentan-2-one 161



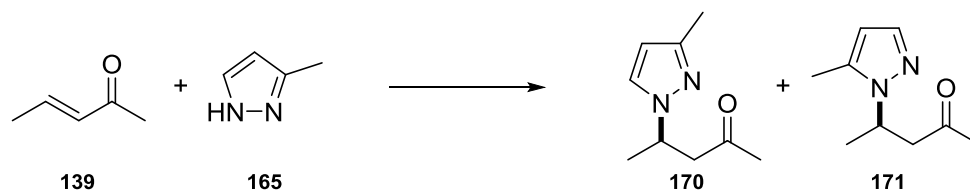
Following general procedure 2, reaction of indazole **148** (60.0 mg, 500 μ mol) with 3-penten-2-one **139** (72.0 μ l, 500 μ mol) for 71 hours to give the crude product. Purification by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 2: 1) yielded **161** (90.0 mg, 90%) as a colourless oil. $[\alpha]_D^{25}$ -32.5 (*c* 0.7, CHCl₃); R_f : 0.5 (light petroleum ether: ethyl acetate; 2: 1); $\nu_{\max}$ / cm⁻¹ (neat) 2980, 1716, 1627, 1514, 1454, 1384; δ_H (400 MHz, CDCl₃) 8.00 (1H, s, ArH), 7.70 (1H, d, *J* 8.5, 2ArH), 7.65 (1H, d, *J* 8.5, ArH), 7.31 - 7.26 (1H, m, 2ArH), 7.10 - 7.05 (1H, m, ArH), 5.20 - 5.06 (1H, m, CHN), 3.46 (1H, dd, *J* 16.0, 4.0, CH_AH_B), 2.97 (1H, dd, *J* 16.0, 4.0, CH_AH_B), 2.10 (3H, s, COCH₃), 1.68 (3H, d, *J* 8.0, CHCH₃); δ_C (100 MHz, CDCl₃) 205.6 (C), 126.0 (CH), 123.8 (C), 122.6 (CH), 121.6 (CH), 121.0 (C), 120.3 (CH), 117.3 (CH), 54.9 (CH), 49.8 (CH₂), 30.5 (CH₃), 21.6 (CH₃); *m/z* (ES) 225 (M+Na⁺, 22 %), 203 (M+H⁺, 100). *m/z* (ES) [M+H]⁺ 203.1181. C₁₂H₁₅N₂O requires 203.1179; R_t HPLC: Chiralcel OD-H; mobile phase, hexane: 2-propanol (9: 1 v/v); flow rate, 1 ml/min; 12.0 min (94.5 %), 13.2 min (5.5 %) 89 % e.e.

3-Methyl-5-phenylpyrazole 168



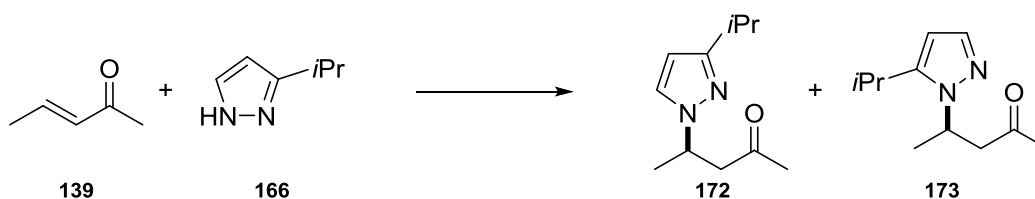
Following general procedure 1, 1-phenyl-1,3-butanedione **169** (1.00 g, 6.20 mmol) was condensed with hydrazine hydrate (600 μ l, 12.4 mmol) to yield **168** (970 mg, 94 %) as a colourless solid. M.p. 125 - 127 °C; Lit m.p. 121 - 122 °C^[126], $\nu_{\max}$ / cm⁻¹ (CHCl₃) 3195, 2955, 1589, 1461; δ_H (400 MHz, CDCl₃) 7.72 (2H, d, *J* 8.0, ArH), 7.38 (2H, t, *J* 8.0, 2ArH), 7.22 (1H, t, *J* 8.0, ArH), 6.35 (1H, s, ArH), 2.32 (3H, s, CH₃); δ_C (100 MHz, CDCl₃) 149.9 (C), 143.9 (C), 132.6 (C), 128.7 (CH), 127.8 (CH), 125.8 (CH), 102.1 (CH), 11.7 (CH₃); *m/z* (ES) 159 (M+H⁺, 100 %). *m/z* (ES) [M+H]⁺ 159.0919. C₁₀H₁₁N₂ requires 159.0917. The ¹H and ¹³C NMR data are in agreement with those previously reported.^[126]

(R)-4-(3-Methylpyrazol-1-yl)pentan-2-one 170 and (R)-4-(5-Methylpyrazol-1-yl)pentan-2-one 171



Following general procedure 2, 3-methylpyrazole **165** (41.0 mg, 500 μmol) was reacted with 3-penten-2-one **139** (72.0 μl , 500 μmol) for 120 hours to give the crude product. Purification by flash chromatography on silica gel (dichloromethane) yielded **170** and **171** as a 7: 3 mixture of regiosomers (80.0 mg, 96 %) as a colourless oil. R_f : 0.4 (dichloromethane); $[\alpha]_D^{26}$ -30.9 (c 0.7 in CHCl_3); ν_{max} / cm^{-1} (neat) 2934, 1717, 1521, 1448, 1417, 1385; δ_{H} (400 MHz, CDCl_3) 5.92 (2H, m, 2ArH), 4.80 - 4.64 (1H, m, CHN), 3.36 (0.3H, dd, J 16.0, 8.0, CH_AH_B), 3.18 (0.7H, dd, J 16.0, 8.0, CH_AH_B), 2.82 - 2.72 (1H, m, CH), 2.30 (0.9H, s, CH_3), 2.24 (2.1H, s, CH_3), 2.05 (3H, 2s, COCH_3), 1.47 (2.1H, d, J 8.0, CHCH_3), 1.39 (0.9H, d, J 8.0, COCH_3); δ_{C} (100 MHz, CDCl_3) 206.5 (minor C), 206.2 (major C), 148.5 (major C), 138.5 (minor CH), 137.8 (minor C), 129.1 (major CH), 104.7 (minor CH), 104.3 (major CH), 53.1 (major CH), 49.9 (major CH_2), 49.3 (minor CH_2), 49.0 (minor CH) 30.6 (minor CH_3), 30.5 (major CH_3), 21.3 (minor CH_3), 21.2 (major CH_3), 13.7 (major CH_3), 10.9 (minor CH_3); m/z (ES) 167 ($\text{M}+\text{H}^+$, 100 %), 189 ($\text{M}+\text{Na}^+$, 22). m/z (ES) $[\text{M}+\text{H}]^+$ 167.1182. $\text{C}_9\text{H}_{15}\text{N}_2\text{O}$ requires 167.1179; R_t HPLC Chiralcel AD-H; mobile phase, hexane: 2-propanol (9: 1 v/v); flow rate, 1 ml/min; Major 4.6 min (3.1 %), 4.8 min (65.3 %) 88 % e.e.; Minor 5.5 min (1.9 %), 5.8 min (29.7 %) 94 % e.e.

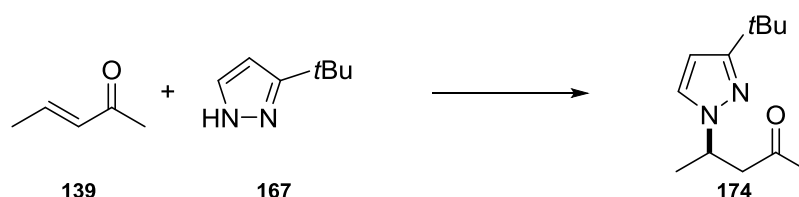
(4R)-(3'-iso-Propylpyrazol-1'-yl)pentan-2-one 172 and (4R)-(5'-iso-propylpyrazol-1-yl)pentan-2-one 173



Following general procedure 2, 3-iso-propylpyrazole **166** (22.0 mg, 200 μmol) was reacted with 3-penten-2-one **139** (29.0 μl , 200 μmol) for 42 hours to give the crude product. Purification by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 3: 2) yielded **172** (24.0 mg, 62 %) as a colourless oil. R_f : 0.5 (light petroleum ether: ethyl acetate; 3: 2); $[\alpha]_D^{23}$ -9.5 (c 0.8 in CHCl_3); ν_{max} (neat)/ cm^{-1} 2964, 1717, 1519, 1457, 1419; δ_{H} (400 MHz, CHCl_3) 7.29 (1H, d, J 2.5, ArH), 5.99 (1H, d, J 2.5, ArH), 4.79 - 4.68 (1H, m, CHN), 3.20 (1H, dd, J 17.0, 7.0, CH_AH_B), 2.97 (1H, m, CH), 2.76 (1H, dd, J 17.0, 6.5, CH_AH_B), 2.07 (3H, s, COCH_3), 1.50 (3H, d, J 7.0, CHCH_3), 1.24 (3H, d, J 7.0,

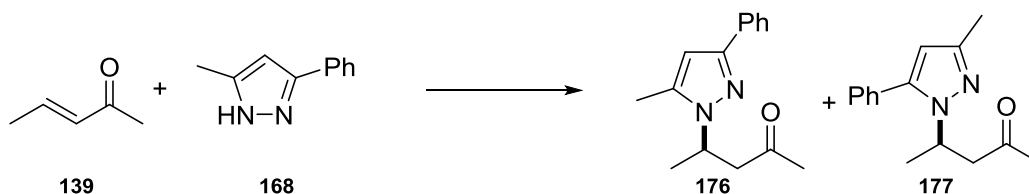
CHCH₃), 1.22 (3H, d, *J* 7.0, CHCH₃); δ_C (100 MHz, CHCl₃) 206.4 (C), 159.2 (C), 128.3 (CH), 101.1 (CH), 53.3 (CH), 50.0 (CH₂), 30.5 (CH₃), 28.0 (CH), 23.1 (CH₃), 21.0 (CH₃); *m/z* (ES) 195 ([M+H]⁺, 100 %); *m/z* (ES) found [M+H]⁺ 195.1499. C₁₁H₁₉N₂O⁺ requires 195.1492; R_t HPLC: Chiralpak AD-H; hexane: 2-propanol, (49: 1 v/v); flow rate, 1 ml/min; 6.0 min (10.5 %), 6.4 min (89.5 %), 79 % e.e. Followed by **173** (7.20 mg, 18 %) as a colourless oil. R_f : 0.4 (light petroleum ether: ethyl acetate; 3: 2); $[\alpha]_D^{23}$ -27.1 (c 0.1 in CHCl₃); $\nu_{\max}$ (neat)/cm⁻¹ 2960, 1718, 1518, 1459, 1418; δ_H (400 MHz, CHCl₃) 7.43 (1H, d, *J* 2.5, ArH), 5.98 (1H, d, *J* 2.5, ArH), 4.88 - 4.78 (1H, m, CHN), 3.37 (1H, dd, *J* 17.5, 8.0, CH_AH_B), 3.15 - 3.07 (1H, m, CHN), 2.87 (1H, dd, *J* 17.5, 6.0, CH_AH_B), 2.08 (3H, s, COCH₃), 1.46 (3H, d, *J* 8.0, CHCH₃), 1.30 (3H, d, *J* 8.0, CHCH₃), 1.25 (3H, d, *J* 7.5, CHCH₃); δ_C (100 MHz, CHCl₃) 206.6 (C), 181.7 (C), 138.4 (CH), 101.7 (CH), 49.5 (CH₂), 49.0 (CH), 30.7 (CH₃), 25.0 (CH), 23.2 (CH₃), 22.5 (CH₃), 21.7 (CH₃); *m/z* (ES) 195 ([M+H]⁺, 100 %); *m/z* (ES) found [M+H]⁺ 195.1497. C₁₁H₁₉N₂O⁺ requires 195.1492; R_t HPLC: Chiralpak AD-H; mobile phase, hexane: 2-propanol (49: 1 v/v); flow rate, 1 ml/min; 7.5 min (2.4 %), 9.0 min (97.6 %) 95 % e.e.

(4*R*)-(3'-*tert*-Butylpyrazol-1'-yl)pentan-2-one **174**



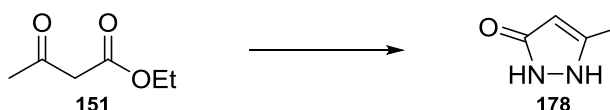
Following general procedure 2, reaction of 3-*tert*-butylpyrazole **167** (25.0 mg, 200 μ mol) with 3-penten-2-one **139** (29.0 μ l, 200 μ mol) for 42 hours to give the crude product. Purification by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 4: 1) yielded **174** (31.0 mg, 75 %) as a colourless oil. R_f : 0.4 (light petroleum ether: ethyl acetate; 4: 1); $[\alpha]_D^{23}$ -28.8 (c 0.9 in CHCl₃); $\nu_{\max}$ (neat)/cm⁻¹ 2960, 1718, 1518, 1459, 1418; δ_H (400 MHz, CHCl₃) 7.27 (1H, d, *J* 2.5, ArH), 6.02 (1H, d, *J* 2.5, ArH), 4.79 - 4.69 (1H, m, CHN), 3.20 (1H, dd, *J* 17.0, 8.0, CH_AH_B), 2.72 (1H, dd, *J* 17.0, 7.0, CH_AH_B), 2.08 (3H, s, COCH₃), 1.50 (3H, d, *J* 7.0, CHCH₃), 1.28 (3H, s, C(CH₃)₃); δ_C (100 MHz, CHCl₃) 206.6 (C), 161.6 (C), 127.5 (CH), 101.1 (CH), 53.5 (CH), 50.0 (CH₂), 32.1 (C), 30.7 (C(CH₃)₃), 21.0 (CH₃); *m/z* (ES) 209 ([M+H]⁺, 100 %); *m/z* (ES) found [M+H]⁺ 209.1650. C₁₂H₂₁N₂O⁺ requires 209.1648; R_t HPLC: Chiralpak AD-H; mobile phase, hexane: 2-propanol (19: 1 v/v); flow rate, 1 ml/min; 5.1 min (8.0 %), 6.2 min (92.0 %) 84 % e.e.

(4*R*)-4-(3'-Phenyl-5'-methylpyrazol-1'-yl)pentan-2-one 176 and (4*R*)-4-(5'-Phenyl-3'-methylpyrazol-1'-yl)pentan-2-one 177



Following general procedure 2, 3-methyl-5-phenylpyrazole **168** (79.0 mg, 500 μ mol) was reacted with 3-penten-2-one **139** (72.0 μ l, 500 μ mol) for 68 hours to give the crude product. Purification by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 7: 3) yielded **176** (36.0 mg, 30 %) as a colourless oil. R_f : 0.6 (light petroleum ether: ethyl acetate; 7: 3); $[\alpha]_D^{26}$ -20.4 (c 0.8 in CHCl_3); ν_{max} cm^{-1} (neat) 2981, 1715, 1551, 1511; δ_{H} (400 MHz, CDCl_3) 7.77 (2H, d, J 8.0, 2ArH), 7.38 (2H, t, J 8.0, 2ArH), 7.27 (1H, t, J 8.0, ArH), 6.26 (1H, s, ArH), 4.84 - 4.74 (1H, m, CHN), 3.49 (1H, dd, J 20.0, 8.0, CH_AH_B), 2.82 (1H, dd, J 20.0, 4.0, CH_AH_B), 2.36 (3H, s, CH_3), 2.10 (3H, s, CH_3), 1.48 (3H, d, J 4.0, CHCH_3); δ_{C} (100 MHz, CDCl_3) 206.7 (C), 150.1 (C), 139.2 (C), 134.1 (C), 128.5 (CH), 127.2 (CH), 125.5 (CH), 102.2 (CH), 49.3 (CH_2), 30.8 (CH_3), 21.4 (CH_3), 11.1 (CH_3). m/z (ES) 243 ($\text{M}+\text{H}^+$, 100 %). m/z (ES) $[\text{M}+\text{H}]^+$ 243.1496. $\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}$ requires 243.1492; R_t HPLC: Chiralpak AD-H; mobile phase, hexane: 2-propanol (49: 1 v/v); flow rate, 1 ml/min; retention times, 6.9 min (13.6 %), 8.3 min (86.4 %) 73 % e.e. Followed by **177** (25.0 mg, 20 %) as a colourless oil. R_f : 0.4 (light petroleum ether: ethyl acetate; 7: 3); $[\alpha]_D^{21}$ -33.7 (c 0.6, CHCl_3); ν_{max} (neat)/ cm^{-1} 2976, 1716, 1496, 1446, 1369; δ_{H} (400 MHz, CDCl_3) 7.49-7.37 (5H, m, ArH), 6.00 (1H, s, CH), 4.88 - 4.77 (1H, m, CHN), 3.36 (1H, dd, J 17.5, 7.5, CH_AH_B), 2.82 (1H, dd, J 17.5, 6.0, CH_AH_B), 2.30 (3H, s, CH_3), 2.08 (3H, s, COCH_3), 1.39 (3H, d, J 6.5, CHCH_3); δ_{C} (100 MHz, CDCl_3) 206.4 (C), 147.9 (C), 144.3 (C), 131.1 (C), 129.1 (CH), 128.6 (CH), 128.4 (CH), 105.7 (CH), 49.6 (CH), 49.3 (CH_2), 30.6 (CH_3), 21.8 (CH_3), 13.7 (CH_3); m/z (ES) 243 ($\text{M}+\text{H}^+$, 100 %); m/z (ES) Found 243.1492. $\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}^+$ requires 243.1492; R_t HPLC: Chiralpak AD-H; mobile phase, hexane: 2-propanol (49: 1 v/v); flow rate, 1 ml/min; retention times, 7.2 min (7.1 %), 8.0 min (92.9 %) 86 % e.e.

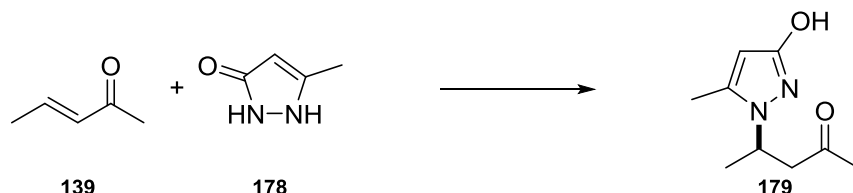
3-Methylpyrazol-5-one 178



Following general procedure 1, ethyl acetoacetate **151** (4.86 ml, 38.4 mmol) was condensed with hydrazine hydrate (2.39 ml, 76.8 mmol) to yield **178** (3.20 g, 80 %) as a colourless solid. M.p. 220 - 222 $^{\circ}\text{C}$; Lit m.p. 222 - 224 $^{\circ}\text{C}$ ^[127]; ν_{max} cm^{-1} (solid) 3406, 1644, 1487; δ_{H} (400 MHz, d_6 -DMSO) 9.45 (2H, br s, 2NH), 5.21 (1H, s, CH), 2.08 (3H, s,

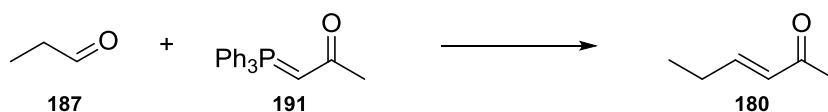
CH₃); δ_C (100 MHz, d₆-DMSO) 161.6 (C), 141.6 (C), 89.8 (CH), 11.5 (CH₃); m/z (ES) 121 (M+Na⁺, 100 %). m/z (ES) [M+Na]⁺ 121.0375. C₄H₆N₂ONa requires 121.0372. The ¹H and ¹³C NMR data are in agreement with those previously reported.^[28]

(4R)-4-(3'-Hydroxy-5'-methylpyrazol-1'-yl)-pentan-2-one **179**



Following general procedure 2, reaction of 3-methylpyrazol-5-one **178** (49.0 mg, 500 μ mol) with 3-penten-2-one **139** (72.0 μ l, 500 μ mol) for 18 hours gave the crude product. Purification by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 4:1) yielded **179** (60 mg, 66 %) as a colourless oil. R_f : 0.5 (light petroleum ether: ethyl acetate; 4:1); $[\alpha]_D^{25} +0.3$ (c 0.7 in CHCl₃); ν_{max} / cm⁻¹ (neat) 2943, 1715, 1540, 1497; δ_H (400 MHz, CDCl₃) 5.36 (1H, s, ArH), 4.72 - 4.64 (1H, m, CHN), 3.26 (1H, dd, *J* 16.0, 8.0, CH_AH_B), 2.75 (1H, dd, *J* 16.0, 8.0, CH_AH_B), 2.28 (3H, s, CH₃), 2.11 (3H, s, COCH₃), 1.41 (3H, d, *J* 8.0, CHCH₃); δ_C (100 MHz, CDCl₃) 206.5 (C), 161.6 (C), 140.4 (C), 90.0 (CH), 48.8 (CH₂), 48.4 (CH), 30.7 (CH₃), 20.9 (CH₃), 11.2 (CH₃); m/z (ES) 183 (M+H⁺, 100 %). m/z (ES) [M+H]⁺ 183.1129. C₉H₁₅N₂O₂ requires 183.1129; R_t HPLC: Chiralpak AD-H; mobile phase, hexane: 2-propanol (19: 1 v/v); flow rate, 1 ml/min; 16.7 min (3.6 %), 25.5 min (96.4 %) 93 % e.e. The ¹H and ¹³C NMR data are in agreement with those previously reported.^[28]

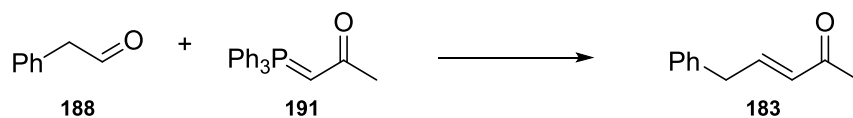
3-Hexen-2-one **180**



To a solution of 1-(triphenylphosphoranylidene)-2-propanone **191** (20.0 g, 64.0 mmol) in dichloromethane (100 ml) was added propionaldehyde **187** (17.0 ml, 141 mmol) and the reaction was stirred at room temperature for 18 hours. The solvent was removed under reduced pressure and the residue triturated with diethyl ether (2 x 125 ml). The resulting solid was collected by filtration and the solution concentrated under reduced pressure. The residue was purified by distillation (b.p. 144 - 146 °C) to yield **180** (5.11 g, 80 %) as a colourless oil. Lit. b.p. 130 - 140 °C^[128]; ν_{max} / cm⁻¹ (neat) 2974, 1675, 1627, 1255; δ_H (400 MHz, CDCl₃) 6.86 (1H, dt, *J* 16.0, 6.5, CH=CHCO), 6.07 (1H, d, *J* 16.0, CH=CHCO), 2.28 - 2.21 (5H, s + m, COCH₃ + CH₂CH₃), 1.08 (3H, t, *J* 6.5, CH₂CH₃); δ_C (100 MHz, CDCl₃) 198.9 (C), 149.8 (CH), 130.4 (CH), 26.8 (CH₃), 25.5 (CH₂), 12.2 (CH₃);

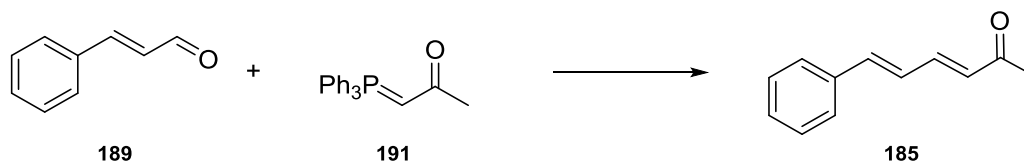
m/z (ES) 197 ($2M+H^+$, 100 %). m/z (ES) $[2M+H]^+$ 197.1551. $C_{12}H_{21}O_2$ requires 197.1536. The ^1H and ^{13}C NMR data are in agreement with those previously reported.^[128]

5-Phenyl-3-penten-2-one **183**



To a solution of 1-(triphenylphosphoranylidene)-2-propanone **191** (5.00 g, 16.0 mmol) in dichloromethane (100 ml) was added phenylacetaldehyde **188** (1.71 ml, 14.5 mmol) and the reaction was stirred at room temperature for 18 hours. The solvent was triturated with diethyl ether (100 ml). The resulting solid was collected by filtration and the solution concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (light petroleum ether: dichloromethane; 1: 1) to yield **183** (640 mg, 25 %) as a colourless oil. R_f : 0.2 (light petroleum ether: dichloromethane; 1: 1); ν_{max}/cm^{-1} (neat) 3029, 1672, 1625, 1495; δ_H (400 MHz, $CDCl_3$) 7.37 - 7.35 (2H, m, 2ArH), 7.30 - 7.23 (1H, m, ArH), 7.22 - 7.18 (2H, m, 2ArH), 6.93 (1H, dt, J 16.0, 8.0 CH=CHCO), 6.09 (1H, dt, J 16.0, 3.0, CH=CHCO), 3.56 (2H, dd, J 8.0, 3.0, CH₂), 2.25 (3H, s, CH₃); δ_C (100 MHz, $CDCl_3$) 198.6 (C), 146.3 (CH), 137.7 (C), 132.0 (CH), 128.7 (CH), 126.8 (CH), 38.8 (CH₂), 26.9 (CH₃); m/z (ES) 183 ($M+Na^+$, 100 %), 161 ($M+H^+$, 62); m/z (ES) Found 183.0785. $C_{11}H_{12}NaO^+$ requires 183.0780. The ^1H and ^{13}C NMR data are in agreement with those previously reported.^[129]

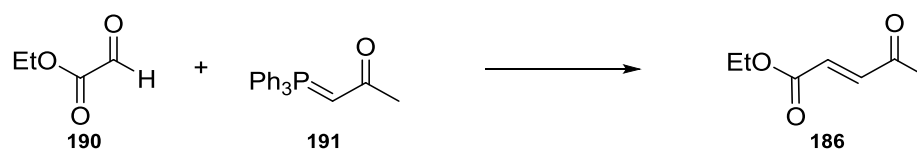
(3E,5E)-6-Phenylhexa-3,5-dien-2-one **185**



Cinnamaldehyde **189** (1.32 g, 10.0 mmol) was dissolved in THF (20 ml) and 1-(triphenylphosphoranylidene)-2-propanone **191** (3.35 g, 10.5 mmol) was added. This was heated at reflux for 18 hours. This was concentrated under reduced pressure and the residue triturated with diethyl ether (100 ml). The resulting solid was removed by filtration and the solution concentrated. The residue was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 17: 3) to yield **185** (890 mg, 52 %) as a yellow solid. M.p. 65 - 69 °C; lit m.p. 67 - 68 °C^[110]; R_f : 0.2 (light petroleum ether: ethyl acetate; 17: 3); $\nu_{max}(CHCl_3)/cm^{-1}$ 2923, 1668, 1652, 1614, 1588, 1495; δ_H (400 MHz, $CDCl_3$) 7.51 (2H, ddd, 7.5, 2.0, 2.0, 2ArH), 7.44 - 7.31 (4H, m, 3ArH + CH), 7.00 (1H, d, J 16.0, CH), 6.94 (1H, dd, J 16.0, 16.0, CH), 6.30 (1H, d, J 16.0, CH), 2.35 (3H, s, COCH₃); δ_C (100 MHz, $CDCl_3$) 198.4 (C), 143.4 (CH), 141.3 (CH), 136.0 (C), 130.5 (CH),

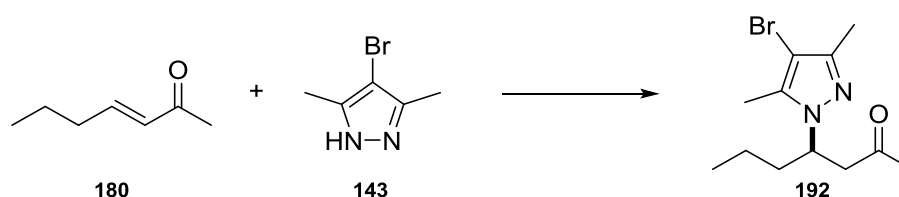
129.2 (2CH), 128.9 (CH), 127.3 (2CH), 126.9 (CH), 27.4 (CH₃); *m/z* (ES) 195 ([M+Na]⁺, 100 %), 173 ([M+H]⁺, 60); *m/z* (ES) found [M+Na]⁺ 195.0782. C₁₂H₁₂NaO⁺ requires 195.0780. The ¹H and ¹³C NMR data are in agreement with those previously reported.^[130]

Ethyl (*E*)-4-oxopent-2-enoate **186**



Ethyl glyoxalate **190** (530 mg, 1.00 ml of a 50 % solution in toluene, 5.16 mmol) was dissolved in toluene (9 ml) and 1-(triphenylphosphoranylidene)-2-propanone **191** (1.70 g, 5.42 mmol) was added. This was stirred at room temperature for 18 hours. This was concentrated under reduced pressure and the residue suspended in diethyl ether (50 ml). The resulting solid was collected by filtration and the solution concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 9: 1) to yield **186** (160 mg, 21 %) as a colourless oil. *R_f*: 0.3 (light petroleum ether: ethyl acetate; 9: 1); *v*_{max} (neat)/cm⁻¹ 2985, 1725, 1703, 1686, 1642, 1157; *δ*_H (400 MHz, CDCl₃) 7.02 (1H, d, *J* 16.0, CH=CHCO), 6.65 (1H, d, *J* 16.0, CH=CHCO), 4.27 (2H, q, *J* 7.0, CH₂CH₃), 2.36 (3H, s, COCH₃), 1.33 (3H, t, *J* 7.0, CH₂CH₃); *δ*_C (100 MHz, CDCl₃) 197.6 (C), 165.5 (C), 139.9 (CH), 131.6 (CH), 61.5 (CH₂), 28.1 (CH₃), 14.1 (CH₃); *m/z* (ES) 165 (M+Na⁺, 48 %), 143 (M+H⁺, 100); *m/z* (ES) found M+H⁺ 143.0692. C₇H₁₁NO₃⁺ requires 143.0703. The ¹H and ¹³C NMR data are in agreement with those previously reported.^[131]

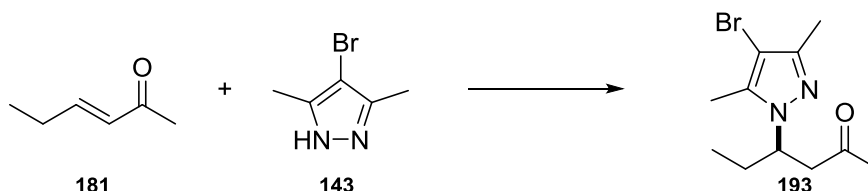
(4*R*)-4-(4'-Bromo-3',5'-dimethylpyrazol-1'-yl)-heptan-2-one **192**



Following general procedure 2, 4-bromo-3,5-dimethylpyrazole **143** (88.0 mg, 500 μmol) with 3-hepten-2-one **180** (65.0 μl, 500 μmol) for 18 hours to give the crude product. Purification by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 4: 1) yielded **192** (132 mg, 92 %) as a colourless oil. *R_f*: 0.4 (light petroleum ether: ethyl acetate; 4: 1); [*α*]_D²⁶ -24.0 (c 0.8 in CHCl₃); *v*_{max} (neat)/cm⁻¹ 2933, 1716, 1602, 1365; *δ*_H (400 MHz, CDCl₃) 4.57 (1H, dddd, *J* 9.5, 9.5, 4.5, 4.5, CHN), 3.34 (1H, dd, *J* 17.5, 9.5, COCH_AH_B), 2.73 (1H, dd, *J* 17.5, 4.5, COCH_AH_B), 2.29 (3H, s, CH₃), 2.19 (3H, s, CH₃), 2.06 (3H, s, COCH₃), 1.89 (1H, dddd, *J* 13.5, 9.5, 9.5, 5.0, CH₂CH_AH_B), 1.64 - 1.54 (1H, m, CH₂CH_AH_B), 1.20 - 0.95 (2H, m, CH₃CH₂), 0.86 (3H, t, *J* 7.0, CH₂CH₃); *δ*_C (100 MHz,

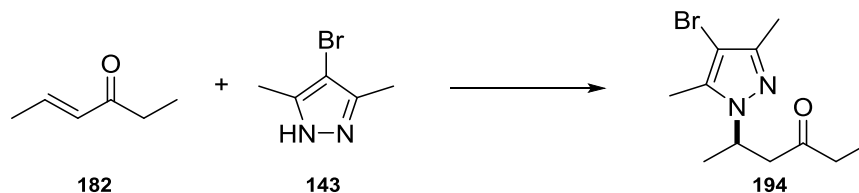
CDCl₃) 206.4 (C), 146.1 (C), 137.9 (C), 93.2 (CH), 54.1 (CH), 48.1 (CH₂), 37.5 (CH₂), 30.6 (CH₃), 19.2 (CH₂), 13.7 (CH₃), 12.4 (CH₃), 10.3 (CH₃); *m/z* (ES) 289 (M(⁸¹Br)+H⁺, 97 %), 287 (M(⁷⁹Br)+H⁺, 100); *m/z* (ES) found 287.0749. C₁₂H₂₀⁷⁹BrN₂O⁺ requires 287.0754; R_t HPLC: Chiralcel OJ-H; mobile phase, hexane: 2-propanol (19: 1 v/v); flow rate, 1 ml/min; 5.0 min (98.5 %), 5.4 min (1.5 %) 97 % e.e.

(4*R*)-4-(4'-Bromo-3',5'-dimethylpyrazol-1'-yl)-hexan-2-one 193



Following general procedure 2, 4-bromo-3,5-dimethylpyrazole **143** (88.0 mg, 500 μmol) was reacted with 3-hexen-2-one **181** (55.0 mg, 500 μmol) for 18 hours to give the crude product. Purification by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 2: 1) yielded **193** (110 mg, 80 %) as a colourless oil. R_f : 0.4 (light petroleum ether: ethyl acetate; 2: 1); [α]_D²⁵ -24.0 (c 0.8 in CHCl₃); ν_{max} (neat)/cm⁻¹ 2934, 1717, 1602, 1546, 1365, 1023; δ_H (400 MHz, CDCl₃) 4.47 (1H, dddd, *J* 9.0, 9.0, 4.5, 4.5, CHN), 3.34 (1H, dd, *J* 17.5, 9.0, COCH_AH_B), 2.73 (1H, dd, *J* 17.5, 4.5, COCH_AH_B), 2.28 (3H, s, CH₃), 2.18 (3H, s, CH₃), 2.05 (3H, s, COCH₃), 1.94 - 1.81 (1H, m, CH₃CH_AH_B), 1.74 - 1.62 (1H, m, CH₃CH_AH_B), 0.70 (3H, t, *J* 7.5, CH₂CH₃); δ_C (100 MHz, CDCl₃) 206.3 (C), 146.1 (C), 138.0 (C), 93.1 (C), 55.6 (CH), 47.9 (CH₂), 30.6 (CH₃), 28.5 (CH₂), 12.4 (CH₃), 10.5 (CH₃), 10.4 (CH₃); *m/z* (ES) 296 (M(⁸¹Br)+Na⁺, 24 %), 295 (M(⁷⁹Br)+Na⁺, 24), 275 (M(⁸¹Br)+H⁺, 98), 273 (M(⁷⁹Br)+H⁺, 100); *m/z* (ES) Found 273.0587. C₁₁H₁₈⁷⁹BrN₂O⁺ requires 273.0597; R_t HPLC: Chiralcel OJ-H; mobile phase, hexane: 2-propanol (19: 1 v/v); flow rate, 1 ml/min; 5.4 min (97.5 %), 6.0 min (2.5 %) 95 % e.e.

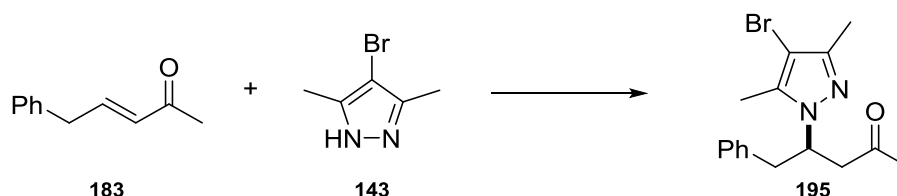
(5*R*)-5-(4'-Bromo-3',5'-dimethylpyrazol-1'-yl)-hexan-3-one 194



Following general procedure 2, 4-bromo-3,5-dimethylpyrazole **143** (88.0 mg, 500 μmol) was reacted with 4-hexen-3-one **182** (57.0 μl, 500 μmol) for 18 hours to give the crude product. Purification by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 4: 1) yielded **194** (102 mg, 75 %) as a colourless oil. R_f : 0.4 (light petroleum ether: ethyl acetate; 4: 1); [α]_D²⁵ -28.4 (c 0.7, CHCl₃); ν_{max} (CHCl₃)/cm⁻¹ 2940, 1715, 1602, 1547, 1379, 1063; δ_H (400 MHz, CDCl₃) 4.80 - 4.70 (1H, m, CHN), 3.31 (1H, dd, *J*

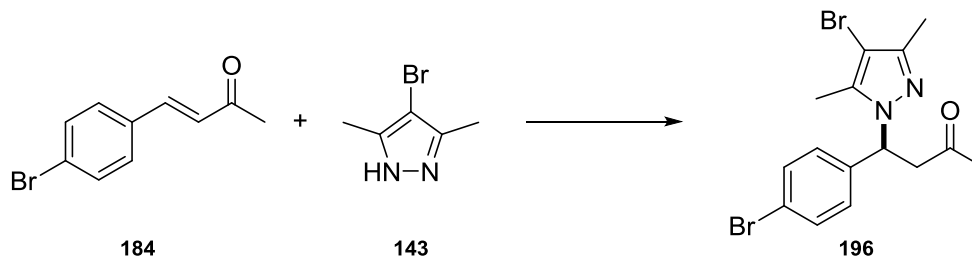
17.5, 8.5, $\text{CH}_\text{A}\text{H}_\text{B}$), 2.73 (1H, dd, J 17.5, 5.0, $\text{CH}_\text{A}\text{H}_\text{B}$), 2.45 - 2.25 (2H, m, CH_2CH_3), 2.27 (3H, s, CH_3), 2.18 (3H, s, CH_3), 1.37 (3H, d, J 7.0, CHCH_3), 0.98 (3H, t, J 7.5, CH_2CH_3); δ_C (100 MHz, CDCl_3) 208.9 (C), 145.9 (C), 139.8 (C), 93.5 (C), 49.9 (CH), 47.7 (CH_2), 36.6 (CH_2), 21.2 (CH_3), 12.4 (CH_3), 10.1 (CH_3), 7.5 (CH_3); m/z (ES) 273 ($\text{M}^{79}\text{Br} + \text{H}^+$, 100 %), 275 ($\text{M}^{81}\text{Br} + \text{H}^+$, 99); m/z (ES) Found 273.0590. $\text{C}_{11}\text{H}_{18}^{79}\text{BrN}_2\text{O}^+$ requires 273.0597; R_f HPLC: Chiralcel OJ-H; mobile phase, hexane: 2-propanol (19: 1 v/v); flow rate, 1 ml/min; 5.4 min (96.6 %), 6.0 min (3.4 %) 93 % e.e.

(4R)-4-(4'-Bromo-3',5'-dimethylpyrazol-1'-yl)-5-phenylpentan-2-one 195



Following general procedure 2, 4-bromo-3,5-dimethylpyrazole **143** (88.0 mg, 500 μmol) was reacted with 5-phenyl-3-penten-2-one **183** (80.0 mg, 500 μmol) for 66 hours to give the crude product. Purification by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 4: 1) yielded **195** (150 mg, 60 %) as a clear oil. R_f : 0.2 (light petroleum ether: ethyl acetate; 4: 1); $[\alpha]_\text{D}^{24} +127.9$ (c 0.7, CHCl_3); ν_max (neat)/ cm^{-1} 2926, 1717, 1602, 1365; δ_H (400 MHz, CDCl_3) 7.24 - 7.15 (3H, m, 3ArH), 6.91 - 6.84 (2H, m, 2ArH), 4.68 (1H, dddd, J 9.5, 9.0, 5.0, 5.0, CHN), 3.48 (1H, dd, J 17.5, 9.0, $\text{COCH}_\text{A}\text{H}_\text{B}$), 3.08 (1H, dd, J 13.5, 9.5, $\text{PhCH}_\text{A}\text{H}_\text{B}$), 2.91 (1H, dd, J 13.5, 5.0, $\text{PhCH}_\text{A}\text{H}_\text{B}$), 2.87 (1H, dd, J 17.5, 5.0, $\text{COCH}_\text{A}\text{H}_\text{B}$), 2.23, (3H, s, CH_3), 2.09 (3H, s, CH_3), 1.76 (3H, s, COCH_3); δ_C (100 MHz, CDCl_3) 206.1 (C), 146.2 (C), 138.5 (C), 137.7 (C), 129.0 (2CH), 128.4 (2CH), 126.8 (CH), 93.0 (C), 56.2 (CH), 47.3 (CH_2), 41.8 (CH_2), 30.6 (CH_3), 12.5 (CH_3), 9.6 (CH_3); m/z (ES) 337 ($\text{M}^{81}\text{Br} + \text{H}^+$, 98 %), 335 ($\text{M}^{79}\text{Br} + \text{H}^+$, 100); m/z (ES) Found 335.0742. $\text{C}_{16}\text{H}_{20}^{79}\text{BrN}_2\text{O}^+$ requires 335.0754; R_f HPLC Chiralcel OJ-H; mobile phase, hexane: 2-propanol (99: 1 v/v); flow rate, 1 ml/min; 12.2 min (98.5 %), 13.3 min (1.5 %) 97 % e.e.

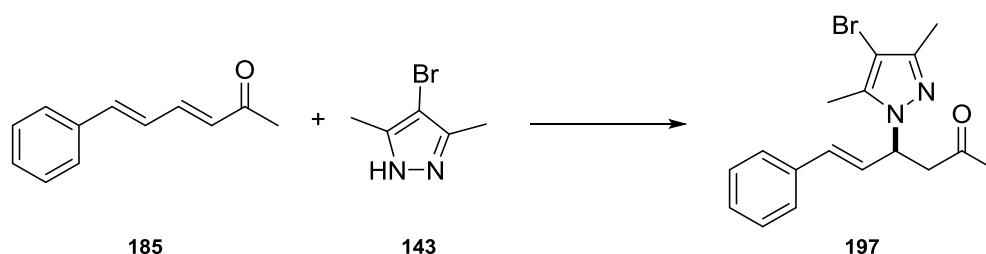
(4S)-4-(4'-Bromo-3',5'-dimethylpyrazol-1'-yl)-4-(4''-bromophenyl)butan-2-one 196



Following general procedure 2, 4-bromo-3,5-dimethylpyrazole **143** (88.0 mg, 500 μmol) was reacted with 4-(4'-bromophenyl)-3-buten-2-one **184** (113 mg, 500 μmol) for 118 hours to give the crude product. Purification by flash chromatography on silica gel

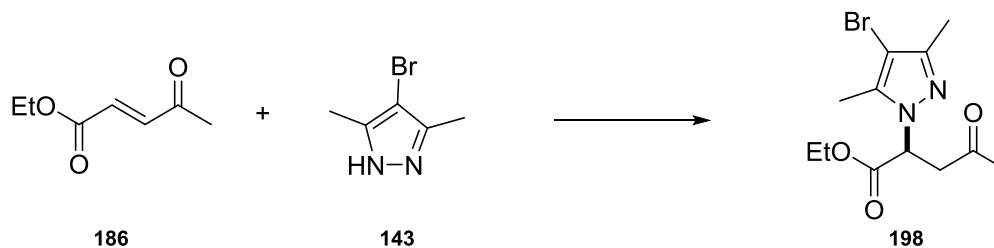
(chloroform) yielded **196** (160 mg, 80%) as a colourless oil. R_f : 0.3 (chloroform); $[\alpha]_D^{24} +23.2$ (c 1.0, CHCl_3); ν_{max} (neat)/ cm^{-1} 2982, 2925, 1718, 1489, 1364; δ_{H} (400 MHz, CDCl_3) 7.45 - 7.39 (2H, m, 2ArH), 7.08 - 7.01 (2H, m, 2ArH), 5.69 (1H, dd, J 9.5, 4.5, CHN), 3.92 (1H, dd, J 17.5, 9.5, CH_AH_B), 2.97 (1H, dd, J 17.5, 4.5, CH_AH_B), 2.21 (3H, s, CH_3), 2.17 (3H, s, CH_3), 2.16 (3H, s, CH_3); δ_{C} (100 MHz, CDCl_3) 205.2 (C), 146.0 (C), 139.5 (C), 137.7 (C), 132.0 (2CH), 128.1 (2CH), 121.8 (C), 94.8 (C), 57.3 (CH), 48.1 (CH_2), 30.6 (CH_3), 12.5 (CH_3), 10.2 (CH_3); m/z (ES) 424 ($\text{M}(2\times {}^{81}\text{Br})+\text{Na}^+$, 46 %), 422 ($\text{M}(1\times {}^{79}\text{Br}, 1\times {}^{81}\text{Br})+\text{Na}^+$, 100), 420 ($\text{M}(2\times {}^{79}\text{Br})+\text{Na}^+$, 48), 402 ($\text{M}(2\times {}^{81}\text{Br})+\text{H}^+$, 37), 400 ($\text{M}(1\times {}^{79}\text{Br}, 1\times {}^{81}\text{Br})+\text{H}^+$, 78), 398 ($\text{M}(2\times {}^{79}\text{Br})+\text{H}^+$, 38); m/z (ES) Found 420.9511. $\text{C}_{15}\text{H}_{16}{}^{79}\text{Br}_2\text{N}_2\text{O}\text{Na}^+$ requires 420.9522; R_t HPLC Chiralpak AD-H; mobile phase, hexane: 2-propanol (19: 1 v/v); flow rate, 1 ml/min; 5.8 min (96.7 %), 6.3 min (3.3 %) 94 % e.e.

(S,E)-4-(4-Bromo-3,5-dimethyl-1H-pyrazol-1-yl)-6-phenylhex-5-en-2-one 197



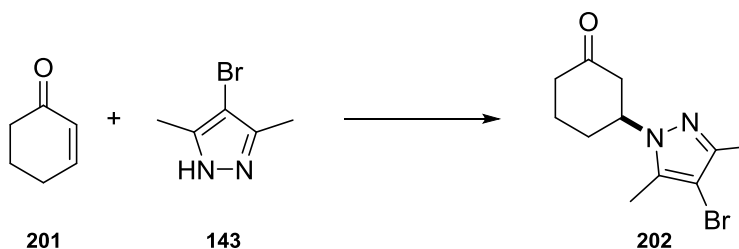
Following general procedure 2, 4-bromo-3,5-dimethylpyrazole **143** (44.0 mg, 100 μmol) was reacted with (3E, 5E)-6-phenylhexa-3,5-dien-2-one **185** (44.0 mg, 100 μmol) for 120 hours to give the crude product. Purification by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 17: 3) yielded **197** (8.00 mg, 23 %) as a light yellow oil. R_f : 0.3 (light petroleum ether: ethyl acetate; 17: 3); $[\alpha]_D^{24} -32.5$ (c 0.6 in CHCl_3); ν_{max} (neat)/ cm^{-1} 2875, 1717, 1671, 1589, 1492; δ_{H} (400 MHz, CHCl_3) 7.35 - 7.21 (5H, m, 5ArH), 6.36 - 6.23 (2H, m, 2CH), 5.33 (1H, ddd, J 8.5, 7.5, 5.0, CHN), 3.67 (1H, dd, J 17.5, 8.5, CH_AH_B), 2.96 (1H, dd, J 17.5, 5.0, CH_AH_B), 2.31 (3H, s, CH_3), 2.22 (3H, s, CH_3), 2.16 (3H, s, COCH_3); δ_{C} (100 MHz, CHCl_3) 205.4 (C), 146.2 (C), 137.7 (C), 136.0 (C), 131.6 (CH), 128.6 (2CH), 128.0 (CH), 127.7 (CH), 126.6 (2CH), 94.2 (C), 56.3 (CH), 47.2 (CH_2), 30.7 (CH_3), 12.4 (CH_3), 10.2 (CH_3); m/z (ES) 371 ($\text{M}^{81}\text{Br}+\text{Na}^+$, 43 %), 369 ($\text{M}^{79}\text{Br}+\text{Na}^+$, 41), 349 ($\text{M}^{81}\text{Br}+\text{H}^+$, 100), 347 ($\text{M}^{79}\text{Br}+\text{H}^+$, 98); m/z (ES) found $[\text{M}^{81}\text{Br}+\text{H}]^+$ 349.0730. $\text{C}_{17}\text{H}_{20}{}^{81}\text{Br}\text{N}_2\text{O}^+$ requires 349.0734. R_t HPLC: Chiralcel OJ-H; mobile phase, hexane: 2-propanol (49: 1 v/v); flow rate, 1.0 ml/min; 10.7 min (10.6 %), 11.6 min (86.9 %) 74 % e.e.

