An Asymmetric Approach Towards 3-Spiropiperidines

Saikiran Ravi

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University of York

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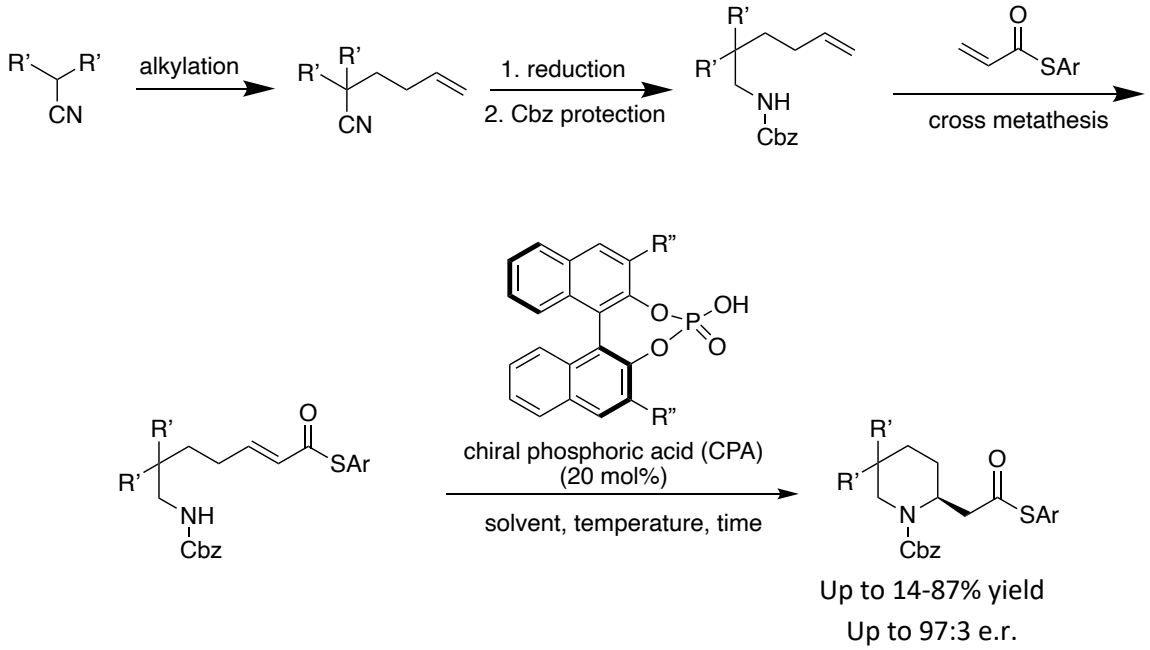
Abstract

In the last few years, asymmetric intramolecular aza-Michael cyclisations have become a well-established method in the synthesis of nitrogen heterocycles. Chiral phosphoric acids (CPA) are known to be versatile catalysts in a variety of asymmetric reactions and have provided access to enantioenriched scaffolds present in natural products and pharmaceutical drugs. Previous work in the Clarke group established the crucial role played by thioesters as Michael acceptors in the aza-Michael reactions catalyzed by CPA resulting in high yields and enantioselectivities in the synthesis of substituted pyrrolidines. The work presented in this thesis expands on the methodology for the synthesis of substituted piperidines. Extensive optimization was required to increase the yield and maintain high enantioselectivity of the piperidines formed. Each of the changes in the thioester functionality, ring substitution, catalyst, time, temperature, and solvent affected the outcome of the reaction and were used to arrive at the final optimized reaction conditions. The methodology was then applied to synthesize a range of 3-spiropiperidines from readily available starting materials resulting in good yields and excellent enantioselectivities (Scheme 1).



Scheme 1 : Asymmetric synthesis of 3-spiropiperidines

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Declaration

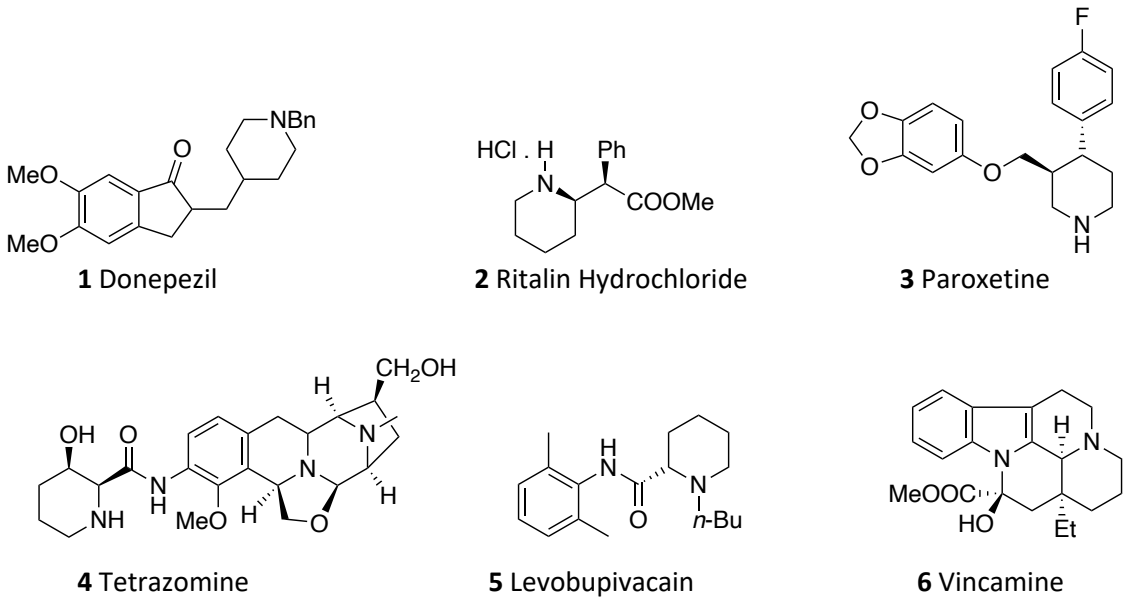
I declare that this thesis is a presentation of original work and I am the sole author. This work has not previously been presented for an award at this, or any other, University. All sources are acknowledged as References.

1. Introduction

1.1 Pharmaceutical relevance of piperidines

Natural products are a source of structural and chemical diversity and have inspired advances in drug discovery.[1] They play an invaluable role in the discovery of drugs particularly in the areas of cancer and infectious diseases.[2] It is reported that around 35% of all medicines have their origins in natural products.[3] A report on the compiled database of all the US FDA approved pharmaceuticals, revealed that nitrogen heterocycles are common drug scaffolds. Out of 1086 unique small molecule drugs, 910 (84%) contained at least one nitrogen atom, while 640 (59%) contained at least one nitrogen heterocycle. Among the 640 pharmaceuticals containing a nitrogen heterocycle, piperidine was found to be the most prevalent, present in a total of 72 of the unique small-molecule drugs, followed by pyridine and piperazine which were a close second and third respectively.[4] While piperidines are the most prevalent nitrogen heterocycles in pharmaceutical compounds, they are also considered the second most common ring systems found in small drug molecules, along with pyridine with benzene being the first.[5]

Piperidines are very useful structural units in pharmaceutical products and they act as linkers between biologically active units or to improve the pharmacokinetic properties of the drug (increasing the *in vivo* solubility and reducing logD values. LogD is a distribution coefficient to measure the lipophilicity of ionizable compounds, where the partition is a function of the pH). They are also incorporated to provide extended H-bonding networks for efficient binding.[6] Some of the functionalised piperidines that are present in pharmaceutical agents and natural products are illustrated in Figure 1. Donepezil **1** is used for the treatment of Alzheimer's disease[7], while Ritalin hydrochloride **2** is administered for the treatment of ADHD in children.[8] Paroxetine **3** has anti-depressant properties,[4] tetrazomine **4** has antitumour and antibiotic properities,[9] levobupivacain **5** is administered as a local anaesthetic drug[10] while vincamine **6** is used for the treatment of primary degenerative and vascular dementia[11] (Figure 1).



1 Donepezil **2** Ritalin Hydrochloride **3** Paroxetine

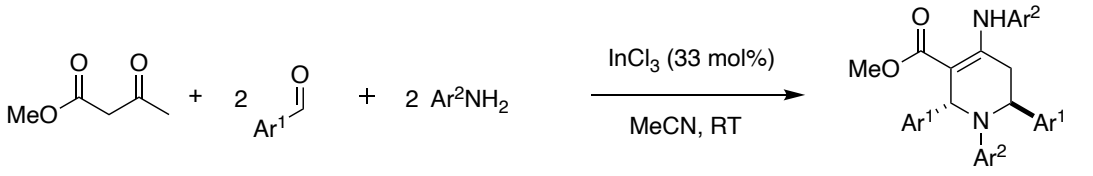
4 Tetrazomine **5** Levobupivacain **6** Vincamine

Figure 1 : Structures of compounds containing piperidine moieties

Studies show that 1,4-substituted piperidines are more prevalent (39%) among the disubstituted piperidines in pharmaceutical compounds[4] owing to the ease of synthesis and the absence of complicating stereochemical issues.[12] It has been found that 2- and 3-substituted piperidines are the fundamental units of many biologically relevant and pharmaceutical compounds. The synthesis of racemic piperidines is well known, but catalytic enantioselective synthesis of piperidine derivatives, especially the 3-substituted, are challenging.[13] Herein, different racemic and asymmetric methods of synthesis of piperidines will be discussed.

1.2 Synthesis of racemic piperidines

Synthesis of heterocycles has been an integral part of the Clarke group's research and it has been applied in the total synthesis of natural products.[14–18] A five-component condensation reaction involving methyl acetoacetate along with an aldehyde and aniline was reported to result in highly substituted piperidines in a pot, atom and step economic (PASE) method (Scheme 2).[19] Aromatic aldehydes with electron donating and withdrawing groups were reacted under the conditions and found to result in high yields. Precipitation of the piperidines from the reaction led to the smooth and easy isolation of the products.



7 **8** **9** **10**

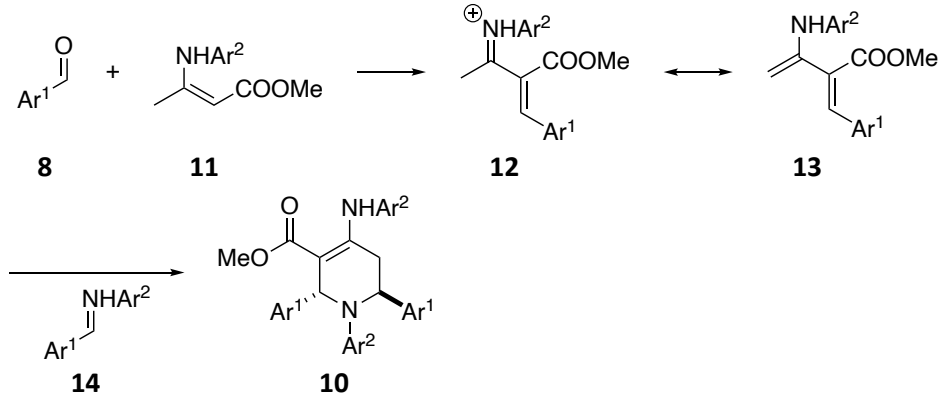
Up to 74% yield

Ar^1 = Ph, 4-$OMeC_6H_4$, 4-$MeO_2CC_6H_4$, 4-$NO_2C_6H_4$, *p*-tolyl, 3-MeC_6H_4, 2-MeC_6H_4, 3- $CF_3C_6H_4$

Ar^2 = Ph, 4-$OMeC_6H_4$, 4-ClC_6H_4,

Scheme 2 : Five component PASE synthesis of piperidines

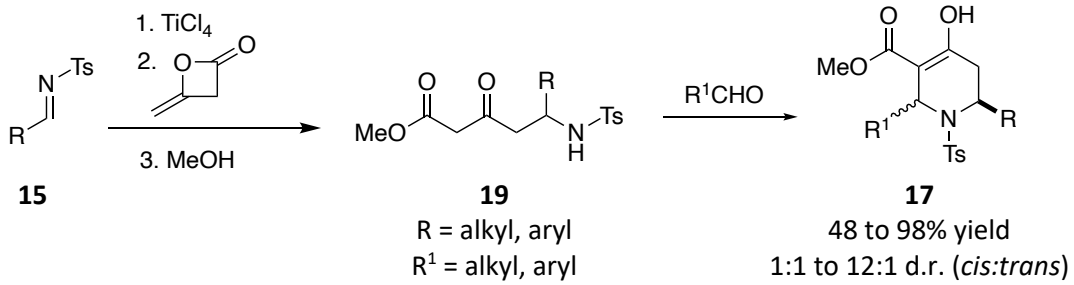
The reaction was catalysed by Lewis acid $InCl_3$ and is assumed to proceed via formation of enamine **11** and imine **14**. The enamine **11** reacts with the aldehyde to form the iminium ion-Knoevenagel product **12** which forms **13** after tautomerization. This then reacts with imine **14** to form the piperidine **10** (Scheme 3).



8 **11** **12** **13** **14** **10**

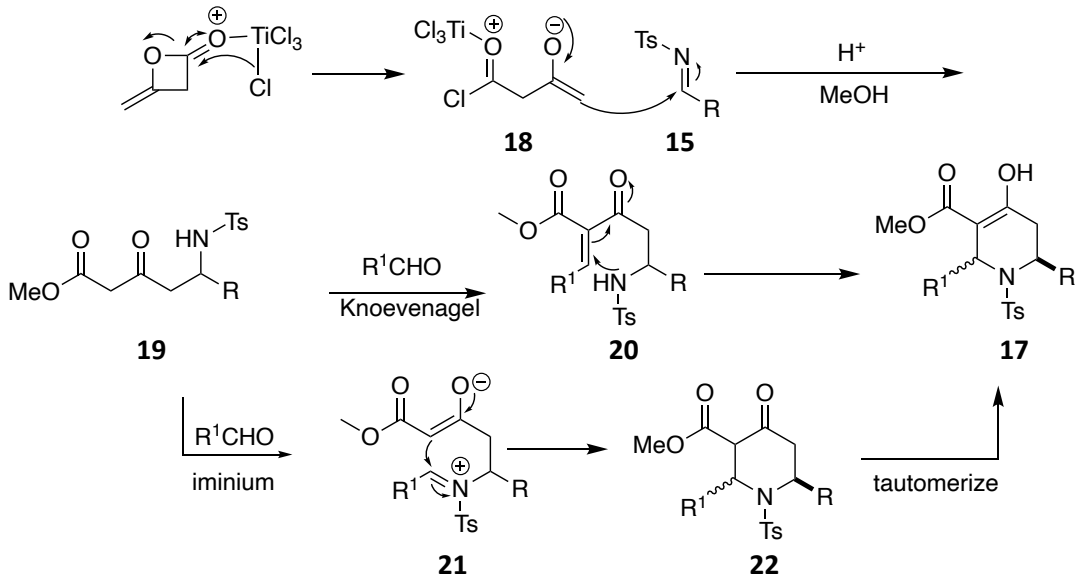
Scheme 3 : Possible mechanism for the PASE synthesis of piperidines

The group then reported a four component one-pot synthesis of 2,6-disubstituted piperid-4-ones [20] which utilised diketene as the nucleophile. [21] The diketene reacted with imine **15** in the presence of $TiCl_4$ to form the Mannich product **19**. This was followed by addition of the aldehyde and cyclisation to form a wide range of substituted piperid-4-ones **17** in high yields (Scheme 4). [20]



Scheme 4 : Four component one pot PASE synthesis of piperid-4-ones

The mechanism commences by activating the diketene by Lewis acid $TiCl_4$ to form **18** which reacts with the imine **15** to form the adduct **19** in the presence of MeOH. It was proposed that the addition of the aldehyde followed by cyclisation to form **17** could go *via* two pathways. It could either react through Knoevenagel condensation and forming intermediate **20** followed by Michael addition to yield **17** or form an iminium ion **21** followed by a Mannich-like attack of the enol form of the ester forming **22**, leading to **17** after tautomerisation (Scheme 5).

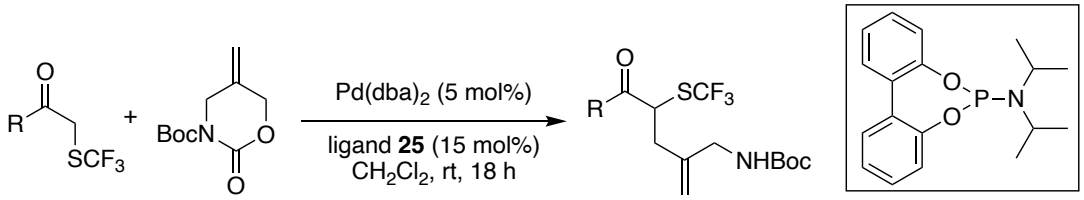


*Scheme 5 : Plausible pathways for the one-pot synthesis of **17** using diketene as the nucleophile*

The reaction was carried out in the presence of aryl and alkyl aldehydes leading to moderate diastereoselectivity with excellent yields for most of the substrates. While the asymmetric synthesis was not attempted, the reaction was developed to be a robust and pot, step and atom economic (PASE) synthesis of highly functionalised piperidines which is a greener approach to access these motifs, making it an attractive method for large scale synthesis.

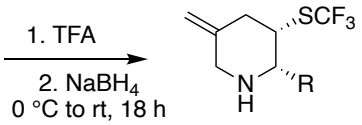
The strong electron-withdrawing power and high lipophilicity exhibited by the SCF_3 group,[22] is known to influence the pharmacological properties in a molecule, and thus are found frequently in pharmaceutical and agrochemical compounds. [22] Harrity and co-workers reported an efficient method to 3-trifluoromethylthio-piperidines in high yields and diastereoselectivities which are important building blocks in drug discovery processes. The method involved a palladium catalysed [4+2] annulation strategy using α-SCF_3 ketones.[23] The strategy began with the allylation-condensation sequence between α-SCF_3 ketones **23** and cyclic carbamate **24** in the presence of $Pd(dba)_2$ and phosphoramidite ligand **25** which reacted smoothly to form the adduct **26**. This was followed by Boc deprotection in the presence of TFA, generating a range of SCF_3 substituted piperidines which were reduced using $NaBH_4$ for smooth isolation and purification (Scheme 6).

Various aryl ketones were subjected to the reaction conditions and products were obtained in high yields, and excellent diastereoselectivities preferring *cis*-selectivity. The reaction was found to be unsuccessful on using ketones with electron-withdrawing groups like 4-nitrophenyl and 4-trifluoromethylphenyl and these reactions led to decomposition in the presence of TFA. One example of an alkyl ketone with ethyl substituent was also carried out but resulted in low yield and selectivity (43%, 3:1 d.r.). While the reaction was successful in the rapid synthesis of functionalised piperidines under mild conditions, the asymmetric version was not explored.



23 **24** **26** ligand **25**

R = Ph, *p*-tolyl, 4-C_6H_4OMe, 2-C_6H_4OMe, 4-C_6H_4Cl, 3-C_6H_4Cl, thiophen-2-yl, Et

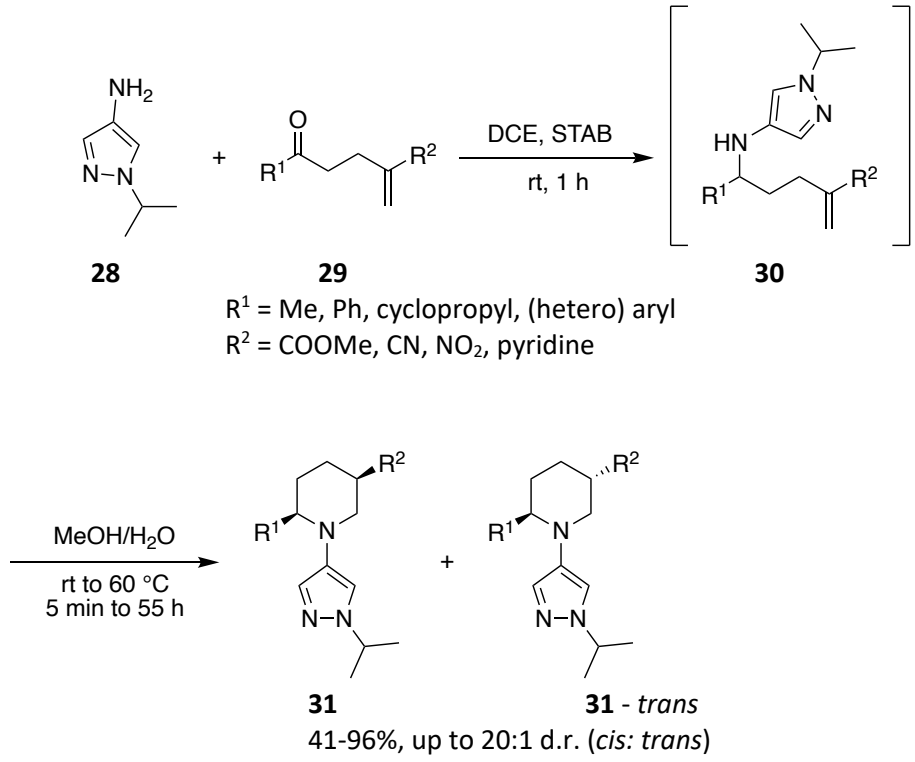


27

Up to 76% yield over three steps
Up to 98:2 d.r.

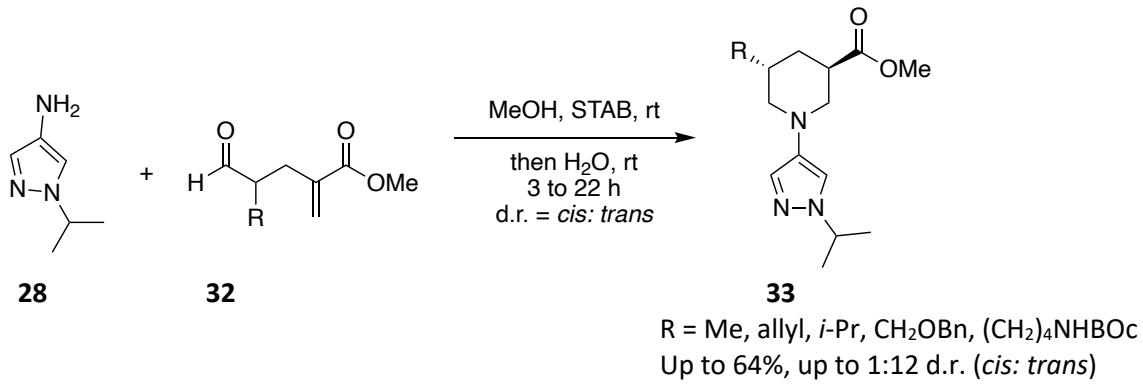
Scheme 6 : Synthesis of SCF_3 substituted piperidines

Recently, researchers at Merck developed a reductive amination/aza-Michael reaction that formed a variety of *N*-aryl and *N*-heteroaryl piperidines with good to excellent yields with diastereoselectivity up to 20:1 d.r.[24] Substrates **28** and **29** underwent reductive amination readily in the presence of sodium triacetoxyborohydride (STAB) in 1,2-dichloroethane (Scheme 7). Excess STAB was quenched with NaOH and on performing a solvent-swap to MeOH/H_2O the aza-Michael cyclisation yielded the substituted piperidine in moderate to excellent yields with diastereoselectivities up to 20:1 d.r. favouring the *cis*- isomer over the *trans* (Scheme 7). The reaction was tolerant to aliphatic ketones and acetophenone derivates. Along with α-β unsaturated esters, the reaction was also successful with cyanoalkenes, nitroalkenes and 2-vinylpyridines, thus exploring the substrate scope on the C-5 position of the piperidine ring.



Scheme 7 : Synthesis of 2,5-cis-piperidine with different ketone and ester substitutions

Extension of the methodology towards substrates containing substituted aldehydes **32** were successful in synthesising 3,5-disubstituted piperidines **33** (Scheme 8). The reductive amination reaction was carried out in MeOH and the next step took place by addition of water, making it a one pot reaction. Although the reaction was successful with different aldehyde substitutions, the major diastereomer was the *trans* isomer rather than the *cis* which was obtained in the method shown in Scheme 7.



Scheme 8 : Substrate scope with different aldehydes

To explain the observed opposite stereoselectivity when using ketone and aldehyde derivatives of the Michael acceptor, the conformations of exocyclic enol intermediates **35** and **38** from the aza-Michael reactions of intermediates **34** and **37** respectively, were analysed using Density Function Thery (DFT)/M06-2X /6-31G**.[25,26] When water molecules were included to account for the hydrogen bonding with the solvent, and Me groups placed in equatorial positions for the lowest energy conformation, the observed diastereoselectivities were explained. The enol protonated equatorially in **35** and **38** due to steric hindrance arising from hydrogen bonding in the axial position in the chair conformations respectively. This led to a *cis*-selective protonation of **35** and a *trans*-selective protonation of **38**, forming **36** and **39** respectively. Thus the protonation of the water-coordinated enol-intermediate was proposed to be the stereo-determining step of the reaction (Figure 2).

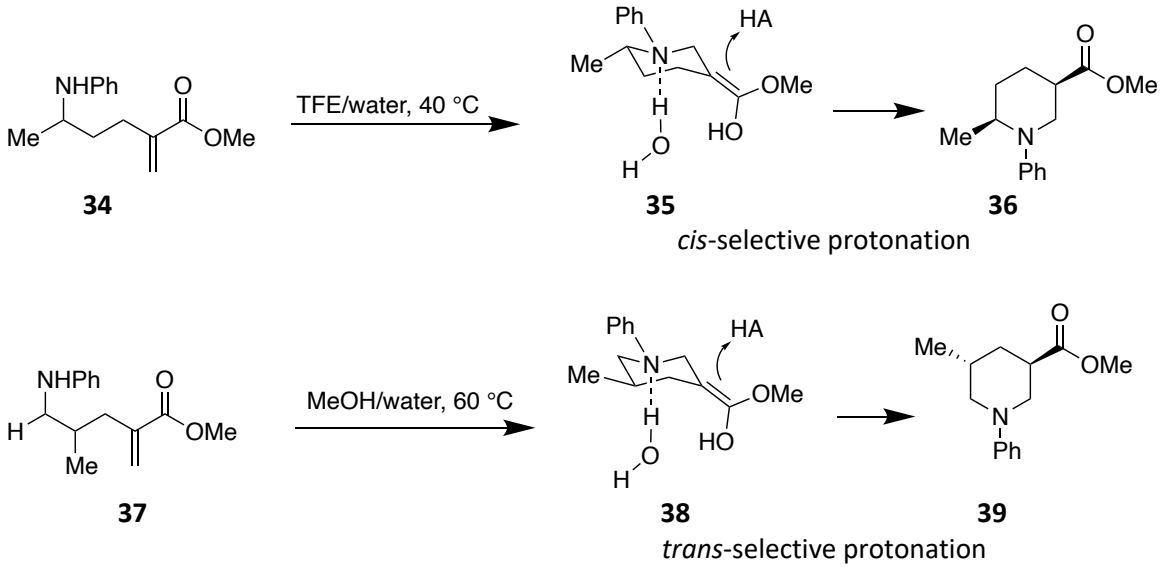
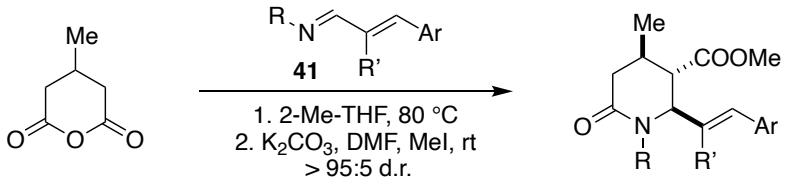


Figure 2 : Stereochemistry elucidation of the cis vs trans piperidines

The reaction was also extensively explored to incorporate different *N*-protecting groups furnishing a wide scope of *N*-aryl and *N*-heteroaryl substituted piperidines which led to medicinally relevant scaffolds. The reaction can be further optimised to improve the diastereoselectivities while also extending it to the asymmetric model to yield compounds with high enantiopurity which are valuable tools in the synthesis of pharmaceutical compounds.

Functionalised 2-oxopiperidines with three contiguous stereocenters **42** were synthesised by Beng and co-workers, based on the stereocontrolled annulation of 1,3-azadiene **41** with 3-methylglutaric anhydride **40** (Scheme 9).[27] The reaction was performed using 2-methyltetrahydrofuran (2-MeTHF) as the solvent. For the ease of purification and characterisation, the initially formed carboxylic acid was converted into the corresponding methyl ester.

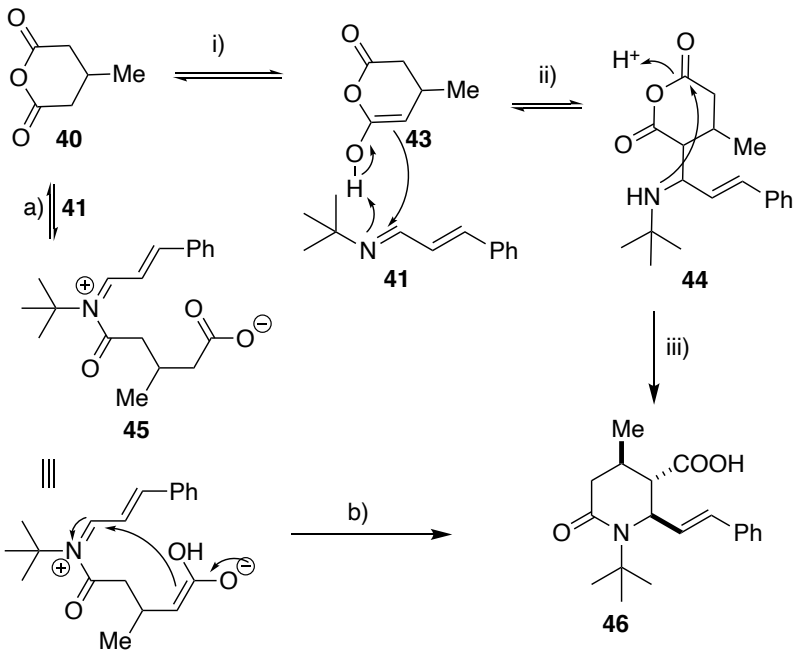


40 R = *t*-Bu, *i*-Pr, allyl, PMP, *p*-tolyl, Ph
R' = H, Me
Ar = Ph, PMP, PNP, 2-OMeC_6H_4, 2-$NO_2C_6H_4$, 4-IC_6H_4, 3-Cl-4-IC_6H_3, 3-$CF_3C_6H_4$,

42
Up to 87% yield
>95:5 d.r.

*Scheme 9 : Annulation of anhydride **40** with azadiene **41***

Studies in the substrate scope revealed that the 1,3-azadienes with electron-donating and electron-withdrawing styryl groups resulted in high yields with with >95:5 d.r. Different *N*-aryl-1,3-azadienes and tri substituted alkenes were also explored which also gave similar results. The reaction resulted in high stereoselectivity at the C-4 position and a high chemoselectivity through the Castagnoli-Cushman reaction in an anhydride-imine pathway. The authors proposed that the reaction proceeds via either of two pathways. The first one involved tautomerization of anhydride **40** [Figure 3 (i)] under thermal conditions to enol **43** which upon Mannich-type addition [Figure 3 (ii)] with **41**, affords **44**. Attack of the secondary amine on the carbonyl carbon leads to an intramolecular aminolysis [Figure 3 (iii)] giving rise to the lactam **42**. The other pathway involves an intermolecular iminolysis of the anhydride with azadiene [Figure 3 (a)] leading to formation of **45** followed by intramolecular Mannich-type addition [Figure 3 (b)], leading to **46**. This was then converted into the corresponding methyl ester **42.**



i) tautomerisation, ii) intermolecular Mannich-type addition, iii) intramolecular aminolysis
a) intermolecular iminolysis, b) intramolecular Mannich-type addition

*Figure 3 : Proposed mechanism for the synthesis of lactam **42***

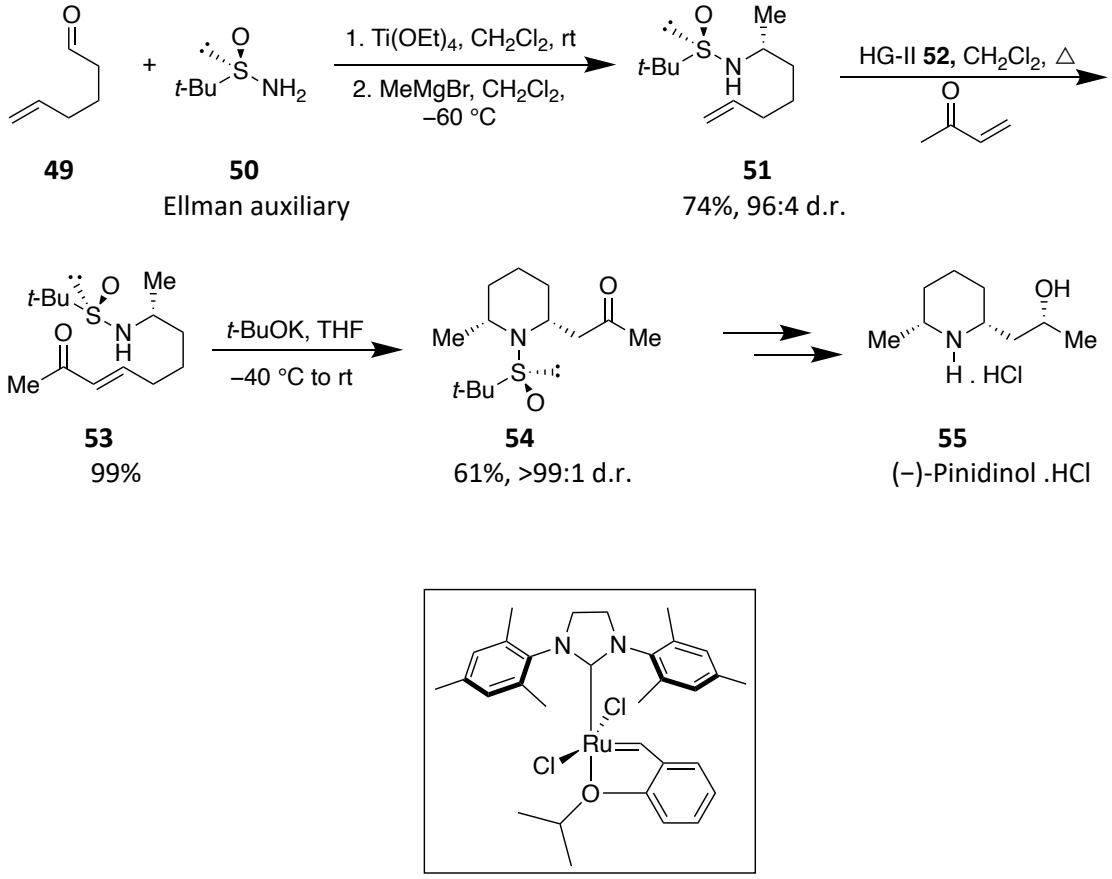
The reaction was proved to be scalable, efficient, versatile and fulfilled pot-step-atom economy criteria and the 2-oxopiperidine products were diversified into desirable scaffolds of pharmaceutical relevance. The asymmetric methodology of this reaction, though unexplored, would also be a very useful tool for both synthetic and medicinal chemists alike.

1.3 Using chiral auxiliaries

The use of a chiral auxiliary involves a temporary introduction of a chiral compound in a molecule that can control the stereochemical outcome of the reaction and is removed at later stages in the synthesis. The temporary chiral compound introduced by the auxiliary helps to direct the chirality at the new stereocenter formed, resulting in the formation of diastereomers, which can be easily separated as they have different physical properties. Different chiral auxiliaries have been used for the synthesis of piperidine containing compounds like the readily available (+)-(*S,S*)-pseudoephedrine **47** which was used for the total synthesis of (*S*)-conine hydrochloride[28] and oxazolidinone type chiral auxiliary **48** for the synthesis of the core motif of the marine-derived alkaloid sarain A[29] (Figure 4).

Figure 4 : Chiral auxiliaries used for the total synthesis of piperidine containing motifs

N-Sulfinyl amines can be good nitrogen-centered nucleophiles as well as useful *S*-chiral auxiliaries as they are readily removed under acidic conditions. Fustero exploited this in the synthesis of chiral substituted piperidines leading to the total synthesis of natural product (−)-pinidinol hydrochloride **55** by using the Ellman auxiliary **50** (Scheme 10).[30] Following the condensation of 5-hexenal with *N*-sulfinyl amine **50** and addition of methyl magnesium bromide, amine **51** was obtained in 74% yield with an excellent selectivity of 96:4 d.r. Cyclisation precursor **53** was obtained in excellent yield under cross metathesis conditions with methyl vinyl ketone in the presence of Hoveyda Grubbs 2nd generation catalyst (HG-II) **52**. Deprotonation with *t*-BuOK at −40 °C yielded 2,6-*cis*-disubstituted piperidine **54** in excellent diastereoselectivity. The relative *cis* stereochemistry of the newly formed stereocenters was confirmed by NOE experiments. This showed that the sulfinyl group played an important role in inducing chirality in the molecule with the sterically bulky *t*-Bu groups blocking the top face so that the cyclisation takes place from the bottom face leading to the desired stereochemistry. The piperidine ring thus formed underwent further transformations to form the HCl salt of (−)-pinidinol **55** (Scheme 10).



49 **50** **51**

Ellman auxiliary

74%, 96:4 d.r.

53 **54** **55**

99% 61%, >99:1 d.r. (−)-Pinidinol .HCl

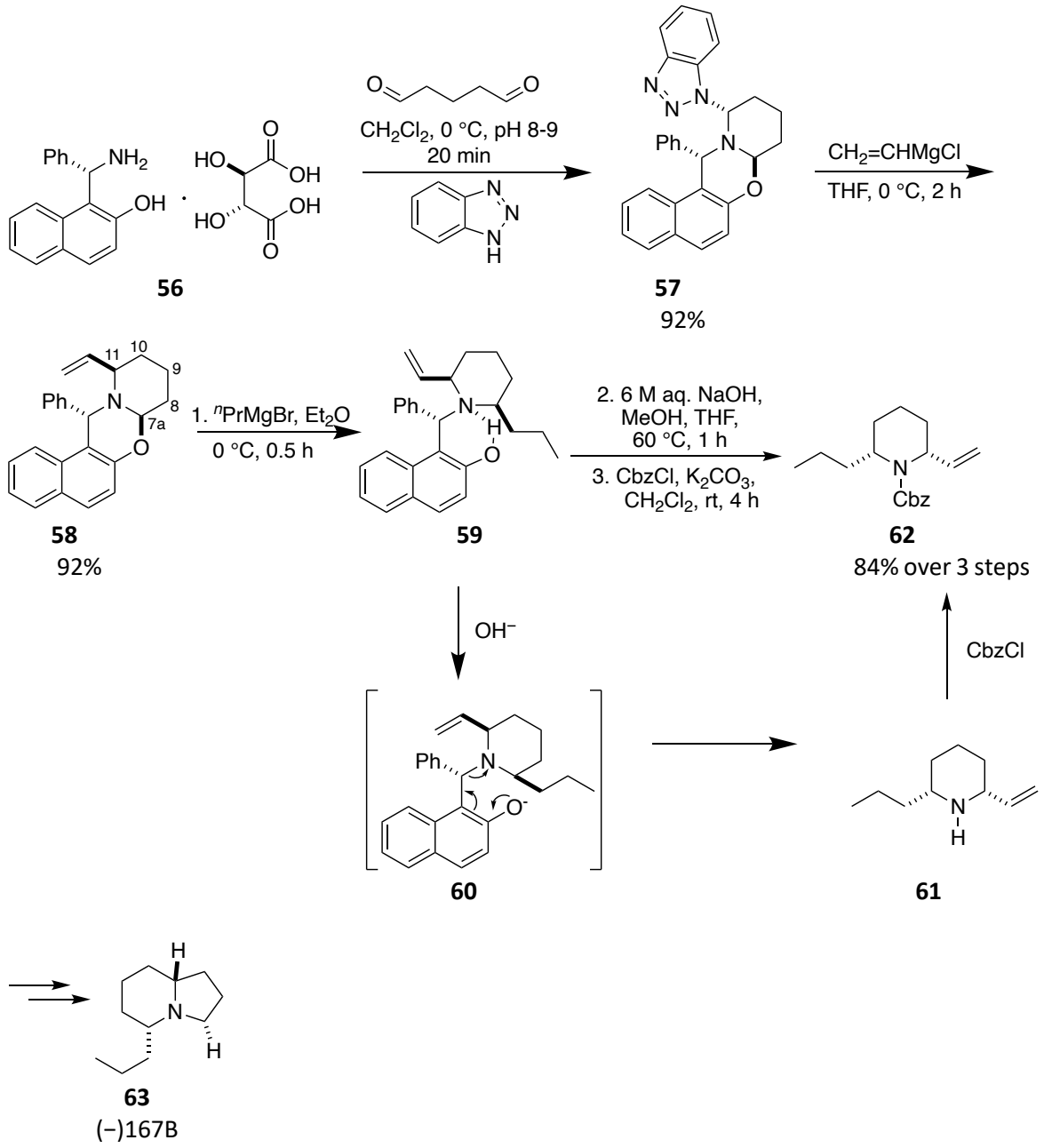
52

Hoveyda Grubbs 2nd generation catalyst (HG-II)

Scheme 10 : N-sulfinyl amines as a chiral auxiliary and N-nucleophile

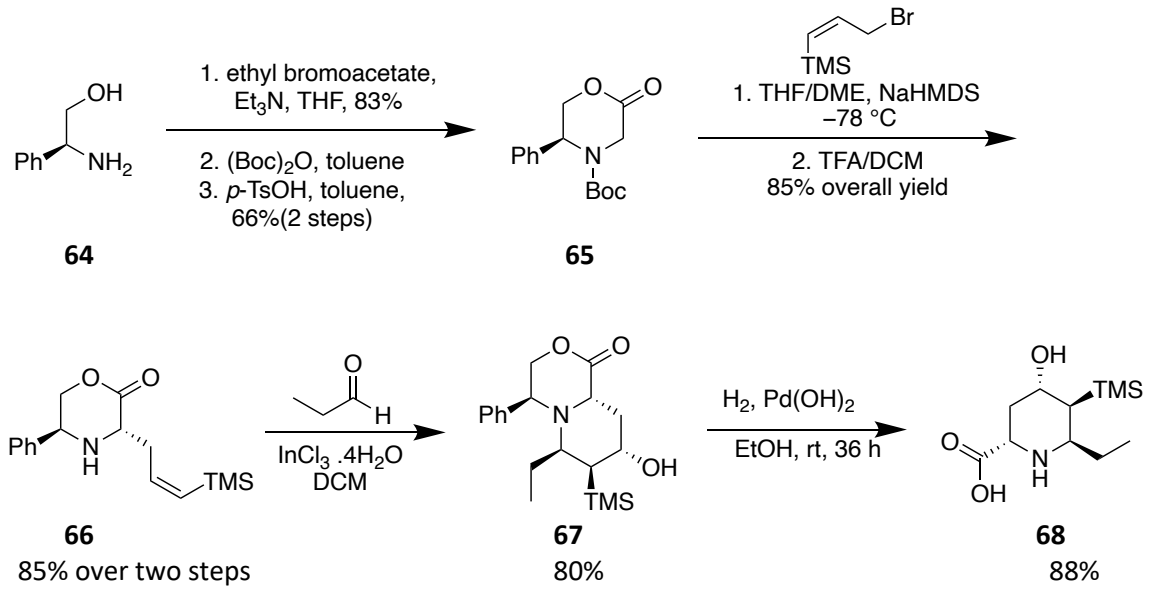
Another efficient procedure to synthesise 2,6-*cis*-disubstituted piperidines bearing an alkene or alkyne substituent used non-racemic Betti base as the chiral auxiliary. The advantage of this methodology was that the chiral auxiliary was removed under non-hydrogenative *N*-debenzylation conditions which allowed the synthesis of alkene substituted piperidines. This method was then extended to the asymmetric total synthesis of indolizidine alkaloids (−)167B **63** (Scheme 11).[31] In this method, the salt of (*S*)-Betti base with L-(+)-tartaric acid **56** was condensed with pentane-1,5-dial and benzotriazole to yield the product **57** as a single diastereomer. The high diastereoselectivity was proposed to be due to the sterically bulky naphthalene unit and the high reactivity of the hydroxyl group in the naphthol moiety of the Betti base.[32] Grignard addition of **57** resulted in an S_N2 substitution to form alkene substituted product **58** obtained as a single diastereomer in 92% yield. This reaction was found to be regioselective depending on the solvent and temperature. In the presence of THF, monoalkylation at C-11 occurred while Et_2O as the

solvent resulted in dialkylation at C-7a and C-11.[31,32] The reaction proceeded smoothly at 0 °C to furnish the single diastereomer, while higher temperatures of 25 °C resulted in a complex mixture containing predominantly the dimer after purification. Further alkylation in the presence of *n*-PrMgBr followed by base catalysed non-hydrogenative *N*-debenzylation in the presence of NaOH/MeOH resulted in the formation of free amine **61** which was protected to form the Cbz-amine **62** in 84% yield over 3 steps. Upon further transformations, indolizidine alkaloid (−)167B **63** was formed in 83% yield. It was hypothesized that while the first alkylation resulted in an S_N2 type substitution due to solvent effects, the second alkylation went through a planar iminium salt intermediate resulting in a C-C bond formation with a retention in configuration **59**.



*Scheme 11 : Betti base derivative as a chiral auxiliary for the total synthesis of (−)167B **63***

The first example of asymmetric aza-silyl-Prins reaction was reported by Dobbs *et al* which resulted in substituted piperidines being formed as single enantiomers.[33] The synthesis utilized a novel chiral auxiliary homoallylic amine **66** which was prepared from (*S*)-phenyl glycinol **64** in three steps that involved *N*-alkylation, Boc protection of the amine followed by acid catalyzed cyclisation resulting in **65**. Alkylation with (*Z*)-(3-bromoprop-1-enyl) trimethylsilane in the presence of NaHMDS followed by Boc-deprotection led to the synthesis of chiral auxiliary **66**. Aza-silyl-Prins cyclisation of this compound was carried out with propionaldehyde in the presence of indium chloride tetrahydrate as the Lewis acid catalyst resulting in trapping of the intermediate carbocation by water instead of elimination of the silane. The key aspect of the reaction is that it resulted in a single diastereomer and enantiomeric product **67**. Catalytic hydrogenation of the product using Pearlman's catalyst led to the synthesis of pipecolic acid derivative **68** in high yield (Scheme 12).[33]

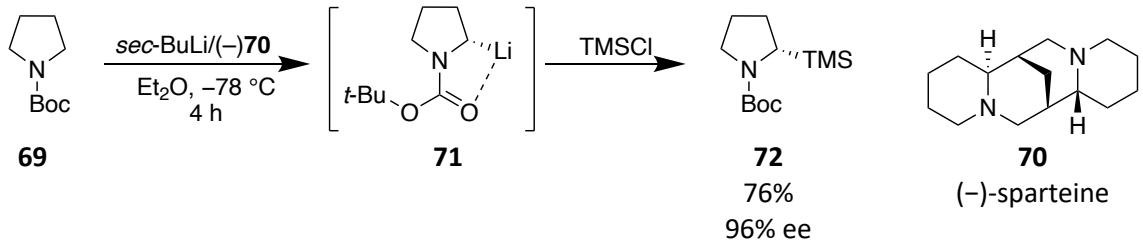


Scheme 12 : Synthesis of pipecolic acid derivatives using asymmetric aza-silyl-Prins reaction

As the chiral auxiliary is not always required in the final product, the use of chiral auxiliaries require extra steps in the overall synthetic route for their introduction as well as removal, making the reaction sequence longer. Since stoichiometric quantities of the chiral auxiliaries are required, they affect the atom economy of the reaction. Oftentimes, the other enantiomer of the chiral auxiliary is not readily available or is far more expensive. This makes it difficult to access selective enantiomers of the target compound.

1.4 Using chiral lithium amide bases

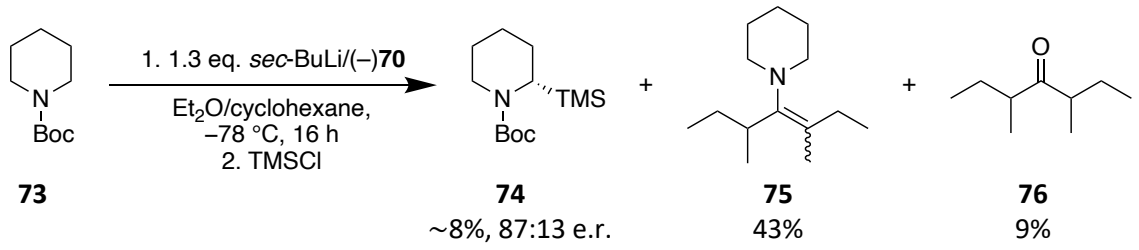
Another method of introduction of the required stereochemistry in a compound can be done using chiral lithium amide bases. These are commonly used lithium amide bases in organic synthesis but contain a stereogenic center. The coordination between lithium and the heteroatom brings the base in close proximity with the substrate and this selectively removes one of two enantiotopic protons, forming a chiral carbanion. Attack of an electrophile results in an enantioenriched compound. Unlike chiral auxiliaries, they don't require a separate step for their removal and thus allow for direct induction of stereochemistry. In the seminal work by Beak and coworkers, *N*-Boc pyrrolidine was asymmetrically deprotonated next to the nitrogen atom in the presence of *sec*-BuLi and (−)-sparteine **70**.[34] The chiral carbanion **71** is stabilized by coordination between the carbonyl oxygen of the Boc group and the Li. This species was trapped with the electrophile TMSCl, resulting in the formation of **72** in 76% yield and an excellent enantioselectivity of 96% ee (Scheme 13).



Scheme 13 : Asymmetric deprotonation of N-Boc pyrrolidine

When this reaction was applied to *N*-Boc piperidines in the presence of *sec*-BuLi and (−)-sparteine **70**, a poor yield of ~8% of the desired product **74** was formed with a reduced enantioselectivity of 87:13 e.r. (Scheme 14) [35]as compared to that with pyrrolidines (Scheme 13).[35] The major product was a mixture of isomeric enamines **75** and 9% of **76**. It was found that the slow rate of the lithiation reaction led to the addition of *sec*-BuLi to the carbamate. Loss of the piperidine ring led to formation of the heptanone **76** while loss of the *t*-butoxide, followed by a second addition of the Grignard reagent and dehydration led to **75**. Computational studies showed that the deprotonation process is slower than that of the analogous reaction with pyrrolidine **69** due to the high activation energy in the

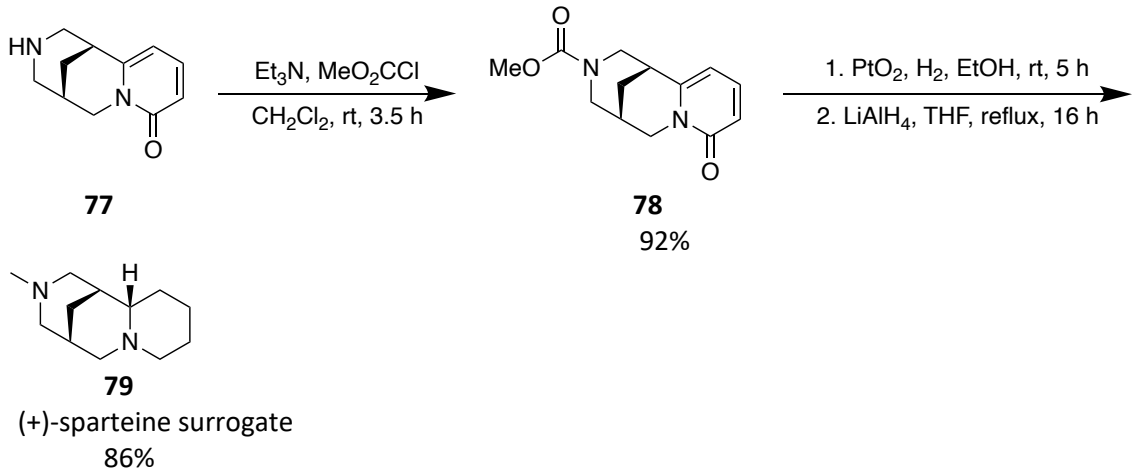
preferential abstraction of the least acidic α-proton in **73**, resulting in the sluggish nature of the lithiation reaction.



73 **74** ~8%, 87:13 e.r. **75** 43% **76** 9%

Scheme 14 : Asymmetric deprotonation of N-Boc piperidine with low yields

O'Brien *et al* reported the synthesis of (+)-sparteine surrogate[36] **79** which was synthesized from the naturally occurring alkaloid (–)-cytisine **77**. The amine was protected using methoxy chloroformate forming the pyridone **78** in 92% yield. Hydrogenation in the presence of Adam's catalyst followed by $LiAlH_4$ reduction yielded the (+)-sparteine surrogate **79** in 86% yield (Scheme 15).



77 **78** 92%

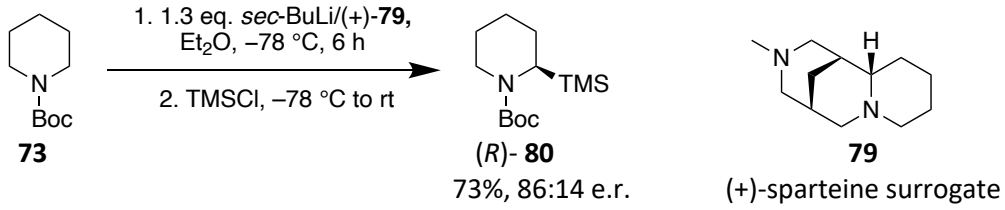
79
(+)-sparteine surrogate
86%

*Scheme 15 : Synthesis of (+)-sparteine surrogate **79***

To probe the feasibility of (+)-sparteine surrogate **79** to function as *ent* (–)-sparteine **70**, *N*-Boc pyrrolidine was asymmetrically deprotonated in the presence of *sec*-BuLi and (+)-sparteine surrogate **79**. It resulted in the same yield and enantioselectivity as obtained with (–)-sparteine but with opposite absolute stereochemistry. This confirmed that (–)-sparteine and of (+)-sparteine surrogate **79** give enantio-complimentary results. This was a very

useful result as (+)-sparteine is not commercially available and attempts to synthesize resulted in limited success.[36]

When this was applied to the lithiation of *N*-Boc piperidine **73** in the presence of *sec*-BuLi and (+)-**79** followed by trapping with Me_3SiCl, compound (*R*)-**80** was formed in 73% yield and 86:14 e.r. (Scheme 16) with better yield and opposite enantioselectivity as obtained with (–)-sparteine in Scheme 14. Thus enantioenriched 2-substituted piperidines were made possible using direct lithiation trapping.[37] In another paper published by the O'Brien group on reactivity of *sec*-BuLi/diamine complexes for lithiation reactions, it was found that *sec*-BuLi/(+)-sparteine surrogate **79** was more reactive that *sec*-BuLi/(–)-sparteine **70**, though the two diamines were similarly sterically bulky.[38] Though chiral lithium amide bases have been successful in the asymmetric lithiation followed by further transformations to synthesise 2-substituted pyrrolidines and piperidines, the direct synthesis of 3-substituted counterparts is not as effective.

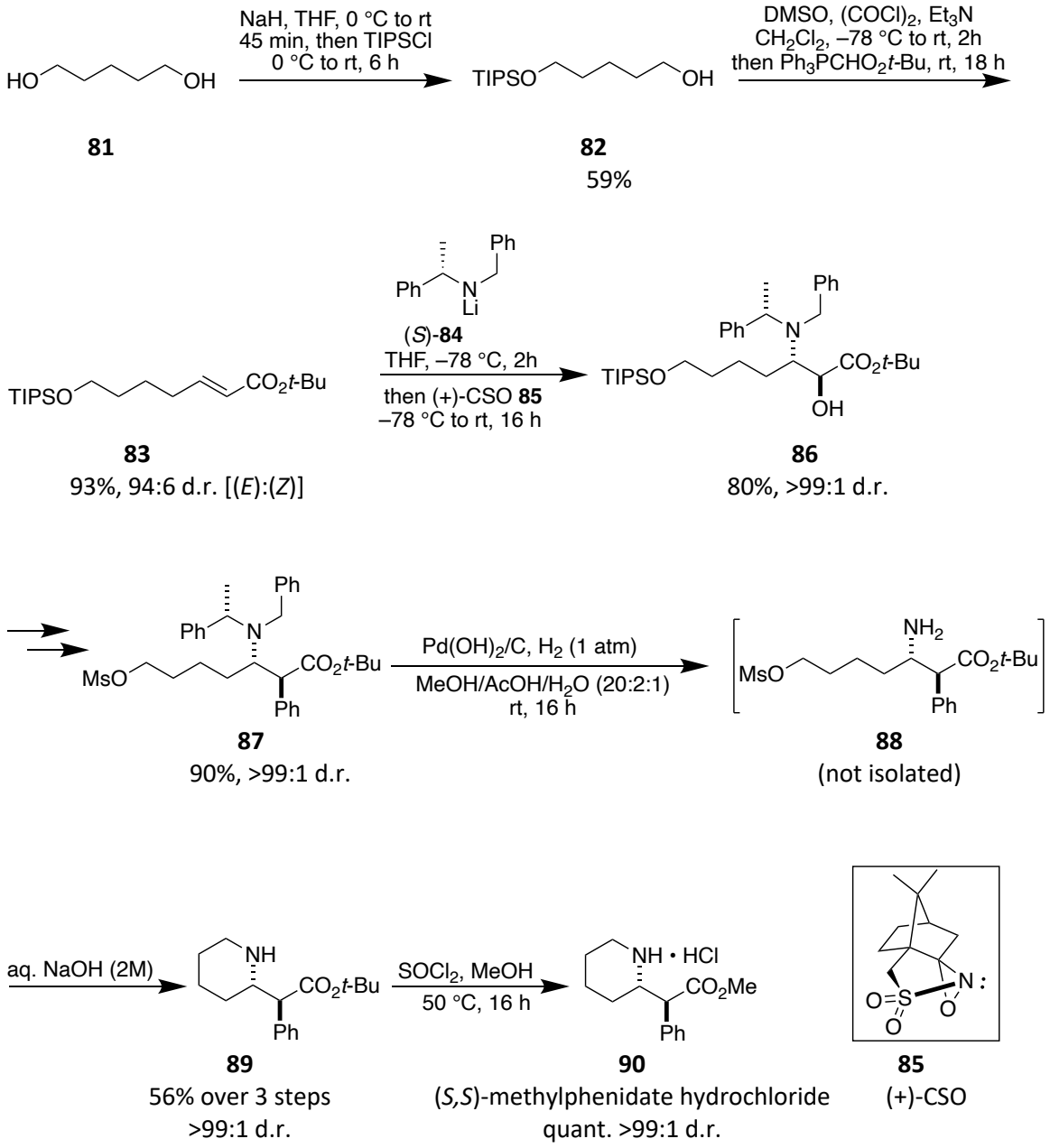


73 (*R*)- **80** 73%, 86:14 e.r. **79** (+)-sparteine surrogate

*Scheme 16 : Lithiation of N-Boc piperidine using (+)-sparteine surrogate **79***

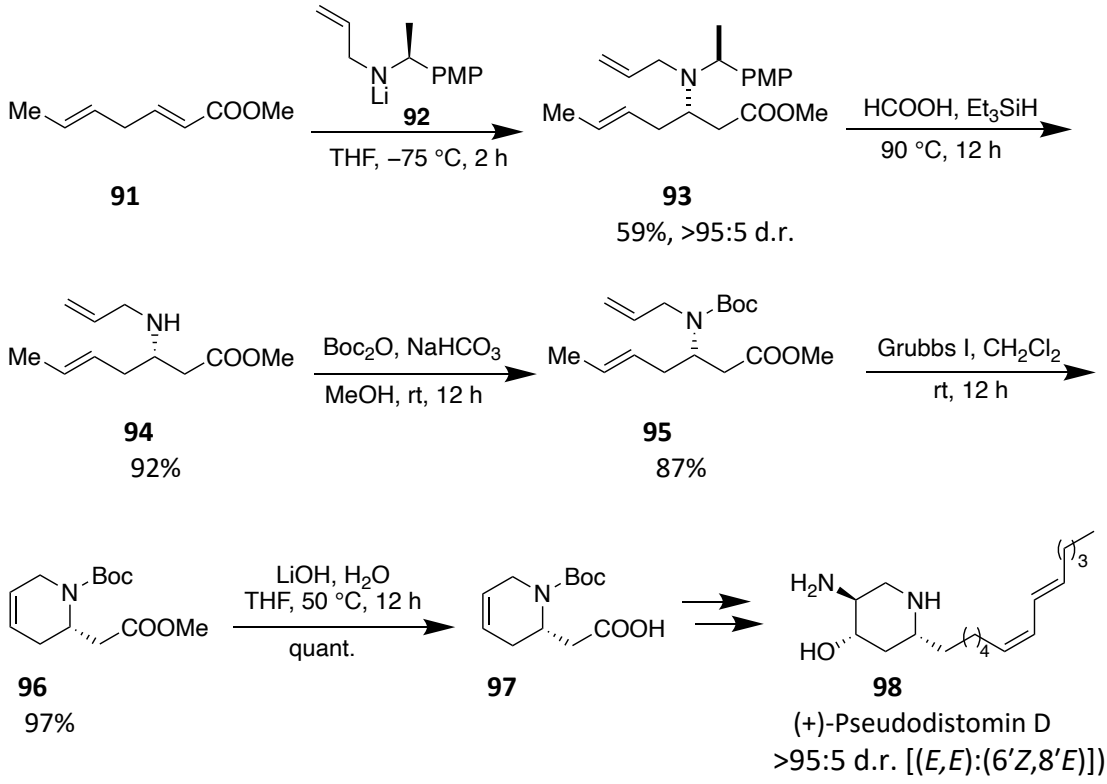
The use of chiral lithium amides are not limited to their uses as bases to abstract enantiotopic protons, but they can also be used in conjugate addition reactions, as homochiral ammonia equivalents, for the asymmetric synthesis of β-amino acid derivatives.[39] Davies and coworkers reported the total synthesis of (*S,S*)-methyl phenidate hydrochloride **90** using chiral lithium amide base **84** to install the stereochemistry at the chiral center.[40] The synthesis of the precursor ζ-silyloxy-α-hydroxy-β-amino ester **86** was prepared in three steps from the commercially available 1,5-pentanediol **81**. Monoprotection of the alcohol with TIPSCl followed by Swern oxidation and Wittig olefination of the resulting aldehyde yielded the α-β unsaturated ester **83** as a mixture of *E/Z* diastereomers with 94:6 d.r. Conjugate addition of the chiral lithium amide base lithium (*S*)-*N*-benzyl-*N*-(a-methylbenzyl)amide **84** to the mixture of isomers **83** was followed by

oxidation of the intermediate lithium β-amino enolate with (+) (camphorsulfonyl) oxaziridine [(+)-CSO] **85** to amino hydroxy ester **86** in >99:1 d.r. Further modifications led to mesylate **87** which upon hydrogenolysis followed by treatment with aq. NaOH yielded piperidine **89** in 56% over three steps in >99:1 d.r. Finally, transesterification in the presence of $SOCl_2$ and MeOH gave (*S,S*)-methylphenidate hydrochloride **90** in quantitative yield in >99:1 d.r. (Scheme 17).



*Scheme 17 : Synthesis of (S,S)-methylphenidate hydrochloride **90***

Davies also reported the total synthesis of (+)-pseudodistomin D **98** which involved the pivotal step of a stereoselective conjugate addition of a chiral lithium amide base to an unsaturated ester.[41] Lithium (*S*)-*N*-allyl-*N*-(α-methyl-*p*-methoxybenzyl) amide **92** (>99% ee) underwent conjugate addition with methyl (*E,E*)-hepta-2,5-dienoate **91** to form the β-amino ester (*S,S*)-**93** in high selectivity of >95:5 d.r. in 59% yield. Selective removal of the *N*-α-methyl-*p*-methoxybenzyl group was carried out in the presence of triethylsilane followed by subsequent Boc protection to form **95** in 87% yield. Treatment with Grubbs I catalyst led to ring closing metathesis to yield tetrahydropyridine **96** which formed the enantiopure carboxylic acid **97** in quantitative yield after ester hydrolysis. Further modifications led to the synthesis of (+)-pseudodistomin D **98** (Scheme 18).



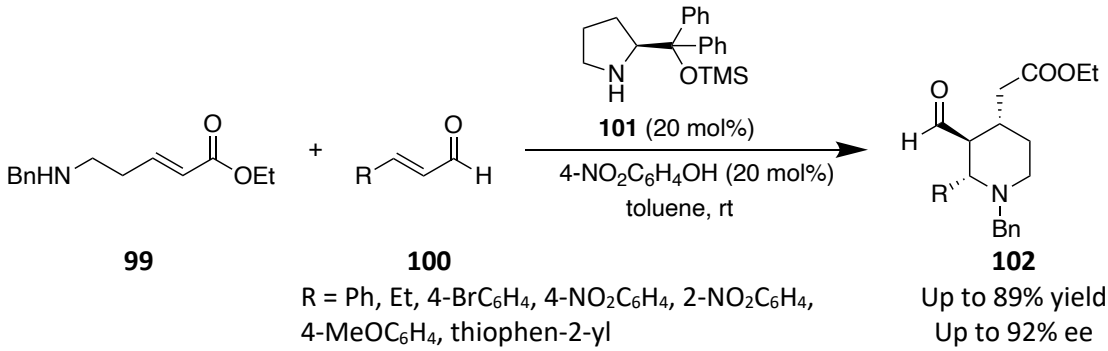
Scheme 18 : Total synthesis of (+)-Pseudodistomin D

While chiral lithium amide bases have been effective in introducing chiral centres in a molecule, the stoichiometric quantities required in the reaction reduce the overall atom economy and the use of cryogenic temperatures may limit its scalability for industrial settings.

1.5 Aza-Michael reaction

Addition of an enolate of a ketone or aldehyde to an α-β unsaturated carbonyl compound was originally defined to be a Michael reaction.[42] Aza-Michael reactions are those where nitrogen is the nucleophile. These reactions have been extensively explored for the synthesis of nitrogen heterocycles.[43,44] Since the pioneering work of Macmillan[45] and List[46] in the use of small organic molecules to catalyse organic reactions, this methodology has gained a lot of attention in organic synthesis. The first efficient intermolecular asymmetric aza-Michael reaction catalysed by an organocatalyst was published by Macmillan[47] after which this reaction has gained immense popularity. Along with metal mediated and biocatalytic reactions, organocatalysis is considered a third pillar that sustains enantioselective catalysis.[48] A forerunner among organocatalysts is the diarylprolinol TMS ether catalyst that is widely used for one-pot asymmetric Michael reactions. Proline-based organocatalysts have been a popular choice in Michael reactions because of their efficiency in the development of enantioenriched compounds arising from their extraordinary catalytic activity.[49]

2,3,4-Trisubstituted piperidines **102** were synthesised in high enantiopurity through an aminocatalytic aza-Michael reaction between ethyl (*E*)-5-(benzylamino)pent-2-enoate **99** and unsaturated aromatic aldehyde **100**. This reaction was catalysed by proline-based organocatalyst trimethylsilylprolinol **101**, in the presence of additive 4-nitrophenol. The reaction was highly diastereoselective and yielded a single diastereomer in a *trans, trans* configuration (Scheme 19).[50] Different alkyl and aryl substituted unsaturated aldehydes were subjected to the reaction conditions and it was found that all of them furnished the desired products as a single diastereomer in high yields and enantioselectivities.



Scheme 19 : Intermolecular aza-Michael reaction to give 2,3,4-trisubstituted piperidines

The proposed reaction mechanism is as shown in Figure 5, where the first Michael addition is the stereo-determining step of the cascade reaction. Due to the sterically bulky catalyst, the *Re*-face of the substrate is shielded, which forces the amine nucleophile to attack on the *Si*-face, resulting in an *S*-configuration on the cyclisation precursor. The stereochemistry of the final product is determined by the second Michael addition, where thermodynamic factors favour all the substituents in the equatorial position, leading it to a *trans, trans* configuration (Figure 5).

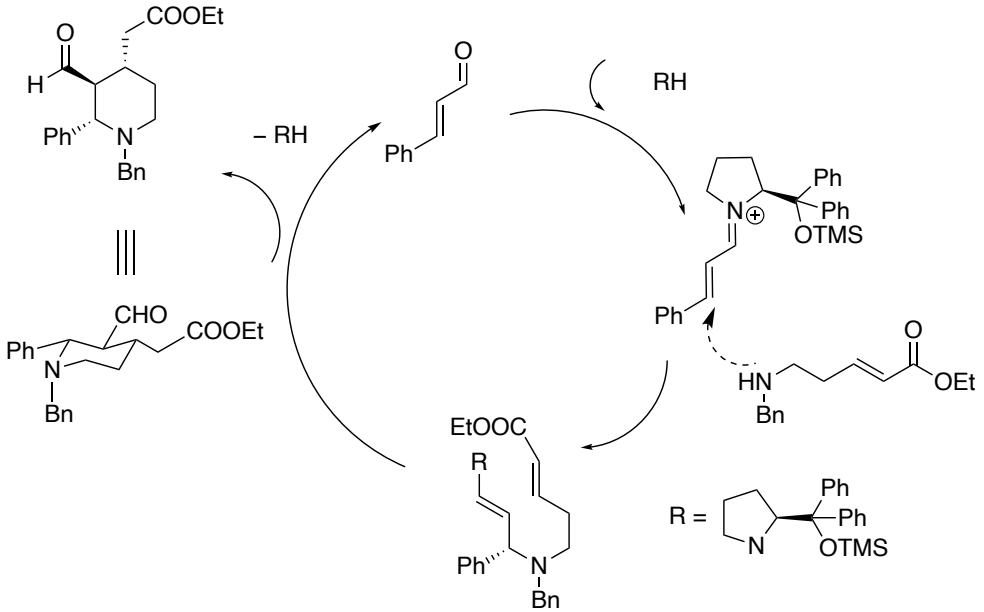


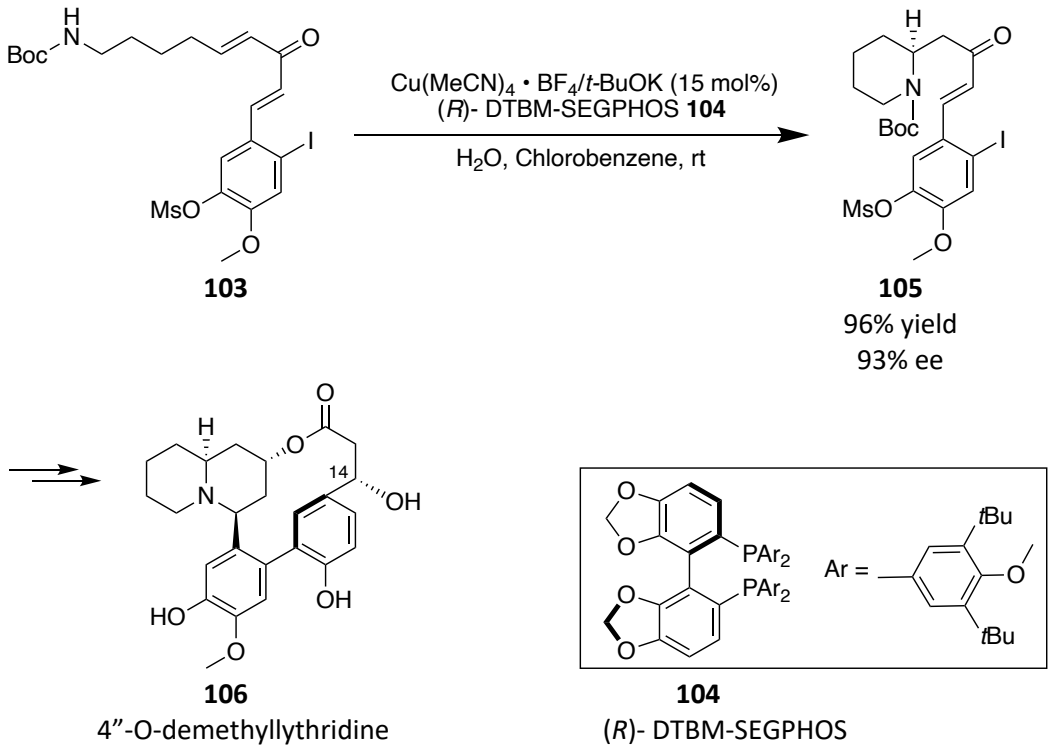
*Figure 5 : Proposed reaction mechanism for the synthesis of **102***

Though aldehydes are useful functional groups, they are quite reactive and over a period of time, tend to undergo partial arial oxidation yielding the corresponding acids, thus making it difficult to handle them. In order to make them bench-stable, the aldehyde would have to be protected or converted to other less reactive functional groups like an alcohol.

1.5.1 Intramolecular aza-Michael reaction

Intramolecular aza-Michael reaction is the most straightforward way to construct a nitrogen heterocycle, including piperidine. The corresponding asymmetric method generates enantioenriched heterocycle containing a substituted nitrogen at the stereocenter, which has made this a very appealing application in the synthesis for biologically important molecules.[51] Most often, stereocontrol/activation is obtained by using a chiral auxiliary or an appropriate chiral catalyst in asymmetric aza-Michael reactions. While some aza-Michael reactions are catalysed by salts of transition metals, metal derived catalysts are not preferred because of possible contamination with toxic heavy metals during large scale synthesis of pharmacologically relevant molecules.[52]

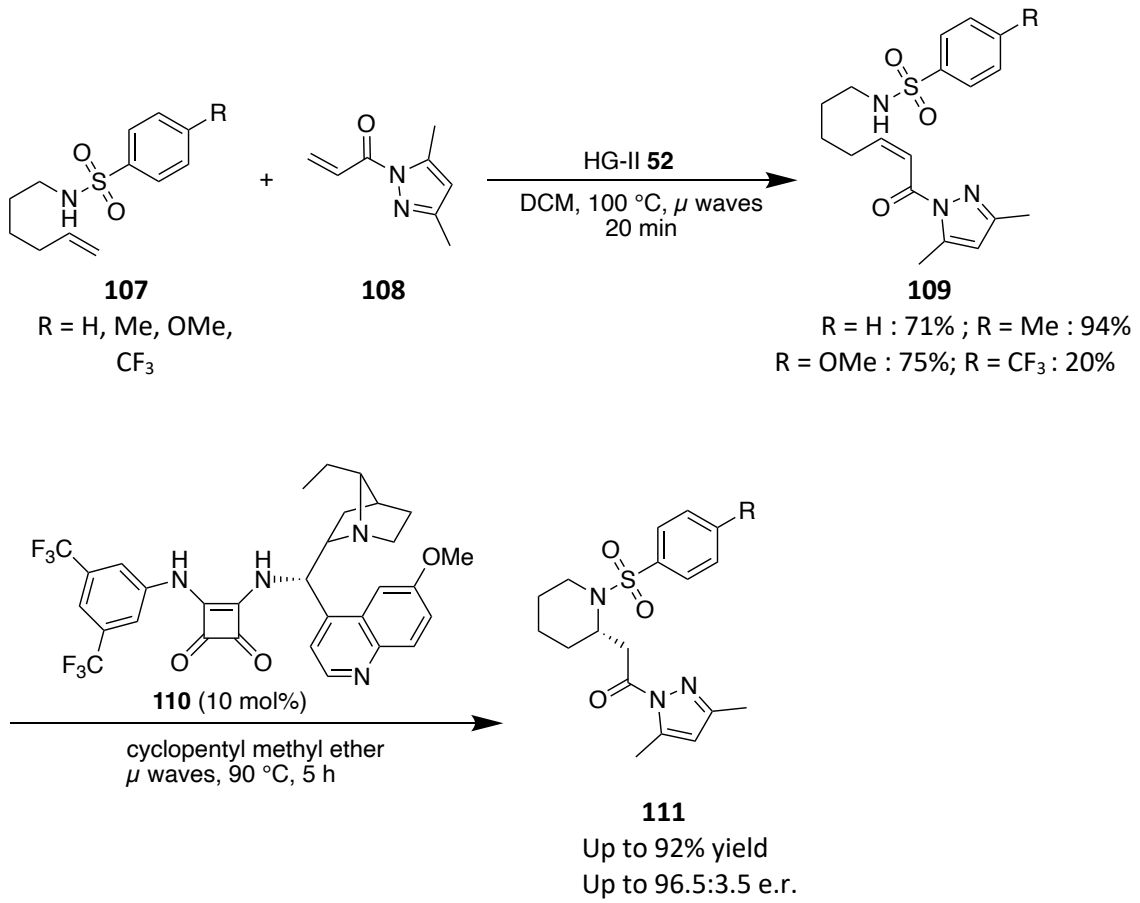
Takayama and Kitajima demonstrated a copper catalysed enantioselective intramolecular aza-Michael reaction as a key step in the total synthesis of quinolizidine alkaloids 4”-O-demethyllythridine **106** and its C-14 epimer.[53] The reaction proceeded smoothly using 15 mol% of CuO*t*-Bu which was generated *in situ* from *t*-BuOK and $Cu(MeCN)_4 \cdot BF_4$ in the presence of chiral catalyst (*R*)- DTBM-SEGPHOS **104** to form the piperidine derivative **105** in excellent yield and enantioselectivity (Scheme 20). Switching the chirality of the catalyst gave access to *ent*-**105** which was crucial in the stereochemistry determination. Piperidine **105** was further modified to give the biphenyl quinolizidine alkaloid **106.**



*Scheme 20: Copper catalysed aza-Michael reaction for the total synthesis of quinolizidine alkaloid **106***

Fustero and del Pozo demonstrated the use of α,β- unsaturated *N*-acyl pyrazoles as activated ester surrogates instead of unsaturated esters as Michael acceptors. Conjugated pyrole amides offer the advantages of being good leaving groups for further transformations. The use of squaramides as catalysts **110** with unsaturated pyrazole derivates **108** as ester surrogates and a sulfonamide protecting group allowed for an effective asymmetric intramolecular Michael reaction leading to substituted piperidines in excellent yields and enantioselectivities (Scheme 21).[54]

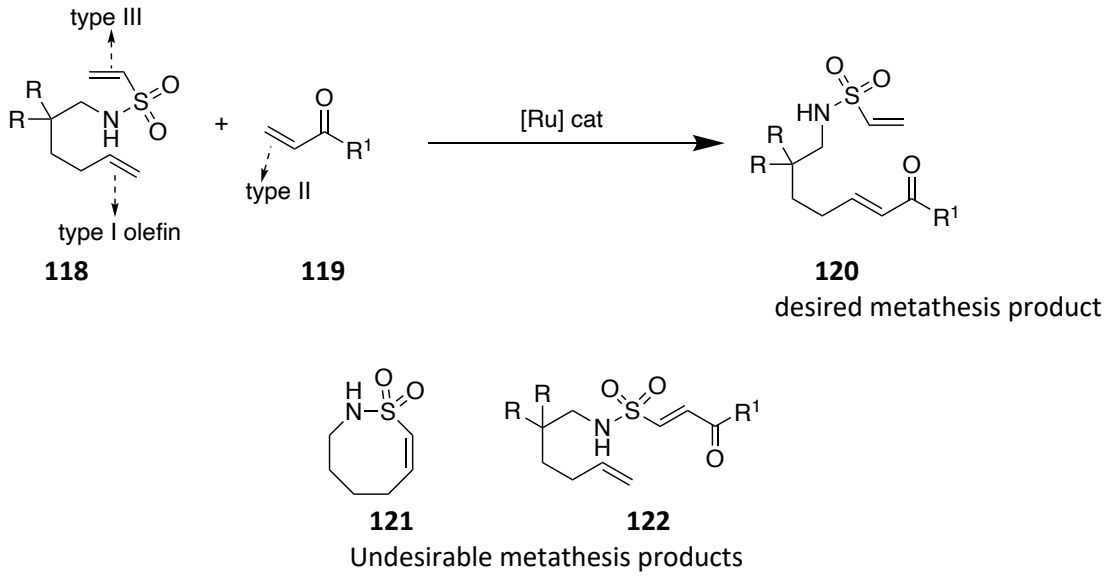
Cyclisation precursor **109** was synthesised from the sulfonamide amine **107** and 3,5-dimethylpyrazol acrylamide **108** under cross-metathesis conditions using HG-II **52** and microwave irradiation at 100 °C in good to excellent yields except for R = CF_3 with 20% yield. When the cyclisation was carried out at room temperature in $CHCl_3$ in the presence of catalyst **110**, the reaction time was five days with moderate yields (48-60%) although with high enantioselectivities (up to 98:2 e.r.). The authors were able to reduce the reaction times by carrying out the reaction under microwave irradiation (4-5 hours), resulting in excellent yields and enantioselectivities of the substituted piperidines (Scheme 21). The methodology was also extended to pyrrolidines which were obtained with high yields and enantioselectivities.



