University of Nottingham
UK | CHINA | MALAYSIA

Synthesis of Cyclic Sulfoximines and Their Application in the Expedient Synthesis of Cyclic Sulfinamides and 3-Pyrrolines

Jon-Paul Ward

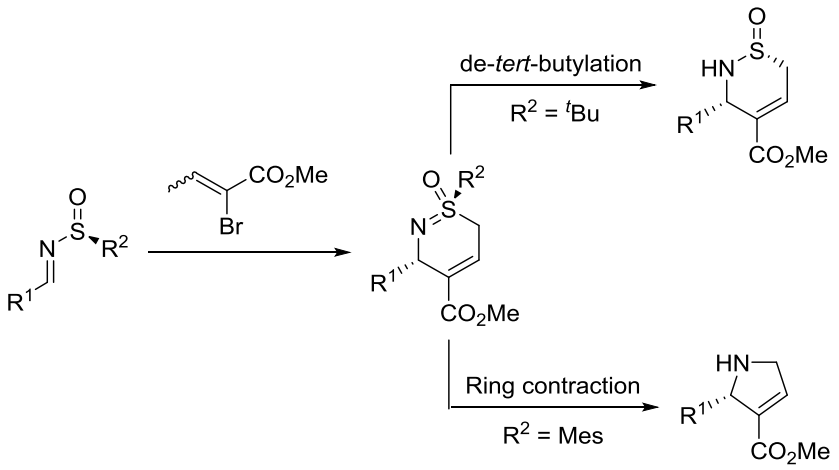
Thesis submitted to the University of Nottingham for the degree of Doctor of Philosophy

SEPTEMBER 2018

Abstract

The synthesis of sulfoximines has been studied since the late 1940s but their application in academia and industry has only started to be exploited over the last 20 years.

In 2013, a novel [2,3]-sigmatropic rearrangement of 2-vinylaziridines to cyclic sulfoximines (R^2 = mesityl or *tert*-butyl) was discovered by the Stockman group. The first project investigates the de-*tert*-butylation of *tert*-butyl sulfoximines (R^2 = *tert*-butyl) to afford the unprecedented chiral cyclic sulfinamides. This has enabled a two-step telescoped protocol to be developed, whereby chiral cyclic sulfinamides can be prepared from readily available *tert*-butyl sulfinimines.



The second project revisits a previous finding within the Stockman group, which was the ring contraction of mesityl cyclic sulfoximines (R^2 = mesityl). The scope of the existing [2,3]-sigmatropic rearrangement to afford mesityl cyclic sulfoximines is expanded. Subsequently, the scope of the novel ring contraction of mesityl cyclic sulfoximines to 3-pyrrolines in one step is greatly expanded.

Finally, the third project concerns the further functionalisation of the cyclic sulfoximine and cyclic sulfinamide products, which were produced during the first and second projects. This small study is only an introduction into the potential of these novel three-dimensional structures.

Acknowledgements

I would like to express my gratitude to my supervisor, Professor Robert Stockman, for giving me the opportunity to work on possibly the most exciting projects in his research group. I am very grateful for the freedom I was allowed in order to pursue my interests and findings along the way.

I would also like to thank all of the people I met during my 3 or so months at Lilly UK in Windlesham. It was a thoroughly rewarding experience and has very much re-enforced my desire to work in the medicinal chemistry sector. I am especially thankful to my industrial supervisor, Dr. Lesley Walton for seemingly making it her priority to make me feel welcome and at home at Lilly UK over those 3 or so months.

A special mention goes to all the past and present Stockman group members for all the knowledge and assistance and, perhaps most importantly, for making the group an enjoyable place to work. In particular, Dr. Ryan Liffey introduced me to Team Lygo (football team) and who I later recruited to help push on the cyclic sulfinamides project.

In particular I would like to thank all of the Post-Docs for their input over the four years. Specifically, Dr. Ross Wilkie, Dr. Johnny Moore and Dr. Thomas Storr for daily input and again Dr. Ross Wilkie, Dr. Thomas Storr and Nessa Carson for proof-reading.

I am very grateful to all the technical staff at the University of Nottingham without whose dedication this would not have been possible.

It goes without saying, but I would like to thank my family and friends for their love and continued support. Special mention to the University of Nottingham Snooker and Pool Club, it was an honour to play with you all whilst we represented the University of Nottingham at National level.

Finally, I would like to thank Lilly UK and the EPSRC for funding this research and the RSC for funding my travel to present this work at the biannual ACS Conference in New Orleans.

Abbreviations

$[\alpha]_D$	specific rotation
Å	Ångström(s)
Ac	acetyl
acac	acetylacetone
aq	aqueous solution
Ar	aryl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
Bz	benzoyl
c	concentration
CDK	cyclin-dependent kinase
cod	1,5-cyclooctadiene
CSA	camphorsulfonic acid
Cyp	cyclopentyl
Δ	difference in
δ	chemical shift
d	doublet
DMF	*N*,*N*-dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
de	diastereomeric excess
ee	enantiomeric excess
equiv.	equivalent(s)
er	enantiomeric ratio
ESI	electrospray ionisation
Et	ethyl
FTIR	fourier transform infrared
g	gram
h	hour

HATU	Hexafluorophosphate azabenzotriazole tetra-methyl uronium
HMDS	hexamethyldisilazide or hexamethyldisilazane
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
i	*iso*
IR	infrared
J	coupling constant
mg	milligram
mL	millilitre
m	multiplet
M	molecular ion
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
Mes	mesityl or 2,4,6-trimethylphenyl
MHz	megahertz
min	minute(s)
mmol	millimole
MS	mass spectrometry
Ms	mesyl or methanesulfonyl
MSH	*O*-(mesitylenesulfonyl)hydroxylamine
m/z	mass to charge ratio
n	*normal*
NMR	nuclear magnetic resonance
Ns	nosyl or *p*-nitrobenzenesulfonyl
ũ	wavenumber
Ph	phenyl
Pr	propyl
ppm	parts per million
q	quartet
R	any group
rt	room temperature
s	singlet

tert or t	*tertiary*
t	triplet
TBS	*tert*-butyldimethylsilyl
TCA	trichloroacetic acid
Tf	triflate or trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TOF	time of flight
p-tol	*para*-tolyl
Ts	4-toluenesulfonyl or tosyl
UV	ultraviolet

Contents

1. Introduction – *Sulfinamides*

1.1 Sulfinamides

Sulfinamides, known previously as sulphinamides or sulfinanilides,[1] are the sulfur equivalent of amides. They are second in an oxidation state family of sulfur-amine compounds, which comprises of sulfenamides **1**, sulfinamides **2** and sulfonamides **3** (Figure 1.1).

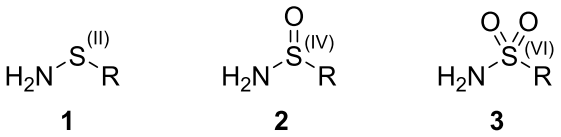
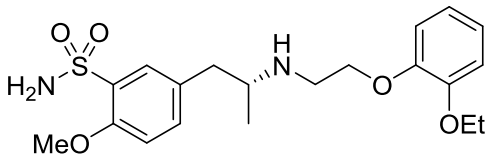


Figure 1.1. Oxidation state family of sulfur-amine compounds.

Initially, sulfinamides (**2**) were used to synthesise sulfonimidoyl chlorides,[2,3] which can be used as intermediates in the syntheses of sulfoximines or sulfonimidamides.[4] In the 1990s, sulfinamides were employed as a chiral ammonia equivalent, such as in the synthesis of the drug Tamsulosin – which is used to treat benign prostatic hyperplasia (BPH) (Figure 1.2).[5,6] In more recent years they have found application as chiral ligands[7] and as organocatalysts.[8]



Tamsulosin

Figure 1.2. Muscle relaxant drug, Tamsulosin.

As the area of sulfinamide chemistry is extensive and one of the primary objectives of this research was the development of enantioselective syntheses, presented herein is only the literature of a similar nature. This

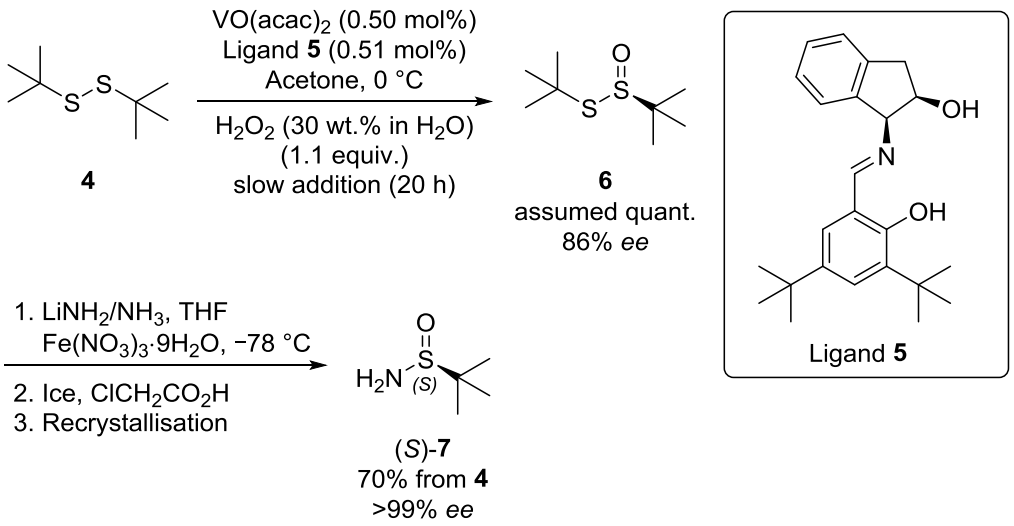
criterion therefore excludes examples that obtain enantiopure products *via* chiral resolutions. A comprehensive review of achiral sulfinamide chemistry up until 1990 was published by Tillett.[9]

1.1.1 Methodologies for the Preparation of Acyclic Sulfinamides

The synthesis of acyclic sulfinamides is well precedented in the literature.[9,10] These methods have been used to prepare sulfinamides from a wide range of sulfur-containing compounds such as: thiols, disulfides and sulfinyl- or sulfonyl-derivatives.

1.1.1.1 Preparation from Sulfenyl Derivatives

The application of chiral sulfinamides as chiral auxiliaries was popularised by Ellman at the end of the 1990s.[5] The Ellman group performed an enantiocontrolled oxidation of *tert*-butyl disulfide **4** with vanadyl acetylacetonate, hydrogen peroxide and a chiral ligand **5** to obtain **6** (Scheme 1.1).[11] Cleavage of the sulfide bond with lithium amide in ammonia, followed by a series of recrystallisations, allowed access to *tert*-butanesulfinamide (*S*)-**7** in 70% yield from **4** in >99% *ee*. The optimised route was published in 2005 and is shown below in Scheme 1.1.[12] In 2010, there were 75 suppliers offering enantiopure *tert*-butanesulfinamide **7** for <£1 per gram.[5]



Scheme 1.1. Optimised synthesis of *tert*-butanesulfinamide **7**.

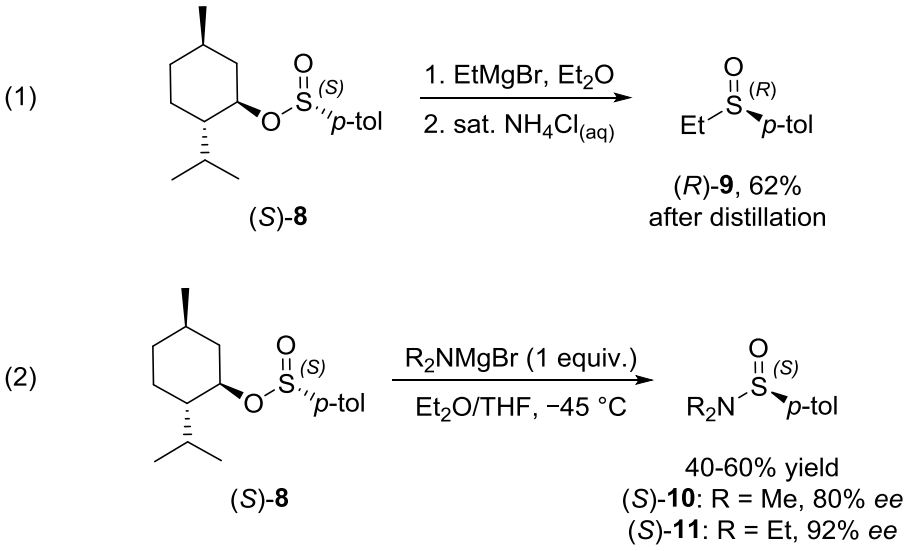
The original route had a number of drawbacks, the biggest being catalyst decomposition in the biphasic mixture due to highly variable peroxide concentration. Changes to the procedure included: the reaction solvent was changed from chloroform to acetone, ligand **5** was found to have an improved selectivity over its predecessor under the new conditions, and the catalyst decomposition was overcome by the slow addition of hydrogen peroxide over 20 h.

As a side note, chiral resolution of racemic *tert*-butanesulfinamide **7** was explored, albeit unsuccessfully, alongside the optimisation of the stereoselective oxidation route.[13]

1.1.1.2 Preparation from Sulfinyl Derivatives

Chiral sulfinyl transfer templates have been routinely used to prepare chiral sulfoxides since Andersen pioneered the use of menthyl *p*-tolylsulfinate (*S*)-**8**, obtained from L-menthol, in 1962 (Scheme 1.2 – equation [1]).[14] In 1968,

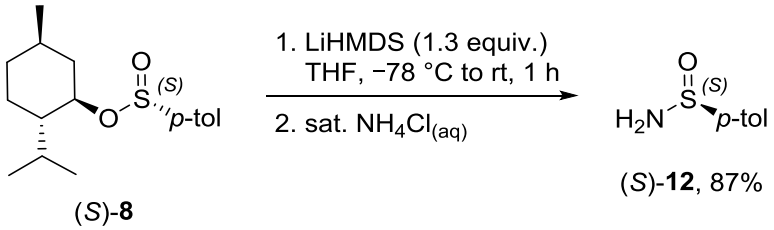
Colonna and co-workers adapted this strategy to prepare the first examples of sulfinamides obtained in high enantioselectivity (Scheme 1.2 – equation [2]).[15] Treatment of sulfinate (*S*)-**8** with bromomagnesium alkylamides afforded sulfinamides (*S*)-**10** and (*S*)-**11** in yields ranging from 40-60% – it was ambiguous if the yields reported referred to the average yields for the chemistry or were specific to an individual example. The enantiomeric excesses of sulfinamides (*S*)-**10** and (*S*)-**11** were determined by conversion to their corresponding sulfoxides, by displacement of the nitrogen with methyllithium, which are known in the literature. The reactions with methyllithium proceeded with inversion of configuration at the sulfur centre. An *iso*-propyl example was investigated, however, reaction of the resulting sulfinamide with methyllithium was unsuccessful and therefore an enantiomeric excess could not be elucidated.



Scheme 1.2. Examples of (*S*)-**8** as a chiral sulfinyl transfer template.

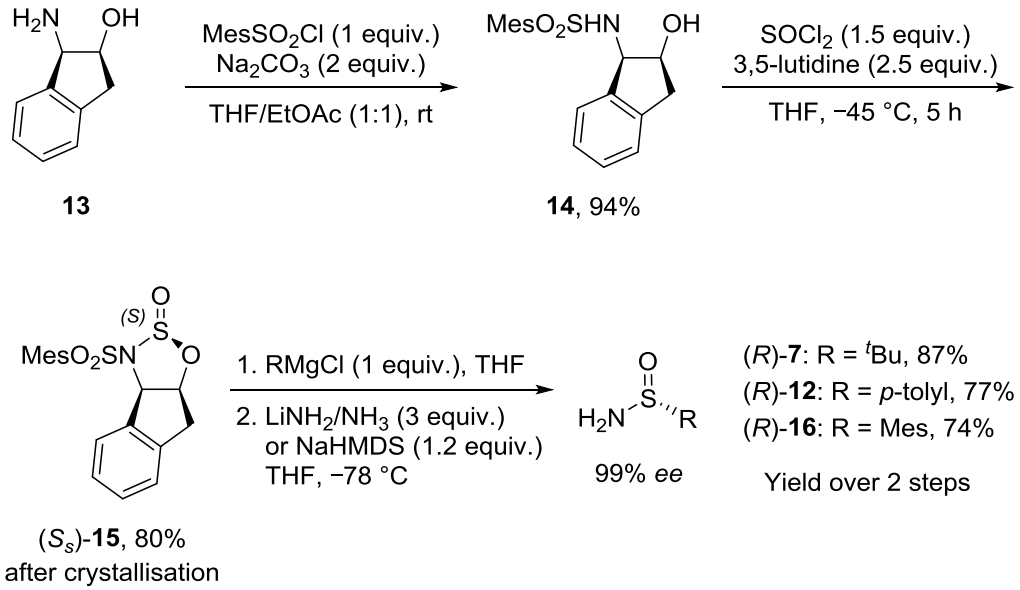
At the same time, Nudelman and Cram investigated the reaction of sulfinate (*S*)-**8** with lithium anilide ($PhHN^-Li^+$).[16] The product was obtained in 41% yield in what was believed to be a high stereospecificity, this postulation was made based upon the observed racemisation of the product when greater than 1 equivalent of lithium anilide was used.

Later, Davis and co-workers also adapted Andersen's strategy by substituting the Grignard reagent for lithium bis(trimethylsilyl)amide[17] to prepare (*S*)-*p*-tolyl sulfinamide (*S*)-**12** in 87% yield (Scheme 1.3).[18]



Scheme 1.3. Application of (*S*)-**8** as a source of chiral sulfinamide (*S*)-**12**.

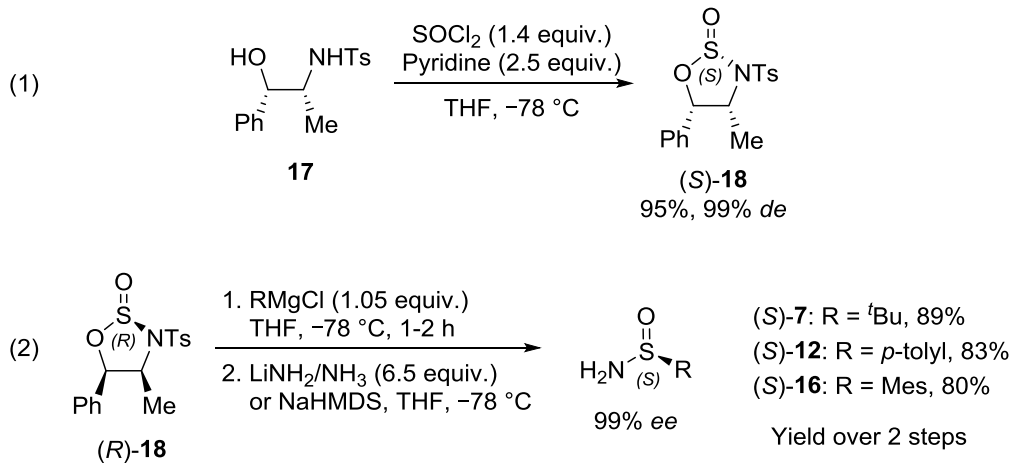
The greatest advancement in the preparation of enantiopure sulfinamides was the development of a chiral auxiliary-based strategy by Senanayake and co-workers at Sepracor in 2002 (Scheme 1.4).[19] Following mesityl sulfonylation of *cis*-1-amino-2-indanol **13**, chiral auxiliary **14** was reacted with thionyl chloride and 3,5-lutidine to afford diastereomerically pure 1,2,3-oxathiazolidine-2-oxide (S_S)-**15** in 80% yield – the other diastereoisomer was an oil. To synthesise enantiopure sulfinamides, chiral template (S_S)-**15** was treated with a Grignard reagent at –45 °C or –78 °C. After purification, the intermediate was then reacted with lithium amide or sodium bis(trimethylsilyl)amide at –78 °C to afford enantiopure (*R*)-sulfinamides (**7**, **12** and **16**) in 74-87% yield over two steps.



Scheme 1.4. Chiral auxiliary-based strategy of Senanayake.

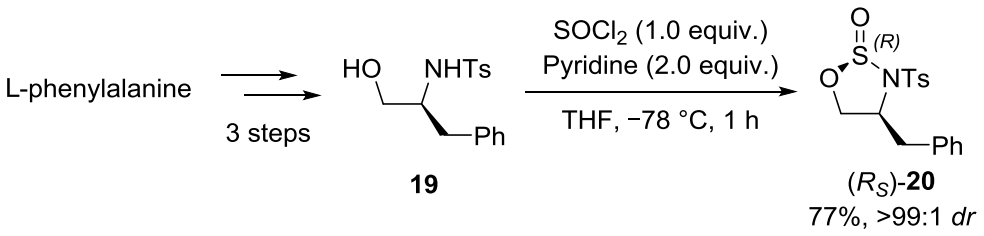
In 2005, Senanayake and co-workers developed a norephedrine-based chiral auxiliary **17** (Scheme 1.5 – equation [1]).[20] The rationale for developing a new chiral auxiliary was due to the high cost of *cis*-1-amino-2-indanol **13** – unless on a multi-ton scale. Conversely, norephedrine is now a highly controlled substance. Nevertheless, *N*-tosyl norephedrine **17** was treated with thionyl chloride and pyridine at –78 °C to afford diastereomerically pure (*S*)-**18** in 95% yield. The enantiomer (*R*)-**18** was used to prepare (*S*)-sulfinamides (**7**, **12** and **16**) in improved yields of 80-89% over two steps (Scheme 1.5 – equation [2]).

In addition, further development of their previous work on chiral auxiliary **14** led to the preparation of the opposite diastereoisomer (R_S)-**15** by using 2,6-*tert*-butyl pyridine instead of 3,5-lutidine.



Scheme 1.5. Second generation chiral auxiliary from norephedrine.

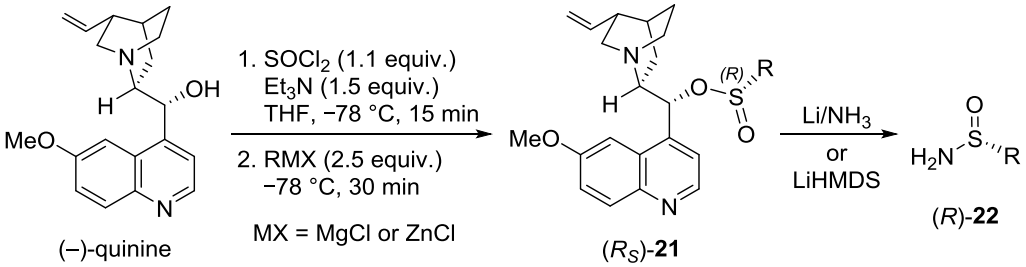
The Stockman group contributed to this area with a chiral auxiliary **19** derived from L-phenylalanine in 3 steps (Scheme 1.6).[21] This extension of the methodology exemplified that chiral templates could be accessed from inexpensive and readily available building blocks. It became apparent that chiral template (R_s)-**20** was prone to epimerisation in aqueous or acidic media. Thus, concentration of the reaction mixture followed by purification over ISOLUTE® nitrile (end-capped) silica gel afforded (R_s)-**20** in 77% yield and >99:1 *dr*.



Scheme 1.6. Stockman group's amino acid derived chiral template (R_s)-**20**.

The latest iteration of Senanayake's chiral auxiliary methodology employed (–)-quinine as the chiral amino alcohol (Table 1.1).[22] This work appeared to overcome the previous limitations in the field which were: the high cost of *cis*-1-amino-2-indanol **13**, the highly controlled access to norephedrine, and the purification instability of the Stockman group's phenylalanine-derived template (R_S)-**20**. The (–)-quinine sulfinates (*R*)-**21** were isolated in excellent yields of 76-94% and 96:4-98:2 *dr* (Table 1.1 , column 4, entries 1-6). Cleavage of the sulfinates with a nucleophilic nitrogen source afforded sulfinamides (*R*)-**22** also in excellent yields (71-92%) and enantioselectivities (85:15-99:1 *er*) (Table 1.1, column 7, entries 1-6). Cleavage conditions of lithium and ammonia were necessary for the more sterically hindered sulfinates.

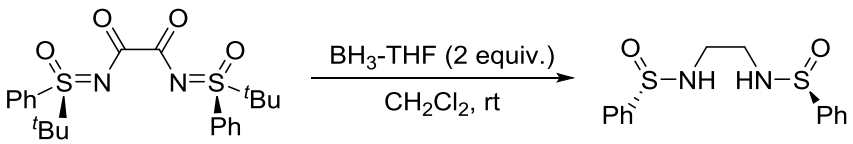
Table 1.1. Third generation chiral auxiliary strategy from Senanayake.



Entry	RMX	(R_S)-**21** Yield/*dr*	Conditions	(*R*)-**22** Yield/*er*
1	^{t}BuMgCl	91%, 98:2	Li/NH_3	79%, >99:1
2	2-Me-2-BuMgCl	92%, 96:4	Li/NH_3	71%, >99:1
3	*p*-TolylZnCl	76%, 96:4	Li/NH_3 LiHMDS	92%, 88:12 84%, >99:1
4	MesZnCl	94%, 96:4	Li/NH_3 LiHMDS	85%, 85:15 82%, 99:1
5	2,4,6-triiso-propylphenylZnCl	80%, 96:4	Li/NH_3	84%, >99:1
6	^{n}BuMgCl	85%, 96:4	LiHMDS	87%, 98:2

1.1.1.3 Preparation from Sulfonyl Derivatives

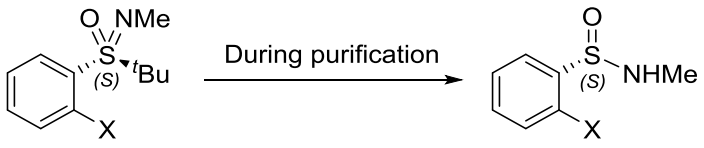
The unintentional isolation of sulfinamides has been prevalent during research into sulfoximines. Whilst preparing bissulfoximine ligands for the palladium-catalysed asymmetric allylic alkylation of 1,3-diphenylpropenyl acetate, Bolm and co-workers observed the de-*tert*-butylation of bissulfoximine **23** to afford **24** when attempting to perform a borane reduction of the bridging carbonyls (Scheme 1.7).[23] The elimination could be explained by diborane's ability to act as a Lewis acid and hydride donor. In addition, the authors proposed that the elimination occurred with retention of configuration at sulfur.



23 **24**, 60%

Scheme 1.7. Serendipitous isolation of bissulfinamide **24**.

Later in 2005, Gaillard and co-workers detected the de-*tert*-butylation of sulfoximines **25** and **26** during their purification (Scheme 1.8).[24] Prior to their purification, sulfoximines **25** and **26** were prepared by *ortho*-lithiation with *n*-butyllithium and subsequent trapping with halogen electrophiles.



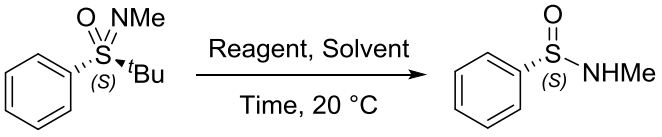
25: R = Cl
26: R = I

27: R = Cl
28: R = I

Scheme 1.8. De-*tert*-butylation of acyclic sulfoximines.

Optimisation of the de-*tert*-butylation conditions for sulfoximine **29** is shown in Table 1.2.

Table 1.2. Investigation into de-*tert*-butylation conditions.



29 **30**

Entry	Conditions	Solvent	Time	**30** Yield (%)
1[a]	KDMO (2 equiv.)	DMSO	30 min	70
2	BH_3 (2 equiv.)	THF	12 h	76
3	$NaBH_4$ (1 equiv.)	$CDCl_3$	5 days	5[b]
4	$NaBH_3CN$ (1 equiv.)	$CDCl_3$	5 days	5[b]
5	$LiAlH_4$ (1 equiv.)	$CDCl_3$	5 days	10[b]
6	$LiAlH_4$ (1 equiv.)	THF	24 h	20[b]
7	$LiAlH_4$ (3 equiv.)	THF	24 h	60[b]
8	$ZnBr_2$ (1 equiv.)	$CDCl_3$	5 days	35[b,c]
9	$MgBr_2$ (1 equiv.)	$CDCl_3$	5 days	43[b,c]
10	$CuCl_2$ (1 equiv.)	$CDCl_3$	5 days	-[c]
11	$Mg(ClO_4)_2$ (1 equiv)	$CDCl_3$	24 h	-[c]
12	$Mg(ClO_4)_2$ (1 equiv)	THF	24 h	84[b] (76)

[a] Performed at 50 °C. [b] Determined by ^1H NMR. [c] Degradation observed.

Employing Harmata's conditions,[25] potassium dimsylate (KDMSO) in dimethylsulfoxide, a 70% yield of sulfinamide **30** was obtained (Table 1.2, entry 1). A weaker base, such as potassium *tert*-butoxide, was unsuccessful. Bolm's conditions, borane-tetrahydrofuran complex, afforded an improved 76% yield (Table 1.2, entry 2). Of the metal hydride donors tested, lithium aluminium hydride gave the best result of 60% yield (Table 1.2, entries 3-7). The application of Lewis acids afforded the sulfinamide **30** in poor yield, except for magnesium perchlorate which gave a 76% yield (Table 1.2, entries 8-12). Similarly, the use of strong Brønsted acids (2 M hydrochloric acid or

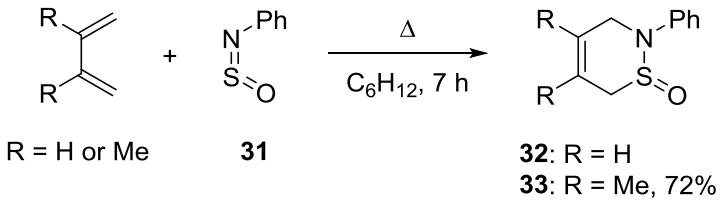
Amberlyst® 15) gave degradation products. Furthermore, the stereoselectivity was only assessed in the borane and magnesium perchlorate reactions (Table 1.2, entries 2 and 12), both products were isolated in 80% *ee* which equates to complete retention of configuration with no erosion of the *ee* of the starting material.