(S)-2-(4'-Bromo-3',5'-dimethylpyrazol-1'-yl)-4-oxopentanoate 198



Following general procedure 2, 4-bromo-3,5-dimethylpyrazole **143** (17.5 mg, 100 μ mol) was reacted with ethyl (E)-4-oxopent-2-enoate **186** (14.3 mg, 100 μ mol) for 168 hours to give the crude product. Purification by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 4: 1) yielded **198** (6.30 mg, 20%) as a colourless oil. R_f ; 0.3 (light petroleum ether: ethyl acetate; 4: 1); $[\alpha]_D^{23}$ -67.2 (c 0.2 in CHCl_3); ν_{max} (neat)/ cm^{-1} 2983, 1745, 1720, 1553, 1474, 1163; δ_{H} (400 MHz, CDCl_3) 5.30 (1H, dd, J 7.5, 6.0, CHN), 4.23 - 4.10 (2H, m, CH_3CH_2), 3.49 (1H, dd, J 17.5, 6.0, CH_AH_B), 3.08 (1H, dd, J 17.5, 7.5, CH_AH_B), 2.32 (3H, s, CH_3), 2.21 (3H, s, CH_3), 2.18 (3H, s, COCH_3), 1.21 (3H, t, J 7.0, CH_3CH_2); δ_{C} (100 MHz, CDCl_3) 204.7 (C), 168.9 (C), 147.1 (C), 138.8 (C), 94.6 (C), 62.1 (CH_2), 56.1 (CH), 43.7 (CH_2), 30.2 (CH_3), 14.0 (CH_3), 12.4 (CH_3), 10.2 (CH_3); m/z (ES) 341 ($\text{M}^{81}\text{Br}+\text{Na}^+$, 48 %), 339 ($\text{M}^{79}\text{Br}+\text{Na}^+$, 50), 319 ($\text{M}^{81}\text{Br}+\text{H}^+$, 99), 317 ($\text{M}^{79}\text{Br}+\text{H}^+$, 100); m/z (ES) Found 317.0478. $\text{C}_{12}\text{H}_{18}^{79}\text{BrN}_2\text{O}_3^+$ requires 317.0495; R_t HPLC Chiralcel OD-H; mobile phase, hexane: 2-propanol (9: 1 v/v); flow rate, 0.9 ml/min; 6.3 min (9.4 %), 7.0 min (90.6 %), 81 % e.e.

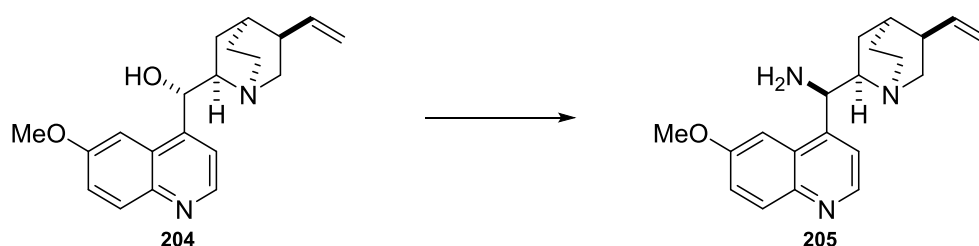
(3S)-(4-Bromo-3,5-dimethylpyrazol-1-yl)cyclohexan-1-one 202



Following general procedure 2, 4-bromo-3,5-dimethylpyrazole **143** (44.0 mg, 250 μ mol) was reacted with 2-cyclohexen-1-one **201** (24.0 μ l, 250 μ mol) for 18 hours to give the crude product. Purification by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 2: 1) yielded **202** (41.0 mg, 61 %) as a colourless solid. M.p. 96 - 99 $^{\circ}\text{C}$; R_f : 0.4 (light petroleum ether: ethyl acetate; 9: 1); $[\alpha]_D^{24}$ -5.6 (c 1.0 in CHCl_3); ν_{max} (CHCl_3)/ cm^{-1} 2951, 1714, 1548, 1473, 1420; δ_{H} (400 MHz, CHCl_3) 4.39 - 4.28 (1H, m, CHN), 3.08 (1H, dd, J 12.0, 11.0, COCH_AH_B), 2.61 (1H, dd, J 12.0, 4.0, COCH_AH_B), 2.46 - 2.38 (2H, m, CH_2), 2.29 - 2.19 (7H, m + 2s, $\text{CH} + 2\text{CH}_3$), 2.18 - 2.02 (2H, m, CH_2), 1.76 - 1.60 (1H, m, CH); δ_{C} (100 MHz, CHCl_3) 208.2 (C), 146.2 (C), 135.9 (CH), 94.3 (C),

56.8 (CH), 47.5 (CH₂), 40.5 (CH₂), 31.2 (CH₂), 22.0 (CH₂), 12.4 (CH₃), 10.1 (CH₃); *m/z* (ES) 295 ([M⁸¹Br+Na]⁺, 48 %), 293 (M⁷⁹Br+Na⁺, 48), 273 (M⁸¹Br+H⁺, 100), 271 (M⁷⁹Br+H⁺, 99); *m/z* (ES) found [M⁸¹Br+H]⁺ 273.0413. C₁₁H₁₆⁸¹BrN₂O⁺ requires 273.0421; R_t HPLC: Chiralpak AD-H; mobile phase, hexane: 2-propanol (9: 1 v/v); flow rate, 1 ml/min; 5.4 min (67.3 %), 6.0 min (32.7 %) 35 % e.e.

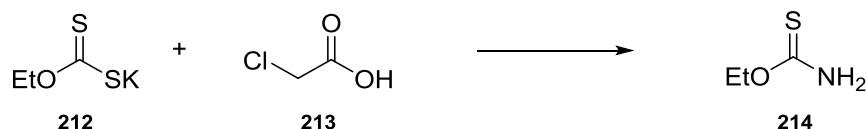
9-Deoxy-9-*epi*-aminoquinidine **205**



Quinidine **204** (1.85 g, 5.70 mmol) and triphenylphosphine (1.79 g, 6.84 mmol) were dissolved in dry THF (27 ml) and the solution was cooled to 0 °C. Diisopropyl azodicarboxylate (1.34 ml, 6.84 mmol) was added in one portion. A solution of diphenylphosphoryl azide (1.48 ml, 6.84 mmol) in dry THF (13 ml) was then added then dropwise and the reaction mixture was allowed to warm to room temperature, then stirred for approximately 20 hours. The solution was then heated to 50 °C and stirred for a further 2 hours. Triphenylphosphine (1.94 g, 7.40 mmol) was then added and the mixture stirred at 50 °C for a further 1 hour until gas evolution had ceased. The solution was then cooled to room temperature and water (1.0 ml) was added, the solution was stirred for 4 hours. Solvents were evaporated under reduced pressure and the residue partitioned between dichloromethane (50 ml) and 2M hydrochloric acid (50 ml). The aqueous phase was washed with dichloromethane (2 x 50 ml). The aqueous phase was then adjusted to pH 9 with an excess of concentrated aqueous ammonia solution (10 ml). The aqueous was extracted with dichloromethane (3 x 50 ml). The later combined organic layers were dried (magnesium sulfate) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate: methanol: triethylamine; 17: 3: 1) to yield **205** (632 mg, 35 %) as a yellow oil. R_f : 0.3 (ethyl acetate: methanol: triethylamine; 17: 3: 1); [α]_D²¹ +60.3 (c 0.8 in CHCl₃); Lit [α]_D²⁰ +79.6 (c 1.0 in CHCl₃)^[132], ν_{max} (neat)/cm⁻¹ 3365, 3075, 2936, 1621, 1589, 1508, 1473, 1227; δ_H (400 MHz, CDCl₃) 8.75 (1H, d, *J* 8.0, C₁₂H), 8.02 (1H, d, *J* 2.0, C₁₈H), 7.70 - 7.44 (2H, m, C₁₁H + C₁₅H), 7.37 (1H, dd, *J* 7.5, 2.0, C₁₆H), 5.87 (1H, ddd, *J* 17.5, 10.0, 6.5 CH=CH₂), 5.12 - 5.03 (2H, m, CH=CH₂), 4.69 (1H, d, *J* 8.0, C₉H), 3.96 (3H, s, OCH₃), 3.18 - 2.91 (5H, m, C₈H + C₆H₂ + C₂H₂), 2.53 (2H, bs, NH₂), 2.33 - 2.24 (1H, m, C₅H), 1.66 - 1.49 (3H, m, C₄H + C₃H₂), 1.20 - 1.07 (1H, m, C₇H), 1.04 - 0.91 (1H, m, C₇H); δ_C (100 MHz, CDCl₃) 157.7 (C₁₇), 147.9 (C₁₂H), 147.3 (C₁₀), 144.7 (C₁₄), 140.6 (CH=CH₂), 131.9 (C₁₈H), 128.6 (C₁₉), 121.7 (C₁₆H), 120.0 (C₁₅H), 114.6 (CH=CH₂), 101.4 (C₉H),

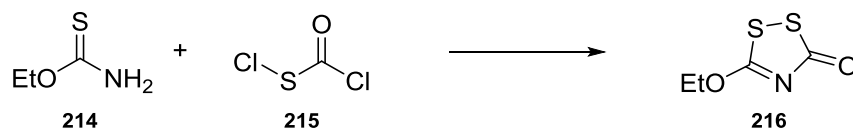
62.5 (C₈H), 55.5 (OCH₃), 49.5 (C₂H₂), 47.4 (C₆H₂), 39.3 (C₅H₂), 27.6 (C₄H), 26.6 (C₃H₂), 25.0 (C₇H₂); *m/z* (ES) 324 (M+H⁺, 100 %); *m/z* (ES) found [M+H]⁺ 324.2057. C₂₀H₂₆N₃O requires 324.2070. The ¹H and ¹³C NMR data are in agreement with those previously reported.^[132]

O-Ethyl thiocarbamate **214**^[71]



A solution of potassium hydroxide (3.36 g, 60.0 mmol) in water (31 ml) was stirred with ethanol (10.3 ml) and carbon disulfide (3.60 ml, 60.0 mmol) was added dropwise over 5 minutes. This was stirred at room temperature for 1 hour. Chloroacetic acid **213** (5.65 g, 60.0 mmol) and sodium hydroxide (2.40 g, 60 mmol) was dissolved in water (23 ml) and added dropwise to crude ethyl xanthanide **212**. This was stirred for 8 hours. Concentrated aqueous ammonia solution (5 ml) was added and stirred for 12 hours. The solution was extracted with diethyl ether (2 x 25 ml). The combined organics were washed with water (50 ml) and 1 M hydrochloric acid (50 ml), dried (magnesium sulfate) and concentrated under reduced pressure. The resulting solid was recrystallised from light petroleum ether at -20 °C to yield **214** (2.50 g, 39 %) as a colourless solid. M.p. 40 - 41 °C; lit m.p. 36 - 38 °C^[71]; $\nu_{\max}(\text{CHCl}_3)/\text{cm}^{-1}$ 3290, 3173, 2978, 1804, 1307; δ_{H} (400 MHz, CDCl₃) 6.52 (1H, bs, NH), 6.04 (1H, bs, NH), 4.48 (2H, q, *J* 7.0, CH₂CH₃), 1.34 (3H, t, *J* 7.0, CH₂CH₃); δ_{C} (100 MHz, CDCl₃) 192.7 (C), 67.8 (CH₂), 14.1 (CH₃); *m/z* (ES) 128 (M+Na⁺, 100 %); *m/z* (ES) found [M+Na]⁺ 128.0146. C₃H₇NNaOS⁺ requires 128.01441. The ¹H and ¹³C NMR data are in agreement with those previously reported.^[71]

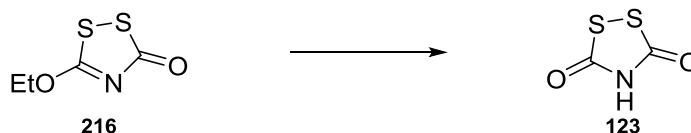
3-Ethoxy-1,2,4-dithiazole-5-one **216**^[71]



O-Ethyl thiocarbamate **214** (2.46 g, 23.4 mmol) was dissolved in diethyl ether (12 ml) was added dropwise over 20 minutes to chlorocarbonylsulfonyl chloride **215** (1.96 ml, 23.4 mmol) dissolved in diethyl ether (117 ml) at 0 °C. This was allowed to warm to room temperature for 90 minutes. This was concentrated under reduced pressure and the residue redissolved in dichloromethane (42 ml). The resulting white solid was removed by filtration and the solution concentrated under reduced pressure. The resulting solid was recrystallized from diethyl ether at -20 °C to yield **216** (1.52 g, 39 %) as a colourless solid. M.p. 54 - 56 °C; lit m.p. 51 - 53 °C^[71]; $\nu_{\max}(\text{CHCl}_3)/\text{cm}^{-1}$ 3000, 1679, 1547, 1271;

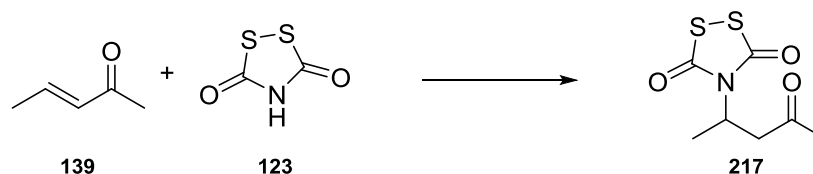
δ_{H} (400 MHz, CDCl_3) 4.68 (1H, q, J 7.0, CH_2CH_3), 1.48 (3H, t, J 7.0, CH_2CH_3); δ_{C} (100 MHz, CDCl_3) 187.6 (C), 179.9 (C), 73.6 (CH_2), 14.3 (CH_3); m/z (ES) 185 ($\text{M}+\text{Na}^+$, 100 %); m/z (ES) found $[\text{M}+\text{Na}]^+$ 185.9673. $\text{C}_4\text{H}_5\text{NNaO}_2\text{S}_2^+$ requires 185.9654. The ^1H and ^{13}C NMR data are in agreement with those previously reported.^[71]

1,2,4-Dithiazole-3,5-dione **123**^[71]



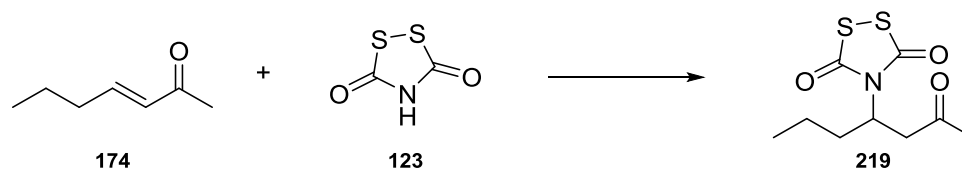
3-Ethoxy-1,2,4-dithiazole-5-one **216** (850 mg, 5.20 mmol) was suspended in concentrated hydrochloric acid (5 ml) which was heated to 110 °C over 40 minutes. After 10 minutes the solution was filtered hot to remove elemental sulfur. The resulting solution was concentrated under reduced pressure to yield a yellow solid. This was recrystallized from toluene to yield **123** (400 mg, 58 %) as a colourless solid. M.p. 142 - 144 °C; lit m.p. 141 - 143 °C^[71]; ν_{max} (CHCl_3)/ cm^{-1} 3368, 1735, 1700, 1683, 1287; δ_{H} (400 MHz, CDCl_3) 8.28 (1H, bs, NH); δ_{C} (100 MHz, CDCl_3) 166.8 (C); m/z (ES) 135 ($\text{M}+\text{H}^+$, 100 %); m/z (ES) found $[\text{M}+\text{H}]^+$ 135.9521. $\text{C}_2\text{H}_2\text{NO}_2\text{S}_2^+$ requires 135.9500. The ^1H and ^{13}C NMR data are in agreement with those previously reported.^[71]

(+)-4'-(4'-Oxopentan-2'-yl)-1,2,4-dithiazolidine-3,5-dione **217**



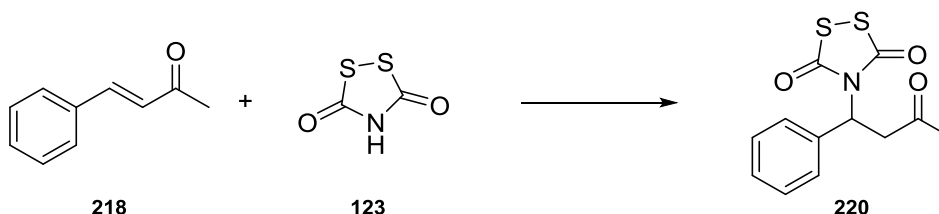
9-Deoxy-9-*epi*-aminoquinine **60** (1.60 mg, 5.00 μmol) was dissolved in toluene (0.7 ml) and a solution of 3-penten-2-one **139** (10.0 μl , 100 μmol) in toluene (0.1 ml) was added. A solution of trifluoroacetic acid (0.750 μl , 10.0 μmol) in toluene (0.2 ml) was added followed by 1,2,4-dithiazole-3,5-dione **123** (13.5 mg, 100 μmol). The solution was stirred for 24 hours, and the solution passed through a silica plug and concentrated under reduced pressure to yield **217** (12.6 mg, 57 %) as a colourless solid. M.p. 81 - 83 °C; ν_{max} (CHCl_3)/ cm^{-1} 2934, 1715, 1645; $[\alpha]_{\text{D}}^{23}$ +27.8 (c 0.4 in CHCl_3); δ_{H} (400 MHz, CDCl_3) 5.00 - 4.89 (1H, m, CHN), 3.28 (1H, dd, J 18.0, 8.0, $\text{CH}_\text{A}\text{H}_\text{B}$), 2.98 (1H, dd, J 18.0, 6.5, $\text{CH}_\text{A}\text{CH}_\text{B}$), 2.15 (3H, s, COCH_3), 1.43 (3H, d, J 7.0, CHCH_3); δ_{C} (100 MHz, CDCl_3) 205.0 (C), 167.6 (C), 50.8 (CH), 45.2 (CH_2), 30.1 (CH_3), 17.4 (CH_3); m/z (ES) 241 ($\text{M}+\text{Na}^+$, 100%); m/z (ES) found $[\text{M}+\text{Na}]^+$ 241.9914. $\text{C}_7\text{H}_9\text{NNaO}_3\text{S}_2^+$ requires 241.9916; R_{f} HPLC Chiralcel OD-H; mobile phase, hexane: 2-propanol (9: 1 v/v); flow rate, 1 ml/min; 17.0 min (16.8 %), 22.6 min (83.2 %) 66 % e.e.

(+)-4'-(2'-Oxoheptan-4'-yl)-1,2,4-dithiazolidine-3,5-dione **219**



9-Deoxy-9-*epi*-aminoquinine **60** (1.60 mg, 5.00 μ mol) was dissolved in toluene (0.8 ml) and 3-hepten-2-one **174** (11.4 mg, 100 μ mol) was added. Trifluoroacetic acid (1.60 μ l, 10.0 μ mol) dissolved in toluene (0.2 ml) was added followed by 1,2,4-dithiazole-3,5-dione **123** (13.5 mg, 100 μ mol). The solution was stirred for 48 hours, and the solution passed through a silica plug and concentrated under reduced pressure to yield **219** (16.7 mg, 67 %) as a colourless oil. $\nu_{\max}$ (neat)/ cm^{-1} 2961, 1719, 1650; $[\alpha]_{\text{D}}^{23}$ +13.8 (c 0.9 in CHCl_3); δ_{H} (400 MHz, CDCl_3) 4.92 - 4.79 (1H, m, CHN), 3.28 (1H, dd, J 18.5, 8.5, $\text{CH}_\text{A}\text{H}_\text{B}$), 2.93 (1H, dd, J 18.5, 6.0, $\text{CH}_\text{A}\text{CH}_\text{B}$), 2.14 (3H, s, COCH_3), 2.05 - 1.91 (1H, m, $\text{CH}_\text{A}\text{CH}_\text{B}\text{CHN}$), 1.67 - 1.53 (1H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{CHN}$), 1.37 - 1.19 (2H, m, CH_2), 0.92 (3H, t, J 8.0, CH_2CH_3); δ_{C} (100 MHz, CDCl_3) 205.1 (C), 167.7 (C), 55.0 (CH), 44.3 (CH_2), 33.2 (CH_2), 30.2 (CH_3), 19.3 (CH_2), 13.6 (CH_3); m/z (ES) 270 ($\text{M}+\text{Na}^+$, 100 %); m/z (ES) found $[\text{M}+\text{Na}]^+$ 270.0227. $\text{C}_9\text{H}_{13}\text{NNaO}_3\text{S}_2^+$ requires 270.0229; R_{f} HPLC Chiralcel OJ-H; mobile phase, hexane: 2-propanol (9: 1 v/v); flow rate, 1 ml/min; 13.6 min (16.6 %), 20.1 min (83.4 %) 67 % e.e.

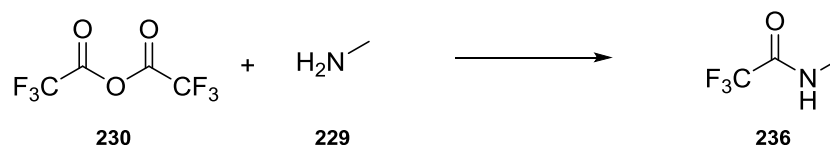
(+)-4'-(3'-Oxo-1'-phenylbutyl)-1,2,4-dithiazolidine-3,5-dione **220**



9-Deoxy-9-*epi*-aminoquinine **60** (0.800 mg, 2.50 μ mol) was dissolved in toluene (0.8 ml) and 4-phenylbuten-2-one **218** (14.6 mg, 100 μ mol) was added. Trifluoroacetic acid (0.380 μ l, 5.00 μ mol) dissolved in toluene (0.2 ml) was added followed by 1,2,4-dithiazole-3,5-dione **123** (13.5 mg, 100 μ mol). The solution was stirred for 101 hours, and the solution passed through a silica plug and concentrated under reduced pressure. The resulting oil was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 9: 1) to yield **220** (4.20 mg, 17 %) as a colourless solid. M.p. 72 - 74 $^{\circ}\text{C}$; R_{f} : 0.3 (light petroleum ether: ethyl acetate; 9: 1); $\nu_{\max}$ (CHCl_3)/ cm^{-1} 2922, 1717, 1646; $[\alpha]_{\text{D}}^{23}$ +0.7 (c 1.1 in CHCl_3); δ_{H} (400 MHz, CDCl_3) 7.49 - 7.42 (2H, m, 2ArH), 7.40 - 7.31 (3H, m, 3ArH), 5.97 (1H, dd, J 9.5, 5.5, CHN), 3.93 (1H, dd, J 18.5, 9.5, $\text{CH}_\text{A}\text{H}_\text{B}$), 3.33 (1H, dd, J 18.5, 5.5, $\text{CH}_\text{A}\text{H}_\text{B}$), 2.22 (3H, s, CH_3); δ_{C} (100 MHz, CDCl_3) 204.5 (C), 167.5

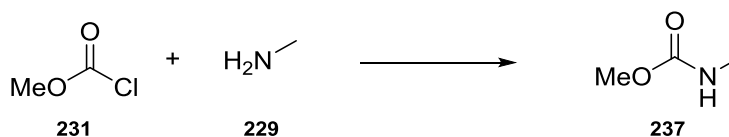
(C), 136.5 (C), 128.9 (2CH), 128.0 (3CH), 57.2 (CH), 43.0 (CH₂), 30.1 (CH₃); *m/z* (ES) 304 (M+Na⁺, 100 %); *m/z* (ES) found [M+Na]⁺ 304.0062. C₁₂H₁₁NNaO₃S₂⁺ requires 304.0073; R_t HPLC Chiralpak AD-H; mobile phase, hexane: 2-propanol (9: 1 v/v); flow rate, 1 ml/min; 10.6 min (69.4 %), 11.8 min (30.6 %) 39 % e.e.

***N*-Methyltrifluoroacetamide 236**



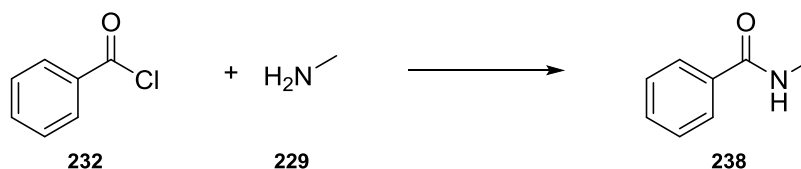
Following general procedure 3, reaction of trifluoroacetic anhydride **230** (1.00 g, 4.80 mmol) yielded **236** (90.0 mg, 13 %) as a colourless solid. M.p. 46 - 48 °C; lit m.p. 45 °C^[133] *v*_{max}/ cm⁻¹ (CHCl₃) 3345, 2979, 1720; δ_H (400 MHz, CDCl₃) 6.55 (1H, bs, NH), 2.96 (3H, d, *J* 5.0, CH₃); δ_C (100 MHz, CDCl₃) 158.1 (C, q, *J* 37), 115.8 (C, q, *J* 286), 26.4 (CH₃); *m/z* (ES) 150 (M+Na⁺, 100 %). *m/z* (ES) [M+Na]⁺ 150.0142. C₃H₅F₃NO⁺ requires 150.0137. The ¹H NMR and ¹³C data is in agreement with those previously reported.^[133]

***N*-Methyl methyl carbamate 237**



Following general procedure 3, reaction of methyl chloroformate **231** (500 mg, 5.30 mmol) yielded **237** (150 mg, 32 %) as a colourless oil. *v*_{max}/ cm⁻¹ (neat) 3445, 2979, 1710, 1290; δ_H (400 MHz, CDCl₃) 4.66 (1H, bs, NH), 3.67 (3H, s, OCH₃), 2.79 (3H, d, *J* 5.0, NCH₃); δ_C (100 MHz, CDCl₃) 157.7 (C), 52.1 (CH₃), 27.6 (CH₃); *m/z* (ES) 112 (M+Na⁺, 100 %). *m/z* (ES) [M+Na]⁺ 112.0373. C₃H₇NNaO₂⁺ requires 112.0369. The ¹H NMR and ¹³C data is in agreement with those previously reported.^[134]

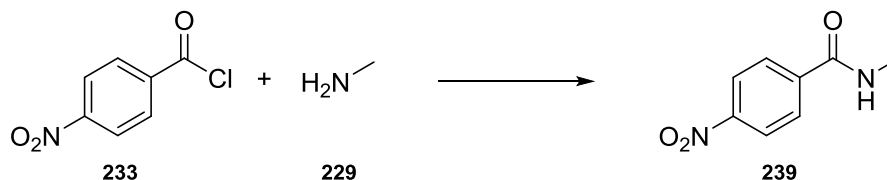
***N*-Methylbenzamide 238**



Following general procedure 3, reaction of benzoyl chloride **232** (1.00 g, 7.10 mmol) yielded **238** (905 mg, 94 %) as a colourless solid. M.p. 81 - 84 °C; lit. m.p. 77 - 78 °C^[135]; *v*_{max}/ cm⁻¹ (neat) 3325, 2924, 1639, 1551; δ_H (400 MHz, CDCl₃) 7.82 - 7.76 (2H, m, 2ArH), 7.55 - 7.49 (1H, m, ArH), 7.48 - 7.41 (2H, m, 2ArH), 6.27 (1H, bs, NH), 3.04 (3H, d, *J*

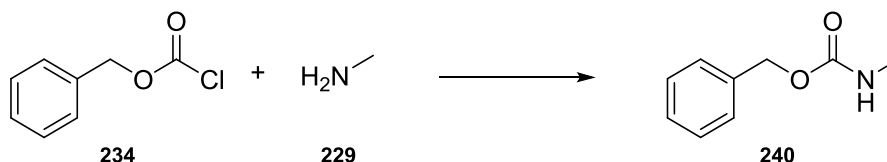
7.0, CH₃); δ_C (100 MHz, CDCl₃) 168.3 (C), 134.7 (C), 131.4 (CH), 128.6 (CH), 126.8 (CH), 26.8 (CH₃); m/z (ES) 158 (M+Na⁺, 97 %), 136 (M+H⁺, 100); m/z (ES) [M+H]⁺ 136.0742. C₈H₁₀NO⁺ requires 136.0757. The ¹H NMR and ¹³C data is in agreement with those previously reported.^[135]

***N*-Methyl-4-nitrobenzamide 239**



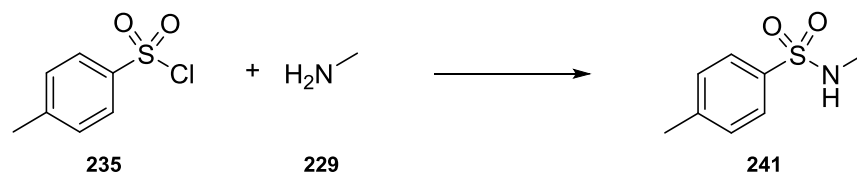
Following general procedure 3, reaction of *m*-nitrobenzoyl chloride **233** (1.00 g, 5.40 mmol) yielded **239** (427 mg, 44 %) as an off white solid. M.p.: 221 - 224 °C; lit. m.p. 222 - 223 °C^[136] $\nu_{\max}/\text{cm}^{-1}$ (solid) 3334, 3079, 1649, 1599, 1553, 1513, 1491; δ_H (400 MHz, d₆-DMSO) 8.78 (1H, bs, NH), 8.31 (2H, dd, *J* 7.5, 2.0, 2ArH), 8.06 (2H, dd, *J* 7.5, 2.0, 2ArH), 2.81 (3H, d, *J* 7.5, CH₃); δ_C (100 MHz, d₆-DMSO) 165.4 (C), 149.4 (C), 140.6 (C), 129.0 (CH), 124.0 (CH), 26.9 (CH₃); m/z (ES) 179 (M-H⁺, 100%). m/z (ES) [M-H]⁺ 179.0470. C₈H₉NaO₃⁺ requires 179.0462. The ¹H NMR and ¹³C data is in agreement with those previously reported.^[136]

***O*-Benzyl-*N*-methylcarbamate 240**



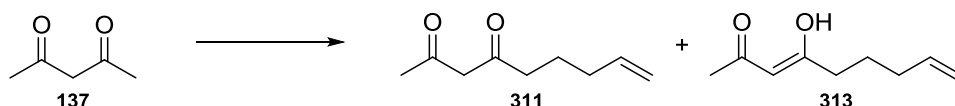
Following general procedure 3, reaction of benzyl chloroformate **234** (1.00 g, 5.90 mmol) yielded **240** (995 mg, 90 %) as a colourless oil. $\nu_{\max}/\text{cm}^{-1}$ (neat) 3345, 2949, 1702, 1537, 1261; δ_H (400 MHz, CDCl₃) 7.44 - 7.28 (5H, m, 5ArH), 5.12 (2H, s, CH₂), 4.84 - 4.59 (1H, bs, NH), 2.82 (3H, s, CH₃); δ_C (100 MHz, CDCl₃) 157.0 (C), 136.7 (C), 128.5 (CH), 128.1 (CH), 66.7 (CH₂), 27.6 (CH₃); m/z (ES) 188 (M+Na⁺, 100 %). m/z (ES) [M+Na]⁺ 188.0687. C₉H₁₁NNaO₂⁺ requires 188.0682. The ¹H NMR and ¹³C data is in agreement with those previously reported.^[137]

N-Methyl-*p*-toluenesulfonamide **241**



Following general procedure 3, reaction of *p*-toluenesulphonyl chloride **235** (1.00 g, 5.30 mmol) yielded **241** (806 mg, 80 %) as a colourless solid. M.p. 84 - 86 °C; lit m.p. 78 °C^[138]; $\nu_{\max}$ / cm⁻¹ (CHCl₃) 3290, 2979, 1710, 1290; δ_{H} (400 MHz, CDCl₃) 7.76 (2H, d, *J* 8.0, 2ArH), 7.33 (2H, d, *J* 8.0, 2ArH), 4.43 (1H, bs, NH), 2.65 (3H, d, *J* 5.5, NCH₃), 2.44 (3H, s, CH₃); δ_{C} (100 MHz, CDCl₃) 143.5 (C), 135.9 (C), 129.7 (CH), 128.1 (CH), 127.3 (CH), 29.3 (CH₃), 21.5 (CH₃); *m/z* (ES) 208 (M+Na⁺, 100 %). *m/z* (ES) [M+Na]⁺ 208.0407. C₈H₁₁NNaO₂S⁺ requires 208.0403. The ¹H NMR and ¹³C data is in agreement with those previously reported.^[139]

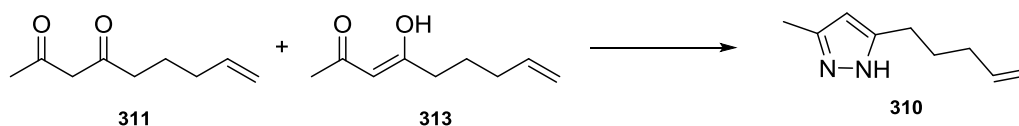
Non-8-ene-2,4-dione **311** and 4-hydroxynona-3,8-dien-2-one **313**^[96]



Pentan-2,4-dione **137** (5.10 ml, 50.0 mmol) was added dropwise to a stirred solution of sodium hydride (2.00 g, 60 % dispersion in mineral oil, washed once with light petroleum ether, 50.0 mmol) in tetrahydrofuran (100 ml) at 0 °C under Argon. The resulting mixture was stirred for 10 minutes at 0 °C, cooled to -20 °C and *n*-butyllithium (20.0 ml, 2.5 M concentration in hexane, 50.0 mmol) was added dropwise to give a pale yellow solution. After 30 minutes at -20 °C, 4-bromobut-1-ene **312** (6.75 g, 50.0 mmol) was added dropwise, allowed to warm to 0 °C then stirred for 3 hours. This was then allowed to warm to room temperature then stirred for 2 hours. The mixture was poured into a mixture of saturated aqueous ammonium chloride (50 ml) and diethyl ether (50 ml). The layers were separated and the aqueous phase was extracted with diethyl ether (2 x 20 ml). The combined organics were dried (magnesium sulfate) and concentrated under reduced pressure. The residue was triturated with petrol (30 ml) and the resulting solid collected by filtration. The filtrate was concentrated and the residue purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 9: 1) to yield **311** and **313** (2.32 g, 30 %) as a 13: 2 mixture of tautomers. *R_f*: 0.5 (light petroleum ether: ethyl acetate; 9: 1). $\nu_{\max}$ / cm⁻¹ (neat) 3419, 3078, 2932, 1726, 1708, 1618, 1418. δ_{H} (400 MHz, CDCl₃) 15.48 (1H, bs, OH **313**), 5.85 - 5.68 (2H, m, CH **311** + **313**), 5.50 (1H, s, CH **313**), 5.07 - 4.97 (4H, m, CH₂ **311** + **313**), 3.57 (2H, s, CH₂ **311**), 2.52 (2H, t, *J* 8.0, CH₂ **311**), 2.29 (2H, t, *J* 8.0, CH₂ **313**), 2.24 (3H, s, CH₃ **311**), 2.14 - 2.03 (7H, s + m, CH₃ **313** + CH₂ **311** + **313**), 1.76 - 1.65 (4H, m, CH₂, **311** + **313**). δ_{C} (100 MHz, CDCl₃) 204.0 (C **311**), 202.0 (C **311**), 193.9 (C **313**), 191.4 (C **313**), 137.8 (CH **313**), 115.5 (CH₂ **311** +

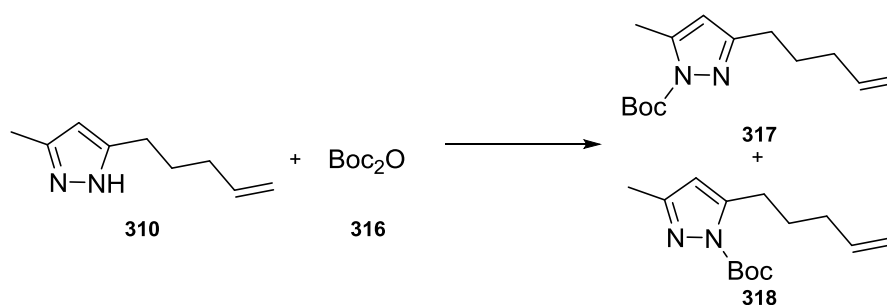
313), 99.9 (CH **311** + **313**), 58.0 (CH₂ **311**), 42.9 (CH₂ **311**), 37.5 (CH₂ **313**), 33.1 (CH₂ **313**), 32.9 (CH₂ **311**), 30.9 (CH₃ **311**), 25.0 (CH₃ **313**), 24.8 (CH₂ **313**), 22.4 (CH₂ **311**). *m/z* (ES) 177 (M+Na⁺, 100 %). *m/z* (ES) [M+Na]⁺ 177.0891. C₉H₁₄NaO₂ requires 177.0886. The ¹H NMR and ¹³C data is in agreement with those previously reported.^[96]

3-(Penten-4'-yl)-5-methylpyrazole **310**



Non-8-ene-2,4-dione **311** and 4-hydroxynona-3,8-dien-2-one **313** (13: 2 tautomer mixture, 2.21 g, 14.0 mmol) were added to a solution of hydrazine hydrate (35 % in water, 2.52 ml, 28.0 mmol) in ethanol (1.2 ml) at 0 °C. This was allowed to warm to room temperature then stirred for 30 minutes. Ethyl acetate (5.0 ml) was added and the layers separated. The organic layer was dried (magnesium sulfate) and concentrated to yield **310** (1.84 g, 85 %) as a light yellow oil. *R_f* : 0.5 (light petroleum ether: ethyl acetate; 9: 1); *v*_{max}/ cm⁻¹ (neat) 3197, 3135, 2930, 1641, 1582; *δ*_H (400 MHz, CDCl₃) 8.94 (1H, bs, NH), 5.89 - 5.74 (2H, m + s, ArH + CH=CH₂), 5.05 - 4.96 (2H, m, CH=CH₂), 2.63 (2H, t, J 8.0, CCH₂CH₂), 2.28 (3H, s, CH₃), 2.15 - 2.08 (2H, m, CHCH₂), 1.78 - 1.70 (2H, m, CH₂); *δ*_C (100 MHz, CDCl₃) 149.0 (C), 144.4 (C), 138.3 (CH), 115.0 (CH₂), 103.1 (CH), 33.3 (CH₂), 28.6 (CH₂), 26.3 (CH₂), 12.3 (CH₃); *m/z* (ES) 151 (M+H⁺, 100 %). *m/z* (ES) [M+H]⁺ 151.1223. C₉H₁₅O₂ requires 151.1230.

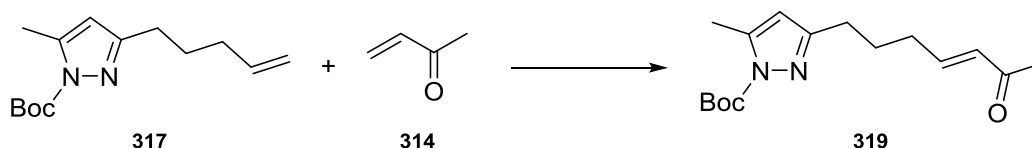
N-Boc-5-methyl-3-(pent-4'-enyl)-pyrazole **317** and *N*-Boc-3-methyl-5-(pent-4'-enyl)-pyrazole **318**



3-(Penten-4'-yl)-5-methylpyrazole **310** (600 mg, 4.00 mmol) was dissolved in dichloromethane (2 ml) and triethylamine (760 μ l, 4.20 mmol) was added. Di-*tert*-butyl dicarbonate **316** (420 μ l, 4.00 mmol) dissolved in dichloromethane (2 ml) and was added dropwise at 0 °C over 10 minutes. This was allowed to warm to room temperature then stirred for 18 hours. This was concentrated under reduced pressure and purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 9: 1) to yield **317** (470 mg, 47 %) as a colourless oil; *R_f* : 0.3 (light petroleum ether: ethyl acetate; 9: 1);

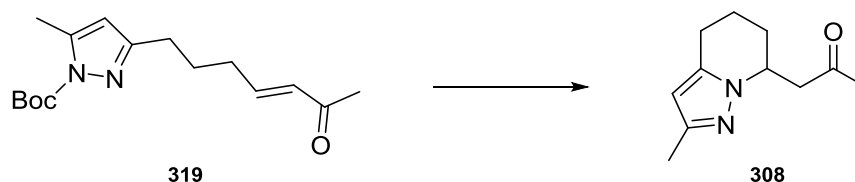
$\nu_{\max}$ (neat)/ cm^{-1} 2979, 1744, 1641, 1579, 1162; δ_{H} (400 MHz, CDCl_3) 5.96 (1H, s, ArH), 5.83 (1H, ddt, J 16.0, 10.5, 8.0, $\text{CH}=\text{CH}_2$), 5.07 - 4.94 (2H, m, $\text{CH}=\text{CH}_2$), 2.65 - 2.58 (2H, m, CCH_2), 2.48 (3H, s, CH_3), 2.12 (2H, dt, J 8.0, 8.0, CHCH_2), 1.78 - 1.68 (2H, m, CH_2), 1.64 (9H, s, $\text{C}(\text{CH}_3)_3$); δ_{C} (100 MHz, CDCl_3) 156.1 (C), 148.9 (C), 143.9 (C), 138.3 (CH), 114.9 (CH_2), 109.2 (CH), 84.6 (C), 33.5 (CH_2), 28.1 (CH_3), 27.9 (CH_2), 14.7 ($\text{C}(\text{CH}_3)_3$); m/z (ES) 273 ($\text{M}+\text{Na}^+$, 100 %); m/z (ES) found $[\text{M}+\text{Na}]^+$ 273.1569. $\text{C}_{14}\text{H}_{22}\text{F}_3\text{N}_2\text{NaO}_2^+$ requires 273.1573. Followed by **318** (260 mg, 26 %) as a colourless oil; R_f : 0.2 (light petroleum ether: ethyl acetate; 9: 1); $\nu_{\max}$ (neat)/ cm^{-1} 2980, 1742, 1641, 1577, 1159; δ_{H} (400 MHz, CDCl_3) 5.96 (1H, s, CH), 5.83 (1H, ddt, J 16.0, 10.5, 8.0, $\text{CH}=\text{CH}_2$), 5.09 - 4.93 (2H, m, $\text{CH}=\text{CH}_2$), 2.94 - 2.84 (2H, m, CCH_2), 2.27 (3H, s, CH_3), 2.14 (2H, dt, J 8.0, 8.0, CHCH_2), 1.79 - 1.69 (2H, m, CH_2), 1.64 (9H, s, $\text{C}(\text{CH}_3)_3$); δ_{C} (100 MHz, CDCl_3) 151.9 (C), 148.8 (C), 148.6 (C), 138.1 (CH), 115.1 (CH_2), 109.3 (CH), 84.6 (C), 33.3 (CH_2), 28.0 (CH_3), 27.6 (CH_2), 14.0 ($\text{C}(\text{CH}_3)_3$); m/z (ES) 273 ($\text{M}+\text{Na}^+$, 100 %); m/z (ES) found $[\text{M}+\text{Na}]^+$ 273.1570. $\text{C}_{14}\text{H}_{22}\text{F}_3\text{N}_2\text{NaO}_2^+$ requires 273.1573.

N*-Boc-(*E*)-5-methyl-3-(6-oxohept-4-en-1-yl)-1*H*-pyrazole **319*



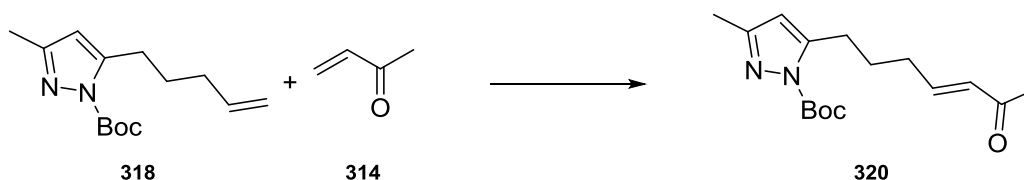
Following general procedure 7, *N*-Boc-5-methyl-3-(pent-4'-enyl)-pyrazole **317** (460 mg, 1.85 mmol) was reacted with methylvinylketone **314** (780 μl , 9.25 mmol) for 18 hours to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 3: 2) to yield **319** (310 mg, 58 %) as a yellow oil. R_f : 0.3 (light petroleum ether: ethyl acetate; 3: 2); $\nu_{\max}$ (neat)/ cm^{-1} 2981, 1744, 1697, 1674, 1627, 1578, 1160; δ_{H} (400 MHz, CDCl_3) 6.80 (1H, dt, J 17.0, 7.5, $\text{CH}=\text{CHCO}$), 6.08 (1H, dt, J 17.0, 2.0, $\text{CH}=\text{CHCO}$), 5.95 (1H, bs, ArH), 2.67 - 2.61 (2H, m, CCH_2), 2.47 (3H, s, CH_3), 2.29 (2H, dt, J 7.5, 7.5, CHCH_2), 2.23 (3H, s, COCH_3), 1.87 - 1.77 (2H, m, CH_2), 1.64 (9H, s, $\text{C}(\text{CH}_3)_3$); δ_{C} (100 MHz, CDCl_3) 198.6 (C), 155.3 (C), 148.8 (C), 147.6 (CH), 144.0 (C), 131.7 (CH), 109.2 (CH), 84.7 (C), 32.0 (CH_2), 28.0 ($\text{C}(\text{CH}_3)_3$), 27.9 (CH_2), 27.3 (CH_2), 26.8 (CH_3), 14.7 (CH_3); m/z (ES) 315 ($\text{M}+\text{Na}^+$, 100 %); m/z (ES) found $[\text{M}+\text{Na}]^+$ 315.1663. $\text{C}_{16}\text{H}_{24}\text{N}_2\text{NaO}_3^+$ requires 315.1679.

($\pm$)-1-(2-methyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridin-7-yl)propan-2-one **308**



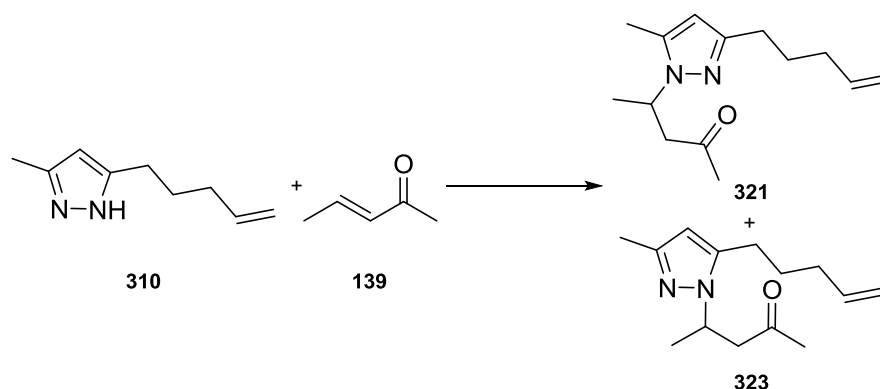
N-Boc-(*E*)-5-methyl-3-(6-oxohept-4-en-1-yl)-1*H*-pyrazole **319** (50.0 mg, 0.170 mmol) was dissolved in dichloromethane (2 ml) and TFA (126 μ l, 1.70 mmol) was added in one portion. After 30 minutes sodium bicarbonate (2 ml) was added. The resulting layers were separated and the aqueous extracted with dichloromethane (2 ml). The combined organic layers were dried (magnesium sulfate) and concentrated under reduced pressure. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 4: 1) to yield **308** (22.0 mg, 67 %) as a colourless oil. R_f : 0.2 (light petroleum ether: ethyl acetate; 4: 1); $\nu_{\max}$ (neat)/ cm^{-1} 2944, 1715, 1547, 1447; δ_{H} (400 MHz, CDCl_3) 5.73 (1H, s, ArH), 4.62 - 4.49 (1H, m, CHN), 3.50 (1H, dd, J 17.5, 4.0, COCH_AH_B), 2.82 - 2.52 (3H, m, CH_2 + COCH_AH_B), 2.31 - 2.16 (7H, m + 2s, CH_AH_B + 2 CH_3), 1.95 - 1.81 (1H, m, CH_AH_B), 1.81 - 1.62 (2H, m, CH_2); δ_{C} (100 MHz, CDCl_3) 206.4 (C), 147.7 (C), 140.2 (C), 102.5 (CH), 53.2 (CH), 48.5 (CH_2), 30.6 (CH_3), 29.2 (CH_2), 22.9 (CH_2), 18.9 (CH_2), 13.6 (CH_3); m/z (ES) 193 ($\text{M}+\text{H}^+$, 100 %); m/z (ES) found $[\text{M}+\text{H}]^+$ 193.1336. $\text{C}_{11}\text{H}_{17}\text{N}_2\text{O}^+$ requires 193.1335.

