Synthesis Of 2-Substituted *N*-Heterocycles *via* Asymmetric Organocatalysed Intramolecular *N*-Conjugate Addition

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Contents

Abbreviations

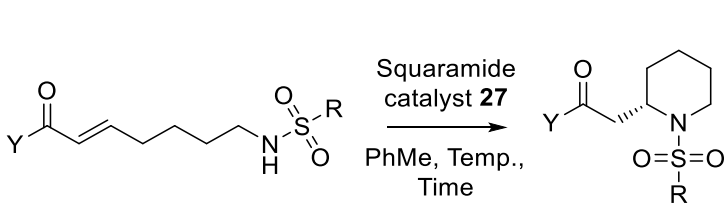
[H]	Reductant/Reduction
[O]	Oxidant/Oxidation
2-Ns	*ortho*-Nitrobenzene sulfonyl
4-Ns	*para*-Nitrobenzene sulfonyl
A	Acid
Ar	Aromatic
B	Base
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
Boc	*tert*-Butyl carboxylate
Brosyl /Bs	4-Bromobenzene sulfonyl
Cbz	Carboxy benzyl
d	Days
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicycloundec-7-ene
DCC	*N,N'*-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCU	Dicyclohexylurea
DIAD	Diisopropyl azodicarboxylate
DMAP	4-Dimethyl aminopyridine
DMF	*N,N*-Dimethyl formamide
DPPA	Diphenyl phosphoryl azide
equiv.	Equivalents
Et	Ethyl
Fmoc	Fluorenylmethyloxycarbonyl
h	Hours
HGII	Hoveyda-Grubbs second generation catalyst
HOMO	Highest Occupied Molecular Orbital

HPLC	High Pressure Liquid Chromatography
^{i}Pr	*iso*-Propyl
LG	Leaving group
LUMO	Lowest Unoccupied Molecular Orbital
Me	Methyl
Ms	Methyl sulfonyl
MS	Molecular sieves
MVK	Methyl vinyl ketone
NMR	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser Effect
Nosyl / Ns	Nitrobenzene sulfonyl
OTBS	*tert*-Butyldimethylsilyl ether
OTMS	Trimethylsilyl ether
PCC	Pyridinium chlorochromate
PG	Protecting group
ppm	Parts per million
p-TSA	*para*-Toluene sulfonic acid
PVK	Phenyl vinyl ketone
RT	Room temperature
Sq	Squaramide catalyst **27**
TBAB	Tetrabutyl ammonium bromide
^{t}Bu	*tert*-Butyl
Temp.	Temperature
TFA	Trifluoroacetic acid
TfOH	Trifluoromethane sulfonic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
Tosyl / Ts	*para*-Toluene sulfonyl

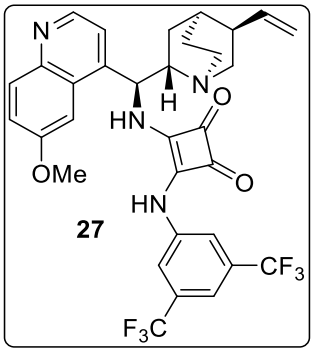
Abstract

This thesis describes the use of cinchona derived squaramide catalyst **27** in the asymmetric intramolecular *N*-conjugate addition of nitrogen nucleophiles with α,β-unsaturated carbonyls.

The first chapter describes investigation of intramolecular *N*-conjugate addition reactions of sulfonamides with aromatic ketones, esters, thioesters and amides generating chiral 2-substituted piperidines, morpholines and oxazinanes. The squaramide catalyst **27** was found to efficiently catalyse the reaction, good yields of cyclic products were obtained with excellent enantioselectivities. Further modification of these products towards natural and drug targets is outlined. A possible mechanism based on observed stereochemistry and in silico modelling of transition states is proposed.

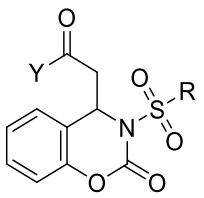


Y = Aromatic, esters, thioesters and amides.
R = Ph, 2-Ns, 4-Ns, Bs, Ts



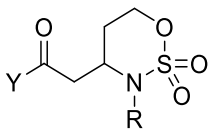
The second chapter describes investigation of altered substrates formed by varying functionality linking the α,β-unsaturated carbonyl to the nitrogen nucleophile. For example, 4-Substitued 3,4-dihydro-2H-benzo[e][1,3]oxazin-2-ones and cyclic sulfamates were synthesised this way, but unfortunately enantioselectivity was poor in this case.

4-substitued 3,4-dihydro-2H-benzo[e][1,3]oxazin-2-ones



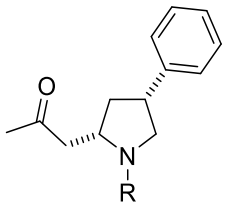
Y = Me, OMe, Ph, SEt
R = Ph, Bn, Ts

cyclic sulfamates



Y = Me, Ph
R = Cbz, Boc, H

Finally the influence of chiral substrates on asymmetric cyclisation was investigated during the synthesis of 2,4-disubstituted pyrrolidines. It was found that the intrinsic diastereoselectivity of the cyclisation is difficult to overcome using asymmetric organocatalysis.



R = Cbz, Ts, Ac

Acknowledgements

I would like to thank my supervisors Prof. Barry Lygo and Dr. James Dowden.

Prof. Barry Lygo made me the sceptical and questioning scientist I am today, whether I wanted to or not. Dr. James Dowden allowed me to express my creativity and convinced me I am better than I think I am.

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A special thanks to Naomi Barton who has always freely supplied me with life advice, guidance and much needed criticism, a debt that no amount of pints at the pub will repay I fear.

Finally thanks to my family and partner Faye Kime for putting up with me for much longer than chemistry has had to.

“Life moves pretty fast.

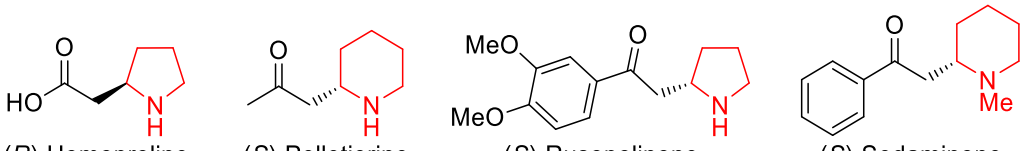
If you don’t stop and look around once in a while, you could miss it”

-Ferris Bueller’s Day Off (1986)

Introduction

N-Heterocycles And Asymmetric Intramolecular *N*-Conjugate Additions

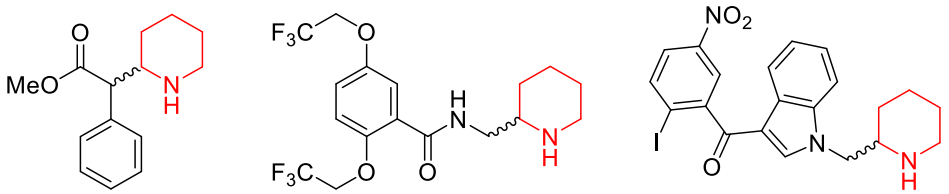
Piperidines and pyrrolidines are among a collection of saturated *N*-heterocyclic rings. These can be found as a common feature of many alkaloid natural products with valued biological activities. However, in nature these compounds are commonly poisonous (Figure 1).



(*R*)-Homoproline **1** (*S*)-Pelletierine **2** (*S*)-Rusopolinone **3** (*S*)-Sedaminone **4**

Figure 1. Small piperidine and pyrrolidine containing natural products

N-Heterocyclic rings have been incorporated in drug design and in marketed products. For example, Ritalin **5** is a central nervous system stimulator, Tambocor **6** is used to treat irregular heart beat (tachycardia) and AM-1241 **7** was a potent pain killer for sufferers of bone cancer. (*R*),(*R*)-Ritalin has been reported by Williard *et al.* to be much more active than its enantiomer.[1] It has been reported by Bingham *et al.* that the (*S*) enantiomer displays more CB_2 receptor agonist properties than the (*R*) enantiomer or the racemic mixture.[2] Despite these differences in biological activity these are often sold as racemates due to a difficulty in enantiopure drug synthesis (Figure 2).



Ritalin **5** Tambocor **6** AM-1241 **7**

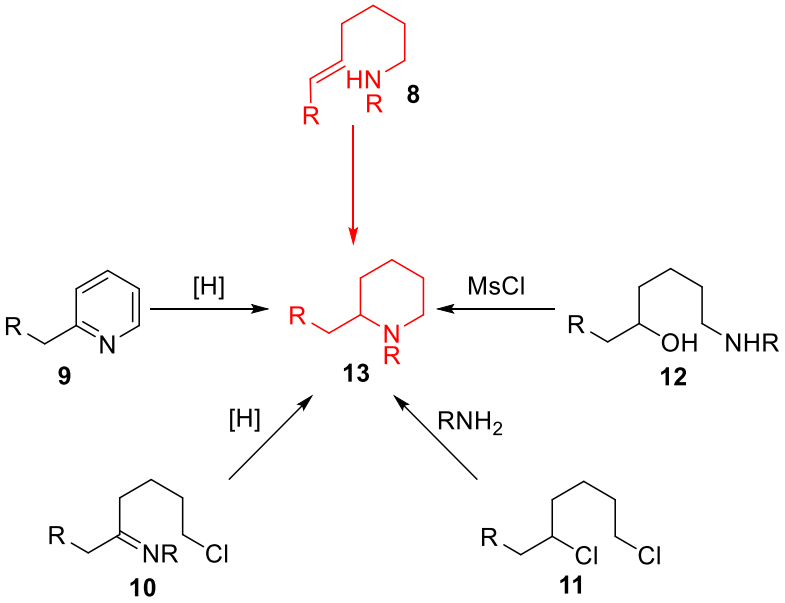
Figure 2. Example drug compounds

Different enantiomers of drug compounds may act differently in the body, sometimes one enantiomer of a drug may be inactive against the drug receptor target (meaning half the material administered is redundant) or even possess more undesirable side effects. For this reason legislators such as the U.S Food

and Drug Administration (FDA) prefer the biological activities of both enantiomers of a drug to be known, even when being sold as a racemic mixture.

The formation of piperidines and other *N*-heterocycles by *N*-conjugate addition with asymmetric catalysts is therefore an area of great interest.[3–15]

Piperidines and other *N*-heterocycles can be synthesised in a variety of ways, some of which are shown below (Scheme 1).



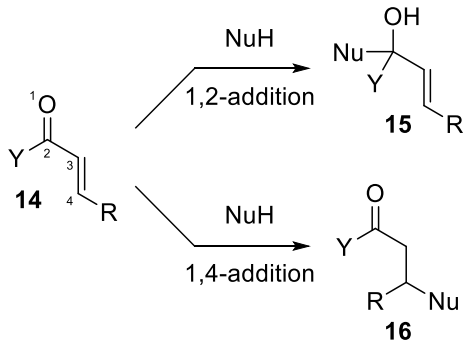
Scheme 1. Synthesis of piperidines 13

Piperidines have been formed through many possible disconnections of the carbon-nitrogen bonds. 1,6-amino alcohols **12** can be converted to a mesylate *in situ* and generate the piperidine upon displacement by the amine.[16–18] 1,6-dichloro compounds **11** can be reacted with primary amines generate the piperidines much the same way.[19–21] Reduction of pyridines **9** or the resulting iminium after imine **10** undergoes ring closure also give piperidines.[22–27] However, our investigations were of the intramolecular *N*-conjugate addition of amine containing olefins **8**.

The conjugate addition of a nucleophile to an α,β-unsaturated carbonyl has been investigated for over a century since Arthur Michael reported the reaction between an enolate and an α,β-unsaturated carbonyl.[28] The mild conditions commonly used in the formation of C-C bonds are of great appeal to chemists.

A new chiral centre is formed during the reaction. The potential to use chiral molecules as catalysts to perform the reaction asymmetrically is therefore of significant interest.

α,β-Unsaturated carbonyl systems **14** can undergo nucleophilic addition at both the 2 and the 4 positions (Scheme 2).



Scheme 2. 1,2-Addition vs 1,4-conjugate addition

Normally alkenes are unreactive to 1,2-nucleophilic addition but when in conjugation with an ester for example, the carbonyl polarises the alkene, activating it towards addition at the 4-position. Reactive carbonyls such as acid chlorides and aldehydes are more likely to undergo 1,2-addition whilst less reactive carbonyls such as ketones, esters and amides prefer to undergo 1,4-addition. Other factors that dictate the nature of the addition are sterics about the alkene; more heavily substituted α,β-unsaturated carbonyls react at the carbonyl and the nature of the nucleophile; softer nucleophiles such as nitrogen and sulfur undergo nucleophilic addition at the 4-position whilst harder nucleophiles such as Grignard's undergo nucleophilic addition at the carbonyl. Resonance forms of the α,β-unsaturated carbonyl show why these carbons are the most electrophilic (Figure 3).

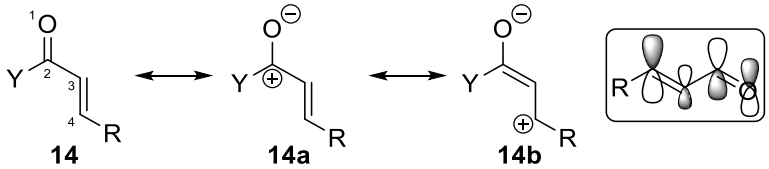
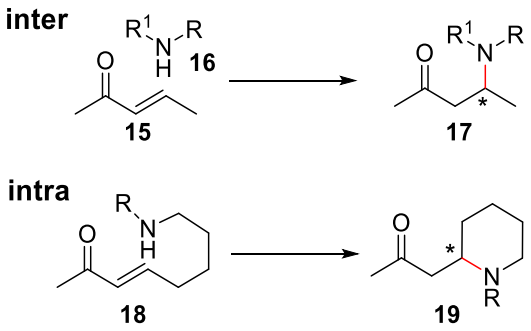


Figure 3. Resonance states and orbitals of α,β-unsaturated carbonyls

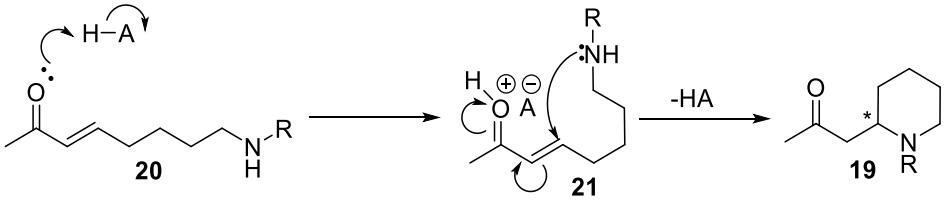
N-Conjugate addition reactions between nitrogen nucleophiles and α,β-unsaturated carbonyls are a useful synthetic method for the formation of carbon–nitrogen bonds. In the case of the intramolecular reaction the result is the formation of a heterocycle (Scheme 3).



Scheme 3. Inter and intramolecular *N*-conjugate addition reactions

These reactions pose a challenge to the synthetic chemist who wishes to control both the competing 1,2-addition reaction and the stereochemistry of the newly formed stereocentre. Asymmetric organocatalysis is one way of both catalysing and imparting stereoselectivity in *N*-conjugate addition reactions by use of small chiral molecules in substoichometric quantities to facilitate a reaction that favours one enantiotopic face of the alkene over the other. A variety of modes may be used to activate either the nucleophile or electrophile in an *N*-conjugate addition reaction as outlined below:

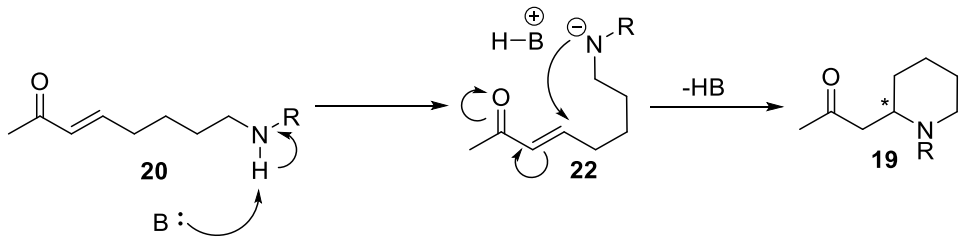
Brønsted acid catalysis: In the presence of acid, the carbonyl of an α,β–unsaturated carbonyl may be protonated. In non-polar media the conjugate base of the acid remains in close proximity to the activated electrophile (Scheme 4).



Scheme 4. Brønsted acid catalysis

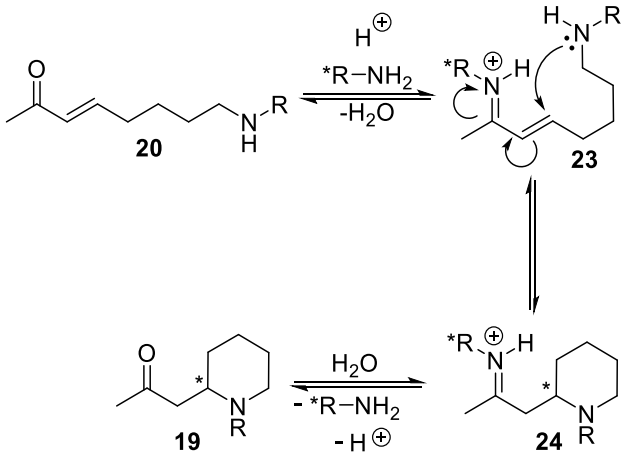
If the conjugate base is chiral then further interactions between the conjugate base and nucleophile could direct conjugate addition to one enantiotopic face of the enone.

Brønsted base catalysis: When base is added, the nitrogen nucleophile can be deprotonated. In non-polar media the conjugate acid of the base remains in close proximity to the activated nucleophile. When the nucleophile undergoes conjugate addition, if the base is chiral then this can again lead to selectivity between the possible enantiomers of the product (Scheme 5).



Scheme 5. Brønsted base catalysis

Iminium catalysis: In the presence of an amine an α,β-unsaturated carbonyl compound may form an iminium species **23** (Scheme 6).



Scheme 6. Iminium catalysis.

The use of an acid co-catalyst is often used to aid formation of the iminium species. After the conjugate addition has taken place, the iminium **24** may readily hydrolyse back to the carbonyl to give the desired product **19**, releasing the catalyst for further reactions. Iminium catalysis can be more complicated

to understand than Brønsted acid and base catalysis due to the number of covalent bonds that must form and break.

Bifunctional catalysts may participate in more than one of the above modes of catalysis (Figure 4).

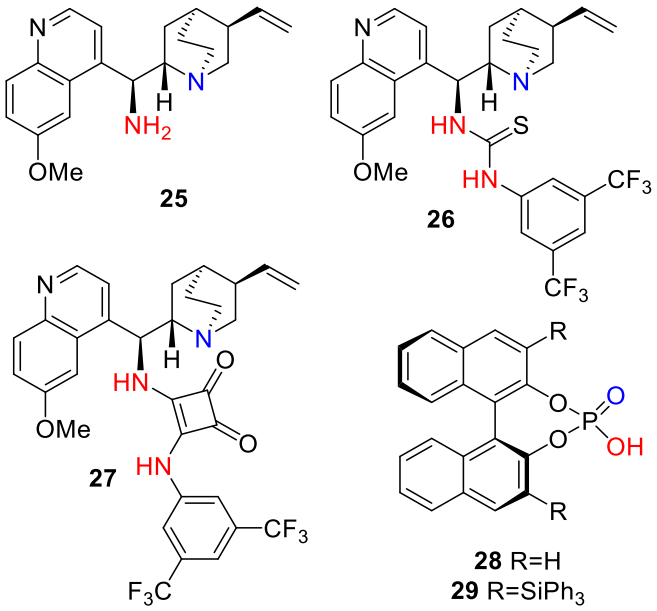


Figure 4. Some examples of potential bifunctional catalysts.

(Red = Brønsted acid/potential iminium, Blue = Brønsted base)

In these examples the Brønsted basic moieties of the catalyst (such as the quinuclidine or lone pair on the P=O oxygen) coordinate to an acidic part of a reactant, while acidic/iminium moieties (e.g. the amine **25**, thiourea **26**, squaramide **27** or P-OH **28** functionalities of each particular catalyst) coordinate to a basic part of the molecule. The activated nucleophile and electrophile are thus arranged within the chiral environment of the catalyst and the reaction takes place. As an example of this bifunctional activity, 9-*epi*aminoquinine **25** can form an iminium intermediate **30** *via* its primary amine, the quinuclidine can then act as a Brønsted acid or base (depending on its protonation state) to activate the nucleophile (Figure 5).

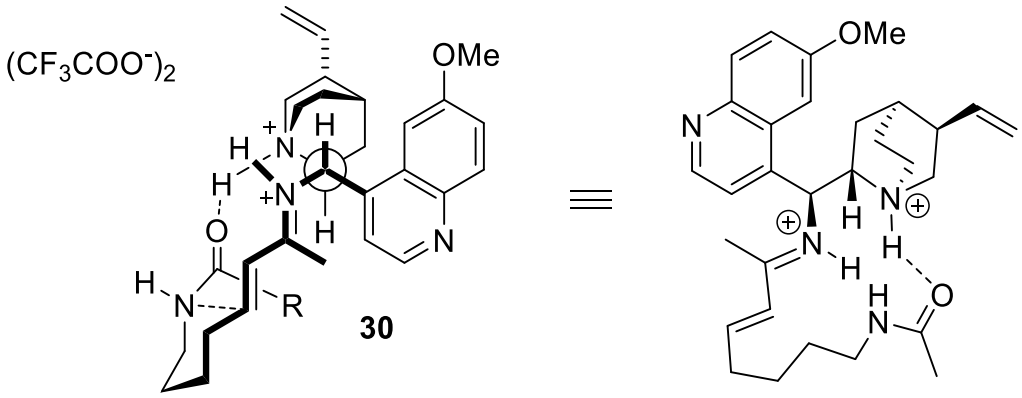


Figure 5. 9-*Epi*aminoquinine 25 acting as a bifunctional catalyst[29]

Modern asymmetric organocatalysis has many examples of cinchona alkaloid derived catalysts.[14] However, their utility for *N*-conjugate additions is relatively recent.

The cinchona alkaloids were first isolated from cinchona bark by Pelletier in 1820.[30] With antimalarial properties, quinine **31** became an attractive target for total synthesis attempts. The first and most famous of which was performed by Doering and Woodward in 1944, their formal synthesis when combined with the work of Rabe and Kindler served as the first total synthesis of quinine. Later asymmetric syntheses by Jacobsen *et al.* would combine asymmetric organocatalysis and natural product synthesis for another total synthesis (Figure 6). [31–34]

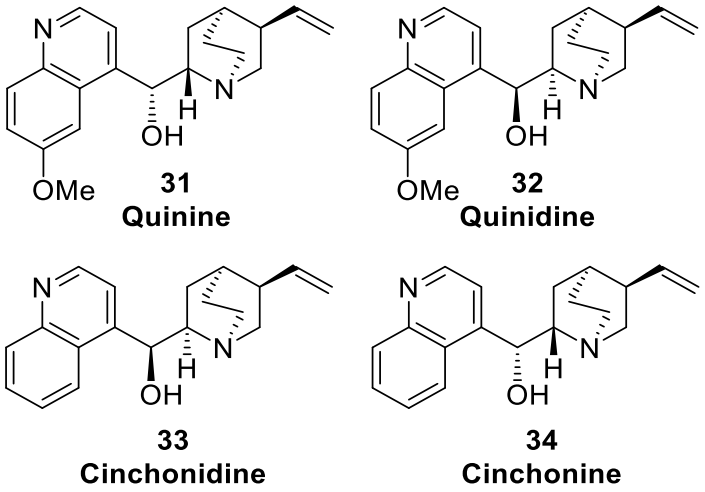
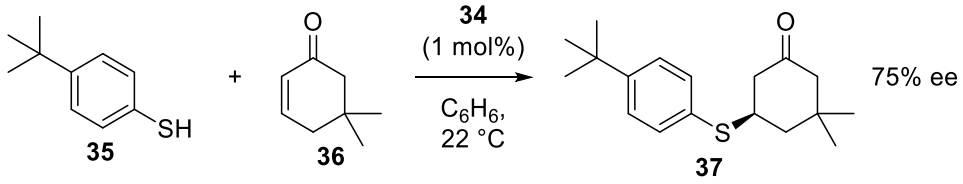


Figure 6. The cinchona alkaloids 31-34

In 1977 Wynberg *et al.* demonstrated that conjugate addition between thiophenols **35** and cycloalkenones **36** could be performed asymmetrically with cinchonine **34** (Scheme 7).[35,36]



Scheme 7. A landmark in hydrogen bonding asymmetric organocatalysis

This reaction has been investigated further more recently by Houk *et al.* was proposed. In silico modelling lead to an alternative transition state being proposed involving bifunctional organocatalysis. In Wynberg *et al.*'s original model **38** the protonated quinuclidine delivers the thiophenol **35** to the enone **36** held by the hydroxyl group of the cinchonine **34**. Houk *et al.* proposed a new model **39** in which the protonated quinuclidine hydrogen bonds to the enone **36** as the hydroxyl of the cinchonine **33** delivers the thiophenolate **35**. This new model proposed by Houk *et al.* was found to be lower in energy (Figure 7).[37]

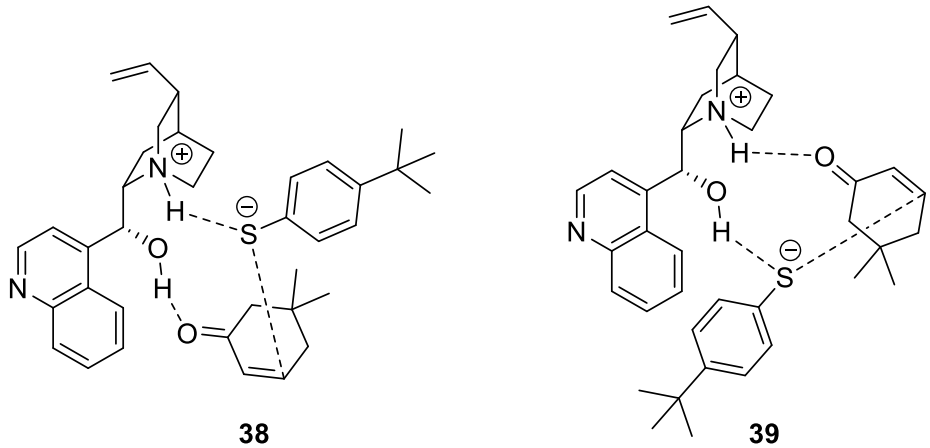
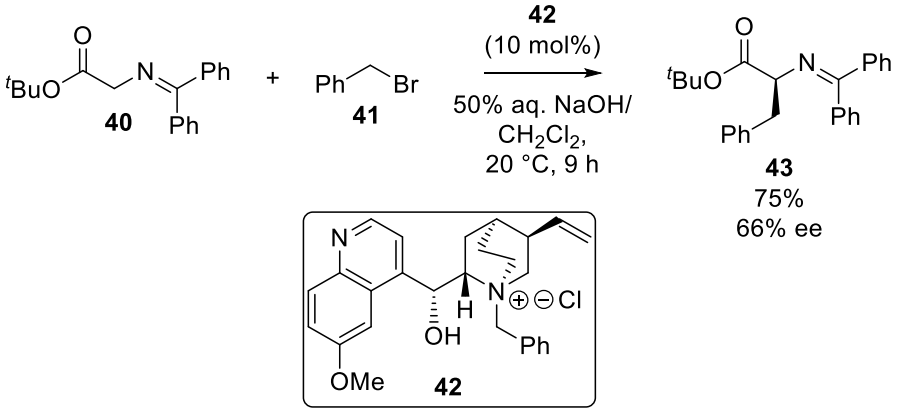


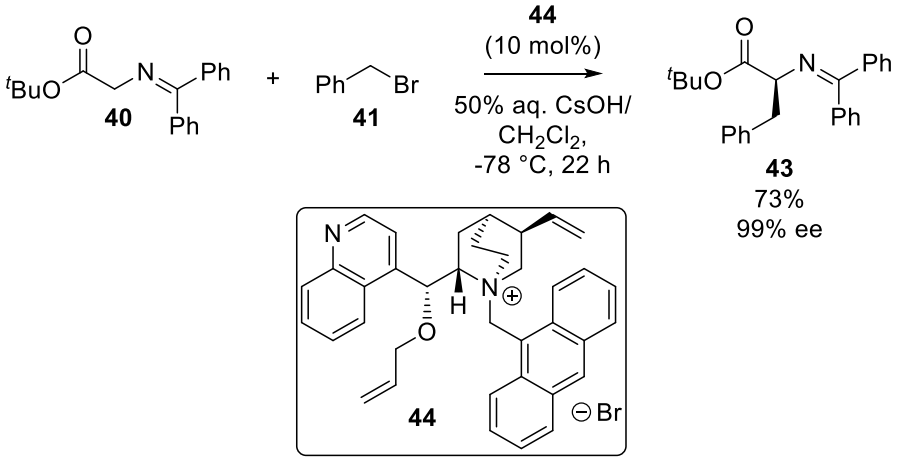
Figure 7. Modelling of the transition state by Wynberg *et al.* and Houk *et al.*

Cinchona alkaloids have since been modified to catalyse a multitude of chemical transformations, including aldol reactions, synthesis of β-lactones, cyanation of ketones, desymmetrisation of cyclic *meso* anhydrides and kinetic resolutions.[38–42] Stand out uses include as a phase transfer catalyst (PTC) for

asymmetric alkylations as described separately by Lygo *et al.* and O'Donnell *et al.* and later improved upon by modifications to the catalyst by Corey *et al.* (Scheme 8 and 9).[43–46]



Scheme 8. Representative PTC cinchona alkaloid 42 catalysed alkylation reaction by O'Donnell *et al.*



Scheme 9. Representative improved reaction by Corey *et al.*

Arguably the most famous and continued use for cinchona alkaloids is for asymmetric dihydroxylation leading to the rational design of modern catalysts such as $(DHQD)_2PHAL$ **45** (Figure 8).[47–49]

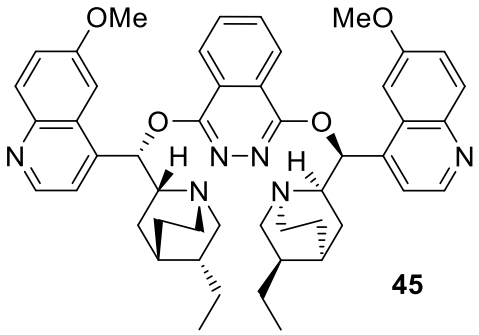
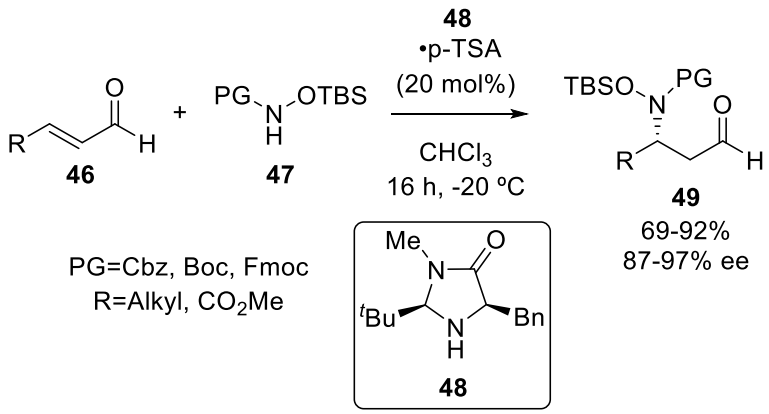


Figure 8. Hydroquinidine 1,4-phthalazinediyl diether 45 or $(DHQD)_2PHAL$

Amine Catalysts In *N*-Conjugate Addition Reactions

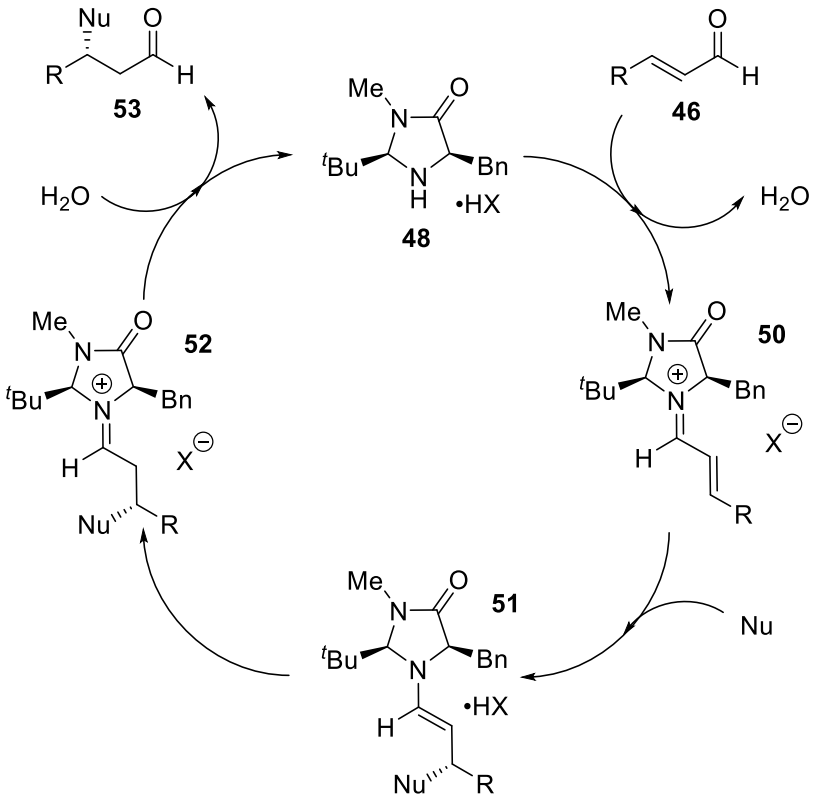
Intermolecular *N*-Conjugate Addition Reactions Using Secondary Amine Catalysts

A seminal example of asymmetric secondary amine catalysed intermolecular *N*-conjugate addition was reported in 2006 by MacMillan *et al.*.[50] It was reported that *N*-siloxycarbamates **47** could be combined with α,β-unsaturated aldehydes (enals) **46** to give β-amino aldehydes **49** with high enantiomeric excess (87-97% ee) (Scheme 10).[51]



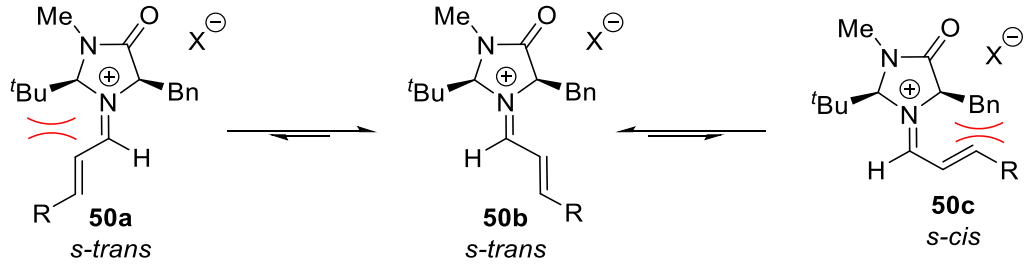
Scheme 10. MacMillan *et al. N*-conjugate addition catalysed by 48

MacMillan *et al*. had previously reported the use of imidazolidinone **48** in asymmetric C-C bond forming in aldol and Diels Alder reactions.[52–54] MacMillan *et al.* had proposed these previous reactions to be controlled by formation of an iminium species **50**, when imidazolidinone **48** condenses with enal **46** (Scheme 11).



Scheme 11. A proposed mechanism for the enantioselectivity of the amine catalyst 48

This iminium species lowers the LUMO of the electrophile and promotes the conjugate addition reaction. The catalyst likely dictates the configuration of species **50**; the steric repulsion is greatest when the alkenes configuration is s-*cis* to the *tert*-butyl group of the imidazolidinone, thus the s-*trans* lower energy (Scheme 12).

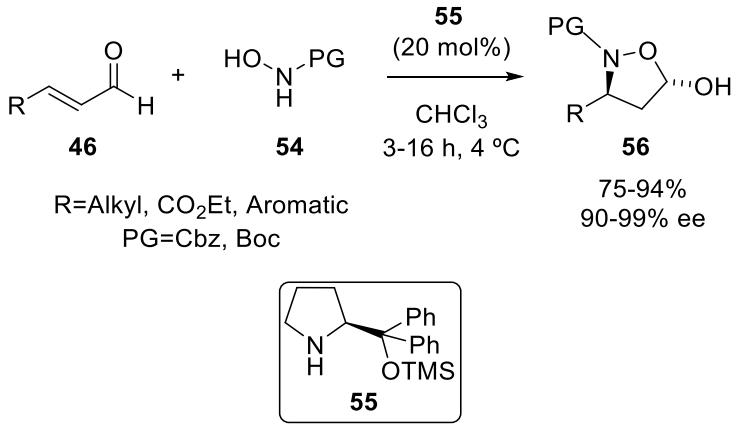


Scheme 12. Most favourable conformation of the iminium 50

Subsequently, when the nucleophile attacks the iminium intermediate **50b**, its approach is less hindered from the *Si* face, thus providing the enantioselectivity to favour enamine **51**. Enamine **51** is in equilibrium with the iminium **52** which

may undergo hydrolysis with the water generated at the start of the reaction to regenerate the catalyst and give the product **53**.

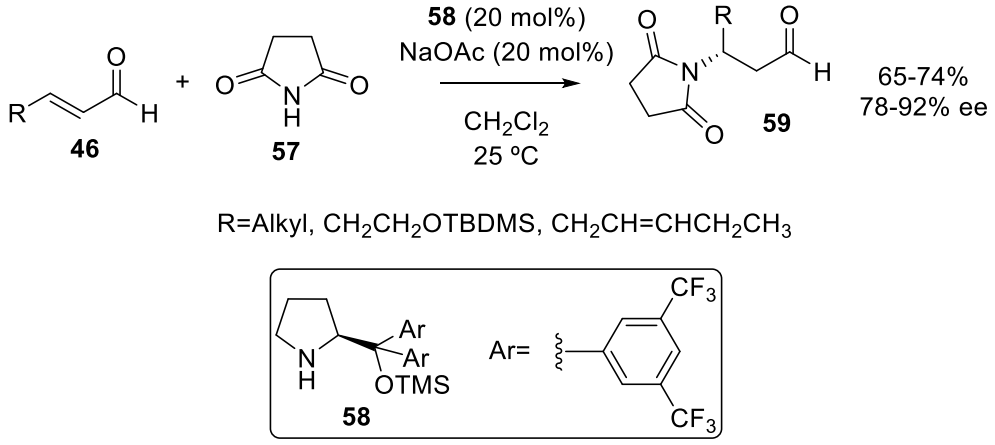
The MacMillan group reported their results shortly before Cordova *et al.* reported a related asymmetric intermolecular *N*-conjugate addition reaction.[55] Cordova *et al.* reported the proline derivative **55** catalysed reactions of hydroxylamine **54** and enal **46**, subsequent intramolecular hemiacetal formation gave hydroxyisoxazolidinone **56** (Scheme 13).



Scheme 13. Cordova *et al.*'s one pot formation of 5-hydroxyisoxazolidine 56

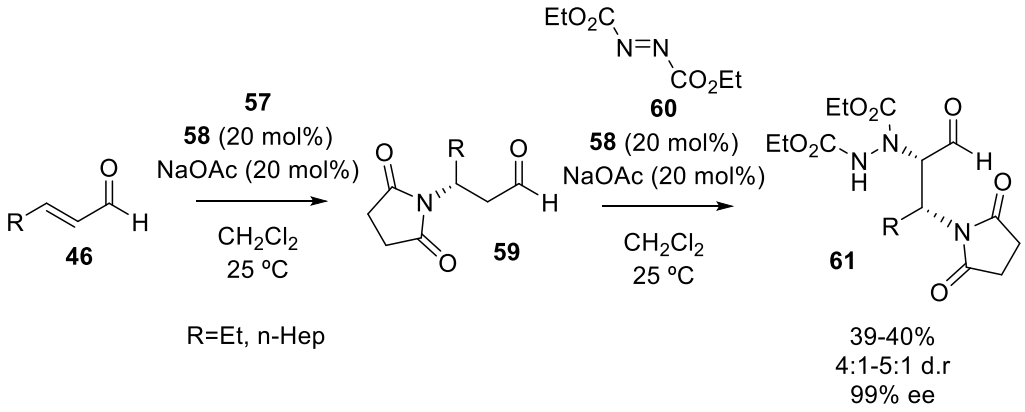
The proline derived catalyst **55** likely acts in a similar manner to that of imidazolidinone **48**. In that an iminium species is formed which is attacked from one diastereotopic face of the conjugated iminium is favoured.[55]

In 2007, Jørgensen *et al*. reported the *N*-conjugate addition of succinimide **57** with enals **46**, catalysed by a proline derived catalyst **58** (Scheme 14).[56]



Scheme 14. Jørgensen *et al.*'s *N*-conjugate addition with succinimide 57

These reactions are appealing as the succinimide functionality could potentially be unmasked to give the free amine thus installing a β-amine in relatively few steps using mild conditions. The group also report that the product can be further functionalised in a tandem reaction with the proline catalyst **58**. Diethyl azodicarboxylate **60** is introduced at the α-position to give the α,β-amine substituted **61** (Scheme 15).



Scheme 15. Further α-functionalisation performed by Jørgensen *et al.*

Further intermolecular *N*-conjugate additions of enals with various nitrogen nucleophiles such as tetrazoles **62**,[57] nucleosides such as Adenine **63**[58] and triazoles **64**[59] have been shown to work well with secondary amine catalysis (Figure 9).

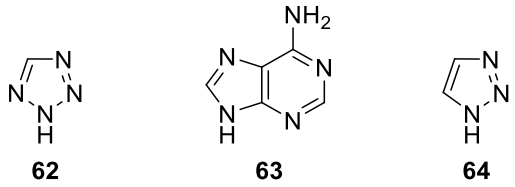
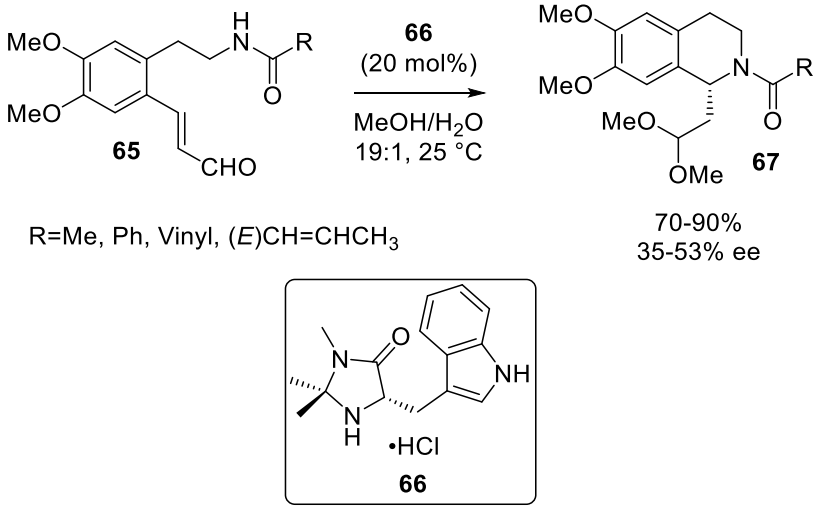


Figure 9. Tetrazole 62,[57] adenine 63[58] and triazole 64[59]

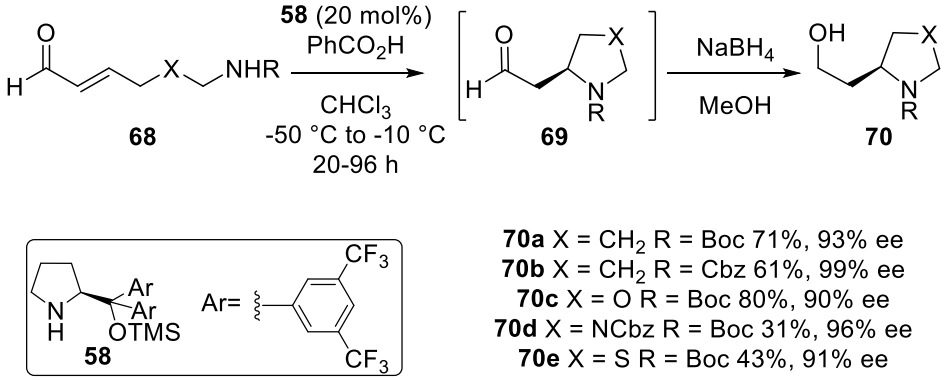
Intramolecular *N*-Conjugate Addition Reactions Using Secondary Amine Catalysts

In 2003, Ihara *et al.* reported asymmetric intramolecular secondary amine catalysed *N*-conjugate addition.[60] The reaction occurred between the amide and enal of compound **65** to give cyclised product **67** in good yields (70-90%) but with poor to moderate enantioselectivity (35-53% ee) (Scheme 16).



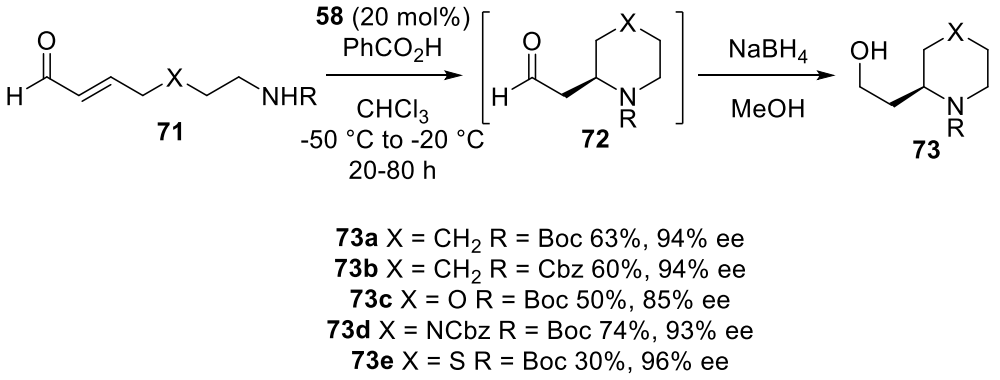
Scheme 16. Intramolecular *N*-conjugate addition reported by Ihara *et al.*

In 2007, Fustero *et al.* reported intramolecular reaction between a nitrogen nucleophile and an enal to form a range of *N*-heterocyclic products (Scheme 17).[61]



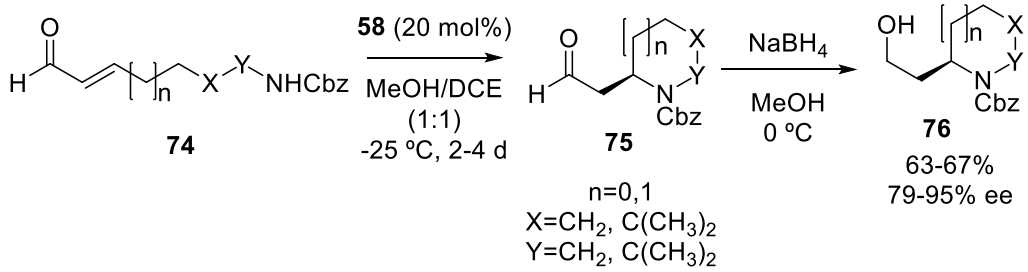
Scheme 17. The cyclisation of substrates to form 5 membered *N*-heterocyclic rings using amine 58

Fustero *et al.* reported reactions of aldehyde **68** and **71** with use of proline derived catalyst **58** and benzoic acid co-catalyst, gave a range of 5 and 6 membered heterocyclic products **70a-70e** and **73a-73e**. The aldehyde intermediates **69** were reported to be unstable for HPLC analysis. To overcome this, the aldehydes were reduced to more stable alcohols **70** (Scheme 17 and 18).[62]



Scheme 18. The cyclisation of substrates to form 6 membered *N*-heterocyclic rings using amine 58

However, Fustero *et al*.'s use of low temperatures, gradual warming over prolonged were not ideal conditions for industrial synthesis. In 2008, Carter *et al*. reported improved conditions compared to those previously reported by Fustero *et al*.. Similar yields and enantioselectivities were obtained in reactions using the same catalyst and similar substrates (Scheme 19). [62]



Scheme 19. Carter *et al.*'s improved conditions

Carter *et al*. used reaction temperatures of -25 °C as opposed to -50 °C and performed reactions in the absence of the acid co-catalyst. Potentially a wider range of substrates could be used that previously wouldn't have tolerated the acid or would have been too unreactive at low temperatures.

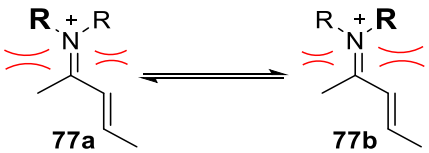
Carter *et al*. also investigated the effect that dimethyl substitution α or β to the nitrogen nucleophile has on the cyclisation. Dimethyl substituents β to the nitrogen appeared to have little effect on yield or enantioselectivity of the five or six membered rings **76**. However, dimethyl substituents on the α position appears to have stopped piperidine formation, whilst the reaction time is doubled with a decrease in enantioselectivity to 11% for the formation of

pyrrolidines. These observations are likely the effect of steric interactions between the methyl groups and the bulky groups on the catalyst.

Problems With Secondary Amine Catalysts

Although useful, secondary amines have limitations for catalysis of *N*-conjugate addition reactions. Though successful with enals, reactions failed to give the same success or levels of enantioselectivity when used with α,β-unsaturated ketone substrates.

When an iminium species is formed from a secondary amine catalyst and an enal, the resulting product favours a configuration in which the largest substituents are arranged *trans* to one another. The difference in steric bulk between a methyl group borne by a ketone and a proton is large; in aldehyde substrates the iminium resulting from a secondary amine catalyst and an enone lacks this configurational selectivity (Scheme 20).

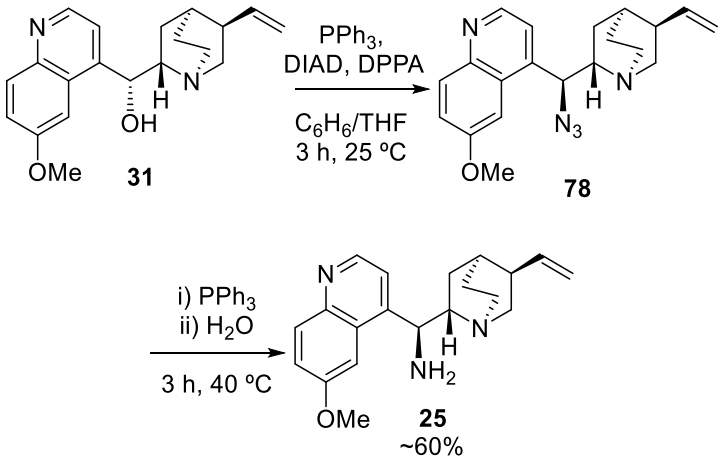


Scheme 20. Lack of configurational selectivity with secondary amines and ketones

This lack of a control over iminium configuration erodes enantioselectivity as the nucleophile may be able to approach either face of the enone.

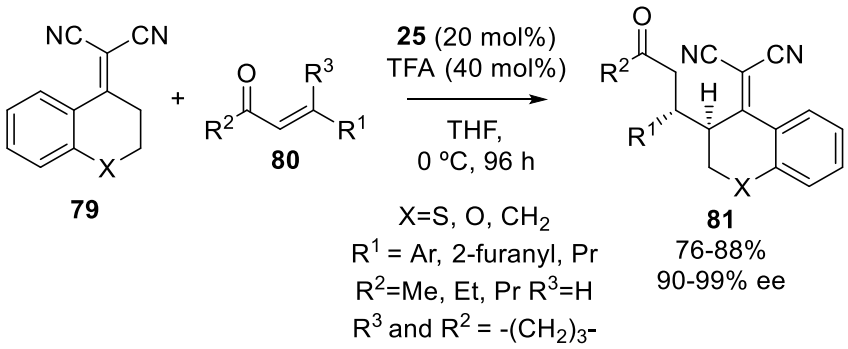
Intermolecular *N*-Conjugate Addition Reactions Using Primary Amine Catalysts

Transformation of the primary alcohol of quinine into an amine at the C-9 position provides new opportunities for reactivity and development of new catalysts.[63] Displacement of a hydroxyl by an azide under Mitsunobu conditions gives the cinchona alkaloid azide **78** with inversion an inversion in stereochemistry. This azide **78** is not normally isolated but immediately converted to amine **25** by a Staudinger reduction using triphenylphosphine and water (Scheme 21).



Scheme 21. Preparation of 9-*epi*aminoquinine 25 from quinine 31

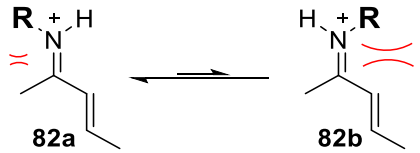
The amine catalyst 9-*epi*aminoquinine **25** has also been reported with a large scope of substrates.[14] In 2007, J.G. Deng *et al*. reported that primary amine of 9-*epi*aminoquinine **25** was able to catalyse the reaction of α,α-dicyanoalkenes **79** with α,β–unsaturated ketones **80**.[64] This was the first time that 9-*epi*aminoquinine **1** was shown to catalyse reactions to such high enantioselectivities (Scheme 22).



Scheme 22. Deng *et al.* 9-*epi*aminoquinine 25 catalysed *N*-conjugate addition reaction

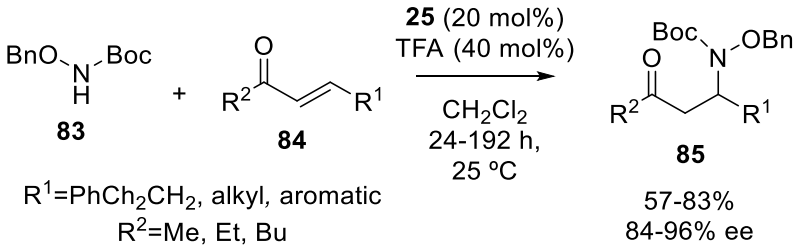
J.G. Deng *et al*. reported that their initial attempts to perform the reaction using secondary amine catalysts were unsuccessful, rationalising that the amines were too bulky and therefore unfavourable for iminium formation.

On the other hand iminiums derived from primary amines have fewer steric clashes between groups either side of the C=N bond thus allowing one configuration to predominate (Scheme 23).



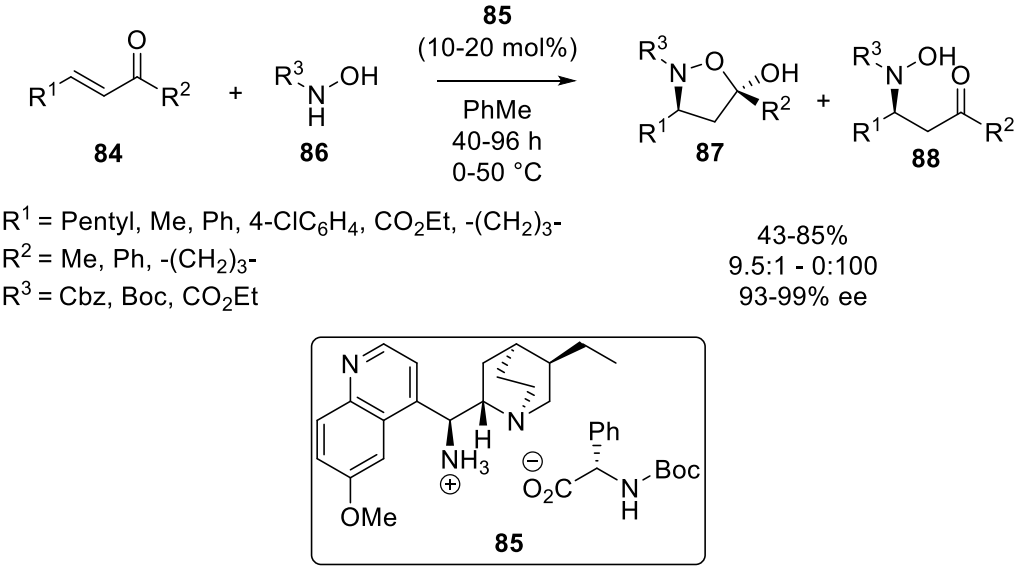
Scheme 23. Conformational selectivity in primary amine derived iminiums from enones

In 2008, L. Deng *et al*. reported the first asymmetric primary amine catalysed intermolecular *N*-conjugate addition reaction.[65] Amine **83** combined with α,β-unsaturated ketone **84** catalysed by amine 9-*epi*aminoquinine **25** giving good yields and enantioselectivity (Scheme 24).



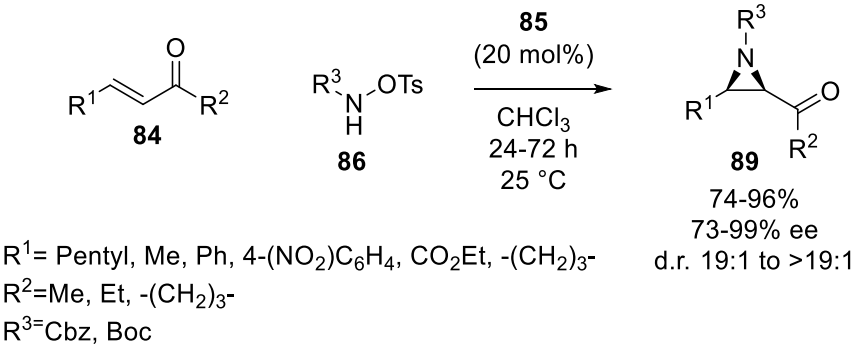
Scheme 24. L. Deng *et al.* report the first *N*-conjugate addition to an enone using amine catalyst 25

In 2008, Melchiorre *et al.* reported intermolecular *N*-conjugate additions between protected hydroxylamine **86** and enones **84** using an amine catalyst derived from 9-*epi*aminoquinine **85** (Scheme 25).[14,66]



Scheme 25. Melchiorre *et al.* *N*-conjugate addition using protected hydroxylamines 86

The ratio between hemiacetal **87** and addition product **88** was highly dependent on the substituent R^2. When R^2 consisted of aliphatic groups the ratio was highly in favour of the formation of the hemiacetal **87**. Aromatic or a cyclic enone shifted the product distribution towards addition product **88**. Melchiorre *et al.* also note that if the hydroxyl group of the hydroxyl amine **86** was replaced with a leaving group then aziridines **89** could be formed (Scheme 26).

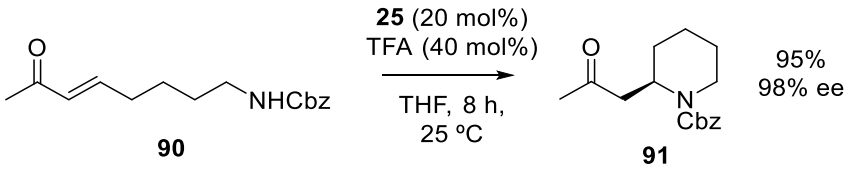


Scheme 26. Aziridine 89 formation

Intramolecular *N*-Conjugate Addition Reactions Using Primary Amine Catalysts

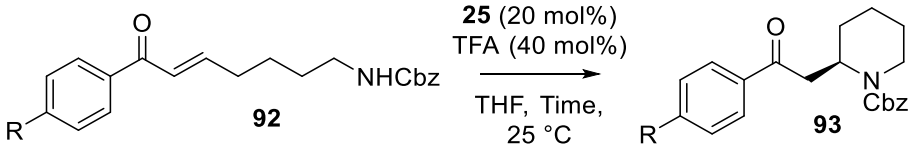
Primary amine 9-*epi*aminoquiinine **25** was soon applied to intramolecular *N*-conjugate addition reactions involving α,β-unsaturated ketones.

In 2011 Fan *et al.* reported that 9-*epi*aminoquinine **25** was capable of promoting cyclisations of substrates such as enone **90** to form piperidines **91** in good yields and high enantioselectivity (Scheme 27).[67]

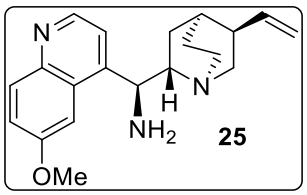


Scheme 27. *N*-Conjugate addition reaction reported by Fan *et al.*

They noted that the aliphatic ketones such as methyl ketones experienced short reaction times in comparison to the aromatic ketones (Scheme 28).

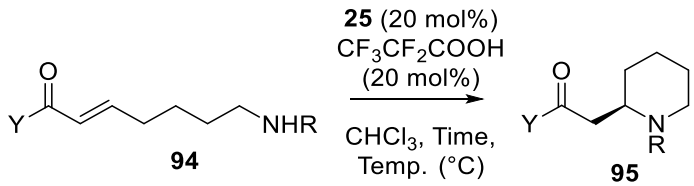


Entry	R	Time (h)	%Yield	% ee
1	H	24	95	96
2	Me	120	75	96
3	OMe	120	0	-
4	NO_2	84	80	85

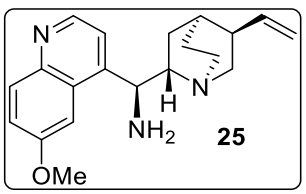


Scheme 28. Cyclising aromatic ketones with 9-*epi*aminoquinine by Fan *et al.*

In this study it was shown that the use of an acid co-catalyst not only increased the rate of the reaction but also the enantioselectivity. Similar observations were reported by Fustero *et al.* using similar conditions (Scheme 29).[29]



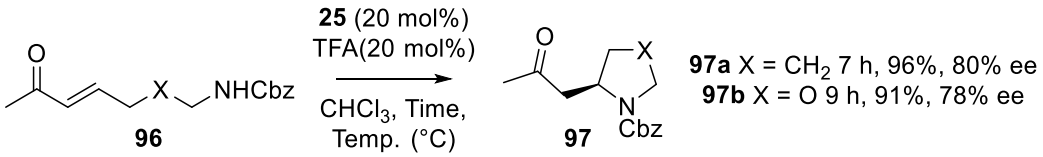
Entry	Y	PG	Temp. (°C)	Time (h)	%Yield	% ee
1	Me	Boc	25	15	92	93
2	Me	Boc	60	1	58	93
3	Ph	Cbz	25	240	97	90
4	Ph	Cbz	60	4	75	84



Scheme 29. Fustero *et al.* *N*-conjugate addition reaction

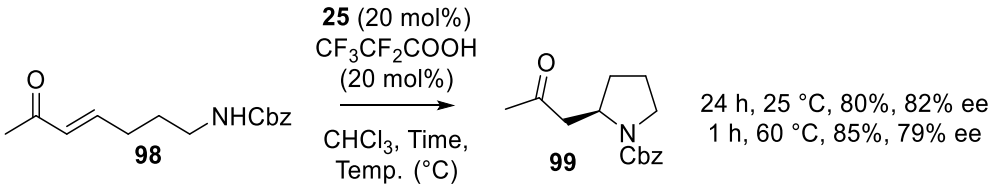
In both reports, the use of methyl ketones resulted in faster formation of the product when compared to the phenyl ketones, presumably because of the slower rate of imine formation associated with phenyl enones.

When pyrrolidine rings were formed rather than six membered rings, the reaction times were similar but the enantioselectivity was lower in the range of 78-82% (Scheme 30).



Scheme 30. Fan *et al.* reactions forming 5-membered rings

Both Fan *et al.* and Fustero *et al.* observed that the enantioselectivity of the pyrrolidines were lower than that of the piperidines (Scheme 31).



Scheme 31. Fustero *et al.* reactions forming 5-membered rings

Iminium formation using primary amines is not without limitations. The key steps involved in the reaction mechanism revolve around covalent bonds being made and broken. The reactions in which large substituents are present within the substrate containing the α,β-unsaturated ketone generally suffer from long reaction times (over a week), large scale industry synthesis cannot afford for reactors to be occupied by one reaction for such time periods. The primary amines also fail to catalyse enantioselective reactions where the α,β-unsaturated carbonyl functionality cannot form imines, such as esters and amides.

Brønsted Acid Catalysts In *N*-Conjugate Addition Reactions

Potential solutions to these problems can be found in different methods of enone activation. Brønsted acid catalysts are able to protonate or partially

protonate the carbonyl of an enal or enone activating it to nucleophilic addition. When combining this mode of activation with a Brønsted base able to accept a proton from the incoming nucleophile, stereoselective *N*-conjugate addition reactions can be performed. Brønsted acid catalysts described in this section contain one of the following functional groups: thioureas **100**, squaramides **101** and phosphoric acids **102** (Figure 10).

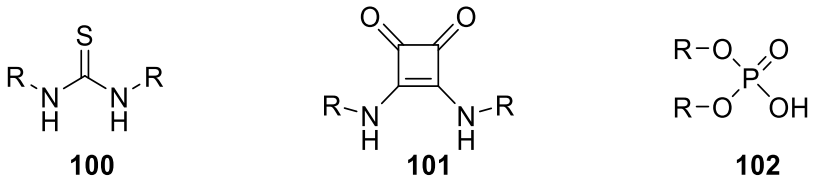


Figure 10. Thioureas, squaramides and phosphoric acids general structures

Unlike amine catalysis, no covalent bonds are broken or formed with respect to the mode of activation. Substrates found previously to be incompatible with imine formation may be compatible with this form catalysis.

Intermolecular Reactions Using Brønsted Acid Catalysts

Thioureas have been shown to catalyse *N*-conjugate addition reactions in good enantioselectivity by Takemoto *et al*. [68] and Jacobsen *et al*. (Figure 11). [69]

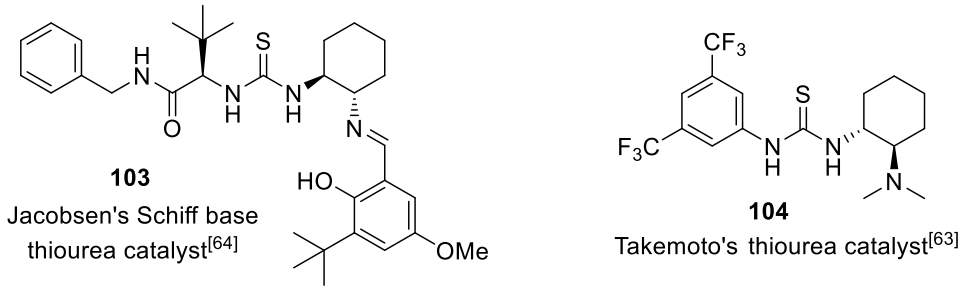
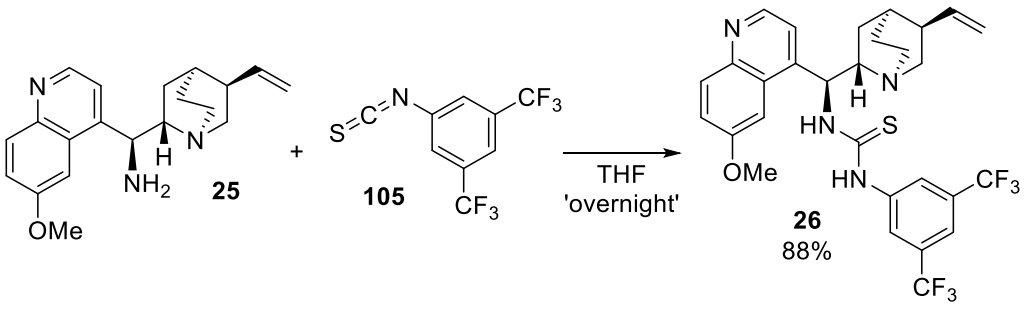


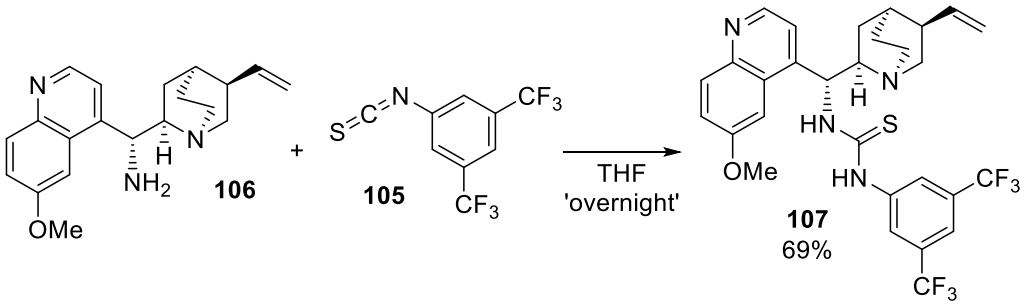
Figure 11. Thiourea catalysts used by Takemoto *et al.* and Jacobsen *et al.*

In 2005, Soos *et al*. reported the synthesis of thiourea catalysts **26** and **61** from amine derived cinchona alkaloids **25** and **107** (Scheme 32).[70]



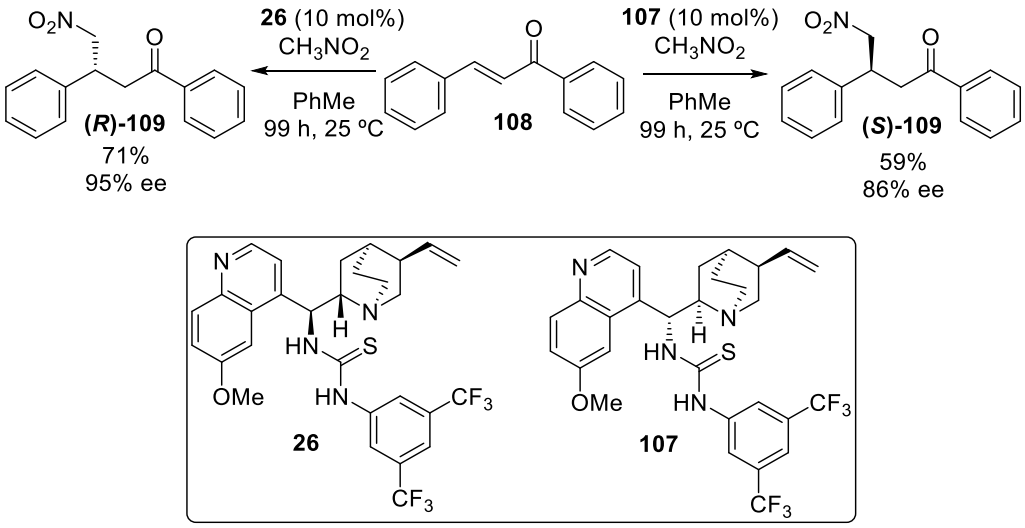
Scheme 32. Catalyst 26 made from 9-*epi*aminoquinine 25

Soos *et al.* prepared 9-*epi*aminoquinidine **25** using a method outlined by Schmidt and Brunner.[71] The thiourea catalyst derived from 9-*epi*aminoquinidine **106** is a different diastereoisomer to that of the thiourea catalyst derived from 9-*epi*aminoquinine **25** differing at C8 and C9 positions (Scheme 33).



Scheme 33. Catalyst 107 made from 9-*epi*aminoquinidine 106

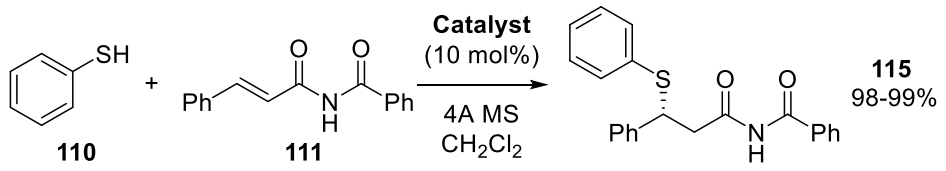
These cinchona thioureas were found to be capable of catalysing asymmetric conjugate additions between nitromethane and chalcone **108** (Scheme 34).



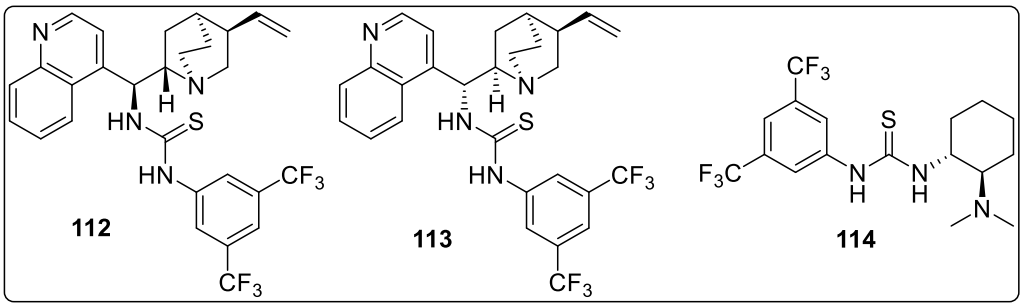
Scheme 34. Cinchonathiourea catalysed conjugate addition

Opposite enantiomers of products were obtained depending which diastereoisomer catalyst was used (catalysts **26** and **107**). These catalysts are capable of hydrogen bonding to the carbonyl of the electrophile *via* the thiourea, whilst the quinuclidine may potential direct the approach of the nitromethane.

In 2005, Li *et al*. investigated thiourea catalysts **112** and **113** in reactions between thiophenols **110** and unsaturated imide **111**. These studies concluded that catalysts **112** and **113** were capable of catalysing this reaction but enantioselectivity was poor compared to previously reported catalyst **114** made by Takemoto *et al.* (Scheme 35).[72]

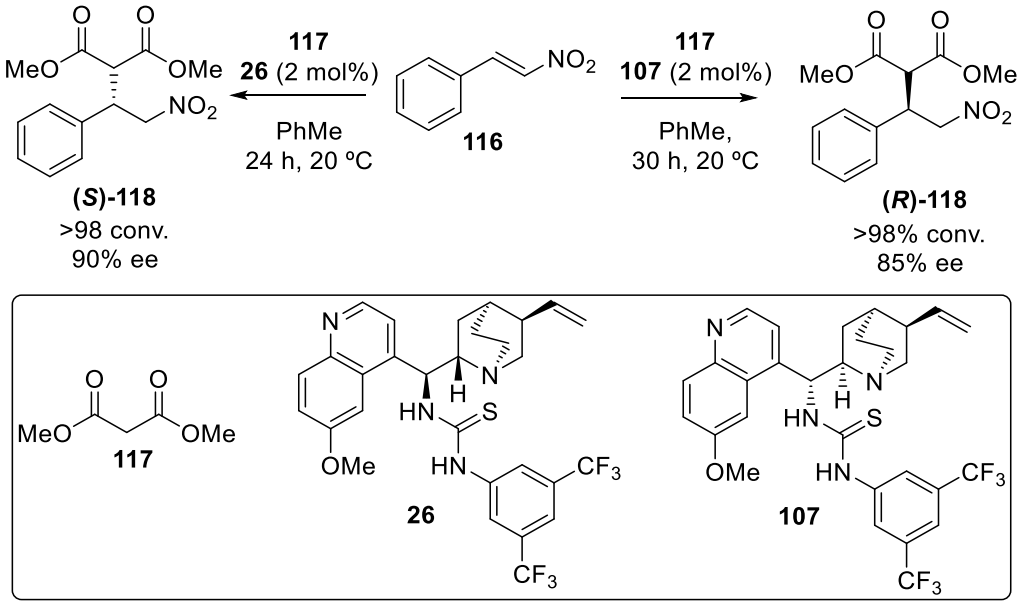


Entry	Catalyst	Temp (ºC)	Time (h)	ee (%)
1	**112**	20	2	7
2	**113**	20	2	17
3	**114**	20	4	60
4	**114**	0	12	67
5	**114**	-40	72	75



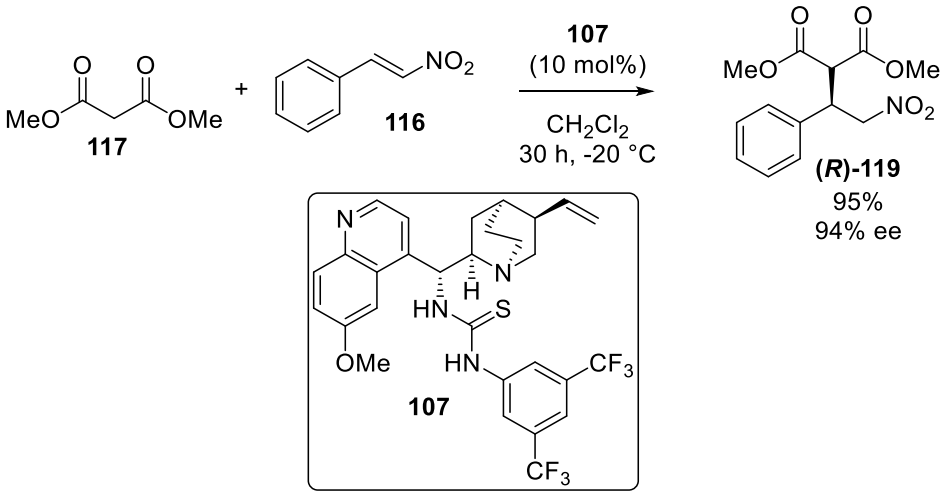
Scheme 35. *N*-Conjugate additions catalysed by thioureas 52, 53 and 56

In 2005, Connon *et al*. reported asymmetric conjugate additions between β-nitrostyrene **116** and malonate **117**. Again the enantiomeric products were obtained depending on which catalyst diastereoisomer was used (Scheme 36).[73]



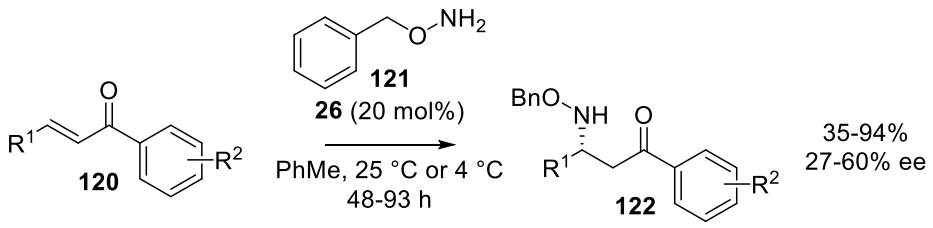
Scheme 36. Example of work by Connon *et al.*

Dixon *et al*. simultaneously reported similar observations in the conjugate addition reaction between malonate **117** and β-nitrostyrene **116** (Scheme 37).[74]



Scheme 37. Example of work by Dixon *et al.*

In 2007 Ricci *et al.* reported that the cinchona thiourea catalyst **26** was capable of promoting asymmetric *N*-conjugate addition reactions between *O*-benzylhydroxylamines **121** and chalcones **120** (Scheme 38).[75]



R^1=H, Me, Bu, ^{t}Bu, 4-$MeOC_6H_4$, 4-ClC_6H_4, 2-Cl, C_6H_4, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 3-MeC_6H_4, 3-$NO_2C_6H_4$, 2-furyl, 1-napthyl
R^2=H, 4-OMe, 4-NO_2, 2-Me

Scheme 38. Thiourea 26 promoted *N*-conjugate addition reaction

Between 2005 and 2008 a vast number of publications describe use of thiourea catalysts to achieve reactions ranging from Michael additions,[76] Morita-Baylis-Hillmann,[77] Friedel-Crafts,[78] Petasis[79] and Diels-Alder reactions.[80]

The attraction of thiourea derived catalysts **123** stems from their ability to potentially hydrogen bond with substrates using potentially both protons of the thiourea moiety. For this reason, Rawal *et al.* proposed that the squaramide unit **124** may prove a versatile moiety due to the extra distance between the protons (Figure 12).[81]

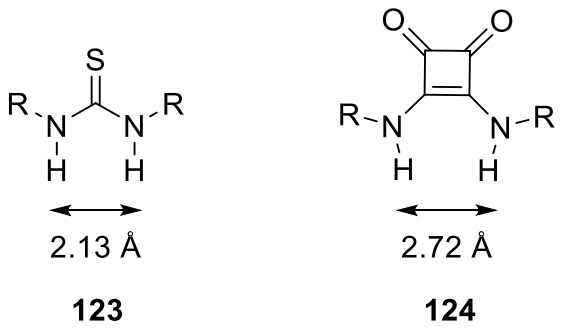
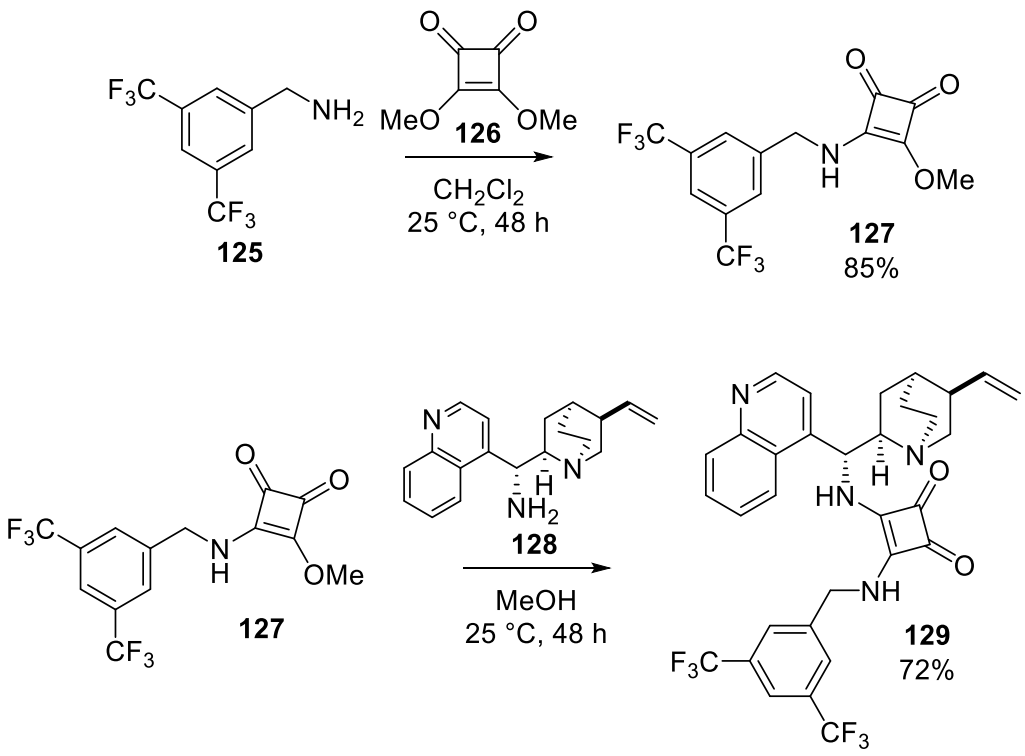


Figure 12. Squaramide distance between protons versus a thiourea

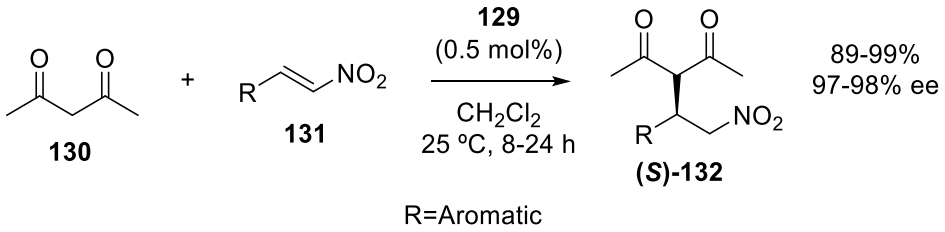
In 2008, Rawal *et al*. reported the synthesis of a cinchonine **33** derived squaramide catalyst **129** (Scheme 39).[81]



Scheme 39. Synthesis of cinchonine squaramide catalyst 73

Benzylamine **125** and dimethylsquarate **126** were reacted in a 1:1 ratio to give product **127**. Product **127** and 9-*epi*aminocinchonidine **128** were then reacted 1:1 to generate the squaramide catalyst **129**.

The squaramide derivatives of cinchonidine **34**, quinine **31** and quinidine **32** were also made the same way. The conjugate addition reaction between dimethyl malonate **130** and various aromatic nitroalkenes **131** proceeded with high enantioselectivity using low catalyst loadings (Scheme 40).

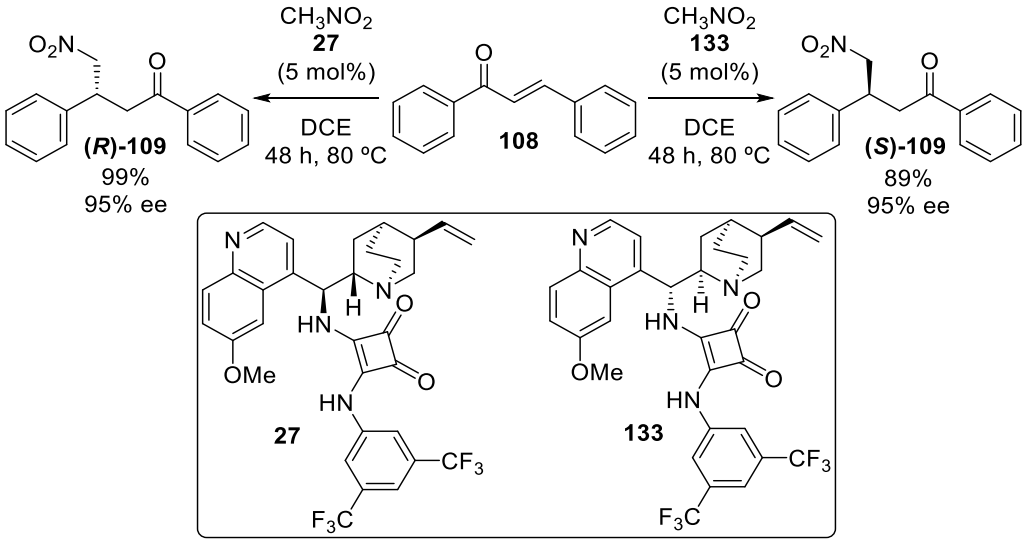


Scheme 40. Squaramide 129 catalysing a reaction with low catalyst loading

These results compared favourably to related experiments described by Dixon *et al*. using the cinchona derived thioureas. Squaramide catalysts may in fact

be a more efficient class of catalysts, giving higher enantioselectivity with a lower loading.

