Asymmetric Synthesis of Functionalised Pyrrolidines and their Application in Total Synthesis

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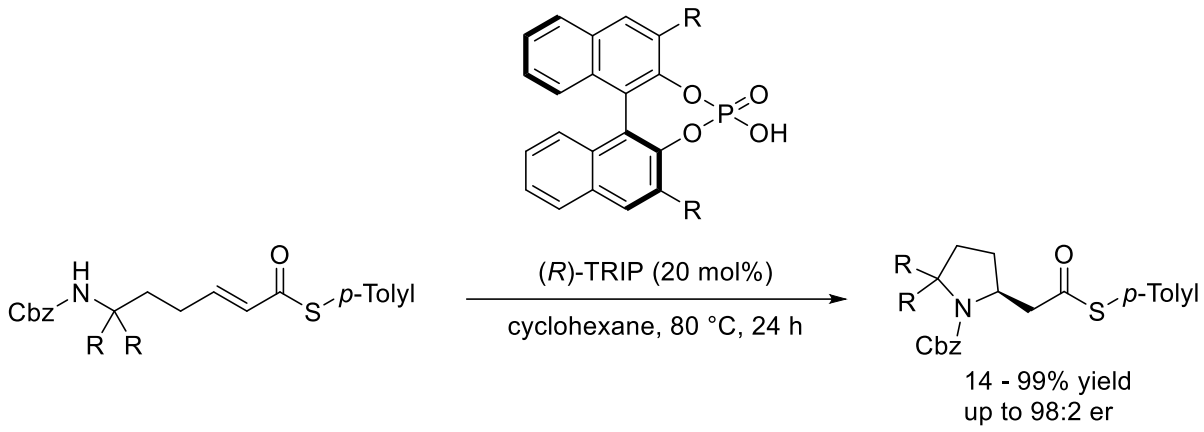
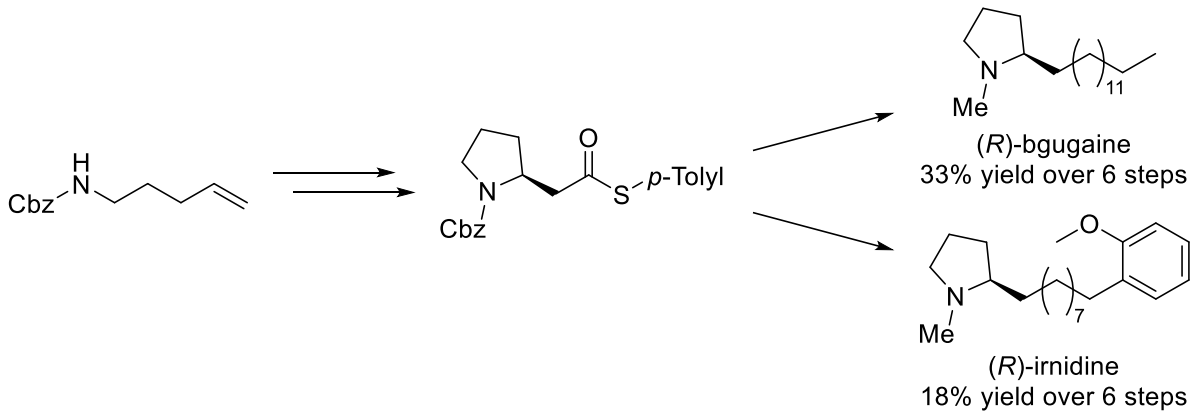
Abstract

The intramolecular aza-Michael reaction has been used effectively in the synthesis of nitrogen heterocycles, with several efforts made in recent years to do so asymmetrically. The selection of the Michael acceptor can play an important role in both the rate and enantioselectivity of the reaction. The research in this thesis demonstrates how the use of a chiral phosphoric acid can catalyse the intramolecular asymmetric aza-Michael reaction of a protected amine with an α,β- unsaturated thioester. The scope of the reaction was demonstrated in the synthesis of 2,2- and 3,3-spirocyclic pyrrolidines in high yields and enantioselectivity (Scheme 1). The synthesis of an unsubstituted pyrrolidine provided the core of two natural products (*R*)-bgugaine and (*R*)-irnidine and both succumbed to total synthesis. (*R*)-Bgugaine was synthesized in a 33% overall yield in 6 steps while (*R*)-irnidine was synthesized for the first time in an overall yield of 18% over 6 steps.



Scheme 1. Asymmetric synthesis of spirocyclic pyrrolidines



Scheme 2. Total synthesis of (R)-bgugaine and (R)-irnidine

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Declaration

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

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

Some of the research outlined in thesis has been published in the following papers:

Asymmetric "Clip-Cycle" Synthesis of Pyrrolidines and Spiropyrrolidines, C. J. Maddocks, K. Ermanis, and P. A. Clarke, *Organic Letters*, 2020, **22**, 8116-8121

Catalytic asymmetric total syntheses of (*R*)-bgugaine and (*R*)-irnidine, C. J. Maddocks and P. A. Clarke, *Tetrahedron*, 2021, **78**, 131789

1. Introduction – The Enantioselective Synthesis of Pyrrolidines

1.1. Pyrrolidines in pharmaceuticals

A recent report on the number of nitrogen heterocycles present in FDA approved pharmaceuticals highlights the prevalence and structural diversity of these compounds.[1] From a database of 1086 unique small molecule drugs, 910 (84%) contained at least one nitrogen atom with 640 (59%) containing a nitrogen heterocycle. Out of these 640, the aromaticity, ring size and substitution patterns were analysed to determine the prevalence of each type of ring system. The most common five-membered non-aromatic nitrogen heterocycle by far was the pyrrolidine, which ranked 5th overall for frequency out of 25 distinct heterocycles.[1] The structure was present in more drugs than all other five-membered non-aromatic nitrogen heterocycles combined. The report also noted that the vast majority (92%) of pyrrolidine drugs showed substitution on the nitrogen atom with 62% substituted at the 2-position as the second most common site of substitution. A common motif present which contains a pyrrolidine ring is that of proline and is seen in many ACE inhibitor drugs used to treat hypertension, such as captopril **1** (Figure 1).[2] The application of pyrrolidine containing drugs is very wide ranging from the antibiotic clindamycin **5**, antihistamine (*S*,*S*)-clemastine **3** and the hepatitis C drug ledipasvir **4**. [3–5] While not used as a drug, the small molecule (-)-kainic acid **2** is useful in studying mammalian nervous system disorders such as epilepsy and Alzheimer's disease.[6,7]

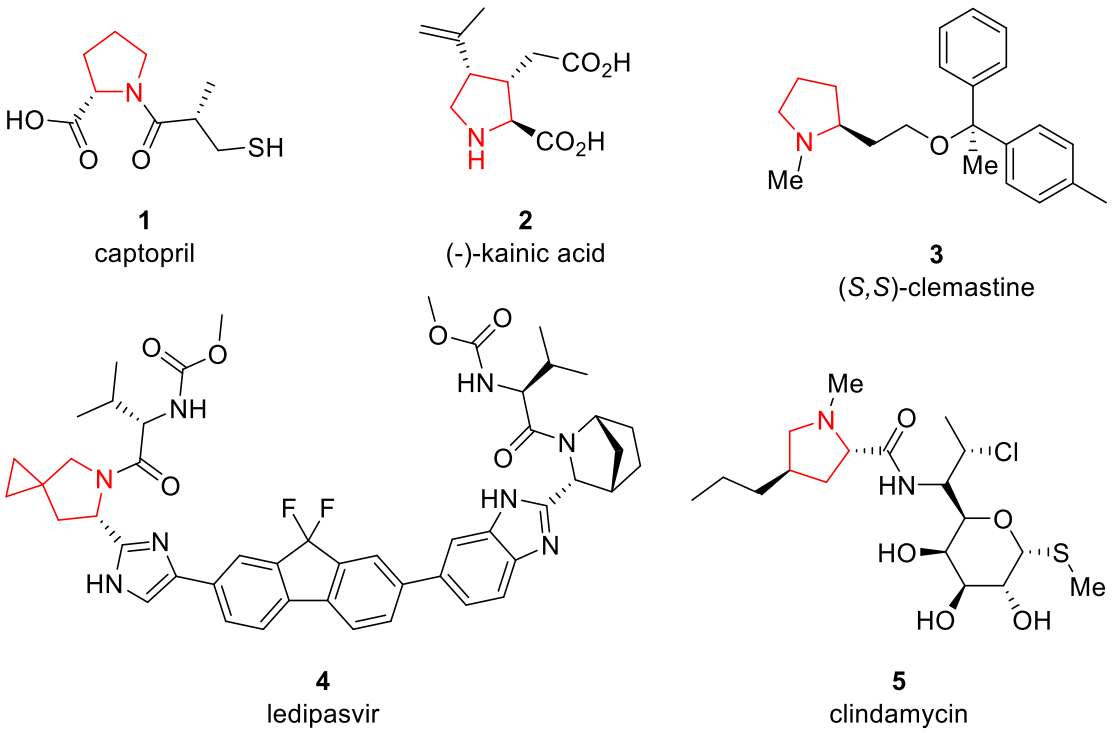


Figure 1. Pyrrolidine containing pharmaceuticals and biologically active molecules

A key feature to note in all the structures shown in Figure 1, is that there is at least one or more stereocenters on the pyrrolidine ring. Over half (56%) of drugs currently in use are chiral, with 88% of these chiral drugs used as a racemate.[8,9] While these drugs are used effectively as a racemate, in recent years there has been efforts to understand the effect of different enantiomers on the body, in terms of efficacy, toxicology and pharmacokinetics.[9,10] As such, in 1992 the FDA released a policy statement indicating new measures for the introduction of chiral drugs involving the study of various properties of both enantiomers in order to gain approval.[11] The policy also suggested using synthetic methods to prepare single enantiomers in order to properly assess the properties of both isomers.

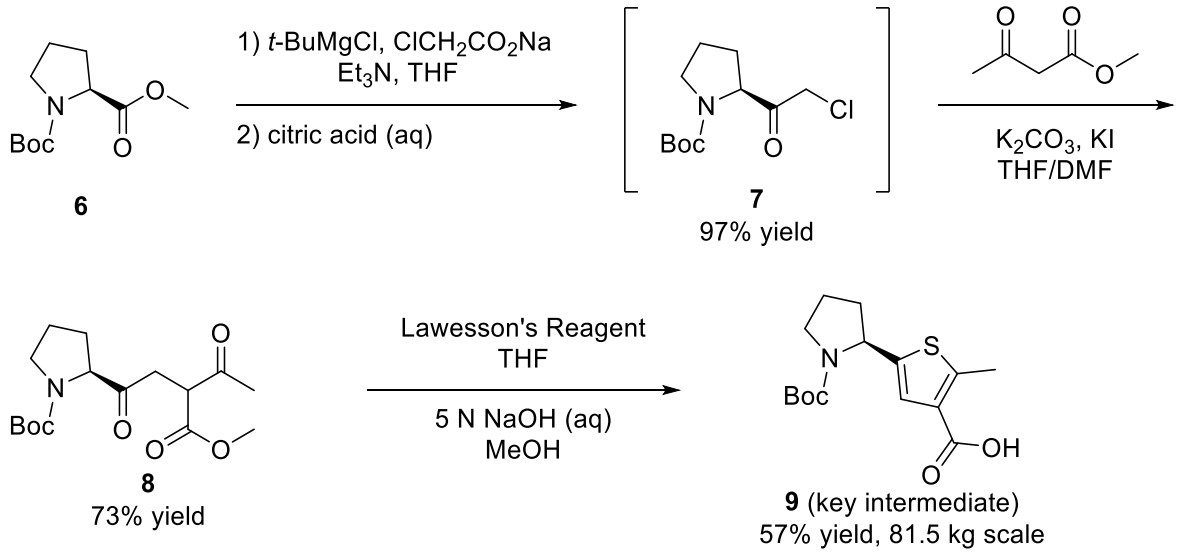
There is a clear need and desire to synthesise compounds as a single enantiomer, or otherwise separate enantiomers for study. Although chiral separation techniques exist, if the specific stereochemistry can be introduced *via* a synthetic step, separation would not be required. Due to the prevalence of *N*-heterocycles in pharmaceutical compounds, the stereoselective synthesis of these motifs has been of interest for several years. Many methods have been developed to enable efficient and stereo-controlled production of pyrrolidines. A selection of

these approaches is presented below to demonstrate the variety of reactions available in the literature.

1.2. Chiral pool synthesis

One of the most direct methods of producing compounds as a single enantiomer is using enantiomerically pure starting material, i.e. using the chiral pool. This typically involves utilising materials widely available in nature as the starting material for a synthetic route in order to form the key chiral structures of a compound.[12] Some common materials from the chiral pool include α-amino acids, carbohydrates, terpenes and hydroxy acids. The chiral pool and derivatives thereof have also been widely used in the field of enantioselective catalysis,[13–15] for example L-proline has been used to catalyse asymmetric aldol reactions since the 1970s.[16]

Building pyrrolidine scaffolds from the chiral pool is possible through various synthetic modifications and one of the most obvious starting materials for this is L-proline.[17] The functionalisation of L-proline has been performed in multiple ways to enable its use as a chiral synthon, such as the Arndt-Eistert homologation,[18] and the Henry-Nef reaction.[19] Due to the low cost and accessibility of L-proline it also makes a very useful starting material for large scale synthesis. A report by Fujieda demonstrates the use of an L-proline derivative in the synthesis of a glucokinase activator, a potential treatment for type 3 diabetes, on a multi-kilo scale (Scheme 3).[20] In the first-generation synthesis of the key intermediate **9** a racemic mixture was obtained and an optical resolution was required to access the desired enantiomer, making the maximum theoretical yield for that step 50%. To get around this in later generation syntheses, *N*-Boc-L-proline methyl ester **6** was functionalised through a chloromethylation to give the α-chloroketone **7** in 97% yield, followed by alkylation with methylacetoacetate to give compound **8** in 73% yield. The use of a sulfating reagent (in this case Lawesson's reagent) allowed for the Paul-Knorr thiophene synthesis of the key intermediate **9** in 57% yield to give 81.5 kg of the product.



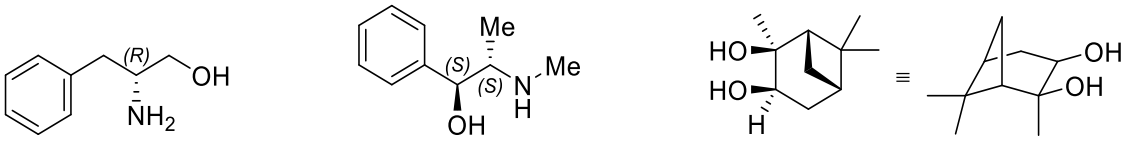
Scheme 3. Synthesis of key intermediate of a glucokinase activator

The key to the success of this application is that the desired stereochemistry of the product matched that of the naturally occurring L-proline which greatly reduces the cost. The unnatural enantiomer, D-proline, can be up to 20x more expensive than the natural enantiomer, which can severely limit accessibility or feasibility.[21] Another limitation when using the chiral pool is that functionalisation around the pyrrolidine ring can be more difficult or involve multistep syntheses. If the functionality of the starting material is not desired in the product (*e.g.* the carboxylic acid group of an amino acid), then extra synthetic steps may be required to remove or modify that group. This can make alternative methods, where unwanted motifs are never present in the molecule during the forward synthesis, particularly attractive.

1.3. Chiral auxiliaries

If an unnatural enantiomer of a pyrrolidine or specific chemical groups are required for the synthesis of a product, then an alternative asymmetric procedure may be required. A way to get around this can be through the use of a chiral auxiliary, where a chiral compound is incorporated into a molecule and then removed later in the synthesis. By having a chiral auxiliary covalently bound to a molecule, any introduction of stereocenters into the compound will result in the potential formation of diastereomers. As diastereomers generally have different physical properties to each other, separation and purification can be much easier than with enantiomers.

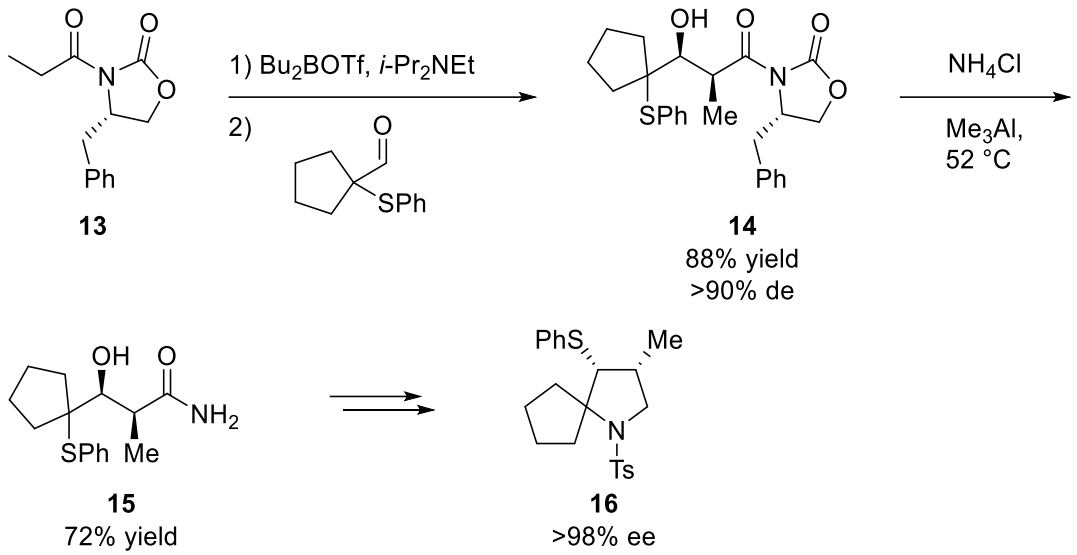
There are many chiral auxiliaries available for asymmetric synthesis and a number of these have been used in the synthesis of pyrrolidines. Both (*R*)-phenylglycinol **10** and (*S,S*)-pseudoephedrine **11** (Figure 2) have both been used in diastereoselective reactions, which have led to the production of single enantiomers of substituted pyrrolidines, after sacrificial loss of the auxiliary.[22,23] Another use for chiral auxiliaries is for the resolution of a racemic mixture. (+)-Pinanediol **12** (Figure 2) has been used to synthesise the boronate ester of racemic *N*-Boc-pyrrolidine-2-boronic acid, allowing for separation and chiral resolution of the two enantiomers.[24] The high price of (+)-pinanediol **12** has also led to the development of processes to enable efficient recycling of the auxiliary.[25]



10 **11** **12**

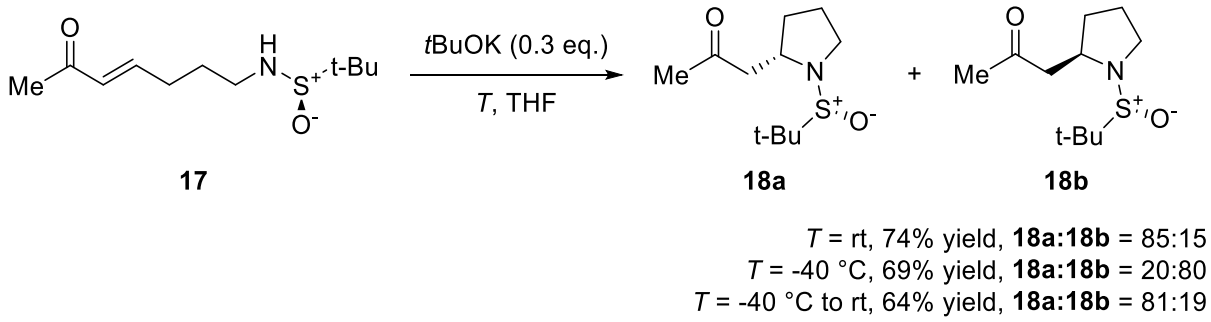
Figure 2. Examples of chiral auxiliaries

One common class of chiral auxiliary is the oxazolidinone, which was popularised by Evans for the use in enantioselective aldol condensations.[26] This oxazolidinone has also been exploited in the synthesis of pyrrolidines by setting up stereocenters within a molecule prior to cyclisation of a pyrrolidine ring. Using the Evans auxiliary, Warren and co-workers were able to achieve an asymmetric aldol reaction with an α-SPh aldehyde to give aldol addition product **14** with high yield and diastereoselectivity (Scheme 4).[27] Removal of the auxiliary from the major diastereomer was achieved through a transamination procedure with ammonium chloride and trimethylaluminium to give amide **15** in 72% yield. Further transformations led to the formation of the spirocyclic pyrrolidine **16** in high enantiomeric excess.



Scheme 4. Use of Evans auxiliary in the synthesis of spirocyclic pyrrolidines

Another example of a well-used auxiliary is the *N*-*tert*-butanesulfinamide (Ellman auxiliary), which was used by Fustero *et. al.* in a base mediated intramolecular aza-Michael reaction for the synthesis of pyrrolidines and piperidines (Scheme 5).[28] The procedure was demonstrated on both methyl vinyl ketones and *tert*-butyl acrylates, but an interesting selectivity was observed when varying the temperature of the reaction. The cyclisation of enone **17** with potassium *tert*-butoxide gave a diastereoselectivity of 85:15 with pyrrolidine **18a** as the major isomer and thermodynamic product when the reaction was performed at room temperature. However, by lowering the temperature to -40 °C, the selectivity was inverted to favour pyrrolidine **18b** as the kinetic product in a ratio of 80:20. This inversion of stereochemistry was possible due to the reversibility of the reaction, which was further demonstrated when the reaction was performed at -40 °C then warmed to room temperature and left for 12 hours. When this was done, the product was isolated as a ratio of 81:19 for **18a** to **18b**, showing conversion of the kinetic product to the thermodynamic over time.



Scheme 5. Use of the Ellman auxiliary in the asymmetric intramolecular aza-Michael reaction

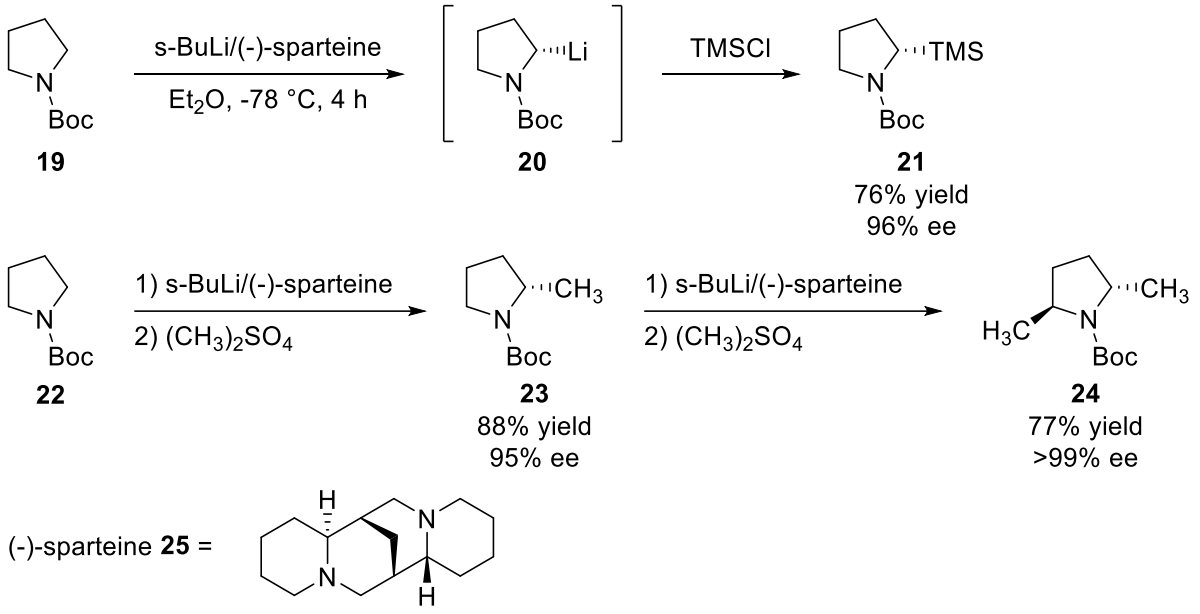
There is clear precedent for the use of chiral auxiliaries to synthesise enantiomerically enriched pyrrolidines. The availability of auxiliaries, especially of both enantiomers, gives a good access to the desired stereochemistry of a molecule, and as most reactions lead to the formation of diastereomers, the purification of a single stereoisomer can also be achieved more easily. However, the inclusion of the auxiliary in the final product is not always required, and due to the stoichiometric quantities needed, the atom economy of the reaction can be significantly reduced. While some auxiliaries can be recycled, this is not always the case and the addition and removal of an auxiliary adds extra steps to a synthetic plan.

1.4. Chiral lithium amide bases

Introduction of the specific stereochemistry needed in a final product can be achieved in a single step through the use of other chiral reagents. A valuable method that can do this is asymmetric induction with chiral lithium amide bases. These reagents are analogous to widely used bases in organic chemistry, such as lithium diisopropylamide, but contain stereogenic centres within the structure of the base. The core structures can be derived from organic molecules, such as α-methylbenzylamine and phenylglycine, or can be isolated from natural sources, as in the case of sparteine. These reagents have found various applications in asymmetric organic synthesis, such as the deprotonation of prochiral ketones and epoxide rearrangement to allylic alcohols.[29] For the asymmetric synthesis of heterocycles, sparteine has been widely used in the enantioselective lithiation of *N*-Boc pyrrolidine.[30]

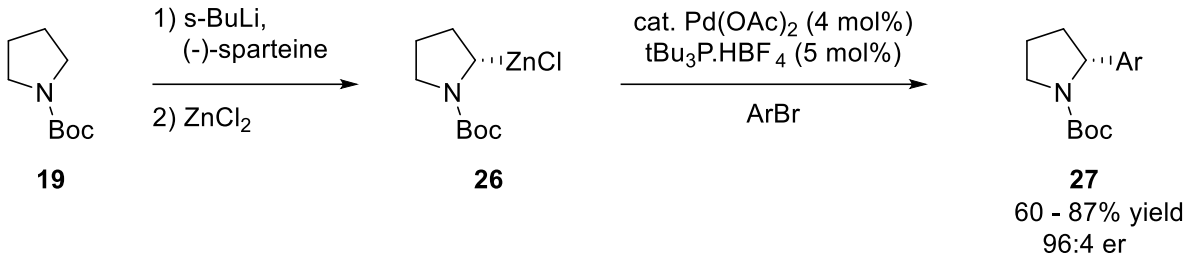
The seminal work by Beak and co-workers demonstrated the use of (-)-sparteine **25** and sec-BuLi to deprotonate *N*-Boc pyrrolidine **19** next to the nitrogen.[31] Asymmetric deprotonation can take place due to the coordination of the lithium cation with the nitrogen atoms of the (-

)-sparteine ligand. The chiral carbanion formed is also stabilised by coordination of the carbonyl of the Boc group to the lithium atom, which helps prevent racemisation of the stereocentre. The lithiated species could then be trapped with an electrophile to give an isolated product in high enantiomeric excess. In the case of TMSCl, this led to the isolation of 2-trimethylsilyl-*N*-Boc pyrroldine **21** in 76% yield and 96% ee. When dimethyl sulfate was used, successive additions were able to take place to introduce methyl groups for a double sparteine-lithiation to give a 2,5-disubstituted pyrrolidine **24** (Scheme 6).[32]



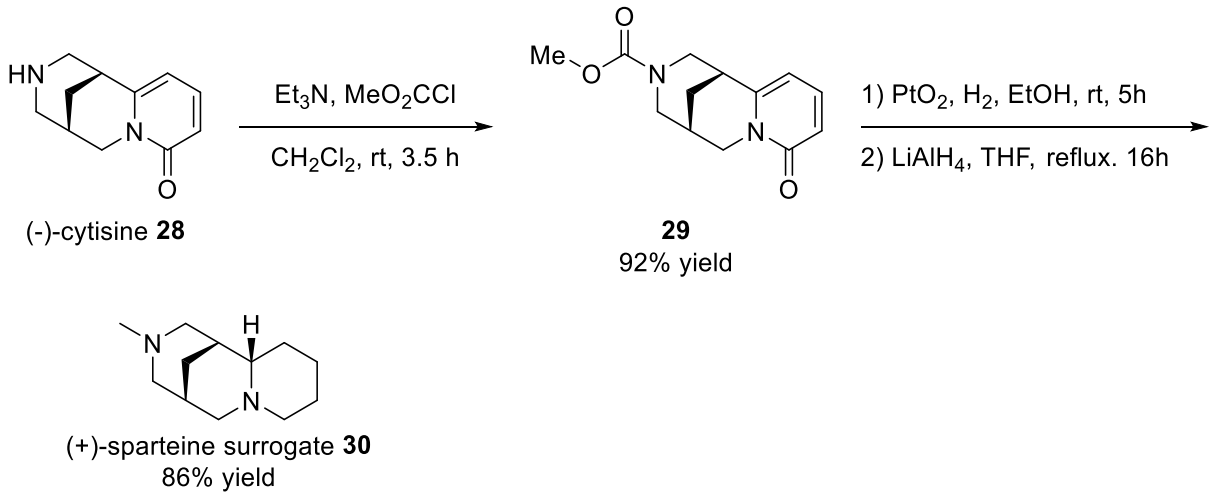
Scheme 6. Sparteine mediated asymmetric lithiation and trapping of N-Boc pyrrolidines

Since this work, there have been various applications of Beak's procedure to the asymmetric synthesis of pyrrolidines. Trapping of the lithiated intermediate with electrophiles has been extended to the boron trifluoride assisted ring opening of ethylene epoxide to create β-homoproline derivatives.[33] Transmetalation can also be performed on the lithiated intermediate to give potential cross coupling partners. Beak demonstrated this in the synthesis of a tributylstannane pyrrolidine with the potential for use in Stille reactions.[32] Another development of the procedure was demonstrated by Campos in a transmetalation to give a chiral zincate **26** that then underwent a Negishi coupling with a variety of substituted aryl bromides (Scheme 7).[34] This led to the formation of α-arylated pyrrolidines **27** with high er and good yields reported for all the bromides tested.



Scheme 7. Pd-catalysed arylation of N-Boc pyrrolidine

While these demonstrate the utility of sparteine, lack of availability of the ligand has led to limitations in its application. In order to overcome this shortage, the synthesis of sparteine like chiral diamines has been investigated by several research groups.[35] One compound that has matched the synthetic capabilities of sparteine is the sparteine surrogate **30** developed by the O'Brien group (Scheme 8).[36] The surrogate is accessible in two steps from the natural product (-)-cytisine **28** extracted *laburnum anagyroides* seeds. When tested in the deprotonation of *N*-Boc pyrrolidine with *sec*-BuLi and trapping with TMSCl, the (+)-sparteine surrogate gave the same enantioselectivity and yields as (-)-sparteine but with the opposite absolute stereochemistry.



Scheme 8. Synthesis of sparteine surrogate

The use of these reagents has enabled easy access to both enantiomers of 2-substituted pyrrolidines and the lithiated intermediates have wide synthetic applications. However, this process is not effective in synthesising 3-substituted pyrrolidines, as the stabilisation of the Boc protecting group is necessary for retaining the enantioselectivity. Similarly, the necessity of the Boc group can also limit the synthetic procedures used. The stoichiometric quantities

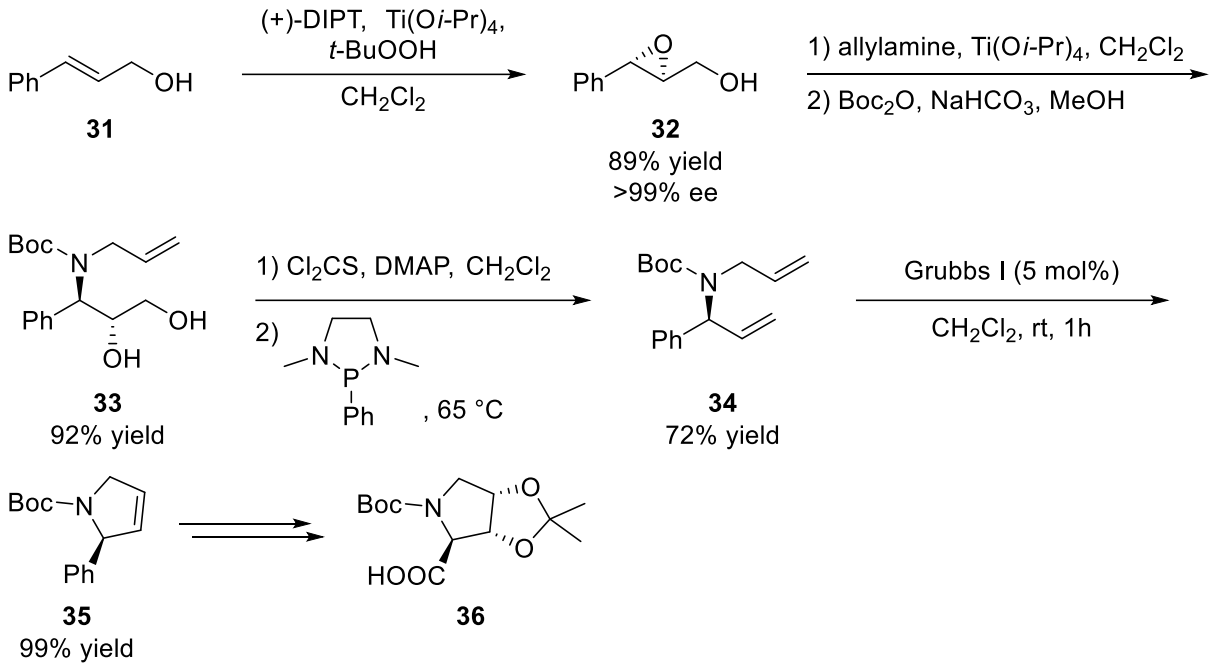
of the ligand can reduce the atom efficiency of the reaction, but unlike using chiral auxiliaries, the ligand does not need to be removed in a separate step and allows for direct introduction of the desired stereocentre. The use of organometallic reagents also warrants the use of cryogenic temperatures which can hinder some applications and limits large scale industrial use.

1.5. Asymmetric transition metal catalysis

A way to combat some of the shortcomings of using stoichiometric reagents, such as chiral auxiliaries and amide bases, is through the use of asymmetric catalysis. With design and optimisation of catalytic systems, low catalyst loading can be achieved which leads to greater atom efficiency of the reaction. It also enables the modification of the selectivity of a reaction to gain access to multiple stereoisomers by variation of the catalyst.[37]

One branch of asymmetric catalysis is that of transition metal catalysed reactions where the chirality is introduced by a chiral ligand around a metal centre. When synthesising pyrrolidines, the ring system can either be introduced at the start of a synthesis (such as when using chiral lithium amide bases) or formed in a cyclisation step. Many asymmetric transition metal catalysed reactions introduce chirality during this cyclisation of pyrrolidines, and this will be the focus of this section. However, it is worth mentioning an important method that introduces the chiral centre before the cyclisation.

A widely used enantioselective reaction is the Sharpless epoxidation, which uses catalytic quantities of a titanium (IV) isopropoxide and a diethyl tartrate ligand with stoichiometric *t*-BuOOH to form an enantioenriched epoxide from allylic alcohols.[38] This technique was exploited by Riera to synthesise allylic amines **34** as a single enantiomer (Scheme 9).[39] The asymmetric epoxidation of cinnamyl alcohol **31** gave epoxide **32** in high yields and enantiomeric excess. Ring opening of the epoxide with allyl amine and Boc protection gave diol **33** in 92% yield, and subsequent deoxygenation gave the bis-allylamine **34** in 72% yield. Using another catalytic process of a ring closing metathesis, the bis-allylamine **34** was subjected to Grubbs first generation catalyst to form pyrrolidine **35** in near quantitative yields. Further manipulations gave access to the proline derivative (2*S*,3*R*,4*S*)-3,4-dihydroxyproline **36** (Scheme 9).



Scheme 9. Synthesis of (2S,3R,4S)-3,4-dihydroxyproline

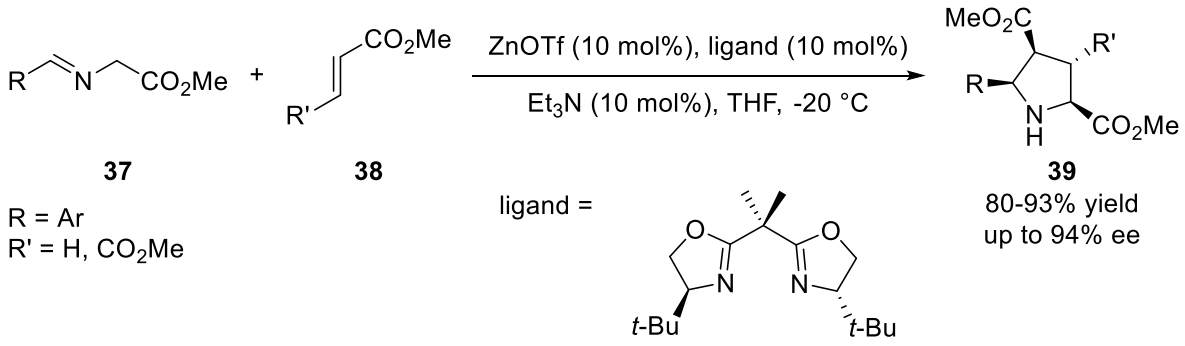
One of the disadvantages of this method is that the desired stereochemistry is introduced in the first step of the reaction. If the opposite enantiomer was required, then the whole synthesis would need to be repeated from the asymmetric epoxidation step. This can make enantiomeric derivatives more difficult to access than methods where the stereochemistry is introduced at a later stage.

1.5.1. Intermolecular cyclisation

Introduction of chirality in the cyclisation step can be achieved both intermolecularly and intramolecularly. Intermolecular reactions can introduce a large amount of functionality in a single step, while intramolecular reactions can offer greater control over the reaction, as well faster rates of reaction. In metal catalysed reactions, the coordination of organic molecules to the metal centre can have multiple effects on the reaction mechanism and scope. For both inter- and intramolecular reactions, the coordination of two or more functional groups to the metal atom can help tether the reactive groups bringing them into closer proximity. This can promote a faster rate of reaction and, by using chiral ligands, potentially introduce chirality into the molecule. In some cases, the metal can also act as a Lewis acid, lowering the LUMO energies of some functional groups, such as carbonyls. A powerful method for synthesising ring systems that utilises the coordinating ability of metals is the cycloaddition reaction. Many

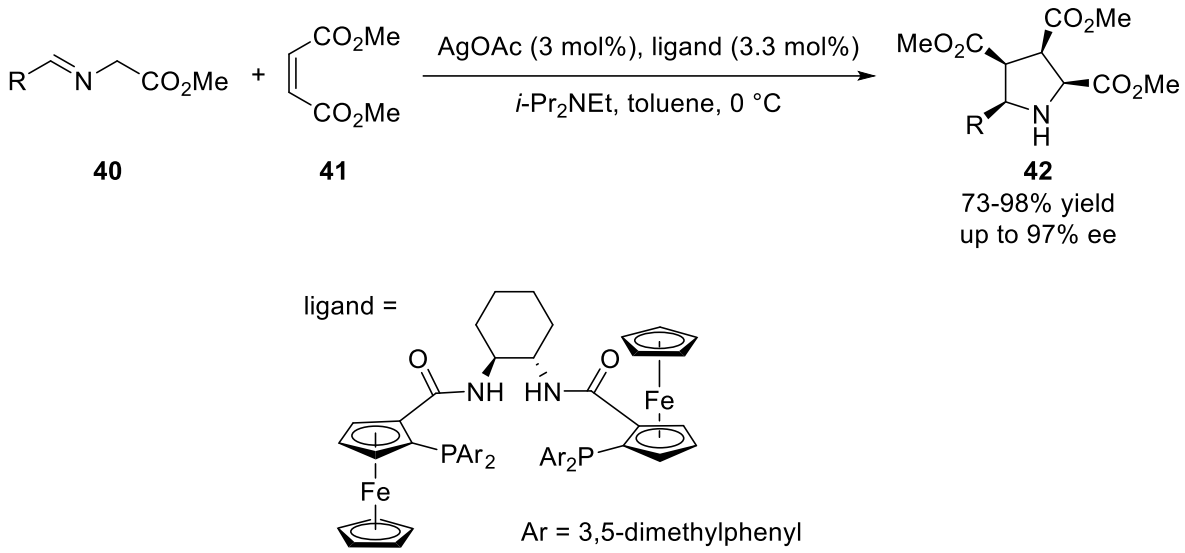
methods have been developed for racemic cyclisations, but the introduction of asymmetry remains challenging. One method that dominates the field of pyrrolidine synthesis is the azomethine dipolar addition.

The dipolar cycloaddition of azomethine ylides onto a dipolarophile can lead to the formation of a number of nitrogen heterocycles, such as pyrrolines and pyrrolidines, and has been known since the 1960s.[40] Two of the earliest catalytic asymmetric examples of this reaction were reported in 2002 by Jørgensen and Zhang in separate reports but with both using chiral ligands and a transition metal catalyst.[41,42] Jørgensen's method utilised a chiral BOX ligand with zinc triflate as the catalyst for the asymmetric cycloaddition of aryl iminoesters **37** with methyl acrylate **38** (Scheme 10).[41] Screening of the reaction conditions showed that zinc triflate was imperative in achieving high enantioselectivity, as when copper triflate was used a racemic product was acquired. It was also shown that using that switching to the ethyl acrylate as the dipolarophile caused a noticeable drop in yields and enantiomeric excess, while *tert*-butyl acrylate led to very poor yields and enantioselectivity.



Scheme 10. Jørgensen azomethine cycloaddition

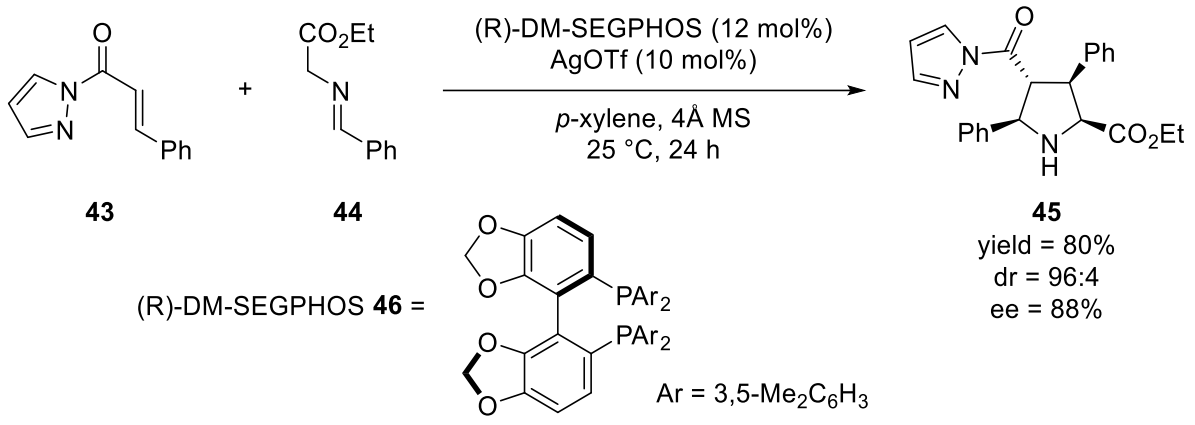
Zhang shortly after demonstrated the use of silver acetate with a chiral bidentate phosphine ligand in the cycloaddition of aryl iminoesters **40** with dimethyl maleate **41** (Scheme 11). [42] The reaction favoured the endo product to give highly substituted pyrrolidines **42** in high yields and enantiomeric excess. The reaction was also extended to alkyl iminoesters, but these required extended reaction times of 48 hours and room temperature in order to go to completion.



Scheme 11. Zhang azomethine cycloaddition

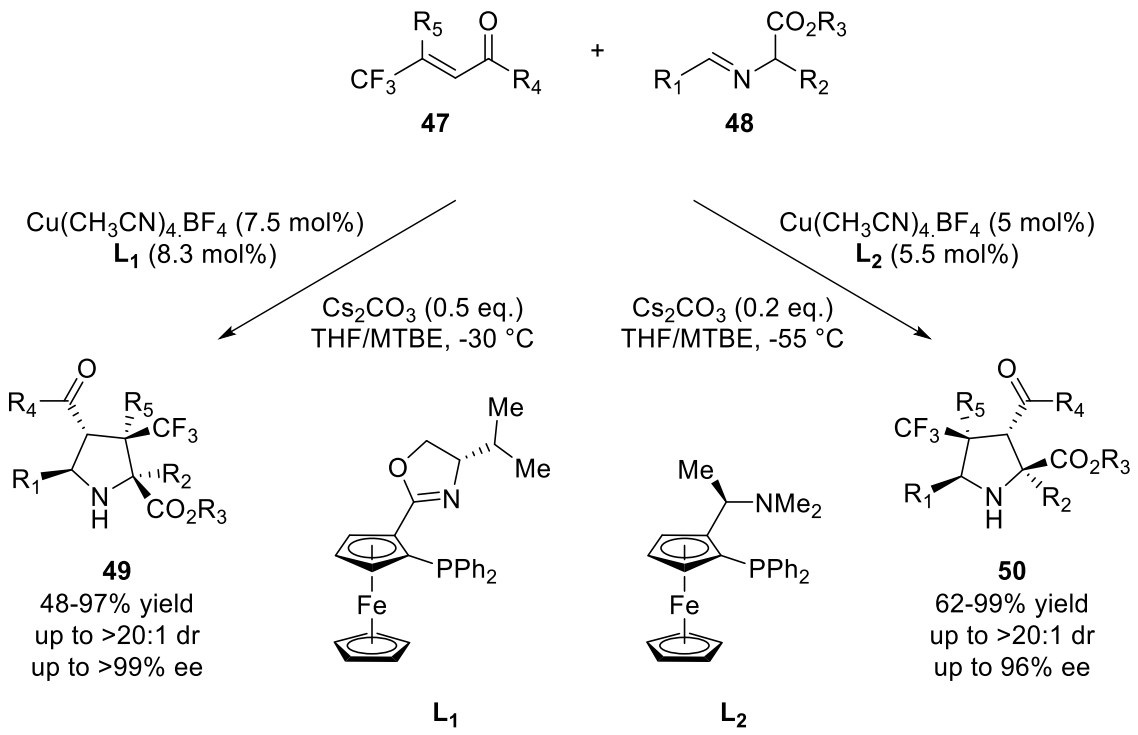
In both of these cycloaddition reactions, the ylide is formed from an iminoester *in situ*. In order to stabilise the ylide and promote the reaction, an electron withdrawing group (such as a methyl ester) is required on the imine. Not only does this allow for easier abstraction of the α-proton by the nitrogen, the carbonyl can stabilise the ylide through coordination to the metal catalyst. Since these initial reports there have been a number of developments into the asymmetric azomethine cycloaddition, and a selection of recent reports are shown below.

A strategy reported by Singh employs (1,3)-dipolar cycloadditions of iminoesters **44** with an unusual α,β-unsaturated pyrazole amide dipolarophile **43** to produce highly substituted pyrrolidines **45** with good enantioselectivity (Scheme 12).[43] After screening multiple ligands, metal salts, and conditions the group found that the chiral ligand (*R*)-DM-SEGPHOS **46** with silver triflate gave the best combination of yield, diastereoselectivity and enantioselectivity. The scope of the reaction was also tested with various aryl and ester substituents giving good to excellent, selectivity. However, when alkyl or alkenyl substituents were introduced at the 5-position or groups other than pyrazole were used on the Michael acceptor, the reaction either did not proceed or gave poorer enantiomeric excess.



Scheme 12. Enantioselective (1,3)-dipolar cycloadditions of azomethine ylides

A related reaction by Zhang shows a similar cycloaddition reaction of iminoesters **48** with aryl enones **47** as electrophiles (Scheme 13).[44] However, the researchers were able to develop an interesting switching of regioselectivity through variation of the catalyst and conditions. The switching ability was aided by the electron withdrawing CF_3 group, which can pull charge from the double bond of the dipolarophile. This leads to both carbons of the double bond being susceptible to nucleophilic attack instead of just the β-carbon. Utilising ligand **L_1** the cycloaddition led to the CF_3 group located in the 3-position of the pyrrolidine **49**, while ligand **L_2** led to the CF_3 in the 4-position **50**. The selectivity was explored through DFT calculations and experimental data to investigate the different coordination modes between the ligands and enones to the copper atom. In the case of **L_1**, both the phosphine and nitrogen atom of the oxazoline coordinate to the nitrogen as a bidentate ligand. This prevents coordination of the enone carbonyl to the metal leading to the formation of pyrrolidine **49**. For ligand **L_2**, the phosphine still coordinates to the copper, but the NMe_2 does not, which allows for the enone carbonyl to interact with the copper atom and drive the selectivity, giving pyrrolidine **50** as the major product. Application of the methodology to a range of substitution on both the enone and the iminoester produced a wide variety of pyrrolidine products with four distinct stereocentres, including two quaternary centres, in high enantioselectivity for all the substrates tested.



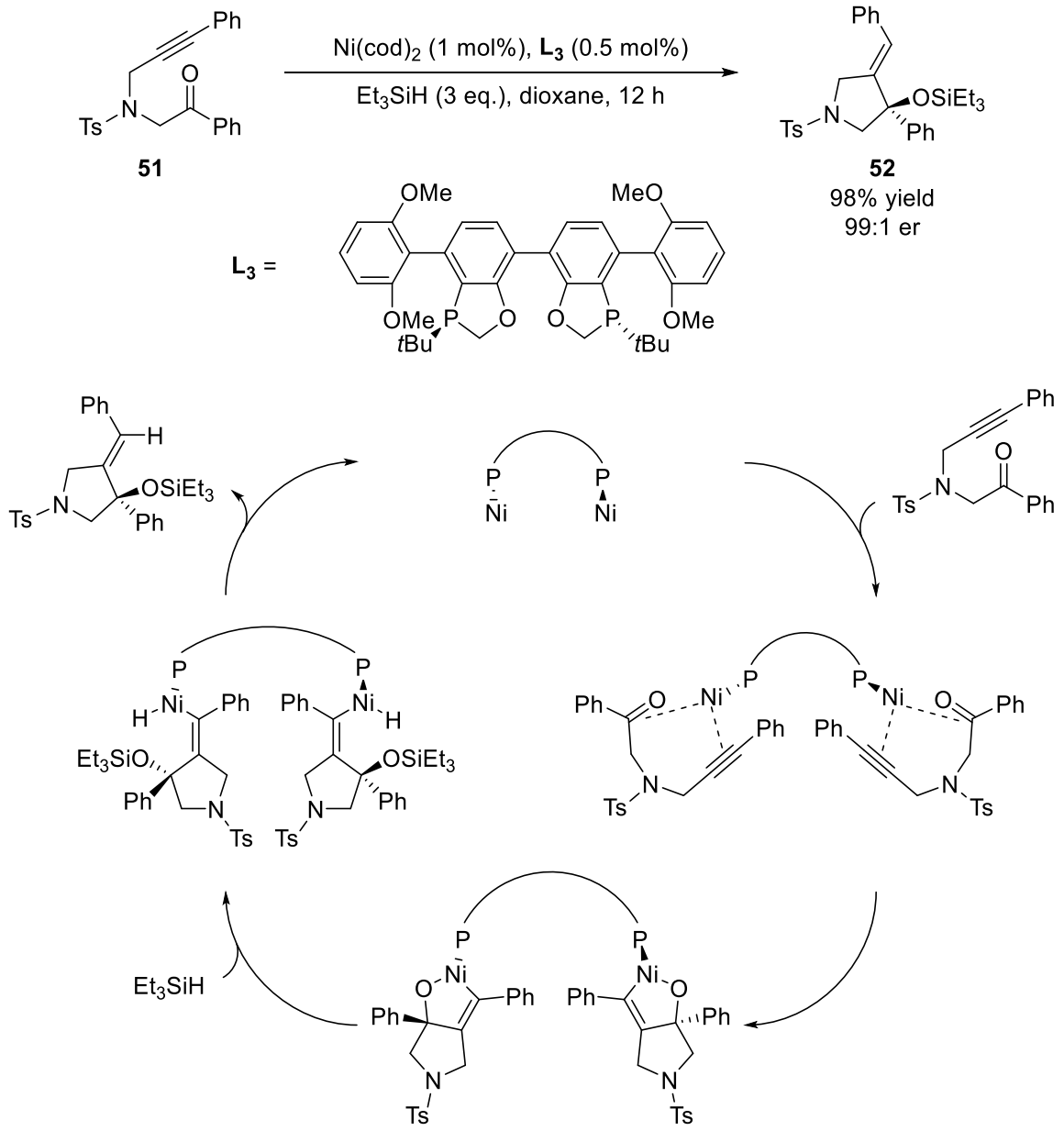
Scheme 13. Asymmetric cycloaddition of iminoesters and enones

1.5.2. Intramolecular cyclisation

While the intermolecular azomethine cycloaddition reaction can be very effective in the asymmetric synthesis of pyrrolidines, the use of intramolecular reactions can offer greater control over reactivity and selectivity. Indeed, the application of the azomethine cycloaddition to an intramolecular reaction has also been widely investigated, with an in-depth review by Coldham and Hufton on this area of research.[45] However, while this reaction is powerful in constructing a pyrrolidine, there are other methods available to the synthetic chemist.

A recent example of an intramolecular cyclisation used to synthesise pyrrolidines is the asymmetric alkyne cycloaddition reaction. In a report by Tang the Nickel-catalysed reductive cyclization of *N*-alkynones **51** was able to produce pyrrolidines containing a tertiary alcohol **52** in high enantiomeric ratio (Scheme 14).[46] The use of a chiral bidentate ligand **L₃** to form a dimeric nickel complex enabled the coordination of two molecules of the *N*-alkynone **51** to the catalyst. When compared to the monodentate version of ligand, the bidentate ligand **L₃** showed enhance reactivity and enantioselectivity. The researchers suggested that the

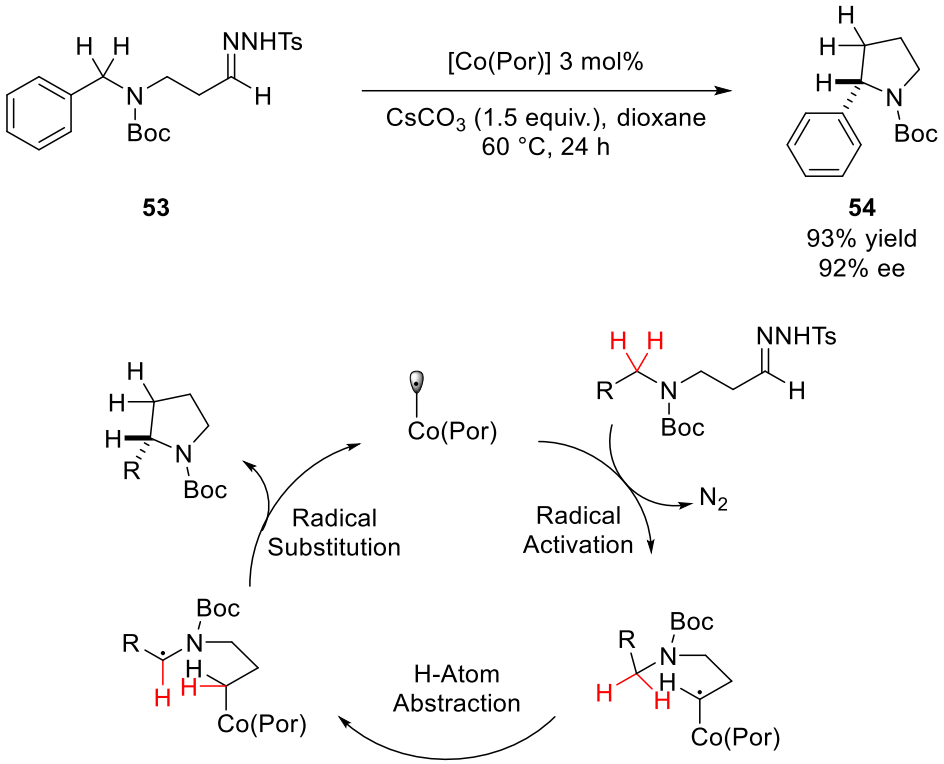
formation of the dimer was crucial to this enantioselectivity, due to the increased steric hindrance during the cycloaddition step.



Scheme 14. Nickel-catalysed enantioselective reductive cyclization of N-alkynones

One other powerful method for constructing ring systems, and one that has garnered much attention in recent years, is a radical cyclisation. Research performed by Zhang demonstrated a newly emerging metalloradical approach to synthesising 5 membered ring systems.[47] The approach differs from a traditional radical cyclisation which proceeds through radical addition followed by H-atom abstraction to give the desired compound. Instead, metalloradical reactions proceed through a different process where a metalloradical firsts abstracts a H-

atom and then undergoes radical substitution to produce the desired compound (Scheme 15). The use of a chiral porphyrin based cobalt complex and suitably bulky R groups on the diazo precursor **53** (aryl, heteroaromatic and cyclohexyl were reported) allows for the production of 2-substituted pyrrolidines **54** with most examples obtaining enantiomeric excesses of >85%. Replacing the *N*-Boc with oxygen, sulphur or carbon enabled synthesis of related 5-membered cycles and demonstrated good yields and enantioselectivity under the reaction conditions. One exception was the formation of a benzyl substituted pyrrolidine which had significantly lower enantioselectivity than other substituents. It is also noted that, besides cyclohexyl, no aliphatic substituents were reported.



Scheme 15. Metalloradical cyclisation for the synthesis of 2-substituted pyrrolidines

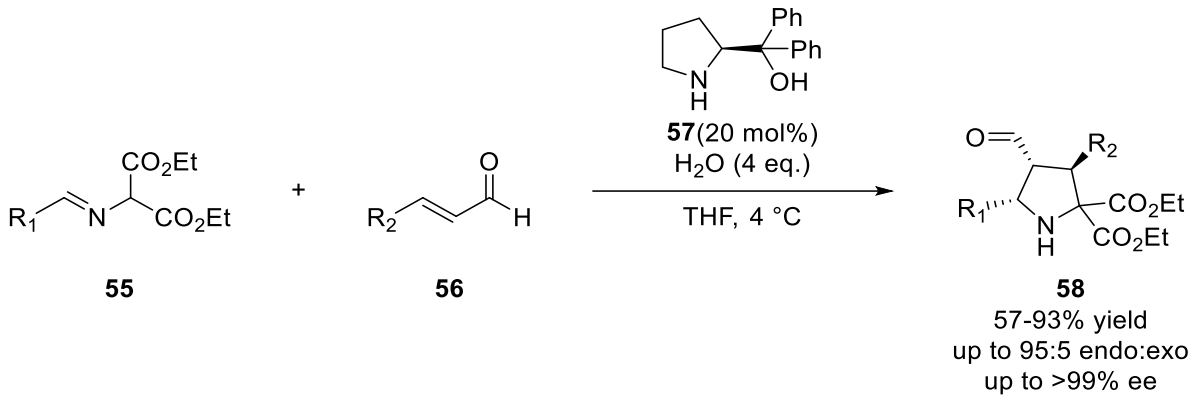
Transition metal catalysed reactions have a clear value in the asymmetric synthesis of pyrrolidines, allowing for fine tuning of a reaction as well as effecting a large variety of transformations. However, in recent years there has been a shift towards a newly growing area; organocatalysis.

1.6. Asymmetric organocatalysis

Metal free acid catalysis has become an area of interest over the past years and offers a few advantages over metal catalysed reaction.[48] Some of the problems that come with the use of transition metals, such as high price, toxicity, pollution, etc. can be overcome by using organocatalysts.[49] These catalysts can also demonstrate less sensitivity to moisture and air often exhibited in transition metal catalysis. The area of asymmetric organocatalysis has been researched as far back as the 1970s,[16] but has been investigated to a much greater degree in recent years as an attractive and green method of synthesis.[50,51] Pyrrolidines, such as proline, have been used effectively as organocatalysts themselves, but methodologies have been developed to synthesise pyrrolidines as scaffolds for natural products and drug candidates.[52]

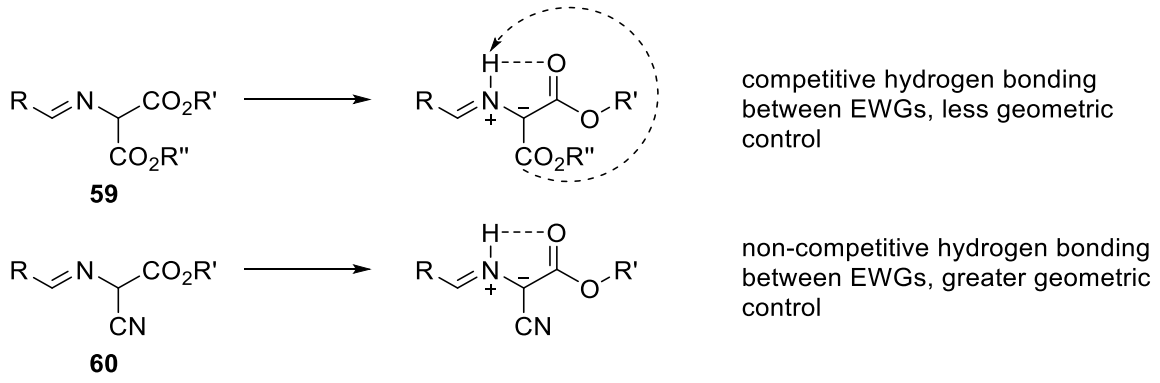
1.6.1. Intermolecular cyclisation

As in the case of transition metal catalysed reactions, organocatalysed reactions can occur both inter- and intramolecularly. While the transition metal catalysed cycloadditions of azomethine ylides have already been explored in the previous section, organocatalysts have also been shown to be efficient in this type of reaction. Research by Vicario demonstrated the first use of a proline derived catalyst **57** in the cycloaddition of azomethine ylides to enals **56** through an iminium intermediate (Scheme 16).[53] The presence of the diethyl esters on the iminoester **55** aids in the formation and stabilisation of the azomethine ylide *in situ*. Iminium formation with prolinol catalyst **57** and enal **56** both lowers the LUMO energy of the dipolarophile and promotes selectivity through attack of the less hindered *Re* face. The methodology was applied to a range of aryl iminoesters and both alkyl and aryl enals, with most examples achieving high yields and enantioselectivity with the endo product favoured in all cases.



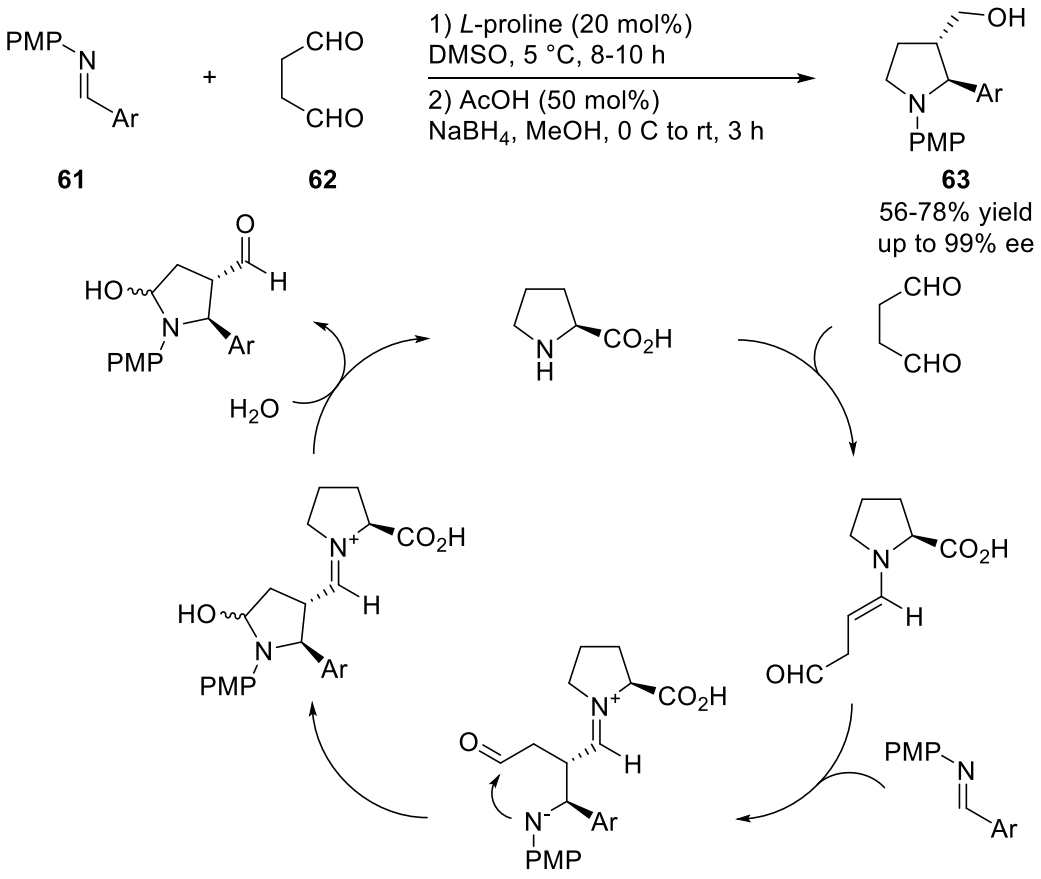
Scheme 16. Asymmetric organocatalysed cycloaddition of azomethine ylides to enals

A later report by Vicario showed that greater diastereoselectivity could be achieved by replacing one of the ethyl esters with a nitrile (Scheme 17).[54] In the 1,3-dipolar addition of azomethine ylides, the geometry of the starting ylide is exclusively what determines the relative stereochemistry of any 2,5-susbitution on the pyrrolidine product. However, there is also a necessity for (mulitiple) electron withdrawing groups on the iminoester for the α-hydrogen to be acidic enough to form the ylide *in situ*. By having two esters on the iminoester **59**, the acidity of the α-hydrogen is increased but there is also competitive hydrogen bonding between the two carbonyl groups. Replacing one ester with a nitrile (**60**) removes the competitive hydrogen bonding as the nitrile does not take part in H-bonding but maintains the acidity of the α-hydrogen. This effectively locks the geometry of the ylide as depicted in Scheme 17 through the H-bonding with the single ester unit. As stated, the ylide geometry is essential for control over the 2,5-relative stereochemistry and the use of the nitrile as an electron withdrawing group lead to greater control of the diastereoselectivity of the dipolar addition.



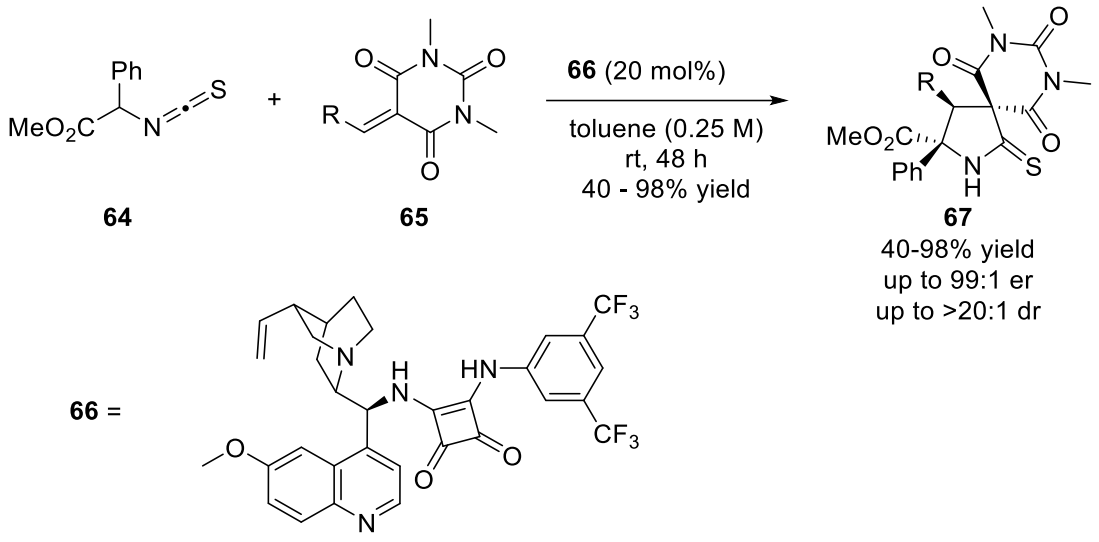
Scheme 17. Electron withdrawing group effect on azomethine geometry

Organocatalysed intermolecular reactions are not just limited to azomethine cycloadditions. An alternative strategy involving a Mannich cyclisation reaction was investigated by Kumar *et al* to synthesise 2,3-disubstituted pyrrolidines **63** (Scheme 18).[55] The authors report the reaction as a formal [3+2] cycloaddition reaction catalysed by L-proline with succinaldehyde **62** as a novel 1,3-carbon dipole. The proposed mechanism is shown in Scheme 18 where L-proline formed an enamine with the succinaldehyde, followed by a Mannich reaction with the aryl imine **61**. Cyclisation onto the second aldehyde formed the pyrrolidine, and removal of the proline with water gave the hemiaminal product. *In situ* reduction of the hemiaminal with sodium borohydride gave the 2,3-disubstituted pyrrolidine **63** in high yields and very high enantioselectivity for most aryl imines tested. The methodology was successful in the reaction of imines derived from electron poor aryl aldehydes, but imines derived from electron rich aryl aldehydes (such as *p*-anisaldehyde) or alkyl aldehydes failed to produce any desired product.



Scheme 18. Proline catalysed Mannich reaction

Recently a strategy for the asymmetric construction of pyrrolidines from an isothiocyanates **64** with barbiturates **65** was developed by Albrecht (Scheme 19).[56] When treated with a chiral organocatalyst **66** featuring a squaramide core and cinchona alkaloid moiety, heterocyclic ring systems could be synthesised with high enantioselectivity. This strategy sets up two quaternary centres (one of which is chiral) and a separate stereogenic centre in a highly functionalised spirocyclic pyrrolidine scaffold **67**. Certain substituents on the barbiturate **65** led to reduced stereoselectivity or afforded lower yields with notable examples; 4-$NO_2C_6H_4$ giving a yield of 52% and er of 82.5:17.5 and *i*-Pr giving a yield of 40%.

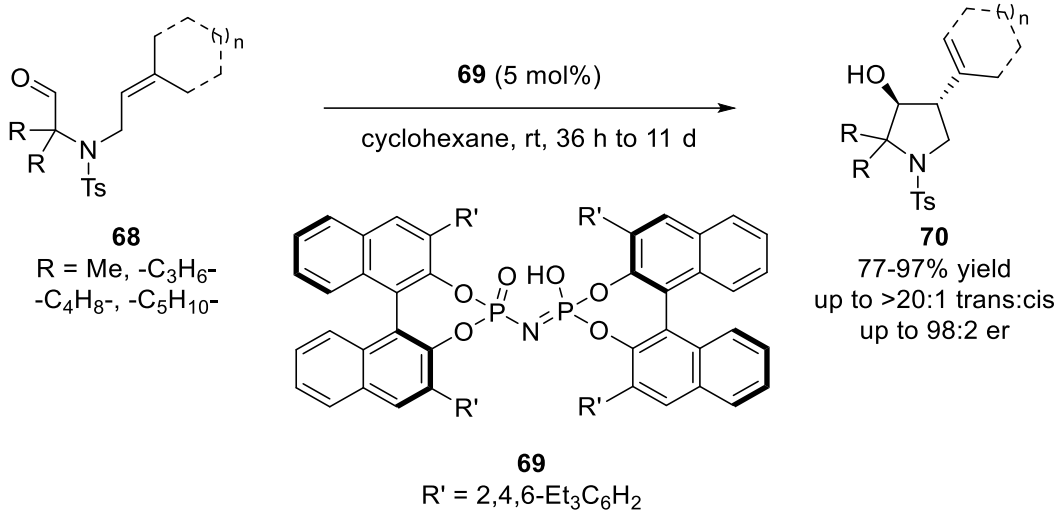


Scheme 19. Isothiocyanate strategy for the synthesis of spirocyclic pyrrolidines.

1.6.2. Intramolecular cyclisation

An organocatalysed intramolecular cyclisation offers some benefits to intermolecular cyclisations, in the same way they do when catalysed by transition metals. Greater selectivity (endo vs exo selectivity can be easier to control) and potential increased reaction rate are some of the advantages that an intramolecular reaction can have. Coupled with the "greener" credentials of organocatalyst, this are of research has been of interest in recent years for constructing heterocyclic rings. As with intermolecular reactions, there a number of methods available, but this section will focus on those reaction where asymmetry is introduced during cyclisation.

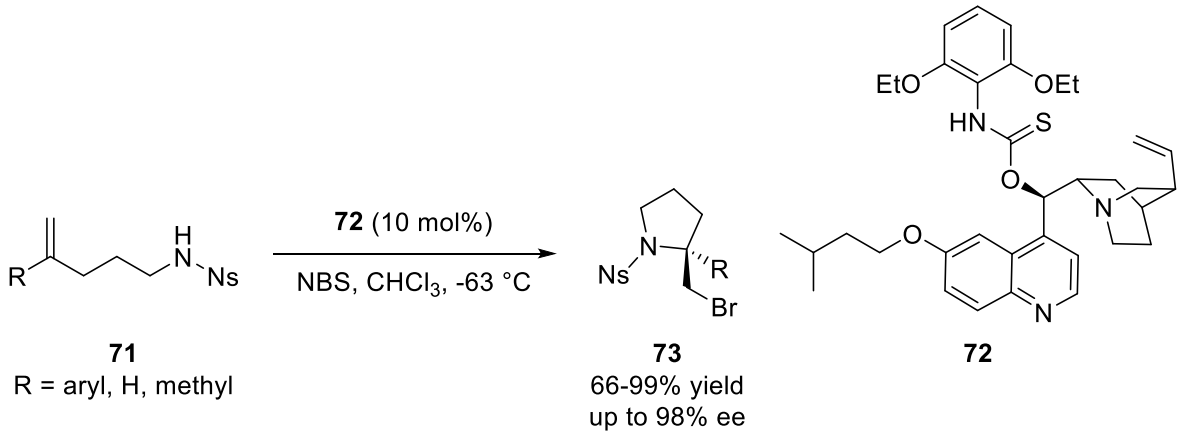
A well-studied reaction in organic chemistry that can be used for the construction of ring systems is the ene reaction. Intermolecular ene reactions are challenging, whereas intramolecular ene reactions have entropic, regio- and stereoselective advantages.[57] A highly enantioselective carbonyl-ene reaction was developed by List for the synthesis of spirocyclic pyrrolidines **70** (Scheme 20).[58] Asymmetric carbonyl-ene reactions had previously been reported with transition metal catalysts, but this research demonstrated the first organocatalysed carbonyl-ene reaction. One of the findings the research group reported was the necessity for the dimeric BINOL based catalyst **69** in order to achieve high enantioselectivity. When a monomeric BINOL based phosphoric or sulfuric acid catalyst was used, high conversions and regioselectivity were achieved but with poor enantioselectivity. DFT calculations suggested that the imido-diphosphate was necessary as both phosphate groups take part in the transition state of the reaction.



Scheme 20. Asymmetric carbonyl-ene cyclisation

Another useful method for synthesising ring systems is through halocyclization. Catalytic enantioselective variations of this reaction have been applied to *O*-heterocycle synthesis since 2003, but extension to *N*-heterocycles was first reported by Yeung in 2011.[59] The application of a quinuclidine thiocarbamate catalyst **72** to *N*-sulfonyl alkenes **71** in the presence of an excess of NBS led to the formation of bromo-pyrrolidines **73** in high yields and very high enantioselectivity (Scheme 21). The structure of the catalyst was key to effecting the cyclisation reaction. In the proposed mechanism the sulfonamide of the starting material coordinated to the nitrogen of the quinuclidine, while the NBS coordinated to the

thiocarbamate. This led to a controlled geometry of the transition state and selective site for the bromination to occur.



Scheme 21. Asymmetric cyclobromination of sulfonyl amines.

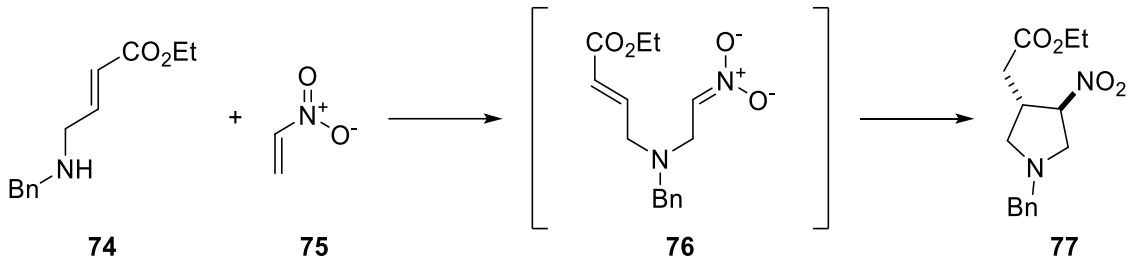
While these reactions offer a flavour of asymmetric pyrrolidine synthesis, one method that has been widely investigated and was of interest to our research group is that of the intramolecular aza-Michael reaction

1.7. Asymmetric intramolecular aza-Michael reactions

The addition of nitrogen containing nucleophiles to Michael acceptors has been widely explored and has enabled the synthesis of pyrrolidines and piperidines in high stereoselectivity.[60,61] The intermolecular aza-Michael reaction has been used to construct chiral amines that can then be used to form pyrrolidines, but a more direct approach is through the intramolecular aza-Michael, as this can introduce chirality in the same step as heterocycle formation. This stereocontrol can come from the substrate itself (*i.e.* from a chiral auxiliary) or from a chiral catalyst and both methods will be examined.

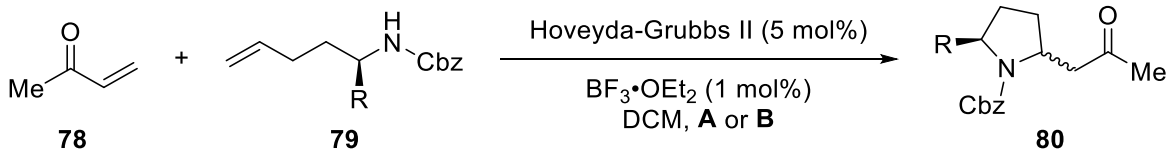
The Michael reaction is an example of a conjugate addition, and an early report by Spalluto shows a tandem intermolecular Michael/intramolecular conjugate addition reaction for the synthesis of pyrrolidines.[62] While this could be argued as not a true intramolecular aza-Michael, it does demonstrate the simplicity with which ring systems can be constructed using these methodologies. Using Michael donor/acceptors **74** and nitroethylene **75** as a Michael acceptor led to the formation of an nitronate intermediate **76** followed by cyclisation to

produce the substituted pyrrolidines **77** (Scheme 22). The *trans* relationship of the nitro- and carbonyl-substituents was confirmed by the reduction of the nitro group to the free amine and subsequent attempts at lactamisation. These attempts were not met with success, resulting in the assignment of the *trans* stereochemistry, as the *cis* isomer would be expected to cyclise. Although this route is not enantioselective, it is diastereoselective with no reports of the *cis* isomer being isolated.



Scheme 22. Intermolecular conjugate addition for the synthesis of pyrrolidines

Although diastereoselective reactions are useful in organic synthesis, greater stereocontrol in a reaction can be desirable. One such method was developed by Fustero where stereoselectivity could be switched depending on the conditions used.[63] Cbz protected amines **79** were synthesised as a single enantiomer through the use of a chiral *tert*-butanesulfinamide auxiliary. A cross metathesis reaction with methyl vinyl ketone **78** was performed in the presence of $BF_3.OEt_2$ as a tandem metathesis/cyclisation reaction to give the pyrrolidine **80** (Scheme 23). One of the most interesting aspects to this reaction is the effect of time and heating on the stereochemistry of the pyrrolidine. When the reaction was heated to a lower temperature of 45 °C over 4 days, the 2,5-*trans* product was isolated, in good to high yields for the R groups tested. However, when the reaction was heated by a microwave to 100 C for 20 mins, high yields were still achieved, but the selectivity was switched in favour of the 2,5-*cis* isomer. While the authors do not comment on the selectivity, it could be conceived that the *trans* isomer is the kinetic product, while the *cis*-isomer is the thermodynamic product and was only accessible at the very high temperatures of 100 °C. Reactions were also performed on achiral Cbz amines which led to racemic pyrrolidine products in generally high yields.



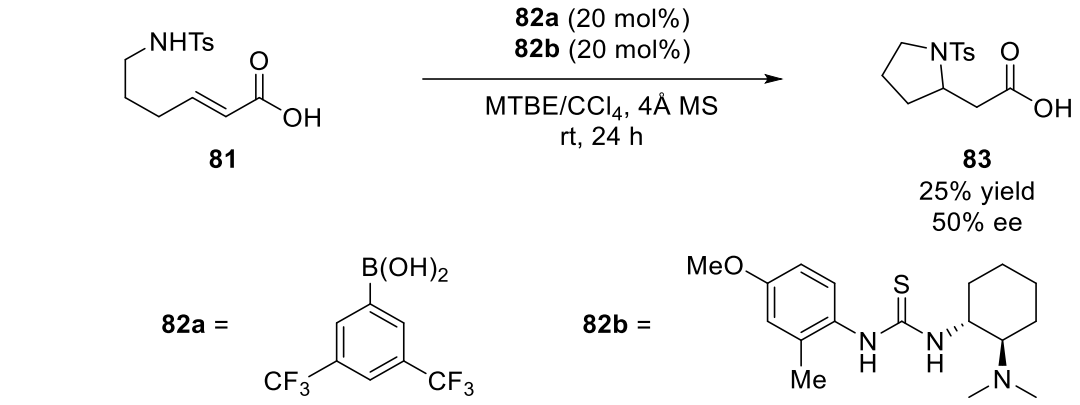
A = 45 °C, 4 days
B = 100 °C, μwave, 20 mins

R	**A** yield (*trans/cis*)	**B** yield (*trans/cis*)
i-Pr	97 (3/1)	81 (1/4)
Ph	98 (6/1)	86 (1/2)
4-MeO-C_6H_4	78 (4/1)	97 (1/2)
CF_3	76 (5/1)	97 (1/3)

Scheme 23. Tandem metathesis and cyclisation reaction of substituted Cbz amines

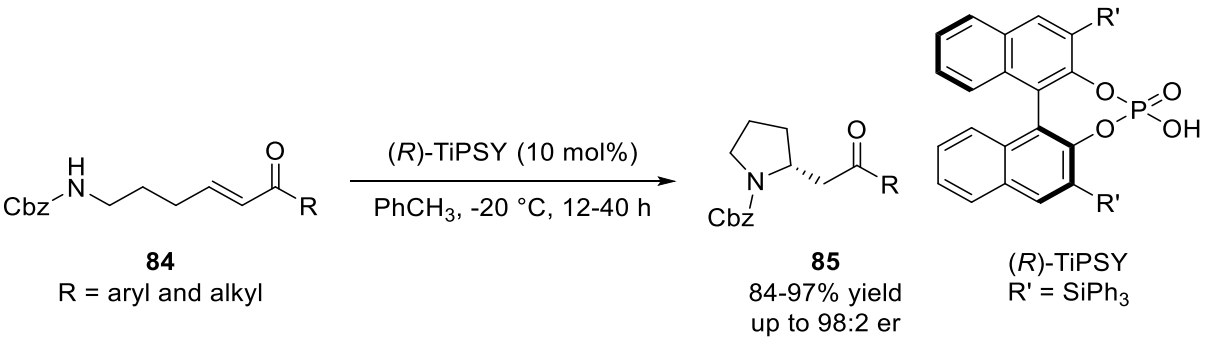
Building in the desired stereochemistry through the use of a chiral auxiliary is a successful method for producing asymmetric pyrrolidines. However, if the opposite enantiomer is required, this could potentially mean a protracted synthetic route that needs to be tailored to each specific product. Therefore, introducing the stereochemistry at a later stage can be advantageous and is most easily achieved with a chiral catalyst in the cyclisation step.

One catalytic method by Azuma *et. al.* utilized a dual system of an aryl boronic acid **82a** and a chiral aminothiourea catalyst **82b** for the intramolecular hetero-Michael reaction with α,β-unsaturated carboxylic acids **81** (Scheme 24).[64] The reaction was successful in the racemic synthesis of pyrrolidines when only the boronic acid was used, although only with sulfonamide protected amines, with no reaction observed for the Cbz protected amine. The oxy-Michael reaction worked well to give a variety of dihydrobenzofuran scaffolds which were obtained with high enantioselectivity when the chiral aminothiourea catalyst **82b** was introduced to the reaction. However, when testing the chiral catalyst, *N*-tosyl pyrrolidine **83** formation gave only moderate ee's (50%) and poor yields (25%). No other asymmetric aza-Michael reaction was reported, which shows the significant limitations of this methodology in the asymmetric synthesis of pyrrolidines.



Scheme 24. Dual aryl boronic acid and aminothiourea catalytic system for heterocycle synthesis.

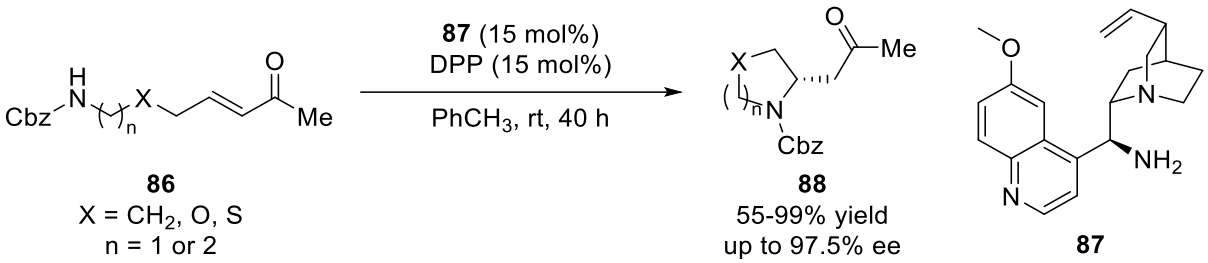
The poor results from this aza-Michael reaction may be due to both the difference in nucleophilicity of the sulfonamide vs. the hydroxyl group, as well as the electrophilicity of the Michael acceptor. Fustero had already demonstrated the capability of methyl vinyl ketone as a Michael acceptor in a non-asymmetric aza-Michael reaction.[63] In a report by Yu, the enhanced reactivity of the enone was explored in the chiral Bronsted acid catalysed cyclisation of enone carbamates.[65] A range of aryl and alkyl enones **84** were synthesised and subjected to the (*R*)-TiPSY catalyst in toluene at -20 °C (Scheme 25). The cyclised pyrrolidines **85** were isolated in high yields and with good enantioselectivity, although some reactions required up to 40 hours to reach completion.



Scheme 25. Enantioselective cyclisation of enone carbamates

A related paper by Yang demonstrated another asymmetric aza-Michael reaction onto enones, but utilising a different catalytic system.[66] The cinchona alkaloid 9-amino-9-deoxy-epi-quinine **87** was used alongside diphenyl hydrogen phosphate (DPP) as a co-catalyst to effect the aza-Michael cyclisation (Scheme 26). In this study only the methyl enone was used as the Michael acceptor, but the cyclisation was extended to synthesise both pyrrolidines and

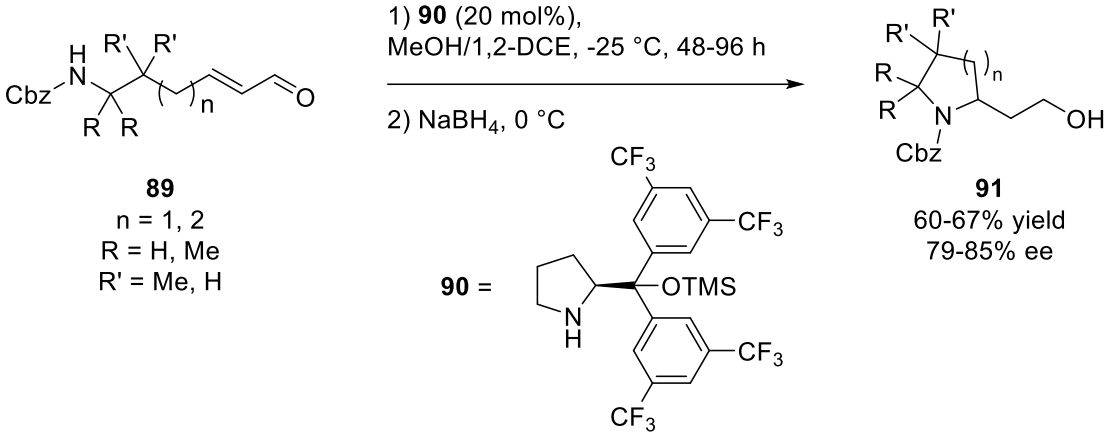
piperidines, as well as the related heterocycles; oxazolidine, thiazolidine, morpholine, and thiomorpholine, all with good enantioselectivity **88**. The advantage of the cocatalyst system over that of (*R*)-TiPSY, is that these reactions were run at room temperature, so cryogenic temperatures did not need to be maintained for extended reaction times.



Scheme 26. Cyclisation of enone carbamates with co-catalyst system

While these systems demonstrate the application of enones in asymmetric aza-Michael reactions, there are some limitations to the procedures. The cyclisations reported both require extended reaction times and did not demonstrate any substitution around the ring. The use of enones also limits the synthetic applications after cyclisation. Any functionality needed in a side chain would necessitate incorporation at the beginning of a synthesis within the enone. Other carbonyl derivatives such as esters and aldehydes offer handles that can be more easily functionalised at a later stage. The use of other Michael acceptors has been explored by other research groups to enable this.

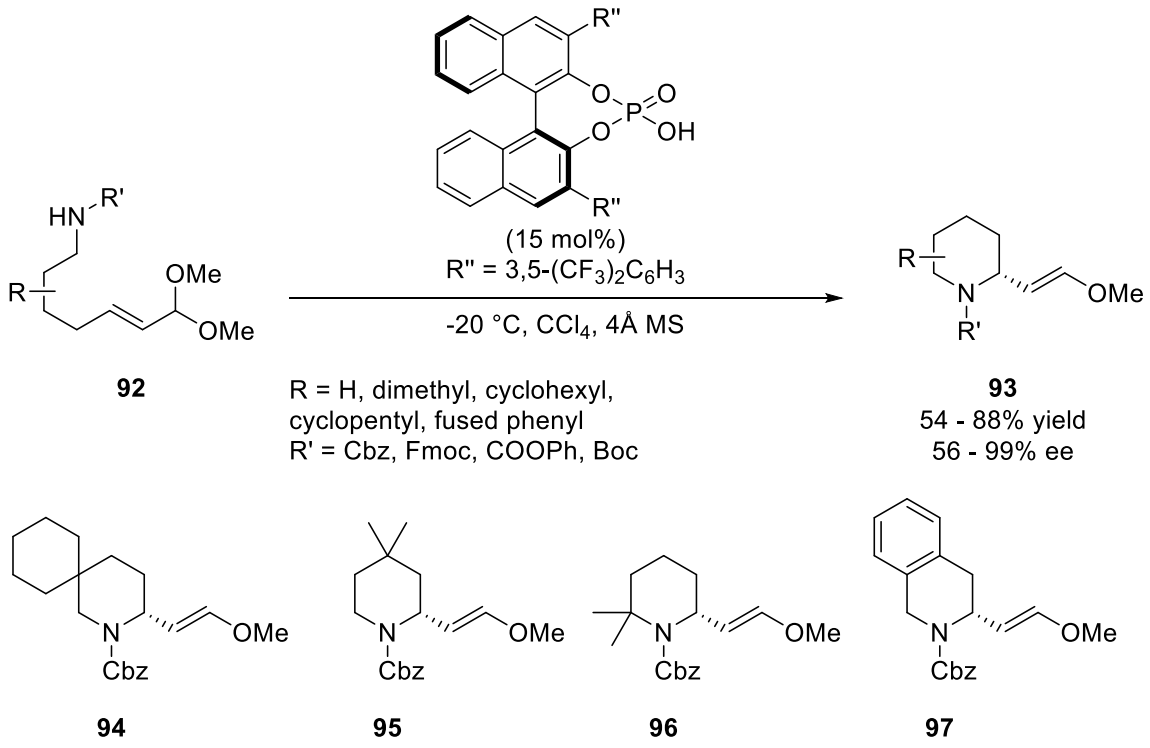
An alternative procedure to synthesise pyrrolidines (and piperidines) through a Michael reaction was reported by Carter using α,β-unsaturated aldehydes **89** (Scheme 27).[67] In the proposed mechanism the proline catalyst **90** forms a chiral α,β-unsaturated iminium species to activate the Michael acceptor and utilises sterically demanding groups to force attack from one side of the molecule. The method was applied to the synthesis of *gem*-dimethyl pyrrolidines and piperidines **91** with most substrates showing good yields and ee's. The exceptions to this was of the 6,6'-dimethylpiperidine which gave poor conversion and the 2,2'-dimethylpyrrolidine which showed a reduced ee of 79%. Also, in order to prevent racemisation or decomposition of the cyclised product, the aldehyde group was reduced to the alcohol with sodium borohydride after cyclisation. While this loses the carbonyl functionality, it does still give a useful handle for further synthesis.