***N*-Boc-(*E*)-3-methyl-5-(6-oxohept-4-en-1-yl)-1*H*-pyrazole 320**



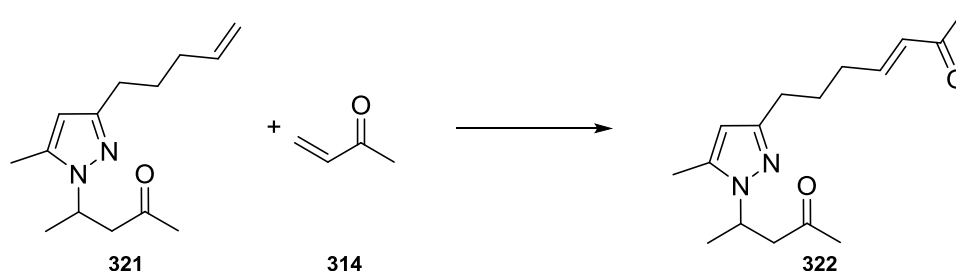
Following general procedure 7, *N*-Boc-5-methyl-3-(pent-4'-enyl)-pyrazole **318** (250 mg, 1.00 mmol) was reacted with methylvinylketone **314** (410 μ l, 5.00 mmol) for 1 hour to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 3: 2) to yield **320** (266 mg, 91 %) as a colourless oil. R_f : 0.3 (light petroleum ether: ethyl acetate; 3: 2); $\nu_{\max}$ (neat)/ cm^{-1} 2933, 1743, 1674, 1627, 1576, 1456, 1155; δ_{H} (400 MHz, CDCl_3) 6.81 (1H, dt, J 16.0, 8.0, $\text{CH}=\text{CHCO}$), 6.11 (1H, dt, J 16.0, 2.0, $\text{CH}=\text{CHCO}$), 5.97 (1H, s, ArH), 2.94 (2H, dt, J 8.0, 8.0, CHCH_2), 2.36 - 2.23 (8H, m + 2s, CCH_2 + 2 CH_3), 1.88 - 1.78 (2H, m, CH_2), 1.65 (9H, s, (CH_3)₃); δ_{C} (100 MHz, CDCl_3) 198.5 (C), 152.0 (C), 148.8 (C), 147.9 (C), 147.2 (CH), 131.7 (CH), 109.5 (CH), 84.8 ($\text{C}(\text{CH}_3)_3$), 31.9 (CH_2), 28.0 ($\text{C}(\text{CH}_3)_3$), 27.5 (CH_2), 27.0 (CH_3), 26.9 (CH_2), 14.0 (CH_3); m/z (ES) 293 ($\text{M}+\text{H}^+$, 100 %), 193 ($\text{M-Boc}+\text{H}^+$, 35); m/z (ES) found $[\text{M}+\text{Na}]^+$ 293.1861. $\text{C}_{16}\text{H}_{25}\text{N}_2\text{O}_3^+$ requires 293.1860.

(±)-4-(5'-methyl-3'-(pent-4-en-1-yl) pyrazol-1-yl)pentan-2-one 321 and (±)-4-(3'-methyl-5'-(pent-4-en-1-yl)pyrazol-1-yl)pentan-2-one 323



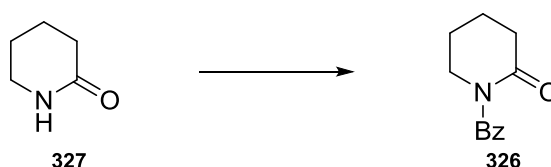
3-(Penten-4-yl)-5-methylpyrazole **310** (300 mg, 2.00 mmol) was dissolved in toluene (12 ml) and 3-penten-2-one **139** (200 μ l, 2.00 mmol) was added. TFA (60.0 μ l, 800 μ mol) was added and the reaction stirred at room temperature for 18 hours. This was then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 3: 1) to yield **321** (174 mg, 37 %) as a colourless oil. R_f : 0.3 (light petroleum ether: ethyl acetate; 3: 1); $\nu_{\max}$ (neat)/ cm^{-1} 2939, 1719, 1641, 1552, 1430; δ_{H} (400 MHz, CDCl_3) 5.82 (1H, ddt, J 16.0, 10.0, 8.0, $\text{CH}=\text{CH}_2$), 5.73 (1H, s, ArH), 5.06 - 4.91 (2H, m, $\text{CH}=\text{CH}_2$), 4.74 - 4.62 (1H, m, CHN), 3.35 (1H, dd, J 17.0, 8.0, COCH_AH_B), 2.78 (1H, dd, J 17.0, 5.5, COCH_AH_B), 2.56 (2H, dt, J 8.0, 8.0, CHCH_2), 2.26 (3H, s, CH_3), 2.14 - 2.02 (5H, m + s, $\text{CCH}_2 + \text{COCH}_3$), 1.74 - 1.62 (2H, m, CH_2), 1.40 (3H, d, J 7.5, CHCH_3); δ_{C} (100 MHz, CDCl_3) 206.8 (C), 152.0 (C), 138.7 (CH), 138.3 (C), 114.5 (CH_2), 103.3 (CH), 49.3 (CH_2), 49.2 (CH), 33.5 (CH_2), 30.7 (CH_3), 29.2 (CH_2), 27.9 (CH_2), 21.3 (CH_2), 11.0 (CH_3); m/z (ES) 235 ($\text{M}+\text{H}^+$, 100 %); m/z (ES) found $[\text{M}+\text{Na}]^+$ 235.1803. $\text{C}_{14}\text{H}_{23}\text{N}_2\text{O}^+$ requires 235.1805; Followed by **323** (204 mg, 44 %) as a colourless oil. R_f : 0.2 (light petroleum ether: ethyl acetate; 3: 1); $\nu_{\max}$ (neat)/ cm^{-1} 2978, 1718, 1641, 1548, 1453; δ_{H} (400 MHz, CDCl_3) 5.90 - 5.76 (2H, m + s, ArH + $\text{CH}=\text{CH}_2$), 5.11 - 5.00 (2H, m, $\text{CH}=\text{CH}_2$), 4.74 - 4.69 (1H, m, CHN), 3.43 (1H, dd, J 18.0, 8.0, COCH_AH_B), 2.87 (1H, dd, J 18.0, 5.5, COCH_AH_B), 2.74 - 2.58 (2H, m, CHCH_2), 2.27 (3H, s, CH_3), 2.20 - 2.12 (2H, m, CCH_2), 2.09 (3H, s, COCH_3), 1.80 - 1.69 (2H, m, CH_2), 1.46 (3H, d, J 7.5, CHCH_3); δ_{C} (100 MHz, CDCl_3) 206.2 (C), 147.3 (C), 144.6 (C), 137.7 (CH), 115.5 (CH_2), 104.0 (CH), 49.3 (CH_2), 49.1 (CH), 33.2 (CH_2), 30.5 (CH_3), 27.5 (CH_2), 24.6 (CH_2), 21.1 (CH_3), 12.9 (CH_3); m/z (ES) 235 ($\text{M}+\text{H}^+$, 100 %); m/z (ES) found $[\text{M}+\text{H}]^+$ 235.1805. $\text{C}_{14}\text{H}_{23}\text{N}_2\text{O}^+$ requires 235.1800.

(E)-7-(5'-methyl-1'-(4'-oxopentan-2'-yl)pyrazol-3'-yl)hept-3-en-2-one 322



Following general procedure 7, 4-(5'-methyl-3'-(pent-4-en-1-yl) pyrazol-1-yl)pentan-2-one **321** (130 mg, 560 μmol) was reacted with methylvinylketone **314** (235 μl , 2.80 mmol) for 1 hour to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 3: 1) to yield **322** (36.0 mg, 23 %) as a colourless oil. R_f : 0.3 (light petroleum ether: ethyl acetate; 3: 1); ν_{max} (neat)/ cm^{-1} 2934, 1716, 1672, 1626, 1557, 1424; δ_{H} (400 MHz, CDCl_3) 6.80 (1H, dt, J 16.0, 8.0, $\text{CH}=\text{CHCO}$), 6.08 (1H, dt, J 16.0, 2.0, $\text{CH}=\text{CHCO}$), 5.73 (1H, s, ArH), 4.75 - 4.64 (1H, m, CHN), 3.35 (1H, dd, J 16.0, 8.0, COCH_AH_B), 2.78 (1H, dd, J 16.0, 5.5, COCH_AH_B), 2.59 (2H, dt, J 8.0, 8.0, CHCH_2), 2.30 - 2.21 (8H, m + 2s, $\text{CCH}_2 + 2\text{CH}_3$), 2.07 (3H, s, COCH_3), 1.83 - 1.72 (2H, m, CH_2), 1.40 (3H, d, J 7.0, CHCH_3); δ_{C} (100 MHz, CDCl_3) 206.6 (C), 198.7 (C), 151.2 (C), 148.2 (CH), 138.5 (CH), 131.4 (CH), 49.2 (CH_2), 48.8 (CH), 32.1 (CH_2), 30.7 (CH_3), 28.2 (CH_2), 26.8 (CH_3), 21.3 (CH_3), 11.0 (CH_3); m/z (ES) 277 ($\text{M}+\text{H}^+$, 100 %); m/z (ES) found $[\text{M}+\text{H}]^+$ 277.1904. $\text{C}_{16}\text{H}_{25}\text{N}_2\text{O}_2^+$ requires 277.1911.

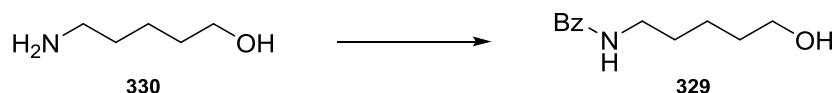
N-Benzoyl- δ -valerolactam 326^[99]



Sodium hydride (60 % w/w dispersion in mineral oil, 490 mg, 12.3 mmol) was washed with light petroleum ether (10 ml) and tetrahydrofuran (10 ml). Tetrahydrofuran (10 ml) was added under an Argon atmosphere. δ -Valerolactam **327** (1.16 g, 11.6 mmol) dissolved in tetrahydrofuran (10 ml) was added in one portion at 0 $^{\circ}\text{C}$. This was stirred at 0 $^{\circ}\text{C}$ for 20 minutes. Benzoyl chloride (1.43 ml, 12.3 mmol) was added dropwise at 0 $^{\circ}\text{C}$ and was allowed to warm to room temperature then stirred for 3 hours. Saturated aqueous ammonium chloride (20 ml) and diethyl ether (20 ml) were added. The resulting layers were separated and the aqueous layer re-extracted with diethyl ether (20 ml). The resulting organics were combined, dried (magnesium sulfate) and concentrated under reduced pressure to yield a colourless solid. This was purified by flash chromatography on silica gel (chloroform: ethyl acetate; 19: 1) to yield **326** (1.19 g, 50 %) as a colourless solid. M.p. 112 - 114 $^{\circ}\text{C}$; Lit. m.p. 111 $^{\circ}\text{C}$ ^[140]; R_f : 0.3 (chloroform: ethyl acetate; 19: 1);

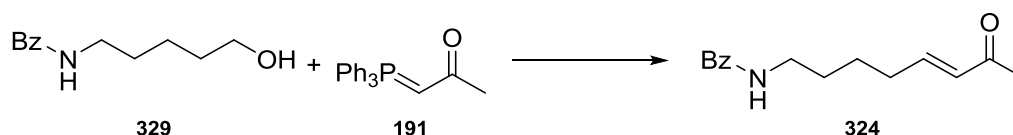
$\nu_{\max}$ (CHCl₃)/cm⁻¹ 2952, 1702, 1677, 1288, 1251; δ_{H} (400 MHz, CDCl₃) 7.67 - 7.33 (5H, m, 5ArH), 3.81 (2H, t, *J* 6.0, NCH₂), 2.57 (2H, t, *J* 6.0, COCH₂), 2.04 - 1.88 (4H, m, 2CH₂); δ_{C} (100 MHz, CDCl₃) 174.7 (C), 173.4 (C), 136.2 (C), 131.5 (CH), 128.2 (CH), 127.9 (CH), 46.1 (CH₂), 34.7 (CH₂), 22.9 (CH₂), 21.5 (CH₂); *m/z* (ES) 226 (M+Na⁺, 100 %), 204 (M+H⁺, 46); *m/z* (ES) found [M+Na]⁺ 226.0829. C₁₂H₁₃NNaO₂⁺ requires 226.0838. The ¹H NMR and ¹³C data is in agreement with those previously reported.^[140]

***N*-(5-Hydroxypentyl)benzamide 329**



Following general procedure 4a, 5-aminopentanol **330** (500 mg, 4.90 mmol) was reacted with benzoyl chloride (600 mg, 5.00 mmol) to give the crude product. This was purified by flash chromatography on silica gel (ethyl acetate) to yield **329** (704 mg, 70 %) as a colourless solid. M.p. 48 - 51 °C; *R_f* : 0.3 (ethyl acetate); $\nu_{\max}$ (CHCl₃)/cm⁻¹ 3316, 2935, 1639, 1546, 1490; δ_{H} (400 MHz, CDCl₃) 7.76 (2H, ddd, *J* 7.5, 2.5, 2.5, 2ArH), 7.50 - 7.34 (3H, m, 3ArH), 6.57 (1H, bs, NH), 3.62 (2H, t, *J* 8.0, OCH₂), 3.43 (2H, dt, *J* 8.0, 8.0, NCH₂), 2.33 (1H, bs, OH), 1.69 - 1.39 (6H, m, 3CH₂); δ_{C} (100 MHz, CDCl₃) 167.8 (C), 134.7 (C), 131.4 (CH), 128.5 (CH), 126.9 (CH), 62.5 (CH₂), 40.0 (CH₂), 32.2 (CH₂), 29.4 (CH₂), 23.2 (CH₂); *m/z* (ES) 230 (M+Na⁺, 100 %), 208 (M+H⁺, 12); *m/z* (ES) found [M+Na]⁺ 230.1156. C₁₂H₁₇NNaO₂⁺ requires 230.1151. The ¹H NMR and ¹³C data is in agreement with those previously reported.^[141]

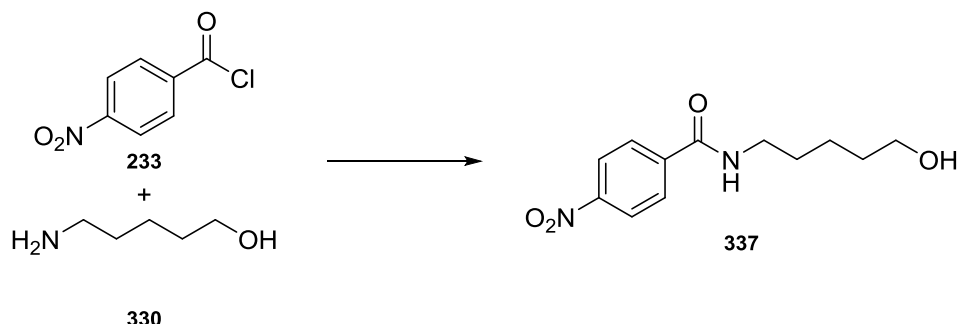
***(E)*-N-(6-Oxo-oct-5-en-1-yl)benzamide 324**



Following general procedure 6, *N*-(5-hydroxypentyl)benzamide **329** (330 mg, 1.60 mmol) was reacted with 1-(triphenylphosphoranylidene)-2-propanone **191** (815 mg, 2.60 mmol) in dichloromethane (14 ml) heated at reflux for 20 hours to give the crude product. Purification by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 3: 7) yielded **324** (136 mg, 32 %) as a yellow solid. M.p. 70 - 72 °C; *R_f* : 0.3 (light petroleum ether: ethyl acetate; 3: 7); $\nu_{\max}$ (CHCl₃)/cm⁻¹ 3327, 2931, 1671, 1639, 1578, 1257; δ_{H} (400 MHz, CDCl₃) 7.77 (2H, dt, *J* 7.5, 2.5, 2.5, 2ArH), 7.55 - 7.35 (3H, m, 3ArH), 6.78 (1H, dt, *J* 16.0, 8.0, CH=CHCO), 6.28 (1H, bs, NH), 6.08 (1H, dt, *J* 16.0, 2.0, CH=CHCO), 3.47 (2H, dt, *J* 8.0, 8.0, CHCH₂), 2.33 - 2.19 (5H, m + s, CH₂ + CH₃), 1.70 - 1.52 (4H, m, 2CH₂); δ_{C} (100 MHz, CDCl₃) 198.6 (C), 167.6 (C), 147.6 (CH), 134.7 (C), 131.6 (CH), 131.4 (CH), 128.6 (CH), 126.8 (CH), 39.7 (CH₂), 32.0 (CH₂), 29.3 (CH₂),

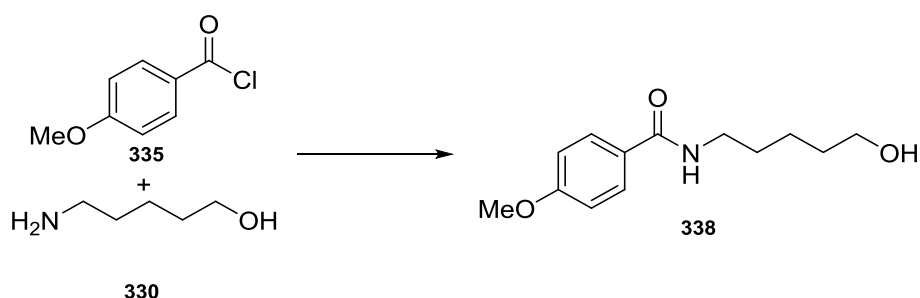
27.0 (CH₃), 25.4 (CH₂); *m/z* (ES) 268 (M+Na⁺, 100 %); *m/z* (ES) found [M+Na]⁺ 268.1306. C₁₅H₁₉NNaO₂⁺ requires 268.1308.

N-(5-Hydroxypentyl)-4'-nitrobenzamide **337**



Following general procedure 4a, 5-aminopentanol **330** (500 mg, 4.90 mmol) was reacted with *p*-nitrobenzoyl chloride **233** (930 mg, 5.00 mmol) to give the crude product. This was purified by flash chromatography on silica gel (chloroform: methanol; 9: 1) to yield **337** (760 mg, 63 %) as a colourless solid. M.p. 116 - 118 °C; Lit. m.p. 102.5 - 103.5 °C^[142], *R_f*: 0.4 (chloroform: methanol; 9: 1); *v*_{max} (CHCl₃)/cm⁻¹ 3427, 2938, 1639, 1600, 1560, 1347; *δ*_H (400 MHz, d₄-MeOD) 8.31 (2H, dd, *J* 7.5, 2.5, 2ArH), 8.01 (2H, dd, *J* 7.5, 2.5, 2ArH), 3.57 (2H, t, *J* 6.5, OCH₂), 3.41 (2H, t, *J* 7.0, NCH₂), 1.72 - 1.39 (6H, m, 3CH₂); *δ*_C (100 MHz, d₄-MeOD) 166.7 (C), 149.6 (C), 140.3 (C), 128.2 (CH), 123.2 (CH), 61.4 (CH₂), 39.8 (CH₂), 31.9 (CH₂), 28.8 (CH₂), 22.9 (CH₂); *m/z* (ES) 275 (M+Na⁺, 100%); *m/z* (ES) found [M+Na]⁺ 275.1001. C₁₂H₁₆N₂NaO₄⁺ requires 275.1002. The ¹H NMR and ¹³C data is in agreement with those previously reported.^[142]

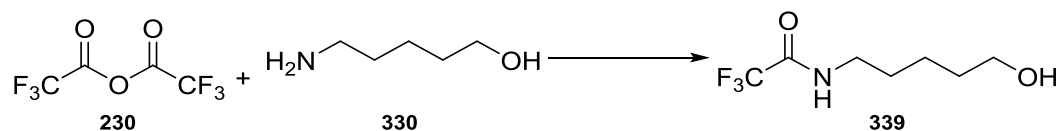
N-(5-Hydroxypentyl)-4'-methoxybenzamide **338**



Following general procedure 4a, 5-aminopentanol **330** (500 mg, 4.90 mmol) was reacted with 4-methoxybenzoyl chloride **335** (850 mg, 5.00 mmol) to yield **338** (1.04 g, 89 %) as a colourless solid. M.p. 73 - 76 °C; *v*_{max} (CHCl₃)/cm⁻¹ 3319, 2934, 1634, 1303, 1180; *δ*_H (400 MHz, CDCl₃) 7.73 (2H, ddd, *J* 8.0, 2.0, 2.0, 2ArH), 6.92 (2H, ddd, *J* 8.0, 2.0, 2.0, 2ArH), 6.11 (1H, bs, NH), 3.86 (3H, s, OCH₃), 3.68 (2H, t, *J* 8.0, OCH₂), 3.47 (2H, dt, *J* 7.5, 7.5, NCH₂), 1.73 - 1.42 (7H, m + s, OH + 3CH₂); *δ*_C (100 MHz, CDCl₃) 167.2 (C), 162.1 (C), 128.7 (CH), 127.0 (C), 113.7 (CH), 62.5 (CH₂), 55.4 (CH₃), 39.9 (CH₂), 32.2

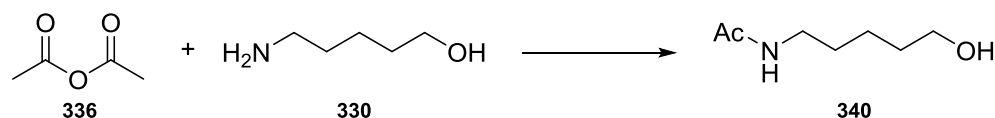
(CH₂), 29.5 (CH₂), 23.2 (CH₂); *m/z* (ES) 260 (M+Na⁺, 100 %); *m/z* (ES) found [M+Na]⁺ 260.1234. C₁₃H₁₉NNaO₃⁺ requires 260.1257.

2',2',2'-Trifluoro-*N*-(5-hydroxypentyl)acetamide **339**^[104]



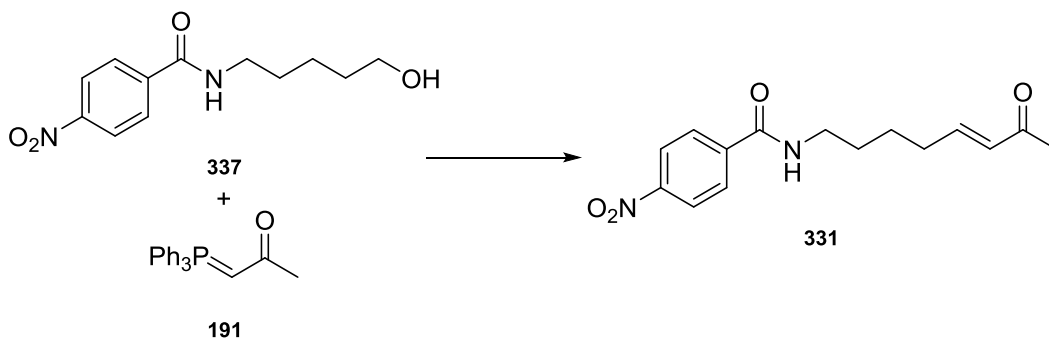
Following general procedure 4b, 5-aminopentanol **330** (500 mg, 4.90 mmol) was reacted with trifluoroacetic anhydride **230** (940 μl, 6.70 mmol) to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 2: 3) to yield **339** (970 mg, 99 %) as a light yellow oil. *R_f*: 0.5 (light petroleum ether: ethyl acetate; 2: 3); *v*_{max} (neat)/cm⁻¹ 3304, 2941, 1707, 1561; *δ*_H (400 MHz, CDCl₃) 6.61 (1H, bs, NH), 3.67 (2H, t, *J* 7.0, OCH₂), 3.38 (2H, dt, *J* 7.0, 7.0, NCH₂), 1.70 - 1.40 (7H, m, OH + 3CH₂); *δ*_C (100 MHz, CDCl₃) 157.4 (C, q, *J* 37), 116.0 (C, q, *J* 286), 62.4 (CH₂), 39.8 (CH₂), 31.8 (CH₂), 28.6 (CH₂), 22.9 (CH₂); *m/z* (ES) 222 (M+Na⁺, 100 %); *m/z* (ES) found [M+Na]⁺ 222.0713. C₇H₁₂F₃NNaO₂⁺ requires 222.0712. The ¹H NMR and ¹³C data is in agreement with those previously reported.^[104]

N-(5-hydroxypentyl)acetamide **340**



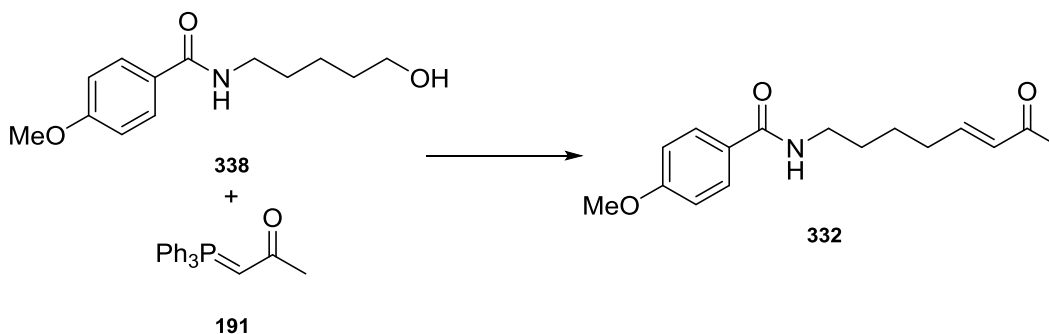
Following general procedure 4b, 5-aminopentanol-1-ol **330** (500 mg, 4.90 mmol) was reacted with acetic anhydride **336** (600 μl, 6.70 mmol) to give the crude product. This was purified by flash chromatography on silica gel (dichloromethane: methanol; 9: 1) to yield **340** (700 mg, 99 %) as a colourless oil. *R_f*: 0.2 (dichloromethane: methanol; 9: 1); *v*_{max} (neat)/cm⁻¹ 3295, 3100, 2936, 1635; *δ*_H (400 MHz, CDCl₃) 6.14 (1H, bs, NH), 3.60 (2H, t, *J* 7.5, OCH₂), 3.21 (2H, dt, *J* 7.5, 7.5, NCH₂), 1.94 (3H, s, CH₃), 1.63 - 1.32 (6H, m, 3CH₂); *δ*_C (100 MHz, CDCl₃) 170.3 (C), 62.3 (CH₂), 39.5 (CH₂), 32.1 (CH₂), 29.2 (CH₂), 23.2 (CH₃), 23.1 (CH₃); *m/z* (ES) 168 (M+Na⁺, 100 %); *m/z* (ES) found [M+Na]⁺ 168.0988. C₇H₁₅NNaO₂⁺ requires 168.0995. The ¹H NMR and ¹³C data is in agreement with those previously reported.^[143]

(E)-N-(6-Oxo-oct-5-en-1-yl)-4'-nitrobenzamide 331



Following general procedure 6, *N*-(5-hydroxypentyl)-4'-nitrobenzamide **337** (750 mg, 3.00 mmol) was reacted with 1-(triphenylphosphoranylidene)-2-propanone **191** (1.52 g, 4.80 mmol) in dichloromethane (26 ml) heated at reflux for 20 hours to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 2: 3) to yield **331** (315 mg, 36 %) as a brown solid. M.p. 91 - 93 °C; R_f : 0.3 (light petroleum ether: ethyl acetate; 2: 3); $\nu_{\max}$ (CHCl₃)/cm⁻¹ 3325, 2938, 1668, 1648, 1601, 1525, 1347; δ_H (400 MHz, CDCl₃) 8.28 (2H, dd, J 7.5, 2.5, 2ArH), 7.94 (2H, dd, J 7.5, 2.5, 2ArH), 6.79 (1H, dt, J 16.0, 7.5, CH=CHCO), 6.44 (1H, bs, NH), 6.08 (1H, d, J 16.0, CH=CHCO), 3.50 (2H, dt, J 7.5, 7.5, CHCH₂), 2.34 - 2.20 (5H, m + s, CH₂ + CH₃), 1.75 - 1.53 (4H, m, 2CH₂); δ_C (100 MHz, CDCl₃) 198.6 (C), 165.5 (C), 149.6 (C), 147.3 (CH), 140.2 (C), 131.7 (CH), 128.1 (CH), 123.8 (CH), 40.1 (CH₂), 31.9 (CH₂), 29.2 (CH₂), 27.0 (CH₃), 25.4 (CH₂); m/z (ES) 313 (M+Na⁺, 100 %); m/z (ES) found [M+Na]⁺ 313.1160. C₁₅H₁₈N₂NaO₄⁺ requires 313.1159.

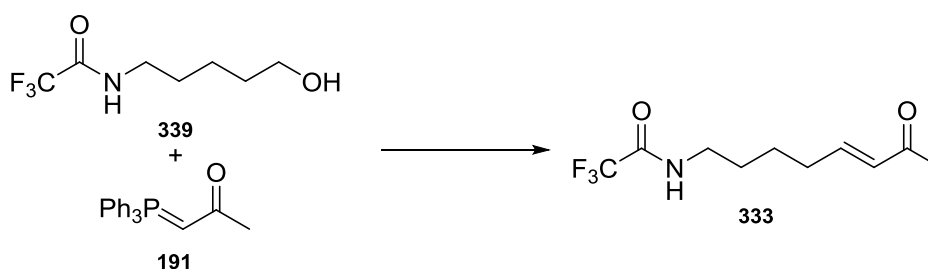
(E)-4'-Methoxy-N-(7-oxooct-5-en-1-yl)benzamide 332



Following general procedure 6, *N*-(5-hydroxypentyl)-4'-methoxybenzamide **338** (1.02 g, 4.30 mmol) was reacted with 1-(triphenylphosphoranylidene)-2-propanone **191** (2.19 g, 6.90 mmol) in chloroform (38 ml) heated at reflux for 20 hours to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 1: 3) to yield **332** (380 mg, 32 %) as a yellow solid. M.p. 92 - 95 °C; R_f : 0.4 (light petroleum ether: ethyl acetate; 1: 3); $\nu_{\max}$ (CHCl₃)/cm⁻¹ 3338, 2938, 1671, 1624, 1608, 1366, 1180; δ_H (400 MHz, CDCl₃) 7.73 (2H, dd, J 8.0, 2.0, 2ArH), 6.91 (2H, dd, J 8.0, 2.0, 2ArH), 6.78 (1H, dt, J 16.0, 8.0, CH=CHCO), 6.17 (1H, bs, NH), 6.08 (1H, dt, J 16.0, 2.0,

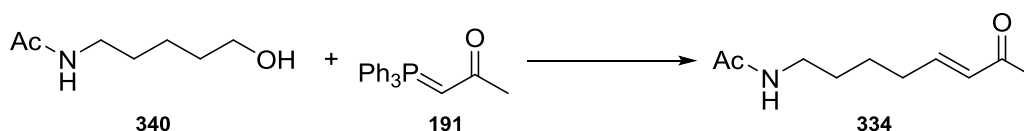
CH=CHCO), 3.85 (3H, s, OCH₃), 3.46 (2H, dt, *J* 8.0, 8.0, CHCH₂), 2.32 - 2.20 (5H, m + s, CH₂ + CH₃), 1.70 - 1.52 (4H, m, 2CH₂); δ_c (100 MHz, CDCl₃) 198.6 (C), 167.1 (C), 162.1 (C), 147.6 (CH), 131.6 (CH), 128.6 (CH), 126.9 (C), 113.8 (CH), 55.4 (CH₃), 39.6 (CH₂), 32.0 (CH₂), 29.4 (CH₂), 26.9 (CH₃), 25.4 (CH₂); *m/z* (ES) 298 (M+Na⁺, 100 %); *m/z* (ES) found [M+Na]⁺ 298.1409. C₁₆H₂₁NNaO₃⁺ requires 298.1414.

(*E*)-2',2',2'-Trifluoro-*N*-(7-oxooct-5-en-1-yl)acetamide **333**



Following general procedure 6, 2',2',2'-trifluoro-*N*-(5-hydroxypentyl)acetamide **339** (950 mg, 4.80 mmol) was reacted with 1-(triphenylphosphoranylidene)-2-propanone **191** (2.43 g, 7.60 mmol) in chloroform (42 ml) heated at reflux for 66 hours to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 3: 2) to yield **333** (560 mg, 49 %) as a yellow oil. *R_f*: 0.3 (light petroleum ether: ethyl acetate; 3: 2); $\nu_{\max}$ (neat)/cm⁻¹ 3309, 2939, 1712, 1672, 1627, 1559; δ_H (400 MHz, CDCl₃) 6.77 (1H, dt, *J* 16.0, 8.0, CH=CHCO), 6.55 (1H, bs, NH), 6.09 (1H, dt, *J* 16.0, 2.0, CH=CHCO), 3.39 (2H, dt, *J* 8.0, 8.0, CHCH₂), 2.32 - 2.22 (5H, m + s, CH₂ + CH₃), 1.70 - 1.49 (4H, m, 2CH₂); δ_c (100 MHz, CDCl₃) 198.6 (C), 157.3 (C, q, *J* 37), 147.0 (CH), 131.7 (CH), 115.8 (C, q, *J* 283), 39.6 (CH₂), 31.8 (CH₂), 28.5 (CH₂), 27.0 (CH₃), 25.1 (CH₂); *m/z* (ES) 260 (M+Na⁺, 100 %); *m/z* (ES) found [M+Na]⁺ 260.0868. C₁₀H₁₄F₃NNaO₂⁺ requires 260.0869.

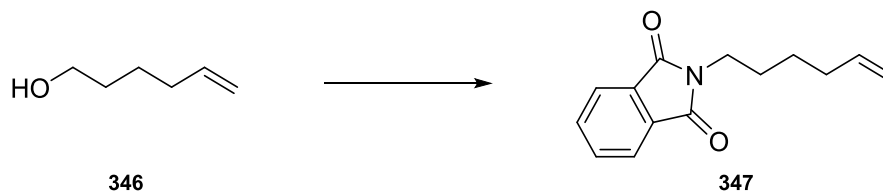
(*E*)-*N*-(7-Oxooct-5-en-1-yl)acetamide **334**



Following general procedure 6, *N*-(5-hydroxypentyl)acetamide **340** (440 mg, 3.00 mmol) was reacted with 1-(triphenylphosphoranylidene)-2-propanone **191** (1.53 g, 4.80 mmol) in chloroform (28 ml) heated at reflux for 44 hours to give the crude product. This was purified by flash chromatography on silica gel (ethyl acetate: methanol; 19: 1) to yield **334** (122 mg, 22 %) as a yellow oil. *R_f*: 0.2 (ethyl acetate: methanol; 19: 1); $\nu_{\max}$ (neat)/cm⁻¹ 3296, 2936, 1669, 1533; δ_H (400 MHz, CDCl₃) 6.78 (1H, dt, *J* 16.0, 8.0, CH=CHCO), 6.08 (1H, dt, *J* 16.0, 2.0, CH=CHCO), 5.53 (1H, bs, NH), 3.26 (2H, dt, *J* 8.0, 8.0, NCH₂), 2.31 - 2.20 (5H, m + s, CH₂ + COCH₃), 1.98 (3H, s, NCOCH₃), 1.60 - 1.46

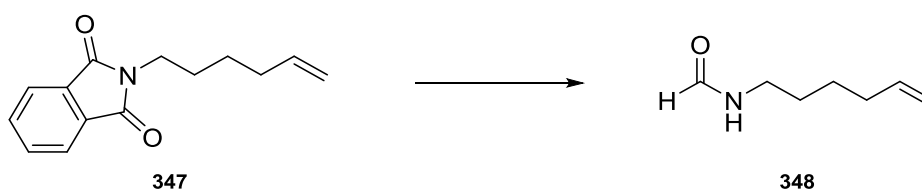
(4H, m, 2CH₂); δ_c (100 MHz, CDCl₃) 198.6 (C), 170.0 (C), 147.5 (CH), 131.6 (CH), 39.3 (CH₂), 32.0 (CH₂), 29.3 (CH₂), 27.0 (CH₃), 25.4 (CH₂), 23.3 (CH₃); m/z (ES) 206 (M+Na⁺, 100 %); m/z (ES) found [M+Na]⁺ 206.1154. C₁₀H₁₇NNaO₂⁺ requires 206.1151.

2-(Hex-5'-en-1'-yl)isoindoline-1,3-dione **347**^[105]



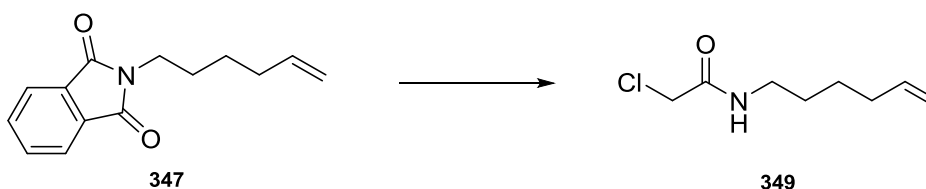
Mesyl chloride (4.30 g, 55.0 mmol) was added dropwise at 0 °C to a solution of 5-hexenol **346** (5.00 g, 50.0 mmol) and triethylamine (8.30 ml, 60.0 mmol) in dichloromethane (150 ml). This was stirred at 0 °C for 1 hour. Water (150 ml) was added and the layers separated. The aqueous layer was extracted with diethyl ether (100 ml), the organics combined, dried (sodium sulfate) and concentrated under reduced pressure to yield the crude mesylated alcohol (8.50 g) as a light yellow oil. This was dissolved in *N,N*-dimethylformamide (150 ml) and potassium phthalamide (9.25 g, 50.0 mmol) was added. This was heated under argon at 90 °C for 4 hours. Water (350 ml) and diethyl ether (250 ml) were added, the layers separated and the aqueous extracted with diethyl ether (200 ml). The organics were combined, dried (sodium sulfate) and concentrated under reduced pressure to yield a yellow oil. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 9: 1) to yield **347** (7.55 g, 68 %) as a colourless solid. M.p. 30 - 32 °C; R_f : 0.3 (light petroleum ether: ethyl acetate; 9: 1); $\nu_{\max}$ (CHCl₃)/cm⁻¹ 2938, 1712, 1640, 1616, 1467, 1396; δ_H (400 MHz, CDCl₃) 7.84 (2H, dd, *J* 5.5, 3.0, 2ArH), 7.71 (2H, dd, *J* 5.5, 3.0, 2ArH), 5.78 (1H, ddt, *J* 16.0, 12.0, 8.0, CH=CH₂), 5.05 - 4.90 (2H, m, CH=CH₂), 3.69 (2H, t, *J* 7.5, NCH₂), 2.10 (2H, dt, *J* 8.0, 8.0, CHCH₂), 1.76 - 1.65 (2H, m, CH₂), 1.50 - 1.39 (2H, m, CH₂); δ_c (100 MHz, CDCl₃) 168.4 (C), 138.3 (CH), 133.9 (CH), 132.2 (C), 123.2 (CH), 114.9 (CH₂), 37.9 (CH₂), 33.2 (CH₂), 28.0 (CH₂), 26.1 (CH₂); m/z (ES) 252 (M+Na⁺, 100 %); m/z (ES) found [M+Na]⁺ 252.0998. C₁₄H₁₅NNaO₂⁺ requires 252.0995. The ¹H NMR and ¹³C data is in agreement with those previously reported.^[105]

N*-(hex-5-en-1-yl)formamide **348*



Hydrazine hydrate (55 %, 1.30 ml, 14.6 mmol) was added dropwise to a solution of 2-(hex-5'-en-1'-yl)isoindoline-1,3-dione **347** (1.11 g, 4.85 mmol) in ethanol (15 ml). The solution was heated at reflux under argon for 40 minutes. The resulting suspension was cooled to room temperature, the solid collected by filtration and washed with ethanol (10 ml). The resulting solution was treated with 12 M hydrochloric acid (1 ml) and concentrated under reduced pressure. The resulting solution was adjusted to pH 10 with 2 M aqueous sodium hydroxide. The solution was extracted with diethyl ether (4 x 5 ml). Methyl formate (10 ml) was added to the combined organic extracts and stirred at room temperature for 18 hours. The solution was concentrated under reduced pressure and the residue purified by flash chromatography on silica gel (ethyl acetate) to yield **348** (370 mg, 59 %) as a colourless oil. R_f : 0.4 (ethyl acetate); $\nu_{\max}$ (neat)/ cm^{-1} 3440, 2925, 2854, 1641; δ_{H} (400 MHz, CDCl_3 , 4: 1 mix of rotamers A and B) 8.17 (0.8H, s, COH rotamer A), 8.13 (0.2H, d, J 12.0, COH rotamer B) 5.90 - 5.47 (2H, m + s, $\text{CH}=\text{CH}_2$ + NH), 5.08 - 4.89 (2H, m, $\text{CH}=\text{CH}_2$), 3.31 (1.6H, dt, J 7.0, 7.0, NCH_2 rotamer A), 3.23 (0.4H, dt, J 7.0, 7.0, NCH_2 rotamer B), 2.08 (2H, dt, J 8.0, 8.0, CHCH_2), 1.61 - 1.38 (4H, m, 2CH_2); δ_{C} (100 MHz, CDCl_3) 164.6 (CH rotamer B), 161.2 (CH rotamer A), 138.3 (CH), 114.9 (CH_2), 41.6 (CH_2 rotamer B), 38.0 (CH_2 rotamer A), 33.3 (CH_2), 30.6 (CH_2 rotamer A), 29.0 (CH_2 rotamer B) 26.1 (CH_2); m/z (ES) 150 ($\text{M}+\text{Na}^+$, 100 %); m/z (ES) found $[\text{M}+\text{Na}]^+$ 150.0882. $\text{C}_7\text{H}_{13}\text{NNaO}^+$ requires 150.0889.

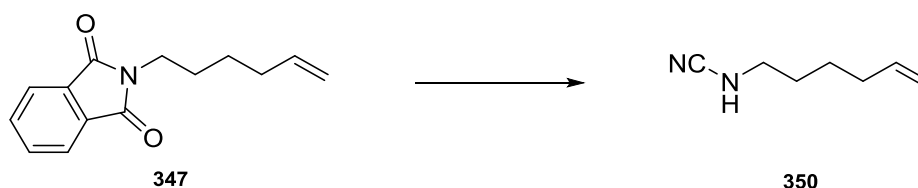
2-Chloro-*N*-(hex-5'-en-1'-yl)acetamide **349**



Hydrazine hydrate (55 %, 1.30 ml, 14.5 mmol) was added dropwise to a solution of 2-(hex-5'-en-1'-yl)isoindoline-1,3-dione **347** (1.11 g, 4.85 mmol) in ethanol (15 ml). The solution was heated at reflux under argon for 20 minutes. The resulting suspension was cooled to room temperature, the solid collected by filtration and washed with ethanol (10 ml). The resulting solution was treated with 12 M hydrochloric acid (1 ml) and concentrated under reduced pressure. The resulting solution was dissolved in water (10 ml) and adjusted to pH 10 with 1 M aqueous sodium hydroxide. The solution was extracted with dichloromethane (4 x 5 ml). The combined organics were added dropwise to a solution of α -chloroacetyl chloride (300 μl , 3.80 mmol) dissolved in dichloromethane (5 ml) at 0 °C. Potassium carbonate (520 mg, 3.80 mmol) was added and the solution allowed to warm to room temperature then stirred for 2 hours. The solution was concentrated under reduced pressure and the residue purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 3: 1) to yield **349** (180 mg, 29 %) as a colourless oil. R_f : 0.3 (light petroleum ether: ethyl acetate; 3: 1); $\nu_{\max}$ (CHCl_3)/ cm^{-1} 3292,

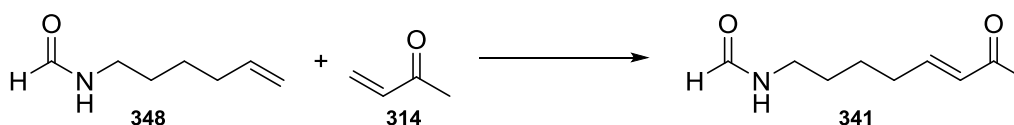
2933, 1658, 1544; δ_{H} (400 MHz, CDCl_3) 6.58 (2H, bs, NH), 5.79 (1H, ddt, J 16.0, 10.5, 7.0, $\text{CH}=\text{CH}_2$), 5.08 - 4.93 (2H, m, $\text{CH}=\text{CH}_2$), 4.05 (2H, s, PhCH_2), 3.32 (2H, dt, J 8.0, 8.0, NCH_2), 2.10 (2H, dt, J 7.0, 7.0, CHCH_2), 1.69 - 1.38 (4H, m, 2CH_2); δ_{C} (100 MHz, CDCl_3) 165.8 (C), 138.2 (CH), 115.0 (CH), 42.7 (CH_2), 39.7 (CH_2), 33.3 (CH_2), 28.8 (CH_2), 26.0 (CH_2); m/z (ES) 200 ($\text{M}^{37}\text{Cl}+\text{Na}^+$, 34 %), 198 [$\text{M}^{35}\text{Cl}+\text{Na}^+$, 100], 178 ($\text{M}^{37}\text{Cl}+\text{H}^+$, 28), 176 ($\text{M}^{35}\text{Cl}+\text{H}^+$, 89); m/z (ES) found $[\text{M}+\text{Na}]^+$ 198.0659. $\text{C}_8\text{H}_{14}^{35}\text{ClNNaO}^+$ requires 198.0656.

N*-(Hex-5-en-1-yl)cyanamide **350*



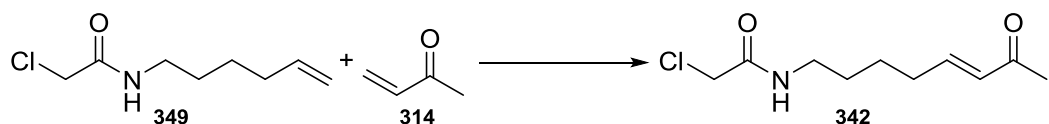
Hydrazine hydrate (55 %, 2.60 ml, 29.1 mmol) was added dropwise to a solution of 2-(hex-5'-en-1'-yl)isoindoline-1,3-dione **347** (2.22 g, 9.70 mmol) in ethanol (30 ml). The solution was heated at reflux under argon for 40 minutes. The resulting suspension was cooled to room temperature, the solid collected by filtration and washed with ethanol (20 ml). The resulting solution was treated with 12 M hydrochloric acid (2 ml) and concentrated under reduced pressure. The resulting solution was adjusted to pH 10 with 2 M aqueous sodium hydroxide. The solution was extracted with diethyl ether (4 x 5 ml). Sodium carbonate (4.18 g, 39.4 mmol) was added to the combined organic extracts and the solution cooled to $-20\text{ }^{\circ}\text{C}$. Cyanogen bromide (2.18 g, 20.6 mmol) dissolved in diethyl ether (5 ml) was added dropwise over 10 minutes and the solution stirred at $-20\text{ }^{\circ}\text{C}$ for 4 hours. The solid was collected by filtration and the solution concentrated under reduced pressure and the residue purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 3: 1) to yield **350** (540 mg, 44 %) as a colourless oil. R_f : 0.3 (light petroleum ether: ethyl acetate; 3: 1); ν_{max} (neat)/ cm^{-1} 3210, 2934, 2221, 1684, 1641; δ_{H} (400 MHz, CDCl_3) 5.86 - 5.71 (1H, ddt, J 16.0, 10.5, 8.0, $\text{CH}=\text{CH}_2$), 5.07 - 4.94 (2H, m, $\text{CH}=\text{CH}_2$), 3.60 (1H, s, NH), 3.09 (2H, dt, J 7.5, 7.5, NCH_2), 2.09 (2H, dt, J 8.0, 8.0, CHCH_2), 1.70 - 1.41 (4H, m, 2CH_2); δ_{C} (100 MHz, CDCl_3) 138.0 (CH), 116.2 (C), 115.2 (CH_2), 46.2 (CH_2), 33.1 (CH_2), 29.1 (CH_2), 25.5 (CH_2); m/z (ES) 147 ($\text{M}+\text{Na}^+$, 100 %); m/z (ES) found $[\text{M}+\text{Na}]^+$ 147.0891. $\text{C}_7\text{H}_{12}\text{N}_2\text{Na}^+$ requires 147.0893.