1.1.2 Methodologies for the Synthesis of Cyclic Sulfinamides

Unsurprisingly, the synthesis of cyclic sulfinamides has proven more challenging. Presented herein are a diverse range of procedures for the synthesis of cyclic sulfinamides. However, prior to this report, there were only two approaches to chiral cyclic sulfinamides that can be considered as general. Moreover, the two general methods are reliant on an aromatic ring, which acts as a tether, to construct the starting material or the cyclic sulfinamide directly.

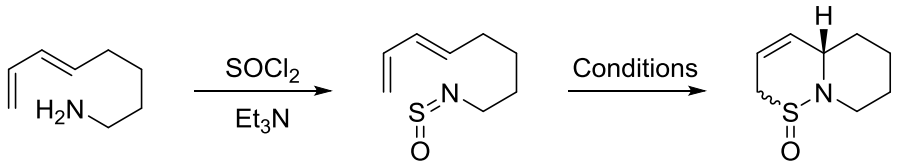
1.1.2.1 Preparation of Achiral Cyclic Sulfinamides

The first cyclic sulfinamides were prepared by Wichterle and Roček in 1953 *via* the Diels-Alder reactions of butadiene or 2,3-dimethylbutadiene and *N*-thionylaniline **31** (Scheme 1.9).[26–28] Two sources corroborate that **32** and **33** were the first examples of cyclic sulfinamide synthesis, however, only the yield of the sulfinamide **33** could be confirmed, which was 72%. The group on the nitrogen had to be electron-withdrawing as alkyl substituents were found to be unsuccessful. In a follow up paper, the same authors investigated different electron withdrawing groups on the nitrogen. The scope was expanded to include ketones, esters and sulfonic acids.[26,29]



Scheme 1.9. First synthesis of a cyclic sulfinamide.

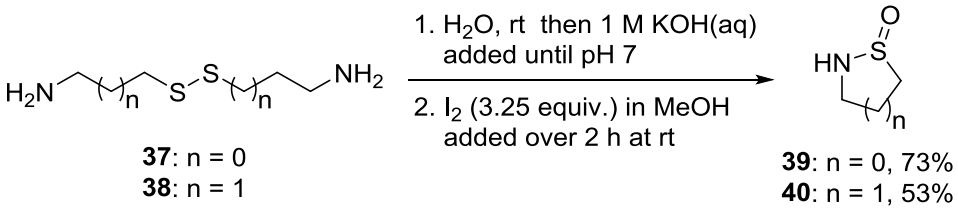
Extension of the original Diels-Alder methodology, of Wichterle and Roček, by Weinreb and Bell investigated the incorporation of an alkyl tether between the diene and dienophile (Scheme 1.10). Treatment of amine **34** with thionyl chloride afforded **35** in 60% yield. The [4+2]-cycloaddition did not proceed under thermal conditions and it wasn't until a Lewis acid or high pressure was applied that the successful preparation of bicyclic sulfinamide **36** was observed. A 2:1 mixture of isomers of **36** was reported in both cases, unfortunately, no indication was given for which was the major.



Scheme 1.10. Bicyclic sulfinamide synthesis using tethered substrate.

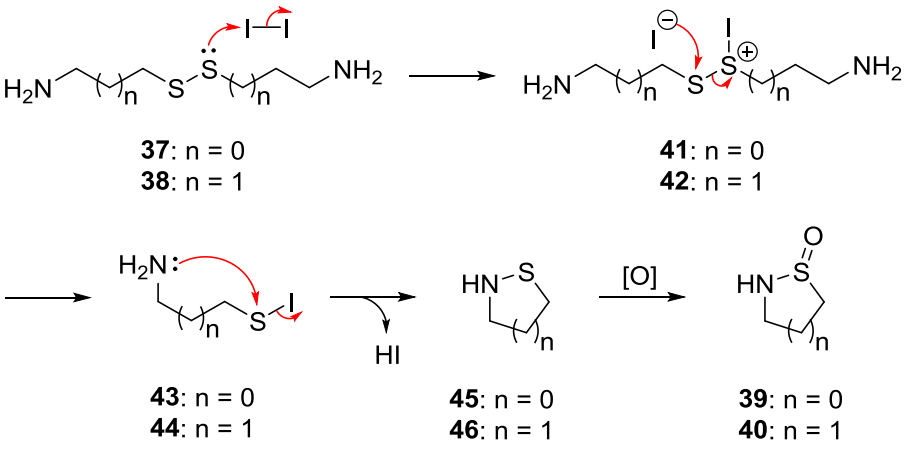
Whilst investigating the oxidative cleavage of disulfides **37** and **38** in aqueous iodine, Doi and Musker reported the unusual isolation of cyclic sulfinamides **39** and **40** (Scheme 1.11).[30] This was the first example of a 5-membered cyclic sulfinamide. The necessity of the potassium hydroxide in the experimental procedure is unclear. Although, for the preparation of the 6-membered cyclic

sulfinamide **40**, the disulfide **38** was prepared as the hydrobromide salt and therefore a salt neutralisation would be necessary in that case.



Scheme 1.11. Synthesis of cyclic sulfinamides **39** and **40**.

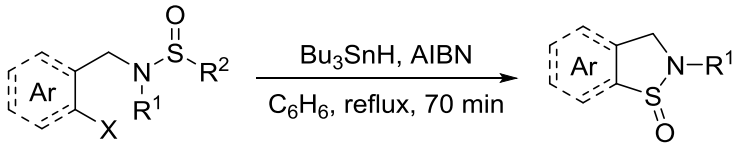
Based on their kinetic studies, the mechanism the authors proposed began with a sulfur atom of disulfide **37** or **38** reacting with a molecule of iodine to give intermediate **41** or **42** (Scheme 1.12). Then, only because the amine(s) were unprotected, **43** or **44** underwent intramolecular cyclisation to allow access to sulfenamide **45** or **46**, which must have subsequently undergone oxidation under the reaction conditions to afford sulfinamide **39** or **40**. The same authors published a follow up paper which included a range of secondary substrates that were used to prepare bicyclic and tricyclic sulfinamides.[29]

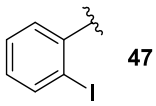
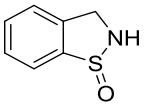
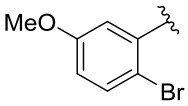
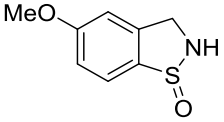
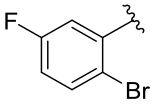
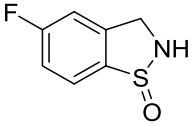
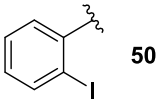
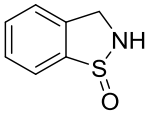
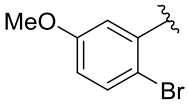
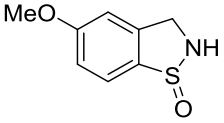
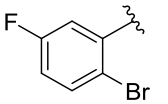
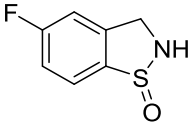
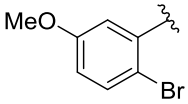
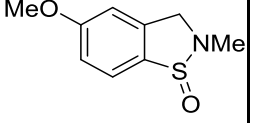
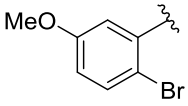
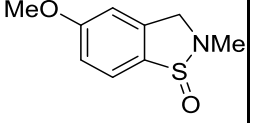


Scheme 1.12. Mechanism for the formation of sulfinamides **39** and **40**.

Malacria and co-workers published the ring-closing synthesis of **47-54** to aryl cyclic sulfinamides **55**-**62** *via* an intramolecular homolytic substitution at sulfur (Table 1.3).[31] Following the slow addition over 1 h of tributyltin hydride and azobisisobutyronitrile (AIBN) to a solution of the sulfinamide **47**-**54** and azobisisobutyronitrile, the reaction was complete in only 10 min.

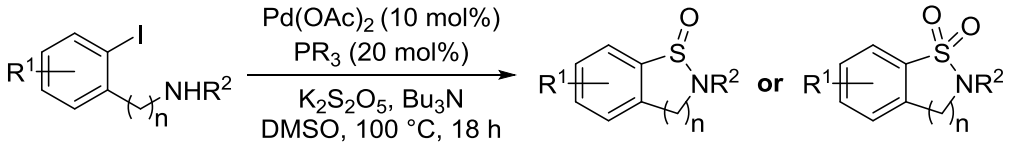
Table 1.3. Intramolecular radical cyclisations of sulfinamides.



Entry	Ar	R^1	R^2	Product		Yield (%)
1	 **47**	H	*p*-tolyl		**55**	58
2	 **48**	H	*p*-tolyl		**56**	66
3	 **49**	H	*p*-tolyl		**57**	63
4	 **50**	H	^{t}Bu		**58**	85
5	 **51**	H	^{t}Bu		**59**	86
6	 **52**	H	^{t}Bu		**60**	85
7	 **53**	Me	*p*-tolyl		**61**	36
8	 **54**	Me	^{t}Bu		**62**	31

Cyclic sulfinamides **55**-**62** were isolated in good yields when R^2 = *p*-tolyl (Table 1.3, entries 1-3). The erosion of yield was due to an unwanted 7-*endo*-cyclisation onto the *p*-tolyl group, instead of the sulfur, followed by rearomatisation. This issue was addressed by simply switching the *p*-tolyl group for a *tert*-butyl group (Table 1.3, entries 4-6). However, it was detrimental to incorporate a methyl group on the nitrogen (Table 1.3, entries 7 and 8). It was postulated that the new major pathway was a 1,5-intramolecular hydrogen abstraction on the methyl group, which led to compound decomposition.

Inspired by the acyclic sulfonamide-forming conditions of Willis and co-workers,[32] Manabe and co-workers developed procedures that upon simple modification, starting from the same aryl halide **63**, allowed access to either cyclic sulfinamides **64** or cyclic sulfonamides **65** (Scheme 1.13).[33]



63

64
14 examples
23-76%

65
13 examples
12-66%

Sulfinamide (64) Method:
$Pd(OAc)_2$ (10 mol%), PCy_3 (20 mol%), $K_2S_2O_5$ (1.5 equiv.), Bu_3N (2.0 equiv.)

Sulfonamide (65) Method:
$Pd(OAc)_2$ (10 mol%), $(^tBu)_3P{\cdot}HBF_4$ (20 mol%), $K_2S_2O_5$ (2.0 equiv.), Bu_3N (1.0 equiv.)

Scheme 1.13. Use of potassium metabisulfite as a sulfinyl/sulfonyl surrogate.

The mechanism for the cross-coupling is believed to be analogous to the Stille-carbonylative cross-coupling.[32] In regard to the mechanism of the sulfinamide **64** oxidation, which does appear similar to the oxidation observed

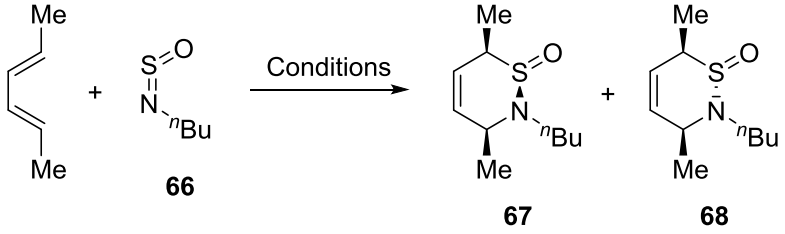
by Doi and Musker,[30] a number of control experiments were performed on sulfinamide **64**. Firstly, re-submission of sulfinamide **64** to the reaction conditions did not afford sulfonamide **65**. Secondly, re-submission of sulfinamide **64** to the reaction conditions with potassium iodide, instead of tributylamine, afforded sulfonamide **65** in dimethylsulfoxide but the reaction did not proceed in dimethylformamide. Lastly, it was shown that half an equivalent of iodine in dimethylsulfoxide at 100 °C gave sulfonamide **65** in 64% yield. These results demonstrated that iodide ions were essential in the oxidation and that dimethylsulfoxide acts as the oxygen donor.

1.1.2.2 Preparation of Chiral Cyclic Sulfinamides

In 1988, alongside their investigation into the Diels-Alder reaction between the tethered diene and dienophile, Weinreb and Bell determined the stereochemical outcome of the Diels-Alder reaction between 1,4-dimethylbutadiene and *N*-thionyl-*n*-butylamine **66** (Table 1.4).[34] The 1,4-dimethylbutadiene reacted with the expected *syn*-selectivity and therefore only afforded two isomers (**67** and **68**), dependent on the *Z* or *E*-geometry of the dienophile (**66**), respectively. The relative stereochemistry of the products was elucidated after ^{1}H NMR experiments with europium as a chiral shift reagent. Lewis acids titanium tetrachloride and boron trifluoride gave exclusively isomer **67**, whereas tin tetrachloride gave a mixture of isomers (Table 1.4, entries 1-3). In contrast, isomer **68** was the major product in the high pressure reactions (Table 1.4, entries 4-7). The authors speculated that

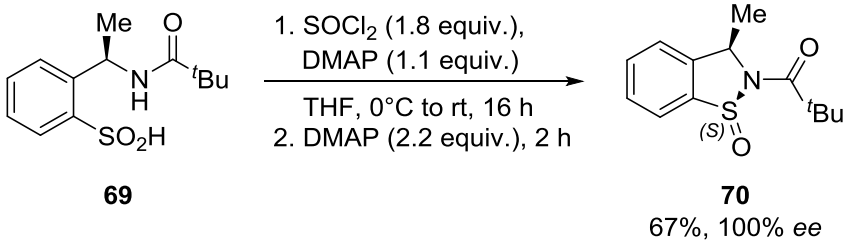
this could be due to some type of complexation of the Lewis acid to the dienophile that leads to reaction under steric control.

Table 1.4. Stereochemical investigation of a DIels-alder reaction.



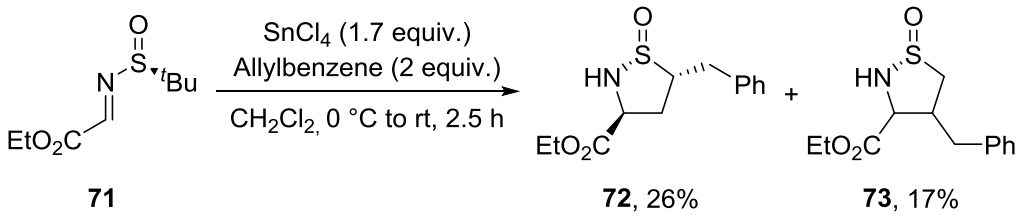
Entry	Conditions	Yield (%)	**67**:**68**
1	$TiCl_4$ (1 equiv.), CH_2Cl_2, –78 °C	27	100:0
2	$SnCl_4$ (0.5 equiv.), CH_2Cl_2, –78 °C	47	40:60
3	BF_3-Et_2O (1 equiv.), CH_2Cl_2, –78 °C	54	100:0
4	Et_2O, rt, 12 kbar	56	11:89
5	C_6H_{12}, rt, 12 kbar	66	12:88
6	CH_2Cl_2, rt, 12 kbar	80	18:82
7	CH_2Cl_2, rt, 6 kbar	22	15:85

In 1991, the Wills group described the preparation of one example of an enantiopure cyclic sulfinamide (Scheme 1.14).[35] Aryl sulfinic acid **69** was cyclised to sulfinamide **70** using thionyl chloride and (4-dimethylamino)pyridine in 67% yield and 100% *ee*. The stereochemistry of the enantiopure **70** was determined by X-ray crystallography.



Scheme 1.14. Cyclisation of **69** to enantiopure cyclic sulfinamide **70**.

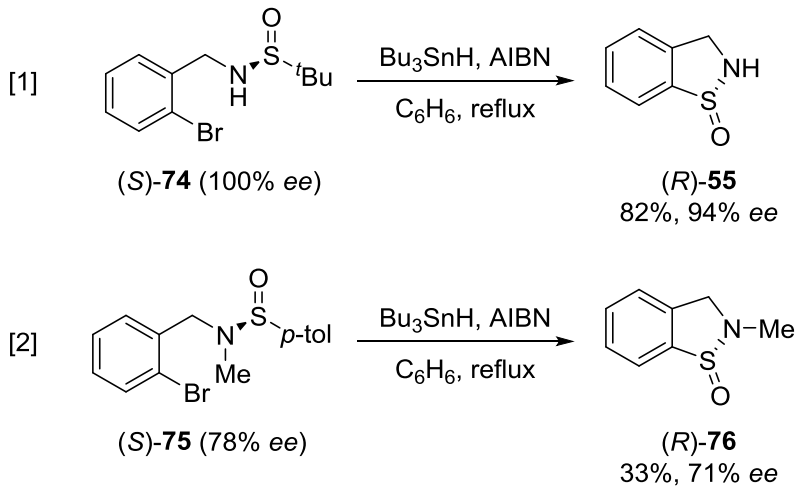
In 2002, Davis and co-workers described one example of an unexpected imino-ene reaction of sulfinimine **71** with tin tetrachloride and allylbenzene that afforded **72** and **73** in 26% and 17% yield, respectively (Scheme 1.15).[36] The relative stereochemistry of **72** was determined by X-ray crystallography and then the absolute stereochemistry was assigned by synthesis of the amino ester – obtained after removal of the sulfinyl group from **72** *via* oxidation and then elimination of the resulting sulfonyl group with Raney-nickel. Only the relative configuration of the sulfinyl group in **73** was assigned, based on an NOE experiment which indicated the benzyl protons were closer to the proton at the alpha position to the ester.



71 **72**, 26% **73**, 17%

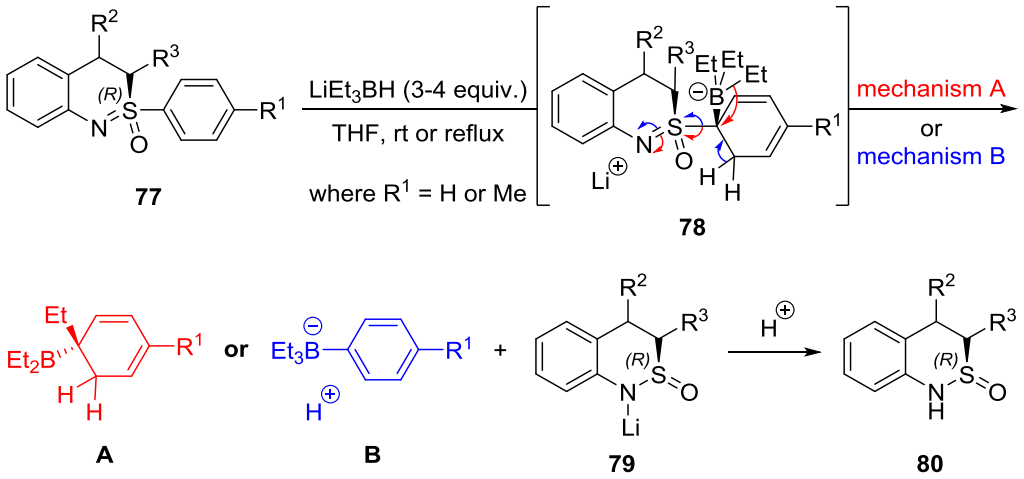
Scheme 1.15. Imino-ene reaction of **71** with allylbenzene.

Three years after their work on the synthesis of racemic aryl cyclic sulfinamides **55**-**62** *via* an intramolecular homolytic substitution at sulfur, Malacria and co-workers used (*S*)-**131** and (*S*)-**132** to investigate enantiopure examples (Scheme 1.16).[37] The authors tentatively assigned the stereochemistry of (*R*)-**112** and (*R*)-**133** based on the results of analogous sulfinate and sulfoxide reactions. Therefore, the products were believed to be formed with inversion of configuration and with only a slight loss in *ee*. Unfortunately, the scope of chemistry was not expanded further.



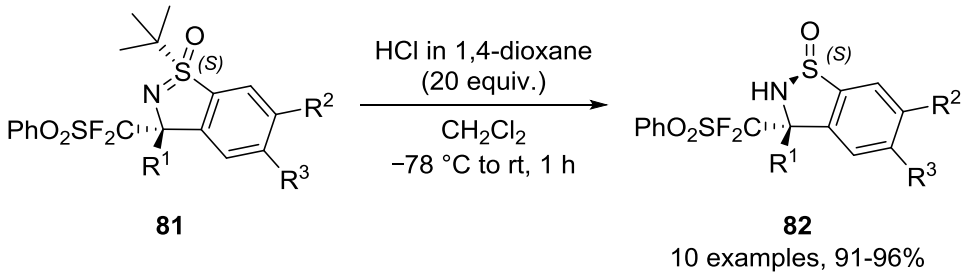
Scheme 1.16. Radical cyclisations with enantiopure substrates.

Harmata and Zheng reported the de-arylation of endocyclic sulfoximines **77** with either a phenyl or *p*-tolyl group on the sulfur.[10] The authors demonstrated a wide functional group tolerance, however, the limitation of this methodology was that the de-arylation was only performed on two types of aromatic substrate. Moreover, substrates with the more electron rich *p*-tolyl group suffered from significantly longer reaction times. Analysis of the crude product from a reaction with a phenyl substrate (R^1 = H) by GC-MS, revealed the production of ethylbenzene in 44% and benzene in 27%. Thus, generalised mechanisms A and B for the de-arylation of **77** *via* dearomatised species **78** were proposed and these are shown in Scheme 1.17. In mechanism A, it was postulated that an ethyl migration in the dearomatised intermediate **78** would give access to **A** and **79**, deborylation of **A** would afford an ethyl benzene byproduct. In mechanism B, elimination of the aryl group from **78** by rearomatisation would afford **B** and **79** and following decomposition of **B**, either by protonation or in the work-up, would afford a benzene byproduct. Finally, protonation of **79** in the work-up would afford sulfinamide **80**.



Scheme 1.17. Generalised mechanisms for the de-arylation of sulfoximine **77**.

In 2014, Hu and co-workers converted sulfoximines **81** into their respective cyclic sulfinamides **82** by elimination of the *tert*-butyl group using excess hydrochloric acid (Scheme 1.18).[38] The authors used 20 equivalents of hydrochloric acid to facilitate this transformation, however no rationale was provided.

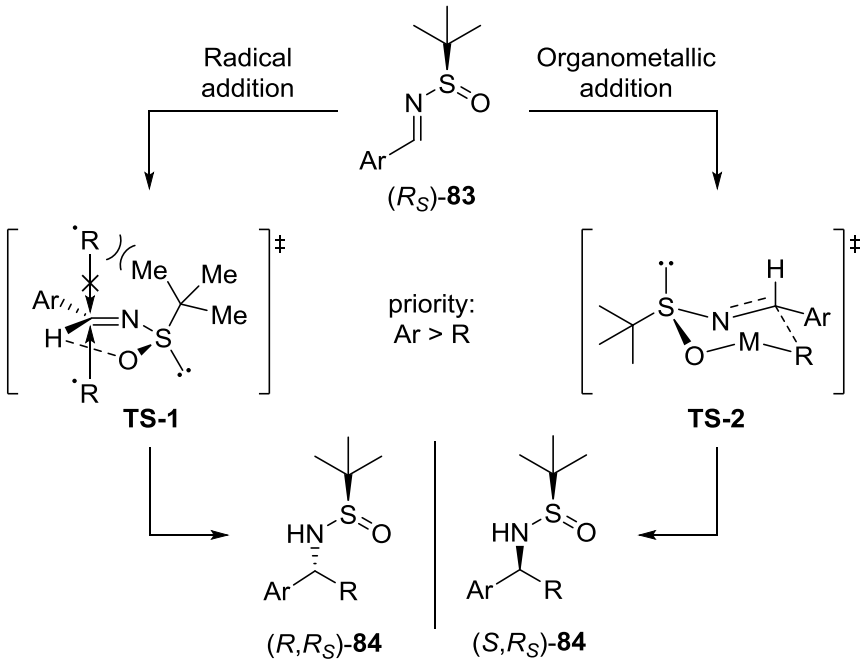


Scheme 1.18. Removal of the *tert*-butyl group to obtain cyclic sulfinamide **82**.

In the same year, Garcia-Ruano and co-workers expanded and improved upon the intramolecular homolytic substitution chemistry of Malacria and co-workers.[39] It was envisaged that the treatment of a range of chiral sulfinamides, obtained after stereospecific radical addition into the requisite

sulfinimines, would provide unequivocal evidence so as to elucidate the stereochemical outcome of intramolecular homolytic substitution reactions.

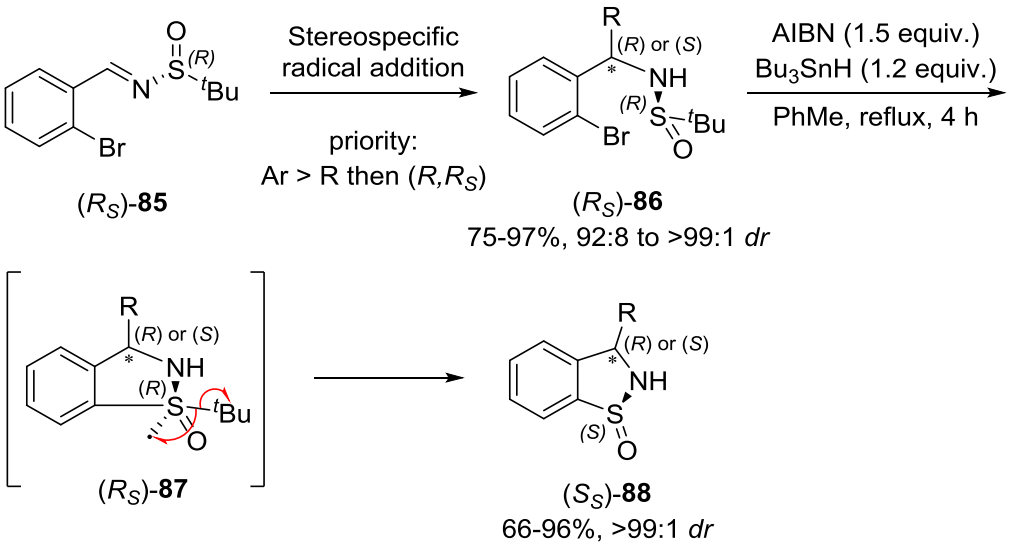
In the chair-like transition state (**TS-2**), the *tert*-butyl group occupies the least hindered equatorial position and the organometallic chelates to the sulfinyl group (Scheme 1.19). This leads to an intramolecular attack of the nucleophile to the *Si*-face of sulfinimine (R_s)-**83** to afford (S,R_s)-**84**.[40] In contrast, nucleophilic radical addition affords the opposite diastereoisomer as attack occurs from the least hindered face (**TS-1**) of sulfinimine (R_s)-**83**, due to an intermolecular addition, to afford (R,R_s)-**84**.



Scheme 1.19. Generalised mechanisms for additions into sulfinimines.

The stereospecific radical addition into sulfinimine (R_s)-**85**, as outlined by **TS-1**, gave access to nine acyclic sulfinamides (R_S)-**86** in 75-97% yield and 92:8 to >99:1 *dr*. These were then subjected to the intramolecular homolytic substitution conditions, that went *via* radical intermediate (R_S)-**87**, to afford

the cyclic sulfinamides (S_S)-**88** in 66-96% yield and excellent *dr* of >99:1 (Scheme 1.20). The absolute stereochemistry of the sulfur centre in the cyclic sulfinamides (S_S)-**88** was revealed by X-ray crystallography and was found to be opposite to that of the starting material.

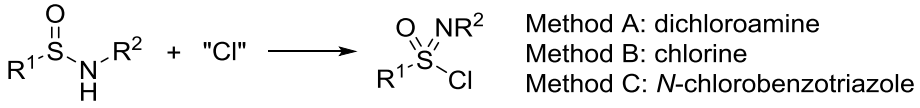


Scheme 1.20. Stereospecific intramolecular homolytic substitution of (R_S)-**85**.

1.1.3 Applications of Sulfinamides

As robust and reproducible syntheses of chiral sulfinamides were not developed until the 1990s, the applications of racemic sulfinamides were very limited and these were reviewed by Tillett.[9] Perhaps the most synthetically useful was the preparation of sulfonimidoyl chlorides. Johnson and co-workers prepared a range of sulfonimidoyl chlorides **89**-**101** using chlorine, *N*-chlorobenzotriazole, and dichloroamine – which was first used by Levchenko and Kirsanov[41] (Table 1.5).[2,3]

Table 1.5. Methods of oxidative chlorination.

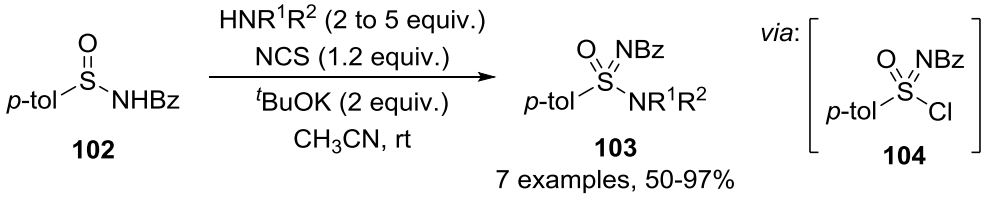


Entry	R^1	R^2	Method	Compound	Yield (%)
1	Me	^{n}Bu	A	**89**	91
2	Me	Ts	A	**90**	73
3	Et	Ts	A	**91**	57
4	CH_2Cl	Ts	B	**92**	89
5	$CHCl_2$	Ts	B	**93**	71
6	Ph	Me	B	**94**	89
7	Ph	H	B	**95**	69
8	Bn	Ph	B	**96**	100
9	Bn	*p*-Cl-Ph	B	**97**	52
10	Bn	2,4,6-Cl_3Ph	B	**98**	77
11	*p*-$CH_3CONHC_6H_4$	Me	B	**99**	~50
12	*p*-$CH_3CONHC_6H_4$	2-pyrimidine	C	**100**	~50
13	*p*-tolyl	$CONH^nBu$	C	**101**	~80

Overall the products were inherently unstable. Compounds **89**, **96** and **97** decomposed within hours at room temperature and thus compounds **99**-**101** were used immediately in further derivatisation reactions – therefore their yields were approximations.