In 2010, Du *et al.* published the use of squaramides **27** and **133** derived from quinine **31** and quinidine **32** cinchona alkaloids in 1,4-conjugate addition reactions (Scheme 41).[82]

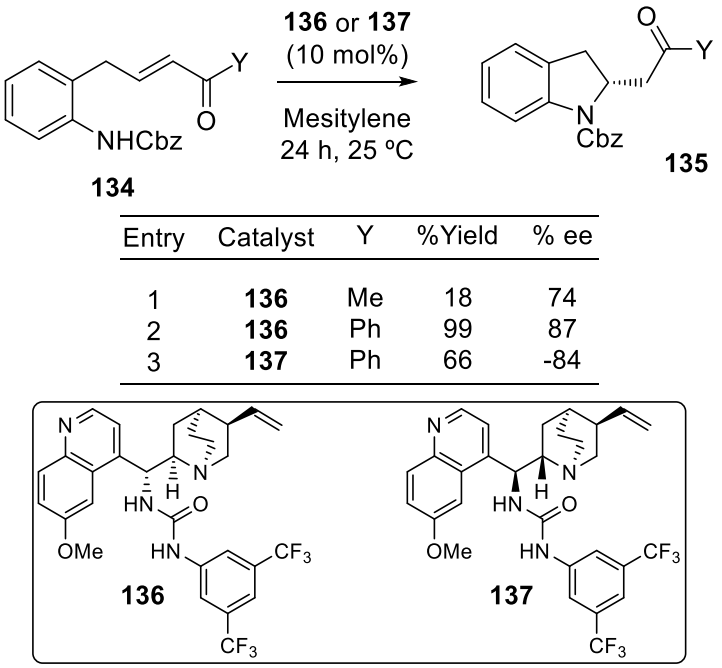


Scheme 41. Squaramide catalysts derived from cinchona alkaloids

They demonstrated that selective formation of enantiomeric products **109** in good yields and enantioselectivity, depending which diastereomeric catalysts was used despite the use of elevated temperatures. A result similar to observations for the thiourea derived catalyst described by Soos *et al.*.[70]

Intramolecular Reactions Using Brønsted Acid Catalysts

In 2013, Matsubara *et al.* reported that the cinchona derived ureas **136** and **137** could promote the intramolecular *N*-conjugate addition of aniline derivatives such as **134** (Scheme 42).[83]



Entry	Catalyst	Y	%Yield	% ee
1	**136**	Me	18	74
2	**136**	Ph	99	87
3	**137**	Ph	66	-84

Scheme 42. Use of the cinchona derived ureas by Matsubara *et al.*

This catalyst worked well with phenyl ketones (Entries 2 and 3). However, conjugate addition reactions of a methyl ketone (Entry 1) was attempted the products were obtained in lower in yield and enantioselectivity.

In 2004, both Terada *et al*. [84] and Akiyama *et al*. [85] reported pioneering studies in the use of BINOL derived phosphoric acids. Since then, these Brønsted acid catalysts have been applied to a range of asymmetric reactions.[86] The chiral axis of the phosphoric acid when combined with large bulky substituents R (typically substituted aromatic rings) creates a chiral environment around the phosphoric acid moiety (Figure 13).

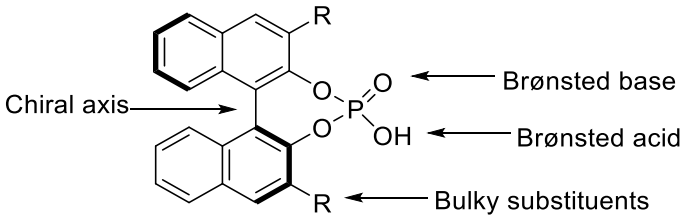
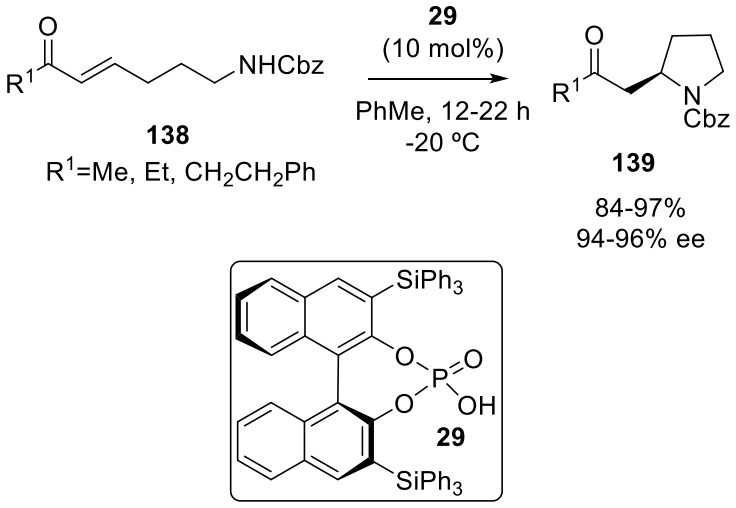


Figure 13.The key features of the BINOL derived phosphoric acids[87]

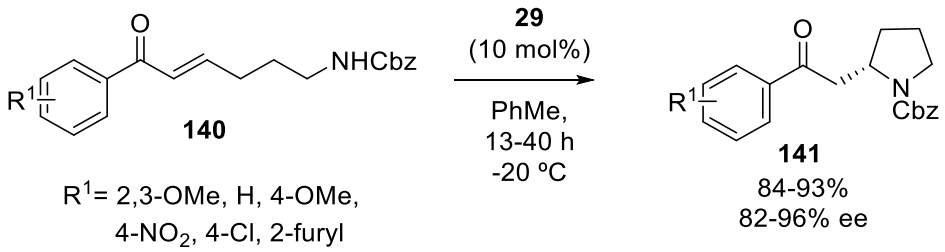
Though these phosphoric acid catalysts have been widely used for asymmetric catalysis, it is only recently that they have been used in intramolecular *N*-conjugate addition reactions.

In 2013 Yu *et al.* reported that BINOL derived phosphoric acid **29** could promote cyclisations of similar substrates in high enantiomeric excess (Scheme 43).[88]



Scheme 43. Chiral phosphoric acid 29 promoted *N*-conjugate addition reactions of enones

BINOL derived phosphoric acid **29** generated pyrrolidines **139** in good yield and enantioselectivity when the enone was aliphatic or aromatic with only a small change in reaction time being the notable difference (Scheme 44).



Scheme 44. Tolerance of aromatic enones

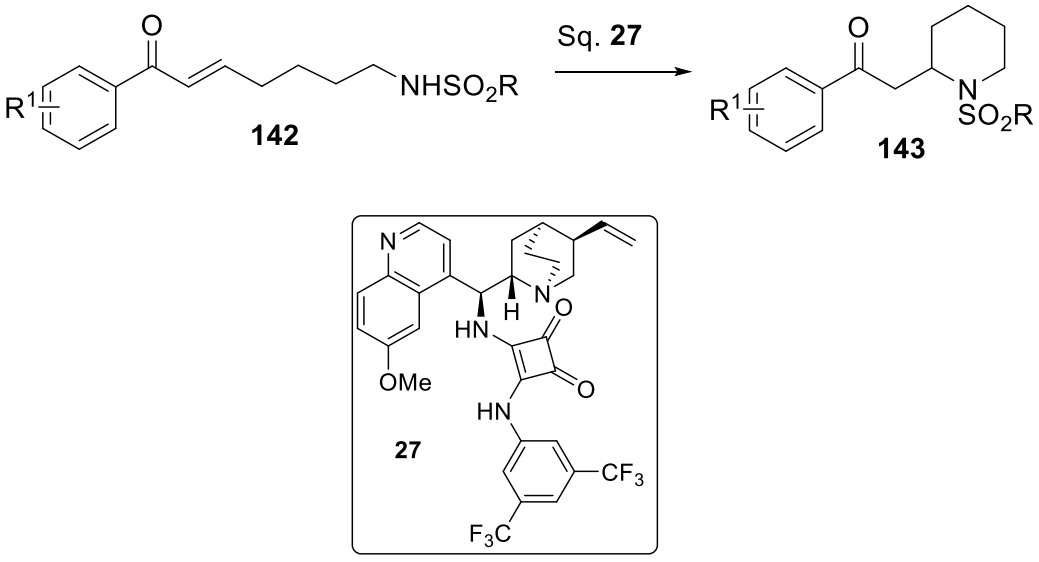
In summary, as the substrate focus has shifted from aldehydes (enals), to methyl ketones (enones), aromatic ketones and currently focuses on α,β-unsaturated esters and amides, the type of catalysis and the catalysts mode of action have had to evolve alongside. This evolution has moved from ineffective but pioneering work with hydrogen bonding catalysts through secondary and

primary amines using iminium catalysis but attention has returned towards better designed and better understood hydrogen bonding catalysts.

Project Aims

Upon commencing work, no literature examples of *N*-conjugate addition between sulfonamides and α,β-unsaturated carbonyls had been reported. The recently reported cinchona derived squaramide catalyst **27** was of great interest as it had been shown to be potentially a better catalyst than the then state-of-the-art cinchona-derived thiourea catalyst **26**.

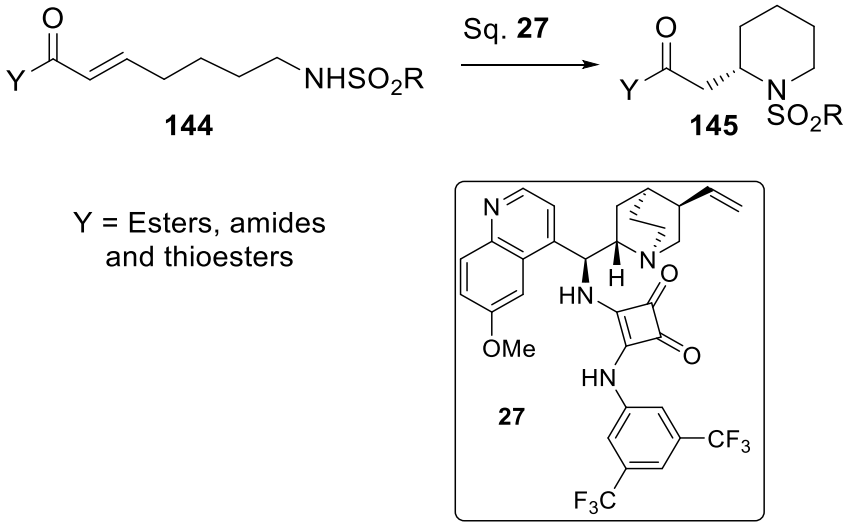
We aimed to investigate the use of the cinchona derived squaramide catalyst **27** in the synthesis of different heterocycles (pyrrolidines, piperidines, and oxazinanes) by the *N*-conjugate addition of a sulfonamide and an α,β-unsaturated carbonyl. Previously aldehydes, methyl and to some extent phenyl ketones were all that was possible using amine derived catalysts. With the use of a potential hydrogen bonding catalyst we set out to look at improving the work on phenyl ketones **142** with regards to lower reaction temperatures and times whilst also attempting to drop the catalyst loading (Scheme 45).



Scheme 45. Investigation of phenyl ketones

Esters, amides and thioesters had not been incorporated into asymmetric synthesis with organocatalysts before and was of keen interest with the

potential to access interesting drug like targets both natural and unnatural (Scheme 46).



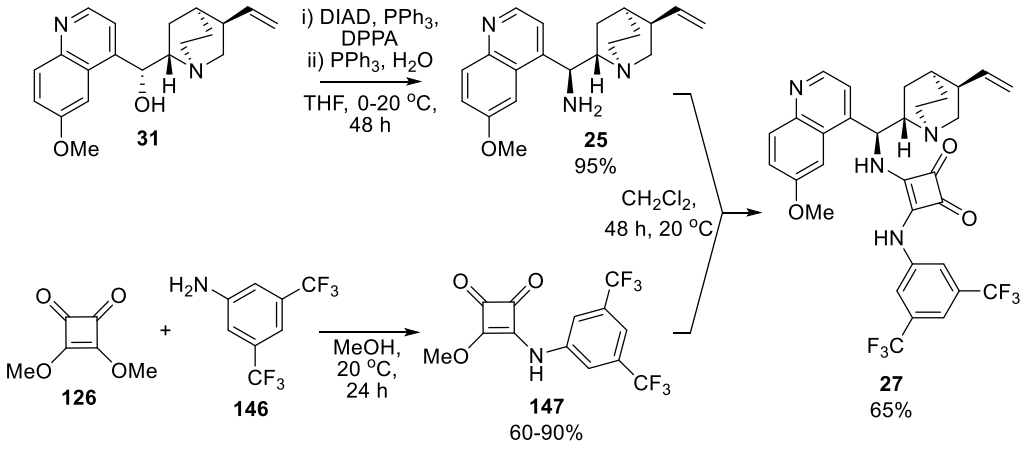
Scheme 46. Esters, amides and thioester incorporation

If this work with simple heterocycles proved successful we aimed to look at heterocycles that had not previously been reported being synthesised by asymmetric organocatalysis.

Results And Discussion – Chapter One

Catalyst Synthesis

The squaramide catalyst **27** is a known compound first synthesised by Rawal *et al.* and Du *et al.* (Scheme 47).[81,82]

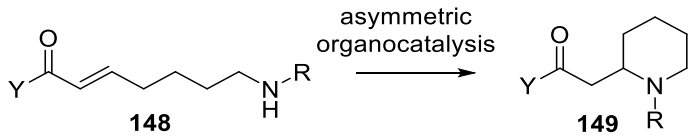


Scheme 47. Synthesis of the squaramide catalyst

Mixing stoichiometric squarate **126** and aniline **146** for a day resulted in clean crystallisation of the desired product **147**. Synthesis of the other chiral part of the catalyst involved conversion of commercially available quinine **31** into 9-*epi*-aminoquinine **25** using a one pot reaction.[63] First, a Mitsunobu reaction replaced the alcohol with an azide whilst inverting the stereochemistry; immediate Staudinger reduction provides clean amine product after simple aqueous work up in 95% yield. It was then subsequently found that if this crude product contained coloured impurities coupling reactions proved difficult. Instead 9-*epi*aminoquinine **25** was purified by flash column chromatography gave a yellow product. Subsequent reaction of the methoxy squarate **147** with this amine **25** proceeded cleanly.

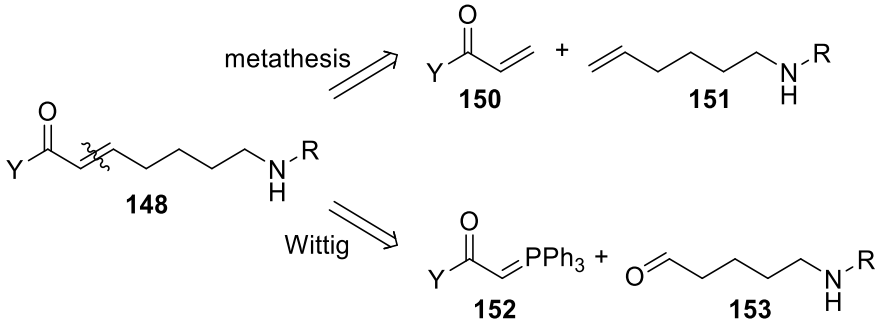
Synthesising The Desired Enones

Our initial investigation focussed on the synthesis of various chiral heterocycles by the use of an intramolecular *N*-conjugate addition (also commonly known as an *aza*-Michael reaction) using asymmetric organocatalysis (Scheme 48).



Scheme 48. Forming piperidines by *N*-conjugate addition

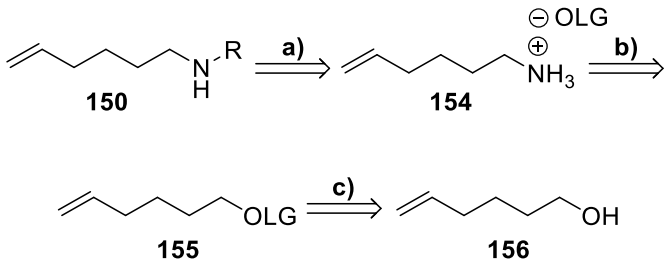
For the chemistry to be both attractive and synthetically useful the starting enone **148** would have to be made by a route with as few steps and with as cheap material as was possible. The synthesis plan typically focussed on the olefin, as many methods to form this require conditions likely to cause premature racemic cyclisation to occur (acid, base, Brønsted acid, Brønsted base, Lewis acid and Lewis base). The clear favourites for the disconnection were the Wittig reaction between an aldehyde **153** and the corresponding phosphonium ylide **152** and a metathesis reaction using Grubbs catalysts between the corresponding alkene **151** and vinyl ketone/ester **150**. Both potential routes were investigated (Scheme 49).



Scheme 49. Two possible methods for olefination

The Metathesis Route Investigated – Synthesising The Precursors

In order to utilise the metathesis reaction the acrylate **150** and amine containing alkene **151** would need to be synthesised. A route was outlined starting from commercially available 6-hexen-1-ol **156** (Scheme 50).

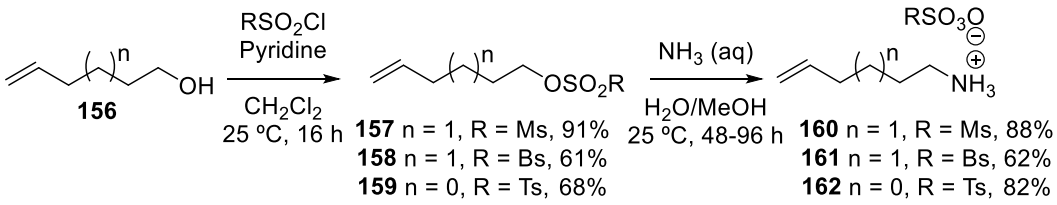


a) Nitrogen functionalisation b) Salt formation c) Oxygen functionalisation

Scheme 50. 6-Hexen-1-ol based retrosynthesis

Starting with 6-hexen-1-ol **156**, *O*-activation with either brosyl, nosyl or mesyl chloride would give the sulfonyl esters **157-159**. This leaving group (LG) could then be displaced by a nitrogen nucleophile, ideally ammonia.[89] Isolation of the product as ammonium salts **160-162** were preferable to the free amine.

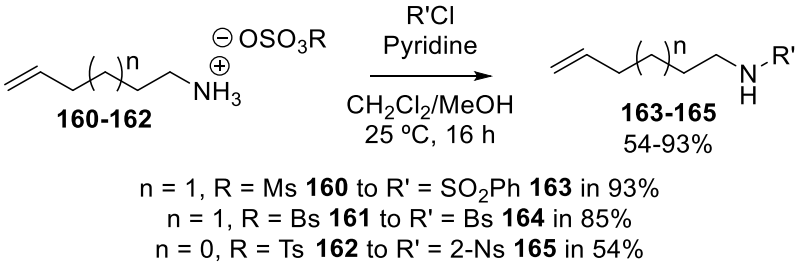
The synthesis began smoothly with the conversion of 6-hexen-1-ol **156** cleanly to the desired sulfonyl esters **157-159** (Scheme 51).



Scheme 51. Formation of the ammonium salt 160-162

The sulfonyl esters were subsequently dissolved in methanol then stirred with excess ammonium hydroxide solution (36%). Conveniently, concentration of this reaction to dryness gave a crystalline solid which was easily isolated after a brief wash with diethyl ether to give the corresponding salts **160-162** in good yield as a manageable solid.

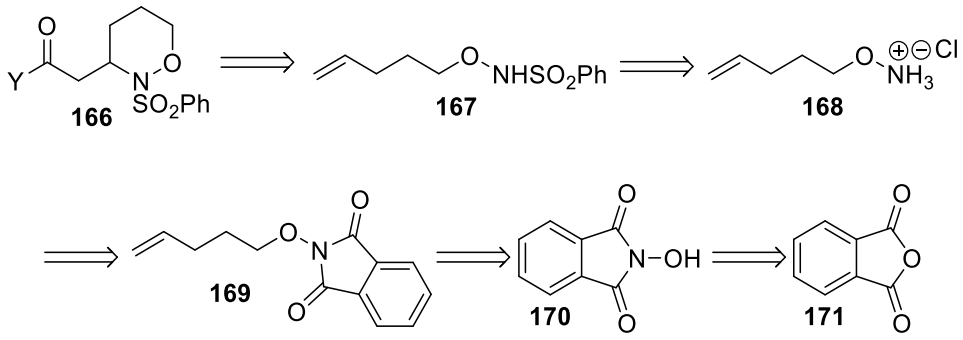
The ammonium salts **160-162** were successfully converted to sulfonamides **163-165** using similar conditions to that of the *O*-functionalisation (Scheme 52). Methanol was added to the reaction to both aid solubility of the ammonium salts and to prevent over *N*-substitution.



n = 1, R = Ms **160** to R' = SO_2Ph **163** in 93%
n = 1, R = Bs **161** to R' = Bs **164** in 85%
n = 0, R = Ts **162** to R' = 2-Ns **165** in 54%

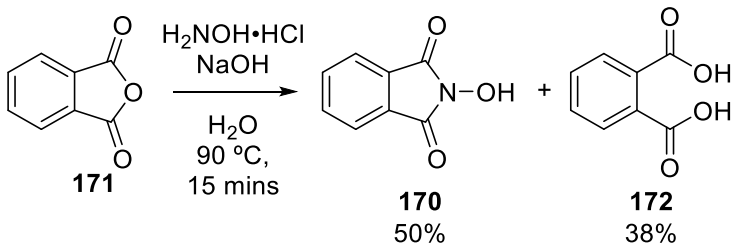
Scheme 52. Diversification of the ammonium salts

This route worked well for the synthesis of compounds containing a simple alkyl chain between the alkene and the nitrogen. However, precursors of morpholine and 1,2-oxazinane precursors required further steps. The 1,2-oxazinane was planned to be synthesised starting from phthalic anhydride **171** (Scheme 53).



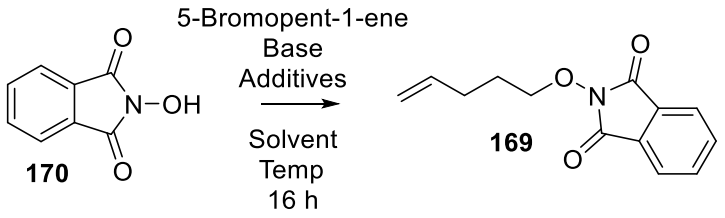
Scheme 53. Retrosynthetic analysis of 1,2-oxazinane precursors from phthalic anhydride 171

Phthalic anhydride was condensed with hydroxylamine hydrochloride.[90] Hydroxyphthalimide **170** could be easily produced with reproducible high purity on scales up to 20 grams (Scheme 54).



Scheme 54. Hydroxyphthalimide 170 synthesis

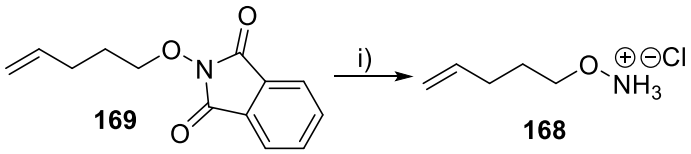
Next alkylation of hydroxyphthalimide **170** with 5-bromopent-1-ene was attempted. The reaction was attempted in acetonitrile, tetrahydrofuran or dichloromethane as solvent but only low levels of alkylation were observed (Entries 1-9). When the reaction was performed in DMF with sodium hydride a bright red colour observed suggests deprotonation of hydroxyphthalimide **170**. In DMF with sodium iodide as an additive a good yield was obtained (Scheme 55).



Entry	Base	Additives	Solvent	Temp (ºC)	% Yield
1	K_2CO_3	None	MeCN	25	>2
2	K_2CO_3	None	MeCN	80	20
3	K_2CO_3	None	THF	66	>2
4	$NaHCO_3$	None	THF	66	0
5	DBU	None	CH_2Cl_2	25	>2
6	DBU	NaI	DMF	70	0
7	^{t}BuOK	None	THF	25	12
8	NaH	NaI	THF	25	>2
9	NaH	NaI	THF	66	11
10	NaH	NaI	DMF	70	89

Scheme 55. Alkylation of hydroxyphthalimide 170

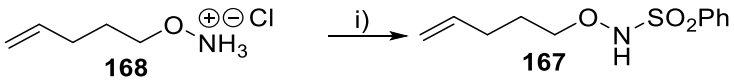
Removal of the phthalimide group using hydrazine and subsequent isolation of the hydrochloride salt **168** was performed in good, reproducible yields (Scheme 56).



i) $H_2NNH_2 \cdot xH_2O$, Et_2O, 4 h, RT then 2M HCl in Et_2O, RT, 15 mins, 70-95%

Scheme 56. Phthalimide removal and salt formation

Next the salt **168** was reacted with benzenesulfonyl chloride to form the desired precursor in good yield (Scheme 57). Methanol which was added for solubility also prevented additional sulfonylation, presumably by intercepting excess electrophile.

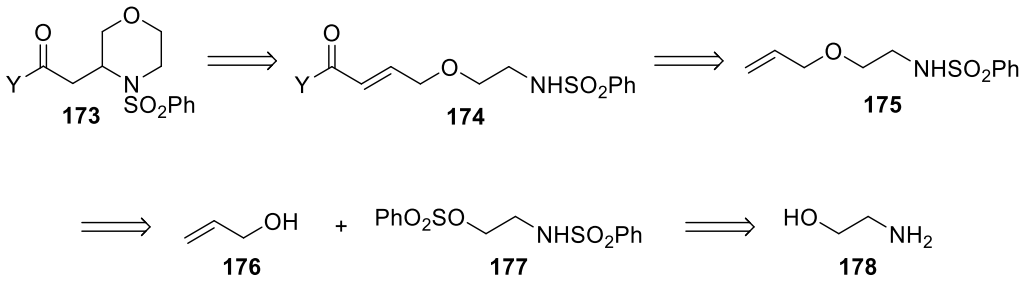


168 **167**

i) $PhSO_2Cl$, Et_3N, CH_2Cl_2, MeOH, 0 ºC, 16 h, 87%

Scheme 57. *N*-Sulfonylation of hydroxylamine salt 168

With the 1,2-oxazinane precursor **167** in hand the next target was the morpholine precursor **174** (Scheme 58).

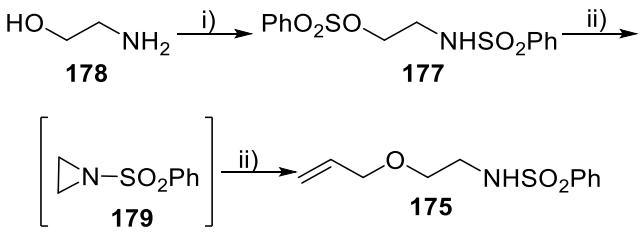


173 **174** **175**

176 **177** **178**

Scheme 58. Retrosynthetic analysis of morpholine 174

The synthesis began with the *O* and *N*-sulfonylation of 2-aminoethanol **178** with benzene sulfonyl chloride. This product was then treated with potassium *tert*-butoxide in order to form the aziridine **179** *in situ,* addition of allyl alcohol lead to the ring opening of the aziridine to give the ether product **175** (Scheme 59).



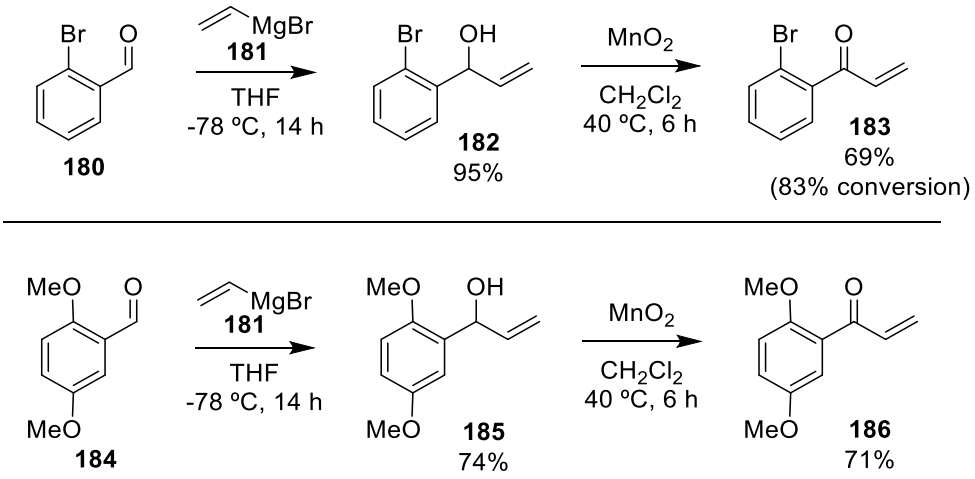
178 **177**

179 **175**

i) $PhSO_2Cl$, pyridine, CH_2Cl_2, RT, 16 h, ~70%
ii) ^tBuOK, allyl alcohol, THF, 0 °C, 64%

Scheme 59. Synthesis of the morpholine precursor 174

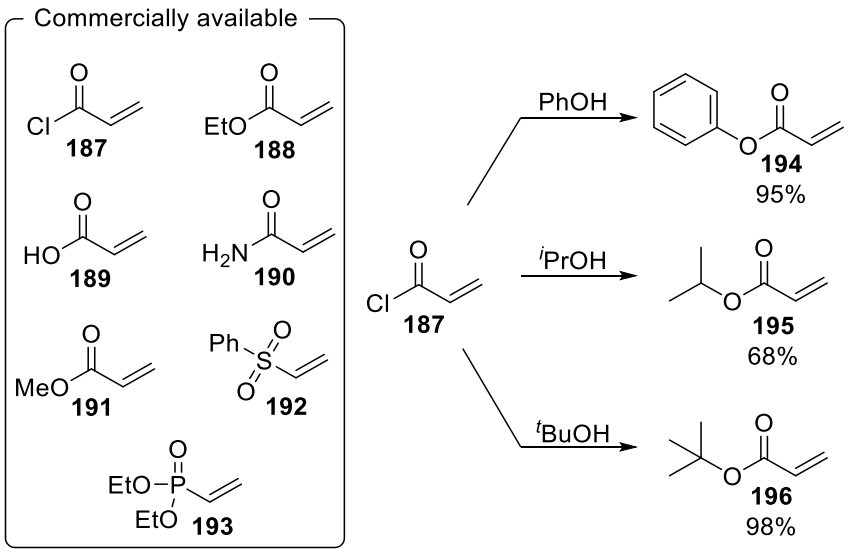
With the nitrogen containing alkenes synthesised in moderate to excellent yields the next cross metathesis step required the corresponding acrylates. Most of these acrylates were commercially available or readily synthesised from available materials. Vinyl phenyl ketones **183** and **186** were synthesised from commercial aldehydes (Scheme 60).



Scheme 60. Synthesis of vinyl phenyl ketones 183 and 186

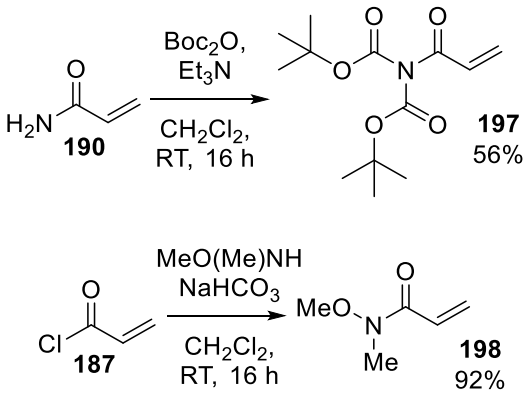
These aldehydes **180** and **184** were smoothly converted into the alcohols **182** and **185** by a Grignard reaction with vinyl magnesium bromide **181**. Subsequent oxidation with manganese dioxide proceeded with reasonable conversion. Though more manganese dioxide was added and longer reaction times were attempted, full conversion was never achieved. Despite this, the isolated yields are acceptable.

Acrylic acid **189**, acryloyl chloride **187**, acrylamide **190**, (vinylsulfonyl)benzene **192**, diethyl vinylphosphonate **193**, methyl and ethyl acrylate **191** and **188** were all commercially available whilst the *iso*-propyl, *tert*-butyl and phenyl acrylates **195**, **196** and **194** were all synthesised from acryloyl chloride **187** and the corresponding alcohol in good yields (Scheme 61).



Scheme 61. Simple acrylate synthesis

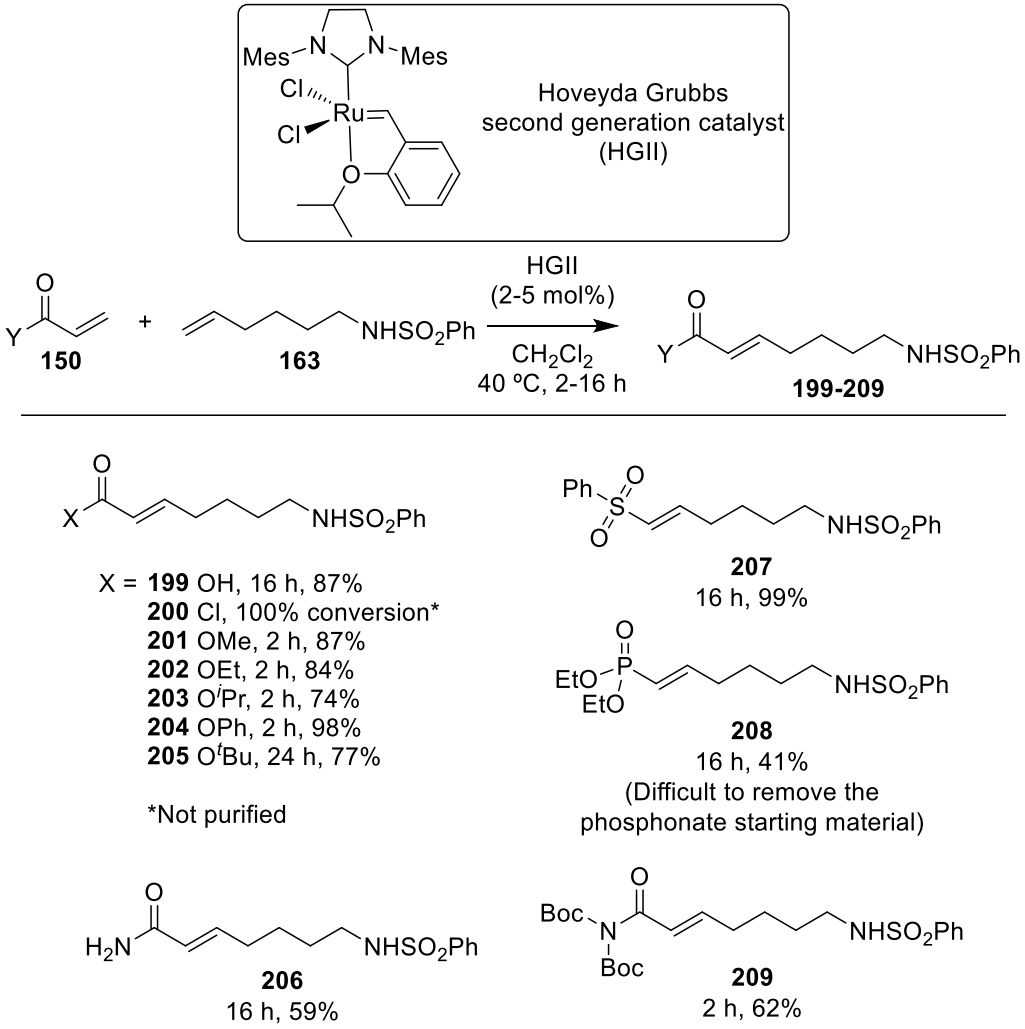
The corresponding acrylamides **197** and **198** were made from commercially available acrylamide **190** or acryloyl chloride **187** in good yields (Scheme 62).



Scheme 62. Simple acrylamide synthesis

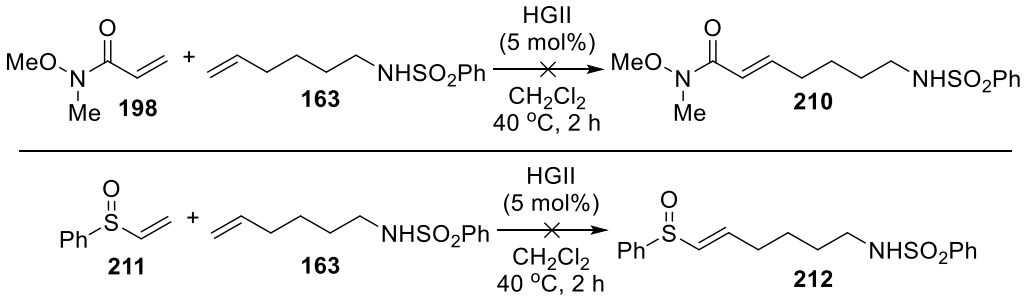
The Metathesis Route Investigated – The Metathesis Reaction

We proceeded to investigate cross metathesis of the terminal alkenes, using Hoveyda-Grubbs second generation catalyst (HGII) in dichloromethane to give the enone products in good to excellent yields (Scheme 63).



Scheme 63. The successful metathesis reactions with acrylates

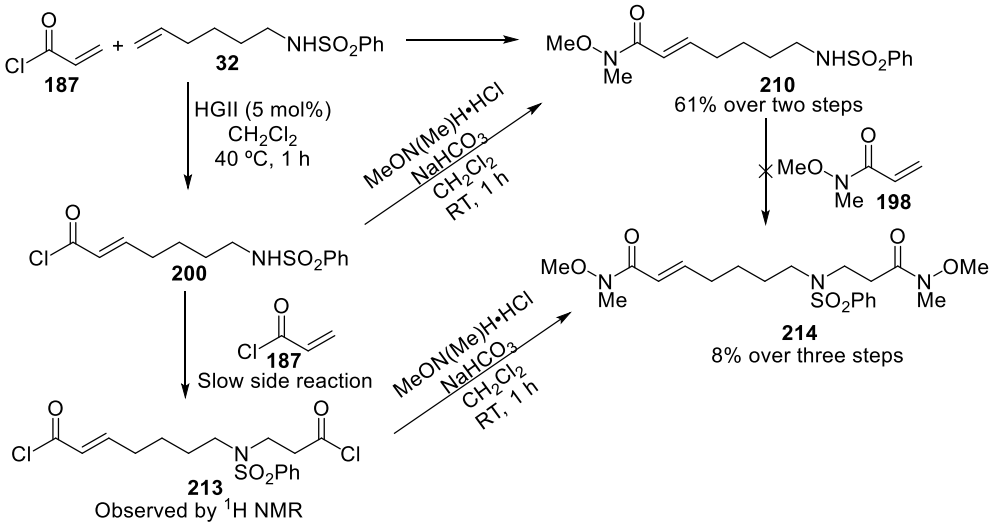
Synthesis of the Weinreb amide **210** was also attempted but the vinyl Weinreb amide **198** would not undergo the metathesis reaction (Scheme 64).



Scheme 64. The unsuccessful metathesis reactions

Instead the acid chloride **200** would be converted to the Weinreb amide **210**. When the acid chloride **187** was mixed with the alkene sulfonamide **163** with HGII, the starting sulfonamide **163** was consumed within an hour, at this point

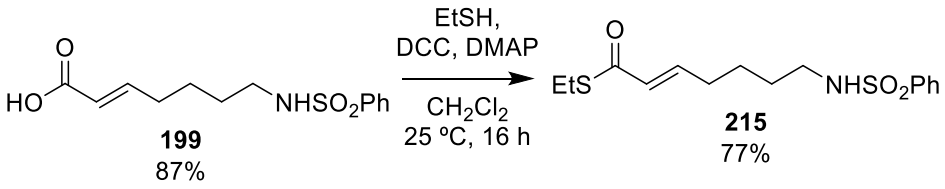
the *N*,*O*-dimethylhydroxylamine hydrochloride salt and sodium hydrogen carbonate were added and within an hour the Weinreb amide enone **210** was observed. Upon purification it was found that a sizable quantity of an impurity **214** was isolated (Scheme 65).



Scheme 65. The route to the Weinreb amide enone 210 and the generation of impurity 214

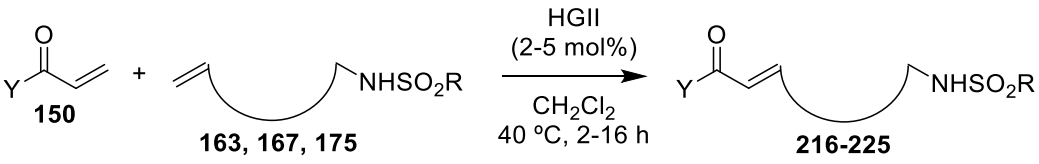
The impurity was found to be the product of intermolecular 1,4-conjugate addition between the sulfonamide moiety and either excess α,β-unsaturated acid chloride **187** or Weinreb amide **198**. When the reaction was left for longer than an hour for the initial metathesis reaction, a side product **213** was observed by ^{1}H NMR spectroscopy. Notably no such adduct was observed when sulfonamide **210** was stirred with the Weinreb amide acrylate **198** in the presence of sodium hydrogen carbonate. This suggested that intermolecular conjugate addition with the sulfonamide only occurs with the acid chloride **187** and not the resulting Weinreb amide acrylate **198**. This impurity was thereby avoided by concentrating the metathesis reaction under reduced pressure to remove excess acid chloride **187** from product **200** then subsequently performing formation of the Weinreb amide **210**.

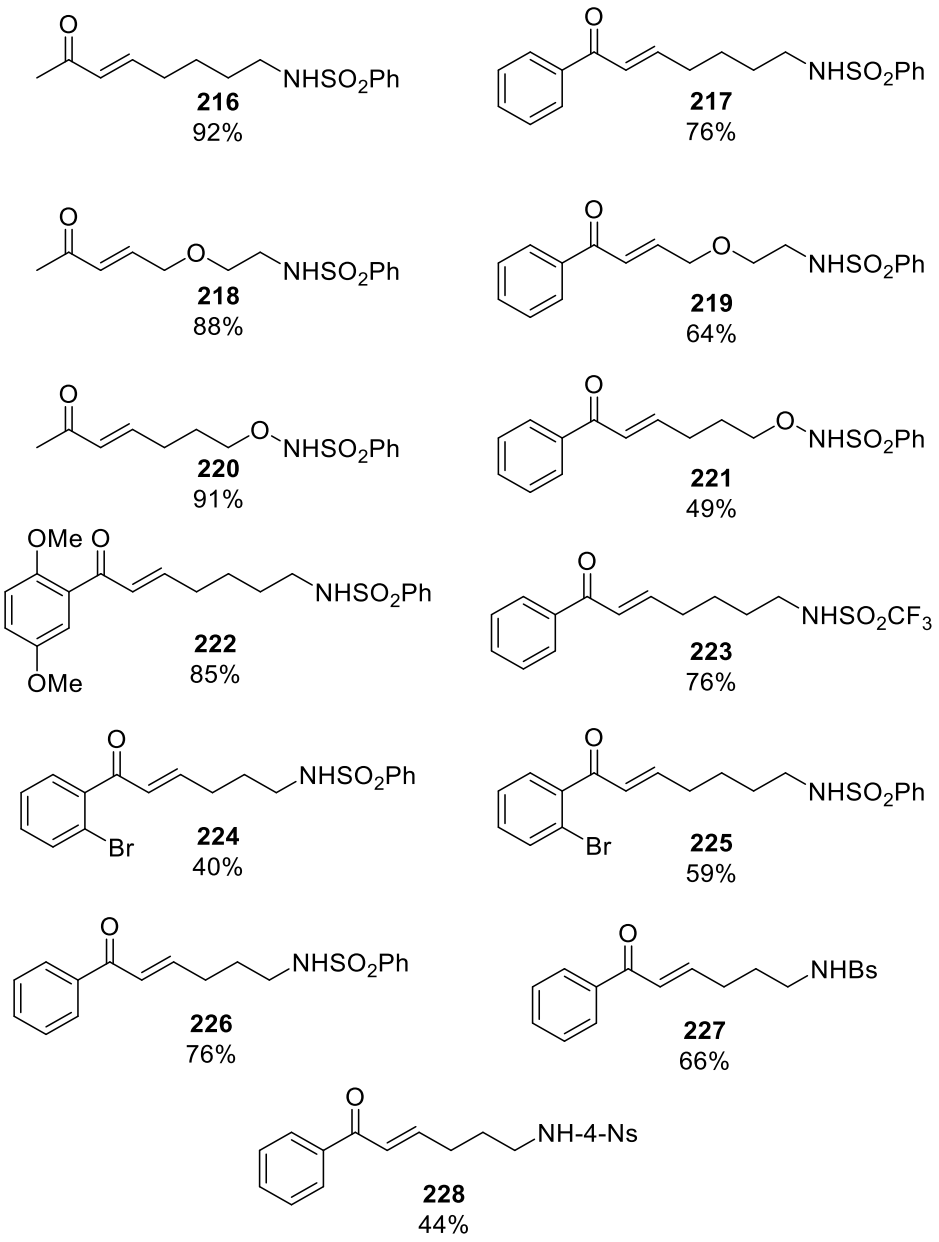
Thioester **215** was prepared from the carboxylic acid **199**, over two steps in acceptable yield (Scheme 66).



Scheme 66. Synthesis of the thioester 215

The phenyl ketones were also synthesised using cross metathesis (Scheme 67).





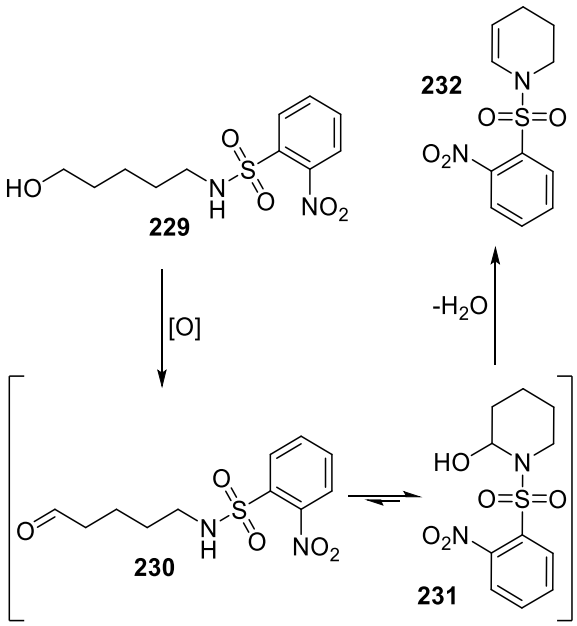
Scheme 67. Synthesis of phenyl ketones by the metathesis reaction

The metathesis route to α,β-unsaturated carbonyls works well using mild conditions but is not without limitations. Among them are the lack of scalability, larger scale reactions gave poorer yields. Some vinyl compounds also appeared to poison the catalyst (likely through co-ordination to the metal)

so are inaccessible to this approach. We therefore considered an alternative route employing a Wittig reaction.

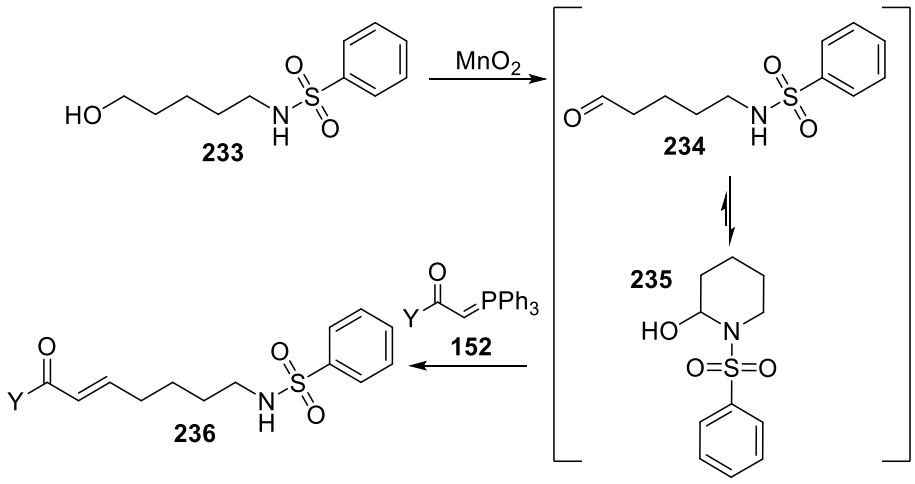
The Wittig Route Investigated – Synthesising The Precursors

Aldehydes required for the Wittig reaction were thought to exist predominantly as the hemiaminal. This makes Wittig reactions with them potentially slow depending on the equilibrium of this position. Furthermore a cyclic enamine product inert to these conditions could form by elimination from the hemiaminal **232** (Scheme 68).



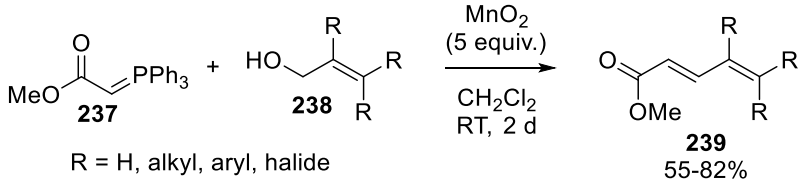
Scheme 68. Oxidation leading to enamine 232 formation *via* condensation

This problem of isolating similar aldehydes had previously been reported as an issue for groups when using PCC as oxidant. Because of this problem the oxidation step of the oxidative Wittig step would need to be investigated in more detail with the planned alcohol substrates in hand. Ideally the hemiaminal would act as no more than a reservoir for the aldehyde and be consumed in the subsequent Wittig reaction before any elimination can occur (Scheme 69).



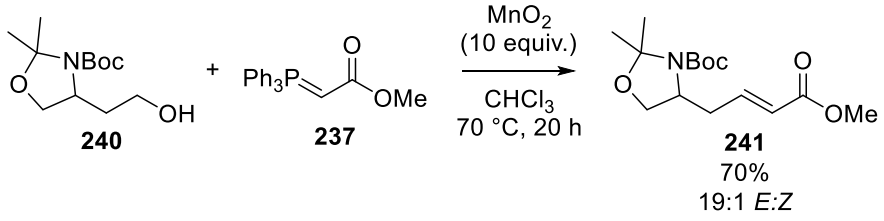
Scheme 69. The one pot oxidation Wittig reaction

Taylor *et al.* had previously shown that alcohols **238** could be oxidised by large equivalents of manganese dioxide in the presence of ylides **237** to generate the corresponding Wittig products **239** without the need to isolate the potentially unstable or reactive aldehydes.[91] This was a vast improvement on Ireland and Norbeck's reported method using a Swern reaction followed by the addition of an ylide to the crude aldehyde because Taylor *et al.* avoid the use of cryogenic conditions and chemicals exhibiting a stench (Scheme 70).[92]



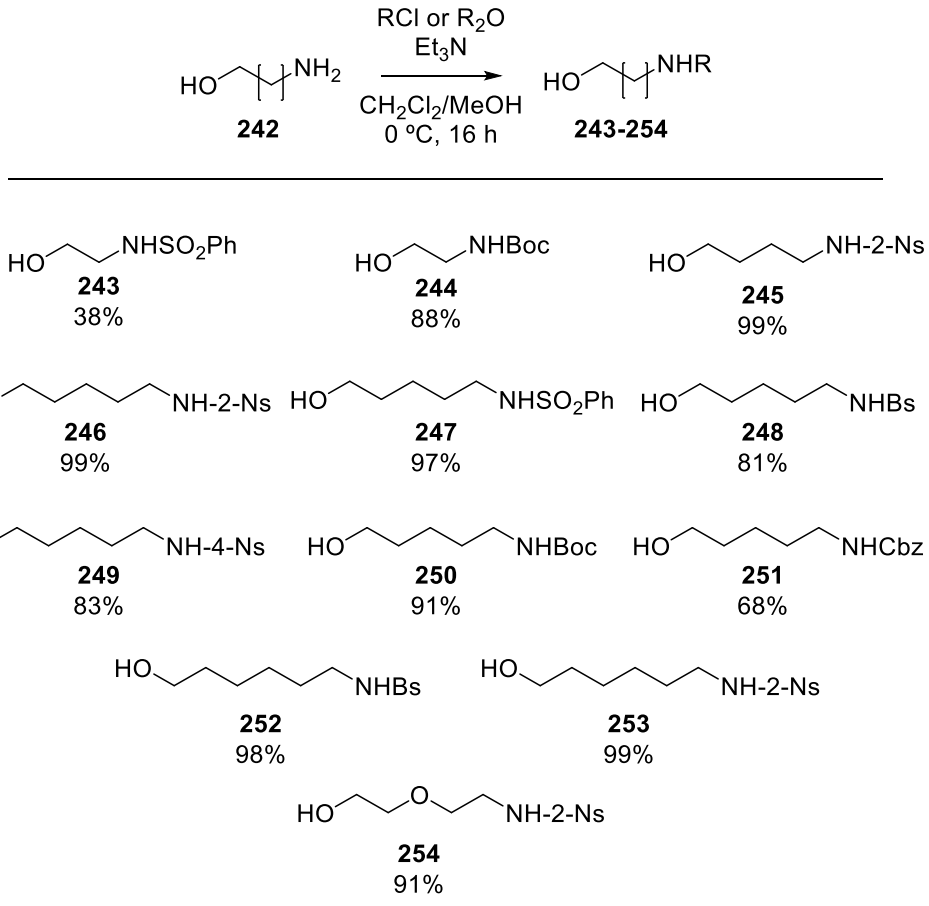
Scheme 70. Taylor *et al.*'s first report of the oxidative Wittig

Taylor *et al.*'s first report of the oxidative Wittig was performed on allylic or conjugated primary alcohols **238**, more recent publications have shown the oxidation to work on less activated alcohols **240** (Scheme 71).[93]



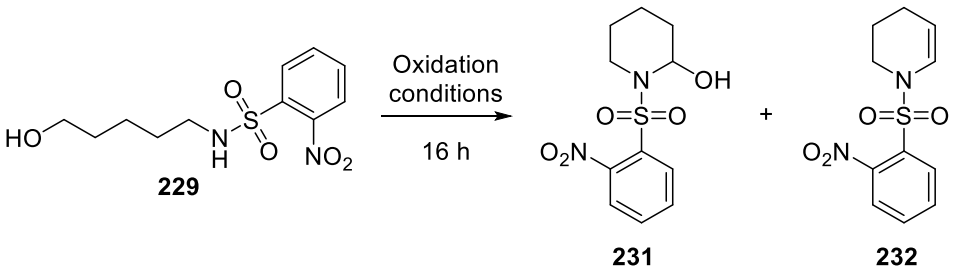
Scheme 71. One pot oxidative Wittig on an unactivated alcohol 240

Before any oxidation could be attempted the starting materials were prepared. Commercial amino alcohols were selectively transformed to the *N*-substituted products **243-254**. When the reactions were performed in dichloromethane with a small amount of methanol present, the reaction gave only the *N*-substituted product with no signs of *O*-substitution. In all cases after an aqueous work up with 2M hydrochloric acid, the desired product was obtained with no further need for purification (Scheme 72).



Scheme 72. Successful *N*-functionalisation

A screen of several potential oxidants quickly confirmed manganese dioxide as the best reagent for use with the one pot oxidation Wittig reaction. Other oxidants such as hypervalent iodine, hydrogen peroxide or Swern conditions were constrained by the need for aqueous work up that typically lead to the elimination of the hemiaminals (Table 1).



Entry	Oxidant	Additives	Temp. (ºC)	Solvent(s)	Conv. (%)[a]	**231**:**232**[a]
1	$NaIO_4$	-	45	$MeOH/H_2O$	0	-
2	$NaIO_4$	Pyridine	45	$MeOH/H_2O$	0	-
3	$PhI(OAc)_2$	Pyridine	0-20	CH_2Cl_2	0	-
4	TEMPO/NaOCl	TBAB	0-20	CH_2Cl_2/H_2O	0	-
5	MnO_2	-	80	$CHCl_3$	70	100:0
6	PCC	-	20	CH_2Cl_2	100[b]	-
7	$(COCl)_2$/DMSO	Et_3N	-78	CH_2Cl_2	100	7:3

[a] Conversion and ratio's of products determined by ^1H NMR spectroscopy of crude reactions.
[b] No products identified or isolated

Table 1. A screen of potential oxidants

Hemiaminal **231** was the only product from manganese dioxide oxidations. Manganese dioxide is cheap, usable in open air in non-anhydrous conditions and was removed by filtration prior to flash column chromatography for work up (Figure 14).

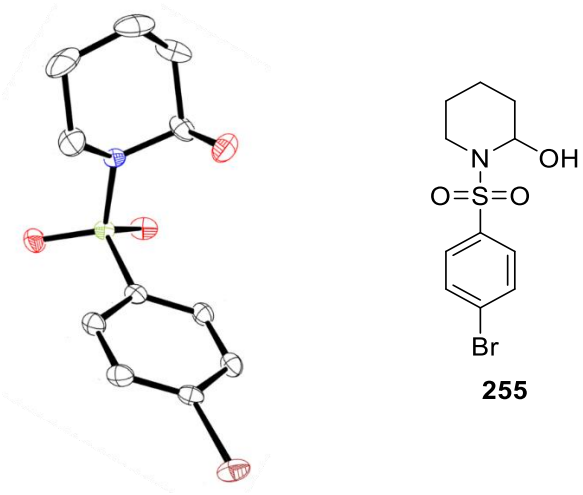
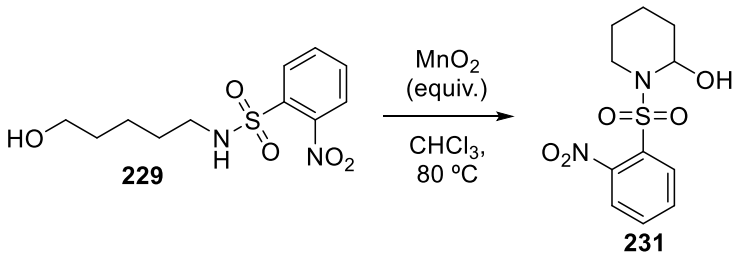


Figure 14. X-Ray structure of the hemiaminal 255

The oxidation of the alcohol **229** to the hemiaminal **231** or the enamine **232** was studied and optimised (Table 2 and Table 3).



Entry	Conc. (M)	Equiv. Of MnO_2	Conv. (%)[a]
1	0.2	2	20-25[b]
2	0.2	4	20-30[b]
3	0.1	8	70
4	0.1	10	87
5	0.1	12	86
6	0.2	8	81
7	0.3	8	79
8	0.4	8	59
9	0.2	10	90
10	0.3	10	86

[a] Conversion and products determined by ^{1}H NMR spectroscopy of crude reactions.
[b] Estimated by relative integration in ^{1}H NMR

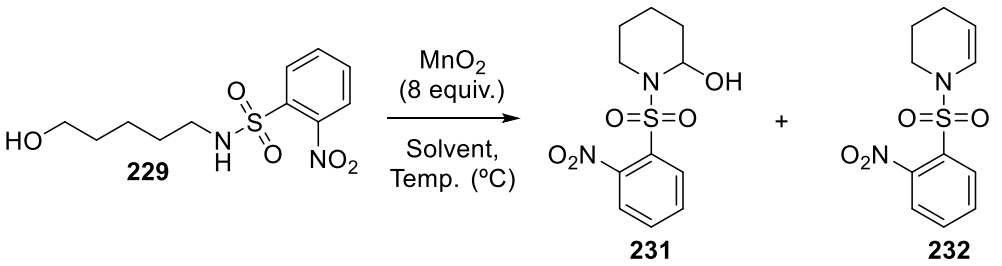
Table 2. The effect of equivalents of oxidant and reaction concentration

It was found that 8 equivalents or more was necessary (Entries 1-5) for good conversion; more oxidant had little effect on yield (Entries 3 and 5).

Next the effect of the concentration was investigated, higher concentrations were tolerated (Entries 3, 6, 7 and 8) with little effect on conversion. However, a concentration of 0.4M (Entry 8) gave a violent reaction with a large amount of powder present, ultimately resulting in lower yields.

Although the best yields were obtained from concentrated reactions of 0.2M and 0.3M with 10 equivalents of oxidant (Entries 9 and 10), the use of extra oxidant and more violent reflux were deemed unnecessary in most situations.

Next, factors such as solvent and additives were investigated (Table 3).



Entry	Solvent(s)	Additives	Temp. (ºC)	Conc. (M)	Conv. (%)[a]	Product(s)(**231**:**232**)[a]
1	THF	-	66	0.1	26-29[b]	100:0
2	PhMe	-	80	0.1	30	1:4
3	PhMe	Pyridine	80	0.1	40	1:3
4	PhMe	-	110	0.1	90	1:2
5	PhMe	-	110	0.2	80	0:100
6	PhMe	-	110	0.3	54	0:100
7	$CHCl_3$	H_2O	61	0.1	25	100:0
8	$CHCl_3$	TFA	61	0.1	14	0:100
9	$CHCl_3$	Pyridine	61	0.1	65	100:0
10	$CHCl_3$	Pyridine	61	0.2	80	100:0

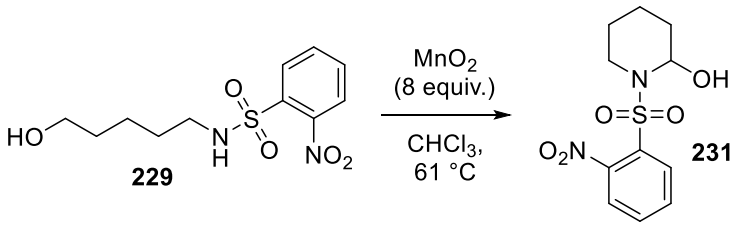
[a] Conversion and products determined by ^{1}H NMR spectroscopy of crude reactions.
[b] Estimated by relative integration in ^{1}H NMR

Table 3. Solvent and additive effects

Tetrahydrofuran and toluene were also investigated as alternate solvents as both are commonly used in Wittig reactions but neither gave satisfactory conversions (Entries 1 and 2).

While similar oxidations gave hemiaminals it has been reported that the addition of pyridine can increase yield of hemiaminal.[94] No significant difference was observed for these conditions (Entries 3, 9 and 10). Water and trifluoroacetic acid were also added to separate oxidation reactions with significant effect. The addition of water gave a homogeneous solution that resulted in a reaction that slowed greatly after initiation (Entry 7). Acid, as mentioned in the literature, causes hemiaminals to undergo elimination to give enamine **232** as the only observable product, but also these conditions cause the manganese to clump.[95–98] The oxidation was performed in toluene at the higher temperatures of 110 °C (Entries 2-4), from which enamine **232** was identified as the major product.

It was decided to use 8 equivalents of manganese dioxide as it best afforded the best combination of conversion with a manageable reflux. The concentration between 0.1M and 0.3M made no real difference to conversion after 16 h but may have an effect on the rate of the reaction, which was investigated next (Table 4).



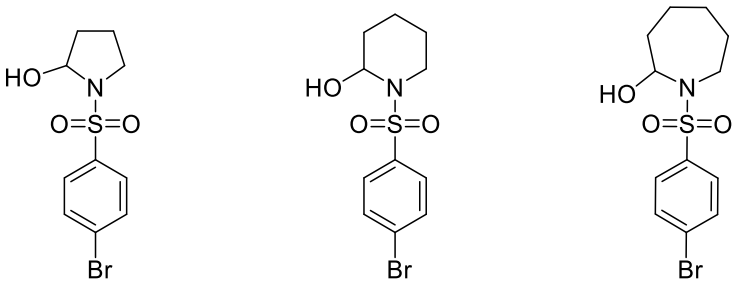
		Concentration (M)		
		0.1	0.2	0.3
Entry	Time (h)	%Conversion[a]		
1	1	42	47	43
2	2	49	53	50
3	4	60	63	60
4	8	63	68	68
5	22	84	82	78

[a] Conversion determined by ^{1}H NMR

Table 4. The effect concentration has on the rate of oxidation

As the results clearly show, the rate of the reaction is independent of concentration; thus the operating concentration could be decided by the solubility of the ylides used for the *in situ* Wittig.

The equilibrium between hemiaminal **231** and aldehyde **230** in solution can be measured in chloroform by ^{1}H NMR. It's likely the more time the product exists as the aldehyde the more likely it is to undergo the Wittig reaction and correspondingly less likely to undergo elimination (Figure 15).

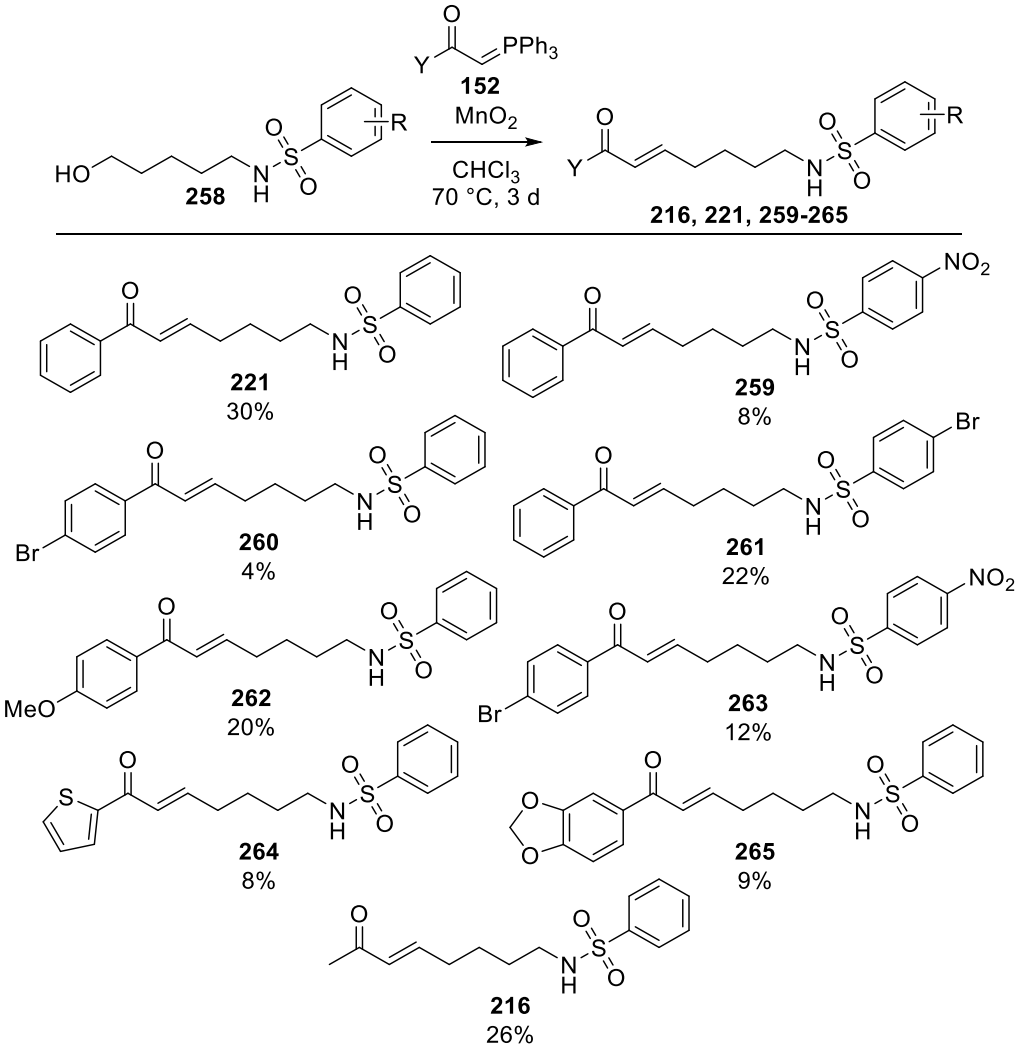


256	**255**	**257**
80% hemiaminal 20% aldehyde	97% hemiaminal 3% aldehyde	3% hemiaminal 97% aldehyde

Figure 15. Effect on ring size on equilibrium between hemiaminal and aldehyde

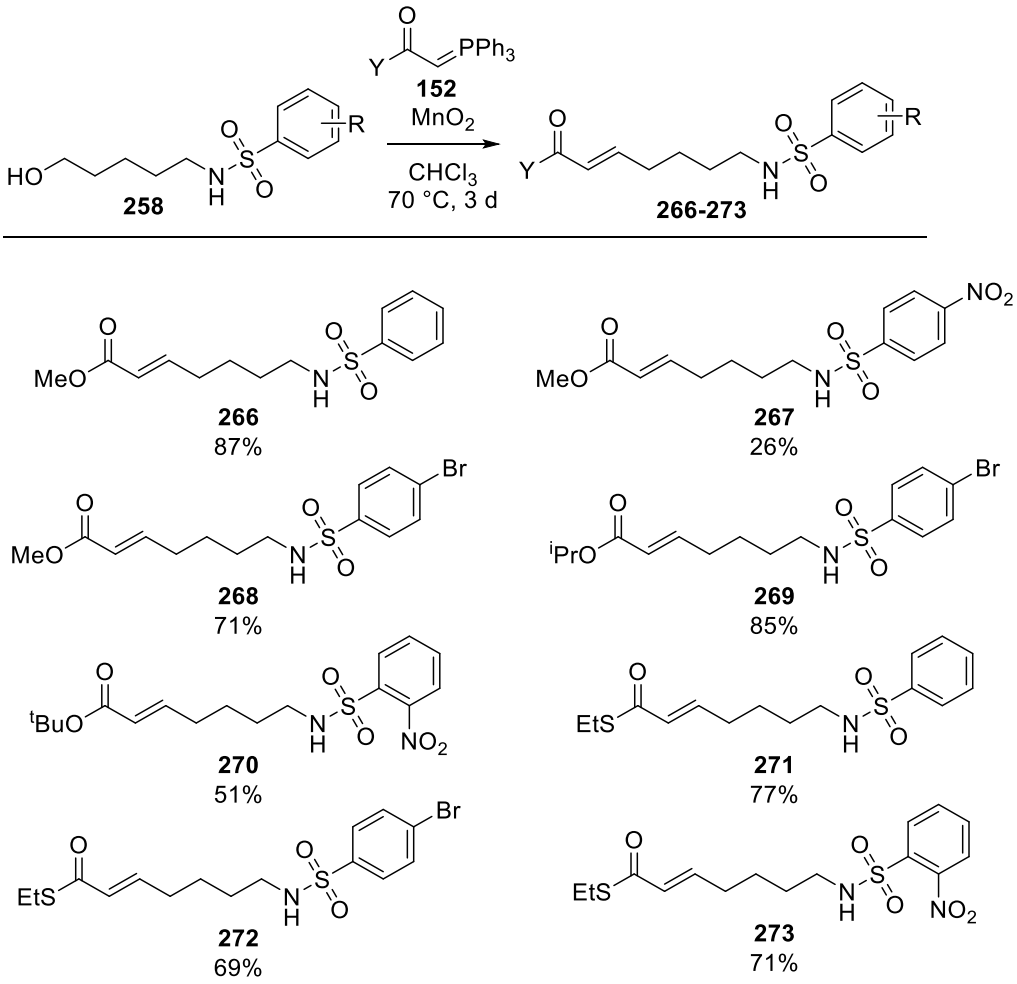
The Wittig Route Investigated – Substrate preparation

With the alcohols in hand, the oxidation in the presence of the ylides was performed (Scheme 73).



Scheme 73. Ketones made by the oxidative Wittig approach

Aromatic ketones **221** and **269-265** and an example methyl ketone **216** were obtained in poor to moderate yields. The racemic cyclised products of these enones account for the mass balance of these reactions, suggesting the enones readily undergo unwanted racemic cyclisation under these conditions. This premature reaction was less of an issue in the synthesis of esters and thioesters *via* the oxidative Wittig (Scheme 74).

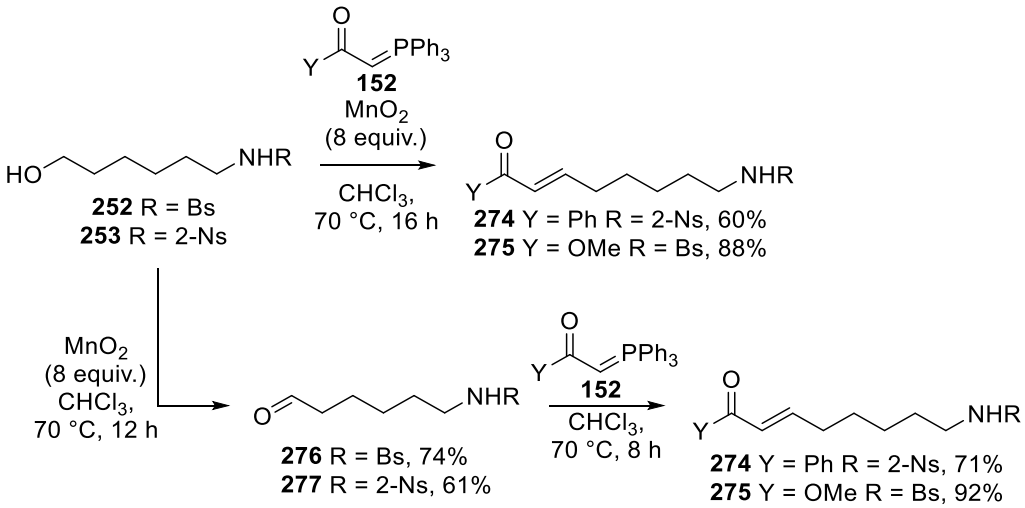


Scheme 74. Esters and thioesters made by the oxidative Wittig approach

Moderate to good yields were obtained for esters **266-270** and thioesters **271-273**. Background cyclisation was seldom observed in the synthesis of esters and only contributed to a small erosion of yield with the thioesters. The formation of the *cis* alkene was observed with esters and thioesters, a typical ratio between *trans* and *cis* being 19:1, unlike the phenyl and methyl ketones in which no *cis* product was observed by ^{1}H NMR. The *cis* alkenes eluted close to the desired *trans* products and were rarely obtained clean by flash column chromatography on silica gel, instead these mixed fractions were sacrificed for the purity of the *trans* products.

The oxidative Wittig reactions were performed on scales between hundreds of milligrams of starting alcohol up to fifty grams (125 mmol) in one instance of the *tert*-butyl ester **270**. The yields and crude ^{1}H NMR of the reactions appeared to be unchanged with increased scale so that the purification technique became the limiting factor.

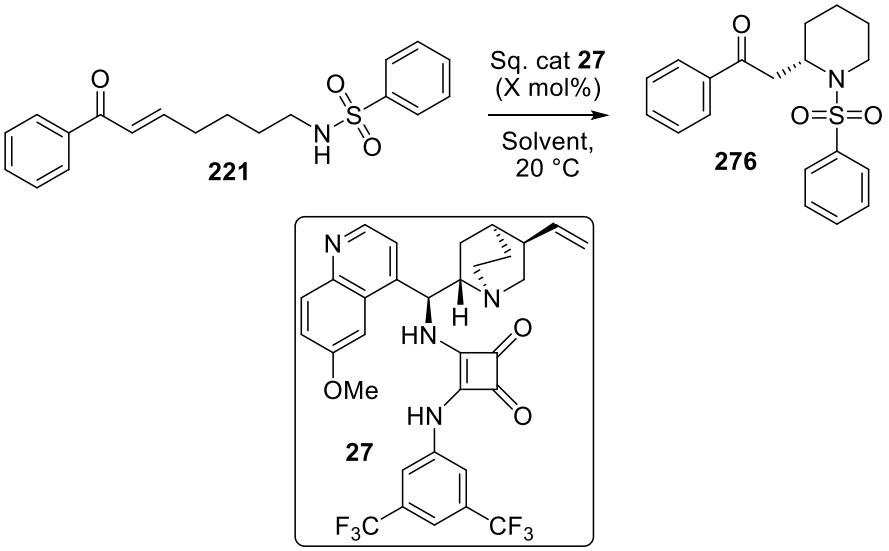
As mentioned earlier, the seven membered ring precursors exist as predominantly the aldehyde (Figure 15). Aldehydes **276** and **277** were isolated in good yields and subsequently converted to phenyl ketone **274** and methyl ester **275** in excellent yields. When the oxidative Wittig reactions were performed to access the same phenyl ketone **274** and methyl ester **275** yields were better than those of the combined two step approach (Scheme 75).



Scheme 75. Comparing the oxidative Wittig to the two step approach

Asymmetric Cyclisations - Phenyl Ketones

With precursors in hand we proceeded to then investigate the choice of solvent for the cyclisation of a phenyl ketone **221** in the presence of the squaramide catalyst **27**. The effect of the solvent polarity and catalyst load on conversion and enantiomeric excess of products were of greatest interest (Table 5).



Entry	Solvent	(X mol%)	Time (h)	%Conversion	%ee	Polarity
1	MeCN	10	168	85	96	35.9
2	MeOH	10	168	39	90	32.7
3	CH_2Cl_2	10	5	100	98	8.9
4	2-MeTHF	10	104	100	98	7.0
5	$CHCl_3$	10	3.5	100	98	4.8
6	EtOAc	10	48	100	99	3.0
7	$(EtO)_2O$	10	23	100	98	2.8
8	PhMe	10	4	100	99	2.4
9	PhMe	5	4	100	99	2.4
10	PhMe	2	6	100	99	2.4
	PhMe	1	12	100	99	2.4

Table 5. Reaction optimisation for a simple phenyl ketone 221

Notably, the overall reaction time increased as the polarity of the solvent increases, with reactions in most polar solvent not reaching completion after a week. Of the non-polar solvents toluene worked best. Although some other solvents gave higher conversions, it was noted that the % ee was not quite as high. It was observed during the catalyst screening that, whilst most or all of the catalyst is soluble in solvents such as chloroform and dichloromethane, reactions carried out in toluene were heterogeneous with little catalyst in

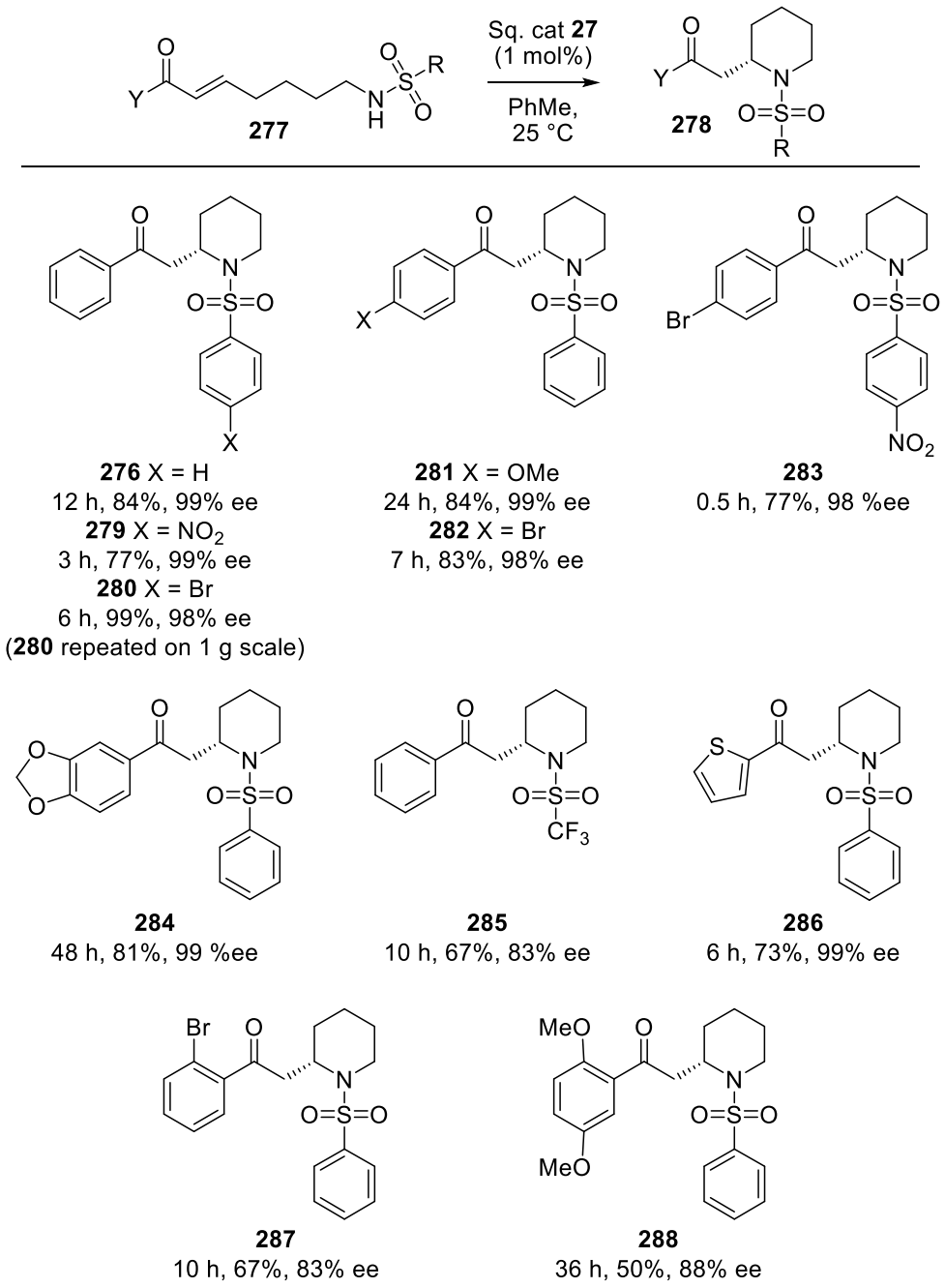
solution. As the reaction times between dichloromethane, chloroform and toluene are all similar but the amount of catalyst in solution differs largely. The amount of catalyst used in the toluene screening experiments was reduced until all the catalyst was found to be in solution.

At 10 and 5 mol% catalyst the reaction is near identical. At 2 mol%, longer reaction times were observed but still no change in % ee. At one mole percent a homogenous solution was obtained, in this case a reaction time is three times that of ten mole percent catalyst loading but still acceptable, while the % ee appears unaffected throughout.

Next the effect of different substituents on the substrate were studied, the key places groups could easily be placed were on the aromatic ring of the phenyl ketone and variation of the sulfonamide group (Scheme 76).

With more electron withdrawing sulfonamides a faster reaction time was observed in the formation of the piperidine, exchanging from a benzene sulfonamide to a brosyl group (*para*-bromobenzene sulfonamide) resulted in the reaction time being halved with no change to enantiomeric excess. Sulfonamides such as nosyl **259** (*para*-nitrobenzene sulfonamide) quartered the reaction time with respect to benzene sulfonamide **221**. However, when substrates featured the trifluoromethyl sulfonamide **223** the rate of reaction unexpectedly reduce and the observed enantiomeric excess fell considerably. This result suggests that a more acidic nitrogen is preferable for cyclisations but that there are limits to how low a pKa is tolerated more generally.

The effect of *para* substituents at the phenyl ring followed a similar trend in that the electron withdrawing groups resulted in faster reactions. Likewise the use of electron donating group such as methoxy groups or the use of a benzo[d][1,3]dioxole produced longer reaction times of the sulfonamide derivatives. Regardless of *para*-substituent the enantiomeric excess remained excellent. It was only when *ortho*-substituents were present on the phenyl ketone that enantioselectivity of the product formation was diminished.



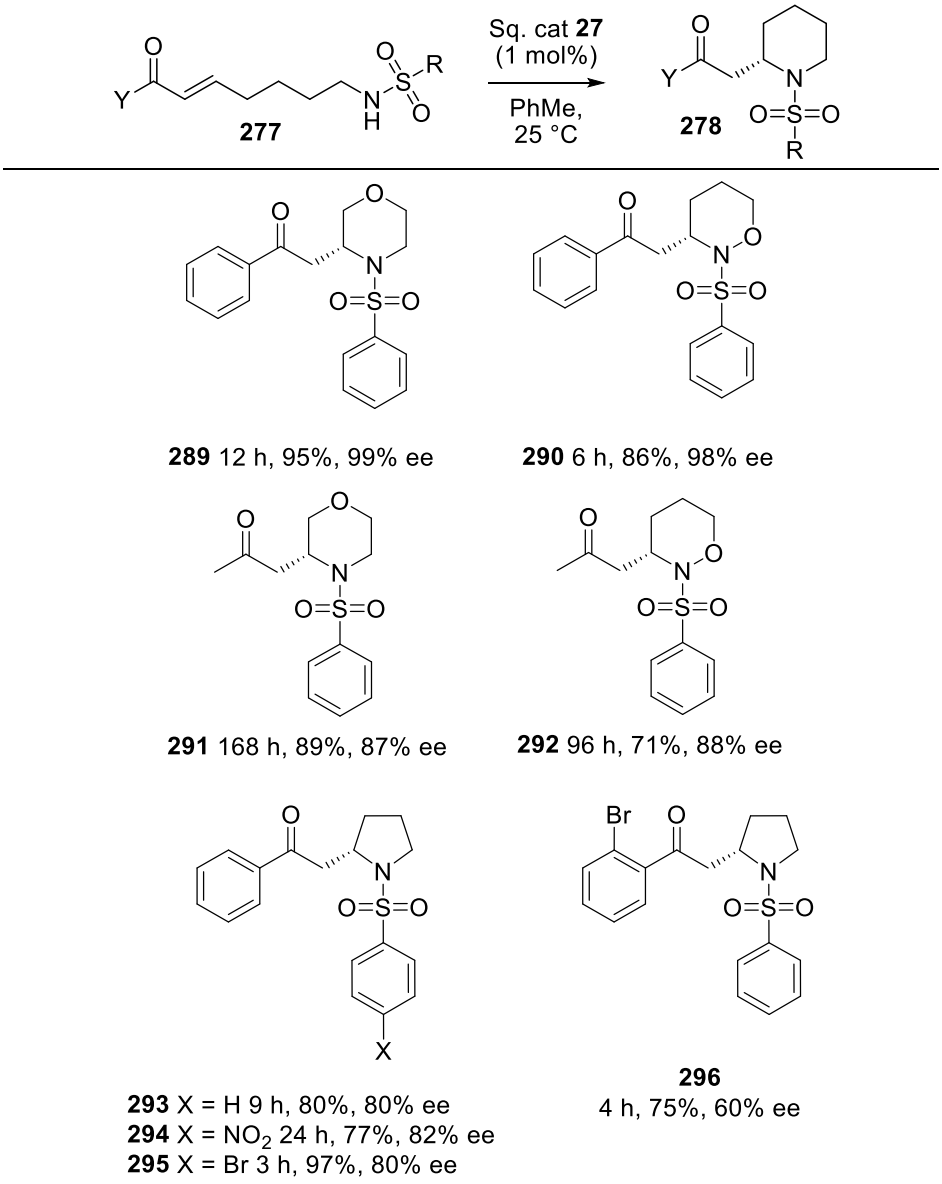
Scheme 76. Asymmetric cyclisations of phenyl ketones

Notably a thiophenyl ketone gave excellent enantioselectivity when cyclised showing its applicability to the synthesis of heterocycles.

The incorporation of an oxygen atom in the tether/linker allows synthesis of morpholines or 1,2-oxazinanes, both substrates gave cyclised products with excellent enantioselectivity with the morpholine reaction proceeding almost analogously to its piperidine equivalent. Reactions leading to oxazinanes were

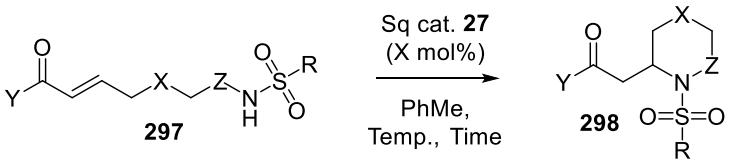
shorter, perhaps due to the α effect, but high enantioselectivities are still obtained in these products none the less (Scheme 77).