Scheme 27. Asymmetric intramolecular hetero-Michael reaction

While aldehydes have great synthetic utility and ability to undergo a large variety of transformations, the sensitivity of aldehydes towards decomposition and potential for scrambling of stereocentres can limit their application. Reduction to an alcohol, as demonstrated by Carter, followed by an oxidation back to the aldehyde can help with long term stability and storage of a compound but this is not an efficient method for synthesis. However, there have been methods developed that allow for retaining carbonyl functionality without the need for an extra step in the synthesis.

In a report by Nagorny, the sensitivity of aldehydes was overcome through the use of a novel Michael acceptor, which enabled the asymmetric synthesis of spirocyclic piperidines.[68] The reaction utilised an unsaturated dimethyl acetal **92**, which *in situ* formed an α,β-unsaturated oxocarbenium ion with the chiral catalyst via loss of methanol. This makes the unsaturated acetal analogous to a protected enal, showing good reactivity towards Michael addition for the formation of the piperidine ring. The use of the acetal group presumably helps to reduce any racemic background reaction that may occur when using the aldehyde equivalent as well as preventing aerobic auto-oxidation which might also be anticipated of unsaturated aldehydes. The enol ether produced in the reaction can be seen as a masked or protected aldehyde to prevent against such decomposition. The methodology was applied to the synthesis of several substituted piperidines **93**, specifically *gem*-dimethyl, fused phenyl, and spiro-cyclopentyl and –cyclohexyl examples (Scheme 28).



Scheme 28. Asymmetric synthesis of spirocyclic piperidines and selected examples of synthesised products

A common trend among the reactions was that extending the reaction time would lead to an increase in selectivity, at the expense of yield. The authors postulated that the presence of small amounts of MeOH that were not adsorbed by the molecular sieves were reacting with the product **93** to form a new saturated acetal product. It is also worth noting that these reactions were performed at -20 °C in CCl_4 which poses both health and procedural concern, due to the toxicity[69] of CCl_4 and the feasibility of running reactions at cryogenic temperatures for long periods of time. The use of CCl_4 would also make this reaction less desirable for use in industrial settings due to the associated health hazards.

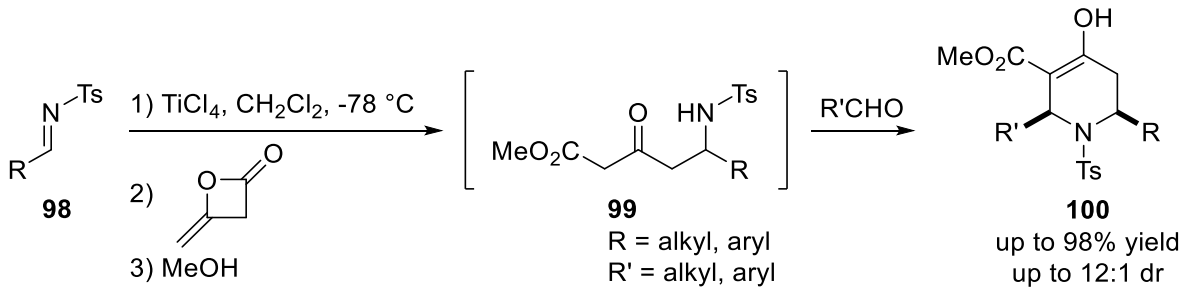
One of the stipulations for improving the enantiomeric excess of the reaction reported by Nagorny, was the reduction of temperatures to allow for greater selectivity, as when performed at room temperature a significant decrease in the enantioselectivity was observed from 71% to 57% ee. This is common in asymmetric reactions, as generally low temperatures lead to an increase in enantioselectivity. However, lower temperatures will also decrease the rate of reaction, so conditions for increasing the rate, while maintaining the selectivity are essential when creating new methodologies. The use of more reactive Michael acceptors, such as enals and enones, can increase reaction rate but can also lead to an increase in

background racemic reactions. If less reactive unsaturated Michael acceptors are needed, then alternatives must be considered. Nagorny's use of unsaturated acetals is one option, although they are not as easy to access as aldehydes and there are limitations to the reaction as previously stated.

2. Asymmetric synthesis of spirocyclic pyrrolidines

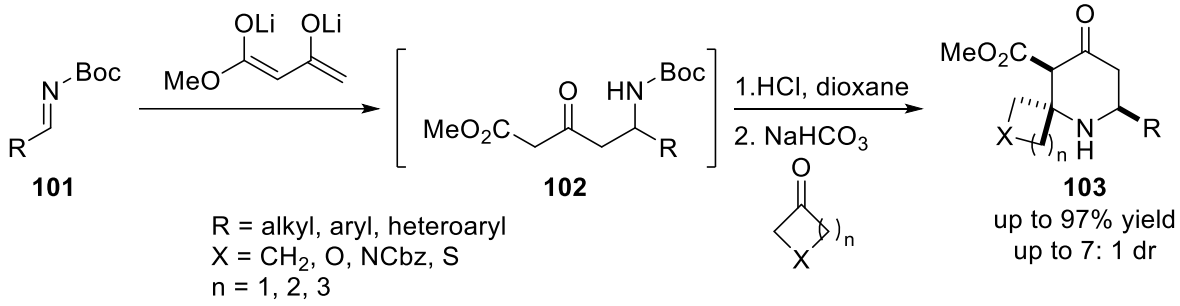
The stereoselective synthesis of heterocycles has been an integral research area within the Clarke group, and has supported efforts towards the total synthesis of natural products.[70–74] Due to the prevalence of heterocyclic rings, especially chiral ring systems, in natural products, there has been substantial interest in the group to devise new strategies to facilitate the construction of these heterocycles.

Expanding on methodologies for the synthesis of tetrahydropyran-4-ones,[75] the one-pot synthesis of functionalised piperidin-4-ones **100** was achieved through ring opening of diketene in the presence of tosyl-aldimines **98** to give a β-amino-ketone intermediate **99.** This intermediate was then intercepted with an aldehyde to give the piperidin-4-one **100** (Scheme 29).[76]



Scheme 29. Multicomponent Maitland-Japp reaction for the synthesis of highly substituted piperidin-4-ones

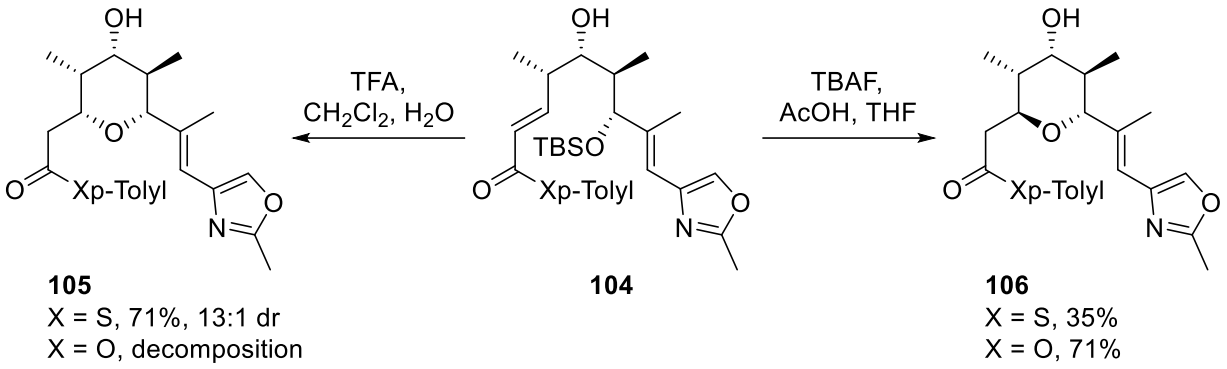
This was then later developed into a synthesis of spirocyclic piperidines by substituting the aldehyde for a cyclic ketone to introduce the spirocyclic functionality (Scheme 30).[77] The use of ketones with *N*-tosyl aldimines inhibited cyclisation of the piperidine under the conditions shown in Scheme 29. However, it was found that the reaction of *N*-Boc imines **101** generated *in situ* with the Weiler dianion allowed for the formation of the Boc protected β-amino-ketone intermediate **102**. The use of Boc instead of tosyl as the nitrogen protecting group allowed for reactivity with ketones and facile synthesis of the functionalised piperidines **103** (Scheme 30).



Scheme 30. Modification of aza-Maitland-Japp reaction for the synthesis of spirocyclic piperidines

Not only does the methodology allow for the formation of highly functionalised piperidines, but the introduction of a spirocyclic motif increases the amount of three-dimensionality, or sp^3 character, of the molecules. This has been of interest in the field of fragment-based drug discovery as it populates an under explored area of chemical space with accessible molecules. By introducing more three-dimensionality into a molecule, drug discovery can identify potential compounds that move away from the more common sp and sp^2 rich systems seen in the majority of "lead-like" molecules.[77]

While this approach allows for novel, highly functionalised fragments to be synthesised with good diastereoselectivity, there are limitations when it comes to synthesising other stereoisomers or single enantiomers. One area of research that has been investigated by the Clarke group is the use of α,β-unsaturated thioesters in intramolecular Michael reactions. The first use of thioesters within the group was employed for the stereodivergent synthesis of 2,6-functionalised tetrahydropyrans as a route towards the C20-C32 core of the phorboxazoles.[71] In the cyclisation of precursor **104** with buffered TBAF conditions, both the oxo- and thioester led to the formation of the 2,6-*trans*-tetrahydropyran **106**. When acidic conditions (CSA or TFA) were used in an attempt to form the 2,6-*cis*-tetrahydropyran **105**, the oxoester showed either decomposition or no cyclisation, while the thioester led to the production of the *cis* product with high selectivity over the *trans* with a 13:1 dr (Scheme 31).



Scheme 31. Stereodivergent synthesis of the C20-C32 tetrahydropyran core of phorboxazoles and the C22 epimer

The utility of the thioester moiety and mechanism of reaction was then further explored through experimental and computational studies.[74] It was found that the 4-hydroxyl group was essential for the stereodivergence seen in this reaction as, under the buffered TBAF conditions, the hydroxyl could participate in hydrogen bonding with the cyclising alkoxide and enable a boat-like transition state **107**, yielding the 2,6-*trans*-tetrahydropyran (Figure 3).

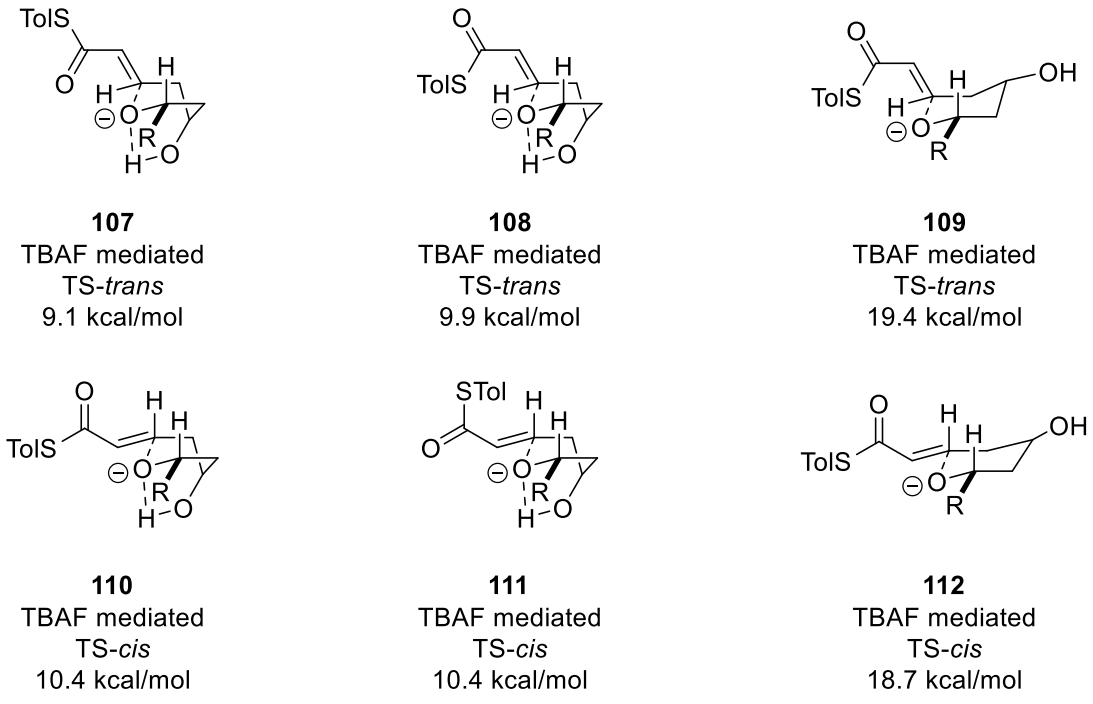
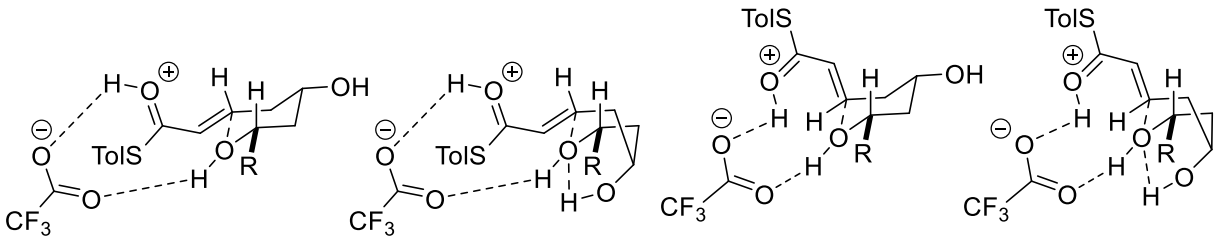


Figure 3. Computational transition states for TBAF mediated cyclisation

Investigation of the acid mediated cyclisation, where decomposition of the oxo-ester was observed, showed that the lowest energy transition state was a chair **113**, where the 4-hydroxyl group did not take part in the cyclisation (Figure 4). The role of the trifluoroacetic

acid was that of a proton shuttle. Protonation of the thioester group increased the electrophilicity of the Michael acceptor, whilst simultaneous deprotonation of the alcohol raised its nucleophilicity. Interestingly, the transition state energy for the oxoester was 7.6 kcal mol^{-1} higher than that of the thioester, making the oxoester rate of cyclisation much slower. This would then allow for competing decomposition pathways to occur, hence the selection of the thioester over the oxoester in the acidic mediated cyclisation.



113
TFA mediated
TS-*cis*-chair
19.3 kcal/mol

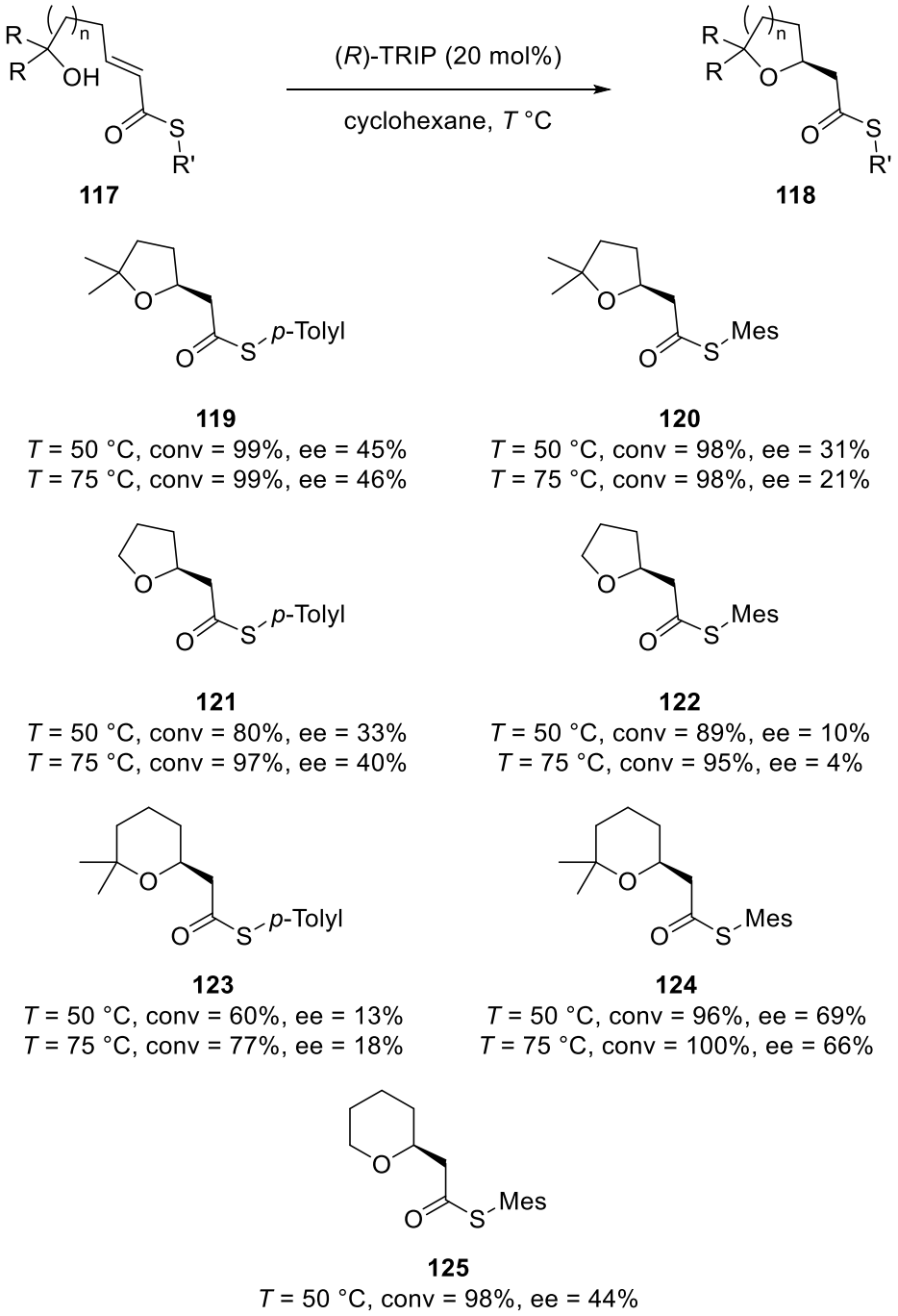
114
TFA mediated
TS-*cis*-boat
25.9 kcal/mol

115
TFA mediated
TS-*trans*-chair
21.7 kcal/mol

116
TFA mediated
TS-*trans*-chair
26.3 kcal/mol

Figure 4. Computational transition states for TFA mediated cyclisation

With this knowledge of the thioester reactivity, the group then examined the possibility of using chiral phosphoric acids (CPAs) as a means of inducing enantioselectivity during the Michael reaction.[78] It was hypothesised that the CPA could replace the trifluoroacetic acid used to catalyse the Michael addition, through a similar proton shuttle mechanism. The cyclisation of 2,2-dimethyl and unsubstituted alcohols, **117** using (*R*)-TRIP as the chiral catalyst, was examined for the synthesis of both THFs and THPs **118** (Scheme 32).[78]



Scheme 32. Asymmetric Michael reaction for the synthesis of THFs and THPs

When cyclised using (*R*)-TRIP in cyclohexane, it was found that both the alcohol substitution and substitution of the thioester played important roles in both the conversion and the selectivity (Scheme 32). For the 2,2-dimethyl THF with *p*-tolyl as the thioester substituent (**119**), full consumption of starting material was observed at both 50 °C and 75 °C with ees of the THF products being 45% and 46% respectively. However, when a mesityl thioester was used (**120**), the ee dropped to 31% for 50 °C and 21% for 75 °C. It was also observed, that

when unsubstituted alcohols were cyclised, both conversions and ees decreased (**121** and **122**). In the case of the 2,2-dimethyl THP synthesis, the cyclisation of the *p*-tolyl thioester (**123**) at 50 °C led to a lower conversion of 60% and an ee of only 13%. For the same reaction with the mesityl thioester (**124**), the conversion reached 96% with an ee of 69%, the highest selectivity achieved in this methodology. When the unsubstituted mesityl THP was synthesised (**125**), the conversion remained high at 98% but ee dropped to 44%.

From this work, we can see that substitution around the alcohol tends to increase the selectivity of the reaction for both THFs and THPs. Modulating the thioester functionality can also allow for tuning of the reaction depending on the intended ring size. With this knowledge and previous reports on asymmetric aza-Michael reactions, we believed that thioesters could offer a middle ground of reactivity between aldehydes and oxoesters. Consequently, we hypothesised that the use of a CPA in the formation of nitrogen heterocycles through aza-Michael addition onto a thioester may be used effectively in the asymmetric synthesis of pyrrolidines.

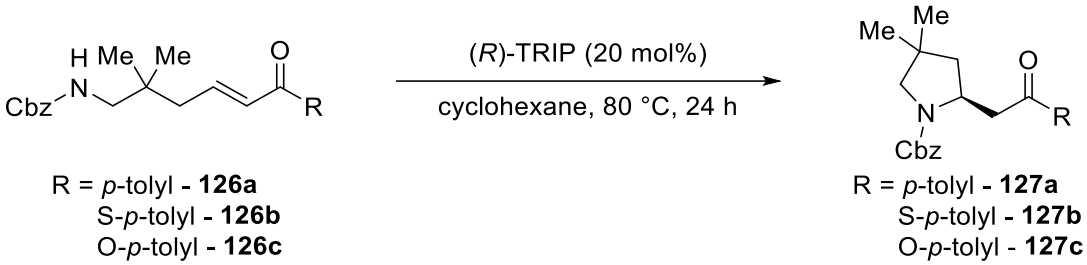
2.1. Comparison of the Michael acceptor reactivity

In order to test the asymmetric aza-Michael reaction and confirm its viability for the asymmetric synthesis of functionalised pyrrolidines, a series of questions needed to be answered:

1. Do thioesters offer advantages over aldehydes/ketones or esters in the intramolecular aza-Michael reaction to form pyrrolidines?
2. What substrate scope can be used to test the limits of the method and what functionality can be introduced into the products?
3. Does varying the reaction conditions, such as catalyst, solvent and temperature, affect the yield and selectivity?

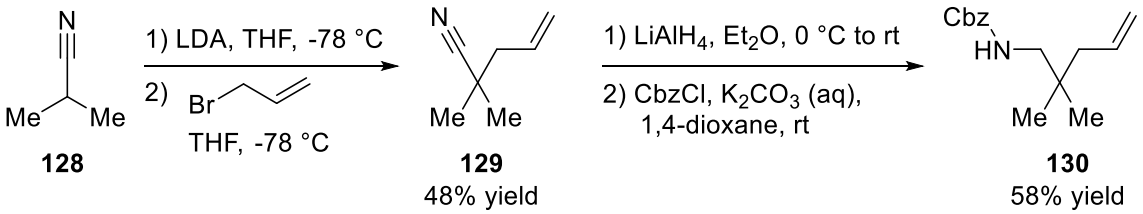
The first step to answering these questions was to synthesise precursors that would allow for testing the thioester moiety against other Michael acceptors. To do this, the 3,3-dimethyl precursors **126** were selected as we anticipated that they would be easily accessible and should offer enhanced rate of cyclisation due to the Thorpe-Ingold effect (Scheme 33).[79,80]

The synthesis of the *p*-tolyl thioester was a well-practiced procedure within the group so was selected for the initial tests and, to allow for a more direct comparison of reactivity, the *p*-tolyl ketone and *p*-tolyl oxoester were also selected for screening.



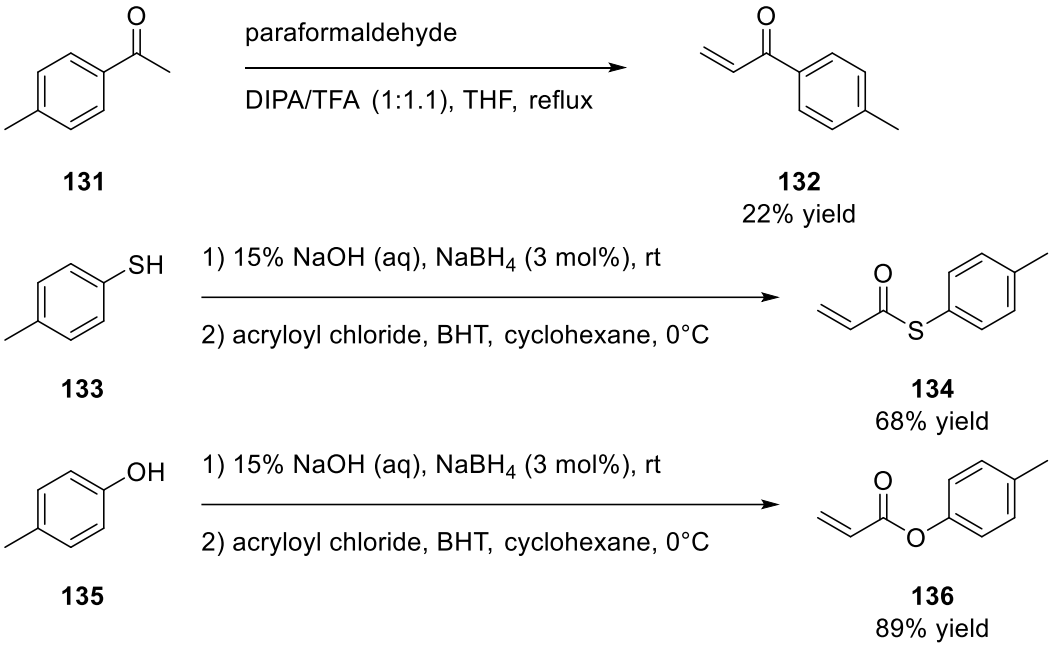
Scheme 33. Proposed precursors for the testing of Michael acceptors

The synthesis of the 3,3-dimethyl substituted compounds was adapted from a literature procedure,[81] where isobutyronitrile **128** was deprotonated with LDA and alkylated with allyl bromide to form the quaternary nitrile **129** in 48% yield. The nitrile was then reduced using lithium aluminium hydride to give the free amine, which was followed by protection with benzyl chloroformate, to afford the Cbz protected amine **130** in 58% yield (Scheme 34).



Scheme 34. Synthesis of 3,3-dimethyl-substituted precursor

The next precursor compounds required were the acrylates which would act as intramolecular Michael acceptors when coupled to the Cbz amine. To this end, enone **132** and thioacrylate **134** were synthesised using literature procedures in 22% and 68% yield respectively.[82,83] While other methods exist for synthesising the acrylate **136,** the same method used for producing thioacrylate **134** was also fruitful in synthesising acrylate **136** in 89% yield (Scheme 35).

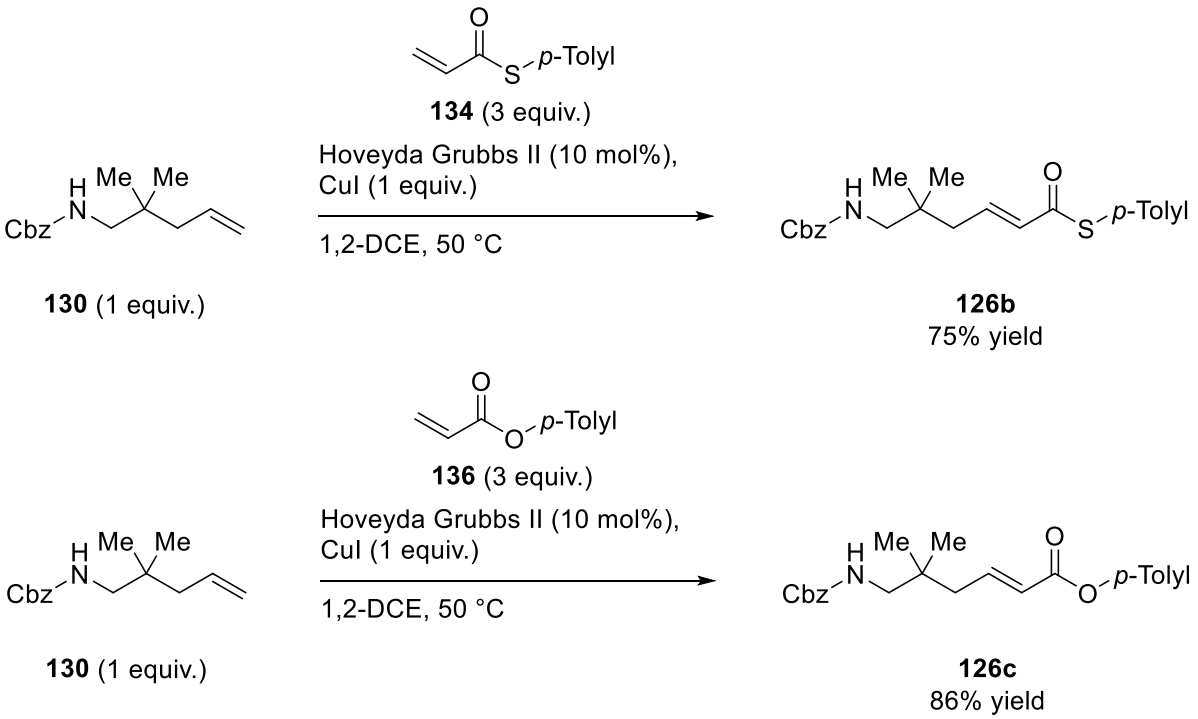


Scheme 35. Synthesis of acrylates

With the Cbz amines and acrylates in hand, the next step was to form the Michael acceptors needed for cyclisation through cross metathesis. Cross metathesis with the relevant thioacrylate has been performed by the group before, however acrylates pose several problems when used for metathesis reactions. A report by Grubbs shows that olefins can be categorized in a general model according to the levels of homodimerization observed and the reactivity of the homodimers when exposed to different metathesis catalysts.[84] Acrylates are categorised as a Type II olefin, which means they homodimerize slowly when subjected to the second-generation Grubbs catalyst. While homodimerization of the Cbz amine occurs rapidly, the homodimer itself is still a candidate for metathesis, as this can then undergo a further reaction with the slower reacting acrylate to form the desired product.

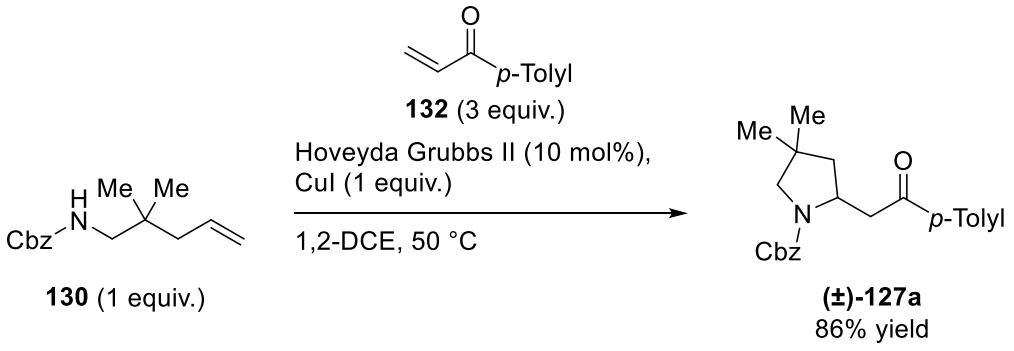
Previous work in the group found that when performing a metathesis with thioacrylates, 1 equivalent of the second-generation Hoveyda-Grubbs catalyst was required.[85] However, the use of 15 mol% copper iodide allowed for effective cross metathesis with 10 mol% of the catalyst. This was effect was originally reported by Lipshtuz showing that the inclusion of copper iodide or sodium iodide in conjunction with Grubbs catalysts, gave a rate enhancement when coupling acrylates with other olefins.[86] This is reported to be due to both the ability of copper (I) to scavenge the phosphine ligand, and the stabilisation effect of the iodide ion on the catalyst. In the case of the reaction of the Cbz amine **130** it was found that

the addition of 1 equivalent of copper iodide led to facile production of the α,β-unsaturated thioester product **126b** in 75% yield (Scheme 36). This procedure was then also applied to the acrylate **136** to yield the α,β-unsaturated ester **126c** in 86% yield.



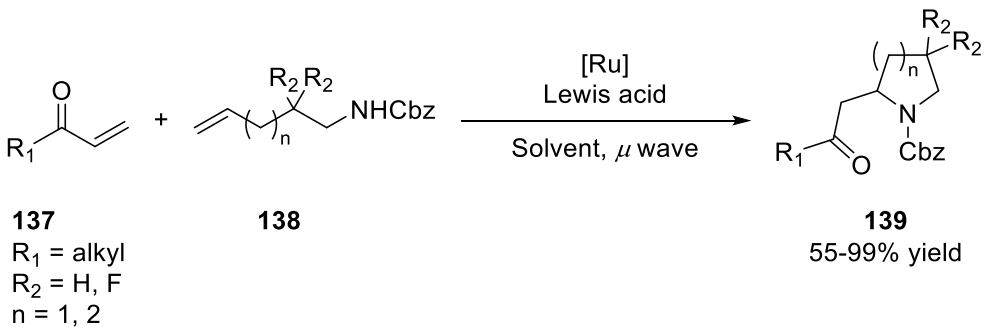
Scheme 36. Cross metathesis procedure for thioacrylates

When Cbz amine **130** was submitted to the metathesis conditions with enone **132**, the only compound isolated was the cyclised pyrrolidine **(±)-127a**, obtained in 88% yield. Though this was unexpected, it does support out initial hypothesis that ketones and aldehydes may be too reactive, and have a significant racemic background reactivity, and are therefore unsuitable as electrophiles in the asymmetric intramolecular aza-Michael reaction.



Scheme 37. Metathesis reaction of p-tolyl enone to form keto-pyrrolidine

A report by Fustero shows a similar metathesis reaction of methyl vinyl ketone and other alkyl enones were coupled to Cbz amines. In the presence of a Lewis acid, and with microwave heating, they were able to obtain high yields of racemic pyrrolidines **139** (Scheme 38).



137
R_1 = alkyl
R_2 = H, F
n = 1, 2

138

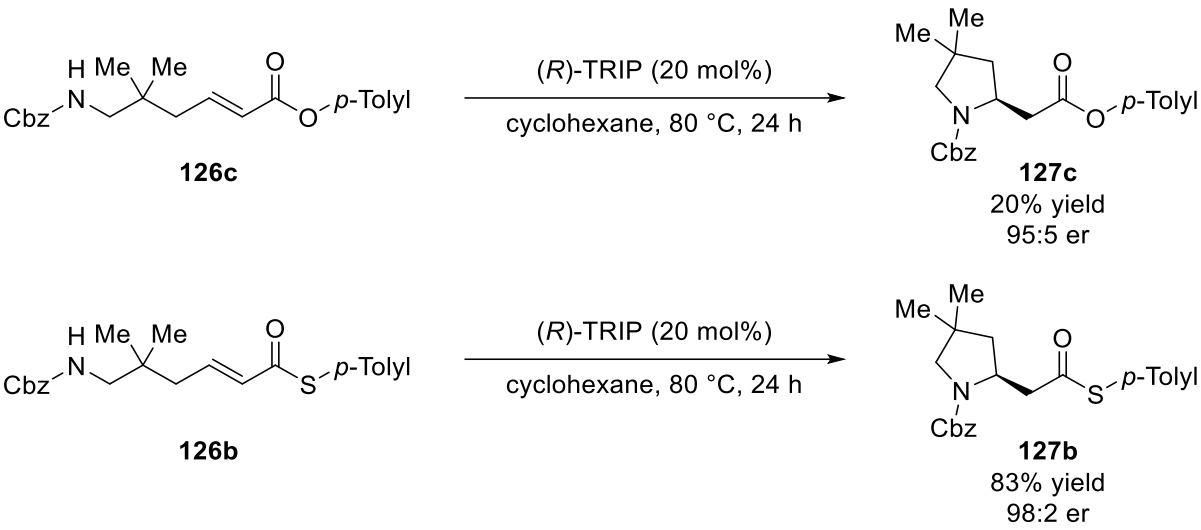
139
55-99% yield

Scheme 38. Tandem metathesis IMAMR of enones

When compared to this report, it is perhaps unsurprising that we obtained a cyclised product **(±) 127a** when using the *p*-tolyl enone under these metathesis conditions. This result also meant that we were not able to submit the enone to asymmetric conditions, as we were unable to isolate the uncyclised product, which lends credence to using less reactive Michael acceptors in stereoselective reactions.

As we had ruled out the use of enones as intramolecular aza-Michael acceptors, the next comparison we wished to draw was between the α,β-unsaturated ester **126c** and α,β-unsaturated thioester **126b**. To do this, conditions were selected based on the previous work in the group on the asymmetric synthesis of tetrahydrofurans.[78] The combination of cyclohexane and (*R*)-TRIP had shown to be fruitful in achieving higher yields and enantioselectivity for the cyclisation of the 5-membered rings. There was also an indication that higher temperatures were not detrimental to the enantioselectivity of the reaction but did offer increased yields. For example, in the case of the 2,2-dimethyl THF synthesis**,** an ee of 45% was achieved at 50 °C and 46% at 75 °C. To that effect, initial screening of the asymmetric reaction was performed at 80 °C as this would be near reflux for cyclohexane and the upper limit for the reaction temperature in this solvent. This would hopefully allow for enantioselective reactions of the α,β-unsaturated thioester **126b** to occur as well as enabling cyclisation of the, theoretically, less reactive α,β-unsaturated ester **126c**. When subjected to these conditions the ester did react but with a low yield of 20%, however, a high enantiomeric

ratio of 95:5 was achieved (**127c**). While this yield was lower than we had hoped, it did lend credence to the hypothesis that the thioesters may offer enhanced reactivity. Gratifyingly, the cyclisation of the thioester led to the formation of pyrrolidine **127b** in a high yield of 83% and with excellent enantioselectivity of 98:2 er. (Scheme 39).



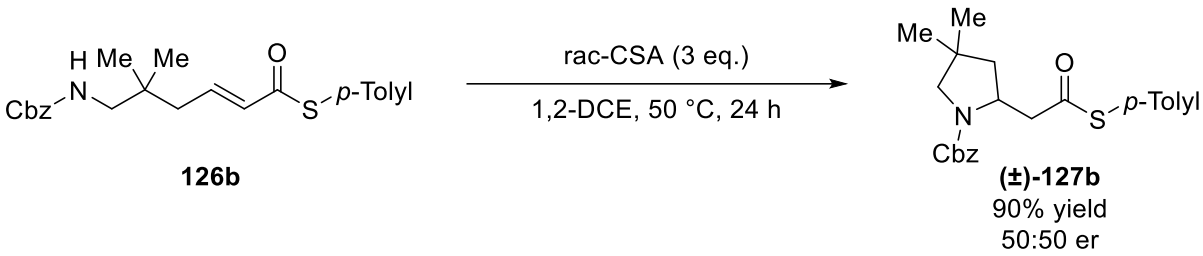
Scheme 39. Asymmetric cyclisation of αβ-unsaturated thioester and αβ-unsaturated ester

This result supports our hypothesis that the thioester sits in a middle ground of reactivity between the ketones/aldehydes and esters. The higher yields observed when using the thioester over esters demonstrate the increased reactivity, while the ability to isolate the α,β-unsaturated thioester means having control over the enantioselectivity of the reaction, which we did not have when using the ketone.

2.1.1. HPLC determination of enantiomeric ratio

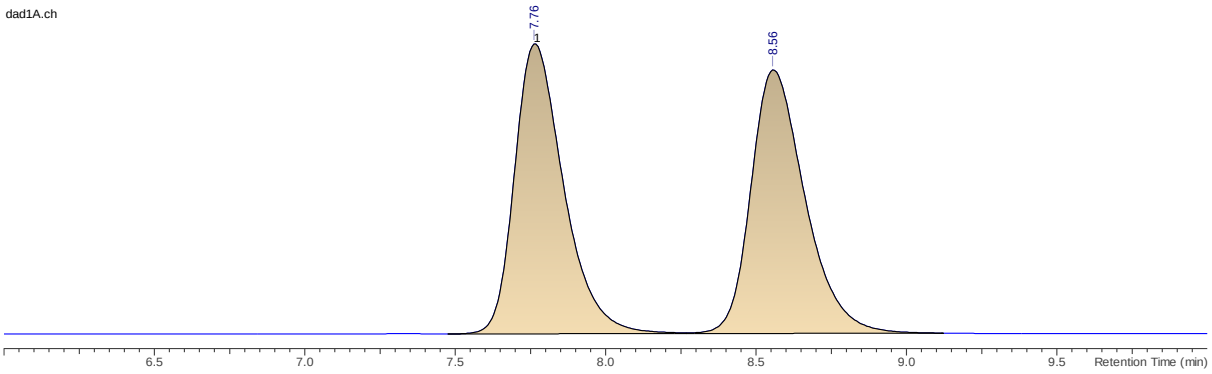
Several methods can be used to determine the enantiomeric ratios in a chiral mixture, but the most appropriate and accessible method for this work was the use of chiral HPLC. The ratios reported in Scheme 39 were determined using this technique.

In order to determine an enantiomeric ratio, a racemic standard is needed to assign the peaks of both enantiomers. To do this, a cyclisation was performed using an excess of racemic (±)-camphorsulfonic acid (rac-CSA), with pyrrolidine **(±)-127b** isolated in 90% yield and an assumed er of 50:50 (Scheme 40).



Scheme 40. Racemic cyclisation of αβ-unsaturated thioester

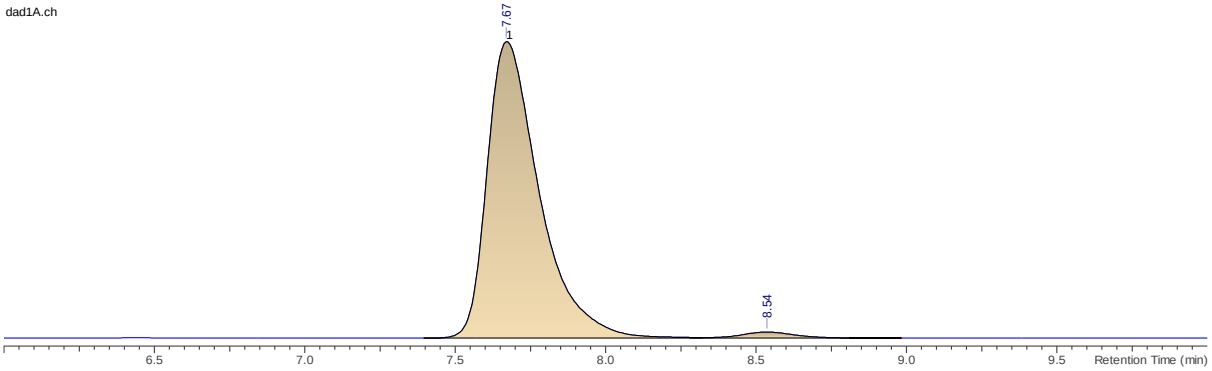
With the racemate in hand, screening of chiral HPLC conditions could be performed. Initial screens were performed by testing a series of CHIRALPAK® columns, namely the IA, IB, IC and IG immobilised polysaccharide columns.[87] In these columns, the polysaccharide stationary phase (either amylose or cellulose) has various organic selector molecules bound to the sugars, and different interaction between the two enantiomers and the selectors enables resolution of the mixture. When developing the method, it was found that varying the chiral column had a greater effect on improving the resolution of the mixture, while changing solvent ratios (hexane/IPA), flow rate or temperature, gave some control over resolution but was more useful in fine-tuning retention times. After screening of conditions, it was found that the CHIRALPAK® IB column eluting with hexane/2-propanol (95:5) at a flow rate of 1.0 mL/min at 25 °C afforded separation of both enantiomers in a short time (Figure 5). The integrated area of both peaks shows a 50:50 ratio confirming that the rac-CSA did indeed afford a racemic mixture.



No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	7.76	4395871.500	49.967	0.289
2	8.55	4401762.000	50.033	0.320

*Figure 5. HPLC chromatogram for cyclisation of pyrrolidine **(±)-127b** with rac-CSA*

With the method developed, the enantiomer ratio of the asymmetric reaction could be determined. Submitting the product of the (*R*)-TRIP reaction to HPLC analysis gave the chromatogram depicted in Figure 6 with the major peak having a retention time of 7.7 mins, and the minor peak at a retention time of 8.5 mins. Integration of the peaks gave an enantiomeric ratio of 98:2.



No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	7.67	10851146.000	97.931	0.302
2	8.54	229300.266	2.069	0.311

*Figure 6. HPLC chromatogram for cyclisation of pyrrolidine **127b** with (R)-TRIP*

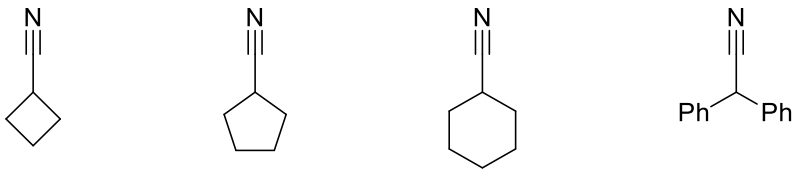
While this method gave excellent separation and resolution for the 3,3-dimethyl substituted pyrrolidine, modification of the conditions or use of alternate chiral columns was easily performed to improve the HPLC traces on other substrates. This data is reported in the experimental section of this thesis.

With these promising results, the next step was to see if the cyclisation conditions were universal for other substituents at the 3,3-position, or would other substrates require screening of the reaction conditions.

2.2. Scope of the reaction for 3,3-disubstitution

The geminal-dimethyl group offered a simplistic substrate for comparing the different Michael acceptors, but altering the substitution at the 3-position could offer greater synthetic complexity and show the limits of the reaction. As discussed earlier, the formation of spirocycles allows for an increase in sp^3 character in a molecule and is of interest in the field of fragment-based drug discovery. Therefore, the introduction of spirocyclic functionality to the pyrrolidine was investigated.

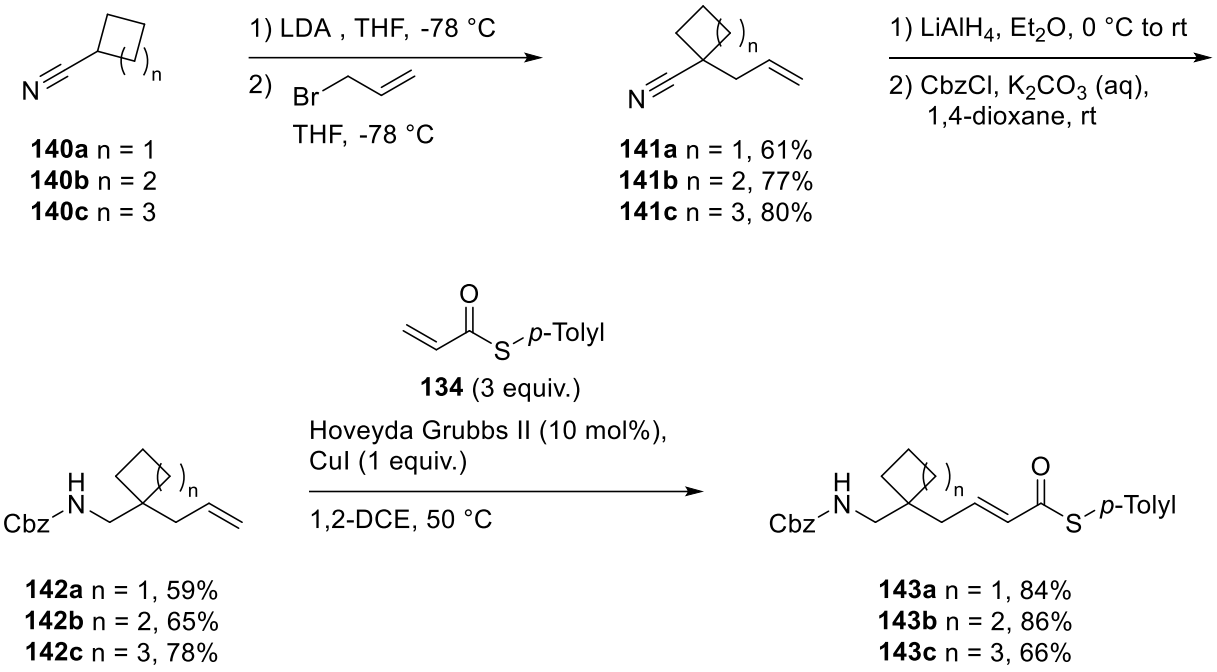
To synthesise the spirocyclic compounds, the procedures used in the production of the geminal dimethyl precursor was used almost directly with only minor modifications required. To modify the 3,3-susbtitution, a range of cycloalkane nitriles, as well as diphenylacetonitrile, were selected to see how they tolerate the cyclisation reaction (Figure 7).



140a **140b** **140c** **140d**

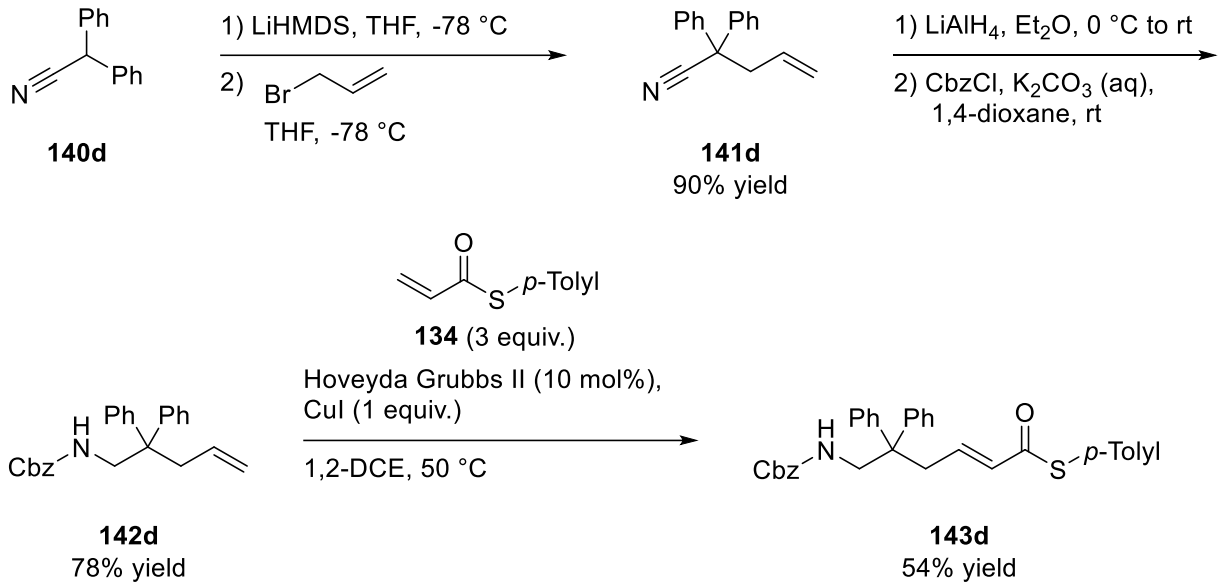
Figure 7. Nitriles selected to test 3,3-subsitutted scope

Following a similar procedure to the dimethyl precursors, the cycloalkyl nitriles were alkylated using LDA and allyl bromide to yield the cyano-alkene. This was then reduced with lithium aluminium hydride and protected with CbzCl in good yields. The metathesis using CuI with the *p*-tolyl thioacrylate gave good yields for the cyclobutyl **143a** and cyclopentyl **143b** precursors (84% and 86% respectively) but a lower yield of 66% for the cyclohexyl **143c** compound (Scheme 41).



Scheme 41. Synthesis of 3,3-spirocyclic precursors

For the diphenyl substituted precursor, the synthetic steps proceeded in much the same way, with the exception that LiHMDS was used for the deprotonation of diphenylacetonitrile **140d** instead of LDA (Scheme 42). The decision to change the base was made for both convenience, as LiHMDS was commercially available as a molar solution, and this specific transformation was reported in the literature with LiHMDS as the base.[88] Alkylation with allyl bromide yielded the cyano-alkene in **141d** in 90% yield. Reduction and protection to give the Cbz amine **142d** followed as for the cycloalkyl products with a good yield of 78%. However, the metathesis of the diphenyl compound gave a lower yield of 54%. While this was lower than the other metathesis reactions, it still allowed for enough material to be isolated to test the cyclisation procedure.



Scheme 42. Synthesis of 3,3-diphenyl precursors

With the precursors in hand, the conditions that had been successfully used to cyclise the 3,3-dimethyl pyrrolidine (cyclohexane, (*R*)-TRIP at 80 °C) were applied to the substrates (Figure 8).

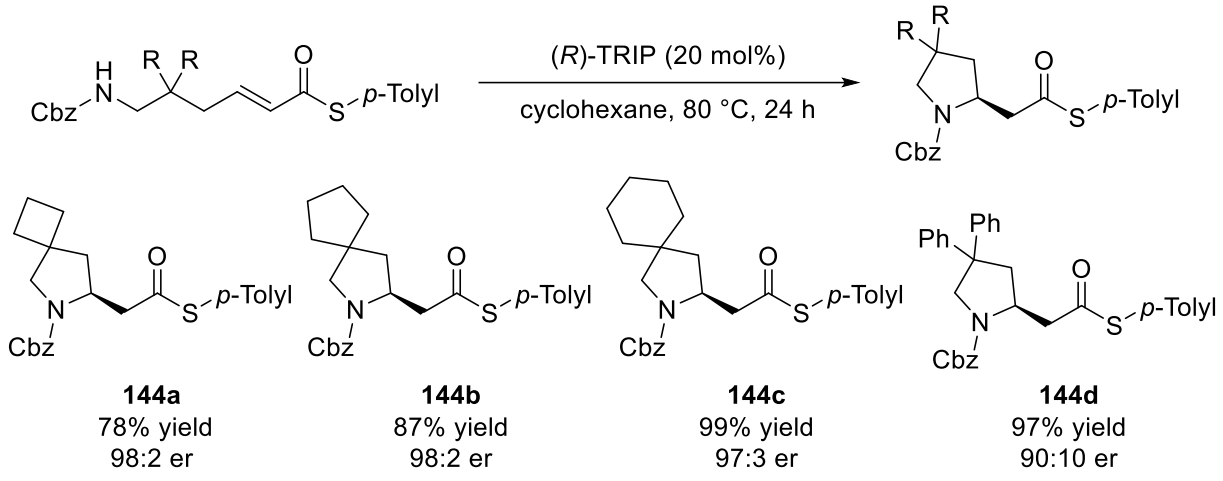


Figure 8. Asymmetric cyclisation to form 3,3-spirocyclic pyrrolidines.

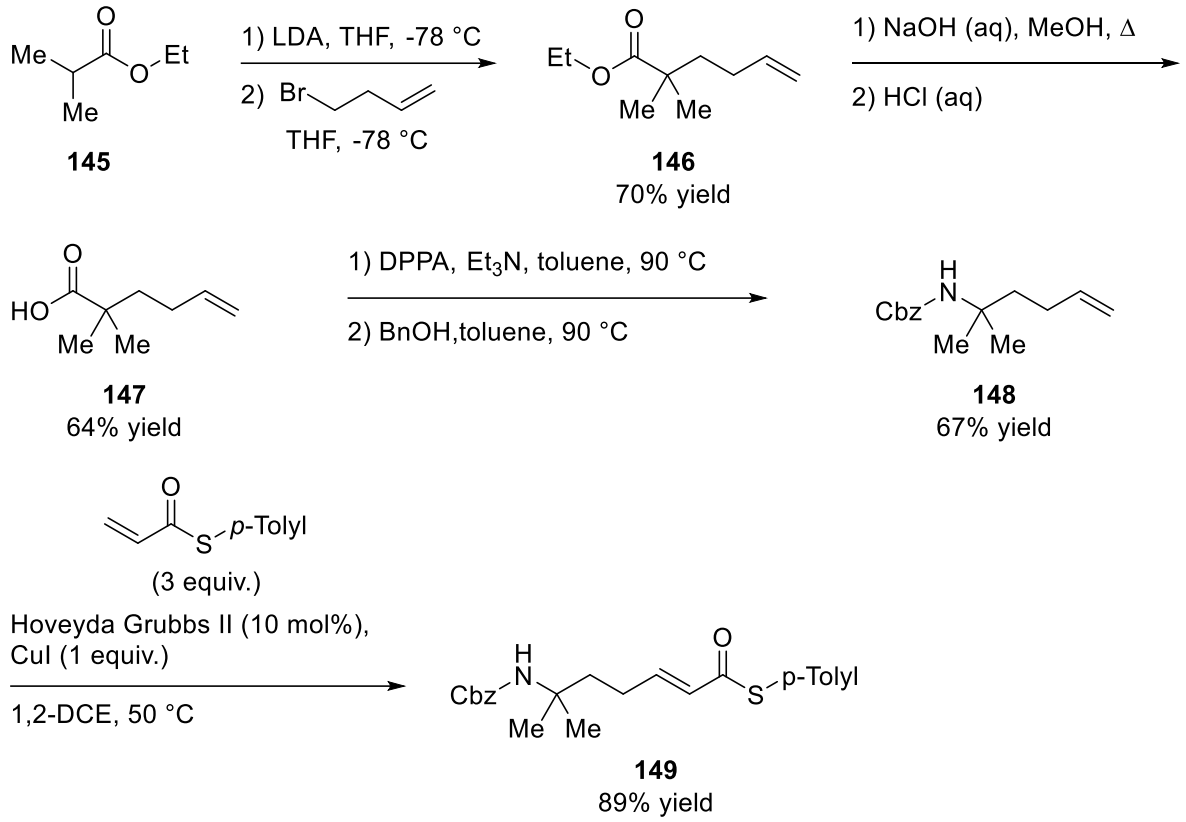
Fortuitously, the (*R*)-TRIP conditions afforded high yields for all the 3,3-disubstituted pyrrolidines, with particularly high yields observed for the 3,3-cyclohexyl spiropyrrolidine **144c** (99%) and for the 3,3-diphenyl substituted pyrrolidine **144d** (97%). Slightly lower yields of 78% for the 3,3-cyclobutyl and 87% for the 3,3-cyclopentyl spiropyrrolidine were observed, but both are good yields and are similar to the yield observed for the 3,3-dimethyl pyrrolidine

127b (83%). The enantioselectivity of the reaction was also very high, with both cyclobutyl and cyclopentyl attaining 98:2 er, and cyclohexyl achieving 97:3 er. The enantioselectivity dropped slightly for the diphenyl pyrrolidine to yield an er of 90:10.

The high yields and enantioselectivity observed for the 3,3-disubstituted pyrrolidines while using (*R*)-TRIP at 80 °C in cyclohexane were very encouraging. It was decided that further screening of reaction conditions would not be useful at this point, as any gains in enantioselectivity or yield would be minimal, and the current set of conditions avoided the use of toxic solvents or bespoke catalysts. However, it was unknown how these results would translate to 2,2-disubstituted compounds.

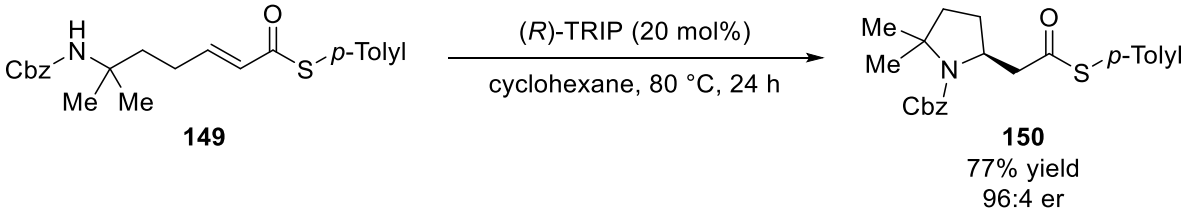
2.3. Scope of the reaction for 2,2-disubstitution

To mirror the reactions performed on the 3,3-disubstituted pyrrolidines, initial tests were performed using the 2,2-dimethyl compounds as a representative example. The approach used to synthesise the 2,2-dimethyl-precursor was to utilise a Curtius rearrangement, as had been reported in the literature.[67,89] The Curtius rearrangement required a carboxylic acid in order to form the intermediate acyl azide, so the first synthetic step was to alkylate ethyl isobutyrate with 4-bromobut-1-ene after deprotonation with LDA (Scheme 43). This formed the alkenyl ester **146** in a good yield of 70%. Subsequent hydrolysis of the ester led to formation of the carboxylic acid **147** in 64% yield, which was then treated with DPPA and Et_3N to form the intermediate acyl azide. Upon heating, the acyl azide underwent the Curtius rearrangement to give an isocyanate with loss of N_2. In the literature reports, this isocyanate is then hydrolysed at reflux with water to produce a free amine. However, as we intended to form the Cbz protected amine at the end of the synthesis, an opportunity for telescoping the reaction arose. To both bypass the amine synthesis, and to reduce the step count of the reaction, benzyl alcohol was added to the reaction after isocyanate formation. Upon heating, this underwent nucleophilic addition to the isocyanate to form the Cbz group *in situ* with a yield of 67% over the two steps. Utilising the same cross metathesis conditions as used for the 3,3-disubstituted compounds, gave the 2,2-dimethyl substituted amino thioester **149** in 89% yield.



Scheme 43. Synthesis of 2,2-dimethyl-substituted precursor through the Curtius rearrangement

With the precursor **149** synthesised, the cyclisation could then be tested. Using the same conditions as the 3,3-disusbsitutted reaction (cyclohexane, (*R*)-TRIP at 80 °C) gave a good yield of 77% (Scheme 44). However, a small drop in er of 96:4 was noted, when compared to 98:2 er for the 3,3-dimethyl pyrrolidine. While this drop is not large, there was potentially room for improvement if conditions were modified.



Scheme 44. Cyclisation of 3,3-dimethyl precursor with (R)-TRIP catalyst

For the screening and optimisation of conditions, there were four parameters that could be changed easily without modification of the substrate; temperature, time, solvent, and catalyst.

The work performed on THFs and THPs used cyclohexane as it was believed the low polarity of the solvent would prevent solvation of the catalyst and interference with the transition state. However, the solubility of more polar substrates in cyclohexane could be problematic, especially at lower temperatures. Therefore, toluene and 1,2-DCE were selected as alternative solvents for screening. Both solvents have high boiling points (110 °C and 84 °C respectively) which could allow for a range of temperatures to be screened and toluene also offers a safer alternative to benzene as an aromatic solvent, while 1,2-DCE has toxicity and carcinogenicity hazards associated with it, however it is useful as a high boiling point chlorinated solvent which could dissolve more polar substrates.

Catalysts were selected based on their commercial availability for two main reasons. Firstly, it allowed for rapid testing of conditions as CPA catalysts require multistep syntheses to make; secondly, if the catalyst can be purchased from a chemical supplier, it becomes more viable in both research and industrial settings. To that end, the catalysts selected were (*R*)-TRIP, (*R*)-TiPSY, (*R*)-phen and (*R*)-anth as shown in Figure 9.

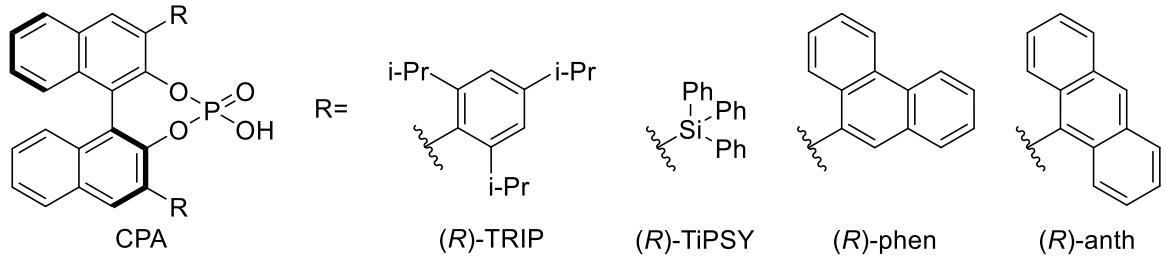
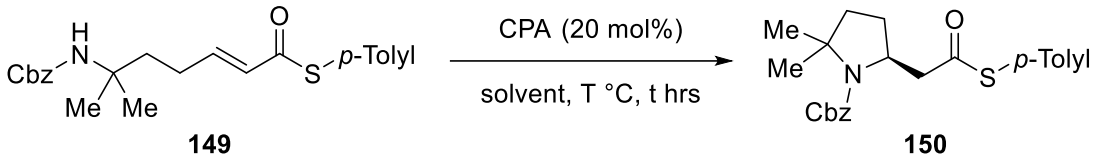


Figure 9. Structure of CPA catalysts used in reaction screening

Initial screening was done by variation of the temperature and the time of the reaction. Table 1, entry 1 shows the already tested conditions of cyclohexane, (*R*)-TRIP at 80 °C for 24 hours, which gave 77% yield and 96:4 er. When the temperature was lowered to 50 °C (Table 1, entry 2), the yield nearly halved to 38%, but no increase in er was observed. Indeed, the er for the reaction dropped marginally to 95:5. The decrease in yield is not particularly surprising as with lower temperatures, the rate of reaction would also be expected to drop. Extending the reaction time to 48 h may be expected to increase the yield, but these conditions only saw a small increase in yield to 46% and a marginal increase in enantioselectivity to 97:3. These slight differences in enantioselectivity are very minor and effectively show that time and

temperature have minimal to no effect on the enantioselectivity of the reaction, but they do have an impact on the yield.

Table 1. Conditions screen for p-tolyl, 2,2-dimethyl pyrrolidine



149 **150**

Entry	CPA	Solvent	T / °C	t / hrs	Yield %	er
1	(*R*)-TRIP	cyclohexane	80	24	77	96:4
2	(*R*)-TRIP	cyclohexane	50	24	38	95:5
3	(*R*)-TRIP	cyclohexane	50	48	46	97:3
4	(*R*)-TRIP	toluene	50	24	18	96:4
5	(*R*)-TRIP	1,2-DCE	50	24	12	95:5
6	(*R*)-TiPSY	cyclohexane	80	24	22	79:21
7	(*R*)-phen	cyclohexane	80	24	21	73:27
8	(*R*)-anth	cyclohexane	80	24	99	81:19

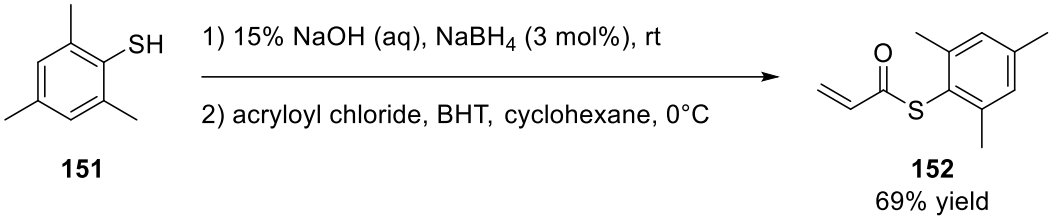
To screen the different solvents in the reaction, the catalyst remained unchanged but the lower temperature of 50 °C was used for 24 hours. The use of the lower temperature would make for easier comparisons for the effect of solvent on the yield and enantioselectivity. If any major increases in yield were observed through varying the solvent, they would be more apparent when increasing from 38 % yield (50 °C) than from 77% yield (80 °C). Any decrease in yield, while less pronounced when using 38% as the baseline, would still be apparent but not as important as those conditions would not be pursued. As can be seen when comparing Table 1, Entries 2, 4, and 5, the effect of solvent had a marked impact on the yield of the reaction, but a negligible effect on the enantioselectivity. Cyclohexane at 50 °C gave a yield of

38%, while both toluene and 1,2-DCE saw a drop to 18 and 12% respectively. The enantiomeric ratio remained at 95:5 for 1,2-DCE and gave a slight increase to 96:4 for toluene.

Cyclohexane at 80 °C for 24 hours seemed to be the ideal conditions for the reaction to achieve high yields while variation of these conditions did not seem to greatly affect the enantioselectivity. While this allows for some flexibility when trying to attain higher yields for the reaction, it seemed that the only way to affect the enantioselectivity would be through catalyst choice. Screening of catalysts (Table 1, Entries 6, 7, and 8) showed moderate enantioselectivity for both (*R*)-TiPSY (79:21 er) and (*R*)-phen (73:27 er) but low yields of 22% and 21% respectively. (*R*)-anth also showed a moderate er of 81:19 but gave an exceptionally high yield of 99%. These results show that the most influential method for affecting enantioselectivity is the choice of catalyst. While the yields of the reactions were also affected, catalyst choice gave the most marked change to enantiomeric ratio for the reaction.

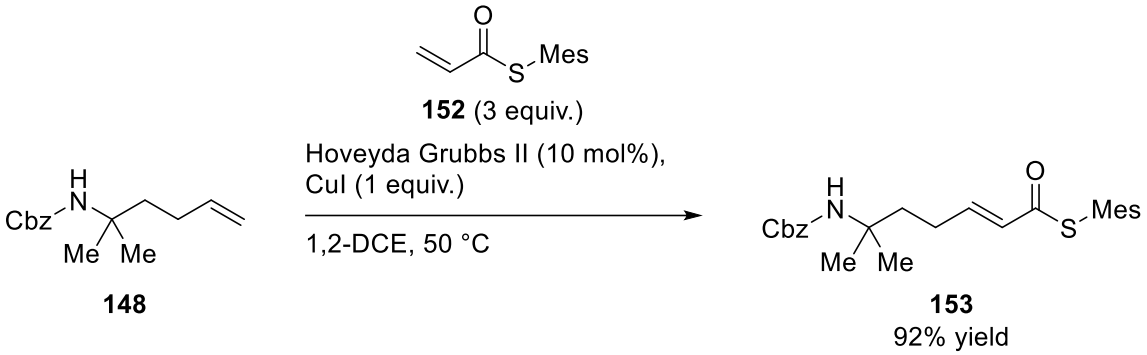
This screen shows that our initial conditions used when synthesising the 3,3,'-dimethyl substituted pyrrolidine were fortunate in also providing high yields and enantioselectivities for the 2,2-diemthyl substituted pyrrolidine. As those initial conditions were based on the asymmetric synthesis of THFs performed in the group,[78] it is gratifying to know that the chemistry can be translated well from the oxy-Michael reaction to the aza-Michael.

Another potential way of affecting the enantioselectivity of the reaction would be to change the substituent on the thioester. In the THF/THP work, changing the *p*-tolyl thiol to mesityl thiol improved enantioselectivity for the tetrahydropyrans, but led to poorer enantioselectivity for tetrahydrofurans (Scheme 32). As the effects of the thiol substituent were unknown for the synthesis of pyrrolidines, this seemed to be a prudent choice for investigation. Mirroring the *p*-tolyl thioacrylate, the mesityl thioacrylate **152** was synthesised from 2,4,6-trimethylthiophenol to give the product in 69% yield (Scheme 45).



Scheme 45. Synthesis of mesityl thioacrylate

The newly formed mesityl thioacrylate could then be coupled to the 2,2-dimethyl Cbz amine **148** under the metathesis conditions, and this proceeded smoothly to give the product **153** in 92% yield (Scheme 46).



Scheme 46. Synthesis of 2,2-dimethyl mesityl thioester precursor

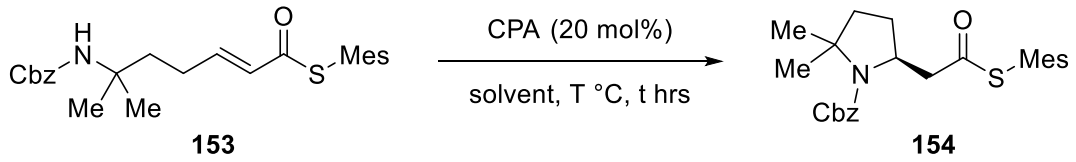
Cyclising the mesityl thioester with (*R*)-TRIP at 80 °C in cyclohexane gave a very high yield of 94% and an er of 92:8 (Table 2, entry 1). The high yield of the reaction is very promising, but the lower enantioselectivity than that of the *p*-tolyl thioester (er 96:4) was deemed to be significant. Therefore, further screening was necessary to see if the selectivity could be improved upon. As the previous screen demonstrated that solvent had minimal effect on enantioselectivity, and that yields were highest when performed with cyclohexane, it was decided to continue only with the cyclohexane and screen temperature, time and catalyst.

As in the case of the *p*-tolyl, reducing the temperature to 50 °C showed a marked decrease in the yield to 41%, but a slight increase in selectivity to give an er of 93:7 (Table 2, entry 2). Extending the reaction time to 48 hours did increase the yield to 68%, but saw a small drop in er to 90:10 (Table 2, entry 3). This ties in with the results seen in Table 1 that increasing the temperature is more beneficial to reaction rate than extending the reaction time, and that the temperature has a small but noticeable effect on enantioselectivity. It is also worth noting

that the mesityl thioester showed higher yields but lower enantioselectivity when compared to the *p*-tolyl thioester when cyclised with (*R*)-TRIP.

Perhaps the largest difference between the *p*-tolyl and mesityl thioester was seen in the results for (*R*)-TiPSY, (*R*)-phen and (*R*)-anth (Table 2, Entries 4, 5, and 6). In all cases the yields and enantiomeric ratios were lower than that of the *p*-tolyl thioester, and all were significantly lower than that of (*R*)-TRIP. The er of 92:8 recorded when (*R*)-TRIP was used does still represents a reasonably high enantioselectivity, though it is a drop from 96:4 when the same conditions were used in the *p*-tolyl thioester. It seems apparent that the added steric bulk from the mesityl group does not lead to any significant gains in enantioselectivity, but with specific catalysts can give increased yields.

Table 2. Conditions screen for mesityl, 2,2-dimethyl pyrrolidine



153 **154**

Entry	CPA	Solvent	T / °C	Time / hrs	Yield %	er
1	(*R*)-TRIP	cyclohexane	80	24	94	92:8
2	(*R*)-TRIP	cyclohexane	50	24	41	93:7
3	(*R*)-TRIP	cyclohexane	50	48	68	90:10
4	(*R*)-TiPSY	cyclohexane	80	24	14	65:35
5	(*R*)-phen	cyclohexane	80	24	5	55:45
6	(*R*)-anth	cyclohexane	80	24	59	59:41

While the screening of the reaction was necessary, it did demonstrate that the initial conditions used for the 3,3-disubstituted pyrrolidines (cyclohexane, (*R*)-TRIP, 80 °C) gave the best results. It also demonstrated that the substitution of the thioester could affect the yields

and enantioselectivity, with the mesityl giving better yields under the (*R*)-TRIP conditions than the *p*-tolyl, but poorer selectivity. For this reaction, the enantioselectivity was given priority over yield and so the *p*-tolyl was selected as the thioester of choice for investigating substitution at the 2-position.

Like the 3,3-disubstituted precursors, the 2,2-disubstituted precursors were synthesised by replacement of the ethyl isobutyrate with the relevant substituted esters. The same carbocycle and diphenyl functionality was included in the selection of substituents, however commercial availability of other esters meant we were able to introduce heterocycles into the precursors, namely 4-tetrahydropyranyl and *N*-Cbz-piperidinyl (Figure 10).

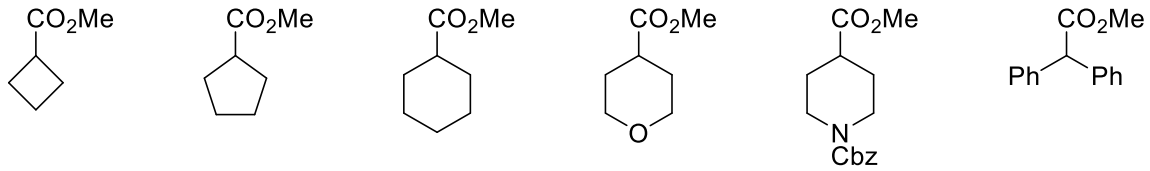
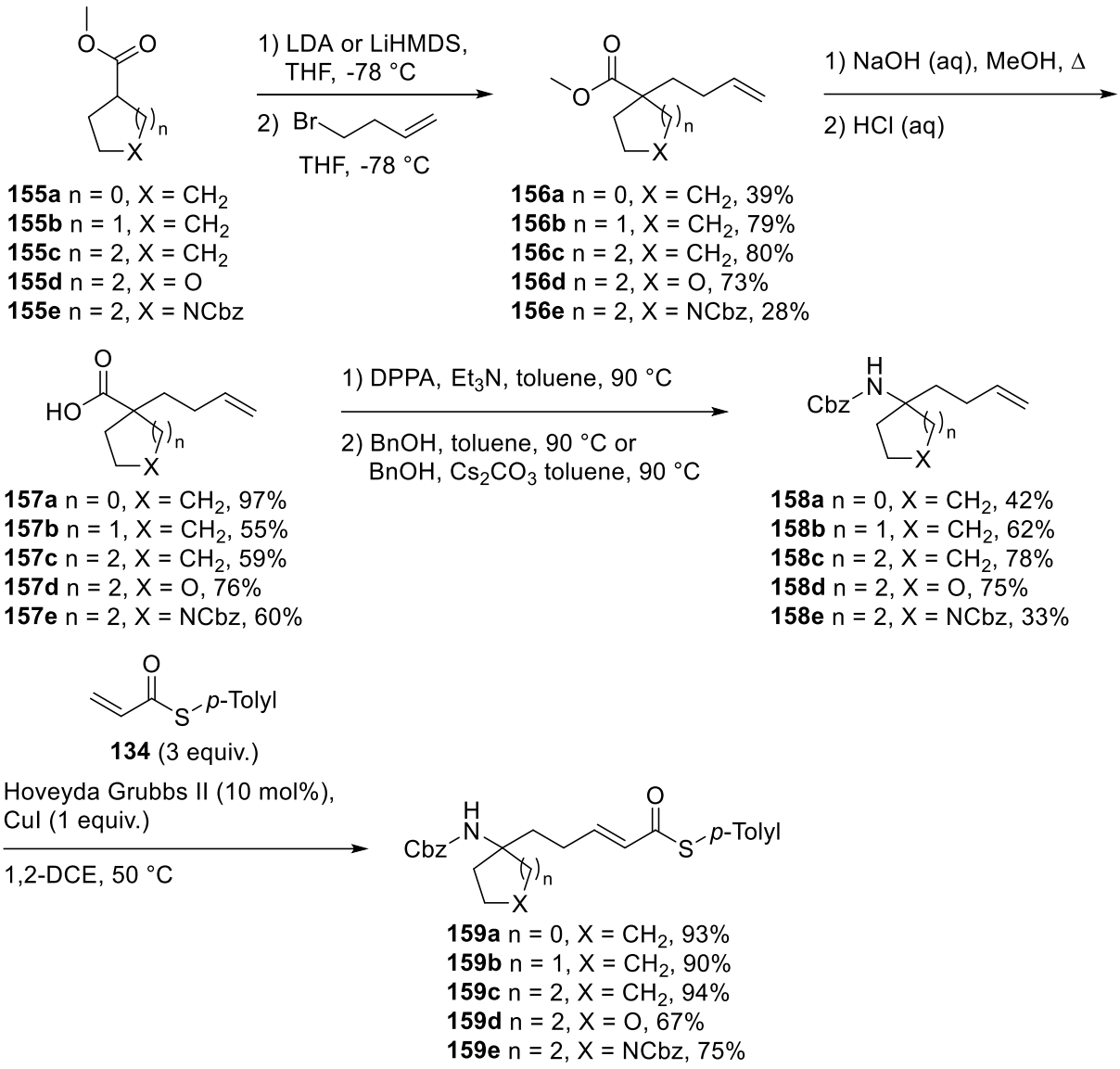


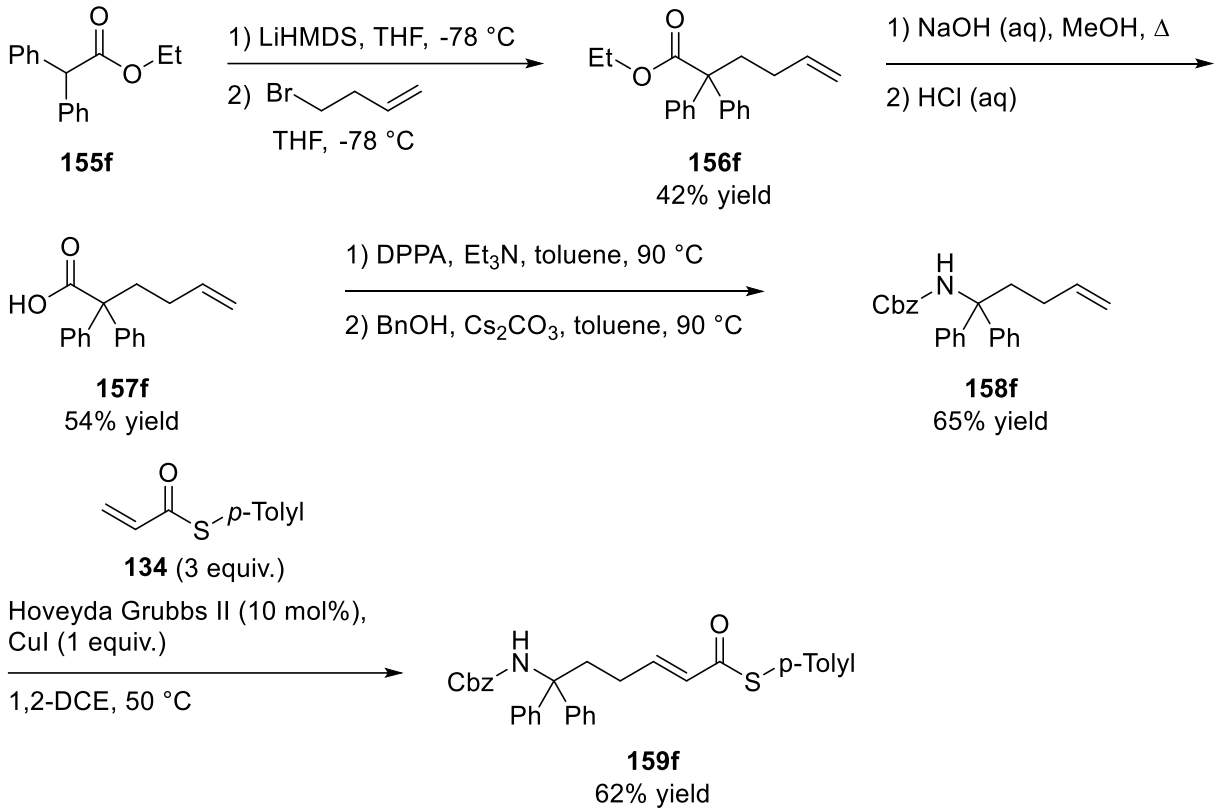
Figure 10. Esters selected to test 2,2-disubstituted scope

These esters were alkylated in the same method as the 2,2-dimethyl substrate (Scheme 43) using LDA and 4-bromobut-1-ene, although in the case of the *N*-Cbz-piperidinyl ester **155e** LiHMDS was used as decomposition occurred with LDA and no product was isolated. (Scheme 47). Following hydrolysis of the ester to the acid, the Curtius rearrangement was again employed. In the case of cyclobutyl **157a**, tetrahydropyranyl **157d**, and *N*-Cbz-piperidinyl **157e** substrates, the addition of Cs_2CO_3 alongside the benzyl alcohol led to better yields of the Cbz amine product. The metathesis proceeded well for most substrates, with especially high yields seen for the carbocyclic precursors (**159a**, **159b**, and **159c**).



Scheme 47. Synthesis of 2,2-disubstituted precursors

For the 2,2-diphenyl ester **155f**, LiHMDS was used for the deprotonation for convenience, and upon alkylation yielded the alkenyl ester **156f** in 42% yield. Hydrolysis of the ester followed the same procedure as for the other substrates and gave the carboxylic acid **157f** in 54% yield. For the Curtius rearrangement, Cs_2CO_3 was also included with the benzyl alcohol, which generated the Cbz amine **158f** in a good yield of 65%. The metathesis conditions also worked well for this substrate and gave the 2,2-diphenyl cyclisation precursor **159f** in a good yield of 62%.



Scheme 48. Synthesis of 2,2-diphenyl precursor

These newly synthesised precursors were then subjected to the cyclisation conditions previously stated (cyclohexane (*R*)-TRIP, 80 °C) (Figure 11).

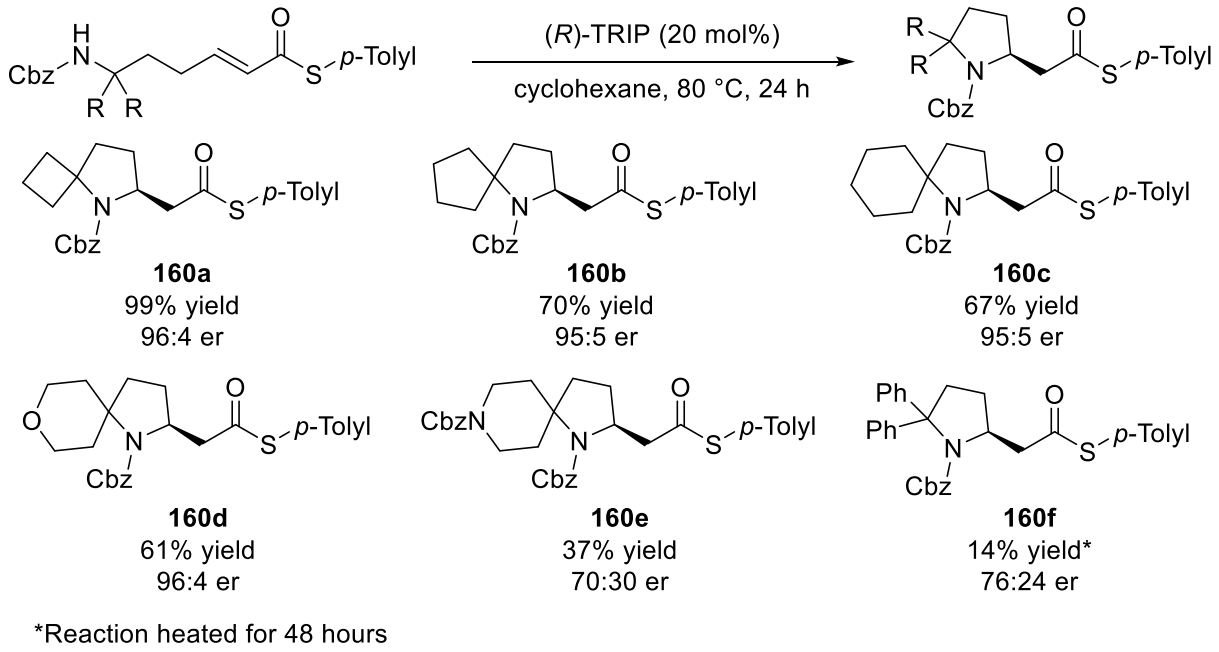


Figure 11. Asymmetric cyclisation to form 2,2- spirocyclic pyrrolidines.

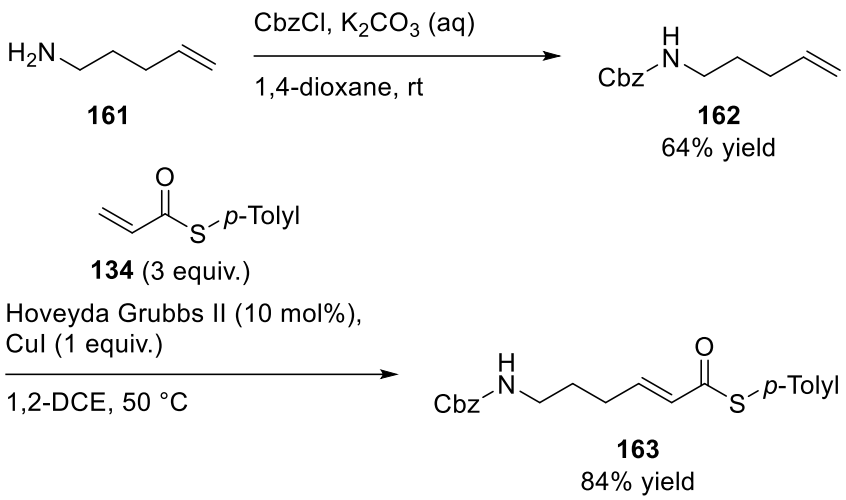
In the case of the 2,2-disubstituted pyrrolidines the cycloalkyl substituents (**160a**, **160b**, and **160c**) gave good to high yields, while maintaining high enantioselectivity. This reflected the results seen for the 2,2-dimethyl pyrrolidine (Table 1, Entry 5) which gave an er of 96:4 and a yield of 77%. Gratifyingly, the introduction of the tetrahydropyranyl spirocycle **160d** gave a good yield of 61% whilst maintaining high enantioselectivity (96:4 er). The *N*-Cbz-piperidinyl **160e** saw a larger drop in yield to 37% and a substantial drop in er to 70:30. This reduction in selectivity and yield was also seen for the 2,2-diphenyl pyrrolidine **160f**, with a very poor yield of 14% and an er of 76:24 attained which was only attained after an extended reaction time of 48 hours.

The lower yields and enantioselectivity observed for the diphenyl **160f** and *N*-Cbz-piperidinyl **160e** pyrrolidines could be due to the increased steric bulk in the transition state of the reaction. Our hopes had been that increasing steric bulk would lead to an increase in selectivity by creating a larger energy gap between the transition states of the reaction which lead to either the (*R*) or (*S*) enantiomer. However, it appears that larger substituents disfavour cyclisation as well as selectivity. The 2,2-diphenyl-pyrroldine **160f** gave particularly poor results, which could be a combination of both steric and electronic factors, although it is unclear as to the degree these different factors affect the reaction. However, the high yields and enantioselectivity observed when synthesising the cycloalkyl and tetrahydropyranyl spiropyrrolidines, was gratifying.

This result coupled with the positive results gained for the 3,3-disubstituted spiropyrrolidines gave us a robust methodology to move forward with. One substrate that had not been tested was that of the unsubstituted pyrrolidine, and this seemed the most obvious compound to try next.

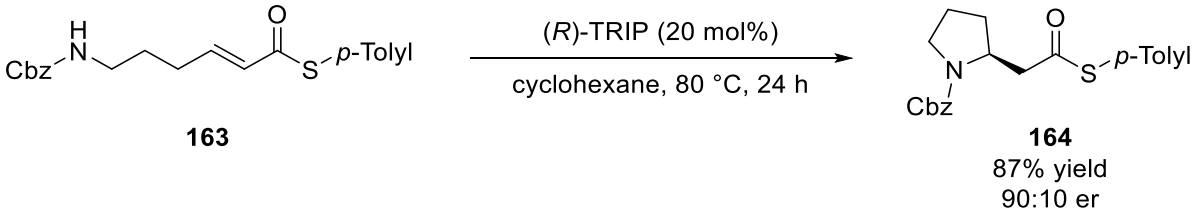
2.4. Synthesis of an unsubstituted pyrrolidine

The formation of the unsubstituted precursor was achieved through protection of 4-penten-1-amine **161** with benzyl chloroformate to give the Cbz amine **162** in 64% yield. Metathesis with the *p*-tolyl thioester gave the unsubstituted precursor **163** in a high yield of 84% (Scheme 49).