In the same year, Johnson and co-workers reported *tert*-butyl hypochlorite as a superior reagent for the oxidative chlorination.[4] Perhaps based on their observations of the compounds shown above, the authors did not isolate the sulfonimidoyl chloride but treated it with an alcohol or amine to prepare the respective sulfonimidate (6 examples, 57-81% yield) or sulfonimidamide (2 examples, 60 and 84% yield), respectively. This became the most widely used method for the synthesis of sulfonimidoyl chlorides.[42]

In 2007, Bolm and Mancheno proposed that *N*-chlorosuccinimide was a safer alternative and demonstrated its applicability on **102** (Scheme 1.21). Seven sulfonimidamides **103** were prepared, *via* an *in situ* formation of sulfonimidoyl chloride **104**, in 50-97% yield [42]

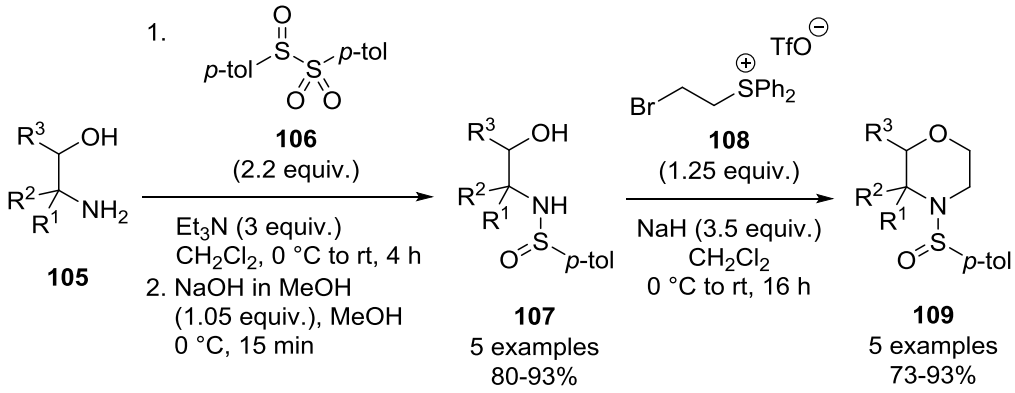


Scheme 1.21. Oxidative chlorination using *N*-chlorosuccinimide.

Aggarwal and co-workers saw the potential of achiral sulfinamides as a protecting group in their synthesis of morpholines from 1,2-amino alcohols.[43] Their rationale against more classical nitrogen protecting groups, such as sulfonyl groups, was their occasional difficulty to remove. Moreover, if there were also functional group incompatibility in the molecule then this would pose a major problem. Therefore, it was desirable to find an easily cleavable functional group as they stated that protecting groups, such as Boc, CBz and Ac, led to side reactions in the final annulation step.

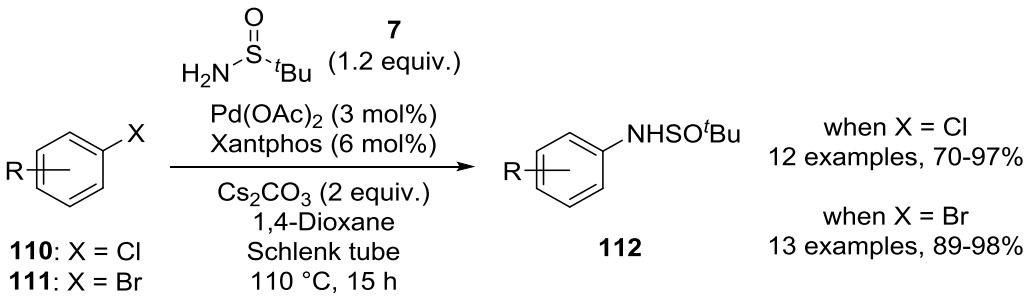
Partial double protection of the amine in amino alcohol **105** was unavoidable, therefore a "double protection/mono-deprotection" strategy was employed (Scheme 1.22). Using excess *p*-tolylsulfinyl-*p*-tolyl sulfone **106** the amine of **105** was doubly-protected. Therefore, following mono-deprotection by treatment with sodium hydroxide, *p*-tolyl sulfinamides **107** were prepared in 80-93% yield. It should be noted that *tert*-butyl and *iso*-propyl sulfinamides were investigated, however, they were unsuccessful in the annulation step.

Subsequent treatment of *p*-tolyl sulfinamides **107** with the now commercially available bromoethylsulfonium salt **108** and sodium hydride, completed the annulation and afforded morpholines **109** in 73-93% yield. Lastly, the efficacy of their methodology was demonstrated in a formal synthesis of the antidepressant drug (*S*,*S*)-reboxetine, marketed by Pfizer.



Scheme 1.22. Sulfinamide employed as a protecting group.

Sivakumar and co-workers demonstrated that sulfinamides could be used as an ammonia surrogate in the palladium-catalysed C-N cross-coupling of aryl halides **110** and **111** and *tert*-butanesulfinamide **7** (Scheme 1.23).[44] All substrates contained at least one electron-withdrawing group and therefore it has to be assumed that this is a limitation. Nevertheless, 12 examples of **112** were prepared from aryl chlorides **110** in excellent yields of 70-97% and 13 examples from aryl bromides **111** in 89-98%. Moreover, the authors demonstrated that indoles could be prepared in one pot, under the same conditions, from aryl bromides *via* C-N cross coupling and then *in situ* intramolecular cyclisation with an alkyne at the *ortho*-position.



Scheme 1.23. Cross-coupling of *tert*-butanesulfinamide **7** with aryl halides.

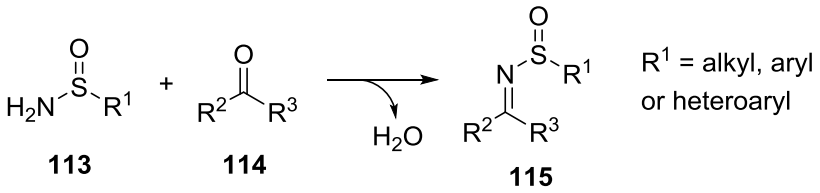
Shortly after, Zeng and co-workers published the palladium-catalysed C-N cross-coupling of enantiopure *tert*-butanesulfinamide **7** with a wider scope than that demonstrated by Sivakumar and co-workers.[45]

Ellman and co-workers popularised the use of enantiopure *tert*-butanesulfinamide **7** as a chiral directing group and/or chiral ammonia equivalent at the end of the 1990s.[5] In 2010, Ellman published a comprehensive review surrounding the synthesis of **7** and its application, primarily *via* the sulfinimine, towards the preparation of chiral amines, chiral β-hydroxyketones, α- and β-amino acid derivatives, aziridines, as well as incorporation into ligands and catalysts. Herein, only a select number of examples from the extensive field of applications of chiral sulfinamides are highlighted.

1.1.3.1 Sulfinimines

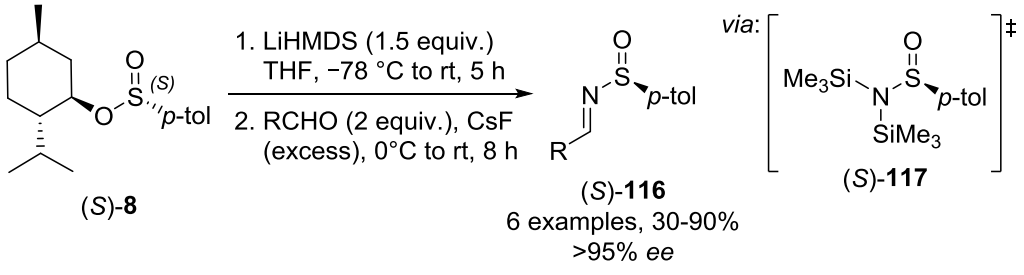
The condensation of a sulfinamide **113** and an aldehyde or ketone **114** with a dehydrating agent affords sulfinimines **115**, also known as *N*-sulfinyl imines (Scheme 1.24).[5] In general, sulfinimines (**115**) are very stable in air and can be purified by column chromatography. The sulfinyl group activates the imine

towards nucleophilic attack and, when the sulfur centre is enantiopure, the large group on the sulfur acts as a powerful chiral directing group offering excellent stereocontrol for diastereoselective reactions. Moreover, the majority of the aforementioned applications of enantiopure *tert*-butanesulfinamide **7** went *via* a sulfinimine (**115**) intermediate.



Scheme 1.24. General mechanism for sulfinimine condensation.

Initially, methods to prepare enantiopure sulfinimines (**115**) did not isolate the sulfinamide prior to performing the sulfinimine condensation (Scheme 1.25).[17] Davis and co-workers treated sulfinate (*S*)-**8** with lithium bis(trimethylsilyl)amide at –78 °C and then after 5 h added excess aldehyde and cesium fluoride at 0 °C and stirred at room temperature for a further 8 h. Following column chromatography, sulfinimines (*S*)-**116** were isolated in yields of 30-90% and >95% *ee*.



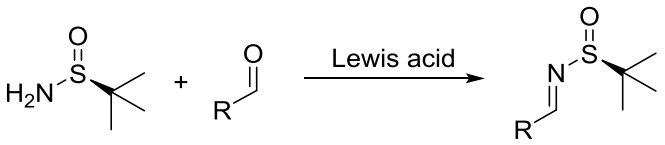
Scheme 1.25. Sulfinimine condensation *via* an *in situ* sulfinamide formation.

In the same publication that disclosed the first enantioselective synthesis of *tert*-butanesulfinamide **7**, Ellman and co-workers also reported the syntheses

of three *tert*-butyl sulfinimines using excess magnesium sulfate (5 equiv.) as a drying agent and pyridinium *p*-toluenesulfonate as an acid catalyst.[11] Ethyl, *iso*-propyl and phenyl *tert*-butyl sulfinimines were prepared in 96%, 90% and 91%, respectively. Molecular sieves, Dean-Stark conditions and sodium sulfate were all unsuccessful therefore it was postulated that the role of the magnesium sulfate was more than just a drying agent. It should be noted that large excesses (1.5-3 equiv.) of the aldehyde were required to achieve high yields.

Optimisation revealed that copper sulfate was effective as a drying agent and Lewis acid therefore an acid catalyst was not required (Table 1.6).[46,47] Moreover, the equivalents of the aldehyde could be reduced to 1.1. Good to excellent yields of sulfinimines **118**-**126** were obtained, even for less reactive substrates (Table 1.6, entries 1-6). In the reaction with 3-pyridinecarboxaldehyde, a blue precipitation was observed immediately upon addition of the aldehyde, which suggested formation of a pyridine-copper complex (Table 1.6, entry 7). Titanium(IV) complexes were even more effective than copper sulfate due to their increased water-scavenging ability and Lewis acidity – titanium ethoxide was found to be the most optimal. Sulfinimines (**124**-**126**) that were previously isolated in poor yields with copper sulfate (Table 1.6, entries 7, 9 and 11) were obtained in excellent yield with titanium ethoxide (Table 1.6, entries 8, 10 and 12).

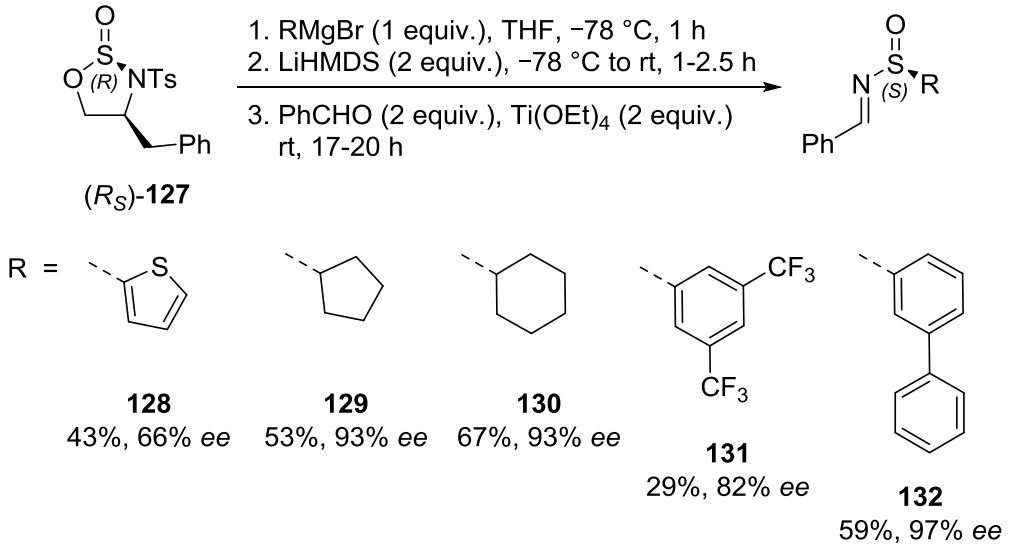
Table 1.6. Lewis acid screen for sulfinimine condensations.



Entry[a]	R	Lewis Acid	Product	Yield (%)
1	Et	$CuSO_4$	**118**	96
2	Bn	$CuSO_4$	**119**	79
3	Ph	$CuSO_4$	**120**	91
4	4-MeOPh	$CuSO_4$	**121**	81
5	CO_2Me	$CuSO_4$	**122**	65
6	2-pyridyl	$CuSO_4$	**123**	95
7	3-pyridyl	$CuSO_4$	**124**	trace
8[b]	3-pyridyl	$Ti(OEt)_4$	**124**	quantitative
9	2-furfuryl	$CuSO_4$	**125**	40
10[b]	2-furfuryl	$Ti(OEt)_4$	**125**	82
11	^{t}Bu	$CuSO_4$	**126**	trace
12[b]	^{t}Bu	$Ti(OEt)_4$	**126**	82

[a] $CuSO_4$ (2 equiv.), aldehyde (1.1 equiv.), CH_2Cl_2, rt.
[b] $Ti(OEt)_4$ (2 equiv.), aldehyde (1.1 equiv.), THF, rt.

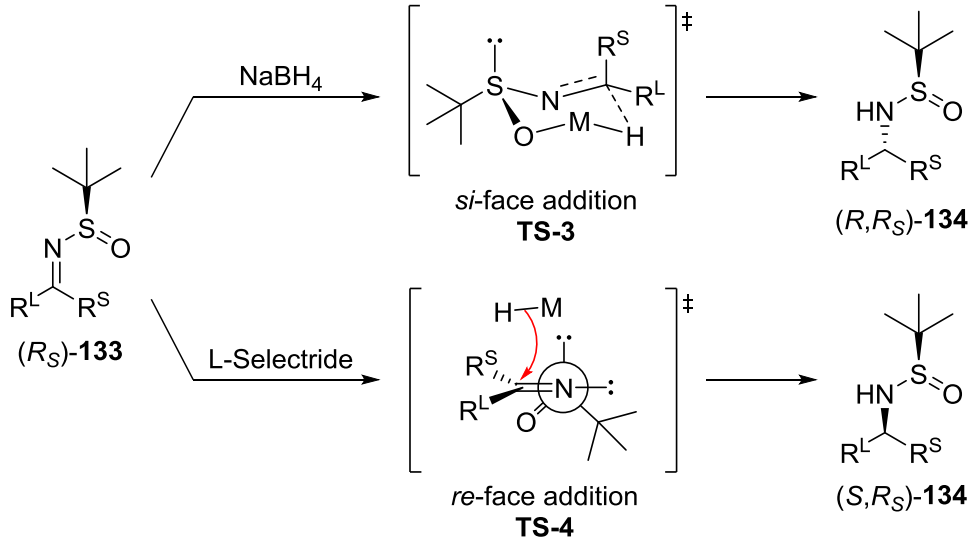
The Stockman group further contributed to the area of sulfinimine synthesis with a multicomponent reaction utilising chiral template (R_S)-**127,** derived from the inexpensive and readily available L-phenylalanine in 4 steps, to afford unusual sulfinimines **128**-**132** in good to high *ee* (Scheme 1.26).[21] The sulfinamide is prepared *in situ* then condensed with an aldehyde which is facilitated by titanium ethoxide. The viability of the multicomponent reaction was further exemplified with the preparation of seventeen (*S*)-mesityl sulfinimines in 33-85% yield and 93-100% *ee*.



Scheme 1.26. Synthesis of unusual sulfinimines using template (R_S)-**127**.

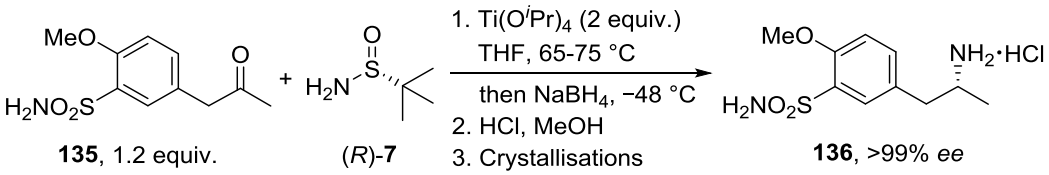
Nucleophilic addition into the sulfinimine has been extensively studied.[5] Addition of Grignards and organometallics proceeds through the chair-like transition state **TS-2**, shown in Scheme 1.19, which leads to attack of the nucleophile from the *Si*-face.

The reduction of *tert*-butyl sulfinimine (R_S)-**133** can be carried out with a chelating or non-chelating metal hydride reducing agent to prepare either diastereoisomer of the sulfinyl amine (R_S)-**134** (Scheme 1.27). Reduction with the chelating sodium borohydride or diisobutylaluminium hydride, delivers the hydride through a six-membered chair-like transition state (**TS-3**) from the *Si*-face to give access to (*R*,R_S)-**134**. Alternatively, the use of the non-chelating L-selectride delivers the hydride from the least hindered face *via* an open transition state (**TS-4**) to give access to (*S*,R_S)-**134**. In these processes the sulfinamide acts as a chiral ammonia surrogate. Finally, deprotection of the sulfinyl group is achieved with hydrochloric acid in methanol.[11]



Scheme 1.27. General mechanisms for the reduction of sulfinimines.

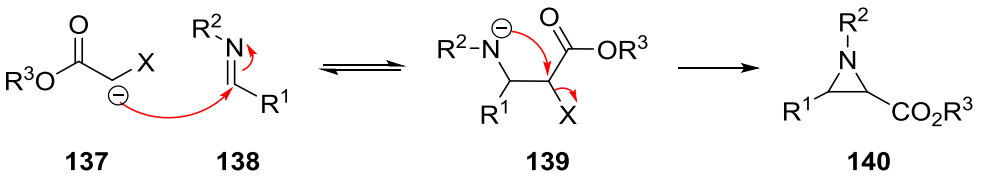
This methodology was exemplified by Reddy and co-workers in an improved synthesis of the antihypertensive drug Tamsulosin, which is also used in the treatment of benign prostatic hyperplasia (BPH).[5,6] The required ketimine was prepared from ketone **135** and sulfinamide (*R*)-**7** with titanium isopropoxide before reduction of the sulfinimine with sodium borohydride (Scheme 1.28). Hydrochloric acid in methanol was used to remove the sulfinyl group and following two crystallisations with dibenzoyl-D-tartrate, amine hydrochloride **136** was isolated in >99% *ee*. At this point the route converged with the original synthesis of Tamsulosin. Surprisingly, percentage yields were not reported in the publication.



Scheme 1.28. Alternative synthesis of Tamsulosin hydrochloride.

1.1.3.2 Aziridines (*aza*-Darzens Aziridination)

First reported by Deyrup in 1969,[48] the *aza*-Darzens reaction is a two-step reaction that begins with reversible addition of α-haloenolate **137** into imine **138** under basic conditions to generate intermediate **139** (Scheme 1.29). This is then followed by irreversible S_N2 displacement of the halide, at the α-position of the ester, by the negatively charged nitrogen to afford aziridine **140**.



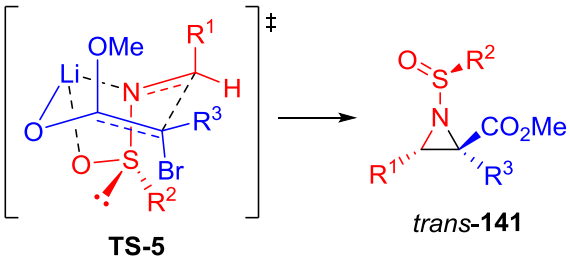
137 **138** **139** **140**

Scheme 1.29. Generalised mechanism of the *aza*-Darzens reaction.

One of the most widely used methods for asymmetric *aza*-Darzens aziridination is by employing a chiral sulfinyl group on the nitrogen.[49–52] Davis and co-workers employed chiral *p*-tolyl sulfinimines in a diastereoselective synthesis of 2,2',3-trisubstituted aziridines *trans*-**141** (Scheme 1.30).[50] To rationalise the observed *trans* stereochemistry of the aziridines, Davis proposed the chair-like transition state **TS-5**. The *Z*-geometry of the lithium enolate was required and was therefore believed to be the kinetic enolate – this hypothesis was supported by a six-membered transition state by Ireland and co-workers.[53] Later, Stockman and co-workers investigated chiral *tert*-butyl sulfinimines and prepared 9 examples of *trans*-**141** in similar yield and *de* (Scheme 1.30).[51,52]

Davis' work: (R^2 = *p*-tolyl)
3 examples, 61-85% yield
trans/*cis* 97:3, (90->95% *de*)

Stockman's work: (R^2 = *tert*-butyl)
9 examples, 38-88% yield
trans/*cis* 50:50-92:8, 90->98% *de*



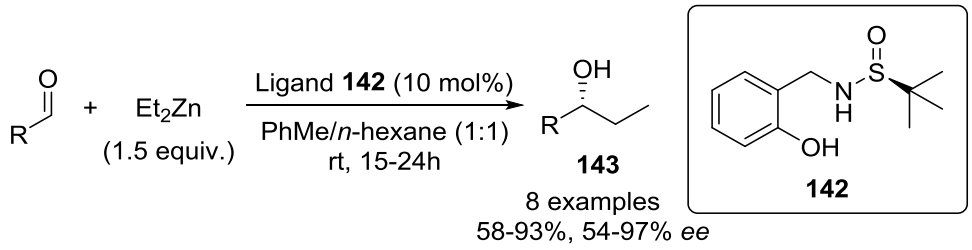
TS-5 *trans*-**141**

Scheme 1.30. Transition state in the synthesis of trisubstituted aziridines.

1.1.3.3 Chiral Ligands and Organocatalysis

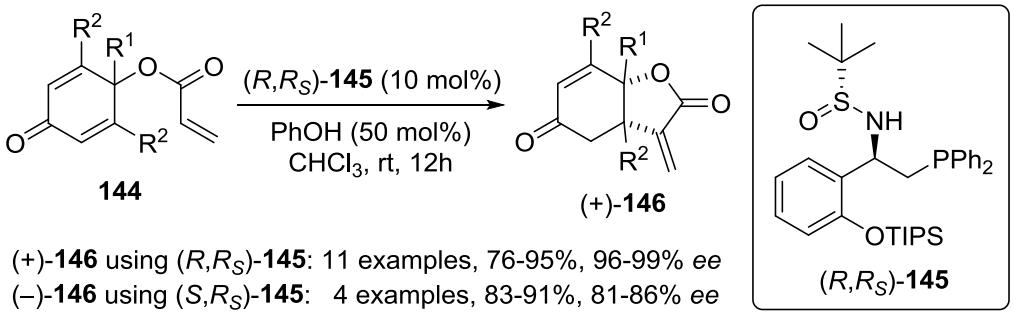
Due to its commercial availability and therefore low cost, *tert*-butansulfinamide **7** has been incorporated into chiral ligands or employed as organocatalysts.[8,54] The design of *tert*-butanesulfinyl-containing ligands and organocatalysts began as early as 2001 and are covered by Ellman in his 2010 review.[5] Hence only a select number of examples from this ever growing field are presented herein.

One example is the catalytic enantioselective addition of diethylzinc to aldehydes reported by Qin and co-workers.[55] Treatment of aldehydes with excess diethylzinc and ligand **142** in a 1:1 mixture of toluene and *n*-hexane at room temperature, afforded alcohols **143** in 58-93% yield and 54-97% *ee* (Scheme 1.31). Aromatic examples gave excellent enantioselectivities (93-97% *ee*), whereas an ethyl linker or an alkene between the aldehyde and phenyl group gave lower enantioselectivities of 70% and 54% *ee*, respectively.



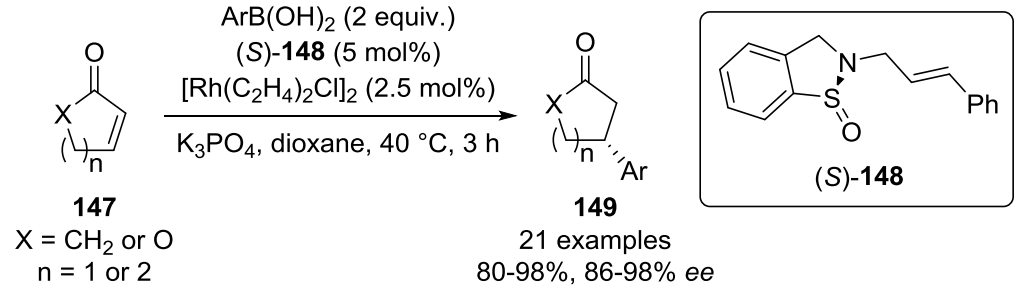
Scheme 1.31. Enantioselective addition of diethylzinc into aldehydes.

Phosphines are routinely used as chiral ligands in asymmetric catalysis due to the ease in their design and construction. Moreover, they can also be used as chiral catalysts for the analogous reasons. Zhang and co-workers designed a set of chiral sulfinamide phosphine catalysts to investigate the dimerisation of the two Michael acceptors in **144**, known as the Rauhut-Currier reaction.[7] Optimisation studies identified phosphine (R,R_S)-**145** as the optimal chiral catalyst. Thus, the scope of the enantioselective intramolecular Rauhut-Currier reaction was investigated with (R,R_S)-**145** and then its diastereoisomer (S,R_S)-**145** (Scheme 1.32). Excellent enantioselectivities (96-99% *ee*) were obtained for (+)-**146** with (R,R_S)-**145**, however a small drop (81-86% *ee*) was observed for (–)-**146** with (S,R_S)-**145**. This suggested that the interaction of the sulfinamide in the reactive intermediate was important to obtain high enantiocontrol.



Scheme 1.32. Use of a sulfinamide as a ligand in the Rauhut-Currier reaction.

Zeng and co-workers designed a range of chiral cyclic sulfinamide-olefin ligands for the rhodium-catalysed asymmetric 1,4-addition of arylboronic acids into cyclic α,β-unsaturated carbonyl compounds (**147**) (Scheme 1.33).[56] Four ligands with a cyclic sulfinamide core were tested and these were prepared using an optimised intramolecular homolytic substitution procedure (Scheme 1.16).[37] The new conditions used a different base, toluene instead of benzene, a reaction temperature of 110 °C and a longer injection time of the azobisisobutyronitrile solution. The best ligand out of the set was (*S*)-**148** and this was prepared in 99% *ee*. Employing (*S*)-**148**, the majority of the scope of the highly enantioselective, rhodium-catalysed asymmetric 1,4-addition was conducted on cyclohexanone with 14 examples of **149** isolated in very good to excellent yield of 80-98% and 91-98% *ee*. Cyclopentenone and 2-furanone also gave good yields and enantioselectivities.

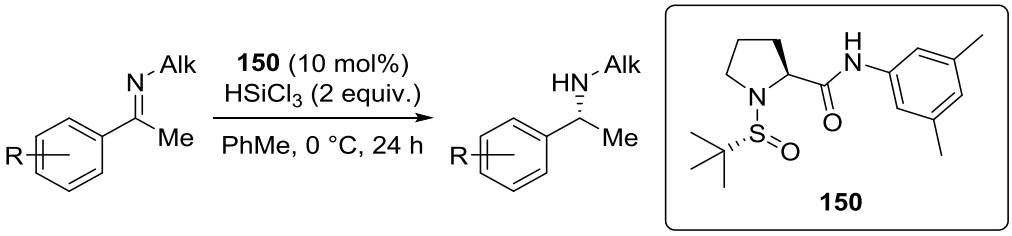


Scheme 1.33. Use of a sulfinamide as a ligand in asymmetric 1,4-addition.

Sun and co-workers developed the first enantioselective organocatalytic reduction of *N*-alkyl imines, that used a *tert*-butanesulfinyl-protected proline catalyst **150**, to obtain amines **151**-**164** (Table 1.7).[8] The *E*:*Z* ratio corresponds to the ratio of isomers of the starting material obtained from the imine condensation – determined by ^{1}H NMR spectroscopy. The catalyst was

prepared by racemic protection of proline and subsequent separation of the diastereoisomers by column chromatography. Overall, a wide variety of *N*-benzyl and *N*-allyl substrates were reduced in high yield and *ee* (Table 1.7, entries 1-11). However, poorer results were obtained for propyl, *iso*-butyl and *para*-methoxybenzyl-protected substrates (Table 1.7, entries 12-14). The enantiomeric excesses were increased by using carbon tetrachloride instead of toluene. Strangely, the authors gave only one enantiomeric excess for a reaction that used two isomers of the ketimine starting material. Moreover, the authors state that they cannot explain how the enantiomeric excess is possible given there were two starting materials.

Table 1.7. Application of a sulfinamide as an organocatalyst.



Entry	R	Alk	Compound	*E*:*Z*[a]	Yield (%)	*ee* (%)
1	H	Bn	**151**	12:1	98	96
2	4-F	Bn	**152**	21:1	80	96
3	3-Cl	Bn	**153**	20:1	98	97
4	3-Br	Bn	**154**	22:1	93	97
5	4-CF_3	Bn	**155**	22:1	94	98
6	4-NO_2	Bn	**156**	40:1	80	>99
7	4-MeO	Bn	**157**	18:1	54	78
8	H	allyl	**158**	10:1	82	92
9	4-Cl	allyl	**159**	18:1	97	89
10	4-NO_2	allyl	**160**	33:1	97	96
11	4-Me	allyl	**161**	9:1	88	83
12	H	Pr	**162**	12:1	67 (60[b])	66 (90[b])
13	H	^{i}Bu	**163**	15:1	56 (80[b])	70 (87[b])
14	H	PMB	**164**	12:1	85 (83[b])	93 (95[b])

[a] Determined by ^{1}H NMR spectroscopy. [b] Repeated with CCl_4 as the solvent.