Scheme 21 : Using N-acyl pyrazole as Michael acceptor to form substituted piperidine

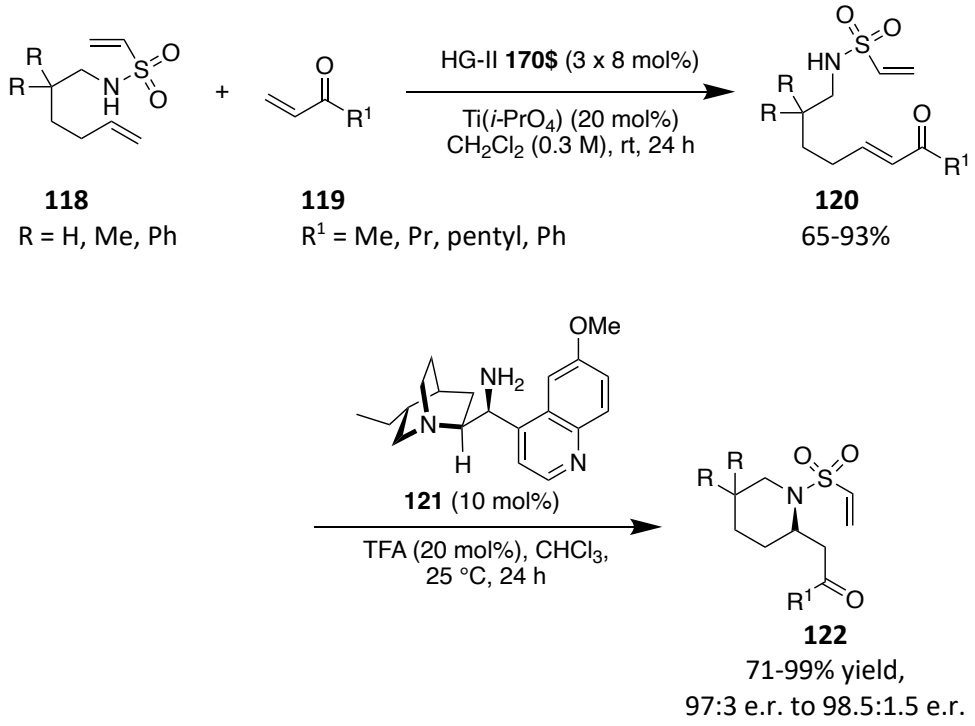
The same authors also made use of a vinyl sulfonamide which played a dual role, as a nitrogen nucleophile and a Michael acceptor, in the asymmetric synthesis of piperidines *via* an intramolecular aza-Michael reaction.[55] The cyclisation precursor was prepared by a cross metathesis reaction between vinyl sulfonamide **118** and the unsaturated ketone **119** (Scheme 22). According to the general model for predicting the selectivity in olefin cross metathesis reactions in the presence of a second-generation ruthenium catalyst reported by Grubbs and co-workers,[56] the reaction could take three possible routes and form either the desired product **120** or the eight membered ring **121** or the cross-metathesis product with the vinyl sulfonamide olefin **122**. The most feasible reaction was between the more reactive isolated olefin in **118** (type I olefin which undergoes rapid homodimerization and forms very reactive homodimers) and the unsaturated ketone **119** (type II olefin, slower homodimerization). This reaction was further promoted by adding an excess of the unsaturated ketone to reduce the homodimerization of the type I olefin. The type III olefin in the vinyl sulfonamide would be poorly reactive under the reaction conditions and unable to react with unsaturated ketone **119** to form **122**. Also, due to the slow formation of the

8-membered ring, product **121** was less favourable and not observed in the reaction (Scheme 22).



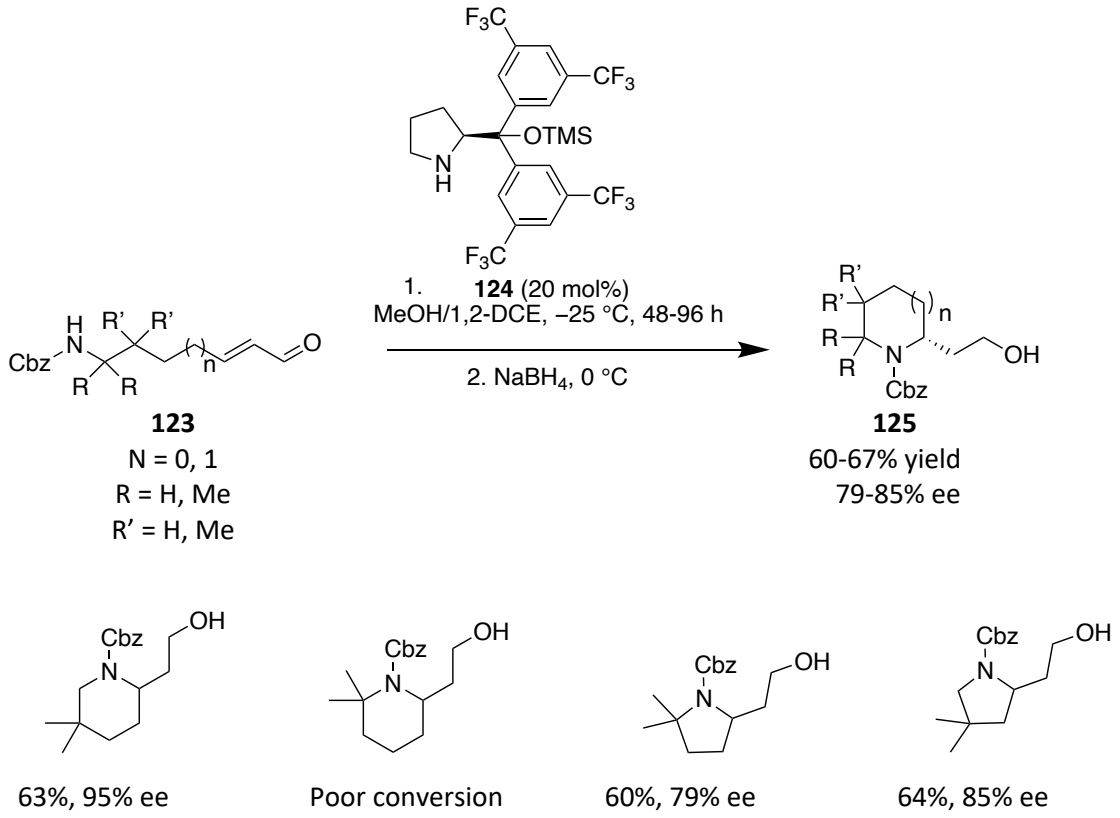
*Scheme 22 : Plausible metathesis reactions between **118** and **119***

The cross-metathesis reaction required the addition of titanium (IV) isopropoxide as a Lewis acid to reduce the basicity of the sulfonamide nitrogen. The reaction was tolerant to H, Me and Ph substitutions on the vinyl sulfonamide **118** resulting in moderate to excellent yields of the cyclisation precursor **120** (Scheme 23). The intramolecular aza-Michael reaction was carried out under mild conditions in the presence of organocatalyst 9-amino-9-deonxy-*epi*-hydroquinine **121** and trifluoroacetic acid (TFA) as a co-catalyst in $CHCl_3$ to form the substituted piperidine in very good yields and excellent enantioselectivities. This methodology was also extended to benzo fused piperidines with high yields and enantioselectivities.



*Scheme 23 : Synthesis of piperidine **122** using vinyl sulfonamide as a nucleophile and a Michael acceptor*

An alternative method to synthesise piperidines and pyrrolidines was demonstrated by Carter where α-β unsaturated aldehydes **123** were used as Michael acceptors catalysed by Jørgensen's trifluoromethyl derivative catalyst **124**.[57] The proposed mechanism involved iminium formation from the catalyst **124** and aldehyde **123** which activated the Michael acceptor, and steric bulk on the catalyst forced the cyclisation from one side of the molecule. It was noticed that halogenated solvents like chloroform and 1,2-DCE and reduced temperatures of −25 °C gave the best yield and enantioselectivity. This method was used to synthesise 2,2'- and 3,3'- disubstituted piperidines and pyrrolidines **125** in high yields and enantioselectivities, with the exception of 2,2'-dimethylpiperidine which gave poor conversions (Scheme 24).

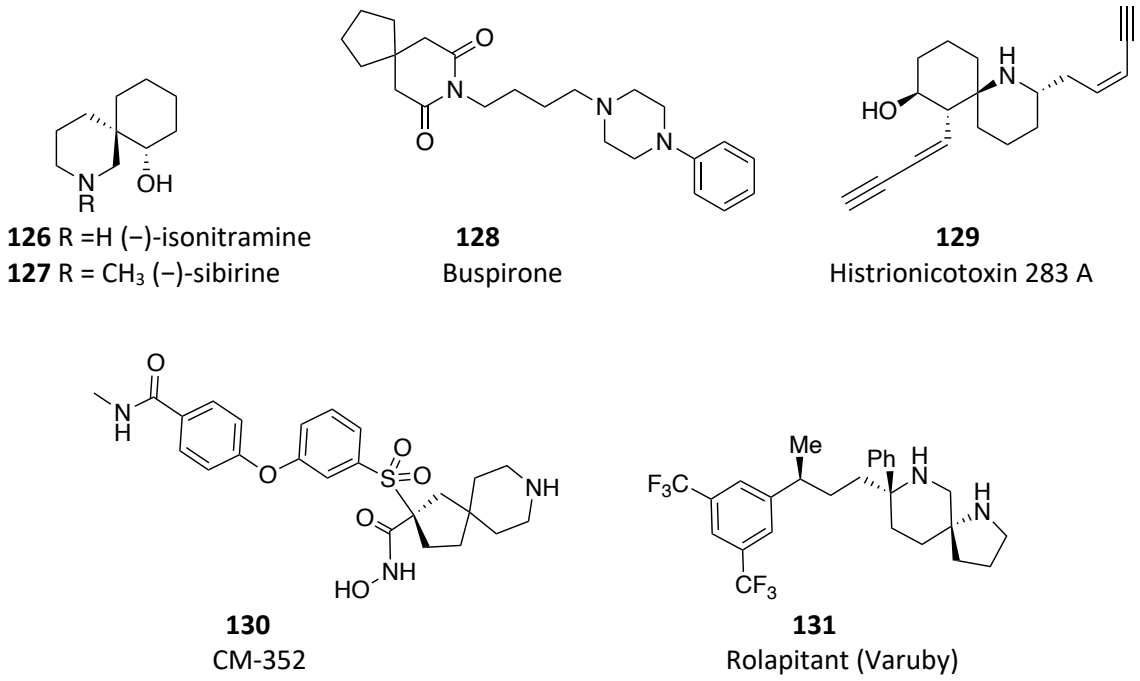


Scheme 24 : Using unsaturated aldehydes as Michael acceptors

While excellent enantioselectivities were obtained using this methodology, the high reactivity of aldehydes as a functional group had to be controlled by using cryogenic temperatures which slowed down the rate of the reaction, extending it to 2-4 days. Although cryogenic temperatures prevented the possibility of unwanted side reactions and by-products, this could be seen as a possible drawback considering industrial scale-up of this process. Another disadvantage of using aldehydes as the Michael acceptor was that it was unstable under the chiral HPLC conditions, so the aldehyde had to be reduced to the corresponding alcohol. While alcohols are useful functional groups, the loss of a carbonyl functionality limits the scope for late-stage diversification.

1.6 Spiropiperidines

Spirocyclic compounds are those in which two cyclic structures are joined by a single atom. Spiropiperidines constitute a privileged motif in the pharmaceutical and agrochemical industry and are considered as building blocks of medicinal chemistry. They are desired for their rigidity, structural complexity and novel intellectual property value.[58] Their rigidity presents the functional groups in defined vectors thus leading to better interactions between the drug and the target molecule. Structures **126** and **127** are γ-amino alcohols that are derived from natural products and desired for their potent biological activity.[59] Buspirone **128** is used to treat anxiety disorders, histrionicotoxin 283 A **129** is an acetylcholine receptor inhibitor,[60] CM352 **130** is a promising drug for the treatment of intracerebral hemorrhage[61] and rolapitant (Varuby) **131** is an antiemetic used to stop chemotherapy induced nausea and vomiting (Figure 6).



126 R =H (−)-isonitramine
127 R = CH_3 (−)-sibirine

128
Buspirone

129
Histrionicotoxin 283 A

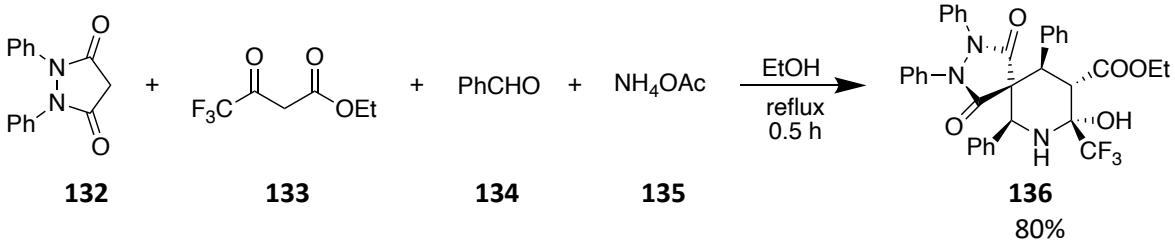
130
CM-352

131
Rolapitant (Varuby)

Figure 6 : Spiropiperidines with pharmaceutical importance

Due to the properties of spiropiperidines, they have become interesting targets for synthesis in the recent years.[62,63] A few recent examples of syntheses of spiropiperidines will be discussed in the following sections.

Song reported a four component one-pot reaction of 1,2-diphenylpyrazolidine-3,5-dione **132**, ethyl 4,4,4-trifluoroacetoacetate **133**, benzaldehyde **134** and ammonium acetate **135** that afforded a highly functionalized substituted spiropiperidine **136** in 80% yield.[64] The key aspect of the reaction was that the products were isolated as single diastereomers although there were four stereocenters generated. The reaction was tolerant towards aldehydes with various electron withdrawing and donating groups and good to excellent yields were obtained for all (Scheme 25).

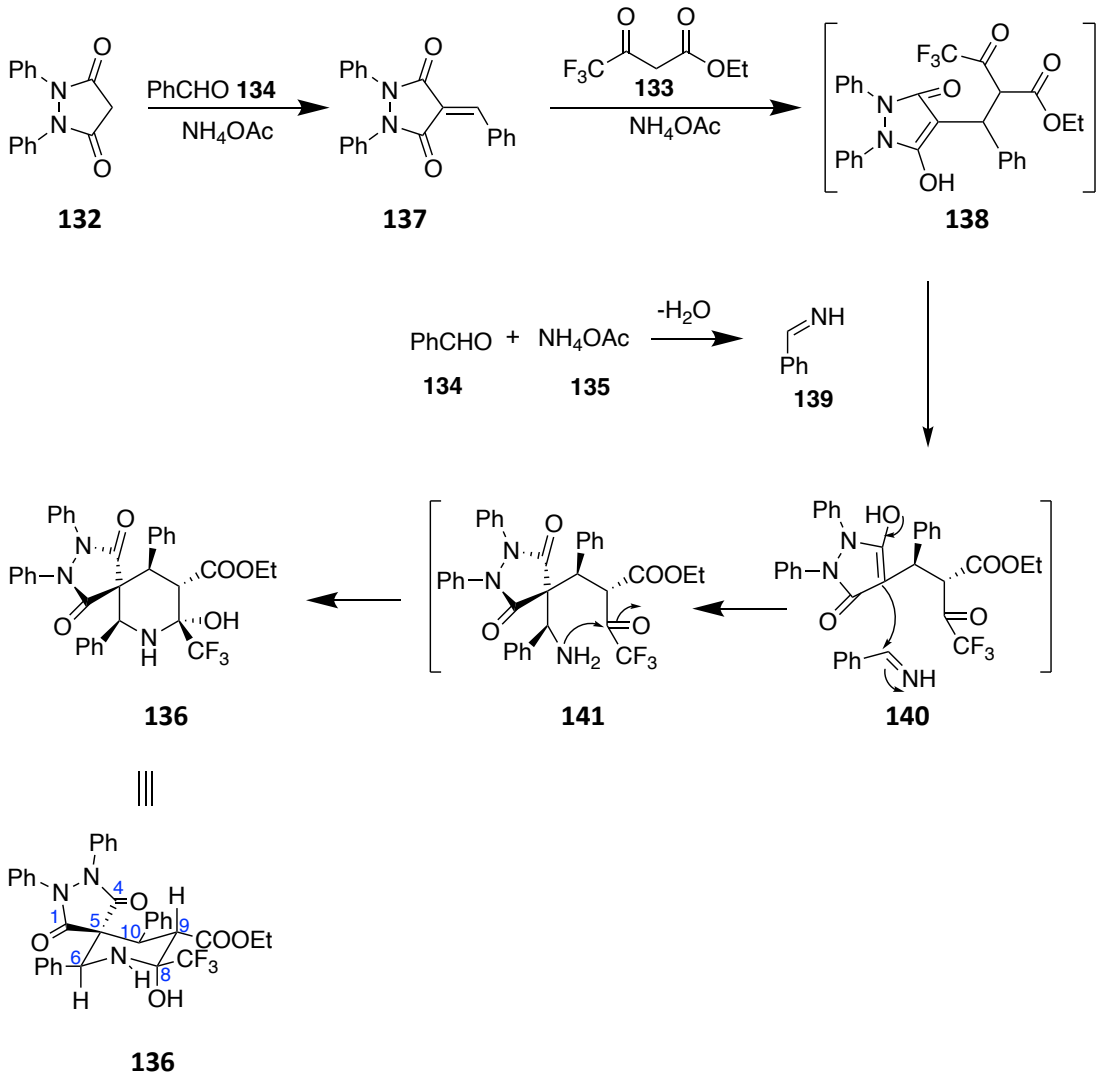


132 **133** **134** **135** **136**

80%

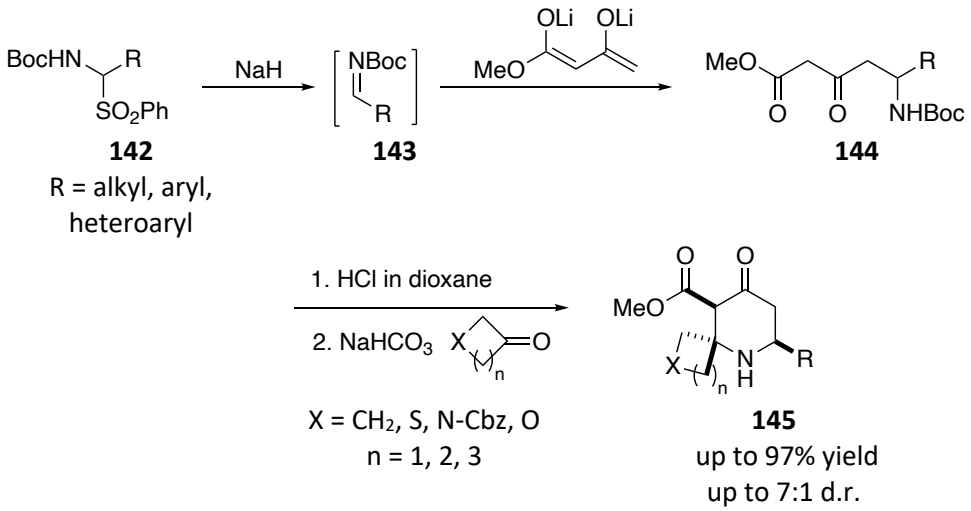
Scheme 25 : One pot synthesis of highly substituted spiropiperidines

A plausible mechanism involves the reaction of **132** with benzaldehyde in the presence of NH_4OAc forming **137** via a Knoevenagel condensation reaction which further undergoes Michael addition with ethyl 4,4,4-trifluoroacetoacetate **133** and NH_4OAc to generate intermediate **138**. This reacts with arylmethanimine **139** formed *in situ* by the reaction of benzaldehyde and NH_4OAc, forming the acyclic intermediate **141** which forms the spiropiperidine **136** as the major product after intramolecular cyclisation (Scheme 26). The single diastereomer was the result of an energetically favourable process intramolecular cyclisation where the piperidine ring adopted an ideal chair conformation. This led to the bulky substituents- 6-aryl, 10-aryl and 9-ethoxycarbonyl group to occupy equatorial sites and the corresponding hydrogens on the carbons to be axially oriented with the stereochemistry being confirmed by X-ray analysis (Scheme 26). Though the reaction scope was well explored, the other diastereomer cannot be accessed through this method. It would require the presence of a chiral reagent/catalyst to induce the required stereochemistry.



*Scheme 26 : Plausible mechanism for the formation of **136***

The Clarke group has reported the synthesis of 2-spiropiperidines, by using *N*-Boc imines and Weiler's dianion. *N*-Boc imines **143** generated *in situ* from the corresponding *N*-Boc sulfone precurors **142** were treated with the Weiler dianion to form the resulting product δ-*N*-Boc-amino-β-ketoester **144**. Boc-deprotection in the presence of HCl in dioxane was followed by cracking the HCl salt using $NaHCO_3$ and reacting it with the corresponding ketone. This allowed for the synthesis of 2-spiropiperidines **145** in high yields and moderate diastereoselectivity (Scheme 27). [58]



Scheme 27 : Synthesis of 2-spiropiperidines

Principal moments of inertia (PMI) analysis gives the measure of the three dimensionality of a molecule represented by the ternary plot as shown in Figure 7[65] showing the three extremes of molecular shape.[66] The top left vertex represents diacetylene like molecules that are purely *sp* hybridised and have a 'rod-like' shape. The bottom vertex of the plot is represented by benzene equivalents that are sp^2 hybridised and have a planar geometry. The top right vertex is occupied by molecules like adamantane that have cage-like structures which are three-dimensional (purely sp^3 hybridised). A molecule with a particular structure can lie anywhere in between these three vertices depending on the degree to which its morphology represents the three shape classes.[67]

Figure 7 is a PMI plot of 35,270 'lead-like' molecules[68] downloaded from the ZINC database having molecular weights <350 and AlogP values <3.5. AlogP is the partition co-efficient of a molecule measured by its solubility in a water/*n*-octanol system. A low AlogP value corresponds to a hydrophilic molecule and a high value implies a lipophilic molecule. Normalized PMI values (lowest energy conformer of the molecules was determined from which moments of interia, *I*, were calculated along x,y, and z axis and normalised PMI values from I_x/I_z and I_y/I_z were obtained)[65] were plotted on a PMI plot and are represented by the blue dots. It is evident that there is an uneven distribution of molecules to the left of the graph, i.e., a majority of the molecules are two-dimensional: linear and planar. The black line in the graph represents a region where 75% of the molecules lie to the left of the

line, clearly showing the disparity in the area of space represented by three-dimensional molecules.

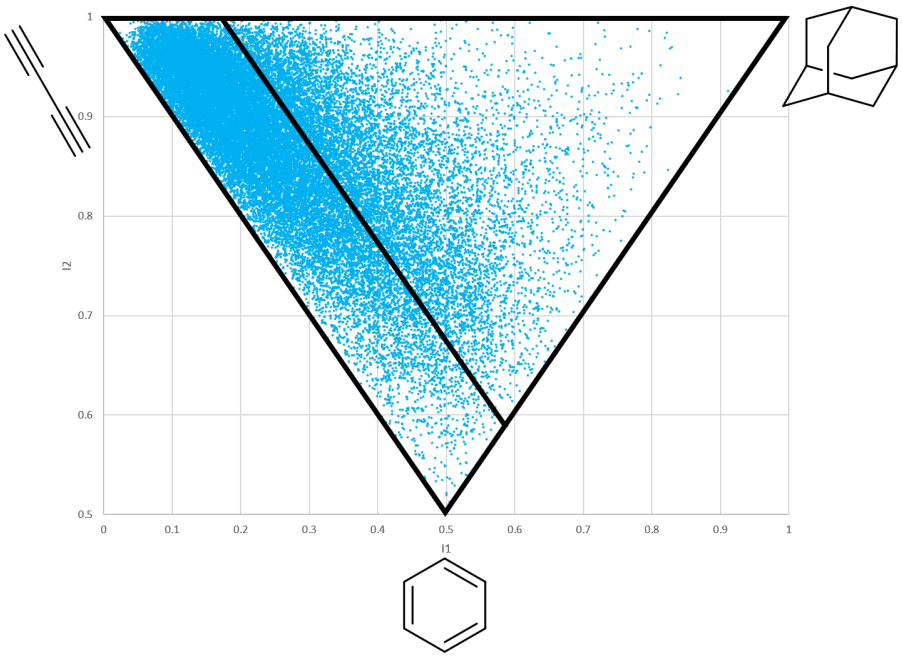


Figure 7 : PMI plot of the ZINC 'lead-like' database

The 2-spiropiperidines **145** synthesized in Scheme 27 were subjected to PMI analysis and were found to be more three-dimensional compared to the 'lead-like' molecules in the ZINC database as they occupied the underexplored areas of sp^3 chemical space. These molecules are shown by the orange dots in Figure 8 where most of them lie to the right of the black line in the ternary plot.[65] Thus, this methodology towards making 2-spiropiperidines was useful towards synthesizing more three dimensional molecules, thus making them important fragments in drug discovery programs and moving away from the more traditional two dimensional, i.e., *sp* and sp^2 rich molecules.[69]

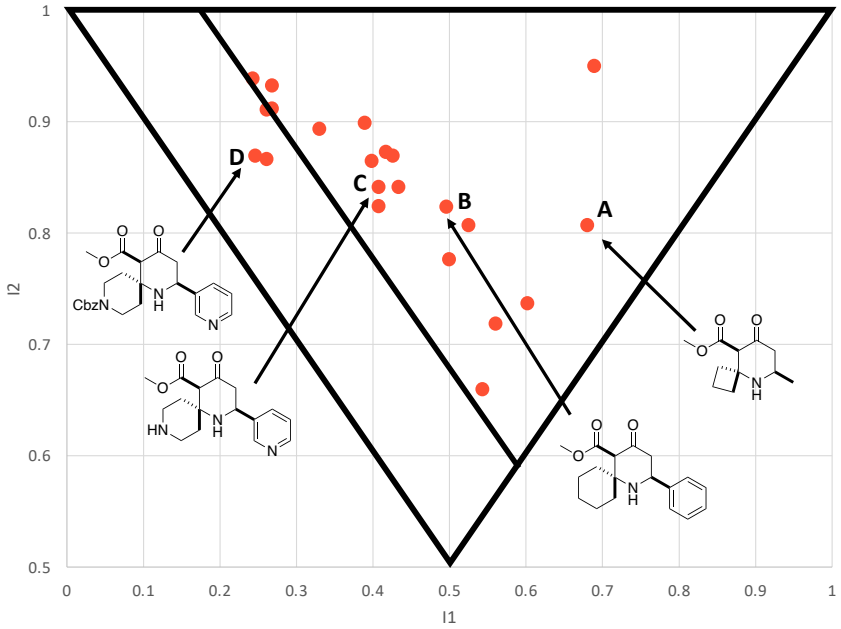
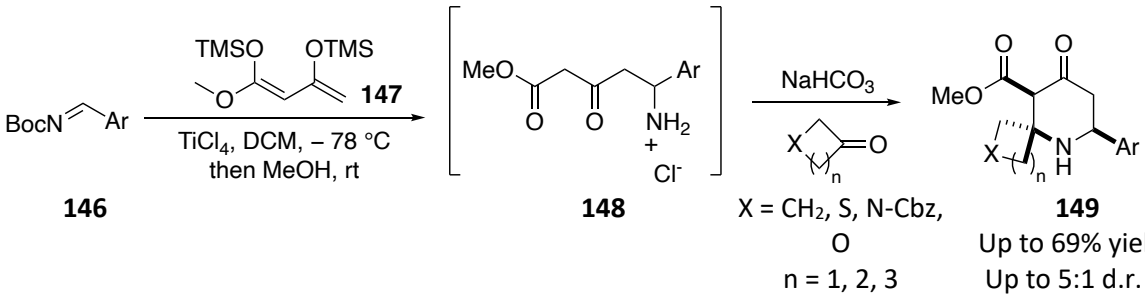


Figure 8 : PMI plot of the 2-spiropiperidines synthesised in Scheme 27 [65]

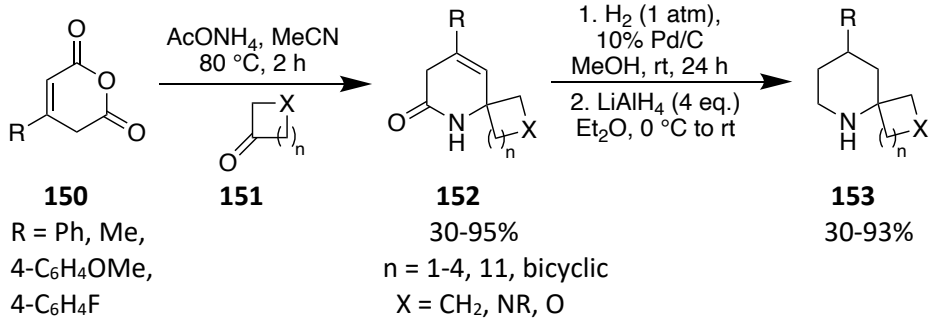
A one pot procedure for the synthesis of 2-spiropiperidines was also developed that utilised modified Maitland-Japp conditions in the presence of Chan's diene **147** as the nucleophile. After the Mannich-like addition product was formed, addition of MeOH led to methanolysis of $TiCl_4$ to generate $Ti(OMe)_4$ along with HCl, which led to Boc deprotection and formed the HCl salt of the amine **148**. Addition of base and ketone led to successful formation of 2-spiropiperidine **149** (Scheme 28).[58]



Scheme 28 : One-pot synthesis of 2-spiropiperidines

Though the methodology was successful in developing fragments that were useful in drug discovery programs, one of the limitations was synthesizing piperidines with high enantiopurity. Although diastereoselective reactions are useful, reactions with high enantiocontrol are desirable.

Recently, Peshkov *et* al published a three-component Castagnoli-Cushman reaction, which synthesised 2-spiropiperidones **152** that were further modified to give 2-spiropiperidines **153** in good to excellent yields. In this method, 3-substituted glutaconic acid anhydride was reacted with various cyclic ketones **151** in the presence of ammonium acetate to form the spiropiperidone **152** in 30-95% yield (Scheme 29). Subsequent hydrogenation followed by reduction from the lactam to the amine using $LiAlH_4$ proceeded smoothly yielding the spiropiperidines **153** in 30-93% yield.[70]



Scheme 29 : Castagnoli–Cushman reaction to synthesise 2-spiropiperidines

The mechanism commences with the Mannich-type reaction of the enol form of the anhydride **154** with the imine **155** formed *in situ* from the reaction of the cyclic ketone and ammonium acetate (Figure 9). The Mannich adduct **156** then undergoes an intramolecular acylation proceeding by the attack of the nitrogen lone pair onto the carbonyl carbon leading to the formation of α-β unsaturated lactam carboxylic acid **157** which upon decarboxylation followed by tautomerization results in the spiropiperidone **152.**[71] The spiropiperidines **153** were further modified at the hindered nitrogen resulting in 2-spiropiperidine amine building blocks which are useful cores for library development.[70]

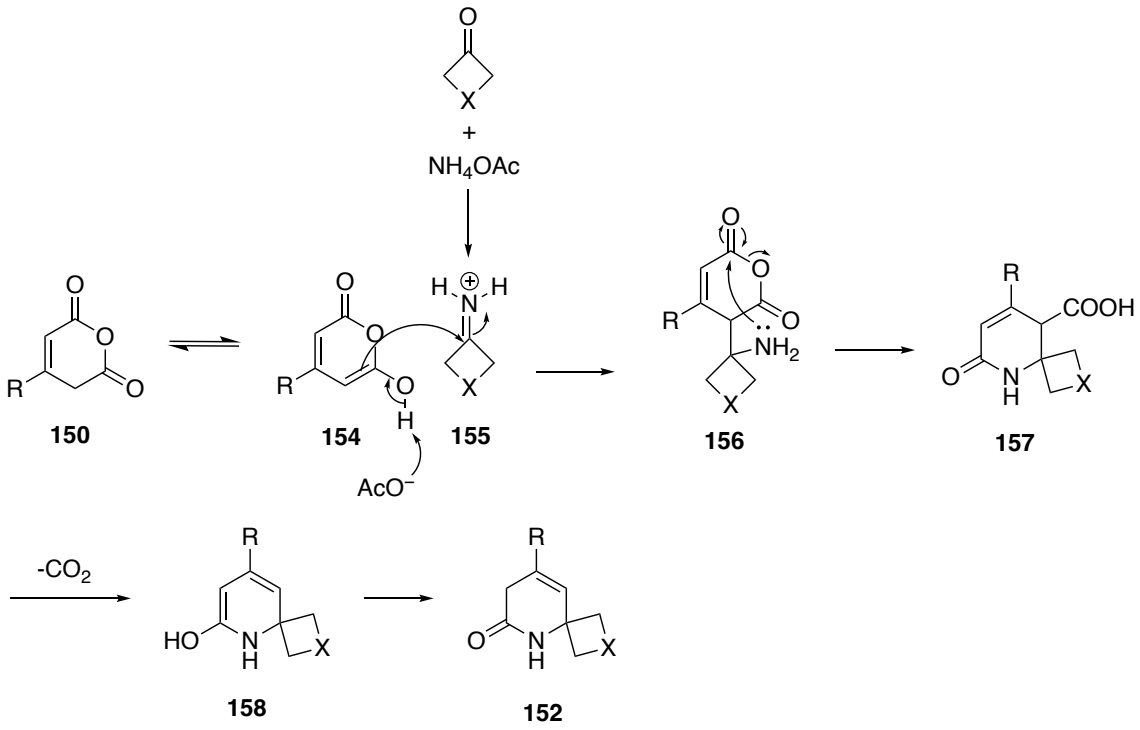


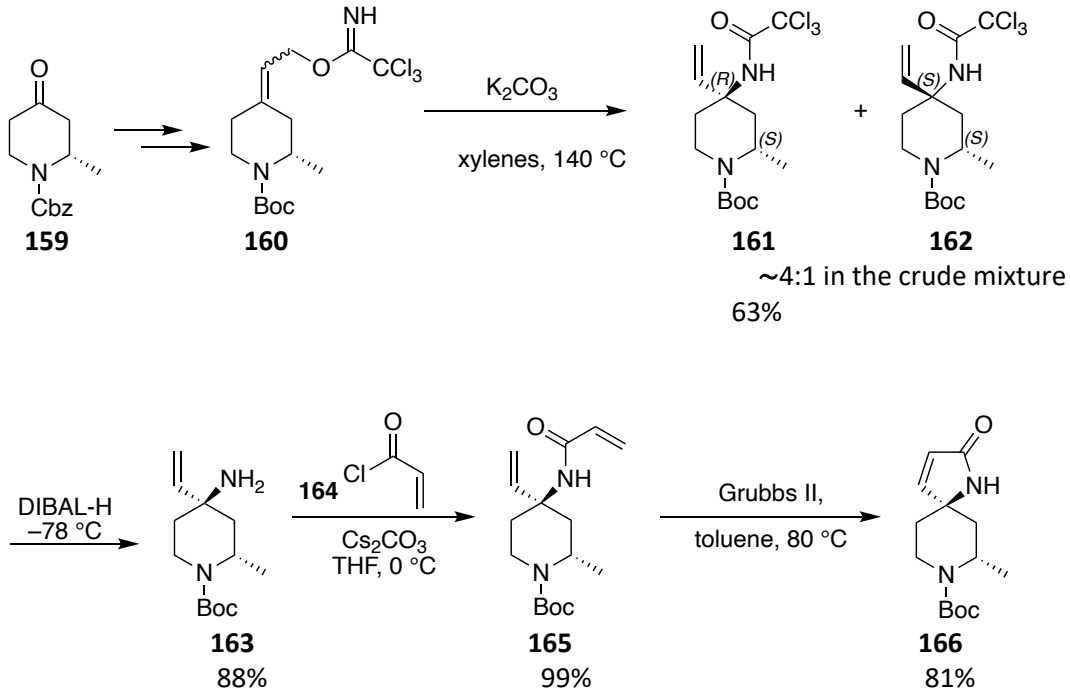
Figure 9 : Proposed mechanism for the Castagnoli–Cushman reaction

The method explores a variety of substituents for building a spirocyclic scaffold in an efficient manner, however, the asymmetric version has not been explored, which could be an attractive feature for drug discovery processes. Enantiopure compounds are crucial for the biological study of the molecules, hence there is a clear need to synthesise spiropiperidines as single enantiomers.

1.6.1 Asymmetric synthesis

One of the direct methods to access chiral spiropiperidines is by using an enantiomerically pure starting material. Researchers from Pfizer and Novartis reported a diastereoselective synthesis of novel spiropiperidine which used a chiral starting material (*S*)-2-methyl-4-oxopiperidine-1-carboxlyate **159** to synthesise the α-β unsaturated lactam containing spiropiperidine **166** as a single diastereomer (Scheme 30).[72] Piperidine **159** underwent modifications to afford isomeric trichloro-imidate **160**. The synthesis then made use of an Overmann rearrangement in the presence of potassium carbonate in xylenes at 140 °C. This reaction played a key role in controlling the stereoselectivity of the chiral carbon as a 4:1 mixture of trichloroacetamide diastereomers **161** and **162** were obtained after 48 hours. Separation of the diastereomers resulted in 63% yield of the major diastereomer **161**, the

stereochemistry of which was confirmed by crystal X-ray analysis. On reduction with DIBAL-H, the primary amine **163** was obtained in 88% yield. Acylation of **163** with acryloyl chloride resulted in the diolefin **165** in excellent yield followed by ring closing metathesis in the presence of Grubbs-II catalyst to furnish the lactam **166** in 81% yield. The authors extended the approach to functionalize the α-position to the carbonyl group in the spiro lactam and were also successful in arylation of the N-H lactams which can be useful for late-stage diversification.



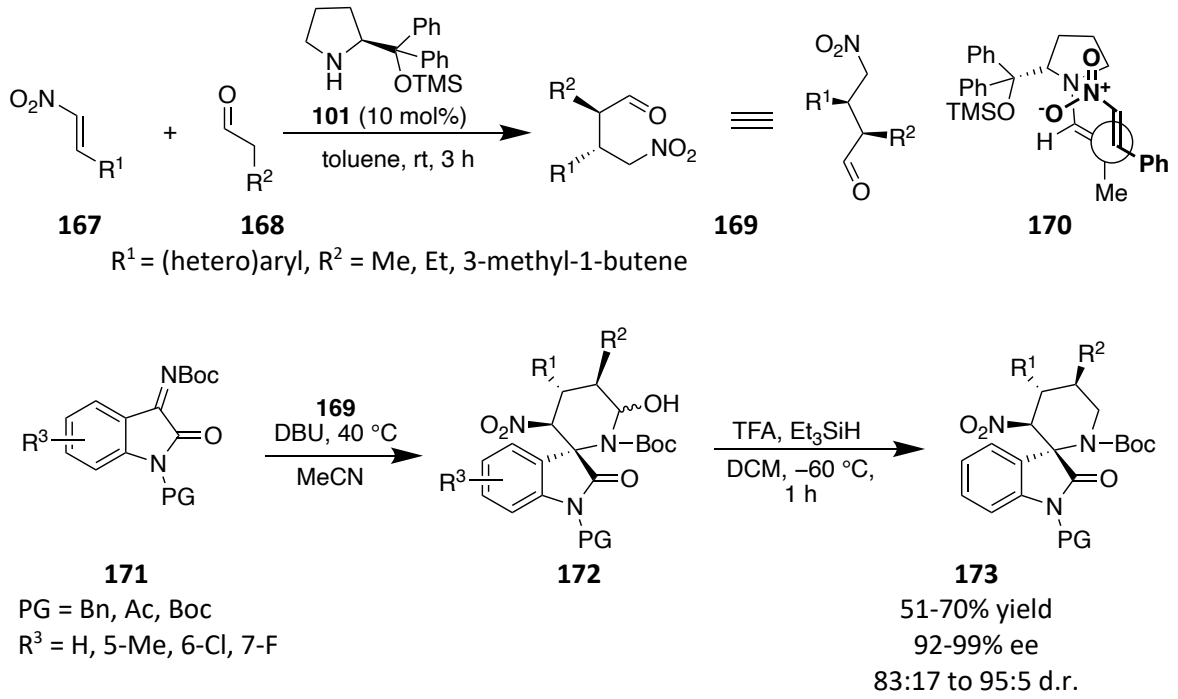
*Scheme 30 : Synthesis of spiropiperidine **166***

One of the drawbacks of this method is that the stereochemistry is introduced in the first step by using a chiral starting material. If the other diastereomer of the spiropiperidine is desired as the major isomer, the entire synthesis would have to be restarted by using the other enantiomer of the starting material. This can make the overall process of accessing selective isomers tedious while also preventing racemisation of the stereocentre throughout the synthetic route as opposed to introducing the stereochemistry in the later stages of the synthesis.

1.6.2 Using organocatalysts

As compared to metal catalysts, organocatalysts are generally considered to be more environmentally friendly and less sensitive to moisture and air.[49] Organocatalysts have been studied as far as in the 1970s,[73] but have been researched in depth in the recent years and are considered to be preferable and a greener method of synthesis.[74,75] Due to their independent pioneering work in the development of asymmetric organocatalysis, David MacMillan and Benjamin List were awarded the Nobel Prize in Chemistry in 2021.

Diphenylprolinol silyl ethers are known to be efficient organocatalysts for the asymmetric Michael reaction of aldehydes and nitroalkenes resulting in excellent diastereo- and enantioselectivities.[76,77] One such example by Peng and co-workers demonstrated the asymmetric synthesis of pharmacologically relevant spiro-oxindole derivative through a cascade Michael/aza-Henry/hemiaminalization cascade reaction in the presence of prolinol based catalyst **101** (Scheme 31).[78]

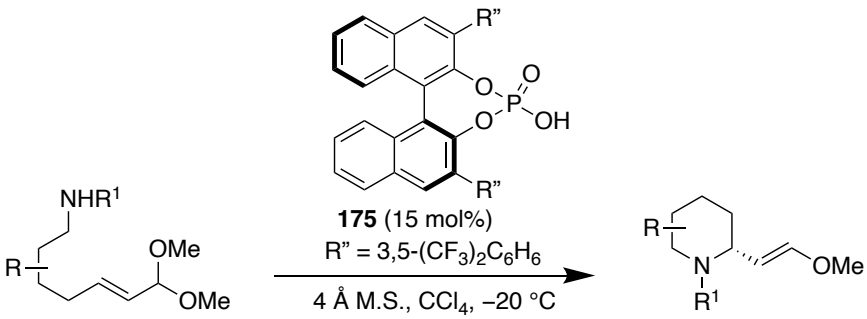


*Scheme 31 : Asymmetric synthesis of spiro-oxindole piperidine derivative **173***

(*E*)-Nitrostyrene **167** was reacted with aldehyde **168** in the presence of Hayashi-Jørgensen secondary amine catalyst **101** to yield the adduct **169**. The bulky α-subsituent on the

pyrrolidine ring as shown in **170** helps in orienting the double bond away from it resulting in an *anti*-enamine configuration. It also shields the *re*-face of the enamine double bond resulting in the attack of the (*E*)- *anti*-enamine (*si*-face) on the *si*-face of the nitrostyrene,[76] as this conformer was identified as energetically most stable in the transition state.[79] An electrostatic interaction between nitro group and the nitrogen atom of the pyrrolidine ring was also proposed to be operating in this transition state.[76] Once **169** was formed a solution of **171** was added in a one-pot procedure leading to successive aza-Henry and hemiaminalization reactions with the facile formation of **172**. Dehydroxylation of **172** in the presence of Et_3SiH and TFA yielded the spiropiperidine oxindole **173** in good to moderate yields with excellent stereoselectivity. The method highlights the synthesis of a highly substituted spiropiperidine in a one-pot cascade reaction with contiguous stereocenters with excellent stereoselectivity. Though the scope of the reaction has been exhaustive regarding various substituted nitrostyrenes, the substrate scope for the aldehydes is limited. An important application of the synthesis was deprotection of the isatin ketimine nitrogen which showed promising antiproliferative activity toward breast cancer cells.

In his report, Nagorny demonstrated that unsaturated acetals were a good alternative to using aldehydes as Michael acceptors which led to the synthesis of functionalized chiral piperidines **176** in excellent yields and enantioselectivities in the presence of CPA **175** (Scheme 32).[80] The use of acetals was a way to control the high reactivity of aldehydes and also made them easier to use, as it eliminated the occurrence of the aerial oxidation of aldehydes to carboxylic acids. The reaction was found to be highly dependent on non-polar solvents leading to high yields and improved selectivity, with carbon tetrachloride giving the best results. Additionally, lowering the temperature to −20 °C prevented any racemisation from taking place. Improved enantioselectivities were obtained with longer reaction times but this led to decreased yields. The reaction scope tolerated different *N*-protecting groups and substitutions on the C-4 and C-5 positions of the piperidine ring.



174

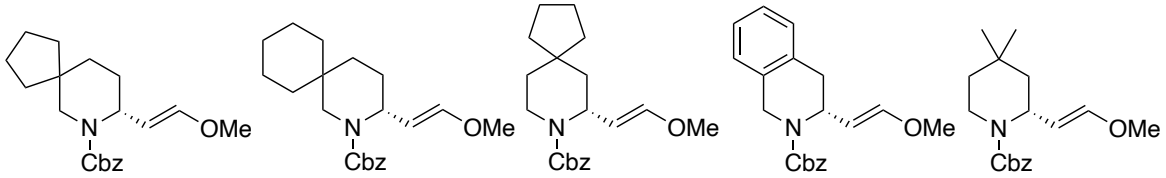
R = H, dimethyl, cyclopentyl, cyclohexyl, fused phenyl

R^1 = Cbz, Fmoc, Boc

176

Up to 88% yield

Up to 99% ee



177	**178**	**179**	**180**	**181**
24 h, 78%, 92% ee 30 h, 73%, 93% ee	24 h, 74%, 95% ee 30 h, 71%, 96% ee	8 h, 77%, 93% ee 12 h, 71%, 95% ee	6 h, 88%, 81% ee 24 h, 73%, 93% ee	14 h, 73%, 95% ee 24 h, 66%, 99% ee

Scheme 32 : Using unsaturated acetals as Michael acceptors

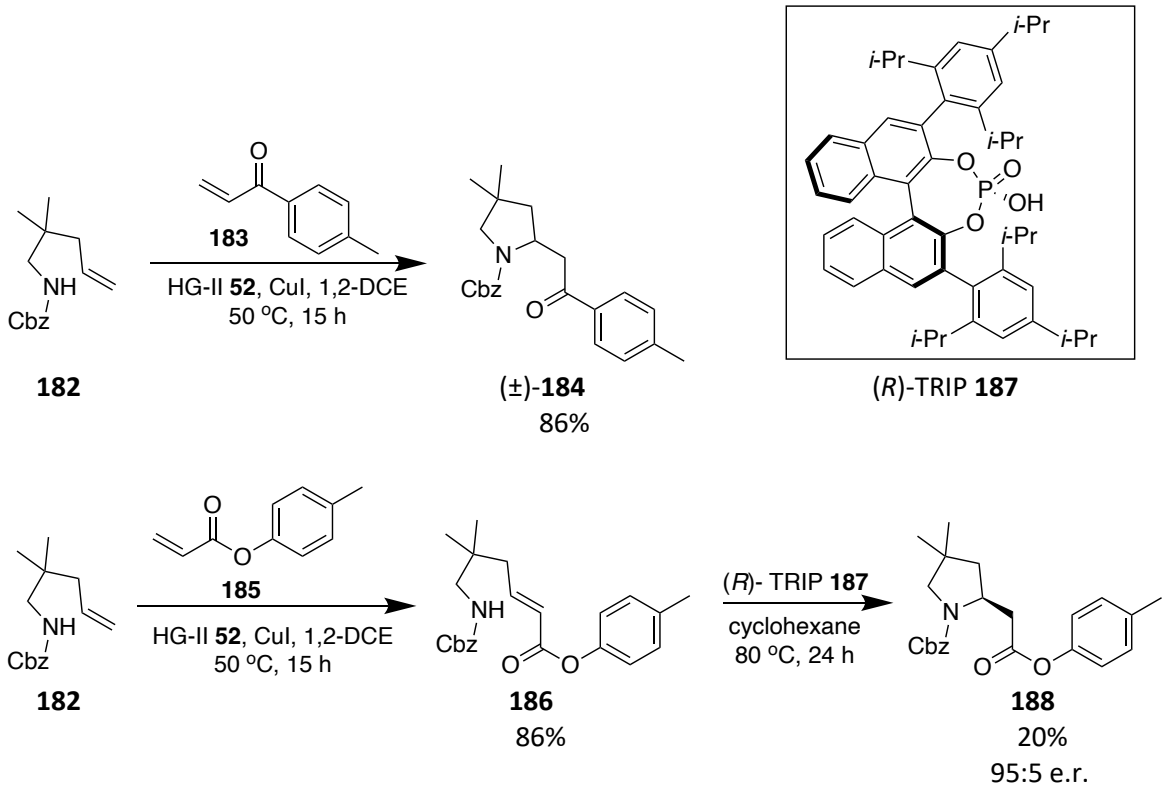
Industrially, the use of CCl_4 would need to be avoided because of its known toxicity. The use of cryogenic temperatures for extended periods of time would also make the process unfeasible for industrial scale up. Safer solvents and non-cryogenic temperatures would be required for a greener approach to synthesizing enantioenriched spiropiperidines.

Before new methods to synthesise spiropiperidines with high yields and enantioselectivities were envisaged, a few criteria needed to be considered - is there a Michael acceptor that can be handled easily? Can the use of CCl_4 as a solvent and cryogenic temperatures for an extended period of time be avoided, and still result in high yields and enantioselectivities of substituted spiropiperidines? The following sections aim to answer these questions in achieving the end result.

2. Results and Discussions

2.1 Use of α-β thioesters as Michael acceptors

One of the key strategies involved in the Clarke group's research is the use of thioesters as Michael acceptors in the asymmetric synthesis of substituted THPs[81] and pyrrolidines.[82] A set of experiments were carried out by a former member of the group, Chris Maddocks, to arrive at the optimised reaction conditions for the asymmetric synthesis of pyrrolidines. A pivotal part of these experiments was in determining an appropriate Michael acceptor. Organocatalysis is known to be one of the most flourishing areas of research in organic chemistry and CPAs are one of the robust organocatalysts that have enabled a variety of asymmetric reactions.[83] Following the reports of Akiyama[84] and Terada,[85] CPAs have become popular choice of catalysts among organic chemists. It was hypothesised that a CPA could be effective in catalysing the aza-Michael reaction to synthesise pyrrolidines enantioselectively.

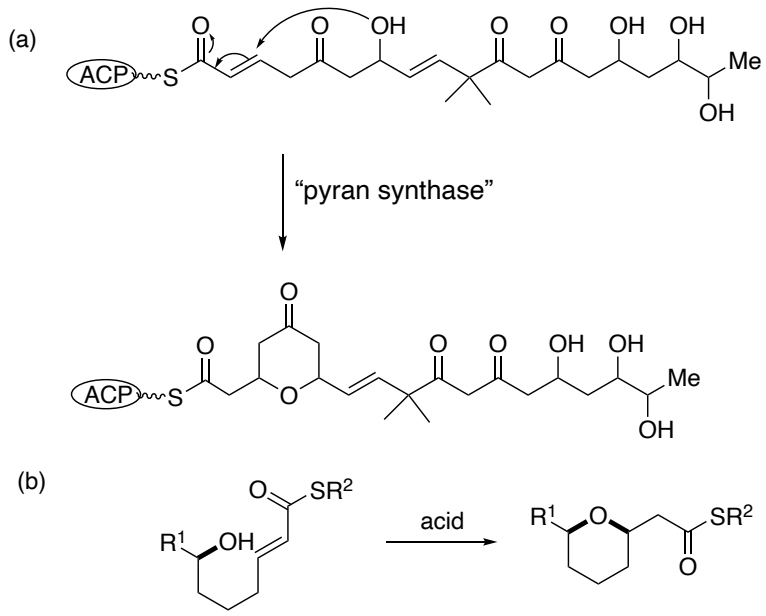


Scheme 33 : Cyclisation with unsaturated ketone and oxo-ester

When Cbz-amine **182** was subjected to metathesis conditions with α-β unsaturated ketone **183** as the Michael acceptor in the presence of HG-II catalyst **52** and CuI, only the racemic

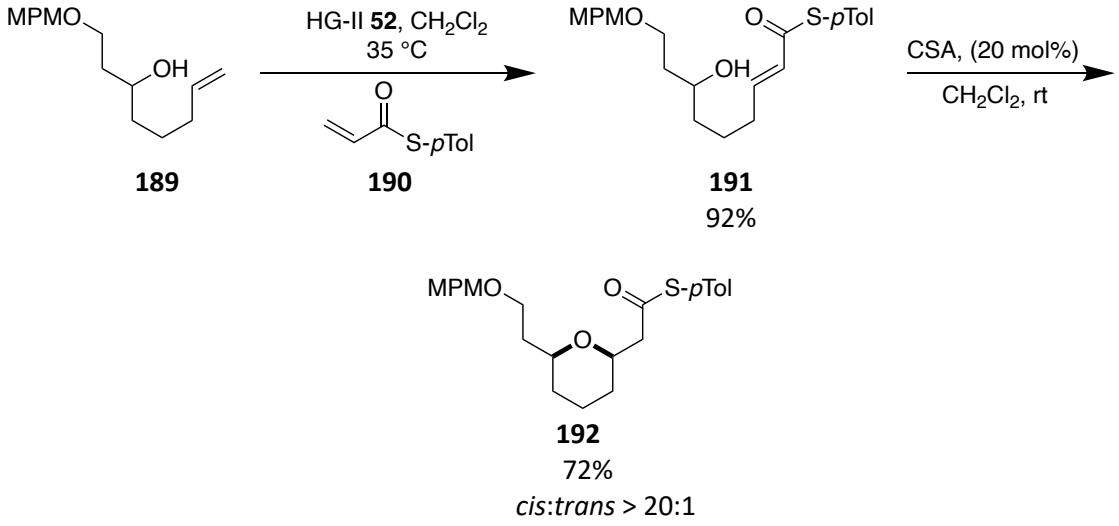
compound **184** was isolated in 86% yield (Scheme 33). This could be due to the high reactivity of ketones which led to the cyclisation reaction of the metathesis product leading to a racemic product. When an α-β unsaturated oxo-ester **185** was used as the Michael acceptor and subjected to metathesis conditions with **182**, metathesis product **186** was obtained in 86% yield. In the presence of (*R*)-TRIP **187** as the catalyst, the cyclised product **188** was formed in an excellent enantioselectivity of 95:5 e.r. but in a poor yield of 20%. The low yield was not surprising considering the low reactivity of an ester due to resonance of the oxygen lone pair of electrons on the carbonyl carbon, making it less electrophilic. However, the high enantioselectivity was an encouraging result, proving that CPAs were a good choice of catalysts for these reaction conditions.

Biosynthetic studies for the polyketide containing tetrahydropyrans showed that it was formed *via* an intramolecular oxa-conjugate cyclisation catalysed by pyran synthase. The acyl carrier protein (ACP) bound to a thioester functioned as a Michael acceptor activated by hydrogen bonding, for the attack by the nucleophilic hydroxyl group (Scheme 34a). [86] Fuwa reasoned that a greater reactivity of α-β unsaturated thioesters with respect to the corresponding oxo-esters played a key role in this reaction. Inspired by the biosynthesis, he proposed a biomimetic methodology for the synthesis of 2,6-*cis*-THPs (Scheme 34b).[86]



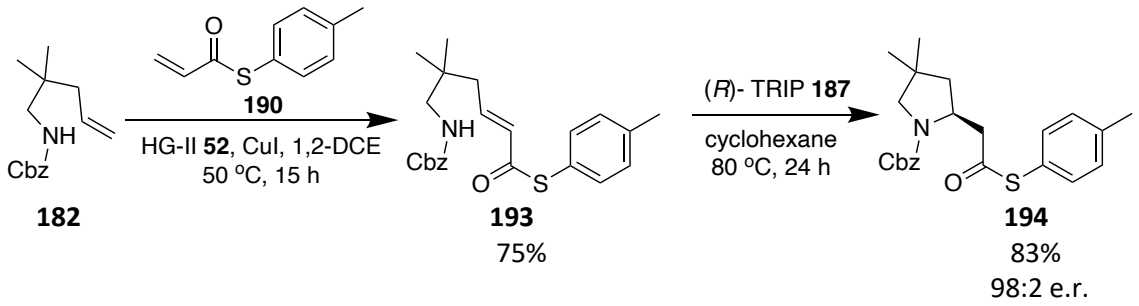
Scheme 34 : (a) Biosynthesis of THPs of polyketide natural products (b) Biomimetic synthesis of 2,6-cis-THPs proposed by Fuwa

Based on the proposed synthesis, hydroxyolefin **189** was subjected to olefin cross metathesis conditions with thioacrylate **190** catalysed by HG-II catalyst **52** to form the cyclisation precursor **191** in an excellent yield of 92% (Scheme 35). Brønsted acid catalysed cyclisation of precursor **191** in the presence of camphor sulfonic acid (CSA) in CH_2Cl_2 led to the synthesis of 2,6-*cis*-substituted tetrahydropyran **192** in 72% yield with d.r. >20:1. The advantage of using thioesters as Michael acceptors was also demonstrated owing to their versatility, by derivatizing them into different functional groups under mild conditions resulting in excellent yields.[86]



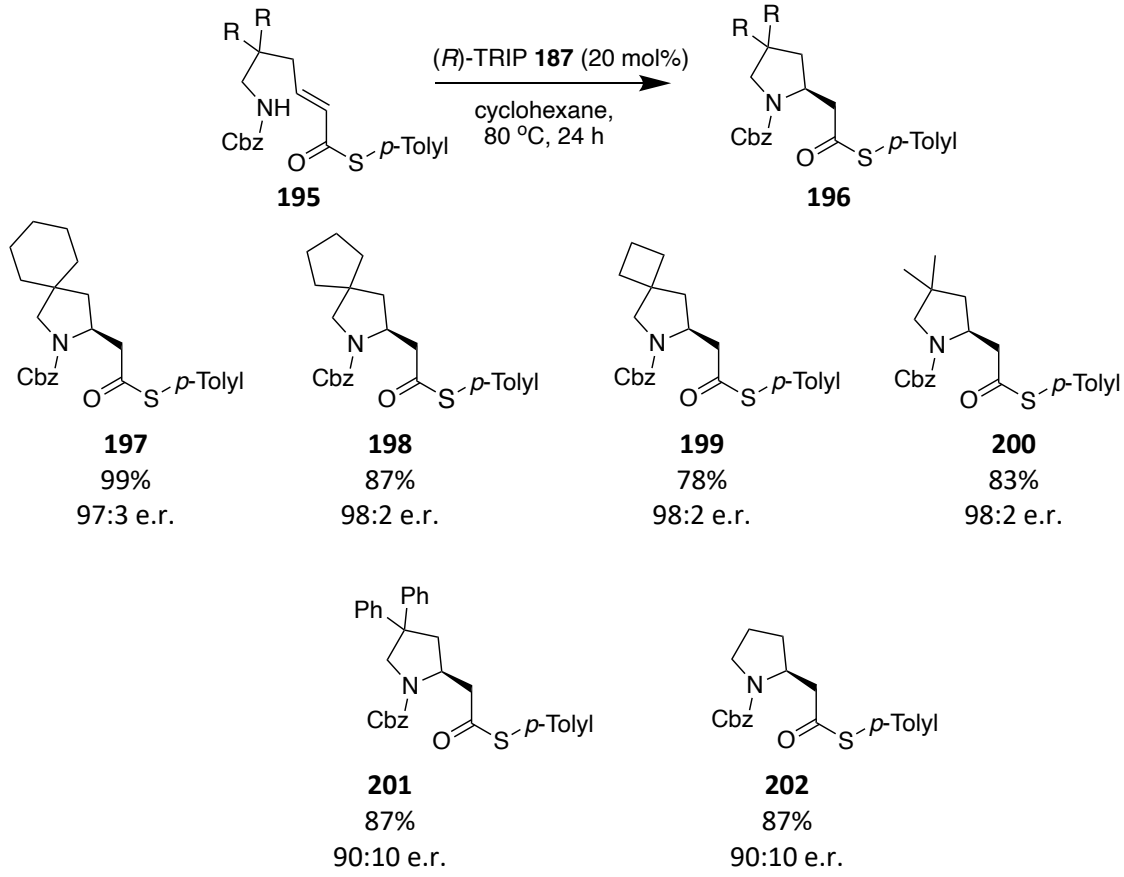
*Scheme 35 : Use of α-β thioesters as Michael acceptors to synthesise 2,6-cis-substituted tetrahydropyran **192***

Building on the interesting reactivity of thioesters, the Clarke group decided to incorporate the thioester functionality in their experiments towards arriving at an appropriate Michael acceptor in synthesis of pyrrolidines. Under metathesis conditions, Cbz-amine **182** and thioester **190** reacted to form the amine-thioester **193** in 75% yield which upon cyclisation in the presence of (*R*)-TRIP resulted in an excellent yield and enantioselectivity of **194** in 83% with 98:2 e.r. (Scheme 36).



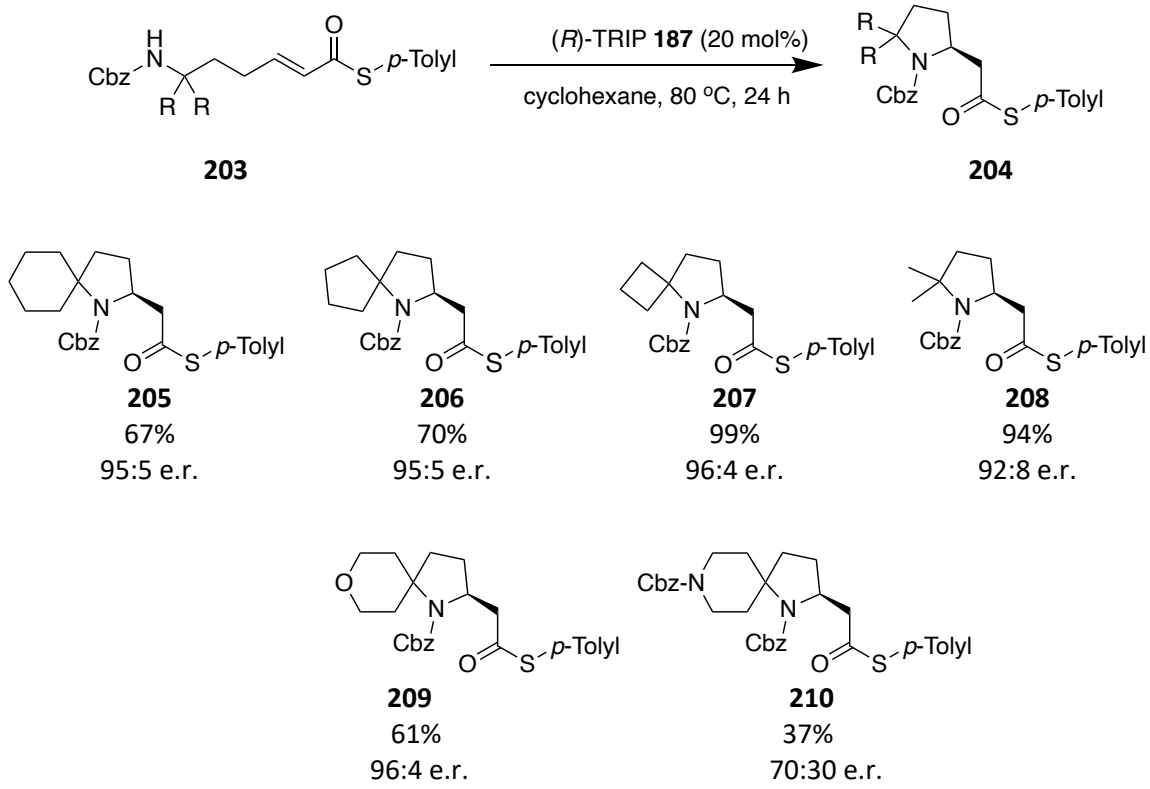
Scheme 36 : Use of thioester as Michael acceptor for the synthesis of pyrrolidines

The contrasting results in the previous Schemes 33-36 provide valuable insight into the relative reactivity of the Michael accepter when conjugated to different carbonyl groups. Of the three carbonyl classes, the carbonyl of an oxo-ester is the least reactive due to the delocalization of lone pair electrons from the oxygen atom onto the carbonyl carbon, making it less electropositive. This is not in the case of an unsaturated ketone, where there is no delocalization of electrons, thus making the carbonyl carbon highly electrophilic leading to an immediate cyclisation of the metathesis product formed in Scheme 33. The reactivity of thioesters falls in between that of a ketone and an ester due to smaller overlap of lone pair electrons on sulfur because of its larger 3p orbital as compared to that of oxygen (2p orbital). This reactivity can be exploited in Michael reactions to synthesise nitrogen and oxygen heterocycles.



Scheme 37 : Asymmetric synthesis of 3,3'-spiropyrrolidines

After optimizing aza-Michael reaction conditions, asymmetric synthesis of spirocyclic pyrrolidines catalyzed by CPAs that used α-β unsaturated thioesters as the Michael acceptors was achieved.[82] This methodology was successful in the synthesis of 3,3'-spiropyrrolidines and 3,3'-disubstituted pyrrolidines with a range of substituents where the amino-thioesters **195** were cyclized in the presence of (*R*)-TRIP **187** to give substituted pyrrolidines **197-202** in high yields and enantioselectivities (Scheme 37). The methodology was extended to 2-spiropyrrolidines yielding them in high enantioselectivities and yields (Scheme 38).



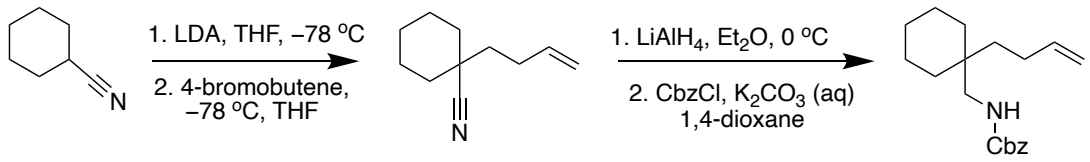
Scheme 38 : Asymmetric synthesis of 2,2-spiropyrrolidines

The next set of questions to be answered involved the feasibility of this methodology to synthesise the six-membered nitrogen heterocycle piperidine and if thioesters, in combination with a CPA, would offer a similar advantage to result in high yields and enantioselectivities for the corresponding substrate scope.

2.2 Asymmetric synthesis of 3-spiropiperidines

2.2.1 Synthesis of precursors

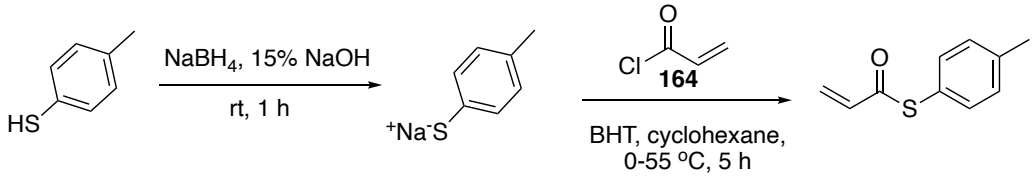
Following the success of the methodology in the synthesis of spiropyrrolidines, it was decided to investigate its applications to the synthesis of spiropiperidines. The synthesis of the 3-spirocyclic substituted piperidine precursors involved a two-part convergent strategy using readily available starting materials. Initial studies began using cyclohexyl as the substituent where cyclohexane carbonitrile **211** was deprotonated in the presence of LDA and alkylated with 4-bromobutene to form **212** in 77% yield. The nitrile was then reduced to the primary amine using lithium aluminium hydride followed by formation of the Cbz-carbamate **213** in the presence of benzyl chloroformate in 78% yield over two steps (Scheme 39).



211 **212** 77% **213** 78%

*Scheme 39 : Synthesis of Cbz-amine **213***

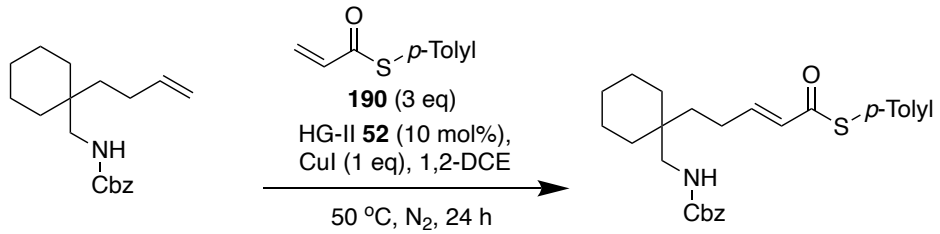
The next step was to synthesize the α-β unsaturated thioester **190** which has been used in the group previously.[18] Thiol **214** was deprotonated by dissolving in aqueous NaOH/$NaBH_4$ to generate the thiolate **215** with $NaBH_4$ added to prevent the formation of disulphides. To this, a solution of acryloyl chloride **164** and 2,4,6-butylated hydroxytoluene (BHT) dissolved in cyclohexane was added and heated to 55 °C. The addition of BHT prevented radical polymerization of the thioester through oxidation of thiol. Thioester **190** was obtained in 51% yield (Scheme 40).



214 **215** **190** 51%

*Scheme 40 : Preparation of thioester **190***

With the Cbz-amine **213** and thioester **190** in hand, the next step was to perform a cross metathesis reaction which would deliver the aza-Michael cyclisation precursor. Grubbs categorized olefins for cross metathesis reactions based on their relative ability to undergo homodimerization and the reactivity of the homodimers towards secondary metathesis conditions.[56] Acrylates fall under the Type-II olefins which undergo slow homodimerization in the presence of second-generation Grubbs catalyst while the Cbz-amines like **213** are Type-I olefins which homodimerize quickly. The homodimer thus formed, further reacts readily under the metathesis conditions to form the cross-metathesis product.



213 **216** 76%

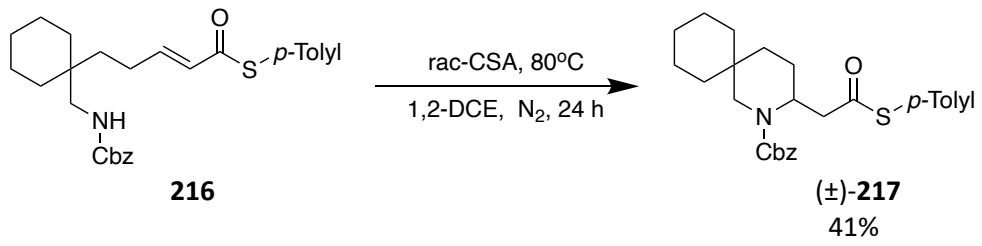
*Scheme 41 : Cross metathesis reaction of amino-thioester **213** with p-tolyl thioester*

Previous work in the group found that one equivalent of the second generation Hoveyda-Grubbs catalyst was required for a cross-metathesis reaction with thioacrylates.[87] However, further work in the group[82] demonstrated that 10 mol% of HG-II catalyst **52** in the presence of copper (I) iodide as a co-catalyst resulted in good-excellent yields of the cross-metathesis product. This was originally reported by Lipshutz who showed that adding sodium iodide or copper iodide as a co-catalyst with Grubbs catalysts had a stabilizing effect which was effective in increasing the rate of olefin cross-metathesis reactions. This is reported to be due to the stabilizing effect of the iodine ion on the catalyst.[88] In this case, adding one equivalent of CuI along with HG-II catalyst **52** led to the facile formation of the cross-metathesis product, amino thioester **216**, in 76% yield (Scheme 41).

2.2.2 Brønsted acid cyclisation of precursors

The next part of the process was to study the asymmetric aza-Michael cyclisation of the precursor which would give an insight into the enantioselectivity of the reaction. To this end, a racemic aza-Micheal cyclisation was carried out on **216** in the presence of excess

racemic camphorsulfonic acid (rac-CSA) and heated to 80 °C in 1,2-DCE which yielded (±)-**217** in 41% yield (Scheme 42).



216 (±)-**217** 41%

*Scheme 42 : Racemic cyclisation of precursor **217***

The proton assignment of **217** is shown in Figure 10 which was arrived at using 1-D and 2-D NMR. Aromatic protons of the Cbz group and the thioester appeared as a multiplet from 7.42−7.10 ppm. The benzylic protons H-17 correspond to the singlet at 5.12 ppm while the proton H-8 formed after cyclisation appeared as a broad peak from 4.91−4.67 ppm. This was confirmed with DEPT (Figure 11) as a positive peak at 48.85 ppm along with C-1 at 21.48 ppm and the aromatic protons as positive peaks. The two protons on C-15 appear as two broad multiplets at 4.24−3.87 ppm and 2.67−2.44 ppm respectively in the ^{1}H NMR (Figure 10). This is confirmed by the COSY spectrum in Figure 12 which shows the H-H coupling of the two protons of H-15 and H-15' with each other. Protons on H-7 were assigned the multiplet from 3.0−2.84 ppm as they showed long-range coupling (HMBC) with the thioester carbon C-6 and the carbon C-8 as shown in Figure 13. The methyl protons (H-1) from the thioester were assigned the singlet at 2.37 ppm.