Scheme 49. Synthesis of the unsubstituted precursor

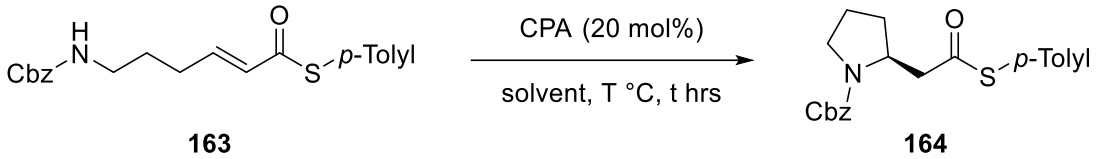
As before the precursor **163** was subjected to the cyclisation conditions of (*R*)-TRIP at 80 °C in cyclohexane. Under these conditions, the substrate cyclised well giving a high yield of 87%, but the selectivity dropped significantly to 90:10 (Scheme 50). Despite the screening for the 2,2-dimethyl substrate resulting in the initial conditions proving to be the best, the lower selectivity observed for the unsubstituted pyrrolidine merited another screen of the conditions.



Scheme 50. Cyclisation of the unsubstituted precursor with (R)-TRIP

Increasing the steric bulk through substitution was theorised to favour certain catalyst transition states, as well as providing a Thorpe-Ingold effect to increase the rate of reaction. Without that substitution, both rates and enantioselectivity could be affected. Certainly, we can see that the enantioselectivity dropped when using the previously optimised conditions, so to ensure a thorough screen, the conditions selected for the screen mirrored those seen in Table 1. The screen for the unsubstituted pyrrolidine synthesis is shown in Table 3.

Table 3. Conditions screen for p-tolyl, unsubstituted pyrrolidine



163 **164**

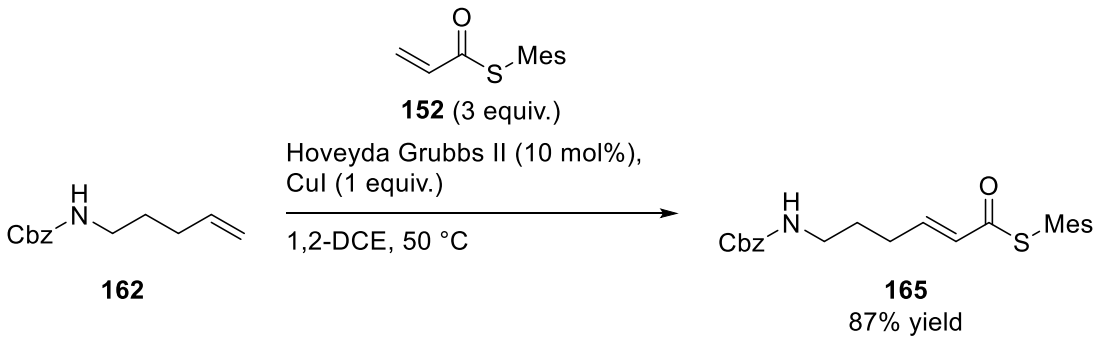
Entry	CPA	Solvent	T / °C	Time / hrs	Yield %	er
1	(*R*)-TRIP	cyclohexane	80	24	87	90:10
2	(*R*)-TRIP	cyclohexane	50	24	88	91:9
3	(*R*)-TRIP	cyclohexane	50	48	43	89:11
4	(*R*)-TRIP	toluene	50	24	42	90:10
5	(*R*)-TRIP	1,2-DCE	50	24	44	88:12
6	(*R*)-TiPSY	cyclohexane	80	24	87	94:6
7	(*R*)-phen	cyclohexane	80	24	73	81:19
8	(*R*)-anth	cyclohexane	80	24	97	78:22

Reducing the temperature of the reaction to 50 °C (Table 3, entry 2) showed almost no change to the reaction conducted at 80 °C, both gave comparable yields and a slight increase in enantioselectivity. Interestingly, when the reaction was conducted for 48 hours (Table 3, Entry 3), instead of increasing the yield, there was a significant drop from 87 % for the 24 hour reaction, to 43%. It was theorised that while extending the reaction time may lead to an increase in the amount of product formed for a more sluggish reaction, extending the time also leads to competing decomposition pathways, possibly through hydrolysis of the thioester. For both toluene and 1,2-DCE, yields were approximately half of that obtained with cyclohexane (Table 3, entries 4 and 5). Likewise, enantioselectivity was only marginally affected, with 1,2-DCE performing slightly poorer than toluene and cyclohexane.

In screening the catalysts, (*R*)-TiPSY (Table 3, entry 6) achieved a yield of 87% to match that of (*R*)-TRIP (Table 3, entry 1), but with an increased er of 94:6. (*R*)-phen gave a slightly lower yield of 73%, but showed a significant decrease in er to 81:19 (Table 3, entry 7). (*R*)-anth showed a near quantitative yield for but also led to a lower er of 78:22 (Table 3, entry 8). The increase in enantioselectivity and high yields for (*R*)-TiPSY suggest that for unsubstituted compounds it is a better catalyst than (*R*)-TRIP

With the discovery that (*R*)-TiPSY gave better results in the case of the *p*-tolyl unsubstituted pyrrolidine, the utility in screening conditions had been demonstrated. One other aspect that warranted investigation was modification of the thioester. While the use of a mesityl thioester did not improve on the *p*-tolyl results for the 2,2-dimethyl pyrrolidine, it was deemed appropriate to test the effect of the thioester substitution on the cyclisation of the unsubstituted pyrrolidine.

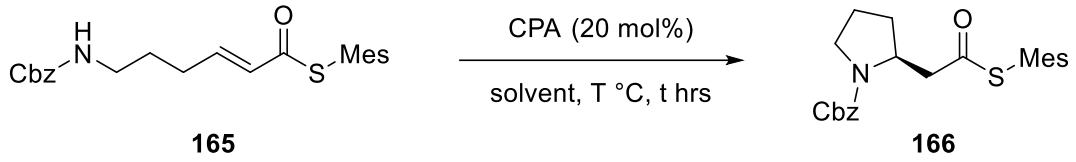
To do this, the unsubstituted Cbz amine **162** was once again submitted to the metathesis conditions, this time with the mesityl thioacrylate. This gave the cyclisation precursor **165** in a high yield of 87% (Scheme 51).



Scheme 51. Synthesis of unsubstituted mesityl thioester precursor

As the effect of solvent had again been shown to be minimal on yield and selectivity, cyclohexane was carried forward for the screen, with toluene and 1,2-DCE not tested. However, temperature, time and catalyst were screened, as shown in Table 4.

Table 4. Conditions screen for mesityl, unsubstituted pyrrolidine



165 **166**

Entry	CPA	Solvent	T / °C	Time / hrs	Yield %	er
1	(*R*)-TRIP	cyclohexane	80	24	91	85:15
2	(*R*)-TRIP	cyclohexane	50	24	62	85:15
3	(*R*)-TRIP	cyclohexane	50	48	91	85:15
4	(*R*)-TiPSY	cyclohexane	80	24	36	93:7
5	(*R*)-phen	cyclohexane	80	24	10	67:33
6	(*R*)-anth	cyclohexane	80	24	89	72:28

When the reaction was performed with (*R*)-TRIP at 80 °C for 24 hours, a high yield of 91% was obtained, but an er of only 85:15 was achieved (Table 4, entry 1). Reduction of the reaction temperature to 50 °C did also reduce the yield to 62%, but the enantioselectivity was unchanged, achieving an er of 85:15 (Table 4, entry 2). Extending the reaction time to 48 hours at 50 °C did increase the yield to 91% but again, no increase in enantioselectivity was observed (Table 4, entry 3).

The use of (*R*)-phen and (*R*)-anth (Table 4, Entries 5 and 6) saw a decrease in both yield and enantioselectivity when compared to (*R*)-TRIP , but (*R*)-TiPSY (Table 4, Entry 4) showed a dramatic increase in er to 93:7. This reflects the results seen for the unsubstituted *p*-tolyl where (*R*)-TiPSY led to a higher enantioselectivity when compared to (*R*)-TRIP (Table 3, Entries 1 and 6). Unfortunately, the yield of the mesityl thioester (36%) was lower when (*R*)-TiPSY was used, meaning any gains from enantioselectivity were outweighed by a lack of synthetic utility.

It is also worth noting that when extended reaction times were used for the unsubstituted *p*-tolyl thioesters, the yield dropped significantly (Table 3, Entry 3), possibly due to hydrolysis of the thioester. In the case of the mesityl thioester, extending the reaction time not only increased the yield (Table 4, Entry 3), it also matched the results seen for the higher temperature reaction (Table 4, Entry 1). This suggests that, while less effective at providing enantioselectivity, the mesityl thioester does seem to be more stable to hydrolysis or decomposition than the *p*-tolyl. By varying the thioester, it was clear that the cyclisation itself was significantly affected, but the stability of the resultant thioester to hydrolysis or decomposition under the reaction conditions was a result worth considering.

2.5. Functionalisation of pyrrolidines

The pyrrolidine substructure offers two main handles that could be used to introduce functionalisation; the thioester and the nitrogen atom. The thioester can be modified in similar ways to an oxoester, such as reduction, hydrolysis or transesterification. The transesterification was of interest as a method for determining the stereochemistry of the stereogenic centre formed in the cyclisation **167** (Figure 12). The simplest modification of the nitrogen was deprotection of the Cbz group to reveal the secondary amine **168**, which could then go undergo further reactions such as reductive aminations or Buchwald Hartwig coupling.[90]

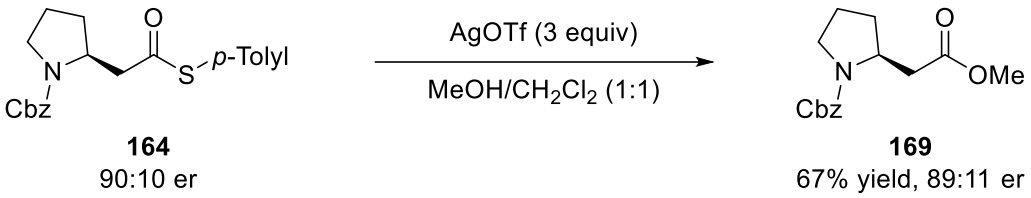
167 **168**

Figure 12. Potential transesterification and deprotection products

2.5.1. Transesterification and confirmation of stereochemistry

One of the aspects of the thioester which made it especially useful for asymmetric synthesis of pyrrolidines, was its comparatively higher reactivity than the ester. While the ester gave lower yields and enantioselectivity than the thioester in the aza-Michael reaction, conversion of the thioester into an ester would enable access to analogues of L-β-homoproline. They could also serve as a linker unit to attach the pyrrolidine subunit onto a larger molecule.

Fortunately, methods have been reported in the literature to produce esters from corresponding thioesters. A report by Hanessian *et. al.* demonstrates a process using AgOTf in MeOH/CH_2Cl_2 to convert a thiophenyl ester into a methyl ester.[91] Using these conditions, the pyrrolidine **164** was converted smoothly into the methyl ester **169** in 67% yield and with minimal change in enantiomeric ratio (Scheme 52).

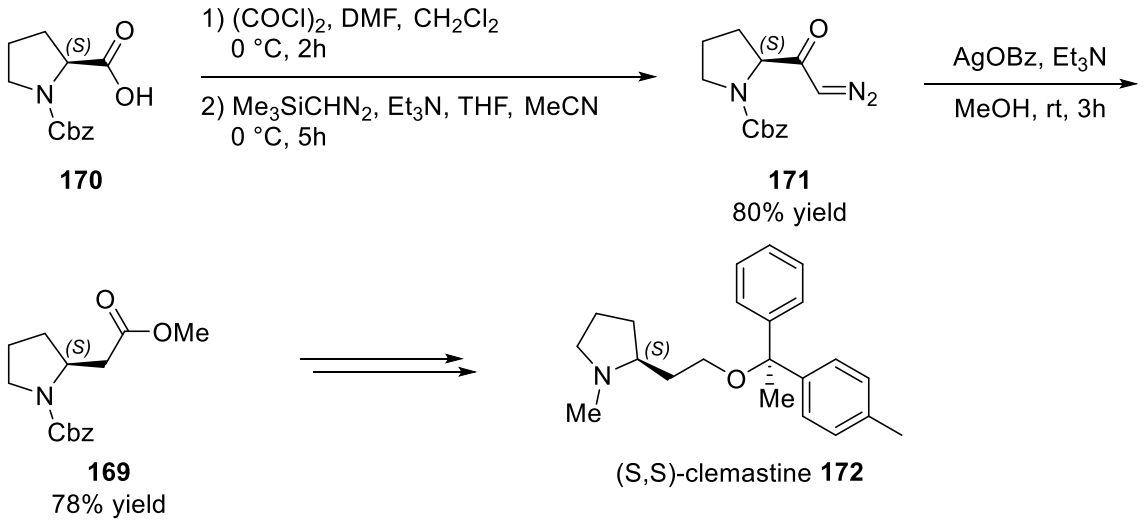


164
90:10 er

169
67% yield, 89:11 er

Scheme 52. Transesterification using silver triflate and methanol

The synthesis of the pyrrolidine methyl ester **169** was performed for two main reasons; firstly, to demonstrate the transesterification procedure, but also to allow for determination of the absolute stereochemistry of the product. In a publication by the Clayden group, they synthesised (*S,S*)-clemastine **172** from L-proline **170** through an Arndt-Eistert extension of the amino acid.[4] They formed the Cbz-methyl ester-protected-β-amino acid **169** as part of the synthesis which matches the structure of the product of the transesterification procedure. (Scheme 53).



170

171
80% yield

169
78% yield

(S,S)-clemastine **172**

Scheme 53. Synthesis of (S,S)-clemastine with β-amino acid intermediate

As this intermediate in the synthesis was derived from an enantiomerically pure source (L-proline), the value for the optical rotation of the molecule would enable the determination of configuration in the (*R*)-TRIP catalysed cyclisation. By discovering the configuration of the stereogenic centre formed in the cyclisation, alternate catalysts could be used, e.g. (*S*)-TRIP, depending on which enantiomer is required in further syntheses. It can also allow for analysis of the transition state and mechanism of the reaction through computational studies.

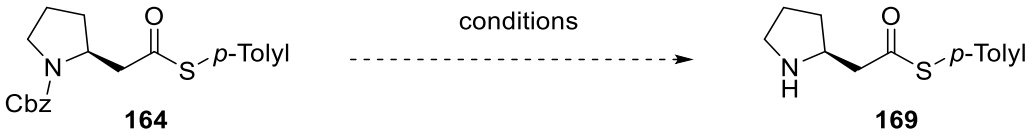
The optical rotation of the methyl ester synthesised from the cyclised thioester was recorded to be $[\alpha]_D^{25}$ -25.4 (c 0.55, $CHCl_3$), with the value for the literature compound as $[\alpha]_D^{25}$ -42.7 (c 1.33, $CHCl_3$).[4] Comparison of the sign of optical rotation with the literature value led to the conclusion that the configurtion of the pyrrolidine methyl ester **169** was (*S*) and therefore the thioester **164** must also be (*S*)- as there appeared to be no racemisation of the stereocentre.

2.5.2. Cbz de-protection

One of the most obvious points of functionalisation on the pyrrolidine ring is that of the nitrogen atom. For functionalisation to take place, the nitrogen must first be deprotected, and the usual methods for the removal of a Cbz group is through hydrogenation. Cbz had been used since the start of the methodology in preference to Boc, mainly due to its stability under acidic conditions as the cyclisation procedures were performed using acid catalysts. However, this stability of the Cbz offers more challenges in its removal. Standard deprotection methods used within the group were the use of 10 mol% Pd/C in methanol under an atmosphere of hydrogen. When tested on the cyclised pyrrolidine **164**, no reaction was observed, and only starting material was recovered (Table 5, entry 1). Replacing the solvent with one of higher polarity has been a variation employed for particularly difficult substrates.[92] However, when acetic acid was used in place of methanol, the results of the reaction were much the same with only starting material recovered and no deprotection observed (Table 5, entry 2). Using an excess of palladium also proved fruitless when 1.1 equivalents of $Pd(OH)_2$ were used in methanol (Table 5, entry 3). Under this set of conditions, no product or starting material was recovered, with only decomposition products observed by NMR. Another method for the removal of Cbz groups is through transfer hydrogenation. This replaces gaseous hydrogen with a chemical source, in this case ammonium formate, as the hydrogen donor. This procedure has shown utility in peptide synthesis and has been

demonstrated in the deprotection of Cbz proline.[93] To test this reaction, a catalytic amount of $Pd(OH)_2/C$ with an excess of ammonium formate was refluxed with the pyrrolidine **164** in ethanol. Unfortunately, this was not productive in yielding the deprotected product, and only decomposition was observed (Table 5, entry 4).

Table 5. Hydrogenation conditions tested for the removal of the Cbz protecting group.

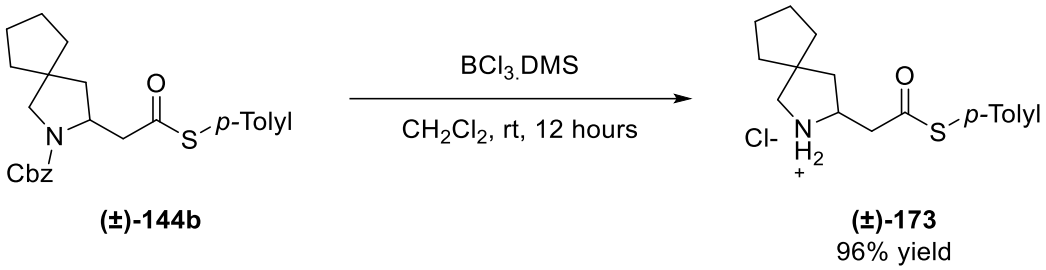


Entry	Pd catalyst (loading)	Solvent/temp	Hydrogen source	Result
1	Pd/C (10 mol%)	MeOH, rt	H_2	No reaction
2	Pd/C (10 mol%)	AcOH, rt	H_2	No reaction
3	$Pd(OH)_2/C$ (1.1 eq)	MeOH, rt	H_2	Decomposition
4	$Pd(OH)_2/C$ (10 mol%)	EtOH, reflux	NH_4CO_2H (10 eq.)	Decomposition

It was theorised that the some of the decomposition observed may have been due to hydrolysis of the thioester in alcoholic solvents. The liberated sulfur may have then gone on to poison the palladium on charcoal, rendering it unable to perform the hydrogenation.[94] As none of the palladium catalysed hydrogenation gave viable methods for deprotection, alternate procedures were investigated.

One procedure proposed, was the use of boron trichloride-dimethyl sulphide complex as a debenzylating reagent.[95] Both boron tribromide and boron trichloride have been used to remove benzyl groups from benzyl protected alcohols and amines. It was reasoned that the benzyl group of the Cbz may undergo deprotection under these conditions to give the resultant carbamic acid, which could then break down releasing CO_2 to generate the deprotected amine. Due to material availability, this process was tested on a racemic 3,3-cyclopentyl pyrrolidine **(±)-144b**. Gratifyingly, when treated with BCl_3.DMS the Cbz was

removed smoothly to generate the HCl salt of the pyrrolidine **(±)-173** in a very high 96% yield (Scheme 54).



(±)-144b **(±)-173** 96% yield

Scheme 54. Cbz deprotection using BCl_3.DMS

2.6. Summary of results

The use of α,β-unsaturated thioesters as Michael acceptors in an intramolecular asymmetric aza-Michael reaction has been demonstrated. Initial comparisons between oxo-esters and ketones showed that the thioester gave better yields and higher enantioselectivity than the other substrates. When using (*R*)-TRIP in the synthesis of 3,3-disubstituted and spirocyclic pyrrolidines, high yields and enantiomeric ratio could be achieved. After a series of optimisations, it was also shown that these same conditions led to the formation of 2,2-disubstituted pyrrolidines as well, although with an overall slightly reduced selectivity when compared with 3,3-disubstituted pyrrolidines. It is unclear as to the exact reason for the difference in selectivity, but the proximity of the substitution, and thus steric bulk, to the nucleophile could be a factor. Screening of the reaction did reveal that the use of (*R*)-TiPSY in the synthesis of unsubstituted pyrrolidines was beneficial, and led to higher enantioselectivity, with only a small loss in yield.

Screening of the reaction conditions showed the extent to which each variable affected the yield and selectivity of the reaction. Solvent choice affected the yield of the reactions, with cyclohexane performing best in all cases, but had little effect on enantioselectivity. Generally, raised temperatures (80 °C instead of 50 °C) increased yield but did not greatly affect the enantioselectivity. Increasing the reaction times from 24 to 48 hours at 50 °C increased yields in the case of the mesityl thioester but not the p-tolyl, possibly due to competing hydrolysis or decomposition reactions. However, when higher temperatures were used (80 °C) the *p*-tolyl thioesters gave higher yields and enantioselectivities than when using mesityl thioesters.

The main factor in determining the enantioselectivity of the reaction was in the catalyst choice, with (*R*)-TiPSY giving the best selectivity for unsubstituted pyrrolidines, and (*R*)-TRIP giving the best selectivity for substituted pyrrolidines.

Through this process of optimisation, we were able to decide upon a general set of conditions for the asymmetric synthesis of spiropyrrolidines; (*R*)-TRIP, cyclohexane, 80 °C for 24 h. These conditions proved to be productive for synthesising a range of spirocyclic and di-substituted pyrrolidines.

Functionalisation of the cyclised products was achieved through a transesterification procedure and deprotection. The transesterification procedure allowed for easy modification of the thioester into the corresponding methyl ester in 67% yield with no appreciable racemisation of the stereocentre observed. Comparison of the specific rotation of the methyl ester allowed for the determination of the absolute configuration of the compound, and thus the stereochemistry of the product of cyclisation, as being the (*S*)-enantiomer. Deprotection of the Cbz group was not possible using traditional hydrogenation conditions, but the use of BCl_3.DMS gave the HCl salt of the pyrrolidine in a very high 96% yield.

3. Expanding the methodology

With a wide substrate scope demonstrated for the asymmetric synthesis of substituted pyrrolidines, further attempts to expand the methodology were investigated. The initial scope gave access to a range of spirocyclic pyrrolidines, a structural motif which can increase the three-dimensionality of a compound. When developing drugs or drug-like compounds, changing the shape or form of a molecule is one way in which the pharmacokinetics can be tuned.[96] Further modification of potential drug-like compounds, such as introduction of heteroatoms or diastereotopic centres, can also help in the tuning of a drugs properties.

One area of interest in synthetic and medicinal chemistry is the incorporation of fluorine atoms into drug molecules. Fluorination of organic molecules is non-trivial and the possibility of introducing fluorine into the pyrrolidine structures **174** and **175** provided an interesting synthetic challenge (Figure 13). Another point of functionalisation was the double bond where introduction of an R group, such as a methyl, could lead to new enantioenriched pyrrolidines **176** or new diastereomeric pyrrolidines **177**. These variations could affect the lipophilicity of the pyrrolidine scaffolds in the case of fluorine, or the branching and steric interactions with the double bond substitution. Both approaches would lead to a greater scope for the methodology, adding complexity to the pyrrolidine scaffolds available using the cyclisation procedure.

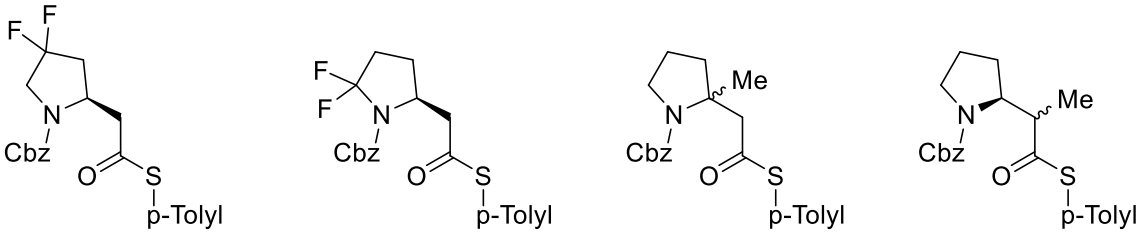


Figure 13. Potential new pyrrolidines using existing procedures

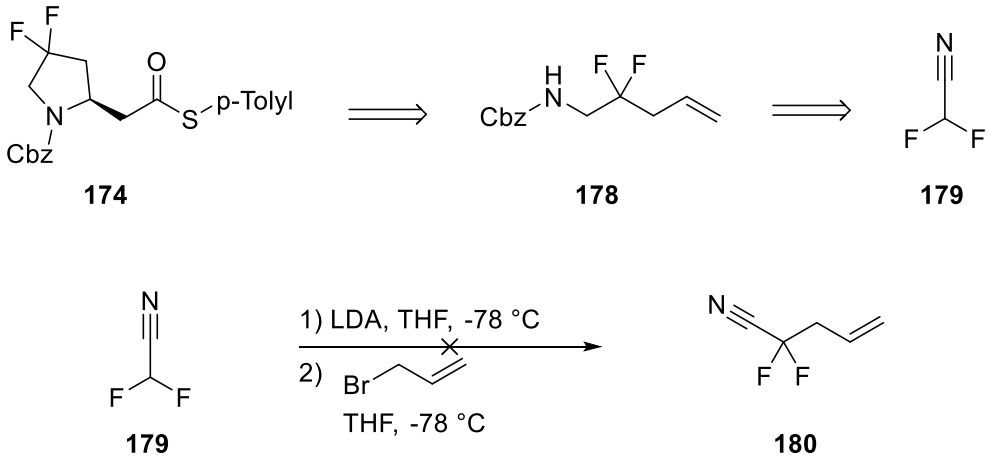
3.1. Di-fluorinated pyrrolidines

Fluorine and its properties are of interest to medicinal chemistry for the pharmacokinetic properties it provides to drugs, and its introduction into organic molecules can be non-trivial.[97,98] The size of the fluorine atom is relatively small (Van der Waal radius of 1.47 Å)

considering the size of a hydrogen atom (1.20 Å),[99] while its electronegativity is 3.98 on the Pauling scale.[100] Replacement of hydrogen in a drug molecule with fluorine has been shown to mimic the steric interactions of hydrogen when binding to a receptor or enzyme.[101] This, coupled with the stability of the C-F bond in comparison to C-H, can lead to an increase in chemical and metabolic stability and enhanced biological activity.[101] While the steric interactions may be small, the electrostatic interaction of the fluorine can also induce a conformational bias in both ring and aliphatic systems, as well as affecting the pKa of functional groups both proximal and distal to the fluorine.[98,102] The presence of fluorine can also increase the lipophilicity of a compound, a property that can affect the solubility and membrane permeability of a drug.[98] For these reasons, it seems clear that the introduction of fluorine to a molecule warrants investigation.

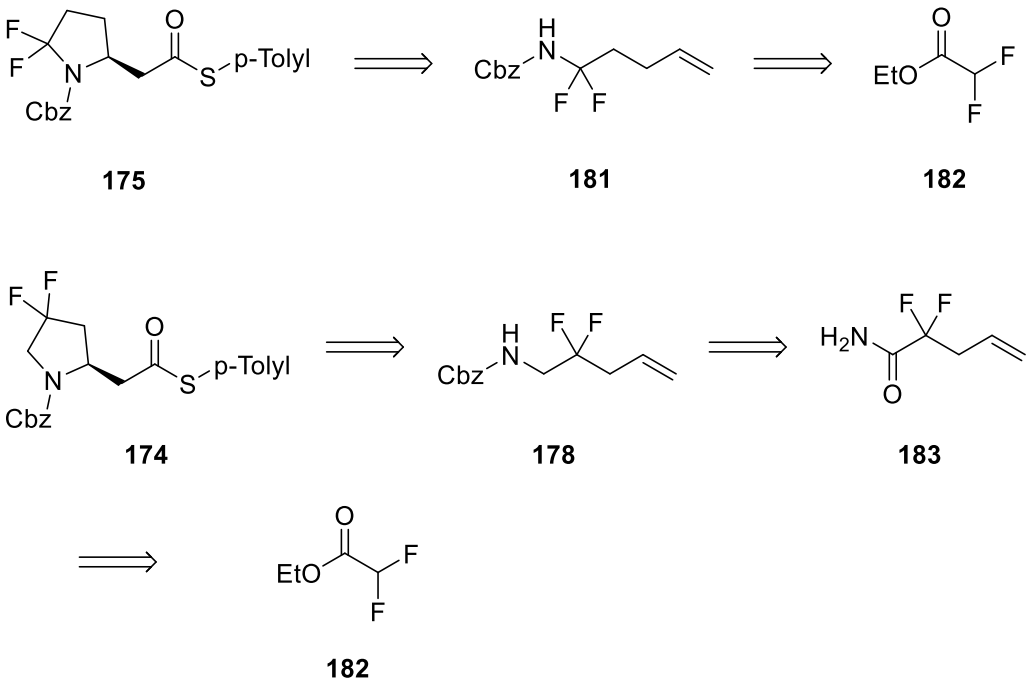
3.1.1. Previous route

In order to synthesise the appropriate precursor, the initial plan was to follow the previous syntheses used for producing the disubstituted pyrrolidines. To begin with difluoroacetonitrile **179** was selected as a starting material for the synthesis of the 3,3-difluoro pyrrolidines (Scheme 55). First, the alkylation procedure of difluoroacetonitrile was tested using LDA to deprotonate the nitrile, followed by addition of allyl bromide. Unfortunately, no product was observed in the reaction (Scheme 55). It was hypothesised, that the nitrile anion may be stabilised by the adjacent fluorine atoms making it less reactive towards nucleophilic addition. Whether this reactivity would be observed when using other fluorinated starting materials remained to be seen.



Scheme 55. Retrosynthetic analysis and forward synthesis of 3,3-difluorinated pyrrolidine

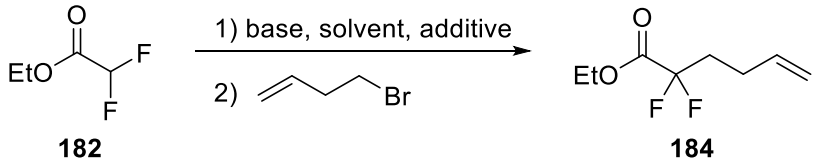
While the nitrile proved unsuccessful, there was hope that the use of ethyl difluoroacetate **182** may be more fruitful in synthesising the 2,2-difluorinated precursor **181** (Scheme 56). Use of the nitrile was non-trivial due to its low boiling point and high volatility. Consequently, a new synthesis for the 3,3-difluorinated precursor **178** was conceived, also from ethyl difluoroacetate **182** giving a common starting material to derive both 2,2- and 3,3-difluoro compounds (Scheme 56).



Scheme 56. Retrosynthetic analysis of 2,2- and 3,3-difluorinated pyrrolidines

As a forward synthesis, the first conditions tested were those previously used when synthesising 2,2-disubstituted pyrrolidines; LDA in THF at -78 °C followed by addition of 4-bromobut-1-ene (Table 6, entry 1). Under these conditions, no product was isolated, and analysis of the crude material did not discern any identifiable compounds. When LDA was replaced with LiHMDS as an alternative non-nucleophilic amine base, the only product observed was the hydrolysed starting material (Table 6, entry 2). Another base commonly used for deprotonation in the formation of enolates is sodium hydride. Under reflux in dry benzene (Table 6, entry 3), the only product recovered was difluoroacetic acid with no alkylated product seen. It was hypothesised that small amounts of water may have entered the reaction and, coupled with high temperatures, resulted in the hydrolysis of the starting material. To try and combat hydrolysis, NaH deprotonation was attempted at -78 °C in dry THF (Table 6, entry 4). Unfortunately this method also resulted in hydrolysis. It was therefore concluded that quenching the reaction with water led to the formation of NaOH during workup which would be the most likely explain the hydrolysis observed.

Table 6. Enolate formation and alkylation with 4-bromobut-1-ene



182 **184**

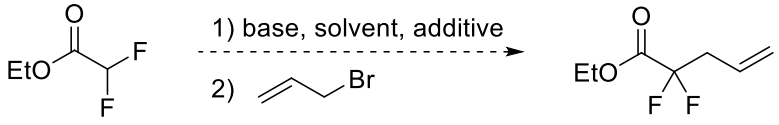
Entry	Base	Solvent	Temp / °C	Additive	Result	Yield %
1	LDA	THF	-78	-	Decomposition	-
2	LiHMDS	THF	-78	-	difluoroacetic acid	62
3	NaH	benzene	80	-	difluoroacetic acid	63
4	NaH	THF	-78	-	difluoroacetic acid	76
5	KHMDS	Toluene	-40	18-crown-6 (premixed)	Decomposition	-
6	KHMDS	Toluene	-40	18-crown-6 (after halide)	Decomposition	-

The lack of product formation may also be due to the stability of the metal enolate, as even at elevated temperatures, no product was observed. To try and counter this, KHMDS was used as a base with 18-crown-6 added as a potassium ionophore. When KHMDS was premixed with the crown ether (Table 6, entry 5), decomposition was observed. The crown ether was also added after the addition of the bromide to the reaction (Table 6, entry 6) to try and break up the potassium enolate in the presence of the bromide. Regrettably, decomposition still

occurred, possibly from side-reactions such as self-condensation or condensation with products.

The results for the reaction with 4-bromobut-1-ene were disappointing and seemed to suggest it may not be possible to synthesise the desired product *via* this route. However, we hypothesised replacement of the 4-bromobut-1-ene with allyl bromide for the synthesis of the 3,3- substrate may provide different results. This was reasoned as allyl halides undergo an S_N2' reaction as opposed to direct 1,2-nucleophilic substitution, which may be more amenable with this enolate.

Table 7. Enolate formation and allylation with allyl bromide



182 **185**

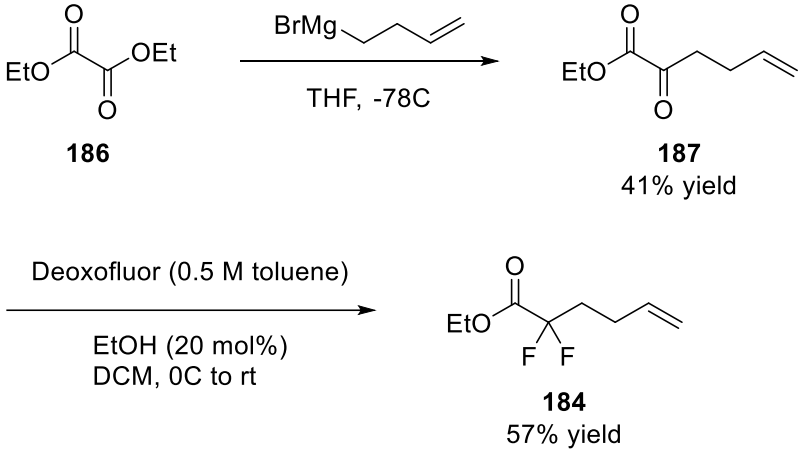
Entry	Base	Solvent	Temp / °C	Additive	Result	Yield %
1	LDA	THF	-78	-	Decomposition	-
2	LiHMDS	THF	-78	-	difluoroacetic acid	77
3	NaH	benzene	80	-	difluoroacetic acid	72
4	NaH	THF	-78	-	difluoroacetic acid	75
5	KHMDS	Toluene	-40	18-crown-6 (premixed)	Decomposition	-
6	KHMDS	Toluene	-40	18-crown-6 (after halide)	Decomposition	-

When the conditions for the reaction with 4-bromobut-1-ene were mirrored with allyl bromide (Table 7), very similar results were observed. When using LDA or KHMDS with 18-crown-6 (Table 7, entries 1,5 and 6) decomposition occurred again, and when LiHMDS or NaH was used, the only observable product was hydrolysed starting material. Overall, this suggests the major difficult in performing this reaction is less to do with the electrophile, but more to do with the formation and stability of the enolate. Therefore, other methods would be required in order to synthesise the difluorinated compounds required.

3.1.2. Synthesis of 2,2-difluoro precursors

Upon investigation of the literature, a report by Fustero *et al.* showed the synthesis of 2,2-difluoro-5-hexenoic acid with the keys step being a difluorination of an α-keto ester.[103] This acid is the same intermediate we were intending to make as a precursor to the Curtius rearrangement, making this procedure much more synthetically viable than the initial plan of direct alkylation of ethyl difluoroacetate. This route would have an additional step but there was clear precedent for the synthesis of the desired compound.

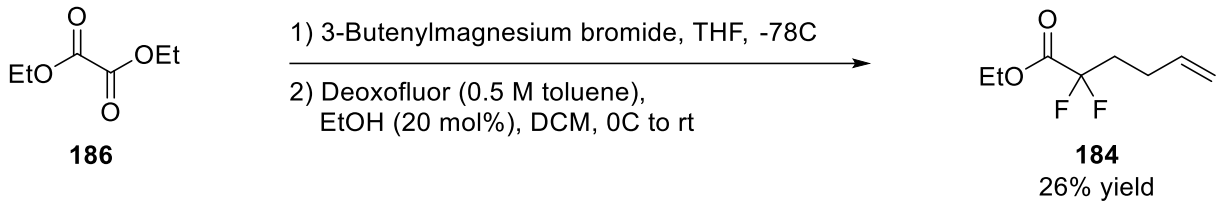
Following the same procedures as Fustero, we were able to obtain the α-keto ester **187** in 41% yield from diethyl oxalate (Scheme 57). The product of the Grignard addition **184** could potentially undergo further addition reactions explaining the lower yield.



Scheme 57. Synthesis of difluorinated ester

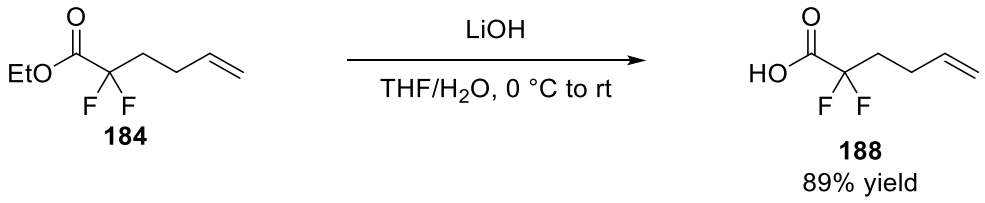
With the α-keto ester in hand, the fluorination step could be performed. This involved the use of the nucleophilic fluorinating agent bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-

Fluor®). The reactivity of this reagent is such that it can convert α-ketones and aldehydes into the corresponding geminal difluoride but leave the ester functionality intact. Gratifyingly, when the α-keto ester was subjected to the fluorination conditions, the difluoroester **184** was revealed in a 57% yield with an overall yield of 23% over the two steps (Scheme 57). While this gave sufficient material to work with, as the α-keto ester was prone to decomposition over time, it was imperative to perform the fluorination soon after isolation. To try and circumvent this instability, the reaction was telescoped to remove the column chromatography step used to purify the α-keto ester. Instead, the Grignard reaction was only treated with an aqueous work-up and the crude material then subjected to fluorination conditions. By performing the reaction over two steps, the yield of the difluorinated ester **184** was marginally increased to 26% from 23% and eliminated the need for chromatography after the first step (Scheme 58).



Scheme 58. Telescoped reaction for the synthesis if the difluorinated ester

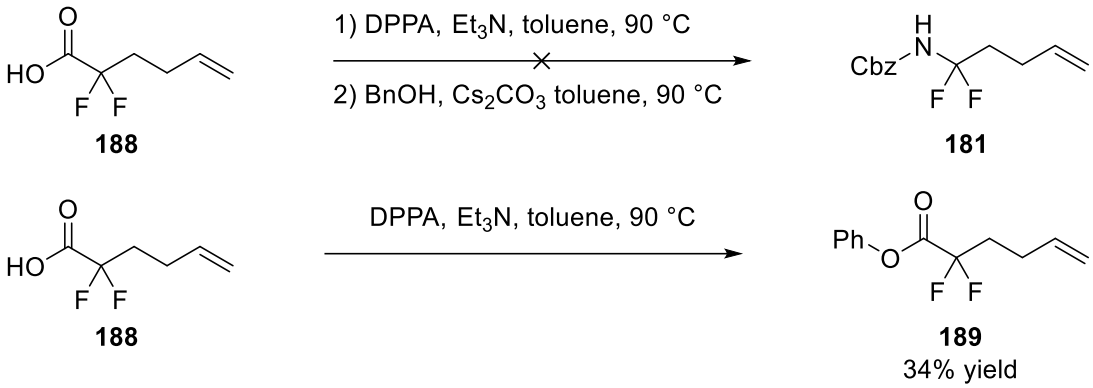
With the ester in hand, the next step was a hydrolysis to give the 2,2-difluoro-5-hexenoic acid. This was readily accessible from the ester through the use of LiOH in THF/H_2O, with the acid obtained in a very high 89% yield.



Scheme 59. Synthesis of 2,2-difluoro-5-hexenoic acid

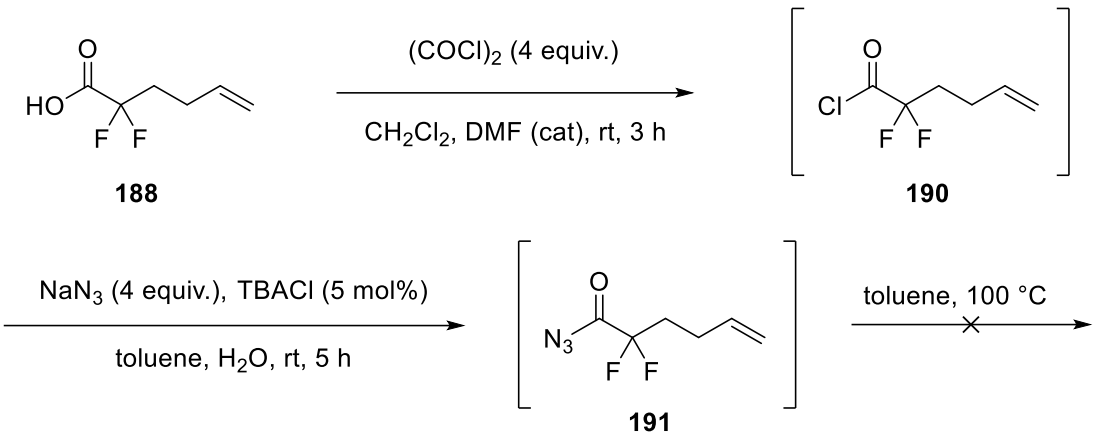
The acid **188** could then be subjected to Curtius rearrangement conditions that had been previously optimised, with DPPA followed by BnOH addition (Scheme 60). However, when using these conditions, no identifiable product could be observed. To try and simplify the reaction, the procedure was performed without the benzyl alcohol allowing for isolation of

the isocyanate product, which could then be subjected to either hydrolysis or benzyl alcohol conditions in a separate step. When the reaction was tested, the only product that was isolated was the difluorinated phenyl ester **189** with no isocyanate observed. It is believed that the DPPA formed the acyl azide as expected, but the intermediate does not undergo decomposition and rearrangement. Instead, the acyl azide is likely intercepted with phenol to give the phenyl ester **189** in 34% yield (Scheme 60). The sources of phenol are most likely from either the DPPA or phosphoryl by-products which may have liberated phenol at the elevated temperatures.



Scheme 60. Attempts at the Curtius rearrangement

To try and prevent the formation of the phenyl ester and to allow for isolation of the isocyanate, the reaction was modified to remove the DPPA. Instead the acyl azide was formed through the synthesis of acyl chloride **190** from acid **188** through the use of oxalyl chloride/DMF followed by sodium azide addition to the crude acyl chloride to give a crude acyl azide **191** (Scheme 61). Further purification of the acyl chloride or the acyl azide was not performed to try and prevent hydrolysis back to the starting carboxylic acid. Formation of the acyl azide was confirmed by infra-red (IR) spectroscopy with a distinctive azide stretch observed at 2148 cm^{-1}. The crude acyl azide was then heated in dry toluene to 100 °C to try and effect the Curtius rearrangement and isolate the isocyanate. This reaction was monitored by taking aliquots for IR analysis at 1, 13 and 20 hours, with an expected isocyanate stretch of 2275-2250 cm^{-1}.

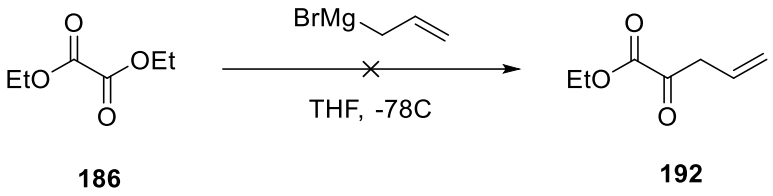


Scheme 61. Alternative procedure for the Curtius rearrangement

After 20 hours of reaction, the azide peak had completely disappeared, but over the course of the reaction no isocyanate was observed by IR and no free amine was recovered on workup. This suggests that the C-C bond which would normally insert into the nitrene is not nucleophilic enough, most likely because of the electrophilicity of the difluoro group. Due to this, a Curtius rearrangement approach will therefore likely be unfruitful for synthesising the 2,2-difluoroamine. Despite investigation of the literature, no alternative procedures were found that may enable the synthesis of a 2,2-difluoroamine, so further attempts at isolating the 2,2-difluoropyrroldine were not pursued.

3.1.3. Synthesis of 3,3-difluoro precursors

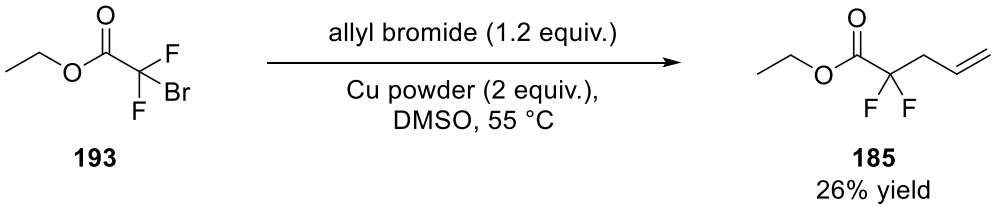
While this approach was not feasible for the 2,2-difluoroamine, there remained the possibility of using the Deoxo-Fluor® procedure in the synthesis of the 3,3-difluoroamine. To do this, the synthesis would need to be modified to use allylmagnesium bromide instead of forming the Grignard reagent from 4-bromobut-1-ene. Unfortunately, addition of allyl Grignard into diethyl oxalate was not successful despite multiple attempts, with only decomposition or multiple side products observed in the reaction (Scheme 62). It was reasoned that the allyl group may undergo a rearrangement to form the conjugated ketone which could then lead to other side reactions.



186 **192**

Scheme 62. Attempted addition of allylmagnesium bromide to diethyl oxalate

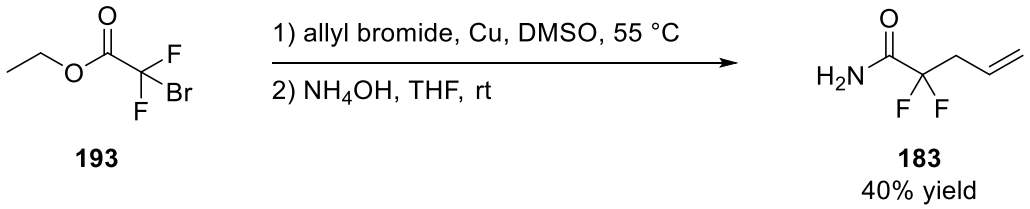
After searching the literature, an alternative procedure was found for the synthesis of the desired difluoroester from ethyl bromodifluoroacetate **193**. The method involved the use of copper powder and allyltributylstannane, with the authors suggesting the formation of a tributyl tin radical abstracting the bromide from ethyl bromodifluoroacetate.[104] This radical could then react further with the allyltributylstannane to form the desired product. However, the report gave no procedure or quantities for the synthesis. Fortunately, further literature investigation found a patent with a very similar method to produce the desired ester.[105] The method employed ethyl iododifluoroacetate and allyl bromide as the coupling reagents, which was much more appealing as it avoided the use of toxic stannanes. Due to availability of materials, ethyl iododifluoroacetate was replaced with ethyl bromodifluoroacetate **193** and the reaction tested. Gratifyingly, the reaction proceeded and the product was obtained in 26% yield (Scheme 63).



193 **185**
26% yield

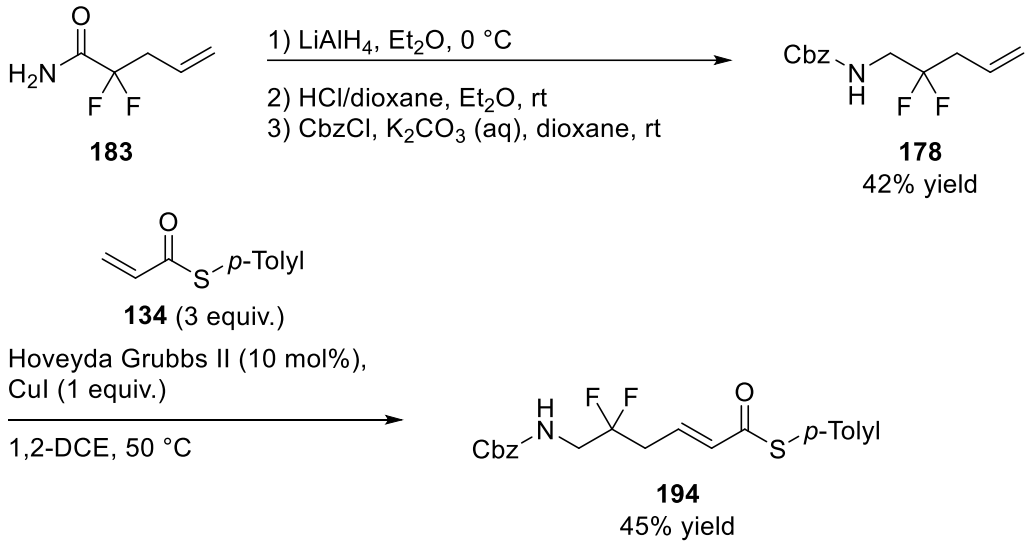
Scheme 63. Allylation of ethyl bromodifluoroacetate

The main difficulty with this reaction was the isolation of the product. The difluorinated ester **185** was volatile and could only be isolated through bulb-to-bulb distillation.[105] The following step in this reaction was the formation of the amide **183** by treatment of the ester with ammonium hydroxide in THF. To try and prevent loss of the ester, the reaction was telescoped to include the amidation of the crude ester after an aqueous workup (Scheme 64). Despite an additional step, the formation of the amide **183** was achieved in 40% yield over two steps, a significant improvement over the isolation of the ester on its own.



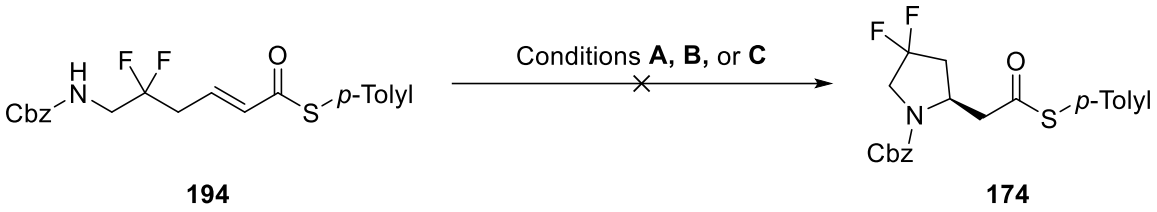
Scheme 64. Telescoped allylation and amidation

To obtain the desired Cbz protected amine, the amide was reduced using $LiAlH_4$ and the resultant amine trapped as the HCl salt. The amine hydrochloride was then 'cracked' with K_2CO_3 and subjected to benzyl chloroformate to give the Cbz protected amine **178** in 42% yield over the 3 steps. The Cbz amine **178** could then be subjected to the metathesis procedure, as had been done for other 3,3-disubstituted substrates, which yielded the metathesis product in a moderate yield of 45% (Scheme 65).



Scheme 65. Reduction and Cbz protection of 2,2-difluoroamide with subsequent metathesis

With the metathesis product in hand, the cyclisation procedure could then be tested. To obtain a racemate of the product for HPLC analysis, the 3,3-difluoro precursor was treated with rac-CSA in DCE at 50 °C. Unfortunately, no reaction was observed, with no product observed in the crude NMR. The reaction was also repeated with both (*R*)-TRIP and (*R*)-TiPSY catalysts in cyclohexane at 80 °C to test the optimised procedure for the asymmetric cyclisation. This also gave no observable product when analysing the crude NMR, with only starting material **194** observed (Scheme 66).



194 **174**

A. rac-CSA (3 equiv.) 1,2-DCE, 50 °C, 24 h
B. (*R*)-TRIP (20 mol%), cyclohexane, 80 °C, 24 h
C. (*R*)-TiPSY (20 mol%), cyclohexane, 80 °C, 24 h

Scheme 66. Attempted cyclisation of 3,3-difluoro pyrrolidine

The difficulty in trying to cyclise the precursor **194** was disappointing and it was reasoned that this poor reactivity was from electronic effects over steric effects. As stated earlier the relative size of the fluorine atom is small, and considering the propensity for sterically bulky substrates, such as the cyclohexyl-spiropyrrolidine to cyclise, steric effects were ruled out as the reason for this lack of reactivity. However, the high electrophilicity of fluorine may have reduced the effective nucleophilicity of the nitrogen atom. From this we can also infer that the 2,2-difluoro pyrrolidine would also be difficult to cyclise as the effects of the fluorine would be even more pronounced when α to the amine. Therefore, it was concluded that the synthesis of difluoro pyrrolidines using this methodology would not be possible.

3.2. Methyl substitution on Michael acceptor

Another avenue of interest was the introduction of a methyl group to the double bond of the Michael acceptor before cyclisation. Methyl substitution at the 5-position of the pyrrolidine would create a tetrasubstituted pyrrolidine giving access to novel enantiomers as well as a new quaternary centre. Introduction of an R group at the position alpha to the carbonyl would result in new diastereomers as analogues of pharmaceutically relevant compounds. A series of patents for kinase inhibitors show several drug molecules that use pyrrolidines as a terminal substructure in the active compounds.[106–109] Typically, the pyrrolidine is synthesised as an analogue of L-β-homoproline which is then coupled to the core of the drug through the carboxylic acid. Some examples of these pyrrolidine sub-units are shown in Figure 14.

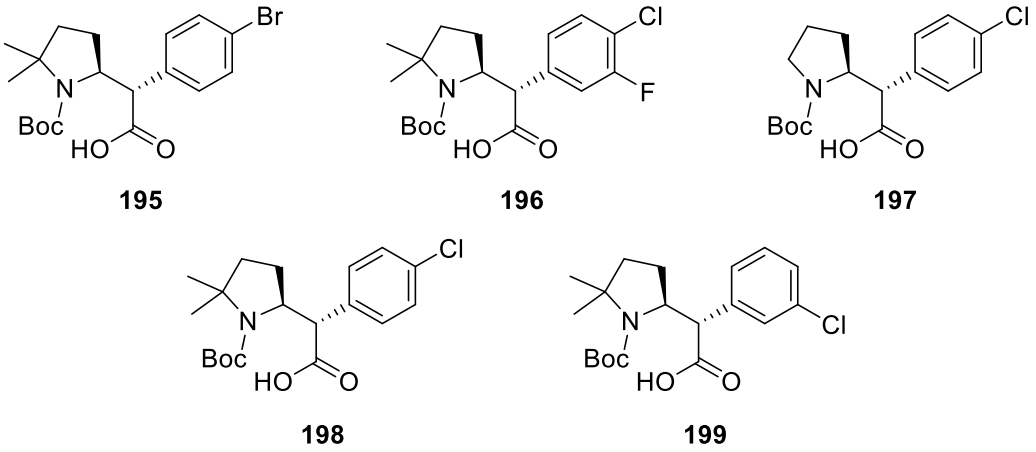
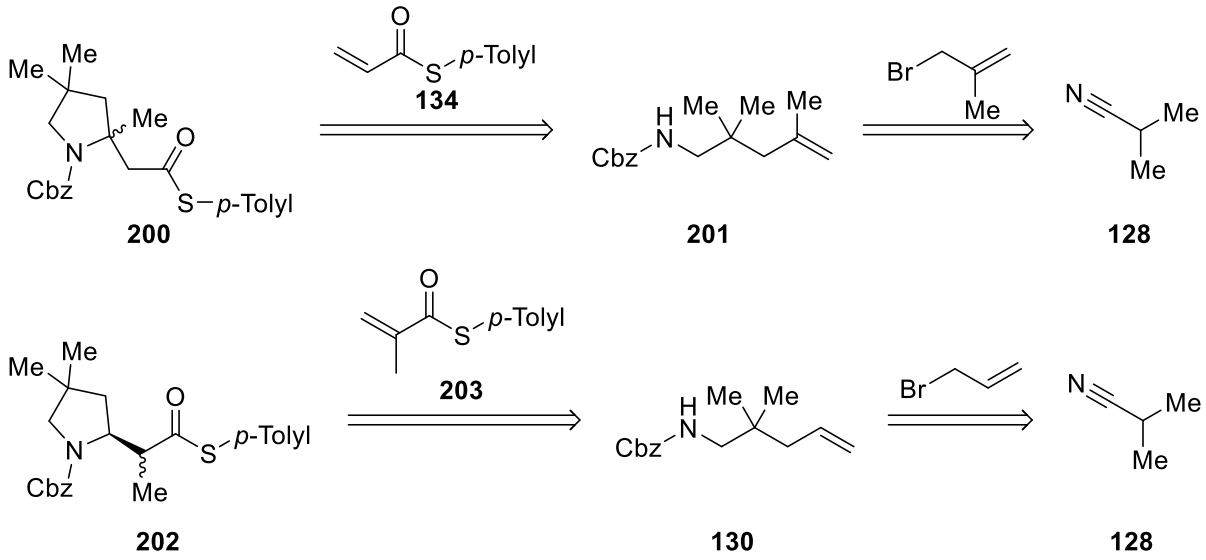


Figure 14. Intermediates in the synthesis of kinase inhibitors

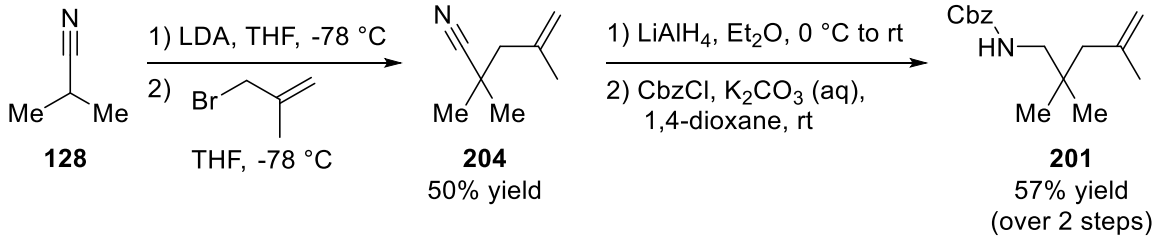
While these examples demonstrate an aryl substitution at the α-position, using methyl as an initial substituent would serve as a benchmark for reaction feasibility and the possibility of further substitution.

To introduce the methyl group, the procedure for the synthesis would have to be modified. To ensure both good conversion and enantioselectivity, it was decided to begin by testing the 3,3-dimethyl precursor, as this had given some of the best results in the initial cyclisation procedure. In order to produce a tetrasubstituted pyrrolidine **200**, the allyl bromide used in the alkylation of isobutyronitrile **128** would have to be replaced with 3-bromo-2-methylpropene. This could then be subjected to the metathesis conditions with the *p*-tolyl thioacrylate to give the double bond with methyl substitution at the β-position to the carbonyl. Introduction of the methyl at the α-position of the carbonyl would be done through modification of the thioester. Replacing acryloyl chloride with methacryloyl chloride would enable the synthesis of the *p*-tolyl 2-methyl-thioacrylate **203** to give the correct substitution (Scheme 67).



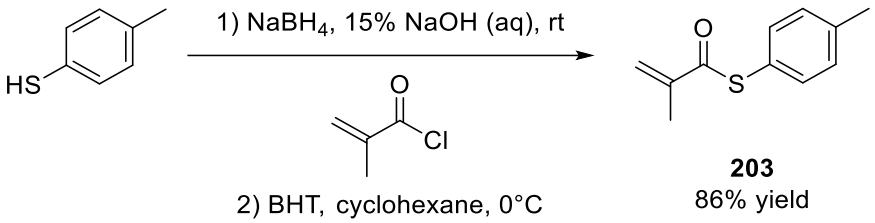
Scheme 67. Retrosynthetic analysis for the introduction of a methyl group onto cyclisation precursors

For the forward synthesis, the modified allylation of isobutyronitrile with 3-bromo-2-methylpropene gave a moderate yield of 50% for the nitrile **204** (Scheme 68). Subsequent reduction with lithium aluminium hydride and protection with benzyl chloroformate gave the Cbz protected amine **201** in 57% yield over the 2 steps.



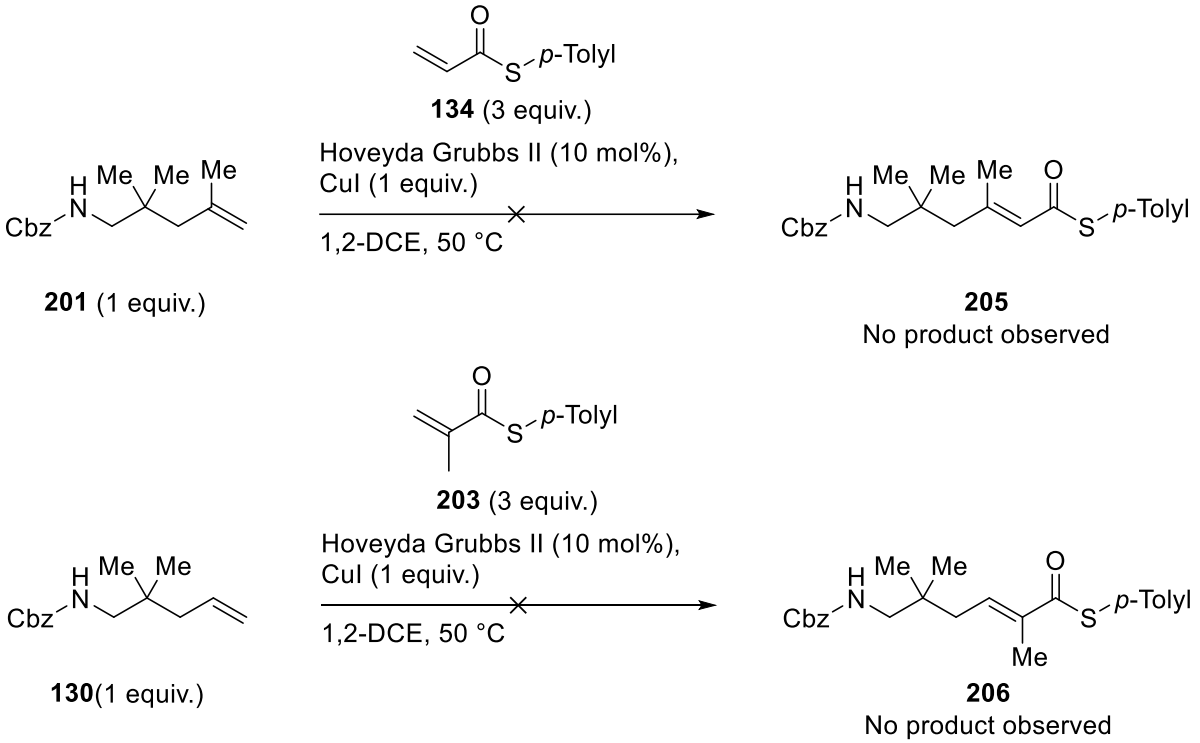
Scheme 68. Forward synthesis of methyl substituted Cbz amine

Similarly, the modification of the thioacrylate synthesis proved fruitful, giving the 2-methyl-thioacrylate **203** in a high yield of 86% (Scheme 69). The yield of this product was noticeably higher than that of the unsubstituted thioacrylate (68%), possibly due to less side reactions of the thioacrylate product. The unsubstituted thioacrylate shows a certain amount of 1,4-addition by-product from attack of the *p*-thiocresol during the reaction, but this is not observed in the methyl substituted thioacrylate.



Scheme 69. Forward synthesis of methyl substituted thioacrylate

With the methyl substituted precursors in hand, the next step was to monitor how each compound performed under the optimised metathesis conditions. Unfortunately, neither metathesis reaction yielded any of the desired product (Scheme 70).



Scheme 70. Attempted metathesis of methyl substituted precursors

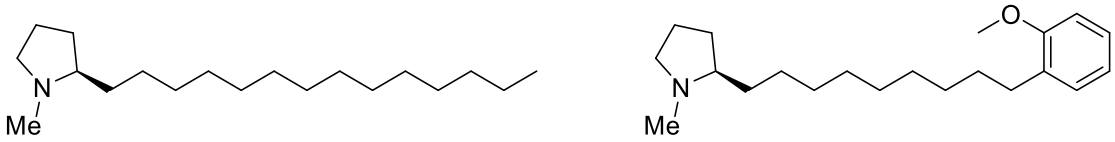
This result was disappointing but perhaps unsurprising. 1,1-disubstituted olefins are known to be less reactive than other monosubstituted olefins, as are α,β-unsaturated olefins, both of which are present in the precursors.[84] No further attempts were made to obtain the methyl substituted precursors using this method as the metathesis did not seem feasible with these substrates. Other synthetic routes for introduction of a methyl group may be possible but would likely involve substantial reworking of the current synthetic route and were not investigated.

3.3. Summary of results

Attempts at introducing fluorine around the pyrrolidine ring were not successful. The synthesis of the 2,2-difluoro precursor was not possible with the methods attempted, but the 3,3-difluoro precursor was synthesised after extensive testing of conditions and literature research. However, when attempting cyclisation under racemic or asymmetric conditions, no product was observed. This lack of reactivity was reasoned to be due to the high electronegativity of the fluorine atom affecting the nucleophilicity of the nitrogen atom, rendering cyclisation difficult. Introduction of methyl groups to the double bond was also met with limited success. Both the methyl substituted thioester and methyl substituted Cbz amine were synthesised readily using previously developed methods, however both compounds failed to undergo the necessary metathesis reaction to produce the cyclisation precursor.

4. Total Synthesis of Natural Products

The presence of pyrrolidine structures in pharmaceuticals has been documented and, according to one study, the pyrrolidine was the most prevalent 5-membered *N*-heterocycle in FDA approved small molecule drugs.[1] Pyrrolidines also feature prominently in many alkaloids which have been the target of total syntheses.[17,110,111] To demonstrate the utility of the pyrrolidine thioesters that have been synthesised, total synthesis of a natural product seemed a good demonstration. After literature examination, two candidates for total synthesis were targeted: (*R*)-bgugaine **207** and (*R*)-irnidine **208** (Figure 15).

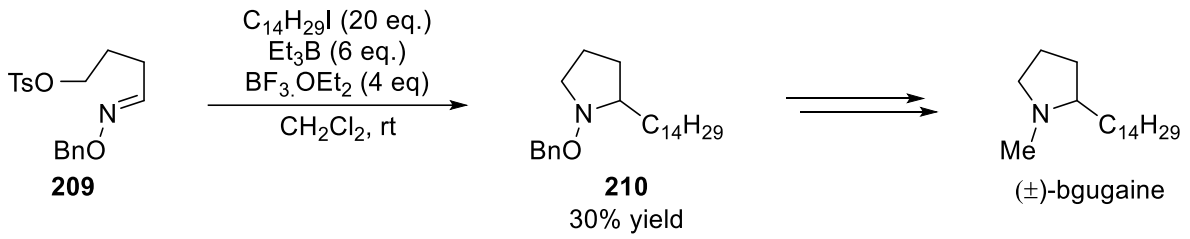


207 (*R*)-Bgugaine **208** (*R*)-Irnidine

Figure 15. Natural products (R)-bgugaine and (R)-irnidine

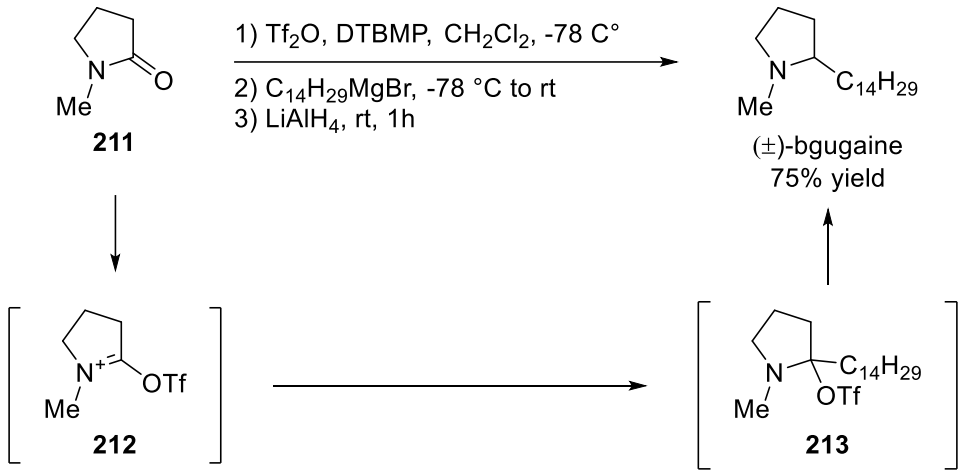
Both (*R*)-bgugaine and (*R*)-irnidine were isolated from the tubers of *Arisarum vulgare,* a plant widespread in Morocco.[112–114] In the initial isolation, these compounds were shown to be toxic in the brine shrimp bioassay (LC_{50} of 1.0 and 1.5 μg/ml respectively), with (*R*)-bgugaine demonstrating both antibacterial and antifungal properties.[112,113] Subsequently, (*R*)-bgugaine was shown to have affinity for binding to DNA as well as being a strong hepatotoxin in both rat liver cells and the human hepatoblastoma cell line $HepG_2$. [115,116] The cytotoxicity effects of bgugaine have also been demonstrated in the mouse mastocytoma cell line P815, and the human laryngeal carcinoma cell line Hep for both the (*R*)- and the (*S*)- enantiomer.[117] The IC_{50} values were recorded for the mastocytoma P815 as 10 and 5 μml^{-1} for (*R*) and (*S*) respectively, with carcinoma Hep requiring 5 and 100 μml^{-1} for (*R*) and (*S*) respectively. It should be noted that the (*R*)-isomer is the natural occurring isomer of bgugaine, and the (*S*)-enantiomer used in this study was acquired through enantioselective synthesis. This makes investigation into methods for asymmetric synthesis particularly useful due to the lack of natural source for the (*S*)-enantiomer, which has also been investigated separately for its cytotoxic effects on MRC-5 fibroblasts.[118] While a few racemic and asymmetric syntheses have been developed for the synthesis of bgugaine, there are no reports of the asymmetric synthesis of irnidine.

The racemic synthesis of bgugaine was achieved by Naito through a radical addition and ionic cyclisation of oxime ethers **209** (Scheme 71).[119] The reaction utilised triethyl borane as a radical initiator to generate an alkyl radical from the alkyl iodide. This radical was then able to add to the oxime to produce a nitrogen centred radical which was quenched by triethyl borane. The nitrogen-borane ionic adduct could then cyclise by displacing the tosylate group with loss of the borane. One of the limitations of the reaction is it uses a large excess of reagents to achieve cyclisation, with 20 equivalents of the alkyl iodide required for only 30% yield.



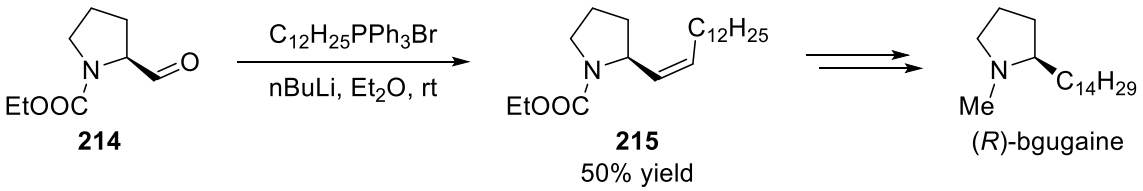
Scheme 71. Radical oxime route to the racemic synthesis of bgugaine

Another synthesis was reported by Huang starting from the lactam **211** (Scheme 72). Activation of the amide was achieved using triflic anhydride and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP). This led to an O-sulfonated iminium intermediate **212** that enabled addition of the Grignard reagent. After the addition, the intermediate triflate **213** was then reduced with lithium aluminium hydride to yield the natural product in 75% yield as a one pot procedure.[120]



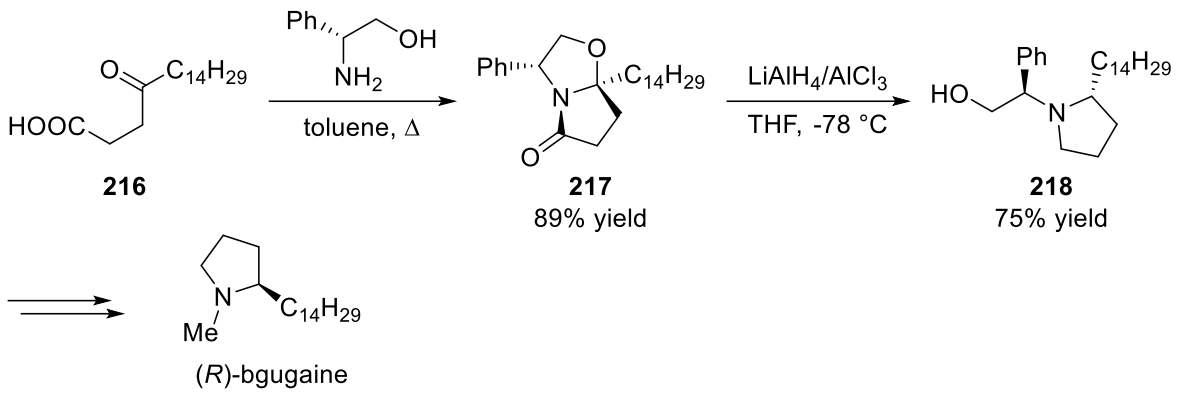
Scheme 72. One-pot reductive alkylation of lactams as a method for the synthesis of racemic bgugaine

For an asymmetric synthesis of bgugaine there have been 3 main methods of introducing the desired stereocentre: using a chiral starting material, a chiral auxiliary, or a chiral ligand during a synthetic step. The use of chiral starting material was demonstrated by Tilve *et.al.* through the use of (*S*)-*N*-carboethoxy prolinal **214**, a derivative of L-proline (Scheme 73).[121] Through a Wittig condensation, the alkyl chain required for (*R*)-bgugaine was installed in a 50% yield with subsequent transformations yielding the natural product. While this method is useful in providing the (*R*)-enantiomer of bgugaine, the (*S*) enantiomer could be more difficult to obtain in larger quantities using this strategy as it would require starting from D-proline. This can add extra costs as the 'unnatural' enantiomer can be up to twenty times more expensive than L-proline.



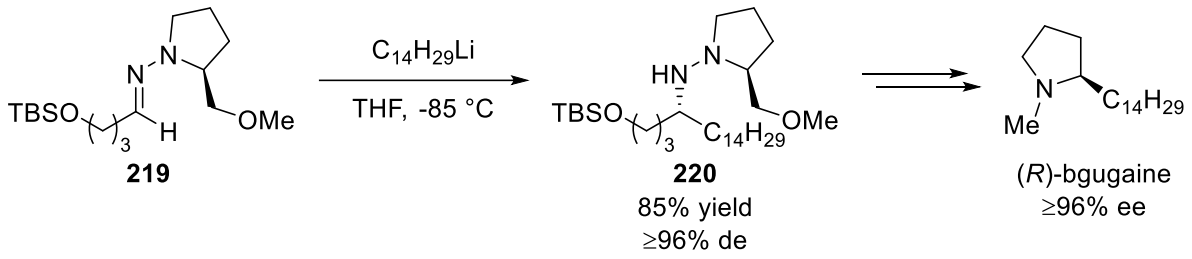
Scheme 73. Asymmetric approach to the synthesis of (R)-bgugaine from chiral starting material

Another method for the introduction of the desired stereocentre, is the use of a chiral auxiliary during the synthesis which is then later removed. One of the main advantages of this method is that the option for synthesizing opposite enantiomers can be more readily available than when using chiral starting materials. The earliest example of the synthesis of (*R*)-bgugaine was reported by Jossang *et.al.* where 4-oxooctadecanoic acid **216** underwent a condensation reaction with (*R*)-phenylglycinol to form the bicyclic lactam **217** in 89% yield (Scheme 74).[122] Treatment of $LiAlH_4/AlCl_3$ simultaneously reduced the lactam carbonyl and selectively ring-opened the oxazole to afford pyrrolidine **218** in 75% yield. Removal of the auxiliary and *N*-methylation led to (*R*)-bgugaine. This methodology has also been employed in the synthesis of the (*S*)-enantiomer to test the biological activity of the unnatural isomer.[117,118]



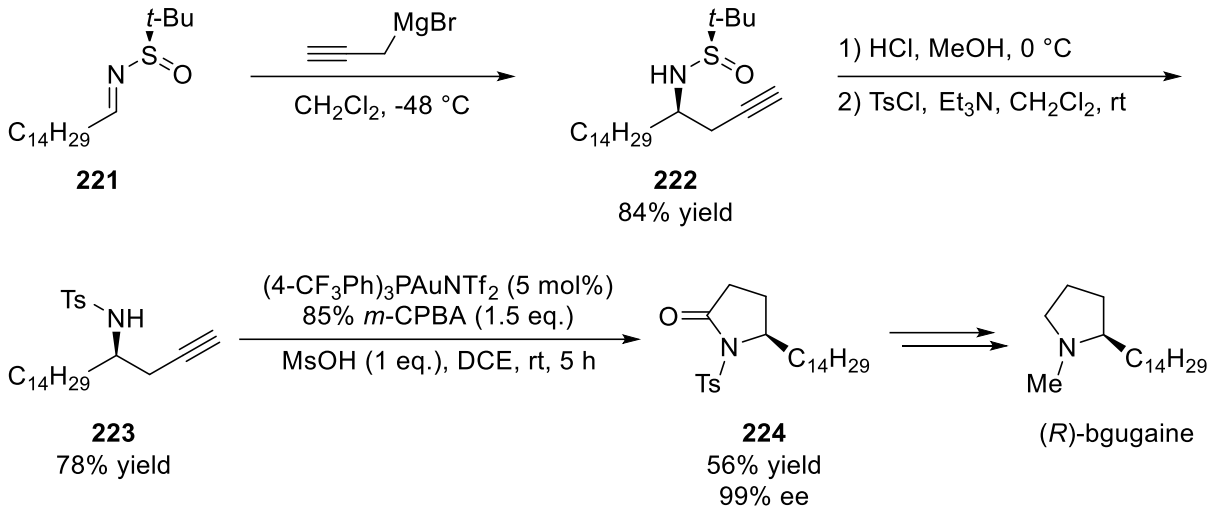
Scheme 74. Asymmetric approaches to the synthesis of (R)-bgugaine using a chiral auxiliary

An alternative approach has been to form chiral amines through nucleophilic addition to chiral imines. One example by Enders and Thiebes utilized the (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) chiral auxiliary to form hydrazone **219** (Scheme 75).[123] Tetradecyl lithium was then used as a nucleophile to give the hydrazide **220** in high diastereoselectivity (≥96% de) and yield (85%). Successive manipulations led to the natural product while maintaining the selectivity in the addition, with (*R*)-bgugaine synthesised with ≥96% ee. The same synthetic steps were used to synthesise (*S*)-bgugaine with an ee of 92% by using the opposite enantiomer of the chiral auxiliary, RAMP.



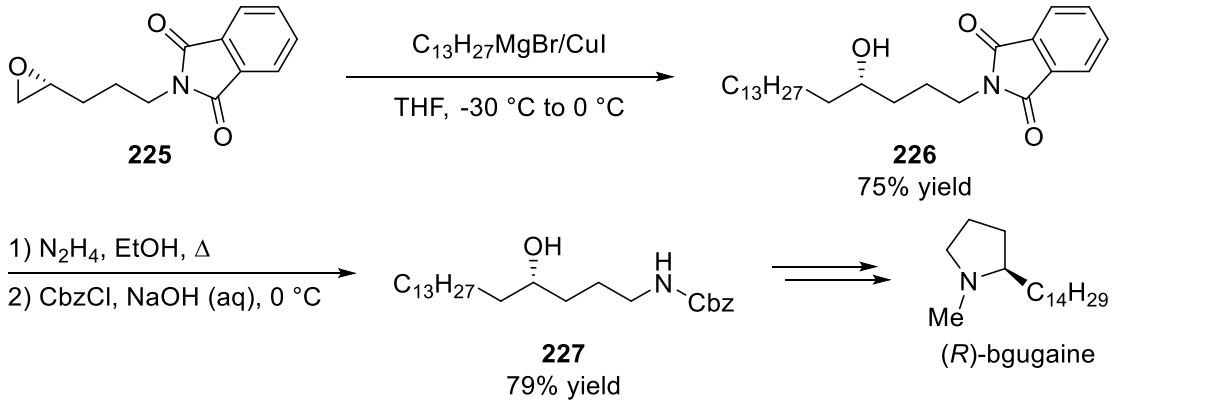
Scheme 75. SAMP approach to asymmetric synthesis of (R)-bgugaine

Another auxiliary used in the synthesis of chiral amines is the 'Ellman' (*R*)-*tert*-butylsulfinamide auxiliary. This approach was exploited by Shu *et.al.* with an asymmetric Grignard addition to the aldimine **221**, to isolate sulfinamide **222** in 84% yield as a single diastereomer (Scheme 76).[124,125] Removal of the auxiliary and replacement with a tosyl protecting group gave the chiral homopropargyl amide **223** in 78% yield over the two steps. This product could then undergo a gold catalyzed oxidative cyclisation to yield the lactam **224** in a moderate 56% yield. Further synthetic steps were taken to isolate (*R*)-bgugaine as a single enantiomer.



Scheme 76. Ellman auxiliary route to the asymmetric synthesis of (R)-bgugaine

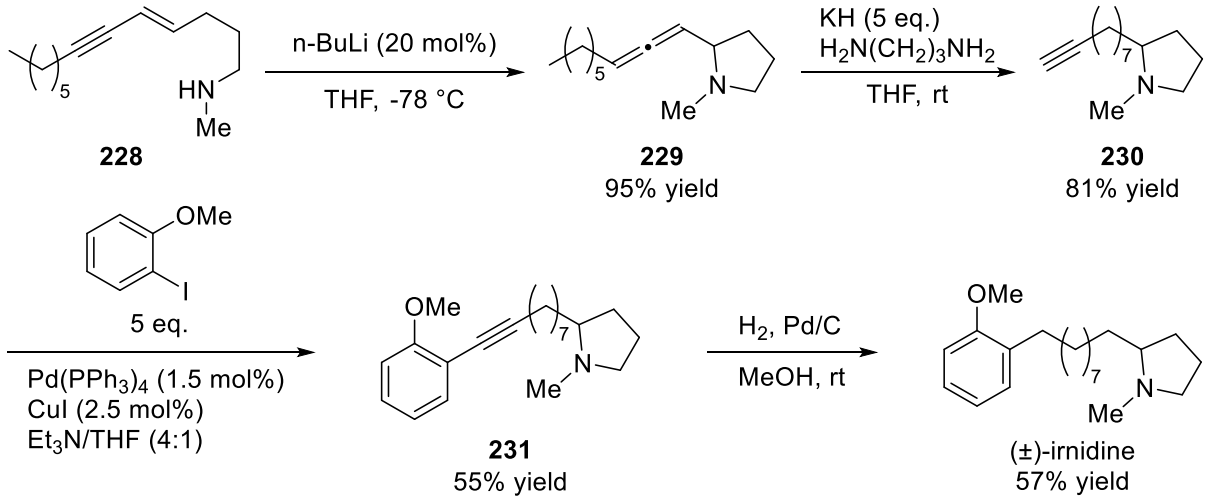
The only other asymmetric synthesis of (*R*)-bgugaine was reported by Takahata *et.al.* and employed a Sharpless asymmetric dihydroxylation and epoxidation to give the epoxide **225**. This could then undergo selective ring-opening with tridecanylmagnesium bromide to give the hydroxy phthalimide **226** in 75% yield, which was subsequently deprotected and reprotected to give the Cbz amine **227** in 79% yield. Further transformations led to the isolation of the natural product and, by modification of the Sharpless asymmetric dihydroxylation catalyst system, (*S*)-bgugaine was also isolated.



Scheme 77. Asymmetric approach to the synthesis of (R)-bgugaine through ring opening of a chiral epoxide

As stated earlier, the asymmetric synthesis of irnidine has not been achieved, but a racemic synthesis has been reported Zhang *et.al.* [126,127] The key step in the formation of the pyrrolidine ring was a base catalysed intramolecular hydroamination of conjugated enyne **228** to give allene **229** in 95% yield (Scheme 78). An alkyne zipper reaction was then used to give the

terminal alkyne **230** in good yield. Sonogashira coupling of 2-iodoanisole and reduction of the alkyne led to the formation of racemic irnidine in reasonable yields.



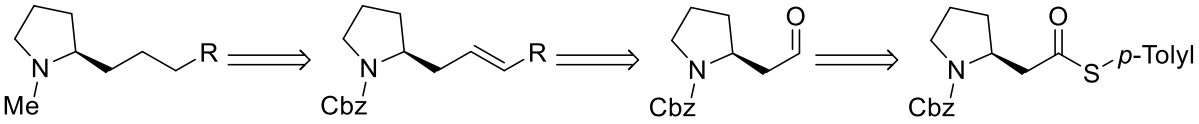
Scheme 78. Racemic synthesis of irnidine

While there are a few examples for the asymmetric synthesis of bgugaine, most introduce the stereocentre with chiral auxiliaries, and the only catalytic system still required stoichiometric quantities of oxidant. The chiral phosphoric acid catalysed cyclisation reported in this thesis offers the opportunity to create a novel catalytic method for the asymmetric synthesis of (*R*)-bgugaine and the first asymmetric synthesis of (*R*)-irnidine from a common intermediate. In order to achieve the highest possible enantiomeric ratio, the unsubstituted pyrrolidine was synthesised using (*R*)-TiPSY as the chiral catalyst to give an er of 94:6 for all starting pyrrolidines in this section.

4.1. Wittig route

The pyrrolidine thioester **164** can supply the core of both bgugaine **207** and irnidine **208**. Therefore, the main transformations required in the synthesis are the introduction of the alkyl chain to the 2-position and the conversion of Cbz to an *N*-methyl group. Access to the *N*-methyl should be simple, as Cbz can be converted directly into a methyl *via* reduction with $LiAlH_4$. Another process can be the removal of the Cbz followed by reductive amination with formaldehyde. The more problematic part of the synthesis is the installation of the sidechain. Initially, it was hoped that the molecule could be synthesised via a Wittig reaction (Scheme 79). Reduction of the thioester **164** to the corresponding aldehyde **234** could then allow for

a Wittig reaction to give alkenes **232** and **233**. Further reductions of the alkene and Cbz could then lead to the natural products.

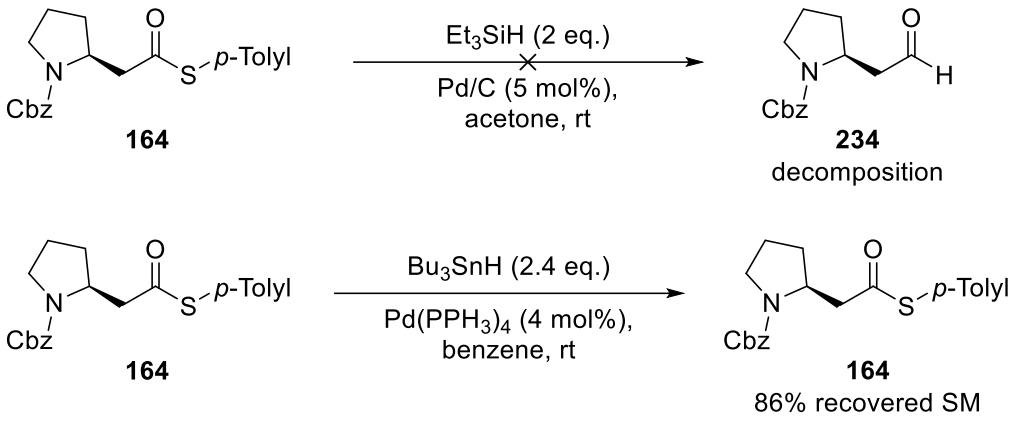


207, 208 **232, 233** **234** **164**

207, 232, R = $C_{11}H_{23}$
208, **233**, R = $(CH_2)_6C_6H_4OMe$

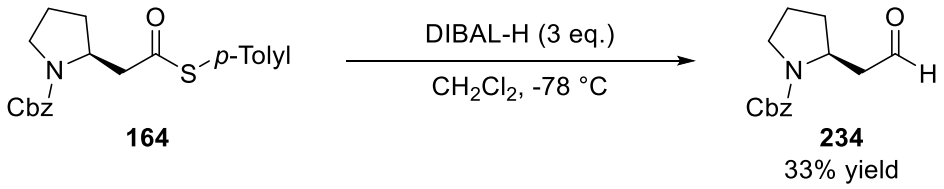
Scheme 79. Retrosynthetic analysis via aldehyde formation and Wittig reaction

The transformation of thioesters into aldehydes offer a few synthetic challenges, mainly controlling the level of reduction, as it can be possible to over reduce the more reactive aldehyde and obtain an alcohol. To try and counter this, methods of reduction have been investigated to reduce thioesters which stop at the aldehyde without over reduction. One of the earliest methods reported is the Fukuyama reduction using triethylsilane as the reducing agent, and was developed as an approach for accessing aldehydes from carboxylic acids without reduction to the alcohol and subsequent oxidation.[128] In the presence of catalytic palladium in acetone, triethylsilane was able to reduce ethyl thioesters to the aldehyde in good to excellent yields. However, when this procedure was attempted on thioester **164**, no aldehyde was formed and only decomposition was observed (Scheme 80). Another similar method was developed shortly after by Sonoda to reduce aryl thioesters in the presence of thioalkenes using tributyltin hydride and a palladium catalyst.[129] Again the conditions were tested on thioester **164** but failed to yield any product with 86% of starting material recovered (Scheme 80).



Scheme 80. Attempts at palladium catalysed reduction of thioester

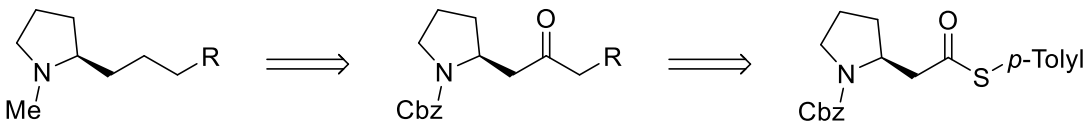
As the palladium reactions were unsuccessful, an alternative approach was considered. The use of DIBAL-H to reduce esters to aldehydes is well practiced in organic synthesis, and there have also been reports of this approach being applied to thioesters.[130] The main difficulty in using this reagent is DIBAL-H can also be used to reduce esters to alcohols if conditions are not controlled. However, by maintaining cryogenic temperatures and using controlled addition of the reducing agent, DIBAL-H was able to reduce the thioester **164** to the aldehyde **234** in 33% yield which matched literature data.[131] While the reduction was successful, the low yield for this reaction was not encouraging and this route was not investigated further.



Scheme 81. Reduction of thioester to aldehyde with DIBAL-H

4.2 Liebeskind-Srogl coupling route

As the Wittig route had been abandoned, other methods for the introduction of the sidechain were researched. One such reaction is the Liebeskind-Srogl coupling, a cross coupling reaction between thioesters and aryl boronic acids to synthesise ketones.[132] The reaction has also been modified to introduce alkyl chains by replacing the boronic acid with a *B*-alkyl-9-BBN derivative.[133] By using the modified procedure it should be possible to couple the correct side chains for the natural products, and then remove the ketone through a deoxygenation procedure (Scheme 82).

