NEW METHODS FOR

COMPLEX MOLECULE SYNTHESIS

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the degree of Doctor of Philosophy
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Declaration of Authorship

I declare that the work contained within this thesis, submitted by myself for the degree of Doctor of Philosophy is my own original work, except where due reference is made and has not previously been submitted by me for a degree at this or any other university.

Rafid Saad Dawood *Prof. Robert A. Stockman*

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Abstract

This thesis is split into three chapters describing syntheses of two types of the pyrrolidine chemical scaffolds and total synthesis of the natural product (+)-monomorine.

The first chapter of this work presents a simple and efficient asymmetric synthesis of novel sp^3-rich pyrrolidine chemical scaffolds over five steps starting from simple ketones. The key step includes using *tert*-butanesulfinamide as a chiral auxiliary to achieve an asymmetric Tsuji-Trost allylation. Following this, cross-metathesis coupling of allyl derivatives with an acrylate ester affords α,β-unsaturated esters. Reduction of the sulfinimine stereoselectively results in the corresponding amide derivatives. The sulfinamides were then employed to synthesise a range of pyrrolidine scaffolds *via* cyclisation under basic conditions. Finally, by removing the directing group and functionalising the ester group, the resulting scaffold core can be further derivatised.

In the second chapter, some of the chemistry of pyrrolidine chemical scaffold that was achieved in the first chapter is used towards an attempted total synthesis of (+)-monomorine, a natural product isolated from the pharaoh ant (*Monomorium pharaonis* L). In addition, different synthetic routes have been employed as well towards achieving this synthesis.

The third and last chapter of this thesis outlines the first attempts to synthesise the spiro-pyrrolidine scaffold starting from 4-bromobutene or 1,7-dichloroheptan-4-one. This type of chemical scaffold will be useful as a versatile intermediate for drug discovery *via* diversification at three different points on *N* atoms. The synthetic route required preparation of protected azocan-5-one (eight-membered ring) as a key material in this route. Different reaction conditions have been attempted; involving investigations into the catalyst, temperature, base, stoichiometry and reaction time. It was observed that the cyclisation to give the desired eight-membered ring is very slow and the yield was low.

Abbreviations

$[\alpha]_D$	specific rotation
α	alpha
Å	angstrom
app.	apparent
β	beta
Boc	*tert*-butyloxycarbonyl
Bpin	bis(pinacolato)diboron
9-BBN	9-borabicyclo[3.3.1]nonane
bpy	2,2’-bipyridine
δ	chemical shift in ppm
CDI	carbonyldiimidazole
ca	circa (Latin = about or around)
Conc.	concentration
COD	1,5-cyclooctadiene
cbz	carboxybenzyl
Cy	cyclohexyl
DMSO	dimethyl sulfoxide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone
DMAP	4-dimethylaminopyridine
de	diastereomeric excess
d	doublet
DNA	deoxyribonucleic acid
DIBAL-H	diisobutylaluminium hydride
DIAD	diisopropyl azodicarboxylate
DME	dimethoxyethane
DMF	dimethylformamide

DMPA	dimethylolpropionic acid
DCE	dichloroethane
DCM	dichloromethane
DCC	*N*,*N*'-dicyclohexylcarbodiimide
dppp	1,3-bis(diphenylphosphino)propane
dppe	1,2-bis(diphenylphosphino)ethane
dppb	1,4-bis(diphenylphosphino)butane
dppf	1,1'-bis(diphenylphosphino)ferrocene
Dpp	diphenylphosphinic
DPPP	diphenyl-1-pyrenylphosphine
Dppbenz	1,2-bis(diphenylphosphanyl)benzene
dr	diastereoisomer
DEAD	diethyl azodicarboxylate
D	dextrorotatory
eq.	equivalent
EDCl	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDG	electron-donating group
ESI	electrospray ionization
ee	enantiomeric excess
er	enantiomeric ratio
E/Z	*trans/cis*
FDA	food and drug administration
FTIR	fourier-transform infrared spectroscopy
γ	gamma
GC	gas chromatography
HMDS	hexamethyldisilamide
HIV	human immunodeficiency virus
HOBt	1-hydroxybenzotriazole hydrate

HRMS	high resolution mass spectrometry
HMPA	hexamethylphosphoramide
Hünig's base	*N,N*-diisopropylethylamine (DIPEA)
h	hour
i	iso
Hz	hertz
HPLC	high performance liquid chromatography
i.e.	for example
IUPAC	international union of pure and applied chemistry
J	coupling constant
LCMS	liquid chromatography-mass spectrometry
LDA	lithium diisopropylamide
liq.	liquid
LAH	lithium aluminium hydride
L	levorotary
M	molarity of solution
Ms	mesylate
MS	mass spectrometry
MOM	methoxymethyl
m	multiplet
m	meta
min.	minute(s)
MHz	mega hertz
mL	millilitre
m.p.	melting point
MW	microwave
MMPP	magnesium monoperoxyphthalic acid
m-CPBA	*m*-chloroperbenzoic acid

NMDA	*N*-methyl-D-aspartate
NOESY	nuclear overhauser effect spectroscopy
NMI	*N*-methylimidazole
n	normal
Naph.	naphthyl
NCS	*N*-chlorosuccinimide
Nu	nucleophile
NMR	nuclear magnetic resonance
Ph	phenyl
Pro-Leu-Gly	proline-Leucine-Glycine
P	para
psi	pound per square inch
ppm	part per million
PCC	pyridinium Chlorochromate
PTSA	*p*-toluenesulfonic acid
r.t.	room temperature
s	singlet
S	sinister (Latin = left)
RSM	recovered of starting material
R	rectus (Latin = right)
$Rh(acac)(Co)_2$	(acetylacetonato)dicarbonylrhodium(I)
L-Selectride	lithium *tri-sec*-butylborohydride
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl
TMEDA	tetramethylethylenediamine
Temp.	temperature
THF	tetrahydrofuran
Ts	tosyl
T.S	transition state

TMM	trimethylenemethane
TFA	trifluoroacetic acid
Tf	trifluoromethanesulfonyl
TBAI	*tetra*-*n*-butylammonium iodide
TBAH	*tetra*-*n*-butylammonium hydroxide
TBAF	*tetra*-*n*-butylammonium fluoride
TBACl	*tetra*-*n*-butylammonium chloride
TLC	thin layer chromatography
TBS	*tert*-butyldimethylsilyl
vs.	versus
W	watt
*	chiral centre

Contents

1. Asymmetric synthesis of pyrrolidine containing chemical scaffolds through the Tsuji-Trost allylation

1.1. Introduction

1.1.1. Sulfinimines

The chiral centre on the sulfur atom is due to the presence of a lone pair, which provides the sulfur a tetrahedral conformation. Chiral sulfoxides have been represented in different ways, but the convention for this report is to delete the lone pair and show the chiral centre *via* the oxygen atom (Figure 1).

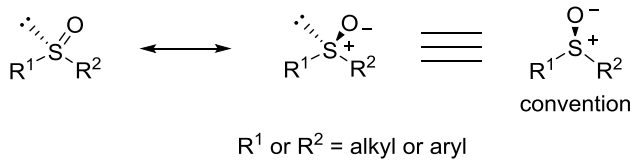
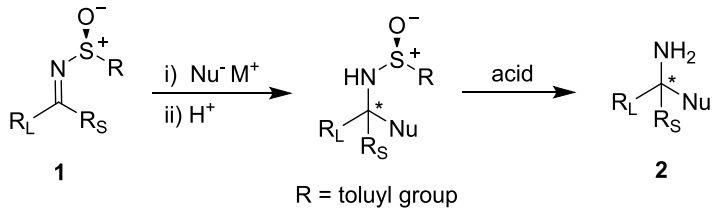


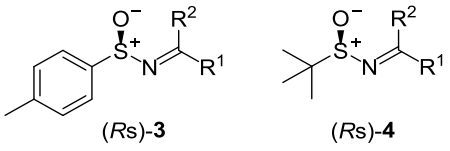
Figure 1: Representation of the chiral sulfoxide group

The sulfinyl is a polar functional group and the length of the S-O bond is about 1.5 Å.[1] The sulfinimine group is more stable towards hydrolysis than other imine-type groups. The stereoselectivity of a nucleophilic addition to sulfinimines can be rationalised by the presence of a stereocentre at α-position to the nitrogen atom. The sulfinyl group shields one face of the imine from nucleophilic attack (Scheme 1). Davis *et al*.[2,3] employed the sulfinimine compounds **1** as intermediate in the synthesis of chiral amines **2**.



Scheme 1: Preparation of chiral amine **2** using sulfinimine **1**

Chiral amines are an important class of organic compounds for the synthesis of complex natural products,[4] materials synthesis[5] and drug discovery.[6] For these reasons, methods to prepare enantiomerically pure compounds that contain an amine functionality have been developed. Chiral sulfinimines have come to the fore as versatile chiral building blocks for the preparation of chiral amines. Davis and co-workers[2] pioneered the use of sulfinimines and developed *p*-toluenesulfinyl imines (*p*-TS-imines) **3** (Figure 2). *Tert*-butanesulfinyl imines (^{t}BS-imines) **4** were later developed by Ellman and co-workers.[7] Many factors have led to the popularity of *p*-TS and ^{t}BS imines in asymmetric reactions, such as the commercial availability of both enantiomers of these two compounds, the wide variety of synthetic methods available from which to prepare amines and their stability and ease of storage as many are crystalline.[8-16] Furthermore, both aromatic and enolisable aliphatic sulfinimines are much more stable to hydrolysis, less prone to tautomerisation and more electrophilic than *N*-alkyl/aryl imines (due to the significant partial positive charge on the sulfur atom) than other imines. Thus, increase in electrophilicity leads to activation of nucleophilic additions by a wide range of reagents (without epimerisation) such as, organo-lithium, -zinc, -magnesium and many others, as well as hydride reagents ($NaBH_4$, $LiAlH_4$, DIBAL-H, L-Selectride and others).



R^1 = H, alkyl or aryl
R^2 = alkyl or aryl

Figure 2: *p*-Toluenesulfinimine **3** and *tert*-butylsulfinimine **4**

Most often, sulfinimines derived from aromatic aldehydes are solids at room temperature while aliphatic sulfinimines are generally obtained as an oil phase. Aliphatic sulfinimines are less stable than aromatic sulfinimines, but no major decomposition is seen before several months.[17] The stability of the aromatic sulfinimines is rationalised by the conjugation of the aromatic ring with the carbon-nitrogen double bond. Thus, the aromatic sulfinimines can be stored in the refrigerator with no significant decomposition.[17] Isolation and purification of both sulfinimines have been achieved easily using conventional silica gel chromatography.[17] *N*-Sulfinyl aldimines were observed as a single isomer at room temperature. Whereas, *N*-sulfinyl ketimines exist as both *E* and *Z* isomers despite planar inversion is noticed. X-ray studies and NMR experiments have shown that the *E*-geometry is favoured.[18]

Davis *et al*.[18] through work on *p*-toluenesulfinyl imines indicated that sulfinimines prefer *E*-geometry due to electrostatic repulsion between the nitrogen lone pair and the oxygen lone pair. Both the R group and the *p*-toluenesulfinyl group prefer to be in the most thermodynamically stable conformation with the less steric congestion. In addition, the imine hydrogen and sulfur oxygen atoms were not aligned and the hydrogen bond length with the oxygen is too large (2.736 Å) to explain the selectivity towards the *E*-isomer (Figure 3).

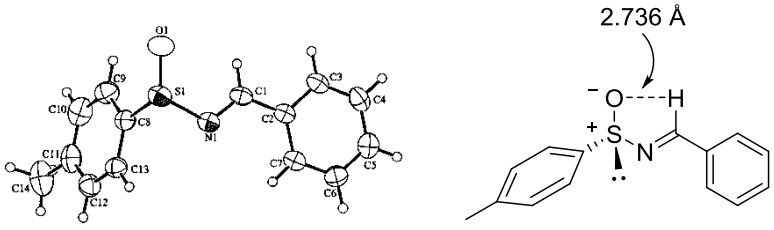


Figure 3: X-ray structure of (*S*,*E*)-*N*-benzylidene-4-methylbenzenesulfinamide[18]

1.1.1.1. Preparation of sulfinimine compounds

There are three methods commonly used to prepare chiral sulfinimines which include, iminolysis of sulfinate esters,[8,19,20] asymmetric oxidation[10,21] and condensation of a sulfinamide with a carbonyl compound, for example aldehydes and ketones (Figure 4).[18,22,23]

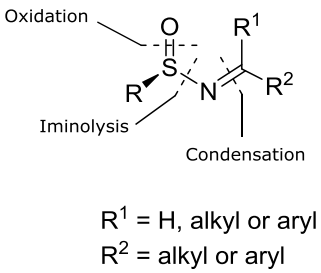
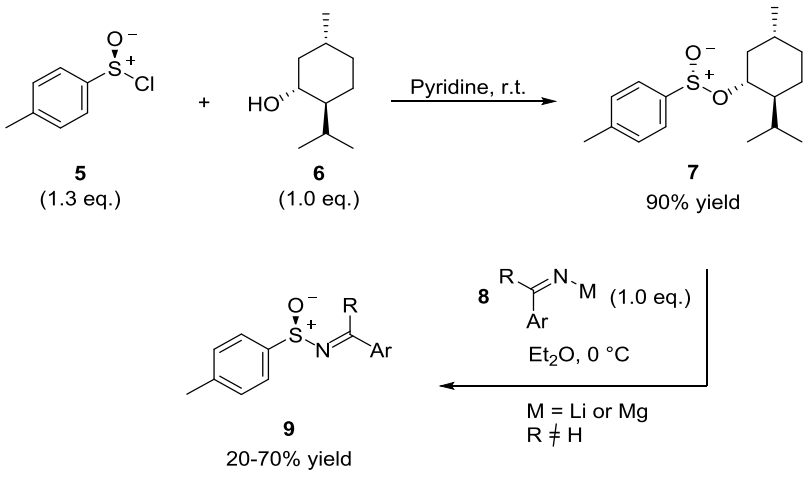


Figure 4: Synthesis of chiral sulfinimines

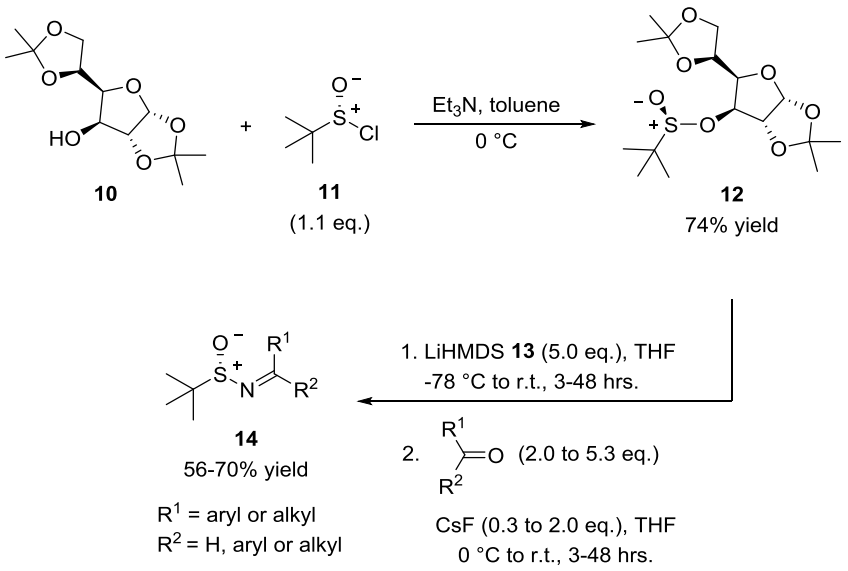
1.1.1.1.1. Iminolysis

The first asymmetric synthesis of a chiral sulfinimine was performed by Cozzi and co-workers[8] using (-)-(*S*)-menthyl *p*-toluenesufinate (Andersen's reagent) **7**, which was prepared by reacting *p*-tolylsulfinyl chloride **5** with (-)-menthol **6**.[24,25] Treatment of **7** with metal ketimines **8** gave the corresponding sulfinimines **9** in an enantiomerically pure form in modest to good yields (Scheme 2).[8]



Scheme 2: Typical iminolysis of Andersen's reagent **7** with metal amides **8**

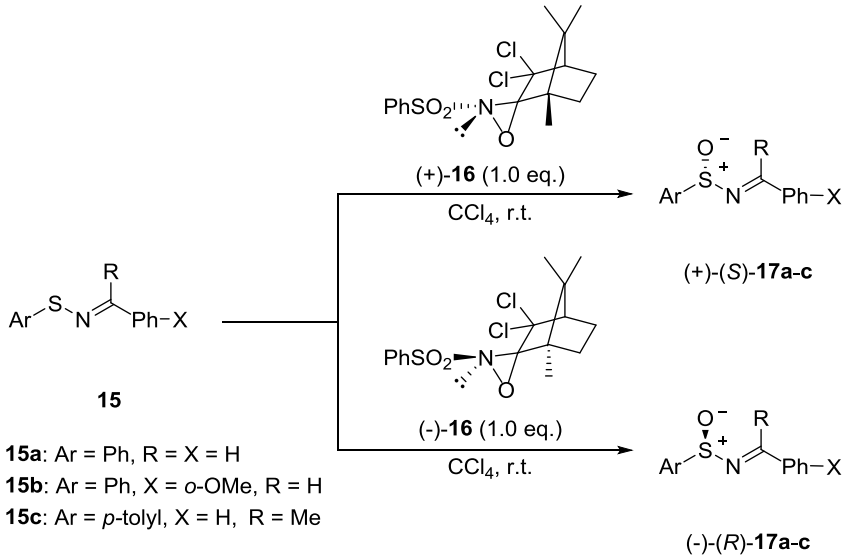
Moreover, in 1996, Cruz and co-workers[26] prepared ^{t}BS-imines **14** in a high enantiopurity. This was done using diacetone-D-glucose (DAG) *tert*-butanesulfinate esters **12**, which was prepared *via* treatment of diacetone-D-glucose (DAG) **10** with *tert*-butanesulfinyl chloride **11**.[19] Compound **12** was reacted with LiHMDS **13**, then treated with various aldehydes and ketones in the presence of cesium fluoride (CsF) to give **14** in yields ranging from 56 to 90% (Scheme 3).[26]



Scheme 3: Preparation of ^{t}BS-imine **14** using diacetone-D-glucose **10**

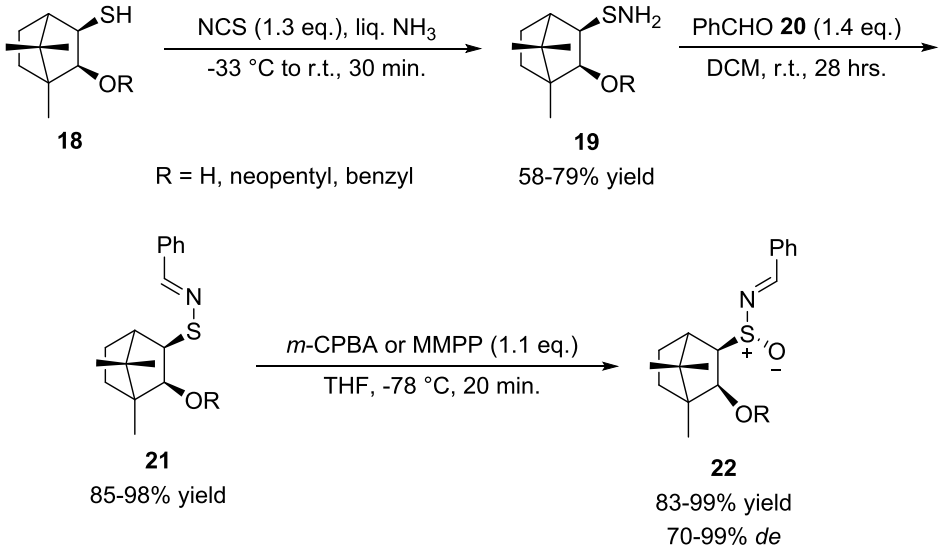
1.1.1.1.2. Oxidation

In 1974, Davis, Friedman and Kluger,[2] reported the first oxidation of the sulfenamides to the corresponding sulfinimines in a racemic mixture using *m*-CPBA. Whereas, the first asymmetric oxidation of sulfenimines to give enantiomerically pure sulfinimine compounds was achieved by Davis *et al*. in 1992.[21] This methodology includes oxidation of sulfenimines **15a**-**c** with stoichiometric amounts of a chiral oxidant *N*-(*R,S*)-9-(phenylsulfonyl)(3,3-dichlorocamphoryl)oxaziridine **16**. Sulfinimines **17a**-**c** were purified by flash chromatography in very good to excellent yields (72-95%) with 88-90% of *ee*. The *ee* was improved to >97% *via* recrystallisation from *n*-hexane (Scheme 4).[21]



Scheme 4: First asymmetric oxidation of sulfenimines **15** to sulfinimines **17**

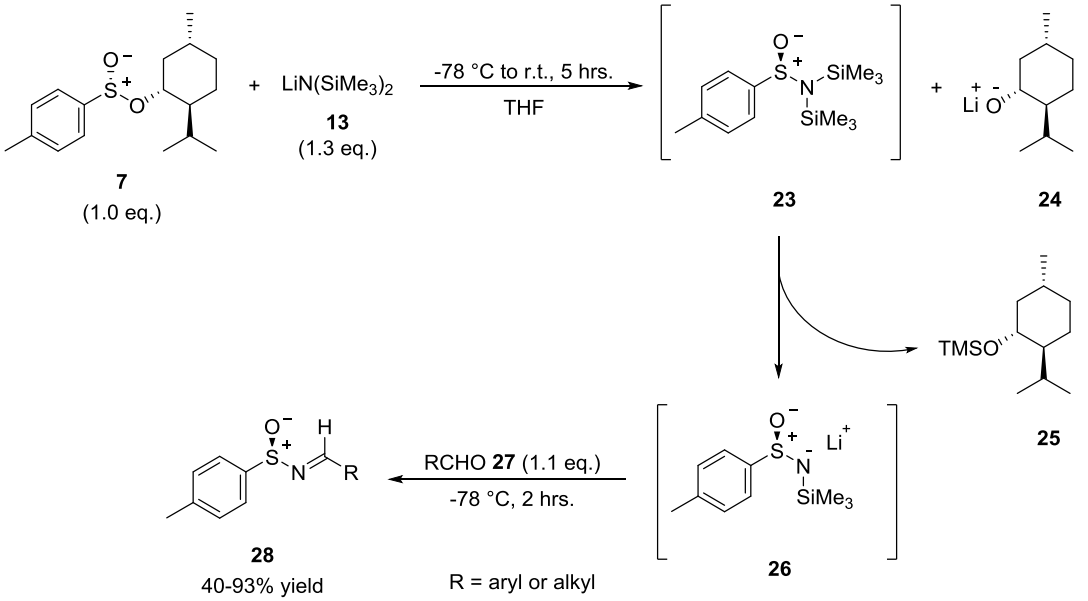
Another asymmetric oxidation of sulfenimines has been reported by Yang *et al*.[10] which used mercapto chiral auxiliaries derived from camphor **18**. When **18** was treated with liquid ammonia in the presence of *N*-chlorosuccinimide, sulfenamides **19** were formed and following condensation with benzaldehyde **20** afforded sulfenimines **21** in very good to excellent yields (85-98%). The stereoselective oxidation of **21** was achieved by two oxidants, *m*-CPBA or MMPP. Both oxidants gave chiral sulfinimines **22** in very good yields (83-99%) and high *de* (70-99%) (Scheme 5).[10]



Scheme 5: Asymmetric synthesis of sulfinimines **22** *via* oxidation of sulfenimines **21** using mercapto chiral auxiliaries

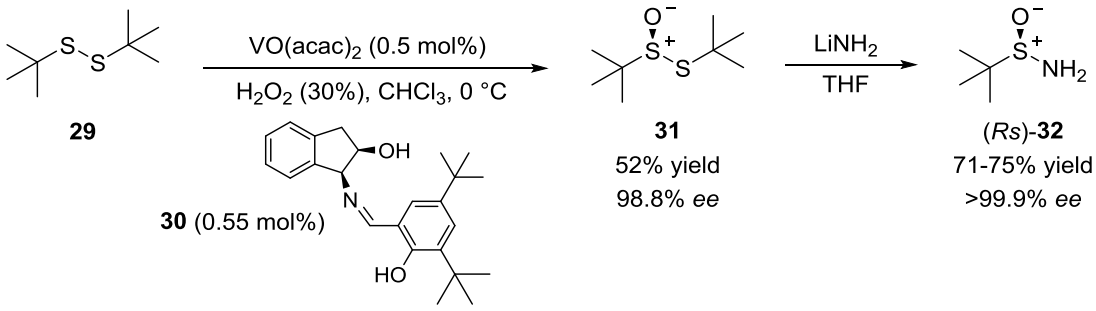
1.1.1.1.3. Condensation

The most common methods to prepare sulfinimines include the condensation between a primary sulfinamide and an aldehyde or ketone. The first preparation of an enantiomerically pure sulfinimine by condensation was by Davis *et al*.[18] by treatment of **7** with LiHMDS **13** to give *N*,*N*-bis(trimethylsilyl)-*p*-toluenesulfinamide **23** and lithium menthoxide **24**. Transilylation between **23** and **24** afforded anion **26**, which was then trapped with aldehydes **27** to give sulfinimines **28** in yields ranging from 40 to 93% (Scheme 6).[18]



Scheme 6: First reported condensation of sulfinamide **26** with aldehydes **27**

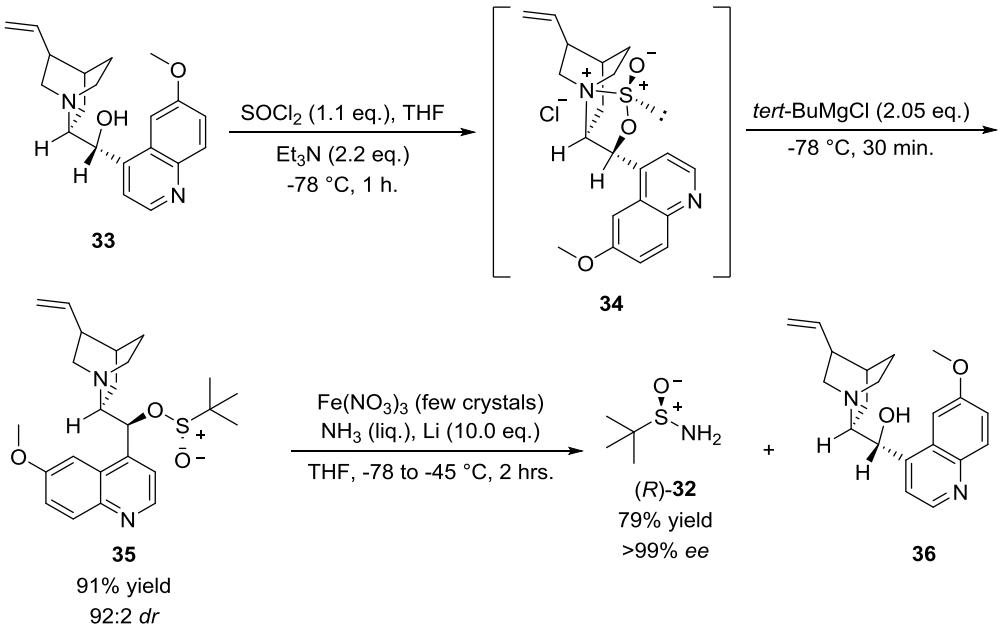
Ellman and co-workers[22] reported the synthesis of (*R*)-*tert*-butanesulfinamide **32** as a single enantiomer in 71-75% overall yield using a simple and cost-effective route (Scheme 7). Reaction between inexpensive *tert*-butyl disulfide **29** and vanadyl acetylacetonate $VO(acac)_2$ in the presence of hydrogen peroxide as a stoichiometric oxidant and **30** as a chiral ligand (prepared *via* one-step procedure from *cis*-1-amino-2-indanol) gave the thiosulfinate ester **31** in 52% yield with 98.8% *ee*. The product **31** was then treated with a solution of lithium amide in THF to give the desired product (R_S)-**32**.[22] This procedure has used to synthesise tonne quantities of enantiomerically pure (*R*s)-**32**.[11,17]



Scheme 7: Tonne-scale synthesis of enantiomerically pure (*R*)-*tert*-butanesulfinamide **32**

Later, Senanayake and co-workers[27] designed and demonstrated a new methodology for the efficient asymmetric synthesis of (*R*)-*tert*-butanesulfinamide **32** in a high *ee* and good yield using quinine sulfonate **35** (*Cinchona alkaloids*) as a chiral auxiliary. The compound **35** was prepared *via* simple method and from cheap starting materials.[24,25] In addition, **35** could be recovered and reused after the reaction, however, treatment of **33** with $SOCl_2$ and Et_3N gave the salt complex of the pseudo oxathiazolidine-2-oxide **34**. Followed by nucleophilic addition of *tert*-BuMgCl afforded *tert*-butanesulfinate **35** in an excellent yield (91%) and high *dr* (98:2, by HPLC-MS), then the major diastereoisomer **35** was separated in >99:1 *dr* using flash column chromatography. The product **35** was then treated with Li/NH_3 in the presence of $Fe(NO_3)_3$ as a catalyst afforded the desired product (R_S)-**32** in >99% *ee* and a good yield (79%). This step included an inversion of

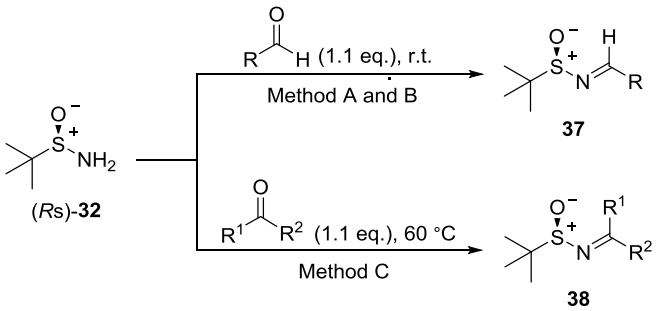
stereochemical configuration at the sulfur centre (Scheme 8). Enantiopure sulfinamides are now commercially available (around £1/g).



Scheme 8: Asymmetric synthesis of (*R*s)-**32** *via* pseudo-five-membered ring oxathiazolidine **34**

The sulfinamide **32** can subsequently be reacted with different ketones or aldehydes to give the corresponding sulfinimines (Scheme 9). Ellman and co-workers.[23] have used three types of Lewis acid catalysts in this condensation. For example, $MgSO_4$ and PPTS gave both aliphatic and aromatic aldimines **37** in very good yields (84-96%) without loss of enantiopurity (analysis by chiral HPLC) (Scheme 9). However, this method used slight excesses of aldehydes (1.1 eq.), particularly with unreactive substrates, and it was unsuitable for ketones (Method A). Furthermore, the use of $CuSO_4$ afforded *tert*-BS-aldimines **37** in modest to excellent yields (40-96%) and required a small excess of reagents with unreactive substrates. However, ketones were unreactive using this methodology (Method B). On the contrary, $Ti(OEt)_4$ was suitable to react with ketones and gave good to excellent yields (73-91%) of *tert*-BS-ketimines **38** (Method C).[23] $Ti(OEt)_4$ had been used as a Lewis acid and water scavenger (ultimately generating titanium dioxide) (Scheme 9).

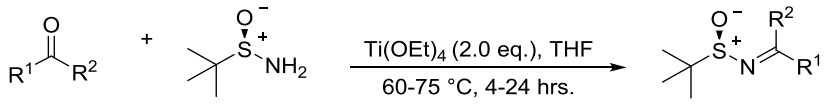
Various other reagents have been explored, such as sodium hydroxide, potassium bisulfate, ytterbium (III) trifluoromethanesulfonate and cesium sulfate. In addition, different reaction conditions have been used, such as using 4 Å molecular sieves (with varying degrees of success). Most of the sulfinimines prepared using these conditions can be handled at room temperature in air and with limited light-sensitivity and found very hydrolytically stable. While some sulfinimines derivatives decompose after a period of weeks at room temperature, the storing at -5 °C under an inert gas (N_2 or Ar) was found to effective in avoiding this problem.[17]



Method A: $MgSO_4$ (5.0 eq.), PPTS (0.05 eq.), DCM, 84-96% yield
Method B: $CuSO_4$ (2.2 eq.), DCM, 40-96% yield
Method C: $Ti(OEt)_4$ (2.0 eq.), THF, 73-91% yield

Scheme 9: Condensation of (*R*s)-**32** with carbonyl compounds

Ellman and co-workers[23,28,29] indicated that the control on ratio of *E:Z* isomers of *N*-*tert*-butanesulfinyl imines **40a**-**h** depending on the steric effects of R^1 and R^2 group at the **40a**-**h**. The ratios were observed as a single *E*-isomer (determined by ^1H NMR spectroscopy in $CDCl_3$) with *N*-*tert*-butanesulfinyl imines (**40a**-**f**). No significant of the steric effect was observed with **40g** and **40h**. Despite the **40g** and **40h** preferred *E*-isomer in 6:1 and 5:1 respectively (Scheme 10).



39a-h (1.1 eq.) + (*R*s)-**32** (1.0 eq.) → **40a-h** 73-89% yield

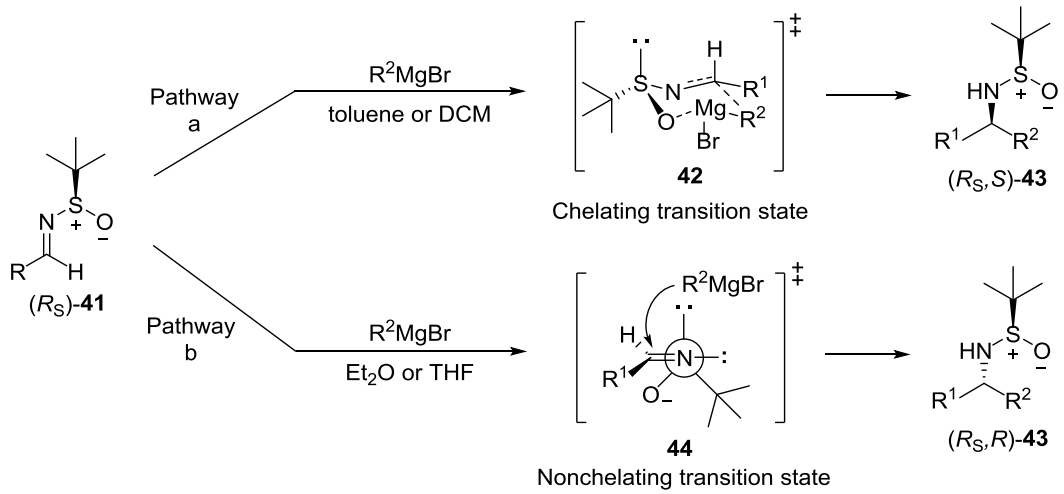
40a: R^1 = Ph, R^2 = Me, 89% yield, single isomer (*E*/*Z*)
40b: R^1 = ^{i}Pr, R^2 = Me, 84% yield, single isomer (*E*/*Z*)
40c: R^1 = ^{i}Pr, R^2 = Bu, 77% yield, single isomer (*E*/*Z*)
40d: R^1 = Ph, R^2 = Bu, 77% yield, single isomer (*E*/*Z*)
40e: R^1 = 2-Npth, R^2 = Me, 73% yield, single isomer (*E*/*Z*)
40f: R^1 = ^{t}Bu, R^2 = Me, 82% yield, single isomer (*E*/*Z*)
40g: R^1 = ^{i}Bu, R^2 = Me, 88% yield, 6:1 (*E*/*Z*)
40h: R^1 = Bu, R^2 = Me, 77% yield, 5:1 (*E*/*Z*)

Scheme 10: Condensation of ketones **39a**-**h** with (*R*s)-**32** to afford **40a**-**h**

1.1.1.2. Reactions of sulfinimine compounds

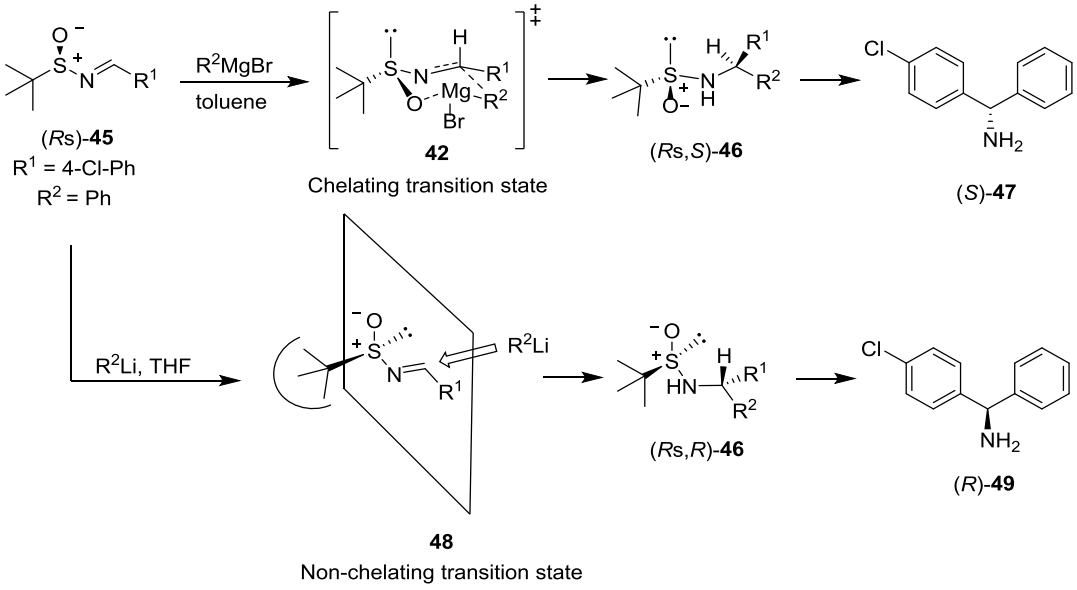
1.1.1.2.1. Reaction with organometallic compounds

1,2-Addition to sulfinimines is a common method for the asymmetric synthesis of amines. The selectivity of 1,2-addition of organometallic compounds to sulfinimines was investigated in several studies.[7,30,31] These studies indicated that the stereo- chemical outcome of the products depended on the transition state models (Scheme 11). As a result, the reaction conditions play a crucial role in which diastereoisomer is favoured. For example, chelated transition state (closed transition state) **42** affords (R_S,*S*)-**43** when using a Grignard reagent in non-coordinating solvents (toluene and DCM) (Scheme 11, pathway a). On the other hand, the open transition state **44** gives (R_S,*R*)-**43**, which is favoured using a Grignard reagent in coordinating solvents (Et_2O and THF) (Scheme 11, pathway b).



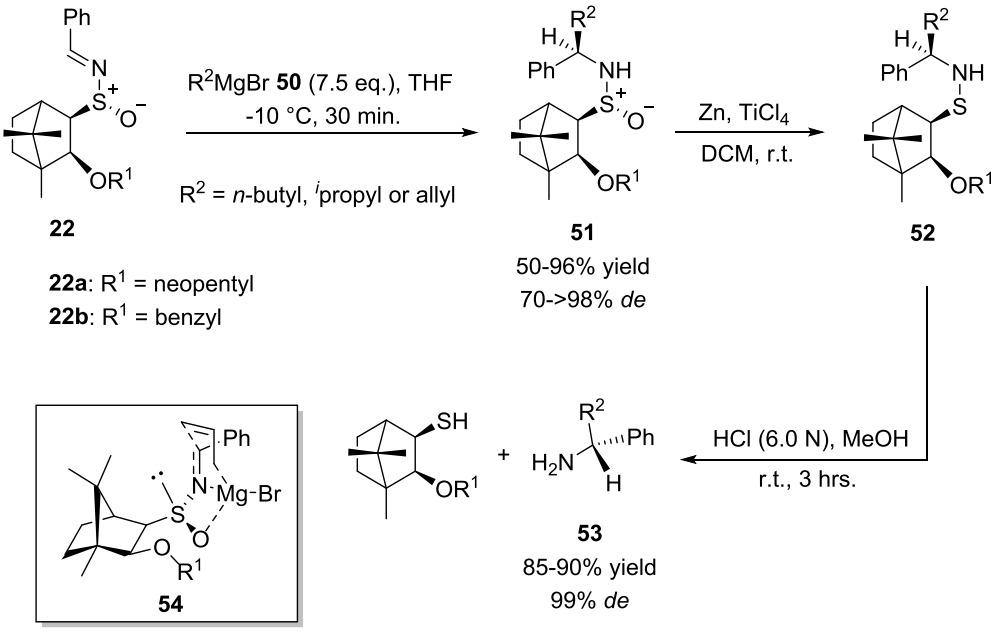
Scheme 11: Transition state models for stereoselectivity in 1,2-additions to sulfinimines **41**

Plobeck and Powell.[31] reported that the addition of a Grignard reagent to a sulfinimines **45** in toluene providing the expected *S*-amine **47** (Scheme 12). This was based on the chelation of magnesium to the oxygen to afford a six-membered transition state **42** as mentioned in Scheme 12. Conversely, in the case of the organolithium reagent, the reaction goes *via* non-chelating transition state (open transition state) **48** and provided *R*-amine **49**, as shown in Scheme 12.



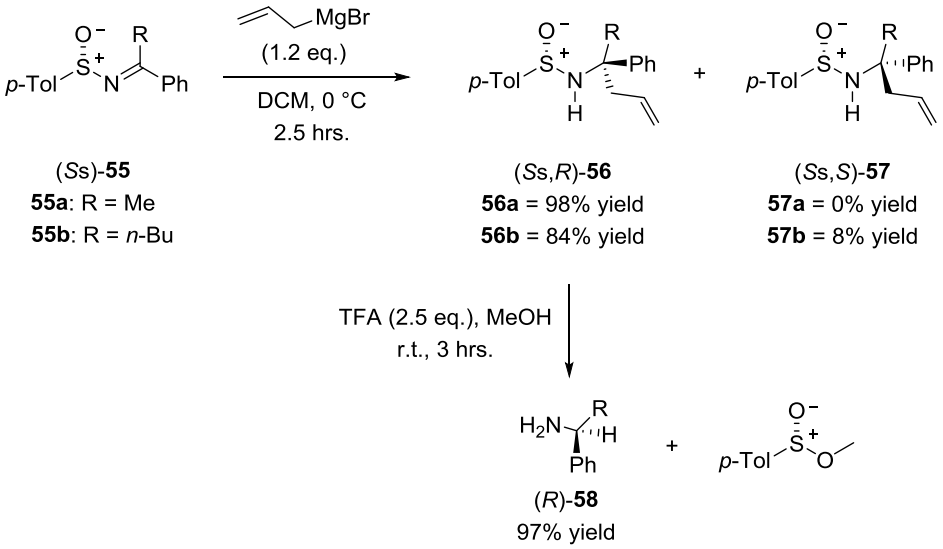
Scheme 12: Addition of Grignard and organolithium reagents to sulfinimines **45**

Yang *et al*. (1994)[10] have demonstrated the asymmetric reaction of camphor derived sulfinaldimines **22** with different types of organometallic reagents **50**. These steps included reacting **22** with Grignard reagents **50** to give **51** in very good to excellent *de* (70->98%) and yields ranging from 50 to 96%. The selectivity was rationalised by the formation of the chair-like transition state **54** shown in Scheme 13, where the oxygen and the nitrogen of the sulfinimine coordinate to the magnesium metal forcing the nucleophilic attack on the *Si* face of the double bond. In addition, they indicated that the selectivity was influenced by the size of the R group of the Grignard reagent **50**. For example, *n*-butyl magnesium bromide afforded 70% *de*, ^{i}propyl (88%) and allyl (>98%). The camphor derivatives **52** were prepared in two steps to give chiral amines **53** without any loss in enantiopurity. The products **51** were then reduced with zinc powder/$TiCl_4$ at room temperature to afford **52**, followed by methanolysis of **52** in a solution of HCl/MeOH (6.0 N) to give the desired products **53** in very good to excellent yields (85-90%) with 99% *de* (Scheme 13).[10]



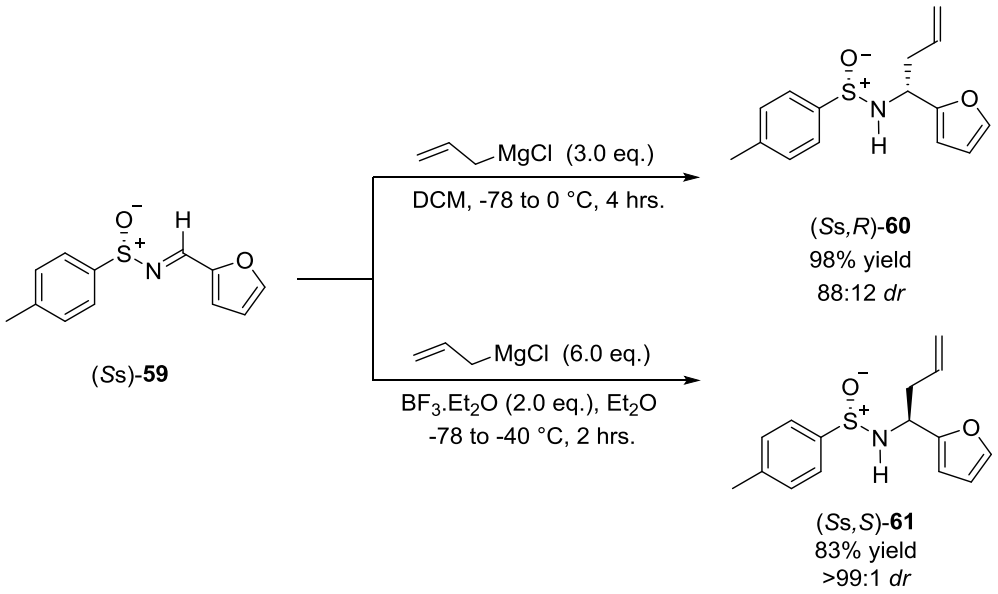
Scheme 13: Yang's *et al*. amine synthesis

Furthermore, Hua *et al*. (1991)[9] reported the reaction between *p*-toluenesulfinyl ketimines **55** and allylmagnesium bromide in DCM gave the corresponding α-branched sulfinamides **56** and **57** with 82 to 100% *de* in very good yields (84-98%). The deprotection of **56** was achieved *via* acid methanolysis which afforded the corresponding amines **58** (Scheme 14).[9]



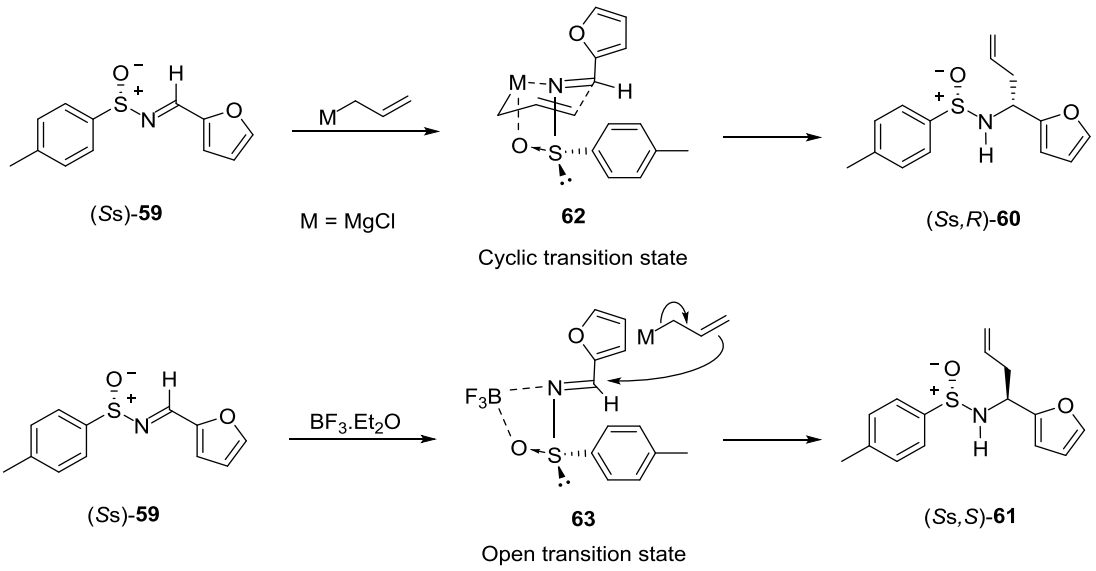
Scheme 14: Hua's *et al*. amine synthesis

Shimizu and co-workers (2002)[32] reported the reaction involving the addition of allyl Grignard reagent to *p*-toluenesulfinyl aldimine **59**. The reaction conditions they used led to a high diastereoselectivity and opposite configuration of the newly afforded chiral centre. Reaction of allylmagnesium chloride with (S_S)-sulfinimine **59** gave (S_S,*R*)-sulfinamide **60** in an excellent yield (98%) with 88:12 *dr*. Conversely, the addition of allylmagnesium chloride in the presence of boron trifluoride diethyl etherate furnished (S_S,*S*)-sulfinamide **61** as the major diastereoisomer (>99:1 *dr*) in a very good yield (83%) (Scheme 15).[32]



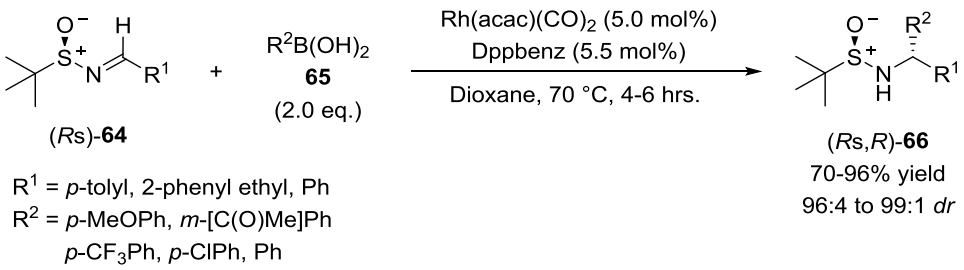
Scheme 15: Addition of allyl Grignard reagent to *p*-toluenesulfinyl aldimine **59**

The use of magnesium in the reaction will lead to a six-membered transition state **62** because the magnesium chelates to the oxygen. This causes the nucleophile to attack at the imine in an open transition state. This led to (S_S,*R*)-sulfinamide **60** as a major isomer. While, it was found the reversal of the diastereofacial selectivity in the second example, therefore gave (S_S,*S*)-sulfinamide **61** as a major isomer. This is due to boron trifluoride etherate coordinating to the oxygen and preventing formation of the six-membered transition state **63**. The selectivity is therefore governed by sterics (Scheme 16).[32]



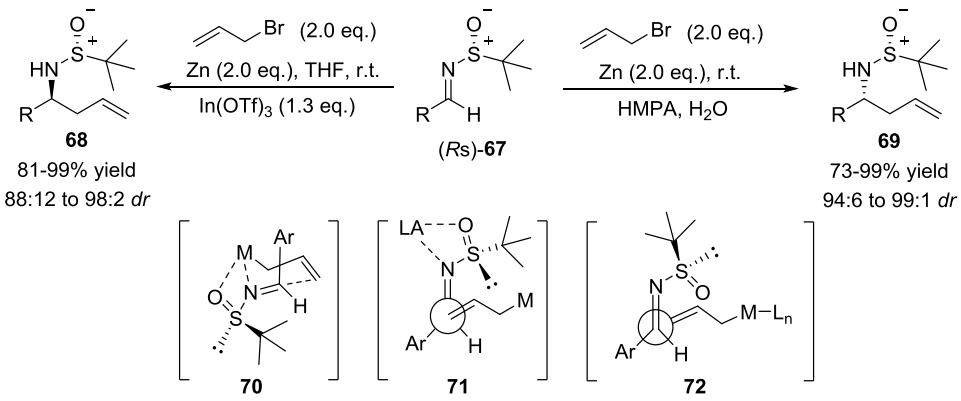
Scheme 16: Reversal of the Grignard addition selectivity

Organolithium and Grignard reagents are commercially available to add to the sulfinimines, especially *tert*-butyl sulfinimines, in an asymmetric synthesis. However, these reagents are extremely strong bases and can cause synthetic problems. Therefore, a method which is tolerant of more functional groups would be desirable. Boronic acids are very useful organometallic reagents for the asymmetric synthesis of α-branched amines, which are stable and easy to prepare. Despite this, arylboronic acids are poor nucleophiles. In 2005, Weix, Shi and Ellman,[33] indicated that the addition of arylboronic acid **65** to (R_S)-*tert*-butyl sulfinimines **64** in the presence of a rhodium(I)-phosphine complex as a catalyst affords the corresponding (R_S,*R*)-sulfinamides **66** overcoming their poor nucleophilicity (Scheme 17).



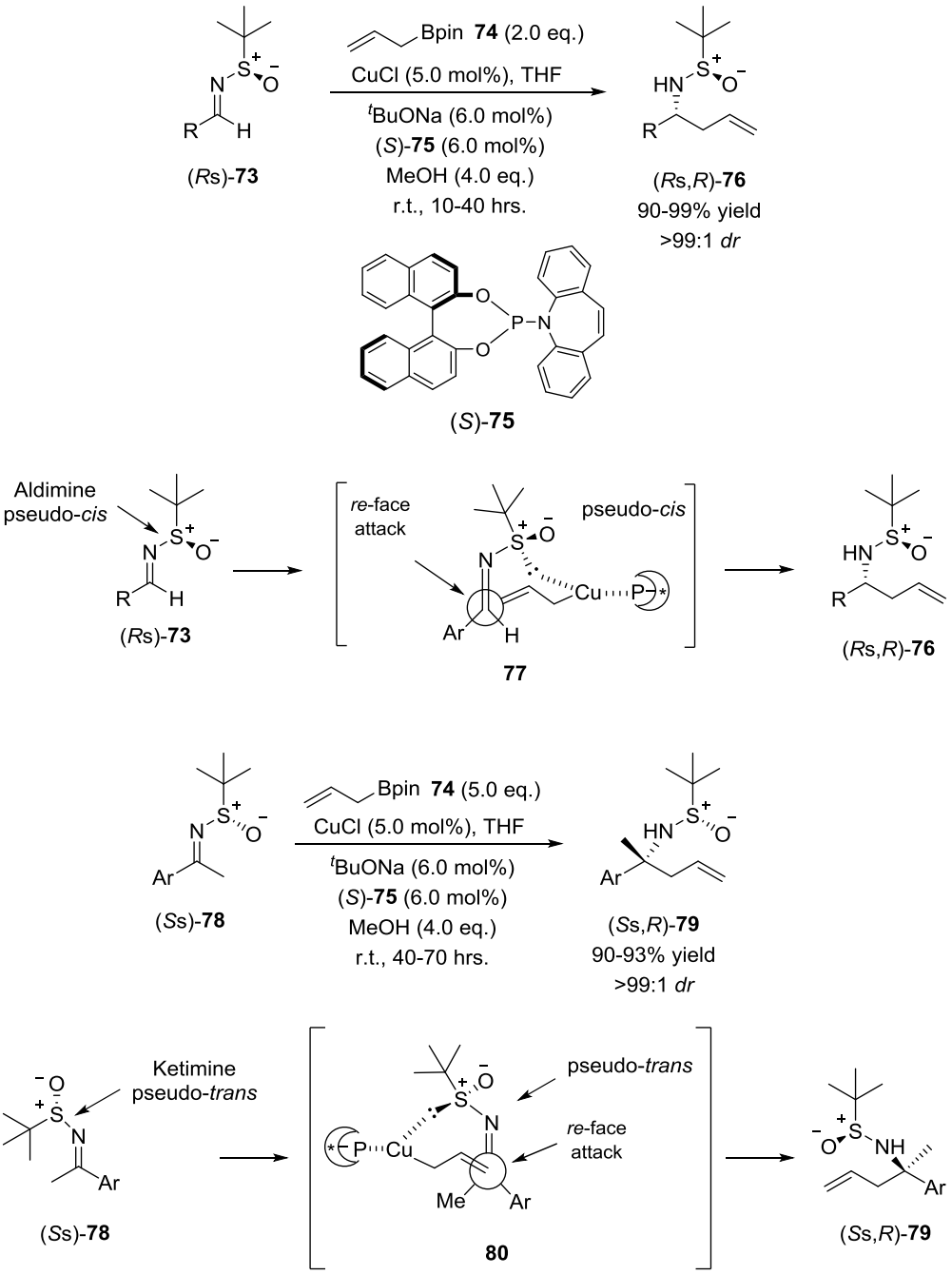
Scheme 17: Addition of arylboronic acids **65** to (*R*s)-sulfinimines **64** to give (*R*s,*R*)-**66**

Sun, Xu and Lin[34] reported a methodology for the synthesis of chiral homoallylic amines **68** and **69** diastereoselectively *via* reaction addition of Zn-mediated allylation to chiral sulfinimines **67** in the presence of THF and $In(OTf)_3$ as a Lewis acid. The selectivity was not rationalised by the formation of the chair-like transition state **70** as reported before with allyllmetal (In and Mg) in which the metal coordinates to the sulfinyl oxygen. As a result, the use of (R_S)-sulfinimines **67** gives (R_S,*S*)-sulfinamide products **68** because of the *Si* face addition will be favoured. In this methodology, the chelation of $In(OTf)_3$ with both sulfinyl oxygen and nitrogen of **67** leads to direct allyl attack selectively through the sterically unblocked *Si*-face affording (R_S,*S*)-sulfinamide products **68** in high *dr* (up to 98:2) and yields ranging from 81 to 99%. These reaction conditions included formation of an acyclic transition state **71** instead of a chair-like transition state **70**. In addition, they indicated that this methodology allows to furnish the opposite (R_S,*R*)-sulfinamide diastereoisomer **69** in high *dr* (up to 99:1) and good to excellent yields (73-99%). This was using HMPA as a Lewis base and some drops of H_2O. The allyllmetal will coordinate to HMPA in place of the sulfinyl oxygen as shown in the transition state **72**. The allyl addition to the less hindered *Re*-face of imine (the *N*-sulfinyl group adopts an approximate synperiplanar configuration) will be favoured to afford **69**.[35-37] The role of H_2O in this methodology is to disrupt the chelation of Zn(II) with the sulfinyl oxygen or nitrogen atoms, which prevents formation of both transition states **70** and **71** (Scheme 18).



Scheme 18: Allylation of *N*-*tert*-butanesulfinyl aldimines **67** using allyl bromide[34]

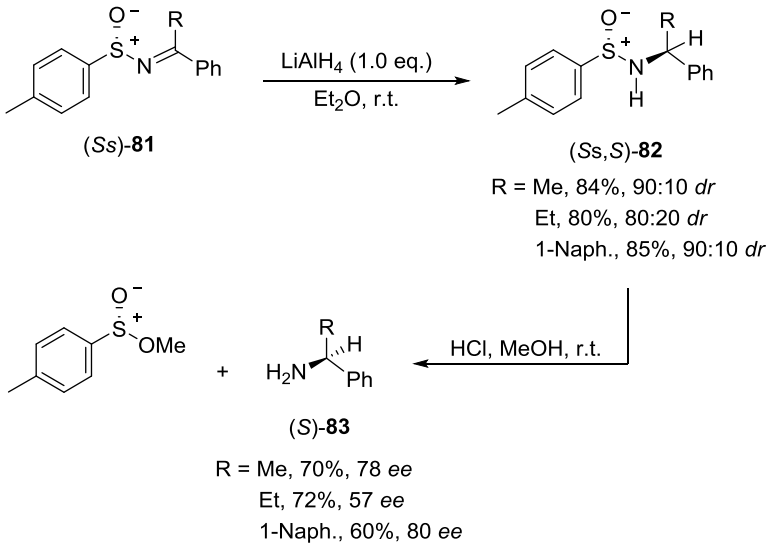
Recently, Zhao *et al.*[38] reported using CuCl as a catalyst and **75** as bulky phosphoramidite ligand in the stereoselective asymmetric allylation of chiral sulfinimine to give the corresponding sulfinamides in excellent *dr* (up to >99:1) and high yields (90-99%) (Scheme 19). Allylboronic acid pinacol ester **74** was employed as an allyl source in this methodology. Interestingly, two different stereochemical outcomes have been observed between (R_S)-aldimine **73** and (S_S)-ketimine **78**, probably due to their conformation difference. In (R_S)-aldimine **73**, the C=N bond is pseudo-*cis* to the S-O bond, allylcopper would selectively direct attack from the sterically unblocked *Re*-face of (R_S)-aldimine **73** to give (R_S,*R*)-sulfinamide **76**. This is because the steric congestion of the *tert*-butyl group of **73** and the pseudo-*cis* conformation between the S-O and C=N bonds on one hand, and steric congestion of by the bulky ligand **75** bonding to copper on the other hand (Scheme 19, **77**). Whilst, the C=N bond is pseudo-*trans* conformation with (S_S)-ketimine **78**,[39] which the addition of allylcopper prefers to attack at *Re*-face of (S_S)-ketimine **78** to provide (S_S,*R*)-sulfinamide **79** (Scheme 19, **80**).[38]



Scheme 19: Stereoselective allylation of *N-tert*-butanesulfinyl imines **73** and **78** using allylboronic acid pinacol ester **74**

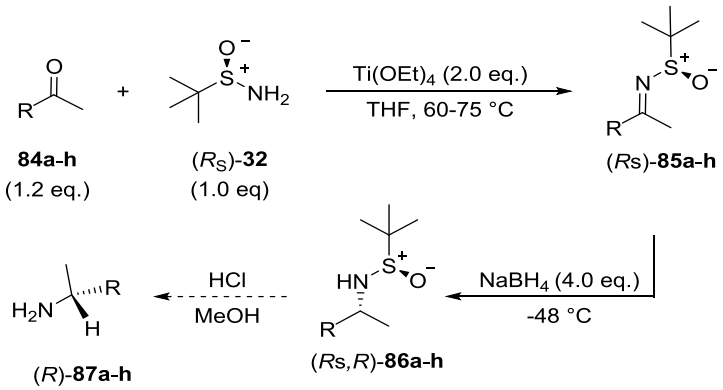
1.1.1.2.2. Hydride reduction

Cinquini and Cozzi[40] reported the first reduction of the chiral (S_S)-sulfinimines **81** using $LiAlH_4$ furnishing the corresponding (S_S,*S*)-sulfinamides **82** in very good yields (80-85%) with *dr* 80:20 to 90:10 (determined by ^1H NMR spectroscopy). Deprotection of sulfinamides **82** *via* acid methanolysis at room temperature afforded the corresponding (*S*)-amines **83** in modest to very good yields (60-72%) with 57-80% *ee* (Scheme 20).[40]



Scheme 20: Reduction of (*Ss*)-sulfinimine **81** using $LiAlH_4$

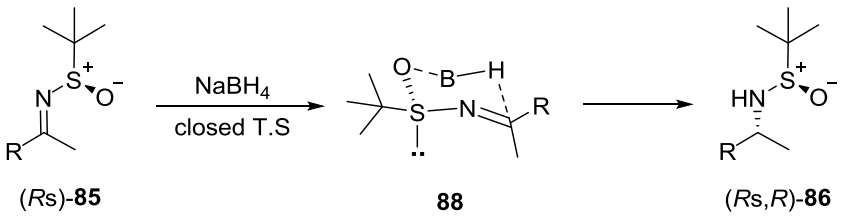
Borg, Cogan and Ellman (1999)[12] reported the first example of the asymmetric synthesis of *tert*-butanesulfinyl-protected amines **86a**-**h** in a one-pot method *via* condensation reaction of different types of ketones **84a**-**h** with (*R*)-*tert*-butanesulfinamide **32**. In the reaction $Ti(OEt)_4$ acts as a Lewis acid and water scavenger. The *E*/*Z* ratio of isolated intermediates **85a**-**h** was assigned using ^1H NMR spectroscopy. Subsequently, *in situ* reduction of **85a**-**h** with $NaBH_4$ provided the *N*-*tert*-butanesulfinyl α-branched amines **86a**-**h** in good yields (66-86%) and high *dr* from 83:17 to 97:3. The deprotection of **86a**-**h** can be achieved by treating **86a**-**h** with HCl/MeOH affording amines **87a**-**h** (Scheme 21).[12]



86a: R = Ph, 78%, 96:4 *dr*
86b: R = *p*-NCPh, 82%, 96:4 *dr*
86c: R = ^{i}Pr, 66%, 97:3 *dr*
86d: R = *n*-Bu, 82%, 83:17 *dr*
86e: R = ^{i}Bu, 74% 92:8 *dr*
86f: R = Bn, 86%, 90:10 *dr*
86h: R = PhCH=CH, 76%, 90:10 *dr*

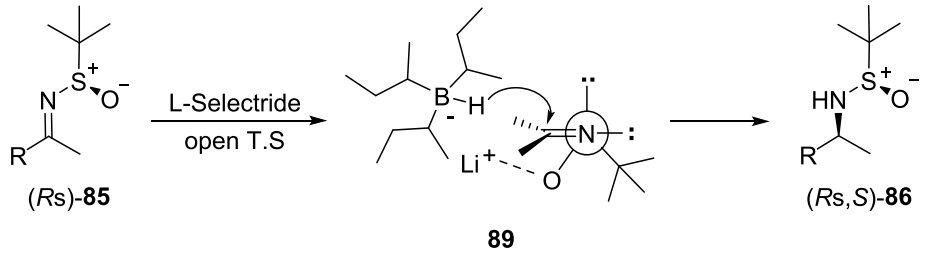
Scheme 21: Reductive amination of acyclic ketones **84a**-**h** using $NaBH_4$ to sulfinamide **86a**-**h** in a one-pot reaction

Later, Colyer *et al.*[41] reported the investigation of the diastereofacial diastereoselective reduction of *N*-*tert*-butanesulfinyl imines (R_S)-**85** to the corresponding sulfinamides **86** using two different reducing reagents ($NaBH_4$ and L-Selectride). Using $NaBH_4$ to reduce (R_S)-**85** gave (R_S,*R*)-**86** diastereoisomer while L-Selectride afforded the opposite diastereoisomer (R_S,*S*)-**86**. This is because the mechanism of this reduction with $NaBH_4$, included the formation of a cyclic transition state **88**. Hence, the hydride (H-) will attack the carbon of the sulfinyl imine directly. The reduction mechanism of (R_S)-**85** with $NaBH_4$ has been outlined in the Scheme 22.



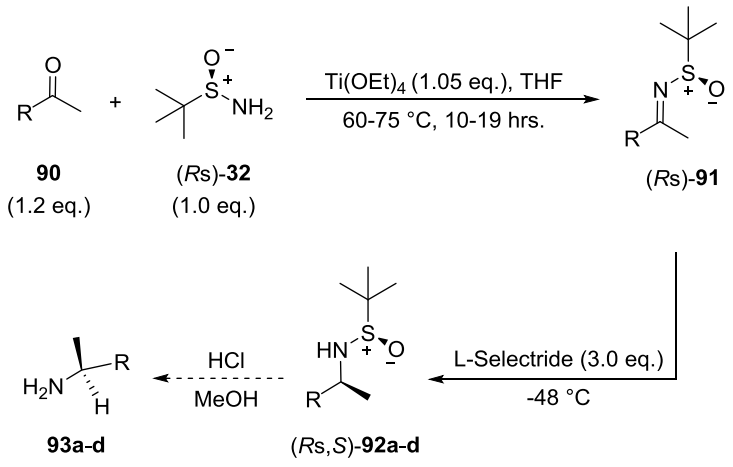
Scheme 22: Mechanistic proposal of sulfinimine (*R*s)-**85** reduction using $NaBH_4$

On the other hand, using L-Selectride includes formation of an acyclic transition state **89**. This is due to steric congestion of the substituents on the boron metal, which is considered a bulky reducing agent.[41] The mechanism of this reduction is described in Scheme 23.



Scheme 23: Mechanistic proposal of (*R*s)-**85** reduction using L-Selectride

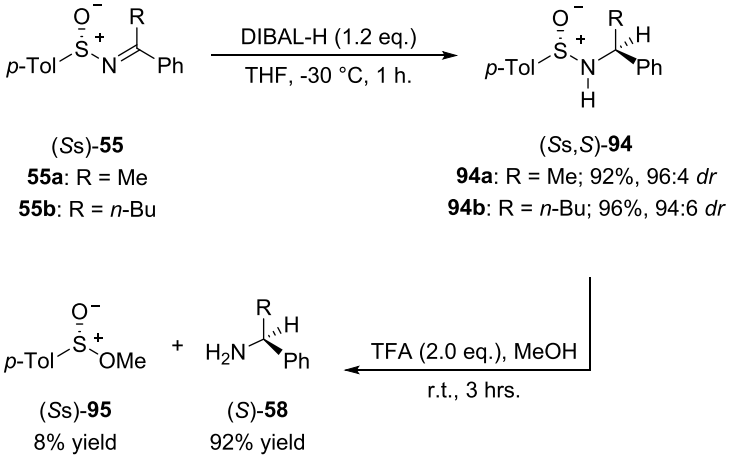
Subsequently, Tanuwidjaja, Peltier and Ellman[42] have reported an asymmetric reductive amination of ketones **90** with L-Selectride in a one-pot reaction. The desired sulfinamide products **92a**-**d** were isolated in high *dr* (up to 97:3) with good yields (70-89%). The stereochemistry determination of **92a**-**d** was based on the previous description by Colyer *et al.*[41] (Scheme 24).



92a: R = Ph; 89%, 97:3 *dr*
92b: R = ^{i}Pr; 76%, 96:4 *dr*
92c: R = *n*-Bu; 72%, 86:14 *dr*
92d: R = ^{i}Bu; 70% 96:4 *dr*

Scheme 24: Reductive amination of acyclic ketones **90** using L-Selectride to sulfinamide (*R*s,*S*)-**92a**-**d** in a one-pot reaction

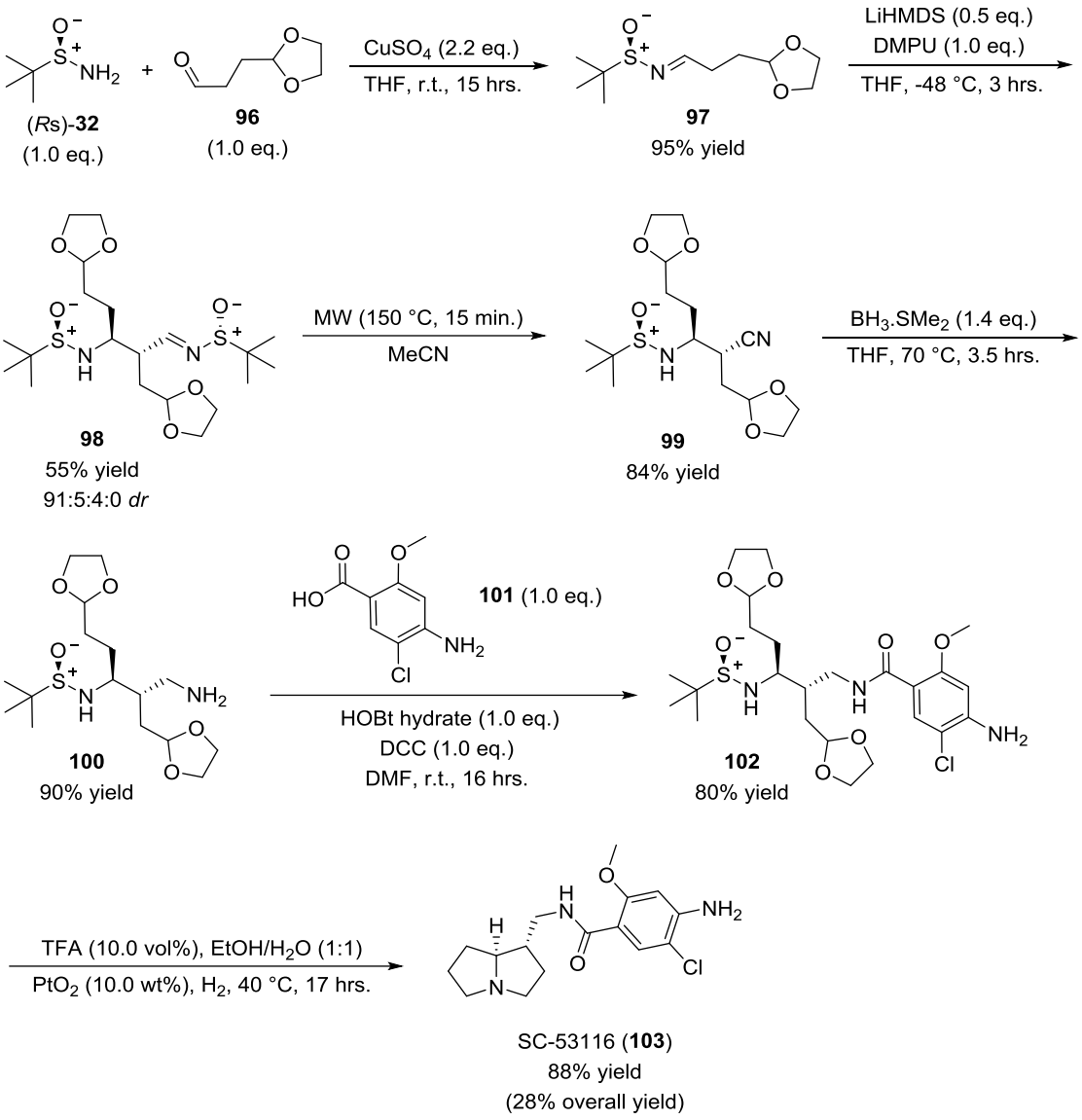
Hua *et al*. (1991)[9] indicated that *p*-toluenesulfinyl ketimines **55** derived from butyl phenyl ketone and acetophenone could be stereoselectively reduced by DIBAL-H. The result provided sulfinamide **94a** in 92% yield and 96:4 *dr* when using acetophenone derivative **55a**, and gave **94b** in 96% yield and 94:6 *dr* with using *n*-butyl phenyl ketone derivative **55b**.[7] The diastereoisomers were readily isolated *via* flash column chromatography. Subsequently, the products **94a** and **94b** then underwent methanolysis with TFA in MeOH at room temperature for 3 hours. This afforded 100% optical pure of amines **58** with yield 92% (Scheme 25).[9]



Scheme 25: Reduction of (*S*s)-**55** using DIBAL-H to afford (*S*s,*S*)-**94**

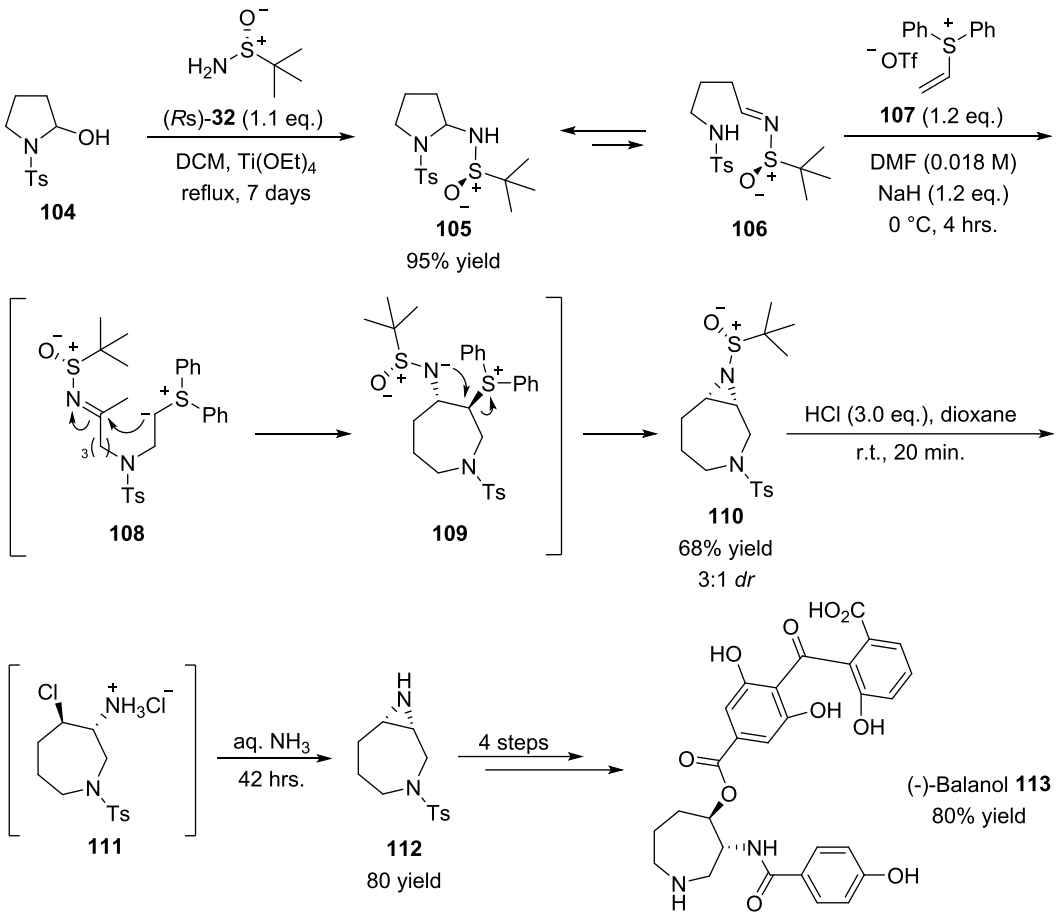
1.1.1.3. Application of sulfinimines in asymmetric synthesis

Recently, many of sulfinimine derivatives have been used as versatile moieties in the asymmetric synthesis of bioactive molecules, natural products, pharmaceuticals and organomaterials. An efficient and elegant approach for synthesis of drug-candidate SC-53116 (**103**) has been reported by Schenkel and Ellman.[43] The first step in this synthesis included preparation of the sulfinimine **97** *via* condensation between (*R*)-*tert*-butanesulfinamide **32** and the appropriate aldehyde **96** in the presence of $CuSO_4$ as a water scavenger and Lewis acid catalyst giving the desired product **97** in an excellent yield (95%). Followed by an intermolecular self-condensation of the **97** using LiHMDS as a base and DMPU as additive to improve the diastereoselectivity afforded **98** in a 55% yield with high *dr* (91:5:4:0, determined by ^{1}H NMR spectroscopy). One group of sulfinimine at **98** was then decomposed to the corresponding nitrile **99** in 84% yield using microwave conditions (150 °C, 15 minutes). The nitrile group at **99** was then reduced under mild conditions with $BH_3.SMe_3$ gave the corresponding amine **100** in a 90% yield. The next step included coupling between **100** and 4-amino-5-chloro-2-methoxybenzoic acid **101** in the presence of HOBt as a coupling reagent provided **102** in a very good yield (80%). The sulfinyl and acetal protecting groups at **102** were then removed using acidic conditions (TFA/H_2O) led simultaneously to the formation of the pyrrolizidine core **103** in 88% yield under acidic reducing conditions. The overall yield of SC-53116 (**103**) was 28% in 6 steps (Scheme 26).



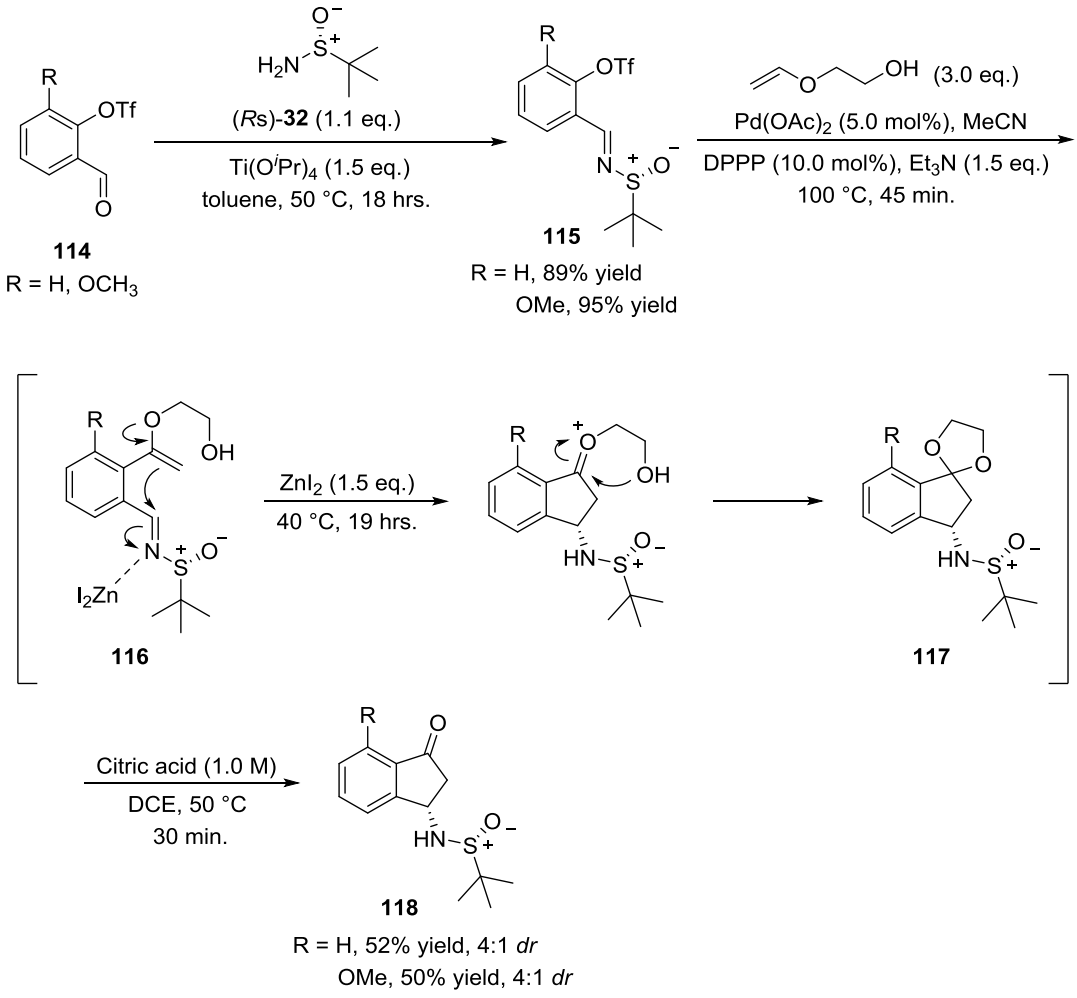
Scheme 26: Schenkel and Ellman synthesis of SC-53116 (**103**)

After two years, Unthank, Hussain and Aggarwal[44] reported the formal synthesis of (-)-balanol **113** (a fungal metabolite produced by the fungus *Verticillium balanoides*). This product **113** plays an important role as a potent inhibitor to the serine/threonine kinases protein kinase A (PKA) and protein kinase C (PKC).[44] The first step in the formal synthesis included preparation sulfinamide **105** in an excellent yield (95%) *via* condensation between hemiaminal **104** and (*R*)-*tert*-butanesulfinamide **32** in the presence of $Ti(OEt)_4$. The product **105** was then treated with diphenyl vinyl sulfonium salt **107** in the presence of NaH as a base to afford hexahydroazepine **110** in 3:1 *dr* with a good yield (68%). The mechanism of this reaction involves deprotonation of the tosyl amide in ring-opened tautomer **106**, followed by conjugate addition to **107**, furnishing the intermediate **108**. Next, an intramolecular nucleophilic addition of the anion to the sulfinimine group at **108** gave **109**. The protected aziridine product **110** was then formed by an intramolecular nucleophilic substitution *via* displacement of diphenyl sulfide by the newly-formed sulfinamide anion at **109**. The mixture of **110** was then separated using silica gel chromatography. X-ray crystallography assigned the minor diastereomer, hence establishing the stereochemistry of the major isomer. Deprotection of **110** using acidic conditions gave the ring-opened form **111**, followed by treatment with NH_3 (aq.) afforded the known chiral aziridine **112** in a very good yield (80%).[45] This concluded the formal synthesis, providing the desired target **113** in eight steps (the shortest route to date) (Scheme 27).



Scheme 27: Aggarwal's formal synthesis of (–)-balanol **113**

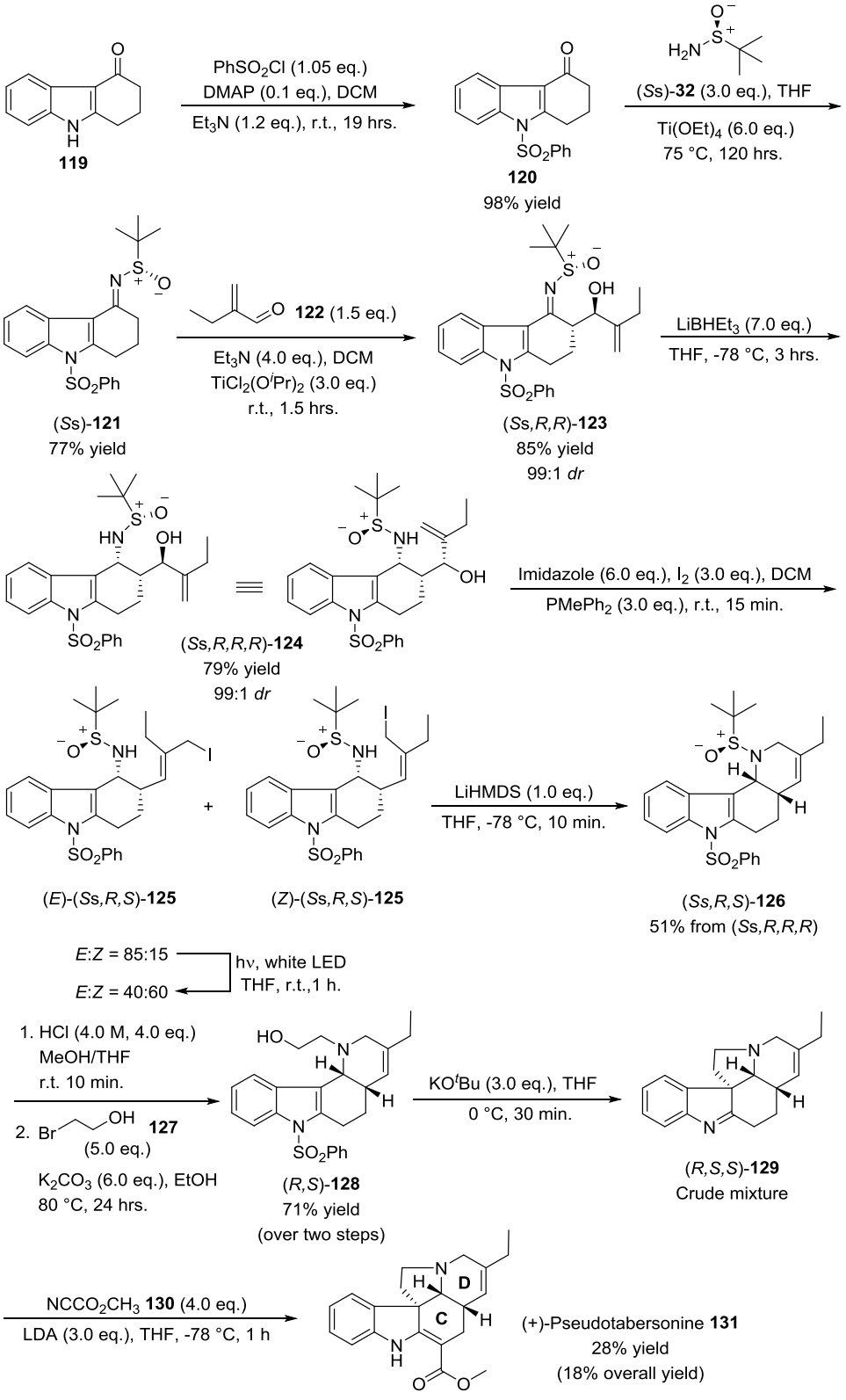
Hallberg and co-workers[46] have reported a novel method for the synthesis of 3-aminoindan-1-ones **118** stereoselectively, which are useful building blocks for the synthesis of HIV-1 protease inhibitors. This method included condensation between salicylic aldehyde triflates **114** and (*R*)-*tert*-butanesulfinamide **32** in the presence of $Ti(O^iPr)_4$ as a Lewis acid gave triflates of salicylic sulfinyl imine **115**. The product **115** was then used as a substrate in an annulation reaction, which is achieved in a one-pot, two-step sequence *via* the Heck coupling. This provided intermediate **116**, followed by selective cyclisation of **116** using ZnI_2 as a selective catalyst which afforded intermediate **117**. The acetal group formed at **117** was then removed using citric acid, furnishing **118** in 4:1 *dr* and 50-52% yield (Scheme 28).



Scheme 28: New approach towards synthesis 3-aminoindan-1-ones **118**

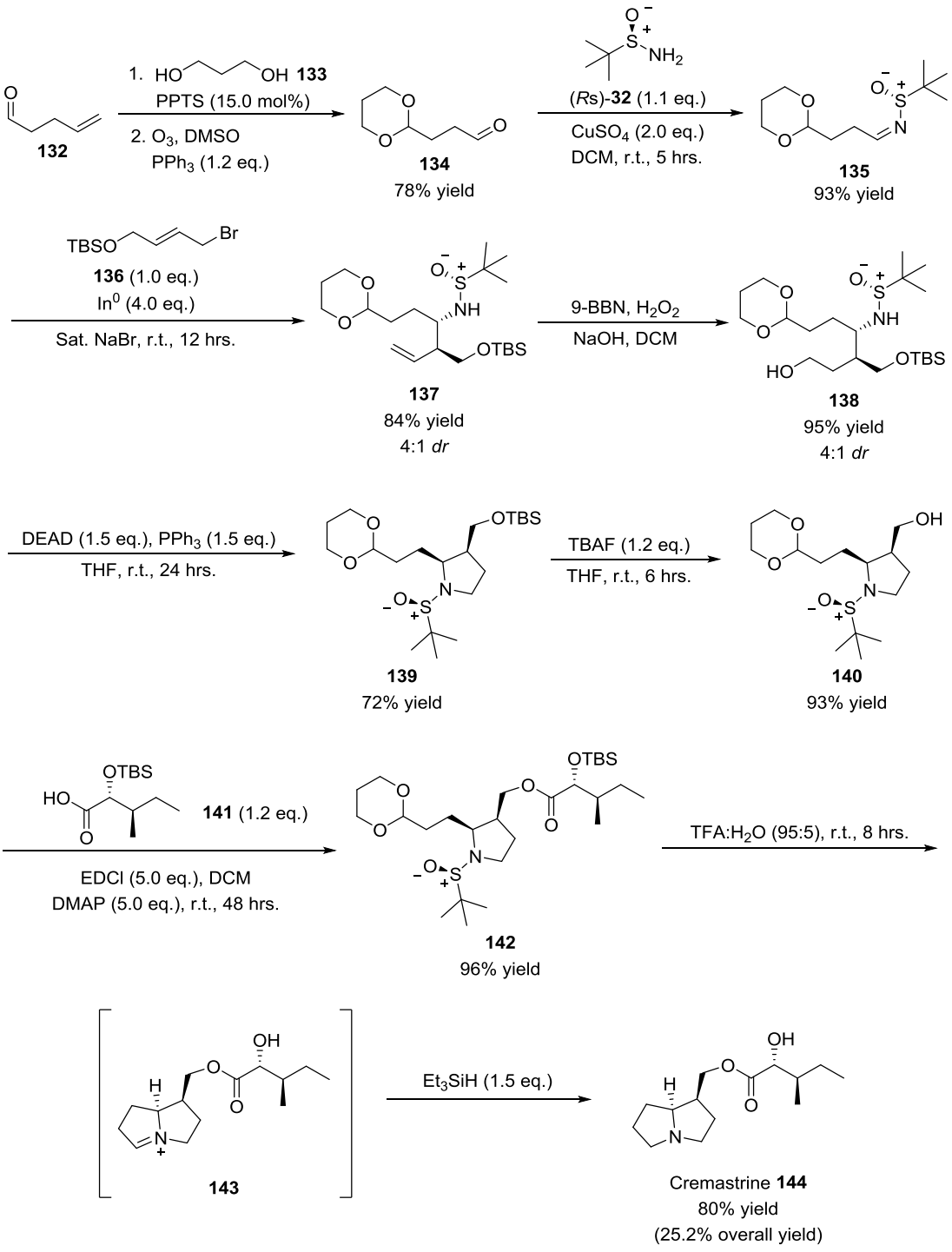
Suna and co-workers[47] have reported the stereoselective synthesis of (+)-pseudotabersonine **131** (a natural product isolated from *Pandaca caducifolia* in 1975.[48] The product **131** belongs to the *Aspidosperma* alkaloids family.[49,50] This type of alkaloid natural product contains a pentacyclic core with a *cis*-junction between the C and D rings. Vincristine is an excellent chemotherapy medication for cancer. The synthetic route included using a common intermediate **121**, which was synthesised over two steps (Scheme 29). *N*-Protection of the commercially available compound **119** gave **120** in an excellent yield (98%), followed by condensation with (*S*)-*tert*-butanesulfinamide **32** (Ellman's protocol) afforded (S_S)-sulfinimine **121** in 77% yield.[23] A diastereoselective aldol-type reaction was then performed between **121** and 2-ethylacrolein **122**, which gave the desired 1,3-iminoalcohol (S_S,*R*,*R*)-**123** in an excellent diastereoselectivity (99:1 *dr*) and very good yield (85%). The next step in this synthesis involved stereoselective reduction of the imine group at **123** to afford (S_S,*R*,*R*,*R*)-**124**, which required the delivery of hydride on the less hindered *Si* face. This was done *via* treatment of **123** with $LiBHEt_3$, and afforded the desired product **124** in 79% yield with an excellent diastereoselectivity (99:1 *dr*). Appel conditions were then applied on (S_S,*R*,*R*,*R*)- **124**, which provided **125** as an inseparable mixture of *E*/*Z* (85:15) isomers. Unfortunately, only the minor *Z*-isomer underwent the S_N2 cyclisation conditions (LiHMDS, -78 °C) giving the desired tetracyclic (S_S,*R,S*)-**126** (12% yield), and no reaction with major *E*-isomer. Gratifyingly, it was observed that the *E*/*Z* ratio could be change from 85:15 to 40:60 using irradiation with visible LED light (1400 1m for 1 hour at room temperature). The cyclisation of the *Z*-enriched **125** in the same conditions (LiHMDS, -78 °C) provided the desired (S_S,*R,S*)-**126** in 51% yield. Hence, deprotection of the chiral auxiliary group of **126** under acidic conditions (4.0 M HCl) afforded the corresponding amine, which was alkylated with 2-bromoethanol **127** to give (*R*,*S*)-**128** in 71% yield over 2 steps. Following this, a one-pot sequence of *N*-deprotection/*O*-sulfonylation, then Bosch-Rubiralta spirocyclisation[51-53] afforded pentacycle (*R,S*,*S*)-**129**. Finally, the crude mixture of

129 was then treated with Mander's reagent **130**[54] (methylcyanoformate) in the presence of LDA as a base, which afforded the desired target **131** in 28% yield (18% overall yield) (Scheme 29).[47]



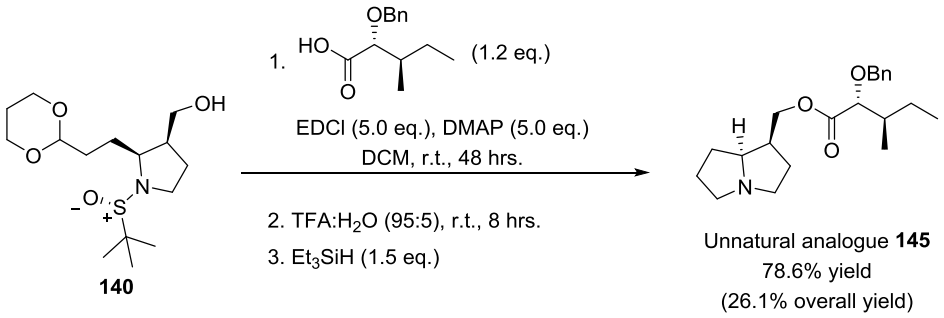
Scheme 29: Stereoselective synthesis of (+)-pseudotabersonine **131**

Lindsley and co-workers[55] reported a novel and concise methodology for the total synthesis of cremastrine **144** and an unnatural analogue **145**. The product **144** is a pyrrolizidine alkaloid isolated from the Japanese tuber (*Cremastra appendiculata*) by Ikeda *et al.*[56] The preliminary biological examination indicated that the compound was a good selective muscarinic acetylcholine receptor subtype 3 inhibtor.[56,57] Firstly, protection of the carbonyl group of 4-pentenal **132** was performed using propane-1,3-diol **133**, followed by ozonolysis giving **134** in 78% yield (Scheme 30). Chiral aldimine **135** was then prepared in an excellent yield (93%) by condensation of **134** with (*R*)-*tert*-butanesulfinamide **32**. The next step involved installing two stereocentres *via* indium mediated allylation using functionalized allyl bromide **136**. The reaction gave **137** in a very good yield (84%) with 4:1 *dr*. Hydroboration-oxidation was then achieved on the terminal alkene of **137**, which afforded the corresponding alcohol **138** in 95% yield. Mitsunobu conditions have then been used with **138**, which furnished substituted pyrrolidine **139** in 72% yield. The product **139** was obtained with a *syn*-stereochemical relationship of the two chiral centres, which was determined by NOESY-NMR spectroscopy. The protecting group at **139** was then removed using TBAF and afforded the corresponding alcohol **140** in 93% yield. Next, a coupling reaction between **140** and **141** provided the ester derivative **142** in 96% yield. Compound **141** was prepared according to literature procedure in a 65% yield over three steps starting from D-isoleucine.[58] Thereafter, global deprotection of three groups (TBS, 1,3-dioxane and chiral auxiliary) and intramolecular condensation/reductive amination was then successfully accomplished in a one-pot reaction when **142** was treated with acidic conditions (TFA:H_2O, 95:5), which gave an intermediate **143**. This was followed by addition of triethyl silane as a reducing agent, which afforded the desired natural product **144** in 80% yield from **142** (an overall yield of 25.2% from **132**) (Scheme 30).



Scheme 30: Total synthesis of cremastrine **144**

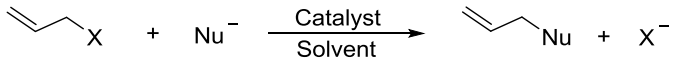
On the other hand, unnatural analogue **145** has been synthesised in 78% yield over three steps starting from **140** (Scheme 31).[55]



Scheme 31: Synthesis of unnatural analogue **145**

1.1.2. Tsuji-Trost allylation

The Tsuji-Trost reaction (sometimes named allylic alkylation or Trost allylic alkylation) is the substitution reaction between a substrate containing a leaving group in an allylic position and carbon nucleophile in the presence of palladium catalyst (Scheme 32).[59]



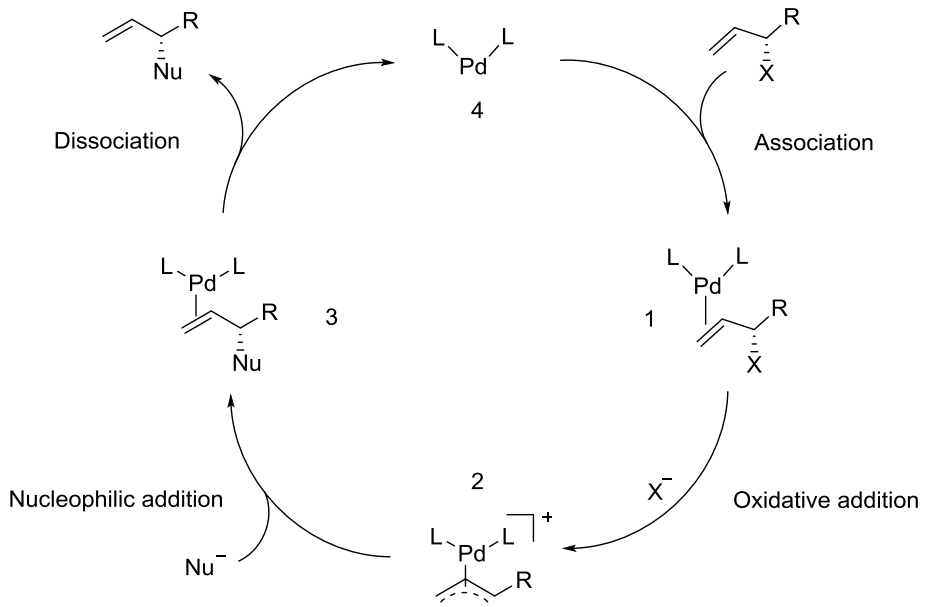
X = OAc, Cl, Br, OCO_2R, OCOR, etc.

Catalyst = $Pd(PPh_3)_4$, $Pd(dba)_3$, $Pd[(C_3H_5)Cl]_2$, $PdCl_2(PPh_3)_2$, $Pd(OAc)_2$, etc.

Scheme 32: Tsuji-Trost reaction

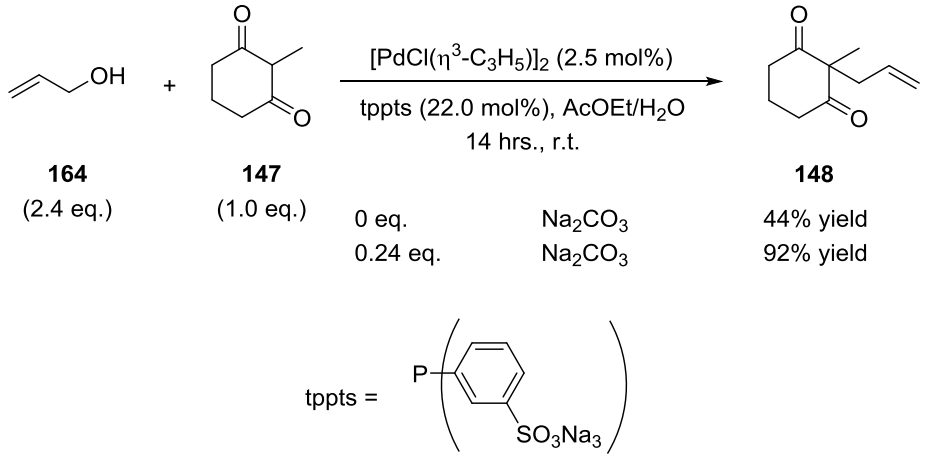
This allylation reaction was discovered in 1965 by Jiro Tsuji[60] and then developed by Barry Trost in 1973.[61] Various types of leaving groups were screened; phosphine ligands,[61] and many different oxygen, carbon and nitrogen-based nucleophiles were also tested. In addition, a broad range of metal complexes instead of palladium were tested. These included molybdenum, iron, platinum, ruthenium, tungsten, rhodium and nickel; however, none were an effective as palladium. This is due to palladium catalyst possessing, excellent stability, high functional group tolerance, and low sensitivity towards water and air in comparison with other metals.[62] Use of different palladium catalysts was led to an improvement in the asymmetric allylic alkylation strategies. These results led to significant developments in many different applications such as natural product synthesis and medicinal chemistry. This is because of the ability to synthesise carbon-carbon, carbon-oxygen and carbon-nitrogen bonds.