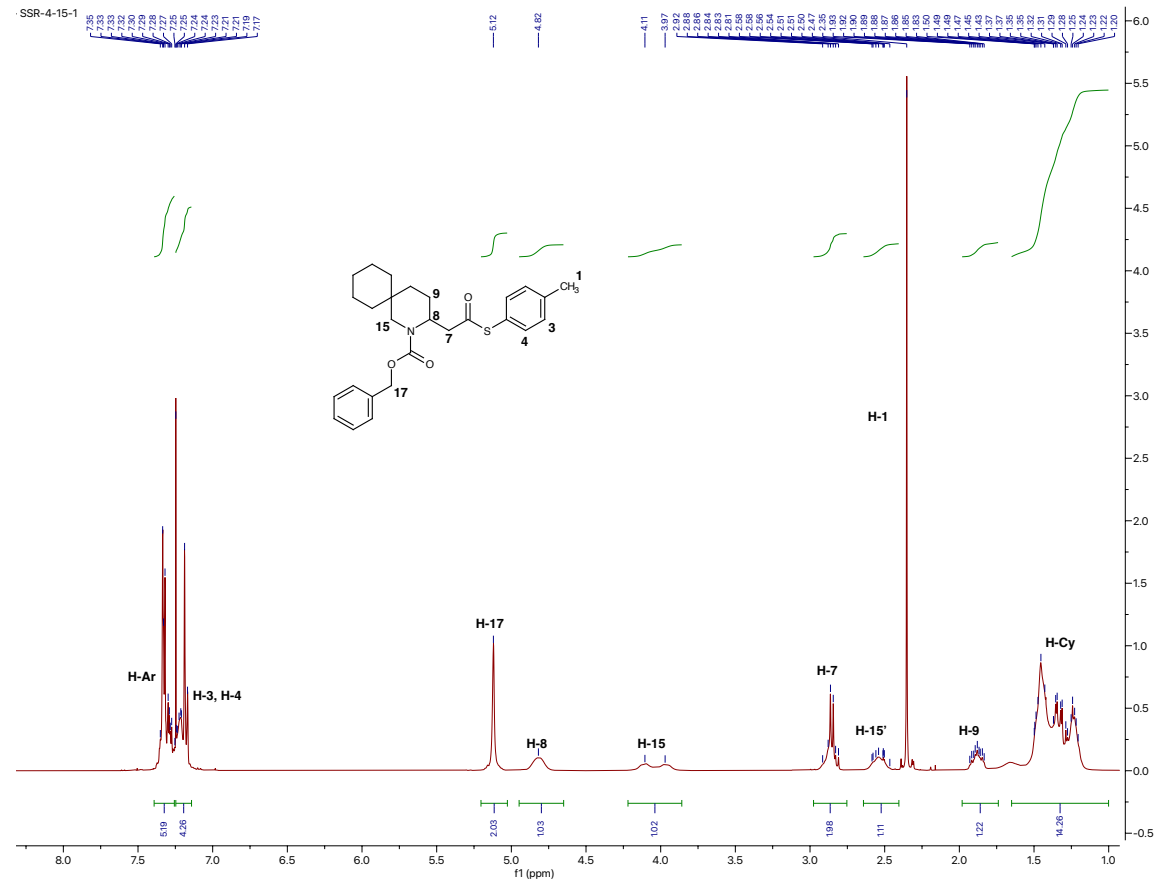


*Figure 10 : ^{1}H NMR spectrum of **217***

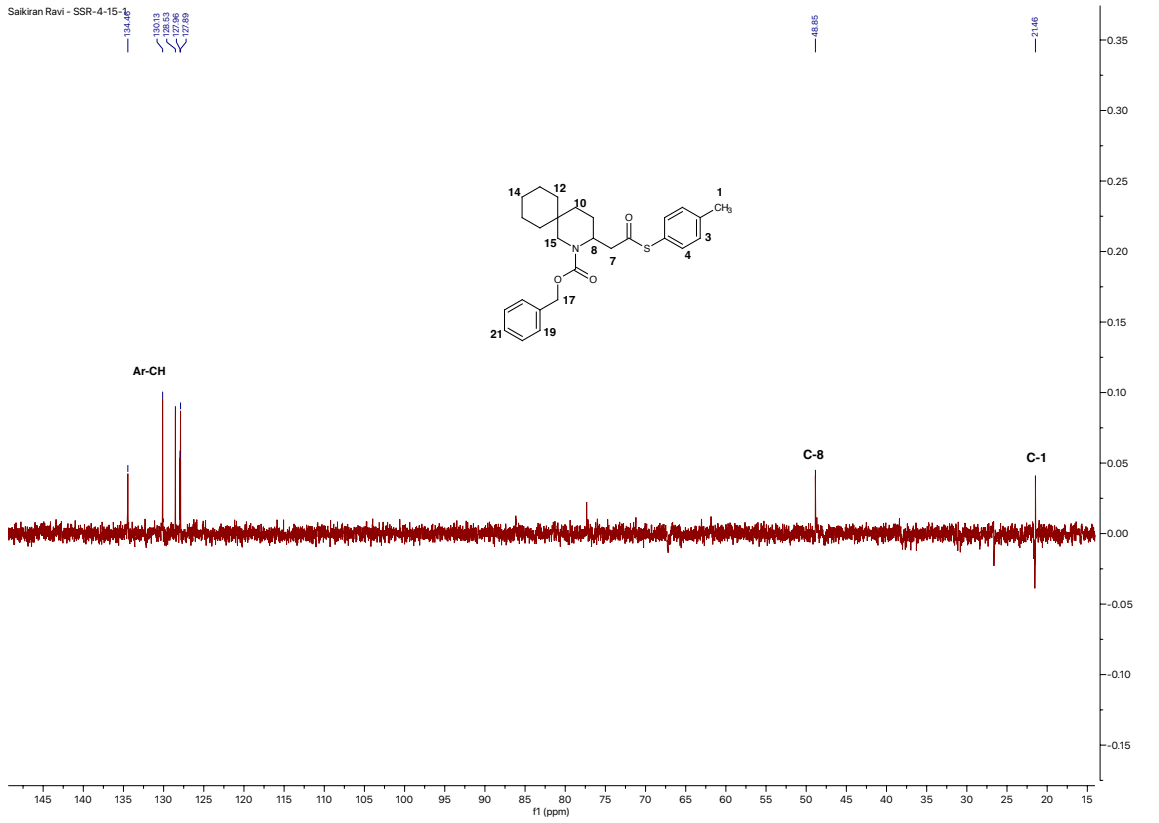


Figure 11 : DEPT for compound 217 showing positive peaks for C-H protons

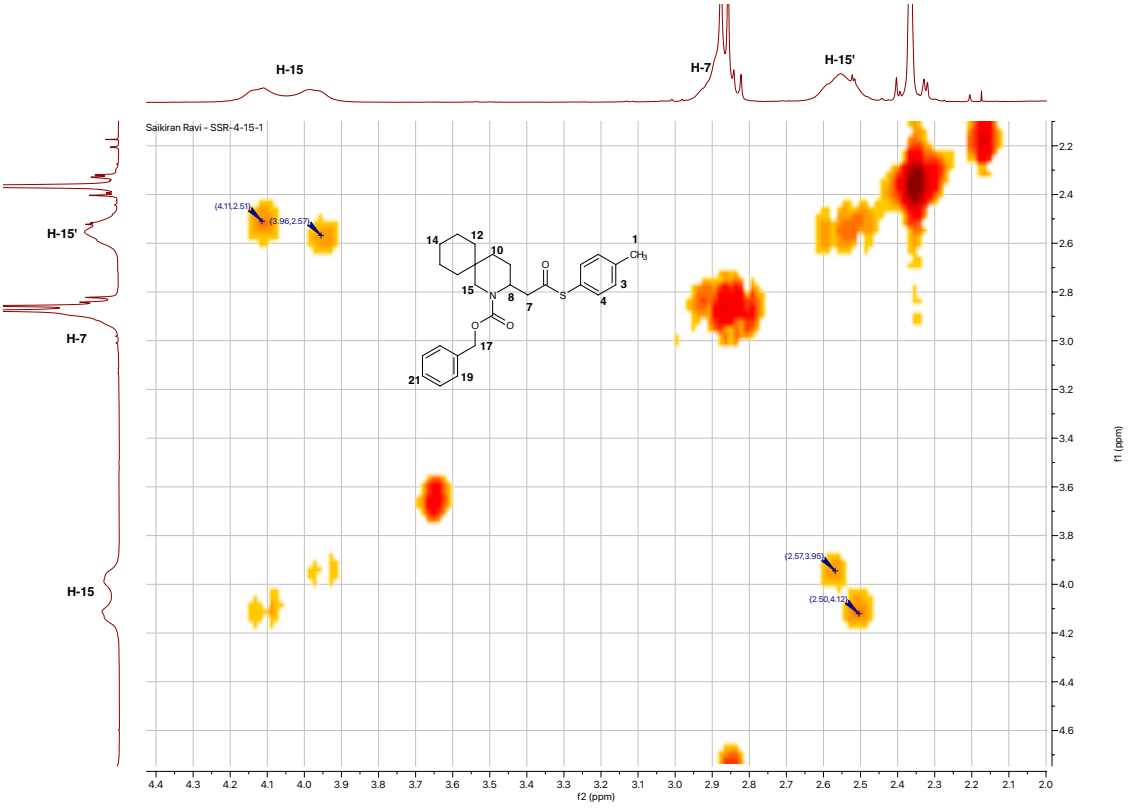


*Figure 12 : COSY spectrum showing correlation between H-15 and H-15' in **217***

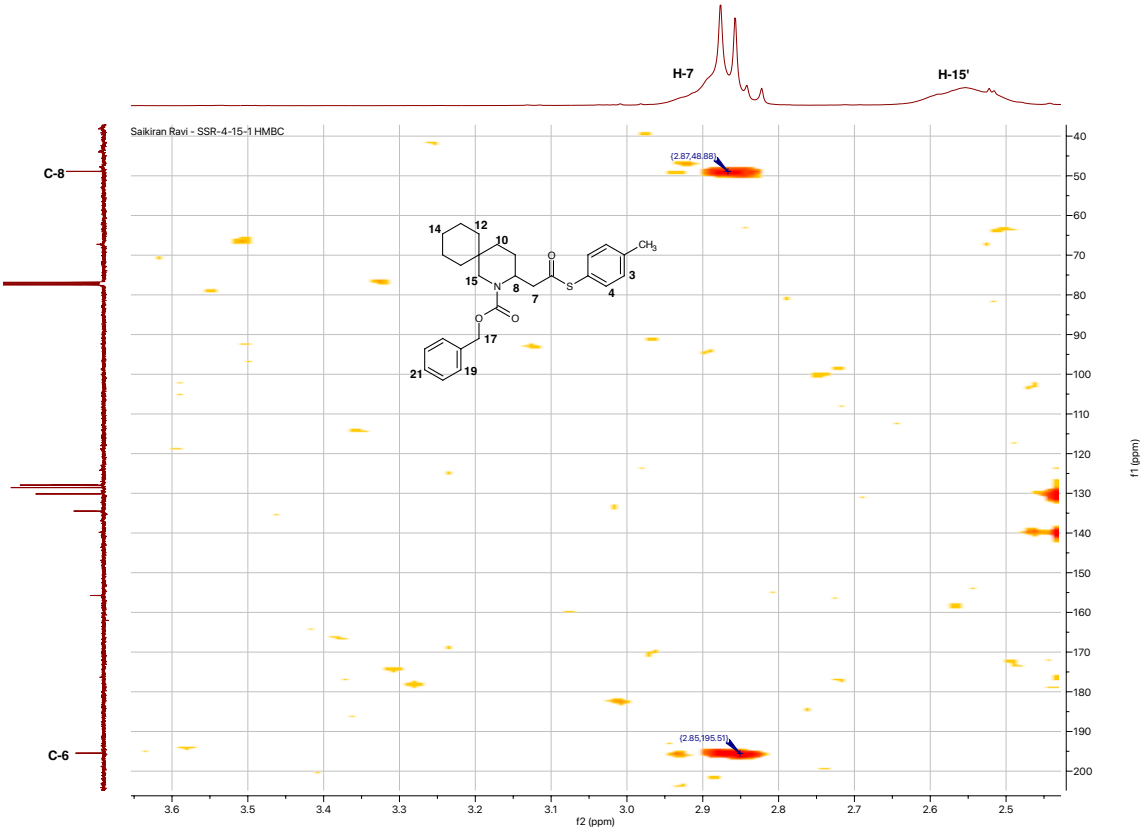
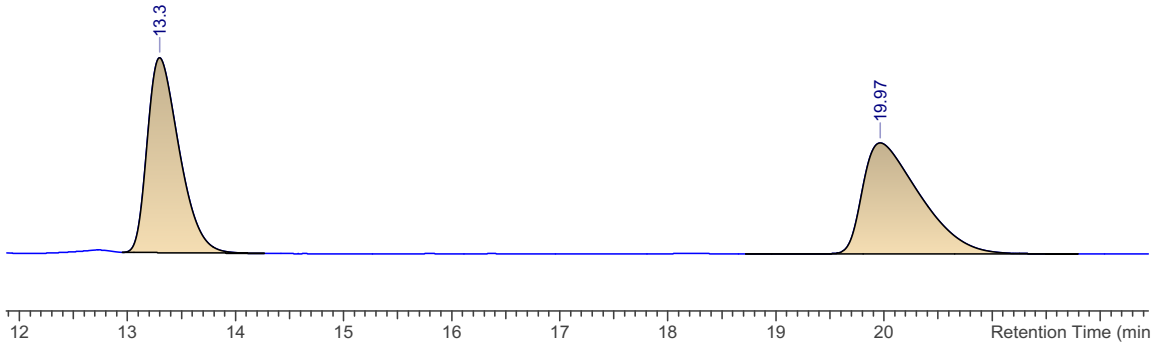


*Figure 13 : HMBC spectrum showing long range bonding between H-7 with C-6 and C-8 in **217***

With the racemic product **217** synthesized and characterised, the next step was to separate the enantiomers *via* chiral HPLC. Chiral chromatography involves the separation of enantiomers based on their interaction with the chiral stationary phase of the column. For the purpose of this study, CHIRALPAK® IA, IB and IC columns were screened to resolve the enantiomers. Different concentrations of the eluent (hexane:IPA), temperatures and flow rate were varied to achieve good separation of the enantiomers as two sharp peaks with equal percentage area. The best separation of enantiomers for **217** was obtained with 95:5 of hexane:2-propanol with a flow rate of 1.0 mL/min on the IB column at 25 °C. As expected, area under the peaks were in the ratio 50:50, confirming the formation of a racemic product (e.r. = 50:50) as shown in Figure 14. The retention time of the peaks were used to compare the enantiomeric ratios of the asymmetric products formed subsequently.

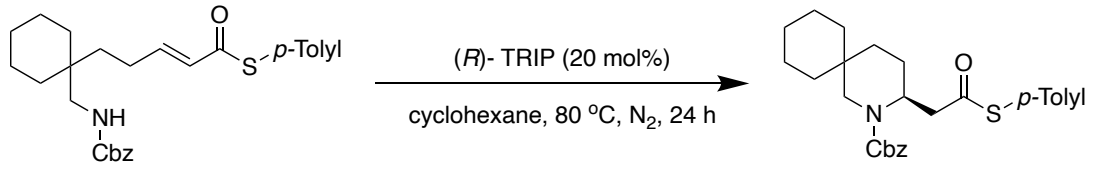


No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	13.30	9500926.000	49.554	0.538
2	19.97	9671766.000	50.446	0.969

HPLC conditions: Chiralpak ® IB Column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 25 °C, λ = 254 nm; e.r. = 50:50

*Figure 14 : Resolution of enantiomers of racemic (±)-**217***

The asymmetric aza-Michael reaction was then carried out using the conditions that were successful in the synthesis of spiropyrrolidines (Scheme 37)[82]. Thus, 20 mol% of the CPA, (*R*)- TRIP, was used as the catalyst with cyclohexane as the solvent and heated to 80 °C for 24 hours (Scheme 43).

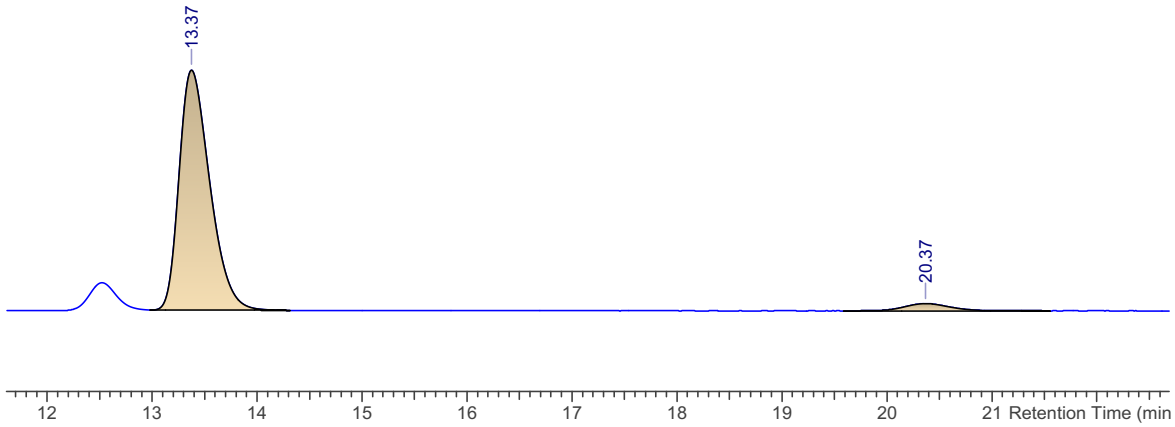


216

217
10%
96:4 e.r.

Scheme 43 : Cyclisation using conditions that were successful for the synthesis of pyrrolidines

It was a delight to obtain **217** with an excellent enantioselectivity of 96:4 e.r. (enantiomeric ratio) (Figure 15) after comparing the retention time of the peaks from the racemic product in Figure 14. While this proved that the (*R*)- TRIP catalyst was efficient in giving high enantioselectivities, it was disappointing to see a yield of 10% (Scheme 43).It was reasoned that the difficulty in forming a six-membered ring as compared to a five-membered counterpart resulted in the low yields. Thus, the next steps were focussed on improving the yields while maintaining high enantioselectivities thus obtained.



No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	13.37	6660466.000	95.691	0.530
2	20.37	299931.688	4.309	0.782

HPLC conditions: Chiralpak ® IB Column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 25 °C, λ = 254 nm; e.r. = 96:4

*Figure 15 : HPLC trace for asymmetrically synthesised **217** with 96:4 e.r.*

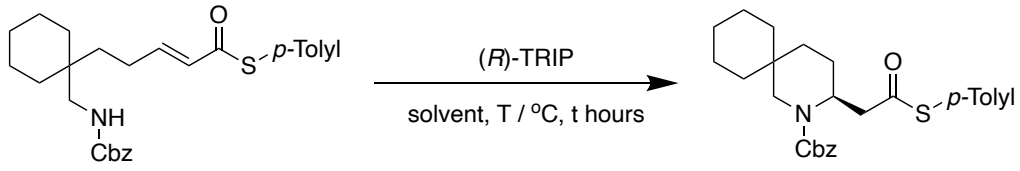
The piperidine **217** obtained asymmetrically in Scheme 43 was arbitrarily assigned an (*S*)-absolute stereochemistry at the chiral centre formed, based on the results obtained with similar methodologies for the asymmetric synthesis of pyrrolidines[82] and THPs[89] in the Clarke group. The confirmation of the stereochemistry of the chiral piperidines will be discussed in a later section in the thesis.

2.3 Optimization of aza-Michael reaction conditions

2.3.1 *p*-tolyl thioester

On careful consideration of the reaction conditions, it was clear that reaction parameters like temperature, time, thioester functionality, catalyst and solvent could influence the enantioselectivity and yield of the reaction. In order to improve the yield, it was decided to change each of these parameters in turn and observe the reaction outcomes (Table 1). Initial screening was done by varying the temperature and solvent.

Table 1 entry 1 shows the conditions that were tested in Scheme 43 which gave a yield of 10% with 96:4 e.r. Increasing the reaction time to 48 hours was marginally successful resulting in a yield of 21%, with no change in the e.r. (entry 2). This showed that though the reaction was sluggish over longer reaction times, excellent enantioselectivities could still be obtained. The next parameter to change was the temperature to test the reaction tolerance at higher temperatures. Increasing the temperature to 95 °C with octane (boiling point 125.6 °C) as the solvent resulted in a marginal increase in yield to 23% with a slight decrease in enantioselectivity to 95:5 e.r. (entry 3). Upon further increase in temperature to 100 °C, the yield improved to 36% with the e.r. at 94:6. This was an encouraging result as high enantioselectivities were being maintained at high temperatures.



216 **217**

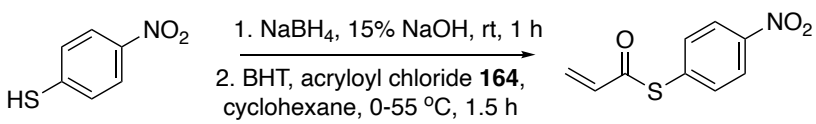
Entry	Solvent	T / °C	t / hours	Yield / %	e.r.
1	cyclohexane	80	24	10	96:4
2	cyclohexane	80	48	21	96:4
3	octane	95	24	23	95:5
4	octane	100	24	36	94:6

Table 1 : Screening reaction conditions with p-tolyl thioester

In conclusion, it was noted that *p*-tolyl thioester **190** in conjunction with (*R*)-TRIP as the catalyst resulted high enantioselectivities, however, a change in time and temperature of the reaction impacted the yield of the product, although very slightly. The reaction needed further optimisation to improve the yield and further parameters needed to be varied in order to achieve this end.

2.3.2 *p*-nitro thioester

Changing the functionality of the thioester was considered in order to improve the yield of the reaction. It was envisaged that an electron-withdrawing group on the *para* position of the aromatic ring of the thioester would make the Michael acceptor more electrophilic, thus increasing the rate of the cyclisation reaction. Thioester **219** was synthesized using the same procedure used in Scheme 40 from 4-nitrothiophenol **218** as shown in Scheme 44.

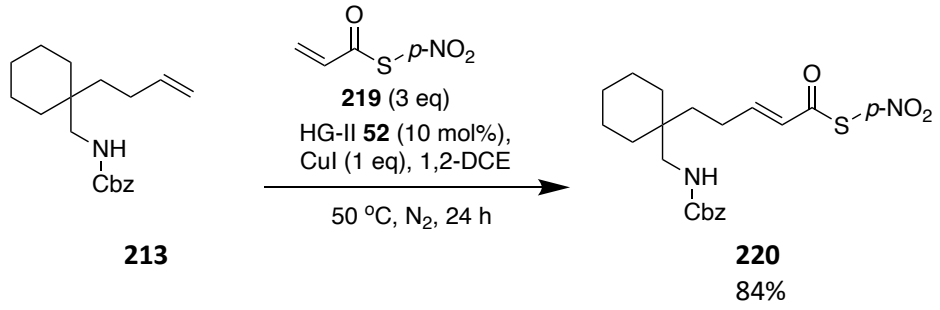


218
4-nitrothiophenol

219
63%

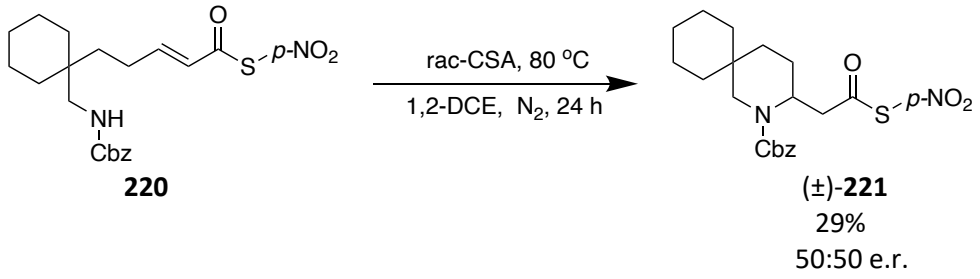
*Scheme 44 : Preparation of thioester **219***

Cross metathesis of the amine **213** with the *p*-nitro thioester **219** with the established conditions resulted in the amino-thioester **220** (Scheme 45) which was subjected to aza-Michael cyclisation reaction subsequently.



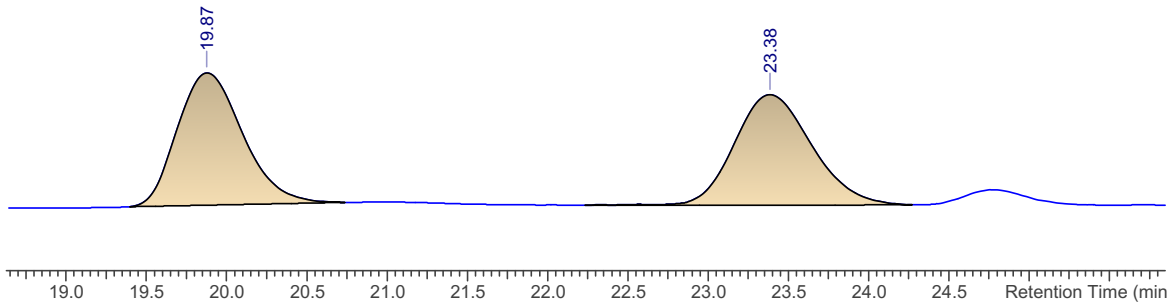
*Scheme 45 : Cross metathesis using thioester **219***

Mirroring the *p*-tolyl substrate, the precursor **220** was cyclised in the presence of rac-CSA to yield the racemic product (±)-**221** in 29% yield (Scheme 46).



*Scheme 46 : Synthesis of (±)- **221***

The enantiomers of the racemic compound were resolved using chiral HPLC as shown in Figure 16. Chiralpak ® IB Column was found to give the best separation between the two peaks of equal areas with a flow rate of 1 mL/min of hexane/2-propanol (95:5) at 40 °C.

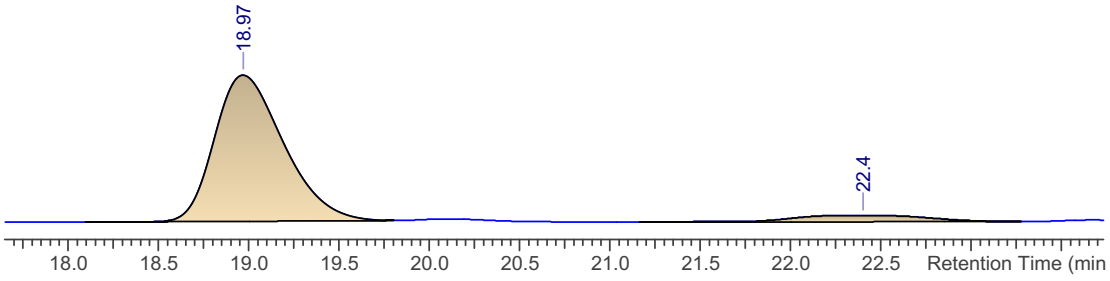


No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	19.87	281308.219	50.259	0.755
2	23.38	278406.219	49.741	0.883

HPLC conditions: Chiralpak ® IB Column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 40 °C, λ = 254 nm; e.r. = 50:50

*Figure 16 : HPLC trace of (±)-**221***

Compound **220** was cyclised using conditions from the cyclization of pyrrolidines, i.e. (*R*)-TRIP as the catalyst in cyclohexane at 80 °C for 24 hours and the product was formed with a low yield of 20% (Table 2, entry 1). The HPLC conditions that resolved the racemic product **221** in Figure 16 was used to separate the enantiomers of the above-mentioned asymmetric reaction. It was found that the product was formed in high enantioselectivity of 92:8 e.r. (Figure 17), although slightly lower than that obtained with *p*-tolyl thioester under the same reaction conditions, i.e., 94:6 e.r.



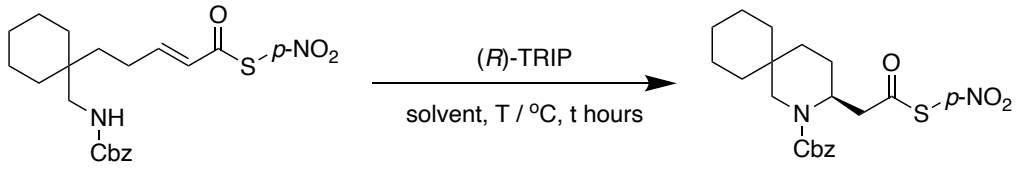
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	18.97	6508034.000	92.470	0.699
2	22.40	529962.938	7.530	1.431

HPLC conditions: Chiralpak ® IB Column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 40 °C, λ = 254 nm; e.r. = 92:8

*Figure 17 : HPLC trace of chiral **221** formed using the conditions: (R)-TRIP, cyclohexane, 80 °C*

Increasing the reaction time to 48 hours proved detrimental as it resulted in a drop in the enantioselectivity to 84:16 e.r. with almost no change in the yield (Table 2, entry 2). Upon changing the solvent to toluene and stirring the reaction at 80 °C for 48 hours, the e.r. further reduced to 71:29 with a yield of 8% (entry 3). It was reasoned that pi-stacking interactions between the solvent and the catalyst led to a drop in the enantioselectivity. Since longer reaction times did not improve the yield or enantioselectivity, it was decided to stop the reaction after 24 hours thereafter.

On increasing the temperature to 95 °C for 24 hours in octane, the high enantioselectivity returned to 93:7 e.r., although with a low yield of 17% (entry 4). The yield was further improved on increasing the temperature to 100 °C in octane at 55% with a slight decrease to 89:11 e.r. (entry 5). It was decided to run the reaction at the same temperature (100 °C) but using microwave radiation as the heat source, which if successful, could help in reducing reaction times while having good yields and enantioselectivities. Instead, the resulting product was isolated with a very poor yield of 9% and it was racemic (entry 6). This could be due to the rapid heating in the microwave which eroded the enantioselectivity as compared to the heating in an oil bath.



220 **221**

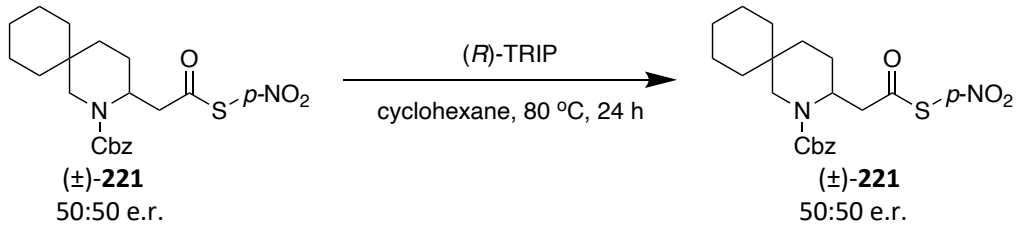
Entry	Solvent	T / °C	t / hours	Yield / %	e.r.
1	cyclohexane	80	24	20	92:8
2	cyclohexane	80	48	21	84:16
3	toluene	80	48	8	71:29
4	octane	95	24	17	93:7
5	octane	100	24	55	90:10
6	octane	100 [a]	1	9	50:50

[a] *microwave*

*Table 2 : Reaction conditions to synthesise **221** asymmetrically*

It was concluded that high temperatures of 100 °C gave a moderate yield of 55% and 90:10 e.r. Although the yield obtained was the best so far, the drop in enantioselectivity from 96:4 e.r. with *p*-tolyl thioester (Table 1, entry 1) was not desirable.

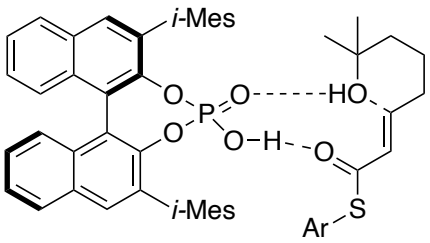
The lower enantioselectivities with the *p*-nitro thioester as compared to the *p*-tolyl counterpart led us to investigate the possibility of a retro-Michael reaction under the reaction conditions. The racemic product **221** was subjected to asymmetric conditions to check for reversibility of the reaction (Scheme 47). It was noted that the product remained racemic which ruled out the possibility of a retro-Michael reaction, leading to the reason for a drop in enantioselectivity still unclear.



*Scheme 47 : Subjecting racemic **221** to asymmetric conditions*

2.3.3 Mesityl thioester

Density Function Theory (DFT) studies on asymmetric synthesis of THPs carried out in the Clarke group[89] showed that the thioester functionality influenced the enantioselectivity of the reaction (Figure 18). In the presence of (*R*)-TRIP as the catalyst, the *p*-tolyl thioester functionality resulted in transition state like structures favouring the (*S*)- enantiomer over the (*R*) enantiomer by a low margin of 1.9 kcal/mol. This finding was corroborated with an experimental low enantioselectivity of 18% ee. On increasing the steric bulk of the thioester by introducing the mesityl thioester, the (*S*)- enantiomer was favoured over the (*R*) enantiomer by an increased margin of >5 kcal/mol which was experimentally proved to result in a higher enantioselectivity of 69% ee (Figure 18).



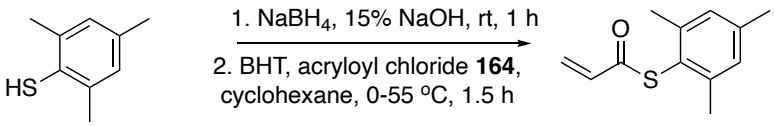
Ar = *p*-tolyl; ΔE = 1.9 kcal/mol
Experimental results - 18% ee

Ar = Mes; ΔE = >5 kcal/mol
Experimental results - 69% ee

Reaction conditions: (*R*)-TRIP, cyclohexane, 50 °C, 24 h

Figure 18 : DFT studies involving TS-like structures for the CPA catalysed synthesis of THPs favouring the (S)-enantiomer, where ΔE relates to the energy difference between R and S enantiomers

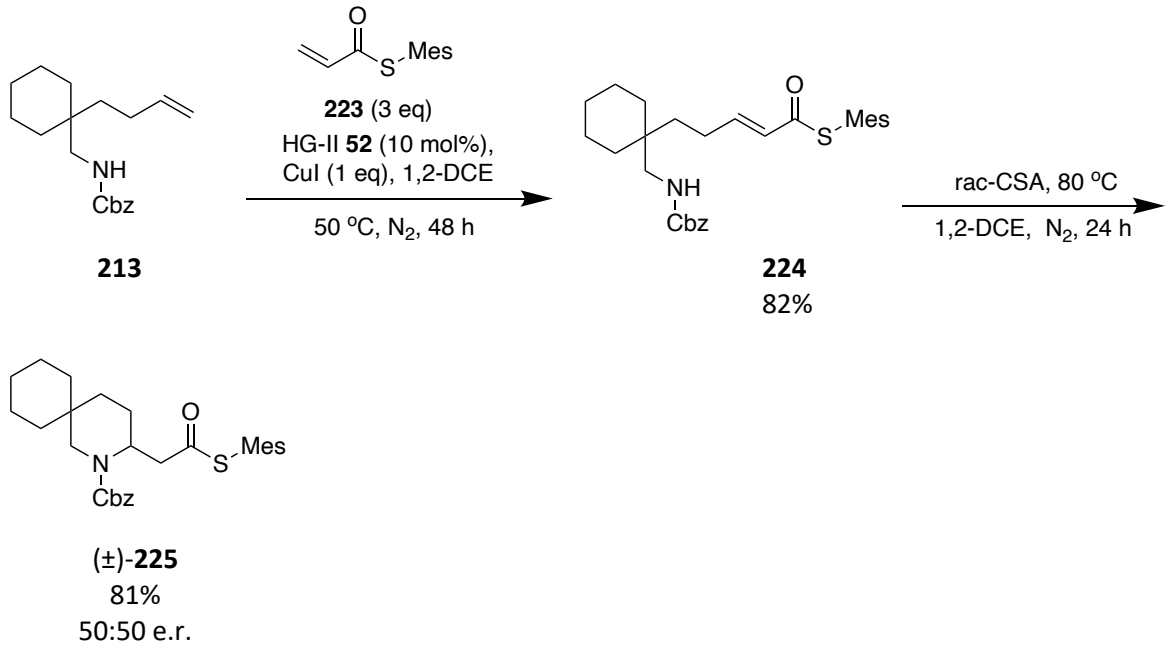
Applying these results to maintain the high enantioselectivities obtained so far for the piperidines and to sustain them when the reactions were run at higher temperatures, the mesityl functionality was introduced to observe its effect on the yield of the reaction.



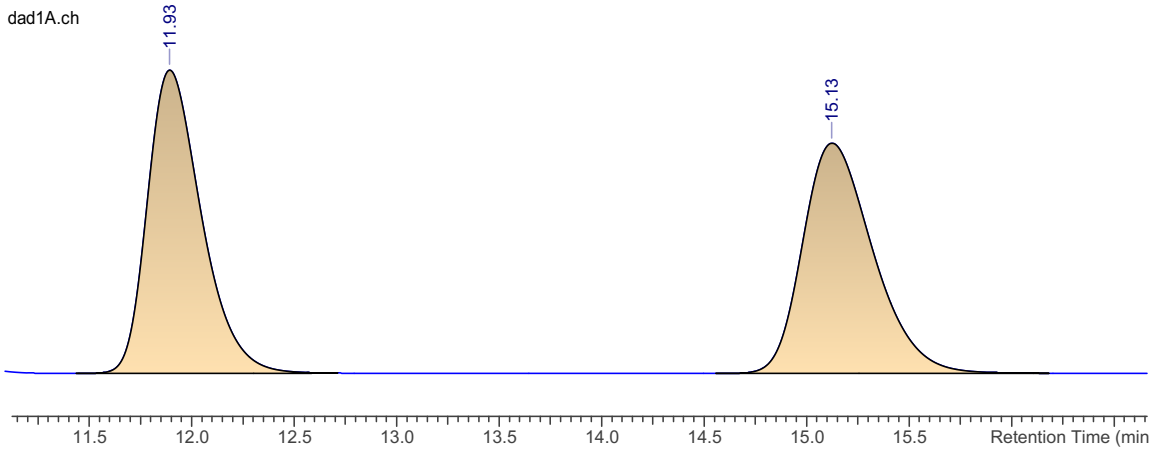
222 **223** 69%

*Scheme 48 : Synthesis of mesityl thioacrylate **223***

Mesityl thioacrylate **223** was synthesized from 2,4,6-trimethylthiophenol **222** in 69% yield (Scheme 48) using the method previously described for the preparation of *p*-tolyl thioester **190**. The thioester **223** was reacted with Cbz amine **213** under metathesis conditions to yield the cyclisation precursor **224** in 82% yield. Amino-thioester **224** was cyclised in the presence of rac-CSA to form the racemic cyclised product **225** (Scheme 49).The two enantiomers were separated using Chiralpak ® IA Column with hexane/2-propanol (95:5) as the eluent, at a flow rate of 1.0 mL/min at 40 °C, giving equal areas under the peaks at 11.9 min and 15.1 min as shown in Figure 19.



*Scheme 49 : Metathesis of Cbz-amine **213** with mesityl thioester **223***



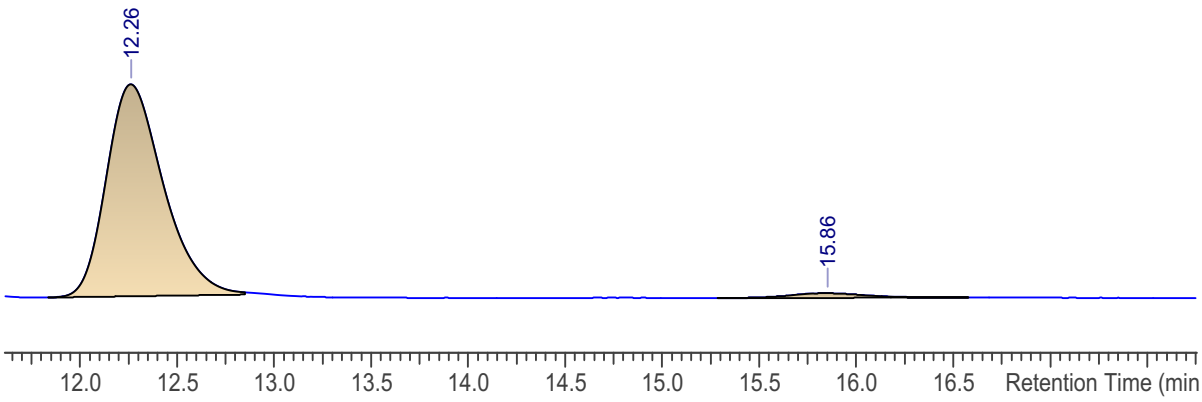
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	11.92	3639067.500	50.289	0.472
2	15.13	3597187.250	49.711	0.620

HPLC conditions: Chiralpak ® IA Column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 40 °C, λ = 254 nm; e.r. = 50:50

*Figure 19 : HPLC trace of (±)-**225***

Cyclisation of the precursor **224** using the conditions from the pyrrolidines project [(*R*)-TRIP, 80 °C, cyclohexane, 24 h] resulted in an excellent enantioselectivity of 97:3 e.r. but with only 15% yield of **225** (Figure 20 and Table 3, entry 1). Since increasing the reaction

time to 48 hours did not improve the yield and resulted in the same enantioselectivity of 97:3 e.r. (entry 2), the reactions were run for 24 hours thereafter. Changing the solvent to heptane (boiling point 98.4 °C) and heating at 80 °C increased the yield to 24% while maintaining the enantioselectivity at 97:3 e.r. (entry 3). This showed that different solvents of similar polarity at the same temperature resulted in similar enantioselectivities. Gratifyingly, an improved yield of 45% was observed when the temperature was increased to 95 °C in heptane, while maintaining high enantioselectivity of 96:4 e.r. (entry 4).

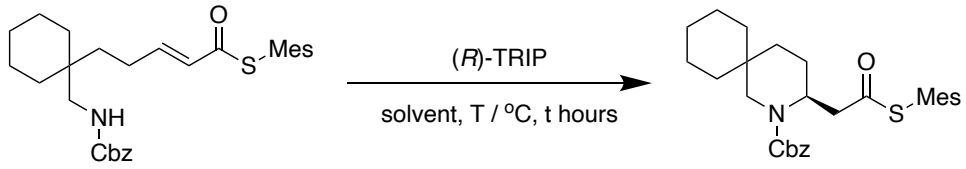


No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	12.26	1063003.625	97.239	0.531
2	15.86	30187.508	2.761	0.689

HPLC conditions: Chiralpak ® IA Column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 40 °C, λ = 254 nm; e.r. = 97:3

*Figure 20 : HPLC trace of **225** under the reaction conditions: (R)-TRIP, 80 °C, cyclohexane, 24 h*

It was encouraging to see excellent enantioselectivities being maintained at high temperatures, so it was decided to further explore the tolerance to higher temperatures. To this end, the solvent was changed to octane (boiling point 125.6 °C) and the reaction was performed at four temperatures: 95 °C, 100 °C , 110 °C and 120 °C. Octane at 95 °C (entry 5) gave similar results to heptane at 95 °C with a yield of 44% with 96:4 e.r., showing that enantioselectivities were unaffected by different solvents of similar polarity at the same temperature. Upon increasing the temperature to 100 °C, the yield and enantioselectivity marginally improved to 47% with 96:4 e.r. respectively (entry 6). Further increments in temperature to 110 °C and 120 °C reduced the enantioselectivity to 95:5 e.r. and 93:7 e.r. respectively, although with increase in yields to 63%, which was the highest yield obtained so far, and 56% respectively (entries 7 and 8).



224 **225**

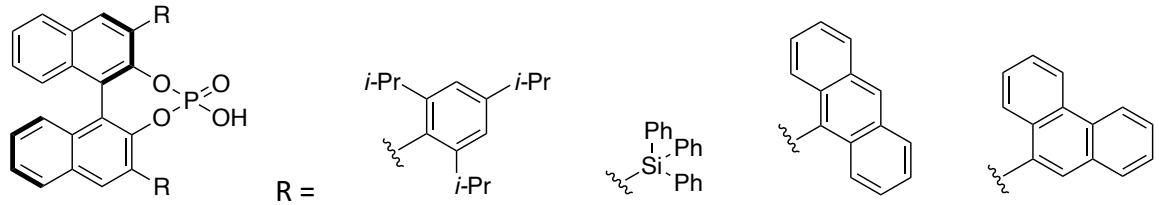
Entry	Solvent	T / °C	t / hours	Yield / %	e.r.
1	cyclohexane	80	24	15	97:3
2	cyclohexane	80	48	14	97:3
3	heptane	80	24	24	97:3
4	heptane	95	24	45	96:4
5	octane	95	24	44	96:4
6	octane	100	24	47	96:4
7	octane	110	24	63	95:5
8	octane	120	24	56	93:7

*Table 3 : Screening of reaction conditions with Cbz amine-mesityl thioester **224***

In conclusion, after comparing the results of the three thioesters from Tables 1-3, it was found that octane at 100 °C with (*R*)-TRIP as the catalyst gave the best balance between yield and enantioselectivity, with each thioester respectively (*p*-tolyl- 36%, 94:6 e.r.; *p*-NO_2- 55%, 90:10 e.r.; Mes- 47%, 96:4 e.r.). Since the best enantioselectivity among the three results was from the mesityl thioester, it was decided to carry out a catalyst screen using this substrate while keeping the other parameters unchanged.

2.3.3.1 Catalyst screen

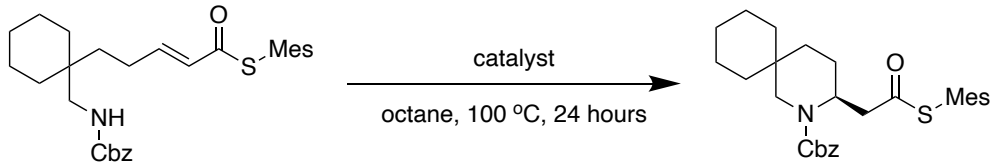
The high enantioselectivities obtained with the mesityl thioester at 100 °C in octane paved way for a catalyst screen to further optimise the yields. Commercially available CPAs were the chosen to avoid their multistep synthesis and thus save time. Three other CPAs apart from (*R*)-TRIP were used in the study as shown in Figure 21.



CPA | R = | **187** (*R*)-TRIP | **226** (*R*)-TiPSY | **227** (*R*)- Anth | **228** (*R*)-Phen

Figure 21 : CPAs used in the study

The catalysts were screened in octane at 100 °C on substrate **224** over 24 hours and the results obtained are shown in Table 4, with entry 1 containing the results obtained using (*R*)-TRIP as the catalyst, as previously discussed.



224 **225**

Entry	Catalyst	Yield / %	e.r.
1	(*R*)-TRIP	47	97:3
2	(*R*)-TiPSY	17	38:62
4	(*R*)-Anth	67	92:8
3	(*R*)- Phen	21	62:38

Table 4 : CPA catalyst screen

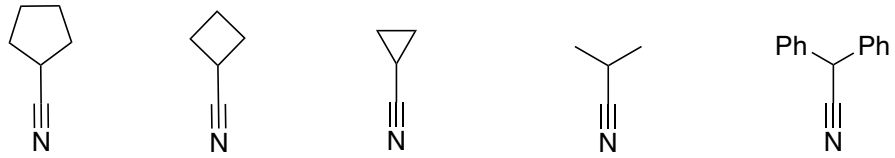
Catalyst (*R*)-TiPSY **226** resulted in the opposite and the lowest enantioselectivity of 38:62 e.r. obtained so far with a poor yield of 17% yield (entry 2). While (*R*)-Anth **227** resulted in an increased yield and enantioselectivity to 67% and 92:8 e.r. respectively, (*R*)- Phen **228** gave a reduced yield and enantioselectivity of 21% and 62:38 e.r. respectively. This confirmed that (*R*)-TRIP was a preferred catalyst as it resulted in better enantioselectivity.

In conclusion, mesityl thioester gave the best balance between yield and enantioselectivity in octane at 95/100 °C in the presence of (*R*)-TRIP as the catalyst.

2.3.3.2 Substrate scope with mesityl thioester

Although yields obtained with octane at 95/100 °C were not high as desired, they were the best obtained so far. Between 95 °C and 100 °C, it was decided to continue further optimisations with the former. With the reaction conditions in hand- (*R*)-TRIP, octane, 95 °C, - the next step was altering the substitution on the third position of the piperidine ring and study the scope and limitations of the reaction under these reaction conditions.

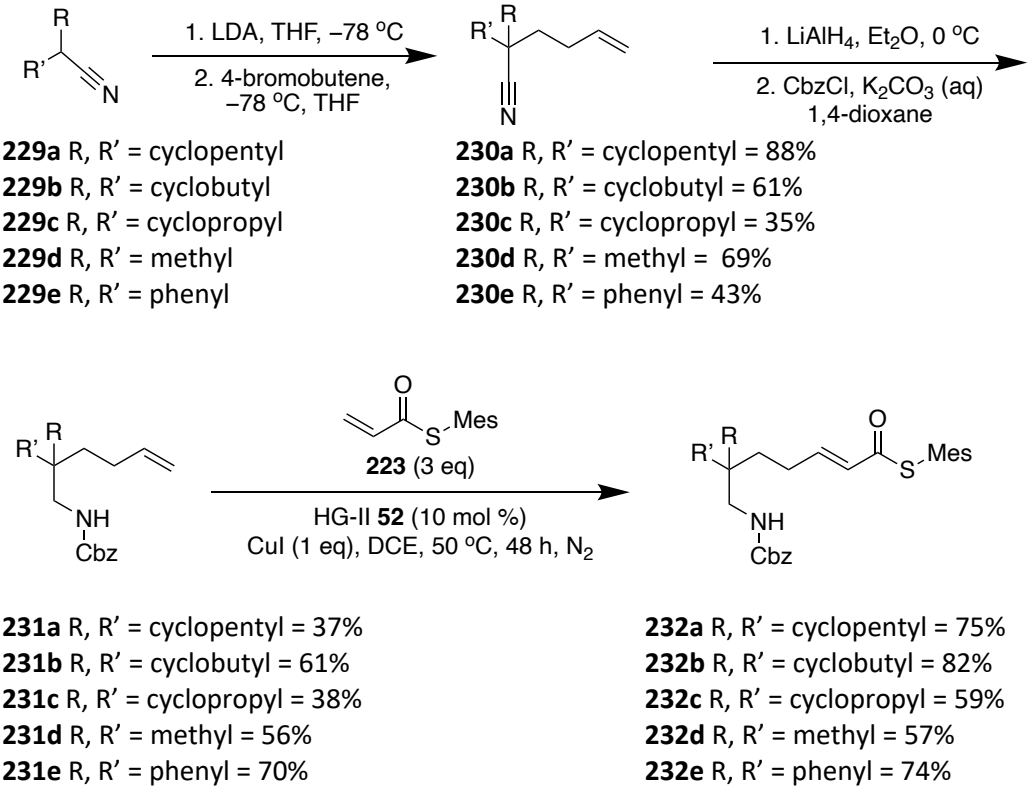
Five different 3,3'-substitution patterns were chosen to give the corresponding disubstituted or spirocyclic piperidines. The following nitriles were used as the starting materials, all of which were commercially available (Figure 22).



229a **229b** **229c** **229d** **229e**

Figure 22 : Nitriles used as starting materials for substrate scope

The synthesis of the respective cyclisation precursors followed a similar procedure to that outlined in Scheme 39 with the only change being the starting material nitriles. The nitriles were alkylated in the presence of LDA followed by 4-bromobutene resulting in the substituted nitriles (**230a-230e**). The alkylated nitriles were reduced to the primary amines using $LiAlH_4$ and protected to yield the corresponding Cbz-carbamates (**231a-231e**), with substrates **231a-231c** synthesised by undergraduate student Freddy Horsfall. On subjecting the Cbz protected amines to metathesis conditions with thioester **223** in the presence of HG-II catalyst **52** and CuI, moderate to excellent yields (57-82%) of metathesis products **232a-232e** were obtained (Scheme 50). The reactions were left for 48 hours in order to achieve maximum consumption of the limiting reagent.



229a R, R' = cyclopentyl
229b R, R' = cyclobutyl
229c R, R' = cyclopropyl
229d R, R' = methyl
229e R, R' = phenyl

230a R, R' = cyclopentyl = 88%
230b R, R' = cyclobutyl = 61%
230c R, R' = cyclopropyl = 35%
230d R, R' = methyl = 69%
230e R, R' = phenyl = 43%

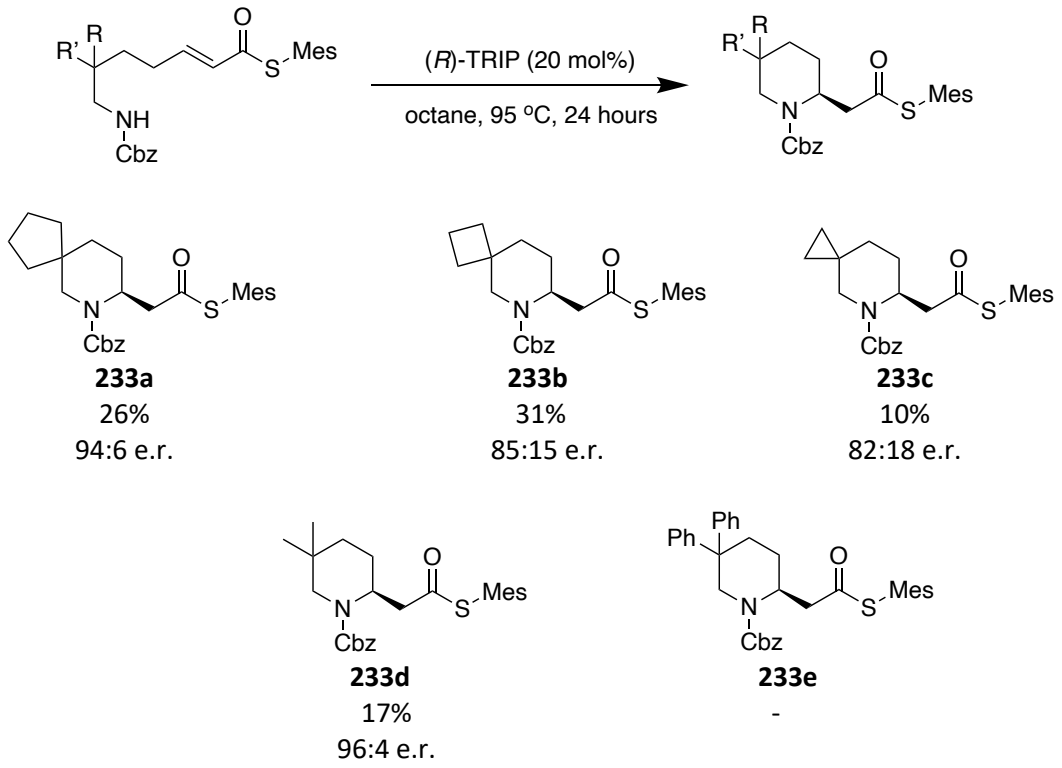
231a R, R' = cyclopentyl = 37%
231b R, R' = cyclobutyl = 61%
231c R, R' = cyclopropyl = 38%
231d R, R' = methyl = 56%
231e R, R' = phenyl = 70%

232a R, R' = cyclopentyl = 75%
232b R, R' = cyclobutyl = 82%
232c R, R' = cyclopropyl = 59%
232d R, R' = methyl = 57%
232e R, R' = phenyl = 74%

Scheme 50 : Synthesis of cyclisation precursors of different substituents

With the precursors in hand, the aza-Michael cyclisation was carried out for the above obtained substrates using the conditions with (*R*)-TRIP as the catalyst in octane at 95 °C (Scheme 51).

While high enantioselectivities were obtained for cyclopentyl **233a** and dimethyl **233d** substituted piperidines, and lower e.r.'s for cyclobutyl **233b** and cyclopropyl **233c** substrates, it was disappointing to see low yields (0-31%) for the substrates. Diphenyl substrate **233e** did not cyclize under the reaction conditions possibly due to steric hindrance by the phenyl groups, and the starting material was recovered (Scheme 51). It was reasoned that the low yields for the other substrates were a combination of the bulky mesityl thioester and the (*R*)-TRIP catalyst. The substrate scope revealed that the optimized reaction conditions were not the best after all, as the highest yield (47%) was obtained with the cyclohexyl substrate, on which the optimization process was carried out.



Scheme 51 : Substrate scope with mesityl thioester

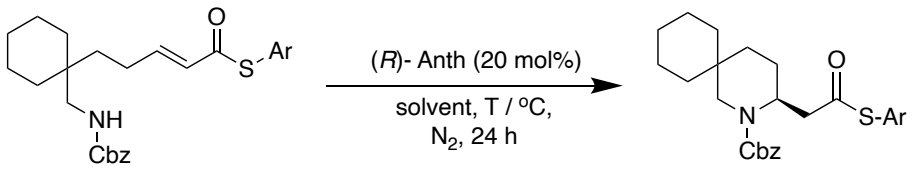
2.3.3.3 (*R*)-Anth catalyst screening

A re-examination of the results of the catalyst screen in Table 4 showed that (*R*)-Anth gave the best yield of 67% although with a slightly lower enantioselectivity of 92:8 (Table 4, entry 3) as compared to that of (*R*)-TRIP catalyst (47%, 97:3 e.r.; Table 4, entry 1). Catalyst (*R*)-Anth gave the second-best result on comparing the enantioselectivities, but it was tested only under one reaction condition- mesityl thioester, octane, 100 °C. It was decided to screen other reaction parameters i.e., thioester, solvent, and temperature, while maintaining the catalyst as (*R*)-Anth.

The three substrates **216, 220** and **224** were subjected to two different conditions - octane at 100 °C and cyclohexane at 80 °C, both using (*R*)-Anth as the catalyst (Table 5). For the ease of comparison, the results obtained with (*R*)-TRIP as the catalyst for the respective reactions conditions are also mentioned, after collating from Tables 1-3. On heating the reaction containing substrate **216** to 100 °C in the presence of octane, **217** was formed in an excellent yield of 80% and a slight reduction in the enantioselectivity at 93:7 e.r. with (*R*)-Anth as compared to that obtained with (*R*)-TRIP as the catalyst (36%, 94:6 e.r. - Table 5, entry 1). With the *p*-nitro substrate **220**, product **221** showed a small improvement in

the yield (55% with (*R*)-TRIP to 65% with (*R*)-Anth) with the same enantioselectivity (89:11 e.r) when either of the catalysts were used (Table 5, entry 2). (*R*)-Anth resulted in better yield of 67% with substrate **224** as compared to 47% from (*R*)-TRIP, while there was a drop in enantioselectivity from 97:3 e.r. in the presence of (*R*)-TRIP to 92:8 (Table 5, entry 3).

These three results showed that while (*R*)-TRIP gave better enantioselectivities, (*R*)-Anth resulted in higher yields at 100 °C with octane as the solvent, although the difference in enantioselectivities was not very large. Also, the *p*-nitro substrate resulted in the same enantioselectivities, for both the catalysts.



entry	Ar (Substrate)	Solvent	T / °C	Yield / % [with (*R*)-Anth]	e.r. [with (*R*)-Anth]	Yield / % [with (*R*)-TRIP]	e.r. [with (*R*)-TRIP]
1	*p*-Tol (**216**)	octane	100	**217** 80	93:7	**217** 36	94:6
2	*p*-NO_2 (**220**)	octane	100	**221** 65	89:11	**221** 55	89:11
3	Mes (**224**)	octane	100	**225** 67	92:8	**225** 47	97:3
4	*p*-Tol (**216**)	cyclohexane	80	**217** 78	96:4	**217** 10	96:4
5	*p*-NO_2 (**220**)	cyclohexane	80	**221** 72	86:14	**221** 20	93:7
6	Mes (**224**)	cyclohexane	80	**225** 36	94:6	**225** 15	98:2

Table 5 : Screening of substrates with (R)-Anth as catalyst

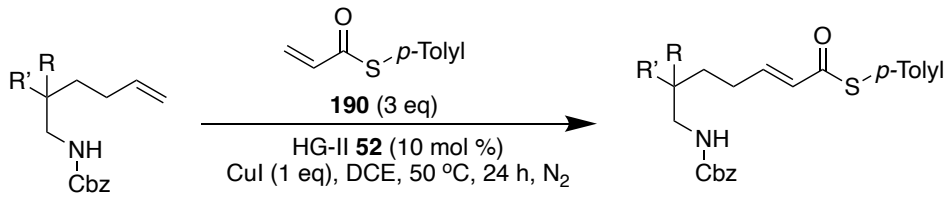
Gratifyingly, **217** was formed with an excellent improvement in yield of 78% in the presence of (*R*)-Anth from only 10% yield with (*R*)-TRIP, in the presence of cyclohexane at 80 °C. Both the catalysts maintained an excellent enantioselectivity of 96:4 e.r. (Table 5, entry 4) under the reaction conditions. Product **221** showed a huge improvement in yield from 20% to 72% but with a drop in enantioselectivity from 93:7 e.r. to 86:14 e.r. when the catalyst was changed from (*R*)-TRIP to (*R*)-Anth respectively (Table 5, entry 5). While **225** was obtained with a drop in enantioselectivity from 98:2 e.r. with (*R*)-TRIP to 94:6 e.r. with (*R*)-Anth, the

yields more than doubled from 15% using (*R*)-TRIP to 36% in the presence of (*R*)-Anth (Table 5, entry 6).

Once again, it was evident that (*R*)-Anth resulted in higher yields, with a drop in enantioselectivities in **221** and **225** as compared to (*R*)-TRIP (entries 5, 6). Since the *p*-tolyl substituted product **217** (entry 4) was formed in improved yields with no drop in enantioselectivity, it was the best result in terms of yield and enantioselectivity obtained so far in the entire optimization process. Thus, the optimized reaction conditions were finalized to be : (*R*)-Anth as the catalyst with cyclohexane as the solvent at 80 °C.

2.4 Scope of the reaction towards 3,3'-disubstituted piperidines

With the optimised reaction conditions for the asymmetric aza-Michael cyclisation achieved, the next step was to synthesise cyclization precursors using the Cbz amines **231a-231e** synthesised previously in Scheme 50. The Cbz amines **231a-231e** were subjected to previously outlined metathesis conditions in the presence of CuI and HG-II catalyst **52** with *p*-tolyl thioester **190** (Scheme 52). On comparing the yields of the substrate obtained with the mesityl thioester **223,** it was observed that the cyclisation precursors **234a-234e** were obtained in higher yields (70-91%). Except for the cyclobutyl substrate **234b** which showed a slight drop in the yield, the others showed improved yields with *p*-tolyl thioester **190** as compared to the mesityl thioester **223**. Lower yields with mesityl thioester could be attributed due to steric hindrance by the mesityl group due to which reactions didn't go to completion even after 48 hours.



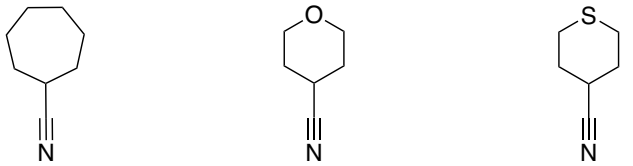
231a R, R' = cyclopentyl
231b R, R' = cyclobutyl
231c R, R' = cyclopropyl
231d R, R' = methyl
231e R, R' = phenyl

234a R, R' = cyclopentyl = 87% (75%)[a]
234b R, R' = cyclobutyl = 80% (82%)[a]
234c R, R' = cyclopropyl = 91% (59%)[a]
234d R, R' = methyl = 70% (57%)[a]
234e R, R' = phenyl = 82% (74%)[a]

[a] Yields obtained with mesityl thioester **223** as mentioned in Scheme 50

Scheme 52 : Metathesis with p-tolyl thioester

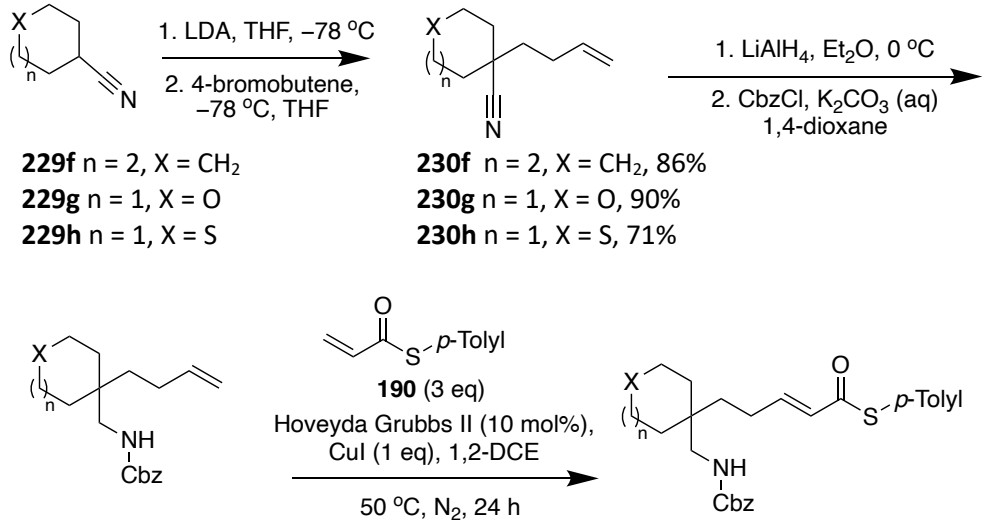
To add to the existing di-substituted/spiro-substituted range, cycloheptyl, 3,3'-THP and 3,3'-tetrahydrothiopyran substitutions were considered starting from the commercially available nitriles **229f, 229g** and **229h** respectively as shown in Figure 23. The cyclisation precursors **234f-234h** were synthesised using the same procedure that was used for the other substrates as outlined in Scheme 50, but using the *p*-tolyl thioester **190** instead.



229f **229g** **229h**

Figure 23 : Commercially available nitriles used for the synthesis of precursors

The nitriles **229f-229h** were alkylated to form **230f-230h** in excellent yields, which further yielded Cbz-amines **231f-231h** via a two-step process by reducing the nitriles to amines in the presence of $LiAlH_4$ followed by Cbz protection in the presence of benzyl chloroformate (Scheme 53). On subjecting the protected amines to metathesis conditions in the presence of thioester **190**, high yields of 64% and 79% were formed with the cycloheptyl **234f** and THP **234g** substrates respectively, while the tetrahydrothiopyran substrate **234h** was formed in a lower yield of 43% and the unreacted starting material amine was recovered.



229f n = 2, X = CH_2
229g n = 1, X = O
229h n = 1, X = S

230f n = 2, X = CH_2, 86%
230g n = 1, X = O, 90%
230h n = 1, X = S, 71%

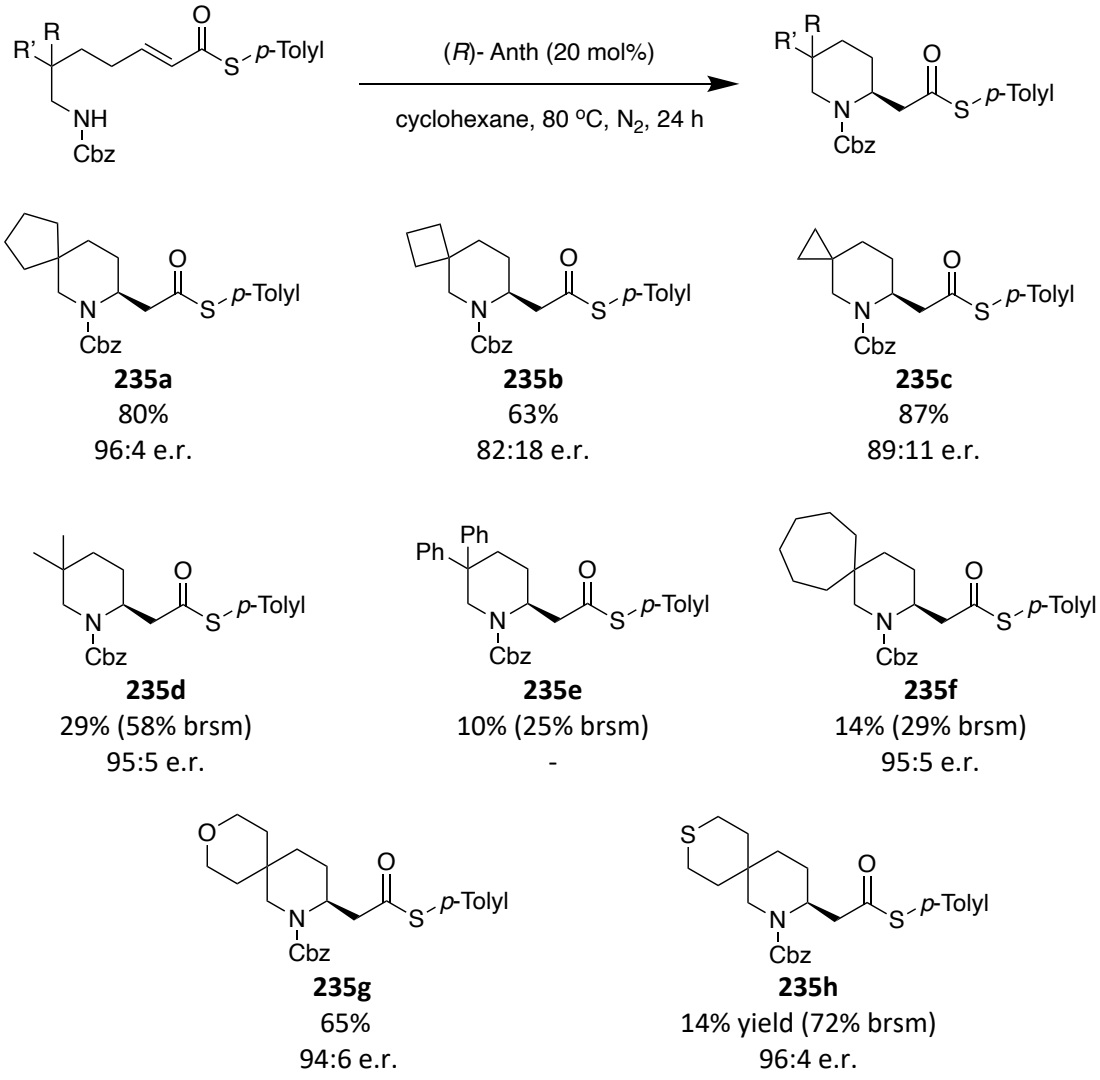
231f n = 2, X = CH_2, 66%
231g n = 1, X = O, 73%
231h n = 1, X = S, 67%

234f n = 2, X = CH_2, 64%
234g n = 1, X = O, 79%
234h n = 1, X = S, 43%

*Scheme 53 : Synthesis of precursors **234f-234h***

2.4.1 Cyclization of precursor substrates

With the eight di-substituted/spiro-substituted precursors in hand, the respective amino-thioesters were cyclized under the optimized reaction conditions – (*R*)-Anth catalyst in cyclohexane at 80 °C as shown in Scheme 54 to obtain compounds **235a-235h.**



Scheme 54 : Substrate scope of the reaction

Gratifyingly, there was a huge improvement in the yield of the substituted piperidines compared to the yields obtained in Scheme 51 while also maintaining excellent enantioselectivities for all the substrates. Among the previously cyclised cycloalkyl substituents, the cyclopentyl substrate **235a** was formed with excellent yield and enantioselectivity with 80% and 96:4 e.r. while the cyclobutyl substrate **235b** was obtained in moderate yields and enantioselectivity of 63% and 82:18 e.r. An excellent yield of 87%

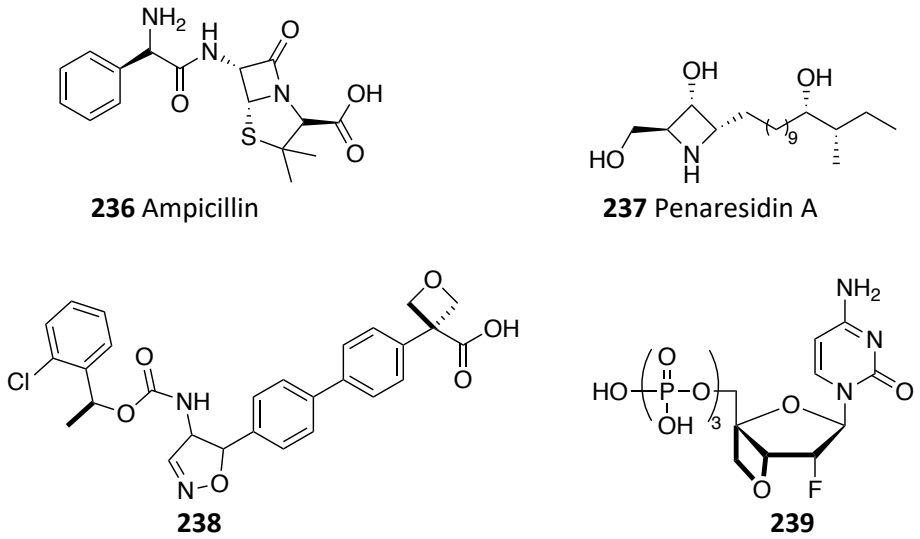
with 89:11 e.r. was obtained with the cyclopropyl substrate **235c**. The *gem*-dimethyl substituted piperidine **235d** was formed in a low yield of 29% (58% brsm) with an excellent enantioselectivity of 95:5 e.r. while the diphenyl substituted compound **235e** showed a very poor conversion in the ^{1}H NMR of the crude reaction mixture. The sluggish nature of the reaction could be attributed to the steric and electronic factors of the phenyl groups. There could also be a possible degradation of the starting material under the reaction conditions as the unreacted starting material could not be completely recovered. Although the product was isolated with difficulty after flash column chromatography, the HPLC chromatogram for the product was very messy, indicating that the product could be degrading on the HPLC column, due to which the enantioselectivity for this substrate couldn't be calculated.

It was observed that bulkier substituents gave rise to excellent enantioselectivity although with low yields. Cycloheptyl substrate **235f** was formed in a low yield (14%) but with excellent enantioselectivity (95:5 e.r.). The poor yield could be because of decomposition of the starting material **234f** under the reaction conditions as shown by the calculated yield based on recovered starting material (29% brsm). The THP (**235g**) and tetrahydrothiopyran (**235h**) substituents were formed in excellent enantioselectivities (94:6 e.r. and 96:4 e.r., respectively). While **235g** was formed in a moderate yield of 65%, the tetrahydrothiopyran substituent **235h** was formed in poor yield of 14%, with the unreacted starting material recovered. Among the three six-membered ring substitution patterns on the piperidine ring, (cyclohexyl- 78%, 96:4 e.r.; THP- 65%, 94:6 e.r.; tetrahydrothiopyran -14%, 96:4 e.r.), it was observed that while all three were formed in excellent enantioselectivities, the varying yields were attributed to electronic factors but couldn't exactly be reasoned out. Solubility factors were ruled out as all three substrates formed homogenous reaction mixtures. The more electronegative oxygen substituent resulted in higher yields than its sulfur counterpart, while the cyclohexyl ring resulted in the highest yield among the three at 78% yield.

2.4.2 Other heterocyclic substitutions

Small molecules like oxetane and azetidine substituents on an underlying scaffold influence the metabolic and physicochemical properties of the molecule and these are highly sought after by medicinal chemists.[90] Ampicillin **236** and Penaresidin A **237** have been found to

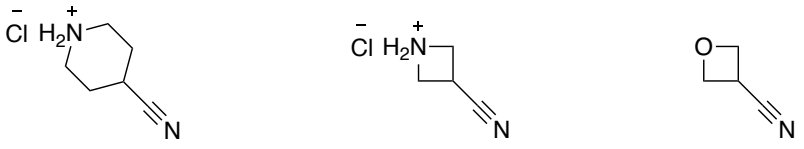
have antibacterial and antioxidant properties[91] while **238** is a Lysophosphatidic acid receptor antagonist[92] and 3,4'-oxetane nucleoside **239** has been reported to be an inhibitor of Hepatitis C virus[93] (Figure 24). Based on these substitution patterns seen in natural products and medicinally relevant compounds, we decided to explore the formation of spiro-piperidine compounds with the following nitriles as starting materials leading to the respective substitutions (Figure 25).



236 Ampicillin **237** Penaresidin A

238 **239**

Figure 24 : Azetidine and oxetane substituents in compounds with biological activity



240 **241** **242**

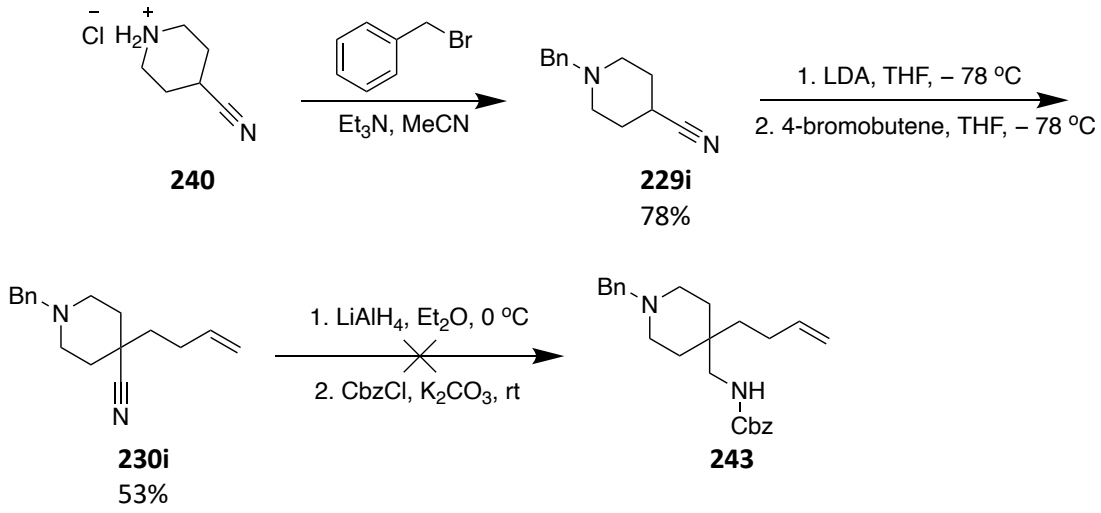
Figure 25 : Commercial nitriles used as starting materials for heterocyclic spiropiperidine substitutions

2.4.2.1 3-spiropiperidine substituted piperidine

It was necessary to protect the nitrogen on the piperidine ring in **240** before proceeding with the alkylation to prevent side products in the further steps. While Cbz group is unaffected in the presence of LDA, it is unstable in the presence of $LiAlH_4$. An alternative protecting group that would be stable under LDA and $LiAlH_4$ reaction conditions had to be

used. Benzyl protecting group was an appropriate choice as it would be stable under both the reaction conditions.

Following the patented procedure,[94] the nitrile **240** was benzyl protected in the presence of bromomethyl benzene and Et_3N in acetonitrile to yield the Bn-protected nitrile **229i** in 78% yield (Scheme 55). The alkylated nitrile **230i** was formed in 53% yield in the presence of LDA and 4-bromobutene. It was reduced to form the primary amine using $LiAlH_4$ followed by Cbz protection in the presence of benzyl chloroformate. The expected product **243** was not formed as there was one extra carbon peak in the ^{13}C NMR spectrum, with two carbonyl carbons (156.8 and 155.4 ppm) instead of just one from the Cbz carbonyl carbon (Figure 26).



*Scheme 55 : Attempt to synthesise **243***

The integration for aromatic protons in the ^1H NMR equalled 10 which was in accordance with 5 protons each from the existing benzyl group and the newly added Cbz protecting group in **243**. But the total number of protons exceeded by 2, and these protons appeared as a singlet at 5.10 ppm, next to the expected singlet from the benzylic protons from the Cbz group at 5.08 ppm (Figure 27). It was also observed that the molecular weight of the compound exceeded by 44 units (Figure 28) which corresponds to a mass equivalent of CO_2.