1. Introduction – *Sulfoximines*

1.2 Sulfoximines

Sulfoximines, known previously as sulfoximides, have the general formula: $R_2S(=O)(=NR)$ (Figure 1.3).[57,58]

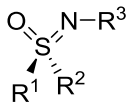
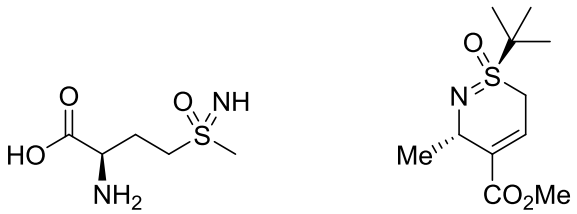


Figure 1.3. General structure of a sulfoximine.

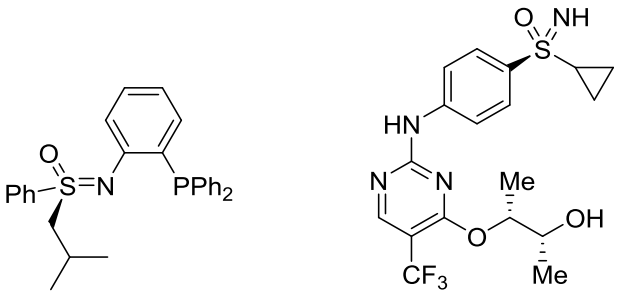
The two structural forms of substituted or unsubstituted sulfoximines can be referred to as acyclic or cyclic, such as methionine sulfoximine **165**[59] and **167**,[60] respectively (Figure 1.4). Additionally, cyclic sulfoximines can be either endo or exocyclic with regard to the sulfur-nitrogen double bond being integrated into or protruding from the ring, respectively.



165 **166**

Figure 1.4. Methionine sulfoximine **165** and cyclic sulfoximine **166**.

The early applications of sulfoximines were as ylide transfer reagents,[61–63] but in recent years they have been applied in asymmetric synthesis as chiral auxiliaries[64] or chiral ligands,[65–67] in agrochemicals for crop protection[68] and in medicinal chemistry, specifically in drug design.[69] Two examples of sulfoximine applications are chiral ligand (*S*)-**167**,[65] and Bayer's anti-cancer candidate BAY1000394 (Figure 1.5).[69,70]



(*S*)-**167**
Chiral Ligand

BAY1000394
pan-CDK inhibitor

Figure 1.5. Chiral ligand (*S*)-**167** and Bayer's pan CDK inhibitor BAY1000394.

1.2.1 Properties of Sulfoximines

In general, sulfoximines are a robust and configurationally stable functional group – which is apparent from their methods of preparation. The sulfoximines versatility is primarily influenced by the nitrogen and its substituent (Figure 1.6).[69]

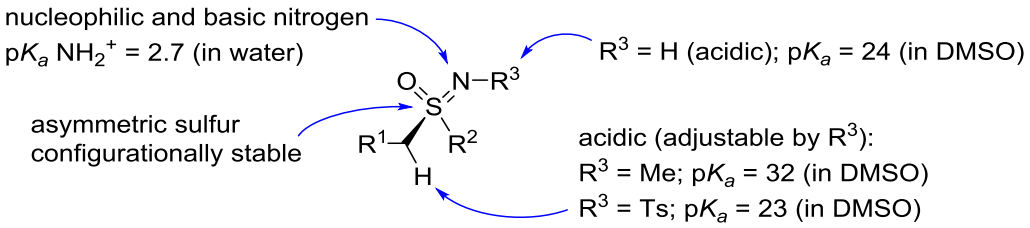


Figure 1.6. Properties of the sulfoximine that lead to its versatility.

The nitrogen imparts chirality at the sulfur atom provided the two R substituents are non-identical. Most importantly, the functional group on the nitrogen (R^3) can be varied to tune the properties of the sulfoximine. For example, a *N*-tosyl group lowers the pK_a of the sulfur's alpha-hydrogens by 9 units, in comparison to a *N*-methyl group, hence *N*-tosyl sulfoximines are utilised as ylide transfer reagents.

Unsubstituted sulfoximines (R^3 = H), sometimes referred to as "free sulfoximines", offer dual functionality. The *NH* group of the sulfoximine can act as a hydrogen bond donor and as a hydrogen bond acceptor. In comparison, a sulfone can only act as a dual hydrogen bond acceptor. Moreover, these properties make sulfoximines more hydrophilic which increases their aqueous solubility, which makes them an attractive group in medicinal chemistry.

The bond lengths and bond angles of sulfoximine **166** are shown in Figure 1.7. The length of the sulfur-oxygen bond (1.46 Å) and sulfur-nitrogen bond (1.52 Å) are close to their double bond lengths of 1.43 Å[71] and 1.54 Å,[72] respectively; this is reflected in their 2D representation.

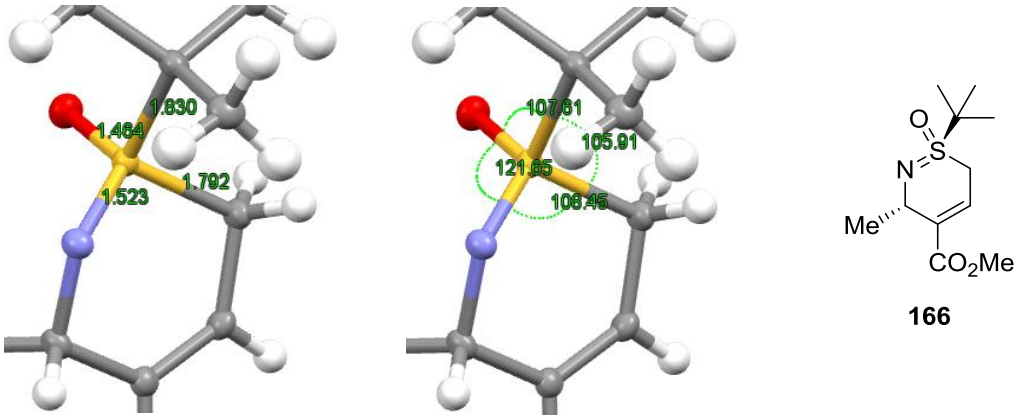
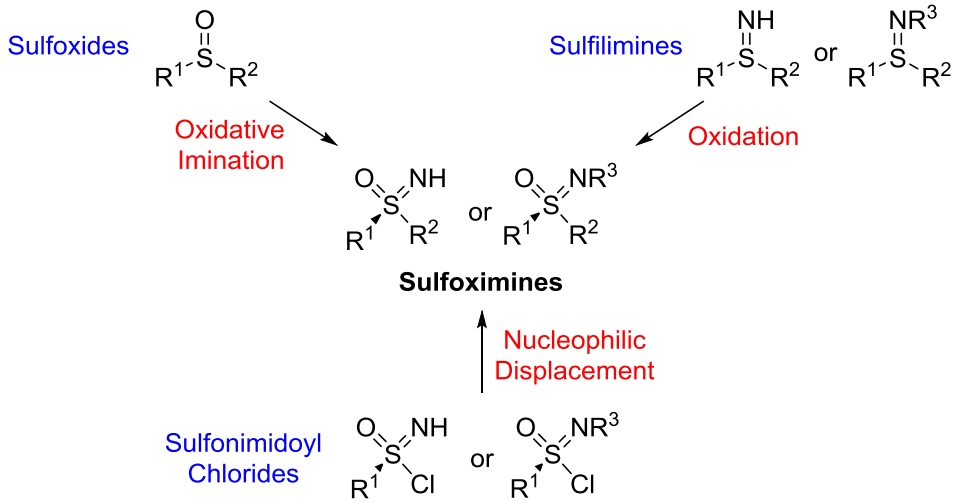


Figure 1.7. Bond lengths (left) and bond angles (right) of sulfoximine **166**.

1.2.2 Established Methods for the Preparation of Sulfoximines

Well established methods for the preparation of sulfoximines are: oxidative imidation of sulfoxides, oxidation of sulfilimines or nucleophilic displacement of sulfonimidoyl chlorides (Scheme 1.34).[57]



Scheme 1.34. Established methods for the synthesis of sulfoximines.

1.2.2.1 Preparation from Sulfoxides

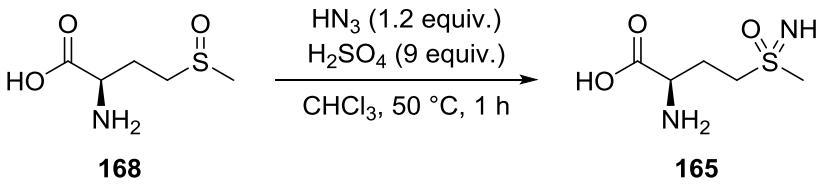
Oxidative imidation, or imination, of a sulfoxide is the simultaneous addition of an amine to form a sulfur-nitrogen double bond whilst oxidising the sulfur centre from sulfur(IV) to sulfur(VI). Initially, azides were used to imidate sulfoxides using a strong acid, such as sulfuric acid[73] or phosphoric acid,[57] as a catalyst. The metal-catalysed imidation of sulfoxides has become the most widely used method for the preparation of enantiopure sulfoximines – due to the larger precedent of chiral sulfoxide synthesis.[74,75]

In 1946, a study of canine behaviour by Mellanby demonstrated that dogs who were fed commercial flour developed canine hysteria.[76] One year later,

Moran reported that the toxic substance was being produced during the bleaching process of wheat flour.[77] This process used nitrogen trichloride and was called agenising.

The toxic substance was first isolated by Bentley and co-workers in 1949.[78] It was not until the following year that the empirical formula was elucidated and thereafter it was postulated that the toxic substance was methionine sulfoximine **165**.[59,73]

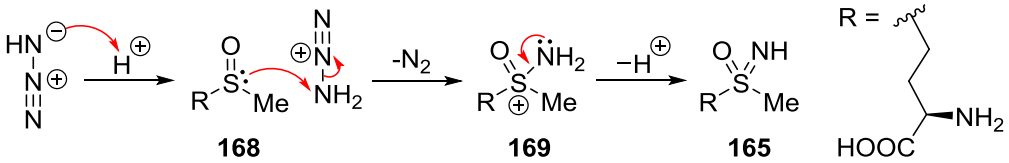
In 1950, Bentley and co-workers reported the successful syntheses of methionine sulfoximine **165** and dimethylsulfoximine using hydrazoic acid.[73] The procedure, that was not disclosed until the following year, was the portion wise addition of hydrazoic acid to a solution of sulfoxide **168** and excess sulfuric acid in chloroform at 50 °C (Scheme 1.35).[79]



Scheme 1.35. Synthesis of Methionine sulfoximine **165**.

Initially it was postulated that the mechanism was analogous to the Schmidt reaction because it performed best under those conditions.[73] Later, Bentley proposed that the mechanism involved nucleophilic attack of sulfoxide **168** on a protonated molecule of hydrazoic acid, thereby releasing nitrogen gas as a byproduct (Scheme 1.36).[79] The resulting intermediate (**169**) liberated a proton to afford methionine sulfoximine **165**. Later, Johnson and Janiga

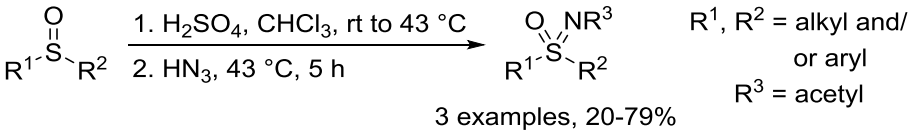
reported that two equivalents of sulfuric acid were essential, otherwise the reaction does not take place.[80]



168 169 165

Scheme 1.36. Proposed mechanism for the oxidative imidation of sulfoxides.

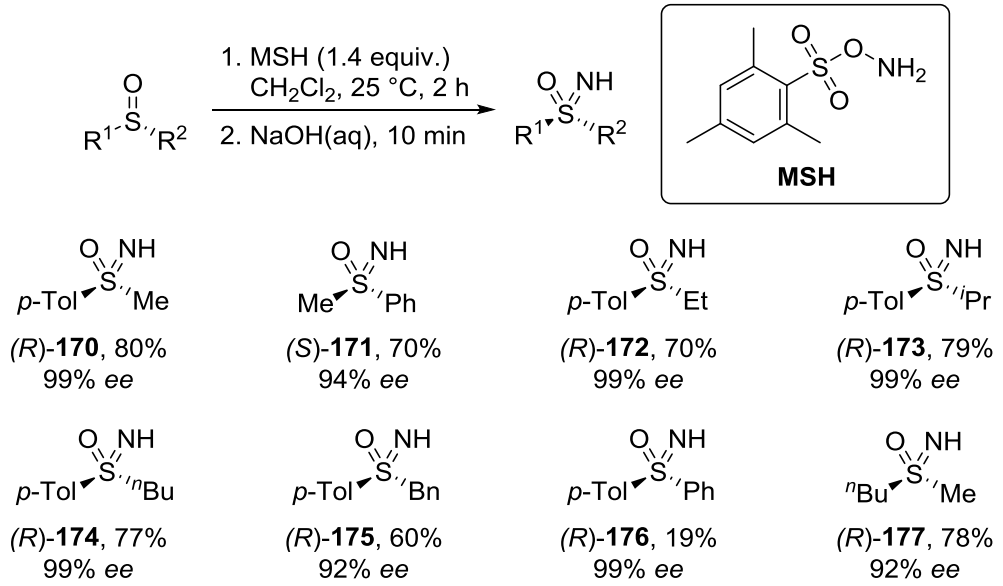
The scope of the sulfoxide and hydrazoic acid reaction was explored by Reiner and co-workers who prepared six examples of aryl and/or alkyl sulfoximines from the corresponding sulfoxides (Scheme 1.37).[81] Unfortunately, half of the yields of the reactions were not reported. Later, Stoss and Satzinger used phosphoric acid as the acid catalyst and the solvent to obtain sulfoximines in good yields.[57]



Scheme 1.37. First synthesis of a range of sulfoximines.

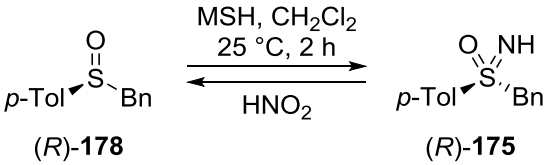
An alternative method to the synthesis of sulfoximines *via* azide chemistry was developed for a number of reasons: (1) the potential dangers that surround azide chemistry (2) during the preparation of enantiopure *NH*-sulfoximines the hydrazoic acid method racimises the sulfoxide prior to imidation[82,83] (3) the deprotection of optically pure *N*-tosyl sulfoximines with concentrated sulfuric acid either fails and/or results in decomposition.[83]

Tamura and co-workers reported the use of *O*-(mesitylenesulfonyl) hydroxylamine (MSH) in dichloromethane at room temperature as a protocol for the oxidative imidation of sulfoxides (Scheme 1.38).[84] This method overcame the problems highlighted previously for the azide chemistry. Johnson employed this methodology to prepare enantiopure sulfoximines **170**-**177** in 92-99% *ee*.[83] The limitation was the stability of *O*-(mesitylenesulfonyl)-hydroxylamine – even at room temperature.[83,85,86]



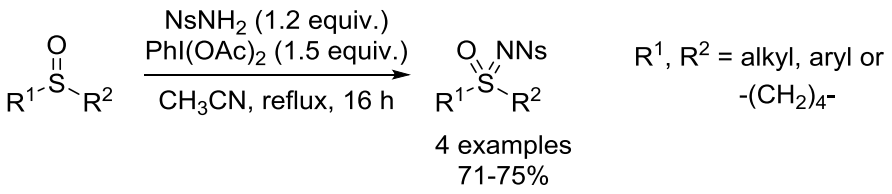
Scheme 1.38. Preparation of chiral sulfoximines **170**-**177** using MSH.

A key observation was that reactions with *O*-(mesitylenesulfonyl)-hydroxylamine occurred with retention of stereochemistry.[87] This was exemplified by Johnson and co-workers *via* the deimidation of sulfoximine (*R*)-**175** by treatment with nitrous acid to afford (*R*)-**178**, which was known to have the (*R*)-stereochemistry (Scheme 1.39).



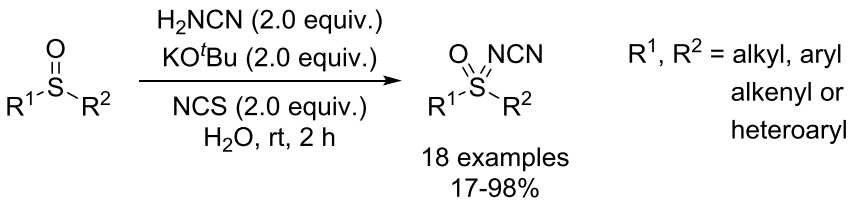
Scheme 1.39. Elucidation of the stereochemistry of (*R*)-**175**.

In 2005, Bolm and Cho described the metal-free imidation of four sulfoxides using an *in situ* nitrogen transfer reagent formed from *para*-nitrobenzenesulfonamide ($NsNH_2$) and iodobenzene diacetate (Scheme 1.40).[88] This work was inspired by Yudin and co-workers who in the same year had used *N*-aminophthalimide.[89] Recently, Bolm and co-workers added cyanamide to this list of nitrogen sources.[90]



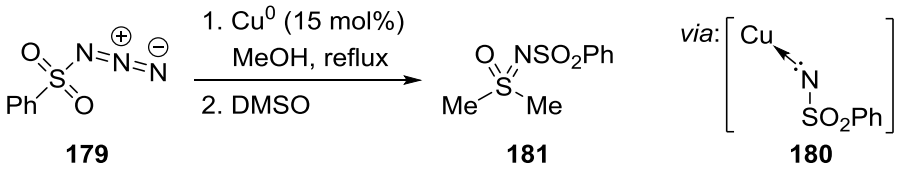
Scheme 1.40. Metal-free oxidative imidation of sulfoxides.

In 2007, Bolm and co-workers slightly altered conditions (*N*-bromosuccinimide, *tert*-butoxide and cyanamide) which were previously used for the imidation of sulfides,[91] towards the preparation of sulfoximines from sulfoxides (Scheme 1.41).[90] Treatment of 20 alkyl and/or aryl examples with *N*-chlorosuccinimide furnished 18 successful examples in 17-98% yield. The two examples that failed were the *ortho*-bromo phenyl and vinyl examples – which was attributed to sterics.



Scheme 1.41. Metal-free oxidative imidation using *N*-chlorosuccinimide.

Synthesising sulfoximines using metal catalysis is an attractive method because reactions are generally carried out using mild conditions.[66] In 1967, Kwart and Kahn developed a copper-catalysed decomposition of benzenesulfonyl azide **179** which generated a copper nitrene **180** *in situ* (Scheme 1.42).[92] In the absence of copper powder the decomposition of azide **179** occurred very slowly. It was postulated that following the decomposition of **179**, *via* the release of nitrogen gas, copper nitrene **180** was trapped by dimethylsulfoxide to afford sulfoximine **181**. Evidence for the formation of the copper-sulfonyl nitrene was provided by Carr and co-workers,[93] who observed the insertion of a *para*-toluenesulfonyl nitrene into dioxane. The nitrene was prepared using chloramine-T and copper powder.

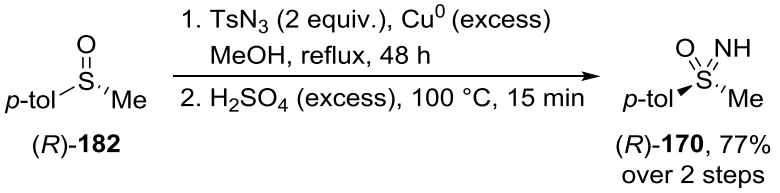


179 **181** **180**

Scheme 1.42. Copper-catalysed synthesis of sulfoximine **181**.

The generality of the methodology was demonstrated by Johnson and co-workers who used tosyl azide in methanol at reflux to prepare 7 alkyl and aryl examples of racemic *N*-tosyl sulfoximines in yields ranging from 52-94%.[94] Furthermore, Johnson and Schroek prepared enantiopure sulfoximine (*R*)-**170**

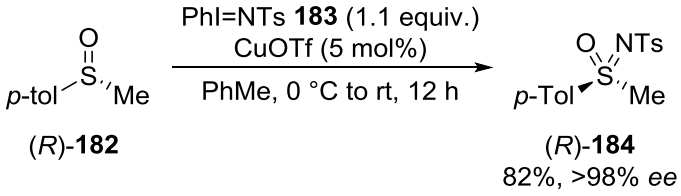
from its requisite sulfoxide (*R*)-**182** in 71% yield over two steps (Scheme 1.43).[82] The stereochemistry was assigned by optical rotation however the optical purity was not determined. The authors demonstrated that imidation proceeded with retention of configuration at the sulfur centre.



Scheme 1.43. Enantiopure sulfoximine obtained using nitrene methodology.

In 1998, Muller and Vogt reported the copper(I) triflate-catalysed imidation of racemic sulfoxides with *N*-tosyliminophenyliodinane (PhI=NTs) **183** as the nitrene source.[95] Six products were obtained in yields that ranged from 79-93%. This procedure was more efficient requiring only 5 mol% of copper(I). Shortly after, the same transformation was reported using copper(II) triflate.[96]

Muller and Vogt then applied their methodology to an enantiopure substrate (Scheme 1.44). Under the same conditions, the stereoselective imidation of (*R*)-**182** afforded sulfoximine (*R*)-**184** in 82% yield and >98% *ee*.

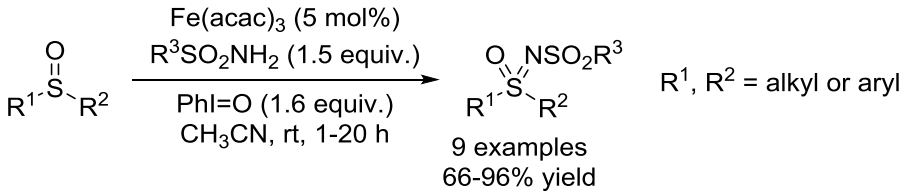


Scheme 1.44. Copper-catalysed imidation of enantiopure sulfoxide (*R*)-**182**.

In the same year, Bach and Körber published the iron(II) chloride-mediated isolation of *N*-Boc-protected sulfoximines from sulfoxides in a single step.[97]

However, it required the use of a large excess of sulfoxide as well as the highly explosive Boc-azide as the nitrene precursor. The authors primarily focused on the use of stoichiometric iron(II) chloride, although select examples using 10 mol% were successful – albeit in slightly lower yield.

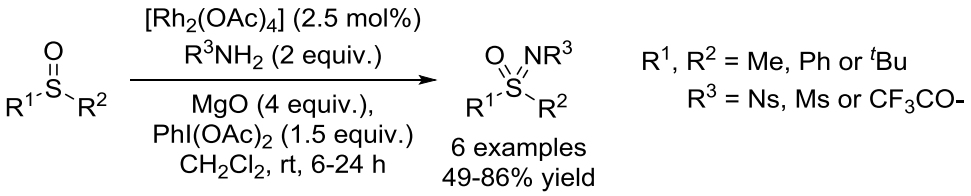
Alternatives were offered by Bolm who initially investigated the same transformation with iron(III) acetylacetonate (Scheme 1.45).[98] Treatment of sulfoxides with catalytic iron(III) and preformed iminating agent, from iodosylbenzene and the sulfonyl amine, led to the isolation of *N*-sulfonyl sulfoximines in good yield. Bolm endeavoured to improve the yields for bulky substrates in a follow up publication.[99] Iron(II) triflate and *N*-nosyl-iminophenyliodinane in acetonitrile at room temperature was used to prepare a range of bulky alkyl, aryl and heteroaryl sulfoximines in 50-96% yield.



Scheme 1.45. Oxidative imidation of sulfoxides using iron(III).

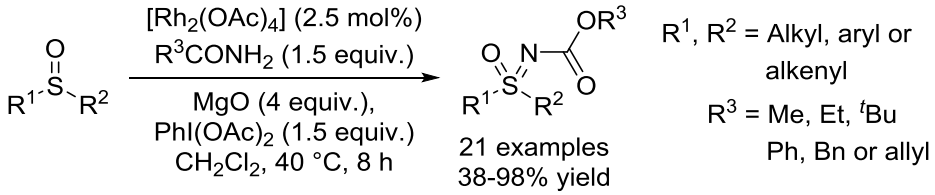
In 2004, Bolm and Okamura described a rhodium-catalysed oxidative imidation of sulfoxides.[100] Imidation of alkyl or arylsulfoxides with rhodium acetate, an amine, magnesium oxide and iodobenzene diacetate in dichloromethane at room temperature for 6-24 h afforded protected sulfoximines in 49-86% yield (Scheme 1.46). The attractiveness of this work was the simplicity of the reaction procedure. Instead of using a potentially dangerous imidating agent, such as *N*-nosyliminophenyliodinane or *O*-

(mesitylenesulfonyl)hydroxylamine (MSH), the imidating agent was formed *in situ* under mild conditions. Finally, the *N*-trifluoroacetyl protecting group can be removed using potassium carbonate in methanol at room temperature in high yield to obtain the versatile *NH*-sulfoximine. The cleavage of the other protecting groups was not investigated.



Scheme 1.46. Rhodium-catalysed imidation of sulfoxides.

Later, the Bull group published an extension of Bolm and Okamura's methodology which greatly expanded its scope.[101] Bull and co-workers prepared a range of *N*-carbamate sulfoximines which included the versatile *N*-Boc and *N*-CBz derivatives (Scheme 1.47). Prior to this work, the only procedure that furnished *N*-Boc sulfoximines was that of Bach and Körber.[97] Even though the cost of the rhodium catalyst is high, the methodology has found widespread application in the pharmaceutical industry.

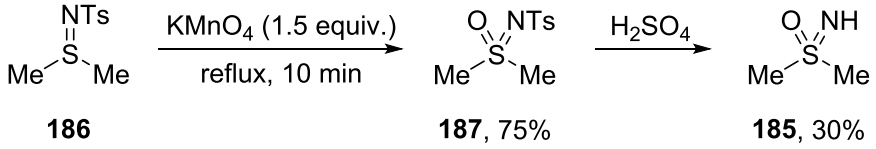


Scheme 1.47. Extension of the rhodium-catalysed imidation methodology.

1.2.2.2 Preparation from Sulfilimines

Achiral or chiral sulfilimines, also known as sulfimides, are prepared from sulfides using a range of imidation conditions such as: *N*-haloamides and similar derivatives, azides, nitrene sources and iminoiodinane-type compounds; all of which were reviewed by Bolm and co-workers in 2015.[74] The application of these methodologies, which covers a number of the aforementioned imidation conditions, towards the synthesis of sulfoximines from sulfoxides are presented herein.

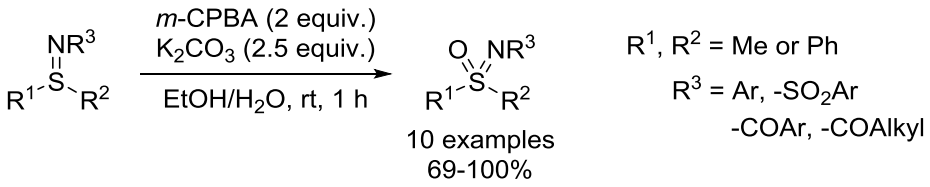
In the same publication that reported the successful synthesis of methionine sulfoximine **165**, Bentley and co-workers also prepared dimethylsulfoximine **185**.[73] Shortly after, Bentley and Whitehead synthesised dimethylsulfoximine **185** *via* a different approach (Scheme 1.48).[102] Starting from sulfilimine **186**, the sulfur centre was oxidised from sulfur(IV) to sulfur(VI) using neutral or alkaline permanganate in 75% yield. Deprotection of the tosyl group of **187** using concentrated sulfuric acid afforded dimethylsulfoximine **185** in only 30% yield. Shortly after, Claus and co-workers improved Bentley's permanganate procedure using an aqueous potassium permanganate-dioxane mixture.[103]



186 **187**, 75% **185**, 30%

Scheme 1.48. Two-step synthesis of dimethylsulfoximine **185**.

In 1979, Huang and Swern optimised the *m*-CPBA oxidation method of Cram and co-workers from 1968,[87] to afford a range of *N*-alkyl, *N*-acyl and *N*-aryl sulfilimines.[104] The optimised conditions used a molar ratio of 1:2:2.5 of sulfilimine/*m*-CPBA/K_2CO_3. The scope was exquisitely demonstrated by the synthesis of a wide variety of *N*-protected sulfoximines in excellent yields of 69-100% (Scheme 1.49). Prior to this work the protecting group scope for sulfoximine chemistry had been exclusively sulfonyl groups.

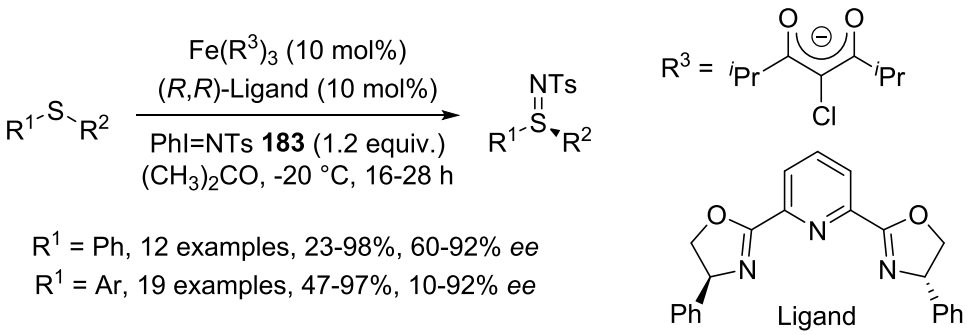


Scheme 1.49. *N*-protected sulfoximines prepared using *m*-CPBA.

Also in 1979, Johnson and Kirchhoff described the use of alkaline hydrogen peroxide (sodium hydroxide and hydrogen peroxide in water) for the oxidation of alkyl and aryl *N*-tosyl sulfilimines.[105] The methodology afforded high yields ranging from 78-98% for substrates with one small alkyl substituent. However, when substrates had two bulky substituents then the yields dropped to 29-65%.