The general catalytic cycle for transition metal-catalysed allylic alkylations is organised in four key steps. These steps are; the formation of metal-olefin complex (association), ionisation (oxidative addition), nucleophilic addition, and decomplexation (regeneration of catalyst or dissociation) (Scheme 33).[63]



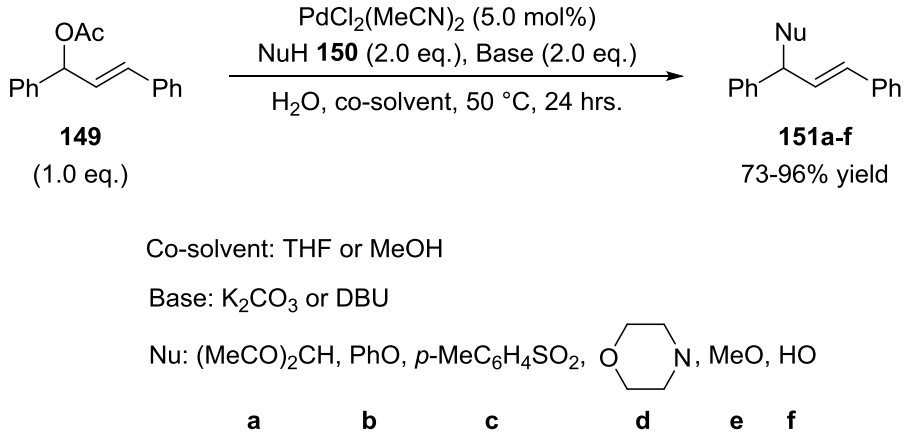
Scheme 33: Mechanism of the Tsuji-Trost reaction

From the literature, it has been observed that there are significant applications of the Tsuji-Trost allylation in organic synthesis. Kinoshita *et al*.[64] indicated the method to prepare 2-allyl-2-methylcyclohexane-1,3-dione **148** *via* the Tsuji-Trost reaction (Scheme 34). This was done by treatment of 2-methylcyclohexane-1,3-dione **147** with allyl alcohol **146** in the presence of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ as a catalyst and tris(*m*-sulfonatophenyl)phosphine trisodium salt (tppts) as ligand. This gave the desired product **148** in a 44% yield. Interestingly, they noticed that addition of a catalytic amount of Na_2CO_3 improved the yield to 92%. This is because Na_2CO_3 prevented transesterification of AcOEt with allyl alcohol, where the reaction occurred in an AcOEt/H_2O biphasic system.[64]



Scheme 34: Reaction of 2-methylcyclohexane-1,3-dione **147** with allyl alcohol **146** *via* Tsuji-Trost reaction

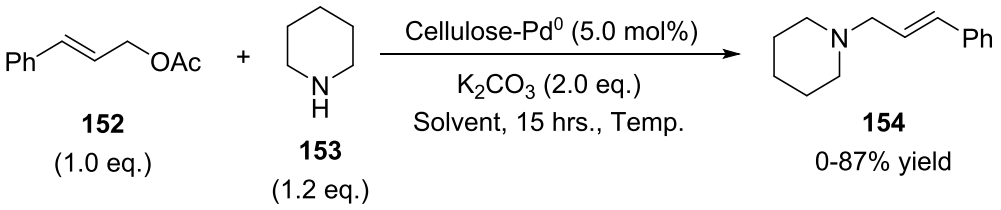
Muzart and co-workers[65] conducted a study on the nucleophilic substitution reaction between 1-acetoxy-1,3-diphenylpropene **149** and different types of nucleophilic reagents **150** in the presence of $PdCl_2(MeCN)_2$ as a catalyst, and K_2CO_3 or DBU as base (Scheme 35).[65] They indicated that the reaction was very slow as **149** needed 6 days to afford **151a** in a 17% yield. After that, the reaction was repeated by using a range of co-solvents. It was observed that they had a significant impact on the selectivity and efficiency of the reaction. For example, using a mixture of water and THF (1:1) afforded 36% yield in 6 days. Conversely, using methanol as co-solvent gave 92% yield in 24 hours.[65]



Scheme 35: Nucleophilic substitution of 1-acetoxy-1,3-diphenylpropene **149** with **150** to give **151a**-**f**

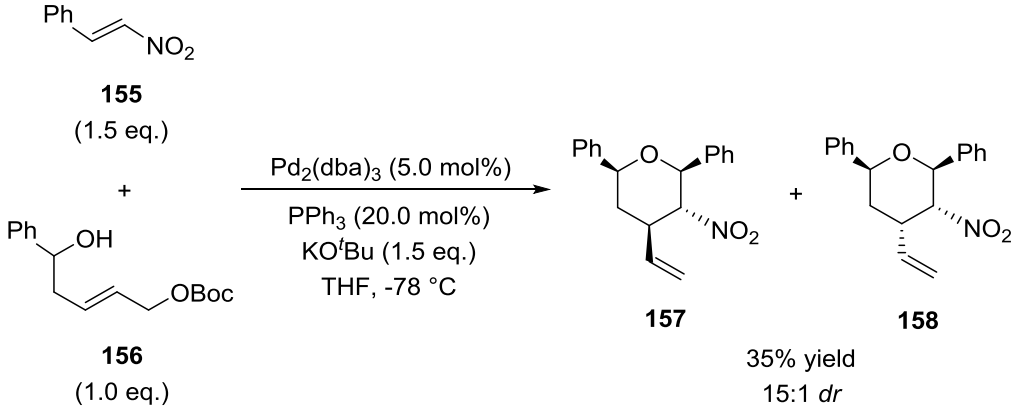
Vaddula *et al*.[66] indicated the optimisation in the reactions conditions of Tsuji-Trost allylation to synthesise allylic amine compounds **154**. This was done using *N*-allylation of piperidine **153** by cinnamyl acetate (allylic substrate) **152** in the presence of K_2CO_3 as a base and cellulose-Pd as catalyst.[66] This catalyst can be a more effective, reusable and cheap alternative than other palladium catalysts. They used various types of solvents and found that DMF at 110 °C (Table 1, entry 4) gave the best result, where it gave 87% yield of compound **154**. This is because the cellulose requires high temperatures to dissolve. Conversely, they observed that using H_2O as a solvent (Table 1, entry 1) was not suitable because it reacted with **152** to give the corresponding alcohol. While, using the other solvents gave a low yield (Table 1, entries 2,3,5 and 6).[66]

Table 1: Solvent assessment for the reaction conditions of **69** with **70**



Entry	Solvent	T (°C)	Yield (%)
1	H_2O	100	0
2	THF	66	10
3	DMF	90	41
4	DMF	110	87
5	MeCN	82	35
6	Toluene	100	16

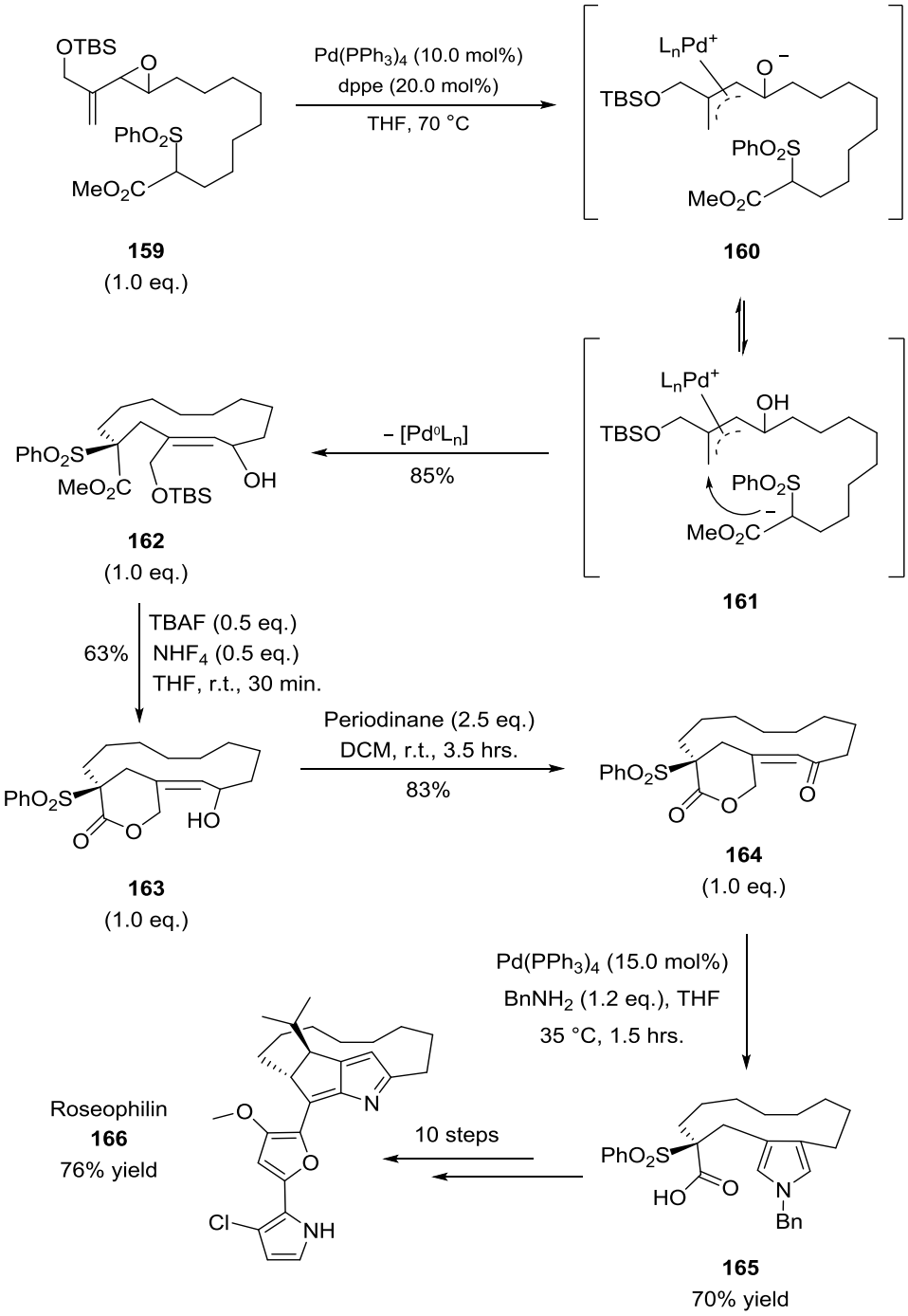
Wang and Menche[67] developed a new method for the Tsuji-Trost reaction between β-nitrostyrene **155** and homoallyl carbonate substrate **156** (Scheme 36).[67] They used $Pd_2(dba)_3$ as a catalyst and KO^{t}Bu as base, the result gave two products **157** and **158** in good *dr* (15:1) with 35% yield.[67]



Scheme 36: Reaction between nitrostyrene **155** and homoallyl carbonate substrate **156** *via* Tsuji-Trost reaction

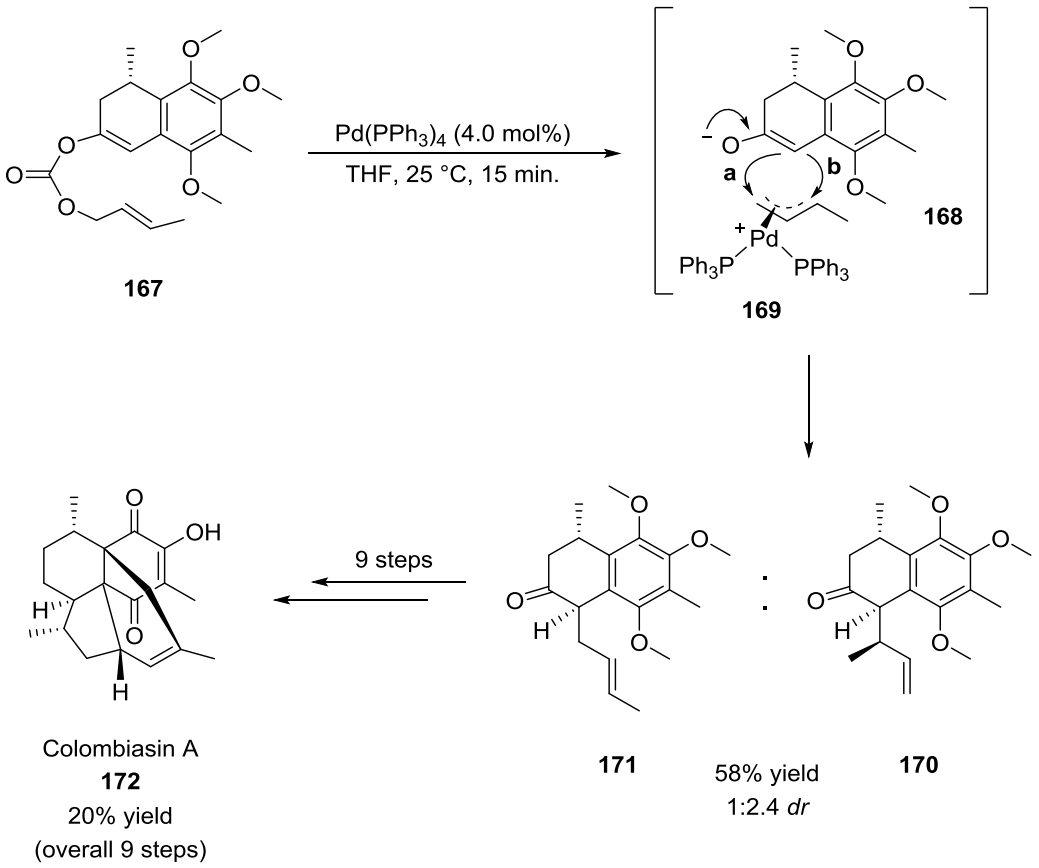
Fürstner and Weintritt[68] demonstrated the method for the preparation of alkaloid roseophilin **166** (an antibiotic isolated from *Streptomyces griscovirides* shown to have antitumor activity)[69] in a unique way. This synthetic method included many steps to synthesise the desired natural product **166**, and two from these steps were for Tsuji-Trost reaction. The first step included preparation of the macrocyclic ring by an intramolecular reaction of the allylic epoxide **159** in the presence of $Pd(PPh_3)_4$ and dppe as a catalyst and ligand respectively, in THF at 70 °C to give **162** in a very good yield (85%) (Scheme 37). In this step there was selectivity in the opening of the allylic epoxide ring to form alkoxide intermediate **160**. Then, **160** gave the stabilised carbanion species **161** *via* proton transfer, followed by a cyclisation of **161** at the least hindered position of the π-allyl system to afford **162**. It was found that the reaction was diastereoselective under normal conditions without the need for an external base to deprotonate the β-sulfone ester group. After that, cyclisation of **162** by using TBAF/NH_4F afforded lactone **163** in a good yield (63%). Subsequent oxidation using a Dess-Martin oxidation

on **163** gave ketone **164** in a very good yield (83%). Another Tsuji-Trost reaction was used with the same catalyst as above in $BnNH_2$ and THF at 35 °C affording metapyrrolocyclophane **165** in a good yield (70%). Subsequently, ten steps had been achieved to afford the desired natural product roseophilin **166** in 76% yield (Scheme 37).[70]



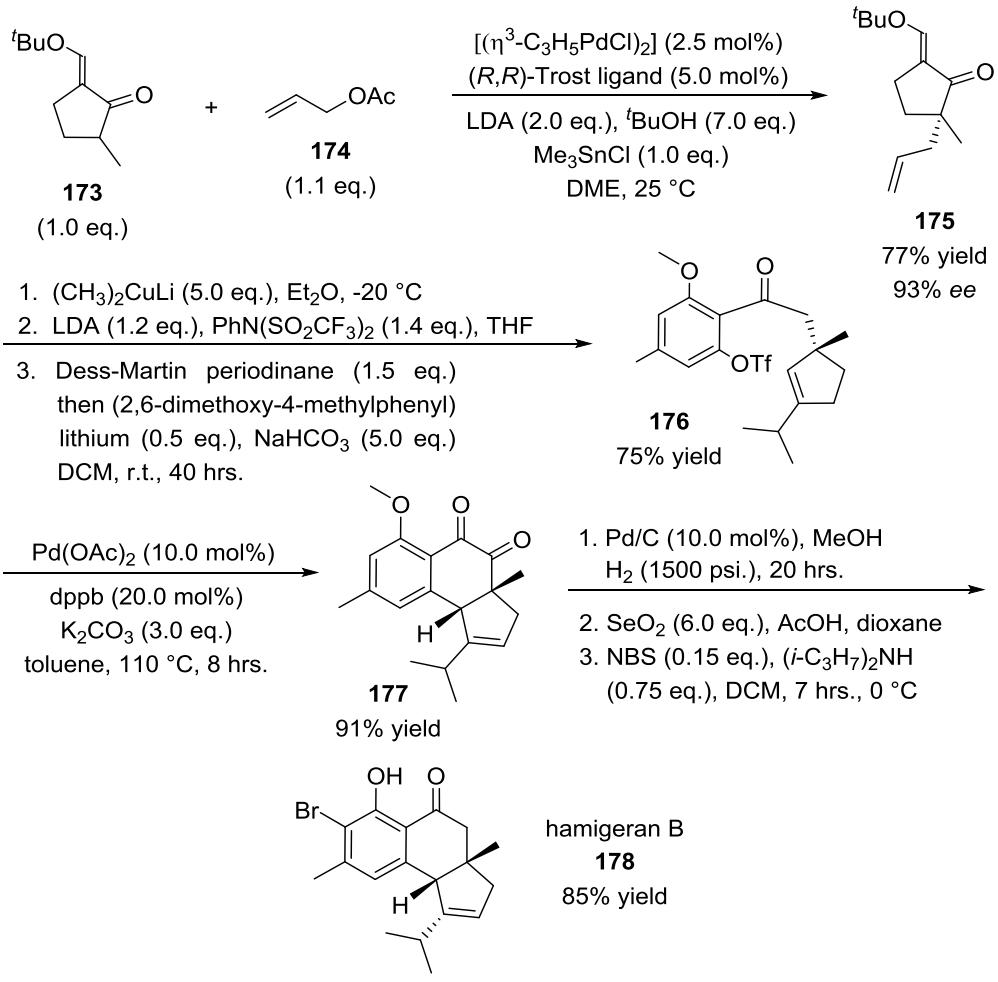
Scheme 37: Synthesis of natural product roseophilin **166**

The preparation of colombiasin A **172** (a marine natural product) was achieved by Nicolaou *et al.* in 2001 *via* regioselective Tsuji-Trost reaction of a crotyl enol carbonate **167** (Scheme 38).[71,72] It was observed that treatment of **167** with $Pd(PPh_3)_4$ in THF at room temperature led to intermediate **168**+**169**, which lead to the production of a mixture of the two regioisomers (**170**:**171**, 2.4:1 *dr*) in good yield (58%). From the literature precedent mentioned that the addition of palladium-catalysed allyl species will occur easily on the less-hindered position of the complex to afford the undesired regioisomer product **171** (Scheme 38, pathway a).[71] Conversely, it was observed that **170** was the major product in this reaction. They suggested that electronic factors may have more of an effect than steric effects due to the secondary carbon atom terminus in the allylic domain of complex **169**. This is due to accumulation of a partial positive charge on the crotyl group in complex **169**; therefore, the attack on the more-substituted carbon is more favourable than the other positions. They indicated that using ligands containing better s-donor potential such as $P(O^iPr)_3$ or dppe, gave a reasonable ratio of regioselectivity which meant formation of the undesired product **171** is observed in lower quantities (Scheme 38, pathway b). Compound **170** followed by nine consecutive steps to afford the desired natural product colombiasin A **172** in an overall yield of 20% (Scheme 38).[71]



Scheme 38: Synthesis of natural product colombiasin A **172**

Trost *et al.* have demonstrated a method to synthesise hamigeran B **178** (a marine sponge derived natural product from *Hamigera tarangaensis*),[73] which can be used as an antiviral agent.[73] This method included using cyclic ketone **173** as a starting material in the synthetic route (Scheme 39). The asymmetric alkylation of **173** with allyl acetate **174** in the presence of $[(\eta^3\text{-}C_3H_5PdCl)_2]$ as a catalyst and (*R*,*R*)-Trost's chiral ligand *via* the Tsuji-Trost reaction afforded α-allyl derivative **175** in a good yield (77%) and high *ee* (93%). Thereafter, the elaboration of **175** to furnish triflate **176** in 75% yield (over three steps). Followed by an intramolecular cyclisation of **176** in the presence of $Pd(OAc)_2$, dppb and K_2CO_3 as a catalyst, ligand and base respectively, in toluene gave product **177** in an excellent yield (91%). Subsequently, three steps had been conducted to produce the desired natural product hamigeran B **178** in a very good yield (85%) (Scheme 39).[73]



Scheme 39: Total synthesis of natural product hamigeran B **178**

1.1.3. Chiral pyrrolidines

Pyrrolidine is a saturated five-membered heterocyclic ring containing one nitrogen atom (also known as tetrahydropyrrole). Compounds containing a pyrrolidine ring usually possess a wide range of biological activities such as, anticancer, antitumor and anti-biotic activity.[74] Specifically, chiral pyrrolidines constitute a large group of heterocyclic organic compounds which are useful building blocks of pharmaceuticals,[75,76] vitamins, dyes, drug candidates, hormones, agrochemicals[77] and alkaloid natural products.[78,79] Furthermore, these compounds have been used as ligands for transition metals, organocatalysts,[80,81,82] and effective chiral controllers in asymmetric synthesis.[83-90]

Many natural products containing chiral pyrrolidines in their structure are found to be associated with a variety of pharmacological and physiological effects such as, (-)-lepadiformine **179**,[91] cocaine **180**,[92] nicotine **181**,[93] (+)-lapidilectine B **182**,[94] (+)-pumilotoxin B **183** and (-)-slaframine **184**[95] (Figure 5).

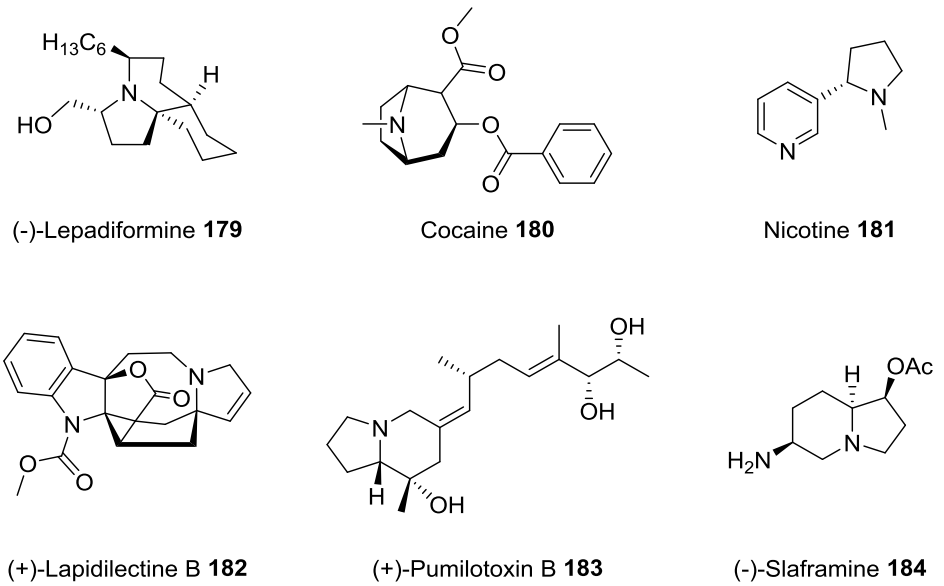
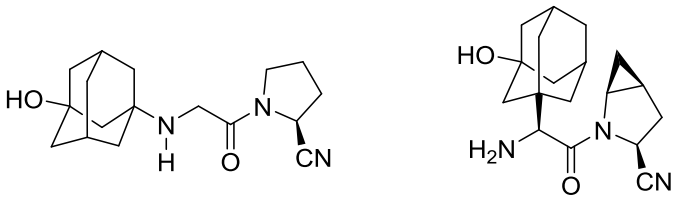


Figure 5: Compounds containing a pyrrolidine ring in their structures and exhibit pharmacological and physiological effects

In addition, two types of dipeptidic inhibitors containing a pyrrolidine ring in their structure, such as vildagliptin **185**[96] and saxagliptin **186**[97] have been authorised by FDA for treatment of Type II diabetes (Figure 6).

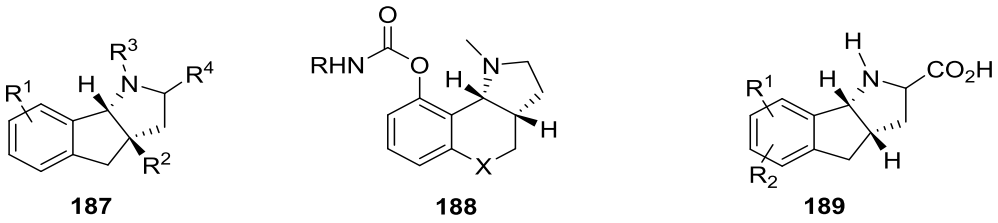


Vildagliptin **185**
(trade names Galvus, Zomelis)

Saxagliptin **186**
(trade name Onglyza)

Figure 6: Structure of Vildagliptin **185** and Saxagliptin **186**

It has been also observed that polycyclic pyrrolidines possess significant biologically activities. For example, substituted indenopyrrolidines **187** behave as antagonists of NMDA receptor[98] or hypoglycemic agents.[99] Moreover, compounds **188** and **189** have been studied as acetylcholinesterase inhibitors[100] and angiotensin converting enzyme inhibitor analogues[101] respectively (Figure 7).



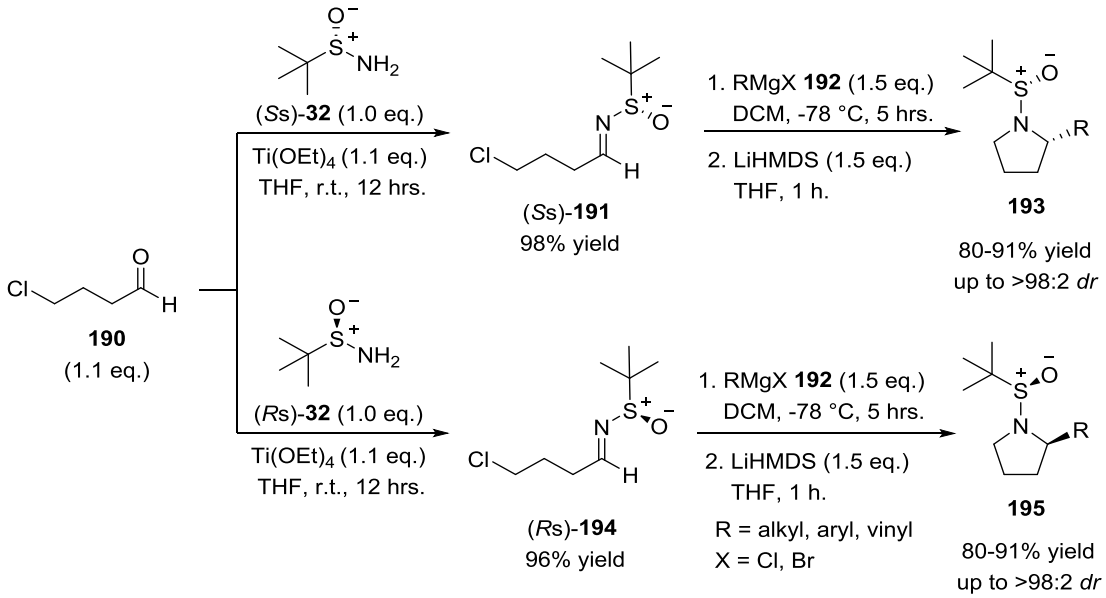
187 **188** **189**

R, R^1, R^2 = H, alkyl or aryl
X = Halogen

Figure 7: General structures of biologically active polycyclic pyrrolidines

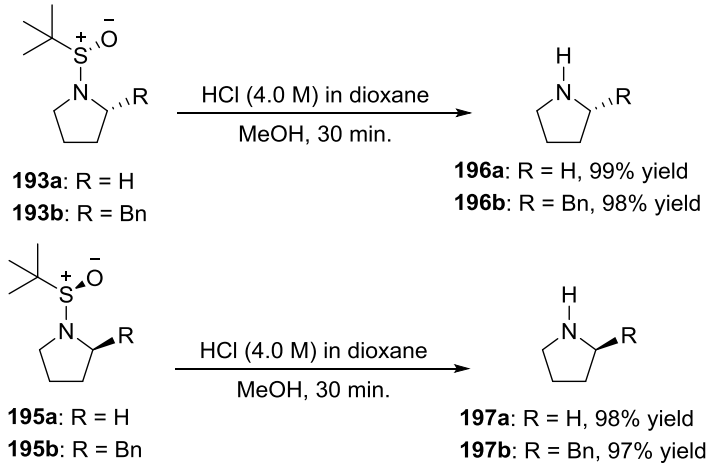
Recently, it has been observed that there is a significant interest in the stereoselective synthesis of chiral pyrrolidines using *p*-toluenesulfinyl imines **3** or *tert*-butanesulfinyl imines **4** as a chiral auxiliary under mild and operationally simple reaction conditions. Reddy and Prashad[102] reported a method to prepare 2-substituted pyrrolidines **193** in high *dr* (up to >98:2) with very good to excellent yields (80-91%) (Scheme 40). This was achieved using (S_S)-chiral *γ*-chloro *N*-*tert*-butanesulfinyl aldimine **191**, which was prepared *via* treatment of 4-chlorobutanal

190 with (*S*)-*tert*-butanesulfinamide **32**.[103] Thereafter, addition of Grignard reagent **192** to **191**, followed by ring cyclisation in a one-pot reaction under basic conditions afforded the desired product **193**. Following the same procedure, the synthesis of the opposite enantiomer, *i.e.* 2-substituted pyrrolidine **195** using (R_S)-γ-chloro *N*-*tert*-butanesulfinyl aldimine **194** was achieved [prepared from (*R*)-*tert*-butanesulfinamide **32**] (Scheme 40).



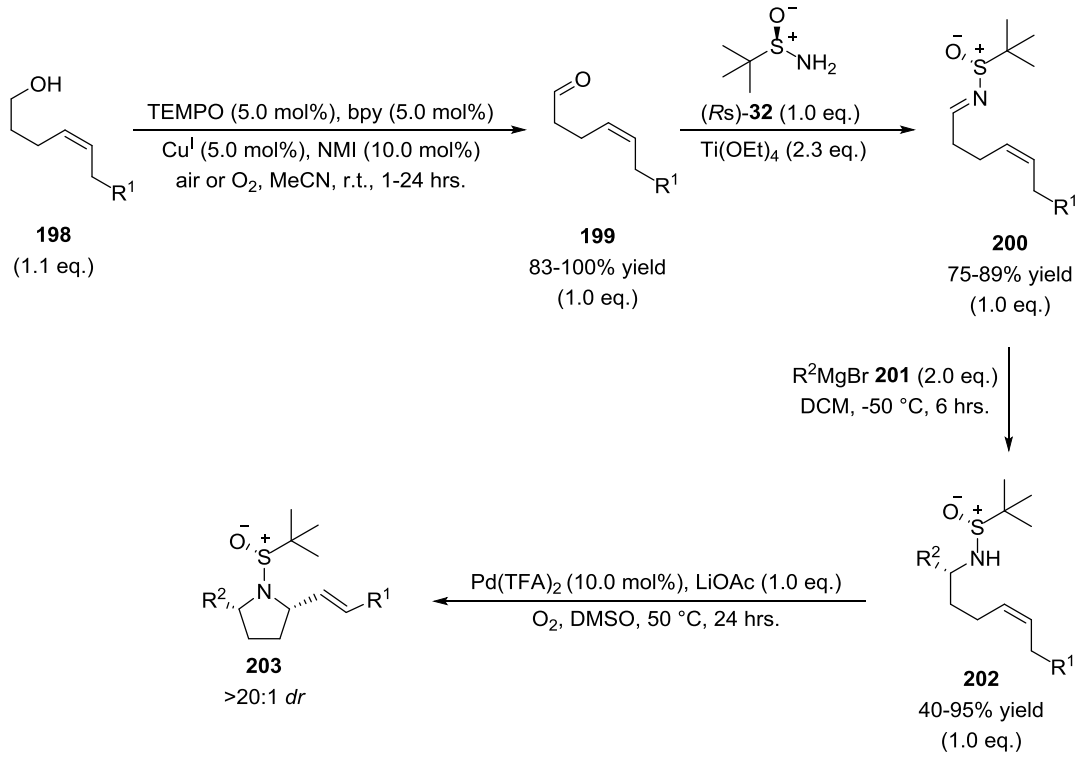
Scheme 40: Preparation of 2-substituted pyrrolidines **193** and **195** *via* reaction between various Grignard reagents 192 with γ-chloro *N*-sulfinyl aldimine (*S*s)-**191** and (*R*s)-**194**

Subsequently, deprotection was achieved by treating **193a**-**b** and **195a**-**b** under mild acidic conditions to furnish free amines **196a**-**b** and **197a**-**b** (Scheme 41).[102]



Scheme 41: Deprotection of the sulfinyl group

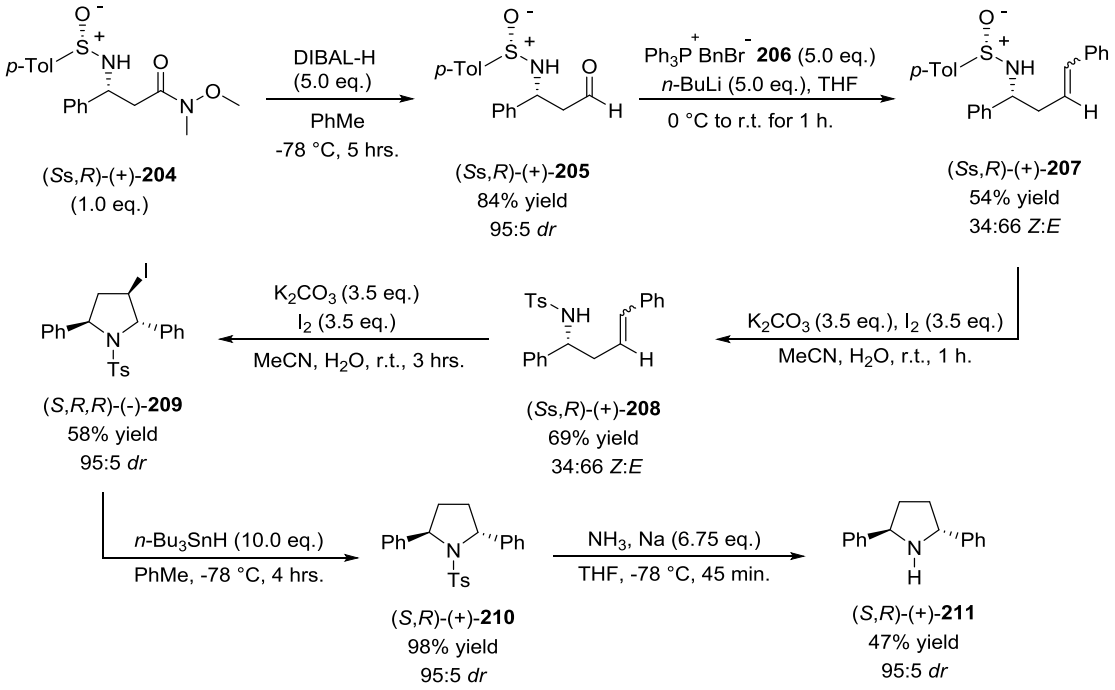
Redford *et al*.[104] reported the preparation of 2,5-disubstituted pyrrolidines **203** in high *dr* (up to >20:1) with yields ranging from medium to very good (54-85%) (Scheme 42). Selective aerobic oxidation of **198** in the presence of bpy, Cu^{I} and TEMPO as a catalysts afforded aldehydes **199**,[105] which were then treated with (*R*)-*tert*-butanesulfinamide **32** to afford the sulfinimine analogues **200** in good yields (75-89%).[17,23] Stereoselective addition of a variety of Grignard reagents **201** to **200** gave a wide range of enantiomerically pure of α-substituted sulfinamides **202** in moderate to excellent yields (40-95%).[17] The final step included an additional aerobic oxidative cyclisation of **202**, but using $Pd(TFA)_2$ as a catalyst and LiOAc as base to furnish desired products **203** (Scheme 42).



203a: R^1 = Ph, R^2 = Me, 85% yield
203b: R^1 = H, R^2 = ^{i}Propyl, 64% yield
203c: R^1 = H, R^2 = Ph, 68% yield
203d: R^1 = H, R^2 = Cl, 71% yield
203e: R^1 = H, R^2 = $PO(OCH_3)_2$, 54% yield
203f: R^1 = H, R^2 = CO_2Me, 80% yield
203h: R^1 = H, R^2 = 2-ethyl-1,3-dioxanyl, 67% yield
203i: R^1 = H, R^2 = allyl, 70% yield

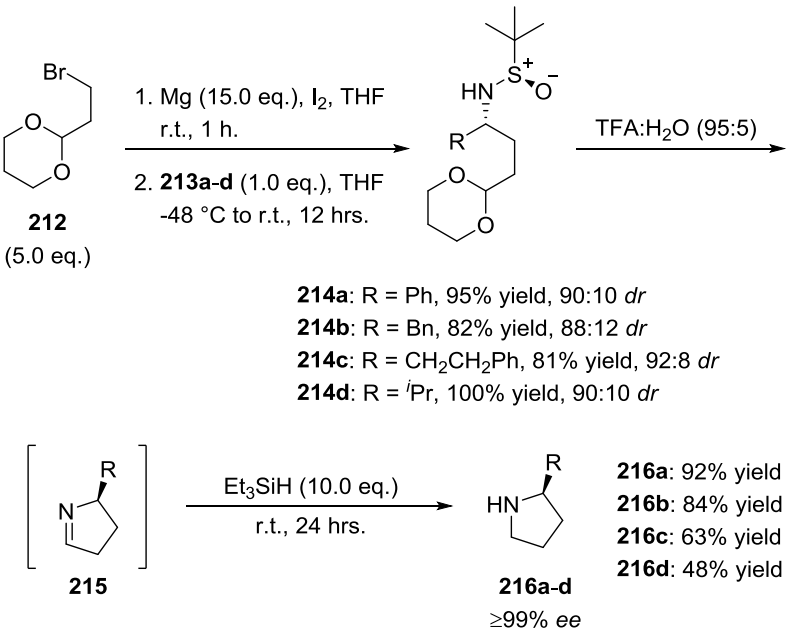
Scheme 42: Synthesis of 2,5-disubstituted pyrrolidines **303** using aerobic oxidation

Davis, Song and Augustine[106] have reported a methodology for the preparation of enantiomerically pure *trans*-2,5-diphenyl pyrrolidine **211** in a high *dr* (>99:1) with 47% yield (Scheme 43). This was accomplished using sulfinimine-derived *N*-sulfinyl *β*-amino Weinreb amide **204** as a starting material. Hence, compound **204** was reduced selectively with DIBAL-H, resulting in the isolation of *N*-sulfinyl *β*-amino aldehyde **205** in a very good yield (84%) and 95:5 *dr*. Homoallylic sulfinamide **207** was then obtained in a mixture of *Z* and *E* isomers (34:66) with 54% yield *via* treatment of **205** with benzyltriphenylphosphonium bromide **206** in the presence of *n*-BuLi as a base. This was followed by the oxidation of the *N*-sulfinyl group of **207** using I_2 in the presence of K_2CO_3, affording the corresponding homoallylic sulfonamide **208** in the same ratio of *Z* and *E* isomers with 69% yield. The next step included iodocyclisation of **208** giving 3-iodo *trans*-2,5-diphenyl pyrrolidine **209** in 58% yield with 95:5 *dr*, which was achieved successfully using the same procedure used in the preparation of **208**. Compound **209** was then reduced using *n*-Bu_3SnH furnishing 2,5-diphenyl-1-tosylpyrrolidine **210** in an excellent yield (98%) with 95:5 *dr*. The final step involved removing the tosyl group of **210** using Na/NH_3 (liq.) to give the desired product **211** in a high diastereoisomeric ratio with 47% yield (Scheme 43).



Scheme 43: Asymmetric synthesis of *trans*-2,5-diphenyl pyrrolidine **211** using *N*-sulfinyl β-amino Weinreb amide **204** as a starting material

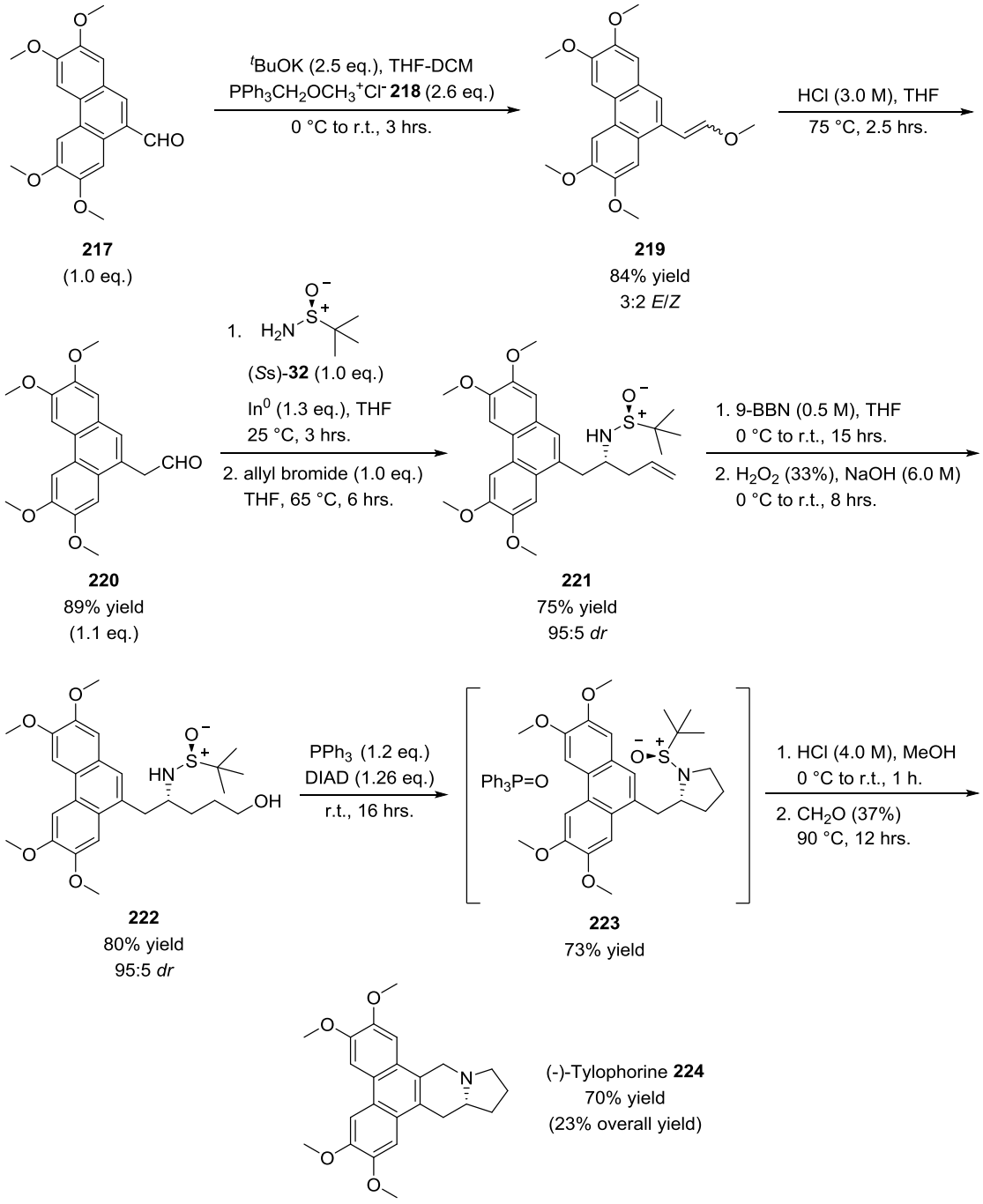
Brinner and Ellman[107] indicated a concise and efficient methodology for the preparation of 2-substituted pyrrolidines **216** enantioselectively (Scheme 44). This was achieved over three steps starting from simple aldehydes. First step included preparation of the Grignard analogue of **212**, followed by a nucleophilic addition of **212** to sulfinimines **213a**-**d** gave the corresponding sulfinamides **214a**-**d** in 82-100% yields and *dr* from 88:2 to 92:8. Sulfinimines **213a**-**d** were prepared *via* Ellman's protocol using appropriate aldehydes.[23] Deprotection of the acetal and chiral auxiliary groups at **214a**-**d** using acidic conditions (TFA/H_2O) has activated the cyclisation to afford an intermediates **215a**-**d**, followed by reduction of imine with Et_3SiH provided **216a**-**d** in one step. The desired products were obtained in 48-92% yields with high *ee* (≥99%, evaluated by HPLC) (Scheme 44).



Scheme 44: Asymmetric synthesis of 2-substituted pyrrolidine derivatives **216a**-**d**

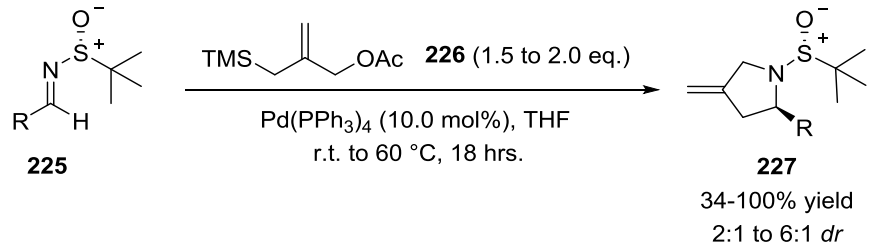
Torrecillas and Gomez[108] reported the total synthesis of (-)-tylophorine **224** (phenanthroindolizidine alkaloid), which is natural product isolated from *Asclepiadaceae* plant family.[109,110] The synthetic route was achieved in nine steps starting from commercially available aldehyde **217** (Scheme 45). First step included Wittig reaction *via* treatment of **217** with ylide derivative **218** gave **219** in a very good yield (84%) with *E*/*Z* 3:2 ratio (determined by ^{1}H NMR spectroscopy). The hydrolysis of **219** using acidic conditions (HCl 3.0 M) was performed to afford the corresponding aldehyde **220** in a very good yield (89%). The product **220** was then condensed with (*S*)-*tert*-butanesulfinamide **32** to give the corresponding sulfinimine, followed by indium-mediated allylation in a one-pot reaction furnished **221** in a high *dr* (95:5) with good yield (75%). Hydroboration-oxidation was then performed on the alkene bond at **221** gave **222** in 80% yield. Subsequently, Mitsunobu conditions employed with **222** provided 73% yield of an inseparable mixture of the desired product **223** and triphenylphosphine oxide by-product. To avoid this problem, the chiral auxiliary group at **223** was then removed under acidic conditions (HCl 4.0 M) afforded the corresponding amine, which was treated with aqueous formaldehyde (37%) in a one-pot reaction

afforded the desired natural product **224** in 70% yield (23% overall yield) (Scheme 45).



Scheme 45: Total synthesis of natural product (-)-tylophorine **224**

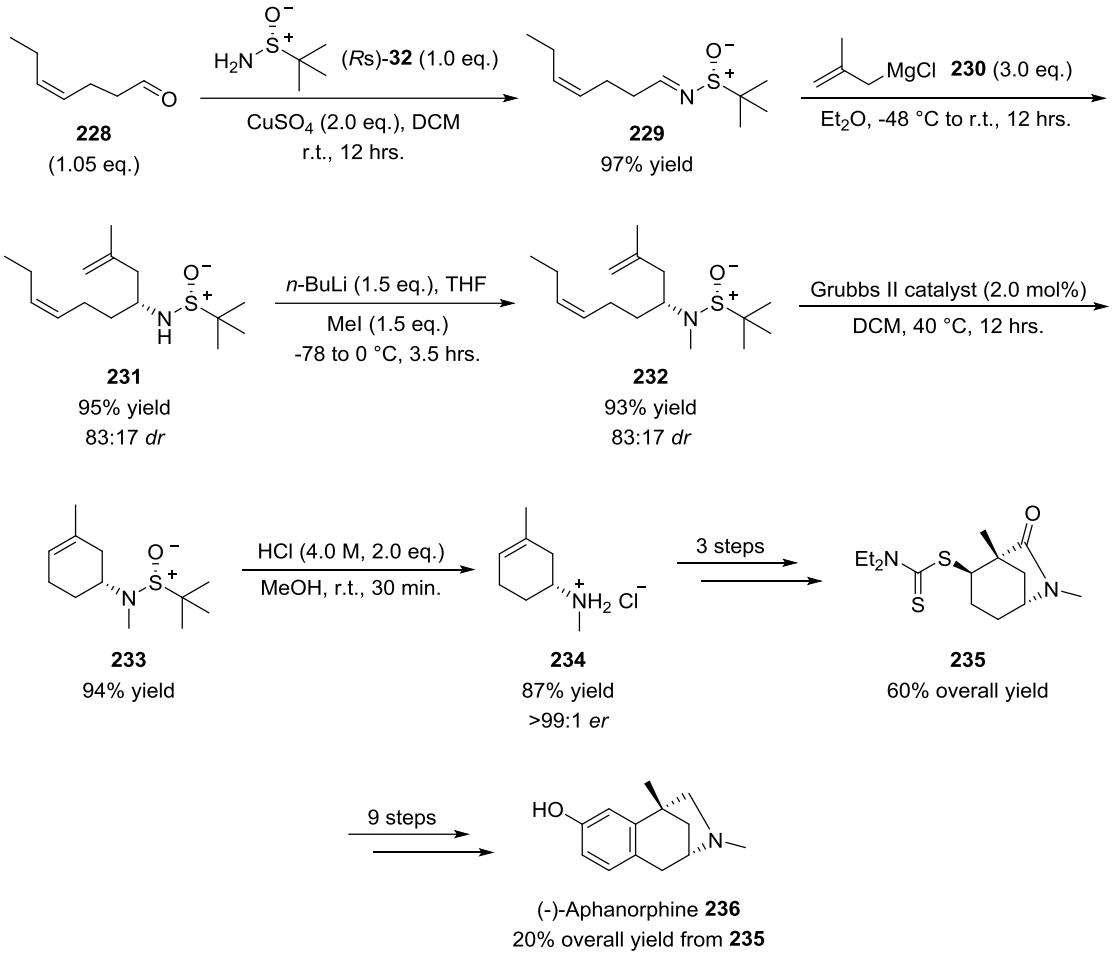
Moreover, in 2013, a methodology for the synthesis of the methylene-pyrrolidine derivatives **227** was reported by Procopiou *et al*.[111] This was done by cycloaddition of chiral sulfinimines **225** with trimethylenemethane (TMM) **226**, which gave the desired products **227** in 2:1 to 6:1 *dr* and 34-100% yields. This type of chemical scaffold is useful as a building block for natural products and pharmaceuticals due to two functional of *N*-protected amine and methylene group, which can be further derivatised (Scheme 46).



Scheme 46: Cycloaddition of chiral *tert*-butanesulfinimines **225** with trimethylenemethane **226** to afford methylene-pyrrolidine derivatives **227**

Grainger and Welsh[112] reported the formal synthesis of (-)-aphanorphine **236** alkaloid natural product, which was isolated from the freshwater blue-green alga *Aphanizomenon flos aquae* by Gulavita *et al*.[113] In order to synthesise a literature product **229**, reaction between 4-heptenal **228** and (*R*)-*tert*-butanesulfinamide **32** gave (R_S)-sulfinimine **229** in an excellent yield (97%). This was followed by nucleophilic addition of Grignard reagent **230** to **229** provided the corresponding sulfinamide **231** in 95% yield and good *dr* (83:17). The stereochemistry of the C-N bond at **231** was determined based on Ellman and workers explanation.[7] *N*-Methylation of **231** was then performed using *n*-BuLi/MeI gave **232** in a 93% yield. Ring closure of **232** *via* cross metathesis reaction afforded the corresponding alkene **233** in an excellent yield (94%). The deprotection of the protecting group at **233** was then conducted using acidic conditions (HCl 4.0 M) and gave the desired literature compound **234** as a single enantiomer (*er* >99:1, evaluated by HPLC) in very good yield (87%). Following this, the pyrrolidine derivative **235** was prepared in 60% yield from **234** *via* three sequences steps. The product **235** was then used as a key intermediate for the synthesis of **236**, which required nine

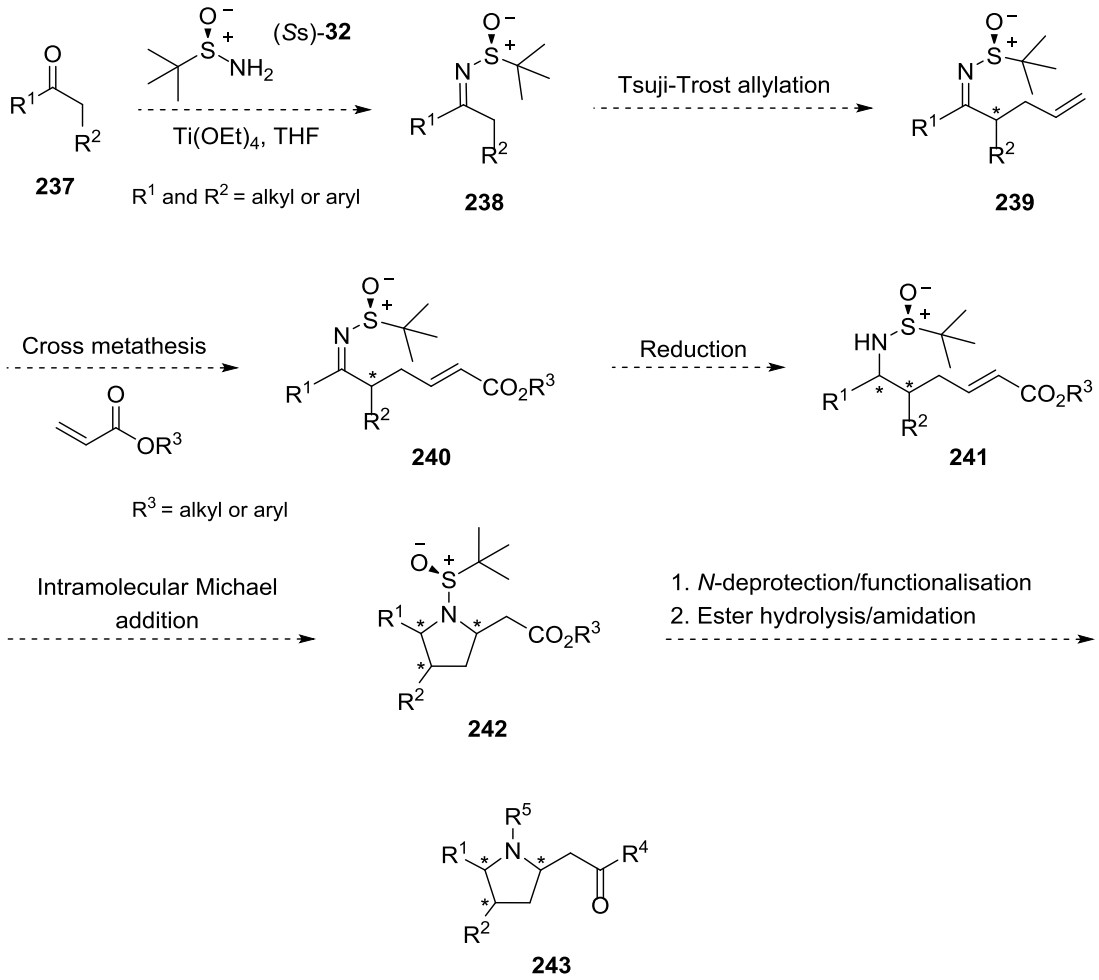
steps to provide **236** in 20% yield (overall yield for nine steps starting from **235**) (Scheme 47).



Scheme 47: Formal synthesis of natural product (-)-aphanorphine **236**

1.1.4. Aims and objectives

The aim of this part is to investigate the potential use of sulfinimines for the stereoselective synthesis of a novel functionalised pyrrolidine-like scaffolds **242**. These compounds can contain a variety of ring systems and heteroatoms bearing useful functionalities which can be further derivatised **243**. Hence, this type of the chemical scaffold would be useful for drug discovery, natural product synthesis and library synthesis due to two points of diversity on the *N* and *O* atoms. In our approach, this will be performed using a range of sulfinimines **238** as starting materials. The starting compounds **238** will be prepared from the condensation of various ketones **237** with (*S*)-*tert*-butanesulfinamide **32** as a chiral auxiliary in the presence of $Ti(OEt)_4$ as a Lewis acid and water scavenger. Compound **238** will be used then to synthesise α-allyl sulfinimines **239** *via* the Tsuji-Trost reaction. Cross metathesis of **239** with an acrylate will be performed to prepare **240**. The next step will include the stereoselective reduction of **240** to afford corresponding sulfinamide derivative **241**. Several reducing agents will be examined in order to synthesise desired products **241** stereoselectively. Intramolecular Michael addition will be performed to deliver the pyrrolidine derivatives **242** under basic conditions. After achieving the synthesis of the pyrrolidine chemical scaffolds, our focus will then turned to further functionalise them. In particular, by taking advantage the two points of diversity at this type of the pyrrolidine chemical scaffold. By removing the chiral auxiliary and functionalising the ester group, the resulting scaffold core can be further derivatised to yield a sp^3-rich pyrrolidine chemical scaffold-like library (Scheme 48).

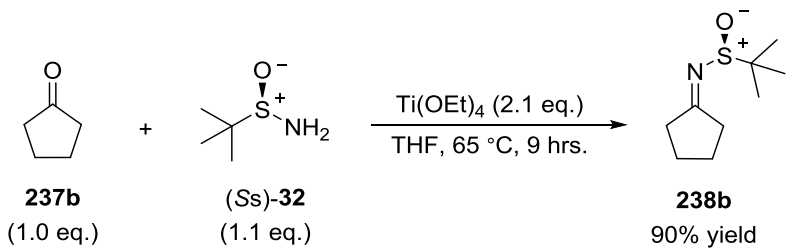


Scheme 48: Proposed strategy for synthesis of pyrrolidine chemical scaffolds **242**

1.2. Results and discussion

In order to obtain the target α-allyl sulfinimine, we proposed using the Tsuji-Trost reaction as an efficient methodology to provide an allyl electrophile. Accordingly, to access these moieties, preparation of the sulfinimine and a substrate containing a leaving group in an allylic position was required.

Synthesis of a range of sulfinimines was achieved successfully *via* the methodology pioneered by Ellman *et al*.,[7] This method included condensation between a suitable ketone **237b** and (*S*)-*tert*-butanesulfinamide **32** in the presence of $Ti(OEt)_4$ as a Lewis acid and water scavenger. From this procedure, we prepared (*S*)-(-)-*N*-cyclopentylidene-2-methylpropane-2-sulfinamide **238b** as a bench mark substrate in order to optimise the Tsuji-Trost allylation (Scheme 49).



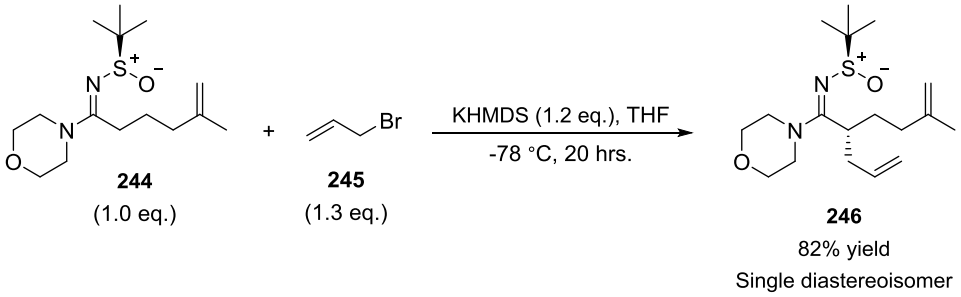
Scheme 49: Synthesis of **238b** by condensation of **237b** with (*S*)-*tert*-butanesulfinamide **32** in the presence of $Ti(OEt)_4$

1.2.1. Optimisation of Tsuji-Trost allylation

Different conditions were investigated varying the allyl source, solvent, base, catalyst, temperature, stoichiometry and reaction time for the purpose of improving this reaction.

1.2.1.1. Allyl source

Kochi and Ellman (2004)[114] reported the asymmetric allylation reaction of *N-tert*-butanesulfinyl amidines **244** at -78 °C by using allyl bromide **245** in the presence of THF and KHMDS as a solvent and base respectively. They reported that the desired product **246** was produced in a very good yield (82%) with a single diastereoisomer (Scheme 50).[114]

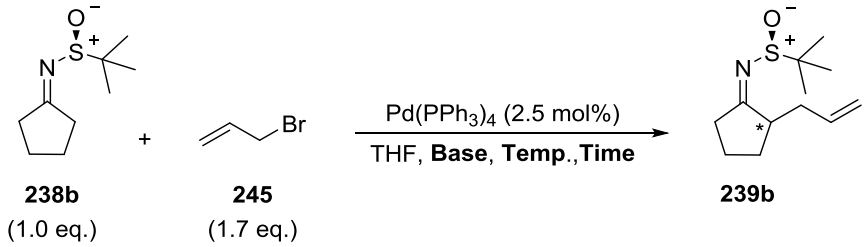


Scheme 50: Asymmetric allylation reaction of *N-tert*-butanesulfinyl amidine **246**

It was envisaged that this reaction could be a successful transformation of sulfinimines into allylated products for two reasons; firstly, we have used an allyl compound containing a good leaving group (Br). Secondly, Kochi and Ellman[114] indicated a similar reaction to synthesise α-allyl sulfinimine derivatives.

Compound **238b** was used as the starting material in our test substrate and treated in the beginning with **245** in the presence of $Pd(PPh_3)_4$ as a catalyst. The bases were Et_3N, KHMDS or Hünig's base (base for deprotonation of the α-hydrogen of **238b**) in different temperatures and reaction times. Unfortunately, we did not observe any conversion for this reaction to the desired product **239b** *via* TLC, HRMS or ^1H NMR spectroscopy (Table 2, entries 1-9).

Table 2: Investigation of **245** attempts on Tsuji-Trost allylation

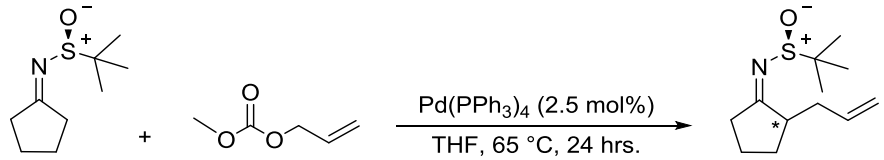


238b (1.0 eq.) + **245** (1.7 eq.) → **239b**

Entry	Base	T (°C)	Time (h)	Yield (%)
1	Et_3N	-78	20	-
2	Et_3N	25	24	-
3	Et_3N	25	48	-
4	Et_3N	65	6	-
5	Et_3N	65	24	-
6	KHMDS	-78	24	-
7	KHMDS	-78	48[1]	-
8	KHMDS	65	24	-
9	Hünig's base	65	24	-

1. Reaction was carried in the absence of $Pd(PPh_3)_4$.

On the contrary, when using allyl methyl carbonate **247** instead of **245** in dry THF in the presence of the same catalyst $Pd(PPh_3)_4$ and Et_3N, it was found the desired product **239b** could be obtained in 66% yield and ratio 3:1 of *dr* (Scheme 51).

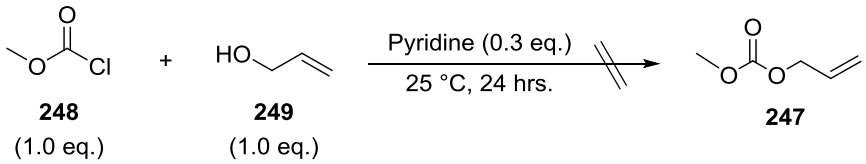


238b (1.0 eq.) + **247** (1.5 eq.) → **239b** 66% yield 3:1 *dr*

Scheme 51: Synthesis of **239b** using allyl methyl carbonate **238b**

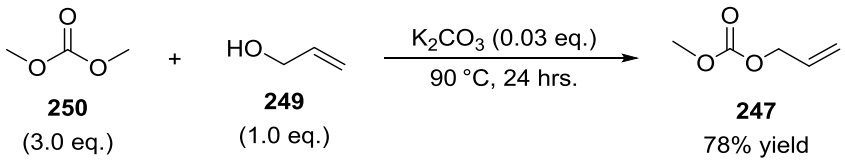
Despite the fact that the carbonate group has a lower ability as a leaving group compared to bromide, it was observed that **247** gave a good result compared with allyl bromide **245** in this reaction.

There were two ways to prepare **247**; the first being the nucleophilic addition of allyl alcohol **249** to methyl chloroformate **248** in the presence of pyridine. Unfortunately, no product was observed in this attempt (Scheme 52).[115]



Scheme 52: Preparation of **247** using methyl chloroformate **248**

The second method for the preparation of **247** was by reaction of allyl alcohol **249** with dimethyl carbonate **250** in the presence of K_2CO_3 as a catalyst at 90 °C. This method was successful and the desired product **247** was separated using distillation in a good yield (78%) (Scheme 53).

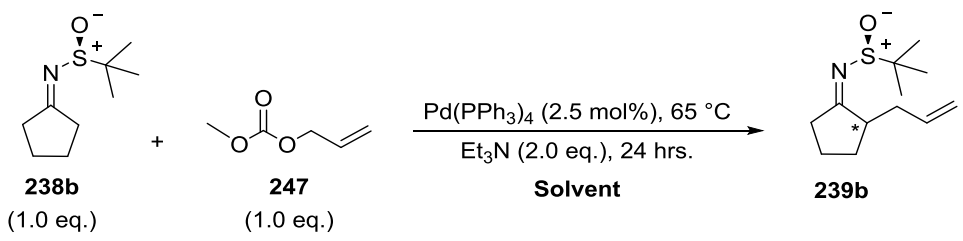


Scheme 53: Preparation of **247** using dimethyl carbonate **250**

1.2.1.2. Solvent choice

We have used different types of solvents (aprotic, protic, polar, non-polar and aromatic) without changing the other factors in order to explore the viability of this methodology. Non-polar solvent (Table 3, entry 1) was not efficient, 20% yield only of the desired product **239b** was obtained with low *dr* (3:1) was observed when *n*-hexane was employed. This is probably due to the solubility of the substrate **238b** and $Pd(PPh_3)_4$, which were only partially dissolved in *n*-hexane. Better results were observed with aromatic and protic solvents (Table 3, entries 3 and 4). Toluene gave **239b** in 44% yield with 4:1 *dr*, and MeOH afforded **239b** in 51% yield with 5:1 *dr*. On the other hand, differentiated results were observed with aprotic solvent, dioxane (Table 3, entry 2) gave **239b** in a good *dr* (6:1) with 47% yield. Low yields have been obtained when DMF, MeCN and DMSO (Table 3, entries 6, 7 and 8) were used, where the desired product **239b** was observed in 31%, 32% and 36% respectively. The solvents were used from bottles, which maybe were not very dry enough to complete the reaction without decomposition of the Pd catalyst. Finally, distilled THF (Na/benzophenone was used to remove the oxygen and moisture) afforded **239b** in the best yield (60%) with 3:1 *dr* (Table 3, entry 5). It was found that THF was the best solvent tested in terms of the yield (60%), while, it was observed that there is no big difference in the *dr* with others. Table 3 summarises our attempts at optimising the solvent choice for the benchmark reaction.

Table 3: Investigation of solvent effects on Tsuji-Trost reaction



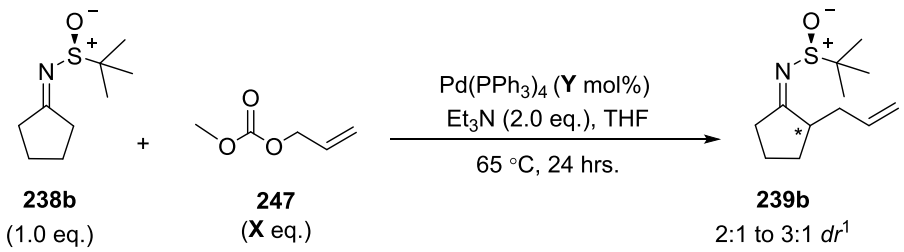
Entry	Solvent	Yield (%)[1]	*dr*[2]
1	*n*-Hexane	20	3:1
2	Dioxane	47	6:1
3	Toluene	44	4:1
4	MeOH	51	5:1
5	THF	60	3:1
6	DMF	31	4:1
7	MeCN	32	2:1
8	DMSO	36	5:1

1. Isolated yield.
2. The *dr* values were determined by ^{1}H NMR spectroscopy.

1.2.1.3. Optimal stoichiometry

The effect of varying stoichiometric quantities of the substrate **238b**, **247** and the catalyst on the yield and *dr* of this reaction was explored. It was observed that using **238b** (1.0 eq.), **247** (1.0 eq.) and 2.5 mol% of $Pd(PPh_3)_4$ affording 60% yield of the desired product **239b** (Table 4, entry 1). On the other hand, using an extra amount of **247** compared with **238b** led to increase in the yield, which 1.5 or 1.7 eq. of **238b** giving **239b** same yield (66%) (Table 4, entries 2 and 3). While using 2.0 eq. of **247** affording **239b** in 64% yield (Table 4, entry 4) with trace amounts of diallyl derivative detected by HRMS. Finally, using extra quantities of $Pd(PPh_3)_4$ (5.0 mol%) was not effective and similar results to using 2.5 mol% (Table 4, entries 5 and 6). It was observed that there was no a great change in the *dr* in the all cases as described in Table 4.

Table 4: Investigation into stoichiometric quantities effect of Tsuji-Trost reaction



238b (1.0 eq.) + **247** (**X** eq.) → **239b** 2:1 to 3:1 *dr*[1]

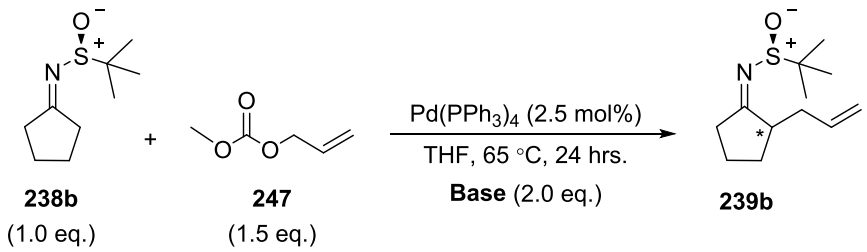
Entry	**247** (X eq.)	Y (mol%)	Yield (%)[2]
1	1	2.5	60
2	1.5	2.5	66
3	1.7	2.5	66
4	2.0	2.5	64
5	1	5	60
6	1.5	5	65

1. The *dr* values were determined by ^{1}H NMR spectroscopy.
2. Isolated yield.

1.2.1.4. Base choice

The reaction conditions were next evaluated with a range of bases to optimise this reaction. The use of Et_3N as a base gave the desired product **239b** in 66% with 3:1 *dr* (Table 5, entry 1). Using non-nucleophilic base (Hünig's base) afforded **239b** in better *dr* (4:1) and 59% yield (Table 5, entry 2). In addition, the reaction performed by using strong bases (LDA and KHMDS) resulted **239b** in 60% and 38% yields respectively with 3:1 to 4:1 *dr* (Table 5, entries 3 and 4). Conversely, the use of KO^{t}Bu gave the desired product **239b** in a low yield (30%) with 3:1 *dr* (Table 5, entry 5). It was found that Hünig's base was most suitable for this reaction, providing good yield and increased *dr* (Table 5, entry 2) as shown in Table 5.

Table 5: Optimisation of base in Tsuji-Trost reaction



238b (1.0 eq.) + **247** (1.5 eq.) → **239b**

Entry	Base	Yield (%)[1]	*dr*[2]
1	Et_3N	66	3:1
2	Hünig's base	59	4:1
3	LDA	60	3:1
4	KHMDS	38	4:1
5	KO^{t}Bu	30	3:1

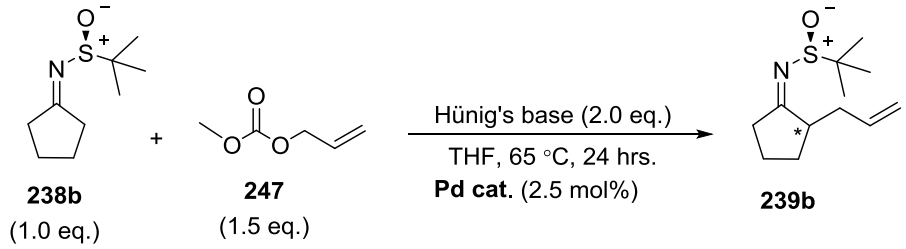
1. Isolated yield.
2. The *dr* values were determined by ^{1}H NMR spectroscopy.

1.2.1.5. Palladium catalyst source

Different types of Pd catalysts were used and it was observed that $Pd(PPh_3)_4$ (Table 6, entry 1) was the most effective, which afforded the desired product **239b** in 59% yield with 4:1 *dr*. But, it is well known that this catalyst is sensitive to air, where it decomposes to give triphenylphosphine (TPP) and triphenylphosphine oxide (TPPO).[116] The abundance of the TPPO is considered a crucial factor to assess the quality of $Pd(PPh_3)_4$ typically in the reaction mixture. On the other hand, there is not any known quantitative method of evaluating the purity of $Pd(PPh_3)_4$ before using, except very crudely according to its colour, which is the best quality of $Pd(PPh_3)_4$ assigned by its appearance as 'canary' yellow crystals. Hence, using any $Pd(PPh_3)_4$ between orange/brown and bright green (due to the presence of various Pd(II) species from decomposition) is not effective enough to complete the reaction.[116] While, other pre-catalysts did not provide any conversion demonstrated by TLC, HRMS or ^{1}H NMR spectroscopy for the crude reaction

mixture (Table 6, entries 2, 3 and 4). Only a trace of the desired product **239b** was observed when we used $Pd_2(dba)_3.CHCl_3$ (Table 6, entry 5). Finally, no desired product **239b** was detected when the reaction carried out without using Pd catalyst (Table 6, entry 6) as can be seen in Table 6.

Table 6: Investigation into Pd(0) source for Tsuji-Trost reaction



238b (1.0 eq.) + **247** (1.5 eq.) → **239b**

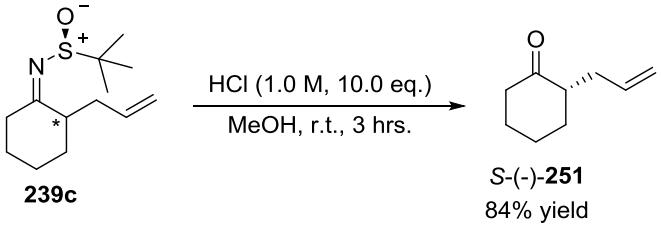
Entry	Pd catalyst	Yield (%)[1]	*dr*[2]
1	$Pd(PPh_3)_4$	59	4:1
2	$Pd(dba)_2$	-	-
3	$Pd(OAc)_2$	-	-
4	$Pd_2(dba)_3$	-	-
5	$Pd_2(dba)_3.CHCl_3$	<5	3:1
6	-	-	-

1. Isolated yield.
2. The *dr* values were determined by ^1H NMR spectroscopy.

From these attempts, it was determined that the optimal conditions currently available to synthesise α-allyl sulfinimine derivatives were THF (solvent), Hünig's base as a base, **247** (allyl source) and $Pd(PPh_3)_4$ as a catalyst.

The mechanism of the Tsuji-Trost allylation favours formation α-allyl sulfinimines **239** as a (*Z*)-isomer. This is due to the coordination of Pd metal of the catalyst to the sulfur or oxygen atom in *tert*-butanesulfinyl group then the carbon nucleophile will add to the allyl group.

The next step in our plan was to assign the stereochemistry of the newly created chiral centre at **239c**. The removal of the chiral auxiliary group on **239c** gave the corresponding chiral allyl ketone **251** as a single enantiomer (*ee* >99%) (Scheme 54). The *ee* value of **251** was tested by GC analysis on a chiral stationary phase. In the literature, the specific rotation of (*S*)-**251** is $[\alpha]_D^{23}$ = -15.8 (c = 3, MeOH), which was used to compare with our recorded value ($[\alpha]_D^{23}$ = -14.9, c = 3, MeOH)[117] (Figure 8 and 9).



239c

S-(-)-**251**
84% yield
>99% *ee*

Scheme 54: The removal of the *tert*-butanesulfinyl chiral auxiliary group on **239c** to give **251**

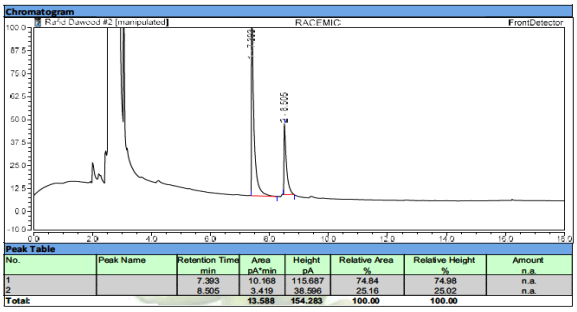


Figure 8: GC-FID analysis of mixture of products **251**

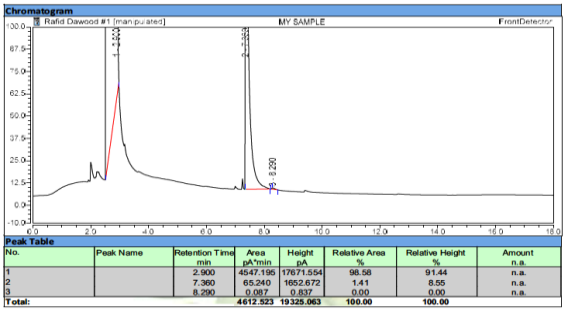
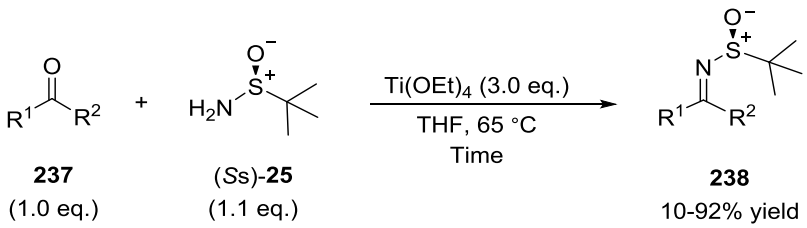


Figure 9: GC-FID analysis of crude product **251**

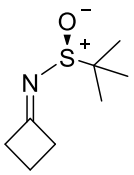
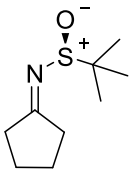
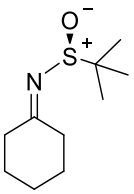
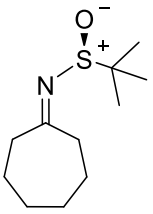
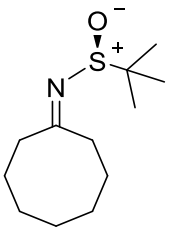
1.2.2. Synthesis of sulfinimines 238

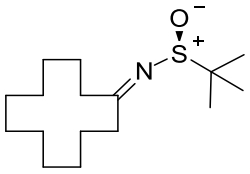
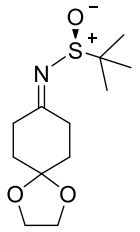
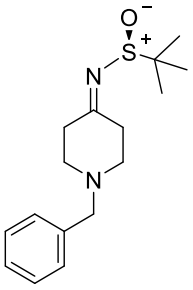
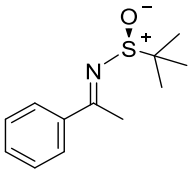
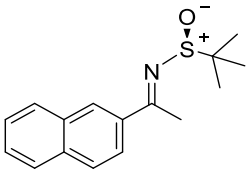
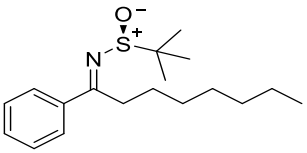
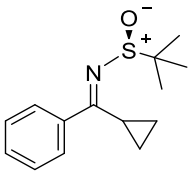
A number of sulfinimines **238** were prepared according to Ellman's methodology as shown in Table 7.[23]

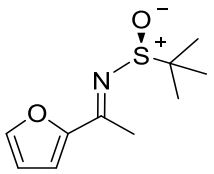
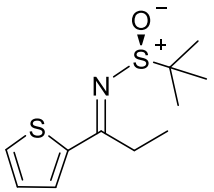
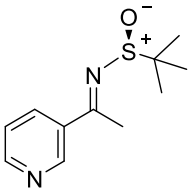
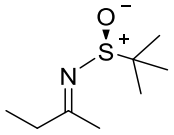
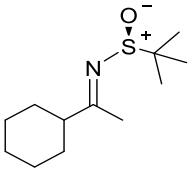
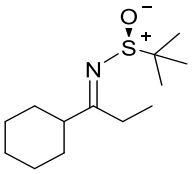
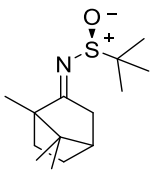
Table 7: Synthesis of sulfinimines **238** for Tsuji-Trost scope exploration

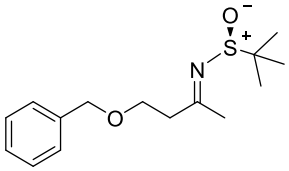
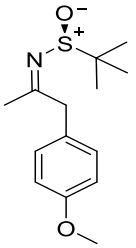
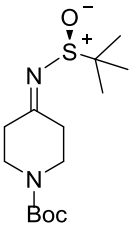
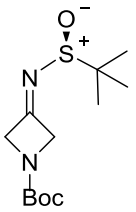
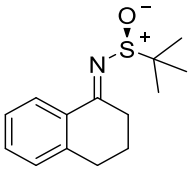
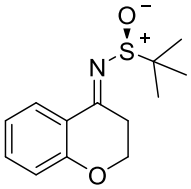
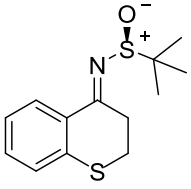


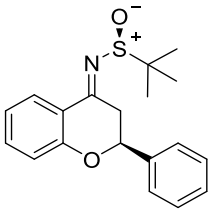
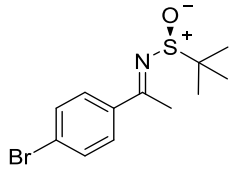
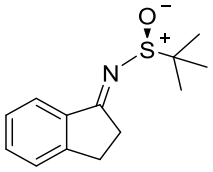
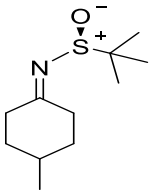
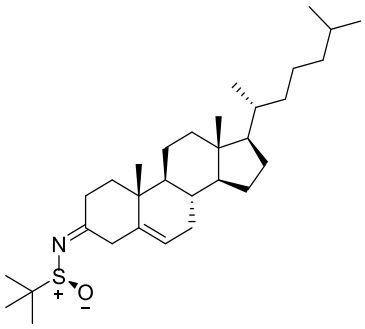
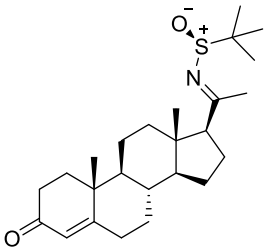
237 (1.0 eq.) | (*Ss*)-**25** (1.1 eq.) | **238** 10-92% yield

Entry	Ketone	R.T.[1] (h)	Yield[2] (%)	Sulfinimine	No.	*Z*/*E*[3]
1	**237a**	6	77		**238a**	N/A
2	**237b**	9	90		**238b**	N/A
3	**237c**	12	68		**238c**	N/A
4	**237d**	9	75		**238d**	N/A
5	**237e**	7	57		**238e**	N/A

Entry	Ketone	R.T.[1] (h)	Yield[2] (%)	Sulfinimine	No.	*Z*/*E*[3]
6	**237f**	5	91		**238f**	N/A
7	**237g**	9	61		**238g**	N/A
8	**237h**	7	51		**238h**	N/A
9	**237i**	6	92		**238i**	single isomer
10	**237j**	5	81		**238j**	single isomer
11	**237k**	9	61		**238k**	single isomer
12	**237l**	8	70		**238l**	1:16

Entry	Ketone	R.T.[1] (h)	Yield[2] (%)	Sulfinimine	No.	*Z*/*E*[3]
13	**237m**	6	90		**238m**	single isomer
14	**237n**	8	61		**238n**	1:8
15	**237o**	6	91		**238o**	single isomer
16	**237p**	5	82		**238p**	1:6
17	**237q**	8	67		**238q**	single isomer
18	**237r**	8	58		**238r**	1:4
19	**237s**	6	10		**238s**	1:2

Entry	Ketone	R.T.[1] (h)	Yield[2] (%)	Sulfinimine	No.	*Z*/*E*[3]
20	**237t**	7	80		**238t**	1:6
21	**237u**	6	79		**238u**	1:3
22	**237v**	5	61		**238v**	N/A
23	**237w**	7	58		**238w**	N/A
24	**237x**	5	86		**238x**	single isomer
25	**237y**	5	91		**238y**	single isomer
26	**237z**	6	90		**238z**	single isomer

Entry	Ketone	R.T.[1] (h)	Yield[2] (%)	Sulfinimine	No.	*Z*/*E*[3]
27	**237aa**	12	89		**238aa**	single isomer
28	**237ab**	5	87		**238ab**	single isomer
29	**237ac**	8	-		**238ac**	-
30	**237ad**	6	66		**238ad**	1:1
31	**237ae**	7	86		**238ae**	1:6
32	**237af**	8	77		**238af**	1:1

1. Reaction time.
2. Isolated yield.
3. *Z/E* ratio determined from the ^{1}H NMR spectroscopy.

It is well known, that the use of ketones in the reaction requires higher temperatures and increased quantities of the Lewis acid when compared to aldehydes, due to the electronic and steric effects.[23] Generally, sulfinimines **238** were obtained in poor to excellent yields (10-92%) by treatment of aromatic, aliphatic and heteroaromatic ketones **237** with (*S*)-*tert*-butanesulfinamide **32** in the presence of $Ti(OEt)_4$ as a desiccant and Lewis acid. The *Z/E* ratio of the sulfinimines **238** was determined by comparison of the integration of the protons in the ^1H NMR spectroscopy of the crude products. In all cases the *E*-isomer was the main product, as report by Ellman and co-workers.[23]

Using symmetrical cyclic ketones **237a**-**f** (Table 7, entries 1-6), the desired products **238a**-**f** were afforded in good to excellent yields (57-91%). It was observed that the large ring size was not an influential factor on the yield because of the substrate **237e** (eight-membered ring) gave **238e** in 57% yield compared to the cyclic ketone **237f** (twelve-membered ring), which was gave **238f** an excellent yield (91%).

Conversely, the substituted cyclic ketone **237s** provided the desired sulfinimine **238s** in a low yield (10%). This is may be due to presence of the bridge bond on the substrate **237s**, creating a strained system (Table 7, entry 19). The sulfinimine bearing acetal-protected carbonyl **237g** afforded **238g** in 61% yield. Moderate yields (51-61%) were observed with the *N*-protected substrates **237h**, **237v** and **237w** (Table 7, entries 8, 22 and 23).

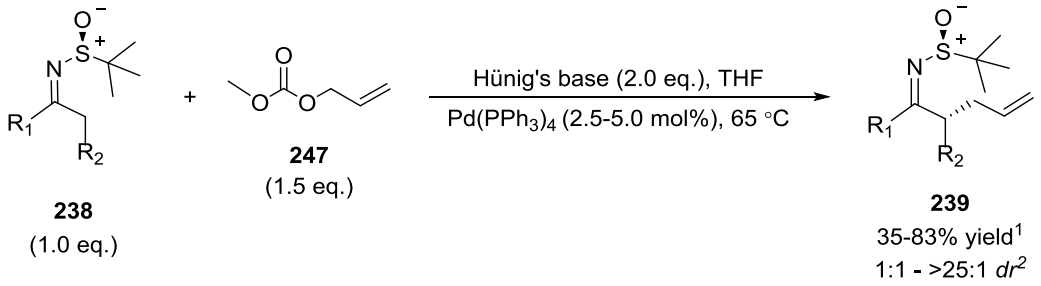
In the case of heterocyclic ketones, sulfinimines **237m**-**o** were obtained in different yields, for example **237m** and **237o** (Table 7, entries 13 and 15) furnished **238m** and **238o** in excellent yields (90% and 91% respectively) as single isomer, while **237n** (Table 7, entry 14) gave **238n** in a moderate yield (61%) in 1:8 of *Z/E*. This is probably due to the substrates **237m** and **237o** bearing methyl as the α-substituent group which is less steric hindrance than **237n** that containing an ethyl group.

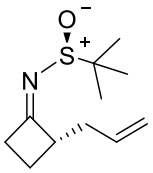
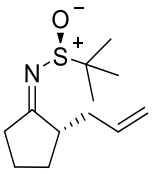
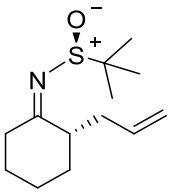
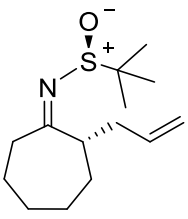
In addition, cyclic-aliphatic substrates, **237q** (Table 7, entry 17) resulted in a 67% isolated yield of the desired product **238q**, compared to **237r** (Table 7, entry 18) which gave **238r** in 58% yield. This is due to the reduced steric and electronic influences in **237q** than **237r**. Moreover, electron-rich ketone **237u** (Table 7, entry 21) gave a good yield (79%) with poor ratio of *Z/E* (1:3). The aliphatic ketone **237p** (Table 7, entry 16) afforded **238p** in a very good yield (82%) with moderate *Z/E* selectivity (1:6). Likewise, the aliphatic ketone **237t** gave **238t** in a slightly reduced yield (80%) compared to **238p**, and the same ratio of *Z/E* (1:6) (Table 7, entry 20). Aromatic ketones (Table 7, entries 9-12 and 28) gave moderate to excellent yields (61-92%) in a single isomer in most cases, which was dependent on the nature of the substrate. However, sulfinimine **238i** was obtained in an excellent yield (92%) (Table 7, entry 9), while sulfinimine **238j** in 81%, and this was due to the bulkiness of the substrate (Table 7, entry 10). In addition, sulfinimine **238k** was isolated in 61% yield (Table 7, entry 11) which is lower than **238i** and **238j** (Table 7, entries 9 and 10) because it contains a long aliphatic carbon chain without methyl as the α-substituent group. Despite the steric effect in **237l**, the desired product **238l** was isolated in a good yield (70%), with very good ratio of *Z/E* (1:16) (Table 7, entry 12). The ketones derived from substituted and unsubstituted aromatic-cyclic aliphatic rings **237x**-**aa** afforded the corresponding sulfinimines **238x**-**aa** in very good yields (86-91%) and as single diastereoisomer (Table 7, entries 24-27). Surprisingly, the sulfinimine **238ac** was not isolated when **237ac** (5,6-fused ring system) was employed (Table 7, entry 29), which may be attributed to the nature of the size of the fused ring system compared with **237x**-**aa** (6,6-fused ring system) (Table 7, entries 24-27). Ketone analogue of cholesterol **237ae** (prepared in 83% yield by oxidation of cholesterol **237AE** with PCC) afforded the corresponding sulfinimine **238ae** in a very good yield (86%) with 1:6 of *Z/E* (Table 7, entry 31). While, progesterone **237af** gave sulfinimine **238af** in a good yield (77%) with 1:1 of *Z/E* (Table 7, entry 32).

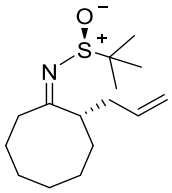
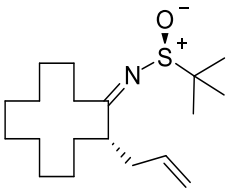
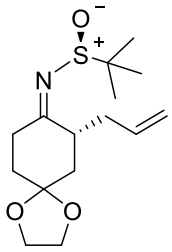
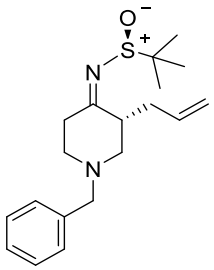
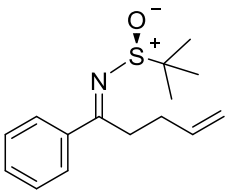
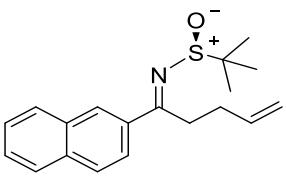
1.2.3. Synthesis of α-allyl sulfinimines 239

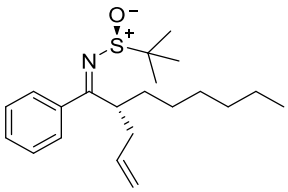
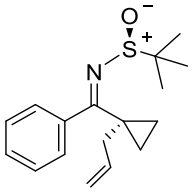
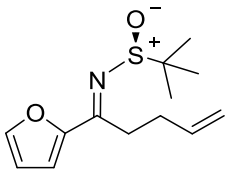
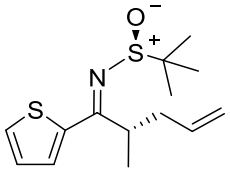
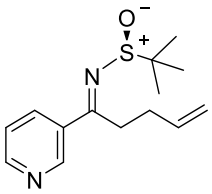
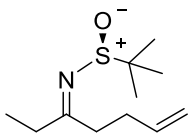
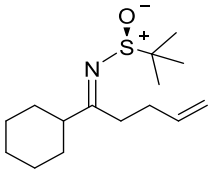
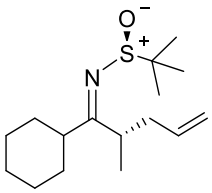
The prepared sulfinimines **238** were subjected to our optimised Tsuji-Trost reaction conditions in order to synthesise α-allyl sulfinimines **239** as described in Table 8.

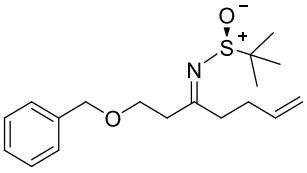
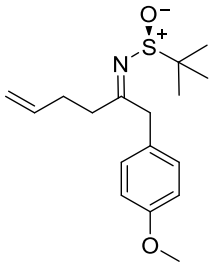
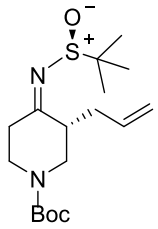
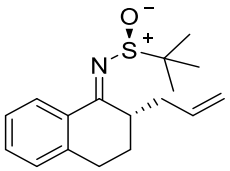
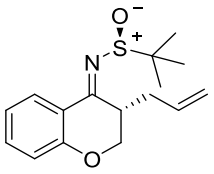
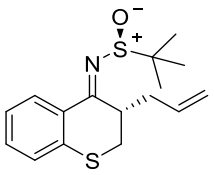
Table 8: Synthesis of α-allyl sulfinimines **239** *via* the Tsuji-Trost

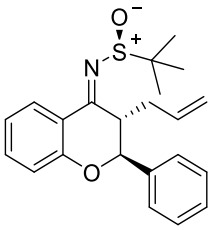
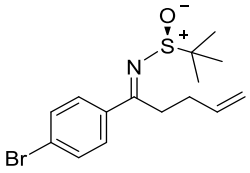
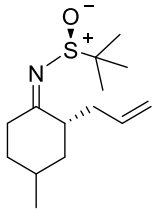
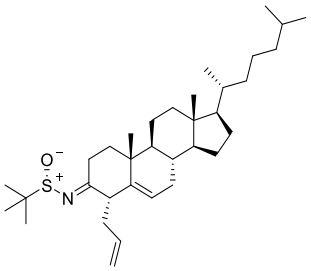
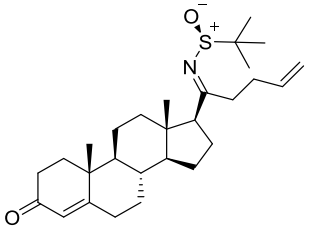


Entry	Sulfinimine	R.T.[1] (h)	Yield[2] (%)	α-Allyl sulfinimine	No.	*dr*[3]
1	**238a**	24	72		**239a**	3:1
2	**238b**	24	59		**239b**	4:1
3	**238c**	30	75		**239c**	20:1
4	**238d**	27	56		**239d**	7:1

Entry	Sulfinimine	R.T.[1] (h)	Yield[2] (%)	α-Allyl sulfinimine	No.	*dr*[3]
5	**238e**	29	57		**239e**	3:1
6	**238f**	20	73		**239f**	2:1
7	**238g**	27	44		**239g**	6:1
8	**238h**	26	38		**239h**	4:1
9	**238i**	20	81		**239i**	N/A
10	**238j**	22	72		**239j**	N/A

Entry	Sulfinimine	R.T.[1] (h)	Yield[2] (%)	α-Allyl sulfinimine	No.	*dr*[3]
11	**238k**	38	36		**239k**	4:1
12	**238l**	96	-		**239l**	-
13	**238m**	20	74		**239m**	N/A
14	**238n**	96	51		**239n**	8:1
15	**238o**	23	72		**239o**	N/A
16	**238p**	21	70		**239p**	N/A
17	**238q**	28	35		**239q**	N/A
18	**238r**	96	-		**239r**	-

Entry	Sulfinimine	R.T.[1] (h)	Yield[2] (%)	α-Allyl sulfinimine	No.	*dr*[3]
19	**238t**	25	72		**239t**	N/A
20	**238u**	144	-		**239u**	-
21	**238v**	13	42		**239v**	3:1
22	**238x**	24	77		**239x**	>25:1
23	**238y**	24	77		**239y**	>25:1
24	**238z**	18	83		**239z**	>25:1

Entry	Sulfinimine	R.T.[1] (h)	Yield[2] (%)	α-Allyl sulfinimine	No.	*dr*[3]
25	**238aa**	23	74		**239aa**	>25:1
26	**238ab**	24	77		**239ab**	N/A
27	**238ad**	24	64		**239ad**	12:1
28	**238ae**	24	38		**239ae**	10:1
29	**238af**	24	51		**239af**	>25:1

1. Reaction time.
2. Isolated yield.
3. The *dr* values were determined by ^{1}H NMR spectroscopy.

A wide range of α-allyl derivatives **239** have been synthesised successfully in yields ranging from medium to very good (35-83%) with good rate of *dr* (up to >25:1). Symmetrical cyclic sulfinimines **239a**-**f** (Table 8, entries 1-6) gave moderate to good yields (56-75%) and *dr* ranging from 2:1 to 20:1. Interestingly, it was observed that the small ring system **238a** (Table 8, entry 1) and large systems **238e** and **238f** (Table 8, entries 5 and 6) gave the desired products **239a**, **239e** and **239f** in low *dr* (2:1 to 3:1) with moderate to good yields (57-73%). Conversely, the sulfinimines bearing a medium ring such as **238b**, **238c** and **238d** afforded the corresponding α-allyl sulfinimines **239b**, **239c** and **239d** in better *dr* (4:1, 20:1 and 7:1 respectively) and moderate to good yields (56-75%) (Table 8, entries 2, 3 and 4).

The allylation of sulfinimine bearing acetal-protected carbonyl **238g** provided **239g** in 44% yield and *dr* 6:1 (Table 8, entry 7). *N*-Bn- and *N*-Boc-protected sulfinimines **238h** and **238v** afforded the corresponding α-allyl derivatives **239h** and **239v** in low *dr* (4:1 and 3:1 respectively) and low yields (38% and 42% respectively) (Table 8, entries 8 and 21). It was observed that *dr* decreased when protected sulfinimine was used (**238h** and **238v**) compared to **238g**. This may be due to increased steric hindrance of the protecting group on these substrates. Notably, diallylation was observed when **238h** and **238v** employed and furnished diallyl undesired products **239ha** and **239va** in 11% and 14% yields respectively.

Aromatic sulfinimine substrates **238i**, **238j** and **238ab** (Table 8, entries 9, 10 and 26) gave the desired α-allyl derivatives **239i**, **239j** and **239ab** in 81%, 72% and 77% yields respectively. In contrast, the aromatic sulfinimine **238k** (Table 8, entry 11) afforded **239k** in a low yield (36%), which may be attributed to a long aliphatic carbon chain. In addition, the aromatic sulfinimine **238l** failed to give the desired product **239l** when employed (Table 8, entry 12), probably due to the increased steric hindrance on the hydrogen at the α-position. In the case of heterocyclic sulfinimines, it was observed that **238m** and **238o** (Table 8, entries 13 and 15)

furnished **239m** and **239o** in good yields (74% and 72% respectively). While, **239n** was isolated in a low yield (51%) with good *dr* (8:1) (Table 8, entry 14).

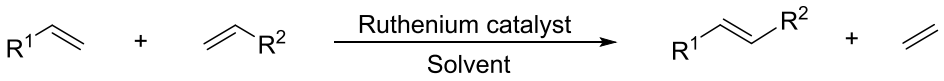
In terms of the aliphatic substrates, the sulfinimine **238p** gave the desired product **239p** cleanly in a good yield (70%) (Table 8, entry 16). While, the substrate **238t** provided **239t** in 72% yield (Table 8, entry 19). We also envisaged that the allylation of **238u** will be performed easily due to the starting material bearing methyl as the α-substituent group. But, unfortunately, the desired product **239u** was not observed after 6 days (Table 8, entry 20).

In the cyclic-aliphatic systems, the substrate **238q** resulted **239q** in 35% yield (Table 8, entry 17), while the desired product **239r** was not detected after 4 days when **238r** was used (Table 8, entry 18). The sulfinimines derived from unsubstituted aromatic-cyclic aliphatic rings **238x**-**z** furnished the corresponding α-allyl derivatives **239x**-**z** in very good yields (77-83%) and excellent *dr* (>25:1) (Table 8, entries 22-24). Although, sulfinimine **238aa** has an extra stereocentre, the desired allyl derivative **239aa** was obtained in an excellent *dr* (>25:1) and 74% yield (Table 8, entry 25).

The sulfinimine derived from cholesterol **238ae** afforded two products; the desired product **239ae** in 38% yield with 10:1 *dr*, and diallyl undesired product **239aea** in 31% yield with 10:1 *dr* (Table 8, entry 28). Finally, the sulfinimine **238af** gave the product **239af** in 51% yield with >25:1 *dr* (Table 8, entry 29).

1.2.4. Cross metathesis reaction 240

Compounds **239** were then used in olefin cross metathesis reaction (CM); an organic reaction between two alkenes (olefins) to afford a new carbon-carbon double bond in the presence of a ruthenium catalyst (Scheme 55).



Scheme 55: General equation of the cross metathesis reaction (CM)

Many types of ruthenium catalyst have used in this reaction such as, Grubbs I catalyst, Grubbs II catalyst, Hoveyda-Grubbs I catalyst and Hoveyda-Grubbs II catalyst (Figure 10).

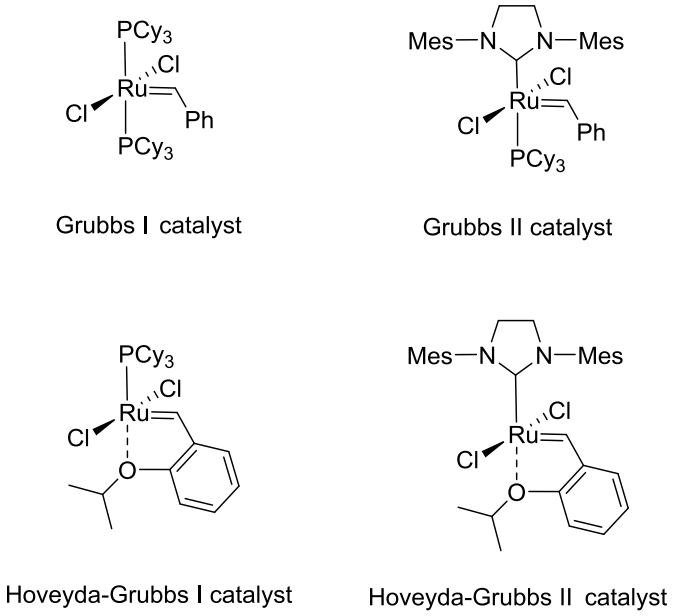
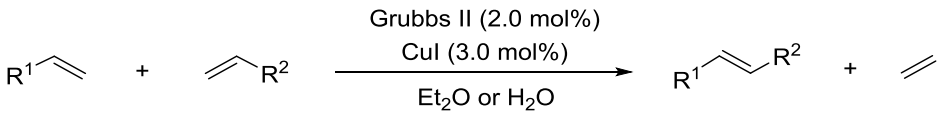


Figure 10: Ruthenium cross metathesis catalyst

Recently, Voigtritter, Ghorai and Lipshutz[118] have reported optimised conditions for the olefin cross metathesis reactions using CuI as a co-catalyst with Grubbs II catalyst in Et_2O or water as a solvent (Scheme 56). They indicated that using CuI increases the rate of the reaction because it serves as a phosphine scavenger (Figure 11). They also reported that using this salt with Hoveyda-Grubbs I catalyst and Hoveyda-Grubbs II catalyst was not effective to improve the rate of the reaction.



Scheme 56: CuI-assisted olefin metathesis reaction (CM)

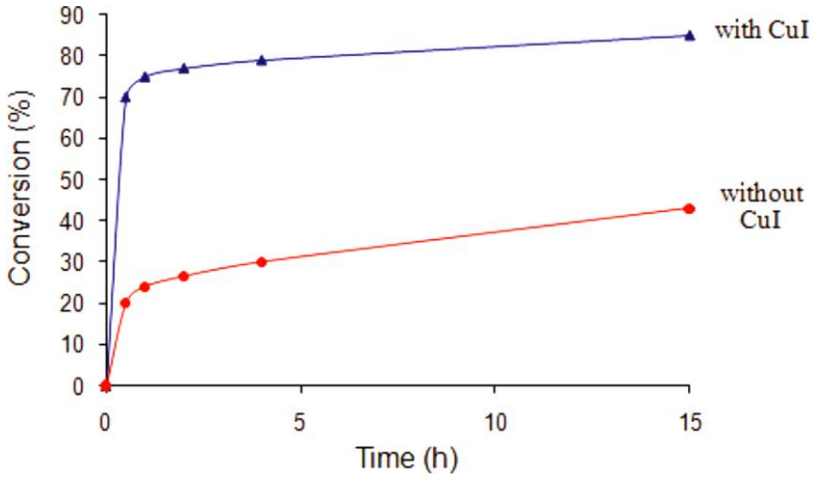
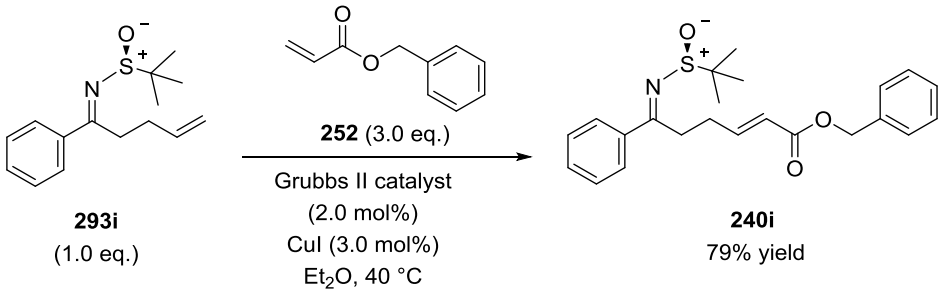


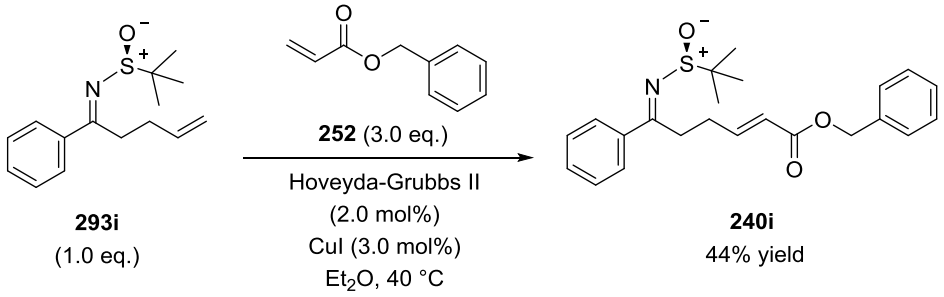
Figure 11: The effect of the CuI on the metathesis reaction between alkenes in the presence of Grubbs catalyst II[118]

In our work, the same conditions have been tested to do coupling between α-allyl sulfinimine **293i** and benzyl acrylate **252**. The desired α,β-unsaturated ester **240i** was isolated in 79% yield (Scheme 57).



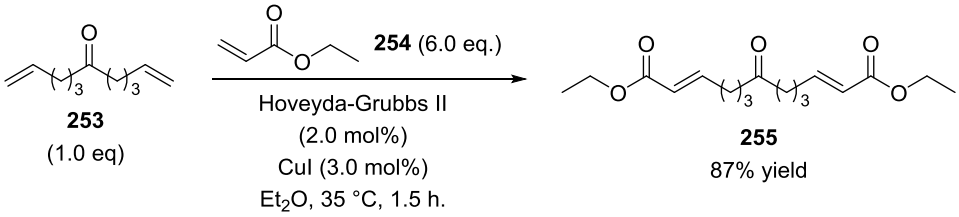
Scheme 57: Cross metathesis reaction using Grubbs II catalyst

After this reaction and before commencing with the scope substrates, Hoveyda-Grubbs II catalyst was used also instead of Grubbs II catalyst to compare the efficiency between them under the same conditions to prepare **240i**, but the isolated yield was lower than the previous procedure (44 *vs*. 79%) (Scheme 58).



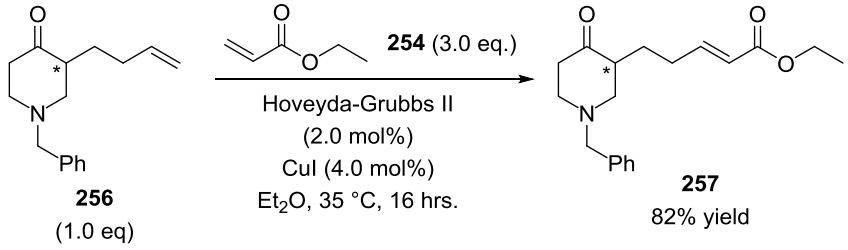
Scheme 58: Cross metathesis reaction using Hoveyda-Grubbs II catalyst

Contrary to Liphutz's report,[118] the Stockman group previously used CuI with Hoveyda-Grubbs II catalyst to improve the rate of the coupling between allyl derivative **253** and ethyl acrylate **254** under cross metathesis conditions. The desired product **255** was isolated in a very good yield (87%) (Scheme 59).



Scheme 59: Stockman's use of Hoveyda-Grubbs II catalyst with CuI in a cross metathesis coupling

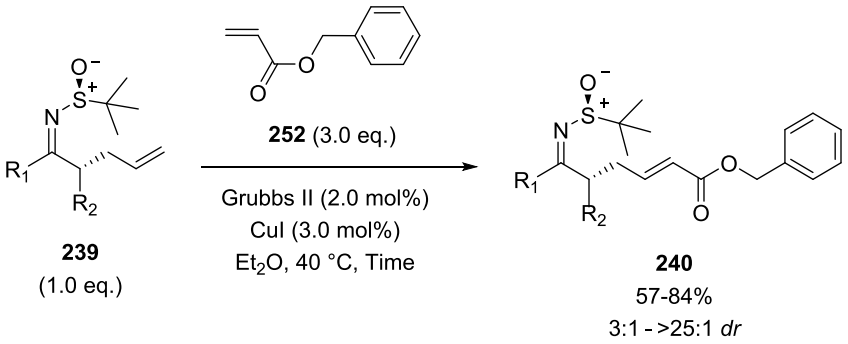
In the same way, the Stockman group prepared α,β-unsaturated ester derivative **257** in 82% yield *via* coupling between allyl derivative **256** and ethyl acrylate **254** in the presence of CuI and Hoveyda-Grubbs II catalyst (Scheme 60).

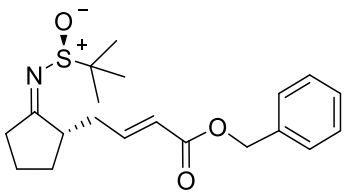
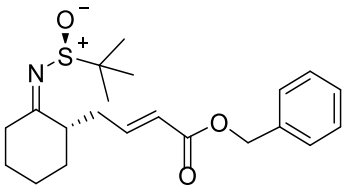
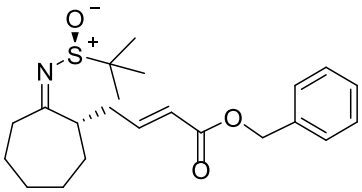
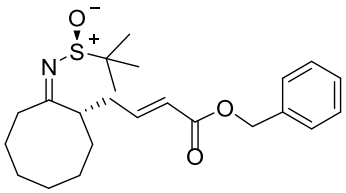
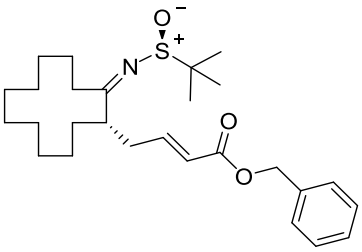
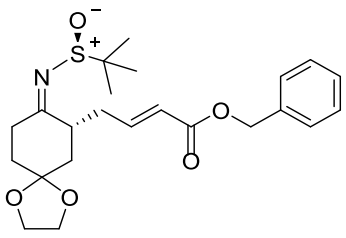


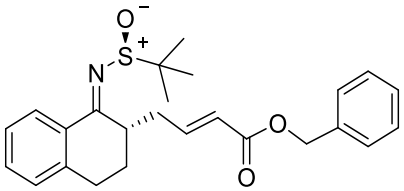
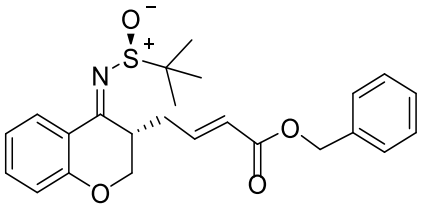
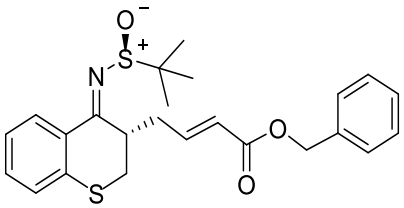
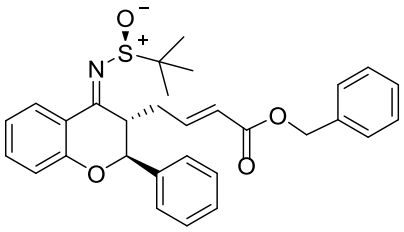
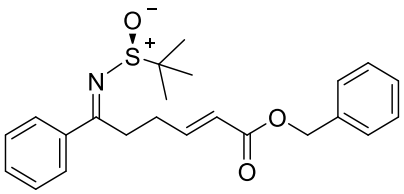
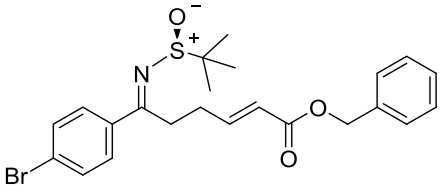
Scheme 60: Cross metathesis of **256** and **254** to afford α,β-unsaturated ester derivative **257** in the presence of CuI and Hoveyda-Grubbs II catalyst

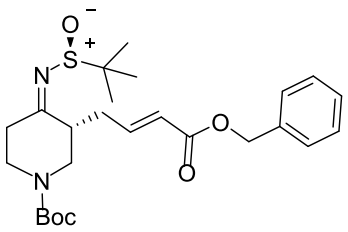
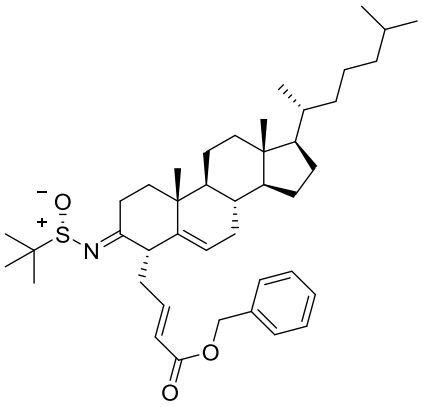
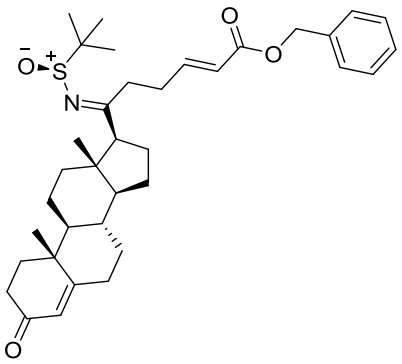
The optimised conditions for the cross metathesis reaction in the presence of Grubbs II catalyst were then applied in our work. Hence, α-allyl sulfinimines **239**, were treated with benzyl acrylate **252** in Et_2O giving the corresponding metathesis adducts **240** in yields ranging from 57 to 84% and *dr* up to >25:1 as described in Table 9.

Table 9: Cross metathesis coupling of **239** with **252** in the presence of Grubbs II catalyst and CuI to provide **240**



Entry	SM	*dr*[1]	R.T.[2] (h)	Cross metathesis adduct	No.	Yield (%)[3]	*dr*[1]
1	**239b**	4:1	3		**240b**	68	4:1
2	**239c**	20:1	8		**240c**	81	20:1
3	**239d**	7:1	7		**240d**	77	7:1
4	**239e**	3:1	7		**240e**	84	4:1
5	**239f**	2:1	5		**240f**	79	3:1
6	**239g**	6:1	5		**240g**	83	5:1

Entry	SM	*dr*[1]	R.T.[2] (h)	Cross metathesis adduct	No.	Yield (%)[3]	*dr*[1]
7	**239x**	>25:1	6		**240x**	75	>25:1
8	**239y**	>25:1	4		**240y**	75	>25:1
9	**239z**	>25:1	4		**240z**	76	>25:1
10	**239aa**	>25:1	7		**240aa**	83	>25:1
11	**239i**	N/A	6		**240i**	79	-
12	**239ab**	N/A	6		**240ab**	76[4]	-

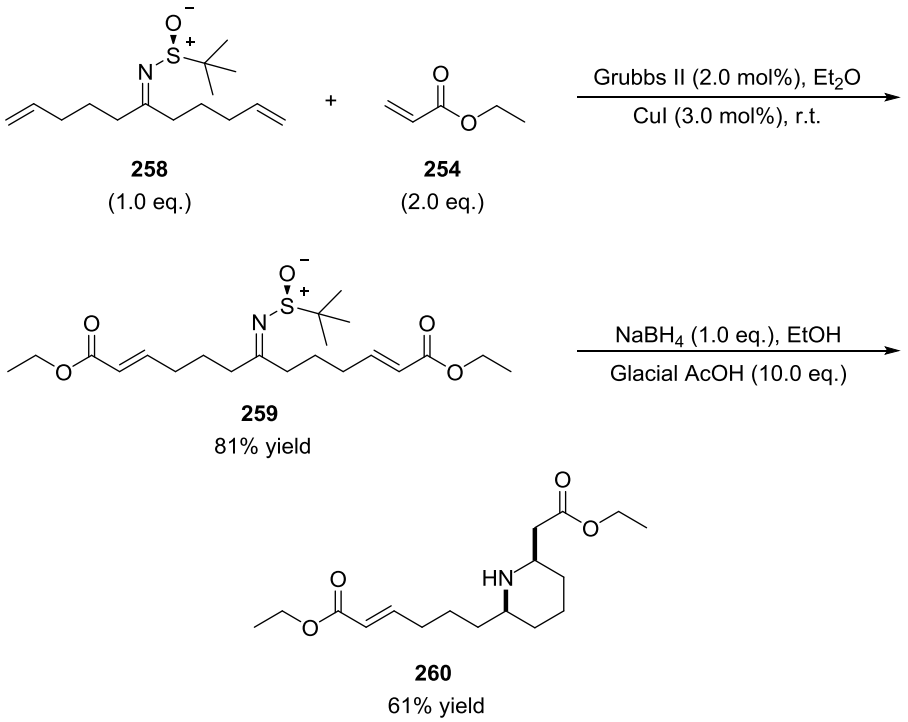
Entry	SM	*dr*[1]	R.T.[2] (h)	Cross metathesis adduct	No.	Yield (%)[3]	*dr*[1]
13	**239v**	3:1	48		**240v**	-	-
14	**239ae**	10:1	12		**240ae**	57	10:1
15	**239af**	1:1	12		**240af**	62	1:1

1. The *dr* values were determined by ^{1}H NMR spectroscopy.
2. Reaction time.
3. Isolated yield.
4. The reaction was carried out in the absence of CuI due to side reactions and poor transformation detected in its presence.

In order to prevent homo coupling of the starting material, extra amounts of benzyl acrylate **252** (3.0 eq.) was used to react with α-allyl sulfinimines **239**. Furthermore, Grubbs II catalyst was found to be selective to give **240** as single *E*-isomer. The addition of the catalyst to the reaction mixture was slow, which prevents the formation of any undesired homo couplings. All the α-allyl derivatives **239** afforded the desired α,β-unsaturated esters **240**, except the substrate **239v**, did not give the corresponding product **240v**. This may be due to the protecting group, which is preventing the coupling with **252** (Table 9, entry 13). Unfortunately, all the products were isolated as an oil and no product was isolated as a solid. Therefore, it was not possible to assign the relative stereochemistry by X-ray crystallographic analysis.

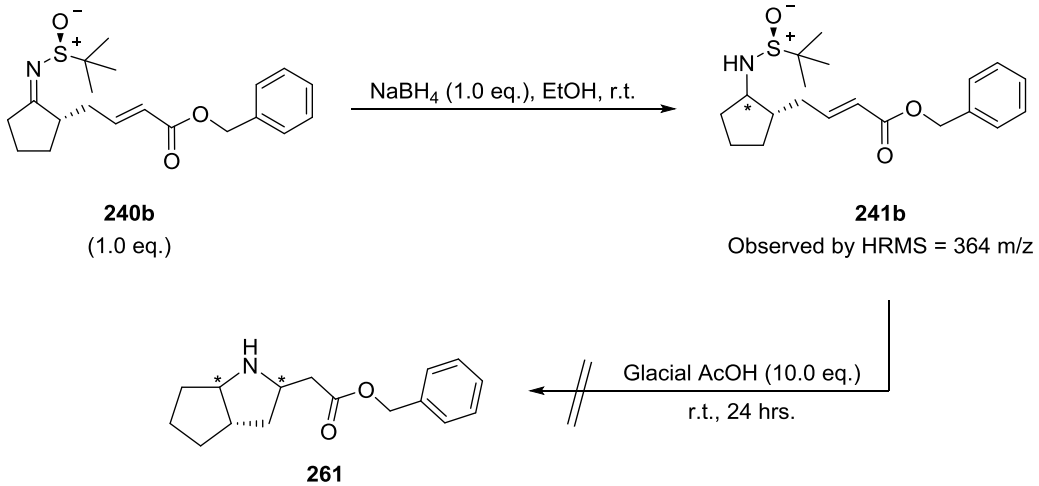
1.2.5. Homo allyl sulfinimines to pyrrolidine chemical scaffolds 242

The next step in this project was to access the pyrrolidine chemical scaffolds **242** from cross metathesis adducts **240** in a one-pot reaction. The Stockman group has previously prepared **260** in a one-pot reaction. This was achieved successfully *via* reducing **259** with $NaBH_4$ followed by removing of the protecting group using glacial AcOH affording the corresponding amine, which was cyclised spontaneously to give **260** in a 61% yield (Scheme 61).[119]



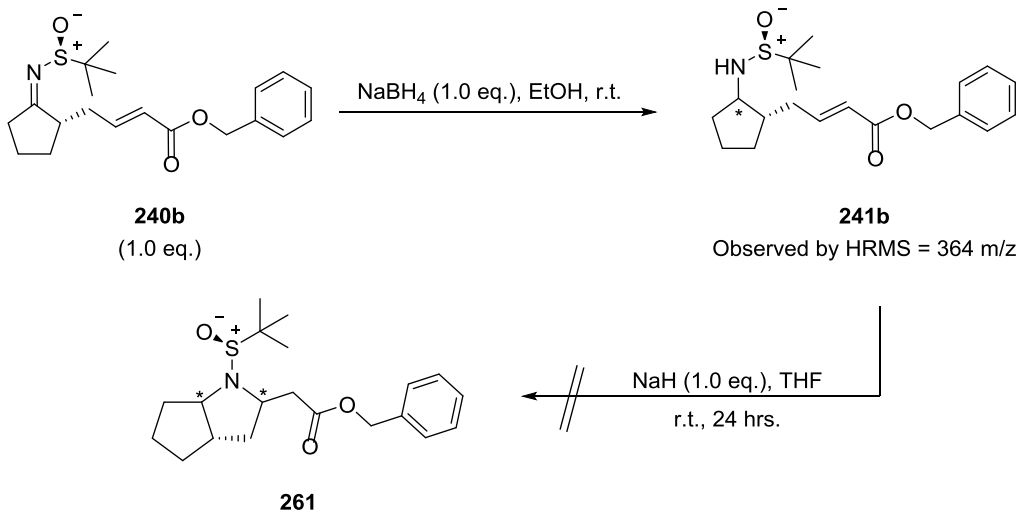
Scheme 61: Preparation of **260** from **258** in a one-pot reaction

The same conditions have been tested on our substrate **240b** to produce **261**. HRMS and ^{1}H NMR spectroscopy showed that there was a conversion to sulfinamide **241b**, but the cyclisation was not observed to provide desired amine derivative **261** (Scheme 62).