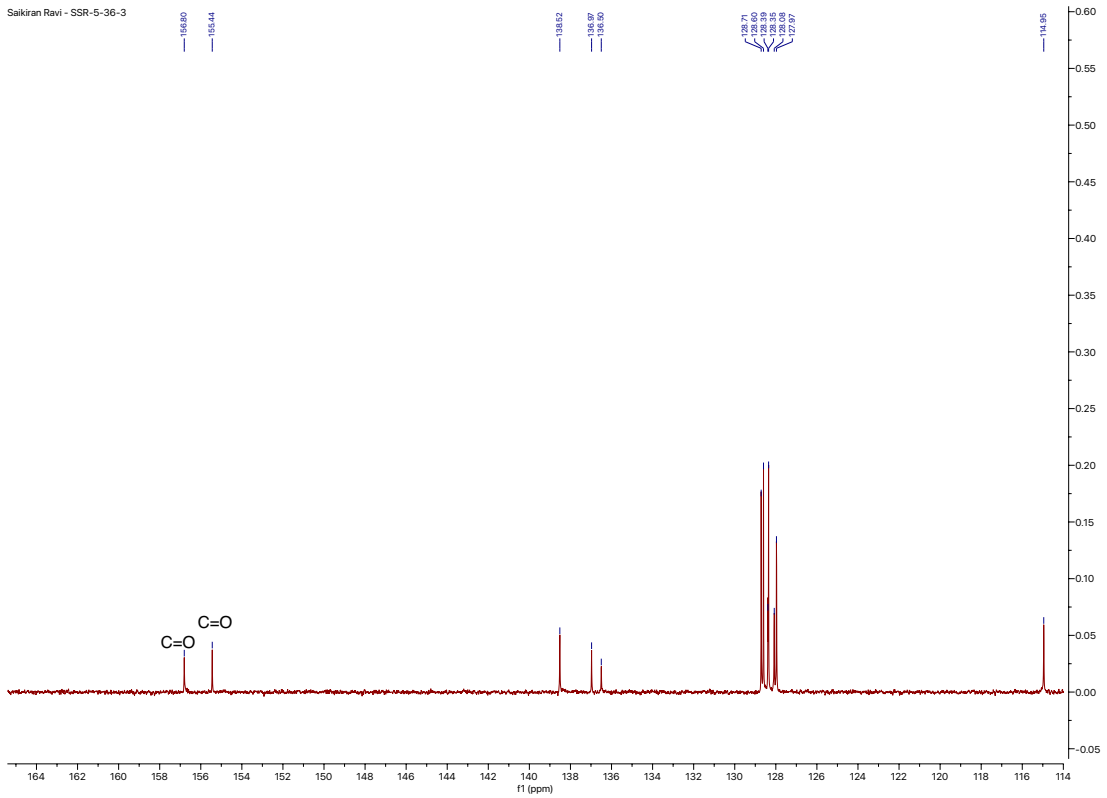


*Figure 26 : 13C NMR of **231i** showing two carbonyl carbon peaks*

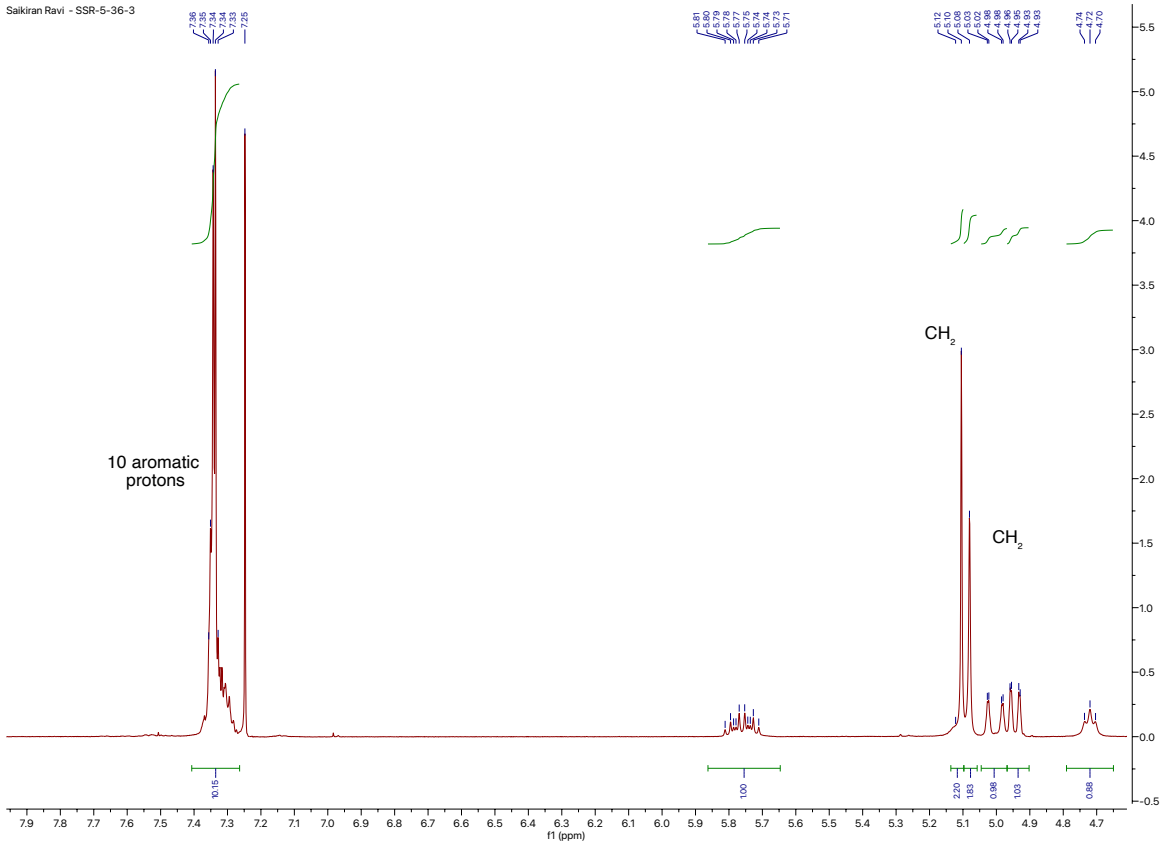


*Figure 27 : ^{1}H NMR of **231i** showing two extra protons appearing as a singlet at 5.12 ppm*

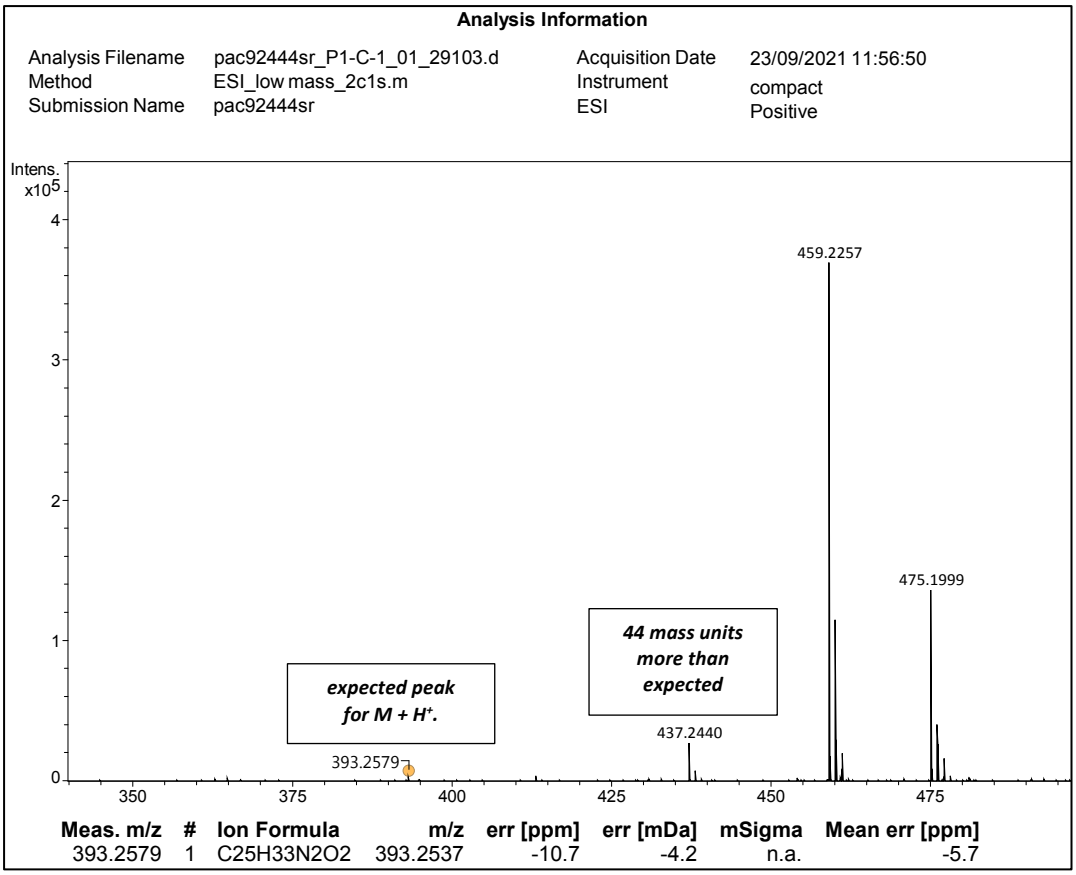


Figure 28 : Mass spectrum peak showing 44 mass units (equivalent to CO_2 molecule) more than the expected molecular weight

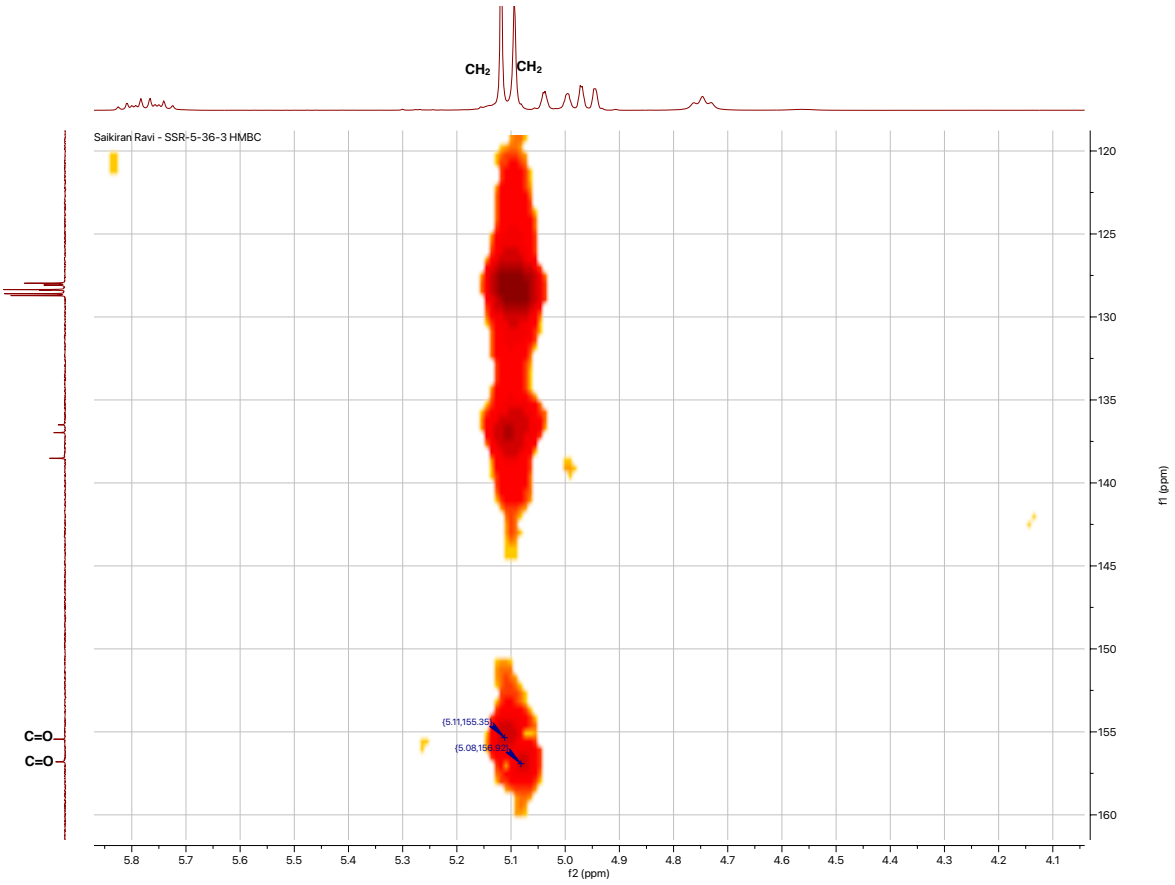
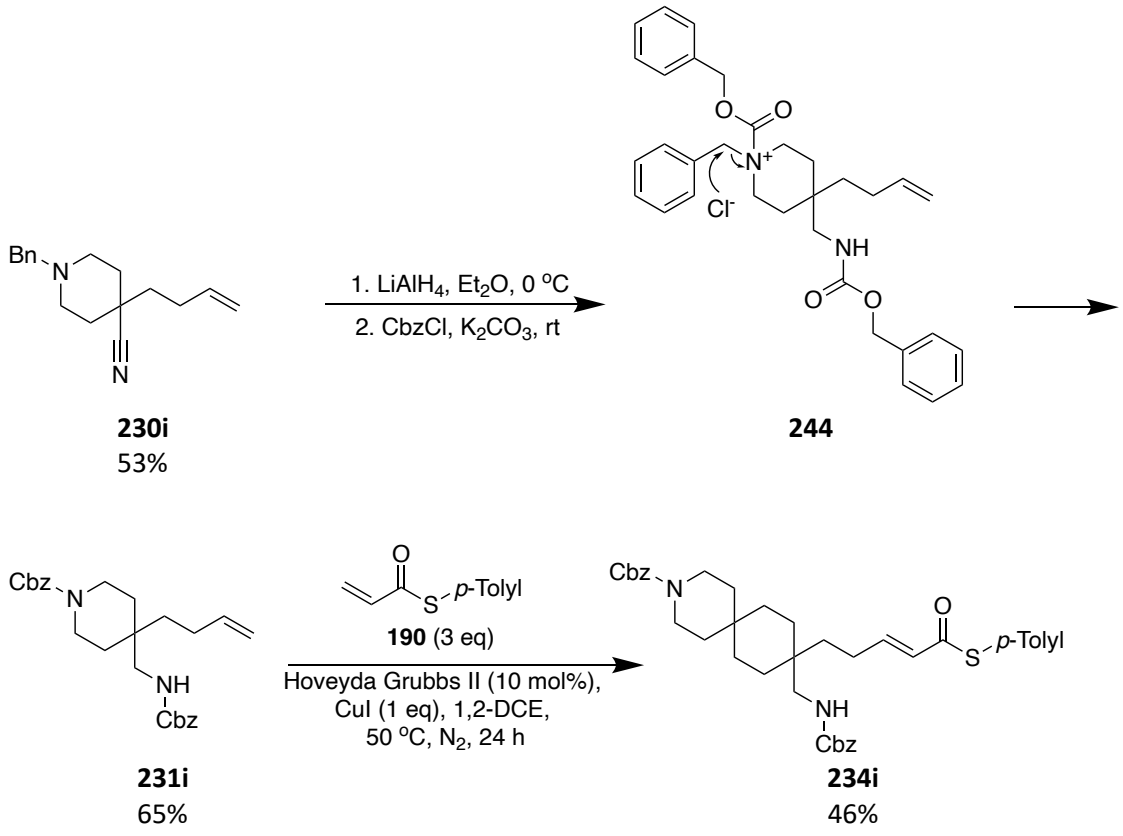


Figure 29 : HMBC correlation between the carbonyl carbons and CH_2 protons

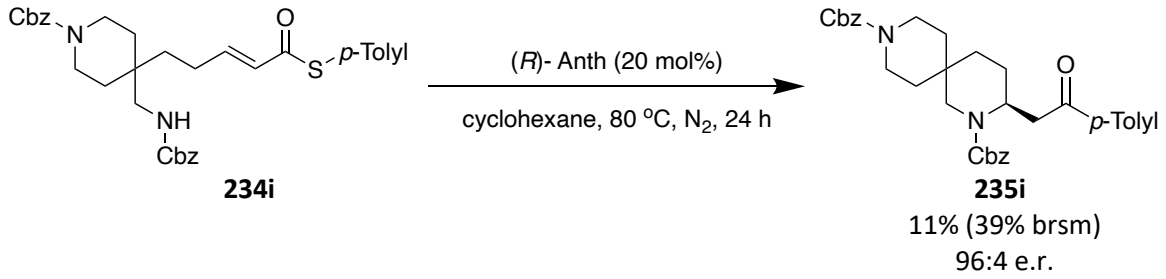
The HMBC of the singlet at 5.12 ppm showed long range coupling with the extra carbonyl carbon peak at 155 ppm as seen in Figure 29, showing that the both the CH_2 peaks were in close proximity to carbonyl groups, which was unexpected as the benzyl CH_2 cannot show a long-range coupling with a C=O group in the expected product **243**.

From the information explained above, it was concluded that the Bn group was replaced by Cbz leading to two *N*-Cbz groups in the molecule after the addition of benzyl chloroformate, thus the extra carbonyl carbon and the excess weight equivalent to a CO_2 molecule. This could be due to the nucleophilic *N*-Bn nitrogen atom attacking the CbzCl to form a quaternary ammonium ion **244** and the Cl^- from the benzyl chloroformate leading to the displacement of the more labile Bn group to form **231i**. Since the change in protecting group wouldn't interfere in the synthesis procedure ahead, it was decided to carry forward with the product as obtained. Upon subjecting the Cbz-amine **231i** to metathesis conditions, a lower yield of 46% of **234i** was obtained and the unreacted starting material was recovered (Scheme 56).



*Scheme 56 : Synthesis of cyclisation precursor **234i***

When the amino-thioester **234i** was subjected to cyclization conditions, the product **235i** was obtained in a low yield (11%, 39% brsm) but with an excellent enantioselectivity of 96:4 e.r. The low yield could be due to a combination effect of the increased steric bulk of the *N*-Cbz piperidine substituent and decomposition of the starting material under the reaction conditions as seen from the yield based on recovered starting material (Scheme 57).

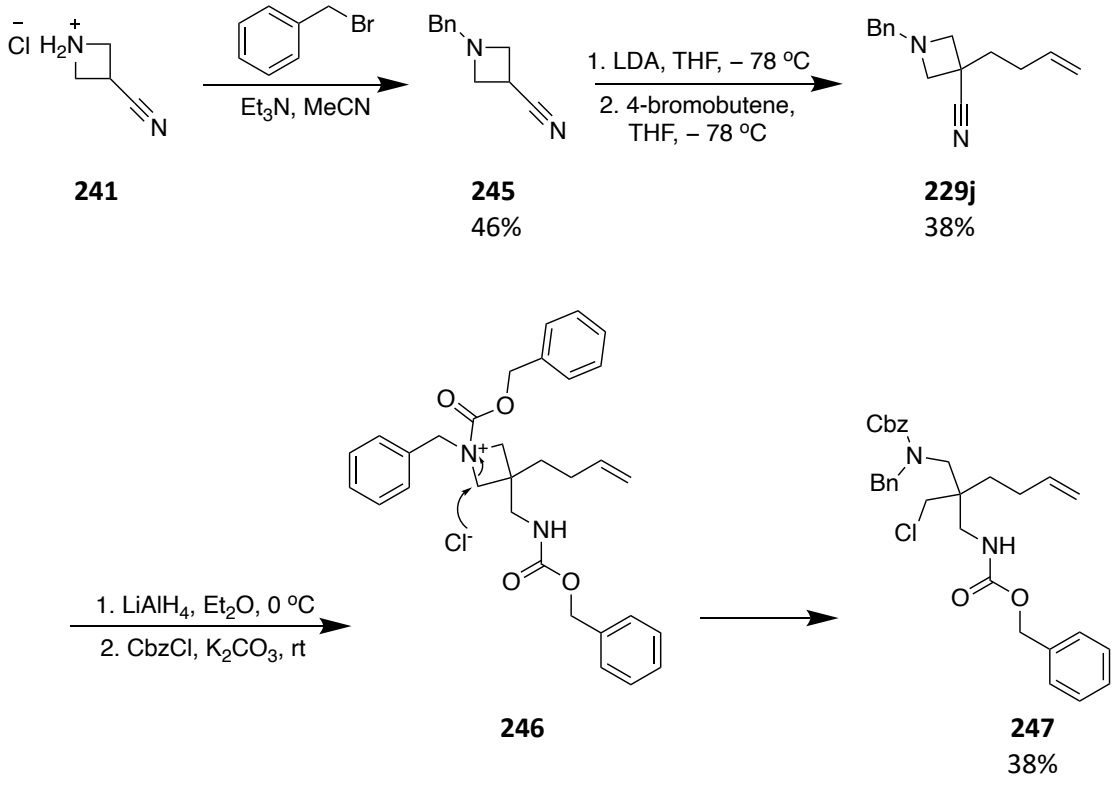


234i **235i**
11% (39% brsm)
96:4 e.r.

Scheme 57 : Cyclisation of N-Cbz piperidine substrate

2.4.2.2 3-spiroazetidine substituted piperidine

As with the piperidine substrate, the nitrile **241** was benzyl protected in the presence of bromomethyl benzene yielding **245** in 46% yield followed by alkylation in 38% yield. Upon reduction of the nitrile with $LiAlH_4$, followed by reaction with benzyl chloroformate to protect the amine, the desired Cbz-amine was not formed and instead the ring opening product **247** was isolated in 38% yield. This could be due to the formation of the ammonium cation due to the nucleophilic benzyl protected nitrogen that attacked CbzCl forming **246**. Due to the ring strain in azetidine, the chloride ion attacked the CH_2 on the ring **246**, leading to the formation of **247** (Scheme 58).



Scheme 58 : Ring opening product formed with azetidine substrate

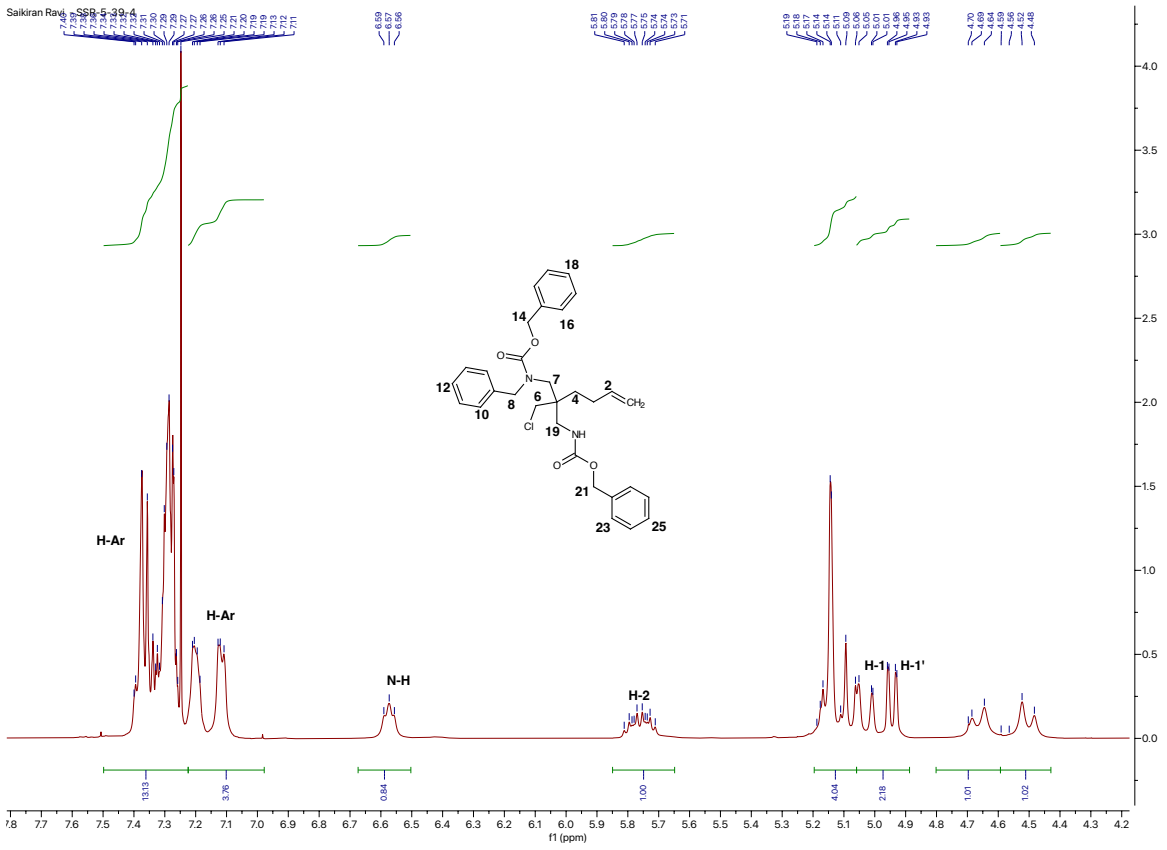


*Figure 30 : Proton NMR of **247***

The complete characterisation of **247** started with the assignment of aromatic protons which was assigned as two multiplets from 7.4-7.3 ppm and 7.2-7.1 ppm in the ^{1}H NMR consisting of a total of 15 protons from the three aromatic rings. The triplet at 6.57 ppm was assigned to the N-H proton. H-2 was assigned the peak at 5.8 ppm with multiplicity doublet of doublet of triplet (ddt) with *J* = 16.8, 10.4, 6.6 Hz. H-1 (*trans*) appeared as multiplet from 5.1 – 5.0 ppm and the H-1' (*cis*) appeared as a doublet of doublet (dd) at 5.0 ppm with *J* = 10.4, 1.9 Hz (Figure 30).

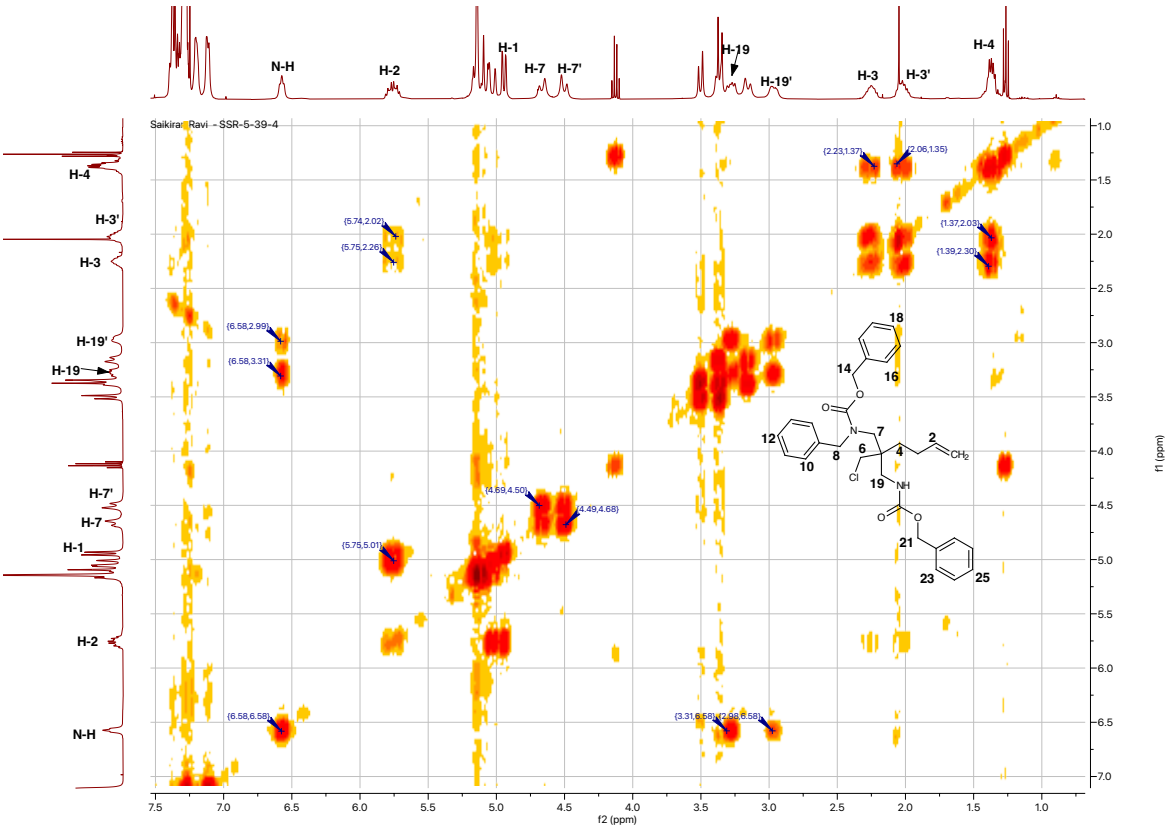


*Figure 31 : COSY spectrum of **247** to show assignment of protons H-7, H-7', H-19, H-19', H-3 and H-4*

From the COSY spectrum, the multiplets at 2.23 ppm and 2.06 ppm were assigned H-3 and H-3' respectively as they showed allylic coupling with protons H-1 and H-2. Protons H-4 were subsequently assigned the multiplet 1.37 ppm as they showed H-H correlation with protons on C-3 (Figure 31). The N-H proton showed an H-H correlation to peaks at 3.31 ppm and 2.98 ppm, integrating to one proton each. Thus, they were assigned H-19 and H-19' as they are adjacent to N-H. Two doublets integrated to one proton each at 4.66 ppm and 4.50 ppm as seen in the ^{1}H NMR in Figure 30, and they showed no correlation to any other proton as seen in the COSY spectrum (Figure 31). From the structure, it can be seen that

the doublets at 4.50 ppm and 4.68 ppm correspond to H-7 and H-7' as they have no neighbouring protons, and they were thus assigned. With the protons H-3, H-4, H-7 and H-19 assigned, the corresponding carbons were assigned their respective peaks from the HMQC spectrum.

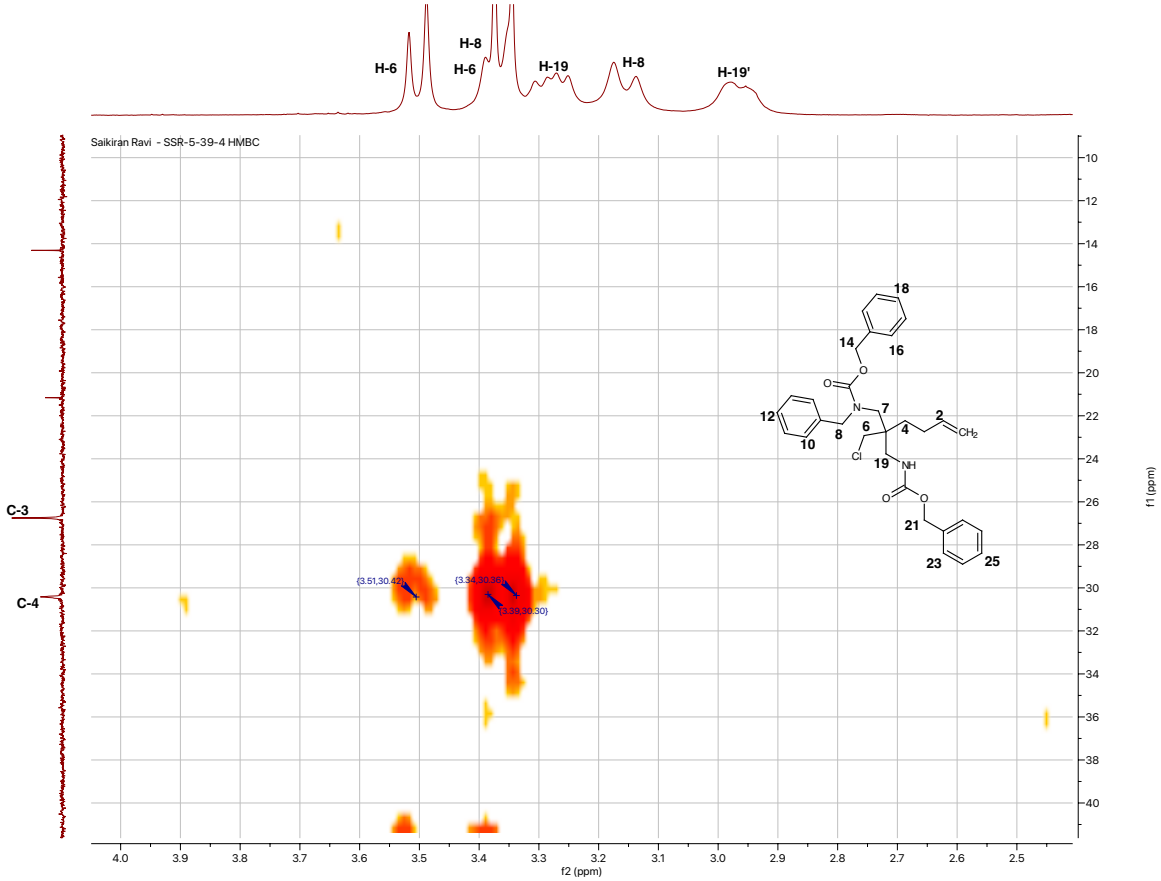


Figure 32 : HMBC spectrum showing long-range coupling between C-4 and H-6 in ***247***

The HMBC spectrum in Figure 32 shows long range coupling between C-4 at 30.4 ppm and the two protons of H-6- one as a doublet at 3.5 ppm and the other in the multiplet from 3.4-3.3 ppm respectively, which confirmed the assignment of the two protons on C-6. Once H-6 was assigned, H-8 was assigned with HMQC. One appeared in the mulitiplet from 3.4-3.3 ppm and the other as a doublet at 3.2 ppm (Figure 33).

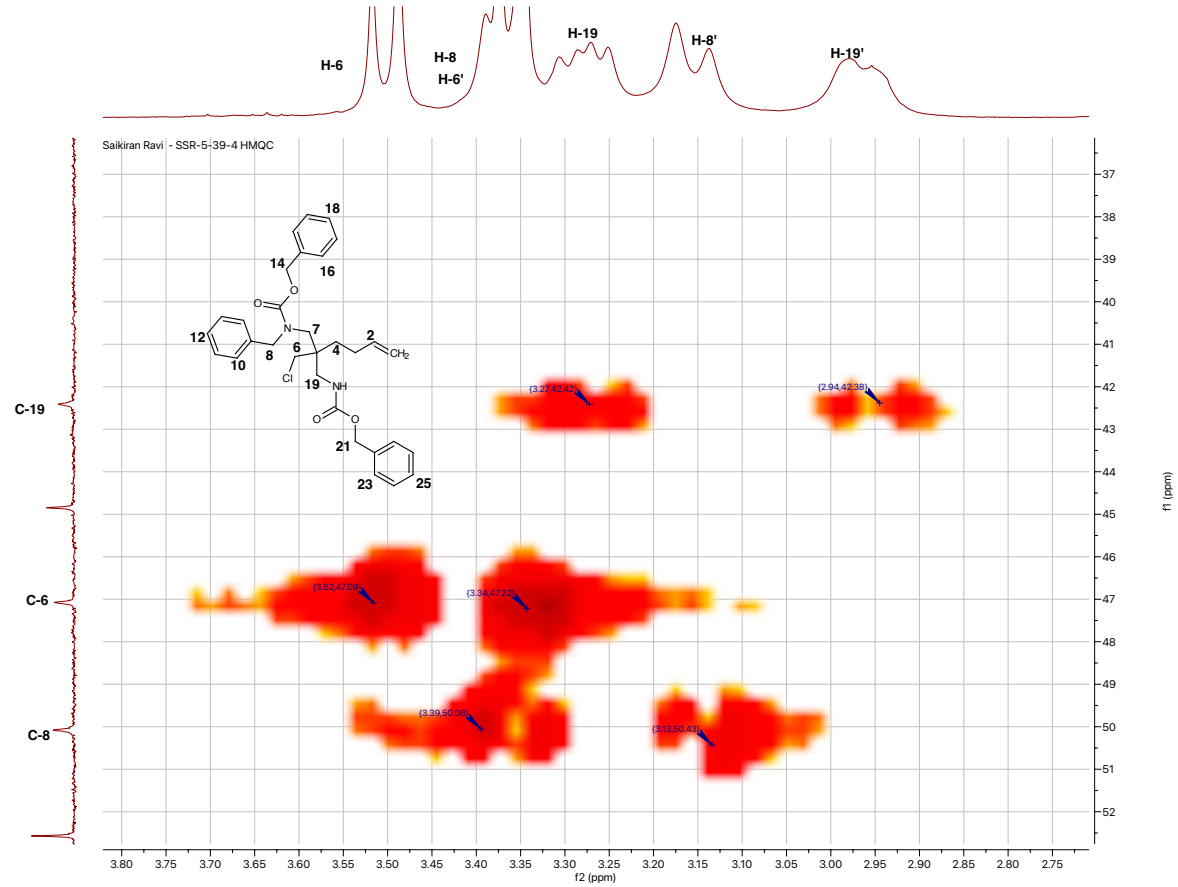


*Figure 33 : HMQC showing assignment of H-6 and H-8 in **247***

The protons H-14 and H-21 were confirmed using HMBC and HMQC spectra. A long-range coupling between H-7' at 4.52 ppm and carbon peak at 158.52 ppm (Figure 34) meant that this was C-13. Subsequently, carbon peak at 156.99 ppm was allotted C-20. This made is easy to assign the protons H-14 and H-21 using HMQC as the peak at 5.14 ppm corresponded to H-14 with C-14 at 68.05 ppm. The H-21 peak was thus assigned 5.07 ppm which correlated with the carbon at 66.67 ppm (Figure 35).

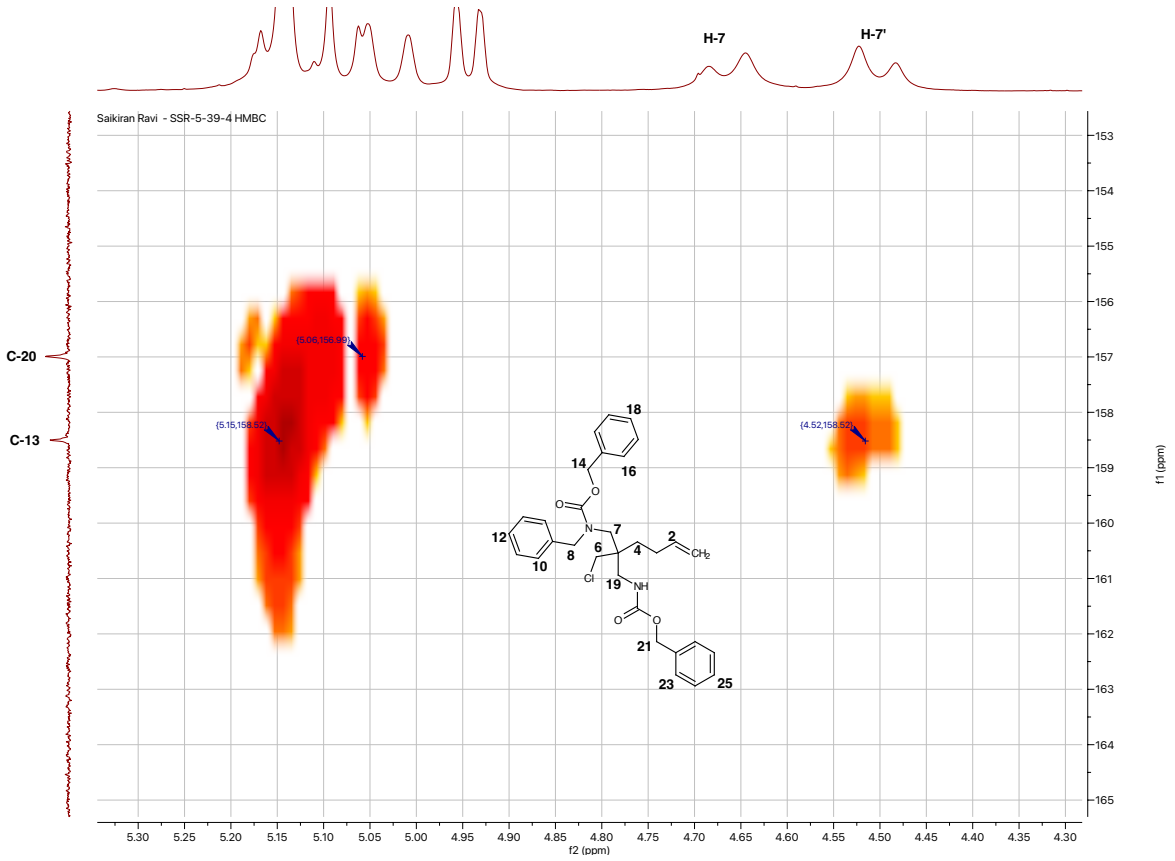


*Figure 34 : HMBC showing long range coupling between H-7' and C-13 in **247***

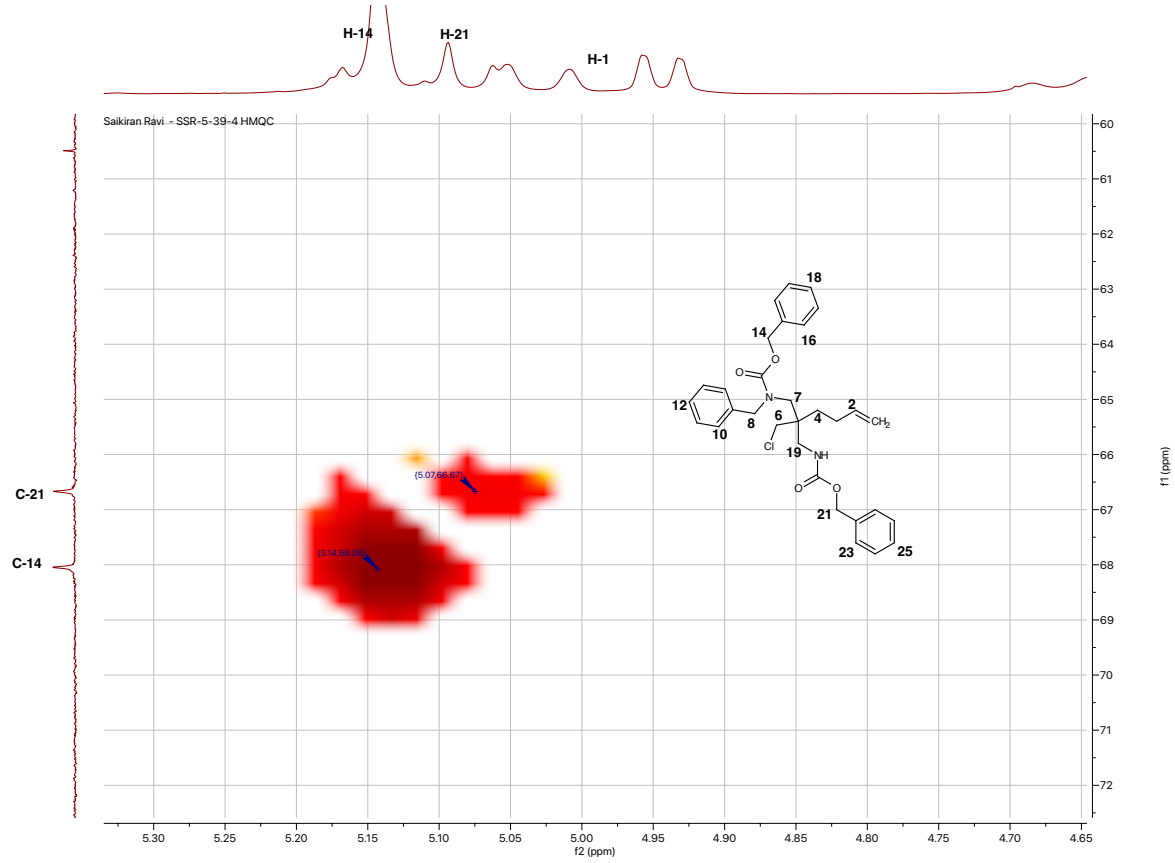
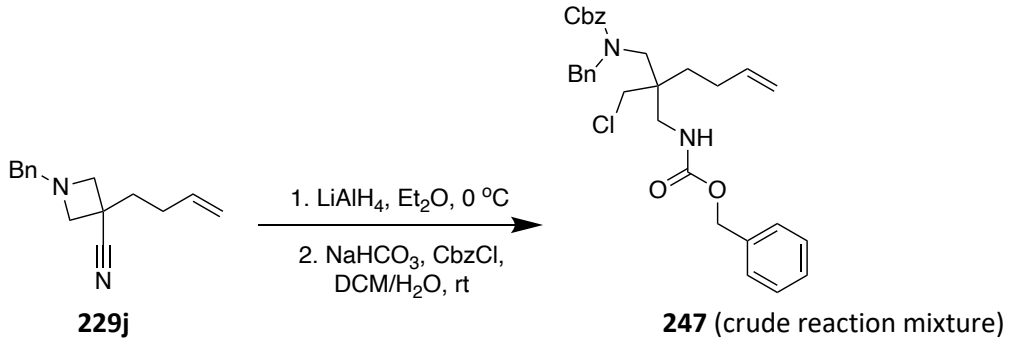


*Figure 35 : HMQC spectrum showing C-14 and C-21 with the respective protons in **247***

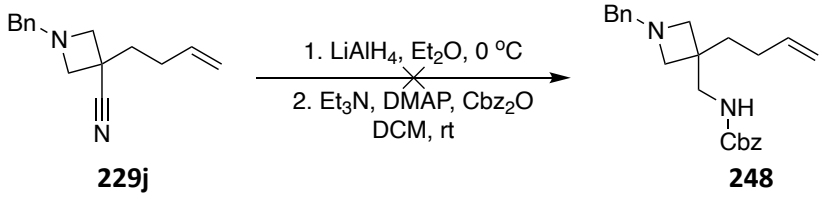
Once the structure of **247** was confirmed, the next step was to avoid its formation and obtain the desired product **248**. To prevent the ring opening of azetidine, the reaction was carried out in a biphasic medium of DCM/water using $NaHCO_3$ and CbzCl [95] so that Cl^- would no longer be in the organic layer but in the aqueous layer as NaCl. But this reaction also led to the ring opening product **247** as seen in the ^1H NMR of the crude reaction mixture (Scheme 59).



229j **247** (crude reaction mixture)

Scheme 59 : Ring opening of azetidine obtained in biphasic medium

Since Cl^- from the benzyl chloroformate caused the ring opening, it was decided to use Cbz anhydride instead. Alkylated nitrile **229j** was reduced to the primary amine in the presence of $LiAlH_4$ followed by reaction with triethylamine, DMAP and Cbz anhydride in DCM but the desired product **248** was not detected by ^1H NMR and mass spectrometry in the crude reaction mixture, with some starting material still left unreacted (Scheme 60). It was not clear as to why this reaction did not work.

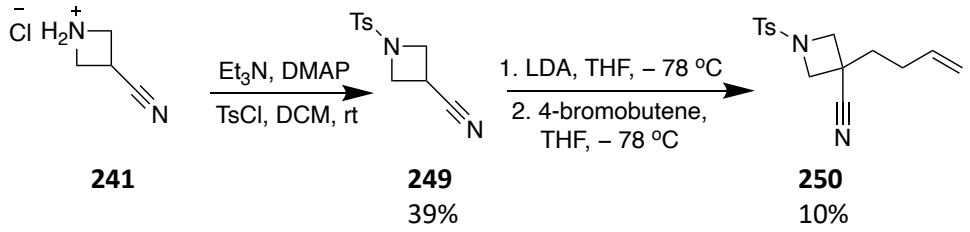


229j **248**

Scheme 60 : Reaction with Cbz anhydride

Since the benzyl protecting group was not compatible with the reaction conditions, it was decided to change the protecting group to tosyl as the lone pairs on nitrogen would be less available. To this end, nitrile **241** was reacted with tosyl chloride in the presence of DMAP

and Et_3N to form the tosyl protected amine **249** in 39% yield. Alkylating the product in the presence of LDA gave **250** in a very poor yield of 10%. The low yield was attributed to the high ring strain on the azetidine ring which was not compatible in the LDA conditions with the tosyl protecting group.



241 **249** 39% **250** 10%

Scheme 61 : Tosyl protecting group on the azetidine ring

No further efforts were carried out on the synthesis of the azetidine substrate due to the ring opening issues and incompatible protecting groups.

2.4.2.3 3-spirooxetane substituted piperidine

Oxetane substitution is often seen in natural products and pharmaceutical compounds. 3-substituted oxetanes are often exploited as useful surrogates to access common functional groups like *gem*-dimethyl and carbonyl units (Figure 36). [90] Due to its high degree of hydrogen bonding ability which influences its physicochemical properties, oxetanes are favoured as important structural motifs in the pharmaceutical industry[96] and was thus chosen as one of the substrates in the project.

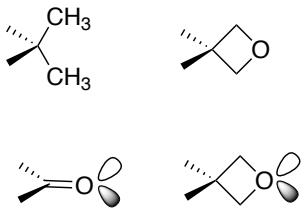
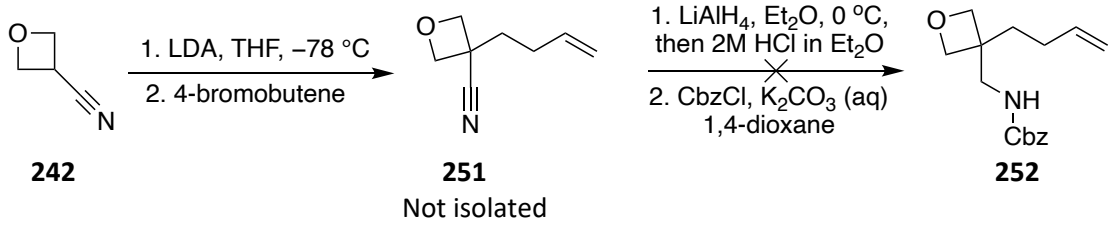


Figure 36 : Oxetanes as surrogates for gem-dimethyl and carbonyl groups

Oxetane-3-carbonitrile **242** was alkylated in the presence of LDA and 4-bromobutene. The ^1H NMR of the crude product **251** looked like the expected product **251** but the mass spectrometry analysis did not show any product, while the IR spectrum showed a broad -OH peak. It was suspected that the ring might have opened. Nevertheless, **251** was taken

through the next step where it was reduced in the presence of $LiAlH_4$ to the primary amine, which was trapped as the corresponding HCl salt in the presence of 2M HCl in Et_2O followed by Cbz protection, but no product was obtained. This could be due to the ring opening of the oxetane under these reaction conditions.



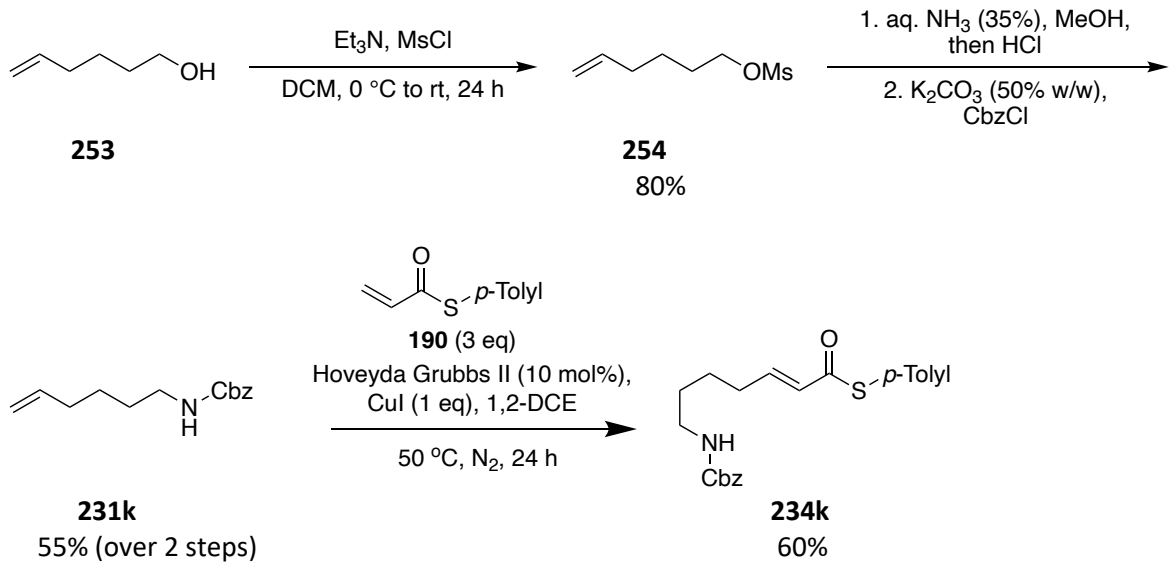
242 **251** Not isolated **252**

*Scheme 62 : Attempts at synthesising the cyclisation precursor **252***

Due to lack of time, the synthesis of this substrate was no longer pursued. Future work in this project would include the synthesis of oxetane substituted piperidine under different reaction conditions.

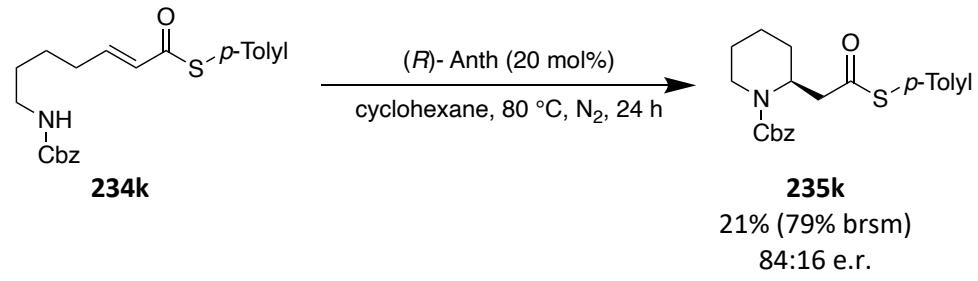
2.5 Unsubstituted piperidine

Increasing the steric bulk on the piperidine ring through substitution favours enhanced cyclisation and enantioselectivity through the Thorpe Ingold effect[97], without which both factors would be affected. In order to study this, an unsubstituted piperidine was synthesised. The synthesis was achieved from 5-hexen-1-ol **253** which was reacted with methanesulfonyl chloride to form the mesylate **254** in 80% yield. Reaction with NH_3 (aq) in the presence of methanol resulted in the free amine which was trapped as the HCl salt. Cracking of the HCl salt was achieved in the presence of K_2CO_3 and the amine was protected to form the Cbz-amine **231k**. Under metathesis conditions with the *p*-tolyl thioester **190**, the unsubstituted Cbz-amine **234k** was formed in 60% yield (Scheme 63).



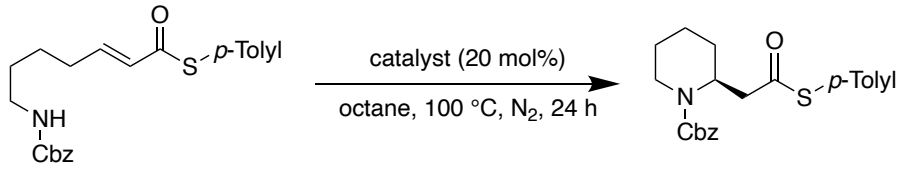
*Scheme 63 : Synthesis of unsubstituted piperidine cyclisation precursor **234k***

With the Cbz-amine in hand, the asymmetric aza-Michael reaction was carried out under the optimised reaction conditions, in the presence of (*R*)-Anth in cyclohexane at 80 °C to yield the unsubstituted piperidine **235k** in 21% yield (79% brsm) and 84:16 e.r. with the unreacted starting material recovered (Scheme 64).



*Scheme 64 : Cyclisation to form unsubstituted piperidine **235k***

The sluggish nature of the reaction was expected because of lack of substitution on the ring. The reaction was carried out with other catalysts to improve the yield of the reaction as shown in Table 6. Catalysts (*R*)-TRIP and (*R*)-TiPSY resulted in poor yields (25% and 2% respectively) as well as low enantioselectivities. The best condition was obtained with (*R*)-Anth, cyclohexane, 80 °C as shown in Scheme 64.



234k **235k**

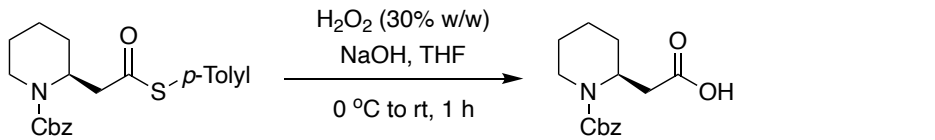
Entry	catalyst	yield (%)	e.r.
1	(*R*)-TRIP	25	31:69
2	(*R*)-TiPSY	2	25:75

Table 6 : Cyclisation of unsubstituted piperidine under different conditions

2.5.1 Confirmation of absolute stereochemistry

One of the advantages of using a thioester is its versatility which was demonstrated by Fuwa,[86] as different functional groups can be accessed under mild conditions. Converting the thioester into the carboxylic acid gives ready access to pipecolic acid derivatives. Literature search demonstrated the transformation of thioester to a carboxylic acid in the presence of hydrogen peroxide and NaOH.[98]

The method was carried out on the unsubstituted cyclised piperidine **235k** in the presence of H_2O_2 and NaOH (aq) to form the *N*-Cbz protected homopipecolic acid **255** in an excellent yield of 92% (Scheme 65). The presence of a carboxylic acid functional group in **255** made it difficult to separate the two enantiomers using chiral HPLC as the product was too polar to be eluted from the column. The positive values of specific rotation retained in the product **255** as in the originally cyclised piperidine **235k** implied that there was no racemization of the stereocentre, though there might have been a small change in enantioselectivity.

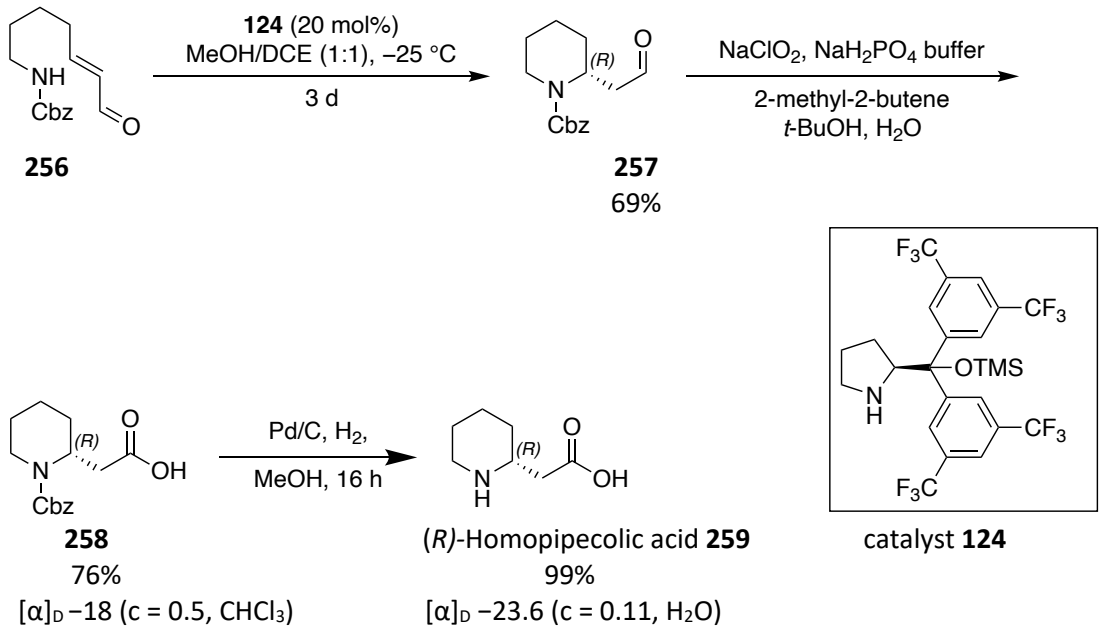


235k
84:16 e.r.
$[\alpha]_D^{20}$ +23.7 (c = 0.5345, $CHCl_3$)

255
92%
$[\alpha]_D^{20}$ +7.14 (c = 0.2055, $CHCl_3$)

Scheme 65 : Hydrolysis of thioester to carboxylic acid

Transformation of the functional group also served the purpose of determining the absolute stereochemistry of the product. A literature search showed the synthesis of **258** by Carter *et al*[57] where the synthesis of (*R)*-Homopipecolic acid was achieved with the *N*-Cbz protected acid (*R*)-**258** being formed in the penultimate step (Scheme 66).

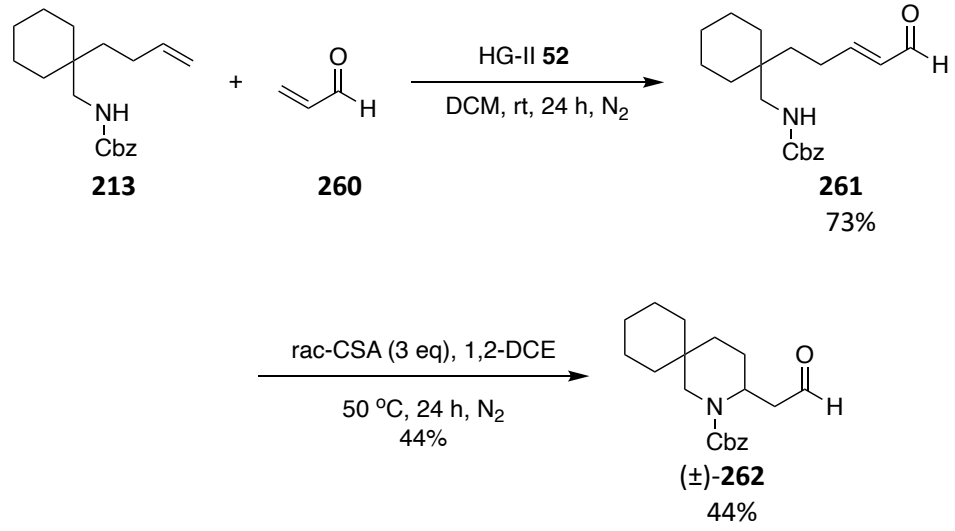


*Scheme 66 : Synthesis of (R)-Homopipecolic **259** acid by Carter and co-workers*

Comparison of the sign of the optical rotation values of **255** $[\alpha]_D^{20}$ +7.14 (c = 0.2055, $CHCl_3$) against that of (*R*)-**258** $[\alpha]_D$ −18 (c = 0.5, $CHCl_3$) led us to the conclusion that the absolute stereochemistry of *N*-Cbz protected homopipecolic acid **255** was (*S*), and therefore the unsubstituted piperidine-thioester **235k** must also be having the (*S*)-stereochemistry at the chiral centre. The stereochemistry was in accordance with the predictions made with results obtained using the same methodology in the Clarke group for the asymmetric synthesis of THPs [89] and pyrrolidines.[82]

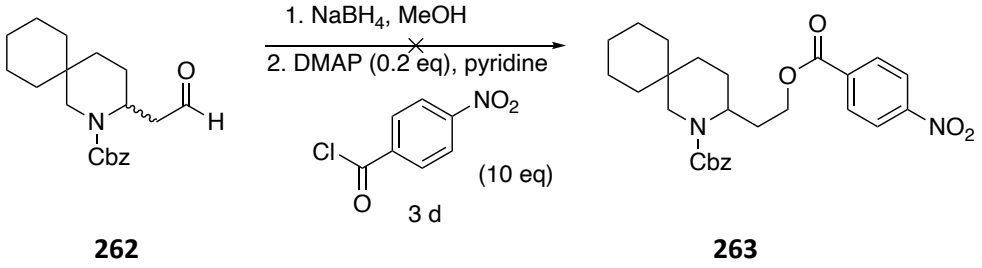
2.6. Aldehydes as Michael acceptors

In order to validate our results that thioesters were the best choice as Michael acceptors for the piperidine substrates too, it was decided to study the impact of aldehydes as the Michael acceptor. Thus, the unsaturated amine **213** was set to olefin cross metathesis conditions with acrolein **260** using HG-II catalyst **52** forming **261** in 73% yield (Scheme 67).



Scheme 67 : Racemic cyclisation of piperidine substrate using aldehyde as the activating group

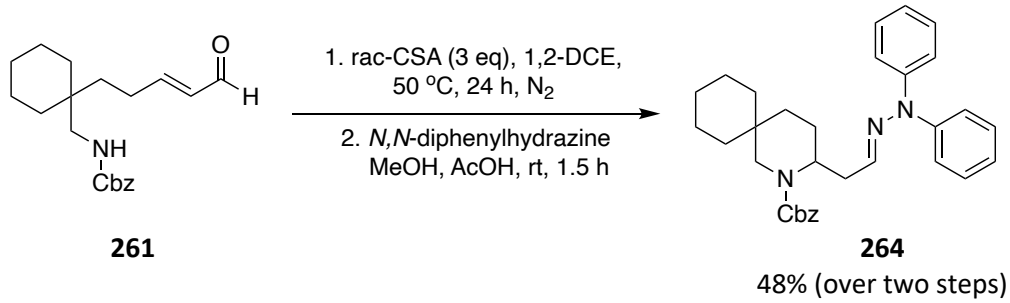
Upon cyclisation in the presence of rac-CSA, compound **262** was formed in 44% yield, but it was very weakly UV active which made it difficult to obtain a clear HPLC chromatogram. It also underwent partial aerial oxidation to the corresponding acid. It was decided to introduce a chromophore to make it UV active and also avoid handling the reactive aldehyde group. Compound **262** was reduced to the corresponding alcohol and then acylated using *p*-nitrobenzoyl chloride (Scheme 68). The desired product **263** could not be isolated even after using 10 eq. of the acyl chloride over a period of three days.



*Scheme 68 : Reduction followed by acylation of **262***

It was then decided to trap the aldehyde **262** using *N,N*-diphenylhydrazine which is commercially available as the HCl salt. One gram of the salt was neutralised with 1M NaOH solution and extracted with DCM which gave the free hydrazine as a deep purple oil. Amino-aldehyde **261** was reacted with rac-CSA at 50 °C in 1,2-DCE as the solvent over 24 hours to form **262**. The crude product was taken forward to the next step without

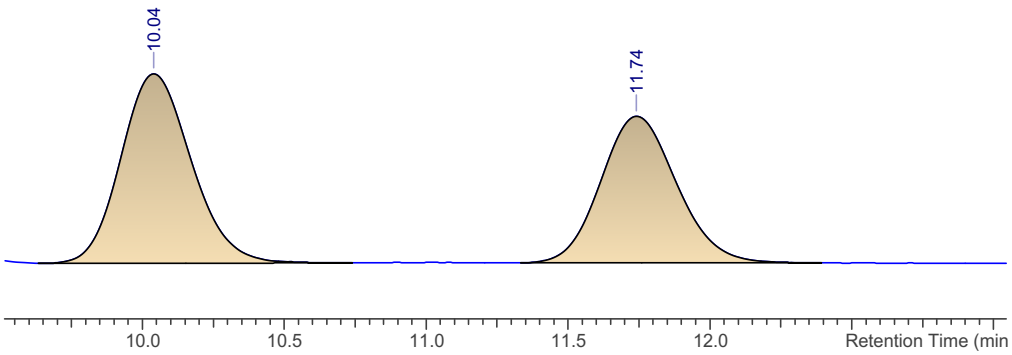
purification and reacted with *N,N*-diphenylhydrazine in the presence of dry MeOH and catalytic glacial acetic acid at room temperature forming compound **264** with 48% yield over two steps (Scheme 69). The two enantiomers were resolved using chiral HPLC conditions- Chiralpak ® IA Column hexane:2-propanol in the ratio 95:5 at 25 °C to give two well separated peaks with equal area percentage (Figure 37).



261 **264**

48% (over two steps)

*Scheme 69: Cyclisation of **261** and trapping it as a hydrazone*



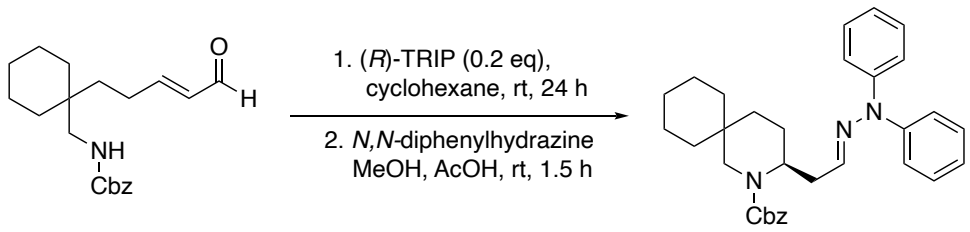
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	10.04	262880.656	54.511	0.453
2	11.74	219368.844	45.489	0.489

HPLC conditions: Chiralpak ® IA Column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 25 °C, λ = 254 nm; e.r = 50:50

*Figure 37 : HPLC trace for (±)-**264***

With the enantiomers resolved, the asymmetric reaction was carried out with (*R*)-TRIP catalyst in cyclohexane at room temperature for 24 hours followed by trapping the crude aldehyde as a hydrazone in the presence of *N,N*-diphenylhydrazine (Scheme 70). Both the reactions went to completion and compound **264** was formed in 49% yield over two steps

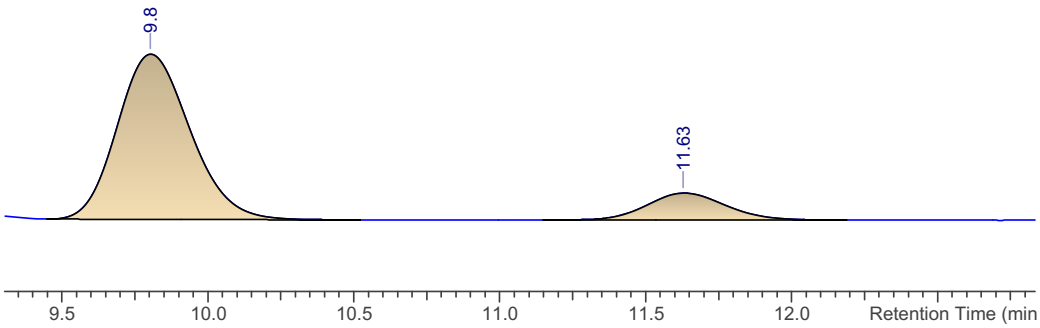
with 85:15 e.r. (Figure 38) which was of lesser enantioselectivity than that obtained with cyclohexyl substituted piperidine with the thioester substrate (96:4 e.r.).



261 **264**

49% (over two steps)
85:15 e.r.

*Scheme 70 : Asymmetric synthesis of **264***



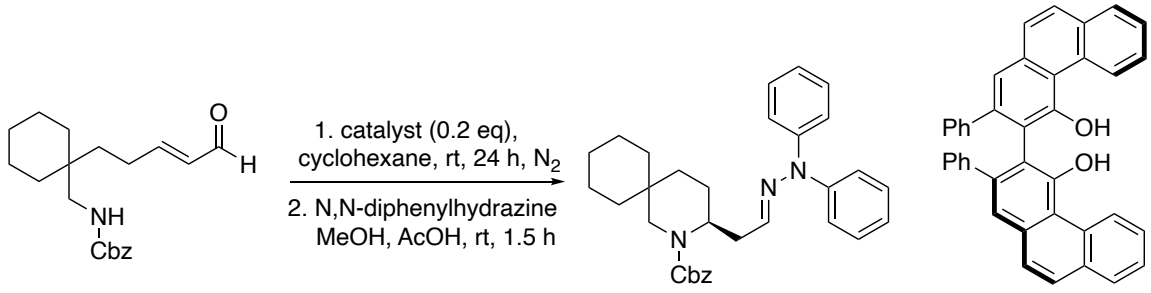
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	9.80	530858.188	84.936	0.458
2	11.63	94149.320	15.064	0.494

HPLC conditions: Chiralpak ® IA Column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 25 ˚C, λ = 254 nm; e.r = 85:15

*Figure 38 : HPLC trace for **264** synthesised asymmetrically*

To improve the yield and enantioselectivity, a catalyst screen was conducted for the aldehyde substrate using catalysts (*R*)-TiPSY, (*R*)-Anth, (*R*)-Phen and (*R*)-VAPOL (Table 7). The catalysts gave moderate yields as shown in Table 7. Catalyst (*R*)-TiPSY gave a poor enantioselectivity of 63:37 e.r. (Table 7, entry 1) while (*R*)- Anth gave similar enantioselectivities as (*R*)-TRIP, 83:17 e.r., but with a higher yield of 70% (Table 7, entry 2) showing that (*R*)- Anth is a better CPA than (*R*)-TRIP for the synthesis of piperidines under these reaction conditions. The catalyst (*R*)-Phen gave a high yield of 83% although with low e.r. of 61:39 (Table 7, entry 3), while (*R*)- VAPOL returned a racemic product (Table 7, entry

4).This study proved that α-β unsaturated thioesters are better Michael acceptors than the corresponding aldehydes.



261 **264** **265**
(*R*)-VAPOL

Entry	Catalyst	% Yield*	e.r.
1	(*R*)-TiPSY **226**	46	63:37
2	(*R*)- Anth **227**	70	83:17
3	(*R*)- Phen **228**	83	61:39
4	(*R*)- VAPOL **265**	66	50:50

* Yield calculated over two steps

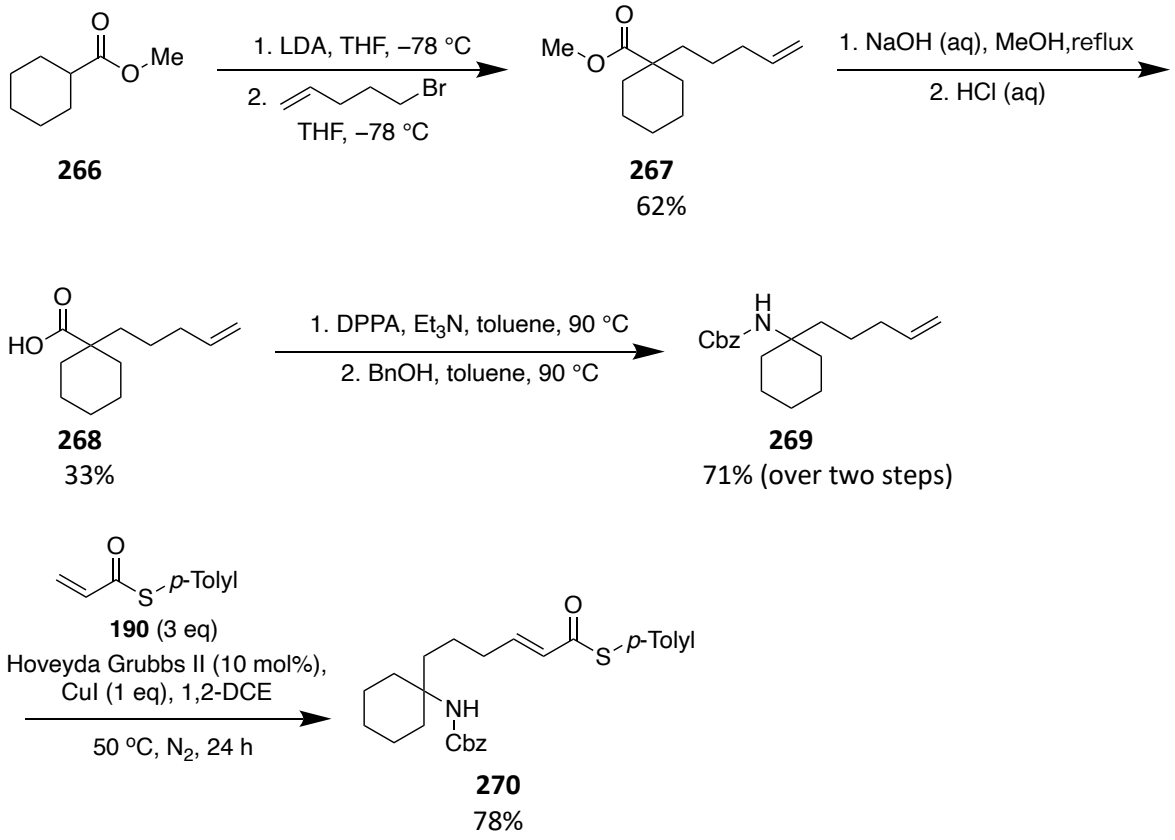
Table 7 : Cyclisation of aldehyde substrate using different CPAs

2.7. Scope of the reaction towards 2-spiropiperidines

It was decided to translate the methodology carried out for the asymmetric synthesis of 2,2'-substituted pyrrolidines[99] towards the synthesis of 2,2'-substituted piperidines. As with the 3-spiropiperidines, it was decided to carry out these reactions on the cyclohexyl substrate followed by the substrate scope after arriving at the optimised reaction conditions. Following literature procedures,[57,100] a Curtius rearrangement would play a key role in installing the primary amine group from the corresponding acid.

Ester **266** was alkylated in the presence of LDA and 5-bromopentene to form the alkylated ester **267** in 62% yield, followed by hydrolysis to form the corresponding acid **268**. The acid was converted into the intermediate acyl azide in the presence of DPPA and Et_3N which on heating formed the isocyanate after loss of N_2. The formation of isocyanate was monitored using IR and it was confirmed with a broad peak at 2275-2250 cm^{-1} with absence of the broad OH peak from the carboxylic acid centred at 3000 cm^{-1}, showing complete consumption of the starting material **268**. To reduce the number of steps in first isolating the free amine by hydrolysis of the isocyanate followed by Cbz-protection, the isocyanate

underwent nucleophilic addition in the presence of benzyl alcohol to yield **269** in 71% yield over two steps. The Cbz-amine was subjected to cross-metathesis conditions with *p*-tolyl thioester **190** to form the cyclisation precursor **270** in 78% yield (Scheme 71).



*Scheme 71 : Synthesis of precursor **270** for 2-spiropiperidine*

The ^{1}H NMR of compound **270** is as shown in Figure 39. As expected, the aromatic protons appeared as a multiplet between 7.3-6.9 ppm. Proton H-8 was assigned the doublet of triplet (dt) peak at 7.0 ppm with J = 15.2, 7.1 Hz followed by H-7 as a doublet with the J = 15.2 Hz. The benzylic protons H-17 and the N-H proton appeared as singlets at 5.06 ppm and 4.52 ppm respectively. The three protons at H-1 were unambiguously assigned the singlet at 2.4 ppm (Figure 39).