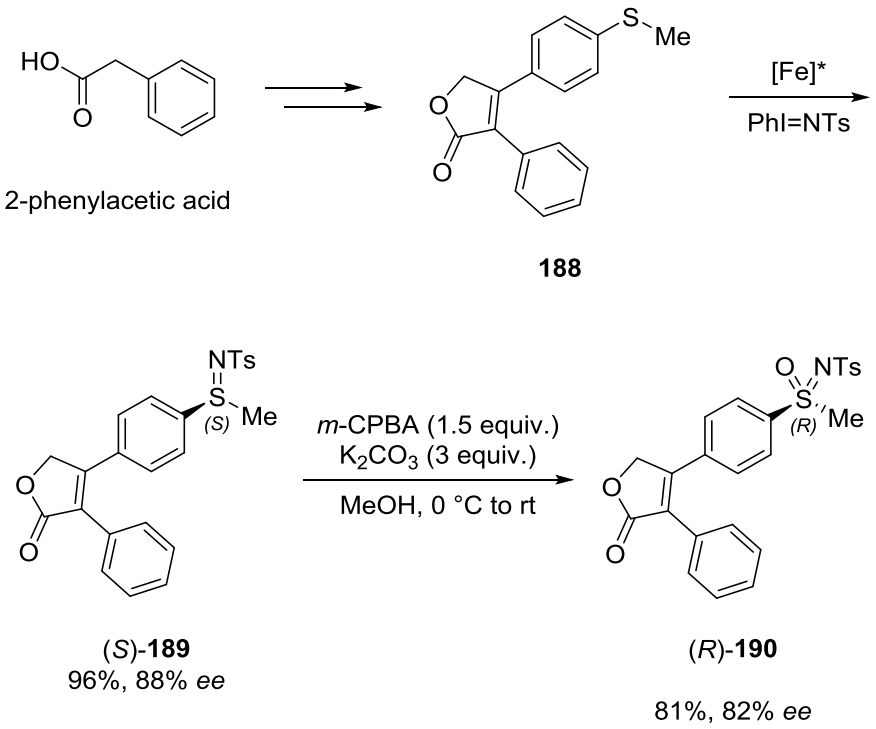
In 2013, Bolm and co-workers prepared chiral sulfilimines by the treatment of sulfides with an Fe^{III} catalyst, chiral ligand and *N*-tosyliminophenyliodinane **183** in acetone at –20 °C (Scheme 1.50).[106] An extensive range of products were afforded in good to excellent yield and up to 92% *ee*. The methodology stood apart from all previous methods from the early 2000s, which employed chiral auxiliaries[107] or catalytic metal-ligand systems that used either

copper,[108] manganese[109] or ruthenium.[110] These methodologies reported moderate to good enantiomeric excesses and the ligands used in the metal-ligand systems required long syntheses.[74]



Scheme 1.50. Synthesis of chiral sulfilimines from sulfides.

Moreover, Bolm applied this methodology in the synthesis of Vioaxx® sulfoximine analogues (Scheme 1.51). Following a literature procedure to convert 2-phenylacetic acid into the sulfide **188** starting material, the iron-catalysed imidation methodology afforded chiral sulfilimine (*S*)-**189** in 96% yield and 88% *ee*. The authors then performed the stereospecific oxidation of (*S*)-**189** with *meta*-chloroperoxybenzoic acid to obtain the Vioaxx® sulfoximine analogue (*R*)-**190** in 81% yield and 82% *ee*.[106]



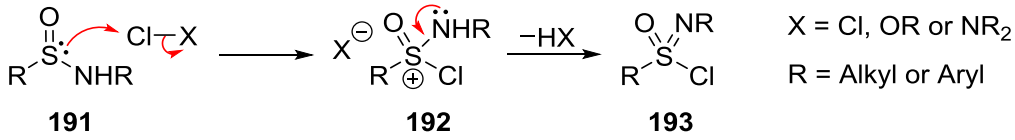
Scheme 1.51. Synthesis of Vioaxx® sulfoximine analogue (*R*)-**190**.

1.2.2.3 Preparation from Sulfonimidoyl Chlorides

Sulfonimidoyl chlorides were first reported by the Levchenko group in 1960,[41] since then there have been an increasing number of methods to synthesise them.

In 1979, Johnson introduced three methods for the preparation of sulfonimidoyl chlorides. Johnson and Wambsgans prepared aryl sulfonimidoyl chlorides from their requisite sulfinamides by treatment with *tert*-butylhypochlorite in carbon tetrachloride at 0 °C in the dark for 30 mins to 1 h.[4] The general mechanism for the oxidative chlorination is shown in Scheme 1.52. The lone pair on the sulfur of **191** attacks an electropositive chlorine atom thereby breaking its existing bond with X (X = Cl, OR or NHR). As a result, the lone pair on the nitrogen in **192** forms a double bond with the sulfur and

the loss of a salt or neutral molecule (HX) affords the sulfonimidoyl chloride **193**.

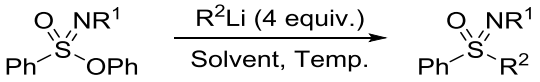


Scheme 1.52. Generalised mechanism for oxidative chlorination.

The second and third methods by Johnson and co-workers used chlorine or *N*-chlorobenzotriazole as the oxidant.[3] The experimental procedure consisted of stirring a solution of the sulfinamide at room temperature and either bubbling through chlorine gas or adding *N*-chlorobenzotriazole. Yields of 52-100% were obtained for nine sulfoximines. The advantage of these methods was the simple experimental procedure. However, seven of the nine products were obtained *via* the method that used toxic chlorine gas.

Sulfoximines can be directly synthesised from sulfonimidoyl chlorides by substitution of the chloride with a nucleophile, such as amines or anilines.[111,112] They can also be prepared in two steps from sulfonimidoyl chlorides *via* substitution of the chloride by phenoxide, which is followed by substitution of the phenoxide by alkyllithiums (Table 1.8).[113] This method gave access to previously unobtainable sulfoximines **194**-**200**, in particular *S*-benzyl and *S*-allyl (Table 1.8, entries 3 and 4).

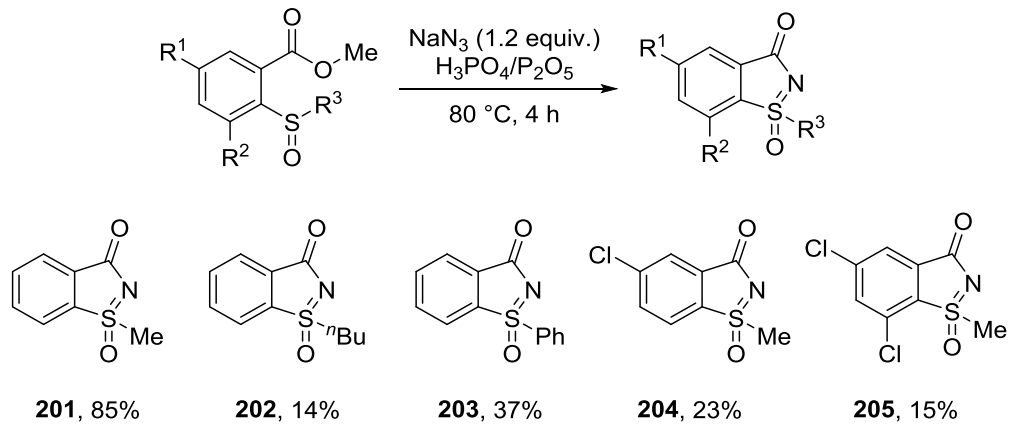
Table 1.8. Substitution of sulfonimidates by alkyllithiums.



Entry	R^1	R^2	Solvent	Temperature	Product	Yield (%)
1	Me	Me	Diethyl ether	rt	**194**	73
2	Me	^{n}Bu	Diethyl ether	rt	**195**	74
3	Me	Bz	Benzene	0 °C	**196**	30
4	Me	allyl	Diethyl ether	0 °C	**197**	71
5	Me	Cyp	pentane	0 °C to rt	**198**	46
6	Ph	Me	Diethyl ether	0 °C	**199**	45
7	Ph	^{n}Bu	Diethyl ether	0 °C	**200**	67

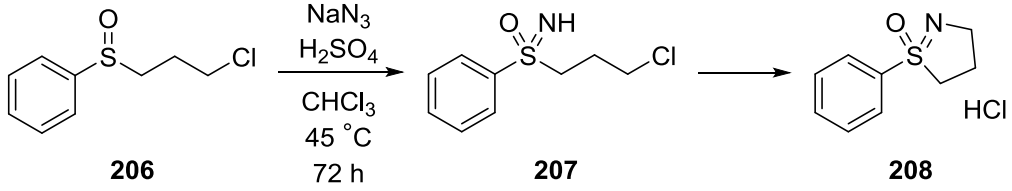
1.2.3 Preparation of Cyclic Sulfoximines

The first cyclic sulfoximines were prepared in 1971. Stoss and Satzinger used sodium azide with polyphosphoric acid as the acid catalyst and solvent to synthesise a range of cyclic sulfoximines **201-205** from their respective methyl 2-sulfinylbenzoates (Scheme 1.53).[114] Later, Stoss and Satzinger extended this methodology to obtain six- and seven-membered rings.[115]



Scheme 1.53. Synthesis of the first cyclic sulfoximines.

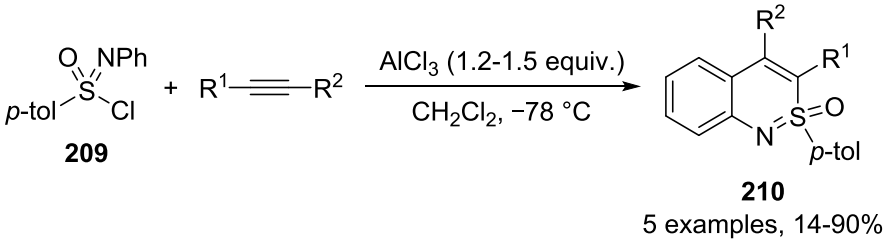
Also in 1979, Johnson and co-workers reported the intramolecular cyclisation of an open-chain sulfoximine to a cyclic sulfoximine (Scheme 1.54).[116] Following the imidation of **206** using the conditions of Bentley and co-workers,[79] sulfoximine **207** underwent slow cyclisation to **208**.



206 **207** **208**

Scheme 1.54. Cyclisation of **207** to obtain cyclic sulfoximine **208**.

The Harmata group has published numerous iterations of their 2,1-benzothiazine synthesis methodology. In 1987, the first iteration was the Lewis acid-catalysed cyclisation of sulfonimidoyl chloride **209** with a range of alkynes in dichloromethane at –78 °C to synthesis sulfoximines **210** (Scheme 1.55).[117] Analysis by ^{1}H NMR indicated that the products (**210**) were isolated as a single isomer.

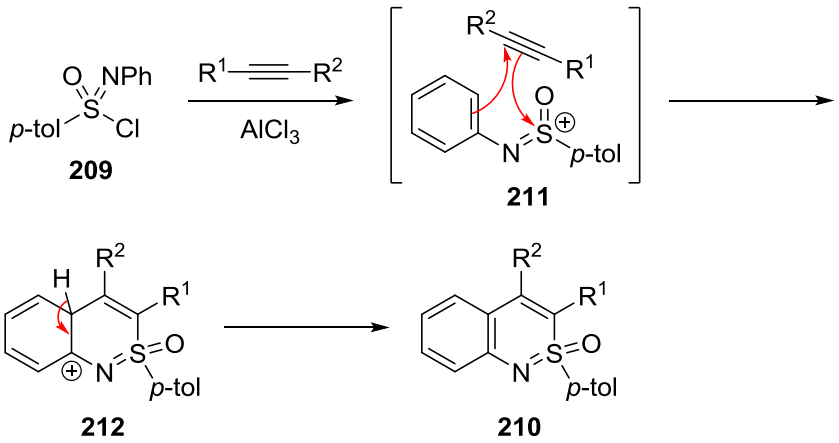


209 **210**
5 examples, 14-90%

Scheme 1.55. Synthesis of 2,1-benzothiazines.

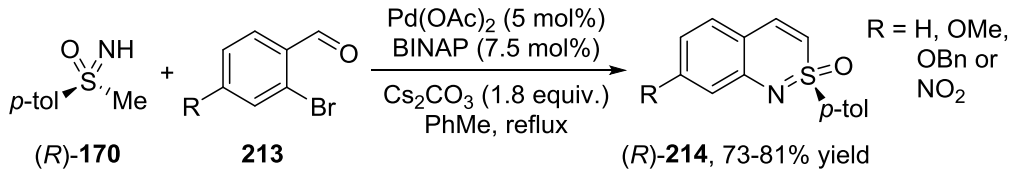
The mechanism was investigated in a follow up paper, in 1991, which also disclosed the same transformation except with alkenes.[118] Harmata and co-workers proposed a concerted cycloaddition between **211** (heterodiene) and the alkyne (or alkene) dienophile (Scheme 1.56). The production of

heterodiene **211** required loss of the chloride from **209** which was facilitated by the Lewis acid. Seven alkyl alkenes were investigated, which included four cycloaliphatic alkenes, although poor product isomer ratios were observed.



Scheme 1.56. Generalised mechanism for the synthesis of 2,1-benzothiazines.

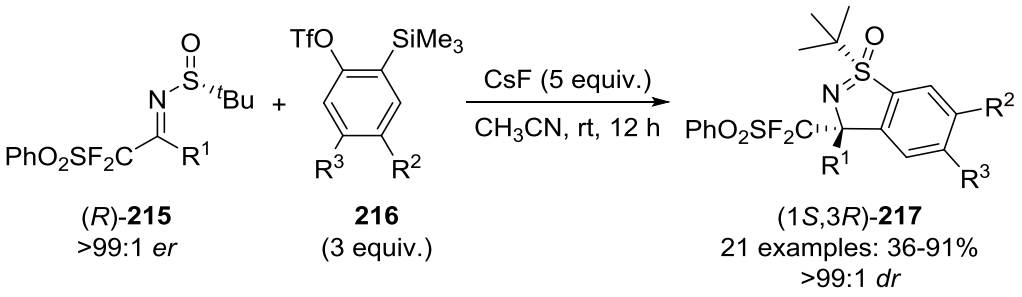
The third iteration was the one-pot cyclisation of aryl bromides **213** and enantiopure *NH*-sulfoximine (*R*)-**170** using Buchwald-Hartwig palladium cross-coupling conditions to prepare (*R*)-**214** in 73-81% yield (Scheme 1.57).[119]



Scheme 1.57. Buchwald-Hartwig cross-coupling then cyclisation.

Hu and co-workers reported an elegant stereoselective [3+2] cycloaddition of benzynes to *N-tert*-butanesulfinimines (*R*)-**215**.[38] The benzyne intermediate was prepared *in situ* following treatment of **216** with cesium fluoride in acetonitrile. Sulfoximines (1*S*,3*R*)-**217** were afforded in moderate to excellent yields (36-91%) and excellent diastereoselectivity (>99:1 *dr*) (Scheme 1.58).

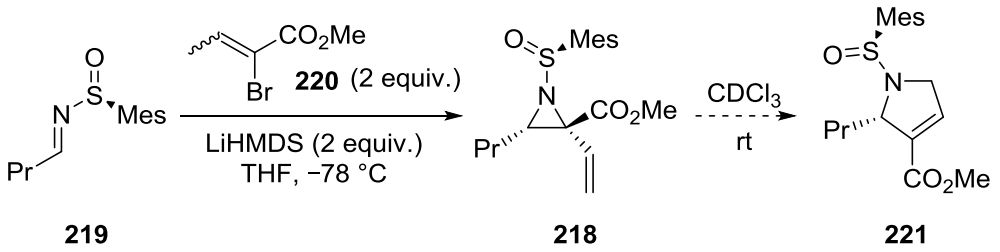
The chemistry tolerated a wide range of electron-donating and electron-withdrawing substituents (R^1) on sulfinimine (*R*)-**215**.



Scheme 1.58. [3+2] cycloaddition of sulfinimines with arynes.

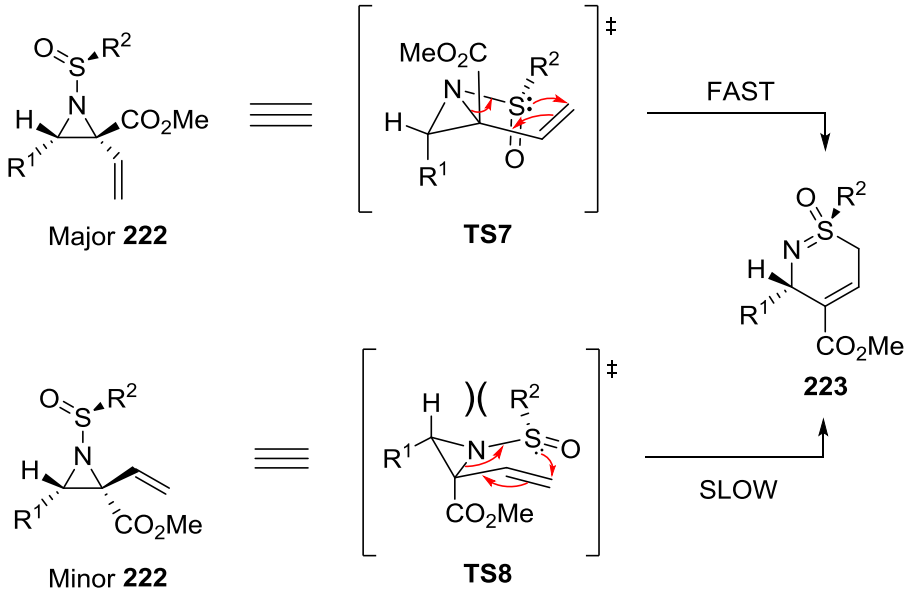
1.2.3.1 Thermal Rearrangement of 2-Vinylaziridines

In 2013, whilst investigating the preparation of trisubstituted 2-vinylazridines **218** from mesityl sulfinimines **219** and **220**, the Stockman group serendipitously discovered their rearrangement to chiral sulfoximines.[60,120] The rearrangement was found to occur when 2-vinylaziridine **218** was left in deuterated chloroform at room temperature for an extended period of time. It was initially postulated that the identity of the product was pyrroline **221** (Scheme 1.59).



Scheme 1.59. Initial hypothesis for the identity of the unknown product.

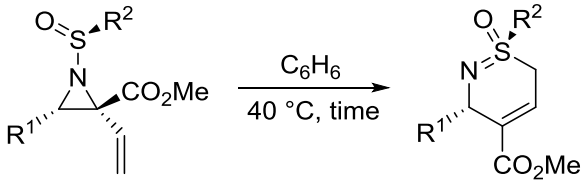
Fortunately, the resulting unknown was crystalline and hence the structure was elucidated by X-ray crystallography.[120] After gathering evidence against a radical or stepwise mechanism, we proposed that the mechanism of the rearrangement was a concerted process: a [2,3]-sigmatropic rearrangement.[120] A kinetic study revealed that the major diastereoisomer of aziridine **222** rearranged approximately 3 times faster than the minor.

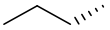
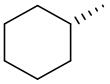
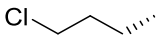
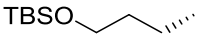
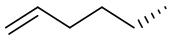
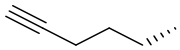
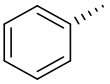


Scheme 1.60. Proposed rearrangements of aziridine **222** to sulfoximine **223**.

The outcome of a study into the rearrangement of aziridine **222** in numerous deuterated NMR solvents, revealed that it proceeded best in apolar solvents, in particular benzene, at 40 °C and 70 °C. The conditions selected for the investigation into the scope were 40 °C in benzene (Table 1.9).

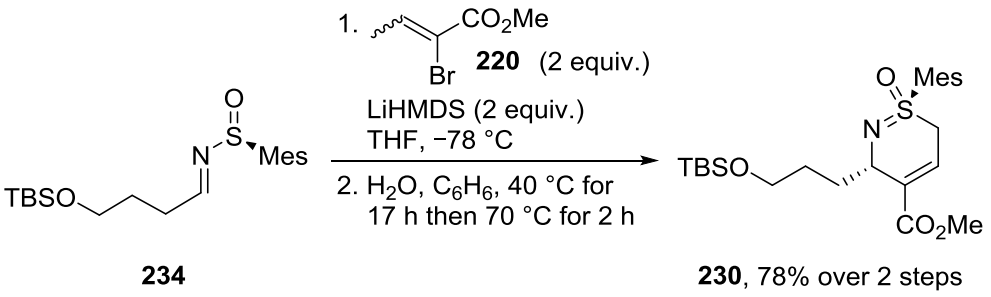
Table 1.9. Scope of the 2-vinylaziridine [2,3]-sigmatropic rearrangement.



Entry	C-3 Position (R^1)	Sulfinyl Group (R^2)	Time (h)	Yield (%)	Product
1		Mes	19	80	**224**
2		Mes	17	82	**225**
3		Mes	24	93	**226**
4		Mes	24	68	**227**
5		Mes	15	77	**228**
6		Mes	15	67	**229**
7		Mes	17	88	**230**
8		Mes	17	97	**231**
9		Mes	8	79	**232**
10		^{t}Bu	23	45	**166**
11		^{t}Bu	108	16	**233**

In summary, the rearrangement was performed on a wide range of *N*-mesitylsulfinyl and *N*-*tert*-butylsulfinyl 2-vinylaziridines. A wide range of functional groups were tolerated at the C-3 position (R^1), however, significantly higher yields were obtained in the reactions that employed mesityl (Table 1.9, entries 1-9) as the directing group versus reactions which employed *tert*-butyl (Table 1.9, entries 10 and 11).

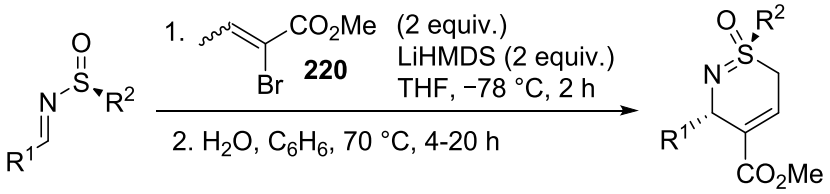
Since the rearrangement of the 2-vinylaziridine was intramolecular, it was envisaged that a one-pot process could be used to prepare sulfoximine **230** as few side reactions could occur. Indeed, the *aza*-Darzens reaction was quenched with water and the resulting mixture allowed to warm to room temperature, benzene was added and the resulting biphasic solution heated to 40 °C and stirred overnight (Scheme 1.61). The reaction did not go to completion therefore the mixture was heated to 70 °C for a further 2 h. The one-pot procedure improved the yield over the 2 steps from 59% to 78%, as well as removing the aziridine purification step.

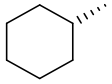
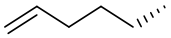
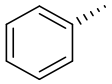
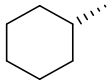
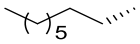
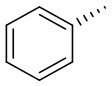
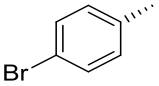
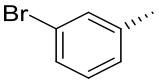
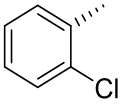
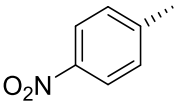
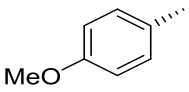
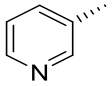
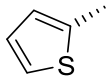
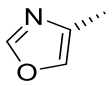


Scheme 1.61. One-pot preparation of **230**.

Thus, the scope of the functional groups at the C-3 position and the tolerance of the two directing groups was investigated in the one-pot method (Table 1.10, column 4).[120,121] The yields were then compared against the two step process (Table 1.10, column 5). Surprisingly, no product was obtained when R^1 = phenyl and R^2 = mesityl (Table 1.10, entry 3). In comparison, a 16% yield was recorded when R^1 = phenyl and R^2 = *tert*-butyl (Table 1.9, entry 11).

Table 1.10. Re-investigation of the scope of the thermal rearrangement.



Entry	R^1	R^2	One-pot Yield (%)	Two-step Yield (%)[a]	Product
1		Mes	49	33	**228**
2		Mes	62	57	**231**
3		Mes	-	-	-
4		^{t}Bu	62	17	**166**
5		^{t}Bu	48	39	**235**
6		^{t}Bu	74	10	**236**
7		^{t}Bu	34	-	**237**
8		^{t}Bu	74	12	**233**
9		^{t}Bu	23	-	**238**
10		^{t}Bu	49	-	**239**
11		^{t}Bu	-[b,c]	-	-
12		^{t}Bu	40	-	**240**
13		^{t}Bu	-	-	-
14		^{t}Bu	36	-	**241**
15		^{t}Bu	-[c]	-	-
16		^{t}Bu	-[c]	-	-

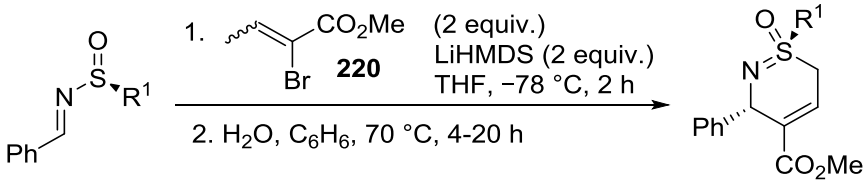
[a] Rearrangement performed at 40 °C. [b] De-*tert*-butylation observed.
[c] Aziridine observed by TLC.

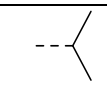
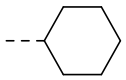
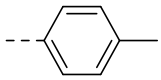
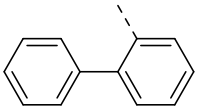
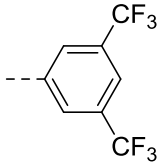
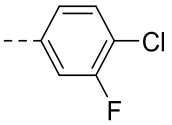
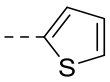
Disappointingly, examples with electron withdrawing groups on the aryl ring gave lower yields (Table 1.10, entries 9-12). Moreover, when R^1 was a substituent with an electron donating group on the aryl ring, no reaction was observed (Table 1.10, entry 13). Whilst the heteroaromatic 2-pyridyl example gave a moderate 36% yield (Table 1.10, entry 14), experiments with thiophene and oxazole substituents were unsuccessful due to decomposition during the aziridine to sulfoximine rearrangement (Table 1.10, entry 15 and 16). Overall, the one-pot procedure greatly improved the yield of the sulfoximine, even though the rearrangement was carried out at the higher temperature of 70 °C (Table 1.10, entries 1, 2, 4-6 and 8).

Exploration of different groups on the sulfur exemplified the capricious nature of the reaction (Table 1.11).

The 2-vinylaziridine rearrangement did not tolerate an *iso*-propyl or cyclohexyl substituent on the sulfur (Table 1.11, entries 1 and 2). Encouragingly, other aryl substituents aside from 3-fluoro-4-chloro-phenyl (Table 1.11, entry 6) gave moderate yields of the respective sulfoximines (Table 1.11, entries 3-5). Again, a heteroaromatic example suffered from decomposition during the 2-vinylaziridine to sulfoximine rearrangement (Table 1.11, entry 7).

Table 1.11. Scope of the directing group tolerated on the sulfur.



Entry	Sulfinyl Group (R^1)	Yield (%)	Product
1		-[a]	-
2		-[a]	-
3		21	**242**
4		37	**243**
5		21	**244**
6		-[a]	-
7		-[a]	-

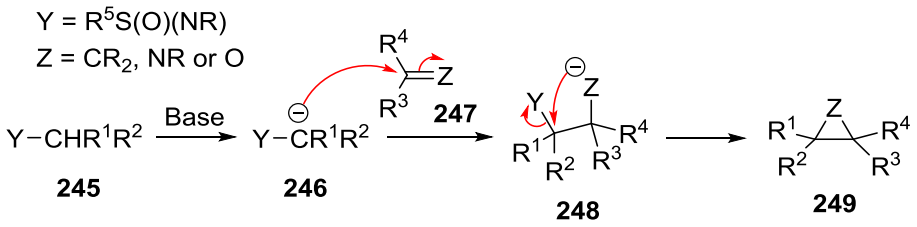
[a] Aziridine intermediate observed by TLC.

In summary, the Stockman group has shown that a thermal rearrangement of 2-vinylaziridines is a general method for the preparation of cyclic sulfoximines (Table 1.9 and Table 1.10). The best results were obtained when R^2 = mesityl but other functional groups were tolerated (Table 1.11).

1.2.4 Applications of Sulfoximines

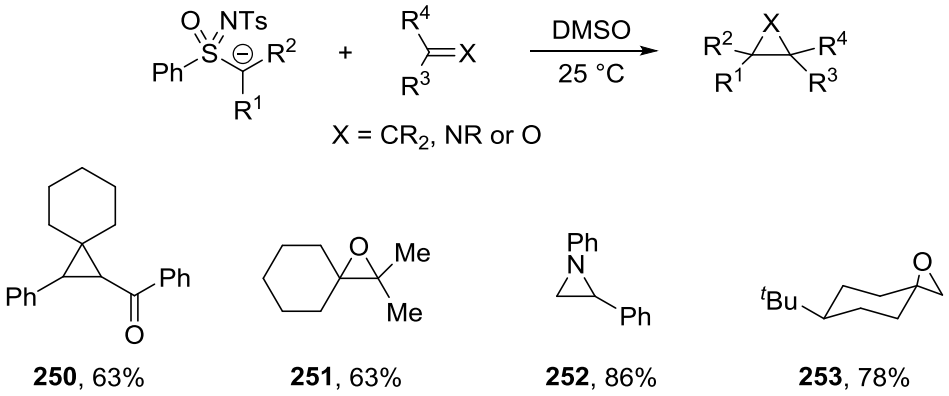
Sulfoximines are a biologically active functional group. This has been known since Bentley identified methionine sulfoximine **165** as the toxic factor in agenised wheat flour.[59,122] The applications of sulfoximines has been studied in particular by: the Johnson group from 1968 to the late 1980s, the Bolm group since the early 1990s and in recent years by the Stockman group and Bull group.