(E)*-N-(7-Oxo-oct-5-en-1-yl)formamide **341*



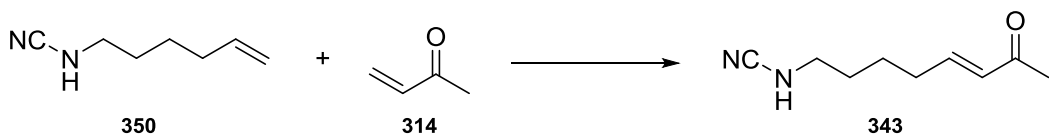
Following general procedure 7, *N*-(hex-5-en-1-yl)formamide **348** (180 mg, 1.40 mmol) was reacted with methylvinylketone **314** (350 μ l, 4.20 mmol) for 2 hours to give the crude product. This was purified by flash chromatography on silica gel (ethyl acetate) to yield **341** (190 mg, 81 %) as a brown oil. R_f : 0.2 (ethyl acetate). $\nu_{\max}$ (neat)/ cm^{-1} 3305, 2937, 2864, 1668, 1627; δ_{H} (400 MHz, CDCl_3) 17: 3 mix of rotamers A and B) 8.18 (0.85H, s, CHO rotamer A), 8.05 (0.15H, d, J 16.0, CHO rotamer B), 6.78 (1H, dt, J 16.0, 7.5, $\text{CH}=\text{CHCO}$), 6.08 (1H, dt, J 16.0, 2.0, $\text{CH}=\text{CHCO}$), 5.65 (1H, bs, NH), 3.33 (1.7H, dt, J 8.0, 8.0, NCH_2 rotamer A), 3.25 (0.3H, dt, J 8.0, 8.0, NCH_2 rotamer B), 2.31 - 2.22 (5H, m + s, $\text{CHCH}_2 + \text{CH}_3$), 1.63 - 1.47 (4H, m, 2CH_2); δ_{C} (100 MHz, CDCl_3) 198.6 (C), 164.5 (CH rotamer A), 161.2 (CH rotamer B), 147.4 (CH rotamer A), 146.9 (CH rotamer B), 131.6 (CH rotamer A), 129.1 (CH rotamer B), 41.5 (CH_2 rotamer B), 37.8 (CH_2 rotamer A), 31.9 (CH_2 rotamer A), 30.9 (CH_2 rotamer B), 29.2 (CH_2), 27.0 (CH_3), 25.3 (CH_2); m/z (ES) 192 ($\text{M}+\text{Na}^+$, 100 %); m/z (ES) found $[\text{M}+\text{Na}]^+$ 192.1001. $\text{C}_9\text{H}_{15}\text{NNaO}_2^+$ requires 192.0995.

(*E*)-2-Chloro-*N*-(7'-oxooct-5'-en-1'-yl)acetamide 342



Following general procedure 7, 2-chloro-*N*-(hex-5'-en-1'-yl)acetamide **349** (160 mg, 900 μ mol) was reacted with methylvinylketone **314** (380 μ l, 4.50 mmol) for 1 hour to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 2: 3) to yield **342** (140 mg, 72 %) as a light brown oil. R_f : 0.3 (light petroleum ether: ethyl acetate; 2: 3); $\nu_{\max}$ (neat)/ cm^{-1} 3305, 2937, 1670, 1627; δ_{H} (400 MHz, CDCl_3) 6.78 (1H, dt, J 17.5, 8.0, $\text{CH}=\text{CHCO}$), 6.61 (1H, bs, NH), 6.09 (1H, dt, J 17.5, 2.0, $\text{CH}=\text{CHCO}$), 4.05 (2H, s, ClCH_2), 3.33 (2H, dt, J 8.0, 8.0, NCH_2), 2.31 - 2.22 (5H, m + s, $\text{CH}_2 + \text{CH}_3$), 1.64 - 1.48 (4H, m, 2CH_2); δ_{C} (100 MHz, CDCl_3) 198.5 (C), 165.9 (C), 147.3 (CH), 131.7 (CH), 42.7 (CH_2), 39.5 (CH_2), 31.9 (CH_2), 29.0 (CH_2), 27.0 (CH_3), 25.3 (CH_2); m/z (ES) 242 ($\text{M}^{37}\text{Cl}+\text{Na}^+$, 33 %), 240 ($\text{M}^{35}\text{Cl}+\text{Na}^+$, 100), 220 ($\text{M}^{37}\text{Cl}+\text{H}^+$, 16), 218 ($\text{M}^{35}\text{Cl}+\text{H}^+$, 53); m/z (ES) found $[\text{M}+\text{Na}]^+$ 240.0761. $\text{C}_{10}\text{H}_{16}^{35}\text{ClNNaO}_2^+$ requires 240.0762.

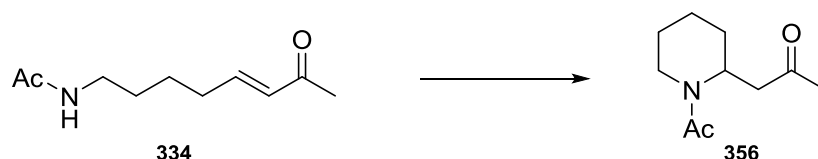
(*E*)-*N*-(7-Oxooct-5-en-1-yl)cyanamide 343



Following general procedure 7, *N*-(hex-5-en-1-yl)cyanamide **350** (250 mg, 2.00 mmol) was reacted with methylvinylketone **314** (830 μ l, 10.0 mmol) for 1 hour to give the crude

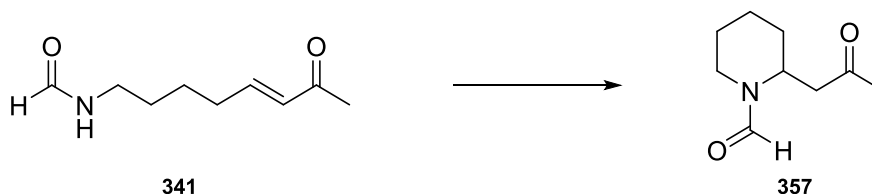
product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 2: 1) to yield **343** (93.0 mg, 28 %) as a brown oil. R_f : 0.4 (light petroleum ether: ethyl acetate; 2: 1); $\nu_{\max}$ (neat)/ cm^{-1} 3425, 2941, 2218, 1638; δ_{H} (400 MHz, CDCl_3) 6.78 (1H, dt, J 16.0, 8.0, $\text{CH}=\text{CHCO}$), 6.08 (1H, dt, J 16.0, 2.0, $\text{CH}=\text{CHCO}$), 4.23 (1H, bs, NH), 3.09 (2H, dt, J 7.0, 7.0, NCH_2), 2.31 - 2.22 (5H, m + s, $\text{CHCH}_2 + \text{CH}_3$), 1.70 - 1.51 (4H, m, 2CH_2); δ_{C} (100 MHz, CDCl_3) 198.9 (C), 147.4 (CH), 131.6 (CH), 116.3 (CH), 45.8 (CH_2), 31.8 (CH_2), 29.1 (CH_2), 27.0 (CH_3), 24.7 (CH_2); m/z (ES) 189 ($\text{M}+\text{Na}^+$, 100 %); m/z (ES) found $[\text{M}+\text{Na}]^+$ 189.1002. $\text{C}_9\text{H}_{14}\text{N}_2\text{NaO}^+$ requires 189.0998.

(+)-1-(1-Acetylpiperidin-2-yl)propan-2-one **356**



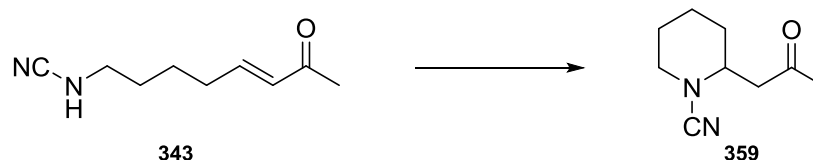
Following general procedure 8, (*E*)-*N*-(7-oxooct-5-en-1-yl)acetamide **334** (18.3 mg, 100 μmol) was stirred in 2-methyltetrahydrofuran (1.0 ml) at 20 °C for 48 hours to yield **356** (15.2 mg, 83 %) as a colourless oil. R_f : 0.5 (ethyl acetate: methanol; 9: 1); $[\alpha]_{\text{D}}^{25} +71.2$ (c 0.4 in CHCl_3); $\nu_{\max}$ (neat)/ cm^{-1} 2932, 1712, 1633; δ_{H} (400 MHz, CDCl_3 , 1: 1 mix of rotamers) 5.32 - 5.20 (0.5H, m, CHN rotamer A), 4.64 - 4.48 (1H, m, $\text{CH}_\text{A}\text{H}_\text{B}$ rotamer A + CHN rotamer B), 3.64 - 3.57 (0.5H, m, $\text{CH}_\text{A}\text{H}_\text{B}$ rotamer B), 2.90 (0.5H, ddd, J 14.0, 14.0, 2.0, $\text{CH}_\text{A}\text{H}_\text{B}$ rotamer A), 2.80 (0.5H, dd, J 16.0, 4.0, $\text{COCH}_\text{A}\text{H}_\text{B}$ rotamer A), 2.73 - 2.47 (1.5H, m, 2CH rotamer B + CH rotamer A), 2.21 (1.5H, s, CH_3 rotamer A), 2.18 (1.5H, s, CH_3 rotamer B), 2.15 (1.5H, s, CH_3 rotamer A), 2.06 (1.5H, s, CH_3 rotamer B), 1.75 - 1.30 (6.5H, m, 3CH_2 rotamer A + $3\text{CH}_2 + \text{CH}$ rotamer B); δ_{C} (100 MHz, CDCl_3 , 1: 1 mix of rotamers) 207.4 (C rotamer A), 205.9 (C rotamer B), 169.4 (C rotamer A), 168.1 (C rotamer B), 49.3 (CH rotamer A), 44.8 (CH rotamer B), 44.3 (CH_2 rotamer A), 44.1 (CH_2 rotamer B), 42.1 (CH_2 rotamer A), 37.0 (CH_2 rotamer B), 31.0 (CH_3 rotamer A), 29.8 (CH_3 rotamer B), 29.3 (CH_2 rotamer A), 28.2 (CH_2 rotamer B), 25.8 (CH_2 rotamer A), 25.3 (CH_2 rotamer B), 21.9 (CH_3 rotamer A), 21.6 (CH_3 rotamer B), 19.2 (CH_2 rotamer A), 18.9 (CH_2 rotamer B); m/z (ES) 206 ($\text{M}+\text{Na}^+$, 100 %); m/z (ES) found $[\text{M}+\text{Na}]^+$ 206.1160. $\text{C}_{14}\text{H}_{19}\text{NNaO}_3\text{S}^+$ requires 206.1151; R_t HPLC Chiralpak AD-H; mobile phase, hexane: 2-propanol (19: 1 v/v); flow rate, 1 ml/min; 17.6 min (5.0 %), 19.9 min (95.0 %) 90 % e.e.

(+)-1-(1-Formylpiperidin-2-yl)propan-2-one **357**



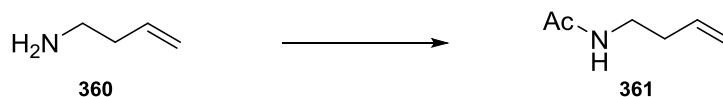
Following general procedure 8, (*E*)-*N*-(7-oxooct-5-en-1-yl)formamide **341** (8.50 mg, 50.0 μ mol) was stirred in tetrahydrofuran (0.5 ml) at room temperature for 144 hours to yield the crude product. This was purified by flash chromatography on silica gel (ethyl acetate) to yield **357** (4.25 mg, 50 %) as a colourless oil. R_f : 0.3 (ethyl acetate); $[\alpha]_D^{26} +41.8$ (c 0.4 in CHCl_3); ν_{max} (neat)/ cm^{-1} 2942, 2864, 1712, 1658; δ_{H} (400 MHz, CDCl_3) 14: 11 mixture of rotamers A and B) 8.11 (0.56H, s, CHO rotamer A), 7.97 (0.44H, s, CHO rotamer B), 5.09 - 4.96 (0.44H, m, CH_N rotamer B), 4.33 - 4.21 (1.12H, m, 2CH rotamer A), 3.44 - 3.35 (0.44H, m, CH_AH_B rotamer B), 3.18 (0.44H, ddd, J 16.0, 12.0, 2.0, CH_AH_B rotamer B), 2.93 (0.56H, dd, J 16.0, 8.0, COCH_AH_B rotamer A), 2.73 - 2.60 (2H, m, 2CH rotamer A + 2CH rotamer B), 2.21 (1.32H, s, CH_3 rotamer B), 2.16 (1.68H, s, CH_3 rotamer A), 1.79 - 1.31 (6H, m, 3 CH_2 rotamer A + 3 CH_2 rotamer B); δ_{C} (100 MHz, CDCl_3) 206.5 (C rotamer A), 205.6 (C rotamer B), 161.6 (CH), A), 49.7 (CH rotamer A), 44.2 (CH₂ rotamer B), 44.0 (CH rotamer B), 42.7 (CH₂ rotamer A), 36.2 (CH₂ rotamer B), 30.8 (CH₃ rotamer A), 30.0 (CH₂ rotamer A), 29.8 (CH₃ rotamer B), 28.0 (CH₂ rotamer B), 26.2 (CH₂ rotamer A), 25.0 (CH₂ rotamer B), 20.1 (CH₂), 19.6 (CH₂ rotamer A); m/z (ES) 192 ($\text{M}+\text{Na}^+$, 100 %); m/z (ES) found $[\text{M}+\text{Na}]^+$ 192.1006. $\text{C}_9\text{H}_{15}\text{NNaO}_2^+$ requires 192.0995; R_t HPLC Chiralcel OD-H; mobile phase, hexane: 2-propanol (9: 1 v/v); flow rate, 1 ml/min; 22.6 min (10.8 %), 31.7 min (89.2 %) 78 % e.e.

(+)-2-(2-Oxopropyl)piperidine-1-carbonitrile 359



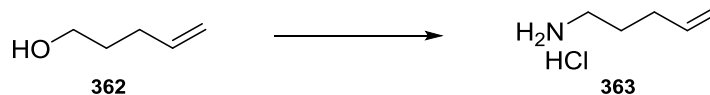
Following general procedure 8, (*E*)-*N*-(7-oxooct-5-en-1-yl)cyanamide **343** (16.6 mg, 100 μ mol) was stirred in tetrahydrofuran (1.0 ml) at room temperature for 18 hours to yield the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 3: 2) to yield **359** (14.3 mg, 89 %) as a colourless oil. R_f : 0.2 (light petroleum ether: ethyl acetate; 3: 2); $[\alpha]_D^{26} +17.5$ (c 0.6 in CHCl_3); ν_{max} (neat)/ cm^{-1} 2941, 2205, 1717; δ_{H} (400 MHz, CDCl_3) 3.50 - 3.40 (2H, m, CNH + CH_AH_B), 3.12 - 3.02 (1H, m, CH_AH_B), 2.98 (1H, dd, J 17.5, 6.5, COCH_AH_B), 2.60 (1H, dd, J 17.5, 7.0, COCH_AH_B), 2.22 (3H, s, CH_3), 1.89 - 1.31 (6H, m, 3 CH_2); δ_{C} (100 MHz, CDCl_3) 204.7 (C), 116.6 (C), 54.4 (CH), 51.1 (CH₂), 47.0 (CH₂), 30.8 (CH₃), 30.3 (CH₂), 24.1 (CH₂), 23.3 (CH₂); m/z (ES) 189 ($\text{M}+\text{Na}^+$, 100 %); m/z (ES) found $[\text{M}+\text{Na}]^+$ 189.1003. $\text{C}_9\text{H}_{14}\text{N}_2\text{NaO}^+$ requires 189.0998; R_t HPLC ChiralpakAD-H; mobile phase, hexane: 2-propanol (19: 1 v/v); flow rate, 1 ml/min; 14.5 min (17.9 %), 15.6 min (82.1 %) 64 % e.e

N-(But-3-en-1-yl)acetamide **361**



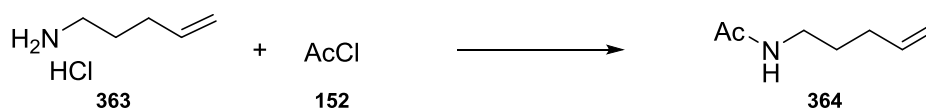
3-But-1-amine **360** (220 μ l, 2.42 mmol) was dissolved in dichloromethane (2 ml) and triethylamine (480 μ l, 2.67 mmol) was added at 0 °C. Acetic anhydride **336** (240 μ l, 2.50 mmol) was added dropwise over 10 minutes and the solution was allowed to warm to room temperature then stirred for 18 hours. The resulting solution was concentrated under reduced pressure to yield the crude product. This was purified by flash chromatography on silica gel (ethyl acetate) to yield **361** (200 mg, 73 %) as a colourless oil. R_f : 0.4 (ethyl acetate); $\nu_{\max}$ (neat)/ cm^{-1} 3292, 2979, 1654, 1558; δ_{H} (400 MHz, CDCl_3) 5.76 (1H, ddt, J 17.0, 10.5, 6.5, $\text{CH}_2=\text{CH}$), 5.55 (1H, bs, NH), 5.14 - 5.06 (2H, m, $\text{CH}_2=\text{CH}$), 3.33 (2H, dt, J 6.5, NCH_2), 2.27 (2H, dtt, J 7.5, 7.5, 2.0, CHCH_2), 1.97 (3H, s, CH_3); δ_{C} (100 MHz, CDCl_3) 170.0 (C), 135.3 (CH), 117.2 (CH_2), 38.5 (CH_2), 33.7 (CH_2), 23.3 (CH_3); m/z (ES) 136 ($\text{M}+\text{Na}^+$, 100 %); m/z (ES) found $[\text{M}+\text{Na}]^+$ 136.0714. $\text{C}_6\text{H}_{11}\text{NNaO}^+$ requires 136.0733. The ^1H NMR is in agreement with that previously reported.^[144]

4-Penten-1-amine hydrochloride **363**^[108]



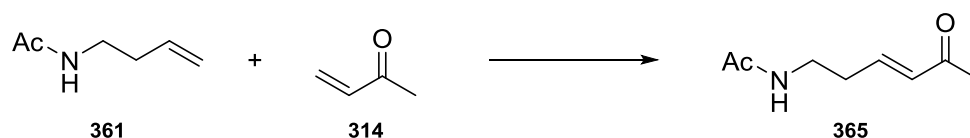
4-Penten-1-ol **362** (1.20 ml, 11.6 mmol), triethylamine (4.90 ml, 34.8 mmol) and DMAP (142 mg, 1.16 mmol) were dissolved in dichloromethane (40 ml) and the solution was cooled to 0 °C. Methanesulfonyl chloride (1.35 ml, 17.4 mmol) was added and the solution stirred at 0 °C for 2 hours. The reaction mixture was washed with water (40 ml) and the aqueous extracted with ethyl acetate (20 ml). The organic phases were combined, dried (magnesium sulfate) and concentrated under reduced pressure. The residue was dissolved in methanol (90 ml) and ammonium hydroxide solution (103 ml) was added. This was stirred at room temperature for 48 hours. This was concentrated under reduced pressure to remove the excess ammonia and methanol. Water (100 ml) was added and the aqueous washed with ethyl acetate (2 x 100 ml). The water phase was acidified with 1M hydrochloric acid (3 ml) and the solution concentrated. This yielded crude product **363** (1.51 g) which was used directly in the next step without further purification.

N-(Pent-4-en-1-yl)acetamide **364**

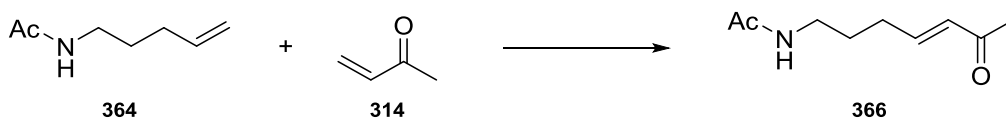


4-Penten-1-amine hydrochloride salt **363** (250 mg, 1.00 mmol) was suspended in dichloromethane (4 ml) and triethylamine (280 μ l, 2.00 mmol) was added at 0 °C. Acetyl chloride **152** (35.0 μ l, 500 μ mol) was then added dropwise. The solution was allowed to warm to room temperature then stirred for 2 hours. This solution was diluted with water (4 ml) and the layers separated. The organic layer was washed with 0.1 M hydrochloric acid (4 ml), dried (magnesium sulfate) and concentrated under reduced pressure to yield the crude product. This was purified by flash chromatography on silica gel (ethyl acetate) to yield **364** (44.0 mg, 70 %) as a colourless oil. R_f : 0.3 (ethyl acetate); $\nu_{\max}$ (neat)/cm⁻¹ 3291, 2934, 1653, 1558; δ_H (500 MHz, CDCl₃) 6.15 (1H, bs, NH), 5.75 (1H, ddt, J 17.0, 10.0, 7.0, CH₂=CH), 5.02 - 4.94 (2H, m, CH=CH₂), 3.20 (2H, t, J 7.0, NCH₂), 2.05 (2H, dt, J 7.0, 7.0, CHCH₂), 1.93 (3H, s, CH₃), 1.61 - 1.54 (2H, m, CH₂); δ_C (125 MHz, CDCl₃) 172.3 (C), 137.7 (CH), 115.1 (CH₂), 39.1 (CH₂), 31.1 (CH₂), 28.7 (CH₂), 23.2 (CH₃). m/z (ES) 128 (M+H⁺, 100 %), 150 (M+Na⁺, 81); m/z (ES) found [M+H]⁺ 128.1037. C₇H₁₄NO⁺ requires 128.1070. The ¹H NMR and ¹³C data is in agreement with those previously reported.^[145]

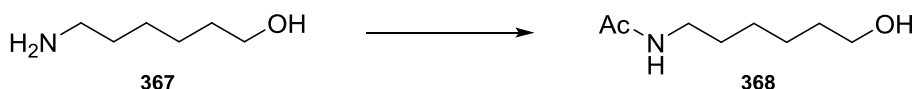
(E)-*N*-(5-Oxohex-3-en-1-yl)acetamide **365**



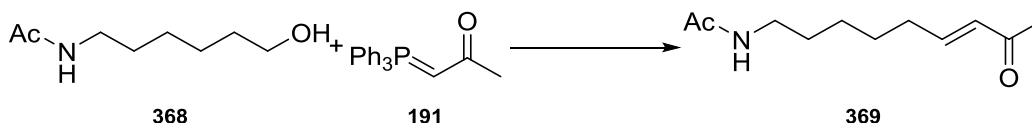
Following general procedure 7, *N*-(but-3-en-1-yl)acetamide **361** (110 mg, 1.00 mmol) was reacted with methylvinylketone **314** (420 μ l, 5.00 mmol) for 2 hours to give the crude product. This was purified by flash chromatography on silica gel (ethyl acetate: methanol; 19: 1) to yield **365** (130 mg, 84 %) as a yellow oil. R_f : 0.2 (ethyl acetate: methanol; 19: 1); $\nu_{\max}$ (neat)/cm⁻¹ 3418, 2935, 1663, 1638, 1557; δ_H (400 MHz, CDCl₃) 6.74 (1H, dt, J 16.0, 7.5, CH=CHCO), 6.12 (1H, dt, J 16.0, 2.0, CH=CHCO), 5.76 (1H, bs, NH), 3.41 (2H, dt, J 6.5, 6.5, NCH₂), 2.45 (2H, dt, J 7.0, 7.0, CHCH₂), 2.25 (3H, s, COCH₃), 1.97 (3H, s, NCOCH₃); δ_C (100 MHz, CDCl₃) 198.3 (C), 170.3 (C), 144.3 (CH), 132.8 (CH), 38.0 (CH₂), 32.7 (CH₂), 27.1 (CH₃), 23.3 (CH₃); m/z (ES) 178 (M+Na⁺, 100 %), 156 (M+H⁺, 44); m/z (ES) found [M+Na]⁺ 178.0843. C₈H₁₃NNaO₂⁺ requires 178.0838.

(E)-N-(6-Oxohept-4-en-1-yl)acetamide 366

Following general procedure 7, *N*-(pent-4-en-1-yl)acetamide **364** (44.0 mg, 350 μ mol) was reacted with methylvinylketone **314** (145 μ l, 1.75 mmol) for 1 hour to give the crude product. This was purified by flash chromatography on silica gel (ethyl acetate: methanol; 49: 1) to yield **366** (47.0 mg, 80 %) as a yellow oil. R_f : 0.2 (ethyl acetate: methanol; 49: 1); $\nu_{\max}$ (neat)/ cm^{-1} 3295, 2935, 1661, 1558; δ_{H} (400 MHz, C_6D_6) 6.41 (1H, dt, J 16.0, 7.0, $\text{CH}=\text{CHCO}$), 5.91 (1H, dt, J 16.0, 2.0, $\text{CH}=\text{CHCO}$), 4.93 (1H, bs, NH), 2.94 (2H, dt, J 6.5, 6.5, NCH_2), 1.87 (3H, s, COCH_3), 1.74 (2H, dt, J 7.0, 7.0, CHCH_2), 1.69 (3H, s, NCOCH_3), 1.28 - 1.16 (2H, m, CH_2); δ_{C} (100 MHz, C_6D_6) 196.4 (C), 168.7 (C), 145.9 (CH), 131.5 (CH), 38.6 (CH_2), 29.4 (CH_2), 28.2 (CH_2), 26.6 (CH_3), 22.7 (CH_3); m/z (ES) 192 ($\text{M}+\text{Na}^+$, 100 %), 170 ($\text{M}+\text{H}^+$, 89); m/z (ES) found $[\text{M}+\text{Na}]^+$ 192.0997. $\text{C}_9\text{H}_{15}\text{NNaO}_2^+$ requires 192.0995.

***N*-(6-hydroxyhexyl)acetamide 367**

Following general procedure 4b, 6-aminohexan-1-ol **367** (570 mg, 4.90 mmol) was reacted with acetic anhydride **336** (600 μ l, 6.70 mmol) to give the crude product. This was purified by flash chromatography on silica gel (methanol: dichloromethane; 9: 1) to yield **368** (470 mg, 61 %) as a colourless solid. M.p. 46 - 48 $^{\circ}\text{C}$; lit m.p. 35 - 37 $^{\circ}\text{C}$ [146], R_f : 0.5 (methanol: dichloromethane; 9: 1); $\nu_{\max}$ (CHCl_3)/ cm^{-1} 3293, 3090, 2933, 1561; δ_{H} (400 MHz, CDCl_3) 5.58 (1H, bs, NH), 3.64 (2H, t, J 6.5, OCH_2), 3.24 (2H, dt, J 7.5, 7.5, NCH_2), 1.97 (3H, s, CH_3), 1.72 (1H, bs, OH), 1.61 - 1.30 (8H, m, 4 CH_2); δ_{C} (100 MHz, CDCl_3) 170.2 (C), 62.7 (CH_2), 39.5 (CH_2), 32.5 (CH_2), 29.6 (CH_2), 26.5 (CH_2), 25.3 (CH_2), 23.3 (CH_3). m/z (ES) 182 ($\text{M}+\text{Na}^+$, 94 %), 160 ($\text{M}+\text{H}^+$, 100); m/z (ES) found $[\text{M}+\text{H}]^+$ 160.1330. $\text{C}_8\text{H}_{18}\text{NO}_2^+$ requires 160.1332. The ^1H NMR and ^{13}C data is in agreement with those previously reported. [146]

(E)-N-(8-Oxonon-6-en-1-yl)acetamide 369

Following general procedure 6, *N*-acetyl-6-aminoheptanol **368** (460 mg, 2.90 mmol) was reacted with 1-(triphenylphosphoranylidene)-2-propanone **191** (1.46 g, 4.60 mmol) in chloroform (25 ml) heated at reflux for 42 hours to give the crude product. This was purified by flash chromatography on silica gel (ethyl acetate: methanol; 19: 1) to yield **369** (170 mg, 29 %) as a yellow oil. R_f : 0.2 (ethyl acetate: methanol; 19: 1); $\nu_{\max}$ (neat)/cm⁻¹ 3297, 2933, 1668, 1557; δ_H (400 MHz, CDCl₃) 6.78 (1H, dt, *J* 16.0, 7.0, CH=CHCO), 6.06 (1H, dt, *J* 16.0, 2.0, CH=CHCO), 5.63 (1H, bs, NH), 3.23 (2H, dt, *J* 6.0, 6.0, NCH₂), 2.23 (3H, s, COCH₃), 2.22 (2H, dt, *J* 7.0, 7.0, CHCH₂), 1.96 (3H, s, NCOCH₃), 1.56 - 1.44 (4H, m, 2CH₂), 1.39 - 1.30 (2H, m, CH₂); δ_C (100 MHz, CDCl₃) 198.7 (C), 170.1 (C), 148.0 (CH), 131.4 (CH), 39.4 (CH₂), 32.3 (CH₂), 29.5 (CH₂), 27.7 (CH₂), 26.9 (CH₃), 26.4 (CH₂), 23.3 (CH₃); m/z (ES) 198 (M+H⁺, 100 %), 220 (M+Na⁺, 75), 417 (2M+Na⁺, 22); m/z (ES) found [M+H]⁺ 198.1490. C₁₁H₂₀NO₂⁺ requires 198.1489.

(+)-1-(1-Acetylpyrrolidin-2-yl)propan-2-one 371



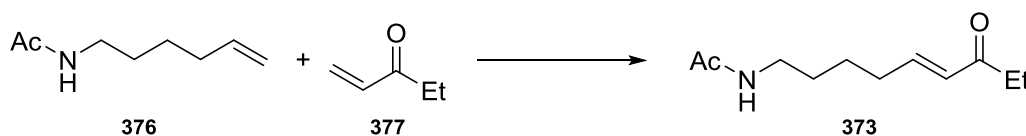
Following general procedure 8, (*E*)-*N*-(6-oxohept-4-en-1-yl)acetamide **366** (8.50 mg, 50.0 μ mol) with trifluoroacetic acid (0.750 μ l, 10.0 μ mol) was stirred in 2-methyltetrahydrofuran (0.5 ml) at 20 °C for 8 hours to yield **371** (8.10 mg, 95 %) as a colourless oil. R_f : 0.3 (ethyl acetate: methanol; 49: 1); $[\alpha]_D^{28}$ +50.4 (c 0.4 in CHCl₃); $\nu_{\max}$ (neat)/cm⁻¹ 2972, 1709, 1623; δ_H (400 MHz, C₆D₆, 17: 3 mixture of rotamers A and B) 4.44 - 4.33 (0.85H, m, CHN rotamer A), 3.95 - 3.81 (0.15H, m, CHN rotamer B), 3.47 - 3.21 (0.30H, m, 2CH rotamer B), 3.06 (0.85H, dd, *J* 16.5, 3.5, CH_AH_B rotamer A), 2.72 - 2.62 (0.85H, m, CH_AH_B rotamer A), 2.57 - 2.48 (0.85H, m, CH rotamer A), 1.98 (0.85H, dd, *J* 16.5, 9.5, COCH_AH_B rotamer A), 1.89 - 1.76 (0.30H, m, 2CH rotamer B), 1.74 (0.45H, s, CH₃ rotamer B), 1.71 (2.55H, s, CH₃ rotamer A), 1.65 (2.55H, s, CH₃ rotamer A), 1.65 - 1.56 (0.6H, m, 2CH₂ rotamer B), 1.50 (0.45H, s, CH₃ rotamer B), 1.41 - 1.09 (3.4H, m, 2CH₂ rotamer A); δ_C (100 MHz, C₆D₆, mixture of rotamers A and B) 205.4 (C rotamer A), 204.2 (C rotamer B), 167.7 (C rotamer A), 166.1 (C rotamer B), 53.5 (CH rotamer B), 53.2 (CH rotamer A), 47.8 (CH₂ rotamer B), 47.0 (CH₂ rotamer A), 46.8 (CH₂ rotamer A), 45.2 (CH₂ rotamer B), 31.5 (CH₂ rotamer B), 30.3 (CH₂ rotamer A), 29.7 (CH₃ rotamer B), 29.5 (CH₃ rotamer A), 23.6 (CH₂ rotamer A), 22.4 (CH₃ rotamer A), 21.6 (CH₃ rotamer B), 21.6 (CH₂ rotamer B); m/z (ES) 192 (M+Na⁺, 95 %), 170 (M+H⁺, 100); m/z (ES) found [M+H]⁺ 170.1175. C₉H₁₆NO₂⁺ requires 170.1176; R_t HPLC Chiralpak OD-H; mobile phase, hexane: 2-propanol (4: 1 v/v); flow rate, 1 ml/min; 8.6 min (4.7 %), 11.0 min (95.3 %) 90 % e.e.

N*-(Hex-5-en-1-yl)acetamide **376*



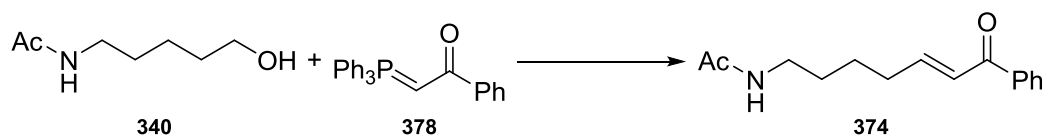
Acetyl chloride **152** (35.0 μ l, 500 μ mol) was added to a solution of 5-hexen-1-amine hydrochloride salt **375** (300 mg, 1.00 mmol) and triethylamine (280 μ l, 2.00 mmol) in dichloromethane (4 ml) at 0 °C. The solution was warmed to room temperature then stirred for 2 hours. This solution was diluted with water (4 ml) and the layers separated. The organic layer was washed with 0.1 M hydrochloric acid (4 ml), dried (magnesium sulfate) and concentrated under reduced pressure to yield the crude product. This was purified by flash chromatography on silica gel (ethyl acetate: methanol; 24: 1) to yield **376** (70.0 mg, 99 %) as a colourless oil. R_f : 0.3 (ethyl acetate: methanol; 24: 1); $\nu_{\max}$ (neat)/cm⁻¹ 3292, 2933, 1641, 1560; δ_H (400 MHz, CDCl₃) 6.30 (1H, bs, NH), 5.72 (1H, ddt, J 17.0, 10.0, 7.0, CH₂=CH), 4.98 - 4.85 (2H, m, CH=CH₂), 3.16 (2H, t, J 7.0, NCH₂), 2.00 (2H, dt, J 7.0, 7.0, CHCH₂), 1.91 (3H, s, CH₃), 1.51 - 1.30 (4H, m, 2CH₂); δ_C (100 MHz, CDCl₃) 170.3 (C), 138.4 (CH), 114.7 (CH₂), 39.4 (CH₂), 33.3 (CH₂), 28.9 (CH₂), 26.1 (CH₂), 23.1 (CH₃). m/z (ES) 164 (M+Na⁺, 100 %), 142 (M+H⁺, 15); m/z (ES) found [M+Na]⁺ 164.1049. C₈H₁₅NNaO⁺ requires 164.1046. The ¹H NMR and ¹³C data is in agreement with those previously reported.^[127]

(E)*-N-(7-Oxonon-5-en-1-yl)acetamide **373*



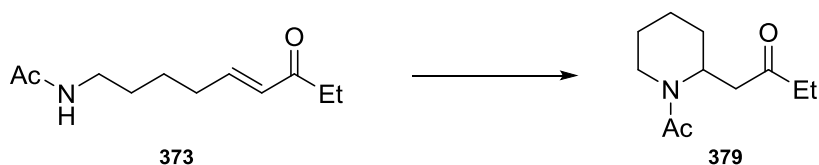
Following general procedure 7, *N*-(hex-5-en-1-yl)acetamide **376** (70.0 mg, 500 μ mol) was reacted with ethylvinylketone **377** (250 μ l, 2.50 mmol) for 1 hour to give the crude product. This was purified by flash chromatography on silica gel (ethyl acetate: methanol; 24: 1) to yield **373** (80.0 mg, 81 %) as a yellow oil. R_f : 0.4 (ethyl acetate: methanol; 24: 1); $\nu_{\max}$ (neat)/cm⁻¹ 3293, 2937, 1656, 1636; δ_H (400 MHz, C₆D₆) 6.58 (1H, dt, J 16.0, 7.0, CH=CHCO), 5.94 (1H, dt, J 16.0, 2.0, CH=CHCO), 5.07 (1H, bs, NH), 3.02 (2H, dt, J 7.0, 7.0, NCH₂), 2.18 (2H, q, J 7.5, CH₂CH₃), 1.80 (2H, dt, J 7.0, 7.0, CHCH₂), 1.63 (3H, s, COCH₃), 1.22 - 1.06 (4H, m, 2CH₂), 1.03 (3H, t, J 7.5, CH₂CH₃); δ_C (100 MHz, C₆D₆) 199.0 (C), 168.8 (C), 145.2 (CH), 130.3 (CH), 38.9 (CH₂), 33.2 (CH₂), 31.7 (CH₂), 29.3 (CH₂), 25.3 (CH₂), 22.7 (CH₃), 8.0 (CH₃); m/z (ES) 220 (M+Na⁺, 100 %), 198 (M+H⁺, 15); m/z (ES) found [M+Na]⁺ 220.1313. C₁₁H₁₉NNaO₂⁺ requires 220.1308.

(E)-N-(7-Oxo-7-phenylhept-5-en-1-yl)acetamide 374



Following general procedure 6, *N*-acetyl-5-aminopentanol **340** (680 mg, 4.80 mmol) was reacted with 1-benzoylmethylene-(triphenylphosphorane) **378** (2.91 g, 7.70 mmol) in chloroform (42 ml) heated at reflux for 18 hours to give the crude product. This was purified by flash chromatography on silica gel (ethyl acetate: methanol; 97: 3) to yield **374** (450 mg, 38 %) as an off white solid. M.p. 72 - 74 °C; R_f : 0.3 (ethyl acetate: methanol; 97: 3); $\nu_{\max}$ (CHCl₃)/cm⁻¹ 3292, 2934, 1655, 1620, 1598; δ_H (400 MHz, CDCl₃) 7.95 - 7.90 (2H, m, 2ArH), 7.59 - 7.43 (3H, m, 3ArH), 7.03 (1H, dt, J 17.0, 7.5, CH=CHCO), 6.89 (1H, dt, J 17.0, 2.0, CH=CHCO), 5.60 (1H, bs, NH), 3.27 (2H, dt, J 8.0, 8.0, NCH₂), 2.35 (2H, dt, J 7.5, 7.5, CHCH₂), 1.98 (3H, s, CH₃), 1.62 - 1.51 (4H, m, 2CH₂); δ_C (100 MHz, CDCl₃) 190.8 (C), 170.1 (C), 149.0 (CH), 137.9 (C), 132.7 (CH), 128.5 (CH), 126.3 (CH), 39.3 (CH₂), 32.3 (CH₂), 29.3 (CH₂), 25.5 (CH₂), 23.3 (CH₃). m/z (ES) 268 (M+Na⁺, 100 %); m/z (ES) found [M+Na]⁺ 268.1313. C₁₅H₁₉NNaO₂⁺ requires 268.1308.

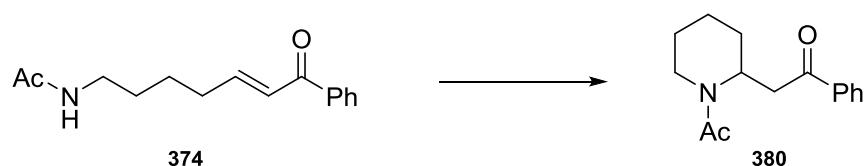
(+)-1-(1-Acetylpiperidin-2-yl)butan-2-one 379



Following general procedure 8, (*E*)-*N*-(7-oxonon-5-en-1-yl)acetamide **373** (19.7 mg, 100 μ mol) was stirred in 2-methyltetrahydrofuran (1.0 ml) at 20 °C for 120 hours to yield the crude product. This was purified by flash chromatography on silica gel (ethyl acetate) to yield **379** (14.7 mg, 75 %) as a colourless oil. R_f : 0.3 (ethyl acetate); $[\alpha]_D^{23}$ +14.8 (c 0.6 in CHCl₃); $\nu_{\max}$ (neat)/cm⁻¹ 2937, 1711, 1632; δ_H (400 MHz, CDCl₃, 11: 9 mixture of rotamers) 5.26 - 5.15 (0.55H, m, CHN rotamer A), 4.64 - 4.45 (1H, m, CH_AH_B rotamer A + CHN rotamer B), 3.65 - 3.53 (0.55H, m, CH_AH_B rotamer A), 3.15 (0.55H, ddd, J 12.0, 12.0, 4.0, CH rotamer A), 2.80 (0.55H, dd, J 16.0, 4.0, COCH_ACH_B rotamer A), 2.74 (0.45H, dd, J 16.0, 4.0, COCH_AH_B rotamer B), 2.68 - 2.34 (4.9H, m, 4CH rotamer A + 6 CH rotamer B), 2.14 (1.35H, s, NCOCH₃ rotamer B), 2.04 (1.65H, s, NCOCH₃ rotamer A), 1.82 - 1.22 (5.45H, m, 5CH rotamer A + 6CH rotamer B), 1.06 (1.35H, t, J 7.5, CH₂CH₃ rotamer B), 1.02 (1.65H, t, J 7.5, CH₂CH₃ rotamer A); δ_C (125 MHz, CDCl₃, mixture of rotamers) 208.8 (C rotamer A), 207.0 (C rotamer B), 169.4 (C rotamer A), 169.3 (C rotamer B), 49.5 (CH rotamer B), 44.9 (CH rotamer A), 43.0 (CH₂ rotamer A), 42.8 (CH₂

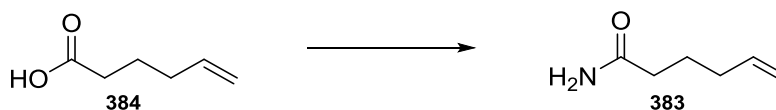
rotamer B), 42.2 (CH₂ rotamer A), 37.1 (CH₂ rotamer B), 36.9 (CH₂ rotamer A), 35.7 (CH₂ rotamer B), 29.4 (CH₂ rotamer B), 28.2 (CH₂ rotamer A), 25.8 (CH₂ rotamer A), 25.4 (CH₂ rotamer B), 21.9 (CH₃ rotamer A), 21.6 (CH₃ rotamer B), 19.3 (CH₂ rotamer B), 18.9 (CH₂ rotamer A), 7.7 (CH₃ rotamer A), 7.6 (CH₃ rotamer B); *m/z* (ES) 220 (M+Na⁺, 100 %), 198 (M+H⁺, 17); *m/z* (ES) found [M+Na]⁺ 220.1315. C₁₁H₁₉NNaO₂⁺ requires 220.1308; R_t HPLC Chiralcel OD-H; mobile phase, hexane: 2-propanol (9: 1 v/v); flow rate, 1 ml/min; 6.7 min (3.5 %), 7.9 min (96.5 %) 93 % e.e.

(+)-2--(1-acetylpiperidin-2-yl)-1-phenylethan-1-one 380



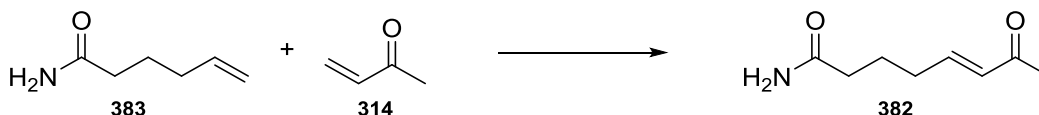
Following general procedure 8, (*E*)-*N*-(7-oxo-7-phenylhept-5-en-1-yl)acetamide **374** (24.5 mg, 100 μmol) was stirred in 2-methyltetrahydrofuran (1.0 ml) at 50 °C for 72 hours to yield the crude product. This was purified by flash chromatography on silica gel (ethyl acetate) to yield **380** (19.0 mg, 78 %) as a colourless oil. [α]_D²⁹ +21.5 (c 0.6 in CHCl₃); R_f : 0.4 (ethyl acetate); ν_{max} (neat)/cm⁻¹ 2937, 1682, 1629, 1448, 1362; δ_{H} (400 MHz, CDCl₃ 1: 1 mixture of rotamers A and B) 8.08 - 8.03 (1H, m, 2ArH rotamer A), 7.98 - 7.92 (1H, m, 2ArH rotamer B), 7.64 - 7.42 (3H, m, 3ArH rotamer A + 3ArH rotamer B), 5.32 - 5.22 (0.5H, m, CHN rotamer A), 4.76 - 4.68 (0.5H, m, CHN rotamer B), 4.65 - 4.56 (0.5H, m, CH_AH_B rotamer A), 3.73 - 3.63 (0.5H, m, CH_AH_B rotamer B), 3.39 (0.5H, dd, *J* 16.0, 8.0, COCH_AH_B rotamer B), 3.32 - 3.11 (2H, m, 2CH rotamer A + 2CH rotamer B), 2.63 (0.5H, ddd, *J* 16.0, 16.0, 2.0, CH_AH_B rotamer A), 2.16 (1.5H, s, CH₃ rotamer B), 2.08 (1.5H, s, CH₃ rotamer A), 1.80 - 1.30 (6H, m, 3CH₂ rotamer A + 3CH₂ rotamer B); δ_{C} (100 MHz, CDCl₃) 198.6 (C rotamer A), 197.6 (C rotamer B), 169.6 (C rotamer A), 169.5 (C rotamer B), 136.8 (C rotamer A), 136.7 (C rotamer B), 133.6 (CH rotamer A), 133.2 (CH rotamer B), 128.8 (2CH rotamer A), 128.7 (2CH rotamer B), 128.5 (2CH rotamer A), 128.0 (2CH rotamer B), 49.9 (CH rotamer B), 45.9 (CH rotamer A), 42.3 (CH₂ rotamer B), 39.2 (CH₂ rotamer A), 39.1 (CH₂ rotamer B), 37.1 (CH₂ rotamer A), 29.4 (CH₂ rotamer B), 27.3 (CH₂ rotamer A), 25.7 (CH₂ rotamer A), 25.4 (CH₂ rotamer B), 22.0 (CH₃ rotamer A), 21.6 (CH₃ rotamer B), 19.3 (CH₂ rotamer A), 18.8 (CH₂ rotamer B); *m/z* (ES) 268 (M+Na⁺, 100 %); *m/z* (ES) found [M+Na]⁺ 268.1315. C₁₅H₁₉NNaO₂⁺ requires 268.1308; R_t HPLC Chiralpak AD-H; mobile phase, hexane: 2-propanol (9: 1 v/v); flow rate, 1 ml/min; 12.0 min (10.9 %), 15.5 min (89.1 %) 78 % e.e.

Hex-5-enamide **383**



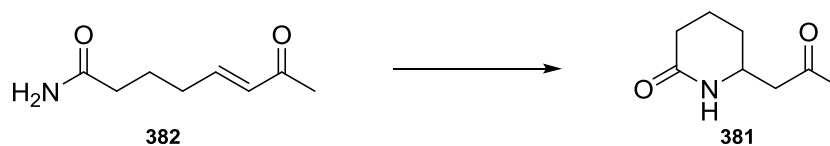
5-Hexenoic acid **384** (420 μ l, 3.50 mmol) was added dropwise to oxalyl chloride (700 μ l). This was stirred for 2 hours at room temperature. This was concentrated under reduced pressure (water bath <30 $^{\circ}$ C) to yield the crude acid chloride. This was added dropwise over 10 minutes to a stirred solution of ammonium hydroxide (5 ml) and stirred for 1 hour. Dichloromethane (5 ml) was added and the layers separated. The aqueous layer was extracted with dichloromethane (2 x 5 ml). The combined organics were dried (magnesium sulfate) and concentrated under reduced pressure to yield **383** (370 mg, 93%) as a colourless solid. M.p. 85 - 87 $^{\circ}$ C; lit m.p. 80 $^{\circ}$ C^[148]; $\nu_{\max}$ (CHCl₃)/cm⁻¹ 3358, 3194, 2953, 1658; δ_{H} (400 MHz, CHCl₃) 5.79 (1H, ddt, *J* 17.0, 10.5, 6.5, CH₂=CH), 5.70 (1H, bs, NH), 5.51 (1H, bs, NH), 5.08 - 4.95 (2H, m, CH=CH₂), 2.23 (2H, t, *J* 8.0, COCH₂), 2.11 (2H, dt, *J* 6.5, 6.5, CHCH₂), 1.80 - 1.69 (2H, m, CH₂); δ_{C} (100 MHz, CHCl₃) 175.5 (C), 135.8 (CH), 115.4 (CH₂), 35.0 (CH₂), 33.1 (CH₂), 24.5 (CH₂); *m/z* (ES) 136 (M+Na⁺, 100 %); *m/z* (ES) found [M+Na]⁺ 136.0728. C₆H₁₁NaNO⁺ requires 136.0733. The ¹H NMR and ¹³C data is in agreement with those previously reported.^[148]

(*E*)-7-Oxo-oct-5-enamide **382**



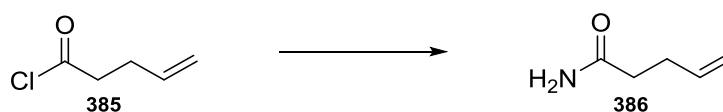
Following general procedure 7, hex-5-enamide **383** (113 mg, 1.00 mmol) was reacted with methylvinylketone **314** (390 μ l, 5.00 mmol) for 2 hours to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 1: 1) to yield **382** (143 mg, 92 %) as an off white solid. M.p. 82 - 84 $^{\circ}$ C; *R_f*: 0.4 (light petroleum ether: ethyl acetate; 1: 1); $\nu_{\max}$ (CHCl₃)/cm⁻¹ 3403, 3304, 2937, 1666, 1625; δ_{H} (400 MHz, CDCl₃) 6.78 (1H, dt, *J* 16.0, 7.0, CH=CHCO), 6.10 (1H, dt, *J* 16.0, 2.0, CH=CHCO), 5.67 - 5.43 (2H, m, NH₂), 2.34 - 2.22 (7H, s + m, CH₃ + 2CH₂), 1.89 - 1.80 (2H, m, CH₂); δ_{C} (125 MHz, CDCl₃) 198.6 (C), 174.6 (C), 147.1 (CH), 131.9 (CH), 34.7 (CH₂), 31.7 (CH₂), 27.0 (CH₃), 23.5 (CH₂); *m/z* (ES) 178 (M+Na⁺, 100 %), 156 (M+H⁺, 18); *m/z* (ES) found [M+Na]⁺ 178.0841. C₈H₁₃NNaO₂⁺ requires 178.0838.