Scheme 62: Synthesis of **261** from **240b** in a one-pot reaction

The reaction conditions were then modified after this attempt *via* addition of NaH to the reaction mixture instead of glacial AcOH to deprotonate the sulfinamide **241b** formed. The desired product **261** was detected by TLC and HRMS, but the ^{1}H NMR spectrum indicated a complex mixture of products formed (Scheme 63).

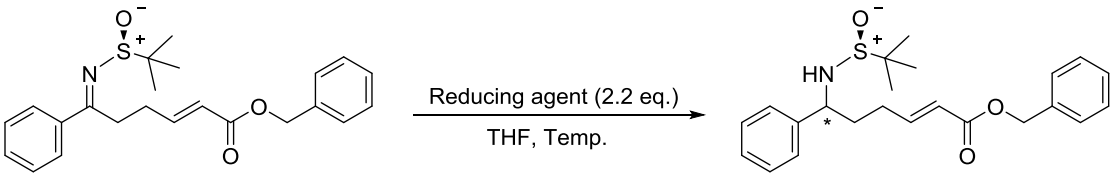


Scheme 63: Synthesis of **261** from **240b** in a one-pot reaction

After these two unfruitful attempts, we decided to obtain the desired pyrrolidine chemical scaffolds **242** *via* two steps in place of one step. Firstly, reduction of sulfinimines **240** stereoselectively to the corresponding sulfinamides **241** and then Michael-intramolecular cyclisation to give the corresponding pyrrolidine chemical scaffolds **242**.

In the beginning, substrate **240i** was chosen as a bench mark substrate to optimise the reaction conditions (Table 10). Different reducing agents were used to explore the best results in terms of yield and *dr*. It was found that DIBAL-H (Table 10, entry 1) was the best reducing agent tested, which gave a good yield (74%) and *dr* >25:1. The starting material was consumed completely within 3 hours. Table 10 summarises our attempts at optimising the reducing agent choice.

Table 10: Reducing agent screen



240i
(1.0 eq.)

241i

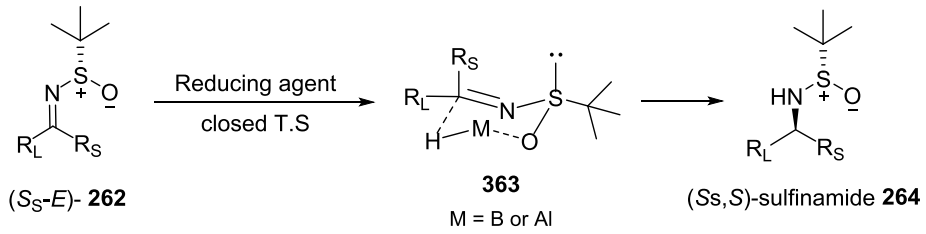
Entry	Reducing agent	R.T.[1] (h)	Temp. (°C)	Yield (%)[2]	*dr*[3]
1	DIBAL-H	3	-78	74	>25:1
2	9-BBN	3	0	67	>25:1
3	L-Selectride	3	-42	65	5:1
4	$LiAlH_4$	6	-42	-	-
5	$NaBH_4$	4	0	38	1:1

1. Reaction time.
2. Isolated yield.
3. The *dr* values were determined by ^{1}H NMR spectroscopy.

The reduction of **240i** with 9-BBN afforded **241i** in an excellent *dr* (>25:1), but the yield was 67% (Table 10, entry 2), which are similar to the results observed with DIBAL-H in terms of the *dr* and a lesser extent in terms of the yield. On the other hand, the *dr* dropped to 5:1 with 65% yield when L-Selectride was used as a reducing agent (Table 10, entry 3). Unfortunately, the desired product **241i** could not be observed by TLC, HRMS or ^{1}H NMR spectroscopy when $LiAlH_4$ was used (Table 10, entry 4). The reduction with $NaBH_4$ gave the desired product **241i** in a 38% yield with low *dr* (1:1) (Table 10, entry 5).

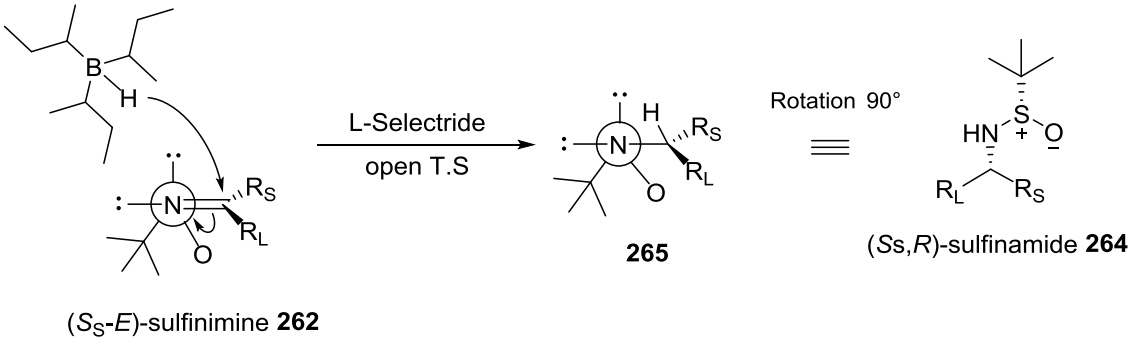
From the literature, the reduction mechanism of the (S_S-*E*)-sulfinimine **262** with $NaBH_4$, 9-BBN, Red-Al or DIBAL-H including formation a cyclic transition state **263**, which is favoured due to arrangment of the *tert*-butyl and R_L groups in a pseudo equatorial conformation. This will afford the corresponding (S_S,*S*)-sulfinamide **264**. The boron or aluminium metal will co-ordinate to oxygen and the hydride

directly will attack the carbon on the opposite face of the sulfur lone pair electron (bottom face) of the sulfinimine **262** to give **264** (Scheme 64).[41]



Scheme 64: Mechanistic proposal of (*S*s-*E*)-sulfinimine **262** reduction *via* formation a cyclic transition state

On the other hand, the reduction of (S_S-*E*)-sulfinimine **262** with L-Selectride giving the opposite (S_S,*R*)-sulfinamide **264** *via* open transition state. This is due to the steric effect of the substituents (*sec*-butyl groups) on the boron metal, which is considered a bulky reducing agent. This prevents the formation of the six-membered transition state **265**. The carbon of the sulfinimine will receive the hydride on the less hindered face (top face). This means, the hydride will attack the carbon on the same face of the sulfur lone pair electron to give the corresponding (S_S,*R*)-sulfinamide **264**. Scheme 65 described the reduction mechanism of (S_S-*E*)-sulfinimine **262** with L-Selectride.[41]



Scheme 65: Mechanistic proposal reduction of (*S*s-*E*)-sulfinimine **262** using L-Selectride *via* open transition state

Whereas, in our work, the mechanism of the Tsuji-Trost allylation favours formation α-allyl sulfinimines **239** as a (*Z*)-isomer as previously mentioned in this chapter. Hence, the reduction of the sulfinimines **240** with DIBAL-H more likely to be *via* open transition state due to difficulty to the formation of the cyclic transition state **263** of the (*Z*)-isomer. The unfavourable interactions of allyl moiety (large group) in the axial position with the substituents (*iso*-butyl group) on the aluminium metal prevents the formation of the six-membered transition state **266** (Figure 12).

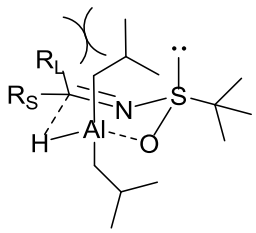
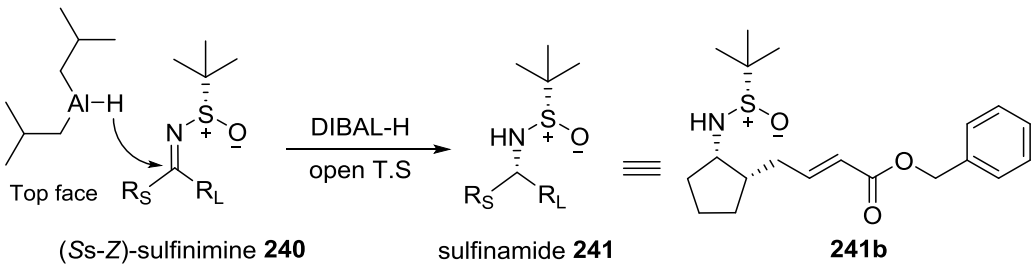


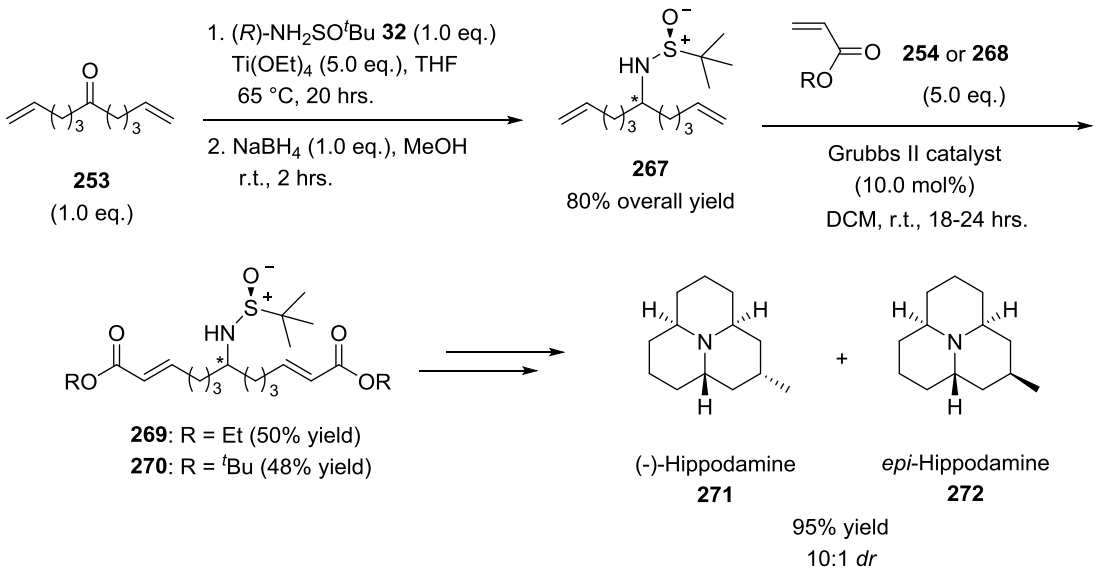
Figure 12: Unfavoured transition state **266**

The hydride of the DIBAL-H favours to attack the electrophilic carbon at less hindered face, and the bonds; C-N and S-O prefer a planar orentiation (flat), which is more stable due to the dipole-dipole interactions. This means, that for **240** (Scheme 66), the *tert*-butyl group will be down, and the sulfur non-bonding electrons will be up when using (*S*)-(-)-*tert*-butylsulfinamide **32** as a chiral auxiliary. Hence, the hydride will attack at the top face (less hindered), which effected by the chiral sulfinyl directing group. Scheme 66 illustrated the reduction mechanism of (S_S-*Z*)-sulfinimine **240** with DIBAL-H.



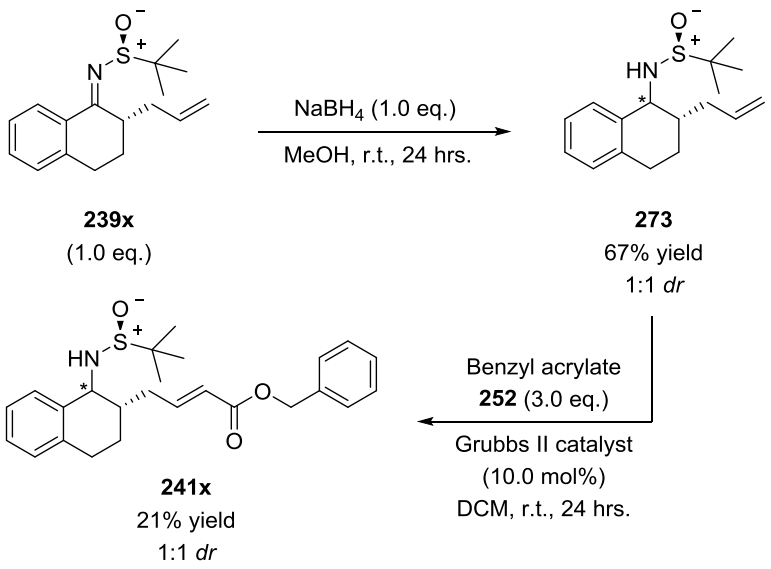
Scheme 66: The reduction mechanism of (*S*s-*E*)-sulfinimine **240** with DIBAL-H

Our plan is to prepare sulfinamide derivative from α-allyl sulfinimine *via* cross metathesis reaction/reduction, but we found in the literature work which includes synthesis of some sulfinamide derivatives similar to our compounds *via* reduction of the sulfinimine then cross metathesis coupling. So, in 2015, Guerola *et al.*[120] have reported the synthesis of the alkaloid products (-)-hippodamine **271** and *epi*-hippodamine **272** (Scheme 67). This synthesis included using compound **267** as a key intermediate, which was prepared over two steps. Condensation of a symmetric ketone **253** with (*R*)-*N*-*tert*-butanesulfinamide **32** in the presence of $Ti(OEt)_4$, followed by reduction with $NaBH_4$ in a one-pot reaction provided sulfinamide **267** in a 80% overall yield. The cross metathesis reaction of double bonds on **267** with ethyl acrylate **254** or *tert*-butyl acrylate **268** in the presence of Grubbs II catalyst furnished **269** and **270** in 50% and 48% yields respectively (Scheme 67).



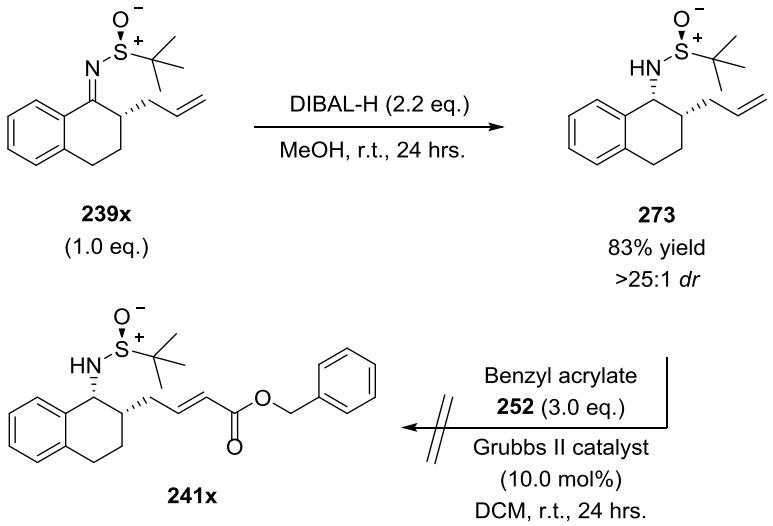
Scheme 67: Reproduced from Guerola *et al*. synthesis of (-)-hippodamine **271** and *epi*-hippodamine **272**[120]

These results prompted us to use the same reducing agent ($NaBH_4$) to see if there is any improvement in the *dr* and yield when reducing the α-allyl sulfinimine **239x** before doing the cross metathesis coupling. Compound **239x** was reduced with $NaBH_4$ in MeOH, affording amide derivative **273** in 67% yield with 1:1 *dr*. Cross metathesis coupling of **273** with benzyl acrylate **252** using Grubbs II catalyst has been achieved gave **241x**, but the yield was low (21%) (Scheme 68).



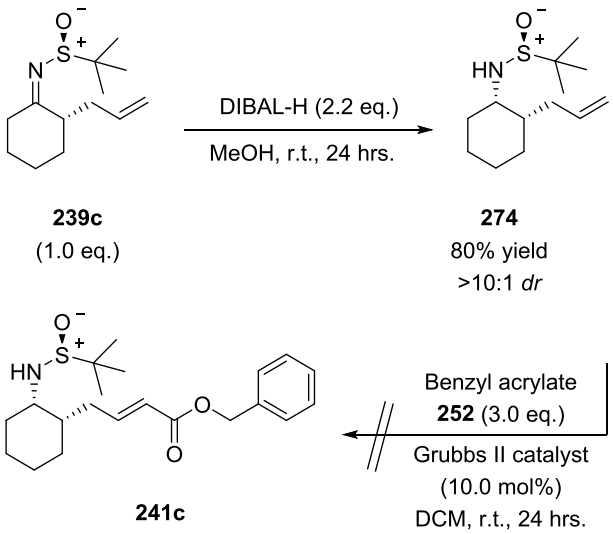
Scheme 68: Preparation of **241x** using a cross metathesis reaction in the presence of Grubbs II catalyst

We therefore turned to use DIBAL-H in place of $NaBH_4$ to reduce α-allyl sulfinimine **239x** before doing the cross metathesis coupling. The desired amide derivative **273** was obtained in a very good yield (83%) with excellent *dr* (>25:1). But, unfortunately, the coupling between **273** and benzyl acrylate **252** in the presence of Grubbs II catalyst did not work to give the desired product **241x** (Scheme 69). This is may be due to the poisoning of the catalyst with amide, which is *via* coordination of the nitrogen atom at amide to ruthenium atom of the catalyst.



Scheme 69: Preparation of **241x** using a cross metathesis reaction in the presence of Grubbs II catalyst

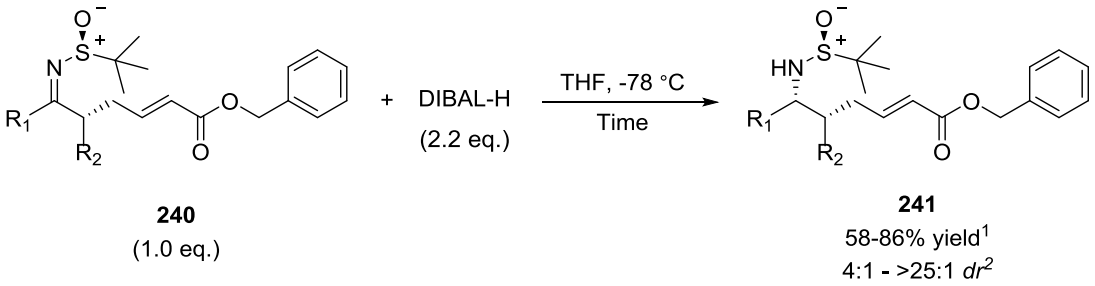
We decided then to test another substrate under the same conditions in order to explore the main reason, which led to failure of the reaction. The substrate **239c** was employed with the same conditions, but unfortunately, the desired product **241c**, could not be detected after 24 hours by HRMS or ^{1}H NMR spectroscopy (Scheme 70). Hence, it was found that this way was not effective to access **241** better than using the cross metathesis reaction/reduction of α-allyl sulfinimine **239**.



Scheme 70: Preparation of **241c** using a cross metathesis reaction in the presence of Grubbs II catalyst

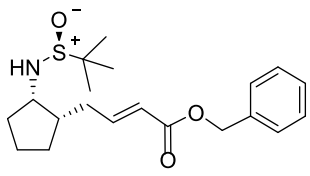
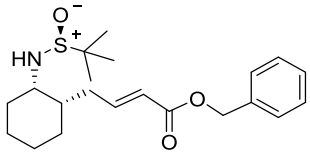
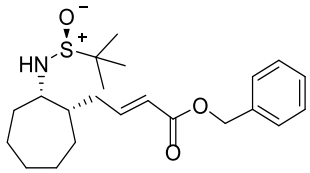
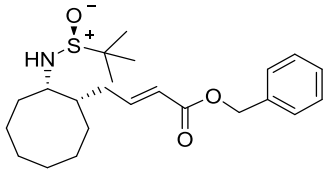
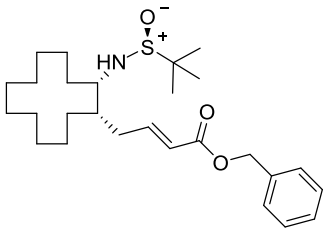
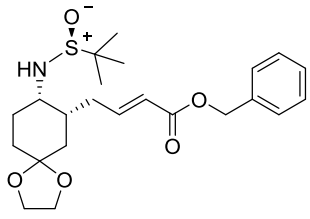
The optimised reduction conditions using DIBAL-H were then applied on sulfinimines **240** as a mixture of diastereoisomers affording the corresponding sulfinamides **241** (Table 11). The *dr* of desired sulfinamides **241** was determined by ^{1}H NMR spectroscopy (up to >25:1) and the yields ranged from 58 to 86%.

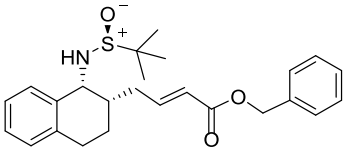
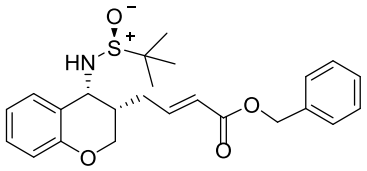
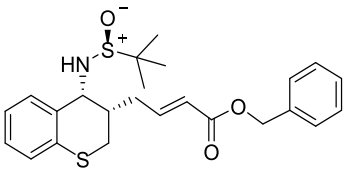
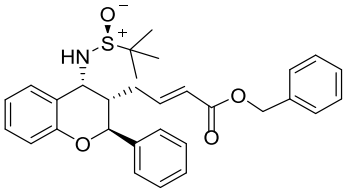
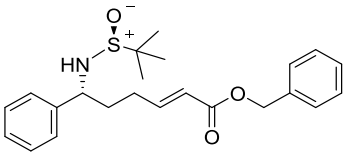
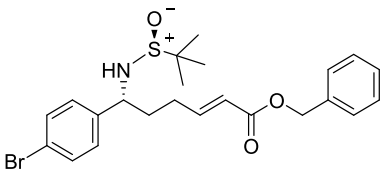
Table 11: Synthesis of sulfinamides **241** *via* reduction of **240** with DIBAL-H



240
(1.0 eq.)

241
58-86% yield[1]
4:1 - >25:1 *dr*[2]

Entry	SM	*dr*[1]	R.T.[2] (h)	Sulfinamide	No.	Yield (%)[3]	*dr*[1]
1	**240b**	4:1	5		**241b**	71	>25:1
2	**240c**	7:1	7		**241c**	75	>25:1
3	**240d**	7:1	6		**241d**	76	10:1
4	**240e**	4:1	6		**241e**	58	10:1
5	**240f**	3:1	5		**241f**	76	>25:1
6	**240g**	5:1	6		**241g**	80	>25:1

Entry	SM	*dr*[1]	R.T.[2] (h)	Sulfinamide	No.	Yield (%)[3]	*dr*[1]
7	**240x**	>25:1	5		**241x**	79	10:1
8	**240y**	>25:1	5		**241y**	86	10:1
9	**240z**	>25:1	5		**241z**	85	>25:1
10	**240aa**	>25:1	6		**241aa**	81	4:1
11	**240i**	N/A	3		**241i**	74	>25:1
12	**240ab**	N/A	3		**241ab**	71	>25:1

1. The *dr* values were determined by ^{1}H NMR spectroscopy of the crude mixture.
2. Reaction time.
3. Isolated yield.

As shown in Table 11, the reduction of sulfinimines **240** with DIBAL-H was found to be diastereoselective to afford the corresponding sulfinamides **241**. The *dr* was observed from 4:1 to >25:1 and the yields ranged from 58-86%. All of the starting materials were consumed completely between 3-7 hours. The chiral sulfinamide **241b** was isolated in *dr* >25:1 and 71% yield when the material **240b** was employed (Table 11, entry 1).

Likewise, the reduction of **240c** afforded **241c** in 75% yield with >25:1 *dr* (Table 11, entry 2). The substrates bearing seven- and eight-membered rings **240d** and **240e** were used and provided the desired products **241d** and **241e** in 76% and 58% yields respectively, and 10:1 *dr* (Table 11, entries 3 and 4). In these two substrates, the spontaneous cyclisation to the corresponding pyrrolidines **242d** and **242e** in the absence of catalyst or base was also detected in trace amounts. In addition, it was observed that there is no major effect of the ring size on the reduction. For example, the reduction of the substrate bearing a twelve-membered ring **240f** led to **241f** in a good yield (76%) with excellent *dr* (>25:1) (Table 11, entry 5), and the substrate **240f** was consumed within 5 hours.

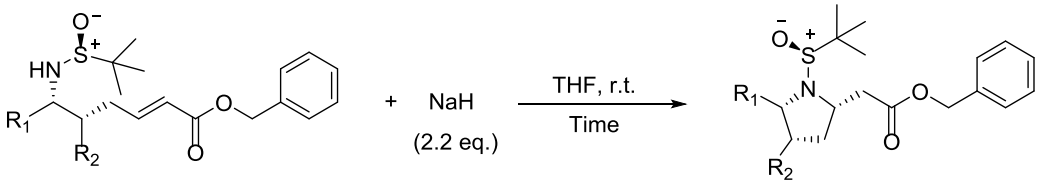
The reduction of substrate bearing acetal-protected carbonyl **240g** afforded **241g** in >25:1 *dr* and a very good yield (80%), proving its stability under these reducing conditions (Table 11, entry 6). Unsubstituted aromatic-cyclic aliphatic ring systems **240x**-**z** gave the corresponding chiral sulfinamides **240x**-**z** in very good yields (79-86%) with *dr* from 10:1 to >25:1 (Table 11, entries 7, 8 and 9). While, the reduction of the substituted aromatic-cyclic aliphatic ring system **240aa** provided the corresponding sulfinamide **241aa** in 81% yield, but the *dr* dropped to 4:1 (Table 11, entry 10). This is probably due to the phenyl group on the ring, which partially blocks the top face. This means a reduction in the effect of the chiral sulfinyl directing group.

Finally, the reduction of the substrates **240i** and **240ab** afforded the corresponding sulfinamides **241i** and **241ab** in good yields 74% and 71% respectively, and excellent *dr* (>25:1) (Table 11, entries 11 and 12). The starting materials **240i** and **240ab** were consumed completely within 3 hours.

In all cases, the reaction was carried out at -78 °C and 2.2 eq. of the reducing agent was used to prevent any reduction of the ester group to corresponding aldehyde or alcohol. In addition, the quench of the reaction should be carried out at -78 °C. The N-H proton of the sulfinamides **241** was observed by ^{1}H NMR spectroscopy and no exchange with deuterated chloroform ($CDCl_3$) was detected.

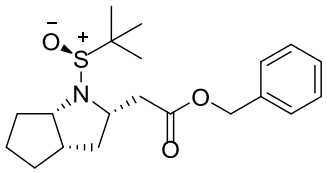
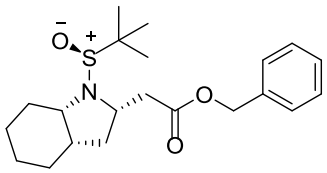
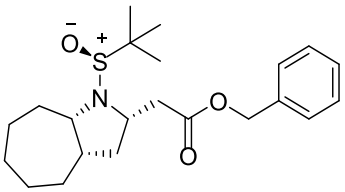
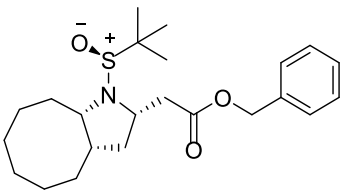
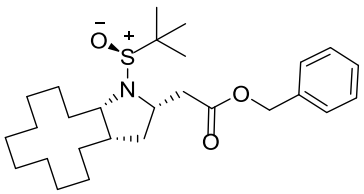
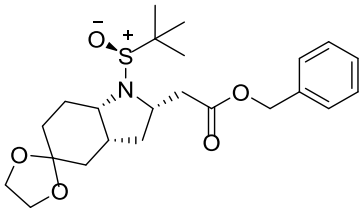
These sulfinamide derivatives **241** were then employed in the next step to prepare the corresponding pyrrolidine chemical scaffolds **242** *via* intramolecular Michael addition in the presence of NaH in THF at room temperature (Table 12). To our delight, all the substrates **241** were transformed into the desired pyrrolidine products **242** in moderate to good yields (53-77%) and were found to proceed with moderate to good diastereoselectivity to yield *cis*-2,5-pyrrolidines as the major diastereoisomer as shown in Table 12. The stereochemistry of the new C-C bond that formed from this reaction was assigned as *S* and will be explained later in this chapter.

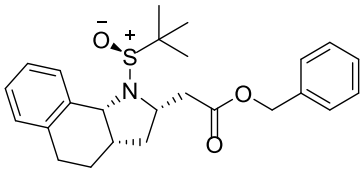
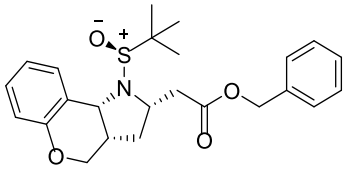
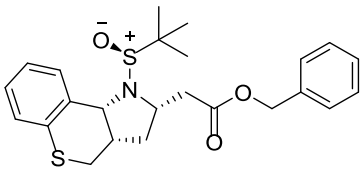
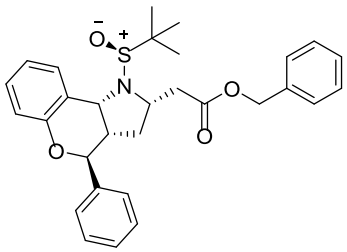
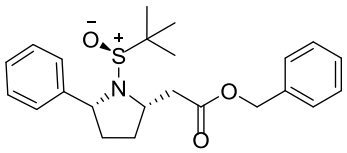
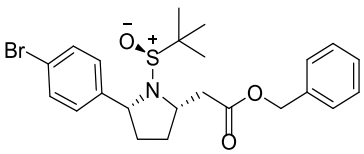
Table 12: Synthesis of pyrrolidine derivatives **242** *via* cyclisation of **241** under basic conditions



241
(1.0 eq.)

242
53-77% yield[1]
2:1 - >25:1 *dr*[2]

Entry	SM	*dr*[1]	R.T.[2] (h)	Pyrrolidine derivative	No.	Yield (%)[3]	*dr*[1]
1	**241b**	>25:1	3		**242b**	77	6:1
2	**241c**	>25:1	4		**242c**	75	2:1
3	**241d**	10:1	5		**242d**	77	3:1
4	**241e**	10:1	5		**242e**	75	5:1
5	**241f**	>25:1	5		**242f**	74	10:1
6	**241g**	>25:1	6		**242g**	76	10:1

Entry	SM	*dr*[1]	R.T.[2] (h)	Pyrrolidine derivative	No.	Yield (%)[3]	*dr*[1]
7	**241x**	10:1	5		**242x**	73	9:1
8	**241y**	10:1	5		**242y**	72	10:1
9	**241z**	>25:1	5		**242z**	71	>25:1
10	**241aa**	4:1	6		**242aa**	71	4:1
11	**241i**	>25:1	3		**242i**	53	>10:1
12	**241ab**	>25:1	3		**242ab**	66	>10:1

1. The *dr* values were determined by ^{1}H NMR spectroscopy.
2. Reaction time.
3. Isolated yield.

As shown in Table 12, in most of the cases *dr* for the pyrrolidine derivatives **242** that were synthesised were lower than observed for the sulfinamide derivatives **241**. This may be due to the intramolecular cyclisation reaction, which includes the formation of a C-N bond. The carbon atom in this bond infers an extra stereocentre on the pyrrolidine ring and this cyclisation was found not to be very selective in most cases to give high *dr* at this centre.

Compound **241b** was used almost as a single diastereoisomer (>25:1) and afforded **242b** in *dr* (6:1) with 77% yield (Table 12, entry 1). All of the substrate **241b** was converted into the desired pyrrolidine product within 3 hours. The substrate **241c** was used in *dr* >25:1 gave **242c** in a good yield (75%), but the *dr* was decreased to 2:1 (Table 12, entry 2).

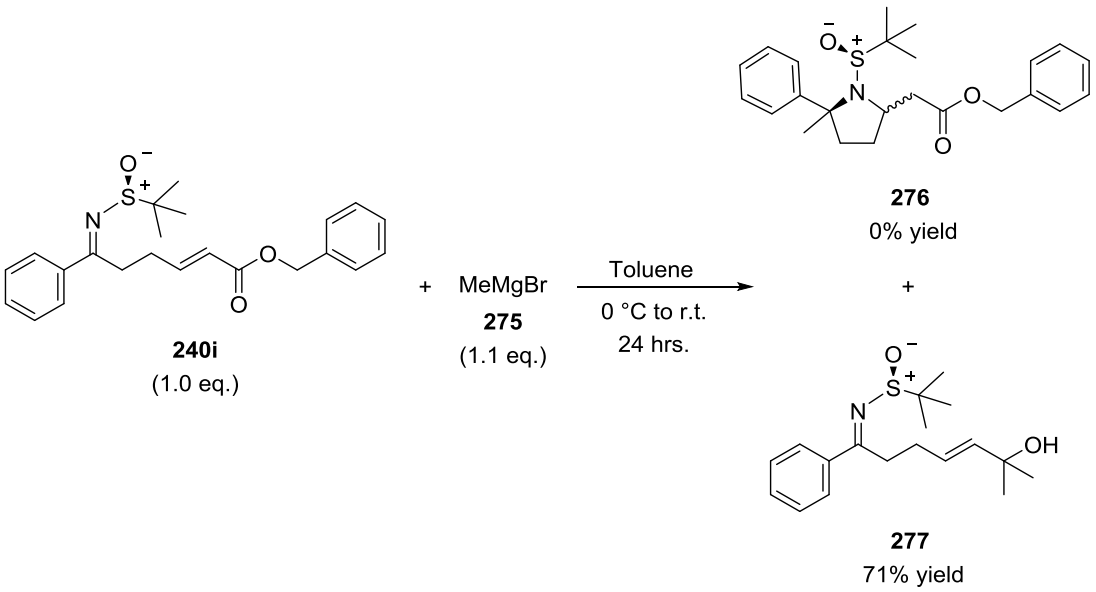
In the same way, the *dr* was decreased when the substrates bearing seven and eight-membered rings were employed. For example, the *dr* dropped from 10:1 to 3:1, and from 10:1 to 5:1 when **241d** and **241e** were used respectively (Table 12, entries 3 and 4). While, the sulfinamide bearing a twelve-membered ring **241f** afforded the desired pyrrolidine scaffold **242f** in a good yield (74%) and 10:1 *dr* (Table 12, entry 5), which the diastereoselectivity of this system was better than five, six, seven and eight systems.

Furthermore, the cyclisation of sulfinamide bearing acetal protected carbonyl **241g** was performed successfully and gave the corresponding pyrrolidine **242g** in 76% yield with 10:1 *dr* (Table 12, entry 6). Unsubstituted aromatic-cyclic aliphatic rings system **241x** and **241y** provided the desired pyrrolidines **242x** and **242y** in good yields (73% and 72% respectively), the *dr* was 9:1 for **242x** and 10:1 for **242y** (Table 12, entries 7 and 8).

Conversely, the desired pyrrolidine **242z** was obtained in the best *dr* (>25:1) and a good yield (71%) when **241z** was employed (Table 12, entry 9). The reason for this probably the size of the sulfur atom present on the heterocycle, which improves the selectivity of the ring cyclisation. While, substituted aromatic-cyclic aliphatic ring system **241aa** afforded the corresponding pyrrolidine **242aa** in a good yield (71%) and without change in the *dr* (4:1) (Table 12, entry 10). This is may be due to the phenyl substituent on **241aa**, which is considered a bulky group and hence increased the selectivity on the opposite face.

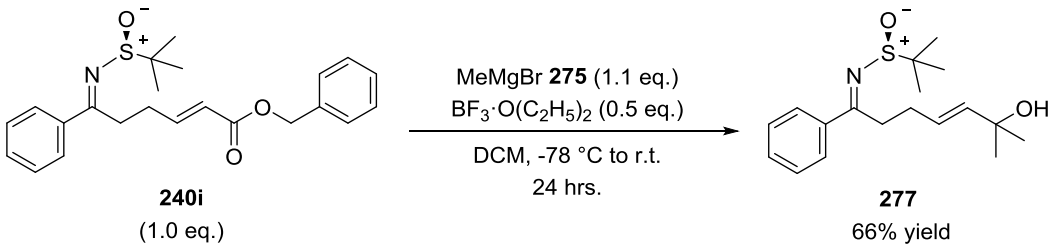
Finally, the substrates derived from aromatic-aliphatic **241i** and **241ab** gave **242i** and **242ab** in 53% and 66% yields respectively, with >10:1 *dr* (Table 12, entries 11 and 12). We did not observe any evidence for reversibility in the cyclisations, and consequently presume they are under kinetic control.

We also envisaged that the nucleophilic addition of MeMgBr **275** in dry toluene to **240i** could give substituted pyrrolidine **276**. Unfortunately, the desired product **276** could not be observed in this attempt and a tertiary alcohol derivative **277** was isolated in a 71% yield (Scheme 71).



Scheme 71: Nucleophilic addition of Grignard reagent **275** to sulfinimine **240i** resulting tertiary alcohol derivative **277**

The conditions were then changed and boron trifluoride diethyl etherate was used as a Lewis acid, which could be used to increase the electrophilicity of the imine group rather than ester group. Unfortunately, the addition also was on the ester carbonyl and afforded the same product **277** in a 66% yield (Scheme 72).



240i
(1.0 eq.)

277
66% yield

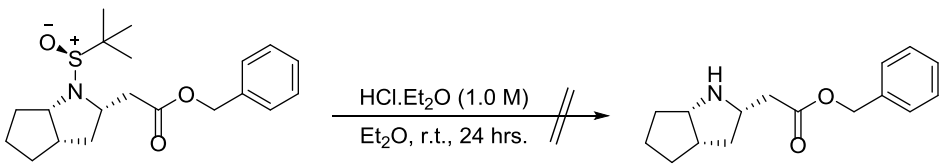
Scheme 72: Nucleophilic addition of Grignard reagent **275** to sulfinimine **240i** in the presence of boron trifluoride diethyl etherate as a Lewis acid resulting tertiary alcohol derivative **277**

1.2.6. Exploration of pyrrolidine chemical scaffolds chemistry

After accomplishing the synthesis of the pyrrolidine chemical scaffolds **242**, our focus was then turned to further functionalise them. In particular, by taking advantage of the two points of diversity that each of the pyrrolidine chemical scaffolds **242** possesses.

1.2.6.1. Deprotection of the chiral auxiliary group and hydrolysis of the ester group at pyrrolidine chemical scaffold

The removal of the *tert*-butanesulfinyl chiral auxiliary group on **242b** to produce **261** was not successful when using conditions HCl in Et_2O. This is possibly because the amine group at the product **261** will react with *tert*-butanesulfinyl chloride formed to give the starting material **242b** (Scheme 73).

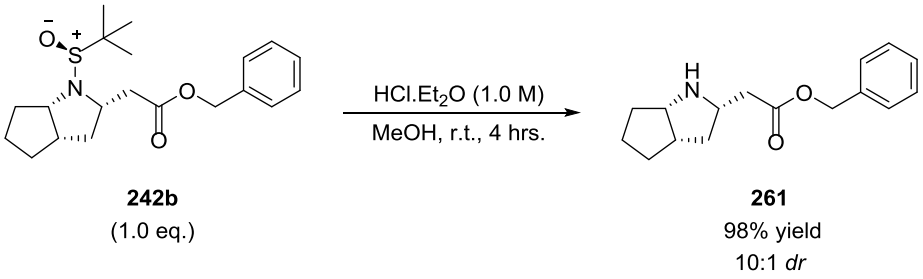


242b
(1.0 eq.)

261

Scheme 73: Unsuccessful removal of the chiral auxiliary on **242b** in Et_2O to give **261**

The reaction conditions were then modified using MeOH in place of Et_2O in order to quench *tert*-butanesulfinyl chloride formed. The deprotection of **242b** in these conditions was accomplished; the desired product **261** was obtained in an excellent yield (98%) with 10:1 *dr* (Scheme 74).

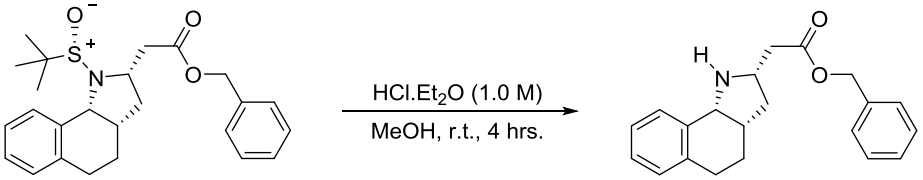


242b
(1.0 eq.)

261
98% yield
10:1 *dr*

Scheme 74: Removal of the chiral auxiliary on **242b** in MeOH to give **261**

The same conditions above were used with **242x** and the desired product **278** was isolated in 99% yield and 10:1 *dr* (Scheme 75).

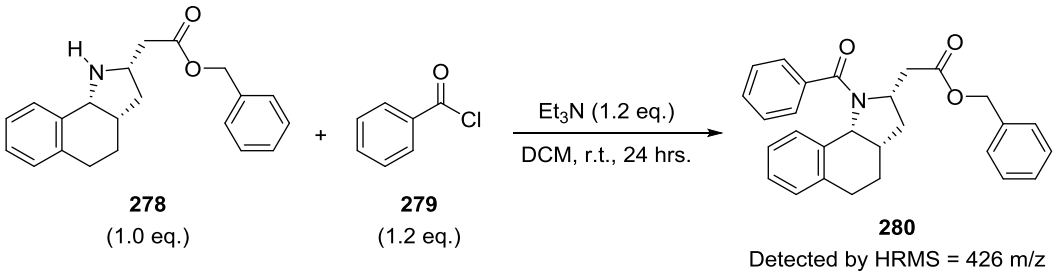


242x
(1.0 eq.)

278
Crude material
99% yield
10:1 *dr*

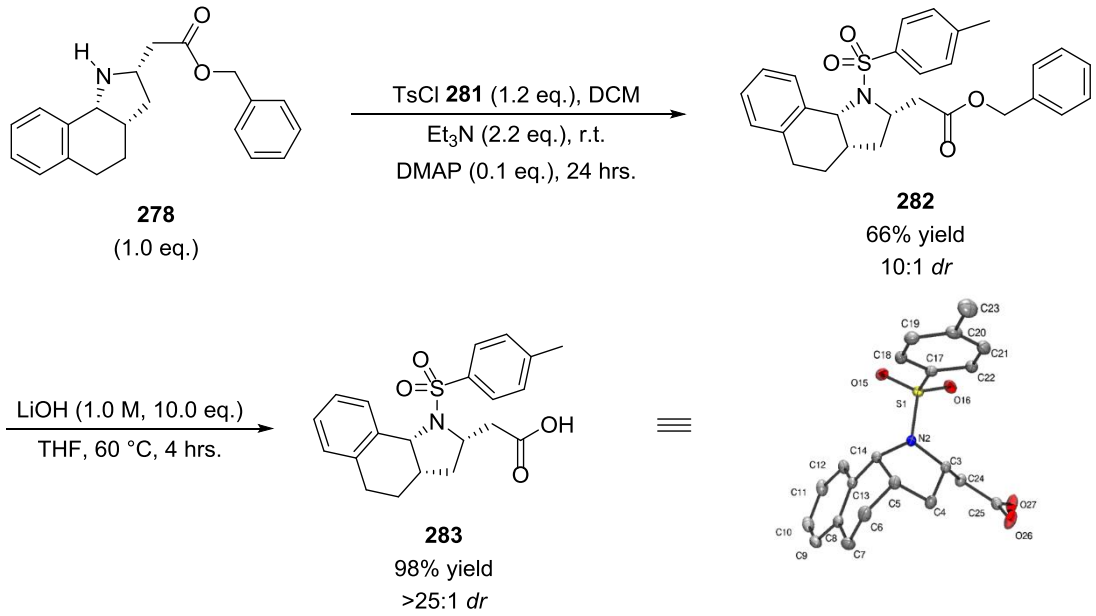
Scheme 75: Removal of the chiral auxiliary at **242x** in MeOH to give **278**

Nucleophilic substitution of **278** with benzoyl chloride **279** in the presence of Et_3N as a base was then attempted to synthesise **280**. ^1H NMR spectroscopy showed there was conversion to the desired amine derivative **280** but not cleanly, as another side product had found. HRMS also detected **280** but it was not the major product (Scheme 76).



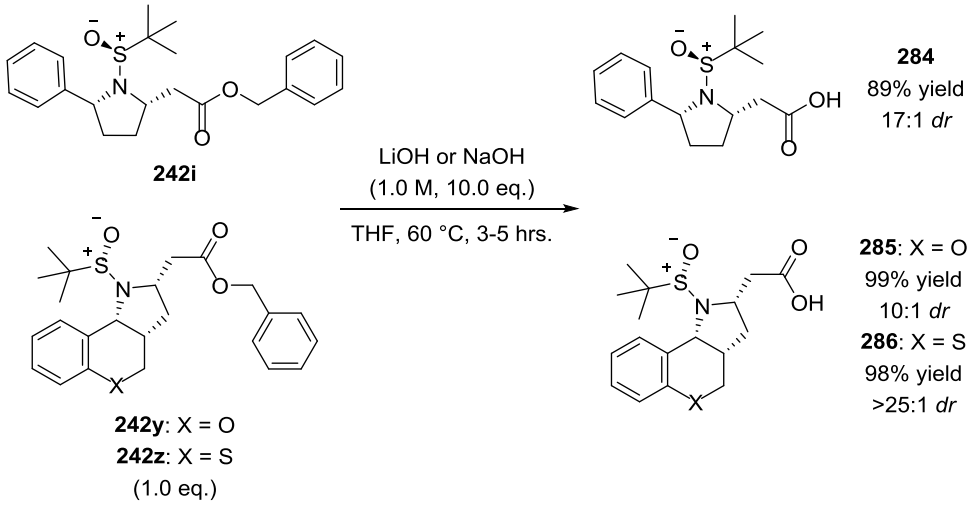
Scheme 76: Nucleophilic substitution of **278** with **279** to afford **280**

Sulfonylation of **278** with TsCl **281** was then performed and afforded **282** in 66% yield and *dr* 10:1 (Scheme 77). Hydrolysis of the ester group at **282** under basic conditions gave the desired carboxylic acid **283** in an excellent yield (98%) and almost as single diastereoisomer (>25:1 *dr*). Fortunately, X-ray crystallographic analysis of **283** confirmed the atoms connectivity and the stereochemistry of the C-C bond created from the Tsuji-Trost allylation, and the C-N bond formed from the sulfinimine reduction. In addition, this gave the stereochemistry of the new C-N bond that was established *via* intramolecular Michael addition (Scheme 77).



Scheme 77: Synthesis of **283** *via* sulfonylation and hydrolysis of the benzyl group at **278**

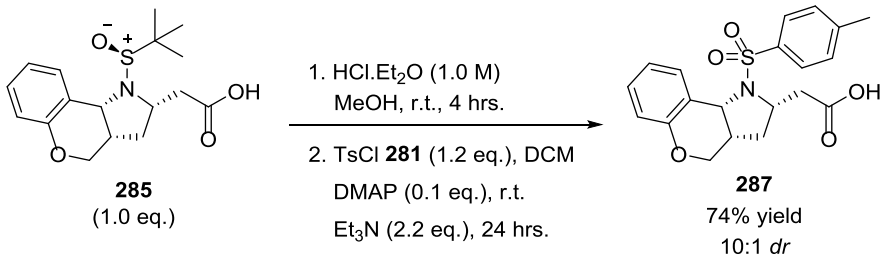
In addition, the benzyl group of **242i**, **242y** and **242z** was removed and afforded the corresponding acids **284**, **285** and **286** in yields ranging from 89 to 99% with *dr* from 10:1 to >25:1. This was achieved using LiOH or NaOH (1.0 M) in THF with heating at 60 °C for 3-5 hours (Scheme 78).



Scheme 78: Hydrolysis of **242i**, **242y** and **242z** to the carboxylic acids **284**, **285** and **286** under basic conditions

The aim of this reaction is conversion of the ester to the corresponding acid, which may be a solid and could be crystallised in order to confirm the stereochemistry by X-ray crystallography. Unfortunately, the desired products **284**, **285** and **286** were obtained as an oil.

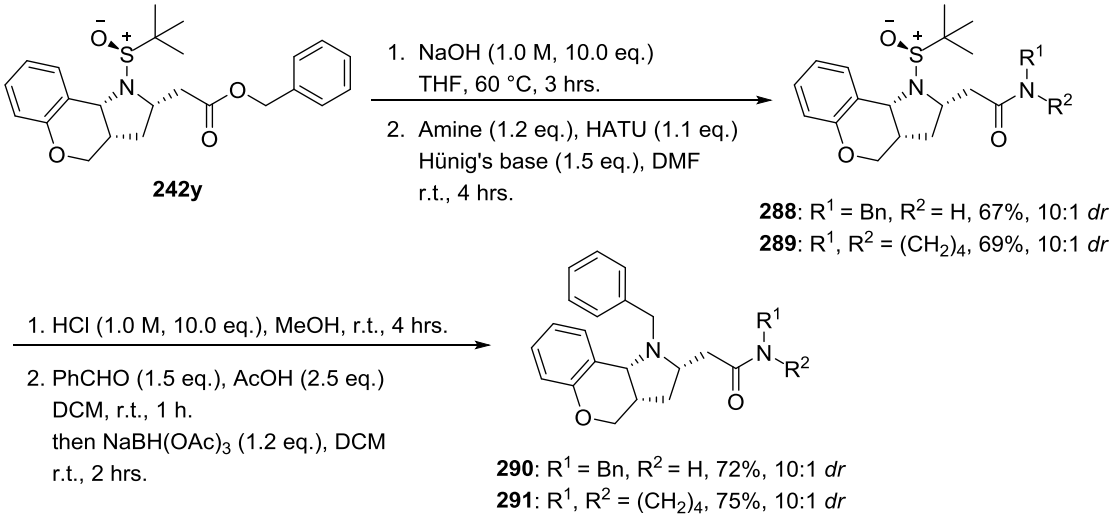
The chiral auxiliary group on **285** was then removed using acidic conditions, which afforded the corresponding amine. This was followed by treatment with TsCl **281** to give the sulfonylated product **287** in 74% yield and 10:1 *dr*. The desired product **287** was obtained as an oil, therefore an X-ray crystal structure could not be obtained (Scheme 79).



Scheme 79: Deprotection and sulfonylation of **285** to give **287**

1.2.6.2. Reductive amination and amidation

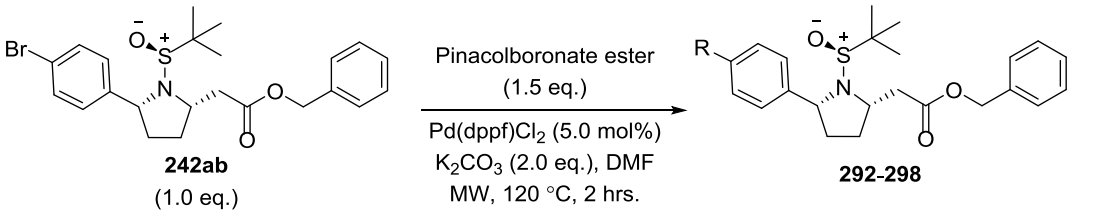
Next, it was decided to investigate the reductive amination on the pyrrolidine chemical scaffold, the synthetic route was scaled up to obtain a total of 3 g of scaffold core **242y**, bearing two points of diversity which can be further functionalised. The conversion of **242y** to the corresponding carboxylic acid was achieved successfully using NaOH (1.0 M). The acid was then coupled with primary and secondary amines in the presence of HATU as a coupling agent and afforded the corresponding amides **288** and **289** in 67% and 69% yields respectively (Scheme 80). The protecting group at amides **288** and **289** was then removed using acidic standard conditions, providing the corresponding amines. This was followed by reductive amination with benzaldehyde in the presence of $NaBH(OAc)_3$ and AcOH in DCM, giving the corresponding substituted tertiary amines **290** and **291** in 72% and 75% yields respectively.



Scheme 80: *N*-alkylation and C-amidation on **242y**

1.2.6.3. Suzuki-Miyaura cross-coupling

In looking for ways of further functionalising, bromide substituted scaffold core **242ab** was derivatised using Suzuki-Miyaura cross-coupling reaction (Scheme 81). In particular, **242ab** was treated with pinacolboronate esters under microwave conditions (120 °C, 2 hours) in the presence of $Pd(dppf)Cl_2$ as a catalyst giving desired products **292**-**296** in yields ranging from 50 to 66%. It was observed that the reaction was successful when aromatic pinacolboronate esters were employed. Conversely, we failed to successfully convert alkyl pinacolboronate esters to their corresponding products **297** and **298**. This is because the alkyl pinacolboronate esters are generally less reactive than aromatic pinacolboronate ester derivatives (Scheme 81).

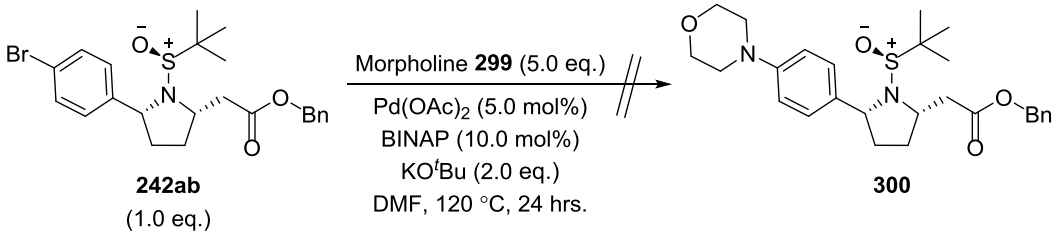


292: R = C_6H_5, 62% yield, >10:1 *dr*
293: R = *p*-$OMeC_6H_4$, 66% yield, >10:1 *dr*
294: R = *p*-$NO_2C_6H_4$, 50% yield, >10:1 *dr*
295: R = 3-furyl, 54% yield, >10:1 *dr*
296: R = 1,2-dihydroacenaphthylene
61% yield, >10:1 *dr*
297: R = 2-ethyl-1,3-dioxolane, 0% yield
298: R = 5-chloropent-1-ynyl, 0% yield

Scheme 81: Suzuki-Miyaura cross-coupling of **242ab** with pinacolboronate esters using microwave conditions

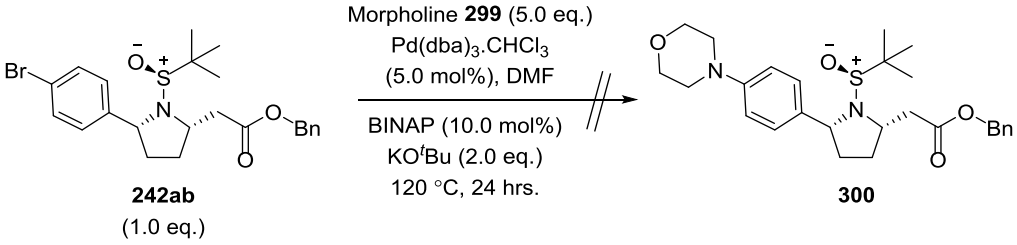
1.2.6.4. Buchwald-Hartwig amination

The possibility of amination at the Br-position of the pyrrolidine ring on **242ab** using Buchwald-Hartwig amination was the next investigation. It was hoped that this position would be easily aminated with morpholine **299** (carbon-nitrogen bond formation) in the presence of $Pd(OAc)_2$ and BINAP as a catalyst and ligand respectively. Unfortunately, the desired aryl amine derivative **300** could not be detected by HRMS or ^1H NMR spectroscopy (Scheme 82).



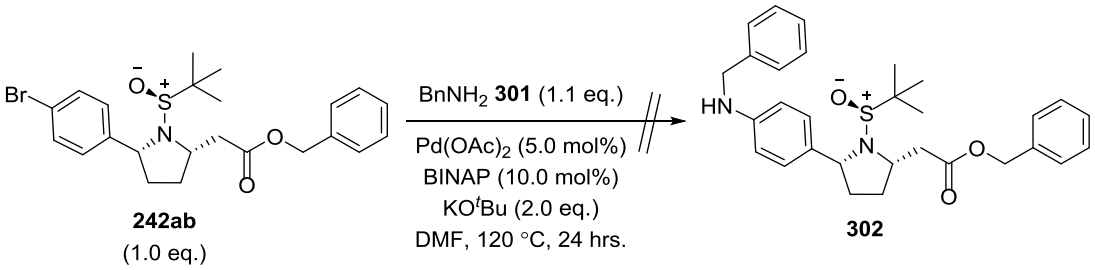
Scheme 82: Buchwald-Hartwig amination of **242ab** with morpholine **299** in the presence of $Pd(OAc)_2$ to afford **300**

We still believed this substrate **242ab** to be suitable for Buchwald-Hartwig amination, however, the reaction conditions were then changed using $Pd(dba)_3.CHCl_3$ instead of $Pd(OAc)_2$. But, only the starting material was observed after 24 hours (Scheme 83).



Scheme 83: Buchwald-Hartwig amination of **242ab** with morpholine **299** in the presence of $Pd(dba)_3.CHCl_3$ to give **300**

Next attempt on this reaction is using benzyl amine **301** in place of morpholine **299** in order to find the problem with this coupling, which might be due to the primary amine being more effective than secondary amine. Unfortunately, the substrate **242ab** could not be converted into aryl amine product **302** using these conditions (Scheme 84).



Scheme 84: Buchwald-Hartwig amination of **242ab** with benzyl amine **301** in the presence of $Pd(OAc)_2$ to afford **302**

1.2.7. Conclusion

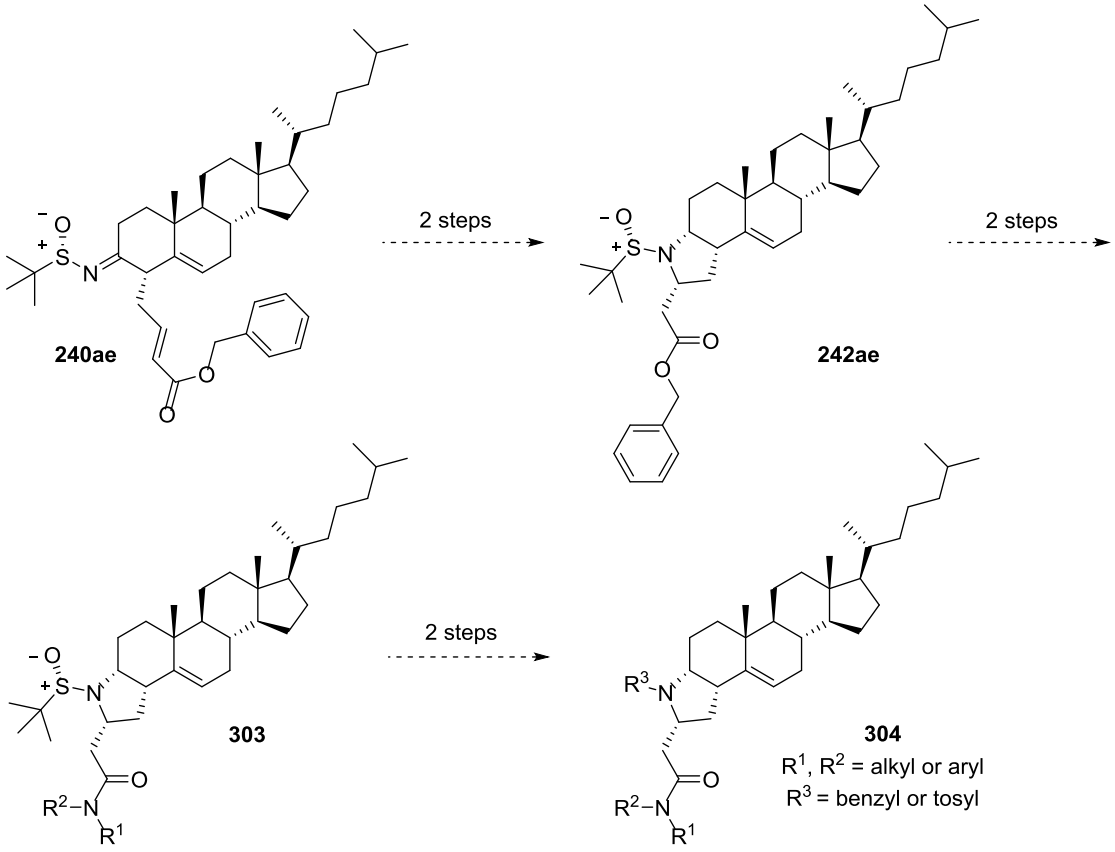
The synthesis of novel pyrrolidine containing chemical scaffolds **242** using sulfinimines **238** has been investigated. A Tsuji-Trost reaction was used in order to obtain α-allyl sulfinimines **239** *via* condensation of sulfinimines **238** with allyl methyl carbonate **247** in the presence of $Pd(PPh_3)_4$ as a catalyst. These products **239** were reacted with benzyl acrylate **252** in a cross metathesis reaction to give the corresponding α,β-unsaturated ester derivatives **240** in good yields (57-84%) and *dr* from 3:1 to >25:1. Stereoselective reduction of the sulfinimine group in substrates **240** have been achieved successfully to afford the corresponding sulfinamides **241** in high *dr* in most cases (up to >25:1), in yields ranging from 58 to 86%.

The sulfinamides **241** were then used to synthesise pyrrolidine scaffolds **242** *via* intramolecular Michael addition in the presence of NaH. The desired pyrrolidine products **242** were isolated in yields between 53 and 77% with *dr* up to >25:1. Furthermore, removal the chiral auxiliary and the hydrolysis of the ester group gave a scaffold core which can be further derivatised. For example, sulfonylation, reductive amination, amidation and Suzuki coupling leading to highly functionalised substrates, has been achieved successfully.

1.2.8. Future work

In the recent years, the steroid and its derivatives have been used as medicines to treat a variety of inflammatory diseases such as eczema, allergies, arthritis and inhalers for asthma. In addition, the steroid and its derivatives have two essential biological roles; a main component in the cell membranes (sometimes called cytoplasmic membrane or plasma membrane) and as a signalling molecule that activates steroid hormone receptors.

Hence, α,β-unsaturated esters derived from cholesterol **240ae** and progesterone **240af** constitute useful intermediates for interesting applications in the future leading to highly functionalised substrates (amine and ester group) for steroid derivatives. The synthesis of these functionalised intermediate compounds can be achieved in only a few simple steps (Scheme 85).

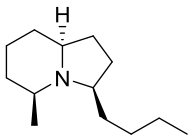


Scheme 85: Potential applications of **240ae** in synthesis

2. Progress towards the total synthesis of natural product (+)-monomorine (305)

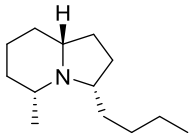
2.1. Introduction

Monomorine is an example of an indolizidine alkaloid containing a sp^3 hybridised nitrogen atom. It has three stereogenic centres at C-3, C-5 and C-9, and therefore could exist as one of eight stereoisomers. (+)-Monomorine **305** is a natural product, whereas (-)-monomorine **306** is a non-natural product (Figure 13).



(+)-Monomorine **305**

(3*R*,5*S*,9*S*)-3-butyl-5-methyloctahydroindolizine



(-)-Monomorine **306**

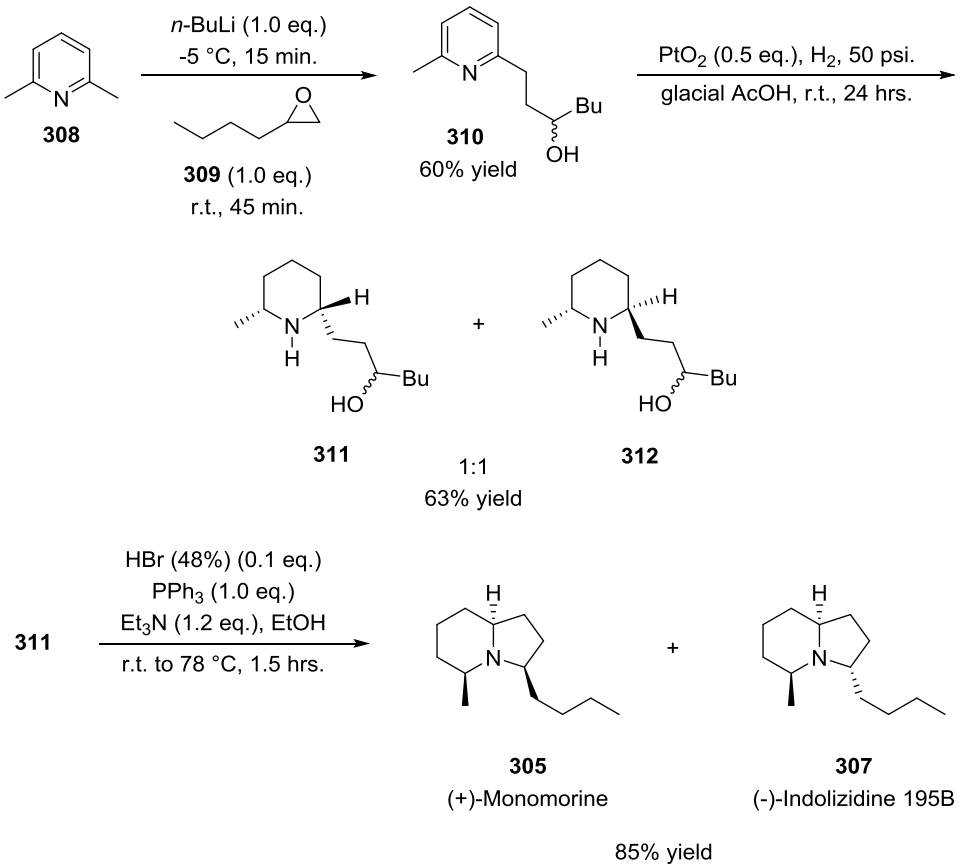
(3*S*,5*R*,9*R*)-3-butyl-5-methyloctahydroindolizine

Figure 13: Structure of (+)-**305** and (-)-**306**-monomorine

(+)-Monomorine **305** is a trail pheromone, isolated for the first time in 1973 by Ritter *et al.* from Pharaoh's ants (*Monomorium pharaonis L*); a small transparent ant (2 mm) with yellow or light brown colour (Figure 14, a).[121] In addition, Gros and co-workers in 1993 detected (+)-monomorine **305** as a mixture with three other diastereoisomers from the skin of *Melanopbyrniscus* frog (Figure 14, b).[122] The absolute configuration of the diastereomers present in this mixture, which was named (-)-indolizidine 195B (**307**) has not been determined yet. On the other hand, (-)-monomorine **306** is a non-natural product. The racemic and the enantioselective synthesis of both (+)-monomorine **305** and (-)-monomorine **306** have been reported.[123-126]

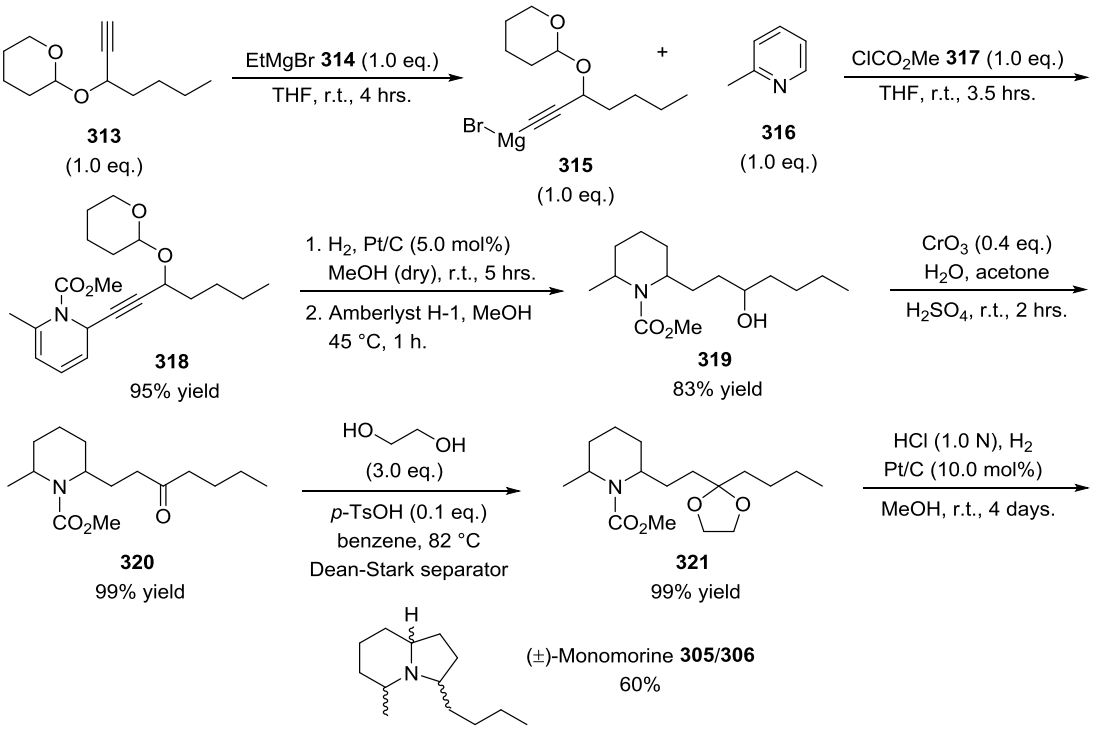
Figure 14: (a) Pharaoh ant (*Monomorium pharaonis L*) (b) Dendrobatidae frog (*Melanopbyrniscus*)

Oliver and Sonnet reported the first total synthesis of a mixture a containing (+)-monomorine **305** and (-)-indolizidine 195B (**307**) in 1974 (Scheme 86).[127,128] The synthetic route was performed using 2,6-lutidine **308** as a starting material. Reaction of **308** with 1,2-epoxyhexane **309** in the presence of *n*-BuLi as a base afforded alcohol **310** in 60% yield. Hydrogenation of the aromatic ring of **310** was then achieved successfully using H_2/PtO_2, affording a mixture of *cis*- and *trans* piperidines **311** and **312** in a 1:1 ratio (63% yield). Separation of the mixture was achieved using spinning band distillation. Furthermore, cyclisation of **311** in the presence of Ph_3P, HBr (48%) and Et_3N furnished a mixture of diastereoisomers of **305** and **307** in a very good yield (85%) (Scheme 86).



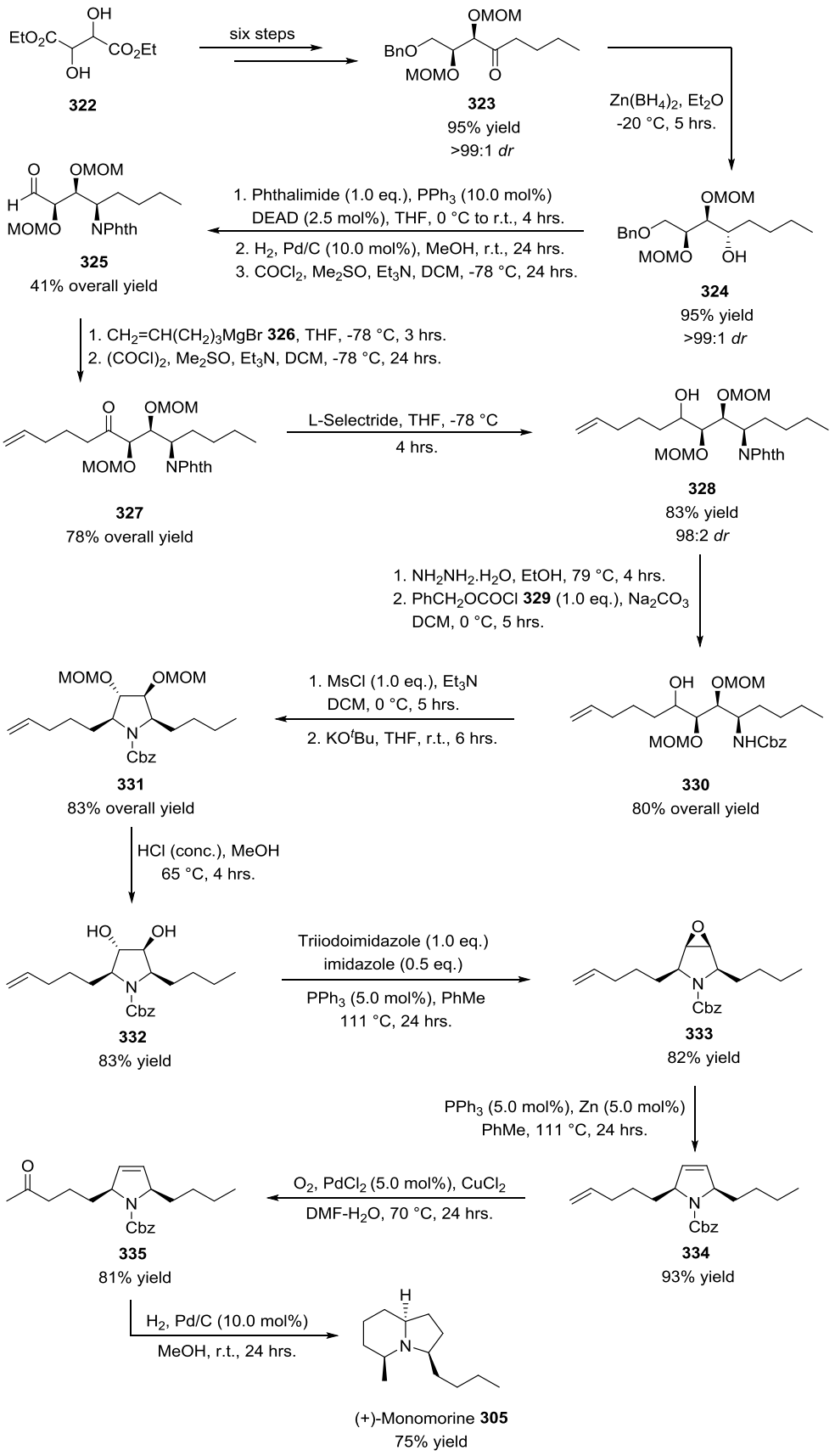
Scheme 86: Total synthesis of (+)-monomorine **305** in a mixture of diastereoisomers with (-)-indolizidine 195B (**307**) by Oliver and Sonnet

Yamaguchi *et al.*[129] published the first total synthesis of (+)-monomorine **305** as a racemic mixture. This was done using 2-methyl pyridine **316** as a starting material (Scheme 87). Hence, compound **316** was treated with 3-(2-tetrahydropyranyloxy) heptynylmagnesium bromide **315** in the presence of methyl chloroformate **317**, affording compound **318** in an excellent yield (95%). In addition, compound **315** was prepared *via* the reaction between 3-(2-tetrahydropyranyloxy)-1-heptyne **313** and EtMgBr **314** in THF. Hydrogenation of **318** over Pt/C in MeOH, followed by deprotection of the hydroxyl group using Amberlyst H-1 in MeOH afforded piperidine derivative **319** in a very good yield (83%). The following step in this synthetic route included a Jones oxidation ($CrO_3.H_3O^+$/acetone) with **319** resulted in the isolation of **320** in 99% yield. Protection of the ketone functionality using ethylene glycol in the presence of *p*-TsOH as a catalyst gave **321** in an excellent yield (99%). Compound **321** was then treated with HCl (1.0 N), followed by reductive cyclisation using H_2 over Pt/C in MeOH affording a racemic mixture of desired product **305** and undesired product **306** in a good yield (60%) (Scheme 87).



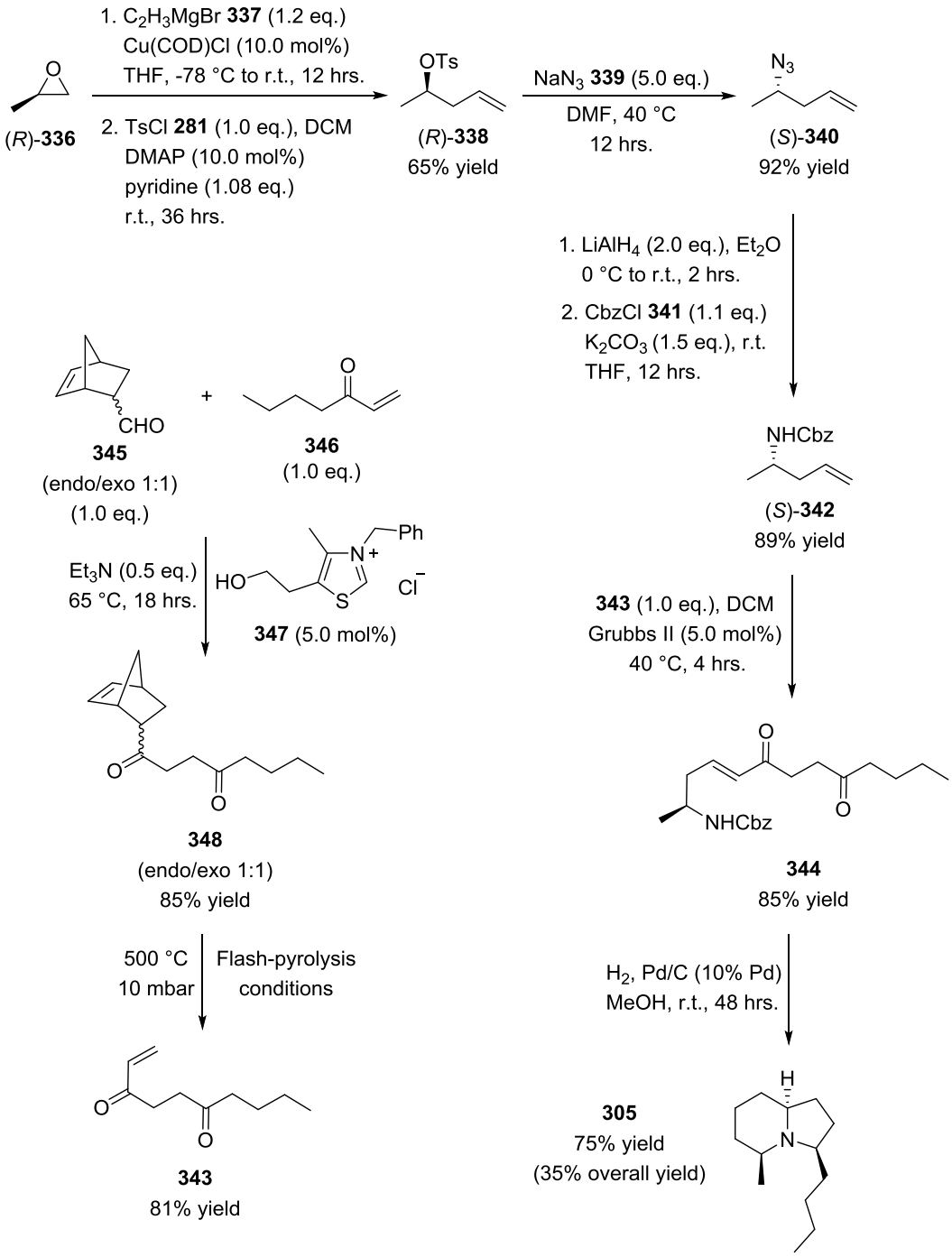
Scheme 87: Yamaguchi's *et al*. synthesis of (±)-monomorine **305**/**306**

The first enantioselective total synthesis of (+)-monomorine **305** was reported in 1988 by Yamazaki and Kibayashi (Scheme 88).[130] This synthetic route required many cascade reactions and several functional group protection and deprotection steps. Ketone **323**, bearing methoxymethyl (MOM) ethers at α and β positions was used, which was synthesised over six steps starting from diethyl L-tartrate **322**.[131] Compound **323** was then reduced with $Zn(BH_4)_2$ in Et_2O at -20 °C to afford alcohol **324** in an excellent yield (95%) with high anti selectivity (>99:1 *dr*). Aldehyde **325** was then obtained in 41% overall yield from **324** over three steps (Scheme 88). Nucleophilic addition of Grignard reagent **326** to **325** followed by a Swern oxidation provided **327** in 78% overall yield. The following step included the reduction of **327** using L-Selectride in THF at -78 °C to give alcohol **328** in an excellent *dr* (98:2) with very good yield (83%). Thereafter, the phthaloyl group of **328** was removed using $(NH_2)_2.H_2O$ in EtOH, followed by protection of the amino group *via* treatment with benzyl chloroformate **329** in DCM at 0 °C affording **330** in 80% overall yield. Mesylation of the hydroxyl group at **330** with MsCl in DCM then ring cyclisation under basic conditions (KO^tBu, THF, room temperature) gave pyrrolidine **331** in a very good yield (83%). Removal of the MOM ether groups on **331**, under acidic conditions (HCl, MeOH) afforded the corresponding alcohol **332** in a very good yield (83%). Compound **332** was then treated with triiodoimidazole and PPh_3 furnishing epoxide derivative **333** in 82% yield. Compound **333** was then deoxygenated in the presence of PPh_3 and Zn under reflux in toluene to provide pyrroline form **334** in an excellent yield (93%). The terminal olefin on **334** was then oxidised selectivity using a Wacker reaction (O_2, $PdCl_2$, $CuCl_2$), affording **335** in 81% yield. The final step in the synthetic route included hydrogenation of **335** over Pd/C in MeOH giving (+)-monomorine **305** as a single enantiomer in good yield (75%) (Scheme 88).



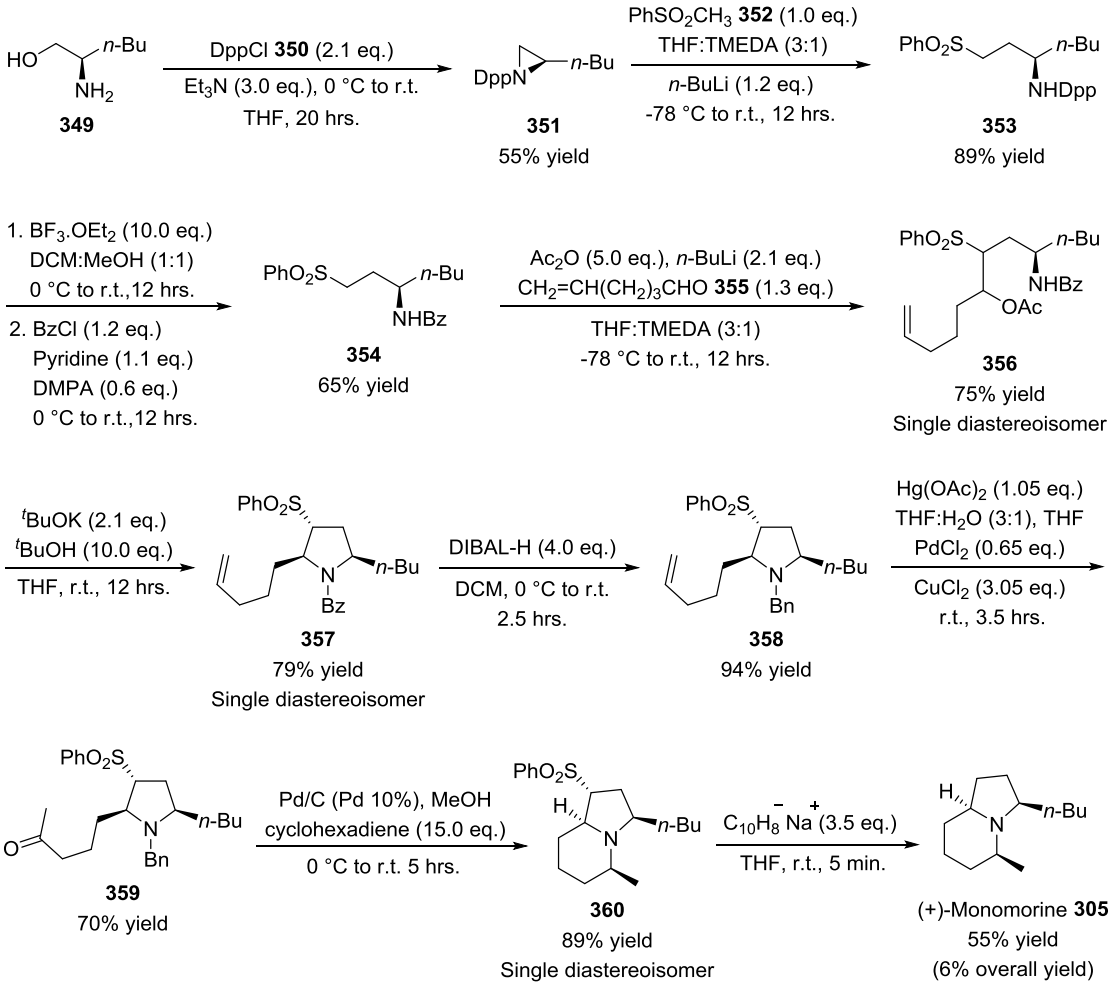
Scheme 88: First enantioselective total synthesis of (+)-monomorine **305** by Yamazaki and Kibayashi

In 2003, a novel and facile an enantioselective synthesis of (+)-monomorine **305** has been reported by Randl and Blechert.[132] The synthetic route included using (*R*)-methyloxirane **336** as a starting material (Scheme 89). Treatment of **336** with a Grignard reagent **337** in the presence of a copper catalyst led to open the ring regioselectively and gave the corresponding alcohol, which was followed by protection of the hydroxyl group with TsCl **281** afforded **338** in 65% yield. Nucleophilic displacement of the OTs group at **338** with sodium azide **339** was then performed provided **340** in an excellent yield (92%) and inverted stereochemistry at the C-N bond. Reduction of the azide group at **340** with $LiAlH_4$ gave amine derivative, which was then directly protected with benzyl chloroformate **341** in a one-pot reaction afforded **342** in a very good yield (89%). Cross metathesis coupling between **342** and **343** provided **344** in 85% yield. The product **343** was prepared from **345** over two steps, which included Michael addition of **345** to oct-1-en-3-one **346** in the presence of **347** gave diketone derivative **348** in 85% yield. Following this, flash-pyrolysis induced retro-Diels-Alder conditions on **348** furnished enone form **343** in a very good yield (81%). Finally, double-reductive cyclisation on **344** has been achieved successfully afforded the desired product **305** in 75% yield (Scheme 89).



Scheme 89: Randl and Blechert's enantioselective synthesis of (+)-monomorine **305** starting from **336**

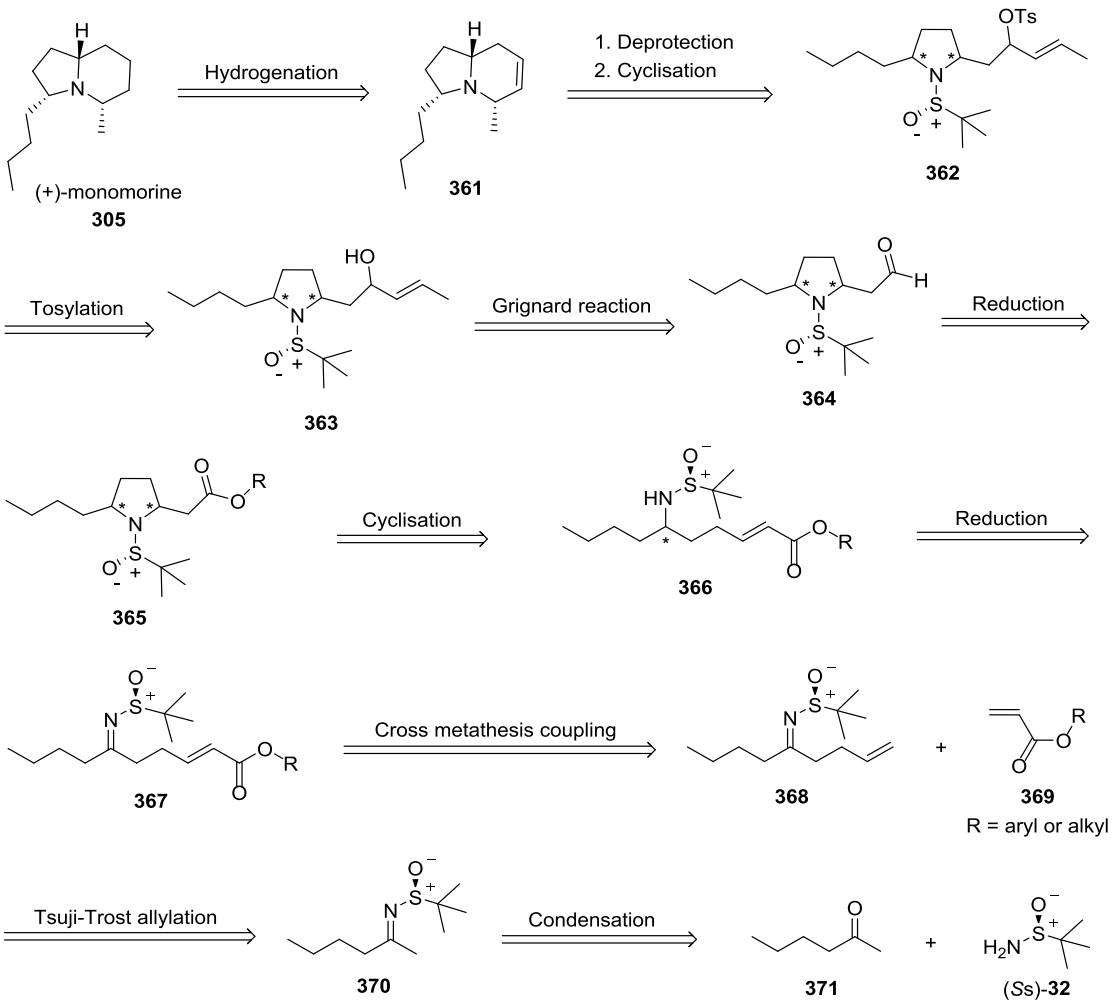
Moreover, Berry *et al.*[133] reported an efficient and new method for the total synthesis of (+)-monomorine **305** enantioselectively. This was done starting from commercially available compound **349** (Scheme 90). Diphenylphosphinylaziridine **351** was obtained in 55% yield by reaction of **349** with DppCl **350** in the presence of Et_3N as a base. The opening of the aziridine ring at **351** was achieved successfully when treated with **352** in the presence of *n*-BuLi as a base gave **353** in a very good yield (89%). Protecting group exchange of Dpp with a Bz group at **353** was then performed and provided **354** in 65% yield (Scheme 90). Treatment of **354** with *n*-BuLi afforded the anionic form of **354**, which was employed as a nucleophile reagent to react with aldehyde **355** provided **356** as a single diastereoisomer with good yield (75%). Elimination and cyclisation was then conducted on **356** in a one-pot reaction. When treated with KO^tBu gave pyrrolidine derivative **357** in 79% yield, which is considered the key intermediate of the synthetic route. The Bz group at **357** was reduced selectively with DIBAL-H to Bn form **358** in a good yield (94%). A Wacker reaction was then applied to oxidise the terminal alkene at **358** to afford **359** in 70% yield. Debenzylation of **359** followed by an intramolecular reductive amination was performed in a one-pot reaction, and afforded **360** as a single diastereoisomer with 89% yield. Final step included desulfonylation of **360** using Na/naphthalene gave the desired natural product **305** in 55% yield (6% overall yield) (Scheme 90).



Scheme 90: Berry's *et al*. enantioselective synthesis of natural product (+)-monomorine **305**

2.1.1. Aims and objectives

The total synthesis of the natural product (+)-monomorine **305** is the third aim of this thesis, using the proposed retrosynthetic analysis shown in Scheme 91. In this regard, the chemistry developed within the first chapter, especially Tsuji-Trost allylation applications on the sulfinimines, will be utilised. We propose a novel approach for the synthesis of (+)-monomorine **305**, which will include using known sulfinimine chemistry, and also display the role of this chiral auxiliary in a route not previously attempted in the (+)-monomorine **305** total synthesis context. Our synthesis approach towards (+)-monomorine **305** could be performed in eleven steps starting from 2-hexanone **371**, which is commercially available and inexpensive. The key step in our synthetic strategy is the preparation of allyl sulfinimine **368**. A variety of methods will be examined in order to synthesise **368** in a high yield and as a single regioisomer. Cross metathesis coupling of **368** with an acrylate ester **369** could be performed to provide the corresponding α,β-unsaturated ester derivative **367**. This will be followed by the reduction of the sulfinimine **367** and subsequent cyclisation of the resulting sulfinamide **366** affording the desired pyrrolidine scaffolds **365**. The reduction of the ester group on **365** will be attempted to give the corresponding aldehyde **364**, which will be used later to react with a Grignard reagent to afford alcohol derivative **363**. Tosylation of the hydroxyl group at **363** should be performed to provide **362**. Removal of the chiral auxiliary on **362** using acidic conditions will be carried out to give the analogue amine of **362**, then a proposed S_N2' intramolecular reaction cascade could then lead to afford **361**. The final step would include hydrogenation of the alkene bond at **361** to give the desired natural product **305** (Scheme 91).

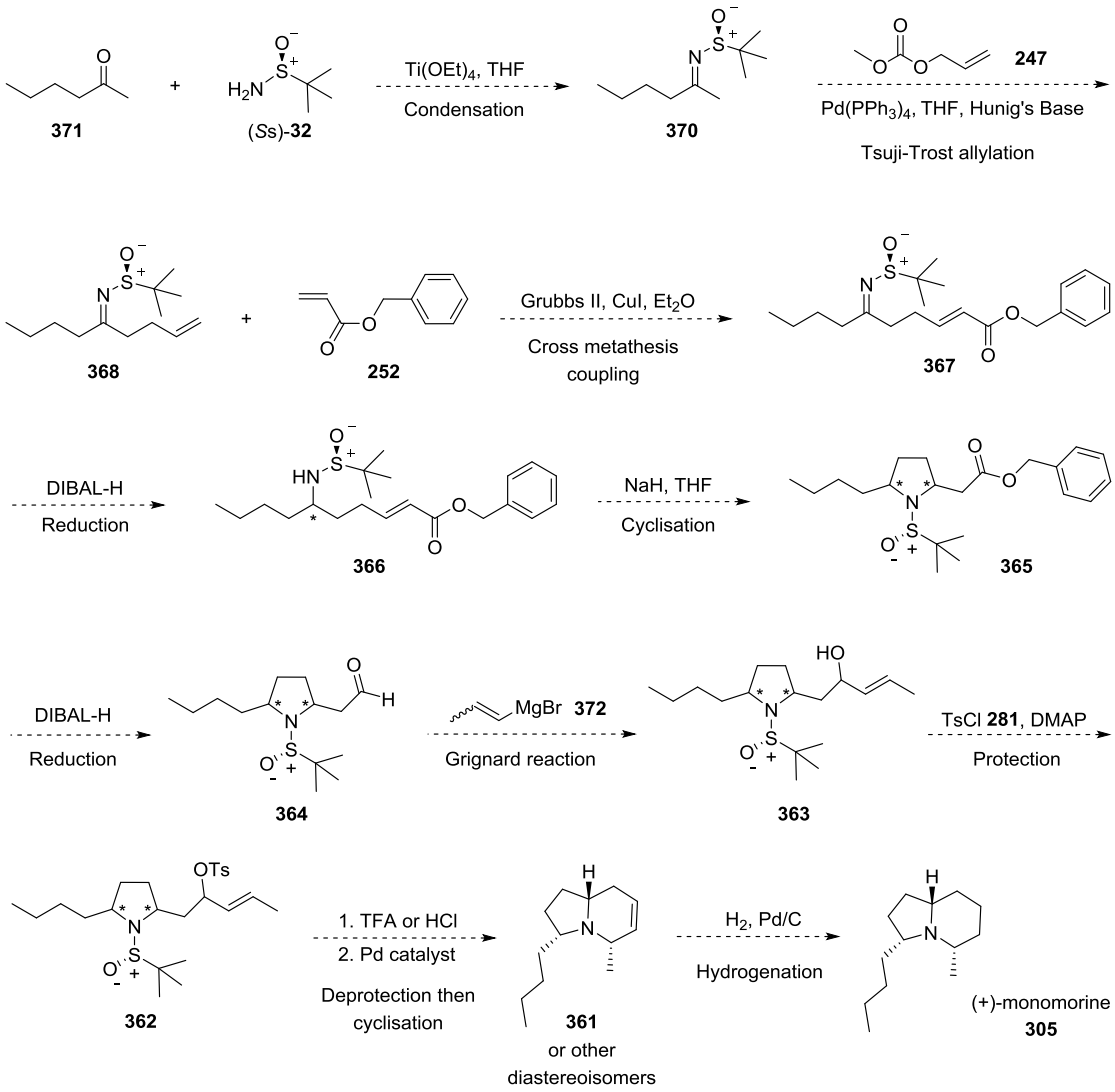


Scheme 91: Retrosynthetic analysis: novel approach towards natural product (+)-monomorine **305**

2.2. Results and discussion

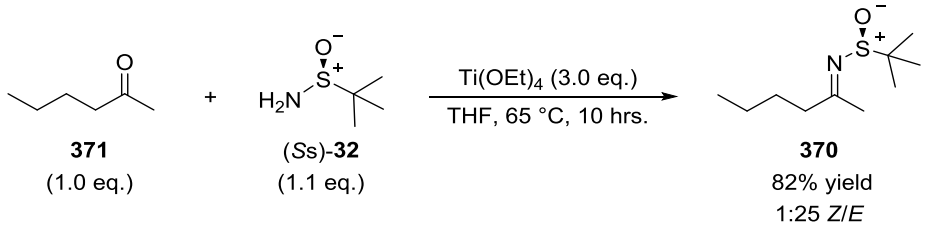
2.2.1. Synthesis of natural product (+)-monomorine 305

The aim of this part of the thesis is to achieve a total synthesis of (+)-monomorine **305** using the proposed synthetic route as described in Scheme 92. There are two key steps in this synthesis; a regioselective allylation of sulfinimine **370** using a Tsuji-Trost reaction to prepare **368**, and a stereoselective reduction of the imine group on **367** to afford sulfinamide **366**. The next step in this project will be synthesis of **365** *via* cyclisation of **366** under basic conditions. The product **365** will be used to prepare the aldehyde derivative **364** ideally in a good yield and high *dr via* reduction the ester group of **365**. If the aldehyde **364** is formed successfully, nucleophilic addition of a Grignard reagent **372** to **364** will be used in order to prepare alcohol derivative **363**. Conversion of the hydroxyl group on **363** to tosylate **362** *via* reaction with TsCl **281** will follow. Removal of the chiral auxiliary on **362** using acidic conditions can at this point be examined to give the analogue amine of **362**. Cyclisation of the analogue amine of **362** to afford **361** using acidic conditions in the presence of a palladium catalyst will be investigated. The last step will be hydrogenation of the alkene bond in **361** with a metal catalysed hydrogenation to give the desired target **305** (Scheme 92).



Scheme 92: Planned retrosynthetic analysis towards natural product (+)-monomorine **305**

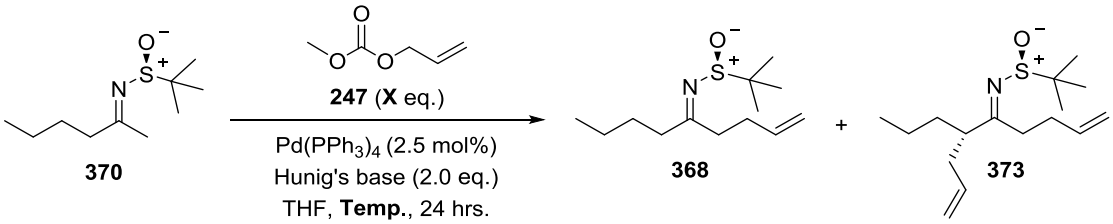
The first reaction in this synthesis included preparation of **370** in a very good yield (82%) *via* condensation between **371** and (*S*)-*tert*-butanesulfinamide **32** using Ellman's methodology[23] (Scheme 93).



Scheme 93: Preparation of **370** by condensation of **371** with (*S*s)-**32**

A variety of conditions were examined to synthesise **368** as a single regioisomer in high yield using a Tsuji-Trost reaction. The amount of allyl methyl carbonate **247** and the temperature were the two main factors that were used to optimise the conditions of this reaction (Table 13).

Table 13: Investigation of conditions effects on Tsuji-Trost reaction

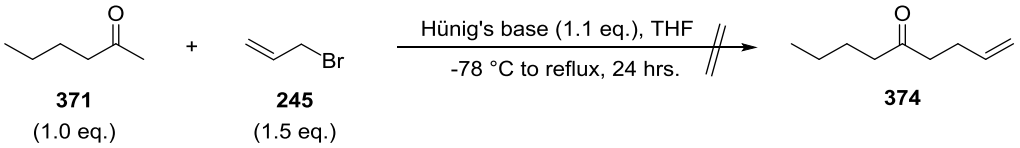


Entry	**247** (X eq.)	T (°C)	Yield **368** (%)[1]	Yield **373** (%)[1]	RSM **370** (%)[1]
1	1.1	Reflux	11	-	66
2	1.5	Reflux	20	-	20
3	1.7	Reflux	20	9	22
4	1.5	60	18	-	21
5	1.5	50	23	-	25
6	1.5	40	15	-	30
7	1.5	r.t.	-	-	RSM
8	1.5	-78	-	-	RSM

1. Isolated yield

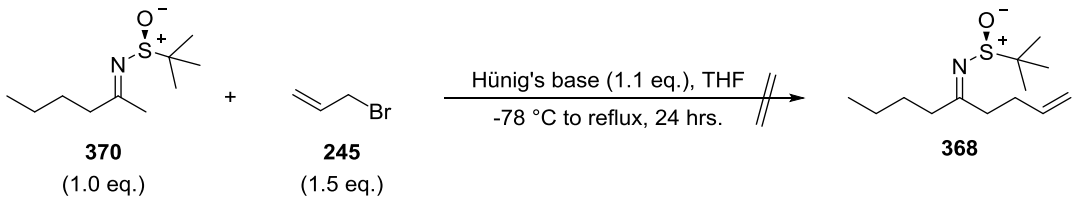
The first reaction in this optimisation was carried out with 1.1 eq. of allyl methyl carbonate **247** at reflux, and gave the desired product **368** in a low yield (11%), with 66% recovered starting material **370** (Table 13, entry 1). The product **368** was isolated in better yield (20%) when the amount of the allyl methyl carbonate **247** was increased to 1.5 eq. at reflux, accompanied with a decrease in the recovered starting material **370** to 20% (Table 13, entry 2). The reaction was then performed using 1.7 eq. of allyl methyl carbonate **247** at reflux, which afforded 20% of the desired product **368** and diallyl undesired product **373** in 9%, with 22% recovered starting material **370** (Table 13, entry 3). It was observed that 1.5 eq. of allyl methyl carbonate **247** was the best amount used in this reaction. Different temperatures were then used with 1.5 eq. of allyl methyl carbonate **247**. The desired product **368** was isolated in 18% when the reaction was carried out at 60 ºC (Table 13, entry 4). The best result was observed when the reaction was carried out at 50 ºC, which afforded 23% yield of the desired product **368** with 25% recovered starting material **370** (Table 13, entry 5). The use of 40 ºC gave a low yield of the desired product **368** (15%) and also increased the recovered starting material **370** to 30% (Table 13, entry 6). Finally, the desired product **368** could not be detected and only the starting material **370** was found when the reaction was carried out at room temperature and -78 ºC (Table 13, entries 7 and 8). Allyl methyl carbonate **247** and the temperature were found to be crucial parameters towards formation the desired product **368**, albeit in a low yield (Table 13).

We have tested other conditions to find better results than the Tsuji-Trost reaction to prepare **368**. 2-Hexanone **371** was treated with allyl bromide **245** in the presence of Hünig's base to give **374**. Thereafter, the product **374** can be converted to **368** using a condensation reaction with (*S*)-*tert*-butanesulfinamide **32**. Unfortunately, the product **374** was not detected by TLC, HRMS or ^{1}H NMR spectroscopy and only the starting material **371** was recovered (Scheme 94).



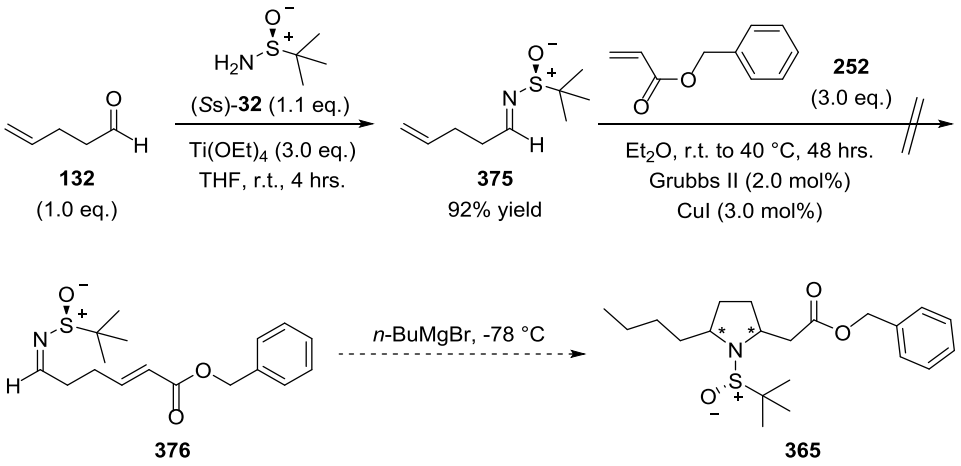
Scheme 94: Preparation of **374** *via* treatment **371** with **245** in the presence of Hünig's base

Compound **370** was also treated with **245** in the presence of Hünig's base to afford **368**. No product was detected from this attempt and only the starting material **370** was recovered (Scheme 95).



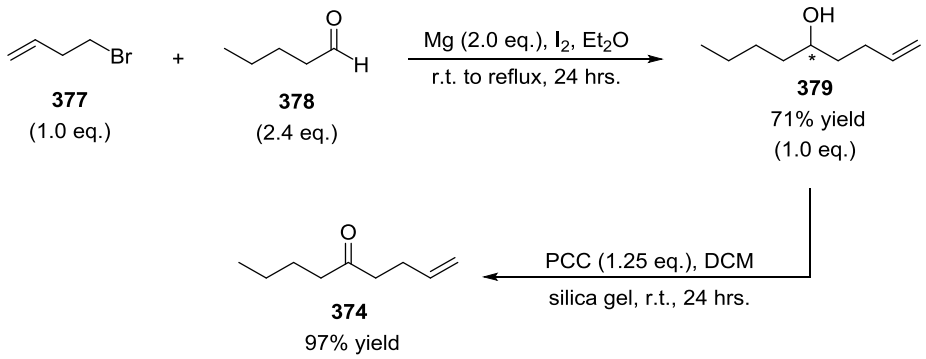
Scheme 95: Synthesis of **368** by condensation of **370** with **245** in the presence of Hünig's base

Next, we also tried to prepare **376** over two steps from **132**, the product **376** could be subjected to a tandem nucleophilic addition/Michael addition to provide the desired pyrrolidine derivative **365**. The condensation between 4-pentenal **132** and (*S*)-*tert*-butanesulfinamide **32** gave the corresponding (S_S)-sulfinimine **375** in 92% yield. This was followed by a cross metathesis reaction between **375** and benzyl acrylate **252** to afford **376**. However, no reaction was observed and only starting materials were recovered after two days (Scheme 96).



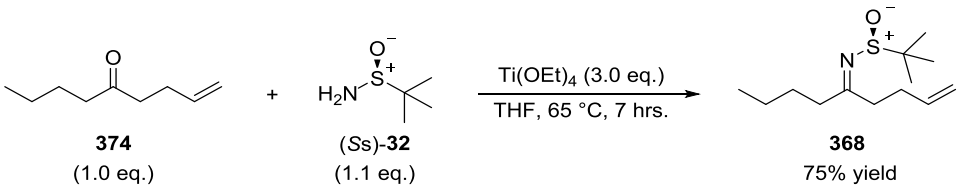
Scheme 96: Synthesis of **365** *via* using a tandem nucleophilic addition/Michael addition

After these attempts, the Grignard analogue of **377** was prepared *via* reaction between 4-bromobutene **377** and magnesium metal in the presence of I_2 as an activator and Et_2O as solvent. Thereafter, nucleophilic addition of Grignard analogue of **377** to pentanal **378**, produced alcohol **379** in a 71% yield. The product **379** was then oxidised with PCC, which gave ketone derivative **374** in an excellent yield (97%). The oxidation step required the addition of silica gel in a 1:1 mass ratio to PCC in order to aid the workup, which includes the removal of sticky black tar of two by-products: chromium deposits and pyridine hydrochloride. Accordingly, the role of the silica gel is an inert adsorbent to adsorb the by-products (Scheme 97).



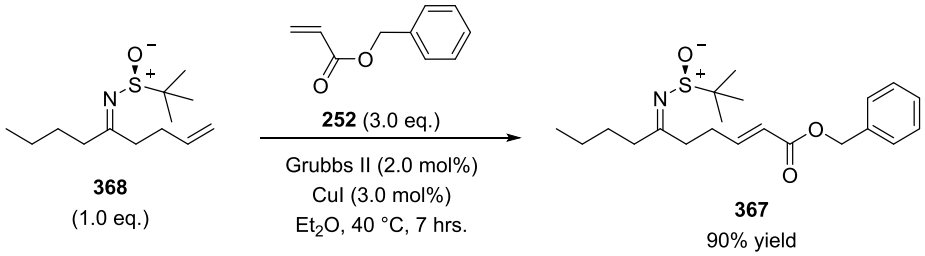
Scheme 97: Preparation of **374** over two steps starting from **377**

Ellman's procedure was then used with **374** which gave the corresponding (S_S)-sulfinimine **368** in a 75% yield (Scheme 98).[23] This route was found to be better than the previously studied Tsuji-Trost reaction. In addition, the desired product **368** was obtained in a good yield (75%) and could be formed without the complications of the regioselectivity associated with the Tsuji-Trost process.



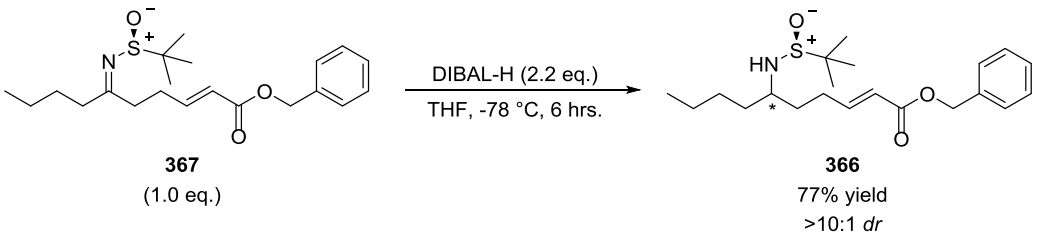
Scheme 98: Preparation of **368** using Ellman's methodology

Following this, benzyl acrylate **252** was used to react with **368** under cross metathesis conditions. The desired product **367** was isolated in an excellent yield (90%) (Scheme 99).



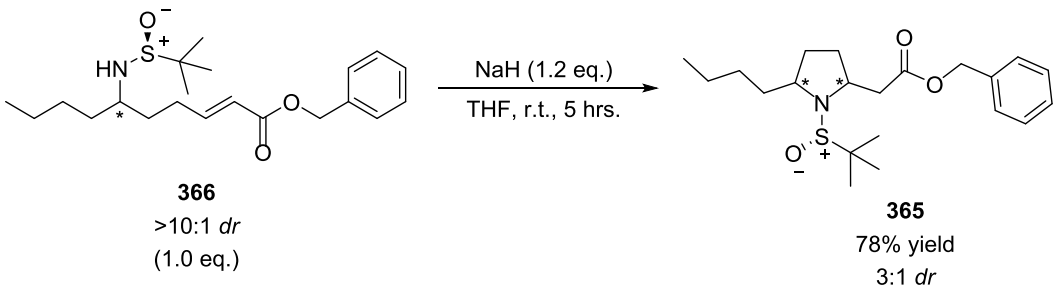
Scheme 99: Synthesis of **367** using a cross metathesis reaction

The imine group of **367** was then reduced stereoselectively with DIBAL-H (previously explained in the chapter one), which furnished the corresponding sulfinamide **366** in a 77% yield with >10:1 *dr* (Scheme 100).