Cyclisations of enones shorter by one methylene gave pyrrolidine products with noticeably lower enantioselectivities. When forming a pyrrolidine with an *ortho* substituent on the phenyl ketone, enantioselectivity was further compromised to give products with poor enantioselectivities.



Scheme 77. Asymmetric cyclisations that demonstrate tolerance for morpholines, oxazinanes and pyrrolidines

Some further investigation of six membered rings formation evaluated whether catalyst loading or temperature affected enantioselectivity (Table 6).



Entry	No.	Y	X	Z	R	(X mol%)	Temp (°C)	Time (h)	% Yield[a]	% ee[b]
1	**218**	Me	O	CH_2	Ph	1	RT	168	89	87
2	**218**	Me	O	CH_2	Ph	1	80	3	87	89
3	**219**	Ph	O	CH_2	Ph	1	RT	12	95	99
4	**220**	Me	CH_2	O	Ph	10	RT	62	59	88
5	**220**	Me	CH_2	O	Ph	1	RT	96	71	88
6	**220**	Me	CH_2	O	Ph	10	80	1.5	63	84
7	**220**	Me	CH_2	O	Ph	1	80	1	43	87
8	**221**	Ph	CH_2	O	Ph	10	RT	6	86	98
9	**221**	Ph	CH_2	O	Ph	1	RT	8	77	95
10	**223**	Ph	CH_2	CH_2	CF_3	10	RT	2	75	87
11	**223**	Ph	CH_2	CH_2	CF_3	1	RT	2	71	87
12	**223**	Ph	CH_2	CH_2	CF_3	1	80	1	82	86

a - Isolated yield b - Determined by HPLC

Table 6. Asymmetric cyclisation of the morpholines and triflate compounds

The effect of catalyst loading or temperature on enantioselectivity was next investigated.

The methyl ketone morpholine **291** was produced at higher temperatures but with little effect on yield or enantioselectivity (Entries 1+2). Phenyl ketone morpholine **289** was obtained in great yield and with good enantioselectivity at room temperature (Entry 3). Similar observations were made for cyclisations to form the methyl and phenyl ketone oxazinanes **290** and **292** (Entries 4-9). Finally, triflate derived phenyl ketone piperidine **285** was obtained with poor enantioselectivity regardless of catalyst loading and temperature (Entries 10-12). These observations are summarised in Figure 16.

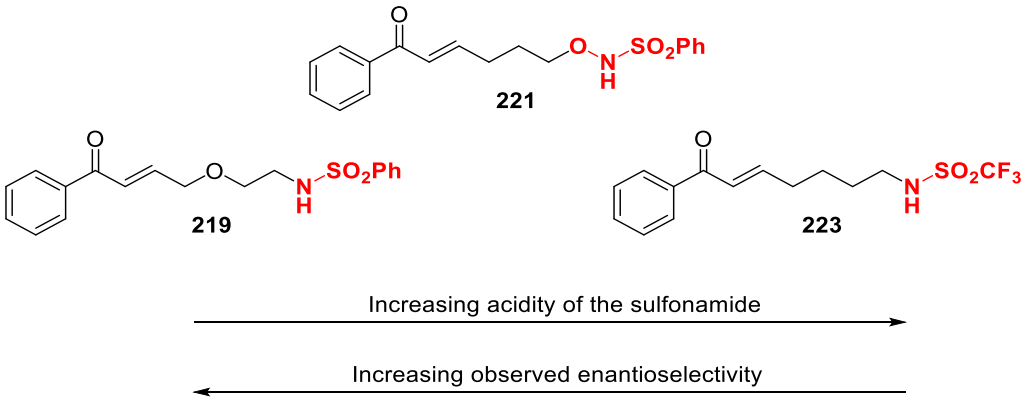
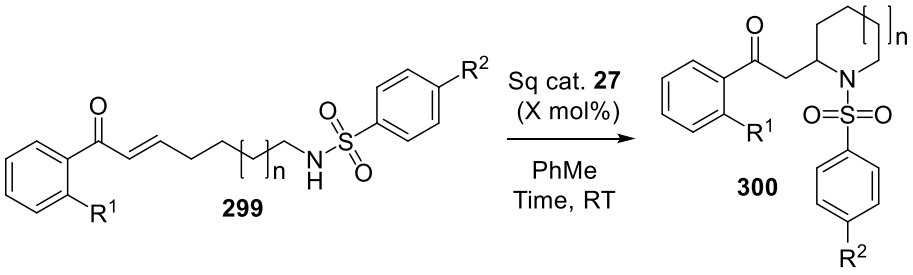


Figure 16. The corresponding change in acidity and the resulting enantioselectivity

Some further work with catalyst loading was performed, these results suggest once again that for phenyl ketone precursors the catalyst loading typically has little effect on enantioselectivity (Table 7).

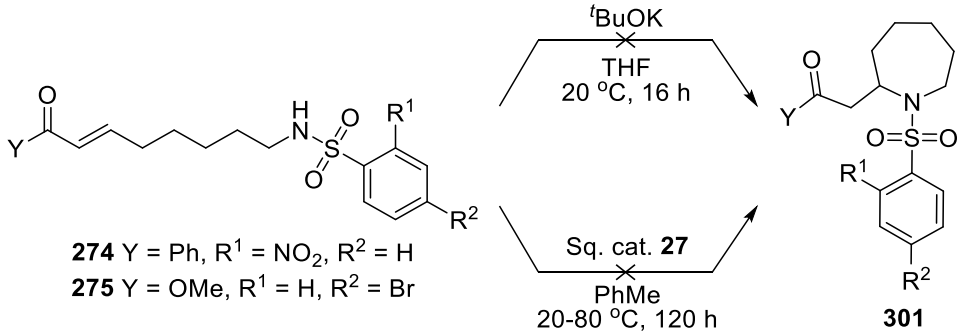


Entry	No.	n	R^1	R^2	(X mol%)	Time (h)	%Yield[a]	%ee[b]
1	**224**	0	Br	H	10	5	75	53
2	**224**	0	Br	H	1	4	36	60
3	**225**	1	Br	H	10	10	67	85
4	**225**	1	Br	H	1	12	52	85
5	**227**	0	H	Br	10	0.5	97	81
6	**228**	0	H	NO_2	10	24[c]	74	82
7	**226**	0	H	H	10	9	80	78
8	**261**	1	H	Br	10	6	94	98
9	**261**	1	H	Br	1	24	98	98
10	**221**	1	H	H	1	12	84	99

[a] Isolated yield [b] Determined by HPLC
[c] Likely a result of solubility issues

Table 7. Further work with the electron withdrawing substituents

After the successful enantioselective production of five and six membered rings, formation of seven membered rings were also investigated. Unfortunately, despite multiple attempts no cyclisation of the enone was observed either using the squaramide catalyst or potassium *tert*-butoxide (Scheme 78).



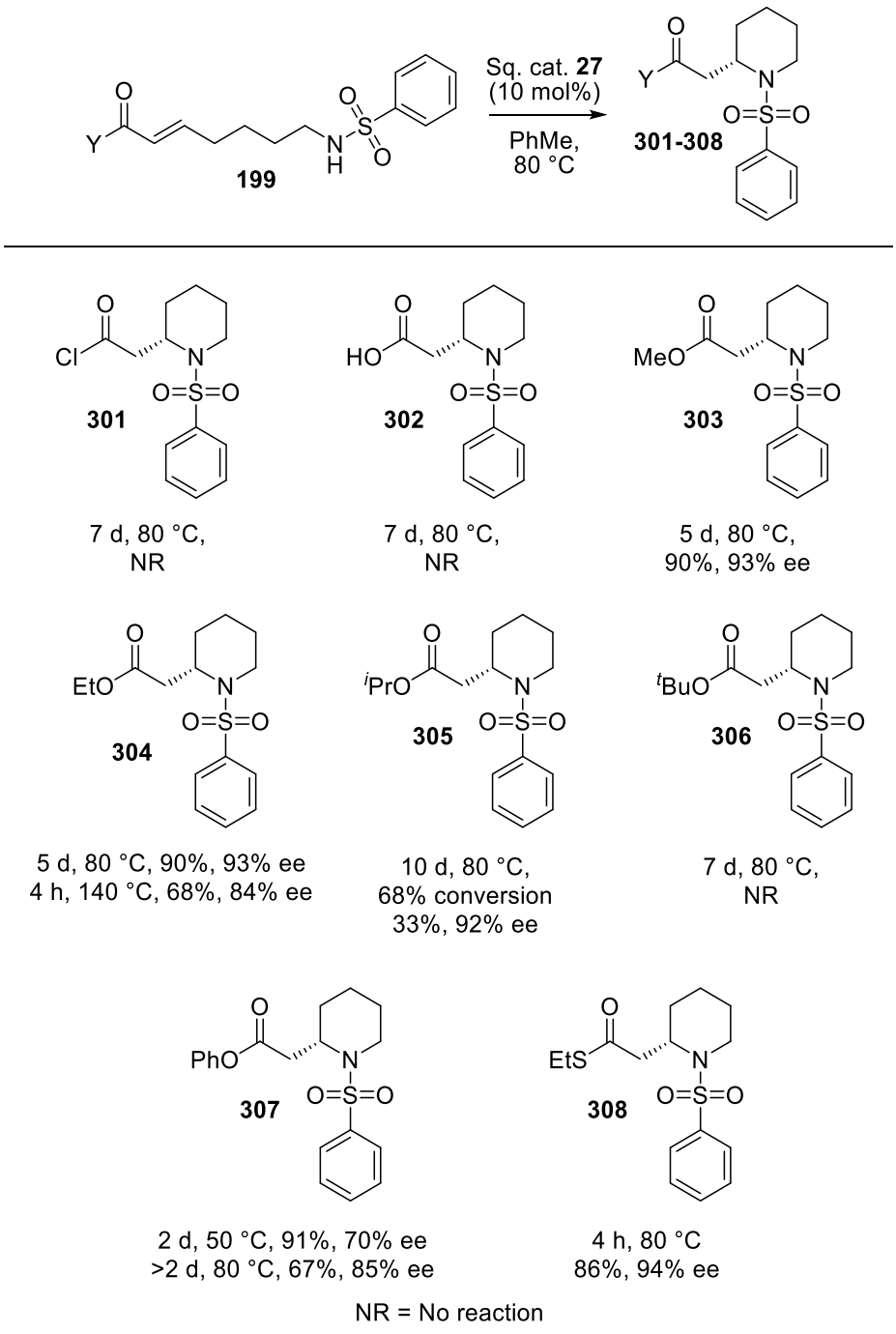
Scheme 78. Attempts towards a seven membered ring

Asymmetric Cyclisations - Esters, Amides, Thioester and others

Aromatic ketones are more easily activated towards *N*-conjugate addition than esters. With methyl ketones the rate at which an amine can condense and form an iminium is higher than that of a phenyl ketone. As many asymmetric organocatalysts rely on the formation of such iminium species to perform the reaction the conjugate addition is rarely seen to work with these more conjugated ketones with reasonable rates. Esters and related functional groups that do not readily undergo iminium formation are poorly represented in the asymmetric organocatalysis literature. The squaramide catalyst does not rely on this bond formation but instead uses hydrogen bonding interactions that esters are compatible.

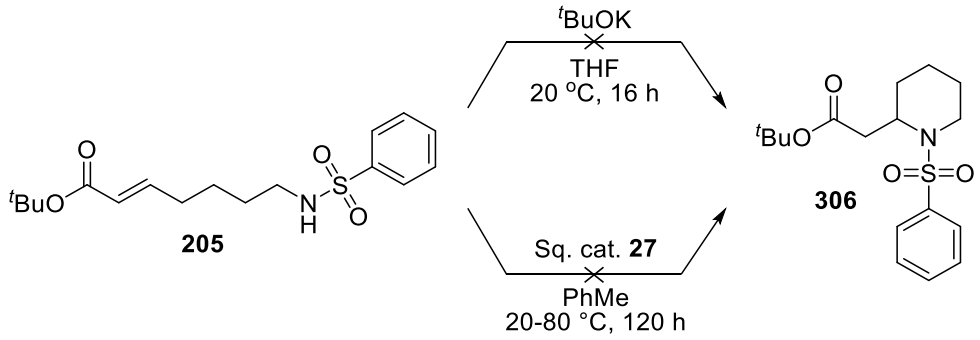
The α,β-unsaturated esters did not undergo cyclisation in the presence of the squaramide catalyst **27** at room temperature. When the reactions were heated, more of the catalyst was found to be soluble in the solution and at 80 °C the catalyst loading could be increased to 10 mol% in toluene. At these temperatures the esters underwent cyclisation slowly albeit stereoselectively (Scheme 79).

Neither acid chloride **200** nor carboxylic acid **199** underwent cyclisation, even after prolonged reaction times. It was also observed that the acid chloride **200** begins to decompose to the carboxylic acid **199** under these conditions. The methyl **201** and ethyl esters **202** both cyclised to give identical enantioselectivities after the same amount of reaction time. Five days is a long time for a reaction at elevated temperatures, yet the observed enantioselectivity was still high under these conditions. Further increases in reaction temperature were investigated. Using a microwave the reaction was super-heated to 140 °C and reached completion after four hours, the measured enantioselectivity dropped in these reactions but was still respectable levels (84% ee). When changing from methyl to ethyl the added bulk of the extra carbon appeared to have no effect on the reaction outcome. However, this is not the case with the *iso*-propyl ester **203**, as after ten days only two thirds of the starting material had been consumed.



Scheme 79. Results from cyclisations of esters with the squaramide catalyst

Despite these very long reaction times, the enantioselectivity was almost identical to that of the other esters (92% ee). The *tert*-butyl ester **205** did not cyclise in the presence of the squaramide catalyst **27**, or when the reaction was instead attempted with several equivalents of strong base such as potassium *tert*-butoxide (Scheme 80).



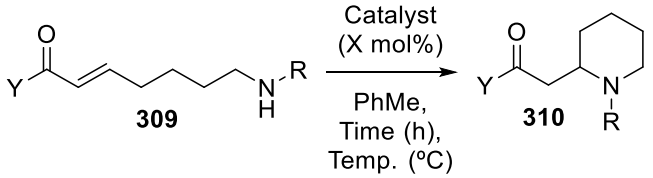
Scheme 80. The *tert*-butyl ester 205 does not cyclise

In terms of steric bulk the phenyl ester **204** is somewhat comparable to the *iso*-propyl **203** or the *tert*-butyl **205** but has a very different electronic influence. After two days at 80 °C the reaction was already complete, but the enantioselectivity for this reaction was the lowest of the esters tested so far. Unexpectedly the phenyl ester **204** cyclised much quicker than the other esters at 80 °C, because of this a lower temperature was investigated as it was thought this would result in a higher enantioselectivity. At 50 °C the reaction was still completed quite quickly in comparison to the other esters, but the enantioselectivity was actually reduced. One explanation could be that the phenyl ester **204** undergoes some positive interaction with the catalyst that the other esters do not.

All of these esters that gave high enantioselectivities suffered from prolonged reaction times, to attempt to tackle this issue a more reactive ester was investigated in the form of a thioester. The 3p orbitals used by the sulfur in the carbon sulfur double bond do not have as good orbital overlap with the carbon 2p orbitals as oxygen, thus resulting in a much longer bond than esters. This lack of conjugation means the thioester is closer to a ketone in terms of reactivity towards nucleophiles. For this reason we believed that the thioester may react analogously as a methyl ketone rather than that of an ester.

Cyclisation of thioester compound **215** reached completion after only 4 hours at 80 °C whilst also giving the highest enantioselectivity observed for all esters. In light of the results obtained from the thioester, further work was performed to explore whether a better enantioselectivity could be achieved and how

these changes compared when performed on the same methyl esters (Table 8).



Entry	No.	Y	R	Catalyst	(X mol%)	Time (h)	Temp. (ºC)	%Yield[a]	%ee[b]
1	**268**	OMe	Bs	**27**	10	48	80	48	88
2	**268**	OMe	Bs	**27**	5	48	80	66	88
3	**268**	OMe	Bs	**26**	10	48	80	71	87
4	**272**	SEt	Bs	**27**	10	2	80	99	94
5	**272**	SEt	Bs	**27**	5	8	80	99	94
6	**272**	SEt	Bs	**27**	10	24	50	77	97
7	**272**	SEt	Bs	**27**	5	26	50	82	97
8	**272**	SEt	Bs	**26**	10	26	50	64	91
9	**273**	SEt	2-Ns	**27**	5	8	80	89	91
10	**273**	SEt	2-Ns	**27**	5	24	50	94	94
11	**273**	SEt	2-Ns	**27**	5	96	25	82	87

[a] Isolated yield.
[b] Determined by chiral HPLC.

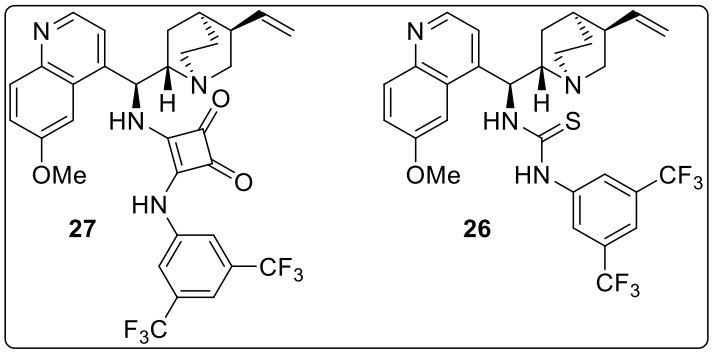
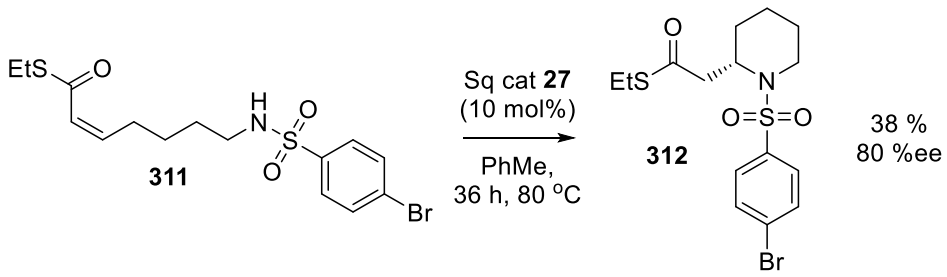


Table 8. Further comparative screening on thioester and methyl esters

A brosyl group was used as the nitrogen functionality as it was hoped that a crystal structure of one of the esters or thioesters could be obtained. Both the ester and thioester brosyl derivatives **268** and **272** were cyclised in a shorter reaction time than there benzenesulfonamide counterparts **266** and **271**. Ester **268** proceeded to completion in only two days while the brosyl derived thioester **272** proceeded in just two hours as compared to four hours for the corresponding benzenesulfonamide **271** (Entries 1 and 4). When the reaction temperature was lowered to 50 °C the reaction time to completion lengthened as expected but an improvement of the enantioselectivity was observed (Entries 4 and 6). The squaramide catalyst **27** was also compared with the

popular thiourea catalyst **26** (Entries 3 and 8). Despite good enantioselectivities the thiourea **26** is not as good as the squaramide **27** in terms of yield and enantioselectivity (Comparing Entries 1 and 3 or Entries 5 and 8). Dropping the catalyst loading to 5 mol% gave almost identical results to 10 mol%. 2-Nosyl derivative **273** was also evaluated as the group is easier to remove than other sulfonamides. The *ortho*-nosyl derivative **273** gave comparable results to the brosyl derivative **272** at both 80 °C and 50 °C (Entries 9 and 10). Cyclisations attempted at 25 °C gave much longer reaction times but no improvement in enantioselectivity was observed (Entry 11). It is likely a temperature between 25 °C and 80 °C offers the ideal compromise for enantioselectivity and reaction rate.

A reaction of much interest was the cyclisation of the *cis* alkene of the thioester that was isolated in a small quantity from the oxidative Wittig (Scheme 81).



Scheme 81. Cyclisation of a *cis* alkene 311 using the squaramide catalyst 27

Although a *cis* alkene **311** doesn't fit the transition state model (shown later), the results of the cyclisation show that the catalyst is still able to impart enantioselectivity upon the product in moderate levels (previous *trans* reaction gave 99% yield, 94% ee in 2 hours).

The cyclisation product featuring a methyl ester and a brosyl group was crystalline and ultimately gave an X-ray crystal structure. The major enantiomer for the esters are the same as that of the phenyl ketones, thus overall the mechanism is assumed to be the same (Figure 17).

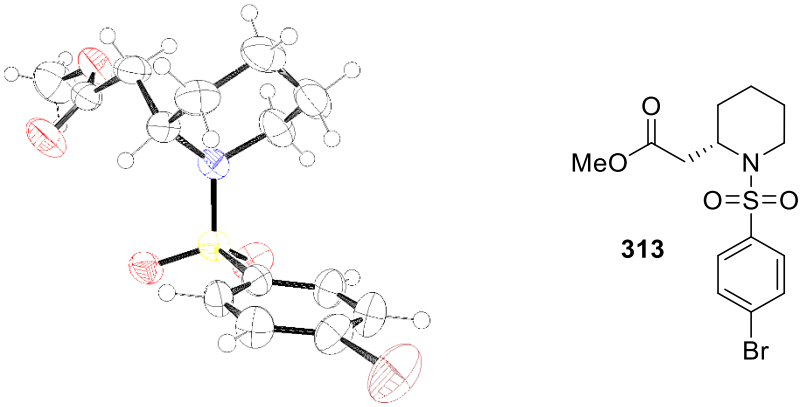
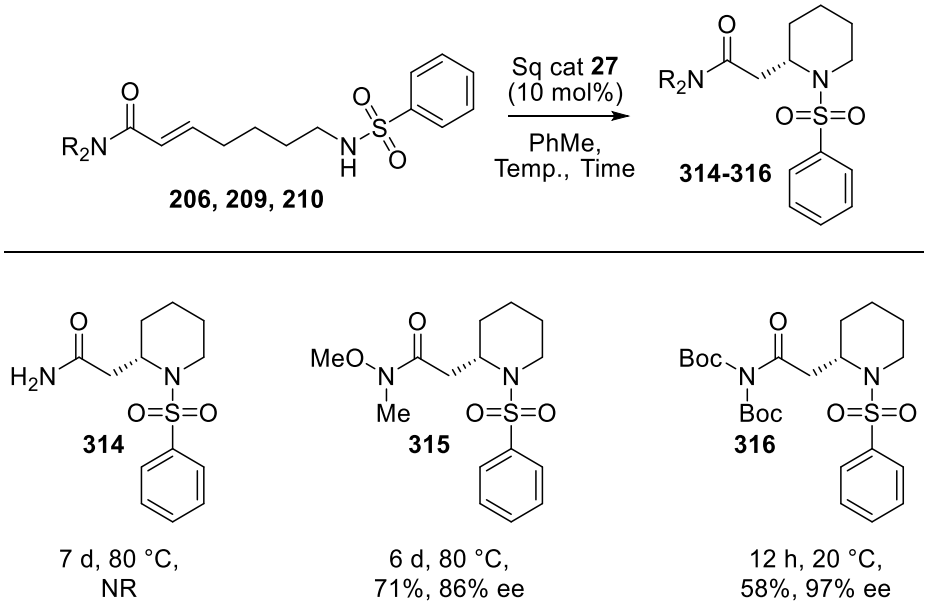


Figure 17. X-Ray crystal structure of methyl ester 313

As well as esters, cyclisations of other conjugated vinyl compounds were investigated, including primary amide **206**, di-Boc protected amide **209** and Weinreb amide **210** (Scheme 82).

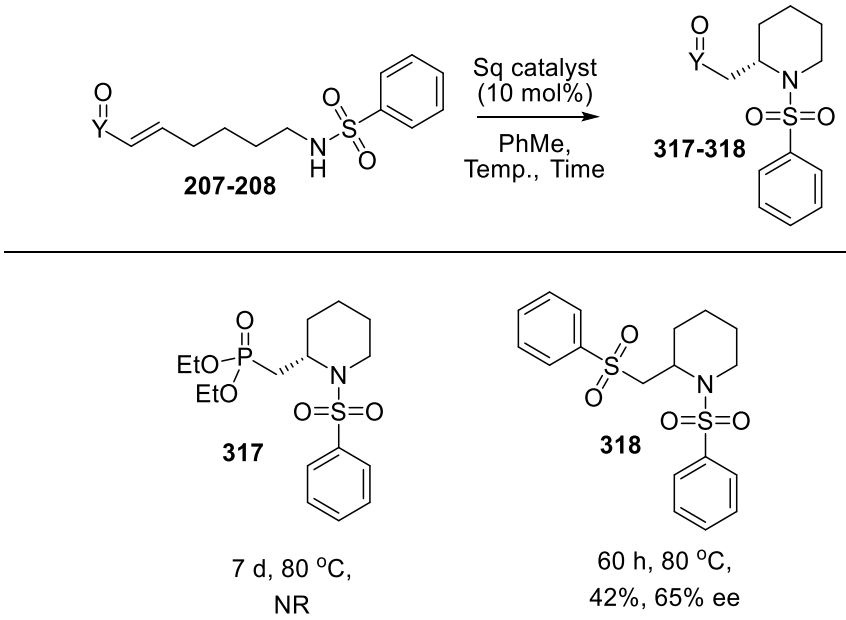


Scheme 82. Amides attempted using squaramide catalyst

Cyclisation of the free amide **206** was unsuccessful; this was expected since the acid chloride **200** and carboxylic acid **199** both gave similar results. Next cyclisation of a Weinreb amide derivative was attempted, the Weinreb amide was slow to cyclise but did so in good yield and with good enantioselectivity. The slow reaction time is most likely the result of the electron rich nature of this functional group. A di-*tert*-butyl dicarbamate **209** was found to cyclise

readily at room temperature in only twelve hours in moderate yield and excellent enantioselectivity. Di-*tert*-butyl dicarbamate **209** worked well but is not an atom efficient route.

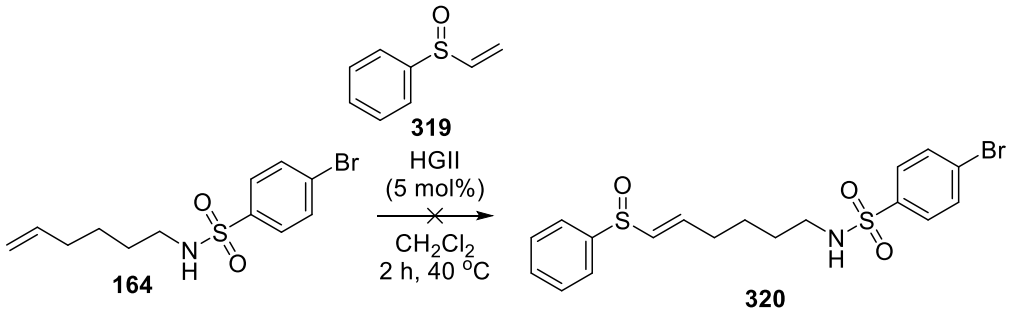
All of the previous compounds have featured a carbonyl as part of the acceptor. Two compounds were made in which this bond was replaced with a sulfone and a phosphonate (Scheme 83).



Scheme 83. Synthesis of sulfone 318 and phosphonate 317 compounds

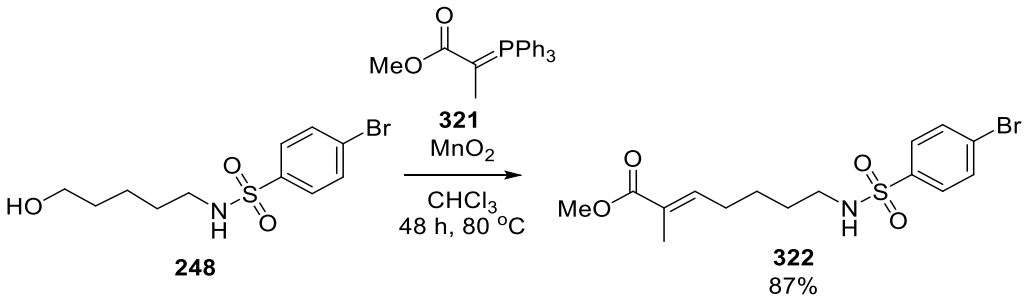
The phosphonate compound **208** did not undergo cyclisation when heated with the squaramide catalyst **27** or when stirred with strong base (potassium *tert*-butoxide). The sulfone **207** proved more successful, reaching completion in two and a half days although the product **318** yield was poor and enantioselectivity modest. A different elution order of peaks to the normal by HPLC and an opposite direction being observed by polarimetry raise the possibility this may be the opposite enantiomer than that expected from preceding experiments on the carbonyls. The presence of a sulfone moiety at both ends of the compound may account for this observation as there is less to distinguish potential binding modes to the catalyst. The synthesis of a sulfoxide derived compound **320** was also attempted but the precursors **164** and **319** do not

undergo the cross metathesis, instead the reaction immediately became purple, suggesting that the metal catalyst was compromised (Scheme 84).



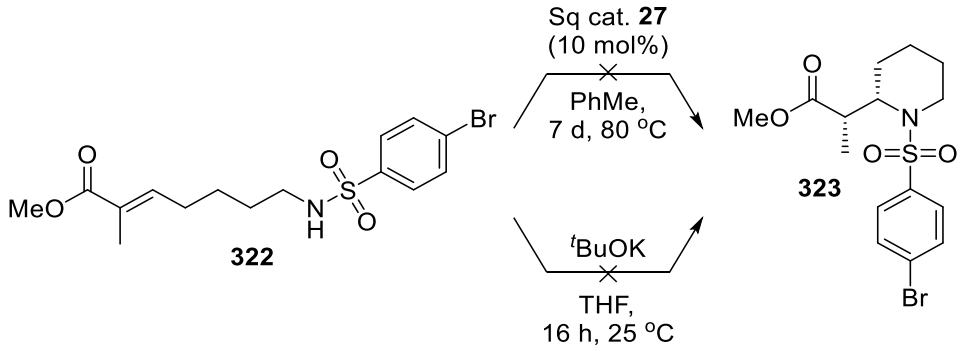
Scheme 84. The attempted metathesis reaction to synthesise the sulfinyl compound

We wanted to explore disubstituted alkenes as potential electrophiles. A substituted phosphorus ylide was prepared to this end **321**.[99] Subsequent oxidative Wittig between the ylide **321** and alcohol **248** gave the trisubstituted alkene **322** in good yields and with no trace of the *cis* isomer by ^{1}H NMR (Scheme 85).



Scheme 85. Synthesis of the trisubstituted alkene

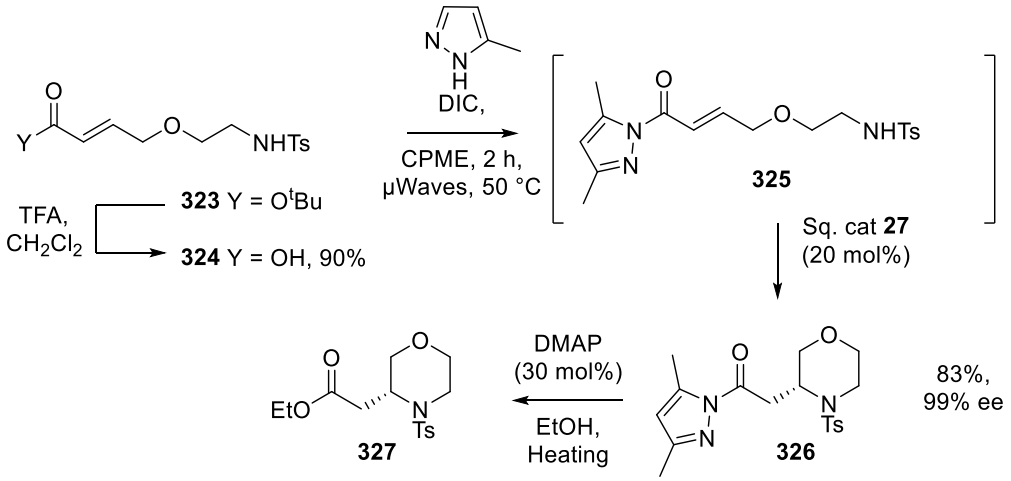
Unfortunately, all attempts to effect cyclisation of this compound **322** proved unsuccessful (Scheme 86).



Scheme 86. Attempted cyclisation of the trisubstituted alkene 322

Time was not available to pursue this further within the project but it is certainly an area that demands more attention especially for the synthesis of potentially biological active small molecules such as Ritalin.

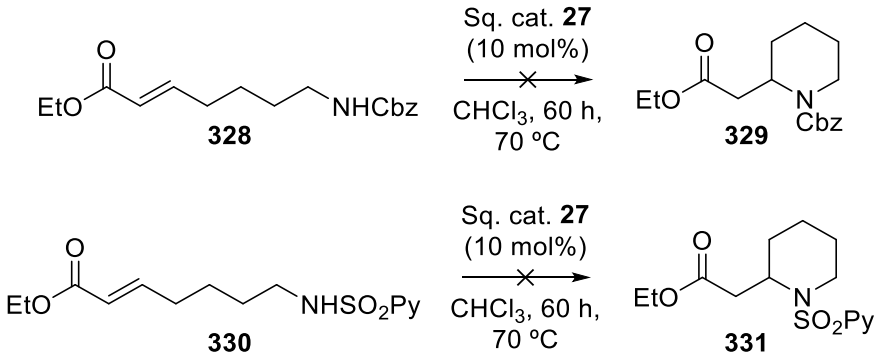
During the end of our investigations a report from Fustero *et al.* contained the preparation of similar heterocycles using the same cinchona derived squaramide catalyst **27** in good yields and enantioselectivities (Scheme 87).[100]



Scheme 87. Fustero *et al.*'s report of similar work involving squaramide catalyst 27

Fustero *et al.* arrived upon the use of conjugated *N*-acyl pyrazoles **325** as several key experiments attempted suggested to them that esters were not compatible with the cinchona derived squaramide catalyst **27**. This incompatibility appears to be as a result of two substrates that did not undergo cyclisation in the presence of the catalyst. However, our investigation has shown that the reason these compounds did not cyclise is due to either the

pyridine sulfonamide or the carbamate, both of which are incompatible with the catalyst (Scheme 88).



Scheme 88. Fustero *et al.*'s incompatible substrates

Had Fustero *et al.* used a compound with either sulfonamide or an ester less bulky than a *tert*-butyl they would have likely observed asymmetric cyclisations occurring. Fustero *et al*.'s synthesis achieves the synthesis of esters but requires the synthesis of a *tert*-butyl ester, subsequent acid cleavage and amide coupling reaction in favour of a more direct route.

Determining a potential mechanism

Several products made in very high enantioselectivity were crystalline, these were recrystallized to enantiopurity as analysed by chiral HPLC. Subsequent X-ray crystallography of these crystals gave the absolute stereochemistry of the chiral centre formed, which was found in all cases have an (*S*) configuration (Figure 18).

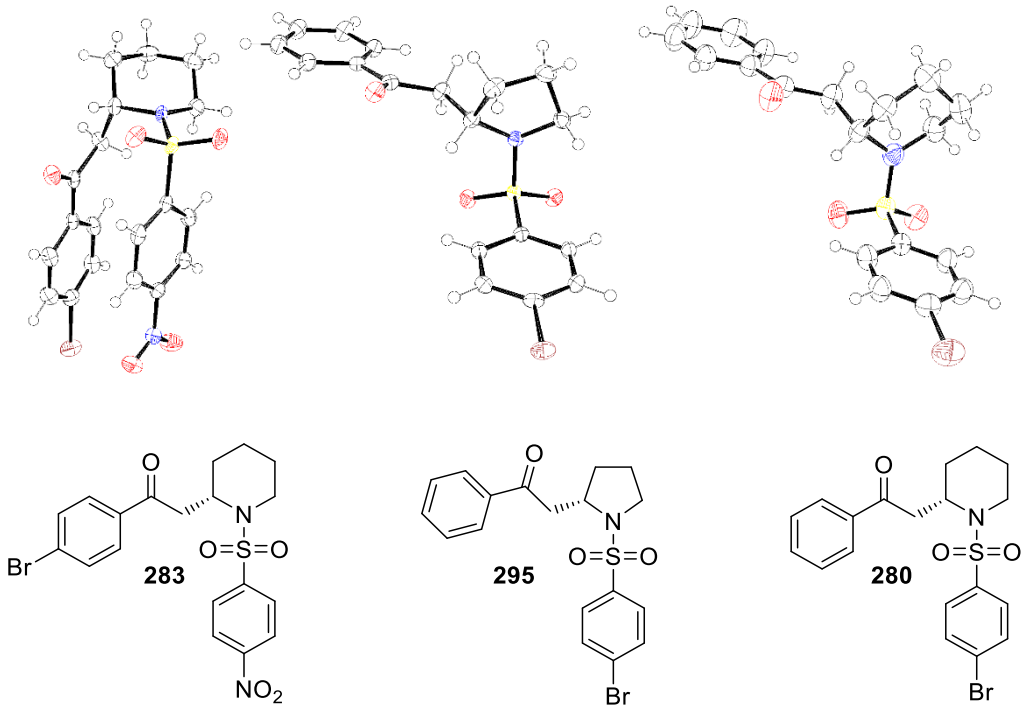
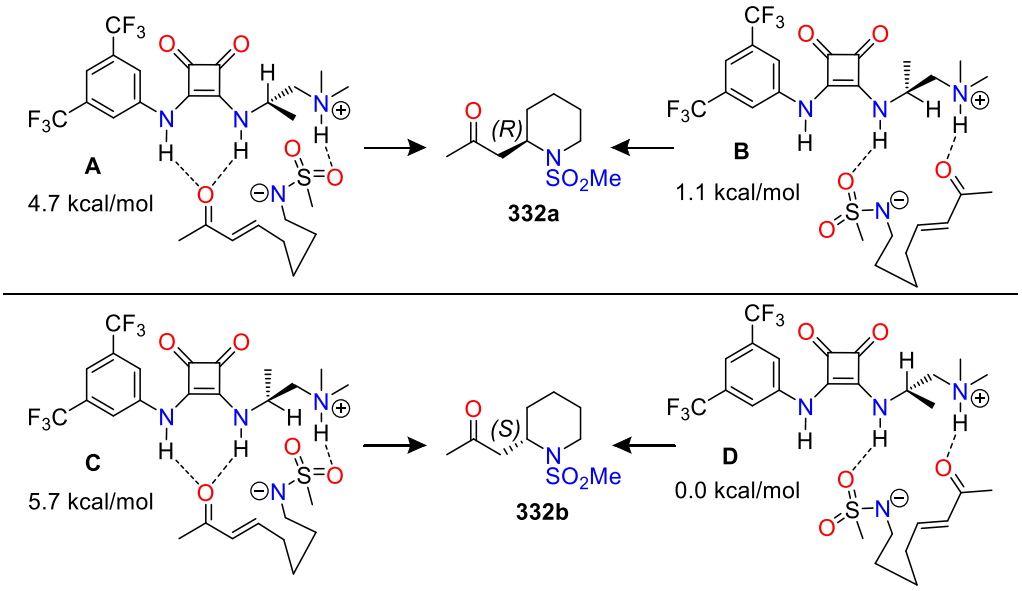


Figure 18. Crystal structures of compounds 283, 295 and 280

We moved on to consider the mechanism. It is suggested that the quinuclidine moiety of the squaramide catalyst deprotonates the sulfonamide resulting in the formation of an ion pair between the deprotonated sulfonamide and the now protonated quinuclidine. Next the *N*-conjugate addition will occur, and it is here that the interactions between two molecules become important for the formation of each enantiomer. Computational work was performed by Barry Lygo (see Appendix) on a simplified version of the two molecules in four different arrangements. Arrangements **A** and **C** both have the sulfonamide substrate oxygen hydrogen bonding to the protonated quinuclidine whereas **B** and **D** involve hydrogen bonds to the carbonyl. The sulfonamide now hydrogen

bonds to the squaramide moiety with the enone now hydrogen bonging to the protonated quinuclidine (Scheme 89).

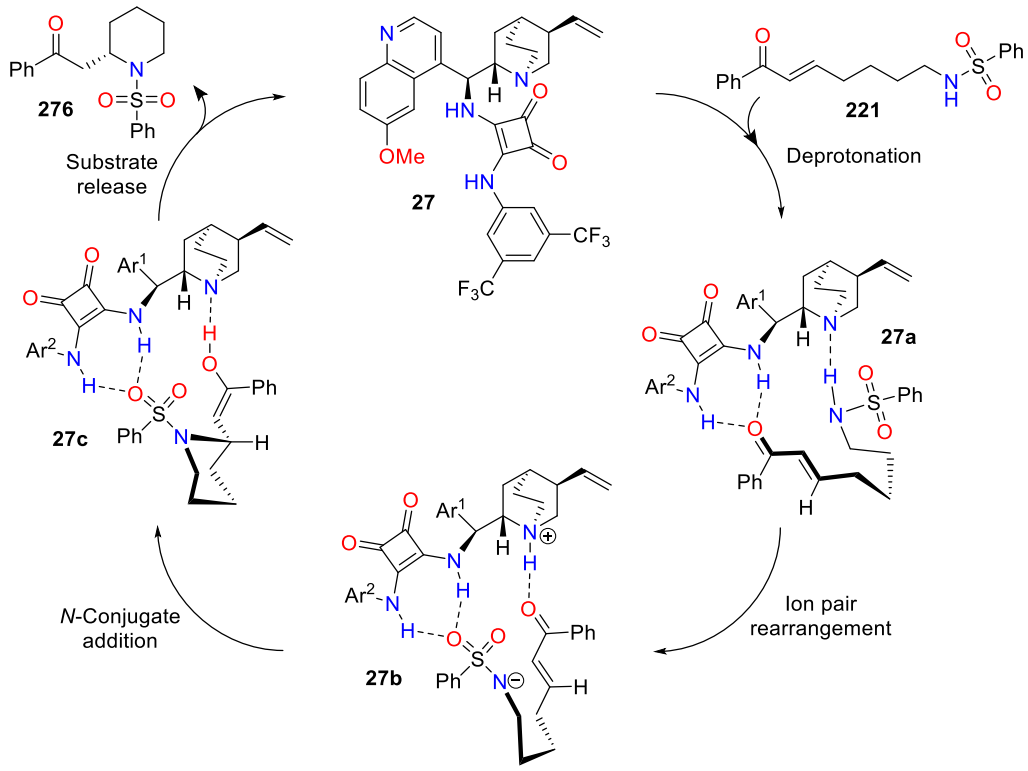


Scheme 89. Relative energies using the B3LYPD3(BJ)/def2-TZVPP//B3LYP/6-316 theoretical model

The difference between **A** and **B**, and **C** and **D** is the arrangement around the squaramide catalysts chiral centre. Depending on its positioning the nitrogen can be delivered from either the front or the back face of the enone. Energies were calculated for all four of these models using B3LYPD3(BJ)/def2-TZVPP//B3LYP/6-316; the lowest energy is represented as 0.0 kcal/mol. The immediate observation is that the relative energies of both the transition states with hydrogen bonding between the enone and the terminal dimethyl amine (**B** and **D**) are much lower by 3.6 and 5.7 kcal/mol than those bonding the sulfonamide (**A** and **C**). The transition state with the lowest energy of all those modelled results in the (*S*) enantiomer, the same identified as the major product by X-ray crystallography. As the computational work, the X-ray crystallography data, optical rotation and order of elution in the HPLC chromatograms all point to the same enantiomer, a confident assignment of the (*S*) enantiomer as the product in these reactions. Products that were not crystalline shared the same characteristic elution order by chiral HPLC traces

and same direction of optical rotation, thus we conclude that in all compounds investigated thus far the major product is the (*S*) enantiomer.

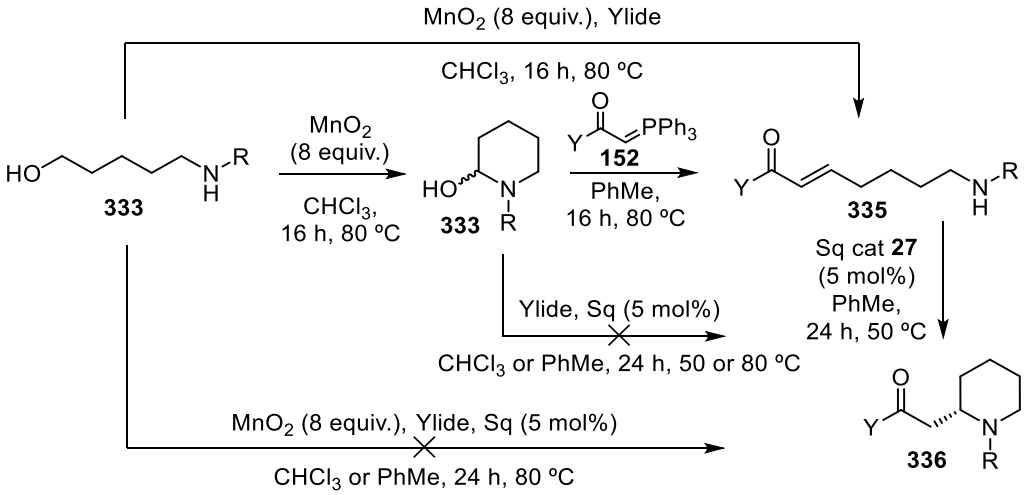
From all of this data we propose a mechanism that starts with the deprotonation of the sulfonamide by the quinuclidine. An energetically favourable ion pair rearrangement follows that leaves the sulfonamide hydrogen bonding with the squaramide moiety and the enone to the protonated quinuclidine. Subsequently, the enone is attacked by the nitrogen from the back face as directed by the chiral centres lowest energy conformation leading to the formation of the (*S*) enantiomer of the chiral centre (Scheme 90).



Scheme 90. Our proposed mechanism for the formation of the (*S*) enantiomer

Further investigation towards telescoped reactions

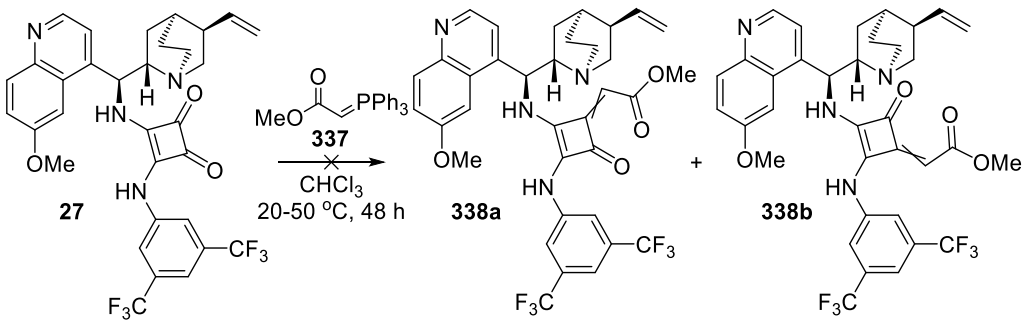
The alcohol can be oxidised in the presence of the ylide with manganese dioxide to generate the enone in one pot. The enone formed can potentially undergo unwanted cyclisation under the reaction conditions or during purification by flash column chromatography. The oxidative Wittig was attempted with the squaramide catalyst **27** present to see if the asymmetric cyclisation would occur in the same reaction vessel (Scheme 91).



Scheme 91. Individual and combined steps of the oxidative Wittig and cyclisation

As described, the oxidation of the alcohols by manganese dioxide to the hemiaminal proceeded in moderate to good yields (~60-80%). The reaction between the hemiaminal and the ylide also proceeds in similar yields (~60-80%). The transformation achieved over these two steps was similar or worse than that progressed using a one pot method. The resulting enone can then be cyclised asymmetrically with the squaramide catalyst in high yields and enantiomeric excess. Unfortunately attempts to include the squaramide catalyst **27** (5 mol%) with the oxidative Wittig yielded predominantly uncyclised material (93% by ^{1}H NMR) and any cyclised material (4%, 7% by ^{1}H NMR) was found to be racemic. It was thought the manganese dioxide oxidant could potentially be altering the catalyst perhaps by co-ordination, thus rendering it inert. However, when the hemiaminal intermediate **334** was reacted with the ylide **152** in the presence of the catalyst **27** still no reaction occurred, perhaps

suggesting that it is the ylide **152** that renders the catalyst inert. Ylide **152** may be reacting with one of the carbonyls on the squaramide moiety. However, reaction attempts at this did not give corresponding reaction products as observed by LC-MS or ^{1}H NMR (Scheme 92).



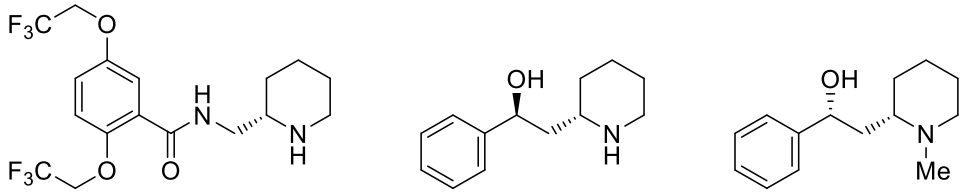
Scheme 92. No reaction between the catalyst 27 and the ylide 337 observed

Instead it is likely that the ylide is simply deprotonating the catalyst, this may also render the catalyst ineffective but would have no observable change by LC-MS and be difficult to detect by ^{1}H NMR.

Further modifications on the phenyl ketones

Generally, the phenyl ketones were cyclised in yields and excellent enantioselectivities typically in the region of 98 and 99% ee. Next, reactions were performed to demonstrate the potential of this reaction to produce drugs or natural products.

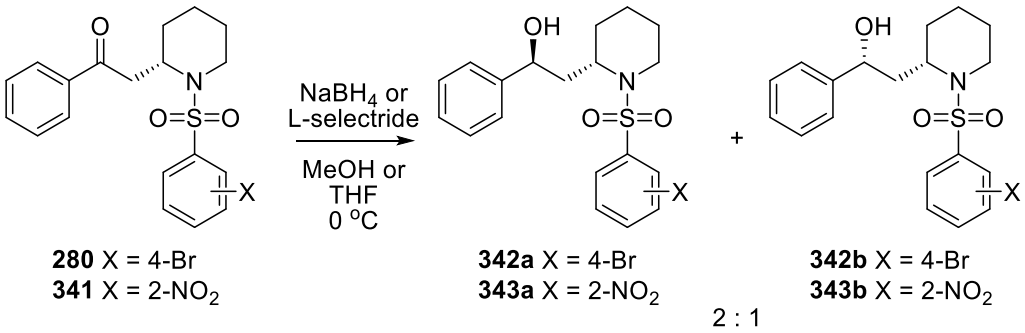
Specifically we chose to work towards formal syntheses of small natural products such as (-)-Norsedamine **339** or (-)-Allosedamine **340** (Figure 19).



7 Tambocor | **339** (-)-Norsedamine | **340** (-)-Allosedamine

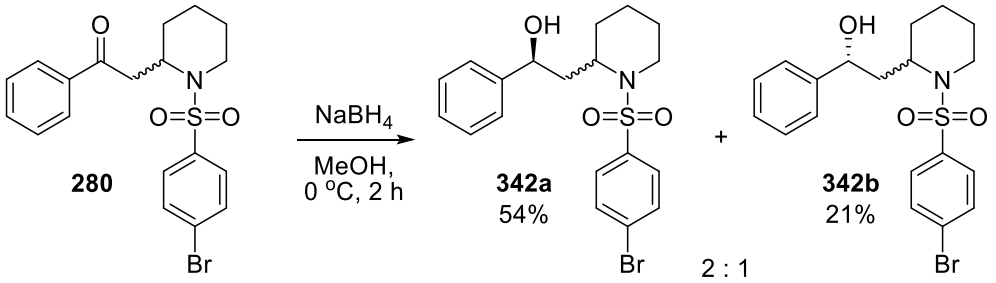
Figure 19. Natural products and drug compounds containing 2-substituted piperidine rings

First, a reduction of the ketone was performed with sodium borohydride in methanol. This gave a mixture of diastereoisomers for the brosyl compound that in this case could be separated by column chromatography but not for the 2-nitrobenzenesulfonyl compound (Scheme 93).



Scheme 93. Reductions of phenyl ketones with sodium borohydride and L-selectride

When the reaction was repeated with racemic starting material the same ratio was once again produced (Scheme 94).



Scheme 94. Reproduced results on racemic compound

The brosyl alcohol **342a** and **342b** were both crystalline and **342a** was successfully recrystallized to afford a crystal structure that allowed stereochemical assignment (Figure 20).

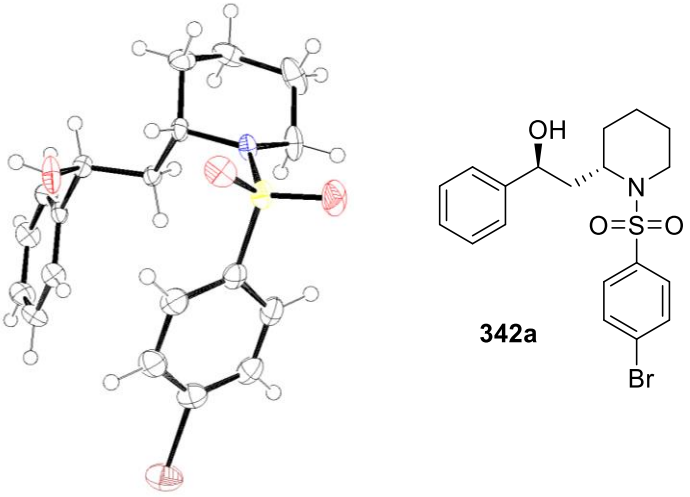
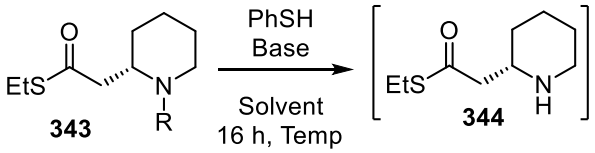


Figure 20. X-Ray crystal of the major diastereoisomer from the reduction

Next a representative deprotection was attempted on some sulfonamide containing piperidines (Table 9).



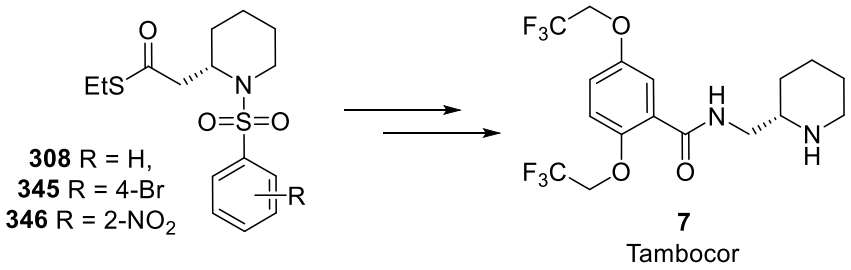
No.	R	Base	Solvent	Temp (ºC)	%Conversion
345	Bs	K_2CO_3	MeCN	25-80	0
345	Bs	Cs_2CO_3	MeCN	25-80	0
345	Bs	Cs_2CO_3	DMF	25-80	0
345	Bs	Cs_2CO_3	DMF	25-80	0
308	SO_2Ph	Cs_2CO_3	DMF	25-80	0
346	2-Ns	Cs_2CO_3	MeCN	25	100

Table 9. Deprotection of sulfonamides

No deprotection was observed when attempting to remove the brosyl group with thiophenol, regardless of conditions used. The benzene sulfonyl group was also not removed using these conditions. However, the *ortho*-nitrobenzene sulfonamide was completely converted to the amine when caesium carbonate was used as a base at room temperature in acetonitrile (Table 9). The presence of the nitro group is essential for stabilising the Meisenhemier complex.

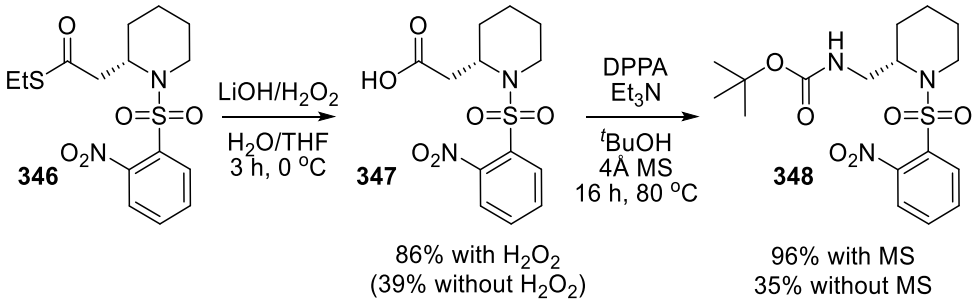
Further modifications of esters and thioesters

As with the phenyl ketones, the esters and thioesters can be easily modified to become the core or part of biologically active compound. A route was undertaken toward the formal enantioselective synthesis of Tambocor **7** with the aim of demonstrating the utility of using the thioesters (Scheme 95).



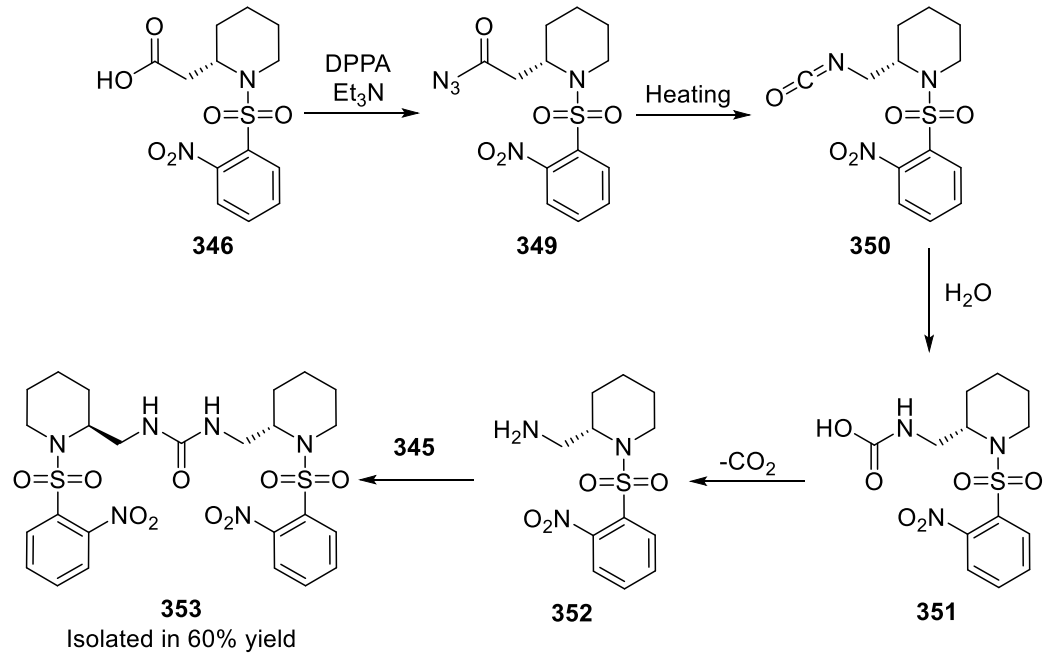
Scheme 95. Towards an enantiorich synthesis of Tambocor 7

After isolating the thioester **346** in good yields and enantioselectivity the thioester was cleaved using aqueous lithium hydroxide and hydrogen peroxide in 86% yield (Scheme 96).



Scheme 96. Towards Tambocor 7

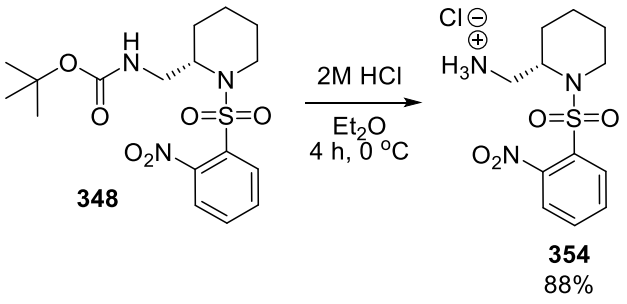
Next, a Curtius rearrangement was achieved using diphenyl phosphoryl azide followed by heating in *tert*-butanol with triethylamine. Initially only a third of the material isolated was found to be the desired carbamate **348** and a side product urea **353** was isolated in 60% yield, likely the result of trace water in the *tert*-butanol (Scheme 97).



Scheme 97. Side product 353 and likely pathway

Any water present in the reaction competes the *tert*-butanol to react with the isocyanate **350** to form a carbamic acid **351**, which then decomposes to the amine **352**, releasing carbon dioxide. From here the resulting primary amine **352** can react with further isocyanate **350** to undesired urea product **353**.

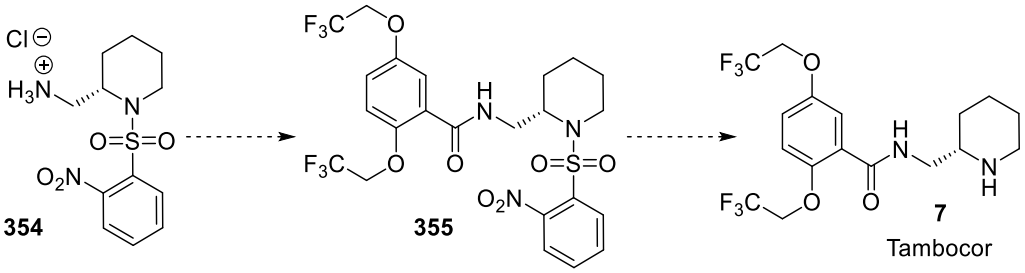
When performed with crushed 4Å molecular sieves the desired Boc protected amine **348** was isolated in good yields (96%), subsequently this carbamate **348** was then deprotected using 2M hydrogen chloride in diethyl ether solution to furnish ammonium salt **354** from the reaction mixture as a powdery white solid in good yield (Scheme 98).



Scheme 98. Boc group cleavage with hydrogen chloride

Work was concluded at this point. Future work would take the hydrochloride salt **354** would then be partnered with an appropriate acid chloride or

carboxylic acid using DCC, the only step left would be the deprotection of the sulfonyl group (Scheme 99).



Scheme 99. Future work that could potentially access Tambocor 7

Investigating Cyclisations Using Factorial Experimental Design

Traditionally chemists optimise reactions only one factor at a time but this can lead to problems as when several variables are tested one after the other only the last variable tested would truly be optimum. For example, a reaction optimised for temperature then concentration will likely not give the best possible result as these variables can interact with one another. The lack of understanding interactions between variables makes a one variable at a time approach unreliable.

Factorial experimental design (FED) otherwise known as design of experiments (DoE) is used in a multivariable reaction to give the best understanding of a response or outcome with the fewest number of experiments. This designs of experiments can be visualised using a cube plot (Figure 21).

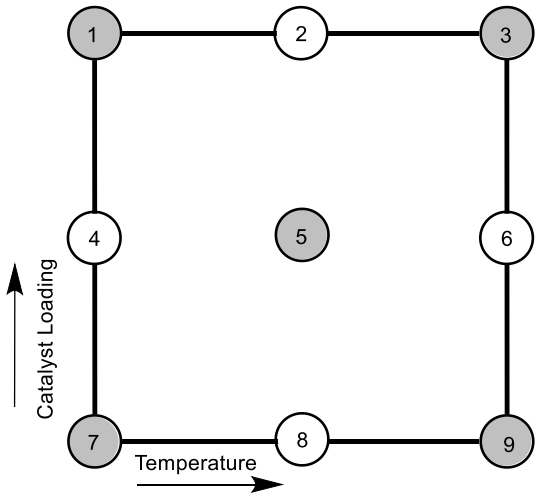


Figure 21. Two factor cube plot

Simple two factor experiments are defined as a 2^2 factorial design (2^k design system in which k is the number of variables). Thus a minimum of six experiments are need, these consist of the corners 1, 3, 7 and 9 and a centre point 5 is also performed twice. This centre point tests for reproducibility of the reactions and allows to further look for curvature in the contour plots generated.

When applying this approach we need to perform $2^4 + 2$ experiments (18 total). We can think of this visually as comparison between two cubes in which all the corners 1, 3, 7, 9, 19, 21, 25 and 27 and the centre 14 are reactions to run and statistical mathematics performed by a computer program compares the cubes and generates data and plots regarding major effects and trends.

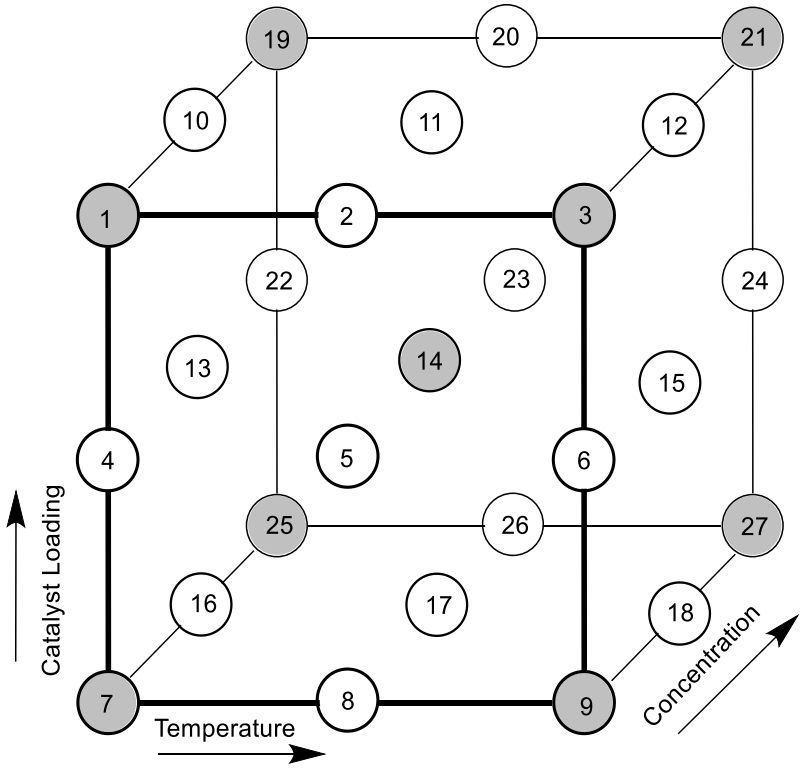
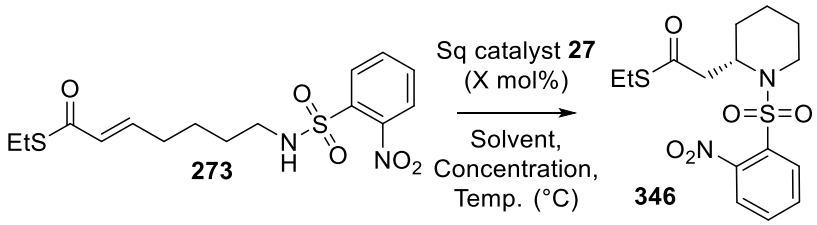


Figure 22. Visualisation of a three factor cube plot

Instead of a full factorial design, a fractional factorial design was performed. With fractional factorial design less experiments are performed than a full design, instead only a carefully chosen few that will reveal trends in the data. Best results are obtained when alternate corners are used, in the figure above these could either be corners 1, 9, 21 and 25 or corners 3, 7, 19 and 27. These

corners are used to better separate the effect of each individual factor and improve the resolution of the design (in this instance referred to as an IV or 2^{4-1} design).

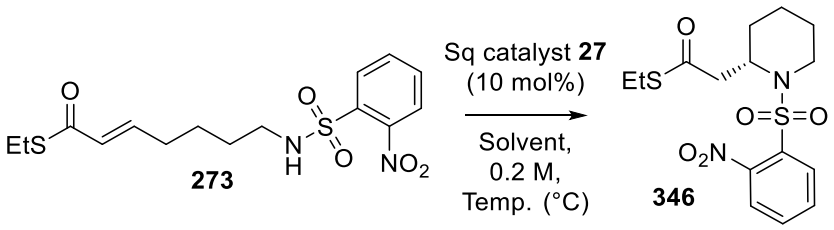
The cyclisation of the 2-nitrobenzene sulfonamide containing thioester compound **273** with the squaramide catalyst **27** was chosen for further study; the thioester product **346** is of interest due to its synthetic versatility (Scheme 100).



Scheme 100. The reaction to better study

Numerical factors to be explored included temperature, catalyst loading and concentration. Solvent as a categorical factor was also studied. The objective of this investigation was to determine what factors were most important for outcomes such as yield, enantiomeric excess and reaction time.

To begin the study another solvent would need to be selected other than toluene. A solvent screen using the thioester **273** in the presence of the squaramide catalyst **27** was performed (Table 10).[101]



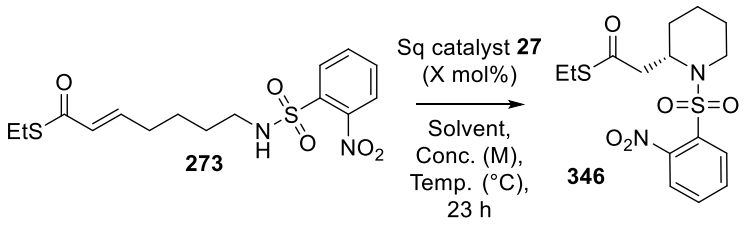
Entry	Solvent	Temp. (°C)	% ee
1	Toluene	40	96
2	Anisole	50	96
3	n-Heptane	50	95
4	Toluene	60	95
5	Toluene	80	94
6	Toluene	80	91
7	MTBE	50	89
8	iPrOAc	50	88
9	MIBK	50	76
10	DMSO	50	12

Table 10. Alternate solvent screen

All solvents chosen were considered to be 'green' by industry and their use in large scale industrial or pharmaceutical synthesis approved.[101] Reactions were run at 50 °C whilst previous toluene experiments were run at a variety of temperatures (40, 60 and 80 °C). Toluene, anisole and n-heptane (Entries 1-6) gave the highest enantioselectivities, these are also the more non-polar solvents. Other solvents (Entries 7-10) gave lower enantioselectivities. From these results further optimisation was performed with both toluene and anisole.

The designed experiments factors were chosen based on previous reactions performed. The temperatures chosen were 40, 60 and 80 °C. A concentration of 0.2M had been used for previous experiments, for this reason values higher and lower than this were also selected for comparison (0.15M, 0.20M and 0.25M). High catalyst loading is undesirable so only values below that previously used were selected (2, 6 and 10 mol%).

A set of 10 factorial experiments were initially performed (Table 11 Entries 1-10). Afterwards additional reactions were performed to explore curvature in the system (Table 11 Entries 11-15).



Entry	Solvent	X mol%	Conc. (M)	Temp. (°C)	Time (h)	%Conv.[a]	%Yield[b]	% ee[c]
1	Anisole	10	0.15	80	5	100	88	92
2	Toluene	2	0.15	80	168	50	46	88
3	Anisole	2	0.15	40	168	30	19	95
4	Toluene	2	0.25	40	168	33	24	94
5	Toluene	10	0.25	80	3	100	87	91
6	Toluene	6	0.20	60	23	100	76	95
7	Toluene	10	0.15	40	45	100	94	97
8	Anisole	2	0.25	80	144	68	42	90
9	Anisole	10	0.25	40	45	100	84	96
10	Toluene	6	0.20	60	23	100	92	95
11	Toluene	6	0.20	80	5	100	71	92
12	Toluene	10	0.20	60	8	100	85	95
13	Toluene	6	0.20	60	8	100	68	94
14	Toluene	2	0.20	60	23	100	69	94
15	Toluene	6	0.20	40	48	82	76	96

[a] As determined by HPLC integrations corrected with m-terphenyl as an internal standard. [b] Isolated yield after flash column chromatography. [c] As determined by HPLC.

Table 11. Factorial experiments to optimise the reaction

The reactions performed can be visualised on a cubic plot with the use of colour as shown in the below figure (Figure 23).

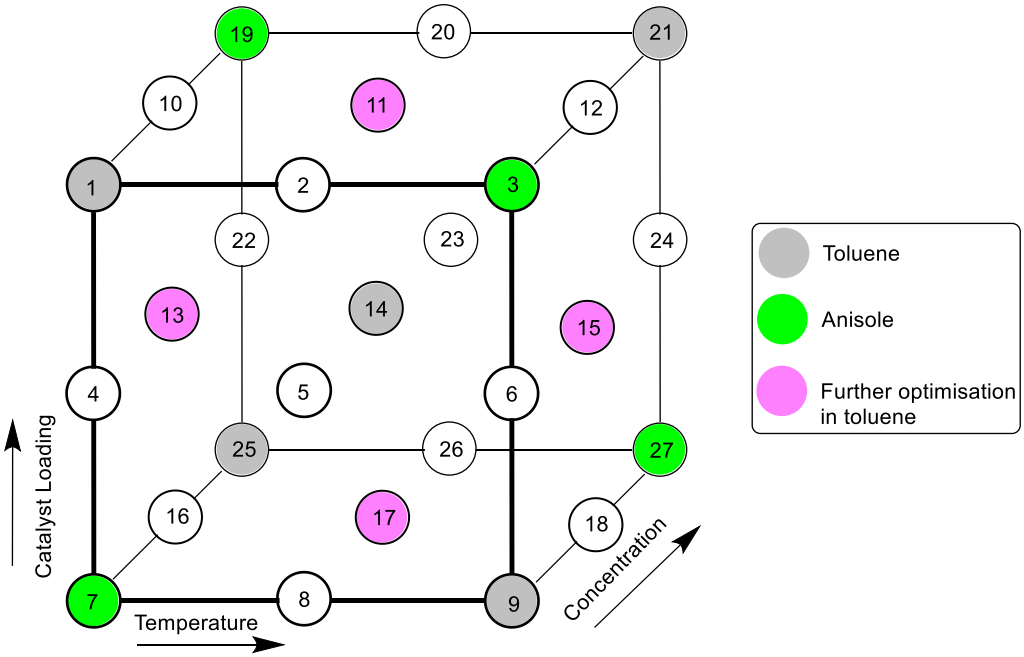


Figure 23. Reactions performed visualised on a cubic plot

The results were processed and the effect of each factor is expressed as the coefficient plot below. The larger the bars value the higher the effect with the direction being whether the effect is a positive or negative on the outcome. The error bars show whether the effect is significant, thus if the error bar is larger than the green bar then the effect can be described as insignificant (Chart 1).

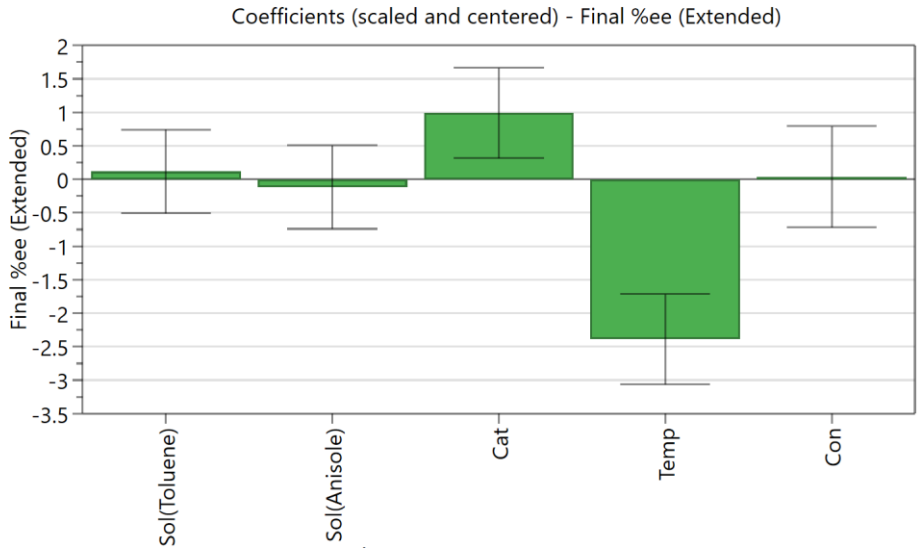


Chart 1. The effect of each factor on enantioselectivity

The choice of solvent between toluene and anisole is shown to be insignificant, this means if a reaction was done in either solvent this would likely not affect the enantiomeric excess of the product. Concentration is also insignificant within the range investigated. Higher catalyst loadings have a positive effect, resulting in improved enantioselectivity. Temperature has a negative effect, with lower temperatures producing better enantioselectivity.

Further analysis of the squared term suggest that as the catalyst charge increases, the less it contributes to the result as shown by the negative catalyst*catalyst term in the below plot. This means adding increasing amounts of catalyst will improve the enantioselectivity less and less (Chart 2).

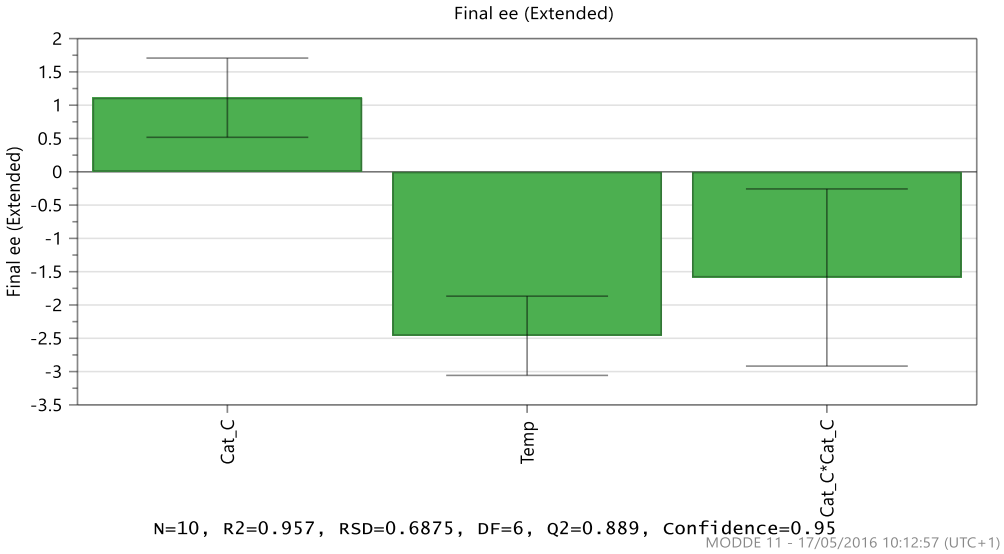


Chart 2. The effect of square terms

A contour plot can be generated to best show the effects temperature and catalyst loading each have on the enantioselectivity. The best results are obtained at low temperatures and high catalyst loadings (Chart 3).

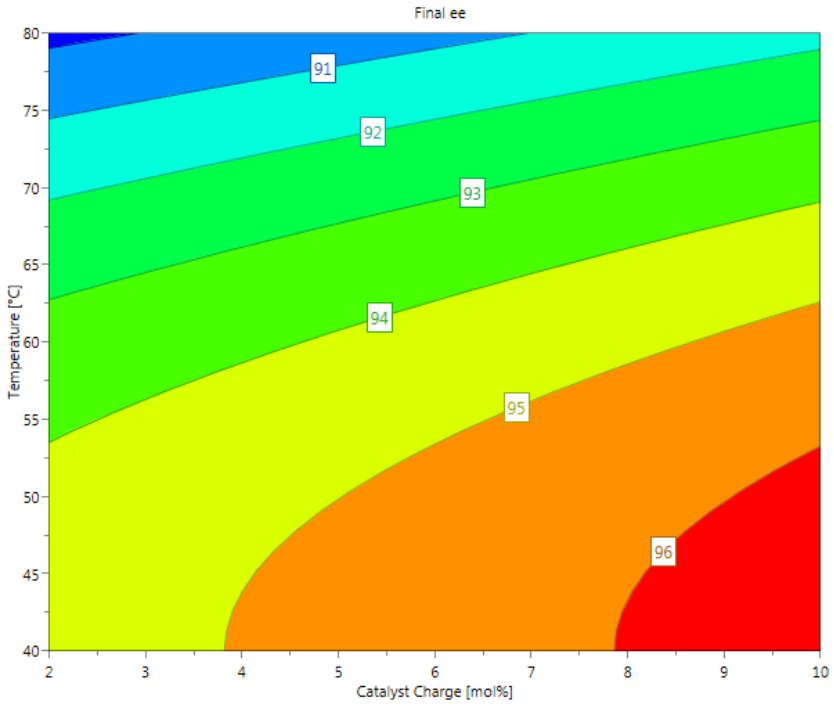


Chart 3. Contour plot of temperature and catalyst charge with respect to enantioselectivity

Coefficient plots were also generated for the factors of catalyst loading and temperatures effect on yield (Chart 4).

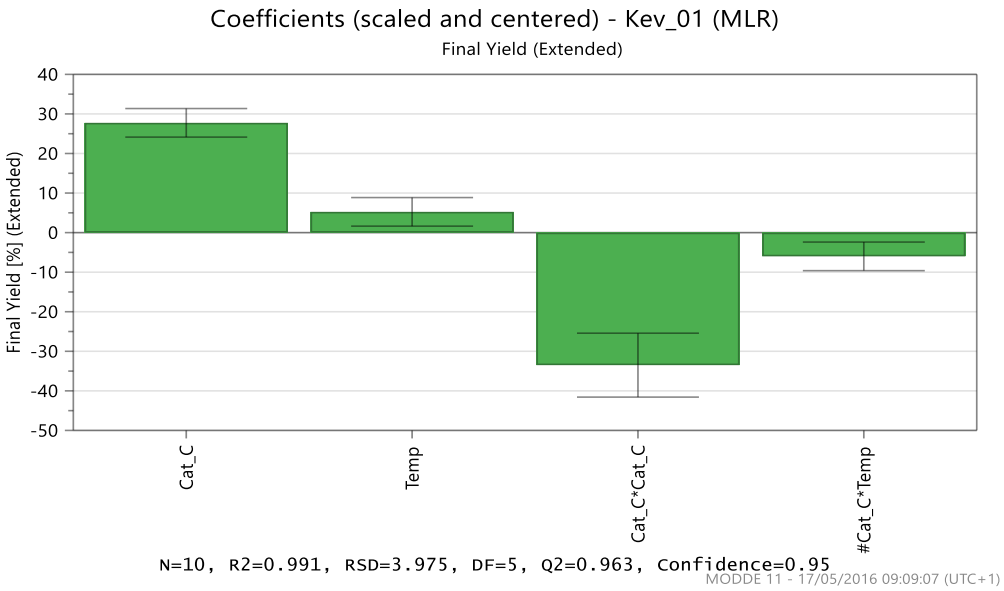


Chart 4. The effect of the variables on final yields

The catalyst loading appears to have a large positive effect on the yield whilst temperature has a small positive effect. The squared values show that once again the more catalyst added, the less effect the factor has on yield, this is also exhibited with the combination of catalyst and temperature. These squared or multiplied terms mean that as the temperature and catalyst charge are increased the yield will increase to a plateau. An interaction plot between temperature and catalyst loading shows that at high catalyst loading, temperature has little to no effect whilst at low catalyst loading the temperature has a larger effect. However, the effect of catalyst loading still has a larger contribution than temperature (Chart 5).

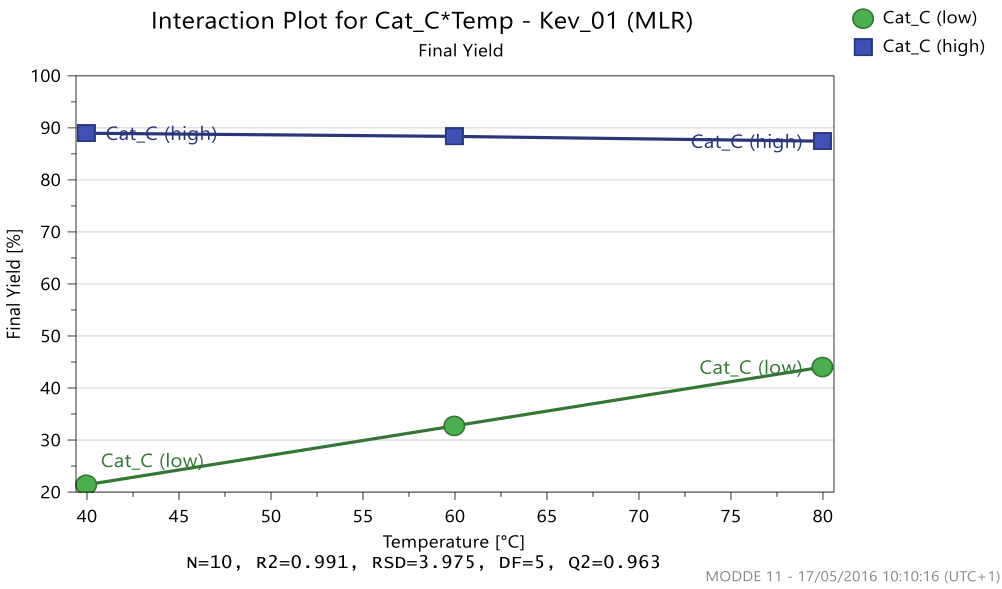


Chart 5. Interaction plot between temperature and catalyst charge on yield

The contour plot shows a simple relationship between increasing temperature and catalyst charge on the yield of the reaction (Chart 6).

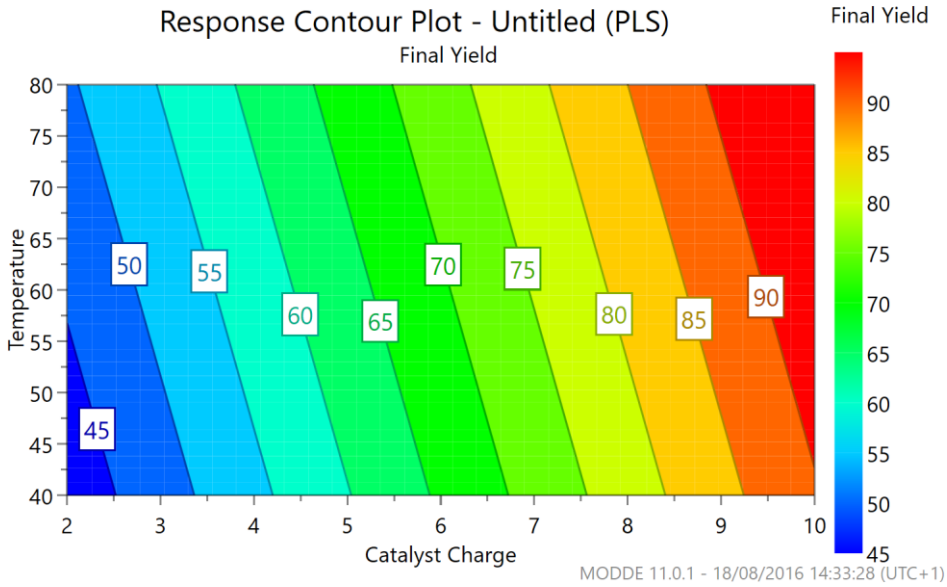


Chart 6. Contour plot of catalyst charge and temperatures effect on yield

The progress of reactions were monitored by HPLC using m-terphenyl as an internal standard. The progress of each reaction after twenty three hours was measured. The resulting coefficient plot shows catalyst loading is more of a positive factor than increasing temperature on the rate of reaction. However, once again the square of catalyst loading is negative meaning increasing

catalyst loadings has less and less of an effect on the rate of the reaction (Chart 7).