6-(2-Oxopropyl)piperidin-2-one **381**



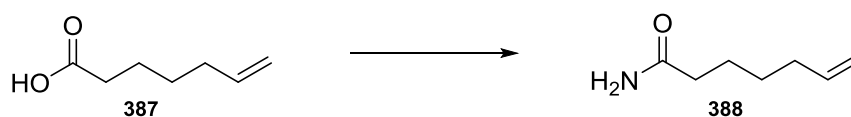
Following general procedure 8, (*E*)-7-oxooct-5-enamide **382** (15.5 mg, 100 μmol) was stirred in tetrahydrofuran (1.0 ml) at 20 $^{\circ}\text{C}$ for 22 hours to yield **381** (12.8 mg, 83 %) as a colourless solid. M.p. 86 - 88 $^{\circ}\text{C}$; R_f : 0.3 (ethyl acetate); $[\alpha]_D^{24}$ -46.9 (c 0.7 in CHCl_3); ν_{max} (CHCl_3)/ cm^{-1} 3398, 2951, 1711, 1651; δ_{H} (400 MHz, CDCl_3) 6.34 (1H, bs, NH), 3.91 - 3.81 (1H, m, CHN), 2.68 (1H, dd, J 18.5, 4.0, COCH_AH_B), 2.61 (1H, dd, J 18.5, 8.0, COCH_AH_B), 2.43 - 2.22 (2H, m, CH_2), 2.16 (3H, s, CH_3), 1.95 - 1.67 (3H, m, 3CH), 1.46 - 1.33 (1H, m, CH); δ_{C} (100 MHz, CDCl_3) 207.0 (C), 171.8 (C), 50.0 (CH_2), 48.3 (CH), 31.5 (CH_2), 30.3 (CH_3), 28.2 (CH_2), 19.4 (CH_2); m/z (ES) 178 ($\text{M}+\text{Na}^+$, 100 %), 156 ($\text{M}+\text{H}^+$, 17); m/z (ES) found $[\text{M}+\text{Na}]^+$ 178.0838. $\text{C}_8\text{H}_{13}\text{NNaO}_2^+$ requires 178.0838; R_t HPLC Chiralcel OJ-H; mobile phase, hexane: ethanol (9: 1 v/v); flow rate, 1 ml/min; 16.2 min (2.5 %), 18.2 min (97.5 %) 95 % e.e.

Pent-4-enamide **386**



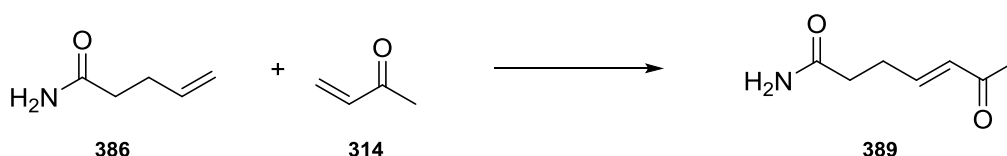
4-Pentenoyl chloride **385** (350 μl , 3.19 mmol) was added dropwise to ammonium hydroxide solution (5 ml). This was stirred at room temperature for 30 minutes. Dichloromethane (5 ml) was added and the layers separated. The aqueous layer was extracted with dichloromethane (2 x 5 ml). The combined organics were dried (magnesium sulphate) and concentrated under reduced pressure to yield **386** (221 mg, 70 %) as a colourless solid. M.p. 103 - 105 $^{\circ}\text{C}$; lit m.p. 105 - 107 $^{\circ}\text{C}$ ^[149]; ν_{max} (CHCl_3)/ cm^{-1} 3356, 3193, 1665, 1634; δ_{H} (400 MHz, CDCl_3) 5.85 (1H, ddt, J 16.5, 10.0, 8.0, $\text{CH}_2=\text{CH}$), 5.78 - 5.39 (2H, 2bs, NH_2), 5.16 - 4.97 (2H, m, $\text{CH}=\text{CH}_2$), 2.44 - 2.30 (4H, m, 2 CH_2); δ_{C} (100 MHz, CDCl_3) 174.8 (C), 136.9 (CH), 115.8 (CH_2), 35.0 (CH_2), 29.3 (CH_2); m/z (ES) 122 ($\text{M}+\text{Na}^+$, 100 %); m/z (ES) found $[\text{M}+\text{Na}]^+$ 122.0580. $\text{C}_5\text{H}_9\text{NNaO}^+$ requires 122.0576. The ^1H NMR and ^{13}C data is in agreement with those previously reported.^[149]

Hept-6-enamide **388**



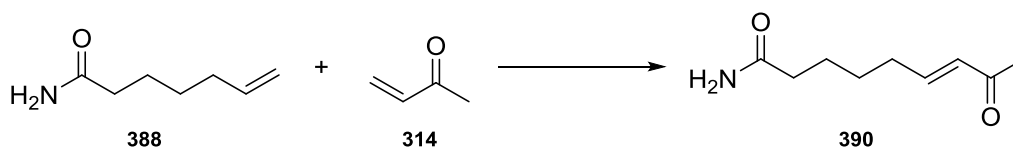
6-Heptenoic acid **387** (470 μ l, 3.50 mmol) was added dropwise to stirred oxalyl chloride (700 μ l). This was stirred at room temperature for 2 hours. This was concentrated under reduced pressure (water bath <30 °C) to yield the crude acid chloride. This was added dropwise over 10 minutes to ammonium hydroxide (5 ml) and stirred for 1 hour. This was diluted with dichloromethane (5 ml) and separated. The aqueous layer was extracted with dichloromethane (2 x 5 ml). The combined organics were dried (magnesium sulfate) and concentrated under reduced pressure to yield **388** (300 mg, 66 %) as a colourless solid. M.p. 88 - 90 °C; $\nu_{\max}$ (CHCl₃)/cm⁻¹ 3359, 3193, 2938, 1661, 1635; δ_{H} (400 MHz, CHCl₃) 5.80 (1H, ddt, *J* 17.0, 10.0, 6.5, CH₂=CH), 5.56 (1H, bs, NH), 5.44 (1H, bs, NH), 5.06 - 4.93 (2H, m, CH=CH₂), 2.24 (2H, t, *J* 7.5, COCH₂), 2.09 (2H, dt, *J* 6.5, 6.5, CHCH₂), 1.73 - 1.61 (2H, m, CH₂), 1.50 - 1.40 (2H, m, CH₂); δ_{C} (100 MHz, CHCl₃) 175.4 (C), 138.4 (CH), 114.8 (CH₂), 35.7 (CH₂), 33.4 (CH₂), 28.4 (CH₂), 25.0 (CH₂); *m/z* (ES) 150 (M+Na⁺, 100 %), 128 (M+H⁺, 50); *m/z* (ES) found [M+Na]⁺ 150.0880. C₇H₁₃NaNO⁺ requires 150.0889.

(E)-6-Oxohept-4-enamide **389**



Following general procedure 7, pent-4-enamide **386** (100 mg, 1.00 mmol) was reacted with methylvinylketone **314** (390 μ l, 5.00 mmol) for 1 hour to give the crude product. This was purified by flash chromatography on silica gel (ethyl acetate: methanol; 9: 1) to yield **389** (92.0 mg, 63 %) as a light brown solid. M.p. 75 - 77 °C; *R_f*: 0.4 (ethyl acetate: methanol; 9: 1); $\nu_{\max}$ (CHCl₃)/cm⁻¹ 3361, 3200, 1668, 1625; δ_{H} (400 MHz, CDCl₃) 6.83 (1H, dt, *J* 17.5, 8.0, CH=CHCO), 6.12 (1H, dt, *J* 17.5, 2.0, CH=CHCO), 5.52 (2H, 2bs, NH₂), 2.59 (2H, dt, *J* 8.0, 8.0, CHCH₂), 2.41 (2H, t, *J* 8.0, COCH₂), 2.25 (3H, s, CH₃); δ_{C} (100 MHz, CDCl₃) 198.5 (C), 173.4 (C), 154.9 (CH), 131.8 (CH), 33.7 (CH₂), 27.6 (CH₂), 27.0 (CH₃); *m/z* (ES) 164 (M+Na⁺, 100 %); *m/z* (ES) found [M+Na]⁺ 164.0681. C₇H₁₁NNaO₂⁺ requires 164.0682.

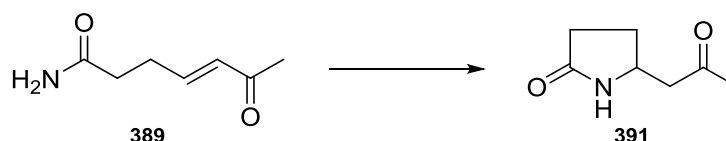
(E)-8-Oxonon-6-enamide **390**



Following general procedure 7, hept-6-enamide **388** (130 mg, 1.00 mmol) was reacted with methylvinylketone **314** (420 μ l, 5.00 mmol) for 1 hour to give the crude product. This was purified by flash chromatography on silica gel (ethyl acetate: methanol; 97: 3) to

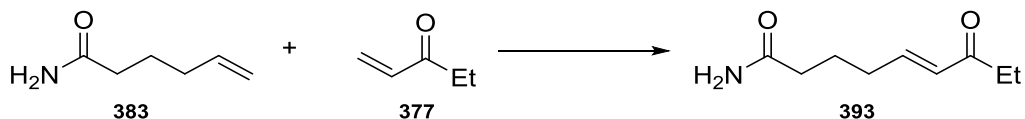
yield **390** (150 mg, 90 %) as a colourless solid. M.p. 102 - 104 °C; R_f : 0.2 (ethyl acetate: methanol; 97: 3); $\nu_{\max}$ (CHCl₃)/cm⁻¹ 3389, 3186, 2936, 1668, 1646; δ_H (400 MHz, CDCl₃) 6.79 (1H, dt, J 16.0, 8.0 CH=CHCO), 6.08 (1H, dt, J 16.0, 2.0 CH=CHCO), 5.66 - 5.40 (2H, m, NH₂), 2.28 - 2.20 (4H, m, 2CH₂), 2.24 (3H, s, CH₃), 1.74 - 1.63 (2H, m, CH₂), 1.59 - 1.49 (2H, m, CH₂); δ_C (100 MHz, CDCl₃) 198.7 (C), 172.7 (C), 147.7 (CH), 131.6 (CH), 35.5 (CH₂), 32.1 (CH₂), 27.6 (CH₂), 26.9 (CH₂), 24.9 (CH₂); m/z (ES) 192 (M+Na⁺, 100 %), 170 (M+H⁺, 39); m/z (ES) found [M+Na]⁺ 192.1001. C₉H₁₅NNaO₂⁺ requires 192.0995.

(-)-5-(2-Oxopropyl)pyrrolidin-2-one **391**



Following general procedure 8, (*E*)-6-oxohept-4-enamide **389** (14.1 mg, 100 μ mol) was stirred in deuterated chloroform (1.0 ml) at 50 °C for 72 hours to give the crude product. This was purified by flash chromatography on silica gel (ethyl acetate: methanol; 4: 1) to yield **391** (5.20 mg, 37 %) as a colourless oil. R_f : 0.4 (ethyl acetate: methanol; 4: 1); $[\alpha]_D^{25}$ -22.5 (c 0.2 in CHCl₃); $\nu_{\max}$ (neat)/cm⁻¹ 3283, 2921, 1715, 1683; δ_H (400 MHz, CDCl₃) 6.07 (1H, bs, NH), 4.06 - 3.96 (1H, m, CHN), 2.79 (1H, dd, J 17.0, 3.5, COCH_AH_B), 2.61 (1H, dd, J 17.0, 9.5, COCH_AH_B), 2.38 - 2.08 (3H, m, 3CH), 2.18 (3H, s, CH₃), 1.80 - 1.65 (1H, m, CH); δ_C (100 MHz, CDCl₃) 207.1 (C), 177.6 (C), 50.1 (CH₂), 49.5 (CH), 30.2 (CH₃), 29.4 (CH₂), 26.6 (CH₂); m/z (ES) 164 (M+Na⁺, 100 %), 142 (M+H⁺, 24); m/z (ES) found [M+Na]⁺ 164.0682. C₇H₁₁NNaO₂⁺ requires 164.0682; R_t HPLC Chiralcel OJ-H; mobile phase, hexane: ethanol (19: 1 v/v); flow rate, 1 ml/min; 34.2 min (14.5 %), 37.8 min (85.5 %) 71 % e.e.

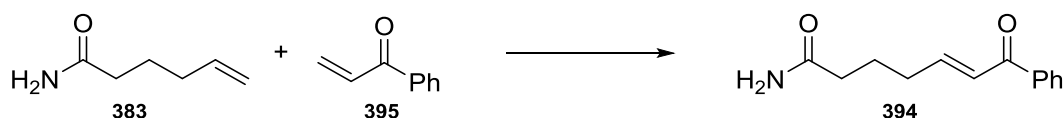
(*E*)-7-Oxonon-5-enamide **393**



Following general procedure 7, hex-5-enamide **383** (113 mg, 1.00 mmol) was reacted with ethylvinylketone **377** (500 μ l, 5.00 mmol) for 1 hour to give the crude product. This was purified by flash chromatography on silica gel (ethyl acetate: methanol; 49: 1) to yield **393** (100 mg, 58 %) as an off white solid. M.p. 72 - 74 °C; R_f : 0.2 (ethyl acetate: methanol; 49: 1); $\nu_{\max}$ (neat)/cm⁻¹ 3362, 3195, 2976, 1696, 1661, 1632; δ_H (400 MHz, C₆D₆) 6.55 (1H, dt, J 16.0, 7.0, CH=CHCO), 6.44 (1H, bs, NH), 5.93 (1H, dt, J 16.0, 2.0, CH=CHCO), 5.04 (1H, bs, NH), 2.16 (2H, q, J 7.5, CH₂CH₃), 1.87 (2H, dt, J 7.0, 7.0, CHCH₂), 1.80 - 1.70 (2H, m, CH₂), 1.61 - 1.51 (2H, m, CH₂), 1.02 (3H, t, J 7.5, CH₂CH₃);

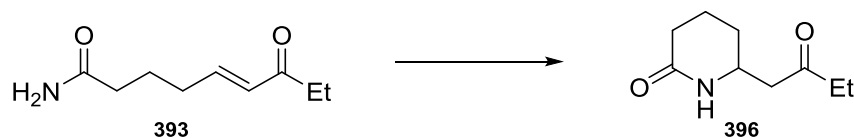
δ_{C} (100 MHz, C_6D_6) 199.2 (C), 174.5 (C), 145.0 (CH), 130.6 (CH), 34.4 (CH_2), 33.1 (CH_2), 31.5 (CH_2), 23.7 (CH), 8.0 (CH_3); m/z (ES) 192 ($\text{M}+\text{Na}^+$, 100 %), 170 ($\text{M}+\text{H}^+$, 18); m/z (ES) found $[\text{M}+\text{Na}]^+$ 192.0999. $\text{C}_9\text{H}_{15}\text{NNaO}_2^+$ requires 192.0995.

(E)-7-Oxo-7-phenylhept-5-enamide **394**



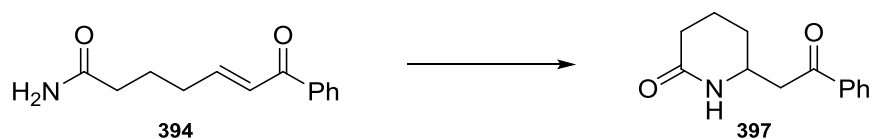
Following general procedure 7, reaction of hex-5-enamide **383** (113 mg, 1.00 mmol) and phenylvinylketone **395** (290 mg, 2.20 mmol) for 2 hours to give the crude product. This was purified by flash chromatography on silica gel (ethyl acetate: methanol; 49: 1) to yield **394** (143 mg, 68 %) as an off white solid. M.p. 74 - 76 °C; R_f : 0.3 (ethyl acetate: methanol; 3: 1); ν_{max} (CHCl_3)/ cm^{-1} 3357, 3195, 2921, 1657, 1630, 1447; δ_{H} (400 MHz, CDCl_3) 7.94 (2H, ddd, J 7.5, 2.0, 2.0, 2ArH), 7.61 - 7.54 (1H, m, ArH), 7.51 - 7.45 (2H, m, 2ArH), 7.05 (1H, dt, J 16.0, 8.0, $\text{CH}=\text{CHCO}$), 6.93 (1H, dt, J 16.0, 2.0, $\text{CH}=\text{CHCO}$), 5.40 (2H, bs, NH_2), 2.41 (2H, dt, J 8.0, 8.0, CHCH_2), 2.30 (2H, t, J 7.5, COCH_2), 1.97 - 1.87 (2H, m, CH_2); δ_{C} (100 MHz, CDCl_3) 190.7 (C), 175.0 (C), 148.3 (CH), 137.8 (C), 132.8 (CH), 128.6 (CH), 126.7 (CH), 34.7 (CH_2), 32.0 (CH_2), 23.7 (CH_2); m/z (ES) 240 ($\text{M}+\text{Na}^+$, 100 %), 218 ($\text{M}+\text{H}^+$, 26); m/z (ES) found $[\text{M}+\text{Na}]^+$ 240.0989. $\text{C}_{13}\text{H}_{15}\text{NNaO}_2^+$ requires 240.0995.

(-)-6-(2-Oxobutyl)piperidin-2-one **396**



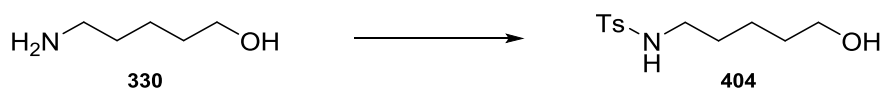
Following general procedure 8, (E)-7-oxonon-5-enamide **393** (17.0 mg, 100 μmol) was stirred in tetrahydrofuran (1.0 ml) at 20 °C for 46 hours to yield **396** (14.0 mg, 82 %) as a colourless solid. M.p. 63 - 65 °C; R_f : 0.3 (ethyl acetate: methanol; 24: 1); $[\alpha]_{\text{D}}^{23}$ -54.7 (c 0.9 in CHCl_3); ν_{max} (CHCl_3)/ cm^{-1} 3078, 2970, 1713, 1660; δ_{H} (400 MHz, CDCl_3) 6.30 (1H, bs, NH), 3.93 - 3.83 (1H, m, CHN), 2.66 (1H, dd, J 17.5, 4.0, $\text{COCH}_\text{A}\text{H}_\text{B}$), 2.58 (1H, dd, J 17.5, 9.5, $\text{COCH}_\text{A}\text{H}_\text{B}$), 2.43 (2H, q, J 8.0, CH_2CH_3), 2.42 - 2.22 (2H, m, CH_2), 1.95 - 1.67 (3H, m, 3CH), 1.46 - 1.32 (1H, m, CH), 1.07 (3H, t, J 8.0, CH_2CH_3); δ_{C} (100 MHz, CDCl_3) 209.8 (C), 171.8 (C), 48.8 (CH_2), 48.3 (CH), 36.4 (CH_2), 31.5 (CH_2), 28.3 (CH_2), 19.4 (CH_2), 7.6 (CH_3); m/z (ES) 192 ($\text{M}+\text{Na}^+$, 100 %); m/z (ES) found $[\text{M}+\text{Na}]^+$ 192.0995. $\text{C}_9\text{H}_{15}\text{NNaO}_2^+$ requires 192.0995; R_t HPLC Chiralcel OD-H; mobile phase, hexane: ethanol (9: 1 v/v); flow rate, 1 ml/min; 14.2 min (2.6 %), 17.1 min (97.4 %) 95 % e.e.

(-)-6-(2-Oxo-2-phenylethyl)piperidin-2-one 397



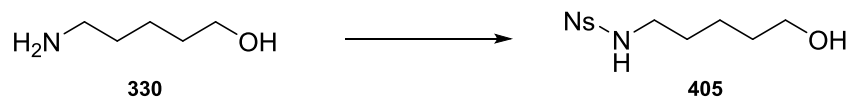
Following general procedure 8, (*E*)-7-oxo-7-phenylhept-5-enamide **394** (10.8 mg, 50.0 μ mol) was stirred in tetrahydrofuran (0.5 ml) at 20 °C for 120 hours to yield the crude product. This was purified by flash chromatography on silica gel (ethyl acetate: methanol; 49: 1) to yield **397** (3.00 mg, 27 %) as a colourless solid. M.p. 154 - 155 °C; R_f : 0.2 (ethyl acetate: methanol; 49: 1); $[\alpha]_D^{22}$ -32.9 (c 0.3 in CHCl_3); $\nu_{\text{max}}(\text{CHCl}_3)/\text{cm}^{-1}$ 3343, 2954, 1678, 1657, 1448, 1430; δ_{H} (400 MHz, CDCl_3) 7.94 (2H, ddd, J 7.5, 2.0, 2.0, 2ArH), 7.65 - 7.57 (1H, m, ArH), 7.53 - 7.44 (2H, m, 2ArH), 6.42 (1H, bs, NH), 4.12 - 4.02 (1H, m, CHN), 3.23 (1H, dd, J 16.0, 4.0, COCH_AH_B), 3.13 (1H, dd, J 16.0, 8.0, COCH_AH_B), 2.48 - 2.26 (2H, m, CH_2), 2.07 - 1.74 (3H, m, 3CH), 1.60 - 1.48 (1H, m, CH); δ_{C} (100 MHz, CDCl_3) 198.2 (C), 171.8 (C), 136.4 (C), 133.7 (CH), 128.8 (CH), 128.0 (CH), 48.7 (CH), 45.4 (CH_2), 31.7 (CH_2), 28.5 (CH_2), 19.5 (CH_2); m/z (ES) 240 ($\text{M}+\text{Na}^+$, 100 %), 218 ($\text{M}+\text{H}^+$, 27); m/z (ES) found $[\text{M}+\text{Na}]^+$ 240.0989. $\text{C}_{13}\text{H}_{15}\text{NNaO}_2^+$ requires 240.0995; R_t HPLC Chiralcel OD-H; mobile phase, hexane: ethanol (9: 1 v/v); flow rate, 1 ml/min; 21.9 min (96.2 %), 24.4 min (3.8 %) 92 % e.e.

***N*-(5-Hydroxypentyl)-4'-methylbenzenesulfonamide 404**



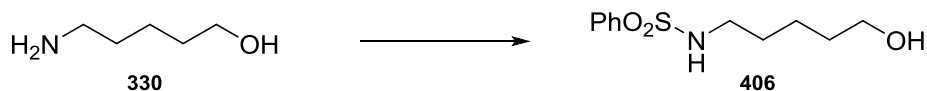
Following general procedure 4a, 5-aminopentanol **330** (500 mg, 4.90 mmol) was reacted with tosyl chloride **401** (950 mg, 5.00 mmol) to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 2: 3) to yield **404** (970 mg, 78 %) as a colourless solid. M.p. 62 - 64 °C; R_f : 0.4 (light petroleum ether: ethyl acetate; 2: 3); $\nu_{\text{max}}(\text{CHCl}_3)/\text{cm}^{-1}$ 3504, 3281, 2938, 1599, 1322; δ_{H} (400 MHz, CDCl_3) 7.75 (2H, d, J 8.0, 2ArH), 7.31 (2H, d, J 8.0, 2ArH), 4.80 (1H, bs, NH), 3.60 (2H, t, J 8.0, OCH_2), 2.94 (2H, dt, J 7.5, 7.5, NCH_2), 2.43 (3H, s, CH_3), 1.66 (1H, bs, OH), 1.56 - 1.45 (4H, m, 2 CH_2), 1.42 - 1.31 (2H, m, CH_2); δ_{C} (100 MHz, CDCl_3) 143.4 (C), 137.0 (C), 129.7 (CH), 127.1 (CH), 62.5 (CH_2), 43.1 (CH_2), 32.0 (CH_2), 29.3 (CH_2), 22.7 (CH_2), 21.5 (CH_3); m/z (ES) 280 ($\text{M}+\text{Na}^+$, 100 %); m/z (ES) found $[\text{M}+\text{Na}]^+$ 280.0980. $\text{C}_{12}\text{H}_{19}\text{NNaO}_3\text{S}^+$ requires 280.0978. The ^1H NMR and ^{13}C data is in agreement with those previously reported.^[150]

N-(5-Hydroxypentyl)-4'-nitrobenzenesulfonamide **405**



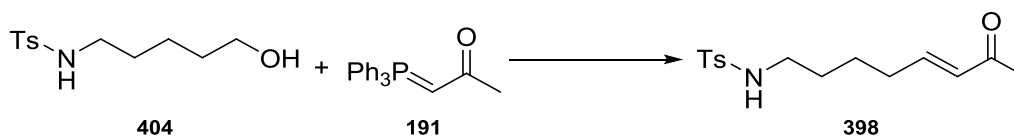
Following general procedure 4a, 5-aminopentanol **330** (500 mg, 4.90 mmol) was reacted with nosyl chloride **402** (1.10 g, 5.00 mmol) to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 1: 4) to yield **405** (880 mg, 63 %) as a light yellow solid. M.p. 89 - 91 °C; R_f : 0.4 (light petroleum ether: ethyl acetate; 1: 4); $\nu_{\max}$ (CHCl₃)/cm⁻¹ 3528, 3295, 2939, 1607, 1530; δ_H (400 MHz, CDCl₃) 8.37 (2H, dd, J 8.0, 2.0, 2ArH), 8.06 (2H, dd, J 8.0, 2.0, 2ArH), 4.99 (1H, t, J 7.0, NH), 3.63 (2H, t, J 6.5, OCH₂), 3.04 (2H, dt, J 7.0, 6.0, NCH₂), 1.61 - 1.33 (5H, m, OH + 2CH₂), 1.42 - 1.31 (2H, m, CH₂); δ_C (100 MHz, CDCl₃) 150.1 (C), 146.0 (C), 128.3 (CH), 124.4 (CH), 62.4 (CH₂), 43.2 (CH₂), 31.7 (CH₂), 29.3 (CH₂), 22.7 (CH₂); m/z (ES) 311 (M+Na⁺, 100%); m/z (ES) found [M+Na]⁺ 311.0675. C₁₁H₁₆N₂NaO₅S⁺ requires 311.0672.

N-(5-Hydroxypentyl)-benzenesulfonamide **406**



Following general procedure 4a, 5-aminopentanol **330** (500 mg, 4.90 mmol) was reacted with benzenesulfonyl chloride **403** (640 μ l, 5.00 mmol) to give the crude product. This was purified by flash chromatography on silica gel (ethyl acetate) to yield **406** (890 mg, 75 %) as a colourless oil. R_f : 0.5 (ethyl acetate); $\nu_{\max}$ (neat)/cm⁻¹ 3508, 3282, 2939, 1447, 1322; δ_H (400 MHz, CDCl₃) 7.90 - 7.84 (2H, m, 2ArH), 7.61 - 7.47 (3H, m, 3ArH), 5.04 (1H, t, J 6.0, NH), 3.59 (2H, t, J 6.5, OCH₂), 2.95 (2H, dt, J 7.0, 7.0, NCH₂), 1.83 (1H, bs, OH), 1.55 - 1.29 (6H, m, 3CH₂); δ_C (100 MHz, CDCl₃) 140.0 (C), 132.6 (CH), 129.1 (CH), 127.0 (CH), 62.4 (CH₂), 43.1 (CH₂), 31.9 (CH₂), 29.2 (CH₂), 22.7 (CH₂); m/z (ES) 266 (M+Na⁺, 100 %); m/z (ES) found [M+Na]⁺ 266.0804. C₁₁H₁₇NNaO₃S⁺ requires 266.0821.

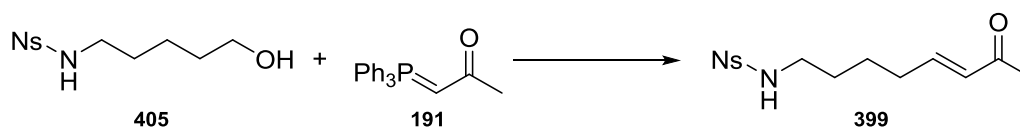
(*E*)-4'-Methyl-*N*-(7-oxooct-5-en-1-yl)benzenesulfonamide **398**



Following general procedure 6, *N*-(5-hydroxypentyl)-4-methylbenzenesulfonamide **404** (930 mg, 3.60 mmol) was reacted with 1-(triphenylphosphoranylidene)-2-propanone **191** (1.84 g, 5.80 mmol) in dichloromethane (32 ml) heated at reflux for 20 hours to give the crude product. This was purified by flash chromatography (light petroleum ether: ethyl acetate; 3: 2) to yield **398** (400 mg, 38 %) as a yellow solid. M.p. 42 - 44 °C; R_f : 0.3 (light

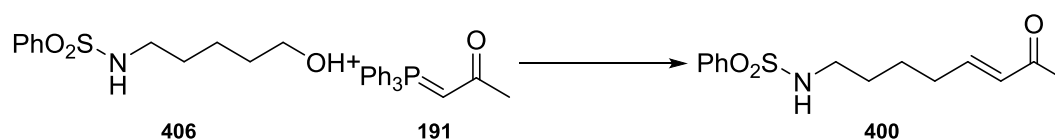
petroleum ether: ethyl acetate; 3: 2); $\nu_{\max}(\text{CHCl}_3)/\text{cm}^{-1}$ 3275, 2935, 1670, 1624, 1598, 1326; δ_{H} (400 MHz, CDCl_3) 7.75 (2H, d, J 8.0, 2ArH), 7.31 (2H, d, J 8.0, 2ArH), 6.72 (1H, dt, J 16.0, 8.0, $\text{CH}=\text{CHCO}$), 6.03 (1H, dt, J 16.0, 2.0, $\text{CH}=\text{CHCO}$), 4.69 (1H, bt, J 4.0, NH), 2.95 (2H, dt, J 8.0, 8.0, CHCH_2), 2.43 (3H, s, CH_3), 2.24 - 2.13 (5H, m + s, CH_2 + CH_3), 1.55 - 1.42 (4H, m, 2CH_2); δ_{C} (100 MHz, CDCl_3) 198.6 (C), 147.3 (CH), 143.5 (CH), 136.9 (C), 131.6 (CH), 129.8 (CH), 127.1 (CH), 42.8 (CH_2), 31.7 (CH_2), 29.1 (CH_2), 26.9 (CH_3), 24.9 (CH_2), 21.5 (CH_3); m/z (ES) 318 ($\text{M}+\text{Na}^+$, 100 %); m/z (ES) found $[\text{M}+\text{Na}]^+$ 318.1136. $\text{C}_{15}\text{H}_{21}\text{NNaO}_3\text{S}^+$ requires 318.1134.

(E)-4'-Nitro-N-(7-oxooct-5-en-1-yl)benzenesulfonamide 399



Following general procedure 6, *N*-(5-hydroxypentyl)-4-nitrobenzenesulfonamide **405** (840 mg, 2.90 mmol) was reacted with 1-(triphenylphosphoranylidene)-2-propanone **191** (1.49 g, 4.70 mmol) in dichloromethane (26 ml) heated at reflux for 20 hours to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 1: 1) to yield **399** (390 mg, 41 %) as a yellow solid. M.p. 65 - 68 °C; R_f : 0.4 (light petroleum ether: ethyl acetate; 1: 1); $\nu_{\max}(\text{CHCl}_3)/\text{cm}^{-1}$ 3277, 2937, 1669, 1624, 1530, 1350; δ_{H} (400 MHz, CDCl_3) 8.37 (2H, dd, J 8.0, 2.0, 2ArH), 8.05 (2H, dd, J 8.0, 2.0, 2ArH), 6.74 (1H, dt, J 16.0, 7.0, $\text{CH}=\text{CHCO}$), 6.06 (1H, dt, J 16.0, 2.0, $\text{CH}=\text{CHCO}$), 4.91 (1H, t, J 6.0, NH), 3.04 (2H, dt, J 7.0, 7.0, CHCH_2), 2.26 - 2.15 (5H, m + s, CH_2 + CH_3), 1.61 - 1.45 (4H, m, 2CH_2); δ_{C} (100 MHz, CDCl_3) 198.6 (C), 150.1 (C), 147.0 (CH), 146.0 (C), 131.7 (CH), 128.3 (CH), 124.5 (CH), 43.1 (CH_2), 31.7 (CH_2), 29.2 (CH_2), 27.0 (CH_3), 24.9 (CH_2); m/z (ES) 349 ($\text{M}+\text{Na}^+$, 100 %); m/z (ES) found $[\text{M}+\text{Na}]^+$ 349.0827. $\text{C}_{14}\text{H}_{18}\text{N}_2\text{NaO}_5\text{S}^+$ requires 349.0829.

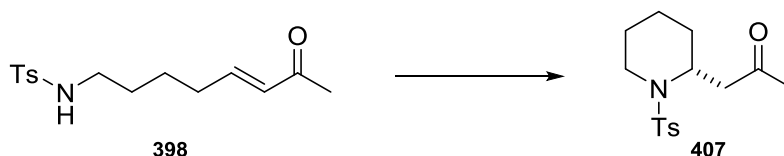
(E)-N-(7-Oxooct-5-en-1-yl)benzenesulfonamide 400



Following general procedure 6, *N*-(5-hydroxypentyl)-benzenesulfonamide **406** (840 mg, 3.50 mmol) was reacted with 1-(triphenylphosphoranylidene)-2-propanone **191** (1.76 g, 5.30 mmol) in chloroform (30 ml) heated at reflux for 44 hours to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 1: 1) to yield **400** (440 mg, 45 %) as an off white solid. M.p. 64 - 66 °C; R_f : 0.3 (light petroleum ether: ethyl acetate; 1: 1); $\nu_{\max}(\text{CHCl}_3)/\text{cm}^{-1}$ 3277, 2928, 1670, 1624, 1328, 1160; δ_{H} (400 MHz, CDCl_3) 7.90 - 7.84 (3H, m, 3ArH), 7.63 - 7.49 (2H, m, 2ArH),

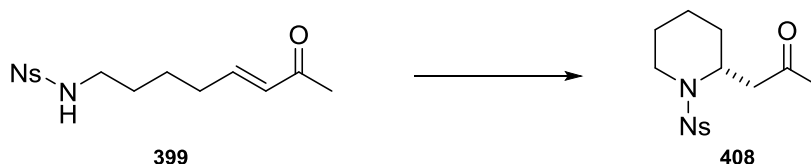
6.72 (1H, dt, *J* 16.0, 7.0, CH=CHCO), 6.04 (1H, dt, *J* 16.0, 2.0, CH=CHCO), 4.56 (1H, bs, NH), 2.98 (2H, dt, *J* 7.0, 7.0, CHCH₂), 2.25 - 2.15 (5H, m + s, CH₂ + CH₃), 1.58 - 1.42 (4H, m, 2CH₂); δ_{C} (100 MHz, CDCl₃) 198.5 (C), 147.2 (CH), 140.0 (C), 132.7 (CH), 131.6 (CH), 129.2 (CH), 127.0 (CH), 42.9 (CH₂), 31.7 (CH₂), 29.2 (CH₂), 27.0 (CH₃), 24.9 (CH₂); *m/z* (ES) 304 (M+Na⁺, 100%); *m/z* (ES) found [M+Na]⁺ 304.0984. C₁₄H₁₉NNaO₃S⁺ requires 304.0970.

(*R*)-1-(1-Tosylpiperidin-2-yl)propan-2-one 407



Following general procedure 8, (*E*)-4-methyl-*N*-(7-oxooct-5-en-1-yl)benzenesulfonamide **398** (15.0 mg, 50.0 μmol) in tetrahydrofuran (0.5 ml) was stirred at room temperature for 22 hours to yield **407** (13.5 mg, 90 %) as a colourless oil. *R_f* : 0.4 (light petroleum ether: ethyl acetate; 3: 2); $[\alpha]_{\text{D}}^{23} +23.7$ (c 1.0 in CHCl₃); ν_{max} (neat)/cm⁻¹ 2941, 1715, 1597, 1336; δ_{H} (400 MHz, CDCl₃) 7.71 (2H, dd, *J* 8.0, 2.5, 2ArH), 7.29 (2H, d, *J* 8.0, 2ArH), 4.56 - 4.48 (1H, m, CHN), 3.82 - 3.74 (1H, m, CH_AH_B), 2.94 (1H, ddd, *J* 12.0, 12.0, 4.0, CH_AH_B), 2.79 (1H, dd, *J* 16.0, 8.0, COCH_AH_B), 2.60 (1H, dd, *J* 16.0, 6.0, COCH_AH_B), 2.42 (3H, s, CH₃), 2.13 (3H, s, COCH₃), 1.58 - 1.22 (6H, m, 3CH₂); δ_{C} (100 MHz, CDCl₃) 206.0 (C), 143.2 (C), 138.1 (C), 129.7 (CH), 127.1 (CH), 48.7 (CH), 43.9 (CH₂), 41.3 (CH₂), 30.3 (CH₃), 27.7 (CH₂), 24.6 (CH₂), 21.5 (CH₃), 18.4 (CH₂); *m/z* (ES) 318 (M+Na⁺, 100 %); *m/z* (ES) found [M+Na]⁺ 318.1122. C₁₅H₂₁NNaO₃S⁺ requires 318.1134; *R_t* HPLC Chiralpak AD-H; mobile phase, hexane: 2-propanol (9: 1 v/v); flow rate, 1 ml/min; 18.5 min (6.2 %), 21.6 min (93.8 %) 88 % e.e. The ¹H NMR and ¹³C data is in agreement with those previously reported.^[151]

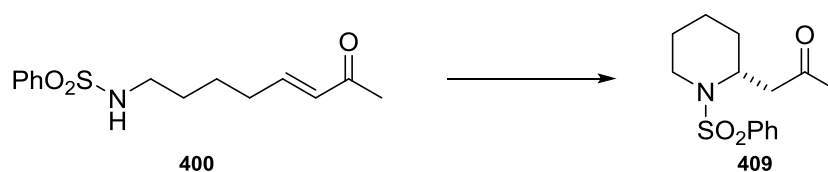
(*R*)-1-(1-Nosylpiperidin-2-yl)propan-2-one 408



Following general procedure 8, (*E*)-4-nitro-*N*-(7-oxooct-5-en-1-yl)benzenesulfonamide **399** (16.3 mg, 50.0 μmol) in tetrahydrofuran (0.5 ml) was stirred at room temperature for 46 hours to yield **408** (15.0 mg, 92 %) as a colourless oil. *R_f* : 0.4 (light petroleum ether: ethyl acetate; 1: 1); $[\alpha]_{\text{D}}^{23} +33.9$ (c 0.6 in CHCl₃); ν_{max} (CHCl₃)/cm⁻¹ 2944, 1715, 1606, 1530, 1350; δ_{H} (400 MHz, CDCl₃) 8.38 (2H, dd, *J* 8.0, 2.0, 2ArH), 8.05 (2H, dd, *J* 8.0, 2.0, 2ArH), 4.63 - 4.55 (1H, m, CHN), 3.90 - 3.81 (1H, m, CH_AH_B), 3.05 (1H, ddd, *J* 14.0,

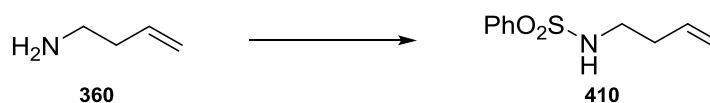
12.0, 3.0, $\text{CH}_\text{A}\text{H}_\text{B}$), 2.88 (1H, dd, J 17.0, 9.0, $\text{COCH}_\text{A}\text{H}_\text{B}$), 2.68 (1H, dd, J 17.0, 5.0, $\text{COCH}_\text{A}\text{H}_\text{B}$), 2.17 (3H, s, CH_3), 1.67 - 1.21 (6H, m, 3CH_2); δ_C (100 MHz, CDCl_3) 205.4 (C), 147.1 (C), 128.2 (CH), 124.4 (CH), 49.1 (CH), 44.2 (CH_2), 41.7 (CH_2), 30.4 (CH_3), 27.9 (CH_2), 24.7 (CH_2), 18.3 (CH_2); m/z (ES) 349 ($\text{M}+\text{Na}^+$, 100 %); m/z (ES) found $[\text{M}+\text{Na}]^+$ 349.0824. $\text{C}_{14}\text{H}_{18}\text{N}_2\text{NaO}_5\text{S}^+$ requires 349.0829; R_t HPLC Chiralpak AD-H; mobile phase, hexane: 2-propanol (4: 1 v/v); flow rate, 1 ml/min; 17.0 min (5.6 %), 21.6 min (94.4 %) 89 % e.e.

(*R*)-1-(1-(Phenylsulfonyl)piperidin-2-yl)propan-2-one 409



Following general procedure 5, (*E*)-*N*-(7-oxooct-5-en-1-yl)benzenesulfonamide **400** (14.0 mg, 50.0 μmol) was stirred in tetrahydrofuran (0.5 ml) at 30 °C for 7 hours to yield **409** (13.0 mg, 93 %) as a colourless oil. R_f : 0.5 (light petroleum ether: ethyl acetate; 3: 2); $[\alpha]_\text{D}^{28} +34.0$ (c 0.3 in CHCl_3); ν_max (neat)/ cm^{-1} 2927, 1715, 1447, 1336, 1157; δ_H (400 MHz, CDCl_3) 7.83 (2H, dd, J 8.0, 2.0, 2ArH), 7.60 - 7.47 (3H, m, 3ArH), 4.58 - 4.50 (1H, m, CHN), 3.85 - 3.78 (1H, m, $\text{CH}_\text{A}\text{H}_\text{B}$), 2.96 (1H, ddd, J 14.0, 12.0, 2.0, $\text{CH}_\text{A}\text{H}_\text{B}$), 2.80 (1H, dd, J 17.0, 10.0, $\text{COCH}_\text{A}\text{H}_\text{B}$), 2.59 (1H, dd, J 17.0, 5.0, $\text{COCH}_\text{A}\text{H}_\text{B}$), 2.12 (3H, s, CH_3), 1.60 - 1.21 (6H, m, 3CH_2); δ_C (100 MHz, CDCl_3) 206.0 (C), 141.1 (C), 132.5 (CH), 129.1 (CH), 127.0 (CH), 48.8 (CH), 44.0 (CH_2), 41.3 (CH_2), 30.3 (CH_3), 27.8 (CH_2), 24.6 (CH_2), 18.4 (CH_2); m/z (ES) 304 ($\text{M}+\text{Na}^+$, 100 %); m/z (ES) found $[\text{M}+\text{Na}]^+$ 304.0984. $\text{C}_{14}\text{H}_{19}\text{NNaO}_3\text{S}^+$ requires 304.0970; R_t HPLC Chiralpak AD-H; mobile phase, hexane: 2-propanol (19: 1 v/v); flow rate, 1 ml/min; 29.1 min (2.5 %), 39.6 min (97.5 %) 95 % e.e.

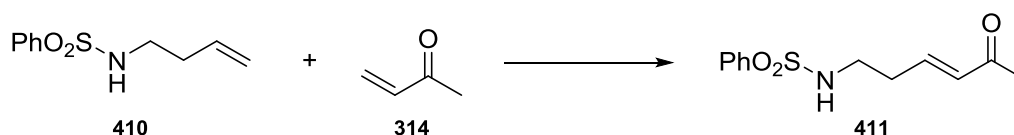
***N*-(But-3-en-1-yl)benzenesulfonamide 410**



Triethylamine (480 μl , 2.67 mmol) was added to a solution of 3-but-1-amine **360** (220 μl , 2.42 mmol) in dichloromethane (2 ml) at 0 °C. Benzenesulfonyl chloride **403** (320 μl , 2.50 mmol) was added dropwise over 10 minutes and the solution warmed to room temperature then stirred for 4 hours. The resulting solution was concentrated under reduced pressure to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 4: 1) to yield **410** (440 mg, 89 %) as a colourless oil. R_f : 0.3 (light petroleum ether: ethyl acetate; 4: 1); ν_max (neat)/ cm^{-1} 3284, 1642, 1447, 1324; δ_H (500 MHz, CDCl_3) 7.91 - 7.81 (2H, m, 2ArH), 7.61 - 7.56 (1H, m,

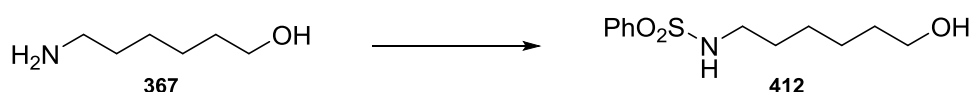
ArH), 7.55 - 7.49 (2H, m, 2ArH), 5.62 (1H, ddt, J 17.0, 10.5, 7.0, $\text{CH}_2=\text{CH}$), 5.08 - 4.99 (2H, m, $\text{CH}=\text{CH}_2$), 4.76 (1H, t, J 6.5, NH), 3.03 (2H, dt, J 6.5, 6.5, NCH_2), 2.20 (2H, dt, J 7.0, 7.0, CHCH_2); δ_{C} (100 MHz, CDCl_3) 139.9 (C), 134.1 (CH), 132.7 (CH), 129.1 (CH), 127.1 (CH), 118.1 (CH_2), 42.2 (CH_2), 33.6 (CH_3); m/z (ES) 445 ($2\text{M}+\text{Na}^+$, 43 %), 234 ($\text{M}+\text{Na}^+$, 100), 212 ($\text{M}+\text{H}^+$, 54); m/z (ES) found $[\text{M}+\text{Na}]^+$ 234.0561. $\text{C}_{10}\text{H}_{13}\text{NNaO}_2\text{S}^+$ requires 280.0559. The ^1H NMR and ^{13}C data is in agreement with those previously reported.^[152]

(*E*)-*N*-(5-Oxohex-3-en-1-yl)benzenesulfonamide **411**



Following general procedure 7, *N*-(but-3-en-1-yl)benzenesulfonamide **410** (210 mg, 1.00 mmol) was reacted with methylvinylketone **314** (420 μl , 5.00 mmol) for 2 hours to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 1: 1) to yield **411** (210 mg, 85 %) as a colourless oil. R_f : 0.3 (light petroleum ether: ethyl acetate; 1: 1); ν_{max} (neat)/ cm^{-1} 3272, 2938, 1672, 1628, 1447, 1327; δ_{H} (400 MHz, CDCl_3) 7.89 - 7.84 (2H, m, 2ArH), 7.63 - 7.57 (1H, m, ArH), 7.55 - 7.49 (2H, m, 2ArH), 6.65 (1H, dt, J 16.0, 7.5 $\text{CH}=\text{CHCO}$), 6.04 (1H, dt, J 16.0, 2.0 $\text{CH}=\text{CHCO}$), 5.15 (1H, bs, NH), 3.13 (2H, dt, J 6.5, 6.5, NCH_2), 2.41 (2H, dt, J 7.5, 7.5, CHCH_2), 2.20 (3H, s, CH_3); δ_{C} (100 MHz, CDCl_3) 198.3 (C), 148.1 (CH), 139.8 (C), 133.3 (CH), 132.9 (CH), 129.2 (CH), 127.0 (CH), 41.6 (CH_2), 32.6 (CH_2), 27.1 (CH_3); m/z (ES) 529 ($2\text{M}+\text{Na}^+$, 33 %), 276 ($\text{M}+\text{Na}^+$, 100), 254 ($\text{M}+\text{H}^+$, 47); m/z (ES) found $[\text{M}+\text{Na}]^+$ 276.0658. $\text{C}_{12}\text{H}_{15}\text{NNaO}_3\text{S}^+$ requires 276.0665.