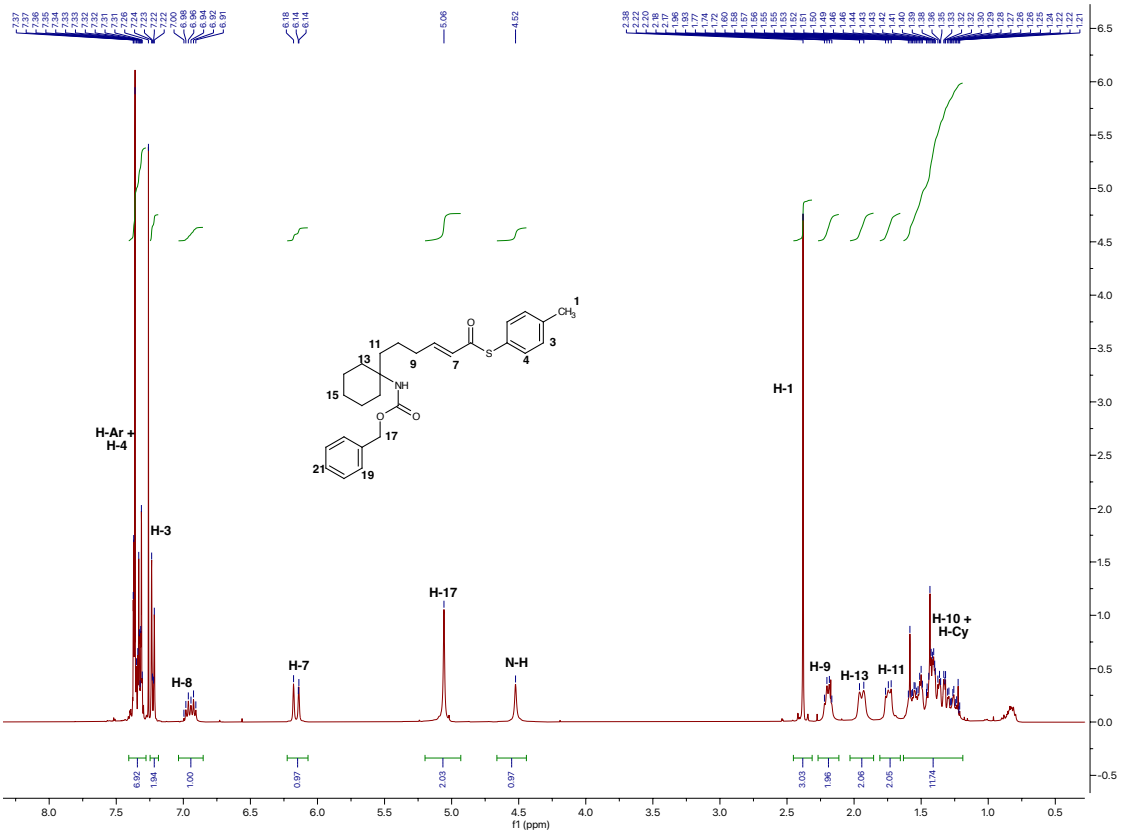


*Figure 39 : 1H NMR of **270***

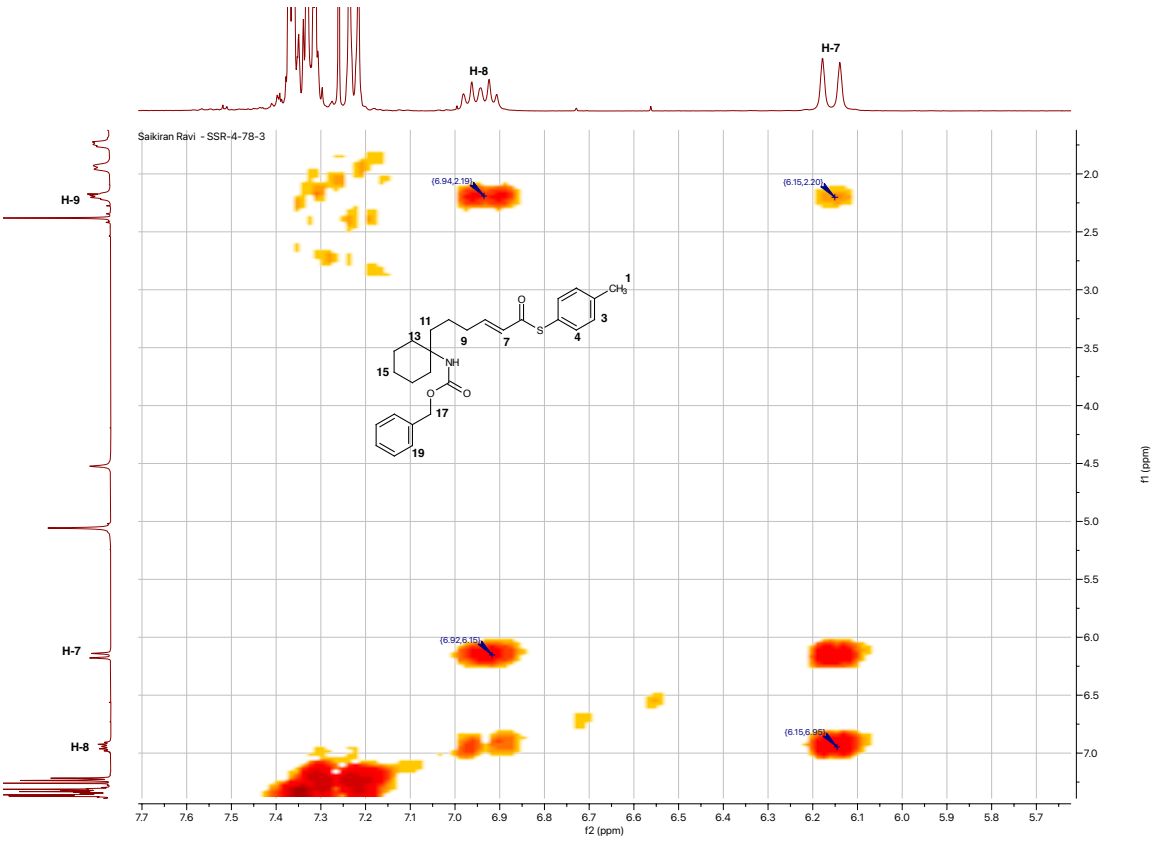


*Figure 40 : COSY spectrum of **270** showing correlation between H-9 and the alkene protons H-8, H-7*

The proton at 2.19 ppm was assigned as H-9 using the COSY spectrum as shown in Figure 40. Cross peaks to H-8 and H-7 correlated to the peak at 2.19 ppm which was thus confirmed to be the allylic protons H-9. Figure 41 shows the portion of the COSY spectrum for the protons H-10 showing H-H corelation with H-9 and H-11. H-9 showed correlation with the peak at 1.40 ppm, thus H-10 appeared in the multiplet 1.6-1.1 ppm. H-11 was assigned similarly, as the peak at 1.40 ppm correlated with the peak at 1.72 ppm. HMBC spectrum in Figure 42 shows the long-range coupling between N-H proton and C-13 which was used to assign the proton H-13.

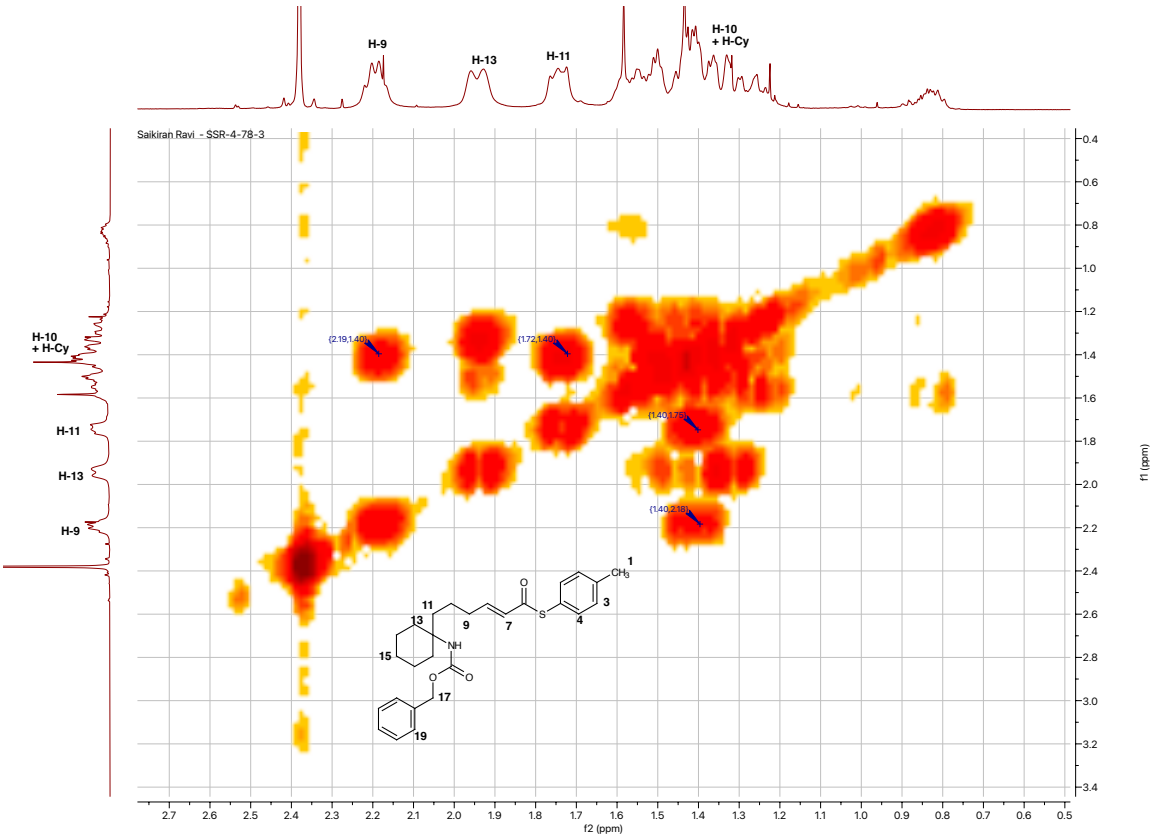


*Figure 41 : COSY spectrum of **270** showing correlation between H-10 with the protons H-9, H-11*

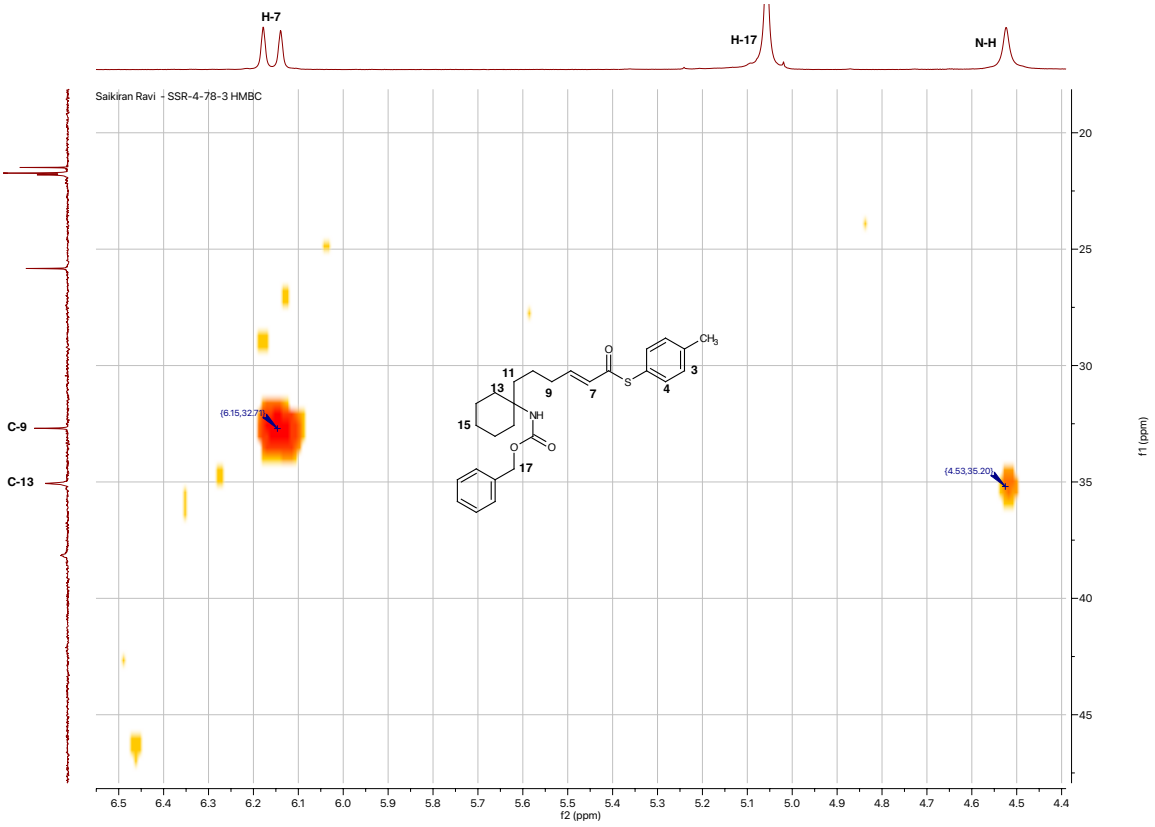
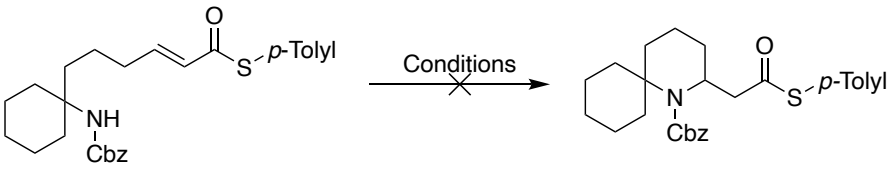


*Figure 42 : HMBC spectrum of **270** to show long range coupling between N-H and C-13*

Once the characterisation of **270** was complete, it was set to racemic cyclisation conditions in the presence of excess rac-CSA in 1,2-DCE at 80 °C for 24 hours but no product was formed (Table 8, entry 1). The reaction was also performed under basic conditions in the presence of *t*-BuOK at −78 °C, 0 °C and rt in THF, either with a very poor conversion making it a difficult column, or no product being formed (Table 8, entries 2-4). As expected, the asymmetric reaction conditions in the presence of (*R*)-Anth also did not form the desired product (Table 8, entry 5). The starting material was recovered in each of the reactions.

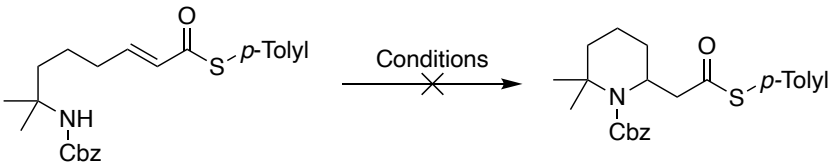


270 **271**

Entry	Conditions	Comments
1	rac-CSA, 1,2-DCE, 80 °C, 24 h	No product
2	*t*-BuOK (2 eq), THF, rt, 3.5 h;	Poor conversion, couldn't isolate product
3	*t* -BuOK (2 eq), THF, −78 °C, 3 h	No product
4	*t*-BuOK (2 eq), THF, 0 °C, 3.5 h	Poor conversion, couldn't isolate product
5	(*R*)-Anth (0.2 eq), cyclohexane, 80 °C, 24 h	No product

*Table 8 : Attempted cyclisation of precursor **270***

This was attributed to the steric bulk on the second position being in proximity with the bulky Cbz group and thus did not cyclise under acidic or basic conditions. The cyclisation precursor for the 2,2-dimethyl substrate **272** which was prepared by Chris Maddocks was also carried out under the conditions shown in Table 9. A very poor conversion was obtained under basic conditions using *t*-BuOK at rt (Table 9, entry 1) and at 0 °C (Table 9, entry 2) and it was difficult to isolate the product by column chromatography. No product was formed on reducing the temperature to –78 °C (Table 9, entry 3) under basic conditions. Using CPA as catalysts resulted in very poor conversion and the product could not be isolated (Table 9, entries 4-6). The unreacted starting material was recovered after each reaction.



272 **190$**

Entry	Conditions	Comments
1	*t*-BuOK (1.6 eq), THF, rt, 3.5h	Poor conversion, couldn't isolate product
2	*t*-BuOK (1.6 eq), THF, 0 °C, 1 h	Poor conversion, couldn't isolate product
3	*t*-BuOK (1.6 eq), THF, –78 °C, 1 h	No product formed.
4	(*R*)-TRIP, cyclohexane, 80 °C, 24 h	Poor conversion ~4%, couldn't isolate product
5	(*R*)-TiPSY, cyclohexane, 80 °C, 24 h	Poor conversion ~ 15%, couldn't isolate product
6	(*R*)-Phen, cyclohexane, 80 °C, 24 h	Poor conversion ~ 14%, couldn't isolate product

*Table 9 : Attempted cyclisation of dimethyl precursor **272** under different reaction conditions*

Due to steric hindrance, the cyclisation of 2,2'-spiropiperidines would need to be optimised separately followed by substrate scope. This would be carried out subsequently in the future.

The current methodology proved unsuccessful for the synthesis of 2-spiropiperidines. In order to drive the cyclisation forward, the reaction would require cryogenic temperatures but this would be disadvantageous for an industrial scale up. Nevertheless, extensive optimisation of reaction conditions would need to be carried out to achieve the end product.

3. Conclusions

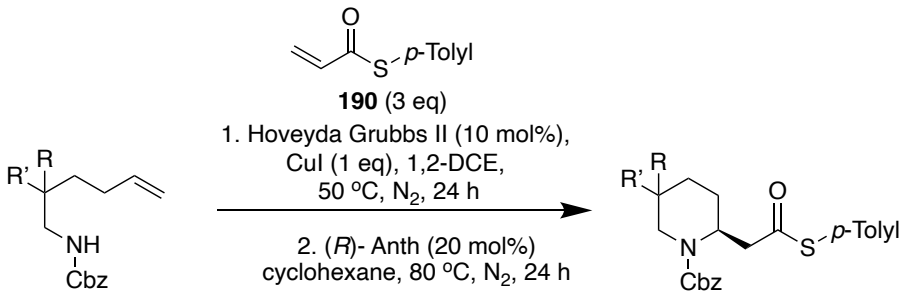
A novel methodology for the asymmetric synthesis of 3-spiropiperidines catalysed by chiral phosphoric acids *via* aza-Michael reaction has been developed during this PhD. Methodology development involved extensive optimization of reaction conditions. The selection of chiral phosphoric acid enabled excellent enantioselectivity from the start, but other parameters needed to be varied in order to improve the yield. Increasing the time of the reaction had no effect on the yield and e.r. of the product. It was also observed that sterically bulky thioester like mesityl functionality and higher temperatures up to 120 °C maintained excellent enantioselectivities, but with low-moderate yields. While (*R*)-TRIP gave excellent enantioselectivities with poor yields, it was found that (*R*)-Anth resulted in higher yields although with slightly reduced enantioselectivities. It was found that the optimized reaction conditions were (*R*)-Anth, cyclohexane, 80 °C, 24 h, using *p*-tolyl thioester as the Michael acceptor.

Using these optimized conditions, a range of substituted 3-spiropiperidines were synthesized in excellent enantioselectivities with a range of yields. Cyclisation precursors containing heterocyclic rings were subjected to the reaction conditions and were found to give acceptable yields. 3-spiroazetidine and 3-spirooxetane substitutions were also attempted but remained unsuccessful either because of decomposition or the ring opening of the substrates. The thioester of the unsubstituted piperidine was hydrolyzed to the corresponding acid which was used to measure the optical rotation and upon comparing with literature values, the absolute stereochemistry of the 3-spiropiperidines synthesized using this methodology was confirmed to be (*S*).

An unsaturated aldehyde was also used as a Michael acceptor to synthesise 3-spiropiperidine in high yield and although with a lower enantioselectivity as compared to thioesters, thus proving thioesters to be a better choice. An attempt to synthesise 2-spiropiperidines using the general methodology was also carried out but was unsuccessful, potentially due to steric bulk, calling for future work in this area.

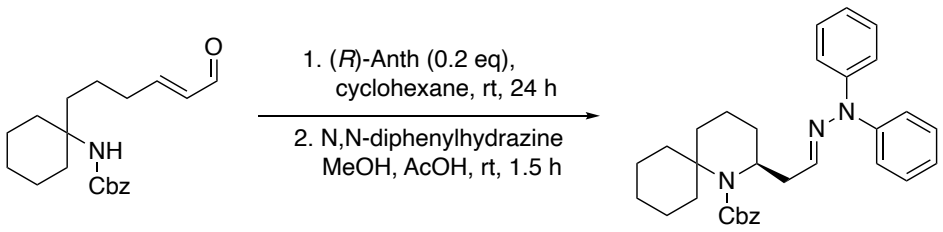
4. Future Work

With the promising methodology for the synthesis of 3-spiropiperidines, a one-pot cascade metathesis/ aza-Michael cyclisation, if successful, would eliminate the need to isolate the metathesis product along with saving time and resources (Scheme 72).



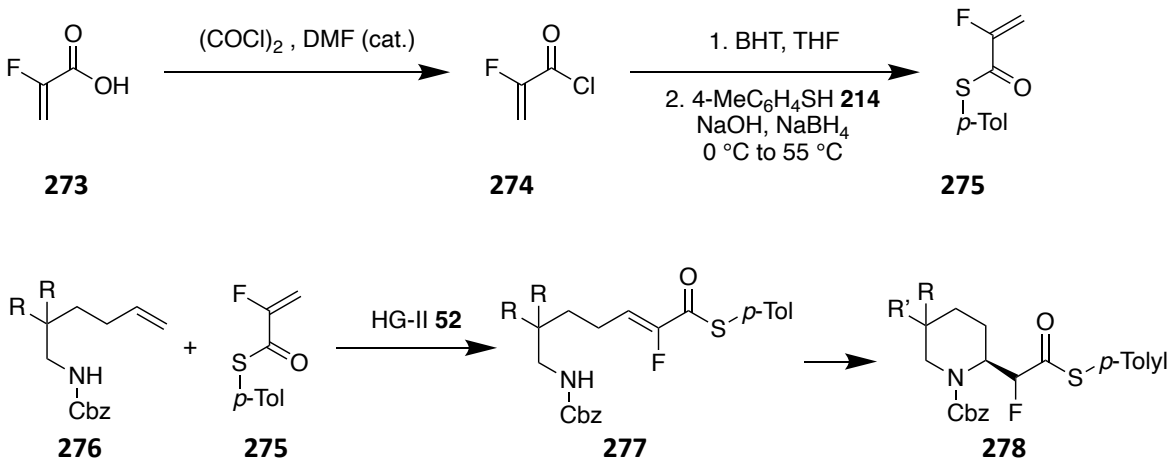
Scheme 72 : One pot cascade reaction for the synthesis of 3-spiropiperidines

The optimization for the synthesis of 2-spiropiperidines needs to be carried out as the methodology was not successful for the substrates **270** and **272** (Table 8 and Table 9). Although the disadvantages of using an aldehyde as the Michael acceptor have been discussed in the thesis, one of the ways to drive the cyclisation forward could be using them in the optimization process, in order to compensate for the steric hindrance between the 2-cyclohexyl substituent and Cbz protecting group (Scheme 73).



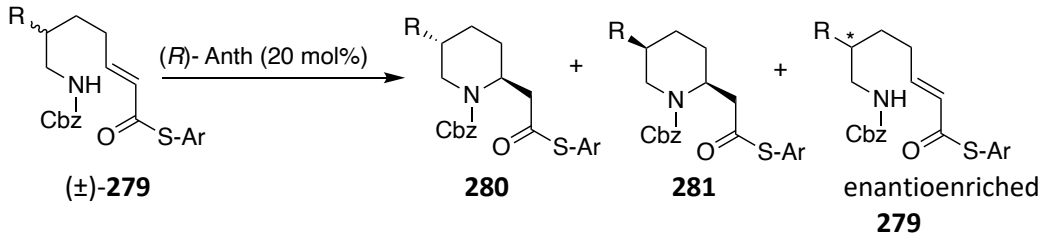
Scheme 73 : Use of unsaturated aldehyde as Michael acceptor towards 2-spiropiperidines

A fluorine-substitution around the piperidine ring would be very important from the medicinal chemistry perspective. A possible method is outlined in Scheme 74 starting with 2-fluoroacrylic acid **273** and converting it to the corresponding acid chloride **274** in the presence of oxalyl chloride and DMF. Thioester **275** can then be synthesised using the procedure outlined in the thesis and can be subjected to metathesis conditions with Cbz-amine **276**. Subsequent cyclisation of **277** would yield the compound **278**.



Scheme 74 : Installing a fluorine substituent around the piperidine ring

Another area of research stemming from this work is the kinetic resolution of racemic chiral precursors to generate enantioenriched compounds (Scheme 75).



*Scheme 75 : Kinetic resolution of (±)-**279** to obtain enantioenriched products*

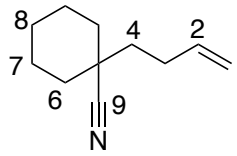
5. Experimental

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 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) and atmospheric pressure chemical ionization (APCI) techniques. Thin layer chromatography was performed on aluminium sheets 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, HmQC techniques. All numbering on the structures below is for the benefit of characterisation and does not necessarily conform to IUPAC rules.

Optimisation

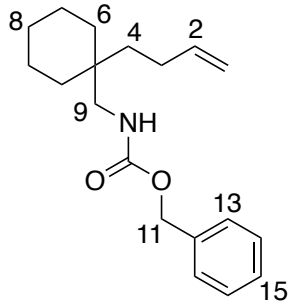
1-(But-3-en-1-yl)cyclohexanecarbonitrile (212)



To a solution of diisopropylamine (2.7 mL, 19.8 mmol, 1.1 eq) in dry THF (10 mL) at –78 °C under N_2 was added *n*-BuLi (1.42 M in hexanes, 15.2 mL, 21.6 mmol, 1.2 eq) and stirred for 50 min. A solution of cyclohexanecarbonitrile (2.1 mL, 18 mmol, 1 eq) in dry THF (10 mL) was added over 5 min at –78 °C and the reaction stirred for 40 mins. 4-Bromobutene (3.7 mL, 36 mmol, 2 eq) was added dropwise over 5 mins at –78 °C and the reaction warmed to room temperature and stirred overnight. The reaction was quenched with 1 M HCl (20 mL) and partitioned with Et_2O (20 mL). The aqueous layer was extracted with Et_2O (20 mL x 2). The combined organics were washed with saturated brine solution (20 mL) and dried over

$MgSO_4$, filtered, and concentrated *in vacuo.* The crude product was purified by flash column chromatography (2% EtOAc/Pet ether) to give the product **212** as a colourless oil (2.26 g, 13.8 mmol, 77% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 5.79 (ddt, *J* = 17.0, 10.1, 6.4 Hz, 1H, H-2), 5.05 (dd, *J* = 17.0, 1.5 Hz, 1H, H-1), 4.96 (dd, *J* = 10.1, 1.5 Hz, 1H, H-1'), 2.28 – 2.16 (m, 2H, H-3), 2.04 – 1.88 (m, 2H, H-6), 1.8 – 1.7 (m, 3H, H-7, H-8), 1.70 – 1.50 (m, 4H, H-7', H-4), 1.30 – 1.07 (m, 3H, H-8', H-6') ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 137.3 (C-2), 123.5 (C-9), 115.3 (C-1), 39.7 (C-4), 38.8 (C-5), 35.7 (C-6), 28.7 (C-3), 25.4 (C-8), 23.0 (C-7) ppm; **IR** (ATR): ν_{max} 3079, 2933, 2858, 2230, 1642, 1453, 1361, 1319, 1271, 1113, 998, 964, 912, 849, 766, 691, 646, 615, 557, 520 cm^{-1}; **HRMS** (APCI) 164.1428 ($M + H^+$. $C_{11}H_{18}N$ requires 164.1433).

1-(But-3-en-1-yl-cyclohexylmethyl) carbamic acid benzyl ester (213)



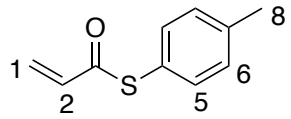
In a flame dried flask, $LiAlH_4$ (697 mg, 18.3 mmol, 1.5 eq) was added and the flask was cooled to 0 °C followed by addition of dry Et_2O (72 mL) under N_2 with continuous stirring. A solution of compound **212** (2.0 g, 12.2 mmol, 1 eq) in dry Et_2O (12 mL) was added over 5 min and the reaction was stirred at 0 °C under N_2 for 45 min and then warmed to room temperature. After 3.5 hours, the reaction mixture was cooled to 0 °C and quenched with water (0.7 mL), followed by addition of NaOH solution (15% w/w, 0.7 mL), followed by water (2.1 mL). The reaction was then warmed to room temperature and left to stir for 15 min after which $MgSO_4$ was added. After the reaction mixture was filtered through Celite®, it was concentrated *in vacuo* to give the amine (1.96 g, 11.7 mmol, 96% yield) which was taken through to the next step without purification.

Amine (1.8 g, 10.7 mmol, 1 eq) was dissolved in 1,4-dioxane (50 mL). To this, K_2CO_3 solution (50% w/w aq, 1.2 mL, 12.9 mmol, 1.2 eq) was added followed by benzyl chloroformate (1.8 mL, 12.9 mmol, 1.2 eq) and the reaction was stirred at room temperature. After 4 hours, the reaction was quenched with water (50 mL) and extracted with dichloromethane (50 mL x 3). The organic layer was washed with brine (50 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo.* The crude product was purified by flash column chromatography

(5% EtOAc/Petroleum ether) to afford **213** as a light-yellow oil (2.5 g, 15.9 mmol, 78% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.43 – 7.27 (m, 5 H, H-13, H-14, H-15), 5.79 (ddt, *J* = 17.1, 10.4, 6.5 Hz, 1 H, H-2), 5.10 (s, 2 H, H-11), 5.00 (dd, *J* = 17.1, 1.5 Hz, 1 H, H-1), 4.93 (dd, *J*= 10.4, 1.5 Hz, 1 H, H-1'), 4.80 (t, *J* = 6.1 Hz, 1 H, N-H), 3.13 (d, *J* = 6.1 Hz, 2 H, H-9), 2.13 – 1.85 (m, 2 H, H-3), 1.55 – 1.38 (m, 6 H, H-7, H-8), 1.37 – 1.18 (m, 6 H, H-4, H-6) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 156.6 (C-10), 139.2 (C-2), 136.5 (C-12), 128.5 (Ar-CH), 128.2 (Ar-CH), 128.1 (Ar-CH), 114.2 (C-1), 66.7 (C-11), 47.0 (C-9), 36.2 (C-4), 34.7 (C-5), 33.4 (C-6), 27.3 (C-3), 26.2 (C-8), 21.4 (C-7) ppm; **IR** (ATR): ν_{max} 3341, 3067, 3033, 2923, 2851, 1698 cm^{-1}; **HRMS** (ESI) 302.2115 (M + H$^+$. $C_{19}H_{28}NO_2$ requires 302.2115).

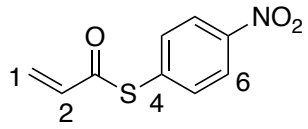
General Procedure A

Thioacrylic acid S-*p*-tolyl ester (190)



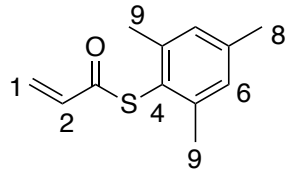
To a solution of NaOH (15% w/w aq. 17 mL, 64 mmol, 2 eq) was added $NaBH_4$ (36 mg, 0.96 mmol, 0.03 eq) and *p*-thiocresol (4 g, 32 mmol, 1 eq) which was then stirred for 1 hour at room temperature. A solution of butylated hydroxytoluene (106 mg, 0.48 mmol, 0.015 eq) and acryloyl chloride (3.90 mL, 48 mmol, 1.5 eq) in cyclohexane (30 mL) was cooled to 0 °C. The aqueous solution of *p*-thiocresol was added dropwise over 5 min to the acryloyl chloride solution and the reaction warmed to room temperature. The reaction was then heated to 55 °C for 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 **190** as a colourless oil (3 g, 0.016 mmol, 51 % yield). **^{1}H 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 *trans*), 5.78 (dd, *J* = 10.0, 1.5 Hz, 1H, H-1 *cis*), 2.41 (s, 3H, H-8) ppm. The compound was found to have identical ^{1}H NMR and ^{13}C NMR peaks as reported.[82]

Thioacrylic acid-S-*p*-nitrothioester (219)



Thioester **219** was synthesised using the **general procedure A** with a solution of NaOH (15% w/w aq. 5.65 mL), $NaBH_4$ (25 mg, 0.661 mmol, 0.05 eq), 4-nitrothiophenol (2 g, 12.8 mmol, 1 eq), butylated hydroxytoluene (42 mg, 0.192 mmol, 0.015 eq), acryloyl chloride (6 mL, 19.58 mmol) dichloromethane (8 mL) and heated at 55 °C for 1.5 hours. Compound **219** yielded as a light yellow solid (1.67 g, 7.98 mmol, 63% yield) after column chromatography (15% EtOAc/hexane) **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 8.31 – 8.23 (m, 2H, H-6), 7.69 – 7.62 (m, 2H, H-5), 6.52 – 6.41 (m, 2H, H-1, H-2), 5.89 (dd, *J* = 6.7, 4.3 Hz, 1H, H-1') ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ ppm 186.3 (C-3), 148.3 (C-7), 135.9 (C-4), 135.0 (C-6), 134.1 (C-2), 129.0 (C-1), 124.1 (C-5) ppm; **IR** (ATR): ν_{max} 3105, 2931, 2856, 1684, 1578, 1598, 1515, 1400, 1478, 1300, 1163, 1111, 1093, 983, 944, 850, 742 cm^{-1}; **HRMS** (APCI) 210.0209.2096 ($M + H^+$. $C_9H_8NO_3S$ requires 210.0219); m.p. 76 –79.5 °C.

Thioacrylic acid 2,4,6-trimethyl-phenyl ester (223)

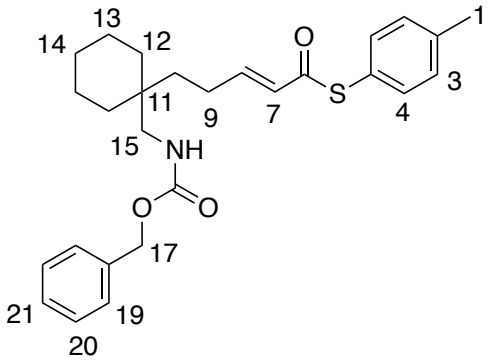


Thioester **223** was synthesised using the **general procedure A** with a solution of NaOH (15% w/w aq. 5.65 mL), $NaBH_4$ (12 mg, 0.318 mmol), 2,4,6-trimethylthiophenol (1.62 g, 10.6 mmol), butylated hydroxytoluene (35 mg, 0.159 mmol), acryloyl chloride (1.31 mL, 16.2 mmol) cyclohexane (6.6 mL). Compound **223** yielded as a pale-yellow oil (1.262 g, 6.12 mmol, 69% yield) after column chromatography (2% Et_2O/hexane). **^{1}H 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 *trans*), 5.76 (dd, *J* = 10.0, 1.2 Hz, 1 H, H-1 *cis*), 2.34 (s, 6 H, H-9), 2.32 (s, 3 H, H-8) ppm. This matched with the reported peaks in the literature.[82]

General Procedure B

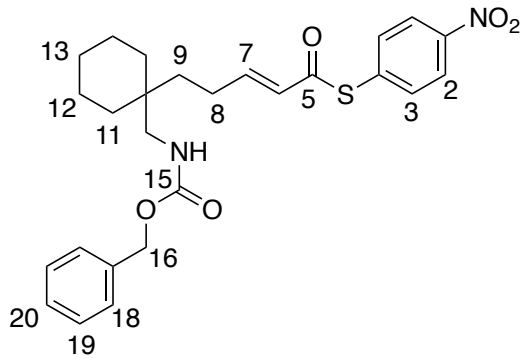
Hoveyda-Grubbs Catalyst™ 2nd generation (0.1 eq), copper iodide (1 eq) and 1,2-dichloroethane (8 mL) were added to a flame dried flask. To this, a solution of thioester (3 eq) in 1,2-dichloroethane (5 mL) was added under a nitrogen atmosphere while stirring, followed by the addition of a solution of Cbz-amine (1 eq) in 1,2 dichloroethane (5 mL). The flask was purged with N_2, and the reaction heated to 50 ^oC for 24 hours, after which the reaction mixture was cooled to room temperature, exposed to air and concentrated *in vacuo.* The crude residue was purified by flash column chromatography to yield the metathesis product**.**

(*E*)-S-*p*-Tolyl-5-(1-((((benzyloxy)carbonyl)amino)methyl)cyclohexyl)pent-2-enethioate (216)



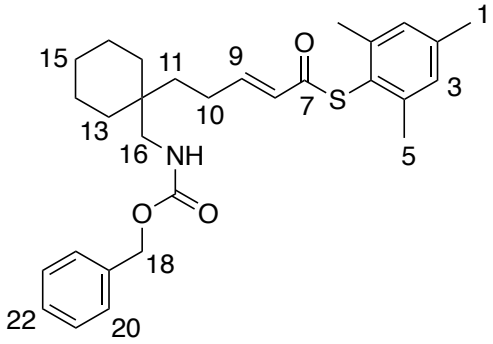
Compound **216** was synthesised using **general procedure B** with thioester **190** (193 mg, 1.082 mmol, 3 eq) copper iodide (68.5 mg, 0.36 mmol, 1 eq) and Hoveyda-Grubbs Catalyst™ 2nd generation (22.5 mg, 0.036 mmol, 0.1 eq), Cbz-amine **213** (109 mg, 0.36 mmol, 1 eq). **216** yielded as a pale-yellow oil (123 mg, 0.272 mmol, 76% yield) after column chromatography (20% Et_2O/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.38 – 7.26 (m, 7H, H-19, H-20, H-21, H-4), 7.21 (d, *J* = 8.1 Hz, 2H, H-3) 6.94 (dt, *J* = 15.5, 6.8 Hz, 1H, H-8), 6.17 (d, *J* = 15.5 Hz, 1H, H-7), 5.09 (s, 2H, H-17), 4.77 (t, *J* = 6.4 Hz, 1H, N-H), 3.10 (d, *J* = 6.4 Hz, 2H, H-15), 2.35 (s, 3H, H-1), 2.21 – 2.10 (m, 2H, H-9), 1.52 – 1.16 (m, 12H, H-10, H-12, H-13, H-14) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 188.6 (C-6), 156.7 (C-16), 147.0 (C-8), 139.6 (C-2), 136.6 (C-18), 134.7 (C-4), 130.0 (C-3), 128.7 (Ar-CH), 128.3 (Ar-CH), 127.8 (C-7), 124.2 (C-5), 67.0 (C-17) 47.1 (C-15), 36.5 (C-11), 33.4 (C-10 + C-12), 26.2 (C-9 + C-14), 21.4 (C-1), 21.4 (C-13) ppm; **IR** (ATR): ν_{max} 3356, 3033, 2926, 2853, 1710, 1681, 1630, 1518, 1494, 1455, 1237, 1130, 1016, 909, 808, 732, 698 cm^{-1}; **HRMS** (ESI) 452.2257 (M + H^+. $C_{27}H_{34}NO_3S$ requires 452.2254).

(*E*)-S-(4-Nitrophenyl)-5-(1-((((benzyloxy)carbonyl)amino)methyl)cyclohexyl)pent-2-enethioate (220)



Compound **220** was synthesised using **general procedure B** with thioester **219** (207 mg, 1.0 mmol, 3 eq), copper iodide (64 mg, 0.334 mmol) and Hoveyda-Grubbs^{TM} 2nd generation catalyst (21 mg, 0.033 mmol), Cbz-amine **213** (101 mg, 0.334 mmol, 1 eq). Compound **220** yielded as a pale brown oil (136 mg, 0.281 mmol, 84% yield) after column chromatography (15% EtOAc/hexane). **^{1}H NMR (**400 MHz, Chloroform-*d*): δ 8.30 – 8.18 (m, 2H, H-2), 7.68 – 7.58 (m, 2H, H-3), 7.38 – 7.23 (m, 5H, H-18, H-19, H-20), 7.03 (dt, *J* = 15.2 Hz, 6.8 Hz, 1H, H-7), 6.32 – 6.00 (d, *J* = 15.2 Hz, 1H, H-6), 5.08 (s, 2H, H-16), 4.87 (t, *J* = 6.6 Hz, 1H, N-H), 3.11 (d, *J* = 6.6 Hz, 2H, H-14), 2.32 – 1.99 (m, 2H, H-8), 1.63 – 1.11 (m, 12H, H-9, H-11, H-12, H-13) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 185.8 (C-5), 156.8 (C-15), 149.0 (C-7), 148.2 (C-1), 136.6 (C-17 + C-4), 134.9 (C-3), 128.7 (Ar-CH), 128.3 (Ar-CH), 128.3 (Ar-CH), 127.4 (C-6), 124.0 (C-2), 67.0 (C-16), 47.1 (C-14), 36.5 (C-10), 33.5 + 33.2 (C-11 + C-9), 26.4 (C-8), 26.2 (C-13), 21.4 (C-12) ppm; **IR (ATR)** 3346, 2925, 2854, 1696, 1628, 1518, 1455, 1342, 1237, 1012, 853, 743, 697 cm^{-1}; **HRMS** (ESI) 505.1767 (M+ Na^{+}. $C_{26}H_{30}N_2NaO_5S$ requires 505.1768).

(*E*)-*S*-Mesityl-5-(1-((((benzyloxy)carbonyl)amino)methyl)cyclohexyl)pent-2-enethioate (224)



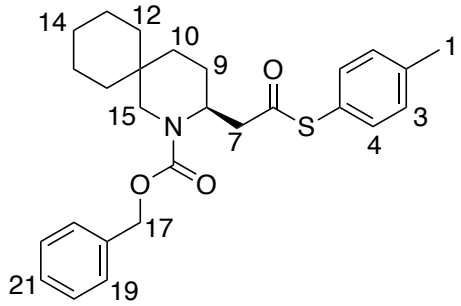
Compound **224** was synthesised using the **general procedure B** with thioester **223** (303 mg, 1.47 mmol, 3 eq), Hoveyda-Grubbs Catalyst™ 2nd generation (31 mg, 0.049 mmol, 0.1 eq) and copper iodide (93.5 mg, 0.491 mmol, 1 eq), Cbz-amine **213** (115 mg, 0.491 mmol, 1 eq) and reaction stopped after 48 h. Compound **224** yielded as a light brown oil (174 mg, 0.362 mmol, 82% yield) after column chromatography (15% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.41 – 7.28 (m, 5H, H-20, H-21, H-22), 6.98 (s, 2H, H-3), 6.97 – 6.91 (m, 1H, H-9), 6.23 (d, *J* = 15.6 Hz, 1H, H-8), 5.11 (s, 2H, H-18), 4.75 (t, *J* = 6.5 Hz, 1H, N-H), 3.14 (d, *J* = 6.5 Hz, 2H, H-16), 2.32 (s, 6H, H-5), 2.30 (s, 3H, H-1), 2.24 – 2.14 (m, 2H, H-10), 1.54 – 1.12 (m, 12H, H-11, H-13, H-14, H-15) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 187.8 (C-7), 156.8 (C-17), 146.5 (C-9), 142.8 (C-6), 139.9 (C-2), 136.6 (C-19), 129.3 (C-3), 128.7 (Ar-CH), 128.3 (Ar-CH), 128.0 (C-8), 123.6 (C-4), 66.9 (C-18), 47.1 (C-16), 36.5 (C-12), 33.5 (C-13, C-11), 26.2 (C-10), 26.1 (C-15), 21.7 (C-5), 21.4 (C-14), 21.2 (C-1) ppm; **IR** (ATR): ν_{max} 3356, 2923, 2852, 1707, 1673, 1630, 1603, 1529, 1454, 1375, 1237, 1129, 1012, 849, 805, 774, 735, 697, 816, 509, 462 cm^{-1}; **HRMS** (ESI) 480.2574 (M + H^{+}.$C_{29}H_{38}NO_3S$ requires 480.2567).

General Procedure C

Racemic: To a solution of amino-thioester (1 eq) in 1,2-DCE (0.02 M) was added rac-CSA (3 eq) and the reaction heated to 80 °C for 24 hours under N_2. The reaction was cooled to room temperature and extracted with DCM (2 x 5 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 to afford the cyclised product

Asymmetric: To a solution of amino-thioester (1 eq) in cyclohexane (0.02 M) was added CPA (0.2 eq) and the reaction heated to 80 °C for 24 hours under N_2. The reaction was quenched with Et_3N (0.2 mL) and cooled to room temperature and concentrated *in vacuo*. The crude material was purified by column chromatography to afford the cyclised product.

(*S*)-Benzyl 3-(2-oxo-2-(p-tolylthio)ethyl)-2-azaspiro[5.5]undecane-2-carboxylate (217)



Racemic: Compound **217** was synthesized using the **general procedure C** using the amino-thioester **216** (29 mg, 0.066 mmol, 1 eq) and rac-CSA (40 mg, 0.18 mmol, 3 eq). Compound **217** yielded as a pale-yellow oil (12 mg, 0.027 mmol, 41% yield) after column chromatography (10% EtOAc/hexane).

Asymmetric (*R*)-TRIP, cyclohexane 80 °C, 24 h

Compound **217** was synthesized using the **general procedure C** using the amino-thioester **216** (20 mg, 0.046 mmol, 1 eq) and (*R*)-TRIP (7 mg, 0.009 mmol, 0.2 eq). Compound **217** yielded as a pale-yellow oil (2 mg, 0.004 mmol, 10% yield, 96:4 e.r.) after column chromatography (10% EtOAc/hexane)

Asymmetric (*R*)-TRIP, cyclohexane 80 °C, 48 h

Compound **217** was synthesized using the **general procedure C** using the amino-thioester **216** (46 mg, 0.105 mmol, 1 eq) and (*R*)-TRIP (16 mg, 0.021 mmol, 0.2 eq). Compound **217** yielded as a pale-yellow oil (9.5 mg, 0.021 mmol, 21% yield, 96:4 e.r.) after column chromatography (10% EtOAc/hexane)

Asymmetric (*R*)-TRIP , octane 95 °C, 24 h

Compound **217** was synthesized using the **general procedure C** using the amino-thioester **216** (29 mg, 0.05 mmol, 1 eq) and (*R*)-TRIP (9 mg, 0.011 mmol, 0.2 eq). Compound **217** yielded as a pale-yellow oil (6.5 mg, 0.013 mmol, 23% yield, 95:5 e.r.) after column chromatography (20% Et_2O/pentane)

Asymmetric (*R*)-TRIP, octane 100 °C, 24 h

Compound **217** was synthesized using the **general procedure C** using the amino-thioester **216** (18 mg, 0.04 mmol, 1 eq) and (*R*)-TRIP (6 mg, 0.008 mmol, 0.2 eq). Compound **217** yielded as a pale-yellow oil (6.5 mg, 0.014 mmol, 36% yield, 94:6 e.r.) after column chromatography (20% Et_2O/pentane)

Asymmetric (*R*)- Anth, octane 100 °C, 24 h

Compound **217** was synthesized using the **general procedure C** using the amino-thioester **216** (22 mg, 0.04 mmol, 1 eq) and (*R*)-TRIP (7 mg, 0.009 mmol, 0.2 eq). Compound **217** yielded as a pale-yellow oil (17 mg, 0.039 mmol, 80% yield, 93:7 e.r.) after column chromatography (20% Et_2O/pentane)

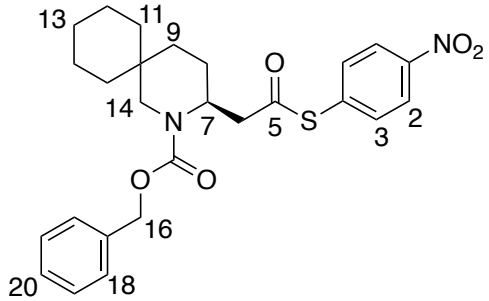
Asymmetric (*R*)-Anth, cyclohexane 80 °C, 24 h

Compound **217** was synthesized using the **general procedure C** using the amino-thioester **216** (29 mg, 0.066 mmol, 1 eq) and (*R*)-Anth (6 mg, 0.009 mmol, 0.2 eq). Compound **217** yielded as a pale-yellow oil (16 mg, 0.036 mmol, 78% yield, 96:4 e.r.) after column chromatography (20% EtOAc/pentane)

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.42 – 7.27 (m, 5H, H-19, H-20, H-21), 7.20 – 7.10 (m, 4H, H-4, H-3), 5.13 (s, 2H, H-17), 4.91 – 4.67 (br. m, 1H, H-8), 4.24 – 3.87 (br. m, 1H, H-15), 3.00 – 2.84 (m, 2H, H-7), 2.67 – 2.44 (br. m, 1H, H-15'), 2.37 (s, 3H, H-1), 1.97 – 1.79 (m, 1H, H-9), 1.58 – 1.12 (m, 13H, H-9', H-10, H-11, H-13, H-14) ppm; **^{13}C NMR** (101 MHz,

Chloroform-*d*): δ 195.4 (C-6), 155.4 (C-16), 139.8 (C-2), 136.9 (C-18), 134.4 (C-4), 130.1 (C-3), 128.5 (Ar-CH), 127.9 (Ar-CH), 127.9 (Ar-CH), 124.1 (C-5), 67.2 (C-17), 48.9 (C-8), 47.8 (C-15), 44.0 (C-7), 38.1 (C-13), 33.1 (C-11), 31.2 (C-12), 30.8 (C-12'), 26.6 (C-10), 23.6 (C-9), 21.7 (C-14), 21.5 (C-13'), 21.4 (C-1) ppm; **IR** (ATR): ν_{max} 2925, 2855, 1694, 1494, 1448, 1421, 1341, 1225, 1147, 1003, 807, 763, 734, 697, 607 cm^{-1}; **HRMS** (ESI) 452.2253 ($M + H^+$. $C_{27}H_{34}NO_3S$ requires 452.2254); **$[\alpha]_D^{20}$** +37.83 (c= 0.7, $CHCl_3$) for 96:4 er with (*R*)-Anth, cyclohexane at 80 °C.

(*S*)-Benzyl-3-(2-((4-nitrophenyl)thio)-2-oxoethyl)-2-azaspiro[5.5]undecane-2-carboxylate (221)



Racemic: Compound **221** was synthesized using the **general procedure C** using the amino-thioester **220** (22 mg, 0.046 mmol, 1 eq) and rac-CSA (32 mg, 0.139 mmol, 3 eq). Compound **221** yielded as a light-yellow oil (6.5 mg, 0.013 mmol, 29% yield) after column chromatography (20% Et_2O/hexane)

Asymmetric (*R*)-TRIP, cyclohexane 80 °C, 24 h

Compound **221** was synthesized using the **general procedure C** using the amino-thioester **220** (27 mg, 0.044 mmol, 1 eq) and (*R*)-TRIP (7 mg, 0.008 mmol, 0.2 eq). Compound **221** yielded as a light-yellow oil (4 mg, 0.009 mmol, 20% yield, 92:8 e.r.) after column chromatography (20% EtOAc/pentane)

Asymmetric (*R*)-TRIP, cyclohexane 80 °C, 48 h

Compound **221** was synthesized using the **general procedure C** using the amino-thioester **220** (25.5 mg, 0.052 mmol, 1 eq) and (*R*)-TRIP (8 mg, 0.01 mmol, 0.2 eq). Compound **221** yielded as a light-yellow (5 mg, 0.01 mmol, 21% yield, 84:16 e.r.) after column chromatography (20% Et_2O/hexane)

Asymmetric (*R*)-TRIP, toluene, 80 °C, 48 h

Compound **221** was synthesized using the **general procedure C** using the amino-thioester **220** (113 mg, 0.234 mmol, 1 eq) and (*R*)-TRIP (35 mg, 0.04 mmol, 0.2 eq). Compound **221** yielded as a light-yellow oil (9 mg, 0.018 mmol, 8% yield, 71:29 e.r.) after column chromatography (30% Et_2O/hexane)

Asymmetric (*R*)-TRIP, octane, 95 °C, 24 h

Compound **221** was synthesized using the **general procedure C** using the amino-thioester **220** (20 mg, 0.042 mmol, 1 eq) and (*R*)-TRIP (6 mg, 0.008 mmol, 0.2 eq). Compound **221** yielded as a light-yellow oil (3 mg, 0.007 mmol, 17% yield, 93:7 e.r.) after column chromatography (20% EtOAc/pentane)

Asymmetric (*R*)-TRIP, octane, 100 °C, 24 h

Compound **221** was synthesized using the **general procedure C** using the amino-thioester **220** (19 mg, 0.038 mmol, 1 eq) and (*R*)-TRIP (6 mg, 0.007 mmol, 0.2 eq). Compound **221** yielded as a light-yellow oil (10 mg, 0.021 mmol, 55% yield, 89:11 e.r.) after column chromatography (20% EtOAc/pentane)

Asymmetric (*R*)-TRIP, octane, 100 °C, microwave, 1 h

Compound **221** was synthesized using the **general procedure C** using the amino-thioester **220** (11 mg, 0.023 mmol, 1 eq) and (*R*)-TRIP (3.5 mg, 0.004 mmol, 0.2 eq). Compound **221** yielded as a light-yellow oil (1 mg, 0.002 mmol, 9% yield, 50:50 e.r.) after column chromatography (20% EtOAc/pentane)

Asymmetric (*R*)-Anth, octane, 100 °C, 24 h

Compound **221** was synthesized using the **general procedure C** using the amino-thioester **220** (18 mg, 0.037 mmol, 1 eq) and (*R*)-Anth (5 mg, 0.007 mmol, 0.2 eq). Compound **221** yielded as a light-yellow oil (12.5 mg, 0.025 mmol, 65% yield, 89:11 e.r.) after column chromatography (20% EtOAc/pentane)

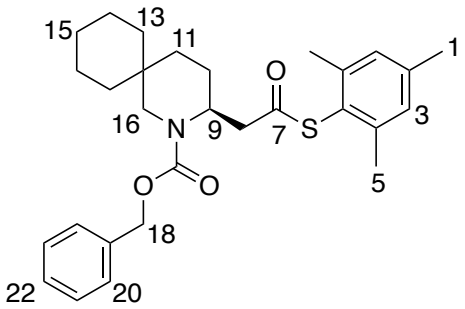
Asymmetric (*R*)-Anth, cyclohexane, 80 °C, 24 h

Compound **221** was synthesized using the **general procedure C** using the amino-thioester **220** (20 mg, 0.04 mmol, 1 eq) and (*R*)-Anth (6 mg, 0.008 mmol, 0.2 eq). Compound **221**

yielded as a light-yellow oil (14 mg, 0.029 mmol, 72% yield, 86:14 e.r.) after column chromatography (20% EtOAc/pentane)

^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.18 (d, *J* = 8.7 Hz, 2H, H-2), 7.64 – 7.39 (br. m, 2H, H-3), 7.38 – 7.20 (m, 5H, H-18, H-19, H-20), 5.13 (s, 2H, H-16), 4.99 – 4.73 (br. m, 1H, H-7), 4.24 – 3.93 (br. m, 1H, H-14), 3.12 – 2.91 (br. m, 1H, H-6), 2.90 – 2.72 (br. m, 1H, H-6'), 2.70 – 2.45 (br. m, 1H, H-14'), 2.06 – 1.85 (br. m, 1H, H-8), 1.56 – 1.07 (m, 13H, H-8', H-9, H-11, H-12, H-13) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 192.7 (C-5), 156.1 (C-15), 148.1 (C-1), 136.8 (C-17), 136.1 (C-4), 134.7 (C-3), 128.5 (Ar-CH), 128.0 (Ar-CH), 127.8 (Ar-CH), 124.0 (C-2), 67.2 (C-16), 49.0 (C-7), 48.0 (C-14), 44.4 (C-6), 38.0 (C-9), 33.1 (C-10), 31.2 (C-11), 30.9 (C-11'), 26.6 (C-13), 24.0 (C-8), 21.7 (C-12) 21.5 (C-12') ppm; **IR** (ATR): ν_{max} 2927, 2854, 1693, 1599, 1578, 1519, 1497, 1448, 1421, 1341, 1302, 1281, 1258, 1225, 1147, 1093, 852, 742 cm^{-1}; **HRMS** (ESI) 483.1955 (M + H^{+}. $C_{26}H_{31}N_2O_5S$ requires 483.1948); **$[\alpha]_D^{20}$** +22.5 (c= 0.2955, $CHCl_3$) for e.r. 90:10, (*R*)-TRIP, octane, 100 °C, 24 h.

(*S*)-Benzyl-3-(2-(mesitylthio)-2-oxoethyl)-2-azaspiro[5.5]undecane-2-carboxylate (225)



Racemic: Compound **225** was synthesized using the **general procedure C** using the amino-thioester **224** (34 mg, 0.071 mmol, 1 eq) and rac-CSA (49.5 mg, 0.213 mmol, 3 eq). Compound **225** yielded as a light-brown oil (28 mg, 0.057 mmol, 81% yield) after column chromatography (20% Et_2O/hexane)

Asymmetric (*R*)-TRIP, cyclohexane 80 °C, 24 h

Compound **225** was synthesized using the **general procedure C** using the amino-thioester **224** (50 mg, 0.103 mmol, 1 eq) and (*R*)-TRIP (16 mg, 0.02 mmol, 0.2 eq). Compound **225** yielded as a light-brown oil (7 mg, 0.014 mmol, 14% yield, 98:2 e.r.) after column chromatography (8% EtOAc /hexane)

Asymmetric (*R*)-TRIP, cyclohexane 80 °C, 48 h

Compound **225** was synthesized using the **general procedure C** using the amino-thioester **224** (54 mg, 0.112 mmol, 1 eq) and (*R*)-TRIP (17 mg, 0.02 mmol, 0.2 eq). Compound **225** yielded as a light-brown oil (7 mg, 0.014 mmol, 14% yield, 97:3 e.r.) after column chromatography (8% EtOAc /hexane)

Asymmetric (*R*)-TRIP, heptane 80 °C, 24 h

Compound **225** was synthesized using the **general procedure C** using the amino-thioester **224** (19 mg, 0.038 mmol, 1 eq) and (*R*)-TRIP (6 mg, 0.007 mmol, 0.2 eq). Compound **225** yielded as a light-brown (4 mg, 0.009 mmol, 24% yield, 97:3 e.r.) after column chromatography (8% EtOAc /hexane)

Asymmetric (*R*)-TRIP, heptane 95 °C, 24 h

Compound **225** was synthesized using the **general procedure C** using the amino-thioester **224** (23 mg, 0.047 mmol, 1 eq) and (*R*)-TRIP (7 mg, 0.009 mmol, 0.2 eq). Compound **225** yielded as a light-brown oil (10 mg, 0.021 mmol, 45% yield, 96:4 e.r.) after column chromatography (8% EtOAc /hexane)

Asymmetric (*R*)-TRIP, octane 95 °C, 24 h

Compound **225** was synthesized using the **general procedure C** using the amino-thioester **224** (24 mg, 0.049 mmol, 1 eq) and (*R*)-TRIP (7 mg, 0.009 mmol, 0.2 eq). Compound **225** yielded as a light-brown oil (11 mg, 0.023 mmol, 48% yield, 96:4 e.r.) after column chromatography (20% Et_2O /hexane)

Asymmetric (*R*)-TRIP, octane 100 °C, 24 h

Compound **225** was synthesized using the **general procedure C** using the amino-thioester **224** (19 mg, 0.039 mmol, 1 eq) and (*R*)-TRIP (6 mg, 0.007 mmol, 0.2 eq). Compound **225** yielded as a light-brown oil (10 mg, 0.02 mmol, 48% yield, 97:3 e.r.) after column chromatography (20% Et_2O /pentane)

Asymmetric (*R*)-TRIP, octane 110 °C, 24 h

Compound **225** was synthesized using the **general procedure C** using the amino-thioester **224** (18 mg, 0.038 mmol, 1 eq) and (*R*)-TRIP (6 mg, 0.007 mmol, 0.2 eq). Compound **225**

yielded as a light-brown oil (11.5 mg, 0.024 mmol, 63% yield, 95:5 e.r.) after column chromatography (8% EtOAc /hexane)

Asymmetric (*R*)-TRIP, octane 120 °C, 24 h

Compound **225** was synthesized using the **general procedure C** using the amino-thioester **224** (13.5 mg, 0.028 mmol, 1 eq) and (*R*)-TRIP (4 mg, 0.005 mmol, 0.2 eq). Compound **225** yielded as a light-brown oil (8 mg, 0.015 mmol, 56% yield, 93:7 e.r.) after column chromatography (8% EtOAc /hexane)

Asymmetric (*R*)-TiPSY, octane 100 °C, 24 h

Compound **225** was synthesized using the **general procedure C** using the amino-thioester **224** (20.5 mg, 0.042 mmol, 1 eq) and (*R*)- TiPSY (6 mg, 0.008 mmol, 0.2 eq). Compound **225** yielded as a light-brown oil (3 mg, 0.007 mmol, 17% yield, 38:62 e.r.) after column chromatography (10% EtOAc /hexane)

Asymmetric (*R*)-Phen, octane 100 °C, 24 h

Compound **225** was synthesized using the **general procedure C** using the amino-thioester **224** (19 mg, 0.039 mmol, 1 eq) and (*R*)- Phen (5.5 mg, 0.007 mmol, 0.2 eq). Compound **225** yielded as a light-brown oil (4 mg, 0.008 mmol, 21% yield, 62:38 e.r.) after column chromatography (20% Et_2O /pentane)

Asymmetric (*R*)-Anth, octane 100 °C, 24 h

Compound **225** was synthesized using the **general procedure C** using the amino-thioester **224** (46.5 mg, 0.096 mmol, 1 eq) and (*R*)- Anth (13.5 mg, 0.019 mmol, 0.2 eq). Compound **225** yielded as a light-brown oil (24.5 mg, 0.05 mmol, 67% yield, 92:8 e.r.) after column chromatography (20% Et_2O /pentane)

Asymmetric (*R*)-Anth, cyclohexane 80 °C, 24 h

Compound **225** was synthesized using the **general procedure C** using the amino-thioester **224** (27 mg, 0.05 mmol, 1 eq) and (*R*)-TRIP (8 mg, 0.011 mmol, 0.2 eq). Compound **225** yielded as a light-brown oil (10 mg, 0.02 mmol, 36% yield, 94:6 e.r.) after column chromatography (20% EtOAc /pentane).

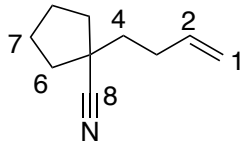
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.48 – 7.26 (m, 5H, H-20, H-21, H-22), 6.96 (s, 2H, H-3), 5.23 – 4.97 (br. m, 2H, H-18), 4.96 – 4.71 (br. s, 1H, H-9), 4.22 – 3.78 (br. m, 1H, H-16), 3.01 – 2.79 (m, 2H, H-8), 2.66 – 2.45 (br. m, 1H, H-16'), 2.29 (s, 3H, H-1), 2.27 (s, 6H, H-5), 1.97 – 1.79 (m, 1H, H-10), 1.57 – 1.12 (m, 13H, H-10', H-11, H-13, H-14, H-15) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 194.4 (C-7), 155.6 (C-17), 142.5 (C-6), 140.1 (C-2), 136.9 (C-19), 129.3 (C-3), 128.5 (C-20), 127.9 (C-21, C-22), 123.6 (C-4), 67.2 (C-18), 48.9 (C-9), 47.8 (C-16), 43.8 (C-8), 38.1 (C-14), 33.1 (C-12), 31.2 (C-13) 30.8 (C-13'), 26.6 (C-11). 23.4 (C-10), 21.7 (C-15), 21.6 (C-5), 21.5 (C-14'), 21.2 (C-1) ppm; **IR** (ATR): ν_{max} 2925, 2854, 1696, 1422, 1342, 1225, 1004, 849, 751, 696, 607 cm^{-1}; **HRMS** (ESI) 480.2581 (M + H^+. $C_{29}H_{38}NO_3S$ requires 480.2567); **$[\alpha]_D^{20}$** +30.47 (c= 0.3825, $CHCl_3$) for er 97:3, (*R*)-TRIP, octane 100 °C, 24 h.

Synthesis of 3,3'-disubstituted precursors

General Procedure D

To a solution of diisopropylamine (19.8 mmol1.1 eq) in dry THF (10 mL) at –78 °C under N_2 was added *n*-BuLi (1.42 M in hexanes, 21.6 mmol 1.2 eq) and stirred for 50 min. A solution of nitrile (18 mmol, 1 eq) in dry THF (10 mL) was added over 5 min at –78 °C and the reaction stirred for 40 mins. 4-Bromobutene (36 mmol, 2 eq) was added dropwise over 5 mins at –78 °C and the reaction warmed to room temperature and stirred overnight. The reaction was quenched with 1 M HCl (20 mL) and partitioned with Et_2O (20 mL). The aqueous layer was extracted with Et_2O (20 mL x 2). The combined organics were washed with saturated brine solution (20 mL) and dried over $MgSO_4$, filtered, and concentrated *in vacuo.* The crude product was purified by flash column chromatography to give the alkylated product.

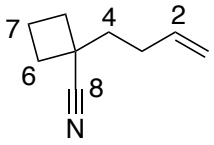
1-(But-3-en-1-yl)cyclopentanecarbonitrile (230a)



Compound **230a** was synthesised using the **general procedure D** with diisopropylamine (2 mL, 12 mmol, 1.1 eq), *n*-BuLi (2.07 M in hexanes, 6 mL, 12 mmol, 1.1 eq), cyclopentane carbonitrile (1.1 mL, 10.5 mmol, 1 eq) and 4-bromobutene (2 mL, 21.0 mmol, 2 eq). Compound **230a** yielded as a colourless oil (1 g, 9 mmol, 88% yield) after column

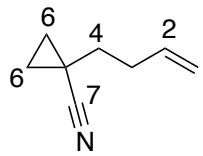
chromatography (5% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 5.80 (ddt, *J* = 16.9, 10.1, 6.4 Hz, 1H, H-2), 5.05 (dd, *J* = 16.9, 1.8 Hz, 1H, H-1), 4.98 (dd, *J* = 10.1, 1.8 Hz, 1H, H-1'), 2.30 – 2.21 (m, 2H, H-3), 2.17 – 2.06 (m, 2H, H-6), 1.88 – 1.78 (m, 2H, H-7), 1.78 – 1.69 (m, 2H, H-7'), 1.69 – 1.63 (m, 2H, H-4), 1.62 – 1.52 (m, 2H, H-6') ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 137.1 (C-2), 125.1 (C-8), 115.4 (C-1), 43.0 (C-5), 38.2 (C-6), 37.8 (C-4), 30.6 (C-3), 24.2 (C-7) ppm; **IR** (ATR): ν_{max} 3083, 2958, 2875, 2231, 1643, 1453, 994, 914 cm^{-1}; **HRMS** (APCI): 150.1280 (M + H^{+}. $C_{10}H_{16}N$ requires 150.1277).

1-(But-3-en-1-yl)cyclobutanecarbonitrile (230b)



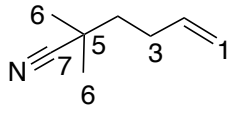
Compound **230b** was synthesised using the **general procedure D** with diisopropylamine (4 mL, 27 mmol, 1.1 eq), *n*-BuLi (2.0 M in hexanes, 14 mL, 27 mmol, 1.2 eq), cyclobutane carbonitrile (2 mL, 25 mmol, 1 eq) and 4-bromobutene (5 mL, 49 mmol, 2 eq). Compound **230b** yielded as a pale-yellow oil (2. g, 15 mmol, 61% yield) after column chromatography (20% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 5.77 (ddt, *J* = 16.8, 10.7, 6.8 Hz, 1H, H-2), 5.04 (dd, *J* = 16.8, 1.5 Hz, 1H, H-1), 4.96 (dd, *J* = 10.7, 1.5 Hz, 1H, H-1'), 2.51 – 2.39 (m, 2H, H-6), 2.19 – 2.12 (m, 2H, H-3), 2.12 – 1.90 (m, 4H, H-6', H-7), 1.81 – 1.72 (m, 2H, H-4) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 136.8 (C-2), 124.4 (C-8), 115.5 (C-1), 37.2 (C-4), 35.7 (C-5), 32.1 (C-6), 29.5 (C-3), 16.8 (C-7) ppm; **IR** (ATR): ν_{max} 3080, 2987, 2944, 2861, 2230, 1643, 1452, 996, 914, 616 cm^{-1}; **HRMS** (APCI): 136.1116 (M + H^{+}. $C_{9}H_{14}N$ requires 136.1120).

1-(But-3-en-1-yl)cyclopropanecarbonitrile (230c)



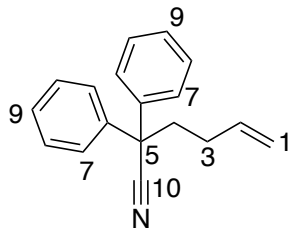
Compound **230c** was synthesised using the **general procedure D** with diisopropylamine (2 mL, 16 mmol, 1.1 eq), *n*-BuLi (2.08 M in hexanes, 8.5 mL, 18 mmol, 1.2 eq), cyclopropane cyanide (1 mL, 15 mmol, 1 eq) and 4-bromobutene (3 mL, 30 mmol, 2 eq). Compound **230c** yielded as a pale-yellow oil (625 mg, 5 mmol, 35% yield) after column chromatography (10% Et_2O/pentane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 5.80 (ddt, *J* = 16.9, 10.5, 6.7 Hz, 1H, H-2), 5.10 (dt, *J* = 16.9, 1.8 Hz, 1H, H-1), 5.00 (dd, *J* = 10.5, 1.8 Hz, 1H, H-1'), 2.40 – 2.30 (m, 2H, H-3), 1.60 – 1.50 (m, 2H, H-4), 1.23 – 1.20 (m, 2H, H-6), 0.81 – 0.78 (m, 2H, H-6) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 136.7 (C-2), 123.3 (C-7), 115.9 (C-1), 34.7 (C-4), 31.8 (C-3) , 13.9 (C-6), 9.5 (C-5) ppm; **IR** (ATR): ν_{max} 3080, 2927, 2237, 1642, 1451, 1430, 1068, 1035, 990, 914, 625, 572 cm^{-1}; **HRMS** (ESI) 122.0962 (M + H$^+$. $C_8H_{12}N$ requires 122.0964).

2,2-Dimethylhex-5-enenitrile (230d)



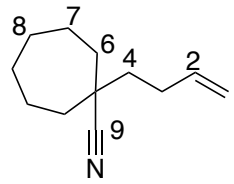
Compound **230d** was synthesised using the **general procedure D** with diisopropylamine (2 mL, 16 mmol, 1.1 eq), *n*-BuLi (1.89 M in hexanes, 9 mL, 17 mmol, 1.2 eq), isobutyronitrile (1 mL, 15 mmol, 1 eq) and 4-bromobutene (3 mL, 29 mmol, 2 eq). Compound **230d** yielded as a pale-yellow oil (1 g, 10 mmol, 69% yield) after column chromatography (10% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 5.80 (ddt, *J* = 17.1, 10.1, 6.5 Hz, 1H, H-2), 5.06 (dd, *J* = 17.1, 1.8 Hz, 1H, H-1), 4.99 (dd, *J* = 10.1, 1.8 Hz, 1H, H-1'), 2.28 – 2.15 (m, 2H, H-3), 1.65 – 1.53 (m, 2H, H-4), 1.34 (s, 6H, H-6) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 137.0 (C-2), 124.9 (C-7), 115.5 (C-1), 40.2 (C-4), 32.2 (C-5), 29.6 (C-3), 26.7 (C-6) ppm; **IR** (ATR): ν_{max} 3082, 2979, 2939, 2234, 1643, 1455, 1370, 1393, 1249, 1208, 996, 914, 773, 629 cm^{-1}; **HRMS** (APCI) 124.1120 (M + H$^+$. $C_8H_{14}N$ requires 124.1120).

2,2-Diphenylhex-5-enenitrile (230e)



Compound **230e** was synthesised using the **general procedure D** with diisopropylamine (3 mL, 17.0 mmol, 1.1 eq), *n*-BuLi (2.36 M in hexanes, 14.5 mL, 19 mmol, 1.2 eq), diphenylacetonitrile (3 g, 15.5 mmol, 1 eq) and 4-bromobutene (1 mL, 36.0 mmol, 2 eq). Compound **230e** yielded as a colourless oil (1.6 g, 7 mmol, 43% yield) after column chromatography (10% Et_2O/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.46 – 7.27 (m, 10H, H-7, H-8, H-9), 5.81 (ddt, *J* = 17.4, 10.3, 6.4 Hz, 1H, H-2), 5.06 (dd, *J* = 17.4, 1.4 Hz, 1H, H-1), 5.00 (dd, *J* = 10.3, 1.4 Hz, 1H, H-1'), 2.52 – 2.42 (m, 2H, H-4), 2.24 – 2.10 (m, 2H, H-3); **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 140.1 (C-6), 136.7 (C-2), 129.0 (Ar-CH), 128.0 (Ar-CH), 127.0 (Ar-CH), 122.3 (C-10), 115.8 (C-1), 51.5 (C-5), 38.9 (C-4), 29.9 (C-3) ppm; **IR** (ATR): ν_{max} 3064, 2934, 2249, 1645, 1600, 1494, 1449, 907, 728, 695, 649, 539 cm^{-1}; **HRMS** (ESI) 270.1255 ($M + Na^+$. $C_{18}H_{17}NNa$ requires 270.1253).

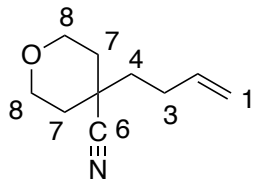
1-(But-3-en-1-yl)cycloheptanecarbonitrile (230f)



Compound **230f** was synthesised using the **general procedure D** with diisopropylamine (1.25 mL, 9 mmol, 1.1 eq), *n*-BuLi (1.89 M in hexanes, 5 mL, 10 mmol, 1.2 eq), cycloheptane carbonitrile (1 g, 8 mmol, 1 eq) and 4-bromobutene (2 mL, 16 mmol, 2 eq). Compound **230f** yielded as a pale-yellow oil (1.2 g, 7 mmol, 86% yield) after column chromatography (10% Et_2O/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 5.80 (ddt, *J* = 16.9, 10.1, 6.5 Hz, 1H, H-2), 5.06 (dd, *J* = 16.9, 1.7 Hz, 1H, H-1), 4.99 (dd, *J* = 10.1, 1.7 Hz, 1H, H-1'), 2.31 – 2.17 (m, 2H, H-3), 2.07 – 1.95 (m, 2H, H-6), 1.77 – 1.63 (m, 6H, H-7, H-8, H-8'), 1.63 – 1.58 (m, 2H, H-4), 1.58 – 1.45 (m, 4H, H-6', H-7') ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 137.3 (C-2), 124.8 (C-9), 115.4 (C-1), 41.3 (C-5), 40.0 (C-4), 38.0 (C-6), 29.5 (C-3), 28.1 (C-7), 23.5 (C-8)

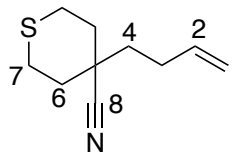
ppm; **IR** (ATR): ν_{max} 3079, 2928, 2858, 2229, 1642, 1462, 1450, 1367, 1150, 995, 912, 851, 683 cm^{-1}; **HRMS** (ESI) 200.1417 ($M + Na^+$. $C_{12}H_{19}NNa$ requires 200.1410).

4-(But-3-en-1-yl)tetrahydro-2H-pyran-4-carbonitrile (230g)



Compound **230g** was synthesised using the **general procedure D** with diisopropylamine (3 mL, 20 mmol, 1.1 eq), *n*-BuLi (2.0 M in hexanes, 11 mL, 21 mmol, 1.2 eq), 4-cyanotetrahydropyran (2 mL, 18 mmol, 1 eq) and 4-bromobutene (4 mL, 36 mmol, 2 eq). Compound **230g** yielded as a pale-yellow oil (3 g, 16 mmol, 90% yield) after column chromatography (15% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 5.75 (ddt, *J* = 16.8, 10.3, 6.5 Hz, 1H, H-2), 5.02 (dd, *J* = 16.8, 1.8 Hz, 1H, H-1), 4.95 (dd, *J* = 10.3, 1.8 Hz, 1H, H-1'), 3.98 – 3.93 (m, 2H, H-8), 3.62 (td, *J* = 12.3, 2.0 Hz, 2H, H-8'), 2.31 – 2.06 (m, 2H, H-3), 1.81 (dd, *J* = 13.5, 2.1 Hz, 2H, H-7), 1.65 – 1.57 (m, 2H, H-4), 1.60 (td, *J* = 13.0, 4.6 Hz, 2H, H-7') ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 136.9 (C-2), 122.5 (C-6), 115.9 (C-1), 64.8 (C-8), 39.6 (C-4), 36.8 (C-5), 35.5 (C-7), 28.4 (C-3) ppm; **IR** (ATR): ν_{max} 3082, 2954, 2854, 2926, 2230, 1642, 1453, 1242, 1109, 1013, 912, 838, 753, 562 cm^{-1}; **HRMS** (ESI) 188.1048 ($M + Na^+$. $C_{10}H_{15}NNaO$ requires 188.1046).

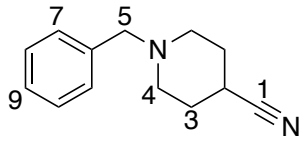
4-(But-3-en-1-yl)tetrahydro-2*H*-thiopyran-4-carbonitrile (230h)



Compound **230h** was synthesised using the **general procedure D** with diisopropylamine (1.21 mL, 8.64 mmol, 1.1 eq), *n*-BuLi (1.89 M in hexanes, 5 mL, 9.43 mmol, 1.2 eq), tetrahydrothiopyran-4-carbonitrile (1 g, 7.86 mmol, 1 eq) and 4-bromobutene (1.6 mL, 15.72 mmol, 2 eq). Compound **230h** yielded as a colourless oil (1.01 g, 5.57 mmol, 71% yield) after column chromatography (15% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-

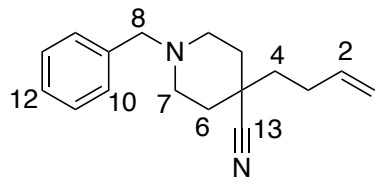
d): δ 5.79 (ddt, *J* = 17.0, 10.5, 6.4 Hz, 1H, H-2), 5.07 (dd, *J* = 17.0, 1.3 Hz, 1H, H-1), 5.01 (dd, *J* = 10.5, 1.3 Hz, 1H, H-1'), 3.00 (td, *J* = 12.5, 2.2 Hz, 2H, H-7), 2.62 – 2.50 (m, 2H, H-7'), 2.30 – 2.17 (m, 4H, H-6, H-3), 1.70 – 1.56 (m, 4H, H-6', H-4) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 136.8 (C-2), 122.1 (C-8), 115.8 (C-1), 39.8 (C-4), 38.6 (C-5), 36.5 (C-6), 28.3 (C-3), 25.3 (C-7) ppm; **IR** (ATR): ν_{max} 3078, 2940, 2912, 2231, 1641, 1452, 1430, 1277, 1141, 996, 939, 916, 616 cm^{-1}; **HRMS** (ESI) 204.0823 (M + Na$^+$. $C_{10}H_{15}NNaS$ requires 204.0817).