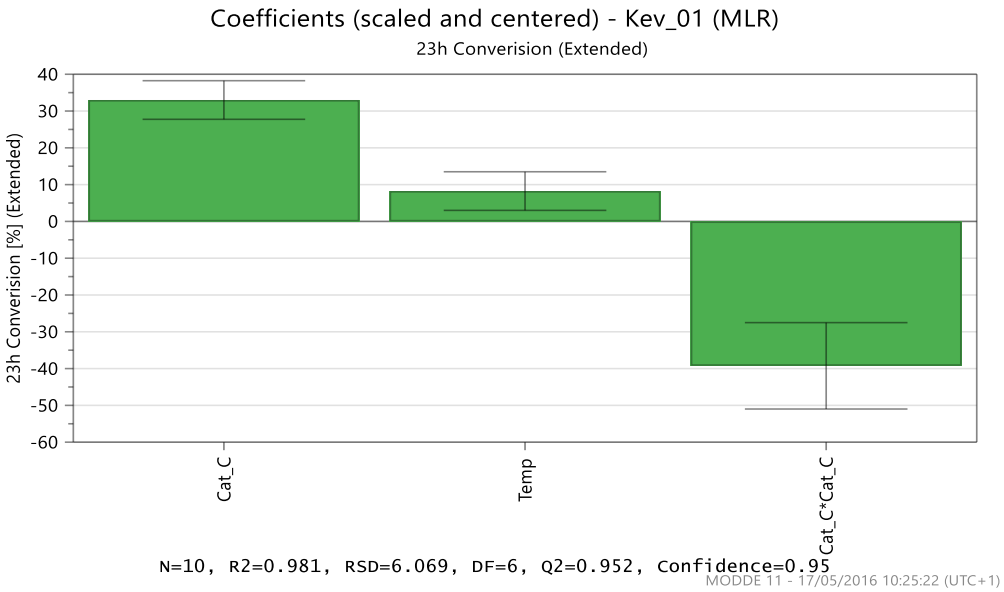


Chart 7. Catalyst loading plays a large role in reaction rate

A contour plot for conversion with regard to catalyst loading and temperature show an ideal rate of reaction can be found between 55 and 75 °C using between 7 and 10 mol% catalyst loading (Chart 8).

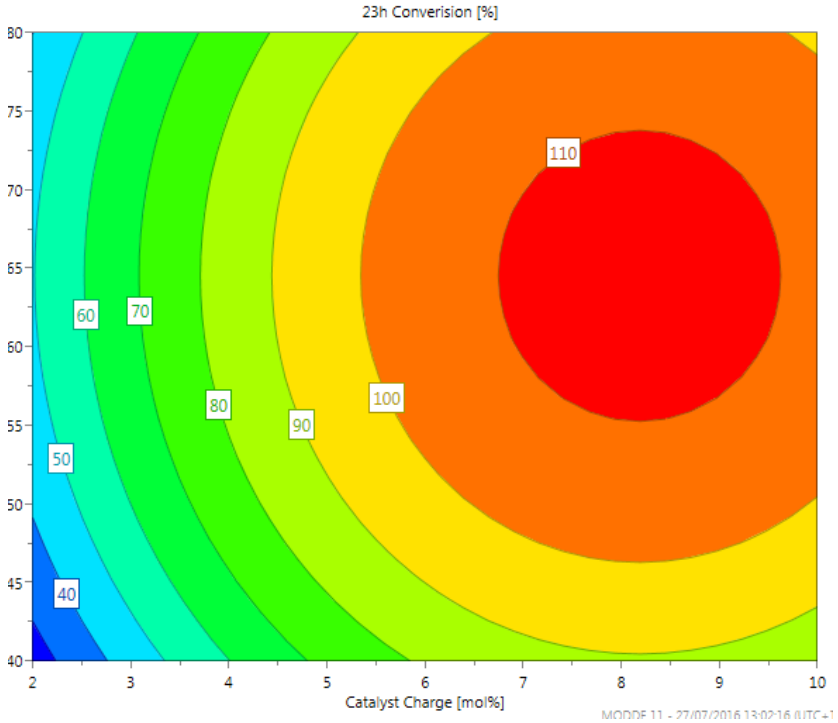


Chart 8. Rate of reaction plot

The contour plot shows that at too high a temperature reduces the conversion, this suggests that the higher temperature disturbs the reaction. There is an interaction between the temperature and the amount of catalyst dissolved in solution, this was measured through a series of experiments.

First, known amounts of the squaramide catalyst **27** were dissolved completely in acetonitrile and its response by LCMS measured relative to an internal standard (*m*-terphenyl). This generated a calibration curve that future solution concentrations could be determined from (Chart 9).

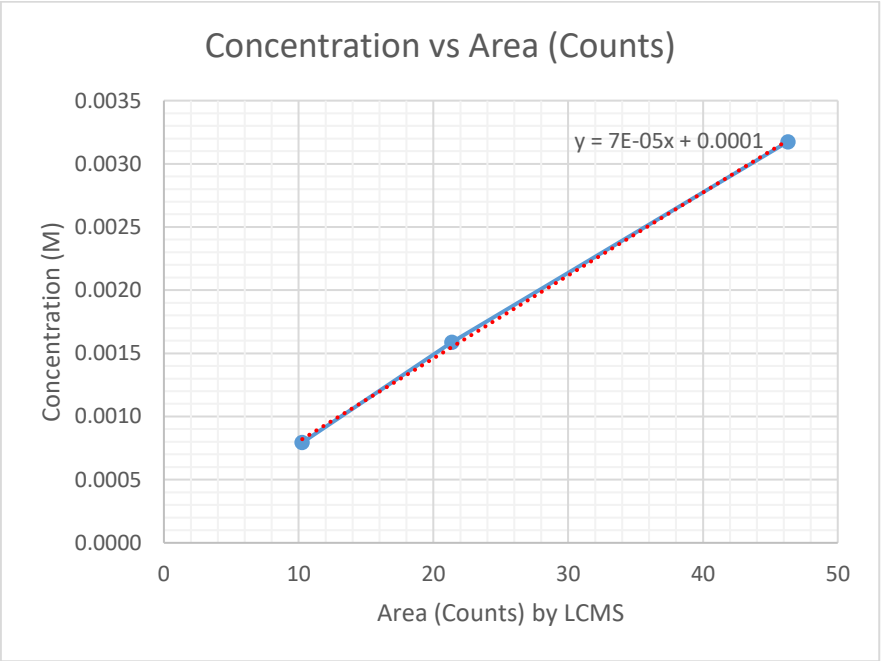
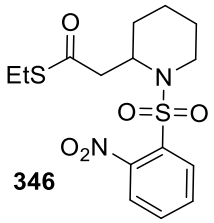


Chart 9. Calibration curve for squaramide dissolved in acetonitrile

Subsequently, squaramide catalyst **27** (25 mg) was suspended in toluene (5 mL). With no cyclised material **346** added the catalyst solubility was poor even when heated to common reaction temperatures of 50 °C and 80 °C (Entries 1-3). Adding amounts of substrate **346** increased the solubility of the squaramide catalyst **27** at room temperature. The addition of substrate resulted in a larger increase in solubility than increasing the temperature (Entries 4-6). By using both added substrate **346** and increasing temperature the solubility of the squaramide catalyst **27** can increase to complete dissolution (Entry 6-8). These results suggest that substrate interaction with the squaramide is

predominantly responsible for drawing catalyst into solution and not temperature (Table 12 and Chart 10).



Entry	**346** Added (mg)	Temp. (°C)	% Sq cat **27** Dissolved
1	0	80	13
2	0	50	7
3	0	20	4
4	20	20	9
5	50	20	16
6	100	20	30
7	100	50	70
8	100	80	100

Table 12. Results of solubility tests on the squaramide catalyst 27

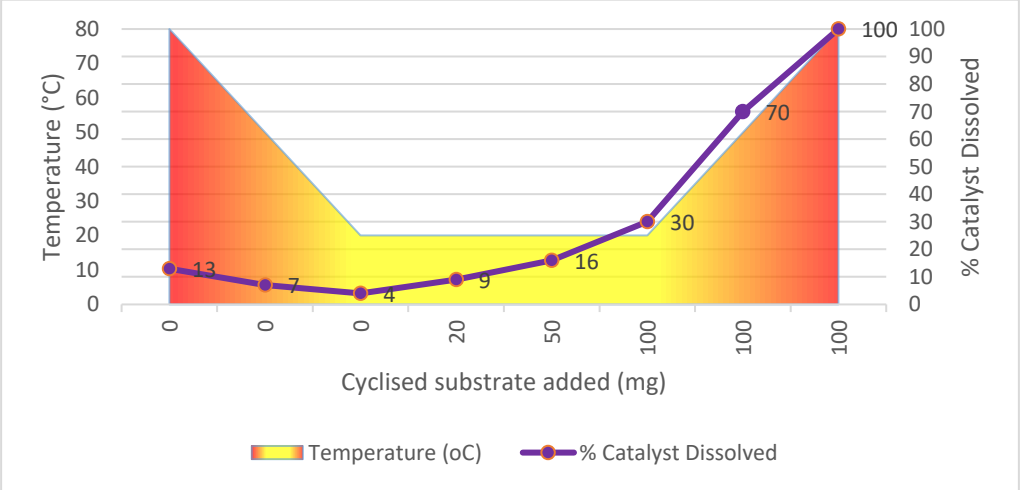


Chart 10. Catalyst concentration in solution with regard to substrate and temperature

Changing the linker

Thus far most of the chemistry has revolved around changing the α,β-unsaturated carbonyl with different functional groups (Figure 24).

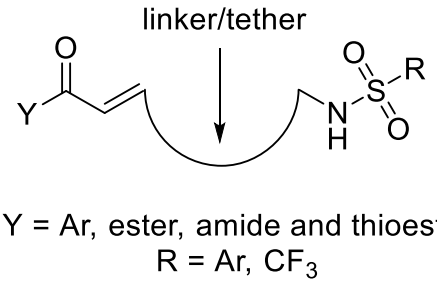
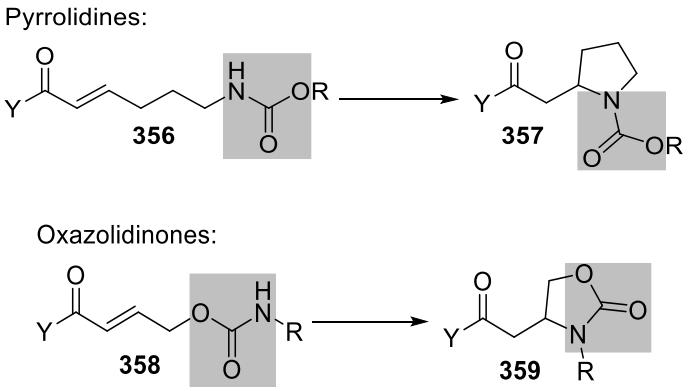


Figure 24. Work so far has done little with changing the tether

The changes made in the linker thus far have been to add an oxygen to make morpholines and oxazinanes and to remove a methylene unit to access five membered rings. These changes have been relatively simple to achieve. Some subsequent novel changes are reported in this chapter which were generally more difficult to achieve.

4-Substitued 3,4-dihydro-2H-benzo[e][1,3]oxazin-2-ones

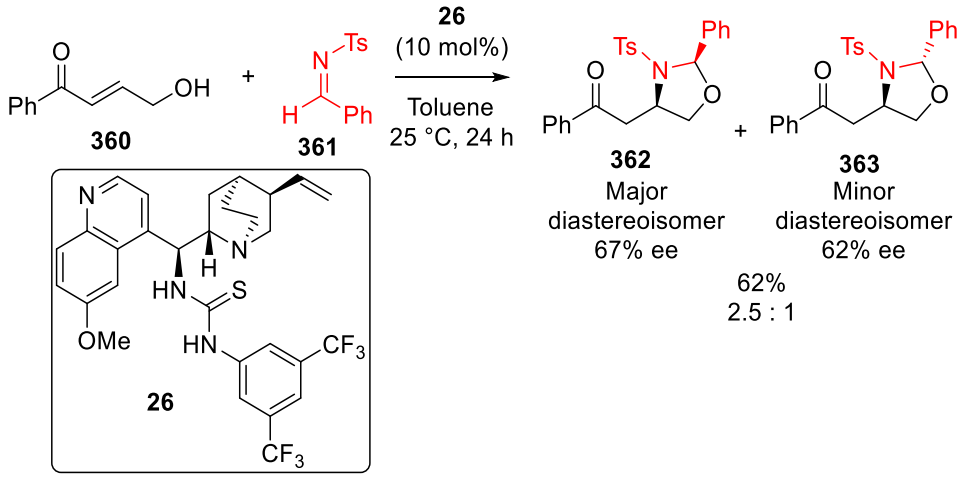
During the work on piperidines and pyrrolidines we contemplated whether the carbamate unit could be reversed. Such that a carbamate would be incorporated into the ring upon conjugate addition (Scheme 101).



Scheme 101. The rationale leading to oxazolidinones from pyrrolidines

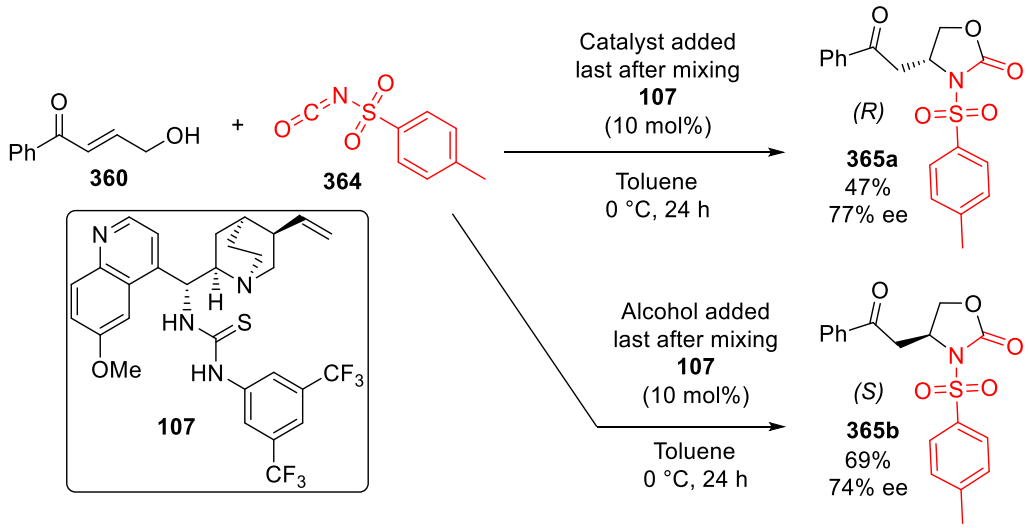
In the beginning, work was being done towards the oxazolidinones. However, this work was stopped after a report emerged from the Matsubara and Asano

et al. group. Previously, Matsubara and Asano *et al.* had reported that the cinchona derived thioureas **26** and **107** were capable of performing *O*-conjugate addition reactions. [102–104] Matsubara and Asano *et al.*'s previous work found that alcohol **360** could be reacted with imine **361** in the presence of cinchona derived thiourea catalyst **26** to generate 1,3-oxazolidines **362** and **363** in moderate yield and enantioselectivity with some diastereomeric selectivity (Scheme 102).[105]



Scheme 102. Matsubara and Asano *et al.*s synthesis of 1,3-oxazolidines

This work lead to Matsubara and Asano *et al.* reporting in 2013 the reaction of the same alcohol **360** with tosyl isocyanate **364** in the presence of cinchona derived thiourea catalyst **107** to generate oxazolidinones **365a** and **365b** in good yields and enantioselectivity. They also found that the order of addition of the alcohol **360**, isocyanate **364** and catalyst **107** would determine which enantiomer was formed (Scheme 103).[106]



Scheme 103. Oxazolidinone work performed by Matsubara and Asano *et al.*

This led to work toward oxazolidinones **359** being stopped, other work towards the larger ringed 1,3-oxazinan-2-ones **366** was continued as these were still unknown in the literature (Figure 25).

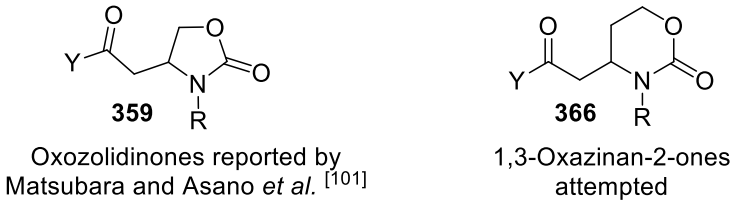
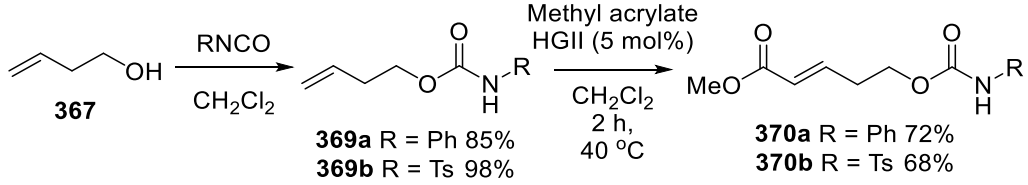


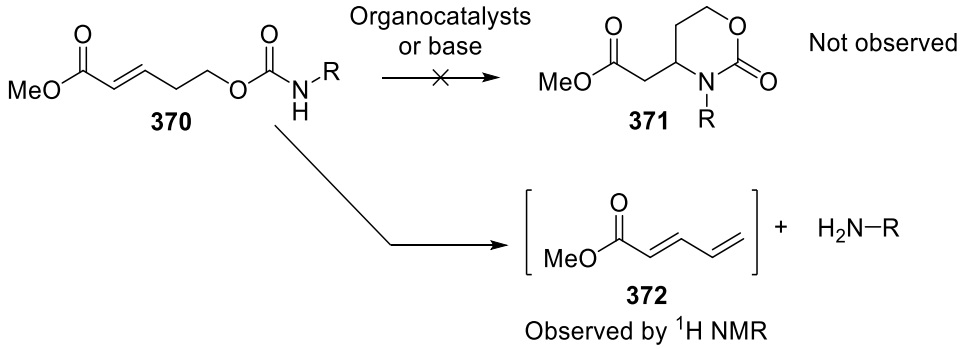
Figure 25. Oxazolidinones 359 and 1,3-oxazinan-2-ones 366

Our route remained the same as we had used for the 5 membered rings but with 3-buten-1-ol **367** instead of allyl alcohol **368**. The reaction with the corresponding isocyanate proceeded cleanly and in good yields. Subsequent metathesis with methyl acrylate gave the compounds **370a** and **370b** to be cyclised in good yields; purification of these molecules was simple as most impurities were either volatile or baseline on flash column chromatography (Scheme 104).



Scheme 104. Synthesis of the 1,3-oxazinan-2-ones precursors

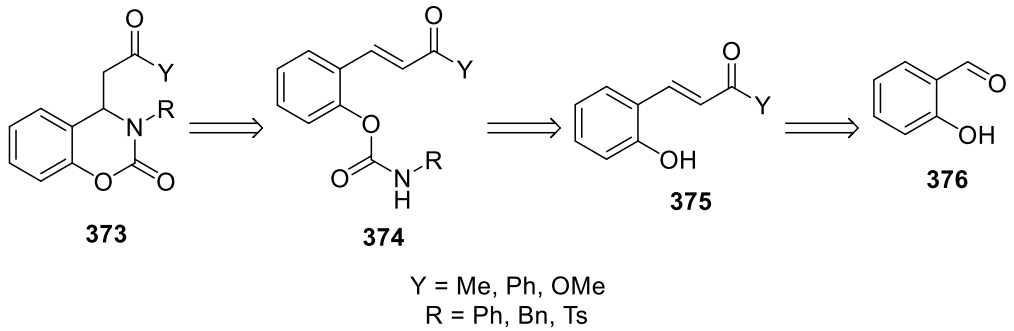
Unfortunately, no desired product **371** was observed by ^{1}H NMR upon treatment of the compounds with either the catalyst or base. Instead in the alkene region of the crude ^{1}H NMR spectrum suggested that the compounds had instead undergone an elimination to generate a diene **372**, these dienes were not isolated (Scheme 105).



Scheme 105. The attempted cyclisation reaction

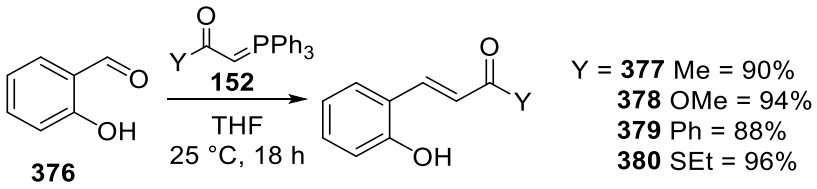
A phenyl group linking the alkene and the carbamate was chosen because it offered the simplest synthesis in principle.

We considered linking groups that could not undergo elimination. The retrosynthesis began with the cleavage of the carbamate, this could be achieved by the reaction of the corresponding phenol and isocyanate. The phenol was itself the result of a Wittig reaction between salicylaldehyde and previously made ylides (Scheme 106).



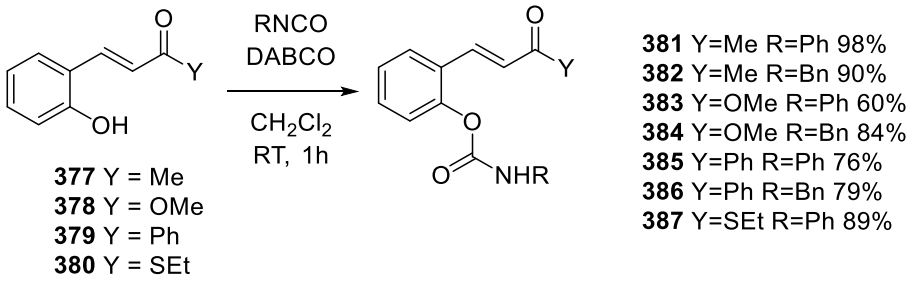
Scheme 106. The retrosynthesis of 373

The Wittig reactions proceeded well with salicylaldehyde **376** in excellent yield (Scheme 107).



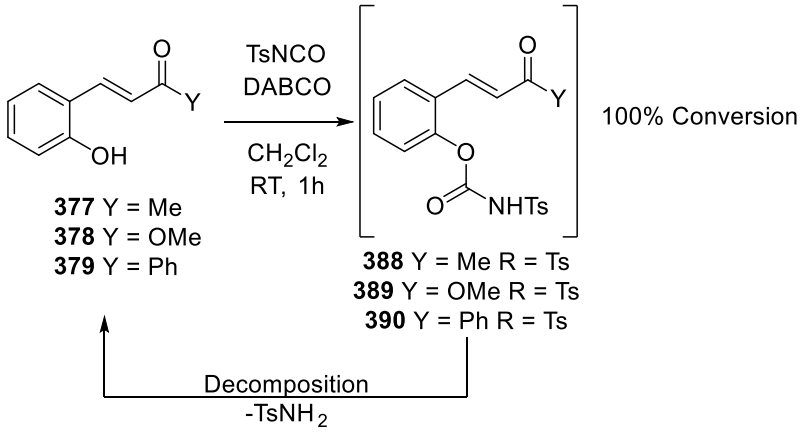
Scheme 107. Wittig reactions on salicylaldehyde 376

The phenols **377**-**380** were then reacted with phenyl and benzyl isocyanate in good to excellent yields, it was found the reaction occurred faster when a catalytic amount of DABCO was added (Scheme 108).



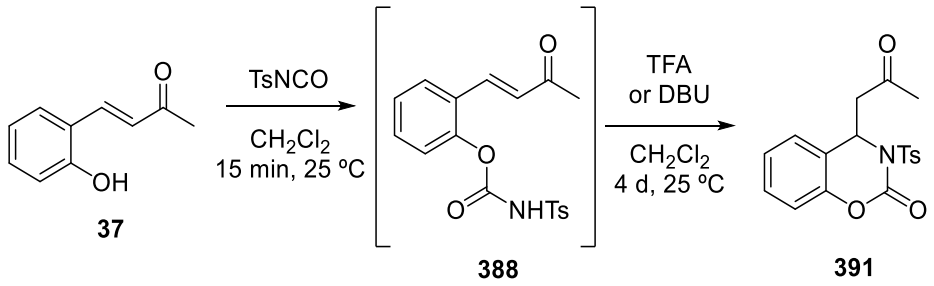
Scheme 108. Formation of the isocyanates from phenols

When the same reaction was attempted with tosyl isocyanate the desired carbamates **388**, **389** and **390** were observed *in situ* by ^{1}H NMR. However, upon concentration of the reaction, flash column chromatography or aqueous work up only the starting phenols **377**, **378** and **379** were isolated along with toluene sulfonamide (Scheme 109).



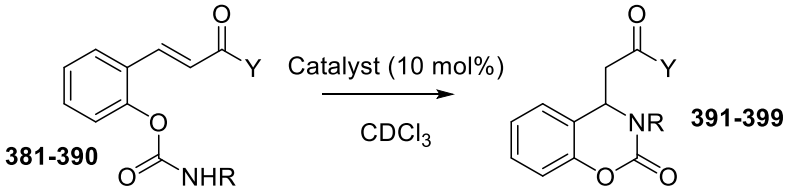
Scheme 109. The instability of the tosyl carbamates 388, 389 and 390

When tosyl isocyanate was mixed in a 1:1 ratio with the phenol **377** then subsequently heated with either acid or base the carbamate **388** underwent racemic *N*-conjugate addition. The cyclised compound **391** was isolated and found to be stable (Scheme 110).



Scheme 110. Stable cyclised compound 391

Unfortunately attempts to cyclise the compounds using a variety of catalysts gave either poor yields or proceeded with poor enantioselectivity (Table 13 and Figure 26).



Y	R	Catalyst	Temp (°C)	Time (h)	Yield (%)	% ee[a]
Ph	Bn	DBU	50	48	0	-
Ph	Bn	TFA	50	48	0	-
Ph	Bn	**34**	50	48	0	-
Ph	Bn	**26**	50	48	0	-
Ph	Bn	**29**	50	48	0	-
Ph	Bn	Cs_2CO_3	25	16	63	0
Ph	Ts	DABCO	50	48	0[b]	-
Ph	Ts	DBU	25	48	0[b]	-
Ph	Ts	TFA	50	24	60	0
Ph	Ts	**34**	25	96	40	0
Ph	Ts	**25**[c]	25	48	55	0
Ph	Ts	**26**	25	96	58	0
Ph	Ts	**29**	50	48	57	0
Me	Bn	Cs_2CO_3	25	16	92	0
Me	Ts	DABCO	50	48	0	-
Me	Ts	DBU	25	48	0	-
Me	Ts	TFA	50	72	35	0
Me	Ts	**34**	50	62	57	0
Me	Ts	**26**	50	62	70	0
Me	Ts	**29**	50	62	74	0
OMe	Ph	Cs_2CO_3	25	16	0	-
OMe	Bn	DABCO	50	48	0	-
OMe	Bn	DBU	50	48	0	-
OMe	Bn	TFA	50	48	0	-
OMe	Bn	Cs_2CO_3	25	16	30	0
OMe	Ts	Cs_2CO_3	25	16	0[b]	-

a Determined by HPLC on a chiral stationary phase (Chiracel AD-H)
b Decomposed to corresponding phenol
c 20 mol% used with TFA (40 mol%) co-catalyst

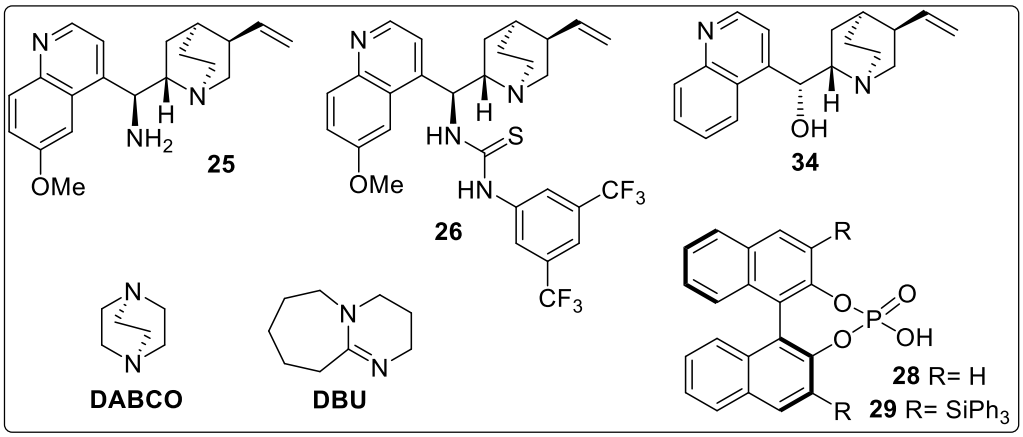


Table 13. Results of asymmetric cyclisation attempts

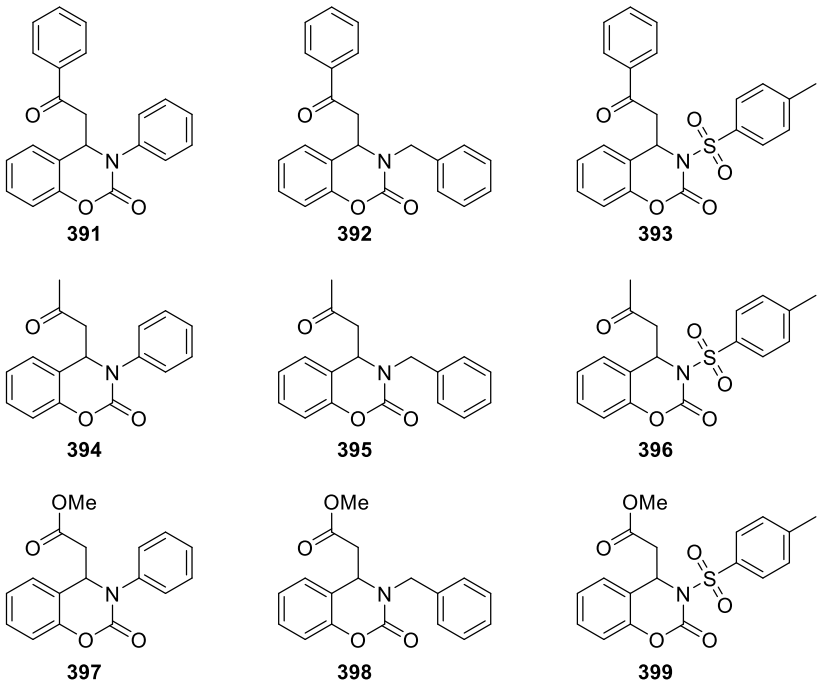


Figure 26. Racemic 4-substitued 3,4-dihydro-2H-benzo[e][1,3]oxazin-2-ones synthesised by *N*-conjugate addition

When the starting nitrogen is substituted with either a phenyl ring (**381**, **383** and **385**) or a benzyl ring (**382**, **384** and **386**) most attempts at cyclisation failed. However, caesium carbonate did promote cyclisation in adequate yields.

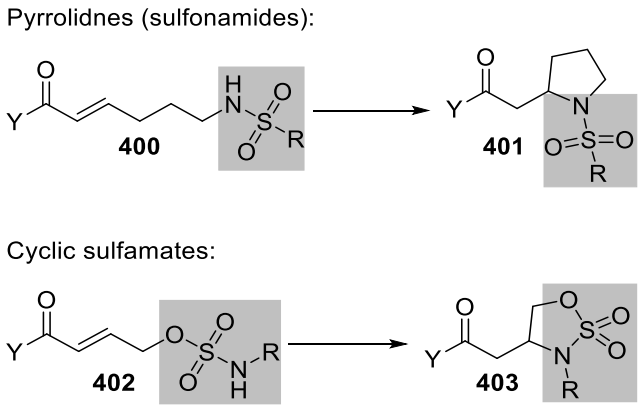
Greater reactivity was observed when the nitrogen was substituted with a tosyl group. Methyl and phenyl ketone derivatives cyclised successfully in the presence of trifluoroacetic acid, although the reaction was slow. The ester derived electrophiles **384, 385** and **389** were less reactive and no cyclisation was observed even for the tosyl derived compound **389**, only decomposition was observed.

Asymmetric catalysts **25**, **26**, **29** and cinchonidine **34** successfully cyclised the methyl and phenyl ketones that contained a nitrogen functionalised with a tosyl group. But no enantioselectivity was observed in any case.

Due to the lack of time, the poor enantioselectivity inhibited further investigation.

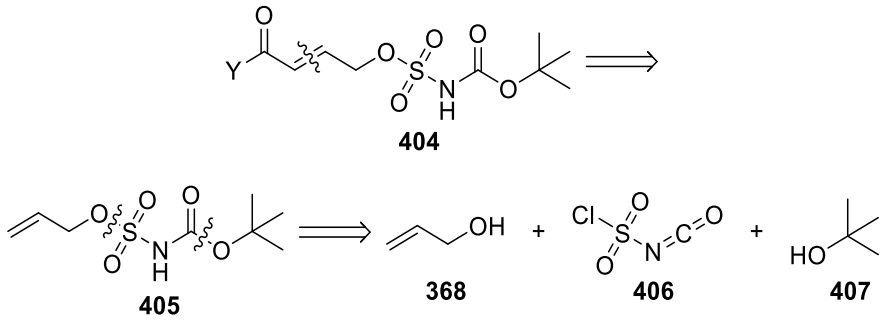
Cyclic Sulfamates

It has been observed that the squaramide catalyst **27** works well with sulfonamide containing compounds, but poor enantioselectivity was observed where the tether replaced sp^3 centres with sp^2 centres and reduced conformational flexibility in the precursor. We decided to investigate since cyclic sulfamates on the other hand keep the tether sp^3 rich (Scheme 111).



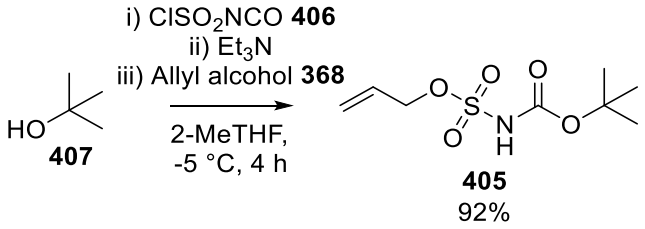
Scheme 111. The rationale leading to sulfamates 403 from pyrrolidines 401

The olefin as before would be installed by a metathesis reaction using Hoveyda-Grubbs II as before. The terminal alkene can be broken down into three smaller compounds easily, by combining allyl alcohol, chlorosulfonyl isocyanate and an alcohol (in this example *tert*-butanol) (Scheme 112).



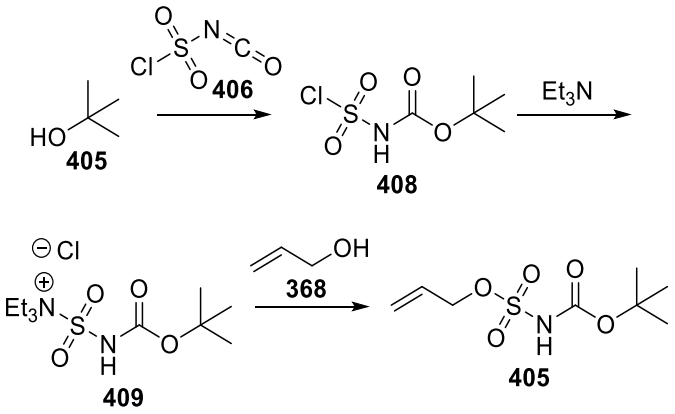
Scheme 112. The retrosynthesis for the sulfamate 404

Conversion of the chlorosulfonyl isocyanate **406** to the sulfamate **405** proceeded in good yield (Scheme 113).[107]



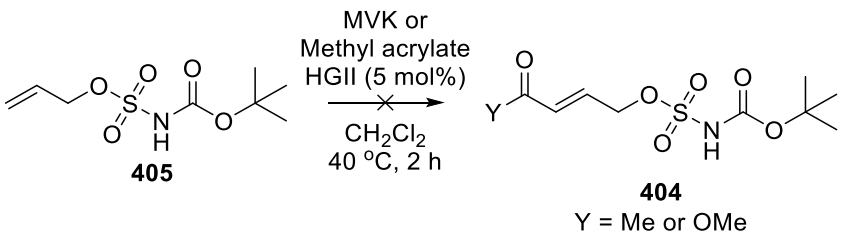
Scheme 113. Formation of the terminal alkene 405

The *tert*-butanol **405** was dissolved in the 2-methyl tetrahydrofuran, this prevented the reaction from freezing. Chlorosulfonyl isocyanate **406** was then added followed by triethylamine after two hours leading to a Burgess salt that appears to be soluble in 2-methyl tetrahydrofuran. Finally allyl alcohol was added to give the desired product cleanly after aqueous work up (Scheme 114).



Scheme 114. The synthesis of the sulfamate alkene 405

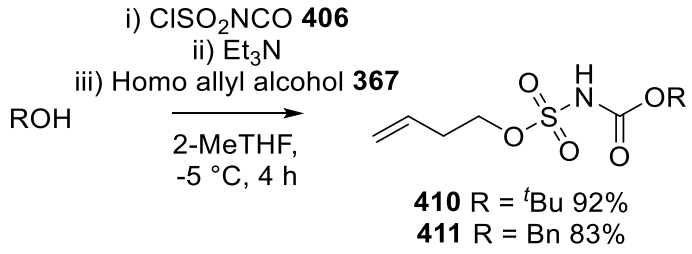
The final step to make the enone target involved the familiar metathesis reaction. Unfortunately, no reaction was observed for this substrate (Scheme 115).



Scheme 115. Failed metathesis reaction

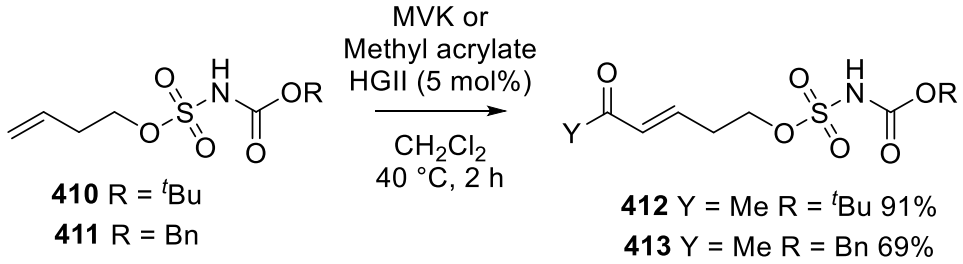
Reactions normally performed with Hoveyda-Grubbs II usually start green then slowly become brown. However, in this case the solution immediately became purple when using both methyl vinyl ketone and methyl acrylate. This is potentially the result of a change in metal coordination and thus poisoning of the catalyst.

Inclusion of another methylene unit, would result in a six membered ring being formed upon cyclisation rather than a five. Synthesis of the homo allyl precursors **410** and **411** proceeded in the same manner with identical yield. The reaction was also performed with benzyl alcohol in good yield, these Boc and Cbz containing alkenes did not require extra purification (Scheme 116).



Scheme 116. Using homo allyl alcohol 367 instead of allyl alcohol 368

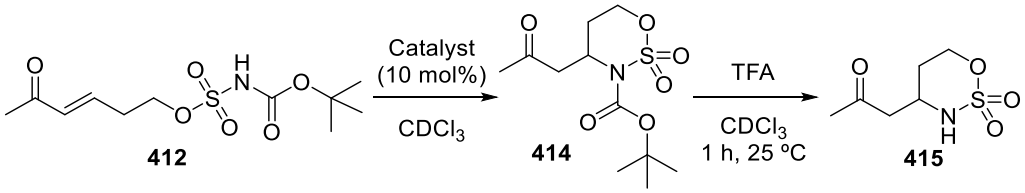
When these new substrates were subjected to metathesis the reaction proceeded well with no purple being observed (Scheme 117).



Scheme 117. Successful metathesis reactions

Heterocycle **414** could be isolated from attempted cyclisations with various catalysts in low yield but unfortunately this molecule proved unstable to chiral HPLC and no enantioselectivities could be measured. It was subsequently found that deprotected compound could be obtained in good yield by

treatment with TFA and this proved to be stable to HPLC, thus all reactions were treated with TFA prior to analysis (Table 14).



Catalyst	Temp (°C)	Time (h)	**414** Yield (%)	**415** Yield (%)	% ee[a]
TFA	25	1	-[b]	95	0
DABCO	50	48	0	-	-
25[c]	25	24	33	92	0
26	50	48	0	-	-
28	50	36	36	90	0
29	50	36	37	90	0

a Determined by HPLC on a chiral stationary phase (Chiracell AD-H)
b Product was directly converted to **415**
c 20 mol% used with TFA (40 mol% co-catalyst

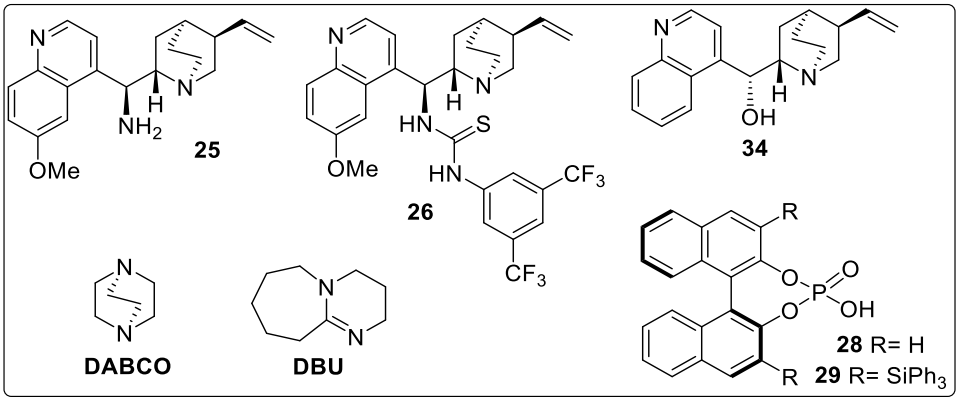
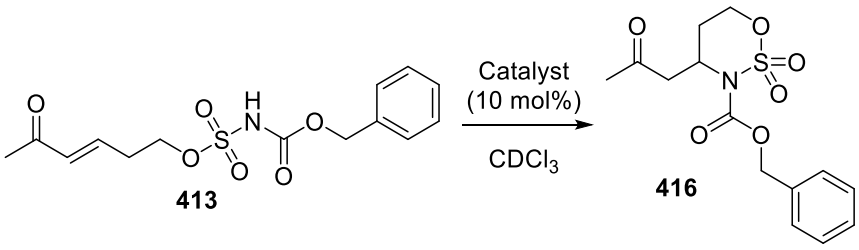


Table 14. Catalyst screening of enone 412 and subsequent deprotection

HPLC analysis of the products all appeared to be racemic. The same trifluoroacetic acid reaction conditions were used for cyclisations to produce racemic Cbz containing cyclic sulfamate **416**, this heterocycle was also stable to HPLC analysis (Table 15).



Entry	Catalyst	Temp (ºC)	Time (h)	Conversion (%)[b]	% ee[c]
1	TFA	25	1	100	0
2	**25**[a]	50	48	100	0
3	**26**	50	24	0	-
4	**27**	50	48	0	-
5	**28**	50	36	100	0
6	**29**	50	36	100	0

a 20 mol% used with TFA (40 mol%) co-catalyst
b Determined by ^{1}H NMR
c Determined by HPLC on a chiral stationary phase (Chiracel AD-H)

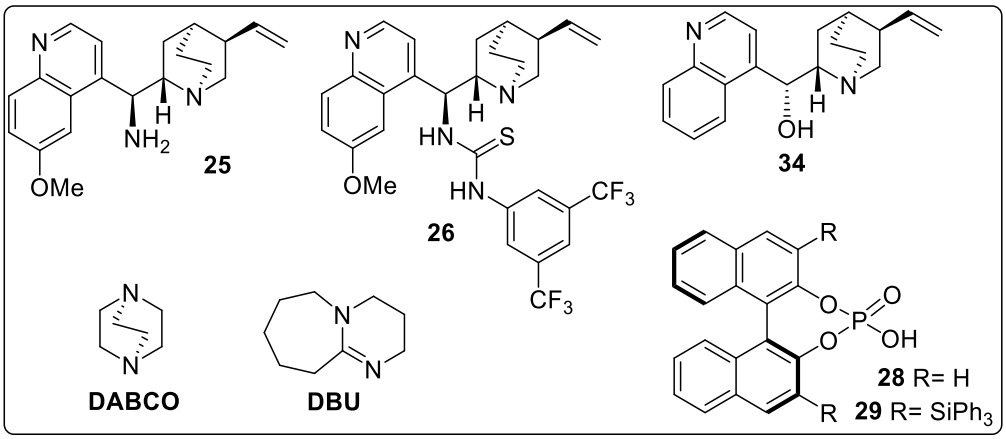


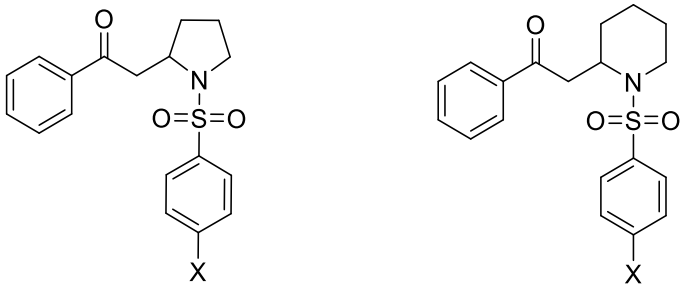
Table 15. The catalytic screening of enone 413

Excellent conversions were achieved to give product **416** but unfortunately no enantioselectivity was observed for this precursor. The *N*-conjugate addition reaction proceeds rapidly with acid catalysts but very slowly with catalysts **25-29**, in all reactions elimination was not observed. At the time of performing this chemistry there was no literature similar to this work, subsequently some similar work has emerged.[108]

2,4-Disubstitued pyrrolidines

Racemic 4-substitution

The pyrrolidines (e.g. **293**, **294** and **295**) previously made using the squaramide catalyst **27** (results and discussion – chapter two) were all produced with significantly lower enantioselectivity when compared to their six membered counterparts (e.g. **276**, **279** and **280**) (Figure 27).

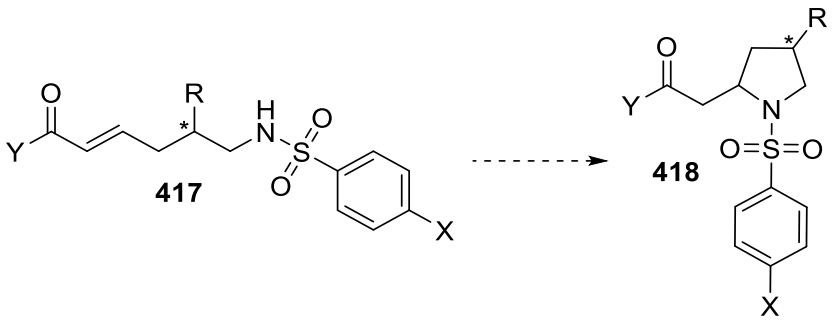


293 X = H 80% ee
294 X = NO_2 82% ee
295 X = Br 80% ee

276 X = H 99% ee
279 X = NO_2 99% ee
280 X = Br 98% ee

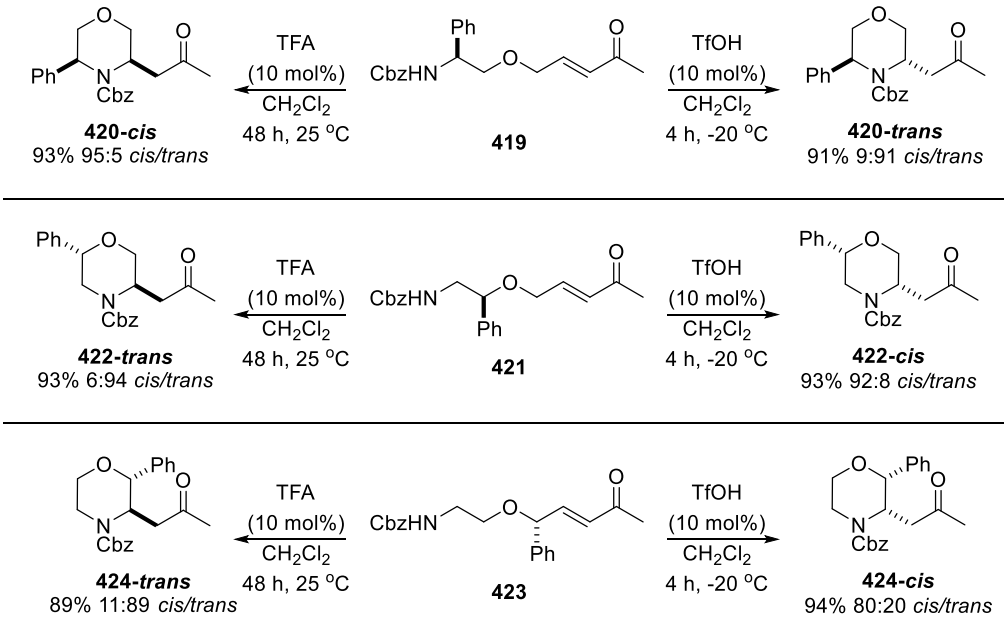
Figure 27. Comparison of the % ee's of 5 and 6 membered rings

We decided to investigate whether the inclusion of a chiral substituent within the tether would have an influence on the enantioselectivity of the new chiral centre formed and perhaps therefore reveal any interactions with catalysts (Scheme 118).



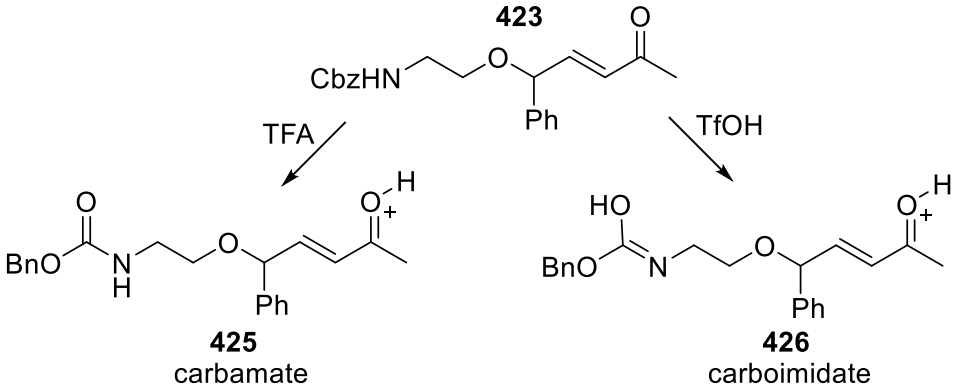
Scheme 118. Inclusion of a chiral centre in the tether

Previous work performed by Young *et al.* had shown that the inclusion of chirality of the tether between the enone and the nitrogen nucleophile in the formation of morpholines would attempt to dictate any stereochemistry formed (Scheme 119).[109,110]

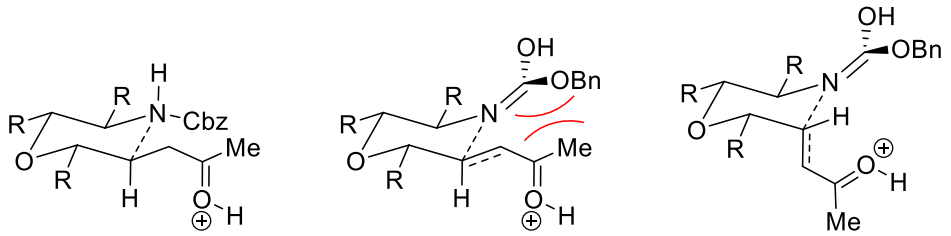


Scheme 119. Work previously performed by Young *et al.*

The rationale given by Young *et al.* for the different diastereoselectivity depending on the choice of acid comes down to the effect the acid has on the compounds. The triflic acid is such a strong acid that it not only protonates the carbonyl but furthermore causes tautomerisation of the carbamate to a carboimidate. However, trifluoroacetic acid only protonates the carbonyl, thus when the compounds cyclise they proceed through different transition states favouring different diastereoisomers (Scheme 120 and 121).

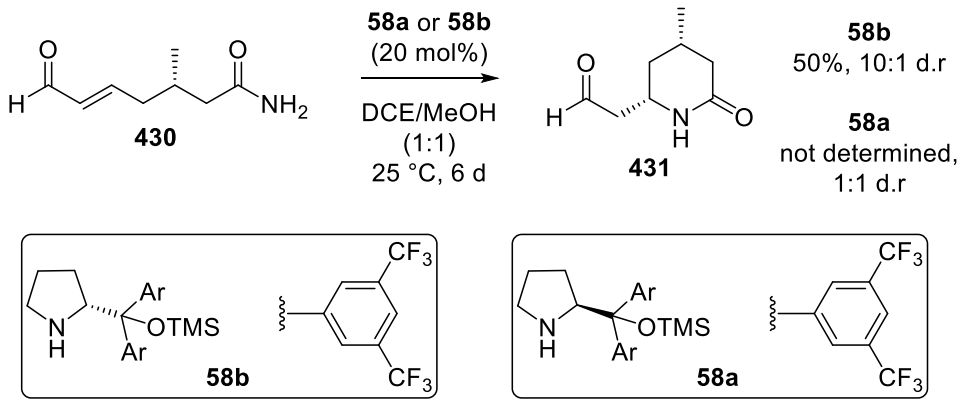


Scheme 120. Carbamate 425 and carboimidate 426



Scheme 121. Proposed effect of the choice of acid used

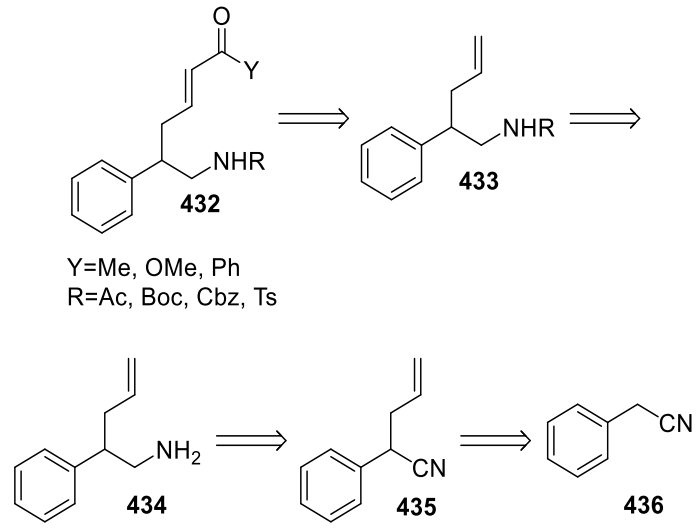
In 2013 Carter *et al*. reported diastereoselective formation of a piperidine **431** under catalyst control (Scheme 122).[111]



Scheme 122. Use of chiral catalyst to dictate the favoured diastereoisomer

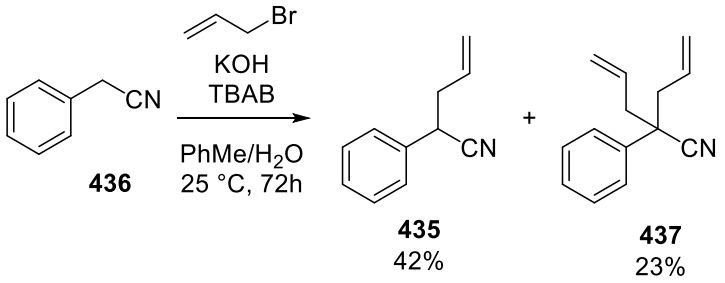
The proline derived catalyst **58b** gave the product as a mixture of diastereoisomers in the ratio of 10:1 towards the desired product. Carter *et al*. also attempted the reaction using the enantiomer of the catalyst, catalyst **58a**, but this only gave a 1:1 ratio, the same as when achiral reaction conditions were used. These results demonstrate that the intrinsic chiral centres of the substrate predominate over the influence of the catalyst. Normally in achiral substrates of this type it would be expected the opposite enantiomer catalyst would give the opposite diastereomeric ratio.

For our investigation, a phenyl ring was our chosen substituent for the chiral moiety in the tether. The initial disconnection is the olefin since carrying it throughout the synthesis would be difficult. The amine was planned to be the product of a reduction of a nitrile originating from benzyl cyanide alkylated with allyl bromide (Scheme 123).



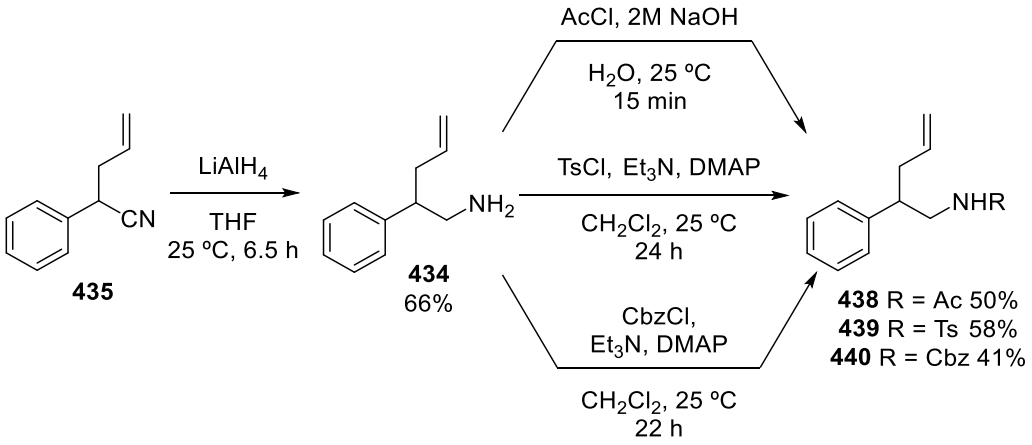
Scheme 123. Retrosynthesis of racemic material 432

The alkylation of benzyl cyanide **436** proceeded in moderate to low yields, typically the dialkylated product **437** was favoured (Scheme 124).[112]



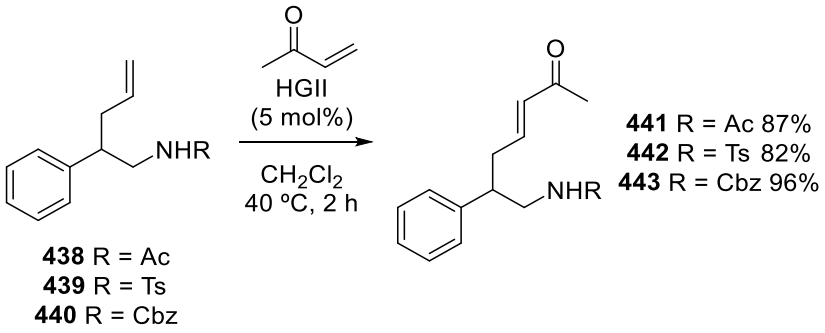
Scheme 124. The allylation of benzyl cyanide 436

Nitrile **435** was then reduced using lithium aluminium hydride to give the primary amine **434**, which was used without further purification because it proved too volatile.[113] Thus amine **434** was successfully converted into acetamide **438**, sulfonamide **439** and carbamate **440** in good yields (Scheme 125).



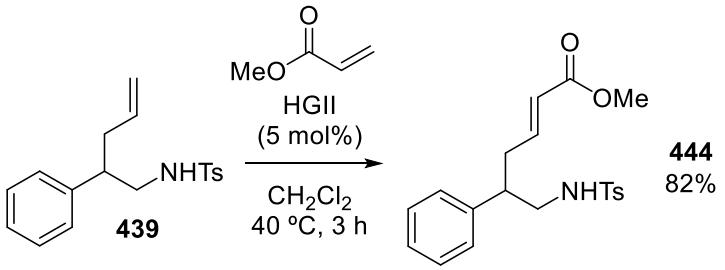
Scheme 125. Synthesis of the functionalised nitrogen compounds

Using Hoveyda-Grubbs second generation catalyst, each of the terminal alkenes **438-440** underwent cross metathesis with methyl vinyl ketone to give methyl enones **441-443** in good yields (Scheme 126).



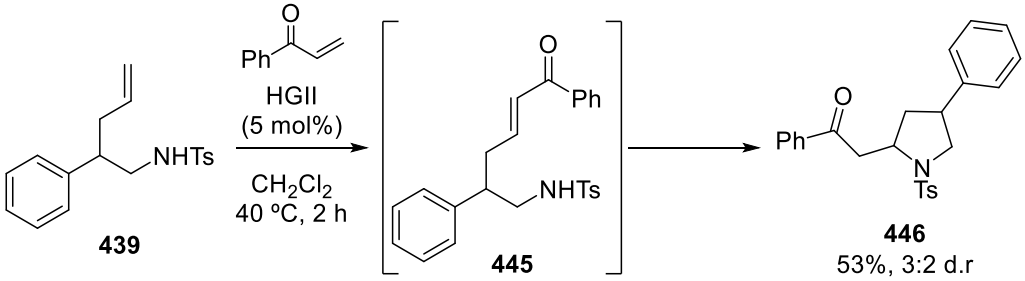
Scheme 126. Successful cross metathesis with methyl vinyl ketone

An ester **444** was also made from the sulfonamide **439** containing precursor with methyl acrylate (Scheme 127).



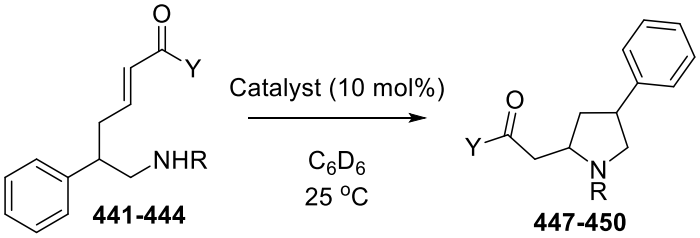
Scheme 127. Successful cross metathesis with methyl acrylate

However, attempts at cross metathesis with the same precursor **439** and phenyl vinyl ketone, gave pyrrolidine **446** as the exclusive product (Scheme 128).



Scheme 128. Successful cross metathesis with phenyl vinyl ketone and immediate cyclisation

With some compounds in hand, conditions for cyclisation were explored. Trifluoroacetic acid and trifluoromethanesulfonic acid were used to cyclise substrates **441-444** to investigate whether the results reported by Young *et al*. with disubstituted morpholines were also applicable to 2,4-disubstituted pyrrolidines.[109,110] Reactions were performed in deuterated benzene as often the substrates could undergo racemic cyclisation in deuterated chloroform due to the potential presence of trace acid (Table 16).



Entry	Compound	Y	R	Catalyst	Time (h)	Yield (%)[a]	*cis:trans*[b]
1	**443**	Me	Cbz	TFA	8	94	98:2
2		Me	Cbz	TfOH	<1	62	70:30
3	**441**	Me	Ac	TFA	16	94	90:10
4		Me	Ac	TfOH	2	64	60:40
5	**442**	Me	Ts	TFA	8	99	75:25
6		Me	Ts	TfOH	<1	81	66:33
7	**444**	OMe	Ts	TFA	48[c]	0	-
8		OMe	Ts	TfOH	<1	100[d]	50:50
9		OMe	Ts	Cs_2CO_3	18	100[d]	60:40
10		OMe	Ts	^{t}BuOK	<1	100[d]	60:40

a Isolated yield. **b** As observed via ^{1}H NMR spectroscopy and/or HPLC. **c** Heated at 55 °C. **d** Conversion

Table 16. Acid and base screening of substrates

Young *et al.* observed the major diastereoisomer to change with the choice of acid. However, for these substrates the *cis* diastereoisomer was observed as the major diastereoisomer upon treatment of the carbamate **443** and acetamide **441** with catalytic TFA.[110] Performing the reactions with TfOH gave diastereomeric ratios closer to 1:1, but selective production of the *trans* diastereoisomer could not be completely achieved. Sulfonamide **442** showed poor diastereoselectivity when cyclised with TFA and TfOH, in both cases the major diastereoisomer was determined to be *cis*. Ester **444** did not undergo cyclisation with TFA and little diastereoselectivity was observed when cyclised with TfOH. Bases were also used to cyclise the ester **444**, these reactions also resulted in small diastereoselectivity to the *cis* product (Figure 28).

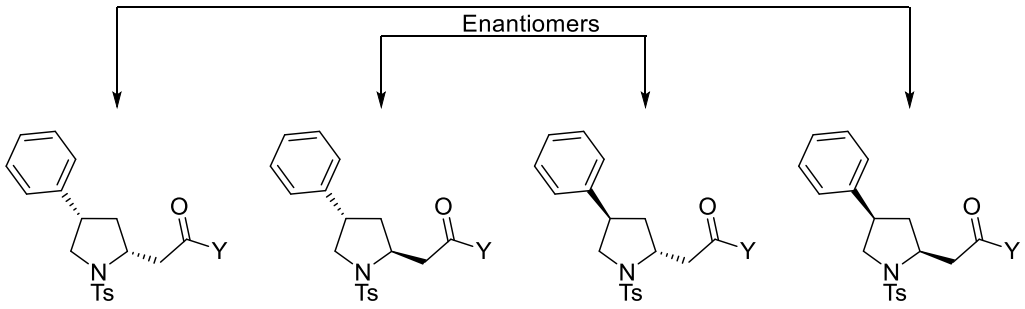
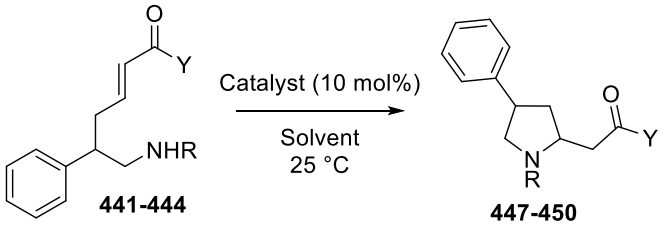


Figure 28. Possible enantiomers and diastereoisomers

When carbamate **443** was cyclised with *9-epi*aminoquinine **25**, a 7:3 mixture of diastereoisomers was produced favouring the *cis* product. The minor *trans* diastereoisomer was produced in 94% ee whilst the major *cis* diastereoisomer was produced in 43% ee. This would support the idea that the different enantiomers of the starting material may interact differently with the catalyst depending on the stereocentre already present in the molecule. Similar observations were made when BINOL derived phosphoric acid **29** was used as catalyst. Both acetamide **441** and sulfonamide **442** when cyclised with 9-*epi*aminoquinine **25** were produced with similar enantioselectivity to that seen for the carbamate **443**. When the reactions of sulfonamide **442** were repeated in deuterated benzene, the enantioselectivities were improved.

Further investigation of this effect required production of enantiomers of each starting material.



No.	Y	R	Catalyst	Solvent	Time (h)	Yield (%)[a]	*cis*:*trans*[b]	maj ee.[b]	min ee.[b]
443	Me	Cbz	**1**[c]	$CDCl_3$	8	98	70:30	-43	-94
	Me	Cbz	**2**	C_6D_6	48[d]	0	-	-	-
	Me	Cbz	**5**	C_6D_6	5	56	66:33	-64	-94
441	Me	Ac	**1**[c]	$CDCl_3$	8	92	70:30	-49	-94
	Me	Ac	**2**	C_6D_6	2[d]	80	80:20	0	0
442	Me	Ts	**1**	$CDCl_3$	120	99	80:20	-12	-55
	Me	Ts	**1**[c]	$CDCl_3$	5	96	60:40	-66	-93
	Me	Ts	**1**[c]	C_6D_6	2	90	50:50	-82	-97
	Me	Ts	**2**	$CDCl_3$	3	99	70:30	30	70
	Me	Ts	**2**	C_6D_6	1	76	66:33	47	85
	Me	Ts	**4**	$CDCl_3$	<1	99	75:25	0	0
	Me	Ts	**5**	$CDCl_3$	3	99	90:10	-4	-32
	Me	Ts	**34**	$CDCl_3$	5	99	80:20	-8	-43
444	OMe	Ts	**4**	C_6D_6	18[d]	0	-	-	-

a Isolated yield. **b** As observed via ^{1}H NMR spectroscopy and/or HPLC.
c 20 mol% used with 20 mol% of TFA as a co-catalyst in reaction.
d Heated at 55 °C.

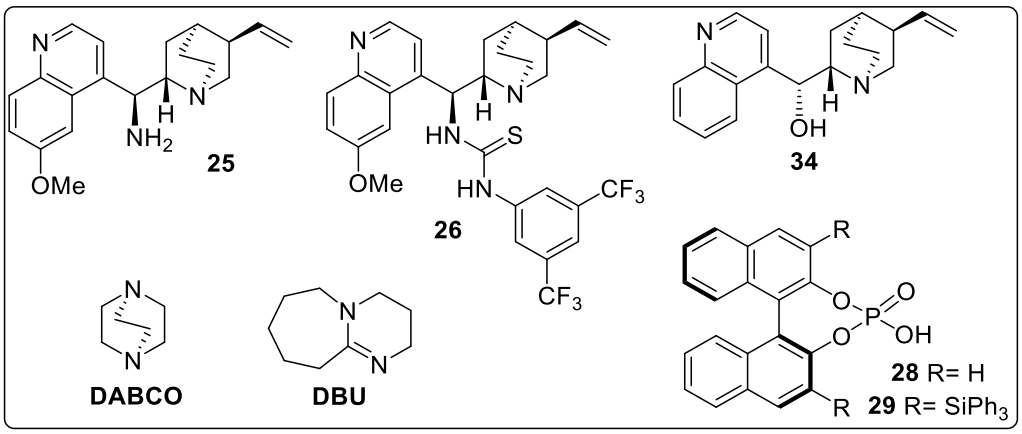
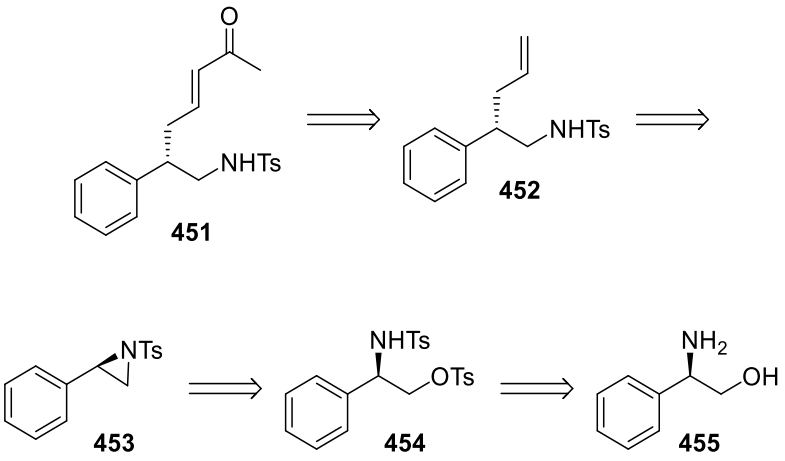


Table 17. The use of chiral catalysts

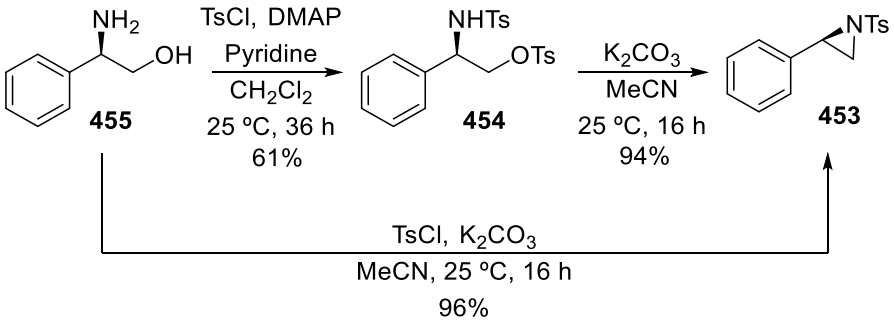
Enantiopure 4-substitution

The route would start with single enantiomers of 2-phenylglycinol **455** (Scheme 129).



Scheme 129. Retrosynthesis of 451 from 2-phenyl glycinol 455

Phenylglycinol **455** was converted to the toluenesulfonamide **454** and gave the product in moderate yield (61%). Subsequent transformation to aziridine **453** proceeded smoothly giving good yields (94%) (Scheme 130).[114]



Scheme 130. Synthesis of azridine 453

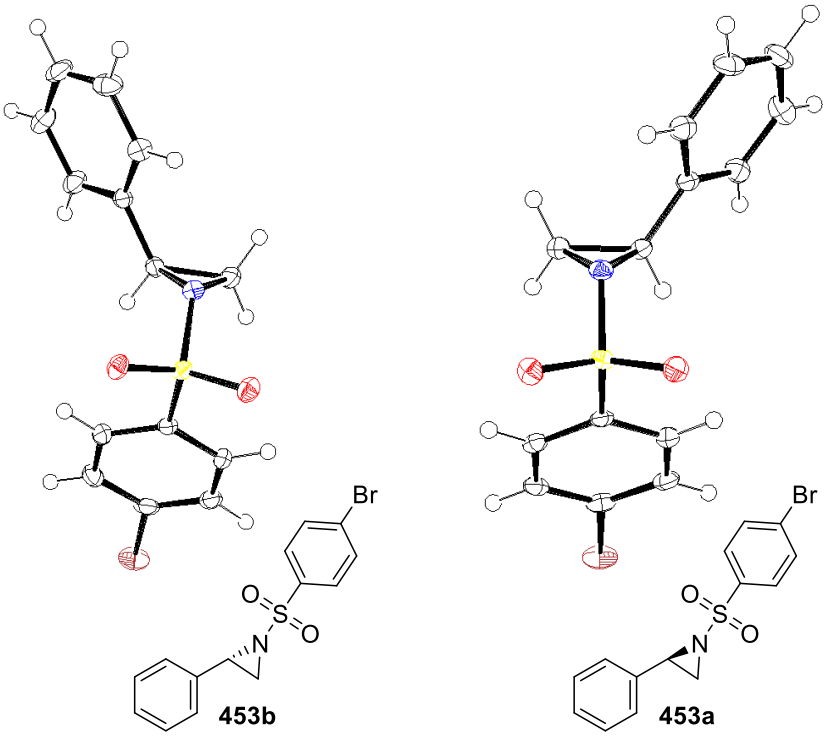
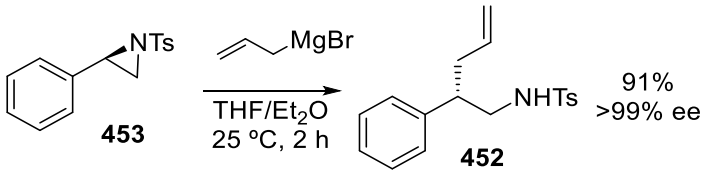


Figure 29. X-Ray of aziridines confirm retention of stereochemistry

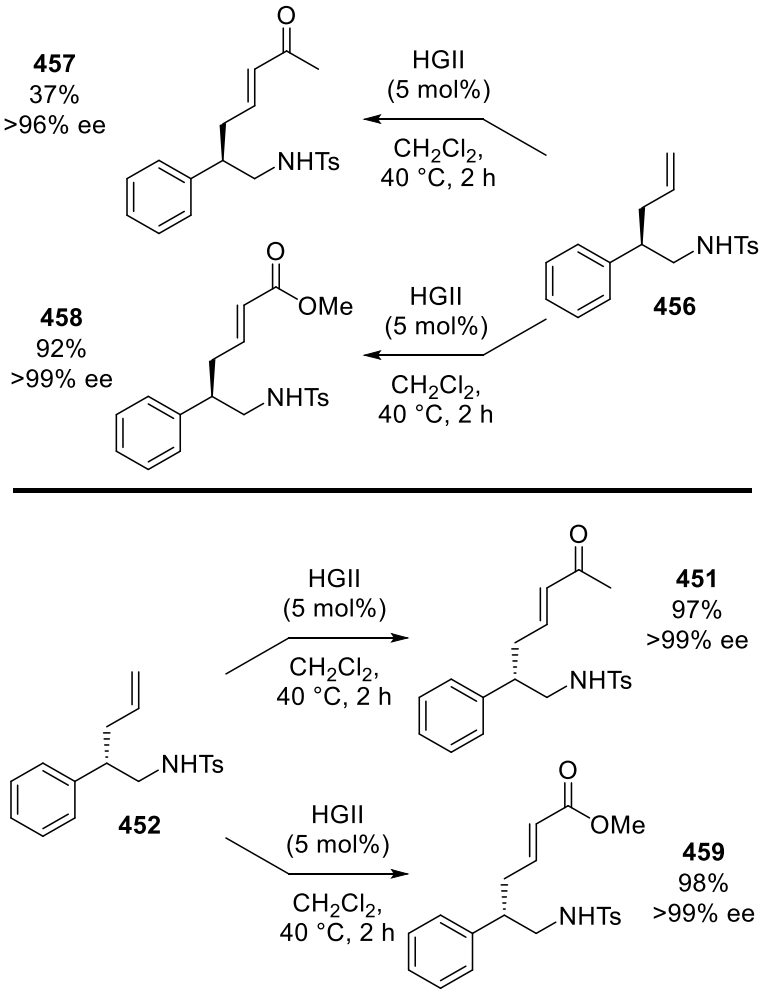
Using potassium carbonate to convert **454** to **453** proceeded cleanly requiring little purification and in good yield (94%). In the aziridination reaction, all substances except the aziridine **453** are insoluble in acetonitrile, therefore simple filtration of the completed reaction gave pure product **453**. Aziridine **453** was reacted with allyl magnesium bromide to give terminal alkene **452** in good yield and enantioselectivity (Scheme 131).[115]



Scheme 131. Ring opening of the aziridine 453

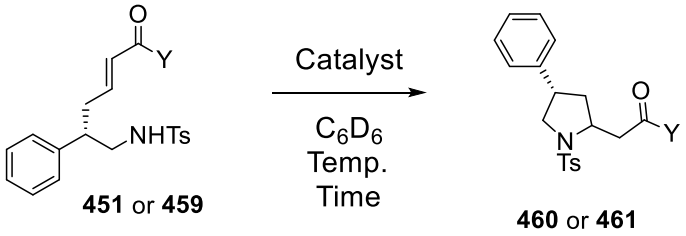
It is proposed that excess of the Grignard reagent is required to act as a Lewis acid and that this causes selectivity for the benzylic position. It was observed that prolonged reaction times could lead to a decrease in the enantiopurity of the product, so the reactions were followed carefully and quenched as soon as determined to be complete. Subsequent cross metathesis proceeded smoothly

giving good yields and a retention of stereochemistry was observed (Scheme 132).[116–118]



Scheme 132. Enantiopure precursors 451, 457-459

With single enantiomers of sulfonamides **451** and **457-459** in hand, they were cyclised using a range of chiral catalysts. Catalysts chosen included primary amine catalysts 9-*epi*aminoquinine **25**, its pseudo enantiomer 9-*epi*aminoquinidine **106**. Brønsted acid catalysts chosen included the thiourea **26**, squaramide **27** and BINOL derived phosphoric acids **28** and **29** (Table 18 and 19).



Entry	Substrate	Y	Catalyst	Temp. (ºC)	Time (h)	*trans:cis*
1	**451**	Me	**25**	25	3	2:98
2	**451**	Me	TFA	25	1	29:71
3	**451**	Me	**28**	25	1	33:66
4	**451**	Me	**29**	25	3	13:87
5	**451**	Me	**26**	25	3	66:33
6	**451**	Me	**27**	25	3	29:71
7	**451**	Me	**106**	25	3	55:45
8	**459**	OMe	**26**	60	66	33:66
9	**459**	OMe	**27**	60	66	60:40

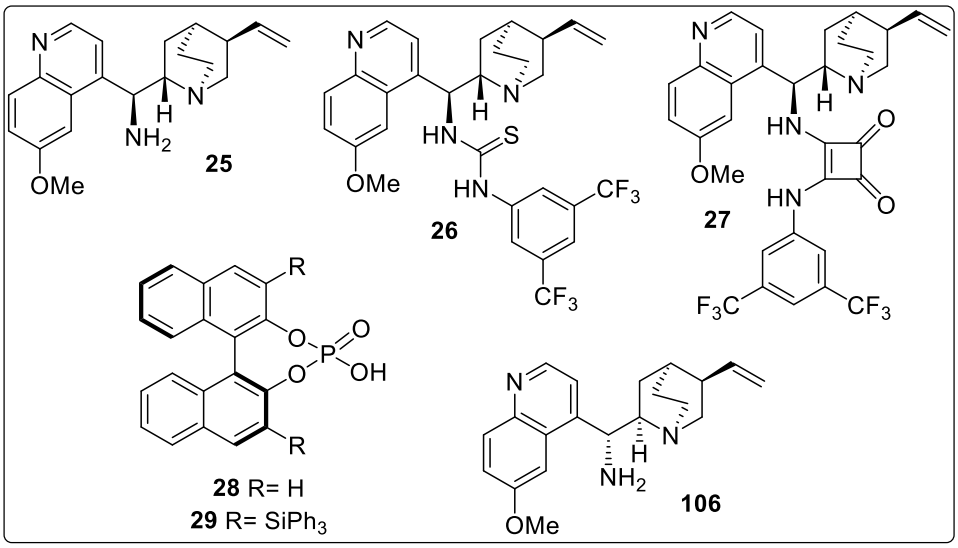
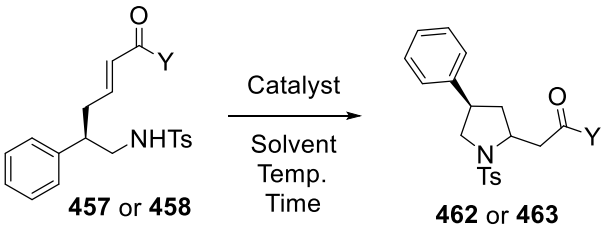


Table 18. Chiral catalyst cyclisations of compounds 451 and 459

Cyclisation with 9-*epi*aminoquinine **25** gave the best result, achieving almost complete selectivity towards the *cis* diastereoisomer. 9-*Epi*aminoquinidine **106** is the pseudo-enantiomer of 9-*epi*aminoquinine **25**, it might be expected that the catalysts would give similar levels of selectivity but for opposite enantiomers. However, when the 9-*epi*aminoquinidine **106** was used the diastereomeric ratio was close to 1:1 (*trans:cis*). BINOL derived phosphoric acid **29** gave good selectivity for the *cis* product **460.** Cinchona thiourea **26** gave the *trans* diastereoisomer **460** as the major product, but only in a 2:1 ratio.

Little diastereoselectivity was observed when ester precursor **461** was cyclised using cinchona thiourea **26** upon heating to give. In this example the catalyst is unable to overcome the intrinsic effects of the phenyl substituent. However, the ester **461** also cyclised upon heating and gave poor diastereoselectivity using the squaramide **27** in favour of the *trans* diastereoisomer. Squaramide catalyst **27** appears more capable than cinchona thiourea **26** in overcoming the intrinsic *cis* diastereoselectivity.

These results suggest that overcoming the formation of the favoured *cis* product **461** is difficult for catalysts but that some are capable of improving the *cis* selectivity for the favoured diastereoisomer.



457 or **458** → **462** or **463**

Entry	Substrate	Y	Catalyst	Temp. (ºC)	Time (h)	*trans:cis*
1	**457**	Me	TFA	25	<1	33:66
2	**457**	Me	**26**	25	5	13:87
3	**457**	Me	**25**	25	3	25:75
4	**457**	Me	**28**	25	<1	40:60
5	**457**	Me	**29**	25	<1	7:93
6	**458**	OMe	**26**	60	66	17:83
7	**458**	OMe	**27**	60	66	13:87

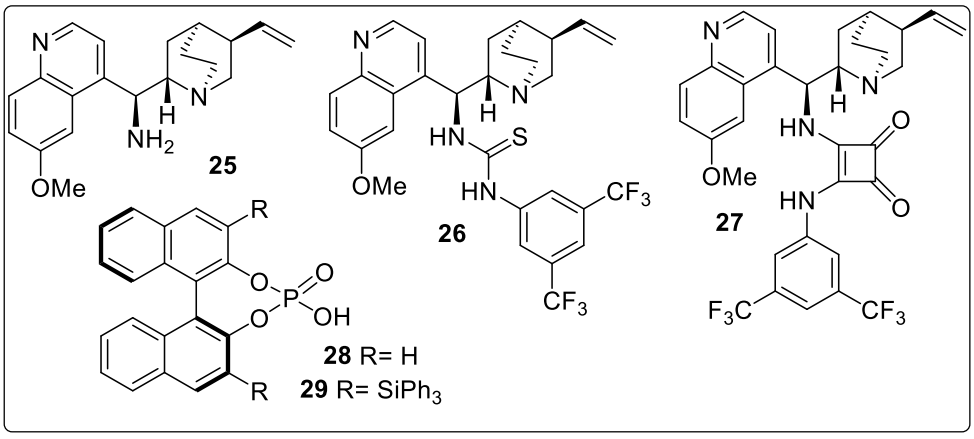


Table 19. Chiral catalysed cyclisations of 457 and 458

Cyclisation of the opposite enantiomer **457** with 9-*epi*aminoquinine **25** did not give the same levels of selectivity seen before producing a 1:2 ratio of *trans*:*cis* diastereoisomers. The only chiral catalysts that gave the *cis* product **462** in good selectivity were cinchona derived thiourea **26** and phosphoric acid **29**, presumably the stereocentre being formed by the catalyst is complementary to the formation of the *cis* diastereoisomer.

BINOL derived phosphoric acid **29** gives the *cis* diastereoisomer with good selectively as observed with the enantiomeric compound **460**. However, if the catalyst was acting as a chiral catalyst it would be expected the results would mimic those obtained using the 9-*epi*aminoquinine **25** as catalyst in which one reaction would be considerably worse in diastereomeric ratio. Instead, these results suggest the catalyst may be participating as Brønsted acid without chiral influence.

When cyclised at 60 °C using the cinchona thiourea catalyst **26**, the ester **458** gave good diastereoselectivity in favour of the *cis* diastereoisomer (1:5). This was improved upon by the use of the squaramide catalyst **27** giving even better *cis* selectivity (1:7).

Relative stereochemistry of the 2,4-disubstitued pyrrolidines

Separation of the diastereoisomers by flash chromatography gave single diastereoisomers that could be characterised. One diastereoisomer contained overlapping ^{1}H NMR signals that made nOe studies difficult, the product was also an oil making X-ray crystallography unlikely. The other diastereoisomer, though still an oil, contained no overlapping proton signals allowing nOe analysis to be performed (Figure 30).