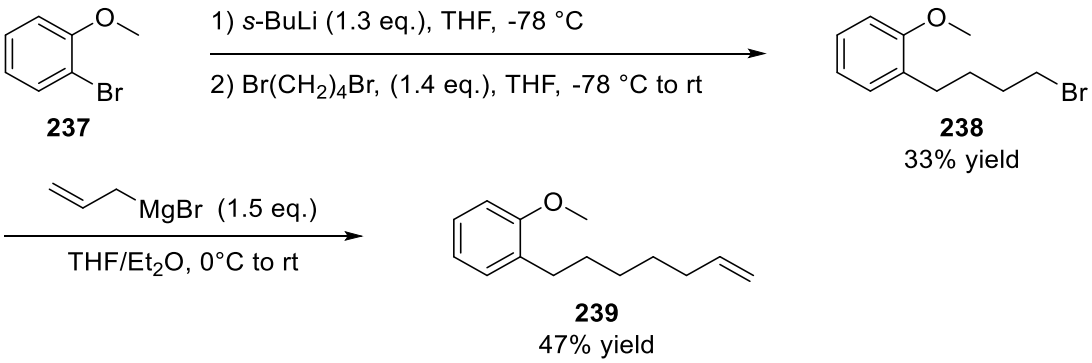


207, 208 **235, 236** **164**

207, 235, R = $C_{11}H_{23}$
208, 236, R = $(CH_2)_6C_6H_4OMe$

Scheme 82. Retrosynthetic analysis via Liebeskind-Srogl coupling and deoxygenation

The alkyl boron reagent can be synthesised readily via the hydroboration of the relevant alkene using 9-BBN under inert conditions to prevent oxidation to the alcohol. To install the sidechain of bgugaine, the alkene required is commercially available 1-dodecene, but the alkene required for irnidine needed to be synthesised. This was achieved through lithiation of 2-bromoanisole **237** with *s*-BuLi followed by alkylation with 1,4-dibromobutane to give bromide **238** in 33% yield (Scheme 83).[134] This low yield is likely due to overreaction with the lithiated anisole, giving a double addition product, as well as difficulties in separating the starting material and product with chromatography. The low yield was offset by the reaction being performed on a multigram scale to give good quantities of material for further reactions. The bromide **238** the underwent nucleophilic substitution with allylmagnesium bromide to give the alkene **239** in 47% yield.



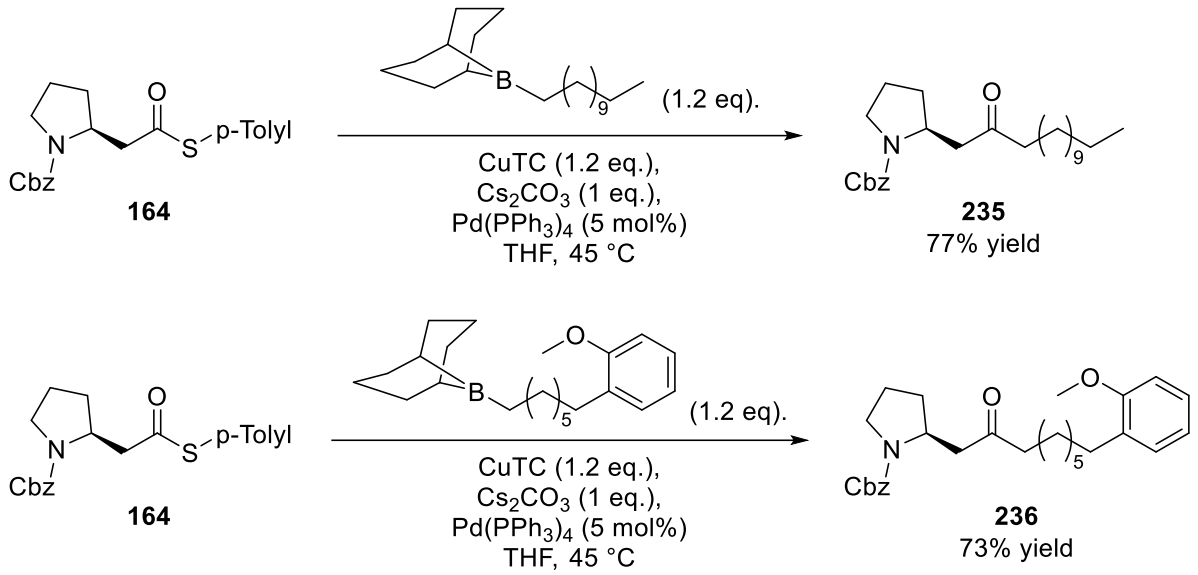
237 **238** 33% yield

239 47% yield

Scheme 83. Alkene synthesis for irnidine sidechain

With the alkene in hand, the Liebeskind-Srogl coupling could be tested. As mentioned earlier, the alkenes could be converted easily into the *B*-alkyl-9-BBN derivative through addition of 9-BBN. This solution of the boron reagent was then added to a degassed solution of the

thioester with CuTC, Cs_2CO_3 and the palladium catalyst. The reaction proceeded smoothly for both reagents, with the dodecyl product **235** isolated in 77% yield and the (2-methoxyphenyl)alkyl product **236** isolated in 73% yield.



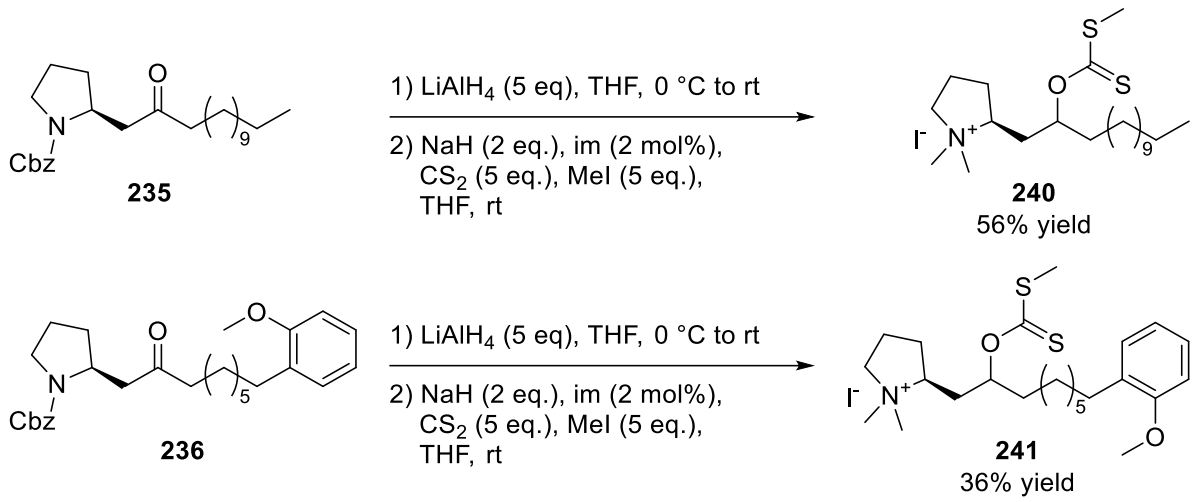
Scheme 84. Liebeskind-Srogl coupling to install the alkyl sidechains of bgugaine and irnidine

4.2.1 Alcohol deoxygenation

Once the ketones were synthesised, the next step was deoxygenation, for which multiple methods exist in the literature. The first of these that was investigated was a Barton-McCombie deoxygenation of a xanthate ester.[135] The deoxygenation occurs when tributyltin hydride and AIBN are used to effect a homolytic cleavage of the C-O bond of a xanthate ester. Quenching of the carbon radical by hydrogen atom transfer then leads to the overall replacement of a C-O bond with C-H. In the case of the Liebeskind-Srogl coupled products, the ketone must be reduced to the secondary alcohol in order to then form the required xanthate ester.

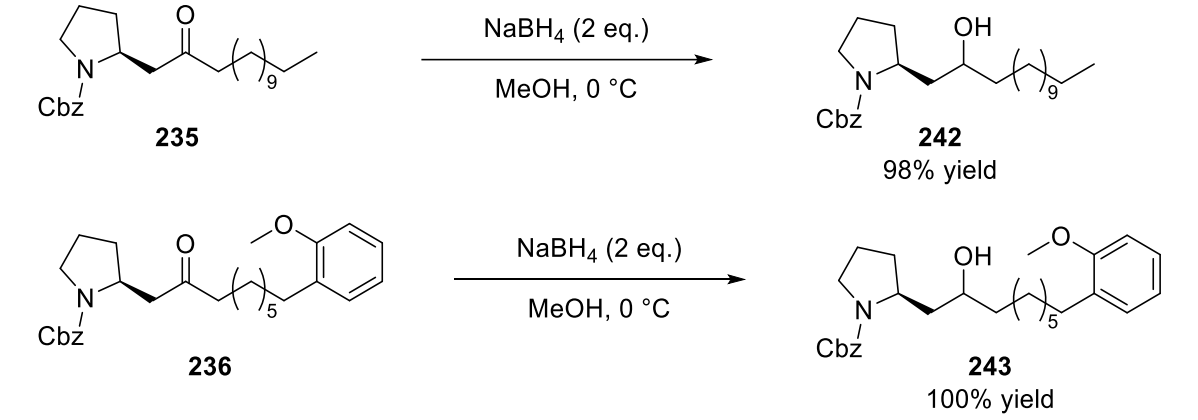
As the natural product had an *N*-methyl group, the global reduction using lithium aluminium hydride would allow for the synthesis of both the secondary alcohol and the reduction of the Cbz. This was done with a large excess of reducing agent and the product used without further purification. The secondary alcohol was deprotonated using sodium hydride/imidazole and intercepted with carbon disulfide to form the xanthate sodium salt, which was then alkylated using methyl iodide to form the xanthate ester. However, the excess of methyl iodide also

produced the quaternary ammonium salts **240** and **241** through over alkylation of the nitrogen in low to moderate yields (Scheme 85).



Scheme 85. Formation of xanthate esters

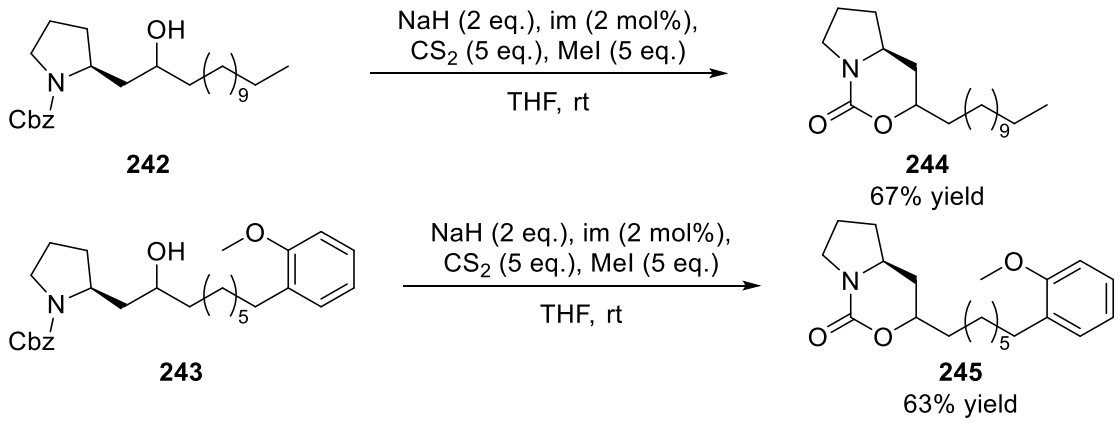
While this reaction was unforeseen, it did indicate that a global reduction strategy would not be useful. Therefore, separate reduction steps would be required, and the ketone was reduced using sodium borohydride. This preceded smoothly giving near quantitative yields for both substrates **242** (98%) and **243** (100%) (Scheme 86).



Scheme 86. Reduction of ketone with sodium borohydride

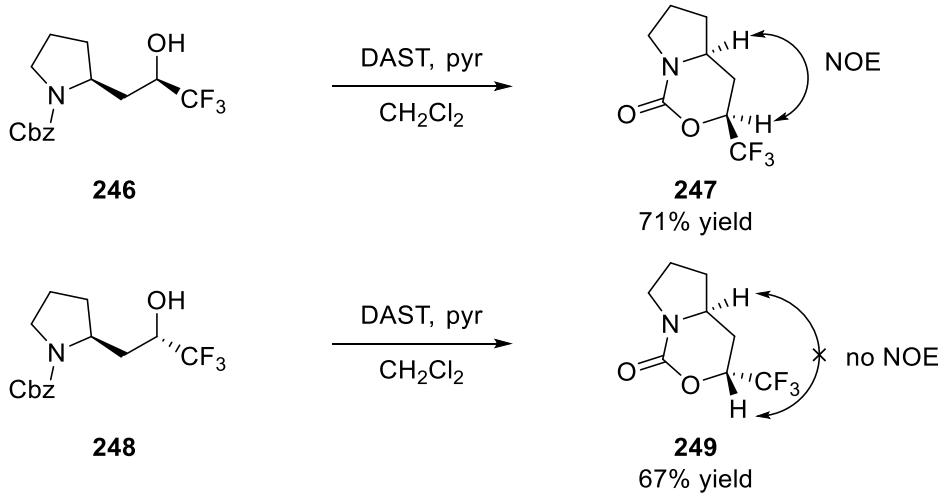
With the secondary alcohols in hand, the formation of the xanthate was tested using the same conditions as before (deprotonation with NaH, trapping with CS_2, and methylation with MeI). While formation of a quaternary ammonium was not observed, another product was formed instead of the xanthate ester. During deprotonation of the secondary alcohols, a cyclization

of the alkoxide onto the Cbz protecting group occurred to form the cyclic carbamates **244** and **245** (Scheme 87). The location of the alcohols meant that a 6-exo-trig ring closure could occur preferentially to an intermolecular reaction with carbon disulfide.



Scheme 87. Attempted formation of xanthate ester and resultant carbamate cyclisation

The cyclisation of alcohols onto a Cbz group has been reported before by Cossy and Pardo as a method of determining the relative stereochemistry of trifluoromethyl pyrrolidines.[136] The use of DAST and pyridine in dichloromethane led to the formation of a bicyclic system from trifluoromethyl pyrrolidines **246** and **248** (Scheme 88). NOE studies allowed the group to determine the relative stereochemistry of the trifluoromethyl group to the proton of the pyrrolidine.



Scheme 88. Studies by Cossy and Pardo into the relative stereochemistry of trifluoromethyl pyrrolidines.

Comparison of the ^{1}H NMR data for the bicyclic products **247** and **249** reported by Cossy and Pardo enabled easier assignment of the bicyclic carbamates synthesised in Scheme 87. Attempted formation of xanthate ester and resultant carbamate cyclisation. Figure 16 shows a section of the ^{1}H NMR of product **244** with the key C-H peaks for the bicyclic product highlighted. The protons assigned as H-7 allow for a determination of the diastereomeric ratio of the sodium borohydride reduction as 6:1, although further NOE studies to determine the relative stereochemistry were not performed, as this was deemed unnecessary for the purposes of the total synthesis.

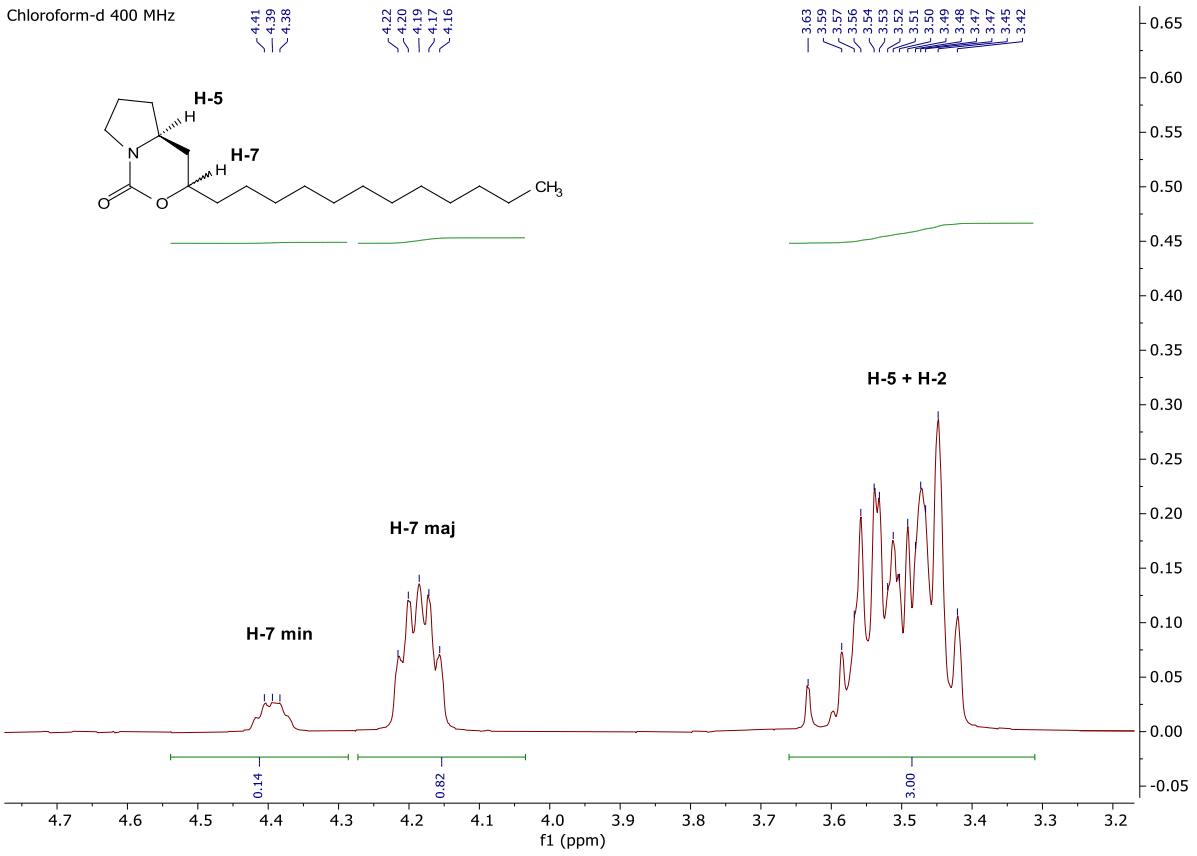
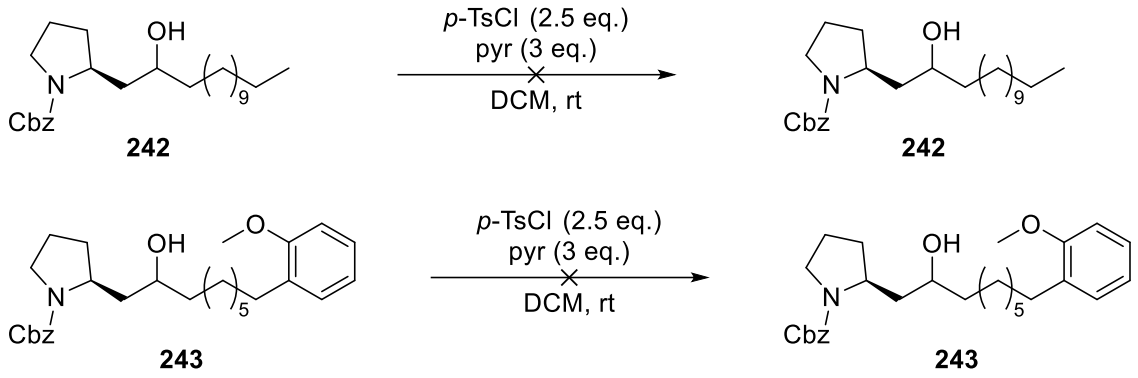


*Figure 16. ^{1}H NMR spectrum of bicyclic carbamate **244** showing key identifying peaks*

This result meant that any steps involving the deprotonation of an alcohol would likely be unproductive when trying to remove the alcohol. To try and counter this, an alternative approach was tested through the tosylation of alcohol **242** and **243**. As pyridine is used in this reaction, it does not deprotonate the alcohol but acts as a base to sequester HCl as a by-product. Unfortunately, no product was isolated from this reaction and starting material was recovered (Scheme 89).



Scheme 89. Attempted tosylation of alcohol

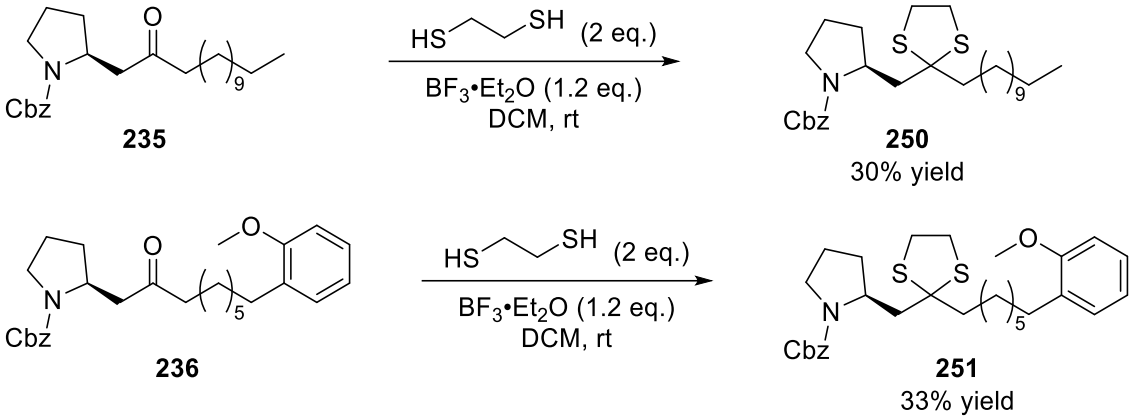
As the alcohols had proved resistant to deoxygenation, efforts were instead focused on the manipulation of the ketone for a more direct removal of the oxygen.

4.2.2 Dithiolane synthesis

One method that can be used to reduce ketones to an alkane is through a desulfurization reaction, which proceeds via the formation of a dithioacetal, followed by reduction with Raney®-Nickel under a hydrogen atmosphere.[137] The desulfurization is seen as a milder version to other related reductions such as the Clemmensen or Wolff-Kishner reductions which generally require more forcing conditions (strong acids or bases, and heat). The desulfurization conditions (Raney®-Nickel/H_2) may also lead to deprotection of the Cbz group, but as there are methods for introduction of the *N*-methyl, this reaction would not affect the overall step count.

The formation of the thioacetal of ketones **235** and **236** was performed using 1,2-ethanedithiol with boron trifluoride diethyl etherate as the Lewis acid.[138] Dithiolanes **250** and **251** were isolated in 30% and 33% yield respectively (Scheme 90). It was theorised that the low yields were due to side reactions of the $BF_3{\cdot}Et_2O$ with the Cbz group, as BCl_3 had been

previously shown to deprotect the pyrrolidine. As the yields were particularly low, this route was not investigated further.



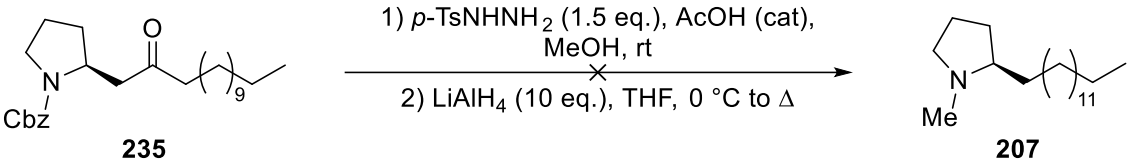
Scheme 90. Synthesis of dithiolanes

4.2.3 Wolff-Kishner reduction

An alternative to the desulfurization reaction that can be used to reduce a ketone to an alkane is the Wolff-Kishner reduction.[139] This reaction is generally performed through the *in situ* generation of a hydrazone from a ketone or an aldehyde using hydrazine hydrate. The hydrazone is then heated in the presence of a strong base to generate the alkane through loss of N_2. While this can be effective in deoxygenating the relevant compound, the forcing conditions can be unsuitable for certain substrates, and functional group tolerance can be low. To circumvent this, a number of modifications have been developed that can use lower temperatures or milder reagents to effect the same result. One such procedure is the Caglioti modification, which uses *p*-tosyl hydrazide in place of hydrazine hydrate and replaces the base with a hydride source.[140] The original conditions tested the deoxygenation of various steroids by forming the tosylhydrazone which was then refluxed in THF (66 °C) in the presence of lithium aluminium hydride to afford the alkane. These conditions were appealing for the synthesis of bgugaine and irnidine, as the use of $LiAlH_4$ would provide a telescoped reaction where both the ketone could be removed and the Cbz group could be converted into the *N*-methyl group required in the product.

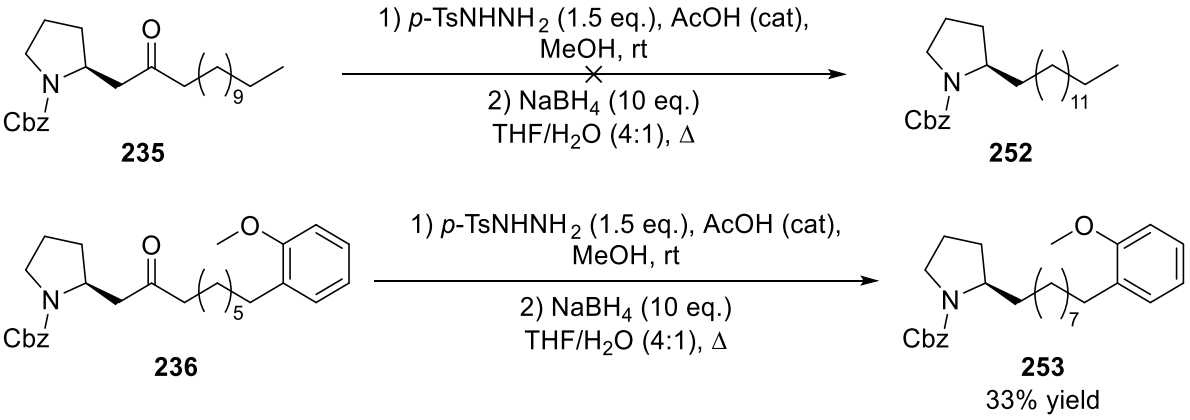
To test this, the tosylhydrazone of ketone **235** was formed through addition of *p*-tosyl hydrazide in MeOH with a catalytic amount of acetic acid. The formation of the hydrazone was monitored by TLC and, once all the ketone had been consumed, the reaction was

quenched. After an aqueous work up the crude hydrazone was passed through a silica pad filtration to remove excess hydrazide and the tosyl hydrazone was used without purification. Subjecting the hydrazone to $LiAlH_4$ conditions resulted in multiple decomposition products, with no isolatable quantity of product (Scheme 91). This reaction was only tested on the dodecyl ketone **235** due to availability of material.



Scheme 91. Attempted Wolff-Kishner reduction using lithium aluminium hydride for global reduction

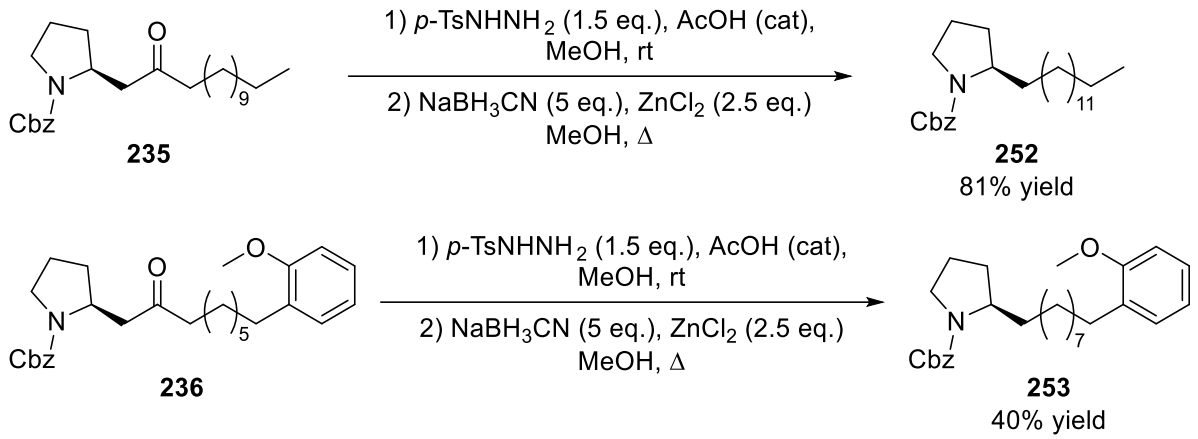
As the $LiAlH_4$ had not been successful, it was deemed prudent to test the reaction in a sequential manner by performing the Wolff-Kishner reduction with a milder reducing agent first, and then convert the Cbz to the *N*-methyl in a separate step. The reaction was tested on both the dodecyl **235** and (2-methoxy-phenyl)-heptanyl **236** ketones with sodium borohydride used as the reducing agent in THF/H_2O. While the reaction failed to yield product for the dodecyl ketone, the irnidine precursor **253** was isolated in 33% yield (Scheme 92).



Scheme 92. Wolf-Kishner reduction using sodium borohydride in THF/H_2O

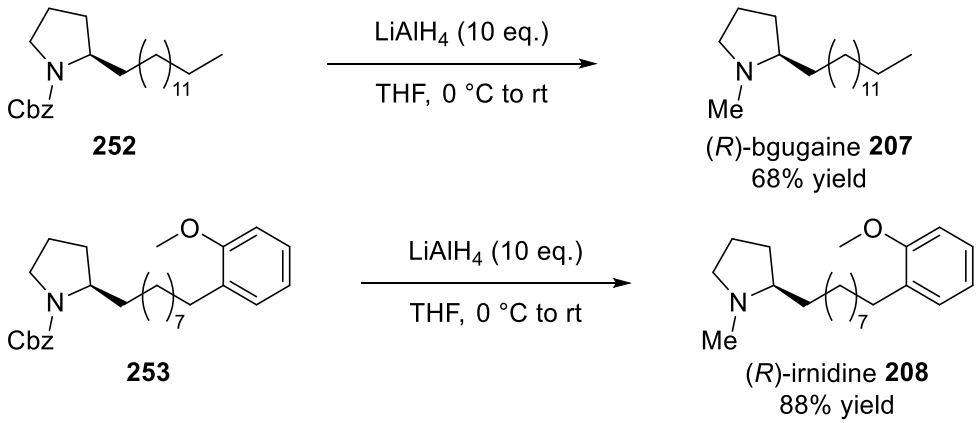
It is unclear as to why this reaction did not work for the dodecyl substrate, but the results for the irnidine precursor were promising. Upon literature investigation, a report by Kim showed the use of zinc-modified cyanoborohydride as a selective reducing agent that could be applied to the deoxygenation of aldehydes and ketones *via* tosylhydrazones.[141] This reducing agent has also been applied to the construction of *Iboga* alkaloids by Sames for the deoxygenation

of sterically hindered tosylhydrazones.[142] Application of this method on dodecyl ketone **235** resulted in a very good yield of 81% for bgugaine precursor **252**, while ketone **236** gave a minor improvement over the sodium borohydride reduction with a yield of 40% the irnidine precursor **253** (Scheme 93). While the improvement for the irnidine precursor was not substantial, the ability to isolate the bgugaine precursor in a high yield using this reaction procedure gives more synthetic viability to this route than the other approaches tested.



Scheme 93. Wolff-Kishner reduction using sodium cyanoborohydride

Reduction of the Cbz group with $LiAlH_4$ had already been demonstrated when attempting the Barton-McCombie deoxygenation previously. Following the same method with an excess of $LiAlH_4$ in THF, revealed (*R*)-bgugaine **207** in 68% yield and (*R*)-irnidine **208** in 88% yield with both compounds matching spectroscopically to the literature (Scheme 94).[112,113]



Scheme 94. Cbz reduction to reveal the natural products

Optical rotations can be used as a measure for the enantiomeric purity of a synthesised compound through calculation of the enantiomeric ratio. The natural products were synthesised from the starting pyrrolidine **164** cyclised by the (*R*)-TiPSY with an enantiomeric ratio of 94:6. Racemisation of the chiral centre of the pyrrolidine was not expected in any of the synthetic steps, but comparison of the optical rotation with the literature reported values would provide a good confirmation. The values measured for each product are listed in Table 8 along with the literature values and form these the enantiomeric ratio calculated. For (*R*)-bgugaine, the er had apparently dropped from 94:6 to 92:8 (entry 1), while for (*R*)-irnidine the er had increased to 95:5 (entry 2). While the calculated values do not exactly match those expected, the difference is not great, and error in either measuring the optical rotation or the concentration of the product being analysed could account for those errors. Importantly, both compounds rotated the plane of polarised light in an l-rotary direction, indicated by the negative sign. Both the measured and literature values demonstrate a negative sign, which shows that the synthesised compounds were both the (*R*) enantiomers.

Table 8. Optical rotations of the natural products compared to literature values

Entry	Compound	Measured $[\alpha]_D^{20}$	Lit. $[\alpha]_D^{20}$	Calculated er	Expected er
1	(*R*)-bgugaine	-35.9° MeOH	-42.5° MeOH [143]	92:8	94:6
2	(*R*)-irnidine	-18.2° $CHCl_3$	-20.0° $CHCl_3$ [113]	95:5	94:6

NMR analysis confirmed the synthesis of the natural products. In the case of (*R*)-bgugaine the ^{1}H NMR showed an integration of 39 protons corresponding to the number of protons in the natural product (Figure 17). A triplet with an integration of 3H was observed at 0.84 ppm, alongside a large peak at 1.34 – 1.06 ppm which integrated to 25H. Both of these peaks are indicative of a long aliphatic chain, as seen in (*R*)-bgugaine. The N-Me group is also distinctly visible at 2.29 ppm integrating to 3H, while the CH_2 protons in the pyrrolidine ring α- to the nitrogen are indicated by the peaks at 3.05 and 2.10 ppm. These assignments are supported by literature assignments performed during the initial isolation.[112]

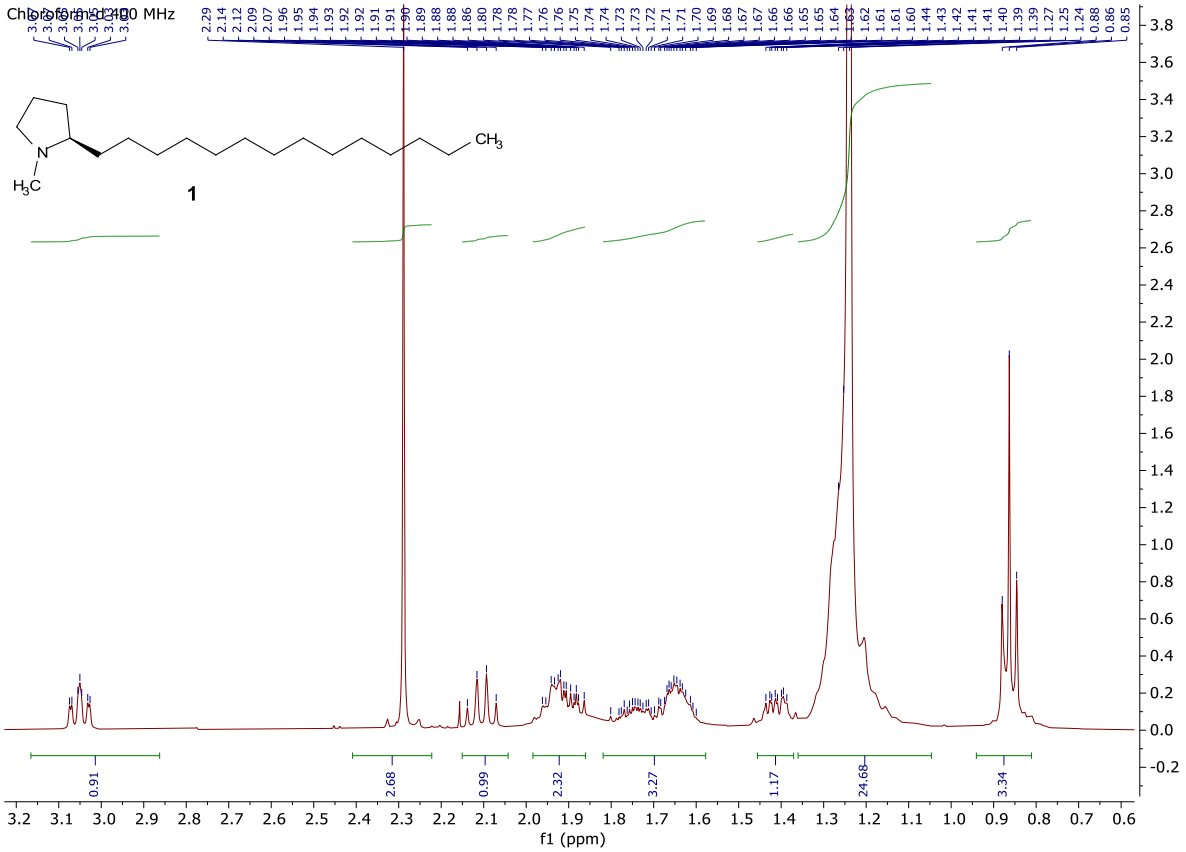


Figure 17. ^{1}H NMR spectrum of (R)-bgugaine

For (*R*)-irnidine assignments of the ^{1}H NMR were performed in a similar way to (*R*)-bgugaine and the ^{1}H NMR spectra for (*R*)-irnidine is shown in Figure 18. Upon integration of the peaks, the total number of protons was calculated as 35, equal to the number of protons in (*R*)-irnidine. The N-Me peak was observed at 2.29 ppm, analogous to that of (*R*)-bgugaine, and the additional CH_3 peak for the O-Me was assigned as the singlet at 3.81 integrating to 3H. The aromatic protons are shown as a zoomed in region in Figure 18, and splitting pattern analysis supports the assignment of an ortho substitution pattern on the aromatic. The CH_2 protons in the pyrrolidine ring α- to the nitrogen are indicated by the peaks at 3.05 and 2.13 ppm, again analogous to those seen in (*R*)-bgugaine. Another indicative peak of the side chain is the triplet at 2.58 integrated to 2H, which corresponds to the CH_2 adjacent to the aromatic. Comparison with the literature supports these assignments and indicates successful synthesis of the natural product.[113]

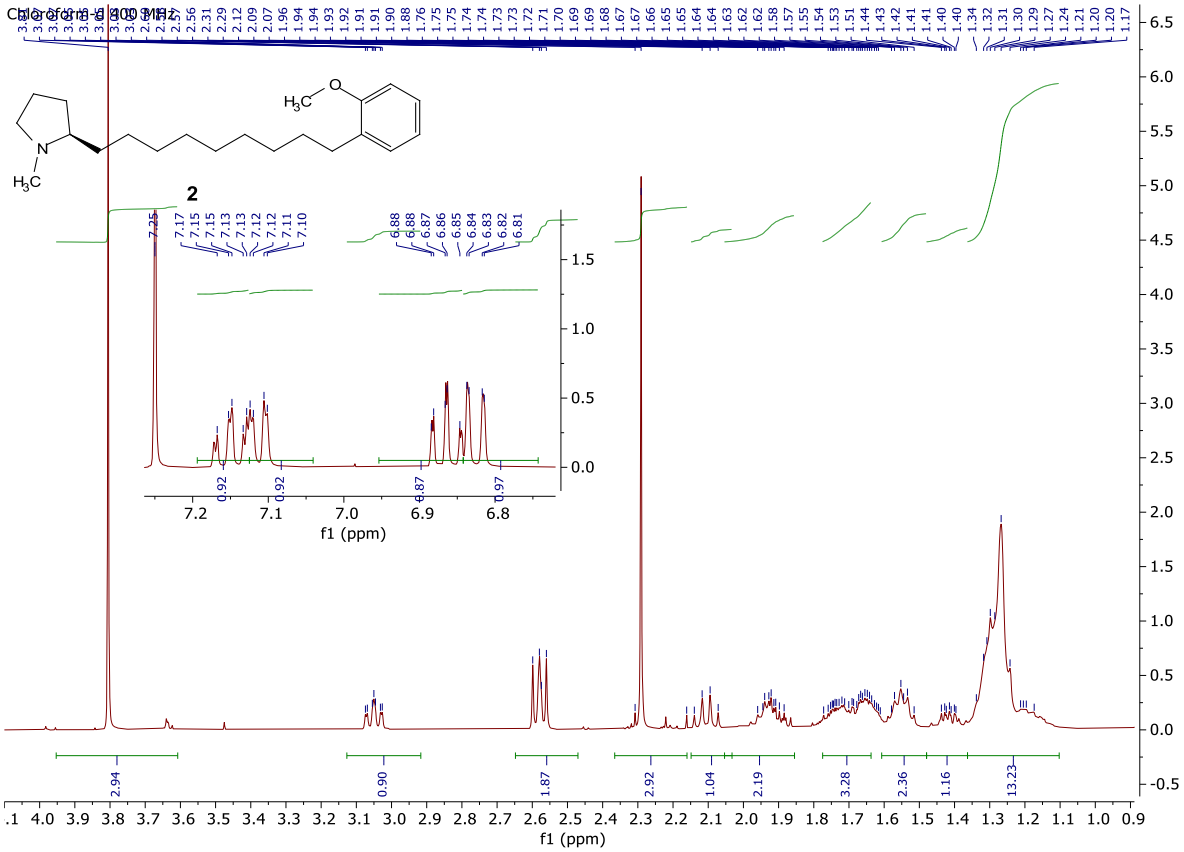


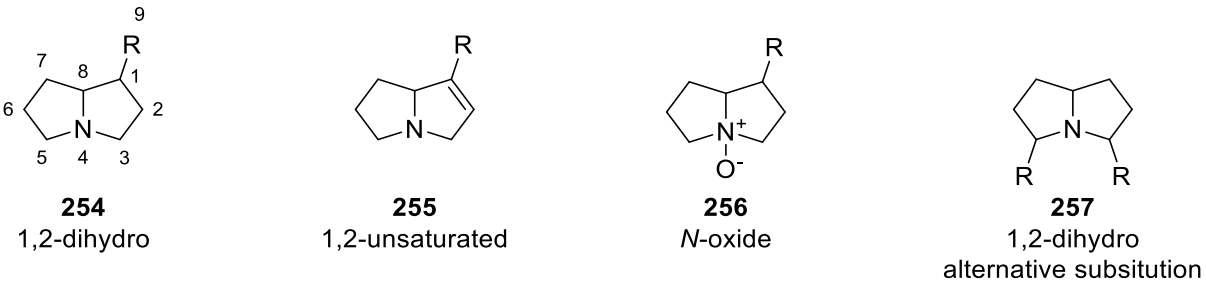
Figure 18. ^{1}H NMR spectrum of (R)-irnidine

4.3. Summary of results

(*R*)-Bgugaine **207** was synthesized in a 33% overall yield in 6 steps from a simple Cbz protected amine **162** while (*R*)-irnidine **208** was synthesized for the first time in an overall yield of 18% over 6 steps. After research into routes *via* a Wittig olefination, a Barton McCombie deoxygenation, and a desulfurization reaction proved unproductive, the asymmetric total synthesis of (*R*)-bgugaine **207** and (*R*)-irnidine **208** was achieved *via* a metathesis and asymmetric cyclisation reaction to give a pyrrolidine core for both molecules. A Liebeskind-Srogl coupling allowed for the selective installation of the side chain required for each natural product. Fine tuning of a Wolf-Kishner reaction enabled and deoxygenation in moderate to high yields and subsequent $LiAlH_4$ reduction allowed access to the natural products in high yields. Analysis of the products and comparison with literature data confirmed the enantioselective synthesis of the natural products, for both natural enantiomers.

5. Desymmetrisation of Prochiral Amines

The total synthesis of (*R*)-bgugaine and (*R*)-irnidine demonstrated a viable synthetic pathway to produce pyrrolidine alkaloids using our methodology. While this is useful for synthesising alkaloids that contain a single pyrrolidine core, there remained the possibility of synthesising another class of alkaloids containing a pyrrolizidine core using this methodology. Pyrrolizidine alkaloids are widely found in nature in plants, microorganisms and animals.[144] They have a range of biological activity and often show toxicity in humans and this activity has been exploited in the development of pharmaceuticals, which will be discussed later.[144] Some general motifs observed for pyrrolizidine alkaloids are shown in Figure 19, and the general atomic numbering shown on compound **254**.[145] Substitution around the pyrrolizidine can vary but the 1,2-unsaturated **255** structures show a general trend of enhanced toxicity from cytochrome P450 3A4 mediated metabolic pathways.[146] The metabolites of various pyrrolizidine alkaloids were shown to induce toxicity in human, pig, rat, and mouse liver microsomes, with humans being particularly susceptible to hepatotoxicity.[147]



254 1,2-dihydro

255 1,2-unsaturated

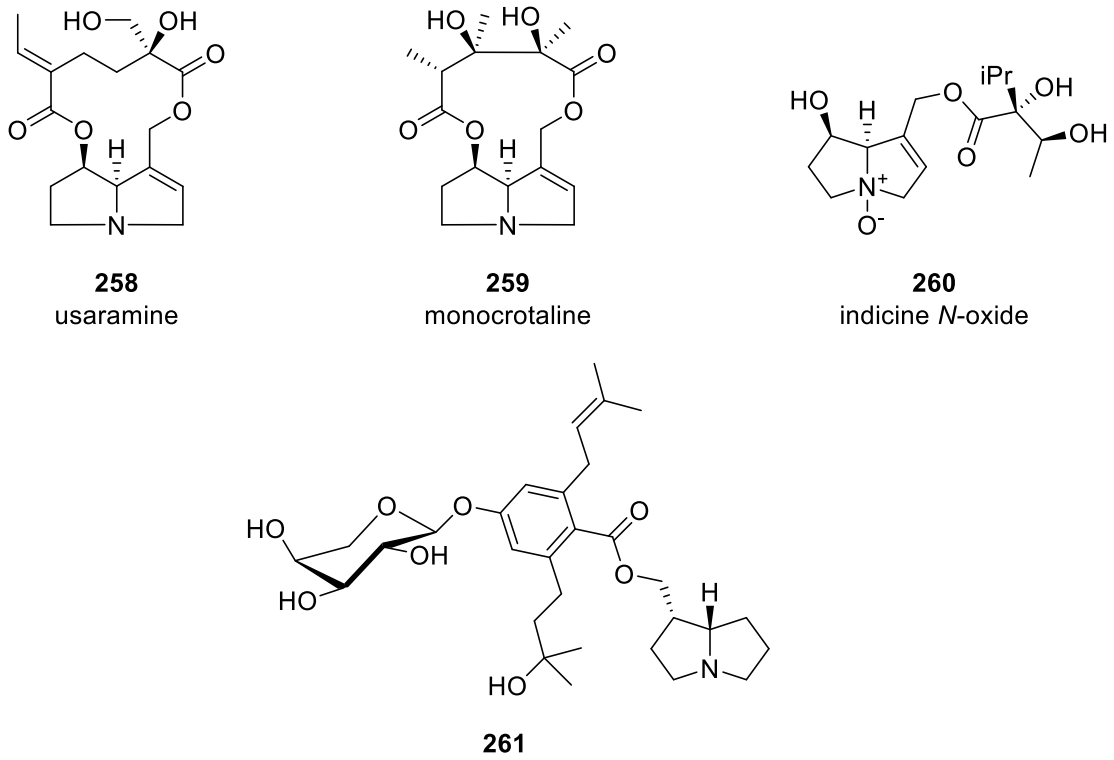
256 *N*-oxide

257 1,2-dihydro alternative subsitution

Figure 19. Structural motifs of pyrrolizidine alkaloids

Despite the toxicity of pyrrolizidine alkaloids, there are a number of examples that show pharmacological properties, including anti-microbial, anti-inflammatory, anti-cancer and anti-HIV activity.[144] Usaramine **258** (Figure 20) is a pyrrolizidine alkaloid isolated from *Crotalaria retusa* seeds and its activity against biofilm formation of *Staphylococcus epidermidis* was studied.[148] While the usaramine did not significantly impact the growth of the bacteria, the formation of biofilm was inhibited by 50% with a dosage of 1 mg/ml.[148] In the same study, another related alkaloid monocrotaline **259** (Figure 20) was extracted from *C. retusa* seeds which showed activity against the parasitic protozoan *Trichomonas vaginalis*. Treatment of the protozoan with monocrotaline **259** at a dosage of 1 mg/ml killed 74% of the parasitic cells

whilst showing no cytotoxicity to vaginal epithelial cells, making it a potential topical treatment for the disease.[148]



258
usaramine

259
monocrotaline

260
indicine *N*-oxide

261

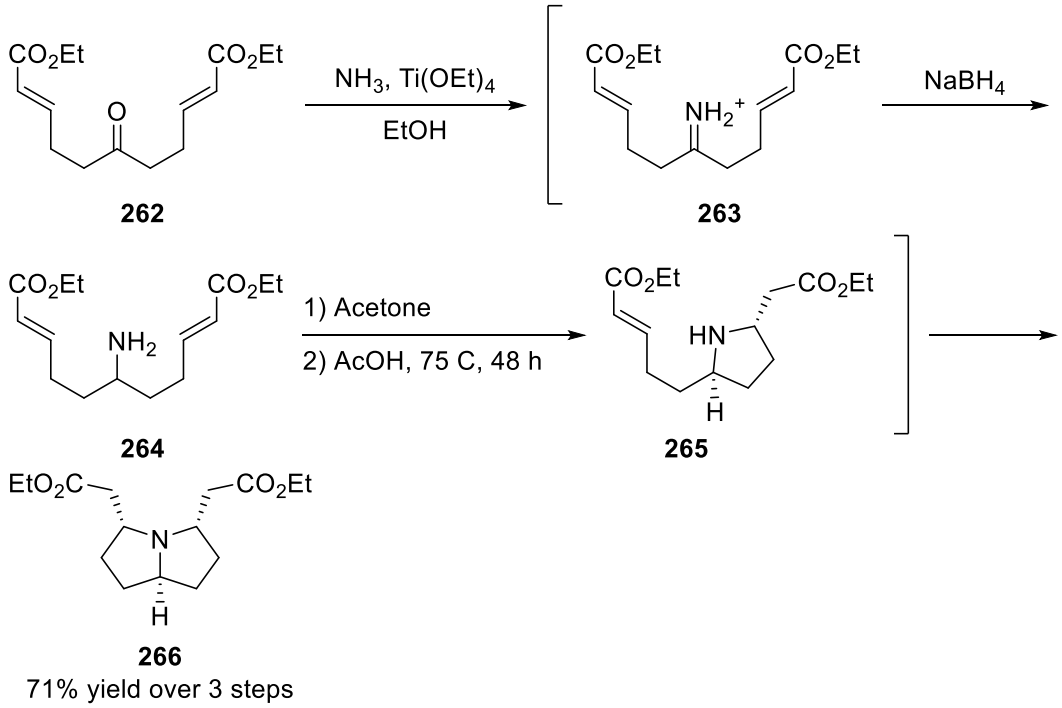
Figure 20. Pyrrolizidine alkaloids with pharmacological applications.

A potential anti-cancer compound that has attracted interest in the treatment of leukaemia is indicine *N*-oxide **260** (Figure 20).[149,150] In one study of 22 patients with acute and chronic leukaemia, the use of indicine *N*-oxide **260** with a dosage between 3.0-3.75 g/m^2 over 5 days resulted in complete remission for 3 patients and partial remission for 2 patients.[149] However, one patient of the 22 suffered liver failure and higher doses were shown to increase the incidence of severe hepatotoxicity. In a phase II clinical trial of 46 patients, lower doses of 2.0-2.5 g/m^2 were given over a 5 day period but showed a reduced response against the cancer when compared to the 3.0 g/m^2 dosage.[150] The trial concluded that, while indicine *N*-oxide **260** is active in the treatment of acute lymphoblastic leukaemia in children, the hepatotoxicity and narrow therapeutic index mean long term administration of the drug may be unsafe. The researchers also suggested that the development of new pyrrolizidine alkaloids, that

demonstrate antileukemic effects whilst reducing hepatotoxicity, would be required before they could be incorporated into treatments for leukaemia.[150]

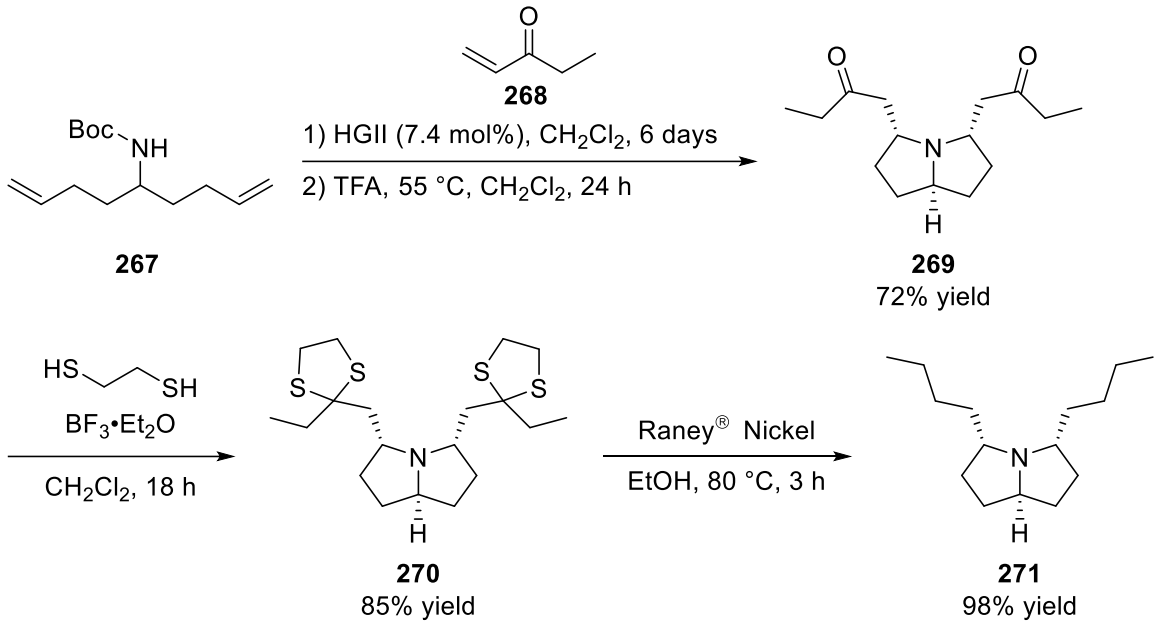
A series of pyrrolizidine alkaloids extracted from *Liparis nervosa* were screened for their ability to inhibit nitric oxide production in macrophages, which plays a role in the immune response.[151] While all the compounds screened showed some level of inhibition to nitric oxide production, alkaloid **261** (Figure 20) showed the strongest inhibitory effect with an IC_{50} of 2.16 ± 0.57 μM, whilst showing no cytotoxicity towards the macrophage. The range of alkaloids was also tested for potential anti-cancer activity, but no inhibition was observed.[151]

It is apparent that having synthetic tools that can enable the formation of novel pyrrolizidine alkaloids can be very useful from a medicinal chemistry perspective. The synthesis of pyrrolizidine alkaloids has been of interest to chemists for a number of years, with several reviews published on recent methodologies.[145,152,153] One possible method for synthesising pyrrolizidines is through intramolecular aza-Michael reactions and this method was demonstrated by the Stockman group in the synthesis of 3,5-disubstituted pyrrolizidines (Scheme 95).[154] Through a one-pot reductive amination of ketone **262** and subsequent double Michael addition, pyrrolizidine **266** was synthesised in 71% yield over 3 steps (Scheme 95).[154]



Scheme 95. Tandem reductive amination-double Michael addition synthesis of pyrrolizidines

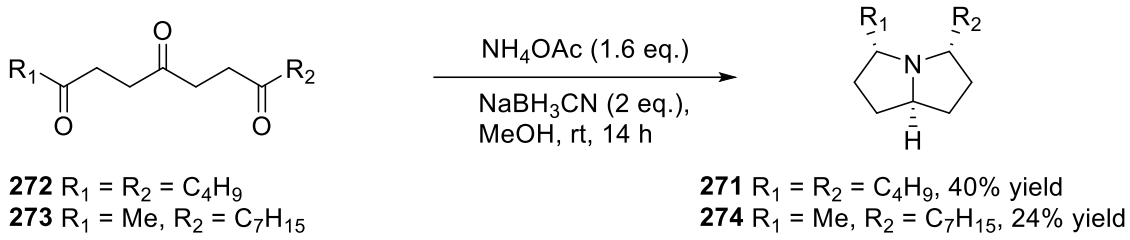
While the initial approach demonstrated the use of α,β-unsaturated ethyl esters as Michael acceptors, the group also showed an alternative procedure utilising α,β-unsaturated ketone (enone) functionality. The use of the enone meant that the previous reductive amination strategy was not feasible, so amine functionality was introduced before the formation of the enone through the synthesis of Boc amine **267** (Scheme 96). Through a one-pot metathesis with enone **268** and TFA mediated double cyclisation, the pyrrolizidine **269** was synthesised in 72% yield. The choice of 1-penten-3-one as the metathesis coupling partner was important, as the number of carbons on the side chains of pyrrolizidine **269** formed the core of the natural product alkaloid *cis*-223B **271**.[155,156] Through formation of dithiolane **270** and subsequent reduction with Raney® Nickel, the natural product **271** was isolated in excellent yields (Scheme 96).[154]



Scheme 96. Double Michael addition and synthesis of alkaloid cis-223B

One distinction to note about Stockman's methodology, is that the procedure forms a *meso* compound. If chirality was introduced during the first cyclisation, it would then be lost during the second cyclisation. While this is not detrimental to the synthesis of alkaloid *cis*-223B **271**, there are some cases where enantio-enrichment may be beneficial. A later paper published by the group shows an adaptation of the reductive amination strategy to synthesise another alkaloid (±)-xenovenine **274** as well as alkaloid *cis*-223B **271** (Scheme 97).[157] This procedure features a triple reductive amination which allowed for the isolation of (±) xenovenine **274** in

24% yield as a single diastereomer. The natural product is not a *meso* compound (there is no plane of symmetry) so an asymmetric reaction could theoretically produce a single enantiomer. However, the conditions used do not allow for this as there is no chiral catalyst or auxiliary that could give the desired stereochemistry.

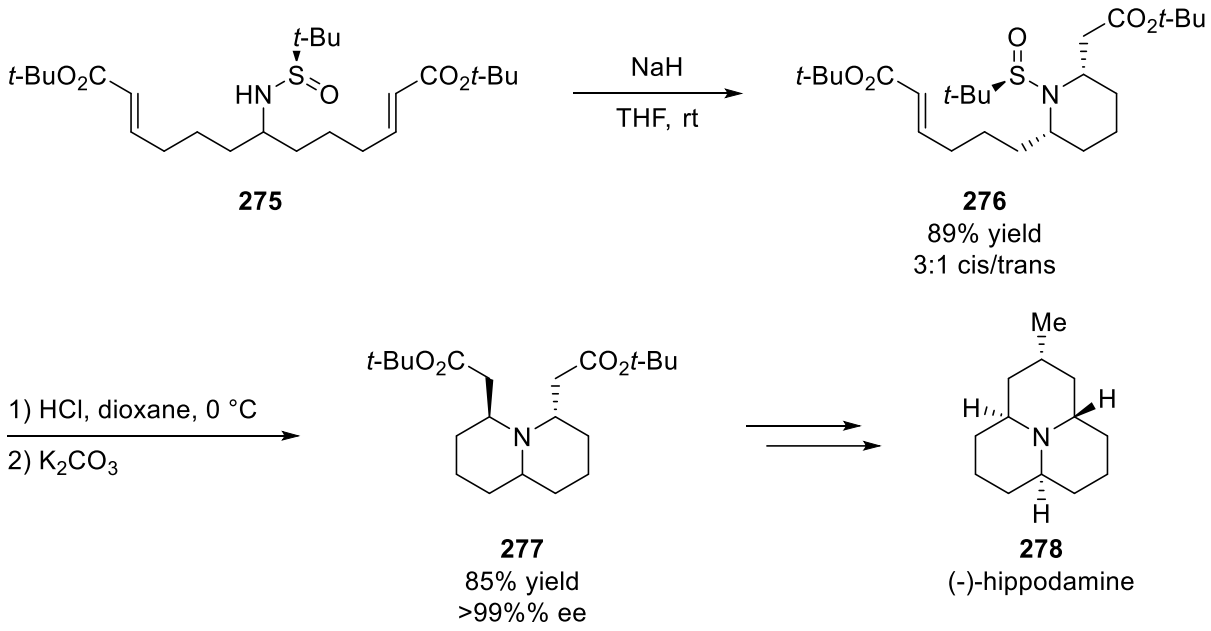


272 $R_1 = R_2 = C_4H_9$
273 R_1 = Me, $R_2 = C_7H_{15}$

271 $R_1 = R_2 = C_4H_9$, 40% yield
274 R_1 = Me, $R_2 = C_7H_{15}$, 24% yield

Scheme 97. Reductive amination strategy for synthesising alkaloid cis-223B and (±) xenovenine

While these strategies were unable to produce single enantiomers, the possibility for the asymmetric synthesis of bicyclic amines has been demonstrated by the Fustero group in the total synthesis of (-)-hippodamine **278** through a desymmetrisation reaction (Scheme 98).[158] The use of a chiral sulfinamide enabled the asymmetric intramolecular aza-Michael reaction of amine **275** to give 2,6-substituted piperidine **276** in 89% yield with a 3:1 cis/trans ratio. Removal of the chiral auxiliary with HCl/dioxane and treatment of the salt with K_2CO_3 led to a second cyclisation to give quinolizidine **277** in 85% yield and >99% ee. The use of the *t*-Bu ester was essential in achieving high enantioselectivity, as when the corresponding ethyl ester was used the ee dropped to 90%. Further transformations gave access to the natural product (-)-hippodamine **278**.[158]

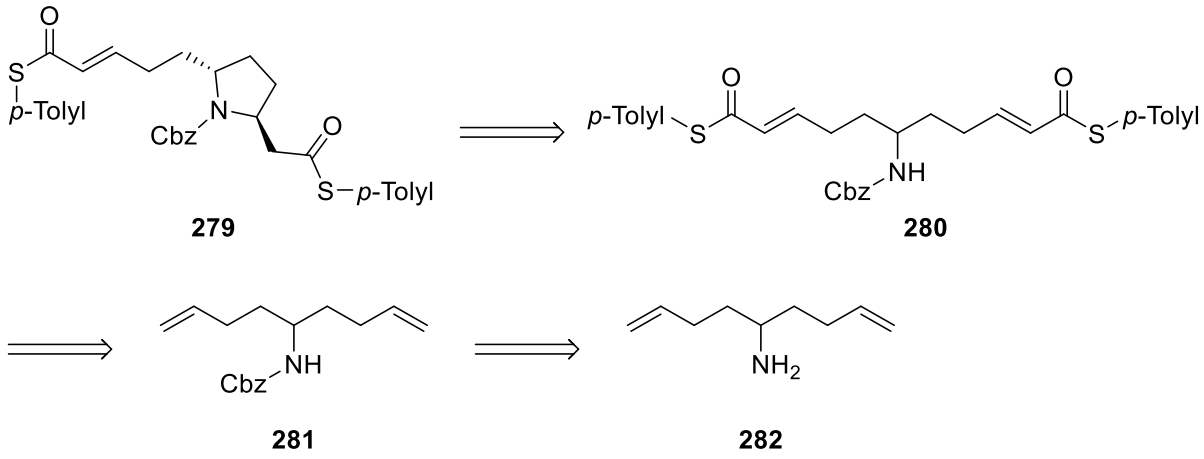


Scheme 98. Asymmetric synthesis of (-)- hippodamine

The formation of a single enantiomer of quinolizidine **277** shows the asymmetric synthesis of bicyclic amines through a desymmetrisation procedure to be possible. In the synthesis of (-)-hippodamine the enantioselectivity was induced through the use of a chiral auxiliary.[158] The work from Stockman showed that the use of enones as Michael acceptors could be used in a metathesis/Michael reaction to effect the synthesis of the racemic pyrrolizidines.[154,157] It was hypothesised that by replacing the enone with a thioacrylate and application of a chiral catalyst would be effective in the asymmetric synthesis of pyrrolizidines.

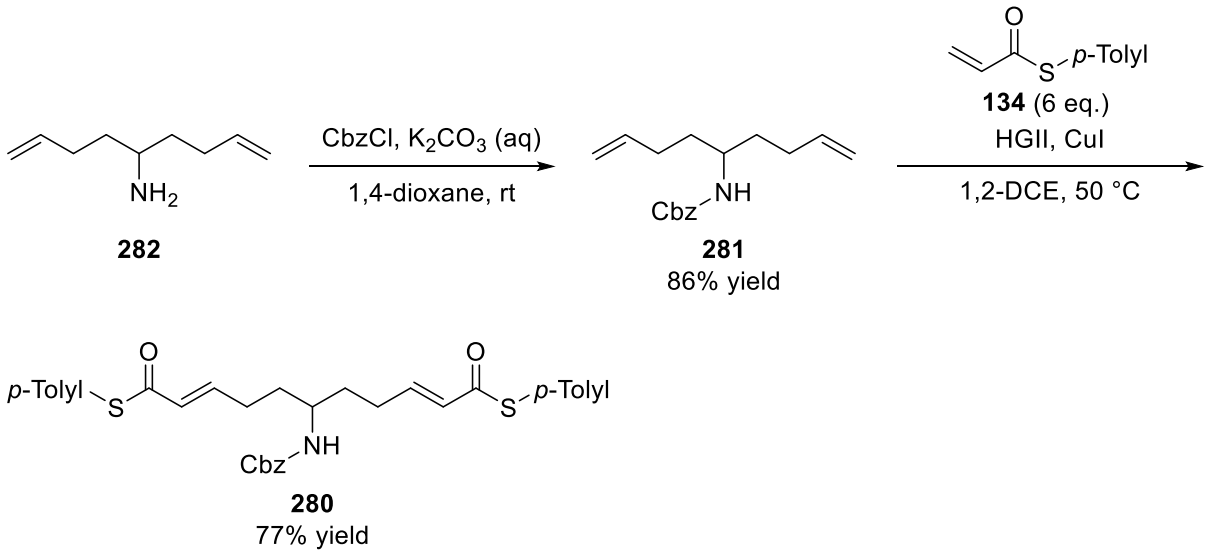
5.1. Synthesis of Precursors

In the work of Stockman, the metathesis reaction of Boc-amine **267** with 1-penten-3-one gave a mix of uncyclised and cyclised products, and so was taken through as a mixture to the deprotection/second cyclisation step to obtain the pyrrolizidine **269** (Scheme 96).[154] In order to perform an asymmetric desymmetrisation reaction with (*R*)-TRIP, the cyclisation precursor **280** needed to be isolated (Scheme 99). The use of a thioacrylate in a metathesis reaction with alkenyl amines without cyclisation has been shown to give high yields in this thesis, and it was decided to use this procedure in the desymmetrisation reaction. To employ the methodology in line with previous reactions, the Cbz protected amine **281** was required through protection of amine **282** (Scheme 99).



Scheme 99. Retrosynthetic analysis for the desymmetrisation reaction

Amine **282** was prepared using literature procedures and protected with benzyl chloroformate to give Cbz amine **281** in 86% yield (Scheme 100).[159] Using an excess of thioacrylate **134**, the metathesis reaction was performed using Hoveyda-Grubbs second generation catalyst and copper iodide to give the cyclisation precursor **280** in 77% yield (Scheme 100).



Scheme 100. Synthesis of achiral pyrrolizidine precursor

5.2. Asymmetric Cyclisation

With the prochiral amine **280** in hand, the cyclisation was tested with both *rac*-CSA and (*R*)-TRIP to give racemic and enantioenriched pyrrolidines and allow for HPLC analysis. Under the racemic conditions **A**, pyrrolidine **279** was isolated in 60% yield as a mixture of diastereomers

(92:8 dr), while asymmetric conditions **B** gave a slightly higher 77% yield and a dr of 92:8 (Scheme 101).

280

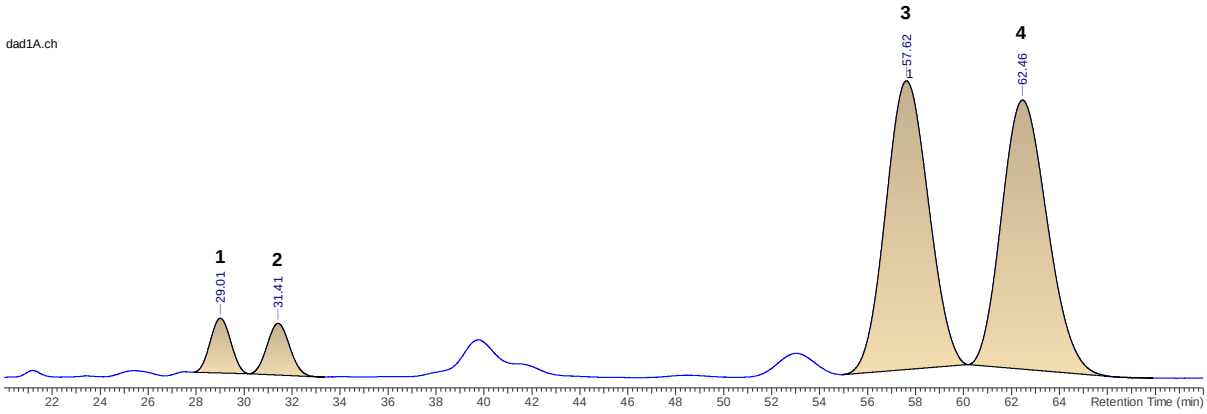
A = *rac*-CSA (3 eq.), 1,2-DCE, 50 °C, 24 h
B = (R)-TRIP (20 mol%), cyclohexane, 80 °C, 24 h

279

A 60% yield, 92:8 dr
B 77% yield, 92:8 dr

Scheme 101. Cyclisation and desymmetrisation reaction to give 2,5-disubstituted-pyrroldine

To determine both the diastereomeric ratio and enantiomer ratios achieved in the reaction, the mixture was analysed by chiral HPLC. Initial screening for the HPLC conditions was performed using the racemic substrate, as each diastereomer should have a 50:50 enantiomeric ratio, which allows for easier determination of product peaks. After screening several HPLC conditions, the CHIRALPAK® IG column gave good separation of both diastereomers, as well as separating each diastereomer into individual enantiomers (Figure 21). In the chromatogram, the two peaks for the minor diastereomer are indicated as peaks **1** and **2** while the major diastereomer peaks shown as peaks **3** and **4**. From this the diastereomeric ratio was calculated as being 92:8, based on the assumption that both diastereomers would have a UV absorption at 254 nm.



No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	29.01	510349.719	4.152	1.611
2	31.41	530868.500	4.319	1.745
3	57.62	5641569.000	45.899	3.349
4	62.46	5608441.500	45.630	3.531

*Figure 21. HPLC chromatogram for cyclisation of pyrrolidine **(±)-279** with rac-CSA*

As a secondary confirmation of the diastereomeric ratio, the NMR spectrum of the diastereomeric mixture was analysed for key peaks. The complexity of the NMR analysis was increased due to the presence of rotamers from the Cbz group. For example, the proton **H-14** is expected to have a splitting pattern of a doublet after coupling to the only adjacent proton **H-13** (Figure 22). However, the alkene signal at 6.3-6.0 ppm which corresponds to **H-14** showed two large doublets, each with a *J* value of 15.5 Hz, a magnitude indicative of a *trans* alkene. The presence of these two doublets is expected for a mixture of diastereomers and the two larger doublets might be assigned as a 50:50 dr for the mixture. However, the presence of smaller overlapping peaks at 6.1-6.0 ppm suggest that these smaller peaks correspond to the minor diastereomer (assigned as **H-14b**), and the larger doublets correspond to the major diastereomer (assigned as **H-14a**) (Figure 22).

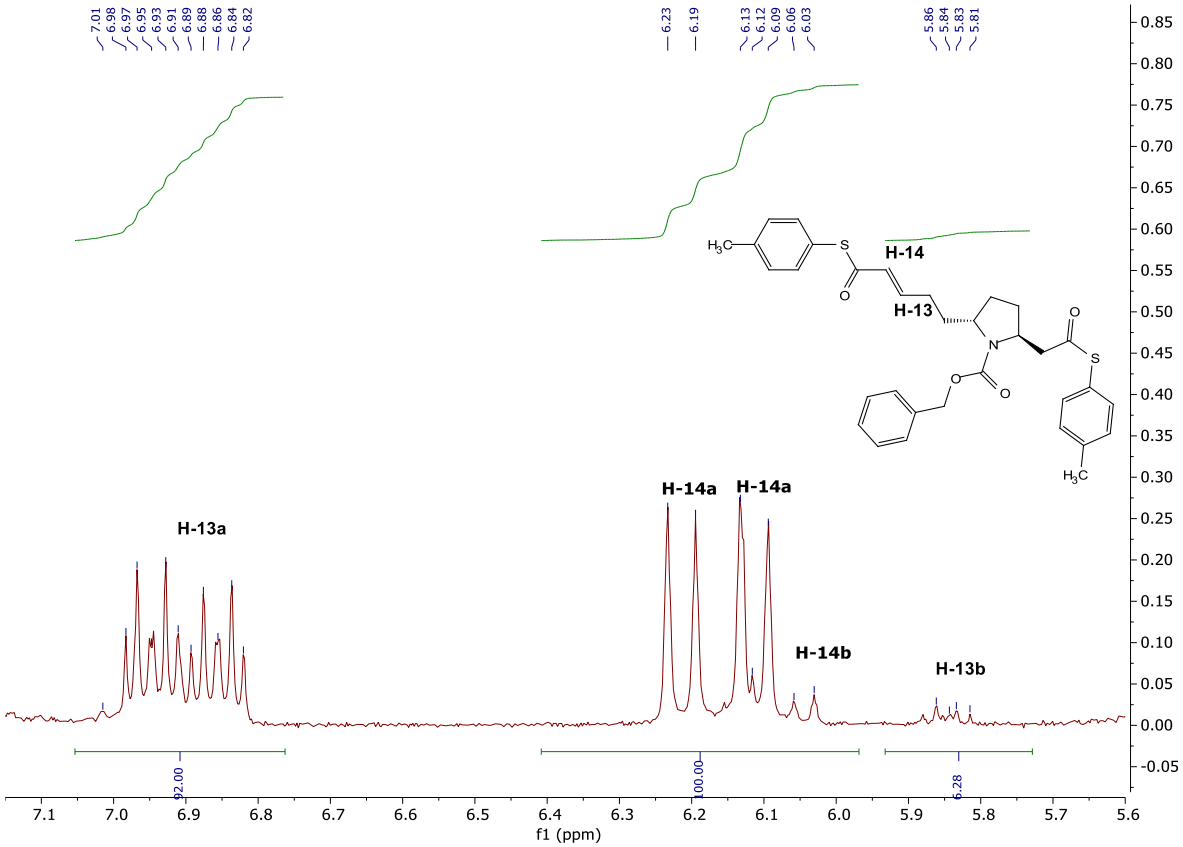


*Figure 22. NMR spectrum of the mixture of diastereomers of cyclised pyrrolidine **279***

The assignments for the alkene proton **H-13** showed even greater evidence for the presence of rotamers and diastereomers. The signal at 7.0-6.8 ppm, can be split into two doublet of triplet signals, a splitting pattern that corresponds with the **H-13a** proton. Like the **H-14a** proton, these two signals correspond to a 50:50 mixture of rotamers, but the peaks for the minor diastereomer **H-13b** were not visible in this region. COSY analysis revealed a minor peak at 5.9-5.8 ppm which showed a coupling to the **H**-**14b** proton and was assigned to the alkene proton for the minor diastereomer, **H-13b** (Figure 23).

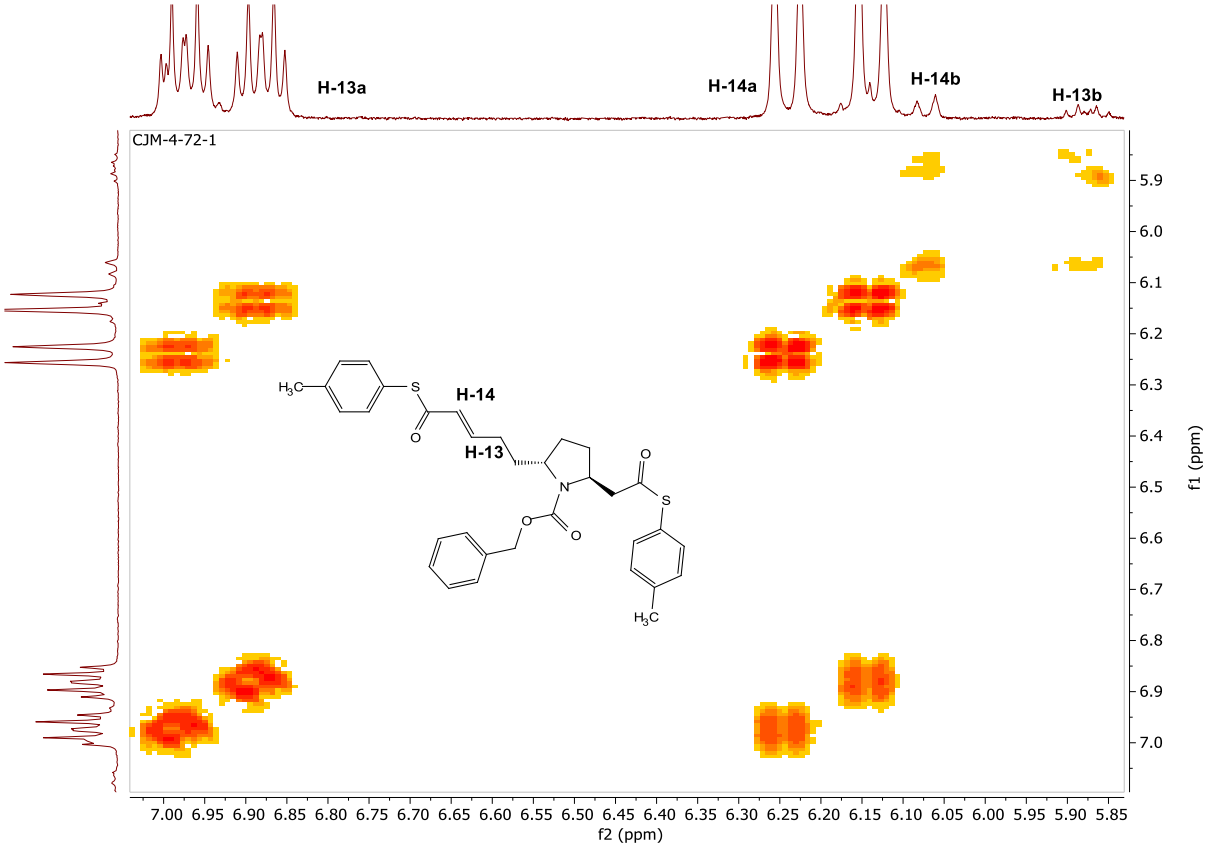


*Figure 23. COSY NMR spectrum of the mixture of diastereomers of cyclised pyrrolidine **279***

With two distinct peaks for the **H-13** protons, the diastereomeric ratio could be confirmed. Integration of all the peaks between 6.3-6.0 ppm and normalisation of the integration value to 100 was used to encompass all the rotameric and diastereomeric signals for **H-14** (Figure 22). Integration of the **H-13a** and **H-13b** peak gave a ratio of 92.0:6.28 which aligned with the value for the diastereomeric ratio of 92:8 dr measured by HPLC.

Confirmation that the peak **H-13b** corresponded to the minor diastereomer and that the minor diastereomer peaks were overlapping peak **H-14** was achieved by isolating the major diastereomer through flash column chromatography. In the initial analysis, the mixture of diastereomers was isolated as a single fraction during chromatography and was compared to the NMR spectrum of the crude reaction mixture to ensure no loss of either diastereomer. Repeating the chromatography allowed for isolation of the major diastereomer in order to compare peak data. The peaks at 5.9-5.8 ppm for proton **H-13b** and at 6.1-6.0 ppm for proton **H-14b** are no longer observed in the NMR spectrum of the major diastereomer (Figure 24) confirming the assignment of the major and minor diastereomers. It also confirms that the

two doublets observed for **H-14** correspond to rotamers and not to diastereomers (Figure 24).

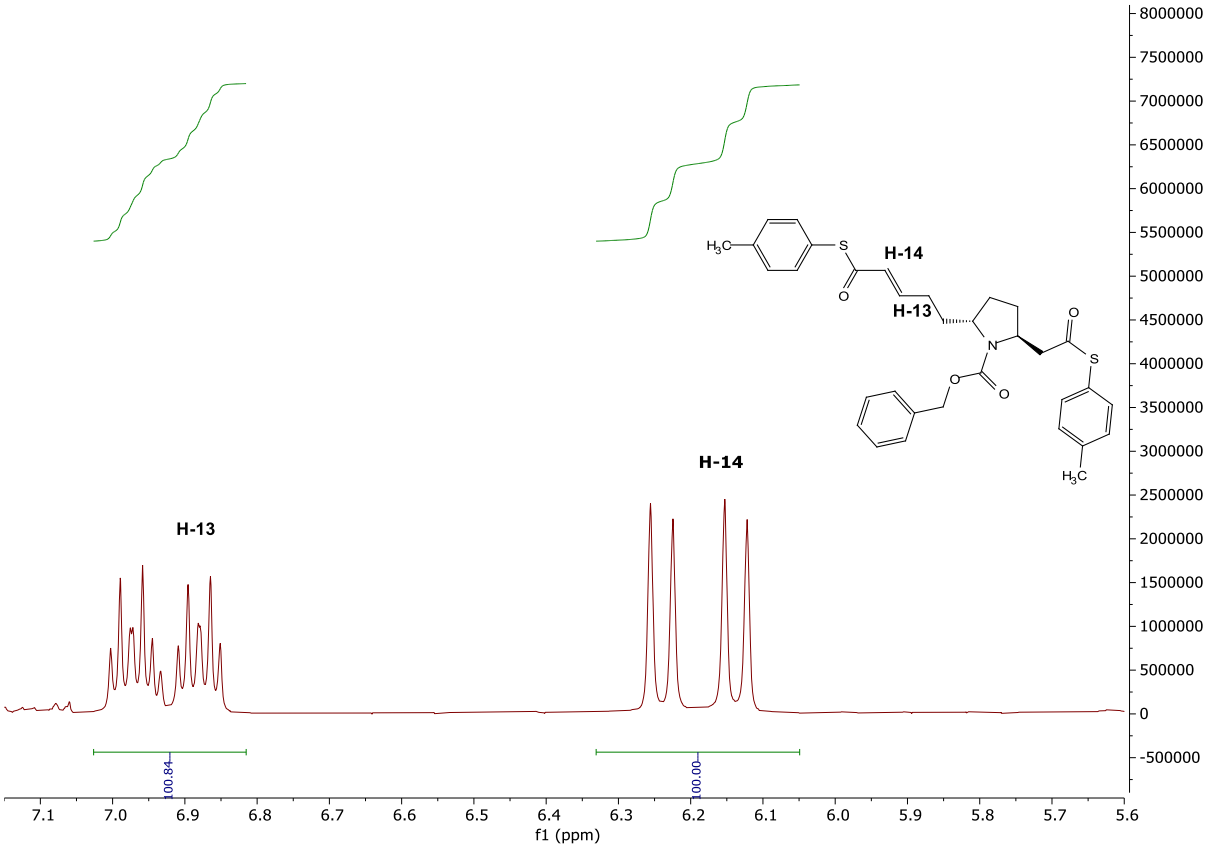
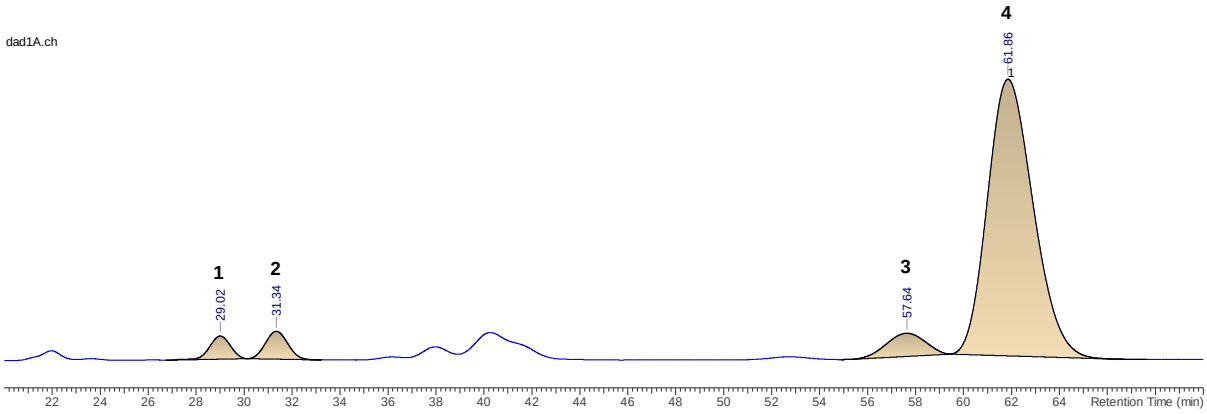


*Figure 24. NMR spectrum of the major diastereomer of cyclised pyrrolidine **279***

With the HPLC conditions decided upon and diastereomeric ratio confirmed for the racemic reaction, the product of the (*R*)-TRIP reaction could be analysed for enantioselectivity. Integration of the chromatogram (Figure 25) showed a diastereomeric ratio of 92:8, the same as the racemic reaction. Calculation of enantioselectivity showed the major diastereomer having a high enantiomeric ratio of 93:7, with the minor diastereomer being less selective with a 56:44 er. This result was very gratifying and demonstrated the potential for this reaction in the asymmetric synthesis of pyrrolizidines.



No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	29.02	444878.438	3.280	1.600
2	31.34	574038.750	4.232	1.736
3	57.64	834827.313	6.155	3.106
4	61.86	11709307.000	86.332	3.516

*Figure 25. HPLC chromatogram for cyclisation of pyrrolidine **279** with (R)-TRIP*

5.2.1 Determination of stereochemistry

With high diastereo- and enantioselectivity achieved, the relative stereochemistry of the reaction needed to be determined. To do this, NOE studies were performed on the molecule to see if there was any through space interaction between protons **H-10** and **H-7** (Figure 26). In the case of a *trans* configuration (**279-trans**), no NOE would be observed between **H-10** and **H-7**, whereas a *cis* configuration (**279-cis**) should show an NOE signal due to the closer proximity of the hydrogen atoms.

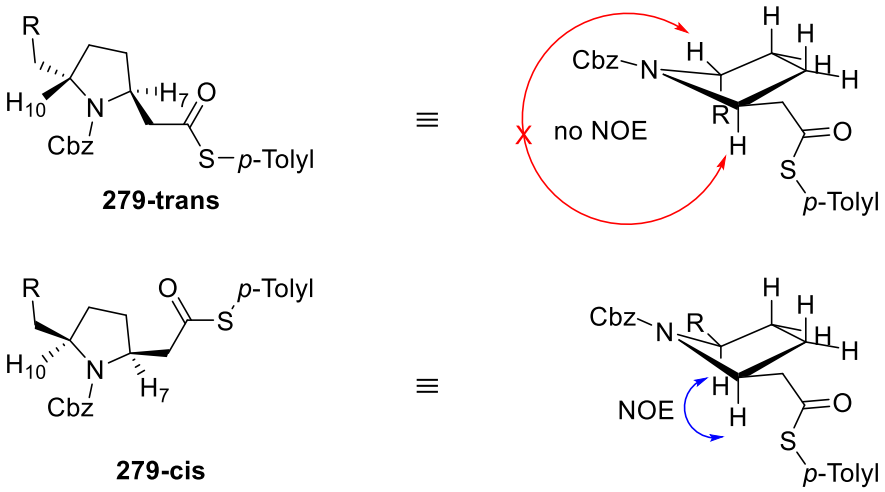


Figure 26. 3D structures and expected NOE resonance for cis and trans diastereomers

This method has been used in literature reports to assign the relative stereochemistry for structurally similar 2,5-disubstituted pyrrolidines **283-trans** and **283-cis** (Figure 27).[160] In the case of pyrrolidine **283-trans** no NOE was observed, while an NOE was measured between H-2 and H-5 for pyrrolidine **283-cis**, although no value was reported.

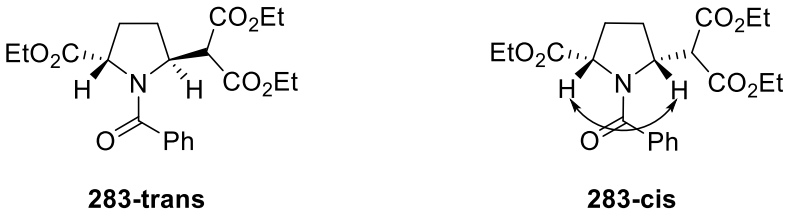


Figure 27. Literature examples of 2,5-disubstituted pyrrolidines.

The peaks in the NMR spectrum associated with **H-7** and **H-10** are seen at 4.32 ppm and 3.87 ppm respectively (Figure 28). When each signal is individually excited, no NOE was seen between the two CH protons as indicated in Figure 28. **H-10** showed an NOE with the CH_2 protons at the α-position to the thioester (3.4-3.0 and 2.7-2.6 ppm) as well as NOEs to the CH_2 protons in the pyrrolidine ring (2.3-1.8 ppm). **H-7** showed NOEs to the CH_2 protons in the pyrrolidine and to the CH_2 protons in the alkenyl side chain (2.3-1.4 ppm). Due to the overlapping multiplets in the CH_2 region, the individual signals were not assigned to specific protons, but this was not necessary for determining the stereochemistry.

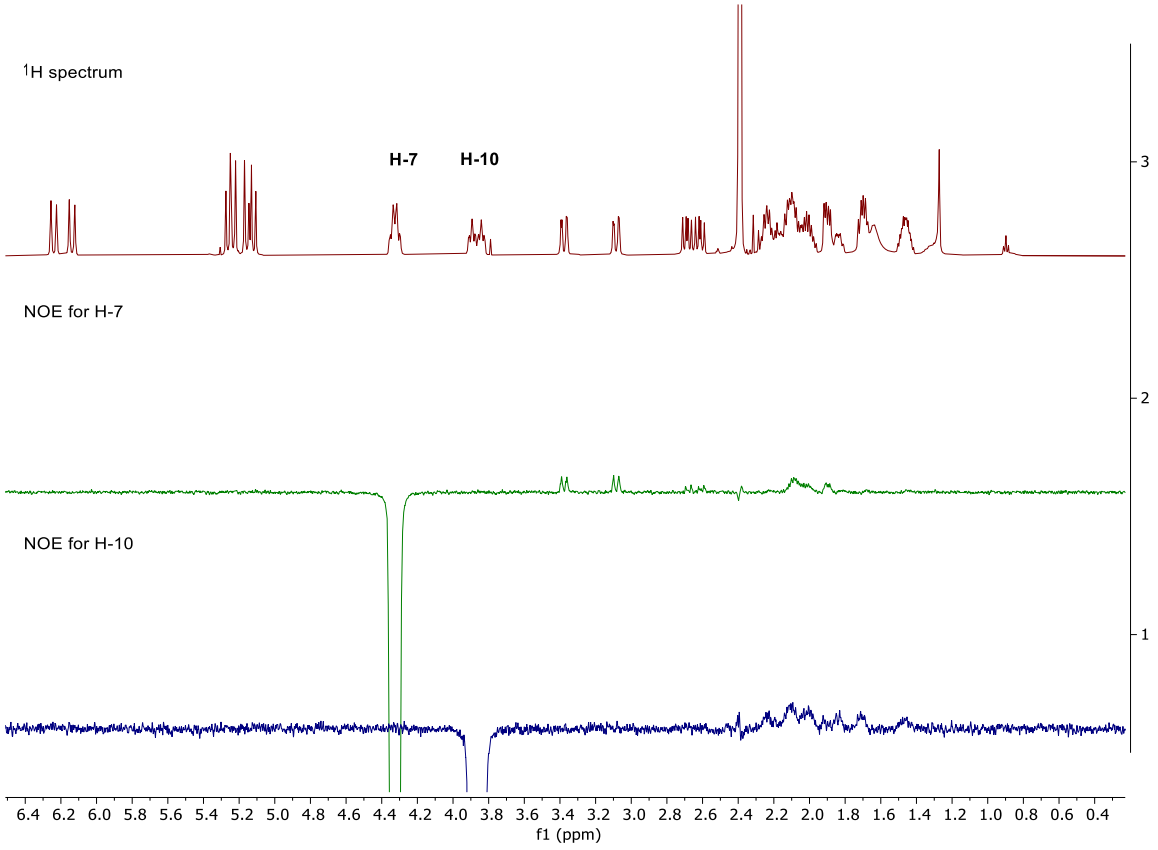
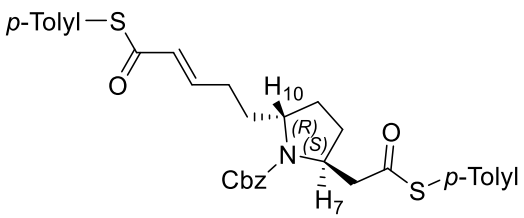


*Figure 28. NMR spectrum and NOE studies of major diastereomer of pyrrolidine **279***

The lack of an NOE between **H-7** and **H-10** suggest that the major diastereomer formed was the 2,5-*trans* pyrrolidine. It was also assumed that the stereochemistry for **H-7** (which was formed from the intramolecular Michael addition of the Cbz amine was (*S*). This was the same stereochemistry as that observed for the unsubstituted pyrrolidine **164**, as both reactions used (*R*)-TRIP as the chiral catalyst. Due to time constraints, the deprotection and cyclisation to form the pyrrolizidine was not attempted.