In 1968, the Johnson group outlined the use of sulfoximines as a nucleophilic ylide transfer reagent **245** (Scheme 1.62).[61] A nucleophilic ylide transfer reaction involves the transfer of the ylide fragment **246** to an electrophilic double bond **247**.[62] The effectiveness of the ylide **248** is dependent on its ability to stabilise the adjacent carbanion and to act as a good leaving group to obtain the desired product **249**.



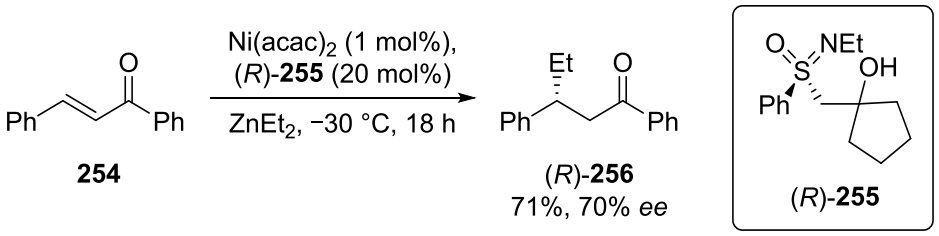
Scheme 1.62. General mechanism for a nucleophilic ylide transfer reaction.

The Johnson group demonstrated that *N*-tosyl sulfoximines were excellent ylide transfer reagents to prepare unusual compounds such as **250-253** (Scheme 1.63).[63] The mechanism was analogous to that of the Darzens reaction.



Scheme 1.63. *N*-Tosyl sulfoximines as nucleophilic ylide transfer reagents.

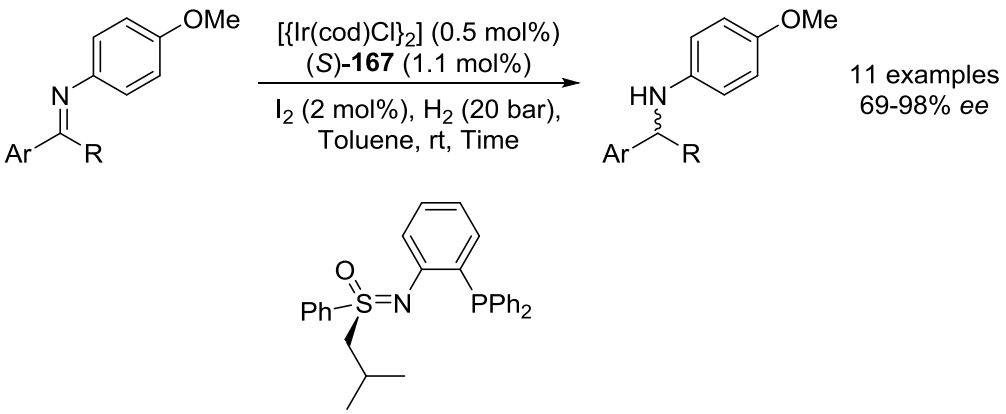
The Bolm group has had a keen interest in the synthesis and applications of sulfoximines since the early 1990s. The Bolm group's earliest publication in this area was the first example of the use of a chiral sulfoximine as a catalyst in an asymmetric reaction.[65] Asymmetric 1,4-addition of diethylzinc into chalcone **254** was achieved using a nickel catalyst and sulfoximine ligand (*R*)-**255** and afforded (*R*)-**256** in 71% yield and 70% *ee* (Scheme 1.64). Out of a catalogue of twenty two sulfoximines made for the ligand screen, sulfoximine (*R*)-**255** gave the best yield and *ee*.



Scheme 1.64. Enantioselective 1,4-addition of diethylzinc using (*R*)-**255**.

Bolm has also applied sulfoximines as a ligand in the iridium-catalysed hydrogenation of imines.[123] This publication outlined an exciting application whereby an iridium(I) catalyst with sulfoximine ligand (*S*)-**167** gave acyclic amine products with full conversion and excellent enantioselectivities of up to

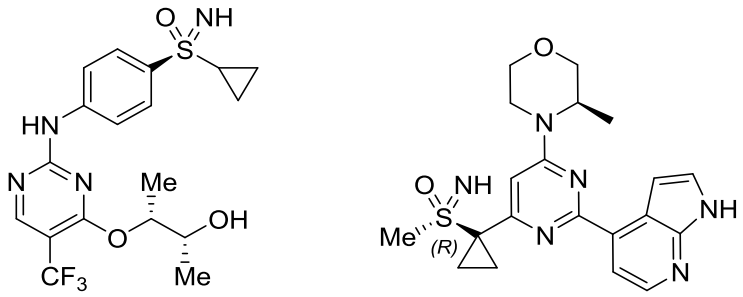
98% *ee*. Bolm primarily focused on imines bearing the *N*-(*para*-methoxy)phenyl group (Scheme 1.65). Aside from one example all the substrates gave excellent enantioselectivities. The rational design for the ligand was to base it on the chiral phosphine ligand that was used by Zhang and Xiao, who obtained up to >99% *ee* for the same transformation.[124]



(*S*)-**167**

Scheme 1.65. Enantioselective hydrogenation of imines employing (*S*)-**167**.

Probably the most exciting application of a sulfoximine to date was Bayer's cyclin-dependent kinase (pan-CDK) inhibitor candidate, BAY 1000394 (Figure 1.8) – its mode of action was the inhibition of the cell-cycle and transcriptional CDKs. Unfortunately, BAY 1000394 failed in Phase III clinical trials.[69,70] Another example of a sulfoximine-containing drug candidate that has gone into clinical trials is AstraZeneca's ataxia telangiectasia and rad3 related (ATR) kinase inhibitor, AZD6738 (Figure 1.8).[125]

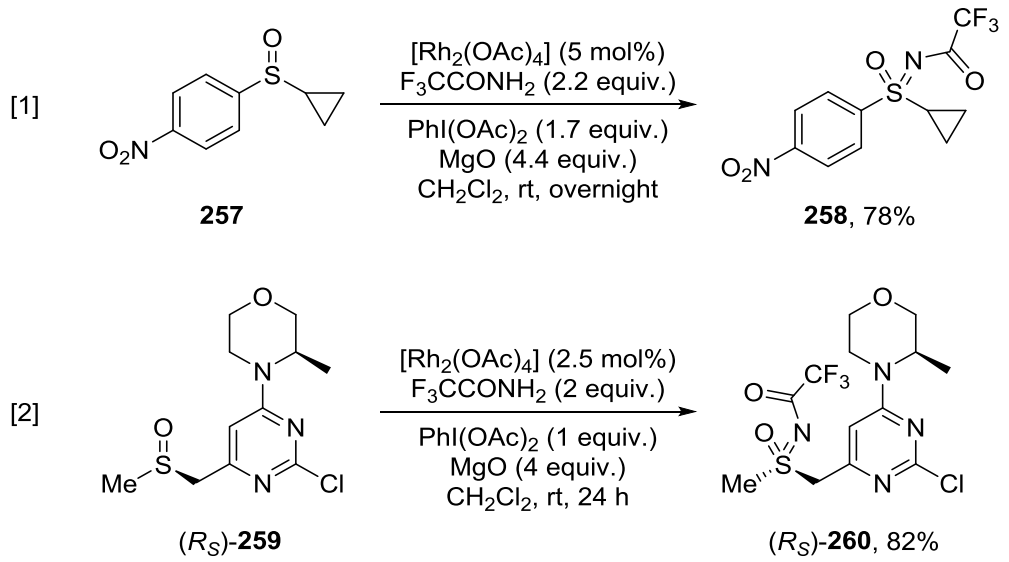


BAY 1000394

AZD6738
ATR Kinase Inhibitor

Figure 1.8. Sulfoximine drug candidates: BAY 1000394 and AZD6738.

A sulfoximine was incorporated into BAY1000394 during the lead optimisation phase.[69] The sulfoximine moeity was prepared from sulfoxide **257** using the rhodium-catalysed methodology of Bolm and Okamura[100] (Scheme 1.66 – equation [1]).[126] Oxidative imidation of **257** afforded **258** in 78% yield. The desired (*R*)-stereoisomer (BAY100394) was obtained by chiral separation at the end of the synthesis. Finally, the rhodium-catalysed methodology was again employed during the synthesis of AZD6738.[125] Thus, treatment of (R_S)-**259** to the conditions of Bolm and Okamura[100] allowed access to enantiopure (R_S)-**260** in an excellent 82% yield (Scheme 1.66 – equation [2]). On this occasion the chiral separation was performed earlier in the synthesis to obtain enantiomerically pure (R_S)-**259**.

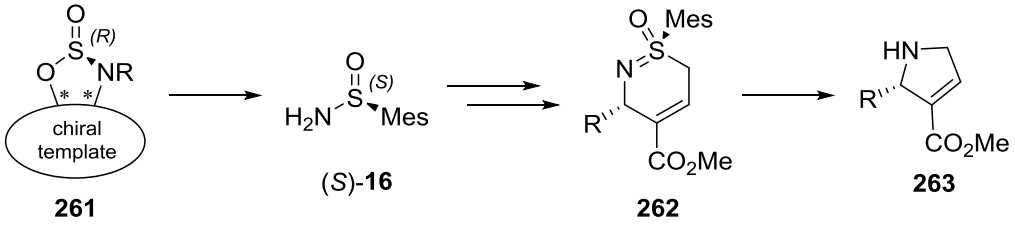


Scheme 1.66. Oxidative imidation of sulfoxides **257** and (R_S)-**259**.

1.3 Aims and Objectives

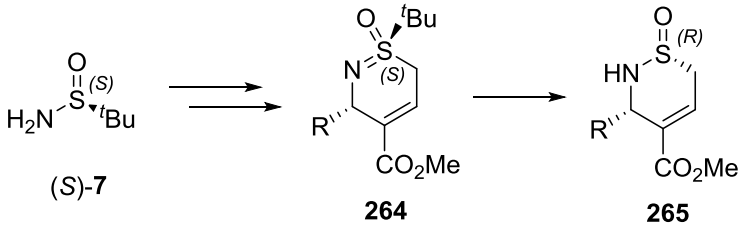
The synopsis for this programme of research was to expand the chemistry of the cyclic sulfoximines afforded from the Stockman group's vinylaziridine rearrangement methodology.[120]

We required (*S*)-mesityl sulfinamide (*S*)-**16**, which had limited availability due to its high cost, and therefore would employ a chiral sulfinyl transfer template **261** (Scheme 1.67). With (*S*)-**16** in hand, we would have access to mesityl cyclic sulfoximines **262** *via* the group's rearrangement methodology. The avenue of research we prioritised was the expansion of the cyclic sulfoximine **262** to 3-pyrroline **263** scope, as only 2 examples had previously been characterised.[60]



Scheme 1.67. Proposed route to expand 3-pyrroline **263** scope.

A second avenue of interest arose during our investigations which led to our published work on the vinylaziridine rearrangement methodology, we obtained low yields of the desired cyclic sulfoximine **264** (Scheme 1.68). The major product was the respective cyclic sulfinamide **265**. As *tert*-butyl sulfinamide (*S*)-**7** is commercially available we wanted to further examine the pathway to this byproduct and thereafter the scope.



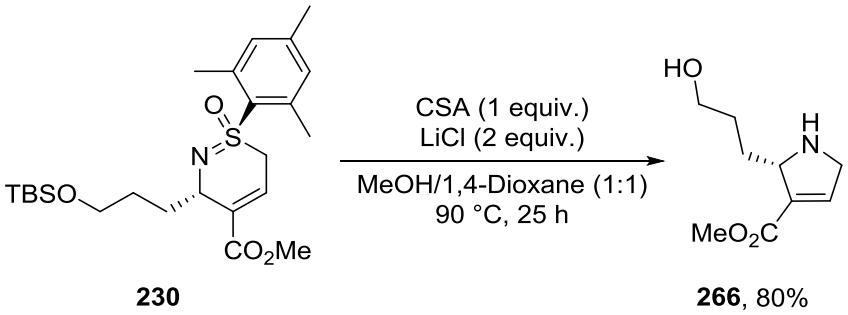
Scheme 1.68. Proposed route to investigate cyclic sulfinamides **265**.

Finally, further functionalisation of the products obtained over the course of this research would be attempted, so as to open new avenues of future interest.

2. Results and Discussion

2.1 Preparation of *NH*-3-Pyrrolines

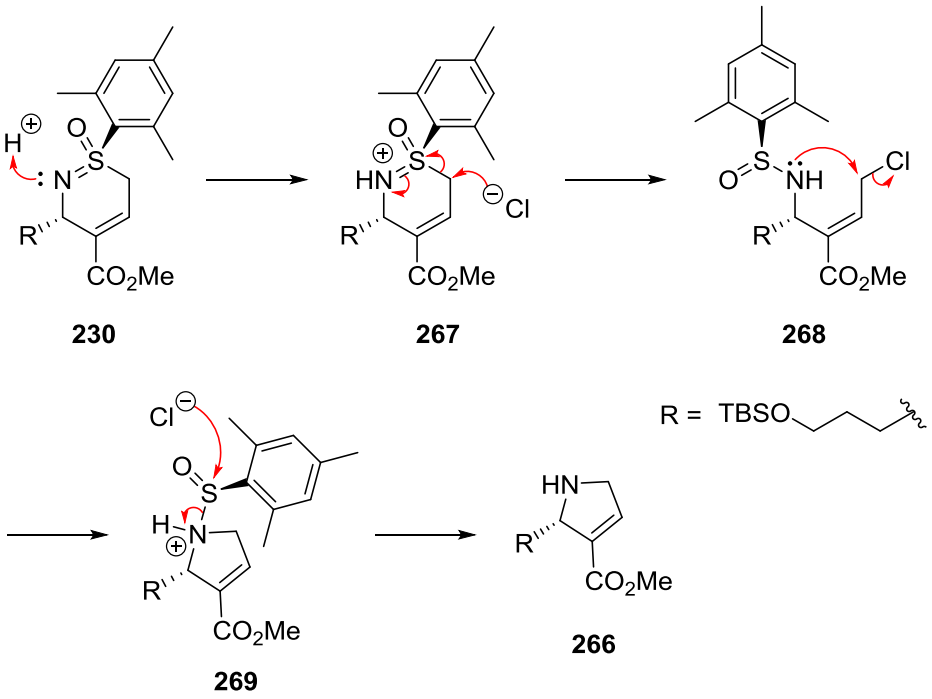
As disclosed by the Stockman group in 2016,[120] the serendipitous discovery of the ring contraction of mesityl cyclic sulfoximine **230** to *NH*-3-pyrroline **266** was reported (Scheme 2.1). Neutralisation of the hydrochloride salt of the crude product with triethylamine and careful purification by normal phase column chromatography afforded pyrroline **266** in 80% yield.



230 **266**, 80%

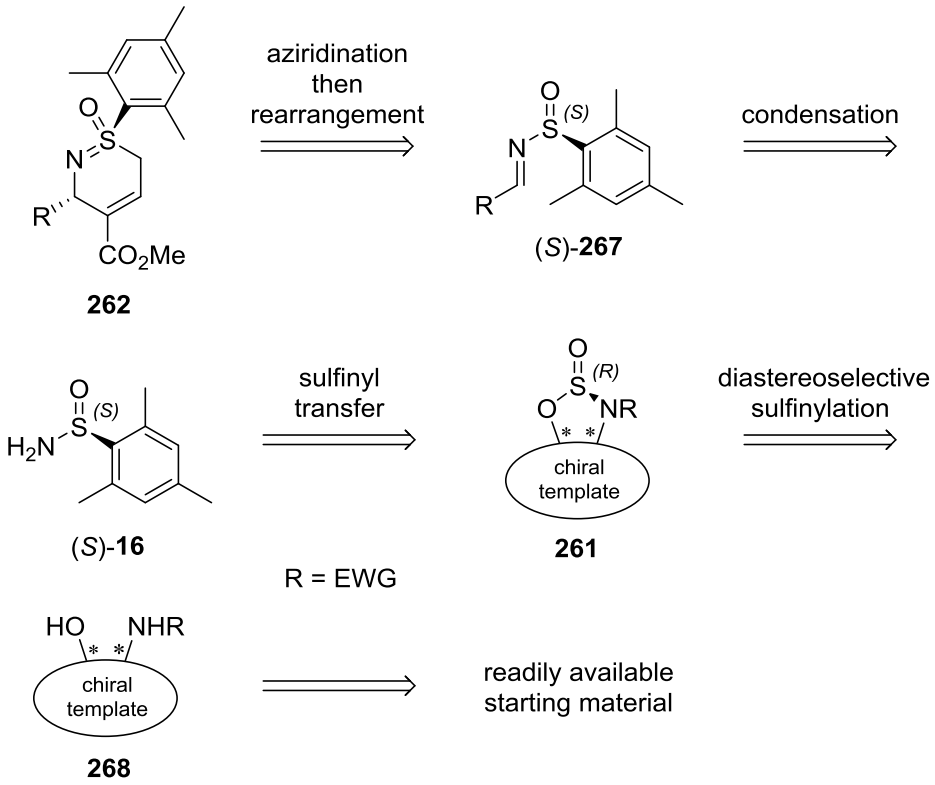
Scheme 2.1. Ring contraction of cyclic sulfoximine **230** to 3-pyrroline **266**.

The proposed mechanism began with protonation of sulfoximine **230** on the nitrogen by camphorsulfonic acid to give **267** (Scheme 2.2).[60] The resulting protonated sulfoximine **267** undergoes ring opening by the addition of chloride. Open-chain sulfinamide **268** then completes a 5-*exo*-*tet* ring closure to afford protected pyrroline **269**. Deprotection of the nitrogen is achieved following addition of chloride to **269** to afford the deprotected pyrroline **266**.



Scheme 2.2. Proposed mechanism of the ring contraction of **230** to **266**.

Investigation into the scope of the ring contraction required the synthesis of the sulfoximines **262**, which in turn can be prepared from their respective sulfinimines (*S*)-**267** *via* the condensation of mesityl sulfinamide (*S*)-**16** and readily accessible aldehydes (Scheme 2.3). Mesityl sulfinamide (*S*)-**16** would be prepared using a chiral template (**261**), which would be afforded following the diastereoselective sulfinylation of amino alcohol **268** – accessed from a readily available starting material.



Scheme 2.3. Retrosynthetic route for the mesityl cyclic sulfoximines **262**.

After considering the aforementioned chiral templates (Chapter 1.1.1.2) for the synthesis of chiral sulfinamides, due to the cost of preparing or buying the *cis*-1-amino-2-indanol for template (R_s)-**15** and the controlled access to norephedrine for template (R_s)-**18**, it was decided that the Stockman group's chiral template (R_s)-**20** would be employed (Figure 2.1).[21] In the Stockman group's paper, from 2011, a four-component one-pot synthesis of (*S*)-mesityl sulfinimines (*S*)-**267** was presented, however, in this research a more modular approach was taken.

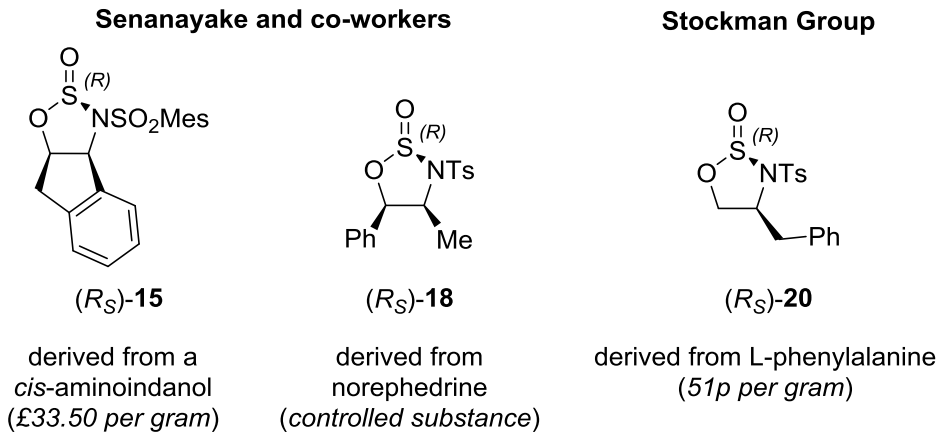
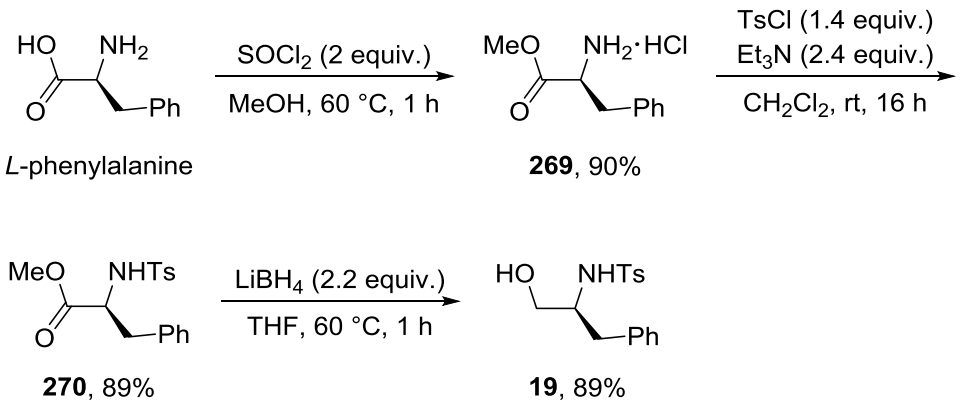


Figure 2.1. Chiral templates used in the preparation of chiral sulfinamides.[127]

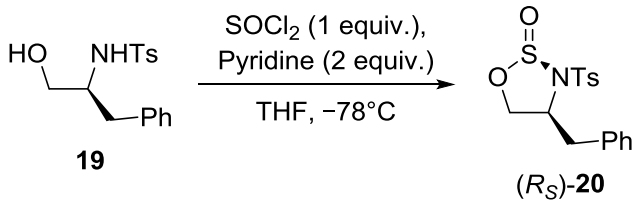
2.1.1 Preparation of Oxathiazolidine 2-oxide Template

The synthesis of template (R_s)-**20** began with the esterification of *L*-phenylalanine using thionyl chloride in methanol (Scheme 2.4). The hydrochloride salt of amine **269** was isolated in 90% yield by crystallisation from methanol with diethyl ether. Sulfonylation of amine **269** proceeded smoothly and *N*-tosyl amine **270** was obtained following column chromatography in excellent yield. Finally, the synthesis of **19** was completed with reduction of the ester functionality, after treatment with lithium borohydride, in an overall yield of 71% over 3 steps on multigram scale.



Scheme 2.4. Synthesis of precursor **19**.

With precursor **19** in hand, the key step was the diastereoselective sulfinylation with thionyl chloride and pyridine (Scheme 2.5). Identity of the desired diastereosiomer (R_S)-**20** was assigned unequivocally *via* a crystal structure in the 2011 paper.[21] Therefore, the diastereoselectivity was ascertained by ^{1}H NMR spectroscopy through integration of the most downfield proton peaks at the alpha position to the oxygen. In initial experiments to replicate the group's procedure, upon filtration of the reaction mixture through Celite® at –20 °C and removal of the solvent, the highest diastereomeric ratio of (R_S)-**20**:(S_S)-**20** observed was a satisfactory 91:9. Stockman and co-workers reported that chiral template (R_S)-**20** was susceptible to epimerisation during aqueous work-up and under acidic conditions.[21] Without access to the ISOLUTE® CN cartridges used in the original publication, previous members of the Stockman group were able to isolate diastereomerically pure (R_S)-**20** following efficient purification through a short silica column. However, mass recovery of (R_S)-**20** suffered and typical yields ranged between 50-60%.

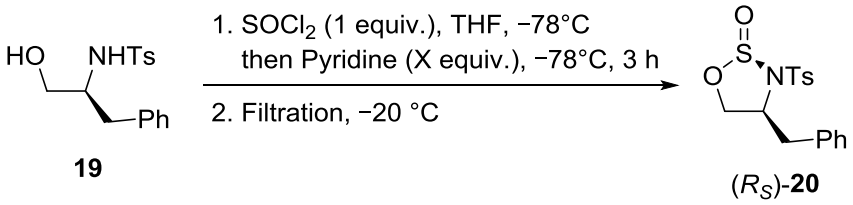


Scheme 2.5. Synthesis of oxathiazolidine 2-oxide (R_S)-**20**.

An in depth investigation of the reaction conditions was deemed prudent so as to determine which factor(s) were causing the product to decompose prior to and/or during purification. Moreover, it was paramount to develop an

effective procedure that delivered clean product – ideally avoiding purification. Examples of the parameters investigated were: concentration, order of addition, time between additions, equivalents of reagents and filtration method to remove the reaction byproduct – pyridinium hydrochloride. The results of these small scale experiments are shown below in Table 2.1. The filtration was performed at –20 °C because at this temperature pyridinium hydrochloride was not soluble in tetrahydrofuran and, as stated previously, it was known that the product epimerised under acidic conditions.[21]

Table 2.1. Improvement of the chiral template (R_S)-**20** synthesis.



19 (R_S)-**20**

Entry	X	Filtration	*dr*[a]	Impurity **271**:(R_S)-**20**[a]
1	2	sintered funnel/Celite®	94:6	3.01:1
2	2	sintered funnel only	89:11	1.18:1
3	2	sintered funnel/silica gel	>99:1	0.46:1
4[b]	2	sintered funnel/silica gel	>99:1	1.30:1
5[c]	2	sintered funnel/silica gel	>99:1	1.26:1
6[d]	2	sintered funnel/silica gel	95:5	1.11:1
7	2.2	sintered funnel/silica gel	>99:1	0.10:1
8	4	sintered funnel/silica gel	>99:1	0.40:1

[a] Determined from crude ^{1}H NMR spectrum. [b] Increased dilution from 0.6 to 0.1 mmol/mL. [c] Reverse order of addition of $SOCl_2$ and pyridine. [d] Delayed addition of pyridine by 15 min.

In most cases, an impurity **271** was being formed in preference to the target product (Table 2.1, entries 1, 2 and 4-6). The impurity **271** had a characteristic apparent double doublet at δ_H 5.50-5.40 ppm in a referenced spectrum (Figure 2.2). There was no correlation between the observed diastereomeric

ratio and the ratio of template (R_S)-**20** and the impurity. However, the diastereomeric ratio was consistently higher in reactions that filtered the reaction mixture through silica gel (Table 2.1, entries 3-8). This was attributed to the effectiveness of the silica gel at removing the pyridinium hydrochloride. Changing the dilution, order of addition or time between the addition of the thionyl chloride and pyridine did not have any effect (Table 2.1, entries 4-6). The best conditions used a small or large excess of pyridine (Table 2.1, entries 7 and 8, respectively). Consequently, the benefit of an excess of pyridine would facilitate complete removal of the hydrochloric acid generated during the reaction. The optimal conditions were 2.2 equivalents of pyridine and, when the reaction was deemed complete and was allowed to warm to –20 °C, a cold filtration through silica gel (Table 2.1, entry 7).

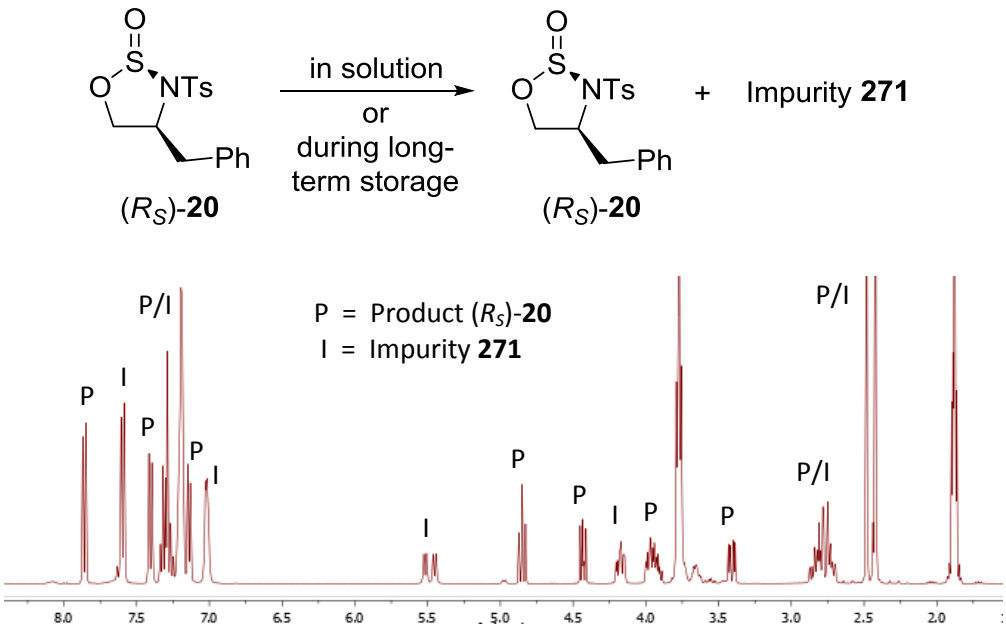


Figure 2.2. ^{1}H NMR spectrum of the crude mixture from Table 2.1, entry 4.

It should be noted that the identity of the impurity was elucidated at a later date, when (R_S)-**20** was stored for long periods (6 months+) the integrity of (R_S)-**20** visually changed from a powdery white solid to a clear gum. Purification of the material led to the isolation of **271** and thus we postulate that the impurity was in fact a dimer which could have either structure **A** or structure **B**, shown in Figure 2.3.

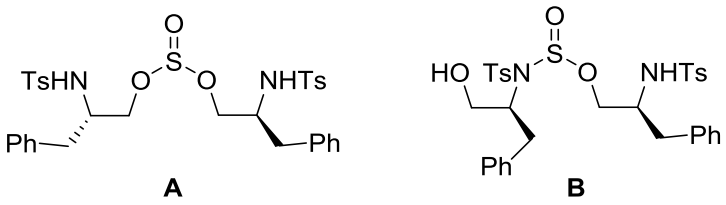


Figure 2.3. Plausible structures **A** and **B** for dimer **271**.

Initially, the observed duplication of the signals in the proton and carbon NMR spectra suggested structure **B**. This is conceivable because structure **A** has C_2 rotation symmetry and thus the carbon chains either side of the bridging sulfinyl moiety would be equivalent. However, further analysis of the 2D NMR experiments indicate that structure **A** is the likely identity of **271**.