1-Benzylpiperidine-4-carbonitrile (229i)



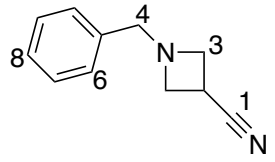
Following the literature procedure,[94] to piperidine-4-carbonitrile hydrochloride (1.86 g, 12.65 mmol, 1 eq) in dry acetonitrile (25 mL) was added bromomethylbenzene (1.5 mL, 12.65 mmol, 1 eq) followed by triethylamine (5.3 mL, 38 mmol, 3 eq) and stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo* and diluted with EtOAC (15 mL). The organic layer was washed with brine (15 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product which was redissolved in dichloromethane (15 mL) and washed with 2M HCl (10 mL x 4). The combined aqueous layers were washed with saturated $NaHCO_3$ solution to pH 9. This was then extracted with dichloromethane (15 mL x 3), washed with brine, dried with Na_2SO_4, filtered and concentrated *in vacuo* to give **229i** as a colourless oil (1.73 g, 9.87 mmol, 78% yield). The data matched the literature values.[101] **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.40 – 7.20 (m, 5H, H-7, H-8, H-9), 3.50 (s, 2H, H-5), 2.80 – 2.50 (br. m, 3H, H-4, H-2), 2.40 – 2.20 (br. m, 2H, H-4'), 2.00 – 1.80 (m, 4H, H-3, H-3') ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 138.0 (C-6), 129.0 (Ar-CH), 128.3 (Ar-CH), 127.2 (Ar-CH), 121.9 (C-1), 63.1 (C-5), 51.4 (C-4), 28.8 (C-3), 26.2 (C-2) ppm; **IR** (ATR): ν_{max} 3028, 2948, 2807, 2763, 2239, 1728, 1467, 1452, 1367, 1316, 1121, 1028, 915, 786, 738, 698, 605, 551, 469 cm^{-1}; **HRMS** (ESI) 201.1385 (M + H$^+$. $C_{13}H_{17}N_2$ requires 201.1386).

Benzyl 4-(but-3-en-1-yl)-4-cyanopiperidine-1-carboxylate (230i)



Compound **230i** was synthesised using the **general procedure D** with diisopropylamine (0.44 mL, 3.15 mmol, 1.1 eq), *n*-BuLi (1.89 M in hexanes, 1.81 mL, 3.43 mmol, 1.2 eq), **229i** (502 mg, 2.86 mmol, 1 eq) and 4-bromobutene (0.6 mL, 5.73 mmol, 2 eq). Compound **230i** yielded as a pale-yellow oil (386 mg, 1.51 mmol, 53% yield) after column chromatography (15% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.38 – 7.26 (m, 5H, H-10, H-11, H-12), 5.82 (ddt, *J* = 16.9, 10.1, 6.4 Hz, 1H, H-2), 5.08 (dd, *J* = 16.9, 1.5 Hz, 1H, H-1), 5.02 (dd, *J* = 10.1, 1.5 Hz, 1H, H-1'), 3.54 (s, 2H, H-8), 2.93 – 2.80 (m, 2H, H-7), 2.30 (td, *J* = 12.6, 2.0 Hz, 2H, H-7'), 2.29 – 2.23 (m, 2H, H-3), 1.97 – 1.88 (m, 2H, H-6), 1.69 – 1.62 (m, 2H, H-4), 1.60 (td, *J* = 13.2, 4.0 Hz, 2H, H-6') ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 138.1 (C-9), 137.0 (C-2), 129.1 (Ar-CH), 128.3 (Ar-CH), 127.2 (Ar-CH), 122.8 (C-13), 115.6 (C-1) , 62.9 (C-8), 50.4 (C-7), 39.2 (C-4), 37.4 (C-5), 35.0 (C-6), 28.7 (C-3) ppm; **IR** (ATR): ν_{max} 3028, 2944, 2923, 2810, 2769, 2231, 1642, 1494, 1453, 1369, 1345, 1301, 1120, 973, 912, 798, 738, 698, 606 cm^{-1}; **HRMS** (ESI) 255.1858 (M + H^{+}. $C_{17}H_{23}N_2$ requires 255.1856).

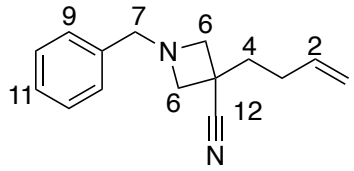
1-Benzylazetidine-3-carbonitrile (245)



Compound **245** was synthesised using the same procedure as **229i** using azetidine-3-carbonitrile hydrochloride (1.5 g, 12.65 mmol, 1 eq), bromomethylbenzene (1.5 mL, 12.65 mmol, 1 eq), triethylamine (5.3 mL, 38 mmol, 3 eq). Compound **245** was obtained as a pale-yellow oil (1 g, 5.8 mmol, 46% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.40 – 7.20 (m, 5H, H-6, H-7, H-8), 3.60 (s, 2H, H-4), 3.50 (t, *J* = 7.3 Hz, 2H, H-3), 3.30 (t, *J* = 7.3 Hz, 2H, H-3'), 3.30 – 3.20 (m, 1H, H-2) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 136.7 (C-5), 128.5 (C-Ar), 128.3 (C-Ar), 127.4 (C-Ar), 120.2 (C-1), 62.9 (C-4), 57.3 (C-3), 18.4 (C-2) ppm; **IR (ATR)**

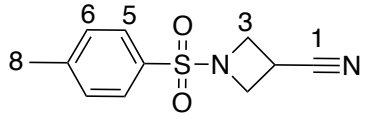
2984, 1736, 1372, 1233, 1043m 938, 917, 786, 634, 607 cm^{-1}; **HRMS** (ESI) 173.1073 ($M+Na^+$. $C_{11}H_{13}N_2$ requires 173.1073).

1-Benzyl-3-(but-3-en-1-yl)azetidine-3-carbonitrile (229j)



Compound **229j** was synthesised using the **general procedure D** with diisopropylamine (0.2 mL, 1.6 mmol, 1.1 eq), *n*-BuLi (2.5 M in hexanes, 0.7 mL, 1.8 mmol, 1.1 eq), nitrile **245** (260 mg, 1.5 mmol, 1 eq) and 4-bromobutene (0.3 mL, 3 mmol, 2 eq) and the reaction quenched with saturated sodium bicarbonate solution (2 mL). Compound **229j** yielded as a colourless oil (129 mg, 0.57 mmol, 38% yield) after column chromatography (15% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.40 – 7.30 (m, 5H, H-9, H-10, H-11), 5.80 (ddt, *J* = 16.9, 10.1, 6.5 Hz, 1H, H-2), 5.10 (dd, *J* = 16.9, 1.6 Hz, 1H, H-1), 5.00 (dd, *J* = 10.1, 1.8 Hz, 1H, H-1'), 3.70 (s, 2H, H-7), 3.50 (d, *J* = 7.5 Hz, 2H, H-6), 3.30 (d, *J* = 7.4 Hz, 2H, H-6'), 2.30 – 2.20 (m, 2H, H-3), 2.10 – 2.00 (m, 2H, H-4) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 136.6 (C-8), 136.3 (C-2), 128.6 (C-Ar), 128.6 (C-Ar), 127.6 (C-Ar), 122.4 (C-12), 116.3 (C-1), 62.6 (C-7), 62.3 (C-6), 35.3 (C-4), 32.1 (C-5), 29.9 (C-3) ppm; **IR (ATR)** 3064, 3030, 2936, 2836, 2235, 1642, 1495, 1453, 1365, 1303, 1225, 1191, 1068, 916, 729, 698 cm^{-1}.

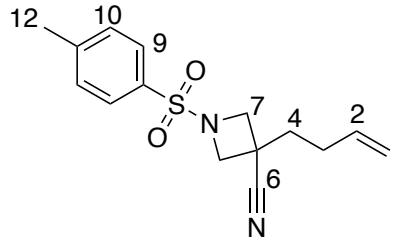
1-Tosylazetidine-3-carbonitrile (249)



To a flame dried flask, was added a solution of azetidine-3-carbonitrile hydrochloride (500 mg, 4.21 mmol, 1 eq), in DCM (10 mL) followed by dropwise addition of a solution of DMAP (51.5 mg, 0.42 mmol, 0.1 eq) in DCM (2 mL) over 2 minutes and Et_3N (1.29 mL, 9.27 mmol, 2.2 eq) and stirred at room temperature for an hour. A solution of tosyl chloride (1.2 g, 6.32 mmol, 1.5 eq) in DCM (12 mL) was added over 10 minutes and left to stir at room temperature overnight. The reaction mixture was concentrated, and the residue was

neutralised with saturated sodium bicarbonate solution and the aqueous layer was extracted with EtOAc (15 mL x 3). Combined organics were washed with brine (15 mL), dried with $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by flash column chromatography (20-60% EtOAc/hexane) to afford **249** as a light-yellow oil (385 mg, 1.62 mmol, 39% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.70 (d, *J* = 8.2 Hz, 2H, H-5), 7.40 (d, *J* = 8.2 Hz, 2H, H-6), 4.10 (t, *J* = 8.5 Hz, 2H, H-3), 3.90 (d, *J* = 8.5 Hz, 2H, H-3'), 3.40 – 3.20 (m, 1H, H-2), 2.50 (s, 2H, H-8) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 145.2 (C-4), 130.8 (C-7), 130.3 (C-6), 128.5 (C-5), 118.2 (C-1), 53.3 (C-3), 21.8 (C-8), 17.0 (C-2) ppm; **IR (ATR)** 2958, 2249, 1348, 1161, 1115, 817, 676, 550 cm^{-1}; **HRMS** (ESI) 237.0695 (M+ H$^+$. $C_{11}H_{13}N_2O_2S$ requires 237.0692).

3-(But-3-en-1-yl)-1-tosylazetidine-3-carbonitrile (250)



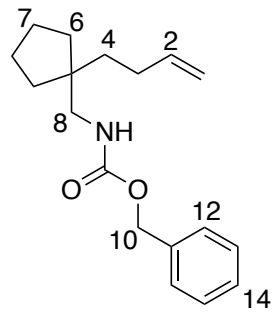
Compound **250** was synthesised using the **general procedure D** with diisopropylamine (0.15 mL, 1.12 mmol, 1.1 eq), *n*-BuLi (2.5 M in hexanes, 0.5 mL, 1.22 mmol, 1.1 eq), nitrile **249** (241 mg, 1.02 mmol, 1 eq) and 4-bromobutene (0.2 mL, 2 mmol, 2 eq) and the reaction quenched with saturated sodium bicarbonate solution (2 mL). Compound **250** yielded as a colourless oil (30 mg, 0.103 mmol, 10% yield) after column chromatography (20% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.80 – 7.60 (m, 2H, H-9), 7.40 (d, *J* = 8.1 Hz, 2H, H-10), 5.70 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1H, H-2), 5.10 (dd, *J* = 17.0, 1.7 Hz, 1H, H-1), 5.00 (dd, *J* = 10.2, 1.7 Hz, 1H, H-1'), 4.00 (d, *J* = 8.3 Hz, 2H, H-7), 3.80 (d, *J* = 8.3 Hz, 2H, H-7'), 2.50 (s, 1H, H-12), 2.20 – 2.10 (m, 2H, H-3), 1.90 – 1.80 (m, 2H, H-4) ppm; **^{13}C NMR** δ (101 MHz, Chloroform-*d*): δ 145.1 (C-11), 135.3 (C-1), 131.0 (C-8), 128.4 (C-9), 120.2 (C-6), 117.1 (C-2), 58.7 (C-7), 35.2 (C-4), 30.5 (C-5), 29.5 (C-3), 21.8 (C-12) ppm; **IR (ATR)** 2926, 1597, 1349, 1161, 1090, 998, 817, 711, 675, 548 cm^{-1}; **HRMS** (ESI) 291.1172 (M+ H$^+$. $C_{15}H_{19}N_2O_2S$ requires 291.1162).

General Procedure E

In a flame dried flask, $LiAlH_4$ (18.3 mmol, 1.5 eq) was added and the flask was cooled to 0 ^oC followed by addition of dry Et_2O (72 mL) under N_2 with continuous stirring. A solution of nitrile (12.2 mmol, 1 eq) in dry Et_2O (12 mL) was added over 5 min and the reaction was stirred at 0 ^oC under N_2 for 45 min and then warmed to room temperature. After 3.5 hours, the reaction mixture was cooled to 0 ^oC and quenched with water (0.7 mL), followed by addition of NaOH solution (15% w/w, 0.7 mL), followed by water (2.1 mL). The reaction was then warmed to room temperature and left to stir for 15 min after which $MgSO_4$ was added. After the reaction mixture was filtered through Celite®, it was concentrated *in vacuo* to give the amine which was taken through to the next step without purification.

Amine (10.7 mmol, 1 eq) was dissolved in 1,4-dioxane (50 mL). To this, K_2CO_3 solution (50% w/w aq, 12.9 mmol, 1.2 eq) was added followed by benzyl chloroformate (12.9 mmol, 1.2 eq) and the reaction was stirred at room temperature. After 4 hours, the reaction was quenched with water (50 mL) and extracted with dichloromethane (50 mL x 3). The organic layer was washed with brine (50 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo.* The crude product was purified by flash column chromatography to afford the Cbz-amine**.**

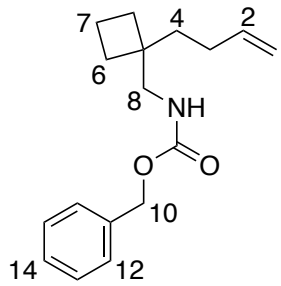
Benzyl ((1-(but-3-en-1-yl)cyclopentyl)methyl)carbamate (231a)



Compound **231a** was synthesised using the **general procedure E** with $LiAlH_4$ (191 mg, 5.03 mmol, 1.5 eq), nitrile **230a** (500 mg, 3.35 mmol, 1 eq) to give the amine as a colourless oil (521 mg, 3.40 mmol) which was Cbz protected with K_2CO_3 solution (50% w/w aq, 1.2 mL, 8.5 mmol, 2.5 eq) and benzyl chloroformate (0.58 mL, 4.08 mmol, 1.2 eq). Compound **231a** yielded as a pale-yellow oil (353 mg, 1.22 mmol, 37% yield over two steps) after column chromatography (10% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.41 – 7.28 (m, 5H, H-12, H-13, H-14), 5.80 (ddt, *J* = 16.9, 10.1, 6.5 Hz, 1H, H-2), 5.10 (s, 2H, H-10), 5.00 (dd,

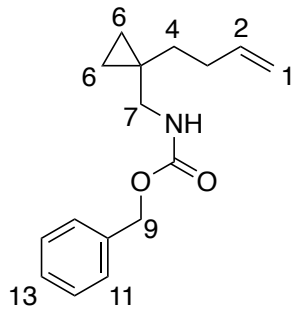
J = 16.9, 1.8 Hz, 1H, H-1), 4.93 (dd, *J* = 10.1, 1.8 Hz, 1H, H-1'), 4.76 (t, *J* = 6.4 Hz, 1H, N-H), 3.12 (d, *J* = 6.4 Hz, 2H, H-8), 2.09 – 1.95 (m, 2H, H-3), 1.68 – 1.54 (m, 4H, H-7), 1.45 – 1.32 (m, 6H, H-4, H-6) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 156.8 (C-9), 139.1 (C-2), 136.7 (C-11), 128.6 (Ar-CH), 128.3 (Ar-CH), 128.2 (Ar-CH), 114.3 (C-1), 66.8 (C-10), 47.5 (C-8), 45.9 (C-5), 37.0 (C-4), 35.5 (C-6), 29.1 (C-3), 25.0 (C-7) ppm; **IR (ATR)**: ν_{max} 3340, 3069, 3034, 2946, 2867, 1703, 1640, 1527, 1454, 1410, 1335, 1238, 1136, 1027, 999, 909, 775, 735, 697, 485 cm^{-1}; **HRMS (ESI):** 310.1775 (M + Na$^+$. $C_{18}H_{25}NNaO_2$ requires 310.1777).

Benzyl ((1-(but-3-en-1-yl)cyclobutyl)methyl)carbamate (231b)



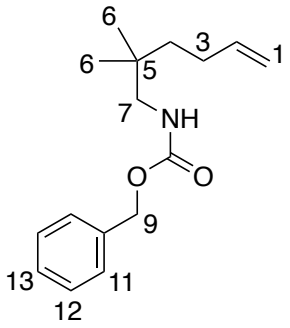
Compound **231b** was synthesised using **general procedure E** with $LiAlH_4$ (421 mg, 11.1 mmol, 1.5 eq), nitrile **230b** (1 g, 7.4 mmol, 1 eq) to give the amine as a colourless oil (1.02 g, 7.35 mmol, 99% yield) which was Cbz protected with K_2CO_3 solution (50% w/w aq, 2.5 mL, 18.37 mmol, 1.2 eq) and benzyl chloroformate (2.6 mL, 18.37 mmol, 1.2 eq). Compound **231b** yielded as a colourless oil (1.22 g, 4.47 mmol, 61% yield) after column chromatography (10% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.43 – 7.27 (m, 5H, H-12, H-13, H-14), 5.82 (ddt, *J* = 17.0, 10.1, 6.9 Hz, 1H, H-2), 5.11 (s, 2H, H-10), 5.02 (dd, *J* = 17.0, 1.8 Hz, 1H, H-1), 4.94 (dd, *J* = 10.1, 1.8 Hz, 1H, H-1'), 4.71 (br. S, 1H, N-H), 3.27 (d, *J* = 6.1 Hz, 2H, H-8), 2.07 – 1.95 (m, 2H, H-3), 1.94 – 1.80 (m, 2H, H-7), 1.80 – 1.67 (m, 4H, H-6), 1.57 – 1.46 (m, 2H, H-4) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 156.9 (C-9), 139.0 (C-2), 136.7 (C-11), 128.7 (Ar-CH), 128.2 (Ar-CH), 128.2 (Ar-CH), 114.4 (C-1), 66.8 (C-10), 47.3 (C-8), 41.8 (C-5), 36.7 (C-4), 29.2 (C-6), 28.4 (C-3), 15.1 (C-7) ppm; **IR (ATR)**: ν_{max} 3339, 3072, 3034, 2931, 2868, 1703, 1640, 1523, 1454, 1344, 1244, 1135, 1004, 910, 853, 775, 739, 697 cm^{-1}; **HRMS (ESI):** 274.1798 (M+ H$^+$. $C_{17}H_{24}NO_2$ requires 274.1802).

Benzyl ((1-(but-3-en-1-yl)cyclopropyl)methyl)carbamate (231c)



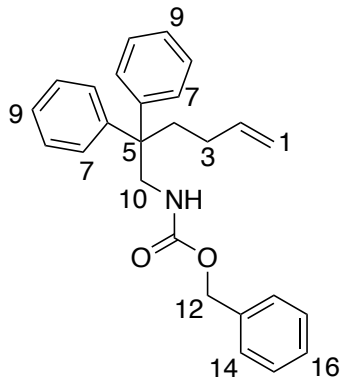
Compound **231c** was synthesised using **general procedure E** with $LiAlH_4$ (490 mg, 13 mmol, 1.5 eq), nitrile **230c** (1.05 g, 8.66 mmol, 1 eq) to give the crude amine which was acidified by addition of 2M HCl in ether (4.8 mL, 1.1 eq) and stirred for 20 hours at room temperature to form the corresponding HCl salt which was used without further purification. The HCl salt of the amine was Cbz protected using K_2CO_3 solution (50% w/w aq, 3 mL, 22 mmol, 1.2 eq) and benzyl chloroformate (3 mL, 22 mmol, 1.2 eq). Compound **231c** yielded as a light-yellow oil (780.5 mg, 3 mmol, 38% yield over two steps) after column chromatography (10% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.43 – 7.28 (m, 5H, H-11, H-12, H-13), 5.81 (ddt, *J* = 17.0, 10.4, 6.6 Hz, 1H, H-2), 5.13 (s, 2H, H-9), 5.01 (dd, *J* = 17.0, 1.8 Hz, 1H, H-1), 4.93 (dd, *J* = 10.4, 1.8 Hz, 1H, H-1'), 4.82 (t, *J* = 6.0 Hz, 1H, N-H), 3.10 (d, *J* = 6.0 Hz, 2H, H-7), 2.22 – 2.02 (m, 2H, H-3), 1.46 – 1.30 (m, 2H, H-4), 0.42 – 0.30 (m, 4H, H-6) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ ppm 156.5 (C-8), 138.7 (C-2), 136.7 (C-10), 128.6 (Ar-CH), 128.2 (Ar-CH), 114.5 (C-1), 66.71 (C-9), 47.1 (C-7), 34.1 (C-4), 31.0 (C-3), 20.0 (C-5), 10.7 (C-6) ppm; **IR** (ATR): ν_{max} 3337, 3072, 2928, 1703, 1640, 1525, 1454, 1240, 1133, 1046, 1015, 995, 910, 775, 735, 697, 627 cm^{-1}; **HRMS** (ESI): 260.1651 (M+ H^+. $C_{16}H_{22}NO_2$ requires 260.1645).

Benzyl (2,2-dimethylhex-5-en-1-yl)carbamate (231d)



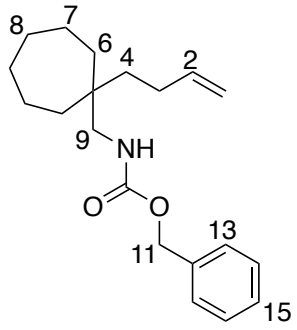
Compound **231d** was synthesised using the **general procedure E** with $LiAlH_4$ (693 mg, 18.2 mmol, 1.5 eq), nitrile **230d** (1.5 g, 12.1 mmol, 1 eq) to give the amine as a colourless oil (643 mg, 5.05 mmol, 41% yield) which was Cbz protected with K_2CO_3 solution (50% w/w aq, 0.83 mL, 6.06 mmol, 1.2 eq) and benzyl chloroformate (1.16 mL, 6.02 mmol, 1.2 eq). Compound **231d** yielded as a light brown oil (739 mg, 2.82 mmol, 56% yield) after column chromatography (5% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.47 – 7.27 (m, 5H, H-11, H-12, H-13), 5.81 (ddt, *J* = 17.0, 10.1, 6.5 Hz, 1H, H-2), 5.11 (s, 2H, H-9), 5.02 (dd, *J* = 17.0, 1.8 Hz, 1H, H-1), 4.93 (dd, *J* = 10.1, 1.8 Hz, 1H, H-1'), 4.76 (t, *J* = 6.4 Hz, N-H), 3.04 (d, *J* = 6.4 Hz, 2H, H-7), 2.17 – 1.77 (m, 2H, H-3), 1.43 – 1.11 (m, 2H, H-4), 0.89 (s, 6H, H-6) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 156.7 (C-8), 139.1 (C-2), 136.6 (C-10), 128.5 (Ar-CH), 128.1 (Ar-CH), 128.1 (Ar-CH), 114.2 (C-1), 66.6 (C-9), 50.9 (C-7), 38.7 (C-4), 34.3 (C-5), 28.3 (C-3), 24.7 (C-6) ppm; **IR** (ATR): ν_{max} 3353, 3071, 3031, 2959, 1701, 1640, 1524, 1454, 1235, 1135, 995, 908, 734, 696 cm^{-1}; **HRMS** (ESI) 284.1617 ($M + Na^+$. $C_{16}H_{23}NnaO_2$ requires 284.1621).

Benzyl (2,2-diphenylhex-5-en-1-yl)carbamate (231e)



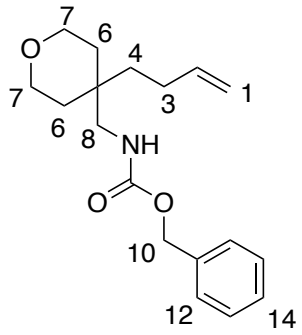
Compound **231e** was synthesised using the **general procedure E** with $LiAlH_4$ (173 mg, 4.5 mmol, 1.5 eq), nitrile **230e** (756 mg, 3.05 mmol, 1 eq) to give the crude product as a colourless oil (908 mg, 3.61 mmol) which was Cbz protected with K_2CO_3 solution (50% w/w aq, 0.5 mL, 4.33 mmol, 1.2 eq) and benzyl chloroformate (0.61 mL, 4.33 mmol, 1.2 eq). Compound **231e** yielded as a pale-yellow oil (825 mg, 2.13 mmol, 70% yield over two steps) after column chromatography (5% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.42 – 7.10 (m, 15H, H-7, H-8, H-9, H-14, H-15, H-16), 5.73 (ddt, *J* = 16.8, 10.1, 6.5 Hz, 1H, H-2), 5.06 (s, 2H, H-12), 4.99 – 4.79 (m, 2H, H-1), 4.30 (t, *J* = 6.1 Hz, 1H, N-H), 3.96 (d, *J* = 6.1 Hz, 2H, H-10), 2.25 – 2.04 (m, 2H, H-4), 1.89 – 1.74 (m, 2H, H-3) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 156.5 (C-11), 145.6 (C-6), 138.7 (C-2), 136.5 (C-13), 128.6 (Ar-CH), 128.4 (Ar-CH), 128.3 (Ar-CH), 128.0 (Ar-CH), 126.5 (Ar-CH), 114.5 (C-1) , 66.8 (C-12), 50.3 (C-5), 47.8 (C-10), 36.2 (C-4), 28.7 (C-3) ppm; **IR** (ATR): ν_{max} 3300, 3030, 2935, 1723, 1640, 1513, 1497, 1455, 1445, 1222, 1074, 1031, 1031, 911, 755, 699, 608 cm^{-1}; **HRMS** (ESI) 386.2121 ($M + H^+$. $C_{26}H_{28}NO_2$ requires 386.2115).

Benzyl ((1-(but-3-en-1-yl)cycloheptyl)methyl)carbamate (231f)



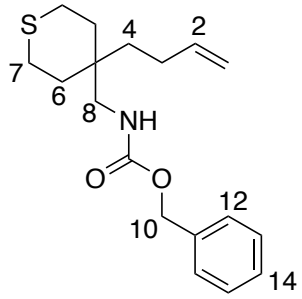
Compound **231f** was synthesised using the **general procedure E** with $LiAlH_4$ (278 mg, 7.32 mmol, 1.5 eq), nitrile **230f** (1.13 g, 6.37 mmol, 1 eq) to give the crude product as a colourless oil (1.16 g, 6.39 mmol). The crude amine (908 mg, 5.008 mmol, 1 eq) was Cbz protected with K_2CO_3 solution (50% w/w aq, 0.83 mL, 6.00 mmol, 1.2 eq) and benzyl chloroformate (0.86 mL, 6.00 mmol, 1.2 eq). Compound **231f** yielded as a colourless oil (1.32 g, 4.18 mmol, 66% yield over two steps) after column chromatography (5% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.44 – 7.27 (m, 5H, H-13, H-14, H-15), 5.79 (ddt, *J* = 16.9, 10.1, 6.5 Hz, 1H, H-2), 5.10 (s, 2H, H-11), 5.00 (dd, *J* = 16.9, 1.8 Hz, 1H, H-1), 4.93 (dd, *J* = 10.1, 1.8 Hz, 1H, H-1'), 4.72 (t, *J* = 6.4 Hz, 1H, N-H), 3.07 (d, *J* = 6.4 Hz, 2H, H-9), 2.07 – 1.88 (m, 2H, H-3), 1.58 – 1.40 (m, 8H, H-7, H-8), 1.41 – 1.32 (m, 4H, H-6), 1.32 – 1.24 (m, 2H, H-4) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 156.8 (C-10), 139.3 (C-2), 136.7 (C-12), 128.7 (Ar-CH), 128.3 (Ar-CH), 128.2 (Ar-CH), 114.3 (C-1), 66.8 (C-11), 48.4 (C-9), 39.5 (C-5), 37.3 (C-4), 36.5 (C-6), 31.0 (C-7), 28.0 (C-3), 22.9 (C-8) ppm; **IR** (ATR): ν_{max} 3342, 2922, 2854, 1707, 1640, 1526, 1460, 1240, 1140, 1002, 908, 735, 697 cm^{-1}; **HRMS** (ESI) 338.2101 ($M + Na^+$. $C_{20}H_{29}NnaO_2$ requires 338.2090).

Benzyl ((4-(but-3-en-1-yl)tetrahydro-2H-pyran-4-yl)methyl)carbamate (231g)



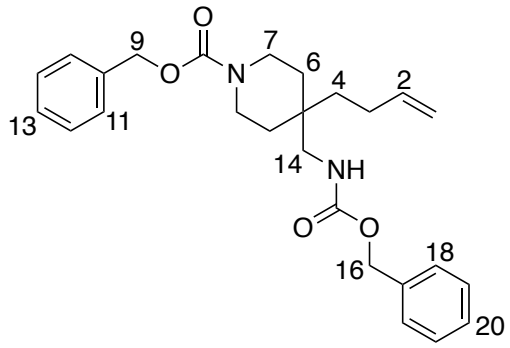
Compound **231g** was synthesised using the **general procedure E** with $LiAlH_4$ (73 mg, 1.93 mmol, 1.5 eq), nitrile **230g** (213 mg, 1.28 mmol, 1 eq) to give the crude product as a colourless oil (334 mg, 1.97 mmol) which was Cbz protected with K_2CO_3 solution (50% w/w aq, 0.32 mL, 2.36 mmol, 1.2 eq) and benzyl chloroformate (0.33 mL, 2.36 mmol, 1.2 eq). Compound **231g** yielded as a colourless oil (283.5 mg, 0.934 mmol, 73% yield over two steps) after column chromatography (20-50% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.45 – 7.28 (m, 5H, H-12, H-13, H-14), 5.79 (ddt, *J* = 17.0, 10.1, 6.4 Hz, 1H, H-2), 5.10 (s, 2H, H-10), 5.03 (dd, *J* = 17.0, 1.8 Hz, 1H, H-1), 4.96 (dd, *J* = 10.1, 1.8 Hz, 1H, H-1'), 4.77 (t, *J* = 6.4 Hz, 1H, N-H), 3.76 – 3.54 (m, 4H, H-7), 3.23 (d, *J* = 6.4 Hz, 2H, H-8), 2.06 – 1.89 (m, 2H, H-3), 1.53 – 1.32 (m, 6H, H-6, H-4) ppm; **^{13}CNMR** (101 MHz, Chloroform-*d*): δ 156.8 (C-9), 138.6 (C-2), 136.5 (C-11), 128.7 (Ar-CH), 128.3 (Ar-CH), 128.3 (Ar-CH), 114.8 (C-1), 67.0 (C-10), 63.5 (C-7), 46.1 (C-8), 34.8 (C-4), 34.6 (C-5), 33.4 (C-6), 27.2 (C-3) ppm; **IR** (ATR): ν_{max} 3329, 2928, 2854, 1705, 1640, 1536, 1453, 1239, 1137, 1104, 1017, 995, 909, 775, 736, 697, 574 cm^{-1}; **HRMS** (ESI) 304.1905 ($M + H^+$. $C_{18}H_{26}NO_3$ requires 304.1907).

Benzyl ((4-(but-3-en-1-yl)tetrahydro-2*H*-thiopyran-4-yl)methyl)carbamate (231h)



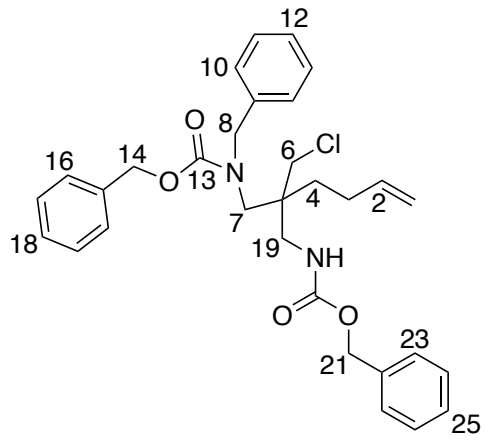
Compound **231h** was synthesised using the **general procedure E** with $LiAlH_4$ (247 mg, 6.24 mmol, 1.5 eq), nitrile **230h** (754 mg, 4.15 mmol, 1 eq) to give the crude product as a pale-yellow oil (874 mg, 4.71 mmol). The crude amine (7034 mg, 3.79 mmol, 1 eq) was Cbz protected with K_2CO_3 solution (50% w/w aq, 0.62 mL, 4.55 mmol, 1.2 eq) and benzyl chloroformate (0.65 mL, 4.55 mmol, 1.2 eq). Compound **231h** yielded as a colourless oil (883.5 mg, 2.76 mmol, 67% yield over two steps) after column chromatography (15% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.44 – 7.29 (m, 5H, H-12, H-13, H-14), 5.78 (ddt, *J* = 17.0, 10.1, 6.5 Hz, 1H, H-2), 5.09 (s, 2H, H-10), 5.02 (dd, *J* = 17.0, 1.8 Hz, 1H, H-1), 4.96 (dd, *J* = 10.1, 1.8 Hz, 1H, H-1'), 4.72 (t, *J* = 6.9 Hz, 1H, N-H), 3.13 (d, *J* = 6.9 Hz, 2H, H-8), 2.71 – 2.50 (m, 4H, H-7), 2.05 – 1.89 (m, 2H, H-3), 1.73 – 1.56 (m, 4H, H-6), 1.42 – 1.30 (m, 2H, H-4) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 156.7 (C-9), 138.6 (C-2), 136.5 (C-11), 128.7 (Ar-CH), 128.5 (Ar-CH), 128.3 (Ar-CH), 114.8 (C-1), 67.0 (C-10), 47.1 (C-8), 35.7 (C-5), 34.2 (C-4, C-6), 26.9 (C-3), 23.2 (C-7) ppm; **IR** (ATR): ν_{max} 3338, 3068, 2925, 1706, 1639, 1528, 1454, 1240, 1144, 999, 912, 774, 736, 697 cm^{-1}; **HRMS** (ESI) 320.1680 ($M + H^+$. $C_{18}H_{26}NO_2S$ requires 320.1679).

Benzyl-4-((((benzyloxy)carbonyl)amino)methyl)-4-(but-3-en-1-yl)piperidine-1-carboxylate (231i)



Compound **231i** was synthesised using the **general procedure E** with $LiAlH_4$ (85 mg, 2.24 mmol, 1.5 eq), nitrile **230i** (381 mg, 1.5 mmol, 1 eq) to give the crude product as a pale-yellow oil (521 mg, 2.26 mmol). The crude amine (447 mg, 1.94 mmol, 1 eq) was Cbz protected with K_2CO_3 solution (50% w/w aq, 0.32 mL, 2.32 mmol, 1.2 eq) and benzyl chloroformate (0.33 mL, 2.32 mmol, 1.2 eq). Compound **231i** yielded as a colourless oil (427 g, 0.98 mmol, 65% yield over two steps) after column chromatography (20-50% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.44 – 7.27 (m, 10H, H-11, H-12, H-13, H-18, H-19, H-20), 5.77 (ddt, *J* = 17.0, 10.5, 6.4 Hz, 1H, H-2), 5.12 (s, 2H, H-9), 5.09 (s, 2H, H-16), 5.02 (dd, *J* = 17.0, 1.8 Hz, 1H, H-1), 4.96 (dd, *J* = 10.5, 1.8 Hz, 1H, H-1'), 4.75 (t, *J* = 6.4 Hz, 1H, N-H), 3.64 – 3.51 (m, 2H, H-7), 3.50 – 3.39 (m, 2H, H-7'), 3.17 (d, *J* = 6.4 Hz, 2H, H-14), 2.08 – 1.89 (m, 2H, H-3), 1.46 – 1.30 (m, 6H, H-4, H-6) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 156.8 (C-15), 155.4 (C-8), 138.5 (C-2), 136.9 (C-10), 136.5 (C-17), 128.7 (Ar-CH), 128.6 (Ar-CH), 128.3 (Ar-CH), 128.3 (Ar-CH), 128.0 (Ar-CH), 127.9 (Ar-CH), 114.9 C-1), 67.1 + 67.0 (C-16 + C-9), 45.9 (C-14), 39.7 (C-7), 35.4 (C-5), 34.3 (C-4), 32.4 (C-6), 27.3 (C-3) ppm; **IR** (ATR): ν_{max} 3335, 2933, 1692, 1538, 1439, 1359, 1244, 1096, 1014, 911, 734, 697 cm^{-1}; **HRMS** (ESI) 459.2261 ($M + Na^+$. $C_{26}H_{32}N_2NaO_4$ requires 459.2254).

Benzyl-benzyl(2-((((benzyloxy)carbonyl)amino)methyl)-2-(chloromethyl)hex-5-en-1-yl)carbamate (247)

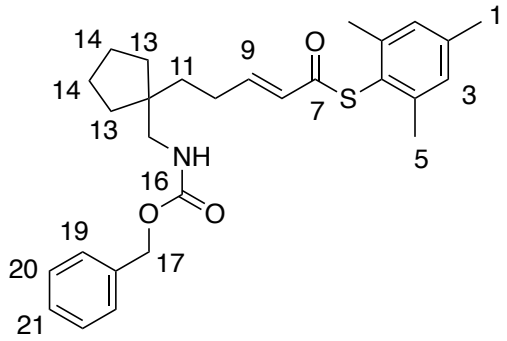


Compound **247** was synthesised using the **general procedure E** with $LiAlH_4$ (67 mg, 1.32 mmol, 1.5 eq), nitrile **229j** (199 mg, 0.88 mmol, 1 eq) to give the crude product as a colourless oil (330 mg, 1.43 mmol) which was Cbz protected with K_2CO_3 solution (50% w/w aq, 0.2 mL, 1.72 mmol, 1.2 eq) and benzyl chloroformate (0.24 mL, 1.72 mmol, 1.2 eq). Compound **247** yielded as a pale-yellow oil (291 mg, 0.543 mmol, 38% yield over two steps) after column chromatography (5% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.40 – 7.30 (m, 11H, H-Ar), 7.20 – 7.10 (m, 4H, H-Ar), 6.60 (t, *J* = 6.8 Hz, 1H, N-H), 5.80 (ddt, *J* = 16.8, 10.4, 6.6 Hz, 2H, H-2), 5.20 – 5.14 (m, 2H, H-14), 5.14 – 5.07 (m, 2H, H-21), 5.10 – 5.00 (m, 1H, H-1), 5.00 (dd, *J* = 10.4, 1.9 Hz, 1H, H-1' *trans*), 4.70 (d, *J* = 16.1 Hz, 1H, H-7), 4.50 (d, *J* = 16.1 Hz, 1H, H-7'), 3.50 (d, *J* = 11.6 Hz, 1H, H-6), 3.40 – 3.30 (m, 2H, H-6, H-8), 3.30 – 3.20 (m, 1H, H-19), 3.20 (d, *J* = 15.1 Hz, 1H, H-8), 3.10 – 2.90 (m, 1H, H-19'), 2.30 – 2.20 (m, 1H, H-3), 2.10 – 2.00 (m, 1H, H-3'), 1.50 – 1.30 (m, 2H, H-4) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 158.5 (C-13), 157.0 (C-20), 138.3 (C-2), 137.4 (C-Ar), 137.0 (C-Ar), 136.0 (C-Ar), 128.7 (Ar-CH), 128.6 (Ar-CH), 128.5 (Ar-CH), 128.3 (Ar-CH), 128.2 (Ar-CH), 128.1 (Ar-CH), 128.0 (Ar-CH), 127.5 (Ar-CH), 127.0 (Ar-CH), 114.8 (C-1), 68.0 (C-14), 66.6 (C-21), 52.5 (C-7), 50.0 (C-8), 47.0 (C-6), 44.8 (C-5), 42.4 (C-19), 30.4 (C-4), 26.7 (C-3) ppm; **IR (ATR)** 2984, 1736, 1447, 1372, 1233, 1043, 917, 938, 786, 634 cm^{-1}; **HRMS** (ESI) m/z (%) 535.2365 (M+ H^+. , 19.2%, $C_{31}H_{36}Cl^{35}N_2O_4$ requires 535.2358).

Substrate scope with mesityl thioester

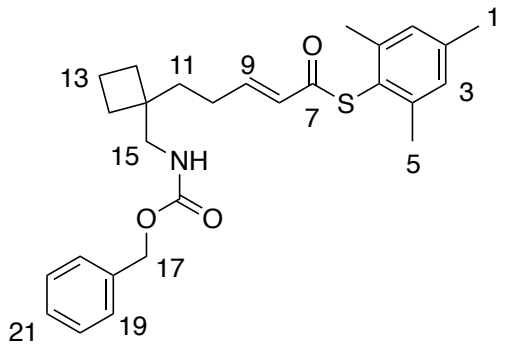
Cyclisation precursors

(*E*)-S-Mesityl-5-(1-((((benzyloxy)carbonyl)amino)methyl)cyclopentyl)pent-2-enethioate (232a)



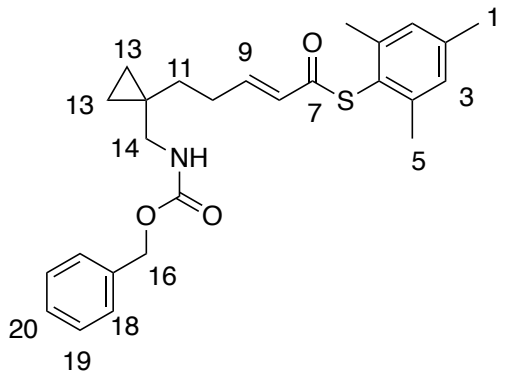
Compound **232a** was synthesised using the **general procedure B** with thioester **223** (210 mg, 1.02 mmol, 3 eq), Hoveyda-Grubbs Catalyst^{TM} 2nd generation (29 mg, 0.034 mmol, 0.1 eq), copper iodide (65 mg, 0.034 mmol, 1 eq) and Cbz-amine **231a** (98 mg, 0.340 mmol, 1 eq), and the reaction stopped after 48 h. Compound **232a** yielded as a pale brown oil (119 mg, 0.254 mmol, 75% yield) after column chromatography (20% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.42 – 7.29 (m, 5H, H-19, H-20, H-21), 6.99 (s, 2H, H-3), 6.98 – 6.92 (m, 1H, H-9), 6.23 (d, *J* = 15.6 Hz, 1H, H-8), 5.12 (s, 2H, H-17), 4.80 (t, *J* = 6.4 Hz, 1H, N-H), 3.14 (d, *J* = 6.4 Hz, 2H, H-15), 2.32 (s, 6H, H-5), 2.30 (s, 3H, H-1), 2.28 – 2.15 (m, 2H, H-10), 1.74 – 1.56 (m, 4H, H-14), 1.55 – 1.44 (m, 2H, H-11), 1.44 – 1.31 (m, 4H, H-13) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ ppm 187.7 (C-7), 156.8 (C-16), 146.2 (C-9), 142.7 (C-6) , 139.9 (C-2), 136.6 (C-18) 129.2 (C-3), 128.6 (Ar-CH), 128.3 (Ar-CH), 128.2 (Ar-CH), 128.0 (C-8), 123.5 (C-4), 66.9 (C-17), 47.3 (C-15), 46.0 (C-12), 35.6 (C-11), 35.5 (C-13), 27.7 (C-10), 24.9 (C-14), 21.7 (C-5), 21.2 (C-1) ppm; **IR** (ATR): ν_{max} 3356, 2948, 2865, 1708, 1683, 1673, 1630, 1454, 1235, 1137, 1010, 850, 805, 697 cm^{-1}; **HRMS** (ESI) 466.2418 (M + H^{+}. $C_{28}H_{36}NO_3S$ requires 466.2410).

(*E*)-S-Mesityl-5-(1-((((benzyloxy)carbonyl)amino)methyl)cyclobutyl)pent-2-enethioate (232b)



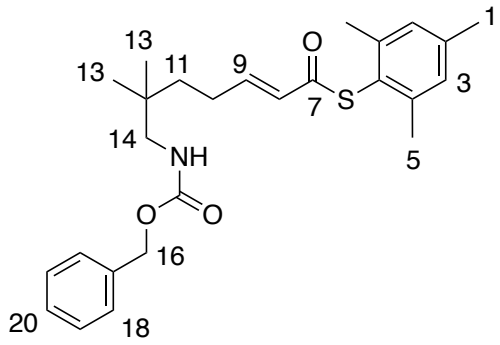
Compound **232b** was synthesised using the **general procedure B** with thioester **223** (142.5 mg, 0.690 mmol, 1.8 eq), Hoveyda-Grubbs Catalyst™ 2nd generation (39 mg, 0.046 mmol, 0.12 eq), copper iodide (44 mg, 0.230 mmol, 0.6 eq) and Cbz-amine **231b** (104 mg, 0.380 mmol, 1 eq), and the reaction stopped after 48 h. Compound **232b** yielded as a light yellow powder (174 mg, 0.362 mmol, 82% yield) after column chromatography (20% Et_2O/hexane).**^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.46 – 7.27 (m, 5H, H-19, H-20, H-21), 7.00 (s, 2H, H-3), 6.98 – 6.90 (m, 1H, H-9), 6.25 (d, *J* = 15.6 Hz, 1H, H-8), 5.12 (s, 1H, H-17), 4.81 (t, *J* = 6.4 Hz, 1H, N-H), 3.29 (d, *J* = 6.4 Hz, 2H, H-15), 2.33 (s, 6H, H-5), 2.31 (s, 3H, H-1), 2.24 – 2.14 (m, 2H, H-10), 1.97 – 1.83 (m, 2H, 1-14), 1.82 – 1.70 (m, 4H, H-13), 1.64 – 1.56 (m, 2H, H-11) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 187.7 (C-7), 156.8 (C-16), 146.1 (C-9), 142.7 (C-6), 139.9 (C-2), 136.5 (C-18), 129.3 (C-3), 129.2 (Ar-CH), 128.6 (Ar-CH), 128.2 (Ar-CH), 128.0 (Ar-CH), 123.5 (C-4), 66.8 (C-17), 46.9 (C-15), 41.8 (C-12), 35.4 (C-11), 29.2 (C-13), 26.9 (C-10), 21.7 (C-5), 21.2 (C-3), 15.0 (C-14) ppm; **IR** (ATR): ν_{max} 3352, 2924, 2854, 1706, 1672, 1630, 1527, 1453, 1375, 1298, 1238, 1132, 1054, 1012, 806, 733 cm^{-1}; **HRMS** (ESI) 452.2261 ($M + H^+$. $C_{27}H_{34}NO_3S$ requires 452.2254); **m.p.** 89 – 91.8 °C.

(*E*)-S-Mesityl-5-(1-((((benzyloxy)carbonyl)amino)methyl)cyclopropyl)pent-2-enethioate (232c)



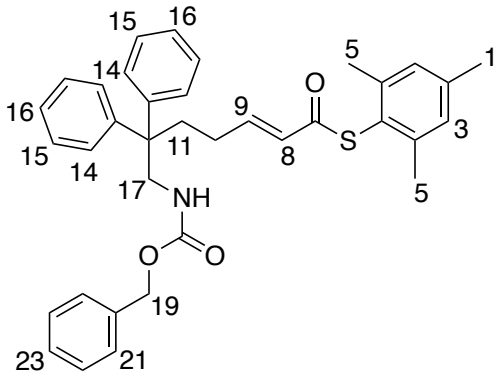
Compound **232c** was synthesised using the **general procedure B** with thioester **223** (239 mg, 1.15 mmol, 3 eq), Hoveyda-Grubbs Catalyst™ 2nd generation (33 mg, 0.038 mmol, 0.1 eq), copper iodide (73.5 mg, 0.386 mmol, 1 eq) and Cbz-amine **231c** (100 mg, 0.386 mmol, 1 eq), and the reaction stopped after 48 h. Compound **232c** yielded as a pale brown oil (100 mg, 0.227 mmol, 59% yield) after column chromatography (20% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.45 – 7.28 (m, 5H, H-18, H-H-19, 20), 7.00 (s, 2H, H-3), 6.98 – 6.92 (m, 1H, H-9), 6.23 (d, *J* = 15.5 Hz, 1H, H-8), 5.13 (s, 2H, H-16), 4.91 (t, *J* = 6.0 Hz, 1H, N-H), 3.12 (d, *J* = 6.0 Hz, 2H, H-14), 2.43 – 2.34 (m, 2H, H-10), 2.33 (s, 6H, H-5), 2.31 (s, 3H, H-1), 1.52 – 1.38 (m, 2H, H-11), 0.49 – 0.29 (m, 4H, H-13) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 187.7 (C-7), 156.6 (C-15), 145.8 (C-9), 142.7 (C-6), 139.8 (C-2), 136.6 (C-17), 129.2 (C-3), 128.6 (Ar-CH), 128.2 (Ar-CH), 128.2 (Ar-CH), 128.1 (C-8), 123.5 (C-4), 66.8 (C-16), 46.7 (C-14), 33.1 (C-11), 29.5 (C-10), 21.6 (C-5), 21.2 (C-1), 20.1 (C-12), 10.8 (C-13) ppm; **IR** (ATR): ν_{max} 3350, 2922, 1700, 1621, 1525, 1454, 1375, 1240, 1131, 991, 805, 698, 623 cm^{-1}; **HRMS** (ESI) 438.2095 (M + H^{+}. $C_{26}H_{32}NO_3S$ requires 438.2097).

(*E*)-S-Mesityl 7-(((benzyloxy)carbonyl)amino)-6,6-dimethylhept-2-enethioate (232d)



Compound **232d** was synthesised using the **general procedure B** with thioester **223** (248 mg, 1.2 mmol, 3 eq), Hoveyda-Grubbs Catalyst™ 2nd generation (34 mg, 0.04 mmol, 0.1 eq) and copper iodide (76 mg, 0.4 mmol, 1 eq), Cbz-amine **231d** (104 mg, 0.4 mmol, 1 eq) and reaction stopped after 48 h. Compound **232d** yielded as a light yellow solid (99 mg, 0.226 mmol, 57% yield) after column chromatography (20-25% Et_2O/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.46 – 7.28 (m, 5H, H-18, H-19, H-20), 7.00 (s, 2H, H-3), 6.98 – 6.92 (m, 1H, H-9), 6.23 (d, *J* = 15.6 Hz, 1H, H-8), 5.12 (s, 2H, H-16), 4.88 (t, *J* = 6.5 Hz, 1H, N-H), 3.06 (d, *J* = 6.5 Hz, 2H, H-14), 2.33 (s, 6H, H-5), 2.31 (s, 3H, H-1), 2.22 (dt, *J* = 16.5, 7.3 Hz, 2H, H-10), 1.47 – 1.31 (m, 2H, H-11), 0.91 (s, 6H, H-13) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 187.7 (C-7), 156.7 (C-15), 146.3 (C-9), 142.7 (C-6), 139.9 (C-2), 136.6 (C-17), 129.2 (C-3), 128.6 (Ar-CH), 128.2 (Ar-CH), 128.1 (Ar-CH), 128.0 (C-8), 123.5 (C-4), 66.8 (C-16), 50.8 (C-14), 37.5 (C-11), 34.5 (C-12), 27.0 (C-10), 24.7 (C-13), 21.6 (C-5), 21.2 (C-1) ppm; **IR** (ATR): ν_{max} 3357, 2958, 1707, 1680, 1602, 1527, 1454, 1234, 1133, 1002, 850, 805, 753, 697, 625 cm^{-1}; **HRMS** (ESI) 440.2262 ($M + H^+$. $C_{26}H_{34}NO_3S$ requires 440.2254); **m.p.** 107 – 109.6 °C.

(*E*)-S-Mesityl 7-(((benzyloxy)carbonyl)amino)-6,6-diphenylhept-2-enethioate (232e)

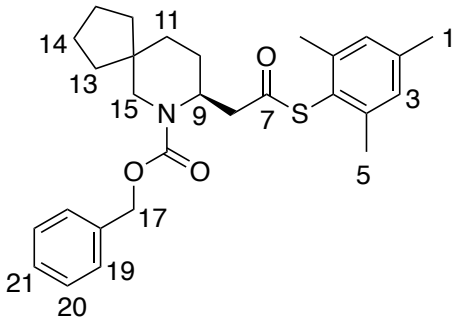


Compound **232e** was synthesised using the **general procedure B** with thioester **223** (129.5 mg, 0.627 mmol, 2.0 eq), Hoveyda-Grubbs Catalyst™ 2nd generation (35 mg, 0.041 mmol, 0.13 eq) and copper iodide (40 mg, 0.209 mmol, 0.6 eq), Cbz-amine **231e** (118 mg, 0.306 mmol, 1 eq). Compound **232e** yielded as a pale-yellow oil (128 mg, 0.227 mmol, 74% yield) after column chromatography (30% Et_2O/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.42 – 7.11 (m, 15H, H-14, H-15, H-16, H-21, H-22, H-23), 6.99 (s, 2H, 3), 6.88 (dt, *J* = 15.5, 6.7 Hz, 1H, H-9), 6.15 (d, *J* = 15.5 Hz, 1H, H-8), 5.09 (s, 2H, H-19), 4.31 (t, *J* = 6.3 Hz, 1H, N-H), 3.99 (d, *J* = 6.3 Hz, 2H, H-17), 2.32 (s, 6H, H-5), 2.30 (s, 3H, H-1), 2.28 – 2.13 (m, 2H, H-11), 2.09 – 1.98 (m, 2H, H-10) ppm; **^{13}CNMR** (101 MHz, Chloroform-*d*): δ 187.7 (C-7), 156.6 (C-18), 145.9 (C-9), 145.3 (C-13), 142.8 (C-6), 139.9 (C-2), 136.4 (C-20), 129.3 (C-3), 128.7 (Ar-CH), 128.6 (Ar-CH), 128.4 (Ar-CH), 128.3 (Ar-CH), 128.1 (C-8), 127.9 (Ar-CH), 126.8 (Ar-CH), 123.5 (C-4), 67.0 (C-19), 50.3 (C-12), 47.6 (C-17), 34.8 (C-11), 27.3 (C-10), 21.7 (C-5), 21.2 (C-1) ppm; **IR** (ATR): ν_{max} 3435, 3027, 2937, 1721, 1681, 1631, 1602, 1514, 1497, 1445. 1454, 1222, 1137, 1029, 1002, 851, 805, 754, 699, 666, 610, 505 cm^{-1}; **HRMS** (ESI) 586.2396 ($M + Na^+$. $C_{36}H_{37}NNaO_3S$ requires 586.2386).

Substrate scope with Mesityl thioester- cyclised compounds

The asymmetric reactions were performed using octane as the solvent at 95 ^{o}C over 24 h

(*S*)-Benzyl-8-(2-(mesitylthio)-2-oxoethyl)-7-azaspiro[4.5]decane-7-carboxylate (233a)

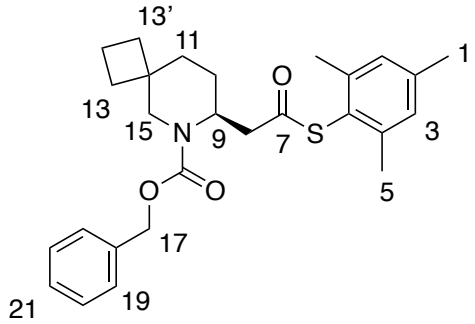


Racemic: Compound **233a** was synthesized using the **general procedure C** using the amino-thioester **232a** (17 mg, 0.036 mmol) and rac-CSA (25 mg, 0.109 mmol, 3 eq). Compound **233a** yielded as a pale-yellow oil (14 mg, 0.031 mmol, 86% yield) after column chromatography (20% EtOAc/pentane).

Asymmetric: Compound **233a** was synthesized using the **general procedure C** using the amino-thioester **232a** (19 mg, 0.041 mmol) and (*R*)-TRIP (6 mg, 0.008 mmol, 0.2 eq). Compound **233a** yielded as a pale-yellow oil (5 mg, 0.01 mmol, 26% yield, 94:6 e.r.) after column chromatography (15% EtOAc/pentane).

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.50 – 7.27 (m, 5H, H-19, H-20, H-21), 6.96 (s, 2H, H-3), 5.27 – 4.99 (br. m, 2H, H-17), 4.98 – 4.75 (br m 1H, H-9), 3.97 – 3.67 (br. m, 1H, H-15), 3.06 – 2.81 (br. m, 2H, H-8), 2.78 – 2.58 (br. m, 1H, H-15'), 2.28 (s, 3H, H-1), 2.26 (s, 6H, H-5), 1.90 – 1.72 (m, 1H, H-10), 1.71 – 1.51 (m, 7H, H-10', H-11, H-13, H-13, H-13', H-14), 1.45 – 1.29 (m, 3H, H-14, H-14', H-14'), 1.24 – 1.11 (m, 1H, H-13') ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 194.4 (C-7), 155.5 (C-16), 142.5 (C-6), 140.1 (C-2), 136.9 (C-18), 129.3 (C-3), 128.5 (Ar-CH), 128.0 (Ar-CH), 127.8 (Ar-CH), 123.5 (C-4), 67.2 (C-17), 48.4 (C-15), 48.3 (C-9), 43.6 (C-8), 42.8 (C-12), 38.7 (C-14), 33.8 (C-13), 31.8 (C-14'), 25.5 (C-10), 25.0 (C-13'), 24.3 (C-11), 21.6 (C-5), 21.2 (C-1) ppm; **IR** (ATR): ν_{max} 2940, 2858, 1696, 1602, 1497, 1420, 1340, 1263, 1205, 1103, 1016, 967, 803, 850, 743, 697, 607, 562 cm^{-1} **HRMS** (ESI) 466.2421 (M + H^{+}. $C_{28}H_{36}NO_3S$ requires 466.2410); **$[\alpha]_D^{20}$** +26.02 (c= 0.204, $CHCl_3$).

(*S*)-Benzyl-7-(2-(mesitylthio)-2-oxoethyl)-6-azaspiro[3.5]nonane-6-carboxylate (233b)

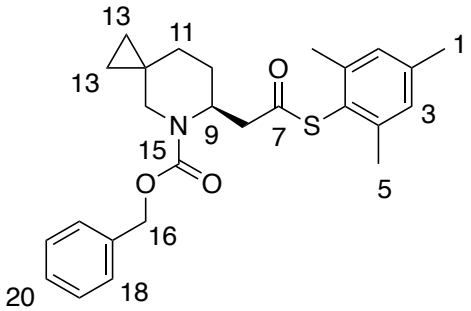


Racemic: Compound **233b** was synthesized using the **general procedure C** using the amino-thioester **232b** (20 mg, 0.044 mmol) and rac CSA (31 mg, 0.132 mmol, 3 eq). Compound **233b** yielded as a pale brown oil (16 mg, 0.035 mmol, 81% yield) after column chromatography (20% Et_2O/pentane).

Asymmetric: Compound **233b** was synthesized using the **general procedure C** using the amino-thioester **232b** (23 mg, 0.051 mmol) and (*R*)-TRIP (8 mg, 0.01 mmol, 0.2 eq). Compound **233b** yielded as a pale brown oil (7 mg, 0.015 mmol, 31% yield, 85:15 e.r.) after column chromatography (20% Et_2O/pentane).

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.47 – 7.22 (m, 5H, H-19, H-20, H-21), 6.96 (s, 2H, H-3), 5.29 – 4.99 (br. m, 2H, H-17), 4.95 – 4.71 (br. m, 1H, H-9), 4.28 – 3.96 (br. m, 1H, H-15), 3.00 – 2.84 (br. m, 2H, H-8), 2.84 – 2.64 (br. m, 1H, H-15'), 2.29 (s, 3H, H-1), 2.26 (s, 6H, H-5), 2.05 – 1.77 (m, 3H, H-13, H-13, H-13'), 1.77 – 1.61 (m, 5H, H-10, H-11, H-13', H-14), 1.58 – 1.47 (m, 2H, H-11', H-14') ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 194.3 (C-7), 155.6 (C-16), 142.5 (C-6), 140.1 (C-2), 136.9 (C-18), 129.3 (C-3), 128.6 (Ar-CH), 128.0 (Ar-CH), 127.8 (Ar-CH), 123.5 (C-4), 67.2 (C-17), 48.6 (C-15), 48.2 (C-9), 42.9 (C-8), 38.4 (C-12), 31.3 (C-14), 30.5 (C-10), 29.6 (C-13), 24.3 (C-11), 21.6 (C-5), 21.2 (C-1), 15.0 (C-13') ppm; **IR** (ATR): ν_{max} 2925, 2853, 1696, 1602, 1498, 1419, 1355, 1335, 1213, 1093, 989, 804, 735, 697, 562 cm^{-1}; **HRMS** (ESI) 452.2262 (M + H$^+$. $C_{27}H_{34}NO_3S$ requires 452.2254); **$[\alpha]_D^{20}$** +17.86 (c= 0.3605, $CHCl_3$).

(*S*)-Benzyl-6-(2-(mesitylthio)-2-oxoethyl)-5-azaspiro[2.5]octane-5-carboxylate (233c)

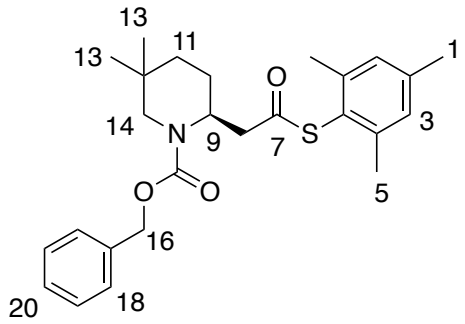


Racemic: Compound **233c** was synthesized using the **general procedure C** using the amino-thioester **232c** (22 mg, 0.049 mmol) and rac CSA (34 mg, 0.148 mmol, 3 eq). Compound **233c** yielded as a pale brown oil (16 mg, 0.036 mmol, 73% yield) after column chromatography (20% EtOAc/pentane).

Asymmetric: Compound **233c** was synthesized using the **general procedure C** using the amino-thioester **232c** (20 mg, 0.046 mmol) and (*R*)-TRIP (7 mg, 0.009 mmol, 0.2 eq). Compound **233c** yielded as a pale brown oil (2 mg, 0.04 mmol, 10% yield, 82:18 e.r.) after column chromatography (15% EtOAc/pentane).

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.46 – 7.27 (m, 5H, H-18, H-19, H-20), 6.96 (s, 2H, H-3), 5.21 – 5.04 (br. m, 2H, H-16), 5.04 – 4.85 (br. m, 1H, H-9), 3.45 – 3.11 (br. m, 2H, H-14), 3.07 – 2.85 (m, 2H, H-8), 2.29 (s, 3H, H-1), 2.27 (s, 6H, H-5), 2.11 (td, *J* = 13.5, 3.7 Hz, 1H, H-11), 1.98 – 1.79 (m, 1H, H-10), 1.76 – 1.63 (m, 1H, H-10'), 0.93 – 0.74 (m, 1H, H-11'), 0.64 – 0.32 (m, 3H, H-13, H-13'), 0.29 – 0.17 (m, 1H, H-13') ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 194.3 (C-7), 155.4 (C-15), 142.5 (C-6), 140.1 (C-2), 136.8 (C-17), 129.3 (C-3), 128.5 (Ar-CH), 128.0 (Ar-CH), 127.9 (Ar-CH), 123.5 (C-4), 67.2 (C-16), 48.6 (C-9), 47.6 (C-14), 43.6 (C-8), 28.4 (C-10), 27.4 (C-11), 21.6 (C-5), 21.2 (C-1), 18.3 (C-12), 12.3, 10.1 (C-13, C-13') ppm; **IR** (ATR): ν_{max} 2923, 2855, 1700, 1418, 1312, 1212, 1011, 850, 697 cm^{-1} **HRMS** (ESI) 438.2097 (M + H^{+}. $C_{26}H_{32}NO_3S$ requires 438.2097); **$[\alpha]_D^{20}$** +13.17 (c= 0.105, $CHCl_3$).

(*S*)-Benzyl-2-(2-(mesitylthio)-2-oxoethyl)-5,5-dimethylpiperidine-1-carboxylate (233d)

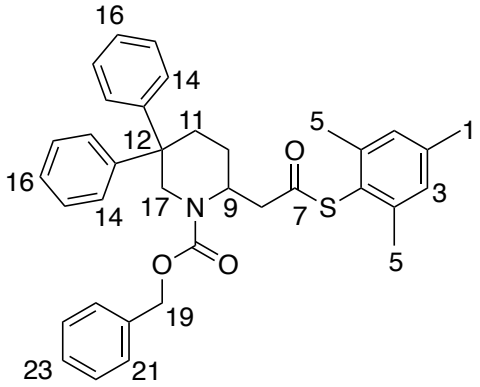


Racemic: Compound **233d** was synthesized using the **general procedure C** using the amino-thioester **232d** (25 mg, 0.057 mmol) and rac CSA (40 mg, 0.173 mmol, 3 eq). Compound **233d** yielded as a colourless oil (11 mg, 0.025 mmol, 45% yield) after column chromatography (10% EtOAc/hexane).

Asymmetric: Compound **233d** was synthesized using the **general procedure C** using the amino-thioester **232d** (27 mg, 0.062 mmol) and (*R*)-TRIP (9 mg, 0.012 mmol, 0.2 eq). Compound **233d** yielded as a colourless oil (5 mg, 0.01 mmol, 17% yield, 96:4 e.r.) after column chromatography (15% EtOAc/pentane).

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.51 – 7.16 (m, 5H, H-18, H-19, H-20), 6.96 (s, 2H, H-3), 5.24 – 4.99 (br. m, 2H, H-16), 4.99 – 4.73 (br. m, 1H, H-9), 3.89 – 3.50 (br. m, 1H, H-14), 2.99 – 2.79 (br. m, 2H, H-8), 2.79 – 2.56 (br. m, 1H, H-14'), 2.28 (s, 3H, H-1), 2.26 (s, 6H, H-5), 1.99 – 1.81 (m, 1H, H-10), 1.54 – 1.45 (m, 2H, H-10', H-11), 1.37 – 1.28 (m, 1H, H-11'), 0.99 – 0.79 (m, 6H, H-13) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 194.3 (C-7), 155.6 (C-15), 142.5 (C-6), 140.1 (C-2), 136.9 (C-17), 129.3 (C-3), 128.5 (Ar-CH), 128.0 (Ar-CH), 127.8 (Ar-CH), 123.5 (C-4) , 67.2 (C-16), 50.3 (C-14), 48.2 (C-9), 43.8 (C-8), 32.5 (C-11), 30.7 (C-12), 29.0 (C-13), 24.1 (C-10), 23.2 (C-13'), 21.6 (C-1), 21.2 (C-5) ppm; **IR** (ATR): ν_{max} 2937, 2862, 1696, 1498, 1454, 1420, 1351, 1335, 1335, 1120, 1097, 1051, 1000, 910, 850, 803, 722, 696, 562 cm^{-1}; **HRMS** (ESI) 440.2256 (M + H^{+}. $C_{26}H_{34}NO_3S$ requires 440.2254); **$[\alpha]_D^{20}$** +18.16 (c= 0.2345, $CHCl_3$).

Benzyl 2-(2-(mesitylthio)-2-oxoethyl)-5,5-diphenylpiperidine-1-carboxylate (233e)



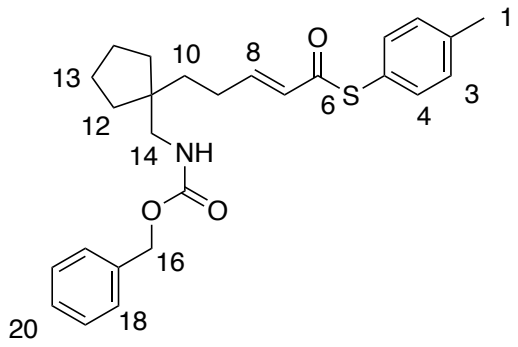
Racemic: To a solution of amino-thioester **232e** (52 mg, 0.092 mmol) in THF (1.02 mL) at 0 ^{o}C was added *t*-BuOK (8 mg, 0.074 mmol, 0.8 eq) and stirred at the same temperature for 2 h. The reaction was quenched with saturated NH_4Cl solution (2 mL) and extracted with Et_2O (10 mL x 3). The combined organics were washed with brine (10 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography (15% EtOAc/pentane) to give **233e** as a colourless oil (35 mg, 0.062 mmol, 68% yield).

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.60 – 7.04 (m, 15H, H-14, H-15, H-16, H-21, H-22, H-23), 6.98 (s, 2H, H-3), 5.52 – 4.58 (m, 4H, H-19, H-17, H-9), 3.25 – 2.72 (m, 3H, H-17', H-8), 2.61 – 2.38 (m, 2H, H-11), 2.29 (br. s, 9H, H-1, H-5), 1.75 – 1.59 (s, 2H, H-10) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 194.3 (C-7), 155.3 (C-18), 147.2 (C-13), 143.8 (C-13'), 142.5 (C-6), 140.2 (C-2), 136.7 (C-20), 129.3 (C-3), 128.6 (Ar-CH), 128.5 (Ar-CH), 128.1 (Ar-CH), 127.7 (Ar-CH), 126.6 (Ar-CH), 126.1 (Ar-CH), 123.5 (C-4), 67.5 (C-19), 48.2 (C-9), 48.1 (C-17), 46.3(C-12), 43.9 (C-8), 29.4 (C-11), 23.6 (C-10), 21.6 (C-5), 21.2 (C-1) ppm; **IR** (ATR): ν_{max} 3064, 3027, 2956, 2923, 2871, 1691, 1600, 1500, 1556, 1419, 1356, 1333, 1271, 1229, 1111, 1022, 963, 909, 851, 730, 698, 574 cm^{-1}; **HRMS** (ESI) 564.2573 (M + H^{+}. $C_{36}H_{38}NO_3S$ requires 564.2567).

Substrate scope with *p*-tolyl thioester

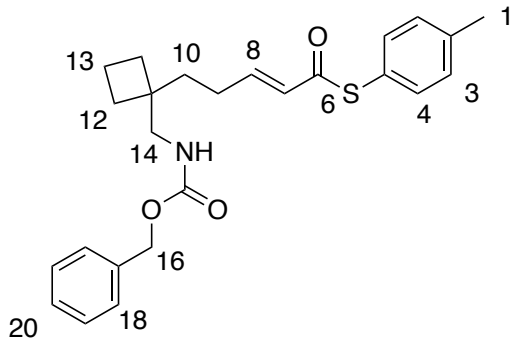
Cyclisation precursors

(*E*)-S-*p*-Tolyl-5-(1-((((benzyloxy)carbonyl)amino)methyl)cyclopentyl)pent-2-enethioate (234a)



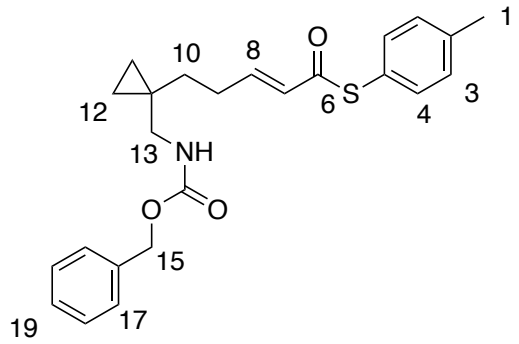
Compound **234a** was synthesised using the **general procedure B** with thioester **190** (195 mg, 1.09 mmol, 3 eq), Hoveyda-Grubbs Catalyst^{TM} 2nd generation (31 mg, 0.036 mmol, 0.1 eq) and copper iodide (69.5 mg, 0.36 mmol, 1 eq), Cbz-amine **231a** (105 mg, 0.36 mmol, 1 eq). Compound **234a** yielded as a pale brown oil (139 mg, 0.317 mmol, 87% yield) after column chromatography (15% EtOAc/hexane) **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.45 – 7.28 (m, 7H, H-18, H-19, H-20, H-4), 7.23 (d, *J* = 8.0 Hz, 2H, H-3), 6.96 (dt, *J* = 15.5, 6.8 Hz, 1H, H-8), 6.18 (d, *J* = 15.5 Hz, 1H, H-7), 5.12 (s, 2H, H-16), 4.82 (t, *J* = 6.4 Hz, 1H, N-H), 3.14 (d, *J* = 6.4 Hz, 2H, H-14), 2.38 (s, 3H, H-1), 2.28 – 2.15 (m, 2H, H-9), 1.73 – 1.51 (m, 4H, H-13), 1.52 – 1.43 (m, 2H, H-10), 1.43 – 1.32 (m, 4H, H-12) ppm; **^{13}CNMR** (101 MHz, Chloroform-*d*): δ 188.5 (C-6), 156.8 (C-15), 146.7 (C-8), 139.6 (C-2), 136.5 (C-17), 134.7 (C-4), 130.0 (C-3), 128.6 (Ar-CH), 128.2 (Ar-CH), 127.7 (C-7), 124.1 (C-5), 66.8 (C-16), 47.3 (C-14), 46.0 (C-11), 35.6 (C-10), 35.5 (C-12), 27.8 (C-9), 24.9 (C-13), 21.4 (C-1) ppm; **IR** (ATR): ν_{max} 3353, 3029, 2946, 2866, 1692, 1630, 1523, 1494, 1453, 1402, 1233, 1135, 1010, 806, 751, 696, 665, 535, 474 cm^{-1}; **HRMS** (ESI) 438.2096 (M + H^{+}. $C_{26}H_{32}NO_3S$ requires 438.2097).

(*E*)-S-*p*-Tolyl-5-(1-((((benzyloxy)carbonyl)amino)methyl)cyclobutyl)pent-2-enethioate (234b)



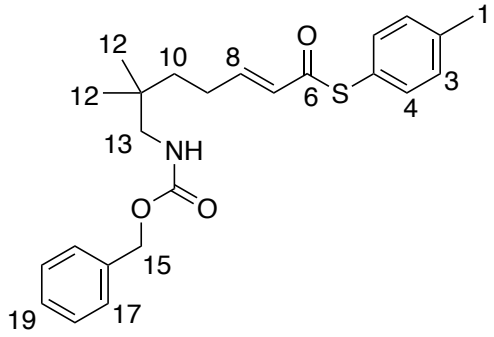
Compound **234b** was synthesised using the **general procedure B** with thioester **190** (202 mg, 1.133 mmol, 3 eq), Hoveyda-Grubbs Catalyst™ 2nd generation (32 mg, 0.037 mmol, 0.1 eq) and copper iodide (72 mg, 0.377 mmol, 1 eq), Cbz-amine **231b** (103 mg, 0.377 mmol, 1 eq). Compound **234b** yielded as a pale brown oil (127 mg, 0.300 mmol, 80% yield) after column chromatography (15% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.46 – 7.29 (m, 7H, H-18, H-19, H-20, H-4), 7.23 (d, *J* = 8.0 Hz, 2H, H-3), 6.98 (dt, *J* = 15.5, 6.8 Hz, 1H, H-8), 6.20 (d, *J* = 15.5 Hz, 1H, H-7), 5.12 (s, 2H, H-16), 4.80 (t, *J* = 6.4 Hz, 1H, N-H), 3.28 (d, *J* = 6.4 Hz, 2H, H-14), 2.38 (s, 3H, H-1), 2.26 – 2.14 (m, 2H, H-9), 1.97 – 1.83 (m, 2H, H-13), 1.81 – 1.68 (m, 4H, H-12), 1.65 – 1.53 (m, 2H, H-10) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 188.5 (C-6), 156.8 (C-15), 146.5 (C-8), 139.6 (C-2), 136.5 (C-17), 134.7 (C-4), 130.0 (C-3), 128.6 (Ar-CH), 128.3 (Ar-CH), 128.2 (Ar-CH), 127.8 (C-7), 124.1 (C-5), 66.8 (C-16), 46.9 (C-14), 41.8 (C-11), 35.4 (C-10), 29.2 (C-12), 27.0 (C-9), 21.4 (C-1), 15.0 (C-13) ppm; **IR** (ATR): ν_{max} 3350, 2927, 1689, 1630, 1526, 1494, 1453, 1238, 1132, 1013, 807, 774, 697, 619, 475 cm^{-1}; **HRMS** (ESI) 424.1958 (M + H^{+}. $C_{25}H_{30}NO_3S$ requires 424.1941).

(*E*)-S-*p*-Tolyl-5-(1-((((benzyloxy)carbonyl)amino)methyl)cyclopropyl)pent-2-enethioate (234c)



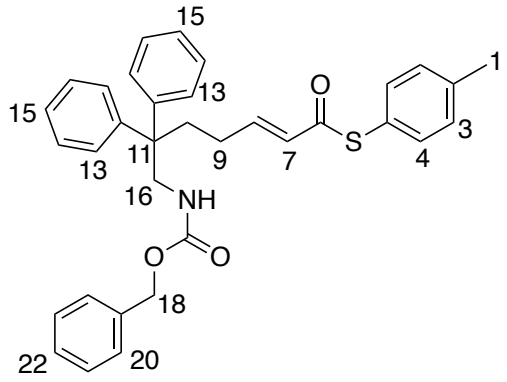
Compound **234c** was synthesised using the **general procedure B** with thioester **190** (214 mg, 1.210 mmol, 3 eq), Hoveyda-Grubbs Catalyst™ 2nd generation (34 mg, 0.040 mmol, 0.1 eq) and copper iodide (76 mg, 0.400 mmol, 1 eq), Cbz-amine **231c** (104 mg, 0.400, 1 eq). Compound **234c** yielded as a pale brown oil (150 mg, 0.365 mmol, 91% yield) after column chromatography (15% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.44 – 7.29 (m, 7H, H-17, H-18, H-19, H-4), 7.23 (d, *J* = 8.1 Hz, 2H, H-3), 6.97 (dt, *J* = 15.5, 6.9 Hz, 1H, H-8), 6.17 (d, *J* = 15.5 Hz, 1H, H-7), 5.13 (s, 2H, H-15), 4.94 (t, *J* = 5.6 Hz, 1H, N-H), 3.11 (d, *J* = 5.6 Hz, 2H, H-13), 2.38 (s, 3H, H-1), 2.37 – 2.28 (m, 2H, H-9), 1.52 – 1.37 (m, 2H, H-10), 0.48 – 0.29 (m, 4H, H-12) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 188.6 (C-6), 156.5 (C-14), 146.2 (C-8), 139.7 (C-2), 136.6 (C-16), 134.7 (C-4), 130.1 (C-3), 128.7 (Ar-CH), 128.3 (Ar-CH), 128.3 (Ar-CH), 127.9 (C-7), 124.1 (C-5), 66.9 (C-15), 46.8 (C-13), 33.2 (C-10), 29.6 (C-9), 21.4 (C-1), 20.1 (C-11), 10.8 (C-12) ppm; **IR** (ATR): ν_{max} 3346, 2922, 1689, 1630, 1519, 1494, 1453, 1234, 1042, 1016, 988, 806, 751, 697, 515, 475 cm^{-1}; **HRMS** (ESI) 410.1791 (M + H^{+}. $C_{24}H_{28}NO_3S$ requires 410.1784).