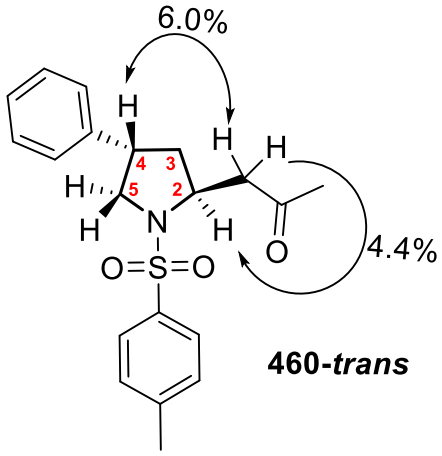
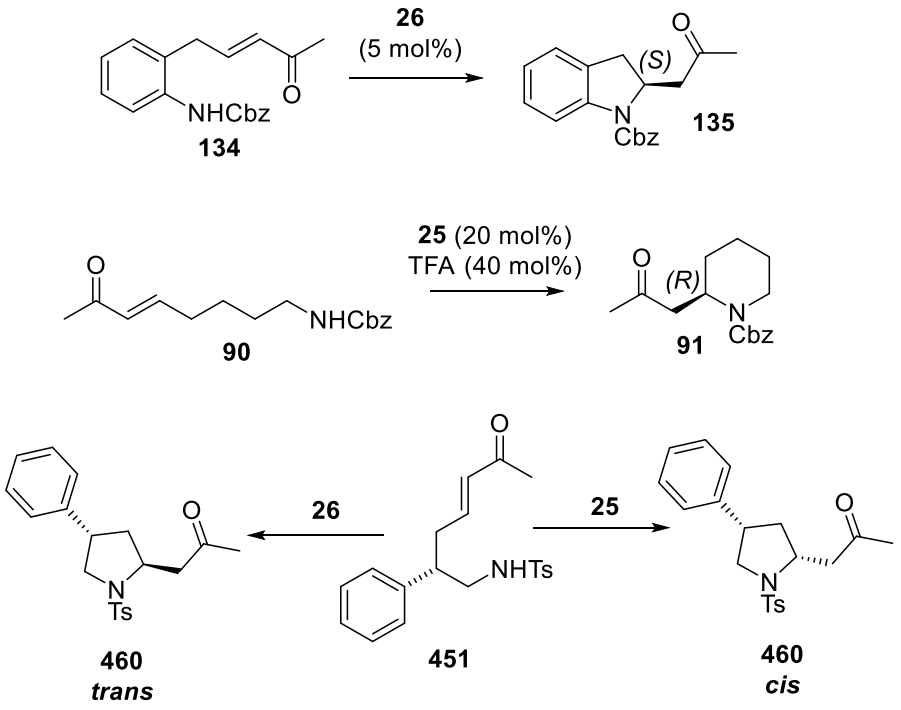


Figure 30. nOe results of the minor diastereoisomer

The stereochemistry of the phenyl group was defined from the aziridine used to construct the cyclisation precursor, this not only allows determination of whether the diastereoisomer formed was *cis* or *trans,* but also the assignment of absolute stereochemistry. Analysis by ^{1}H NMR using nOe analysis suggests that the proton on the C-4 position of the pyrrolidine is in proximity of one of the protons adjacent to the carbonyl. In turn, this strongly indicates that the phenyl group is on the opposite face to the substituent at the C-2 position. The proton on the C-2 carbon is not shown interacting with the proton on the C-4 carbon.

There are also comparable literature compounds made using catalysts **25** and **26** that suggest the stereochemistry seen here is likely correct (Scheme 133).



Scheme 133. Previously reported stereochemistry from reactions using catalysts 25 and 26

Fan *et al.* found that the (*R*) enantiomer of the piperidine **91** was formed in their experiments with 9-*epi*aminoquinine **25**.[67] Matsubara *et al.* suggest that the *(S)* enantiomer of the indoline **135** is formed with the cinchona thiourea **26**.[83] In the case of methyl enone **451** it is likely that the 9-*epi*aminoquinine catalyst **25** generates the *cis* diastereoisomer as the catalyst appears to generate the (*R*) enantiomer and that the cinchona thiourea catalyst **25** generates the *trans* isomer as it has been shown to generate the (*S*) enantiomer.

When the uncyclised precursors containing the phenyl substituent are arranged in an envelope like transition state the *cis* diastereoisomer arises placing both the phenyl and α,β-unsaturated carbonyl equatorial so that the 1,3-diaxial interaction is minimised between the two positions (Figure 31).

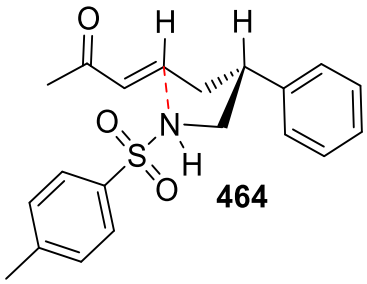


Figure 31. Possible chair like complex

Summary

We have shown that the squaramide catalyst **27** can be used generate 2-substituted piperidines, morpholines and oxazinanes through the asymmetric *N*-conjugate addition of sulfonamides with α,β-unsaturated phenyl ketones, methyl ketones, esters, thioesters and amides in good yields and good to excellent enantioselectivity with as low as 1 mol% catalyst loading with phenyl ketones. Using energy calculations and the determined absolute stereochemistry of the products we have also proposed a mechanism by which the products likely form.

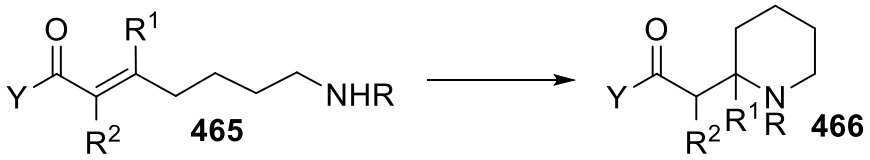
We have further utilised factorial experimental design to explore which factors are most important to the reaction and how they can affect the reaction times, yields and enantiomeric excess.

This same approach has also been attempted with the synthesis of 4-substitued 3,4-dihydro-2H-benzo[e][1,3]oxazin-2-ones and cyclic sulfamates but with no impartment of enantioselectivity from the catalyst suggesting that changes in the tether can have a profound effect on the chemistry.

Finally, investigation into the effects of pre-existing stereocentres has found that the intrinsic selectivity of even simple compounds results in an overriding of the effects of an external asymmetric organocatalyst in the synthesis of 2,4-disubstituted pyrrolidines.

Future Work

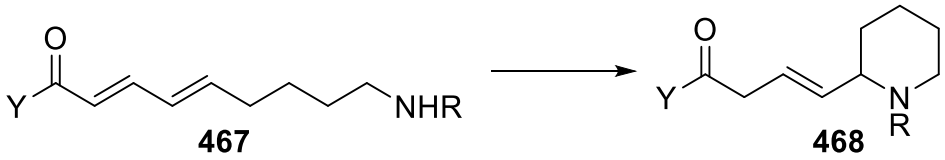
Despite unsuccessful work with more substituted alkenes, the area deserves more study (Scheme 134).



Y = Esters, amides, thioesters, aliphatic and aromatic ketones
R = Sulfonamides and carbamates

Scheme 134. More substituted alkenes

Another area of interest is the γ-functionalisation of dienes (Scheme 135).



Scheme 135. γ-functionalisation of dienes

Experimental

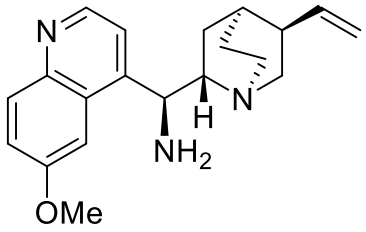
General Information

All solvents and reagents were used as supplied from commercial sources or where appropriate purified by standard techniques. Melting points (m.p.) were determined using a Stuart SMP3 electrothermal apparatus and are uncorrected against a standard. Optical rotations were measured on a Bellingham and Stanley ADP440 polarimeter at wavelength 589 nm, corresponding to the sodium line D, and at the temperature indicated and are given in units of 10^{-1} deg cm^2 g^{-1}. Infrared (IR) spectra were recorded using a Perkin-Elmer 1600 FT-IR spectrometer in the range 4000 – 600 cm^{-1}. Spectra were recorded as neat samples (liquid film) or as chloroform solutions as indicated. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on Bruker spectrometers (AV400, AV(III)400, AV(III)400HD, AV(III)500 and DPX400) at ambient temperature. All chemical shifts (δ) were referenced to the deuterium lock, or 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; sept = septet; m = multiplet; br = broad, or any combination of those. All coupling constants *J* are reported in Hertz. All ^{13}C NMR spectra were acquired using broadband decoupled mode and assignments were determined using DEPT135 and DEPT90 sequences. Assignment of peaks were assisted by COSY, HMQC and/or HMBC experiments. Mass spectra were obtained on a Bruker microTOF (electrospray ionisation ES) machine. High performance liquid chromatography (HPLC) was performed using a Varian ProStar chromatograph and a Hewlett-Packard Series 1100 with chiral analytical 4.6 x 250 mm chiralcel columns (AD-H, OJ-H, OD-H and AS-H) with a guard column attached using conditions outlined in the relevant experimental procedures. Flash chromatography was carried out using silica gel 60 (230-400 mesh) using solvents specified. Analytical thin layer chromatography (TLC) was performed using pre-coated glass backed plates (silica gel 60 with F254). Plates were visualised using short-wave UV followed by staining with potassium permanganate. Petroleum ether refers to light petroleum ether 40-60 °C. Ether refers to diethyl ether.

Ylides used were synthesised using typical literature procedures.[104] Acrylates used for cross metathesis reactions were prepared using literature methods.[119] α,β-Unsaturated phenyl ketone compounds **221**, **259**, **260**, **262-265** and phenyl ketone containing piperidines **276**-**284** and **286** were previously synthesised by a fellow member of the Lygo group Christopher Davison whilst working on the same project.[120]

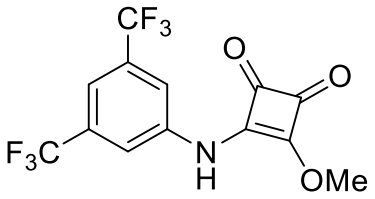
Squaramide Catalyst Synthesis

9-*epi*aminoquinine **25**



Quinine **31** (6.00 g, 18.5 mmol) and triphenylphosphine (5.82 g, 22.2 mmol) were dissolved in dry tetrahydrofuran (100 mL). The solution was then cooled to 0 °C and diisopropyl diazodicarboxylate (4.49 g, 22.2 mmol) was added in one portion. A solution of diphenyl phosphoryl azide (6.11 g, 22.2 mmol) in dry tetrahydrofuran (50 mL) was then added drop-wise to the cooled reaction solution. After complete addition the reaction was allowed to warm to room temperature and stirred for 16 h. The reaction was then heated to 50 °C for 2 h. Triphenylphosphine (6.31 g, 24.1 mmol) was added and the reaction held at 50 °C for a further 2 h. The reaction was then cooled to room temperature and water (2.0 mL) added before stirring for 16 h at room temperature. The reaction was then diluted with dichloromethane (100 mL) and 1M hydrochloric acid (100 mL). The aqueous layer was washed with dichloromethane (2 x 50 mL) then adjusted to pH 9 with 18 M aqueous ammonia (19 mL). The aqueous was then extracted with dichloromethane (3 x 50 mL) and the combined organics were dried over magnesium sulfate and concentrated under reduced pressure to yield a crude product which was purified by flash column chromatography on silica gel (50:39:10:1, petroleum ether/ethyl acetate/ethanol/18M aqueous ammonia to 39:10:1, ethyl acetate/ethanol/18M aqueous ammonia) to give the product **25** (3.71 g, 62%) as a pale yellow oil. $[\alpha]_D^{23}$ +78.0 (*c* 0.7, $CHCl_3$), (lit. $[\alpha]_D^{25}$ +80 (*c* 1.1, $CHCl_3$)) [63]; *Rf* 0.1 (39:10:1, ethyl acetate/ethanol/18M aqueous ammonia); $\nu_{max}(CHCl_3)/cm^{-1}$ 3365, 2939, 1621, 1589, 1508, 1474, 1358, 1231, 1029; δ_H (400 MHz, $CDCl_3$) 8.76 (1H, d, *J* 4.5, ArH), 8.05 (1H, d, *J* 9.5, ArH), 7.67 (1H, br s, ArH), 7.47 (1H, br. d, *J* 4.0, ArH), 7.40 (1H, dd, *J* 9.0, 3.0, ArH), 5.82 (1H, ddd, *J* 17.0, 10.5, 7.5, CH), 5.03-4.97 (2H, m, CH_2), 4.61 (1H, br d, *J* 9.5, C*H*N), 3.98 (3H, s, CH_3), 3.33-3.07 (3H, m, CH and CH_2), 2.87-2.79 (2H, m, CH_2), 2.34-2.28 (1H, m, CH), 1.98 (2H, br. s, NH_2), 1.66-1.64 (1H, m, CH), 1.60-1.55 (2H, m, *C*H_2), 1.48-1.42 (1H, m, CH_2), 0.82-0.76 (1H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 157.5 (C), 147.7 (CH), 147.0 (C), 144.7 (C), 141.7 (CH), 131.6 (CH), 128.7 (C), 121.1 (CH), 119.9 (CH), 114.2 (CH_2), 102.0 (CH), 61.7 (CH), 56.2 (CH_2), 55.4 (CH_3), 52.7 (CH), 40.8 (CH_2), 39.7 (CH), 28.1 (CH_2), 27.5 (CH), 25.9 (CH_2); *m/z* (ESI) 324 ($M+H^+$, 100%); *m/z* (ESI) Found $[M+H]^+$ 324.2058. $C_{20}H_{26}N_3O^+$ requires 324.2070. The ^1H and ^{13}C NMR data are in agreement with that previously reported.[121]

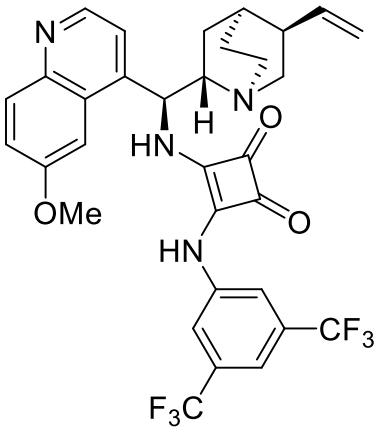
3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione **147**



Product was made using literature procedure.[82]

Recrystallised from petroleum ether/diethyl ether (7:3, petroleum ether/ethyl acetate) to give the product **147** (2.91 g, 85%) as a white solid. ν_{max} ($CHCl_3$)/cm^{-1} 3374, 1815, 1735, 1607, 1458, 1386, 1359; m.p. 191-197 °C (lit. m.p. 179-181 °C)[82]; δ_H (400MHz, DMSO-d6) 11.18 (1H, br.s, NH), 8.04 (2H, s, ArH), 7.78 (1H, s, ArH), 4.41 (3H, s, CH_3); δ_C (100MHz, DMSO-d6) 187.8 (C), 185.1 (C), 180.5 (C), 169.6 (C), 140.8 (C), 131.9 (C, q, J_{CF} 33.0), 123.5 (C, q, J_{CF} 273.0), 119.9 (CH), 116.7 (CH), 61.4 (CH_3); *m/z* (ESI) 362 ($M+Na^+$, 100), 340 ($M+H^+$, 17%); *m/z* (ESI) found $[M+Na]^+$ 362.0223. $C_{13}H_7O_3F_6NNa^+$ requires 362.0222.

The Squaramide Catalyst: 3-((3,5-Bis(trifluoromethyl)phenyl)amino)-4-(9'-*epi*-9'-amino-9'-deoxyquinine)cyclobut-3-ene-1,2-dione **27**



To a solution of 9-*epi*-aminoquinine **25** (288 mg, 0.89 mmol) in dichloromethane (5 mL) was added 3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione **147** (302 mg, 0.89 mmol). The resulting mixture was stirred at room temperature for 72 h, then filtered to give the product **27** (419 mg, 75%) as a colourless solid. $[\alpha]_D^{24}$ -61.4 (*c* 0.85, (DMSO), (lit. $[\alpha]_D^{25}$ -52.8 (*c* 0.5, DMSO)) [82]; m.p. 213-218 °C (lit. m.p. 227-228 °C)[82]; ν_{max}($CHCl_3$)/cm^{-1} 3215, 2930; 1793, 1684, 1601, 1557, 1437, 1380, 1278, 1181, 1134; δ_H (400 MHz, DMSO) 10.19 (1H, br s, NH), 8.82 (1H, d, *J* 4.5, ArH), 8.32 (1H, br s, NH), 8.00-7.96 (3H, m, ArH), 7.75 (1H, br s, ArH), 7.67 (1H, d, *J* 4.5, ArH), 7.65 (1H, s, ArH), 7.45 (1H, dd, *J* 9.5, 2.5, ArH), 6.03-5.94 (2H, m, CHN and C*H*CH_2), 5.04 (1H, d, *J* 17.5, CH_2), 4.99 (1H, d, *J* 10.5, CH_2), 3.95 (3H, s, CH_3), 3.50-3.44 (1H, m, CH), 3.30-3.25 (1H, m, CH_2), 3.23-3.17 (1H, m, CH_2), 2.73-2.61 (2H,

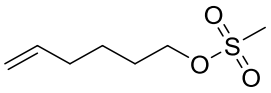
m, CH_2), 2.33-2.25 (1H, m, CH), 1.60-1.45 (4H, m, CH_2 and CH), 0.72-0.67 (1H, m, CH_2); δ_C (100 MHz, DMSO) 185.2 (C), 180.6 (C), 169.1 (C), 163.2 (C), 158.4 (C), 148.2 (CH), 144.8 (C), 143.5 (C), 142.6 (CH), 141.3 (C), 132.0 (CH), 131.7 (C, q, J_{CF} 33), 127.9 (C), 123.6 (C, q, J_{CF} 273.0), 122.4 (CH), 120.0 (CH), 118.8 (C), 115.3 (CH), 114.8 (CH_2), 101.9 (CH), 59.4 (CH), 56.1 (CH_3), 56.1 (CH_2), 53.8 (CH), 40.6 (CH_2), 39.9 (CH), 27.7 (CH_2), 27.8 (CH), 26.5 (CH_2); *m/z* (ESI) 631 ($M+H^+$, 100%); *m/z* (ESI) Found $[M+H]^+$ 631.2137. $C_{32}H_{29}F_6N_4O_3^+$ requires 631.2138. ^1H and ^{13}C NMR data is in agreement with that previously reported.[82]

Metathesis and oxidative Wittig precursors and related compounds

General procedure for sulfonylation reactions

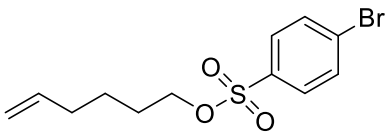
To a solution of alkene alcohol (1 equiv.) in dichloromethane (2.3M) was added pyridine (2 equiv.) followed by portionwise addition of the corresponding sulfonyl chloride (1.5 equiv.). The solution was then stirred for 16 h at room temperature. The solution was then washed with 2M hydrochloric acid (3 x equal volume to CH_2Cl_2), saturated aqueous sodium hydrogen carbonate (4 x equal volume to CH_2Cl_2), dried over magnesium sulfate and concentrated under reduced pressure. The residue was then purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate) to give the sulfonyl ester.

Hex-5-en-1-yl methanesulfonate **157**



Aqueous work up gave product **157** (6.14 g, 91%) as a pale yellow oil. *Rf* 0.3 (9:1, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 1599, 1359, 1189; δ_H (400 MHz, $CDCl_3$) 5.81 (1H, ddt, *J* 17.0, 10.5, 6.5, 6.5, CH), 5.11-4.96 (2H, m, $C=CH_2$), 4.23 (2H, t, *J* 6.5, CH_2O), 3.02 (3H, s, CH_3), 2.19-2.07 (2H, m, CH_2), 1.86-1.73 (2H, m, CH_2), 1.63-1.48 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 137.9 (CH), 115.2 (CH_2), 69.9 (CH_2), 37.4 (CH_3), 33.0 (CH_2), 28.5 (CH_2), 24.6 (CH_2); *m/z* (ESI) 201 ($M+Na^+$, 100%), 179 ($M+H^+$, 39%); *m/z* (ESI) found 201.0549. $C_7H_{14}O_3SNa^+$ requires 201.0556.

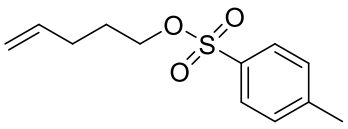
Hex-5-en-1-yl 4-bromobenzenesulfonate **158**



Aqueous work up gave product **158** (2.45 g, 61%) as a pale yellow oil. *Rf* 0.42 (9:1, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3080, 3043, 2942, 2863, 1916, 1641, 1578, 1474, 1391, 1365, 1277, 1178, 1096, 1070, 1013, 994, 921; δ_H (400 MHz, $CDCl_3$) 7.82-7.75 (2H, m, ArH), 7.74-7.68 (2H, m, ArH), 5.73 (1H, ddt, *J* 17.0, 10.5, 6.5, CH), 5.02-4.92 (2H, m, $C=CH_2$), 4.08 (2H, t, *J* 6.5, CH_2O),

2.07-1.98 (2H, m, CH_2), 1.72-1.64 (2H, m, CH_2), 1.48-1.38 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 137.8 (CH), 135.2 (C), 132.6 (CH), 129.3 (CH), 128.9 (C), 115.2 (CH_2), 71.0 (CH_2), 32.9 (CH_2), 28.2 (CH_2), 24.5 (CH_2); *m/z* (ESI) 343 ($M^{81}Br+Na^+$, 100), 341 ($M^{79}Br+Na^+$, 99%); *m/z* (ESI) found 342.9794. $C_{12}H_{15}{}^{81}BrNO_2SNa^+$ requires 342.9797.

Pent-4-en-1-yl 4-methylbenzenesulfonate **159**

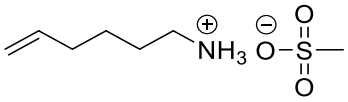


Aqueous work up gave product **159** (3.78 g, 68%) as a pale yellow oil. *Rf* 0.3 (19:1, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3081, 3067, 3045, 1642, 1599, 1359, 1189; δ_H (400 MHz, $CDCl_3$) 7.81 (2H, d, *J* 8.0, ArH), 7.37 (2H, d, *J* 8.0, ArH), 5.77-5.65 (1H, m, C=CH), 5.02-4.93 (2H, m, $C=CH_2$), 4.05 (2H, t, *J* 6.5, CH_2O), 2.47 (3H, s, CH_3), 2.14-2.06 (2H, m, CH_2), 1.81-1.72 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 144.7 (C), 136.6 (CH) 133.2 (C), 129.8 (CH), 127.9 (CH), 115.9 (CH_2), 69.8 (CH_2), 29.4 (CH_2), 28.0 (CH_2), 21.6 (CH_3); *m/z*(ESI) 263 ($M+Na^+$, 100%), 241 ($M+H^+$, 94%); *m/z*(ESI) found 263.0704. $C_{12}H_{16}O_3SNa^+$ requires 263.0712.

General procedure for ammonium salt formation reactions

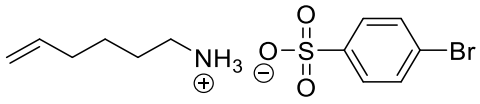
The corresponding sulfonyl ester was dissolved in a mixture of aqueous ammonium hydroxide solution and methanol (3:2, 60 mM) and stirred at room temperature for 72 h then concentrated under reduced pressure. The crude solid was then recrystallized in hot diethyl ether to give the product salt.

Hex-5-en-1-aminium methanesulfonate **160**



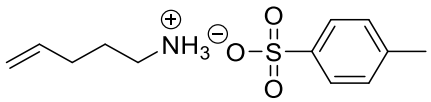
Rotary evaporation gave product **160** (4.80 g, 88%) as a pale yellow solid. m.p. 118 °C; δ_H (400 MHz, $CDCl_3$) 7.56 (3H, br.s, NH_3), 5.80 (1H, ddt, *J* 17.0, 10.5, 6.5, CH), 5.09-4.96 (2H, m, $C=CH_2$), 2.98 (2H, br. t, *J* 6.5, CH_2N), 2.78 (3H, s, CH_3), 2.15-2.07 (2H, m, CH_2), 1.78-1.68 (2H, m, CH_2), 1.55-1.45 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 137.8 (CH), 115.2 (CH_2), 39.8 (CH_2), 39.3 (CH_3), 33.0 (CH_2), 26.9 (CH_2), 25.6 (CH_2); *m/z*(ESI) 100 (M^+, 100%); *m/z*(ESI) found 100.1096. $C_7H_{14}N^+$ requires 100.1121.

Hex-5-en-1-aminium 4-bromobenzenesulfonate **161**



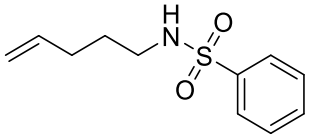
Rotary evaporation gave product **161** (2.94 g, 62%) as a colourless solid. m.p. 163 °C; δ_H (400 MHz, MeOD-d4) 7.83-7.73 (2H, m, ArH), 7.68-7.54 (2H, m, ArH), 5.82 (1H, ddt, *J* 17.0, 10.5, 7.0, C=CH), 5.09-4.97 (2H, m, C=CH_2), 2.93 (2H, t, *J* 7.0, CH_2O), 2.16-2.06 (2H, m, CH_2), 1.72-1.60 (2H, m, CH_2), 1.53-1.43 (2H, m, CH_2); δ_C (100 MHz, MeOD-d4) 144.2 (C), 137.7 (C), 131.1 (CH), 127.5 (CH), 124.0 (CH), 114.3 (CH_2), 39.3 (CH_2), 32.8 (CH_2), 26.6 (CH_2), 25.3 (CH_2).

Pent-4-en-1-aminium 4-methylbenzenesulfonate) **162**



Rotary evaporation gave product **162** (3.49 g, 82%) as a pale yellow solid. m.p. 161 °C; δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J* 8.0, ArH), 7.71 (3H, br.s, NH_3), 7.21 (2H, d, *J* 8.0, ArH), 5.61 (1H, ddt, *J* 17.0, 10.5, 6.5, CH), 4.99-4.90 (2H, m, C=CH_2), 2.78 (2H, br.t, *J* 6.5, CH_2N), 2.39 (3H, s, $ArCH_3$), 2.01-1.93 (2H, m, CH_2), 1.68-1.58 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 141.1 (C), 140.9 (C), 136.5 (CH), 129.1 (CH), 125.9 (CH), 115.8 (CH_2), 39.4 (CH_2), 30.3 (CH_2), 26.4 (CH_2), 21.4 (CH_3); *m/z* (ESI) 86 (M^+, 100%); *m/z* (ESI) found 86.0915. $C_5H_{12}N^+$ requires 86.0964.

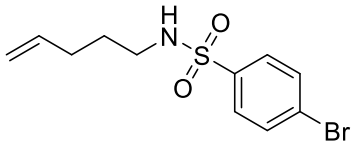
N-(Pent-4-enyl)benzenesulfonamide **163b**



Benzene sulfonamide (1.0 g, 6.40 mmol) and potassium carbonate (1.6 g, 11.6 mmol) were stirred in *N*,*N*-dimethylformamide (10 mL). 5-Bromo-1-pentene (864 mg, 5.80 mmol) was dissolved in *N*,*N*-dimethylformamide (5 mL) and added drop-wise to the reaction mixture over 5 minutes. The reaction mixture was then heated to 40 °C for 6.5 hours. It was then quenched with water (45 mL) and extracted with diethyl ether (90 mL). The organics were then washed with water (35 mL), brine (35 mL) and dried over sodium sulfate. The residue was then purified by gradient elution flash column chromatography on silica gel (17:3 to 7:3, petroleum ether/ethyl acetate) to give the product **163b** (574 mg, 44%) as a colourless oil. ν_{max} ($CHCl_3$)/cm^{-1} 3286, 3070, 2936, 1447, 1324, 1160, 1094; δ_H (400 MHz, $CDCl_3$) 7.91-7.85 (2H, m, ArH), 7.62-7.49 (3H, m, ArH), 5.71 (1H, ddt, *J* 17.0 10.5 6.5, CH_2CHCH_2), 5.01-4.93 (2H, m, CH_2CH), 4.54 (1H, t, *J* 5.5, N*H*), 2.98 (2H, dt, *J* 7.0 7.0, CH_2NH), 2.10-2.01 (2H, m, $CHCH_2CH_2$), 1.63-1.53 (2H, m, $CH_2CH_2CH_2$); δ_C (100 MHz, $CDCl_3$) 140.0 (C), 137.1 (C), 132.6 (C),

129.1 (CH), 127.0 (CH), 115.6 (CH_2), 42.7 (CH_2), 30.6 (CH_2), 26.7 (CH_2); *m/z* (ESI) 248 ($M+Na^+$, 100%), 226 ($M+H^+$, 87); *m/z* (ESI) Found 248.0718. $C_{11}H_{15}NNaO_2S^+$ requires 248.0716.

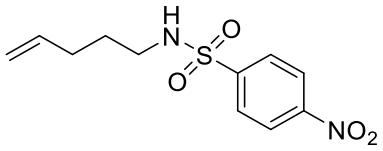
4-Bromo-*N*-(pent-4-en-1-yl)benzenesulfonamide **164b**



Followed general procedure for *N*-functionalisation.

Purified by flash column chromatography on silica gel (9:1, petroleum ether/ethyl acetate) to give the product **164b** (312 mg, 85%) as a low melting colourless solid. *Rf* 0.2 (9:1, petroleum ether/ethyl acetate); $\nu_{max}(CHCl_3)/cm^{-1}$ 3392, 3081, 3045, 2936, 1577, 1473, 1439, 1411, 1390, 1338, 1164; δ_H (400 MHz, $CDCl_3$) 7.76 (2H, d, *J* 8.5, ArH), 7.68 (2H, d, *J* 8.5, ArH), 5.73 (1H, ddt, *J* 17.0, 10.5, 7.0, C=CH), 5.05-4.95 (2H, m, $C=CH_2$), 4.66 (1H, t, *J* 7.0, NH), 2.99 (2H, dt, *J* 7.0, 7.0, CH_2N), 2.08 (2H, dt, *J* 7.0, 7.0, $C=CCH_2$), 1.60 (2H, tt, *J* 7.0, 7.0, CH_2); δ_C (100 MHz, $CDCl_3$) 139.1 (C), 137.0 (CH), 132.3 (CH), 128.7 (CH), 127.6 (C), 115.8 (CH_2), 42.7 (CH_2), 30.7 (CH_2), 28.7 (CH_2); *m/z* (ESI) 328 ($M+Na^+$, 25%), 326 ($M+Na^+$, 23%), 306 ($M^{81}Br+H^+$, 100%), 304 ($M^{79}Br+H^+$, 96); *m/z* (ESI) found 305.9972. $C_{11}H_{15}{}^{81}BrNO_2S^+$ requires 305.9981.

4-Nitro-*N*-(pent-4-en-1-yl)benzenesulfonamide **165c**

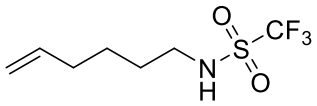


Made by literature procedure.[122]

4-Nitrobenzene sulfonamide (1.26 mg, 6.25 mmol) was added to a solution of pent-4-en-1-yl 4-methylbenzenesulfonate (1.00 g, 4.17 mmol) and potassium carbonate (1.73 g, 12.5 mmol) in *N*,*N*-dimethylformamide (14 mL). The slurry was then heated at 70 °C for 3 h. Water (8 mL) was added and extracted with dichloromethane (2 x 15 mL), the organic was the washed with water (2 x 15 mL), brine (2 x 15 mL), dried over magnesium sulfate then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (4:1, petroleum ether/ethyl acetate) to give the product **165c** (686 mg, 61%) as a yellow solid. m.p. 63-66 °C (lit m.p. 66-67.5 °C)[123]; *Rf* 0.3 (4:1, petroleum ether/ethyl acetate); ν_{max} $(CHCl_3)/cm^{-1}$ 3691, 3606, 3391, 3080, 3044, 2928, 1604, 1533, 1413, 1350, 1166; δ_H (400 MHz, $CDCl_3$) 8.39 (2H, d, *J* 9.0, ArH), 8.08 (2H, d, *J* 9.0, ArH), 5.73 (1H, ddt, *J* 17.0, 10.0, 7.0, C=CH), 5.06-4.96 (2H, m, $C=CH_2$), 4.68 (1H, br.t, *J* 7.0, NH), 3.06 (2H, dt, *J* 7.0 7.0, CH_2N), 2.13-2.05 (2H, m, CH_2), 1.63 (2H, tt, *J* 7.0, 7.0, CH_2); δ_C (100 MHz, $CDCl_3$) 150.1

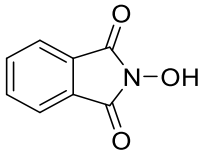
(C), 146.0 (C), 136.9 (CH), 128.3 (CH), 124.4 (CH), 116.0 (CH_2), 42.8 (CH_2), 30.6 (CH_2), 28.8 (CH_2); *m/z*(ESI) 293 ($M+Na^+$, 100%); *m/z* (ESI) found 293.0564. $C_{11}H_{14}N_2O_4SNa^+$ requires 293.0566.

1,1,1-Trifluoro-*N*-(hex-5-en-1-yl)methanesulfonamide **165d**



Triflic anhydride (0.43 mL, 2.56 mmol) was added dropwise to a 0 °C solution of hex-5-en-1-aminium methanesulfonate (500 mg, 2.56 mmol), triethylamine (1 mL, 7.68 mmol) and dichloromethane (10 mL) and allowed to stir for 4 h. Water (10 mL) was added, the organic separated, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (9:1, petroleum ether/ethyl acetate) to give the product **165d** (293 mg, 49%) as a pale yellow oil. *Rf* 0.42 (9:1, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3387, 3080, 2979, 1428, 1375, 609; δ_H (400 MHz, $CDCl_3$) 5.79 (1H, ddt, *J* 17.0, 10.5, 7.0, C=CH), 5.10-4.97 (2H, m, $C=CH_2$), 4.86 (1H, br.s, NH), 3.33 (2H, br.t, *J* 6.5, CH_2N), 2.17-2.08 (2H, m, $CH_2C=C$), 1.71-1.58 (2H, m, CH_2), 1.54-1.41 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 137.7 (CH), 119.6 (C, q, J_{CF} 320.0), 115.3 (CH_2), 44.4 (CH_2), 32.9 (CH_2), 29.5 (CH_2), 25.4 (CH_2).

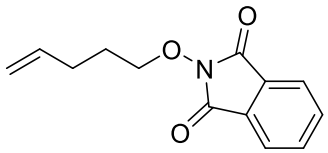
2-Hydroxyisoindoline-1,3-dione **170**



Made by literature procedure.[90]

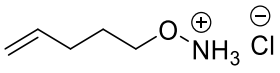
Phthalic anhydride **171** (3.00 g, 20.3 mmol), hydroxylamine hydrochloride (1.65 g, 24.3 mmol) and sodium hydroxide (972 mg, 24.3 mmol) were dissolved in water (30 mL). The solution was heated to 90 °C for 15 minutes, the solution became clear and orange then colourless precipitate developed. The precipitate was isolated by filtration under vacuum and dried to give the product **170** (1.72 g, 52%) as a colourless solid. m.p. 240-244 °C (lit m.p. 240-241 °C)[124]; *Rf* 0.23 (19:1, dichloromethane/methanol); ν_{max} ($CHCl_3$)/cm^{-1} 3960, 3606, 1732, 1602; δ_H (400 MHz, MeOD-d4) 7.87-7.79 (4H, m, ArH); δ_C (100 MHz, MeOD-d4) 164.5 (C), 135.2 (CH), 129.1 (C), 122.7 (CH); *m/z*(ESI) 186 ($M+Na^+$, 100%), 164 ($M+H^+$, 15%); *m/z*(ESI) found 186.0175. $C_8H_5NO_3Na^+$ requires 186.0162.

2-(Pent-4-en-1-yloxy)isoindoline-1,3-dione **169**



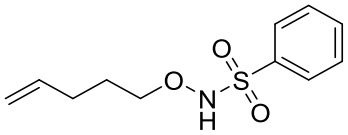
Hydroxypthallimide **170** (500 mg, 3.07 mmol) in *N*,*N*-dimethylformamide (7 mL) was added dropwise to a 0 °C solution of sodium hydride in mineral oil (123 mg, 3.07 mmol) in *N*,*N*-dimethylformamide (3 mL), gas evolved and the suspension was allowed to stir at 0 °C for 30 mins. Sodium iodide (46 mg, 0.31 mmol) and 5-bromopentene (686 mg, 4.60 mmol) was added drop-wise to the 0 °C suspension. The suspension was then heated at 70 °C for 14 h. The suspension was then quenched with water (10 mL) and the solution extracted with dichloromethane (2 x 25 mL). The organics were combined and washed with brine (5 x 30 mL), dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (9:1, petroleum ether/ethyl acetate) to give the product **169** (633 mg, 89%) as a colourless oil. *Rf* 0.34 (17:3, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3011, 2927, 2855, 1790, 1733, 1603, 1188, 992; δ_H (400 MHz, $CDCl_3$) 7.88-7.75 (4H, m, ArH), 5.86 (1H, ddt, *J* 17.0, 10.5, 6.5, C=CH), 5.15-5.00 (2H, m, $C=CH_2$), 4.24 (2H, t, *J* 6.5, CH_2O), 2.31 (2H, dtt, *J* 8.0, 6.5, 1.5, $CH_2C=C$), 1.95-1.87 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 163.7 (C), 137.4 (CH), 134.5 (CH), 129.0 (C), 123.5 (CH), 115.6 (CH_2), 76.44 (CH_2), 29.7 (CH_2), 27.4 (CH_2); *m/z* (ESI) 254 ($M+Na^+$, 100%), 232 ($M+H^+$, 34); *m/z* (ESI) found 254.0775. $C_{13}H_{13}NO_3Na^+$ requires 254.0778.

O-(Pent-4-en-1-yl)hydroxylammonium chloride **168**



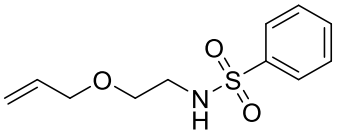
Hydrazine hydrate (162 mg, 3.24 mmol) was added to a solution of 2-(pent-4-en-1-yloxy)isoindoline-1,3-dione **169** (500 mg, 2.16 mmol) in diethyl ether (10 mL) and allowed to stir at room temperature for 2 h, the resulting precipitate was removed by filtration and 2M hydrogen chloride in diethyl ether (5 mL, 10 mmol) was added to the resulting solution. The hydrochloride salt **168** (297 mg, 99%) was obtained by filtration and used without further purification. δ_H (400 MHz, $CDCl_3$) 5.86 (1H, ddt, *J* 17.0, 10.5, 6.5, C=CH), 5.13-5.00 (2H, m, $C=CH_2$), 4.07 (2H, t, *J* 6.5, CH_2O), 2.25-2.14 (2H, m, CH_2), 1.86-1.75 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 136.9 (CH), 114.7 (CH_2), 74.3 (CH_2), 29.3 (CH_2), 26.6 (CH_2); *m/z* (ESI) 102 (M^+, 100%); *m/z* (ESI) found 102.0918. $C_5H_{12}NO^+$ requires 102.0913.

N-(Pent-4-en-1-yloxy)benzenesulfonamide **167**



Benzene sulfonyl chloride (484 mg, 2.00 mmol) was added drop-wise to a 0 °C solution of *O*-(pent-4-en-1-yl)hydroxylamine hydrochloride salt (200 mg, 1.45 mmol), triethylamine (0.49 mL, 3.51 mmol) in methanol (4 mL) and dichloromethane (5 mL), the solution was then allowed to stir at room temperature for 16 h. Dichloromethane (25 mL) was added washed with 2M hydrochloric acid (2 x 25 mL), dried over magnesium sulfate then concentrated under reduced pressure. The residue was then purified by flash column chromatography on silica gel (4:1, petroleum ether/ethyl acetate) to give the product **167** (301 mg, 87%) as a colourless oil. *Rf* 0.28 (4:1, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3285, 3074, 3045, 2944, 1641, 1478, 1386, 1334, 1172; δ_H (400 MHz, $CDCl_3$) 8.00-7.93 (2H, m, ArH), 7.72-7.66 (1H, m, ArH), 7.63-7.56 (2H, m, ArH), 7.07 (1H, br.s, NH), 5.80 (1H, ddt, *J* 17.0, 10.5, 7.0, C=CH), 5.07-4.97 (2H, m, C=CH_2), 4.03 (2H, t, *J* 6.5, CH_2O), 2.14-2.06 (2H, m, CH_2), 1.77-1.65 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 137.6 (CH), 133.8 (C), 129.1 (CH), 128.5 (CH), 115.2 (CH_2), 76.9 (CH_2), 29.9 (CH_2), 27.3 (CH_2); *m/z*(ESI) 264 ($M+Na^+$, 100%), 242 ($M+H^+$, 12%); *m/z*(ESI) found 264.0681. $C_{11}H_{15}NO_3SNa^+$ requires 264.0665.

N-(2-(Allyloxy)ethyl)benzenesulfonamide **175**



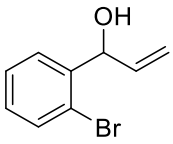
Potassium *tert*-butoxide (985 mg, 8.79 mmol) was added in one addition to a solution of 2-(phenylsulfonamido)ethyl benzenesulfonate (1.00 g, 2.93 mmol) and allyl alcohol (340 mg, 5.86 mmol) in tetrahydrofuran (10 mL), the solution was then allowed to stir for 18 h at room temperature. Water (10 mL) and dichloromethane (10 mL) were added and the organic further washed with 2M hydrochloric acid (2 x 10 mL), dried over magnesium sulfate then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (4:1, petroleum ether/ethyl actetate) to give product **175** (452 mg, 64%) as a colourless oil. *Rf* 0.45 (7:3, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3366, 3011, 2927, 2958, 1602, 1331, 1163, 1091; δ_H (400 MHz, $CDCl_3$) 7.92-7.87 (2H, m, ArH), 7.63-7.58 (1H, m, ArH), 7.57-7.51 (2H, m, ArH), 5.84 (1H, ddt, *J* 17.0, 10.5, 6.0, CH), 5.27-5.16 (2H, m, CH_2), 4.91 (1H, br. t, *J* 6.0, NH), 3.91 (2H, dt, *J* 6.0, 1.5, CHC*H*$_2$O), 3.48 (2H, t, *J* 6.0, CH_2O), 3.18 (2H, td, *J* 6.0, 6.0, CH_2N); δ_C (100 MHz, $CDCl_3$) 139.9 (C), 134.0 (CH), 132.7 (CH), 129.0 (CH), 127.0 (CH), 117.7 (CH_2), 72.1 (CH_2), 68.1

(CH_2), 43.0 (CH_2); *m/z* (ESI) 264 ($M+Na^+$, 100%), 242 ($M+H^+$, 22); *m/z* (ESI) found 264.0661. $C_{11}H_{15}NSO_3rNa^+$ requires 264.0665.

General procedure for vinyl magnesium Grignard addition to aldehydes

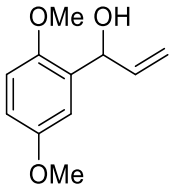
1M Vinyl magnesium bromide (1.2 equiv.) was added slowly to a -78 °C solution of the corresponding aldehyde (1 equiv.) in tetrahydrofuran (0.8M), the solution was then allowed to warm and stir at room temperature for 14 h at which point saturated aqueous ammonium chloride (half volume of THF used) was added. Dichloromethane (volume of THF used) was added then washed with water (volume of THF used), dried over magnesium sulfate then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel in the solvent systems outlined for individual products.

1-(2-Bromophenyl)prop-2-en-1-ol **182**



The residue was purified by flash column chromatography on silica gel (9:1, petroleum ether/ethyl acetate) to give the product **182** (3.26 g, 95%) as a colourless oil. *Rf* 0.39 (9:1, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3603, 3069, 3011, 2923, 1469, 1441, 1018, 652; δ_H (400 MHz, $CDCl_3$); 7.62-7.49 (2H, m, ArH), 7.34 (1H, ddd, *J* 7.5, 7.5, 1.5, ArH), 7.15 (1H, ddd, *J* 7.5, 7.5, 1.5, ArH), 6.02 (1H, ddd, *J* 17.0, 10.5, 7.0, CH), 5.60 (1H, br.d, *J* 5.0, ArCH), 5.39 (1H, dt, *J* 17.0, 1.5, C=C*Ha*Hb), 5.23 (1H, dt, *J* 10.5, 1.5, C=CHa*Hb*), 2.95 (1H, br.s, ArOH); δ_C (100 MHz, $CDCl_3$) 141.6 (C), 138.4 (CH), 132.8 (CH), 129.1 (CH), 128.0 (CH), 127.9 (CH), 122.6 (C), 115.7 (CH_2), 73.5 (CH); *m/z* (ESI) 237 ($M+Na^+$, ^{81}Br, 51%), 235 ($M+Na^+$, ^{79}Br, 48), 215 ($M+H^+$, ^{81}Br, 98), 213 ($M+H^+$, ^{79}Br, 100); *m/z*(ESI) found 212.9889. $C_9H_9O^{79}Br^+$ requires 212.9910.

1-(2,5-Dimethoxyphenyl)prop-2-en-1-ol **185**



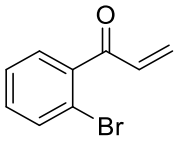
The residue was purified by flash column chromatography on silica gel (4:1, petroleum ether/ethyl acetate) to give the product **185** (860 mg, 74%) as a yellow oil. R_f 0.16 (1:4, ethyl acetate/petroleum ether); ν_{max}(neat)/cm^{-1} 3672, 3602, 3086, 3046, 2957, 2837, 1500, 1465, 1279, 1122; δ_H (400 MHz, $CDCl_3$) 6.92 (1H, d, *J* 3.0, ArH), 6.85 (1H, d, *J* 8.0, ArH), 6.80 (1H, dd, *J* 8.0, 3.0, ArH), 6.13 (1H, ddd, *J* 17.0, 10.5, 5.5, CHO), 5.43-5.37 (1H, m, CH), 5.34 (1H, dt, *J* 17.0, 1.5, CH), 5.20 (1H, dt, *J* 10.5, 1.5), 3.84 (3H, s, OCH_3), 3.79 (3H, s, OCH_3); δ_c (100

MHz, $CDCl_3$) 153.8 (C), 150.9 (C), 139.3 (CH), 131.9 (C), 114.7 (CH_2), 113.5 (CH), 113.0 (CH), 111.9 (CH), 71.6 (CH), 56.0 (CH_3), 55.7 (CH_3); *m/z* (ESI) 217 ($M+Na^+$ 100%), 177 (M^+-OH fragment 29%); *m/z* (ESI) Found 217.0853. $C_{11}H_{14}O_3Na^+$ requires 217.0835.

General procedure for benzylic alcohol oxidation with manganese dioxide

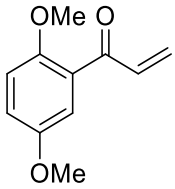
Benzylic alcohol (1 equiv.) and activated manganese dioxide (10 equiv.) in chloroform (0.2M) were heated at reflux for 24 h then passed through Celite and concentred under reduced pressure. The residue was purified by flash column chromatography on silica gel in the solvent systems outlined for individual products.

1-(2-Bromophenyl)prop-2-en-1-one **183**



The residue was purified by flash column chromatography on silica gel (9:1, petroleum ether/ethyl acetate) to give the product **183** (755 mg, 69%) as a pale yellow oil. *Rf* 0.43 (9:1, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3098, 3059, 3011, 1666, 1605, 1468, 1430, 1296; δ_H (400 MHz, $CDCl_3$) 7.63 (1H, dd, *J* 8.0, 1.0, ArH), 7.43-7.30 (3H, m, 3 x ArH), 6.75 (1H, dd, *J* 17.5, 10.5, C=CH), 6.17-6.06 (2H, m, $C=CH_2$); δ_C (100 MHz, $CDCl_3$) 195.2 (C), 140.2 (C), 136.1 (CH), 133.4 (CH), 132.5 (CH_2), 131.5 (CH), 129.1 (CH), 127.2 (CH), 119.4 (C); *m/z* (ESI) 235 ($M+Na^+$, ^{81}Br, 38%), 233 ($M+Na^+$, ^{79}Br, 35%), 213 ($M+H^+$, ^{81}Br, 98%), 211 ($M+H^+$, ^{79}Br, 100%); *m/z*(ESI) found 210.9783. $C_9H_8O^{79}Br^+$ requires 210.9753.

1-(2,5-Dimethoxyphenyl)prop-2-en-1-one **186**

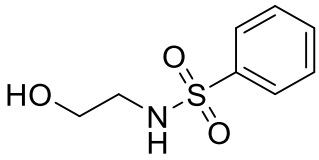


The residue was purified by flash column chromatography on silica gel (4:1, petroleum ether/ethyl acetate) to give the product **186** (583 mg, 71%) as an orange oil. R_f 0.35 (4:1, petroleum ether/ethyl acetate); ν_{max}(neat)/cm^{-1} 3085, 3058, 3007, 2960, 1661, 1598, 1496, 1465, 1418, 1278, 1124; δ_H (400 MHz, $CDCl_3$) 7.16 (1H, d, *J* 3.0, ArH), 7.10-7.01 (2H, m, ArH), 6.93 (1H, d, *J* 9.0, ArH), 6.31 (1H, dd, *J* 17.0, 2.0, CH), 5.82 (1H, dd, *J* 10.5, 2.0, CH), 3.85 (3H, s, OCH_3), 3.81 (3H, s, OCH_3); δ_c (100 MHz, $CDCl_3$) 192.8 (C), 153.5 (C), 152.7 (C), 136.5 (CH), 128.8 (CH_2), 128.4 (C), 119.4 (CH), 114.4 (CH), 113.3 (CH), 56.3 (CH_3), 55.8 (CH_3); *m/z* (ESI) 215 ($M+Na^+$ 100%), 193 ($M+H^+$ 21%); *m/z* (ESI) Found 215.0697. $C_{11}H_{12}O_3Na^+$ requires 215.0679.

General procedure for *N*-functionalisation

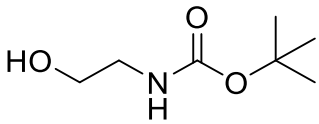
To a solution of amine (1 equiv.) in dichloromethane (2.3M) and methanol (10 equiv.) was added triethylamine (2 equiv.) followed by portionwise addition of the corresponding sulfonyl chloride, di-*tert*-butyl dicarbonate, benzyl chloroformate, acetyl chloride, acetic anhydride (1.5 equiv.). The solution was then stirred for 16 h at room temperature. The solution was then washed with 2M hydrochloric acid (3 x equal volume to CH_2Cl_2), saturated aqueous sodium hydrogen carbonate (4 x equal volume to CH_2Cl_2), dried over magnesium sulfate and concentrated under reduced pressure. Some products were purified by flash column chromatography but most were clean after aqueous work up.

N-(2-Hydroxyethyl)benzenesulfonamide **243**



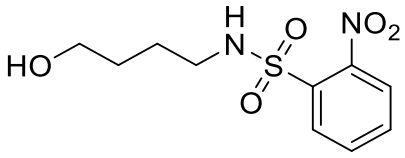
Aqueous work up gave product **243** (2.47 g, 38%) as colourless oil. R_f 0.3 (7:3, ethyl acetate/petroleum ether); ν_{max}(neat)/cm^{-1} 3285, 2938, 2866, 2361, 2344, 1162; δ_H (400 MHz, $CDCl_3$) 7.91-7.84 (2H, m, ArH), 7.61-7.55 (1H, m, ArH), 7.54-7.48 (2H, m, ArH), 5.91 (1H, br.s, NH), 3.68 (2H, t, *J* 5.0, CH_2O), 3.29 (1H, br.s, OH), 3.08 (2H, t, *J* 5.0, CH_2N); δ_c (100 MHz, $CDCl_3$) 139.6 (C), 132.8 (CH), 129.2 (CH), 127.0 (CH), 61.2 (CH_2), 45.3 (CH_2); *m/z* (ESI) 224 (M+Na$^+$ 100%), 202 (M+H$^+$ 17%); *m/z* (ESI) Found 224.0357. $C_8H_{11}O_3SNa^+$ requires 224.0352.

tert-Butyl (2-hydroxyethyl)carbamate **244**



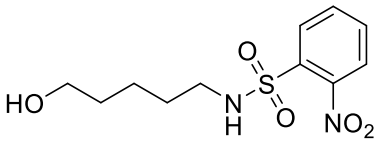
Aqueous work up gave product **244** (4.60 g, 88%) as colourless oil. R_f 0.22 (7:3, petroleum ether/ ethyl acetate); δ_H (400 MHz, $CDCl_3$) 5.15 (1H, br. t, NH), 3.72-3.61 (2H, m, CH_2O), 3.33-3.15 (3H, m, CH_2N and NH), 1.45 (9H, s, 3 x CH_3); δ_c (100 MHz, $CDCl_3$) 158.9 (C), 79.6 (C), 62.3 (CH_2), 43.1 (CH_2), 28.4 (CH_3); *m/z* (ESI) 345 (2M+Na$^+$, 76), 184 (M+Na$^+$ 100%); *m/z* (ESI) Found 184.0951. $C_7H_{15}O_3NNa^+$ requires 184.0944.

N-(4-Hydroxybutyl)-2-nitrobenzenesulfonamide **245**



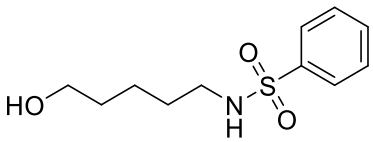
Obtained the product **245** (6.11 g, 99%) as a colourless solid. m.p. 98-104 °C; *Rf* 0.22 (2:1, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3625, 3371, 3010, 2941, 2892, 1551, 1211; δ_H (400 MHz, $CDCl_3$) 8.17-8.09 (1H, m, ArH), 7.91-7.81 (1H, m, ArH), 7.79-7.70 (2H, m, ArH), 5.71 (1H, br. t, *J* 6.0, NH), 3.65 (2H, t, *J* 6.0, CH_2O), 3.15 (td, *J* 7.0, 6.0, CH_2N), 1.89 (1H, s, OH), 1.71-1.53 (4H, m, 2 x CH_2); δ_C (100 MHz, $CDCl_3$) 148.1 (C), 133.7 (C), 133.6 (CH), 132.8 (CH), 131.0 (CH), 125.3 (CH), 62.1 (CH_2), 43.6 (CH_2), 29.4 (CH_2), 26.4 (CH_2); *m/z* (ESI) 297 ($M+Na^+$, 100%); *m/z* (ESI) found [$M+Na^+$] 297.0518. $C_{10}H_{14}N_2O_5SNa^+$ requires 297.0516.

N-(5-Hydroxypentyl)-2-nitrobenzenesulfonamide **246**



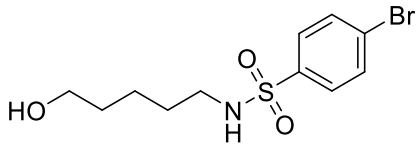
Aqueous work up gave product **246** (41.2 g, 99%) as a waxy low melting solid. m.p. 75-82 °C; R_f 0.28 (3: 2, petroleum ether/ethyl acetate); ν_{max}($CHCl_3$)/cm^{-1} 3629, 3376, 3022, 2940, 2888, 1543, 1419, 1360, 1200, 1171, 1065, 597; δ_H (400 MHz, $CDCl_3$) 4.05 (2H, s, CH_2), 2.98 (2H, q, *J* 7.5, CH_2), 1.32 (3H, t, *J* 7.5, CH_3); δ_C (100 MHz, $CDCl_3$) 148.0 (C), 133.7 (CH), 133.6 (C), 132.8 (CH), 131.0 (CH), 125.3 (CH), 62.4 (CH_2), 43.7 (CH_2), 31.9 (CH_2), 29.3 (CH_2), 22.7 (CH_2); *m/z* (ESI) 311 ($M+Na^+$ 100%), 599 (M_2+Na^+ 18%); *m/z* (ESI) Found 311.0643. $C_{11}H_{16}N_2O_5SNa^+$ requires 311.0672.

N-(5-Hydroxypentyl)benzenesulfonamide **247**



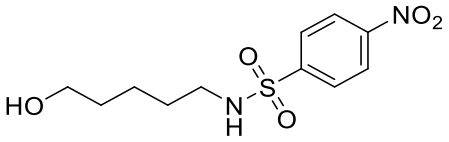
Aqueous work up gave product **247** (5.84 g, 97%) as a colourless oil. ν_{max}(neat)/cm^{-1} 3282, 2938, 2866, 2360, 2342, 1447, 1322, 1157, 1093; δ_H (400 MHz, CD_3Cl) 7.89-7.86 (2H, m, ArH), 7.60-7.50 (3H, m, ArH), 4.97 (1H, br t, *J* 6.0, NH), 3.59 (2H, t, *J* 6.0, C*H*$_2$OH) 2.96 (2H, dt, *J* 6.5, 6.0, C*H*$_2$NH), 1.74 (1H, br s, OH), 1.54-1.47 (m, 4H, CH_2), 1.40-1.32 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 140.0 (C), 132.6 (CH), 129.1 (CH), 127.0 (CH), 62.5 (CH_2), 43.1 (CH_2), 31.9 (CH_2), 29.2 (CH_2), 22.7 (CH_2); *m/z* (ESI) 266 [($M+Na^+$, 100%), 244 ($M+H^+$, 44%) (M_2+Na^+, 23%)]; *m/z* (ESI) Found 266.0811. $C_{11}H_{17}NO_3SNa^+$ requires 266.0821.

4-Bromo-*N*-(5-hydroxypentyl)benzenesulfonamide **248**



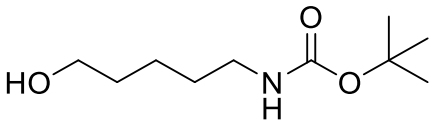
Aqueous work up gave product **248** (5.03 g, 81%) as a colourless crystalline solid. m.p. 55 ^{o}C; *Rf* 0.3 (19:1, dichloromethane/methanol); ν_{max} ($CHCl_3$)/cm^{-1} 3627, 3392, 3011, 2941, 2865, 1577, 1164, 607; δ_H (400 MHz, $CDCl_3$) 7.76 (2H, d, *J* 8.0, ArH), 7.68 (2H, d, *J* 8.0, ArH), 4.63 (1H, t, *J* 6.5, NH), 3.65 (2H, t, *J* 6.5, CH_2O), 3.00 (2H, dt.*J* 6.5, 6.5, CH_2N), 2.32 (1H, s, OH), 1.76-1.20 (6H, m, 3xCH_2); δ_C (100 MHz, $CDCl_3$) 139.0 (C), 132.4 (CH), 128.6 (CH), 127.5 (C), 62.3 (CH_2), 43.0 (CH_2), 31.8 (CH_2), 29.1 (CH_2), 22.7 (CH_2); *m/z* (ESI) 669 ($2M^{81}Br^{81}Br+Na^+$), 667 ($2M^{81}Br^{79}Br+Na^+$), 665 ($2M^{79}Br^{79}Br+Na^+$), 346 ($M^{81}Br+Na^+$, 65%), 344 ($M^{79}Br+Na^+$, 62), 324 ($M^{81}Br+H^+$, 40), 322 ($M^{79}Br+H^+$, 38); *m/z* (ESI) found 345.9905. $C_{11}H_{16}NO_3S^{81}BrNa^+$ requires 345.9906.

N-(5-Hydroxypentyl)-4-nitrobenzenesulfonamide **249**



Aqueous work up gave product **249** (1.15 g, 83%) as a colourless solid. m.p. 90 ^{o}C; R_f 0.2 (2: 1, petroleum ether/ethyl acetate); ν_{max}($CHCl_3$)/cm^{-1} 3626, 3391, 3043, 2941, 2868, 1608, 1537, 1350, 1165; δ_H (400 MHz, $CDCl_3$) 8.37 (2H, d, *J* 9.0, ArH), 8.06 (2H, d, *J* 9.0, ArH), 5.19 (1H, t, *J* 6.0, NH), 3.62 (2H, t, *J* 6.0, C*H*$_2$OH), 3.03 (2H, dt, *J* = 6.0, 6.0, CH_2N), 1.77 (1H, brs, OH), 1.54 (4H, m, CH_2), 1.40 (2H, m, CH_2); δ_C (100 MHz, CD_3Cl) 150.1 (C), 146.0 (C), 128.3 (CH), 124.4 (CH), 62.4 (CH_2), 43.2 (CH_2), 31.7 (CH_2), 29.3 (CH_2), 22.7 (CH_2); *m/z* (ESI) 311 ($M+Na^+$ 100%), 599 (M_2+Na^+ 18%); *m/z* (ESI) Found 311.0643. $C_{11}H_{16}N_2O_5SNa^+$ requires 311.0672.

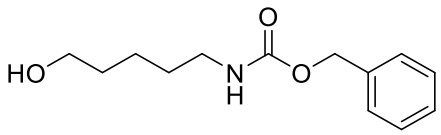
tert-Butyl (5-hydroxypentyl)carbamate **250**



Purified by flash column chromatography (4:1 chloroform/ethyl acetate) to give the product **250** (537 mg, 91%) as a colourless oil. R_f 0.28 (4: 1, petroleum ether/ethyl acetate); δ_H (400 MHz, $CDCl_3$) 4.57 (1H, br. s, NH), 3.67 (2H, t *J* 6.5, CH_2O), 3.17-3.12 (2H, m, CH_2N), 1.66-1.37 (6H, m), 1.46 (9H, s, 3xCH_3); δ_C (100 MHz, $CDCl_3$) 156.13 (C), 82.55 (C), 62.31 (CH_2), 39.97 (CH_2), 32.84 (CH_2), 30.63 (CH_2), 28.03 (CH_3), 23.44 (CH_2); *m/z* (ESI) 170.0785 (17.9%), 226.1418 (100%),

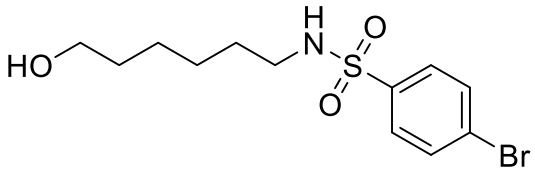
227.1446 (11.5%). *m/z* (ESI) found [M+Na$^+$] 226.1418, $C_{10}H_{21}NO_3Na^+$ requires 226.1414.

Benzyl (5-hydroxypentyl)carbamate **251**



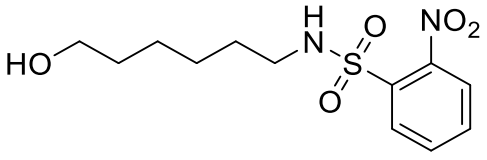
The residue was purified by flash column chromatography on silica gel (4:1 chloroform/ethyl acetate) to give the product **251** (328.7 mg, 68%) as a colourless oil. R_f 0.3 (4: 1, petroleum ether/ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.39-7.31 (5H, m, ArH), 5.14 (1H, br.s, NH), 5.12 (2H, s, CH_2), 4.81 (1H, br. s, OH), 3.66 (2H, t *J* 6.5, CH_2), 3.24 (2H, dt *J* 6.5, 6.5, CH_2), 1.59-1.55 (4H, m), 1.44-1.41 (2H, m); δ_C (100 MHz, $CDCl_3$) 156.54 (C), 136.71 (C), 128.63 (CH), 128.23 (CH), 66.67 (CH_2), 62.78 (CH_2), 40.94 (CH_2), 32.30 (CH_2), 29.84 (CH_2), 22.96 (CH_2); *m/z* (ESI) 260.1253 (100%), 261.1291 (14.5%), 394.1648 (10.9%); *m/z* (ESI) found [M+Na$^+$] 260.1253, $C_{13}H_{19}NO_3Na^+$ requires 260.1257.

4-Bromo-*N*-(6-hydroxyhexyl)benzenesulfonamide **252**



Aqueous work up gave product **252** (2.82 g, 98%) as a colourless solid. m.p. 104-106 °C; R_f 0.22 (19:1, dicloromethane/methanol); $\nu_{max}(CHCl_3)/cm^{-1}$ 3622, 3392, 3033, 2939, 1577, 1410, 1390, 1337, 1222, 1164, 1092, 1069, 806; δ_H (400 MHz, $CDCl_3$) 7.78-7.73 (2H, m, ArH), 7.71-7.65 (2H, m, ArH), 4.67 (1H, br.t, *J* 5.5, NH), 3.64 (2H, t, *J* 6.5, CH_2O), 2.98 (2H, dt, *J* 7.0, 7.0, CH_2N), 1.70-1.24 (9H, m, 4 x CH_2 and OH); δ_C (100 MHz, $CDCl_3$) 139.1 (C), 132.4 (CH), 128.6 (CH), 127.6 (C), 62.7 (CH_2), 43.1 (CH_2), 32.4 (CH_2), 29.5 (CH_2), 26.2 (CH_2), 25.2 (CH_2); *m/z* (ESI) 358 ($M^{79}Br+Na^+$ 97%), 360 ($M^{81}Br+Na^+$ 100%); *m/z* (ESI) Found 360.0076. $C_{12}H_{18}NO_3S^{81}BrNa^+$ requires 360.0063.

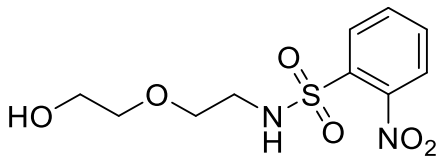
N-(6-Hydroxyhexyl)-2-nitrobenzenesulfonamide **253**



Aqueous work up gave product **253** (3.01 g, 99%) as a colourless solid. m.p. 79-81 °C; R_f 0.3 (19: 1, dichloromethane/methanol); $\nu_{max}(CHCl_3)/cm^{-1}$ 3626, 3381,

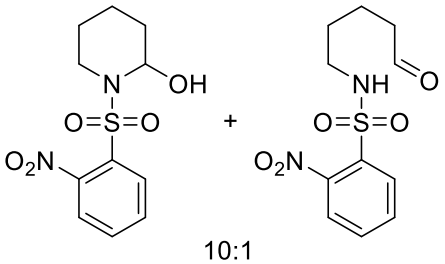
3019, 2939, 2880, 1542, 1417, 1361, 1199, 1171, 1065, 595; δ_H (400 MHz, $CDCl_3$) 8.20-8.12 (1H, m, ArH), 7.93-7.85 (1H, m, ArH), 7.83-7.71 (2H, m, ArH), 5.31 (1H, br.t, *J* 5.5, NH), 3.64 (2H, t, *J* 6.5, CH_2O), 3.13 (2H, dt, *J* 7.0, 6.5, CH_2N), 1.64-1.28 (9H, m, 4 x CH_2 and OH); δ_C (100 MHz, $CDCl_3$) 148.1 (C), 133.8 (C), 133.5 (CH), 132.8 (CH), 131.1 (CH), 125. (CH), 62.7 (CH_2), 43.7 (CH_2), 32.4 (CH_2), 29.5 (CH_2), 26.2 (CH_2), 25.2 (CH_2); *m/z* (ESI) 325 ($M+Na^+$ 100%); *m/z* (ESI) Found 325.0849. $C_{12}H_{18}N_2O_5SNa^+$ requires 325.0829.

N-(2-(2-Hydroxyethoxy)ethyl)-2-nitrobenzenesulfonamide **254**



Obtained the product **254** (1.34 g, 91%) as a colourless solid. m.p. 66-69 °C; *Rf* 0.26 (19:1, dichloromethane/methanol); ν_{max} ($CHCl_3$)/cm^{-1} 3607, 3375, 3039, 3016, 2931, 2895, 2875, 1543, 1414, 1361, 1171, 1125, 1059, 854, 597; δ_H (400 MHz, $CDCl_3$) 8.20-8.11 (1H, m, ArH), 7.92-7.85 (1H, m, ArH), 7.82-7.70 (2H, m, ArH), 6.06 (1H, br. t, *J* 5.5, NH), 3.69 (2H, t, *J* 5.0, C*H*$_2$OH), 3.58 (2H, t, *J* 5.0, C*H*$_2$O), 3.50 (2H, t, *J* 5.0, CH_2O), 3.33 (2H, dt, *J* 5.0, 5.0, CH_2N), 2.29 (1H, s, OH); δ_C (100 MHz, $CDCl_3$) 148.0 (C), 133.8 (C), 133.7 (CH), 132.8 (CH), 131.0 (CH), 125.4 (CH), 72.3 (CH_2), 69.1 (CH_2), 61.6 (CH_2), 43.6 (CH_2); *m/z* (ESI) 313 ($M+Na^+$, 100%); *m/z* (ESI) found [$M+Na^+$] 313.0466. $C_{10}H_{14}N_2O_6SNa^+$ requires 313.0465.

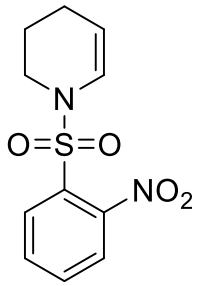
1-((2-nitrophenyl)sulfonyl)piperidin-2-ol **231** (and **232**)



A suspension of *N*-(5-hydroxypentyl)-2-nitrobenzenesulfonamide **229** (400 mg, 1.38 mmol) and manganese oxide (1.2 g, 13.8 mmol) in chloroform (6.66 mL) was heated at 80 ºC for 16 h then the reaction was cooled and the manganese dioxide allowed to settle. The solution was then carefully removed by pipette and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (1:1, petroleum ether/ethyl acetate) to give the product **231/232** (330 mg, 83%) as an observed 10:1 mixture of hemiaminal and aldehyde (denoted by an * in NMR data) by ^{1}H NMR. *Rf* 0.53 (3:7, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3579, 3027, 2951, 2874, 1727, 1547, 1372, 1347, 1166, 1053; δ_H (400 MHz, $CDCl_3$) 9.75* (1H, t, *J* 1.5, CHO), 8.17-8.12* (1H, m, ArH), 8.08-8.02 (1H, m, ArH), 7.90-7.85* (1H, m, ArH), 7.79-7.61 (3H, m, ArH and ArH*), 5.55* (1H, m, NCH), 5.38 (1H, br.t, *J* 6.0, NH),

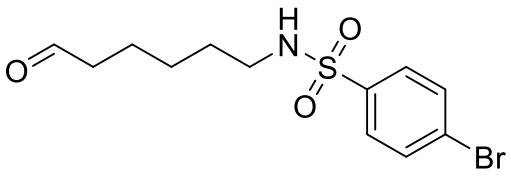
3.62 (1H, br.d, NC*Ha*Hb), 3.32-3.21 (2H, m, NCHa*Hb* and CH), 3.13* (1H, dt, *J* 6.5, 6.5, CH_2N), 2.50-2.45* (1H, m, *CH_2*CHO), 1.92 (1H, m, CH), 1.82-1.54 (6H, m, CH_2's and CH_2's*); δ_C (100 MHz, $CDCl_3$) 147.7 (C), 133.8 (CH), 132.8 (C), 132.0 (CH), 131.0 (CH), 124.4 (CH), 76.7 (CH), 40.8 (CH_2), 31.4 (CH_2), 24.9 (CH_2), 17.2 (CH_2); *m/z* (ESI) 309 ($M+Na^+$, 100%); *m/z* (ESI) found ($M+Na^+$) 309.0524. $C_{11}H_{14}N_2O_5SNa^+$ requires 309.0156;

1-((2-Nitrophenyl)sulfonyl)-1,2,3,4-tetrahydropyridine **232**



A suspension of *N*-(5-hydroxypentyl)-2-nitrobenzenesulfonamide **229** (400 mg, 1.38 mmol) and manganese dioxide (1.2 g, 11.0 mmol) was heated at 80 °C for 16 h before allowing to cool to room temperature. Trifluoroacetic acid (5 drops) was added and the suspension allowed to stand for 2 h. The solution was carefully decanted from the manganese dioxide and concentrated under reduced pressure. The residue was then purified by flash column chromatography on silica gel (2:1, petroleum ether/ethyl acetate) to give the product **232** (134 mg, 34%) as a bright yellow powder. m.p. 79-81 °C *Rf* 0.4 (2:1, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3034, 3008, 2958, 2938, 2847, 1547, 1373, 1173; δ_H (400 MHz, $CDCl_3$) 8.01-7.94 (1H, m, ArH), 7.77-7.69 (2H, m, ArH), 7.68-7.62 (1H, m, ArH), 6.65 (1H, dt, *J* 8.5, 1.5, CHN), 5.10 (1H, dt, *J* 8.5, 4.5, CH), 3.61-3.54 (2H, m, CH_2N), 2.04 (2H, tdd, *J* 6.0, 4.0, 2.0, CH_2), 1.83 (2H, tt, *J* 6.0, 6.0, CH_2); δ_C (100 MHz, $CDCl_3$) 148.2 (C), 133.8 (CH), 131.8 (C), 131.7 (CH), 130.4 (CH), 124.2 (CH), 108.8 (CH), 44.3 (CH_2), 21.3 (CH_2), 20.9 (CH_2); *m/z* (ESI) 291 ($M+Na^+$, 100%), 269 ($M+H^+$, 53); *m/z* (ESI) found ($M+Na^+$) 291.0403. $C_{11}H_{12}N_2O_4SNa^+$ requires 291.0410.

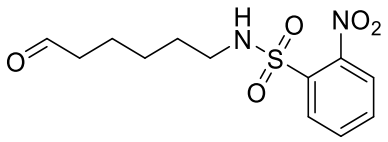
4-Bromo-*N*-(6-oxohexyl)benzenesulfonamide **276**



Purified by flash column chromatography on silica gel (3:2, petroleum ether/ethyl acetate) to give the product aldehyde **276** (338 mg, 74%) as a pale yellow oil. *Rf* 0.41 (3:2, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3392, 3036, 3020, 2943, 2865, 2730, 1723, 1577, 1473, 1411, 1390, 1338; δ_H (400 MHz, $CDCl_3$) 9.75 (1H, t, *J* 1.5, CHO), 7.77-7.63 (4H, m, ArH), 4.95 (1H, t, *J* 6.0,

NH), 2.96 (2H, td, *J* 7.0, 6.0, CH_2N), 2.42 (2H, td, *J* 7.0, 1.5, $OCCH_2$), 1.63-1.45 (4H, m, 2 x CH_2) 1.40-1.21 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 202.4 (CH), 139.1 (C), 132.4 (CH), 128.6 (CH), 127.6 (C), 43.6 (CH_2), 42.9 (CH_2), 29.3 (CH_2), 25.9 (CH_2), 21.3 (CH_2); *m/z* (ESI) 358 ($M^{81}Br+Na^+$, 100%), 356 ($M^{79}Br+Na^+$, 99%); *m/z* (ESI) found [$M+Na^+$] 357.09908. $C_{12}H_{16}{}^{81}BrNO_3SNa^+$ requires 357.9906.

2-Nitro-*N*-(6-oxohexyl)benzenesulfonamide **277**



A suspension of *N*-(6-hydroxyhexyl)-2-nitrobenzenesulfonamide **253** (420 mg, 1.39 mmol) and manganese dioxide (1.2 g, 13.9 mmol) in chloroform (6.66 mL) were heated at 80 °C for 16 h then allowed to cool. The solution was decanted once the manganese dioxide settled and concentrated under reduced pressure. The residue was then purified by flash column chromatography on silica gel (3:2, petroleum ether/ethyl acetate) to give the product **277** (257 mg, 61%) as a pale yellow oil. *Rf* 0.3 (3:2, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3381, 3027, 2944, 2866, 2729, 1723, 1543, 1417, 1361; δ_H (400 MHz, $CDCl_3$) 9.74 (1H, t, *J* 1.5, CHO), 8.16-8.10 (1H, m, ArH), 7.90-7.83 (1H, m, ArH), 7.80-7.72 (2H, m, 2 x ArH), 5.35 (1H, br.t, *J* 6.0, NH), 3.11 (2H, dt, *J* 7.0, 7.0, CH_2N), 2.42 (2H, td, *J* 7.0, 1.5, CH_2CHO), 1.68-1.48 (4H, m, 2 x CH_2), 1.46-1.29 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 202.3 (CH), 148.1 (C), 133.6 (CH and C), 132.8 (CH), 131.0 (CH), 125.4 (CH), 43.6 (CH_2), 43.5 (CH_2), 29.4 (CH_2), 25.9 (CH_2), 21.4 (CH_2); *m/z* (ESI) 323 ($M+Na^+$, 52%); *m/z* (ESI) found [$M+Na^+$] 323.0669. $C_{12}H_{16}N_2O_5SNa^+$ requires 309.0672.

α,β-Unsaturated Methyl and Phenyl Ketones

General procedure for oxidation/Wittig

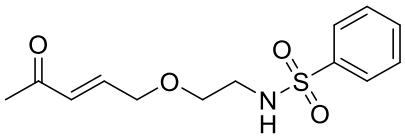
Alcohol (1 equiv.), ylide (1.2-1.5 equiv.) and manganese dioxide (8 equiv.) were suspended in a solution of chloroform (0.2M with respect to the alcohol). The suspension was heated to 70 °C and reaction progression followed by TLC and ^1H NMR. After consumption of starting material and hemiaminal the suspension is cooled to room temperature and filtered through Celite. The resulting solution was then concentrated under reduced pressure and the residue purified by flash column chromatography on silica gel in the solvent systems outlined for individual products.

General procedure for cross metathesis reactions

Hoveyda-Grubbs second generation catalyst (2-5 mol%) in dichloromethane (1/4 of total solvent, final volume 0.2M with respect to alkene) was added to a solution of alkene (1 equiv.) and methyl vinyl ketone/phenyl vinyl ketone/methylacrylate etc. (5-8 equiv.) in dichloromethane (3/4 of final volume) at 30 °C. The solution was heated at reflux for 1 h then concentrated

under reduced pressure. The residue was purified by flash column chromatography in the solvent system outlined for each individual compound.

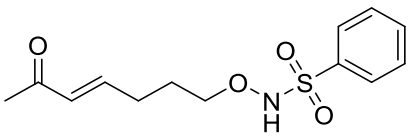
(*E*)-*N*-(2-((4-Oxopent-2-en-1-yl)oxy)ethyl)benzenesulfonamide **218**



Followed general procedure for cross metathesis reactions.

Purified by gradient elution flash column chromatography on silica gel (100%, dichloromethane to 19:1, dichloromethane/methanol) to give the product **218** (206 mg, 88%) as a light green oil. *Rf* 0.2 (7:3, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3390, 3011, 2928, 2874, 1678, 1164; δ_H (400 MHz, $CDCl_3$) 7.94-7.88 (2H, m, ArH), 7.66-7.60 (1H, m, ArH), 7.59-7.54 (2H, m, ArH), 6.72 (1H, dt, *J* 16.0, 4.5, CH), 6.25 (1H, dt, *J* 16.0, 2.0, CH), 4.94 (1H, br. t, *J* 6.0, NH), 4.12 (2H, dd, *J* 4.5, 2.0, CHC*H*$_2$O), 3.55 (2H, t, *J* 5.0, CH_2O), 3.22 (2H, dt, *J* 5.0, 6.0, CH_2N); δ_C (100 MHz, $CDCl_3$) 198.0 (C), 142.0 (CH), 139.9 (C), 132.8 (CH), 130.5 (CH), 129.2 (CH), 127.0 (CH), 69.8 (CH_2), 69.2 (CH_2), 43.0 (CH_2), 27.4 (CH_3); *m/z* (ESI) 306 ($M+Na^+$, 100%), 284 ($M+H^+$, 27%); *m/z*(ESI) found 306.0758. $C_{13}H_{17}NSO_4Na^+$ requires 306.0770.

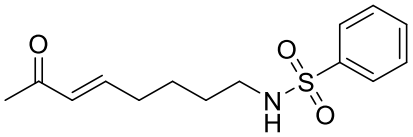
(*E*)-*N*-((6-Oxohept-4-en-1-yl)oxy)benzenesulfonamide **220**



Followed general procedure for cross metathesis reactions.

Purified by flash column chromatography on silica gel (7:3. petroleum ether/ethyl acetate) to give the product **220** (320 mg, 91%) as a light brown oil. *Rf* 0.23 (7:3, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3390, 3011, 2929, 2874, 1698, 1678, 1361, 1163; δ_H (400 MHz, $CDCl_3$) 7.97-7.91 (2H, m, ArH), 7.71-7.65 (1H, m, ArH), 7.61-7.55 (2H, m, ArH), 7.30 (1H, br.s, NH), 6.78 (1H, dt, *J* 16.0, 7.0, C=CH), 6.08 (1H, dt, *J* 16.0, 1.5, C=CH), 4.04 (2H, t, *J* 6.5, CH_2O), 2.32-2.24 (2H, m, CH_2), 2.24 (3H, s, CH_3), 1.84-1.76 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 198.7 (C), 146.9 (CH), 135.7 (C), 133.9 (CH), 131.7 (CH), 129.1 (CH), 128.5 (CH), 76.4 (CH_2), 28.8 (CH_2), 27.0 (CH_3), 26.5 (CH_2); *m/z*(ESI) 306 ($M+Na^+$, 100%), 284 ($M+H^+$, 96%); *m/z*(ESI) found 306.0766. $C_{13}H_{17}NO_4SNa^+$ requires 306.0770.

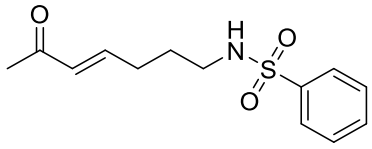
(*E*)-*N*-(7-Oxooct-5-en-1-yl)benzenesulfonamide **221**



Followed general procedure for oxidative Wittig reactions.

Purified by flash column chromatography on silica gel (2:1, petroleum ether/ethyl acetate). The resulting product was further purified by recrystallisation from ethyl acetate/petroleum ether to give the product **221** (0.15 g, 26%) as a colourless solid. m.p. 62 °C; R_f 0.2 (2:1, petroleum ether/ethyl acetate); ν_{max}(neat)/cm^{-1} 3276, 2938, 2865, 1670, 1625, 1447, 1363, 1159; δ_H (400 MHz, $CDCl_3$) 7.89-7.86 (2H, m, ArH), 7.61-7.57 (1H, m, ArH), 7.54-7.50 (2H, m, ArH), 6.72 (1H, dt, *J* 16.0, 7.0, CH), 6.03 (1H, dt, *J* 16.0, 1.5, CH), 4.79 (1H, t, *J* 6.0, NH), 2.97 (2H, td, *J* 6.5, 6.0, CH_2), 2.23 (3H, s, CH_3), 2.18 (2H, dtd, *J* 7.0, 7.0, 1.5 Hz, CH_2), 1.53-1.45 (4H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 198.6 (C), 147.3 (CH), 140.0 (C), 132.7 (CH), 131.6 (CH), 129.2 (CH), 127.0 (CH), 42.9 (CH_2), 31.7 (CH_2), 29.1 (CH_2), 27.0 (CH_3), 24.9 (CH_2); *m/z* (ESI) 304 (M+Na$^+$ 100%), 282 (M+H$^+$ 17%); *m/z* (ESI) Found 304.0961. $C_{14}H_{19}NO_3SNa^+$ requires 304.0978.

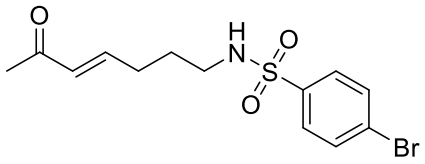
(*E*)-*N*-(6-Oxohept-4-en-1-yl)benzenesulfonamide **226**



Followed general procedure for cross metathesis reactions.

Purified by gradient elution flash column chromatography on silica gel (4:1 to 1:1, petroleum ether/ethyl acetate) to give the product **226** (60 mg, 92%) as a colourless oil; R_f 0.4 (1:1 ethyl acetate/petroleum ether); ν_{max} (neat) / cm^{-1} 3276, 2936, 1670, 1625, 1447, 1327, 1159, 1094; δ_H (400 MHz, C_6D_6) 7.89-7.80 (2H, m, Ar*H*), 7.04-6.95 (3H, m, Ar*H*), 6.26 (1H, dt, *J* 16.0 7.0, OCC*H*=CH), 5.82 (1H, dt, *J* 16.0 1.0, OCCH=C*H*), 4.70-4.57 (1H, br s, N*H*), 2.53 (2H, td, *J* 6.5 6.5, CH_2NH), 1.85 (3H, s, CH_3CO), 1.64 (2H, tdd, *J* 7.0 7.0 1.0, CH=CHCH_2), 1.09 (2H, tt, *J* 7.0 7.0, $CH_2CH_2CH_2$); δ_C (100 MHz, C_6D_6) 196.5 (C), 145.3 (CH), 141.0 (C), 132.1 (CH), 131.7 (CH), 128.9 (CH), 127.1 (CH), 42.3 (CH_2), 28.8 (CH_2), 26.6 (CH_2), 27.9 (CH_3); *m/z* (ES+) 290 (M+Na$^+$, 100%), 268 (M+H$^+$, 81); *m/z* (ES+) Found 290.0817. $C_{13}H_{17}NNaO_3S^+$ requires 290.0821.

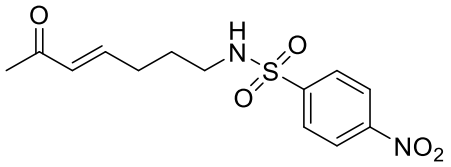
(*E*)-4-Bromo-*N*-(6-oxohept-4-en-1-yl)benzenesulfonamide **227**



Followed general procedure for cross metathesis reactions.

Purified by flash column chromatography on silica gel (7:3 petroleum ether/ethyl acetate) to give the product **227** (112 mg, 90%) as a colourless oil. *Rf* 0.24 (3:2, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1}3393, 3011, 2942, 2873, 1729, 2695, 1673, 1628, 1390, 1165, 607; δ_H (400 MHz, $CDCl_3$) 7.58 (2H, d, *J* 9.0, ArH), 7.23 (2H, d, *J* 9.0, ArH), 6.40 (1H, dt, *J* 16.0, 7.0, CH), 5.95 (1H, dt, *J* 16.0, 1.5, CH), 4.55 (1H, t, 7.0, NH), 2.57 (2H, dt, *J* 7.0, 7.0, CH_2N), 1.98 (2H, s, CH_3), 1.76 (2H, dtd, *J* 7.0, 7.0, 1.5, CH_2), 1.19 (2H, tt, *J* 7.0, 7.0, CH_2); δ_C (100 MHz, $CDCl_3$) 196.4 (C), 145.1 (CH), 137.9 (C), 132.0 (CH), 131.5 (CH), 129.0 (CH), 127.6 (C), 126.9 (CH), 42.1 (CH_2), 28.6 (CH_2), 27.7 (CH_2), 26.5 (CH_3); *m/z*(ESI) 370 ($M+Na^+$, 100%), 368 ($M+Na^+$, 99%), 348 ($M+H^+$, 46%), 346 ($M+H^+$, 43%); *m/z*(ESI) found 369.9902. $C_{13}H_{16}{}^{81}BrNO_3SNa^+$ requires 369.9906.