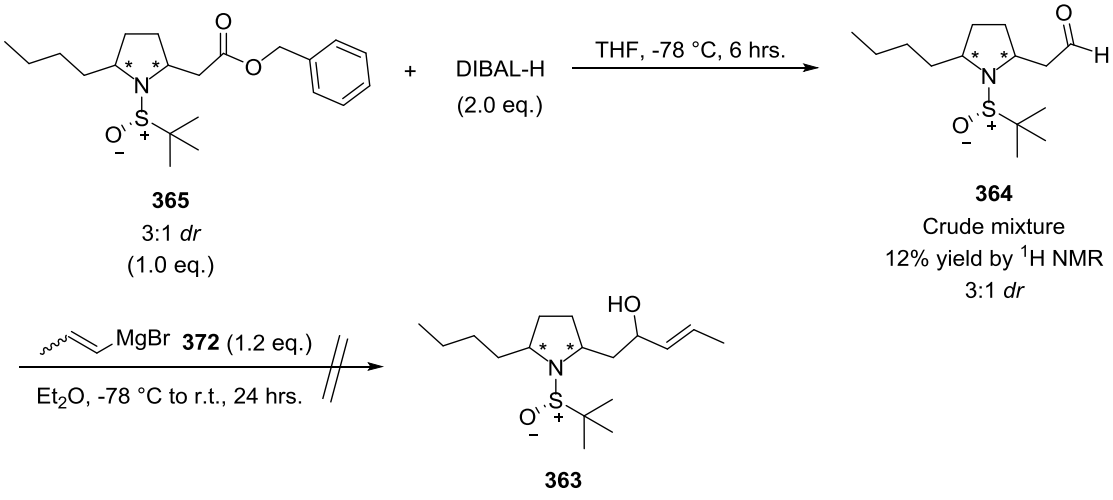
Scheme 100: Preparation of **366** *via* reduction of **367** with DIBAL-H

The cyclisation of **366** to give the pyrrolidine derivative **365** was then achieved successfully *via* treatment with NaH in THF. The desired product **365** was isolated in a 78% yield with 3:1 *dr* (Scheme 101).



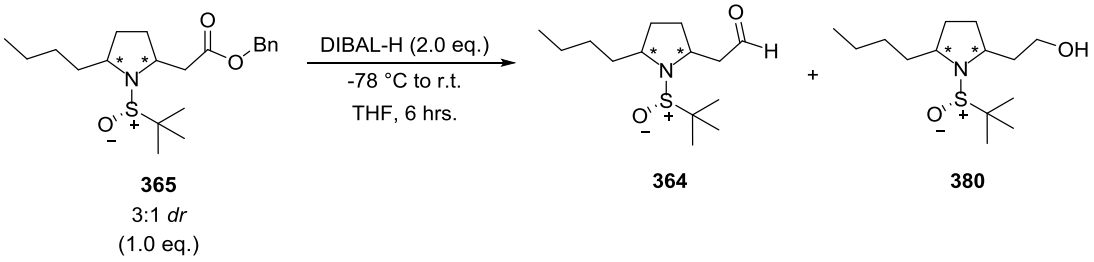
Scheme 101: Synthesis of **365** *via* cyclisation of **366** with NaH

Reduction of **365** with DIBAL-H afforded the corresponding aldehyde **364** in a low yield (12%) with 3:1 *dr*. Due to difficulty in purification of the aldehyde, the crude material of **364** was then used to react with a Grignard reagent **372** to afford the corresponding alcohol **363**. Unfortunately, the desired product **363** could not be observed by HRMS or ^{1}H NMR spectroscopy (Scheme 102).



Scheme 102: Preparation of **363** starting from **365** over two steps

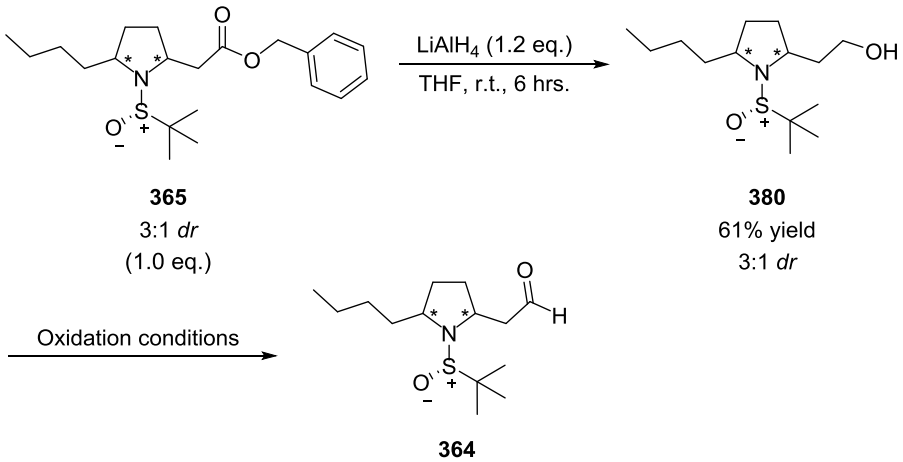
After this attempt, the reduction of **365** with DIBAL-H at -78 ºC was repeated, then the reaction was left to warm to room temperature, to see the stability of the benzyl group under these conditions. Unfortunately, a mixture of the aldehyde desired product **364** and the corresponding alcohol **380** was detected by HRMS and ^{1}H NMR spectroscopy of the crude mixture (Scheme 103). Therefore, it was found that the reduction chemoselectivity of DIBAL-H on **365** at room temperature was not good enough to afford the desired aldehyde **364** in one step.



Scheme 103: Reduction of **365** with DIBAL-H to afford the corresponding aldehyde **364**

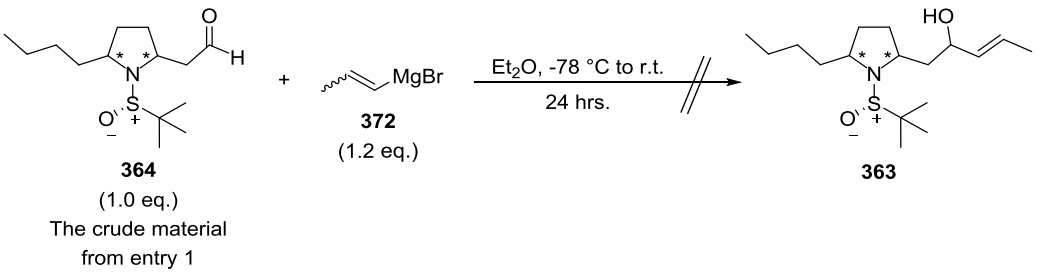
Our focus then turned to preparing the desired aldehyde **364** in two steps in place of one step. So, the ester group at **365** was reduced to the corresponding alcohol **380** using a strong reducing agent ($LiAlH_4$), which gave **380** in a 61% yield. This was followed by oxidation using different types of conditions as described in Table 14.

Table 14: Oxidation conditions of alcohol **380** to aldehyde **364**



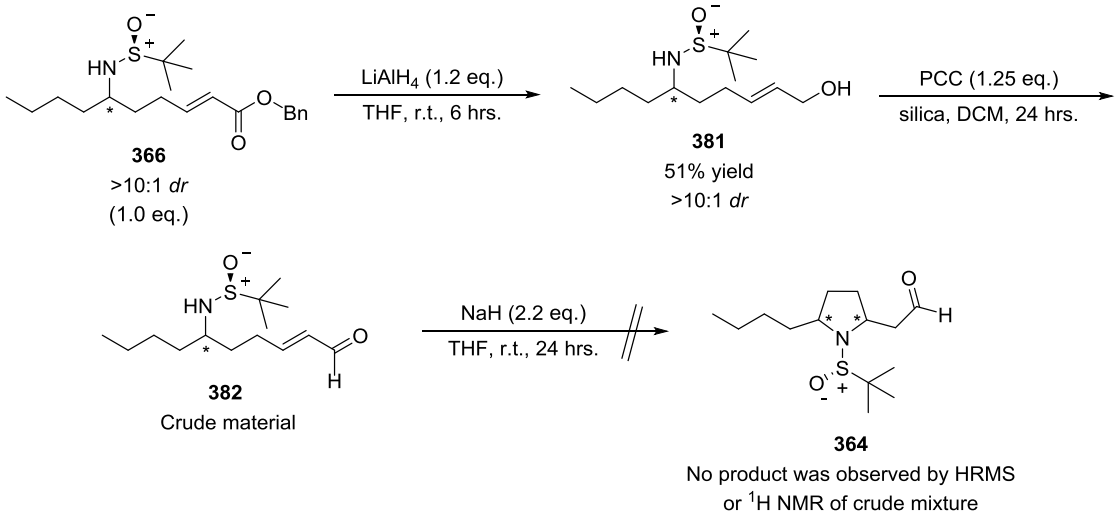
Entry	Oxidation Conditions	Result
1	Oxalyl chloride (2.5 eq.) DMSO, DCM, Et_3N, -78 °C to r.t., 24 hrs.	Detected by HRMS
2	PCC (1.25 eq.), silica gel, DCM, r.t., 24 hrs.	-
3	Dess-Martin's periodinane (1.1 eq.) DCM, r.t., 24 hrs.	-
4	TEMPO (0.1 eq.), NCS (1.5 eq.), TBACl (0.1 eq.) K_2CO_3 (0.05 M), DCM, $NaHCO_3$ (0.5 M), r.t., 24 hrs.	-

We envisaged that the oxidation using Swern conditions (Table 14, entry 1) could be successful to give **364**. But, unfortunately, the desired aldehyde **364** was detected by HRMS only, and ^{1}H NMR spectroscopy of crude material indicated a complex mixture of products formed. Likewise, the oxidation of **380** with PCC was not effective to afford the desired aldehyde **364**. This may be due to the presence of the sulfur atom at the chiral auxiliary group, or oxidation of the chiral auxiliary group (Table 14, entry 2). Furthermore, the desired aldehyde **364** was not observed when Dess-Martin's periodinane was employed, and only the starting material **380** was observed (Table 14, entry 3). Finally, the same result was observed when TEMPO was used as an oxidant (Table 14, entry 4). From these results, the oxidation of **380** was not effective to give **364**. However, the crude material obtained from the oxidation of **380** using Swern conditions (Table 14, entry 1) was then used to react with a Grignard reagent **372** to explore the possibility of detecting the target alcohol **363** (Scheme 104). Unfortunately, the desired product **363** could not be observed by HRMS or ^{1}H NMR spectroscopy, which may be due to the impurities present with the sample of **364** used.



Scheme 104: Nucleophilic addition of Grignard reagent **372** to **364** to afford alcohol **363**

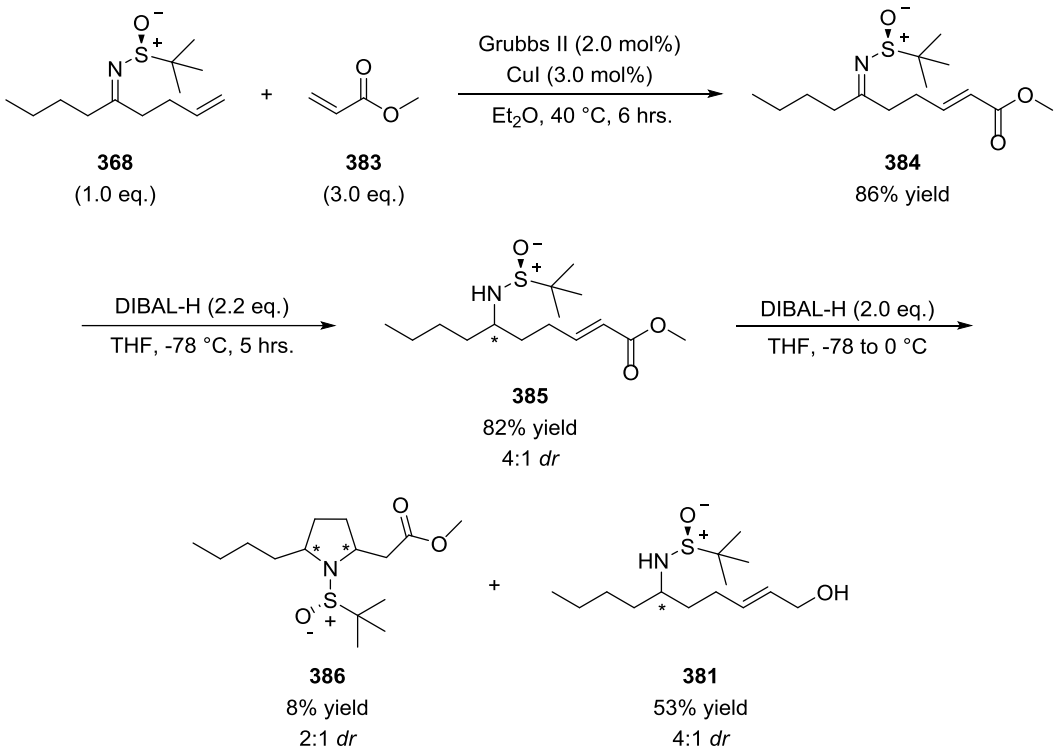
Another route was also explored to provide **364**, starting from **366** over three steps. Reduction to give alcohol derivative **381**, followed by oxidation to afford the corresponding aldehyde **382** and then cyclisation using basic conditions to furnish **364**. The reduction of **366** with $LiAlH_4$ was achieved successfully to afford **381** in 51% yield with >10:1 *dr*. The product **381** was then oxidised with PCC, and the crude material of the aldehyde **382** was used direct in the next step without purification by chromatography due to the instability of **382**. But, unfortunately, the intramolecular Michael addition of **382** did not work to give **364** (Scheme 105). However, the transformation to aldehyde **364** was observed in a low yield (Scheme 102) and this is may be due to the stability of the benzyl group present in **366**.



Scheme 105: Preparation of **364** starting from **366**

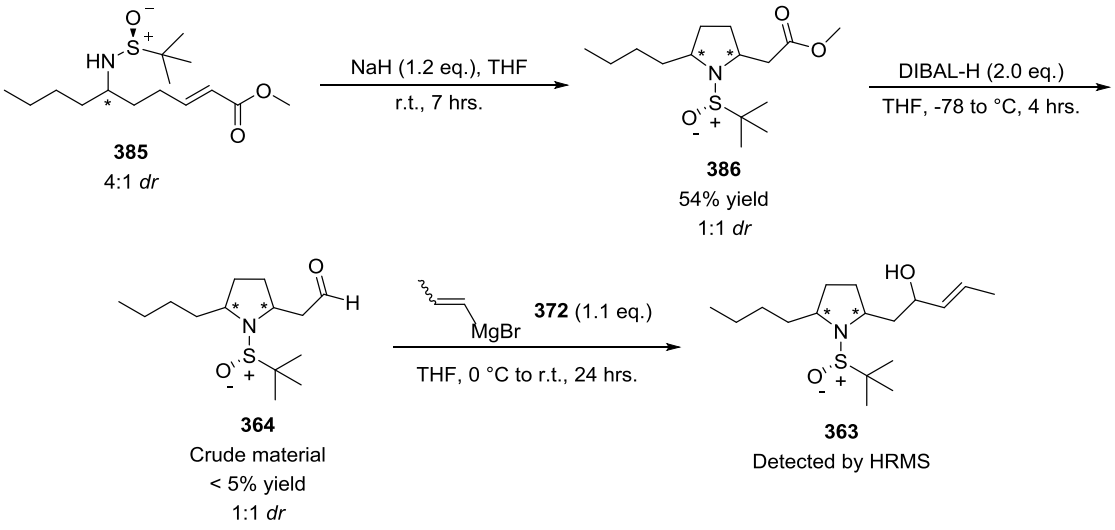
It was then decided to use **383** in place of **252**, which may be easier to give **364** in a high yield. In order to obtain **364**, compound **368** was treated with methyl acrylate **383** under cross metathesis conditions, which gave **384** in a very good yield (86%). The imine group on **384** was then reduced stereoselectively with DIBAL-H, to afford the corresponding sulfinamide **385** in 82% yield with 4:1 *dr*. The next step included using the same reducing agent (DIBAL-H, 2.0 eq.) with the product **385** to reduce the ester group to the corresponding aldehyde **382**, which can be cyclised later under basic conditions to give the desired pyrrolidine **364**.

Unfortunately, a mixture of product was isolated are the corresponding alcohol **381** in 53% yield with 4:1 *dr* and the desired pyrrolidine derivative **386** was obtained in 8% yield with 2:1 *dr* (Scheme 106). It was found that there was no chemoselectivity on the reduction to afford **386** from **385** using DIBAL-H. In addition, this route was not effective to synthesise **386** in an acceptable yield and *dr*.



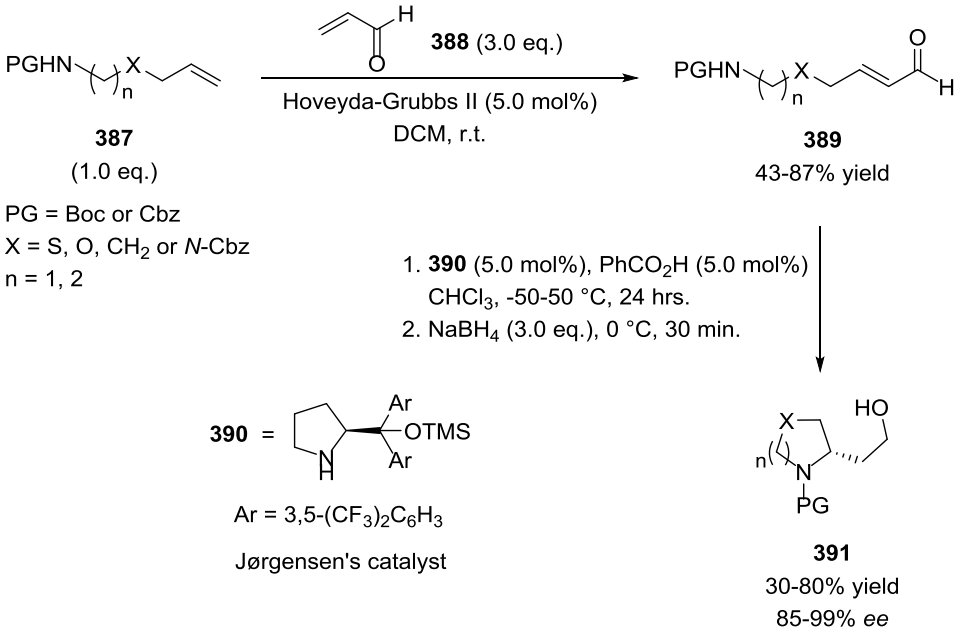
Scheme 106: Preparation of **381** over three steps starting from **368**

The cyclisation of **385** was then achieved successfully under basic conditions, which afforded the corresponding pyrrolidine derivative **386** in 54% yield with 1:1 *dr*. This was followed by reduction of **386** with DIBAL-H, which gave the corresponding aldehyde **364** in a low yield (<5%) with 1:1 *dr*. A Grignard reagent **372** was then added to **364** to give **363**. Unfortunately, only a trace amount of the desired product **363** was detected by HRMS (Scheme 107).



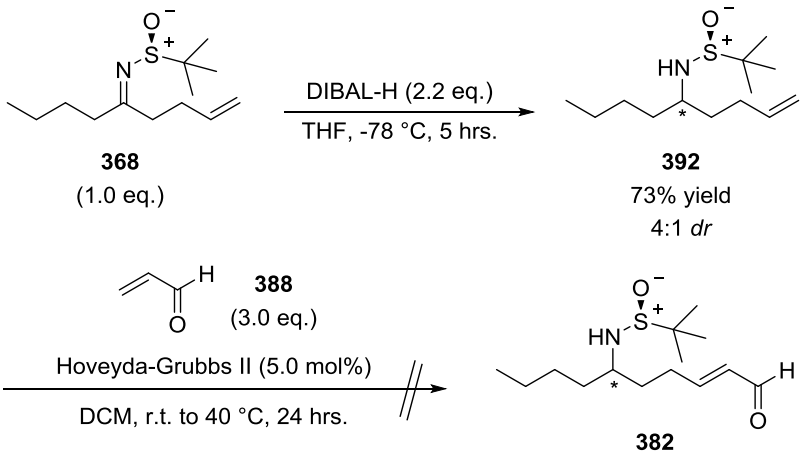
Scheme 107: Preparation of **363** starting from **385**

We decided then to find another way to access **363** in a high yield and *dr*. From the literature, Fustero *et al*.[134] have reported a methodology for enantioselective organocatalytic intramolecular aza-Michael reaction (IMAMR). This methodology was used to synthesise several five- and six-membered heterocycles **391** over three steps, starting from the corresponding unsaturated amine analogue compounds **387**. The first step of our strategy included a cross metathesis coupling of a range of protected amines **387** with acrolein **388** in the presence of Hoveyda-Grubbs II catalyst. This furnished α,β-unsaturated aldehydes a bearing protected amine group **389** in yields ranging from 43 to 87%. IMAMR was then applied on **389** in the presence of Jørgensen's catalyst **390** as an enantioselective organocatalysed reaction, followed by reduction with $NaBH_4$, which afforded the desired five- and six-membered ring heterocycles **391** containing oxygen, nitrogen and sulfur in 30-80% yields and with 85-99% *ee* (Scheme 108).



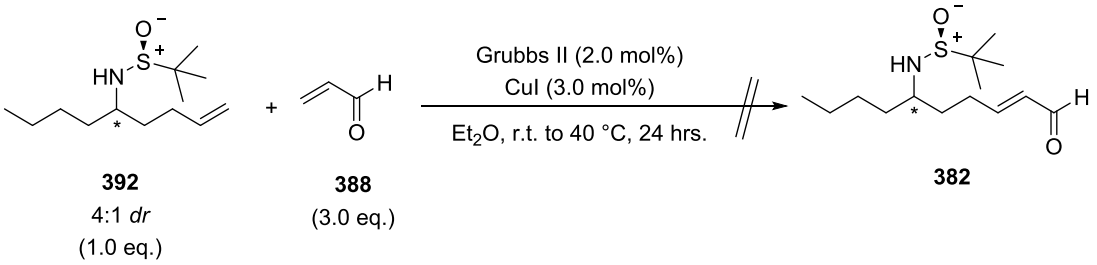
Scheme 108: Synthesis of five- and six-membered heterocycles **391** enantioselectively *via* intramolecular aza-Michael reaction

In our work, the product **368** was reduced with DIBAL-H, which gave **392** in 73% yield with 4:1 *dr*. The same conditions that used to synthesise **389** was then applied on **392** to afford α,β-unsaturated aldehyde derivative **382**. Unfortunately, the desired product **382** could not be detected by HRMS or ^{1}H NMR spectroscopy of the crude mixture and only the starting materials **392** and **388** were observed (Scheme 109).



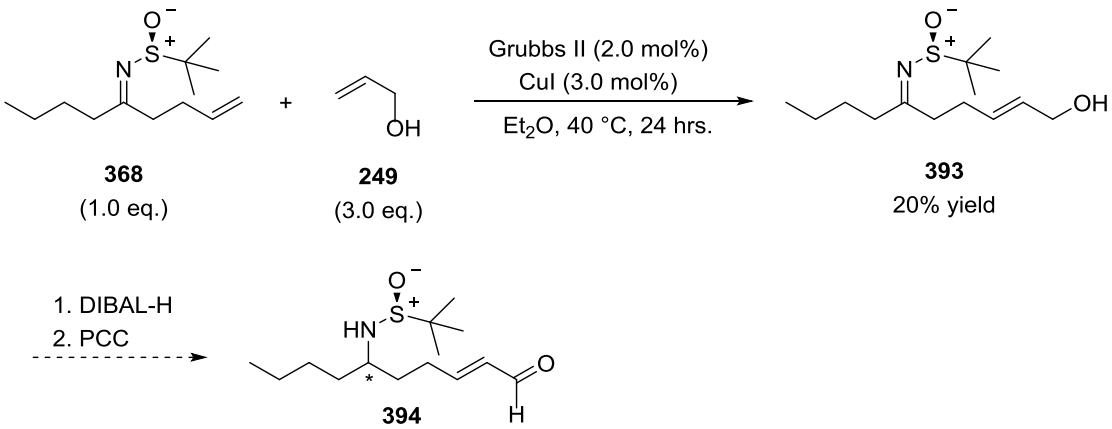
Scheme 109: Preparation of **382** *via* cross metathesis reaction of **392** with **388** in the presence of Hoveyda-Grubbs II catalyst

After this attempt, Grubbs II catalyst was used in place of Hoveyda-Grubbs II catalyst, using the same conditions. Unfortunately, the desired product **382** was also not detected (Scheme 110). This may be attributed to poisoning of the catalyst with sulfinamide **392**, which is initiated *via* coordination of the nitrogen atom in the sulfinamide group to the ruthenium atom of the catalyst.



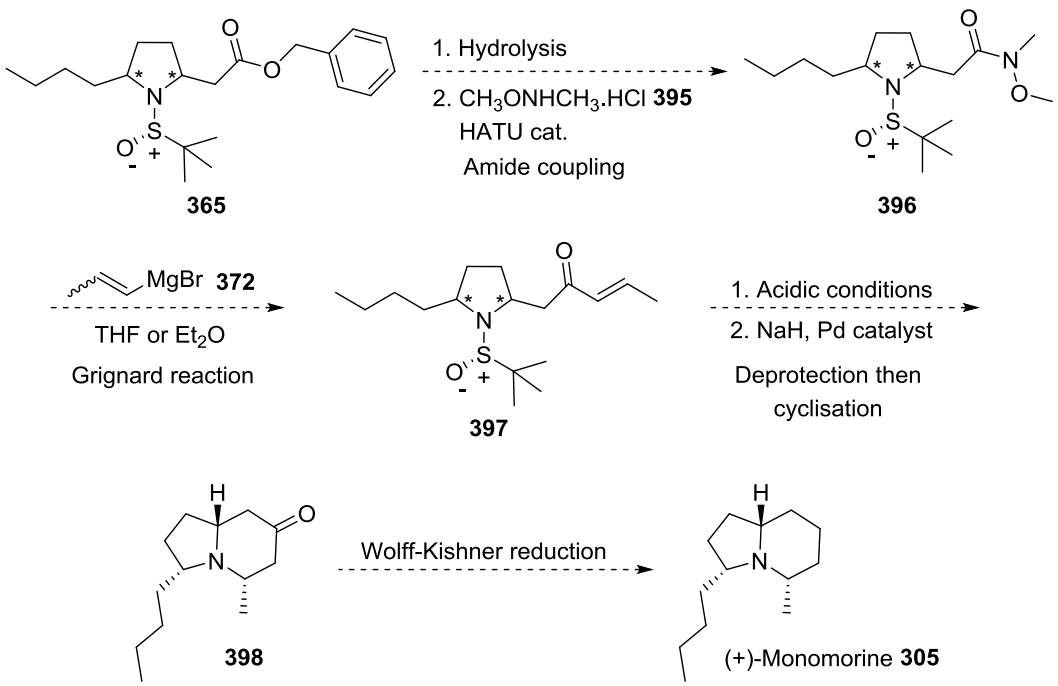
Scheme 110: Preparation of **382** *via* cross metathesis reaction of **392** with **388** in the presence of Grubbs II catalyst

As we found the cross metathesis coupling was not effective with those substrates to afford desired product **382**, it was attempted to use another route to access **382**. This route included a condensation between **368** and **249** using a cross metathesis reaction, which gave **393** in a low yield (20%). This yield was not suffecient to use **393** in the next step, which includes reduction of sulfinimine group with DIBAL-H to furnish the sufinamide analogue of **393** then oxidation with PCC to afford the corresponding aldehyde **394** (Scheme 111).



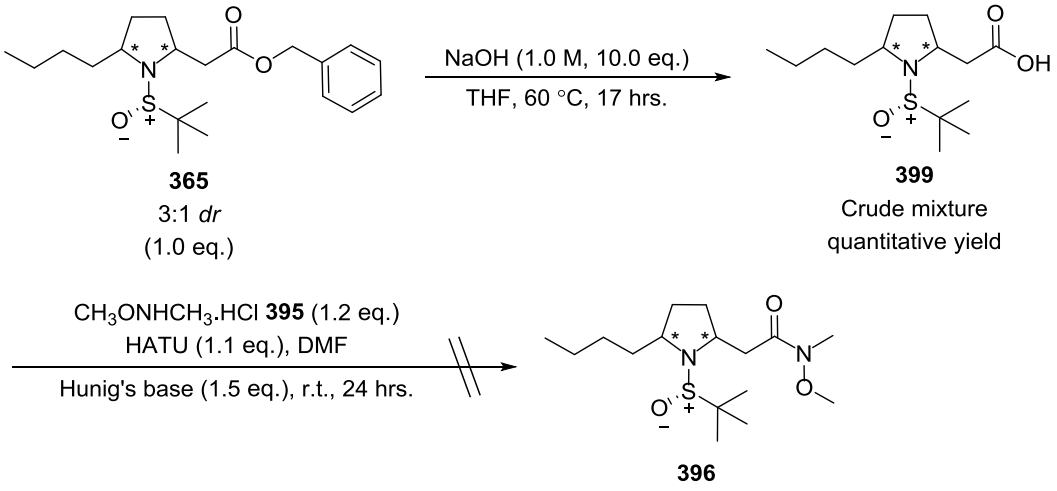
Scheme 111: Preparation of **393** *via* condensation of **368** with **249** using cross metathesis reaction

We therefore decided to probe alternatives, and another synthetic route was proposed, which included hydrolysis of the ester group at **365** using basic conditions to afford the corresponding acid. Amide coupling will be performed between the crude acid derivative and *N*,*O*-dimethylhydroxylamine hydrochloride **395** to give Weinreb amide derivative **396**. Next, nucleophilic addition of Grignard reagent **372** to **396** will be carried out, affording the desired ketone **397**. Deprotection and cyclisation of **397** will be achieved in a one-pot reaction to furnish **398**. The final step in this synthetic route includes reduction of the carbonyl group at **398** using Wolff-Kishner conditions to access the desired natural product (+)-monomorine **305** (Scheme 112).



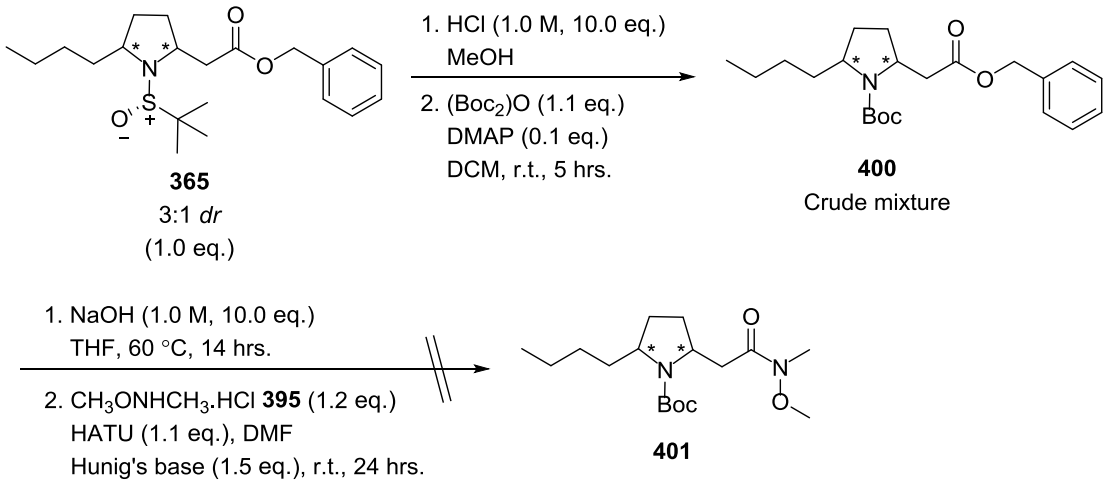
Scheme 112: Proposed synthetic route of natural product (+)-monomorine **305**

The hydrolysis of the ester group at **365** was achieved successfully using NaOH (1.0 M), which gave acid **399** in a quantitative yield. The crude mixture of **399** was then used to do an amide coupling with *N*,*O*-dimethyl hydroxylamine hydrochloride **395** in the presence of HATU as a coupling agent to form the corresponding Weinreb amide **396** (Scheme 113). Unfortunately, the desired product **396** could not be detected by HRMS or ^{1}H NMR spectroscopy. This may be due to the protecting group at **399**, which potentially affects the coupling with **395** through steric hinderance.



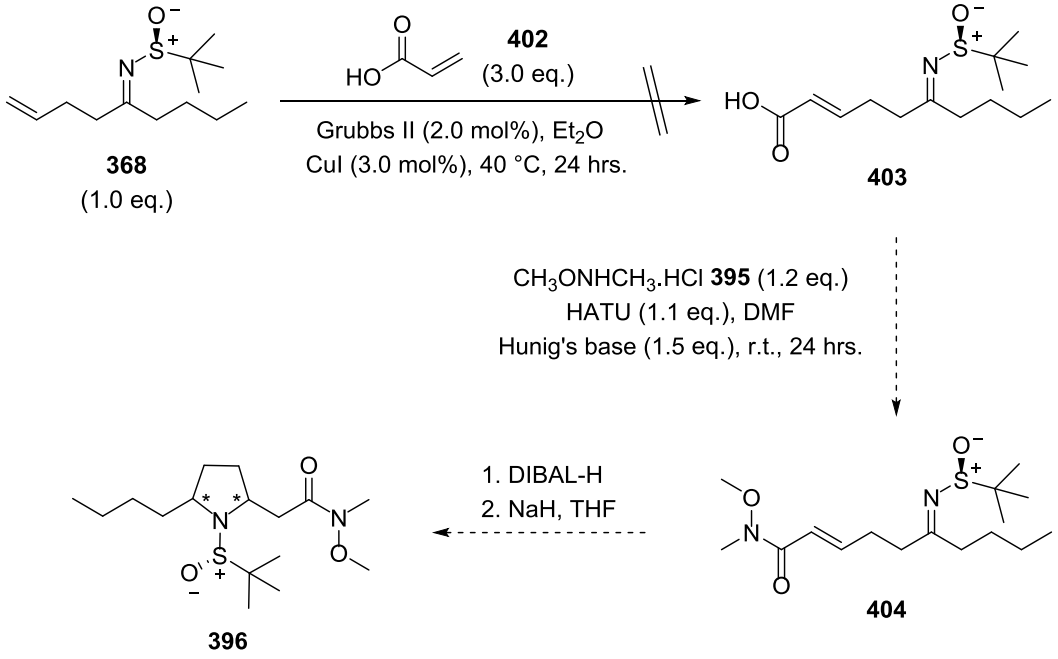
Scheme 113: Preparation of amide derivative **396** from **365** over two steps

We wanted then to explore the main reason for the unsuccessful coupling of **399** with **395**, by replacing the protecting group in **399** with a Boc group. This was done by removal of the *tert*-butanesulfinyl group in **365** using acidic conditions, which gave the amine analogue of **365**. This was treated with $(Boc)_2O$, which afforded the desired protected pyrrolidine **400**. Thereafter, hydrolysis of the ester group in **400** provided the corresponding acid analogue of **400**, which was monitored by HRMS and TLC. Disappointingly, no reaction was observed to give **401** when the acid was treated with *N*,*O*-dimethylhydroxylamine hydrochloride **395** (Scheme 114). Hence, the problem was not the type of the protecting group at the substrate.



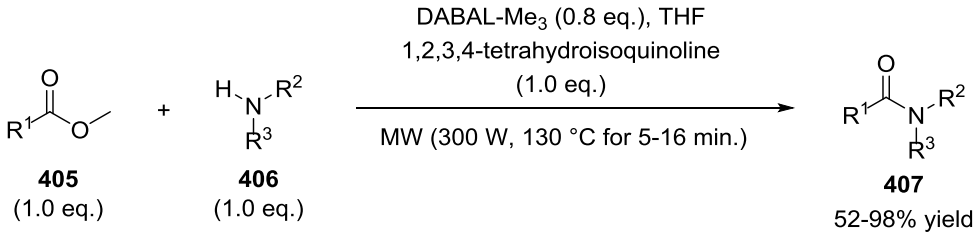
Scheme 114: Preparation of amide derivative **401** from Boc-protected substrate **400**

We also tried to prepare the acid **403** as an open chain to use instead of **399** (cyclic chain) to do the amidation reaction, to see if this affected the coupling with *N*,*O*-dimethylhydroxylamine hydrochloride **395**. Unfortunately, the cross metathesis coupling between **368** and acrylic acid **402** in the presence of Grubbs II catalyst to provide **403** was unsuccessful (Scheme 115).



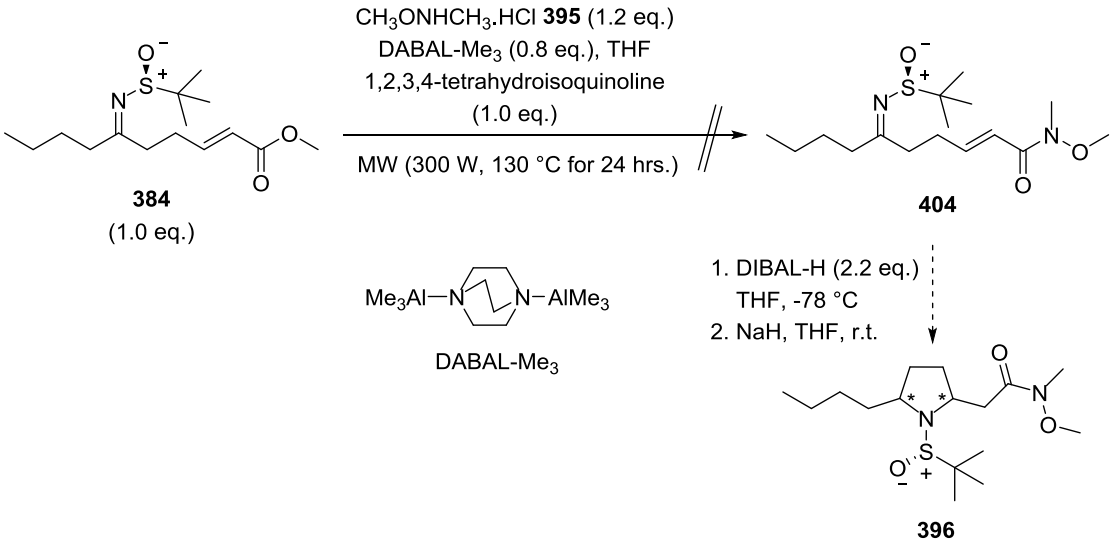
Scheme 115: Preparation of amide derivative **396** from **368** over four steps

Glynn, Bernier and Woodward[135] reported a methodology for the synthesis of tertiary amide derivatives **407** *via* coupling between secondary amines **406** and ester derivatives **405** in the presence of DABAL-Me_3 as a catalyst, using microwave irradiation. The desired amides **407** were isolated in moderate to excellent yields (52-98%) (Scheme 116).



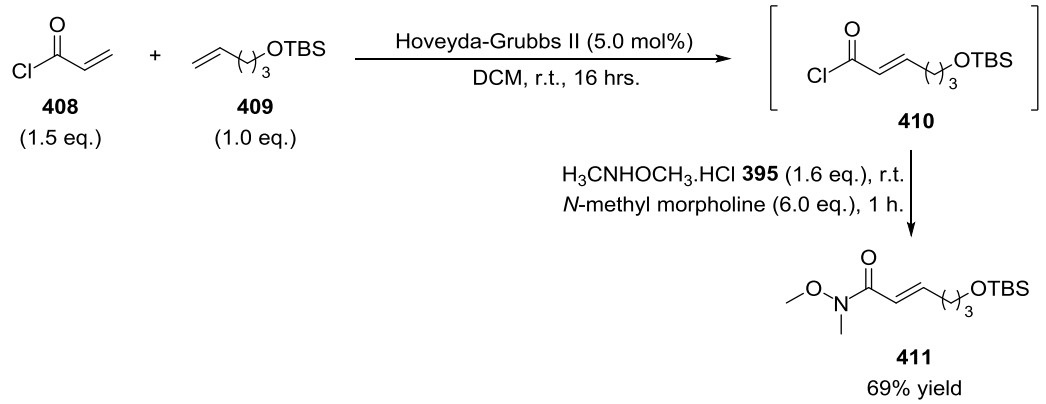
Scheme 116: Preparation of various tertiary amides **407** under microwave heating in the presence of DABAL-Me_3

In our work, we tried running the same reaction conditions reported in Scheme 116. The substrate **384** was treated with *N*,*O*-dimethylhydroxylamine hydrochloride **395** to give the corresponding amide **404**, which will be reduced to the corresponding sulfinamide and then subjected to the intramolecular Michael addition conditions to afford **396**. But, unfortunately, the coupling did not work to form the desired product **404** (Scheme 117).



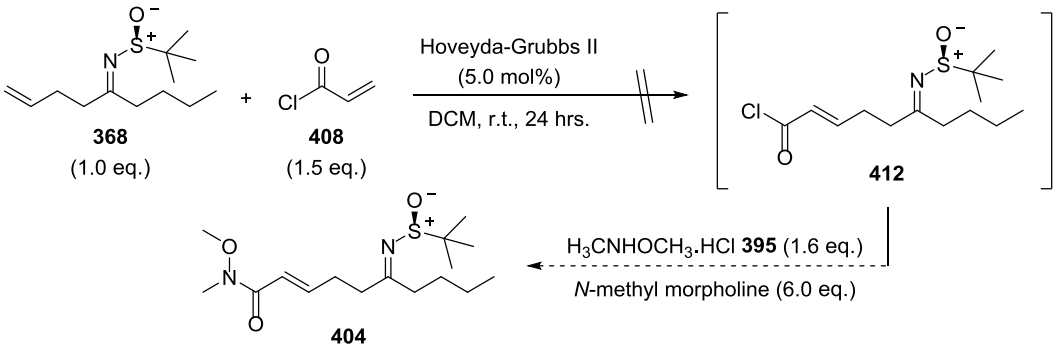
Scheme 117: Preparation of amide derivative **396** under microwaveheating in the presence of DABAL-Me_3

In 2009, Ferrie, Bouzbouz and Cossy[136] published a methodology for the synthesis of a wide range of α,β-unsaturated amide derivatives such as **411**. This was done *via* simple one-pot reaction, which included a cross metathesis coupling between acryloyl chloride **408** and terminal alkene **409**, to give α,β-unsaturated acid chloride **410** as an intermediate. *N*,*O*-Dimethyl hydroxylamine hydrochloride **395** in the presence of *N*-methyl morpholine was then added as a nucleophile to quench **410**, which gave the desired derivative **411** in 69% yield (Scheme 118).



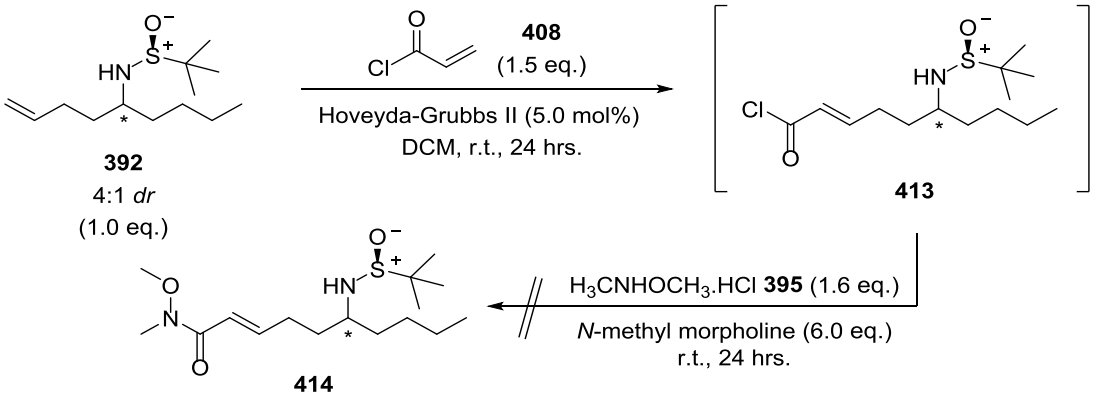
Scheme 118: Synthesis of **411** in a one-pot reaction *via* cross metathesis coupling then nucleophilic substitution

This methodology was explored in our work in order to synthesise **404**, which could be useful material in the synthetic route of the natural product **305**. Homo allyl sulfinimine **368** was treated with acryloyl chloride **408** in the presence of Hoveyda-Grubbs II catalyst to afford the desired intermediate **412**. Unfortunately, HRMS, TLC and ^{1}H NMR spectroscopy of the reaction mixture did not detect the intermediate **412** (Scheme 119).



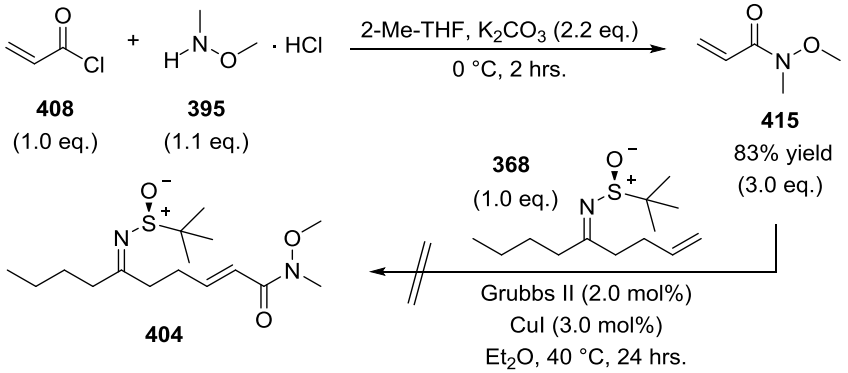
Scheme 119: Synthesis of **404** in a one-pot reaction from **368** using Ferrie's *et al*. methodology

After this attempt, homo allyl sulfinamide **392** was employed in place of **368**, but the same result was observed. However, compound **395** was then added to the reaction mixture to check if there was any conversion to desired product **414** despite the fact that **413** could not be detected. No product **414** was observed after 24 hours (Scheme 120).



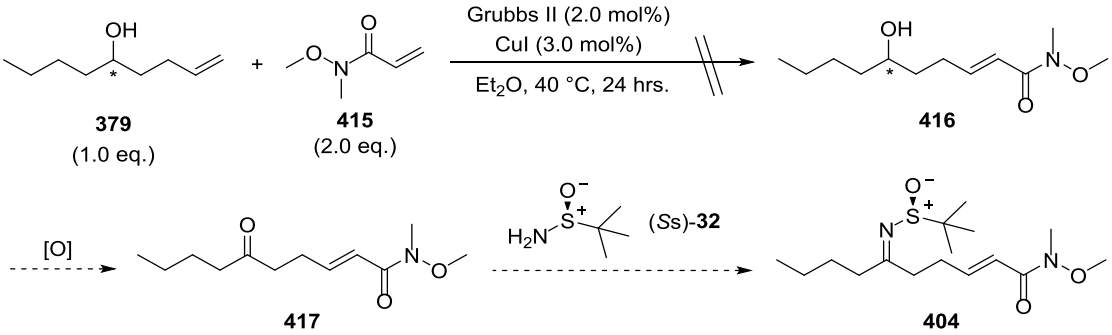
Scheme 120: Synthesis of **414** in a one-pot reaction from **392** using Ferrie's *et al*. methodology

Weinreb amide **415** was then prepared to react with **368** to furnish **404**, which is considered a useful material, which could react with a Grignard reagent to afford the desired ketone. The compound **415** was prepared in a very good yield (83%) *via* nucleophilic substitution reaction between acryloyl chloride **408** and *N*,*O*-dimethylhydroxylamine hydrochloride **395**.[137] Cross metathesis reaction of **415** with **368** was then attempted to give **404**. Unfortunately, the transformation to provide the desired product **404** was not successful as determined by TLC, HRMS or ^{1}H NMR spectroscopy (Scheme 121).



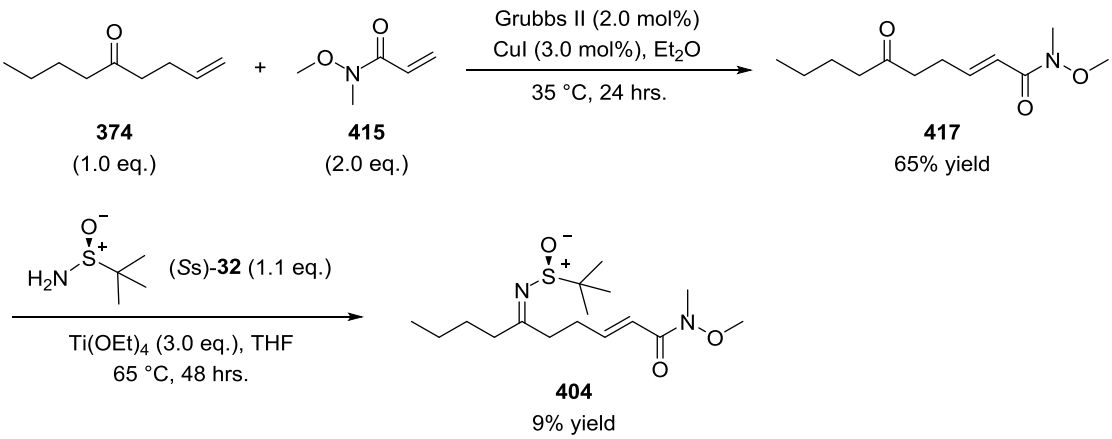
Scheme 121: Synthesis of **404** using a Weinreb amide **415**

Next, non-1-en-5-ol **379** was used to react with **415** instead of **368** to provide **416** under cross metathesis conditions. The product **416** could be useful to oxidise the hydroxyl group to ketone **417**, followed by a condensation reaction with (*S*)-*tert*-butanesulfinamide **32** to give (*S*S)-sulfinimine **404**. Disappointingly, no reaction was also observed with this attempt (Scheme 122).



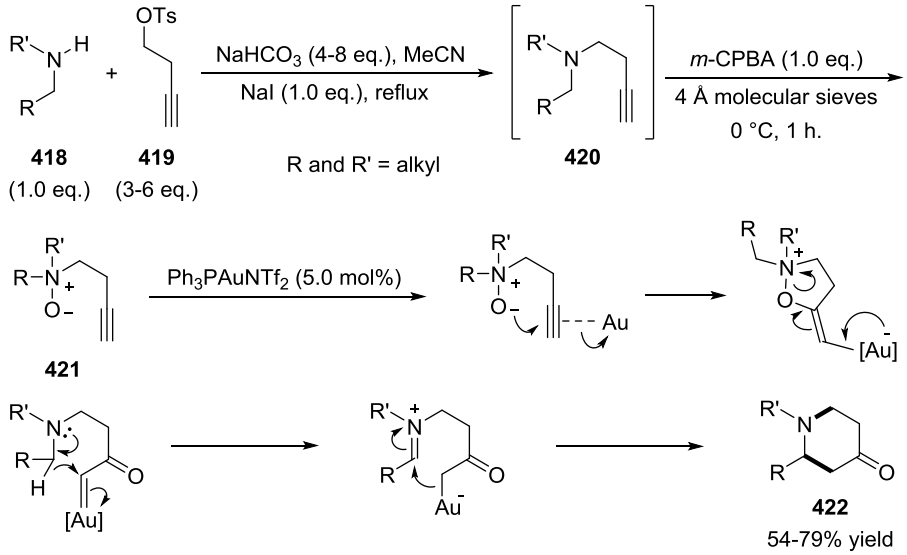
Scheme 122: Synthesis of **404** starting from homoallyl alcohol **379**

Following this attempt, homoallyl ketone **374** was then employed in place of **379** to react with **415**, and the desired amide **417** was obtained in 65% yield. Thereafter, the condensation of **417** with (*S*)-*tert*-butanesulfinamide **32** has been performed under standard conditions, but only 9% yield of the desired α,β-unsaturated amide **404** was isolated (Scheme 123). This yield discouraged us to explore further reactions in this synthetic route.



Scheme 123: Synthesis of **404** starting from homoallyl ketone **374**

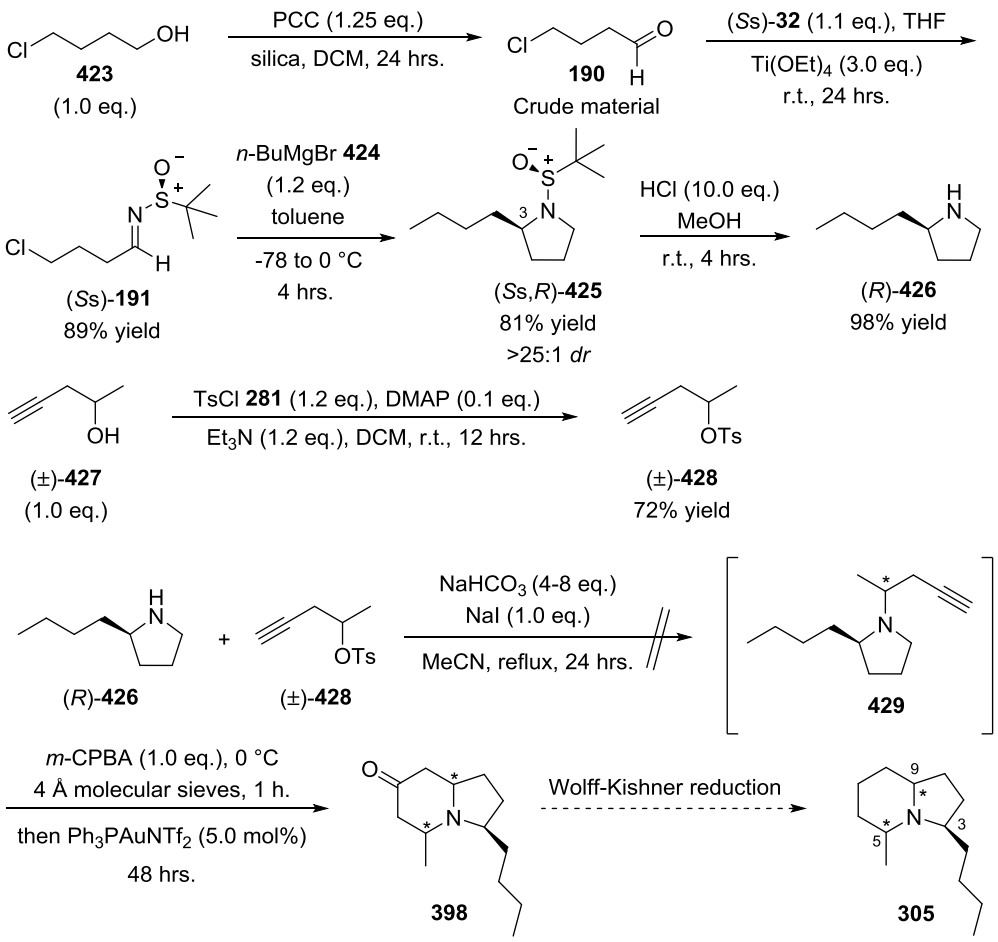
From the literature, Cui, Peng and Zhang,[138] have reported a methodology for the synthesis of piperidin-4-one derivatives **422**. This was done by nucleophilic substitution of tosylate derivative **419** with secondary amines **418**, giving tertiary amines **420** as intermediates, followed by oxidation with *m*-CPBA to form the tertiary amine *N*-oxide forms **421**. A gold catalyst was then added to activate the intramolecular cyclisation of **421** to give **422** in a one-pot reaction. A wide range of the piperidin-4-one derivatives **422** were isolated in moderate to very good yields (54-79%) (Scheme 124).



Scheme 124: Synthesis and mechanism of **422** *via* one-pot reaction

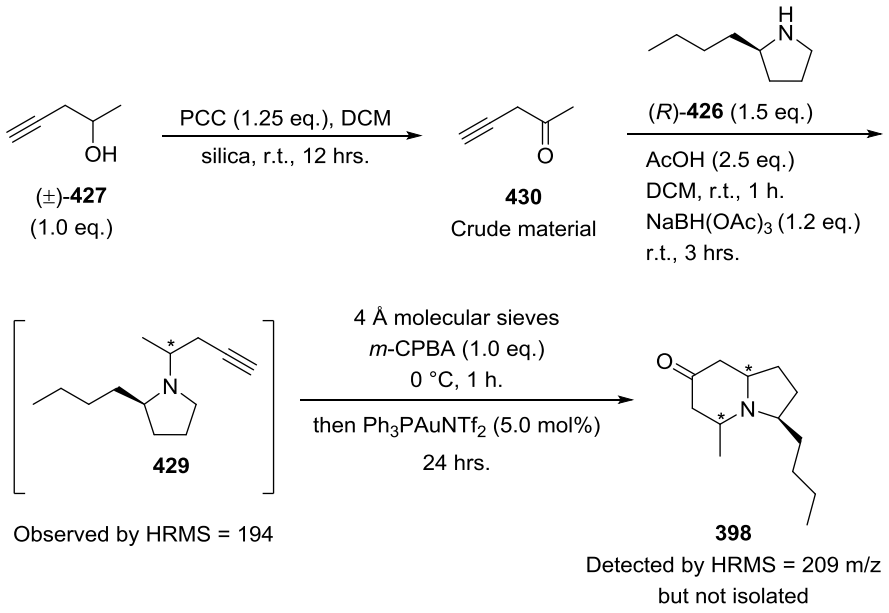
In our work, we decided to synthesise the two suitable substrates to use in this reaction to access **398**, which the carbonyl group in **398** could later be reduced using Wolff-Kishner conditions to give the desired (+)-monomorine **305** albeit in a mixture of diastereoisomers (Scheme 125). The two substrates are pyrrolidine derivative **426** as a secondary amine and tosylate derivative **428**. The product **426** was prepared over a sequence of four steps from 4-chlorobutanol **423**, which was oxidised with PCC to the corresponding aldehyde **190**. The crude material of **190** was then condensed with (*S*)-*tert*-butanesulfinamide **32**, which gave (S_S)-sulfinimine **191** in 89% yield. This was followed by a cascade reaction between **191** and *n*-BuMgBr **424**, which afforded the desired pyrrolidine (S_S,*R*)-

425 in 81% yield and a high *dr* (>25:1). The stereochemistry of C-3 (according to the monomorine IUPAC numbering, see Figure 13) was assigned as *R* according to the research reported by Ellman and co-workers[7,17], which is the same stereochemistry required on the desired natural product **305**. The removal of chiral auxiliary in **425** was performed using acidic conditions and gave the corresponding (*R*)-amine **426** in 98% yield. While the substrate **428** was prepared in 72% yield *via* reaction between (±)-pent-4-yn-2-ol **427** and TsCl **281**. Thereafter, the same conditions for the nucleophilic substitution that were mentioned in Scheme 124 have been used in the reaction between **426** and **428**, to give the intermediate **429** (Scheme 125). Unfortunately, the intermediate **429** could not be observed by HRMS or ^{1}H NMR spectroscopy under reflux for 24 hours, and only starting materials **426** and **428** were recovered. However, *m*-CPBA and $Ph_3PAuNTf_2$ were then added to the reaction mixture to check if there is any conversion to desired product **398** despite **429** did not observed, no product **398** was observed after 48 hours (Scheme 125).



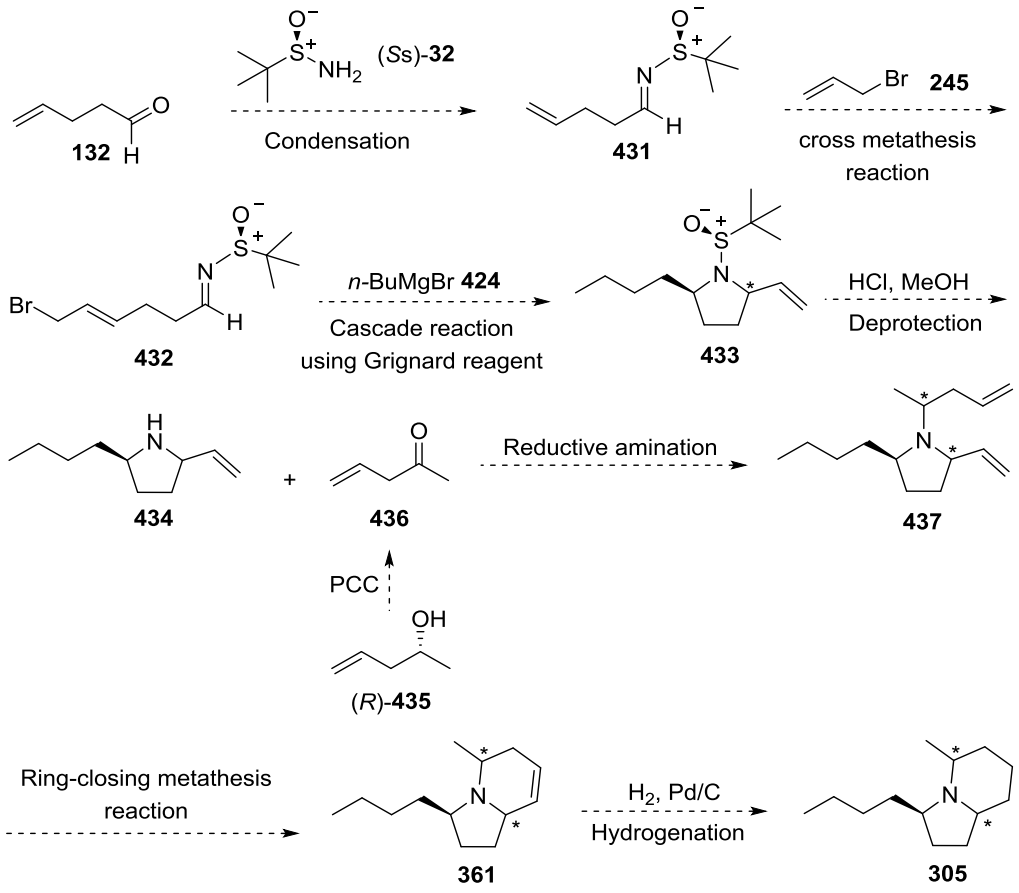
Scheme 125: Synthesis of **398** using a gold catalyst in a one-pot reaction

We then turned to prepare the intermediate **429** using a different way instead of the nucleophilic substitution. Reductive amination of **426** with **430** has been attempted to provide **429**. The substrate **430** was prepared by oxidation of (±)-**427** with PCC, which afforded **430** as a volatile compound. This was used in a reductive amination reaction without further purification. The reductive amination reaction was monitored by HRMS and TLC and showed conversion to the desired tertiary amine **429**. This was followed by addition of *m*-CPBA then $Ph_3PAuNTf_2$ to the reaction mixture. The desired product **398** was detected by HRMS only, and never isolated successfully after purification (Scheme 126).



Scheme 126: Synthesis of **398** using a gold catalyst in a one-pot reaction

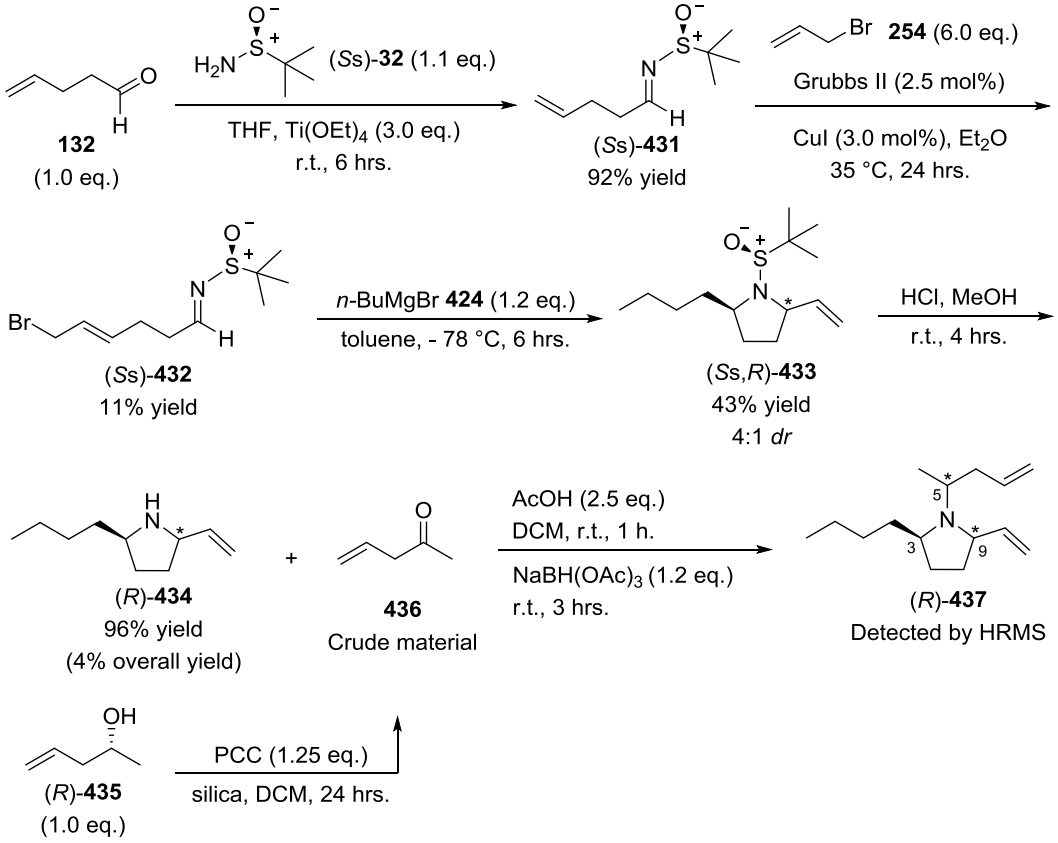
However, our plan was then changed to prepare pyrrolidine derivative **434**, which could be used in the reductive amination with pent-4-en-2-one **436** to provide **437**. The product **436** could be accessed *via* oxidation of (*R*)-pent-4-en-2-ol **435** with PCC. On the other hand, the preparation of **434** in four steps from **132** could be achieved, which condensation between 4-pentenal **132** and (*S*)-*tert*-butanesulfinamide **32** are giving (S_S)-sulfinimine **431**. Then, cross metathesis of **431** with allyl bromide **245** will be used to form **432**, which we could subject to a cascade reaction *via* nucleophilic addition of *n*-BuMgBr **424** to provide **433**. Removal of the protecting group at **433** using acidic conditions will be used to afford the corresponding amine **434**. Reductive amination will be attempted on this substrate **434** with **436** to give **437**. Following this, ring-closing metathesis of **437** in the presence of Grubbs II catalyst will be performed to give **361**. Finally, hydrogenation of the alkene bond in **361** to afford **305** will be conducted (Scheme 127).



Scheme 127: Synthesis of **305** starting from **132**

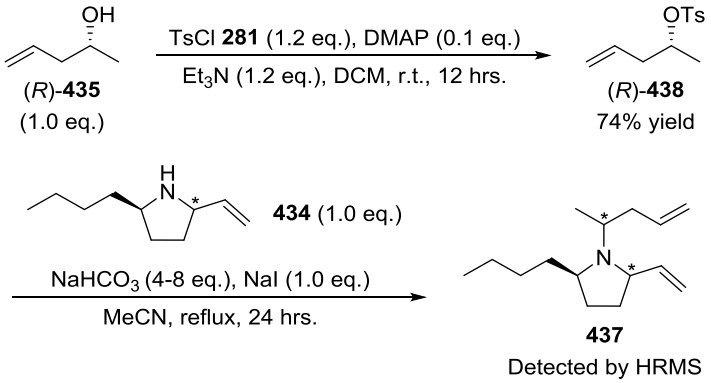
The oxidation of (*R*)-pent-4-en-2-ol **435** with PCC was achieved successfully and gave the corresponding ketone **436**, which was used in the reductive amination reaction without further purification due to volatility of the compound. Whereas the pyrrolidine derivative **434** was synthesised in 4% overall yield from **132**. The condensation of **132** with (*S*)-*tert*-butanesulfinamide **32** gave the desired (S_S)-sulfinimine **431** in an excellent yield (92%), which was used then to do coupling with allyl bromide **245** under cross metathesis conditions. This afforded the corresponding cross metathesis adduct **432** in a low yield (11%) (Scheme 128). A cascade reaction promoted by nucleophilic addition of *n*-BuMgBr **424** to **432**, followed by an intramolecular S_N2' furnished **433** in 43% yield with 4:1 *dr.* The stereochemistry of C-3 at **433** was assigned according to the report by Ellman and co-workers.[7,17] However, no information was obtained about the stereochemistry at C-9 formed by cyclisation. The removal of the *tert*-

butanesulfinyl chiral auxiliary group on **433** was then performed using acidic conditions, which gave **434** in 96% yield (4% overall yield). Reductive amination was then conducted between **434** and **436** to provide **437**, but, disappointingly, the desired product **437** was detected by HRMS only and could not be isolated using flash column chromatography over silica gel (Scheme 128).



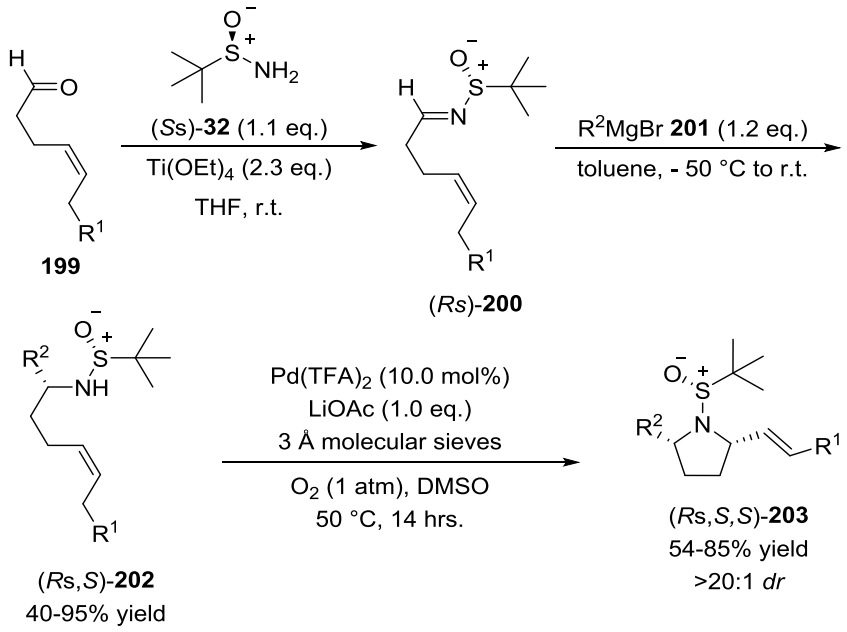
Scheme 128: Our work to synthesise **437** starting from **305**

After this attempt, tosylation of alcohol **435** was then performed, which gave the tosylated alcohol **438** in a good yield (74%). Nucleophilic substitution of **434** with **438** was then attempted in place of reductive amination to form **437**. Unfortunately, a similar result to Scheme 128 was observed, as the desired product **437** was detected by HRMS only (Scheme 129).



Scheme 129: Synthesis of **437** using a tosylated alcohol **438**

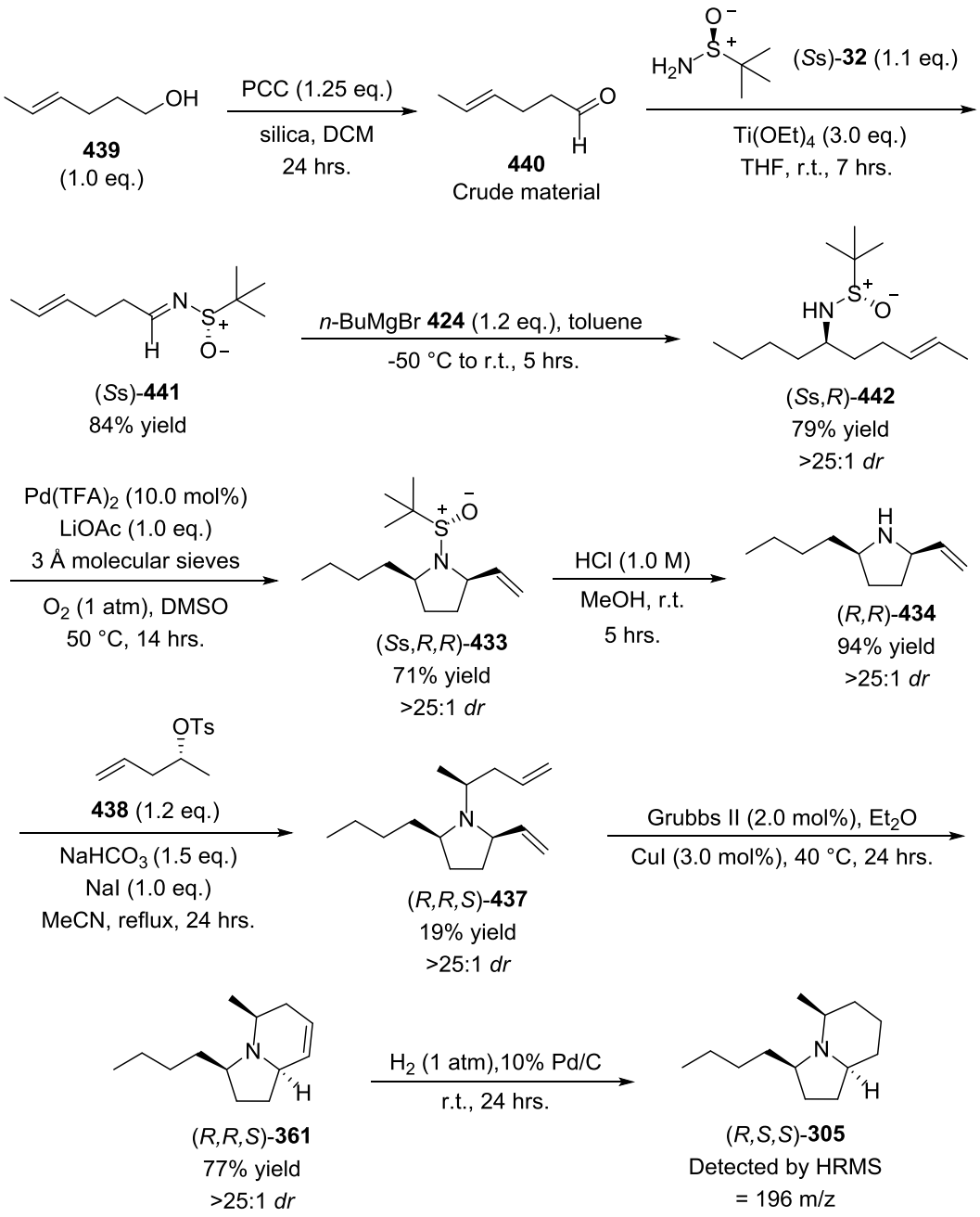
We decided then to find another way to obtain the product **433** in a high yield, *dr* and assign the stereochemistry of C-9 at the desired natural product **305**, which could make optimisation of the reaction conditions easier with respect to the nucleophilic substitution of **434** with **438** to provide **437**. However, Redford *et al*.[104] reported a methodology for the synthesis of *cis*-2,5-disubstituted pyrrolidine derivatives **203** stereoselectively using a Wacker aerobic oxidation in the presence of $Pd(TFA)_2$ and LiOAc as a catalyst and base respectively. In the beginning, they prepared a wide range of (R_S)-alkenes-**200** bearing *tert*-butanesulfinamide as a chiral auxiliary, which were made by condensation of **199** with (*R*)-*tert*-butanesulfinamide **32**. This afforded (R_S)-sulfinimines **200**, which was followed by a nucleophilic addition of R^2MgBr **201** to **200** stereoselectively. This gave the corresponding (R_S,*S*)-sulfinamides **202** in yields ranging from 40 to 95%. The stereochemistry of the new chiral centre was assigned according to the literature.[7,17] The products (R_S,*S*)-**202** were then employed as substrates for the oxidative cyclisation, which furnished the desired pyrrolidine derivatives (R_S,*S*,*S*)-**203** in moderate to very good yields (54-85%). In addition, they indicated that the reaction conditions used gave (R_S,*S*,*S*)-**203** in a high diastereoisomeric ratio (>20:1 *dr*) with *cis*-configuration (Scheme 130).



Scheme 130: Stereoselective synthesis of *cis*-2,5-disubstituted pyrrolidines **203** *via* Wacker aerobic oxidation

Hence, we envisioned taking advantage of the Wacker aerobic oxidative cyclisation of **442** to access **433**. The desired product **433** could be obtained in a high yield and *dr*, with the desired stereochemistry at C-3 and C-9. So, to access our target **305**, we decided to prepare **441** over two steps. Oxidation of alcohol **439** with PCC gave aldehyde **440**. This was then condensed with (*S*)-*tert*-butanesulfinamide **32**, which afforded the corresponding (S_S)-sulfinimine **441** in very good yield (84%). The product **441** was considered a useful substrate to react with a Grignard reagent **424** to form the corresponding sulfinamide **442**, with opposite stereochemistry at the new chiral centre. This step was then performed successfully and afforded **442** in 79% yield with an excellent *dr* (>25:1). Next, Wacker oxidation conditions were then applied on **442**, which gave the desired pyrrolidine derivative **433** in a good yield (71%) with very high diastereoisomeric ratio (>25:1 *dr*). Following this, removal of the directing group at **433** was then achieved using acidic conditions, which gave the corresponding amine **434** in an excellent yield (94%) and >25:1 *dr*. Nucleophilic substitution of **434** with **438** in the presence of NaI was then performed, and the desired product **437** was isolated in a low yield (19%) with >25:1 *dr*. Ring closing metathesis was then applied on

437 in the presence of Grubbs II catalyst, and this afforded **361** in 77% yield with >25:1 *dr*. Finally, hydrogenation of the alkene bond in **361** was then performed, and the desired natural product **305** was detected by HRMS, but could not be isolated using flash column chromatography over silica gel (Scheme 131).



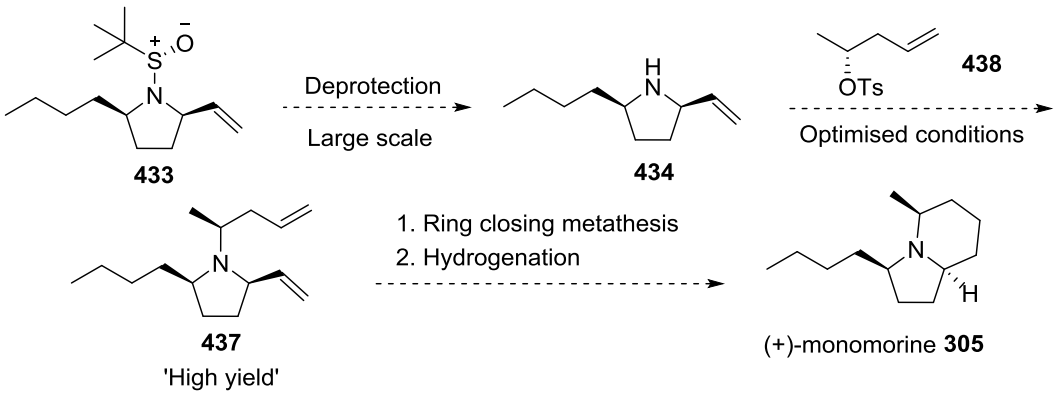
Scheme 131: Asymmetric synthesis of (+)-monomorine **305** starting from **439**

2.2.2. Conclusion

In conclusion, efforts were focused on the application of the pyrrolidine chemical scaffolds chemistry for the synthesis of a natural product (+)-monomorine **305**. Cyclisation of sulfinamide **366** *via* intramolecular Michael addition afforded pyrrolidine core **365** in a good yield. Subsequently, different strategies were fruitlessly employed on **365** for a more efficient synthesis of the corresponding aldehyde **364** or amide **396**. However, different alternative routes have been explored towards performing the asymmetric synthesis of this natural product. A Wacker aerobic oxidative cyclisation was applied on **442** and afforded **433** in a good yield with the desired stereochemistry at C-3 and C-9. Deprotection, nucleophilic substitution, ring closing metathesis and hydrogenation were then performed on **433**. Unfortunately, in no case was the desired natural product **305** isolated using flash column chromatography, albeit detected by HRMS.

2.2.3. Future work

In order to complete the total synthesis of natural product (+)-monomorine **305**, clearly gram scale quantities of the pyrrolidine derivative **433** would be required. Following this, similar steps could be performed to access **305** as previously described in Scheme 131. In this regard, the optimisation of the key step: stereospecific nucleophilic substitution of the tosyl group at **438** with **434** to provide **437** in a high yield should be considered (Scheme 132).



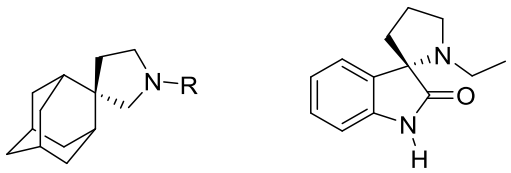
Scheme 132: Synthesis of (+)-monomorine **305** stereoselectively starting from **433**

3. Studies towards the synthesis of spiro-pyrrolidine chemical scaffolds

3.1. Introduction

Spiro compounds are molecules containing two rings or more linked by one shared atom (the spiroatom). Spiro compounds are present in numerous natural products,[139] and represent an important class of naturally occurring substances found to be associated with a wide range of biological activities.[140]

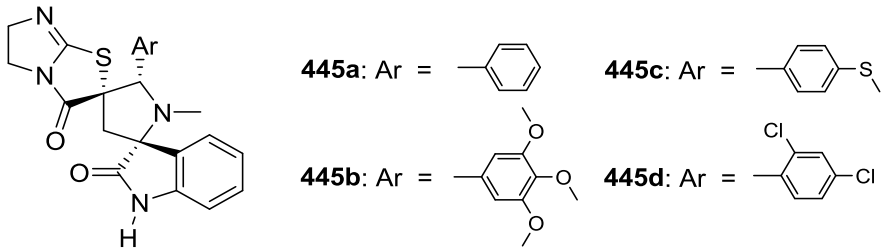
Spiro-pyrrolidines are class of spiro compounds which have shown significant biological activities. In particular, adamantanespiro-3-pyrrolidines **443** have an antiviral activity against Influenza A_2,[141] and oxindole-3-spiropyrrolidine **444**, showed similar behaviour as lidocaine, a local anesthetic and antiarrhythmic drug (Figure 15).[142]



443 **444**

Figure 15: Structure of adamantanespiro-3-pyrrolidines **443** and oxindole-3-spiropyrrolidine **444**

It has also been reported that some spiro-pyrrolidine derivatives **445a**-**d** exhibit biological activities such as, carcinogenic and antiviral activity, a DNA cross-linker, hepatotoxicity and antimycobacterials (Figure 16).[143-145]



445a-d

Figure 16: Molecular structures of novel spiro pyrrolidine analogues

In addition, it has been observed that some types of spiro-pyrrolidines **446**-**453** show a wide range of significant bioactivities. For example, the spiro-pyrrolidine **446** was used as an anti-tumoral,[146] **447** as an anti-microbial and as an anti-cancer activities,[147] **448** as an anti-inflammatory,[148] **449** as an acetylcholinesterase-inhibitor,[149] **450** as an anti-bacterial.[150,151] The compound **451** was found to mimic Pro-Leu-Gly-NH_2, which behaves as a negative allosteric modulator of dopamine D2 receptor.[152] While, the spiro-pyrrolidines **452** and **453** exhibited potent anticancer activity (Figure 17).[153,154]

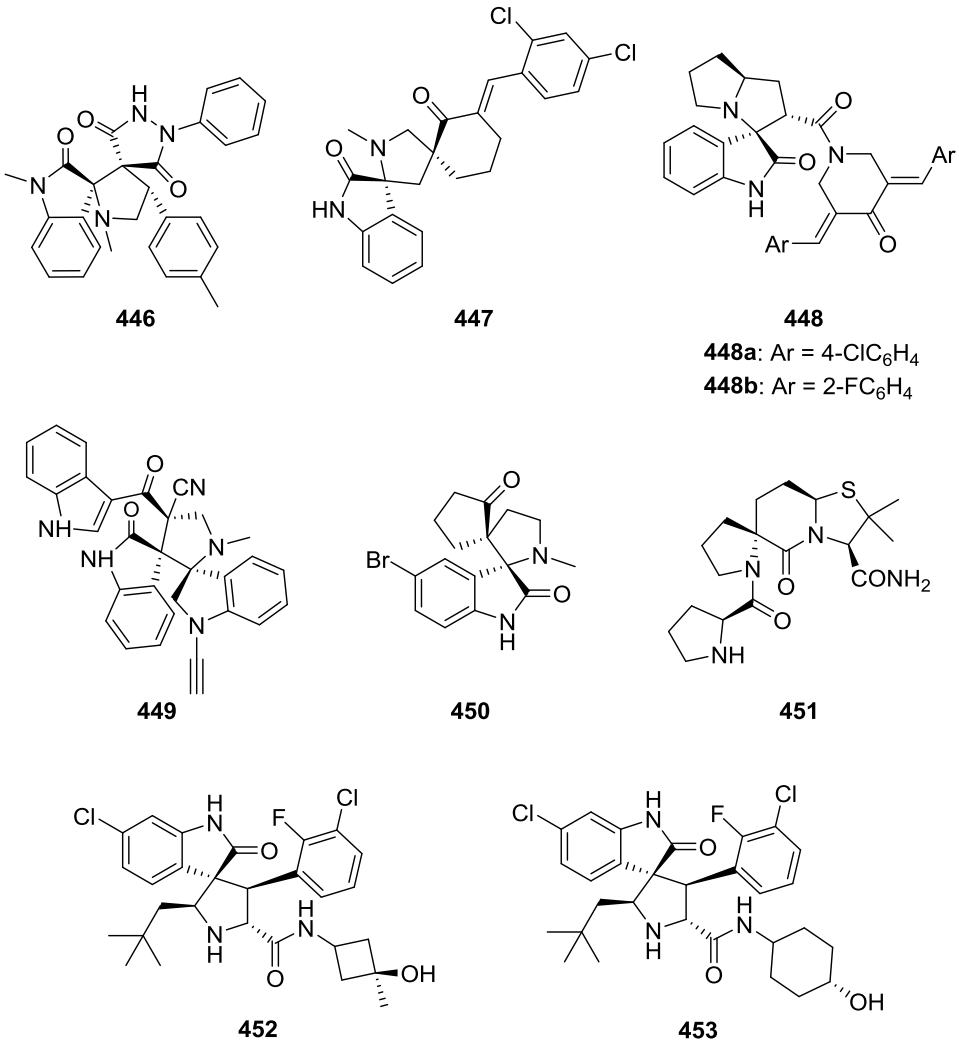


Figure 17: Some examples of biologically active compounds containing a spiro-pyrrolidine motif

Many spiro-pyrrolidines have been isolated from natural products and have displayed important biological activities. For example, horsfiline **454** an oxindole alkaloid natural product containing a spiro-[indole-pyrrolidone] nucleus, was isolated from *Horsfieldia superba* (a tree from Malaysia) by Bodo and co-workers in 1991.[155] This compound was employed as a cell-cycle-specific cytostatic agent that arrests mitosis and metaphase by acting as a spindle poison. Furthermore, it was found to be effective as an analgesic and in cancer chemotherapy (Figure 18).[156-158]

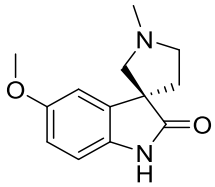
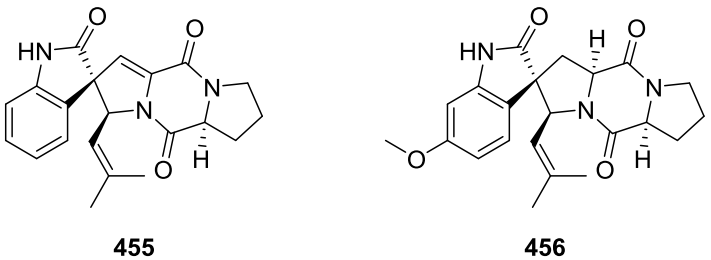


Figure 18: Structure of horsfiline **454**

Two natural products, spirotryprostatin A **455** and spirotryprostatin B **456** were isolated for the first time from *Aspergillus fumigatus* BM939 by Cui, Kakeya and Osada in 1996 (Figure 19).[159,160] These two natural products effectively inhibit the cell cycle in the G2/M phase with half-maximal inhibitory concentrations (MIC) of 14.0 and 197.5 μM for **455** and **456** respectively. Furthermore, the natural product **456** was found to be an inhibititor for the growth of human promyelocytic leukemia HL-60 cells with MICs and human chronic myelogenous leukemia K562 cells of 10 and 35 μg/mL respectively.[159,160]

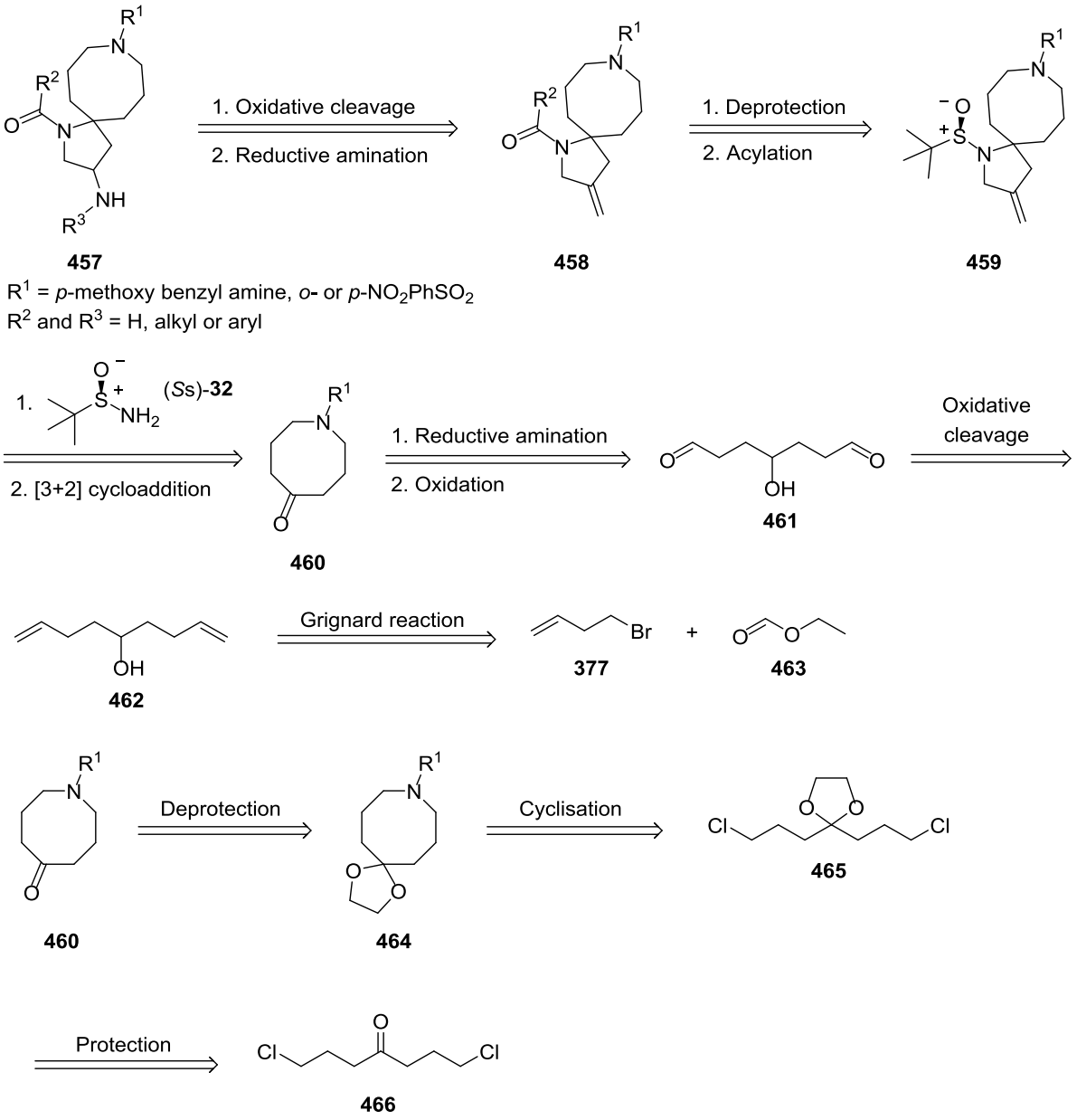


455 **456**

Figure 19: Structures of spiro-pyrrolidine products natural products are spirotryprostatin A **455** and spirotryprostatin B **456**

3.1.1. Aims and objectives

The aim of this project is to synthesise the spiro-pyrrolidine scaffold **457** which contains functionalities for further elaboration. Therefore, this type of chemical scaffold will be useful as a versatile intermediate for drug discovery *via* diversification at the three points of diversity on *N* atoms. Synthesis of **457** will be attempted from commercially available compounds; 4-bromobutene **377** or 1,7-dichloroheptan-4-one **466**. The desired target **457** contains a densely-functionalised bicyclic core with a spirocyclic centre, which can be generated in a diastereoselective manner. The interesting step in this synthetic route is the [3+2] cycloaddition of trimethylenemethane (TMM) **468** to ketamine to afford **459** in the presence of $Pd(PPh_3)_4$ as a catalyst,[111] which includes forming a spiro-pyrrolidine system in a single step (Scheme 133).



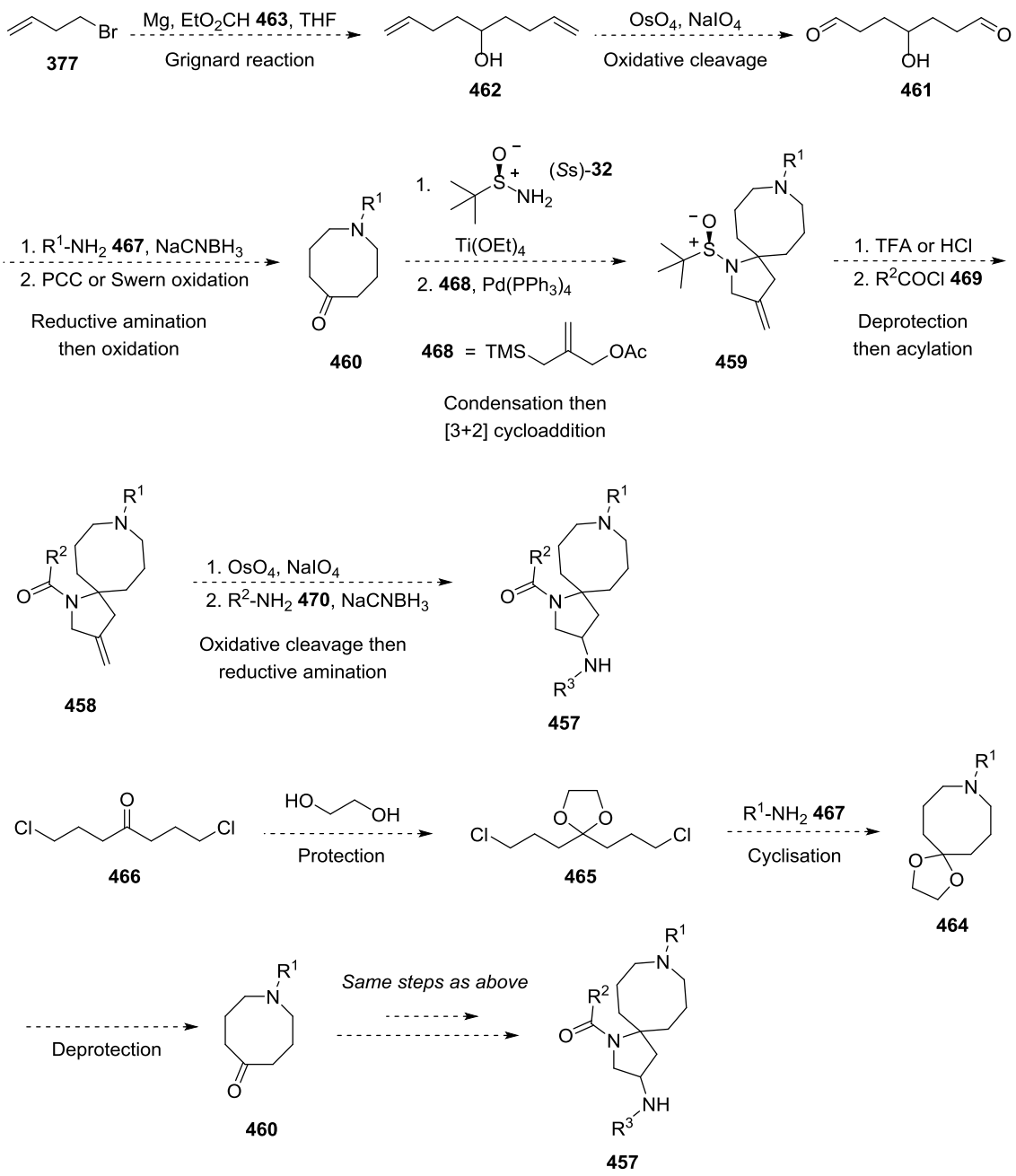
Scheme 133: Planned retrosynthetic analysis towards **457** starting from **377** or **466**

3.2. Results and discussion

3.2.1. Synthesis of spiro-pyrrolidine chemical scaffolds

Spiro-pyrrolidine **457***,* is an interesting bicyclic amide system, which could serve as a chemical scaffold for the synthesis of "lead-like" compound libraries for drug discovery programme.

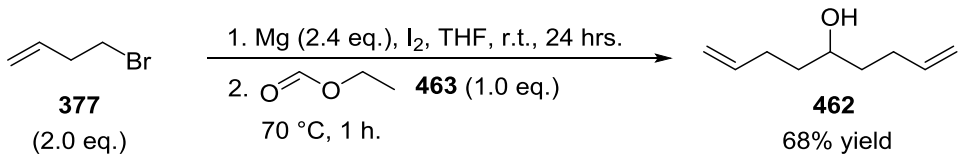
It has been proposed to use one of two routes to synthesise the desired product **457**. The product **460** was designed to be a key intermediate in both synthetic routes. The first route includes using 4-bromobutene **377** as a starting material to prepare **457**, whereas 1,7-dichloroheptan-4-one **466** will be used as a starting material in the second route (Scheme 134).



R^1 = *p*-methoxy benzyl amine, *o*- or *p*-NO_2PhSO_2
R^2 and R^3 = H, alkyl or aryl

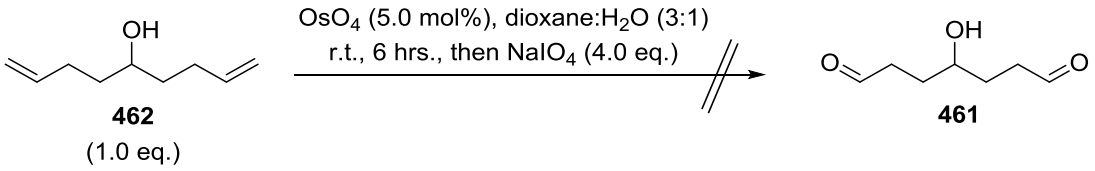
Scheme 134: Proposed synthesis of **457** starting from **377** or **466**

Investigations were started with the first route; the Grignard analogue of **377** was prepared and added to ethyl formate **463**, to give the symmetrical diene alcohol derivative **462** in a good yield (68%) (Scheme 135).



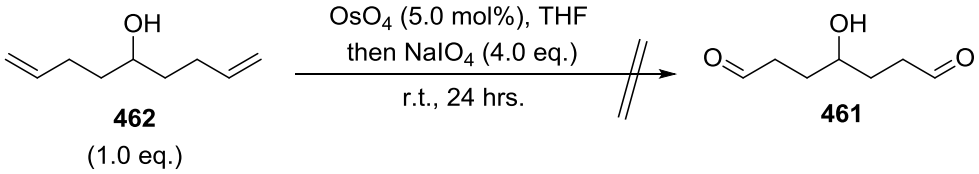
Scheme 135: Preparation of undeca-1,10-dien-6-ol **462**

The oxidative cleavage of the alkene bonds on **462** to afford aldehyde **461** was then attempted using OsO_4 in dioxane:H_2O (3:1). The desired product **461** could not be observed *via* TLC, HRMS or ^1H NMR spectroscopy (Scheme 136).



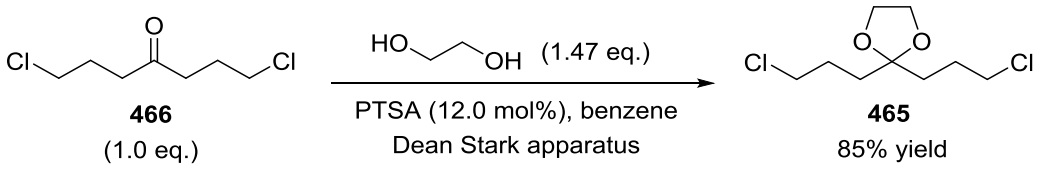
Scheme 136: Attempted oxidation of the alkene bonds of undeca-1,10-dien-6-ol **462** to aldehyde **461** using OsO_4

The reaction conditions were then modified using THF instead of dioxane:H_2O. The desired product **461** was not detected after 24 hours (Scheme 137).



Scheme 137: Attempted synthesis of **461** from undeca-1,10-dien-6-ol **462** in a one-pot reaction

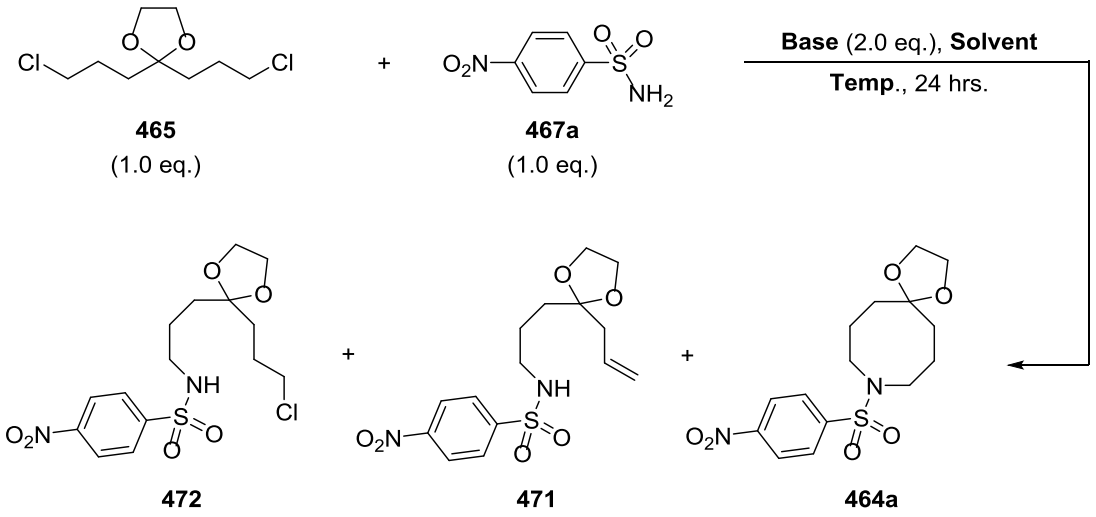
Next, the second route was investigated, as it is theorised that it could be easier to access the intermediate **460**. The ketone group in **466** was protected as an acetal **465**. This was carried out using ethylene glycol in the presence of *p*-toluenesulfonic acid (PTSA) as a catalyst, which afforded **465** in a very good yield (85%) (Scheme 138).



Scheme 138: Preparation of 1,7-dichloroheptan-4-one ethylene ketal **465**

In the next step, it was attempted to synthesise **464a** *via* condensation of **465** with *p*-nitrobenzenesulfonamide **467a** under basic conditions (Table 15). Different conditions were tested to obtain the desired product **464a** (Table 15).

Table 15: Investigation into the synthesis of **464a** using **467a**



Entry	Base	Base pkaH	Solvent	T (°C)	**464a**	**471**	**472**	SM[1] **465**/**467a**
1	K_2CO_3	10.25	DMF	r.t.	-	-	-	RSM
2	K_2CO_3	10.25	DMF	153	-	trace	-	RSM
3	Et_3N	10.75	DMF	r.t.	-	-	-	RSM
4	Et_3N	10.75	DMF	80	-	-	-	RSM
5	LiOH	13.6	THF	r.t.	-	-	-	RSM
6	LiOH	13.6	DMF	153	-	-	-	-
7	NaH	*ca*. 35	DMF	80	-	-	1:1[2]	

1. The starting material was observed using TLC and ^{1}H NMR spectroscopy for crude mixture.
2. The ratio of the products was based upon ^{1}H NMR spectroscopy of crude material.

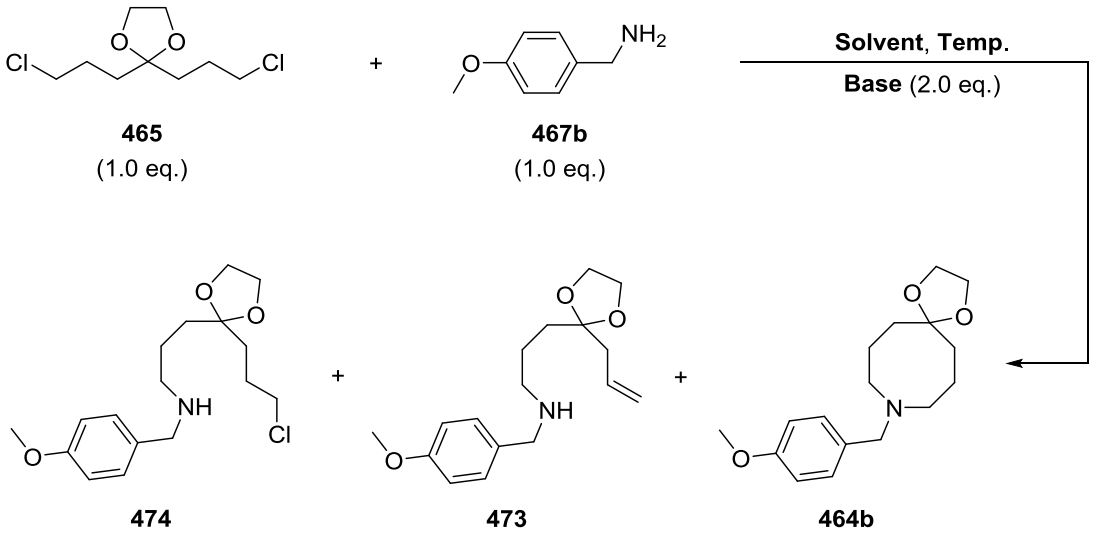
The use of K_2CO_3 as a base and DMF as a solvent at room temperature was not effective to give the desired product **464a**, and only the starting materials **465** and **467a** were recovered (Table 15, entry 1). The reaction was then repeated at 153 °C (Table 15, entry 2), but, no desired product **464a** was observed and only starting materials **465** and **467a** were recovered. Trace amount of undesired alkene derivative **471** was detected by HRMS and ^{1}H NMR spectroscopy. Et_3N was then employed in place of K_2CO_3, which is more basic and could be more reactive. The desired product **464a** was not detected when the reaction carried out at room temperature or 80 °C (Table 15, entries 3 and 4). Stronger base was then used (LiOH) to deprotonate the sulfonamide group on **467a**, which is could make the anion of **467a** more reactive towards nucleophilic substitution (Table 15, entry 5). But, no product **464a** was detected and only the starting materials **465** and **467a** were detected. While, heating at reflux using DMF as a solvent was unsuccessful to afford the desired product **464a**, and no starting material **465** was recovered by TLC or ^{1}H NMR spectroscopy (Table 15, entry 6). Presumably, the high temperature led to degradation of the starting material **465**. Finally, analysis by ^{1}H NMR spectroscopy of the crude material showed a ratio 1:1 of the starting

material **465** and intermediate **472**, when the reaction was carried out at 80 °C in the presence of NaH as a base (Table 15, entry 7).

The attempts to obtain **464a** were unsuccessful and this is may be attributed to the sulfone group on **467a**, which reduces the nucleophilicity at the amine towards nucleophilic substitution with **465**.

We envisaged that synthesis of protected azocan-5-one **464b** could be achieved using *p*-methoxybenzyl amine **467b** in place of **467a**. The compound **467b** can be considered more nucleophilic than **467a** and will encourage the nucleophilic substitution on **465**. Different conditions were tested after this attempt to synthesise the desired product **464b**, including changing the base, solvent and the temperature. However, all the conditions employed with this reaction were found to be unsuccessful (Table 16).

Table 16: Reactions conditions of ring cyclisation to synthesise **464b**



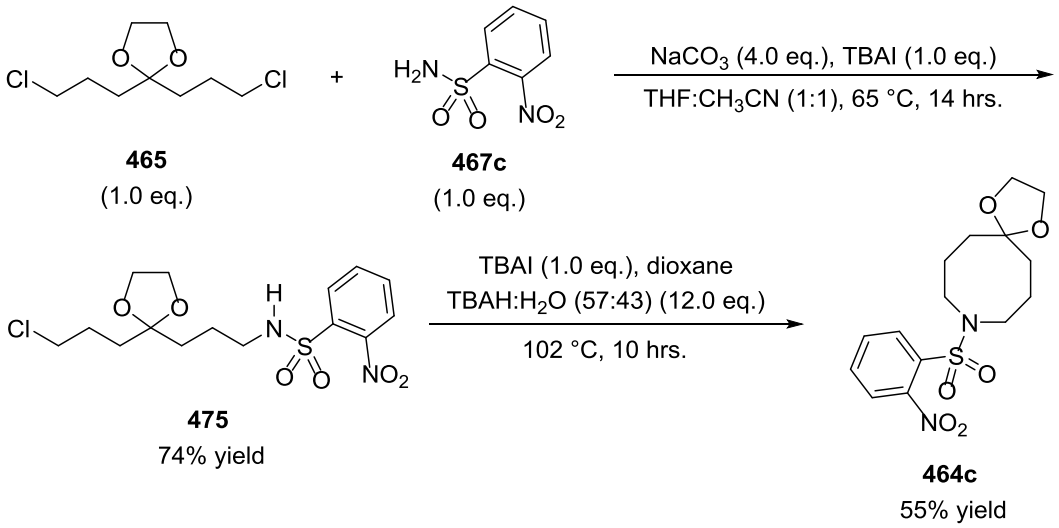
Entry	Base	Base pkaH	Solvent	T (°C)	Time (h)	Yield **473** (%)[1]	Yield **474** (%)[1]	Yield **464b** (%)[1]	SM (%) **465**
1	K_2CO_3	10.25	DMF	r.t.	24	-	-	-	RSM
2	KO^tBu	*ca*. 17	DMF	r.t.	24	-	-	-	RSM
3	K_2CO_3	10.25	DMF	50	24	6:0:0:1[2]			
4	K_2CO_3	10.25	DMF	80	24	20	-	-	39
5	K_2CO_3	10.25	DMF	100	24	16	20	-	-
6	KO^tBu	*ca*. 17	DMF	80	24	15	7	-	25
7	K_2CO_3	10.25	H_2O	50[3]	5	-	-	-	RSM

1. Yield based on ^{1}H NMR spectroscopy of isolated material.
2. The ratio of the products was based upon ^{1}H NMR spectroscopy of crude material.
3. The experiment was conducted using microwave conditions.

When the reaction was carried out at room temperature in two different bases K_2CO_3 and KO^tBu, no reaction was observed and only starting materials were recovered (Table 16, entries 1 and 2). While the alkene derivative **473** was observed when the reaction was performed at higher temperatures. The formation of **473** is due to the acidic proton at the α-position of the chlorine atom, which is easy to remove at high temperatures. For example, when the reaction was carried out at 50 °C using K_2CO_3 as a base gave a ratio 6:1 of **473**:**465** and the desired product **464b** was not detected (Table 16, entry 3). When the temperature rose to 80 °C, the desired product **464b** was not observed, and the undesired alkene derivative **473** was isolated in a 20% yield with 39% recovered of the starting material **465** (Table 16, entry 4). The desired product **464b** was not observed in these conditions, and two undesired compounds were isolated; **473** and **474** in 16% and 20% yields respectively (Table 16, entry 5). The use of KO^tBu at 80 °C resulted in 15% of **473**, 7% of **474** and 25% recovered of the starting material **465** (Table 16, entry 6). Finally, microwave conditions also did not afford the

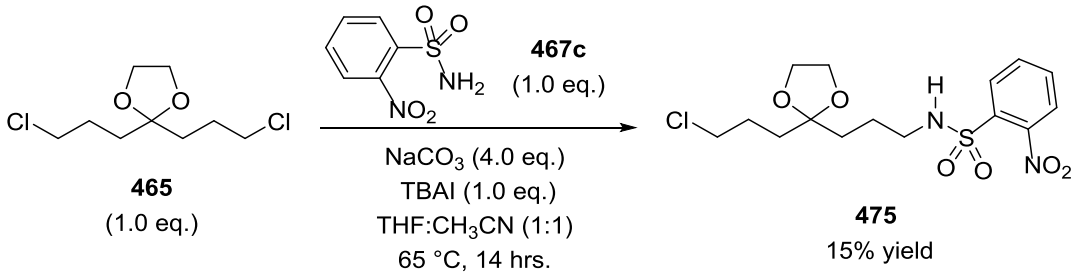
desired product **464b** and only the starting materials were observed after 5 hours at 50 °C (Table 16, entry 7).

Recently, Galicia and Maldonado[161] have reported the synthesis of **464c**, which could be useful in the synthetic route. This was achieved successfully over two steps starting from **465**. Treatment of **465** with *o*-nitrobenzenesulfonamide **467c** in the presence of tetrabutyl ammonium iodide (TBAI) and $NaCO_3$ afforded **475** as an oil in good yield (74%). Followed by a cyclisation of **475** using tetrabutyl ammonium hydroxide (TBAH) and TBAI gave the desired product **464c** in a 55% yield (Scheme 139).