(*E*)-S-*p*-Tolyl 7-(((benzyloxy)carbonyl)amino)-6,6-dimethylhept-2-enethioate (234d)



Compound **234d** was synthesised using the **general procedure B** with thioester **190** (214 mg, 1.210 mmol, 3 eq), Grubbs Catalyst™ 2nd generation (29.5 mg, 0.034 mmol, 0.1 eq) and copper iodide (66 mg, 0.34 mmol, 1 eq), Cbz-amine **231d** (91 mg, 0.348 mmol, 1 eq). Compound **234d** yielded as a pale-yellow oil (100 mg, 0.242 mmol, 70% yield) after column chromatography (10-12% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.44 – 7.27 (m, 7H, H-17, H-18, H-19, H-4), 7.23 (d, *J* = 7.9 Hz, 2H, H-3), 6.96 (dt, *J* = 15.5, 6.8 Hz, 1H, H-8), 6.18 (d, *J* = 15.5 Hz, 1H, H-7), 5.11 (s, 2H, H-15), 4.78 (t, *J* = 6.6 Hz, 1H, N-H), 3.05 (d, *J* = 6.6 Hz, 2H, H-13), 2.38 (s, 3H, H-1), 2.29 – 2.11 (m, 2H, H-9), 1.43 – 1.30 (m, 2H, H-10), 0.90 (s, 6H, H-12) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 188.6 (C-6), 156.8 (C-14), 146.7 (C-8), 139.7 (C-2), 136.6 (C-16), 134.7 (C-4), 130.1 (C-3), 128.7 (Ar-CH), 128.3 (Ar-CH), 127.8 (C-7), 124.1 (C-5), 66.9 (C-15), 50.8 (C-13), 37.5 (C-10), 34.6 (C-11), 27.1 (C-9), 24.8 (C-12), 21.4 (C-1) ppm; **IR** (ATR): ν_{max} 3346, 2943, 2864, 1694, 1630, 1523, 1494, 1454, 1233, 1133, 1003, 806, 752, 697, 620, 474 cm^{-1}; **HRMS** (ESI) 412.1933 (M + H^{+}. $C_{24}H_{30}NO_3S$ requires 412.1941).

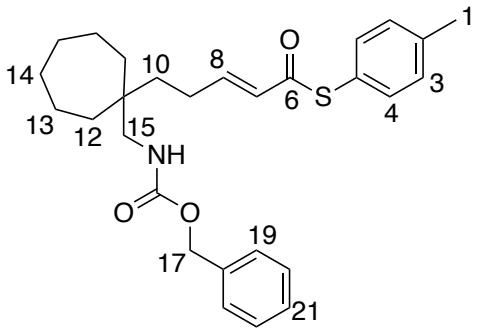
(*E*)-S-*p*-Tolyl 7-(((benzyloxy)carbonyl)amino)-6,6-diphenylhept-2-enethioate (234e)



Compound **234e** was synthesised using the **general procedure B** with thioester **190** (144 mg, 0.805 mmol, 3 eq), Hoveyda-Grubbs Catalyst™ 2nd generation (23 mg, 0.026 mmol,

0.1 eq) and copper iodide (51 mg, 0.268 mmol, 1 eq), Cbz-amine **231e** (103.5 mg, 0.268 mmol, 1 eq). Compound **234e** yielded as a pale-yellow oil (117 mg, 0.219 mmol, 82% yield) after column chromatography (15% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.40 – 7.08 (m, 19H, H-3, H-4, H-13, H-14, H-15, H-20, H-21, H-22), 6.86 (dt, *J* = 15.6, 6.7 Hz, 1H, H-8), 6.10 (d, *J* = 15.6 Hz, 1H, H-7), 5.08 (s, 2H, H-18), 4.29 (t, *J* = 6.2 Hz, 1H, N-H), 3.98 (d, *J* = 6.2 Hz, 2H, H-16), 2.38 (s, 3H, H-1), 2.27 – 2.10 (m, 2H, H-10), 2.07 – 1.94 (m, 2H, H-9) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 188.6 (C-6), 156.6 (C-17), 146.3 (C-8), 145.3 (C-12), 139.7 (C-2), 136.4 (C-19), 134.7 (C-4), 130.1 (C-3), 128.7 (Ar-CH), 128.6 (Ar-CH), 128.4 (Ar-CH), 127.9 (C-7, Ar-CH), 126.8 (Ar-CH), 124.2 (C-5), 67.0 (C-18), 50.3 (C-11), 47.6 (C-16), 34.9 (C-10), 27.5 (C-9), 21.4 (C-1) ppm; **IR** (ATR): ν_{max} 3464, 3064, 3030, 2940, 1720, 1682, 1631, 1514, 1445, 1495, 1223, 996, 808, 755, 699 cm^{-1}; **HRMS** (EsI) 558.2083 (M + Na^{+}. $C_{34}H_{33}NNaO_3S$ requires 558.2073).

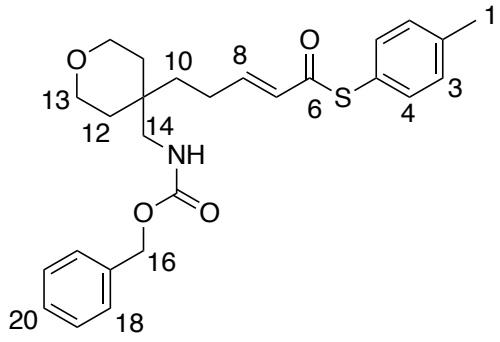
(*E*)-*S*-*p*-Tolyl-5-(1-((((benzyloxy)carbonyl)amino)methyl)cycloheptyl)pent-2-enethioate (234f)



Compound **234f** was synthesised using the **general procedure B** with thioester **190** (182 mg, 1.01 mmol, 3 eq), Hoveyda-Grubbs Catalyst^{TM} 2nd generation (28 mg, 0.033 mmol, 0.1 eq) and copper iodide (64.5 mg, 0.33 mmol, 1 eq), Cbz-amine **231f** (107 mg, 0.33 mmol, 1 eq). Compound **234f** yielded as a light brown oil (101 mg, 0.216 mmol, 64% yield) after column chromatography (20% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.41 – 7.27 (m, 7H, H-19, H-20, H-21, H-4), 7.22 (d, *J* = 8.0 Hz, 2H, H-3), 6.96 (dt, *J* = 15.6, 6.8 Hz, 1H, H-8), 6.18 (d, *J* = 15.6 Hz, 1H, H-7), 5.11 (s, 2H, H-17), 4.72 (d, *J* = 6.4 Hz, 1H, N-H), 3.05 (d, *J* = 6.4 Hz, 2H, H-15), 2.38 (s, 3H, H-1), 2.26 – 2.11 (m, 2H, H-9), 1.57 – 1.40 (m, 8H, H-13, H-14), 1.40 – 1.27 (m, 6H, H-10, H-12) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 188.6 (C-6), 156.8 (C-16), 146.9 (C-8), 139.7 (C-2), 136.6 (C-18), 134.7 (C-4), 130.1 (C-3), 128.7 (Ar-

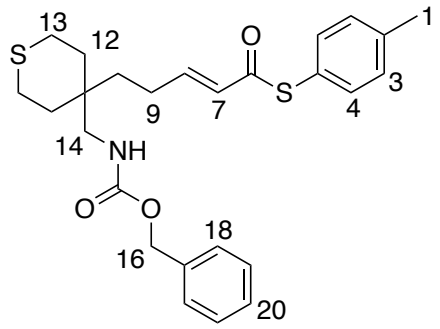
CH), 128.3 (Ar-CH), 127.8 (C-7), 124.2 (C-5), 66.9 (C-17), 48.2 (C-15), 39.6 (C-11), 36.4 (C-12), 36.0 (C-10), 30.9 (C-13), 26.7 (C-9), 22.8 (C-14), 21.4 (C-1) ppm; **IR** (ATR): ν_{max} 3356, 3032, 2919, 2853, 1694, 1630, 1524, 1494, 1458, 1235, 1136, 1014, 806, 697, 615 cm^{-1}; **HRMS** (ESI) 488.2238 (M + Na^+. $C_{28}H_{35}NNaO_3S$ requires 488.2230).

(*E*)-S-*p*-Tolyl-5-(4-((((benzyloxy)carbonyl)amino)methyl)tetrahydro-2H-pyran-4-yl)pent-2-enethioate (234g)



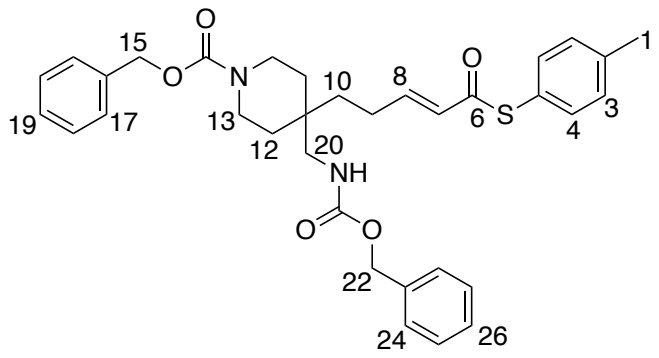
Compound **234g** was synthesised using the **general procedure B** with thioester **190** (156 mg, 0.875 mmol, 3 eq), Hoveyda-Grubbs Catalyst™ 2nd generation (25 mg, 0.029 mmol, 0.1 eq), copper iodide (55 mg, 0.29 mmol, 1 eq), Cbz-amine **231g** (88.5 mg, 0.29 mmol, 1 eq). Compound **234g** yielded as a colourless oil (104.5 mg, 0.230 mmol, 79% yield) after column chromatography (25-40% EtOAc/hexane) **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.43 – 7.29 (m, 7H, H-18, H-19, H-20, H-4), 7.23 (d, *J* = 8.2 Hz, 2H, H-3), 6.94 (dt, *J* = 15.5, 6.8 Hz, 1H, H-8), 6.19 (d, *J* = 15.5 Hz, 1H, H-7), 5.11 (s, 2H, H-16), 4.80 (t, *J* = 6.8 Hz, 1H, N-H), 3.81 – 3.44 (m, 4H, H-13), 3.23 (d, *J* = 6.8 Hz, 2H, H-14), 2.38 (s, 3H, H-1), 2.25 – 2.14 (m, 2H, H-9), 1.54 – 1.47 (m, 2H, H-10), 1.47 – 1.31 (m, 4H, H-12) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 188.5 (C-6), 156.8 (C-15), 146.0 (C-8), 139.8 (C-2), 136.4 (C-17), 134.7 (C-4), 130.1 (C-3), 128.7 (Ar-CH), 128.4 (Ar-CH), 128.3 (Ar-CH), 128.1 (C-7), 124.0 (C-5), 67.1 (C-16), 63.4 (C-13), 46.2 (C-14), 34.7 (C-11), 33.5 (C-10), 33.3 (C-12), 25.9 (C-9), 21.4 (C-1) ppm; **IR** (ATR): ν_{max} 3342, 2932, 1700, 1630, 1536, 1494, 1453, 1241, 1139, 1105, 1017, 808, 737, 618, 475 cm^{-1}; **HRMS** (ESI) 454.2053 (M + H^+. $C_{26}H_{32}NO_4S$ requires 454.2047).

(*E*)-*S*-*p*-Tolyl-5-(4-((((benzyloxy)carbonyl)amino)methyl)tetrahydro-2*H*-thiopyran-4-yl)pent-2-enethioate (234h)



Compound **234h** was synthesised using the **general procedure B** with thioester **190** (180 mg, 1.01 mmol, 3 eq), Hoveyda-Grubbs Catalyst™ 2nd generation (29 mg, 0.033 mmol, 0.1 eq) and copper iodide (64 mg, 0.33 mmol, 1.1 eq), Cbz-amine **231h** (108 mg, 0.33 mmol, 1 eq). Compound **234h** yielded as a pale-yellow oil (68 mg, 0.144 mmol, 43% yield (50% brsm)) after column chromatography (15% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.42 – 7.28 (m, 7H, H-18, H-19, H-20, H-4), 7.23 (d, *J* = 7.7 Hz, 2H, H-3), 6.93 (dt, *J* = 15.5, 6.8 Hz, 1H, H-8), 6.20 (d, *J* = 15.5 Hz, 1H, H-7), 5.10 (s, 2H, H-16), 4.74 (t, *J* = 6.7 Hz, 1H, N-H), 3.15 (d, *J* = 6.7 Hz, 2H, H-14), 2.72 – 2.50 (m, 4H, H-13), 2.38 (s, 3H, H-1), 2.27 – 2.11 (m, 2H, H-9), 1.74 – 1.62 (m, 4H, H-12), 1.48 – 1.39 (m, 2H, H-10) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 188.5 (C-6), 156.8 (C-15), 146.0 (C-8), 139.8 (C-2), 136.4 (C-17), 134.7 (C-4), 130.1 (C-3), 128.7 (Ar-CH), 128.4 (Ar-CH), 128.3 (Ar-CH), 128.1 (C-7), 124.0 (C-5), 67.1 (C-16), 47.0 (C-14), 35.8 (C-11), 34.1 (C-12), 33.0 (C-10), 25.6 (C-9), 23.2 (C-13), 21.4 (C-1) ppm; **IR** (ATR): ν_{max} 3356, 2924, 1701, 1630, 1529, 1492, 1453, 1240, 1146, 1016, 985, 808, 735, 698 cm^{-1}; **HRMS** (ESI) 492.1649 (M + Na^{+}. $C_{26}H_{31}NNaO_3S_2$ requires 492.1638).

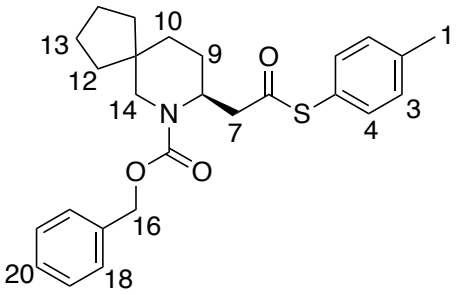
(*E*)-Benzyl-4-((((benzyloxy)carbonyl)amino)methyl)-4-(5-oxo-5-(*p*-tolylthio)pent-3-en-1-yl)piperidine-1-carboxylate (234i)



Compound **234i** was synthesised using the **general procedure B** with thioester **190** (155 mg, 0.87 mmol, 3.3 eq), Hoveyda-Grubbs Catalyst^{TM} 2nd generation (25 mg, 0.029 mmol, 0.1 eq) and copper iodide (55 mg, 0.29 mmol, 1.1 eq), Cbz-amine **231i** (114 mg, 0.26 mmol, 1 eq). Compound **234i** yielded as a brown oil (70.45 mg, 0.12 mmol, 46% yield (58% brsm)) after column chromatography (20-40% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.40 – 7.29 (m, 12H, H-17, H-18, H-19, H-24, H-25, H-26, H-4), 7.22 (d, *J* = 8.0 Hz, 2H, H-3), 6.93 (dt, *J* = 15.5, 6.7 Hz, 1H, H-8), 6.19 (d, *J* = 15.5 Hz, 1H, H-7), 5.13 (s, 2H, H-15), 5.11 (s, 2H, H-22), 4.94 – 4.85 (m, 1H, N-H), 3.64 – 3.50 (m, 2H, H-13), 3.50 – 3.37 (m, 2H, H-13'), 3.28 – 3.06 (br. m, 2H, H-20), 2.38 (s, 3H, H-1), 2.26 – 2.11 (m, 2H, H-9), 1.50 – 1.40 (m, 2H, H-10), 1.40 – 1.30 (br. m, 4H, H-12) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 188.5 (C-6), 156.8 (C-21), 155.3 (C-14), 145.8 (C-8), 139.7 (C-2), 136.8 (C-23), 136.4 (C-16), 134.6 (C-4), 130.1 (C-3), 128.6 (Ar-CH), 128.5 (Ar-CH), 128.3 (Ar-CH), 128.3 (Ar-CH), 128.1 (Ar-CH), 128.0 (Ar-CH), 127.9 (C-7), 124.0 (C-5), 67.1 + 67.0 (C-15 + C-22), 45.9 (C-20), 39.5 (C-13), 35.5 (C-11), 33.0 (C-10), 32.3 (C-12), 25.9 (C-9), 21.4 (C-1) ppm; **IR** (ATR): ν_{max} 3339, 2931, 1684, 1531, 1537, 1495, 1439, 1359, 1277, 1241, 1094, 1017, 753, 697, 808, 607 cm^{-1}; **HRMS** (ESI) 609.2402 (M + Na^{+}. $C_{34}H_{38}N_2NaO_5S$ requires 609.2394).

Substrate scope with Mesityl thioester- cyclised compounds

(*S*)-Benzyl 8-(2-oxo-2-(*p*-tolylthio)ethyl)-7-azaspiro[4.5]decane-7-carboxylate (235a)

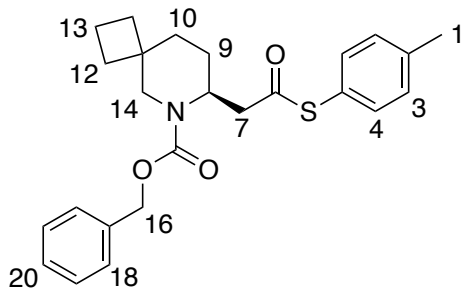


Racemic: Compound **235a** was synthesized using the **general procedure C** using the amino-thioester **234a** (21 mg, 0.047 mmol, 1 eq) and rac-CSA (33 mg, 0.143 mmol, 3 eq). Compound **235a** yielded as a light brown oil (19.5 mg, 0.044 mmol, 93% yield) after column chromatography (15% EtOAc/pentane).

Asymmetric: Compound **235a** was synthesized using the **general procedure C** using the amino-thioester **234a** (18.5 mg, 0.042 mmol, 1 eq) and (*R*)-Anth (6 mg, 0.008 mmol, 0.2 eq). Compound **235a** yielded as a light-brown oil (15 mg, 0.033 mmol, 80% yield, 96:4 e.r.) after column chromatography (15% EtOAc/pentane).

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.40 – 7.30 (m, 5H, H-18, H-19, H-20), 7.30 – 7.20 (br. m, 2H, H-4), 7.20 (d, *J* = 7.8 Hz, 2H, H-3), 5.27 – 5.01 (br. m, 2H, H-16), 4.98 – 4.68 (br. m, 1H, H-8), 4.02 – 3.55 (br. m, 1H, H-14), 2.89 (d, *J* = 7.7 Hz, 2H, H-7), 2.78 – 2.56 (br. m, 1H, H-14'), 2.36 (s, 3H, H-1), 1.91 – 1.72 (m, 1H, H-9), 1.72 – 1.46 (m, 7H, H-9', H-10, H-12, H-12', H-13), 1.48 – 1.28 (br. m, 3H, H-13, H-13'), 1.28 – 1.08 (br. m, 1H, H-12') ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 195.4 (C-6), 155.7 (C-15), 139.8 (C-2), 136.9 (C-17), 134.4 (C-4), 130.1 (C-3), 128.5 (Ar-CH), 128.0 (Ar-CH), 127.8 (Ar-CH), 124.1 (C-5), 67.2 (C-16), 48.4 (C-14), 48.2 (C-8), 43.5 (C-7), 42.7 (C-11), 38.7 (C-13), 33.8 (C-12), 31.8 (C-13'), 25.7 (C-9), 25.0 (C-12'), 24.3 (C-10), 21.4 (C-1) ppm; **IR** (ATR): ν_{max} 2924, 2855, 1695, 1420, 1340, 1265, 1150, 1106, 1013, 807, 737, 696, 606, 474 cm^{-1}; **HRMS** (ESI) 438.2101 (M + H^{+}. $C_{26}H_{32}NO_3S$ requires 438.2097); **$[\alpha]_D^{20}$** +47.5 (c= 0.7285, $CHCl_3$).

(*S*)-Benzyl 7-(2-oxo-2-(p-tolylthio)ethyl)-6-azaspiro[3.5]nonane-6-carboxylate (235b)

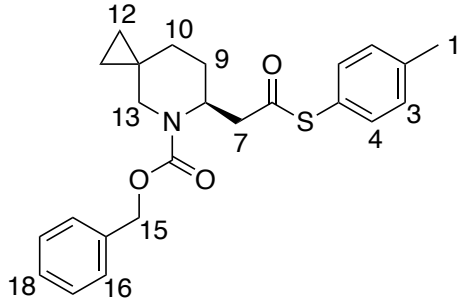


Racemic: Compound **235b** was synthesized using the **general procedure C** using the amino-thioester **234b** (21 mg, 0.049 mmol, 1 eq) and rac-CSA (35 mg, 0.149 mmol, 3 eq). Compound **235b** yielded as a light-brown oil (18 mg, 0.042 mmol, 84% yield) after column chromatography (15% EtOAc/pentane).

Asymmetric: Compound **235b** was synthesized using the **general procedure C** using the amino-thioester **234b** (20 mg, 0.047 mmol, 1 eq), (*R*)-Anth (6.5 mg, 0.009 mmol, 0.2 eq). Compound **235b** yielded as a light-brown oil (12.5 mg, 0.029 mmol, 63% yield, 82:18 e.r.) after column chromatography (15% EtOAc/pentane).

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.42 – 7.27 (m, 5H, H-18, H-19, H-20), 7.26 – 7.21 (m, 2H, H-4), 7.19 (d, *J* = 8.0 Hz, 2H, H-3), 5.23 – 4.99 (br. m, 2H, H-16), 4.92 – 4.62 (br. m, 1H, H-8), 4.25 – 3.95 (br. m, 1H, H-14), 2.84 (d, *J* = 7.7 Hz, 2H, H-7), 2.81 – 2.62 (br. m, 1H, H-14'), 2.37 (s, 3H, H-1), 2.09 – 1.77 (m, 3H, H-12, H-12'), 1.77 – 1.58 (m, 5H, H-9, H-10, H-12', H-13), 1.58 – 1.41 (m, 2H, H-10', H-13') ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 195.3 (C-6), 155.7 (C-15), 139.8 (C-2), 136.8 (C-17), 134.4 (C-4), 130.1 (C-3), 128.5 (Ar-CH), 128.0 (Ar-CH), 127.8 (Ar-CH), 124.1 (C-5), 67.3 (C-16), 48.6 (C-14), 48.1 (C-8), 43.3 (C-7), 38.3 (C-11), 31.3 (C-13), 30.5 (C-9), 29.7 (C-12), 24.5 (C-10), 21.4 (C-1), 15.0 (C-12') ppm; **IR** (ATR): ν_{max} 2922, 2850, 1694, 1494, 1418, 1334, 1287, 1230, 1195, 1096, 1056, 1027, 989, 918, 807, 746, 697 cm^{-1}; **HRMS** (ESI) 424.1946 (M + H^{+}. $C_{25}H_{30}NO_3S$ requires 424.1941); **$[\alpha]_D^{20}$** +31.5 (c= 0.59, $CHCl_3$).

(*S*)-Benzyl 6-(2-oxo-2-(p-tolylthio)ethyl)-5-azaspiro[2.5]octane-5-carboxylate (235c)

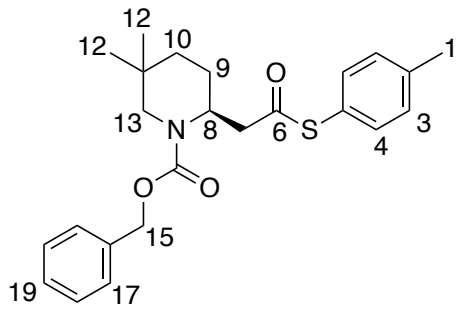


Racemic: Compound **235c** was synthesized using the **general procedure C** using the amino-thioester **234c** (20 mg, 0.047 mmol, 1 eq) and rac-CSA (33 mg, 0.143 mmol, 3 eq). Compound **235c** yielded as a light-brown oil (16 mg, 0.038 mmol, 80% yield) after column chromatography (15% EtOAc/pentane).

Asymmetric: Compound **235c** was synthesized using the **general procedure C** using the amino-thioester **234c** (17.5 mg, 0.042 mmol, 1 eq), (*R*)-Anth (6 mg, 0.008 mmol, 0.2 eq). Compound **235c** yielded as a light-brown oil (15 mg, 0.037 mmol, 87% yield, 89:11 e.r.) after column chromatography (15% EtOAc/pentane).

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.40 – 7.27 (m, 5H, H-16, H-17, H-18), 7.26 – 7.21 (br. m, 2H, H-4), 7.19 (d, *J* = 8.2 Hz, 2H, H-3), 5.20 – 5.03 (m, 2H, H-15), 5.02 – 4.81 (br. m, 1H, H-8), 3.48 – 3.07 (br. m, 2H, H-13), 3.03 – 2.82 (m, 2H, H-7), 2.37 (s, 3H, H-1), 2.10 (ddd, *J* = 13.6, 13.6, 3.7 Hz, 1H, H-10), 1.97 – 1.82 (m, 1H, H-9), 1.79 – 1.61 (m, 1H, H-9'), 0.90 (ddd, *J* = 13.4, 3.7, 3.7 Hz, 1H, H-10'), 0.66 – 0.28 (m, 3H, H-12, H-12'), 0.28 – 0.14 (m, 1H, H-12') ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 195.4 (C-6), 155.4 (C-14), 139.8 (C-2), 136.8 (C-16), 134.4 (C-4), 130.1 (C-3), 128.5 (Ar-CH), 128.0 (Ar-CH), 127.9 (Ar-CH), 124.1 (C-5), 67.3 (C-15), 48.6 (C-8), 47.6 (C-13), 43.7 (C-7), 28.3 (C-10), 27.6 (C-9), 21.4 (C-1), 18.2 (C-11), 12.4 (C-12), 10.19 (C-12') ppm; **IR** (ATR): ν_{max} 2928, 2856, 1697, 1494, 1418, 1342, 1303, 1211, 1145, 1110, 1011, 975, 743, 697, 605, 473 cm^{-1}; **HRMS** (ESI) 410.1794 (M + H^{+}. $C_{24}H_{28}NO_3S$ requires 410.1784); **$[\alpha]_D^{20}$** +24.3 (c= 0.715, $CHCl_3$).

(*S*)-Benzyl 5,5-dimethyl-2-(2-oxo-2-(p-tolylthio)ethyl)piperidine-1-carboxylate (235d)

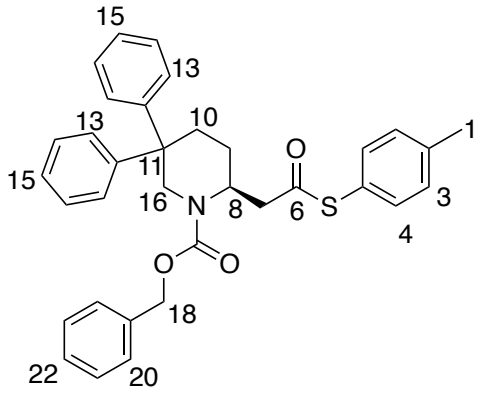


Racemic: Compound **235d** was synthesized using the **general procedure C** using the amino-thioester **234d** (23 mg, 0.055 mmol, 1 eq) and rac-CSA (39 mg, 0.166 mmol, 3 eq). Compound **235d** yielded as a pale-yellow oil (11.5 mg, 0.028 mmol, 51% yield) after column chromatography (10% EtOAc/hexane).

Asymmetric: Compound **235d** was synthesized using the **general procedure C** using the amino-thioester **234d** (25 mg, 0.058 mmol, 1 eq), (*R*)-Anth (8 mg, 0.012 mmol, 0.2 eq). Compound **235d** yielded as a pale-yellow oil (7.14 mg, 0.017 mmol, 29% yield (58% brsm), 95:5 e.r.) after column chromatography (15% EtOAc /pentane).

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.45 – 7.27 (m, 5H, H-17, H-18, H-19), 7.30 – 7.20 (br. m, 2H, H-4), 7.20 (d, *J* = 8.1 Hz, 2H, H-3), 5.25 – 5.00 (br. m, 2H, H-15), 5.00 – 4.73 (br. m, 1H, H-8), 3.89 – 3.50 (br. m, 1H, H-13), 2.86 (d, *J* = 7.9 Hz, 2H, H-7), 2.77 – 2.55 (br. m, 1H, H-13'), 2.37 (s, 3H, H-1), 2.01 – 1.80 (m, 1H, H-9), 1.55 – 1.37 (m, 2H, H-9', H-10), 1.36 – 1.26 (m, 1H, H-10'), 0.92 (d, *J* = 11.7 Hz, 6H, H-12) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 195.4 (C-6), 155.7 (C-14), 139.8 (C-2), 136.9 (C-16), 134.4 (C-4), 130.1 (C-3), 128.5 (Ar-CH), 128.0 (Ar-CH), 127.8 (Ar-CH), 124.1 (C-5), 67.2 (C-15), 50.3 (C-13), 48.2 (C-8), 43.5 (C-7), 32.5 (C-10), 30.6 (C-11), 29.0 (C-12), 24.4 (C-9), 23.2 (C-12'), 21.4 (C-1) ppm; **IR** (ATR): ν_{max} 2922, 1696, 1494, 1454, 1420, 1336, 1285, 1205, 1180, 1098, 1052, 999, 806, 752, 696, 606, 473 cm^{-1}; **HRMS** (ESI) 412.1947 (M + H^{+}. $C_{24}H_{30}NO_3S$ requires 412.1941); **$[\alpha]_D^{20}$** +34.6 (c= 0.506, $CHCl_3$).

Benzyl 2-(2-oxo-2-(*p*-tolylthio)ethyl)-5,5-diphenylpiperidine-1-carboxylate (235e)

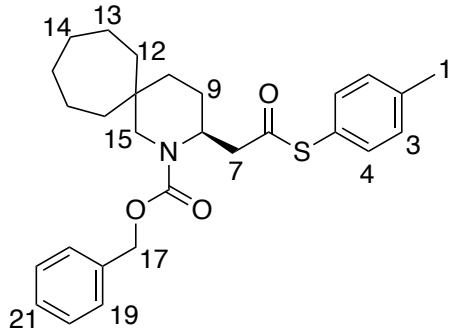


Racemic: Compound **235e** was synthesised using the **general procedure C** using the amino-thioester **234e** (41 mg, 0.076 mmol, 1 eq) and *t*-BuOK (6.83 mg, 0.06 mmol, 0.8 eq). Compound **235e** yielded as a colourless oil (24.65 mg, 0.046 mmol, 61% yield) after column chromatography (15% EtOAc/pentane).

Asymmetric: Compound **235e** was synthesized using the **general procedure C** using the amino-thioester **234e** (21 mg, 0.039 mmol, 1 eq) and (*R*)-Anth (6 mg, 0.008 mmol, 0.2 eq). Compound **235e** yielded as a colourless oil (2 mg, 0.004 mmol, 10% yield, 25% brsm) after column chromatography (15% EtOAc/pentane).

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.58 – 6.93 (m, 19H, H-3, H-4, H-13, H-14, H-15, H-20, H-21, H-22), 5.53 – 4.82 (m, 3H, H-18, H-16), 4.82 – 4.64 (br. m, 1H, H-8), 3.23 – 2.76 (m, 3H, H-7, H-16'), 2.60 – 2.38 (m, 2H, H-10), 2.35 (s, 3H, H-1), 1.78 – 1.58 (br. m, 2H, H-9) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 195.3 (C-6), 155.3 (C-17), 147.2 (C-12), 143.8 (C-12'), 139.9 (C-2), 136.7 (C-19), 134.4 (C-4), 130.1 (C-3), 128.6 (Ar-CH), 128.5 (Ar-CH), 128.1 (Ar-CH), 127.7 (Ar-CH), 126.6 (Ar-CH), 126.1 (Ar-CH), 124.0 (C-5), 67.5 (C-18), 48.1 (C-8), 47.9 (C-16), 46.3 (C-11), 43.8 (C-7), 29.5 (C-10), 24.0 (C-9), 21.4 (C-1) ppm; **IR** (ATR): ν_{max} 3030, 2938, 2871, 1696, 1495, 1446, 1419, 1341, 1229, 1111, 1074, 1056, 1023, 964, 910, 808, 752, 699, 631, 576 cm^{-1}; **HRMS** (ESI) 536.2266 (M + H^{+}. $C_{34}H_{34}NO_3S$ requires 536.2254).

(*S*)-Benzyl 3-(2-oxo-2-(p-tolylthio)ethyl)-2-azaspiro[5.6]dodecane-2-carboxylate (235f)

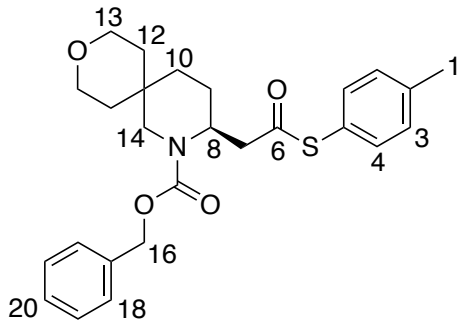


Racemic: Compound **235f** was synthesized using the **general procedure C** using the amino-thioester **234f** (21 mg, 0.045 mmol) and rac-CSA (31 mg, 0.135 mmol, 3 eq). Compound **235f** yielded as a pale-yellow oil (16 mg, 0.035 mmol, 78% yield) after column chromatography (15% EtOAc/pentane).

Asymmetric: Compound **235f** was synthesized using the **general procedure C** using the amino-thioester **234f** (24 mg, 0.051 mmol) and (*R*)-Anth (7 mg, 0.01 mmol, 0.2 eq). Compound **235f** yielded as a pale-yellow oil (3.5 mg, 0.007 mmol, 14% yield, (29% brsm), 95:5 e.r.) after column chromatography (15% EtOAc/pentane).

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.40 – 7.30 (m, 5H, H-19, H-20, H-21), 7.30 – 7.20 (m, 2H, H-4), 7.20 (d, *J* = 7.9 Hz, 2H, H-3), 5.30 – 5.00 (br. m, 2H), 4.90 – 4.70 (br. m, 1H, H-8), 4.00 – 3.70 (br. m, 1H, H-15), 2.90 (d, *J* = 7.8 Hz, 2H, H-7), 2.70 – 2.40 (br. m, 1H, H-15), 2.40 (s, 3H, H-1), 2.00 – 1.80 (m, 1H, H-9), 1.80 – 1.10 (m, 15H, H-10, H-12, H-12' H-13, H-13', H-14, H-14') ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ ppm 195.4 (C-6), 155.8 (C-2), 139.8 (C-2), 136.9 (C-18), 134.4 (C-4), 130.1 (C-3), 128.5 (Ar-CH), 127.9 (Ar-CH), 127.8 (Ar-CH), 124.1 (C-5), 67.2 (C-17), 48.9 (C-15), 48.7 (C-8), 43.9 (C-7), 40.6, 36.2 (C-11), 33.6, 32.0, 30.7, 30.6, 23.8 (C-9), 22.7, 22.6, 21.4 (C-1) ppm; **IR** (ATR): ν_{max} 2932, 2854, 1694, 1443, 1421, 1341, 1239, 1105, 1032, 1003, 912, 763, 735, 697, 606, 534 cm^{-1}; **HRMS** (ESI) 466.2423 (M + H^{+}. $C_{28}H_{36}NO_3S$ requires 466.2410); **$[\alpha]_D^{20}$** +11.54 (c= 0.207, $CHCl_3$).

(*S*)-Benzyl-3-(2-oxo-2-(p-tolylthio)ethyl)-9-oxa-2-azaspiro[5.5]undecane-2-carboxylate (235g)

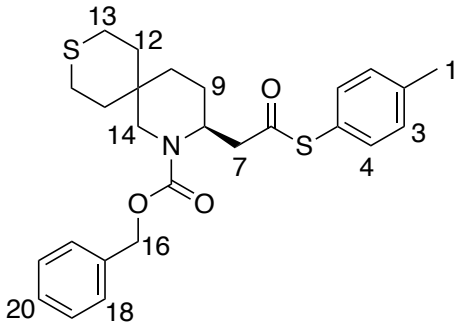


Racemic: Compound **235g** was synthesized using the **general procedure C** using the amino-thioester **234g** (21 mg, 0.047 mmol) and rac-CSA (33 mg, 0.141 mmol, 3 eq). Compound **235g** yielded as a pale-yellow oil (13 mg, 0.028 mmol, 60% yield) after column chromatography (60% Et_2O/pentane).

Asymmetric: Compound **235g** was synthesized using the **general procedure C** using the amino-thioester **234g** (20 mg, 0.043 mmol), (*R*)-Anth (6 mg, 0.008 mmol, 0.2 eq). Compound **235g** yielded as a pale-yellow oil (13 mg, 0.027, 65% yield, 94:6 e.r.) after column chromatography (60% Et_2O/pentane).

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.46 – 7.27 (m, 5H, H-18, H-19, H-20), 7.30 – 7.20 (m, 2H, H-4), 7.20 (d, *J* = 7.8 Hz, 2H, H-3), 5.29 – 4.96 (br. m, 2H, H-16), 5.00 – 4.71 (br. m, 1H, H-8), 4.49 – 3.96 (br. m, 1H, H-14), 3.82 – 3.36 (br. m, 4H, H-13), 3.02 – 2.79 (m, 2H, H-7), 2.74 – 2.46 (br. m, 1H, H-14'), 2.37 (s, 3H, H-1), 1.99 – 1.78 (m, 1H, H-9), 1.71 – 1.29 (m, 7H, H-9', H-10, H-12) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 195.2 (C-6), 155.6 (C-15), 139.9 (C-2), 136.6 (C-17), 134.4 (C-4), 130.1 (C-3), 128.6 (Ar-CH), 128.1 (Ar-CH), 124.0 (C-5), 67.5 (C-16), 64.0 (C-13), 63.3 (C-13'), 48.7 (C-8), 46.8 (C-14), 43.6 (C-7), 37.4 (C-10), 31.5 (C-12), 31.2 (C-11), 30.44 (C-12'), 23.3 (C-9), 21.4 (C-1) ppm; **IR** (ATR): ν_{max} 2920, 2850, 1694, 1494, 1422, 1342, 1303, 1268, 1234, 1221, 1156, 1105, 1017, 808, 753, 698, 609, 534, 474 cm^{-1}; **HRMS** (ESI) 454.2055 (M + H^+. $C_{26}H_{32}NO_4S$ requires 454.2047); **$[\alpha]_D^{20}$** +33.3 (c= 0.602, $CHCl_3$).

(*S*)-Benzyl-3-(2-oxo-2-(*p*-tolylthio)ethyl)-9-thia-2-azaspiro[5.5]undecane-2-carboxylate (235h)

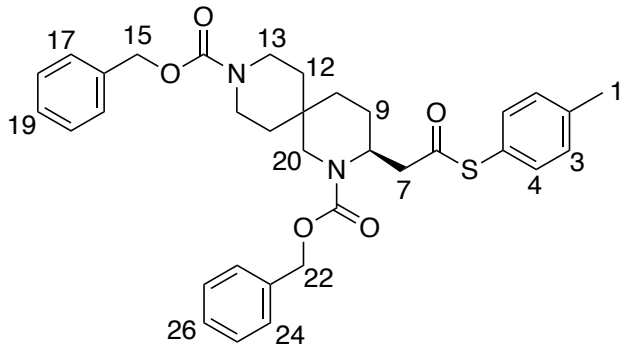


Racemic: Compound **235h** was synthesized using the same procedure as **233e** using the amino-thioester **234h** (22 mg, 0.046 mmol, 1 eq) and *t*-BuOK (4 mg, 0.036 mmol, 0.8 eq). Compound **235h** yielded as a colourless oil (14.5 mg, 0.030 mmol, 70% yield) after column chromatography (15% EtOAc/pentane).

Asymmetric: Compound **235h** was synthesized using the **general procedure C** using the amino-thioester **234h** (19 mg, 0.039 mmol, 1 eq) and (*R*)-Anth (5.5 mg, 0.008 mmol, 0.2 eq). **235h** yielded as a colourless oil (3 mg, 0.005 mmol, 14% yield, (72% brsm) 96:4 e.r.) after column chromatography (15% EtOAc/pentane).

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.38 – 7.27 (m, 5H, H-18, H-19, H-20), 7.26 – 7.21 (m, 2H, H-4), 7.20 (d, *J* = 8.0 Hz, 2H, H-3), 5.24 – 5.04 (br. m, 2H, 16), 4.91 – 4.71 (br. m, 1H, H-8), 4.31 – 3.86 (br. m, 1H, H-14), 2.99 – 2.78 (m, 2H, H-7), 2.80 – 2.41 (br. m, 5H, H-14', H-13, H-13'), 2.37 (s, 3H, H-1), 1.98 – 1.81 (m, 1H, H-9), 1.81 – 1.58 (br. m, 4H, H-12, H-12'), 1.54 – 1.40 (m, 2H, H-9', H-10), 1.34 (td, *J* = 13.3, 3.7 Hz, 2H, H-10') ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 195.2 (C-6), 155.6 (C-15), 139.9 (C-2), 136.7 (C-17), 134.4 (C-4), 130.1 (C-3), 128.6 (Ar-CH), 128.1 (Ar-CH), 128.0 (Ar-CH), 124.0 (C-5), 67.4 (C-16), 48.8 (C-8), 47.0 (C-14), 43.8 (C-7), 38.7 (C-12), 32.3 (C-12'), 32.2 (C-11), 30.2 (C-10), 23.7 (C-13), 23.2 (C-13'), 21.4 (C-1) ppm; **IR** (ATR): ν_{max} 2927, 1695, 1494, 1424, 1278, 1215, 1015, 808, 749, 668 cm^{-1}; **HRMS** (ESI) 492.1641 (M + Na^{+}. $C_{26}H_{31}NNaO_3S_2$ requires 492.1638); **$[\alpha]_D^{20}$** +10.41 (c= 0.1685, $CHCl_3$).

(*S*)-Dibenzyl-3-(2-oxo-2-(p-tolylthio)ethyl)-2,9-diazaspiro[5.5]undecane-2,9-dicarboxylate (235i)



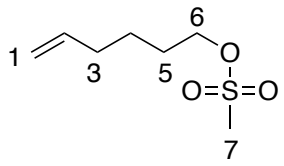
Racemic: Compound **235i** was synthesized using the **general procedure C** using the amino-thioester **234i** (20 mg, 0.034 mmol, 1 eq) and rac-CSA (26 mg, 0.111 mmol, 3.2 eq). Compound **235i** yielded as a pale-yellow oil (14 mg, 0.023 mmol, 69% yield) after column chromatography (35% EtOAc/pentane).

Asymmetric: Compound **235i** was synthesized using the **general procedure C** using the amino-thioester **234i** (24 mg, 0.040 mmol, 1 eq) and (*R*)-Anth (6 mg, 0.008 mmol, 0.22 eq). Compound **235i** yielded as a pale-yellow oil (2.5 mg, 0.004 mmol, 11% yield (39% brsm), 96:4 e.r.) after column chromatography (35% EtOAc/pentane).

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.42 – 7.27 (m, 10H, H-17, H-18, H-19, H-24, H-25, H-26), 7.26 – 7.21 (m, 2H, H-4), 7.19 (d, *J* = 8.1 Hz, 2H, H-3), 5.28 – 4.99 (br. m, 4H, H-15, H-22), 4.86 (br. s, 1H, H-8), 4.34 – 3.89 (br. M, 1H, H-20), 3.78 – 3.19 (br. m, 4H, H-13, H-13'), 3.03 – 2.78 (br. m, 2H, H-7), 2.76 – 2.49 (m, 1H, H-20'), 2.37 (s, 3H, H-1), 1.99 – 1.78 (br. m, 1H, H-9), 1.57 – 1.44 (m, 3H, H-9', H-10), 1.44 – 1.26 (m, 4H, H-12, H-12') ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 195.2 (C-6), 155.6 + 155.4 (C-14 + C-21), 139.9 (C-2), 136.9 (C-23), 136.4 (C-16), 134.4 (C-4), 130.1 (C-3), 128.6 (Ar-CH), 128.6 (Ar-CH), 128.2 (Ar-CH), 128.1 (Ar-CH), 127.9 (Ar-CH), 124.0 (C-5), 67.5 + 67.1 (C-15 + C-22), 48.7 (C-8), 43.7 (C-7), 40.1 (C-20), 39.5 (C-13), 36.5 (C-12), 32.0 (C-11), 30.6 (C-10), 23.5 (C-9), 21.4 (C-1) ppm; **IR** (ATR): ν_{max} 2929, 2866, 1693, 1495, 1425, 1278, 1246, 1229, 1152, 1092, 1012, 808, 735, 697 cm^{-1}; **HRMS** (ESI) 587.2590 (M + H^{+}. $C_{34}H_{39}N_2O_5S$ requires 587.2574); **$[\alpha]_D^{20}$** +10.62 (c= 0.189, $CHCl_3$).

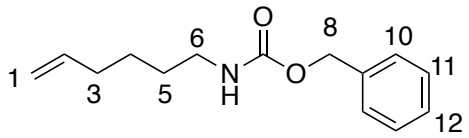
Unsubstituted piperidine

Hex-5-en-1-yl methanesulfonate (254)



In a flame dried flask, 5-hexene-1-ol (0.5 mL, 4.2 mmol, 1 eq) and Et_3N (2.34 mL, 16.8 mmol, 4 eq) were added to dichloromethane (25 mL) and cooled to 0 °C. Methanesulfonyl chloride (0.4 mL, 6.3 mmol, 1.5 eq) was added at 0 °C and the reaction was warmed to room temperature and stirred for 24 hours. The reaction was concentrated and co-concentrated with toluene *in vacuo* to form the crude residue which was purified with flash column chromatography (20% EtOAc/hexane) to yield compound **254** as a colourless oil (595 mg, 3.34 mmol, 80% yield) **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 5.74 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1H, H-2), 5.00 (dd, *J* = 17.0, 1.8 Hz, 1H, H-1), 4.90 (dd, *J* = 10.2, 1.8 Hz, 1H, H-1'), 4.18 (t, *J* = 6.5 Hz, 2H, H-6), 2.96 (s, 3H, H-7), 2.13 – 1.99 (m, 2H, H-3), 1.81 – 1.64 (m, 2H, H-5), 1.55 – 1.41 (m, 2H, H-4) ppm; **^{13}CNMR** (101 MHz, Chloroform-*d*): δ 137.8 (C-2), 115.1 (C-1), 70.0 (C-6), 37.2 (C-7), 32.9 (C-3), 28.4 (C-5), 24.5 (C-4) ppm. This matches the data reported in the literature.[102]

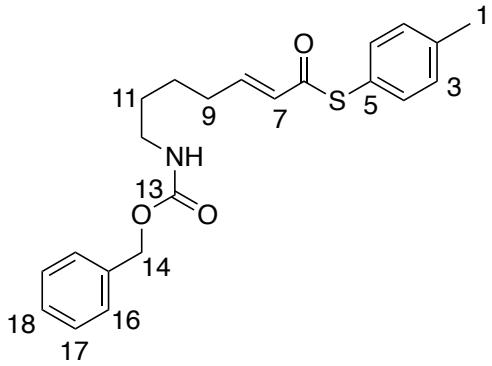
Benzyl hex-5-en-1-ylcarbamate (231k)



To a solution of aq. NH_3 (35%, 20 mL) and methanol (10 mL), the mesylate **254** (252 mg, 1.41 mmol, 1 eq) was added and stirred at room temperature for 24 hours. The reaction mixture was extracted with Et_2O (20 mL x 4) and the combined organics were washed with 2 M HCl (10 mL x 4), dried with Na_2SO_4, filtered and concentrated *in vacuo* to give the HCl salt of the amine (688 mg, 5.09 mmol) which was taken through the next step without further purification. The salt was dissolved in water (1 mL) and Cbz protected using the **general procedure E** solution (50% w/w aq, 0.8 mL, 6.11 mmol, 1.2 eq) and benzylchloroformate (0.8 mL, 6.11 mmol, 1.2 eq). Compound **231k** yielded as a colourless oil (179 mg, 0.77 mmol, 55% yield over two steps) after column chromatography (5%

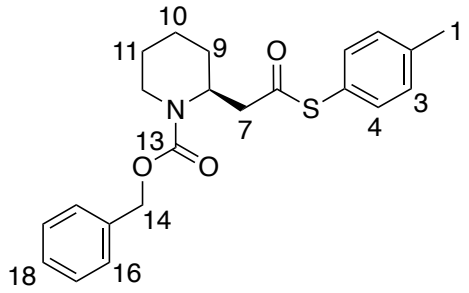
EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.46 – 7.26 (m, 5H, H-10, H-11, H-12), 5.78 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H, H-2), 5.09 (s, 2H, H-8), 5.03 – 4.92 (m, 2H, H-1), 4.72 (br. s, 1H, N-H), 3.20 (q, *J* = 6.7 Hz, 2H, H-6), 2.07 (m, 2H, H-3), 1.57 – 1.46 (m, 2H, H-5), 1.46 – 1.35 (m, 2H, H-4) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 156.1 (C-7), 138.5 (C-2), 136.7 (C-9), 128.6 (Ar-CH), 128.2 (Ar-CH), 128.2 (Ar-CH), 114.9 (C-1), 66.7 (C-8), 41.0 (C-6), 33.4 (C-3), 29.5 (C-5), 26.0 (C-4) ppm; **IR** (ATR): ν_{max} 3334, 3066, 3033, 2932, 2859, 1679, 1640, 1530, 1455, 1413, 1248, 1113, 1024, 995, 911,776, 735, 696, 639 cm^{-1}; **HRMS** (ESI) 234.1490 (M + H$^+$. $C_{14}H_{20}NO_2$ requires 234.1489).

(*E*)-S-*p*-tolyl 7-(((benzyloxy)carbonyl)amino)hept-2-enethioate (234k)



Compound **234k** was synthesised using the **general procedure B** with thioester **190** (90 mg, 0.506 mmol, 3 eq), Hoveyda-Grubbs Catalyst™ 2nd generation (10.5 mg, 0.016 mmol, 0.1 eq), copper iodide (32 mg, 0.168 mmol, 1 eq), Cbz-amine **231k** (39 mg, 0.168 mmol, 1 eq). Compound **234k** yielded as a pale-yellow oil (39 mg, 0.101 mmol, 60% yield) after column chromatography (10-20% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.41 – 7.27 (m, 7H, H-16, H-17, H-18, H-4), 7.21 (d, *J* = 8.0 Hz, 2H, H-3), 6.93 (dt, *J* = 15.5, 6.9 Hz, 1H, H-8), 6.16 (d, *J* = 15.5 Hz, 1H, H-7), 5.09 (s, 2H, H-14), 4.80 (t, *J* = 6.4 Hz, 1H, N-H), 3.19 (Q, *J* = 6.4 Hz, 2H, H-12), 2.37 (s, 3H, H-1), 2.28 – 2.13 (m, 2H, H-9), 1.74 – 1.40 (br. m, 4H, H-10, H-11) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 188.6 (C-6), 156.5 (C-13), 145.8 (C-8), 139.7 (C-2), 136.6 (C-15), 134.7 (C-4), 130.1 (C-3), 128.6 (Ar-CH), 128.2 (C-7, Ar-CH), 124.0 (C-5), 66.7 (C-14), 40.8 (C-12), 31.9 (C-9), 29.6 (C-11), 25.1 (C-10), 21.4 (C-1) ppm; **IR** (aTR): ν_{max} 3343, 2924, 2854, 1697, 1246, 808 cm^{-1}; **HRMS** (ESI) 406.1445 (M + Na$^+$. $C_{22}H_{25}NNaO_3S$ requires 406.1447).

(*S*)-Benzyl 2-(2-oxo-2-(p-tolylthio)ethyl)piperidine-1-carboxylate (235k)



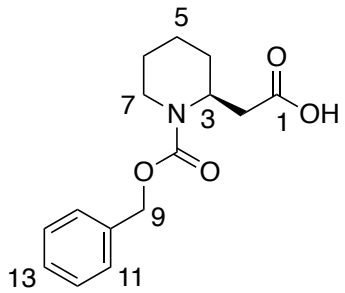
Racemic: Compound **235k** was synthesized using the **general procedure C** using the amino-thioester **234k** (40 mg, 0.104 mmol, 1 eq) and rac-CSA (73 mg, 0.312 mmol, 3 eq). Compound **235k** yielded as a pale-yellow oil (17 mg, 0.044 mmol, 43% yield) after column chromatography (20% EtOAc/hexane).

Asymmetric: Compound **235k** was synthesized using the **general procedure C** using the amino-thioester **234k** (48mg, 0.124 mmol, 1 eq), (*R*)-Anth (17.5 mg, 0.024 mmol, 0.2 eq). Compound **235k** yielded as a pale-yellow oil (10 mg, 0.026 mmol, 21% yield (79% brsm), 84:16 e.r.) after column chromatography (40% Et_2O/pentane).

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.39 – 7.29 (m, 5H, H-16, H-17, H-18), 7.25 – 7.21 (br. m, 2H, H-4), 7.19 (d, *J* = 7.8 Hz, 2H, H-3), 5.20 (d, *J* = 12.4 Hz, 1H, H-14), 5.10 (d, *J* = 12.4 Hz, 1H, H-14') 4.92 – 4.77 (br. m, 1H, H-8), 4.21 – 3.95 (br. m, 1H, H-12), 2.99 – 2.80 (m, 3H, H-7, H-12'), 2.36 (s, 3H, H-1), 1.80 – 1.60 (m, 4H, H-9, H-9', H-10, H-11), 1.6 – 1.5 (m, 1H, H-10'), 1.50 – 1.40 (m, 1H, H-11') ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 195.4 (C-6), 155.4 (C-13), 139.8 (C-2), 136.8 (C-15), 134.4 (C-4), 130.1 (C-3), 128.6 (Ar-CH), 128.0 (Ar-CH), 127.9 (Ar-CH), 124.1 (C-5), 67.2 (C-14), 48.8 (C-8), 43.8 (C-7), 39.8 (C-12), 28.2 (C-9), 25.3 (C-11), 21.4 (C-1), 18.9 (C-10) ppm; **IR** (ATR): ν_{max} 2925, 2853, 1704, 1533, 1456, 1260, 1085, 1022, 803, 736, 700 cm^{-1}; **HRMS** (ESI) 384.1633 ($M + H^+$. $C_{22}H_{26}NO_3S$ requires 384.1628); **$[\alpha]_D^{20}$** +23.7 (c= 0.5345, $CHCl_3$).

Determination of absolute stereochemistry

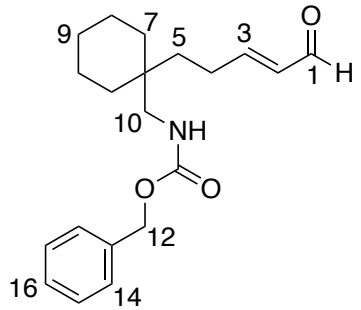
(*S*)-2-(1-((Benzyloxy)carbonyl)piperidin-2-yl)acetic acid (255)



To compound **235k** (10.75 mg, 0.03 mmol, 1 eq) in THF (1.5 mL) was added aq. H_2O_2 (30% w/w, 4 µL, 0.112 mmol, 4 eq) at 0 °C and stirred for 15 min at 0 °C. Aq. NaOH (0.22 M, 0.38 mL, 0.084 mmol, 3 eq) was added at at 0 °C and the reaction warmed to room temperature and stirred for 1 hour. The reaction was quenched with water (15 mL) and the aqueous layer extracted with Et_2O (15 mL x 3). The combined aqueous layers were acidified to pH 2 with 2M HCl and extracted with EtOAc (15 mL x 3). The combined organic layers were washed with saturated sodium metabisulfite solution (10 mL), followed by saturated brine solution (10 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo.* The crude material was purified by column chromatography (50% EtOAc/hexane) to afford **255** as a colourless oil (7 mg, 0.025 mmol, 92% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.40 – 7.30 (m, 5H, H-11, H-12, H-13), 5.10 (s, 2H, H-9), 4.90 – 4.70 (m, 1H, H-3), 4.20 – 4.00 (br. m, 1H, H-7), 3.00 – 2.80 (m, 1H, H-7'), 2.70 – 2.50 (m, 2H, H-2), 1.80 – 1.60 (m, 4H, H-4, H-5, H-6), 1.60 – 1.50 (m, 1H, H-5'), 1.50 – 1.40 (m, 1H, H-6') ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 175.8 (C-1), 155.6 (C-8), 136.8 (C-10), 128.6 (Ar-CH), 128.0 (Ar-CH), 127.9 (Ar-CH), 67.3 (C-9), 48.1 (C-3), 39.7 (C-7), 35.1 (C-2), 28.3 (C-4), 25.3 (C-6), 18.8 (C-5) ppm; **IR** (ATR): ν_{max} 3035, 2937, 2862, 1731, 1697, 1426, 1319, 1263, 1170, 1138, 1093, 1044, 1015, 766, 697 cm^{-1}; **HRMS** (ESI) 278.1392 ($M + H^+$. $C_{15}H_{20}NO_4$ requires 278.1387); **$[\alpha]_D^{20}$** +7.14 (c= 0.2055, $CHCl_3$) [lit. $[\alpha]_D$ -18 (c=0.5, $CHCl_3$) for (*R*)-isomer][57]

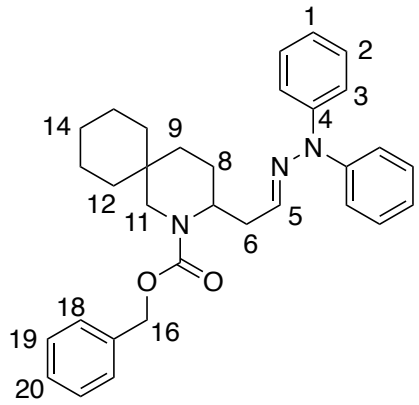
Aldehyde substrates

(*E*)-Benzyl ((1-(5-oxopent-3-en-1-yl)cyclohexyl)methyl)carbamate (261)



Compound **261** was synthesised using the **general procedure B** with acrolein (0.4 mL, 7 mmol, 20 eq), Hoveyda-Grubbs Catalyst^{TM} 2nd generation (22 mg, 0.035 mmol, 0.1 eq), Cbz-amine **213** (105 mg, 0.35 mmol, 1 eq) in DCM (18 mL) and stirred at rt for 24 hours. Compound **261** yielded as a pale brown oil (84 mg, 0.253 mmol, 73% yield) after column chromatography (20% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 9.50 (d, *J* = 8.2 Hz, 1H, H-1), 7.40 – 7.30 (m, 5H, H-14, H-15, H-16), 6.80 (dt, *J* = 15.7, 6.7 Hz, 1H, H-3), 6.10 (dd, *J* = 15.7, 8.2 Hz, 1H, H-2), 5.10 (s, 2H, H-12), 4.80 (t, *J* = 6.6 Hz, 1H, N-H), 3.10 (d, *J* = 6.5 Hz, 2H, H-10), 2.4 – 2.2 (m, 2H, H-4), 1.60 – 1.20 (m, 12H, H-5, H-7, H-7', H-8, H-8', H-9) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 194.2 (C-1), 159.4 (C-3), 156.8 (C-11), 136.6 (C-13), 132.8 (C-2), 128.6 (Ar-CH), 128.3 (Ar-CH), 128.2 (Ar-CH), 66.8 (C-12), 47.0 (C-10), 36.5 (C-6), 33.4 (C-7), 33.1 (C-5), 26.8 (C-4), 26.1 (C-9), 21.4 (C-8) ppm; **IR** (ATR): ν_{max} 2926, 2870, 1735, 1535, 1435, 1245, 1160, 763, 704 cm^{-1}; **HRMS** (ESI) 330.2058 (M + H^{+}. $C_{20}H_{28}NO_3$ requires 330.2064).

(*E*)-Benzyl-3-(2-(2,2-diphenylhydrazono)ethyl)-2-azaspiro[5.5]undecane-2-carboxylate (264)



Racemic: Compound **264** was synthesized using the **general procedure C** using the compound **261** (67 mg, 0.204 mmol, 1 eq) and rac-CSA (142 mg, 0.612 mmol, 3 eq). The crude residue (68 mg, 0.306 mmol) was dissolved in dry MeOH (3 mL) and added to *N*,*N*-diphenylhydrazine (46 mg, 0.24 mmol, 1.2 eq) followed by 2-3 drops of glacial acetic acid. The reaction was stirred at room temperature for 3 hours and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (10% Et_2O/Hexane) to afford **264** as a dark brown oil (48 mg, 0.1 mmol, 48% over two steps).

Asymmetric : Compound **264** was synthesized using the **general procedure C** using the compound **261** (75 mg, 0.23 mmol, 1 eq) and (*R*)-TRIP (34 mg, 0.045 mmol, 0.2 eq) at rt for 24 hours. The crude residue (101 mg, 0.306 mmol) was dissolved in dry MeOH (3 mL) and added to *N*,*N*-diphenylhydrazine (68 mg, 0.37 mmol, 1.2 eq) followed by 2-3 drops of drops of glacial acetic acid. The reaction was stirred at room temperature for 1 hour and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (7% EtOAc/Hexane) to afford **264** as a pale brown oil (53 mg, 0.107 mmol, 49% yield over two steps, 85:15 e.r.)

Asymmetric : (*R*)-TiPSY

Compound **264** was synthesized using the same procedure as above using the Cbz amine-aldehyde **261** (24 mg, 0.072 mmol, 1 eq) and (*R*)-TiPSY (12.5 mg, 0.014 mmol, 0.2 eq) and *N*,*N*-diphenylhydrazine (28 mg, 0.15 mmol, 1.3 eq) . Compound **264** yielded as a pale brown oil (17 mg, 0.033 mmol, 46% yield over two steps, 63:37 e.r.) after column chromatography (10% Et_2O/hexane).

Asymmetric : (*R*)-Anth

Compound **264** was synthesized using the same procedure as above using the Cbz amine-aldehyde **261** (20 mg, 0.06 mmol, 1 eq) and (*R*)-Anth (9 mg, 0.012 mmol, 0.2 eq) and *N*,*N*-diphenylhydrazine (20 mg, 0.11 mmol, 1.3 eq) . Compound **264** yielded as a pale brown oil (21 mg, 0.042 mmol, 70% yield over two steps, 83:17 e.r.) after column chromatography (10% Et_2O/hexane).

Asymmetric : (*R*)-Phen

Compound **264** was synthesized using the same procedure as above using the Cbz amine-aldehyde **261** (18.5 mg, 0.05 mmol, 1 eq) and (*R*)- Phen (8 mg, 0.011 mmol, 0.2 eq) and *N*,*N*-diphenylhydrazine (20 mg, 0.11 mmol, 1.3 eq). Compound **264** yielded as a pale brown oil (23 mg, 0.046 mmol, 83% yield over two steps, 61:39 e.r.) after column chromatography (15% Et_2O/hexane).

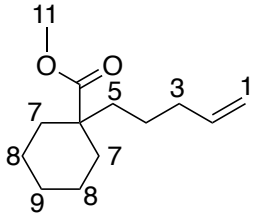
Asymmetric : (*R*)-VAPOL

Compound **264** was synthesized using the same procedure as above using the Cbz amine-aldehyde **261** (26 mg, 0.08 mmol, 1 eq) and (*R*)- VAPOL (10 mg, 0.016 mmol, 0.2 eq) and *N*,*N*-diphenylhydrazine (27.5 mg, 0.15 mmol, 1.3 eq). Compound **264** yielded as a pale brown oil (26.5 mg, 0.053 mmol, 66% yield over two steps, 50:50 e.r.) after column chromatography (10% Et_2O/hexane).

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.33 (t, *J* = 7.8 Hz, 4H, H-2), 7.29 – 7.18 (m, 5H, H-18, H-19, H-20), 7.10 (t, *J* = 7.4 Hz, 2H, H-1), 7.03 (d, *J* = 7.8 Hz, 4H, H-3), 6.44 (t, *J* = 5.5 Hz, 1H, H-5), 5.16 – 4.81 (m, 2H, H-16), 4.50 – 4.34 (m, 1H, H-7), 4.12 – 3.84 (m, 1H, H-11), 2.83 – 2.47 (m, 2H, H-11', H-6), 2.46 – 2.30 (m, 1H, H-6'), 1.91 – 1.68 (m, 1H, H-8), 1.54 – 1.10 (m, 13H, H-8', H-9, H-12, H-13, H-14) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 155.8 (C-15), 144.1 (C-4), 136.7(C-5 + C-17), 129.8 (C-2), 128.5, 127.8, 127.4 (Ar C-H), 124.1 (C-1), 122.4 (C-3), 66.9 (C-16), 49.0(C-7), 47.5 (C-11), 38.1 (C-13), 33.4 (C-6), 33.0 (C-10), 31.1 (C-12), 30.7 (C-12'), 26.7 (C-9), 23.2 (C-8), 21.7 (C-14), 21.6 (C-13') ppm; **IR** (ATR): ν_{max} 3061, 3033, 2925, 2853, 1693, 1589, 1495, 1450, 1423 cm^{-1}; **HRMS** (ESI) 496.2963 ($M + H^+$. $C_{32}H_{38}N_3O_2$ requires 496.2959); **HPLC** CHIRALPAK^{TM} IA column hexane:IPA= (5:95), flow rate 1.0 mL/min, 25 ^oC, λ= 254, t_R (major)= 9.804, t_R (minor)=11.631; **$[\alpha]_D^{20.8}$** +37.58 (c 0.3575, $CHCl_3$) for 85:15 e.r with (*R*)-TRIP as the catalyst.

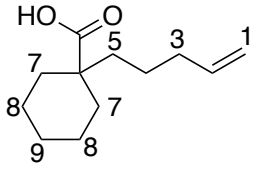
Synthesis of 2,2'-disubstituted precursors

Methyl 1-(pent-4-en-1-yl)cyclohexanecarboxylate (267)



Compound **267** was synthesised using the **general procedure D** with diisopropylamine (1.5 mL, 11 mmol, 1.1 eq), n-BuLi (1.82 M in hexanes, 6 mL, 11 mmol, 1.1 eq), methyl cyclohexylcarboxylate (1.5 mL, 10 mmol, 1 eq) and 5-bromobutene (1.2 mL, 10 mmol, 1 eq). Compound **267** yielded as a colourless oil (1.3 g, 6.2 mmol, 62% yield) after column chromatography (5% Et_2O/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 5.80 (ddt, *J* = 17.0, 10.1, 6.5 Hz, 1H, H-2), 5.00 (dd, *J* = 17.0, 1.7 Hz, 1H, H-1), 5.00 – 4.90 (m, 1H, H-1'), 3.70 (s, 3H, H-11), 2.10 – 2.00 (m, 2H, H-8), 2.00 – 1.90 (m, 2H, H-3), 1.60 – 1.50 (m, 2H, H-7, H-9), 1.50 – 1.40 (m, 2H, H-5), 1.30 – 1.10 (m, 8H, H-4, H-7, H-7', H-8', H-9') ppm; **^{13}C NMR** δ (101 MHz, Chloroform-*d*): δ 177.4 (C-10), 138.6 (C-2), 114.6 (C-1), 51.5 (C-11), 47.0 (C-6), 40.4 (C-5), 34.2 (C-8), 34.1 (C-3), 26.0 (C-9), 23.4 (C-4), 23.3 (C-7) ppm; **IR (ATR)** 2932, 2856, 1727, 1452, 1214, 745, 668 cm^{-1}.

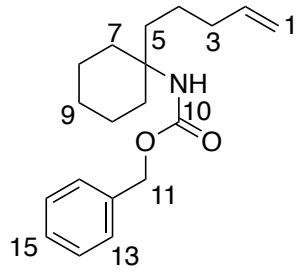
1-(Pent-4-en-1-yl)cyclohexanecarboxylic acid (268)



To a solution of alkenyl ester **267** (898 mg, 4.3 mmol, 1 eq) in MeOH (10 ml) was added NaOH (20% w/w, 2.5 ml) and reaction heated to reflux while stirring overnight. 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 20 mL). Combined organics were dried with $MgSO_4$, filtered and concentrated *in vacuo*, to yield acid **268** (275 mg, 1.4 mmol, 33% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 5.80 (ddt, *J* = 16.9, 10.4, 6.7 Hz, 1H, H-2), 5.00 (dd, *J* = 17.0, 1.8 Hz, 1H, H-1), 4.90 (dd, *J* = 10.4, 1.8 Hz, 1H, H-1'), 2.10 – 1.90 (m, 4H, H-3, H-8), 1.70 – 1.50 (m, 5H, H-

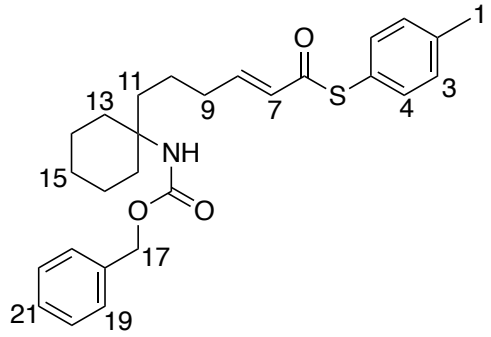
5, H-7, H-9), 1.50 – 1.30 (m, 4H, H-4, H-7'), 1.30 – 1.20 (m, 3H, H-8', H-9') ppm; **^{13}C NMR** δ (101 MHz, Chloroform-*d*): δ 184.2 (C-10), 138.2 (C-2), 114.7 (C-1), 46.8 (C-6), 39.8 (C-5), 34.1 (C-3), 33.9 (C-8), 26.0 (C-9), 23.3 (C-4), 23.2 (C-7) ppm; **IR (ATR)** 2932, 2856, 1693, 1453, 1242, 908, 752 cm^{-1}; **HRMS** (ESI) 219.1363 (M+ Na^+. $C_{12}H_{20}NaO_2$ requires 219.1356).

Benzyl ((1-(pent-4-en-1-yl)cyclohexyl)methyl)carbamate (269)



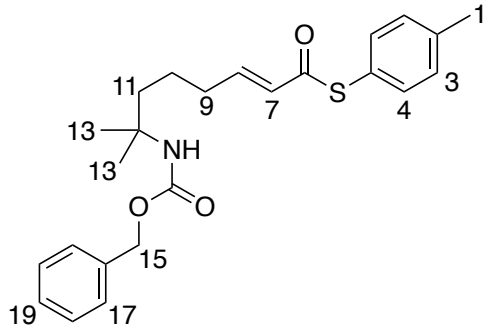
To a solution of carboxylic acid **268** (0.6 mmol, 1 eq)) in dry toluene (6 mL) under N_2 was added Et_3N (0.7 mmol, 1.2 eq, 1 mL) and DPPA (0.65 mmol, 1.1 eq, 0.15 mL) and the reaction heated to 90 °C for 2 hours. Benzyl alcohol (0.9 mmol, 1.5 eq, 1 mL) was added and reaction stirred at 90 °C for 64 hours. Reaction was quenched with H_2O (5 mL) and extracted with EtOAc (10 x 30 mL). Combined organics were washed with saturated brine solution (2 x 10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. Compound **269** yielded as a pale brown oil (127 mg, 0.4 mmol, 71% yield) was obtained after flash column chromatography 20% (EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.40 – 7.30 (m, 5H, H-13, H-14, H-15), 5.80 (ddt, *J* = 16.9, 10.6, 6.8 Hz, 1H, H-2), 5.00 (s, 2H, H-11), 5.0 – 5.0 (m, 1H, H-1), 5.0 – 4.9 (m, 1H, H-1'), 4.5 (s, 1H, N-H), 2.1 – 2.0 (m, 2H, H-3), 2.0 – 1.9 (m, 2H, H-7), 1.8 – 1.6 (m, 2H, H-5), 1.6 – 1.3 (m, 10H, H-4, H-7', H-8, H-8', H-9) ppm; **^{13}C NMR** δ 154.5 (C-10), 139.0 (C-2), 137.0 (C-12), 128.6 (Ar-CH), 128.1 (Ar-CH), 114.5 (C-1), 66.0 (C-11), 54.9 (C-6), 38.0 (C-5), 35.0 (C-7), 34.1 (C-3), 25.9 (C-9), 22.6 (C-4), 21.8 (C-8) ppm; **IR (ATR)** 2921, 2853, 1735, 1499, 1455, 1376, 1248, 909 cm^{-1}; **HRMS** (ESI) 302.2115 (M+ H^+. $C_{19}H_{28}NO_2$ requires 302.2115).

(*E*)-*S*-*p*-tolyl 6-(1-(((benzyloxy)carbonyl)amino)cyclohexyl)hex-2-enethioate (270)



Compound **270** was synthesised using the **general procedure B** with thioester **190** (200 mg, 1.1 mmol, 3 eq), Hoveyda-Grubbs Catalyst™ 2nd generation (32 mg, 0.038 mmol, 0.1 eq) and copper iodide (72 mg, 0.38 mmol, 1 eq), Cbz-amine **269** (115 mg, 0.38 mmol, 1 eq). Compound **270** yielded as a pale brown oil (133 mg, 0.3 mmol, 78% yield) after column chromatography (15% Et_2O/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.40 – 7.30 (m, 7H, H-4, H-19, H-20, H-21), 7.24 – 7.19 (m, 2H, H-3), 7.0 (dt, *J* = 15.2, 7.1 Hz, 1H, H-8), 6.20 (d, *J* = 15.2 Hz, 1H, H-7), 5.10 (s, 2H, H-17), 4.50 (s, 1H, N-H), 2.40 (s, 3H, H-1), 2.30 – 2.10 (m, 2H, H-9), 2.00 – 1.90 (m, 2H, H-13), 1.80 – 1.70 (m, 2H, H-11), 1.60 – 1.10 (m, 10H, H-10, H-13', H-14, H-14' H-15) ppm; **^{13}C NMR** δ 188.7 (C-6), 154.3 (C-16), 146.5 (C-8), 139.7 (C-2), 136.9 (C-18), 134.7 (C-4), 130.1 (C-3), 128.6 (Ar-CH), 128.2 (Ar-CH), 128.1 (Ar-CH), 128.0 (C-7), 124.2 (C-5), 66.2 (C-17), 54.7 (C-12), 38.1 (C-11), 35.0 (C-13), 32.7 (C-9), 25.8 (C-15), 21.8 (C-10), 21.7 (C-14), 21.4 (C-1) ppm; **IR (ATR)** 3362, 2928, 2856, 1721, 1683, 1631, 1495, 1453, 1245, 1090, 1019, 970, 807, 737, 697 cm^{-1}; **HRMS** (ESI) 452.2262 (M+ H^+. $C_{27}H_{34}NO_3S$ requires 452.2254).

(*E*)-*S*-*p*-Tolyl 7-(((benzyloxy)carbonyl)amino)-7-methyloct-2-enethioate (272)



Compound **272** was synthesised by Chris Maddocks by using **general procedure B** with thioester **190** (214 mg, 1.2 mmol, 3 eq), copper iodide (76 mg, 0.4 mmol, 1 eq) and

Hoveyda-Grubbs^{TM} 2nd generation catalyst (25 mg, 0.04 mmol, 0.1 eq), Cbz-amine (105 mg, 0.4 mmol, 1 eq). Compound **272** yielded as a pale brown oil (139 mg, 0.338 mmol, 84% yield) after column chromatography (10% EtOAc/hexane).

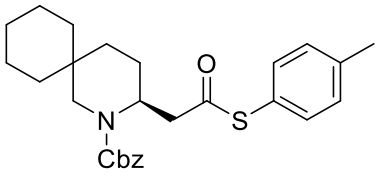
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.40 – 7.30 (m, 7H, H-4, H-17, H-18, H-19), 7.20 (d, *J* = 8.1 Hz, 2H, H-3), 6.90 (dt, *J* = 15.6, 6.9 Hz, 1H, H-8), 6.20 (d, *J* = 15.6 Hz, 1H, H-7), 5.00 (s, 2H, H-15), 4.60 (s, 1H, N-H), 2.40 (s, 3H, H-1), 2.30 – 2.10 (m, 2H, H-9), 1.80 – 1.60 (m, 2H, H-11), 1.50 – 1.40 (m, 2H, H-10), 1.30 (s, 6H, H-13) ppm; **^{13}C NMR** δ (101 MHz, Chloroform-*d*): δ 188.6 (C-6), 154.6 (C-14), 146.1 (C-8), 139.7 (C-2), 134.7 (C-4), 130.1 (C-3), 128.6, 128.2, 128.1 (C-7), 124.1 (C-5), 66.2 (C-15), 52.8 (C-12), 39.7 (C-11), 32.5 (C-9), 27.2 (C-13), 22.7 (C-10), 21.4 (C-1) ppm; **IR (ATR)** 3360, 2927, 1720, 1631, 1508, 1455, 1260, 1073, 808, 697 cm^{-1}; **HRMS** (ESI) 412.1948 (M+ H^{+}. $C_{24}H_{30}NO_3S$ requires 412.1941).