The absence of proton to carbon correlations in the HSQC spectrum of **271** confirmed that the two doublets, at approximately 5.5 ppm, were individual protons bonded to separate heteroatoms (Figure 2.4). The COSY spectrum of **271** (Figure 2.5) indicated that these heteroatoms were adjacent to a carbon which the HSQC spectrum identified as a carbon bonded to only one proton (red correlation at approximately 3.7 ppm – Figure 2.4). Thus, this was evidence for structure **A**. Although, the presence of two separate sets of correlations in the COSY spectrum is more evidence in favour of two

inequivalent carbon chains in **271** and thereby structure **B**. Overall, the evidence for structure **A** from the 2D NMR experiments was incontrovertible. Therefore, it was postulated that the splitting observed in the NMR spectra arose from the conformation that **271** occupied in the solution of chloroform.

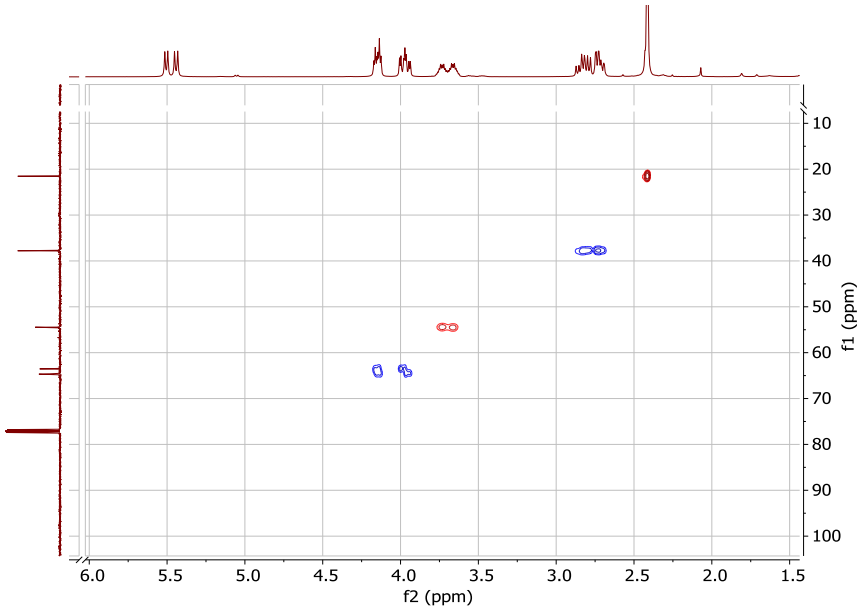


Figure 2.4. HSQC spectrum of **271**.

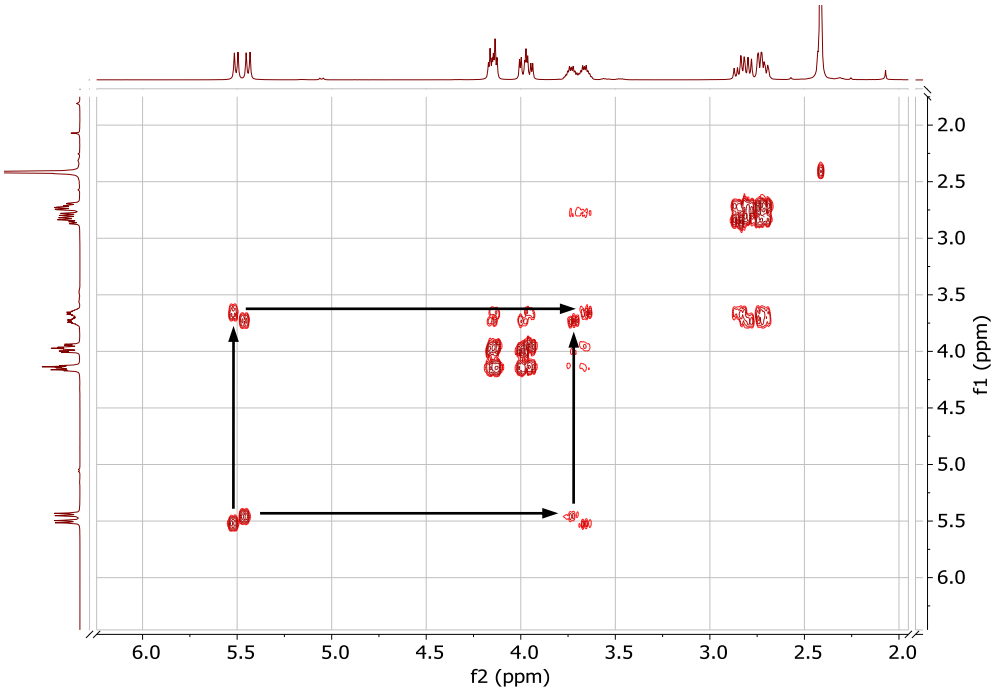
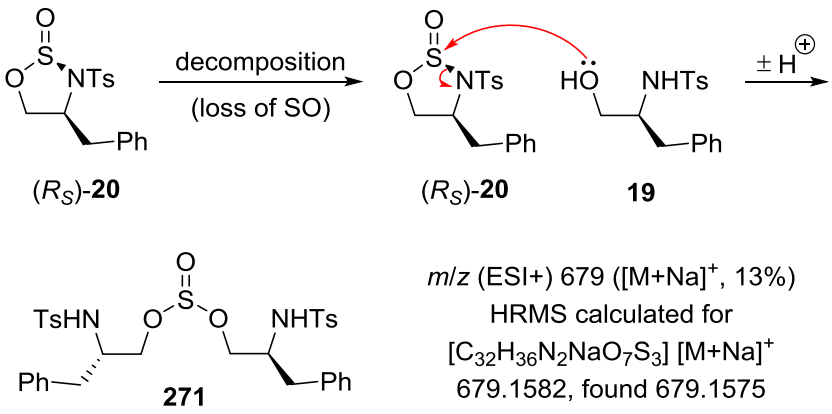


Figure 2.5. COSY spectrum of **271**.

Therefore, we propose that decomposition of (R_S)-**20** would liberate a molecule of **19**. By design, the alcohol in **19** is more nucleophilic due to the electron withdrawing group on the amine. This subsequently can undergo ring opening of (R_S)-**20** and, following proton transfer, afford dimer **271**. A very similar mechanism can be proposed for the formation of dimer **271** in solution with an acid.



Scheme 2.6. Proposed formation of dimer **271**.

After much experimentation, trace levels of dimer **271** were removed from the crude material following efficient filtration through a silica plug and washing with dichloromethane. Pleasingly, there was no change in the diastereomeric ratio of template (R_S)-**20**. The differences in the ^{1}H NMR spectra between the crude material and after the silica plug filtration can be seen in Figure 2.6.

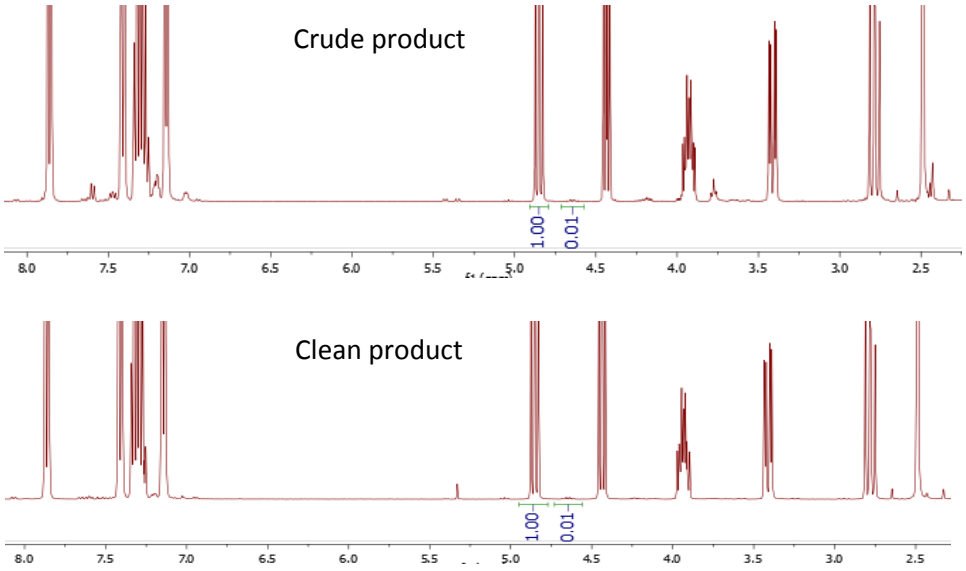
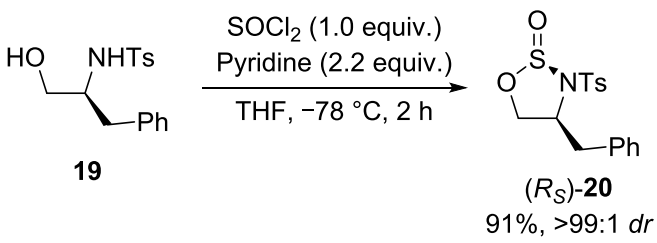


Figure 2.6. Before and after silica plug filtration of template (R_S)-**20**.

In summary, a range of parameters for the reaction of amine **19** with thionyl chloride and pyridine in THF at –78 °C was investigated. Chiral template (R_S)-**20** was afforded in 99% yield in excellent purity on a 66 mmol scale without purification (Top spectrum of Figure 2.6). Although, material of analytical purity was obtained in 91% yield following a second short purification through silica gel (Bottom spectrum of Figure 2.6). This was a significant improvement upon the 77% yield from the original publication that used specialised nitrile end-capped silica gel.[21] The optimised conditions are shown in Scheme 2.7. Furthermore, the reaction time was later reduced to 1 h in accordance with the literature.



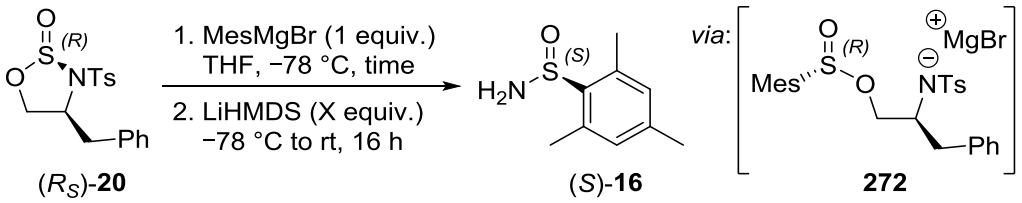
Scheme 2.7. Optimised conditions for the synthesis of template (R_S)-**20**.

2.1.2 Preparation of (*S*)-Mesityl Sulfinamide

With template (R_S)-**20** in hand, sulfinyl transfer *via* addition of a Grignard reagent followed by a second addition of a nucleophilic nitrogen source, which cleaves the sulfinyl moiety from the template, could be investigated. The reaction proceeds with retention of configuration at the sulfur centre.

Indanol-based template (R_S)-**15** had previously been utilised by Senanayake and co-workers to prepare mesityl sulfinamide (*S*)-**16** in 80% yield and >99% *ee* over two steps.[19] Whilst investigating template (R_S)-**20** in 2011, we telescoped these two steps to obtain chiral sulfinamides from such templates (Table 2.2).[21] The telescoped procedure used mesityl magnesium bromide in tetrahydrofuran at –78 °C followed by lithium bis(trimethylsilyl)amide at –78 °C, which was then allowed to warm to room temperature. With this knowledge in hand, it was decided to revisit the reaction so as to maximise the yields of every step in our synthesis.

Table 2.2. Improvement of the mesityl sulfinamide (*S*)-**16** one-pot reaction.

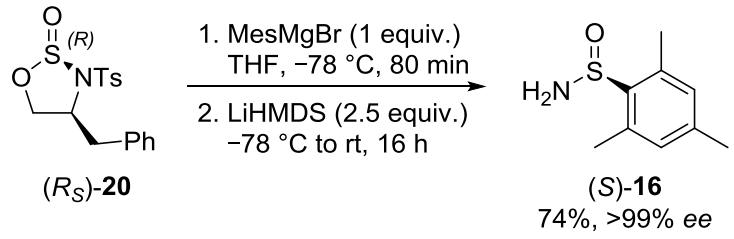


(R_S)-**20** (*S*)-**16** **272**

Entry	time (mins)	X	Yield (%)
1	120	2	63
2	120	2.5	49
3	60	2.5	72
4	80	2.5	74

Initial experiments appeared to suggest that the equivalents of lithium bis(trimethylsilyl)amide had an impact on the yield of the reaction (Table 2.2, entries 1 and 2). Although, it was postulated that the source of the lower yield(s) was more likely due to a second addition of the Grignard reagent thus forming the mesityl sulfoxide. This problem was circumvented by following the reaction more closely by thin layer chromatography and addition of the lithium bis(trimethylsilyl)amide immediately after the template (R_S)-**20** was consumed (Table 2.2, entries 3 and 4). Chiral HPLC demonstrated that the enantiomeric excesses of all samples were >99%.

In summary, the best example of the two-step one-pot reaction gave mesityl sulfinamide (*S*)-**16** in 74% yield and very high enantiomeric excess (Scheme 2.8). Our findings were comparable to the indanol-based template (R_S)-**15**[19] and the norephedrine-based template (R_S)-**18** from Senanayake and co-workers,[20] which both obtained yields of 80%.



(R_S)-**20** (*S*)-**16**
74%, >99% *ee*

Scheme 2.8. Synthesis of sulfinamide (*S*)-**16** from template (R_S)-**20**.

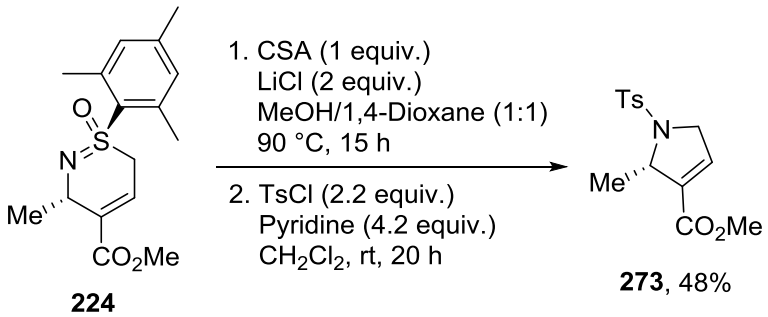
2.1.3 Isolation of the 3-Pyrrolines

With our established methodology to prepare mesityl sulfoximines **262**, a reproducible procedure for the isolation of the 3-pyrrolines **263** was next investigated. The purification of these compounds was found to be extremely

challenging and despite numerous attempts, not discounting attempts by previous members of the Stockman group, the column chromatography originally described could not be reproduced. Therefore, a new method for their isolation was highly sought.

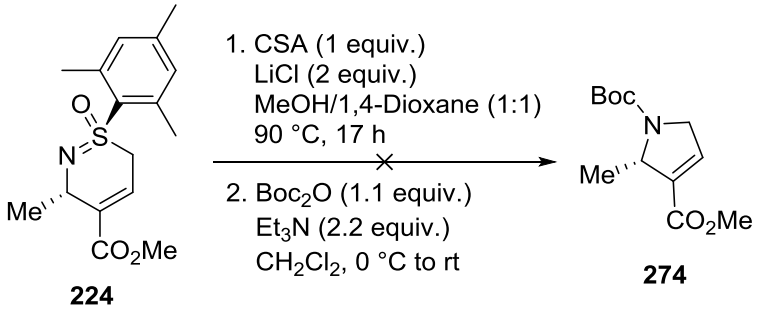
Precipitation of the pyrrolines as their hydrochloride salt was attempted during the initial investigation into this area by the Stockman group. Nevertheless, for completion, this strategy was attempted again. As before, acid-base work up proved unsuccessful due to the high solubility of the unprotected pyrroline.

To continue their formal synthesis of trachelanthamidine, a previous member of the Stockman group isolated pyrroline **273** as the tosylate using tosyl chloride and triethylamine.[128] Using this concept, pyrroline **273** was isolated in a comparable yield (Scheme 2.9). Interestingly, it was found that the stirring rate during the ring contraction step was critical, unless the stirring speed of the hotplate was on maximum (>900 rpm) then the reaction rate was generally very slow.



Scheme 2.9. Ring contraction/tosyl protection to afford pyrroline **273**.

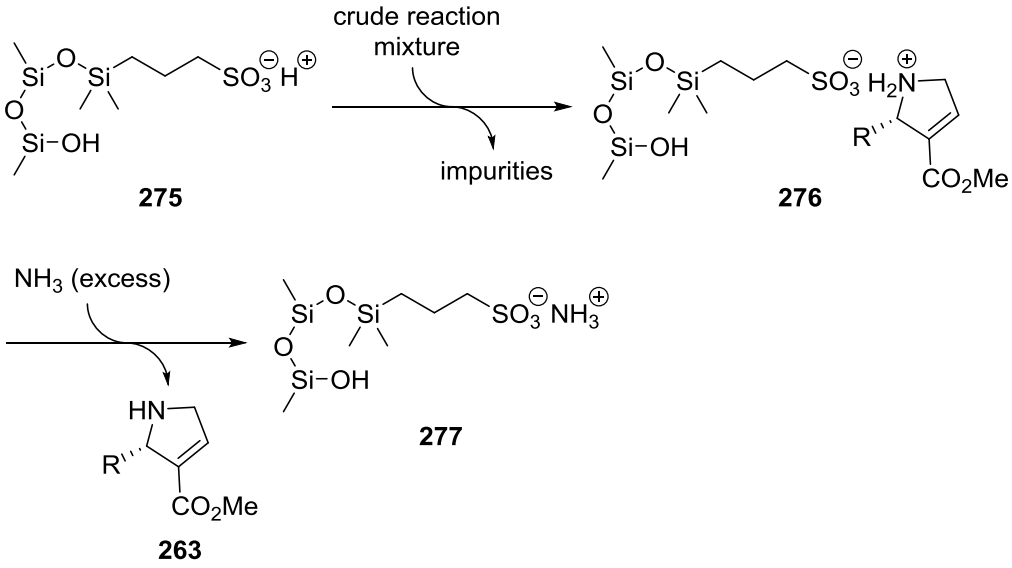
Next, the synthesis of pyrroline **274**, which included a carbamate protecting group, was explored. Following a similar procedure, the crude pyrroline was treated with Boc anhydride and triethylamine, surprisingly however, no product was observed (Scheme 2.10). Replication of the reaction with the addition of catalytic 4-(dimethylamino)pyridine was also unsuccessful. All reactions gave a complex mixture of unrecognisable products.



Scheme 2.10. Attempted Boc protection to afford pyrroline **274**.

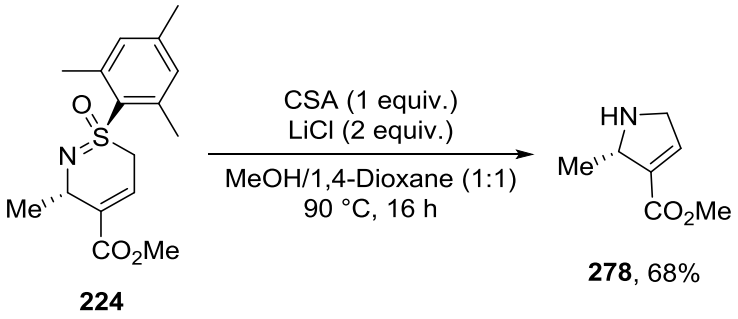
Protection with benzyl was not investigated, due to concern over the removal of the protecting group, as there is literature precedent for the hydrogenation of the alkene in these substrates.[129]

Lastly, the application of a Biotage® cation exchange sorbent ISOLUTE® SCX-2 was investigated.[130] The silica gel is modified with a propylsulfonic acid terminus **275**, designed to extract basic compounds from aqueous solution *via* strong retention after cation exchange **276** (Scheme 2.11). The desired analyte **263** is then eluted by elimination of the charge on the analyte using high pH.



Scheme 2.11. Mechanism of the ISOLUTE® SCX-2 sorbent purification.

Pleasingly, performing an ISOLUTE® SCX-2 extraction on the crude reaction mixture afforded clean pyrroline **278** in 68% yield (Scheme 2.12).



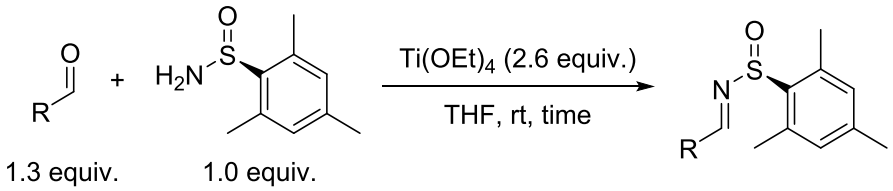
Scheme 2.12. Isolation of pyrroline **278** *via* ISOLUTE® SCX-2 purification.

Overall, the concerns surrounding the feasibility of a protection/deprotection strategy, which would be complicated further should the conditions for deprotection perform unwanted side reactions, were deemed not viable. Moreover, there was the undesirable increase in the number of reaction steps solely for the isolation of clean **263**. Thus, it was decided to use the ISOLUTE® SCX-2 purification due to its simplicity and ease of isolation of our key material.

2.1.4 Scope

In order to explore the two-step telescoped procedure, the synthesis of sulfinimines from readily available or readily accessible aldehydes, was required. Using the well precedented sulfinimine condensation conditions of Ellman and co-workers,[5,46] titanium ethoxide in tetrahydrofuran at room temperature, sulfinimines (**234**, **279**-**289**) were obtained in satisfactory to excellent yields of 41-92% (Table 2.3). In agreement with the literature, all examples were prepared exclusively as the *E*-isomer. It was deemed not necessary to optimise the examples that gave lower yields.

Table 2.3. Scope of mesityl sulfinimine condensation.

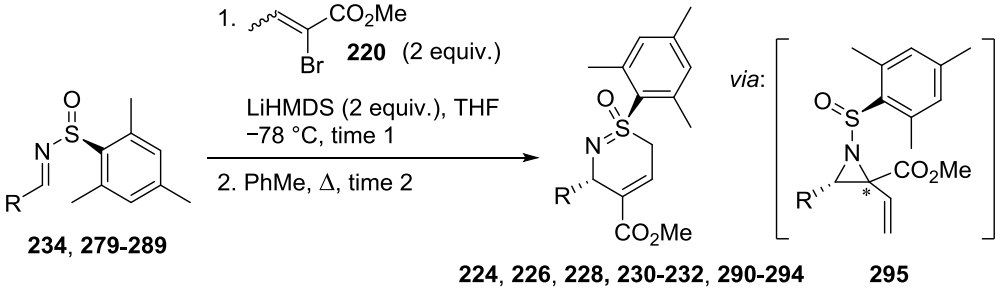


Entry	R	time (h)	Compound	Yield (%)
1	Me	22	**279**	41
2		15	**280**	68
3		15	**281**	56
4	Cl	41	**282**	66
5	TBSO	64	**283**	78
6[a]	TBSO	48	**234**	78
7	BocHN	23	**284**	62
8	CBzHN	22	**285**	68
9	PhthN	18	**286**	66
10		18	**287**	88
11		14	**288**	92
12	Cbz N	69	**289**	71

[a] Performed by Dr. Toni Moragas.

With sulfinimines **234**, **279**-**289** in hand, the scope of the [2,3]-sigmatropic rearrangement of mesityl 2-vinylaziridines to mesityl cyclic sulfoximines was expanded (Table 2.4).

Table 2.4. Scope of the telescoped two-step sulfoximine methodology.



234, **279-289** **224**, **226**, **228, 230-232**, **290-294** **295**

Entry	R	time 1 (h)	Δ (°C)	time 2 (h)	Compound	Yield (%)
1	Me	1.5	70	2	**224**	57
2		3	50	22	**232**	56
3		3.25	50	18	**231**	43
4	Cl	2	70	2	**–**	0
5	TBSO	3	50	21	**290**	52
6[a]	TBSO	3	70[b]	2	**230**	78
7	BocHN	2.5	70	3	**291**	20
8	CBzHN	3	50	6	**292**	34
9	PhthN	2	50	18	**293**	40
10		1.5	50	19	**226**	61
11		2	70	3	**228**	55
12	Cbz N	4	50	6	**294**	42

[a] Performed by Dr. Toni Moragas. [b] Heated at 40 °C for 17 h before heating to 70 °C.

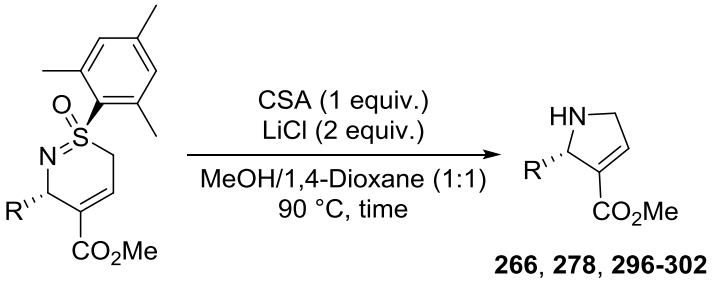
Similarly, the progress of the aziridination was followed by thin layer chromatography and the average reaction duration was 2-3 h (Table 2.4, column 3). The optimal temperature for the mesityl aziridine **295** rearrangement was not elucidated definitively. Initially, a reaction temperature of 40 degrees was used for the TBS-protected butyl alcohol, however, the reaction rate proved too slow and thus the temperature was elevated to 70 degrees for 2 h to push the reaction to completion (Table 2.4, entry 6). Initially, a reaction temperature of 70 degrees was employed. However, if there was a concern about the stability of the substrate/product under the reaction conditions then 50 degrees was employed. Overall, there was no strong evidence to suggest that the lower reaction temperature of 50 degrees was necessary (Table 2.4, column 4).

Alkyl examples were successful, when R = methyl, a 57% yield of sulfoximine **224** was obtained over the 2 steps – which corresponds to 75% per step (Table 2.4, entry 1). Alkyne and alkene substrates were tolerated in 56% and 43% yield, respectively (Table 2.4, entries 2 and 3). In the case of the halide example, the sulfoximine was observed in high yield in the crude ^{1}H NMR spectrum. However, the desired product decomposed prior to, during and post-column chromatography to a complex mixture (Table 2.4, entry 4). TBS-protected propyl and butyl alcohols were obtained, following column chromatography, in good and very good yields of 52% and 78%, respectively (Table 2.4, entries 5 and 6). Mono- and di-substituted amine examples were successful albeit in lower yields of 20-40% (Table 2.4, entries 7-9). More sterically hindered substrates, such as *iso*-propyl and cyclohexyl, were also

tolerated in good yield (Table 2.4, entries 10 and 11). Pleasingly, when R = CBz-protected piperidine, sulfoximine **294** was isolated in 42% yield over 2 steps (Table 2.4, entry 12).

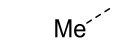
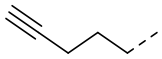
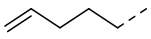
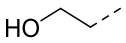
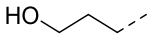
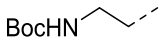
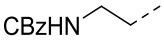
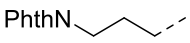
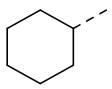
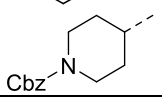
With sulfoximines **224**, **226**, **228**, **230-232**, **290-294** in hand, the scope of the novel ring contraction was expanded and pyrrolines **266**, **278**, **296**-**302** were obtained following SCX-2 purification in 41-80% yield (Table 2.5).

Table 2.5. Scope of mesityl sulfoximine ring contraction methodology.



224, **226**, **228**, **230-232**, **290-294**

266, **278**, **296-302**

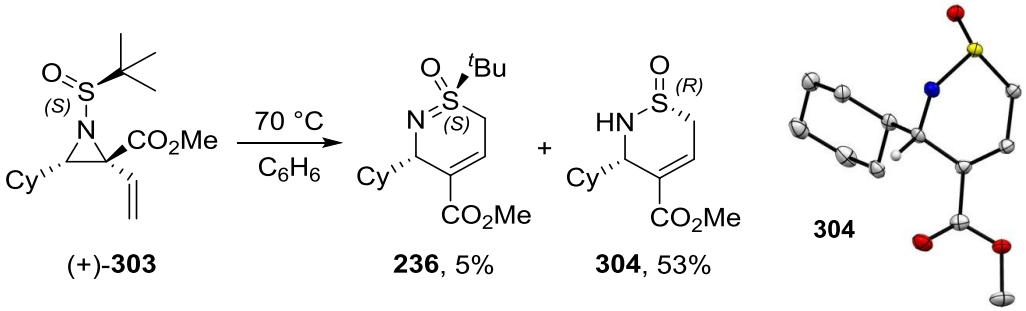
Entry	R	time (h)	Compound	Yield (%)
1		16	**278**	68
2		23	**296**	77
3		18	**297**	72
4		24	–	0
5[a]		25	**266**	80
6		26	–	Not clean
7		19	**298**	80
8		22	**299**	61
9		19	**300**	41
10		18	**301**	57
11		15	**302**	53

[a] Performed by Dr. Toni Moragas.

The ring contraction demonstrated wide applicability for all functional groups tested (Table 2.5). Alkyl (R = methyl) and unsaturated substrates gave good to excellent yields of 68-77% (Table 2.5, entries 1-3). In the next two examples, the *tert*-butyldimethylsilyl groups were deprotected under the reaction conditions before the ring contraction took place. However, only pyrroline **266** was isolated cleanly following column chromatography in an excellent 80% yield – this was one of the rare occasions these compounds were purified by that method successfully (Table 2.5, entry 5). The product isolated from the reaction with the propyl alcohol substrate always gave a complex mixture – this was repeated in triplicate (Table 2.5, entry 4). It was postulated that the pendant alcohol may form the six-membered lactone, which could lead to dimerisation or polymerisation side reactions. Carboxybenzyl- and phthalimide-protected amine pyrrolines were afforded in 80% and 61%, respectively (Table 2.5, entries 7 and 8). Disappointingly, the *tert*-butyloxycarbonyl-protected example contained an impurity and thus a yield, which would have been lower than the other examples, could not be recorded (Table 2.5, entry 6). The identity of the impurity is most likely to be the deprotected Boc compound. Perhaps unsurprisingly, the more sterically hindered examples gave lower yields of 41-57% (Table 2.5, entries 9-11).