Scheme 139: Galicia and Maldonado synthesis of **464c** over two steps starting from **465**[161]

Encouraged by this literature, the same conditions were investigated to prepare **464c**. Compound **475** was obtained in 15% yield (Scheme 140).



Scheme 140: Preparation of **475** *via* condensation of **465** with **467c**

The product **475** was crystallised and the structure was then confirmed by X-ray crystallographic analysis (Figure 20).

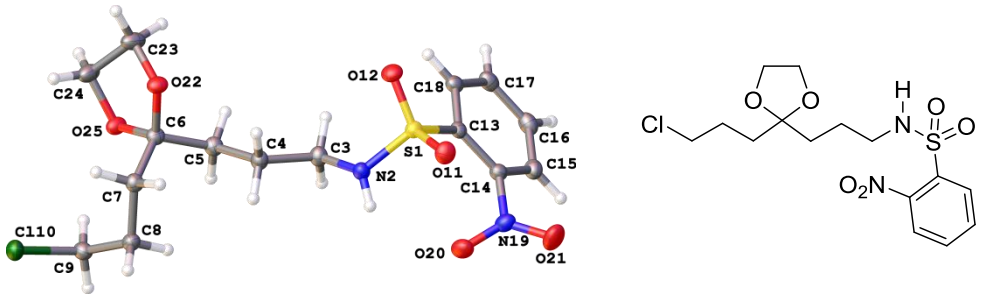
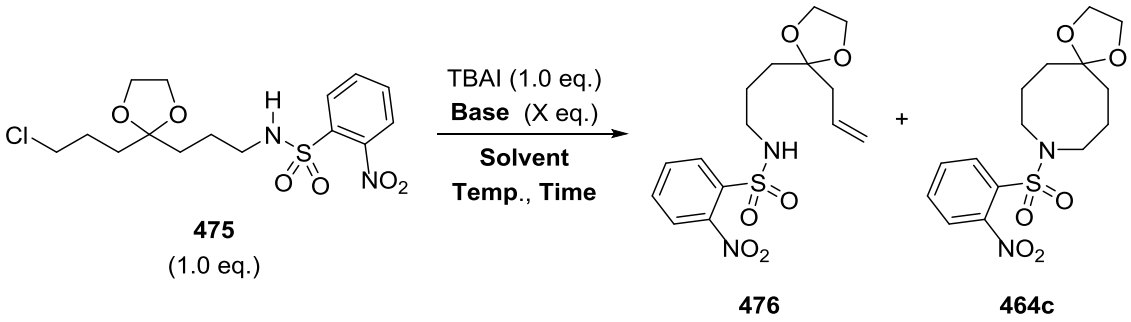


Figure 20: X-ray crystal structure of **475**

Different conditions were then used to synthesise the desired product **464c** *via* cyclisation of **475**. Table 17 summarises our attempts to prepare **464c**.

Table 17: Optimisation of reactions conditions to synthesise **464c** *via* cyclisation of **475** under basic conditions



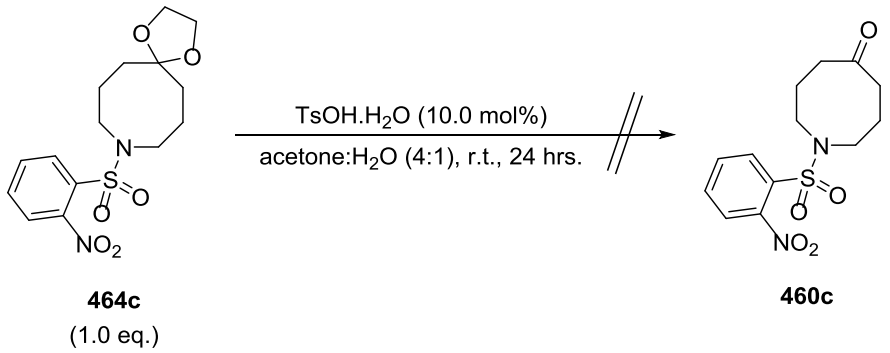
Entry	Solvent	Base	Base pka	Base (X eq.)	Temp. (°C)	Time (h)	RSM **475** (%)[1]	Yield **476** (%)[1]	Yield **464c** (%)[1]
1	Dioxane	TBAH	*ca*. 14	6	102	24	complex mixture		9
2	Dioxane	TBAH	*ca*. 14	12	102	24	19	11	8
3	Dioxane	TBAH	*ca*. 14	3	102	48	35	12	-
4	Dioxane	TBAH	*ca*. 14	3	r.t.	24	RSM[3]		
5	Dioxane	NaH	*ca*. 35	1.1	r.t.	24	RSM[3]		
6	Dioxane	TBAH	*ca*. 14	1.1	102	24	1:2:0[2]		
7	Dioxane	TBAH	*ca*. 14	15	102	24	1:7:0[2]		
8	MeCN: Dioxane	TBAH	*ca*. 14	5	60	24	1:1:0[2]		
9	THF	NaH	*ca*. 35	1.1	66	24	RSM[3]		

1. Isolated yield.
2. The ratio of the products was based upon ^{1}H NMR spectroscopy of crude material.
3. The starting material was observed using TLC.

The reactions were performed in the presence of TBAI, which served to activate the substrate **475** *via* formation an iodo intermediate.[162] The desired product **464c** was obtained in a 9% yield with complex mixture of undesired alkene product **476** and starting material **475** when the reaction was carried out at 102 °C for 24 hours with TBAH as a base in dioxane (Table 17, entry 1). No significant change in the yield (8%) was observed when the amount of the base was increased (12.0 eq. of TBAH), but the alkene derivative **476** was isolated in 11% yield with 19% of recovered starting material **475** (Table 17, entry 2). Only the undesired alkene derivative **476** was isolated in 12% yield and 35% recovered starting material **475** when the reaction was carried out for 48 hours at 102 °C using 3.0 eq. of TBAH (Table 17, entry 3). Only the starting material **475** was observed *via* TLC when the reaction was carried out at room temperature using TBAH or NaH as a

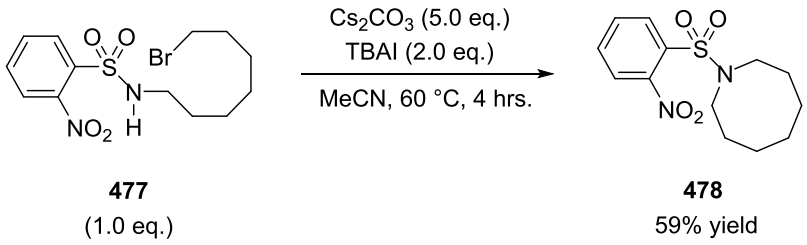
base (Table 17, entries 4 and 5). ^{1}H NMR spectroscopy of the crude mixtures showed no desired product **464c** and a mixture of alkene derivative **476** and the starting material **475** in different ratios when the reaction was carried out at 102 °C and different eqs. of the base (Table 17, entries 6 and 7). However, the transformation to the alkene derivative **476** was found to be quicker when using an extra amount of base; the ratio was 1:2 (**475**:**476**) in 1.1 eq. of TBAH compared to 1:7 (**475**:**476**) in 15.0 eq. of TBAH (Table 17, entries 6 and 7). No desired product **464c** was observed when the reaction was performed in MeCN:dioxane and TBAH at 60 °C and same ratio of the **475** to **476** was detected by ^{1}H NMR spectroscopy of the crude mixture (Table 17, entry 8). Only the starting material **475** was observed *via* ^{1}H NMR spectroscopy of the crude mixture when using THF as a solvent and NaH as base at 66 °C (Table 17, entry 9). As a result, it was observed that this reaction is very slow in spite of use TBAH or NaH as a base and TBAI to increase the reaction rate *via* changing the chloride with iodide, which is better a leaving group (Table 17).

The optimisation of the reaction conditions attempted to prepare the desired product **464c** were unsuccessful (only 9% yield). Therefore, the isolated amount of **464c** (5 mg) was then used in the next step. Hydrolysis of the acetal protecting group on **464c** was then attempted *via* treatment with $TsOH.H_2O$ to give the corresponding ketone **460c**. Unfortunately, the desired product **460c** was not detected using HRMS, TLC or ^1H NMR spectroscopy (Scheme 141).



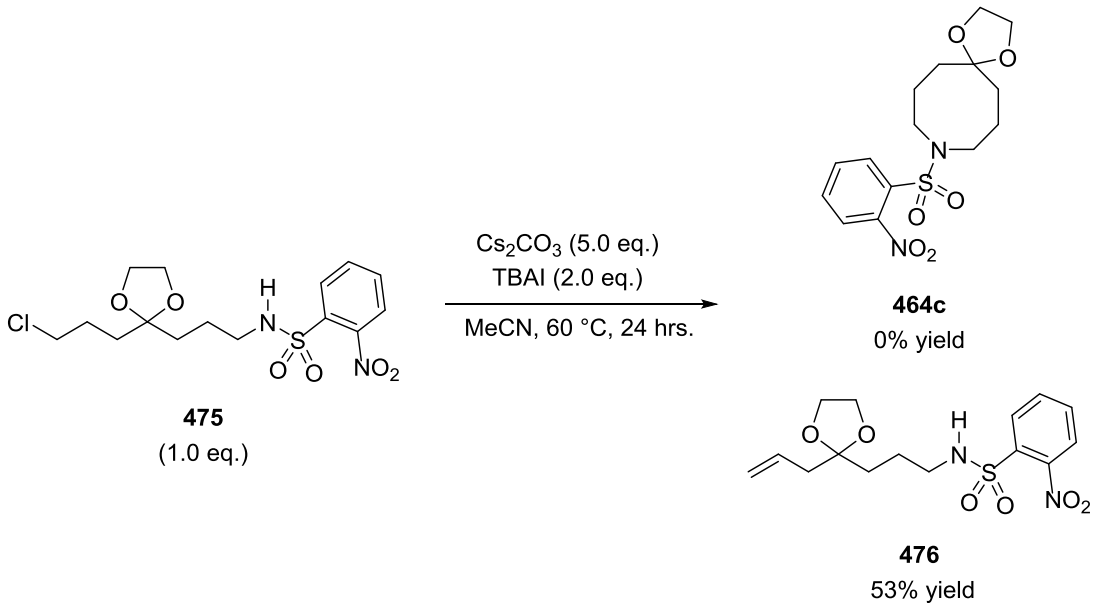
Scheme 141: Hydrolysis of acetal group of **464c** using TsOH.H2O to ketone **460c**

Kan *et al*.[163] have reported the total synthesis of lipogrammistin-A natural product. The synthetic route included cyclisation of *N*-(7-Bromoheptyl)-2-nitrobenzenesulfonamide **477** afforded 1-(2-nitrobenzenesulfonyl)-azocane **478** in a good yield (59%). This was done using Cs_2CO_3 as a base and TBAI with heating at 60 °C for 4 hours (Scheme 142).



Scheme 142: Kan's *et al*. preparation of **478** *via* cyclisation of **477** under basic conditions[163]

The same conditions were then tested in our project using **475** to afford **464c**. Unfortunately, the desired product **464c** was not observed and formed only alkene undesired product **476** in a 53% yield (Scheme 143).



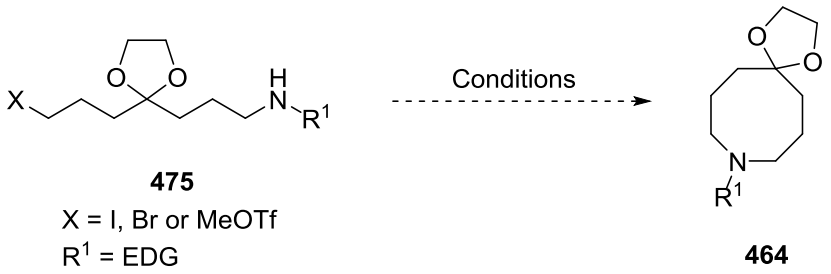
Scheme 143: Attempted intramolecular cyclisation of **475** under basic conditions resulting alkene derivative **476**

3.2.2. Conclusion

The attempts regarding the formation of protected azocan-5-one **464a** and **464b** were unsuccessful using *p*-nitrobenzenesulfonamide **467a** and *p*-methoxybenzyl amine **467b** respectively. The intermolecular nucleophilic substitution reaction of *o*-nitrobenzenesulfonamide **467c** with protected acetal compound **465** was achieved successfully and gave the desired product **475** albeit in a low yield (15%). The product **475** was confirmed by X-ray crystallography. Unfortunately, intramolecular nucleophilic substitution reaction afforded only 9% yield of the desired product **464c** when various conditions were screened using **475**. As yet, no significant progress towards the synthesis of spiro-pyrrolidine chemical scaffolds **457** has been made.

3.2.3. Future work

The synthesis of the protected azacon-5-one **464c** was achieved *via* intramolecular cyclisation of **475** in the presence of TBAH as a base, in a poor yield (9%) (Table 17). The yield of the reaction should be improved in order to establish an efficient synthesis. In this regard, the use of a more activated substrate could be useful to improve the yield of the reaction and minimise the formation of side-products. The use of different atoms or groups on the **475** would be screened, such as using iodine, bromine or trifluoromethanesulfonate group in place of chlorine, which are better leaving groups than chlorine. At the same time, the use of electron-donating groups instead of *o*-nitrobenzenesulfonyl could activate the intramolecular cyclisation on the substrate **475** to provide **464** (Scheme 144).



475
X = I, Br or MeOTf
R^1 = EDG

464

Scheme 144: Studies towards the optimisation of the synthesis of **464**

4. Conclusion

During the studies introduced in this course, several investigations have been employed in the aim of synthesis of new complex molecules. These investigations included using *tert*-butanesulfinamide as a chiral auxiliary for asymmetric synthesis.

In the first study, the use of Ellman's *tert*-butylsulfinimines for the synthesis of α-allyl sulfinimines **239**, using the Tsuji-Trost allyation has been achieved successfully. Followed this, the synthesis of novel sp^3-rich pyrrolidine containing chemical scaffolds **242** has been performed over three sequence steps, starting from the α-allyl sulfinimines **239**. The desired pyrrolidine products **242** were isolated in moderate to good yields (53-77%) with *dr* up to >25:1. Ring-formation was found to proceed with moderate to good diastereoselectivity to yield *cis*-2,5-pyrrolidines as the major diastereoisomer. Having in hand pyrrolidine products, a range of further derivatisation such as, amidation, reductive amination, sulfonylation and Suzuki coupling to furnish highly functionalised substrates, has been performed successfully.

Although the pyrrolidine chemical scaffolds **242** have been confirmed as a simple and efficient method for fabricating many interesting and diverse scaffolds, the attempts in the total synthesis of the natural product (+)-monomorine **305** was not very effective using this chemistry. Therefore, several synthetic routes were then explored towards achieving this total synthesis. As a result, the desired natural product **305** was detected by HMRS, but not isolated using flash column chromatography. The synthetic route could be scaled up easily to afford large quantities of **433** from commercially inexpensive starting materials, which would be easier to isolate or even identify the desired natural product **305** *via* NMR spectroscopy after purification by flash column chromatography. The studies towards these ends are currently ongoing and the results will be reported when complete.

Finally, the investigations into the synthesis of spiro-pyrrolidine scaffold **457** were unsuccessful. Different strategies were fruitlessly attempted to synthesise the products azocan-5-one **464a** and **464b** were unfruitful using *p*-nitrobenzenesulfonamide **467a** and *p*-methoxybenzylamine **467b** respectively. Whereas, the product **475** was obtained in a low yield (15%) *via* an intermolecular nucleophilic substitution reaction of *o*-nitrobenzenesulfonamide **467c** with protected acetal compound **465**. Subsequently, the intramolecular nucleophilic substitution reaction of **475** was not very successful, which afforded the desired product **464c** in a low yield (9%). However, attempts to carry out the cyclisation through use of the substrates **467a**, **467b** and **475** either failed or gave a poor yield.

5. Experimental

5.1. General experimental procedures

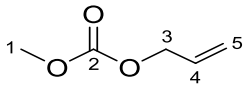
All reagents were purchased from commercial sources and used without additional purification unless stated otherwise. Tetrahydrofuran was freshly distilled over sodium and benzophenone under nitrogen gas. Anhydrous DMF, benzene, MeOH, CH_3CN and dioxane were purchased; THF and Et_2O were degassed and dried over alumina under nitrogen. All reactions were conducted in flame-dried glassware under an inert atmosphere of nitrogen or argon. Brine is a saturated aqueous solution of sodium chloride. Petroleum ether refers to light petroleum ether (b.p. 40-60 °C), and water refers to deionised water. Solvents evaporation was performed using a rotary evaporator under reduced pressure.

TLC was performed on Merck silica gel 60 F_{254} and visualised by UV lamp and aqueous alkaline potassium permanganate. Flash column chromatography was performed over silica gel Fluka 60 or Merck aluminium oxide 90. Preparative thin layer chromatography was performed over silica gel plates Merck 60. Microwave reactions were performed using a Biotage Initiator 2.0 reactor. ^{1}H and ^{13}C NMR spectral data were recorded using a Bruker DPX300, Bruker DPX400, Bruker AV400, Bruker AV(III)400, Bruker AV(III)400HD or AV(III)500 spectrometer. Chemical shifts are quoted in ppm downfield from tetramethylsilane (TMS) as internal standard or deuterated chloroform either in ^{1}H NMR or ^{13}C NMR as reference (δ_H 7.26 ppm or δ_C 77.16 ppm respectively). Multiplicities in the ^{1}H NMR spectra are described as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad; coupling constant values *J* are given in Hertz. Infrared spectral data were recorded using a Perkin-Elmer 1600 FTIR spectrometer. Mass spectrometry data were recorded using a Bruker MicroTOF spectrometer in ESI mode.

Melting points are uncorrected and were recorded in open capillary tubes using Stuart scientific SMP20. Elemental microanalyses for carbon, hydrogen and nitrogen were recorded on an Exeter analytical CE-440 elemental analyser. Specific rotation values were measured at ambient temperature in $CHCl_3$ or MeOH solutions on an ADP-440 digital polarimeter using a sodium lamp at 589 nm and a 2 mL capacity cell with 10 cm path length.

All yields refer to isolated material, homogenous by TLC or NMR unless otherwise stated. Where isomeric compounds are present in purified materials, the ratios have been determined by ^{1}H NMR analysis where possible. In most cases the ^{1}H NMR data is reported for only the major isomer. Compound names are assigned according to standard IUPAC nomenclature. The numbering in the compound names was later modified to fit an alternative numbering system. In some cases, the compound numbering does not agree with the alternative numbering system. The analysis of the crude product **251** was performed on a Bruker Trace 1310 series GC equipped with an autosampler and chirasil Dex CB (25 m × 0.25 mm × 0.25 μm) column. X-ray analysis study was performed by Dr. William Lewis and Prof. Sandy Blake at the University of Nottingham.

Preparation of allyl methyl carbonate (247)

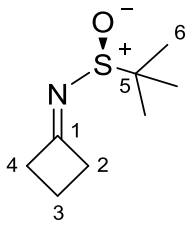


To a mixture of allyl alcohol **249** (6.8 mL, 100 mmol, 1.0 eq.) and dimethyl carbonate **250** (25.25 mL, 300 mmol, 3.0 eq.) was added potassium carbonate (415 mg, 3 mmol, 3.0 mol%) at room temperature with stirring. The reaction mixture was heated to reflux (90 °C) for 24 hours. Distillation of the reaction mixture (temperature 127 °C) afforded title compound **247** (8.86 mL, 78 mmol, 78%) as a colourless liquid. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2958, 2856 (C-H_{ali}), 1751 (C=O), 1650 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.88 (1H, ddt, *J* = 16.2, 10.4 and 5.6, 4-H), 5.30 (1H, dd, *J* = 16.2 and 1.4, 5-H_a), 5.21 (1H, dd, *J* = 10.4 and 1.4, 5-H_b), 4.57 (2H, dt, *J* = 5.6 and 1.4, 3-H), 3.73 (3H, s, 1-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 155.7 (C2), 131.7 (C4), 119.0 (C5), 68.6 (C3), 54.9 (C1); CHN Found: C, 51.4%; H, 7.2%, $C_5H_8O_3$ requires: C, 51.7%; H, 6.9%.

5.2. General procedure A: Synthesis of sulfinimines 238.

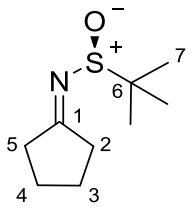
To a solution of titanium (IV) ethoxide (3.48-113 mmol, 3.0 eq.) in anhydrous THF (25-160 mL), were added the ketones **237** (1.16-37.67 mmol, 1.0 eq.) and the mixture was stirred at room temperature for 15 minutes. Followed by the slow addition of (*S*)-(-)-*tert*-butyl-sulfinamide **32** (1.28-41.44 mmol, 1.1 eq.), and the reaction mixture was heated to 65 °C. When the reaction had reached completion, as mentioned by TLC, the reaction was allowed to cool at room temperature. The reaction was then quenched with brine (30-50 mL) and the resulting slurry solution was filtered through a pad of Celite®, and the filter cake was washed with ethyl acetate (5-25 mL). The filtrate was then transferred to a separating funnel where the organic layer was washed with brine (5-25 mL). The aqueous layer was extracted once with ethyl acetate (15-25 mL), and the combined organic extracts were over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. Flash column chromatography afforded desired sulfinimines **238**.[17,23]

(*S*S)-*N*-cyclobutylidene-2-methylpropane-2-sulfinamide (238a)



General procedure A was followed using cyclobutanone **237a** (493 μL, 6.6 mmol, 1.0 eq.), titanium (IV) ethoxide (4.15 mL, 19.8 mmol, 3.0 eq.) and (*S*)-(-)-*tert*-butyl-sulfinamide **32** (880 mg, 7.26 mmol, 1.1 eq.) in anhydrous THF (30 mL). The crude product was obtained as a yellow oil and purified by flash column chromatography over silica gel (eluting with 5:1 petroleum ether/ethyl acetate) to give **238a** (881 mg, 5.1 mmol, 77%) as a pale yellow oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2960, 2867 (C-H_{ali}), 1663 (C=N), 1080 (S-O); $[\alpha]_D^{22}$ = 400.8 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 3.54-3.42 (1H, m, 2-H_a), 3.31-3.19 (1H, m, 2-H_b), 3.18-3.01 (2H, m, 4-H), 2.14-2.04 (2H, m, 3-H), 1.15 (9H, s, 6-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 186.8 (C1), 56.7 (C5), 40.5 (C2 or C4), 39.9 (C2 or C4), 22.2 (C6), 15.1 (C3); ESI-MS m/z = 369.16 ($2M+Na^+$, 22.1), 347.18 ($2M+H^+$, 5.5), 196.07 ($M+Na^+$, 100), 174.09 ($M+H^+$, 75.3); HRMS (ESI) m/z = 196.0778 (calculated for $C_8H_{15}NOSNa^+$ = 196.0767). Data consistent with literature.[164]

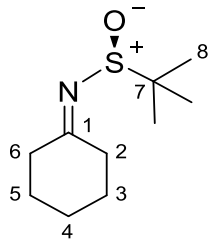
(*S*S)-*N*-cyclopentylidene-2-methylpropane-2-sulfinamide (238b)



General procedure A was followed using cyclopentanone **237b** (1.77 mL, 20 mmol, 1.0 eq.), titanium (IV) ethoxide (12.6 mL, 60 mmol, 3.0 eq.) and (*S*)-(-)-*tert*-butyl-sulfinamide **32** (2.67 g, 22 mmol, 1.1 eq.) in anhydrous THF (30 mL). The crude product was obtained as a yellow oil and purified by flash column chromatography over silica gel (eluting with 6:1 petroleum ether/ethyl acetate) to

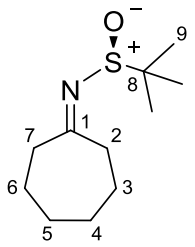
give **238b** (3.37 g, 18 mmol, 90%) as a clear yellow oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2901, 2849 (C-H_{ali}), 1687 (C=N), 1077 (S-O); $[\alpha]_D^{19}$ = -20.3 (*c* = 0.1 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ_H = 2.89 (1H, dt, *J* = 19.1 and 7.7, 2-H_a), 2.58-2.48 (3H, m, 2-H_b and 5-H), 1.94-1.84 (2H, m, 3-H), 1.81-1.73 (2H, m, 4-H), 1.22 (9H, s, 7-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 195.0 (C1), 56.4 (C6), 39.0 (C2), 49.5 (C5), 25.8 (C4), 23.7 (C3), 22.3 (C7); ESI-MS m/z = 397.19 ($2M+Na^+$, 49.5), 375.21 ($2M+H^+$, 21.2), 210.09 ($M+Na^+$, 42.5), 188.11 ($M+H^+$, 100); HRMS (ESI) m/z = 188.1104 (calculated for $C_9H_{18}NOS^+$ = 188.1104). Data consistent with literature.[164]

(*S*S)-*N*-cyclohexylidene-2-methylpropane-2-sulfinamide (238c)



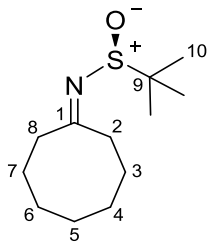
General procedure A was followed using cyclohexanone **237c** (2.07 mL, 20 mmol, 1.0 eq.), titanium (IV) ethoxide (12.6 mL, 60 mmol, 3.0 eq.) and (*S*)-(-)-*tert*-butyl-sulfinamide **32** (2.66 g, 22 mmol, 1.1 eq.) in anhydrous THF (25 mL). The crude product was obtained as a yellow oil and purified by flash column chromatography over silica gel (eluting with 6:1 petroleum ether/ethyl acetate) to give **238c** (2.74 g, 13.6 mmol, 68%) as a yellow oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2935, 2861 (C-H_{ali}), 1675 (C=N), 1070 (S-O); $[\alpha]_D^{19}$ = -13.2 (*c* = 0.1 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ_H = 3.04 (1H, dt, *J* = 16.8 and 6.0, 2-H_a), 2.79 (1H, dt, *J* = 16.8 and 6.2, 2-H_b), 2.65-2.55 (2H, m, 6-H), 1.81-1.55 (6H, m, 3-H, 4-H and 5-H), 1.23 (9H, s, 8-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 191.8 (C1), 56.0 (C7), 42.1 (C2 or C6), 36.5 (C2 or C6), 29.8 (C3 or C5), 26.3 (C3 or C5), 25.3 (C4), 22.1 (C8); ESI-MS m/z = 403.24 ($2M+H^+$, 27.3), 202.12 ($M+H^+$, 100); HRMS (ESI) m/z = 202.1276 (calculated for $C_{10}H_{20}NOS^+$ = 202.1260). Data consistent with literature.[164]

(*S*S)-*N*-cycloheptylidene-2-methylpropane-2-sulfinamide (238d)



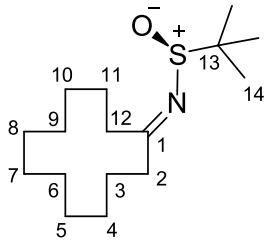
General procedure A was followed using cycloheptanone **237d** (778 μL, 6.6 mmol, 1.0 eq.), titanium (IV) ethoxide (4.15 mL, 19.8 mmol, 3.0 eq.) and (*S*)-(-)-*tert*-butyl-sulfinamide **32** (880 mg, 7.26 mmol, 1.1 eq.) in anhydrous THF (30 mL). The crude product was obtained as a yellow oil and purified by flash column chromatography over silica gel (eluting with 1:1 petroleum ether/ethyl acetate) to give **238d** (1.07 mg, 4.95 mmol, 75%) as a clear yellow oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2927, 2857 (C-H_{ali}), 1666 (C=N), 1073 (S-O); $[\alpha]_D^{22}$ = 173.3 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 3.02 (1H, dt, *J* = 12.0 and 6.4, 2-H_a), 2.77 (1H, dt, *J* = 12.0 and 6.2, 2-H_b), 2.65-2.53 (2H, m, 7-H), 1.78-1.50 (8H, m, 3-H, 4-H, 5-H and 6-H), 1.21 (9H, s, 9-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 191.7 (C1), 55.9 (C8), 42.0 (C2), 36.4 (C7), 29.73 (C3 or C6), 29.67 (C3 or C6), 26.2 (C4 or C5), 25.3 (C4 or C5), 22.1 (C9); ESI-MS m/z = 453.26 ($2M+Na^+$, 100), 431.27 ($2M+H^+$, 11.6), 238.12 ($M+Na^+$, 73.9), 216.14 ($M+H^+$, 40.7); HRMS (ESI) m/z = 453.2617 (calculated for $C_{22}H_{42}N_2O_2S_2Na^+$ = 453.2580). Data consistent with literature.[164]

(*S*S)-*N*-cyclooctylidene-2-methylpropane-2-sulfinamide (238e)



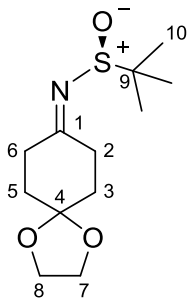
General procedure A was followed using cyclooctanone **237e** (869 μL, 6.6 mmol, 1.0 eq.), titanium (IV) ethoxide (4.15 mL, 19.8 mmol, 3.0 eq.) and (*S*)-(-)-*tert*-butyl-sulfinamide **32** (880 mg, 7.26 mmol, 1.1 eq.) in anhydrous THF (25 mL). The crude product was obtained as a yellow oil and purified by flash column chromatography over silica gel (eluting with 5:1 petroleum ether/ethyl acetate) to give **238e** (863 mg, 3.76 mmol, 57%) as a pale yellow oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2925, 2859 (C-H_{ali}), 1640 (C=N), 1074 (S-O); $[\alpha]_D^{22}$ = 141.6 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 2.87-2.78 (1H, m, 2-H_a), 2.76-2.67 (1H, m, 2-H_b), 2.54-2.39 (2H, m, 8-H), 1.92-1.70 (4H, m, 3-H and 7-H), 1.54-1.40 (5H, m, 4-H, 5-H_a and 6-H), 1.38-1.25 (1H, m, 5-H_b), 1.19 (9H, s, 10-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 193.9 (C1), 56.1 (C9), 40.7 (C2), 34.6 (C8), 27.2 (C3 or C7), 27.0 (C3 or C7), 26.3 (C4 or C6), 25.9 (C4 or C6), 25.0 (C5), 22.2 (C10); ESI-MS m/z = 481.29 ($2M+Na^+$, 84.5), 459.30 ($2M+H^+$, 6.2), 252.13 ($M+Na^+$, 100), 230.15 ($M+H^+$, 44.8); HRMS (ESI) m/z = 252.1398 (calculated for $C_{12}H_{23}NOSNa^+$ = 252.1393).

(*S*S)-*N*-cyclododecylidene-2-methylpropane-2-sulfinamide (238f)



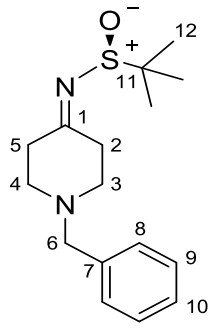
General procedure A was followed using cyclodocecanone **237f** (5 g, 27.4 mmol, 1.0 eq.), titanium (IV) ethoxide (17.23 mL, 82.2 mmol, 3.0 eq.) and (*S*)-(-)-*tert*-butyl-sulfinamide **32** (3.65 g, 30.14 mmol, 1.1 eq.) in anhydrous THF (150 mL). The crude product was obtained as a white solid and purified by flash column chromatography over silica gel (eluting with 6:1 petroleum ether/ethyl acetate) to give **238f** (7.12 g, 24.9 mmol, 91%) as a white solid, m.p. = 60-62 °C. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2929, 2864 (C-H_{ali}), 1704 (C=N), 1083 (S-O); $[\alpha]_D^{23}$ = -23.4 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 3.03-2.89 (1H, m, 2-H_a or 12-H_a), 2.70-2.48 (2H, m, 2-H or 12-H), 2.46-2.34 (1H, m, 2-H_b or 12-H_b), 1.94-1.78 (1H, m, 3-H or 11-H), 1.76-1.52 (3H, m, 3-H and 11-H), 1.46-1.26 (14H, m, 4-H, 5-H, 6-H, 7-H, 8-H, 9-H and 10-H), 1.23 (9H, s, 14-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 189.4 (C1), 56.2 (C13), 35.5 (C2 or C12), 35.4 (C2 or C12), 26.2 (C3 or C11), 26.1 (C3 or C11), 24.7 (C4 or C5 or C6 or C7 or C8 or C9 or C10), 24.4 (C4 or C5 or C6 or C7 or C8 or C9 or C10), 23.9 (C4 or C5 or C6 or C7 or C8 or C9 or C10), 22.9 (C4 or C5 or C6 or C7 or C8 or C9 or C10), 22.7 (C4 or C5 or C6 or C7 or C8 or C9 or C10), 22.6 (C4 or C5 or C6 or C7 or C8 or C9 or C10), 22.4 (C14), 22.2 (C4 or C5 or C6 or C7 or C8 or C9 or C10); ESI-MS m/z = 593.41 ($2M+Na^+$, 34.1), 571.43 ($2M+H^+$, 11.3), 308.20 ($M+Na^+$, 11.2), 286.22 ($M+H^+$, 100.0); HRMS (ESI) m/z = 286.2205 (calculated for $C_{16}H_{32}NOS^+$ = 286.2199).

(*S*S)-2-methyl-*N*-(1,4-dioxaspiro[4.5]decan-8-ylidene)propane-2-sulfinamide (238g)



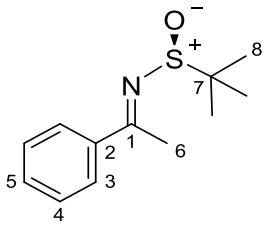
General procedure A was followed using 1,4-cyclohexanedione monoethyleneacetal **237g** (1.03 g, 6.6 mmol, 1.0 eq.), titanium (IV) ethoxide (4.15 mL, 19.8 mmol, 3.0 eq.) and (*S*)-(-)-*tert*-butyl-sulfinamide **32** (880 mg, 7.26 mmol, 1.1 eq.) in anhydrous THF (100 mL). The crude product was obtained as a yellow solid and purified by flash column chromatography over silica gel (eluting with 1:1 petroleum ether/ethyl acetate) to afford **238g** (1.04 mg, 4.03 mmol, 61%) as a pale yellow solid, m.p. = 76-78 °C. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2957, 2886 (C-H_{ali}), 1655 (C=N), 1260, 1031 (C-O-C), 1088 (S-O); $[\alpha]_D^{19}$ = -1.73 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 3.99 (4H, s, 7-H and 8-H), 3.09 (1H, ddd, *J* = 14.1, 7.9 and 5.4, 2-H_a), 2.87 (1H, ddd, *J*= 14.1, 8.3 and 5.6, 2-H_b), 2.60 (2H, t, *J* = 6.8, 6-H), 1.96-1.81 (4H, m, 3-H and 5-H), 1.22 (9H, s, 10-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 185.9 (C1), 107.1 (C4), 64.7 (C7 or C8), 64.6 (C7 or C8), 56.4 (C9), 37.6 (C2), 35.3 (C3 or C5), 34.7 (C3 or C5), 30.6 (C6), 22.1 (C10); ESI-MS m/z = 541.23 (2M+Na^+, 9.4), 282.11 (M+Na^+, 100), 260.13 (M+H^+, 40.4); HRMS (ESI) m/z = 282.1135 (calculated for $C_{12}H_{21}NO_3SNa^+$= 282.1134).

(*S*S)-*N*-(1-benzylpiperidin-4-ylidene)-2-methylpropane-2-sulfinamide (238h)



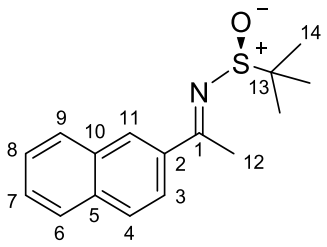
General procedure A was followed using 1-benzyl-4-piperidone **237h** (1.22 mL, 6.6 mmol, 1.0 eq.), titanium (IV) ethoxide (4.15 mL, 19.8 mmol, 3.0 eq.) and (*S*)-(-)-*tert*-butyl-sulfinamide **32** (880 mg, 7.26 mmol, 1.1 eq.) in anhydrous THF (40 mL). The crude product was obtained as a deep yellow oil and purified by flash column chromatography over silica gel (eluting with 1:1 petroleum ether/ethyl acetate) to afford **238h** (984 mg, 3.37 mmol, 51%) as a as yellow gum. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3084, 3060 (C-H_{aro}), 2955, 2865 (C-H_{ali}), 1625 (C=N), 1073 (S-O); $[\alpha]_D^{21}$ = 75.1 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.35-7.27 (5H, m, 8-H, 9-H and 10-H), 3.56 (2H, s, 6-H), 3.12-3.02 (1H, m, 3-H or 4-H), 2.85 (1H, dt, *J* = 14.4 and 6.1, 3-H or 4-H), 2.71-2.60 (4H, m, 2-H and 5-H), 2.57-2.51 (2H, m, 3-H or 4-H), 1.22 (9H, s, 12-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 185.2 (C1), 138.2 (C7), 129.1 (C8 or C9 or C10), 128.5 (C8 or C9 or C10), 127.4 (C8 or C9 or C10), 62.2 (C6), 56.5 (C11), 53.8 (C3 or C4), 53.3 (C3 or C4), 39.9 (C2 or C5), 33.9 (C2 or C5), 22.3 (C12); ESI-MS m/z = 315.14 ($M+Na^+$, 2.7), 293.16 ($M+H^+$, 100); HRMS (ESI) m/z = 293.1671 (calculated for $C_{16}H_{25}N_2OS^+$ = 293.1682).

(*S*S)-2-methyl-*N*-(1-phenylethylidene)propane-2-sulfinamide (238i)



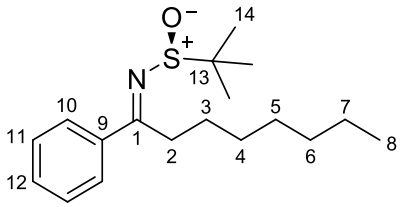
General procedure A was followed using acetophenone **237i** (817 μL, 7 mmol, 1.0 eq.), titanium (IV) ethoxide (4.4 mL, 21 mmol, 3.0 eq.) and (*S*)-(-)-*tert*-butyl-sulfinamide **32** (933 mg, 7.7 mmol, 1.1 eq.) in anhydrous THF (30 mL). The crude product was obtained as a yellow solid and purified by flash column chromatography over silica gel (eluting with 6:1 petroleum ether/ethyl acetate) to give **238i** (1.44 g, 6.44 mmol, 92%; single isomer) as a yellow solid, m.p. = 40-42 °C. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3063, 3026 (C-H_{aro}), 2960, 2866 (C-H_{ali}), 1685 (C=N), 1067 (S-O); $[\alpha]_D^{19}$ = -21.3 (*c* = 0.1 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.92 (2H, d, *J* = 7.5, 3-H), 7.50-7.45 (1H, m, 5-H), 7.44-7.38 (2H, m, 4-H), 2.80 (3H, s, 6-H), 1.36 (9H, s, 8-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 176.6 (C1), 138.9 (C2), 131.8 (C3 or C4 or C5), 128.6 (C3 or C4 or C5), 127.4 (C3 or C4 or C5), 57.6 (C7), 22.7 (C8), 20.0 (C6); ESI-MS m/z = 469.19 ($2M+Na^+$, 100), 447.21 ($2M+H^+$, 11.3), 246.09 ($M+Na^+$, 73.7), 224.11 ($M+H^+$, 60.8); HRMS (ESI) m/z = 469.1966 (calculated for $C_{24}H_{34}N_2O_2S_2Na^+$ = 469.1954); CHN Found: C, 64.8%; H, 7.6%; N, 6.0%, $C_{12}H_{17}NOS$ requires: C, 64.5%; H, 7.7%; N, 6.3%. Data consistent with literature.[41]

(S_S,*E*)-2-methyl-*N*-(1-(naphthalen-2-yl)ethylidene)propane-2-sulfinamide (238j)



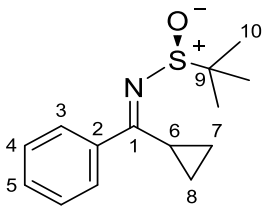
General procedure A was followed using 2-acetonaphthone **237j** (1.19 g, 7 mmol, 1.0 eq.), titanium (IV) ethoxide (4.4 mL, 21 mmol, 3.0 eq.) and (*S*)-(-)-*tert*-butyl-sulfinamide **32** (933 mg, 7.7 mmol, 1.1 eq.) in anhydrous THF (40 mL). The crude product was obtained as a yellow solid and purified by flash column chromatography over silica gel (eluting with 6:1 petroleum ether/ethyl acetate) to afford **238j** (1.55 g, 5.67 mmol, 81%; single isomer) as a yellow solid, m.p. = 133-135 °C. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3057, 3022 (C-H_{aro}), 2959, 2864 (C-H_{ali}), 1647 (C=N), 1067 (S-O); $[\alpha]_D^{19}$ = -12.29 (*c* = 0.1 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ_H = 8.30 (1H, s, 11-H), 8.07 (1H, dd, *J* = 8.8 and 1.5, 3-H), 7.94-7.90 (1H, m, 4-H), 7.88-7.83 (2H, m, 6-H and 9-H), 7.59-7.51 (2H, m, 7-H and 8-H), 2.89 (3H, s, 12-H), 1.36 (9H, s, 14-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 176.3 (C1), 136.3 (C5 or C10), 135.0 (C5 or C10), 132.8 (C2), 132.3 (C4), 129.4 (C6 or C9), 128.3 (C6 or C9), 128.1 (C7 or C8), 127.8 (C11), 126.8 (C7 or C8), 124.0 (C3), 57.7 (C13), 22.7 (C14), 19.9 (C12); ESI-MS m/z = 569.22 ($2M+Na^+$, 62.0), 547.24 ($2M+H^+$, 7.9), 296.10 ($M+Na^+$, 100), 274.12 ($M+H^+$, 84.3); HRMS (ESI) m/z = 296.1072 (calculated for $C_{16}H_{19}NOSNa^+$ = 296.1080). Data consistent with literature.[164]

(*S*$_S$,*E*)-2-methyl-*N*-(1-phenyloctylidene)propane-2-sulfinamide (238k)



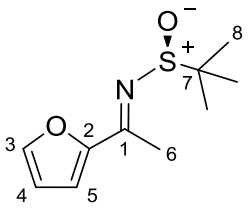
General procedure A was followed using octanophenone **237k** (1.44 mL, 6.6 mmol, 1.0 eq.), titanium (IV) ethoxide (4.15 mL, 19.8 mmol, 3.0 eq.) and (*S*)-(-)-*tert*-butyl-sulfinamide **32** (880 mg, 7.26 mmol, 1.1 eq.) in anhydrous THF (40 mL). The crude product was obtained as a yellow oil and purified by flash column chromatography over silica gel (eluting with 3:1 petroleum ether/ethyl acetate) to give **238k** (1.24 g, 4.03 mmol, 61%; single isomer) as a yellow oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3062, 3012 (C-H_{aro}), 2926, 2856 (C-H_{ali}), 1642 (C=N), 1075 (S-O); $[\alpha]_D^{22}$ = 37.9 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.84 (2H, d, *J* = 7.0, 10-H), 7.50-7.39 (3H, m, 11-H and 12-H), 3.27-3.20 (1H, m, 2-H_a), 3.14-3.05 (1H, m, 2-H_b), 1.73-1.58 (2H, m, 3-H), 1.50-1.38 (2H, m, 4-H), 1.30 (9H, s, 14-H), 1.30-1.19 (6H, m, 5-H, 6-H and 7-H), 0.85 (3H, t, *J* = 6.9, 8-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 180.4 (C1), 138.0 (C9), 131.5 (C10 or C11 or C12), 128.6 (C10 or C11 or C12), 127.5 (C10 or C11 or C12), 57.4 (C13), 32.6 (C2), 31.7 (C3), 29.9 (C4), 29.0 (C5), 28.8 (C6), 22.7 (C7), 22.6 (C14), 14.1 (C8); ESI-MS m/z = 637.38 (2M+Na^+, 73.4), 615.40 (2M+H^+, 8.4), 330.18 (M+Na^+, 100), 308.20 (M+H^+, 68.3); HRMS (ESI) m/z = 330.1876 (calculated for $C_{18}H_{29}NOSNa^+$ = 330.1862).

(S_S,*E*)-*N*-(cyclopropyl(phenyl)methylene)-2-methylpropane-2-sulfinamide (238l)



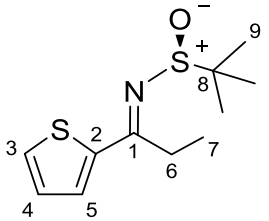
General procedure A was followed using phenyl cyclopropyl ketone **237l** (912 μL, 6.6 mmol, 1.0 eq.), titanium (IV) ethoxide (4.15 mL, 19.8 mmol, 3.0 eq.) and (*S*)-(-)-*tert*-butyl-sulfinamide **32** (880 mg, 7.26 mmol, 1.1 eq.) in anhydrous THF (30 mL). The crude product was obtained as a yellow oil and purified by flash column chromatography over silica gel (eluting with 1:1 petroleum ether/ethyl acetate) to give **238l** (1.15 g, 4.62 mmol, 70%; 1:16 *cis* vs. *trans*) as a yellow solid, m.p. = 41-43 °C. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3082, 3002 (C-H_{aro}), 2959, 2865 (C-H_{ali}), 1668 (C=N), 1073 (S-O); $[\alpha]_D^{19}$ = -6.6 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.51-7.43 (2H, m, 3-H), 7.42-7.38 (3H, m, 4-H and 5-H), 2.36-1.88 (1H, m, 6-H), 1.18 (9H, s, 10-H), 1.15-0.99 (4H, m, 7-H and 8-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 188.8 (C1), 138.2 (C2), 139.9 (C3 or C4 or C5), 128.3 (C3 or C4 or C5), 127.3 (C3 or C4 or C5), 56.1 (C9), 22.7 (C6), 22.1 (C10), 12.3 (C7 or C8), 11.7 (C7 or C8); ESI-MS m/z = 521.22 ($2M+Na^+$, 28.0), 499.24 ($2M+H^+$, 3.3), 272.10 ($M+Na^+$, 100), 250.12 ($M+H^+$, 43.6); HRMS (ESI) m/z = 272.1074 (calculated for $C_{14}H_{19}NOSNa^+$ = 272.1080).

(S_S,*E*)-*N*-(1-(furan-2-yl)ethylidene)-2-methylpropane-2-sulfinamide (238m)



General procedure A was followed using 2-acetyl furan **237m** (702 μL, 7 mmol, 1.0 eq.), titanium (IV) ethoxide (4.4 mL, 21 mmol, 3.0 eq.) and (*S*)-(-)-*tert*-butyl-sulfinamide **32** (933 mg, 7.7 mmol, 1.1 eq.) in anhydrous THF (30 mL). The crude product was obtained as a yellow oil and purified by flash column chromatography over silica gel (eluting with 6:1 petroleum ether/ethyl acetate) to afford **238m** (1.34 g, 6.3 mmol, 90%; single isomer) as a yellow oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2960, 2866 (C-H_{ali}), 1674 (C=N), 1225, 1029 (C-O-C), 1068 (S-O); $[\alpha]_D^{20}$ = 19.0 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.56 (1H, dd, *J* = 1.7 and 0.7, 3-H), 7.05 (1H, dd, *J* = 3.4 and 0.7, 5-H), 6.51 (1H, dd, *J* = 3.4 and 1.7, 4-H), 2.65 (3H, s, 6-H), 1.29 (9H, s, 8-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 166.3 (C1), 153.3 (C2), 145.9 (C3), 114.7 (C4 or C5), 112.5 (C4 or C5), 57.7 (C7), 22.6 (C8), 18.9 (C6); ESI-MS m/z = 449.15 (2M+Na^+, 87.9), 236.08 (M+Na^+, 100), 214.09 (M+H^+, 29.0); HRMS (ESI) m/z = 236.0726 (calculated for $C_{10}H_{15}NO_2SNa^+$ = 236.0716).

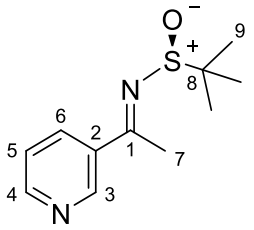
(S_S,*E*)-2-methyl-*N*-(1-(thiophen-2-yl)propylidene)propane-2-sulfinamide (238n)



General procedure A was followed using 2-propionyl thiophene **237n** (411 μL, 3.3 mmol, 1.0 eq.), titanium (IV) ethoxide (2.08 mL, 9.9 mmol, 3.0 eq.) and (*S*)-(-)-*tert*-butyl-sulfinamide **32** (440 mg, 3.63 mmol, 1.1 eq.) in anhydrous THF (35 mL). The crude product was obtained as a yellow oil and purified by flash column

chromatography over silica gel (eluting with 5:1 petroleum ether/ethyl acetate) to give **238n** (490 mg, 2.01 mmol, 61%; 1:8 *cis* vs. *trans*) as a pale yellow oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2937, 2874 (C-H_{ali}), 1665 (C=N), 1067 (S-O); $[\alpha]_D^{19}$ = -51.8 (*c* = 0.1 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.50 (1H, dd, *J* = 3.8 and 1.1, 3-H), 7.47 (1H, dd, *J* = 5.1 and 1.1, 5-H), 7.07 (1H, dd, *J* = 5.1 and 3.8, 4-H), 3.23-3.05 (2H, m, 6-H), 1.35 (3H, t, *J* = 7.7, 7-H), 1.29 (9H, s, 9-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 175.6 (C1), 145.0 (C2), 132.1 (C3), 129.5 (C4 or C5), 128.0 (C4 or C5), 57.6 (C8), 27.8 (C6), 22.6 (C9), 13.8 (C7); ESI-MS m/z = 509.13 ($2M+Na^+$, 32.8), 487.15 ($2M+H^+$, 2.4), 266.06 ($M+Na^+$, 100), 244.08 ($M+H^+$, 45.1); HRMS (ESI) m/z = 266.0642 (calculated for $C_{11}H_{17}NOS_2Na^+$ = 266.0644). Data consistent with literature.[111]

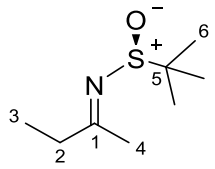
(*S*$_S$,*E*)-2-methyl-*N*-(1-(pyridin-3-yl)ethylidene)propane-2-sulfinamide (238o)



General procedure A was followed using 3-acetyl pyridine **237o** (726 μL, 6.6 mmol, 1.0 eq.), titanium (IV) ethoxide (4.15 mL, 19.8 mmol, 3.0 eq.) and (*S*)-(-)-*tert*-butyl-sulfinamide **32** (880 mg, 7.26 mmol, 1.1 eq.) in anhydrous THF (40 mL). The crude product was obtained as a yellow oil and purified by flash column chromatography over silica gel (eluting with 1:1 petroleum ether/ethyl acetate) to afford **238o** (1.33 g, 5.94 mmol, 90%; single isomer) as a yellow amorphous solid. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3037, 3009 (C-H_{pyr}), 2960, 2866 (C-H_{ali}), 1643 (C=N), 1071 (S-O); $[\alpha]_D^{19}$ = -21.3 (*c* = 0.1 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ_H = 9.06 (1H, s, 3-H), 8.67 (1H, dd, *J* = 4.8 and 1.5, 4-H), 8.13 (1H, dd, *J* = 8.1 and 1.5, 6-H), 7.34 (1H, ddd, *J* = 8.1, 4.8 and 0.8, 5-H), 2.77 (3H, s, 7-H), 1.30 (9H, s, 9-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 174.4 (C1), 152.3 (C3), 148.7 (C4),

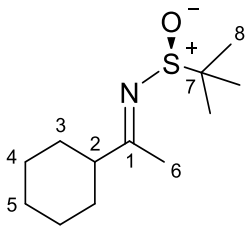
134.5 (C6), 134.3 (C2), 123.4 (C5), 57.9 (C8), 22.6 (C9), 19.7 (C7); ESI-MS m/z = 471.18 ($2M+Na^+$, 10.7), 449.20 ($2M+H^+$, 4.8), 247.08 ($M+Na^+$, 35.6), 225.10 ($M+H^+$, 100); HRMS (ESI) m/z = 225.1057 (calculated for $C_{11}H_{17}N_2OS^+$ = 225.1056).

(*S*$_S$,*E*)-*N*-(butan-2-ylidene)-2-methylpropane-2-sulfinamide (238p)



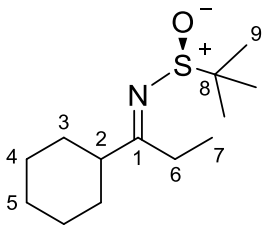
General procedure A was followed using 2-butanone **237p** (627 μL, 7 mmol, 1.0 eq.), titanium (IV) ethoxide (4.4 mL, 21 mmol, 3.0 eq.) and (*S*)-(-)-*tert*-butyl-sulfinamide **32** (933 mg, 7.7 mmol, 1.1 eq.) in anhydrous THF (35 mL). The crude product was obtained as a colourless oil and purified by flash column chromatography over silica gel (eluting with 6:1 petroleum ether/ethyl acetate) to give **238p** (1 g, 5.74 mmol, 82%; 1:6 *cis* vs. *trans*) as a colourless oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2932, 2872 (C-H_{ali}), 1642 (C=N), 1073 (S-O); $[\alpha]_D^{19}$ = 163.1 (*c* = 0.1 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ_H = 2.37 (2H, m, 2-H), 2.25 (3H, s, 4-H), 1.21 (9H, s, 6-H), 1.08 (3H, t, *J* = 7.3, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 186.1 (C1), 56.3 (C5), 36.7 (C2), 22.8 (C4), 22.2 (C6), 9.9 (C3); ESI-MS m/z = 373.19 ($2M+Na^+$, 100), 351.21 ($2M+H^+$, 16.8), 198.09 ($M+Na^+$, 14.4); HRMS (ESI) m/z = 373.1953 (calculated for $C_{16}H_{34}N_2O_2S_2{}^+Na$ = 373.1954). Data consistent with literature.[39]

(*S*$_S$,*E*)-*N*-(1-cyclohexylethylidene)-2-methylpropane-2-sulfinamide (238q)



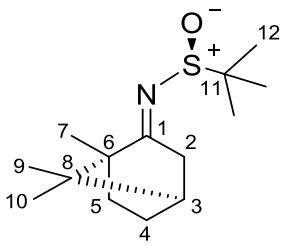
General procedure A was followed using cyclohexyl methyl ketone **237q** (963 μL, 7 mmol, 1.0 eq.), titanium (IV) ethoxide (4.4 mL, 21 mmol, 3.0 eq.) and (*S*)-(-)-*tert*-butyl-sulfinamide **32** (933 mg, 7.7 mmol, 1.1 eq.) in anhydrous THF (35 mL). The crude product was obtained as a colourless oil and purified by flash column chromatography over silica gel (eluting with 5:1 petroleum ether/ethyl acetate) to afford **238q** (1.08 g, 4.69 mmol, 67%; single isomer) as a colourless oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2929, 2854 (C-H_{ali}), 1632 (C=N), 1076 (S-O); $[\alpha]_D^{22}$ = 206.3 (*c* = 0.1 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ_H = 2.25 (3H, s, 6-H), 2.21-2.11 (1H, m, 2-H), 1.85-1.70 (4H, m, 3-H), 1.67-1.59 (1H, m, 4-H), 1.34-1.23 (3H, m, 4-H), 1.22-1.19 (1H, m, 5-H_a), 1.18 (9H, s, 8-H), 1.16-1.07 (1H, m, 5-H_b); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 188.5 (C1), 56.4 (C7), 51.3 (C2), 30.2 (C3 or C4 or C5), 30.0 (C3 or C4 or C5), 26.0 (C3 or C4 or C5), 22.2 (C8), 21.5 (C6); ESI-MS m/z = 481.29 ($2M+Na^+$, 71.3), 459.30 ($2M+H^+$, 14.6), 252.13 ($M+Na^+$, 53.0), 230.15 ($M+H^+$, 100); HRMS (ESI) m/z = 230.1577 (calculated for $C_{12}H_{24}NOS^+$ = 230.1573).

(S_S,*E*)-*N*-(1-cyclohexylpropylidene)-2-methylpropane-2-sulfinamide (238r)



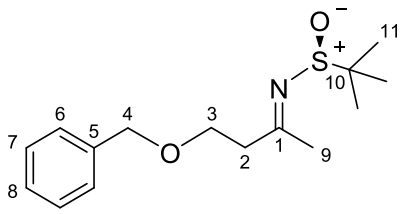
General procedure A was followed using cyclohexyl ethyl ketone **237r** (1.02 mL, 6.6 mmol, 1.0 eq.), titanium (IV) ethoxide (4.15 mL, 19.8 mmol, 3.0 eq.) and (*S*)-(-)-*tert*-butyl-sulfinamide **32** (880 mg, 7.26 mmol, 1.1 eq.) in anhydrous THF (35 mL). The crude product was obtained as a pale yellow oil and purified by flash column chromatography over silica gel (eluting with 5:1 petroleum ether/ethyl acetate) to give **238r** (932 mg, 3.83 mmol, 58%; 1:4 *cis* vs. *trans*) as a pale yellow oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2929, 2854 (C-H_{ali}), 1644 (C=N), 1077 (S-O); $[\alpha]_D^{22}$ = 78.4 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 2.77-2.60 (2H, m, 6-H), 2.46-2.20 (1H, m, 2-H), 1.86-1.73 (3H, m, 3-H), 1.71-1.63 (1H, m, 3-H), 1.41-1.20 (6H, m, 4-H and 5-H), 1.21 (9H, s, 9-H), 1.19-1.12 (3H, m, 7-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 192.6 (C1), 56.5 (C8), 48.9 (C2), 30.8 (C6), 28.5 (C3 or C4 or C5), 26.2 (C3 or C4 or C5), 26.0 (C3 or C4 or C5), 22.4 (C9), 12.0 (C7); ESI-MS m/z = 266.15 ($M+Na^+$, 100), 244.17 ($M+H^+$, 30.0); HRMS (ESI) m/z = 266.1551 (calculated for $C_{13}H_{25}NOSNa^+$ = 266.1549). Data consistent with literature.[111]

(*S*S)-2-methyl-*N*-((1*R*,4*R*,*E*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)propane-2-sulfinamide (238s)



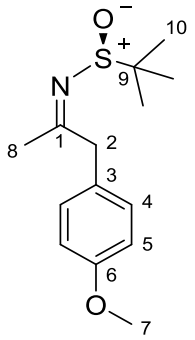
General procedure A was followed using (*R*)-(+)-camphor **237s** (989 g, 6.5 mmol, 1.0 eq.), titanium (IV) ethoxide (4.09 mL, 19.5 mmol, 3.0 eq.) and (*S*)-(-)-*tert*-butyl-sulfinamide **32** (867 mg, 7.15 mmol, 1.1 eq.) in anhydrous THF (40 mL). The crude product was obtained as a deep yellow oil and purified by flash column chromatography over silica gel (eluting with 4:1 petroleum ether/ethyl acetate) to afford **238s** (166 mg, 650 μmol, 10%; 1:2 *cis* vs. *trans*) as a clear yellow oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2977, 2966, 2891, 2844 (C-H_{ali}), 1711 (C=N), 1089 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 3.13-3.04 (1H, m, 3-H), 2.27 (1H, dd, *J* = 18.8, 5.0, 2-H_a), 1.97 (1H, dd, *J* = 18.8, 4.4, 2-H_b), 1.90-1.81 (1H, m, 5-H_a), 1.78-1.68 (1H, m, 5-H_b), 1.38 (1H, ddd, *J* = 13.2, 9.4 and 4.1, 4-H_a), 1.32-1.26 (1H, m, 4-H_b), 1.23 (9H, s, 12-H), 0.97 (3H, s, 7-H or 9-H or 10-H), 0.94 (3H, s, 7-H or 9-H or 10-H), 0.84 (3H, s, 7-H or 9-H or 10-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 194.6 (C1), 57.5 (C6 or C8 or C11), 57.0 (C6 or C8 or C11), 47.4 (C6 or C8 or C11), 44.3 (C3), 40.0 (C2 or C4 or C5), 32.3 (C2 or C4 or C5), 27.1 (C2 or C4 or C5), 22.6 (C12), 19.8 (C7 or C9 or C10), 19.1 (C7 or C9 or C10), 11.3 (C7 or C9 or C10); ESI-MS m/z = 533.32 (2M+Na^+, 14.2), 511.33 (2M+H^+, 2.2), 278.15 (M+Na^+, 11.0), 256.17 (M+H^+, 100); HRMS (ESI) m/z = 256.1734 (calculated for $C_{14}H_{26}NOS^+$ = 256.1730).

(*S*$_S$,*E*)-*N*-(4-(benzyloxy)butan-2-ylidene)-2-methylpropane-2-sulfinamide (238t)



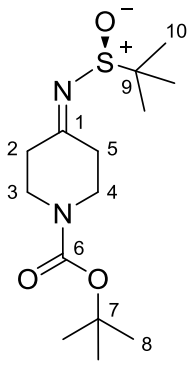
General procedure A was followed using 4-benzyloxy-2-butanone **237t** (573 μL, 3.3 mmol, 1.0 eq.), titanium (IV) ethoxide (2.08 mL, 9.9 mmol, 3.0 eq.) and (*S*)-(-)-*tert*-butyl-sulfinamide **32** (440 mg, 3.63 mmol, 1.1 eq.) in anhydrous THF (40 mL). The crude product was obtained as a yellow oil and purified by flash column chromatography over silica gel (eluting with 3:1 petroleum ether/ethyl acetate) to afford **238t** (743 mg, 2.64 mmol, 80%; 1:6 *cis* vs. *trans*) as a yellow oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3055, 3011 (C-H_{aro}), 2959, 2867 (C-H_{ali}), 1713 (C=N), 1171, 1029 (C-O-C), 1083 (S-O); $[\alpha]_D^{22}$ = 63.4 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.36-7.27 (5H, m, 6-H, 7-H and 8-H), 4.50 (2H, s, 4-H), 3.84-3.74 (2H, m, 3-H), 2.80-2.67 (2H, m, 2-H), 2.34 (3H, s, 9-H), 1.21 (9H, s, 11-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 183.0 (C1), 138.1 (C5), 128.5 (C6 or C7), 127.8 (C6 or C7 and C8), 73.3 (C4), 66.7 (C3), 56.6 (C10), 43.3 (C2), 23.6 (C9), 22.3 (C11); ESI-MS m/z = 585.27 ($2M+Na^+$, 6.1), 304.13 ($M+Na^+$, 66.2), 282.15 ($M+H^+$, 100); HRMS (ESI) m/z = 282.1521 (calculated for $C_{15}H_{24}NO_2S^+$ = 282.1522).

(*S*$_S$,*Z*)-*N*-(1-(4-methoxyphenyl)propan-2-ylidene)-2-methylpropane-2-sulfinamide (238u)



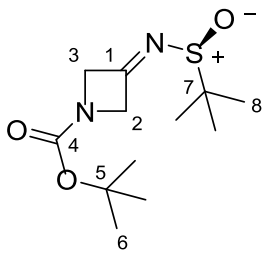
General procedure A was followed using 4-methoxyphenylacetone **237u** (539 μL, 3.5 mmol, 1.0 eq.), titanium (IV) ethoxide (2.2 mL, 10.5 mmol, 3.0 eq.) and (*S*)-(-)-*tert*-butyl-sulfinamide **32** (467 mg, 3.85 mmol, 1.1 eq.) in anhydrous THF (40 mL). The crude product was obtained as a yellow oil and purified by flash column chromatography over silica gel (eluting with 5:1 petroleum ether/ethyl acetate) to give **238u** (739 mg, 2.77 mmol, 79%) as a yellow oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3088, 3021 (C-H_{aro}), 2959, 2837 (C-H_{ali}), 1651 (C=N), 1249, 1033 (C-O-C), 1067 (S-O); $[\alpha]_D^{19}$ = 54.2 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.14-7.08 (2H, m, 4-H or 5-H), 6.88-6.81 (2H, m, 4-H or 5-H), 3.78 (3H, s, 7-H), 3.67-3.54 (2H, m, 2-H), 2.26 (3H, s, 8-H), 1.19 (9H, s, 10-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 183.8 (C1), 158.8 (C6), 130.4 (C4 or C5), 127.8 (C3), 114.2 (C4 or C5), 56.7 (C9), 55.4 (C7), 49.4 (C2), 29.2 (C8), 22.3 (C10); ESI-MS m/z = 557.24 ($2M+Na^+$, 12.2), 290.11 ($M+Na^+$, 100), 268.13 ($M+H^+$, 53.2); HRMS (ESI) m/z = 290.1179 (calculated for $C_{14}H_{21}NO_2SNa^+$ = 290.1185).

***Tert*-butyl-(S_S)-4-((*tert*-butylsulfinyl)imino)piperidine-1-carboxylate (238v)**



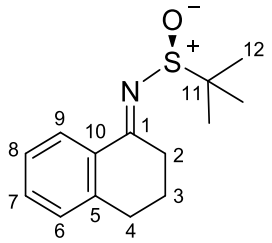
General procedure A was followed using *N*-(*tert*-butoxycarbonyl)-4-piperidone **237v** (2.49 g, 12.5 mmol, 1.0 eq.), titanium (IV) ethoxide (7.86 mL, 37.5 mmol, 3.0 eq.) and (*S*)-(-)-*tert*-butyl-sulfinamide **32** (1.67 g, 13.75 mmol, 1.1 eq.) in anhydrous THF (30 mL). The crude product was obtained as a yellow oil and purified by flash column chromatography over silica gel (eluting with 1:1 petroleum ether/ethyl acetate) to afford **238v** (2.3 g, 7.63 mmol, 61%) as a pale yellow oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2975, 2928, 2869 (C-H_{ali}), 1691 (C=O), 1653 (C=N), 1071 (S-O); $[\alpha]_D^{23}$ = +88.1 (*c* = 1.0 g/100 mL in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 3.70 (2H, dt, *J* = 12.3 and 6.3, 3-H or 4-H), 3.58 (2H, app. ddd, *J* = 13.8, 7.7 and 6.1, 3-H or 4-H), 3.10 (1H, ddd, *J* = 14.8, 6.3 and 5.0, 5-H_a), 2.82 (1H, ddd, *J* = 14.8, 7.7 and 5.1, 5-H_b), 2.52 (1H, t, *J* = 6.1, 2-H_a), 2.44 (1H, t, *J* = 6.1, 2-H_b), 1.46 (9H, s, 8-H), 1.24 (9H, s, 10-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 183.5 (C1), 154.5 (C6), 80.4 (C7), 56.7 (C9), 41.3 (C3 or C4), 39.6 (C3 or C4), 33.7 (C2 and C5), 28.5 (C8), 22.3 (C10); ESI-MS m/z = 627.32 (2M+Na^+, 18.2), 325.15 (M+Na^+, 100), 303.17 (M+H^+, 39.3); HRMS (ESI) m/z = 325.1568 (calculated for $C_{14}H_{26}N_2NaO_3S^+$ = 325.1556).

***Tert*-butyl-(S_S)-3-((*tert*-butylsulfinyl)imino)azetidine-1-carboxylate (238w)**



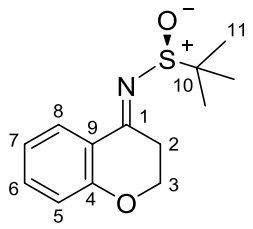
General procedure A was followed using *tert*-butyl 3-oxoazetidine-1-carboxylate **237w** (199 mg, 1.16 mmol, 1.0 eq.), titanium (IV) ethoxide (730 μL, 3.48 mmol, 3.0 eq.) and (*S*)-(-)-*tert*-butyl-sulfinamide **32** (155 mg, 1.28 mmol, 1.1 eq.) in anhydrous THF (25 mL). The crude product was obtained as a deep yellow oil and purified by flash column chromatography over silica gel (eluting with 3:1 petroleum ether/ethyl acetate) to give **238w** (185 mg, 673 μmol, 58%; 1:2 *cis* vs. *trans*) as a clear yellow oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2977, 2930, 2869 (C-H_{ali}), 1828 (C=O), 1710 (C=N), 1057 (S-O); $[\alpha]_D^{23}$ = +67.8 (*c* = 1.0 g/100 mL in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.18-5.08 (1H, m, 2-H_a or 3-H_a), 5.00-4.93 (1H, m, 2-H_b or 3-H_b), 4.75 (2H, t, *J* = 2.7, 2-H or 3-H), 1.45 (9H, s, 6-H), 1.25 (9H, s, 8-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 171.5 (C1), 156.0 (C4), 80.7 (C5), 65.3 (C2 or C3), 60.5 (C2 or C3), 58.2 (C7), 28.4 (C6), 22.5 (C8); ESI-MS m/z = 571.25 ($2M+Na^+$, 23.9), 297.12 ($M+Na^+$, 100); HRMS (ESI) m/z = 297.1245 (calculated for $C_{12}H_{22}N_2NaO_3S^+$ = 297.1243).

(*S*S)-*N*-(3,4-dihydronaphthalen-1(2H)-ylidene)-2-methylpropane-2-sulfinamide (238x)



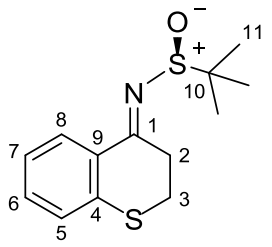
General procedure A was followed using 1-tetralone **237x** (4.97 g, 34 mmol, 1.0 eq.), titanium (IV) ethoxide (21.38 mL, 102 mmol, 3.0 eq.) and (*S*)-(-)-*tert*-butyl-sulfinamide **32** (4.53 g, 37.4 mmol, 1.1 eq.) in anhydrous THF (150 mL). The crude product was obtained as a deep brown oil and purified by flash column chromatography over silica gel (eluting with 4:1 petroleum ether/ethyl acetate) to afford **238x** (7.29 g, 29.24 mmol, 86%; single isomer) as a clear brown oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3063, 3024 (C-H_{aro}), 2978, 2947, 2866 (C-H_{ali}), 1651 (C=N), 1081 (S-O); $[\alpha]_D^{23}$ = -33.7 (*c* = 0.1 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ_H = 8.17 (1H, dd, *J* = 7.7 and 1.3, 9-H), 7.38 (1H, td, *J* = 7.7 and 1.1, 8-H), 7.28-7.22 (1H, m, 7-H), 7.18 (1H, dd, *J* = 7.6 and 1.1, 6-H), 3.29 (1H, ddd, *J* = 17.5, 9.2 and 4.8, 2-H_a), 3.06 (1H, ddd, *J* = 17.5, 7.4 and 4.5, 2-H_b), 2.92-2.83 (2H, m, 4-H), 2.09-1.91 (2H, m, 3-H), 1.33 (9H, s, 12-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 177.1 (C1), 142.4 (C10), 133.2 (C5), 132.1 (C8), 129.1 (C6), 127.2 (C9), 126.6 (C7), 57.3 (C11), 32.5 (C2), 29.7 (C4), 22.6 (C3), 22.7 (C12); ESI-MS m/z = 521.22 ($2M+Na^+$, 42.8), 272.10 ($M+Na^+$, 100), 250.12 ($M+H^+$, 16.5); HRMS (ESI) m/z = 272.1084 (calculated for $C_{14}H_{19}NOSNa^+$ = 272.1080). Data consistent with literature.[41]

(*S*S,*E*)-*N*-(chroman-4-ylidene)-2-methylpropane-2-sulfinamide (238y)



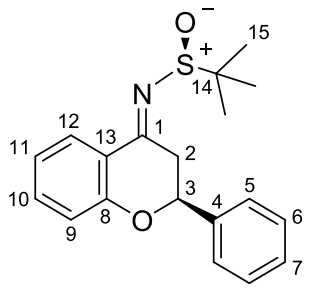
General procedure A was followed using 4-chromanone **237y** (5 g, 33.7 mmol, 1.0 eq.), titanium (IV) ethoxide (21.19 mL, 101.1 mmol, 3.0 eq.) and (*S*)-(-)-*tert*-butyl-sulfinamide **32** (4.49 g, 37.07 mmol, 1.1 eq.) in anhydrous THF (150 mL). The crude product was obtained as a deep brown oil and purified by flash column chromatography over silica gel (eluting with 3:1 petroleum ether/ethyl acetate) to give **238y** (7.7 g, 30.67 mmol, 91%; single isomer) as a clear brown oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3071, 3038 (C-H_{aro}), 2982, 2878 (C-H_{ali}), 1712 (C=N), 1231, 1109 (C-O-C), 1070 (S-O); $[\alpha]_D^{23}$ = +46.0 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.99 (1H, d, *J* = 8.2, 8-H), 7.38 (1H, app. t, *J* = 7.7, 7-H), 6.97 (1H, app. t, *J* = 7.7, 6-H), 6.91 (1H, d, *J* = 8.2, 5-H), 4.44-4.26 (2H, m, 3-H), 3.50 (1H, ddd, *J* = 17.3, 8.7 and 4.6, 2-H_a), 3.27 (1H, ddd, *J* = 17.3, 7.0 and 4.3, 2-H_b), 1.32 (9H, s, 11-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 169.8 (C1), 159.3 (C4), 134.3 (C7), 127.0 (C8), 121.4 (C6), 121.2 (C9), 118.1 (C5), 65.6 (C3), 58.1 (C10), 30.8 (C2), 22.7 (C11); ESI-MS m/z = 525.18 (2M+Na^+, 100), 274.08 (M+Na^+, 50.2), 252.10 (M+H^+, 96.1); HRMS (ESI) m/z = 525.1856 (calculated for $C_{26}H_{34}N_2NaO_4S_2^+$ = 525.1852); CHN Found: C, 61.8%; H, 6.9%; N, 5.9%. $C_{13}H_{17}NO_2S$ requires: C, 62.1%; H, 6.8%; N, 5.6%.

(*S*S,*E*)-2-methyl-*N*-(thiochroman-4-ylidene)propane-2-sulfinamide (238z)



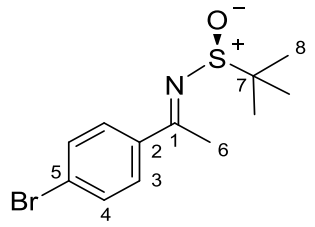
General procedure A was followed using 4-thiochromanone **237z** (6 g, 36.5 mmol, 1.0 eq.), titanium (IV) ethoxide (22.95 mL, 109.5 mmol, 3.0 eq.) and (*S*)-(-)-*tert*-butyl-sulfinamide **32** (4.87 g, 40.15 mmol, 1.1 eq.) in anhydrous THF (150 mL). The crude product was obtained as a deep green solid and purified by flash column chromatography over silica gel (eluting with 5:1 petroleum ether/ethyl acetate) to give **238z** (8.78 g, 32.85 mmol, 90%; single isomer) as a green solid, m.p. = 98-100 °C. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3056, 3016 (C-H_{aro}), 2976, 2957, 2921, 2862 (C-H_{ali}), 1680 (C=N), 1068 (S-O); $[\alpha]_D^{23}$ = +58.1 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.17 (1H, dd, *J* = 8.1 and 1.1, 8-H), 7.29 (1H, ddd, *J* = 8.2, 7.1 and 1.1, 6-H), 7.22 (1H, dd, *J* = 8.2 and 1.5, 5-H), 7.12 (1H, ddd, *J* = 8.1, 7.1 and 1.5, 7-H), 3.66 (1H, ddd, *J* = 17.2, 8.6 and 4.4, 2-H_a), 3.45 (1H, ddd, *J* = 17.2, 8.5 and 4.6, 2-H_b), 3.14-3.05 (2H, m, 3-H), 1.33 (9H, s, 11-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 172.8 (C1), 139.3 (C9), 131.8 (C6), 131.5 (C4), 129.0 (C8), 128.2 (C5), 125.1 (C7), 58.1 (C10), 32.5 (C3), 26.1 (C2), 22.8 (C11); ESI-MS m/z = 557.14 ($2M+Na^+$, 30.0), 290.06 ($M+Na^+$, 34.2), 268.08 ($M+H^+$, 100); HRMS (ESI) m/z = 268.0822 (calculated for $C_{13}H_{18}NOS_2^+$ = 268.0824); CHN Found: C, 58.7%; H, 6.2%; N, 5.0%. $C_{13}H_{17}NOS_2$ requires: C, 58.4%; H, 6.4%; N, 5.2%.

(S_S)-2-methyl-*N*-((*S*,*E*)-2-phenylchroman-4-ylidene)propane-2-sulfinamide (238aa)



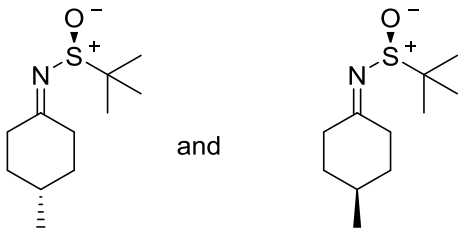
General procedure A was followed using flavanone **237aa** (5 g, 22.3 mmol, 1.0 eq.), titanium (IV) ethoxide (14 mL, 66.9 mmol, 3.0 eq.) and (*S*)-(-)-*tert*-butyl-sulfinamide **32** (2.97 g, 24.53 mmol, 1.1 eq.) in anhydrous THF (150 mL). The crude product was obtained as a yellow solid and purified by flash column chromatography over silica gel (eluting with 6:1 petroleum ether/ethyl acetate) to afford **238aa** (6.5 g, 19.85 mmol, 89%; single isomer) as a yellow solid, m.p. = 82-84 °C. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3064, 3033 (C-H_{aro}), 2977, 2921, 2863 (C-H_{ali}), 1677 (C=N), 1224, 1117 (C-O-C), 1055 (S-O); $[\alpha]_D^{23}$ = +12.4 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.02 (1H, dd, *J* = 8.2 and 1.7, Ar-H), 7.48 (2H, dd, *J* = 8.2 and 1.2, Ar-H), 7.44-7.34 (4H, m, Ar-H), 7.04-6.98 (2H, m, Ar-H), 5.24 (1H, dd, *J* = 12.9 and 2.8, 3-H), 3.80 (1H, dd, *J* = 17.5 and 2.8, 2-H_a), 3.34 (1H, dd, *J* = 17.5 and 12.9, 2-H_b), 1.32 (9H, s, 15-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 169.7 (C1), 159.1 (C4 or C8 or C13), 138.9 (C4 or C8 or C13), 134.5 (C5 or C6 or C7 or C9 or C10 or C11 or C12), 128.9 (C5 or C6 or C7 or C9 or C10 or C11 or C12), 128.8 (C5 or C6 or C7 or C9 or C10 or C11 or C12), 127.0 (C5 or C6 or C7 or C9 or C10 or C11 or C12), 126.5 (C5 or C6 or C7 or C9 or C10 or C11 or C12), 121.7 (C5 or C6 or C7 or C9 or C10 or C11 or C12), 121.0 (C4 or C8 or C13), 118.4 (C5 or C6 or C7 or C9 or C10 or C11 or C12), 78.1 (C3), 58.4 (C14), 37.7 (C2), 22.8 (C15); ESI-MS m/z = 677.24 ($2M+Na^+$, 21.8), 350.11 ($M+Na^+$, 27.3), 328.13 ($M+H^+$, 100); HRMS (ESI) m/z = 328.1370 (calculated for $C_{19}H_{22}NO_2S^+$ = 328.1366); CHN Found: C, 70.0%; H, 6.3%; N, 4.2%. $C_{19}H_{21}NO_2S$ requires: C, 69.7%; H, 6.5%; N, 4.3%.

(*S*S)-*N*-(1-(4-bromophenyl)ethylidene)-2-methylpropane-2-sulfinamide (238ab)



General procedure A was followed using 4-bromo acetophenone **237ab** (7.5 gm, 37.67 mmol, 1.0 eq.), titanium (IV) ethoxide (23.69 mL, 113 mmol, 3.0 eq.) and (*S*)-(-)-*tert*-butyl-sulfinamide **32** (5.02 g, 41.44 mmol, 1.1 eq.) in anhydrous THF (160 mL). The crude product was obtained as a yellow solid and purified by flash column chromatography over silica gel (eluting with 3:1 petroleum ether/ethyl acetate) to afford **238ab** (9.9 g, 32.77 mmol, 87%; single isomer) as a yellow solid, m.p. = 101-103 °C. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3064, 3056, 3033 (C-H_{aro}), 2978, 2922, 2863 (C-H_{ali}), 1685 (C=N), 1062 (S-O), 1091 (C-Br); $[\alpha]_D^{19}$ = -57.9 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.73 (2H, d, *J* = 8.5, 4-H), 7.54 (2H, d, *J* = 8.5, 3-H), 2.73 (3H, s, 6-H), 1.30 (9H, s, 8-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 175.3 (C1), 137.7 (C2 or C5), 131.8 (C3), 128.9 (C4), 126.6 (C2 or C5), 57.7 (C7), 22.7 (C8), 19.7 (C6); ESI-MS m/z = 629.01 ($2M+Na^+$, 15.3), 326.00 ($M+Na^+$, 100), 304.01 ($M+H^+$, 78.1); HRMS (ESI) m/z = 326.0002 (calculated for $C_{12}H_{16}{}^{81}BrNNaOS^+$ = 326.0008); CHN Found: C, 48.0%; H, 5.1%; N, 4.3%, $C_{12}H_{16}BrNOS$ requires: C, 47.7%; H, 5.3%; N, 4.6%. Data consistent with literature.[41]

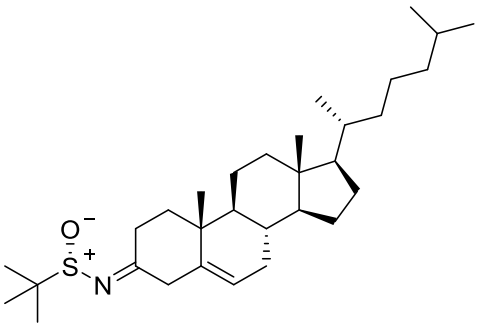
(*S*S)-2-methyl-*N*-((*R*,*Z*)-4-methylcyclohexylidene)propane-2-sulfinamide (A-238ad) and (*S*S)-2-methyl-*N*-((*S*,*E*)-4-methylcyclohexylidene) propane-2-sulfinamide (B-238ad)



A-238ad **B-238ad**

General procedure A was followed using a racemic mixture of 4-methylcyclohexanone **237ad** (1.09 mL, 8.9 mmol, 1.0 eq.), titanium (IV) ethoxide (5.6 mL, 26.7 mmol, 3.0 eq.) and (*S*)-(-)-*tert*-butyl-sulfinamide **32** (1.19 g, 9.79 mmol, 1.1 eq.) in anhydrous THF (50 mL). The crude product was obtained as a deep yellow oil and purified by flash column chromatography over silica gel (eluting with 1:1 petroleum ether/ethyl acetate) affording **238ad** (1.26 g, 5.87 mmol, 66%; 1:1 mixture of sulfinimine isomers) as a yellow oil. The peaks have been reported according to both isomers. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2955, 2927, 2905, 2868 (C-H_{ali}), 1711 (C=N), 1031 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 3.42 (0.5H, ddd, *J* = 14.2, 6.1 and 3.6), 3.31 (0.5H, ddd, *J* = 14.2, 6.1 and 3.6), 2.52 (1H, ddd, *J* = 14.2, 6.3 and 3.8), 2.41-2.31 (1.5H, m), 2.14 (0.5H, td, *J* = 13.7 and 5.0), 2.01-1.89 (2H, m), 1.81-1.71 (1H, m), 1.41-1.26 (2H, m), 1.22 (9H, s), 0.96 (3H, d, *J* = 6.5); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 189.1 (C), 188.5 (C), 56.3 (C), 55.9 (C), 40.0 (CH_2), 39.9 (CH_2), 35.8 (CH_2), 35.7 (CH_2), 35.4 (CH_2), 35.1 (CH_2), 33.6 (CH_2), 33.5 (CH_2), 31.7 (CH), 31.5 (CH), 22.23 (CH_3), 22.20 (CH_3), 21.24 (CH_3), 21.21 (CH_3); ESI-MS m/z = 453.25 (2M+Na^+, 16.2), 431.27 (2M+H^+, 11.6), 238.12 (M+Na^+, 35.8) 216.14 (M+H^+, 100); HRMS (ESI) m/z = 216.1417 (calculated for $C_{11}H_{22}NOS^+$ = 216.1417).

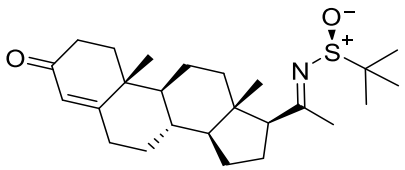
(S_S)-*N*-((8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methyl heptan-2-yl)-1,2,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3H-cyclopenta[a]phenanthren-3-ylidene)-2-methylpropane-2-sulfinamide (238ae)



General procedure A was followed using **237ae** (800 mg, 2.08 mmol, 1.0 eq.), titanium (IV) ethoxide (1.3 mL, 6.24 mmol, 3.0 eq.) and (*S*)-(-)-*tert*-butyl-sulfinamide **32** (277 mg, 2.29 mmol, 1.1 eq.) in anhydrous THF (50 mL). The crude product was obtained as a deep yellow oil and purified by flash column chromatography over silica gel (eluting with 2:1 petroleum ether/ethyl acetate) affording **238ae** (873 mg, 1.79 mmol, 86%; 1:6 *cis* vs. *trans*) as a yellow solid. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2946, 2867 (C-H_{ali}), 1680 (C=N), 1615 (C=C), 1077 (S-O); $[\alpha]_D^{23}$ = +31.4 (*c* = 1.0 g/100 mL in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.81 (1H, s), 4.34 (2H, d, *J* = 2.7), 2.58-2.47 (1H, m), 2.44-2.34 (1H, m), 2.10-2.01 (3H, m), 1.99-1.89 (2H, m), 1.83 (1H, ddd, *J* = 13.0, 7.6 and 3.9), 1.72 (1H, dd, *J* = 14.3 and 4.5), 1.68-1.61 (2H, m), 1.48 (9H, s), 1.37 (3H, s), 1.33-1.22 (5H, m), 1.23-1.19 (1H, m), 1.18-1.14 (3H, m), 1.13-1.08 (3H, m), 1.06-0.96 (3H, m), 0.91 (3H, d, *J* = 6.5), 0.87 (3H, d, *J* = 1.8), 0.85 (3H, d, *J* = 1.8), 0.74 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 200.6 (C), 168.6 (C), 126.5 (CH), 73.4 (CH), 59.2 (C), 56.3 (CH), 56.0 (CH), 53.8 (CH), 42.7 (C), 39.7 (CH_2), 39.6 (CH_2), 38.7 (CH_2), 38.1 (C), 37.2 (CH_2), 36.3 (CH_2), 35.9 (CH), 34.4 (CH_2), 29.9 (CH), 28.3 (CH_2), 28.2 (CH_2), 24.34 (CH_2), 24.28 (CH_3), 24.0 (CH_2), 23.0 (CH_3), 22.7 (CH_3), 21.1 (CH_2), 19.7 (CH_3), 18.8 (CH_3), 12.2 (CH_3); ESI-MS m/z = 488.39

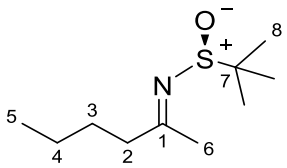
(M+H$^+$, 100); HRMS (ESI) m/z = 488.3926 (calculated for $C_{31}H_{54}NOS^+$ = 488.3921).

(*S*$_S$)-*N*-1-((8*S*,9*S*,10*R*,13*S*,14*S*,17*S*)-10,13-dimethyl-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethyl idene)-2-methylpropane-2-sulfinamide (238af)



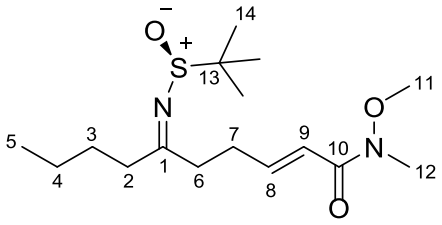
General procedure A was followed using **237af** (2.99 g, 9.5 mmol, 1.0 eq.), titanium (IV) ethoxide (6 mL, 28.5 mmol, 3.0 eq.) and (*S*)-(-)-*tert*-butyl-sulfinamide **32** (1.27 g, 10.45 mmol, 1.1 eq.) in anhydrous THF (70 mL). The crude product was obtained as a deep yellow oil and purified by flash column chromatography over silica gel (eluting with 3:1 petroleum ether/ethyl acetate) affording **238af** (3.06 g, 7.32 mmol, 77%; 1:1 *cis* vs. *trans*) as a yellow oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2963, 2939, 2875, 2856 (C-H_{ali}), 1698 (C=O), 1659 (C=N), 1612 (C=C), 1055 (S-O); $[\alpha]_D^{23}$ = +16.3 (*c* = 1.0 g/100 mL in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.91 (1H, s), 2.65-2.42 (2H, m), 2.39-2.14 (4H, m), 2.10 (3H, s), 2.03 (1H, d, *J* = 8.1), 1.98-1.76 (3H, m), 1.73-1.63 (2H, m), 1.61-1.49 (3H, m), 1.46-1.37 (2H, m), 1.32-1.22 (1H, m), 1.21 (9H, s), 1.11 (3H, d, *J* = 7.6), 1.05-0.85 (2H, m), 0.63 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 209.5 (C), 178.2 (C), 165.5 (C), 124.2 (CH), 63.6 (CH), 56.1 (CH), 53.5 (CH), 44.0 (C), 38.8 (CH_2), 35.7 (CH), 35.4 (CH_2), 33.3 (CH_2), 32.8 (CH_2), 32.3 (CH_2), 31.6 (CH_3), 26.7 (CH_2), 24.4 (CH_2), 22.9, (C) 22.4 (C), 22.3 (CH_3), 21.3 (CH_2), 17.7 (CH_3), 13.4 (CH_3); ESI-MS m/z = 857.53 (2M+Na$^+$, 19.0), 835.55 (2M+H$^+$, 16.9), 440.25 (M+Na$^+$, 63.0), 418.27 (M+H$^+$, 100); HRMS (ESI) m/z = 418.2772 (calculated for $C_{25}H_{40}NO_2S^+$ = 418.2774).

(*S*$_S$,*E*)-*N*-(hexan-2-ylidene)-2-methylpropane-2-sulfinamide (370)



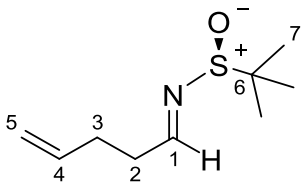
General procedure A was followed using 2-hexanone **371** (1.23 mL, 10 mmol, 1.0 eq.), titanium (IV) ethoxide (6.29 mL, 30 mmol, 3.0 eq.) and (*S*)-(-)-*tert*-butyl-sulfinamide **32** (1.33 g, 11 mmol, 1.1 eq.) in anhydrous THF (30 mL). The crude product was obtained as a deep brown oil and purified by flash column chromatography over silica gel (eluting with 4:1 petroleum ether/ethyl acetate) to afford **370** (1.67 g, 8.2 mmol, 82%; 1:25 *cis* vs. *trans*) as a clear brown oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2957, 2929, 2870 (C-H_{ali}), 1720 (C=N), 1071 (S-O); $[\alpha]_D^{23}$ = -11.4 (*c* = 1.0 g/100 mL in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$), *E*-isomer δ_H = 2.41-2.29 (2H, m, 2-H), 2.25 (3H, s, 6-H), 1.54-1.46 (2H, m, 3-H), 1.37-1.23 (2H, m, 4-H), 1.17 (9H, s, 8-H), 0.85 (3H, t, *J* = 7.4, 5-H); *Z*-isomer δ_H = 2.13-2.07 (2H, m, 2-H), 2.64 (3H, t, *J* = 7.9, 6-H), 1.54-1.46 (2H, m, 3-H), 1.37-1.23 (2H, m, 4-H), 1.17 (9H, s, 8-H), 0.85 (3H, t, *J* = 7.4, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 185.6 (C1), 56.2 (C7), 43.2 (C2), 27.7 (C3), 22.9 (C6), 22.2 (C4), 22.1 (C8), 13.9 (C5); ESI-MS m/z = 429.25 ($2M+Na^+$, 28.3), 226.12 ($M+Na^+$, 100), 204.14 ($M+H^+$, 15.7); HRMS (ESI) m/z = 226.1240 (calculated for $C_{10}H_{21}NOSNa^+$ = 226.1236). Data consistent with literature.[23]

(2*E*,6*Z*)-6-(((*S*$_S$)-*tert*-butylsulfinyl)imino)-*N*-methoxy-*N*-methyldec-2-enamide (404)



General procedure A was followed using **417** (1 g, 4.4 mmol, 1.0 eq.), titanium (IV) ethoxide (2.77 mL, 13.2 mmol, 3.0 eq.) and (*S*)-(-)-*tert*-butyl-sulfinamide **32** (587 mg, 4.84 mmol, 1.1 eq.) in anhydrous THF (30 mL). The crude product was obtained as a deep yellow oil and purified by flash column chromatography over silica gel (eluting with 2:1 petroleum ether/ethyl acetate) to afford **404** (131 mg, 396 μmol, 9%; 1:20 *cis* vs. *trans*) as a pale yellow oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2945, 2908, 2887, 2860, 2838 (C-H_{ali}), 1666 (C=N), 1651 (C=O), 1622 (C=C), 1087 (S-O); $[\alpha]_D^{23}$ = -44.7 (*c* = 1.0 g/100 mL in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 6.31-6.25 (1H, m, 8-H), 6.20-6.14 (1H, m, 9-H), 3.64 (3H, s, 11-H or 12-H), 3.22 (3H, s, 11-H or 12-H), 2.95-2.84 (2H, m, 7-H), 2.64 (2H, t, *J* = 7.1, 2-H or 6-H), 2.45 (2H, t, *J* = 7.6, 2-H or 6-H), 1.41-1.22 (4H, m, 3-H and 4-H), 0.95 (3H, t, *J* = 7.0, 5-H), 1.19 (9H, s, 14-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 187.2 (C1), 156.9 (C10), 131.2 (C8), 129.1 (C9), 56.8 (C13), 54.1 (C11), 50.2 (C12), 33.6 (C2 or C6 or C7), 29.1 (C2 or C6 or C7), 28.2 (C2 or C6 or C7), 26.3 (C3 or C4), 25.4 (C3 or C4), 22.1 (C14), 14.3 (C5); ESI-MS m/z = 683.38 ($2M+Na^+$, 100), 661.40 ($2M+H^+$, 16.3), 353.18 ($M+Na^+$, 55.2), 331.20 ($M+H^+$, 41.9); HRMS (ESI) m/z = 683.3849 (calculated for $C_{32}H_{60}N_4NaO_6S_2^+$ = 683.3846).

(*S*$_S$,*E*)-2-methyl-*N*-(pent-4-en-1-ylidene)propane-2-sulfinamide (431)

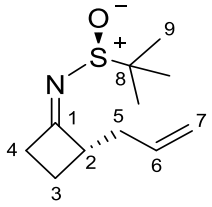


General procedure A was followed using 4-pentenal **132** (2 mL, 20.2 mmol, 1.0 eq.), titanium (IV) ethoxide (12.7 mL, 60.6 mmol, 3.0 eq.) and (*S*)-(-)-*tert*-butyl-sulfinamide **32** (2.69 g, 22.22 mmol, 1.1 eq.) in anhydrous THF (50 mL). The crude product was obtained as a yellow oil and purified by flash column chromatography over silica gel (eluting with 7:1 petroleum ether/ethyl acetate) to give **431** (3.48 g, 18.58 mmol, 92%; single isomer) as a pale yellow oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3110 (C-H_{alkene}), 2978, 2958, 2924, 2903, 2867, 2815 (C-H_{ali}), 1641 (C=N), 1620 (C=C), 1083 (S-O); $[\alpha]_D^{21}$ = -275.5 (*c* = 1.0 g/100 mL in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.06 (1H, t, *J* = 4.4, 1-H), 5.82 (1H, ddt, *J* = 17.0, 10.2 and 7.0, 4-H), 5.06 (1H, ddd, *J* = 17.0, 3.2 and 1.5, 5-H_a), 5.01 (1H, ddd, *J* = 10.2, 2.7 and 1.5, 5-H_b), 2.61 (2H, td, *J* = 7.0 and 4.4, 2-H), 2.43-2.34 (2H, m, 3-H), 1.17 (9H, s, 7-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 168.9 (C1), 136.8 (C4), 115.9 (C5), 56.6 (C6), 35.3 (C2), 29.4 (C3), 22.4 (C7); ESI-MS m/z = 397.19 ($2M+Na^+$, 7.1), 375.21 ($2M+H^+$, 6.6), 210.09 ($M+Na^+$, 36.3), 188.11 ($M+H^+$, 100); HRMS (ESI) m/z = 188.1106 (calculated for $C_9H_{18}NOS^+$ = 188.1104); CHN Found: C, 57.4%; H, 9.4%; N, 7.5%. $C_9H_{17}NOS$ requires: C, 57.7%; H, 9.2; N, 7.5%.

5.3. General procedure B: Synthesis of α-allyl sulfinimines 239 and 368.

A flame-dried round bottom flask equipped with a magnetic stirring-bar was purged with nitrogen gas and charged with sulfinimines **238** and **370** (308 μmol-23.2 mmol, 1.0 eq.) in anhydrous THF (25-150 mL). Hunig's base (616 μmol-46.4 mmol, 2.0 eq.) was added to the reaction mixture and stirred at room temperature for 30 minutes. Allyl methyl carbonate **247** (462 μmol-34.8 mmol, 1.5 eq.) and $Pd(PPh_3)_4$ (8-580 μmol, 2.5-5.0 mol%) were then added slowly to the reaction under nitrogen gas and stirred for 15 minutes at room temperature. The mixture was then heated to reflux for 13-96 hours. This was followed by the addition of silica gel (1-10 g) and the resulting suspension was concentrated *in vacuo*. Flash column chromatography afforded desired α-allyl sulfinimines **239** and **368**.

(*S*S)-*N*-((*S*,*Z*)-2-allylcyclobutylidene)-2-methylpropane-2-sulfinamide (239a)

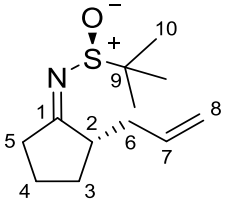


General procedure B was followed using **238a** (87 mg, 500 μmol, 1.0 eq.), Hunig's base (174 μL, 1 mmol, 2.0 eq.), allyl methyl carbonate **247** (85 μL, 750 μmol, 1.5 eq.) and $Pd(PPh_3)_4$ (29 mg, 25 μmol, 5.0 mol%) in anhydrous THF (25 mL). Purification by flash column chromatography over silica gel (eluting with 7:1 petroleum ether/ethyl acetate) gave **239a** (77 mg, 360 μmol, 72%) as a yellow oil. The product was isolated as a 3:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2953, 2865 (C-H_{ali}), 1662 (C=N), 1640 (C=C), 1080 (S-O); ^1H NMR (400 MHz, $CDCl_3$) δ_H = 5.89-5.75 (1H, m, 6-H), 5.14-5.01 (2H, m, 7-H), 3.35 (1H, ddd, *J* = 18.9, 10.1 and 7.2, 4-H_a), 3.12 (1H, ddd, *J* = 18.9, 9.7 and 6.7, 4-H_b), 2.38-2.33 (2H, m, 5-H), 2.32-

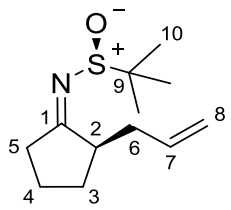
2.29 (1H, m, 2-H), 2.01-1.88 (2H, m, 3-H), 1.24 (9H, s, 9-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 188.5 (C1), 135.0 (C6), 116.8 (C7), 57.1 (C8), 52.5 (C2), 37.1 (C3 or C4 or C5), 36.2 (C3 or C4 or C5), 22.5 (C9), 21.5 (C3 or C4 or C5); ESI-MS m/z = 449.22 ($2M+Na^+$, 23.3), 236.10 ($M+Na^+$, 100), 214.12 ($M+H^+$, 23.6); HRMS (ESI) m/z = 236.1087 (calculated for $C_{11}H_{19}NOSNa^+$ = 236.1080).

(*S*$_S$)-*N*-((*S*,*Z*)-2-allylcyclopentylidene)-2-methylpropane-2-sulfinamide (239b)

General procedure B was followed using **238b** (94 mg, 500 μmol, 1.0 eq.), Hunig's base (174 μL, 1 mmol, 2.0 eq.), allyl methyl carbonate **247** (85 μL, 750 μmol, 1.5 eq.) and $Pd(PPh_3)_4$ (15 mg, 13 μmol, 2.5 mol%) in anhydrous THF (50 mL). Purification by flash column chromatography over silica gel (eluting with 6:1 petroleum ether/ethyl acetate) gave **239b** [67 mg, 295 μmol, 59%, mixture of diastereoisomers (4:1)] as a clear yellow oil.

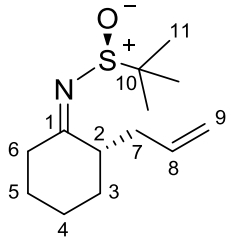


Major: 48 mg, 210 μmol, 42%, IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2926, 2872 (C-H_{ali}), 1678 (C=N), 1637 (C=C), 1080 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.85-5.73 (1H, m, 7-H), 5.05 (1H, ddd, *J* = 17.0, 3.2 and 1.5, 8-H_a), 5.01-4.96 (1H, m, 8-H_b), 2.81-2.73 (2H, m, 5-H), 2.62-2.54 (1H, m, 6-H_a), 2.52-2.42 (1H, m, 2-H), 2.14-2.05 (1H, m, 6-H_b), 2.03-1.90 (2H, m, 3-H_a and 4-H_a), 1.73-1.53 (1H, m, 4-H_b), 1.44-1.34 (1H, m, 3-H_b), 1.23 (9H, s, 10-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 194.4 (C1), 136.4 (C7), 116.4 (C8), 56.8 (C9), 49.5 (C2), 36.4 (C6), 34.2 (C5), 29.6 (C3), 23.5 (C4), 22.4 (C10); ESI-MS m/z = 477.25 ($2M+Na^+$, 50.2), 455.27 ($2M+H^+$, 15.4), 250.12 ($M+Na^+$, 30.2), 228.14 ($M+H^+$, 100); HRMS (ESI) m/z = 228.1425 (calculated for $C_{12}H_{22}NOS^+$ = 228.1417).



Minor: 19 mg, 85 μmol, 17%, IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2926, 2871 (C-H_{ali}), 1677 (C=N), 1636 (C=C), 1080 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.80 (1H, dddd, *J* = 17.1, 10.2, 7.4 and 6.3, 7-H), 5.12-4.99 (2H, m, 8-H), 3.16-3.05 (1H, m, 5-H_a), 2.67-2.50 (2H, m, 2-H and 5-H_b), 2.19-1.87 (2H, m, 6-H), 1.79-1.68 (1H, m, 3-H_a), 1.59-1.52 (1H, m, 3-H_b), 1.49-1.29 (2H, m, 4-H), 1.24 (9H, s, 10-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 195.9 (C1), 136.3 (C7), 116.5 (C8), 56.4 (C9), 49.3 (C2), 35.7 (C6), 33.9 (C5), 29.4 (C3), 23.1 (C4), 22.3 (C10); ESI-MS m/z = 477.25 ($2M+Na^+$, 62.7), 455.27 ($2M+H^+$, 21.1), 250.12 ($M+Na^+$, 25.0), 228.14 ($M+H^+$, 100); HRMS (ESI) m/z = 228.1423 (calculated for $C_{12}H_{22}NOS^+$ = 228.1417).

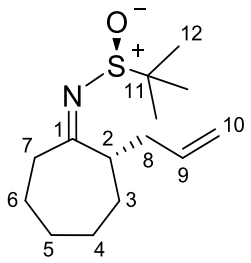
(*S*$_S$)-*N*-((*S*,*Z*)-2-allylcyclohexylidene)-2-methylpropane-2-sulfinamide (239c)



General procedure B was followed using **238c** (100 mg, 500 μmol, 1.0 eq.), Hunig's base (174 μL, 1 mmol, 2.0 eq.), allyl methyl carbonate **247** (85 μL, 750 μmol, 1.5 eq.) and $Pd(PPh_3)_4$ (15 mg, 13 μmol, 2.5 mol%) in anhydrous THF (50 mL). Purification by flash column chromatography over silica gel (eluting with 6:1 petroleum ether/ethyl acetate) gave **239c** (91 mg, 375 μmol, 75%) as a colourless oil. The product was isolated as a 20:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2930, 2859 (C-H_{ali}), 1679 (C=N), 1618 (C=C), 1075 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.88-

5.73 (1H, m, 8-H), 5.05-4.97 (2H, m, 9-H), 3.45 (1H, app. dt, *J* = 7.2 and 3.8, 2-H), 2.63-2.53 (1H, m, 6-H_a), 2.39-2.29 (1H, m, 6-H_b), 2.19-1.94 (4H, m, 3-H or 5-H and 7-H), 1.85-1.77 (1H, m, 3-H_a or 5-H_a), 1.70-1.64 (1H, m, 3-H_b or 5-H_b), 1.63-1.50 (2H, m, 4-H), 1.23 (9H, s, 11-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 189.8 (C1), 137.1 (C8), 116.3 (C9), 56.5 (C10), 49.4 (C2), 35.4 (C6), 34.8 (C3 or C5 or C7), 34.6 (C3 or C5 or C7), 28.8 (C3 or C5 or C7), 25.2 (C4), 22.4 (C11); ESI-MS m/z = 505.28 ($2M+Na^+$, 4.8), 264.13 ($M+Na^+$, 100), 242.15 ($M+H^+$, 37.8); HRMS (ESI) m/z = 264.1383 (calculated for $C_{13}H_{23}NOSNa^+$ = 264.1393).

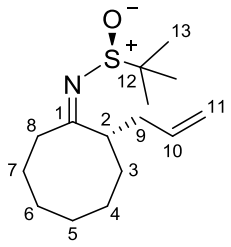
(*S*$_S$)-*N*-((*S*,*Z*)-2-allylcycloheptylidene)-2-methylpropane-2-sulfinamide (239d)



General procedure B was followed using **238d** (108 mg, 500 μmol, 1.0 eq.), Hunig's base (174 μL, 1 mmol, 2.0 eq.), allyl methyl carbonate **247** (85 μL, 750 μmol, 1.5 eq.) and $Pd(PPh_3)_4$ (29 mg, 25 μmol, 5.0 mol%) in anhydrous THF (25 mL). Purification by flash column chromatography over silica gel (eluting with 1:1 petroleum ether/ethyl acetate) gave **239d** (72 mg, 280 μmol, 56%) as a deep yellow oil. The product was isolated as a 7:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2926, 2856 (C-H_{ali}), 1660 (C=N), 1614 (C=C), 1073 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.74 (1H, dddd, *J* = 17.0, 10.2, 6.9 and 6.5, 9-H), 5.05-4.95 (2H, m, 10-H), 2.98-2.89 (1H, m, 2-H), 2.80 (1H, ddd, *J* = 14.3, 6.9 and 4.4, 8-H_a), 2.63-2.53 (1H, m, 8-H_b), 2.51-2.41 (1H, m, 3-H_a), 2.15-2.05 (1H, m, 3-H_b), 1.95-1.71 (4H, m, 4-H and 7-H), 1.69-1.57 (1H, m, 6-H_a), 1.39-1.26 (3H, m, 5-H and 6-H_b), 1.23 (9H, s, 12-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 191.8 (C1), 136.7 (C9), 116.5 (C10),

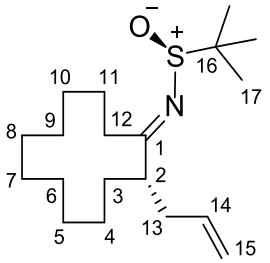
56.5 (C11), 50.3 (C2), 38.0 (C8), 35.0 (C3), 32.4 (C4 or C7), 28.9 (C4 or C7), 27.6 (C3 or C5), 25.4 (C3 or C5), 22.5 (C12); ESI-MS m/z = 533.32 ($2M+Na^+$, 44.7), 278.15 ($M+Na^+$, 100), 256.17 ($M+H^+$, 23.7); HRMS (ESI) m/z = 278.1542 (calculated for $C_{14}H_{25}NOSNa^+$ = 278.1549).

(S_S)-*N*-((*S*,*Z*)-2-allylcyclooctylidene)-2-methylpropane-2-sulfinamide (239e)



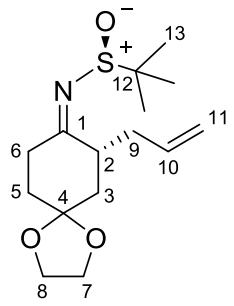
General procedure B was followed using **238e** (115 mg, 500 μmol, 1.0 eq.), Hunig's base (174 μL, 1 mmol, 2.0 eq.), allyl methyl carbonate **247** (85 μL, 750 μmol, 1.5 eq.) and $Pd(PPh_3)_4$ (29 mg, 25 μmol, 5.0 mol%) in anhydrous THF (60 mL). Purification by flash column chromatography over silica gel (eluting with 4:1 petroleum ether/ethyl acetate) gave **239e** (77 mg, 285 μmol, 57%) as a yellow oil. The product was isolated as a 3:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2925, 2857 (C-H_{ali}), 1640 (C=N), 1608 (C=C), 1073 (S-O); ^1H NMR (400 MHz, $CDCl_3$) δ_H = 5.78-5.62 (1H, m, 10-H), 5.04-4.93 (2H, m, 11-H), 2.94-2.82 (1H, m, 8-H_a), 2.65-2.45 (2H, m, 2-H and 8-H_b), 2.36 (1H, dt, *J* = 13.4 and 6.6, 9-H_a), 2.12 (1H, dt, *J* = 13.4 and 7.1, 9-H_b), 2.06-1.93 (1H, m, 3-H_a), 1.87-1.71 (2H, m, 3-H_b and 7-H_a), 1.66-1.55 (3H, m, 4-H and 7-H_b), 1.52-1.37 (4H, m, 5-H and 6-H), 1.22 (9H, s, 13-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 194.7 (C1), 136.4 (C10), 116.7 (C11), 56.5 (C12), 49.6 (C2), 39.3 (C9), 35.1 (C8), 34.2 (C3 or C7), 33.1 (C3 or C7), 32.4 (C4 or C5 or C6), 26.0 (C4 or C5 or C6), 25.1 (C4 or C5 or C6), 22.5 (C13); ESI-MS m/z = 561.35 ($2M+Na^+$, 6.7), 539.37 ($2M+H^+$, 10.9), 292.17 ($M+Na^+$, 19.7), 270.18 ($M+H^+$, 100.0); HRMS (ESI) m/z = 270.1888 (calculated for $C_{15}H_{28}NOS^+$ = 270.1886).

(*S*S)-*N*-((*S*,*E*)-2-allylcyclododecylidene)-2-methylpropane-2-sulfinamide (239f)



General procedure B was followed using **238f** (5 g, 17.5 mmol, 1.0 eq.), Hunig's base (6.1 mL, 35 mmol, 2.0 eq.), allyl methyl carbonate **247** (2.98 mL, 26.25 mmol, 1.5 eq.) and $Pd(PPh_3)_4$ (506 mg, 438 μmol, 2.5 mol%) in anhydrous THF (100 mL). The yellow reaction mixture was purified by flash column chromatography over silica gel (eluting with 6:1 petroleum ether/ethyl acetate) to afford **239f** (4.16 g, 12.78 mmol, 73%) as a yellow oil. The product was isolated as a 2:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2927, 2908, 2860 (C-H_{ali}), 1698 (C=N), 1613 (C=C), 1068 (S-O); ^1H NMR (400 MHz, $CDCl_3$) δ_H = 5.77 (1H, ddt, *J* = 17.1, 9.9 and 7.1, 14-H), 5.10-5.01 (2H, m, 15-H), 3.49-3.39 (1H, m, 2-H), 2.83-2.64 (1H, m, 12-H_a), 2.45-2.31 (1H, m, 12-H_b), 2.30-1.93 (3H, m, 3-H or 11-H), 1.91-1.67 (1H, m, 3-H or 11-H), 1.66-1.28 (16H, m, 4-H, 5-H, 6-H, 7-H, 8-H, 9-H, 10-H and 13-H), 1.25 (9H, s, 17-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 191.4 (C1), 136.2 (C14), 117.0 (C15), 56.4 (C16), 45.0 (C2), 40.4 (C13), 37.7 (C12), 34.4 (C3 or C11), 30.1 (C3 or C11), 26.9 (C4 or C5 or C6 or C7 or C8 or C9 or C10), 26.8 (C4 or C5 or C6 or C7 or C8 or C9 or C10), 24.8 (C4 or C5 or C6 or C7 or C8 or C9 or C10), 24.6 (C4 or C5 or C6 or C7 or C8 or C9 or C10), 24.0 (C4 or C5 or C6 or C7 or C8 or C9 or C10), 23.8 (C4 or C5 or C6 or C7 or C8 or C9 or C10), 22.5 (C17), 22.4 (C4 or C5 or C6 or C7 or C8 or C9 or C10); ESI-MS m/z = 673.47 ($2M+Na^+$, 6.2), 348.23 ($M+Na^+$, 10.4), 326.25 ($M+H^+$, 100.0); HRMS (ESI) m/z = 326.2509 (calculated for $C_{19}H_{36}NOS^+$ = 326.2512).