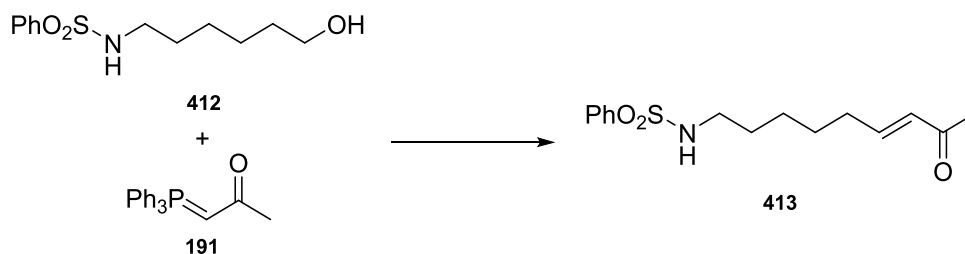
N-(6-Hydroxyhexyl)benzenesulfonamide **412**



Following general procedure 4b, 6-aminohexan-1-ol **367** (570 mg, 4.90 mmol) was reacted with benzenesulfonyl chloride **403** (820 μl , 6.70 mmol) to give a yellow oil. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 3: 2) to yield **412** (1.20 g, 99 %) as a colourless oil. R_f : 0.4 (light petroleum ether: ethyl acetate; 3: 2); ν_{max} (neat)/ cm^{-1} 3508, 3283, 2935, 1447, 1322; δ_{H} (400 MHz, CDCl_3) 7.90 - 7.85 (2H, m, 2ArH), 7.62 - 7.48 (3H, m, 3ArH), 4.59 (1H, bs, NH), 3.61 (2H, t, J 6.5, OCH_2), 2.97 (2H, dt, J 6.5, 6.5, NCH_2), 1.57 - 1.27 (9H, m, OH + 4 CH_2); δ_{C} (100 MHz, CDCl_3) 140.0 (C), 132.6 (CH), 129.1 (CH), 127.0 (CH), 62.6 (CH_2), 43.1 (CH_2), 32.4 (CH_2), 29.5 (CH_2), 26.2 (CH_2), 25.1 (CH_2); m/z (ES) 537 ($2\text{M}+\text{Na}^+$, 60 %), 280 ($\text{M}+\text{Na}^+$,

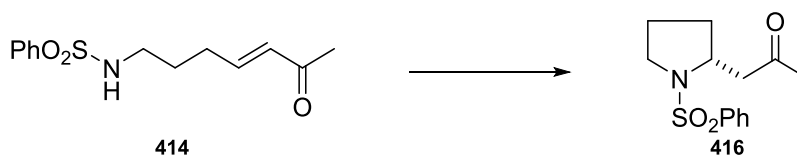
100), 258 ($M+H^+$, 75); m/z (ES) found $[M+Na]^+$ 280.0972. $C_{12}H_{19}NNaO_3S^+$ requires 280.0978.

(E)-N-(8-Oxonon-6-en-1-yl)benzenesulfonamide 413



Following general procedure 6, N-(6-hydroxyhexyl)-benzenesulfonamide **412** (1.20 g, 4.85 mmol) was reacted with 1-(triphenylphosphoranylidene)-2-propanone **191** (2.43 g, 7.70 mmol) in chloroform (42 ml) heated at reflux for 20 h to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 3: 2) to yield **413** (670 mg, 48 %) as a yellow oil. R_f : 0.3 (light petroleum ether: ethyl acetate; 3: 2); ν_{max} (neat)/ cm^{-1} 3277, 2936, 1670, 1625, 1446, 1327; δ_H (400 MHz, $CDCl_3$) 7.90 - 7.85 (2H, m, 2ArH), 7.61 - 7.49 (3H, m, 3ArH), 6.74 (1H, dt, J 16.0, 8.0, $CH=CHCO$), 6.04 (1H, dt, J 16.0, 2.0, $CH=CHCO$), 4.76 (1H, bs, NH), 2.95 (2H, dt, J 8.0, 8.0, NCH_2), 2.23 (3H, s, CH_3), 2.17 (2H, dt, J 8.0, 8.0, $CHCH_2$), 1.53 - 1.24 (6H, m, 3 CH_2); δ_C (100 MHz, $CDCl_3$) 198.7 (C), 147.9 (CH), 140.0 (C), 132.6 (CH), 131.5 (CH), 129.1 (CH), 127.0 (CH), 43.0 (CH_2), 32.2 (CH_2), 29.4 (CH_2), 27.5 (CH_2), 26.9 (CH_3), 26.0 (CH_2); m/z (ES) 613 ($2M+Na^+$, 64 %), 318 ($M+Na^+$, 96), 296 ($M+H^+$, 100); m/z (ES) found $[M+H]^+$ 296.1304. $C_{15}H_{22}NO_3S^+$ requires 366.1315.

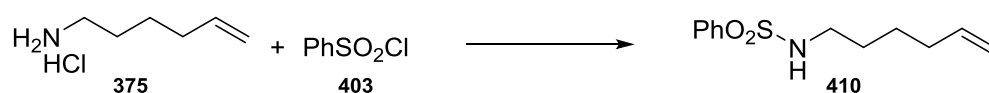
(R)-1-(1-(Phenylsulfonyl)pyrrolidin-2-yl)propan-2-one 416



Following general procedure 8, (E)-N-(6-oxohept-4-en-1-yl)benzenesulfonamide **414** (18.0 mg, 70.0 μ mol) with trifluoroacetic acid (1.00 μ l, 7.00 μ mol) was stirred in tetrahydrofuran (0.7 ml) at 30 °C for 5 hours to yield **416** (16.5 mg, 92 %) as a colourless oil. R_f : 0.3 (light petroleum ether: ethyl acetate; 7: 3); $[\alpha]_D^{26} +119.1$ (c 0.6 in $CHCl_3$); ν_{max} ($CHCl_3$)/ cm^{-1} 2959, 1712, 1446, 1337; δ_H (400 MHz, $CDCl_3$) 7.86 - 7.81 (2H, m, 2ArH), 7.64 - 7.50 (3H, m, 3ArH), 3.99 - 3.91 (1H, m, CHN), 3.49 - 3.42 (1H, m, CH_AH_B), 3.26 (1H, dd, J 18.0, 3.5, $COCH_AH_B$), 3.14 - 3.07 (1H, m, CH_AH_B), 2.61 (1H, dd, J 18.0, 9.5, $COCH_AH_B$), 2.18 (3H, s, CH_3), 1.87 - 1.70 (2H, m, CH_2), 1.59 - 1.43 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 207.2 (C), 136.8 (C), 132.8 (CH), 129.1 (CH), 127.6 (CH), 55.9 (CH),

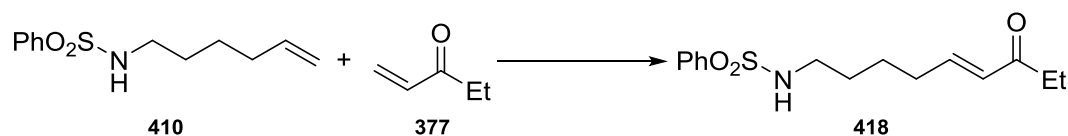
50.6 (CH₂), 49.2 (CH₂), 32.1 (CH₂), 30.6 (CH₃), 23.8 (CH₂); *m/z* (ES) 557 (2M+Na⁺, 34 %), 290 (M+Na⁺, 97), 268 (M+H⁺, 100); *m/z* (ES) found [M+H]⁺ 268.0999. C₁₃H₁₈NO₃S⁺ requires 268.1002; R_f HPLC Chiralpak OD-H; mobile phase, hexane: 2-propanol (4: 1 v/v); flow rate, 1 ml/min; 10.1 min (3.3 %), 16.7 min (96.7 %) 94 % e.e. The ¹H NMR and ¹³C data is in agreement with those previously reported.^[151]

***N*-(Hex-5-en-1-yl)benzenesulfonamide 410**



Benzenesulfonyl chloride **403** (64.0 μl, 0.500 mmol) was added to a solution of 5-hexen-1-amine hydrochloride salt **375** (300 mg, 1.00 mmol) and triethylamine (280 μl, 2.00 mmol) in dichloromethane (4 ml) at 0 °C. The reaction was allowed to warm to room temperature then stirred for 2 hours. Water (4 ml) was added and the layers separated. The organic layer was washed with 0.1 M hydrochloric acid (4 ml), dried (magnesium sulfate) and concentrated under reduced pressure to yield a light yellow oil. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 4: 1) to yield **410** (102 mg, 86 %) as a colourless oil. R_f : 0.3 (light petroleum ether: ethyl acetate; 4: 1); *v*_{max} (neat)/cm⁻¹ 3288, 2936, 1640, 1447, 1425, 1325; δ_H (400 MHz, CDCl₃) 7.91 - 7.83 (2H, m, 2ArH), 7.60 - 7.43 (3H, m, 3ArH), 5.75 (1H, ddt, *J* 17.0, 10.5, 6.5, CH₂=CH), 5.18 (1H, t, *J* 6.5, NH), 4.96 - 4.85 (2H, m, CH=CH₂), 2.92 (2H, dt, *J* 7.0, 7.0, NCH₂), 1.95 (2H, dt, *J* 6.5, 6.5, CHCH₂), 1.51 - 1.28 (4H, m, 2CH₂); δ_C (100 MHz, CDCl₃) 140.0 (C), 138.2 (CH), 132.6 (CH), 129.1 (CH), 127.0 (CH), 114.9 (CH₂), 43.1 (CH₂), 33.1 (CH₂), 28.9 (CH₂), 25.7 (CH₂); *m/z* (ES) 262 (M+Na⁺, 100 %), 240 (M+H⁺, 15); *m/z* (ES) found [M+Na]⁺ 262.0875. C₁₂H₁₇NNaO₂S⁺ requires 262.0872. The ¹H NMR and ¹³C data is in agreement with those previously reported.^[153]

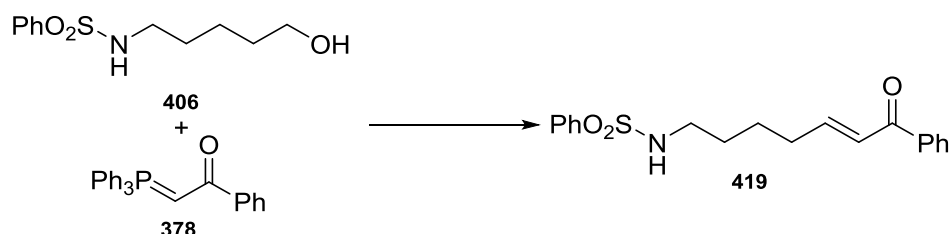
***(E)*-N-(7-Oxonon-5-en-1-yl)benzenesulfonamide 418**



Following general procedure 7, *N*-(hex-5-en-1-yl)benzenesulfonamide **410** (102 mg, 410 μmol) was reacted with ethylvinylketone **377** (200 μl, 2.00 mmol) for 1 hour to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 3: 2) to yield **418** (102 mg, 86 %) as a yellow oil. R_f : 0.4 (light petroleum ether: ethyl acetate; 3: 2); *v*_{max} (neat)/cm⁻¹ 3274, 2938, 1667, 1627, 1447, 1327; δ_H (400 MHz, C₆D₆) 7.90 - 7.31 (2H, m, 2ArH), 7.03 - 6.98 (3H, m, 3ArH), 6.41 (1H, dt, *J* 16.0, 7.0, CH=CHCO), 5.87 (1H, dt, *J* 16.0, 2.0, CH=CHCO), 4.55 (1H, t, *J* 6.5, NH), 2.59 (2H, dt, *J* 7.0, 7.0, NCH₂), 2.17 (2H, q, *J* 7.5, CH₂CH₃), 1.63 (2H, dt, *J* 7.0, 7.0,

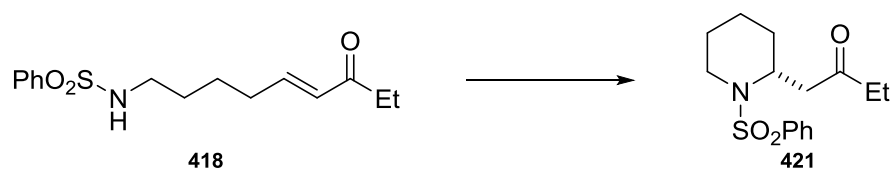
CHCH₂), 1.04 (3H, t, *J* 7.5, CH₂CH₃), 1.01 - 0.83 (4H, m, 2CH₂); δ_C (100 MHz, C₆D₆) 199.0 (C), 144.9 (CH), 141.1 (C), 132.0 (CH), 130.3 (CH), 128.8 (CH), 127.1 (CH), 42.7 (CH₂), 33.2 (CH₂), 31.4 (CH₂), 28.9 (CH₂), 24.8 (CH₂), 8.0 (CH₃); *m/z* (ES) 318 (M+Na⁺, 100 %); *m/z* (ES) found [M+Na]⁺ 318.1129. C₁₅H₂₁NNaO₃S⁺ requires 318.1134.

(*E*)-*N*-(7-Oxo-7-phenylhept-5-en-1-yl)benzenesulfonamide 419



Following general procedure 6, *N*-(5-hydroxypentyl)-benzenesulfonamide **406** (1.18 g, 4.85 mmol) was reacted with benzoylmethylene-(triphenylphosphorane) **378** (2.91 g, 7.70 mmol) in chloroform (42 ml) heated at reflux for 96 h to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 2: 3) to yield **419** (530 mg, 32 %) as an off white solid; M.p. 82 - 84 °C; *R_f* : 0.3 (light petroleum ether: ethyl acetate; 2: 3); $\nu_{\max}$ (CHCl₃)/cm⁻¹ 3273, 2936, 1666, 1617, 1597, 1578; δ_H (400 MHz, CDCl₃) 7.98 - 7.82 (4H, m, 4ArH), 7.65 - 7.40 (6H, m, 6ArH), 6.97 (1H, dt, *J* 16.0, 7.0, CH=CHCO), 6.85 (1H, dt, *J* 16.0, 2.0, CH=CHCO), 4.57 (1H, t, *J* 7.5, NH), 3.00 (2H, dt, *J* 7.5, 7.5, NCH₂), 2.29 (2H, dt, *J* 7.0, 7.0, CHCH₂), 1.59 - 1.47 (4H, m, 2CH₂); δ_C (100 MHz, CDCl₃) 190.7 (C), 148.6 (CH), 140.0 (C), 137.9 (C), 132.7 (CH), 129.2 (CH), 128.6 (CH), 128.5 (CH), 126.4 (CH), 43.0 (CH₂), 32.1 (CH₂), 29.2 (CH₂), 25.1 (CH₂); *m/z* (ES) 366 (M+Na⁺, 100 %); *m/z* (ES) found [M+Na]⁺ 366.1130. C₁₉H₂₁NNaO₃S⁺ requires 366.1134.

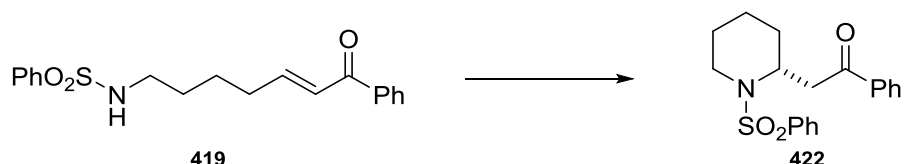
(*R*)-1-(1-(Phenylsulfonyl)piperidin-2-yl)butan-2-one 421



Following general procedure 8, (*E*)-*N*-(7-oxonon-5-en-1-yl)benzenesulfonamide **418** (29.5 mg, 100 μ mol) was stirred in tetrahydrofuran (1.0 ml) at 30 °C for 8 hours to yield **421** (25.0 mg, 85 %) as a colourless oil. *R_f* : 0.3 (light petroleum ether: ethyl acetate; 3: 1); $[\alpha]_D^{23} +12.4$ (c 0.5 in CHCl₃); $\nu_{\max}$ (neat)/cm⁻¹ 2939, 1712, 1446, 1413, 1355; δ_H (400 MHz, CDCl₃) 7.87 - 7.78 (2H, m, 2ArH), 7.61 - 7.44 (3H, m, 3ArH), 4.58 - 4.50 (1H, m, CHN), 3.87 - 3.78 (1H, m, CH_AH_B), 2.96 (1H, ddd, *J* 12.0, 12.0, 4.0, CH_AH_B), 2.78 (1H, dd, *J* 16.0, 9.5, COCH_AH_B), 2.56 (1H, dd, *J* 16.0, 4.5, COCH_AH_B), 2.39 (2H, q, *J* 7.5, CH₂CH₃), 1.62 - 1.17 (6H, m, 3CH₂), 1.02 (3H, t, *J* 7.5, CH₂CH₃); δ_C (100 MHz, CDCl₃)

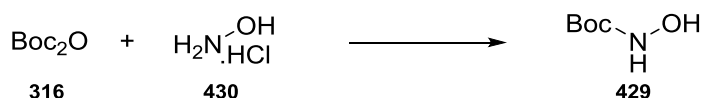
208.6 (C), 141.1 (C), 132.4 (CH), 129.1 (CH), 127.0 (CH), 48.9 (CH), 42.6 (CH₂), 41.3 (CH₂), 36.4 (CH₂), 27.8 (CH₂), 24.7 (CH₂), 18.4 (CH₂), 7.6 (CH₃); *m/z* (ES) 318 (M+Na⁺, 100 %); *m/z* (ES) found [M+Na]⁺ 318.1123. C₁₅H₂₁NNaO₃S⁺ requires 318.1134; R_t HPLC Chiralcel OD-H; mobile phase, hexane: 2-propanol (9: 1 v/v); flow rate, 1 ml/min; 12.4 min (1.6 %), 14.9 min (98.4 %) 97 % e.e.

(R)-1-Phenyl-2-(1-(phenylsulfonyl)piperidin-2-yl)ethan-1-one 422



Following general procedure 8, (*E*)-*N*-(7-oxo-7-phenylhept-5-en-1-yl)benzenesulfonamide **419** (34.0 mg, 100 μmol) was stirred in tetrahydrofuran (1.0 ml) at 50 °C for 72 hours to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 3: 1) to yield **422** (20.0 mg, 58 %) as a colourless oil. R_f : 0.4 (light petroleum ether: ethyl acetate; 3: 1); [α]_D²⁸ +27.6 (c 0.9 in CHCl₃); ν_{max}(neat)/cm⁻¹ 2938, 1722, 1682, 1587, 1288; δ_H (400 MHz, CDCl₃) 7.92 (2H, dd, *J* 8.0, 2.0, 2ArH), 7.84 (2H, dd, *J* 8.0, 2.0, 2ArH), 7.61 - 7.51 (3H, m, 3ArH), 7.61 - 7.51 (3H, m, 3ArH), 4.74 - 4.66 (1H, m, CHN), 3.99 - 3.78 (1H, m, CH_AH_B), 3.36 (1H, dd, *J* 17.0, 12.0, COCH_AH_B), 3.15 (1H, dd, *J* 17.0, 6.0, COCH_AH_B), 3.08 (1H, ddd, *J* 13.0, 13.0, 2.5, CH_AH_B), 2.12 (3H, s, CH₃), 1.70 - 1.27 (6H, m, 3CH₂); δ_C (100 MHz, CDCl₃) 197.6 (C), 141.1 (C), 136.6 (C), 133.4 (CH), 132.4 (CH), 129.1 (CH), 128.7 (CH), 128.2 (CH), 127.0 (CH), 49.5 (CH), 41.5 (CH₂), 39.0 (CH₂), 27.5 (CH₂), 24.8 (CH₂), 18.4 (CH₂); *m/z* (ES) 366 (M+Na⁺, 100 %); *m/z* (ES) found [M+Na]⁺ 366.1136. C₁₉H₂₁NNaO₃S⁺ requires 366.1134; R_t HPLC Chiralpak AD-H; mobile phase, hexane: 2-propanol (4: 1 v/v); flow rate, 1 ml/min; 11.4 min (4.2 %), 32.1 min (95.8 %) 92 % e.e.

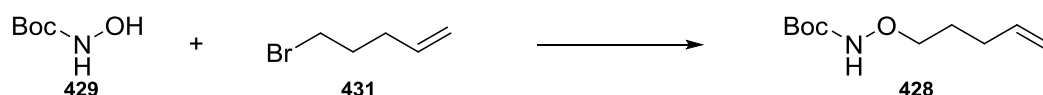
***N*-Boc-hydroxylamine 429^[111]**



Water (0.5 ml) was added to a suspension of hydroxylamine hydrochloride **430** (2.40 g, 35.0 mmol) and sodium carbonate (2.42 g, 23.0 mmol) in diethyl ether (15 ml). The suspension was stirred at room temperature for 1 hour, then cooled to 0 °C. A solution of di-*tert*-butyldicarbonate **316** (5.00 g, 23.0 mmol) dissolved in diethyl ether (5 ml) was added dropwise over 10 minutes and allowed to warm temperature then stirred for 16 hours. The suspension was filtered and the resulting solid washed with diethyl ether (2 x 10 ml). The combined organics were concentrated under reduced pressure to yield a

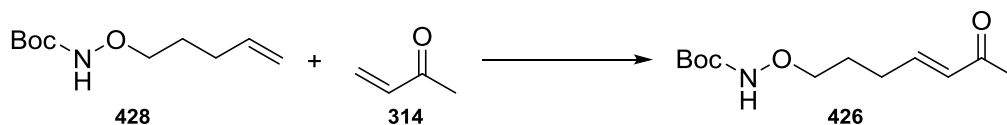
colourless oil. Cyclohexane (10 ml) was added and the resulting solid filtered and dried to yield **429** (2.81 g, 92 %) as a colourless solid. M.p. 58 - 60 °C; Lit M.p. 52 - 54 °C^[111]; $\nu_{\max}$ (CHCl₃)/cm⁻¹ 3309, 2981, 1717, 1370; δ_{H} (400 MHz, CDCl₃) 7.07 (1H, bs, NH), 6.92 (1H, bs, OH), 1.48 (9H, s, C(CH₃)₃); δ_{C} (100 MHz, CDCl₃) 158.8 (C), 62.2 (C), 28.2 (C(CH₃)₃). m/z (ES) 156 (M+Na⁺, 100 %); m/z (ES) found [M+Na]⁺ 156.0625. C₅H₁₁NNaO₃⁺ requires 156.0631. The ¹H NMR and ¹³C data is in agreement with those previously reported.^[111]

tert*-Butyl-pent-4-en-1-yloxycarbamate **428*^[112]



Following general procedure 5, 5-bromobut-1-ene **431** (1.01 ml, 8.50 mmol) was reacted with *N*-Boc hydroxylamine **429** (1.00 g, 7.40 mmol) and DBU (1.16 ml, 7.80 mmol) to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 9: 1) to yield **428** (860 mg, 58 %) as a colourless oil. R_f : 0.3 (light petroleum ether: ethyl acetate; 9: 1); $\nu_{\max}$ (neat)/cm⁻¹ 3292, 2979, 1719, 1642, 1369; δ_{H} (400 MHz, CDCl₃) 7.09 (1H, bs, NH), 5.82 (1H, ddt, J 16.0, 10.0, 8.0, CH=CH₂), 5.09 - 4.95 (2H, m, CH=CH₂), 3.87 (2H, t, J 8.0, OCH₂), 2.16 (2H, dt, J 8.0, 8.0, CHCH₂), 1.78 - 1.69 (2H, m, CH₂), 1.49 (9H, s, C(CH₃)₃); δ_{C} (100 MHz, CDCl₃) 156.9 (C), 137.9 (CH), 115.0 (CH₂), 81.6 (C), 76.2 (CH₂), 30.0 (CH₂), 28.2 ((CH₃)₃), 27.2 (CH₂); m/z (ES) 224 (M+Na⁺, 100 %); m/z (ES) found [M+Na]⁺ 224.1258. C₁₀H₁₉NNaO₃⁺ requires 224.1257. The ¹H NMR and ¹³C data is in agreement with those previously reported.^[112]

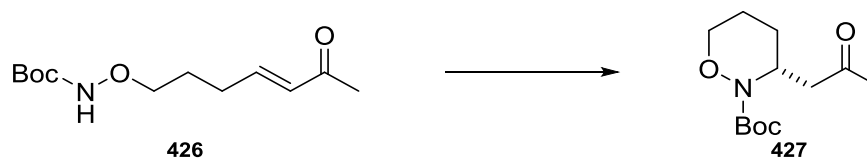
(E)*-tert-Butyl-(6-oxohept-4-en-1-yl)oxycarbamate **426*



Following general procedure 7, *tert*-butyl-(pent-4-en-1-yl)oxycarbamate **428** (150 mg, 750 μ mol) was reacted with methylvinylketone **314** (315 μ l, 3.75 mmol) for 3 hours to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 1: 1) to yield **426** (100 mg, 58 %) as a brown oil. R_f : 0.5 (light petroleum ether: ethyl acetate; 1: 1); $\nu_{\max}$ (neat)/cm⁻¹ 3284, 2978, 1718, 1673, 1627, 1367; δ_{H} (400 MHz, CDCl₃) 7.16 (1H, bs, NH), 6.82 (1H, dt, J 16.0, 8.0, CH=CHCO), 6.10 (1H, dt, J 16.0, 2.0, CH=CHCO), 3.88 (2H, t, J 7.0, OCH₂), 2.41 - 2.32 (2H, m, CHCH₂), 2.25 (3H, s, CH₃), 1.86 - 1.76 (2H, m, CH₂), 1.48 (9H, s, (CH₃)₃); δ_{C} (100 MHz, CDCl₃) 198.6 (C), 156.9 (C), 147.2 (CH), 131.6 (CH), 81.8 (C), 75.7 (CH₂), 28.9

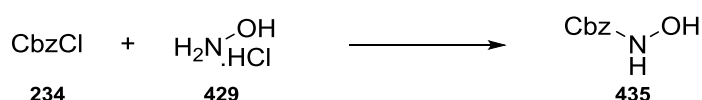
(CH₂), 28.2 ((CH₃)₃), 27.0 (CH₃), 26.6 (CH₂); *m/z* (ES) 266 (M+Na⁺, 100 %), 210 (99); *m/z* (ES) found [M+Na]⁺ 266.1371. C₁₂H₂₁NNaO₄⁺ requires 266.1363. The ¹H NMR and ¹³C data is in agreement with those previously reported.^[95]

(R)-tert-Butyl-3-(2-oxopropyl)-1,2-oxazinane-2-carboxylate **427**



Following general procedure 8, (*E*)-tert-butyl-(6-oxohept-4-en-1-yl)oxycarbamate **426** (12.2 mg, 50.0 μmol) was stirred in 2-methyltetrahydrofuran (0.5 ml) at 20 °C for 7 hours to yield **427** (11.0 mg, 90 %) as a colourless oil. *R_f* : 0.6 (light petroleum ether: ethyl acetate; 1: 1); [α]_D²³ +34.8 (c 0.7 in CHCl₃); lit. [α]_D²⁰ +28.2 (c 1.3 in CHCl₃, 90 % ee)^[95]; *v*_{max} (neat)/cm⁻¹ 2977, 1717, 1368; δ_H (400 MHz, CDCl₃) 4.69 - 4.61 (1H, m, CHN), 4.04 - 3.97 (1H, m, CH_AH_B), 3.87 (1H, ddd, *J* 14.0, 12.0, 3.0, CH_AH_B), 2.99 (1H, dd, *J* 17.0, 6.0, COCH_AH_B), 2.79 (1H, dd, *J* 17.0, 8.0, COCH_AH_B), 2.18 (3H, s, COCH₃), 2.07 - 1.81 (2H, m, CH₂), 1.68 - 1.60 (1H, m, CH), 1.57 - 1.47 (10H, m + s, (CH₃)₃ + CH); δ_C (100 MHz, CDCl₃) 206.6 (C), 154.5 (C), 81.8 (C), 71.2 (CH₂), 50.4 (CH), 43.8 (CH₂), 30.5 (CH₃), 28.3 ((CH₃)₃), 25.3 (CH₂), 19.9 (CH₂); *m/z* (ES) 266 (M+Na⁺, 100 %); *m/z* (ES) found [M+Na]⁺ 266.1366. C₁₂H₂₁NNaO₄⁺ requires 266.1363; *R_t* HPLC Chiralpak AD-H; mobile phase, hexane: 2-propanol (19: 1 v/v); flow rate, 1 ml/min; 9.5 min (98.7 %), 10.5 min (1.3 %) 97 % e.e. The ¹H NMR and ¹³C data is in agreement with those previously reported.^[95]

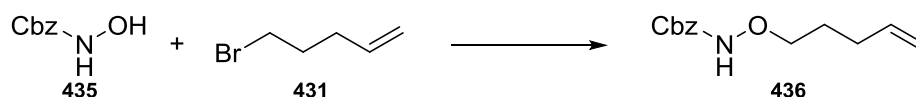
***N*-Cbz-hydroxylamine **435**^[114]**



Water (7.5 ml) was added to a suspension of hydroxylamine hydrochloride **429** (2.40 g, 35.0 mmol) and potassium carbonate (4.80 g, 35.0 mmol) in diethyl ether (7.5 ml). The suspension was stirred at room temperature for 1 hour, then cooled to 0 °C. Benzyl formate **234** (3.30 ml, 23.0 mmol) was added dropwise over 10 minutes and the solution allowed to warm temperature then stirred for 16 hours. The resulting solid was collected by filtration and the resulting solid washed with diethyl ether (10 ml). The combined organics were concentrated under reduced pressure to yield **435** (2.07 g, 54 %) as a colourless solid. M.p. 78 - 80 °C; *v*_{max} (CHCl₃)/cm⁻¹ 3291, 1717, 1269; δ_H (400 MHz, CDCl₃) 7.43 - 7.29 (6H, m + s, 5ArH + NH), 5.18 (2H, s, PhCH₂); δ_C (100 MHz, CDCl₃) 159.2 (C), 135.4 (C), 128.7 (2CH), 128.4 (3CH), 67.9 (CH₂); *m/z* (ES) 190 (M+Na⁺, 100

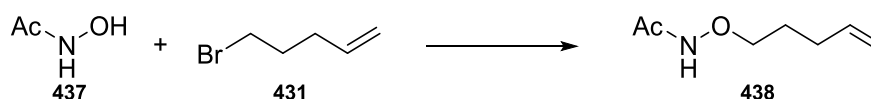
%); m/z (ES) found $[M+Na]^+$ 190.0479. $C_8H_9NNaO_3^+$ requires 190.0475. The ^1H NMR and ^{13}C data is in agreement with those previously reported.^[114]

Benzyl pent-4-en-1-yloxycarbamate **436**

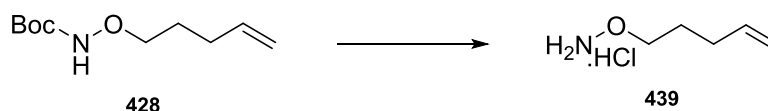


DBU (2.50 ml, 16.7 mmol) was added dropwise to a solution of 5-bromopent-1-ene **431** (230 μ l, 2.00 mmol) and *N*-Cbz-hydroxylamine **435** (840 mg, 5.00 mmol) in dichloromethane (1.0 ml) at 0 °C. The solution was allowed to warm to room temperature then stirred for 16 hours. Ethyl acetate (30 ml) was added and washed with water (20 ml) and brine (20 ml). The organic layer was dried (magnesium sulfate) and concentrated under reduced pressure to yield a crude light yellow oil. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 17: 3) to yield **436** (160 mg, 34 %) as a colourless oil. R_f : 0.3 (light petroleum ether: ethyl acetate; 17: 3); ν_{max} (neat)/ cm^{-1} 3273, 2944, 1723, 1640, 1256; δ_H (400 MHz, $CDCl_3$) 7.42 - 7.08 (6H, m, 5ArH + NH), 5.86 (1H, ddt, J 16.5, 10.5, 8.0, $CH_2=CH$), 5.19 (2H, s, $PhCH_2$), 5.09 - 4.95 (2H, m, $CH=CH_2$), 3.90 (2H, t, J 8.0, OCH_2), 2.15 (2H, dt, J 8.0, 8.0, $CHCH_2$), 1.78 - 1.69 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 157.5 (C), 137.8 (CH), 135.7 (C), 128.6 (CH), 128.4 (CH), 128.3 (CH), 115.1 (CH_2), 76.4 (CH_2), 67.5 (CH_2), 29.9 (CH_2), 27.1 (CH_2); m/z (ES) 258 ($M+Na^+$, 100%); m/z (ES) found $[M+Na]^+$ 258.1101. $C_{13}H_{17}NNaO_3^+$ requires 258.1101.

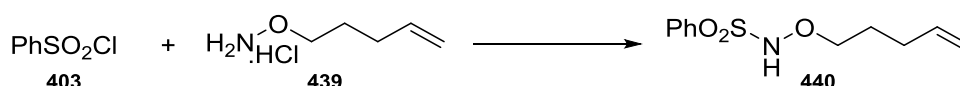
N-(Pent-4-en-1-yloxy)acetamide **438**



Following general procedure 5, 5-bromobut-1-ene **431** (350 μ l, 3.41 mmol) was reacted with *N*-acetohydroxymic acid **437** (220 mg, 2.96 mmol) and DBU (460 μ l, 3.11 mmol) to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 1: 9) to yield **438** (230 mg, 54 %) as a colourless oil. R_f : 0.4 (light petroleum ether: ethyl acetate; 1: 9); ν_{max} (neat)/ cm^{-1} 3188, 2943, 1665, 1087; δ_H (400 MHz, $CDCl_3$, 3: 2 mixture of rotamers) 9.11 - 8.03 (1H, bs, NH), 5.81 (1H, ddt, J 17.0, 10.0, 8.0, $CH_2=CH$), 5.12 - 4.90 (2H, m, $CH=CH_2$), 3.96 - 3.76 (2H, m, OCH_2), 2.15 (2H, dt, J 8.0, 8.0, $CHCH_2$), 2.11 (1.2H, bs, minor CH_3), 1.91 (1.8H, bs, major CH_3), 1.78 - 1.69 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 168.0 (C), 137.7 (CH), 115.2 (CH_2), 78.1 (CH_2), 29.9 (CH_2), 27.1 (CH_2), 19.9 (CH_3); m/z (ES) 166 ($M+Na^+$, 100 %); m/z (ES) found $[M+Na]^+$ 166.0833. $C_7H_{13}NNaO_2^+$ requires 166.0838.

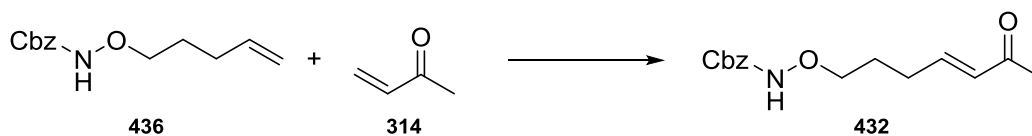
O-(Pent-4-en-1-yl)hydroxylamine hydrochloride salt 439

tert-Butyl (pent-4-en-1-yloxy)carbamate **428** (200 mg, 1.00 mmol) was dissolved in 1 M hydrochloric acid in diethyl ether (4.00 ml, 4.00 mmol) and stirred for 16 hours. The resulting suspension was concentrated and triturated with diethyl ether (3 ml). The resulting solid was collected by filtration to yield **439** (84.0 mg, 61 %) as a colourless solid. M.p. 146 - 149 °C; $\nu_{\max}$ (solid)/cm⁻¹ 3146, 2910, 2848, 1643, 1023; δ_{H} (400 MHz, d₄-MeOD) 5.87 (1H, ddt, *J* 16.5, 10.5, 8.0, CH=CH₂), 5.16 - 5.00 (2H, m, CH=CH₂), 4.07 (2H, t, *J* 6.5, OCH₂), 2.20 (2H, dt, *J* 8.0, 8.0, CHCH₂), 1.86 - 1.76 (2H, m, CH₂); δ_{C} (100 MHz, d₄-MeOD) 136.9 (CH), 114.7 (CH₂), 74.3 (CH₂), 29.3 (CH₂), 26.6 (CH₂); *m/z* (ES) 124 (M+Na⁺, 100 %); *m/z* (ES) found [M+Na]⁺ 124.0736. C₅H₁₁NNaO⁺ requires 124.0733.

N-(Pent-4-en-1-yloxy)benzenesulfonamide 440

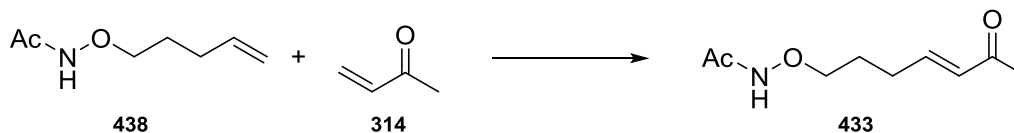
O-(Pent-4-en-1-yl)hydroxylamine hydrochloride **439** (260 mg, 1.90 mmol) was dissolved in dichloromethane (11 ml) and triethylamine (1.02 ml, 5.70 mmol) was added. Benzenesulfonyl chloride **403** (270 μ l, 2.10 mmol) was added at 0 °C and allowed to warm to room temperature then stirred for 3 hours. Dichloromethane (14 ml) was added and the layer washed with water (25 ml). The organic layer was dried (magnesium sulfate) and concentrated under reduced pressure. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 4: 1) to yield **440** (170 mg, 37 %) as a colourless oil. *R_f* : 0.3 (light petroleum ether: ethyl acetate; 4: 1); $\nu_{\max}$ (neat)/cm⁻¹ 3225, 2944, 1641, 1478, 1448, 1170; δ_{H} (400 MHz, CHCl₃) 7.95 (2H, dd, *J* 7.5, 2.0, 2ArH), 7.70 - 7.64 (1H, m, ArH), 7.57 (2H, ddd, *J* 7.5, 7.5, 2.0, 2ArH), 6.95 (1H, bs, NH), 5.79 (1H, ddt, *J* 17.0, 10.5, 6.5, CH=CH₂), 5.05 - 4.95 (2H, m, CH=CH₂), 4.02 (2H, t, *J* 6.5, OCH₂), 2.08 (2H, dt, *J* 6.5, 6.5, CHCH₂), 1.75 - 1.65 (2H, m, CH₂); δ_{C} (100 MHz, CHCl₃) 137.6 (CH), 136.7 (C), 133.8 (CH), 129.1 (CH), 128.5 (CH), 115.2 (CH₂), 77.0 (CH₂), 29.9 (CH₂), 21.3 (CH₂); *m/z* (ES) 264 (M+Na⁺, 100 %), 242 (M+H⁺, 19); *m/z* (ES) found [M+Na]⁺ 264.0661. C₁₁H₁₅NNaO₃S⁺ requires 264.0665.

(E)-Benzyl (6-oxohept-4-en-1-yl)oxycarbamate 432



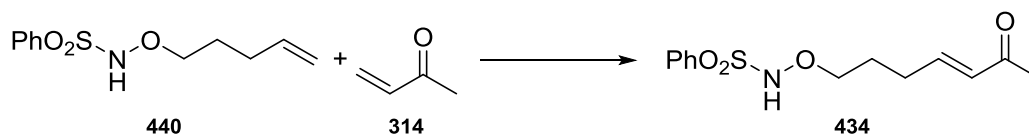
Following general procedure 7, benzyl pent-4-en-1-yloxy carbamate **436** (150 mg, 640 μmol) was reacted with methylvinylketone **314** (275 μl , 3.02 mmol) for 1 hour to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 3: 2) to yield **432** (140 mg, 77 %) as a light yellow oil. R_f : 0.4 (light petroleum ether: ethyl acetate; 3: 2); ν_{max} (neat)/ cm^{-1} 3265, 2950, 1726, 1697, 1670, 1625, 1256; δ_{H} (400 MHz, CDCl_3) 7.44 - 7.29 (6H, m, 5ArH + NH), 6.80 (1H, dt, J 16.0, 7.0, $\text{CH}=\text{CHCO}$), 6.09 (1H, dt, J 16.0, 2.0, $\text{CH}=\text{CHCO}$), 5.19 (2H, s, PhCH_2), 3.92 (2H, t, J 7.0, OCH_2), 2.35 (2H, dt, J 7.0, 7.0, CHCH_2), 2.25 (3H, s, CH_3), 1.86 - 1.66 (2H, m, CH_2); δ_{C} (100 MHz, CDCl_3) 198.6 (C), 157.6 (C), 147.1 (CH), 135.6 (C), 131.7 (CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 75.9 (CH_2), 67.6 (CH_2), 28.8 (CH_2), 27.0 (CH_3), 26.5 (CH_2); m/z (ES) 300 ($\text{M}+\text{Na}^+$, 100 %); m/z (ES) found $[\text{M}+\text{Na}]^+$ 300.1187. $\text{C}_{15}\text{H}_{19}\text{NNaO}_4^+$ requires 300.1206. The ^1H NMR and ^{13}C data is in agreement with those previously reported.^[95]

(E)-N-((6-Oxohept-4-en-1-yl)oxy)acetamide 433



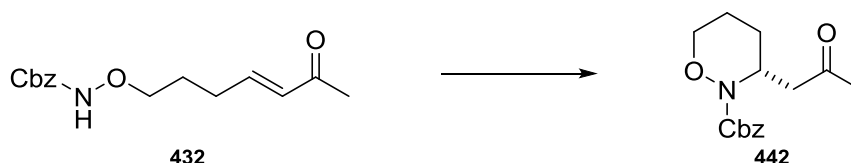
Following general procedure 7, *N*-(pent-4-en-1-yloxy)acetamide **438** (210 mg, 1.47 mmol) was reacted with methylvinylketone **314** (580 μl , 7.35 mmol) for 2 hours to give the crude product. This was purified by flash chromatography on silica gel (ethyl acetate: methanol; 9: 1) to yield **433** (190 mg, 71 %) as a brown oil. R_f : 0.3 (ethyl acetate: methanol; 9: 1); ν_{max} (neat)/ cm^{-1} 3214, 2956, 1669, 1089; δ_{H} (400 MHz, CDCl_3) 8.83 (1H, bs, NH), 6.83 (1H, dt, J 17.0, 8.0, $\text{CH}=\text{CHCO}$), 6.10 (1H, d, J 17.0, $\text{CH}=\text{CHCO}$), 3.92 (2H, m, OCH_2), 2.36 (2H, dt, J 8.0, 8.0, CHCH_2), 2.25 (3H, s, COCH_3), 1.91 (3H, bs, NCOCH_3), 1.87 - 1.76 (2H, m, CH_2); δ_{C} (100 MHz, CDCl_3) 199.0 (C), 168.3 (C), 147.5 (CH), 131.7 (CH), 75.4 (CH_2), 28.8 (CH_2), 26.9 (CH_3), 26.4 (CH_2), 19.8 (CH_3); m/z (ES) 208 ($\text{M}+\text{Na}^+$, 100 %); m/z (ES) found $[\text{M}+\text{Na}]^+$ 208.0943. $\text{C}_9\text{H}_{15}\text{NNaO}_3^+$ requires 208.0944.

(E)-N-((6-Oxohept-4-en-1-yl)oxy)benzenesulfonamide 434



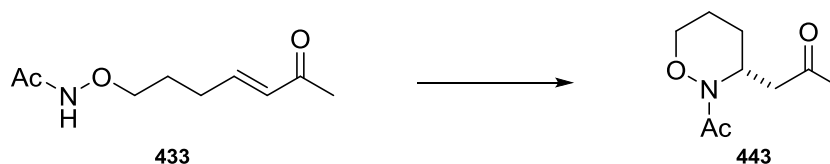
Following general procedure 7, *N*-(pent-4-en-1-yloxy)benzenesulfonamide **440** (160 mg, 0.700 mmol) was reacted with methylvinylketone **314** (275 μ l, 3.30 mmol) for 2 hours to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 13: 7) to yield **434** (160 mg, 86 %) as an off white solid. M.p. 77 - 79 $^{\circ}$ C; R_f : 0.4 (light petroleum ether: ethyl acetate; 17: 3); $\nu_{\max}$ (CHCl₃)/cm⁻¹ 3209, 2941, 1665, 1624, 1477, 1170; δ_H (400 MHz, CDCl₃) 7.96 - 7.92 (2H, m, 2ArH), 7.71 - 7.50 (3H, m, 3ArH), 7.01 (1H, bs, NH), 6.77 (1H, dt, *J* 16.0, 7.0, CH=CHCO), 6.08 (1H, dt, *J* 16.0, 2.0, CH=CHCO), 4.04 (2H, t, *J* 6.5, OCH₂), 2.31 - 2.15 (5H, m + s, CH₃ + CHCH₂), 1.84 - 1.74 (2H, m, CH₂); δ_C (100 MHz, CDCl₃) 198.6 (C), 146.8 (CH), 137.2 (C), 133.9 (CH), 131.7 (CH), 129.2 (CH), 128.5 (CH), 76.4 (CH₂), 28.8 (CH₂), 27.0 (CH₃), 26.6 (CH₂); *m/z* (ES) 306 (M+Na⁺, 100 %), 284 (M+H⁺, 52); *m/z* (ES) found [M+Na]⁺ 306.0763. C₁₃H₁₇NNaO₄S⁺ requires 306.0770.

(R)-Benzyl 3-(2-oxopropyl)-1,2-oxazinan-2-carboxylate 442



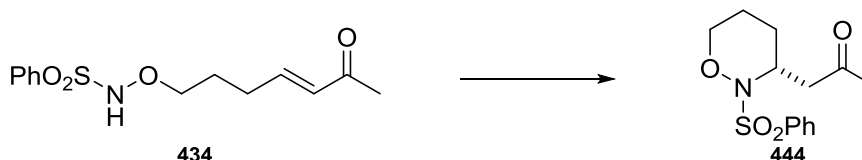
Following general procedure 8, (E)-benzyl (6-oxohept-4-en-1-yl)oxycarbamate **432** (13.9 mg, 50.0 μ mol) was stirred in 2-methyltetrahydrofuran (0.5 ml) at 20 $^{\circ}$ C for 22 hours to yield **442** (12.5 mg, 90 %) as a colourless oil. R_f : 0.2 (light petroleum ether: ethyl acetate; 3: 2); $[\alpha]_D^{23} +35.4$ (c 0.6 in CHCl₃); lit. $[\alpha]_D^{20} +43.1$ (c 1.2 in CHCl₃, 96 % ee);^[95] $\nu_{\max}$ (neat)/cm⁻¹ 2951, 1717, 1446, 1091; δ_H (400 MHz, CDCl₃) 7.43 - 7.28 (5H, m, 5ArH), 5.24 (1H, d, *J* 8.0, PhCH_AH_B), 5.18 (1H, d, *J* 8.0, PhCH_AH_B), 4.80 - 4.66 (1H, m, CHN), 4.09 - 3.98 (1H, m, CH_AH_B), 3.87 (1H, ddd, *J* 12.0, 12.0, 2.0, CH_AH_B), 2.99 (1H, dd, *J* 17.5, 8.0, COCH_AH_B), 2.82 (1H, dd, *J* 17.5, 8.0, COCH_AH_B), 2.15 (3H, s, CH₃), 2.08 - 1.81 (2H, m, CH₂), 1.70 - 1.49 (2H, m, CH₂); δ_C (100 MHz, CDCl₃) 206.2 (C), 155.0 (C), 136.1 (C), 128.6 (CH), 128.2 (CH), 128.1 (CH), 71.8 (CH₂), 67.7 (CH₂), 50.4 (CH), 43.7 (CH₂), 30.4 (CH₃), 25.3 (CH₂), 19.9 (CH₂); *m/z* (ES) 300 (M+Na⁺, 100 %), 278 (M+H⁺, 81); *m/z* (ES) found [M+Na]⁺ 300.1186. C₁₅H₁₉NNaO₄⁺ requires 300.1206; R_t HPLC Chiralcel OJ-H; mobile phase, hexane: 2-propanol (9: 1 v/v); flow rate, 1 ml/min; 20.6 min (97.8 %), 24.1 min (2.2 %) 96 % e.e. The ¹H NMR and ¹³C data is in agreement with those previously reported.^[95]

(R)-1-(2-Acetyl-1,2-oxazinan-3-yl)propan-2-one 443



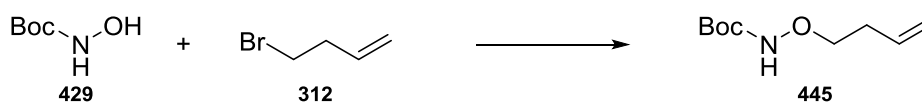
Following general procedure 8, (*E*)-*N*-((6-oxohept-4-en-1-yl)oxy)acetamide **433** (18.5 mg, 100 μ mol) was stirred in deuterated chloroform (1.0 ml) at 20 °C for 72 hours to yield **443** (14.0 mg, 77 %) as a colourless oil. R_f : 0.4 (ethyl acetate: methanol; 9: 1); $[\alpha]_D^{24} +28.5$ (c 0.4 in CHCl_3); $\nu_{\text{max}}(\text{CHCl}_3)/\text{cm}^{-1}$ 2954, 1714, 1652, 1036; δ_{H} (400 MHz, CDCl_3) 5.12 - 5.03 (1H, m, CHN), 4.15 - 4.07 (1H, m, CH_AH_B), 3.80 (1H, ddd, J 12.0, 12.0, 2.0, CH_AH_B), 2.88 (1H, dd, J 16.0, 7.0, COCH_AH_B), 2.80 (1H, dd, J 16.0, 5.0, COCH_AH_B), 2.18 (3H, s, CH_3), 2.08 (3H, s, CH_3), 2.07 - 1.97 (1H, m, CH), 1.93 - 1.81 (1H, m, CH), 1.76 - 1.68 (1H, m, CH), 1.62 - 1.53 (1H, m, CH); δ_{C} (100 MHz, CDCl_3) 206.2 (C), 169.4 (C), 72.9 (CH_2), 46.4 (CH), 43.7 (CH_2), 30.1 (CH_3), 25.3 (CH_2), 20.0 (CH_2); m/z (ES) 208 ($\text{M}+\text{Na}^+$, 100 %); m/z (ES) found $[\text{M}+\text{Na}]^+$ 208.0945. $\text{C}_9\text{H}_{15}\text{NNaO}_3^+$ requires 208.0944; R_t HPLC Chiralcel OJ-H; mobile phase, hexane: 2-propanol (49: 1 v/v); flow rate, 1 ml/min; 39.2 min (75.8 %), 44.8 min (24.2 %) 52 % e.e.