279

*Figure 29. Assigned stereochemistry for pyrrolidine **279***

6. Conclusions

A novel asymmetric synthesis of spirocyclic pyrrolidines has been presented through an intramolecular aza-Michael reaction catalysed by a chiral phosphoric acid, (*R*)-TRIP. The use of an α,β-unsaturated thioester as a Michael acceptor provided higher yields than the ester analogue, and better enantioselectivity than the enone analogue. The scope of the cyclisation was demonstrated through the synthesis of a range of 2,2- and 3,3-spirocyclic and disubstituted pyrrolidines. Generally high yields and enantioselectivities were observed for cycloalkyl substituents, with heterocyclic and diphenyl substituents giving poorer yields and selectivity. Deprotection and transesterification conditions were found for the pyrrolidines, and formation of the methyl ester enabled the absolute stereochemistry to be assigned as (*S*).

Adaptation of the synthesis of the cyclisation precursors enabled the introduction of 3,3-difluoro functionality, although cyclisation of the fluorinated precursor was ultimately unsuccessful. This was hypothesized to be due to the high electronegativity of the fluorine atoms reducing the nucleophilicity of the nitrogen. Attempts at introducing a methyl group onto the double bond of the Michael acceptor were unsuccessful during the metathesis reaction used to make the cyclisation precursors. Alternative approaches to install a methyl group were not attempted due to time constraints and this avenue of research was considered a lower priority.

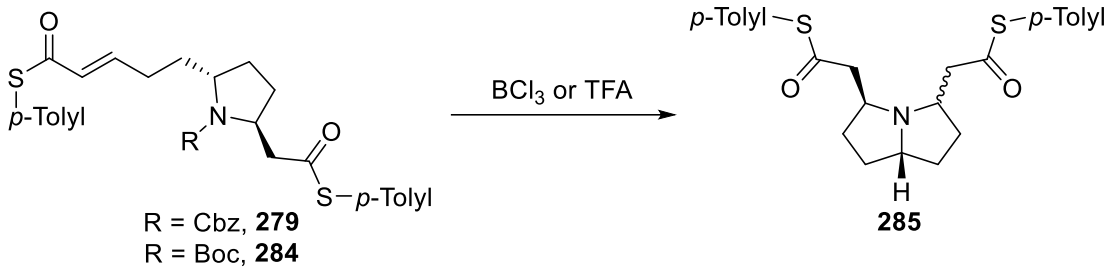
The formation of an unsubstituted pyrrolidine was achieved using (*R*)-TiPSY as a catalyst. This unsubstituted pyrrolidine was an analogue of β-homo-proline and could form the core structure of several pyrrolidine alkaloids. To that end, the total synthesis of (*R*)-bgugaine and (*R*)-irnidine was accomplished over 6 steps in 33% and 18% yield respectively. This was achieved through a Liebeskind-Srogl coupling to install the relevant side-chain of the natural product followed by Wolff-Kishner reduction and $LiAlH_4$ reduction to yield both natural products. This marks only the second catalytic asymmetric synthesis of (*R*)-bgugaine and the first asymmetric synthesis of (*R*)-irnidine.

The application of the methodology towards the synthesis of natural products was extended to a desymmetrisation reaction for the asymmetric synthesis of pyrrolizidines. Initial work

demonstrated that the asymmetric cyclisation could be applied to an prochiral amine and resulted in isolation of the pyrrolidine in high yields, diastereoselectivity and enantioselectivity. The relative stereochemistry was determined through NMR and NOE analysis of the major diastereomer which indicated a trans relationship between the CH protons at the 2,5 positions of the pyrrolidine.

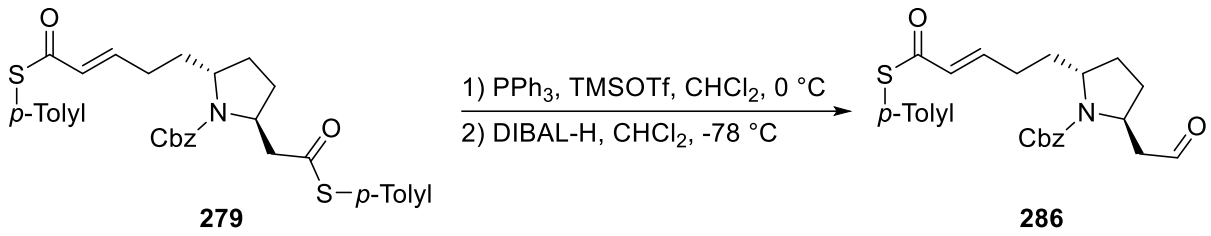
7. Future work

With promising initial work having been completed with the desymmetrisation procedure, the next step would be to investigate the deprotection and second cyclisation to form the pyrrolizidine **285**. Deprotection could be performed with BCl_3 as this was shown to be effective in removal of the Cbz group for the spirocyclic pyrrolidines. Alternatively, replacement of the Cbz with Boc may allow for a milder deprotection and second cyclisation (Scheme 102).



Scheme 102. Possible deprotection/cyclisation conditions to form pyrrolizidines

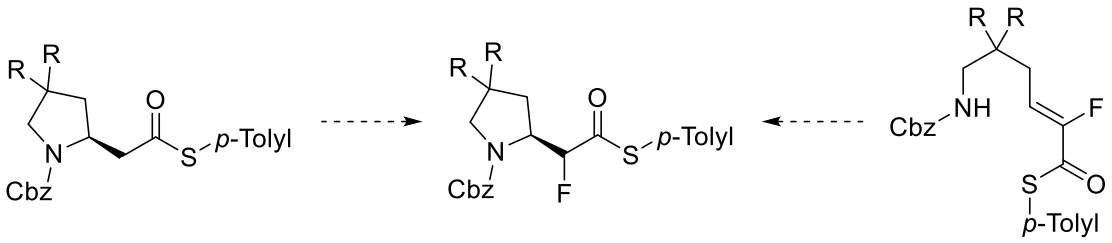
The key to this synthesis will be the determination of the stereochemistry of the final pyrrolizidine. If the pyrrolizidine formed is a *meso* compound, then any chirality installed in the first cyclisation will be lost. This may be prevented by using a chiral catalyst in the second cyclisation to force a specific chirality at the cyclisation position, but this may be a kinetically disfavoured reaction. An alternative would be to functionalise the pyrrolidine before the second cyclisation on one of the thioester groups (Scheme 103). This should be possible through exploitation of the thioester vs α,β-unsaturated thioester reactivity. A report by Fujioka that utilises PPh_3 and TMSOTf to form an *in situ* protecting group for an enone whilst reducing a ketone on the same molecule.[161] The similar reactivity of thioesters to ketones should allow for a similar strategy to selectively reduce the saturated thioester. Following deprotection and second cyclisation, there would be no plane of symmetry in the molecule, eliminating the possibility of forming the meso product.



279 **286**

Scheme 103. Functionalisation through selective thioester reduction

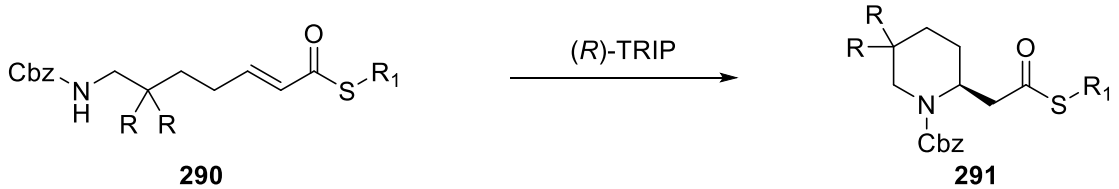
Attempts to install a methyl group onto the double bond or fluorine around the pyrrolidine ring were not met with success. However, the possibility of introducing further substitution, especially fluorine, into the pyrrolidine is still of interest from a medicinal chemistry perspective. This could be potentially be done before or after cyclisation (Scheme 104).



287 **289** **288**

Scheme 104. Installation of a heteroatom onto the pyrroldine

Another area of interest is the application of the α,β-unsaturated thioester as a Michael acceptor in the cyclisation of piperidines (Scheme 105). The selectivity observed in the pyrrolidine cyclisation have the potential to form enantioenriched piperidines, although modifications may be required to the procedure. Changing the substitution of the thioester may be necessary in order to improve yields or selectivity, but this tuning ability is what makes the thioester an appealing motif.



290 **291**

Scheme 105. Potential application of the α,β-unsaturated thioester Michael acceptor in the synthesis of piperidines.

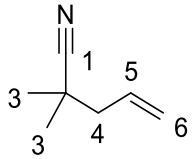
8. Experimental

General Experimental

Unless otherwise noted all compounds were bought from commercial suppliers and used without further purification. Where a solvent is described as “dry” it was purified by PureSolv alumina columns from Innovative Technologies. Melting points were determined using a Stuart SMP3 apparatus. Infra-red spectra were acquired on a ThermoNicolet Avatar 370 FT-IR spectrometer. Nuclear magnetic resonance spectra were recorded on a Jeol ECS-400, a Jeol 500 Avance III HD 500 or a Jeol AV500 at ambient temperature. Coupling constants (*J*) are quoted in Hertz. Mass spectrometry was performed by the University of York mass spectrometry service using electron spray ionisation (ESI) technique. Thin layer chromatography was performed on glass-backed plates coated with Merck Silica gel 60 F_{254}. The plates were developed using ultraviolet light, acidic aqueous ceric ammonium molybdate or basic aqueous potassium permanganate. Liquid chromatography was performed using forced flow (flash column) with the solvent systems indicated. The stationary phase was silica gel 60 (220–240 mesh) supplied by Fluorochem or silica gel Merck TLC grade 11695 supplied by Sigma-Aldrich. NMR assignments were made using 2D NMR including COSY, HMBC, HSQC techniques which can be accessed at DOI: 10.15124/a01fe9be-9b9e-43ac-8a21-20a9075784c5. All numbering on the structures below is for the benefit of characterisation and does not necessarily conform to IUPAC rules.

Screening of Michael acceptors in the intramolecular aza-Michael reaction

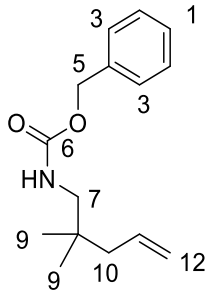
2,2-dimethyl-pent-4-enenitrile (129)



To a solution of diisopropylamine (8.59 ml, 61.3 mmol) in dry THF (25 ml) at -78 °C under N_2 was added n-BuLi (2.5 M in hexanes, 66.8 mmol) and the solution stirred for 45 mins. A solution of isobutyronitrile (5 ml, 55.7 mmol) in THF (25 ml) was added over 5 mins at -78 °C and reaction stirred for 45 mins. Allyl bromide (5.30 ml, 61.3 mmol) was added over 2 min at -78 °C and the reaction warmed to room temperature. The reaction was stirred overnight and

quenched with 1 M HCl (40 ml). The reaction was partitioned with diethyl ether (30 ml) and aqueous phase extracted with diethyl ether (3 x 50 ml), Organic fractions were combined, washed with saturated brine solution (2 x 50 ml), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Crude product was purified by bulb to bulb vacuum distillation (25 °C, 0.2 mbar) to give **129** as a pale yellow oil (2.93 g, 26.9 mmol, 48% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.88 (ddt, *J* = 16.8, 10.1, 7.3 Hz, 1 H, H-5), 5.23 (dq, *J* = 10.1, 1.5 Hz, 1 H, H-6), 5.19 (dq, *J* = 16.8, 1.5 Hz, 1 H, H-6), 2.28 (dd, *J* = 7.3, 1.5 Hz, 2 H, H-4), 1.35 (s, 6 H, H-3) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 132.2 (C-5), 124.7 (C-1), 119.9 (C-6), 45.0 (C-4), 32.1 (C-2), 26.2 (C-3) ppm; IR (ATR): ν_{max} 3082, 2980, 2937, 2235, 1643, 1469, 1418, 1391, 1370, 1279, 1254, 1192, 1122, 1083, 1048, 996, 932, 888, 874, 718, 633, 613, 565 cm^{-1}; HRMS (APCI) 110.0961 (M + H$^+$. $C_7H_{12}N$ requires 110.0964)

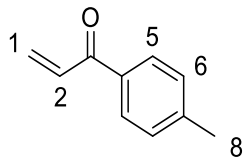
(2,2-dimethyl-pent-4-enyl)-carbamic acid benzyl ester (130)



To a suspension of $LiAlH_4$ (484 mg, 12.75 mmol) in dry diethyl ether (25 ml) at 0 °C under N_2 was added nitrile **129** (928 mg, 8.50 mmol) in dry diethyl ether (25 ml) over 5 mins and the reaction stirred at 0 °C for 30 mins. The reaction was then warmed to room temperature and stirred overnight. The reaction was cooled to 0 °C and quenched with H_2O (0.5 ml), followed by NaOH solution (15% w/w aq, 0.5 ml), followed by H_2O (1.5 ml) and the reaction warmed to rt. $MgSO_4$ was added and the suspension was filtered through Celite®, followed by washings with diethyl ether (50 ml). The filtrate was concentrated *in vacuo* to give the amine as a colourless oil (641 mg, 5.66 mmol, 67% yield) which was used without further purification. Amine (430 mg, 3.78 mmol) was dissolved in dioxane (10 ml) to which was added K_2CO_3 solution (50% w/w aq, 1.20 g, 4.53 mmol) followed by benzyl chloroformate (0.65 ml, 4.53 mmol) and the reaction stirred at room temperature for 4 hours. The reaction was quenched with H_2O (10 ml) and portioned with CH_2Cl_2 (10 ml). The aqueous phase was extracted with CH_2Cl_2 (2 x 10 ml) and organic fractions combined. The combined organics were washed with

saturated brine solution (10 ml), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (10% EtOAc/hexane) to afford **130** as a pale brown oil (801 mg, 3.24 mmol, 86% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.29 - 7.41 (m, 5 H, Ar-H), 5.82 (ddt, *J* = 16.9, 10.1, 7.3 Hz, 1 H, H-11), 5.11 (s, 2 H, H-5), 5.06 (dq, *J* = 10.1, 1.5 Hz, 1 H, H-12), 5.03 (dq, *J* = 16.9, 1.5 Hz, 1 H, H-12), 4.80 (br. s., 1 H, NH), 3.04 (d, *J* = 6.4 Hz, 2 H, H-7), 1.98 (d, *J* = 7.3 Hz, 2 H, H-10), 0.89 (s, 6 H, H-9) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 156.7 (C-6), 136.6 (C-4), 134.7 (C-11), 128.5 (Ar-CH), 128.2 (Ar-CH), 128.1 (Ar-CH), 117.6 (C-12), 66.7 (C-5), 50.8 (C-7), 44.3 (C-10), 34.7 (C-8), 24.7 (C-9) ppm; IR (ATR): ν_{max} 3340, 3071, 3033, 2960, 2929, 1703, 1639, 1520, 1468, 1455, 1410, 1389, 1367, 1323, 1242, 1137, 1090, 1039, 1028, 997, 914, 775, 751, 735, 696, 623, 574, 509, 462 cm^{-1}; HRMS (ESI) 248.1644 (M + H$^+$. $C_{15}H_{22}NO_2$ requires 248.1645), 270.1458 (M + Na$^+$. $C_{15}H_{21}NNaO_2$ requires 270.1464)

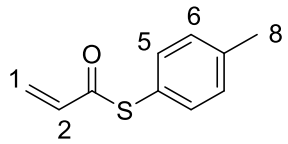
1-p-Tolyl-propenone (132)



To a solution of 4'-methylacetophenone (2.0 ml, 15.0 mmol) and paraformaldehyde (0.9 g, 30 mmol) in THF (15 ml) was added diisopropylammonium trifluoroacetate (3.23 g, 15 mmol) and trifluoroacetic acid (0.12 ml, 1.5 mmol). The reaction was heated to reflux for 2 hours, cooled to room temperature and a second portion of paraformaldehyde (0.9 g, 30 mmol) was added. The reaction was heated to reflux for a further 8 hours, then cooled to room temperature and solvent was removed *in vacuo*. The reaction was partitioned between diethyl ether (20 ml) and 1M HCl (aq) (20 ml). The organic fraction was washed with 1M NaOH (20 ml) and saturated brine solution (20 ml), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (5% EtOAc/hexane) to afford **132** as a colourless oil (493 mg, 3.37 mmol, 22% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.87 (d, *J* = 7.8 Hz, 2 H, H-5), 7.29 (d, *J* = 7.8 Hz, 2 H, H-6), 7.17 (dd, *J* = 17.2, 10.7 Hz, 1 H, H-2), 6.44 (dd, *J* = 17.2, 1.5 Hz, 1 H, H-1), 5.91 (dd, *J* = 10.7, 1.5 Hz, 1 H, H-1), 2.43 (s, 3 H, H-8) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 190.6 (C-3), 144.0 (C-7), 134.8 (C-4), 132.4 (C-2), 129.8 (C-1), 129.4 (C-6), 128.9 (C-5), 21.8 (C-8) ppm; IR (ATR): ν_{max} 3031, 2922

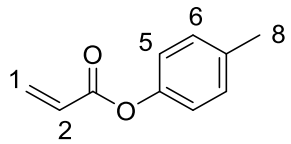
1666, 1603, 1570, 1409, 1398, 1311, 1289, 1235, 1211, 1180, 1120, 1038, 1021, 1001, 980, 966, 844, 768, 726, 700, 637, 599, 526 cm^{-1}; HRMS (APCI) 147.0806 ($M + H^+$. $C_{10}H_{11}O$ requires 147.0804).

Thioacrylic acid S-p-tolyl ester (134)



To a solution of NaOH (15% w/w aq. 20 ml) was added $NaBH_4$ (0.05 g, 1.32 mmol) and *p*-thiocresol (5.46 g, 44 mmol) which was then stirred for 3 hours. A solution of butylated hydroxytoluene (0.145g, 0.66 mmol) and acryloyl chloride (5.36 ml, 66 mmol) in cyclohexane (30 ml) was cooled to 0 °C. The aqueous solution of *p*-thiocresol was added dropwise to the acyrolyol chloride solution and the reaction warmed to room temperature. The reaction was then heated to 55 °C for 2.5 hours. After this time the reaction was cooled to room temperature and extracted with Et_2O (80 ml). The combined organics were washed with saturated $NaHCO_3$ solution (100 ml) and saturated brine solution (100 ml), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (2% Et_2O/hexane) to afford **134** as a pale yellow oil (5.37 g, 30.1 mmol, 68 % yield). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.36 (d, *J* = 8.4 Hz, 2H, H-5), 7.26 (d, *J* = 8.4 Hz, 2H, H-6), 6.48 (dd, *J* = 17.5, 10.0 Hz, 1H, H-2), 6.40 (dd, *J* = 17.5, 1.5 Hz, 1H, H-1), 5.78 (dd, *J* = 10.0, 1.5 Hz, 1H, H-1), 2.41 (s, 3H, H-8) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 188.9 (C-3), 139.7 (C-7), 134.5 (C-5), 134.3 (C-2), 130.0 (C-6), 127.2 (C-1), 123.5 (C-4), 21.3 (C-8) ppm; IR (ATR): ν_{max} 3023, 2921, 1681, 1611, 1597, 1493, 1447, 1393, 1304, 1276, 1160, 986, 940, 803, 722, 704, 627, 528, 470 cm^{-1}; HRMS (ESI) 179.0536 ($M + H^+$. $C_{10}H_{11}OS$ requires 179.0536).

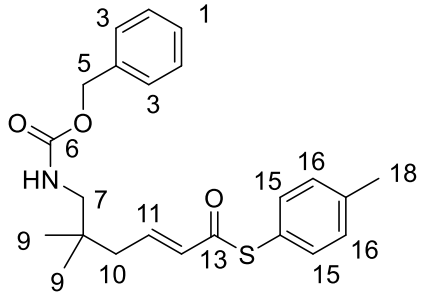
Acrylic acid *p*-tolyl ester (136)



To a solution of NaOH (15% w/w aq. 22.4 ml) was added $NaBH_4$ (0.048 g, 1.26 mmol) and *p*-cresol (4.4 ml, 42 mmol) which was then stirred for 3 hours. A solution of butylated hydroxytoluene (0.139 g, 0.63 mmol) and acryloyl chloride (5.12 ml, 63 mmol) in cyclohexane

(30 ml) was cooled to 0 °C. The aqueous solution of *p*-cresol was added dropwise to the acyrolyl chloride solution and the reaction warmed to room temperature. The reaction was then heated to 55 °C for 2.5 hours. After this time the reaction was cooled to room temperature and extracted with Et_2O (80 ml). The combined organics were washed with saturated $NaHCO_3$ solution (100 ml) and saturated brine solution (100 ml), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (10 % Et_2O/hexane) to afford **136** as a colourless oil (6.07 g, 37.4 mmol, 89% yield) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.20 (d, *J* = 8.4 Hz, 2 H, H-6), 7.03 (d, *J* = 8.4 Hz, 2 H, H-5), 6.61 (dd, *J* = 17.5, 1.5 Hz, 1 H, H-1), 6.33 (dd, *J* = 17.5, 10.7 Hz, 1 H, H-2), 6.01 (dd, *J* = 10.7, 1.5 Hz, 1 H, H-1), 2.37 (s, 3 H, H-8) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.8 (C-3), 148.3 (C-4), 135.5 (C-7), 132.4 (C-1), 129.9 (C-6), 128.0 (C-2), 121.2 (C-5), 20.9 (C-8) ppm; IR (ATR): ν_{max} 3035, 2924, 1739, 1634, 1506, 1402, 1293, 1251, 1196, 1165, 1146, 1104, 1068, 1018, 981, 938, 897, 845, 801, 755, 703, 671, 614, 501 cm^{-1}; HRMS (APCI) 163.0748 (M + H$^+$. $C_{10}H_{11}O_2$ requires 163.0754).

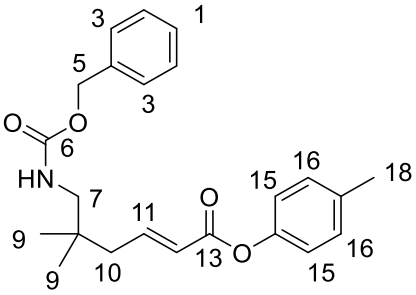
6-Cbz-amino-5,5-dimethyl-hex-2-enethioic acid S-p-tolyl ester (126b)



A solution of thioester **134** (165 mg, 0.924 mmol) in 1,2-DCE (7.5 ml) was added under N_2 to a dry flask containing Hoveyda-Grubbs Catalyst™ 2nd generation (19.3 mg, 0.0308 mmol) and copper iodide (58.7 mg, 0.308 mmol) while stirring. A solution of Cbz-amine **130** (76.2 mg, 0.308 mmol) in 1,2-DCE (7.5 ml) was added under N_2 and the reaction heated to 50 °C for 16 hours. The reaction was then cooled to room temperature, exposed to air and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (8% EtOAc/hexane) to afford **126b** as a colourless residue (92.2 mg, 0.232 mmol, 75% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.35 - 7.43 (m, 5 H, Ar-H), 7.33 (d, *J* = 8.1 Hz, 2 H, H-15), 7.24 (d, *J* = 8.1 Hz, 2 H, H-16), 6.98 (dt, *J* = 15.2, 8.2 Hz, 1 H, H-11), 6.20 (d, *J* = 15.2 Hz, 1 H, H-12), 5.12 (s, 2 H, H-5), 4.85 (t, *J* = 6.7 Hz, 1 H, NH), 3.08 (d, *J* = 6.7 Hz, 2 H, H-7), 2.39 (s, 3 H, H-18), 2.15 (d, *J* = 8.2

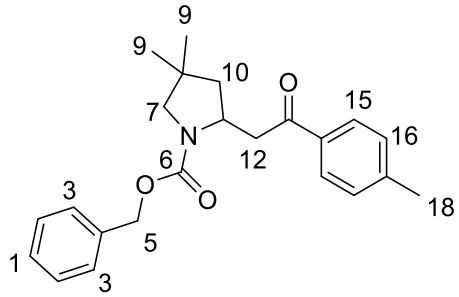
Hz, 2 H, H-10), 0.95 (s, 6 H, H-9) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 188.2 (C-13), 156.7 (C-6), 142.5 (C-11), 139.6 (C-17), 136.4 (C-4), 134.5 (C-15), 130.3 (C-12), 130.0 (C-16), 128.5 (Ar-CH), 128.2 (Ar-CH), 128.2 (Ar-CH), 123.9 (C-14), 66.8 (C-5), 51.2 (C-7), 42.4 (C-10), 35.8 (C-8), 24.7 (C-9), 21.3 (C-18) ppm; IR (ATR): ν_{max} 3346, 3063, 3031, 2959, 2926, 2871, 1698, 1630, 1523, 1494, 1467, 1455, 1392,1368, 1336, 1238, 1181, 1163, 1135, 1117, 1081, 1042, 1016, 888, 808, 775, 736, 697, 647, 619, 575, 534, 475 cm^{-1}; HRMS (ESI) 398.1792 (M + H$^+$. $C_{23}H_{28}NO_3S$ requires 398.1784), 420.1609 (M + Na$^+$. $C_{23}H_{27}NNaO_3S$ requires 420.1604).

6-Cbz-amino-5,5-dimethyl-hex-2-enoic acid p-tolyl ester (126c)



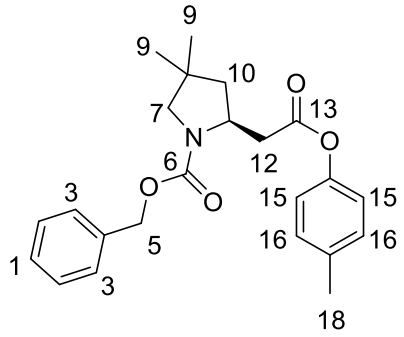
A solution of ester **136** (238 mg, 1.465 mmol) in 1,2-DCE (7.5 ml) was added under N_2 to a dry flask containing Hoveyda-Grubbs Catalyst™ 2nd generation (30.6 mg, 0.0488 mmol) and copper iodide (92.9 mg, 0.488 mmol) while stirring. A solution of Cbz-amine **130** (121 mg, 0.488 mmol) in 1,2-DCE (7.5 ml) was added under N_2 and the reaction heated to 50 °C for 16 hours. The reaction was then cooled to room temperature, exposed to air and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (12% EtOAc/hexane) to afford **126c** as a brown oil (161 mg, 0.422 mmol, 86% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.29 - 7.43 (m, 5 H, Ar-H), 7.18 (d, *J* = 8.4 Hz, 2 H, H-16), 7.16 (dt, *J* = 15.3, 7.6 Hz, 1 H, H-11), 7.00 (d, *J* = 8.4 Hz, 2 H,H-15), 6.04 (d, *J* = 15.3 Hz, 1 H, H-12), 5.12 (s, 2 H, H-5), 4.83 (t, *J* = 6.7 Hz, 1 H, NH), 3.10 (d, *J* = 6.7 Hz, 2 H, H-7), 2.36 (s, 3 H, H-18), 2.21 (d, *J* = 7.6 Hz, 2 H, H-10), 0.97 (s, 6 H, H-9) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.9 (C-13), 156.8 (C-6), 148.6 (C-14), 147.6 (C-11), 136.6 (C-4), 135.5 (C-17), 130.1 (C-16), 128.7 (Ar-CH), 128.4 (Ar-CH), 128.4 (Ar-CH), 123.5 (C-12), 121.4 (C-15), 67.0 (C-5), 51.3 (C-7), 42.7 (C-10), 35.8 (C-8), 24.9 (C-9), 21.0 (C-18) ppm; IR (ATR): ν_{max} 3356, 3033, 2960, 1721, 1650, 1531, 1507, 1455, 1391, 1369, 1313, 1241, 1198, 1167, 1132, 1075, 1040, 1018, 982, 821, 775, 736, 697, 510 cm^{-1}; HRMS (ESI) 382.2010 (M + H$^+$. $C_{23}H_{28}NO_4$ requires 382.2013), 399.2273 (M + NH_4^+. $C_{23}H_{31}N_2O_4$ requires 399.2278), 404.1827 (M + Na$^+$. $C_{23}H_{27}NNaO_4$ requires 404.1832).

***N*-Cbz-3,3-Dimethyl-5-(2-oxo-2-p-tolyl-ethyl)-pyrrolidine ((±)-127a)**



A solution of enone **132** (206 mg, 1.407 mmol) in 1,2-DCE (7.5 ml) was added under N_2 to a dry flask containing Hoveyda-Grubbs Catalyst™ 2nd generation (29.4 mg, 0.0469 mmol) and copper iodide (89.3 mg, 0.469 mmol) while stirring. A solution of Cbz-amine **130** (116 mg, 0.469 mmol) in 1,2-DCE (7.5 ml) was added under N_2 and the reaction heated to 50 °C for 16 hours. The reaction was then cooled to room temperature, exposed to air and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (10% EtOAc/hexane) to afford **(±)-127a** as a pale brown oil (147 mg, 0.402 mmol, 86% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.90 (d, *J* = 7.8 Hz, 1.2H, H-15, *rotamer 1*), 7.70 (d, *J* = 7.8 Hz, 0.8H, H-15, *rotamer 2*), 7.39-7.27 (m, 5H, Ar-H), 7.24 (d, *J* = 7.8 Hz, 1.2H, H-16, *rotamer 1*), 7.14 (d, *J* = 7.8 Hz, 0.8H, H-16, *rotamer 2*), 5.21 – 5.06 (m, 2H, H-5), 4.41 – 4.26 (m, 1H, H-11), 4.07 (dd, *J* = 15.4, 3.6 Hz, 0.6H H-12, *rotamer 1*), 3.73 (dd, *J* = 15.4, 3.6 Hz, 0.4H, H-12, *rotamer 2*), 3.49 (d, *J* = 10.6 Hz, 0.4H, H-7, *rotamer 2*), 3.38 (d, *J* = 10.6 Hz, 0.6H, H-7, *rotamer 1*), 3.06 (d, *J* = 10.6 Hz, 1H, H-7'), 2.90 – 2.75 (m, 1H, H-12'), 2.39 (s, 3H, H-18), 2.11 – 1.99 (m, 1H, H-10), 1.54 – 1.42 (m, 1H, H-10'), 1.07 (s, 3H, H-9), 0.99 (s, 3H, H-9') ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 198.6(198.2) (C-13), 155.2 (C-6), 144.1(144.0) (C-17), 137.0(136.7) (C-4), 134.5(134.3) (C-14), 129.4 (C-16), 128.7(128.6) (C-15), 128.5(128.3) (Ar-CH), 128.3(128.2) (Ar-CH), 128.0(127.8) (Ar-CH),67.1(66.7) (C-5), 59.4(59.3) (C-7), 54.9(54.2) (C-11), 46.9(45.9) (C-10), 45.1(43.8) (C-12), 37.6(37.3) (C-8), 26.5(26.4) (C-9), 26.2(26.1) (C-9'), 21.7 (C-18) ppm; IR (ATR): ν_{max} 3033, 2957, 2870, 1698, 1681, 1607, 1573, 1498, 1449, 1412, 1356, 1302, 1204, 1178, 1100, 1038, 1001, 810, 770, 752, 698, 584, 462 cm^{-1}; HRMS (ESI) 366.2060 (M + H^{+}. $C_{23}H_{28}NO_3$ requires 366.2064); 388.1879 (M + Na^{+}. $C_{23}H_{27}NNaO_3$ requires 388.1883)

_N_-Cbz-3,3-dimethyl-(_S_)-5-p-Tolyloxycarbonylmethyl-pyrrolidine (127c)



Racemic

A solution of amino-ester **126c** (19.9 mg, 0.052 mmol) in 1,2-DCE (5 ml) was added to rac-CSA (36.3 mg, 0.156 mmol) under N_2 and the reaction heated to 50 °C for 24 hours. The reaction was cooled to room temperature, quenched with Et_3N (0.2 ml) and concentrated *in vacuo*. The crude material was analysed by NMR to show 8% conversion.

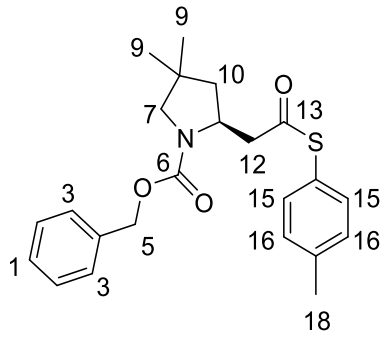
Asymmetric

A solution of amino-ester **126c** (22.1 mg, 0.0579 mmol) in cyclohexane (2.9 ml, 0.02M) was added to (*R*)-TRIP (8.72 mg, 0.0116 mmol) under N_2 and the reaction heated to 80 °C for 24 hours. The reaction was then cooled to room temperature and concentrated *in vacuo*. The crude material was purified by column chromatography (2% Et_2O/hexane) to afford **127c** as a colourless oil (4.5 mg, 0.0118 mmol, 20% yield, 95:5 er).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.26 (m, 5H, Ar-H), 7.14 (d, J = 8.1 Hz, 2H, H-16), 6.94 (d, J = 8.1 Hz, 1.2H, H-15, *rotamer 1*), 6.89 (d, J = 8.1 Hz, 0.8H, H-15, *rotamer 2*), 5.24 – 5.07 (m, 2H, H-5), 4.36 – 4.17 (m, 1H, H-11), 3.50 (d, J = 10.7 Hz, 0.4H, H-7, *rotamer 2*), 3.40 (d, J = 10.7 Hz, 0.6H, H-7, *rotamer 1*), 3.33 (dd, J = 15.7, 4.0 Hz, 0.6H, H-12, *rotamer 1*), 3.15 (dd, J = 15.7, 4.0 Hz, 0.4H, H-12, *rotamer 2*), 3.09 (d, J = 10.7 Hz, 0.6H, H-7', *rotamer 1*), 3.08 (d, J = 10.7 Hz, 0.4H, H-7', *rotamer 2*), 2.74 (dd, J = 15.7, 8.4 Hz, 0.6H, H-12', *rotamer 1*), 2.68 (dd, J = 15.7, 8.4 Hz, 0.4H, H-12', *rotamer 2*), 2.32 (s, 3H, H-18), 2.06 (dd, *J* = 12.8, 7.4 Hz, 1H, H-10), 1.69 (dd, J = 12.8, 8.8 Hz, 0.4H, H-10', *rotamer 2*), 1.63 (dd, J = 12.8, 8.8 Hz, 0.6H, H-10', *rotamer 1*), 1.11 (s, 1.2H, H-9, *rotamer 2*), 1.09 (s, 1.8H, H-9, *rotamer 1*), 1.01 (s, 3H, H-9') ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.3 (C-13), 155.2 (C-6), 148.4 (C-14), 137.1 (C-4)135.5 (C-17), 130.0 (C-16), 128.6(128.5) (Ar-CH), 128.0 (Ar-CH), 127.9(127.8) (Ar-CH), 121.3(121.2) (C-15), 67.1(66.8) (C-5), 59.4 (C-7), 54.4(53.8) (C-11), 46.3(45.5) (C-10), 40.1(38.9) (C-12), 37.5 (C-8), 26.4(26.1) (C-9), 21.0 (C-18) ppm; IR (ATR): ν_{max} 3034, 2957,

2923, 2870, 1756, 1701, 1507, 1433, 1413, 1357, 1303, 1198, 1166, 1137, 1101, 1041, 1019, 1003, 946, 914, 827, 769, 752, 698, 613, 505 cm^{-1}; HRMS (ESI) 382.2019 (M + H^+. $C_{23}H_{28}NO_4$ requires 382.2013), 404.1837 (M + Na^+. $C_{23}H_{27}NNaO_4$ requires 404.1832), 420.1575 (M + K^+. $C_{23}H_{27}KNO_4$ requires 420.1572); $[\alpha]_D^{20}$ -35.1° (c 0.225, $CHCl_3$).

_N_-Cbz-3,3-dimethyl-(_S_)-5-p-Tolylsulfanylcarbonylmethyl-pyrrolidine (127b)



Racemic

A solution of amino-thioester **126b** (19.2 mg, 0.048 mmol) in 1,2-DCE (5 ml) was added to rac-CSA (33.7 mg, 0.145 mmol) under N_2 and the reaction heated to 50 °C for 24 hours. The reaction was cooled to room temperature and extracted with DCM (10 ml). The organic fraction was washed with saturated $NaHCO_3$ solution (10 ml), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (8% EtOAc/hexane) to afford **127b** as a yellow oil (17.2 mg, 0.043 mmol, 90% yield).

Asymmetric

A solution of amino-thioester **126b** (19.5 mg, 0.049 mmol) in cyclohexane (0.02M) was added to (*R*)-TRIP (7.4 mg, 0.098 mmol) under N_2 and the reaction heated to 80 °C for 24 hours. The reaction was then cooled to room temperature, quenched with Et_3N (0.2 ml) and concentrated *in vacuo*. The crude material was purified by column chromatography (8% EtOAc/hexane) to afford **127b** as a yellow oil (16.2 mg, 0.041 mmol, 83% yield, 98:2 er).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.29 (m, 5H, Ar-H), 7.24 (m, 4H, H-15, H-16), 5.27 – 5.12 (m, 2H, H-5), 4.25 (m, 1H, H-11), 3.54 (dd, *J* = 15.2, 3.7 Hz, 0.6H, H-12, *rotamer 1*), 3.49 (d, *J* = 10.7 Hz, 0.4H, H-7, *rotamer 2*), 3.38 (d, *J* = 10.7 Hz, 0.6H, H-7, *rotamer 1*), 3.28 (dd, *J* = 15.2, 3.7Hz, 0.4H, H-12, *rotamer 2*), 3.06 (d, *J* = 10.7 Hz, 0.4H, H-7', *rotamer 2*), 3.05 (d, *J* = 10.7 Hz, 0.6H, H-7', *rotamer 1*), 2.87 (dd, *J* = 15.2, 8.7 Hz, 0.6H, H-12', *rotamer 1*), 2.78 (dd, *J* = 15.2, 8.7 Hz, 0.4H, H-12', *rotamer 2*), 2.38 (s, 3H, 18), 2.01 (dd, *J* = 12.9, 7.5 Hz, 1H, H-10),

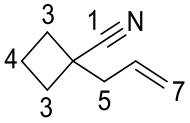
1.64 (m, 1H, H-10'), 1.11 (s, 1.2 H, H-9, *rotamer 2*), 1.11 (s, 1.8 H, H-9, *rotamer 1*), 1.00 (s, 3H, H-9') ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 196.0(195.9) (C-13), 155.1 (C-6), 139.9(139.7) (C-17), 137.0 (C-4), 134.5(134.5) (C-15), 130.2(130.1) (C-16), 128.7(128.6) (Ar-CH), 128.1(128.0) (Ar-CH), 127.8 (Ar-CH), 124.2(124.0) (C-14), 67.1(66.8) (C-5), 59.5(59.3) (C-7), 54.8(54.3) (C-11), 48.7(47.3) (C-12), 46.2(45.2) (C-10), 37.5(37.2) (C-8), 26.4(26.3) (C-9), 26.1(26.0) (C-9'), 21.4 (C-18) ppm; IR (ATR): ν_{max} 3032, 2956, 2925, 2869, 1698, 1598, 1494, 1454, 1410, 1355, 1328, 1285, 1210, 1179, 1101, 1039, 984, 807, 769, 697, 610, 533, 474 cm^{-1}; HRMS (ESI) 398.1785 (M + H$^+$. $C_{23}H_{28}NO_3S$ requires 398.1784); 420.1602 (M + Na$^+$. $C_{23}H_{27}NNaO_3S$ requires 420.1604); $[\alpha]_D^{20}$ -66.3° (c 0.81, $CHCl_3$).

Synthesis of 3,3-disubstituted precursors

General procedure A

To a solution of diisopropylamine (61.3 mmol) in dry THF (25 ml) at -78 °C under N_2 was added n-BuLi (2.5 M in hexanes, 66.8 mmol) and the solution stirred for 45 mins. A solution of nitrile (55.7 mmol) in THF (25 ml) was added over 5 mins at -78 °C and reaction stirred for 45 mins. Allyl bromide (61.3 mmol) was added over 2 min at -78 °C and the reaction warmed to room temperature. The reaction was stirred overnight and quenched with 1 M HCl (40 ml). The reaction was partitioned with diethyl ether (30 ml) and aqueous phase extracted with diethyl ether (3 x 50 ml), Organic fractions were combined, washed with saturated brine solution (2 x 50 ml), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Crude product was purified by column chromatography to yield the nitrile product.

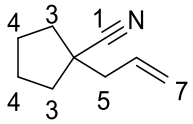
1-Allyl-cyclobutanecarbonitrile (141a)



141a was synthesised using **general procedure A** with diisopropylamine (1.54 ml, 11 mmol), n-BuLi (2.5 M in hexanes, 12 mmol), cyclobutanecarbonitrile (0.93 ml, 10 mmol) and allyl bromide (1.73 ml, 20 mmol). **141a** yielded as a colourless oil (737 mg, 6.08 mmol, 61% yield) after column chromatography (2% EtOAc/hexane). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.82 (ddt, *J* = 16.9, 10.1, 7.3 Hz, 1 H, H-6), 5.22 (m, 2 H, H-7), 2.43 - 2.57 (m, 4 H, H-3, H-5), 1.96 - 2.23 (m, 4 H, H-3, H-4) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 131.9 (C-6), 124.3 (C-1),

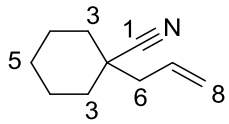
119.4 (C-7), 41.8, (C-5), 35.0, (C-2), 31.3 (C-3), 16.5 (C-4) ppm; IR (ATR): ν_{max} 3081, 2982, 2947, 2230, 1642, 1432, 1293, 1245, 1175, 992, 921, 719, 569 cm^{-1}; HRMS (APCI) 122.0966 (M + H^+. $C_8H_{12}N$ requires 122.0964)

1-Allyl-cyclopentanecarbonitrile (141b)



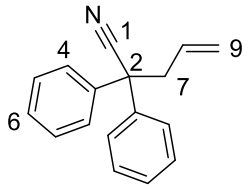
141b was synthesised using **general procedure A** with diisopropylamine (1.54 ml, 11 mmol), n-BuLi (2.5 M in hexanes, 12 mmol), cyclopentanecarbonitrile (1.04 ml, 10 mmol) and allyl bromide (1.73 ml, 20 mmol). **141b** yielded as a colourless oil (1.05 g, 7.73 mmol, 77% yield) after column chromatography (2% EtOAc/hexane). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.81 - 6.01 (m, 1 H, H-6), 5.15 - 5.26 (m, 2 H, H-7), 2.34 (d, *J* = 7.6 Hz, 2 H, H-5), 2.06 - 2.15 (m, 2 H, H-3), 1.79 - 1.91 (m, 2 H, H-4), 1.72 - 1.80 (m, 2 H, H-4), 1.62 - 1.71 (m, 2 H, H-3) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 132.9 (C-6), 125.1 (C-1), 119.2 (C-7), 42.5 (C-2), 42.4 (C-5), 37.5 (C-3), 24.2 (C-4) ppm; IR (ATR): ν_{max} 3081, 2965, 2875, 2231, 1643, 1453, 1417, 1323, 994, 922, 717, 597, 570, 484, 467 cm^{-1}; HRMS (ESI) 136.1124 (M + H^+. $C_9H_{14}N$ requires 136.1121)

1-Allyl-cyclohexanecarbonitrile (141c)



141c was synthesised using **general procedure A** with diisopropylamine (1.54 ml, 11 mmol), n-BuLi (2.5 M in hexanes, 12 mmol), cyclohexanecarbonitrile (1.19 ml, 10 mmol) and allyl bromide (1.73 ml, 20 mmol). **141c** yielded as a colourless oil (1.20 g, 8.04 mmol, 80% yield) after column chromatography (2% EtOAc/hexane). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.89 (ddt, *J* = 17.1, 10.0, 7.3 Hz, 1 H, H-7), 5.18 (dq, *J* = 17.1, 1.5 Hz, 1 H, H-8), 5.21 (dq, *J* = 10.0, 0.9 Hz, 1 H, H-8), 2.29 (d, *J* = 7.3 Hz, 2 H, H-6), 1.96 (m, 2 H, H-3), 1.54 - 1.81 (m, 5 H, H-4, H-5), 1.15 - 1.30 (m, 3 H, H-3, H-5) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 131.9 (C-7), 123.4 (C-1), 119.6 (C-8), 44.6 (C-6), 38.8 (C-2), 35.3 (C-3), 25.3 (C-5), 23.0 (C-4) ppm; IR (ATR): ν_{max} 3080, 2933, 2859, 2230, 1642, 1451, 1417, 1351, 1306, 1265, 1141, 1114, 1083, 996, 974, 920, 847, 714, 652, 569, 521 cm^{-1}; HRMS (APCI) 150.1283 (M + H^+. $C_{10}H_{16}N$ requires 150.1277)

2,2-diphenyl-pent-4-enenitrile (141d)



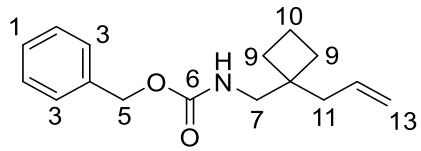
LiHMDS (1M in THF, 12.4 ml, 12.4 mmol) was diluted in dry THF (20 ml) under N_2 and cooled to -78 °C. A solution of diphenyl acetonitrile (2 g, 10.3 mmol) in THF (20 ml) was added at -78 °C over 5 mins and the reaction stirred for 45 mins. Allyl bromide (0.99 ml, 11.4 mmol) was added over 1 min at -78 °C and the reaction warmed to room temperature. The reaction was stirred overnight and quenched with 1 M HCl (40 ml). The reaction was partitioned with diethyl ether (40 ml) and aqueous phase extracted with diethyl ether (2 x 40 ml), Organic fractions were combined, washed with saturated brine solution (40 ml), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (4% EtOAc/hexane) to afford **141d** as a colourless oil (2.17 g, 9.31 mmol, 90% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.19 - 7.39 (m, 10 H, Ar-H), 5.67 (ddt, *J* = 17.5, 10.0, 6.9Hz, 1 H, H-8), 5.17 (d, *J* = 17.5 Hz, 1 H, H-9), 5.13 (d, *J* = 10.0 Hz, 1 H, H-9), 3.10 (d, *J* = 6.9 Hz, 2 H, H-7) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 139.7 (C-3), 131.8 (C-8), 128.8 (Ar-CH), 127.9 (Ar-CH), 127.0 (Ar-CH), 121.9 (C-1), 120.4 (C-9), 51.7 (C-2), 43.9 (C-7) ppm; IR (ATR): ν_{max} 3063, 2237, 1642, 1598, 1494, 1449, 1189, 1087, 1033, 991, 753, 697, 668, 636, 539 cm^{-1}; HRMS (ESI) 256.1108 (M + Na^+. $C_{17}H_{15}NNa$ requires 256.1097).

General procedure B

To a suspension of $LiAlH_4$ (12.75 mmol) in dry diethyl ether (25 ml) at 0 °C under N_2 was added nitrile (8.50 mmol) in dry diethyl ether (25 ml) over 5 mins and the reaction stirred at 0 °C for 30 mins. The reaction was then warmed to room temperature and stirred overnight. The reaction was cooled to 0 °C and quenched with H_2O (0.5 ml), followed by NaOH solution (15% w/w aq, 0.5 ml), followed by H_2O (1.5 ml) and the reaction warmed to rt. $MgSO_4$ was added and the suspension was filtered through Celite®, followed by washings with diethyl ether (50 ml). The filtrate was concentrated *in vacuo* to give the amine purification (5.66 mmol, 67% yield) which was used without further purification. Amine (4.78 mmol) was dissolved in dioxane (10 ml) to which was added K_2CO_3 solution (50% w/w aq, 4.53 mmol) followed by

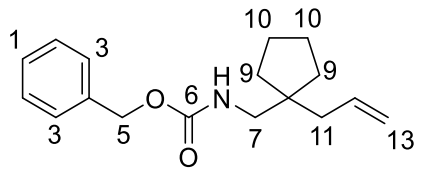
benzyl chloroformate (4.53 mmol) and the reaction stirred at room temperature for 4 hours. The reaction was quenched with H_2O (10 ml) and portioned with CH_2Cl_2 (10 ml). The aqueous phase was extracted with CH_2Cl_2 (2 x 10 ml) and organic fractions combined. The combined organics were washed with saturated brine solution (10 ml), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (3.24 mmol, 86% yield).

(1-Allyl-cyclobutylmethyl)-carbamic acid benzyl ester (142a)



Nitrile **141a** (209 mg, 1.72 mmol) was reduced using **general procedure B** with $LiAlH_4$ (98 mg, 2.59 mmol) to give the amine as a pale yellow oil (201 mg, 1.61 mmol, 93% yield). Amine (97 mg, 0.78 mmol) was Cbz protected with K_2CO_3 solution (50% w/w aq, 258 mg, 0.94 mmol) and benzyl chloroformate (0.13 ml, 0.94 mmol). **142a** yielded as a colourless oil (127 mg, 0.49 mmol, 63% yield) after column chromatography (10% EtOAc/hexane). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.29 - 7.43 (m, 5 H, Ar-H), 5.81 (ddt, *J* = 17.0, 10.0, 7.3 Hz, 1 H, H-12), 5.11 (s, 2 H, H-5), 5.03 - 5.10 (m, 2 H, H-13), 4.78 (br. s., 1 H, NH), 3.26 (d, *J* = 6.5 Hz, 2 H, H-7), 2.20 (d, *J* = 7.3 Hz, 2 H, H-11), 1.83 - 1.95 (m, 2 H, H-10), 1.73 - 1.82 (m, 4 H, H-9) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 156.8 (C-6), 136.6 (C-4), 134.5 (C-12), 128.5 (Ar-CH), 128.2 (Ar-CH), 128.1 (Ar-CH), 117.4 (C-13), 66.7 (C-5), 47.8 (C-7), 42.1 (C-11), 41.7 (C-8), 28.6 (C-9), 14.9 (C-10) ppm; IR (ATR): ν_{max} 3338, 3070, 3033, 2975, 2930, 1697, 1639, 1536, 1454, 1412, 1359, 1307, 1246, 1135, 997, 913, 774, 735, 696, 612, 486 cm^{-1}; HRMS (ESI) 282.1454 (M + Na$^+$. $C_{16}H_{21}NNaO_2$ requires 282.1464)

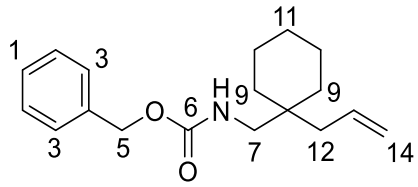
(1-Allyl-cyclopentylmethyl)-carbamic acid benzyl ester (142b)



Nitrile **141b** (264 mg, 1.95 mmol) was reduced using **general procedure B** with $LiAlH_4$ (111 mg, 2.93 mmol) to give the amine as a pale yellow oil (266 mg, 1.91 mmol, 98% yield). Amine

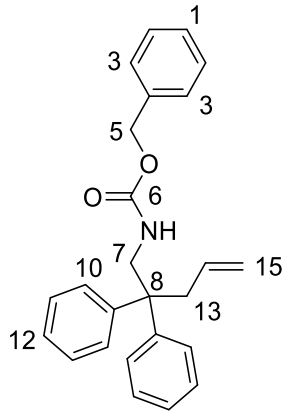
(124 mg, 0.88 mmol) was Cbz protected with K_2CO_3 solution (50% w/w aq, 294 mg, 1.06 mmol) and benzyl chloroformate (0.15 ml, 1.06 mmol). **142b** yielded as a colourless oil (158 mg, 0.58 mmol, 66% yield) after column chromatography (10% EtOAc/hexane). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.29 - 7.47 (m, 5 H, Ar-H), 5.74 - 5.90 (m, 1 H, H-12), 5.11 (s, 2 H, H-5), 5.02 - 5.09 (m, 2 H, H-13), 4.81 (br. s., 1 H, NH), 3.13 (d, *J* = 6.4 Hz, 2 H, H-7), 2.09 (d, *J* = 7.3 Hz, 2 H, H-11), 1.55 - 1.70 (m, 4 H, H-10), 1.33 - 1.48 (m, 4 H, H-9) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 156.7 (C-6), 136.6 (C-4), 135.5 (C-12), 128.5 (Ar-CH), 128.2 (Ar-CH), 128.1 (Ar-CH), 117.4 (C-13), 66.7 (C-5), 48.0 (C-7), 46.2 (C-8), 42.4 (C-11), 35.0 (C-9), 24.8 (C-10) ppm; IR (ATR): ν_{max} 3339, 3070, 3033, 2950, 2867, 1701, 1638, 1521, 1454, 1411, 1332, 1239, 1137, 913, 774, 735, 696 cm^{-1}; HRMS (ESI) 296.1612 (M + Na$^+$. $C_{17}H_{23}NNaO_2$ requires 296.1621).

(1-Allyl-cyclohexylmethyl)-carbamic acid benzyl ester (142c)



Nitrile **141c** (252mg, 1.69 mmol) was reduced using **general procedure B** with $LiAlH_4$ (96 mg, 2.53 mmol) to give the amine as a pale yellow oil (249 mg, 1.62 mmol, 96% yield). Amine (119 mg, 0.78 mmol) was Cbz protected with K_2CO_3 solution (50% w/w aq, 258 mg, 0.93 mmol) and benzyl chloroformate (0.13 ml, 0.93 mmol). **142c** yielded as a colourless oil (182 mg, 0.633 mmol, 81% yield) after column chromatography (10% EtOAc/hexane). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.29 - 7.44 (m, 5 H, Ar-H), 5.83 (ddt, *J* = 15.6, 11.0, 7.3 Hz, 1 H, H-13), 5.10 - 5.14 (m, 2 H, H-5), 5.01 - 5.09 (m, 2 H, H-13), 4.76 (br. s., 1 H, NH), 3.13 (d, *J* = 6.4 Hz, 2 H, H-7), 2.05 (d, *J* = 7.3 Hz, 2 H, H-12), 1.44 - 1.59 (m, 4 H, H-10), 1.36 - 1.44 (m, 2 H, H-11), 1.23 - 1.35 (m, 4 H, H-9) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 156.7 (C-6), 136.6 (C-4), 134.5 (C-13), 128.5 (Ar-CH), 128.2 (Ar-CH), 128.1 (Ar-CH), 117.5 (C-14), 66.7 (C-5), 47.4 (C-7), 40.6 (C-12), 36.9 (C-8), 33.2 (C-9), 26.1 (C-11), 21.4 (C-10) ppm; IR (ATR): ν_{max} 3341, 3069, 3033, 2924, 2852, 1703, 1638, 1518, 1454, 1412, 1239, 1130, 1077, 1077, 1019, 1000, 912, 847, 824, 774, 751, 734, 696, 613, 462 cm^{-1}; HRMS (ESI) 310.1764 (M + Na$^+$. $C_{18}H_{25}NNaO_2$ requires 310.1777).

(2,2-diphenyl-pent-4-enyl)-carbamic acid benzyl ester (142d)

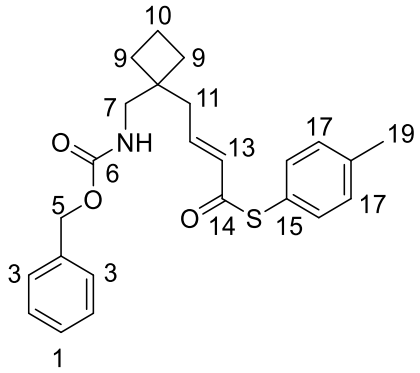


Nitrile **141d** (1.64 g, 7.03 mmol) was reduced using **general procedure B** with $LiAlH_4$ (400 mg, 10.5 mmol) to give the amine as a pale yellow oil (1.66 g, 6.99 mmol, 99% yield). Amine (1.20 g, 5.03 mmol) was Cbz protected with K_2CO_3 solution (50% w/w aq, 1.60 g, 6.04 mmol) and benzyl chloroformate (0.86 ml, 6.04 mmol). **142d** yielded as a colourless oil (1.47 g, 3.97 mmol, 79% yield) after column chromatography (5% EtOAc/hexane). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.11 - 7.43 (m, 15 H, Ar-H), 5.44 (ddt, *J* = 16.9, 10.1, 7.3 Hz, 1 H, H-14), 5.06 (s, 2 H, H-5), 4.93 - 5.02 (m, 2 H, H-15), 4.35 (t, *J* = 6.0 Hz, 1 H, NH), 3.95 (d, *J* = 6.0 Hz, 2 H, H-7), 2.88 (d, *J* = 7.3 Hz, 2 H, H-13) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 156.2 (C-6), 145.2 (C-9), 136.4 (C-4), 133.7 (C-14), 128.5 (Ar-CH), 128.3 (Ar-CH), 128.2 (Ar-CH), 128.2 (Ar-CH), 128.0 (Ar-CH), 126.5 (Ar-CH), 118.6 (C-15), 66.7 (C-5), 50.2 (C-8), 47.6 (C-7), 41.6 (C-13) ppm; IR (ATR): ν_{max} 3433, 3060, 3030, 2936, 1721, 1639, 1598, 1510, 1496, 1405, 1358, 1219, 1142, 1100, 1071, 1030, 1000, 971, 916, 843, 754, 735, 695, 655, 578, 529, 491, 464 cm^{-1}; HRMS (ESI) 372.1969 (M + H$^+$. $C_{25}H_{26}NO_2$ requires 372.1958), 394.1784 (M + Na$^+$. $C_{25}H_{26}NNaO_2$ requires 394.1784)

General procedure C

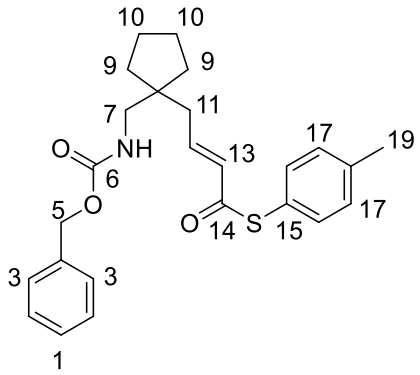
A solution of thioester **134** (0.924 mmol) in 1,2-DCE (7.5 ml) was added under N_2 to a dry flask containing Hoveyda-Grubbs Catalyst™ 2nd generation (0.0308 mmol) and copper iodide (0.308 mmol) while stirring. A solution of Cbz-amine (0.308 mmol) in 1,2-DCE (7.5 ml) was added under N_2 and the reaction heated to 50 °C for 16 hours. The reaction was then cooled to room temperature, exposed to air and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to afford the product (0.232 mmol, 75% yield)

6-Cbz-amino-5,5-cyclobutyl-hex-2-enethioic acid S-p-tolyl ester (143a)



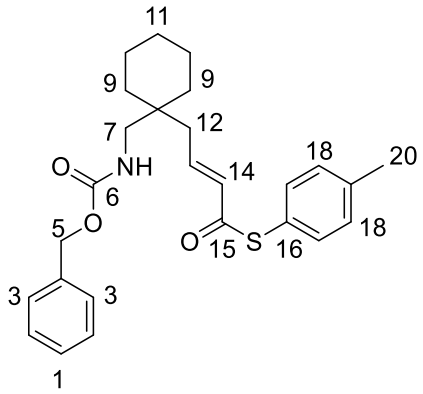
143a was synthesised using **general procedure C** with thioester **134** (118 mg, 0.66 mmol), Hoveyda-Grubbs Catalyst™ 2nd generation (13.8 mg, 0.022 mmol), copper iodide (41.9 mg, 0.22 mmol) and Cbz-amine **142a** (57 mg, 0.22 mmol). **143a** yielded as a green oil (76 mg, 0.19 mmol, 84% yield) after column chromatography (8% EtOAc/hexane). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 - 7.40 (m, 5 H, Ar-H), 7.32 (d, *J* = 7.6 Hz, 2 H, H-16), 7.23 (d, *J* = 7.6 Hz, 2 H, H-17), 6.96 (dt, *J* = 15.3, 7.6 Hz, 1 H, H-12), 6.23 (d, *J* = 16.0 Hz, 1 H, H-13), 5.12 (s, 2 H, H-5), 4.79 (br. s, 1 H, NH), 3.28 (d, *J* = 6.1 Hz, 2 H, H-7), 2.39 (s, 3 H, H-19), 2.36 (d, *J* = 7.6 Hz, 2 H, H-11), 1.87 - 1.98 (m, 2 H, H-10), 1.78 - 1.87 (m, 4 H, H-9) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 188.3 (C-14), 156.7 (C-6), 142.3 (C-12), 139.6 (C-18), 136.4 (C-4), 134.6 (C-16), 130.1 (C-13), 130.0 (C-17), 128.6 (Ar-CH), 128.2 (Ar-CH), 128.2 (Ar-CH), 123.9 (C-15), 66.9 (C-5), 48.0 (C-7), 42.3 (C-8), 40.3 (C-11), 28.6 (C-9), 21.4 (C-19), 14.9 (C-10) ppm; IR (ATR): ν_{max} 3349, 3032, 2930, 1695, 1629, 1532, 1494, 1454, 1335, 1243, 1134, 1045, 1003, 979, 808, 774, 736, 697, 619, 597, 533, 477 cm^{-1}; HRMS (ESI) 432.1609 (M + Na^{+}. $C_{24}H_{27}NNaO_3S$ requires 432.1604)

6-Cbz-amino-5,5-cyclopentyl-hex-2-enethioic acid S-p-tolyl ester (143b)



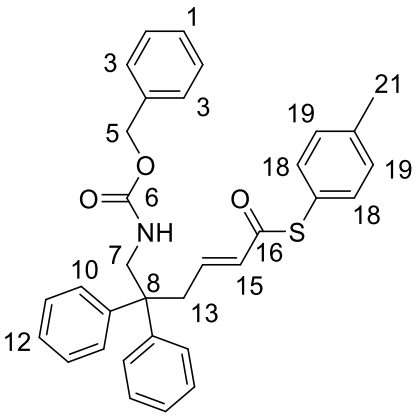
143b was synthesised using **general procedure C** with thioester **134** (118 mg, 0.66 mmol), Hoveyda-Grubbs Catalyst™ 2nd generation (13.8 mg, 0.022 mmol), copper iodide (41.9 mg, 0.22 mmol) and Cbz-amine **142b** (60 mg, 0.22 mmol). **143b** yielded as a green oil (81 mg, 0.19 mmol, 86% yield) after column chromatography (8% EtOAc/hexane). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 - 7.42 (m, 5 H, Ar-H), 7.32 (d, *J* = 7.8 Hz, 2 H, H-16), 7.23 (d, *J* = 7.8 Hz, 2 H, H-17), 6.97 (dt, *J* = 15.3, 7.6 Hz, 1 H, H-12), 6.21 (d, *J* = 15.3 Hz, 1 H, H-13), 5.12 (s, 2 H, H-5), 4.79 (br. s, 1 H, NH), 3.15 (d, *J* = 6.1 Hz, 2 H, H-7), 2.39 (s, 3 H, H-19), 2.25 (d, *J* = 7.6 Hz, 2 H, H-11), 1.60 - 1.70 (m, 4 H, H-10), 1.36 - 1.54 (m, 4 H, H-9) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 188.3 (C-14), 156.7 (C-6), 143.2 (C-12), 139.6 (C-18),136.4 (C-4), 134.6 (C-16), 130.1 (C-13), 130.0 (C-17), 128.6 (Ar-CH), 128.2 (Ar-CH), 128.2 (Ar-CH), 123.9 (C-15), 66.9 (C-5), 48.3 (C-7), 47.0 (C-8), 40.6 (C-11), 35.0 (C-9), 24.8 (C-10), 21.4 (C-19) ppm; IR (ATR): ν_{max} 3345, 3032, 2950, 2867, 1695, 1629, 1534, 1494, 1239, 1140, 1005, 889, 807, 774, 735, 697, 617, 447 cm^{-1}; HRMS (ESI) 446.1774 (M + Na^{+}. $C_{25}H_{29}NNaO_3S$ requires 446.1760).

6-Cbz-amino-5,5-cyclohexyl-hex-2-enethioic acid S-p-tolyl ester (143c)



143c was synthesised using **general procedure C** with thioester **134** (120 mg, 0.68 mmol), Hoveyda-Grubbs Catalyst™ 2nd generation (14.1 mg, 0.023 mmol), copper iodide (42.9 mg, 0.23 mmol) and Cbz-amine **142c** (65 mg, 0.23 mmol). **143c** yielded as a colourless oil (66.2 mg, 0.15 mmol, 66% yield) after column chromatography (8% EtOAc/hexane). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.29 - 7.42 (m, 5 H, Ar-H), 7.32 (d, *J* = 7.6 Hz, 2 H, H-17), 7.23 (d, *J* = 7.6 Hz, 2 H, H-18), 7.00 (dt, *J* = 15.3, 7.6 Hz, 1 H, H-13), 6.21 (d, *J* = 15.3 Hz, 1 H, H-14), 5.12 (s, 2 H, H-5), 4.75 (t, *J* = 6.4 Hz, 1 H, NH), 3.16 (d, *J* = 6.4 Hz, 2 H, H-7), 2.39 (s, 3 H, H-20), 2.21 (d, *J* = 7.6 Hz, 2 H, H-12), 1.40 - 1.60 (m, 6 H, H-10, H-11), 1.24 - 1.39 (m, 4 H, H-9) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 188.2 (C-15), 156.6 (C-6), 142.6 (C-13), 139.6 (C-19), 136.4 (C-4), 134.6 (C-17), 130.0 (C-14), 130.0 (C-18), 128.5 (Ar-CH), 128.2 (Ar-CH), 128.2 (Ar-CH), 123.9 (C-16), 66.9 (C-5), 47.6 (C-7), 39.0 (C-12), 38.2 (C-8), 33.2 (C-9), 25.9 (C-11), 21.3 (C-10), 21.3 (C-20) ppm; IR (ATR): ν_{max} 3346, 3063, 3031, 2924, 2853, 1692, 1627, 1598, 1529, 1494, 1454, 1401, 1361, 1336, 1303, 1238, 1147, 1132, 1105, 1091, 1061, 1015, 981, 918, 882, 848, 835, 807, 774, 752, 734, 697, 646, 617, 597, 576, 533, 475 cm^{-1}; HRMS (ESI) 438.2105 (M + H^{+}. $C_{26}H_{32}NO_3S$ requires 438.2097), 460.1925 (M + Na^{+}. $C_{26}H_{31}NNaO_3S$ requires 460.1917).

6-Cbz-amino-5,5-diphenyl-hex-2-enethioic acid S-p-tolyl ester (143d)



143d was synthesised using **general procedure C** with thioester **134** (276 mg, 1.55 mmol), Hoveyda-Grubbs Catalyst™ 2nd generation (32.4 mg, 0.0517 mmol), copper iodide (98.5 mg, 0.517 mmol) and Cbz-amine **142d** (192 mg, 0.517 mmol). **143d** yielded as a pale brown oil (146 mg, 0.280 mmol, 54% yield) after column chromatography (8% EtOAc/hexane). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.13 - 7.38 (m, 19 H, Ar-H), 6.60 (dt, *J* = 16.0, 7.6 Hz, 1 H, H-14), 6.07 (d, *J* = 16.0 Hz, 1 H, H-15), 5.06 (s, 2 H, H-5), 4.34 (t, *J* = 6.1 Hz, 1 H, NH), 3.94 (d, *J* = 6.1 Hz, 2 H, H-7), 2.98 (d, *J* = 7.6 Hz, 2 H, H-13), 2.35 (s, 3 H, H-21) ppm; ^{13}C NMR (101 MHz,

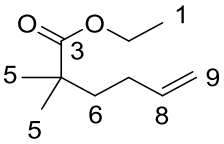
Chloroform-*d*) δ 188.1 (C-16), 156.2 (C-6), 144.18 (C-9), 141.5 (C-14), 139.5 (C-20), 136.2 (C-4), 134.5 (C-18), 130.9 (C-15), 129.9 (C-19), 128.6 (Ar-CH), 128.6 (Ar-CH), 128.3 (Ar-CH), 128.2 (Ar-CH), 127.8 (Ar-CH), 126.9 (Ar-CH), 124.0 (C-17), 66.9 (C-5), 50.9 (C-8), 48.3 (C-7), 40.2 (C-13), 21.3 (C-21) ppm; IR (ATR): ν_{max} 3432, 3030, 2924, 1722, 1685, 1630, 1513, 1495, 1445, 1224, 1139, 1072, 1017, 910, 808, 755, 734, 699, 476 cm^{-1}; HRMS (ESI) 522.2091 ($M + H^+$. $C_{33}H_{32}NO_3S$ requires 522.2097), 544.1913 ($M + Na^+$. $C_{33}H_{31}NNaO_3S$ requires 544.1917)

Synthesis of 2,2-disubstituted precursors

General procedure D

To a solution of diisopropylamine (10.8 mmol) in dry THF (5 ml) at -78 °C under N_2 was added n-BuLi (2.5 M in hexanes, 10.8 mmol) and the solution stirred for 45 mins. A solution of ester (9.9 mmol) in THF (5 ml) was added over 5 mins at -78 °C and the reaction stirred for 45 mins. 4-bromo-1-butene (1.00 ml, 9.9 mmol) was added over 1 min at -78 °C and the reaction warmed to room temperature. The reaction was stirred overnight and quenched with 1 M HCl (10 ml). The reaction was partitioned with diethyl ether (30 ml) and aqueous phase extracted with diethyl ether (2 x 30 ml), organic fractions were combined, washed with saturated brine solution (30 ml), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to afford the product (6.93 mmol, 70% yield)

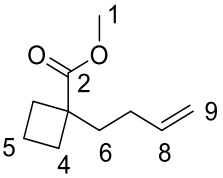
2,2-dimethyl-hex-5-enoic acid ethyl ester (146)



146 was synthesised using **general procedure D** with diisopropylamine (1.51 ml, 10.8 mmol), n-BuLi (2.5 M in hexanes, 10.8 mmol), ethyl isobutyrate (1.33 ml, 9.9 mmol) and 4-bromo-1-butene (1.00 ml, 9.9 mmol). **146** yielded as a colourless oil (1.18 g, 6.93 mmol, 70% yield) after column chromatography (5% EtOAc/hexane). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.80 (ddt, *J* =16.8, 9.9, 6.9 Hz, 1 H, H-8), 5.01 (dq, *J* = 16.8, 1.5 Hz, 1 H, H-9), 4.94 (dq, *J* = 9.9, 1.5 Hz, 1 H, H-9), 4.12 (q, *J* = 7.6 Hz, 2 H, H-2), 1.95 - 2.04 (m, 2 H, H-7), 1.59 - 1.66 (m, 2 H, H-6), 1.25 (t, *J* = 7.6 Hz, 3 H, H-1), 1.18 (s, 6 H, H-5) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 177.8 (C-3), 138.5 (C-8), 114.4 (C-9), 60.2 (C-2), 42.0 (C-4), 39.8 (C-6), 29.3 (C-7), 25.1 (C-5), 14.2 (C-1) ppm;

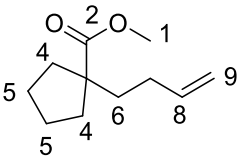
IR (ATR): ν_{max} 2978, 2938, 1726, 1641, 1473, 1450, 1473, 1386, 1365, 1319, 1280, 1199, 1143, 1094, 1027, 996, 909, 863, 774, 646, 580, 556, 503 cm^{-1}; HRMS (APCI) 171.1373 ($M + H^+$. $C_{10}H_{19}O_2$ requires 171.1380).

1-But-3-enyl-cyclobutanecarboxylic acid methyl ester (156a)



156a was synthesised using **general procedure D** with diisopropylamine (0.68 ml, 4.82 mmol), n-BuLi (2.5 M in hexanes, 4.82 mmol), methyl cyclobutane carboxylate (0.5 ml, 4.38 mmol) and 4-bromo-1-butene (0.45 ml, 4.38 mmol). **156a** yielded as a colourless oil (285 mg, 1.69 mmol, 39% yield) after column chromatography (2% EtOAc/hexane). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.80 (ddt, *J* = 16.8, 9.9, 6.1 Hz, 1 H, H-8), 5.01 (dq, *J* = 16.8, 1.5 Hz, 1 H, H-9), 4.94 (dq, *J* = 9.9, 1.5 Hz, 1 H, H-9), 3.69 (s, 3 H, H-1), 2.37 - 2.49 (m, 2 H, H-4), 1.83 - 1.99 (m, 8 H, H-4, H-5, H-6, H-7) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 177.5 (C-2), 138.2 (C-8), 114.6 (C-9), 51.6 (C-1), 47.4 (C-3), 37.2 (C-6), 30.0 (C-4), 29.3 (C-7), 15.6 (C-5) ppm; IR (ATR): ν_{max} 3077, 2948, 2869, 1731, 1693, 1641, 1434, 1329, 1283, 1244, 1201, 1142, 1112, 994, 911, 806, 692, 637, 458 cm^{-1};

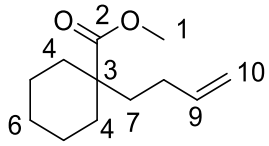
1-But-3-enyl-cyclopentanecarboxylic acid methyl ester (156b)



156b was synthesised using **general procedure D** with diisopropylamine (1.54 ml, 11 mmol), n-BuLi (2.5 M in hexanes, 11 mmol), methyl cyclopentane carboxylate (1.28 g, 10 mmol) and 4-bromo-1-butene (1.00 ml, 10 mmol). **156b** yielded as a colourless oil (1.44 g, 7.89 mmol, 79% yield) after column chromatography (2% EtOAc/hexane). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.78 (ddt, *J* = 16.9, 10.5, 6.9 Hz, 1 H, H-8), 5.00 (dq, *J* = 16.9, 1.5 Hz, 1 H, H-9), 4.93 (dq, *J* = 10.5, 1.5 Hz, 1 H, H-9), 3.67 (s, 3 H, H-1), 2.07 - 2.19 (m, 2 H, H-4), 1.92 - 2.01 (m, 2 H, H-7), 1.67 - 1.75 (m, 2 H, H-6), 1.58 - 1.67 (m, 4 H, H-5), 1.43 - 1.53 (m, 2 H, H-4) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 178.2 (C-2), 138.4 (C-8), 114.4 (C-9), 53.8 (C-3), 51.7 (C-1), 38.4 (C-6),

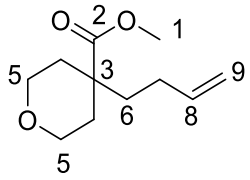
36.0 (C-4), 30.3 (C-7), 24.9 (C-5); IR (ATR): ν_{max} 3078, 2951, 2871, 1730, 1641, 1452, 1339, 1255, 1196, 1162, 994, 910 cm^{-1}.

1-But-3-enyl-cyclohexanecarboxylic acid methyl ester (156c)



156c was synthesised using **general procedure D** with diisopropylamine (1.54 ml, 11 mmol), n-BuLi (2.5 M in hexanes, 11 mmol), methyl cyclohexane carboxylate (1.45 ml, 10 mmol) and 4-bromo-1butene (1.00 ml, 10 mmol). **156c** yielded as a colourless oil (1.56 g, 7.97 mmol, 80% yield) after column chromatography (2% EtOAc/hexane). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.76 (ddt, *J* = 16.9, 10.0, 6.3 Hz, 1 H, H-9), 4.99 (dq, *J* = 16.9, 1.5 Hz, 1 H, H-10), 4.93 (dq, *J* = 10.0, 1.5 Hz, 1 H, H-10), 3.68 (s, 3 H, H-1), 2.03 - 2.14 (m, 2 H, H-4), 1.90 - 2.00 (m, 2 H, H-8), 1.50 - 1.64 (m, 5 H, H-5, H-6, H-7), 1.16 - 1.40 (m, 5 H, H-4, H-5, H-6) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 177.1 (C-2), 138.5 (C-9), 114.4 (C-10), 51.4 (C-1), 46.8 (C-3), 39.7 (C-7), 34.2 (C-4), 28.5 (C-8), 25.9 (C-6), 23.2 (C-5); IR (ATR): ν_{max} 3078, 2930, 2854, 1727, 1641, 1453, 1432, 1364, 1330, 1292, 1275, 1194, 1156, 1134, 1040, 995, 959, 909, 891, 850, 800, 765, 1649, 620, 567, 514 cm^{-1}; HRMS (APCI) 197.1543 ($M + H^+$. $C_{12}H_{21}O_2$ requires 197.1536).

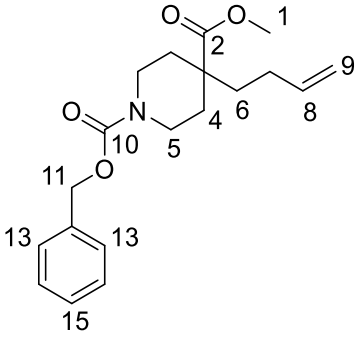
4-But-3-enyl-tetrahydro-pyran-4-carboxylic acid methyl ester (156d)



156d was synthesised using **general procedure D** with diisopropylamine (1.54 ml, 11 mmol), n-BuLi (2.5 M in hexanes, 11 mmol), methyl tetrahydro-2H-pyran-4-carboxylate (1.54 ml, 10 mmol) and 4-bromo-1-butene (1.00 ml, 10 mmol). **156d** yielded as a colourless oil (1.45 g, 7.32 mmol, 73% yield) after column chromatography (10% EtOAc/hexane). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.75 (ddt, *J* = 16.9, 10.5, 6.4 Hz, 1 H, H-8), 5.00 (dq, *J* = 16.9, 1.5 Hz, 1 H, H-9), 4.95 (dq, *J* = 10.5, 1.5 Hz, 1 H, H-9), 3.83 (ddd, *J* = 11.7, 4.4, 4.1 Hz, 2 H, H-5), 3.72 (s, 3 H, H-1), 3.43 (ddd, *J* = 11.7, 2.3 Hz, 2 H, H-5), 2.10 (ddd, *J* = 13.7, 4.4, 2.3 Hz, 2 H, H-4), 1.91 - 2.02 (m, 2 H, H-7), 1.59 - 1.67 (m, 2 H, H-6), 1.52 (ddd, *J* = 13.7, 11.7, 4.1 Hz, 2 H, H-4) ppm; ^{13}C

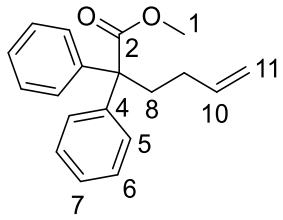
NMR (101 MHz, Chloroform-*d*) δ 176.1 (C-2), 137.8 (C-8), 114.8 (C-9), 65.4 (C-5), 51.8 (C-1), 44.8 (C-3), 39.9 (C-6), 34.2 (C-4), 28.1 (C-7); IR (ATR): ν_{max} 3078, 2954, 2852, 1728, 1641, 1452, 1389, 1337, 1299, 1242, 1210, 1194, 1152, 1108, 1034, 1015, 997, 982, 912, 888, 840, 802, 775, 600, 561, 491, 462 cm^{-1}; HRMS (ESI) 211.1150 (M + Na^+. $C_{11}H_{18}NaO_3$ requires 211.1150).

4-But-3-enyl-piperidine-1,4-dicarboxylic acid 1-benzyl ester 4-methyl ester (156e)



LiHMDS (1M in THF, 22.9 ml, 22.9 mmol) was diluted in dry THF (50 ml) under N_2 and cooled to -78 °C. A solution of N-Cbz-4-piperidinecarboxylic acid methyl ester (5.298 mg, 19.1 mmol) in THF (50 ml) was added at -78 °C over 5 mins and the reaction stirred for 45 mins. 4-bromo-1-butene (2.91 ml, 28.7 mmol) was added over 1 min at -78 °C and the reaction warmed to room temperature. The reaction was stirred overnight and quenched with 1 M HCl (100 ml). The reaction was partitioned with diethyl ether (100 ml) and aqueous phase extracted with diethyl ether (2 x 100 ml), Organic fractions were combined, washed with saturated brine solution (100 ml), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (20% EtOAc/hexane) to afford **156e** as a colourless oil (1.77 g, 5.33 mmol, 28% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.28 - 7.41 (m, 5 H, Ar-H), 5.74 (ddt, *J* = 16.8, 10.7, 6.9 Hz, 1 H, H-8), 5.12 (s, 2 H, H-11), 5.00 (dq, *J* = 16.8, 1.5 Hz, 1 H, H-9), 4.95 (dq, *J* = 10.7, 1.5 Hz, 1 H, H-9), 3.89 - 4.07 (m, 2 H, H-5), 3.71 (s, 3 H, H-1), 2.80 - 3.05 (m, 2 H, H-5), 2.10 - 2.22 (m, 2 H, H-4), 1.89 - 2.02 (m, 2 H, H-7), 1.55 - 1.65 (m, 2 H, H-6), 1.30 - 1.47 (m, 2 H, H-4) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 175.7 (C-2), 155.2 (C-10), 137.7 (C-8), 136.8 (C-12), 128.5 (Ar-CH), 127.9 (Ar-CH), 127.8 (Ar-CH), 114.9 (C-9), 67.0 (C-11), 51.8 (C-1), 45.5 (C-3), 41.5 (C-5), 39.5 (C-6), 33.3 (C-4), 28.2 (C-7) ppm; IR (ATR): ν_{max} 2948, 1726, 1699, 1641, 1497, 1472, 1430, 1360, 1338, 1278, 1246, 1226, 1145, 1093, 1015, 912, 767, 603, 556 cm^{-1}; HRMS (ESI) 332.1848 (M + H^+. $C_{19}H_{26}NO_4$ requires 332.1856), 354.1666 (M + Na^+. $C_{19}H_{24}NNaO_4$requires 354.1676).

2,2-diphenyl-hex-5-enoic acid methyl ester (156f)

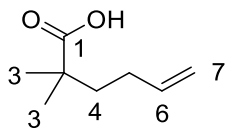


156f was synthesised using the same procedure as **156e** with LiHMDS (1M in THF, 10.6 ml, 10.6 mmol) methyl diphenylacetate (2.0 g, 8.84 mmol) and 4-bromo-1butene (1.00 ml, 10 mmol). **156f** yielded as a colourless oil (1.03 g, 3.67 mmol, 42% yield) after column chromatography (2% EtOAc/hexane). ^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm 7.26 - 7.41 (m, 10 H, Ar-H), 5.81 (ddt, *J* = 16.8, 9.9, 6.5 Hz, 1 H, H-10), 5.01 (dq, *J* = 16.8, 1.5 Hz, 1 H, H-11), 4.96 (dq, *J* = 9.9, 1.5 Hz, 1 H, H-11), 3.72 (s, 3 H, H-1), 2.45 - 2.57 (m, 2 H, H-8), 1.79 - 1.91 (m, 2 H, H-9) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 174.7 (C-2), 142.7 (C-4), 138.3 (C-10), 128.9 (Ar-CH), 127.9 (Ar-CH), 126.8 (Ar-CH), 114.5 (C-11), 60.1 (C-3), 52.3 (C-1), 37.3 (C-8), 29.6 (C-9) ppm; IR (ATR): ν_{max} 3024, 3060, 2950, 1729, 1640, 1598, 1495, 1445, 1221, 1121, 1063, 1033, 913, 784, 760, 699, 602, 576, 502, 481 cm^{-1}; HRMS (ESI) 281.1528 (M + H^{+}. $C_{19}H_{21}O_2$ requires 281.1536), 303.1356 (M + Na^{+}. $C_{19}H_{20}NaO_2$ requires 303.1356).

General procedure E

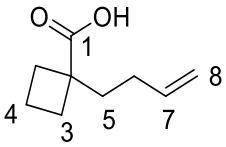
To a solution of alkenyl ester (5.9 mmol) in MeOH (10 ml) was added NaOH (20% w/w, 2.5 ml) and reaction heated to reflux while stirring for 3 hours. Reaction was cooled to room temperature and diluted with H_2O (10 ml) and extracted with diethyl ether (20 ml). The aqueous layer was acidified to pH 1 with 3M HCl (8 ml), extracted with diethyl ether (3 x 25 ml). Combined organics were dried with $MgSO_4$, filtered and concentrated *in vacuo*, and product used without further purification (3.8 mmol, 64% yield).

2,2-dimethyl-hex-5-enoic acid (147)



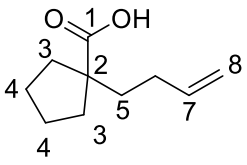
147 was synthesised using **general procedure E** with ester **146** (1.00 g, 5.9 mmol). **147** yielded as a colourless oil (539 mg, 3.8 mmol, 64% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.93 (s, 1 H, COOH), 5.81 (ddt, *J* = 17.0, 10.7, 6.9 Hz, 1 H, H-6), 5.03 (dq, *J* = 17.0, 1.5 Hz, 1 H, H-7), 4.95 (dq, *J* = 10.7, 1.5 Hz, 1 H, H-7), 2.02 - 2.11 (m, 2 H, H-5), 1.62 - 1.69 (m, 2 H, H-4), 1.22 (s, 6 H, H-3) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 184.8 (C-1), 138.3 (C-6), 114.6 (C-7), 42.0 (C-2), 39.5 (C-4), 29.2 (C-5), 24.9 (C-3) ppm; IR (ATR): ν_{max} 3078, 2941, 2976, 1696, 1642, 1476, 1452, 1409, 1367, 1287, 1218, 1177, 994, 909, 788, 644, 549 cm^{-1}; HRMS (ESI) 141.0927 (M - H. $C_8H_{13}O_2$ requires 141.0921).

1-But-3-enyl-cyclobutanecarboxylic acid (157a)



157a was synthesised using **general procedure E** with ester **156a** (220 mg, 1.31 mmol). **157a** yielded as a colourless oil (196 mg, 1.27 mmol, 97% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.33 (br. s, 1 H, COOH), 5.83 (ddt, *J* = 16.9, 10.4, 6.2 Hz, 1 H, H-7), 5.05 (dq, *J* = 16.9, 1.5 Hz, 1 H, H-8), 4.97 (dq, *J* = 10.4, 1.5 Hz, 1 H, H-8), 2.39 - 2.56 (m, 2 H, H-3), 1.99 - 2.11 (m, 2 H, H-6), 1.86 - 1.98 (m, 6 H, H-3, H-4, H-5) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 183.6 (C-1), 138.1 (C-8), 114.7 (C-7), 47.3 (C-2), 36.9 (C-5), 30.0 (C-3), 29.2 (C-6), 15.6 (C-4) ppm; IR (ATR): ν_{max} 3078, 2985, 2939, 2869, 1693, 1641, 1450, 1408, 1328, 1286, 1253, 1226, 1153, 1035, 994, 910, 780, 742, 684, 636, 552 cm^{-1}; HRMS (ESI) 153.0923 (M – H^{+}. $C_9H_{13}O_2$ requires 153.0921).

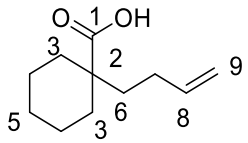
1-But-3-enyl-cyclopentanecarboxylic acid (157b)



157b was synthesised using **general procedure E** with ester **156b** (1.20 g, 6.58 mmol). **157b** yielded as a colourless oil (613 mg, 3.64 mmol, 55% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.03 (br. s., 1 H, COOH), 5.81 (ddt, *J* = 17.0, 10.4, 6.5 Hz, 1 H, H-7), 5.03 (dq, *J* = 17.0, 1.5 Hz, 1 H, H-8), 4.95 (dq, *J* = 10.4, 1.5 Hz, 1 H, H-8), 2.11 - 2.22 (m, 2 H, H-3), 2.01 - 2.10 (m, 2 H,

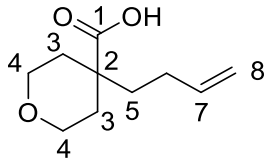
H-6), 1.71 - 1.79 (m, 2 H, H-5), 1.61 - 1.70 (m, 4 H, H-4), 1.48 - 1.57 (m, 2 H, H-3) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 184.7 (C-1), 138.3 (C-7), 114.5 (C-8), 53.6 (C-2), 38.1 (C-5), 36.1 (C-3), 30.2 (C-6), 25.0 (C-4) ppm; IR (ATR): ν_{max} 3078, 2953, 2872, 1693, 1641, 1453, 1406, 1338, 1281, 1219, 991, 910, 786, 643, 509 cm^{-1}; HRMS (ESI) 167.1077 (M – H$^+$. $C_{10}H_{15}O_2$ requires 167.1078), 191.1038 (M + Na$^+$. $C_{10}H_{16}NaO_2$ requires 191.1043).

1-But-3-enyl-cyclohexanecarboxylic acid (157c)



157c was synthesised using **general procedure E** with ester **156c** (1.10 g, 5.60 mmol). **157c** yielded as a white solid (599 mg, 3.29 mmol, 59% yield)**.** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.61 (br. s., 1 H, COOH), 5.80 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1 H, H-8), 5.02 (dq, *J* = 17.1, 1.8 Hz, 1 H, H-9), 4.95 (dq, *J* = 10.2, 1.8 Hz, 1 H, H-9), 1.98 - 2.15 (m, 4 H, H-3,H-7), 1.54 - 1.69 (m, 5 H, H-4, H-5, H-6), 1.34 - 1.49 (m, 2 H, H-4), 1.17 - 1.33 (m, 3 H, H-3, H-5) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 182.89 (C-1), 138.3 (C-8), 114.6 (C-9), 46.6 (C-2), 39.3 (C-6), 33.9 (C-3), 28.4 (C-7), 25.9 (C-5), 23.1 (C-4) ppm; IR (ATR): ν_{max} 3078, 2931, 2856, 1695 1642, 1455, 1407, 1244, 1214, 1165, 11.39, 995, 910, 850, 751, 570 cm^{-1}; HRMS (ESI) 181.1232 (M - H. $C_{11}H_{17}O_2$ requires 181.1234); mp. 39.8-41.6 °C.

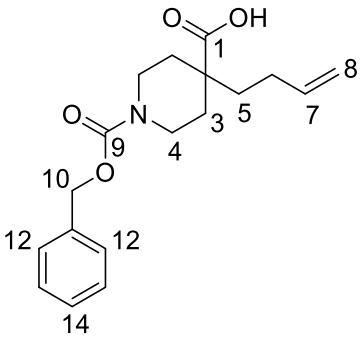
4-But-3-enyl-tetrahydro-pyran-4-carboxylic acid (157d)



157d was synthesised using **general procedure E** with ester **156d** (1.10 g, 5.60 mmol). **157d** yielded as a white solid (789 mg, 4.28 mmol, 76% yield)**.** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.79 (br s, 1 H, COOH), 5.79 (ddt, *J* = 17.1, 10.4, 6.5 Hz, 1 H, H-7), 5.04 (dq, *J* = 17.1, 1.8 Hz, 1 H, H-8), 4.98 (dq, *J* = 10.4, 1.8 Hz, 1 H, H-8), 3.87 (dt, *J* = 12.2, 3.8 Hz, 2 H, H-4), 3.52 (ddd, *J* = 12.2, 11.6, 1.9 Hz, 2 H, H-4), 2.11 (ddd, *J* = 13.7, 3.8, 1.9 Hz, 2 H, H-3), 2.01 - 2.08 (m, 2 H, H-6), 1.65 - 1.74 (m, 2 H, H-5), 1.57 (ddd, *J* = 13.7, 11.6, 3.8 Hz, 2 H, H-3) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 180.7 (C-1), 137.7 (C-8), 115.1 (C-7), 65.3 (C-4), 44.6 (C-2), 39.6 (C-5),

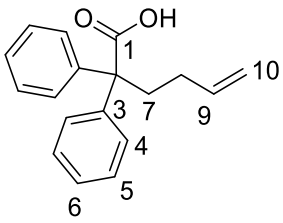
33.9 (C-3), 28.0 (C-6) ppm; IR (ATR): ν_{max} 3072, 2972, 2939, 2910, 2883, 2732, 2598, 1725, 1641, 1452, 1442, 1425, 1383, 1335, 1301, 12847, 1267, 1240, 1219, 1197, 1159, 1089, 1022, 975, 910, 891, 782, 746, 596, 558 cm^{-1}; HRMS (ESI) 183.1031 (M - H. $C_{10}H_{15}O_3$ requires 183.1027); mp. 62.1-63.1°C.