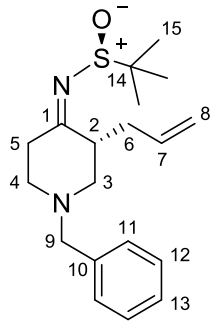
(*S*S)-*N*-((*R*,*Z*)-7-allyl-1,4-dioxaspiro[4.5]decan-8-ylidene)-2-methyl propane-2-sulfinamide (239g)



General procedure B was followed using **238g** (129 mg, 500 μmol, 1.0 eq.), Hunig's base (174 μL, 1 mmol, 2.0 eq.), allyl methyl carbonate **247** (85 μL, 750 μmol, 1.5 eq.) and $Pd(PPh_3)_4$ (29 mg, 25 μmol, 5.0 mol%) in anhydrous THF (40 mL). Purification by flash column chromatography over silica gel (eluting with 2:1 petroleum ether/ethyl acetate) gave **239g** (66 mg, 220 μmol, 44%) as yellow oil. The product was isolated as a 6:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2956, 2927 (C-H_{ali}), 1685 (C=N), 1626 (C=C), 1227, 1051 (C-O-C), 1074 (S-O); ^1H NMR (400 MHz, $CDCl_3$) δ_H = 5.77 (1H, dddd, *J* = 11.1, 9.1, 7.8 and 6.3, 10-H), 5.09-5.02 (1H, m, 11-H_a), 5.01-4.92 (1H, m, 11-H_b), 4.04-3.94 (4H, m, 7-H and 8-H), 3.45 (1H, tt, *J* = 8.3 and 5.4, 2-H), 2.82-2.70 (1H, m, 6-H_a), 2.66-2.50 (2H, m, 6-H_b and 9-H_a), 2.14-1.92 (3H, m, 3-H and 5-H_a), 1.80 (1H, ddd, *J* = 13.2, 7.8 and 4.6, 9-H_b), 1.66-1.56 (1H, m, 5-H_b), 1.25 (9H, s, 13-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 187.7 (C1), 136.4 (C10), 117.0 (C11), 107.4 (C4), 64.9 (C7 or C8), 64.7 (C7 or C8), 56.7 (C12), 45.2 (C2), 41.0 (C5), 35.1 (C3), 34.9 (C9), 30.4 (C6), 22.4 (C13); ESI-MS m/z = 621.30 ($2M+Na^+$, 9.8), 322.14 ($M+Na^+$, 100), 300.16 ($M+H^+$, 22.7); HRMS (ESI) m/z = 322.1441 (calculated for $C_{15}H_{25}NO_3SNa^+$= 322.1447).

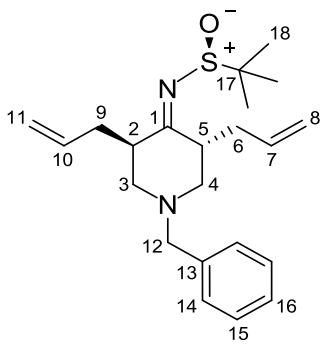
(*S*S)-*N*-((*R*,*Z*)-3-allyl-1-benzylpiperidin-4-ylidene)-2-methylpropane-2-sulfinamide (239h) and (*S*S)-*N*-((3*R*,5*R*)-3,5-diallyl-1-benzylpiperidin-4-ylidene)-2-methylpropane-2-sulfinamide (239ha)

General procedure B was followed using **238h** (146 mg, 500 μmol, 1.0 eq.), Hunig's base (174 μL, 1 mmol, 2.0 eq.), allyl methyl carbonate **247** (85 μL, 750 μmol, 1.5 eq.) and $Pd(PPh_3)_4$ (29 mg, 25 μmol, 5.0 mol%) in anhydrous THF (25 mL). Purification by flash column chromatography over silica gel (eluting with 1:1 petroleum ether/ethyl acetate) affording a mixture of two regioisomers; monoallyl regioisomer (desired product) **239h** (63 mg, 190 μmol, 38%) and diallyl regioisomer (undesired product) **239ha** (20 mg, 55 μmol, 11%) as a yellow oil.



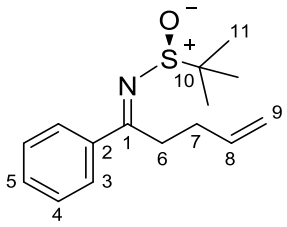
The desired product **239h** was isolated as a 4:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3063, 3028 (C-H_{aro}), 2956, 2868 (C-H_{ali}), 1637 (C=N), 1619 (C=C), 1074 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.36-7.29 (5H, m, 11-H, 12-H and 13-H), 5.81-5.67 (1H, m, 7-H), 5.03-4.95 (2H, m, 8-H), 3.61 (1H, d, *J* = 13.5, 9-H_a), 3.48 (1H, d, *J* = 13.5, 9-H_b), 3.38 (1H, ddd, *J* = 13.6, 6.1 and 4.6, 4-H_a), 2.95 (1H, ddd, *J* = 11.3, 4.6 and 1.7, 3-H_a), 2.90-2.77 (1H, m, 6-H_a), 2.75 (1H, t, *J* = 6.1, 5-H_a), 2.64-2.52 (2H, m, 2-H and 4-H_b), 2.50-2.42 (1H, m, 6-H_b), 2.33-2.20 (1H, m, 3-H_b), 2.14-2.06 (1H, m, 5-H_b), 1.24 (9H, s, 15-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 186.5 (C1), 138.2 (C10), 136.3 (C7), 129.0 (C11 or C12 or C13), 128.5 (C11 or C12 or C13), 127.4 (C11 or C12 or C13), 116.7 (C8), 62.1 (C9), 59.3 (C3), 56.7 (C14), 54.1 (C6), 47.9 (C2), 41.5 (C5), 33.6 (C4), 22.5 (C15); ESI-MS m/z = 355.18

(M+Na^+, 4.4), 333.19 (M+H^+, 100); HRMS (ESI) m/z = 333.1997 (calculated for $C_{19}H_{29}N_2OS^+$ = 333.1995).



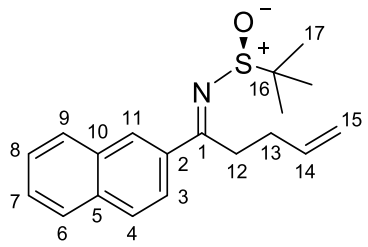
The undesired product **239ha** was isolated as a 3:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3081, 3067, 3022 (C-H_{aro}), 2971, 2923, 2844 (C-H_{ali}), 1643 (C=N), 1623, 1619 (C=C), 1072 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.40-7.20 (5H, m, 14-H, 15-H and 16-H), 5.86-5.56 (2H, m, 7-H and 10-H), 5.06-4.86 (4H, m, 8-H and 11-H), 3.93-3.83 (1H, m, 5-H), 3.60 (1H, d, *J* = 13.2, 12-H_a), 3.39 (1H, d, *J* = 13.2, 12-H_b), 3.20-3.10 (1H, m, 2-H), 2.95-2.79 (2H, m, 3-H or 4-H), 2.64-2.44 (3H, m, 3-H or 4-H and 6-H_a or 9-H_a), 2.34-2.14 (2H, m, 6-H or 9-H), 2.01-1.85 (1H, m, 6-H_b or 9-H_b) 1.27 (9H, s, 18-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 188.9 (C1), 138.5 (C13), 136.6 (C7 or C10), 135.3 (C7 or C10), 128.9 (C14 or C15), 128.4 (C14 or C15), 127.3 (C16), 117.5 (C8 or C11), 116.4 (C8 or C11), 62.1 (C12), 60.5 (C3 or C4), 56.9 (C3 or C4), 56.6 (C17), 43.8 (C5), 41.3 (C2), 36.4 (C6 or C9), 32.7 (C6 or C9), 22.5 (C18); ESI-MS m/z = 373.23 (M+H^+, 100); HRMS (ESI) m/z = 373.2307 (calculated for $C_{22}H_{33}N_2OS^+$ = 373.2308).

(*S*S,*E*)-2-methyl-*N*-(1-phenylpent-4-en-1-ylidene)propane-2-sulfinamide (239i)



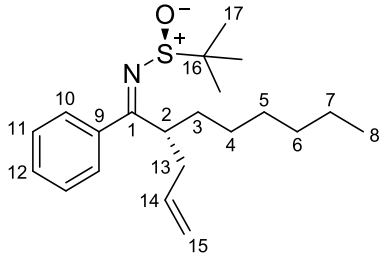
General procedure B was followed using **238i** (112 mg, 500 μmol, 1.0 eq.), Hunig's base (174 μL, 1 mmol, 2.0 eq.), allyl methyl carbonate **247** (85 μL, 750 μmol, 1.5 eq.) and $Pd(PPh_3)_4$ (15 mg, 13 μmol, 2.5 mol%) in anhydrous THF (50 mL). Purification by flash column chromatography over silica gel (eluting with 6:1 petroleum ether/ethyl acetate) gave **239i** (107 mg, 405 μmol, 81%; single isomer) as a colourless oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3065, 3033 (C-H_{aro}), 2959, 2824 (C-H_{ali}), 1686 (C=N), 1640 (C=C), 1075 (S-O); $[\alpha]_D^{19}$ = -24.2 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.83 (2H, d, *J* = 5.7, 3-H), 7.51-7.41 (3H, m, 4-H and 5-H), 5.88 (1H, ddt, *J* = 17.0, 10.2 and 6.6, 8-H), 5.06 (1H, ddd, *J* = 17.0, 3.2 and 1.4, 9-H_a), 5.01 (1H, ddd, *J* = 10.2, 2.9 and 1.4, 9-H_b), 3.42-3.34 (1H, m, 7-H_a), 3.28-3.18 (1H, m, 7-H_b), 2.51-2.34 (2H, m, 6-H), 1.32 (9H, s, 11-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 179.3 (C1), 137.9 (C8), 136.7 (C2), 131.7 (C3 or C4), 128.6 (C3 or C4), 127.6 (C5), 115.8 (C9), 57.7 (C10), 32.7 (C6), 31.8 (C7), 22.8 (C11); ESI-MS m/z = 549.25 ($2M+Na^+$, 10.0), 286.12 ($M+Na^+$, 85.4), 264.14 ($M+H^+$, 100); HRMS (ESI) m/z = 264.1413 (calculated for $C_{15}H_{22}NOS^+$ = 264.1417).

(*S*S,*E*)-2-methyl-*N*-(1-(naphthalen-2-yl)pent-4-en-1-ylidene)propane-2-sulfinamide (239j)



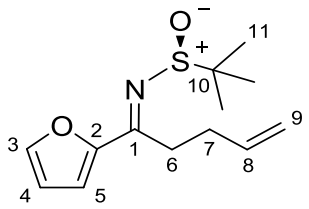
General procedure B was followed using **238j** (137 mg, 500 μmol, 1.0 eq.), Hunig's base (174 μL, 1 mmol, 2.0 eq.), allyl methyl carbonate **247** (85 μL, 750 μmol, 1.5 eq.) and $Pd(PPh_3)_4$ (29 mg, 25 μmol, 5.0 mol%) in anhydrous THF (25 mL). Purification by flash column chromatography over silica gel (eluting with 6:1 petroleum ether/ethyl acetate) gave **239j** (113 mg, 360 μmol, 72%; single isomer) as a yellow oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3060, 3037 (C-H_{aro}), 2979, 2865 (C-H_{ali}), 1640 (C=N), 1629 (C=C), 1074 (S-O); $[\alpha]_D^{22}$ = +53.8 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.26 (1H, s, 11-H), 8.00 (1H, d, *J* = 7.4, 3-H), 7.93 (1H, d, *J* = 7.4, 4-H), 7.86 (2H, d, *J* = 8.7, 6-H and 9-H), 7.57-7.50 (2H, m, 7-H and 8-H), 5.93 (1H, ddt, *J* = 17.0, 10.2 and 6.6, 14-H), 5.09 (1H, dd, *J* = 17.0 and 1.4, 15-H_a), 5.04 (1H, dd, *J* = 10.2 and 1.4, 15-H_b), 3.59-3.50 (1H, m, 13-H_a), 3.38-3.29 (1H, m, 13-H_b), 2.65-2.40 (2H, m, 12-H), 1.36 (9H, s, 17-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 179.0 (C1), 136.7 (C14), 135.9 (C5 or C10), 135.2 (C5 or C10), 134.9 (C2), 132.8 (C3 or C4 or C6 or C7 or C8 or C9 or C11), 129.3 (C3 or C4 or C6 or C7 or C8 or C9 or C11), 128.5 (C3 or C4 or C6 or C7 or C8 or C9 or C11), 128.0 (C3 or C4 or C6 or C7 or C8 or C9 or C11), 127.8 (C3 or C4 or C6 or C7 or C8 or C9 or C11), 126.8 (C3 or C4 or C6 or C7 or C8 or C9 or C11), 124.4 (C3 or C4 or C6 or C7 or C8 or C9 or C11), 115.9 (C15), 57.8 (C16), 32.9 (C12), 31.7 (C13), 22.9 (C17); ESI-MS m/z = 649.29 ($2M+Na^+$, 33.4), 627.30 ($2M+H^+$, 22.9), 336.13 ($M+Na^+$, 17.1), 314.15 ($M+H^+$, 100); HRMS (ESI) m/z = 314.1579 (calculated for $C_{19}H_{24}NOS^+$ = 314.1573).

(S_S)-*N*-((*R*,*E*)-2-allyl-1-phenyloctylidene)-2-methylpropane-2-sulfinamide (239k)



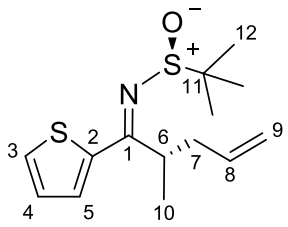
General procedure B was followed using **238k** (154 mg, 500 μmol, 1.0 eq.), Hunig's base (174 μL, 1 mmol, 2.0 eq.), allyl methyl carbonate **247** (85 μL, 750 μmol, 1.5 eq.) and $Pd(PPh_3)_4$ (29 mg, 25 μmol, 5.0 mol%) in anhydrous THF (25 mL). Purification by flash column chromatography over silica gel (eluting with 3:1 petroleum ether/ethyl acetate) gave **239k** (63 mg, 180 μmol, 36%) as a yellow oil. The product was isolated as a 4:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3077, 3061 (C-H_{aro}), 2927, 2857 (C-H_{ali}), 1640 (C=N), 1621 (C=C), 1083 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.44-7.37 (3H, m, 10-H, 11-H or 12-H), 7.36-7.24 (2H, m, 10-H, 11-H or 12-H), 5.85-5.72 (1H, m, 14-H), 5.09-4.99 (2H, m, 15-H), 3.22-3.03 (1H, m, 2-H), 2.57-2.40 (1H, m, 13-H_a), 2.37-2.15 (1H, m, 13-H_b), 1.81-1.69 (1H, m, 3-H_a), 1.58-1.44 (1H, m, 3-H_b), 1.38-1.30 (2H, m, 4-H), 1.29-1.18 (6H, m, 5-H, 6-H and 7-H), 1.22 (9H, s, 17-H), 0.89-0.82 (3H, m, 8-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 188.4 (C1), 138.7 (C9), 136.1 (C14), 129.6 (C10 or C11 or C12), 128.2 (C10 or C11 or C12), 126.9 (C10 or C11 or C12), 117.0 (C15), 56.4 (C16), 37.2 (C2), 31.8 (C13), 31.7 (C3), 29.5 (C4), 29.4 (C5), 27.5 (C6), 22.7 (C7), 22.3 (C17), 14.2 (C8); ESI-MS m/z = 370.21 ($M+Na^+$, 100), 348.23 ($M+H^+$, 44.5); HRMS (ESI) m/z = 370.2174 (calculated for $C_{21}H_{33}NOSNa^+$ = 370.2175).

(*S*S,*E*)-*N*-(1-(furan-2-yl)pent-4-en-1-ylidene)-2-methylpropane-2-sulfinamide (239m)



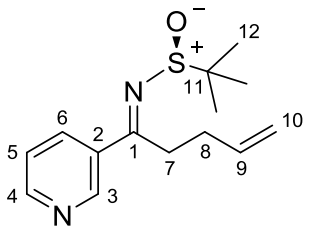
General procedure B was followed using **238m** (107 mg, 500 μmol, 1.0 eq.), Hunig's base (174 μL, 1 mmol, 2.0 eq.), allyl methyl carbonate **247** (85 μL, 750 μmol, 1.5 eq.) and $Pd(PPh_3)_4$ (15 mg, 13 μmol, 2.5 mol%) in anhydrous THF (25 mL). Purification by flash column chromatography over silica gel (eluting with 6:1 petroleum ether/ethyl acetate) gave **239m** (94 mg, 370 μmol, 74%; single isomer) as a yellow oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2959, 2866 (C-H_{ali}), 1678 (C=N), 1640 (C=C), 1226, 1013 (C-O-C), 1076 (S-O); $[\alpha]_D^{23}$ = -66.1 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.56 (1H, d, *J* = 1.7, 3-H), 7.02 (1H, d, *J* = 3.6, 5-H), 6.51 (1H, dd, *J* = 3.6 and 1.7, 4-H), 5.88 (1H, ddt, *J* = 17.1, 10.2 and 6.6, 8-H), 5.08 (1H, ddd, *J* = 17.1, 3.2 and 1.4, 9-H_a), 5.00 (1H, ddd, *J* = 10.2, 2.8 and 1.4, 9-H_b), 3.27-3.18 (1H, m, 7-H_a), 3.14-3.01 (1H, m, 7-H_b), 2.54-2.40 (2H, m, 6-H), 1.29 (9H, s, 11-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 168.9 (C1), 150.9 (C2), 145.8 (C3), 136.7 (C8), 115.8 (C5), 114.7 (C9), 112.5 (C4), 57.8 (C10), 32.9 (C6), 31.6 (C7), 22.7 (C11); ESI-MS m/z = 529.21 ($2M+Na^+$, 7.1), 276.10 ($M+Na^+$, 68.7), 254.12 ($M+H^+$, 100); HRMS (ESI) m/z = 254.1211 (calculated for $C_{13}H_{20}NO_2S^+$ = 254.1209).

(*S*S)-2-methyl-*N*-((*S*,*E*)-2-methyl-1-(thiophen-2-yl)pent-4-en-1-ylidene) propane-2-sulfinamide (239n)



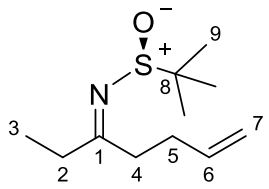
General procedure B was followed using **238n** (122 mg, 500 μmol, 1.0 eq.), Hunig's base (174 μL, 1 mmol, 2.0 eq.), allyl methyl carbonate **247** (85 μL, 750 μmol, 1.5 eq.) and $Pd(PPh_3)_4$ (29 mg, 25 μmol, 5.0 mol%) in anhydrous THF (25 mL). Purification by flash column chromatography over silica gel (eluting with 2:1 petroleum ether/ethyl acetate) gave **239n** (72 mg, 255 μmol, 51%) as a yellow oil. The product was isolated as a 8:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2927, 2868 (C-H_{ali}), 1676 (C=N), 1641 (C=C), 1071 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.65 (1H, d, *J* = 4.1, 3-H), 7.48 (1H, d, *J* = 4.8, 5-H), 7.09 (1H, dd, *J* = 4.8 and 4.1, 4-H), 5.85-5.70 (1H, m, 8-H), 5.07 (1H, ddd, *J* = 6.8, 3.2 and 1.5, 9-H_a), 5.04-4.99 (1H, m, 9-H_b), 4.10-3.40 (1H, m, 6-H), 2.71-2.59 (1H, m, 7-H_a), 2.48-2.28 (1H, m, 7-H_b), 1.37 (3H, d, *J* = 3.8, 10-H), 1.29 (9H, s, 12-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 175.6 (C1), 145.0 (C2), 135.8 (C8), 132.2 (C3), 129.5 (C4 or C5), 127.9 (C4 or C5), 117.2 (C9), 57.7 (C11), 29.1 (C6), 26.8 (C7), 22.6 (C12), 13.9 (C10); ESI-MS m/z = 589.20 ($2M+Na^+$, 5.1), 306.09 ($M+Na^+$, 100), 284.11 ($M+H^+$, 57.1); HRMS (ESI) m/z = 306.0963 (calculated for $C_{14}H_{21}NOS_2Na^+$ = 306.0957).

(*S*S,*E*)-2-methyl-*N*-(1-(pyridin-3-yl)pent-4-en-1-ylidene)propane-2-sulfinamide (239o)



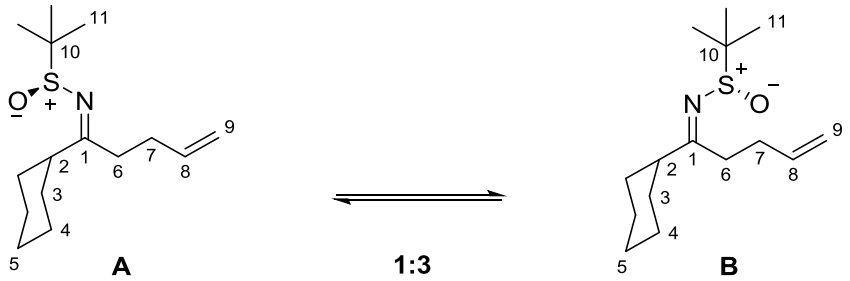
General procedure B was followed using **238o** (112 mg, 500 μmol, 1.0 eq.), Hunig's base (174 μL, 1 mmol, 2.0 eq.), allyl methyl carbonate **247** (85 μL, 750 μmol, 1.5 eq.) and $Pd(PPh_3)_4$ (29 mg, 25 μmol, 5.0 mol%) in anhydrous THF (25 mL). Purification by flash column chromatography over silica gel (eluting with 4:1 petroleum ether/ethyl acetate) gave **239o** (95 mg, 360 μmol, 72%; single isomer) as a yellow-orange oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3077, 3020 (C-H_{pyr}), 2960, 2866 (C-H_{ali}), 1640 (C=N), 1611 (C=C), 1079 (S-O); $[\alpha]_D^{22}$ = -13.8 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 9.03 (1H, s, 3-H), 8.68 (1H, d, *J* = 4.8, 4-H), 8.08 (1H, d, *J* = 7.5, 6-H), 7.36 (1H, dd, *J* = 7.5 and 4.8, 5-H), 5.85 (1H, ddt, *J* = 11.8, 9.9 and 6.7, 9-H), 5.06 (1H, dd, *J* = 11.8 and 1.8, 10-H_a), 5.01 (1H, dd, *J* = 9.9 and 1.8, 10-H_b), 3.46-3.34 (1H, m, 8-H_a), 3.32-3.20 (1H, m, 8-H_b), 2.52-2.32 (2H, m, 7-H), 1.32 (9H, s, 12-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 177.1 (C1), 152.1 (C3), 148.9 (C4), 136.2 (C9), 134.8 (C6), 133.5 (C2), 123.5 (C5), 116.3 (C10), 58.1 (C11), 32.5 (C8), 31.6 (C7), 22.9 (C12); ESI-MS m/z = 287.11 ($M+Na^+$, 18.5), 265.13 ($M+H^+$, 100); HRMS (ESI) m/z = 265.1366 (calculated for $C_{14}H_{21}N_2OS^+$ = 265.1369).

(*S*$_S$,*Z*)-*N*-(hept-6-en-3-ylidene)-2-methylpropane-2-sulfinamide (239p)



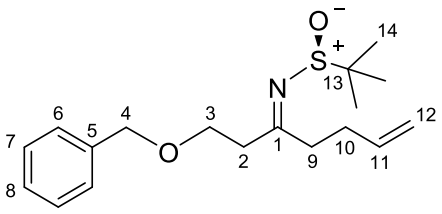
General procedure B was followed using **238p** (88 mg, 500 μmol, 1.0 eq.), Hunig's base (174 μL, 1 mmol, 2.0 eq.), allyl methyl carbonate **247** (85 μL, 750 μmol, 1.5 eq.) and $Pd(PPh_3)_4$ (29 mg, 25 μmol, 5.0 mol%) in anhydrous THF (25 mL). Purification by flash column chromatography over silica gel (eluting with 6:1 petroleum ether/ethyl acetate) gave **239p** (75 mg, 350 μmol, 70%; *circa*. 1:1 mixture of *cis* and *trans* isomers) as a colourless oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2925, 2869 (C-H_{ali}), 1641 (C=N), 1626 (C=C), 1032 (S-O); $[\alpha]_D^{23}$ = +23.5 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.87-5.75 (1H, m, 6-H), 5.10-4.95 (2H, m, 7-H), 2.88-2.64 (2H, m, 5-H), 2.57-2.30 (4H, m, 2-H and 4-H), 1.26 (9H, s, 9-H), 1.20-1.05 (3H, m, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 188.8, 188.3, 137.6, 136.8, 115.9, 115.3, 56.5, 56.4, 41.5, 39.5, 36.1, 35.6, 34.5, 31.6, 30.0, 29.5, 28.0, 22.4, 22.2, 11.9, 10.0 (21 out of a possible 18 carbon resonances observed). ESI-MS m/z = 453.25 ($2M+Na^+$, 100), 431.27 ($2M+H^+$, 7.4), 238.12 ($M+Na^+$, 90.3), 216.14 ($M+H^+$, 51.9); HRMS (ESI) m/z = 453.2592 (calculated for $C_{22}H_{42}N_2O_2S_2Na^+$ = 453.2580).

(S_S,*E*)-*N*-(1-cyclohexylpent-4-en-1-ylidene)-2-methylpropane-2-sulfinamide (239q)



General procedure B was followed using **238q** (115 mg, 500 μmol, 1.0 eq.), Hunig's base (174 μL, 1 mmol, 2.0 eq.), allyl methyl carbonate **247** (85 μL, 750 μmol, 1.5 eq.) and $Pd(PPh_3)_4$ (29 mg, 25 μmol, 5.0 mol%) in anhydrous THF (25 mL). Purification by flash column chromatography over silica gel (eluting with 3:1 petroleum ether/ethyl acetate) gave **239q** (47 mg, 175 μmol, 35% as a 1:3 ratio of A:B rotamers) as a colourless oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2929, 2854 (C-H_{ali}), 1638 (C=N), 1619 (C=C), 1076 (S-O); $[\alpha]_D^{22}$ = +88.3 (*c* = 0.1 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ_H = 5.81 (1H, ddt, *J* = 16.8, 10.2 and 6.4, 8-HA + 8-HB), 5.09-4.93 (2H, m, 2x9-HA + 2x9-HB), 3.34 (1H, m, 2-HA), 2.84 (1H, dtd, *J* = 12.0, 7.9 and 6.4, 7-HB_a), 2.70 (1H, dtd, *J* = 12.0, 7.9 and 6.4, 7-HB_b), 2.48 (2H, m, 7-HA + 7-HB), 2.33 (2H, dt, *J* = 14.4 and 7.9, 2x6-HA + 2x6-HB), 2.24 (1H, m, 2-HB), 1.87-1.62 (5H, m, 3,4,5-HA+B), 1.41-1.10 (5H, m, 3,4,5-HA+B), 1.21 (9H, s, 11-HA + 11-HB); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 190.6 (C1), 136.9 (C8), 115.7 (C9), 56.7 (C10), 49.5 (C2), 34.5 (C7), 31.7 (C6), 30.8 (C3 or C4 or C5), 26.2 (C3 or C4 or C5), 26.0 (C3 or C4 or C5), 22.5 (C11); ESI-MS m/z = 561.35 ($2M+Na^+$, 6.5), 292.16 ($M+Na^+$, 100), 270.18 ($M+H^+$, 49.9); HRMS (ESI) m/z = 292.1699 (calculated for $C_{15}H_{27}NOSNa^+$ = 292.1706).

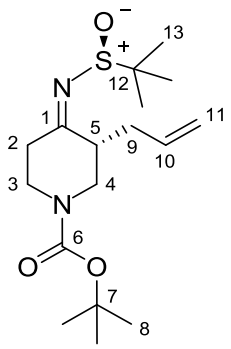
(*S*S,*E*)-*N*-(1-(benzyloxy)hept-6-en-3-ylidene)-2-methylpropane-2-sulfinamide (239t)



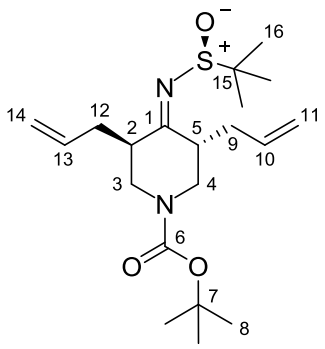
General procedure B was followed using **238t** (141 mg, 500 μmol, 1.0 eq.), Hunig's base (174 μL, 1 mmol, 2.0 eq.), allyl methyl carbonate **247** (85 μL, 750 μmol, 1.5 eq.) and $Pd(PPh_3)_4$ (29 mg, 25 μmol, 5.0 mol%) in anhydrous THF (25 mL). Purification by flash column chromatography over silica gel (eluting with 3:1 petroleum ether/ethyl acetate) gave **239t** (116 mg, 360 μmol, 72%; 1:4 *cis* vs. *trans*) as a yellow oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3065, 3030 (C-H_{aro}), 2957, 2863 (C-H_{ali}), 1703 (C=N), 1625 (C=C), 1189, 1028 (C-O-C), 1075 (S-O); $[\alpha]_D^{23}$ = +44.2 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.36-7.26 (5H, m, 6-H, 7-H and 8-H), 5.90-5.71 (1H, m, 11-H), 5.10-5.94 (2H, m, 12-H), 4.50 (2H, s, 4-H), 3.83-3.73 (2H, m, 3-H), 3.04 (1H, ddt, *J* = 19.8, 12.6 and 6.4, 10-H_a), 2.86-2.76 (1H, m, 10-H_b), 2.73 (1H, dt, *J* = 14.0 and 6.8, 2-H_a), 2.60 (1H, dd, *J* = 14.0 and 6.6, 2-H_b), 2.43-2.28 (2H, m, 9-H), 1.23 (9H, s, 14-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 186.0 (C1), 138.1 (C5), 135.3 (C11), 128.5 (C6 or C7 or C8), 127.8 (C6 or C7 or C8), 127.7 (C6 or C7 or C8), 117.3 (C12), 73.4 (C4), 66.3 (C3), 56.9 (C13), 43.2 (C2), 33.9 (C10), 23.6 (C9), 22.4 (C14); ESI-MS m/z = 665.34 ($2M+Na^+$, 1.7), 344.16 ($M+Na^+$, 100), 322.18 ($M+H^+$, 24.8); HRMS (ESI) m/z = 344.1650 (calculated for $C_{18}H_{27}NO_2SNa^+$ = 344.1655).

***Tert*-butyl-(*R*,*Z*)-3-allyl-4-(((S$_S$)-*tert*-butylsulfinyl)imino)piperidine-1-carboxylate (239v) and *tert*-butyl-(3*R*,5*R*)-3,5-diallyl-4-(((*S*$_S$)-*tert*-butyl sulfinyl) imino)piperidine-1-carboxylate (239va)**

General procedure B was followed using **238v** (2.81 g, 9.3 mmol, 1.0 eq.), Hunig's base (3.24 mL, 18.6 mmol, 2.0 eq.) and allyl methyl carbonate **247** (1.59 mL, 13.95 mmol, 1.5 eq.) and $Pd(PPh_3)_4$ (269 mg, 233 μmol, 2.5 mol%) in anhydrous THF (150 mL). The deep orange reddish reaction mixture was purified by flash column chromatography over silica gel (eluting with 3:1 petroleum ether/ethyl acetate) to give a mixture of two regioisomers; monoallyl regioisomer (desired product) **239v** (1.34 g, 3.9 mmol, 42%) and diallyl regioisomer (undesired product) **239va** (498 mg, 1.3 mmol, 14%) as an orange reddish oil.

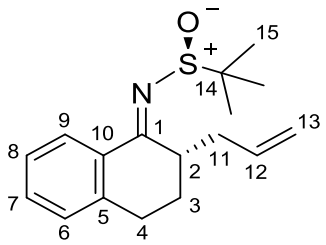


The desired product **239v** was isolated as a 3:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2975, 2929, 2870 (C-H_{ali}), 1697 (C=O), 1652 (C=N), 1621 (C=C), 1075 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.77 (1H, ddt, *J* = 14.4, 10.1 and 7.0, 10-H), 5.15-5.03 (2H, m, 11-H), 4.09-3.76 (1H, m, 4-H_a), 3.71 (1H, app. t, *J* = 6.1, 4-H_b), 3.65-2.65 (4H, m, 3-H, 5-H and 9H_a), 2.58-2.47 (1H, m, 2-H_a), 2.43 (1H, app. t, *J* = 6.1, 9-H_b), 2.18-1.98 (1H, m, 2-H_b), 1.49 (9H, s, 8-H), 1.27 (9H, s, 13-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 185.4 (C1), 154.6 (C6), 135.3 (C10), 117.5 (C11), 80.5 (C7), 56.9 (C12), 48.3 (C5), 41.3 (C4), 33.4 (C3), 33.1 (C2), 29.0 (C9), 28.5 (C8), 22.4 (C13); ESI-MS m/z = 365.18 ($M+Na^+$, 77.3), 343.20 ($M+H^+$, 100); HRMS (ESI) m/z = 343.2058 (calculated for $C_{17}H_{31}N_2O_3S^+$ = 343.2050).



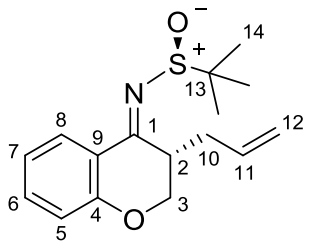
The undesired product **239va** was isolated as a 3:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2955, 2929, 2866 (C-H_{ali}), 1724 (C=O), 1657 (C=N), 1621 (C=C), 1073 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.92-5.72 (2H, m, 10-H and 13-H), 5.15-5.02 (4H, m, 11-H and 14-H), 4.60-3.61 (4H, m, 3-H and 4-H), 2.57-2.42 (4H, m, 9-H and 12-H), 2.36-2.26 (1H, m, 2-H or 5-H), 2.13-2.03 (1H, m, 2-H or 5-H), 1.48 (9H, s, 8-H), 1.26 (9H, s, 16-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 186.7 (C1), 154.7 (C6), 135.0 (C10 and C13), 117.4 (C11 and C14), 80.6 (C7), 57.3 (C15), 49.6 (C2 or C5), 43.4 (C2 or C5), 41.1 (C3 or C4), 32.5 (C3 or C4), 31.5 (C9 or C12), 28.5 (C8), 24.4 (C9 or C12), 22.6 (C16); ESI-MS m/z = 405.21 ($M+Na^+$, 13.6), 383.23 ($M+H^+$, 100); HRMS (ESI) m/z = 383.2360 (calculated for $C_{20}H_{35}N_2O_3S^+$ = 383.2363).

(*S*S)-*N*-((*S*,*E*)-2-allyl-3,4-dihydronaphthalen-1(2H)-ylidene)-2-methyl propane-2-sulfinamide (239x)



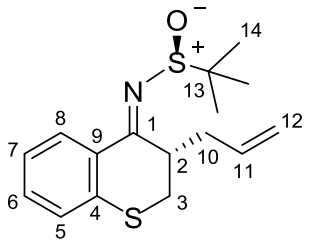
General procedure B was followed using **238x** (170 mg, 681 μmol, 1.0 eq.), Hunig's base (237 μL, 1.36 mmol, 2.0 eq.), allyl methyl carbonate **247** (166 μL, 1.02 mmol, 1.5 eq.) and $Pd(PPh_3)_4$ (20 mg, 17 μmol, 2.5 mol%) in anhydrous THF (30 mL). The brown reaction mixture was purified by flash column chromatography over silica gel (eluting with 3:1 petroleum ether/ethyl acetate) to give **239x** (152 mg, 524 μmol, 77%) as a pale brown oil. The product was isolated as a >25:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3069, 3022 (C-H_{aro}), 2955, 2923, 2854 (C-H_{ali}), 1727 (C=N), 1612 (C=C), 1073 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.08 (1H, dd, *J* = 7.7 and 1.1, 6-H or 9-H), 7.38 (1H, app. td, *J* = 7.7 and 1.4, 7-H or 8-H), 7.25-7.21 (1H, m, 7-H or 8-H), 7.18 (1H, d, *J* = 7.7, 6-H or 9-H), 5.87 (1H, dddd, *J* = 15.3, 11.7, 8.2 and 6.1, 12-H), 5.12-5.09 (1H, m, 13-H_a), 5.08-5.04 (1H, m, 13-H_b), 4.24-4.14 (1H, m, 2-H), 3.08-2.94 (1H, m, 11-H_a), 2.75 (1H, app. dt, *J* = 17.3 and 3.7, 11-H_b), 2.49-2.39 (1H, m, 4-H_a), 2.29-2.19 (1H, m, 4-H_b), 2.09-2.01 (2H, m, 3-H), 1.34 (9H, s, 15-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 178.5 (C1), 141.0 (C10), 135.7 (C12), 132.5 (C5), 131.9 (C7 or C8), 129.2 (C6 or C9), 127.6 (C6 or C9), 126.6 (C7 or C8), 117.5 (C13), 57.9 (C14), 36.5 (C2), 33.7 (C11), 25.1 (C4), 24.0 (C3), 23.0 (C15); ESI-MS m/z = 601.28 ($2M+Na^+$, 41.4), 312.13 ($M+Na^+$, 100), 290.15 ($M+H^+$, 21.2); HRMS (ESI) m/z = 312.1393 (calculated for $C_{17}H_{23}NOSNa^+$ = 312.1393).

(*S*)-*N*-((*S*$_S$,*E*)-3-allylchroman-4-ylidene)-2-methylpropane-2-sulfinamide (239y)



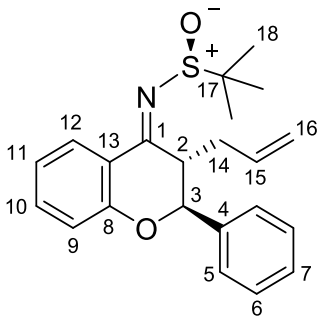
General procedure B was followed using **238y** (5 g, 19.9 mmol, 1.0 eq.), Hunig's base (6.93 mL, 39.8 mmol, 2.0 eq.), allyl methyl carbonate **247** (3.4 mL, 29.85 mmol, 1.5 eq.) and $Pd(PPh_3)_4$ (575 mg, 498 μmol, 2.5 mol%) in anhydrous THF (150 mL). The brown reaction mixture was purified by flash column chromatography over silica gel (eluting with 8:1 petroleum ether/ethyl acetate) to afford **239y** (4.47 g, 15.32 mmol, 77%) as a brown oil. The product was isolated as a >25:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3079, 3053 (C-H_{aro}), 2958, 2933, 2873 (C-H_{ali}), 1712 (C=N), 1640 (C=C), 1230, 1107 (C-O-C), 1060 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.93 (1H, dd, *J* = 8.3 and 1.6, 8-H), 7.38 (1H, ddd, *J* = 8.3, 7.2 and 1.2, 7-H), 7.00-6.95 (1H, m, 6-H), 6.90 (1H, dd, *J* = 8.1 and 1.2, 5-H), 5.89 (1H, dddd, *J* = 17.0, 10.0, 8.9 and 5.5, 11-H), 5.23-5.12 (2H, m, 12-H), 4.40 (1H, dd, *J* = 11.6 and 1.5, 3-H_a), 4.17 (1H, dd, *J* = 11.6 and 1.6, 3-H_b), 3.65-3.55 (1H, m, 2-H), 2.62-2.53 (1H, m, 10-H_a), 2.46-2.36 (1H, m, 10-H_b), 1.34 (9H, s, 14-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 172.8 (C1), 158.4 (C4), 134.7 (C11), 134.2 (C7), 127.4 (C8), 121.4 (C6), 120.1 (C9), 118.6 (C12), 117.9 (C5), 66.9 (C3), 58.4 (C13), 39.5 (C2), 34.7 (C10), 23.0 (C14); ESI-MS m/z = 314.11 ($M+Na^+$, 21.7), 292.13 ($M+H^+$, 100); HRMS (ESI) m/z = 292.1364 (calculated for $C_{16}H_{22}NO_2S^+$ = 292.1366); CHN Found: C, 65.7%; H, 7.5%; N, 4.8%. $C_{16}H_{21}NO_2S$ requires: C, 66.0%; H, 7.3%; N, 5.0%.

(*S*)-*N*-((*S*$_S$,*E*)-3-allylthiochroman-4-ylidene)-2-methylpropane-2-sulfinamide (239z)



General procedure B was followed using **238z** (3.98 g, 14.9 mmol, 1.0 eq.), Hunig's base (5.2 mL, 29.8 mmol, 2.0 eq.), allyl methyl carbonate **247** (2.54 mL, 22.35 mmol, 1.5 eq.) and $Pd(PPh_3)_4$ (430 mg, 373 μmol, 2.5 mol%) in anhydrous THF (150 mL). The deep yellow reaction mixture was purified by flash column chromatography over silica gel (eluting with 6:1 petroleum ether/ethyl acetate) to afford **239z** (3.8 g, 12.37 mmol, 83%) as a bright yellow oil. The product was isolated as a >25:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3075, 3060 (C-H_{aro}), 2977, 2958, 2920, 2864 (C-H_{ali}), 1697 (C=N), 1639 (C=C), 1068 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.10 (1H, dd, *J* = 8.2 and 1.2, 8-H), 7.31-7.25 (1H, m, 6-H), 7.17 (1H, dd, *J* = 7.5 and 1.1, 5-H), 7.10 (1H, ddd, *J* = 8.2, 7.5 and 1.1, 7-H), 5.86 (1H, dddd, *J* = 17.0, 10.8, 8.7 and 5.7, 11-H), 5.22 (1H, dd, *J* = 17.0 and 1.2, 12-H_a), 5.13 (1H, dd, *J* = 10.8 and 1.2, 12-H_b), 4.05 (1H, dddd, *J* = 10.6, 7.4, 3.5 and 2.9, 2-H), 3.42 (1H, dd, *J* = 13.6 and 2.9, 3-H_a), 2.95 (1H, dd, *J* = 13.6 and 3.5, 3-H_b), 2.69-2.57 (1H, m, 10-H_a), 2.51-2.41 (1H, m, 10-H_b), 1.35 (9H, s, 14-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 175.4 (C1), 138.5 (C9), 134.8 (C11), 131.8 (C6), 129.8 (C4), 129.6 (C8), 127.4 (C5), 124.7 (C7), 118.5 (C12), 58.3 (C13), 36.8 (C2), 34.1 (C10), 28.6 (C3), 23.0 (C14); ESI-MS m/z = 637.20 ($2M+Na^+$, 5.1), 330.09 ($M+Na^+$, 24.6), 308.11 ($M+H^+$, 100.0); HRMS (ESI) m/z = 308.1140 (calculated for $C_{16}H_{22}NOS_2^+$= 308.1137); CHN Found: C, 62.9%; H, 6.7%; N, 4.3%. $C_{16}H_{21}NOS_2$ requires: C, 62.5%; H, 6.9%; N, 4.6%.

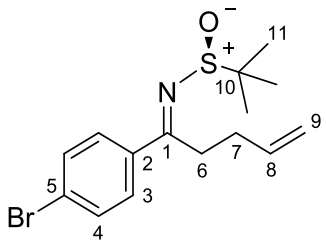
(S_S)-*N*-((2*S*,3*S*,*E*)-3-allyl-2-phenylchroman-4-ylidene)-2-methylpropane -2-sulfinamide (239aa)



General procedure B was followed using **238aa** (4 g, 12.2 mmol, 1.0 eq.), Hunig's base (4.25 mL, 24.4 mmol, 2.0 eq.), allyl methyl carbonate **247** (2.1 mL, 18.3 mmol, 1.5 eq.) and $Pd(PPh_3)_4$ (352 mg, 305 μmol, 2.5 mol%) in anhydrous THF (150 mL). The deep red reaction mixture was purified by flash column chromatography over silica gel (eluting with 6:1 petroleum ether/ethyl acetate) to give **239aa** (3.32 g, 9.03 mmol, 74%) as a deep red oil. The product was isolated as a >25:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3061, 3032 (C-H_{aro}), 2980, 2909, 2863 (C-H_{ali}), 1692 (C=N), 1613 (C=C), 1208, 1125 (C-O-C), 1076 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.75 (1H, dd, *J* = 8.0 and 1.7, Ar-H), 7.43-7.36 (3H, m, Ar-H), 7.25-7.20 (2H, m, Ar-H), 7.19-7.14 (1H, m, Ar-H), 7.03 (1H, dd, *J* = 8.3 and 1.0, Ar-H), 6.93-6.87 (1H, m, Ar-H), 6.17-6.08 (1H, m, 15-H), 5.53 (1H, br s, 3-H), 5.24-5.19 (1H, m, 16-H_a), 5.18-5.13 (1H, m, 16-H_b), 4.99-4.89 (1H, m, 2-H), 2.66-2.51 (2H, m, 14-H), 1.17 (9H, s, 18-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 169.9 (C1), 160.6 (C4 or C8 or C13), 138.8 (C4 or C8 or C13), 134.6 (C5 or C6 or C7 or C9 or C10 or C11 or C12), 134.2 (C15), 128.6 (C5 or C6 or C7 or C9 or C10 or C11 or C12), 127.6 (C5 or C6 or C7 or C9 or C10 or C11 or C12), 127.0 (C5 or C6 or C7 or C9 or C10 or C11 or C12), 126.5 (C5 or C6 or C7 or C9 or C10 or C11 or C12), 121.2 (C5 or C6 or C7 or C9 or C10 or C11 or C12), 120.4 (C4 or C8 or C13), 118.9 (C16), 118.1 (C5 or C6 or C7 or C9 or C10 or C11 or C12), 77.8 (C3), 60.6 (C2), 59.0 (C17), 35.0 (C14), 23.1 (C18); ESI-MS m/z = 390.14

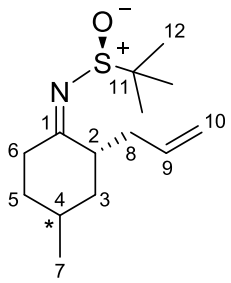
(M+Na$^+$, 10.3), 368.16 (M+H$^+$, 100); HRMS (ESI) m/z = 368.1679 (calculated for $C_{22}H_{26}NO_2S^+$ = 368.1679); CHN Found: C, 71.6%; H, 6.7%; N, 3.6%. $C_{22}H_{25}NO_2S$ requires: C, 71.9%; H, 6.5%; N, 3.4%.

(*S*$_S$,*E*)-*N*-(1-(4-bromophenyl)pent-4-en-1-ylidene)-2-methylpropane-2-sulfinamide (239ab)



General procedure B was followed using **238ab** (7 g, 23.2 mmol, 1.0 eq.), Hunig's base (8.08 mL, 46.4 mmol, 2.0 eq.), allyl methyl carbonate **247** (3.95 mL, 34.8 mmol, 1.5 eq.) and $Pd(PPh_3)_4$ (670 mg, 580 μmol, 2.5 mol%) in anhydrous THF (150 mL). Purification by flash column chromatography over silica gel (eluting with 8:1 petroleum ether/ethyl acetate) gave **239ab** (6.11 g, 17.86 mmol, 77%; single isomer) as a clear yellow oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3076, 3033 (C-H_{aro}), 2977, 2921, 2864 (C-H_{ali}), 1667 (C=N), 1639 (C=C), 1072 (S-O), 1088 (C-Br); $[\alpha]_D^{19}$ = -15.3 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.69 (2H, d, *J* = 8.1, 4-H), 7.56 (2H, d, *J* = 8.1, 3-H), 5.86 (1H, ddt, *J* = 16.8, 10.1 and 6.6, 8-H), 5.09-4.99 (2H, m, 9-H), 3.48-3.32 (1H, m, 7-H_a), 3.29-3.13 (1H, m, 7-H_b), 2.50-2.30 (2H, m, 6-H), 1.32 (9H, s, 11-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 178.1 (C1), 136.8 (C2), 136.5 (C8), 132.0 (C3), 129.1 (C4), 126.5 (C5), 116.1 (C9), 57.9 (C10), 32.6 (C6), 31.6 (C7), 22.8 (C11); ESI-MS m/z = 366.03 (M+Na$^+$, 74.1), 344.05 (M+H$^+$, 100); HRMS (ESI) m/z = 344.0509 (calculated for $C_{15}H_{21}{}^{81}BrNOS^+$ = 344.0501).

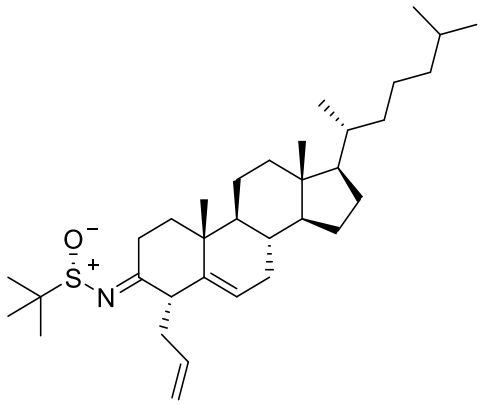
(*S*S)-*N*-((2*R*,*Z*)-2-allyl-4-methylcyclohexylidene)-2-methylpropane-2-sulfinamide (239ad)



General procedure B was followed using **238ad** (801 mg, 3.72 mmol, 1.0 eq.), Hunig's base (1.3 mL, 7.44 mmol, 2.0 eq.), allyl methyl carbonate **247** (634 μL, 5.58 mmol, 1.5 eq.) and $Pd(PPh_3)_4$ (107 mg, 93 μmol, 2.5 mol%) in anhydrous THF (50 mL). The deep yellow reaction mixture was purified by flash column chromatography over silica gel (eluting with 4:1 petroleum ether/ethyl acetate) affording **239ad** (608 mg, 2.38 mmol, 64%) as a pale yellow oil. The product was isolated as a 12:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2952, 2925, 2867 (C-H_{ali}), 1716 (C=N), 1623 (C=C), 1074 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.81 (1H, dddd, *J* = 17.0, 10.2, 8.0 and 6.0, 9-H), 5.05-4.96 (2H, m, 10-H), 3.62-3.52 (1H, m, 6-H_a), 2.65-2.55 (1H, m, 8-H_a), 2.36 (1H, ddt, *J* = 12.6, 7.2 and 5.1, 2-H), 2.11-1.91 (4H, m, 3-H_a, 5-H_a, 6-H_b and 8-H_b), 1.84-1.75 (1H, m 4-H), 1.44-1.27 (2H, m, 3-H_b and 5-H_b), 1.24 (9H, s, 12-H), 0.94 (3H, d, *J* = 6.5, 7-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 189.7 (C1), 137.3 (C9), 116.2 (C10), 56.5 (C11), 48.7 (C2), 43.2 (C3 or C5), 36.8 (C3 or C5), 35.2 (C8), 34.3 (C6), 32.4 (C4), 22.4 (C12), 21.3 (C7); ESI-MS m/z = 533.31 ($2M+Na^+$, 17.6), 278.15 ($M+Na^+$, 100), 256.17 ($M+H^+$, 29.9); HRMS (ESI) m/z = 278.1550 (calculated for $C_{14}H_{25}NNaOS^+$ = 278.1549).

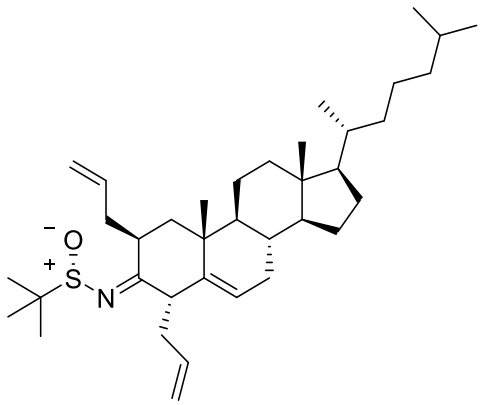
(*S*S)-*N*-((4*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-4-allyl-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-1,2,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3H-cyclopenta[a]phenanthren-3-ylidene)-2-methylpropane-2-sulfinamide (239ae) and (*S*S)-*N*-((2*S*,4*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-2,4-diallyl-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-1,2,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3H-cyclopenta[a]phenanthren-3-ylidene)-2-methyl propane-2-sulfinamide (239aea)

General procedure B was followed using **238ae** (150 mg, 308 μmol, 1.0 eq.), Hunig's base (107 μL, 616 μmol, 2.0 eq.) and allyl methyl carbonate **247** (53 μL, 462 μmol, 1.5 eq.) and $Pd(PPh_3)_4$ (9 mg, 8 μmol, 2.5 mol%) in anhydrous THF (40 mL). The deep yellow reaction mixture was purified by flash column chromatography over silica gel (eluting with 7:1 petroleum ether/ethyl acetate) affording a mixture of two regioisomers; monoallyl regioisomer (desired product) **239ae** (62 mg, 117 μmol, 38%) and diallyl regioisomer (undesired product) **239aea** (54 mg, 95 μmol, 31%) as a yellow oil.



The desired product **239ae** was isolated as a 10:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2949, 2933, 2866 (C-H_{ali}), 1660 (C=N), 1620 (C=C), 1076 (S-O); ^1H NMR (400 MHz, $CDCl_3$) δ_H = 5.88 (1H, ddt, *J* = 17.1, 10.2 and 6.6), 5.42 (1H, d, *J* = 4.9), 5.06 (1H, dd, *J* = 17.1 and 1.4), 4.99 (1H, dd, *J* = 10.2 and 1.4), 3.28-3.18 (1H, m), 3.10 (1H, ddd, *J* = 15.2, 7.3 and 4.6), 2.71 (1H, dt, *J* = 13.6 and 6.3), 2.57-2.47

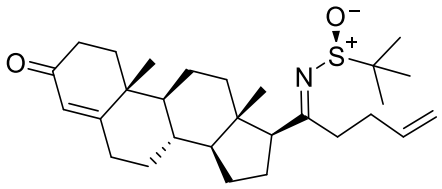
(1H, m), 2.29 (1H, dt, *J* = 13.6 and 6.8), 2.12 (1H, ddd, *J* = 12.4, 4.6 and 2.2), 2.04 (1H, dt, *J* = 12.4 and 3.2), 1.90-1.80 (2H, m), 1.69 (1H, ddd, *J* = 13.8, 9.4 and 4.7), 1.65-1.60 (1H, m), 1.55-1.43 (5H, m), 1.42-1.32 (4H, m), 1.25 (9H, s), 1.19-0.98 (12H, m), 0.94 (3H, d, *J* = 6.5), 0.90 (3H, d, *J* = 1.8), 0.88 (3H, d, *J* = 1.8), 0.71 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 189.6 (C), 141.8 (C), 137.7 (CH), 121.5 (CH), 115.7 (CH_2), 56.9 (C), 56.6 (CH), 56.2 (CH), 50.3 (CH), 47.9 (CH), 42.5 (C), 39.9 (CH_2), 39.7 (CH_2), 38.1 (C), 36.5 (CH_2), 36.3 (CH_2), 35.9 (CH), 32.0 (CH_2), 31.7 (CH), 31.3 (CH_2), 31.2 (CH_2), 28.4, (CH_2) 28.2 (CH), 24.3 (CH_2), 24.0 (CH_2), 23.0 (CH_3), 22.7 (CH_3), 22.4 (CH_3), 21.7 (CH_2), 21.1 (CH_3), 18.8 (CH_3), 12.1 (CH_3); ESI-MS m/z = 550.40 ($M+Na^+$, 81.1), 528.42 ($M+H^+$, 100); HRMS (ESI) m/z = 528.4233 (calculated for $C_{34}H_{58}NOS^+$ = 528.4234).



The undesired product **239aea** was isolated as a 10:1 mixture of diastereomers; only data for the major diastereomer is shown. IR υ_{max}($CHCl_3$)/cm^{-1} (neat) = 2944, 2933, 2866 (C-H_{ali}), 1678 (C=N), 1656 (C=C), 1073 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.69 (1H, dddd, *J* = 17.1, 10.4, 8.2 and 6.8), 5.57 (1H, ddd, *J* = 17.1, 12.1 and 7.5), 5.48 (1H, dd, *J* = 4.9 and 2.5), 5.04-4.96 (2H, m), 4.93-4.89 (1H, m), 4.88-4.84 (1H, m), 3.03-2.85 (3H, m), 2.51 (1H, dd, *J* = 13.9 and 6.7), 2.25 (1H, dd, *J* = 13.9 and 8.3), 2.16-2.08 (2H, m), 2.05-1.98 (1H, m), 1.94-1.74 (3H, m), 1.66 (1H, dd, *J* = 10.3 and 2.4), 1.63-1.59 (1H, m), 1.54-1.44 (4H, m), 1.41-1.31 (5H, m), 1.27 (9H, s), 1.18-1.08 (7H, m), 1.06-0.95 (4H, m), 0.91 (3H, d, *J* = 6.5), 0.87 (3H, d, *J* = 1.8), 0.86 (3H, d, *J* = 1.8), 0.73 (3H, d, *J* = 6.1); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 190.7 (C), 144.3 (C), 136.1 (CH), 133.8 (CH), 122.2 (CH),

118.4 (CH_2), 116.7 (CH_2), 57.1 (CH), 56.33 (CH), 56.27 (C), 54.1 (C), 50.0 (CH_2), 49.0 (CH), 42.5 (C), 41.2 (CH_2), 39.9 (CH_2), 39.7 (CH_2), 36.3 (CH_2), 36.1 (CH), 35.9 (CH), 31.9 (CH), 31.3 (CH_2), 31.2 (CH), 30.2 (CH_2), 28.4 (CH_2), 28.2 (CH), 24.3 (CH_2), 24.0 (CH_2), 23.0 (CH_3), 22.7 (CH_3), 22.6 (CH_3), 21.5 (CH_2), 19.1 (CH_3), 18.8 (CH_3), 12.1 (CH_3); ESI-MS m/z = 590.43 ($M+Na^+$, 63.3), 568.45 ($M+H^+$, 100); HRMS (ESI) m/z = 568.4542 (calculated for $C_{37}H_{62}NOS^+$ = 568.4547).

(*S*$_S$)-*N*-(1-((8*S*,9*S*,10*R*,13*S*,14*S*,17*S*)-10,13-dimethyl-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)pent-4-en-1-ylidene)-2-methylpropane-2-sulfinamide (239af)

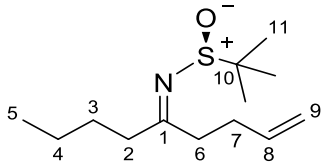


General procedure B was followed using **238af** (501 mg, 1.2 mmol, 1.0 eq.), Hunig's base (418 μL, 2.4 mmol, 2.0 eq.), allyl methyl carbonate **247** (205 μL, 1.8 mmol, 1.5 eq.) and $Pd(PPh_3)_4$ (35 mg, 30 μmol, 2.5 mol%) in anhydrous THF (50 mL). The yellow reddish reaction mixture was purified by flash column chromatography over silica gel (eluting with 2:1 petroleum ether/ethyl acetate) affording **239af** (280 mg, 612 μmol, 51%; 1:1 *cis* vs. *trans*) as a pale brown oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2966, 2942, 2875, 2854 (C-H_{ali}), 1698 (C=O), 1662 (C=N), 1616 (C=C), 1096 (S-O); ^1H NMR (400 MHz, $CDCl_3$) δ_H = 6.80-6.72 (1H, m), 5.96-5.70 (1H, m), 5.18-4.98 (2H, m), 3.66 (1H, dtd, *J* = 13.2, 6.6 and 4.1), 3.09 (1H, qd, *J* = 7.4 and 4.3), 2.84-2.64 (1H, m), 2.65-2.45 (2H, m), 2.43-2.33 (1H, m), 2.32-2.22 (1H, m), 2.21-2.15 (1H, m), 2.11 (3H, s), 2.08-1.98 (2H, m), 1.95-1.81 (1H, m), 1.76-1.61 (4H, m), 1.53 (3H, d, *J* = 6.7), 1.44 (3H, d, *J* = 6.7), 1.25 (9H, s), 1.12 (3H, d, *J* = 10.2), 0.65 (3H, d, *J* = 3.2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 209.5, 178.3, 165.9, 162.6, 136.8, 116.7, 63.6, 57.2, 56.2, 53.8, 50.5, 44.0, 42.0, 39.6, 38.8, 37.9, 35.5, 32.9, 31.6, 24.4, 22.4, 20.9, 18.8,

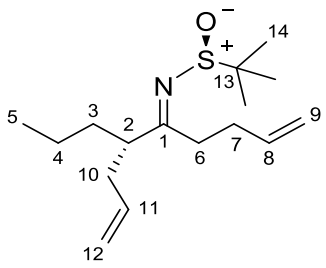
17.5, 13.4, 12.1; ESI-MS m/z = 937.59 (2M+Na^+, 4.1), 480.28 (M+Na^+, 44.7), 458.30 (M+H^+, 100); HRMS (ESI) m/z = 458.3088 (calculated for $C_{28}H_{44}NO_2S^+$ = 458.3087).

(S_S,*Z*)-2-methyl-*N*-(non-1-en-5-ylidene)propane-2-sulfinamide (368) and (S_S)-2-methyl-*N*-((*S*,*E*)-4-propylnona-1,8-dien-5-ylidene)propane-2-sulfinamide (373)

General procedure B was followed using **370** (100 mg, 492 μmol, 1.0 eq.), Hunig's base (171 μL, 984 μmol, 2.0 eq.) and allyl methyl carbonate **247** (84 μL, 738 μmol, 1.5 eq.) and $Pd(PPh_3)_4$ (14 mg, 12 μmol, 2.5 mol%) in anhydrous THF (25 mL). The yellow reaction mixture was purified by flash column chromatography over silica gel (eluting with 3:1 petroleum ether/ethyl acetate) to afford a mixture of regioisomers; monoallyl regioisomer (desired product) **368** (28 mg, 113 μmol, 23%; single isomer) and diallyl regioisomer (undesired product) **373** (13 mg, 44 μmol, 9%) as a pale yellow oil.



The desired product **368**; IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2958, 2929, 2871 (C-H_{ali}), 1715 (C=N), 1618 (C=C), 1066 (S-O); $[\alpha]_D^{23}$ = -44.0 (*c* = 1.0 g/100 mL in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.89-5.75 (1H, m, 8-H), 5.10-4.95 (2H, m, 9-H), 2.90-2.64 (2H, m, 7-H), 2.54 (1H, dt, *J* = 13.4 and 6.9, 6-H_a), 2.47-2.30 (3H, m, 2-H and 6-H_b), 1.63-1.53 (2H, m, 3-H), 1.46-1.34 (2H, m, 4-H), 1.25 (9H, s, 11-H), 0.95 (3H, t, *J* = 7.0, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 188.0 (C1), 137.6 (C8), 115.3 (C9), 56.4 (C10), 41.0 (C2 or C6), 40.1 (C2 or C6), 36.6 (C7), 29.6 (C3), 23.1 (C4), 22.4 (C11), 14.0 (C5); ESI-MS m/z = 509.32 (2M+Na^+, 12.5), 266.15 (M+Na^+, 100), 244.17 (M+H^+, 23.4); HRMS (ESI) m/z = 266.1547 (calculated for $C_{13}H_{25}NOSNa^+$ = 266.1549); CHN Found: C, 64.5%; H, 10.6%; N, 5.5%, $C_{13}H_{25}NOS$ requires: C, 64.2%; H, 10.4%; N, 5.8%.



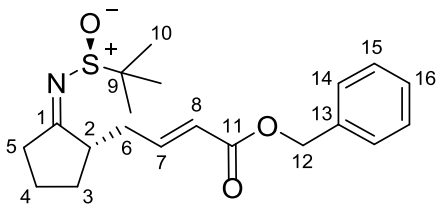
The undesired product **373** was isolated as a 10:1 mixture of diastereomers; only data for the major diastereomer is shown; IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2957, 2928, 2871 (C-H_{ali}), 1671 (C=N), 1640, 1633 (C=C), 1075 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.89-5.67 (2H, m, 8-H and 11-H), 5.12-4.96 (4H, m, 9-H and 12-H), 2.90-2.65 (1H, m, 7-H_a), 2.63-2.48 (1H, m, 7-H_b), 2.46-2.41 (1H, m, 2-H), 2.40-2.25 (3H, m, 6-H and 10-H_a), 2.24-2.17 (1H, m, 10-H_b), 1.58-1.51 (2H, m, 3-H), 1.48-1.33 (2H, m, 4-H), 1.24 (9H, s, 14-H), 0.95-0.85 (3H, m, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 185.9 (C1), 136.0 (C8 or C11), 135.9 (C8 or C11), 117.2 (C9 or C12), 117.0 (C9 or C12), 56.6 (C13), 37.7 (C2), 37.5 (C6), 36.9 (C7 or C10), 36.7 (C7 or C10), 29.0 (C3), 23.2 (C4), 22.6 (C14), 14.4 (C5); ESI-MS m/z = 284.20 ($M+H^+$, 100); HRMS (ESI) m/z = 284.2049 (calculated for $C_{16}H_{30}NOS^+$ = 284.2043).

5.4. General procedure C: Cross metathesis reaction 240, 367, 393, 384, 417 and 432.

A flame-dried two-neck round bottom flask equipped with a condenser and a rubber septum containing a stirring bar was charged with α-allyl sulfinimines **239**, homoallyl sulfinimine **368**, homoallyl ketone **374** and sulfinimine **431** (95 μmol-7.2 mmol, 1.0 eq.), benzyl acrylate **252**, allyl alcohol **249** methyl acrylate **383**, *N*-methoxy-*N*-methylacrylamide **415** and allyl bromide **245** (12 μmol-19.2 mmol, 2.0-6.0 eq.), CuI (3-216 μmol, 3.0 mol%) in anhydrous Et_2O (10-25 mL) under an argon atmosphere and stirred for 15 minutes. The reaction was then heated to reflux (40 °C), and Grubbs II catalyst (2-144 μmol, 2.0 mol%) in anhydrous Et_2O (15-150 mL) was added slowly to the reaction mixture over 1 hour. When the

reaction had reached completion, as determined by TLC, the mixture was allowed to cool to room temperature. This was followed by the addition of silica gel (1-8 g) and the resulting suspension was concentrated *in vacuo* and the residue was purified by flash column chromatography to provide the corresponding metathesis adducts **240**, **367**, **393**, **384**, **417** and **432**.[118]

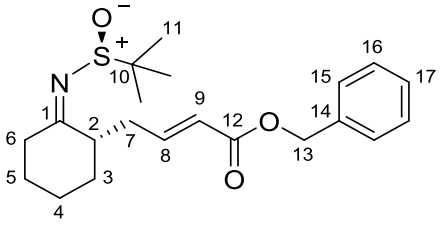
Benzyl-(*E*)-4-((*S,Z*)-2-(((S$_S$)-*tert*-butylsulfinyl)imino)cyclopentyl)but-2-enoate (240b)



General procedure C was followed using **239b** (114 mg, 500 μmol, 1.0 eq.), benzyl acrylate **252** (230 μL, 1.5 mmol, 3.0 eq.), CuI (3 mg, 15 μmol, 3.0 mol%) and Grubbs II catalyst (9 mg, 10 μmol, 2.0 mol%) in anhydrous Et_2O (20 mL). The deep brown reaction mixture was purified by flash column chromatography over silica gel (eluting with 2:1 petroleum ether/ethyl acetate) to afford **240b** (123 mg, 340 mmol, 68%) as a brown oil. The product was isolated as a 4:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)$/ cm^{-1} (neat) = 3064, 3033 (C-H_{aro}), 2959, 2873 (C-H_{ali}), 1719 (C=O), 1637 (C=N), 1078 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.38-7.29 (5H, m, 14-H, 15-H and 16-H), 7.01 (1H, ddd, *J* = 15.6, 8.3 and 7.3, 7-H), 5.91 (1H, ddd, *J* = 15.6, 4.4 and 1.5, 8-H), 5.16 (2H, s, 12-H), 2.83-2.78 (1H, m, 5-H_a), 2.77-2.68 (1H, m, 5-H_b), 2.66-2.54 (1H, m, 2-H), 2.43-2.35 (1H, m, 6-H_a), 2.32-2.17 (1H, m, 6-H_b), 2.10-2.02 (1H, m, 3-H_a), 2.01-1.90 (1H, m, 4-H_a), 1.78-1.60 (1H, m, 4-H_b), 1.41-1.31 (1H, m, 3-H_b), 1.21 (9H, s, 10-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 193.4 (C1), 166.2 (C11), 147.5 (C7), 136.1 (C13), 128.7 (C14 or C15), 128.33 (C14 or C15), 128.31 (C16), 122.6 (C8), 66.2 (C12), 56.9 (C9), 48.8 (C2), 34.7 (C6), 33.9 (C5), 30.1 (C3), 23.4 (C4), 22.4 (C10); ESI-MS m/z = 745.33 (2M+Na^+,

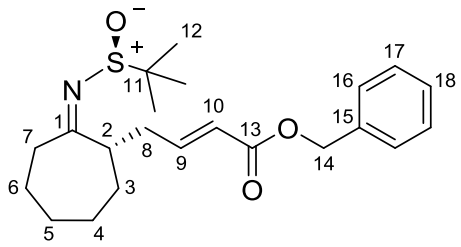
27.7), 384.16 (M+Na$^+$, 64.3), 362.17 (M+H$^+$, 100); HRMS (ESI) m/z = 362.1794 (calculated for $C_{20}H_{28}NO_3S^+$ = 362.1784).

Benzyl-(*E*)-4-((*S*,*Z*)-2-(((*S*$_S$)-*tert*-butylsulfinyl)imino)cyclohexyl)but-2-enoate (240c)



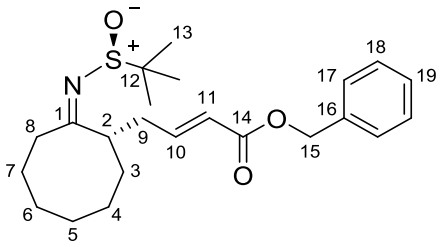
General procedure C was followed using **239c** (302 mg, 1.25 mmol, 1.0 eq.), benzyl acrylate **252** (574 μL, 3.75 mmol, 3.0 eq.), CuI (7 mg, 38 μmol, 3.0 mol%) and Grubbs II catalyst (21 mg, 25 μmol, 2.0 mol%) in anhydrous Et_2O (50 mL). The deep yellow mixture was purified by flash column chromatography over silica gel (eluting with 3:1 petroleum ether/ethyl acetate) to afford **240c** (380 mg, 1.01 mmol, 81%) as a pale yellow oil. The product was isolated as a 20:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)$/ cm^{-1} (neat) = 3066, 3033 (C-H$_{aro}$), 2931, 2860 (C-H$_{ali}$), 1714 (C=O), 1653 (C=N), 1625 (C=C), 1067 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.36-7.30 (5H, m, 15-H, 16-H and 17-H), 6.99 (1H, ddd, *J* = 15.5, 7.9 and 6.5, 8-H), 5.86 (1H, dt, *J* = 15.5 and 1.3, 9-H), 5.15 (2H, s, 13-H), 3.56-3.46 (1H, m, 2-H), 2.78-2.68 (1H, m, 6-H$_a$), 2.42 (1H, dt, *J* = 11.4 and 6.5, 6-H$_b$), 2.19-1.97 (4H, m, 3-H or 5-H and 7-H), 1.85-1.78 (1H, m, 3-H$_a$ or 5-H$_a$), 1.70-1.50 (2H, m, 4-H$_a$ and 3-H$_b$ or 5-H$_b$), 1.41-1.31 (1H, m, 4-H$_b$), 1.20 (9H, s, 11-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 188.8 (C1), 166.3 (C12), 148.3 (C8), 136.2 (C14), 128.6 (C15 or C16), 128.34 (C15 or C16), 128.30 (C17), 122.5 (C9), 66.2 (C13), 56.5 (C10), 48.7 (C2), 35.3 (C6), 34.8 (C3 or C5 or C7), 33.8 (C3 or C5 or C7), 28.7 (C3 or C5 or C7), 25.4 (C4), 22.3 (C11); ESI-MS m/z = 398.17 (M+Na$^+$, 14.7), 376.19 (M+H$^+$, 100.0); HRMS (ESI) m/z = 376.1938 (calculated for $C_{21}H_{30}NO_3S^+$ = 376.1941).

Benzyl-(*E*)-4-((*S*,*Z*)-2-(((*S*$_S$)-*tert*-butylsulfinyl)imino)cycloheptyl)but-2-enoate (240d)



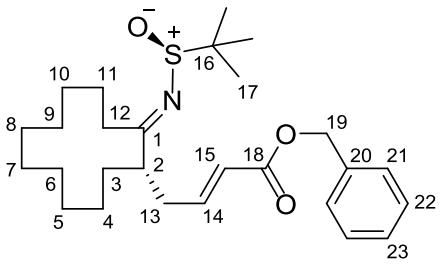
General procedure C was followed using **239d** (220 mg, 860 μmol, 1.0 eq.), benzyl acrylate **252** (395 μL, 2.58 mmol, 3.0 eq.), CuI (5 mg, 26 μmol, 3.0 mol%) and Grubbs II catalyst (15 mg, 17 μmol, 2.0 mol%) in anhydrous Et_2O (30 mL). The deep yellow reaction mixture was purified by flash column chromatography over silica gel (eluting with 3:1 petroleum ether/ethyl acetate) to afford **240d** (258 mg, 662 μmol, 77%) as a pale yellow oil. The product was isolated as a 7:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)$/ cm^{-1} (neat) = 3063, 3034 (C-H_{aro}), 2926, 2857 (C-H_{ali}), 1718 (C=O), 1653 (C=N), 1611 (C=C), 1072 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.39-7.29 (5H, m, 16-H, 17-H and 18-H), 7.01-6.89 (1H, m, 9-H), 5.87 (1H, d, *J* = 15.6, 10-H), 5.16 (2H, s, 14-H), 3.09-2.87 (1H, m, 2-H), 2.85-2.66 (2H, m, 8-H), 2.61-2.41 (1H, m, 3-H_a), 2.36-2.19 (1H, m, 3-H_b), 1.96-1.74 (4H, m, 4-H and 7-H), 1.71-1.59 (1H, m, 6-H_a), 1.46-1.27 (3H, m, 5-H and 6-H_a), 1.21 (9H, s, 12-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 190.7 (C1), 166.3 (C13), 147.9 (C9), 136.2 (C15), 128.7 (C16 or C17), 128.4 (C16 or C17), 128.3 (C18), 122.7 (C10), 66.2 (C14), 56.6 (C11), 49.6 (C2), 36.2 (C8), 35.5 (C3), 33.0 (C4 or C7), 28.6 (C4 or C7), 27.7 (C5 or C6), 25.2 (C5 or C6), 22.4 (C12); ESI-MS m/z = 412.19 ($M+Na^+$, 10.2), 390.21 ($M+H^+$, 100); HRMS (ESI) m/z = 390.2107 (calculated for $C_{22}H_{32}NO_3S^+$ = 390.2097).

Benzyl-(*E*)-4-((*S*,*Z*)-2-(((*S*$_S$)-*tert*-butylsulfinyl)imino)cyclooctyl)but-2-enoate (240e)



General procedure C was followed using **239e** (400 mg, 1.48 mmol, 1.0 eq.), benzyl acrylate **252** (679 μL, 4.44 mmol, 3.0 eq.), CuI (9 mg, 44 μmol, 3.0 mol%) and Grubbs II catalyst (25 mg, 30 μmol, 2.0 mol%) in anhydrous Et_2O (50 mL). The brown oil reaction mixture was purified by flash column chromatography over silica gel (eluting with 3:1 petroleum ether/ethyl acetate) to afford **240e** (502 mg, 1.24 mmol, 84%) as a pale brown oil. The product was isolated as a 4:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3064, 3033 (C-H_{aro}), 2925, 2859 (C-H_{ali}), 1719 (C=O), 1653 (C=N), 1607 (C=C), 1071 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.37-7.27 (5H, m, 17-H, 18-H and 19-H), 6.95-6.85 (1H, m, 10-H), 5.85 (1H, dt, *J* = 15.6 and 1.3, 11-H), 5.15 (2H, s, 15-H), 3.01-2.83 (1H, m, 8-H_a), 2.75-2.65 (1H, m, 2-H), 2.60-2.48 (2H, m, 8-H_b and 9-H_a), 2.29 (1H, ddd, *J* = 13.4, 7.9 and 6.1, 9-H_b), 2.07-1.95 (1H, m, 3-H_a), 1.87-1.75 (3H, m, 3-H_b and 7-H), 1.62-1.52 (2H, m, 4-H), 1.51-1.38 (4H, m, 5-H and 6-H), 1.21 (9H, s, 13-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 193.6 (C1), 166.1 (C14), 147.3 (C10), 136.1 (C16), 128.6 (C17 or C18), 128.4 (C17 or C18), 128.3 (C19), 122.9 (C11), 66.2 (C15), 56.7 (C12), 48.6 (C2), 40.8 (C9), 37.2 (C8), 34.5 (C3 or C7), 33.6 (C3 or C7), 27.1 (C4 or C5 or C6), 25.7 (C4 or C5 or C6), 25.1 (C4 or C5 or C6), 22.4 (C13); ESI-MS m/z = 426.20 ($M+Na^+$, 11.4), 404.22 ($M+H^+$, 100); HRMS (ESI) m/z = 404.2256 (calculated for $C_{23}H_{34}NO_3S^+$ = 404.2254).

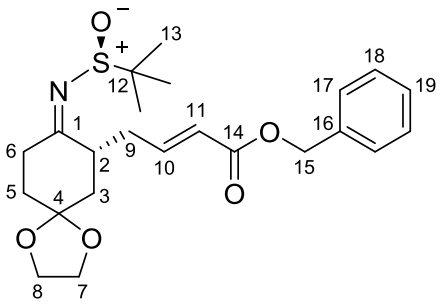
Benzyl-(*E*)-4-((*S*,*E*)-2-(((*S*$_S$)-*tert*-butylsulfinyl)imino)cyclododecyl)but-2-enoate (240f)



General procedure C was followed using **239f** (661 mg, 2.03 mmol, 1.0 eq.), benzyl acrylate **252** (914 μL, 6.09 mmol, 3.0 eq.), CuI (12 mg, 61 μmol, 3.0 mol%) and Grubbs II catalyst (35 mg, 41 μmol, 2.0 mol%) in anhydrous Et_2O (100 mL). The deep yellow reaction mixture was purified by flash column chromatography over silica gel (eluting with 6:1 petroleum ether/ethyl acetate) to give **240f** (737 mg, 1.6 mmol, 79%) as a yellow oil. The product was isolated as a 3:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3074, 3028 (C-H_{aro}), 2925, 2860 (C-H_{ali}), 1731 (C=O), 1695 (C=N), 1617 (C=C), 1072 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.42-7.27 (5H, m, 21-H, 22-H and 23-H), 6.96 (1H, dt, *J* = 15.5 and 7.4, 14-H), 6.01-5.82 (1H, m, 15-H), 5.17 (2H, s, 19-H), 3.53-3.37 (1H, m, 2-H), 2.90-2.62 (1H, m, 12-H_a), 2.52-2.42 (1H, m, 12-H_b), 2.40-2.01 (3H, m, 3-H or 11-H), 1.86-1.66 (1H, m, 3-H or 11-H), 1.64-1.27 (16H, m, 4-H, 5-H, 6-H, 7-H, 8-H, 9-H, 10-H and 13-H), 1.22 (9H, s, 17-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 190.3 (C1), 166.1 (C18), 146.9 (C14), 136.1 (C20), 128.7 (C21 or C22), 128.4 (C21 or C22), 128.3 (C23), 123.2 (C15), 66.3 (C19), 56.6 (C16), 44.3 (C2), 40.4 (C13), 38.1 (C12), 34.0 (C3 or C11), 30.1 (C3 or C11), 26.6 (C4 or C5 or C6 or C7 or C8 or C9 or C10), 26.5 (C4 or C5 or C6 or C7 or C8 or C9 or C10), 24.8 (C4 or C5 or C6 or C7 or C8 or C9 or C10), 24.6 (C4 or C5 or C6 or C7 or C8 or C9 or C10), 23.9 (C4 or C5 or C6 or C7 or C8 or C9 or C10), 23.7 (C4 or C5 or C6 or C7 or C8 or C9 or C10), 22.5 (C17), 22.1 (C4 or C5 or C6 or C7 or C8 or C9 or C10); ESI-MS

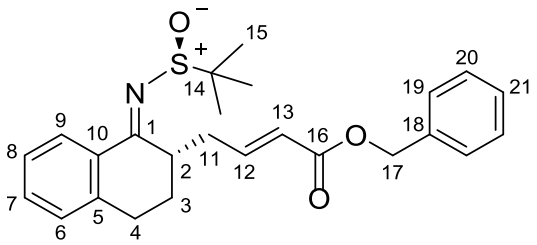
m/z = 941.55 (2M+Na^+, 8.8), 482.27 (M+Na^+, 100), 460.28 (M+H^+, 24.0); HRMS (ESI) m/z = 482.2706 (calculated for $C_{27}H_{41}NNaO_3S^+$ = 482.2699).

Benzyl-(*E*)-4-((*R*,*Z*)-8-(((*S*$_S$)-*tert*-butylsulfinyl)imino)-1,4-dioxaspiro[4.5] decan-7-yl)but-2-enoate (240g)



General procedure C was followed using **339g** (470 mg, 1.57 mmol, 1.0 eq.), benzyl acrylate **252** (721 μL, 4.71 mmol, 3.0 eq.), CuI (9 mg, 47 μmol, 3.0 mol%) and Grubbs II catalyst (27 mg, 31 μmol, 2.0 mol%) in anhydrous Et_2O (50 mL). The deep brown reaction mixture was purified by flash column chromatography over silica gel (eluting with 2:1 petroleum ether/ethyl acetate) to give **240g** (565 mg, 1.3 mmol, 83%) as a brown oil. The product was isolated as a 5:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)$/ cm^{-1} (neat) = 3064, 3032 (C-H_{aro}), 2955, 2930, 2888 (C-H_{ali}), 1712 (C=O), 1651 (C=N), 1642 (C=C), 1264, 1101 (C-O-C), 1041 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.96-7.82 (5H, m, 17-H, 18-H and 19-H), 7.05-6.90 (1H, m, 10-H), 5.88 (1H, d, *J* = 15.7, 11-H), 5.15 (2H, s, 15-H), 3.99 (4H, s, 7-H and 8-H), 3.50 (1H, tt, *J* = 8.4 and 5.4, 2-H), 2.96-2.54 (3H, m, 6-H and 9-H_a), 2.30-2.10 (1H, m, 9-H_b), 2.07-1.90 (2H, m, 3-H), 1.81-1.74 (1H, m, 5-H_a), 1.71-1.58 (1H, m, 5-H_b), 1.21 (9H, s, 13-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 186.3 (C1), 166.3 (C14), 147.7 (C10), 136.2 (C16), 128.7 (C17 or C18), 128.35 (C17 or C18), 128.34 (C19), 122.8 (C11), 107.3 (C4), 66.3 (C15), 65.0 (C7 or C8), 64.7 (C7 or C8), 56.9 (C12), 45.0 (C2), 42.1 (C5), 35.6 (C3), 33.5 (C9), 30.4 (C6), 22.4 (C13); ESI-MS m/z = 456.18 (M+Na^+, 100), 434.19 (M+H^+, 15.2); HRMS (ESI) m/z = 456.1823 (calculated for $C_{23}H_{31}NNaO_5S^+$ = 456.1815).

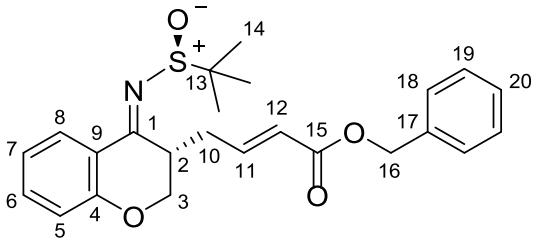
Benzyl-(*E*)-4-((*S*,*E*)-1-(((*S*$_S$)-*tert*-butylsulfinyl)imino)-1,2,3,4-tetra hydronaphthalen-2-yl)but-2-enoate (240x)



General procedure C was followed using **239x** (100 mg, 350 μmol, 1.0 eq.), benzyl acrylate **252** (161 μL, 1.05 mmol, 3.0 eq.), CuI (2 mg, 11 μmol, 3.0 mol%) and Grubbs II catalyst (6 mg, 7 μmol, 2.0 mol%) in anhydrous Et_2O (50 mL). The deep reddish brown reaction mixture was purified by flash column chromatography over silica gel (eluting with 8:1 petroleum ether/ethyl acetate) to afford **240x** (111 mg, 263 μmol, 75%) as a reddish brown oil. The product was isolated as a >25:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3061, 3033 (C-H_{aro}), 2944, 2870 (C-H_{ali}), 1717 (C=O), 1653 (C=N), 1608 (C=C), 1060 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.08 (1H, d, *J* = 8.0, 6-H or 9-H), 7.41-7.31 (6H, m, 7-H or 8-H and 19-H, 20-H, 21-H), 7.27-7.22 (1H, m, 7-H or 8-H), 7.18 (1H, d, *J* = 7.7, 6-H or 9-H), 7.06 (1H, ddd, *J* = 15.4, 9.0 and 6.5, 12-H), 5.96 (1H, d, *J* = 15.4, 13-H), 5.21-5.13 (2H, m, 17-H), 3.87 (1H, app. ddd, *J* = 11.0, 6.5 and 3.5, 2-H), 3.07-2.96 (1H, m, 11-H_a), 2.80-2.76 (1H, m, 11-H_b), 2.75-2.70 (1H, m, 4-H_a), 2.50-2.38 (1H, m, 4-H_b), 2.09-1.97 (2H, m, 3-H), 1.34 (9H, s, 15-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 178.5 (C1), 166.1 (C16), 146.0 (C12), 140.6 (C5 or C10), 136.2 (C5 or C10), 132.3 (C18), 132.2 (C13), 129.4 (C6 or C7 or C8 or C9 or C19 or C20 or C21), 128.7 (C6 or C7 or C8 or C9 or C19 or C20 or C21), 128.4 (C6 or C7 or C8 or C9 or C19 or C20 or C21), 128.3 (C6 or C7 or C8 or C9 or C19 or C20 or C21), 127.8 (C6 or C7 or C8 or C9 or C19 or C20 or C21), 126.8 (C6 or C7 or C8 or C9 or C19 or C20 or C21), 123.5 (C6 or C7 or C8 or C9 or C19 or C20 or C21), 66.3 (C17), 57.9 (C14), 38.7 (C2), 33.5 (C11), 24.7 (C4), 23.8 (C3), 22.9 (C15); ESI-MS m/z =

869.36 (2M+Na^+, 5.8), 446.17 (M+Na^+, 100), 424.19 (M+H^+, 11.5); HRMS (ESI) m/z = 446.1761 (calculated for $C_{25}H_{29}NO_3SNa^+$ = 446.1760).

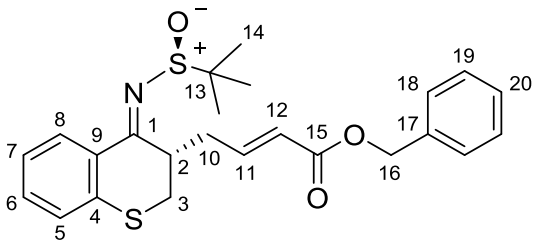
Benzyl-(*E*)-4-((*S*,*E*)-4-(((*S*$_S$)-*tert*-butylsulfinyl)imino)chroman-3-yl)but-2-enoate (240y)



General procedure C was followed using **239y** (1.19 g, 4.1 mmol, 1.0 eq.), benzyl acrylate **252** (1.88 mL, 12 μmol, 3.0 eq.), CuI (23 mg, 123 μmol, 3.0 mol%) and Grubbs II catalyst (70 mg, 82 μmol, 2.0 mol%) in anhydrous Et_2O (100 mL). The deep brown reaction mixture was purified by flash column chromatography over silica gel (eluting with 8:1 petroleum ether/ethyl acetate) to give **240y** (1.31 g, 3.08 mmol, 75%) as a brown oil. The product was isolated as a >25:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3064, 3034 (C-H_{aro}), 2986, 2877 (C-H_{ali}), 1716 (C=O), 1654 (C=N), 1612 (C=C), 1252, 1128 (C-O-C), 1063 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.91 (1H, dd, *J* = 8.0 and 1.4, Ar-H), 7.42-7.28 (6H, m, Ar-H), 7.06 (1H, ddd, *J* = 15.5, 9.0 and 6.0, 11-H), 6.98 (1H, app. t, *J* = 7.5, Ar-H), 6.91 (1H, d, *J* = 8.3, Ar-H), 6.02 (1H, d, *J* = 15.5, 12-H), 5.17 (2H, s, 16-H), 4.31 (1H, dd, *J* = 11.8 and 1.1, 3-H_a), 4.18 (1H, dd, *J* = 11.8 and 1.4, 3-H_b), 3.78-3.68 (1H, m, 2-H), 2.77-2.68 (1H, m, 10-H_a), 2.64-2.54 (1H, m, 10-H_b), 1.34 (9H, s, 14-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 171.6 (C1), 166.0 (C15), 158.2 (C4), 145.2 (C11), 136.1 (C17), 134.3 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 128.7 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 128.4 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 128.3 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 127.4 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 124.5 (C12), 121.7 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 119.9 (C9), 118.0 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 67.0

(C16), 66.3 (C3), 58.6 (C13), 38.8 (C2), 33.1 (C10), 23.0 (C14); ESI-MS m/z = 873.32 (2M+Na^+, 59.7), 448.15 (M+Na^+, 100), 426.17 (M+H^+, 76.7); HRMS (ESI) m/z = 448.1556 (calculated for $C_{24}H_{27}NNaO_4S^+$ = 448.1553).

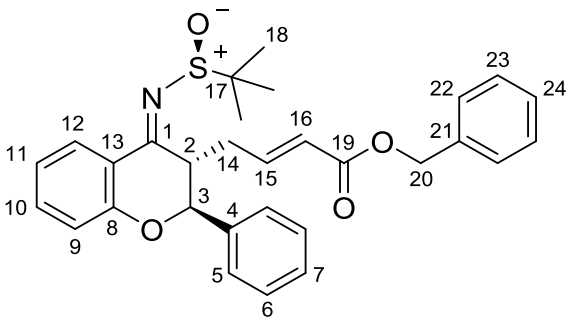
Benzyl-(*E*)-4-((*S*,*E*)-4-(((*S*$_S$)-*tert*-butylsulfinyl)imino)thiochroman-3-yl) but-2-enoate (240z)



General procedure C was followed using **239z** (800 mg, 2.6 mmol, 1.0 eq.), benzyl acrylate **252** (1.19 mL, 7.8 mmol, 3.0 eq.), CuI (15 mg, 78 μmol, 3.0 mol%) and Grubbs II catalyst (44 mg, 52 μmol, 2.0 mol%) in anhydrous Et_2O (150 mL). The deep brown reaction mixture was purified by flash column chromatography over silica gel (eluting with 6:1 petroleum ether/ethyl acetate) to give **240z** (873 mg, 1.98 mmol, 76%) as a brown oil. The product was isolated as a >25:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)$/ cm^{-1} (neat) = 3060, 3032 (C-H_{aro}), 2976, 2958, 2923, 2864 (C-H_{ali}), 1717 (C=O), 1679 (C=N), 1653 (C=C), 1070 (S-O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H = 8.08 (1H, dd, *J* = 8.1 and 1.0, Ar-H), 7.40-7.24 (6H, m, Ar-H), 7.17 (1H, d, *J* = 7.9, Ar-H), 7.14-7.08 (1H, m, Ar-H), 7.03 (1H, ddd, *J* = 15.5, 8.9 and 6.2, 11-H), 6.05 (1H, d, *J* = 15.5, 12-H), 5.17 (2H, s, 16-H), 4.24-4.14 (1H, m, 2-H), 3.44 (1H, dd, *J* = 13.8 and 2.7, 3-H_a), 2.90-2.76 (2H, m, 3-H_b and 10-H_a), 2.67-2.57 (1H, m, 10-H_b), 1.34 (9H, s, 14-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 174.1 (C1), 166.0 (C15), 145.4 (C11), 138.2 (C4 or C9 or C17), 136.1 (C4 or C9 or C17), 131.9 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 129.7 (C4 or C9 or C17), 129.6 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 128.7 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 128.4 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 128.3 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 127.6 (C5 or C6 or C7 or C8 or C18 or C19 or C20),

124.9 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 124.4 (C12), 66.3 (C16), 58.6 (C13), 36.2 (C2), 32.5 (C10), 28.9 (C3), 23.0 (C14); ESI-MS m/z = 905.27 ($2M+Na^+$, 28.2), 464.13 ($M+Na^+$, 100), 442.15 ($M+H^+$, 61.4); HRMS (ESI) m/z = 464.1324 (calculated for $C_{24}H_{27}NNaO_3S_2^+$ = 464.1325).

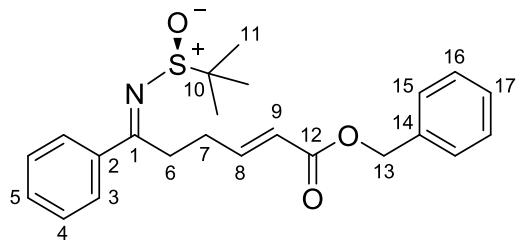
Benzyl-(*E*)-4-((2*S*,3*S*,*E*)-4-(((*S*$_S$)-*tert*-butylsulfinyl)imino)-2-phenyl chroman-3-yl)but-2-enoate (240aa)



General procedure C was followed using **239aa** (600 mg, 1.63 mmol, 1.0 eq.), benzyl acrylate **252** (748 μL, 4.89 mmol, 3.0 eq.), CuI (9 mg, 50 μmol, 3.0 mol%) and Grubbs II catalyst (28 mg, 33 μmol, 2.0 mol%) in anhydrous Et_2O (70 mL). The deep brown reaction mixture was purified by flash column chromatography over silica gel (eluting with 5:1 petroleum ether/ethyl acetate) to afford **240aa** (679 mg, 1.35 mmol, 83%) as a deep brown oil. The product was isolated as a >25:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3076, 3062, 3034 (C-H_{aro}), 2959, 2924, 2862 (C-H_{ali}), 1719 (C=O), 1652 (C=N), 1610 (C=C), 1234, 1122 (C-O-C), 1050 (S-O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.73 (1H, d, *J* = 7.9, Ar-H), 7.42-7.32 (6H, m, Ar-H), 7.30-7.24 (4H, m, Ar-H), 7.23-7.11 (2H, m, Ar-H), 7.03 (1H, d, *J* = 8.4, Ar-H), 6.92 (1H, dt, *J* = 15.6 and 7.8, 15-H), 6.07 (1H, d, *J* = 15.6, 16-H), 5.50 (1H, d, *J* = 6.0, 3-H), 5.24-5.10 (2H, m, 20-H), 4.53 (1H, td, *J* = 7.6 and 6.0, 2-H), 2.99-2.65 (2H, m, 14-H), 1.28 (9H, s, 18-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 170.6 (C1), 165.0 (C19), 157.3 (C4 or C8 or C13 or C21), 144.2 (C15), 135.2 (C4 or C8 or C13 or C21), 135.1 (C4 or C8 or C13 or C21), 133.4 (C5 or C6 or C7 or C9 or C10 or C11 or C12 or C22 or C23 or C24), 128.0 (C4 or C8 or C13 or C21),

127.8 (C5 or C6 or C7 or C9 or C10 or C11 or C12 or C22 or C23 or C24), 127.7 (C5 or C6 or C7 or C9 or C10 or C11 or C12 or C22 or C23 or C24), 127.7 (C5 or C6 or C7 or C9 or C10 or C11 or C12 or C22 or C23 or C24), 127.5 (C5 or C6 or C7 or C9 or C10 or C11 or C12 or C22 or C23 or C24), 127.4 (C5 or C6 or C7 or C9 or C10 or C11 or C12 or C22 or C23 or C24), 126.5 (C5 or C6 or C7 or C9 or C10 or C11 or C12 or C22 or C23 or C24), 123.5 (C5 or C6 or C7 or C9 or C10 or C11 or C12 or C22 or C23 or C24), 120.7 (C5 or C6 or C7 or C9 or C10 or C11 or C12 or C22 or C23 or C24), 119.0 (C5 or C6 or C7 or C9 or C10 or C11 or C12 or C22 or C23 or C24), 117.0 (C16), 76.6 (C3), 66.0 (C20), 65.4 (C2), 57.7 (C17), 37.8 (C14), 22.0 (C18); ESI-MS m/z = 524.18 ($M+Na^+$, 28.4), 502.20 ($M+H^+$, 100); HRMS (ESI) m/z = 502.2045 (calculated for $C_{30}H_{32}NO_4S^+$ = 502.2047).

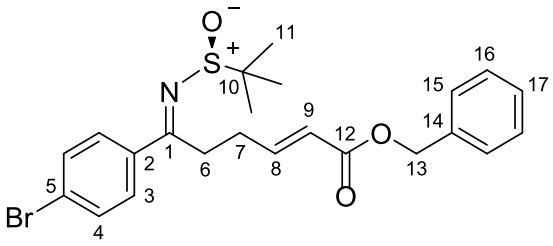
Benzyl-(2*E*,6*E*)-6-(((*S*$_S$)-*tert*-butylsulfinyl)imino)-6-phenylhex-2-enoate (240i)



General procedure C was followed using **239i** (395 mg, 1.5 mmol, 1.0 eq.), benzyl acrylate **252** (688 μL, 4.5 mmol, 3.0 eq.), CuI (9 mg, 45 μmol, 3.0 mol%) and Grubbs II catalyst (25 mg, 30 μmol, 2.0 mol%) in anhydrous Et_2O (50 mL). The yellow reaction mixture was purified by flash column chromatography over silica gel (eluting with 6:1 petroleum ether/ethyl acetate) to afford **240i** (471 mg, 1.19 mmol, 79%; single isomer) as a yellow oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3063, 3033 (C-H_{aro}), 2958, 2864 (C-H_{ali}), 1719 (C=O), 1688 (C=N), 1613 (C=C), 1073 (S-O); $[\alpha]_D^{23}$ = -22.4 (*c* = 1.0 g/100 mL in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.79 (2H, d, *J* = 7.4, 3-H), 7.51-7.40 (3H, m, 4-H and 5-H), 7.39-7.29 (5H, m, 15-H, 16-H and 17-H), 7.04 (1H, dt, *J* = 15.6 and 6.8, 8-H), 5.92 (1H, dt, *J* = 15.6 and 1.5, 9-H), 5.17 (2H, s, 13-H), 3.42-3.33 (2H, m, 7-H), 2.68-2.50 (2H, m, 6-H),

1.32 (9H, s, 11-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 193.4 (C1), 166.1 (C12), 147.1 (C8), 137.6 (C14), 136.2 (C2), 131.9 (C3 or C4), 128.9 (C3 or C4), 128.7 (C15 or C16 or C17), 128.31 (C15 or C16 or C17), 128.29 (C15 or C16 or C17), 127.4 (C5), 122.2 (C9), 66.2 (C13), 58.1 (C10), 31.2 (C6), 30.7 (C7), 22.9 (C11); ESI-MS m/z = 817.33 ($2M+Na^+$, 7.8), 420.16 ($M+Na^+$, 100), 398.17 ($M+H^+$, 25.1); HRMS (ESI) m/z = 420.1609 (calculated for $C_{23}H_{27}NO_3SNa^+$ = 420.1604).

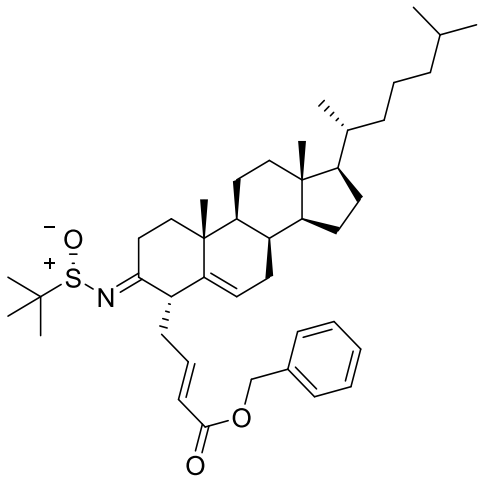
Benzyl-(2*E*,6*E*)-6-(4-bromophenyl)-6-(((*S*$_S$)-*tert*-butylsulfinyl)imino)hex-2-enoate (240ab)



General procedure C was followed using **239ab** (513 mg, 1.5 mmol, 1.0 eq.), benzyl acrylate **252** (689 μL, 4.5 mmol, 3.0 eq.) and Grubbs II catalyst (25 mg, 30 μmol, 2.0 mol%) in anhydrous Et_2O (50 mL). The deep brown reaction mixture was purified by flash column chromatography over silica gel (eluting with 4:1 petroleum ether/ethyl acetate) to give **240ab** (543 mg, 1.14 mmol, 76%; single isomer) as a brown oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3089, 3032, 3009 (C-H_{aro}), 2977, 2924, 2866 (C-H_{ali}), 1716 (C=O), 1654 (C=N), 1634 (C=C), 1071 (S-O), 1088 (C-Br); $[\alpha]_D^{23}$ = -14.3 (*c* = 1.0 g/100 mL in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.66 (2H, d, *J* = 7.5, Ar-H), 7.56 (2H, d, *J* = 8.6, Ar-H), 7.42-7.29 (5H, m, Ar-H), 7.02 (1H, dt, *J* = 15.6 and 6.8, 8-H), 5.91 (1H, d, *J* = 15.6, 9-H), 5.17 (2H, s, 13-H), 3.49-3.20 (2H, m, 7-H), 2.73-2.43 (2H, m, 6-H), 1.31 (9H, s, 11-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 176.6 (C1), 166.1 (C12), 146.8 (C8), 136.5 (C2), 136.1 (C14), 132.2 (C3 or C4 or C15 or C16 or 17), 128.9 (C3 or C4 or C15 or C16 or 17), 128.7 (C3 or C4 or C15 or C16 or 17), 128.4 (C3 or C4 or C15 or C16 or 17), 128.3 (C3 or C4 or C15 or C16 or 17), 126.7 (C5), 122.4 (C9), 66.3 (C13), 58.3 (C10), 31.2 (C6), 30.5 (C7), 22.9 (C11); ESI-MS m/z = 977.15

(2M+Na^+, 43.4), 500.06 (M+Na^+, 69.9), 478.08 (M+H^+, 100); HRMS (ESI) m/z = 478.0866 (calculated for $C_{23}H_{27}{}^{81}BrNO_3S^+$ = 478.0869).

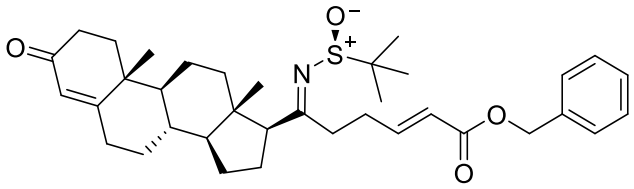
Benzyl-4-((4*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-3-(((*S*$_S$)-*tert*-butylsulfinyl) imino)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11, 12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-4-yl) but-2-enoate (240ae)



General procedure C was followed using **239ae** (50 mg, 95 μmol, 1.0 eq.), benzyl acrylate **252** (44 μL, 285 μmol, 3.0 eq.), CuI (1 mg, 3 μmol, 3.0 mol%) and Grubbs II catalyst (2 mg, 2 μmol, 2.0 mol%) in anhydrous Et_2O (15 mL). The yellow reaction mixture was purified by flash column chromatography over silica gel (eluting with 3:1 Et_2O/petroleum ether affording **240ae** (36 mg, 54 μmol, 57%) as a pale yellow oil. The product was isolated as a 10:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3064, 3031 (C-H_{aro}), 2976, 2962, 2923, 2889, 2862 (C-H_{ali}), 1726 (C=O), 1687 (C=N), 1639, 1616 (C=C), 1076 (S-O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.40-7.30 (5H, m), 7.10-6.99 (1H, m), 5.89 (1H, d, *J* = 15.8), 5.39-5.33 (1H, m), 5.16 (2H, s), 3.34-3.24 (1H, m), 3.16-3.06 (1H, m), 2.90-2.78 (1H, m), 2.55-2.35 (2H, m), 2.13-1.96 (2H, m), 1.93-1.78 (2H, m), 1.52-1.44 (4H, m), 1.40-1.30 (4H, m), 1.28-1.23 (4H, m), 1.19 (9H, s), 1.15-0.98 (11H, m), 0.91 (3H, d, *J* = 6.5), 0.87 (3H, d, *J* = 1.8), 0.85 (3H, *J* = 1.8), 0.71 (3H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C

= 188.9 (C), 166.5 (C), 149.2 (C), 141.5 (C), 136.3 (CH), 128.7 (CH), 128.4 (CH), 128.3 (CH), 122.0 (CH), 121.7 (CH), 66.2 (CH_2), 60.6 (C), 56.8 (CH), 56.2 (CH), 49.5 (CH), 48.0 (CH), 42.5 (C), 41.5 (C), 39.8 (CH_2), 39.7 (CH_2), 36.9 (CH_2), 36.3 (CH_2), 35.9 (CH), 32.0 (CH_2), 31.6 (CH), 31.3 (CH_2), 29.7 (CH_2), 28.4 (CH_2), 28.2 (CH), 24.3 (CH_2), 24.0 (CH_2), 23.0 (CH_3), 22.7 (CH_3), 22.3 (CH_3), 21.6 (CH_2), 21.1 (CH_3), 18.8 (CH_3), 12.1 (CH_3); ESI-MS m/z = 684.44 ($M+Na^+$, 100), 662.46 ($M+H^+$, 52.5); HRMS (ESI) m/z = 684.4431 (calculated for $C_{42}H_{63}NNaO_3S^+$ = 684.4421).

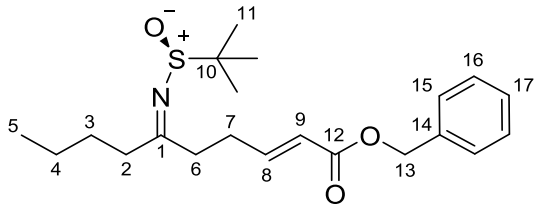
Benzyl-6-(((*S*S)-*tert*-butylsulfinyl)imino)-6-((8*S*,9*S*,10*R*,13*S*,14*S*,17*S*)-10,13-dimethyl-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradeca hydro-1H -cyclo penta[a]phenanthren-17-yl)hex-2-enoate (240af)



General procedure C was followed using **239af** (300 mg, 656 μmol, 1.0 eq.), benzyl acrylate **252** (301 μL, 1.97 mmol, 3.0 eq.), CuI (4 mg, 20 μmol, 3.0 mol%) and Grubbs II catalyst (11 mg, 13 μmol, 2.0 mol%) in anhydrous Et_2O (50 mL). The deep yellow reaction mixture was purified by flash column chromatography over silica gel (eluting with 4:1 to 2:1 petroleum ether/ethyl acetate) affording **240af** (241 mg, 407 μmol, 62%) as a pale yellow oil. The product was isolated as a 1:1 mixture of diastereomers. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3134, 3117 (C-H_{alkene}), 3098, 3091, 3054, 3032 (C-H_{aro}), 2932, 2888, 2874, 2851 (C-H_{ali}), 1717, 1702 (C=O), 1654 (C=N), 1614 (C=C), 1069 (S-O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.43-7.30 (5H, m), 7.0-6.97 (1H, m), 6.86-6.72 (1H, m), 5.92 (1H, d, *J* = 15.7), 5.18 (2H, m), 2.88-2.68 (2H, m), 2.51 (1H, t, *J* = 8.7), 2.46-2.36 (1H, m), 2.34-2.28 (1H, m), 2.27-2.14 (2H, m), 2.12 (3H, m), 2.07-1.97 (2H, m), 1.91 (1H, dd, *J* = 13.1 and 4.0), 1.87-1.77 (1H, m), 1.75-1.61 (4H, m), 1.54-1.46 (3H, m), 1.45-1.39 (3H, m), 1.21 (9H, s), 1.18-1.11 (3H, m), 0.65 (3H, d, *J* = 4.4); ^{13}C

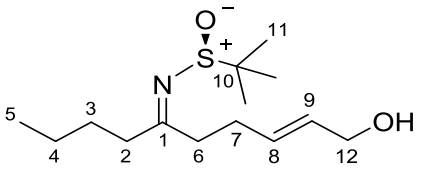
NMR (125 MHz, $CDCl_3$) δ_C = 209.5, 177.2, 166.3, 166.1, 148.2, 136.2, 128.7, 128.4, 128.3, 122.9, 116.6, 66.3, 63.6, 56.8, 56.2, 54.2, 44.0, 41.5, 39.2, 36.2, 33.0, 31.6, 29.2, 27.8, 24.5, 22.8, 20.6, 19.6, 17.8, 14.5, 13.5, 11.6; ESI-MS m/z = 614.32 ($M+Na^+$, 90.2), 592.34 ($M+H^+$, 100); HRMS (ESI) m/z = 592.3455 (calculated for $C_{36}H_{50}NO_4S^+$ = 592.3455).

Benzyl-(2*E*,6*Z*)-6-(((*S*$_S$)-*tert*-butylsulfinyl)imino)dec-2-enoate (367)



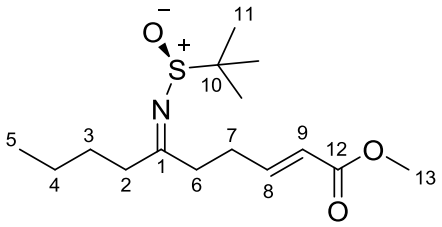
General procedure C was followed using **368** (50 mg, 205 μmol, 1.0 eq.), benzyl acrylate **252** (94 μL, 615 μmol, 3.0 eq.), CuI (1 mg, 6 μmol, 3.0 mol%) and Grubbs II catalyst (4 mg, 4 μmol, 2.0 mol%) in anhydrous Et_2O (50 mL). The yellow reaction mixture was purified by flash column chromatography over silica gel (eluting with 6:1 petroleum ether/ethyl acetate) to give **367** (70 mg, 185 μmol, 90%; single isomer) as a pale yellow oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3066, 3033 (C-H_{aro}), 2956, 2929, 2868 (C-H_{ali}), 1715 (C=O), 1654 (C=N), 1621 (C=C), 1067 (S-O); $[\alpha]_D^{23}$ = +26.7 (*c* = 1.0 g/100 mL in MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.40-7.27 (5H, m, 15-H, 16-H and 17-H), 7.07-6.92 (1H, m, 8-H), 5.95-5.85 (1H, m, 9-H), 5.16 (2H, s, 13-H), 2.97-2.73 (1H, m, 7-H_a), 2.72-2.32 (5H, m, 2-H, 6-H and 7-H_b), 1.63-1.50 (2H, m, 3-H), 1.42-1.32 (2H, m, 4-H), 1.22 (9H, s, 11-H), 0.92 (3H, t, *J* = 7.3, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 186.8 (C1), 166.3 (C12), 148.5 (C8), 136.2 (C14), 128.7 (C15 or C16), 128.3 (C15 or C16), 128.0 (C17), 121.8 (C9), 66.2 (C13), 56.5 (C10), 38.9 (C2 or C6), 36.6 (C2 or C6), 29.6 (C7), 27.8 (C3), 23.0 (C4), 22.4 (C11), 13.9 (C5); ESI-MS m/z = 400.19 ($M+Na^+$, 15.6), 378.20 ($M+H^+$, 100); HRMS (ESI) m/z = 378.2096 (calculated for $C_{21}H_{32}NO_3S^+$ = 378.2097).

(*S*S)-*N*-10-hydroxydec-8-en-5-ylidene)-2-methylpropane-2-sulfinamide (393)



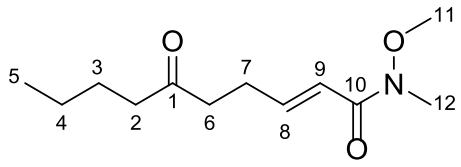
General procedure C was followed using **368** (50 mg, 206 μmol, 1.0 eq.), allyl alcohol **249** (42 μL, 618 μmol, 3.0 eq.), CuI (1 mg, 6 μmol, 3.0 mol%) and Grubbs II catalyst (4 mg, 4 μmol, 2.0 mol%) in anhydrous Et_2O (20 mL). The deep brown reaction mixture was purified by flash column chromatography over silica gel (eluting with 2:1 petroleum ether/ethyl acetate) to give **393** (11 mg, 41 μmol, 20%; single isomer) as a brown oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3350 (O-H), 2922, 2852 (C-H_{ali}), 1720 (C=N), 1643 (C=C), 1055 (S-O); $[\alpha]_D^{23}$ = +26.7 (*c* = 0.1 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ_H = 5.78-5.68 (2H, m, 8-H and 9-H), 4.17-4.07 (2H, m, 12-H), 2.95-2.15 (6H, m, 2-H, 6-H and 7-H), 1.67-1.59 (1H, m, 3-H_a), 1.51-1.33 (3H, m, 3-H_b and 4-H), 1.28 (9H, s, 11-H), 0.96 (3H, t, *J* = 6.5, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 188.2 (C1), 137.8 (C9), 115.5 (C8), 61.1 (C12), 56.5 (C10), 40.3 (C2 or C6 or C7), 36.7 (C2 or C6 or C7), 35.9 (C2 or C6 or C7), 29.7 (C3), 23.2 (C4), 22.5 (C11), 14.0 (C5); ESI-MS m/z = 569.34 ($2M+Na^+$, 4.4), 296.16 ($M+Na^+$, 35.8), 274.18 ($M+H^+$, 100); HRMS (ESI) m/z = 274.1837 (calculated for $C_{14}H_{28}NO_2S^+$ = 274.1835).