(R)-1-(2-(Phenylsulfonyl)-1,2-oxazinan-3-yl)propan-2-one 434



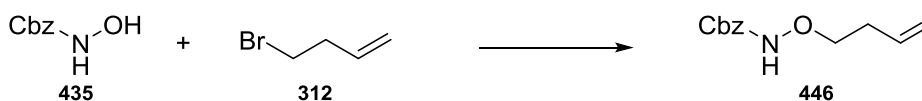
Following general procedure 8, (*E*)-*N*-((6-oxohept-4-en-1-yl)oxy)benzenesulfonamide **434** (14.1 mg, 50.0 μ mol) was stirred in 2-methyltetrahydrofuran (0.5 ml) at 20 °C for 7 hours to yield **444** (13.0 mg, 92 %) as a colourless oil. R_f : 0.4 (light petroleum ether: ethyl acetate; 3: 2); $[\alpha]_D^{23} +15.9$ (c 0.7 in CHCl_3); $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 2924, 1715, 1585, 1447, 1165; δ_{H} (400 MHz, CDCl_3) 7.91 (2H, dd, J 7.0, 2.0, 2ArH), 7.66 - 7.48 (3H, m, 3ArH), 4.66 - 4.59 (1H, m, CHN), 4.05 (1H, ddd, J 12.0, 12.0, 2.0, CH_AH_B), 3.96 - 3.89 (1H, m, CH_AH_B), 3.09 (1H, dd, J 17.5, 5.0, COCH_AH_B), 2.83 (1H, dd, J 17.5, 8.0, COCH_AH_B), 2.14 (3H, s, CH_3), 2.08 - 1.97 (1H, m, CH), 1.95 - 1.82 (1H, m, CH), 1.78 - 1.69 (1H, m, CH), 1.57 - 1.49 (1H, m, CH); δ_{C} (100 MHz, CDCl_3) 205.7 (C), 137.7 (C), 133.5 (CH), 128.9 (CH), 128.5 (CH), 71.6 (CH_2), 51.2 (CH), 43.3 (CH_2), 30.5 (CH_3), 26.8 (CH_2), 20.1 (CH_2); m/z (ES) 306 ($\text{M}+\text{Na}^+$, 100 %), 284 ($\text{M}+\text{H}^+$, 60); m/z (ES) found $[\text{M}+\text{Na}]^+$ 306.0763. $\text{C}_{13}\text{H}_{17}\text{NNaO}_4\text{S}^+$ requires 306.0770; R_t HPLC Chiralpak OD-H; mobile phase, hexane: 2-propanol (49: 1 v/v); flow rate, 1 ml/min; 25.7 min (0.9 %), 28.0 min (99.1 %) 98 % e.e.

tert*-Butyl-(but-3-en-1-yloxy)carbamate **445*



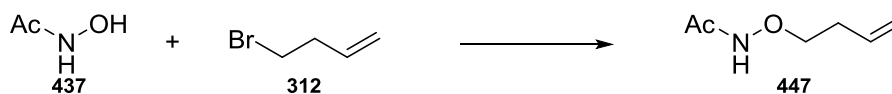
Following general procedure 5, 5-bromobut-1-ene **312** (350 μ l, 3.41 mmol) was reacted with *N*-Boc hydroxylamine **429** (400 mg, 2.96 mmol) and DBU (460 μ l, 3.11 mmol) to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 9: 1) to yield **445** (230 mg, 41 %) as a colourless oil. R_f : 0.3 (light petroleum ether: ethyl acetate; 9: 1); $\nu_{\max}$ (neat)/ cm^{-1} 3290, 2981, 1720, 1642, 1168; δ_{H} (400 MHz, CDCl_3) 7.12 (1H, bs, NH), 5.83 (1H, ddt, J 17.0, 10.5, 7.0, $\text{CH}_2=\text{CH}$), 5.17 - 5.05 (2H, m, $\text{CH}=\text{CH}_2$), 3.92 (2H, t, J 7.5, OCH_2), 2.15 (2H, dt, J 7.0, 7.0, CH_2), 1.49 (9H, s, $\text{C}(\text{CH}_3)_3$); δ_{C} (100 MHz, CDCl_3) 156.9 (C), 134.4 (CH), 116.9 (CH_2), 81.7 (C), 75.7 (CH_2), 32.6 (CH_2), 28.2 (CH_3)₃; m/z (ES) 210 ($\text{M}+\text{Na}^+$, 100 %); m/z (ES) found $[\text{M}+\text{Na}]^+$ 210.1106. $\text{C}_9\text{H}_{17}\text{NNaO}_3^+$ requires 210.1101. The ^1H NMR and ^{13}C data is in agreement with those previously reported.^[154]

Benzyl (but-3-en-1-yloxy)carbamate **446**



Following general procedure 5, 4-bromobut-1-ene **312** (350 μ l, 3.41 mmol) was reacted with *N*-Cbz hydroxylamine **435** (400 mg, 2.96 mmol) and DBU (460 μ l, 3.11 mmol) to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 4: 1) to yield **446** (240 mg, 37 %) as a colourless oil. R_f : 0.3 (light petroleum ether: ethyl acetate; 4: 1); $\nu_{\max}$ (neat)/ cm^{-1} 3276, 2943, 1723, 1642, 1455, 1113; δ_{H} (400 MHz, CDCl_3) 7.44 - 7.30 (6H, m, 5ArH + NH), 5.81 (1H, ddt, J 17.0, 10.5, 7.0, $\text{CH}_2=\text{CH}$), 5.19 (2H, s, PhCH_2), 5.17 - 5.05 (2H, m, $\text{CH}=\text{CH}_2$), 3.95 (2H, t, J 6.5, OCH_2), 2.42 (2H, dt, J 7.0, 7.0, CHCH_2); δ_{C} (100 MHz, CDCl_3) 157.5 (C), 135.6 (C), 134.2 (CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 117.0 (CH_2), 75.9 (CH_2), 67.5 (CH_2), 32.5 (CH_2); m/z (ES) 244 ($\text{M}+\text{Na}^+$, 100 %); m/z (ES) found $[\text{M}+\text{Na}]^+$ 244.0943. $\text{C}_{12}\text{H}_{15}\text{NNaO}_3^+$ requires 244.0944.

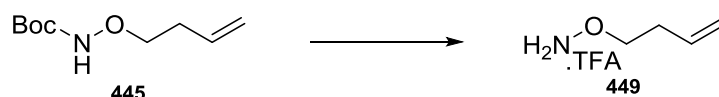
N*-(But-3-en-1-yloxy)acetamide **447*



Following general procedure 5, 4-bromobut-1-ene **312** (350 μ l, 3.41 mmol) was reacted with acetohydroxamic acid **437** (220 mg, 2.96 mmol) and DBU (460 μ l, 3.11 mmol) to

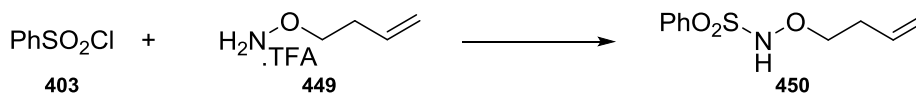
give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 1: 9) to yield **447** (153 mg, 40 %) as a colourless oil. R_f : 0.2 (light petroleum ether: ethyl acetate; 1: 9); $\nu_{\max}$ (neat)/ cm^{-1} 3194, 2981, 1666, 1087; δ_{H} (400 MHz, CDCl_3) (7: 3 mixture of rotamers A and B) 8.65 (0.7H, bs, NH rotamer A), 8.41 (0.3H, bs, NH rotamer B), 5.81 (1H, ddt, J 17.0, 10.5, 7.0, $\text{CH}_2=\text{CH}$), 5.21 - 4.98 (2H, m, $\text{CH}=\text{CH}_2$), 4.08 - 3.91 (2H, m, OCH_2), 2.42 (2H, dt, J 7.0, 7.0, CHCH_2), 2.12 (0.9H, s, CH_3 rotamer B), 1.91 (2.1H, s, CH_3 rotamer A); δ_{C} (100 MHz, CDCl_3 , mixture of rotamers A and B) 175.2 (C rotamer B), 168.2 (C rotamer A), 134.1 (CH rotamer A), 133.7 (CH rotamer B), 117.6 (CH_2 rotamer B), 117.1 (CH_2 rotamer A), 76.3 (CH_2 rotamer B), 75.6 (CH_2 rotamer A), 32.5 (CH_2 rotamer A), 29.7 (CH_2 rotamer B), 19.9 (CH_3 rotamer A), 19.1 (CH_3 rotamer B); m/z (ES) 152 ($\text{M}+\text{Na}^+$, 100 %), 130 ($\text{M}+\text{H}^+$, 45); m/z (ES) found $[\text{M}+\text{Na}]^+$ 152.0672. $\text{C}_6\text{H}_{11}\text{NNaO}_2^+$ requires 152.0682.

O-(Hex-5-en-1-yl)hydroxylamine trifluoroacetic acid salt **449**



tert-Butyl (but-3-en-1-yloxy)carbamate **445** (190 mg, 1.00 mmol) was dissolved in dichloromethane (10 ml) and trifluoroacetic acid (370 μl , 5.00 mmol) was added and stirred for 42 hours. This was concentrated under reduced pressure to yield **449** (190 mg, 94 %) as a crude yellow oil to be used directly in the next step. $\nu_{\max}$ (neat)/ cm^{-1} 3423, 1645, 1204; δ_{H} (500 MHz, d_4 -MeOD) 5.84 (1H, ddt, J 17.0, 10.5, 6.5, $\text{CH}=\text{CH}_2$), 5.23 - 5.09 (2H, m, $\text{CH}=\text{CH}_2$), 4.09 (2H, t, J 6.5, OCH_2), 2.11 (2H, dt, J 6.5, 6.5, CHCH_2); δ_{C} (125 MHz, d_4 -MeOD) 161.2 (C, q, J 35), 132.9 (CH), 116.8 (CH_2), 116.6 (C, q, J 290), 74.0 (CH_2), 31.7 (CH_2); m/z (ES) 87 (M^+ , 100 %); m/z (ES) found $[\text{M}]^+$ 87.0682. $\text{C}_4\text{H}_9\text{NO}^+$ requires 87.0684.

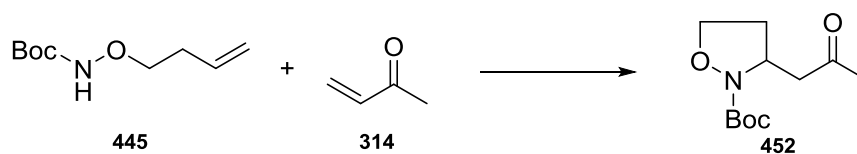
N-(But-3-en-yloxy)benzenesulfonamide **450**



Benzenesulfonyl chloride **403** (170 μl , 1.03 mmol) was added to a solution of O-(hex-5-en-1-yl)hydroxylamine trifluoroacetic acid salt **449** (190 mg, 940 μmol) and triethylamine (288 μl , 2.06 mmol) in dichloromethane (7.5 ml) at 0 $^{\circ}\text{C}$. The solution was allowed to warm to room temperature then stirred for 4 hours. This solution was concentrated under reduced pressure to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 17: 3) to yield **450** (103 mg, 50 %) as a colourless oil. R_f : 0.2 (light petroleum ether: ethyl acetate; 17: 3); $\nu_{\max}$ (neat)/ cm^{-1} 3221, 2967, 1642, 1448, 1332, 1170; δ_{H} (400 MHz, CDCl_3) 7.97 - 7.91 (2H, m, 2ArH), 7.70 -

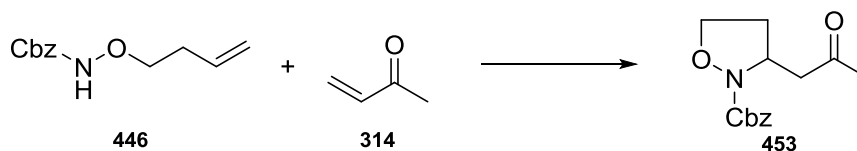
7.53 (3H, m, 3ArH), 6.96 (1H, bs, NH), 5.75 (1H, ddt, J 17.0, 10.5, 7.0, $\text{CH}_2=\text{CH}$), 5.14 - 5.03 (2H, m, $\text{CH}=\text{CH}_2$), 4.07 (2H, t, J 7.0, OCH_2), 2.38 (2H, dt, J 7.0, 7.0, CHCH_2); δ_{C} (100 MHz, CDCl_3) 136.6 (C), 134.2 (CH), 133.8 (CH), 129.1 (CH), 128.6 (CH), 117.1 (CH_2), 76.4 (CH_2), 32.6 (CH_2); m/z (ES) 561 ($2\text{M}+\text{Na}^+$, 34 %), 250 ($\text{M}+\text{Na}^+$, 100), 228 ($\text{M}+\text{H}^+$, 16); m/z (ES) found $[\text{M}+\text{Na}]^+$ 250.0507. $\text{C}_{10}\text{H}_{13}\text{NNaO}_3\text{S}^+$ requires 250.0508.

tert-Butyl-3-(2-oxopropyl)isoxazolidine-2-carboxylate **452**



Following general procedure 7, *tert*-butyl (but-3-en-1-yloxy)carbamate **445** (220 mg, 1.15 mmol) was reacted with methylvinylketone **314** (480 μl , 5.75 mmol) for 2 hours to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 3: 2) to yield **452** (100 mg, 37 %) as a colourless oil. R_f : 0.4 (light petroleum ether: ethyl acetate; 3: 2); ν_{max} (neat)/ cm^{-1} 2981, 1714, 1165; δ_{H} (400 MHz, CDCl_3) 4.55 - 4.47 (1H, m, CHN), 4.04 (1H, ddd, J 10.0, 10.0, 2.0, $\text{CH}_\text{A}\text{H}_\text{B}$), 3.79 - 3.71 (1H, m, $\text{CH}_\text{A}\text{H}_\text{B}$), 2.98 (1H, dd, J 17.5, 6.0, $\text{COCH}_\text{A}\text{H}_\text{B}$), 2.61 (1H, dd, J 17.5, 8.5, $\text{COCH}_\text{A}\text{H}_\text{B}$), 2.60 - 2.50 (1H, m, CH), 2.18 (3H, s, COCH_3), 1.95 - 1.84 (1H, m, CH), 1.49 (9H, s, $(\text{CH}_3)_3$); δ_{C} (100 MHz, CDCl_3) 206.8 (C), 157.4 (C), 82.5 (C), 68.8 (CH_2), 55.6 (CH), 49.2 (CH_2), 34.9 (CH_2), 30.5 (CH_3), 28.2 ($(\text{CH}_3)_3$); m/z (ES) 252 ($\text{M}+\text{Na}^+$, 100 %); m/z (ES) found $[\text{M}+\text{Na}]^+$ 252.1211. $\text{C}_{11}\text{H}_{19}\text{NNaO}_4^+$ requires 252.1206.

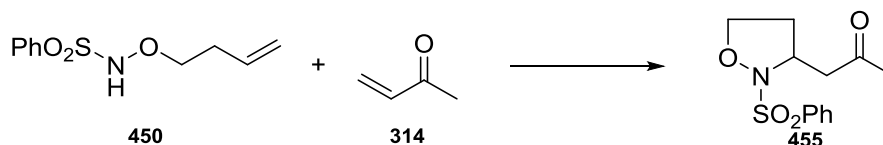
Benzyl 3-(2-oxopropyl)isoxazolidine-2-carboxylate **453**



Following general procedure 7, benzyl (but-3-en-1-yloxy)carbamate **446** (221 mg, 1.00 mmol) was reacted with methylvinylketone **314** (415 μl , 5.00 mmol) for 2 hours to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 3: 2) to yield **453** (149 mg, 57 %) as a colourless oil. R_f : 0.4 (light petroleum ether: ethyl acetate; 3: 2); ν_{max} (CHCl_3)/ cm^{-1} 2957, 1714, 1587, 1498, 1071; δ_{H} (500 MHz, CDCl_3) 7.42 - 7.29 (5H, m, 5ArH), 5.19 (2H, s, PhCH_2), 4.60 - 4.53 (1H, m, CHN), 4.06 (1H, ddd, J 10.0, 10.0, 2.0, $\text{CH}_\text{A}\text{H}_\text{B}$), 3.79 - 3.71 (1H, m, $\text{CH}_\text{A}\text{H}_\text{B}$), 2.99 (1H, dd, J 17.0, 5.0, $\text{COCH}_\text{A}\text{H}_\text{B}$), 2.62 (1H, dd, J 17.0, 9.0, $\text{COCH}_\text{A}\text{H}_\text{B}$), 2.60 - 2.52 (1H, m, CH), 2.14 (3H, s, CH_3), 1.95 - 1.84 (1H, m, CH); δ_{C} (100 MHz, CDCl_3) 206.4 (C), 157.8 (C), 135.7 (C), 128.6 (CH), 128.4 (CH), 128.2 (CH), 69.3 (CH_2), 68.0 (CH_2), 55.6 (CH),

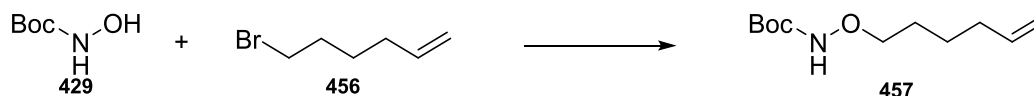
49.0 (CH₂), 34.9 (CH₂), 30.4 (CH₃); *m/z* (ES) 544 (2M+Na⁺, 73 %), 286 (M+Na⁺, 100), 264 (M+H⁺, 25); *m/z* (ES) found [M+Na]⁺ 286.1045. C₁₄H₁₇NNaO₄⁺ requires 286.1050.

1-(2-(Phenylsulfonyl)isoxazolidin-3-yl)propan-2-one **455**



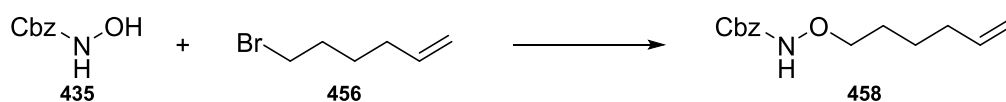
Following general procedure 7, *N*-(but-3-en-yloxy)benzenesulfonamide **450** (90.0 mg, 410 μmol) was reacted with methylvinylketone **314** (170 μl, 2.05 mmol) for 1 hour to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 3: 2) to yield **455** (75.0 mg, 70 %) as a colourless oil. *R_f*: 0.4 (light petroleum ether: ethyl acetate; 3: 2); *v*_{max}(neat)/cm⁻¹ 2967, 1714, 1448, 1415, 1168; δ_H (500 MHz, CDCl₃) 8.00 - 7.94 (2H, m, 2ArH), 7.71 - 7.65 (1H, m, ArH), 7.60 - 7.54 (2H, m, 2ArH), 4.57 - 4.49 (1H, m, CHN), 3.95 (1H, ddd, *J* 10.0, 10.0, 2.0, CH_AH_B), 3.87 - 3.80 (1H, m, CH_AH_B), 3.10 (1H, dd, *J* 17.5, 4.5, COCH_AH_B), 2.62 (1H, dd, *J* 17.5, 9.0, COCH_AH_B), 2.57 - 2.50 (1H, m, CH), 2.20 (3H, s, CH₃), 1.95 - 1.88 (1H, m, CH); δ_C (125 MHz, CDCl₃) 205.8 (C), 135.5 (C), 134.0 (CH), 129.3 (CH), 69.7 (CH₂), 56.0 (CH), 49.1 (CH₂), 35.2 (CH₂), 30.4 (CH₃); *m/z* (ES) 292 (M+Na⁺, 56 %), 270 (M+H⁺, 100); *m/z* (ES) found [M+H]⁺ 270.0789. C₁₂H₁₆NO₄S⁺ requires 270.0795.

tert-Butyl (hex-5-en-1-yloxy)carbamate **457**



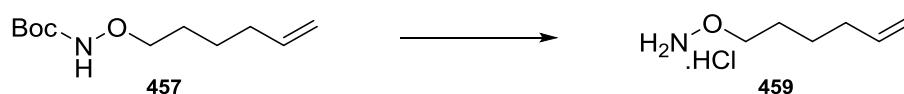
Following general procedure 5, 6-bromohex-1-ene **456** (460 μl, 3.41 mmol) was reacted with *N*-Boc hydroxylamine **429** (400 mg, 2.96 mmol) and DBU (460 μl, 3.11 mmol) to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 9: 1) to yield **457** (250 mg, 42 %) as a colourless oil. *R_f*: 0.4 (light petroleum ether: ethyl acetate; 9: 1); *v*_{max}(neat)/cm⁻¹ 3293, 2979, 1720, 1641, 1167; δ_H (400 MHz, CDCl₃) 7.14 (1H, bs, NH), 5.79 (1H, ddt, *J* 17.0, 10.5, 7.0, CH₂=CH), 5.05 - 4.92 (2H, m, CH=CH₂), 3.85 (2H, t, *J* 6.5, OCH₂), 2.08 (2H, dt, *J* 8.0, 8.0, CHCH₂), 1.76 - 1.61 (2H, m, CH₂), 1.53 - 1.40 (11H, s + m, CH₂ + (CH₃)₃); δ_C (100 MHz, CDCl₃) 158.9 (C), 138.5 (CH), 114.7 (CH₂), 81.6 (C), 78.6 (CH₂), 33.5 (CH₂), 28.2 (CH₂), 27.6 (CH₃)₃, 25.2 (CH₂); *m/z* (ES) 238 (M+Na⁺, 100 %); *m/z* (ES) found [M+Na]⁺ 238.1412. C₁₁H₂₁NNaO₃⁺ requires 238.1414.

Benzyl (hex-en-1-yloxy)carbamate **458**



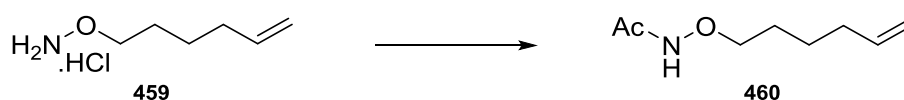
Following general procedure 5, 6-bromohex-1-ene **456** (460 μ l, 3.41 mmol) was reacted with *N*-Cbz hydroxylamine **435** (500 mg, 2.96 mmol) and DBU (460 μ l, 3.11 mmol) to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 17: 3) to yield **458** (360 mg, 49 %) as a colourless oil. R_f : 0.2 (light petroleum ether: ethyl acetate; 17: 3); $\nu_{\max}$ (neat)/ cm^{-1} 3277, 2938, 1724, 1640, 1456, 1114; δ_{H} (400 MHz, CDCl_3) 7.42 - 7.30 (6H, m, 5ArH + NH), 5.79 (1H, ddt, J 17.0, 10.5, 7.0, $\text{CH}_2=\text{CH}$), 5.19 (2H, s, PhCH_2), 5.05 - 4.92 (2H, m, $\text{CH}=\text{CH}_2$), 3.89 (2H, t, J 6.5, OCH_2), 2.08 (2H, dt, J 7.0, 7.0, CHCH_2), 1.70 - 1.60 (2H, m, CH_2), 1.53 - 1.42 (2H, m, CH_2); δ_{C} (100 MHz, CDCl_3) 157.5 (C), 138.5 (CH), 135.7 (C), 128.6 (CH), 128.4 (CH), 128.3 (CH), 114.8 (CH_2), 77.9 (CH_2), 67.5 (CH_2), 33.4 (CH_2), 27.4 (CH_2), 25.1 (CH_2). m/z (ES) 521 ($2\text{M}+\text{Na}^+$, 66 %), 272 ($\text{M}+\text{Na}^+$, 100), 250 ($\text{M}+\text{H}^+$, 17); m/z (ES) found $[\text{M}+\text{Na}]^+$ 272.1254. $\text{C}_{14}\text{H}_{19}\text{NNaO}_3^+$ requires 272.1257.

O-(Hex-5-en-1-yl)hydroxylamine hydrochloride **459**



tert-Butyl (hex-5-en-1-yloxy)carbamate **457** (780 mg, 3.80 mmol) was dissolved in 1M hydrochloric acid in diethyl ether (15.2 ml, 15.2 mmol) and stirred for 192 hours. The resulting solid was collected by filtration to yield **459** (376 mg, 66 %) as a colourless solid. M.p. 128 - 130 $^{\circ}\text{C}$; $\nu_{\max}$ (CHCl_3)/ cm^{-1} 3418, 2959, 1641, 1150; δ_{H} (400 MHz, $\text{d}_4\text{-MeOD}$) 5.82 (1H, ddt, J 17.0, 10.5, 7.0, $\text{CH}=\text{CH}_2$), 5.07 - 4.94 (2H, m, $\text{CH}=\text{CH}_2$), 4.04 (2H, t, J 6.5, OCH_2), 2.11 (2H, dt, J 7.0, 7.0, CHCH_2), 1.75 - 1.65 (2H, m, CH_2), 1.56 - 1.45 (2H, m, CH_2); δ_{C} (100 MHz, $\text{d}_4\text{-MeOD}$) 137.9 (CH), 114.1 (CH_2), 74.9 (CH_2), 32.9 (CH_2), 26.8 (CH_2), 24.6 (CH_2); m/z (ES) 116 ($\text{M}+\text{H}^+$, 100 %); m/z (ES) found $[\text{M}+\text{H}]^+$ 116.1030. $\text{C}_6\text{H}_{14}\text{NO}^+$ requires 116.1070.

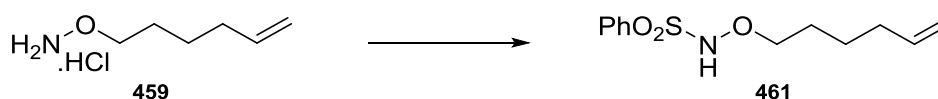
N-(Hex-5-en-1-yloxy)acetamide **460**



O-(Hex-5-en-1-yl)hydroxylamine hydrochloride **459** (170 mg, 1.20 mmol) was dissolved in dichloromethane (7.5 ml) and triethylamine (540 μ l, 3.00 mmol) was added. Acetic anhydride **289** (120 μ l, 1.30 mmol) was added at 0 $^{\circ}\text{C}$ and allowed to warm to room

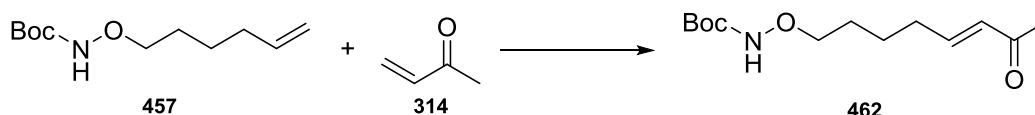
temperature then stirred for 2 hours. This was concentrated under reduced pressure and purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 9: 1) to yield **460** (150 mg, 85 %) as a colourless oil. R_f : 0.4 (light petroleum ether: ethyl acetate; 9: 1); $\nu_{\max}(\text{CHCl}_3)/\text{cm}^{-1}$ 3191, 2941, 1666, 1186; δ_{H} (400 MHz, CHCl_3) (7: 3 ratio of rotamers A and B) 8.79 (0.7H, bs, NH rotamer A), 8.58 (0.3H, bs, NH rotamer B), 5.78 (1H, ddt, J 17.0, 10.0, 6.5, $\text{CH}=\text{CH}_2$), 5.07 - 4.87 (2H, bm, $\text{CH}=\text{CH}_2$), 3.95 - 3.48 (2H, m, OCH_2), 2.08 (2H, dt, J 6.5, 6.5, CHCH_2), 2.07 (0.9H, bs, CH_3 rotamer B), 1.90 (2.1H, bs, CH_3 rotamer A), 1.71 - 1.59 (2H, m, CH_2), 1.53 - 1.41 (2H, m, CH_2); δ_{C} (100 MHz, CHCl_3) 168.0 (C), 138.4 (CH), 114.8 (CH_2), 76.7 (CH_2), 33.4 (CH_2), 27.3 (CH_2), 25.1 (CH_2), 19.9 (CH_3); m/z (ES) 180 ($\text{M}+\text{Na}^+$, 100 %), 158 ($\text{M}+\text{H}^+$, 37); m/z (ES) found $[\text{M}+\text{Na}]^+$ 180.1000. $\text{C}_8\text{H}_{15}\text{NNaO}_2^+$ requires 180.0995.

N*-(Hex-5-en-1-yloxy)benzenesulfonamide **461*



O-(Hex-5-en-1-yl)hydroxylamine hydrochloride **459** (170 mg, 1.20 mmol) was dissolved in dichloromethane (7.5 ml) and triethylamine (540 μl , 3.00 mmol) was added. Benzenesulfonyl chloride **403** (160 μl , 1.30 mmol) was added at 0 °C and allowed to warm to room temperature then stirred for 2 hours. This was concentrated under reduced pressure and purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 4: 1) to yield **461** (160 mg, 53 %) as a colourless oil. R_f : 0.4 (light petroleum ether: ethyl acetate; 4: 1); $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 3223, 2940, 1640, 1586, 1478, 1170; δ_{H} (400 MHz, CHCl_3) 7.94 (2H, dd, J 7.5, 2.0, 2ArH), 7.70 - 7.64 (1H, m, ArH), 7.60 - 7.53 (2H, m, 2ArH), 7.00 (1H, bs, NH), 5.78 (1H, ddt, J 17.0, 10.5, 6.5, $\text{CH}=\text{CH}_2$), 5.04 - 4.92 (2H, m, $\text{CH}=\text{CH}_2$), 4.00 (2H, t, J 6.5, OCH_2), 2.05 (2H, dt, J 6.5, 6.5, CHCH_2), 1.65 - 1.55 (2H, m, CH_2), 1.46 - 1.36 (2H, m, CH_2); δ_{C} (100 MHz, CHCl_3) 138.4 (CH), 136.7 (C), 133.8 (CH), 129.1 (CH), 128.5 (CH), 114.8 (CH_2), 77.4 (CH_2), 33.3 (CH_2), 27.4 (CH_2), 25.0 (CH_2); m/z (ES) 278 ($\text{M}+\text{Na}^+$, 100 %), 256 ($\text{M}+\text{H}^+$, 23); m/z (ES) found $[\text{M}+\text{Na}]^+$ 278.0814. $\text{C}_{12}\text{H}_{17}\text{NNaO}_3\text{S}^+$ requires 278.0821.

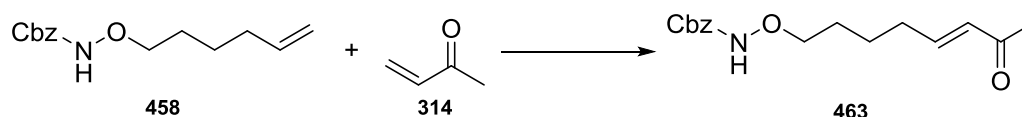
tert*-Butyl (*E*)-((7-oxooct-5-en-1-yl)oxy)carbamate **462*



Following general procedure 7, *tert*-butyl (hex-5-en-1-yloxy)carbamate **457** (220 mg, 1.00 mmol) was reacted with methylvinylketone **314** (420 μl , 5.00 mmol) for 2 hours to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 7: 3) to yield **462** (220 mg, 81 %) as a yellow oil. R_f : 0.3

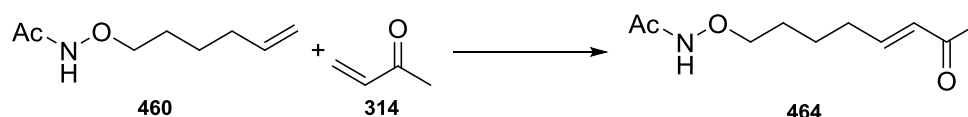
(light petroleum ether: ethyl acetate; 7: 3); $\nu_{\max}$ (neat)/ cm^{-1} 3278, 2935, 1720, 1673, 1626, 1169; δ_{H} (400 MHz, CDCl_3) 7.15 (1H, bs, NH), 6.79 (1H, dt, J 16.0, 7.5, $\text{CH}=\text{CHCO}$), 6.08 (1H, dt, J 16.0, 2.0, $\text{CH}=\text{CHCO}$), 3.87 (2H, t, J 7.0, OCH_2), 2.27 (2H, dt, J 7.5, 7.5, CHCH_2), 2.24 (3H, s, COCH_3), 1.71 - 1.55 (4H, m, 2CH_2), 1.48 (9H, s, $\text{C}(\text{CH}_3)_3$); δ_{C} (100 MHz, CDCl_3) 198.6 (C), 156.9 (C), 147.8 (CH), 131.6 (CH), 81.7 (C), 76.3 (CH_2), 32.1 (CH_2), 28.2 ($\text{C}(\text{CH}_3)_3$), 27.6 (CH_2), 26.9 (CH_3), 24.5 (CH_3); m/z (ES) 537 ($2\text{M}+\text{Na}^+$, 21 %), 280 ($\text{M}+\text{Na}^+$, 100); m/z (ES) found $[\text{M}+\text{Na}]^+$ 280.1519. $\text{C}_{13}\text{H}_{23}\text{NNaO}_4^+$ requires 280.1519.

Benzyl (*E*)-((7-oxooct-5-en-1-yl)oxy)carbamate **463**



Following general procedure 7, benzyl (hex-5-en-1-yl)oxy carbamate **458** (249 mg, 1.00 mmol) was reacted with methylvinylketone **314** (415 μl , 5.00 mmol) for 1 hour to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 3: 2) to yield **463** (265 mg, 91 %) as a yellow oil. R_f : 0.4 (light petroleum ether: ethyl acetate; 3: 2); $\nu_{\max}$ (neat)/ cm^{-1} 3270, 2944, 1728, 1671, 1625, 1498, 1114; δ_{H} (400 MHz, CDCl_3) 7.48 (1H, bs, NH), 7.40 - 7.29 (5H, m, 5ArH), 6.77 (1H, dt, J 16.0, 7.0, $\text{CH}=\text{CHCO}$), 6.07 (1H, dt, J 16.0, 2.0, $\text{CH}=\text{CHCO}$), 5.18 (2H, s, PhCH_2), 3.89 (2H, t, J 6.0, OCH_2), 2.25 (2H, dt, J 7.0, 7.0, CHCH_2), 2.24 (3H, s, CH_3), 1.73 - 1.52 (4H, m, 2CH_2); δ_{C} (100 MHz, CDCl_3) 198.7 (C), 157.5 (C), 147.7 (CH), 135.6 (C), 131.6 (CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 76.5 (CH_2), 67.5 (CH_2), 30.0 (CH_2), 27.5 (CH_2), 26.9 (CH_3), 24.5 (CH_2); m/z (ES) 605 ($2\text{M}+\text{Na}^+$, 27 %), 314 ($\text{M}+\text{Na}^+$, 100), 292 ($\text{M}+\text{H}^+$, 38); m/z (ES) found $[\text{M}+\text{Na}]^+$ 314.1355. $\text{C}_{16}\text{H}_{21}\text{NNaO}_4^+$ requires 314.1363.

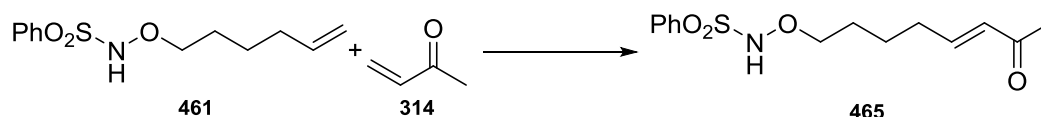
(*E*)-*N*-((7-Oxo-oct-5-en-1-yl)oxy)acetamide **464**



Following general procedure 7, *N*-(hex-5-en-1-yl)oxy acetamide **460** (140 mg, 900 μmol) was reacted with methylvinylketone **314** (380 μl , 4.50 mmol) for 1 hour to give the crude product. This was purified by flash chromatography on silica gel (ethyl acetate) to yield **464** (110 mg, 61 %) as a colourless oil. R_f : 0.2 (ethyl acetate); $\nu_{\max}$ (neat)/ cm^{-1} 3481, 2942, 1670, 1173; δ_{H} (400 MHz, CDCl_3) (7: 3 ratio of rotamers A and B) 8.29 (0.7H, bs, NH rotamer A), 8.14 (0.3H, bs, NH rotamer B), 6.79 (1H, dt, J 16.0, 7.5 $\text{CH}=\text{CHCO}$), 6.09 (1H, dt, J 16.0, 2.0 $\text{CH}=\text{CHCO}$), 3.91 (2H, m, OCH_2), 2.28 (2H, dt, J 7.5, 7.5, CHCH_2), 2.25 (3H, s, COCH_3), 2.10 (0.9H, s, NCOCH_3 rotamer B), 1.91 (2.1H, s, NCOCH_3 rotamer A), 1.72 - 1.55 (4H, m, 2CH_2); δ_{C} (100 MHz, CDCl_3) 198.8 (C), 167.8 (C), 147.8 (CH),

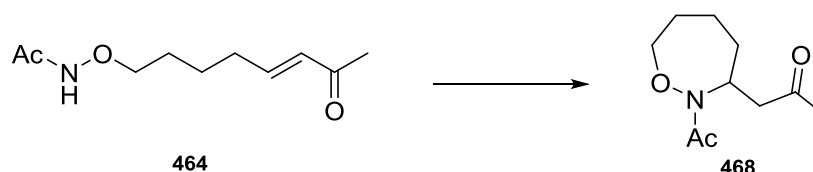
131.6 (CH), 76.7 (CH₂), 32.0 (CH₂), 27.5 (CH₃), 27.0 (CH₃), 24.4 (CH₂), 19.6 (CH₃); *m/z* (ES) 222 (M+Na⁺, 100 %), 200 (M+H⁺, 40); *m/z* (ES) found [M+Na]⁺ 222.1103. C₁₀H₁₇NNaO₃⁺ requires 222.1101.

(*E*)-*N*-((7-Oxo-oct-5-en-1-yl)oxy)benzenesulfonamide **465**



Following general procedure 7, *N*-(hex-5-en-1-yloxy)benzenesulfonamide **461** (140 mg, 560 μmol) was reacted with methylvinylketone **314** (230 μl, 2.80 mmol) for 1 hour to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 3: 2) to yield **465** (140 mg, 87 %) as a colourless solid. M.p. 84 - 86 °C; *R_f* : 0.3 (light petroleum ether: ethyl acetate; 3: 2); *v*_{max} (CHCl₃)/cm⁻¹ 3209, 2943, 1667, 1624, 1448, 1170; δ_H (400 MHz, CDCl₃) 7.95 - 7.90 (2H, m, 2ArH), 7.69 - 7.63 (1H, m, ArH), 7.59 - 7.53 (2H, m, 2ArH), 7.20 (1H, bs, NH), 6.77 (1H, dt, *J* 16.0, 7.5 CH=CHCO), 6.07 (1H, dt, *J* 16.0, 2.0 CH=CHCO), 4.01 (2H, dt, *J* 6.5, 6.5, OCH₂), 2.24 (3H, s, CH₃), 2.23 (2H, dt, *J* 7.5, 7.5, CHCH₂), 1.68 - 1.45 (4H, m, 2CH₂); δ_C (100 MHz, CDCl₃) 198.8 (C), 147.9 (CH), 136.7 (C), 133.8 (CH), 131.5 (CH), 129.1 (CH), 128.5 (CH), 77.1 (CH₂), 31.9 (CH₂), 27.5 (CH₂), 27.0 (CH₃), 24.3 (CH₂); *m/z* (ES) 320 (M+Na⁺, 100 %), 298 (M+H⁺, 56); *m/z* (ES) found [M+Na]⁺ 320.0910. C₁₄H₁₉NNaO₄S⁺ requires 320.0927.

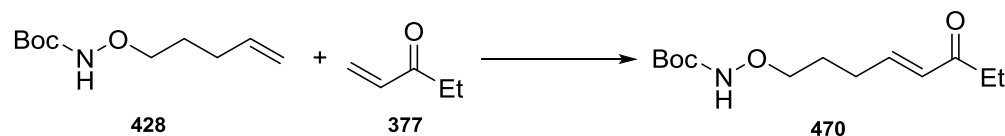
(+)-1-(2-Acetyl-1,2-oxazepan-3-yl)propan-2-one **468**



Following general procedure 8, ((*E*)-*N*-((7-oxo-oct-5-en-1-yl)oxy)acetamide **464** (20.0 mg, 100 μmol) was stirred in 2-methyltetrahydrofuran (1.0 ml) at 20 °C for 72 hours to give the crude product. This was purified by flash chromatography on silica gel (ethyl acetate) to yield **468** (10.0 mg, 50 %) as a colourless oil. *R_f* : 0.4 (ethyl acetate); [α]_D²⁴ +81.9 (c 0.5 in CHCl₃); *v*_{max} (neat)/cm⁻¹ 2933, 1713, 1657, 1163; δ_H (400 MHz, CDCl₃) 4.83 - 4.73 (1H, m, CHN), 4.23 - 4.14 (1H, m, CH_AH_B), 3.76 - 3.69 (1H, m, CH_AH_B), 2.78 (1H, dd, *J* 16.0, 6.0 COCH_AH_B), 2.56 (1H, dd, *J* 16.0, 7.5 COCH_AH_B), 2.15 (3H, s, CH₃), 2.14 (3H, s, CH₃), 1.90 - 1.42 (6H, m, 3CH₂); δ_C (125 MHz, CDCl₃) 206.7 (C), 172.3 (C), 77.3 (CH₂), 53.5 (CH), 47.0 (CH₂), 32.2 (CH₂), 30.5 (CH₂), 30.3 (CH₃), 23.6 (CH₂), 20.5 (CH₃); *m/z* (ES) 222 (M+Na⁺, 100 %), 200 (M+H⁺, 35); *m/z* (ES) found [M+Na]⁺ 222.1105. C₁₀H₁₇NNaO₃⁺ requires 222.1101; *R_t* HPLC: Chiralcel OD-H; mobile phase, hexane: 2-

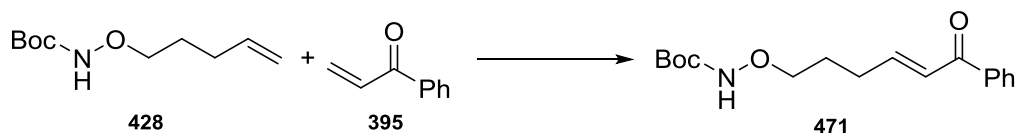
propanol (19: 1 v/v); flow rate, 1.0 ml/min; 14.3 min (16.4 %), 16.4 min (83.6 %) 67 % e.e.

tert*-Butyl (*E*)-((6-oxooct-4-en-1-yl)oxy)carbamate **470*



Following general procedure 7, *tert*-butyl-(pent-4-en-1-yl)oxycarbamate **428** (175 mg, 920 μ mol) was reacted with ethylvinylketone **377** (455 μ l, 4.58 mmol) for 1 hour to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 3: 1) to yield **470** (220 mg, 93 %) as a yellow oil. R_f : 0.3 (light petroleum ether: ethyl acetate; 3: 1); $\nu_{\max}$ (CHCl₃)/cm⁻¹ 3300, 2978, 1698, 1670, 1630, 1168; δ_H (400 MHz, C₆D₆) 6.98 (1H, bs, NH), 6.59 (1H, dt, *J* 16.0, 6.5, CH=CHCO), 5.96 (1H, dt, *J* 16.0, 2.0, CH=CHCO), 3.62 (2H, dt, *J* 6.5, 6.5, OCH₂), 2.16 (2H, q, *J* 8.0, CH₂CH₃), 1.98 (2H, dt, *J* 6.5, 6.5, CHCH₂), 1.48 - 1.38 (2H, m, CH₂), 1.36 (9H, s, C(CH₃)₃), 1.02 (3H, t, *J* 8.0, CH₂CH₃); δ_C (100 MHz, C₆D₆) 199.0 (C), 156.8 (C), 144.9 (CH), 130.5 (CH), 80.5 (C), 75.2 (CH₂), 33.1 (CH₂), 28.7 (CH₂), 28.0 (C(CH₃)₃), 26.6 (CH₂), 8.0 (CH₃); *m/z* (ES) 280 (M+Na⁺, 100 %); *m/z* (ES) found [M+Na]⁺ 280.1514. C₁₃H₂₃NNaO₄⁺ requires 280.1519.

tert*-Butyl (*E*)-((6-oxo-6-phenylhex-4-en-1-yl)oxy)carbamate **471*



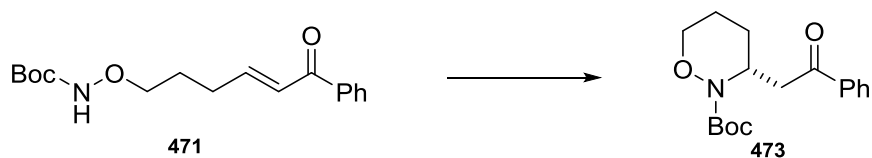
Following general procedure 7, *tert*-butyl (pent-4-en-1-yl)oxycarbamate **428** (200 mg, 1.00 mmol) was reacted with phenylvinylketone **395** (270 mg, 2.00 mmol) for 2 hours to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 3: 1) to yield **471** (200 mg, 65 %) as a light yellow oil. R_f : 0.3 (light petroleum ether: ethyl acetate; 3: 1); $\nu_{\max}$ (neat)/cm⁻¹ 3301, 2932, 1719, 1669, 1620, 1578, 1167; δ_H (400 MHz, CDCl₃) 7.96 (2H, dd, *J* 7.0, 2.0, 2ArH), 7.61 - 7.46 (3H, m, 3ArH), 7.20 (1H, bs, NH), 7.08 (1H, dt, *J* 16.0, 7.0, CH=CHCO), 6.96 (1H, dt, *J* 16.0, 2.0, CH=CHCO), 3.94 (2H, t, *J* 7.0, OCH₂), 2.49 (2H, dt, *J* 7.0, 7.0, CHCH₂), 1.94 - 1.84 (2H, m, CH₂), 1.51 (9H, s, C(CH₃)₃); δ_C (100 MHz, CDCl₃) 190.8 (C), 157.0 (C), 148.5 (CH), 137.9 (C), 132.7 (CH), 128.6 (CH), 128.3 (CH), 126.5 (CH), 81.8 (C), 75.7 (CH₂), 29.2 (CH₂), 28.2 (CH₃), 26.7 (CH₂); *m/z* (ES) 328 (M+Na⁺, 100 %); *m/z* (ES) found [M+Na]⁺ 328.1503. C₁₇H₂₃NNaO₄⁺ requires 328.1519.

(R)-tert-Butyl 3-(2-oxobutyl)-1,2-oxazinane-2-carboxylate 472

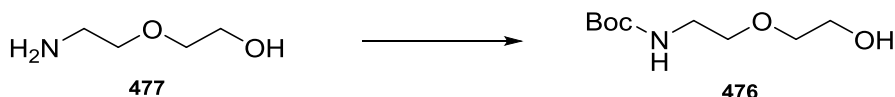


Following general procedure 8, *tert*-butyl (E)-((6-oxooct-4-en-1-yl)oxy)carbamate **470** (25.7 mg, 100 μ mol) was stirred in 2-methyltetrahydrofuran (1.0 ml) at 20 °C for 22 hours to yield **472** (25.1 mg, 98 %) as a colourless oil. R_f : 0.4 (light petroleum ether: ethyl acetate; 3: 1); $[\alpha]_D^{23} +24.0$ (c 0.8 in CHCl_3); $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 2977, 1716, 1168; δ_{H} (400 MHz, CDCl_3) 4.69 - 4.61 (1H, m, CHN), 4.04 - 3.96 (1H, m, CH_AH_B), 3.86 (1H, ddd, J 12.0, 12.0, 4.0, CH_AH_B), 2.96 (1H, dd, J 16.0, 4.0, COCH_AH_B), 2.76 (1H, dd, J 16.0, 8.0, COCH_AH_B), 2.46 (2H, m, CH_2CH_3), 2.06 - 1.92 (1H, m, CH), 1.91 - 1.79 (1H, m, CH), 1.67 - 1.46 (2H, m, CH_2), 1.49 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.04 (3H, t, J 8.0, CH_2CH_3); δ_{C} (100 MHz, CDCl_3) 209.2 (C), 154.4 (C), 81.5 (C), 71.2 (CH_2), 50.5 (CH), 42.4 (CH_2), 36.6 (CH_2), 28.3 ($(\text{CH}_3)_3$), 25.3 (CH_2), 20.0 (CH_2), 7.7 (CH_3); m/z (ES) 280 ($\text{M}+\text{Na}^+$, 100 %), 258 ($\text{M}+\text{Na}^+$, 13); m/z (ES) found $[\text{M}+\text{Na}]^+$ 280.1515. $\text{C}_{13}\text{H}_{23}\text{NNaO}_4^+$ requires 280.1519; R_t HPLC Chiralpak AD-H; mobile phase, hexane: 2-propanol (9: 1 v/v); flow rate, 1 ml/min; 6.2 min (99.2 %), 6.7 min (0.8 %) 98 % e.e.