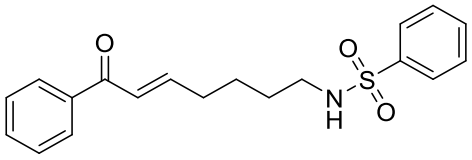
(*E*)-4-Nitro-*N*-(6-oxohept-4-en-1-yl)benzenesulfonamide **228**



Followed general procedure for cross metathesis reactions.

Purified by flash column chromatography on silica gel (7:3, petroleum ether/ethyl acetate) to give the product **228** (228 mg, 99%) as a pale brown solid. m.p. 115-118 ^oC; *Rf* 0.2 (7:3, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3391, 3105, 3008, 2944, 2873, 1732, 1695, 1628, 1608, 1535, 1415, 1350, 1166; δ_H (400 MHz, $CDCl_3$) 8.39 (2H, d, *J* 9.0, ArH), 8.07 (2H, d, *J* 9.0, ArH), 6.74 (1H, dt, *J* 16.0, 7.0, CH), 6.09 (1H, dt, *J* 16.0, 1.5, CH), 4.98 (1H, br.t, *J* 7.0, NH), 3.07 (2H, dt, *J* 7.0, 7.0, CH_2N), 2.34-2.27 (2H, m, CH_2), 2.26 (3H, s, CH_3), 1.74 (2H, tt, *J* 7.0, 7.0, CH_2); δ_C (100 MHz, $CDCl_3$) 198.5 (C), 150.1 (C), 145.8 (CH), 132.0 (CH), 128.3 (CH), 124.5 (CH), 42.7 (CH_2), 29.1 (CH_2), 28.3 (CH_2), 27.2 (CH_3); *m/z*(ESI) 335 ($M+Na^+$, 100%), 313 ($M+H^+$, 43%); *m/z*(ESI) found 355.0676. $C_{13}H_{16}N_2O_5SNa^+$ requires 335.0672.

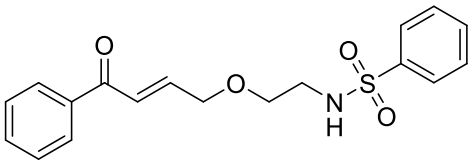
(*E*)-*N*-(7-Oxo-7-phenylhept-5-en-1-yl)benzenesulfonamide **217**



Followed general procedure for oxidative Wittig reactions.

Purified by flash column chromatography on silica gel (2:1, petroleum ether/ethyl acetate) to give the product **217** (2.47 g, 30%) as a colourless solid. m.p. 85 °C; R_f 0.2 (2:1, petroleum ether/ethyl acetate); ν_{max}(neat)/cm^{-1} 3274, 2938, 1666, 1618, 1447, 1327, 1158; δ_H (400 MHz, $CDCl_3$) 7.93-7.86 (4H, m, ArH), 7.60-7.46 (6H, m, ArH), 6.97 (1H, dt, *J* 15.5, 7.0, CH), 6.87-6.83 (1H, m, CH), 4.51 (1H, t, *J* 6.0, NH), 3.03-2.98 (2H, m, CH_2N), 2.31-2.27 (2H, m, CH_2), 1.56-1.52 (4H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 190.7 (C), 148.7 (CH), 139.9 (C), 137.8 (C), 132.8 (CH), 132.7 (CH), 129.2 (CH), 128.6 (CH), 128.6 (CH), 127.0 (CH), 126.3 (CH), 43.0 (CH_2), 32.1 (CH_2), 29.2 (CH_2), 25.1 (CH_2); *m/z* (ESI) 344 (M+H$^+$ 100%), 366 (M+Na$^+$ 21%); *m/z* (ESI) Found 344.1310. $C_{19}H_{22}NO_3S^+$ requires 344.1315.

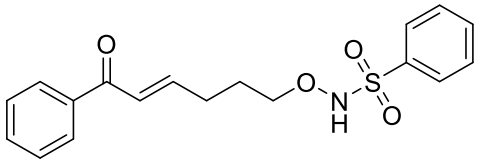
(*E*)-*N*-(2-((4-Oxo-4-phenylbut-2-en-1-yl)oxy)ethyl)benzenesulfonamide **219**



Followed general procedure for cross metathesis reactions.

Purified by flash column chromatography on silica gel (7:3, petroleum ether/ethyl acetate) to give the product **219** (91 mg, 64%) as a pale brown oil. *Rf* 0.2 (7:3, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3391, 3087, 3011, 3008, 2943, 2930, 2874, 2865, 1669, 1598, 1163; δ_H (400 MHz, $CDCl_3$) 7.99-7.94 (2H, m, ArH), 7.93-7.88 (2H, m, ArH), 7.64-7.48 (6H, m, ArH), 7.09 (1H, dt, *J* 15.5, 2.0, CH), 6.97 (1H, dt, *J* 15.5, 4.5, CH), 4.91 (1H, br. t, *J* 6.0, NH), 4.20 (2H, dd, *J* 4.5, 2.0, CHC*H*$_2$O), 3.59 (2H, t, *J* 5.0, CH_2O), 3.25 (2H, td, *J* 5.0, 6.0, CH_2N); δ_C (100 MHz, $CDCl_3$) 190.1 (C), 143.3 (CH), 139.9 (C), 137.5 (C), 133.1 (CH), 132.8 (CH), 129.2 (CH), 128.7 (2 x CH), 127.0 (CH), 125.3 (CH), 70.2 (CH_2), 69.2 (CH_2), 43.0 (CH_2); *m/z*(ESI) 368 (M+Na$^+$, 100%), 346 (M+H$^+$, 8%); *m/z*(ESI) found 368.0922. $C_{18}H_{19}NSO_4Na^+$ requires 368.0927.

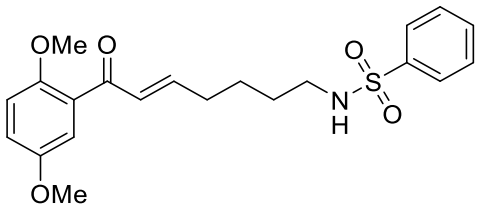
(*E*)-*N*-((6-Oxo-6-phenylhex-4-en-1-yl)oxy)benzenesulfonamide **221**



Followed general procedure for cross metathesis reactions.

Purified by flash column chromatography on silica gel (7:3, petroleum ether/ethyl acetate) to give the product **221** (228 mg, 49%) as a pale yellow oil. *Rf* 0.27 (3:2, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3285, 3067, 3011, 2949, 1671, 1621, 1448, 1387, 1335, 1172; δ_H (400 MHz, C_6D_6) 8.07-8.01 (2H, m, ArH), 7.95-7.90 (2H, m, ArH), 7.25-7.17 (3H, m, ArH), 7.11-7.00 (5H, m, ArH), 6.78 (1H, dt, *J* 15.0, 1.5, C=CH), 6.35 (1H, br.s, NH), 3.82 (2H, t, *J* 6.5, CH_2O), 2.01-1.92 (2H, m, CH_2), 1.50-1.40 (2H, m, CH_2); δ_C (100 MHz, C_6D_6) 189.6 (C), 147.9 (CH), 138.2 (C), 137.7 (C), 133.1 (CH), 132.4 (2 x CH), 128.7 (CH), 128.6 (CH), 128.5 (2 x CH), 128.1 (CH), 127.8 (CH), 127.6 (CH), 126.2 (CH), 76.1 (CH_2), 28.9 (CH_2), 26.5 (CH_2); *m/z*(ESI) 368 (M+Na^+, 52%), 346 (M+H^+, 100%); *m/z*(ESI) found 346.1123. $C_{18}H_{20}NO_4S^+$ requires 346.1108.

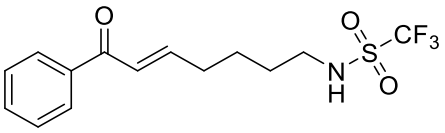
(*E*)-*N*-(7-(2,5-Dimethoxyphenyl)-7-oxohept-5-en-1-yl)benzenesulfonamide **222**



Followed general procedure for cross metathesis reactions.

Purified by gradient flash column chromatography on silica gel (gradient elution 7:3, petroleum ether/ethyl acetate to 2:1, petroleum ether/ethyl acetate) to give the product **222** (260 mg, 85%) as a pale yellow oil. R_f 0.08 (7:3, petroleum ether/ethyl acetate); ν_{max}($CHCl_3$)/cm^{-1} 3392, 3053, 3006, 2943, 1659, 1619, 1604, 1495, 1413, 1163; δ_H (400 MHz, $CDCl_3$) 7.92-7.85 (2H, m, ArH), 7.62-7.48 (3H, m, ArH), 7.08 (1H, d, *J* 3.0, ArH), 7.01 (1H, dd, *J* 9.0, 3.0, ArH), 6.91 (1H, d, *J* 9.0, ArH), 6.81 (1H, dt, *J* 15.5, 6.5, CH), 6.69 (1H, dt, *J* 15.0, 1.0, CH), 4.55 (1H, br.t, *J* 6.5, NH), 3.83 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 2.99 (2H, dt, *J* 6.5, 6.5, CH_2N), 2.24 (2H, dtd, 7.0, 6.5, 1.0, *CH_2*CH), 1.59-1.44 (4H, m, 2 x CH_2); δ_c (100 MHz, $CDCl_3$) 192.8 (C), 153.5 (C), 152.3 (C), 147.4 (CH), 139.9 (C), 132.7 (CH), 130.9 (CH), 129.5 (C), 129.1 (CH), 127.0 (CH), 118.8 (CH), 114.4 (CH), 113.3 (CH), 56.4 (CH_3), 55.9 (CH_3), 43.0 (CH_2), 31.8 (CH_2), 29.1 (CH_2), 25.0 (CH_2); *m/z* (ESI) 426 (M+Na^+ 100%), 404 (M+H^+ 42%); *m/z* (ESI) Found 426.1348. $C_{21}H_{25}NO_5SNa^+$ requires 426.1346.

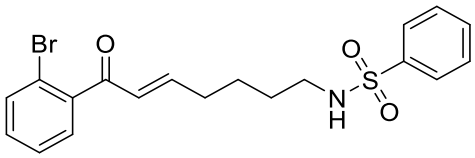
(*E*)-1,1,1-Trifluoro-*N*-(7-oxo-7-phenylhept-5-en-1-yl)methanesulfonamide **223**



Followed general procedure for cross metathesis reactions.

Purified by flash column chromatography on silica gel (4:1, petroleum ether/ethyl acetate) to give the product **223** (162 mg, 76%) as a yellow oil. *Rf* 0.13 (9:1, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3386, 3011, 2942, 2866, 1670, 1621, 1428, 1375, 609; δ_H (400 MHz, $CDCl_3$) 7.93 (2H, dd, *J* 7.0, 1.5, ArH), 7.63-7.58 (1H, m, ArH), 7.54-7.47 (2H, m, ArH), 7.05 (1H, dt, *J* 15.5, 6.5, C=CH), 6.94 (1H, dt, *J* 15.5, 1.5, C=CH), 4.96 (1H, br.s, NH), 3.43-3.33 (2H, dt, *J* 6.5, 6.5, CH_2), 2.40 (2H, dt, *J* 6.5, 6.5, CH_2), 1.77-1.58 (4H. m, 2 x CH_2); δ_C (100 MHz, $CDCl_3$) 190.8 (C), 148.3 (CH), 137.7 (C), 132.9 (2 x CH), 128.6 (CH), 126.5 (CH), 119.8 (C, q, *J* 320.0, CF_3), 44.2 (CH_2), 32.0 (CH_2), 29.8 (CH_2), 24.8 (CH_2); *m/z* (ESI) 358 ($M+H^+$, 72%), 336 ($M+H^+$, 100%); *m/z* (ESI) found 336.0889. $C_{14}H_{18}F_3NO_3S^+$ requires 336.0876.

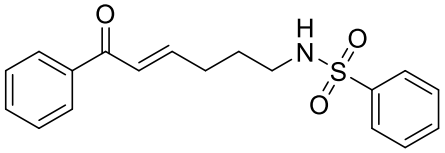
(*E*)-*N*-(7-(2-Bromophenyl)-7-oxohept-5-en-1-yl)benzenesulfonamide **225**



Followed general procedure for cross metathesis reactions.

Purified by flash column chromatography on silica gel (7:3, petroleum ether/ethyl acetate) to give the product **225** (158 mg, 59%) as a pale brown oil. *Rf* 0.40 (3:2, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3392, 3011, 2939, 2864, 1656, 1618, 1446, 1331, 1162, ; δ_H (400 MHz, $CDCl_3$) 7.92-7.85 (2H, m, ArH), 7.67-7.58 (2H, m, ArH), 7.58-7.51 (2H, m, ArH), 7.44-7.37 (1H, m, ArH), 7.36-7.30 (2H, m, ArH), 6.62 (1H, dt, *J* 16.0, 7.0, CH), 6.42 (1H, d, *J* 16.0, CH), 4.46 (1H, br.t, *J* 6.0, NH), 2.99 (2H, dt, *J* 6.5, 6.5, CH_2N), 2.26 (2H, dt, *J* 7.0, 6.5, CH_2), 1.58-1.44 (4H, m, 2xCH_2); δ_C (100 MHz, $CDCl_3$) 195.0 (C), 151.6 (CH), 140.9 (C), 139.9 (C), 133.3 (CH), 132.7 (CH), 131.2 (CH), 130.6 (CH), 129.2 (CH), 128.9 (CH), 127.3 (CH), 127.0 (CH), 119.3 (C), 42.9 (CH_2), 30.0 (CH_2), 29.2 (CH_2), 24.7 (CH_2); *m/z*(ESI) 446 (^{81}Br, $M+Na^+$, 40%), 444 (^{79}Br, $M+Na^+$, 39%), 424 (^{81}Br, $M+H^+$, 100%), 422 (^{79}Br, $M+H^+$, 97%); *m/z*(ESI) found 424.0439. $C_{19}H_{21}{}^{81}BrNO_3S^+$ requires 424.0400.

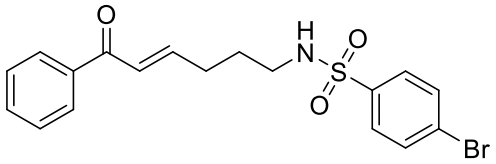
(*E*)-N-(6-Oxo-6-phenylhex-4-en-1-yl)benzenesulfonamide **226**



Followed general procedure for cross metathesis reactions.

Purified by flash column chromatography on silica gel (3:1, petroleum ether/ethyl acetate) to give the product **226** (111 mg, 76%) as a light brown oil. *Rf* 0.4 (3:2, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3690, 3393, 3011, 2941, 2872, 1671, 1651, 1622, 1600, 1579, 1448, 1332, 1163; δ_H (400 MHz, C_6D_6) 8.07 (2H, dd, *J* 8.0, 1.5, ArH), 7.94-7.86 (2H, m, ArH), 7.30-7.18 (3H, m, ArH), 7.09-7.03 (3H, m, ArH), 6.98 (1H, dt, *J* 15.0, 7.0, CH), 6.77 (1H, dt, *J* 15.0, 1.5, CH), 4.13-4.04 (1H, br.m, NH), 2.59 (2H, dt, *J* 7.0, 7.0, CH_2N), 1.86 (2H, dtd, *J* 7.0, 7.0, 1.5, CH_2), 1.15 (2H, tt, *J* 7.0, 7.0, CH_2); δ_C (100 MHz, $CDCl_3$) 189.1 (C), 147.1 (CH), 141.1 (C), 138.3 (C), 132.4 (2 x CH), 132.0 (CH), 127.8 (2 x CH), 127.0 (CH), 126.4 (CH), 42.1 (CH_2), 29.1 (CH_2), 27.9 (CH_2); *m/z*(ESI) 352 ($M+Na^+$, 100%), 330 ($M+H^+$, 6%); *m/z*(ESI) found 352.0974. $C_{18}H_{19}NO_3SNa^+$ requires 352.0978.

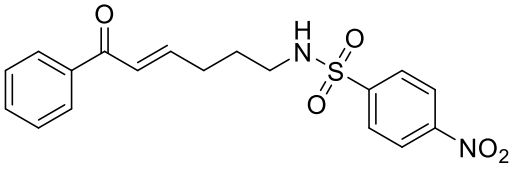
(*E*)-4-Bromo-*N*-(6-oxo-6-phenylhex-4-en-1-yl)benzenesulfonamide **227**



Followed general procedure for cross metathesis reactions.

Purified by flash column chromatography on silica gel (7:3, petroleum ether/ethyl acetate) to give the product **227** (118 mg, 66%) as a colourless oil. *Rf* 0.4 (3:2, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1}3690, 3392, 3008, 2944, 2873, 1670, 1652, 1622, 1599, 1577, 1339, 1164, 607; δ_H (400 MHz, $CDCl_3$) 8.08-8.03 (2H, m, ArH), 7.61 (2H, d, *J* 8.5, ArH), 7.29-7.20 (5H, m,ArH), 7.03 (1H, dt, *J* 15.0, 7.0, CH), 6.83 (1H, dt, *J* 15.0, 1.5, CH), 4.80 (1H, br.t, *J* 7.0, NH), 2.65 (2H, dt, *J* 7.0, 7.0, CH_2N), 1.97 (2H, dtd, *J* 7.0, 7.0, 1.5, CH_2), 1.31 (2H, tt, *J* 7.0, 7.0, CH_2); δC (100 MHz, $CDCl_3$) 189.4 (C), 147.3 (CH), 139.8 (C), 138.1 (C), 132.5 (CH), 132.2 (CH), 128.6 (CH), 127.1 (C), 126.5 (CH), 42.20 (CH_2), 29.2 (CH_2), 27.9 (CH_2); *m/z*(ESI) 432 ($M+Na^+$, 100%, ^{81}Br), 431 ($M+Na^+$, 95%, ^{80}Br); *m/z*(ESI) found 432.0074. $C_{18}H_{18}NO_3S^{81}BrNa^+$ requires 432.0063.

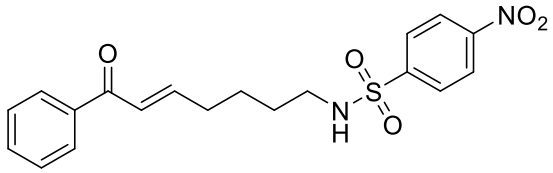
(*E*)-4-Nitro-*N*-(6-oxo-6-phenylhex-4-en-1-yl)benzenesulfonamide **228**



Followed general procedure for cross metathesis reactions.

Purified by recrystallisation from petroleum ether/ethyl acetate to give the product **228** (153 mg, 55%) as an off white powder. m.p. 124-126 °C; *Rf* 0.3 (3:2, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3392, 3105, 3008, 2938, 2873, 1671, 1651, 1622, 1607, 1534, 1350, 1166, 1093, 611; δ_H (400 MHz, $CDCl_3$) 8.37 (2H, d, *J* 9.0, ArH), 8.08 (2H, d, *J* 9.0, ArH), 7.94 (2H, d, *J* 8.5, ArH), 7.60 (1H, dddd, *J* 7.5, 7.5, 1.0, 1.0, ArH), 7.50 (2H, dd, *J* 7.5, 7.5, ArH), 7.03-6.89 (2H, m, HC=CH), 4.89 (1H, br.t, *J* 7.0, NH), 3.11 (2H, dt, *J* 7.0, 7.0, CH_2N), 2.41 (2H, dtd, *J* 7.0, 7.0, 1.0, C=CH_2), 1.80 (2H, tt, *J* 7.0, 7.0, CH_2); δ_C (100 MHz, $CDCl_3$) 190.4 (C), 150.1 (C), 147.1 (CH), 145.9 (C), 137.6 (C), 133.0 (CH), 128.7 (CH), 128.6 (CH), 128.3 (CH), 126.9 (CH), 124.5 (CH), 42.7 (CH_2), 29.5 (CH), 28.4 (CH); *m/z*(ESI) 397 (M+Na^+, 100%), 375 (M+H^+, 62%); *m/z*(ESI) found 397.0802. $C_{18}H_{18}N_2O_5SNa^+$ requires 397.0829.

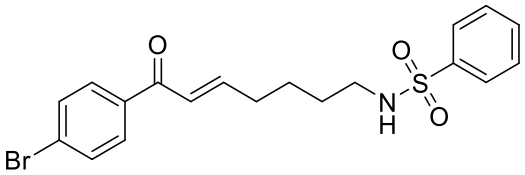
(*E*)-*N*-(7-Oxo-7-phenylhept-5-en-1-yl)-4-nitrobenzenesulfonamide **259**



Followed general procedure for oxidative Wittig reactions.

Purified by flash column chromatography on silica gel (2:1, petroleum ether/ethyl acetate). The resulting product was recrystalised from petroleum ether/ethyl acetate to give the product **259** (110 mg, 8%) as a light yellow solid. m.p. 110 °C; R_f 0.2 (2:1, petroleum ether/ethyl acetate); ν_{max}($CHCl_3$)/cm^{-1} 3278, 2938, 2865, 1666, 1616, 1529, 1349, 1163; δ_H (400 MHz, $CDCl_3$) 8.39-8.36 (2H, m, ArH), 8.07-8.04 (2H, m, ArH), 7.93-7.91 (2H, m, ArH), 7.58 (1H, dddd, *J* 7.5, 7.5, 2.0, 2.0 ArH), 7.50-7.47 (2H, m, ArH), 6.99 (1H, dt, *J* 15.5, 6.5, CH), 6.88 (1H, dt, *J* 15.5, 1.0, CH), 4.65 (1H, t, *J* 6.5, NH), 3.09-3.04 (2H, m, CH_2), 2.35-2.31 (2H, m, CH_2), 1.60-1.56 (4H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 190.7 (C), 150.1 (C), 148.5 (CH), 146.0 (C), 137.7 (C), 132.9 (CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 126.4 (CH), 124.5 (CH), 43.2 (CH_2), 32.0 (CH_2), 29.3 (CH_2), 25.0 (CH_2); *m/z* (ESI) 411 (M+Na^+ 100%); *m/z* (ESI) Found 411.0990. $C_{19}H_{20}N_2O_5SNa^+$ requires 411.0985.

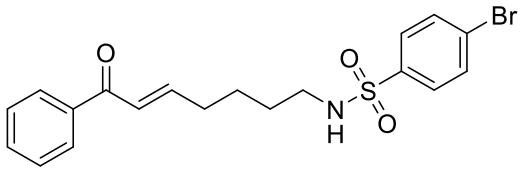
(*E*)-*N*-(7-(4-Bromophenyl)-7-oxohept-5-en-1-yl)benzenesulfonamide **260**



Followed general procedure for oxidative Wittig reactions.

Purified by column chromatography on silica gel (9:1, toluene/ethyl acetate). The resulting product was recrystalised from petroleum ether/ethyl acetate to give the product **260** (80 mg, 4%) as a colourless solid. m.p. 95 °C; R_f 0.2 (9:1, toluene/ethyl acetate); $\nu_{max}(CHCl_3)/cm^{-1}$ 3393, 3010, 2924, 2867, 1731, 1669, 1619, 1586, 1331, 1162; δ_H (400 MHz, $CDCl_3$) 7.88-7.86 (2H, m, ArH), 7.81-7.78 (2H, m, ArH), 7.63-7.51 (5H, m, ArH), 6.99 (1H, dt, *J* 15.5, 7.0, CH), 6.82 (1H, dt, *J* 15.5, 1.0, CH), 4.34 (1H, t, *J* 6.0, NH), 3.04-2.99 (2H, m, CH_2), 2.32-2.28 (2H, m, CH_2), 1.57-1.53 (4H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 189.5 (C), 149.3 (CH), 136.5 (C), 132.7 (CH), 131.9 (CH), 130.1 (C), 129.2 (CH), 127.9 (C), 127.0 (CH), 125.8 (CH), 42.9 (CH_2), 32.1 (CH_2), 29.2 (CH_2), 25.0 (CH_2); *m/z* (ESI) 446 ($M^{81}Br+Na^+$, 100%), 444 ($M^{79}Br+Na^+$, 95); *m/z* (ESI) Found 446.0232. $C_{19}H_{20}{}^{81}BrNO_3SNa^+$ requires 446.0219.

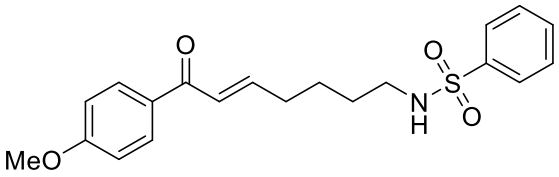
(*E*)-4-Bromo-*N*-(7-oxo-7-phenylhept-5-en-1-yl)benzenesulfonamide **261**



Followed general procedure for oxidative Wittig reactions.

Purified by flash column chromatography on silica gel (4:1, petroleum ether/ethyl acetate). The resulting product was further purified by recrystallisation from petroleum ether/ethyl acetate to give the product **261** (855 mg, 22%) as a pale yellow solid. m.p. 84-87 °C; *Rf* 0.3 (7:3, petroleum ether/ethyl acetate); ν_{max} $(CHCl_3)/cm^{-1}$ 3011, 2947, 2868, 1711, 1684, 1156, 621; δ_H (400 MHz, $CDCl_3$) 7.94 (2H, d, *J* 8.0 ArH), 7.75 (2H, d, *J* 8.0, ArH), 7.68 (2H, d, *J* 8.0, ArH), 7.62-7.55 (1H, m, ArH), 7.53-7.47 (2H, m, ArH), 7.00 (1H, dt, *J* 16.0, 6.5, CH), 6.89 (1H, dt, *J* 16.0, 1.5, CH), 4.39 (1H, t, *J* 6.5, NH), 3.06-2.98 (2H, m, CH_2), 2.37-2.28 (2H, m, CH_2), 1.65-1.48 (4H, m, 2xCH_2); δ_C (100 MHz, $CDCl_3$) 190.7 (C), 148.5 (CH), 139.0 (C), 137.8 (C), 132.8 (CH), 132.5 (CH), 128.6 (CH), 128.5 (CH), 127.7 (C), 126.4 (CH), 43.0 (CH_2), 32.1 (CH_2), 29.2 (CH_2), 25.1 (CH_2); *m/z* (ESI) 446 ($M^{81}Br+Na^+$, 40%), 444 ($M^{79}Br+Na^+$, 39%), 424 ($M^{81}Br+H^+$, 49%), 422 ($M^{79}Br+H^+$, 46%); *m/z* (ESI) found 446.0221. $C_{19}H_{20}NSO_3{}^{81}BrNa^+$ requires 446.0219.

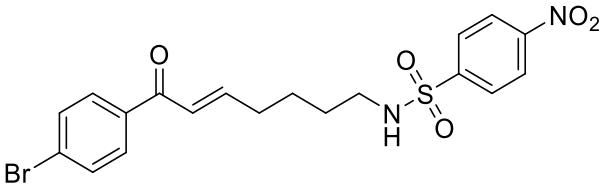
(*E*)-*N*-(7-(4-Methoxyphenyl)-7-oxohept-5-en-1-yl)benzenesulfonamide **262**



Followed general procedure for oxidative Wittig reactions.

Purified by flash column chromatography on silica gel (1:1, petroleum ether/ethyl acetate). The resulting product was recrystalised from petroleum ether/ethyl acetate to give the product **262** (371 mg, 20%) as a pale yellow solid. m.p. 84 °C; R_f 0.2 (1:1, petroleum ether/ethyl acetate); $\nu_{max}(CHCl_3)/cm^{-1}$ 3392, 3011, 2939, 1666, 1618, 1599, 1332, 1260, 1168; δ_H (400 MHz, $CDCl_3$) 7.96-7.92 (2H, m, ArH), 7.88-7.86 (2H, m, ArH), 7.59-7.49 (3H, m, ArH), 6.98-6.91 (3H, m, ArH), 6.86 (1H, dt, *J* 15.5, 1.0, CH), 4.63 (1H, t, *J* 6.0, NH), 3.88 (3H, s, CH_3), 3.02-2.97 (2H, m, CH_2), 2.29-2.24 (2H, m, CH_2), 1.54-1.52 (4H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 188.9 (C), 171.2 (C), 147.6 (CH), 140.0 (C), 132.7 (CH), 130.9 (CH), 130.7 (C), 129.2 (CH), 127.0 (CH), 126.0 (CH), 113.8 (CH), 55.5 (CH_3), 43.0 (CH_2), 32.0 (CH_2), 29.2 (CH_2), 25.1 (CH_2); *m/z* (ESI) 396 ($M+Na^+$ 100%); *m/z* (ESI) Found 396.1240. $C_{20}H_{23}NO_4SNa^+$ requires 396.1240.

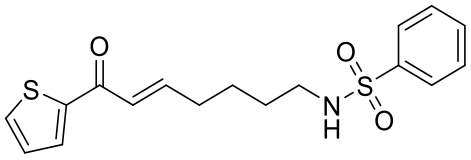
(*E*)-*N*-(7-(4-Bromophenyl)-7-oxohept-5-en-1-yl)-4-nitrobenzenesulfonamide **263**



Followed general procedure for oxidative Wittig reactions.

Purified by flash column chromatography on silica gel (2:1, petroleum ether/ethyl acetate). The resulting product was recrystallised from petroleum ether/ethyl acetat to give the product **263** (180 mg, 12%) as a light brown solid. m.p. 95 °C; R_f 0.2 (2:1, petroleum ether/ethyl acetate); $\nu_{max}(CHCl_3)/cm^{-1}$ 3392, 3011, 2942, 2867, 1670, 1619, 1586, 1534, 1350, 1166; δ_H (400 MHz, $CDCl_3$) 8.39-8.35 (2H, m, ArH), 8.08-8.03 (2H, m, ArH), 7.79-7.76 (2H, m, ArH), 7.63-7.60 (2H, m, ArH), 6.99 (1H, dt, *J* 15.5, 7.0 CH), 6.83 (1H, dt, *J* 15.5, 1.0, CH), 4.82 (1H, t, *J* 6.0, NH), 3.08-3.03 (2H, m, CH_2), 2.34-2.30 (2H, m, CH_2), 1.61-1.53 (4H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 189.4 (C), 150.1 (C), 149.0 (CH), 145.9 (C), 136.4 (C), 131.9 (CH), 130.1 (CH), 128.3 (CH), 128.0 (C), 125.9 (CH), 124.5 (CH), 43.1 (CH_2), 32.1 (CH_2), 29.3 (CH_2), 25.0 (CH_2); *m/z* (ESI) 491 ($M^{81}Br+Na^+$, 100%), 489 ($M^{79}Br+Na^+$, 94); *m/z* (ESI) Found 491.0062. $C_{19}H_{19}{}^{81}BrN_2O_5SNa^+$ requires 491.0070.

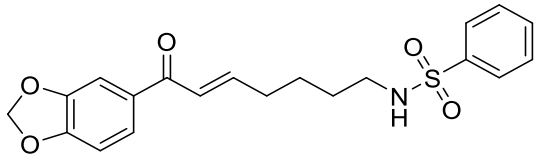
(*E*)-*N*-(7-Oxo-7-(thiophen-2-yl)hept-5-en-1-yl)benzenesulfonamide **264**



Followed general procedure for oxidative Wittig reactions.

Purified by flash column chromatography on silica gel (2:1, petroleum ether/ethyl acetate). The resulting product was recrystalised from petroleum ether/ethyl acetate to give the product **264** (170 mg, 8%) as a pale yellow solid. m.p. 90 °C; R_f 0.2 (2:1, petroleum ether/ethyl acetate); $\nu_{max}(CHCl_3)/cm^{-1}$ 3393, 3011, 2942, 1659, 1614, 1416, 1332, 1162; δ_H (400 MHz, $CDCl_3$) 7.89-7.86 (2H, m, ArH), 7.76 (1H, dd, *J* 4.0, 1.0, ArH), 7.66 (1H, dd, *J* 5.0, 1.0, ArH), 7.60-7.50 (3H, m, ArH), 7.16 (1H, dd, *J* 5.0, 4.0, ArH), 7.02 (1H, dt, *J* 15.5, 7.0, CH), 6.77 (1H, dt, *J* 15.5, 1.5, CH), 4.65 (1H, t, *J* 6.0, NH), 2.97 (2H, m, CH_2), 2.30-2.25 (2H, m, CH_2), 1.55-1.52 (4H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 182.2 (C), 147.9 (CH), 145.0 (C), 139.9 (C), 133.9 (CH), 132.7 (CH), 132.0 (CH), 129.2 (CH), 128.2 (CH), 127.0 (CH), 125.8 (CH), 42.9 (CH_2), 31.9 (CH_2), 29.1 (CH_2), 25.0 (CH_2); *m/z* (ESI) 350 ($M+H^+$ 100%), 372 ($M+Na^+$ 94%); *m/z* (ESI) Found 350.0875. $C_{20}H_{23}NO_4SNa^+$ requires 350.0879.

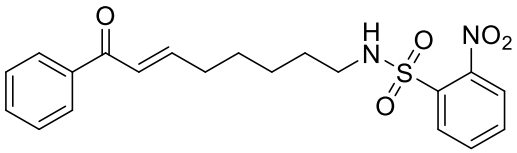
(*E*)-*N*-(7-(Benzo[*d*][1,3]dioxol-5-yl)-7-oxohept-5-en-1-yl)benzenesulfonamide **265**



Followed general procedure for oxidative Wittig reactions.

Purified by flash column chromatography on silica gel (7:3, petroleum ether/ ethyl acetate). The resulting product was recrystalised from petroleum ether/ethyl acetate to give the product **265** (180 mg, 9%) as a colourless solid. m.p. 101 °C; R_f 0.2 (7:3, petroleum ether/ethyl acetate); $\nu_{max}(CHCl_3)/cm^{-1}$ 3393, 3011, 2929, 2858, 1664, 1621, 1602, 1444, 1358, 1251, 1162; δ_H (400 MHz, $CDCl_3$) 7.89-7.86 (2H, m, ArH), 7.60-7.50 (4H, m, ArH), 7.44 (1H, d, *J* 1.5, ArH), 6.95 (1H, dt, *J* 15.5, 7.0, CH), 6.87 (1H, d, *J* 8.0, ArH), 6.81 (1H, dt, *J* 15.5, 1.5, CH), 6.05 (2H, s, CH_2), 4.59 (1H, t, *J* 6.0, NH), 3.02-2.99 (2H, m, CH_2), 2.29-2.24 (2H, m, CH_2), 1.54-1.52 (4H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 188.4 (C), 151.7 (C), 148.3 (C), 147.9 (CH), 140.0 (C), 132.7 (CH), 132.6 (C), 129.2 (CH), 127.0 (CH), 125.9 (C), 124.8 (CH), 108.4 (CH), 107.9 (CH), 101.9 (CH_2), 43.0 (CH_2), 32.0 (CH_2), 29.2 (CH_2), 25.1 (CH_2); *m/z* (ESI) 410 ($M+Na^+$ 100%); *m/z* (ESI) Found 410.1032. $C_{20}H_{21}NO_5SNa^+$ requires 410.1033.

(*E*)-2-Nitro-*N*-(8-oxo-8-phenyloct-6-en-1-yl)benzenesulfonamide **274**

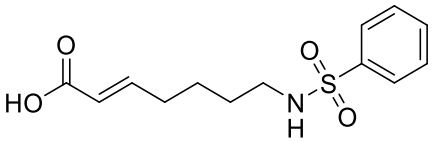


Followed general procedure for oxidative Wittig reactions.

Purified by flash column chromatography on silica gel (13:7, petroleum ether/ethyl acetate) to give the product **274** (381 mg, 60%) as a colourless oil; R_f 0.25 (3:2 petroleum ether/ ethyl acetate); ν_{max} ($CHCl_3$) / cm^{-1} 3691, 3382, 3086, 3049, 3041, 2934, 2860, 1668, 1620, 1542, 1418, 1361, 1301, 1171; δ_H (400 MHz, $CDCl_3$) 8.20-8.11 (1H, m, ArH), 8.00-7.92 (2H, m, ArH), 7.90-7.82 (1H, m, ArH), 7.80-7.68 (2H, m, ArH), 7.62-7.54 (1H, m, ArH), 7.53-7.45 (2H, m, ArH), 7.06-6.95 (1H, m, CH), 6.88 (1H, dt, *J* 15.5, 1.5, CH), 5.31 (1H, br.t, *J* 5.5, NH), 3.13 (2H, dt, *J* 7.0, 7.0, CH_2), 2.31 (2H, dt, *J* 7.0, 7.0, CH_2), 1.65-1.33 (6H, m, 3 x CH_2); δ_C (100 MHz, $CDCl_3$) 190.8 (C), 149.2 (CH), 137.9 (C), 133.7 (C), 133.6 (CH), 132.8 (CH), 132.7 (CH), 131.1 (CH), 128.6 (CH), 128.5 (CH), 126.2 (CH), 125.4 (CH), 43.7 (CH_2), 32.5 (CH_2), 29.4 (CH_2), 27.6 (CH_2), 26.1 (CH_2); *m/z* (ESI) 425 ($M+Na^+$, 100%), 403 ($M+H^+$, 18); *m/z* (ESI) found ($M+Na^+$) 425.1167. $C_{20}H_{22}N_2O_5SNa^+$ requires 425.1142.

α,β-Unsaturated Acids, Esters, Thioesters, Amides etc.

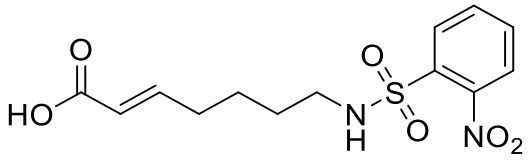
(*E*)-7-(Phenylsulfonamido)hept-2-enoic acid **199**



Followed general procedure for cross metathesis reactions.

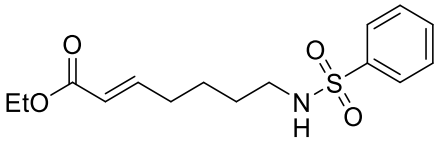
Purified by flash chromatography on silica gel (1:1, petroleum ether/ethyl acetate) to give the product **199** (192 mg, 87%) as a pale brown solid. R_f 0.3 (19:1 dichloromethane/methanol); δ_H (400 MHz, $CDCl_3$) 7.92-7.86 (2H, m, ArH), 7.65-7.52 (3H, m, ArH), 7.01 (1H, dt, *J* 15.5, 7.0, CH), 5.82 (1H, dt, *J* 15.5, 1.5, CH), 4.69 (1H, t, *J* 6.0, NH), 3.01 (2H, dt, *J* 7.0, 6.0, CH_2N), 2.22 (2H, dtd, *J* 7.0, 7.0, 1.5, CH_2CH), 1.58-1.40 (4H, m, 2 x CH_2); δ_C (100 MHz, $CDCl_3$) 171.2 (C), 151.2 (CH), 139.9 (C), 132.7 (CH), 129.2 (CH), 127.0 (CH), 121.0 (CH), 42.8 (CH_2), 31.6 (CH_2), 29.0 (CH_2), 24.7 (CH_2); *m/z* (ESI) 282 ($M-H^+$ 100%); *m/z* (ESI) Found 282.0801. $C_{13}H_{16}NO_4S^-$ requires 282.0806.

(*E*)-7-((2-nitrophenyl)sulfonamido)hept-2-enoic acid **199b**



tert-Butyl (*E*)-7-((2-nitrophenyl)sulfonamido)hept-2-enoate **205b** (3.29 g, 8.57 mmol) was dissolved in dichloromethane (43 mL) and trifluoroacetic acid (3.3 mL, 43.0 mmol, 5 equiv.) was added and the reaction allowed to stir for 16 h. The solution was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient elution 3:2, petroleum ether/ethyl actetae to neat ethyl acetate) to give the product **199b** (2.42 g, 86%) as a white solid. m.p.. 121-127 °C. R_f 0.13 (3: 2, petroleum ether/ethyl acetate); $\nu_{max}(CHCl_3)/cm^{-1}$ 3525, 3380, 1727, 1697, 1655, 1542, 1419, 1361, 1170; δ_H (400 MHz, DMSO-d6) 12.14 (1H, s, COOH), 8.08 (1H, t, *J* 6.0, NH), 8.03-7.98 (1H, m, ArH), 7.97-7.92 (1H, m, ArH), 7.90-7.81 (2H, m, ArH), 6.75 (1H, dt, *J* 15.5, 7.0, CH), 5.72 (1H, d, *J* 15.5, CH), 2.91 (2H, dt, *J* 7.0, 6.5, CH_2N), 2.11 (2H, br.dt, *J* 7.0, 7.0, *CH*$_2$CH), 1.46-1.32 (4H, m, 2 x CH_2); δ_C (100 MHz, $CDCl_3$) 167.5 (C), 148.9 (CH), 148.2 (C), 134.4 (CH), 133.3 (C), 133.0 (CH), 129.9 (CH), 124.8 (CH), 122.6 (CH), 42.8 (CH_2), 31.2 (CH_2), 29.0 (CH_2), 24.9 (CH_2); *m/z* (ESI) 351 ($M+Na^+$ 100%); *m/z* (ESI) Found 351.0618. $C_{13}H_{16}N_2O_6SNa^+$ requires 351.0621.

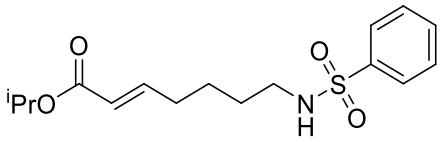
Ethyl (*E*)-7-(phenylsulfonamido)hept-2-enoate **202**



Followed general procedure for oxidative Wittig reactions.

Purified by flash column chromatography on silica gel (4:1, petroleum ether/ethyl acetate) to give the product **202** (165 mg, 84%) as a light brown oil. R_f 0.17 (4:1, petroleum ether/ethyl acetate); $\nu_{max}(CHCl_3)/cm^{-1}$ 3392, 3283, 3011, 2985, 2941, 2866, 1710, 1655, 1370, 1180; δ_H (400 MHz, $CDCl_3$) 7.94-7.82 (2H, m, ArH), 7.66-7.49 (3H, m, ArH), 6.88 (1H, dt, *J* 15.5, 7.0, CH), 5.78 (1H, dt, *J* 15.5, 1.5, CH), 4.61 (1H, t, *J* 6.0, NH), 4.19 (2H, q, *J* 7.0, OC*H*$_2$CH$_3$), 2.99 (2H, q, *J* 6.5, NCH_2), 2.17 (2H, qd, *J* 7.0, 1.5, CH*CH*$_2$), 1.56-1.40 (4H, m, 2 CH_2), 1.30 (3H, t, *J* 7.0, OCH_2*CH*$_3$); δ_C (100 MHz, $CDCl_3$) 166.6 (C), 148.2 (CH), 139.9 (C), 132.7 (CH), 129.1 (CH), 127.0 (CH), 121.8 (CH), 60.2 (CH_2), 42.9 (CH_2), 31.4 (CH2), 29.0 (CH_2), 24.9 (CH_2), 14.3 (CH_3); *m/z* (ESI) 334 ($M+Na^+$ 100%), 312 ($M+H^+$ 97%); *m/z* (ESI) Found 334.1086. $C_{15}H_{21}NO_4SNa^+$ requires 334.1083.

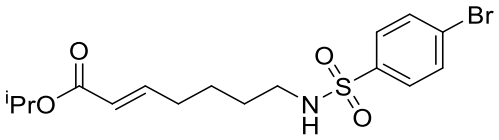
Isopropyl (*E*)-7-(phenylsulfonamido)hept-2-enoate **203**



Followed general procedure for oxidative Wittig reactions.

Purified by flash column chromatography on silica gel (7:3, petroleum ether/ethyl acetate) to give the product **203** (90 mg, 74%) as a light brown oil. R_f 0.31 (7:3, petroleum ether/ethyl acetate); $\nu_{max}(CHCl_3)/cm^{-1}$ 3392, 3009, 2984, 2940, 2866, 1707, 1655, 1331, 1311, 1162, 909; δ_H (400 MHz, $CDCl_3$) 7.93-7.85 (2H, m, ArH), 7.64-7.50 (3H, m, ArH), 6.86 (1H, dt, *J* 15.5, 7.0, CH), 5.76 (1H, dt, *J* 15.5, 1.5, CH), 5.06 (1H, sept, *J* 6.5, *CH*CH_3), 4.61 (1H, t, *J* 6.5, NH), 2.98 (2H, dt, *J* 6.5, 6.5, CH_2N), 2.16 (2H, dtd, *J* 7.0, 7.0, 1.5, CH*CH*$_2$), 1.56-1.41 (4H, m, 2 x CH2), 1.28 (6H, d, *J* 6.5, 2 x CH*CH*$_3$); δ_C (100 MHz, $CDCl_3$) 166.1 (C), 147.8 (CH), 139.9 (C), 132.7 (CH), 129.2 (CH), 127.0 (CH), 122.3 (CH), 67.5 (CH), 42.9 (CH_2), 31.4 (CH_2), 29.1 (CH_2), 24.9 (CH_2), 21.9 (CH_3); *m/z* (ESI) 348 ($M+Na^+$ 100%), 326 ($M+H^+$ 33%); *m/z* (ESI) Found 348.1237. $C_{16}H_{23}NO_4SNa^+$ requires 348.1240.

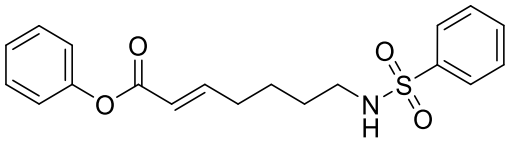
Isopropyl (*E*)-7-((4-bromophenyl)sulfonamido)hept-2-enoate **203b**



Followed general procedure for oxidative Wittig reactions.

Purified by flash column chromatography on silica gel (3:2, petroleum ether/ethyl acetate) to give the product **203b** (667 mg, 84%) as a brown oil. R_f 0.29 (3:2, petroleum ether/ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.77-7.64 (4H, m, ArH), 6.88 (1H, dt, *J* 15.5, 7.0, CH), 5.78 (1H, dt, *J* 15.5, 1.5, CH), 5.05 (6H, hept., *J* 6.0, *CH*$(CH_3)_2$), 5.00 (1H, t, *J* 6.0, NH), 2.97 (2H, dt, *J* 7.0, 6.0, CH_2N), 2.17 (2H, dtd, *J* 7.0, 7.0, 1.5, *CH*$_2$CH), 1.58-1.41 (4H, m, 2 x CH_2);δ_C (100 MHz, $CDCl_3$) 166.2 (C), 147.8 (CH), 139.1 (C), 132.4 (CH), 128.6 (CH), 127.6 (C), 122.3 (CH), 67.6 (CH), 42.9 (CH_2), 31.4 (CH_2), 29.0 (CH_2), 24.9 (CH_2), 21.9 (CH_3); *m/z* (ESI) 428 ($M^{81}Br+Na^+$ 100%), 426 ($M^{79}Br+Na^+$, 98), 406 ($M^{81}Br+H^+$ 66%), 404 ($M^{79}Br+H^+$, 65); *m/z* (ESI) Found 428.0329. $C_{16}H_{22}NO_4S^{81}BrNa^+$ requires 428.0325.

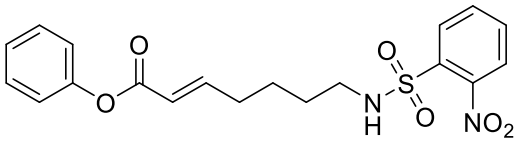
Phenyl (*E*)-7-(phenylsulfonamido)hept-2-enoate **204**



Followed general procedure for cross metathesis reactions.

Purified by flash column chromatography on silica gel (7:3, petroleum ether/ethyl acetate) to give the product **204** (213 mg, 98%) as a light brown oil. R_f 0.17 (4:1, petroleum ether/ethyl acetate); $\nu_{max}(CHCl_3)/cm^{-1}$ 3393, 3043, 2942, 1730, 1653, 1594, 1493, 1447, 1410, 1194, 1163; δ_H (400 MHz, $CDCl_3$) 7.93-7.88 (2H, m, ArH), 7.64-7.52 (3H, m, ArH), 7.43-7.37 (2H, m, ArH), 7.28-7.23 (1H, m, ArH), 7.15-7.05 (3H, m, ArH + CH), 5.99 (1H, dt, *J* 15.5, 1.5, CH), 4.71 (1H, t, *J* 6.5, NH), 3.01 (2H, dt, J 6.5, 6.5, CH_2N), 2.26 (2H, dtd, *J* 7.0, 7.0, 1.5, CH2CH), 1.58-1.48 (4H, m, 2 x CH_2); δ_C (100 MHz, $CDCl_3$) 164.9 (C), 152.3 (C), 150.7 (CH), 139.9 (C), 132.8 (CH), 129.4 (CH), 129.1 (CH), 127.1 (CH), 125.7 (CH), 121.1 (CH), 119.4 (CH), 42.9 (CH_2), 31.7 (CH_2), 29.2 (CH_2), 24.8 (CH_2); *m/z* (ESI) 382 ($M+Na^+$ 100%), 360 ($M+H^+$ 37%); *m/z* (ESI) Found 382.1094. $C_{19}H_{21}NO_4SNa^+$ requires 382.1083.

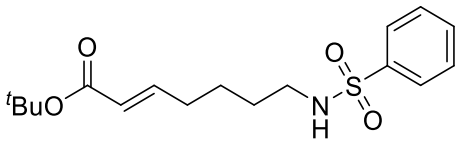
Phenyl (*E*)-7-((2-nitrophenyl)sulfonamido)hept-2-enoate **204b**



To a 0 °C suspension of (*E*)-7-((2-nitrophenyl)sulfonamido)hept-2-enoic acid (200 mg, 0.61 mmol) and oxalyl chloride (92 mg, 0.73 mmol) in dichloromethane (5 mL) was added two drops of DMF. Bubbling commenced immediately and the solution was allowed to warm to room temperature, after 2.5 h the solution was homogenous and was no longer evolving gas. The solution was concentrated under reduced pressure to obtain the acid chloride as a yellow oil. Dichloromethane (3 mL) was added followed dropwise addition of phenol (63 mg, 0.67 mmol) and pyridine (53 mg, 0.67 mmol) in dichloromethane (2 mL). After 2 h the solution was concentrated under reduced pressure and the residue purified by flash column chromatography on silica gel (3:2, petroleum ether/ethyl acetate) to give the product **204b** (101.6 mg, 41%) as a pale yellow oil. *Rf* 0.4 (3:2, petroleum ether/ethyl acetate); δ_H (400 MHz, $CDCl_3$) 8.20-8.09 (1H, m, ArH), 7.90-7.82 (1H, m, ArH), 7.80-7.67 (2H, m, ArH), 7.40 (2H, dddd, *J* 8.0, 8.0, 1.5, 1.5, ArH), 7.24 (1H, dddd, *J* 8.0, 8.0, 1.5, 1.5, ArH), 7.15-7.11 (2H, m, ArH), 7.09 (1H, dt, *J* 15.5, 7.0, CH), 6.00 (1H, dt, *J* 15.5, 1.5, CH), 5.40 (1H, br.t, *J* 6.0, NH), 3.14 (2H, dt, *J* 6.5, 6.5, CH_2N), 2.28 (2H, dtd, *J* 7.0, 7.0, 1.5, CH_2CH), 1.66-1.49 (4H, m, 2 x CH_2's); δ_C (100 MHz, $CDCl_3$) 164.9 (C), 150.7 (C), 150.6 (CH), 148.1 (C), 133.7 (CH), 133.6 (C), 132.9 (CH), 131.0 (CH), 129.4 (CH), 125.8 (CH), 125.4 (CH), 121.6 (CH), 121.1 (CH), 43.5

(CH_2), 31.7 (CH_2), 29.1 (CH_2), 24.8 (CH_2); *m/z* (ESI) 427 ($M+Na^+$, 100%); *m/z* (ESI) found [$M+Na^+$] 427.0928. $C_{19}H_{20}N_2O_6SNa^+$ requires 427.0934.

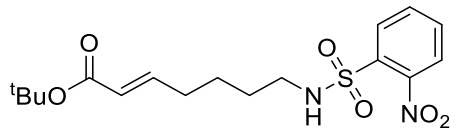
tert-Butyl (*E*)-7-(phenylsulfonamido)hept-2-enoate **205**



Followed general procedure for oxidative Wittig reactions.

Purified by flash column chromatography on silica gel (7:3, petroleum ether/ethyl acetate) to give the product **205** (3.41 g, 66%) as a dark brown oil. R_f 0.33 (7:3, petroleum ether/ethyl acetate); $\nu_{max}(CHCl_3)/cm^{-1}$ 3392, 3011, 2982, 2937, 2866, 1705, 1635, 1369, 1161, 909; δ_H (400 MHz, $CDCl_3$) 7.92-7.86 (2H, m, ArH), 7.64-7.50 (3H, m, ArH), 6.78 (1H, dt, *J* 15.5, 7.0, CH), 5.71 (1H, dt, *J* 15.5, 1.5, CH), 4.59 (1H, t, *J* 6.5, NH), 2.98 (2H, dt, *J* 6.5, 6.5, CH_2N), 2.13 (2H, dtd, J 7.0, 7.0, 1.5, CH_2CH), 1.52-1.42 (13H, m, 2 x CH_2 + 3 x CH_3); δ_C (100 MHz, $CDCl_3$) 165.9 (C), 146.8 (CH), 139.9 (C), 132.7 (C), 129.1 (CH), 127.0 (CH), 123.6 (CH), 80.2 (C), 43.0 (CH_2), 31.3 (CH_2), 29.1 (CH_2), 28.2 (CH_3), 24.9 (CH_2); *m/z* (ESI) 362 ($M+Na^+$ 100%), 342 ($M+H^+$ 38%); *m/z* (ESI) Found 362.1395. $C_{17}H_{25}NO_4SNa^+$ requires 362.1397.

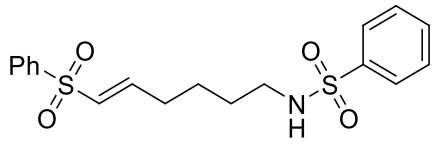
tert-Butyl (*E*)-7-((2-nitrophenyl)sulfonamido)hept-2-enoate **205b**



Followed general procedure for oxidative Wittig reactions.

Purified by flash column chromatography on silica gel (7:3, petroleum ether/ethyl acetate) to give the product **205b** (1.3 g, 51%) as a light brown oil. R_f 0.28 (7:3, petroleum ether/ethyl acetate); $\nu_{max}(CHCl_3)/cm^{-1}$ 3381, 3042, 3017, 2981, 2938, 1705, 1653, 1543, 1417, 1367, 1170; δ_H (400 MHz, $CDCl_3$) 8.19-8.10 (1H, m, ArH), 7.92-7.83 (1H, m, ArH), 7.79-7.71 (2H, m, ArH), 6.77 (1H, dt, *J* 15.5, 7.0, CH), 5.71 (1H, dt, *J* 15.5, 1.5, CH), 5.33 (1H, br.t, *J* 6.0, NH), 3.12 (2H, dt, *J* 7.0, 6.5, CH_2N), 2.16 (2H, dtd, *J* 7.0, 7.0, 1.5, *CH_2*CH), 1.62-1.52 (4H, m, 2 x CH_2), 1.49 (9H, s, 3 x CH_3); δ_C (100 MHz, $CDCl_3$) 165.9 (C), 148.1 (C), 146.7 (CH), 133.7 (C), 133.6 (CH), 132.8 (CH), 131.1 (CH), 125.4 (CH), 123.6 (CH), 80.2 (C), 43.6 (CH_2), 31.3 (CH_2), 29.1 (CH_2), 28.2 (CH_3) 24.9 (CH_2); *m/z* (ESI) 407 ($M+Na^+$ 100%); *m/z* (ESI) Found 407.1251. $C_{17}H_{24}N_2O_6SNa^+$ requires 407.1247.

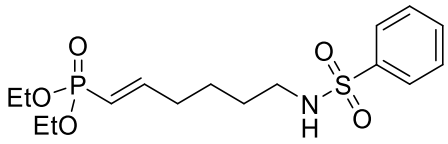
(*E*)-*N*-(6-(Phenylsulfonyl)hex-5-en-1-yl)benzenesulfonamide **207**



Followed general procedure for cross metathesis reactions.

Purified by flash column chromatography on silica gel (3:2, petroleum ether/ethyl acetate) to give the product **207** (201 mg, 99%) as a pale yellow oil. R_f 0.25 (3:2, petroleum ether/ ethyl acetate); $\nu_{max}(CHCl_3)/cm^{-1}$ 3393, 3044, 2943, 2866, 2340, 1627, 1448, 1411, 1321, 1162, 1147; δ_H (400 MHz, $CDCl_3$) 7.92-7.83 (4H, m, ArH), 7.67-7.50 (6H, m, ArH), 6.93 (1H, dt, *J* 15.0, 7.0, 7.0, CH), 6.31 (1H, dt, *J* 15.0, 1.5, CH), 4.68 (1H, br.t, *J* 6.0, NH), 2.96 (2H, dt, *J* 7.0, 7.0, CH_2N), 2.21 (2H, dtd, *J* 7.0, 7.0, 1.5, *CH*$_2$CH), 1.51-1.46 (4H, m, 2 x CH_2); δ_c (100 MHz, $CDCl_3$) 146.1 (CH), 140.5 (C), 139.8 (C), 133.4 (CH), 132.7 (CH), 130.9 (CH), 129.3 (CH), 129.2 (CH), 127.6 (CH), 127.0 (CH), 42.8 (CH_2), 30.8 (CH_2), 29.0 (CH_2), 24.5 (CH_2); *m/z* (ESI) 402 ($M+Na^+$ 100%); *m/z* (ESI) Found 402.0807. $C_{18}H_{21}NO_4S_2Na^+$ requires 402.0804.

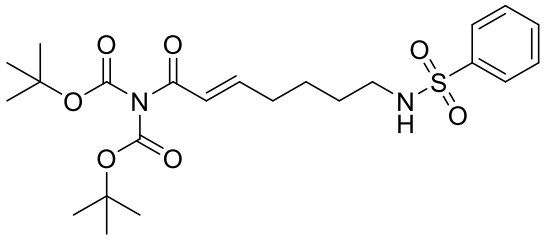
Diethyl (*E*)-(6-(phenylsulfonamido)hex-1-en-1-yl)phosphonate **208**



Followed general procedure for cross metathesis reactions.

Purified by flash column chromatography on silica gel (Gradient elution from 9:1 to 3:2, petroleum ether/ethyl acetate) to give the product **208** (104 mg, 41%) as a pale yellow oil. Some starting diethyl vinylphosphonate remained as the compound streaks heavily throughtout the column. R_f 0.2 (9:1, petroleum ether/ ethyl acetate); $\nu_{max}(CHCl_3)/cm^{-1}$ 3690, 3394, 2993, 1632, 1602, 1447, 1394, 1331, 1163, 1028, 967; ; δ_H (400 MHz, $CDCl_3$) 7.91-7.85 (2H, m, ArH), 7.63-7.49 (3H, m, ArH), 6.76-6.65 (1H, m, CH), 5.69-5.55 (1H, m, CH), 4.92 (1H, br.t, *J* 6.0, NH), 4.14-4.02 (4H, m, 2 x OCH_2), 2.96 (2H, dt, *J* 7.0, 6.0, CH_2N), 2.23-2.15 (2H, m, *CH*$_2$CH), 1.57-1.42 (4H, m, 2 x CH_2), 1.33 (6H, t, *J* 7.0, 2 x CH_3); δ_c (100 MHz, $CDCl_3$) 152.8 (C), 152.7 (C), 140.0 (C), 132.6 (CH), 129.1 (CH), 127.0 (CH), 118.4 (CH), 116.5 (CH), 61.7 (CH_2), 61.6 (CH_2), 42.9 (CH_2), 33.5 (CH_2), 33.3 (CH_2), 29.0 (CH_2), 24.7 (CH_2), 16.4 (CH_2), 16.3 (CH_2); δ_P (162 MHz, $CDCl_3$) 18.42; *m/z* (ESI) 398 ($M+Na^+$ 100%), 376 ($M+H^+$, 38); *m/z* (ESI) Found 398.1175. $C_{16}H_{26}NO_5SPNa^+$ requires 398.1162.

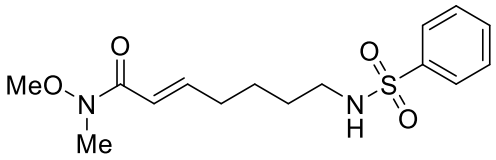
tert-Butyl (*E*)-(7-(phenylsulfonamido)hept-2-enoyl)dicarbamate **209**



Followed general procedure for cross metathesis reactions.

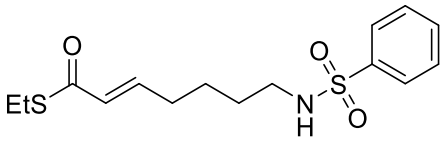
Purified by flash column chromatography on silica gel (3:2, petroleum ether/ethyl acetate) to give the product **209** (131 mg, 62%) as a pale yellow oil. R_f 0.3 (3:2, petroleum ether/ethyl acetate); $\nu_{max}(CHCl_3)/cm^{-1}$ 3392, 2985, 2938, 1775, 1744. 1686, 1636, 1310, 1252, 1124, 1094; δ_H (400 MHz, $CDCl_3$) 7.94-7.84 (2H, m, ArH), 7.65-7.49 (3H, m, ArH), 7.00 (1H, dt, *J* 15.5, 7.0, CH), 6.72 (1H, dt, *J* 15.5, 7.0, CH), 4.67 (1H, br. T, *J* 6.5, NH), 2.98 (2H, dt, *J* 6.5, 6.5, CH_2N), 2.26-2.18 (2H, m, $CH\mathit{CH_2}$), 1.64-1.40 (22H, m, 2 x Boc, 2 x CH_2); δ_c (100 MHz, $CDCl_3$) 166.1 (C), 149.8 (CH), 149.7 (C), 139.9 (C), 132.7 (CH), 129.2 (CH), 127.0 (CH), 122.6 (CH), 84.7 (C), 42.9 (CH_2), 31.8 (CH_2), 28.9 (CH_2), 27.6 (CH_3), 24.8 (CH_2); *m/z* (ESI) 505 ($M+Na^+$ 100%); *m/z* (ESI) Found 505.1987. $C_{23}H_{34}N_2O_7SNa^+$ requires 505.1979;

(*E*)-*N*-Methoxy-N-methyl-7-(phenylsulfonamido)hept-2-enamide **210**



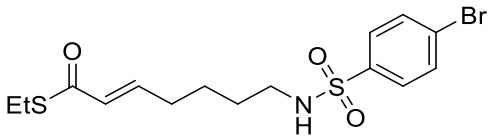
Followed general procedure for cross metathesis reactions to form the acid chloride **200**. The crude acid chloride was then dissolved in dichloromethane (5 mL/mmol) and *N,O*-dimethylhydroxylamine hydrochloride (1.1 equiv.) and sodium hydrogen carbonate (2 equiv.) was added and the suspension stirred at room temperature for 1 h. The suspension was then filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (1:1, petroleum ether/ethyl acetate) to give the product **210** (322 mg, 61%) as a colourless oil. R_f 0.18 (7:3, petroleum ether/ ethyl acetate); $\nu_{max}(CHCl_3)/cm^{-1}$ 3692, 3395, 2991, 1714, 1661, 1627, 1413, 1177; δ_H (400 MHz, $CDCl_3$) 7.93-7.85 (2H, m, ArH), 7.62-7.57 (1H, m, ArH), 7.57-7.50 (2H, m, ArH), 6.90 (1H, dt, *J* 15.0, 7.0, CH), 6.39 (1H, br.d, *J* 15.0, CH), 4.73 (1H, br.t, *J* 6.0, NH), 3.71 (3H, s, NCH_3), 3.25 (3H, s, OCH_3), 2.98 (2H, dt, *J* 7.0, 6.5, CH_2N), 2.21 (2H, dtd, *J* 7.0, 7.0, 1.5, $\mathit{CH_2}CH$), 1.57-1.44 (4H, m, 2 x CH_2); δ_c (100 MHz, $CDCl_3$) 166.8 (C), 146.7 (CH), 140.0 (C), 132.6 (CH), 129.1 (CH), 127.0 (CH), 119.3 (CH), 61.7 (CH_3), 43.0 (CH_2), 32.4 (br. CH_3), 31.8 (CH_2), 29.1 (CH_2), 25.2 (CH_2); *m/z* (ESI) 349 ($M+Na^+$ 100%); *m/z* (ESI) Found 349.1192. $C_{15}H_{22}N_2O_4SNa^+$ requires 349.1192.

S-Ethyl (*E*)-7-(phenylsulfonamido)hept-2-enethioate **215**



To a 0 °C suspension of (*E*)-7-(phenylsulfonamido)hept-2-enoic acid (227 mg, 0.79 mmol) and ethanethiol (147 mg, 2.37 mmol, 3 equiv.) in dichloromethane (4 mL)was added DCC (179 mg, 0.87 mmol, 1.1 equiv.) in one addition. After 16 h the precipitated DCU was removed by filtration and the solution concentrated under reduced pressure. The residue was then purified by flash column chromatography on silica gel (7:3, petroleum ether/ethyl acetate) to give the product **215** (199 mg, 77%) as a light yellow oil. R_f 0.3 (7:3, petroleum ether/ethyl acetate); $\nu_{max}(CHCl_3)/cm^{-1}$ 3392, 3008, 2935, 2867, 1665, 1631, 1448, 1412, 1331, 1162; δ_H (400 MHz, $CDCl_3$) 7.93-7.83 (2H, m , ArH), 7.62-7.47 (3H. m. ArH), 6.77 (1H, dt, *J* 15.5, 7.0, CH), 6.03 (1H, dt, *J* 15.5, 1.5, CH), 5.15 (1H, t, *J* 6.5, NH), 2.99-2.88 (4H, m, SCH_2 + CH_2N), 2.12 (2H, qd, *J* 7.0, 1.5, *CH_2*CH), 1.53-1.37 (4H, m, 2 x CH_2), 1.26 (2H, t, *J* 7.5, CH_3); δ_C (100 MHz, $CDCl_3$) 190.1 (C), 144.2 (CH), 139.9 (C), 132.7 (CH), 129.1 (CH), 129.0 (CH), 127.0 (CH), 42.8 (CH_2), 31.4 (CH_2), 29.0 (CH_2), 24.8 (CH_2), 23.1 (CH_2), 14.8 (CH_3); *m/z* (ESI) 350 ($M+Na^+$ 100%); *m/z* (ESI) Found 350.0860. $C_{15}H_{21}NO_3S_2Na^+$ requires 350.0855.

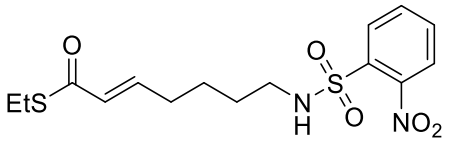
S-Ethyl (*E*)-7-((4-bromophenyl)sulfonamido)hept-2-enethioate **215b**



Followed general procedure for oxidative Wittig reactions.

Purified by flash column chromatography on silica gel (3:2, petroleum ether/ethyl acetate) to give the product **215b** (1.21 g, 69%) as a yellow oil. R_f 0.35 (3:2, petroleum ether/ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.78-7.66 (4H, m, ArH), 6.83 (1H, dt, *J* 15.5, 7.0, CH), 6.10 (1H, dt, *J* 15.5, 1.5, CH), 4.54 (1H, t, *J* 6.0, NH), 3.05-2.92 (4H, m, SCH_2 + CH_2N), 2.20 (2H, ttd, *J* 7.0, 7.0, 1.5, *CH_2*CH), 1.59-1.43 (4H, m, 2 x CH_2), 1.31 (3H, t, *J* 7.0, CH_3); δ_C (100 MHz, $CDCl_3$) 190.1 (C), 143.9 (CH), 139.0 (C), 132.5 (CH), 129.2 (CH), 128.6 (CH), 127.7 (C), 43.0 (CH_2), 31.4 (CH_2), 29.1 (CH_2), 24.9 (CH_2), 23.1 (CH_2), 14.8 (CH_3); *m/z* (ESI) 430($M^{81}Br+Na^+$ 100%), 428 ($M^{79}Br+Na^+$ 97), 408 ($M^{81}Br+H$, 55), 406 ($M^{79}Br+H^+$, 53); *m/z* (ESI) Found 429.9955. $C_{15}H_{20}NO_3{}^{81}BrSNa^+$ requires 429.9940.

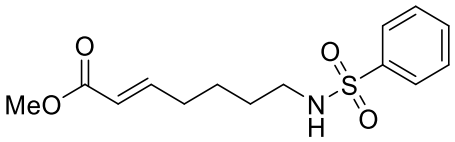
S-Ethyl (*E*)-7-((2-nitrophenyl)sulfonamido)hept-2-enethioate **215c**



Followed general procedure for oxidative Wittig reactions.

Purified by flash column chromatography on silica gel (7:3, petroleum ether/ethyl acetate) to give the product **215c** (2.28 g, 71%) as a dark yellow solid. m.p. 55-58 °C; R_f 0.24 (3:1, petroleum ether/ethyl acetate); $\nu_{max}(CHCl_3)/cm^{-1}$ 3382, 3026, 2935, 2873, 1665, 1631, 1542, 1418, 1361; δ_H (400 MHz, $CDCl_3$) 8.17-8.12 (1H, m, ArH), 7.91-7.85 (1H, m, ArH), 7.80-7.73 (2H, m, ArH), 6.79 (1H, dt, *J* 15.5, 7.0, CH), 6.07 (1H, dt, 15.5, 1.5, CH), 5.31 (1H, br. t, *J* 6.0, NH), 3.13 (2H, td, *J* 7.0, 6.0, CH_2N), 2.96 (2H, q, *J* 7.5, SCH_2), 2.19 (2H, dtd, *J* 7.0, 7.0, 1.5, $C=CCH_2$), 1.61-1.46 (4H, m, 2 x CH_2), 1.29 (3H, t, *J* 7.5, CH_3); δ_C (100 MHz, $CDCl_3$) 190.0 (C), 148.0 (C), 143.9 (CH), 133.7 (C), 133.6 (CH), 132.8 (CH), 131.0 (CH), 129.2 (CH), 125.4 (CH), 43.5 (CH_2), 31.4 (CH_2), 29.1 (CH_2), 24.8 (CH_2), 23.1 (CH_2), 14.8 (CH_3); *m/z* (ESI) 395 ($M+Na^+$, 100%), 373 ($M+H^+$, 6); *m/z* (ESI) Found 395.0734. $C_{15}H_{21}N_2O_5S_2Na^+$ requires 395.0706.

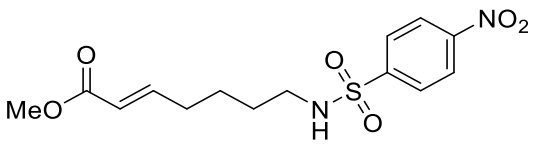
Methyl (*E*)-7-(phenylsulfonamide)hept-2-enoate **266**



Followed general procedure for oxidative Wittig reactions.

Purified by flash chromatography on silica gel (2:1, petroleum ether/ethyl acetate) to give the product **266** (445 mg, 87%) as a colourless oil. R_f 0.2 (2:1, petroleum ether/ethyl acetate); ν_{max}(neat)/cm^{-1} 3284, 2948, 1720, 1655, 1447, 1326, 1159; δ_H (400 MHz, $CDCl_3$) 7.89-7.86 (2H, m, ArH), 7.62-7.58 (1H, m, ArH), 7.56-7.51 (2H, m, ArH), 6.88 (1H, dt, *J* 15.5, 7.0, CH), 5.78 (1H, dt, *J* 15.5, 1.5, CH), 4.43 (1H, br s, NH), 3.20 (3H, s, CH_3), 2.98 (2H, dt, *J* 7.0, 7.0, CH_2N), 2.19-2.14 (2H, m, CH_2), 1.54-1.42 (4H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 166.9 (C), 148.4 (CH), 140.0 (C), 132.7 (CH), 129.2 (CH), 127.0 (CH), 121.5 (CH), 51.5 (CH_3), 42.9 (CH_2), 31.5 (CH_2), 29.1 (CH_2) 24.9 (CH_2); *m/z* (ESI) 320 ($M+Na^+$ 100%); *m/z* (ESI) Found 320.0913. $C_{14}H_{19}NO_4SNa^+$ requires 320.0927.

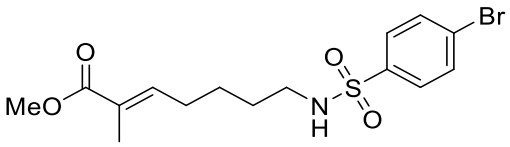
Methyl (*E*)-7-(4-nitrophenylsulfonamide)hept-2-enoate **267**



Followed general procedure for oxidative Wittig reactions.

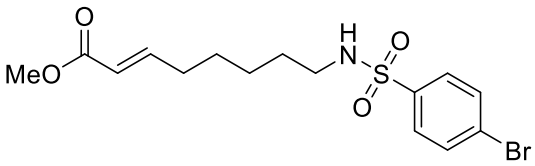
Purified by flash column chromatography on silica gel (2:1, petroleum ether/ethyl acetate). The resulting product was recrystalised from petroleum ether/ethyl acetate to give the product **267** (380 mg, 26%) as a colourless solid. m.p. 100 °C; R_f 0.2 (2:1, petroleum ether/ethyl acetae); $\nu_{max}(CHCl_3)/cm^{-1}$ 3392, 3045, 2950, 2867, 1718, 1534, 1350, 1166; δ_H (400 MHz, $CDCl_3$) 8.40-8.37 (2H, m, ArH), 8.08-8.05 (2H, m, ArH), 6.88 (1H, dt, *J* 15.5, 7.0, CH), 5.79 (1H, dt, *J* 15.5, 1.0, CH), 4.74 (1H, t, *J* 6.0, NH), 3.73 (3H, s, CH_3), 3.06-3.01 (2H, m, CH_2), 2.22-2.17 (2H, m, CH_2), 1.57-1.43 (4H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 166.9 (C), 150.1 (C), 148.2 (CH), 146.0 (C), 128.3 (CH), 124.5 (CH), 121.6 (CH), 51.5 (CH_3), 43.1 (CH_2), 31.4 (CH_2), 29.2 (CH_2), 24.9 (CH_2); *m/z* (ESI) 365 ($M+Na^+$ 100%); *m/z* (ESI) Found 365.0765. $C_{14}H_{18}N_2O_6SNa^+$ requires 365.0778.

Methyl (*E*)-7-((4-bromophenyl)sulfonamido)-2-methylhept-2-enoate **322**



Purified by flash column chromatography on silica gel (3:2, petroleum ether/ethyl acetate) to give the product **322** (343 mg, 87%) as a pale yellow oil. R_f 0.4 (3:2, petroleum ether/ethyl acetate); $\nu_{max}(CHCl_3)/cm^{-1}$ 3690, 3394, 2991, 2950, 1720, 1599, 1441, 1337, 1166; δ_H (400 MHz, $CDCl_3$) 7.81-7.61 (4H, m, ArH), 6.69 (1H, tq, *J* 7.5, 1.5, CH), 4.73 (1H, br.t, *J* 6.0, NH), 3.76 (3H, s, OCH_3), 2.99 (2H, dt, *J* 7.0, 6.5, *CH*$_2$N), 2.16 (2H, dt, *J* 7.0, 7.0, *CH*$_2$CH), 1.82 (3H, d, *J* 1.5, CH_3), 1.58-1.42 (4H, m, 2 x CH_2); δ_c (100 MHz, $CDCl_3$) 168.6 (C), 141.4 (CH), 139.1 (C), 132.4 (CH), 128.9 (C), 128.6 (CH), 128.2 (C), 127.6 (C), 51.8 (CH_3), 43.0 (CH_2), 29.2 (CH_2), 27.9 (CH_2), 25.5 (CH_2), 12.4 (CH_3); *m/z* (ESI) 414 ($M^{81}Br+Na^+$ 100%), 412 ($M^{79}Br+Na^+$, 98); *m/z* (ESI) Found 414.0161. $C_{15}H_{20}NO_4S^{81}BrNa^+$ requires 414.0168.

Methyl (*E*)-8-((4-bromophenyl)sulfonamido)oct-2-enoate **275**



Followed general procedure for oxidative Wittig reactions.

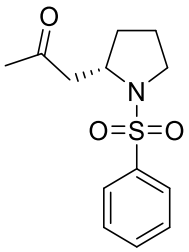
Purified by flash column chromatography on silica gel (4:1, petroleum ether/ethyl acetate) to give the product **275** (628 mg, 88%) as a colourless oil; R_f 0.31 (7:3 petroleum ether/ ethyl acetate); ν_{max} ($CHCl_3$) / cm^{-1} 3691, 3392, 2937, 2861, 1717, 1658, 1577, 1337, 1279, 1211, 1164, 1070, 607; δ_H (400 MHz, $CDCl_3$) 7.76-7.71 (2H, m, ArH), 7.69-7.63 (2H, m, ArH), 6.91 (1H, dt, *J* 15.5, 7.0, CH), 5.80 (1H, dt, *J* 15.5, 1.5, CH), 4.94 (1H, t, *J* 6.0, NH), 3.73 (3H, s, OCH_3), 2.94 (2H, dt, *J* 7.0, 7.0, CH_2), 2.16 (2H, dtd, *J* 7.0, 7.0, 1.5, CH_2), 1.53-1.36 (4H, m, 2 x CH_2), 1.34-1.23 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 167.1 (C), 149.0 (CH), 139.1 (C), 132.4 (CH), 128.6 (CH), 127.5 (C), 121.2 (CH), 51.5 (CH_3), 43.1 (CH_2), 31.9 (CH_2), 29.4 (CH_2), 27.4 (CH_2), 26.0 (CH_2); *m/z* (ESI) 414 ($M^{81}Br+Na^+$, 100%), 412 ($M^{79}Br+Na^+$, 93%); *m/z* (ESI) found [$M+Na^+$] 414.0172. $C_{15}H_{20}{}^{81}BrNO_4SNa^+$ requires 414.0168.

Cyclic Methyl and Phenyl Ketones

General procedure for cyclisations using the Squaramide catalyst 27

A solution of enone (0.1 mmol) and the squaramide catalyst **27** (1-10 mol%) in toluene (0.2M) was stirred until the starting material is no longer present by TLC. The product was then purified by flash column chromatography on silica gel in the solvent systems outlined for individual products.

(*S*)-1-(1-(Phenylsulfonyl)-2-pyrrolidinyl)-2-propanone **293a**

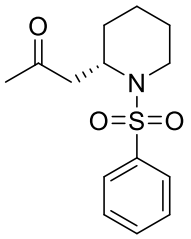


Followed general procedure for cyclisations using the Squaramide catalyst **27**.

Purified by flash column chromatography on silica gel (7:3, petroleum ether/ethyl acetate) to give the product **293a** (26.3 mg, 99%) as a colourless oil. $[\alpha]^{23}$ –70 (*c* 0.7, $CHCl_3$, 40% ee); ν_{max} (neat) / cm^{-1} 2972, 1711, 1446, 1337, 1161, 1074; δ_H (400 MHz, $CDCl_3$), 7.87-7.80 (2H, m, Ar*H*), 7.66-7.49 (3H, m, Ar*H*), 4.00-3.90 (1H, m, C*H*N), 3.52-3.42 (1H, m, CH_aH_bN), 3.26 (1H, dd, J 17.5

3.5, OCCH_aH$_b$), 3.16-3.06 (1H, m, CH_bH$_a$N), 2.69 (1H, dd, *J* 17.5 9.5, OCCH_bH$_a$), 2.18 (3H, s, CH_3CO), 1.90-1.41 (4H, m, CH_2CH_2); δ_C (100 MHz, $CDCl_3$) 207.1 (C), 136.8 (C), 132.8 (CH), 129.1 (CH), 127.6 (CH), 55.9 (CH), 50.6 (CH_2), 49.2 (CH_2), 32.1 (CH_2), 30.6 (CH_3), 23.8 (CH_2); *m/z* (ES+) 290 (M+Na^+, 75%), 268 (M+H^+, 100); *m/z* (ES+) Found 268.0997. $C_{13}H_{18}NO_3S^+$ requires 268.1002. HPLC: Chiralcel OD-H; mobile phase, hexane/2-propanol (4:1 v/v); flow rate, 1 mL/min; 9.9 min (70%), 16.7 min (30%), 40% ee.

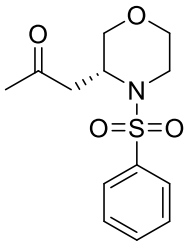
(*S*)-1-(1-(Benzenesulfonyl)piperidin-2-yl)-2-propanone **276a**



Followed general procedure for cyclisations using the Squaramide catalyst **27**.

Purified by flash column chromatography on silica gel (2:1, petroleum ether/ethyl acetate) to give the product **276a** (23 mg, 82%) as a colourless solid. m.p. 75 °C; $[\alpha]_D^{25}$ -22.1 (*c* 0.74, $CHCl_3$, 90% ee); *R*f 0.3 (2:1, petroleum ether/ethyl acetate); ν_{max}(neat)/cm^{-1} 2940, 2863, 1712, 1446; δ_H (400 MHz, $CDCl_3$) 7.85-7.82 (2H, m, ArH), 7.59-7.55 (1H, m, ArH), 7.53-7.49 (2H, m, ArH), 4.56-4.52 (1H, m, CH), 3.84-3.79 (1H, m, CH_2), 2.96 (1H, ddd, *J* 14.0, 13.0, 2.5, CH_2), 2.80 (1H, dd, *J* 16.5, 9.5, CH_2), 2.59 (1H, dd, *J* 16.5, 4.5 CH_2), 2.12 (3H, s, CH_3), 1.57-1.26 (6H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 205.9 (C), 141.1 (C), 132.4 (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* (ESI) 304 (M+Na^+ 100%), 282 (M+H^+ 47%); *m/z* (ESI) Found 304.0962. $C_{14}H_{19}NO_3SNa^+$ requires 304.0978; HPLC: Chiralcel OD-H; mobile phase, hexane/2-propanol (9:1 v/v); flow rate, 1 mL/min; 15.3 min (95%), 20.0 min (5%), 90% ee.

(*S*)-1-(4-(phenylsulfonyl)morpholin-3-yl)propan-2-one **291**

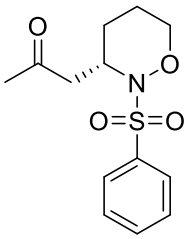


Followed general procedure for cyclisations using the Squaramide catalyst **27**.

Purified by flash column chromatography on silica gel (3:2, petroleum ether/ethyl acetate) to give the product **291** (21.2 mg, 75%) as a colourless oil. $[\alpha]^{23}$ -35 (*c* 0.7, $CHCl_3$, 87% ee); *Rf* 0.4 (3:2, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3692, 3009, 2973, 2926, 2867, 1716, 1332, 1164; δ_H (400 MHz,

$CDCl_3$) 7.87-7.82 (2H, m, ArH), 7.67-7.60 (1H, m, ArH), 7.59-7.53 (2H, m, ArH), 7.32-7.26 (1H, m, CH), 3.81 (1H, dd, *J* 11.5, 3.0, CH), 3.69 (1H, d, *J* 12.0, CH), 3.64-3.57 (1H, m, CH), 3.49-3.35 (2H, m, 2xCH), 3.27-3.19 (1H, m, CH), 3.19 (1H, dd, *J* 18.0, 10.0, CH), 2.50 (1H, ddd, *J* 18.0, 2.5, 2.5, CH), 2.13 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 205.7 (C), 140.3 (C), 132.9 (CH), 129.3 (CH), 127.1 (CH), 69.0 (CH_2), 66.4 (CH_2), 48.8 (CH), 41.7 (CH_2), 41.3 (CH_2), 30.3 (CH_2); *m/z*(ESI) 306 ($M+Na^+$, 100%), 284 ($M+H^+$, 23%); *m/z*(ESI) found 306.0764. $C_{13}H_{17}NSO_4Na^+$ requires 306.0770; HPLC: Chiralcel AD-H; mobile phase, hexane/2-propanol (9:1 v/v); flow rate, 1 mL/min; 26.3 min (6.5%), 27.7 min (93.5%) 87% ee.

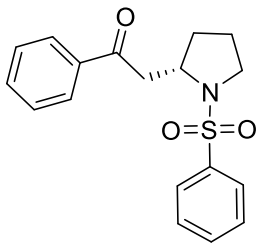
(*S*)-1-(2-(Phenylsulfonyl)-1,2-oxazinan-3-yl)propan-2-one **292**



Followed general procedure for cyclisations using the Squaramide catalyst **27**.

Purified by flash column chromatography on silica gel (3:2, petroleum ether/ethyl acetate) to give the product **292** (12.1 mg, 43%) as a colourless oil. $[\alpha]^{22}$ -21 (*c* 0.7, $CHCl_3$, 87% ee); *Rf* 0.38 (3:2, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2953, 2932, 1717, 1448, 1363, 1166, 1090; δ_H (400 MHz, $CDCl_3$) 7.96-7.89 (2H, m, ArH), 7.67-7.61 (1H, m, ArH), 7.58-7.51 (2H, m, ArH), 4.69-4.60 (1H, m, CH), 4.07 (1H, ddd, *J* 11.5, 11.5, 3.0, CHC*Ha*Hb), 3.98-3.91 (1H, m, CHCHa*Hb*), 3.12 (1H, dd, *J* 17.5, 5.0, COC*Ha*Hb), 2.85 (1H, dd, *J* 17.5, 8.0, COCHa*Hb*), 2.16 (3H, s, CH_3), 2.11-1.99 (1H, m, CH), 1.97-1.84 (1H, m, CH), 1.80-1.72 (1H, m, CH), 1.59-1.51 (1H, m, CH); δ_C (100 MHz, $CDCl_3$) 205.7 (C), 137.7 (C), 133.4 (CH), 128.9 (CH), 128.5 (CH), 71.6 (CH_2), 51.1 (CH), 43.3 (CH_2), 30.5 (CH_3), 26.7 (CH_2), 20.1 (CH_2); *m/z* (ESI) 306 ($M+Na^+$, 29%), 284 ($M+H^+$, 100%); *m/z* (ESI) found 284.0957. $C_{13}H_{18}NO_4S^+$ requires 284.0951; HPLC: Chiralcel OJ-H; mobile phase, hexane/2-propanol (7:3 v/v); flow rate, 1 mL/min; 24.8 min (6.5%), 27.7 min (93.5%) 87% ee.

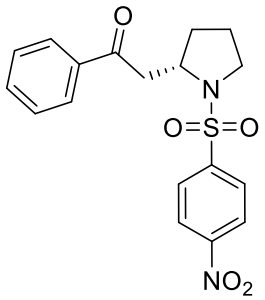
(*S*)-1-Phenyl-2-(1-(phenylsulfonyl)pyrrolidin-2-yl)ethanone **293**



Followed general procedure for cyclisations using the Squaramide catalyst **27**.