4-But-3-enyl-piperidine-1,4-dicarboxylic acid 1-benzyl ester (157e)



157e was synthesised using **general procedure E** with ester **156e** (1.51 g, 4.56 mmol). **157e** yielded as a colourless oil (872 mg, 2.75 mmol, 60% yield)**.** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.28 - 7.47 (m, 5 H, Ar-H), 5.77 (ddt, *J* = 17.1, 10.4, 6.5 Hz, 1 H, H-7), 5.13 (s, 2 H, H-10), 5.03 (dq, *J* = 17.1, 1.5 Hz, 1 H, H-8), 4.97 (dq, *J* = 10.4, 1.5 Hz, 1 H, H-8), 3.87 - 4.13 (m, 2 H, H-4), 2.92 - 3.18 (m, 2 H, H-4), 2.10 - 2.21 (m, 2 H, H-3), 2.00 - 2.08 (m, 2 H, H-6), 1.59 - 1.76 (m, 2 H, H-5), 1.34 - 1.52 (m, 2 H, H-3) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 180.8 (C-1), 155.3 (C-9), 137.5 (C-7), 136.7 (C-11), 128.5 (Ar-CH), 128.0 (Ar-CH), 127.9 (Ar-CH), 115.1 (C-8), 67.1 (C-10), 45.3 (C-2), 41.5 (C-4), 39.2 (C-5), 33.0 (C-3), 28.1 (C-6) ppm; IR (ATR): ν_{max} 3072, 2936, 1727, 1699, 1670, 1477, 1451, 1362, 1279, 1188, 1151, 1107, 1013, 958, 912, 856, 764, 734, 698, 602, 557, 460 cm^{-1}; HRMS (ESI) 318.1692(M + H^+. $C_{18}H_{24}NO_4$ requires 318.1700), 340.1510 (M + Na^+. $C_{18}H_{23}NNaO_4$requires 340.1519).

2,2-diphenyl-hex-5-enoic acid (157f)



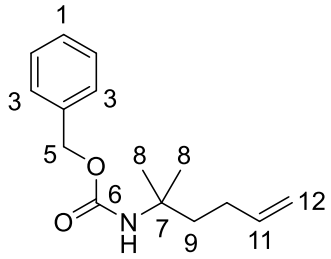
157F was synthesised using **general procedure E** with ester **156f** (1.51 g, 4.56 mmol). **157F** yielded as a white solid (356 mg, 1.34 mmol, 54% yield)**.** ^{1}H NMR (400 MHz, Chloroform-*d*) δ

11.64 (br. s., 1 H, COOH), 7.18 - 7.41 (m, 10 H, Ar-H), 5.76 (ddt, *J* = 17.2, 10.3, 6.1 Hz, 1 H, H-9), 4.96 (dq, *J* = 17.2, 1.5 Hz, 2 H, H-10), 4.92 (dq, *J* = 10.3, 1.5 Hz, 2 H, H-10), 2.40 - 2.54 (m, 2 H, H-7), 1.74 - 1.90 (m, 2 H, H-8) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 180.1 (C-1), 142.2 (C-3), 138.2 (C-9), 129.0 (Ar-CH), 128.0 (Ar-CH), 127.0 (Ar-CH), 114.6 (C-10), 60.0 (C-2), 37.1 (C-7), 29.6 (C-8) ppm; IR (ATR): ν_{max} 3061, 2975, 1698, 1640, 1600, 1495, 1445, 1398, 1262, 1217, 1033, 1003, 913, 759, 724, 698, 591, 502 cm^{-1}; HRMS (ESI) 267.1381 (M + H$^+$. $C_{18}H_{19}O_2$ requires 267.1380), 289.1190 (M + Na$^+$. $C_{18}H_{18}NaO_2$ requires 289.1199), 265.1299 (M - H$^+$. $C_{18}H_{17}O_2$ requires 265.1234); mp. 135.0-137.2 °C.

General Procedure F

To a solution of carboxylic acid (2.10 mmol) in dry toluene (15 ml) under N_2 was added Et_3N (2.52 mmol) and DPPA (2.31 mmol) and the reaction heated to 90 °C for 2 hours. Benzyl alcohol (3.15 mmol) was added and reaction stirred at 90 °C for 96 hours. Reaction was quenched with H_2O (20 ml) and extracted with EtOAc (2 x 30 ml). Combined organics were washed with saturated brine solution (2 x 30 ml), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1.40 mmol, 67% yield).

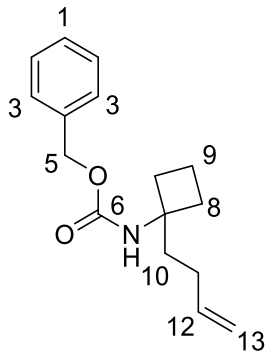
(1,1-dimethyl-pent-4-enyl)-carbamic acid benzyl ester (148)



148 was synthesised using **general procedure F** with acid **147** (299 mg, 2.10 mmol), Et_3N (0.35 ml, 2.52 mmol), DPPA (0.50 ml, 2.31 mmol) and benzyl alcohol (0.33 ml, 3.15 mmol). **148** yielded as a colourless oil (346 mg, 1.40 mmol, 67% yield) after column chromatography (5% EtOAc/hexane). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.28 - 7.42 (m, 5 H, Ar-H), 5.81 (ddt, *J* = 16.8, 10.7, 6.9, Hz, 1 H, H-11), 5.06 (s, 2 H, H-5), 5.02 (dq, *J* = 17.5, 1.5 Hz, 2 H, H-12), 4.95 (dq, *J* = 10.7, 1.5 Hz, 1 H, H-12), 4.67 (br. s., 1 H, NH), 1.99 - 2.10 (m, 2 H, H-10), 1.70 - 1.82 (m, 2 H, H-9), 1.31 (s, 6 H, H-8) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.5 (C-6), 138.5 (C-11),

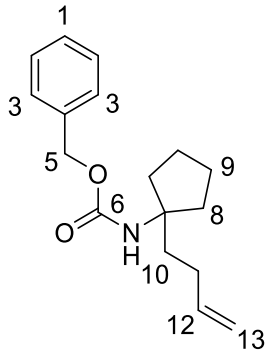
136.7 (C-4), 128.5 (Ar-CH), 128.0 (Ar-CH), 128.0 (Ar-CH), 114.5 (C-12), 66.0 (C-5), 52.7 (C-7), 39.4 (C-9), 28.5 (C-10), 27.0 (C-8) ppm; IR (ATR): ν_{max} 3346, 3066, 3033, 2973, 1703, 1640, 1505, 1453, 1387, 1365, 1314, 1259, 1214, 1071, 1028, 909, 777, 737, 696, 602, 475 cm^{-1}; HRMS (ESI) 248.1637 ($M + H^+$. $C_{15}H_{22}NO_2$ requires 248.1645), 270.1455 ($M + Na^+$. $C_{15}H_{21}NNaO_2$ requires 270.1464).

(1-But-3-enyl-cyclobutyl)-carbamic acid benzyl ester (158a)



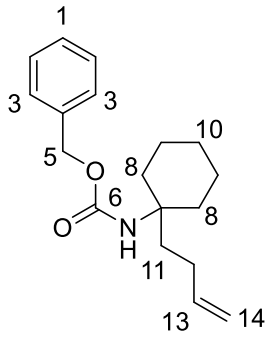
158a was synthesised using **general procedure F** with acid **157a** (106 mg, 0.687 mmol), Et_3N (0.12 ml, 0.824 mmol), DPPA (0.16 ml, 0.756 mmol) and benzyl alcohol (0.11 ml, 1.03 mmol). Cs_2CO_3 (270 mg, 0.824 mmol) was added after 90 hours of stirring. **158a** yielded as a colourless oil (75 mg, 0.289 mmol, 42% yield) after column chromatography (8% EtOAc/hexane). ^1H NMR (400 MHz, Chloroform-*d*) δ ppm 7.29 - 7.44 (m, 5 H, Ar-H), 5.84 (ddt, *J* = 17.5, 9.9, 6.9, 6.9 Hz, 1 H, H-12), 5.08 (s, 2 H, H-5), 5.03 (dq, *J* = 17.5, 1.5 Hz, 3 H, H-13), 4.95 (dq, *J* = 9.9, 1.5 Hz, 1 H, H-13), 4.87 (br. s., 1 H, NH), 2.12 - 2.32 (m, 2 H, H-8), 1.99 - 2.09 (m, 4 H, H-8, H-11), 1.86 - 1.98 (m, 3 H, H-9, H-10), 1.72 - 1.85 (m, 1 H, H-9) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.4 (C-6), 138.5 (C-12), 136.7 (C-4), 128.5 (Ar-CH), 128.0 (Ar-CH), 128.0 (Ar-CH), 114.5 (C-13), 66.1 (C-5), 56.7 (C-7), 36.5 (C-10), 32.6 (C-8), 28.3 (C-11), 14.6 (C-9) ppm; IR (ATR): ν_{max} 3332, 3066, 3032, 2979, 2939, 1697, 1640, 1518, 1498, 1454, 1402, 1372, 1336, 1248, 1234, 1069, 1027, 995, 909, 775, 736, 696, 631, 595, 489 cm^{-1}; HRMS (ESI) 260.1651 ($M + H^+$. $C_{16}H_{22}NO_2$ requires 260.1645), 282.1467 ($M + Na^+$. $C_{16}H_{21}NNaO_2$ requires 282.1464).

(1-But-3-enyl-cyclopentyl)-carbamic acid benzyl ester (158b)



158b was synthesised using **general procedure F** with acid **157b** (313 mg, 1.86 mmol), Et_3N (0.31 ml, 2.23 mmol), DPPA (0.44 ml, 2.05 mmol) and benzyl alcohol (0.29 ml, 2.79 mmol). **158b** yielded as a colourless oil (314 mg, 1.15 mmol, 62% yield) after column chromatography (5% EtOAc/hexane). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.28 - 7.45 (m, 5 H, Ar-H), 5.82 (ddt, *J* = 17.5, 9.9, 6.1 Hz, 1 H, H-12), 5.06 (s, 2 H, H-5), 5.01 (dq, *J* = 17.5, 1.8 Hz, 1 H, H-13), 4.93 (dq, *J* = 9.9, 1.8 Hz, 1 H, H-13), 4.64 (br. s., 1 H, NH), 2.00 - 2.17 (m, 2 H, H-11), 1.78 - 1.98 (m, 4 H, H-8, H-10), 1.51 - 1.76 (m, 6 H, H-8, H-9) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.6 (C-6), 138.8 (C-12), 136.7 (C-4), 128.5 (Ar-CH), 128.0 (Ar-CH), 128.0 (Ar-CH), 114.3 (C-13), 66.0 (C-5), 64.0 (C-7), 38.0 (C-10), 36.7 (C-8), 29.5 (C-11), 23.4 (C-9) ppm; IR (ATR): ν_{max} 3343, 3062, 3032, 2953, 2871, 1697, 1640, 1522, 1499, 1453, 1403, 1372, 1334, 1307, 1251, 1215, 1091, 1026, 1003, 960, 909, 736, 696, 675, 620, 597, 578, 557, 473, 465 cm^{-1}; HRMS (ESI) 296.1622 (M + Na^+. $C_{17}H_{23}NNaO_2$ requires 296.1621).

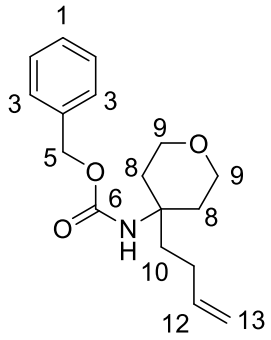
(1-But-3-enyl-cyclohexyl)-carbamic acid benzyl ester (158c)



158c was synthesised using **general procedure F** with acid **157c** (287 mg, 1.57 mmol), Et_3N (0.26 ml, 1.88 mmol), DPPA (0.37 ml, 1.73 mmol) and benzyl alcohol (0.24 ml, 2.36 mmol). **158c** yielded as a colourless oil (353 mg, 1.23 mmol, 78% yield) after column chromatography (5% EtOAc/hexane). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.28 - 7.44 (m, 5 H, Ar-H), 5.81 (ddt,

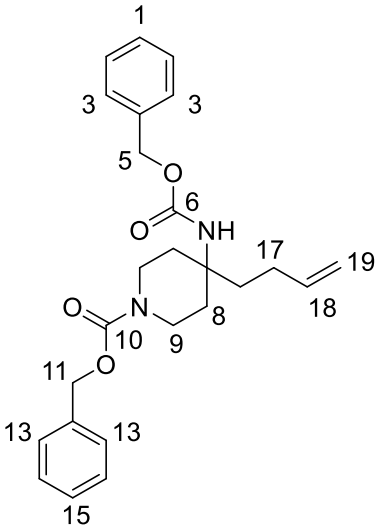
J = 16.8, 10.7, 6.1 Hz, 1 H, H-13), 5.06 (s, 2 H, H-5), 4.99 (dq, *J* = 16.8, 1.5 Hz, 1 H, H-14), 4.92 (dq, *J* = 10.7, 1.5 Hz, 1 H, H-14), 4.52 (br. s., 1 H, NH), 1.89 - 2.09 (m, 4 H, H-8, H-12), 1.75 - 1.87 (m, 2 H, H-11), 1.16 - 1.59 (m, 8 H, H-8, H-9, H-10) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.4 (C-6), 138.9 (C-13), 136.8 (C-4), 128.5 (Ar-CH), 128.0 (Ar-CH), 128.0 (Ar-CH), 114.2 (C-14), 66.0 (C-5), 54.7 (C-7), 37.5 (C-11), 34.9 (C-8), 27.6 (C-12), 25.7 (C-10), 21.6 (C-9) ppm; IR (ATR): ν_{max} 3450, 3347, 3074, 3032, 2980, 2930, 2856, 1706, 1640, 1523, 1505, 1452, 1393, 1379, 1328, 1282, 1243, 1214, 1090, 1076, 1000, 965, 909, 774, 737, 696, 598, 482, 473, 482 cm^{-1}; HRMS (ESI) 310.1776 (M + Na$^+$. $C_{18}H_{25}NNaO_2$ requires 310.1777)

(4-But-3-enyl-tetrahydro-pyran-4-yl)-carbamic acid benzyl ester (158d)



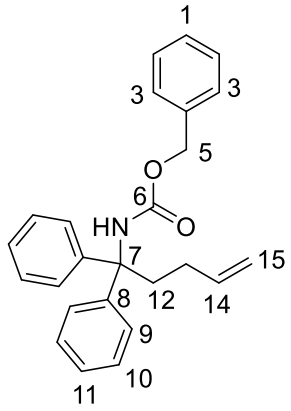
158d was synthesised using **general procedure F** with acid **157d** (300 mg, 1.63 mmol), Et_3N (0.27 ml, 1.96 mmol), DPPA (0.39 ml, 1.79 mmol) and benzyl alcohol (0.253 ml, 2.45 mmol). Cs_2CO_3 (411 mg, 1.26 mmol) was added after 90 hours of stirring. **158d** yielded as a white solid (354 mg, 1.22 mmol, 75% yield) after column chromatography (10% EtOAc/hexane). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.29 - 7.47 (m, 5 H, Ar-H), 5.80 (ddt, *J* = 16.8, 10.7, 6.7 Hz, 1 H, H-12), 5.07 (s, 2 H, H-5), 5.01 (dq, *J* = 16.8, 1.5 Hz, 1 H, H-13), 4.95 (dq, *J* = 10.7, 1.5 Hz, 1 H, H-13), 4.57 (br. s., 1 H, NH), 3.76 (ddd, *J* = 11.8, 4.6, 3.4 Hz, 2 H, H-9), 3.61 (ddd, *J* = 11.8, 11.4, 2.3 Hz, 2 H, H-9), 2.01 - 2.10 (m, 2 H, H-11), 1.99 (ddd, *J* = 13.8, 3.4, 2.3 Hz, 2 H, H-8), 1.80 - 1.91 (m, 2 H, H-10), 1.66 (ddd, *J* = 13.8, 11.4, 4.6 Hz, 2 H, H-8) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.4 (C-6), 138.3 (C-12), 136.5 (C-4), 128.5 (Ar-CH), 128.2 (Ar-CH), 128.0 (Ar-CH), 114.7 (C-13), 66.3 (C-5), 63.4 (C-9), 52.6 (C-7), 37.7 (C-10), 35.3 (C-8), 27.3 (C-11) ppm; IR (ATR): ν_{max} 3328, 3065, 3034, 2952, 2587, 2139, 1701, 1640, 1529, 1453, 1358, 1332, 1250, 1235, 1215, 1105, 1073, 1023, 986, 945, 911, 848, 777, 740, 697, 617, 597, 537, 492, 468 cm^{-1}; HRMS (ESI) 312.1562 (M + Na$^+$. $C_{17}H_{23}NNaO_3$ requires 312.1570; mp. 78.1-80.6 °C

4-Benzyloxycarbonylamino-4-but-3-enyl-piperidine-1-carboxylic acid benzyl ester (158e)



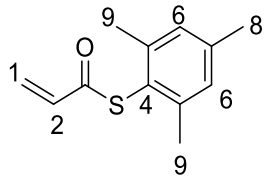
158e was synthesised using **general procedure F** with acid **157e** (610 mg, 1.92 mmol), Et_3N (0.32 ml, 2.31 mmol), DPPA (0.46 ml, 2.11 mmol) and benzyl alcohol (0.30 ml, 2.88 mmol). Cs_2CO_3 (751 mg, 2.31 mmol) was added after 90 hours of stirring. **158e** yielded as a colourless oil (270 mg, 0.640 mmol, 33% yield) after column chromatography (20% EtOAc/hexane). ^{1}H NMR (400 MHz, Chloroform-*d*): 7.28 - 7.46 (m, 10 H, Ar-H), 5.78 (ddt, *J* = 16.8, 10.7, 6.9 Hz, 1 H, H-18), 5.13 (s, 2 H, H-11), 5.07 (s, 2 H, H-5), 5.00 (dq, *J* = 16.8, 1.5 Hz, 1 H, H-19), 4.95 (dq, *J* = 10.7, 1.5 Hz, 1 H, H-19), 4.55 (br. s., 1 H, NH), 3.79 - 3.99 (m, 2 H, H-9), 3.00 - 3.22 (m, 2 H, H-9'), 1.96 - 2.16 (m, 4 H, H-8, H-17), 1.70 - 1.92 (m, 2 H, H-16), 1.45 - 1.60 (m, 2 H, H-8') ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 155.2 (C-10), 154.5 (C-6), 138.2 (C-18), 136.7 (C-12), 136.4 (C-4), 128.7 (Ar-CH), 128.6 (Ar-CH), 128.3 (Ar-CH), 128.2 (Ar-CH), 128.1 (Ar-CH), 128.0 (Ar-CH), 114.8 (C-19), 67.2 (C-11), 66.4 (C-5), 53.3 (C-7), 39.7 (C-9), 37.5 (C-16), 34.4 (C-8), 27.6 (C-17) ppm; IR (ATR): ν_{max} 3331, 3032, 2931, 1681, 1531, 1497, 1452, 1360, 1333, 1274, 1247, 1218, 1168, 1088, 1068, 1026, 911, 737, 697, 603, 456 cm^{-1}; HRMS (ESI) 423.2275 (M + H$^+$. $C_{25}H_{31}N_2O_4$ requires 423.2278), 445.2092 (M + Na$^+$. $C_{25}H_{30}N_2NaO_4$requires 445.2098)

(1,1-diphenyl-pent-4-enyl)-carbamic acid benzyl ester (158f)



158f was synthesised using **general procedure F** with acid **157f** (244 mg, 0.916 mmol), Et_3N (0.15 ml, 1.10 mmol), DPPA (0.22 ml, 1.01 mmol) and benzyl alcohol (0.14 ml, 1.37 mmol). Cs_2CO_3 (358 mg, 1.10 mmol) was added after 90 hours of stirring. **158f** yielded as a white solid (222 mg, 0.598 mmol, 65% yield) after column chromatography (8% EtOAc/hexane). ^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm 7.17 - 7.38 (m, 15 H, Ar-H), 5.80 (ddt, *J* = 16.8, 10.7, 6.9 Hz, 1 H, H-14), 5.71 (s, 1 H, NH), 5.03 (s, 2 H, H-5), 4.98 (dq, *J* = 16.8, 1.5 Hz, 1 H, H-15), 4.94 (dq, *J* = 10.7, 1.5 Hz, 1 H, H-15), 2.61 - 2.79 (m, 2 H, H-12), 1.87 - 2.00 (m, 2 H, H-13) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.6(C-6), 145.1 (C-8), 138.0 (C-14), 136.5 (C-4), 128.5 (Ar-CH), 128.2 (Ar-CH), 128.0 (Ar-CH), 128.0 (Ar-CH), 126.9 (Ar-CH), 126.5 (Ar-CH), 114.8 (C-15), 66.5 (C-5), 64.1 (C-7),37.3 (C-12), 28.6 (C-13) ppm; IR (ATR): ν_{max} 3340, 3061, 3031, 2936, 1735, 1639, 1584, 1491, 1401, 1332, 1242, 1221, 1086, 1061, 1010, 911, 755, 698, 644, 590, 517 cm^{-1}; HRMS (ESI) 372.1949 (M + H$^+$. $C_{25}H_{26}NO_2$ requires 372.1958), 394.1769 (M + Na$^+$. $C_{25}H_{26}NNaO_2$requires 394.1777); mp. 92.1-94.6 °C

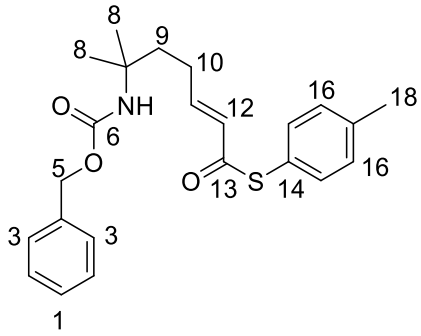
Thioacrylic acid 2,4,6-trimethyl-phenyl ester (152)



152 was synthesised using the same procedure as **134** with a solution of NaOH (15% w/w aq. 5 ml), $NaBH_4$ (0.010 g, 0.27 mmol), 2,4,6-trimethylthiophenol (1.36 g, 8.93 mmol), butylated hydroxytoluene (0.030 g, 0.13 mmol) and acryloyl chloride (1.08 ml, 13.34 mmol). **152** yielded as a pale-yellow oil (1.262 g, 6.12 mmol, 69% yield) after column chromatography (2%

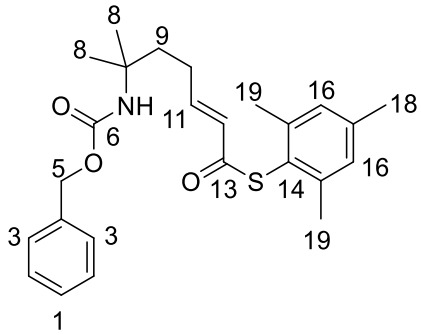
Et_2O/hexane). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.01 (s, 2 H, H-6), 6.50 (dd, *J* = 17.5, 10.0 Hz, 1 H, H-2), 6.40 (dd, *J* = 17.5, 1.2 Hz, 1 H, H-1), 5.76 (dd, *J* = 10.0, 1.2 Hz, 1 H, H-1), 2.34 (s, 6 H, H-9), 2.32 (s, 3 H, H-8) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 188.1 (C-3), 142.6 (C-4), 134.5 (C-2), 129.2 (C-6), 129.1 (C-7), 126.9 (C-1), 123.0 (C-5), 21.5 (C-9), 21.1 (C-8) ppm; IR (ATR): ν_{max} 2952, 2920, 1681, 1612, 1603, 1463, 1375, 1299, 1160, 1031, 994, 940, 850, 726, 631, 558 cm^{-1}; HRMS (ESI) 207.0838 ($M + H^+$. $C_{12}H_{15}OS$ requires 207.0838)

6-Cbz-amino-6,6-dimethyl-hex-2-enethioic acid S-p-tolyl ester (149)



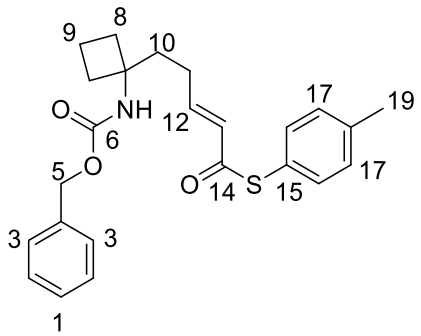
149 was synthesised using **general procedure C** with thioester **134** (214 mg, 1.20 mmol), Hoveyda-Grubbs Catalyst™ 2nd generation (25.1 mg, 0.040 mmol), copper iodide (76.2 mg, 0.40 mmol) and Cbz-amine **148** (100 mg, 0.40 mmol). **149** yielded as a pale green oil (141 mg, 0.355 mmol, 89% yield) after column chromatography (8% EtOAc/hexane). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.28 - 7.40 (m, 5 H, Ar-H), 7.32 (d, *J* = 8.0 Hz, 2 H, H-15), 7.23 (d, *J* = 8.0 Hz, 2 H, H-16), 6.98 (dt, *J* = 16.0, 6.9 Hz, 1 H, H-11), 6.18 (d, *J* = 16.0 Hz, 1 H, H-12), 5.06 (s, 2 H, H-5), 4.64 (br. s., 1 H, NH), 2.39 (s, 3 H, H-18), 2.21 (td, *J* = 8.4, 6.9 Hz, 2 H, H-10), 1.89 (t, *J* = 8.4 Hz, 2 H, H-9), 1.28 - 1.36 (m, 6 H, H-8) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 188.4 (C-13), 154.5 (C-6), 146.1 (C-11), 139.6 (C-17), 136.5 (C-4), 134.6 (C-15), 130.0 (C-16), 128.6 (Ar-CH), 128.1 (Ar-CH), 128.1 (Ar-CH), 127.9 (C-12), 124.0 (C-14), 66.2 (C-5), 52.6 (C-7), 37.8 (C-9), 27.3 (C-10), 27.3 (C-8), 21.3 (C-18) ppm; IR (ATR): ν_{max} 3358, 3031, 2969, 2925, 1722, 1685, 1631, 1521, 1495, 1453, 1399, 1388, 1365, 1303, 1262, 1213, 1180, 1089, 1072, 1036, 1017, 1002, 985, 928, 808, 778, 738, 697, 649, 634, 315, 578, 533, 475 cm^{-1}; HRMS (ESI) 420.1601 ($M + Na^+$. $C_{23}H_{27}NNaO_3S$ requires 420.1604)

6-Cbz-amino-6,6-dimethyl-hex-2-enethioic acid S-2,4,6-trimethyl-phenyl ester (153)



153 was synthesised using **general procedure C** with thioester **152** (248 mg, 1.20 mmol), Hoveyda-Grubbs Catalyst™ 2nd generation (25.1 mg, 0.040 mmol), copper iodide (76.2 mg, 0.40 mmol) and Cbz-amine **148** (100 mg, 0.40 mmol). **153** yielded as a dark green oil (157 mg, 0.37 mmol, 92% yield) after column chromatography (5% EtOAc/hexane). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.29 - 7.43 (m, 5 H, Ar-H), 6.99 (s, 2 H, H-16), 6.92 - 7.03 (m, 1 H, H-11), 6.22 (d, *J* = 15.3 Hz, 1 H, H-12), 5.06 (s, 2 H, H-5), 4.65 (br. s., 1 H, NH), 2.32 (s, 6 H, H-19), 2.30 (s, 3 H, J-18), 2.17 - 2.26 (m, 2 H, H-10), 1.85 - 1.95 (m, 2 H, H-9), 1.31 (s, 6 H, H-8) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 187.5 (C-13), 154.5 (C-6), 145.6 (C-11), 142.7 (C-14), 139.8 (C-17), 136.5 (C-4), 129.2 (C-16), 128.5 (Ar-CH), 128.5 (Ar-CH), 128.1 (Ar-CH), 128.1 (C-12), 123.4 (C-15), 66.2 (C-5), 52.6 (C-7), 37.8 (C-9), 27.3 (C-10), 27.2 (C-8), 21.6 (C-19), 21.1 (C-18) ppm; IR (ATR): ν_{max} 3358, 3030, 2969, 2924, 1723, 1681, 1631, 1602, 1523, 1454, 1388, 1365, 1299, 1262, 1213, 1178, 1087, 1072, 1030, 1003, 929, 850, 806, 778, 738, 715, 697, 634, 578, 564 507, 486, 472 cm^{-1}; HRMS (ESI) 448.1910 (M + Na^{+}. $C_{25}H_{31}NNaO_3S$ requires 448.1917

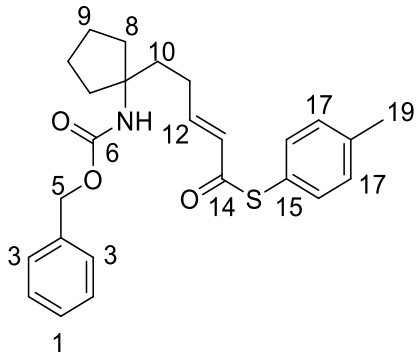
6-Cbz-amino-6,6-cyclobutyl-hex-2-enethioic acid S-p-tolyl ester (159a)



159a was synthesised using **general procedure C** with thioester **134** (118 mg, 0.66 mmol), Hoveyda-Grubbs Catalyst™ 2nd generation (13.8 mg, 0.022 mmol), copper iodide (41.9 mg, 0.22 mmol) and Cbz-amine **158a** (57 mg, 0.22 mmol). **159a** yielded as a pale brown oil (83.6 mg, 0.204 mmol, 93% yield) after column chromatography (8% EtOAc/hexane). ^{1}H NMR (400

MHz, Chloroform-*d*) δ 7.34 - 7.45 (m, 5 H, Ar-H), 7.32 (d, *J* = 8.2 Hz, 2 H, H-16), 7.23 (d, *J* = 8.2 Hz, 2 H, H-17), 7.00 (dt, *J* = 15.6, 5.9 Hz, 1 H, H-12), 6.19 (d, *J* = 15.6 Hz, 1 H, H-13), 5.08 (s, 2 H, H-5), 4.90 (br. s., 1 H, NH), 2.39 (s, 3 H, H-19), 2.12 - 2.29 (m, 4 H, H-8, H-11), 1.98 - 2.10 (m, 4 H, H-8, H-10), 1.91 - 1.97 (m, 1 H, H-9), 1.76 - 1.87 (m, 1 H, H-9) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 188.4 (C-14), 154.3 (C-6), 146.1 (C-12), 139.6 (C-18), 136.4 (C-4), 134.6 (C-16), 130.0 (C-17), 128.5 (Ar-CH), 128.1 (Ar-CH), 128.1 (Ar-CH), 127.9 (C-13), 124.0 (C-15), 66.3 (C-5), 56.5 (C-7), 35.4 (C-10), 32.8 (C-8), 27.0 (C-11), 21.3 (C-19), 14.7 (C-9) ppm; IR (ATR): ν_{max} 3346, 3030, 2938, 3854, 1689, 1630, 1598, 1513, 1494, 1453, 1399, 1376, 1303, 1273, 1247, 1181, 1154, 1084, 1060, 1028, 1016, 982, 807, 737, 697, 649, 618, 535, 475 cm^{-1}; HRMS (ESI) 410.1770 (M + H$^+$. $C_{24}H_{28}NO_3S$ requires 410.1784), 432.1590 (M + Na$^+$. $C_{24}H_{27}NNaO_3S$ requires 432.1604)

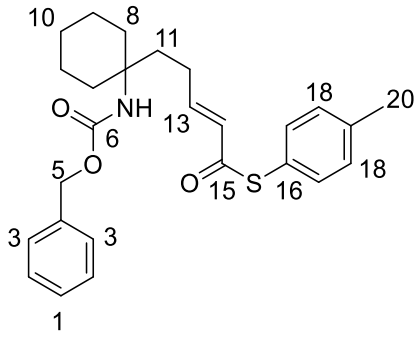
6-Cbz-amino-6,6-cyclopentyl-hex-2-enethioic acid S-p-tolyl ester (159b)



159b was synthesised using **general procedure C** with thioester **134** (126 mg, 0.71 mmol), Hoveyda-Grubbs Catalyst™ 2nd generation (14.8 mg, 0.024 mmol), copper iodide (44.9 mg, 0.24 mmol) and Cbz-amine **158b** (65 mg, 0.24 mmol). **159b** yielded as a pale green oil (90 mg, 0.21 mmol, 90% yield) after column chromatography (8% EtOAc/hexane). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 - 7.47 (m, 5 H, Ar-H), 7.32 (d, *J* = 8.3 Hz, 2 H, H-16), 7.23 (d, *J* = 8.3 Hz, 2 H, H-17), 7.00 (dt, *J* = 15.6, 6.4 Hz, 1 H, H-12), 6.17 (d, *J* = 15.6 Hz, 1 H, H-13), 5.07 (s, 2 H, H-5), 4.65 (br. s., 1 H, NH), 2.35 - 2.43 (m, 3 H, H-19), 2.17 - 2.28 (m, 2 H, H-11), 1.97 - 2.07 (m, 2 H, H-10), 1.87 - 1.97 (m, 2 H, H-9), 1.65 - 1.79 (m, 4 H, H-8), 1.53 - 1.65 (m, 2 H, H-9) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 188.4 (C-14), 154.6 (C-6), 146.4 (C-12), 139.6 (C-18), 136.5 (C-4), 134.6 (C-16), 130.0 (C-17), 128.5 (Ar-CH), 128.1 (Ar-CH), 128.1 (Ar-CH), 127.8 (C-13), 124.0 (C-15), 66.2 (C-5), 63.8 (C-7), 38.1 (C-8), 35.5 (C-10), 28.2 (C-11), 23.3 (C-9), 21.3 (C-19) ppm; IR (ATR): ν_{max} 3355, 3030, 2953, 2870, 1690, 1630, 1520, 1495, 1453, 1399, 1304,

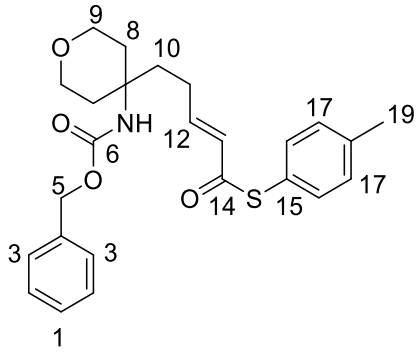
1244, 1181, 1092, 1017, 807, 738, 697, 621, 535, 476 cm^{-1}; HRMS (ESI) 446.1757 ($M + Na^+$. $C_{25}H_{29}NNaO_3S$ requires 446.1760)

6-Cbz-amino-6,6-cyclohexyl-hex-2-enethioic acid S-p-tolyl ester (159c)



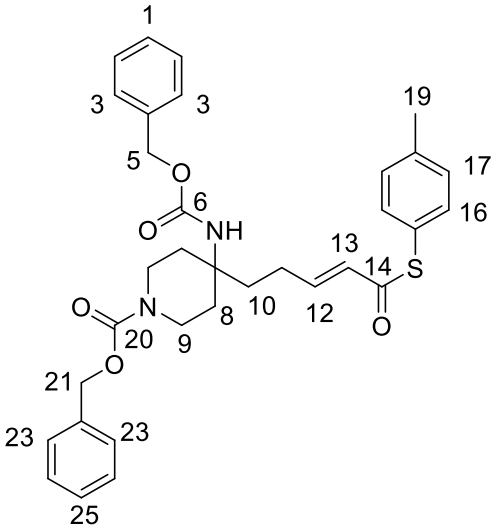
159c was synthesised using **general procedure C** with thioester **134** (128 mg, 0.72 mmol), Hoveyda-Grubbs Catalyst™ 2nd generation (15.0 mg, 0.024 mmol), copper iodide (45.5 mg, 0.24 mmol) and Cbz-amine **158c** (69 mg, 0.24 mmol). **159c** yielded as a pale green oil (98 mg, 0.22 mmol, 94% yield) after column chromatography (8% EtOAc/hexane). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34 - 7.42 (m, 5 H, Ar-H), 7.32 (d, *J* = 8.2 Hz, 2 H, H-17), 7.23 (d, *J* = 8.2 Hz, 2 H, H-18), 6.99 (dt, *J* = 15.1, 6.9 Hz, 1 H, H-13), 6.16 (d, *J* = 15.1 Hz, 1 H, H-14), 5.07 (s, 2 H, H-5), 4.56 (br. s., 1 H, NH), 2.39 (s, 3 H, H-20), 2.13 - 2.26 (m, 2 H, H-12), 1.84 - 2.04 (m, 4 H, H-8, H-11), 1.50 - 1.68 (m, 3 H, H-9, H-10), 1.20 - 1.49 (m, 5 H, H-8, H-9, H-10) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 188.4 (C-15), 154.3 (C-6), 146.6 (C-13), 139.5 (C-19), 136.6 (C-14), 134.6 (C-17), 129.9 (C-18), 128.5 (Ar-CH), 128.1 (Ar-CH), 128.1 (Ar-CH), 127.7 (C-14), 124.0 (C-16), 66.2 (C-5), 54.5 (C-7), 36.4 (C-11), 34.9 (C-8), 26.4 (C-12), 25.6 (C-10), 21.5 (C-9), 21.3 (C-20) ppm; IR (ATR): ν_{max} 3359, 3030, 2928, 2856, 1720, 1685, 1630, 1495, 1452, 1399, 1328, 1305, 1281, 1237, 1208, 1168, 1149, 1130, 1091, 1076, 1039, 1029, 1016, 987, 968, 923, 807, 738, 697, 646, 618, 535, 509, 474 cm^{-1}; HRMS (ESI) 460.1935 ($M + Na^+$. $C_{26}H_{31}NNaO_3S$ requires 460.1917)

6-Cbz-amino-6,6-(tetrahydropyran-4-yl)-hex-2-enethioic acid S-p-tolyl ester (159d)



159d was synthesised using **general procedure C** with thioester **134** (135 mg, 0.76 mmol), Hoveyda-Grubbs Catalyst™ 2nd generation (15.7 mg, 0.025 mmol), copper iodide (47.6 mg, 0.25 mmol) and Cbz-amine **158d** (73 mg, 0.25 mmol). **159d** yielded as a pale brown oil (74 mg, 0.17 mmol, 67% yield) after column chromatography (20% EtOAc/hexane). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34 - 7.44 (m, 5 H, Ar-H), 7.32 (d, *J* = 7.6 Hz, 2 H, H-16), 7.23 (d, *J* = 7.6 Hz, 2 H, H-17), 6.96 (dt, *J* = 16.0, 6.1 Hz, 1 H, H-12), 6.16 (d, *J* = 16.0 Hz, 1 H, H-13), 5.08 (s, 2 H, H-5), 4.62 (br. s, 1 H, NH), 3.77 (ddd, *J* = 12.2, 4.6, 3.0 Hz, 2 H, H-9), 3.61 (ddd, *J* = 12.2, 11.4, 2.3 Hz, 2 H, H-9), 2.39 (s, 3 H, H-19), 2.14 - 2.24 (m, 2 H, H-11), 1.98 (ddd, *J* = 14.0, 3.0, 2.3 Hz, 2 H, H-8), 1.90 - 2.05 (m, 2 H, H-10), 1.66 (ddd, *J* = 14.0, 11.4, 4.6 Hz, 2 H, H-8) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 188.3 (C-14), 154.4 (C-6), 145.7 (C-12), 139.6 (C-18), 136.3 (C-4), 134.6 (C-16), 130.0 (C-17), 128.6 (Ar-CH), 128.3 (Ar-CH), 128.1 (Ar-CH), 128.0 (C-13), 123.9 (C-15), 66.5 (C-5), 63.3 (C-9), 52.4 (C-7), 36.8 (C-10), 35.2 (C-8), 26.0 (C-11), 21.3 (C-19) ppm; IR (ATR): ν_{max} 3355, 3031, 2951, 2925, 2856, 1719, 1679, 1630, 1597, 1524, 1494, 1452, 1393, 1357, 1332, 1303, 1260, 1234, 1212, 1190, 1157, 1104, 1089, 1072, 1018, 992, 935, 911, 847, 808, 778, 737, 697, 647, 625, 580, 535, 475 cm^{-1}; HRMS (ESI) 440.1886 (M + H^{+}. $C_{25}H_{30}NO_4S$ requires 440.1890), 462.1705 (M + Na^{+}. $C_{25}H_{29}NNaO_4S$ requires 462.1710)

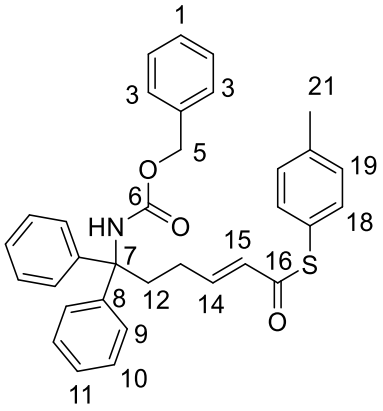
6-Cbz-amino-6,6-(*N*-Cbz-piperidin-4-yl)-hex-2-enethioic acid S-p-tolyl ester (159e)



159e was synthesised using **general procedure C** with thioester **134** (123.5 mg, 0.69 mmol), Hoveyda-Grubbs Catalyst™ 2nd generation (11.9 mg, 0.023 mmol), copper iodide (44.0 mg, 0.23 mmol) and Cbz-amine **158e** (97.6 mg, 0.23 mmol). **159e** yielded as a colourless oil (99 mg, 0.173 mmol, 75% yield) after column chromatography (50% Et_2O/hexane).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.30 (m, 10H, Ar-H), 7.29 (d, *J* = 8.2 Hz, 2H, H-16), 7.21 (d, *J* = 8.2 Hz, 2H, H-17), 6.92 (dt, *J* = 15.4, 6.6 Hz, 1H, H-12), 6.13 (d, *J* = 15.4 Hz, 1H, H-13), 5.11 (s, 2H, H-21), 5.05 (s, 2H, H-5), 4.52 (br. s, 1H, NH), 4.03 – 3.80 (m, 2H, H-9), 3.19 – 2.93 (m, 2H, H-9'), 2.36 (s, 3H, H-19), 2.22 – 2.12 (m, 2H, H-11), 2.09 – 1.97 (m, 2H, H-10), 1.96 – 1.80 (m, 2H, H-8), 1.58 – 1.42 (m, 2H, H-8') ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 188.4 (C-14), 155.3 (C-20), 154.6 (C-6), 145.6 (C-12), 139.8 (C-18), 136.8 (C-22), 136.4 (C-4), 134.7 (C-16), 130.1 (C-17), 128.7 (Ar-CH), 128.6 (Ar-CH), 128.4 (C-13), 128.3 (Ar-CH), 128.2 (Ar-CH), 128.2 (Ar-CH), 128.0 (Ar-CH), 124.0 (C-15), 67.3 (C-21), 66.7 (C-5), 53.3 (C-7), 39.6 (C-9), 36.6 (C-10), 34.4 (C-8), 26.2 (C-11), 21.4 (C-19) ppm; IR (ATR): ν_{max} 3339, 3032, 2933, 1684, 1631, 1526, 1496, 1437, 1360, 1333, 1243, 1214, 1164, 1069, 1017, 972, 808, 713, 737, 697, 603, 538, 475 cm^{-1}; HRMS (ESI) 573.2429 (M + H$^+$. $C_{33}H_{37}N_2O_5S$ requires 573.2418), 590.2694 (M + NH_4^+. $C_{33}H_{40}N_3O_5S$ requires 590.2683), 595.2247 (M + Na$^+$. $C_{33}H_{36}N_3NaO_5S$ requires 595.2237), 611.1983 (M + K$^+$. $C_{33}H_{36}KN_3O_5S$ requires 611.1977)

6-Cbz-amino-6,6-diphenyl-hex-2-enethioic acid S-p-tolyl ester (159f)



159f was synthesised using **general procedure C** with thioester **134** (184 mg, 1.03 mmol), Hoveyda-Grubbs Catalyst™ 2nd generation (21.6 mg, 0.0345 mmol), copper iodide (65.6 mg, 0.345 mmol) and Cbz-amine **158f** (128 mg, 0.345 mmol). **159f** yielded as a pale yellow oil (112 mg, 0.21 mmol, 62% yield) after column chromatography (12% EtOAc/hexane). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.19 - 7.40 (m, 19 H, Ar-H), 6.92 (dt, *J* = 15.3, 6.9 Hz, 1 H, H-14), 6.10 (d, *J* = 15.3 Hz, 1 H, H-15), 5.72 (s, 1 H, NH), 5.02 (s, 2 H, H-5), 2.73 - 2.90 (m, 2 H, H-12), 2.37 (s, 3 H, H-21), 2.07 - 2.17 (m, 2 H, H-13) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 188.3 (C-16), 154.6 (C-6), 145.7 (C-14), 144.9 (C-8), 139.6 (C-20), 136.2 (C-4), 134.6 (C-18), 130.0 (C-19), 128.5 (Ar-CH), 128.4 (Ar-CH), 128.2 (Ar-CH), 128.2 (Ar-CH), 128.0 (C-14), 127.1 (Ar-CH), 126.3 (Ar-CH), 124.0 (C-17), 66.7 (C-5), 63.9 (C-7), 35.7 (C-12), 27.2 (C-13), 21.3 (C-21) ppm; IR (ATR): ν_{max} 3346, 3030, 2925, 1731, 1682, 1630, 1492, 1446, 1399, 1304, 1236, 1213, 1130, 1086, 1043, 1030, 1001, 910, 808, 776, 755, 734, 698, 647, 590, 475 cm^{-1}; HRMS (ESI) 522.2102 (M + H^{+}. $C_{33}H_{32}NO_3S$ requires 522.2097), 544.1918 (M + Na^{+}. $C_{33}H_{31}NNaO_3S$ requires 544.1917)

Asymmetric cyclisation of 3,3-disubstituted pyrrolidines

General procedure G

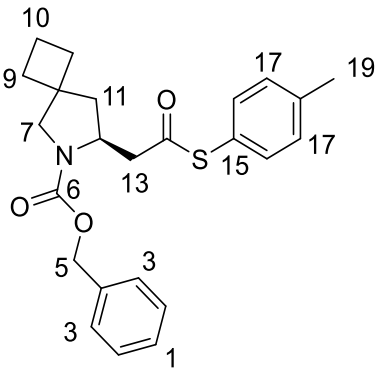
Racemic

A solution of amino-thioester (0.048 mmol) in 1,2-DCE (5 ml) was added to rac-CSA (0.145 mmol) under N_2 and the reaction heated to 50 °C for 24 hours. The reaction was cooled to room temperature and extracted with DCM (10 ml). The organic fraction was washed with saturated $NaHCO_3$ solution (10 ml), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (0.043 mmol, 90% yield).

Asymmetric

A solution of amino-thioester (0.049 mmol) in cyclohexane (0.02M) was added to (R)-TRIP (0.098 mmol) under N_2 and the reaction heated to 80 °C for 24 hours. The reaction was then cooled to room temperature, quenched with Et_3N (0.2 ml) and concentrated *in vacuo*. The crude material was purified by column chromatography (0.041 mmol, 83% yield).

_N_-Cbz-(_S_)-7-p-Tolylsulfanylcarbonylmethyl-6-aza-spiro[3.4]octane (144a)



Racemic

144a was synthesised using **general procedure G** with amino-thioester **143a** (9.1 mg, 0.022 mmol) and rac-CSA (15.5 mg, 0.067 mmol). **144a** yielded as a colourless oil (7.1 mg, 0.017 mmol, 78% yield) after column chromatography (8% EtOAc/hexane).

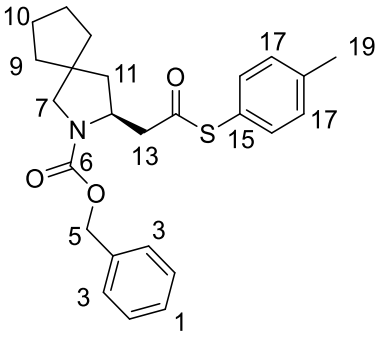
Asymmetric

144a was synthesised using **general procedure G** with amino-thioester **143a** (12.9 mg, 0.031 mmol) and (*R*)-TRIP (4.7 mg, 0.0063 mmol). **144a** yielded as a colourless oil (10.0 mg, 0.024 mmol, 78% yield, 98:2 er) after column chromatography (8% EtOAc/hexane).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.40 – 7.28 (m, 5H, Ar-H), 7.28 – 7.13 (m, 4H, H-16, H-17), 5.20 – 5.09 (m, 2H, H-5), 4.25 – 4.13 (m, 1H, H-12), 3.54 (d, *J* = 10.8 Hz, 0.4H, H-7, *rotamer 2*), 3.49 (d, *J* = 10.8 Hz, 0.6H, H-7, *rotamer 1*), 3.46 (dd, *J* = 14.8, 3.7 Hz, 0.6H, H-13, *rotamer 1*), 3.42 (d, *J* = 10.8 Hz, 0.4H, H-7'), 3.37 (d, *J* = 10.7 Hz, 0.6H, H-7'), 3.19 (dd, *J* = 14.8, 3.7 Hz, 0.4H, H-13, *rotamer 2*), 2.73 (dd, *J* = 14.8, 9.8 Hz, 0.4H, H-13', *rotamer 2*), 2.66 (dd, *J* = 14.8, 9.8 Hz, 0.6H, H-13', *rotamer 1*), 2.36 (s, 3H, H-19), 2.20 – 2.08 (m, 1H, H-11), 2.06 – 1.95 (m, 2H, H-9), 1.95 – 1.78 (m, 5H, H-9', H-10, H-11') ppm; ^{13}C NMR (101 MHz Chloroform-*d*) δ 196.1 (C-14), 155.0 (C-6), 140.0(139.8) (C-18), 136.9(136.7) (C-4), 134.5 (134.4) (C-16), 130.2 (130.1) (C-17), 128.7 (128.6) (Ar-CH), 128.1 (Ar-CH), 128.0 (127.9) (Ar-CH), 124.2(124.0) (C-15), 67.1 (66.8) (C-5), 58.4 (58.1) (C-7), 54.8 (54.4) (C-12), 48.3 (47.1) (C-13), 44.0 (43.5) (C-8), 43.5 (42.8) (C-

11), 32.3 (32.0, 31.6) (C-9), 21.4 (C-19), 16.5 (16.4) (C-10) ppm; IR (ATR): ν_{max} 3031, 2923, 2852, 1699, 1598, 1494, 1446, 1409, 1356, 1340, 1282, 1210, 1165, 1127, 1093, 807, 769, 750, 697, 606, 566, 523, 474 cm^{-1}; HRMS (ESI) 410.1783 (M + H^+. $C_{24}H_{28}NO_3S$ requires 410.1784); 432.1599 (M + Na^+. $C_{24}H_{27}NNaO_3S$ requires 432.1604); $[\alpha]_D^{20}$ -29.9° (c 0.50, $CHCl_3$).

_N_-Cbz-(_S_)-3-p-Tolylsulfanylcarbonylmethyl-2-aza-spiro[4.4]nonane (144b)



Racemic

144b was synthesised using **general procedure G** with amino-thioester **143b** (9.0 mg, 0.021 mmol) and rac-CSA (14.8 mg, 0.064 mmol). **144b** yielded as a colourless oil (8.7 mg, 0.021 mmol, 97% yield) after column chromatography (8% EtOAc/hexane).

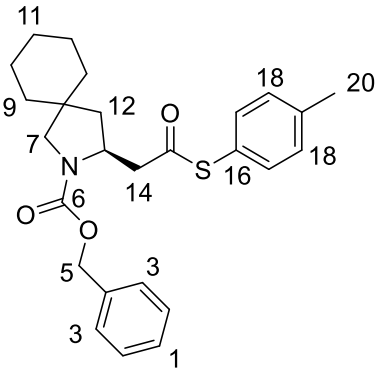
Asymmetric

144b was synthesised using **general procedure G** with amino-thioester **143b** (15.0 mg, 0.035 mmol) and (*R*)-TRIP (5.3 mg, 0.0071 mmol). **144b** yielded as a colourless oil (13.0 mg, 0.031 mmol, 87% yield, 98:2 er) after column chromatography (8% EtOAc/hexane).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.50 – 7.28 (m, 5H, Ar-H), 7.28 – 7.12 (m, 4H, H-16, H-17), 5.24 – 5.04 (m, 2H, H-5), 4.25 – 4.07 (m, 1H, H-12), 3.54 (dd, *J* = 15.2, 3.7 Hz, 0.6H, H-13, *rotamer 1*), 3.46 (d, *J* = 10.7 Hz, 0.4H, H-7, *rotamer 2*), 3.38 (d, *J* = 10.7 Hz, 0.6H, H-7, *rotamer 1*), 3.28 (dd, *J* = 15.2, 3.7 Hz, 0.4H, H-13, *rotamer 2*), 3.14 (d, *J* = 10.7 Hz, 1H, H-7'), 2.83 (dd, *J* = 15.2, 9.1 Hz, 0.6H, H-13', *rotamer 1*), 2.76 (dd, *J* = 15.2, 9.1 Hz, 0.4H, H-13', *rotamer 2*), 2.36 (s, 3H, H-19), 2.15 – 2.00 (m, 1H, H-11), 1.77 (dd, *J* = 12.7, 8.1 Hz, 0.6H, H-11', *rotamer 1*), 1.71 (dd, *J* = 12.7, 8.1 Hz, 0.4H, H-11', *rotamer 2*), 1.67 –1.35 (m, 8H, H9, H-10) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 196.1 (C-14), 155.0 (C-6), 139.9(139.7) (C-18), 136.9 (C-4), 134.5(134.4) (C-16), 130.2(130.1) (C-17), 128.7(128.6) (Ar-CH), 128.1 (128.0) (Ar-CH), 128.0(127.9) (Ar-CH), 124.2 (C-15), 67.1(66.8) (C-5), 58.2(58.0) (C-7), 55.1(54.5) (C-12), 48.6(47.3) (C-13), 48.5(48.3)

(C-8), 44.2(43.4) (C-11), 37.7(36.2) (C-9), 24.9(24.7) (C-10), 21.4 (C-19) ppm; IR (ATR): ν_{max} 2923, 2857, 1701, 1494, 1448, 1410, 1356, 1284, 1210, 1175, 1111, 978, 807, 769, 697, 605, 533, 475 cm^{-1}; HRMS (ESI) 424.1944 ($M + H^+$. $C_{25}H_{30}NO_3S$ requires 424.1941); 446.1756 ($M + Na^+$. $C_{25}H_{29}NNaO_3S$ requires 446.1760); $[\alpha]_D^{20}$ -54.7° (c 0.67 $CHCl_3$).

_N_-Cbz-(_S_)-3-p-Tolylsulfanylcarbonylmethyl-2-aza-spiro[4.5]decane (144c)



Racemic

144c was synthesised using **general procedure G** with amino-thioester **143c** (8.9 mg, 0.020 mmol) and rac-CSA (14.2 mg, 0.061 mmol). **144c** yielded as a pale-yellow oil (8.8 mg, 0.020 mmol, 99% yield) after column chromatography (8% EtOAc/hexane).

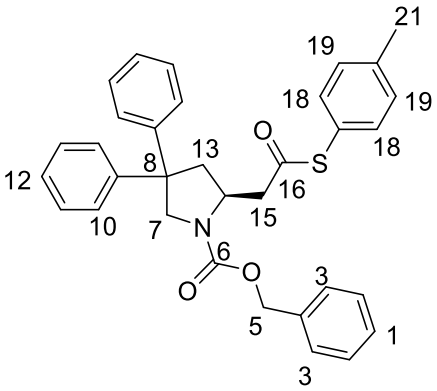
Asymmetric

144c was synthesised using **general procedure G** with amino-thioester **143c** (14.0 mg, 0.032 mmol) and (*R*)-TRIP (4.8 mg, 0.0064 mmol). **144c** yielded as a pale-yellow oil (13.8 mg, 0.032 mmol, 99% yield, 97:3 er) after column chromatography (8% EtOAc/hexane).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.40 – 7.29 (m, 5H, Ar-H), 7.28 – 7.16 (m, 4H, H-17, H-18), 5.27 – 5.05 (m, 2H, H-5), 4.19 (dddd, *J* = 9.1, 8.4, 7.8, 3.7 Hz, 1H, H-13), 3.64 (d, *J* = 11.1 Hz, 0.4H, H-7, *rotamer 2*), 3.55 (d, *J* = 11.1 Hz, 0.6H, H-7, *rotamer 1*), 3.51 (dd, *J* = 15.0, 3.7 Hz, 0.6H, H-14, *rotamer 1*), 3.25 (dd, *J* = 15.0, 3.7 Hz, 0.4H, H-14, *rotamer 2*), 2.98 (d, *J* = 11.1 Hz, 1H, H-7'), 2.81 (dd, *J* = 15.0, 9.1 Hz, 0.6H, H-14', *rotamer 1*), 2.73 (dd, *J* = 15.0, 9.1 Hz, 0.4H, H-14', *rotamer 2*), 2.36 (s, 3H, H-20), 2.35 – 1.94 (m, 1H, H-12), 1.64 – 1.23 (m, 11H, H-9, H-10, H-11, H-12') ppm; ^{13}C NMR (101 MHz, CHLOROFORM-*D*) δ 196.1 (C-15), 155.1 (C-6), 139.8 (C-19), 137.0(136.7) (C-4), 134.5 (C-17), 130.1 (C-18), 128.7(128.6) (Ar-CH), 128.1(128.0) (Ar-CH), 127.8 (Ar-CH), 124.2 (C-16), 67.1(66.8) (C-5), 57.0 (C-7), 54.1(53.6) (C-13), 48.9(47.5) (C-14), 41.4(41.1) (C-8), 36.4 (C-12), 34.6 (C-9), 26.1 (C-11), 23.8(22.8) (C-10), 21.4 (C-20) ppm; IR (ATR): ν_{max} 2922, 2852, 1698, 1598, 1494, 1450, 1411, 1358, 1325, 1283, 1255, 1196, 1170,

1115, 1016, 975, 807, 768, 750, 697, 609, 533, 474 cm^{-1}; HRMS (ESI) 438.2087 (M + H^+. $C_{26}H_{32}NO_3S$ requires 438.2097); 460.1903 (M + Na^+. $C_{26}H_{31}NNaO_3S$ requires 460.1917); $[\alpha]_D^{20}$ -46.1° (c 0.68, $CHCl_3$).

_N_-Cbz-3,3-diphenyl-(_S_)-5-p-Tolylsulfanylcarbonylmethyl-pyrrolidine (144d)



Racemic

144d was synthesised using **general procedure G** with amino-thioester **143d** (19.4 mg, 0.037 mmol) and rac-CSA (25.9 mg, 0.112 mmol). **144d** yielded as a colourless oil (18.3 mg, 0.035 mmol, 94% yield) after column chromatography (10% EtOAc/hexane).

Asymmetric

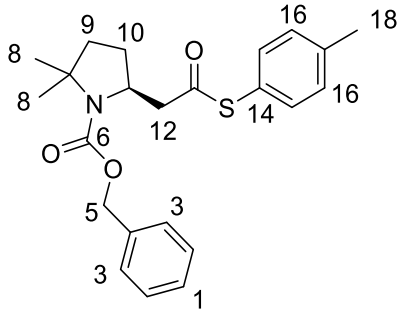
144d was synthesised using **general procedure G** with amino-thioester **143d** (21.7 mg, 0.042 mmol) and (*R*)-TRIP (6.3 mg, 0.0083 mmol). **144d** yielded as a colourless oil (21.1 mg, 0.040 mmol, 97% yield, 90:10 er) after column chromatography (10% EtOAc/hexane).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 – 7.06 (m, 19H, Ar-H), 5.32 – 5.04 (m, 2H, H-5), 4.66 (dd, *J* = 11.6, 1.8 Hz, 0.4H, H-7, *rotamer 2*), 4.53 (dd, *J* = 11.6, 1.8 Hz, 0.6H, H-7, *rotamer 1*), 4.13-3.96 (m, 1H, H-14), 3.72 (d, *J* = 11.7 Hz, 0.6H, H-7', *rotamer 1*), 3.70 (d, *J* = 11.7 Hz, 0.4H, H-7', *rotamer 2*), 3.50 (dd, *J* = 15.3, 3.4 Hz, 0.6H, H-15, *rotamer 1*), 3.26 (dd, *J* = 15.3, 3.4 Hz, 0.4H, H-15, *rotamer 2*), 3.05 – 2.93 (m, 1H, H-13), 2.84 (dd, *J* = 15.3, 9.0 Hz, 0.6H H-15', *rotamer 1*), 2.74 (dd, *J* = 15.3, 9.0 Hz, 0.4H H-15', *rotamer 2*), 2.58 (dd, *J* = 12.8, 9.0 Hz, 0.4H, H-13', *rotamer 2*), 2.51 (dd, *J* = 12.8, 9.0 Hz, 0.6H, H-13', *rotamer 1*), 2.36 (s, 3H, H-21) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 196.2(196.0) (C-16), 155.1(154.7) (C-6), 145.3(144.6) (C-9), 140.0(139.8) (C-20), 136.9(136.6) (C-4), 134.6(134.5) (C-18), 130.2(130.1) (C-19), 128.8(128.7) (Ar-CH), 128.7(128.6) (Ar-CH), 128.2(128.1) (Ar-CH), 128.1(127.8) (Ar-CH), 126.8(126.7) (Ar-CH), 126.6(126.4) (Ar-CH), 124.1(124.0) (C-17), 67.2(67.0) (C-5), 56.0 (C-7), 54.2(53.7) (C-14),

52.9(52.7) (C-8), 47.9(46.7) (C-15), 44.3(43.2) (C-13), 21.4 (C-21) ppm; IR (ATR): ν_{max} 3029, 2923, 1698, 1598, 1494, 1446, 1411, 1357, 1270, 1212, 1180, 1130, 1102, 1030, 1009, 981, 911, 807, 768, 751, 729, 698, 651, 608, 585, 530, 474 cm^{-1}; HRMS (ESI) 522.2100 ($M + H^+$. $C_{33}H_{32}NO_3S$ requires 522.2097); 544.1913 ($M + Na^+$. $C_{33}H_{31}NNaO_3S$ requires 544.1917); $[\alpha]_D^{20}$ -69.1° (c 0.585, CHCl3)

Asymmetric cyclisation of 2,2-disubstituted pyrrolidines

***N*-Cbz-2,2-dimethyl-(*S*)-5-p-Tolylsulfanylcarbonylmethyl-pyrrolidine (150)**



Racemic

A solution of amino-thioester **149** (21.6 mg, 0.054 mmol) in 1,2-DCE (5 ml) was added to rac-CSA (37.9 mg, 0.163 mmol) under N_2 and the reaction heated to 50 °C for 24 hours. The reaction was cooled to room temperature and extracted with DCM (10 ml). The organic fraction was washed with saturated $NaHCO_3$ solution (10 ml), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (10% EtOAc/hexane) to afford **150** as a colourless oil (12.3 mg, 0.031 mmol, 57% yield).

Asymmetric – (R)-TRIP, 80 °C

A solution of amino-thioester **149** (11.7 mg, 0.029 mmol) in cyclohexane (0.02M) was added to (*R*)-TRIP (4.4 mg, 0.0059 mmol) under N_2 and the reaction heated to 80 °C for 24 hours. The reaction was then cooled to room temperature, quenched with Et_3N (0.2 ml) and concentrated *in vacuo*. The crude material was purified by column chromatography (5% EtOAc/hexane) to afford **150** as a colourless oil (9.0 mg, 0.023 mmol, 77% yield, 96:4 er).

Asymmetric – (R)-TiPSY, 80 °C

150 was synthesised using the same procedure as the (*R*)-TRIP conditions with amino-thioester **149** (11.5 mg, 0.029 mmol) and (*R*)-TiPSY (5.0 mg, 0.0058 mmol). **150** yielded as a

colourless oil (2.5 mg, 0.0063 mmol, 22% yield, 76:24 er) after column chromatography (5% EtOAc/hexane).

Asymmetric – (R)-TRIP, 50 °C

150 was synthesised using the same procedure as the (*R*)-TRIP conditions with amino-thioester **149** (22.3 mg, 0.056 mmol) and (*R*)-TRIP (8.5 mg, 0.011 mmol) and the reaction was heated to 50 °C for 24 hours. **150** yielded as a colourless oil (8.5 mg, 0.021 mmol, 38% yield, 95:5 er) after column chromatography (5% EtOAc/hexane).

Asymmetric – (R)-TRIP, 50 °C, toluene

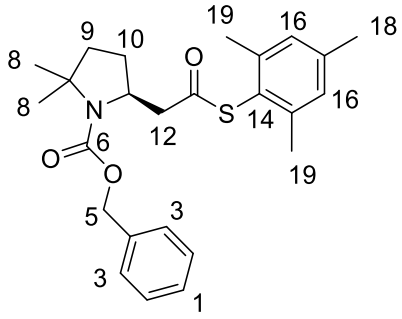
150 was synthesised using the same procedure as the (*R*)-TRIP conditions with amino-thioester **149** (19.5 mg, 0.049 mmol) and (*R*)-TRIP (7.4 mg, 0.0098 mmol) in toluene (0.02M) and the reaction was heated to 50 °C for 24 hours. **150** yielded as a colourless oil (3.6 mg, 0.0091 mmol, 18% yield, 96:4 er) after column chromatography (5% EtOAc/hexane).

Asymmetric – (R)-TRIP, 50 °C, 1,2-DCE

150 was synthesised using the same procedure as the (*R*)-TRIP conditions with amino-thioester **149** (20.1 mg, 0.051 mmol) and (*R*)-TRIP (7.6 mg, 0.010 mmol) in 1,2-DCE (0.02M) and the reaction was heated to 50 °C for 24 hours. **150** yielded as a colourless oil (2.5 mg, 0.0063 mmol, 12% yield, 95:5 er) after column chromatography (5% EtOAc/hexane).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 – 7.25 (m, 5H, Ar-H), 7.24 – 7.17 (m, 4H, H-15, H-16), 5.18 – 5.10 (m, 2H, H-5), 4.42 – 4.33 (m, 1H, H-11), 3.29 (dd, *J* = 14.9, 3.5 Hz, 0.4H, H-12, *rotamer 2*), 3.06 (dd, *J* = 14.9, 3.5 Hz, 0.6H, H-12, *rotamer 1*), 2.71 – 2.58 (m, 1H, H-12'), 2.36 (s, 3H, H-18), 2.12 – 1.95 (m, 1H, H-10), 1.95 – 1.82 (m, 1H, H-9), 1.81 – 1.72 (m, 2H, H-9', H-10'), 1.50 (s, 1.8H, H-8, *rotamer 1*), 1.40 (s, 1.2H, H-8, *rotamer 2*), 1.33 (s, 1.8H, H-8', *rotamer 1*), 1.26 (s, 1.2H, H-8', *rotamer 2*) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 195.8 (C-13), 153.3 (C-6), 139.9 (C-17), 136.9 (C-4), 134.4 (C-15), 130.1 (C-16), 128.6 (Ar-CH), 128.1 (Ar-CH), 127.9(127.9) (Ar-CH), 124.0 (C-14), 67.0(66.4) (C-5), 61.8 (C-7), 57.6(56.5) (C-11), 48.1(47.0) (C-12), 40.3(39.0) (C-9), 29.1(28.2) (C-8), 27.1(26.6) (C-10), 26.3(24.9) (C-8'), 21.4 (C-18) ppm; IR (ATR): ν_{max} 2960, 2923, 2852, 1702, 1494, 1456, 1399, 1347, 1304, 1258, 1214, 1182, 1144, 1071, 1004, 807, 770, 697, 676, 598 cm^{-1}; HRMS (ESI) 398.1772 (M + H^{+}. $C_{23}H_{28}NO_3S$ requires 398.1784); 420.1588 (M + Na^{+}. $C_{23}H_{27}NNaO_3S$ requires 420.1604); $[\alpha]_D^{20}$ +6.12° (c 0.215, $CHCl_3$) for 96:4 er

_N_-Cbz-2,2-dimethyl-(_S_)-5-(2,4,6-trimethyl-phenylsulfanylcarbonylmethyl)-pyrrolidine (154)



Racemic

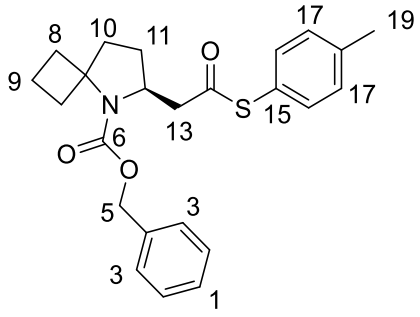
154 was synthesised using **general procedure G** with amino-thioester **153** (14.1 mg, 0.033 mmol) and rac-CSA (23.1 mg, 0.099 mmol). **154** yielded as a colourless oil (9.2 mg, 0.22 mmol, 65% yield) after column chromatography (8% EtOAc/hexane).

Asymmetric

154 was synthesised using **general procedure G** with amino-thioester **153** (13.2 mg, 0.031 mmol) and (*R*)-TRIP (4.7 mg, 0.0062 mmol). **154** yielded as a colourless oil (12.4 mg, 0.029 mmol, 94% yield, 92:8 er) after column chromatography (5% EtOAc/hexane).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 – 7.25 (m, 5H, Ar-H), 6.96 (s, 2H, H-16), 5.21 – 5.08 (m, 2H, H-5), 4.52 – 4.28 (m, 1H, H-11), 3.38 (dd, *J* = 14.7, 3.4 Hz, 0.4H, H-12, *rotamer 2*), 3.11 (dd, *J* = 14.7, 3.4 Hz, 0.6H, H-12, *rotamer 1*), 2.63 (dd, *J* = 14.7, 10.0 Hz, 1H, H-12'), 2.27 (s, 6H, H-19), 2.24 (s, 3H, H-18), 2.13 – 1.97 (m, 1H, H-10), 1.97 – 1.83 (m, 1H, H-9), 1.82 – 1.71 (m, 2H, H-9', H-10'), 1.50 (s, 1.8H, H-8, *rotamer 1*), 1.40 (s, 1.2H, H-8, *rotamer 2*), 1.33 (s, 1.8H, H-8', *rotamer 1*), 1.27 (s, 1.2H, H-8', *rotamer 2*) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 194.8 (C-13), 153.3 (C-6), 142.5(142.4) (C-14), 140.1 (C-17), 136.9 (C-4), 129.3 (C-16), 128.6 (Ar-CH), 128.1(128.0) (Ar-CH), 127.9(127.8) (Ar-CH), 123.5 (C-15), 67.0(66.4) (C-5), 61.7(61.2) (C-7), 57.8(56.7) (C-11), 48.1(47.1) (C-12), 40.3(39.0) (C-9), 29.1(28.2) (C-8), 26.9(26.4) (C-10), 26.3(24.8) (C-8'), 21.7 (C-19), 21.2 (C-18) ppm; IR (ATR): ν_{max} 2963, 1694, 1602, 1498, 1455, 1398, 1346, 1302, 1283, 1259, 1212, 1184, 1144, 1070, 1029, 1003, 971, 907, 850, 820, 770, 734, 715, 697, 676, 600, 554 cm^{-1}; HRMS (ESI) 426.2100 (M + H^{+}. $C_{25}H_{32}NO_3S$ requires 426.2097), 448.1919 (M + Na^{+}. $C_{25}H_{31}NNaO_3S$ requires 448.1917), 464.1658 (M + K^{+}. $C_{25}H_{31}KNO_3S$ requires 464.1656); $[\alpha]_D^{20}$ +20.6° (c 0.435, $CHCl_3$)

N-Cbz-(*S*)-6-p-Tolylsulfanylcarbonylmethyl-5-aza-spiro[3.4]octane (160a)



Racemic

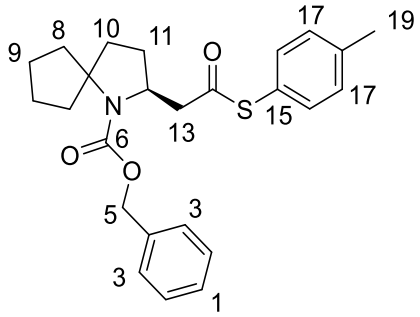
160a was synthesised using **general procedure G** with amino-thioester **159a** (19.2 mg, 0.047 mmol) and rac-CSA (32.7 mg, 0.14 mmol). **160a** yielded as a yellow oil (13.2 mg, 0.032 mmol, 69% yield) after column chromatography (5% EtOAc/hexane).

Asymmetric

160a was synthesised using **general procedure G** with amino-thioester **159a** (19.4 mg, 0.047 mmol) and (*R*)-TRIP (7.1 mg, 0.0095 mmol). **160a** yielded as a yellow oil (19.2 mg, 0.047 mmol, 99% yield, 96:4 er) after column chromatography (5% EtOAc/hexane).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.49 – 7.27 (m, 5H, Ar-CH), 7.25 – 7.17 (m, 4H, H-16, H-17), 5.34 – 5.08 (m, 2H, H-5), 4z.31 (s, 1H, H-12), 3.39 – 2.54 (m, 4H, H-13, H-8), 2.36 (s, 3H, H-19), 2.25 – 2.14 (m, 1H, H-10), 2.04 – 1.89 (m, 1H, H-11), 1.89 – 1.79 (m, 2H, H-9, H-10'), 1.79 – 1.67 (m, 2H, H-11', H-8'), 1.67 – 1.56 (m, 2H, H-8', H-9') ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 195.9 (C-14), 154.0 (C-6), 139.8 (C-18), 136.8 (C-4), 134.4 (C-16), 130.1 (C-17), 128.6 (Ar-CH), 128.0 (Ar-CH), 128.0 (Ar-CH), 124.0 (C-15), 67.1(66.4) (C-5), 64.3 (C-7), 57.5(56.4) (C-12), 47.9 (C-13), 37.5 (C-10), 33.0(32.8) (C-8), 26.9(26.4) (C-11), 21.4 (C-19), 13.6 (C-9) ppm; IR (ATR): ν_{max} 2929, 2870, 1696, 1598, 1494, 1453, 1397, 1349, 1319, 1302, 1266, 1203, 1181, 1170, 1105, 1040, 1028, 1005, 972, 939, 913, 807, 770, 746, 697, 658, 600, 533, 474 cm^{-1}; HRMS (ESI) 410.1788 (M + H^{+}. $C_{24}H_{28}NO_3S$ requires 410.1784); 432.1601(M + Na^{+}. $C_{24}H_{27}NNaO_3S$ requires 432.1604); $[\alpha]_D^{20}$ +5.61° (c 0.585, $CHCl_3$)

_N_-Cbz-(_S_)-2-p-Tolylsulfanylcarbonylmethyl-1-aza-spiro[4.4]nonane (160b)



Racemic

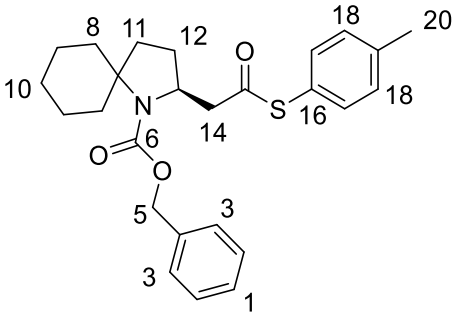
160b was synthesised using **general procedure G** with amino-thioester **159b** (10.0 mg, 0.024 mmol) and rac-CSA (16.5 mg, 0.071 mmol). **160b** yielded as a colourless oil (8.7 mg, 0.021 mmol, 87% yield) after column chromatography (5% EtOAc/hexane).

Asymmetric

160b was synthesised using **general procedure G** with amino-thioester **159b** (15.5 mg, 0.037 mmol) and (*R*)-TRIP (5.5 mg, 0.0073 mmol). **160b** yielded as a colourless oil (10.8 mg, 0.025 mmol, 70% yield, 95:5 er) after column chromatography (5% EtOAc/hexane).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 – 7.27 (m, 5H, Ar-H), 7.27 – 7.16 (m, 4H, H-16, H-17), 5.21 – 5.10 (m, 2H, H-5), 4.41 – 4.30 (m, 1H, H-12), 3.28 (dd, *J* = 14.9, 3.8 Hz, 0.3H, H-13, *rotamer 2*), 3.07 (dd, *J* = 14.9, 3.8 Hz, 0.7H, H-13, *rotamer 1*), 2.73 – 2.60 (m, 1H, H-13'), 2.60 – 2.45 (m, 0.7H, H-8, *rotamer 1*), 2.36 (s, 3H, H-19), 2.60 – 2.26 (m, 0.3H, H-8, *rotamer 2*), 2.20 – 1.64 (m, 7H, H-8, H-9, H-10, H-11), 1.56 – 1.32 (m, 4H, H-8', H-9') ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 195.8 (C-14), 153.0 (C-6), 139.8 (C-18), 136.8 (C-4), 134.3 (C-16), 130.0 (C-17), 128.5(128.3) (Ar-CH), 128.0 (Ar-CH), 127.9(127.8) (Ar-CH), 124.0 (C-15), 71.2 (C-7), 67.0(66.2) (C-5), 57.0 (56.1) (C-12), 47.8(47.0) (C-13), 40.9(39.2) (C-10), 37.2(35.4) (C-8), 27.7(27.1) (C-11), 25.0(24.8) (C-9), 21.3 (C-19) ppm; IR (ATR): ν_{max} 3032, 2923, 2853, 1698, 1598, 1494, 1449, 1399, 1350, 1327, 1302, 1236, 1208, 1172, 1104, 1057, 1028, 1015, 990, 915, 807, 770, 733 ,697, 648, 602, 533, 475 cm^{-1}; HRMS (ESI) 424.1926 (M + H^{+}. $C_{25}H_{30}NO_3S$ requires 424.1941); 446.1742 (M + Na^{+}. $C_{25}H_{29}NNaO_3S$ requires 446.1760); $[\alpha]_D^{20}$ +4.14° (c 0.55, $CHCl_3$)

_N_-Cbz-(_S_)-2-p-Tolylsulfanylcarbonylmethyl-1-aza-spiro[4.5]decane (160c)



Racemic

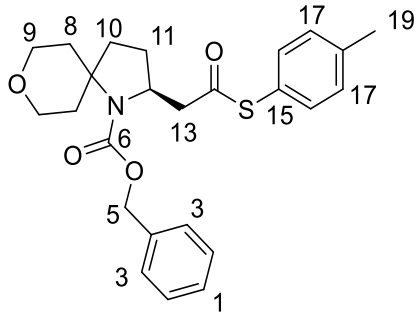
160c was synthesised using **general procedure G** with amino-thioester **159c** (10.9 mg, 0.025 mmol) and rac-CSA (17.4 mg, 0.075 mmol). **160c** yielded as a colourless oil (9.1 mg, 0.021 mmol, 83% yield) after column chromatography (5% EtOAc/hexane).

Asymmetric

160c was synthesised using **general procedure G** with amino-thioester **159c** (15.0 mg, 0.034 mmol) and (*R*)-TRIP (5.2 mg, 0.0069 mmol). **160c** yielded as a colourless oil (10.1 mg, 0.023 mmol, 67% yield, 96:4 er) after column chromatography (5% EtOAc/hexane).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 – 7.27 (m, 5H, Ar-H), 7.27 – 7.16 (m, 4H, H-17, H-18), 5.21 – 5.09 (m, 2H, H-5), 4.46 – 4.34 (m, 1H, H-13), 3.26 (dd, *J* = 14.6, 3.2 Hz, 0.3H, H-14, *rotamer 2*), 3.05 (dd, *J* = 14.6, 3.2 Hz, 0.7H, H-14, *rotamer 1*), 2.74 – 2.64 (m, 0.7H, H-8, *rotamer 1*), 2.61 (dd, *J* = 14.6, 10.5 Hz, 1H, H-14'), 2.50 – 2.41 (m, 0.3H, H-8, *rotamer 2*), 2.36 (s, 3H, H-20), 2.34 – 2.25 (m, 0.7H, H-10, *rotamer 1*), 2.17 (dd, *J* = 12.4, 6.8 Hz, 1H, H-11), 2.12 – 2.00 (m, 0.3H, H-10, *rotamer 2*), 2.00 – 1.84 (m, 1H, H-12), 1.81 – 1.73 (m, 1H, H-12'), 1.73 – 1.56 (m, 4H, H-9, H-11'), 1.44 – 1.13 (m, 5H, H-8', H-9', H-10') ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 195.8 (C-15), 153.2 (C-6), 139.9 (C-19), 137.0 (C-4), 134.4 (C-17), 130.1 (C-18), 128.6 (Ar-CH), 128.0 (Ar-CH), 127.9 (Ar-CH), 124.1 (C-16), 66.3(65.8) (C-5), 57.4 (C-7), 56.3 (C-13), 48.1(47.0) (C-14), 37.9(36.9) (C-8), 34.4(33.2) (C-11), 32.3(30.8) (C-10), 27.1(26.4) (C-12), 25.1(24.5, 24.3) (C-9), 21.4 (C-20) ppm; IR (ATR): ν_{max} 2923, 2854, 1701, 1494, 1454, 1397, 1347, 1301, 1280, 1209, 1155, 1108, 1027, 1002, 807, 769, 697, 599, 476 cm^{-1}; HRMS (ESI) 438.2086 (M + H^{+}. $C_{26}H_{32}NO_3S$ requires 438.2097); 460.1907 (M + Na^{+}. $C_{26}H_{31}NNaO_3S$ requires 460.1917); $[\alpha]_D^{20}$ +13.6° (c 0.39, $CHCl_3$)

_N_-Cbz-(_S_)-2-p-Tolylsulfanylcarbonylmethyl-8-oxa-1-aza-spiro[4.5]decane (160d)



Racemic

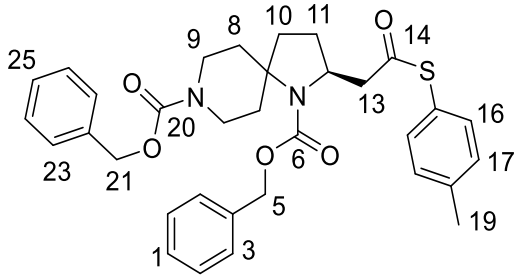
160d was synthesised using **general procedure G** with amino-thioester **159d** (9.7 mg, 0.022 mmol) and rac-CSA (15.4 mg, 0.066 mmol). **160d** yielded as a pale-yellow oil (3.7 mg, 0.0084 mmol, 38% yield) after column chromatography (30% EtOAc/hexane).

Asymmetric

160d was synthesised using **general procedure G** with amino-thioester **159d** (12.8 mg, 0.029 mmol) and (*R*)-TRIP (4.4 mg, 0.0058 mmol). **160d** yielded as a pale-yellow oil (7.8 mg, 0.018 mmol, 61% yield, 96:4 er) after column chromatography (30% EtOAc/hexane).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.50 – 7.27 (m, 5H, Ar-CH), 7.26 – 7.15 (m, 4H, H-16, H-17), 5.27 – 5.07 (m, 2H, H-5), 4.55 – 4.35 (m, 1H, H-12), 4.13 – 3.74 (m, 2H, H-9), 3.46 (ddd, *J* = 12.5, 12.1, 2.4 Hz, 1H, H-9'), 3.38 (ddd, *J* = 12.5, 12.1, 2.4 Hz, 1H, H-9'), 3.29 – 3.21 (m, 0.3H, H-13, *rotamer 2*), 3.16 – 3.08 (m, 0.7H, H-10, *rotamer 1*), 3.08 – 2.99 (m, 0.7H, H-13, *rotamer 1*), 2.92 – 2.80 (m, 0.3H, H-10, *rotamer 2*), 2.78 – 2.68 (m, 0.7H, H-8, *rotamer 1*), 2.62 (dd, *J* = 14.6, 10.2 Hz, 1H, H-13'), 2.54 – 2.49 (m, 0.3H, H-8, *rotamer 2*), 2.36 (s, 3H, H-19), 2.30 (dd, *J* = 12.3, 6.6 Hz, 1H, H-8), 2.03 – 1.90 (m, 1H, H-11), 1.90 – 1.80 (m, 1H, H-11'), 1.80 – 1.71 (m, 1H, H-8'), 1.32 – 1.11 (m, 2H, H-8', H-10') ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 195.7 (C-14), 153.2 (C-6), 140.0 (C-18), 136.8 (C-4), 134.4 (C-16), 130.2 (C-17), 128.6 (Ar-CH), 128.0 (Ar-CH), 128.0 (Ar-CH), 123.9 (C-15), 67.0(66.5) (C-5), 66.1(66.0) (C-9), 63.0 (C-7), 56.4 (C-12) 48.1 (C-13), 37.2 (C-10), 32.9(31.8) (C-8), 26.9 (C-11), 21.4 (C-19) ppm; IR (ATR): ν_{max} 2957, 2922, 2851, 1697, 1598, 1494, 1452, 1397 , 1349, 1302, 1281, 1228, 1208, 119, 1104, 1052, 1027, 1001, 921, 862, 841, 807, 734, 697, 682, 600, 549, 534, 474 cm^{-1}; HRMS (ESI) 440.1892 (M + H^{+}. $C_{25}H_{30}NO_4S$ requires 440.1890); 462.1704 (M + Na^{+}. $C_{25}H_{39}NNaO_4S$ requires 462.1710); 478.1443 (M + Na^{+}. $C_{25}H_{39}KNO_4S$ requires 478.1449); $[\alpha]_D^{20}$ +9.89° (c 0.635, $CHCl_3$)

(*S*)-2-p-Tolylsulfanylcarbonylmethyl-1,8-diaza-spiro[4.5]decane-1,8-dicarboxylic acid dibenzyl ester (160e)



Racemic

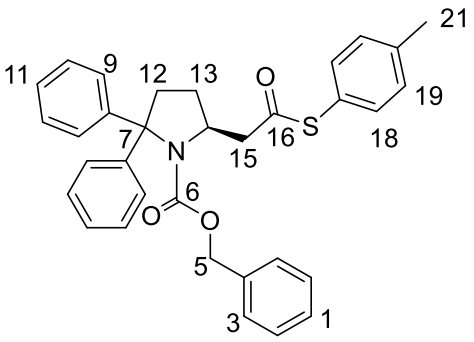
160e was synthesised using **general procedure G** with amino-thioester **159e** (21.4 mg, 0.037 mmol) and rac-CSA (26.0 mg, 0.112 mmol). **160e** yielded as a yellow oil (0.8 mg, 0.0014 mmol, 4% yield) after column chromatography (20% EtOAc/hexane to 100% EtOAc).

Asymmetric

160e was synthesised using **general procedure G** with amino-thioester **159e** (54.7 mg, 0.096 mmol) and (*R*)-TRIP (14.4 mg, 0.019 mmol). **160e** yielded as a yellow oil (20.5 mg, 0.0358 mmol, 37% yield, 70:30 er) after column chromatography (40% Et_2O/hexane).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.79 – 7.24 (m, 10H, Ar-H), 7.24 – 7.03 (m, 4H, H-16, H-17), 5.25 – 4.86 (m, 4H, H-5, H-21), 4.63 – 4.36 (m, 1H, H-12), 4.33 – 3.72 (m, 2H, H-9), 3.37 – 3.01 (m, 1H, H-13), 3.00 – 2.45 (m, 5H, H-8H-9', H-10, H-13'), 2.36 (s, 3H, H-19), 2.27 – 2.15 (m, 1H, H-10'), 2.11 – 1.90 (m, 1H, H-11), 1.90 – 1.80 (m, 1H, H-11'), 1.81 – 1.65 (m, 1H, H-8), 1.40 – 1.23 (m, 2H, H-8') ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 195.7 (C-14), 155.1 (C-20), 153.1 (C-6), 140.0 (C-18), 136.8 (C-22), 136.5 (C-4), 134.4 (C-16), 130.2 (C-17), 128.7 (Ar-CH), 128.6 (Ar-CH), 128.1 (Ar-CH), 128.1 (Ar-CH), 128.0 (Ar-CH), 128.0 (Ar-CH), 123.9 (C-15), 67.2 (C-21), 66.6 (C-7), 63.8 (C-5), 56.4 (C-12), 48.1 (C-13), 42.0 (C-9), 34.2 (C-8), 32.4 (C-10), 26.9, (C-11), 21.4 (C-19) ppm; IR (ATR): ν_{max} 2924, 1699, 1496, 1432, 1358, 1244, 1159, 1074, 808, 738, 697 cm^{-1}; HRMS (ESI) 595.2233 (M + Na$^+$. $C_{33}H_{36}N_2NaO_5S$ requires 595.2237); 611.1991 (M + K$^+$. $C_{33}H_{36}KN_2O_5S$ requires 611.1977); $[\alpha]_D^{20}$ -13.8° (c 0.225, $CHCl_3$)

_N_-Cbz-2,2-diphenyl-(_S_)-5-p-Tolylsulfanylcarbonylmethyl-pyrrolidine (160f)



Racemic

A solution of amino-thioester **159f** (22.2 mg, 0.0426 mmol) in THF (2 ml) was added to NaH 60% dispersion in mineral oil (3.4 mg, 0.0852 mmol) under N_2 at 0 °C and the reaction stirred for 2 hours. The reaction was quenched with H_2O (0.5 ml) and diluted with EtOAc (10 ml). The solution was dried with $MgSO_4$, filtered and the solids washed with EtOAc (2 x 10 ml) and concentrated *in vacuo*. The crude material was purified by column chromatography (10% EtOAc/hexane) to afford **160f** as a colourless oil (21.3 mg, 0.0408 mmol, 96% yield).