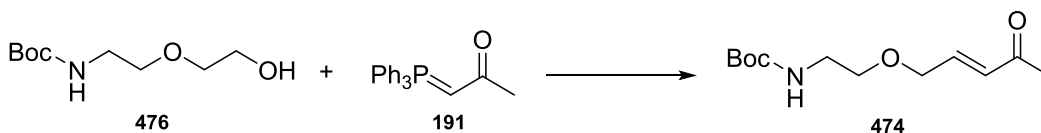
(R)-1-(2-(Boc)-1,2-oxazinan-3-yl)propan-2-one 473



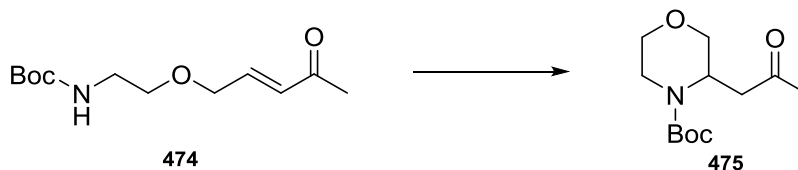
Following general procedure 8, *tert*-butyl (E)-((6-oxo-6-phenylhex-4-en-1-yl)oxy)carbamate **471** (15.3 mg, 50.0 μ mol) was stirred in 2-methyltetrahydrofuran (0.5 ml) at 20 °C for 192 hours to yield **473** (12.5 mg, 81 %) as a colourless oil. R_f : 0.3 (light petroleum ether: ethyl acetate; 3: 1); $[\alpha]_D^{23} +14.2$ (c 0.9 in CHCl_3); $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 2867, 1693, 1597, 1449, 1088; δ_{H} (400 MHz, CDCl_3) 7.99 (2H, dd, J 7.0, 2.0, 2ArH), 7.61 - 7.41 (3H, m, 3ArH), 4.87 - 4.78 (1H, m, CHN), 4.11 - 4.02 (1H, m, CH_AH_B), 3.92 (1H, ddd, J 12.0, 12.0, 2.0, CH_AH_B), 3.48 (1H, dd, J 16.5, 7.0, COCH_AH_B), 3.39 (1H, dd, J 16.5, 9.5, COCH_AH_B), 2.13 - 1.84 (2H, m, CH_2), 1.63 - 1.48 (2H, m, CH_2), 1.46 (9H, s, $\text{C}(\text{CH}_3)_3$); δ_{C} (100 MHz, CDCl_3) 198.1 (C), 154.3 (C), 136.9 (C), 133.3 (CH), 128.7 (CH), 128.2 (CH), 81.5 (C), 71.4 (CH_2), 51.1 (CH), 38.8 (CH_2), 28.3 ($(\text{CH}_3)_3$), 25.5 (CH_2), 20.1 (CH_2); m/z (ES) 328 ($\text{M}+\text{Na}^+$, 100 %); m/z (ES) found $[\text{M}+\text{Na}]^+$ 328.1503. $\text{C}_{17}\text{H}_{23}\text{NNaO}_4^+$ requires 328.1519; R_t HPLC Chiralpak AD-H; mobile phase, hexane: 2-propanol (9: 1 v/v); flow rate, 1 ml/min; 9.2 min (92.1 %), 10.5 min (7.9 %) 84 % e.e.

tert-Butyl-(2-(2-hydroxyethoxy)ethyl)carbamate 477

Following general procedure 4b, 2-(aminoethoxy)ethanol **477** (490 μ l, 4.90 mmol) was reacted with di-*tert*-butyl dicarbonate **316** (1.46 g, 6.70 mmol) to give the crude product. This was purified by flash chromatography (ethyl acetate) to yield **476** (990 mg, 99 %) as a colourless oil. R_f : 0.5 (ethyl acetate); $\nu_{\max}$ (neat)/ cm^{-1} 3349, 2977, 1692, 1528, 1367; δ_{H} (400 MHz, CDCl_3) 5.16 (1H, s, NH), 3.73 - 3.69 (2H, m, OCH_2), 3.57 - 3.50 (4H, m, 2OCH_2), 3.34 - 3.24 (2H, m, NCH_2), 2.76 (1H, s, OH), 1.42 (9H, s, $(\text{CH}_3)_3$); δ_{C} (100 MHz, CDCl_3) 156.2 (C), 79.3 (C), 72.3 (CH_2), 70.3 (CH_2), 61.6 (CH_2), 40.4 (CH_2), 28.4 ($(\text{CH}_3)_3$); m/z (ES) 228 ($\text{M}+\text{Na}^+$, 100 %); m/z (ES) found $[\text{M}+\text{Na}]^+$ 228.1217. $\text{C}_9\text{H}_{19}\text{NNaO}_4^+$ requires 228.1206. The ^1H NMR and ^{13}C data is in agreement with those previously reported.^[155]

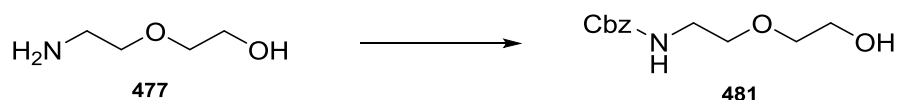
(E)-tert-Butyl-(2-((4-oxopent-2-en-1-yl)oxy)ethyl)carbamate 474

Following general procedure 6, *tert*-butyl-(2-(2-hydroxyethoxy)ethyl)carbamate **476** (1.00 g, 4.90 mmol) was reacted with 1-(triphenylphosphoranylidene)-2-propanone **191** (2.47 g, 7.80 mmol) in chloroform (42 ml) heated at reflux for 42 hours to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 3: 2) to yield **474** (250 mg, 21 %) as a yellow oil. R_f : 0.3 (light petroleum ether: ethyl acetate; 3: 2); $\nu_{\max}$ (neat)/ cm^{-1} 3352, 2932, 1699, 1680, 1635, 1172; δ_{H} (400 MHz, CDCl_3) 6.77 (1H, dt, J 17.0, 6.5, $\text{CH}=\text{CHCO}$), 6.30 (1H, dt, J 17.0, 2.5, $\text{CH}=\text{CHCO}$), 4.88 (1H, bs, NH), 4.18 (2H, dd, J 6.5, 2.5, CHCH_2), 3.55 (2H, t, J 6.5, OCH_2), 3.35 (2H, dt, J 6.5, 6.5, NCH_2), 2.28 (3H, s, COCH_3), 1.45 (9H, s, $\text{C}(\text{CH}_3)_3$); δ_{C} (100 MHz, CDCl_3) 198.0 (C), 155.9 (C), 142.6 (CH), 130.4 (CH), 79.5 (C), 70.2 (CH_2), 69.7 (CH_2), 40.4 (CH_2), 28.4 ($\text{C}(\text{CH}_3)_3$), 27.3 (CH_3); m/z (ES) 266 ($\text{M}+\text{Na}^+$, 100 %); m/z (ES) found $[\text{M}+\text{Na}]^+$ 266.1346. $\text{C}_{12}\text{H}_{21}\text{NNaO}_4^+$ requires 266.1363.

(+)-1-(N-Boc-morpholin-2-yl)propan-2-one 475

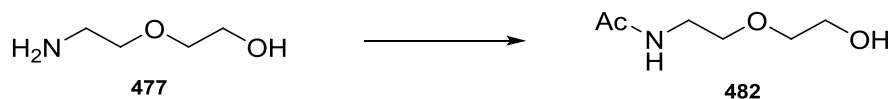
Following general procedure 8, (*E*)-*tert*-butyl-(2-((4-oxopent-2-en-1-yl)oxy)ethyl)carbamate **474** (12.1 mg, 50.0 μ mol) was stirred in diethyl carbonate (0.5 ml) at 20 °C for 22 hours to yield **475** (11.5 mg, 96 %) as a colourless oil. R_f : 0.4 (light petroleum ether: ethyl acetate; 3: 2); $[\alpha]_D^{23} +16.3$ (c 0.8 in CHCl_3); ν_{max} (neat)/ cm^{-1} 2930, 1693, 1169; δ_{H} (400 MHz, CDCl_3) 4.44 - 4.31 (1H, m, CHN), 3.87 - 3.64 (3H, m, 3CH), 3.55 (1H, dd, J 12.0, 4.0, COCH_AH_B), 3.43 (1H, ddd, J 12.0, 12.0, 4.0, CH_AH_B), 3.13 - 2.98 (2H, m, CH_2), 2.64 - 2.50 (1H, m, CH), 2.17 (3H, s, COCH_3), 1.44 (9H, s, $\text{C}(\text{CH}_3)_3$); δ_{C} (100 MHz, CDCl_3) 206.6 (C), 154.5 (C), 95.7 (CH), 80.5 (C), 69.0 (CH_2), 66.8 (CH_2), 42.4 (CH_2), 30.4 (CH_3), 30.3 (CH_2), 28.3 ($\text{C}(\text{CH}_3)_3$); m/z (ES) 266 ($\text{M}+\text{Na}^+$, 100 %); m/z (ES) found $[\text{M}+\text{Na}]^+$ 266.1358. $\text{C}_{12}\text{H}_{21}\text{NNaO}_3^+$ requires 266.1363; R_t HPLC Chiralpak AD-H; mobile phase, hexane: 2-propanol (19: 1 v/v); flow rate, 1 ml/min; 7.6 min (98.8 %), 8.4 min (1.2 %) 98 % e.e.

Benzyl 2-(2-hydroxyethoxy)ethylcarbamate **481**



Following general procedure 4b, 2-(aminoethoxy)ethanol **477** (490 mg, 4.90 mmol) was reacted with benzyl chloroformate **234** (950 μ l, 6.70 mmol) to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 1: 9) to yield **481** (1.16 g, 99 %) as a colourless oil. R_f : 0.4 (light petroleum ether: ethyl acetate; 1: 9); ν_{max} (neat)/ cm^{-1} 3411, 2941, 1701, 1124; δ_{H} (400 MHz, CDCl_3) 7.41 - 7.21 (5H, m, 5ArH), 5.39 (1H, bs, NH), 5.10 (2H, s, PhCH_2), 3.71 (2H, dt, J 6.5, 6.5, HOCH_2), 3.59 - 3.50 (4H, m, 2 OCH_2), 3.40 (2H, dt, J 7.5, 7.5, NCH_2), 2.52 (1H, bs, OH); δ_{C} (125 MHz, CDCl_3) 156.6 (C), 136.5 (C), 128.5 (CH), 128.2 (CH), 72.3 (CH_2), 70.1 (CH_2), 66.8 (CH_2), 61.7 (CH_2), 40.9 (CH_2); m/z (ES) 262 ($\text{M}+\text{Na}^+$, 100 %); m/z (ES) found $[\text{M}+\text{Na}]^+$ 262.1048. $\text{C}_{12}\text{H}_{17}\text{NNaO}_4^+$ requires 262.1050. The ^1H NMR and ^{13}C data is in agreement with those previously reported.^[156]

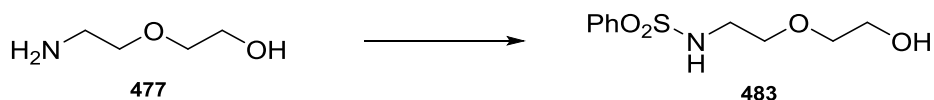
N-(2-(2-Hydroxyethoxy)ethyl)acetamide **482**



Following general procedure 4b, 2-(aminoethoxy)ethanol **477** (490 mg, 4.90 mmol) was reacted with acetic anhydride **336** (632 μ l, 6.70 mmol) to give the crude product. This was purified by flash chromatography on silica gel (dichloromethane: methanol; 9: 1) to yield **482** (713 mg, 99 %) as a colourless oil. R_f : 0.2 (dichloromethane: methanol; 9: 1); ν_{max} (neat)/ cm^{-1} 3396, 2938, 1564, 1123; δ_{H} (400 MHz, CDCl_3) 6.49 (1H, bs, NH), 3.73 (2H, dt, J 6.5, HOCH_2), 3.59 - 3.52 (4H, m, 2 OCH_2), 3.44 (2H, dt, J 7.5, 7.5, NCH_2), 3.12

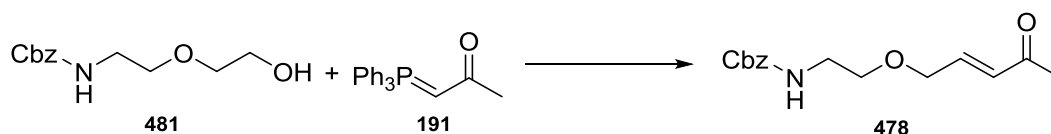
(1H, bt, *J* 6.5, OH), 1.98 (3H, s, CH₃); δ_{C} (100 MHz, CDCl₃) 170.7 (C), 72.3 (CH₂), 69.8 (CH₂), 61.6 (CH₂), 39.4 (CH₂), 23.1 (CH₃); *m/z* (ES) 170 (M+Na⁺, 100 %); *m/z* (ES) found [M+Na]⁺ 170.0790. C₆H₁₃NNaO₃⁺ requires 170.0788.

N-(2-(2-Hydroxyethoxy)ethyl)benzenesulfonamide **483**



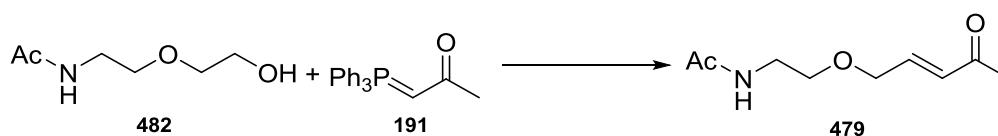
Following general procedure 4b, 2-(aminoethoxy)ethanol **477** (490 mg, 4.90 mmol) was reacted with benzenesulfonyl chloride **403** (850 μ l, 6.70 mmol) to give the crude product. This was purified by flash chromatography on silica gel (ethyl acetate) to yield **483** (1.17 g, 99 %) as a colourless oil. *R_f*: 0.5 (ethyl acetate). ν_{max} (neat)/cm⁻¹ 3282, 2926, 1447, 1324, 1160; δ_{H} (400 MHz, CDCl₃) 7.93 - 7.85 (2H, m, 2ArH), 7.62 - 7.48 (3H, m, 3ArH), 5.61 (1H, t, 6.0, NH), 3.75 - 3.67 (2H, m, OCH₂), 3.56 - 3.46 (4H, m, 2OCH₂), 3.16 (2H, dt, *J* 6.0, 6.0, NCH₂), 2.52 (1H, t, *J* 6.0, OH); δ_{C} (100 MHz, CDCl₃) 140.0 (C), 132.7 (CH), 129.1 (CH), 127.0 (CH), 72.2 (CH₂), 69.3 (CH₂), 61.6 (CH₂), 43.0 (CH₂); *m/z* (ES) 268 (M+Na⁺, 100 %); *m/z* (ES) found [M+Na]⁺ 268.0610. C₁₀H₁₅NNaO₄S⁺ requires 268.0614.

Benzyl (*E*)-(2-((4-oxopent-2-en-1-yl)oxy)ethyl)carbamate **478**



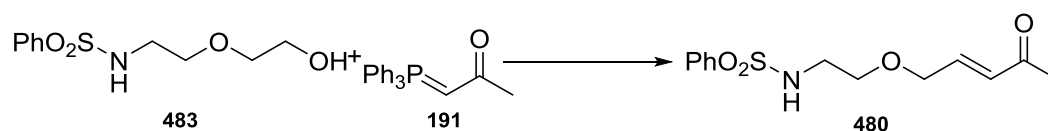
Following general procedure 6, benzyl (2-(2-hydroxyethoxy)ethyl)carbamate **481** (1.16 g, 4.90 mmol) was reacted with 1-(triphenylphosphoranylidene)-2-propanone **191** (2.47 g, 7.80 mmol) in chloroform (42 ml) heated at reflux for 96 hours to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 3: 2) to yield **478** (270 mg, 20 %) as a yellow oil. *R_f*: 0.3 (light petroleum ether: ethyl acetate; 3: 2); ν_{max} (neat)/cm⁻¹ 3413, 2929, 1700, 1674, 1634, 1132; δ_{H} (400 MHz, CDCl₃) 7.41 - 7.29 (1H, m, 5ArH), 6.75 (1H, dt, *J* 16.0, 4.5, CH=CHCO), 6.28 (1H, dt, *J* 16.0, 2.0, CH=CHCO), 5.14 (1H, bs, NH), 5.11 (2H, bs, PhCH₂), 4.17 (2H, dd, *J* 4.5, 2.0, CHCH₂), 3.57 (2H, t, *J* 5.5, OCH₂), 3.43 (2H, dt, *J* 5.5, 5.5, NCH₂), 2.27 (3H, s, CH₃); δ_{C} (100 MHz, CDCl₃) 198.1 (C), 156.4 (C), 142.5 (CH), 136.5 (C), 130.4 (CH), 128.6 (CH), 128.2 (CH), 69.9 (CH₂), 69.7 (CH₂), 66.8 (CH₂), 40.9 (CH₂), 27.4 (CH₃); *m/z* (ES) 300 (M+Na⁺, 100 %); *m/z* (ES) found [M+Na]⁺ 300.1200. C₁₅H₁₉NNaO₄⁺ requires 300.1206.

(*E*)-*N*-(2-((4-Oxopent-2-en-1-yl)oxy)ethyl)acetamide **479**



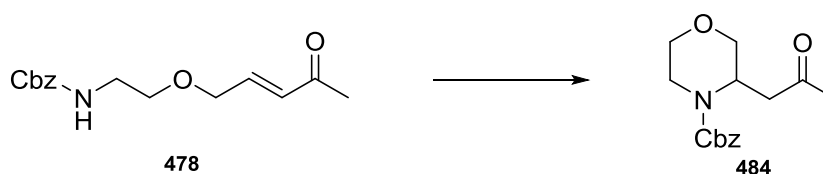
Following general procedure 6, *N*-(2-(2-hydroxyethoxy)ethyl)acetamide **482** (680 mg, 4.62 mmol) was reacted with 1-(triphenylphosphoranylidene)-2-propanone **191** (2.35 g, 7.40 mmol) in chloroform (40 ml) heated at reflux for 42 hours to give the crude product. This was purified by flash chromatography on silica gel (ethyl acetate: methanol; 19: 1) to yield **479** (185 mg, 21 %) as a yellow oil. R_f : 0.3 (ethyl acetate: methanol; 19: 1); $\nu_{\max}$ (neat)/cm⁻¹ 3307, 2872, 1658, 1555, 1120; δ_H (500 MHz, C₆D₆) 6.31 (1H, dt, J 16.0, 4.0, CH=CHCO), 6.20 (1H, dt, J 16.0, 2.0, CH=CHCO), 5.36 (1H, bs, NH), 3.54 (2H, dd, J 4.0, 2.0, CHCH₂), 3.25 (2H, dt, J 5.5, 5.5, NCH₂), 3.10 (2H, t, J 5.5, OCH₂) 1.85 (3H, s, COCH₃), 1.57 (3H, s, NCOCH₃); δ_C (125 MHz, C₆D₆) 196.1 (C), 168.8 (C), 141.9 (CH), 130.0 (CH), 69.6 (CH₂), 69.0 (CH₂), 39.1 (CH₂), 26.5 (CH₃), 22.4 (CH₃); m/z (ES) 208 (M+Na⁺, 100 %); m/z (ES) found [M+Na]⁺ 208.0946. C₉H₁₅NNaO₃⁺ requires 208.0944.

(*E*)-*N*-(2-((4-Oxopent-2-en-1-yl)oxy)ethyl)benzenesulfonamide **480**



Following general procedure 6, *N*-(2-(2-hydroxyethoxy)ethyl)benzenesulfonamide **483** (1.17 g, 4.90 mmol) was reacted with 1-(triphenylphosphoranylidene)-2-propanone **191** (2.47 g, 7.80 mmol) in chloroform (42 ml) heated at reflux for 42 hours to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 1: 1) to yield **480** (215 mg, 16 %) as a yellow oil. R_f : 0.4 (light petroleum ether: ethyl acetate; 1: 1); $\nu_{\max}$ (neat)/cm⁻¹ 3275, 2872, 1673, 1634, 1447, 1162; δ_H (500 MHz, C₆D₆) 7.90 - 7.83 (2H, m, 2ArH), 7.04 - 6.98 (3H, m, 3ArH), 6.28 (1H, dt, J 16.0, 4.5, CH=CHCO), 6.14 (1H, dt, J 16.0, 2.0, CH=CHCO), 5.46 (1H, bt, J 5.5, NH), 3.45 (2H, dd, J 4.5, 2.0, CHCH₂), 3.00 (2H, t, J 5.5, OCH₂), 2.89 (2H, dt, J 5.5, 5.5, NCH₂), 1.89 (3H, s, CH₃); δ_C (125 MHz, C₆D₆) 196.6 (C), 141.7 (CH), 140.9 (C), 131.9 (CH), 130.1 (CH), 128.8 (CH), 127.0 (CH), 69.2 (CH₂), 68.9 (CH₂), 42.8 (CH₂), 26.6 (CH₃); m/z (ES) 306 (M+Na⁺, 100 %); m/z (ES) found [M+Na]⁺ 306.0760. C₁₃H₁₇NNaO₄S⁺ requires 306.0770.

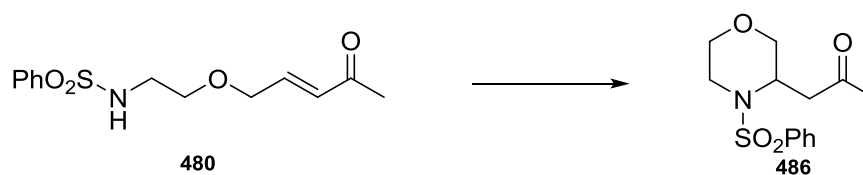
(+)-1-(4-Cbz-morpholin-3-yl)propan-2-one **484**



Following general procedure 8, benzyl (*E*)-(2-((4-oxopent-2-en-1-yl)oxy)ethyl)carbamate **478** (27.7 mg, 100 μ mol) was stirred in diethyl carbonate (1.0 ml) at 20 °C for 22 hours to yield **484** (25.1 mg, 91 %) as a colourless oil. R_f : 0.4 (light petroleum ether: ethyl acetate; 3: 2); $[\alpha]_D^{21}$ +24.0 (c 0.7 in CHCl₃); $\nu_{\max}$ (neat)/cm⁻¹ 2861, 1701, 1456, 1420,

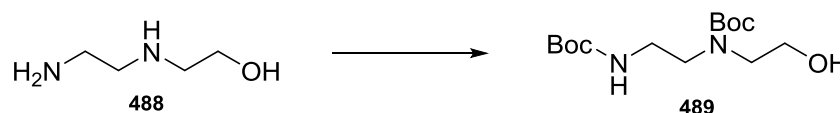
1162; δ_{H} (400 MHz, CDCl_3) 7.42 - 7.29 (5H, m, 5ArH), 5.16 (1H, d, J 16.0, PhCH_AH_B), 5.12 (1H, d, J 16.0, PhCH_AH_B), 4.54 - 4.44 (1H, m, CHN), 3.95 - 3.68 (3H, m, 3CH), 3.59 (1H, m, CH_AH_B), 3.46 (1H, dd, J 16.0, 12.0, COCH_ACH_B), 3.27 - 3.03 (2H, m, CH_2), 2.69 - 2.45 (1H, m, CH), 2.15 (3H, bs, CH_3); δ_{C} (100 MHz, CDCl_3) 206.4 (C), 155.1 (C), 136.4 (C), 128.6 (CH), 128.2 (CH), 128.0 (CH), 68.9 (CH_2), 67.4 (CH_2), 66.7 (CH_2), 47.4 (CH), 42.3 (CH_2), 40.0 (CH_2), 30.4 (CH_3); m/z (ES) 300 ($\text{M}+\text{Na}^+$, 100 %); m/z (ES) found $[\text{M}+\text{Na}]^+$ 300.1198. $\text{C}_{15}\text{H}_{19}\text{NNaO}_4^+$ requires 300.1206; R_{f} HPLC Chiralpak OD-H; mobile phase, hexane: 2-propanol (9: 1 v/v); flow rate, 1 ml/min; 13.8 min (1.9 %), 15.6 min (98.1 %) 96 % e.e.

(+)-1-(4-(Phenylsulfonyl)morpholin-3-yl)propan-2-one 486



Following general procedure 8, (*E*)-*N*-(2-((4-oxopent-2-en-1-yl)oxy)ethyl)benzenesulfonamide **480** (28.3 mg, 100 μmol) was stirred in diethyl carbonate (1.0 ml) at 20 °C for 22 hours to yield **486** (25.0 mg, 88 %) as a colourless oil. R_{f} : 0.4 (light petroleum ether: ethyl acetate; 3: 2); $[\alpha]_{\text{D}}^{23} +51.7$ (c 0.7 in CHCl_3); ν_{max} (neat)/ cm^{-1} 2862, 1714, 1447, 1413, 1349, 1164; δ_{H} (400 MHz, CDCl_3) 7.87 - 7.77 (2H, m, 2ArH), 7.65 - 7.48 (3H, m, 3ArH), 4.29 - 4.23 (1H, m, CHN), 3.79 (1H, dd, J 12.0, 4.0, COCH_AH_B), 3.69 - 3.55 (2H, m, 2CH), 3.46 - 3.41 (1H, m, CH_AH_B), 3.37 (1H, ddd, J 12.0, 12.0, 4.0, CH_AH_B), 3.24 - 3.12 (2H, m, 2CH), 2.51 - 2.43 (1H, m, CH), 2.10 (3H, s, CH_3); δ_{C} (100 MHz, CDCl_3) 205.8 (C), 140.3 (C), 132.9 (C), 129.4 (CH), 127.1 (CH), 69.0 (CH_2), 66.4 (CH_2), 48.8 (CH), 41.7 (CH_2), 41.3 (CH_2), 30.4 (CH_3); m/z (ES) 306 ($\text{M}+\text{Na}^+$, 100 %); m/z (ES) found $[\text{M}+\text{Na}]^+$ 306.0758. $\text{C}_{13}\text{H}_{17}\text{NNaO}_4\text{S}^+$ requires 306.0770; R_{f} HPLC Chiralpak AD-H; mobile phase, hexane: 2-propanol (9: 1 v/v); flow rate, 1 ml/min; 26.7 min (98.1 %), 29.8 min (1.9 %) 96 % e.e.

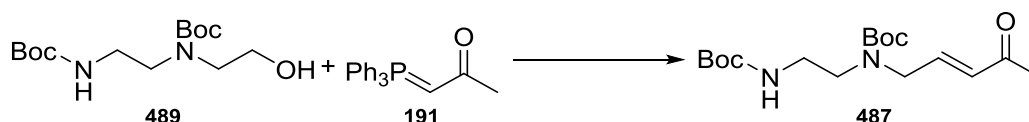
***tert*-Butyl-(2-((*tert*-butoxycarbonyl)amino)ethyl)(2-hydroxyethyl)carbamate 489**



Following general procedure 4b, *N*-(2-hydroxyethyl)ethylenediamine **488** (490 μl , 4.90 mmol) was reacted with di-*tert*-butyl-dicarbonate (2.52 g, 11.5 mmol) to give the crude product. This was purified by flash chromatography on silica gel (ethyl acetate) to yield **489** (1.49 g, 99 %) as a colourless oil. R_{f} : 0.5 (ethyl acetate); ν_{max} (neat)/ cm^{-1} 3360, 2933, 1684, 1171; δ_{H} (400 MHz, CDCl_3) 5.05 (1H, bs, NH), 4.89 (1H, s, OH), 3.83 - 3.64

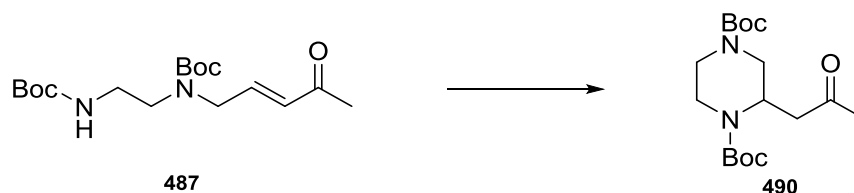
(2H, m, OCH₂), 3.48 - 3.21 (6H, m, 3NCH₂), 1.47 (9H, s, (CH₃)₃), 1.43 (9H, s, (CH₃)₃); δ_C (100 MHz, CDCl₃) 156.6 (C), 79.5 (C), 62.2 (CH₂), 51.5 (CH₂), 48.4 (CH₂), 40.1 (CH₂), 28.4 ((CH₃)₃); m/z (ES) 327 (M+Na⁺, 100 %); m/z (ES) found [M+Na]⁺ 327.1892. C₁₄H₂₈N₂NaO₅⁺ requires 327.1890. The ¹H NMR and ¹³C data is in agreement with those previously reported.^[157]

(*E*)-*tert*-Butyl-(2-((*tert*-butoxycarbonyl)amino)ethyl)(4-oxopent-2-en-1-yl)carbamate **487**



Following general procedure 6, *tert*-butyl-(2-((*tert*-butoxycarbonyl)amino)ethyl)(2-hydroxyethyl)carbamate **489** (1.00 g, 4.90 mmol) was reacted with 1-(triphenylphosphoranylidene)-2-propanone **191** (2.47 g, 7.80 mmol) in chloroform (42 ml) heated at reflux for 42 hours to give the crude product. This was purified by flash chromatography on silica gel (light petroleum ether: ethyl acetate; 3: 2) to yield **487** (51.0 mg, 31 %) as a yellow solid. M.p. 64 - 66 °C; R_f : 0.2 (light petroleum ether: ethyl acetate; 3: 2); $\nu_{\max}$ (CHCl₃)/cm⁻¹ 3361, 2933, 1698, 1683, 1634, 1170; δ_H (400 MHz, CDCl₃) 6.67 (1H, dt, J 16.0, 8.0, CH=CHCO), 6.07 (1H, dt, J 16.0, 2.0, CH=CHCO), 4.93 (1H, s, NH), 4.09 - 3.95 (2H, m, CHCH₂), 3.40 - 3.15 (4H, m, 2CH₂), 2.27 (3H, s, COCH₃), 1.44 (18H, bs, 2C(CH₃)₃); δ_C (100 MHz, CDCl₃) 198.0 (C), 155.9 (C), 142.7 (CH), 131.3 (CH), 80.7 (C), 48.3 (CH₂), 46.7 (CH₂), 39.4 (CH₂), 28.3 (C(CH₃)₃), 27.3 (CH₃); m/z (ES) 365 (M+Na⁺, 100 %); m/z (ES) found [M+Na]⁺ 365.2052. C₁₇H₃₀N₂NaO₅⁺ requires 365.2047.

(+)-1-(*N,N'*-(Di-Boc)-piperazin-2-yl)propan-2-one **490**



Following general procedure 8, (*E*)-*tert*-butyl-(2-((*tert*-butoxycarbonyl)amino)ethyl)(4-oxopent-2-en-1-yl)carbamate **487** (17.1 mg, 50.0 μ mol) was stirred in diethyl carbonate (0.5 ml) at 20 °C for 22 hours to yield **490** (15.8 mg, 92 %) as a colourless solid. M.p. 146 - 148 °C; R_f : 0.4 (light petroleum ether: ethyl acetate; 3: 2); $[\alpha]_D^{23}$ +11.2 (c 0.7 in CHCl₃); $\nu_{\max}$ (CHCl₃)/cm⁻¹ 2977, 1695, 1169; δ_H (400 MHz, CDCl₃) 4.65 - 4.45 (1H, m, CHN), 4.12 - 3.69 (3H, m, 3CH), 3.05 - 2.66 (4H, m, 2CH₂), 2.53 - 2.39 (1H, m, CH), 2.17 (3H, s, COCH₃), 1.43 (18H, s, 2C(CH₃)₃); δ_C (100 MHz, CDCl₃) 205.9 (C), 155.0 (C), 154.5 (C), 80.6 (C), 80.3 (C), 68.0 (CH₂), 47.6 (CH), 46.4 (CH₂), 42.5 (CH₂), 30.4 (CH₃), 28.3

(C(CH₃)₃), 25.6 (CH₂); *m/z* (ES) 365 (M+Na⁺, 100 %); *m/z* (ES) found [M+Na]⁺ 365.2057.
C₁₇H₃₀N₂NaO₅⁺ requires 365.2047; R_t HPLC Chiralpak AD-H; mobile phase, hexane: 2-propanol (49: 1 v/v); flow rate, 1 ml/min; 18.2 min (97.4 %), 20.4 min (2.6 %) 95 % e.e.

Chapter 4: References

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Chapter 6: Crystallography Data for 202

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Bourhis, L.J., Dolomanov, O.V., Gildea, R.J., Howard, J.A.K.,
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(2013). in preparation.

Dolomanov, O.V., Bourhis, L.J., Gildea, R.J., Howard, J.A.K. &
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(2009), J. Appl. Cryst. 42, 339-341.

Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.
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They are only intended as comments.
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  'x+1/2, -y+1/2, -z'

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Version 1.171.37.31 (release 14-01-2014 CrysAlis171 .NET)
(compiled Jan 14 2014,18:38:05)
Numerical absorption correction based on gaussian integration over
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Empirical absorption correction using spherical harmonics,
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Reflections were merged by SHELXL according to the crystal
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(compiled Jan 14 2014,18:38:05)
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Flack x determined using 922 quotients [(I+)-(I-)]/[(I+)+(I-)]
(Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
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  At 1.5 times of:
    All C(H,H,H) groups
2.a Ternary CH refined with riding coordinates:
  C1(H1)
2.b Secondary CH2 refined with riding coordinates:
  C2(H2A,H2B), C4(H4A,H4B), C5(H5A,H5B), C6(H6A,H6B)
2.c Idealised Me refined as rotating group:
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H2B H 0.0836 0.2867 0.6524 0.024 Uiso 1 1 calc R . . . . .
C3 C 0.0489(4) 0.3866(4) 0.73634(12) 0.0199(6) Uani 1 1 d . . . . .
C4 C 0.2310(4) 0.3436(4) 0.76763(10) 0.0211(5) Uani 1 1 d . . . . .
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H4B H 0.2119 0.3589 0.8104 0.025 Uiso 1 1 calc R . . . . .
C5 C 0.3948(4) 0.4683(5) 0.74776(12) 0.0231(6) Uani 1 1 d . . . . .
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H5B H 0.5148 0.4228 0.7650 0.028 Uiso 1 1 calc R . . . . .
C6 C 0.4121(4) 0.4714(5) 0.68076(12) 0.0212(6) Uani 1 1 d . . . . .
H6A H 0.5165 0.5548 0.6690 0.025 Uiso 1 1 calc R . . . . .
H6B H 0.4416 0.3458 0.6662 0.025 Uiso 1 1 calc R . . . . .
O7 O -0.1016(3) 0.3992(3) 0.76182(9) 0.0300(5) Uani 1 1 d . . . . .
N8 N 0.2373(4) 0.5542(2) 0.58993(7) 0.0145(4) Uani 1 1 d . . . . .
N9 N 0.2417(4) 0.3974(3) 0.55666(8) 0.0192(4) Uani 1 1 d . . . . .
C10 C 0.2442(5) 0.4561(3) 0.50128(9) 0.0178(4) Uani 1 1 d . . . . .
C11 C 0.2445(5) 0.6498(3) 0.50024(9) 0.0147(4) Uani 1 1 d . . . . .
C12 C 0.2402(4) 0.7112(3) 0.55740(10) 0.0146(4) Uani 1 1 d . . . . .
C13 C 0.2461(6) 0.3242(3) 0.45088(11) 0.0263(6) Uani 1 1 d . . . . .
H13A H 0.3573 0.2438 0.4539 0.039 Uiso 1 1 calc GR . . . . .
H13B H 0.2515 0.3935 0.4140 0.039 Uiso 1 1 calc GR . . . . .
H13C H 0.1309 0.2489 0.4517 0.039 Uiso 1 1 calc GR . . . . .
Br14 Br 0.24356(4) 0.80225(3) 0.43371(2) 0.01920(9) Uani 1 1 d . . . . .
.
C15 C 0.2397(5) 0.9013(3) 0.58227(10) 0.0203(5) Uani 1 1 d . . . . .
H15A H 0.1425 0.9102 0.6128 0.031 Uiso 1 1 calc GR . . . . .
H15B H 0.2120 0.9905 0.5511 0.031 Uiso 1 1 calc GR . . . . .
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C6 0.0158(14) 0.0293(17) 0.0186(14) 0.0015(12) 0.0011(10) -0.0045(12)
O7 0.0225(11) 0.0412(13) 0.0264(11) 0.0130(10) 0.0092(9) 0.0037(10)
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C12 0.0140(11) 0.0154(10) 0.0144(10) 0.0021(8) 0.0011(13) -0.0006(14)
C13 0.0399(16) 0.0216(12) 0.0174(11) -0.0051(9) 0.0028(14) -0.001(2)
Br14 0.02153(14) 0.02322(14) 0.01285(13) 0.00570(8) 0.00033(14)
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C15 0.0278(14) 0.0148(10) 0.0184(10) -0.0005(8) 0.0025(14) -0.0015(16)

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All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

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C1 C6 1.524(4) . ?
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C2 H2B 0.9900 . ?
C2 C3 1.508(4) . ?
C3 C4 1.503(4) . ?
C3 O7 1.214(3) . ?
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C4 H4B 0.9900 . ?
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C10 C13 H13B 109.5 . . ?
C10 C13 H13C 109.5 . . ?
H13A C13 H13B 109.5 . . ?
H13A C13 H13C 109.5 . . ?
H13B C13 H13C 109.5 . . ?
C12 C15 H15A 109.5 . . ?
C12 C15 H15B 109.5 . . ?
C12 C15 H15C 109.5 . . ?
H15A C15 H15B 109.5 . . ?
H15A C15 H15C 109.5 . . ?

```

H15B C15 H15C 109.5 . . ?

loop_

_geom_torsion_atom_site_label_1
_geom_torsion_atom_site_label_2
_geom_torsion_atom_site_label_3
_geom_torsion_atom_site_label_4
_geom_torsion
_geom_torsion_site_symmetry_1
_geom_torsion_site_symmetry_2
_geom_torsion_site_symmetry_3
_geom_torsion_site_symmetry_4
_geom_torsion_publ_flag
C1 C2 C3 C4 -48.3(4) ?
C1 C2 C3 O7 133.0(3) ?
C1 N8 N9 C10 177.8(3) ?
C1 N8 C12 C11 -178.0(3) ?
C1 N8 C12 C15 2.3(5) ?
C2 C1 C6 C5 -60.3(3) ?
C2 C1 N8 N9 -51.2(4) ?
C2 C1 N8 C12 127.4(3) ?
C2 C3 C4 C5 46.4(4) ?
C3 C4 C5 C6 -50.6(4) ?
C4 C5 C6 C1 58.1(3) ?
C6 C1 C2 C3 54.7(3) ?
C6 C1 N8 N9 72.2(3) ?
C6 C1 N8 C12 -109.1(3) ?
O7 C3 C4 C5 -134.9(3) ?
N8 C1 C2 C3 179.2(2) ?
N8 C1 C6 C5 176.8(2) ?
N8 N9 C10 C11 1.0(4) ?
N8 N9 C10 C13 -179.0(3) ?
N9 N8 C12 C11 0.7(3) ?
N9 N8 C12 C15 -179.0(3) ?
N9 C10 C11 C12 -0.6(5) ?
N9 C10 C11 Br14 -178.9(2) ?
C10 C11 C12 N8 -0.1(4) ?
C10 C11 C12 C15 179.6(4) ?
C12 N8 N9 C10 -1.1(4) ?
C13 C10 C11 C12 179.4(3) ?
C13 C10 C11 Br14 1.1(7) ?
Br14 C11 C12 N8 178.3(2) ?
Br14 C11 C12 C15 -2.0(5) ?

_shelx_res_file

;

TITL

CELL 1.54184 7.060672 7.239275 22.7974 90 90 90

ZERR 4 0.000547 0.000501 0.001714 0 0 0

LATT -1

SYMM 0.5-X,-Y,0.5+Z

SYMM -X,0.5+Y,0.5-Z

SYMM 0.5+X,0.5-Y,-Z

SFAC C H N O Br

UNIT 44 60 8 4 4

L.S. 12

```

PLAN 20
TEMP -153
MORE -1
BOND $H
CONF
fmap 2 53
acta
OMIT -6 6 9
OMIT 0 8 1
REM <HKL>C:/Users/pczwl/Dropbox/Organic/ABBLCB/ABBLCB.hkl</HKL>

WGHT 0.024800 0.444400
FVAR 4.41528
C1 1 0.226662 0.538204 0.653891 11.00000 0.02156
0.01626 =
0.00930 0.00165 0.00132 0.00164
AFIX 13
H1 2 0.198428 0.663417 0.670222 11.00000 -1.20000
AFIX 0
C2 1 0.063348 0.409091 0.670751 11.00000 0.01564
0.02901 =
0.01579 0.00730 -0.00041 -0.00250
AFIX 23
H2A 2 -0.057097 0.459917 0.655462 11.00000 -1.20000
H2B 2 0.083646 0.286667 0.652448 11.00000 -1.20000
AFIX 0
C3 1 0.048894 0.386607 0.736339 11.00000 0.01983
0.02084 =
0.01893 0.00502 0.00242 -0.00207
C4 1 0.231014 0.343587 0.767625 11.00000 0.02114
0.02774 =
0.01432 0.00624 -0.00076 -0.00366
AFIX 23
H4A 2 0.265353 0.213024 0.760293 11.00000 -1.20000
H4B 2 0.211888 0.358884 0.810370 11.00000 -1.20000
AFIX 0
C5 1 0.394794 0.468320 0.747763 11.00000 0.01938
0.03329 =
0.01651 0.00306 -0.00438 -0.00223
AFIX 23
H5A 2 0.373130 0.595470 0.762274 11.00000 -1.20000
H5B 2 0.514770 0.422823 0.764978 11.00000 -1.20000
AFIX 0
C6 1 0.412061 0.471386 0.680756 11.00000 0.01584
0.02928 =
0.01859 0.00149 0.00112 -0.00447
AFIX 23
H6A 2 0.516512 0.554786 0.669013 11.00000 -1.20000
H6B 2 0.441592 0.345807 0.666197 11.00000 -1.20000
AFIX 0
O7 4 -0.101557 0.399218 0.761821 11.00000 0.02254
0.04116 =
0.02638 0.01304 0.00917 0.00372
N8 3 0.237301 0.554173 0.589928 11.00000 0.02015
0.01398 =
0.00951 0.00065 0.00176 0.00017
N9 3 0.241683 0.397442 0.556665 11.00000 0.02793
0.01383 =

```

```

      0.01570   -0.00181    0.00067    0.00152
C10   1      0.244176    0.456097    0.501276    11.00000    0.01879
0.01895 =
      0.01554   -0.00147    0.00123    0.00071
C11   1      0.244472    0.649834    0.500243    11.00000    0.01411
0.01647 =
      0.01348    0.00374    0.00037    0.00171
C12   1      0.240185    0.711152    0.557399    11.00000    0.01397
0.01540 =
      0.01437    0.00206    0.00110   -0.00060
C13   1      0.246126    0.324225    0.450879    11.00000    0.03986
0.02159 =
      0.01740   -0.00510    0.00277   -0.00062
AFIX 137
H13A  2      0.357339    0.243786    0.453885    11.00000   -1.50000
H13B  2      0.251464    0.393513    0.413986    11.00000   -1.50000
H13C  2      0.130854    0.248866    0.451704    11.00000   -1.50000
AFIX   0
BR14  5      0.243563    0.802253    0.433705    11.00000    0.02153
0.02322 =
      0.01285    0.00570    0.00033    0.00041
C15   1      0.239651    0.901344    0.582267    11.00000    0.02779
0.01485 =
      0.01841   -0.00050    0.00246   -0.00152
AFIX 137
H15A  2      0.142506    0.910242    0.612840    11.00000   -1.50000
H15B  2      0.212007    0.990514    0.551077    11.00000   -1.50000
H15C  2      0.364088    0.928453    0.599252    11.00000   -1.50000
AFIX   0
HKLF  4

REM
REM R1 = 0.0195 for 2301 Fo > 4sig(Fo) and 0.0204 for all 2360
data
REM 138 parameters refined using 0 restraints

END

WGHT      0.0248      0.4444

REM Highest difference peak 0.352, deepest hole -0.255, 1-sigma
level 0.060
Q1   1   0.2463  0.5460  0.6238  11.00000  0.05   0.35
Q2   1   0.1589  0.4594  0.6596  11.00000  0.05   0.26
Q3   1   0.0684  0.3926  0.7007  11.00000  0.05   0.24
Q4   1   0.2522  0.3911  0.4792  11.00000  0.05   0.21
Q5   1   0.3159  0.7076  0.5223  11.00000  0.05   0.21
Q6   1  -0.0059  0.8758  0.5546  11.00000  0.05   0.21
Q7   1   0.3288  0.4627  0.6621  11.00000  0.05   0.21
Q8   1   0.2339  0.8141  0.4799  11.00000  0.05   0.21
Q9   1   0.5001  0.5273  0.5620  11.00000  0.05   0.21
Q10  1   0.2308  0.5404  0.4937  11.00000  0.05   0.20
Q11  1   0.4909  0.4394  0.6578  11.00000  0.05   0.19
Q12  1   0.2422  0.8025  0.3805  11.00000  0.05   0.19
Q13  1   0.1428  0.3935  0.7564  11.00000  0.05   0.18
Q14  1   0.1790  0.7017  0.5205  11.00000  0.05   0.18
Q15  1   0.0070  0.4248  0.6582  11.00000  0.05   0.18
Q16  1  -0.0005  0.5367  0.5585  11.00000  0.05   0.18

```

Q17	1	0.4117	0.5430	0.4329	11.00000	0.05	0.17
Q18	1	0.1799	0.2821	0.8388	11.00000	0.05	0.17
Q19	1	0.4949	0.8782	0.5575	11.00000	0.05	0.17
Q20	1	0.2542	0.6398	0.5762	11.00000	0.05	0.17

REM The information below was added by Olex2.

REM

REM R1 = 0.0195 for 2301 Fo > 4sig(Fo) and 0.0204 for all 16622 data

REM n/a parameters refined using n/a restraints

REM Highest difference peak 0.35, deepest hole -0.25

REM Mean Shift 0, Max Shift -0.001.

REM +++ Tabular Listing of Refinement Information +++

REM R1_all = 0.0204

REM R1_gt = 0.0195

REM wR_ref = 0.0503

REM GOOF = 1.090

REM Shift_max = -0.001

REM Shift_mean = 0

REM Reflections_all = 16622

REM Reflections_gt = 2301

REM Parameters = n/a

REM Hole = -0.25

REM Peak = 0.35

REM Flack = -0.006(12)

;

loop_

_exptl_crystal_face_index_h

_exptl_crystal_face_index_k

_exptl_crystal_face_index_l

_exptl_crystal_face_perp_dist

_exptl_oxdiff_crystal_face_indexfrac_h

_exptl_oxdiff_crystal_face_indexfrac_k

_exptl_oxdiff_crystal_face_indexfrac_l

_exptl_oxdiff_crystal_face_x

_exptl_oxdiff_crystal_face_y

_exptl_oxdiff_crystal_face_z

4 0 7 0.0348 3.9840 0.0145 7.0669 0.0380 0.7505 -0.6483

-1 4 -8 0.0648 -0.9947 3.9977 -8.0411 -0.9383 -0.2354 0.3603

2 -4 4 0.0743 2.0030 -3.9963 4.0552 0.7648 0.0965 -0.6279

-1 -4 9 0.0756 -1.0069 -4.0031 9.0097 1.0625 0.1156 0.0464

-4 0 8 0.0726 -4.0160 -0.0085 7.9400 0.4394 0.1011 0.9234

-1 -1 -14 0.0431 -0.9669 -1.0094 -14.0170 -0.2169 -0.9599 -0.1408

-3 0 -10 0.0425 -2.9779 -0.0127 -10.0524 -0.1797 -0.8326 0.3991

1 1 14 0.0434 0.9669 1.0094 14.0170 0.2169 0.9599 0.1408

-4 2 4 0.0721 -4.0135 1.9918 3.9274 -0.0528 0.0275 1.0065

4 0 -5 0.0390 4.0096 0.0097 -4.9386 -0.3439 0.0692 -0.8684

0 -5 0 0.0733 0.0150 -5.0047 0.0269 0.9123 -0.3839 -0.3911

-3 -4 3 0.0795 -2.9936 -4.0113 2.9751 0.9639 -0.4016 0.3247

1 3 10 0.0648 0.9694 3.0097 10.0044 -0.2753 0.8864 0.2239

-2 2 -12 0.0390 -1.9799 1.9913 -12.0481 -0.6545 -0.7043 0.3247

2 0 -13 0.0359 2.0272 0.0007 -12.9741 -0.5062 -0.5615 -0.6268