Purified by flash column chromatography on silica gel (7:3, petroleum ether/ethyl acetate) to give the product **293** (26.3 mg, 80%) as a colourless oil. $[\alpha]^{23}$–80 (*c* 1.0, $CHCl_3$, 80% ee); *Rf* 0.4 (3:2, petroleum ether/ethyl acetate); δ_H (400 MHz, $CDCl_3$) 8.04 (2H, dd, *J* 8.5, 1.5, ArH), 7.89 (2H, dd, *J* 8.5, 1.5, ArH), 7.66-7.48 (6H, m, ArH), 4.21-4.15 (1H, m, CH), 3.88 (1H, dd, *J* 17.0, 3.0, COC*Ha*Hb), 3.59-3.51 (1H, m, NC*Ha*Hb), 3.19 (1H, dd, *J* 17.0, 10.5, NCHa*Hb*), 3.19-3.11 (1H, m, NCHa*Hb*), 1.92-1.78 (2H, m, CH_2), 1.73-1.53 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 1.98.5 (C), 136.8 (C), 138.6 (C), 133.4 (CH), 132.8 (CH), 129.2 (CH), 128.7 (CH), 128.2 (CH), 127.6 (CH), 56.7 (CH), 49.2 (CH_2), 46.2 (CH_2), 31.9 (CH_2), 23.8 (CH_2); ν_{max} ($CHCl_3$)/cm^{-1} 3064, 3008, 2980, 2957, 2877, 1711, 1682, 1598, 1581, 1412, 1335, 1162, 1094, 621; *m/z* (ESI) 352 ($M+Na^+$, 100), 330 ($M+H^+$, 20%); *m/z* (ESI) found 352.0977. $C_{18}H_{19}NO_3SNa^+$ requires 352.0978; HPLC: Chiralcel OD-H; mobile phase, hexane/2-propanol (4:1 v/v); flow rate, 1 mL/min; 9.1 min (90%), 13.2 min (10%), 80% ee.

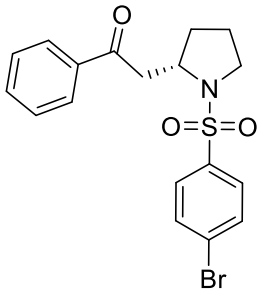
(*S*)-2-(1-((4-Nitrophenyl)sulfonyl)pyrrolidin-2-yl)-1-phenylethan-1-one **294**



Followed general procedure for cyclisations using the Squaramide catalyst **27**.

Purified by flash column chromatography on silica gel (7:3, petroleum ether/ethyl acetate) to give the product **294** (27.8 mg, 77%) as a colourless solid. $[\alpha]^{25}$-171 (*c* 0.5, $CHCl_3$, 82% ee); m.p. 170-174 °C; *Rf* 0.6 (3:2, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3008, 1710, 1682, 1599, 1355, 1165; δ_H (400 MHz, $CDCl_3$) 8.41 (2H, *J* 9.0, ArH), 8.07 (2H, d, *J*9.0, ArH), 8.01 (2H, d, *J* 8.5, ArH), 7.63 (1H, dddd, *J* 7.0, 7.0, 1.5, 1.5, ArH), 7.55-7.49 (2H, m, ArH), 4.20 (1H, dddd, *J* 10.5, 7.0, 3.5, 3.5, CH), 3.84 (1H, dd, *J* 17.5, 3.5, COC*Ha*Hb), 3.66-3.58 (1H, m, C*Ha*Hb), 3.22 (1H, dd, *J* 17.5, 10.5, COHa*Hb*), 3.18-3.11 (1H, m, CHa*Hb*), 1.97-1.88 (2H, m, CH_2), 1.80-1.57 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 198.1 (C), 150.2 (C), 142.7 (C), 136.4 (C), 133.6 (CH), 128.8 (CH), 128.1 (CH), 124.4 (CH), 57.0 (CH), 49.4 (CH_2), 45.7 (CH_2), 32.1 (CH_2), 23.8 (CH_2); *m/z*(ESI) 397 ($M+Na^+$, 100%); *m/z*(ESI) found 397.0834. $C_{18}H_{18}N_2O_5SNa^+$ requires 397.0829; HPLC: Chiralcel OD-H; mobile phase, hexane/ethanol (7:3 v/v); flow rate, 1 mL/min; 12.5 min (91%), 15.6 min (9%) 82% ee.

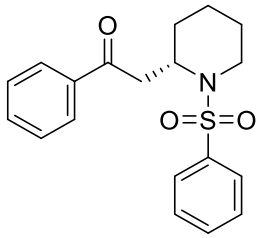
(*S*)-2-(1-((4-Bromophenyl)sulfonyl)pyrrolidin-2-yl)-1-phenylethanone **295**



Followed general procedure for cyclisations using the Squaramide catalyst **27**.

Purified by flash column chromatography on silica gel (9:1, petroleum ether/ethyl acetate) to give the product **295** (39.4 mg, 97%) as a colourless oil. $[\alpha]^{23}$ -85 (*c* 1.0, $CHCl_3$, 80% ee); *Rf* 0.5 (7:3, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3045, 2981, 2956, 2878, 1682, 1576, 1370, 1164, 625; δ_H (400 MHz, $CDCl_3$) 8.05-7.99 (2H, m, ArH), 7.77-7.67 (4H, m, ArH), 7.62 (1H, dddd, *J* 7.0, 7.0, 1.5, 1.5, ArH), 7.55-7.48 (2H, m, ArH), 4.15 (1H, dddd, *J* 10.5, 7.0, 3.5, 3.5, CH), 3.84 (1H, dd, *J* 17.0, 3.0, COC*Ha*Hb), 3.59-3.51 (1H, m, NC*Ha*Hb), 3.19 (1H, dd, *J* 17.0, 10.5, COCHa*Hb*), 3.15-3.07 (1H, m, NCHa*Hb*), 1.95-1.81 (2H, m, CH_2), 1.71-1.57 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 198.4 (C), 136.5 (C), 135.9 (C), 133.5 (CH), 132.5 (CH), 129.1 (CH), 128.7 (CH), 128.1 (CH), 127.9 (C), 56.8 (CH), 49.3 (CH_2), 46.0 (CH_2), 32.0 (CH_2), 23.8 (CH_2); *m/z* (ESI) 432 ($M^{81}Br+Na^+$, 84%), 430 ($M^{79}Br+Na^+$, 76%), 410 ($M^{81}Br+H^+$, 62%), 408 ($M^{79}Br+H^+$, 54%); *m/z* (ESI) found 432.0093. $C_{13}H_{18}{}^{81}BrNO_3S^+$ requires 430.0083; HPLC: Chiralcel OD-H; mobile phase, hexane/2-propanol (4:1 v/v); flow rate, 1 mL/min; 10.3 min (90%), 9.5 min (10%) 80% ee.

(*S*)-1-Phenyl-2-(1-(phenylsulfonyl)piperidin-2-yl)ethan-1-one **276**

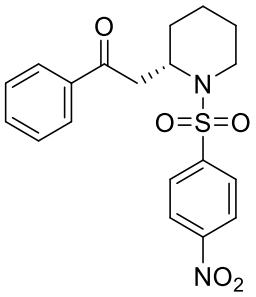


Followed general procedure for cyclisations using the Squaramide catalyst **27**.

Purified by flash column chromatography on silica gel (7:3, petroleum ether/ethyl acetate) to give the product **276** (67 mg, 84%) as a colourless solid. m.p. 132 °C; $[\alpha]_D^{23}$ -37.0 (*c* 0.84, $CHCl_3$, 99% ee); *R*f 0.2 (7:3, petroleum ether/ethyl acetate); ν_{max}(neat)/cm^{-1} 2939, 1681, 1447, 1328, 1288, 1155; δ_H (400 MHz, $CDCl_3$) 7.93-7.91 (2H, m, ArH), 7.85-7.83 (2H, m, ArH), 7.60-7.52 (2H,

m, ArH), 7.49-7.46 (4H, m, ArH), 4.72-4.69 (1H, m, CHN), 3.91-3.87 (1H, m, CH_cH$_d$), 3.37 (1H, dd, *J* 16.0, 11.0, CH_aH$_b$), 3.16 (1H, dd, *J* 16.0, 3.5, CH$_a$$H_b$), 3.08 (1H, ddd, *J* 13.0, 13.0, 2.5, CH$_c$$H_d$), 1.64-1.52 (5H, m, CH$_2$), 1.42-1.31 (1H, m, CH$_2$); δ_c (100 MHz, $CDCl_3$) 197.6 (C), 141.1 (C), 136.5 (C), 133.4 (CH), 132.4 (CH), 129.1 (CH), 128.7 (CH), 128.2 (CH), 127.0 (CH), 49.5 (CH), 41.5 (CH$_2$), 39.0 (CH$_2$), 27.5 (CH$_2$), 24.8 (CH$_2$), 18.4 (CH$_2$); *m/z* (ESI) 366 (M+Na$^+$ 100%); *m/z* (ESI) Found 366.1131. $C_{19}H_{21}NO_3SNa^+$ requires 366.1134; HPLC: Chiralcel AD-H; mobile phase, hexane/2-propanol (4:1 v/v); flow rate, 1.0 ml/min; 12.0 min (99.3%), 35.5 min (0.7%), 99% ee.

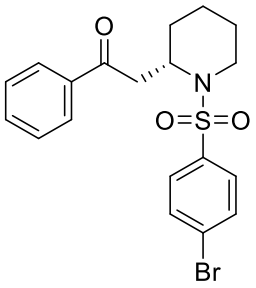
(*S*)-2-(1-((4-Nitrophenyl)sulfonyl)piperidin-2-yl)-1-phenylethan-1-one **279**



Followed general procedure for cyclisations using the Squaramide catalyst **27**.

Purified by flash column chromatography on silica gel (7:3, petroleum ether/ethyl acetate) to give the product **279** (60 mg, 77%) as a colourless solid. m.p. 150 °C; $[\alpha]_D^{23}$ -63.5 (*c* 0.84, $CHCl_3$, 99% ee); *R*f 0.3 (7:3, petroleum ether/ethyl acetate); ν_{max}(neat)/cm^{-1} 2948, 2870, 1684, 1532, 1350, 1159; δ_H (400 MHz, $CDCl_3$) 8.29-8.26 (2H, m, ArH), 8.00-7.97 (2H, m, ArH), 7.90-7.87 (2H, m, ArH), 7.61-7.58 (1H, m, ArH), 7.49-7.45 (2H, m, ArH), 4.77-4.74 (1H, m, CH), 3.95-3.90 (1H, m, CH$_2$), 3.35 (1H, dd, *J* 16.0, 9.0, CH$_2$), 3.23-3.12 (2H, m, CH$_2$), 1.69-1.54 (5H, m, CH$_2$), 1.42-1.33 (1H, m, CH$_2$); δ_c (100 MHz, $CDCl_3$) 197.0 (C), 149.8 (C), 147.0 (C), 136.3 (C), 133.6 (CH), 128.8 (CH), 128.1 (CH), 124.3 (CH), 50.0 (CH), 41.8 (CH$_2$), 39.1 (CH$_2$), 28.1 (CH$_2$), 25.0 (CH$_2$), 18.4 (CH$_2$); *m/z* (ESI) 411 (M+Na$^+$, 100%); *m/z* (ESI) Found 411.0984. $C_{19}H_{20}N_2O_5SNa^+$ requires 411.0985; HPLC: Chiralcel AD-H; mobile phase, hexane/2-propanol (1:1 v/v); flow rate, 1.0 ml/min; 10.7 min (99.3%), 32.8 min (0.7%), 99% ee.

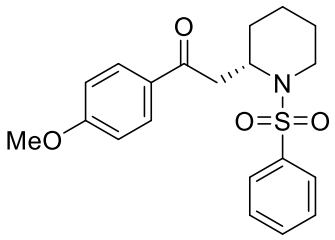
(*S*)-2-(1-((4-Bromophenyl)sulfonyl)piperidin-2-yl)-1-phenylethan-1-one **280**



Followed general procedure for cyclisations using the Squaramide catalyst **27**.

Purified by flash column chromatography on silica gel (9:1, petroleum ether/ethyl acetate) to give the product **280** (987 mg, 99%) as a colourless solid. m.p. 180-183 °C; $[\alpha]^{22}$ -22 (*c* 0.8, $CHCl_3$, 98% ee); *Rf* 0.53 (7:3, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3692, 3011, 2947, 2868, 1711, 1684, 1156, 621; δ_H (400 MHz, $CDCl_3$) 7.95-7.89 (2H, m, ArH), 7.72-7.68 (2H, m, ArH), 7.64-7.57 (3H, m, ArH), 7.53-7.46 (2H, m, ArH), 4.74-4.64 (1H, m, CH), 3.92-3.83 (1H, m, C*Ha*), 3.37 (1H, dd, *J* 16.0, 10.0, COC*Ha*Hb), 3.18 (1H, dd, *J* 16.0, 4.0, COC*Ha*Hb), 3.10 (1H, ddd, *J* 13.5, 13.5, 2.5, CHa*Hb*), 1.75-1.48 (8H, m), 1.46-1.30 (1H, m); δ_C (100 MHz, $CDCl_3$) 197.4 (C), 140.1 (C), 136.4 (C), 133.5 (CH), 132.3 (CH), 128.7 (CH), 128.5 (CH), 128.1 (CH), 127.3 (C), 49.6 (CH), 41.5 (CH_2), 39.0 (CH_2), 27.7 (CH_2), 24.9 (CH_2), 18.4 (CH_2); *m/z*(ESI) 446 ($M^{81}Br+Na^+$, 100%), 444 ($M^{79}Br+Na^+$, 89), 424 ($M^{81}Br+H^+$, 35), 422 ($M^{79}Br+H^+$, 38); *m/z*(ESI) found 446.0234. $C_{19}H_{20}{}^{81}BrNO_3S^+$ requires 446.0239; HPLC: Chiralcel OD-H; mobile phase, hexane/2-propanol (9:1 v/v); flow rate, 1 mL/min; 15.3 min (98.9%), 18.2 min (1.1%) 98% ee.

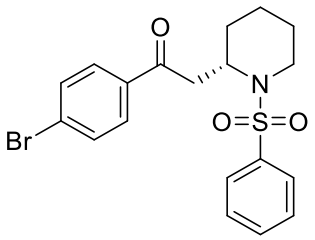
(*S*)-1-(4-Methoxyphenyl)-2-(1-(phenylsulfonyl)piperidin-2-yl)ethan-1-one **281**



Followed general procedure for cyclisations using the Squaramide catalyst **27**.

Purified by flash column chromatography on silica gel (7:3, petroleum ether/ethyl acetate) to give the product **281** (62 mg, 84%) as a white solid. m.p. 96 °C; $[\alpha]_D^{23}$ -42.4 (*c* 1.0, $CHCl_3$, 99% ee); *Rf* 0.3 (7:3, petroleum ether/ethyl acetate); ν_{max}(neat)/cm^{-1} 3009, 2945, 2867, 1672, 1600, 1262, 1171, 1156; δ_H (400 MHz, $CDCl_3$) 7.92-7.90 (2H, m, ArH), 7.85-7.83 (2H, m, ArH), 7.55-7.52 (1H, m, ArH), 7.49-7.45 (2H, m, ArH), 6.95-6.93 (2H, m, ArH), 4.69-4.66 (1H, m, CH), 3.88-3.85 (4H, m, CH_2 and CH_3), 3.29 (1H, dd, *J* 15.5, 10.5, C$H_a$$H_b$), 3.13-3.04 (2H, m, CH$_a$*H$_b$* and CH_2), 1.63-1.48 (5H, m, CH_2), 1.40-1.30 (1H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 196.2 (C), 163.7 (C), 141.1 (C), 132.4 (CH), 130.6 (CH), 129.6 (C) 129.1 (CH), 127.0 (CH), 113.9 (CH), 55.5 (CH_3), 49.7 (CH), 41.4 (CH_2), 38.8 (CH_2), 27.4 (CH_2), 24.8 (CH_2), 18.4 (CH_2); *m/z* (ESI) 396 ($M+Na^+$ 100%); *m/z* (ESI) Found 410.1030. $C_{20}H_{21}NO_5SNa^+$ requires 410.1033; HPLC: Chiralcel AD-H; mobile phase, hexane/2-propanol (1:1 v/v); flow rate, 1.0 ml/min; 9.4 min (99.6%), 16.9 min (0.4%), 99% ee.

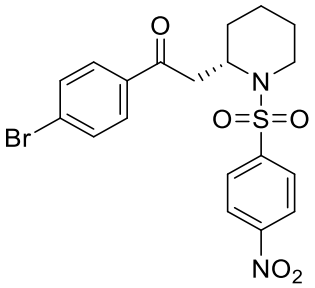
(*S*)-1-(4-Bromophenyl)-2-(1-(phenylsulfonyl)piperidin-2-yl)ethan-1-one **282**



Followed general procedure for cyclisations using the Squaramide catalyst **27**.

Purified by flash column chromatography on silica gel (7:3, petroleum ether/ethyl acetate) to give the product **282** (70 mg, 83%) as a colourless oil. $[\alpha]_D^{23}$ -42.9 (*c* 0.9, $CHCl_3$, 98% ee); *Rf* 0.3 (7:3, petroleum ether/ethyl acetate); ν_{max}(neat)/cm^{-1} 3012, 2947, 2868, 1684, 1586, 1156, 909; δ_H (400 MHz, $CDCl_3$) 7.86-7.80 (4H, m, ArH), 7.65-7.63 (2H, m, ArH), 7.59-7.55 (1H, m, ArH), 7.52-7.48 (2H, m, ArH), 4.86-4.70 (1H, m, CH), 3.91-3.87 (1H, m, C$H_a$$H_b$), 3.33 (1H, dd, *J* 10.0, 16.0, C$H_c$$H_d$), 3.17 (1H, dd, *J* 16.0, 4.0, CH_cH_d), 3.09 (1H, ddd, *J* 13.5, 13.5, 2.5, CH_aH_b), 1.65-1.53 (5H, m, CH_2), 1.42-1.33 (1H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 196.6 (C), 141.0 (C), 135.2 (C), 132.5 (CH), 132.0 (CH), 129.7 (CH), 129.1 (CH), 128.6 (C), 126.9 (CH), 49.5 (CH), 41.4 (CH_2), 39.1 (CH_2), 27.5 (CH_2), 24.7 (CH_2), 18.4 (CH_2); *m/z* (ESI) 446 ($M^{81}Br+Na^+$, 100%), 444 ($M^{79}Br+Na^+$, 99); *m/z* (ESI) Found 446.0219. $C_{19}H_{20}{}^{81}BrNO_3SNa^+$ requires 446.0219; HPLC: Chiralcel AD-H; mobile phase, hexane/2-propanol (1:1 v/v); flow rate, 1.0 ml/min; 8.9 min (99.1%), 19.5 min (0.9%), 98% ee.

(*S*)-1-(4-Bromophenyl)-2-(1-((4-nitrophenyl)sulfonyl)piperidin-2-yl)ethan-1-one **283**

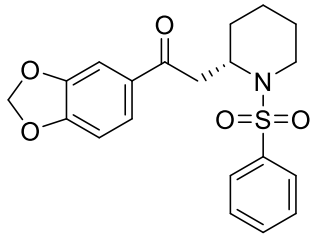


Followed general procedure for cyclisations using the Squaramide catalyst **27**.

Purified by flash column chromatography on silica gel (7:3, petroleum ether/ethyl acetate) to give the product **283** (83 mg, 77%) as a colourless solid. m.p. 157 °C; $[\alpha]_D^{23}$ -76.5 (*c* 0.75, $CHCl_3$, 98% ee); *Rf* 0.3 (7:3, petroleum ether/ethyl acetate); ν_{max}(neat)/cm^{-1} 3045, 2948, 2871, 1685, 1533, 1349, 1158; δ_H (400 MHz, $CDCl_3$) 8.32-8.29 (2H, m, CH_2), 8.01-7.98 (2H, m, CH_2), 7.80-7.76 (2H, m, CH_2), 7.64-7.60 (2H, m, CH_2), 4.72-4.69 (1H, m, CH), 3.92-3.88 (1H, m, CH_2), 3.33 (1H, dd, *J* 16.0, 9.0, CH_2), 3.23-3.11 (2H, m, CH_2), 1.68-1.51 (5H,

m, CH_2), 1.38-1.29 (1H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 196.1 (C), 149.9 (C), 147.0 (C), 135.0 (C), 132.1 (CH), 129.6 (CH), 128.9 (C), 128.1 (CH), 124.4 (CH), 49.9 (CH), 41.8 (CH_2), 39.3 (CH_2), 27.9 (CH_2), 24.9 (CH_2), 18.4 (CH_2); *m/z* (ESI) 491 ($M^{81}Br+Na^+$, 100%), 489 ($M^{79}Br+Na^+$, 94); *m/z* (ESI) Found 491.0067. $C_{19}H_{19}{}^{81}BrN_2O_5SNa^+$ requires 491.0070; HPLC: Chiralcel AD-H; mobile phase, hexane/2-propanol (1:1 v/v); flow rate, 1.0 ml/min; 13.0 min (99.0%), 29.1 min (1.0%), 98% ee.

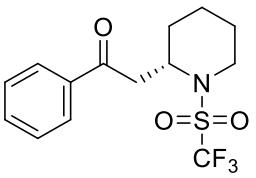
(*S*)-1-(Benzo[d][1,3]dioxol-5-yl)-2-(1-(phenylsulfonyl)piperidin-2-yl)ethan-1-one **284**



Followed general procedure for cyclisations using the Squaramide catalyst **27**.

Purified by flash column chromatography on silica gel (4:1, petroleum ether/ethyl acetate) to give the product **284** (63 mg, 81%) as a white solid. m.p. 138 °C; $[\alpha]_D^{23}$ -42.9 (*c* 0.9, $CHCl_3$, 99% ee); *Rf* 0.4 (7:3, petroleum ether/ethyl acetate); ν_{max}(neat)/cm^{-1} 3011, 2946, 2870, 1674, 1445, 1252, 1158; δ_H (400 MHz, $CDCl_3$) 7.85-7.83 (2H, m, ArH), 7.56-7.46 (4H, m, ArH), 7.39 (1H, d, *J* 1.0, ArH), 6.86 (1H, d, *J* 8.0, ArH), 6.06 (2H, s, CH_2), 4.67-4.62 (1H, m, CH), 3.89-3.85 (1H, m, CH_aH_b), 2.31-3.24 (1H, dd, *J* 15.5, 10.5, CH_2), 3.11-3.03 (2H, m, CH_2), 1.62-1.50 (5H, m, CH_2), 1.40-1.32 (1H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 195.6 (C), 152.0 (CH), 148.3 (C), 141.1 (C), 132.4 (CH), 131.5 (C), 129.1 (CH), 127.0 (CH), 124.6 (CH), 107.9 (CH), 101.9 (CH_2), 49.8 (CH), 41.4 (CH_2), 38.8 (CH_2), 27.4 (CH_2), 24.8 (CH_2), 18.4 (CH_2); *m/z* (ESI) 410 ($M+Na^+$ 100%); *m/z* (ESI) Found 410.1030. $C_{20}H_{21}NO_5SNa^+$ requires 410.1033; HPLC: Chiralcel AD-H; mobile phase, hexane/2-propanol (1:1 v/v); flow rate, 1.0 ml/min; 9.4 min (99.8%), 16.9 min (0.2%), 99% ee.

(*S*)-1-Phenyl-2-(1-((trifluoromethyl)sulfonyl)piperidin-2-yl)ethan-1-one **285**

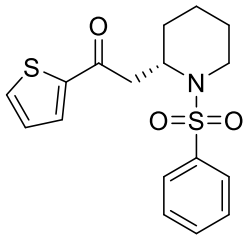


Followed general procedure for cyclisations using the Squaramide catalyst **27**.

Purified by flash column chromatography on silica gel (9:1, petroleum ether/ethyl acetate) to give the product **285** (25.2 mg, 75%) as a colourless solid. $[\alpha]^{22}$ -10.6 (*c* 0.7, $CHCl_3$, 86% ee); m.p. 98-101 °C; *Rf* 0.30 (9:1, petroleum

ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3045, 2952, 2866, 1686, 1388, 625; δ_H (400 MHz, $CDCl_3$) 8.00 (2H, dd, *J* 8.0, 1.5, ArH), 7.63 (1H, dddd, *J* 8.0, 7.5, 1.5, 1.5, ArH), 7.55-7.49 (2H, m, ArH), 4.88-4.67 (1H, m, CH), 3.97-3.88 (1H, m, COC*Ha*Hb), 3.60 (1H, dd, *J* 16.0, 10.5, COCHa*Hb*), 3.36-3.19 (2H, m, CH_2), 1.94-1.51 (6H, m, 3 x CH_2); δ_C (100 MHz, $CDCl_3$) 196.5 (C), 136.3 (C), 133.7 (CH), 128.9 (CH), 128.2 (CH), 119.8 (C, q, *J* 320, CF_3), 51.6 (CH), 43.2 (CH_2), 39.7 (br. CH_2), 27.7 (br. CH_2), 25.1 (br. CH_2), 17.9 (CH_2); *m/z* (ESI) 358 ($M+H^+$, 41%), 336 ($M+H^+$, 100%); *m/z*(ESI) found 336.0876. $C_{14}H_{18}F_3NO_3S^+$ requires 336.0876; HPLC: Chiralcel OD-H; mobile phase, hexane/2-propanol (9:1 v/v); flow rate, 1 mL/min; 6.0 min (93%), 8.3 min (7%) 86% ee.

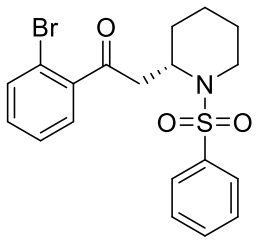
(*S*)-2-(1-(Phenylsulfonyl)piperidin-2-yl)-1-(thiophen-2-yl)ethan-1-one **286**



Followed general procedure for cyclisations using the Squaramide catalyst **27**.

Purified by flash column chromatography on silica gel (7:3, petroleum ether/ethyl acetate) to give the product **286** (46 mg, 73%) as a white solid. m.p. 73 °C; $[\alpha]_D^{23}$ -16.5 (*c* 0.9, $CHCl_3$, 99% ee); *Rf* 0.3 (7:3, petroleum ether/ethyl acetate); ν_{max}(neat)/cm^{-1} 2947, 2867, 1659, 1416, 1156; δ_H (400 MHz, $CDCl_3$) 7.86-7.83 (2H, m, ArH), 7.75 (1H, *J* 4.0, 1.0, dd, ArH), 7.65 (1H, dd, *J* 5.0, 1.0, ArH), 7.56-7.52 (1H, m, ArH), 7.50-7.46 (2H, m, ArH), 7.14 (1H, dd, *J* 5.0, 4.0, ArH), 4.69-4.66 (1H, m, CH), 3.88-3.84 (1H, m, CH_aH$_b$), 3.27 (1H, dd, J 15.0, 10.5, CH_cH$_d$), 3.13-3.03 (2H, m, CH$_a$$H_b$ and CH$_c$$H_d$), 1.67-1.52 (5H, m, CH_2), 1.42-1.32 (1H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 190.4 (C), 144.1 (C), 141.0 (C), 134.2 (CH), 132.5 (CH), 129.1 (CH), 128.3 (CH), 127.0 (CH), 49.9 (CH), 41.4 (CH_2), 39.9 (CH_2), 27.5 (CH_2), 24.8 (CH_2), 18.3 (CH_2); *m/z* (ESI) 372 ($M+Na^+$ 100%) 350 ($M+H^+$ 68%); *m/z* (ESI) Found 372.0691. $C_{17}H_{19}NO_3S_2Na^+$ requires 372.0699; HPLC: Chiralcel AD-H; mobile phase, hexane/2-propanol (1:1 v/v); flow rate, 1.0 ml/min; 6.6 min (99.5%), 27.5 min (0.5%), 99% ee.

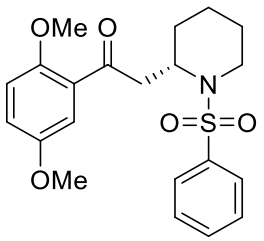
(*S*)-1-(2-Bromophenyl)-2-(1-(phenylsulfonyl)piperidin-2-yl)ethan-1-one **287**



Followed general procedure for cyclisations using the Squaramide catalyst **27**.

Purified by flash column chromatography on silica gel (9:1, petroleum ether/ethyl acetate) to give the product **287** (28.3 mg, 67%) as a colourless oil. $[\alpha]^{21}$ -47.1 (*c* 0.7, $CHCl_3$, 83% ee); *Rf* 0.61 (3:2, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3045, 2947, 2867, 1701, 1328, 1175, 1156; δ_H (400 MHz, $CDCl_3$) 7.88-7.82 (2H, m, ArH), 7.62-7.54 (2H, m, ArH), 7.53-7.47 (2H, m, ArH), 7.41-7.26 (3H, m, ArH), 4.74-4.66 (1H, m, CH), 3.91-3.82 (1H, m, C*Ha*Hb), 3.39 (1H, dd, *J* 17.0, 10.0, COC*Ha*Hb), 2.99 (1H, dd, *J* 17.0, 4.0, COHa*Hb*), 2.96 (1H, ddd, 13.5, 13.5, 2.5, CHa*Hb*), 1.75-1.45 (5H, m), 1.44-1.28 (1H, m); δ_C (100 MHz, $CDCl_3$) 201.2 (C), 141.2 (C), 141.0 (C), 133.7 (CH), 132.4 (CH), 131.8 (CH), 129.1 (CH), 128.5 (CH), 127.6 (CH), 127.0 (CH), 118.5 (C), 49.0 (CH), 42.8 (CH_2), 41.4 (CH_2), 27.7 (CH_2), 24.7 (CH_2), 18.4 (CH_2); *m/z* (ESI) 446 ($M^{81}Br+Na^+$, 100%), 444 ($M^{79}Br+Na^+$, 97), 424 ($M^{81}Br+H^+$, 68), 422 ($M^{79}Br+H^+$, 67); *m/z* (ESI) found 446.0212. $C_{19}H_{20}{}^{81}BrNO_3SNa^+$ requires 446.0219; HPLC: Chiralcel OD-H; mobile phase, hexane/2-propanol (9:1 v/v); flow rate, 1 mL/min; 18.8 min (91.5%), 23.4 min (8.5%) 83% ee.

(*S*)-1-(2,5-Dimethoxyphenyl)-2-(1-(phenylsulfonyl)piperidin-2-yl)ethan-1-one **288**

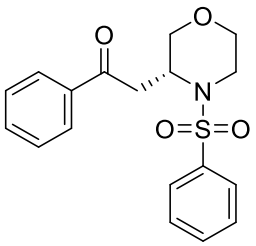


Followed general procedure for cyclisations using the Squaramide catalyst **27**.

Purified by flash column chromatography on silica gel (7:3, petroleum ether/ethyl acetate) to give the product **288** (20.2 mg, 50%) as a colourless oil. $[\alpha]_D^{23}$ -45.2 (*c* 1.0, $CHCl_3$, 88% ee); *Rf* 0.3 (7:3, petroleum ether/ethyl acetate); ν_{max}(neat)/cm^{-1} 3010, 2945, 2877, 1665, 1601, 1259, 1170, 1161; δ_H (400 MHz, $CDCl_3$) 7.86-7.82 (2H, m, ArH), 7.56-7.51 (1H, m ArH), 7.50-7.45 (2H, m, ArH), 7.22 (1H, d, *J* 3.5, ArH), 7.05 (1H, dd, 9.0, 3.5, ArH), 6.91 (1H, d, *J* 9.0, ArH), 4.79-4.72 (1H, m, NCH), 3.89-3.86 (1H, m, NC*Ha*Hb), 3.85 (3H, s, OCH_3), 3.82 (3H, s,

OCH_3), 3.44 (1H, dd, *J* 16.5, 10.0, COC*Ha*Hb), 3.13 (1H, dd, *J* 16.5, 4.0, COCHa*Hb*), 3.08-2.99 (1H, m, NCHa*Hb*), 1.66-1.50 (5H, m, 2.5 x CH_2), 1.43-1.31 (1H, , 0.5 x CH_2); δ_c (100 MHz, $CDCl_3$) 192.8 (C), 153.5 (C), 152.3 (C), 147.4 (CH), 139.9 (C), 132.7 (CH), 130.9 (CH), 129.5 (C), 129.2 (CH), 127.0 (CH), 118.8 (CH), 114.4 (CH), 113.3 (CH), 56.4 (CH), 55.9 (CH), 43.1 (CH_2), 43.0 (CH_2), 31.8 (CH_2), 29.1 (CH_2), 25.0 (CH_2); *m/z* (ESI) 404 ($M+H^+$, 100%); *m/z* (ESI) Found 404.1520. $C_{21}H_{27}NO_5S^+$ requires 404.1520; HPLC: Chiralcel AD-H; mobile phase, hexane/2-propanol (4:1 v/v); flow rate, 1.0 ml/min; 25.9 min (97.8%), 29.3 min (2.2%), 96% ee.

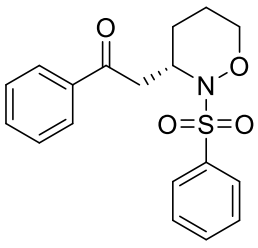
(*S*)-1-Phenyl-2-(4-(phenylsulfonyl)morpholin-3-yl)ethan-1-one **289**



Followed general procedure for cyclisations using the Squaramide catalyst **27**.

Purified by flash column chromatography on silica gel (7:3, petroleum ether/ethyl acetate) to give the product **289** (32.8 mg, 95%) as a colourless oil. $[\alpha]^{22}$ -84 (*c* 0.8, $CHCl_3$, 99% ee); *Rf* 0.4 (3:2, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3011, 2926, 2866, 1684, 1599, 1448, 1165, 944; δ_H (400 MHz, $CDCl_3$) 7.92-7.83 (4H, m, ArH), 7.63-7.56 (2H, m, ArH), 7.55-7.44 (4H, m, ArH), 4.55-4.47 (1H, m, CH), 3.87 (1H, dd, *J* 11.0, 3.0, CH), 3.80 (1H, d, *J* 12.0, CH), 3.73 (1H, dd, *J* 16.0, 10.5, C*Ha*Hb), 3.72-3.65 (1H, m, CH), 3.54 (1H, dd, *J* 12.0, 3.0, 2.0, CH), 3.46 (1H, ddd, *J* 12.0, 12.0, 3.0, CH), 3.34 (1H, ddd, *J* 12.0, 12.0, 3.0, CH); δ_C (100 MHz, $CDCl_3$) 197.3 (C), 140.3 (C), 136.5 (C), 133.5 (CH), 132.8 (CH), 129.4 (CH), 128.7 (CH), 128.0 (CH), 127.1 (CH), 69.1 (CH_2), 66.5 (CH_2), 49.4 (CH), 41.3 (CH_2), 36.7 (CH_2); *m/z*(ESI) 368 ($M+Na^+$, 100%), 346 ($M+H^+$, 31%); *m/z* (ESI) found 368.0917. $C_{18}H_{19}NSO_4Na^+$ requires 368.0927; HPLC: Chiralcel OD-H; mobile phase, hexane/2-propanol (9:1 v/v); flow rate, 1 mL/min; 27.3 min (99.3%), 33.9 min (0.7%) 99% ee.

(*S*)-1-Phenyl-2-(2-(phenylsulfonyl)-1,2-oxazinan-3-yl)ethan-1-one **292**

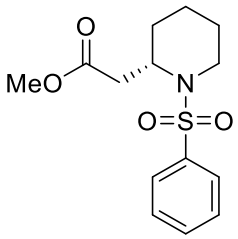


Followed general procedure for cyclisations using the Squaramide catalyst **27**.

Purified by flash column chromatography on silica gel (7:3, petroleum ether/ethyl acetate) to give the product **292** (39.9 mg, 86%) as a colourless oil. $[\alpha]^{21}$ -41 (*c* 0.7, $CHCl_3$, 98% ee); *Rf* 0.38 (7:3, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3067, 3044, 2953, 2933, 1685, 1599, 1448, 1365, 1333, 1167, 1093; δ_H (400 MHz, $CDCl_3$) 7.98-7.88 (4H, m, ArH), 7.63-7.55 (2H, m, ArH), 7.53-7.43 (4H, m, ArH), 4.92-4.81 (1H, m, CH), 4.09 (1H, ddd, *J* 11.0 11.0, 3.0, OC*Ha*Hb), 4.05-3.97 (1H, m, OCHa*Hb*), 3.64 (1H, dd, *J* 17.0, 4.0, (CO)C*Ha*Hb), 3.42 (1H, dd, *J* 17.0, 9.0, (CO)CHa*Hb*), 2.16-2.06 (1H, m, CH), 2.05-1.92 (1H, m, CH), 1.90-1.82 (1H, m, CH), 1.56-1.45 (1H, m, CH); δ_C (100 MHz, $CDCl_3$) 197.4 (C), 137.8 (C), 136.7 (C), 133.4 (CH), 128.9 (CH), 128.7 (CH), 128.5 (CH), 128.2 (CH), 71.9 (CH_2), 51.8 (CH), 38.1 (CH_2), 26.6 (CH_2) 20.1 (CH_2); *m/z*(ESI) 368 ($M+Na^+$, 25%), 346 ($M+H^+$, 100%); *m/z*(ESI) found 346.1107. $C_{18}H_{20}NO_4S^+$ requires 346.1108; HPLC: Chiralcel OD-H; mobile phase, hexane/2-propanol (9:1 v/v); flow rate, 1 mL/min; 14.6 min (99%), 18.4 min (1%) 98% ee.

Cyclic Esters, Thioesters, Amides etc.

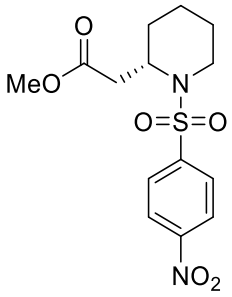
(*S*)-Methyl 2-(1-(phenylsulfonyl)piperidin-2-yl)acetate **303**



Followed general procedure for cyclisations using the Squaramide catalyst **27**.

Purified by flash column chromatography on silica gel (2:1, petroleum ether/ethyl acetate) to give the product **303** (21 mg, 71%) as a colourless oil. $[\alpha]_D^{25}$ -11.1 (*c* 0.45, $CHCl_3$, 92% ee); *Rf* 0.3 (2:1, petroleum ether/ethyl acetate); ν_{max}(neat)/cm^{-1} 2926, 2854, 1735, 1446; δ_H (400 MHz, $CDCl_3$) 7.86-7.84 (2H, m, ArH), 7.58-7.49 (3H, m, ArH), 4.57-4.54 (1H, m, CHN), 3.83 (1H, dd, *J* 13.5, 3.5, C$H_a$$H_b$), 3.64 (3H, s, CH_3), 3.01-2.94 (1H, m, CH_aH_b), 2.64 (1H, dd, *J* 15.0, 9.0, CH_2), 2.52 (1H, dd, *J* 15.0, 6.0, CH_2), 1.59-1.29 (6H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 171.2 (C), 141.2 (C), 132.4 (CH), 129.1 (CH), 127.0 (CH), 51.8 (CH_3), 49.8 (CH), 41.0 (CH_2), 35.0 (CH_2), 27.2 (CH_2), 24.6 (CH_2), 18.3 (CH_2); *m/z* (ESI) 320 [($M+Na^+$ 100%), 298 ($M+H^+$ 81%), (M_2+Na^+ 29%)]; *m/z* (ESI) Found 320.0905. $C_{14}H_{19}NO_4SNa^+$ requires 320.0927; HPLC: Chiralcel AD-H; mobile phase, hexane/2-propanol (9:1 v/v); flow rate, 1.0 ml/min; 14.2 min (96.0%), 18.0 min (4.0%), 92% ee.

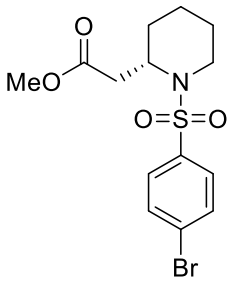
(*S*)-Methyl 2-(1-(phenylsulfonyl)piperidin-2-yl)acetate **303a**



Followed general procedure for cyclisations using the Squaramide catalyst **27**.

Purified by flash column chromatography on silica gel (7:3, petroleum ether/ethyl acetate) to give the product **303a** (25 mg, 73%) as a colourless solid; m.p. 80 °C; $[\alpha]_D^{23}$ -25.1 (*c* 0.75, $CHCl_3$, 88% ee); *Rf* 0.3 (7:3, petroleum ether/ethyl acetate); ν_{max}(neat)/cm^{-1} 2951, 2872, 1735, 1533, 1349, 1160, 909; δ_H (400 MHz, $CDCl_3$) 8.37-8.34 (2H, m, ArH), 8.05-8.02 (2H, m, ArH), 4.60-4.56 (1H, m, CH), 3.88-3.83 (1H, m, CH_2), 3.65 (3H, s, CH_3), 3.04 (1H, ddd, *J* 14.0, 14.0, 2.0, CH_2), 2.65 (1H, dd, *J* 15.0, 6.5, CH_2), 2.56 (1H, dd, *J* 15.0, 6.5, CH_2), 1.63-1.52 (5H, m, CH_2), 1.37-1.27 (1H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 170.9 (C), 147.2 (C), 128.2 (2 x CH), 124.4 (CH), 52.0 (CH_3), 50.2 (CH), 41.3 (CH_2), 35.3 (CH_2), 28.0 (CH_2), 24.8 (CH_2), 18.2 (CH_2); *m/z* (ESI) 365 ($M+Na^+$ 100%), 343 ($M+H^+$ 94%); *m/z* (ESI) Found 365.0774. $C_{14}H_{18}N_2O_6SNa^+$ requires 365.0778; HPLC: Chiralcel AD-H; mobile phase, hexane/2-propanol (1:1 v/v); flow rate, 1.0 ml/min; 8.8 min (93.8%), 11.0 min (6.2%), 88% ee.

(*S*)-Methyl 2-(1-((4-bromophenyl)sulfonyl)piperidin-2-yl)acetate **313**

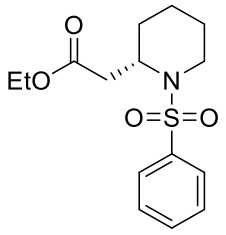


Followed general procedure for cyclisations using the Squaramide catalyst **27**.

Purified by flash column chromatography on silica gel (7:3, petroleum ether/ethyl acetate) to give the product **313** (17.9 mg, 66%) as a colourless solid; m.p. 108-115 °C; $[\alpha]_D^{23}$ -51.9 (*c* 1.0, $CHCl_3$, 88% ee); *Rf* 0.34 (7:3, petroleum ether/ethyl acetate); ν_{max}($CHCl_3$)/cm^{-1} 2931, 2860, 1735, 1381; δ_H (400 MHz, $CDCl_3$) 7.76-7.63 (4H, m, ArH), 4.56 (1H, t, *J* 6.0, NH), 3.90-3.72 (1H, m, NCH), 3.68 (3H, s, OCH_3), 3.05-2.96 (1H, m, *CHa*Hb), 2.67 (1H, dd, *J* 15.0, 9.0, C*Ha*Hb), 2.57 (1H, dd, *J* 15.0, 6.0, CHa*Hb*), 1.65-1.22 (6H, m, 3 x CH_2); δ_c (100 MHz, $CDCl_3$) 171.1 (C), 140.3 (C), 132.4 (CH), 128.6 (CH), 127.3 (C), 51.9 (CH_3), 49.9 (CH), 41.1 (CH_2), 35.1 (CH_2), 27.8 (CH_2), 26.7 (CH_2), 18.3 (CH_2); *m/z* (ESI)

400 ($M^{81}Br+Na^+$, 100%), 398 ($M^{79}Br+Na^+$, 99%), 378 ($M^{81}Br+H^+$, 24), 376 ($M^{79}Br+H^+$, 22); *m/z* (ESI) Found 400.0015. $C_{14}H_{18}N^{81}BrO_4SNa^+$ requires 400.0012; HPLC: Chiralcel AD-H; mobile phase, hexane/2-propanol (4:1 v/v); flow rate, 1.0 ml/min; 13.4 min (93.9%), 16.6 min (6.1%), 88% ee.

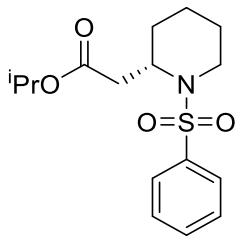
(*S*)-Ethyl 2-(1-(phenylsulfonyl)piperidin-2-yl)acetate **304**



Followed general procedure for cyclisations using the Squaramide catalyst **27**.

Purified by flash column chromatography on silica gel (7:3, petroleum ether/ethyl acetate) to give the product **304** (21.6 mg, 70%) as a colourless oil; $[\alpha]_D^{22}$ -18.0 (*c* 1.00, $CHCl_3$, 93% ee); *Rf* 0.4 (7:3, petroleum ether/ethyl acetate); $\nu_{max}(CHCl_3)/cm^{-1}$ 2930, 2855, 1731, 1455; δ_H (400 MHz, $CDCl_3$) 7.89-7.84 (2H, m, ArH), 7.61-7.49 (3H, m, ArH), 4.61-4.53 (1H, m, NCH), 4.16-4.08 (2H, m, OCH_2), 3.84 (1H, ddd, *J* 13.5, 3.5, 1.5, C*Ha*Hb), 2.99 (1H, ddd, *J* 13.5, 3.5, 1.5, CHa*Hb*), 2.65 (1H, dd, *J* 15.0, 9.0, COC*Ha*Hb), 2.51 (1H, dd, *J* 15.0, 6.0, COCHa*Hb*), 1.68-1.30 (6H, m, 3 x CH_2), 1.27 (3H, t, *J* 7.0); δ_c (100 MHz, $CDCl_3$) 170.8 (C), 141.2 (C), 133.4 (CH), 129.1 (CH), 127.0 (CH), 60.7 (CH_2), 49.8 (CH), 41.0 (CH_2), 35.1 (CH_2), 27.7 (CH_2), 24.6 (CH_2), 18.3 (CH_2), 14.2 (CH_3); ; *m/z* (ESI) 334 ($M+Na^+$ 100%), 312 ($M+H^+$ 51%); *m/z* (ESI) Found 334.1079. $C_{15}H_{21}NO_4SNa^+$ requires 334.1083; HPLC: Chiralcel AD-H; mobile phase, hexane/2-propanol (9:1 v/v); flow rate, 1.0 ml/min; 16.1 min (97.1%), 21.9 min (2.9%), 93% ee.

(*S*)-*Iso*-propyl 2-(1-(phenylsulfonyl)piperidin-2-yl)acetate **305**

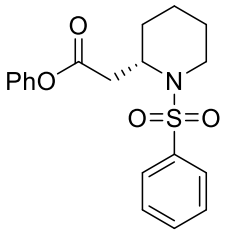


Followed general procedure for cyclisations using the Squaramide catalyst **27**.

Purified by flash column chromatography on silica gel (7:3, petroleum ether/ethyl acetate) to give the product **305** (40.1 mg, 99%) as a colourless oil; $[\alpha]_D^{23}$ -28.5 (*c* 1.00, $CHCl_3$, 94% ee); *Rf* 0.26 (7:3, petroleum ether/ethyl acetate); $\nu_{max}(CHCl_3)/cm^{-1}$ 2933, 2854, 1720, 1462; δ_H (400 MHz, $CDCl_3$) 7.90-7.86 (2H, m, ArH), 7.61-7.50 (3H, m, ArH), 5.00 (1H, sept, *J* 6.5, O*CH*$(CH_3)_2$), 4.62-4.53 (1H, m, CH), 3.84 (1H, dd, *J* 14.0, 3.5, NC*Ha*Hb), 2.98 (1H, td, *J* 13.5, 2.5, NCHa*Hb*), 2.63 (1H, dd, *J* 15.0, 9.5, COC*Ha*Hb), 2.47 (1H, dd, *J* 15.0, 5.5,

COCHa*Hb*), 1.62-1.46 (6H, m, 3 x CH_2), 1.34-1.17 (6H, dd, *J* 6.0, 4.0, 2 x CH_3); δ_c (100 MHz, $CDCl_3$) 170.4 (C), 141.2 (C), 132.4 (CH), 129.1 (CH), 127.0 (CH), 49.8 (CH), 41.0 (CH_2), 35.6 (CH_2), 29.7 (CH_2), 27.6 (CH_2), 24.6 (CH_2), 21.8 (CH_3), 18.3 (CH); *m/z* (ESI) 348 ($M+Na^+$, 100%), 326 ($M+H^+$, 33); *m/z* (ESI) Found 348.1237. $C_{16}H_{23}NO_4SNa^+$ requires 348.1240; HPLC: Chiralcel AD-H; mobile phase, hexane/2-propanol (4:1 v/v); flow rate, 1.0 ml/min; 8.0 min (97.2%), 12.0min (2.8%), 94% ee.

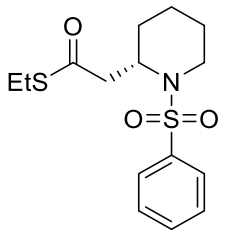
(*S*)-Phenyl 2-(1-(phenylsulfonyl)piperidin-2-yl)acetate **307**



Followed general procedure for cyclisations using the Squaramide catalyst **27**.

Purified by flash column chromatography on silica gel (7:3, petroleum ether/ethyl acetate) to give the product **307** (23.9 mg, 67%) as a colourless oil; $[\alpha]_D^{24}$ -12.2 (*c* 1.00, $CHCl_3$, 85% ee); *Rf* 0.37 (7:3, petroleum ether/ethyl acetate); $\nu_{max}(CHCl_3)/cm^{-1}$ 2927, 2857, 2843, 2771, 1742, 1444, 1390; δ_H (400 MHz, $CDCl_3$) 7.92-7.87 (2H, m, ArH), 7.61-7.56 (1H, m, ArH), 7.55-7.49 (2H, m, ArH), 7.42-7.36 (2H, m, ArH), 7.27-7.22 (1H, m, ArH), 7.14-7.08 (2H, m, ArH), 4.76-4.71 (1H, m *NCH*), 3.88 (1H, ddd, *J* 14.0, 4.5, 2.0, NC*Ha*Hb), 3.09 (1H, ddd, *J* 14.0, 13.0, 2.5, NCHa*Hb*), 2.91-2.79 (2H, m, COC*Ha*Hb and COCHa*Hb*), 1.72-1.32 (6H, m, 3 x CH_2); δ_c (100 MHz, $CDCl_3$) 169.3 (C), 150.5 (C), 141.1 (C), 132.5 (CH), 129.4 (CH), 129.2 (CH), 127.0 (CH), 125.9 (CH), 121.6 (CH), 49.9 (CH), 41.1 (CH_2), 35.4 (CH_2), 29.7 (CH_2), 27.8 (CH_2), 24.4 (CH_2), 18.3 (CH_2); *m/z* (ESI) 382 ($M+Na^+$ 54%), 360 ($M+H^+$ 100%); *m/z* (ESI) Found 360.1266. $C_{19}H_{22}N_2O_4S^+$ requires 360.1264; HPLC: Chiralcel AD-H; mobile phase, hexane/2-propanol (4:1 v/v); flow rate, 1.0 ml/min; 8.0 min (95.9%), 12.0 min (4.1%), 92% ee.

(*S*)-Ethyl 2-(1-(phenylsulfonyl)piperidin-2-yl)ethanethioate **308**

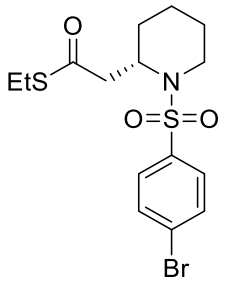


Followed general procedure for cyclisations using the Squaramide catalyst **27**.

Purified by flash column chromatography on silica gel (7:3, petroleum ether/ethyl acetate) to give the product **308** (28.3 mg, 86%) as a pale yellow oil; $[\alpha]_D^{22}$ -22.7 (*c* 1.00, $CHCl_3$, 94% ee); *Rf* 0.3 (4:1, petroleum ether/ethyl

acetate); $\nu_{max}(CHCl_3)/cm^{-1}$ 2930, 2865, 1718, 1400; δ_H (400 MHz, $CDCl_3$) 7.91-7.81 (2H, m, ArH), 7.61-7.47 (3H, m, ArH), 4.62-4.45 (1H, m, NCH), 3.85 (1H, dd, *J* 14.0, 4.0, NC*Ha*Hb), 2.95 (1H, ddd, *J* 14.0, 4.0, 2.0, CHa*Hb*), 2.92-2.82 (3H, m, COC*Ha*Hb and SCH_2), 2.66 (1H, dd, *J* 14.0, 5.5, COCHa*Hb*), 1.66-1.31 (6H, m, 3 x CH_2), 1.25 (3H, t, *J* 7.5, CH_3); δ_c (100 MHz, $CDCl_3$) 196.4 (C), 141.0 (C), 132.4 (CH), 129.1 (CH), 127.0 (CH), 50.1 (CH), 43.7 (CH_2), 41.1 (CH_2), 27.5 (CH_2), 24.7 (CH_2), 23.5 (CH_2), 18.3 (CH_2), 14.6 (CH_3); *m/z* (ESI) 350 ($M+Na^+$ 100%), 328 ($M+H^+$ 23%); *m/z* (ESI) Found 350.0858. $C_{15}H_{21}N_1O_3S_2Na^+$ requires 350.0855; HPLC: Chiralcel AD-H; mobile phase, hexane/2-propanol (4:1 v/v); flow rate, 1.0 ml/min; 8.5 min (97.2%), 15.8 min (2.8%), 94% ee.

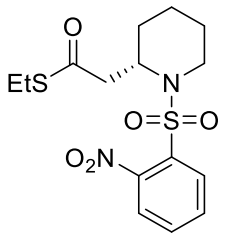
(*S*)-Ethyl 2-(1-((4-bromophenyl)sulfonyl)piperidin-2-yl)ethanethioate **345**



Followed general procedure for cyclisations using the Squaramide catalyst **27**.

Purified by flash column chromatography on silica gel (7:3, petroleum ether/ethyl acetate) to give the product **345** (40.1 mg, 99%) as a colourless oil; $[\alpha]_D^{21}$ -31.3 (*c* 1.00, $CHCl_3$, 94% ee); *Rf* 0.55 (7:3, petroleum ether/ethyl acetate); $\nu_{max}(CHCl_3)/cm^{-1}$ 2935, 2860, 1718, 1404; δ_H (400 MHz, $CDCl_3$) 7.74-7.69 (2H, m, ArH), 7.68-7.63 (2H, m, ArH), 4.61-4.54 (1H, m, CH), 3.86-3.76 (1H, m, NC*Ha*Hb), 2.96 (1H, td, *J* 13.5, 2.5, NCHa*Hb*), 2.91-2.81 (3H, m, SCH_2 and COC*Ha*Hb), 2.69 (1H, dd, *J* 14.5, 6.0, COCHa*Hb*), 1.67-1.49 (5H, m, 2.5 x CH_2), 1.47-1.32 (1H, m, 0.5 x CH_2), 1.25 (3H, t, *J* 7.5, CH_3); δ_c (100 MHz, $CDCl_3$) 196.3 (C), 140.2 (C), 132.4 (CH), 128.6 (CH), 127.3 (C), 50.2 (CH), 43.8 (CH_2), 41.1 (CH_2), 27.7 (CH_2), 24.8 (CH_2), 23.6 (CH_2), 18.3 (CH_2), 14.6 (CH_3); *m/z* (ESI) 430 ($M^{81}Br+Na^+$, 98%), 428 ($M^{79}Br+Na^+$, 100), 408 ($M^{81}Br+H^+$, 31%), 406 ($M^{79}Br+H^+$, 31); *m/z* (ESI) Found 427.9968. $C_{15}H_{20}NO_3S_2{}^{79}BrNa^+$ requires 427.9960; HPLC: Chiralcel AD-H; mobile phase, hexane/2-propanol (4:1 v/v); flow rate, 1.0 ml/min; 10.0 min (96.9%), 20.9 min (3.1%), 94% ee.

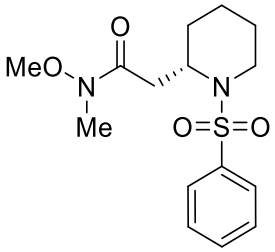
S-Ethyl (*S*)-2-(1-((2-nitrophenyl)sulfonyl)piperidin-2-yl)ethanethioate **346**



Followed general procedure for cyclisations using the Squaramide catalyst **27**.

Purified by flash column chromatography on silica gel (3:2, petroleum ether/ethyl acetate) to give the product **346** (115 mg, 97%) as a pale yellow oil; $[\alpha]_D^{21}$ -27.8 (*c* 1.00, $CHCl_3$, 94% ee); *Rf* 0.27 (3:2, petroleum ether/ethyl acetate); $\nu_{max}(CHCl_3)/cm^{-1}$ 3383, 3021, 2935, 2865, 1722, 1409; δ_H (400 MHz, $CDCl_3$) 8.21-8.07 (1H, m, ArH), 7.79-7.59 (3H, m, ArH), 4.58-4.44 (1H, m, CH), 3.90-3.76 (1H, m, NC*Ha*Hb), 3.13-2.95 (2H, m, NCHa*Hb* and COC*Ha*Hb), 2.88-2.72 (3H, m, COCHa*Hb* and SCH_2), 1.88-1.44 (6H, m, 3 x CH_2), 1.21 (3H, t, *J* 7.0, CH_3); δ_c (100 MHz, $CDCl_3$) 196.3 (C), 147.7 (C), 133.8 (C), 133.5 (CH), 131.9 (CH), 131.3 (CH), 124.3 (CH), 50.6 (CH), 44.0 (CH_2), 41.7 (CH_2), 27.8 (CH_2), 25.2 (CH_2), 23.5 (CH_2), 18.3 (CH_2), 14.6 (CH_3); *m/z* (ESI) 395 (M+Na^+, 100); *m/z* (ESI) Found 395.0741. $C_{15}H_{20}N_2O_5S_2Na^+$ requires 395.0706; HPLC: Chiralcel AD-H; mobile phase, hexane/2-propanol (7:3 v/v); flow rate, 1.0 ml/min; 9.2 min (97.1%), 11.2 min (2.9%), 94% ee.

(*S*)-*N*-methoxy-*N*-methyl-2-(1-(phenylsulfonyl)piperidin-2-yl)acetamide **315**

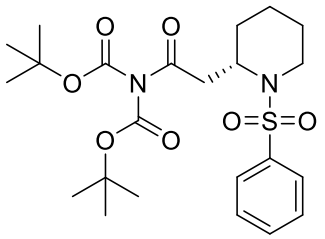


Followed general procedure for cyclisations using the Squaramide catalyst **27**.

Purified by flash column chromatography on silica gel (7:3, petroleum ether/ethyl acetate) to give the product **315** (23 mg, 71%) as a pale yellow oil. $[\alpha]_D^{23}$ -14.3 (*c* 1.00, $CHCl_3$, 86% ee); *Rf* 0.37 (7:3, ethyl acetate/petroleum ether); $\nu_{max}(CHCl_3)/cm^{-1}$ 2930, 2858, 1740, 1390; δ_H (400 MHz, $CDCl_3$) 7.91-7.85 (2H, m, ArH), 7.61-7.48 (3H, m, ArH), 4.65-4.55 (1H, m, CH), 3.88 (1H, br.dd, *J* 13.5, 3.5, N*CHa*Hb), 3.69 (3H, s, OCH_3), 3.17 (3H, s, NCH_3), 3.07 (1H, td, *J* 13.5, 2.5, NCHa*CHb*), 2.86 (1H, dd, *J* 15.0, 10.0, CO*CHa*CHb), 2.63 (1H, dd, *J* 15.0, 5.0, COCHa*CHb*), 1.69-1.15 (6H, m, 3 x CH_2); δ_c (100 MHz, $CDCl_3$) 171.4 (C), 141.3 (C), 132.3 (CH), 129.0 (CH), 127.0 (CH), 61.4 (CH_3), 49.5 (CH), 41.3 (CH_2), 32.7 (CH_2), 32.0 (CH_3), 27.7 (CH_2), 24.8 (CH_2), 18.4 (CH_2); *m/z* (ESI) 349 (M+Na^+ 100%), 327 (M+H^+ 51%); *m/z* (ESI) Found 349.1199. $C_{15}H_{22}N_2O_4SNa^+$ requires

349.1199; HPLC: Chiralcel AD-H; mobile phase, hexane/2-propanol (3:2 v/v); flow rate, 1.0 ml/min; 6.9 min (92.9%), 23.8 min (7.1%), 86% ee.

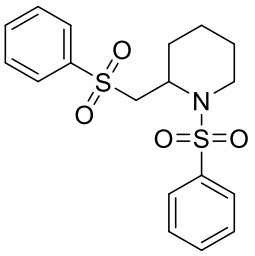
(*S*)-*tert*-Butyl (2-(1-(phenylsulfonyl)piperidin-2-yl)acetyl)dicarbamate **316**



Followed general procedure for cyclisations using the Squaramide catalyst **27**.

Purified by flash column chromatography on silica gel (7:3, petroleum ether/ethyl acetate) to give the product **316** (27.9 mg, 58%) as a colourless oil; $[\alpha]_D^{23}$ -17.6 (*c* 1.00, $CHCl_3$, 97% ee); *Rf* 0.4 (7:3, petroleum ether/ethyl acetate); $\nu_{max}(CHCl_3)/cm^{-1}$ 2985, 2944, 2870, 1777, 1753, 1710, 1371, 1250, 929; δ_H (400 MHz, $CDCl_3$) 7.89-7.83 (2H, m, ArH), 7.58-7.47 (3H, m, ArH), 4.72-4.62 (1H, m, CH), 3.86 (1H, dd, *J* 13.5, 3.0, C*Ha*HbN), 3.33 (1H, dd, *J* 17.0, 10.0, (CO)C*Ha*Hb), 2.99 (1H, ddd, *J* 13.5, 13.5, 2.5, CHa*Hb*N), 2.85 (1H, dd, *J* 17.0, 4.0, (CO)CHa*Hb*) 1.72-1.20 (24H, m, 2 x Boc, 3 x CH_2); δ_c (100 MHz, $CDCl_3$) 171.5 (C), 149.3 (C), 141.1 (C), 132.3 (CH), 129.1 (CH), 127.0 (CH), 84.9 (C), 48.7 (CH), 41.5 (CH_2), 37.1 (CH_2) 27.6 (CH_2) 27.5 (CH_3), 24.7 (CH_2), 18.4 (CH_2); *m/z* (ESI) 505 ($M+Na^+$ 100%); *m/z* (ESI) Found 505.1987. $C_{23}H_{34}N_2O_7SNa^+$ requires 505.1979; HPLC: Chiralcel AD-H; mobile phase, hexane/2-propanol (9:1 v/v); flow rate, 1.0 ml/min; 8.5 min (98.3%), 14.2 min (1.7%), 97% ee.

1-(Phenylsulfonyl)-2-((phenylsulfonyl)methyl)piperidine **318**



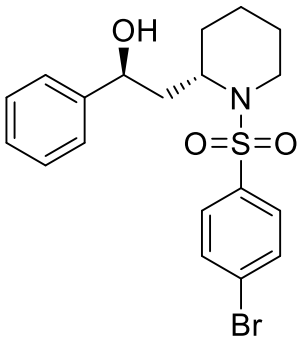
Purified by flash column chromatography on silica gel (7:3, petroleum ether/ethyl acetate) to give the product **318** (25.9 mg, 65%) as a colourless oil; $[\alpha]_D^{24}$ +6.3 (*c* 1.20, $CHCl_3$, 65% ee); *Rf* 0.4 (3:2, petroleum ether/ ethyl acetate); $\nu_{max}(CHCl_3)/cm^{-1}$ 2941, 2933, 2847, 2782, 1161, 901; δ_H (400 MHz, $CDCl_3$) 7.96-7.87 (2H, m, ArH), 7.76-7.68 (3H, m, ArH), 7.66-7.54 (3H, m, ArH), 7.53-7.45 (2H, m, ArH), 4.56-4.50 (1H, m, NCH), 3.85-3.77 (1H, m, N*CHa*Hb), 3.52 (1H, dd, *J* 14.0, 10.0, CO*CHa*Hb), 3.13 (1H, ddd, *J* 13.5, 3.5, 1.0, NCHa*Hb*), 2.77 (1H, td, *J* 13.5, 3.0, COCHa*Hb*), 2.10-2.03 (1H, m, CH), 1.71-1.32 (5H, m, 2 x CH_2 and 0.5 x CH_2); δ_c (100 MHz, $CDCl_3$) 140.3 (C), 139.3 (C), 134.0 (CH), 132.7 (CH), 129.4 (CH), 129.2 (CH), 128.1 (CH), 127.0 (CH), 55.4 (CH_2), 47.9 (CH), 41.4 (CH_2), 27.5

(CH_2), 24.5 (CH_2), 18.1 (CH_2); *m/z* (ESI) 402 ($M+Na^+$ 100%), 380 ($M+H^+$, 41); *m/z* (ESI) Found 402.0813. $C_{18}H_{21}NO_4S_2Na^+$ requires 402.0804; HPLC: Chiralcel AD-H; mobile phase, hexane/2-propanol (3:2 v/v); flow rate, 1.0 ml/min; 11.6 min (17.3%), 13.5 min (82.7%), 65% ee.

Borohydride reduction of phenyl ketones

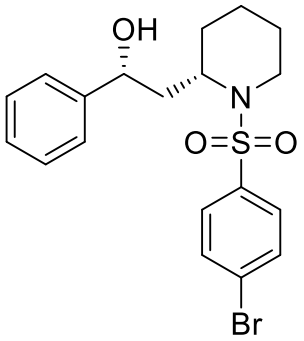
To a solution of phenyl ketone in dichloromethane/methanol (1:1, 0.2M) was added sodium borohydride (2 equiv.) and the reaction monitored by TLC. After 2 h hydrochloric acid (2M, equal volume to reaction solvent) was added and extracted with dichlormethane (3 x reaction volume), dried over magnesium sulfate, concentrated under reduced pressure and the residue purified by flash column chromatography on silica gel (9:1, petroleum ether/ethyl acetate) to give the two diastereoisomers.

(*S*)-2-((*S*)-1-((4-bromophenyl)sulfonyl)piperidin-2-yl)-1-phenylethan-1-ol **342a**



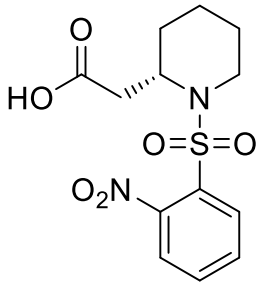
Obtained product (35.7 mg, 68%) as a low melting colourless solid. *Rf* 0.34 (7:3, petroleum ether/ethylacetate); δ_H (400 MHz, $CDCl_3$) 7.84-7.77 (2H, m, ArH), 7.74-7.67 (2H, m, ArH), 7.45-7.36 (4H, m, ArH), 7.34-7.27 (2H, m, ArH), 4.92-4.84 (1H, m, OCH), 4.43-4.35 (1H, m, NC*Ha*Hb), 4.05-3.96 (1H, m, NCHa*Hb*), 3.50 (1H, d, *J* 4.5, OH), 3.16 (1H, td, *J* 14.0, 2.5, OCC*Ha*Hb), 2.24 (1H, ddd, *J* 14.0, 12.0, 2.5, OCCHa*Hb*), 1.72-1.01 (6H, m, 3 x CH_2); δ_c (100 MHz, $CDCl_3$) 144.0 (C), 140.7 (C), 132.6 (CH), 128.5 (CH), 128.4 (CH), 127.4 (CH), 127.3 (C), 69.6 (CH), 50.1 (CH), 41.1 (CH_2), 40.0 (CH_2), 28.0 (CH_2), 24.1 (CH_2), 18.6 (CH_2); *m/z* (ESI) 448 ($M^{81}Br+Na^+$ 98%), 446 ($M^{79}Br+Na^+$, 100); *m/z* (ESI) Found 446.0385. $C_{19}H_{22}NO_3S^{79}BrNa^+$ requires 446.0396.

(*R*)-2-((*S*)-1-((4-bromophenyl)sulfonyl)piperidin-2-yl)-1-phenylethan-1-ol **342b**



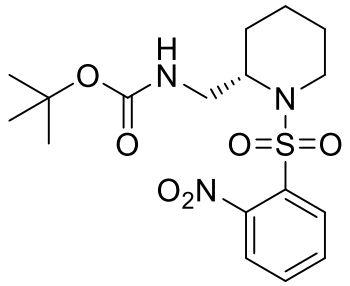
Obtained product (16.7 mg, 32%) as a low melting colourless solid.*Rf* 0.29 (7:3, petroleum ether/ethylacetate); δ_H (400 MHz, $CDCl_3$) 7.78-7.71 (2H, m, ArH), 7.68-7.63 (2H, m, ArH), 7.40-7.30 (5H, m, ArH), 4.75 (1H, dd, *J* 8.5, 4.5, OCH), 4.31 (1H, dt, *J* 6.0, 6.0, NC*Ha*Hb), 3.82 (1H, dd, *J* 14.0, 4.0, NCHa*Hb*), 3.06 (1H, td, *J* 13.5, 2.5, CH), 2.47 (1H, br.s, OH), 2.08-1.98 (1H, m, COC*Ha*Hb), 1.95-1.86 (1H, m, COCHa*Hb*), 1.62-1.15 (6H, m, 3 x CH_2); δ_c (100 MHz, $CDCl_3$) 144.4 (C), 140.6 (C), 132.4 (CH), 128.7 (CH), 128.6 (CH), 127.7 (CH), 127.2 (C), 125.9 (CH), 72.2 (CH), 50.8 (CH), 41.1 (CH_2), 39.4 (CH_2), 27.5 (CH_2), 24.5 (CH_2), 18.3 (CH_2).

(*S*)-2-(1-((2-Nitrophenyl)sulfonyl)piperidin-2-yl)acetic acid **346**



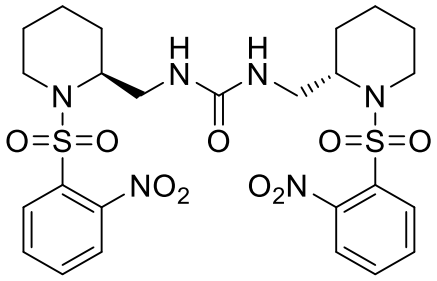
Purified by flash column chromatography on silica gel (7:3, petroleum ether/ethyl acetate) to give the product **346** (542 mg, 86%) as a low melting crystalline solid. *Rf* 0.2 (19:1, dichloromethane/methanol); δ_H (400 MHz, $CDCl_3$) 8.21-8.06 (1H, m, ArH), 7.83-7.68 (3H, m, ArH), 4.54-4.43 (1H, m, CH), 3.90-3.78 (1H, m, C$H_a$$H_b$N), 3.12-3.01 (1H, m, $CH_a$$H_b$N), 2.78 (1H, dd, *J* 15.0, 8.0, COC$H_a$$H_b$), 2.68 (1H, dd, *J* 15.0, 5.0, $COCH_a$$H_b$), 1.90-1.42 (6H, m, 3 x CH_2); δ_c (100 MHz, $CDCl_3$) 176 (C), 147.7 (C), 133.7 (C), 133.6 (CH), 131.9 (CH), 131.2 (CH), 124.2 (CH), 50.0 (CH), 41.6 (CH_2), 35.0 (CH_2), 28.1 (CH_2), 25.2 (CH_2), 18.2 (CH_2); *m/z* (ESI) 327 (M^-, 100%); *m/z* (ESI) Found 327.0628. $C_{13}H_{15}N_2O_6S^-$ requires 327.0656.

tert-Butyl (*S*)-((1-((2-nitrophenyl)sulfonyl)piperidin-2-yl)methyl)carbamate **348**



Rf 0.4 (7:3, petroleum ether/ethylacetate); $\nu_{max}(CHCl_3)/cm^{-1}$ 3443, 2949, 2873, 2150, 1708, 1545, 1517, 1369, 1344, 1164; δ_H (400 MHz, $CDCl_3$) 8.13-8.05 (1H, m, ArH), 7.76-7.62 (3H, m, ArH), 4.81 (1H, br. t, *J* 6.0, NH), 4.12-4.04 (1H, m, NCH), 3.83-3.73 (1H, m, NC*Ha*Hb), 3.59-3.49 (1H, m, NCHa*Hb*), 3.31-3.14 (2H, NHC*Ha*Hb and NHCHa*Hb*), 1.78-1.58 (6H, m, 3 x CH_2), 1.41 (9H, s, 3 x CH_3); δ_c (100 MHz, $CDCl_3$) 156.0 (C), 147.9 (C), 134.3 (C), 133.3 (CH), 131.8 (CH), 130.9 (CH), 124.3 (CH), 79.4 (C), 53.5 (CH), 41.3 (CH_2), 39.5 (CH_2), 28.4 (CH_3), 26.1 (CH_2), 25.0 (CH_2), 18.6 (CH_2); *m/z* (ESI) 422 ($M+Na^+$ 100%), 400 ($M+H^+$, 58); *m/z* (ESI) Found 422.1349. $C_{17}H_{25}N_3O_6SNa^+$ requires 422.1356.

1,3-Bis(((S)-1-((2-nitrophenyl)sulfonyl)piperidin-2-yl)methyl)urea **353**



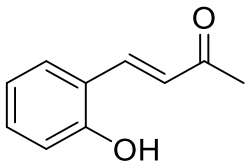
Pale white solid. *Rf* 0.28 (3:2, dichloromethane/methanol);δ_H (400 MHz, $CDCl_3$) 8.15-8.02 (1H, m, ArH), 7.81-7.61 (3H, m, ArH), 4.65-4.54 (1H, m, CH), 4.09-4.00 (1H, m, CH), 3.78-3.69 (1H, m, CH), 3.65-3.44 (1H, m, CH), 3.32-3.10 (2H, m, CH_2), 1.82-1.50 (6H, m, 3 x CH_2); δ_c (100 MHz, $CDCl_3$) 157.7 (C), 147.6 (C), 134.1 (C), 133.4 (CH), 131.9 (CH), 131.0 (CH), 124.3 (CH), 53.6 (CH), 41.4 (CH_2), 39.3 (CH_2), 26.1 (CH_2), 25.0 (CH_2), 18.6 (CH_2); *m/z* (ESI) 647 ($M+Na^+$ 66%), 625 ($M+H^+$, 100); *m/z* (ESI) Found 625.1753. $C_{25}H_{33}N_6O_9S_2^+$ requires 625.1745.

2-Hydroxychalcones

General procedure for the synthesis of hydroxychalcones by a Wittig reaction

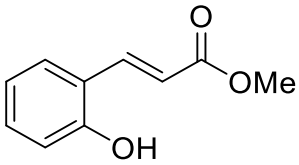
To a solution of salicylaldehyde (1 equiv.) in tetrahydrofuran or dichloromethane (0.5M) was added the corresponding ylide (1.1 equiv.) in portion wise additions at room temperature. The solution was then allowed to stir at room temperature for 16 h before concentrating under reduced pressure and purified by flash column chromatography on silica gel in the solvent systems outlined for individual products.

(*E*)-4-(2-Hydroxyphenyl)but-3-en-2-one **377**



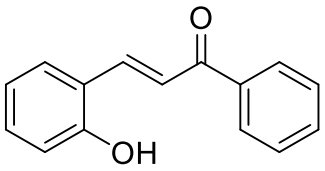
Purified by flash column chromatography on silica gel (2:1, diethyl ether/petroleum ether) to give the product **377** (2.20 g, 90%) as a pink crystalline solid. *Rf* 0.4 (2:1, diethyl ether/petroleum ether); ν_{max} ($CHCl_3$)/cm^{-1} 3591, 3008, 1668, 1645, 1622, 1604; m.p. 141-142 °C (lit. m.p. 139-140 °C)[125]; δ_H (400MHz, $CDCl_3$) 7.86 (1H, d, *J* 16.5, C=CH), 7.49 (1H, dd, *J* 8.0, 1.5, ArH), 7.27 (1H, ddd, *J* 7.5, 7.5, 1.5, ArH), 7.12 (1H, br.s, OH), 7.03 (1H, d, *J* 16.5, C=CH), 6.98-6.89 (2H, m, ArH), 2.44 (3H, s, CH_3); δ_C (100MHz, MeOD) 200.6 (C), 157.1 (C), 140.3 (CH), 131.6 (CH), 128.4 (CH), 126.1 (CH), 121.2 (C), 119.5 (CH), 115.7 (CH), 25.6 (CH_3); *m/z* (ESI) 185 ($M+Na^+$,100), 163 ($M+H^+$, 54%); *m/z* (ESI) found $[M+Na]^+$ 185.0575. $C_{10}H_{10}O_2Na^+$ requires 185.0573.

(*E*)-Methyl 3-(2-hydroxyphenyl)acrylate **378**



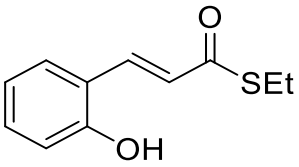
Purified by flash column chromatography on silica gel (19:1, petroleum ether/ethyl acetate) to give the product **378** (1.75 g, 94%) as a colourless crystalline solid, a mixture of *E/Z* isomers (19:1). *Rf* 0.3 (4:1, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3592, 3341, 3011, 1705, 1633, 1606; m.p. 143-145 °C (lit. m.p. 136-137 °C)[126]; δ_H (400MHz, $CDCl_3$) 8.06 (1H, d, *J* 16.0, C=CH), 7.47 (1H, dd, *J* 8.0, 1.5, ArH), 7.26 (1H, ddd, *J* 8.0, 8.0, 1.5, ArH), 6.93 (1H, ddd, *J* 8.0, 8.0, 1.0, ArH), 6.87 (1H, dd, *J* 8.0, 1.0, ArH), 6.66 (1H, d, *J* 16.0, C=CH), 6.52 (1H, br.s, OH), 3.84 (3H, s, OCH_3); δ_C (100MHz, $CDCl_3$) 168.8 (C), 155.3 (C), 140.8 (CH), 131.5 (CH), 129.2 (CH), 121.7 (C), 120.8 (CH), 118.1 (CH), 116.4 (CH), 51.8 (CH_3); *m/z* (ESI) 379 (42), 201 ($M+Na^+$, 100), 179 ($M+H^+$, 38%); *m/z* (ESI) found $[M+Na]^+$ 201.0533. $C_{10}H_{10}O_3Na^+$ requires 201.0522.

(*E*)-3-(2-Hydroxyphenyl)-1-phenylprop-2-en-1-one **379**



Purified by flash column chromatography on silica gel (9:9:2, petroleum ether/dichloromethane/ethyl acetate) to give the product **379** (2.35 g, 88%) as a lime green solid. *Rf* 0.4 (9:9:2 petroleum ether/dichloromethane/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3591, 3009, 1661, 1602; m.p. 153-157 °C (lit. m.p. 154-154.3 °C)[127]; δ_H (400MHz, $CDCl_3$) 8.20 (1H, d, *J* 16.0, C=CH), 8.08-8.02 (2H, m, ArH), 7.72 (1H, d, *J* 16.0, C=CH), 7.64-7.57 (2H, m, ArH), 7.55-7.48 (2H, m, ArH), 7.32-7.25 (1H, m, ArH), 7.00-6.92 (2H, m, ArH), 6.70 (1H, br.s, ArOH); δ_C (100 MHz, $CDCl_3$) 190.9 (C), 155.7 (C), 140.9 (CH), 138.4 (C), 132.8 (CH), 131.8 (CH), 129.5 (CH), 128. 7 (CH), 128.6 (CH), 122.9 (CH), 122.3 (CH), 121.0 (CH), 116.6 (CH); *m/z* (ESI) 471 ($2M+Na^+$, 100%), 247 ($M+Na^+$, 55), 225 ($M+H^+$, 76); *m/z* (ESI) found $[M+H]^+$ 225.0917. $C_{15}H_{13}O_2^+$ requires 225.0910.

S-Ethyl (*E*)-3-(2-hydroxyphenyl)prop-2-enethioate **380**



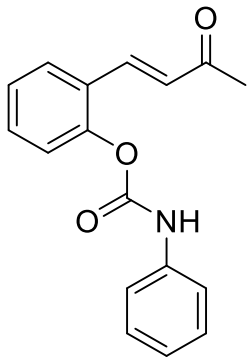
Purified by flash column chromatography on silica gel (4:1, petroleum ether /ethyl acetate) to give the product **380** (3.26 g, 96%) as an off white solid. *Rf* 0.43 (7:3 petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3591, 3041, 3028, 2974, 2933, 2875, 1664, 1647, 1609, 1587, 1458, 1326; m.p. 84-87 °C; δ_H (400MHz, $CDCl_3$) 8.00 (1H, d, *J* 16.0, C=CH), 7.49 (1H, dd, *J* 8.0, 1.5, ArH), 7.26 (1H, ddd, *J* 8.0,7.5, 1.5, ArH), 6.93 (1H, d, *J* 16.0, C=CH), 6.92 (1H, ddd, *J* 7.5, 7.5, 1.0, ArH), 6.88 (1H, dd, *J* 8.0, 1.0, ArH), 6.78 (1H, br.s, ArOH), 3.05 (2H, q, *J* 7.5, CH_2), 1.35 (3H, t. *J* 7.5, CH_3); δ_C (100MHz, $CDCl_3$) 192.3 (C), 155.9 (C), 136.5 (CH), 131.8 (CH), 129.3 (CH), 125.5 (CH), 121.4 (C), 120.8 (CH), 116.5 (CH), 23.5 (CH_2), 14.8 (CH_3); *m/z* (ESI) 231 ($M+Na^+$, 100%); *m/z* (ESI) found $[M+Na]^+$ 231.0453. $C_{11}H_{12}O_2SNa^+$ requires 231.0450.

2-Hydroxychalcone derived carbamates

General procedure for the formation of phenyl and benzyl carbamates

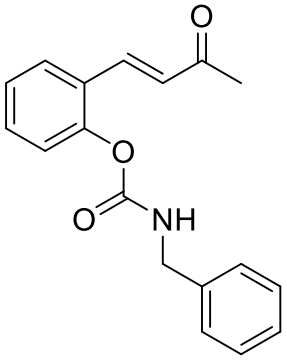
To a 0 °C solution of the hydroxychalcones (1 equiv.) and triethyl amine (1.1 equiv.) in dichloromethane (0.5M) was added the corresponding isocyanate (1 equiv.) dropwise and allowed to stir for 30 mins. The solution was then concentrated under reduced pressure and purified by flash column chromatography on silica gel in the solvent systems outlined for individual products.

(*E*)-4-((Phenylcarbamoyl)oxy)phenyl)but-3-en-2-one **381**



Purified by flash column chromatography on silica gel (9:9:2, dichloromethane/petroleum ether/ethyl acetate) to give the product **381** (85.8 mg, 98%) as a colourless oil. *Rf* 0.4 (9:9:2, dichloromethane/petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3430, 3011, 1758, 1689, 1670, 1646, 1605, 1181; δ_H (400 MHz, $CDCl_3$) 7.80-7.69 (1H, d, *J* 16.5, C=CH), 7.64 (1H, dd, *J* 7.5, 1.5, ArH), 7.57 (1H, br.s, NH), 7.49 (2H, m, ArH), 7.46-7.40 (1H, m, ArH), 7.38-7.29 (2H, m, ArH), 7.27-7.22 (2H, m, ArH) 7.13 (1H, dd, *J* 7.5, 7.5, ArH), 6.76 (1H, d, *J* 16.5, C=CH), 2.36 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 198.5 (C), 151.2 (C), 149.3 (C), 137.1 (C), 136.7 (CH), 131.3 (CH), 129.0 (CH), 128.5 (CH), 127.4 (CH), 127.3 (C), 126.1 (CH), 124.0 (CH), 123.2 (CH), 118.9 (CH), 27.7 (CH_3); *m/z* (ESI) 304 ($M+Na^+$, 100%), 282 ($M+H^+$, 20); *m/z* (ESI) found [$M+Na^+$] 304.0921. $C_{17}H_{15}NO_3Na^+$ requires 304.0944.

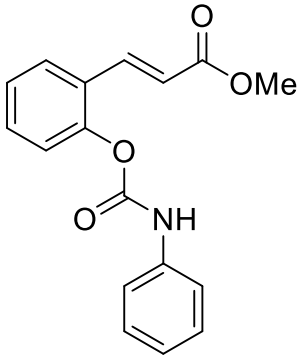
(*E*)-4-((Benzylcarbamoyl)oxy)phenyl)but-3-en-2-one **382**



Purified by flash column chromatography on silica gel (3:1, petroleum ether/ethyl acetate) to give the product **382** (53.1 mg, 90%) as a colourless crystalline solid. *Rf* 0.3 (1:1, petroleum ether/ethyl acetate); m.p. 108-111 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3445, 3009, 1746, 1689, 1672, 1607, 1512, 1481, 1455, 1186; δ_H (400 MHz, $CDCl_3$) 7.68 (1H, d, *J* 16.5, C=CH), 7.64 (1H, dd, *J* 8.0, 1.5, ArH), 7.45-7.29 (6H, m, ArH), 7.28-7.15 (2H, m, ArH), 6.73 (1H, d, *J* 16.5, C=CH), 5.82 (1H, t, *J* 6.0, NH), 4.47 (2H, d, *J* 6.0, $ArCH_2$), 2.33 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 198.3 (C), 154.2 (C), 149.9 (C), 137.9 (C), 137.0 (CH), 131.3 CH), 128.8 (CH), 128.6 (CH), 127.8 (CH), 127.7 (CH), 127.5 (CH), 127.4 (C), 126.0 (CH), 123.3 (CH),

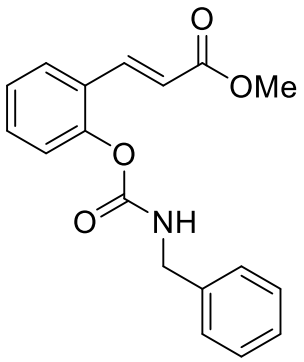
45.4 (CH_2), 27.7 (CH_3); *m/z* (ESI) 318 ($M+Na^+$,100%), 296 ($M+H^+$, 11); *m/z* (ESI) found $[M+Na]^+$ 318.1089. $C_{18}H_{17}NO_3Na^+$ requires 318.1101.