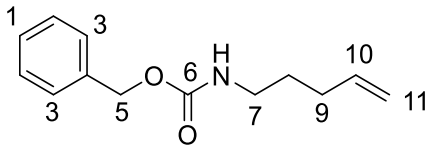
Asymmetric

160f was synthesised using **general procedure G** with amino-thioester **159f** (18.4 mg, 0.0353 mmol) and (*R*)-TRIP (5.3 mg, 0.00705 mmol) and the reaction was stirred at 80 °C for 48 hours. **160f** yielded as a colourless oil (2.5 mg, 0.00479 mmol, 14% yield, 77:23 er) after column chromatography (10% EtOAc/hexane).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.66 – 7.18 (m, 14H, Ar-H), 7.17 – 6.50 (m, 5H, Ar-H), 5.45 – 4.40 (m, 3H, H-5, H-14), 3.78 (d, *J* = 15.0 Hz, 0.6H, H-15, *rotamer 1*), 3.45 (d, *J* = 15.0 Hz, 0.4H, H-15, *rotamer 2*), 2.83 (dd, *J* = 15.0, 10.2 Hz, 1H, H-15'), 2.78 – 2.67 (m, 1H, H-12), 2.51 (dt, *J* = 12.7, 5.5 Hz, 1H, H-12'), 2.37 (s, 3H, H-21), 2.08 – 1.92 (m, 1H, H-13), 1.78 – 1.65 (m, 1H, H-13') ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 195.9 (C-16), 155.1 (C-6), 143.6(143.2) (C-8), 139.8 (C-20), 134.6 (C-18), 130.2 (C-19), 128.6 (Ar-CH), 128.2 (Ar-CH), 127.9 (Ar-CH), 127.8 (Ar-CH), 127.7 (Ar-CH), 126.9 (Ar-CH), 124.0 (C-17), 74.3 (C-7), 66.7 (C-5), 57.5 (C-14), 47.4 (C-15), 45.3 (C-12), 29.8(28.1) (C-13), 21.5 (C-21) ppm; IR (ATR): ν_{max} 3059, 3030, 2953, 1686, 1598, 1493, 1447, 1399, 1343, 1287, 1241, 1211, 1128, 1059, 1032, 1026, 996, 910, 807, 755, 697, 647, 616, 593, 535, 475 cm^{-1}; HRMS (ESI) 522.2099 (M + H$^+$. $C_{33}H_{32}NO_3S$ requires 522.2099); 544.1920 (M + Na$^+$. $C_{33}H_{31}NNaO_3S$ requires 544.1917); 560.1658 (M + K$^+$. $C_{33}H_{31}NKO_3S$ requires 560.1656); $[\alpha]_D^{20}$ -8.63° (c 0.115, $CHCl_3$)

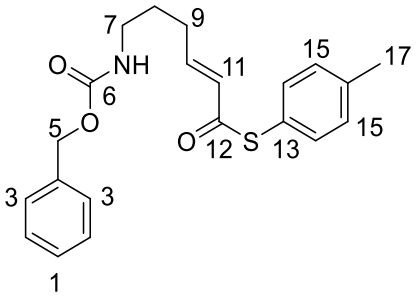
Asymmetric cyclisation of unsubstituted pyrrolidines

Pent-4-enyl-carbamic acid benzyl ester (162)



To a solution of 4-penten-1-amine (154 mg, 1.81 mmol) in dioxane (5 ml) was added K_2CO_3 solution (50% w/w aq, 600mg, 2.17 mmol) followed by benzyl chloroformate (0.39 ml, 2.72 mmol) and the reaction stirred at room temperature for 4 hours. The reaction was quenched with H_2O (5 ml) and portioned with CH_2Cl_2 (5 ml). The aqueous phase was extracted with CH_2Cl_2 (2 x 5 ml) and organic fractions combined. The combined organics were washed with saturated brine solution (5 ml), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (10% EtOAc/hexane) to afford **162** as a colourless oil (254 mg, 1.16 mmol, 64% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.28 - 7.45 (m, 5 H, Ar-H) 5.80 (ddt, *J* = 17.5, 10.7, 6.9 Hz, 1 H, H-10), 5.11 (s, 2 H, H-5), 5.04 (dd, *J* = 17.5, 1.5 Hz, 1 H, H-11), 4.99 (dd, *J* = 10.7, 1.5 Hz, 1 H, H-11), 4.79 (br. s, 1 H, NH), 3.22 (q, *J* = 6.9 Hz, 2 H, H-7), 2.10 (td, *J* = 7.2, 6.9 Hz, 2 H, H-9), 1.62 (tt, *J* = 7.2, 6.9 Hz, 2 H, H-8) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 156.3 (C-6), 137.7 (C-10), 136.6 (C-4), 128.5 (Ar-CH), 128.1 (Ar-CH), 128.1 (Ar-CH), 115.2 (C-11), 66.6 (C-5), 40.5 (C-7), 30.9 (C-9), 29.0 (C-8) ppm; IR (ATR): ν_{max} 3334, 3066, 3033, 2935, 1697, 1640, 1532, 1454, 1414, 1369, 1254, 1137, 1041, 1027, 1002, 912, 776, 736, 696, 638, 485 cm^{-1}; HRMS (ESI) 242.1149 (M + Na$^+$. $C_{13}H_{17}NNaO_2$ requires 242.1151).

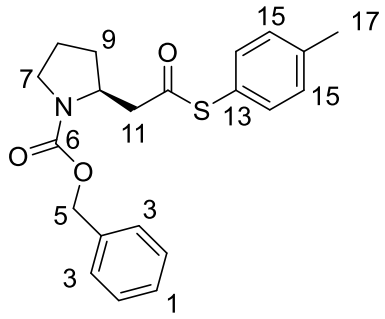
6-Cbz-amino-hex-2-enethioic acid S-p-tolyl ester (163)



163 was synthesised using **general procedure C** with thioester **134** (235 mg, 1.32 mmol), Hoveyda-Grubbs Catalyst™ 2nd generation (27.6 mg, 0.044 mmol), copper iodide (83.8 mg,

0.44 mmol) and Cbz-amine **162** (96.6 mg, 0.44 mmol). **163** yielded as a brown solid (137 mg, 0.37 mmol, 84% yield) after column chromatography (20% EtOAc/hexane). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.29 - 7.42 (m, 5 H, Ar-H), 7.32 (d, *J* = 7.6 Hz, 2 H, H-14), 7.23 (d, *J* = 7.6 Hz, 2 H, H-15), 6.95 (dt, *J* = 16.0, 6.6 Hz, 1 H, H-10), 6.20 (d, *J* = 16.0 Hz, 1 H, H-11), 5.11 (s, 2 H, H-5), 4.80 (br. s., 1 H, NH), 3.25 (q, *J* = 7.1 Hz, 2 H, H-7), 2.39 (s, 3 H, H-17), 2.28 (td, *J* = 7.1, 6.6 Hz, 2 H, H-9), 1.72 (quin, *J* = 7.1 Hz, 2 H, H-8) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 188.4 (C-12), 156.4 (C-6), 144.9 (C-10), 139.7 (C-16), 136.4 (C-4), 134.6 (C-14), 130.0 (C-15), 128.5 (Ar-CH), 128.5 (Ar-CH), 128.3 (Ar-CH), 128.2 (C-11), 123.9 (C-13), 66.7 (C-5), 40.5 (C-7), 29.4 (C-9), 28.4 (C-8), 21.3 (C-17) ppm; IR (ATR): ν_{max} 3345, 3032, 2980, 2884, 1720, 1691, 1631, 1597, 1524, 1494, 1454, 1399, 1378 1336, 1248, 1140, 1104, 1091, 1026, 1017, 992, 808, 776, 752, 737, 697, 635, 649, 615, 476 cm^{-1}; HRMS (ESI) 392.1292 (M + Na^{+}. $C_{21}H_{23}NNaO_3S$ requires 392.1291); mp. 71.5-72.5 °C

_N_-Cbz-(_S_)-2-p-Tolylsulfanylcarbonylmethyl-pyrrolidine (164)



Racemic

164 was synthesised using **general procedure G** with amino-thioester **163** (22.6 mg, 0.061 mmol) and rac-CSA (42.6 mg, 0.184 mmol). **164** yielded as a yellow oil (19.2 mg, 0.052 mmol, 85% yield) after column chromatography (10% EtOAc/hexane).

Asymmetric – (R)-TRIP, 80 °C

164 was synthesised using **general procedure G** with amino-thioester **163** (98.8 mg, 0.27 mmol) and (*R*)-TRIP (40.3 mg, 0.056 mmol). **164** yielded as a yellow oil (86.3 mg, 0.23 mmol, 87% yield, 90:10 er) after column chromatography (10% EtOAc/hexane).

Asymmetric - (R)-TiPSY, 80 °C

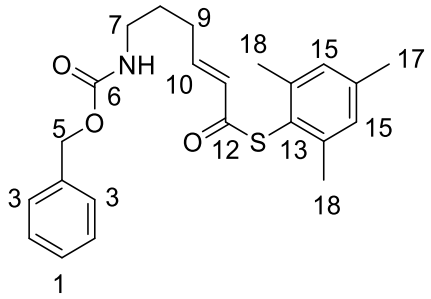
164 was synthesised using **general procedure G** with amino-thioester **163** (9.9 mg, 0.027 mmol) and (*R*)-TiPSY (4.6 mg, 0.0054 mmol). **164** yielded as a yellow oil (8.7 mg, 0.024 mmol, 87% yield, 94:6 er) after column chromatography (10% EtOAc/hexane).

Asymmetric - (R)-TRIP, 50 °C

164 was synthesised using **general procedure G** with amino-thioester **163** (20.0 mg, 0.054 mmol) and (*R*)-TRIP (8.2 mg, 0.11 mmol) and the reaction was heated to 50 °C for 24 hours. **164** yielded as a yellow oil (18.5 mg, 0.050 mmol, 93% yield, 91:9 er) after column chromatography (10% EtOAc/hexane).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.30 - 7.44 (m, 5 H, Ar-H), 7.25 - 7.30 (m, 2 H, H-14), 7.16 - 7.24 (m, 2 H, H-15), 5.08 - 5.26 (m, 2 H, H-5), 4.21 - 4.35 (m, 1 H, H-10), 3.38 - 3.51 (m, 2 H, H-7), 3.33 (dd, *J* = 14.9, 3.4 Hz, 0.5 H, *rotamer 1*, H-11), 3.10 (dd, *J* = 14.9, 3.4 Hz, 0.5 H, *rotamer 2*, H-11), 2.75 (dd, *J* = 15.3, 9.9 Hz, 0.5 H, *rotamer 1*, H-11), 2.68 (dd, *J* = 15.3, 9.9 Hz, 0.5 H, *rotamer 2*, H-11), 2.38 (s, 3 H, H-17), 1.99 - 2.15 (m, 1 H, H-9), 1.78 - 1.98 (m, 3 H, H-9, H-8) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 195.8(195.7) (C-12), 154.6(154.5) (C-6), 139.8(139.4) (C-16), 136.8(136.6) (C-4), 134.4(134.3) (C-14), 130.0(130.0) (C-15), 128.5 (Ar-CH), 128.4 (Ar-CH), 127.9(127.8) (Ar-CH), 124.1(123.9) (C-13), 66.9(66.7) (C-5), 55.0(54.4) (C-10), 47.7(46.7) (C-11), 46.7(46.4) (C-7), 30.9(30.2) (C-9), 23.6(22.8) (C-8), 21.3(C-17) ppm; IR (ATR): ν_{max} 3031, 2955, 2923, 1697, 1597, 1494, 1449, 1409, 1356, 1336, 1306, 1281, 1211, 1181, 1160, 1060, 1009, 985, 916, 879, 807, 768, 751, 697, 603, 551, 533, 474 cm^{-1}; HRMS (ESI) 370.1467 (M + H^{+}. $C_{21}H_{24}NO_3S$ requires 370.1471); 392.1289 (M + Na^{+}. $C_{21}H_{23}NNaO_3S$ requires 392.1291); $[\alpha]_D^{25}$ -21.6° (c 1.035, $CHCl_3$) for 90:10 er.

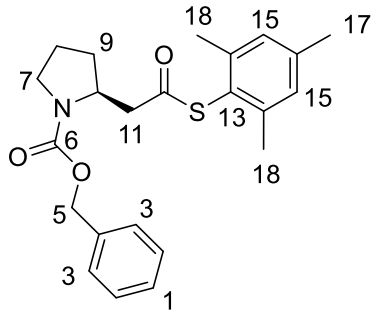
_N_-Cbz-6-amino-hex-2-enethioic acid 2,4,6-trimethyl-phenyl ester (165)



165 was synthesised using **general procedure C** with thioester **152** (308 mg, 1.49 mmol), Hoveyda-Grubbs Catalyst™ 2nd generation (31.1 mg, 0.050 mmol), copper iodide (94.7 mg, 0.50 mmol) and Cbz-amine **162** (109 mg, 0.50 mmol). **165** yielded as a pale brown solid (171 mg, 0.43 mmol, 87% yield) after column chromatography (15% EtOAc/hexane). ^{1}H NMR (400

MHz, Chloroform-*d*): δ7 .29 - 7.45 (m, 5 H, Ar-H), 6.99 (s, 2 H,H-15), 6.95 (dt, *J* = 15.6, 6.4 Hz, 1 H, H-10), 6.24 (d, *J* = 15.6 Hz, 1 H, H-11), 5.12 (s, 2 H, H-5), 4.75 - 4.88 (br. s., 1 H, NH), 3.25 (q, *J* = 6.4 Hz, 1 H, H-7), 2.32 (s, 6 H, H-18), 2.31 (s, 3 H, H-17), 2.28 (td, *J* = 7.3, 6.4 Hz, 2 H, H-9), 1.72 (tt, *J* = 7.3, 6.4 Hz, 2 H, H-8) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 187.6 (C-12), 156.4 (C-6), 144.5 (C-10), 142.6 (C-13), 139.9 (C-16), 136.4 (C-4), 129.2 (C-15), 128.5 (C-11), 128.5 (Ar-CH), 128.5 (Ar-CH), 128.1 (Ar-CH), 123.3 (C-14), 66.7 (C-5), 40.5 (C-7), 29.4 (C-9), 28.3 (C-8), 21.6 (C-18), 21.1 (C-17) ppm; IR (ATR): ν_{max} 3346, 3063, 3031, 2925, 2732, 1720, 1699, 1684, 1630, 1602, 1586, 1527, 1454, 1246, 1189, 1139, 1102, 1026, 992, 931, 914, 851, 798, 776, 753, 736, 715, 697, 645, 633, 614, 578, 565, 506, 489, 475, 459 cm^{-1}; HRMS (ESI) 420.1595 (M + Na$^+$. $C_{23}H_{27}NNaO_3S$ requires 420.1604); mp. 66.4-68.0 °C

_N_-Cbz-(_S_)-2-(2,4,6-Trimethyl-phenylsulfanylcarbonylmethyl)-pyrrolidine (166)



166 was synthesised using **general procedure G** with amino-thioester **165** (14.0 mg, 0.035 mmol) and rac-CSA (24.5 mg, 0.106 mmol). **166** yielded as a colourless oil (10.9 mg, 0.027 mmol, 78% yield) after column chromatography (15% EtOAc/hexane).

Asymmetric

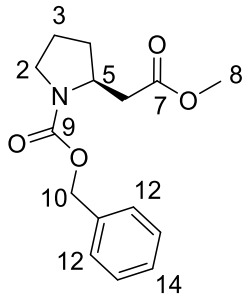
166 was synthesised using **general procedure G** with (*R*)-TRIP (3.9 mg, 0.0052 mmol) and amino-thioester **165** (10.3 mg, 0.026 mmol) **166** yielded as a colourless oil (9.4 mg, 0.024 mmol, 91% yield, er 84:16) after column chromatography (10% EtOAc/hexane).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.26 (m, 5H, Ar-H), 6.96 (s, 2H, H-15), 5.24 – 5.08 (m, 2H, H-5), 4.32 – 4.23 (m, 1H, H-10), 3.46 – 3.39 (m, 2H, H-7), 3.36 (dd, *J* = 14.8, 3.3 Hz, 0.5H, *rotamer 1*, H-11), 3.11 (dd, *J* = 14.8, 3.3 Hz, 0.5H, *rotamer 2*, H-11), 2.75 (dd, *J* = 14.8,

9.9 Hz, 0.5H, *rotamer 1*, H-11'), 2.67 (dd, *J* = 14.8, 9.9 Hz, 0.5H, *rotamer 2*, H-11'), 2.28 (s, 6H, H-18), 2.26 (s, 3H, H-17), 2.11 – 1.99 (m, 1H, H-9), 1.96 – 1.76 (m, 3H, H-8, H-9') ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 195.1 (C-12), 154.7 (C-6), 142.4 (C-13), 140.0 (C-16), 136.5 (C-4), 129.3 (C-15), 128.6 (Ar-CH), 128.1 (Ar-CH), 128.0 (Ar-CH), 123.6 (C-14), 67.1(66.8) (C-5), 55.3(54.7) (C-10), 47.8(46.9) (C-7), 46.8(46.6) (C-11), 31.0(30.3) (C-9), 23.8(22.8) (C-8), 21.7 (C-18), 21.2 (C-17) ppm; IR (ATR): ν_{max} 2923, 2853, 1700, 1602, 1411, 1356, 1187, 1100, 1009, 850, 769, 698 cm^{-1}; HRMS (ESI) 398.1788 (M + H$^+$. $C_{23}H_{28}NO_3S$ requires 398.1784); 420.1601 (M + Na$^+$. $C_{23}H_{27}NNaO_3S$ requires 420.1604); 436.1344 (M + K$^+$. $C_{23}H_{27}KNO_3S$ requires 436.1343); $[\alpha]_D^{20}$ -11.9° (c 0.49, $CHCl_3$)

Determination of the absolute stereochemistry

***N*-Cbz-(*S*)-2-Methoxycarbonylmethyl-pyrrolidine (169)**



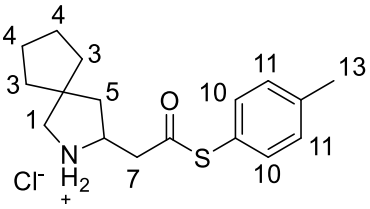
To solution of pyrrolidine **164** (21.8 mg, 0.059 mmol, 90:10 er) in dry MeOH/DCM (1:1, 1ml) was added AgOTf (45.5 mg, 0.177 mmol) and the reaction was stirred for 3 hours. After that time the reaction was diluted with Et_2O (5 ml) and filtered through a silica plug followed by Et_2O (3 x 15 ml). The combined filtrate was concentrated *in vacuo* and the crude residue was purified by flash column chromatography (20% EtOAc/hexane) to afford **169** as a pale-yellow oil (10.9 mg, 0.039 mmol, 67% yield, 89:11 er).

^{1}H NMR (400 MHz, Chloroform-*d*): 7.28 - 7.41 (m, 5 H, Ar-H), 5.15 (m, 2 H, H-10), 4.18 - 4.30 (m, 1 H, H-5), 3.67 (s, 1.8 H, *rotamer 1*, H-8), 3.64 (s, 1.2 H, *rotamer 2*, H-8), 3.38 - 3.50 (m, 2 H, H-2), 2.99 (dd, *J* = 15.2, 3.9 Hz, 0.6 H, H-6 *rotamer 1*), 2.81 (dd, *J* = 15.2, 3.9 Hz, 0.4 H, H-6 *rotamer 2*), 2.29 - 2.42 (m, 1 H, H-6'), 2.02 - 2.16 (m, 1 H, H-4), 1.98 – 1.83 (m, 2H, H-3), 1.83 – 1.72 (m, 1H, H-4') ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 171.9(171.7) (C-7), 154.7(154.0) (C-9), 136.9(136.7) (C-11), 128.4 (Ar-CH), 127.9 (Ar-CH), 127.8 (Ar-CH), 66.8(66.6) (C-10), 54.5(54.0) (C-5), 51.6 (C-8), 46.8(46.4) (C-2), 39.1(38.1) (C-6), 31.3(30.6) (C-4), 23.5(22.7) (C-3) ppm; IR (ATR): ν_{max} 3032, 2953, 2880, 1736, 1699, 1498, 1436, 1411, 1336, 1306, 1284,

1255, 1189, 1168, 1116, 1098, 1064, 1017, 975, 918, 825, 769, 751, 698, 604, 552, 485 cm^{-1}; HRMS (ESI) 300.1205 (M + Na^+. $C_{15}H_{19}NNaO_4$ requires 300.1206); $[\alpha]_D^{20}$ -25.4° (c 0.545, $CHCl_3$) [lit. $[\alpha]_D^{20}$ -33.0° (c 0.54, $CHCl_3$) for (S)-isomer][136]

Cbz deprotection

3-p-Tolylsulfanylcarbonylmethyl-2-azonia-spiro[4.4]nonane chloride ((±)-173)

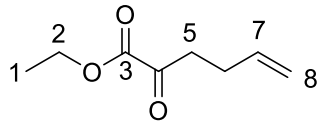


Pyrrolidine **(±)-144b** (32.9 mg, 0.0777 mmol) was dissolved in dry CH_2Cl_2 (0.78 ml) and added to a solution of BCl_3.DMS (97.5 mg, 0.544 mmol) in CH_2Cl_2 (0.27 ml) at room temperature under N_2. The reaction was stirred at room temperature for 12 hours, then diluted with CH_2Cl_2 (15 ml) and quenched with saturated $NaHCO_3$ (aq) (10 ml). The aqueous fraction was extracted with CH_2Cl_2 (3 x 10 ml) and the combined organic fractions were washed with saturated brine solution (10 ml), dried with Na_2SO_4, filtered, and concentrated *in vacuo* to give **(±)-173** as a pale yellow solid (24.2 mg, 0.0744 mmol, 96% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.97 – 9.48 (m, 2H, NH_2^+), 7.31 (d, *J* = 8.0 Hz, 2H, H-10), 7.17 (d, *J* = 8.0 Hz, 2H, H-11), 3.95 (dt, *J* = 11.3, 6.4 Hz, 1H, H-6), 3.50 (dd, *J* = 17.0, 6.9 Hz, 1H, H-7), 3.17 (dd, *J* = 17.0, 6.6 Hz, 1H, H-7'), 3.04 (t, *J* = 5.4 Hz, 2H, H-1), 2.32 (s, 3H, H-13), 2.04 (dd, *J* = 13.0, 6.6 Hz, 1H, H-5), 1.72 – 1.42 (m, 9H, H-3, H-4, H-5') ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 195.4 (C-8), 140.1 (C-12), 134.8 (C-10), 130.2 (C-11), 123.4 (C-9), 55.4 (C-6), 55.0 (C-1), 49.2 (C-2), 45.1 (C-7), 43.1 (C-5), 37.6 (C-3), 36.5 (C-3'), 24.7 (C-4), 24.6 (C-4'), 21.4 (C-13) ppm; IR (ATR): ν_{max} 3398, 2949, 2868, 2711, 1701, 1596, 1493, 1401, 1305, 1270, 1181, 1039, 978, 808, 764, 610, 534, 476 cm^{-1}; HRMS (ESI) 290.1574 (M + H^+. $C_{17}H_{24}NOS$ requires 290.1573); mp. 168-171 °C

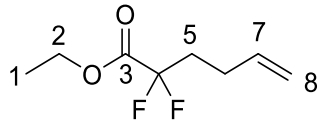
Synthesis of fluorinated amines

ethyl 2-oxo-5-hexenoate (187)



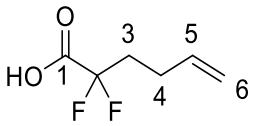
A dry flask was charged with magnesium turnings (1.34 g, 55 mmol) and a single crystal of iodine (~50 mg) under N_2, followed by addition of dry diethyl ether (50 ml) and the flask placed in a water bath to control the temperature of the reaction. 4-bromo-1-butene (5.05 ml, 50 mmol) was added dropwise with rapid stirring and an exotherm was observed. The reaction was stirred at room temperature for 6 hours to allow for complete formation of the Grignard reagent. In a separate dry flask, diethyl oxalate (5.49 ml, 50 mmol) in dry diethyl ether (75 ml) was cooled to -78 °C under N_2. The Grignard reagent was then transferred to the flask containing the diethyl oxalate solution via cannula addition and the reaction was allowed to warm to room temperature overnight with stirring. The reaction was quenched with saturated NH_4Cl (aq) solution (50 ml) and extracted with diethyl ether (2 x 50 ml). The combined organic fractions were washed with saturated NH_4Cl (aq) solution (50 ml) and H_2O (2 x 50 ml), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified using flash column chromatography (10% EtOAc/hexane) to give **187** as a pale-yellow oil (2.05 g, 13.1 mmol, 26% yield).^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.79 (ddt, *J* = 16.9, 10.2, 6.4 Hz, 1H, H-7), 5.05 (ddt, *J* = 16.9, 1.7, 1.3 Hz, 1H, H-8), 4.99 (ddt, *J* = 10.2, 1.7, 1.3 Hz, 1H, H-8'), 4.30 (q, *J* = 7.1 Hz, 2H, H-2), 2.93 (t, *J* = 7.3 Hz, 2H, H-5), 2.37 (tdt, *J* = 7.3, 6.4, 1.7 Hz, 2H, H-6), 1.34 (t, *J* = 7.1 Hz, 3H, H-1) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 193.9 (C-4), 161.1 (C-3), 136.2 (C-7), 116.0 (C-8), 62.5 (C-2), 38.5 (C-5), 27.0 (C-6), 14.1 (C-1) ppm; IR (ATR): ν_{max} 2984, 1793, 1725, 1642, 1445, 1401, 1370, 1277, 1246, 1064, 1025, 999, 915, 856, 731, 681, 637 cm^{-1}; HRMS (APCI) 157.086244 (M + H$^+$. $C_8H_{13}O_3$ requires 157.085921)

ethyl 2,2-difluoro-5-hexenoate (184)



A solution of keto-ester **187** (2.04 g, 13.1 mmol) in dry CH_2Cl_2 (45 ml) was cooled to 0 °C under N_2. To this solution was charged catalytic ethanol (0.15 ml, 2.62 mmol), followed by dropwise addition of Bis(2-methoxyethyl)aminosulfur trifluoride solution (50 wt% in toluene, 8.15 ml, 22.1 mmol), after which the reaction was allowed to warm to room temperature overnight. The reaction was quenched with saturated $NaHCO_3$ (aq) solution (50 ml) and extracted with CH_2Cl_2 (2 x 50 ml). The combined organic fractions were washed with 2M HCl (2 x 50 ml) and saturated brine solution (50ml), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified using flash column chromatography (5% EtOAc/hexane) to give **184** as a pale-yellow oil (1.34 g, 7.50 mmol, 57% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.81 (ddt, *J* = 17.1, 10.2, 6.5 Hz, 1H, H-7), 5.08 (dq, *J* = 17.1, 1.4 Hz, 1H, H-8), 5.03 (dq, *J* = 10.2, 1.4 Hz, 1H, H-8'), 4.33 (q, *J* = 7.1 Hz, 2H, H-2), 2.30 – 2.21 (m, 2H, H-6), 2.21 – 2.11 (m, 2H, H-5), 1.36 (t, *J* = 7.1 Hz, 3H, H-1) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 164.2 (t, $^2J_{CF}$ = 32.8 Hz, C-3), 135.9 (C-7), 116.0 (t, $^1J_{CF}$ = 250.4 Hz, C-4), 115.9 (C-8), 62.8 (C-2), 33.8 (t, $^2J_{CF}$ = 23.4 Hz, C-5), 25.7 (t, $^3J_{CF}$ = 4.8 Hz, C-6), 14.0 (C-1) ppm; ^{19}F NMR (471 MHz, Chloroform-*d*) δ -106.1 (t, J_{FH} = 16.2 Hz, 2F) ppm

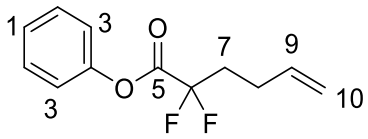
2,2-difluoro-5-hexenoic acid (188)



A solution of fluoro-ester **184** (1.32 g, 7.41 mmol) in THF (20 ml) was added to LiOH (0.933 g, 22.2 mmol) in H_2O (5 ml) at 0 °C and the reaction was allowed to warm to room temperature overnight. The reaction was diluted with H_2O (25 ml) and extracted with diethyl ether (25 ml). The aqueous fraction was then acidified to pH 1 with 2M HCl and extracted with diethyl ether (3 x 25 ml). The combined second extraction was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to give **188** as a colourless oil (0.985 g, 6.56 mmol, 89% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.06 (br s, 1H, COOH), 5.83 (ddt, *J* = 17.1, 10.2, 6.3 Hz, 1H, H-5), 5.11 (dq, *J* = 17.1, 1.5 Hz, 1H, H-6), 5.06 (dq, *J* = 10.2, 1.5 Hz, 1H, H-6'), 2.38 – 2.26 (m, 2H, H-4), 2.26 – 2.10 (m, 2H, H-3) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 168.2 (t, $^2J_{CF}$ = 33.7 Hz, C-1), 135.6 (C-5), 116.2 (C-6), 115.7 (t, $^1J_{CF}$ = 250.1 Hz, C-2), 33.6 (t, $^2J_{CF}$ = 23.0 Hz, C-3), 25.6 (t, $^3J_{CF}$ = 4.7 Hz, C-4) ppm; ^{19}F NMR (471 MHz, Chloroform-*d*) δ -106.7 (t, J_{FH} = 16.3 Hz, 2F) ppm; IR (ATR): ν_{max}

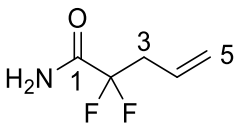
3084, 2982, 2940, 2533, 1752, 1644, 1450, 1420, 1365, 1269, 1191, 1156, 1082, 1045, 994, 955, 877, 771, 690, 655, 609, 554 cm^{-1}; HRMS (ESI) 149.0421 (M - H. $C_6H_7F_2O_2$ requires 149.0420)

phenyl 2,2-difluoro-5-hexenoate (189)



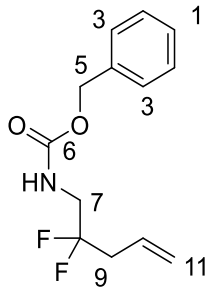
To a solution of fluoro-acid **188** (149 mg, 0.99 mmol) in toluene (10 ml) was added triethylamine (0.17 ml, 1.19 mmol) and diphenylphosporyl azide (0.24 ml, 1.09 mmol) under N_2. The reaction was heated to 90 °C for 2 hours, after which the reaction was cooled to room temperature, quenched with H_2O (10 ml) and extracted with ethyl acetate (2 x 20 ml). The combined organic fractions were washed with H_2O (2 x 20 ml) and saturated brine solution (2 x 20ml), dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified using flash column chromatography (2-50% EtOAc/hexane) to give **189** as a pale-yellow oil (77 mg, 0.34 mmol, 34% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.52 – 7.36 (m, 2H, H-2), 7.34 – 7.24 (m, 1H, H-1), 7.23 – 7.12 (m, 2H, H-3), 5.85 (ddt, *J* = 17.1, 10.4, 6.2 Hz, 1H, H-9), 5.13 (dd, *J* = 17.1, 1.5 Hz, 1H, H-10), 5.07 (dd, *J* = 10.4, 1.5 Hz, 1H, H-10'), 2.42 – 2.24 (m, 4H, H-7, H-8) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.7 (t, $^2J_{CF}$ = 33.7 Hz, C-5), 149.9 (C-4), 135.7 (C-9), 129.8 (C-2), 126.9 (C-1), 121.0 (C-3), 116.4 (C-10), 116.2 (t, $^1J_{CF}$ = 251.1 Hz, C-6), 34.0 (t, $^2J_{CF}$ = 23.2 Hz, C-7), 25.9 (t, $^3J_{CF}$ = 4.8 Hz, C-8) ppm; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -106.6 (t, J_{FH} = 16.0 Hz, 2F) ppm; IR (ATR): ν_{max} 3081, 2936, 2199, 2159, 1780, 1742, 1644, 1591, 1492, 1457, 1419, 1340, 1295, 1262, 1208, 1187, 1160, 1141, 1072, 1047, 1025, 1001, 954, 853, 810, 745, 687, 635, 608, 575, 555, 527, 499 cm^{-1}; HRMS (APCI) 227.087301 (M + H^+. $C_{12}H_{13}F_2O_2$ requires 227.087813)

2,2-Difluoropent-4-enamide (183)



To a dry flask was added copper powder (5.95 g, 93.6 mmol) followed by anhydrous DMSO (30 ml) and ethyl difluorobromoacetate (6 ml, 46.8 mmol) and the reaction heated to 55 °C for 1 hour. Allyl bromide (4.86 ml, 56.2 mmol) was added and the reaction stirred at 55 °C for 24 hours. The reaction was quenched with saturated brine solution (200 ml) and extracted with Et_2O (3 x 100 ml). The combined organics were washed with saturated brine solution (2 x 100 ml) and 2M HCl (100 ml), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was dissolved in THF (15 ml) and ammonium hydroxide solution (15 ml) was added dropwise and the reaction was stirred at room temperature for 15 hours. After stirring the reaction was quenched with H_2O (30 mL) and concentrated to remove excess ammonia and organic solvents, followed by extraction with CH_2Cl_2 (4 x 50 ml). The combined organic fractions were washed with H_2O (2 x 50 ml) and saturated brine solution (2 x 50 ml), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (30% EtOAc/hexane) to afford **183** as a orange solid (758 mg, 5.61 mmol, 12% yield over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.46 – 5.83 (m, 2H, NH_2), 5.75 (ddt, *J* = 17.9, 9.9, 6.8 Hz, 1H, H-4), 5.30 (d, *J* = 17.9 Hz, 1H, H-5), 5.27 (d, *J* = 9.9 Hz, 1H, H-5'), 2.85 (td, *J* = 16.9, 6.8 Hz, 2H, H-3) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.2 (t, $^2J_{CF}$ = 30.5 Hz, C-1), 127.1 (t, $^3J_{CF}$ = 5.4 Hz, C-4), 122.1 (C-5), 116.9 (t, $^1J_{CF}$ = 253.1 Hz, C-2), 38.4 (t, $^2J_{CF}$ = 23.9 Hz, C-3) ppm; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -105.8 (t, J_{FH} = 16.8 Hz, 2F) ppm; IR (ATR): ν_{max} 3386, 3198, 1684, 1622, 1648, 1448, 1432, 1318, 1300, 1257, 1180, 1157, 1098, 1032, 992, 932, 885, 811, 774, 741, 676, 625, 606, 536, 481 cm^{-1}; HRMS (APCI) 136.056206 (M + H$^+$. $C_5H_8F_2NO$ requires 136.056847), mp. 33-35 °C

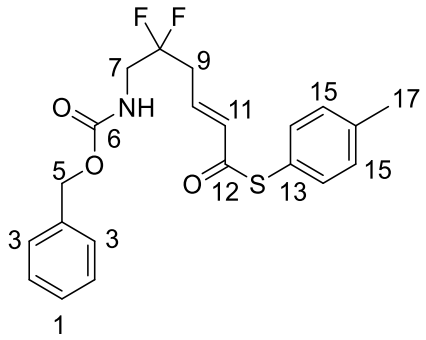
_N_-Cbz-2,2-difluoro-4-pentenamine (178)



To a suspension of $LiAlH_4$ (77 mg, 2.03 mmol) in dry diethyl ether (2.5 ml) at 0 °C under N_2 was added amide **183** (137 mg, 1.01 mmol) in dry diethyl ether (2.5 ml) over 5 mins and the

reaction stirred at 0 °C for 30 mins. The reaction was then warmed to room temperature and stirred for 1.5 hours. The reaction was cooled to 0 °C and quenched with H_2O (0.1 ml), followed by NaOH solution (15% w/w aq, 0.1 ml), followed by H_2O (0.3 ml) and the reaction warmed to rt. $MgSO_4$ was added and the suspension was filtered through Celite®, followed by washings with diethyl ether (10 ml). To the ether solution was added 4M HCl in dioxane (0.75 ml) dropwise and solution concentrated *in vacuo* to give the amine HCl salt as a colourless oil (114 mg) which was used without further purification. Amine HCl salt (93 mg) was dissolved in dioxane (10 ml) to which was added K_2CO_3 solution (50% w/w aq, 408 mg, 1.48 mmol) followed by benzyl chloroformate (0.10 ml, 0.708 mmol) and the reaction stirred at room temperature for 13 hours. The reaction was quenched with H_2O (10 ml) and portioned with CH_2Cl_2 (10 ml). The aqueous phase was extracted with CH_2Cl_2 (2 x 10 ml) and organic fractions combined. The combined organics were washed with saturated brine solution (10 ml), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (15% EtOAc/hexane) to afford **178** as a white solid (108 mg, 0.423 mmol, 42% yield over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 – 7.27 (m, 5H, Ar-H), 5.80 (ddt, *J* = 16.8, 10.0, 7.3 Hz, 1H, H-10), 5.23 (d, *J* = 16.8 Hz, 1H, H-11), 5.22 (d, *J* = 10.0 Hz, 1H, H-11'), 5.12 (s, 2H, H-5), 5.09 (s, 1H, NH), 3.57 (td, *J* = 13.9, 6.6 Hz, 2H, H-7), 2.63 (td, *J* = 16.3, 7.3 Hz, 2H, H-9) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 156.4 (C-6), 136.2 (C-4), 128.7 (Ar-CH), 128.5 (t, $^3J_{CF}$ = 5.9 Hz, C-10), 128.4 (Ar-CH), 128.3 (Ar-CH), 121.8 (t, $^1J_{CF}$ = 244.0 Hz, C-8)121.1 (C-11), 67.4 (C-5), 45.1 (t, $^2J_{CF}$ = 29.6 Hz, C-7), 39.1 (t, $^2J_{CF}$ = 24.7 Hz, C-9) ppm; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -103.72 (p, J_{FH} = 15.0 Hz, 2F) ppm; IR (ATR): ν_{max} 3332, 3035, 2952, 1710, 1645, 1532, 1455, 1431, 1388, 1341, 1248, 1164, 1120, 1005, 927, 880, 806, 776, 738, 698, 547, 481 cm^{-1}; HRMS (ESI) 278.0964 (M + Na$^+$. $C_{13}H_{15}F_2NNaO_2$ requires 278.0963), mp. 40-41 °C

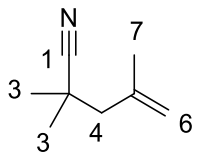
6-Cbz-amino-5,5-difluoro-hex-2-enethioic acid S-p-tolyl ester (194)



194 was synthesised using **general procedure C** with thioester **134** (106 mg, 0.90 mmol), Hoveyda-Grubbs Catalyst™ 2nd generation (18.8 mg, 0.030 mmol), copper iodide (57.1 mg, 0.30 mmol) and Cbz-amine **178** (76.5 mg, 0.30 mmol). **194** yielded as a pale brown oil (55.1 mg, 0.136 mmol, 45% yield) after column chromatography (30% EtOAc/hexane). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.40 – 7.32 (m, 5H, Ar-H), 7.30 (d, *J* = 8.2 Hz, 2H, H-14), 7.22 (d, *J* = 8.2 Hz, 2H, H-15), 6.88 (dt, *J* = 15.5, 7.5 Hz, 1H, H-10), 6.30 (d, *J* = 15.5 Hz, 1H, H-11), 5.16 (s, 1H, NH), 5.13 (s, 2H, H-5), 3.59 (td, *J* = 13.2, 6.6 Hz, 2H, H-7), 2.78 (td, *J* = 16.4, 7.5 Hz, 2H, H-9), 2.38 (s, 3H, H-17) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 188.0 (C-12), 156.4 (C-6), 140.0 (C-16), 136.0 (C-4), 134.7 (t, $^{3}J_{CF}$ = 5.2 Hz, C-10), 134.6 (C-14), 132.6 (C-11), 130.2 (C-15), 128.7 (Ar-CH), 128.5 (Ar-CH), 128.3 (Ar-CH), 123.7 (C-13), 120.02 (t, $^{1}J_{CF}$ = 242.6 Hz, C-8), 67.5 (C-5), 45.36 (t, $^{2}J_{CF}$ = 30.2 Hz, C-7), 37.35 (t, $^{2}J_{CF}$ = 25.0 Hz, C-9), 21.5 (C-17) ppm; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -102.6 (p, *J* = 14.9 Hz, 2F) ppm; IR (ATR): ν_{max} 3341, 3032, 2952, 1708, 1682, 1639, 1597, 1523, 1494, 1455, 1427, 1399, 1240, 1240, 1164, 1107, 1060, 1004, 973, 896, 835, 808, 774, 754, 737, 697, 646, 619, 575, 538, 489, 475 cm^{-1}; HRMS (ESI) 428.1092 (M + Na^{+}. $C_{21}H_{21}F_2NNaO_3S$ requires 428.1102).

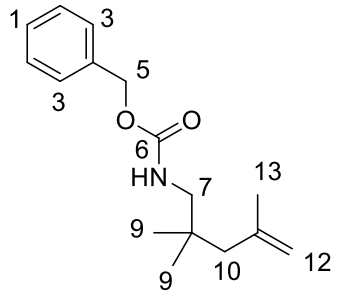
Michael acceptor methyl substitution

2,2,4-Trimethyl-pent-4-enenitrile (204)



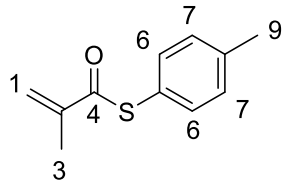
204 was synthesised using **general procedure A** diisopropylamine (4.29 ml, 30.6 mmol), n-BuLi (2.5 M in hexanes, 33.4 mmol), isobutyronitrile (2.5 ml, 27.9 mmol) and 3-bromo-2-methylpropene (3.09 ml, 30.6 mmol). **204** yielded as a colourless oil (1.73 g, 14.1 mmol, 50% yield) after column chromatography (1% EtOAc/hexane). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.95 - 5.00 (m, 1 H, H-6), 4.83 - 4.85 (m, 1 H, H-6), 2.26 (s, 2 H, H-4), 1.90 (s, 3 H, H-7), 1.37 (s, 6 H, H-3) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 140.6 (C-5), 125.4 (C-1), 116.1 (C-6), 48.5 (C-4), 31.3 (C-20), 27.0 (C-3), 23.6 (C-7) ppm; IR (ATR): ν_{max} 3078, 2978, 2937, 2234, 1711, 1645, 1469, 1449, 1390, 1378, 1369, 1292, 1260, 1197, 1134, 1028, 898, 826, 739, 668, 610, 503 cm^{-1}; HRMS (APCI) 124.112127 (M + H^{+}. $C_8H_{14}N$ requires 124.112076)

(2,2,4-Trimethyl-pent-4-enyl)-carbamic acid benzyl ester (201)



Nitrile **204** (426 mg, 3.46 mmol) was reduced using **general procedure B** with $LiAlH_4$ (197 mg, 5.19 mmol) to give the amine as a pale-yellow oil (320 mg, 2.52 mmol, 73% yield). Amine (163 mg, 1.28 mmol) was Cbz protected with K_2CO_3 solution (50% w/w aq, 425 mg, 1.54 mmol) and benzyl chloroformate (0.22 ml, 1.54 mmol). **201** yielded as a colourless oil (260 mg, 1.00 mmol, 78% yield) after column chromatography (8% EtOAc/hexane). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.30 - 7.41 (m, 5 H), 5.11 (s, 2 H), 4.87 - 4.91 (m, 1 H), 4.83 (br. s., 1 H), 4.64 - 4.71 (m, 1 H), 3.07 (d, *J* = 6.4 Hz, 2 H), 1.97 (s, 2 H), 1.79 (s, 3 H), 0.87 - 0.95 (m, 6 H) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 156.7 (C-6), 142.8 (C-11), 136.6 (C-4), 128.5 (Ar-CH), 128.2 (Ar-CH), 128.1 (Ar-CH), 114.8 (C-12), 66.7 (C-5), 51.4 (C-7), 47.5 (C-10), 35.3 (C-8), 25.3 (C-9), 25.2 (C-13) ppm; IR (ATR): ν_{max} 3343, 3070, 3033, 2962, 1702, 1640, 1521, 1468, 1455, 1407, 1389, 1374, 1331, 1240, 1180, 1132, 1049, 1002, 892, 824, 774, 751, 735, 696, 574, 495, 460 cm^{-1}; HRMS (ESI) 262.1799 (M + H^{+}. $C_{16}H_{24}NO_2$ requires 262.1802), 284.1619 (M + Na^{+}. $C_{16}H_{23}NNaO_2$ requires 284.1621)

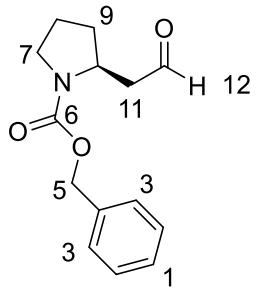
2-Methyl-thioacrylic acid S-p-tolyl ester (203)



203 was synthesised using the same procedure as **134** with a solution of NaOH (15% w/w aq. 5.2 ml), $NaBH_4$ (0.011 g, 0.292 mmol), *p*-thiocresol (1.21 g, 9.74 mmol), butylated hydroxytoluene (0.032 g, 0.146 mmol) and methacryloyl chloride (1.07 ml, 14.6 mmol). **203** yielded as a yellow oil (1.61 g, 8.35 mmol, 86% yield) after column chromatography (1% Et_2O/hexane).^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 (d, *J* = 7.6 Hz, 2 H, H-6), 7.25 (d, *J* = 7.6 Hz, 2 H, H-7), 6.22 (s, 1 H, H-1), 5.70 (s, 1 H, H-1), 2.40 (s, 3 H, H-9), 2.02 (s, 3 H, H-3) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 191.9 (C-4), 143.5 (C-2), 139.6 (C-8), 134.9 (C-6), 130.0 (C-7), 124.0 (C-5), 123.6 (C-1), 21.3 (C-9), 18.2 (C-3) ppm; IR (ATR): ν_{max} 2923, 1676, 1630, 1598, 1493, 1449, 1400, 1375, 1281, 1181, 1104, 1023, 1017, 983, 969, 933, 904, 887, 807, 655, 605, 526, 474 cm^{-1}; HRMS (ESI) 215.0503 ($M + Na^+$. $C_{11}H_{12}NNaOS$ requires 215.0501)

Total Syntheses of Irnidine and Bgugaine

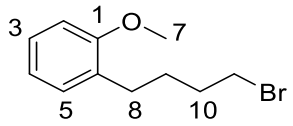
***N*-Cbz-(*S*)-2-(2-oxoethyl)pyrrolidine (234)**



A solution of pyrrolidine **164** (72.9 mg, 0.197 mmol) in CH_2Cl_2 (0.4 M) was cooled to -78 °C and a solution of DIBAL-H (1 M in hexanes, 0.6 ml) was added dropwise with and stirred for 1 h. The reaction was quenched with MeOH (1 ml) at -78 °C and allowed to warm to room temperature. The reaction was partitioned with an aqueous solution of Rochelle's salt (2 ml) and extracted with CH_2Cl_2 (3 x 10 ml). The combined organic fraction was dried with $MgSO_4$,

filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (15% EtOAc/hexane) to afford **234** as a colourless oil (15.9 mg, 0.0643 mmol, 33% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.78 (s, 0.6H, H-12, *rotamer 1*), 9.66 (s, 0.4H, H-12, *rotamer 2*), 7.43 – 7.26 (m, 5H, Ar-H), 5.16 – 5.04 (m, 2H, H-5), 4.33 – 4.28 (m, 1H, H-10), 3.54 – 3.35 (m, 2H, H-7), 2.98 (dd, *J* = 16.5, 3.7 Hz, 0.6H, H-11, *rotamer 1*), 2.81 (dd, *J* = 16.5, 3.7 Hz, 0.4H, H-11, *rotamer 2*), 2.49 (dd, *J* = 16.5, 7.6 Hz, 1H, H-11'), 2.19 – 2.06 (m, 1H, H-9), 1.91 – 1.80 (m, 2H, H-8), 1.70 – 1.62 (m, 1H, H-9') ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 200.9(200.7) (C-12), 155.0 (C-6), 136.9(136.6) (C-4), 128.6 (Ar-CH), 128.2(128.1) (Ar-CH), 128.0 (Ar-CH), 67.1(66.9) (C-5), 53.1(52.3) (C-10), 49.4(48.7) (C-11), 46.9(46.5) (C-7), 32.1(31.3) (C-9), 23.8(23.1) (C-8) ppm; IR (ATR): ν_{max} 2955, 1722, 1697, 1414, 1357, 1337, 1187, 1104, 729, 698 cm^{-1}; HRMS (ESI) 248.1278 (M + H^{+}. $C_{14}H_{18}NO_3$ requires 248.1281); 270.1100 (M + Na^{+}. $C_{14}H_{17}NNaO_3$ requires 270.1101); 286.0838 (M + K^{+}. $C_{14}H_{17}KNO_3$ requires 286.0840); $[\alpha]_D^{20}$ -31.3° (c 0.35, $CHCl_3$)

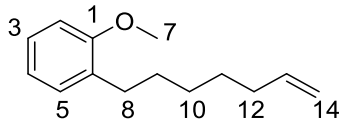
2-(4-bromobutyl)anisole (238)



A solution of 2-bromoanisole (2.0 ml, 16.0 mmol) in dry THF (30 ml) was cooled to -78°C under N_2 and s-BuLi (1.4 M in cyclohexane, 20.9 mmol) was added over 10 minutes. The solution was stirred for 2 hours then quenched with 1,4-dibromobutane (2.7 ml, 22.5 mmol) and allowed to warm to room temperature overnight. The reaction was quenched with water (30 ml) and extracted with Et_2O (3 x 20 ml). The organic fractions were combined, washed with water (2 x 30 ml) and saturated brine solution (30 ml), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (0-2% Et_2O/hexane) to give **238** as a colourless oil (1.29 g, 5.31 mmol, 33 % yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.17 (ddd, *J* = 8.0, 7.8, 1.8 Hz, 1H, H-3), 7.11 (dd, *J* = 7.3, 1.8 Hz, 1H, H-5), 6.88 (ddd, *J* = 7.8, 7.3, 1.2 Hz, 1H, H-4), 6.84 (dd, *J* = 7.8, 1.2 Hz, 1H, H-2), 3.81 (s, 3H, H-7), 3.42 (t, *J* = 6.9 Hz, 2H, H-11), 2.63 (t, *J* = 7.4 Hz, 2H, H-8), 1.98 – 1.82 (m, 2H, H-10), 1.77 – 1.67 (m, 2H, H-9) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.5 (C-1), 130.3 (C-6), 129.9 (C-5), 127.2 (C-3), 120.5 (C-4), 110.3 (C-2), 55.3 (C-7), 34.0 (C-11), 32.6 (C-10), 29.3 (C-8), 28.5 (C-9) ppm; IR (ATR): ν_{max} 2937, 2859, 2835, 1601, 1587, 1493, 1463, 1438, 1289, 1241, 1176, 1133, 1108,

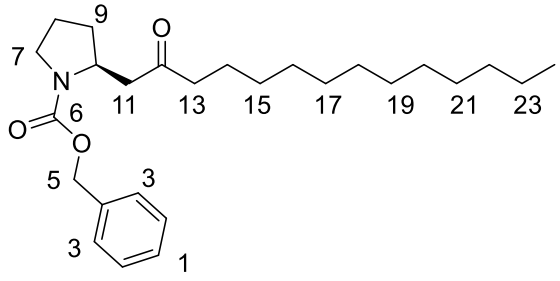
1051, 1032, 752, 644, 559 cm^{-1}; HRMS (APCI) 243.0368 (M + H^+. $C_{11}H_{16}{}^{79}BrO$ requires 243.0379), 245.0341 (M + H^+. $C_{11}H_{16}{}^{81}BrO$ requires 245.0359).

1-Hept-6-enyl-2-methoxy-benzene (239)



A solution of **238** (0.93 g, 3.8 mmol) in dry THF (5.7 ml) was cooled to 0 °C under N_2. Allylmagnesium bromide (1 M in Et_2O, 5.7 mmol) was then added dropwise over 5 minutes, and the reaction allowed to warm to room temperature overnight with stirring. The reaction was quenched with NH_4Cl (aq) (10 ml) and extracted with Et_2O (3 x 20 ml). The combined organic fractions were washed with NH_4Cl (aq) (20 ml) and saturated brine solution (20 ml), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (0-1% Et_2O/hexane) to give **239** as a colourless oil (0.37 g, 1.8 mmol, 47 % yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.16 (ddd, *J* = 8.0, 7.8, 1.8 Hz, 1H, H-3), 7.12 (dd, *J* = 7.3, 1.8 Hz, 1H, H-5), 6.87 (dd, *J* = 7.8, 7.3 Hz, 1H, H-4), 6.83 (d, *J* = 8.0 Hz, 1H, H-2), 5.81 (ddt, *J* = 17.0, 10.1, 6.6 Hz, 1H, H-13), 4.98 (dd, *J* = 17.0, 2.0 Hz, 1H, H-14), 4.92 (dd, *J* = 10.1, 2.0 Hz, 1H, H-14'), 3.81 (s, 3H, H-7), 2.59 (t, *J* = 8.0 Hz, 2H, H-8), 2.04 (td, *J* = 7.2, 6.6 Hz, 2H, H-12), 1.64 – 1.53 (m, 2H, H-9), 1.48 – 1.29 (m, 4H, H-10, H-11) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.5 (C-1), 139.3 (C-13), 131.3 (C-6), 129.8 (C-5), 126.9 (C-3), 120.4 (C-4), 114.2 (C-14), 110.3 (C-2), 55.3 (C-7), 33.9 (C-12), 30.2 (C-8), 29.8 (C-9), 29.2 (C-11), 28.9 (C-10) ppm; IR (ATR): ν_{max} 3074, 2998, 2926, 2855, 2835, 1640, 1601, 1587, 1493, 1463, 1433, 1325, 1289, 1240, 1177, 1160, 1128, 1050, 1031, 993, 908, 816, 749, 730, 636, 566, 539, 463 cm^{-1}; HRMS (APCI) 205.157932 (M + H^+. $C_{14}H_{21}O$ requires 205.158692)

***N*-Cbz-(*S*)-2-(2-Oxo-tetradecyl)-pyrrolidine (235)**

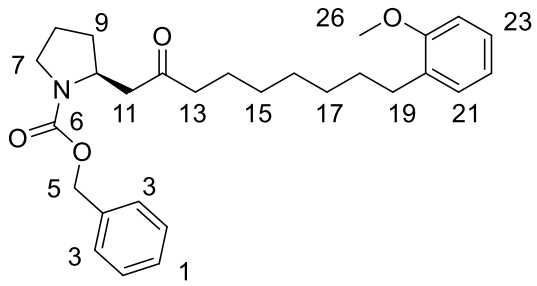


1-Dodecene (0.22 ml, 1.0 mmol) was cooled to 0 °C under N_2 and a solution of 9-BBN (0.5 M in THF, 1.00 mmol) was added dropwise. The solution stirred for 1 hour at 0 °C and 2 hours at room temperature to afford the dodecyl-borane solution (0.5 M, 1.00 mmol).

A degassed solution of pyrrolidine **164** (38.2 mg, 0.103 mmol, 94:6 er) in dry THF (0.1 M) was added to CuTC (23.7 mg, 0.124 mmol), $Pd(PPh_3)_4$ (6.0 mg, 0.00517 mmol), and Cs_2CO_3 (36.5 mg, 0.103 mmol) under N_2 followed by dodecyl-borane solution (0.5 M, 0.248 ml, 0.124 mmol). The solution was then degassed and backfilled with N_2 3 times and heated to 45 °C for 20 hours. The reaction was cooled to room temperature, diluted with Et_2O (20 ml) and partitioned with 2M HCl (10 ml). The organic fraction was washed with 2M NH_3 (3 x 10 ml) and saturated brine solution (10 ml), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (10% EtOAc/hexane) to give **235** as a colourless oil (32.9 mg, 0.0792 mmol, 77 % yield)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 – 7.26 (m, 5H, Ar-H), 5.19 – 5.04 (m, 2H, H-5), 4.23 – 4.15 (m, 1H, H-10), 3.50 – 3.34 (m, 2H, H-7), 3.14 (dd, *J* = 16.2, 3.3 Hz, 0.6H, *rotamer 1*, H-11), 2.86 (dd, *J* = 16.2, 3.3 Hz, 0.4H, *rotamer 2*, H-11), 2.49 – 2.31 (m, 2H, H-11', H-13), 2.30 – 2.20 (m, 1H, H-13'), 2.15 – 2.01 (m, 1H, H-9), 1.92 – 1.74 (m, 2H, H-8), 1.72 – 1.56 (m, 1H, H-9'), 1.55 – 1.36 (m, 3H, CH_2), 1.34 – 1.10 (m, 17H, CH_2), 0.86 (t, *J* = 6.8 Hz, 3H, H-24) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 209.9(209.7) (C-12), 154.7 (C-6), 137.0 (C-4), 128.6 (Ar-CH), 128.0 (Ar-CH), 127.9 (Ar-CH), 66.9(66.7) (C-5), 54.2(53.4) (C-10), 47.6(46.8) (C-11), 46.6(46.5) (C-7), 43.5(43.3) (C-13), 32.1(32.0) (C-9), 31.7(31.0) (C-22), 29.7 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 26.3 (CH_2), 23.8(22.9) (C-14), 23.7(22.8) (C-8), 22.1(C-23), 14.2 (C-24) ppm; IR (ATR): ν_{max} 3406, 2923, 2853, 1701, 1498, 1452, 1410, 1357, 1338, 1300, 1211, 1183, 1103, 1029, 977, 916, 875, 769, 734, 697, 600, 552, 460 cm^{-1}; HRMS (ESI) 416.3156 (M + H$^+$. $C_{26}H_{42}NO_3$ requires 416.3159); 438.2976 (M + Na$^+$. $C_{26}H_{41}NNaO_3$ requires 438.2979); 454.2705 (M + K$^+$. $C_{26}H_{41}NKO_3$ requires 454.2718); $[\alpha]_D^{20}$ -20.2° (c 1.00, $CHCl_3$)

***N*-Cbz-(*S*)-2-[9-(2-Methoxy-phenyl)-2-oxo-nonyl]-pyrrolidine (236)**



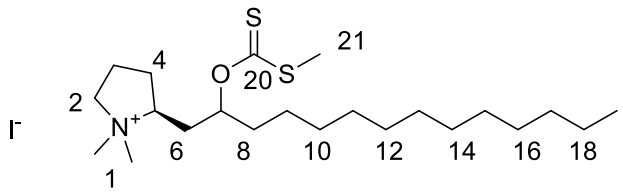
Olefin **239** (43.1 mg, 0.211 mmol) was cooled to 0 °C under N_2 and a solution of 9-BBN (0.5 M in THF, 0.211 mmol) was added dropwise. The solution stirred for 1 hour at 0 °C and 2 hours at room temperature to afford the **239-borane** solution (0.5 M, 0.211 mmol).

A degassed solution of pyrrolidine **164** (64.8 mg, 0.176 mmol, 94:6 er) in dry THF (0.1 M) was added to CuTC (40.2 mg, 0.211 mmol), $Pd(PPh_3)_4$ (10.2 mg, 0.0088 mmol), and Cs_2CO_3 (62.1 mg, 0.176 mmol) under N_2 followed by **239-borane** solution (0.5 M, 0.422 ml, 0.211 mmol). The solution was then degassed and backfilled with N_2 3 times and heated to 45 °C for 20 hours. The reaction was cooled to room temperature, diluted with Et_2O (20 ml) and partitioned with 2M HCl (10 ml). The organic fraction was washed with 2M NH_3 (3 x 10 ml) and saturated brine solution (10 ml), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (15% EtOAc/hexane) to give **236** as a colourless oil (58.1 mg, 0.129 mmol, 73 % yield)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 – 7.26 (m, 5H, Ar-H), 7.16 (dd, *J* = 8.2, 7.6 Hz, 1H, H-23), 7.12 (d, *J* = 7.4 Hz, 1H, H-21), 6.87 (dd, *J* = 7.6, 7.4 Hz, 1H, H-22), 6.83 (d, *J* = 8.2 Hz, 1H, H-24), 5.22 – 5.05 (m, 2H, H-5), 4.25 – 4.16 (m, 1H, H-10), 3.80 (s, 3H, H-26), 3.44 – 3.36 (m, 2H, H-7),3.15 (dd, *J* = 16.7, 3.4 Hz, 0.6H, *rotamer 1*, H-11), 2.86 (dd, *J* = 16.7, 3.4 Hz, 0.4H *rotamer 2*, H-11), 2.59 (t, *J* = 7.6 Hz, 2H, H-19), 2.44 – 2.34 (m, 2H, H-11', H-13), 2.29 – 2.21 (m, 1H, H-13'), 2.16 – 2.02 (m, 1H, H-9), 1.87 – 1.79 (m, 2H, H-8), 1.71 – 1.62 (m, 1H, H-9'), 1.58 – 1.42 (m, 3H, H-18, H-14), 1.40 – 1.13 (m, 7H, H-14', H-15, H-16, H-17) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 209.8(209.6) (C-12), 157.5 (C-25), 154.7 (C-6), 137.0(136.8) (C-4), 131.3 (C-20), 129.8 (C-21), 128.6 (Ar-CH), 128.1 (Ar-CH), 128.0(127.9) (Ar-CH), 126.9 (C-23), 120.4 (C-22), 110.3 (C-24), 66.9(66.7) (C-5), 55.3 (C-26), 54.2(53.4) (C-10), 47.6(46.8) (C-11), 46.6(46.5) (C-7), 43.4(43.3) (C-13), 31.8(31.0) (C-9), 30.2 (C-19), 29.9 (C-18), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 23.8 (C-14), 23.7(22.9) (C-8) ppm; IR (ATR): ν_{max} 2928, 2855, 1698, 1600, 1493, 1455, 1411, 1356, 1336, 1241, 1178, 1103, 1049, 1029, 752, 698 cm^{-1}; HRMS (ESI) 452.2795 (M + H$^+$.

$C_{28}H_{38}NO_4$ requires 452.2795); 474.2616 (M + Na^+. $C_{28}H_{37}NNaO_4$ requires 474.2615); 490.2356 (M + K^+. $C_{28}H_{37}NKO_4$ requires 490.2354); $[\alpha]_D^{20}$ -22.6° (c 1.00, $CHCl_3$)

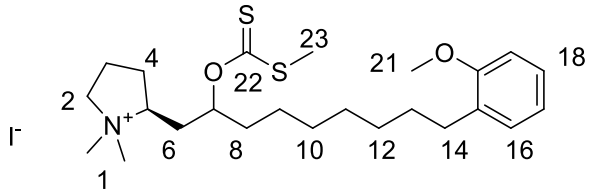
1,1-Dimethyl-(*S*)-2-(2-methylsulfanylthiocarboxyoxy-tetradecyl)-pyrrolidinium iodide (mixture of diastereomers) (240)



A solution of pyrrolidine ketone **235** (39.0 mg, 0.0938 mmol) in dry THF (0.5 mL) was added dropwise to a stirred solution of $LiAlH_4$ (17.8 mg, 0.469 mmol) in dry THF (0.5 mL) at 0 °C under N_2. The reaction was stirred at 0 °C for 1 hour then allowed to warm to room temperature and stirred overnight. The reaction was cooled to 0 °C and diluted with diethyl ether (2 ml) quenched with H_2O (0.1 ml), followed by NaOH solution (15% w/w aq, 0.1 ml), followed by H_2O (0.3 ml) and the reaction warmed to rt. $MgSO_4$ was added and the suspension was filtered through Celite®, followed by washings with diethyl ether (10 ml). The filtrate was concentrated *in vacuo* and the crude residue was further purified by silica plug filtration (1:10:90 NH_3/MeOH/DCM) to give crude the hydroxy pyrrolidine (22.7 mg, 0.0763 mmol). The hydroxy pyrrolidine was dissolved in dry THF (1 mL) and added to NaH (60% in mineral oil, 6.1 mg, 0.153 mmol) and imidazole (0.1 mg, 0.00153 mmol) in a dry flask under N_2 at room temperature and the reaction was stirred for 30 mins. Carbon disulfide (0.023 mL, 0.381 mmol) was added dropwise and the reaction stirred for 30 mins, followed by dropwise addition of methyl iodide (0.024 ml, 0.381 mmol). The reaction was stirred for 16 hours, then quenched with H_2O (1 mL) and partitioned with diethyl ether (20 mL). The organic fraction was washed with H_2O (20 mL) and saturated brine solution (20 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified using sodium iodide coated silica gel, eluting with 5% MeOH/CH_2Cl_2.[162] The isolated salt was then washed on a charcoal column with water, followed by MeOH to remove excess sodium iodide, then isolated by washing with 1:1 MeOH/CH_2Cl_2 to give the quaternary ammonium **240** as a pale-orange oil (27.8 mg, 0.0525 mmol, 56% yield over two steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.83 – 5.70 (m, 1H, H-7), 4.33 (dt, *J* = 11.4, 5.4 Hz, 0.7H, H-2, *diastereomer 1*), 4.24 (ddd,

J = 11.1, 8.1, 2.5 Hz, 0.3H, H-2, *diastereomer 2*), 3.90 – 3.54 (m, 2H, H-2', H-5), 3.53 (s, 0.9H, H-1, *diastereomer 1*), 3.47 (s, 2.1H, H-1, *diastereomer 2*), 3.20 (s, 2.1H, H-1', *diastereomer 1*), 3.11 (s, 0.9H, H-1', *diastereomer 2*), 2.56 (s, 2.1H, H-21, *diastereomer 1*), 2.55 (s, 0.9H, H-21, *diastereomer 2*), 2.47 – 2.36 (m, 1H, H-6), 2.28 – 2.10 (m, 2H, H-3), 2.10 – 1.64 (m, 4H, H-6, H-8, CH_2), 1.37 – 1.09 (m, 19H, CH_2), 0.84 (t, *J* = 6.7 Hz, 3H, H-19) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 216.7(215.9) (C-20), 81.1(80.2) (C-7), 73.9(73.4) (C-5), 67.1(66.6) (C-2), 51.7(51.5) (C-1), 45.7(45.3) (C-1'), 34.5(34.2) (C-8), 33.0(32.9) (C-6), 32.0 (C-17), 29.7 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.2(28.0) (C-4), 25.2(25.1) (C-9), 22.8 (C-18), 19.8(19.6) (C-3), 19.5(19.3) (C-21), 14.2 (C-19) ppm; IR (ATR): ν_{max} 3454, 2923, 2853, 1467, 1221, 1206, 1128, 1051, 965, 722 cm^{-1}; HRMS (ESI) 402.2858 (M^+. $C_{22}H_{44}NOS_2$ requires 402.2859);

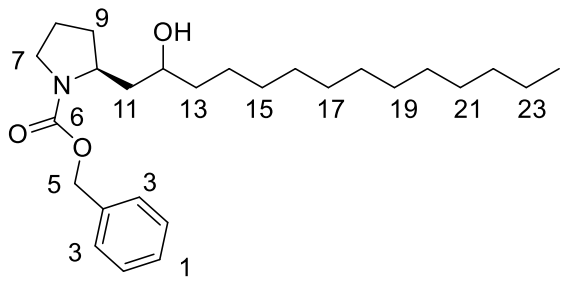
(*S*)-2-[9-(2-Methoxy-phenyl)-2-methylsulfanylthiocarboxyoxy-nonyl]-1,1-dimethyl-pyrrolidinium iodide (mixture of diastereomers) (241)



A solution of pyrrolidine ketone **236** (50.7 mg, 0.112 mmol) in dry THF (0.5 mL) was added dropwise to a stirred solution of $LiAlH_4$ (21.3 mg, 0.561 mmol) in dry THF (0.5 mL) at 0 °C under N_2. The reaction was stirred at 0 °C for 1 hour then allowed to warm to room temperature and stirred overnight. The reaction was cooled to 0 °C and diluted with diethyl ether (2 ml) quenched with H_2O (0.1 ml), followed by NaOH solution (15% w/w aq, 0.1 ml), followed by H_2O (0.3 ml) and the reaction warmed to rt. $MgSO_4$ was added and the suspension was filtered through Celite®, followed by washings with diethyl ether (10 ml). The filtrate was concentrated *in vacuo* and the crude residue was further purified by silica plug filtration (1:10:90 NH_3/MeOH/DCM) to give crude the hydroxy pyrrolidine (33.6 mg, 0.101 mmol). The hydroxy pyrroldine was dissolved in dry THF (1 mL) and added to NaH (60% in mineral oil, 8.1 mg, 0.201 mmol) and imidazole (0.2 mg, 0.00201 mmol) in a dry flask under N_2 at room temperature and the reaction was stirred for 30 mins. Carbon disulfide (0.03 mL, 0.504 mmol) was added dropwise and the reaction stirred for 30 mins, followed by dropwise addition of

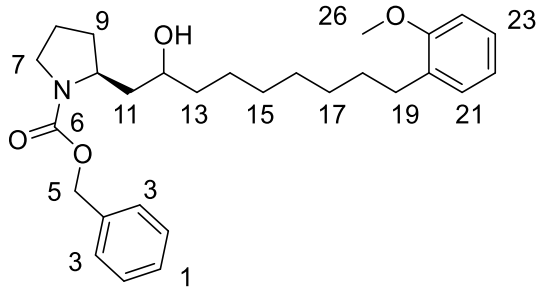
methyl iodide (0.03 ml, 0.504 mmol). The reaction was stirred for 16 hours, then quenched with H_2O (1 mL) and partitioned with diethyl ether (20 mL). The organic fraction was washed with H_2O (20 mL) and saturated brine solution (20 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified using sodium iodide coated silica gel, eluting with 5% MeOH/CH_2Cl_2.[162] The isolated salt was then washed on a charcoal column with water, followed by MeOH to remove excess sodium iodide, then isolated by washing with 1:1 MeOH/CH_2Cl_2 to give the quaternary ammonium **241** as a yellow oil (22.6 mg, 0.0400 mmol, 36% yield over two steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.13 (ddd, *J* = 8.2, 7.6, 1.8 Hz, 1H, H-18), 7.09 (dd, *J* = 7.3, 1.8 Hz, 1H, H-16), 6.84 (dd, *J* = 7.6, 7.3 Hz, 1H, H-17), 6.81 (d, *J* = 8.2 Hz, 1H, H-19)5.81 – 5.73 (m, 1H, H-7), 4.36 – 4.27 (m, 0.7H, H-2, *diastereomer 1*), 4.27 – 4.18 (m, 0.3H, H-2, *diastereomer 2*),3.89 – 3.80 (m, 0.3H, H-5, *diastereomer 1*), 3.78 (s, 3H, H-21), 3.76 – 3.64 (m, 1H, H-2), 3.62 – 3.53 (m, 0.7H, H-5 *diastereomer 2*), 3.51 (s, 0.9H, H-1, *diastereomer 1*), 3.46 (s, 2.1H, H-1, *diastereomer 2*),3.19 (s, 2.1H, H-1', *diastereomer 1*), 3.10 (s, 0.9H, H-1', *diastereomer 2*), 2.56 (s, 3H, H-23), 2.55 (t, *J* = 7.8 Hz, 2H, H-14),2.46 – 2.36 (m, 1H, H-6),2.28 – 2.10 (m, 2H, H-3), 2.07 – 2.00 (m, 1H, H-6'), 2.00 – 1.79 (m, 3H, H-8, CH_2), 1.79 – 1.67 (m, 1H, H-8'), 1.56 – 1.48 (m, 2H, H-13), 1.42 – 1.24 (m, 8H, CH_2) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 216.7(216.0) (C-22), 157.5 (C-20), 131.3 (C-15), 129.8 (C-16), 126.9 (C-18), 120.4 (C-17), 110.3 (C-19), 81.1(80.2) (C-7), 73.4 (C-5), 67.1 (C-2), 55.4 (C-21), 51.7 (C-1), 45.7 (C-1'), 34.5(34.2) (C-8), 33.0(32.8) (C-6), 30.2 (C-14), 29.8 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.2 (C-4), 25.2(25.1) (C-9), 19.8 (C-3), 19.6 (C-23) ppm; IR (ATR): ν_{max} 3452, 2926, 2854, 1706, 1599, 1492, 1464, 1289, 1241, 1223, 1125, 1052, 965, 754 cm^{-1}; HRMS (ESI) 438.2496 (M^+. $C_{24}H_{40}NO_2S_2$ requires 438.2495)

_N_-Cbz-(_S_)-2-(2-Hydroxy-tetradecyl)-pyrrolidine (mixture of diastereomers) (242)



A solution of pyrrolidine ketone **235** (47.8 mg, 0.115 mmol) in dry MeOH (5 mL) was cooled to 0 °C and $NaBH_4$ (8.7 mg, 0.230 mmol) was added portion wise. The reaction was stirred for 1 hour, then quenched with 2M HCl (5 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were washed with saturated aqueous $NaHCO_3$ solution (2 x 20 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo* without further purification to give **242** as a colourless oil (47.3 mg, 0.113 mmol, 98% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.26 (m, 5H, Ar-H), 5.19 – 5.05 (m, 2H, H-5), 4.71–4.14 (m, 0.4H, OH), 4.14–3.14 (m, 4H, H-7, H-10, H-12), 2.07 – 1.55 (m, 5H, CH_2), 1.57 –1.02 (m, 23H, CH_2), 0.91 – 0.77 (m, 3H, H-24) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.0(155.6) (C-6), 137.0(136.8) (C-4), 128.6(128.6) (Ar-CH), 128.1(128.0) (Ar-CH), 128.0(127.9) (Ar-CH), 70.8(70.3)(67.7) (C-12), 67.2(66.9) (C-5), 56.2(54.7) (C-10), 46.4(46.3) (C-7), 43.9(43.5) (CH_2), 38.2(37.1) (CH_2), 32.1(32.0) (CH_2), 31.3 (CH_2), 29.9(29.8) (CH_2), 29.7(CH_2), 29.7(CH_2), 29.5(CH_2), 27.5(26.9) (CH_2), 26.3(26.2) (CH_2), 25.8 (CH_2), 23.9 (CH_2), 22.8 (CH_2), 22.1 (CH_2), 14.2 (C-24) ppm; IR (ATR): ν_{max} 3418, 2922, 2852, 1681, 1498, 1453, 1411, 1357, 1337, 1300, 1260, 1211, 1187, 1164, 1101, 1029, 979, 912, 870, 803, 768, 732, 696, 675, 602 cm^{-1}; HRMS (ESI) 418.3319 (M + H$^+$. $C_{26}H_{44}NO_3$ requires 418.3316); 440.3135 (M + Na$^+$. $C_{26}H_{43}NNaO_3$ requires 440.3135).

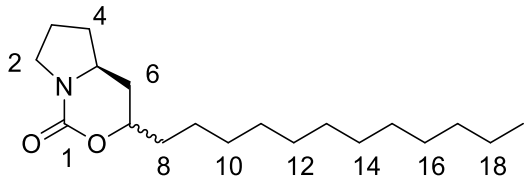
_N_-Cbz-(_S_)-2-[2-Hydroxy-9-(2-methoxy-phenyl)-nonyl]-pyrrolidine (mixture of diastereomers) (243)



A solution of pyrrolidine ketone **236** (90.0 mg, 0.199 mmol) in dry MeOH (5 mL) was cooled to 0 °C and $NaBH_4$ (15.1 mg, 0.399 mmol) was added portion wise. The reaction was stirred for 1 hour, then quenched with 2M HCl (5 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were washed with saturated aqueous $NaHCO_3$ solution (2 x 20

mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo* without further purification to give **243** as a colourless oil (90.3 mg, 0.199 mmol, 100% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.25 (m, 5H, Ar-H), 7.16 (ddd, *J* = 7.8, 7.8, 1.8 Hz, 1H, H-23), 7.12 (dd, *J* = 7.5, 1.8 Hz, 1H, H-21), 6.88 (ddd, *J* = 7.8, 7.5, 1.1 Hz, 1H, H-22), 6.84 (dd, *J* = 7.8, 1.1 Hz, 1H, H-24), 5.23 – 5.01 (m, 2H, H-5), 4.69 (s, 0.3H, O-H), 4.32 – 3.98 (m, 1H, H-10), 3.81 (s, 3H, H-26), 3.69 – 3.47 (m, 1H, H-12), 3.47 – 3.29 (m, 2H, H-7), 2.60 (t, *J* = 7.5 Hz, 2H, H-19), 2.10 – 1.24 (m, 18H, CH_2) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.5(157.0) (C-25), 155.6(155.0) (C-6), 137.0(136.8) (C-4), 131.4 (C-20), 129.8 (C-21), 128.6(128.6) (Ar-CH), 128.1(128.1) (Ar-CH), 128.0(127.9) (Ar-CH), 126.9 (C-23), 120.4 (C-22), 110.3 (C-24), 70.8(70.3) (C-12 *diastereomer 1*), 69.8(67.7) (C-12 *diastereomer 2*),67.2(66.9) (C-5), 56.2(54.7) (C-10), 55.3 (C-26), 46.5(46.3) (C-7), 43.9(43.5) (CH_2), 38.2(37.1) (CH_2), 32.1(31.3) (CH_2), 30.2(30.0) (CH_2), 30.0(29.9) (CH_2), 29.8(29.8) (CH_2), 29.7(29.6) (CH_2), 26.2(25.8) (CH_2), 23.9(23.7) (CH_2),22.4(22.1) (CH_2) ppm; IR (ATR): ν_{max} 3424, 2924, 2853 , 1678, 1600, 1587, 1493, 1454, 1411, 1356, 1336, 1290, 1240, 1212, 1187, 1162, 1101, 1049, 1029, 978, 913, 871, 808, 768, 751, 697, 675, 603, 542, 464 cm^{-1}; HRMS (ESI) 454.2954 (M + H^+. $C_{28}H_{40}NO_4$ requires 454.2952); 476.2773 (M + Na^+. $C_{28}H_{39}NNaO_4$ requires 476.2771).

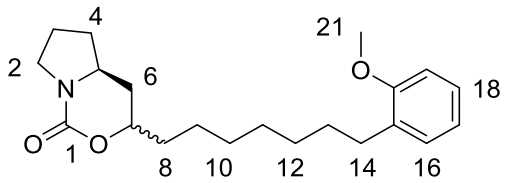
3-Dodecyl-hexahydro-pyrrolo[1,2-c][1,3]oxazin-1-one (mixture of diastereomers) (244)



A solution of hydroxy pyrrolidine **242** (47.3 mg, 0.113 mmol) in dry THF (2 mL) was added to NaH (60% in mineral oil, 9.1 mg, 0.227 mmol) and imidazole (0.2 mg, 0.00227 mmol) in a dry flask under N_2 at room temperature and the reaction was stirred for 30 mins. Carbon disulfide (0.04 mL, 0.566 mmol) was added dropwise and the reaction stirred for 30 mins, followed by dropwise addition of methyl iodide (0.04 ml, 0.566 mmol). The reaction was stirred for 16 hours, then quenched with H_2O (2 mL) and partitioned with CH_2Cl_2 (20 mL). The organic fraction was washed with 1M HCl (20 mL), saturated aqueous $NaHCO_3$ solution (20 mL), and

H_2O (20 mL) dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified with flash column chromatography (25-75% EtOAC/hexane) to give **244** as a white solid (23.4 mg, 0.0756 mmol, 67% yield, 5:1 dr). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.44 – 4.35 (m, 0.1H, H-7 *diastereomer 1*), 4.24 – 4.13 (m, 0.9H, H-7 *diastereomer 2*), 3.62 – 3.40 (m, 3H, H-2, H-5), 2.19 – 1.90 (m, 3H, CH_2), 1.84 – 1.61 (m, 2H, CH_2), 1.61 – 1.13 (m, 23H, CH_2), 0.86 (t, *J* = 6.7 Hz, 3H, H-19) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 153.5 (C-1), 77.5 (C-7), 56.6 (C-5), 46.5 (C-2), 35.3 (CH_2), 33.8 (CH_2), 33.3 (CH_2), 32.0 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 24.9 (CH_2), 23.1 (CH_2), 22.8 (CH_2), 14.2 (C-19) ppm; IR (ATR): ν_{max} 2954, 2917, 2849, 1688, 1519, 1463, 1437, 1378, 1324, 1306, 1243, 1200, 1155, 1127, 1050, 1015, 971, 905, 887, 802, , 754, 729, 670, 655, 631, 588, 523, 483, 458 cm^{-1}; HRMS (ESI) 310.2740 (M + H$^+$. $C_{19}H_{36}NO_2$ requires 310.2741); 332.2555 (M + Na$^+$. $C_{19}H_{35}NNaO_2$ requires 332.2560); mp. 63.1-66.4 °C

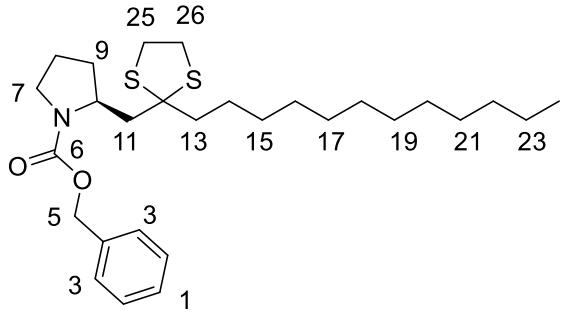
3-[7-(2-Methoxy-phenyl)-heptyl]-hexahydro-pyrrolo[1,2-c][1,3]oxazin-1-one (mixture of diastereomers) (245)



A solution of hydroxy pyrrolidine **243** (90.3 mg, 0.199 mmol) in dry THF (2 mL) was added to NaH (60% in mineral oil, 15.9 mg, 0.398 mmol) and imidazole (0.3 mg, 0.00398 mmol) in a dry flask under N_2 at room temperature and the reaction was stirred for 30 mins. Carbon disulfide (0.06 mL, 0.995 mmol) was added dropwise and the reaction stirred for 30 mins, followed by dropwise addition of methyl iodide (0.06 ml, 0.995 mmol). The reaction was stirred for 16 hours, then quenched with H_2O (2 mL) and partitioned with CH_2Cl_2 (20 mL). The organic fraction was washed with 1M HCl (20 mL), saturated aqueous $NaHCO_3$ solution (20 mL), and H_2O (20 mL) dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified with flash column chromatography (25-75% EtOAC/hexane) to give **245** as a pale yellow oil (43.0 mg, 0.124 mmol, 63% yield, 7:1 dr). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.14 (ddd, *J* = 7.8, 7.4, 1.8 Hz, 1H, H-16), 7.10 (dd, *J* = 7.4, 1.8 Hz, 1H, H-18), 6.86 (dd, *J* = 7.4, 7.4 Hz, 1H, H-17), 6.82 (d, *J* = 7.8 Hz, 1H, H-19), 4.50 – 4.30 (m, 0.1H, H-7 *diastereomer 1*), 4.27 –

4.11 (m, 0.9H, H-7 *diastereomer 2*), 3.80 (s, 3H, H-21), 3.66 – 3.35 (m, 3H, H-2, H-5), 2.58 (t, *J* = 7.8 Hz, 2H, H-14), 2.17 – 2.05 (m, 2H, CH_2), 2.03 – 1.91 (m, 1H, CH_2), 1.86 –1.43 (m, 7H, CH_2), 1.43 – 1.17 (m, 8H, CH_2) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.5 (C-20), 153.5 (C-1), 131.3 (C-15), 129.8 (C-16), 126.9 (C-18), 120.4 (C17), 110.3(C19), 77.5 (C-7), 56.6(55.3) (C-5), 55.4 (C-21), 46.5 (C-2), 35.3 (CH_2), 33.8 (CH_2), 33.3 (C-4), 30.2 (C-14), 29.9 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 24.9 (CH_2), 23.1 (C-3) ppm; IR (ATR): ν_{max} 2925, 2854, 1689, 1600, 1587, 1493, 1462, 1423, 1370, 1342, 1312, 1289, 1240, 1201, 1176, 1117, 1049, 1029, 924, 887, 753, 653, 568, 477 cm^{-1}; HRMS (ESI) 346.2375 (M + H$^+$. $C_{21}H_{32}NO_3$ requires 346.2377); 368.2194 (M + Na$^+$. $C_{21}H_{31}NNaO_3$ requires 368.2196).