Methyl-(2*E*,6*Z*)-6-(((*S*$_S$)-*tert*-butylsulfinyl)imino)dec-2-enoate (384)



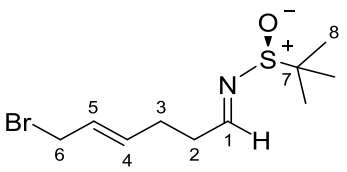
General procedure C was followed using **368** (601 mg, 2.47 mmol, 1.0 eq.), methyl acrylate **383** (672 μL, 7.41 mmol, 3.0 eq.), CuI (14 mg, 74 μmol, 3.0 mol%) and Grubbs II catalyst (42 mg, 49 μmol, 2.0 mol%) in anhydrous Et_2O (50 mL). The deep brown reaction mixture was purified by flash column chromatography over silica gel (eluting with 4:1 petroleum ether/ethyl acetate) to afford **384** (640 mg, 2.12 mmol, 86%; single isomer) as a brown oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2955, 2929, 2866 (C-H_{ali}), 1724 (C=O), 1657 (C=N), 1612 (C=C), 1073 (S-O); $[\alpha]_D^{23}$ = -14.4 (*c* = 1.0 g/100 mL in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.02-6.89 (1H, m, 8-H), 5.90-5.78 (1H, m, 9-H), 3.71 (3H, s, 13-H), 2.89-2.64 (2H, m, 7-H), 2.59-2.49 (1H, m, 6-H_a), 2.44-2.28 (3H, m, 2-H and 6-H_b), 1.63-1.53 (2H, m, 3-H), 1.43-1.30 (2H, m, 4-H), 1.22 (9H, s, 11-H), 0.92 (3H, t, *J* = 7.2, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 186.9 (C1), 167.0 (C12), 148.1 (C8), 121.7 (C9), 56.5 (C10), 51.6 (C13), 38.9 (C2 or C6), 36.6 (C2 or C6), 29.6 (C7), 27.8 (C3), 23.0 (C4), 22.4 (C11), 13.9 (C5); ESI-MS m/z = 324.16 ($M+Na^+$, 30.5), 302.17 ($M+H^+$, 100); HRMS (ESI) m/z = 302.1791 (calculated for $C_{15}H_{28}NO_3S^+$ = 302.1784).

(*E*)-*N*-methoxy-*N*-methyl-6-oxodec-2-enamide (417)



General procedure C was followed using **374** (1 g, 7.2 mmol, 1.0 eq.), *N*-methoxy-*N*-methylacrylamide **415** (1.66 g, 14.4 mmol, 2.0 eq.), CuI (41 mg, 216 μmol, 3.0 mol%) and Grubbs II catalyst (122 mg, 144 μmol, 2.0 mol%) in anhydrous Et_2O (50 mL). The yellow reaction mixture was purified by flash column chromatography over silica gel (eluting with 5:1 petroleum ether/ethyl acetate) to give **417** (1.06 g, 4.68 mmol, 65%) as a pale yellow oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2988, 2977, 2946, 2924, 2850 ($C\text{-}H_{ali}$), 1730 ($C{=}O_{ketone}$), 1649 ($C{=}O_{amide}$), 1602 (C=C); ^1H NMR (400 MHz, $CDCl_3$) δ_H = 6.33-6.23 (1H, m, 8-H), 6.22-6.12 (1H, m, 9-H), 3.70 (3H, s, 11-H or 12-H), 3.24 (3H, s, 11-H or 12-H), 2.92-2.82 (2H, m, 7-H), 2.62 (2H, t, *J* = 7.2, 2-H or 6-H), 2.43 (2H, t, *J* = 7.4, 2-H or 6-H), 1.38-1.26 (4H, m, 3-H and 4-H), 0.92 (3H, t, *J* = 7.3, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 210.8 (C1), 155.2 (C10), 130.6 (C8), 129.4 (C9), 53.9 (C11), 50.0 (C12), 33.4 (C2 or C6 or C7), 28.9 (C2 or C6 or C7), 28.4 (C2 or C6 or C7), 26.1 (C3 or C4), 25.1 (C3 or C4), 14.0 (C5); ESI-MS m/z = 477.29 ($2M+Na^+$, 18.2), 250.14 ($M+Na^+$, 100), 228.15 ($M+H^+$, 42.2); HRMS (ESI) m/z = 250.1415 (calculated for $C_{12}H_{21}NNaO_3^+$ = 250.1414).

(*S*S)-*N*-((1*E*,4*E*)-6-bromohex-4-en-1-ylidene)-2-methylpropane-2-sulfinamide (432)

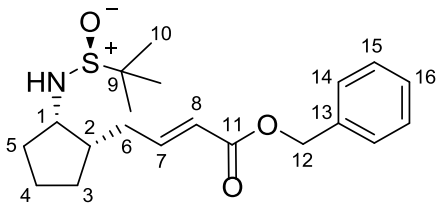


General procedure C was followed using **431** (600 mg, 3.2 mmol, 1.0 eq.), allyl bromide **245** (1.66 mL, 19.2 mmol, 6.0 eq.), CuI (18 mg, 96 μmol, 3.0 mol%) and Grubbs II catalyst (54 mg, 64 μmol, 2.0 mol%) in anhydrous Et_2O (75 mL). The yellow reaction mixture was purified by flash column chromatography over silica gel (eluting with 9:1 petroleum ether/ethyl acetate) to give **432** (99 mg, 352 μmol, 11%; single isomer) as a pale yellow oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3108 (C-H_{alkene}), 2981, 2962, 2923, 2900, 2888, 2826 (C-H_{ali}), 1667 (C=N), 1622 (C=C), 1088 (S-O), 744 (C-Br); $[\alpha]_D^{21}$ = -275.5 (*c* = 1.0 g/100 mL in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.14 (1H, t, *J* = 4.6, 1-H), 5.66-5.44 (2H, m, 4-H and 5-H), 2.79-2.62 (2H, m, 6-H), 2.58-2.51 (2H, m, 2-H), 2.39-2.31 (2H, m, 3-H), 1.27 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 169.3 (C1), 129.4 (C5), 126.6 (C4), 56.6 (C7), 36.1 (C6), 34.5 (C2), 28.2 (C3), 21.9 (C8); ESI-MS m/z = 585.04 ($2M+Na^+$, 11.9), 563.06 ($2M+H^+$, 100), 304.01 ($M+Na^+$, 67.2), 282.03 ($M+H^+$, 35.1); HRMS (ESI) m/z = 563.0618 (calculated for $C_{20}H_{37}{}^{81}Br_2N_2O_2S_2^+$ = 563.0617).

5.5. General procedure D: Synthesis sulfinamides 241, 273, 274, 366, 385 and 392.

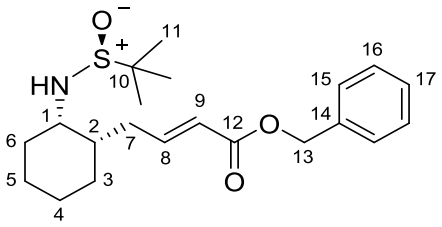
To a solution of sulfinimines **239c**, **239x**, **240**, **367**, **384** and **368** (199 μmol-4.41 mmol, 1.0 eq.) in anhydrous THF (20-50 mL) under argon atmosphere at -78 °C, DIBAL-H (1.0 M in THF or toluene, 438 μmol-9.7 mmol, 2.2 eq.) was added slowly. After completion of the addition, the mixture was stirred at room temperature. The reaction was monitored by TLC (petroleum ether/ethyl acetate) until no sulfinimine remained. Saturated aqueous solution of NH_4Cl (15-30 mL) was then added to the reaction mixture at -78 °C, and stirred for 5 minutes, ethyl acetate (10-20 mL) was added before the layers were separated, and the aqueous layer was washed with ethyl acetate (2 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ before filtration and concentrating *in vacuo*. Flash column chromatography (petroleum ether/ethyl acetate) gave desired products **241**, **273**, **274**, **366**, **385** and **392**.

Benzyl-(*E*)-4-((1*S*,2*S*)-2-(((*S*S)-*tert*-butylsulfinyl)amino)cyclopentyl)but-2-enoate (241b)



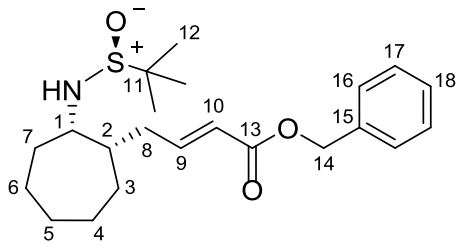
General procedure D was followed using **240b** (1.59 g, 4.41 mmol, 1.0 eq.) and DIBAL-H (1.0 M in THF, 9.7 mL, 9.7 mmol, 2.2 eq.) in anhydrous THF (40 mL). The crude product was obtained as a yellow oil and purified by flash column chromatography over silica gel (eluting with 2:1 petroleum ether/ethyl acetate) to give **241b** (1.14 g, 3.13 mmol, 71%) as a pale yellow oil. The product was isolated as a >25:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3203 (N-H), 3064, 3033 (C-H_{aro}), 2954, 2911, 2869 (C-H_{ali}), 1717 (C=O), 1651 (C=C), 1025 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.39-7.29 (5H, m, 14-H, 15-H and 16-H), 6.98 (1H, dt, *J* = 15.0 and 7.0, 7-H), 5.92 (1H, dt, *J* = 15.0 and 1.4, 8-H), 5.17 (2H, s, 12-H), 3.37-3.28 (1H, m, 1-H), 3.15 (1H, d, *J* = 4.9, N-H), 2.62-2.53 (1H, m, 5-H_a), 2.20-2.10 (1H, m, 2-H), 2.05-1.97 (1H, m, 5-H_b), 1.95-1.85 (2H, m, 6-H), 1.71-1.54 (3H, m, 3-H and 4-H), 1.33-1.23 (1H, m, 3-H or 4-H), 1.18 (9H, s, 10-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 166.4 (C11), 148.1 (C7), 136.2 (C13), 128.7 (C14 or C15), 128.4 (C14 or C15), 128.3 (C16), 122.5 (C8), 66.2 (C12), 62.2 (C1), 55.6 (C9), 46.2 (C2), 36.2 (C6), 33.2 (C5), 30.0 (C3 or C4), 22.7 (C3 or C4), 22.0 (C10); ESI-MS m/z = 749.36 (2M+Na^+, 38.4), 727.37 (2M+H^+, 7.7), 386.17 (M+Na^+, 36.3), 364.19 (M+H^+, 100); HRMS (ESI) m/z = 364.1957 (calculated for $C_{20}H_{30}NO_3S^+$ = 364.1941).

Benzyl-(*E*)-4-((1*S*,2*S*)-2-(((*S*S)-*tert*-butylsulfinyl)amino)cyclohexyl)but-2-enoate (241c)



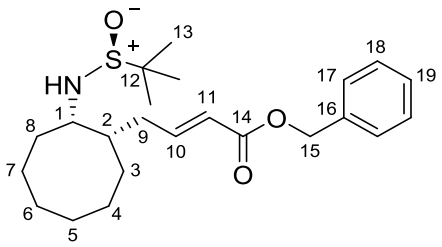
General procedure D was followed using **240c** (293 mg, 780 μmol, 1.0 eq.) and DIBAL-H (1.0 M in THF, 1.72 mL, 1.72 mmol, 2.2 eq.) in anhydrous THF (30 mL). The crude product was obtained as a deep yellow oil and purified by flash column chromatography over silica gel (eluting with 3:1 petroleum ether/ethyl acetate) to give **241c** (221 mg, 585 μmol, 75%) as a pale yellow oil. The product was isolated as a >25:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3227 (N-H), 3067, 3029 (C-H_{aro}), 2952, 2913, 2875 (C-H_{ali}), 1715 (C=O), 1654 (C=C), 1065 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.40-7.35 (5H, m, 15-H, 16-H and 17-H), 7.03 (1H, ddd, *J* = 15.5, 7.9 and 6.5, 8-H), 5.90 (1H, dt, *J* = 15.5 and 1.3, 9-H), 5.19 (2H, s, 13-H), 4.40-4.30 (1H, m, 1-H), 3.99-3.89 (1H, m, N-H), 3.60-3.52 (1H, m, 2-H), 2.77 (1H, dtd, *J* = 12.9, 6.5 and 1.4, 6-H_a), 2.46 (1H, dt, *J* = 12.9 and 6.5, 6-H_b), 2.23-2.03 (4H, m, 3-H and 7-H), 1.90-1.81 (1H, m, 4-H_a or 5-H_a), 1.72-1.57 (2H, m, 4-H or 5-H), 1.47-1.36 (1H, m, 4-H_b or 5-H_b), 1.20 (9H, s, 11-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 166.6 (C12), 148.6 (C8), 136.5 (C14), 128.9 (C15 or C16), 128.6 (C15 or C16), 128.5 (C17), 122.8 (C9), 66.5 (C13), 61.1 (C1), 56.8 (C10), 49.0 (C2), 35.6 (C6), 35.0 (C3 or C5 or C7), 34.1 (C3 or C5 or C7), 29.0 (C3 or C5 or C7), 25.7 (C4), 22.6 (C11); ESI-MS m/z = 777.39 ($2M+Na^+$, 23.8), 755.41 ($2M+H^+$, 4.7), 400.19 ($M+Na^+$, 100), 378.20 ($M+H^+$, 77.1); HRMS (ESI) m/z = 400.1921 (calculated for $C_{21}H_{31}NNaO_3S^+$ = 400.1917).

Benzyl-(*E*)-4-((1*S*,2*S*)-2-(((*S*S)-*tert*-butylsulfinyl)amino)cycloheptyl)but-2-enoate (241d)



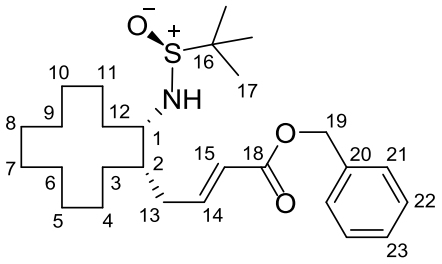
General procedure D was followed using **240d** (150 mg, 385 μmol, 1.0 eq.) and DIBAL-H (1.0 M in toluene, 847 μL, 847 μmol, 2.2 eq.) in anhydrous THF (30 mL). The crude product was obtained as a yellow oil and purified by flash column chromatography over silica gel (eluting with 3:1 petroleum ether/ethyl acetate) to give **241d** (115 mg, 293 μmol, 76%) as a pale yellow oil. The product was isolated as a 10:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3406 (N-H), 3066, 3032 (C-H_{aro}), 2927, 2860 (C-H_{ali}), 1734 (C=O), 1619 (C=C), 1053 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.39-7.26 (5H, m, 16-H, 17-H and 18-H), 7.02-6.87 (1H, m, 9-H), 5.87 (1H, d, *J* = 14.9, 10-H), 5.16 (2H, s, 14-H), 3.39-3.26 (1H, m, 1-H), 3.20 (1H, d, *J* = 9.2, N-H), 3.08-2.91 (1H, m, 2-H), 2.83-2.64 (2H, m, 8-H), 2.63-2.44 (1H, m, 3-H_a), 2.39-2.17 (1H, m, 3-H_b), 1.94-1.71 (4H, m, 4-H and 7-H), 1.72-1.57 (1H, m, 6-H_a), 1.44-1.26 (3H, m, 5-H and 6-H_b), 1.21 (9H, s, 12-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 166.1 (C13), 147.7 (C9), 136.1 (C15), 128.5 (C16 or C17), 128.3 (C16 or C17), 128.2 (C18), 122.8 (C10), 66.3 (C14), 56.7 (C11), 52.4 (C1), 39.1 (C2), 36.4 (C8), 35.4 (C3), 33.1 (C4 or C7), 28.7 (C4 or C7), 27.6 (C5 or C6), 25.3 (C5 or C6), 22.2 (C12); ESI-MS m/z = 414.20 ($M+Na^+$, 11.2), 392.22 ($M+H^+$, 100); HRMS (ESI) m/z = 392.2253 (calculated for $C_{22}H_{34}NO_3S^+$ = 392.2254).

Benzyl-(*E*)-4-((1*S*,2*S*)-2-(((*S*S)-*tert*-butylsulfinyl)amino)cyclooctyl)but-2-enoate (241e)



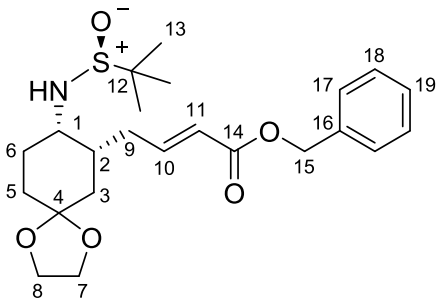
General procedure D was followed using **240e** (201 mg, 498 μmol, 1.0 eq.) and DIBAL-H (1.0 M in toluene, 1.1 mL, 1.1 mmol, 2.2 eq.) in anhydrous THF (30 mL). The crude product was obtained as a deep brown oil and purified by flash column chromatography over silica gel (eluting with 1:1 petroleum ether/ethyl acetate) to give **241e** (117 mg, 289 μmol, 58%) as a pale brown oil. The product was isolated as a 10:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3296 (N-H), 3065, 3032 (C-H_{aro}), 2926, 2861 (C-H_{ali}), 1720 (C=O), 1611 (C=C), 1052 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.33-7.25 (5H, m, 17-H, 18-H and 19-H), 6.99-6.90 (1H, m, 10-H), 5.85 (1H, d, *J* = 15.6, 11-H), 5.10 (2H, s, 15-H), 3.52-3.41 (1H, m, 1-H), 3.19-3.10 (1H, m, N-H), 2.95-2.86 (1H, m, 8-H_a), 2.35-2.20 (2H, m, 2-H and 8-H_b), 2.19-2.09 (2H, m, 9-H), 1.50-1.40 (3H, m, 3-H and 7-H_a), 1.29-1.19 (7H, m, 4-H, 5-H, 6-H and 7-H_b), 1.18 (9H, s, 13-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 166.5 (C14), 148.8 (C10), 136.4 (C16), 128.9 (C17 or C18), 128.6 (C17 or C18), 128.2 (C19), 122.0 (C11), 66.5 (C15), 56.7 (C12), 45.6 (C1), 41.4 (C2), 39.1 (C9), 36.9 (C8), 34.9 (C3 or C7), 33.9 (C3 or C7), 27.0 (C4 or C5 or C6), 25.4 (C4 or C5 or C6), 25.0 (C4 or C5 or C6), 22.6 (C13); ESI-MS m/z = 833.45 ($2M+Na^+$, 3.2), 811.47 ($2M+H^+$, 11.6), 428.22 ($M+Na^+$, 70.9), 406.24 ($M+H^+$, 100); HRMS (ESI) m/z = 406.2415 (calculated for $C_{23}H_{36}NO_3S^+$ = 406.2410).

Benzyl-(*E*)-4-((1*S*,2*S*)-2-(((*S*S)-*tert*-butylsulfinyl)amino)cyclododecyl) but-2-enoate (241f)



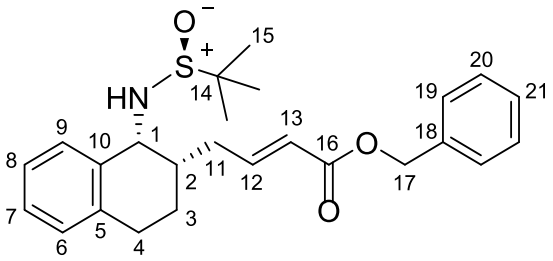
General procedure D was followed using **240f** (100 mg, 218 μmol, 1.0 eq.) and DIBAL-H (1.0 M in THF, 480 μL, 480 μmol, 2.2 eq.) in anhydrous THF (50 mL). The crude product was obtained as a deep yellow oil and purified by flash column chromatography over silica gel (eluting with 4:1 petroleum ether/ethyl acetate) to afford **241f** (76 mg, 166 μmol, 76%) as a pale yellow oil. The product was isolated as a >25:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3260 (N-H), 3062, 3032 (C-H_{aro}), 2932, 2901, 2862, 2851 (C-H_{ali}), 1719 (C=O), 1621 (C=C), 1075 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.47-7.28 (5H, m, 21-H, 22-H and 23-H), 6.99 (1H, dt, *J* = 15.6 and 7.2, 14-H), 5.91 (1H, d, *J* = 15.6, 15-H), 5.20 (2H, s, 19-H), 4.21-4.01 (1H, m, 1-H), 3.46 (1H, d, *J* = 3.5, N-H), 3.13-2.99 (1H, m, 2-H), 2.78-2.66 (1H, m, 12-H_a), 2.62-2.42 (1H, m, 12-H_b), 2.29-1.86 (3H, m, 3-H or 11-H), 1.84-1.67 (1H, m, 3-H or 11-H), 1.62-1.22 (16H, m, 4-H, 5-H, 6-H, 7-H, 8-H, 9-H, 10-H and 13-H), 1.26 (9H, s, 17-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 165.9 (C18), 146.7 (C14), 136.0 (C20), 128.5 (C21 or C22), 128.2 (C21 or C22), 128.1 (C23), 123.0 (C15), 66.1 (C19), 56.4 (C16), 44.1 (C1), 40.9 (C2), 40.2 (C13), 37.9 (C12), 33.8 (C3 or C11), 29.9 (C3 or C11), 26.5 (C4 or C5 or C6 or C7 or C8 or C9 or C10), 26.4 (C4 or C5 or C6 or C7 or C8 or C9 or C10), 24.6 (C4 or C5 or C6 or C7 or C8 or C9 or C10), 24.5 (C4 or C5 or C6 or C7 or C8 or C9 or C10), 23.8 (C4 or C5 or C6 or C7 or C8 or C9 or C10), 23.5 (C4 or C5 or C6 or C7 or C8 or C9 or C10), 22.3 (C17), 21.9 (C4 or C5 or C6 or C7 or C8 or C9 or C10); ESI-MS m/z = 945.58 (2M+Na^+, 24.1), 923.59 (2M+H^+, 9.0), 484.28 (M+Na^+, 19.9), 462.30 (M+H^+, 100); HRMS (ESI) m/z = 462.3042 (calculated for $C_{27}H_{44}NO_3S^+$ = 462.3036).

Benzyl-(*E*)-4-((7*R*,8*S*)-8-(((*S*S)-*tert*-butylsulfinyl)amino)-1,4-dioxaspiro [4.5]decan-7-yl)but-2-enoate (241g)



General procedure D was followed using **240g** (100 mg, 230 μmol, 1.0 eq.) and DIBAL-H (1.0 M in THF, 506 μL, 506 μmol, 2.2 eq.) in anhydrous THF (30 mL). The crude product was obtained as a brown oil and purified by flash column chromatography over silica gel (eluting with 2:1 petroleum ether/ethyl acetate) to afford **241g** (80 mg, 184 μmol, 80%) as a pale brown oil. The product was isolated as a >25:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3304 (N-H), 3063, 3032 (C-H_{aro}), 2950, 2927, 2885 (C-H_{ali}), 1717 (C=O), 1652 (C=C), 1264, 1107 (C-O-C), 1010 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.44-7.31 (5H, m, 17-H, 18-H and 19-H), 6.99 (1H, dt, *J* = 15.5 and 7.2, 10-H), 6.00 (1H, d, *J* = 15.5, 11-H), 5.25-5.15 (2H, m, 15-H), 3.99-3.89 (4H, m, 7-H and 8-H), 3.61-3.51 (1H, m, 1-H), 3.12 (1H, d, *J* = 3.9, N-H), 2.47-2.35 (1H, m, 9-H_a), 2.26-2.09 (2H, m, 2-H and 9-H_b), 2.05-1.95 (1H, m, 6-H_a), 1.87-1.67 (2H, m, 5-H_a and 6-H_b), 1.66-1.47 (3H, m, 3-H and 5-H_b), 1.24 (9H, s, 13-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 166.3 (C14), 147.0 (C10), 136.2 (C16), 128.7 (C17 or C18), 128.4 (C17 or C18), 128.3 (C19), 123.4 (C11), 108.4 (C4), 66.3 (C15), 64.6 (C7 or C8), 64.5 (C7 or C8), 55.8 (C12), 52.5 (C1), 38.6 (C2), 35.6 (C3), 34.8 (C9), 29.6 (C5), 28.2 (C6), 22.7 (C13); ESI-MS m/z = 893.40 (2M+Na^+, 59.6), 458.19 (M+Na^+, 52.8), 436.21 (M+H^+, 100); HRMS (ESI) m/z = 436.2152 (calculated for $C_{23}H_{34}NO_5S^+$ = 436.2152); CHN Found: C, 63.2%; H, 7.7%; N, 3.3%, $C_{23}H_{33}NO_5S$ requires: C, 63.4%; H, 7.6%; N, 3.2%.

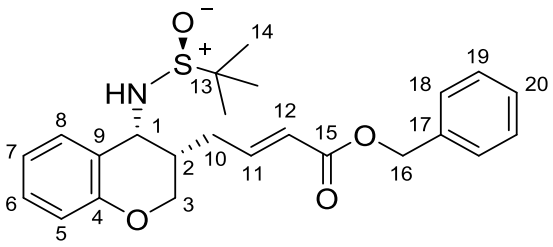
Benzyl-(*E*)-4-((1*R*,2*S*)-1-(((*S*S)-*tert*-butylsulfinyl)amino)-1,2,3,4-tetra hydronaphthalen-2-yl)but-2-enoate (241x)



General procedure D was followed using **240x** (500 mg, 1.18 mmol, 1.0 eq.) and DIBAL-H (1.0 M in THF, 2.6 mL, 2.6 mmol, 2.2 eq.) in anhydrous THF (20 mL). The crude product was obtained as a reddish brown oil and purified by flash column chromatography over silica gel (eluting with 1:1 petroleum ether/ethyl acetate) to give **241x** (397 mg, 932 μmol, 79%) as a reddish brown oil. The product was isolated as a 10:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3256 (N-H), 3061, 3032 (C-H_{aro}), 2926, 2865 (C-H_{ali}), 1718 (C=O), 1652 (C=C), 1043 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.57 (1H, d, *J* = 7.0, 6-H or 9-H), 7.42-7.29 (5H, m, 19-H, 20-H and 21-H), 7.25-7.16 (2H, m, 7-H and 8-H), 7.09 (1H, d, *J* = 7.9, 6-H or 9-H), 7.07-6.97 (1H, m, 12-H), 5.91 (1H, d, *J* = 15.7, 13-H), 5.19 (2H, s, 17-H), 4.26 (1H, app. t, *J* = 4.7, 1-H), 3.36 (1H, d, *J* = 4.7, N-H), 2.81-2.71 (2H, m, 11-H), 2.54-2.42 (1H, m, 2-H), 2.16-2.04 (2H, m, 4-H), 1.63-1.53 (2H, m, 3-H), 1.24 (9H, s, 15-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 166.3 (C16), 147.6 (C12), 137.2 (C5 or C10), 136.2 (C5 or C10), 136.0 (C18), 130.6 (C13), 129.2 (C6 or C7 or C8 or C9 or C19 or C20 or C21), 128.7 (C6 or C7 or C8 or C9 or C19 or C20 or C21), 128.5 (C6 or C7 or C8 or C9 or C19 or C20 or C21), 128.4 (C6 or C7 or C8 or C9 or C19 or C20 or C21), 127.8 (C6 or C7 or C8 or C9 or C19 or C20 or C21), 127.1 (C6 or C7 or C8 or C9 or C19 or C20 or C21), 123.1 (C6 or C7 or C8 or C9 or C19 or C20 or C21), 66.3 (C17), 58.5 (C14), 56.2 (C1), 40.1 (C2), 34.1 (C11), 26.4 (C4), 23.3 (C3), 23.0 (C15); ESI-MS m/z = 873.39 ($2M+Na^+$, 30.5), 448.19 ($M+Na^+$, 100), 426.20

(M+H$^+$, 9.3); HRMS (ESI) m/z = 448.1919 (calculated for $C_{25}H_{31}NO_3SNa^+$ = 448.1917).

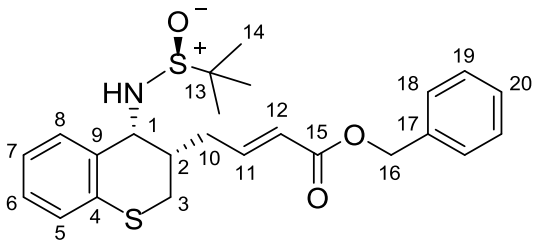
Benzyl-(*E*)-4-((3*S*,4*R*)-4-(((*S*$_S$)-*tert*-butylsulfinyl)amino)chroman-3-yl)but-2-enoate (241y)



General procedure D was followed using **240y** (150 mg, 353 μmol, 1.0 eq.) and DIBAL-H (1.0 M in THF, 777 μL, 777 μmol, 2.2 eq.) in anhydrous THF (50 mL). The crude product was obtained as a yellow oil and purified by flash column chromatography over silica gel (eluting with 1:1 petroleum ether/ethyl acetate) to afford **241y** (130 mg, 304 μmol, 86%) as a pale yellow oil. The product was isolated as a 10:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3302 (N-H), 3067, 3035 (C-H_{aro}), 2979, 2927, 2881, 2856 (C-H_{ali}), 1714 (C=O), 1655 (C=C), 1253, 1123 (C-O-C), 1046 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.40-7.30 (6H, m, Ar-H), 7.23-7.15 (1H, m, Ar-H), 7.12-7.02 (1H, m, 11-H), 6.97-6.97 (1H, m, Ar-H), 6.82 (1H, dd, *J* = 8.3 and 1.0, Ar-H), 6.01 (1H, d, *J* = 15.6, 12-H), 5.18 (2H, s, 16-H), 4.68 (1H, dd, *J* = 9.7 and 4.6, 1-H), 4.15 (1H, dd, *J* = 11.4 and 2.6, 3-H_a), 4.08 (1H, dd, *J* = 11.4 and 6.6, 3-H_b), 3.55 (1H, d, *J* = 9.7, N-H), 2.62-2.52 (1H, m, 10-H_a), 2.51-2.41 (1H, m, 2-H), 2.29-2.20 (1H, m, 10-H_b), 1.26 (9H, s, 14-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 166.1 (C15), 154.5 (C4), 146.0 (C11), 136.1 (C17), 131.1 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 130.0 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 128.7 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 128.5 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 128.4 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 123.8 (C12), 121.7 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 120.8 (C9), 117.2 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 66.4 (C16), 64.0 (C3),

56.0 (C13), 53.1 (C1), 38.2 (C2), 31.3 (C10), 22.8 (C14); ESI-MS m/z = 877.35 ($2M+Na^+$, 27.2), 450.17 ($M+Na^+$, 35.5), 428.18 ($M+H^+$, 100); HRMS (ESI) m/z = 428.1894 (calculated for $C_{24}H_{30}NO_4S^+$ = 428.1890).

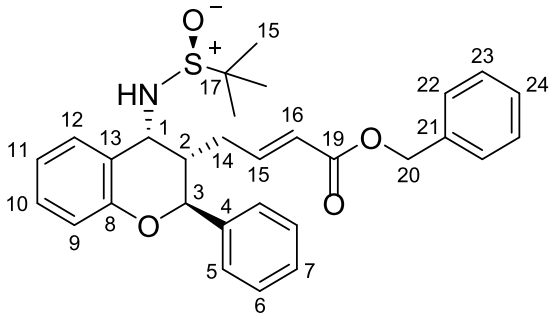
Benzyl-(*E*)-4-((3*S*,4*R*)-4-(((*S*S)-*tert*-butylsulfinyl)amino)thiochroman-3-yl)but-2-enoate (241z)



General procedure D was followed using **240z** (100 mg, 227 μmol, 1.0 eq.) and DIBAL-H (1.0 M in THF, 499 μL, 499 μmol, 2.2 eq.) in anhydrous THF (30 mL). The crude product was obtained as a deep yellow oil and purified by flash column chromatography over silica gel (eluting with 2:1 petroleum ether/ethyl acetate) to afford **241z** (86 mg, 193 μmol, 85%) as a pale yellow oil. The product was isolated as a >25:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3251 (N-H), 3064, 3050, 3034, 3008 (C-H_{aro}), 2954, 2926, 2869 (C-H_{ali}), 1719 (C=O), 1656 (C=C), 1072 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.40-7.36 (4H, m, Ar-H), 7.35-7.32 (1H, m, Ar-H), 7.31 (1H, dd, *J* = 7.7 and 1.2, Ar-H), 7.21-7.05 (3H, m, Ar-H), 6.99 (1H, ddd, *J* = 15.3, 8.0 and 6.8, 11-H), 5.95 (1H, d, *J* = 15.3, 12-H), 5.18 (2H, s, 16-H), 4.36-4.29 (1H, m, 1-H), 3.47 (1H, dd, *J* = 12.9 and 3.0, 3-H_a), 3.17 (1H, d, *J* = 1.9, N-H), 2.65 (1H, ddd, *J* = 12.9, 3.7 and 1.0, 3-H_b), 2.48-2.40 (1H, m, 2-H), 2.38-2.28 (1H, m, 10-H_a), 2.21-2.11 (1H, m, 10-H_b), 1.21 (9H, s, 14-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 166.2 (C15), 146.3 (C11), 136.1 (C4 or C9 or C17), 133.3 (C4 or C9 or C17), 132.8 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 130.3 (C4 or C9 or C17), 128.8 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 128.7 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 128.5 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 128.4 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 126.8 (C5 or C6 or C7 or C8

or C18 or C19 or C20), 125.2 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 123.8 (C12), 66.4 (C16), 55.8 (C13), 55.6 (C1), 35.0 (C2), 32.0 (C10), 24.7 (C3), 22.8 (C14); ESI-MS m/z = 466.14 ($M+Na^+$, 13.0), 444.16 ($M+H^+$, 100); HRMS (ESI) m/z = 444.1664 (calculated for $C_{24}H_{30}NO_3S_2^+$ = 444.1662).

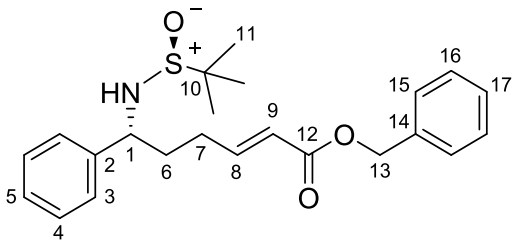
Benzyl-(*E*)-4-((2*S*,3*S*,4*R*)-4-(((*S*$_S$)-*tert*-butylsulfinyl)amino)-2-phenyl chroman-3-yl)but-2-enoate (241aa)



General procedure D was followed using **240aa** (100 mg, 199 μmol, 1.0 eq.) and DIBAL-H (1.0 M in THF, 438 μL, 438 μmol, 2.2 eq.) in anhydrous THF (30 mL). The crude product was obtained as a yellow oil and purified by flash column chromatography over silica gel (eluting with 3:1 petroleum ether/ethyl acetate) to give **241aa** (81 mg, 161 μmol, 81%) as a pale yellow oil. The product was isolated as a 4:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3393 (N-H), 3075, 3040 (C-H_{aro}), 2996, 2931, 2859 (C-H_{ali}), 1707 (C=O), 1639 (C=C), 1226, 1124 (C-O-C), 1071 (S-O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.77 (1H, d, *J* = 8.0, Ar-H), 7.41-7.31 (10H, m, Ar-H), 7.26-7.18 (2H, m, Ar-H), 7.02 (1H, dd, *J* = 9.0 and 6.4, Ar-H), 6.78-6.68 (1H, m, 15-H), 5.68 (1H, d, *J* = 16.1, 16-H), 5.16 (2H, s, 20-H), 4.99 (1H, d, *J* = 8.3, 3-H), 4.54-4.31 (1H, m, 1-H), 3.41 (1H, app. d, *J* = 8.1, 2-H), 2.54-2.45 (1H, m, N-H), 2.43-2.28 (2H, m, 14-H), 1.17 (9H, s, 15-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 171.3, 165.8, 154.6, 145.1, 138.8, 136.1, 130.8, 129.6, 129.0, 128.8, 128.7, 128.6, 128.5, 128.4, 127.2, 126.8, 126.1, 123.8, 123.2, 122.0, 117.0, 80.4, 66.3, 60.6, 56.6, 56.4, 53.6, 46.2, 41.5, 33.9, 31.9, 29.9, 29.2, 29.1, 27.8, 23.9, 23.0,

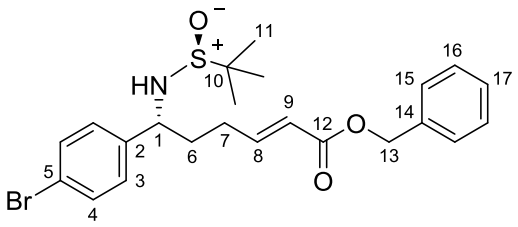
22.84, 22.80, 21.2, 20.6, 19.6, 14.44, 14.41 (44 out of a possible 48 carbon resonances observed; overlayed 24 carbon signals); ESI-MS m/z = 526.20 ($M+Na^+$, 14.6), 504.22 ($M+H^+$, 100); HRMS (ESI) m/z = 504.2202 (calculated for $C_{30}H_{34}NO_4S^+$ = 504.2203).

Benzyl-(*R*,*E*)-6-(((*S*$_S$)-*tert*-butylsulfinyl)amino)-6-phenylhex-2-enoate (241i)



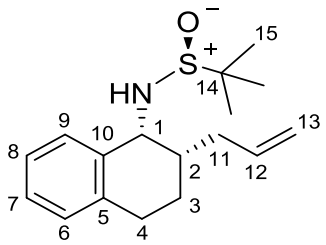
General procedure D was followed using **240i** (120 mg, 302 μmol, 1.0 eq.) and DIBAL-H (1.0 M in THF, 664 μL, 664 μmol, 2.2 eq.) in anhydrous THF (20 mL). The crude product was obtained as a colourless oil and purified by flash column chromatography over silica gel (eluting with 3:1 petroleum ether/ethyl acetate) to give **241i** (89 mg, 223 μmol, 74%) as a colourless oil. The product was isolated as a >25:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3223 (N-H), 3088, 3063, 3031 (C-H_{aro}), 2954, 2927, 2867 (C-H_{ali}), 1718 (C=O), 1653 (C=C), 1053 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.41-7.31 (10H, m, 3-H, 4-H, 5-H, 15-H, 16-H and 17-H), 6.97 (1H, dt, *J* = 15.7 and 6.6, 8-H), 5.84 (1H, dt, *J* = 15.7 and 1.5, 9-H), 5.19 (2H, s, 13-H), 4.43-4.37 (1H, m, 1-H), 3.43 (1H, d, *J* = 3.3, N-H), 2.23-1.93 (4H, m, 6-H and 7-H), 1.26 (9H, s, 11-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 166.3 (C12), 148.6 (C8), 141.7 (C14), 136.2 (C2), 129.0 (C3 or C4), 128.7 (C3 or C4), 128.4 (C15 or C16 or C17), 128.3 (C15 or C16 or C17), 128.4 (C15 or C16 or C17), 127.3 (C5), 121.6 (C9), 66.2 (C13), 58.6 (C1), 55.9 (C10), 34.8 (C6 or C7), 28.5 (C6 or C7), 22.8 (C11); ESI-MS m/z = 821.36 ($2M+Na^+$, 16.1), 799.38 ($2M+H^+$, 7.8), 422.17 ($M+Na^+$, 100), 400.19 ($M+H^+$, 58.3); HRMS (ESI) m/z = 422.1768 (calculated for $C_{23}H_{29}NO_3SNa^+$ = 422.1760).

Benzyl-(*R*,*E*)-6-(4-bromophenyl)-6-(((*S*S)-*tert*-butylsulfinyl)amino)hex-2-enoate (241ab)



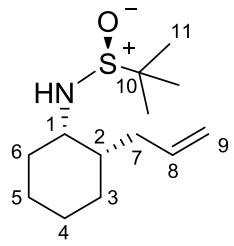
General procedure D was followed using **240ab** (100 mg, 210 μmol, 1.0 eq.) and DIBAL-H (1.0 M in THF, 462 μL, 462 μmol, 2.2 eq.) in anhydrous THF (40 mL). The crude product was obtained as a deep brown oil and purified by flash column chromatography over silica gel (eluting with 1:2 petroleum ether/ethyl acetate) to afford **241ab** (71 mg, 149 μmol, 71%) as a brown oil. The product was isolated as a >25:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3218 (N-H), 3089, 3063, 3032 (C-H_{aro}), 2948, 2901, 2865 (C-H_{ali}), 1714 (C=O), 1651 (C=C), 1068 (S-O), 1092 (C-Br); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.53-7.47 (2H, m, Ar-H), 7.41-7.35 (5H, m, Ar-H), 7.23-7.18 (2H, m, Ar-H), 6.94 (1H, dt, *J* = 15.6 and 6.7, 8-H), 5.83 (1H, dt, *J* = 15.6 and 1.3, 9-H), 5.18 (2H, s, 13-H), 4.38-4.31 (1H, m, 1-H), 3.37 (1H, d, *J* = 4.0, N-H), 2.23-2.03 (3H, m, 6-H_a and 7-H), 1.93-1.83 (1H, m, 6-H_b), 1.24 (9-H, s, 11-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 166.2 (C12), 148.2 (C8), 140.8 (C2), 136.1 (C14), 132.2 (C3 or C4 or C15 or C16 or 17), 129.0 (C3 or C4 or C15 or C16 or 17), 128.7 (C3 or C4 or C15 or C16 or 17), 128.44 (C3 or C4 or C15 or C16 or 17), 128.41 (C3 or C4 or C15 or C16 or 17), 122.2 (C5), 121.9 (C9), 66.3 (C13), 58.2 (C1), 56.1 (C10), 34.7 (C6), 28.4 (C7), 22.7 (C11); ESI-MS m/z = 981.18 ($2M+Na^+$, 18.9), 502.08 ($M+Na^+$, 100), 480.10 ($M+H^+$, 51.8); HRMS (ESI) m/z = 502.0852 (calculated for $C_{23}H_{28}{}^{81}BrNNaO_3S^+$ = 502.0845); CHN Found: C, 58.0%; H, 5.5%; N, 3.1%, $C_{23}H_{28}BrNO_3S$ requires: C, 57.7%; H, 5.9%; N, 2.9%.

(*S*S)-*N*-((1*R*,2*S*)-2-allyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-methyl propane-2-sulfinamide (273)



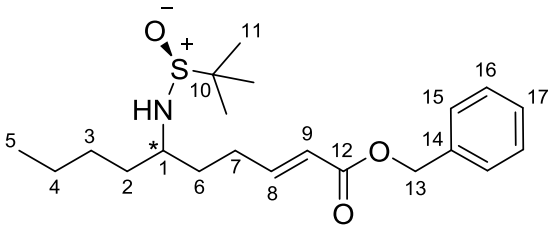
General procedure D was followed using **239x** (100 mg, 346 μmol, 1.0 eq.) and DIBAL-H (1.0 M in THF, 761 μL, 761 μmol, 2.2 eq.) in anhydrous THF (20 mL). The crude product was obtained as a reddish brown oil and purified by flash column chromatography over silica gel (eluting with 1:1 petroleum ether/ethyl acetate) to afford **273** (84 mg, 287 μmol, 83%) as a reddish brown oil. The product was isolated as a >25:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3228 (N-H), 3072, 3018 (C-H_{aro}), 2976, 2925, 2865 (C-H_{ali}), 1639 (C=C), 1057 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.39-7.34 (1H, m, 6-H or 7-H or 8-H or 9-H), 7.23-7.14 (2H, m, 6-H or 7-H or 8-H or 9-H), 7.13-7.09 (1H, m, 6-H or 7-H or 8-H or 9-H), 5.89 (1H, ddt, *J* = 16.8, 10.1 and 6.3, 12-H), 5.17-5.06 (2H, m, 13-H), 4.52 (1H, dd, *J* = 8.1 and 3.3, 1-H), 3.59 (1H, d, *J* = 8.1, N-H), 2.99 (1H, dt, *J* = 17.6 and 6.3, 11-H_a), 2.88 (1H, dt, *J* = 17.6 and 6.1, 11-H_b), 2.81-2.71 (1H, m, 2-H), 2.44-2.34 (1H, m, 4-H_a), 2.16-2.09 (1H, m, 4-H_b), 1.87-1.78 (1H, m, 3-H_a), 1.77-1.68 (1H, m, 3-H_b), 1.22 (9H, s, 15-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 137.1 (C12), 136.9 (C5 or C10), 136.8 (C5 or C10), 129.7 (C6 or C7 or C8 or C9), 129.3 (C6 or C7 or C8 or C9), 127.7 (C6 or C7 or C8 or C9), 125.9 (C6 or C7 or C8 or C9), 116.8 (C13), 58.3 (C1), 56.5 (C14), 38.8 (C2), 35.1 (C11), 27.4 (C4), 23.7 (C3), 23.0 (C15); ESI-MS m/z = 605.32 ($2M+Na^+$, 16.9), 314.15 ($M+Na^+$, 100), 292.17 ($M+H^+$, 14.1); HRMS (ESI) m/z = 314.1552 (calculated for $C_{17}H_{25}NOSNa^+$ = 314.1549).

(S_S)-*N*-((1*S*,2*S*)-2-allylcyclohexyl)-2-methylpropane-2-sulfinamide (274)



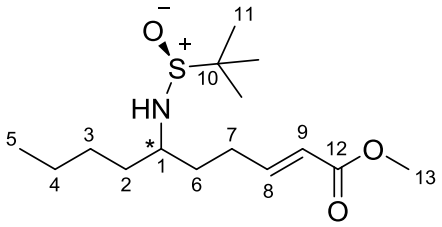
General procedure D was followed using **239c** (200 mg, 829 μmol, 1.0 eq.) and DIBAL-H (1.0 M in toluene, 1.82 mL, 1.82 mmol, 2.2 eq.) in anhydrous THF (20 mL). The crude product was obtained as a yellow oil and purified by flash column chromatography over silica gel (eluting with 2:1 petroleum ether/ethyl acetate) to afford **274** (161 mg, 663 μmol, 80%) as yellow oil. The product was isolated as a >10:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3239 (N-H), 2924, 2854 (C-H_{ali}), 1638 (C=C), 1055 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.76 (1H, ddd, *J* = 16.8, 11.1 and 7.1, 8-H), 5.12-4.96 (2H, m, 9-H), 3.55-3.45 (1H, m, 1-H), 3.19 (1H, d, *J* = 8.3, N-H), 2.20-2.10 (1H, m, 6-H_a), 2.01-1.78 (2H, m, 6-H_b and 3-H, 4-H, 5-H or 7-H), 1.75-1.56 (4H, m, 2-H and 3-H, 4-H, 5-H or 7-H), 1.54-1.46 (2H, m, 3-H, 4-H, 5-H or 7-H), 1.34-1.26 (2H, m, 3-H, 4-H, 5-H or 7-H), 1.24 (9H, s, 11-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 137.4 (C8), 116.1 (C9), 56.8 (C10), 55.8 (C6), 53.6 (C1), 41.0 (C2), 32.4 (C3 or C4 or C5 or C7), 30.5 (C3 or C4 or C5 or C7), 27.4 (C3 or C4 or C5 or C7), 23.0 (C11), 15.4 (C3 or C4 or C5 or C7); ESI-MS m/z = 509.32 ($2M+Na^+$, 100), 487.33 ($2M+H^+$, 48.8), 266.15 ($M+Na^+$, 47.6), 244.17 ($M+H^+$, 49.5); HRMS (ESI) m/z = 509.3212 (calculated for $C_{26}H_{50}N_2NaO_2S_2^+$ = 509.3206).

Benzyl-(*E*)-6-(((*S*$_S$)-*tert*-butylsulfinyl)amino)dec-2-enoate (366)



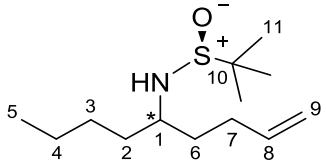
General procedure D was followed using **367** (500 mg, 1.32 mmol, 1.0 eq.) and DIBAL-H (1.0 M in THF, 2.9 mL, 2.9 mmol, 2.2 eq.) in anhydrous THF (40 mL). The crude product was obtained as a yellow oil and purified by flash column chromatography over silica gel (eluting with 1:1 petroleum ether/ethyl acetate) to give **366** (386 mg, 1.02 mmol, 77%) as a pale yellow oil. The product was isolated as a >10:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3238 (N-H), 3065, 3033 (C-H_{aro}), 2955, 2932, 2869 (C-H_{ali}), 1719 (C=O), 1653 (C=C), 1044 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.40-7.30 (5H, m, 15-H, 16-H and 17-H), 7.01 (1H, ddd, *J* = 15.6, 10.3 and 4.7, 8-H), 5.92 (1H, dt, *J* = 15.6 and 1.5, 9-H), 5.17 (2H, s, 13-H), 3.53-3.47 (1H, m, 1-H), 3.25-3.16 (1H, m, N-H), 2.99-2.91 (1H, m, 7-H_a), 2.42-2.26 (1H, m, 7-H_b), 1.79-1.65 (2H, m, 2-H or 6-H), 1.55-1.45 (2H, m, 2-H or 6-H), 1.34-1.27 (4H, m, 3-H and 4-H), 1.21 (9H, s, 11-H), 0.89-0.84 (3H, m, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 166.5 (C12), 149.1 (C8), 136.2 (C14), 128.7 (C15 or C16), 128.4 (C15 or C16), 128.3 (C17), 127.9 (C9), 66.2 (C13), 56.7 (C10), 55.5 (C1), 35.8 (C2 or C6), 34.8 (C2 or C6), 29.2 (C7), 27.8 (C3), 22.8 (C4), 22.7 (C11), 14.2 (C5); ESI-MS m/z = 402.20 ($M+Na^+$, 5.4), 380.22 ($M+H^+$, 100); HRMS (ESI) m/z = 380.2255 (calculated for $C_{21}H_{34}NO_3S^+$ = 380.2254).

Methyl-(*E*)-6-(((*S*S)-*tert*-butylsulfinyl)amino)dec-2-enoate (385)



General procedure D was followed using **384** (100 mg, 332 μmol, 1.0 eq.) and DIBAL-H (1.0 M in THF, 730 μL, 730 μmol, 2.2 eq.) in anhydrous THF (20 mL). The crude product was obtained as a deep red oil and purified by flash column chromatography over silica gel (eluting with 1:1 petroleum ether/ethyl acetate) to give **385** (83 mg, 272 μmol, 82%) as a reddish brown oil. The product was isolated as a 4:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3225 (N-H), 2953, 2931, 2862 (C-H_{ali}), 1724 (C=O), 1656 (C=C), 1050 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 6.95 (1H, dt, *J* = 15.6 and 6.9, 8-H), 5.83 (1H, d, *J* = 15.6, 9-H), 3.72 (3H, s, 13-H), 3.28-3.18 (1H, m, 1-H), 2.95 (1H, d, *J* = 6.5, N-H), 2.38-2.18 (2H, m, 7-H), 1.69 (1H, dddd, *J* = 14.2, 9.6, 6.5 and 4.7, 6-H_a), 1.61-1.47 (3H, m, 2-H and 6-H_b), 1.38-1.28 (4H, m, 3-H and 4-H), 1.21 (9H, s, 11-H), 0.90 (3H, t, *J* = 7.0, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 167.1 (C12), 148.9 (C8), 121.5 (C9), 56.2 (C10), 56.0 (C1), 51.6 (C13), 36.3 (C2), 34.1 (C6), 28.4 (C7), 28.0 (C3), 22.8 (C4), 22.7 (C11), 14.1 (C5); ESI-MS m/z = 326.17 ($M+Na^+$, 24.5), 304.19 ($M+H^+$, 100); HRMS (ESI) m/z = 304.1946 (calculated for $C_{15}H_{30}NO_3S^+$ = 304.1941).

(*S*S)-2-methyl-*N*-(non-1-en-5-yl)propane-2-sulfinamide (392)



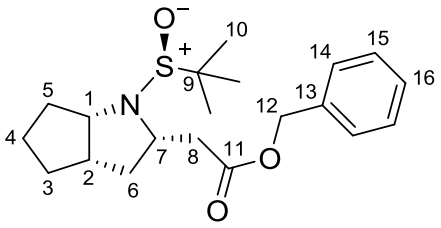
General procedure D was followed using **368** (300 mg, 1.23 mmol, 1.0 eq.) and DIBAL-H (1.0 M in THF, 2.71 mL, 2.71 mmol, 2.2 eq.) in anhydrous THF (50 mL). The crude product was obtained as a yellow oil and purified by flash column

chromatography over silica gel (eluting with 3:1 petroleum ether/ethyl acetate) to give **392** (220 mg, 898 μmol, 73%) as a yellow oil. The product was isolated as a 4:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3212 (N-H), 2956, 2922, 2872, 2855 (C-H_{ali}), 1638 (C=C), 1042 (S-O); ^1H NMR (400 MHz, $CDCl_3$) δ_H = 5.87-5.74 (1H, m, 8-H), 5.09-4.93 (2H, m, 9-H), 3.28-3.16 (1H, m, 1-H), 2.95 (1H, d, *J* = 6.9, N-H), 2.23-1.97 (2H, m, 7-H), 1.89-1.63 (4H, m, 2-H and 6-H), 1.38-1.26 (4H, m, 3-H and 4-H), 1.21 (9H, s, 11-H), 0.94-0.85 (3H, m, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 138.4 (C8), 115.0 (C9), 56.4 (C1), 55.9 (C10), 36.3 (C2 or C6), 35.0 (C2 or C6), 29.9 (C7), 27.9 (C3), 22.84 (C4), 22.80 (C11), 14.1 (C5); ESI-MS m/z = 268.17 ($M+Na^+$, 23.2), 246.18 ($M+H^+$, 100); HRMS (ESI) m/z = 246.1887 (calculated for $C_{13}H_{28}NOS^+$ = 246.1886).

5.6. General procedure E: Synthesis of pyrrolidine derivatives 242, 365 and 386.

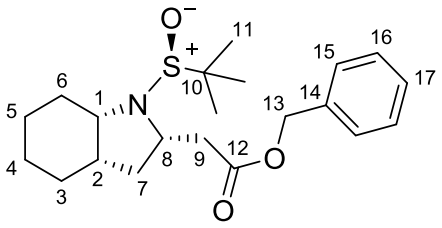
A flame-dried round bottom flask equipped with a magnetic stirring-bar was purged with argon gas and charged with a solution of sulfinamides **241**, **366** and **385** (164 μmol-1.6 mmol, 1.0 eq.) in anhydrous THF (15-50 mL). The reaction mixture was stirred at room temperature for 10 minutes before slowly adding of a suspension of NaH (60% dispersion in mineral oil, 197 μmol-1.92 mmol, 1.2 eq.) in anhydrous THF (5 mL). The reaction mixture was then stirred for 3-6 hours before adding NH_4Cl (saturated aqueous solution, 15 mL). The organic phase was extracted with ethyl acetate (2 × 20 mL), washed with brine (15 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Flash column chromatography (petroleum ether/ethyl acetate) afforded the desired pyrrolidine products **242**, **365** and **386**.

Benzyl-2-((2*S*,3a*S*,6a*S*)-1-((*S*$_S$)-*tert*-butylsulfinyl)octahydrocyclopenta [b]pyrrol-2-yl)acetate (242b)



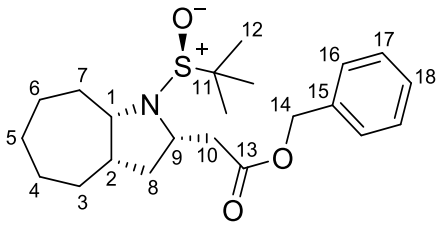
General procedure E was followed using **241b** (582 mg, 1.6 mmol, 1.0 eq.) and NaH (60% dispersion in mineral oil, 77 mg, 1.92 mmol, 1.2 eq.) in anhydrous THF (30 mL). The crude product was obtained as a yellow oil and purified by flash column chromatography over silica gel (eluting with 2:1 petroleum ether/ethyl acetate) to afford **242b** (448 mg, 1.23 mmol, 77%) as a pale yellow oil. The product was isolated as a 6:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3066, 3033 (C-H_{aro}), 2954, 2927, 2865 (C-H_{ali}), 1732 (C=O), 1062 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.38-7.28 (5H, m, 14-H, 15-H and 16-H), 5.14-5.07 (2H, m, 12-H), 4.38-4.25 (1H, m, 1-H), 4.21-4.09 (1H, m, 7-H), 3.45-3.36 (1H, m, 2-H), 2.76-2.64 (1H, m, 8-H_a), 2.45 (1H, app. dd, *J* = 15.8 and 10.6, 8-H_b), 1.90-1.76 (2H, m, 6-H), 1.67-1.47 (6H, m, 3-H, 4-H and 5-H), 1.28 (9H, s, 10-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 171.6 (C11), 136.0 (C13), 128.7 (C14 or C15), 128.34 (C16), 128.27 (C14 or C15), 66.3 (C12), 65.6 (C1), 58.9 (C7), 57.7 (C9), 40.3 (C2), 38.0 (C8), 34.1 (C6), 32.5 (C3 or C4 or C5), 29.8 (C3 or C4 or C5), 24.8 (C3 or C4 or C5), 23.5 (C10); ESI-MS m/z = 749.36 (2M+Na^+, 10.2), 386.17 (M+Na^+, 10.3), 364.19 (M+H^+, 100); HRMS (ESI) m/z = 364.1940 (calculated for $C_{20}H_{30}NO_3S^+$ = 364.1941).

Benzyl-2-((2*S*,3a*S*,7a*S*)-1-((*S*$_S$)-*tert*-butylsulfinyl)octahydro-1H-indol-2-yl)acetate (242c)



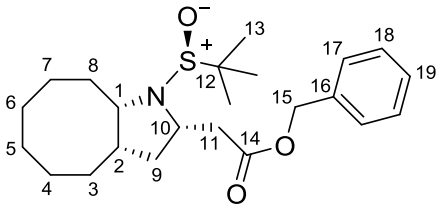
General procedure E was followed using **241c** (100 mg, 265 μmol, 1.0 eq.) and NaH (60% dispersion in mineral oil, 13 mg, 318 μmol, 1.2 eq.) in anhydrous THF (20 mL). The crude product was obtained as a reddish brown oil and purified by flash column chromatography over silica gel (eluting with 4:1 petroleum ether/ethyl acetate) to afford **242c** (75 mg, 199 μmol, 75%) as a reddish brown oil. The product was isolated as a 2:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3074, 3033 (C-H_{aro}), 2956, 2927, 2857 (C-H_{ali}), 1733 (C=O), 1059 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.40-7.27 (5H, m, 15-H, 16-H and 17-H), 5.11 (2H, s, 13-H), 4.75-4.65 (1H, m, 1-H), 4.32 (1H, ddd, *J* = 8.9, 5.7 and 2.4, 8-H), 2.86-2.79 (1H, m, 2-H), 2.67-2.57 (1H, m, 9-H_a), 2.52-2.41 (1H, m, 9-H_b), 2.06-1.99 (1H, m, 6-H_a), 1.92-1.84 (1H, m, 6-H_b), 1.82-1.67 (4H, m, 3-H and 7-H), 1.60-1.50 (2H, m, 4-H or 5-H), 1.45-1.27 (2H, m, 4-H or 5-H), 1.22 (9H, s, 11-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 171.1 (C12), 135.9 (C14), 128.7 (C15 or C16), 128.3 (C15 or C16), 127.1 (C17), 70.6 (C1), 66.5 (C13), 56.2 (C10), 49.4 (C8), 42.6 (C9), 42.1 (C2), 37.0 (C6), 33.2 (C3 or C7), 29.7 (C3 or C7), 25.9 (C4 or C5), 24.9 (C4 or C5), 23.9 (C11); ESI-MS m/z = 400.19 ($M+Na^+$, 19.9), 378.20 ($M+H^+$, 100); HRMS (ESI) m/z = 378.2093 (calculated for $C_{21}H_{32}NO_3S^+$ = 378.2097).

Benzyl-2-((2*S*,3a*S*,8a*S*)-1-((*S*$_S$)-*tert*-butylsulfinyl)decahydrocyclohepta [b]pyrrol-2-yl)acetate (242d)



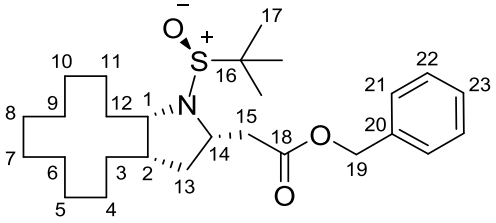
General procedure E was followed using **241d** (627 mg, 1.6 mmol, 1.0 eq.) and NaH (60% dispersion in mineral oil, 77 mg, 1.92 mmol, 1.2 eq.) in anhydrous THF (15 mL). The crude product was obtained as a yellow oil and purified by flash column chromatography over silica gel (eluting with 2:1 petroleum ether/ethyl acetate) to afford **242d** (482 mg, 1.23 mmol, 77%) as a pale yellow oil. The product was isolated as a 3:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3063, 3034 (C-H_{aro}), 2925, 2855 (C-H_{ali}), 1732 (C=O), 1065 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.37-7.30 (5H, m, 16-H, 17-H and 18-H), 5.10 (2H, s, 14-H), 4.31 (1H, ddd, *J* = 10.9, 7.0 and 3.7, 1-H), 3.86-3.78 (1H, m, 9-H), 3.75-3.45 (2H, m, 10-H), 3.36-3.25 (1H, m, 2-H), 2.58-2.48 (2H, m, 8-H), 2.35-2.26 (2H, m, 3-H), 1.92-1.72 (4H, m, 4-H and 7-H), 1.71-1.63 (1H, m, 6-H_a), 1.58-1.41 (3H, m, 5-H and 6-H_b), 1.30 (9H, s, 12-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 171.3 (C13), 136.0 (C15), 128.7 (C16 or C17), 128.4 (C16 or C17), 128.2 (C18), 66.3 (C14), 57.9 (C11), 50.1 (C1), 41.9 (C9), 40.8 (C10), 37.2 (C2), 31.4 (C8), 30.9 (C3), 28.5 (C4 or C7), 26.7 (C4 or C7), 25.0 (C5 or C6), 23.8 (C5 or C6), 21.2 (C12); ESI-MS m/z = 414.20 ($M+Na^+$, 10.4), 392.22 ($M+H^+$, 100); HRMS (ESI) m/z = 392.2252 (calculated for $C_{22}H_{34}NO_3S^+$ = 392.2254).

Benzyl-2-((2*S*,3a*S*,9a*S*)-1-((*S*$_S$)-*tert*-butylsulfinyl)decahydro-1H-cyclo octa[b]pyrrol-2-yl)acetate (242e)



General procedure E was followed using **241e** (107 mg, 264 μmol, 1.0 eq.) and NaH (60% dispersion in mineral oil, 13 mg, 317 μmol, 1.2 eq.) in anhydrous THF (25 mL). The crude product was obtained as a yellow oil and purified by flash column chromatography over silica gel (eluting with 2:1 petroleum ether/ethyl acetate) affording **242e** (80 mg, 198 μmol, 75%) as a pale yellow oil. The product was isolated as a 5:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3065, 3033 (C-H_{aro}), 2921, 2855 (C-H_{ali}), 1734 (C=O), 1077 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.40-7.27 (5H, m, 17-H, 18-H and 19-H), 5.13-5.07 (2H, m, 15-H), 4.32-4.12 (1H, m, 1-H), 3.52 (1H, ddt, *J* = 11.0, 8.0 and 5.3, 10-H), 2.56-2.46 (2H, m, 11-H), 2.21-2.05 (1H, m, 2-H), 1.94-1.85 (2H, m, 8-H or 9-H), 1.76-1.62 (4H, m, 3-H or 7-H and 8-H or 9-H), 1.55-1.41 (4H, m, 4-H and 3-H or 7-H), 1.40-1.30 (4H, m, 5-H and 6-H), 1.19 (9H, s, 13-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 171.0 (C14), 135.8 (C16), 128.7 (C17 or C18), 128.5 (C17 or C18), 128.4 (C19), 72.0 (C1), 66.6 (C15), 56.9 (C12), 49.8 (C10), 43.0 (C8 or C9), 41.0 (C2), 39.8 (C8 or C9), 35.0 (C11), 29.2 (C3 or C4 or C7), 28.0 (C3 or C4 or C7), 27.8 (C3 or C4 or C7), 27.0 (C5 or C6), 26.8 (C5 or C6), 23.7 (C13); ESI-MS m/z = 428.22 ($M+Na^+$, 61.6), 406.24 ($M+H^+$, 100); HRMS (ESI) m/z = 406.2411 (calculated for $C_{23}H_{36}NO_3S^+$ = 406.2410).

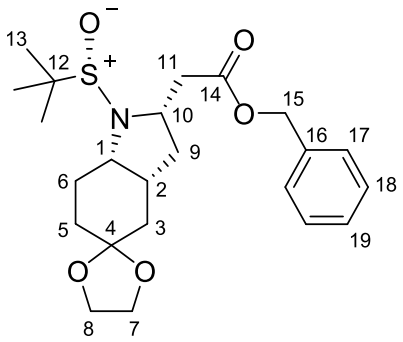
Benzyl-2-((2*S*,3a*S*,13a*S*)-1-((*S*S)-*tert*-butylsulfinyl)tetradecahydro-1H-cyclododeca[b]pyrrol-2-yl)acetate (242f)



General procedure E was followed using **241f** (100 mg, 217 μmol, 1.0 eq.) and NaH (60% dispersion in mineral oil, 10 mg, 260 μmol, 1.2 eq.) in anhydrous THF (30 mL). The crude product was obtained as a yellow oil and purified by flash column chromatography over silica gel (eluting with 5:1 petroleum ether/ethyl acetate) to give **242f** (74 mg, 161 μmol, 74%) as a pale yellow oil. The product was isolated as a 10:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^1$(neat) = 3062, 3033 (C-$H_{aro}$), 2971, 2943 (C-$H_{ali}$), 1712 (C=O), 1089 (S-O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.44-7.31 (5H, m, 21-H, 22-H and 23-H), 5.13 (2H, s, 19-H), 4.39-4.26 (1H, m, 1-H), 3.59-3.49 (1H, m, 14-H), 2.91 (1H, ddt, *J* = 15.1, 5.9 and 3.2, 12-H_a), 2.54 (1H, m, 12-H_b), 2.27 (1H, dd, *J* = 12.4 and 7.9, 15-H_a), 2.17-2.01 (1H, m, 2-H), 1.78-1.58 (3H, m, 3-H and 13-H_a), 1.55-1.27 (18H, m, 4-H, 5-H, 6-H, 7-H, 8-H, 9-H, 10-H, 11-H and 13-H_b and 15-H_b), 1.23 (9H, s, 17-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 166.3 (C18), 135.9 (C20), 128.7 (C21 or C22), 128.5 (C21 or C22), 128.4 (C23), 71.7 (C1), 66.5 (C19), 57.7 (C16), 48.1 (C14), 45.6 (C2), 44.5 (C12), 39.1 (C15), 31.1 (C13), 27.1 (C3 or C4 or C5 or C6 or C7 or C8 or C9 or C10 or C11), 26.6 (C3 or C4 or C5 or C6 or C7 or C8 or C9 or C10 or C11), 25.6 (C3 or C4 or C5 or C6 or C7 or C8 or C9 or C10 or C11), 24.69 (C3 or C4 or C5 or C6 or C7 or C8 or C9 or C10 or C11), 24.66 (C3 or C4 or C5 or C6 or C7 or C8 or C9 or C10 or C11), 24.0 (C3 or C4 or C5 or C6 or C7 or C8 or C9 or C10 or C11), 23.9 (C17), 23.8 (C3 or C4 or C5 or C6 or C7 or C8 or C9 or C10 or C11), 23.4 (C3 or C4 or C5 or C6 or C7 or C8 or C9 or C10 or C11), 23.3 (C3 or C4 or C5 or C6 or C7 or

C8 or C9 or C10 or C11); ESI-MS m/z = 945.58 ($2M+Na^+$, 42.0), 484.28 ($M+Na^+$, 82.2), 462.30 ($M+H^+$, 100); HRMS (ESI) m/z = 462.3047 (calculated for $C_{27}H_{44}NO_3S^+$ = 462.3036).

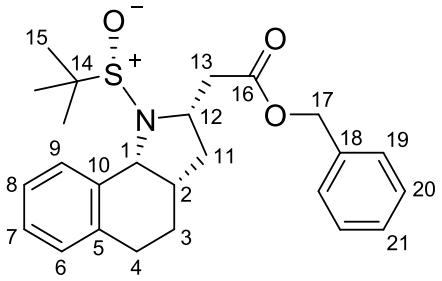
Benzyl-2-((2*S*,3a*R*,7a*S*)-1-((*S*$_S$)-*tert*-butylsulfinyl)octahydrospiro[indole-5, 2'-[1,3]dioxolan]-2-yl)acetate (242g)



General procedure E was followed using **241g** (131 mg, 300 μmol, 1.0 eq.) and NaH (60% dispersion in mineral oil, 14 mg, 360 μmol, 1.2 eq.) in anhydrous THF (30 mL). The crude product was obtained as a yellow oil and purified by flash column chromatography over silica gel (eluting with 3:1 petroleum ether/ethyl acetate) to give **242g** (99 mg, 228 μmol, 76%) as a pale yellow oil. The product was isolated as a 10:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^1$(neat) = 3070, 3031 (C-$H_{aro}$), 2955, 2902, 2844 (C-$H_{ali}$), 1719 (C=O), 1223, 1049 (C-O-C) 1064 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.41-7.29 (5H, m, 17-H, 18-H and 19-H), 5.10 (2H, s, 15-H), 4.38-4.28 (1H, m, 1-H), 3.96-3.83 (4H, m, 7-H and 8-H), 3.78-3.69 (1H, m, 10-H), 2.56-2.26 (3H, m, 2-H and 11-H), 2.18-2.02 (2H, m, 9-H), 1.98-1.85 (1H, m, 5-H_a or 6-H_a), 1.82-1.72 (1H, m, 5-H_a or 6-H_a), 1.67-1.57 (3H, m, 3-H and 5-H_b or 6-H_b), 1.48-1.37 (1H, m, 5-H_b or 6-H_b), 1.31 (9H, s, 13-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 166.3 (C14), 136.2 (C16), 128.7 (C17 or C18), 128.4 (C17 or C18), 128.3 (C19), 108.0 (C4), 66.3 (C15), 64.6 (C7 or C8), 64.5 (C7 or C8), 60.6 (C1), 57.9 (C12), 55.8 (C10), 49.1 (C2 or C11), 40.3 (C2 or C11), 39.3 (C3), 35.7 (C9), 33.3 (C5 or C6), 31.4 (C5 or C6), 21.1 (C13); ESI-MS m/z = 458.19 ($M+Na^+$,

62.6), 436.21 ($M+H^+$, 100); HRMS (ESI) m/z = 436.2163 (calculated for $C_{23}H_{34}NO_5S^+$ = 436.2152).

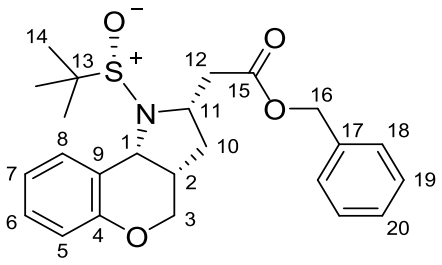
Benzyl-2-((2*S*,3a*S*,9b*R*)-1-((*S*$_S$)-*tert*-butylsulfinyl)-2,3,3a,4,5,9b-hexa hydro-1H-benzo[g]indol-2-yl)acetate (242x)



General procedure E was followed using **241x** (100 mg, 235 μmol, 1.0 eq.) and NaH (60% dispersion in mineral oil, 11 mg, 282 μmol, 1.2 eq.) in anhydrous THF (25 mL). The crude product was obtained as a yellow oil and purified by flash column chromatography over silica gel (eluting with 4:1 petroleum ether/ethyl acetate) to afford **242x** (73 mg, 172 μmol, 73%) as a pale yellow oil. The product was isolated as a 9:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3084, 3032 (C-H_{aro}), 2929, 2863 (C-H_{ali}), 1731 (C=O), 1061 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.40-7.07 (9H, m, 6-H, 7-H, 8-H, 9-H, 19-H, 20-H and 21-H), 5.13 (2H, s, 17-H), 4.77 (1H, d, *J* = 8.2, 1-H), 4.44-4.36 (1H, m, 12-H), 3.74 (1H, dd, *J* = 16.0 and 3.0, 13-H_a), 2.76-2.61 (2H, m, 11-H_a and 13-H_b), 2.56-2.47 (1H, m, 11-H_b), 2.01-1.88 (2H, m, 2-H and 4-H_a), 1.76-1.66 (2H, m, 3-H_a and 4-H_b), 1.48-1.36 (1H, m, 3-H_b), 0.98 (9H, s, 15-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 171.9 (C16), 140.0 (C5 or C10 or C18), 134.7 (C5 or C10 or C18), 133.0 (C5 or C10 or C18), 128.8 (C6 or C7 or C8 or C9 or C19 or C20 or C21), 128.7 (C6 or C7 or C8 or C9 or C19 or C20 or C21), 128.3 (C6 or C7 or C8 or C9 or C19 or C20 or C21), 127.9 (C6 or C7 or C8 or C9 or C19 or C20 or C21), 127.8 (C6 or C7 or C8 or C9 or C19 or C20 or C21), 127.1 (C6 or C7 or C8 or C9 or C19 or C20 or C21), 125.6 (C6 or C7 or C8 or C9 or C19 or C20 or C21), 66.3 (C17), 61.2 (C1), 58.3 (C14), 56.0 (C12), 38.1

(C13), 36.0 (C4), 34.0 (C2), 28.3 (C11), 26.1 (C3), 24.2 (C15); ESI-MS m/z = 873.39 (2M+Na^+, 2.8), 448.19 (M+Na^+, 11.2), 426.20 (M+H^+, 100); HRMS (ESI) m/z = 426.2095 (calculated for $C_{25}H_{32}NO_3S^+$ = 426.2097).

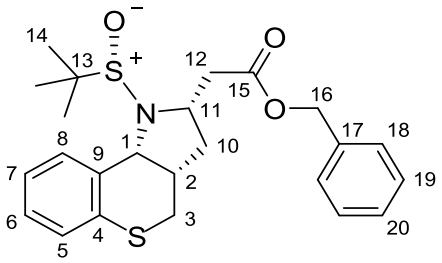
Benzyl-2-((2*S*,3a*S*,9b*R*)-1-((*S*$_S$)-*tert*-butylsulfinyl)-1,2,3,3a,4,9b-hexa hydrochromeno[4,3-b]pyrrol-2-yl)acetate (242y)



General procedure E was followed using **241y** (70 mg, 164 μmol, 1.0 eq.) and NaH (60% dispersion in mineral oil, 8 mg, 197 μmol, 1.2 eq.) in anhydrous THF (30 mL). The crude product was obtained as a yellow oil and purified by flash column chromatography over silica gel (eluting with 1:1 petroleum ether/ethyl acetate) to give **242y** (50 mg, 118 μmol, 72%) as a yellow oil. The product was isolated as a 10:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3067, 3054, 3035 (C-H_{aro}), 2980, 2929, 2880, 2855 (C-H_{ali}), 1713 (C=O), 1254, 1122 (C-O-C), 1047 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.43 (1H, d, *J* = 7.5, Ar-H), 7.40-7.27 (5H, m, Ar-H), 7.19 (1H, t, *J* = 7.4, Ar-H), 6.92 (1H, t, *J* = 7.4, Ar-H), 6.83 (1H, d, *J* = 8.1, Ar-H), 5.13 (2H, s, 16-H), 4.81 (1H, d, *J* = 6.7, 1-H), 4.44-4.34 (1H, m, 11-H), 4.00 (1H, dd, *J* = 11.1 and 3.9, 3-H_a), 3.86 (1H, dd, *J* = 11.1 and 7.5, 3-H_b), 3.80 (1H, dd, *J* = 16.2 and 2.9, 12-H_a), 2.76-2.59 (2H, m, 2-H, 12-H_b), 2.14-2.04 (1H, ddd, *J* = 10.4, 7.6 and 2.7, 10-H_a), 1.88 (1H, ddd, *J* = 10.4, 7.5 and 2.5, 10-H_b), 1.12 (9H, s, 14-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 171.5 (C15), 155.2 (C4 or C9 or C17), 136.0 (C4 or C9 or C17), 133.3 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 129.5 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 128.7 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 128.4 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 128.3 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 121.3 (C4 or C9 or C17), 120.7 (C5

or C6 or C7 or C8 or C18 or C19 or C20), 117.2 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 66.5 (C16), 66.4 (C3), 59.0 (C13), 57.7 (C1), 56.1 (C11), 39.7 (C12), 34.7 (C2), 33.4 (C10), 24.8 (C14); ESI-MS m/z = 877.35 ($2M+Na^+$, 27.2), 450.17 ($M+Na^+$, 40.2), 428.19 ($M+H^+$, 100); HRMS (ESI) m/z = 428.1901 (calculated for $C_{24}H_{30}NO_4S^+$ = 428.1890).

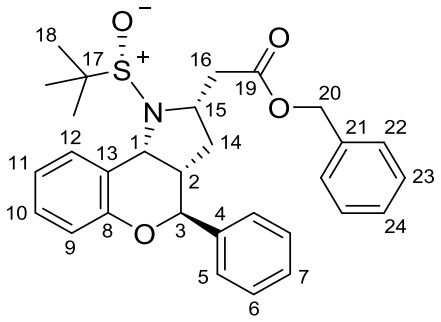
Benzyl-2-((2*S*,3a*S*,9b*R*)-1-((*S*$_S$)-*tert*-butylsulfinyl)-1,2,3,3a,4,9b-hexa hydrothio chromeno[4,3-b]pyrrol-2-yl)acetate (242z)



General procedure E was followed using **241z** (100 mg, 227 μmol, 1.0 eq.) and NaH (60% dispersion in mineral oil, 11 mg, 272 μmol, 1.2 eq.) in anhydrous THF (50 mL). The crude product was obtained as a yellow oil and purified by flash column chromatography over silica gel (eluting with 3:1 petroleum ether/ethyl acetate) to give **242z** (71 mg, 161 μmol, 71%) as a yellow oil. The product was isolated as a >25:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3063, 3034 (C-H_{aro}), 2954, 2924, 2885 (C-H_{ali}), 1721 (C=O), 1072 (S-O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.41-7.27 (5H, m, Ar-H), 7.15 (1H, app. t, *J* = 7.4, Ar-H), 7.01-6.83 (2H, m, Ar-H), 6.80 (1H, d, *J* = 8.2, Ar-H), 5.02 (2H, app. q, *J* = 12.3, 16-H), 4.79 (1H, d, *J* = 7.5, 1-H), 4.49-4.39 (1H, m, 11-H), 3.41-3.32 (2H, m, 3-H_a), 2.99-2.90 (2H, m, 3-H_b), 2.77-2.67 (1H, m, 2-H), 2.53-2.40 (2H, m, 10-H_a and 12-H_a), 1.87-1.75 (2H, m, 10-H_b and 12-H_b), 1.30 (9H, s, 14-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 170.9 (C15), 154.5 (C4 or C9 or C17), 135.8 (C4 or C9 or C17), 129.7 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 129.2 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 128.7 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 128.4 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 128.3 (C5 or C6 or C7 or C8 or C18 or C19 or C20),

123.3 (C4 or C9 or C17), 121.5 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 117.4 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 66.5 (C16), 65.7 (C1), 58.7 (C13), 50.4 (C11), 43.3 (C10 or C12), 38.8 (C2), 34.4 (C10 or C12), 32.7 (C3), 23.9 (C14); ESI-MS m/z = 466.14 ($M+Na^+$, 20.9), 444.16 ($M+H^+$, 100); HRMS (ESI) m/z = 444.1665 (calculated for $C_{24}H_{30}NO_3S_2^+$ = 444.1662).

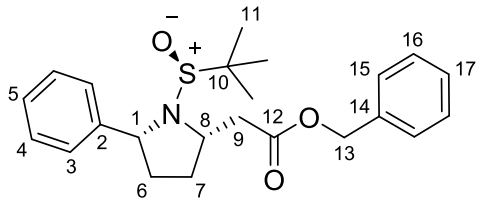
Benzyl-2-((2*S*,3a*S*,4*S*,9b*R*)-1-((*S*$_S$)-*tert*-butylsulfinyl)-4-phenyl-1,2,3,3a ,4, 9b-hexahydrochromeno[4,3-b]pyrrol-2-yl)acetate (242aa)



General procedure E was followed using **241aa** (200 mg, 398 μmol, 1.0 eq.) and NaH (60% dispersion in mineral oil, 19 mg, 478 μmol, 1.2 eq.) in anhydrous THF (40 mL). The crude product was obtained as a deep yellow oil and purified by flash column chromatography over silica gel (eluting with 3:1 petroleum ether/ethyl acetate) to afford **242aa** (142 mg, 283 μmol, 71%) as a pale yellow oil. The product was isolated as a 4:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^1$(neat) = 3088, 3064, 3033 (C-H_{aro}), 2977, 2925, 2869, 2857 (C-H_{ali}), 1732 (C=O), 1231, 1113 (C-O-C), 1068 (S-O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.48-7.39 (2H, m, Ar-H), 7.38-7.32 (3H, m, Ar-H), 7.31-7.27 (5H, m, Ar-H), 7.25-7.17 (2H, m, Ar-H), 7.05-6.95 (2H, m, Ar-H), 5.34 (2H, s, 20-H), 5.02 (1H, d, *J* = 7.6, 3-H), 4.51-4.31 (1H, m, 1-H), 4.04-3.97 (1H, m, 15-H), 3.09-2.90 (1H, m, 2-H), 2.50-2.32 (1H, m, 14-H_a), 2.10-2.05 (1H, m, 16-H_a), 1.90-1.66 (2H, m, 14-H_b and 16-H_b), 1.34 (9H, s, 18-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 170.9 (C19), 154.4 (C4 or C8 or C13 or C21), 139.6 (C4 or C8 or C13 or C21), 129.6 (C5 or C6 or C7 or C9 or C10 or C11 or C12 or C22 or C23 or C24), 129.3 (C4 or C8 or C13 or C21), 128.8 (C5 or C6 or C7 or C9 or C10 or

C11 or C12 or C22 or C23 or C24), 128.7 (C4 or C8 or C13 or C21), 128.6 (C5 or C6 or C7 or C9 or C10 or C11 or C12 or C22 or C23 or C24), 128.4 (C5 or C6 or C7 or C9 or C10 or C11 or C12 or C22 or C23 or C24), 128.3 (C5 or C6 or C7 or C9 or C10 or C11 or C12 or C22 or C23 or C24), 127.8 (C5 or C6 or C7 or C9 or C10 or C11 or C12 or C22 or C23 or C24), 125.6 (C5 or C6 or C7 or C9 or C10 or C11 or C12 or C22 or C23 or C24), 123.0 (C5 or C6 or C7 or C9 or C10 or C11 or C12 or C22 or C23 or C24), 121.7 (C5 or C6 or C7 or C9 or C10 or C11 or C12 or C22 or C23 or C24), 117.7 (C5 or C6 or C7 or C9 or C10 or C11 or C12 or C22 or C23 or C24), 76.1 (C3), 67.3 (C1 or C15), 60.6 (C20), 58.7 (C17), 50.0 (C1 or C15), 44.8 (C2), 43.5 (C16), 31.3 (C14), 23.9 (C18); ESI-MS m/z = 526.20 ($M+Na^+$, 100), 504.22 ($M+H^+$, 33.7); HRMS (ESI) m/z = 526.2027 (calculated for $C_{30}H_{33}NNaO_4S^+$ = 526.2023).

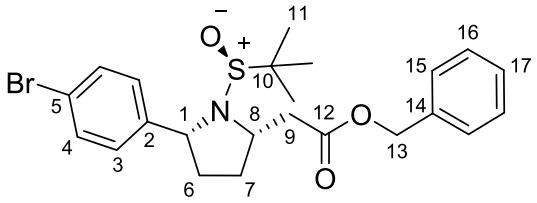
Benzyl-2-((2*S*,5*R*)-1-((*S*$_S$)-*tert*-butylsulfinyl)-5-phenylpyrrolidin-2-yl) acetate (242i)



General procedure E was followed using **241i** (120 mg, 300 μmol, 1.0 eq.) and NaH (60% dispersion in mineral oil, 14 mg, 360 μmol, 1.2 eq.) in anhydrous THF (30 mL). The crude product was obtained as a yellow oil and purified by flash column chromatography over silica gel (eluting with 2:1 petroleum ether/ethyl acetate) to afford **242i** (64 mg, 159 μmol, 53%) as a yellow oil. The product was isolated as a >10:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3062, 3030 (C-H_{aro}), 2962, 2869 (C-H_{ali}), 1735 (C=O), 1069 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.40-7.18 (10H, m, 3-H, 4-H, 5-H, 15-H, 16-H and 17-H), 5.20-5.16 (1H, m, 1-H), 5.15 (2H, app. d, *J* = 5.7, 13-H), 4.27-4.17 (1H, m, 8-H), 2.96 (1H, dd, *J* = 15.2 and 5.7, 9-H_a), 2.71 (1H, dd, *J* = 15.2 and 8.7, 9-H_b), 2.24-2.14 (1H, m, 6-H_a), 2.13-2.04

(1H, m, 7-H_a), 1.84-1.76 (1H, m, 6-H_b), 1.61-1.51 (1H, m, 7-H_b), 0.99 (9H, s, 11-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 170.9 (C12), 144.7 (C14), 135.7 (C2), 128.8 (C3 or C4), 128.7 (C3 or C4), 128.61 (C15 or C16 or C17), 128.56 (C15 or C16 or C17), 126.8 (C15 or C16 or C17), 126.7 (C5), 66.7 (C13), 64.8 (C8), 57.3 (C10), 56.4 (C1), 41.8 (C9), 37.0 (C6), 29.7 (C7), 23.4 (C11); ESI-MS m/z = 821.36 (2M+Na^+, 28.5), 422.17 (M+Na^+, 100); HRMS (ESI) m/z = 422.1765 (calculated for $C_{23}H_{29}NO_3SNa^+$ = 422.1760).

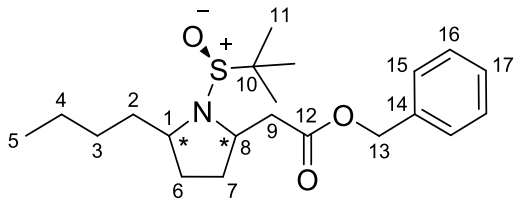
Benzyl-2-((2*S*,5*R*)-5-(4-bromophenyl)-1-((*S*$_S$)-*tert*-butylsulfinyl)pyrrolidine -2-yl)acetate (242ab)



General procedure E was followed using **241ab** (301 mg, 629 μmol, 1.0 eq.) and NaH (60% dispersion in mineral oil, 30 mg, 755 μmol, 1.2 eq.) in anhydrous THF (50 mL). The crude product was obtained as a deep yellow oil and purified by flash column chromatography over silica gel (eluting with 1:1 petroleum ether/ethyl acetate) to give **242ab** (199 mg, 415 μmol, 66%) as a yellow oil. The product was isolated as a >10:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3085, 3062, 3032 (C-H_{aro}), 2960, 2903, 2867 (C-H_{ali}), 1732 (C=O), 1072 (S-O), 1089 (C-Br); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.44-7.40 (2H, m, Ar-H), 7.39-7.31 (5H, m, Ar-H), 7.16-7.11 (2H, m, Ar-H), 5.20-5.14 (2H, m, 13-H), 5.13-5.09 (1H, m, 1-H), 4.21 (1H, tt, *J* = 8.7 and 5.9, 8-H), 2.92 (1H, dd, *J* = 15.2 and 5.9, 9-H_a), 2.67 (1H, dd, *J* = 15.2 and 8.7, 9-H_b), 2.24-2.14 (1H, m, 6-H_a), 2.13-2.05 (1H, m, 7-H_a), 1.79-1.71 (1H, m, 6-H_b), 1.53 (1H, ddt, *J* = 11.9, 8.7 and 5.9, 7-H_b), 0.98 (9H, s, 11-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 170.8 (C12), 143.8 (C2), 135.6 (C14), 131.6 (C3 or C4 or C15 or C16 or C17), 128.8 (C3 or C4 or C15 or C16 or C17), 128.6 (C3 or C4 or C15 or C16 or C17), 128.54 (C3 or C4 or C15 or C16 or C17), 128.51 (C3 or C4

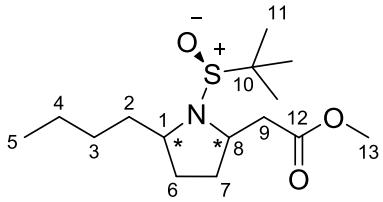
or C15 or C16 or C17), 120.6 (C5), 66.8 (C13), 64.8 (C8), 57.3 (C10), 55.8 (C1), 41.7 (C9), 36.8 (C6), 29.6 (C7), 23.3 (C11); ESI-MS m/z = 981.18 ($2M+Na^+$, 14.8), 502.08 ($M+Na^+$, 100), 480.10 ($M+H^+$, 48.8); HRMS (ESI) m/z = 502.0850 (calculated for $C_{23}H_{28}{}^{81}BrNNaO_3S^+$ = 502.0845).

Benzyl-2-(5-butyl-1-((*S*$_S$)-*tert*-butylsulfinyl)pyrrolidin-2-yl)acetate (365)



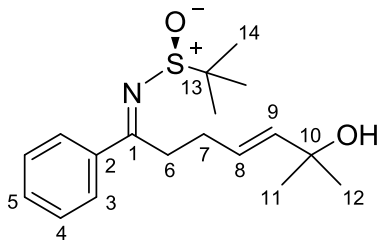
General procedure E was followed using **366** (100 mg, 264 μmol, 1.0 eq.) and NaH (60% dispersion in mineral oil, 13 mg, 317 μmol, 1.2 eq.) in anhydrous THF (40 mL). The crude product was obtained as a deep yellow oil and purified by flash column chromatography over silica gel (eluting with 3:1 petroleum ether/ethyl acetate) to afford **365** (78 mg, 206 μmol, 78%) as a pale yellow oil. The product was isolated as a 3:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3063, 3034 (C-H_{aro}), 2957, 2929, 2870 (C-H_{ali}), 1731 (C=O), 1059 (S-O); ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.40-7.27 (5H, m, 15-H, 16-H and 17-H), 5.19 (2H, s, 13-H), 4.13-3.91 (1H, m, 8-H), 3.83-3.69 (1H, m, 1-H), 3.68-3.53 (2H, m, 9-H), 2.18-1.75 (5H, m, 2-H_a, 6-H and 7-H), 1.73-1.56 (3H, m, 2-H_b and 3-H), 1.55-1.35 (2H, m, 4-H), 1.25 (9H, m, 11-H), 0.89 (3H, t, *J* = 6.5, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 171.0 (C12), 135.8 (C14), 128.8 (C15 or C16), 128.5 (C15 or C16), 128.4 (C17), 66.5 (C13), 63.9 (C8), 57.0 (C10), 54.3 (C1), 43.5 (C9), 36.0 (C2 or C6 or C7), 30.1 (C2 or C6 or C7), 29.2 (C2 or C6 or C7), 27.8 (C3), 23.6 (C11), 20.6 (C4), 14.5 (C5); ESI-MS m/z = 402.20 ($M+Na^+$, 5.9), 380.22 ($M+H^+$, 100); HRMS (ESI) m/z = 380.2250 (calculated for $C_{21}H_{34}NO_3S^+$ = 380.2254).

Methyl 2-(5-butyl-1-((*S*$_S$)-*tert*-butylsulfinyl)pyrrolidin-2-yl)acetate (386)



General procedure E was followed using **385** (300 mg, 989 μmol, 1.0 eq.) and NaH (60% dispersion in mineral oil, 47 mg, 1.19 mmol, 1.2 eq.) in anhydrous THF (40 mL). The crude product was obtained as a yellow oil and purified by flash column chromatography over silica gel (eluting with 3:1 petroleum ether/ethyl acetate) to afford **386** (161 mg, 530 μmol, 54%) as a pale yellow oil. The product was isolated as a 1:1 mixture of diastereomers. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2966, 2931, 2873, 2847 (C-H_{ali}), 1729 (C=O), 1071 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 4.18-4.09 (1H, m, 8-H), 3.85-3.77 (1H, m, 1-H), 3.70 (3H, s, 13-H), 3.65-3.54 (2H, m, 9-H), 2.22-1.78 (4H, m, 6-H and 7-H), 1.72-1.69 (2H, m, 2-H), 1.65-1.57 (2H, m, 3-H), 1.54-1.37 (2H, m, 4-H), 1.22 (9H, m, 11-H), 0.91 (3H, t, *J* = 6.5, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 167.9 (C12), 63.5 (C8), 56.7 (C10), 59.9 (C1), 51.5 (C13), 44.1 (C9), 35.6 (C2 or C6 or C7), 33.9 (C2 or C6 or C7), 28.6 (C2 or C6 or C7), 27.8 (C3 or C4), 23.1 (C3 or C4), 21.9 (C11), 14.4 (C5); ESI-MS m/z = 629.36 ($2M+Na^+$, 14.1), 326.17 ($M+Na^+$, 12.3), 304.19 ($M+H^+$, 100); HRMS (ESI) m/z = 304.1958 (calculated for $C_{15}H_{30}NO_3S^+$ = 304.1941).

(*S*S)-*N*-((1*E*,4*E*)-6-hydroxy-6-methyl-1-phenylhept-4-en-1-ylidene)-2-methylpropane-2-sulfinamide (277)

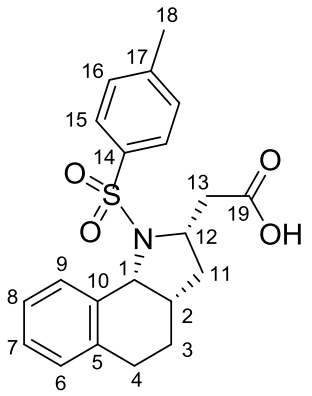


To a solution of α,β-unsaturated ester **240i** (119 mg, 300 μmol, 1.0 eq.) in anhydrous Et_2O (20 mL) under argon atmosphere at 0 °C, MeMgBr **275** (1.72 M in Et_2O, 174 μL, 300 μmol, 1.0 eq.) was then added dropwise. After completion of the addition, the mixture was heated to reflux (40 °C) for 24 hours. The reaction was then cooled to room temperature and added NH_4Cl (saturated aqueous solution, 15 mL). The organic layer was then separated with ethyl acetate (3 × 15 mL) and dried over anhydrous $MgSO_4$ before filtration and concentrating *in vacuo*. Flash column chromatography over silica gel (petroleum ether/ethyl acetate, 6:1) gave the pure product **277** (68 mg, 213 μmol, 71%; single isomer) as a yellow oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3368 (O-H), 3064, 3029 (C-H_{aro}), 2971, 2869 (C-H_{ali}), 1684 (C=N), 1621 (C=C), 1042 (S-O); $[\alpha]_D^{23}$ = +71.3 (*c* = 1.0 g/100 mL in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.85 (2H, d, *J* = 6.6, 3-H), 7.50-7.40 (3H, m, 4-H and 5-H), 5.66 (1H, d, *J* = 15.6, 9-H), 5.57 (1H, dt, *J* = 15.6 and 6.6, 8-H), 3.41-3.19 (2H, m, 7-H), 2.45-2.30 (2H, m, 6-H), 2.14-2.06 (1H, m, O-H), 1.30 (9H, s, 14-H), 1.26 (3H, s, 11-H or 12-H), 1.25 (3H, s, 11-H or 12-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 192.1 (C1), 140.2 (C9), 137.7 (C2), 131.8 (C3 or C4), 128.8 (C3 or C4), 127.8 (C5), 124.8 (C8), 70.4 (C10), 57.4 (C13), 32.4 (C7), 30.9 (C6), 29.8 (C11 or C12), 29.6 (C11 or C12), 22.7 (C14); ESI-MS m/z = 665.34 (2M+Na^+, 86.5), 643.35 (2M+H^+, 5.7), 344.16 (M+Na^+, 100), 322.18 (M+H^+, 7.1); HRMS (ESI) m/z = 344.1657 (calculated for $C_{18}H_{27}NO_2SNa^+$ = 344.1655).

5.7. General Procedure F: Hydrolysis of the ester to afford corresponding acids 283, 284, 285 and 286.

To a solution of esters **282**, **242i**, **242y** and **242z** (120-468 μmol, 1.0 eq.) in anhydrous THF (10-40 mL) at room temperature, LiOH or NaOH (1.0 M, 1.2-4.68 mmol, 10.0 eq.) was added. The reaction mixture was heated at 60 °C for 2-5 hours. A solution of aqueous NH_4Cl (1.0 M, 10 mL) was then added and the organic layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over anhydrous Mg_2SO_4 and concentrated *in vacuo*.

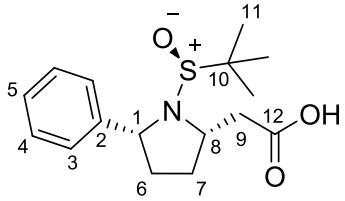
2-((2*S*,3a*S*,9b*R*)-1-tosyl-2,3,3a,4,5,9b-hexahydro-1H-benzo[g]indol-2-yl)acetic acid (283)



General procedure F was followed using **282** (70 mg, 147 μmol, 1.0 eq.) in anhydrous THF (10 mL) and LiOH (1.0 M, 1.47 mL, 1.47 mmol, 10.0 eq.). The reaction mixture was heated at 60 °C for 4 hours. The crude product **283** was then crystallised as a white colour (56 mg, 144 μmol, 98%) from the crude mixture using Et_2O (10 mL), m.p. = 228-230 °C. The product was isolated as a >25:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3269 (O-H), 3064, 3028 (C-H_{aro}), 2923, 2852 (C-H_{ali}), 1706 (C=O), 1344, 1091 (S=O); ^1H NMR (500 MHz, $CDCl_3$) δ_H = 7.88 (1H, d, *J* = 7.8, 6-H or 9-H), 7.81 (2H, d, *J* = 8.1, 15-H or 16-H), 7.37 (2H, d, *J* = 8.1, 15-H or 16-H), 7.31-7.27 (1H, m, 6-H or 9-H), 7.18 (1H, app. t, *J* = 7.3, 7-H or 8-H), 7.03 (1H, app. d, *J* = 7.5, 7-H or 8-H), 4.75 (1H, d, *J* = 7.3, 1-H), 3.97 (1H, tdd,

J = 13.2, 10.3 and 3.9, 12-H), 3.22 (1H, dd, *J* = 16.7 and 3.9, 13-H_a), 2.72 (1H, ddd, *J* = 16.3, 10.3 and 5.5, 11-H_a), 2.64-2.55 (1H, m, 11-H_b), 2.46 (3H, s, 18-H), 2.24 (1H, dd, *J* = 16.7 and 10.3, 13-H_b), 2.20-2.11 (1H, m, 4-H_a), 1.89 (1H, ddd, *J* = 19.4, 10.7 and 5.5, 4-H_b), 1.78-1.67 (1H, m, 2-H), 1.62-1.52 (1H, m, 3-H_a), 1.47-1.37 (1H, m, 3-H_b); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 174.6 (C19), 144.0 (C5 or C10 or C14 or C17), 135.7 (C5 or C10 or C14 or C17), 135.7 (C5 or C10 or C14 or C17), 134.8 (C5 or C10 or C14 or C17), 130.1 (C6 or C7 or C8 or C9 or C15 or C16), 129.7 (C6 or C7 or C8 or C9 or C15 or C16), 128.2 (C6 or C7 or C8 or C9 or C15 or C16), 127.8 (C6 or C7 or C8 or C9 or C15 or C16), 127.2 (C6 or C7 or C8 or C9 or C15 or C16), 126.9 (C6 or C7 or C8 or C9 or C15 or C16), 61.6 (C1), 57.6 (C12), 42.4 (C13), 36.3 (C2), 35.4 (C4), 24.8 (C11), 23.0 (C3), 21.8 (C18); ESI-MS m/z = 408.12 ($M+Na^+$, 100), 386.14 ($M+H^+$, 8.4); HRMS (ESI) m/z = 408.1237 (calculated for $C_{21}H_{23}NNaO_4S^+$ = 408.1240).

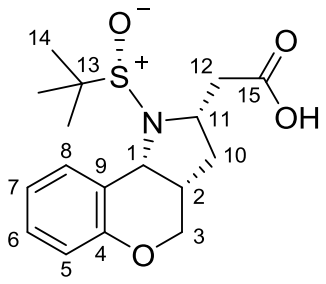
2-((2*S*,5*R*)-1-((*S*$_S$)-*tert*-butylsulfinyl)-5-phenylpyrrolidin-2-yl)acetic acid (284)



General procedure F was followed using **242i** (48 mg, 120 μmol, 1.0 eq.) in anhydrous THF (10 mL) and LiOH (1.0 M, 1.2 mL, 1.2 mmol, 10.0 eq.). The reaction mixture was heated at 60 °C for 2 hours. The crude residue was purified by flash column chromatography over silica gel (eluting with 5:1 petroleum ether/ethyl acetate) to give **284** (33 mg, 107 μmol, 89%) as a yellow oil. The product was isolated as a 17:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3446 (O-H), 3062, 3030 (C-H_{aro}), 2962, 2869 (C-H_{ali}), 1734 (C=O), 1069 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.37-7.12 (5H, m, 3-H, 4-H and 5-H), 5.18 (1H, t, *J* = 8.2, 1-H), 4.23 (1H, tt,

J = 8.7 and 5.7, 8-H), 2.96 (1H, dd, *J* = 15.5 and 5.9, 9-H_a), 2.73 (1H, dd, *J* = 15.5 and 8.2, 9-H_b), 2.26-2.16 (2H, m, 6-H_a and 7-H_a), 1.87-1.77 (1H, m, 6-H_b), 1.66-1.55 (1H, m, 7-H_b), 1.03 (9H, s, 11-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 176.2 (C12), 130.3 (C2), 128.6 (C3 or C4), 126.84 (C3 or C4), 126.76 (C5), 64.5 (C8), 57.5 (C10), 56.7 (C1), 41.4 (C9), 36.9 (C6), 29.6 (C7), 23.4 (C11); ESI-MS m/z = 641.26 ($2M+Na^+$, 100), 332.13 ($M+Na^+$, 79.6), 310.14 ($M+H^+$, 30.2); HRMS (ESI) m/z = 641.2699 (calculated for $C_{32}H_{46}N_2NaO_6S_2^+$ = 641.2689).

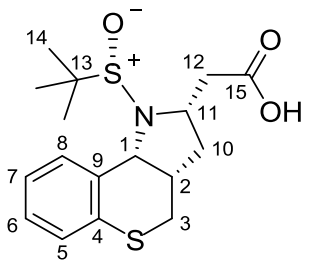
2-((2*S*,3a*S*,9b*R*)-1-((*S*$_S$)-*tert*-butylsulfinyl)-1,2,3,3a,4,9b-hexahydro chromeno[4,3-b]pyrrol-2-yl)acetic acid (285)



General procedure F was followed using **242y** (200 mg, 468 μmol, 1.0 eq.) in anhydrous THF (40 mL) and NaOH (1.0 M, 4.68 mL, 4.68 mmol, 10.0 eq.). The reaction mixture was heated at 60 °C for 4 hours. The crude product of acid (156 mg, 463 μmol, 99%) was obtained as a yellow oil. The compound **285** was used in the next step without further purification. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3380 (O-H), 3058, 3036 (C-H_{aro}), 2956, 2926, 2868 (C-H_{ali}), 1718 (C=O), 1260, 1129 (C-O-C), 1038 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.30 (1H, d, *J* = 7.7, 5-H or 8-H), 7.21-7.11 (1H, m, 6-H or 7-H), 6.91 (1H, app. td, *J* = 7.7 and 1.1, 6-H or 7-H), 6.81 (1H, dd, *J* = 8.2 and 1.1, 5-H or 8-H), 4.79 (1H, d, *J* = 7.6, 1-H), 4.47-4.37 (1H, m, 11-H), 4.19 (2H, d, *J* = 7.6, 3-H), 3.98 (1H, dt, *J* = 13.2 and 9.3, 12-H_a), 3.86-3.78 (1H, m, 12-H_b), 2.73 (1H, dtd, *J* = 8.8, 7.6 and 6.2, 2-H), 2.39 (1H, ddd, *J* = 16.0, 8.8 and 6.2, 10-H_a), 1.75 (1H, ddd, *J* = 16.0, 7.6 and 6.0, 10-H_b), 1.31 (9H, s, 14-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 171.0 (C15), 154.5 (C4), 129.8 (C5 or C6 or C7 or C8), 129.2 (C5 or C6 or C7 or C8), 123.4 (C9), 121.4

(C5 or C6 or C7 or C8), 117.4 (C5 or C6 or C7 or C8), 65.4 (C3), 58.7 (C13), 57.4 (C1), 56.4 (C11), 43.3 (C12), 38.8 (C2), 34.4 (C10), 23.9 (C14); ESI-MS m/z = 697.25 ($2M+Na^+$, 47.7), 675.27 ($2M+H^+$, 26.1), 360.12 ($M+Na^+$, 100), 338.14 ($M+H^+$, 36.2); HRMS (ESI) m/z = 360.1239 (calculated for $C_{17}H_{23}NNaO_4S^+$ = 360.1240).

2-((2*S*,3a*S*,9b*R*)-1-((*S*$_S$)-*tert*-butylsulfinyl)-1,2,3,3a,4,9b-hexahydrothiochromeno[4,3-b]pyrrol-2-yl)acetic acid (286)



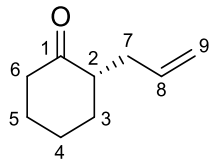
General procedure F was followed using **242z** (100 mg, 226 μmol, 1.0 eq.) in anhydrous THF (30 mL) and LiOH (1.0 M, 2.26 mL, 2.26 mmol, 10.0 eq.). The reaction mixture was heated at 60 °C for 5 hours. The crude residue was purified by flash column chromatography over silica gel (eluting with 2:1 petroleum ether/ethyl acetate) to afford **286** (78 mg, 221 μmol, 98%) as a brown oil. The product was isolated as a >25:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3344 (O-H), 3061, 3027 (C-H_{aro}), 2955, 2923, 2857 (C-H_{ali}), 1725 (C=O), 1038 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.29 (1H, d, *J* = 7.5, Ar-H), 7.19-7.11 (2H, m, Ar-H), 7.09-7.03 (1H, m, Ar-H), 4.57-4.47 (1H, m, 1-H), 4.43-4.32 (2H, m, 11-H and 12-H_a), 4.30-4.23 (1H, m, 12-H_b), 3.46 (1H, dd, *J* = 12.8 and 3.2, 3-H_a), 2.90 (1H, dd, *J* = 12.8 and 2.9, 3-H_b), 2.75-2.65 (1H, m, 2-H), 2.49-2.40 (1H, m, 10-H_a), 2.18-2.09 (1H, m, 10-H_b), 1.31 (9H, s, 14-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 172.8 (C15), 133.6 (C4 or C9), 132.7 (C5 or C6 or C7 or C8), 130.7 (C4 or C9), 129.3 (C5 or C6 or C7 or C8), 128.6 (C5 or C6 or C7 or C8), 126.8 (C5 or C6 or C7 or C8), 65.2 (C1), 55.8 (C13), 50.8 (C11), 43.5 (C12), 42.9 (C10), 38.1 (C2), 32.1 (C3), 23.7 (C14);

ESI-MS m/z = 729.21 (2M+Na^+, 100), 707.23 (2M+H^+, 61.1), 376.10 (M+Na^+, 12.7), 354.11 (M+H^+, 14.8); HRMS (ESI) m/z = 729.2137 (calculated for $C_{34}H_{46}N_2NaO_6S_4^+$ = 729.2131.

5.8. General procedure G: Removal of the chiral auxiliary to give corresponding ketones and amines 251, 261, 426, 434 and 479.

To a solution of **239b, 239c**, **242b**, **425** and **433** (138 μmol-8.17 mmol, 1.0 eq.) in anhydrous MeOH (5-50 mL) at 0 °C, was added HCl (1.0 M in Et_2O, 1.38-40.85 mmol, 5.0-10.0 eq.) was then added slowly over 30 minutes. After completion of the addition, the reaction mixture was stirred at room temperature for 3-5 hours, after which TLC indicated the consumption of the starting material. Then, a saturated solution of aqueous $NaHCO_3$ (15 mL) was added and the organic layer was extracted with ethyl acetate (2 × 15 mL). The combined organic layers were dried over anhydrous Mg_2SO_4 and concentrated *in vacuo* to provide crude of the ketone and amine, which was purified using flash column chromatography over silica gel to provide the desired products **251**, **261**, **426**, **434** and **479**.

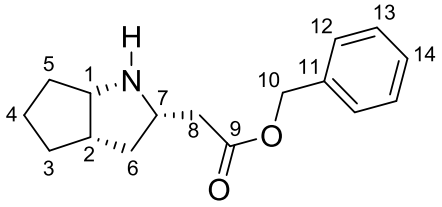
(*S*)-2-allylcyclohexanone (251)



General procedure G was followed using **239c** (100 mg, 415 μmol, 1.0 eq.) and HCl (1.0 M in Et_2O, 4.15 mL, 4.15 mmol, 10.0 eq.) in anhydrous MeOH (10 mL). The crude product **251** was obtained as a yellow oil and purified by flash column chromatography over silica gel (eluting with 10:1 petroleum ether/ethyl acetate) to afford **251** (48 mg, 349 μmol, 84%) as a pale yellow oil. Enantiomeric excess (*ee*) = 99.7%, determined by chiral GC-Lipodex E column of the crude product. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2927, 2857 (C-H_{ali}), 1708 (C=O), 1639 (C=C); $[\alpha]_D^{23}$

= -14.9 (*c* = 3 in MeOH), which was compared to the literature value, -15.8 (*c* = 3 in MeOH)[117,165]; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.78 (1H, dddd, *J* = 16.8, 9.9, 7.6 and 6.7, 8-H), 5.06-4.97 (2H, m, 9-H), 2.54 (1H, tt, *J* = 8.1 and 5.9, 2-H), 2.43-2.28 (3H, m, 6-H and 7-H_a), 2.16-2.11 (1H, m, 7-H_b), 2.10-2.01 (1H, m, 3-H_a or 5-H_a), 2.00-1.92 (1H, m, 3-H_a or 5-H_a), 1.88-1.80 (1H, m, 3-H_b or 5-H_b), 1.72-1.57 (2H, m, 4-H_a and 3-H_b or 5-H_b), 1.44-1.30 (1H, m, 4-H_b); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 212.6 (C1), 136.6 (C8), 116.3 (C9), 50.4 (C2), 42.2 (C6), 33.9 (C3 or C4 or C5 or C7), 33.5 (C3 or C4 or C5 or C7), 28.1 (C3 or C4 or C5 or C7), 25.1 (C3 or C4 or C5 or C7); CHN Found: C, 79.9%; H, 10.1%. $C_9H_{14}O$ requires: C, 78.2%; H, 10.2%. Data consistent with literature.[117]

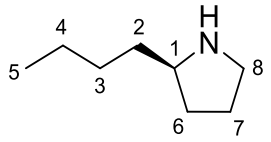
Benzyl-2-((2*S*,3a*S*,6a*S*)-octahydrocyclopenta[b]pyrrol-2-yl)acetate (261)



General procedure G was followed using **242b** (50 mg, 138 μmol, 1.0 eq.) and HCl (1.0 M in Et_2O, 1.38 mL, 1.38 mmol, 10.0 eq.) in anhydrous MeOH (5 mL). The crude product **261** was obtained as a yellow oil and purified by flash column chromatography over silica gel (eluting with 3:1 petroleum ether/ethyl acetate) to give **261** (35 mg, 135 μmol, 98%) as a yellow oil. The product was isolated as a 10:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3428 (N-H), 3083, 3042 (C-H_{aro}), 2957, 2923, 2854 (C-H_{ali}), 1714 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.75-7.66 (2H, m, 12-H or 13-H), 7.56-7.48 (3H, m, 12-H or 13-H and 14-H), 5.16 (2H, s, 10-H), 4.40-4.22 (2H, m, N-H and 1-H or 7-H), 4.17-3.96 (1H, m, 1-H or 7-H), 3.42-3.33 (1H, m, 2-H), 2.77-2.65 (2H, m, 8-H), 1.63-1.52 (2H, m, 6-H), 1.45-1.05 (6H, m, 3-H, 4-H and 5-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 169.6 (C9), 134.0 (C11), 126.7 (C12 or C13), 126.3 (C14), 126.3 (C12 or C13), 64.3 (C10), 63.6 (C1 or C7), 56.9 (C1

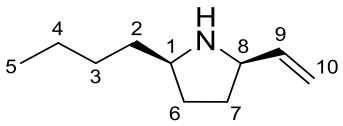
or C7), 40.2 (C2), 38.3 (C8), 36.1 (C3 or C4 or C5 or C6), 32.1 (C3 or C4 or C5 or C6), 30.5 (C3 or C4 or C5 or C6), 21.5 (C3 or C4 or C5 or C6); ESI-MS m/z = 260.16 ($M+H^+$, 100); HRMS (ESI) m/z = 260.1650 (calculated for $C_{16}H_{22}NO_2^+$ = 260.1645).