6. Appendices

HPLC data

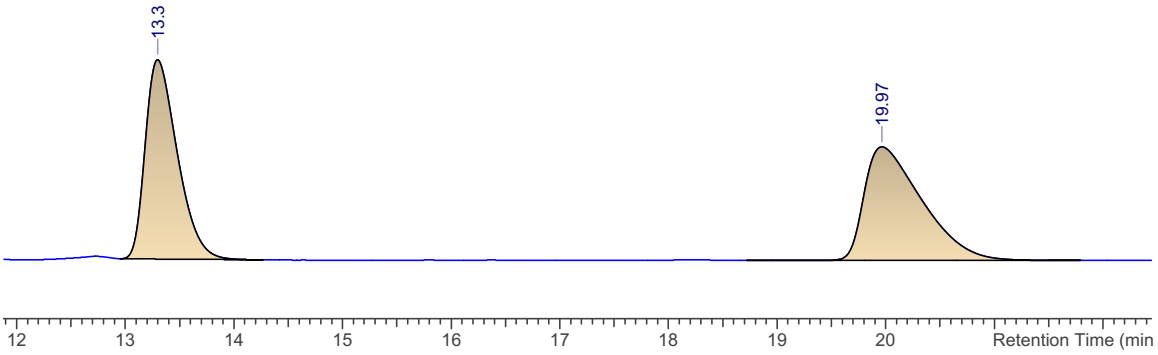
Optimisation

(*S*)-Benzyl 3-(2-oxo-2-(p-tolylthio)ethyl)-2-azaspiro[5.5]undecane-2-carboxylate (217)



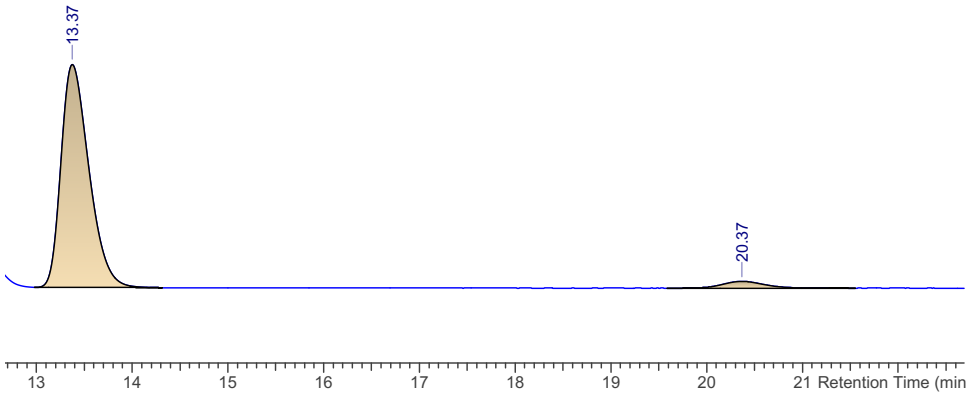
217

HPLC conditions: Chiralpak ® IB Column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 25 °C, λ = 254 nm; tR 13.3 min (major), 20.3 min (minor) (*R*)-TRIP, cyclohexane 80 °C, 24 h, e.r. = 96:4.



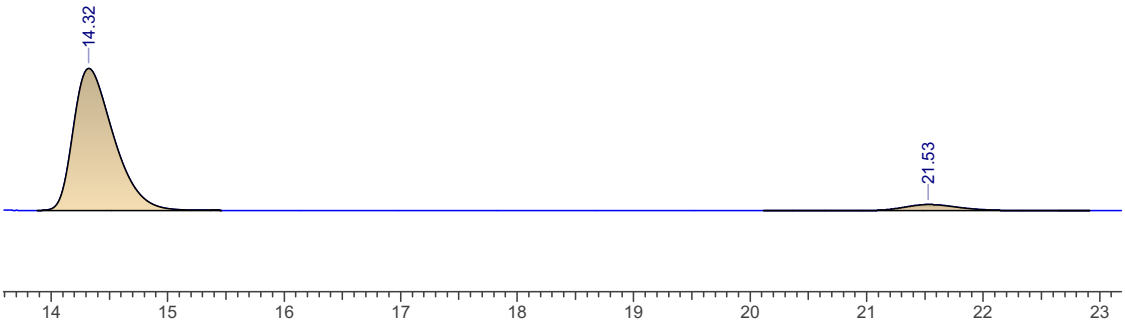
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	13.30	9500926.000	49.554	0.538
2	19.97	9671766.000	50.446	0.969

(*R*)-TRIP, cyclohexane 80 °C, 24 h, e.r. = 96:4.



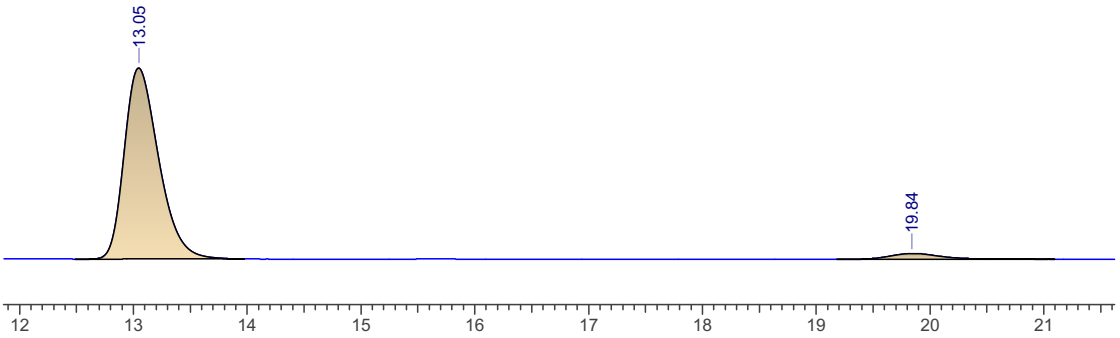
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	13.37	6660466.000	95.691	0.530
2	20.37	299931.688	4.309	0.782

(*R*)-TRIP, octane, 100 °C, 24 h, e.r. = 94:6



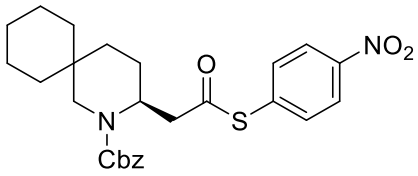
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	14.32	7307619.500	94.267	0.626
2	21.53	444424.781	5.733	0.860

(*R*)-Anth, cyclohexane, 80 °C, 24 h, e.r. = 96:4



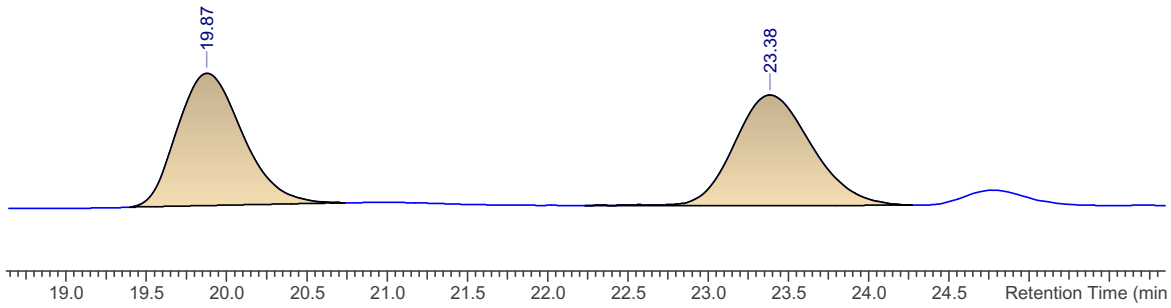
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	13.05	4184735.500	95.741	0.546
2	19.84	186159.891	4.259	0.781

(*S*)-Benzyl 3-(2-((4-nitrophenyl)thio)-2-oxoethyl)-2-azaspiro[5.5]undecane-2-carboxylate (221)



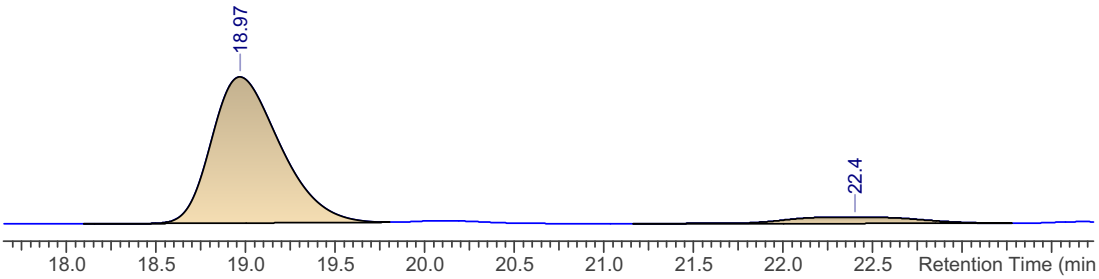
221

HPLC data: Chiralpak ® IB Column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 40 °C, λ = 254 nm; tR 19.8 min (major), 23.38 min (minor)



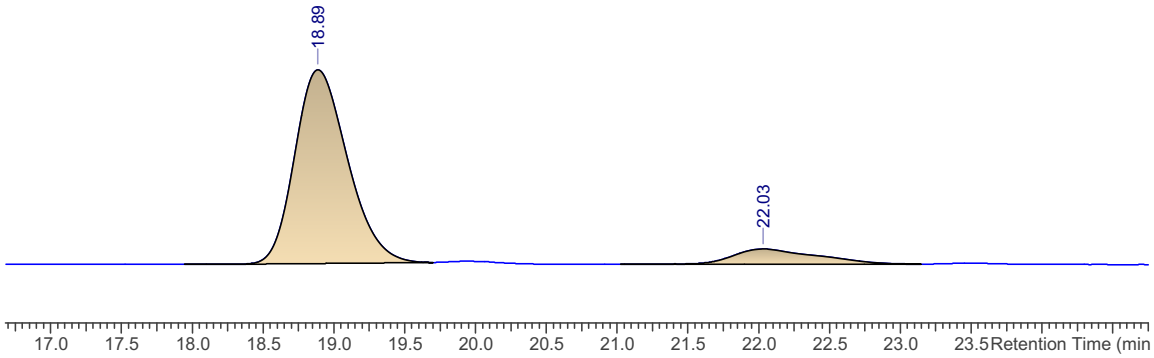
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	19.87	281308.219	50.259	0.755
2	23.38	278406.219	49.741	0.883

(*R*)-TRIP, cyclohexane, 80 °C, 24 h, e.r. = 92:8



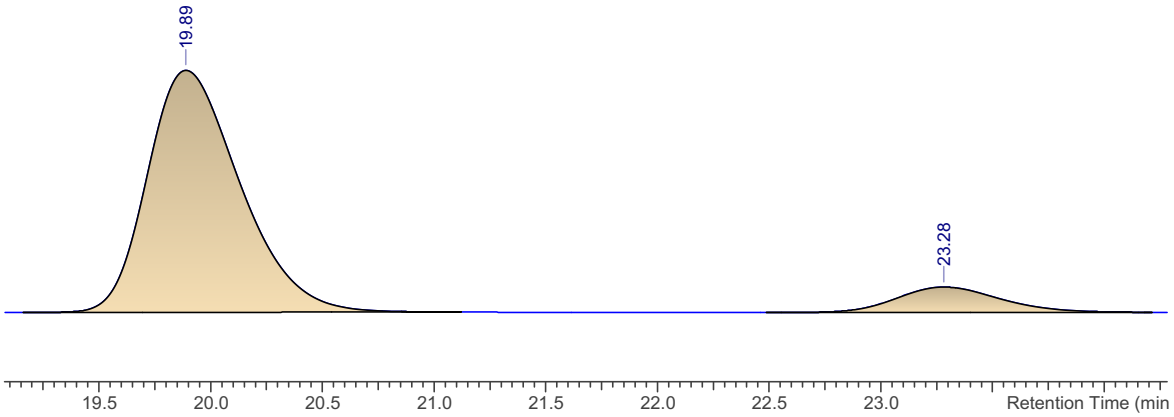
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	18.97	6508034.000	92.470	0.699
2	22.40	529962.938	7.530	1.431

(*R*)-TRIP, octane, 100 °C, 24 h, e.r. = 89:11



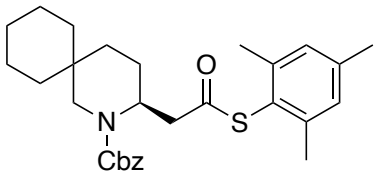
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	18.89	2803674.000	88.835	0.681
2	22.03	352373.969	11.165	1.136

(*R*)-Anth, octane, 100 °C, 24 h, e.r. = 89:11



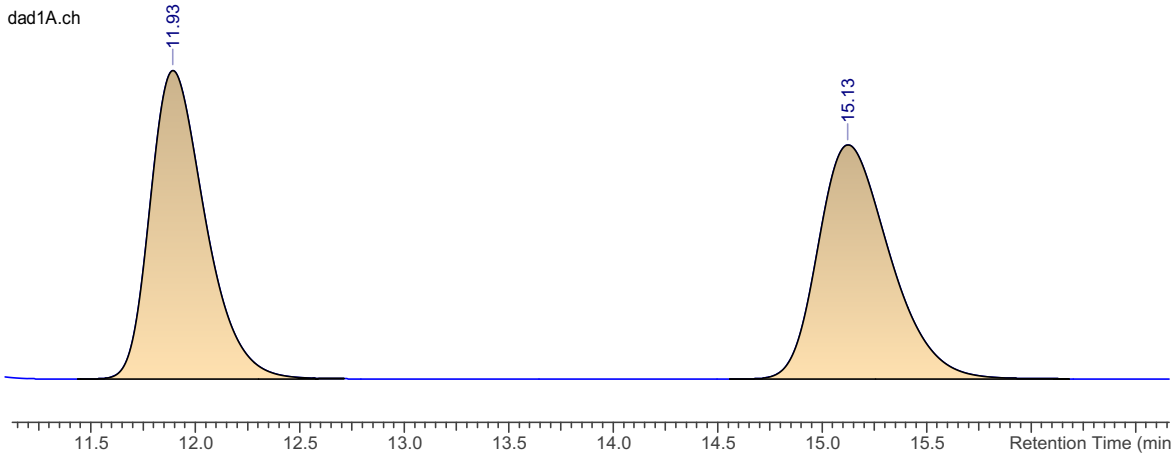
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	19.89	6203331.500	89.470	0.756
2	23.28	730083.438	10.530	0.844

(*S*)-Benzyl 3-(2-(mesitylthio)-2-oxoethyl)-2-azaspiro[5.5]undecane-2-carboxylate (225)



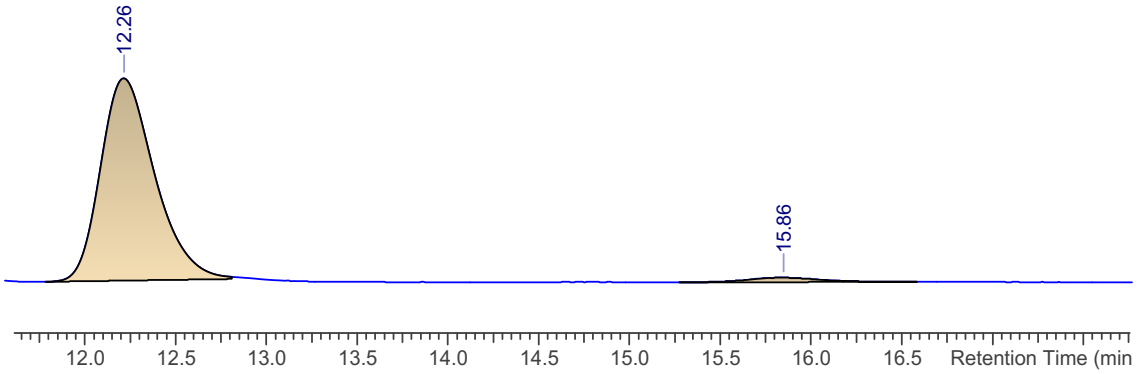
225

HPLC conditions: Chiralpak ® IA Column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 40 °C, λ = 254 nm; tR 12.0 min (major), 15.3 min (minor)



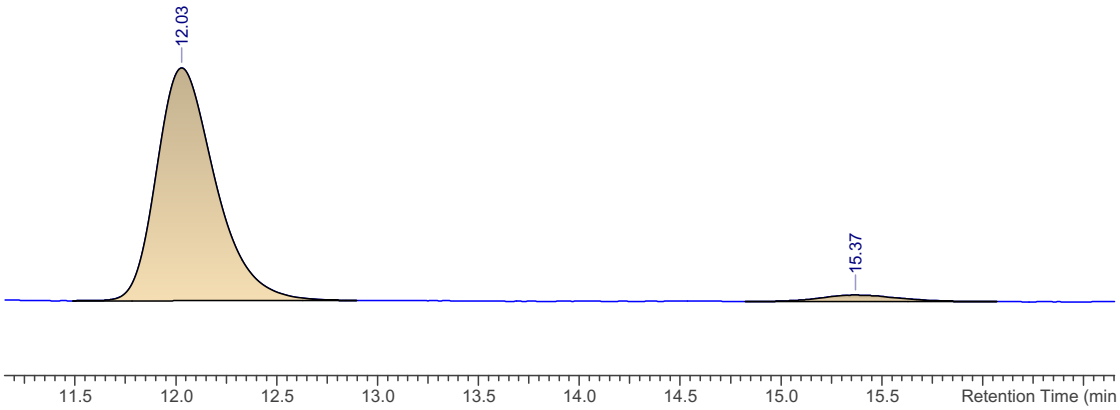
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	11.92	3639067.500	50.289	0.472
2	15.13	3597187.250	49.711	0.620

(*R*)-TRIP, cyclohexane, 80 °C, 24 h, e.r = 97:3



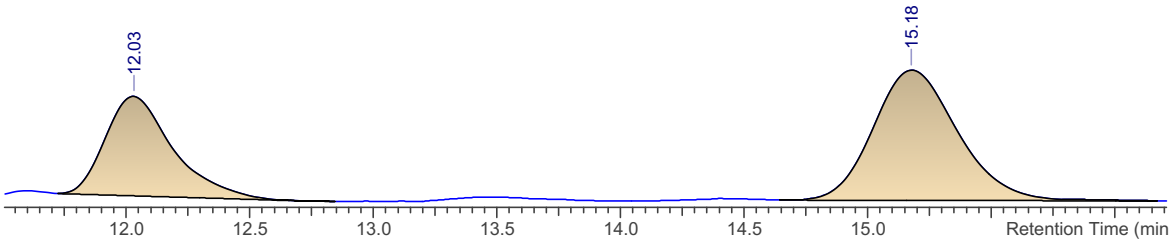
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	12.26	1063003.625	97.239	0.531
2	15.86	30187.508	2.761	0.689

(*R*)-TRIP, octane, 100 °C, 24 h, e.r. = 96:4



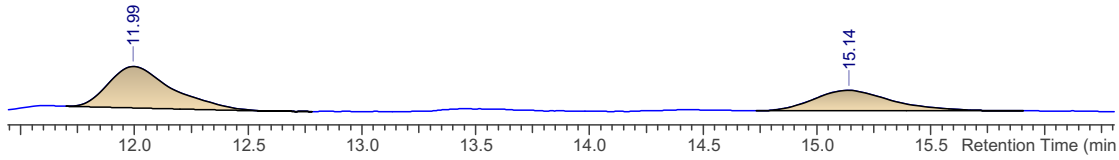
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	12.03	1472033.250	96.365	0.520
2	15.37	55526.348	3.635	0.711

(*R*)-TiPSY, octane, 100 °C, 24 h, e.r. = 38:62



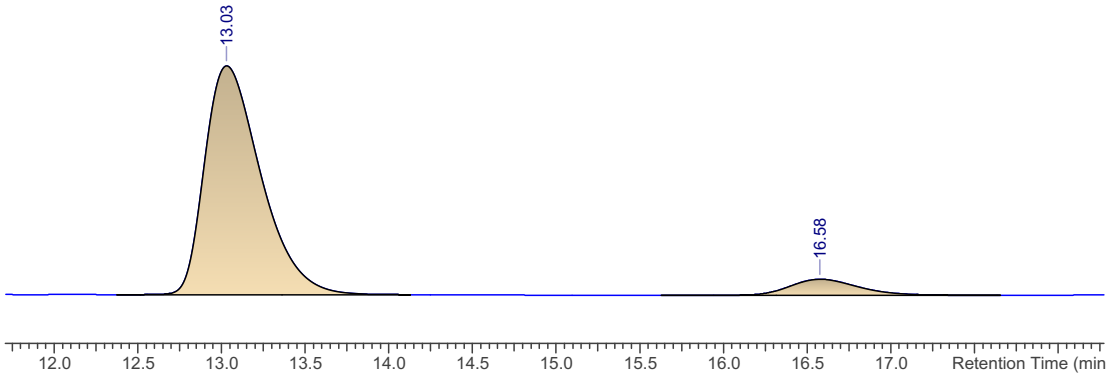
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	12.03	271485.656	37.952	0.477
2	15.18	443862.563	62.048	0.618

(*R*)-Phen, octane, 100 °C, 24 h, e.r. = 62:38



No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	11.99	128061.117	62.365	0.480
2	15.14	77281.563	37.635	0.605

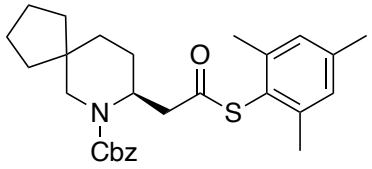
(*R*)-Anth, octane, 100 °C, 24 h, e.r. = 92:8



No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	13.03	9609169.000	92.230	0.610
2	16.58	809506.312	7.770	0.739

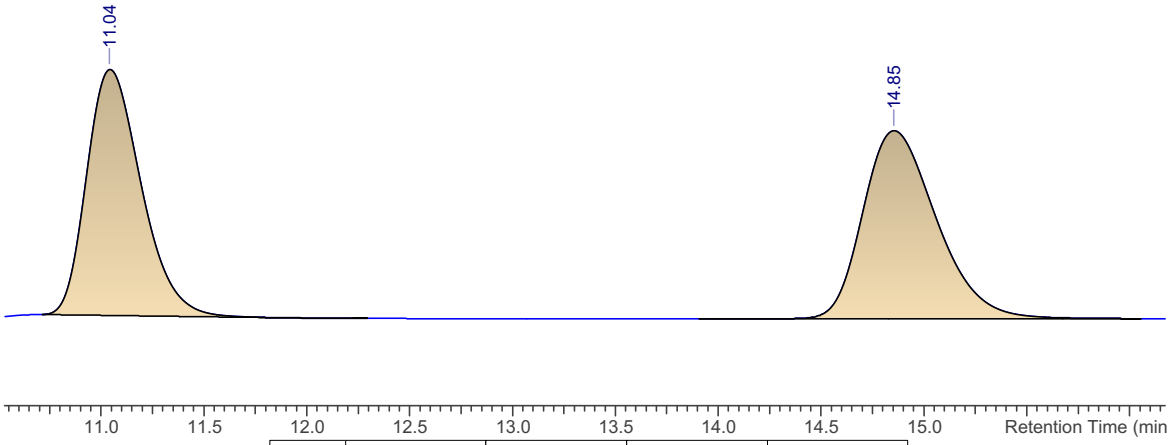
Substrate scope with Mes thioester

Benzyl 8-(2-(mesitylthio)-2-oxoethyl)-7-azaspiro[4.5]decane-7-carboxylate (233a)

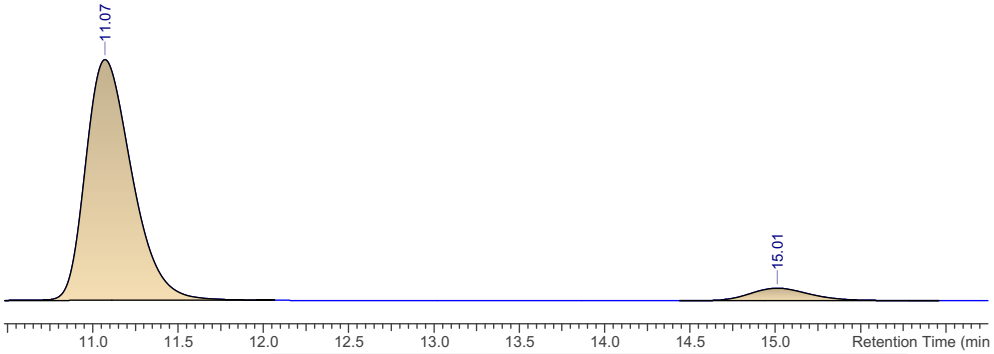


233a

HPLC conditions: Chiralpak ® IA Column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 40 °C, λ = 254 nm; tR 11.0 min (major), 15.0 min (minor) (*R*)-TRIP, octane, 95 °C, 24 h, e.r. = 94:6.

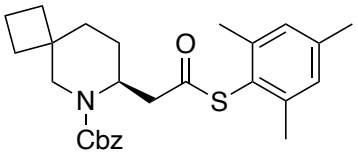


No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	11.04	3266700.000	49.254	0.483
2	14.85	3365722.250	50.747	0.650



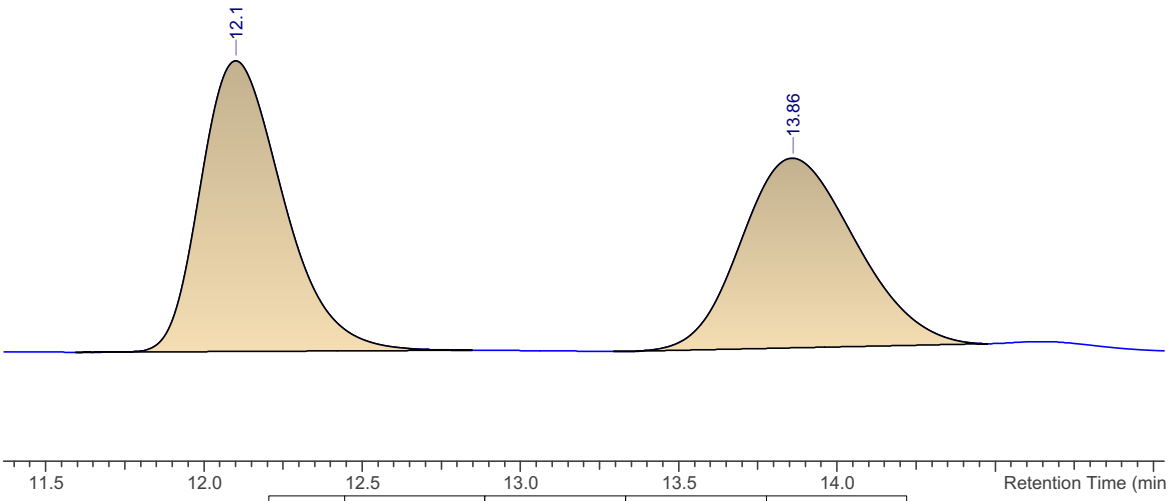
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	11.07	4612624.500	93.688	0.491
2	15.01	310777.563	6.312	0.638

Benzyl 7-(2-(mesitylthio)-2-oxoethyl)-6-azaspiro[3.5]nonane-6-carboxylate (233b)

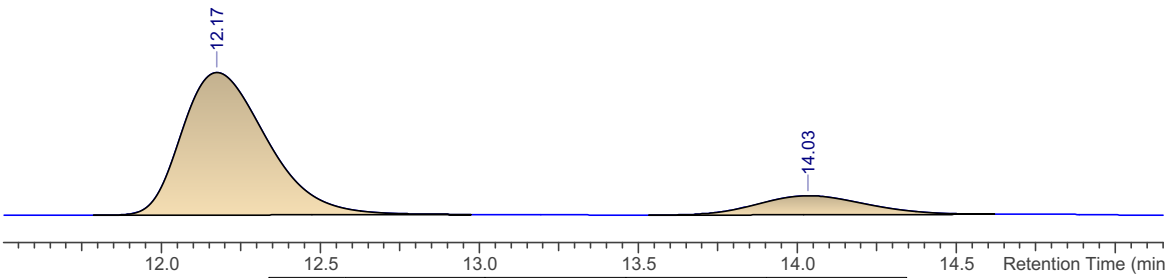


233b

HPLC conditions: Chiralpak ® IA Column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 40 °C, λ = 254 nm; tR 12.1 min (major), 14.0 min (minor) (*R*)-TRIP, octane, 95 °C, 24 h, e.r. = 85:15

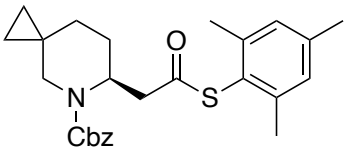


No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	12.10	3632919.250	52.481	0.475
2	13.86	3289396.500	47.519	0.673



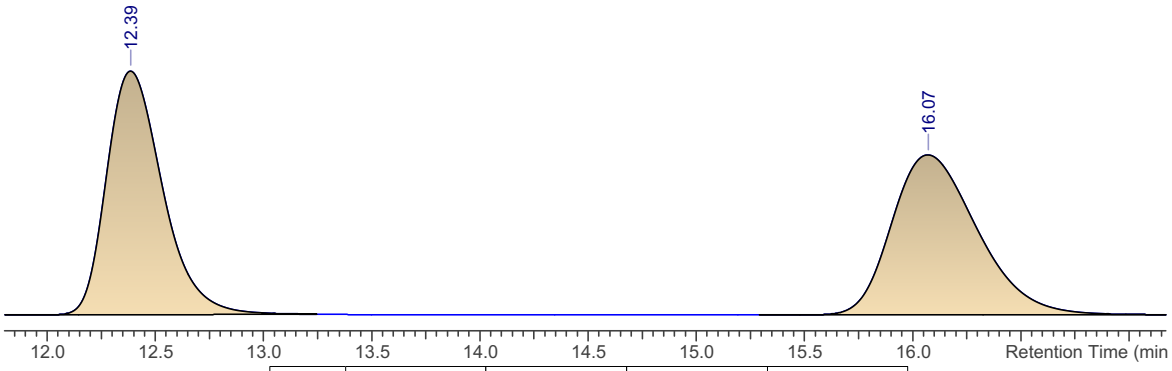
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	12.17	5435925.500	85.398	0.490
2	14.03	929465.813	14.602	0.636

Benzyl 6-(2-(mesitylthio)-2-oxoethyl)-5-azaspiro[2.5]octane-5-carboxylate (233c)

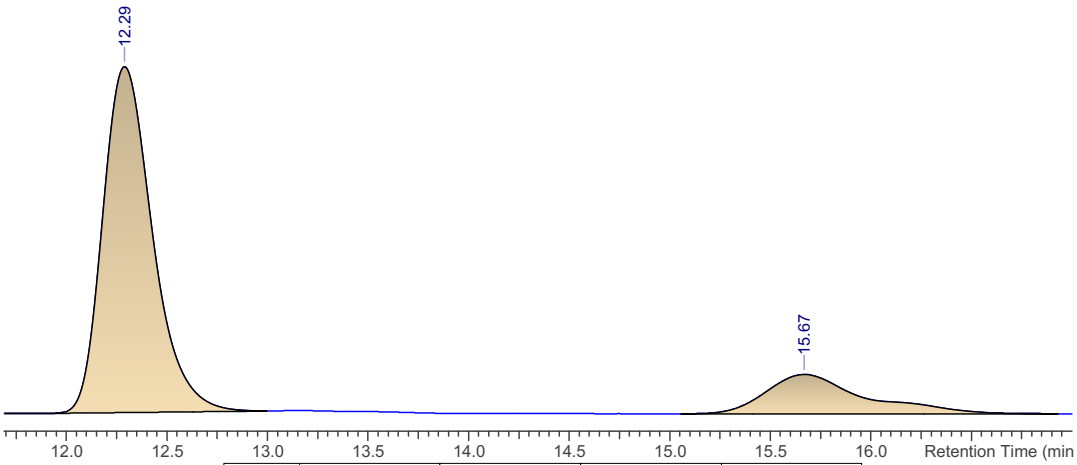


233c

HPLC conditions: Chiralpak ® IA Column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 40 °C, λ = 254 nm; tR 12.2 min (major), 15.6 min (minor) (*R*)-TRIP, octane, 95 °C, 24 h, e.r. = 82:18

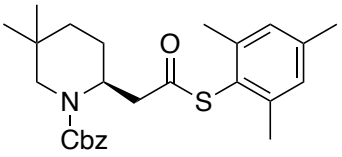


No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	12.39	3636244.750	49.869	0.467
2	16.07	3655409.750	50.131	0.724



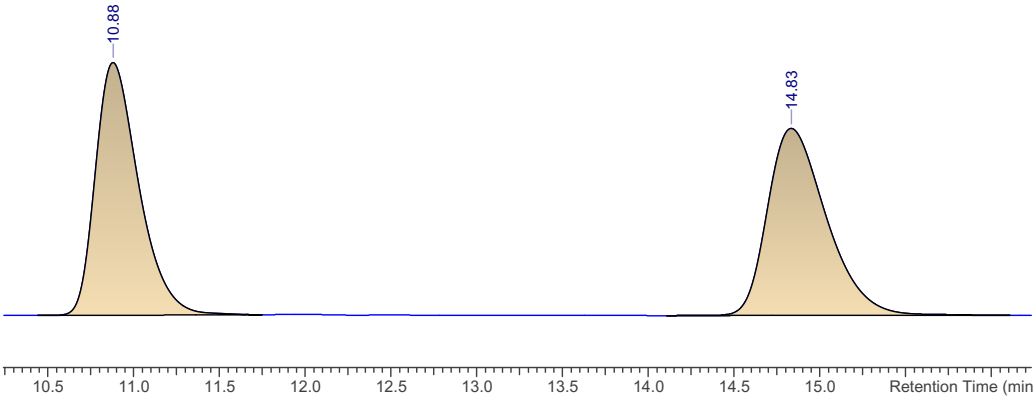
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	12.29	3081322.750	81.728	0.444
2	15.67	688902.250	18.272	0.769

Benzyl 2-(2-(mesitylthio)-2-oxoethyl)-5,5-dimethylpiperidine-1-carboxylate (233d)

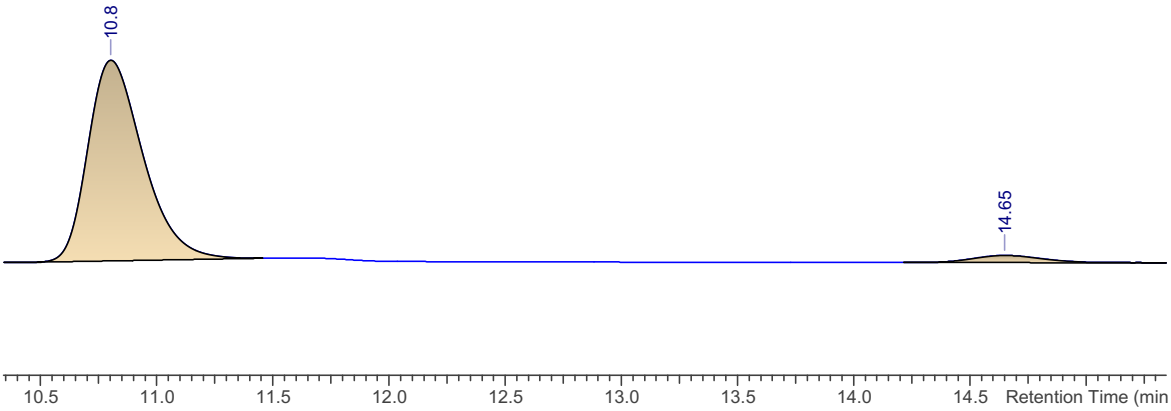


233d

HPLC conditions: Chiralpak ® IA Column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 40 °C, λ = 254 nm; tR 10.8 min (major), 14.6 min (minor) (*R*)-TRIP, octane, 95 °C, 24 h, e.r. = 96:4.



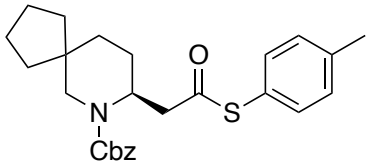
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	10.88	5537202.500	49.788	0.453
2	14.83	5584418.500	50.212	0.622



No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	10.80	5615645.500	95.710	0.428
2	14.65	251703.875	4.290	0.546

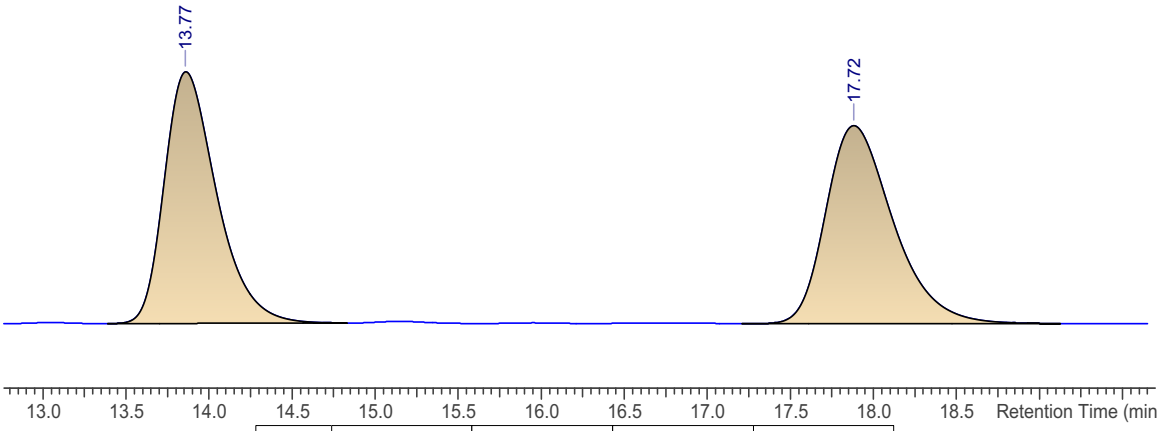
Substrate scope with *p*-Tol thioester

(*S*)-Benzyl 8-(2-oxo-2-(*p*-tolylthio)ethyl)-7-azaspiro[4.5]decane-7-carboxylate (235a)

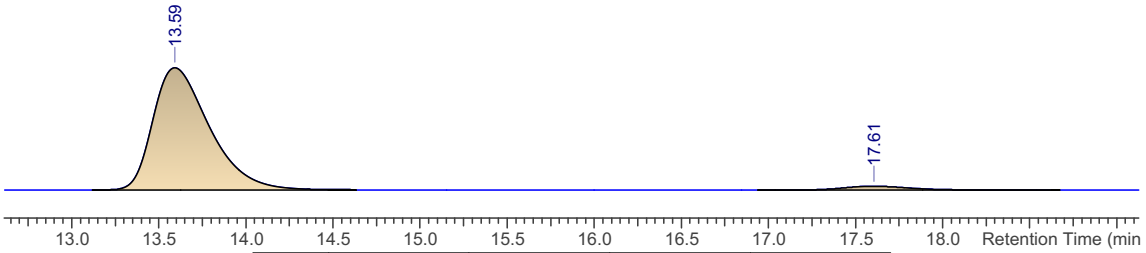


235a

HPLC conditions: Chiralpak ® IA Column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 40 °C, λ = 254 nm; tR 13.77 min (major), 17.72 min (minor) e.r. = 96:4

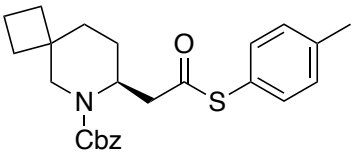


No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	13.77	4339710.500	49.719	0.555
2	17.72	4388849.000	50.281	0.714



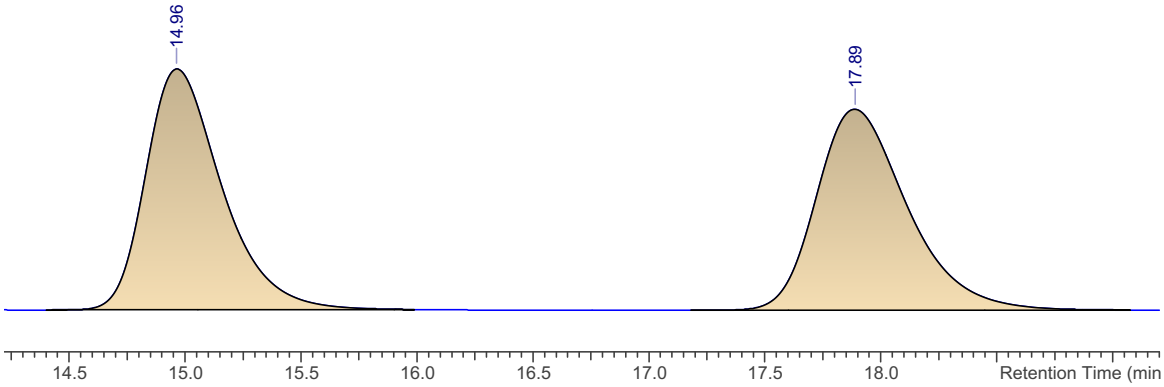
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	13.59	8679875.000	96.287	0.582
2	17.61	334694.563	3.713	0.689

(*S*)-Benzyl 7-(2-oxo-2-(p-tolylthio)ethyl)-6-azaspiro[3.5]nonane-6-carboxylate (235b)

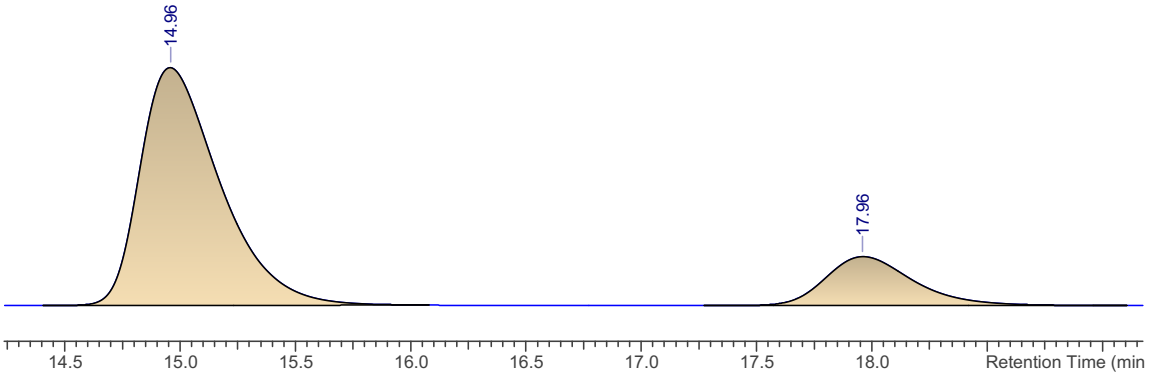


235b

HPLC conditions: Chiralpak ® IA Column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 40 °C, λ = 254 nm; tR 14.96 min (major), 17.96 min (minor) e.r. = 82:18.

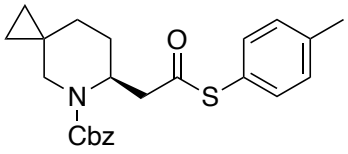


No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	14.96	4267824.500	50.034	0.586
2	17.89	4262097.500	49.966	0.704



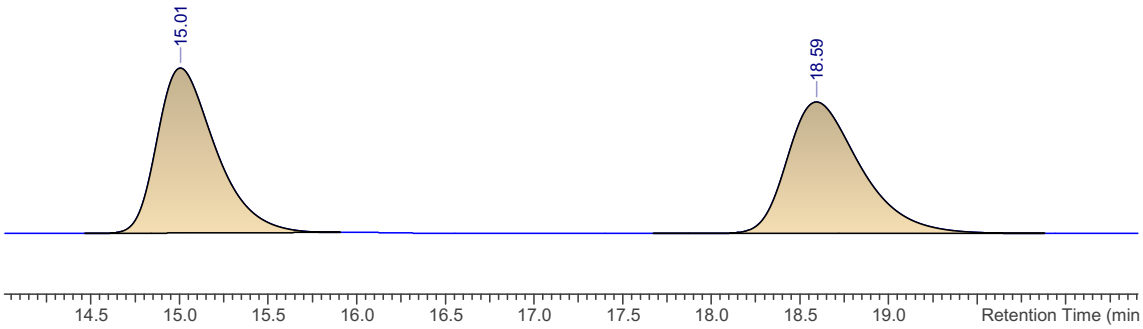
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	14.96	10361550.000	81.538	0.623
2	17.96	2346110.250	18.462	0.679

(*S*)-Benzyl 6-(2-oxo-2-(p-tolylthio)ethyl)-5-azaspiro[2.5]octane-5-carboxylate (235c)

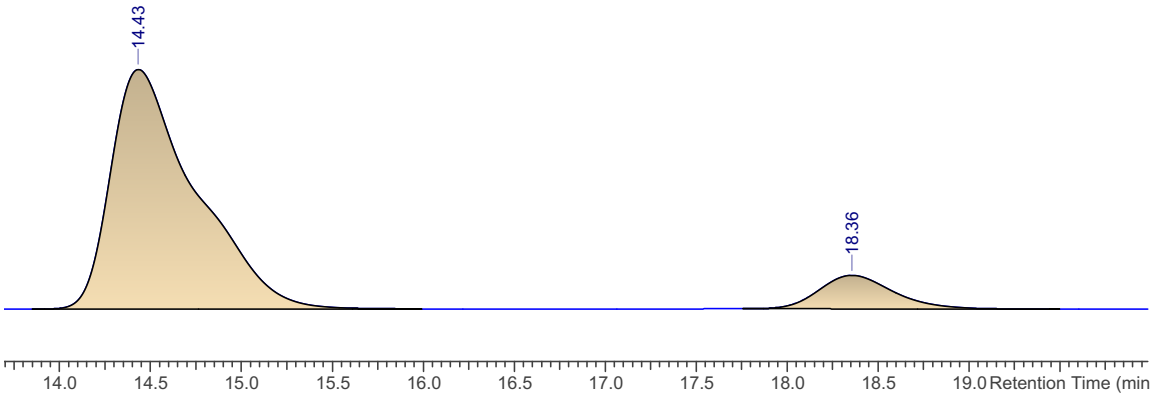


235c

HPLC conditions: Chiralpak ® IA Column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 40 °C, λ = 254 nm; tR 14.43 min (major), 18.36 min (minor) e.r. = 89:11

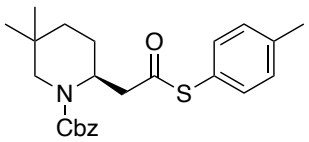


No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	15.01	7303541.500	50.069	0.590
2	18.59	7283321.000	49.931	0.736



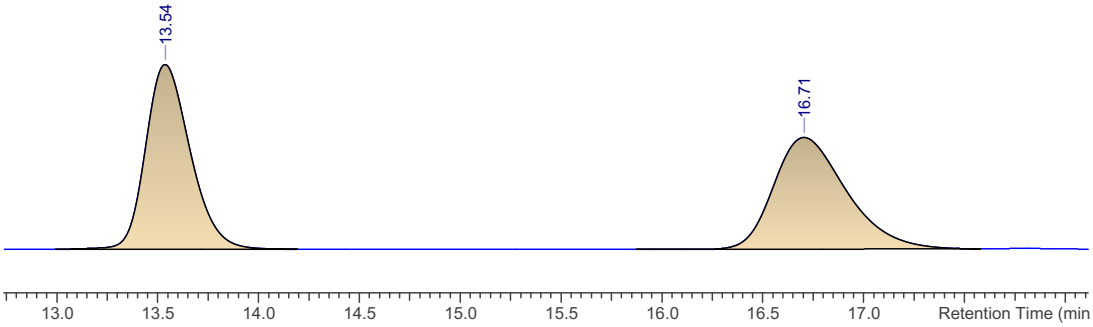
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	14.43	9134949.000	89.087	0.800
2	18.36	1119040.375	10.913	0.733

(*S*)-Benzyl 5,5-dimethyl-2-(2-oxo-2-(p-tolylthio)ethyl)piperidine-1-carboxylate (235d)

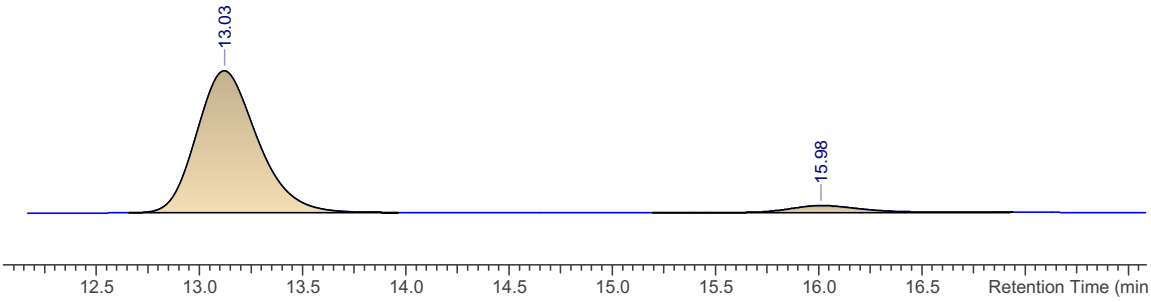


235d

HPLC conditions: Chiralpak ® IA Column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 40 °C, λ = 254 nm; tR 13.54 min (major), 16.71 min (minor) e.r. = 95:5

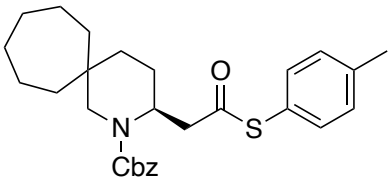


No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	13.54	5282031.000	50.351	0.399
2	16.71	5208444.500	49.649	0.651



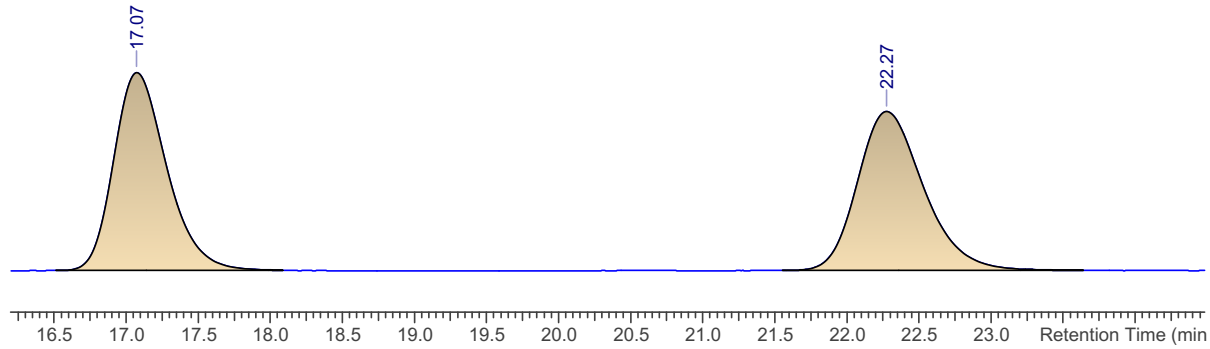
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	13.03	10260320.000	94.670	0.544
2	15.98	577684.375	5.330	0.618

(*S*)-Benzyl 3-(2-oxo-2-(p-tolylthio)ethyl)-2-azaspiro[5.6]dodecane-2-carboxylate (235f)

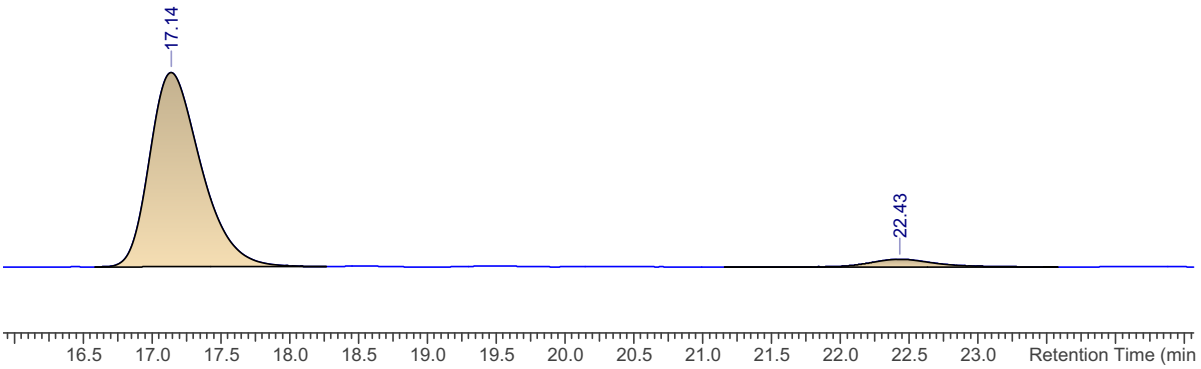


235f

HPLC conditions: Chiralpak ® IA Column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 40 °C, λ = 254 nm; tR 17.07 min (major), 22.27 min (minor) e.r. = 95:5

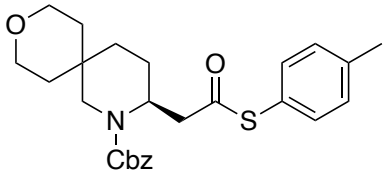


No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	17.07	2093842.875	49.943	0.662
2	22.27	2098596.000	50.057	0.825



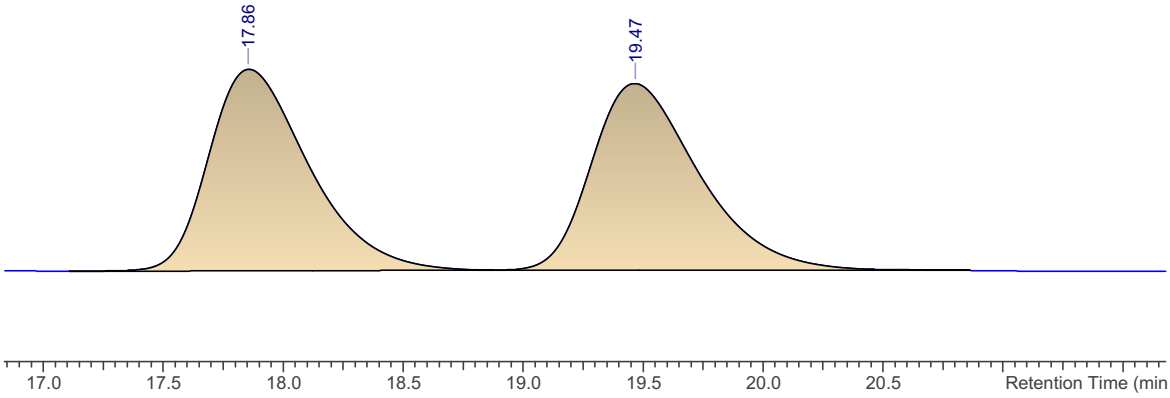
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	17.14	4523534.000	94.806	0.672
2	22.43	247808.266	5.194	0.836

(*S*)-Benzyl-3-(2-oxo-2-(p-tolylthio)ethyl)-9-oxa-2-azaspiro[5.5]undecane-2-carboxylate (235g)

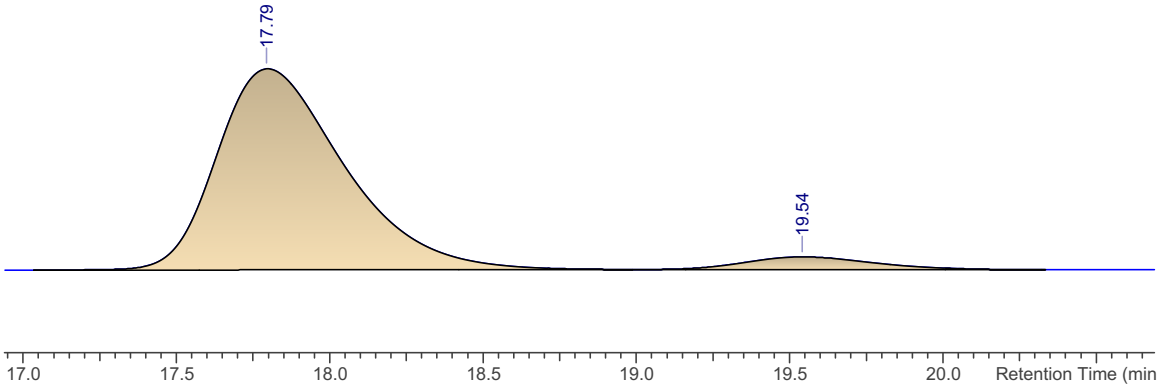


235g

HPLC conditions: Chiralpak ® IA Column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 40 °C, λ = 254 nm; tR 17.79 min (major), 19.54 min (minor) e.r. = 94:6.

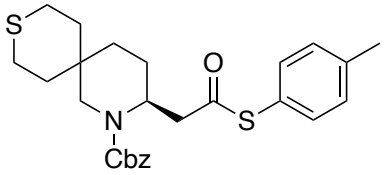


No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	17.86	7152566.500	50.054	0.753
2	19.47	7137064.000	49.946	0.808



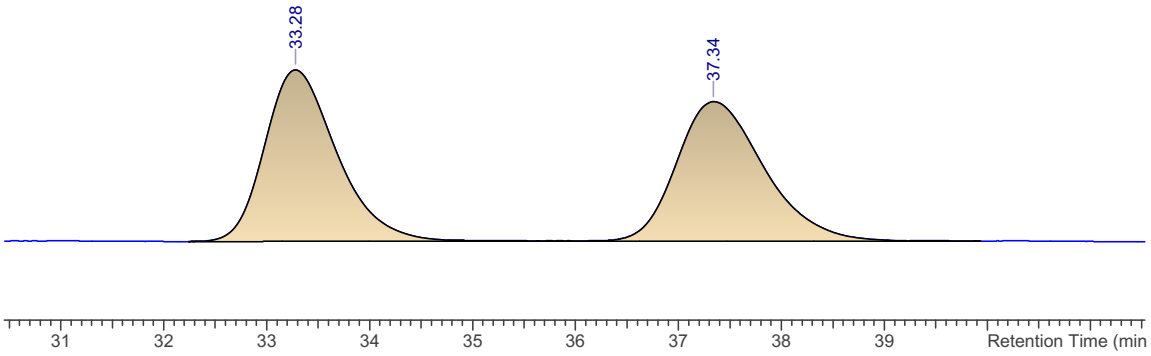
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	17.79	7691958.000	94.003	0.748
2	19.54	490726.250	5.997	0.768

(*S*)-Benzyl-3-(2-oxo-2-(*p*-tolylthio)ethyl)-9-thia-2-azaspiro[5.5]undecane-2-carboxylate (235h)

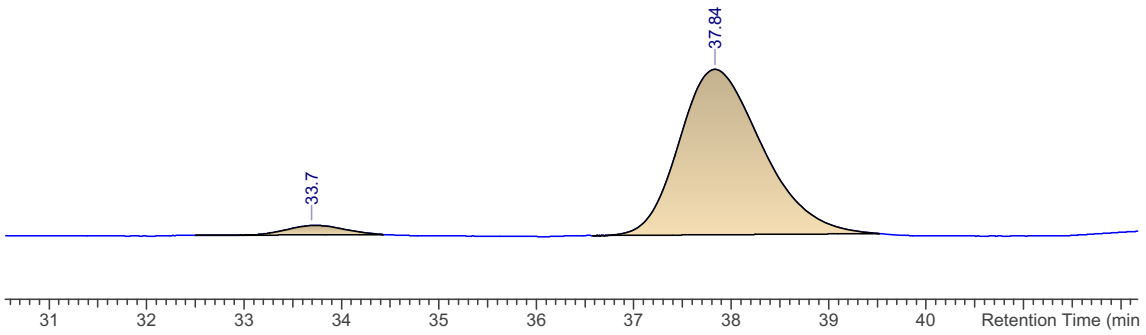


235h

HPLC conditions: Chiralpak ® IA Column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 40 °C, λ = 254 nm; tR 33.7 min (minor), 37.8 min (major) e.r. = 96:4

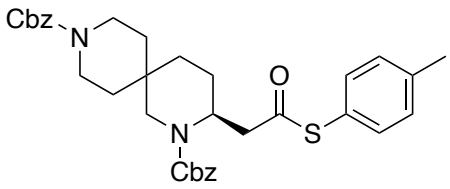


No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	33.28	9957055.000	50.324	1.256
2	37.34	9828861.000	49.676	1.535



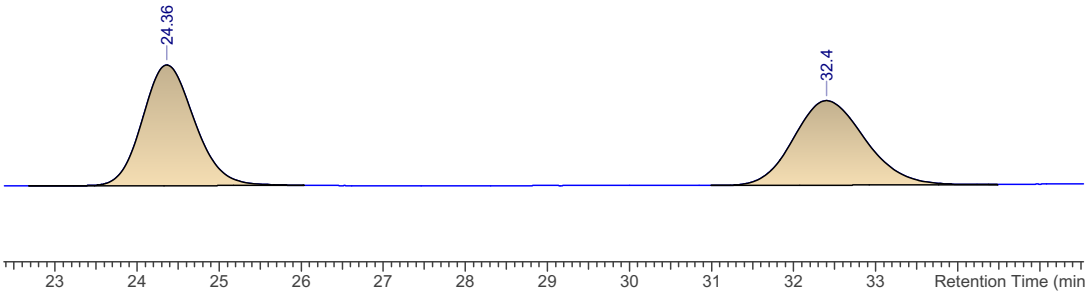
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	33.69	305050.063	3.797	1.117
2	37.83	7728554.000	96.203	1.551

(*S*)-Dibenzyl-3-(2-oxo-2-(p-tolylthio)ethyl)-2,9-diazaspiro[5.5]undecane-2,9-dicarboxylate (235i)

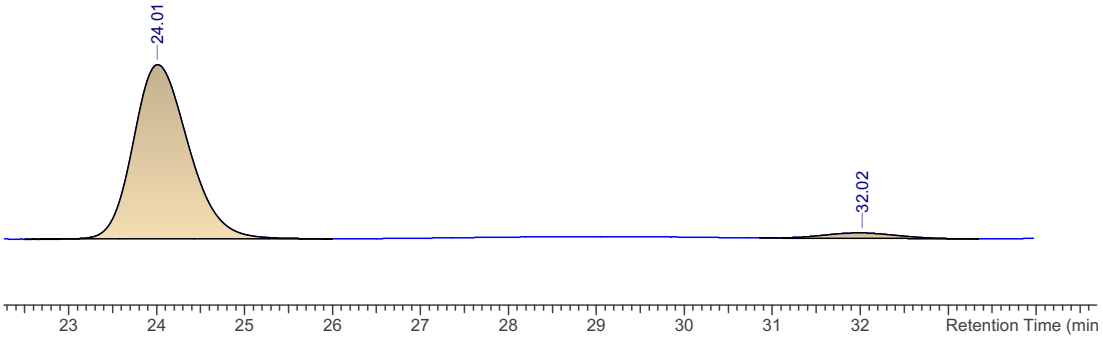


235i

HPLC conditions: Chiralpak ® IB Column, hexane/2-propanol (80:20), flow rate: 1.0 mL/min, 40 °C, λ = 210 nm; tR 24.01 min (major), 32.02 min (minor) e.r. = 96:4

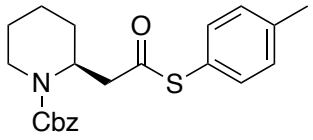


No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	24.36	6668052.500	51.031	1.152
2	32.40	6398717.500	48.969	1.593



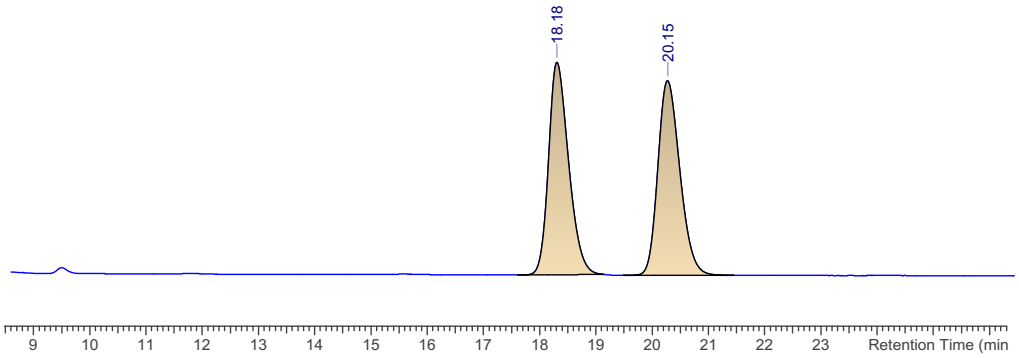
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	24.01	19113494.000	96.104	1.140
2	32.02	774905.063	3.896	1.518

(*S*)-Benzyl 2-(2-oxo-2-(p-tolylthio)ethyl)piperidine-1-carboxylate (235k)

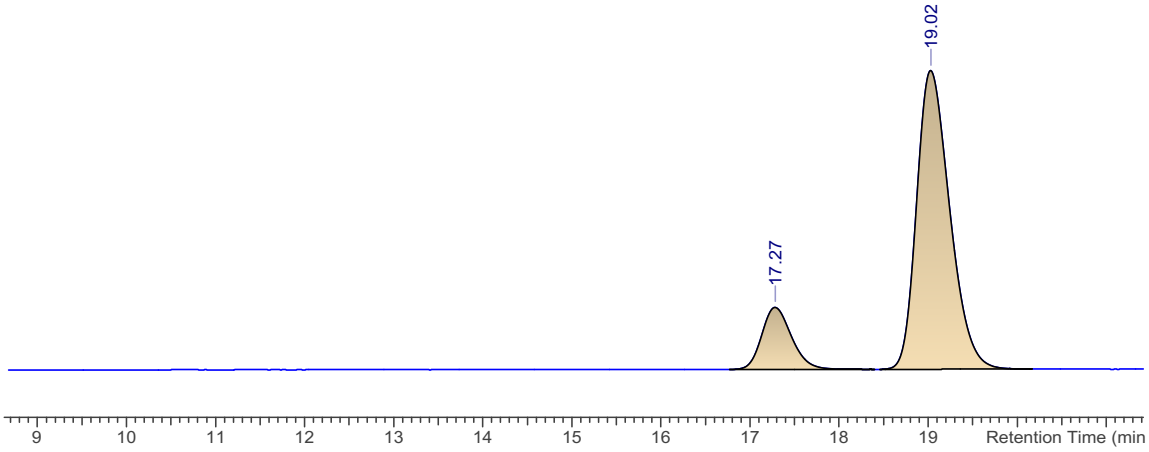


235k

HPLC conditions: Chiralpak ® IB Column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 40 °C, λ = 254 nm; tR 17.27 min (minor), 19.02 min (major) e.r. = 84:16



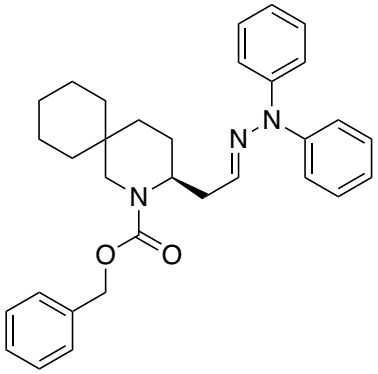
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	18.18	3614383.750	49.876	0.638
2	20.15	3632293.250	50.124	0.709



No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	17.27	1043379.250	15.725	0.605
2	19.02	5591787.500	84.275	0.678

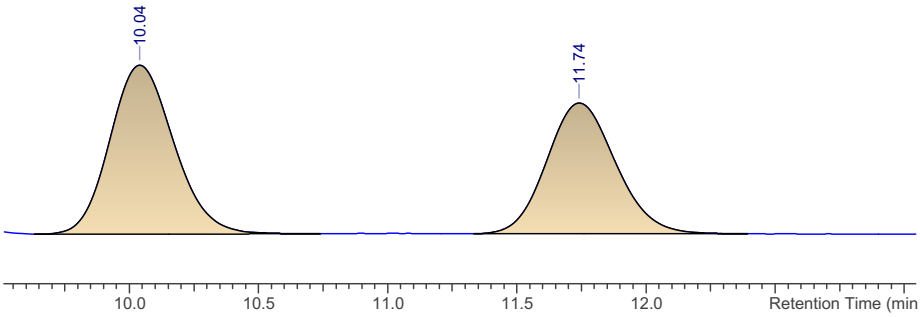
Aldehyde

(*E*)-Benzyl-3-(2-(2,2-diphenylhydrazono)ethyl)-2-azaspiro[5.5]undecane-2-carboxylate (264)



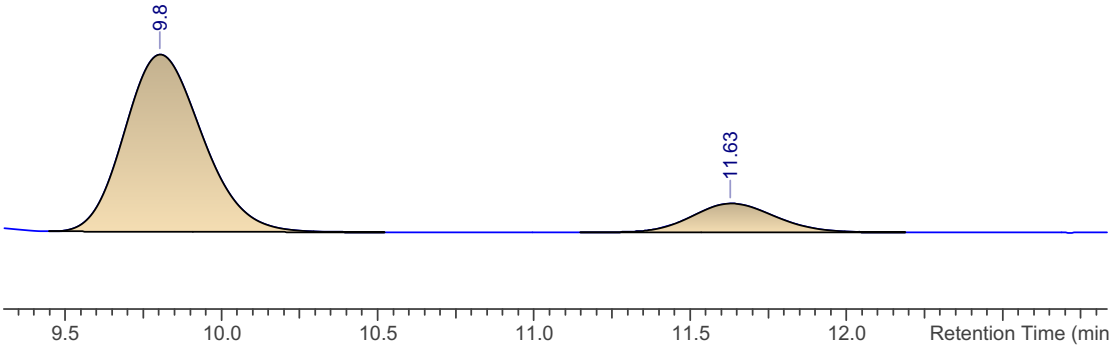
264

HPLC conditions: Chiralpak ® IA Column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 25 °C, λ = 254 nm; tR 9.8 min (minor), 11.6 min (major)



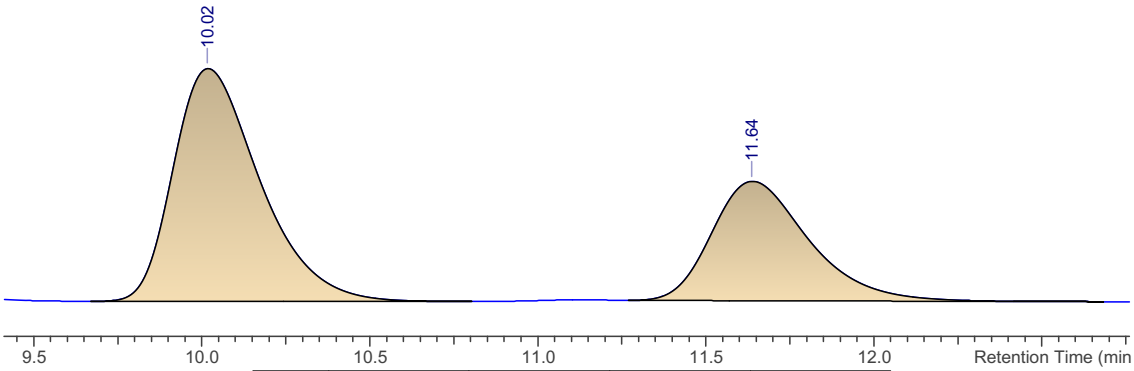
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	10.04	262880.656	54.511	0.453
2	11.74	219368.844	45.489	0.489

(*R*)-TRIP e.r. = 85:15



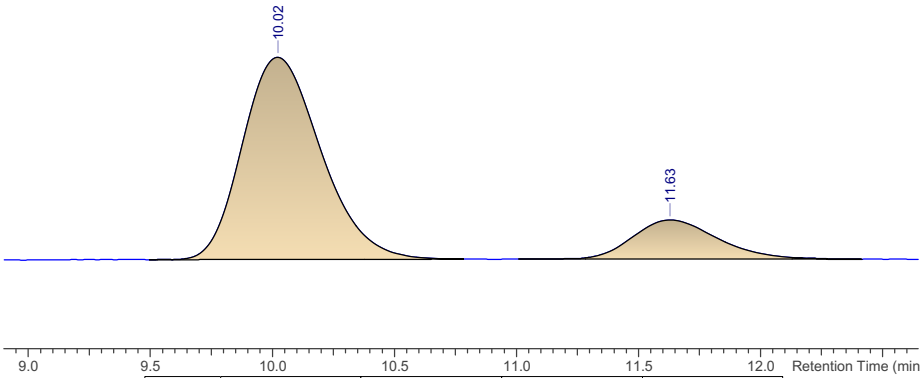
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	9.80	530858.188	84.936	0.458
2	11.63	94149.320	15.064	0.494

(*R*)-TiPSY e.r. = 63:37



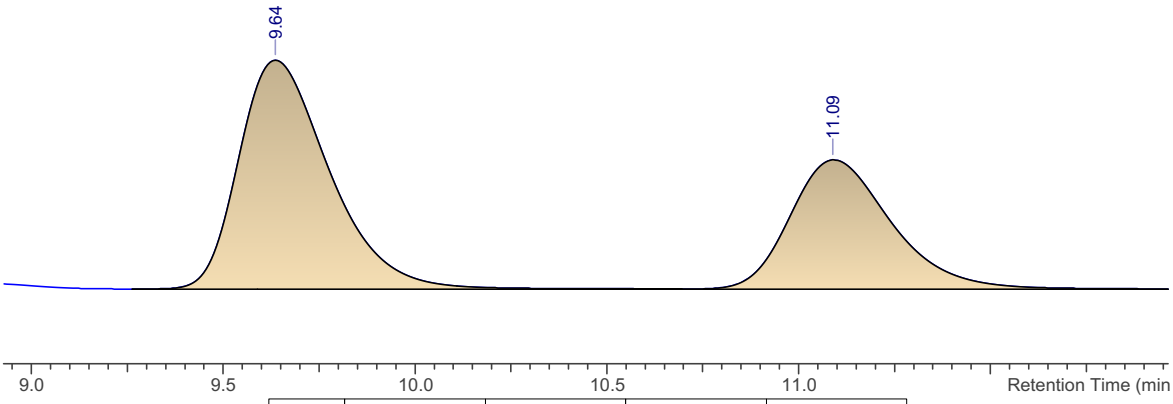
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	10.02	8073929.000	63.461	0.465
2	11.64	4648652.000	36.539	0.516

(*R*)-Anth e.r. = 83:17



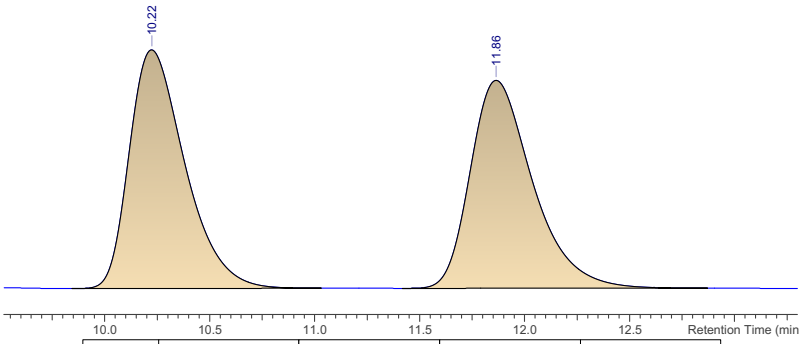
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	10.02	771533.250	82.617	0.591
2	11.63	162332.703	17.383	0.636

(*R*)-Phen e.r. = 61:39



No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	9.64	9466697.000	61.187	0.425
2	11.09	6005076.000	38.813	0.474

(*R*)-VAPOL e.r. = 50:50



No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	10.22	8649588.000	50.507	0.479
2	11.86	8475915.000	49.493	0.530

7. Abbreviations

(*R*)-Anth	(*R*)-3,3'-bis(9-anthracenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate
(*R*)-DTBM-SEGPHOS	(*R*)-(−)-5,5'-Bis[di(3,5-di-tert-butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole
(*R*)-Phen	(*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
(*R*)-VAPOL	(*R*)-2,2'-Diphenyl-3,3'-(4-biphenanthrol)
1,2-DCE	1,2-dichloroethane
2-MeTHF	2-methyltetrahydrofuran
4 Å M.S.	4 Ångstrom molecular sieves
AchE	acetylcholinesterase inhibition
ACP	acyl carrier protein
APCI	atmospheric pressure chemical ionization
aq	aqueous
Ar	aryl
atm	atmospheres
BHT	butylated hydroxy toluene (2,6-di-t-butyl-4-methylphenol)
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Boc	tert-butyloxycarbonyl
brsm	based on recovered starting material
cat.	catalyst
Cbz	carboxybenzyl
COSY	corelated spectroscopy
CPA	chiral phosphoric acid
CSA	camphor sulfonic acid
CSO	camphorsulfonyl oxaziridine
d	doublet
d.r.	diastereomeric ratio
DCM	dichloromethane
dd	doublet of doublet
ddt	doublet of doublet of triplet
DEPT	distortionless enhancement by polarization transfer
DFT	Density Function Theory
DMAP	4-dimethylaminopyridine
DME	dimethylether

DMF	dimethyl formamide
DMSO	dimethylsulfoxide
DPPA	diphenylphosphoryl azide
e.r.	enantiomeric ratio
ee	enantiomeric excess
eq.	equivalents
ESI	electron spray ionisation
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
FDA	U.S. Food and Drug Administration
Fmoc	fluorenylmethyloxycarbonyl chloride
gem	geminal
HG-II	Hoveyda Grubbs 2nd generation
HMBC	heteronuclear multiple bond coherence
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple quantum coherence
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz
h	hours
i-Mes	Isopropyl mesityl
i-Pr	isopropyl
IPA	isopropyl alcohol
IR	infrared
J	coupling constant
LDA	lithium diisopropylamide
m	multiplet
m.p.	melting point
Me	methyl
MeOH	methanol
Mes	mesityl (1,3,5-trimethylbenzene)
mesityl	1,3,5-trimethylbenzene
mol	molar
Ms	mesyl
n-Bu	*n*-butyl
NaHMDS	sodium bis(trimethylsilyl)amide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
OMe	methoxy
OTf	trifluoromethanesulfonate
p-NO_2	para-nitro
p-Tolyl	para-tolyl
$Pd(dba)_2$	Bis(dibenzylideneacetone)palladium(0)

Ph	phenyl
PMI	Principal moments of inertia
PMP	para-methoxyphenyl
PNP	para-nitrophenyl
ppm	parts per million
quant.	quantitative
rac-	racemic
rt	room temperature
s	singlet
SCF_3	trifluoromethylthio
S_N2	substitution nuclear bimolecular
STAB	sodium triacetoxyborohydride
t	triplet
t-Bu	tert-butyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TIPSCl	triisopropylsilyl chloride
TLC	thin layered chromatography
TMS	trimethylsilyl
μ	micro

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