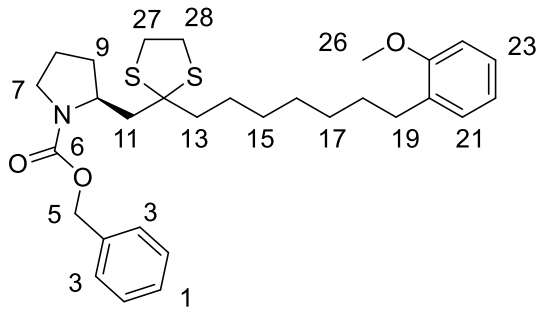
_N_-Cbz-(_S_)-2-(2-Dodecyl-[1,3]dithiolan-2-ylmethyl)-pyrrolidine (250)



Pyrrolidine ketone **235** (42.4 mg, 0.102 mmol) and 1,2-ethanedithiol (0.17 ml, 2.04 mmol) was dissolved in dry CH_2Cl_2 (0.7 mL, 0.16M) under N_2. $BF_3.Et_2O$ (0.15 ml, 1.22 mmol) was added dropwise and the reaction stirred for 4 hours. The reaction was quenched with acetone (0.6 ml), diluted with saturated aqueous $NaHCO_3$ solution (10 mL), and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic fractions were dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (10% EtOAc/hexane) to give **250** as a colourless oil (14.9 mg, 0.0303 mmol, 30% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.23 (m, 5H, Ar-H), 5.18 – 5.05 (m, 2H, H-5), 4.20 – 4.01 (m, 1H, H-10), 3.43 – 3.30 (m, 2H, H-7), 3.32 – 3.00 (m, 4H, H-25, H-26), 2.52 (d, *J* = 14.2 Hz, 0.5H, H-11), 2.31 (d, *J* = 14.2 Hz, 0.5H, H-11), 2.11 – 2.07 (m, 1H, H-9), 2.01 – 1.76 (m, 6H, CH_2), 1.55 – 1.00 (m, 20H, CH_2), 0.86 (t, *J* = 6.7 Hz, 3H, H-24) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.8 (C-6), 134.9 (C-4), 128.5 (Ar-CH), 127.9 (Ar-CH), 127.8 (Ar-CH), 69.8 (C-12), 66.9 (66.6) (C-5), 56.4 (55.8) (C-10), 46.0 (C-7), 45.4 (C-11), 44.6 (CH_2), 39.6 (C-25), 39.1 (C-26), 32.1(31.6) (C-9), 32.0 (CH_2), 29.8 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 26.8 (CH_2), 24.0(23.2) (C-8), 22.8 (C-23), 14.2 (24) ppm; IR

(ATR): ν_{max} 2923, 2852, 1700, 1497, 1455, 1408, 1356, 1337, 1186, 1029, 768, 750, 697, 602 cm^{-1}; HRMS (ESI) 492.2950 (M + H^+. $C_{28}H_{46}NO_2S_2$ requires 492.2964); 514.2778 (M + Na^+. $C_{28}H_{45}NNaO_2S_2$ requires 514.2784); 530.2717 (M + K^+. $C_{28}H_{45}KNO_2S_2$ requires 530.2733); $[\alpha]_D^{25}$ -23.6° (c 0.71, $CHCl_3$)

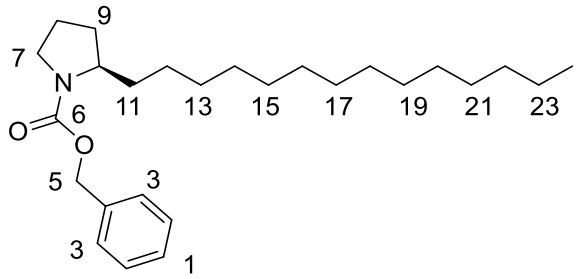
_N_-Cbz-(_S_)-2-{2-[7-(2-Methoxy-phenyl)-heptyl]-[1,3]dithiolan-2-ylmethyl}-pyrrolidine (251)



Pyrrolidine ketone **236** (55.9 mg, 0.124 mmol) and 1,2-ethanedithiol (0.21 ml, 2.48 mmol) was dissolved in dry CH_2Cl_2 (0.8 mL, 0.16M) under N_2. $BF_3.Et_2O$ (0.18 ml, 1.49 mmol) was added dropwise and the reaction stirred for 4 hours. The reaction was quenched with acetone (0.6 ml), diluted with saturated aqueous $NaHCO_3$ solution (10 mL), and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic fractions were dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (15% EtOAc/hexane) to give **251** as a colourless oil (21.3 mg, 0.0404 mmol, 33% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.25 (m, 5H, Ar-H), 7.15 (ddd, *J* = 8.1, 7.4, 1.8 Hz, 1H, H-23), 7.11 (dd, *J* = 7.3, 1.8 Hz, 1H, H-21), 6.87 (dd, *J* = 7.4, 7.3 Hz, 1H, H-22), 6.83 (d, *J* = 8.1 Hz, 1H, H-24), 5.19 – 5.02 (m, 2H, H-5), 4.21 – 4.03 (m, 1H, H-10), 3.80 (s, 3H, H-26), 3.47 – 3.31 (m, 2H, H-7), 3.32 – 3.01 (m, 4H, H-27, H-28), 2.58 (t, *J* = 7.5 Hz, 2H, H-19), 2.52 (d, *J* = 14.2 Hz, 0.5H, H-11, *rotamer 1*), 2.31 (d, *J* = 14.6 Hz, 0.5H, H-11, *rotamer 2*), 2.11 – 2.07 (m, 1H, H-9), 2.03 – 1.75 (m, 6H, CH_2), 1.59 – 1.12 (m, 10H, CH_2) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.5 (C-25), 154.8 (C-6), 131.4 (C-20), 129.8 (C-21),128.5 (Ar-CH), 128.1 (Ar-CH), 127.9 (Ar-CH), 126.8 (C-23), 120.4 (C-22), 110.3 (C-24), 69.8 (C-12), 67.0(66.5) (C-5), 56.4(55.7) (C-10), 55.3 (C-26), 46.0 (45.3) (C-11), 44.6 (CH_2), 39.6 (C-27), 39.0 (C-28), 32.1 (31.6) (C-9), 30.2 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 26.8 (CH_2), 24.0(23.2) (C-8) ppm; IR (ATR): ν_{max} 2927, 2854, 1698, 1493, 1455, 1409, 1356, 1336, 1288, 1241, 1185, 1101, 1050, 1030, 752, 697, 602 cm^{-1}; HRMS (ESI)

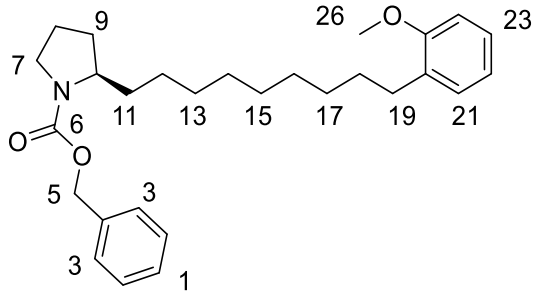
528.2609 (M + H^+. $C_{30}H_{42}NO_3S_2$ requires 528.2601); 550.2426 (M + Na^+. $C_{30}H_{41}NNaO_3S_2$ requires 550.2420); $[\alpha]_D^{20}$ -20.8° (c 0.915, $CHCl_3$)

_N_-Cbz-(R)-2-Tetradecyl-pyrrolidine (252)



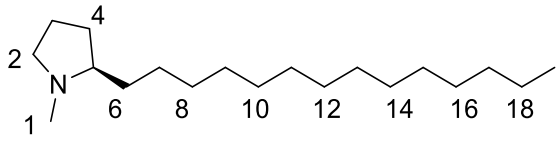
Ketone **235** (48.4 mg, 0.116 mmol) was dissolved in MeOH (5 ml) and added to *p*-toluenesulfonyl hydrazide (32.5 mg, 0.175 mmol) followed by AcOH (cat. ~0.1 ml). The reaction was stirred at room temperature for 24 hours, then concentrated *in vacuo*. The crude material was filtered through a pad of silica (25% EtOAc/hexane) to give the tosylhydrazone as a brown residue (59.4 mg, 0.102 mmol, 88 % yield). A portion of the tosylhydrazone (16.5 mg, 0.0283 mmol) in anhydrous MeOH (1 ml) was added to $NaBH_3CN$ (8.9 mg, 0.141 mmol) and $ZnCl_2$ (9.6 mg, 0.0707 mmol) under N_2 and the reaction heated to reflux for 16 hours. The reaction was quenched with 5% NaOH (aq) (5 ml) extracted with Et_2O (3 x 10 ml). The combined organic fractions were washed with water (10 ml) and saturated brine solution (10 ml), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (10% Et_2O/hexane) to give **252** as a yellow oil (9.2 mg, 0.0229 mmol, 81 % yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46 – 7.25 (m, 5H, Ar-H), 5.20 – 5.05 (m, 2H, H-5), 3.89 – 3.74 (m, 1H, H-10), 3.50 – 3.31 (m, 2H, H-7), 2.01 – 1.61 (m, 5H, CH_2), 1.38 – 1.00 (m, 25H, CH_2), 0.87 (t, *J* = 7.4 Hz, 3H, H-24) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.1 (C-6), 128.5 (Ar-CH), 128.0 (Ar-CH), 127.9 (Ar-CH), 66.7(66.5) (C-5), 58.2(57.4) (C-10), 46.7(46.3) (C-7), 34.6(34.0) (CH_2), 32.0 (CH_2), 30.6(30.4) (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 26.5 (CH_2), 26.3 (CH_2), 23.9 (CH_2), 23.1 (CH_2), 22.8 (C-23), 14.2 (C-24) ppm; IR (ATR): ν_{max} 2923, 2853, 1703, 1618, 1456, 1410, 1357, 1334, 1185, 1100, 768, 696 cm^{-1}; HRMS (ESI) 402.3372 (M + H^+. $C_{26}H_{44}NO_2$ requires 402.3367); 424.3185 (M + Na^+. $C_{26}H_{43}NNaO_2$ requires 424.3186); $[\alpha]_D^{20}$ -22.8° (c 0.285, $CHCl_3$)

***N*-Cbz-(*R*)-2-[9-(2-Methoxy-phenyl)-nonyl]-pyrrolidine (253)**



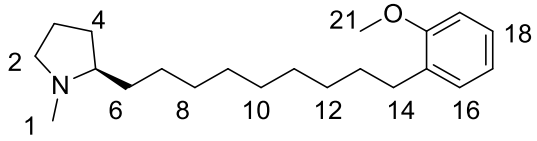
Ketone **236** (55.0 mg, 0.122 mmol) was dissolved in MeOH (5 ml) and added to *p*-toluenesulfonyl hydrazide (34.0 mg, 0.183 mmol) followed by AcOH (cat. ~0.1 ml). The reaction was stirred at room temperature for 24 hours, then concentrated *in vacuo*. The crude material was filtered through a pad of silica (30% EtOAc/hexane) to give the tosylhydrazone as a brown residue (66.8 mg, 0.108 mmol, 88 % yield). A portion of the tosylhydrazone (5.7 mg, 0.00920 mmol) in anhydrous MeOH (1 ml) was added to $NaBH_3CN$ (2.9 mg, 0.0460 mmol) and $ZnCl_2$ (3.1 mg, 0.0230 mmol) under N_2 and the reaction heated to reflux for 16 hours. The reaction was quenched with 5% NaOH (aq) (5 ml) extracted with Et_2O (3 x 10 ml). The combined organic fractions were washed with water (10 ml) and saturated brine solution (10 ml), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (15% Et_2O/hexane) to give **253** as a yellow oil (1.6 mg, 0.00366 mmol, 40 % yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.25 (m, 5H, Ar-H), 7.15 (dd, *J* = 8.4, 7.8 Hz, 1H, H-23), 7.12 (d, *J* = 7.6 Hz, 1H, H-21), 6.87 (t, *J* = 7.8, 7.6 Hz, 1H, H-22), 6.83 (d, *J* = 8.4 Hz, 1H, H-24), 5.20 – 5.05 (m, 2H, H-5), 3.89 – 3.77 (m, 1H, H-10), 3.81 (s, 3H, H-26), 3.52 – 3.31 (m, 2H, H-7), 2.58 (t, *J* = 7.8 Hz, 2H, H-19), 1.98 – 1.61 (m, 5H, CH_2), 1.59 – 1.51 (m, 2H, CH_2), 1.42 – 1.13 (m, 13H, CH_2) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.5 (C-25), 154.9 (C-6), 131.4 (C-20), 129.8 (C-21), 128.5 (Ar-CH), 127.9 (Ar-CH), 127.9 (Ar-CH), 126.8 (C-23), 120.4 (C-22), 110.3 (C-24), 66.5 (C-5), 58.2 (C-10), 55.3 (C-26), 46.7 (C-7), 34.0(C-11), 30.7 (C-9), 30.2(C-19), 29.9 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 26.4 (C-12), 23.9 (CH_2), 23.1 (C-8) ppm; IR (ATR): ν_{max} 2924, 2853, 1701, 1601, 1587, 1493, 1455, 1410, 1356, 1334, 1288, 1259, 1241, 1178, 1097, 1050 1029, 913, 864, 802, 763, 751, 697, 600 cm^{-1}; HRMS (ESI) 460.2819 (M + Na$^+$. $C_{28}H_{39}NNaO_3$ requires 460.2822); $[\alpha]_D^{20}$ -24.4° (c 0.20, CHCl3)

(*R*)-Bgugaine (207)



A solution of pyrrolidine **252** (9.2 mg, 0.0229 mmol) in dry THF (0.25 ml) was added to a solution of $LiAlH_4$ (8.7 mg, 0.229 mmol) in dry THF (0.25 ml) at 0 °C under N_2. The reaction was allowed to warm to room temperature with stirring for 15 hours. The reaction was cooled to 0 °C, diluted with Et_2O (5 ml), quenched with 5% NaOH solution (0.1 ml) and dried with $MgSO_4$. The mixture wa filtered through celite and concentrated *in vacuo*. The crude material was purified by column chromatography (1:10:90 NH_3/MeOH/DCM) to give **207** as a yellow oil (4.4 mg, 0.0156 mmol, 68% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.05 (ddd, *J* = 9.1, 7.8, 2.2 Hz, 1H, H-2), 2.29 (s, 3H, H-1), 2.10 (ddd, *J* = 9.1, 9.1, 8.7 Hz, 1H, H-2'), 1.99 – 1.84 (m, 2H, H-5, CH_2), 1.80 – 1.69 (m, 1H, CH_2), 1.69 – 1.58 (m, 2H, CH_2), 1.48 – 1.34 (m, 1H, CH_2), 1.34 – 1.06 (m, 25H, CH_2), 0.84 (t, *J* = 7.1 Hz, 3H, H-19) ppm;^{13}C NMR (101 MHz, Chloroform-*d*) δ 66.5 (C-5), 57.3 (C-2), 40.4 (C-1), 33.8 (C-6), 31.9 (C-17), 30.8 (C-4), 30.0 (C-8), 29.7-29.6 (C-9-C-15), 29.4 (C-16), 26.7 (C-7), 22.7 (C-18), 21.8 (C-3), 14.1 (C-19) ppm; IR (ATR): ν_{max} 2922, 2852, 2772, 1457, 1376, 1350, 1215, 1163, 1114, 1042, 896, 721, 573 cm^{-1}; HRMS (ESI) 282.3159 (M + H$^+$. $C_{19}H_{40}N$ requires 282.3155); $[\alpha]_D^{20}$ -35.9° (c 0.22, MeOH) (lit. $[\alpha]_D^{20}$ -42.5° (c 1.65, MeOH))[143]

(*R*)-Irnidine (208)

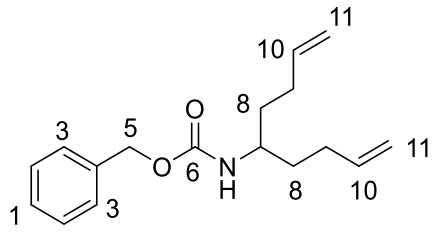


A solution of pyrrolidine **253** (10.8 mg, 0.0247 mmol) in dry THF (0.25 ml) was added to a solution of $LiAlH_4$ (9.4 mg, 0.247 mmol) in dry THF (0.25 ml) at 0 °C under N_2. The reaction was allowed to warm to room temperature with stirring for 15 hours. The reaction was cooled to 0 °C, diluted with Et_2O (5 ml), quenched with 5% NaOH solution (0.1 ml) and dried with $MgSO_4$. The mixture wa filtered through celite and concentrated *in vacuo*. The crude material was purified by column chromatography (1:10:90 NH_3/MeOH/DCM) to give **208** as a yellow oil (6.9 mg, 0.0217 mmol, 88% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.15 (td, *J* = 8.2, 7.4, 1.8 Hz, 1H, H-18), 7.11 (dd, *J* = 7.3, 1.8 Hz, 1H, H-16), 6.86 (ddd, *J* = 7.4, 7.3, 1.2 Hz, 1H, H-17), 6.83

(dd, *J* = 8.2, 1.2 Hz, 1H, H-19), 3.81 (s, 3H, H-21), 3.05 (ddd, *J* = 9.5, 7.8, 2.1 Hz, 1H, H-2), 2.58 (t, *J* = 7.8 Hz, 2H, H-14), 2.29 (s, 3H, H-1), 2.18 – 2.05 (m, 1H, H-2'), 2.04 – 1.84 (m, 2H, H-5, CH_2), 1.84 – 1.60 (m, 3H, CH_2), 1.60 – 1.50 (m, 2H, CH_2), 1.49 – 1.11 (m, 14H, CH_2) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.4 (C-20), 131.3 (C-15), 129.7 (C-16), 126.7 (C-18), 120.2 (C-17), 110.1 (C-19), 66.6 (C-5), 57.2 (C-2), 55.2 (C-21), 40.2 (C-1), 33.5 (C-6), 30.6 (C-4), 30.1 (C-14), 30.0 (C-13), 29.8 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 26.7 (C-7), 21.7 (C-3) ppm; IR (ATR): ν_{max} 2925, 2853, 2775, 1672, 1601, 1493, 1463, 1289, 1241, 1176, 1127, 1050, 1031, 751 cm^{-1}; HRMS (ESI) 318.2790 (M + H$^+$. $C_{21}H_{36}NO$ requires 318.2791); $[\alpha]_D^{20}$ -18.2° (c 0.165, $CHCl_3$) (lit. $[\alpha]_D^{25}$ -20° (c 0.30, $CHCl_3$))[113]

Desymmetrisation procedures

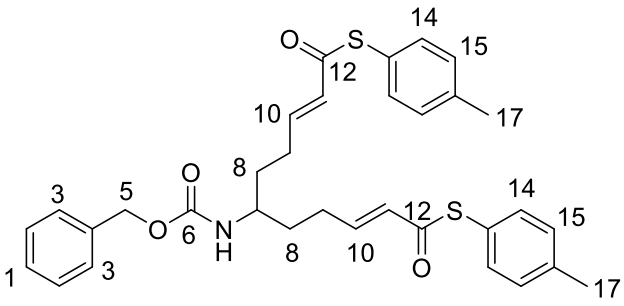
***N*-Cbz-1-(but-3-enyl)pent-4-enylamine (281)**



1-(but-3-enyl)pent-4-enylamine **282** was synthesised using previously reported procedures.[163] A solution of 1-(but-3-enyl)pent-4-enylamine **282** (150 mg, 1.08 mmol) was dissolved in 1,4-dioaxane (5 ml) and added to a stirred solution of K_2CO_3 (178 mg, 1.29 mmol) in H_2O (0.18 ml). Benzyl chloroformate (0.18 ml, 1.29 mmol) was added dropwise to the reaction and stirred for 18 hours. The reaction was diluted with H_2O (5 ml) and extracted with CH_2Cl_2 (3 x 5 ml). The combined organics were washed with saturated brine solution (5 ml), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (10% EtOAc/hexane) to give Cbz-amine **281** as a colourless oil (253 mg, 0.925 mmol, 86% yield).^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.44 – 7.26 (m, 5H, Ar-H), 5.79 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 2H, H-10), 5.08 (s, 2H, H-5), 5.00 (dd, *J* = 16.8, 1.9 Hz, 2H, H-11), 4.95 (dd, *J* = 10.2, 1.9 Hz, 2H, H-11'), 4.51 (d, *J* = 9.5 Hz, 1H, NH), 3.74 – 3.60 (m, 1H, H-7), 2.20 – 2.00 (m, 4H, H-9), 1.69 – 1.52 (m, 2H, H-8), 1.52 – 1.39 (m, 2H, H-8') ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 156.1 (C-6), 138.1 (C-10), 136.7 (C-4), 128.6 (Ar-CH), 128.2(Ar-CH), 128.1 (Ar-CH), 115.1 (C-11), 66.7 (C-5), 50.7 (C-7), 34.7 (C-8), 30.2 (C-9) ppm; IR (ATR): ν_{max}

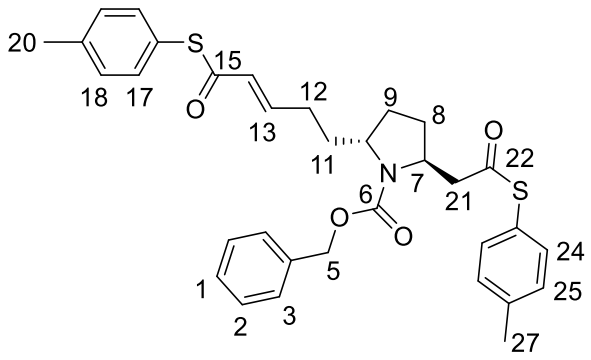
3321, 3074, 2935, 2852, 1691, 1640, 1531, 1451, 1415, 1330, 1299, 1243, 1215, 1045, 1027, 993, 909, 774, 735, 696, 642, 458 cm^{-1}; HRMS (ESI) 274.1798 ($M + H^+$. $C_{17}H_{24}NO_2$ requires 274.1802), 296.1616 ($M + Na^+$. $C_{17}H_{23}NNaO_2$ requires 296.1621), 312.1359 ($M + K^+$. $C_{17}H_{23}KNO_2$ requires 312.1360)

***N*-Cbz-6-amino-undeca-2,9-diene-bis-thioic acid di-S-p-tolyl ester (280)**



A solution of thioester **134** (363 mg, 2.04 mmol) in 1,2-DCE (7.5 ml) was added under N_2 to a dry flask containing Hoveyda-Grubbs Catalyst™ 2nd generation (21.2 mg, 0.034 mmol) and copper iodide (57.1 mg, 0.34 mmol) while stirring. A solution of Cbz-amine **281** (92.8 mg, 0.34 mmol) in 1,2-DCE (7.5 ml) was added under N_2 and the reaction heated to 50 °C for 7 hours. The reaction was then cooled to room temperature, exposed to air and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (10-50% EtOAc/hexane) to afford **280** as a pale brown oil (150 mg, 0.261 mmol, 77% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.49 – 7.32 (m, 5H, Ar-H), 7.31 (d, *J* = 7.8 Hz, 4H, H-14), 7.22 (d, *J* = 7.8 Hz, 4H, H-15), 6.93 (dt, *J* = 15.7, 6.9 Hz, 2H, H-10), 6.18 (d, *J* = 15.7 Hz, 2H, H-11), 5.22 – 5.01 (m, 2H, H-5), 4.62 (d, *J* = 9.4 Hz, 1H, NH), 3.88 – 3.55 (m, 1H, H-7), 2.37 (s, 6H, H-17), 2.32 – 2.17 (m, 4H, H-9), 1.81 – 1.58 (m, 2H, H-8), 1.58 – 1.34 (m, 2H, H-8') ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 188.5 (C-12), 156.2 (C-6), 145.2 (C-10), 139.8 (C-16), 136.5 (C-4), 134.7 (C-14), 130.1 (C-15), 128.7 (Ar-CH), 128.4 (Ar-CH), 128.3 (Ar-CH), 128.2 (C-11), 124.1 (C-13), 67.0 (C-5), 51.0 (C-7), 34.1 (C-8), 29.0 (C-9), 21.5 (C-17) ppm; IR (ATR): ν_{max} 3345, 3030, 2931, 1683, 1630, 1525, 1493, 1449, 1287, 1237, 1140, 1053, 1016, 975, 807, 738, 698, 649, 536, 475 cm^{-1}; HRMS (ESI) 596.1900 ($M + Na^+$. $C_{33}H_{35}NNaO_4S_2$ requires 596.1900), 612.1640 ($M + K^+$. $C_{33}H_{35}KNO_4S_2$ requires 612.1639)

N-Cbz-(*R*)-2-(4-p-Tolylsulfanylcarbonyl-but-3-enyl)-(*S*)-5-p-tolylsulfanylcarbonylmethyl-pyrrolidine (279)



Racemic

A solution of amino-thioester **280** (22.1 mg, 0.039 mmol) in 1,2-DCE (5 ml) was added to rac-CSA (22.6 mg, 0.116 mmol) under N_2 and the reaction heated to 50 °C for 24 hours. The reaction was cooled to room temperature and extracted with DCM (10 ml). The organic fraction was washed with saturated $NaHCO_3$ solution (10 ml), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (25% EtOAc/hexane) to afford **279** as a colourless oil (14.7 mg, 0.026 mmol, 60% yield).

Asymmetric

A solution of amino-thioester **280** (36.2 mg, 0.0631 mmol) in cyclohexane (0.02M) was added to (*R*)-TRIP (9.5 mg, 0.0126 mmol) under N_2 and the reaction heated to 80 °C for 24 hours. The reaction was then cooled to room temperature, quenched with Et_3N (0.2 ml) and concentrated *in vacuo*. The crude material was purified by column chromatography (20% Et_2O/hexane) to afford **279** as a colourless oil (27.7 mg, 0.048 mmol, 77% yield, dr 92:8, major er: 93:7, minor er: 56:44).

Major diastereomer:

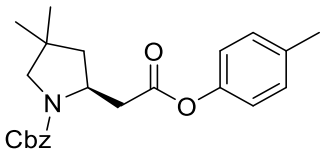
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.50 – 7.17 (m, 13H, Ar-H), 6.97 (dt, *J* = 15.5, 6.7 Hz, 0.5H, H-13, *rotamer 1*), 6.88 (dt, *J* = 15.5, 6.7 Hz, 0.5H, H-13, *rotamer 2*), 6.24 (d, *J* = 15.5 Hz, 0.5H, H-14, *rotamer 1*), 6.14 (d, *J* = 15.5 Hz, 0.5H, H-14, *rotamer 2*), 5.29 – 5.08 (m, 2H, H-5), 4.38 – 4.28 (m, 1H, H-7), 3.94 – 3.79 (m, 1H, H-10), 3.38 (dd, *J* = 14.8, 3.2 Hz, 0.5H, H-21, *rotamer 1*), 3.08 (dd, *J* = 14.8, 3.2 Hz, 0.5H, H-21, *rotamer 2*), 2.69 (dd, *J* = 14.8, 9.7 Hz, 0.5H, H-21', *rotamer 1*), 2.62 (dd, *J* = 14.8, 9.7 Hz, 0.5H, H-21', *rotamer 2*), 2.39 (s, 6H, H-20, H-27), 2.30 – 1.76 (m,

6H, CH_2), 1.76 – 1.65 (m, 1H, CH_2), 1.53 – 1.39 (m, 1H, CH_2) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ195.9(195.8) (C-22), 188.4(188.3) (C-15), 154.0(153.8) (C-6), 145.3, 145.0 (C-13), 139.9, 139.7 (C-19), 139.7, 139.6 (C-26), 136.6(136.6) (C-4), 134.6(134.5) (C-17), 134.4(134.3) (C-24), 130.1(130.1) (C-18), 130.0(130.0) (C-25), 128.6(128.6) (Ar-CH), 128.2(128.2) (Ar-CH), 128.1(128.1) (Ar-CH), 128.1(128.1) (C-14), 124.1(124.1) (C-16), 124.0(123.9) (C-23), 66.9(66.9) (C-5), 57.9(57.2) (C-10), 55.1(54.6) (C-7), 47.1(45.6) (C-21), 32.2(30.9) (C-11), 29.4, (29.3) (C-12), 28.3(27.4) (C-8), 27.4(26.5) (C-9), 21.4 (C-20, C-27) ppm; IR (ATR): ν_{max} 3030, 2923, 2853, 1693, 1631, 1597, 1493, 1453, 1404, 1353, 1330, 1304, 1210, 1181, 1116, 1102, 1060, 1016, 989, 807, 771, 752, 733, 698, 647, 603, 534, 474 cm^{-1}; HRMS (ESI) 574.2069 ($M + H^+$. $C_{33}H_{36}NO_4S_2$ requires 574.2080), 591.2339 ($M + NH_3^+$. $C_{33}H_{39}N_2O_4S_2$ requires 591.2346), 596.1895 ($M + Na^+$. $C_{33}H_{35}NNaO_4S_2$ requires 596.1900), 612.1656 ($M + K^+$. $C_{33}H_{35}KNO_4S_2$ requires 612.1639); $[\alpha]_D^{20}$ -16.6° (c 1.00, $CHCl_3$).

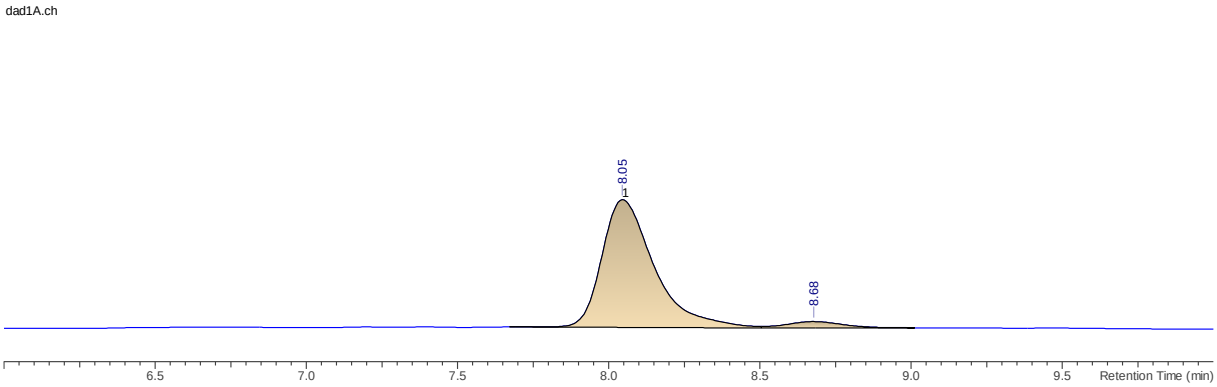
9 Appendices

9.1. HPLC data for cyclised compounds

N-Cbz-3,3-dimethyl-(*S*)-5-p-Tolyloxycarbonylmethyl-pyrrolidine (127c)

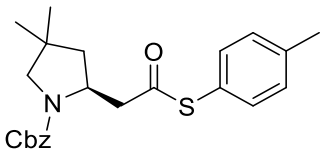


HPLC analysis CHIRALPAK IB column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 25 °C, λ = 254 nm; tR 8.1 min (major), 8.7 min (minor) er = 95:5

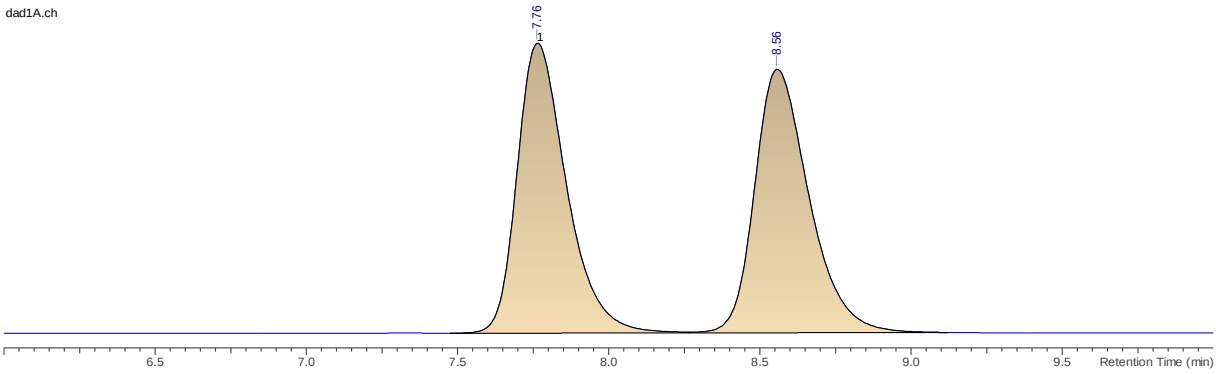


No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	8.05	325636.750	94.962	0.297
2	8.68	17277.719	5.038	0.333

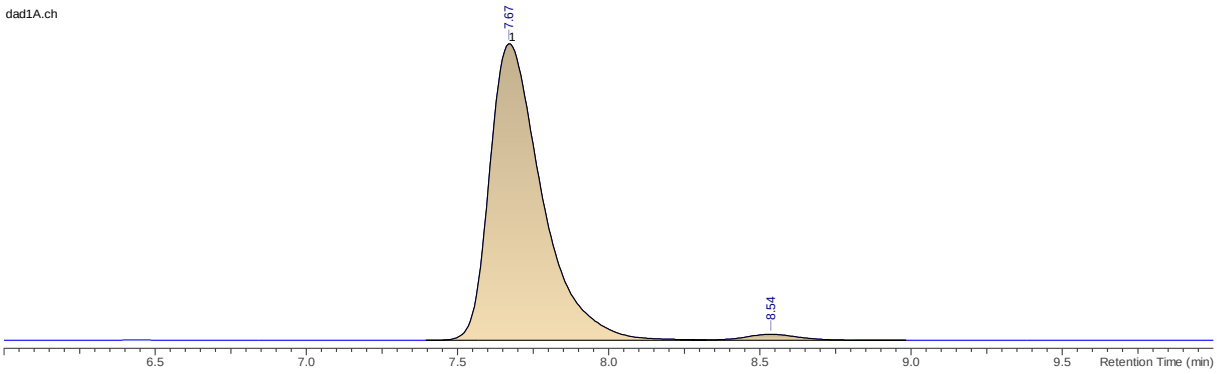
_N_-Cbz-3,3-dimethyl-(_S_)-5-p-Tolylsulfanylcarbonylmethyl-pyrrolidine (127b)



HPLC analysis CHIRALPAK IB column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 25 °C, λ = 254 nm; tR 7.7 min (major) and 8.5 min (minor), er = 98:2

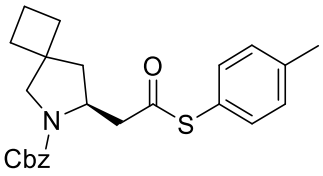


No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	7.76	4395871.500	49.967	0.289
2	8.55	4401762.000	50.033	0.320

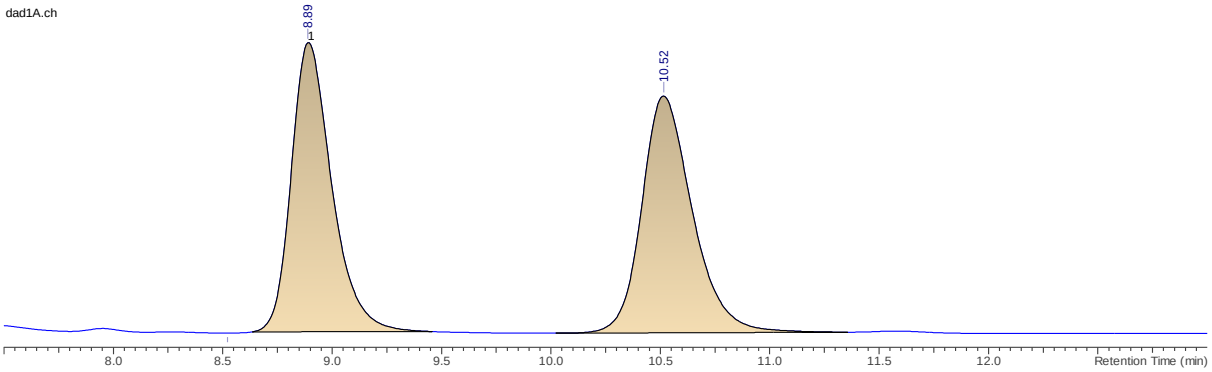


No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	7.67	10851146.000	97.931	0.302
2	8.54	229300.266	2.069	0.311

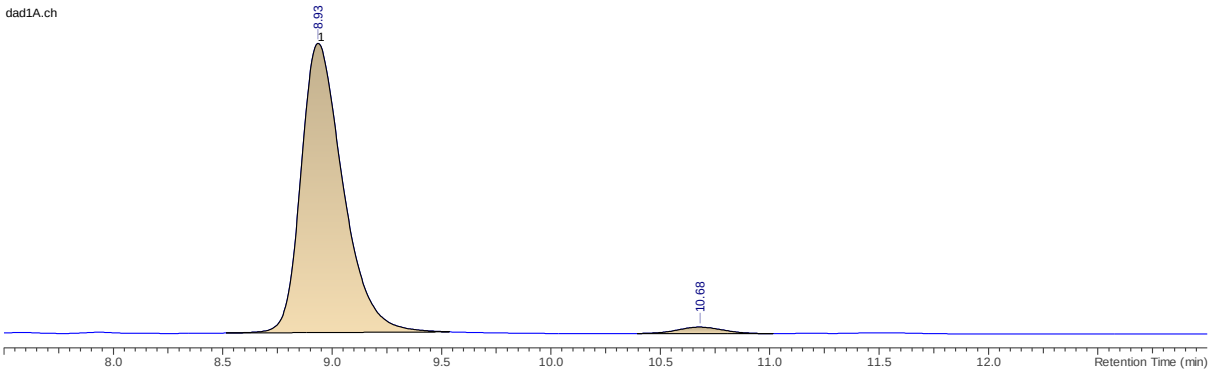
_N_-Cbz-(_S_)-7-p-Tolylsulfanylcarbonylmethyl-6-aza-spiro[3.4]octane (144a)



HPLC analysis CHIRALPAK IB column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 25 °C, λ = 254 nm; tR 8.9 min (major) and 10.6 min (minor), er = 98:2

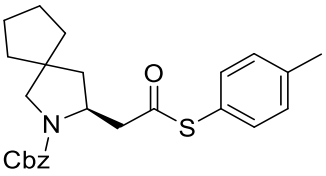


No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	8.89	2444530.250	49.414	0.327
2	10.52	2502497.250	50.586	0.407

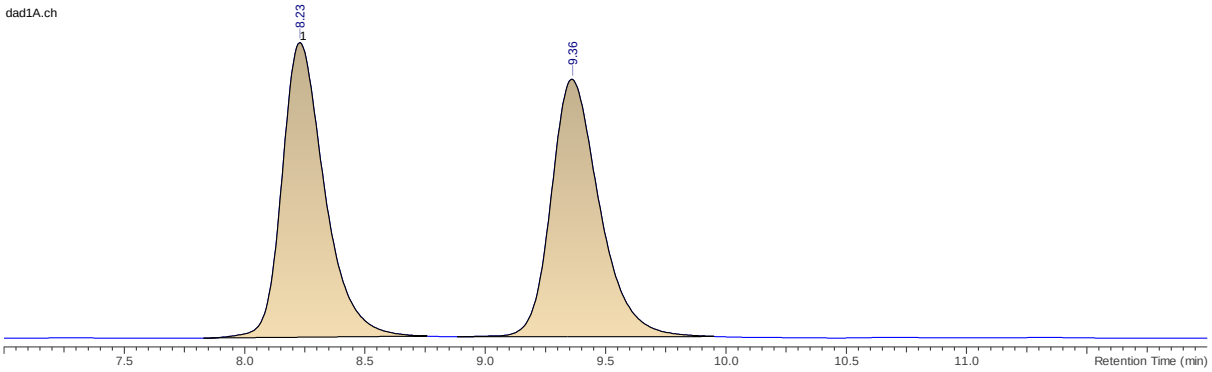


No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	8.93	6110395.500	97.677	0.340
2	10.68	145340.750	2.323	0.380

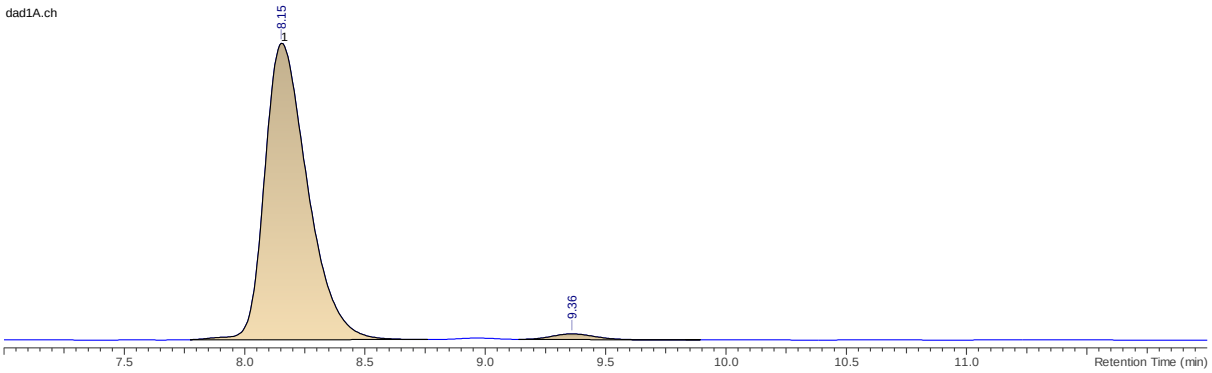
_N_-Cbz-(_S_)-3-p-Tolylsulfanylcarbonylmethyl-2-aza-spiro[4.4]nonane (144b)



HPLC analysis CHIRALPAK IB column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 25 °C, λ = 254 nm; tR 8.2 min (major) and 9.4 min (minor), er = 98:2

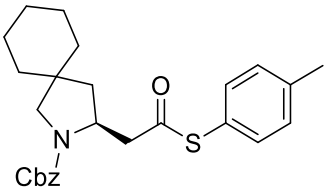


No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	8.23	2949471.000	50.196	0.309
2	9.36	2926389.250	49.804	0.354

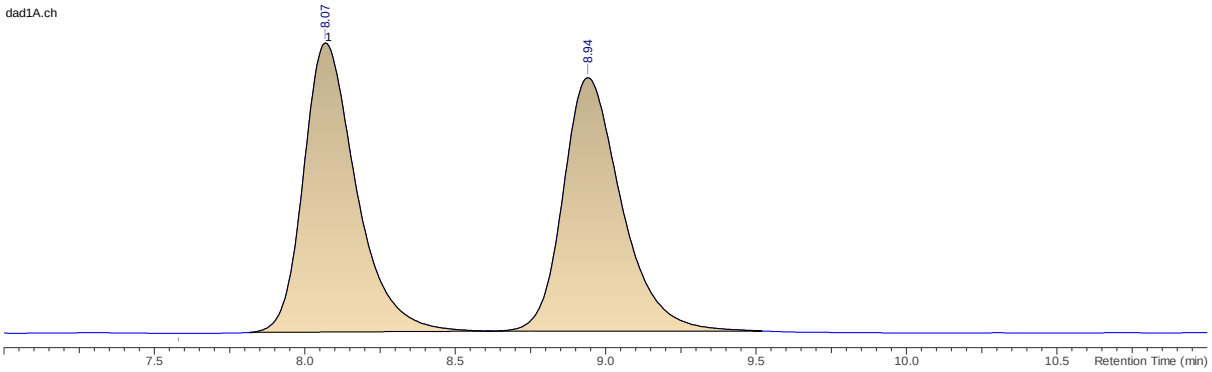


No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	8.15	8030335.000	98.139	0.319
2	9.36	152250.188	1.861	0.325

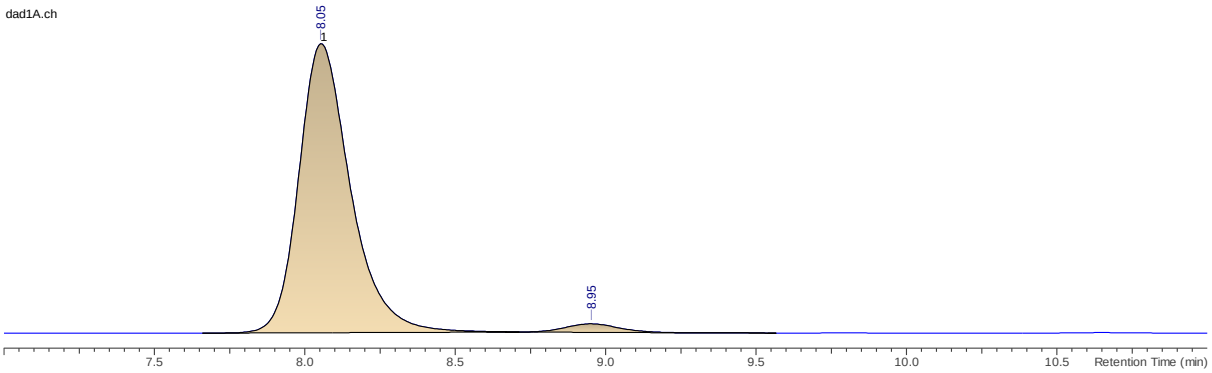
_N_-Cbz-(_S_)-3-p-Tolylsulfanylcarbonylmethyl-2-aza-spiro[4.5]decane (144c)



HPLC analysis CHIRALPAK IB column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 25 °C, λ = 254 nm; tR 8.1 min (major) and 8.9 min (minor), er = 97:3

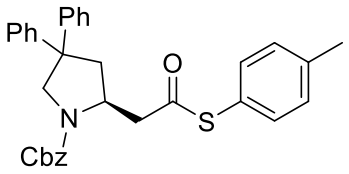


No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	8.07	3063161.000	50.784	0.306
2	8.94	2968525.000	49.216	0.340

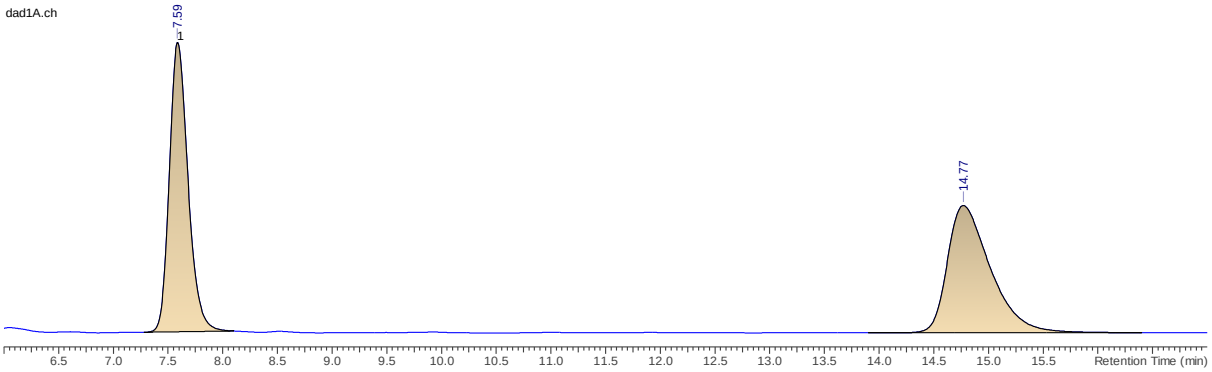


No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	8.05	1187544.500	97.045	0.300
2	8.95	36158.422	2.955	0.322

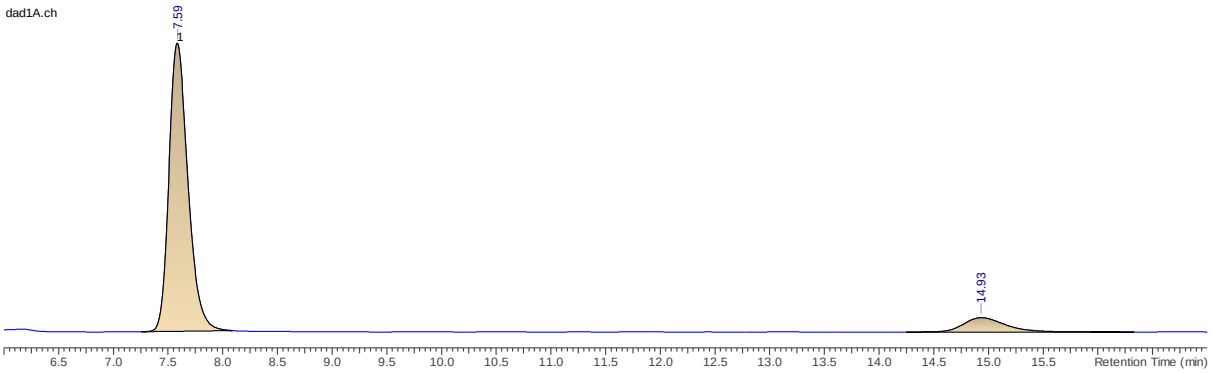
_N_-Cbz-3,3-diphenyl-(_S_)-5-p-Tolylsulfanylcarbonylmethyl-pyrrolidine (144d)



HPLC analysis CHIRALPAK IB column, hexane/2-propanol (80:20), flow rate: 1.0 mL/min, 25 °C, λ = 254 nm; tR 7.6 min (major) and 14.8 min (minor), er = 90:10

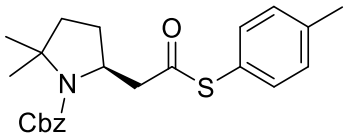


No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	7.59	2987208.500	49.646	0.304
2	14.77	3029823.250	50.354	0.694

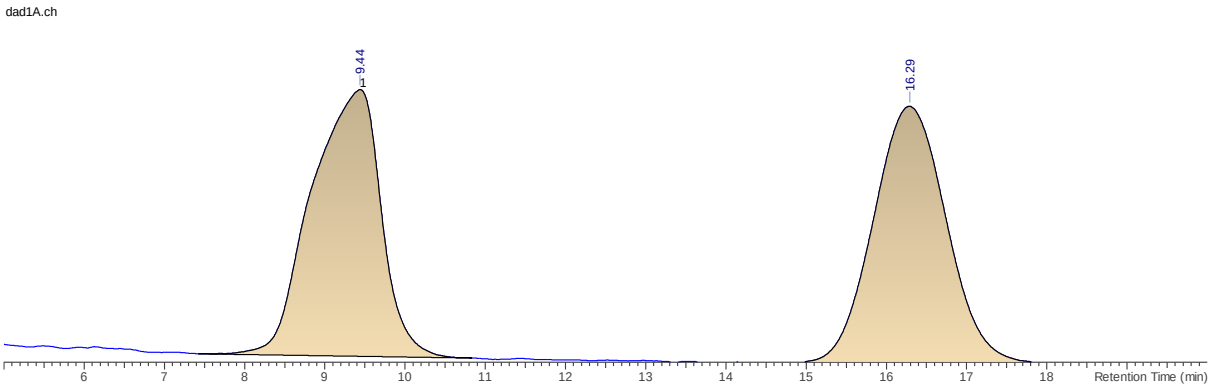


No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	7.59	6442181.000	89.927	0.310
2	14.93	721584.188	10.073	0.679

_N_-Cbz-2,2-dimethyl-(_S_)-5-p-Tolylsulfanylcarbonylmethyl-pyrrolidine (150)

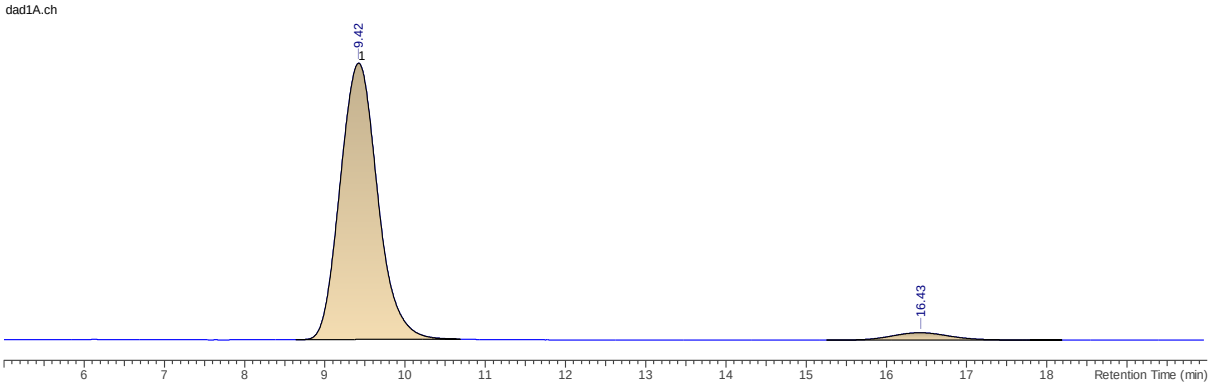


HPLC analysis CHIRALPAK IC column, hexane/2-propanol (80:20), flow rate: 1.0 mL/min, 25 °C, λ = 254 nm; tR 9.4 min (major) and 16.3 min (minor), er = 96:4



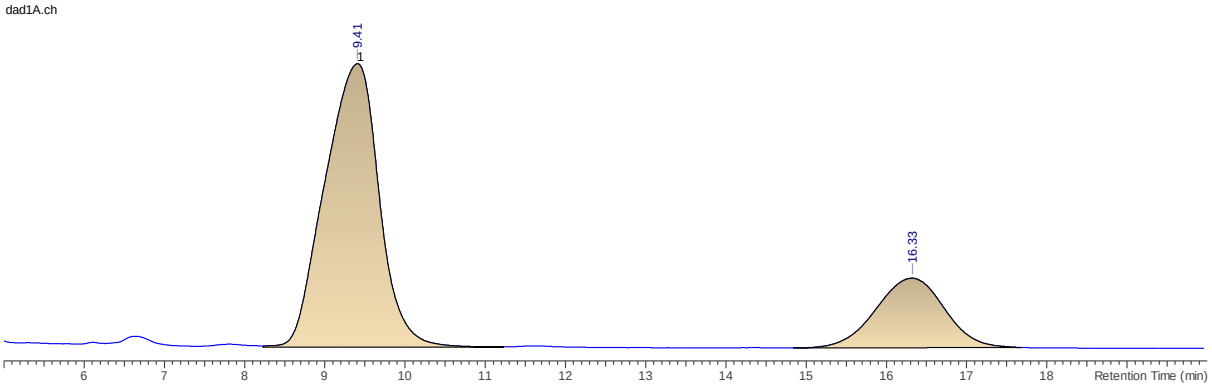
No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	9.44	4442656.000	49.614	1.695
2	16.29	4511810.500	50.386	1.682

(_R_)-TRIP, 80 °C



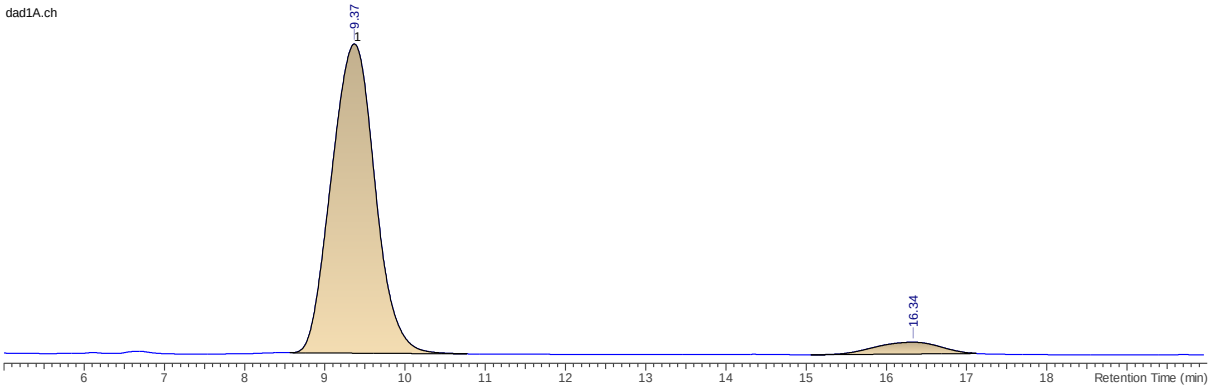
No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	9.42	19048088.000	96.075	0.848
2	16.43	778222.750	3.925	1.305

(*R*)-TiPSY, 80 °C er = 76:24



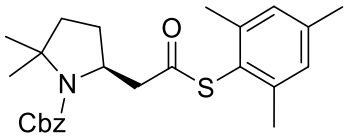
No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	9.41	7742961.500	76.345	1.269
2	16.33	2399111.500	23.655	1.578

(*R*)-TRIP, 50 °C er = 95:5

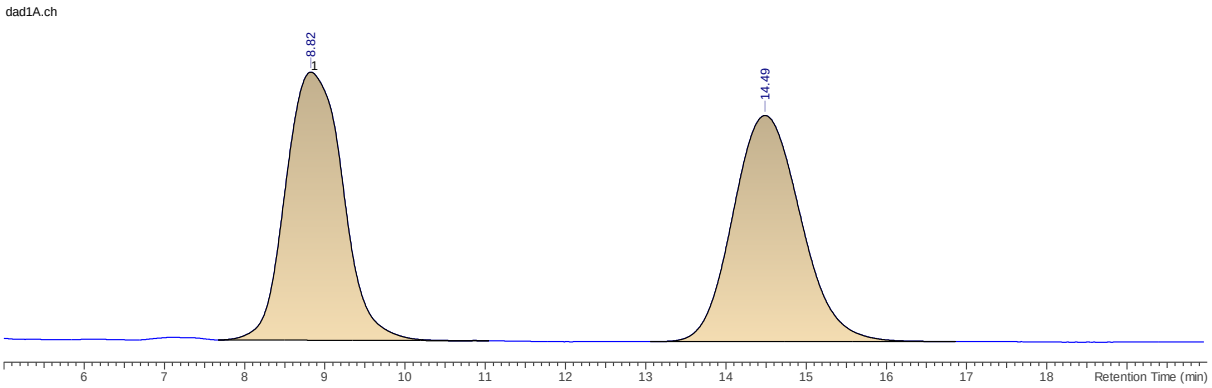


No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	9.37	26652556.000	94.640	1.007
2	16.34	1509538.125	5.360	1.575

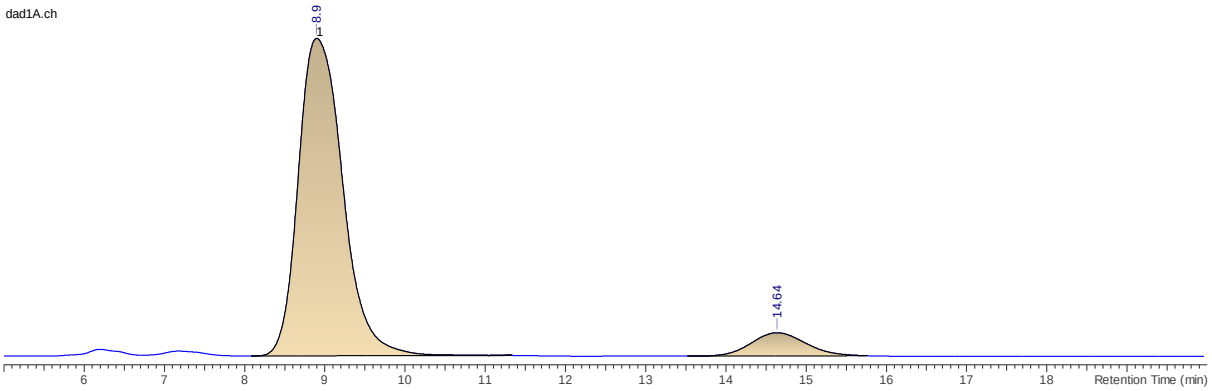
_N_-Cbz-2,2-dimethyl-(_S_)-5-(2,4,6-trimetyhl-phenylsulfanylcarbonylmethyl)-pyrrolidine (154)



HPLC analysis CHIRALPAK IC column, hexane/2-propanol (80:20), flow rate: 1.0 mL/min, 25 °C, λ = 254 nm; tR 8.8 min (major) and 14.5 min (minor), er = 92:8

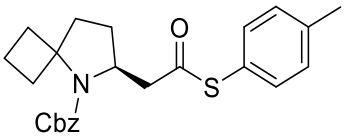


No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	8.82	11354936.000	49.911	1.323
2	14.49	11395396.000	50.089	1.554

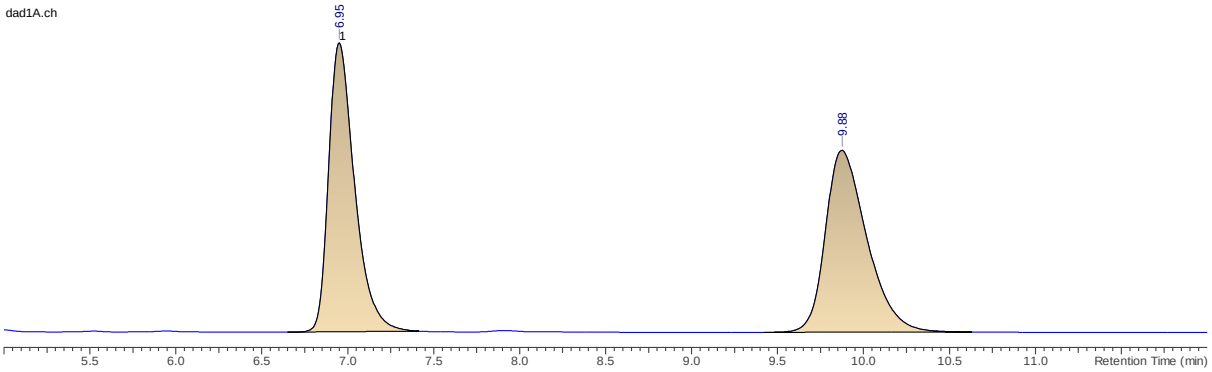


No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	8.90	26545430.000	91.823	1.004
2	14.64	2363939.500	8.177	1.245

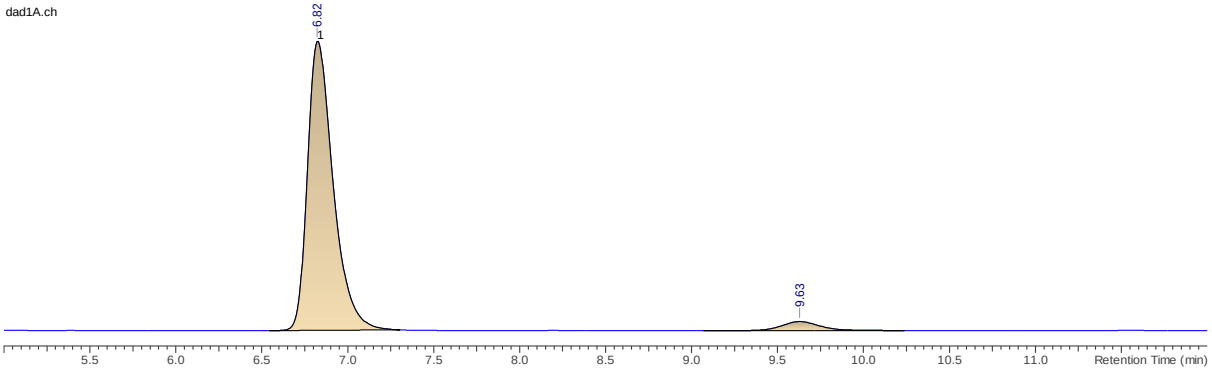
N-Cbz-(*S*)-6-p-Tolylsulfanylcarbonylmethyl-5-aza-spiro[3.4]octane (160a)



HPLC analysis CHIRALPAK IB column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 25 °C, λ = 254 nm; tR 6.9 min (major) and 9.7 min (minor), er = 96:4

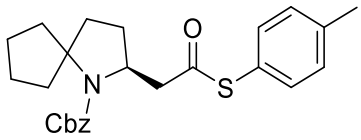


No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	6.95	5707584.000	49.875	0.266
2	9.88	5736213.000	50.125	0.430

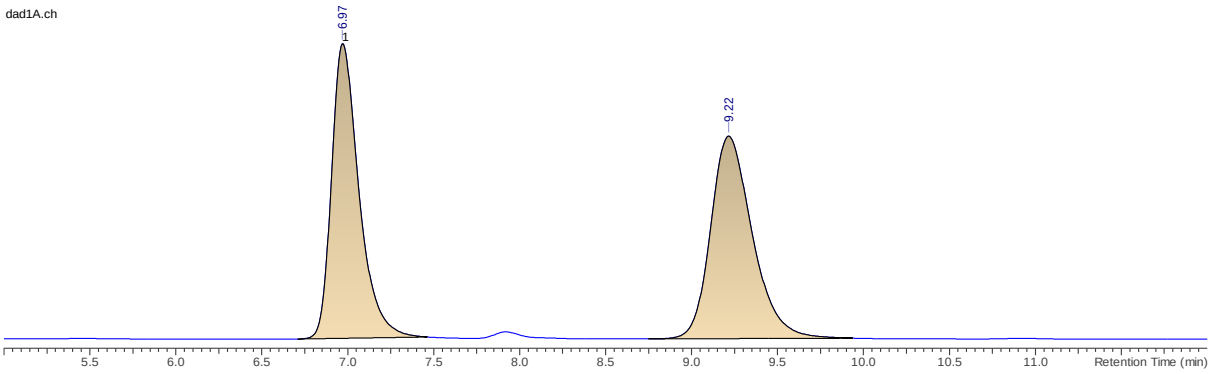


No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	6.82	5138018.500	95.609	0.264
2	9.63	235959.891	4.391	0.390

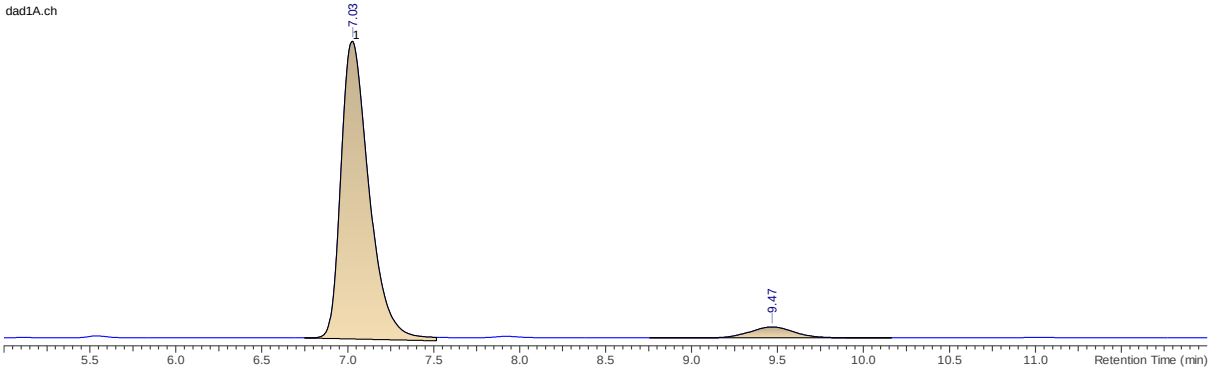
_N_-Cbz-(_S_)-2-p-Tolylsulfanylcarbonylmethyl-1-aza-spiro[4.4]nonane (160b)



HPLC analysis CHIRALPAK IB column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 25 °C, λ = 254 nm; tR 7.0 min (major) and 9.3 min (minor), er = 95:5

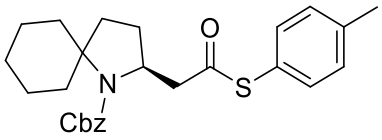


No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	6.97	2636100.250	48.918	0.279
2	9.22	2752741.250	51.082	0.430

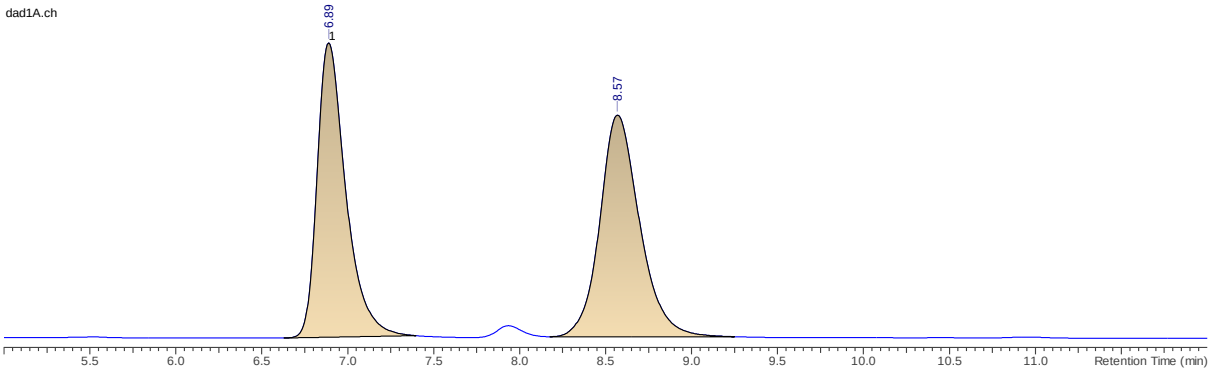


No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	7.03	8773789.000	94.521	0.289
2	9.47	508575.313	5.479	0.470

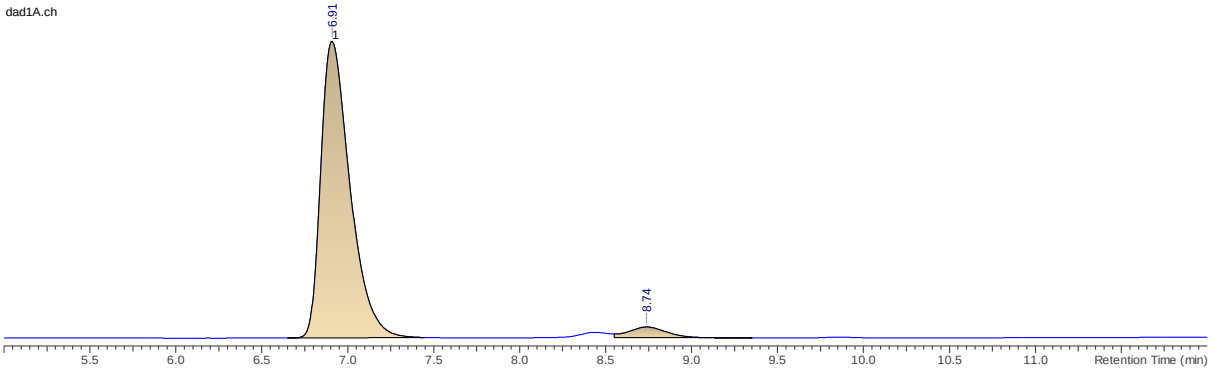
_N_-Cbz-(_S_)-2-p-Tolylsulfanylcarbonylmethyl-1-aza-spiro[4.5]decane (160c)



HPLC analysis CHIRALPAK IB column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 25 °C, λ = 254 nm; tR 6.9 min (major) and 8.6 min (minor), er = 95:5

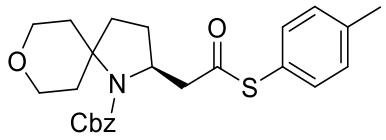


No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	6.89	2331830.750	48.834	0.291
2	8.57	2443199.750	51.166	0.405

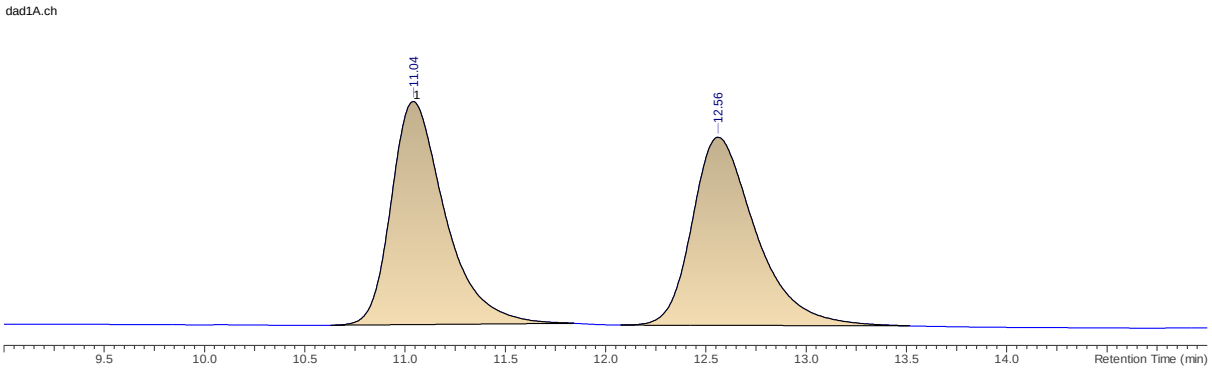


No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	6.91	10262474.000	95.675	0.304
2	8.74	463948.750	4.325	0.412

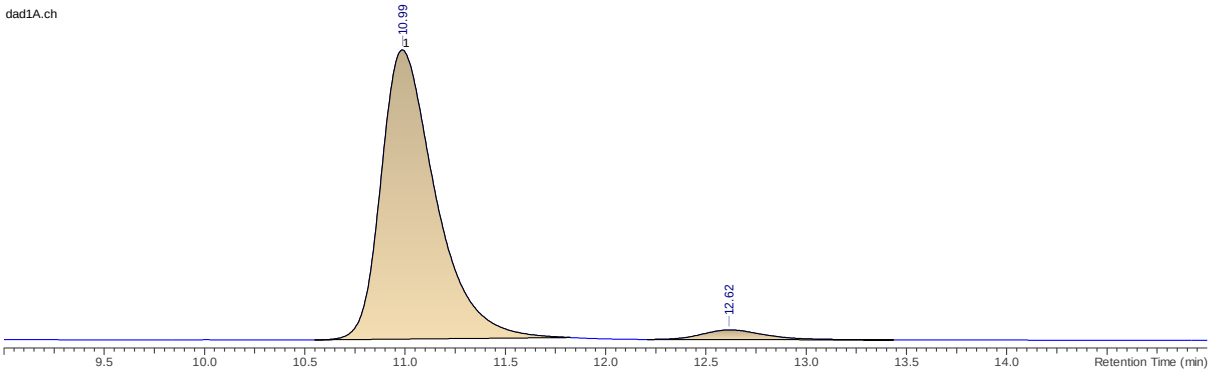
_N_-Cbz-(_S_)-2-p-Tolylsulfanylcarbonylmethyl-8-oxa-1-aza-spiro[4.5]decane (160d)



HPLC analysis CHIRALPAK IB column, hexane/2-propanol (80:20), flow rate: 1.0 mL/min, 25 °C, λ = 254 nm; tR 11.0 min (major) and 12.6 min (minor), er = 96:4

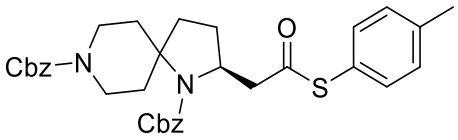


No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	11.04	1795499.875	50.167	0.468
2	12.56	1783541.500	49.833	0.553

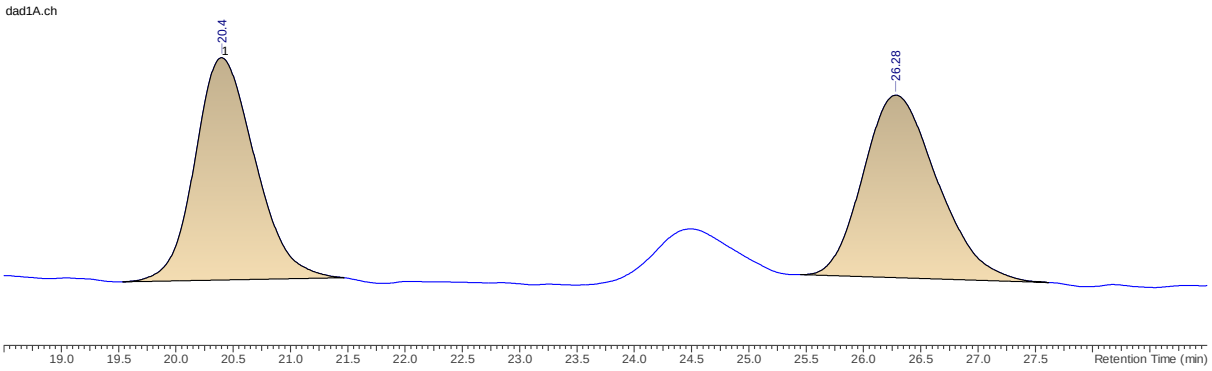


No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	10.99	4534995.000	96.293	0.475
2	12.62	174587.828	3.707	0.552

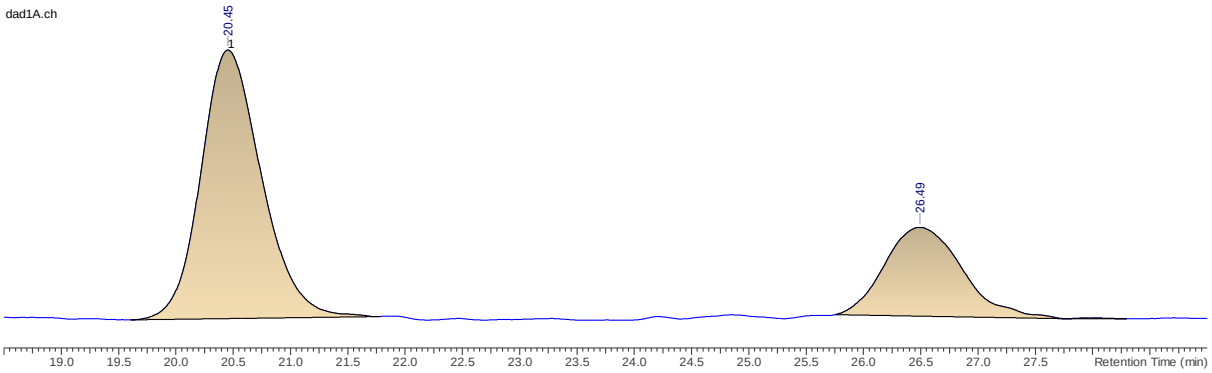
(*S*)-2-p-Tolylsulfanylcarbonylmethyl-1,8-diaza-spiro[4.5]decane-1,8-dicarboxylic acid dibenzyl ester (160e)



HPLC analysis CHIRALPAK IB column, hexane/2-propanol (80:20), flow rate: 1.0 mL/min, 25 °C, λ = 254 nm; tR 20.4 min (major) and 26.4 min (minor), er = 70:30

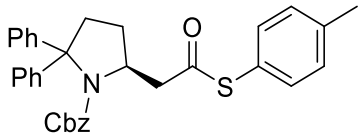


No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	20.40	1139909.500	49.641	0.948
2	26.28	1156413.500	50.359	1.188

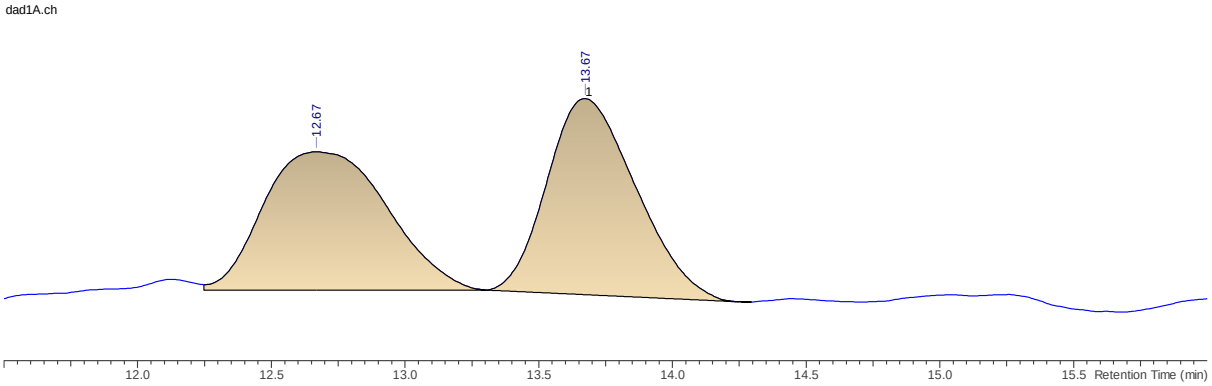


No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	20.45	1121332.500	70.284	0.950
2	26.49	474094.906	29.716	1.235

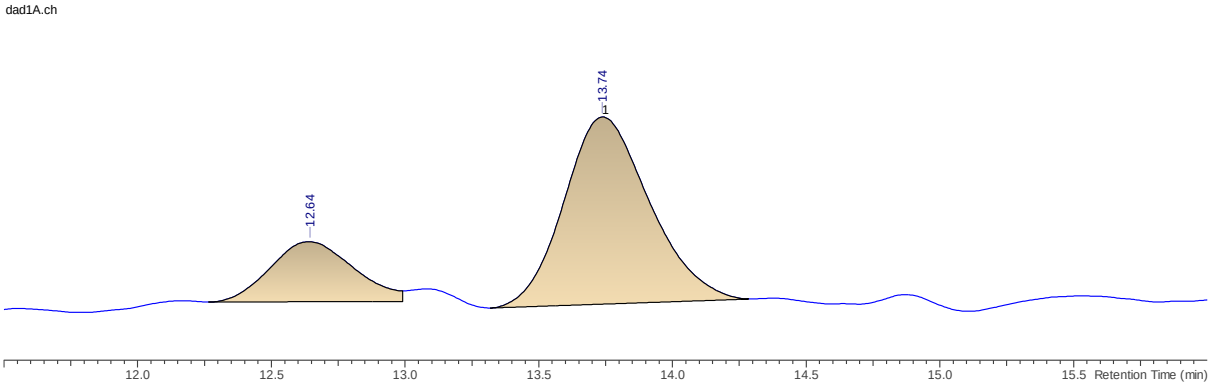
_N_-Cbz-2,2-diphenyl-(_S_)-5-p-Tolylsulfanylcarbonylmethyl-pyrrolidine (160f)



HPLC analysis CHIRALPAK IB column, hexane/2-propanol (80:20), flow rate: 1.0 mL/min, 25 °C, λ = 254 nm; tR 12.6 min (minor), 13.7 min (major) and 57.7 (starting material), er = 76:24

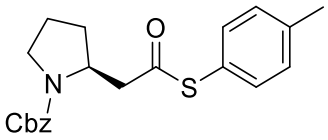


No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	12.67	119961.375	49.566	0.890
2	13.67	122064.375	50.434	0.623

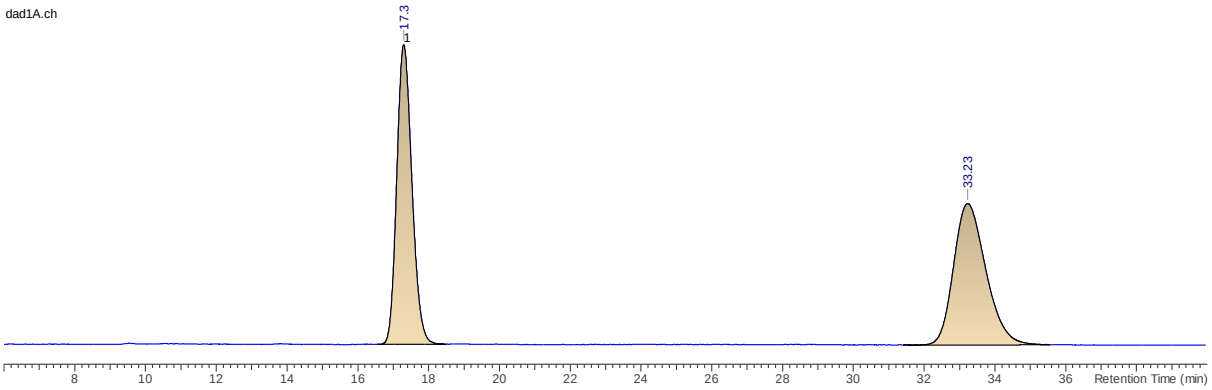


No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	12.64	42114.402	23.827	0.585
2	13.74	134632.922	76.173	0.584

_N_-Cbz-(_S_)-2-p-Tolylsulfanylcarbonylmethyl-pyrrolidine (164)

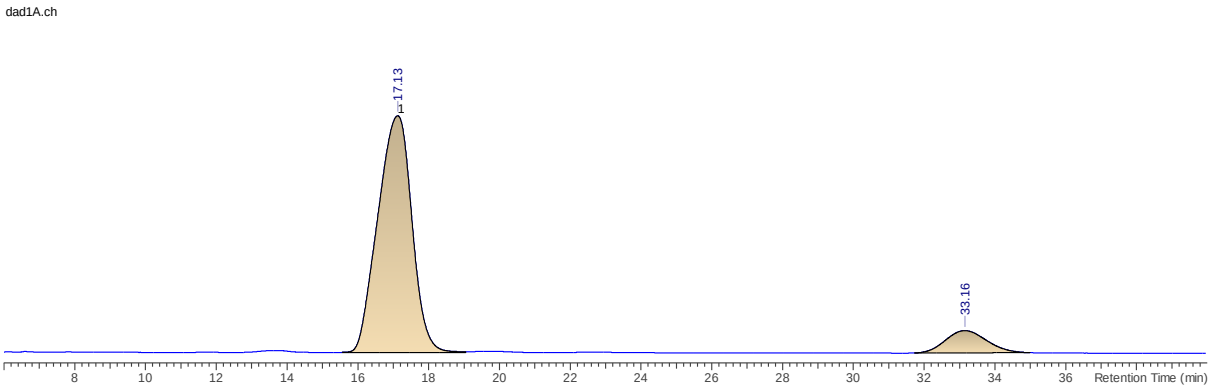


HPLC analysis CHIRALPAK IC column, hexane/2-propanol (80:20), flow rate: 1.0 mL/min, 25 °C, λ = 254 nm; tR 17.1 min (major) and 33.1 min (minor), er = 90:10



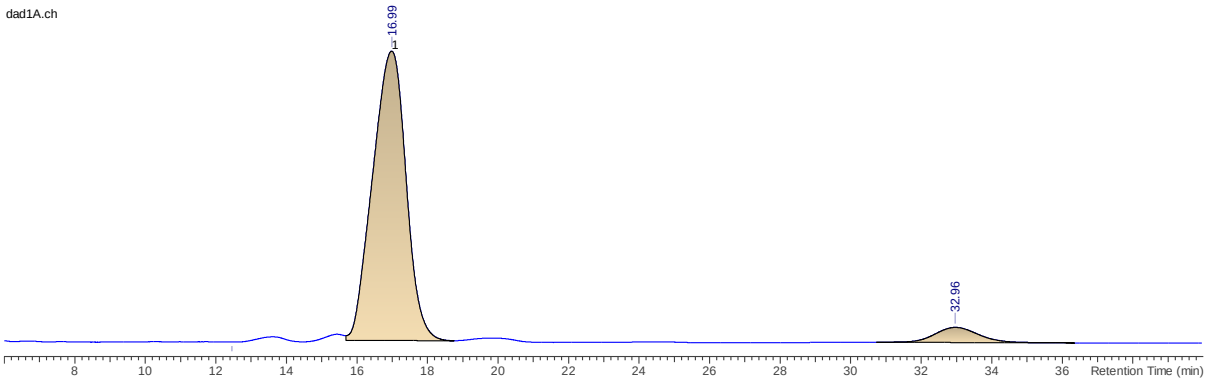
No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	17.30	3642330.000	49.879	0.780
2	33.23	3659963.000	50.121	1.650

(_R_)-TRIP, 80 °C



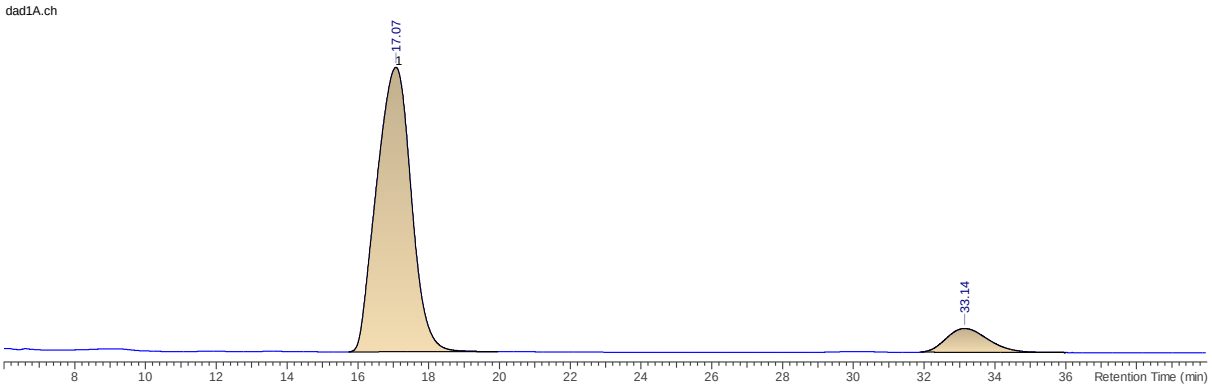
No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	17.13	33881044.000	89.855	1.808
2	33.16	3825307.250	10.145	2.156

(*R*)-TiPSY, 80 °C er = 94:6



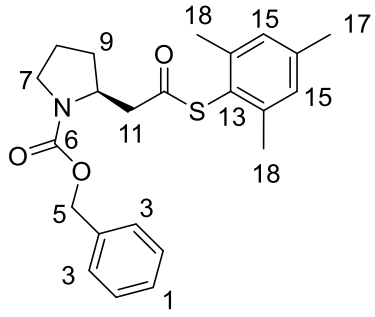
No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	16.99	43907212.000	93.627	1.778
2	32.96	2988478.500	6.373	2.227

(*R*)-TRIP, 50 °C er = 91:9

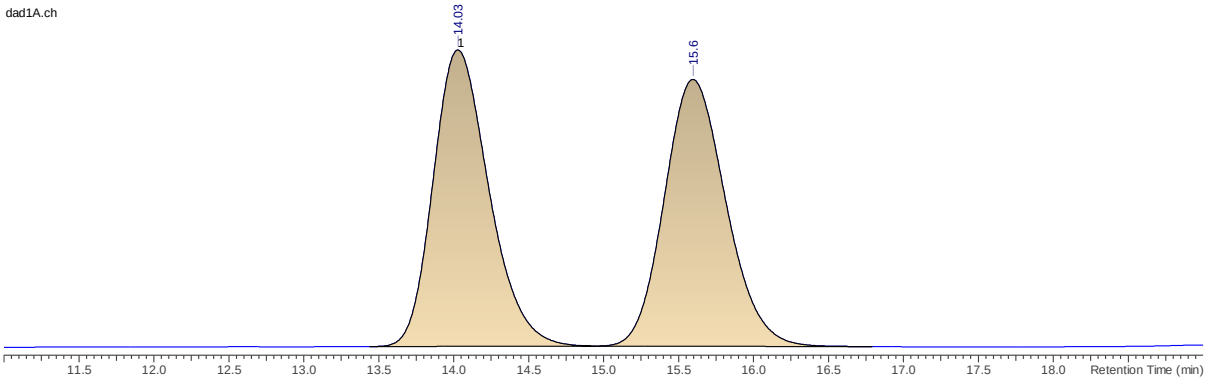


No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	17.07	83726000.000	90.807	1.846
2	33.14	8475707.000	9.193	2.190

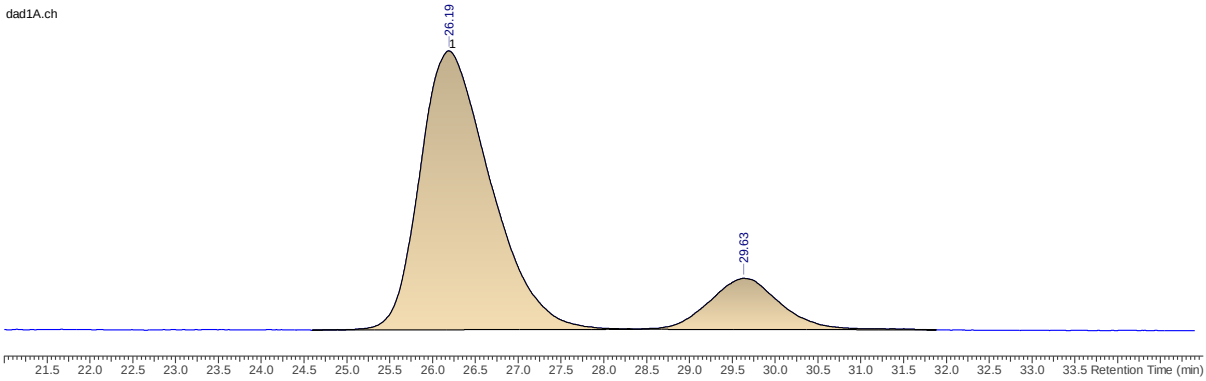
_N_-Cbz-(_S_)-2-(2,4,6-Trimethyl-phenylsulfanylcarbonylmethyl)-pyrrolidine (166)



HPLC analysis CHIRALPAK IB column, hexane/2-propanol (97:3), flow rate: 1.0 mL/min, 25 °C, λ = 254 nm; tR 14.0 min (major), 15.6 min (minor), er = 84:16

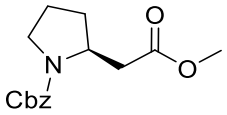


No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	14.03	4092547.250	50.141	0.675
2	15.60	4069504.000	49.859	0.751

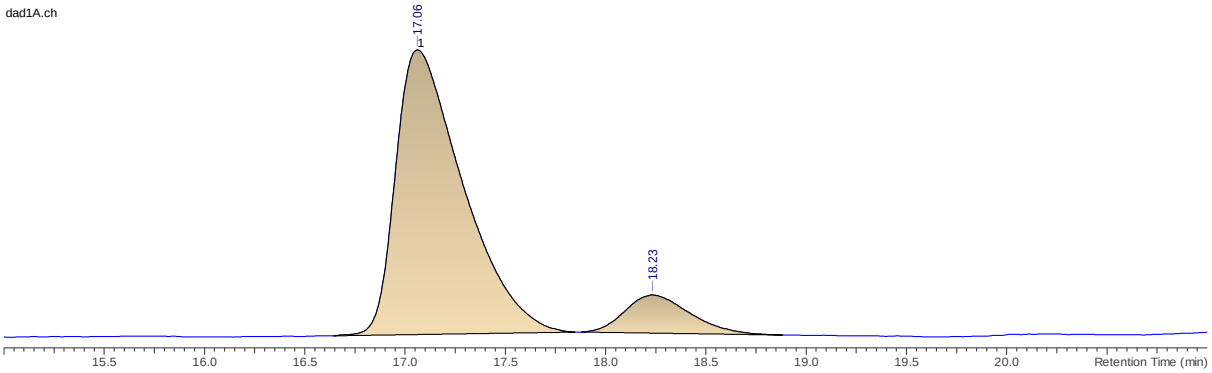


No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	26.19	3932123.500	84.434	1.496
2	29.63	724938.438	15.566	1.476

_N_-Cbz-(_S_)-2-Methoxycarbonylmethyl-pyrrolidine (169)

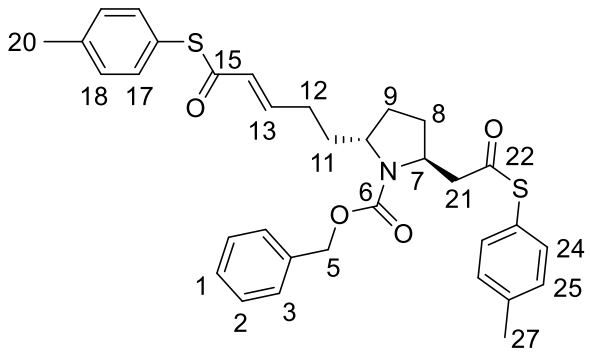


HPLC analysis CHIRALPAK IB column, hexane/2-propanol (99:1), flow rate: 1.0 mL/min, 25 °C; tR 17.1 min for (S)-enantiomer (major) and 18.2 min for (R)-enantiomer (minor), er = 89:11

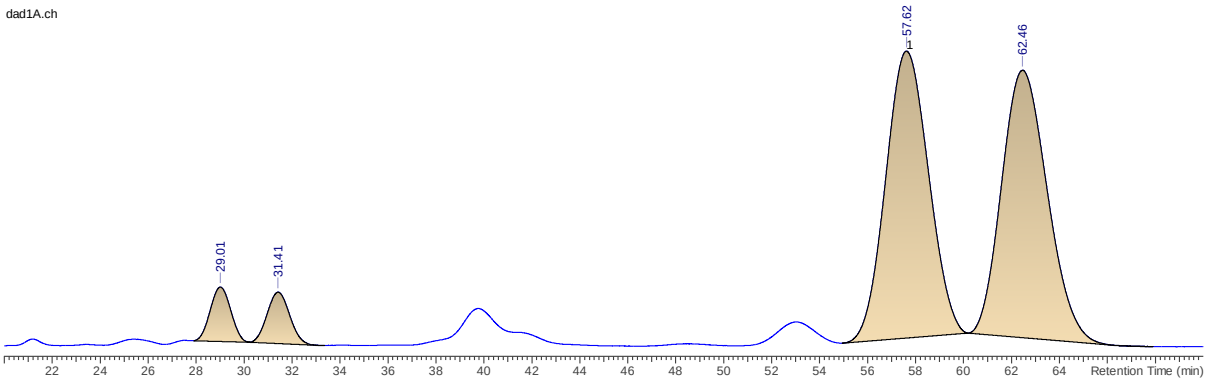


No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	17.06	312242.625	88.576	0.608
2	18.23	40272.551	11.424	0.594

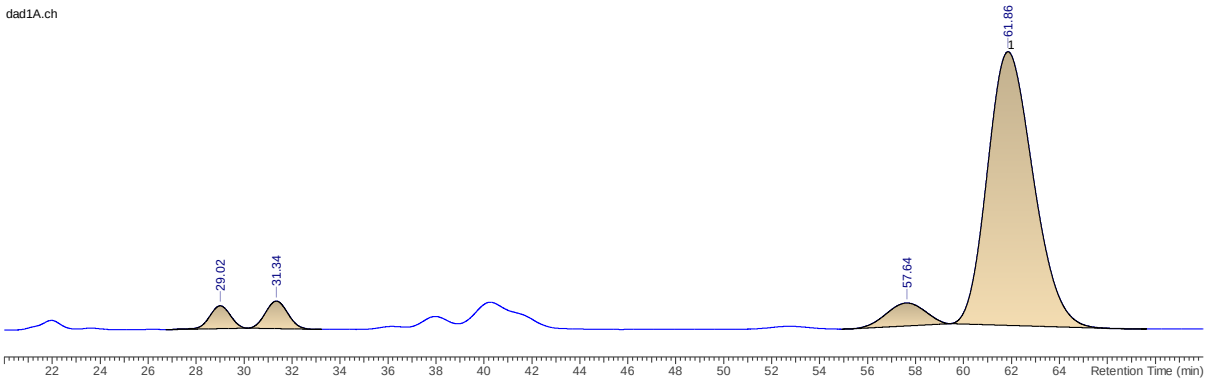
N-Cbz-(*R*)-2-(4-p-Tolylsulfanylcarbonyl-but-3-enyl)-(*S*)-5-p-tolylsulfanylcarbonylmethyl-pyrrolidine (279)



HPLC analysis CHIRALPAK IG column, hexane/2-propanol (50:50), flow rate: 0.7 mL/min, 25 °C, λ = 254 nm; tR 29 min (minor diastereomer, minor enantiomer), 31 min (minor diastereomer, major enantiomer), 58 min (major diastereomer, minor enantiomer) and 62 min (major diastereomer, major enantiomer), dr 92:8, major er: 93:7, minor er: 56:44).



No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	29.01	510349.719	4.152	1.611
2	31.41	530868.500	4.319	1.745
3	57.62	5641569.000	45.899	3.349
4	62.46	5608441.500	45.630	3.531



No.	tR	Peak Area (Y units*ms)	Area Percent	Width
1	29.02	444878.438	3.280	1.600
2	31.34	574038.750	4.232	1.736
3	57.64	834827.313	6.155	3.106
4	61.86	11709307.000	86.332	3.516

10. Abbreviations

(*R*)-anth	(*R*)-3,3'-Bis(9-anthracenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate
(*R*)-phe	(*R*)-3,3'-Bis(9-phenanthryl)-1,1'-binaphthalene-2,2'-diyl hydrogen phosphate
(*R*)-TiPSY	(*R*)-3,3'-Bis(triphenylsilyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate
(*R*)-TRIP	(*R*)-3,3'-Bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate
1,2-DCE	1,2-dichloroethane
4Å MS	4 Ångström molecular sieves
Ac	acetyl
AIBN	azobisisobutyronitrile
APCI	atmospheric pressure chemical ionization
aq	aqueous
Ar	aryl
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Boc	tert-butyloxycarbonyl
bp	boiling point
Bu	n-butyl
Bz	benzoyl
Cbz	carboxybenzyl
conv	conversion
COSY	correlated spectroscopy
CuTC	copper(I)-thiophene-2-carboxylate
Cy	cyclohexyl
d	doublet
DAST	diethylaminosulfur trifluoride
DIBAL-H	diisobutylaluminium hydride
DIPT	diisopropyl tartrate
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethylsulfoxide
DPP	diphenyl hydrogen phosphate
DPPA	diphenylphosphoryl azide
dr	diastereomeric ratio
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
ee	enantiomeric excess
eq.	equivalents
er	enantiomeric ratio
ESI	electrospray ionisation
Et	ethyl
FDA	U.S. Food and Drug Administration
Fmoc	fluorenylmethyloxycarbonyl chloride
gem	geminal

HIV	human immunodeficiency virus
HMBC	heteronuclear multiple bond coherence
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
IC50	half maximal inhibitory concentration
i-Pr	isopropyl
IR	infra-red
J	coupling constant (Hz)
KHMDS	potassium bis(trimethylsilyl)amide
LC50	median lethal concentration
LCMS	liquid chromatography mass spectrometry
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
m	multiplet
*m*CPBA	*m*-chloroperoxybenzoic acid
Me	methyl
Mes	mesityl (1,3,5-trimethylbenzene)
Mp	melting point
Ms	mesyl
MTBE	methyl *tert*-butyl ether
NBS	*N*-bromosuccinimide
n-Bu	*n*-butyl
NMR	nuclear magnetic resonance
Ns	*p*-nitrobenzenesulfonyl
Ph	phenyl
PMP	*p*-methoxyphenyl
Pr	propyl
q	quartet
rac-CSA	racemic camphorsulfonic acid
rt	room temperature
s	singlet
sat	saturated
s-Bu	sec-butyl
t	triplet
TBACl	tetrabutylammonium chloride
TBAF	tetrabutylammonium fluoride
t-Bu	tert-butyl
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl
µW	microwaves

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