(*R*)-2-butylpyrrolidine (426)



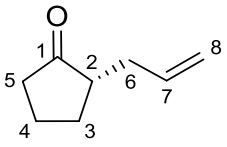
General procedure G was followed using **425** (250 mg, 1.08 mmol, 1.0 eq.) and HCl (1.0 M in Et_2O, 10.8 mL, 10.8 mmol, 10.0 eq.) in anhydrous MeOH (5 mL). The crude product **426** was obtained as a yellow oil and purified by flash column chromatography over silica gel (eluting with 95:5 DCM/MeOH) to afford **426** (135 mg, 1.06 mmol, 98%) as a pale yellow oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3237 (N-H), 2924, 2854 (C-H_{ali}); $[\alpha]_D^{23}$ = +21.2 (*c* = 1.0 g/100 mL in MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ_H = 9.85-8.85 (1H, m, N-H), 3.55-3.15 (3H, m, 1-H and 8-H), 2.28-2.08 (2H, m, 6-H_a and 7-H_a), 2.03-1.87 (2H, m, 2-H), 1.83-1.59 (2H, m, 6-H_b and 7-H_b), 1.50-1.25 (4H, m, 3-H or 4-H), 0.89 (3H, s, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 60.6 (C1), 45.0 (C8), 31.9 (C6 or C7), 30.4 (C6 or C7), 29.0 (C2), 23.7 (C3 or C4), 22.3 (C3 or C4), 13.9 (C5); ESI-MS m/z = 128.14 ($M+H^+$, 100); HRMS (ESI) m/z = 128.1440 (calculated for $C_8H_{18}N^+$ = 128.1434).

(2*R*,5*R*)-2-butyl-5-vinylpyrrolidine (434)



General procedure G was followed using **433** (2.1 g, 8.17 mmol, 1.0 eq.) and HCl (1.0 M in Et_2O, 40.85 mL, 40.85 mmol, 5.0 eq.) in anhydrous MeOH (50 mL). The crude product **434** was obtained as a deep yellow oil and purified by flash column chromatography over silica gel (eluting with 90:10 DCM/MeOH) to give **434** (1.18 g, 7.68 mmol, 94%) as a pale yellow oil. The product was isolated as a >25:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3229 (N-H), 2967, 2929, 2861 (C-H_{ali}), 1685 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.70 (1H, ddd, *J* = 17.2, 10.8 and 7.4, 9-H), 5.45 (1H, dd, *J* = 17.2 and 1.2, 10-H_a), 5.29 (1H, dd, *J* = 10.8 and 1.2, 10-H_b), 3.90-3.79 (1H, m, 8-H), 3.68-3.59 (1H, m, 1-H), 2.24-2.12 (1H, m, 7-H_a), 1.81-1.70 (3H, m, 6-H, 7-H_b), 1.61-1.51 (2H, m, 2-H), 1.43-1.30 (4H, m, 3-H and 4-H), 0.92 (3H, t, *J* = 7.0, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 127.2 (C9), 116.7 (C10), 63.6 (C8), 60.4 (C1), 36.4 (C2 or C6 or C7), 31.5 (C2 or C6 or C7), 29.9 (C2 or C6 or C7), 26.4 (C3), 25.5 (C4), 13.7 (C5); ESI-MS m/z = 329.29 ($2M+Na^+$, 33.1), 307.31 ($2M+H^+$, 9.2), 176.14 ($M+Na^+$, 55.9), 154.15 ($M+H^+$, 100); HRMS (ESI) m/z = 154.1593 (calculated for $C_{10}H_{20}N^+$ = 154.1590).

(*S*)-2-allylcyclopentanone (479)



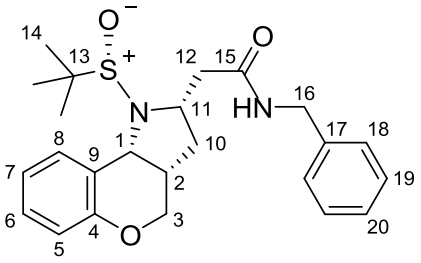
General procedure G was followed using **239b** (114 mg, 502 μmol, 1.0 eq.) and HCl (1.0 M in Et_2O, 5.02 mL, 5.02 mmol, 10.0 eq.) in anhydrous MeOH (20 mL). The crude product **479** was obtained as a yellow oil and purified by flash column chromatography over silica gel (eluting with 8:1 petroleum ether/ethyl acetate) to

give **479** (54 mg, 437 μmol, 87%) as a pale yellow oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2932, 2860 (C-H_{ali}), 1707 (C=O), 1640 (C=C); $[\alpha]_D^{23}$ = -166 (*c* = 2.0 g/100 mL in Et_2O), which was compared to the literature value, +189 (c = 2.03, Et_2O for *R* isomer)[165]; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.90 (1H, ddt, *J* = 17.0, 10.2 and 6.5, 7-H), 5.08 (1H, ddd, *J* = 17.0, 3.2 and 1.6, 8-H_a), 5.01 (1H, dd, *J* = 10.2 and 1.6, 8-H_b), 3.07 (2H, t, *J* = 6.1, 5-H), 2.68-2.62 (1H, m, 2-H), 2.54-2.44 (2H, m, 6-H), 2.19-2.09 (3H, m, 3-H or 4-H and 3-H_a or 4-H_a), 1.92-1.82 (1H, m, 3-H_b or 4-H_b); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 199.6 (C1), 137.4 (C7), 115.4 (C8), 37.9 (C5), 28.3 (C2 or C3 or C4 or C6), 21.6 (C2 or C3 or C4 or C6), 21.2 (C2 or C3 or C4 or C6), 14.3 (C2 or C3 or C4 or C6). Data consistent with literature.[166]

5.9. General Procedure H: *N*-Amidation.

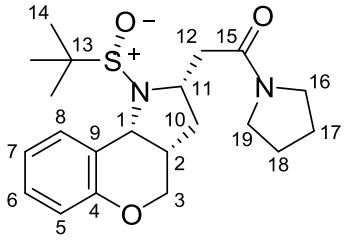
The carboxylic acid **285** (297-356 μmol, 1.0 eq.), Hunig's base (446-539 μmol, 1.5 eq.) and the appropriate amine (356-427 μmol, 1.2 eq.) were stirred in DMF (7 mL) and the solution cooled to 0 °C before dropwise addition of a solution of HATU (327-392 μmol, 1.1 eq.) in DMF (3 mL). The reaction mixture was stirred at room temperature for 4-6 hours under an inert argon atmosphere before being diluted with ethyl acetate (10 mL) and washed successively with 2.0 M HCl (3 × 10 mL), saturated aqueous $NaHCO_3$ solution (10 mL), brine (10 mL) then dried over anhydrous $MgSO_4$. Filtration and removal of solvents *in vacuo* gave the crude material which was purified by flash column chromatography to afford the desired products **288** and **289**.

_N_-benzyl-2-((2_S_,3a_S_,9b_R_)-1-((_S_S)-_tert_-butylsulfinyl)-1,2,3,3a,4,9b-hexa hydro chromeno[4,3-b]pyrrol-2-yl)acetamide (288)



General procedure H was followed using **285** (100 mg, 297 μmol, 1.0 eq.), Hunig's base (78 μL, 446 μmol, 1.5 eq.), benzyl amine (39 μL, 356 μmol, 1.2 eq.) and HATU (124 mg, 327 μmol, 1.1 eq.). The crude product **288** was obtained as a yellow oil and purified by flash column chromatography over silica gel (eluting with 1:3 petroleum ether/ethyl acetate) to give **288** (85 mg, 199 μmol, 67%) as a pale yellow oil. The product was isolated as a 10:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3276 (N-H), 3062, 3031 (C-H_{aro}), 2959, 2926, 2869 (C-H_{ali}), 1649 (C=O), 1223, 1091 (C-O-C), 1046 (S-O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.45-7.30 (4H, m, Ar-H), 7.25-7.09 (2H, m, Ar-H), 7.01-6.78 (3H, m, Ar-H), 5.92-5.76 (1H, m, N-H), 4.57-4.42 (2H, m, 16-H), 4.36-4.26 (2H, m, 1-H and 11-H), 4.24-4.18 (1H, m, 3-H_a), 4.17-4.04 (1H, m, 3-H_b), 3.98-3.77 (1H, m, 12-H_a), 3.41-3.20 (1H, m, 12-H_b), 2.49-2.35 (1H, m, 10-H_a), 2.32-2.10 (2H, m, 2-H and 10-H_b), 1.19 (9H, s, 14-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 169.9 (C15), 154.6 (C4 or C9 or C17), 141.5 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 132.9 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 131.1 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 128.8 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 128.1 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 127.7 (C4 or C9 or C17), 126.1 (C4 or C9 or C17), 121.6 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 117.2 (C5 or C6 or C7 or C8 or C18 or C19 or C20), 65.9 (C16), 64.1 (C3), 55.9 (C13), 53.0 (C1), 51.8 (C11), 43.7 (C12), 38.1 (C2), 31.2 (C10), 22.8 (C14); ESI-MS m/z = 449.18 ($M+Na^+$, 100), 427.20 ($M+H^+$, 75.6); HRMS (ESI) m/z = 449.1879 (calculated for $C_{24}H_{30}N_2NaO_3S^+$ = 449.1869).

2-((2*S*,3a*S*,9b*R*)-1-((*S*$_S$)-*tert*-butylsulfinyl)-1,2,3,3a,4,9b-hexahydro chromeno [4,3-b]pyrrol-2-yl)-1-(pyrrolidin-1-yl)ethan-1-one (289)

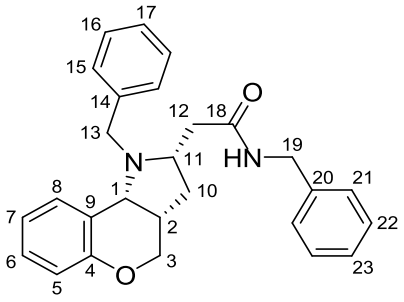


General procedure H was followed using **285** (120 mg, 356 μmol, 1.0 eq.), Hunig's base (93 μL, 539 μmol, 1.5 eq.), pyrrolidine (35 μL, 427 μmol, 1.2 eq.) and HATU (149 mg, 392 μmol, 1.1 eq.). The crude product **289** was obtained as a deep yellow oil and purified by flash column chromatography over silica gel (eluting with 9:1 ethyl acetate/MeOH) to afford **289** (96 mg, 246 μmol, 69%) as a pale yellow oil. The product was isolated as a 10:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3072, 3063, 3033 (C-H_{aro}), 2959, 2950, 2871 (C-H_{ali}), 1635 (C=O), 1220, 1089 (C-O-C), 1055 (S-O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.36 (1H, d, *J* = 7.6, Ar-H), 7.19-7.11 (1H, m, Ar-H), 6.92 (1H, dt, *J* = 7.7 and 1.0, Ar-H), 6.80 (1H, dd, *J* = 8.2 and 1.0, Ar-H), 4.82 (1H, d, *J* = 7.7, 1-H), 4.65-4.52 (1H, m, 11-H), 4.18 (2H, d, *J* = 6.1, 3-H), 3.75 (2H, app. t, *J* = 6.5, 12-H), 3.03-2.67 (4H, m, 16-H and 19-H), 2.59-2.49 (1H, m, 2-H), 2.24-2.13 (1H, m, 10-H_a), 1.87-1.69 (5H, m, 10-H_b, 17-H and 18-H), 1.31 (9H, s, 14-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 168.9 (C15), 154.8 (C4), 130.2 (C5 or C6 or C7 or C8), 129.0 (C5 or C6 or C7 or C8), 124.2 (C9), 121.3 (C5 or C6 or C7 or C8), 117.2 (C5 or C6 or C7 or C8), 65.7 (C3), 58.6 (C13), 57.6 (C1), 51.7 (C11), 46.3 (C16 or C19), 45.5 (C16 or C19), 42.6 (C12), 38.7 (C2), 34.5 (C10), 26.0 (C17 or C18), 24.5 (C17 or C18), 24.0 (C14); ESI-MS m/z = 413.18 ($M+Na^+$, 100), 391.20 ($M+H^+$, 49.6); HRMS (ESI) m/z = 413.1873 (calculated for $C_{21}H_{30}N_2NaO_3S^+$ = 413.1869).

5.10. General procedure I: Reductive amination.

The amine products **288** and **289** (175-187 μmol, 1.0 eq.) was dissolved in DCE (5 mL) in a 5 mL round bottom flask. Benzaldehyde (263-281 μmol, 1.5 eq.) and acetic acid (437-468 μmol, 2.5 eq.) were added and the resulting mixture stirred at room temperature for 2 hours. A solution of sodium triacetoxyborohydride (210-224 μmol, 1.2 eq.) in DCE (5 mL) was added dropwise. The reaction mixture was stirred overnight at room temperature then washed with 1.0 M HCl (2 × 10 mL). The aqueous phase was basified using saturated aqueous $NaHCO_3$ solution then extracted with ethyl acetate (2 × 10 mL), washed with water (2 × 10 mL), and the combined extracts, dried over anhydrous $MgSO_4$, filtered and solvent removed *in vacuo*. Flash column chromatography (petroleum ether/ethyl acetate) afforded the desired products **290** and **291**.

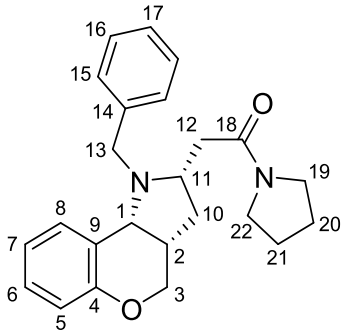
***N*-benzyl-2-((2*S*,3a*S*,9b*R*)-1-benzyl-1,2,3,3a,4,9b-hexahydrochromeno [4,3-b] pyrrol-2-yl)acetamide (290)**



General procedure G was followed using **288** (100 mg, 235 μmol, 1.0 eq.), anhydrous MeOH (10 mL) and HCl (1.0 M in Et_2O, 2.35 mL, 2.35 mmol, 10.0 eq.). The amine intermediate (71 mg, 221 μmol, 94%) was obtained as a yellow oil. The crude amine was then used in the next step without further purification. General procedure I was then followed using amine intermediate (60 mg, 187 μmol, 1.0 eq.), benzaldehyde (29 μL, 281 μmol, 1.5 eq.), acetic acid (27 μL, 468 μmol, 2.5 eq.) sodium triacetoxyborohydride (48 mg, 224 μmol, 1.2 eq.). The crude product **290** was obtained as yellow oil and purified by flash column

chromatography over silica gel (eluting with 1:2 petroleum ether/ethyl acetate) to give **290** (56 mg, 135 μmol, 72%) as a pale yellow oil. The product was isolated as a 10:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3274 (N-H), 3077, 3065, 3033 (C-H_{aro}), 2951, 2926, 2824 (C-H_{ali}), 1647 (C=O), 1222, 1096 (C-O-C); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.52-7.42 (1H, m, Ar-H), 7.40-7.30 (4H, m, Ar-H), 7.24-7.19 (3H, m, Ar-H), 7.16-7.08 (3H, m, Ar-H), 6.93-6.80 (3H, m, Ar-H), 5.77 (1H, app. d, *J* = 5.9, N-H), 4.55-4.45 (2H, m, 19-H), 4.22 (1H, d, *J* = 4.8, 1-H), 4.17 (1H, app. d, *J* = 6.9, 11-H), 4.09 (1H, dd, *J* = 13.8 and 6.1, 3-H_a), 4.02-3.92 (1H, m, 3-H_b), 3.77-3.71 (2H, m, 13-H), 2.68-2.58 (1H, m, 12-H_a), 2.51 (1H, dd, *J* = 15.9 and 6.9, 12-H_b), 2.35 (1H, ddd, *J* = 15.9, 6.9 and 6.0, 10-H_a), 2.05-1.99 (2H, m, 2-H and 10-H_b); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 171.0 (C18), 156.7 (C4 or C9 or C14 or C20), 139.0 (C4 or C9 or C14 or C20), 131.1 (C5 or C6 or C7 or C8 or C15 or C16 or C17 or C21 or C22 or C23), 128.9 (C4 or C9 or C14 or C20), 128.7 (C5 or C6 or C7 or C8 or C15 or C16 or C17 or C21 or C22 or C23), 128.7 (C5 or C6 or C7 or C8 or C15 or C16 or C17 or C21 or C22 or C23), 128.4 (C4 or C9 or C14 or C20), 128.3 (C5 or C6 or C7 or C8 or C15 or C16 or C17 or C21 or C22 or C23), 128.1 (C5 or C6 or C7 or C8 or C15 or C16 or C17 or C21 or C22 or C23), 127.7 (C5 or C6 or C7 or C8 or C15 or C16 or C17 or C21 or C22 or C23), 127.3 (C5 or C6 or C7 or C8 or C15 or C16 or C17 or C21 or C22 or C23), 121.6 (C5 or C6 or C7 or C8 or C15 or C16 or C17 or C21 or C22 or C23), 120.8 (C5 or C6 or C7 or C8 or C15 or C16 or C17 or C21 or C22 or C23), 117.2 (C5 or C6 or C7 or C8 or C15 or C16 or C17 or C21 or C22 or C23), 68.4 (C3), 65.7 (C13 or C19), 61.5 (C13 or C19), 53.8 (C1 or C11), 51.7 (C1 or C11), 42.0 (C12), 35.2 (C2), 32.1 (C10); ESI-MS m/z = 435.20 ($M+Na^+$, 1.5), 413.22 ($M+H^+$, 100); HRMS (ESI) m/z = 413.2234 (calculated for $C_{27}H_{29}N_2O_2^+$ = 413.2224).

2-((2*S*,3a*S*,9b*R*)-1-benzyl-1,2,3,3a,4,9b-hexahydrochromeno[4,3-b] pyrrol-2-yl)-1-(pyrrolidin-1-yl)ethan-1-one (291)



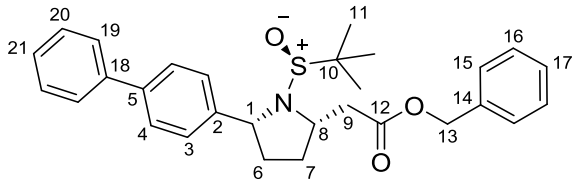
General procedure G was followed using **289** (100 mg, 256 μmol, 1.0 eq.), anhydrous MeOH (10 mL) and HCl (1.0 M in Et_2O, 2.56 mL, 2.56 mmol, 10.0 eq.). The amine intermediate (72 mg, 251 μmol, 98%) was obtained as a deep yellow oil. The crude amine was then used in the next step without further purification. General procedure I was then followed using amine intermediate (50 mg, 175 μmol, 1.0 eq.), benzaldehyde (27 μL, 263 μmol, 1.5 eq.), acetic acid (25 μL, 437 μmol, 2.5 eq.) sodium triacetoxyborohydride (45 mg, 210 μmol, 1.2 eq.). The crude product **291** was obtained as a yellow oil and purified by flash column chromatography over silica gel (eluting with 1:2 petroleum ether/ethyl acetate) to afford **291** (49 mg, 131 μmol, 75%) as a pale yellow oil. The product was isolated as a 10:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3075, 3059, 3028 (C-H_{aro}), 2959, 2928, 2805 (C-H_{ali}), 1724 (C=O), 1242, 1118 (C-O-C); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.24-7.19 (4H, m, Ar-H), 7.18-7.04 (3H, m, Ar-H), 6.83 (1H, d, *J* = 8.0, Ar-H), 6.76 (1H, app. t, *J* = 7.3, Ar-H), 4.28-4.12 (3H, m, 1-H, 3-H_a and 11-H), 4.06 (1H, dd, *J* = 10.7 and 3.8, 3-H_b), 3.78-3.63 (2H, m, 12-H), 3.45-3.30 (2H, m, 13-H), 3.11-2.98 (1H, m, 19-H_a), 2.93-2.84 (1H, m, 19-H_b), 2.55-2.41 (2H, m, 2-H and 22-H_a), 2.20 (1H, ddd, *J* = 15.7, 8.3 and 4.9, 10-H_a), 1.96 (1H, dd, *J* = 15.7, 8.4 and 4.7, 10-H_b), 1.89-1.69 (5H, m, 20-H, 21-H and 22-H_b); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 170.2 (C18), 155.0 (C4), 141.1 (C14), 131.6 (C5 or C6 or C7 or C8 or 15 or C16 or C17), 128.8 (C5 or C6 or C7 or C8 or 15 or C16 or C17), 128.6 (C5 or C6

or C7 or C8 or 15 or C16 or C17), 128.2 (C5 or C6 or C7 or C8 or 15 or C16 or C17), 126.8 (C5 or C6 or C7 or C8 or 15 or C16 or C17), 123.7 (C9), 120.2 (C5 or C6 or C7 or C8 or 15 or C16 or C17), 116.8 (C5 or C6 or C7 or C8 or 15 or C16 or C17), 67.4 (C3), 61.4 (C13), 57.7 (C1 or C11), 53.5 (C1 or C11), 46.5 (C19 or C22), 45.5 (C19 or C22), 42.4 (C12), 34.5 (C2), 33.6 (C10), 26.0 (C20 or C21), 24.5 (C20 or C21); ESI-MS m/z = 399.20 ($M+Na^+$, 1.3), 377.22 ($M+H^+$, 100); HRMS (ESI) m/z = 377.2228 (calculated for $C_{24}H_{29}N_2O_2^+$ = 377.2224).

5.11. General procedure J: Suzuki-Miyaura coupling.

Pyrrolidine derivative **242ab** (126 μmol, 1.0 eq.), aryl boronic acid pinacol ester (189 μmol, 1.5 eq.), $Pd(dppf)Cl_2$ (7 μmol, 5.5 mol%) and K_2CO_3 (252 μmol, 2.0 eq.) in anhydrous DMF (5 mL) were mixed in a microwave vial. The reaction mixture was then stirred under microwave irradiation at 120 °C for 2 hours. The mixture was cooled to room temperature and diluted with saturated solution of $NaHCO_3$ (5 mL). The organic layer was then extracted with ethyl acetate (5 mL), washed with brine (5 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. Flash column chromatography (petroleum ether/ethyl acetate) gave the desired products **292**-**296**.

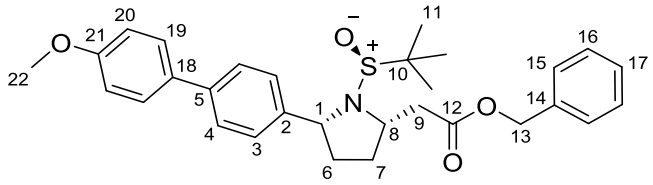
Benzyl-2-((2*S*,5*R*)-5-([1,1'-biphenyl]-4-yl)-1-((*S*S)-*tert*-butylsulfinyl) pyrrolidin-2-yl)acetate (292)



General procedure J was followed using **242ab** (60 mg, 126 μmol, 1.0 eq.), phenylboronic acid pinacol ester (39 mg, 189 μmol, 1.5 eq.), Pd(dppf)Cl_2 (5 mg, 7 μmol, 5.5 mol%) and K_2CO_3 (35 mg, 252 μmol, 2.0 eq.) in anhydrous DMF (5 mL). The crude product was obtained as a deep black oil and purified by flash column chromatography over silica gel (eluting with 1:1 petroleum ether/ethyl acetate) affording **292** (37 mg, 78 μmol, 62%) as a colourless oil. The product was isolated as a >10:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3061, 3030 (C-H_{aro}), 2960, 2868 (C-H_{ali}), 1733 (C=O), 1070 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.58 (2H, d, *J* = 7.5, Ar-H), 7.53 (2H, d, *J* = 8.2, Ar-H), 7.44 (2H, app. t, *J* = 7.5, Ar-H), 7.40-7.30 (8H, m, Ar-H), 5.21 (1H, dd, *J* = 7.8, 6.0, 1-H), 5.19-5.10 (2H, m, 13-H), 4.29-4.20 (1H, m, 8-H), 2.98 (1H, dd, *J* = 15.2 and 5.7, 9-H_a), 2.74 (1H, dd, *J* = 15.2 and 8.7, 9-H_b), 2.28-2.17 (1H, m, 6-H_a), 2.16-2.06 (1H, m, 7-H_a), 1.90-1.80 (1H, m, 6-H_b), 1.64-1.54 (1H, m, 7-H_b), 1.02 (9H, s, 11-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 170.9 (C12), 143.7 (C2), 140.7 (C5 or C18), 139.6 (C5 or C18), 135.7 (C14), 128.9 (C3 or C4 or C15 or C16 or C17 or C19 or C20 or C21), 128.8 (C3 or C4 or C15 or C16 or C17 or C19 or C20 or C21), 128.6 (C3 or C4 or C15 or C16 or C17 or C19 or C20 or C21), 128.6 (C3 or C4 or C15 or C16 or C17 or C19 or C20 or C21), 127.4 (C3 or C4 or C15 or C16 or C17 or C19 or C20 or C21), 127.2 (C3 or C4 or C15 or C16 or C17 or C19 or C20 or C21), 127.2 (C3 or C4 or C15 or C16 or C17 or C19 or C20 or C21), 127.1 (C3 or C4 or C15 or C16 or C17 or C19 or C20 or C21), 66.8 (C13), 64.6 (C8), 57.3 (C10), 56.2 (C1), 41.9 (C9), 37.0 (C6), 29.7 (C7), 23.4 (C11); ESI-MS m/z = 973.42 (2M+Na^+, 24.5), 498.20

(M+Na^+, 100), 476.22 (M+H^+, 8.5); HRMS (ESI) m/z = 498.2082 (calculated for $C_{29}H_{33}NNaO_3S^+$ = 498.2073).

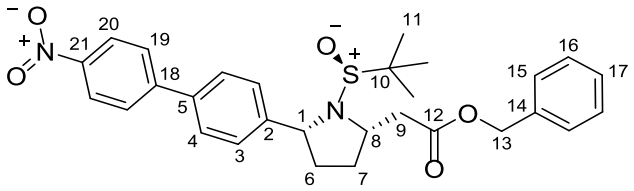
Benzyl-2-((2*S*,5*R*)-1-((*S*$_S$)-*tert*-butylsulfinyl)-5-(4'-methoxy-[1,1'-bi phenyl]-4-yl)pyrrolidin-2-yl)acetate (293)



General procedure J was followed using **242ab** (60 mg, 126 μmol, 1.0 eq.), 4-methoxyphenylboronic acid pinacol ester (44 mg, 189 μmol, 1.5 eq.), Pd(dppf)Cl_2 (5 mg, 7 μmol, 5.5 mol%) and K_2CO_3 (35 mg, 252 μmol, 2.0 eq.) in anhydrous DMF (5 mL). The crude product was obtained as a deep black oil and purified by flash column chromatography over silica gel (eluting with 1:1 petroleum ether/ethyl acetate) affording **293** (42 mg, 83 μmol, 66%) as a yellow oil. The product was isolated as a >10:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3062, 3033 (C-H_{aro}), 2954, 2925, 2866, 2856 (C-H_{ali}), 1733 (C=O), 1246, 1177 (C-O-C), 1067 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$,) δ_H = 7.62-7.45 (4H, m, Ar-H), 7.43-7.27 (7H, m, Ar-H), 6.97 (2H, d, *J* = 8.8, Ar-H), 5.25-5.20 (1H, m, 1-H), 5.19-5.11 (2H, m, 13-H), 4.30-4.15 (1H, m, 8-H), 3.85 (3H, s, 22-H), 2.98 (1H, dd, *J* = 15.2 and 5.7, 9-H_a), 2.74 (1H, dd, *J* = 15.2 and 8.7, 9-H_b), 2.27-2.17 (1H, m, 6-H_a), 2.15-2.06 (1H, m, 7-H_a), 1.88-1.78 (1H, m, 6-H_b), 1.66-1.56 (1H, m, 7-H_b), 1.02 (9H, s, 11-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 170.8 (C12), 159.2 (C21), 142.9 (C2), 139.1 (C5 or C18), 135.6 (C5 or C18), 133.2 (C14), 128.7 (C3 or C4 or C15 or C16 or C17 or C19 or C20), 128.5 (C3 or C4 or C15 or C16 or C17 or C19 or C20), 128.4 (C3 or C4 or C15 or C16 or C17 or C19 or C20), 128.0 (C3 or C4 or C15 or C16 or C17 or C19 or C20), 127.1 (C3 or C4 or C15 or C16 or C17 or C19 or C20), 126.6 (C3 or C4 or C15 or C16 or C17 or C19 or C20), 114.2 (C3 or C4 or C15 or C16 or C17 or C19 or C20), 66.6 (C13), 64.6 (C8), 57.2 (C10), 56.0 (C1), 55.4 (C22), 41.7

(C9), 36.9 (C6), 29.6 (C7), 23.3 (C11); ESI-MS m/z = 528.21 ($M+Na^+$, 100), 506.23 ($M+H^+$, 21.7); HRMS (ESI) m/z = 528.2184 (calculated for $C_{30}H_{35}NNaO_4S^+$ = 528.2179).

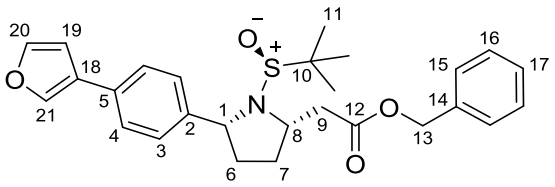
Benzyl-2-((2*S*,5*R*)-1-((*S*$_S$)-*tert*-butylsulfinyl)-5-(4'-nitro-[1,1'-biphenyl]-4-yl)pyrrolidin-2-yl)acetate (294)



General procedure J was followed using **242ab** (60 mg, 126 μmol, 1.0 eq.), 4-nitrophenylboronic acid pinacol ester (47 mg, 189 μmol, 1.5 eq.), $Pd(dppf)Cl_2$ (5 mg, 7 μmol, 5.5 mol%) and K_2CO_3 (35 mg, 252 μmol, 2.0 eq.) in anhydrous DMF (5 mL). The crude product was obtained as a deep black oil and purified by flash column chromatography over silica gel (eluting with 1:2 petroleum ether/ethyl acetate) affording **294** (33 mg, 63 μmol, 50%) as a pale yellow oil. The product was isolated as a >10:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3085, 3064, 3010 (C-H_{aro}), 2965, 2930, 2863 (C-H_{ali}), 1733 (C=O), 1485, 1345 (NO_2), 1061 (S-O); ^1H NMR (500 MHz, $CDCl_3$) δ_H = 8.33 (2H, dd, *J* = 8.8 and 1.9, Ar-H), 7.76 (2H, dd, *J* = 8.8 and 6.7, Ar-H), 7.61 (2H, dd, *J* = 8.3 and 6.7, Ar-H), 7.46-7.36 (7H, m, Ar-H), 5.30-5.24 (1H, m, 1-H), 5.19 (2H, app. q, *J* = 12.2, 13-H), 4.31-4.24 (1H, m, 8-H), 2.97 (1H, dd, *J* = 15.2 and 5.9, 9-H_a), 2.73 (1H, dd, 15.2 and 8.6, 9-H_b), 2.32-2.22 (1H, m, 6-H_a), 2.18-2.11 (1H, m, 7-H_a), 1.91-1.83 (1H, m, 6-H_b), 1.68-1.58 (1H, m, 7-H_b), 1.05 (9H, s, 11-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 170.8 (C12), 147.2 (C21), 145.8 (C2), 137.2 (C5 or C18), 135.7 (C5 or C18), 131.0 (C14), 129.0 (C3 or C4 or C15 or C16 or C17 or C19 or C20), 128.8 (C3 or C4 or C15 or C16 or C17 or C19 or C20), 128.7 (C3 or C4 or C15 or C16 or C17 or C19 or C20), 127.7 (C3 or C4 or C15 or C16 or C17 or C19 or C20), 127.64 (C3 or C4 or C15 or C16 or C17 or C19 or C20), 127.55 (C3 or C4 or C15 or C16 or C17 or C19 or

C20), 124.3 (C3 or C4 or C15 or C16 or C17 or C19 or C20), 66.8 (C13), 64.9 (C8), 57.4 (C10), 56.1 (C1), 41.8 (C9), 37.0 (C6), 29.8 (C7), 23.4 (C11); ESI-MS m/z = 543.19 ($M+Na^+$, 100), 521.21 ($M+H^+$, 23.2); HRMS (ESI) m/z = 543.1932 (calculated for $C_{29}H_{32}N_2NaO_5S^+$ = 543.1924).

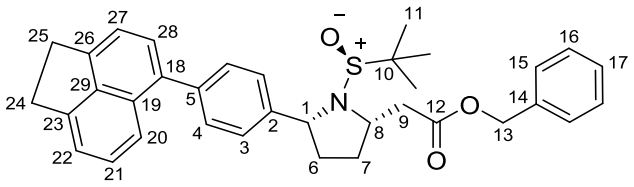
Benzyl-2-((2*S*,5*R*)-1-((*S*$_S$)-*tert*-butylsulfinyl)-5-(4-(furan-3-yl)phenyl) pyrrolidin-2-yl)acetate (295)



General procedure J was followed using **242ab** (60 mg, 126 μmol, 1.0 eq.), 3-furylboronic acid pinacol ester (37 mg, 189 μmol, 1.5 eq.), $Pd(dppf)Cl_2$ (5 mg, 7 μmol, 5.5 mol%) and K_2CO_3 (35 mg, 252 μmol, 2.0 eq.) in anhydrous DMF (5 mL). The crude product was obtained as a deep black oil and purified by flash column chromatography over silica gel (eluting with 1:1 petroleum ether/ethyl acetate) affording **295** (32 mg, 68 μmol, 54%) as a yellow oil. The product was isolated as a >10:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3141, 3119, 3110 (C-H_{alkene}), 3062, 3015 (C-H_{aro}), 2962, 2929, 2870 (C-H_{ali}), 1732 (C=O), 1263, 1162 (C-O-C), 1068 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.75 (1H, d, *J* = 4.1, Ar-H), 7.53-7.35 (7H, m, Ar-H), 7.33-7.26 (3H, m, Ar-H), 6.74-6.68 (1H, m, Ar-H), 5.26-5.21 (1H, m, 1-H), 5.19-5.13 (2H, m, 13-H), 4.31-4.17 (1H, m, 8-H), 2.96 (1H, dd, *J* = 15.1 and 5.7, 9-H_a), 2.72 (1H, dd, *J* = 15.1 and 8.6, 9-H_b), 2.31-2.18 (1H, m, 6-H_a), 2.17-2.07 (1H, m, 7-H_a), 1.88-1.79 (1H, m, 6-H_b), 1.68-1.54 (1H, m, 7-H_b), 1.03 (9H, s, 11-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 170.9 (C12), 143.9 (C2), 143.5 (C3 or C4 or C15 or C16 or C17 or C19 or C20 or C21), 138.6 (C14), 135.7 (C18), 130.9 (C5), 128.8 (C3 or C4 or C15 or C16 or C17 or C19 or C20 or C21), 128.6 (C3 or C4 or C15 or C16 or C17 or C19 or C20 or C21), 128.5 (C3 or C4 or C15 or C16 or C17 or C19 or C20 or C21), 127.3 (C3 or C4 or C15 or C16 or C17 or C19 or C20 or C21),

127.2 (C3 or C4 or C15 or C16 or C17 or C19 or C20 or C21), 126.0 (C3 or C4 or C15 or C16 or C17 or C19 or C20 or C21), 108.9 (C3 or C4 or C15 or C16 or C17 or C19 or C20 or C21), 66.8 (C13), 64.7 (C8), 57.3 (C10), 56.2 (C1), 41.9 (C9), 37.0 (C6), 29.6 (C7), 23.4 (C11); ESI-MS m/z = 953.38 ($2M+Na^+$, 20.3), 488.18 ($M+Na^+$, 100), 466.20 ($M+H^+$, 13.6); HRMS (ESI) m/z = 488.1871 (calculated for $C_{27}H_{31}NNaO_4S^+$ = 488.1866).

Benzyl-2-((2*S*,5*R*)-1-((*S*S)-*tert*-butylsulfinyl)-5-(4-(1,2-dihydroace naphthylen-5-yl)phenyl)pyrrolidin-2-yl)acetate (296)



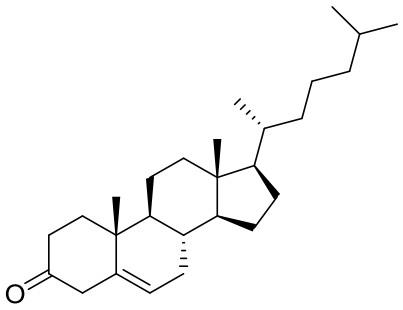
General procedure J was followed using **242ab** (60 mg, 126 μmol, 1.0 eq.), 2-(1,2-dihydroacenaphthylen-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (53 mg, 189 μmol, 1.5 eq.), $Pd(dppf)Cl_2$ (5 mg, 7 μmol, 5.5 mol%) and K_2CO_3 (35 mg, 252 μmol, 2.0 eq.) in anhydrous DMF (5 mL). The crude product was obtained as a deep black oil and purified by flash column chromatography over silica gel (eluting with 1:3 petroleum ether/ethyl acetate) affording **296** (42 mg, 77 μmol, 61%) as a yellow oil. The product was isolated as a >10:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)$/ cm^{-1} (neat) = 3082, 3063, 3031 (C-H_{aro}), 2958, 2944, 2926, 2868 (C-H_{ali}), 1732 (C=O), 1065 (S-O); ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.68 (1H, d, *J* = 8.4, Ar-H), 7.49 (2H, d, *J* = 8.1, Ar-H), 7.47-7.28 (11H, m, Ar-H), 5.26 (1H, dd, *J* = 7.9 and 6.8, 1-H), 5.23-5.11 (2H, m, 13-H), 4.26 (1H, tdd, *J* = 13.1, 5.4 and 3.6, 8-H), 3.49-3.40 (4H, m, 24-H and 25-H), 3.01 (1H, dd, *J* = 15.3 and 5.4, 9-H_a), 2.77 (1H, dd, *J* = 15.3 and 3.6, 9-H_b), 2.32-2.22 (1H, m, 6-H_a), 2.16-2.10 (1H, m, 7-H_a), 1.96-1.88 (1H, m, 6-H_b), 1.72-1.62 (1H, m, 7-H_b), 1.06 (9H, s, 11-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 171.0 (C12), 146.4 (C23 or C26), 145.8 (C23 or C26), 143.3 (C2), 139.8 (C5 or C14 or C18 or C19 or C29), 138.9 (C5 or C14 or C18 or

C19 or C29), 135.7 (C5 or C14 or C18 or C19 or C29), 135.3 (C5 or C14 or C18 or C19 or C29), 129.8 (C3 or C4 or C15 or C16 or C17 or C20 or C21 or C22 or C27 or C28), 128.8 (C3 or C4 or C15 or C16 or C17 or C20 or C21 or C22 or C27 or C28), 128.7 (C3 or C4 or C15 or C16 or C17 or C20 or C21 or C22 or C27 or C28), 128.62 (C3 or C4 or C15 or C16 or C17 or C20 or C21 or C22 or C27 or C28), 128.60 (C3 or C4 or C15 or C16 or C17 or C20 or C21 or C22 or C27 or C28), 128.2 (C3 or C4 or C15 or C16 or C17 or C20 or C21 or C22 or C27 or C28), 126.82 (C5 or C14 or C18 or C19 or C29), 126.79 (C3 or C4 or C15 or C16 or C17 or C20 or C21 or C22 or C27 or C28), 120.9 (C3 or C4 or C15 or C16 or C17 or C20 or C21 or C22 or C27 or C28), 119.5 (C3 or C4 or C15 or C16 or C17 or C20 or C21 or C22 or C27 or C28), 119.3 (C3 or C4 or C15 or C16 or C17 or C20 or C21 or C22 or C27 or C28), 66.8 (C13), 64.8 (C8), 57.4 (C10), 56.3 (C1), 41.9 (C9), 37.0 (C6), 30.7 (C24 or C25), 30.2 (C24 or C25), 29.8 (C7), 23.5 (C11); ESI-MS m/z = 574.23 ($M+Na^+$, 100); HRMS (ESI) m/z = 574.2384 (calculated for $C_{35}H_{37}NNaO_3S^+$ = 574.2386); CHN Found: C, 76.4%; H, 6.2%; N, 2.4%. $C_{35}H_{37}NO_3S$ requires: C, 76.2%; H, 6.8%; N, 2.5%.

5.12. General procedure K: Oxidation of alcohol to the coressponding ketones 237ae, 374 and 430.

To a solution of alcohols **237AE**, **379** and **427** (5.17-35.15 mmol, 1.0 eq.) in DCM (30-50 mL), PCC (6.46-43.94 mmol, 1.25 eq.) and silica gel (1.39-9.47 g) were added. The reaction mixture was stirred overnight. The reaction mixture was then filtered through a pad of silica gel and washed with ethyl acetate (20-50 mL). The solvent was removed *in vacuo* to give the crude mixture as a brown-green oil. The crude mixture was then purified by flash column chromatography over silica gel (eluting with petroleum ether/ethyl acetate) to afford the desired ketones **237ae**, **374** and **430**.

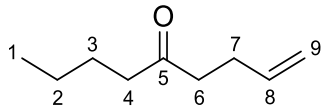
8*S*,9*S*,10*R*,13*R*,14*S*,17*R*-10,13-dimethyl-17-(*R*)-6-methylheptan-2-yl)-1,2,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3H-cyclopenta[a] phenanthren-3-one (237ae)



General procedure K was followed using cholesterol **237AE** (2 g, 5.17 mmol, 1.0 eq.) in DCM (50 mL), PCC (1.39 g, 6.46 mmol, 1.25 eq.) and silica gel (1.39 g). The orange reddish crude mixture was purified by flash column chromatography over silica gel (eluting with 3:1 petroleum ether/ethyl acetate) affording **237ae** (1.65 g, 4.29 mmol, 83%) as a white solid. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2945, 2909, 2887, 2860, 2838 (C-H_{ali}), 1718 (C=O), 1643 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.37 (1H, dd, *J* = 4.9 and 2.2), 3.35-3.25 (1H, m), 2.84 (3H, dd, *J* = 16.4 and 2.1), 2.55-2.45 (1H, m), 2.37-2.27 (1H, m), 2.11-2.01 (1H, m), 1.87 (1H, dtd, *J* = 13.3, 9.6 and 5.9), 1.88-1.49 (7H, m), 1.45-1.25 (5H, m), 1.21 (3H,

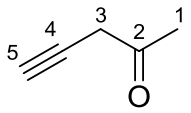
s), 1.18-1.01 (8H, m), 0.95 (3H, d, *J* = 6.5), 0.90 (3H, d, *J* = 1.7), 0.88 (3H, d, *J* = 1.7), 0.73 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 210.4 (C), 138.7 (C), 123.0 (CH), 56.7 (CH), 56.6 (CH), 49.3 (CH), 48.5 (CH_2), 42.5 (C), 39.8 (CH_2), 39.6 (CH_2), 37.8 (CH_2), 37.04 (CH_2), 37.0 (C), 36.3 (CH_2), 35.9 (CH), 32.1 (CH), 31.9 (CH_2), 28.4 (CH_2), 28.1 (CH), 24.4 (CH_2), 24.0 (CH_2), 23.0 (CH_3), 22.7 (CH_3), 21.5 (CH_2), 19.3 (CH_3), 18.8 (CH_3), 12.0 (CH_3); ESI-MS m/z = 791.66 ($2M+Na^+$, 100), 769.68 ($2M+H^+$, 28.2), 407.32 ($M+Na^+$, 24.7), 385.34 ($M+H^+$, 37.3); HRMS (ESI) m/z = 791.6690 (calculated for $C_{54}H_{88}NaO_2^+$ = 791.6677).

Non-1-en-5-one (374)



General procedure K was followed using **379** (5 g, 35.15 mmol, 1.0 eq.) in DCM (50 mL), PCC (9.47 g, 43.94 mmol, 1.25 eq.) and silica gel (9.47 g). The green browinsh crude mixture was then purified by flash column chromatography over silica gel (eluting with 30:1 petroleum ether/ethyl acetate) to afford the desired ketone **374** (4.78 g, 34.1 mmol, 97%) as a green oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2958, 2931, 2873 (C-H_{ali}), 1714 (C=O), 1641 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.81 (1H, ddt, *J* = 16.9, 10.2 and 6.5, 8-H), 5.03 (1H, dd, *J* = 16.9 and 1.0, 9-H_a), 4.97 (1H, dd, *J* = 10.2 and 1.0, 9-H_b), 2.50 (2H, t, *J* = 7.3, 6-H), 2.40 (2H, t, *J* = 7.8, 4-H), 2.32 (2H, dtd, *J* = 14.0, 7.3 and 6.5, 7-H), 1.56 (2H, app. ddt, *J* = 15.1, 7.8 and 7.1, 3-H), 1.37-1.22 (2H, m, 2-H), 0.90 (3H, t, *J* = 6.9, 1-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 210.7 (C5), 137.4 (C8), 115.3 (C9), 42.8 (C4), 41.9 (C6), 27.9 (C7), 26.1 (C3), 22.5 (C2), 14.0 (C1).

Pent-4-yn-2-one (430)

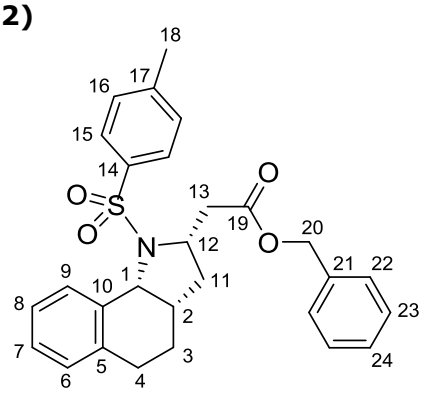


General procedure K was followed using (±)-pent-4-yn-2-ol **427** (892 μl, 10.6 mmol, 1.0 eq.) in DCM (30 mL), PCC (2.86 g, 13.25 mmol, 1.25 eq.) and silica gel (2.86 g). Due to volatility of the desired product **430**, the solvent was then evaporated carefully under reduce pressure and the crude material used in the next step without further purification. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3287 (C-H_{alkyne}), 2953, 2924, 2869, 2852 (C-H_{ali}), 2121 (C≡C), 1728 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.75 (1H, t, *J* = 6.5, 5-H), 5.22 (2H, d, *J* = 6.5, 3-H), 2.24 (3H, s, 1-H).

5.13. General procedure L: Sulfonylation.

A suspension of amine or alcohol (214 μmol-42.4 mmol, 1.0 eq.) and DMAP (21 μmol-4.24 mmol, 0.1 eq.) in DCM (15-100 mL) was cooled to 0 °C then Et_3N (471 μmol-50.88 mmol, 1.2-2.2 eq.) was added dropwise to the reaction mixture followed by the dropwise addition a solution of *p*-TsCl (257 μmol-50.88 mmol, 1.2 eq.) in DCM (5-20 mL) at 0 °C. The reaction mixture was allowed to room temperature overnight. After completion of reaction monitored by TLC, then the suspension was filtered through a short pad of silica gel and washed the silica bed with sufficient amount of DCM. Then the solvent was removed under reduced pressure to give the crude product and it was absorbed on silica straightaway to load the column. And the product was purified by flash column chromatography using petroleum ether/ethyl acetate to give the pure products **282**, **287**, **428** and **438** in yields 66-89%.

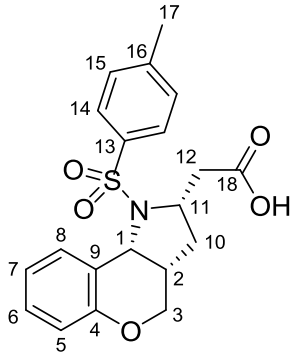
Benzyl-2-((2*S*,3a*S*,9b*R*)-1-tosyl-2,3,3a,4,5,9b-hexahydro-1H-benzo[g] indol-2-yl)acetate (282)



General procedure G was followed using **242x** (150 mg, 353 μmol, 1.0 eq.), anhydrous MeOH (15 mL) and HCl (1.0 M in Et_2O, 3.53 mL, 3.53 mmol, 10.0 eq.). The crude amine **278** (112 mg, 349 μmol, 99%) was obtained as a yellow oil. General procedure L was then followed using crude amine **278** (100 mg, 312 μmol, 1.0 eq.) in DCM (15 mL), Et_3N (97 μL, 686 μmol, 2.2 eq.), DMAP (4 mg, 31 μmol, 0.1 eq.) and *p*-TsCl **281** (71 mg, 374 μmol, 1.2 eq.) were added and stirred for 14 hours. The crude mixture was then purified by flash column chromatography using silica gel (eluting with 3:1 petroleum ether/ethyl acetate) to give desired product **282** (98 mg, 206 μmol, 66%) as a yellow oil. The product was isolated as a 10:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3065, 3033 (C-H_{aro}), 2933, 2899, 2863 (C-H_{ali}), 1728 (C=O), 1343, 1106 (S=O); ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.87 (1H, d, *J* = 7.7, Ar-H), 7.81 (2H, d, *J* = 7.7, Ar-H), 7.40-7.28 (7H, m, Ar-H), 7.23 (1H, d, *J* = 7.6, Ar-H), 7.16 (1H, t, *J* = 7.4, Ar-H), 7.02 (1H, d, *J* = 7.4, Ar-H), 5.08-4.98 (2H, m, 20-H), 4.75 (1H, d, *J* = 7.3, 1-H), 4.07-3.97 (1H, m, 12-H), 3.41 (1H, dd, *J* = 16.3 and 4.1, 13-H_a), 2.72 (1H, dd, *J* = 16.3 and 5.6, 13-H_b), 2.58 (1H, ddd, *J* = 16.4, 7.4 and 4.1, 11-H_a), 2.46 (3H, s, 18-H), 2.41 (1H, ddd, *J* = 16.4, 7.2 and 4.3, 11-H_b), 2.18-2.08 (1H, m, 4-H_a), 1.89 (1H, ddd, *J* = 14.0, 10.7 and 5.5, 4-H_b), 1.83-1.69 (1H, m, 2-H), 1.61-1.51 (1H, m, 3-H_a), 1.45-1.36 (1H, m, 3-H_b); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 171.3 (C19), 143.9 (C5 or C10 or C14 or C17 or C21), 135.9 (C5 or C10 or C14 or C17 or C21), 135.8 (C5 or C10 or C14 or C17

or C21), 135.8 (C5 or C10 or C14 or C17 or C21), 135.0 (C5 or C10 or C14 or C17 or C21), 130.1 (C6 or C7 or C8 or C9 or C15 or C16 or C22 or C23 or C24), 129.6 (C6 or C7 or C8 or C9 or C15 or C16 or C22 or C23 or C24), 128.7 (C6 or C7 or C8 or C9 or C15 or C16 or C22 or C23 or C24), 128.4 (C6 or C7 or C8 or C9 or C15 or C16 or C22 or C23 or C24), 128.3 (C6 or C7 or C8 or C9 or C15 or C16 or C22 or C23 or C24), 128.1 (C6 or C7 or C8 or C9 or C15 or C16 or C22 or C23 or C24), 127.8 (C6 or C7 or C8 or C9 or C15 or C16 or C22 or C23 or C24), 127.2 (C6 or C7 or C8 or C9 or C15 or C16 or C22 or C23 or C24), 126.9 (C6 or C7 or C8 or C9 or C15 or C16 or C22 or C23 or C24), 66.4 (C20), 61.6 (C1), 57.8 (C12), 43.1 (C13), 36.3 (C4), 35.6 (C2), 24.9 (C11), 23.1 (C3), 21.7 (C18); ESI-MS m/z = 498.17 ($M+Na^+$, 100), 476.19 ($M+H^+$, 66.9); HRMS (ESI) m/z = 498.1707 (calculated for $C_{28}H_{29}NNaO_4S^+$ = 498.1710).

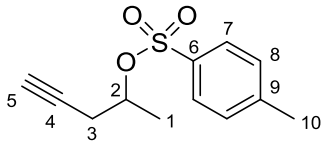
2-((2*S*,3a*S*,9b*R*)-1-tosyl-1,2,3,3a,4,9b-hexahydrochromeno[4,3-b]pyrrol-2-yl) acetic acid (287)



General procedure G was followed using **285** (100 mg, 296 μmol, 1.0 eq.), anhydrous MeOH (15 mL) and HCl (1.0 M in Et_2O, 2.96 mL, 2.96 mmol, 10.0 eq.). The crude amine (68 mg, 293 μmol, 99%) was obtained as a yellow oil. General procedure L was then followed using crude amine (50 mg, 214 μmol, 1.0 eq.) in DCM (15 mL), Et_3N (66 μL, 471 μmol, 2.2 eq.), DMAP (3 mg, 21 μmol, 0.1 eq.) and *p*-TsCl **281** (59 mg, 257 μmol, 1.2 eq.) were added and stirred for 14 hours. The crude mixture was then purified by flash column chromatography using silica gel (eluting with 10:1 petroleum ether/ethyl acetate) to afford the desired product

287 (61 mg, 158 μmol, 74%) as a brown oil. The product was isolated as a 10:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3380 (O-H), 3058, 3036 (C-H_{aro}), 2956, 2926, 2868 (C-H_{ali}), 1718 (C=O), 1260, 1038 (C-O-C), 1160, 1010 (S=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.86-7.73 (3H, m, Ar-H), 7.37 (2H, d, *J* = 7.8, Ar-H), 7.16 (1H, app. t, *J* = 7.5, Ar-H), 7.00 (1H, app. t, *J* = 7.5, Ar-H), 6.74 (1H, d, *J* = 8.1, Ar-H), 4.93 (1H, d, *J* = 6.9, 1-H), 4.13-3.95 (3H, m, 3-H and 11-H), 3.89-3.80 (1H, m, 12-H_a), 3.74-3.64 (1H, m, 12-H_b), 2.46 (3H, s, 17-H), 2.33-2.23 (1H, m, 2-H), 2.11 (1H, ddd, *J* = 16.5, 10.1 and 6.5, 10-H_a), 1.87-1.70 (1H, m, 10-H_b); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 171.3 (C18), 153.7 (C4), 144.1 (C13 or C16), 135.0 (C13 or C16), 132.3 (C5 or C6 or C7 or C8 or C14 or C15), 131.2 (C5 or C6 or C7 or C8 or C14 or C15), 130.2 (C5 or C6 or C7 or C8 or C14 or C15), 128.7 (C5 or C6 or C7 or C8 or C14 or C15), 127.7 (C5 or C6 or C7 or C8 or C14 or C15), 122.1 (C9), 116.7 (C5 or C6 or C7 or C8 or C14 or C15), 64.6 (C3), 60.6 (C1), 57.8 (C11), 50.8 (C12), 36.4 (C2), 33.1 (C10), 21.7 (C17); ESI-MS m/z = 797.21 ($2M+Na^+$, 7.1), 775.23 ($2M+H^+$, 15.1), 410.10 ($M+Na^+$, 100), 388.12 ($M+H^+$, 71.9); HRMS (ESI) m/z = 410.1029 (calculated for $C_{20}H_{21}NNaO_5S^+$ = 410.1033).

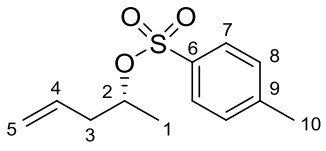
Pent-4-yn-2-yl 4-methylbenzenesulfonate (428)



The title compound **428** was prepared according to general procedure L using (±)-pent-4-yn-2-ol **427** (4 mL, 42.4 mmol, 1.0 eq.) in DCM (100 mL), Et_3N (7.1 mL, 50.88 mmol, 1.2 eq.), DMAP (518 mg, 4.24 mmol, 0.1 eq.) and *p*-TsCl **281** (9.7 g, 50.88 mmol, 1.2 eq.) were added and stirred for 12 hours. The crude mixture was then purified by flash column chromatography using silica gel (eluting with 15:1 petroleum ether/ethyl acetate) to afford **428** as a pale yellow oil (7.27 g, 30.53 mmol, 72%). IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3288 (C-H_{alkyne}), 3125 (C≡C),

3090, 3045, 3033 (C-H_{aro}), 2983, 2935, 2829 (C-H_{ali}), 1346, 1096 (S=O); $[\alpha]_D^{21}$ = -1.7 (*c* = 1.0 g/100 mL in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.79 (2H, d, *J* = 8.2, 7-H or 8-H), 7.33 (2H, dd, *J* = 8.2 and 0.6, 7-H or 8-H), 4.71-4.61 (1H, m, 2-H), 2.49 (1H, dd, *J* = 5.2 and 2.7, 3-H_a), 2.46 (1H, dd, *J* = 7.1 and 2.7, 3-H_b), 2.44 (3H, s, 10-H), 1.95 (1H, t, *J* = 2.7, 5-H), 1.36 (3H, d, *J* = 6.3, 1-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 144.8 (C6 or C9), 133.8 (C6 or C9), 129.8 (C7 or C8), 127.7 (C7 or C8), 78.3 (C2), 76.8 (C4), 71.4 (C5), 26.3 (C3), 21.5 (C10), 19.8 (C1); ESI-MS m/z = 499.12 (2M+Na^+, 36.5), 277.03 (2M+H^+, 9.8), 261.05 (M+Na^+, 100), 239.07 (M+H^+, 35.6); HRMS (ESI) m/z = 261.0553 (calculated for $C_{12}H_{14}NaO_3S^+$ = 261.0556).

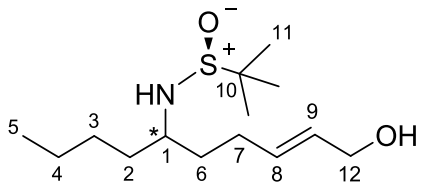
Pent-4-en-2-yl-4-methylbenzenesulfonate (438)



The title compound **438** was prepared according to general procedure L using (*R*)-pent-4-en-2-ol **435** (2 mL, 19.4 mmol, 1.0 eq.) in DCM (75 mL), Et_3N (3.25 mL, 23.28 mmol, 1.2 eq.), DMAP (237 mg, 1.94 mmol, 0.1 eq.) and *p*-TsCl **281** (4.44 g, 23.28 mmol, 1.2 eq.) were added and stirred for 12 hours. The crude mixture was then purified by flash column chromatography using silica gel (eluting with 10:1 petroleum ether/ethyl acetate) to give **438** as a colourless oil (3.45 g, 14.36 mmol, 74%). IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3172, 3140 (C-H_{alkene}), 3080, 3032, 3008 (C-H_{aro}), 2983, 2965, 2881, 2855 (C-H_{ali}), 1644 (C=C), 1349, 1098 (S=O); $[\alpha]_D^{23}$ = -47.2 (*c* = 1.0 g/100 mL in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.78 (2H, d, *J* = 8.3, 7-H or 8-H), 7.35-7.30 (2H, m, 7-H or 8-H), 5.66-5.63 (1H, m, 4-H), 5.06-5.02 (1H, m, 5-H_a), 5.00-4.97 (1H, m, 5-H_b), 4.63-4.56 (1H, m, 2-H), 2.44 (3H, s, 10-H), 2.39-2.23 (2H, m, 3-H), 1.25 (3H, d, *J* = 6.3, 1-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 144.5 (C6 or C9), 134.3 (C6 or C9), 132.2 (C4), 129.7 (C7 or C8), 127.7 (C7 or C8), 118.6 (C5), 79.3 (C2), 40.7 (C3), 21.5 (C10), 20.2 (C1);

ESI-MS m/z = 503.15 ($2M+Na^+$, 30.6), 263.07 ($M+Na^+$, 100); HRMS (ESI) m/z = 263.0715 (calculated for $C_{12}H_{16}NaO_3S^+$ = 263.0712).

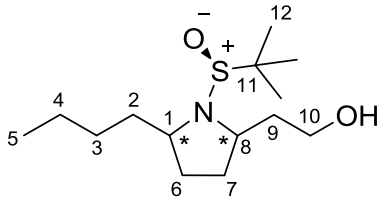
(S_S)-*N*-10-hydroxydec-8-en-5-yl)-2-methylpropane-2-sulfinamide (381)



To a solution of **366** (400 mg, 1.32 mmol, 1.0 eq.) in anhydrous THF (50 mL) at room temperature. A solution of $LiAlH_4$ (60 mg, 1.58 mmol, 1.2 eq.) in anhydrous THF (10 mL) was then added slowly to the reaction mixture. After completion of the addition, the mixture was stirred at room temperature. The reaction was monitored by TLC (petroleum ether/ethyl acetate) until no sulfinimine remained. Saturated aqueous solution of NH_4Cl (30 mL) was then added to the reaction mixture and stirred for 10 minutes. Ethyl acetate (20 mL) was added before the layers were separated, and the aqueous layer was washed with ethyl acetate (2 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$ before filtration and concentrating *in vacuo*. The crude residue was purified by flash column chromatography over silica gel (eluting with 10:1 petroleum ether/ethyl acetate) to provide **381** (185 mg, 673 μmol, 51%) as a clear yellow oil. The product was isolated as a >10:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3446 (O-H), 3201 (N-H), 2941, 2912, 2851 (C-H_{ali}), 1632 (C=C), 1079 (S-O); ^1H NMR (400 MHz, $CDCl_3$) δ_H = 5.75-5.56 (1H, m, 9-H), 4.13-4.03 (1H, m, 8-H), 3.86-3.60 (1H, m, 1-H), 3.33-3.11 (1H, m, N-H), 2.97 (1H, d, *J* = 6.0, 12-H_a), 2.26-1.95 (1H, m, 12-H_b), 1.89-1.67 (1H, m, 7-H_a), 1.66-1.48 (5H, m, 2-H, 6-H and 7-H_b), 1.40-1.27 (4H, m, 3-H and 4-H), 1.22 (9H, s, 11-H), 0.98-0.82 (3H, m, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 132.5 (C9), 129.8 (C8), 63.8 (C12), 56.1 (C10), 55.9 (C1), 36.3 (C2 or C6), 35.1 (C2 or C6), 30.9 (C7), 28.4 (C3), 27.9 (C4), 22.9 (C11), 14.1 (C5);

ESI-MS m/z = 573.37 (2M+Na^+, 21.0), 298.18 (M+Na^+, 80.1), 276.19 (M+H^+, 100); HRMS (ESI) m/z = 276.1988 (calculated for $C_{14}H_{30}NO_2S^+$ = 276.1992).

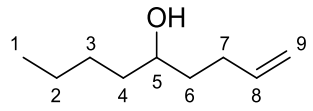
2-(5-butyl-1-((*S*$_S$)-*tert*-butylsulfinyl)pyrrolidin-2-yl)ethan-1-ol (380)



To a solution of **365** (250 mg, 660 μmol, 1.0 eq.) in anhydrous THF (20 mL) at room temperature. A solution of $LiAlH_4$ (50 mg, 1.32 mmol, 2.0 eq.) in anhydrous THF (5 mL) was then added slowly to the reaction mixture. After completion of the addition, the mixture was stirred at room temperature. The reaction was monitored by TLC (petroleum ether/ethyl acetate) until no sulfinimine remained. Saturated aqueous solution of NH_4Cl (20 mL) was then added to the reaction mixture and stirred for 5 minutes. Ethyl acetate (25 mL) was added before the layers were separated, and the aqueous layer was washed with ethyl acetate (2 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ before filtration and concentrating *in vacuo*. The crude residue was purified by flash column chromatography over silica gel (eluting with 1:1 petroleum ether/ethyl acetate) to provide **380** (111 mg, 403 μmol, 61%) as a pale yellow oil. The product was isolated as a 3:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3391 (O-H), 2954, 2928, 2861 (C-H_{ali}), 1039 (S-O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 4.05-3.78 (1H, m, 1-H or 8-H), 3.66-3.53 (1H, m, 1-H or 8-H), 2.95-2.73 (2H, m, 10-H), 1.90-1.76 (1H, m, 9-H_a), 1.74-1.46 (5H, m, 6-H, 7-H and 9-H_b), 1.44-1.27 (6H, m, 2-H, 3-H and 4-H), 1.23 (9H, s, 12-H), 0.89 (3H, t, *J* = 6.7, 5-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 67.6 (C1 or C8), 60.9 (C1 or C8), 57.1 (C11), 50.9 (C10), 38.9 (C6 or C7 or C9), 38.4 (C6 or C7 or C9), 31.9 (C6 or C7 or C9), 29.6 (C2 or C3 or C4), 28.6 (C2 or C3 or C4), 23.8 (C12), 22.8 (C2 or C3 or C4), 14.2 (C5); ESI-MS m/z =

573.37 (2M+Na^+, 21.7), 298.18 (M+Na^+, 90.7), 276.19 (M+H^+, 100); HRMS (ESI) m/z = 276.1991 (calculated for $C_{14}H_{30}NO_2S^+$ = 276.1992).

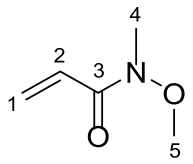
Non-1-en-5-ol (379)



A flame-dried round bottom flask equipped with a magnetic stirring-bar was purged with nitrogen gas and charged with magnesium (4 g, 166 mmol, 2.0 eq.) and anhydrous Et_2O (150 mL). To this was added a small amount of iodine crystals and the reaction mixture was then stirred for 15 minutes at room temperature, forming a colourless suspension. 4-Bromo-1-butene **377** (8.4 mL, 83 mmol, 1.0 eq.) was then added slowly. The solution was then stirred at room temperature for 2 hours. A solution of pentanal **378** (21.2 mL, 199.2 mmol, 2.4 eq.) in anhydrous Et_2O (50 mL) was then added dropwise over 2 hours, and the reaction mixture was stirred for a further 2 hours at room temperature then heated to reflux (40 °C) overnight. The reaction was cooled to room temperature and added to ice (15-20 g) followed by HCl (2.0 M). The organic layer was then extracted with Et_2O (2 × 50 mL) and washed with aqueous solution of $NaHSO_3$, $NaHCO_3$ and H_2O then dried over anhydrous $MgSO_4$ and filtered before evaporation the solvent *in vacuo* to provide the crude mixture. Distillation of the reaction crude mixture (85 °C/20 mbar) afforded **379** (8.38 gm, 58.93 mmol, 71%) as a colourless oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3364 (OH), 2956, 2922, 2852 (C-H_{ali}), 1659 (C=C); $[\alpha]_D^{23}$ = -47.2 (*c* = 1.0 g/100 mL in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.82 (1H, ddt, *J* = 16.9, 9.8 and 6.6, 8-H), 5.03 (1H, dddd, *J* = 16.9, 3.9, 3.1 and 1.6, 9-H_a), 4.99-4.94 (1H, m, 9-H_b), 3.67-3.57 (1H, m, 5-H), 2.50 (1H, app. t, *J* = 7.5, 6-H_a), 2.40 (1H, app. t, *J* = 7.5, 6-H_b), 2.36-2.28 (1H, m, 7-H_a), 2.26-2.07 (1H, m, 7-H_b), 1.60-1.50 (2H, m, 4-H), 1.48-1.38 (2H, m, 3-H), 1.34-1.29 (2H, m, 2-H), 0.93-0.88 (3H, m, 1-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 138.8 (C8), 114.9

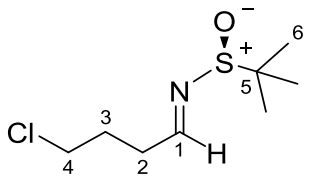
(C9), 71.7 (C5), 42.8 (C6), 37.3 (C4), 30.2 (C7), 28.0 (C3), 22.9 (C2), 14.2 (C1). Data consistent with literature.[167]

_N_-methoxy-_N_-methylacrylamide (415)



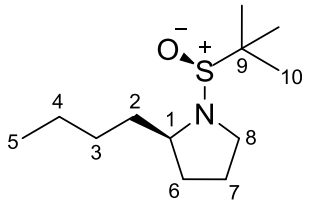
To a solution of acryloyl chloride **408** (994 μL, 12.3 mmol, 1.0 eq.) in 2-MeTHF (15 mL), *N*,*O*-dimethylhydroxylamine hydrochloride (DMHA) **395** (826 mg, 13.53 mmol, 1.1 eq.) was added. The mixture was then cooled to 0 °C before adding an aqueous solution of K_2CO_3 (3.74 g, 27.06 mmol, 2.2 eq.) in a 1:1 H_2O/2-MeTHF (20 mL) was added over 5 minutes. The reaction mixture was stirred for 2 hours at room temperature and then HCl (1.0 M, 12.3 mL, 12.3 mmol, 1.0 eq.) was added. The organic phase was separated and dried over anhydrous $MgSO_4$. The solvent was then removed under reduce pressure to give the desired product **415** (1.18 g, 10.21 mmol, 83%) as a light brown oil, which was used in the next step without further purification. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2973, 2939, 2910 (C-H_{ali}), 1725 (C=O), 1653 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 6.66 (1H, dd, *J* = 17.1 and 10.4, 2-H), 6.35 (1H, dd, *J* = 17.1 and 2.2, 1-H_a), 5.68 (1H, dd, *J* = 10.4 and 2.2, 1-H_b), 3.64 (3H, s, 5-H), 3.19 (3H, s, 4-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 166.4 (C3), 129.0 (C1), 125.9 (C2), 61.7 (C5), 32.3 (C4); CHN Found: C, 52.4%; H, 7.9%; N, 11.8%. $C_5H_9NO_2$ requires: C, 52.2%; H, 7.9%; N, 12.2%. Data consistent with literature.[137]

(*S*S,*E*)-*N*-(4-chlorobutylidene)-2-methylpropane-2-sulfinamide (191)



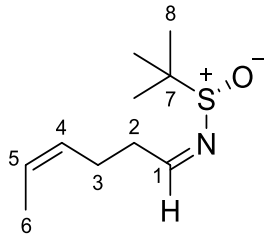
General procedure K was followed using 4-chloro-1-butanol **423** (5 mL, 50.2 mmol, 1.0 eq.), DCM (50 mL), PCC (13.5 g, 62.75 mmol, 1.25 eq.) and silica gel (13.5 g). The solvent was then evaporated under reduce pressure and the aldehyde crude material **190** was then used in the next step without further purification. General procedure A was then followed using aldehyde intermediate **190** (2 g, 18.9 mmol, 1.0 eq.), titanium (IV) ethoxide (11.89 mL, 56.7 mmol, 3.0 eq.) and (*S*)-(-)-*tert*-butyl-sulfinamide **32** (2.52 g, 20.79 mmol, 1.1 eq.) in anhydrous THF (50 mL). The crude product was obtained as a deep yellow oil and purified by flash column chromatography over silica gel (eluting with 6:1 petroleum ether/ethyl acetate) to afford **191** (3.52 g, 16.82 mmol, 89%; single isomer) as a yellow oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2961, 2927, 2903, 2867, 2869 (C-H_{ali}), 1722 (C=N), 1071 (S-O); $[\alpha]_D^{22}$ = +230.3 (*c* = 1.0 g/100 mL in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.07 (1H, t, *J* = 4.0, 1-H), 3.59 (2H, td, *J* = 6.4 and 1.9, 4-H), 2.72-2.61 (2H, m, 2-H), 2.14-2.06 (2H, m, 3-H), 1.16 (9H, s, 6-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 168.0 (C1), 56.7 (C5), 44.1 (C4), 33.2 (C2), 28.0 (C3), 22.4 (C6); ESI-MS m/z = 419.13 ($2M+H^+$, 7.7), 232.05 ($M+Na^+$, 16.7), 210.07 ($M+H^+$, 100); HRMS (ESI) m/z = 210.0711 (calculated for $C_8H_{17}{}^{35}ClNOS^+$ = 210.0714). Data consistent with literature.[102]

(*R*)-2-butyl-1-((*S*$_S$)-*tert*-butylsulfinyl)pyrrolidine (425)



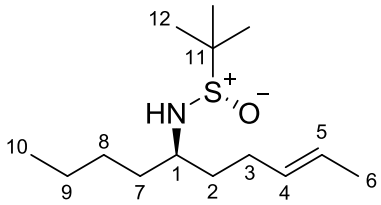
To a solution of **191** (803 mg, 3.83 mmol, 1.0 eq.) in anhydrous toluene (50 mL) at -78 °C under nitrogen and stirred for 10 minutes, was added slowly a solution of *n*-BuMgBr **424** (2.0 M in toluene, 2.3 mL, 4.6 mmol, 1.2 eq.) over 30 minutes at –78 °C. The reaction mixture was then stirred for 4 hours at same temperature before warming to 0 °C and quenched with saturated solution of Na_2SO_4 (30 mL). The organic layer was then extracted with ethyl acetate (3 × 25 mL), washed with water and dried over anhydrous $MgSO_4$ before filtration and concentrating *in vacuo*. The crude residue was purified by flash column chromatography over silica gel (eluting with 5:1 to 4:1 petroleum ether/ethyl acetate) to afford the desired product **425** as a yellow oil (718 mg, 3.1 mmol, 81%). The product was isolated as a >25:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2959, 2932, 2872 (C-H_{ali}), 1054 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 3.72 (1H, ddd, *J* = 10.2, 8.5 and 3.8, 8-H_a), 3.56-3.46 (1H, m, 1-H), 2.72 (1H, ddd, *J* = 10.2, 8.6 and 6.8, 8-H_b), 1.98 (1H, app. ddd, *J* = 18.5, 6.8 and 4.3, 7-H_a), 1.84 (1H, ddt, *J* = 10.8, 6.6 and 3.8, 6-H_a), 1.75-1.55 (2H, m, 2-H_a and 6-H_b), 1.46-1.37 (1H, m, 7-H_b), 1.51.24 (5H, m, 2-H_b, 3-H and 4-H), 1.19 (9H, s, 10-H), 0.89 (3H, t, *J* = 7.0, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 65.9 (C1), 57.2 (C9), 41.6 (C8), 36.8 (C2), 31.5 (C7), 28.5 (C3 or C4), 26.4 (C6), 24.1 (C3 or C4), 22.9 (C10), 14.2 (C5); ESI-MS m/z = 485.32 ($2M+Na^+$, 81.0), 463.33 ($2M+H^+$, 38.6), 254.15 ($M+Na^+$, 100), 232.17 ($M+H^+$, 60.2); HRMS (ESI) m/z = 254.1550 (calculated for $C_{12}H_{25}NNaOS^+$ = 254.1549); CHN Found: C, 62.2%; H, 10.9%; N, 5.7%. $C_{12}H_{25}NOS$ requires: C, 62.3%; H, 10.9%; N, 6.1%. Data consistent with literature.[102]

(*S*S)-*N*-((1*Z*,4*Z*)-hex-4-en-1-ylidene)-2-methylpropane-2-sulfinamide (441)



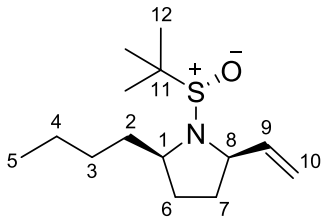
General procedure K was followed using hex-4-en-1-ol **339** (5 mL, 42.5 mmol, 1.0 eq.), DCM (100 mL), PCC (11.45 g, 53.13 mmol, 1.25 eq.) and silica gel (11.45 g). The solvent was then evaporated under reduce pressure and the aldehyde crude material **440** was then used in the next step without further purification. General procedure A was then followed using aldehyde intermediate **440** (4.5 g, 45.9 mmol, 1.0 eq.), titanium (IV) ethoxide (28.9 mL, 137.7 mmol, 3.0 eq.) and (*S*)-(-)-*tert*-butyl-sulfinamide **32** (6.12 g, 50.5 mmol, 1.1 eq.) in anhydrous THF (160 mL). The crude product was obtained as a deep green oil and purified by flash column chromatography over silica gel (eluting with 10:1 petroleum ether/ethyl acetate) to give **441** (7.76 g, 38.57 mmol, 84%; single isomer) as a green oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3104 (C-H_{alkene}), 2978, 2962, 2918, 2899, 2885 (C-H_{ali}), 1669 (C=N), 1621 (C=C), 1081 (S-O); $[\alpha]_D^{23}$ = -47.2 (*c* = 1.0 g/100 mL in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.04 (1H, t, *J* = 4.6, 1-H), 5.55-5.35 (2H, m, 4-H and 5-H), 2.61-2.51 (2H, m, 2-H), 2.31 (2H, ddd, *J* = 13.4, 6.6 and 6.6, 3-H), 1.62 (3H, d, *J* = 5.9, 6-H), 1.17 (9H, s, 8-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 169.1 (C1), 129.2 (C4 or C5), 126.4 (C4 or C5), 56.4 (C7), 35.9 (C2), 28.3 (C3), 22.3 (C8), 17.8 (C6); ESI-MS m/z = 425.22 ($2M+Na^+$, 12.9), 224.10 ($M+Na^+$, 100), 202.12 ($M+H^+$, 16.6); HRMS (ESI) m/z = 224.1081 (calculated for $C_{10}H_{19}NNaOS^+$ = 224.1080). Data consistent with literature.[104]

(S_S)-*N*-((*R*,*E*)-dec-8-en-5-yl)-2-methylpropane-2-sulfinamide (442)



To a solution of **441** (3.2 g, 15.9 mmol, 1.0 eq.) in anhydrous toluene (50 mL) under nitrogen atmosphere at -78 °C, *n*-BuMgBr **424** (2.0 M in toluene, 9.55 mL, 19.1 mmol, 1.2 eq.) was then added dropwise. After completion of the addition, the reaction mixture was stirred for 3 hours at -78 °C before adding NH_4Cl (saturated aqueous solution, 40 mL). The organic layer was then separated with ethyl acetate (3 × 20 mL) and dried over anhydrous $MgSO_4$ before filtration and concentrating *in vacuo*. The crude material was purified by flash column chromatography over silica gel (eluting with 4:1 petroleum ether/ethyl acetate) gave the pure product **442** (3.26 g, 12.56 mmol, 79%) as a pale yellow oil. The product was isolated as a >25:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3213 (N-H), 2954, 2928, 2857 (C-H_{ali}), 1636 (C=C), 1048 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.51-5.31 (2H, m, 4-H and 5-H), 3.23-3.13 (1H, m, 1H), 2.97 (1H, d, *J* = 6.7, N-H), 2.09-1.96 (2H, m, 2-H or 7-H), 1.64-1.58 (3H, m, 6-H), 1.53-1.38 (4H, m, 2-H or 7-H and 3-H), 1.34-1.24 (4H, m, 8-H and 9-H), 1.18 (9H, s, 12-H), 0.90-0.83 (3H, m, 10-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 130.7 (C4 or C5), 125.7 (C4 or C5), 56.3 (C1), 55.8 (C11), 36.0 (C2 or C3 or C7), 35.3 (C2 or C3 or C7), 28.8 (C2 or C3 or C7), 27.6 (C8 or C9), 22.8 (C12), 22.7 (C8 or C9), 18.0 (C6), 14.1 (C10); ESI-MS m/z = 541.38 ($2M+Na^+$, 100), 519.40 ($2M+H^+$, 38.9), 282.18 ($M+Na^+$, 47.4), 260.20 ($M+H^+$, 45.5); HRMS (ESI) m/z = 541.3837 (calculated for $C_{28}H_{58}N_2NaO_2S_2^+$ = 541.3832).

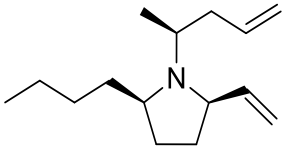
(2*R*,5*R*)-2-butyl-1-((*S*s)-*tert*-butylsulfinyl)-5-vinylpyrrolidine (433)



LiOAc (508 mg, 7.7 mmol, 1.0 eq.), 3Å molecular sieves (150 mg), $Pd(TFA)_2$ (256 mg, 770 μmol, 10.0 mol%) and anhydrous DMSO (25 mL) were weighed into a thick-walled culture tube. The tube was purged with O_2 for 30 minutes. The sulfinamide substrate **442** (2 g, 7.7 mmol, 1.0 eq.) in anhydrous DMSO (25 mL) was then added slowly over 45 minutes. The reaction mixture was then heated to 50 °C under ballon of O_2 for 24 hours. After completion of the reaction (monitored by TLC and LCMS), the reaction mixture was diluted with Et_2O to give the suspension and it was filtered through a short pad of silica gel and the silica was washed with Et_2O and ethyl acetate. The organic solvent was evaporated under reduce pressure and the organic layer washed with H_2O followed by the brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to give the crude product **433**. Purification using flash column chromatography over silica gel (eluting with 2:1 petroleum ether/ethyl acetate) gave the desired product **433** (1.41 g, 5.47 mmol, 71%) as a yellow oil. The product was isolated as a >25:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)$/ cm^{-1} (neat) = 3109 (C-H_{alkene}), 2956, 2930, 2862 (C-H_{ali}), 1642 (C=C), 1064 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.71 (1H, ddd, *J* = 17.3, 10.1 and 7.4, 9-H), 5.16-5.08 (1H, m, 10-H_a), 5.03-4.96 (1H, m, 10-H_b), 4.12-4.02 (1H, m, 8-H), 3.91-3.81 (1H, m, 1-H), 2.13-2.03 (1H, m, 7-H_a), 1.74-1.65 (3H, m, 6-H and 7-H_b), 1.63-1.59 (1H, m, 2-H_a), 1.54-1.44 (1H, m, 2-H_b), 1.40-1.25 (4H, m, 3-H and 4-H), 1.19 (9H, s, 12-H), 0.89 (3H, t, *J* = 7.1, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 141.9 (C9), 114.7 (C10), 69.6 (C8), 56.8 (C11), 54.0 (C1), 35.7 (C2), 31.4 (C6), 30.6 (C7), 29.6 (C3 or C4), 23.6 (C12), 22.8 (C3 or C4), 14.2 (C5); ESI-MS

m/z = 537.35 (2M+Na^+, 18.8), 280.17 (M+Na^+, 100), 258.18 (M+H^+, 41.3); HRMS (ESI) m/z = 280.1703 (calculated for $C_{14}H_{27}NNaOS^+$ = 280.1706).

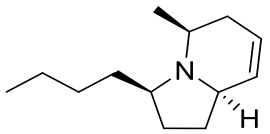
(2*R*,5*R*)-2-butyl-1-((*S*)-pent-4-en-2-yl)-5-vinylpyrrolidine (437)



To a solution of pyrrolidine derivative **434** (150 mg, 980 μmol, 1.0 eq.) and $NaHCO_3$ (123 mg, 1.47 mmol, 1.5 eq.) in anhydrous DMF (20 mL) at room temperature. A mixture of **438** (283 mg, 1.18 mmol, 1.2 eq.) and NaI (147 mg, 980 μmol, 1.0 eq.) in anhydrous DMF (20 mL) was then added slowly to the reaction mixture. After completion of the addition, the mixture was stirred at room temperature. The reaction was monitored by TLC (petroleum ether/ethyl acetate) and LCMS until no starting material **434** remained. Saturated aqueous solution of NH_4Cl (40 mL) was then added to the reaction mixture and stirred for 15 minutes. Ethyl acetate (20 mL) was added before the layers were separated, and the aqueous layer was washed with ethyl acetate (2 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$ before filtration and concentrating *in vacuo*. The crude residue was purified by flash column chromatography over silica gel (eluting with 5:1 petroleum ether/ethyl acetate) to provide **437** (41 mg, 186 μmol, 19%) as a pale yellow oil. The product was isolated as a >25:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2963, 2939, 2875, 2856 (C-H_{ali}), 1689, 1659 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 6.01-5.75 (1H, m), 5.60-5.34 (3H, m), 5.16-5.02 (2H, m), 2.54-2.44 (1H, m), 2.34-2.16 (2H, m), 1.94-1.74 (2H, m), 1.72-1.67 (6H, m), 1.65-1.52 (3H, m), 1.48-1.29 (4H, m), 0.99 (3H, t, *J* = 6.9); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 127.6 (CH), 125.7 (CH), 118.4 (CH_2), 117.0 (CH_2), 48.5 (CH), 47.3 (CH), 46.9 (CH), 32.1 (CH_2), 28.8 (CH_2), 28.6 (CH_2), 28.4 (CH_2), 18.0 (CH_2), 17.7 (CH_2), 15.2 (CH_3), 13.6 (CH_3); ESI-MS m/z = 465.41 (2M+Na^+, 100), 443.43 (2M+H^+, 44.2),

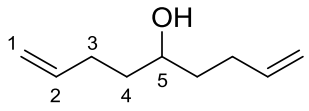
244.20 (M+Na^+, 20.9), 222.22 (M+H^+, 3.3); HRMS (ESI) m/z = 465.4182 (calculated for $C_{30}H_{54}N_2Na^+$ = 465.4179).

(3R,5S,8aR)-3-butyl-5-methyl-1,2,3,5,6,8a-hexahydroindolizine (361)



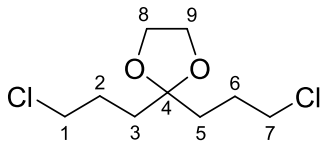
A flame-dried two-neck round bottom flask equipped with a condenser and a rubber septum containing a stirring bar was charged with **437** (75 mg, 339 μmol, 1.0 eq.) in anhydrous Et_2O (25 mL) under an argon atmosphere. A solution of Grubbs II catalyst (6 mg, 7 μmol, 2.0 mol%) in anhydrous Et_2O (25 mL) was then added slowly to the reaction mixture. The reaction was then heated to reflux (40 °C) for 24 hours, the mixture was then allowed to cool to room temperature. This was followed by the addition of silica gel (1 g) and the resulting suspension was concentrated *in vacuo* and the deep yellow residue was purified by flash column chromatography over silica gel (eluting with 6:1 petroleum ether/ethyl acetate) to afford **361** (50 mg, 261 μmol, 77%) as a pale yellow oil. The product was isolated as a >25:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2967, 2929, 2861 (C-H_{ali}), 1658 (C=C); ^1H NMR (400 MHz, $CDCl_3$) δ_H = 5.65-5.55 (1H, m), 5.50-5.40 (1H, m), 3.55-3.46 (3H, m), 2.40-2.33 (1H, m), 2.31-2.22 (1H, m), 2.10-2.02 (1H, m), 1.71-1.61 (2H, m), 1.56-1.46 (2H, m), 1.40-1.30 (5H, m), 1.22 (3H, d, *J* = 7.0), 0.91 (3H, t, *J* = 6.8); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 126.9 (CH), 118.0 (CH), 67.2 (CH), 27.0 (CH), 25.1 (CH), 25.0 (CH_2), 22.5 (CH_2), 22.1 (CH_2), 22.0 (CH_2), 20.5 (CH_2), 18.6 (CH_2), 17.9 (CH_3), 15.9 (CH_3); ESI-MS m/z = 409.35 (2M+Na^+, 8.1), 387.37 (2M+H^+, 22.5), 216.17 (M+Na^+, 100), 194.19 (M+H^+, 59.3); HRMS (ESI) m/z = 216.1719 (calculated for $C_{13}H_{23}NNa^+$ = 216.1723).

Nona-1,8-dien-5-ol (462)



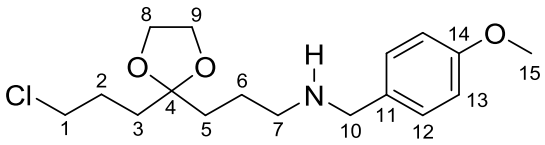
A flame-dried round bottom flask equipped with a magnetic stirring-bar was purged with nitrogen gas and charged with magnesium (2.57 g, 105.6 mmol, 1.2 eq.) and anhydrous THF (40 mL). A small amount of iodine crystals was then added, and the reaction mixture was stirred for 10 minutes at room temperature, forming a colourless suspension. 4-Bromo-1-butene **377** (8.93 mL, 88 mmol, 1.0 eq.) was then added slowly. The solution was then stirred at room temperature for 12 hours. A solution of ethyl formate **463** (3.55 mL, 44 mmol, 0.5 eq.) in anhydrous Et_2O (50 mL) was then added dropwise over 3 hours, and the reaction mixture was stirred for a further 12 hours at room temperature then heated to reflux (70 °C) for 1 hour. The reaction mixture was cooled to room temperature and quenched with saturated solution of NH_4Cl (100 mL) and the organic layer extracted with Et_2O (3 × 50 mL). The combined organic extracts were then concentrated *in vacuo* and the resulting residue charged with potassium hydroxide solution (15%, 100 mL) and heating to reflux for 6 hours. Following, the mixture was extracted with Et_2O, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*, which gave the desired product **462** (8.39 g, 59.84 mmol, 68%) as a colourless oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3346 (O-H), 2977, 2933, 2860 (C-H_{ali}), 1641 (C=C); ^1H NMR (400 MHz, $CDCl_3$) δ_H = 5.83 (2H, ddt, *J* = 17.0, 10.2 and 6.7, 2-H), 5.03 (2H, dtd, *J* = 17.0, 3.4 and 1.9, 1-H_a), 4.97 (2H, ddt, *J* = 10.2, 1.9 and 1.2, 1-H_b), 3.67-3.59 (1H, m, 5-H), 2.17-2.07 (4H, m, 3-H), 1.60-1.40 (4H, m, 4-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 138.9 (C2), 114.7 (C1), 71.8 (C5), 37.0 (C3 or C4), 33.9 (C3 or C4); ESI-MS m/z = 303.22 ($2M+Na^+$, 100), 281.24 ($2M+H^+$, 33.9); HRMS (ESI) m/z = 303.2290 (calculated for $C_{18}H_{32}NaO_2^+$ = 303.2295); CHN Found: C, 76.8%; H, 11.3%. $C_9H_{16}O$ requires: C, 77.1; H, 11.5%.

1,7-dichloroheptan-4-one ethylene ketal (465)

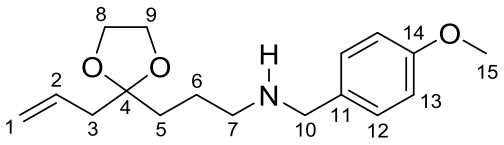


A flame-dried round bottom flask equipped with a magnetic stirring-bar, Dean Stark trap and a reflux condenser was charged with 1,7-dichloroheptan-4-one **466** (43.93 g, 240 mmol, 1.0 eq.), benzene (150 mL), ethylene glycol (19.73 mL, 352.8 mmol, 1.47 eq.) and then *p*-TsOH.H_2O (571 mg, 3 mmol, 1.25 mol%) was added in one portion to the reaction mixture. The mixture was heated to reflux for 4 hours. The azeotrope mixture of ethylene glycol, water, and benzene was collected in the trap and removed periodically by means of the stopcock. The reflux was continued until no further azeotrope was evolved. When the reaction had reached completion, the mixture was allowed to cool to room temperature. H_2O (30 mL) was then added to the mixture, followed by a solution of aqueous $NaHCO_3$ and the organic layer was separated with ethyl acetate (3 × 25 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to provide the crude residue as a yellow oil. Distillation of the crude mixture (120 °C, 0.8 mmHg) afforded title compound **465** (46.3 mL, 204 mmol, 85%) as a clear yellow oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2961, 2883 (C-H_{ali}), 1211, 1056 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 3.94 (4H, s, 8-H and 9-H), 3.55 (4H, t, *J* = 6.5, 1-H and 7-H), 1.90-1.81 (4H, m, 2-H and 6-H), 1.78-1.71 (4H, m, 3-H and 5-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 110.9 (C4), 65.1 (C8 and C9), 45.3 (C1 and C7), 34.5 (C2 and C6), 27.2 (C3 and C5); CHN Found: C, 47.7%; H, 7.3%, $C_9H_{16}Cl_2O_2$ requires: C, 47.6%; H, 7.1%. Data consistent with literature.[168]

3-(2-(3-chloropropyl)-1,3-dioxolan-2-yl)-*N*-(4-methoxybenzyl)propan-1-amine (474) and 3-(2-allyl-1,3-dioxolan-2-yl)-*N*-(4-methoxybenzyl) propan-1-amine (473)



474

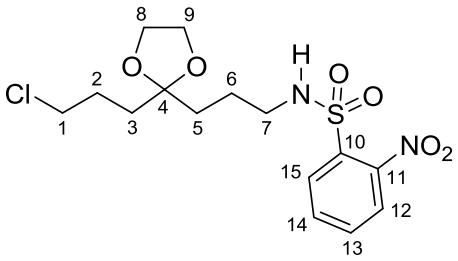


473

To a solution of 1,7-dichloroheptan-4-one ethylene ketal **465** (10 g, 44 mmol, 1.0 eq.) in DMF (20 mL) under argon atmosphere at room temperature. *p*-Methoxy benzyl amine **467b** (5.75 mL, 44 mmol, 1.0 eq.) was then added dropwise to the reaction mixture. After stirring for 15 minutes, K_2CO_3 (12.16 g, 88 mmol, 2.0 eq.) was added followed by heating at 100 °C for 24 hours. Et_2O/H_2O (1:1) (30 mL) was then added to the reaction mixture and the aqueous layer was extracted with H_2O (3 × 15 mL). The residue organic layer was dried over anhydrous $MgSO_4$ before filtration and concentrated *in vacuo*. Flash column chromatography over silica gel (eluent with 8:1 petroleum ether/ethyl acetate) affording two products; **474** (2.89 g, 8.8 mmol, 20%) as a yellow oil and **473** (2.05 g, 7.04 mmol, 16%) as a yellow oil. Product **474**; IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3321 (N-H), 3033, 3010 (C-H_{aro}), 2954, 2884, 2836 (C-H_{ali}), 1247, 1067 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.19 (2H, d, *J* = 8.2, 12-H or 13-H), 6.78-6.82 (2H, m, 12-H or 13-H), 5.03 (1H, br s, N-H), 4.26 (2H, t, *J* = 5.6, 1-H), 4.09 (2H, m, 7-H), 3.91 (3H, s, 15-H), 3.88 (4H, s, 8-H and 9-H), 2.53 (2H, d, *J* = 7.1, 10-H), 1.73-1.60 (8H, m, 2-H, 3-H, 5-H and 6-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 156.8 (C14), 130.8 (C11), 129.0 (C12 or C13), 114.1 (C12 or C13), 111.1 (C4), 65.1 (C8 and C9), 55.4 (C15), 44.6 (C1 and C7), 43.8 (C10), 33.6 (C2 and C6), 23.7 (C3 and C5); ESI-MS m/z = 328.16 ($M+H^+$, 100); HRMS (ESI) m/z = 328.1675 (calculated for $C_{17}H_{27}{}^{35}ClNO_3{}^+$ = 328.1674). Product **473**; IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3293 (N-H), 3051, 3002 (C-H_{aro}), 2999, 2931, 2861 (C-H_{ali}), 1656 (C=C), 1245, 1062 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.83-7.78 (2H, m, 12-H or 13-H), 7.00-6.95

(2H, m, 12-H or 13-H), 5.86-5.72 (1H, m, 2-H), 5.11-5.03 (2H, m, 1-H), 5.01 (1H, br s, N-H), 3.95-3.89 (4H, m, 8-H and 9-H), 3.86 (3H, s, 15-H), 3.38-3.36 (2H, m, 3-H or 7-H), 2.82-2.72 (2H, m, 3-H or 7-H), 2.32-2.25 (2H, m, 10-H), 1.71-1.50 (4H, m, 5-H and 6-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 161.0 (C14), 129.9 (C11), 129.4 (C12 or C13), 129.3 (C12 or C13), 125.1 (C2), 113.9 (C1), 111.3 (C4), 65.1 (C8 and C9), 55.4 (C15), 53.5 (C3 or C7 or C10), 49.6 (C3 or C7 or C10), 45.4 (C3 or C7 or C10), 35.1 (C5 or C6), 27.3 (C5 or C6); ESI-MS m/z = 292.19 ($M+H^+$, 100); HRMS (ESI) m/z = 292.1911 (calculated for $C_{17}H_{26}NO_3^+$ = 292.1907).

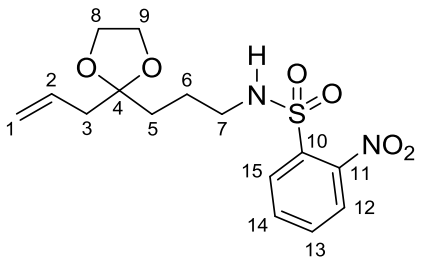
_N_-(3-(2-(3-chloropropyl)-1,3-dioxolan-2-yl)propyl)-2-nitrobenzene sulfonamide (475)



In a two-neck round bottom flask with 2-nitrobenzenesulfonamide **467c** (3.64 g, 18 mmol, 1.0 eq.), 1,7-dichloroheptan-4-one ethylene ketal **465** (4 g, 18 mmol, 1.0 eq.), Na_2CO_3 (9.54 g, 90 mmol, 5.0 eq.) and *n*-Bu_4NI (6.64 g, 18 mmol, 1.0 eq.) in a 1:1 THF/CH_3CN (120 mL) were added. The mixture was heated at 65 °C for 24 hours, cooled at room temperature. H_2O (30 mL) was then added and the solvent removed under reduced pressure. The residue was diluted with brine (30 mL), extracted with ethyl acetate (3 × 30 mL), dried with anhydrous Na_2SO_4 and then concentrated *in vacuo*. The crude residue was purified by flash column chromatography over silica gel (eluting with 1:1:0.1 petroleum ether/ethyl acetate/Et_3N) to afford **475** (1.06 g, 2.7 mmol, 15%) as a yellow solid, m.p. = 65-67 °C. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3333 (N-H), 3096, 3045, 3011 (C-H_{aro}), 2958, 2925, 2883 (C-H_{ali}), 1553, 1341 (NO_2), 1212, 1124 (C-O-C), 1362, 1061 (S=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.16-8.10 (1H, m, 12-H or 13-H or 14-H

or 15-H), 7.89-7.83 (1H, m, 12-H or 13-H or 14-H or 15-H), 7.76-7.71 (2H, m, 12-H or 13-H or 14-H or 15-H), 5.52 (1H, t, *J* = 6.1, N-H), 3.94-3.90 (4H, m, 8-H and 9-H), 3.53 (2H, t, *J* = 6.4, 1-H), 3.13 (2H, td, *J* = 7.1 and 6.1, 7-H), 1.84-1.76 (2H, m, 2-H), 1.72-1.58 (6H, m, 3-H, 5-H and 6-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 148.2 (C10 or C11), 134.0 (C10 or C11), 133.6 (C12 or C13 or C14 or C15), 132.9 (C12 or C13 or C14 or C15), 131.2 (C12 or C13 or C14 or C15), 125.5 (C12 or C13 or C14 or C15), 110.8 (C4), 65.1 (C8 and C9), 45.3 (C1), 43.9 (C7), 34.3 (C2 or C3 or C5 or C6), 34.0 (C2 or C3 or C5 or C6), 27.2 (C2 or C3 or C5 or C6), 24.0 (C2 or C3 or C5 or C6); ESI-MS m/z = 807.15 ($2M+Na^+$, 26.6), 415.06 ($M+Na^+$, 100), 393.08 ($M+H^+$, 5.2); HRMS (ESI) m/z = 415.0693 (calculated for $C_{15}H_{21}{}^{35}ClN_2O_6SNa^+$ = 415.0701). Data consistent with literature.[161]

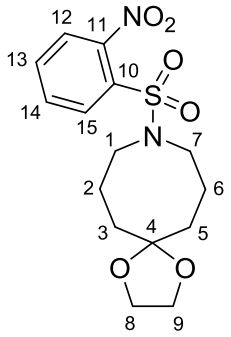
***N*-(3-(2-allyl-1,3-dioxolan-2-yl)propyl)-2-nitrobenzenesulfonamide (476)**



In a 100 mL round bottom flask compound **475** (60 mg, 153 μmol, 1.0 eq.) and *n*-Bu_4NI (113 mg, 306 μmol, 2.0 eq.) were dissolved in MeCN (15 mL). $CsCO_3$ (249 mg, 765 μmol, 5.0 eq.) was then added and the mixture was heated at 60 °C for 24 hours. After cooling at room temperature, the volatiles were concentrated *in vacuo* and the residue was purified by flash column chromatography over silica gel (eluting with 7:3:0.5 petroleum ether/ethyl acetate/Et_3N) to give **476** (29 mg, 81 μmol, 53%) as a yellow oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3336 (N-H), 3083, 3022 (C-H_{aro}), 2956, 2924, 2854 (C-H_{ali}), 1641 (C=C), 1541, 1343 (NO_2), 1261, 1125 (C-O-C), 1363, 1062 (S=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.15-8.11 (1H, m, 12-H or 13-H or 14-H or 15-H), 7.87-7.83 (1H, m, 12-H or 13-H or 14-H or 15-H), 7.75-7.70 (2H, m, 12-H or 13-H or 14-H or 15-H), 5.75 (1H, ddt, *J* = 16.2, 11.8 and 7.2, 2-H), 5.52 (1H, t, *J* = 5.9, N-H), 5.19-5.10 (1H, m, 1-H_a), 5.07-

5.03 (1H, m, 1-H_b), 3.98-3.88 (4H, m, 8-H and 9-H), 3.12 (2H, dt, *J* = 7.0 and 5.9, 7-H), 2.31 (2H, d, *J* = 7.2, 3-H), 1.66-1.63 (4H, m, 5-H and 6-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 134.1 (C10 or C11), 133.6 (C12 or C13 or C14 or C15), 133.2 (C10 or C11), 133.1 (C12 or C13 or C14 or C15), 132.9 (C12 or C13 or C14 or C15), 131.2 (C12 or C13 or C14 or C15), 125.5 (C2), 118.5 (C1), 110.6 (C4), 65.2 (C8 and C9), 44.0 (C7), 42.1 (C3), 33.9 (C5 or C6), 29.9 (C5 or C6); ESI-MS m/z = 379.09 ($M+Na^+$, 100); HRMS (ESI) m/z = 379.0931 (calculated for $C_{15}H_{20}N_2NaO_6S^+$ = 379.0934).

9-((2-nitrophenyl)sulfonyl)-1,4-dioxa-9-azaspiro[4.7]dodecane (464c)



In a 100 mL two-neck round bottom flask with compound **475** (60 mg, 153 μmol, 1.0 eq.) and *n*-Bu_4NI (57 mg, 153 μmol, 1.0 eq.) were dissolved in dioxane (15 mL). A solution of *n*-Bu_4NOH in water (57%, 918 μL, 918 μmol, 6.0 eq.) was then added and the mixture was refluxed for 24 hours before cooling to room temperature. The volatiles were concentrated *in vacuo* and the residue was purified by flash column chromatography over silica gel (eluent with 1:1:0.1 petroleum ether/ethyl acetate/Et_3N) to afford **464c** (5 mg, 14 μmol, 9%) as a yellow oil. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3063, 3029, 3011 (C-H_{aro}), 2999, 2944, 2908 (C-H_{ali}), 1440, 1329 (NO_2), 1226, 1121 (C-O-C), 1329, 1051 (S=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.98-7.93 (1H, m, 12-H or 13-H or 14-H or 15-H), 7.70-7.64 (2H, m, 12-H or 13-H or 14-H or 15-H), 7.63-7.53 (1H, m, 12-H or 13-H or 14-H or 15-H), 3.92 (4H, s, 8-H and 9-H), 3.36 (4H, t, *J* = 6.0, 1-H and 7-H), 1.93-1.82 (8H, m, 2-H, 3-H, 5-H and 6-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 147.2

(C10 or C11), 133.9 (C10 or C11), 133.6 (C12 or C13 or C14 or C15), 132.5 (C12 or C13 or C14 or C15), 131.4 (C12 or C13 or C14 or C15), 126.1 (C12 or C13 or C14 or C15), 111.3 (C4), 65.3 (C8 and C9), 44.7 (C1 and C7), 34.8 (C2 and C6 or C3 and C5), 26.6 (C2 and C6 or C3 and C5); ESI-MS m/z = 379.09 ($M+Na^+$, 100); HRMS (ESI) m/z = 379.0932 (calculated for $C_{15}H_{20}N_2NaO_6S^+$= 379.0934). Data consistent with literature.[161]

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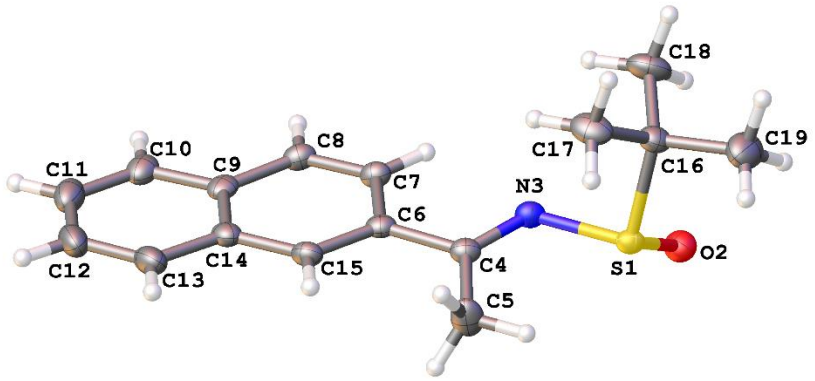
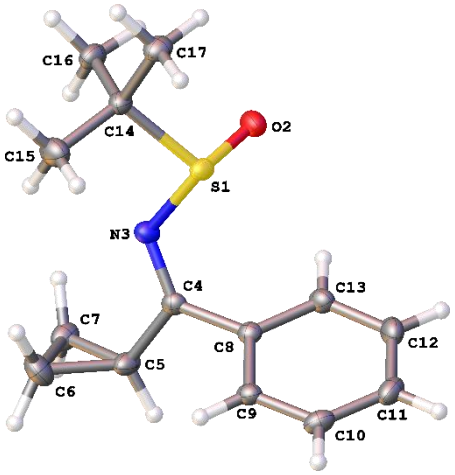
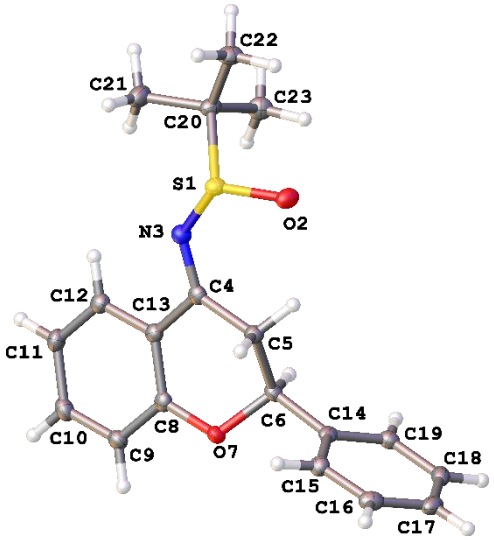
7. Appendix A: X-rays



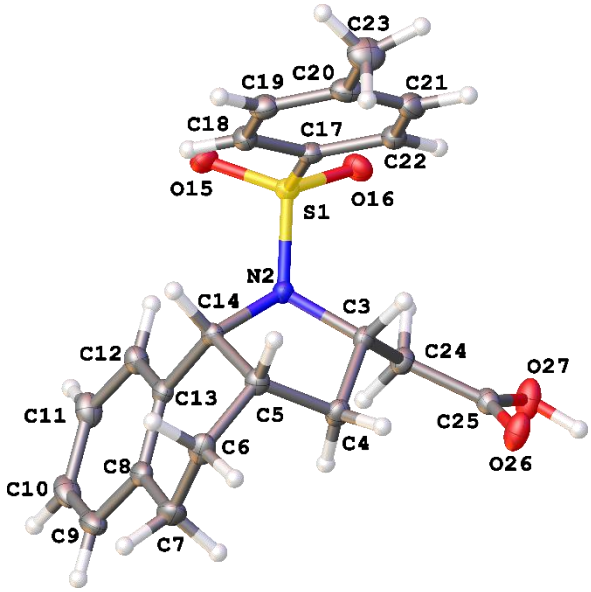
Compound number	**238j**
Identification code	RSDRSA
Empirical formula	$C_{16}H_{19}NOS$
Formula weight	273.38
Temperature/K	120(2)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	9.3691(5)
b/Å	12.0081(7)
c/Å	13.1503(7)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1479.47(14)
Z	4
ρ_{calc}g/cm^3	1.227
μ/mm^{-1}	1.865
F(000)	584.0
Crystal size/mm^3	0.8033 × 0.6373 × 0.5492
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	9.976 to 148.292
Index ranges	$-11 \le h \le 10$, $-14 \le k \le 13$, $-16 \le l \le 11$
Reflections collected	5448
Independent reflections	2900 [R_{int} = 0.0319, R_{sigma} = 0.0334]
Data/restraints/parameters	2900/0/177
Goodness-of-fit on F^2	1.062
Final R indexes [I>=2σ (I)]	R_1 = 0.0325, wR_2 = 0.0865
Final R indexes [all data]	R_1 = 0.0330, wR_2 = 0.0869
Largest diff. peak/hole / e Å^{-3}	0.27/-0.30
Flack parameter	0.019(11)



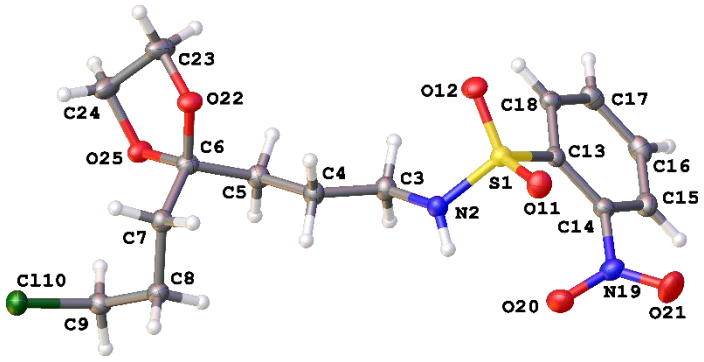
Compound number	**238l**
Identification code	RSDRSI
Empirical formula	$C_{14}H_{19}NOS$
Formula weight	249.36
Temperature/K	120(2)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	7.8638(3)
b/Å	10.9643(4)
c/Å	15.7767(5)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1360.28(8)
Z	4
ρ_{calc}g/cm^3	1.218
μ/mm^{-1}	1.975
F(000)	536.0
Crystal size/mm^3	0.502 × 0.343 × 0.212
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	9.824 to 146.918
Index ranges	$-8 \leq h \leq 9$, $-11 \leq k \leq 13$, $-17 \leq l \leq 19$
Reflections collected	4971
Independent reflections	2664 [R_{int} = 0.0211, R_{sigma} = 0.0267]
Data/restraints/parameters	2664/0/157
Goodness-of-fit on F^2	1.078
Final R indexes [I>=2σ (I)]	R_1 = 0.0243, wR_2 = 0.0640
Final R indexes [all data]	R_1 = 0.0244, wR_2 = 0.0640
Largest diff. peak/hole / e Å^{-3}	0.14/-0.24
Flack parameter	-0.005(8)



Compound number	**238aa**
Identification code	RSDRSK
Empirical formula	$C_{19}H_{21}NO_2S$
Formula weight	327.43
Temperature/K	120(2)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	5.5239(2)
b/Å	9.1638(3)
c/Å	32.2744(14)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1633.74(11)
Z	4
ρ_{calc}g/cm^3	1.331
μ/mm^{-1}	1.830
F(000)	696.0
Crystal size/mm^3	0.475 × 0.113 × 0.1
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	10.034 to 148.554
Index ranges	$-6 \le h \le 4$, $-11 \le k \le 11$, $-39 \le l \le 38$
Reflections collected	9327
Independent reflections	3259 [R_{int} = 0.0318, R_{sigma} = 0.0320]
Data/restraints/parameters	3259/0/211
Goodness-of-fit on F^2	1.035
Final R indexes [I>=2σ (I)]	R_1 = 0.0296, wR_2 = 0.0752
Final R indexes [all data]	R_1 = 0.0323, wR_2 = 0.0768
Largest diff. peak/hole / e Å^{-3}	0.19/-0.26
Flack parameter	-0.006(11)



Compound number	**283**
Identification code	RSDRSD
Empirical formula	$C_{21}H_{23}NO_4S$
Formula weight	385.46
Temperature/K	120(2)
Crystal system	orthorhombic
Space group	$P2_12_12$
a/Å	17.5392(7)
b/Å	11.2447(4)
c/Å	9.5802(4)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1889.44(12)
Z	4
ρ_{calc}g/cm^3	1.355
μ/mm^{-1}	1.749
F(000)	816.0
Crystal size/mm^3	0.43 × 0.202 × 0.142
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	9.232 to 147.41
Index ranges	$-21 \leq h \leq 21$, $-14 \leq k \leq 10$, $-11 \leq l \leq 11$
Reflections collected	13424
Independent reflections	3766 [R_{int} = 0.0262, R_{sigma} = 0.0218]
Data/restraints/parameters	3766/0/248
Goodness-of-fit on F^2	1.062
Final R indexes [I>=2σ (I)]	R_1 = 0.0270, wR_2 = 0.0697
Final R indexes [all data]	R_1 = 0.0273, wR_2 = 0.0699
Largest diff. peak/hole / e Å^{-3}	0.19/-0.34
Flack parameter	0.004(6)



Compound number	**475**
Identification code	RSDRSC
Empirical formula	$C_{15}H_{21}N_2O_6SCl$
Formula weight	392.85
Temperature/K	120(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	11.89958(14)
b/Å	18.3432(2)
c/Å	8.25880(11)
α/°	90
β/°	103.5467(12)
γ/°	90
Volume/Å^3	1752.55(4)
Z	4
ρ_{calc}g/cm^3	1.489
μ/mm^{-1}	3.365
F(000)	824.0
Crystal size/mm^3	0.545 × 0.408 × 0.181
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	7.642 to 153.788
Index ranges	$-13 \leq h \leq 15$, $-23 \leq k \leq 18$, $-9 \leq l \leq 10$
Reflections collected	9224
Independent reflections	3588 [R_{int} = 0.0188, R_{sigma} = 0.0151]
Data/restraints/parameters	3588/0/230
Goodness-of-fit on F^2	1.093
Final R indexes [I>=2σ (I)]	R_1 = 0.0342, wR_2 = 0.0865
Final R indexes [all data]	R_1 = 0.0345, wR_2 = 0.0866
Largest diff. peak/hole / e Å^{-3}	0.34/-0.46