(*E*)-Methyl 3-(2-((phenylcarbamoyl)oxy)phenyl)acrylate **383**



Purified by flash column chromatography on silica gel (9:9:2, petroleum ether/dichloromethane/ethyl acetate) to give the product **383** (70.1 mg, 60%) as a colourless oil. *Rf* 0.4 (9:9:2, petroleum ether/dichloromethane/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3430, 3065, 3011, 2953, 1758, 1713, 1638, 1602, 1526, 1485, 1440, 1322, 1281, 1191; δ_H (400 MHz, $CDCl_3$) 7.93 (1H, d, *J* 16.0, C=CH), 7.64 (1H, dd, *J* 8.0, 1.5, ArH), 7.59 (1H, br.s, NH), 7.55-7.51 (2H, m, ArH), 7.45-7.40 (1H, m, ArH), 7.39-7.31 (2H, m, ArH), 7.30-7.25 (2H, m, ArH), 7.13 (1H, dd, *J* 7.5, 7.5, ArH), 6.50 (1H, d, *J* 16.0, C=CH), 3.82 (3H, s, OCH_3); δ_C (100 MHz, $CDCl_3$) 167.3 (C), 151.2 (C), 149.1 (C), 138.4 (CH), 137.3 (C), 131.2 (CH), 129.2 (CH), 127.6 (CH), 127.4 (C), 126.2 (CH), 124.1 (CH), 123.3 (CH), 119.8 (CH), 118.9 (CH), 51.8 (CH_3); *m/z* (ESI) 320 ($M+H^+$, 100%); *m/z* (ESI) found $[M+H^+]$ 320.0881. $C_{17}H_{15}NO_4^+$ requires 320.0893.

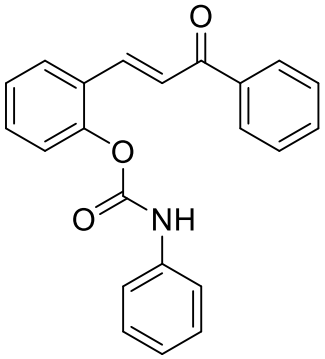
(*E*)-Methyl 3-(2-((benzylcarbamoyl)oxy)phenyl)acrylate **384**



Purified by flash column chromatography on silica gel (dichloromethane) to give the product **384** (365 mg, 84%) as a colourless oil. *Rf* 0.4 (dichloromethane); ν_{max} ($CHCl_3$)/cm^{-1} 3445, 3067, 3011, 2953, 1745, 1714, 1637, 1605, 1512, 1481, 1455, 1185; δ_H (400 MHz, $CDCl_3$) 7.87 (1H, d, *J* 16.0, C=CH), 7.65-7.59 (1H, m, ArH), 7.43-7.30 (6H, m, 6 x ArH), 7.26-7.21 (2H, m, ArH), 6.47 (1H, d, *J* 16.0, C=CH), 5.55 (1H, t, *J* 6.0, NH), 4.48 (2H, d, *J* 6.0, $ArCH_2$), 3.81 (3H, s, OCH_3); δ_C (100 MHz, $CDCl_3$) 167.3 (C), 154.1 (C), 149.6 (C), 138.6

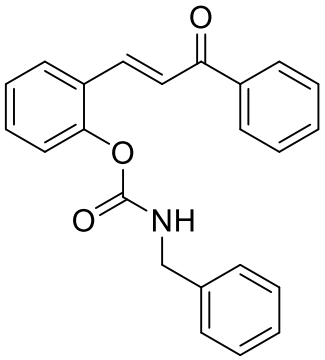
(CH), 137.8 (C), 131.1 (CH), 128.8 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 127.4 (C), 125.9 (CH), 123.3 (CH), 119.7 (CH), 51.8 (CH_3), 45.4 (CH_2); *m/z* (ESI) 334 ($M+Na^+$, 100%), 312 ($M+H^+$, 49); *m/z* (ESI) found $[M+Na]^+$ 334.1038. $C_{18}H_{17}NO_4Na^+$ requires 334.1050.

(*E*)-1-Phenyl-3-(2-((phenylcarbamoyl)oxy)phenyl)prop-2-en-1-one **385**



Purified by flash column chromatography on silica gel (6:3:1, petroleum ether/dichloromethane/ethyl acetate) to give the product **385** (58.0 mg, 76%) as a colourless solid. *Rf* 0.5 (6:3:1, petroleum ether/dichloromethane/ethyl acetate); m.p. 108-112 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3429, 3065, 3011, 1758, 1665, 1641, 1606, 1577, 1181; δ_H (400 MHz, $CDCl_3$) 8.03 (1H, d, *J* 16.0, C=CH), 8.02-7.97 (1H, m, ArH), 7.79 (1H, dd, *J* 8.0, 1.5, ArH), 7.60-7.53 (1H, m, ArH), 7.53 (1H, d, *J* 16.0, C=CH), 7.49-7.40 (5H, m, C=CH and ArH), 7.39-7.26 (5H, m, ArH and NH) 7.18-7.13 (1H, m, ArH); δ_C (100 MHz, $CDCl_3$) 190.6 (C), 151.1 (C), 149.5 (C), 138.2 (CH), 137.9 (C), 137.1 (C), 132.8 (CH), 131.3 (CH), 129.1 (CH), 128.6 (CH), 128.6 (CH), 128.0 (C), 127.6 (CH), 126.2 (CH), 124.0 (CH), 123.4 (CH), 118.9 (CH); *m/z* (ESI) 366 ($M+Na^+$, 100%), 344 ($M+H^+$, 38); *m/z* (ESI) found $[M+Na^+]$ 366.1098. $C_{22}H_{17}NO_3Na^+$ requires 366.1101.

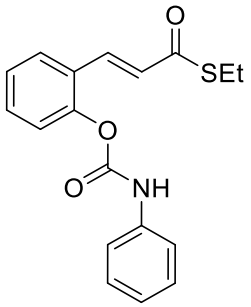
(*E*)-1-Phenyl-3-(2-((benzylcarbamoyl)oxy)phenyl)prop-2-en-1-one **386**



Purified by flash column chromatography on silica gel (47.5:47.5:5, petroleum ether/dichloromethane/ethyl acetate) to give the product **386** (49.2 mg, 79%) as a colourless solid. *Rf* 0.4 (47.5:47.5:5, petroleum ether/dichloromethane/ethyl acetate); m.p. 140-142 °C; δ ν_{max} ($CHCl_3$)/cm^{-1} 3445, 3066, 3011, 1745, 1665, 1639, 1606, 1512, 1480, 1455, 1185; δ_H (400

MHz, $CDCl_3$) 8.07-7.98 (3H, m, C=CH and 2 x ArH), 7.82-7.75 (1H, m, ArH), 7.64-7.58 (1H, m, ArH), 7.58 (1H, d, *J* 16.0, C=CH) 7.56-7.47 (2H, m, ArH), 7.45 (1H, ddd, *J* 8.0, 8.0, 1.5, ArH), 7.44-7.25 (7H, m, ArH) 5.69 (1H, br.s., NH), 4.48 (2H, d, *J* 6.0, $ArCH_2$); δ_C (100 MHz, $CDCl_3$) 190.4 (C), 154.2 (C), 150.1 (C), 138.4 (CH), 138.1 (C), 137.7 (C), 132.9 (CH), 131.3 (CH), 128.9 (CH), 128.7 (CH), 128.6 (CH), 128.0 (C), 127.8 (CH), 127.7 (CH), 127.6 (CH), 125.9 (CH), 123.8 (CH), 123.4 (CH), 45.5 (CH_2); *m/z* (ESI) 380 ($M+Na^+$,100%), 358 ($M+H^+$, 61); *m/z* (ESI) found $[M+Na]^+$ 380.1260. $C_{23}H_{19}NO_3Na^+$ requires 380.1257.

S-Ethyl (E)-3-(2-((phenylcarbamoyl)oxy)phenyl)prop-2-enethioate **387**



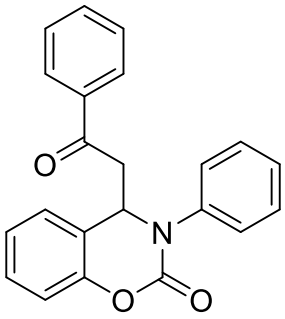
Purified by flash column chromatography on silica gel (3:1, petroleum ether /ethyl acetate) to give the product **387** (420 mg, 89%) as a colourless oil. *Rf* 0.4 (3:1, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3430, 2933, 1759, 1666, 1604, 1525, 1484, 1441, 1180; δ_H (400 MHz, $CDCl_3$) 7.84 (1H, d, *J* 16.0, C=CH), 7.66 (1H, dd, *J* 8.0, 1.5, ArH), 7.52-7.41 (3H, m, ArH and NH), 7.40-7.24 (5H, m, ArH), 7.14 (1H, dd, *J* 7.0, 7.0, ArH), 6.75 (1H, d, *J* 16.0, C=CH), 3.03 (2H, q, *J* 7.5, CH_2), 1.33 (3H, t, *J* 7.5, CH_3); δ_C (100 MHz, $CDCl_3$) 190.1 (C), 149.6 (C), 138.2 (C), 137.9 (C), 137.1 (C), 133.5 (CH), 131.3 (CH), 129.2 (CH), 127.5 (CH), 126.8 (CH), 126.2 (CH), 124.1 (CH), 123.3 (CH), 119.0 (CH), 23.5 (CH_2), 14.7 (CH_3); *m/z* (ESI) 366 ($M+Na^+$, 100%), 344 ($M+H^+$, 38); *m/z* (ESI) found $[M+Na^+]$ 366.1098. $C_{22}H_{17}NO_3Na^+$ requires 366.1101.

3,4-Dihydro-2H-benzo[e][1,3]oxazin-2-ones

General procedure for the cyclisation of 2-hydroxychalcone carbamates

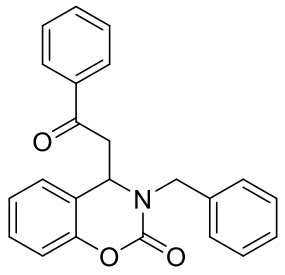
To a solution of the carbamate (1 equiv.) in dichloromethane (0.2M) was added caesium carbonate (0.1 equiv.), and then stirred for 30 mins. The suspension was then concentrated under reduced pressure and purified by flash column chromatography in the solvent system outlined for each individual compound.

3,4-Dihydro-4-(2-oxo-2-phenylethyl)-3-phenyl-2*H*-1,3-benzoxazin-2-one **391**



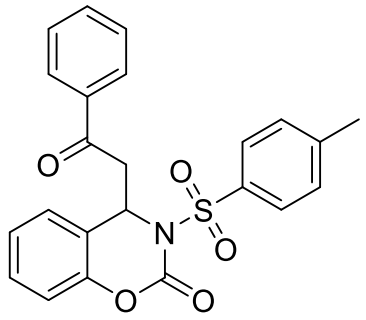
Purified by recrystallisation (4:1, petroleum ether/ethyl acetate) to give the product **391** (282 mg, 69%) as a colourless solid. *Rf* 0.3 (4:1, petroleum ether/ethyl acetate); m.p. 192-194 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3003, 1753, 1665, 1604, 1187; δ_H (400 MHz, $CDCl_3$) 7.83-7.77 (2H, m, ArH), 7.55 (1H, dddd, *J* 7.5, 7.5, 1.5, 1.5, ArH), 7.48-7.41 (6H, m, ArH), 7.40-7.31 (3H, m, ArH), 7.19-7.16 (1H, d, *J* 7.5, ArH), 7.12 (1H, ddd, *J* 7.5, 7.5, 1.0, ArH), 5.58 (1H, dd, *J* 8.5, 3.5, CH), 3.62 (1H, dd, *J* 17.0, 8.5, C*Ha*Hb), 3.54 (1H, dd, *J* 17.0, 3.5, CHa*Hb*); δ_C (100 MHz, $CDCl_3$) 196.3 (C), 150.6 (C), 149.9 (C), 140.2 (C), 136.3 (C), 133.7 (CH), 129.6 (CH), 129.4 (CH), 128.7 (CH), 128.0 (CH), 127.8 (CH), 127.0 (CH), 126.3 (CH), 124.5 (CH), 122.9 (C), 116.6 (CH), 58.1 (CH), 44.1 (CH_2); *m/z* (ESI) 366 ($M+Na^+$,34%), 344 ($M+H^+$, 100); *m/z* (ESI) found $[M+H]^+$ 344.1276. $C_{22}H_{18}NO_3^+$ requires 344.1281.

3-Benzyl-4-(2-oxo-2-phenylethyl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-2-one **392**



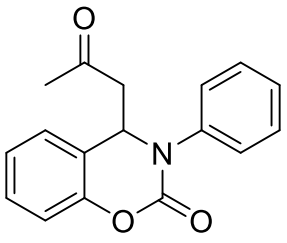
Purified by flash column chromatography on silica gel (7:3, petroleum ether /ethyl acetate) to give the product **392** (22.5 mg, 63%) as a colourless solid. *Rf* 0.5 (7:3, petroleum ether/ethyl acetate); m.p. 161-168 °C; δ_H (400 MHz, $CDCl_3$) 7.84-7.78 (2H, m, ArH), 7.61-7.54 (1H, m, ArH), 7.48-7.41 (2H, m, ArH), 7.39-7.25 (6H, m, ArH), 7.18 (1H, dd, *J* 7.5, 1.5, ArH), 7.13 (1H, dd, *J* 8.0, 1.0, ArH), 7.06 (1H, ddd, *J* 7.5, 7.5, 1.0, ArH), 5.16-5.12 (1H, m, NCH), 5.12 (1H, d, *J* 15.0, PhC*Ha*Hb), 4.42 (1H, d, *J* 15.0, PhCHa*Hb*), 3.41 (1H, dd, *J* 17.5, 7.0, (CO)C*Ha*Hb), 3.39 (1H, dd, *J* 17.5, 5.0, (CO)CHa*Hb*); δ_C (100 MHz, $CDCl_3$) 196.6 (C), 152.1 (C), 149.9 (C), 136.3 (C), 136.0 (C), 135.7 (CH), 129.1 (CH), 128.9 (CH), 128.7 (CH), 128.6 (CH), 128.3 (CH), 125.9 (CH), 124.4 (CH), 123.5 (C), 116.5 (CH), 53.1 (CH), 51.0 (CH_2), 44.8 (CH_2); *m/z* (ESI) 380 ($M+Na^+$, 100%), 296 ($M+H^+$, 40); *m/z* (ESI) found $[M+Na^+]$ 380.1219 $C_{23}H_{19}NO_3Na^+$ requires 380.1257.

3,4-Dihydro-4-(2-oxo-2-phenylethyl)-3-toluene sulfonyl-2*H*-1,3-benzoxazin-2-one **393**



Tosyl isocyanate (39.4 mg, 0. 20 mmol) in dichloromethane (1 mL) was added to a mixture (*E*)-3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one **379** (32.4 mg, 0.20 mmol) in dichloromethane (4 mL). After 15 min of vigorous stirring, all solid dissolved into the solution. DBU (0.1 mL) was added and the solution was stirred for 4 d then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (47.5:47.5:5, petroleum ether/dichloromethane/ethyl acetate) to give the product **393** (38.6 mg, 60%) as colourless oil. *Rf* 0.2 (9:9:2, petroleum ether/dichloromethane/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3069, 1754, 1687, 1619, 1596, 1363, 1174; δ_H (400MHz, $CDCl_3$) 8.00-7.94 (2H, m, 2 x ArH), 7.88-7.81 (2H, m, 2 x ArH), 7.56 (1H, dddd, *J* 7.5, 7.5, 1.5, 1.5, ArH), 7.49-7.39 (3H, m, 3 x ArH), 7.32-7.24 (3H, m, 3 x ArH), 7.13 (1H, ddd, *J* 7.5, 7.5, 1.0, ArH), 7.04 (1H, dd, *J* 8.0, 1.0, ArH), 6.26 (1H, dd, *J* 9.0, 3.0, CH), 3.71 (1H, dd, *J* 17.5, 9.0, C*Ha*Hb), 3.60 (1H, dd, *J* 17.5, 3.0, CHa*Hb*), 2.41 (3H, s, $ArCH_3$); δ_C (100MHz, $CDCl_3$) 195.2 (C), 148.9 (C), 146.9 (C), 145.7 (C), 136.0 (C), 134.8 (C), 133.7 (CH), 129.7 (CH), 129.6 (CH), 129.4 (CH), 128.8 (CH), 128.1 (CH), 127.0 (CH), 125.1 (CH), 122.6 (C), 116.5 (CH), 53.7 (CH), 45.8 (CH_2), 21.7 (CH_3); *m/z* (ESI) 444 ($M+Na^+$, 100%), 422 ($M+H^+$, 34); *m/z* (ESI) found $[M+Na]^+$ 444.0883. $C_{23}H_{19}NO_5SNa^+$ requires 444.0876.

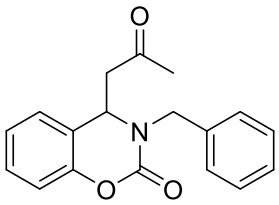
3,4-Dihydro-4-(2-oxopropyl)-3-phenyl-2*H*-1,3-benzoxazin-2-one **394**



Purified by recrystallisation from hot methanol to give the product **394** (603 mg, 58%) as a pink crystalline solid. m.p. 178-180 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3009, 2959, 2927, 1719, 1619, 1600, 1496, 1462, 1416; δ_H (400 MHz, $CDCl_3$) 7.51-7.45 (2H, m, ArH), 7.45-7.39 (2H, m, ArH), 7.38 (2H, m, ArH), 7.34-7.26 (1H, m, ArH), 7.21-7.15 (2H, m, ArH), 5.35 (1H, dd, *J* 8.0, 4.5, CH), 3.07 (1H, dd, *J* 17.0, 4.5, C*Ha*Hb), 3.01 (1H, dd, *J* 17.0, 8.0, CHa*Hb*) 2.02 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 204.9 (C), 150.3 (C), 149.8 (C), 140.1 (C), 129.6 (CH), 129. 5 (CH),

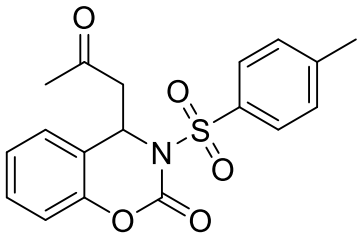
127.9 (CH), 127.1 (CH), 126.1 (CH), 124.5 (CH), 122.7 (C), 116.7 (CH), 57.6 (CH), 48.7 (CH_2), 31.0 (CH_3); *m/z* (ESI) 304 ($M+Na^+$,100%), 282 ($M+H^+$, 28); *m/z* (ESI) found $[M+Na]^+$ 304.0940. $C_{23}H_{19}NO_3Na^+$ requires 304.0944.

3-Benzyl-4-(2-oxopropyl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-2-one **395**



Purified by flash column chromatography on silica gel (7:3, petroleum ether /ethyl acetate) to give the product **395** (27 mg, 92%) as a colourless oil. *Rf* 0.3 (7:3, petroleum ether/ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.38-7.26 (6H, m, ArH), 7.14-7.05 (3H, m, ArH), 5.00 (1H, d, *J* 15.0, PhC*Ha*Hb), 4.91 (1H, dd, *J* 7.0, 5.0, NCH), 4.43 (1H, d, *J* 15.0, PhCHa*Hb*), 2.88-2.83 (2H, m, $(CO)CH_2$), 2.00 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 205.2 (C), 152.0 (C), 149.8 (C), 136.0 (C), 128.9 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 125.7 (CH), 125.6 (CH), 123.2 (C), 116.5 (CH), 52.7 (CH), 51.1 (CH_2), 49.4 (CH_2), 30.3 (CH_3) ; *m/z* (ESI) 318 ($M+Na^+$, 100%), 296 ($M+H^+$, 40); *m/z* (ESI) found $[M+Na^+]$ 318.1093 $C_{18}H_{17}NO_3Na^+$ requires 318.1101.

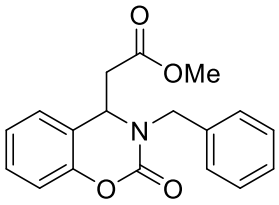
3,4-Dihydro-4-(2-oxopropyl)-3-toluene sulfonyl-2*H*-1,3-benzoxazin-2-one **396**



Tosyl isocyanate (39.4 mg, 0. 20 mmol) in dichloromethane (1 mL) was added to a mixture (*E*)-4-(2-hydroxyphenyl)but-3-en-2-one **396** (32.4 mg, 0.20 mmol) in dichloromethane (4 mL). After 15 min of vigorous stirring, all of the solid dissolved into the solution. Trifluoroacetic acid (0.1 mL) was added and the reaction was stirred for 4 d then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (47.5:47.5:5, petroleum ether/dichloromethane/ethyl acetate) to give the product **396** (25.6 mg, 36%) as colourless oil. *Rf* 0.2 (47.5:47.5:5, petroleum ether/dichloromethane/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 2927, 2855, 1753, 1723, 1596; δ_H (400MHz, $CDCl_3$) 7.97-7.93 (2H, m, ArH), 7.40 (1H, dd, *J* 7.5, 1.5, ArH), 7.36-7.24 (3H, m, 3 x ArH), 7.16 (1H, ddd, *J* 7.0, 7.0, 1.0, ArH), 7.03 (1H, dd, *J* 8.0, 1.0, ArH), 6.01 (1H, dd, *J* 8.5, 3.5, CH), 3.16 (1H, dd, *J* 18.0, 8.5, C*Ha*Hb), 3.09 (1H, dd, *J* 18.0, 3.5, CHa*Hb*), 2.43 (3H, s, $ArCH_3$), 2.06 (3H, s, $(CO)CH_3$); δ_C (100MHz, $CDCl_3$) 203.8 (C), 148.8 (C), 146.7 (C), 145. 8 (C), 134.7 (C), 129.6 (CH), 129. 5 (CH), 129.4 (CH), 126. 8 (CH), 125.1 (CH), 122.4 (C), 116.5 (CH), 53.1 (CH),

50.3 (CH_2). 30.5 (CH_3), 21.7 (CH_3); *m/z* (ESI) 382.0727 ($M+Na^+$,100), 360.0903 ($M+H^+$, 43%); *m/z* (ESI) found $[M+Na]^+$ 382.0727. $C_{18}H_{17}NO_5SNa^+$ requires 382.0720.

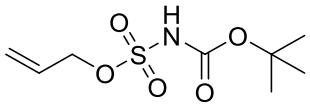
Methyl 2-(3-benzyl-2-oxo-3,4-dihydro-2H-benzo[e][1,3]oxazin-4-yl)acetate **398**



Purified by flash column chromatography on silica gel (7:3, petroleum ether /ethyl acetate) to give the product **398** (8 mg, 33%) as a colourless oil. *Rf* 0.6 (7:3, petroleum ether/ ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.41-7.26 (6H, m, ArH), 7.16-7.05 (3H, m, ArH), 5.19 (1H, d, *J* 15.0, PhC*Ha*Hb), 4.78 (1H, dd, *J* 7.5, 4.5, NCH), 4.35 (1H, d, *J* 15.0, PhCHa*Hb*), 3.65 (3H, s, OCH_3), 2.78 (1H, dd, *J* 17.0, 4.5, (CO)C*Ha*Hb), 2.72 (1H, dd, *J* 17.0, 7.5, (CO)CHa*Hb*); δ_C (100 MHz, $CDCl_3$) 170.2 (C), 151.7 (C), 149.8 (C), 135.8 (C), 129.4 (CH), 128.9 (CH), 128.7 (CH), 127.3 (CH), 125.5 (CH), 124.4 (CH), 121.9 (C), 116.6 (CH), 53.8 (CH), 52.0 (CH_3), 50.7 (CH_2), 40.3 (CH_2); *m/z* (ESI) 334 ($M+Na^+$, 100%), 312 ($M+H^+$, 50); *m/z* (ESI) found $[M+Na^+]$ 334.1032 $C_{18}H_{17}NO_4Na^+$ requires 334.1050.

Cyclic Sulfamates

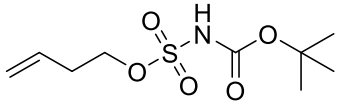
Allyl *tert*-butoxycarbonylsulfamate **405**



Chlorosulfonyl isocyanate (0.30 mL, 3.53 mmol) was added dropwise to a stirred solution of *tert*-butanol (0.37 mL, 3.90 mmol) in 2-methyltetrahydrofuran (6 mL) at -3 °C and was stirred for 30 mins. Allyl alcohol (0.20 mL mL, 3.00 mmol) was added dropwise followed by triethylamine (0.6 mL, 4.2 mmol) dropwise to the 0 °C solution then stirred for 1 h. Potassium hydrogen sulfate (3.20 g) in water (20 mL) was added and the solution was allowed to stir at room temperature for 1 h in which a white precipitate developed. Ethyl acetate (20 mL) was added and the organic layer was washed with water (20 mL), brine (20 mL), dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (7:3, petroleum ether/ethyl acetate) to give the product **405** (771 mg, 92%) as a colourless oil. *Rf* 0.4 (7:3, petroleum ether/ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.42 (1H, br.s, NH), 5.99 (1H, ddt, *J* 17.0, 10.5, 6.0, C=CH), 5.50 (1H, ddt, *J* 17.0, 1.5, 1.5, C=C*Ha*Hb), 5.40 (1H, ddt, *J* 10.5, 1.5, 1.5, C=CHa*Hb*), 4.87 (2H, ddd, *J* 6.0, 1.5, 1.5, OCH_2), 1.53 (9H, s, 3 x CH_3); δ_C (100 MHz, $CDCl_3$) 148.7 (C), 129.9 (CH), 121.1 (CH_2), 84.7 (C), 74.1 (CH_2),

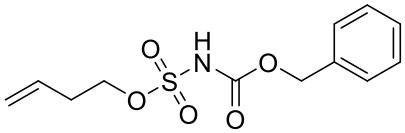
27.9 (CH_3); *m/z* (ESI) 260 ($M+Na^+$, 100%); *m/z* (ESI) found [$M+Na^+$] 260.0559, $C_8H_{15}NO_5SNa^+$ requires 260.0563.

But-3-en-1-yl *tert*-butoxycarbonylsulfamate **410**



Chlorosulfonyl isocyanate (1.5 mL, 17.7 mmol) was added dropwise to a stirred solution of *tert*-butanol (1.8 mL, 19.1 mmol) in methyltetrahydrofuran (12 mL) at -3 °C and was stirred for 30 mins. 3-Buten-1-ol (1.25 mL, 14.7 mmol) was added dropwise followed by triethylamine (2.9 mL, 20.6 mmol) dropwise to the 0 °C solution then stirred for 1 h. Potassium hydrogen sulfate (3.20 g) in water (20 mL) was added and the solution was allowed to stir at room temperature for 1 h in which a white precipitate developed. Ethyl acetate (20 mL) was added and the organic layer was washed with water (20 mL), brine (20 mL), dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (7:3, petroleum ether/ ethyl acetate) to give the product **410** (3.39 g, 92%) as a colourless oil. *Rf* 0.3 (4:1, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3395, 2985, 1758, 1643, 1430, 1371, 1316; δ_H (400 MHz, $CDCl_3$) 8.41 (1H, br.s, NH), 5. 81 (1H, ddt, *J* 17.0, 10.5, 7.0, CH), 5.23-5.12 (2H, m, $C=CH_2$), 4.40 (2H, dd, *J* 7.0, 1.0, CH_2O), 2.54 (2H, dt, *J* 7.0, 7.0, $CH_2C=C$), 1.52 (9H, s, 3 x CH_3); δ_C (100 MHz, $CDCl_3$) 147.2 (C), 132.3 (CH), 118.5 (CH_2), 84.7 (C), 72.8 (CH_2), 33.1 (CH_2), 28.1 (CH_3); *m/z* (ESI) 274 ($M+Na^+$, 100%); *m/z* (ESI) found [$M+Na^+$] 274.0729, $C_9H_{17}NO_5SNa^+$ requires 274.0720.

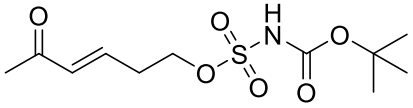
But-3-en-1-yl (benzyloxy)carbonylsulfamate **411**



Benzyl alcohol (1.35 mL, 12.9 mmol) was added dropwise to a solution of chlorosulfonylisocyanate (2.00 g, 14.1 mmol) in methyltetrahydrofuran (10 mL) at -5 °C and allowed to stir for 1 h. 3-Buten-1-ol (1.00 mL, 11.75 mmol) in methyltetrahydrofuran (10 mL) was added dropwise at 0 °C followed by dropwise addition of triethylamine (2.30 mL, 16.5 mmol) and the solution was allowed to stir at room temperature for 2 h in which time a white precipitate developed. Potassium hydrogen sulfate (3.00 g) in water (20 mL) was added and the solution was stirred vigorously before ethyl acetate (20 mL) was added. The organic phase was further washed with water (20 mL), brine (20 mL), dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (4:1, petroleum ether/ethyl acetate) to give the product **411** (2.78 g, 83%) as a colourless oil. *Rf* 0.2 (4:1, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1}

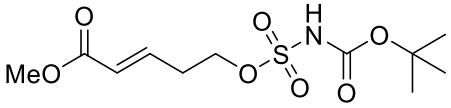
3389, 3010, 1764, 1438, 1181; δ_H (400 MHz, $CDCl_3$) 7.66 (1H, br.s, NH), 7.42-7.35 (5H, m, ArH), 5.73 (1H, ddt, *J* 17.0, 10.5, 7.0, CH), 5.24 (2H, s, $ArCH_2$), 5.17 (1H, ddt, *J* 17.0, 1.5, 1.0, C=C*Ha*Hb) 5.14 (1H, ddt, 10.5, 1.5, 1.0, C=CHa*Hb*), 4.39 (2H, t *J* 6.5, CH_2O), 2.48 (2H, dtdd, *J* 7.0, 6.5, 1.0, 1.0, OCH_2CH_2); δ_C (100 MHz, $CDCl_3$) 150.1 (C), 134.3 (C), 132.0 (CH), 128.9 (CH), 128.8 (CH), 128.5 (CH), 118.6 (CH_2), 73.3 (CH_2), 69.1 (CH_2), 33.0 (CH_2); *m/z* (ESI) 308 ($M+Na^+$, 100%); *m/z* (ESI) found [$M+Na^+$] 308.0562, $C_{12}H_{15}NO_5SNa^+$ requires 308.0563.

(*E*)-5-Oxohex-3-en-1-yl *tert*-butoxycarbonylsulfamate **412**



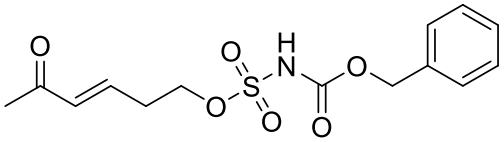
Purified by flash column chromatography on silica gel (3:2, petroleum ether, ethyl acetate) to give the product **412** (343 mg, 92%) as a colourless oil. *Rf* 0.3 (7:3, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3283, 3010, 1715, 1422, 1370, 1191; δ_H (400 MHz, $CDCl_3$) 7.72 (1H, br.s, NH), 6.79 (1H, dt, *J* 16.0, 7.0, C=C*H*-CH_2), 6.22 (1H, dt, *J* 16.0, 1.5, (CO)C*H*=CH), 4.52 (2H, t, *J* 6.5, CH_2O), 2.71 (2H, dtd, *J* 6.5, 6.5, 1.5, $C=CCH_2$), 2.29 (3H, s, CH_3), 1.53 (9H, s, 3 x CH_3); δ_C (100 MHz, $CDCl_3$) 198.2 (C), 148.9 (C), 141.1 (CH), 133.8 (CH), 84.8 (C), 71.4 (CH_2), 31.8 (CH_2), 28.4 (CH_3), 27.1 (CH_3); *m/z* (ESI) 316 ($M+Na^+$, 100%); *m/z* (ESI) found [$M+Na^+$] 316.0829, $C_{11}H_{19}NO_6SNa^+$ requires 316.0825.

(*E*)-Methyl 5-*tert*-butoxycarbonylsulfamate pent-2-enoate **412a**



Purified by flash column chromatography on silica gel (7:3, petroleum ether, ethyl acetate) to give the product **412a** (275 mg, 70%) as a colourless oil. *Rf* 0.2 (7:3, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3392, 2985, 1724, 1663, 1436, 1372; δ_H (400 MHz, $CDCl_3$) 7.79 (1H, br.s, NH), 6.92 (1H, dt, *J* 16.0, 7.0, C=C*H*-CH_2), 5.97 (1H, dt, *J* 16.0, 1.5, (CO)C*H*=CH), 4.48 (2H, t, *J* 6.5, CH_2O), 3.75 (3H, s, OCH_3), 2.69 (2H, dtd, *J* 6.5, 6.5, 1.5, $C=CCH_2$), 1.52 (9H, s, 3xCH_3); δ_C (100 MHz, $CDCl_3$) 166.4 (C), 148.9 (C), 143.2 (CH), 123.9 (CH), 84.8 (C), 72.5 (CH_2), 51.7 (CH_3), 31.5 (CH_2), 28.1 (CH_3); *m/z* (ESI) 332 ($M+Na^+$, 100%); *m/z* (ESI) found [$M+Na^+$] 332.0758, $C_{11}H_{19}NO_7SNa^+$ requires 332.0775.

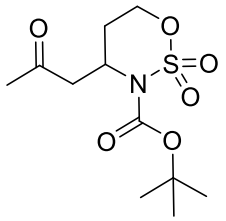
(*E*)-5-Oxohex-3-en-1-yl (benzyloxy)carbonylsulfamate **413**



Purified by flash column chromatography on silica gel (19:1, dichloromethane/methanol) to give the product **413** (288 mg, 69%) as a pale

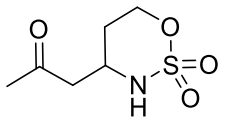
yellow oil. *Rf* 0.4 (19:1, dichloromethane/methanol); ν_{max} ($CHCl_3$)/cm^{-1} 3386, 3011, 2966, 1763, 1713, 1699, 1677, 1632, 1588, 1161; δ_H (400 MHz, $CDCl_3$) 8.51 (1H, br.s, NH), 7.43-7.31 (5H, m, ArH), 6.73 (1H, dt, *J* 16.0, 7.0, CH_2CH), 6.16 (1H, dt, *J* 16.0, 1.5, (CO)CH), 5.23 (2H, s, $ArCH_2$), 4.48 (2H, t, *J* 6.5, OCH_2), 2.64 (2H, dtd, *J* 7.0, 6.5, 1.5, OCH_2CH_2), 2.26 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 198.6 (C), 150.3 (C), 141.2 (CH), 134.4 (C), 133.7 (CH), 128.9 (CH), 128.8 (CH), 128.5 (CH), 71.7 (CH_2), 69.0 (CH_2), 31.6 (CH_2), 27.1 (CH_3); *m/z* (ESI) 350 ($M+Na^+$, 100%), 328 ($M+H^+$, 23); *m/z* (ESI) found [$M+Na^+$] 350.0657. $C_{14}H_{17}NO_6SNa^+$ requires 350.0669.

tert-Butyl 4-(2-oxopropyl)-1,2,3-oxathiazinane-3-carboxylate 2,2-dioxide **414**



(*E*)-5-Oxohex-3-en-1-yl *tert*-butoxycarbonylsulfamate **412** (29 mg, 0.1 mmol) and BINOL phosphoric acid **28** (3.4 mg, 0.01 mmol) in deuterated chloroform were heated at 50 °C for 36 h. The solution was then concentrated under reduced pressure and purified by flash column chromatography on silica gel (3:2, petroleum ether/ethyl acetate) to give the product **414** (10.4 mg, 36%) as a yellow oil. *Rf* 0.2 (3:2, petroleum ether/ethyl acetate); δ_H (400 MHz, $CDCl_3$) 5.08-5.00 (1H, m, NCH), 4.71 (1H, ddd, *J* 28.0, 10.5, 5.5, NCHC*Ha*Hb), 4.65 (1H, ddd, *J* 12.0, 7.0, 3.5, NCHCHa*Hb*), 3.11 (1H, dd, *J* 18.0, 10.0, (CO)C*Ha*Hb), 2.97 (1H, dd, *J* 18.0, 4.0, (CO)C*Ha*Hb), 2.58-2.47 (1H, m, OC*Ha*Hb), 2.22 (3H, s, CH_3), 2.11 (1H, ddt, *J* 15.0, 5.0, 3.0), 1.56 (9H, s, 3 x CH_3); δ_C (100 MHz, $CDCl_3$) 205.3 (C), 150.3 (C), 85.5 (C), 69.6 (CH_2), 52.5 (CH), 45.6 (CH_2), 30.4 (CH_3), 27.9 (CH_3), 26.0 (CH_2); *m/z* (ESI) 332 ($M+H^+$, 100%); *m/z* (ESI) found [$M+Na^+$] 332.0763, $C_{11}H_{19}NO_6SNa^+$ requires 332.0775.

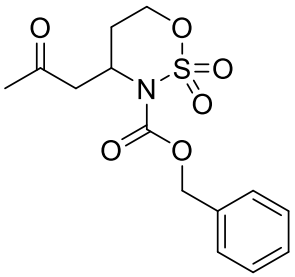
1-(2,2-dioxido-1,2,3-oxathiazinan-4-yl)propan-2-one **415**



(*E*)-5-Oxohex-3-en-1-yl *tert*-butoxycarbonylsulfamate **414** (29 mg, 0.1 mmol) and trifluoroacetic acid (1.1 mg, 0.01 mmol) in deuterated chloroform were heated at 50 °C for 36 h. The solution was then concentrated under reduced pressure then purified by flash column chromatography on silica gel (7:3, petroleum ether/ethyl acetate) to give the product **415** (10.4 mg, 36%) as a yellow oil. *Rf* 0.2 (7:3, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3287, 1715, 1602, 1465, 1422, 1369, 1192; δ_H (400 MHz, $CDCl_3$) 5.18 (1H, d, *J* 10.0, NH), 4.73 (1H, td, *J* 12.0, 2.5, NC*Ha*Hb), 4.56 (1H, ddd, *J* 12.0, 5.0, 2.5, NCHa*Hb*),

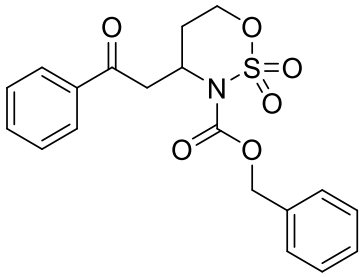
4.13-4.02 (1H, m, NCH), 2.84 (1H, dd, *J* 20.0, 5.0, (CO)C*Ha*Hb), 2.78 (1H, dd, *J* 20.0, 6.0, (CO)CHa*Hb*), 2.22 (3H, s, CH_3), 2.07-1.90 (1H, m, OC*Ha*Hb), 1.75 (1H, ddt, *J* 14.0, 2.5, 2.5, OCHa*Hb*; δ_C (100 MHz, $CDCl_3$) 206.8 (C), 67.9 (CH_2), 52.2 (CH), 46.4 (CH_2), 30.4 (CH_3), 28.4 (CH_2); *m/z* (ESI) 216 ($M+Na^+$, 100%); *m/z* (ESI) found [$M+Na^+$] 216.0309, $C_6H_{11}NO_4SNa^+$ requires 216.0301.

Benzyl 4-(2-oxopropyl)-1,2,3-oxathiazinane-3-carboxylate 2,2-dioxide **416**



Trifluoroacetic acid (6.97 mg, 0.06 mmol) in chloroform (0.3 mL) was added (*E*)-5-oxohex-3-en-1-yl (benzyloxy)carbonylsulfamate **413** (20 mg, 0.06 mmol) in chloroform (0.3 mL), the solution was then heated at 50 °C for 48 h. The solution was then concentrated under reduced pressure, the residue was purified by flash column chromatography on silica gel (9:9:2, petroleum ether/dichloromethane/ethyl acetate) to give the product **416** (4.6 mg, 23%) as a pale yellow oil. *Rf* 0.33 (9:9:2, petroleum ether/dichloromethane/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 2927, 1729, 1397, 1289, 1176; δ_H (400 MHz, $CDCl_3$) 7.45-7.32 (5H, m, ArH), 5.37 (1H, d, *J* 12.5, ArC*Ha*Hb), 5.32 (1H, d, *J* 12.5, ArCHa*Hb*), 5.11 (1H, ddddd, *J* 10.5, 5.5, 3.5, 3.0, 0.5, CH), 4.74 (1H, ddd, *J* 11.5, 11.0, 5.0, O*CHa*CHb), 4.67 (1H, dddd, *J* 11.5, 7.0, 3.5, 0.5, OCHa*CHb*), 3.12 (1H, dd, *J* 18.0, 10.5, (CO)*CHa*CHb), 2.94 (1H, ddd, *J* 18.0, 3.5, 1.0, (CO)CHa*CHb*), 2.53 (1H, ddddd, *J* 15.0, 11.0, 7.0, 5.5, 1.0, OCH_2C*Ha*Hb), 2.12 (3H, s, CH_3), 2.11 (1H, dddd, *J* 15.0, 5.0, 3.5, 3.0, OCH_2CHa*Hb*); δ_C (100 MHz, $CDCl_3$) 205.1 (C), 151.7 (C), 134.6 (C), 128.6 (CH), 127.9 (CH), 69.9 (CH_2), 69.6 (CH_2), 53.2 (CH), 45.3 (CH_2), 30.3 (CH_3), 29.7 (CH_2), 25.9 (CH_2); *m/z* (ESI) 350 ($M+Na^+$, 100%); *m/z* (ESI) found [$M+Na^+$] 350.0652. $C_{14}H_{17}NO_6SNa^+$ requires 350.0669.

Benzyl 4-(2-oxo-2-phenylethyl)-1,2,3-oxathiazinane-3-carboxylate 2,2-dioxide **416a**



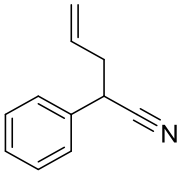
But-3-en-1-yl (benzyloxy)carbonylsulfamate **411** (365 mg, 1.28 mmol), (*E*)-1-phenylbut-2-en-1-one (166 mg, 1.41 mmol) and Hoveyda-Grubbs second

generation catalyst (20.0 mg, 0.032 mmol) in dichloromethane (20 mL) were heated at reflux for 18 h. The solution was concentrated under reduced pressure, the residue was purified by flash column chromatography on silica gel (9:1, petroleum ether/ethyl acetate) to give the product **416a** (40 mg, 8%) as a pale yellow oil. *Rf* 0.4 (7:3, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3044, 2962, 1734, 1684, 1598, 1396, 1289, 1177; δ_H (400 MHz, $CDCl_3$) 7.99-7.93 (2H, m, ArH), 7.61 (1H, dddd, *J* 7.5, 7.5, 1.5, 1.5, ArH), 7.51-7.46 (2H, m, ArH), 7.44-7.40 (2H, m, ArH), 7.39-7.29 (3H, m, ArH), 5.34 (1H, d, *J* 12.5, ArC*Ha*Hb), 5.28 (1H, d, *J* 12.5, ArCHa*Hb*), 5.31 (1H, dddd, *J* 10.5, 5.5, 3.5, 2.5, CH) 4.80 (1H, ddd, *J* 11.5, 11.5, 5.0, O*CHa*Hb), 4.68 (1H, ddd, *J* 11.5, 7.0, 3.0, OCHa*Hb*), 3.64 (1H, dd, *J* 17.5, 10.5, (CO)C*Ha*Hb), 3.48 (1H, ddd, 17.5, 3.5, 1.0, (CO)CHa*Hb*), 2.60 (1H, ddddd, *J* 15.0, 11.5, 7.0, 5.5, 1.0, OCH_2C*Ha*Hb), 2.21 (1H, dddd, *J* 15.0, 5.0, 3.0, 2.5, OCH_2CHa*Hb*); δ_C (400 MHz, $CDCl_3$) 196.7 (C), 151.7 (C), 136.0 (C), 134.6 (C), 133.88 (CH), 128.9 (CH), 128.7 (CH), 128.6 (CH), 128.2 (CH), 128.0 (CH), 70.1 (CH_2), 69.7 (CH_2), 54.1 (CH), 40.6 (CH_2), 25.8 (CH_2); *m/z* (ESI) 412 ($M+Na^+$, 100%); *m/z* (ESI) found [$M+Na^+$] 412.0811. $C_{19}H_{19}NO_6SNa^+$ requires 412.0825.

Synthesis of 2,4-Disubstituted Pyrrolidinones

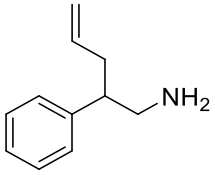
Racemic compound synthesis

2-Phenylpent-4-enenitrile **435**



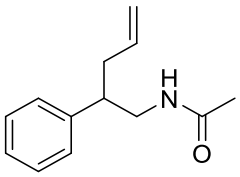
Allyl bromide (3.30 mL, 38.2 mmol) was added dropwise to a vigorously stirred solution of benzyl cyanide **436** (5.00 g, 42.7 mmol), potassium hydroxide (2.39 g, 42.7 mmol), tetrabutyl ammonium bromide (0.500 g, 1.55 mmol) in toluene (50 mL) and water (5 mL), the solution was vigorously stirred for a further 72 h. The organic phase was washed with water (2 x 20 mL), brine (20 mL), dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (19:1, petroleum ether/diethyl ether) to give the product **435** (2.78 g, 42%) as a colourless oil. Rf 0.5 (4:1, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3069, 3011, 2245, 1643, 1601; δ_H (400 MHz, $CDCl_3$) 7.43-7.32 (5H, m, ArH), 5.82 (1H, ddt, *J* 17.0, 10.5, 7.0, C=CH), 5.24-5.17 (2H, m, $C=CH_2$), 3.87 (1H, dd, *J* 8.0, 6.5, CH), 2.68-2.62 (2H, m, CH_2); δ_C (400 MHz, $CDCl_3$) 135.2 (C), 132.6 (CH), 129.1 (CH), 128.2 (CH), 127.4 (CH), 120.3 (C), 119.4 (CH_2), 39.9 (CH_2), 37.5 (CH); *m/z* (ESI) 180 ($M+Na^+$, 100%), 158 ($M+H^+$, 16%); *m/z* (ESI) found [$M+Na^+$] 180.0785. $C_{11}H_{11}NNa^+$ requires 180.0784.

2-Phenylpent-4-en-1-amine **434**



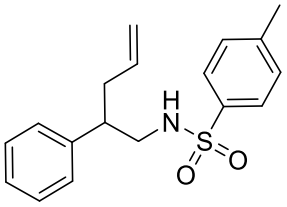
2-Phenylpent-4-enenitrile **435** (1.48 g, 9.43 mmol) in tetrahydrofuran (5 mL) was added dropwise to a stirred suspension of lithium aluminium hydride (0.72 mg, 18.8 mmol) in tetrahydrofuran at 0 °C (10 mL), the suspension was then allowed to stir for 6.5 h at room temperature. The solution was quenched with sequential additions of water (1 mL), 4M aqueous sodium hydroxide (1 mL) and water (3 mL). Precipitate was removed by filtration. Chloroform (20 mL) was added then washed with brine (20 mL), dried over magnesium sulfate then concentrated under reduced pressure to obtain the product **434** (1.00 g, 66%) as a colourless oil. Rf 0.2 (9:1, dichloromethane/methanol); δ_H (400 MHz, $CDCl_3$) 7.35-7.16 (5H, m, ArH), 5.69 (1H, ddt, *J* 17.0, 10.5, 7.0, C=CH), 5.03-4.91 (2H, m, C=CH_2), 2.97 (1H, dd, *J* 13.0, 5.0, C*Ha*Hb), 2.86 (1H, 13.0, 9.0, CHa*Hb*), 2.73-2.64 (1H, m, CH), 2.46-2.31 (2H, m, C=C-CH_2), 1.05 (2H, br.s, NH_2); δ_C (400 MHz, $CDCl_3$) 143.1 (C), 136.6 (CH), 128.5 (CH), 128.0 (CH), 126.5 (CH), 116.1 (CH_2), 49.5 (CH), 47.5 (CH_2), 38.4 (CH_2); *m/z* (ESI) 162 ($M+H^+$, 100%); *m/z* (ESI) found [$M+H^+$] 162.1277. $C_{11}H_{16}N^+$ requires 162.1265.

N-(2-Phenylpent-4-en-1-yl)acetamide **438**



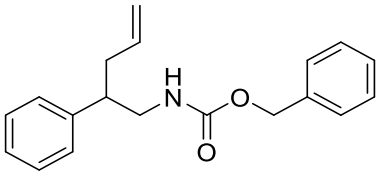
Acetyl chloride (0.48 mL, 6.80 mmol) was added dropwise to a solution of 2-phenylpent-4-en-1-amine **434** (1.00 g, 6.20 mmol) in 2M aqueous sodium hydroxide (4.96 mL) at room temperature. The solution was vigorously shaken for 15 mins, then extracted with dichloromethane (3 x 20 mL), dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient elution of 3:2, petroleum ether/ethyl acetate followed by 19:1, dichloromethane/methanol) to give the product **438** (0.65 g, 50%) as a pale yellow oil. *Rf* 0.2 (3:2, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3445, 3066, 2929, 1731, 1668, 1519; δ_H (400 MHz, $CDCl_3$)7.43-7.17 (5H, m, ArH), 5.69 (1H, ddt, *J* 17.0, 10.0, 7.0, C=CH), 5.41 (1H, br.s, NH), 5.00 (2H, m, C=CH_2), 3.83-3.74 (1H, m, NC*Ha*Hb), 3.24 (1H, ddd, *J* 13.5, 9.0, 4.5, NCHa*Hb*), 2.94-2.84 (1H, m, ArCH), 2.51-2.34 (2H, m, C=CCH_2), 1.89 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 170.1 (C), 141.1 (C), 135.8 (CH), 128.7 (CH), 127.8 (CH), 126.9 (CH), 116.7 (CH_2), 45.4 (CH), 44.5 (CH_2), 38.5 (CH_2), 23.2 (CH_3); *m/z* (ESI) 226 ($M+Na^+$, 100%), 204 ($M+H^+$, 77%); *m/z* (ESI) found [$M+Na^+$] 226.1202. $C_{13}H_{17}NONa^+$ requires 226.1202.

4-Methyl-*N*-(2-phenylpent-4-en-1-yl)benzenesulfonamide **439**



Tosyl chloride (506 mg, 2.66 mmol) in dichloromethane (5 mL) was added dropwise to a 0 °C solution of 2-phenylpent-4-en-1-amine **434** (390 mg, 2.42 mmol), triethylamine (0.51 mL, 3.63 mmol) and 4-dimethylaminopyridine (20.0 mg, 0.16 mmol) in dichloromethane (5 mL), the solution was then stirred at room temperature 24 h. Saturated aqueous ammonium chloride (20 mL) was added and then the separated aqueous layer was extracted with dichloromethane (2 x 10 mL), the organic fractions were combined, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient elution 19:1 to 9:1, petroleum ether/ethyl acetate) to give the product **439** (442 mg, 58%) as a yellow crystalline solid. *Rf* 0.2 (9:1, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3372, 1600, 1333, 1160; m.p 62-68 °C (lit., m.p. 62-64 °C)[118]; δ_H (400 MHz, $CDCl_3$) 7.67 (2H, d, *J* 8.5, ArH), 7.37-7.23 (5H, m, ArH), 7.05 (2H, d, *J* 8.5, ArH), 5.63 (1H, ddt, *J* 17.0, 10.0, 7.0, C=CH), 5.04-4.95 (2H, m, $C=CH_2$), 4.30-4.22 (1H, br.m., NH), 3.34 (1H, ddd, *J* 13.0, 8.0, 5.5, NC*Ha*Hb), 3.03 (1H, ddd, *J* 13.0, 9.0, 4.5, NCHa*Hb*), 2.84-2.75 (1H, m, ArCH), 2.47 (3H, s, $ArCH_3$), 2.43-2.29 (2H, m, $C=CCH_2$); δ_C (100 MHz, $CDCl_3$) 143 (C), 141.0 (C), 137.0 (C), 135.4 (CH), 129.7 (CH), 128.9 (CH), 127.7 (CH), 127.2 (CH), 117.1 (CH_2), 47.7 (CH_2), 45.3 (CH), 38.1 (CH_2), 21.5 (CH_3); *m/z* (ESI) 338 ($M+Na^+$, 100%), 316 ($M+H^+$, 77%); *m/z* (ESI) found [$M+Na^+$] 338.1194. $C_{18}H_{21}SNO_2Na^+$ requires 338.1185. HPLC: Chiralcel AD-H; mobile phase, hexane/2-propanol (9: 1 v/v); flow rate, 1.0 ml/min; 14.3 min (50%), 16.7 min (50%).

Benzyl (2-phenylpent-4-en-1-yl)carbamate **440**



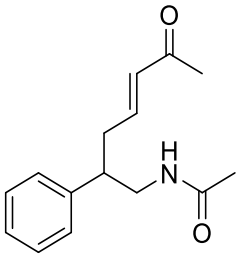
Benzyl chloroformate (1.11 g, 6.50 mmol) in dichloromethane (6 mL) was added dropwise to a stirred solution of 2-phenylpent-4-en-1-amine **434** (1.00 g, 6.21 mmol), triethylamine (0.90 mL, 6.50 mmol), 4-dimethylaminopyridine (20 mg, 0.16 mmol) in dichloromethane (6 mL) at 0 °C. The solution became cloudy, the solution was allowed to stir at room temperature for 22 h. 2M Hydrochloric acid (12 mL) was added, the organic phase was separated and washed with water (15 mL), dried over magnesium sulfate then concentrated under reduced pressure. The residue was purified by flash column

chromatography on silica gel (9:1, petroleum ether /ethyl acetate) to give the product **440** (0.75 g, 41 %) as a colourless oil. *Rf* 0.4 (4:1, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3445, 3067, 1718, 1515, 1242; δ_H (400 MHz, $CDCl_3$) 7.41-7.29 (7H, m, ArH), 7.27-7.22 (1H, m, ArH), 7.20-7.15 (2H, m, ArH), 5.70 (1H, ddt, *J* 17.0, 10.0, 7.0, C=CH), 5.08 (2H, br.s., $ArCH_2$), 5.06-4.95 (2H, m, $C=CH_2$), 4.63 (1H, br.s., NH), 3.70-3.60 (1H, m, NC*Ha*Hb), 3.27 (1H, ddd, 13.5, 9.0, 5.0, NCHa*Hb*), 2.94-2.82 (1H, m, CH), 2.48-2.34 (2H, m, $C=CCH_2$); δ_C (400 MHz, $CDCl_3$) 156.3 (C), 142.0 (C), 135.8 (CH), 128.7 (CH), 128.5 (CH), 128.1 (CH), 127.8 (CH), 126.9 (CH), 116.7 (CH_2), 66.7 (CH_2), 46.0 (CH_2), 45.8 (CH), 38.2 (CH_2); *m/z* (ESI) 318 ($M+Na^+$, 100%); *m/z* (ESI) found [$M+Na^+$] 318.1461. $C_{19}H_{21}NO_2Na^+$ requires 318.1465.

General procedure for the metathesis

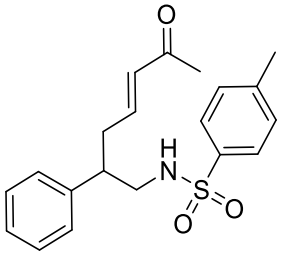
Hoveyda-Grubbs second generation catalyst (2-5 mol%) in dichloromethane (1/4 of total solvent, final volume 0.2M with respect to alkene) was added to a solution of alkene (1 equiv.) and methyl vinyl ketone/phenyl vinyl ketone/methylacrylate etc. (5-8 equiv.) in dichloromethane (3/4 of final volume) at 30 °C. The solution was heated at reflux for 1 h then concentrated under reduced pressure. The residue was purified by flash column chromatography in the solvent system outlined for each individual compound.

(*E*)-*N*-(6-Oxo-2-phenylhept-4-en-1-yl)acetamide **441**



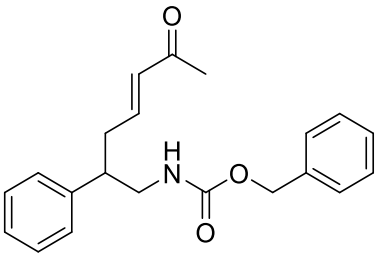
Purified by flash column chromatography (gradient elution, neat dichloromethane to 19:1 dichloromethane/methanol) to give the product **441** (211 mg, 87%) as a brown oil. *Rf* 0.5 (19:1, dichloromethane/methanol); ν_{max} ($CHCl_3$)/cm^{-1} 3690, 3447, 3011, 2932, 1672, 1628, 1519; δ_H (400 MHz, $CDCl_3$) 7.38-7.24 (3H, m, ArH), 7.21-7.15 (2H, m, ArH), 6.63 (1H, dt, *J* 16.0, 7.0, C=CH), 6.02 (1H, dt, *J* 16.0, 1.5, C=CH), 5.55 (1H, br. t, NH), 3.75 (1H, ddd, *J* 13.5, 7.0, 6.0, NC*Ha*Hb), 3.25 (1H, ddd, *J* 13.5, 9.0, 5.0, NCHa*Hb*), 2.99 (1H, ddt, *J* 9.0, 9.0, 6.0, CH), 2.66-2.48 (2H, m, CH_2), 2.16 (3H, s, CH_3), 1.89 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 198.4 (C), 170.2 (C),145.0 (CH), 141.1 (C), 132.8 (CH), 129.0 (CH), 127.6 (CH), 127.3 (CH), 44.9 (CH), 44.6 (CH_2), 36.7 (CH_2), 26.9 (CH_3), 23.2 (CH_3); *m/z* (ESI) 268 ($M+Na^+$, 100%), 246 ($M+H^+$, 45%); *m/z* (ESI) found [$M+Na^+$] 268.1312. $C_{15}H_{19}NO_2Na^+$ requires 268.1308.

(*E*)-4-Methyl-*N*-(6-oxo-2-phenylhept-4-en-1-yl)benzenesulfonamide **442**



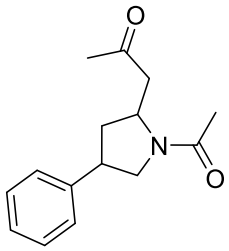
Purified by flash column chromatography on silica gel (gradient elution 4:1 to 3:2, petroleum ether/ethyl acetate) to give the product **442** (93 mg, 82%) as colourless needles. *Rf* 0.3 (3:2, petroleum ether/ethyl acetate); m.p. 116-118 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3378, 3011, 2929, 1673, 1628, 1600, 1335, 1161; δ_H (400 MHz, $CDCl_3$) 7.68 (2H, d, *J* 8.0, ArH), 7.35-7.23 (5H, m, ArH), 7.07 (2H, d, *J* 8.0, ArH), 6.57 (1H, dt, *J* 16.0, 7.0, (CO)C=CH), 5.99 (1H, d, *J* 16.0, (CO)CH), 4.51 (1H, dd, *J* 7.5, 4.5, NH), 3.32-3.22 (1H, m, NC*Ha*Hb), 3.08 (1H, ddd, *J* 13.0, 8.0, 4.5, NCHa*Hb*), 2.97-2.87 (1H, m, ArCH), 2.67-2.57 (1H, m, C=CC*Ha*Hb), 2.55-2.47 (1H, m, C=CCHa*Hb*), 2.45 (3H, s, $ArCH_3$), 2.16 (3H, s, $COCH_3$); δ_C (100 MHz, $CDCl_3$) 198.3 (C), 144.5 (CH), 143.6 (C), 140.0 (C), 136.8 (C), 133.0 (CH), 129.8 (CH), 129.1 (CH), 127.6 (CH), 127.1 (CH), 47.9 (CH_2), 44.9 (CH), 36.2 (CH_2), 27.0 (CH_3), 21.5 (CH_3); *m/z* (ESI) 380 ($M+Na^+$, 100%); *m/z* (ESI) found [$M+Na^+$] 380.1297. $C_{20}H_{23}NSO_3Na^+$ requires 380.1291.

(*E*)-Benzyl (6-oxo-2-phenylhept-4-en-1-yl)carbamate **443**



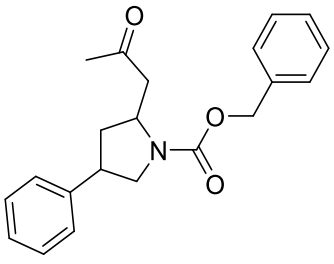
Purified by flash column chromatography on silica gel (4:1, petroleum ether/ethyl acetate) to give the product **443** (218 mg, 96%) as a pale yellow oil. *Rf* 0.3 (7:3, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3447, 3012, 1719, 1672, 1515; δ_H (400 MHz, $CDCl_3$)7.41-7.13 (10H, m, ArH), 6.65 (1H, dt, *J* 16.0, 7.0, COCH=C*H*), 6.05 (1H, dt, *J* 16.0, COCH), 5.10 (2H, s, $ArCH_2$), 4.70 (1H, br.s, NH), 3.64 (1H, dt, *J* 13.5, 7.0, NC*Ha*Hb), 3.32 (1H, ddd, *J* 13.5, 9.0, 5.0, NCHa*Hb*), 3.06-2.95 (1H, m, CH), 2.69-2.50 (2H, m, $C=CCH_2$), 2.18 (3H, s, CH_3); δ_C (100 MHz, C_6D_6) 196.2 (C), 159.1 (C), 144.0 (CH), 141.5 (C), 137.2 (C), 132.8 (CH), 128.7 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 127.8 (CH), 127.6 (CH), 127.0 (CH), 66.5 (CH_2), 46.2 (CH_2), 45.2 (CH), 36.0 (CH_2), 26.3 (CH_3); *m/z* (ESI) 360 ($M+Na^+$, 100%); *m/z* (ESI) found [$M+Na^+$] 360.1582. $C_{21}H_{23}NO_3Na^+$ requires 360.1570.

1-(1-Acetyl-4-phenylpyrrolidin-2-yl)propan-2-one **447**



9-*Epi*aminoquinine **25** (6.46 mg, 0.02 mmol) and trifluoroacetic acid (2.28 mg, 0.02 mmol) in deuterated chloroform (0.2 mL) were added to a solution of (*E*)-*N*-(6-oxo-2-phenylhept-4-en-1-yl)acetamide **441** (24.5 mg, 0.10 mmol) in deuterated chloroform (0.4 mL) at room temperature. After 8 h the solution was filtered through a small plug of silica and concentrated under reduced pressure to give the product **447** (22.6 mg, 92%) as a pale yellow oil, determined to be a 7:3 mixture of diastereoisomers. *Rf* 0.4 (7:3, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3090, 1693 (br), 1420, 909; δ_H (400 MHz, $CDCl_3$) 7.43-7.18 (5H, m, ArH), 4.67-4.58 (0.3H, m, minor CH), 4.57-4.42 (0.1H, m), 4.41-4.28 (0.7H, m, major CH maj), 3.95-3.84 (1H, m), 3.59-3.49 (1H, m), 3.46-3.20 (2H, m), 2.77 (1H, dd, *J* 17.5, 8.0, CH_2) 2.70 (0.6H, dd, *J* 13.0, 8.0, CH_2), 2.56 (0.3H, dd, *J* 16.5, 9.5, CH_2), 2.38-2.06 (1H, m), 2.21 (1H, s, minor CH_3), 2.17 (2H, s, major CH_3), 2.09 (2H, s, major CH_3), 2.07 (1H, s, minor CH_3), 1.86 (0.6H, ddd, *J* 12.5, 12.5, 9.5); δ_C (100 MHz, $CDCl_3$) 207.1 (C), 169.1 (C), 139.9 (C), 129.0 (CH), 127.3 (CH), 126.9 (CH), 54.6 (CH_2), 54.1 (CH), 47.2 (CH_2), 43.4 (CH), 39.3 (CH_2), 30.5 (CH_3), 23.4 (CH_3); *m/z* (ESI) 360 ($M+Na^+$, 100%); *m/z* (ESI) found [$M+Na^+$] 360.1574. $C_{21}H_{23}NO_3Na^+$ requires 360.1570; HPLC: Chiralcel AD-H; mobile phase, hexane/ethanol (49:1 v/v); flow rate, 1.0 ml/min; 35.4 min (50.0%), 41.1 min (16.4%), 47.7 min, (0.02%), 54.6 min (33.58%), 50% major *ee,* 99% minor *ee*.

Benzyl 2-(2-oxopropyl)-4-phenylpyrrolidine-1-carboxylate **449**

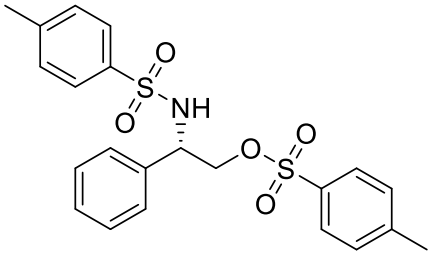


Phosphoric acid catalyst **29** (*ortho*-triphenylsilyl variant of Terada-Akiyama catalyst) (2.50 mg, 3.00 μmol) in deuterated benzene (0.2 mL) was added to a solution of (*E*)-benzyl (6-oxo-2-phenylhept-4-en-1-yl)carbamate **443** (10 mg, 0.03 mmol) in deuterated benzene (0.4 mL) at room temperature. After 5 h the solution was filtered through a small plug of silica and sodium hydrogen carbonate then concentrated under reduced pressure to give the products **449** (5.6 mg, 56%) as a yellow oil, determined to be a 2:1 mixture of

diastereoisomers. *Rf* 0.4 (7:3, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3090, 1693 (br), 1420, 909; δ_H (400 MHz, $CDCl_3$) 7.50-7.02 (10H, m, ArH), 5.35-5.04 (2H, br.s, CH_2), 4.52-3.84 (1.7H, m), 3.59-3.13 (2.4H, m), 2.85-2.49 (1.5H, m), 2.37-1.98 (3.2H, m), 1.84-1.71 (0.7H, m), 1.61 (2H, br.s, maj CH_3), 1.28 (1H, br.s, min CH_3), 0.96-0.80 (0.4H, m); *m/z* (ESI) 360 ($M+Na^+$, 100%); *m/z* (ESI) found [$M+Na^+$] 360.1574. $C_{21}H_{23}NO_3Na^+$ requires 360.1570; HPLC: Chiralcel OD-H; mobile phase, hexane/ethanol (49:1 v/v); flow rate, 1.0 ml/min; 27.1 min (57.7%, major), 30.5 min (12.5%, major), 35.3 min (0.3%, minor), 37.9 min (29.5%, minor). 64% major *ee,* 98% minor *ee*.

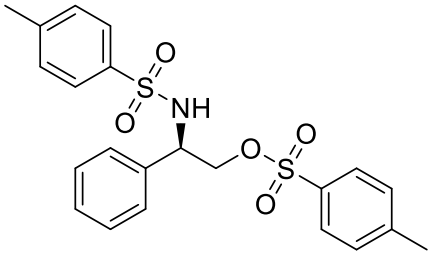
Enantiopure compound synthesis

(*S*)-2-(4-Methylphenylsulfonamido)-2-phenylethyl 4-methylbenzenesulfonate **454**



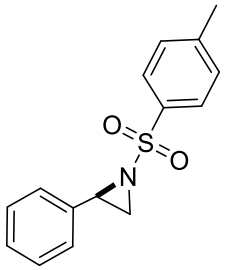
(S)-2-Phenyl glycinol **455** (1.00 g, 7.30 mmol) in dichloromethane (5 mL) was added dropwise to a 0 °C solution of tosyl chloride (3.47 g, 18.3 mmol), pyridine (1.75 mL, 21.9 mmol), 4-dimethylaminopyridine (89 mg, 0.73 mmol) in dichloromethane (5 mL) and stirred for 36 h at room temperature. Hydrochloric acid (2M, 30 mL) was added to the solution then the organic was washed with further hydrochloric acid (2M, 4 x 50 mL), dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient elution 9:1 to 3:2, petroleum ether/ethyl acetate) to give the product **454** (2.00 g, 61%) as a colourless crystalline solid. *Rf* 0.3 (2:1, petroleum ether/ethyl acetate); m.p 116-121 °C (lit., m.p. 100-102 °C)[128]; ν_{max} ($CHCl_3$)/cm^{-1} 3375, 2955, 1599, 1496, 1455, 1366, 1191, 1176; δ_H (400 MHz, $CDCl_3$) 7.63 (2H, d, *J* 8.5, ArH), 7.59 (2H, d, *J* 8.5, ArH), 7.28 (2H, d, *J* 8.0, ArH), 7.23-7.13 (5H, m, ArH), 7.03 (2H, d, *J* 7.0, ArH), 5.53 (1H, d, *J* 7.0, NH), 4.55 (1H, dt, *J* 6.0, 6.0, OC*Ha*Hb), 4.21-4.08 (2H, m, OCHa*Hb* and NCH), 2.44 (3H, s, CH_3), 2.39 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 145.2 (C), 143.5 (C), 137.0 (C), 136.0 (C), 132.2 (C), 129.9 (CH), 129.5 (CH), 128.7 (CH), 129.3 (CH),127.9 (CH), 127.1 (CH), 127.0 (CH), 71.23 (CH_2), 56.4 (CH), 21.7 (CH_3), 21.5 (CH_3); *m/z* (ESI) 468 ($M+Na^+$, 100%); *m/z* (ESI) found [$M+Na^+$] 468.0911. $C_{22}H_{23}NO_5S_2Na^+$ requires 468.0910; $[\alpha]_D^{24}$ 30.5 (*c* 1.0, $CHCl_3$).

(*R*)-2-(4-Methylphenylsulfonamido)-2-phenylethyl 4-methylbenzenesulfonate **454**



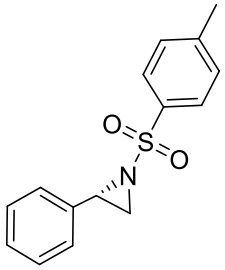
Identical to enantiomer **454** except for optical rotation.$[\alpha]_D^{24}$ -31.9 (*c* 1.0, $CHCl_3$).

(*R*)-2-Phenyl-1-tosylaziridine **453a**



Tosyl chloride (1.04 g, 5.47 mmol) in dichloromethane (5 mL) was added dropwise to a 0 °C solution of (*R*)-2-phenyl glycinol **455** (0.30 g, 2.19 mmol), triethylamine (0.91 mL, 6.57 mmol), 4-dimethylaminopyridine (2 mg, 0.016 mmol) in dichloromethane (5 mL), the solution became cloudy and was left to stir for 18 h at room temperature. The solution was then washed with saturated aqueous ammonium chloride solution (10 mL), the aqueous phase was then extracted with chloroform (10 mL), the organics combined, dried over magnesium sulfate and concentrated under reduced pressure. The residue was then purified by flash column chromatography on silica gel (9:1 petroleum ether/ethyl acetate) and recrystallised from from hexane/dichloromethane to give the product **453a** (0.35 g, 59%) as a colourless crystalline solid. *Rf* 0.4 (4:1, petroleum ether/ethyl acetate); m.p. 79-82 °C (lit., m.p. 82-84 °C)[129]; ν_{max} ($CHCl_3$)/cm^{-1} 3692, 3045, 1599, 1498, 1461, 1326, 1161; δ_H (400 MHz, $CDCl_3$) 7.90 (2H, d, *J* 8.0, ArH), 7.36 (2H, d, *J* 8.0, ArH), 7.34-7.22 (5H, m, ArH), 3.81 (1H, dd, *J* 7.0, 4.5, ArCH), 3.02 (1H, d, *J* 7.0, NC*Ha*Hb), 2.47 (3H, s, $ArCH_3$), 2.42 (1H, d, *J* 4.5, NCHa*Hb*); δ_C (100 MHz, $CDCl_3$) 144.7 (C), 135.1 (C) 135.0 (C), 129.8 (CH), 128.6 (CH), 128.0 (CH), 126.6 (CH), 41.1 (CH), 35.9 (CH_2), 21.7 (CH_3); *m/z* (ESI) 296 ($M+Na^+$, 100%), 274 ($M+H^+$, 83); *m/z* (ESI) found [$M+Na^+$] 296.0705. $C_{15}H_{15}NO_2SNa^+$ requires 296.0716. HPLC: Chiralcel OJ-H; mobile phase, hexane/2-propanol (4:1 v/v); flow rate, 1.0 ml/min; 38.7 min (100%) >99% ee.

(*S*)-2-phenyl-1-tosylaziridine **453b**



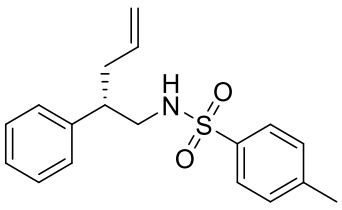
Potassium carbonate (316 mg, 2.29 mmol) was added in one addition to a solution of (*S*)-2-(4-methylphenylsulfonamido)-2-phenylethyl 4-methylbenzenesulfonate **454** (850 mg, 1.91 mmol) in acetonitrile (10 mL), the solution was then stirred for 22 h room temperature. A precipitate developed and was removed with filtration, the filtrate was then concentrated under reduced pressure to give the product **453b** (487 mg, 94%) as a colourless crystalline solid. *Rf* 0.6 (2:1, petroleum ether/ethyl acetate); m.p 79-81 °C (lit., m.p. 82-84 °C)[129]; δ_H (400 MHz, $CDCl_3$) 7.88 (2H, d, *J* 8.5, ArH), 7.34 (2H, d, *J* 8.5, ArH), 7.32-7.20 (5H, m, ArH), 3.79 (1H, dd, *J* 7.0, 4.5, CH), 2.99 (1H, d, *J* 7.0, C*Ha*Hb), 2.45 (3H, s, CH_3), 2.39 (1H, d, *J* 4.5, CHa*Hb*). HPLC: Chiralcel OJ-H; mobile phase, hexane/2-propanol (4:1 v/v); flow rate, 1 ml/min; 30.6 min (100%), >99% ee.

General procedure for ring opening of aziridines with allyl magnesium bromide

To a portion of magnesium turnings (8 equiv.) was added allyl bromide (4 equiv.) in diethyl ether (5 mL/mmol of bromide) at a rate at which the solution was kept at a gentle reflux, after the solution was titrated against iodine in lithium chloride saturated tetrahydrofuran.[130]

The allyl magnesium bromide solution in ether (4 equiv.) was added to a stirred solution of the aziridine (1 equiv.) in tetrahydrofuran (10 mL/mmol of aziridine) at 0 °C, a precipitate formed, the resulting solution was allowed to stir for 24 h at room temperature. The solution was quenched with saturated aqueous ammonium chloride solution (1 mL/mL of tetrahydrofuran). The solution was then extracted with dichloromethane (2 x 20 mL) and organic phases combined, dried over magnesium sulfate and concentrated under reduced pressure. The residues were then purified by flash column chromatography.

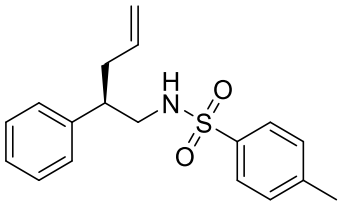
(*R*)-4-Methyl-*N*-(2-phenylpent-4-en-1-yl)benzenesulfonamide **452**



General procedure was followed to give the product **452** (317 mg, 92%) as a colourless solid. HPLC trace gave *ee* as 86%, recrystallization from petroleum

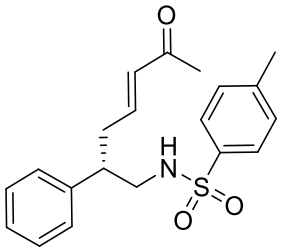
ether/diethyl ether gave the product (168 mg, 50%) with >99% enantiopurity. All data presents the same as that of sulfonamide **439** with the exception of optical rotation. $[\alpha]_D^{23}$ -1.43 (*c* 0.7, $CHCl_3$, 99% ee); HPLC: Chiralcel AD-H; mobile phase, hexane/2-propanol (9:1 v/v); flow rate, 1 ml/min; 14.4 min (1.2%), 20.2 min (98.8%) 98% ee.

(*S*)-4-Methyl-*N*-(2-phenylpent-4-en-1-yl)benzenesulfonamide **456**



General procedure was followed to give the product **456** (84%) as a colourless crystalline solid. All data presents the same as that of sulfonamide **439** with the exception of optical rotation. $[\alpha]_D^{23}$ 1.0 (*c* 0.7, $CHCl_3$, >99% ee); HPLC: Chiralcel AD-H; mobile phase, hexane/2-propanol (9:1 v/v); flow rate, 1 ml/min; 13.4 min (100%) >99% ee.

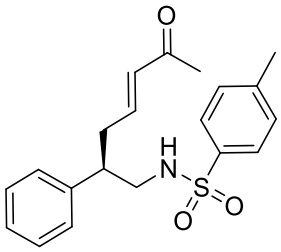
(*E*)-4-Methyl-*N*-(6-oxo-2-phenylhept-4-en-1-yl)benzenesulfonamide **451**



Follwed general procedure for cross metathesis reactions.

Purified by flash column chromatography on silica gel (gradient elution 4:1 to 3:2, petroleum ether/ethyl acetate) to give the product **451** (111 mg, 97%) as colourless needles. HPLC: Chiralcel AD-H; mobile phase, hexane/2-propanol (9 :1 v/v); flow rate, 1 ml/min; 31.5 min (1.5%), 42.9 min (98.5%) 97% ee.

(*E*)-4-Methyl-*N*-(6-oxo-2-phenylhept-4-en-1-yl)benzenesulfonamide **457**

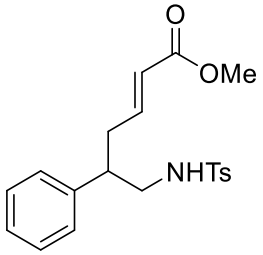


Follwed general procedure for cross metathesis reactions.

Purified by flash column chromatography on silica gel (gradient elution 4:1 to 3:2, petroleum ether/ethyl acetate) to give the product **457** (232 mg, 37%) as

colourless needles. HPLC: Chiralcel AD-H; mobile phase, hexane/2-propanol (9 :1 v/v); flow rate, 1 ml/min; 31.3 min (98%), 42.5 min (2%) 96% ee.

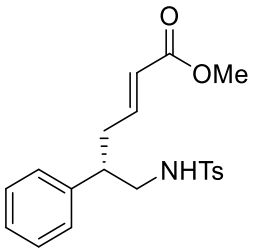
(*E*)-Methyl 6-(4-methylphenylsulfonamido)-5-phenylhex-2-enoate **458/459**



Follwed general procedure for cross metathesis reactions.

Purified by flash column chromatography on silica gel (4:1, petroleum ether/ethyl acetate) to give the product **458/459** (489 mg, 82%) as a pale yellow oil. *Rf* 0.1 (4:1, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3377, 3008, 2952, 2930, 1718, 1659, 1600; δ_H (400 MHz, $CDCl_3$) 7.67 (2H, d, *J* 8.0, ArH),7.35-7.22 (5H, m, ArH), 7.05 (2H, d, *J* 8.0, ArH), 6.73 (1H, dt, *J* 15.5, 7.5, (CO)C=CH), 5.75 (1H, dt, *J* 15.5, 1.5, (CO)CH), 4.39 (1H, dd, *J* 8.0, 4.5, NH), 3.69 (3H, s, OCH_3), 3.28 (1H, ddd, *J* 13.0, 8.0, 6.0, NC*Ha*Hb), 3.06 (1H, ddd, *J* 13.0, 8.5, 4.5, NCHa*Hb*), 2.87 (1H, tt, *J* 8.5, 6.0, ArCH), 2.61-2.43 (2H, m, CHC*Ha*Hb and CHCHa*Hb*), 2.45 (3H, s, $ArCH_3$); δ_C (100 MHz, $CDCl_3$) 166.6 (C), 145.6 (CH), 143.6 (C), 140.0 (C), 136.8 (C), 129.8 (CH), 129.1 (CH), 127.6 (CH), 127.1 (CH), 123.0 (CH), 51.5 (CH_3), 47.9 (CH_2), 44.7 (CH), 36.0 (CH_2), 21.5 (CH_3); *m/z* (ESI) 396 ($M+Na^+$, 100%); *m/z* (ESI) found [$M+Na^+$] 396.1245. $C_{20}H_{23}NO_4SNa^+$ requires 396.1240; HPLC: Chiralcel AD-H; mobile phase, hexane/2-propanol (4:1 v/v); flow rate, 1.0 ml/min; 13.2 min (50%), 17.1 min (50%), 0% ee..

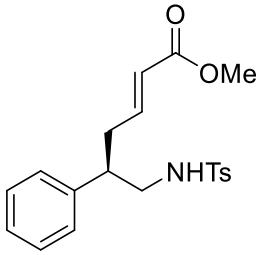
(*S*)-(*E*)-Methyl 6-(4-methylphenylsulfonamido)-5-phenylhex-2-enoate **459**



Follwed general procedure for cross metathesis reactions.

Purified by flash column chromatography on silica gel (4:1, petroleum ether/ethyl acetate) to give the product **459** (348 mg, 98%) as a colourless oil. $[\alpha]_D^{24}$ 8.6 (*c* 0.7, $CHCl_3$); HPLC: Chiralcel AD-H; mobile phase, hexane/2-propanol (4:1 v/v); flow rate, 1.0 ml/min; 16.8 min (100%), >99% ee.

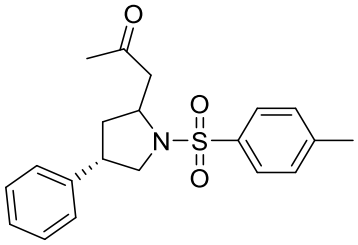
(*R*)-(*E*)-Methyl 6-(4-methylphenylsulfonamido)-5-phenylhex-2-enoate **458**



Follwed general procedure for cross metathesis reactions.

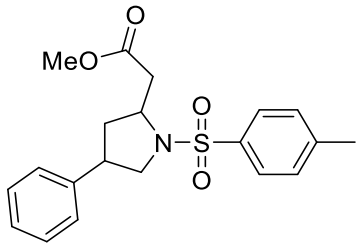
Purified by flash column chromatography on silica gel (4:1, petroleum ether/ethyl acetate) to give the product **458** (109 mg, 92%) as a colourless oil. $[\alpha]_D^{24}$ -3.7 (*c* 0.7, $CHCl_3$). HPLC: Chiralcel AD-H; mobile phase, hexane/2-propanol (4:1 v/v); flow rate, 1.0 ml/min; 13.1 min (100%), >99% ee..

1-(4-Phenyl-1-tosylpyrrolidin-2-yl)propan-2-one **448**



9-*Epi*aminoquinine **25** (6.46 mg, 0.02 mmol) and trifluoroacetic acid (2.28 mg, 0.02 mmol) in deuterated benzene (0.2 mL) were added to (*E*)-4-methyl-*N*-(6-oxo-2-phenylhept-4-en-1-yl)benzenesulfonamide **444** (35.6 mg, 0.10 mmol) in deuterated benzene (0.4 mL). After 3h the solution filtered through a plug of silica gel and concentrated under reduced pressure to give the product **448** (32.2 mg, 90%) as a dark yellow oil. δ_H (400 MHz, $CDCl_3$) 7.80 (2H, d, *J* 8.5, ArH), 7.40 (2H, d, *J* 8.0, ArH), 7.33-7.21 (3H, m, ArH), 7.10 (2H, d, 8.0, ArH), 4.04 (1H, dtd, *J* 12.5, 9.0, 3.5, CH), 3.85-3.78 (1H, m, NC*Ha*Hb), 3.52-3.39 (2H, m, NCHa*Hb* and (CO)C*Ha*Hb), 2.84 (1H, dd, *J* 18.0, 9.0, (CO)CHa*Hb*), 2.67-2.53 (2H, m, C*Ha*Hb and CH), 2.49 (3H, s, CH_3), 2.22 (3H, s, CH_3), 1.78-1.66 (1H, m, CHa*Hb*); δ_C (100 MHz, $CDCl_3$) 207.0 (C), 143.8 (C), 139.3 (C), 134.3 (C), 129.9 (CH), 128.7 (CH), 127.7 (CH), 127.1 (CH), 126.9 (CH), 56.9 (CH), 54.9 (CH_2), 50.7 (CH_2), 42.7 (CH), 40.5 (CH_2), 30.7 (CH_3), 21.6 (CH_3); HPLC: Chiralcel AS-H; mobile phase, hexane/2-propanol (9:1 v/v); flow rate, 1.0 ml/min; 65.5 min (98.4%), 85.4 min (1.6%), 97% ee.

Methyl 2-(4-phenyl-1-tosylpyrrolidin-2-yl)acetate **450**



Potassium *tert*-butoxide (0.3 mg, 0.0027 mmol) was added to a solution of (*E*)-methyl 6-(4-methylphenylsulfonamido)-5-phenylhex-2-enoate **450** (10 mg, 0.027 mmol) in deuterated benzene. After 10 mins the solution was passed through a plug of silica and concentrated under reduced pressure to obtain the products (9.2 mg, 92%, 3:2 mixture of diastereoisomers) as a pale yellow oil. *Rf* 0.4 (7:3, petroleum ether/ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3377, 3008, 2952, 1718, 1659, 1599, 1335; δ_H (400 MHz, $CDCl_3$) 7.83 (1.2H, d, *J* 8.0, ArH), 7.78 (0.8H, d, *J* 8.0, ArH), 7.42-7.19 (5H, m, ArH), 7.12 (1.2H, d, *J* 8.0, ArH), 7.07 (0.8H, d, *J* 8.0, ArH), 4.23-4.16 (0.4H, m, NCH), 4.11-4.02 (0.6H, m, NCH), 3.96-3.80 (1H, m), 3.74 (1.2H, s, OCH_3) 3.73 (1.8H, s, OCH_3), 3.57-3.47 (0.4H, m), 3.47-3.38 (0.6H, m), 3.29 (0.6H, dd, *J* 16.5, 4.0, (CO)C*Ha*Hb), 3.19 (0.4H, dd, *J* 16.5, 4.0, (CO)C*Ha*Hb), 2.97 (0.4H, dd, *J* 11.0, 9.0, (CO)CHa*Hb*), 2.75-2.44 (2.2H, m), 2.49 (1.8H, s, $ArCH_3$), 2.48 (1.2H, s, $ArCH_3$), 2.14-2.05 (0.4H, m), 1.94-1.82 (1H, m), 0.95-0.82 (0.4H, m); δ_C (100 MHz, $CDCl_3$) 171.7 (C), 171.6 (C), 139.2 (C), 139.1 (C), 134.6 (C), 133.5 (C), 129.9 (CH), 129.8 (CH), 128.7 (CH), 127.7 (CH), 127.6 (CH), 127.1 (CH), 127.0 (CH), 126.9 (CH), 57.3 (CH), 56.4 (CH), 55.2 (CH_2), 55.1 (CH_2), 51.7 (CH_3), 51.6 (CH_3), 42.9 (CH), 41.5 (CH_2), 41.3 (CH_2), 40.1 (CH_2), 37.9 (CH_2), 21.6 (CH_3); *m/z* (ESI) 396 ($M+Na^+$, 100%); *m/z* (ESI) found [$M+Na^+$] 396.1245. $C_{20}H_{23}NO_4SNa^+$ requires 396.1240.

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