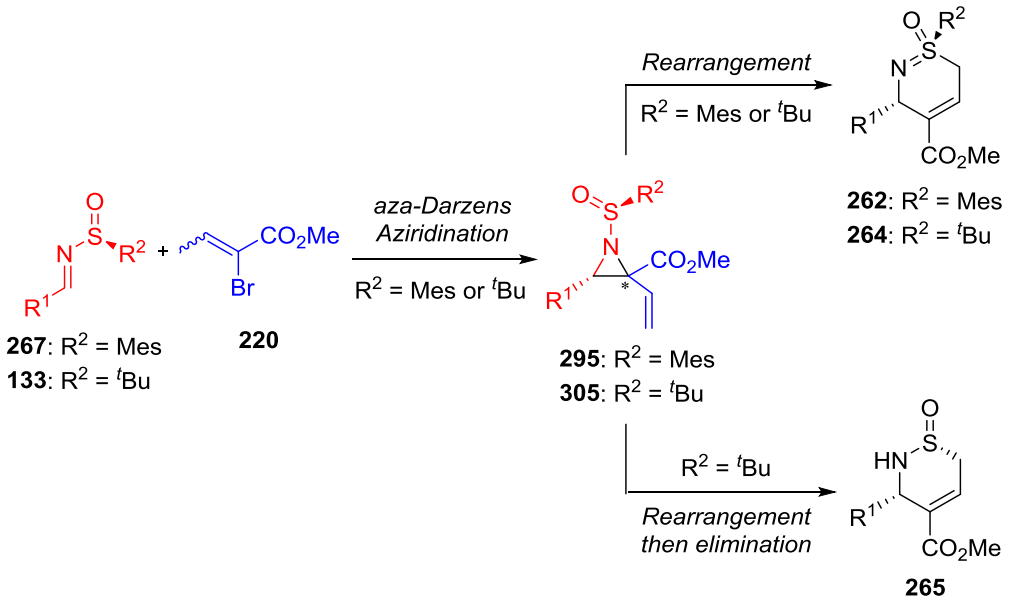
2.2 Preparation of Chiral Cyclic Sulfinamides

Whilst investigating the [2,3]-sigmatropic rearrangement of aziridine **303** we obtained sulfoximine **236** in only 5% yield. [120] On further examination of the reaction mixture, we identified the major product as cyclic sulfinamide **304** and its structure and absolute stereochemistry were confirmed by X-ray crystallography (Scheme 2.13).



Scheme 2.13. Formation of **304** (left) and crystal structure of **304** (right).

As de-*tert*-butylation occurred so readily, it was envisaged that the transformation could be induced in a controlled fashion. Furthermore, there are only a select number of methods for the stereoselective preparation of chiral cyclic sulfinamides (See Chapter 1.1.2.2). The true elegance of our approach would be that either cyclic sulfoximines (**262** and **264**) or cyclic sulfinamides (**265**) could be synthesised using our vinylaziridine (**295** or **305**) to sulfoximine rearrangement methodology – dependent on which set of conditions were used (Scheme 2.14).[120]



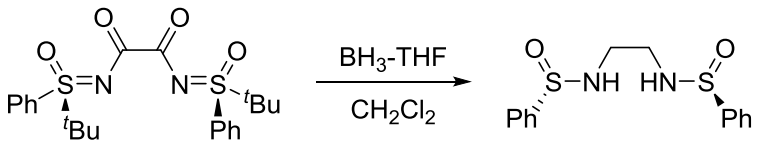
Scheme 2.14. Our approach to sulfoximines **262** and **264** and sulfinamides **265**.

As we have already published our work on mesityl cyclic sulfoximines **262** (See Chapter 1.2.3.1),[120] it was decided to investigate further the de-*tert*-butylation of our *tert*-butyl cyclic sulfoximines **264** (Scheme 2.13). Our methodology would ideally be to remove the *tert*-butyl group from our cyclic sulfoximines **264** at room temperature under mild, non-anhydrous or air sensitive conditions to afford cyclic sulfinamides **265**. The investigation into the de-*tert*-butylation of the *tert*-butyl sulfoximines **264** to cyclic sulfinamides **265** and our postulations regarding the mechanism, that facilitated the loss of the *tert*-butyl group, is presented herein.

2.2.1 Chemically-induced de-*tert*-butylation

Chemically-induced de-*tert*-butylation is well known in the literature (See Chapter 1.1.1.3 and Chapter 1.1.2.2), with a comprehensive review on the subject published by Gaillard and co-workers in 2005.[24] Of these, the most interesting was that of Bolm and co-workers who observed the serendipitous

de-*tert*-butylation of bissulfoximine **306** whilst attempting to reduce the two amide groups with borane (Scheme 1.7).[123] Instead, bissulfinamide **307** was isolated in good yield.

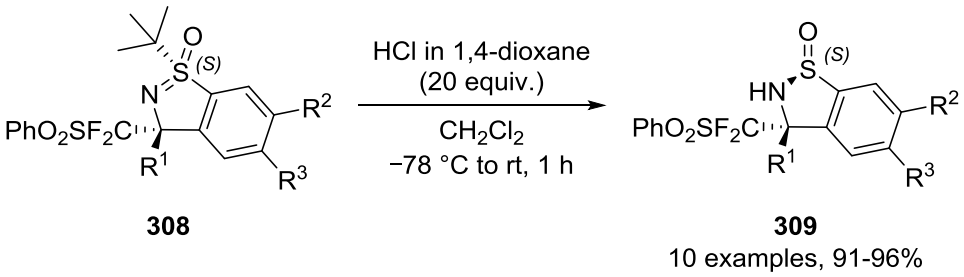


306 **307**, 60%

Scheme 1.7. Serendipitous de-*tert*-butylation of **306** using borane.

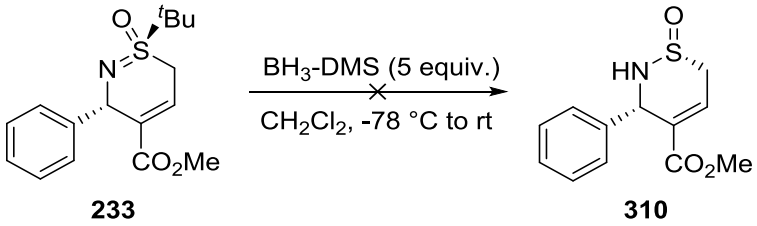
The review by the Gaillard group included their own investigations into de-*tert*-butylation conditions (Table 1.2).[24] These centred around the application of metal hydrides (such as lithium aluminium hydride and sodium borohydride) as bases and Lewis acids (such as metal(II) halides of zinc, magnesium and copper, as well as magnesium perchlorate). Overall, their attempts were not very successful and therefore their findings appeared inconclusive. It is understandable why Gaillard and co-workers did not investigate strong bases as *n*-butyllithium was used to perform the lithium-halogen exchange, prior to electrophilic trapping.

Later in 2014, Hu and co-workers promoted the de-*tert*-butylation of sulfoximines **308** with excess hydrochloric acid to afford cyclic sulfinamides **309** (Scheme 1.18).[38]



Scheme 1.18. Removal of the *tert*-butyl group to obtain cyclic sulfinamide **309**.

With this knowledge of the literature in hand, we first chose to follow the procedure of Bolm and co-workers,[123] unfortunately, the experimental procedure for the transformation was not disclosed in either Bolm's or Gaillard's publication. Therefore, sulfoximine **233** was treated with excess borane in dichloromethane at –78 °C to room temperature, disappointingly, no product **310** was observed (Scheme 2.15).



Scheme 2.15. Attempted de-*tert*-butylation of **233** using borane.

Various conditions for de-*tert*-butylation were investigated by the Gaillard group. One such method employed a strong reducing agent as a base: excess lithium aluminium hydride (3 equivalents) in tetrahydrofuran at 20 °C for 24 h.[24] When these conditions were applied to our substrate **311** consumption of the starting material was observed after 5 h but, following a Rochelle salt work-up, a complex mixture of products was isolated. Interestingly, mass spectrometry analysis identified two products which were related to the

starting material and desired product (Figure 2.7). Alcohol **312** would be afforded by 1,4-addition of hydride to the double bond followed by complete ester reduction. Similarly, **313** would be obtained by de-*tert*-butylation to the desired product followed by 1,4-addition of hydride and then complete ester reduction.

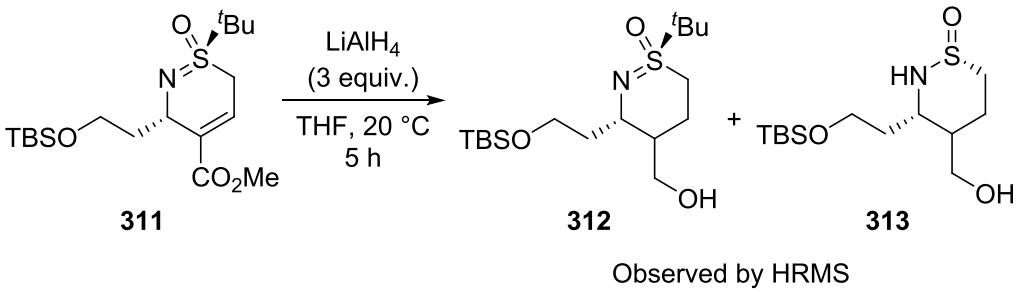


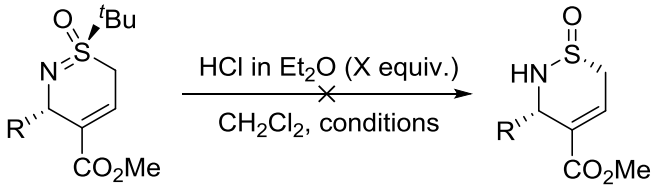
Figure 2.7. 1,2-Addition and 1,4-addition products.

Furthermore, the use of milder bases such as potassium *tert*-butoxide and sodium hydroxide led to decomposition of the starting material. When *tert*-butoxide was used the decomposition product, observed by mass spectrometry, no longer contained a sulfinyl group. Similarly, in the reaction with sodium hydroxide, ^{1}H NMR analysis revealed a decomposition product with two alkenes that did not contain the sulfinyl-amide functional group, which is known in the literature.[131] In addition, the ester hydrolysis product was observed by mass spectrometry and ^{1}H NMR analysis.

As described earlier, Hu and co-workers used excess hydrochloric acid to facilitate de-*tert*-butylation (Scheme 1.32).[38] When this reaction was carried out on our substrate **311** however, a complex mixture was observed (Table 2.6, entry 1). In the case of **166**, when the equivalents of hydrochloric acid

were reduced and the temperature of the reaction increased to room temperature, a small amount of the desired product was detected by ^{1}H NMR spectroscopy (Table 2.6, entry 2).

Table 2.6. Attempted de-*tert*-butylation using excess hydrochloric acid.

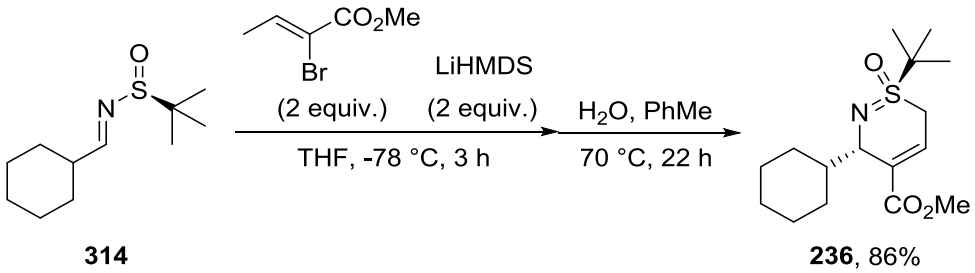


Entry	R	Substrate	X	Conditions	Observations
1	TBSO	**311**	20	–78 °C to rt	Complex mixture
2	Me	**166**	2	rt	Complex mixture Product observed by ^{1}H NMR

After reviewing the results of the above experiments, it was concluded that an in-depth thermal study of the observed de-*tert*-butylation of cyclic sulfoximines **264** was prudent as the desired transformation occurred under those conditions.

2.2.2 Thermal Study

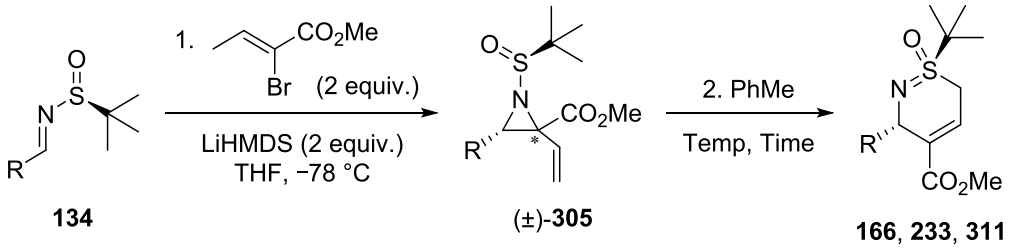
In order to carry out a thermal study, we first needed to prepare the *tert*-butyl sulfoximine starting materials. Thus, using the one-pot procedure previously reported by the Stockman group on readily accessible *tert*-butyl sulfinimines (Table 1.10),[120] sulfoximine **236** was obtained in an improved 86% yield (Scheme 2.16). An early modification was the use of toluene instead of benzene. It should be noted that this reaction used tetrahydrofuran that had not been dried either by sodium wire, solvent towers or by a tetrahydrofuran-sodium still.



Scheme 2.16. One-pot preparation of sulfoximine **236** in high yield.

Even though the one-pot procedure afforded moderate to very good yields for the examples previously investigated (Table 1.10), we were interested in alternative conditions for the rearrangement of vinylaziridine (±)-**305** to cyclic sulfoximines **166**, **233** and **311** (Table 2.7).

Table 2.7. Alternative conditions for the vinylaziridine (±)-**305** rearrangement.



Entry	R	Temp (°C)	Time	Product	Yield (%)
1	Me	30	9 days	**166**	60
2	TBSO	30	70 h	**311**	38
3		40	8 days	**233**	22

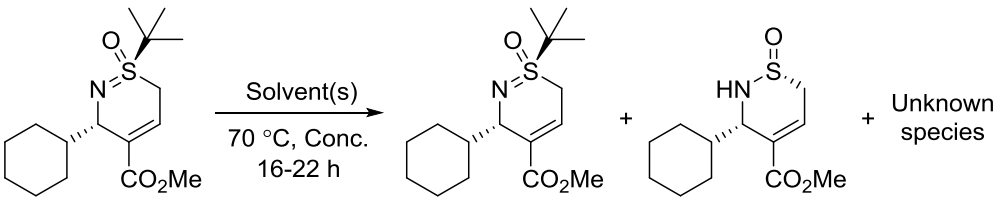
In general, reaction times were greatly increased with only a small improvement in the yields. When R = methyl, the yield of **166** was improved from 45% (Table 1.9, entry 10) to 60%. Unfortunately, the reaction time dramatically increased from 23 h to 9 days (Table 2.7, entry 1). When R = phenyl, the yield of **233** was slightly improved from 16% (Table 1.9, entry 11)

to 22%, with the reaction time increasing by almost a factor of two – from 4.5 days to 8 days (Table 2.7, entry 3). Moreover, the extended reaction times did not necessarily lead to full consumption of the starting material.

As optimisation of the sigmatropic rearrangement step proved to be ineffective, *tert*-butyl sulfoximines **264** were prepared using the one-pot procedure described previously in Scheme 2.16.

To ascertain why the conditions of the one-pot procedure led to exclusive isolation of the sulfoximine, a degradation study was designed. It is conceivable that the *tert*-butyl sulfoximines **236** would be stable if subjected to the same conditions that led to its formation, following the rearrangement of its respective vinylaziridine. The resilience of sulfoximine **236** to degradation under a wide range of conditions is shown in Table 2.8.

Table 2.8. Degradation study of *tert*-butyl sulfoximine **236**.



236 **236** **304** **315**

Entry	Solvent(s)	Conc. (M)	**236**:**304**:**315**[a] (%)	Total (%)
1	PhMe/THF/Water 10:5:1	0.017	74 : 20 : 0	94
2	PhMe/THF/Water 10:5:1 (repeat)	0.017	65 : 30 : 0	95
3	PhMe/THF 2:1	0.017	79 : 4 : 1	84
4	PhMe	0.017	73 : 18 : 0	92
5	PhMe (repeat)	0.017	52 : 35 : 0	87
6	PhMe/THF/Water 10:5:1	0.10	83 : 5 : 1	89
7	PhMe/THF/Water 10:5:1 (repeat)	0.10	48 : 40 : 3	90
8	PhMe/THF 2:1	0.10	27 : 41 : 7	75
9	PhMe	0.10	27 : 47 : 2	76

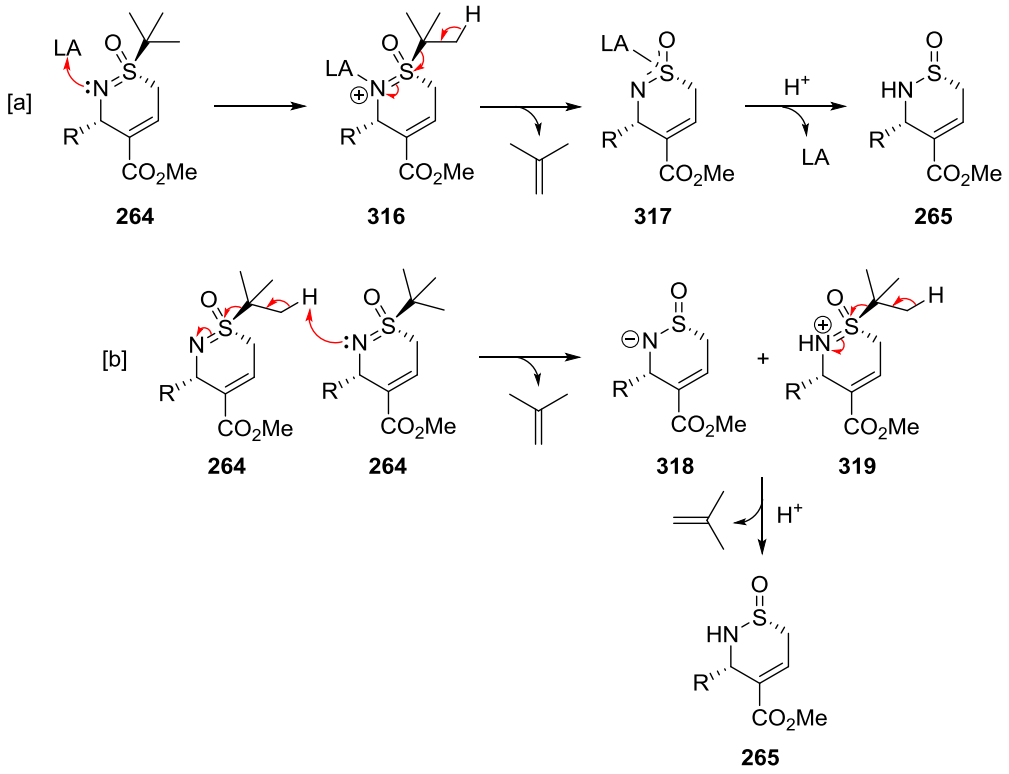
[a] Determined from the crude ^{1}H NMR spectrum using pyrazine as an internal standard. Complete recovery was assumed so as to derive the ratio of the products.

Replication of the conditions at the end of the one-pot reaction agreed favourably (Table 2.8, entry 1). It was not overlooked that there would be impurities remaining in the reaction mixture from the aziridination step. Sulfoximine **236** was also the prominent product when the reaction was carried out without water or without tetrahydrofuran and water (Table 2.8, entries 3 and 4 respectively). In general, when the concentration of the reaction mixture was increased to 0.10 M then sulfinamide **304** was observed in higher quantities (Table 2.8, entries 6, 8 and 9). It was noted that a third species **315**, that was related to **304**, was observed in the reaction but the identity could not be elucidated at this stage.

If this study was indeed the correct method for evaluating the observed anomaly with the one-pot reaction, then there is a case for dilution as the prominent factor (Table 2.8, entries 1-5). It is conceivable therefore that an intermolecular de-*tert*-butylation mechanism is a possibility. However, there was a major concern about the reproducibility of the experiments (Table 2.8, compare entries 1 and 2, 4 and 5, 6 and 7).

We postulated that a ^{1}H NMR spectroscopy study would give a better understanding of the reaction profile and mechanism – such as the presence of reaction intermediates. The parameters examined were the application of heating (40 °C) and the addition of a Lewis acid (boron trifluoride). Performing the reaction at 40 °C would allow the reaction profile to be easily monitored as high levels of de-*tert*-butylation are observed at higher temperatures, such as 70 °C. It was envisaged that a Lewis acid would remove electron density

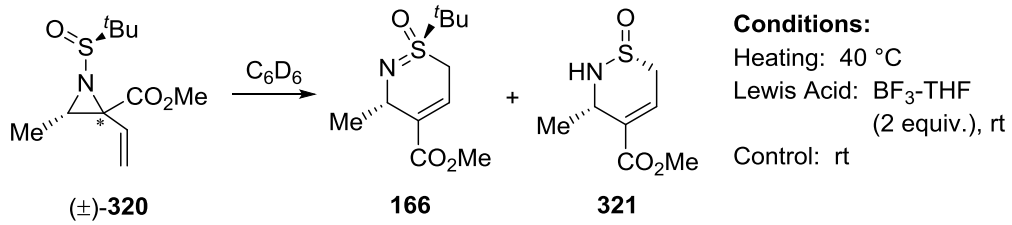
from the sulfur of sulfoximine **264**, thereby leading to a cascade that liberates isobutene from **316** to afford **317**, which allows access to **265** during the work-up (Scheme 2.17 – mechanisms [a]). However, the preliminary results from the one-pot reaction study suggest dilution is a factor (Table 2.8). This means an intermolecular deprotonation of the *tert*-butyl group could not be discounted at this stage (Scheme 2.17 – mechanism [b]). In the intermolecular process, sulfoximine **264** abstracts a proton from another molecule of **264** *via* the more Lewis basic nitrogen to give **318** and **319**. Thus, following elimination of isobutene and proton transfer to **318** affords two molecules of **265**.



Scheme 2.17. Plausible mechanisms for the loss of the *tert*-butyl group: [a] Lewis acid facilitated. [b] Intermolecular.

The progress of the reaction was monitored at intervals by ^{1}H NMR spectroscopy. The percentage conversion was determined by integration of the characteristic peaks of aziridine (±)-**320**, sulfoximine **166** and sulfinamide **321** (5.48 ppm, 6.67 ppm and 6.53 ppm, respectively) relative to one another – not against an internal standard.

In summary the experiments were: heating at 40 °C, addition of 2 equivalents of boron trifluoride and a control at room remperature. All experiments were ran in deuterated benzene and the latter experiments were ran at room temperature (19 °C) (Scheme 2.18).



Scheme 2.18. NMR study into de-*tert*-butylation of sulfoximine **166**.

The results for the control and heating at 40 °C are shown below in Figure 2.8 and Figure 2.9, respectively. Due to the facile rearrangement of the major diastereomer (+)-**320** of the aziridine to sulfoximine **166**, the integration of sulfoximine **166** at the start of the experiments was not zero.

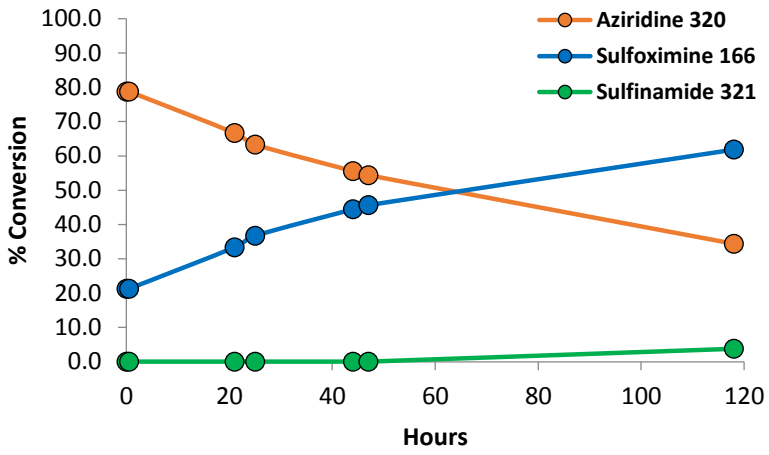


Figure 2.8. Thermal study – control experiment.

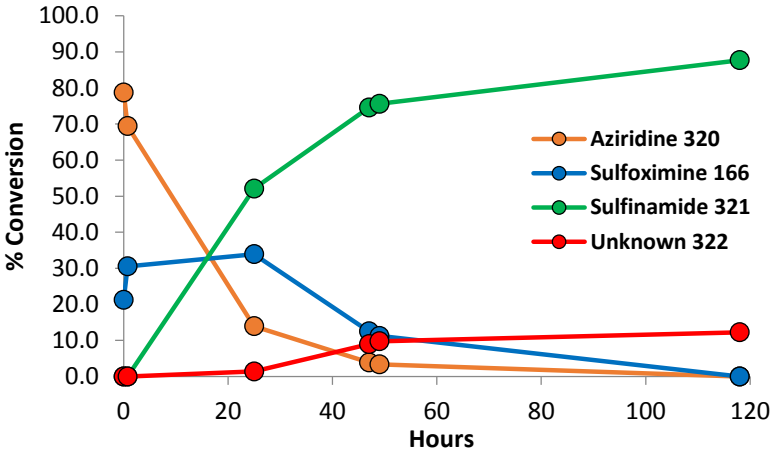


Figure 2.9. Thermal study – 40 °C experiment.

In the control experiment, there was slow conversion of aziridine (±)-**320** to sulfoximine **166** (Figure 2.8), between 48 and 120 hours approximately 4% conversion to sulfinamide **321** was observed**.** Heating the reaction at 40 °C greatly accelerated both rearrangement and elimination processes (Figure 2.9). After 49 hours approximately 83% of the reaction mixture was sulfinamide **321**. Initially, the amount of sulfoximine **166** increased between 0 and 25 h, after which time the de-*tert*-butylated product **321** became the major species.

As was observed in the degradation study of **236** (Table 2.8), between 24 and 48 hours, an unknown species **322** was observed in a significant quantity and thus could not be disregarded (Figure 2.9). The unknown species **322** was not noticed in the 24 hour NMR spectrum, however, by the end of the reaction only sulfinamide **321** and unknown **322** were present in an approximate ratio of 9:1.

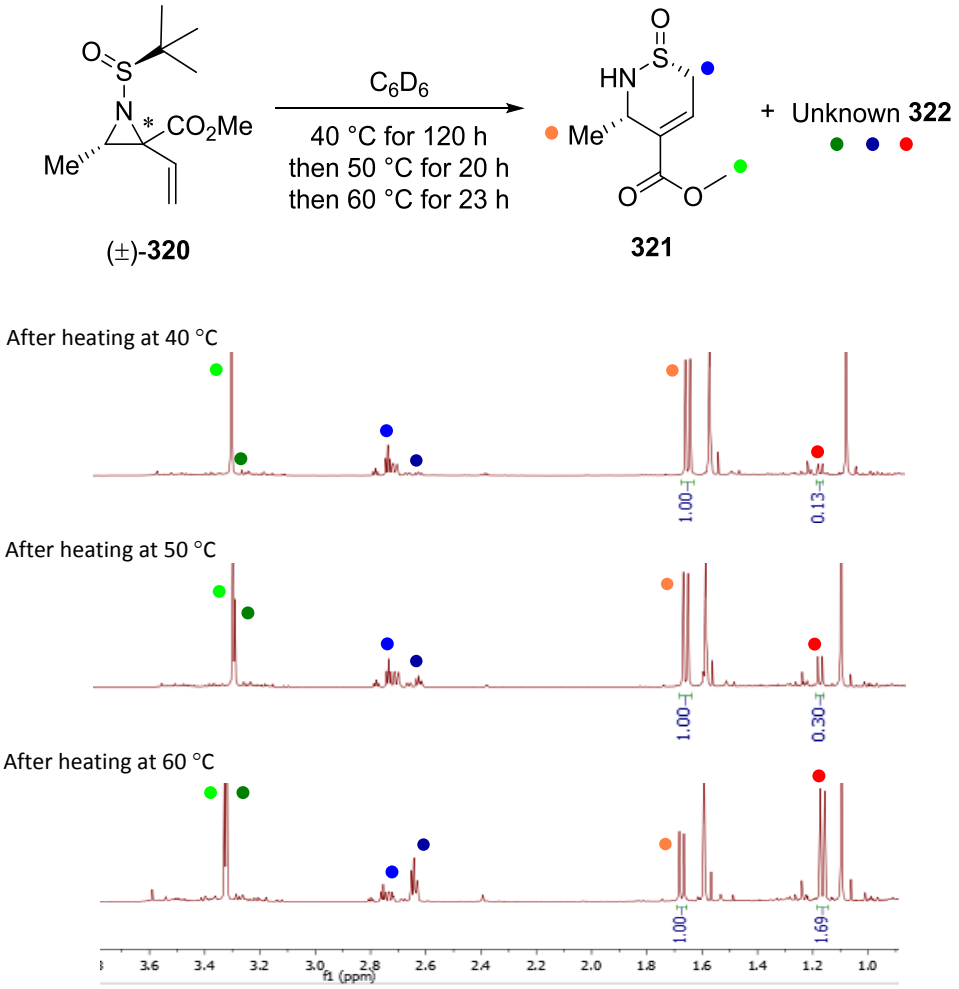


Figure 2.10. Monitoring of the formation of unknown **322** by ^{1}H NMR analysis.

To ascertain if the unknown **322** was formed by heating, the sample from the 40 °C experiment was heated at 50 °C for 20 h (Figure 2.10). The top spectrum in Figure 2.10 shows the levels of **321** and unknown **322** after the experiment

at 40 °C (Figure 2.9). The ratio of sulfinamide **321** and unknown **322** increased from 7.7:1 to 3.3:1 (Figure 2.10, middle spectrum). As expected, heating the sample again at 60 °C for 23 h increased the ratio of sulfinamide **321** and unknown **322** from 3.3:1 to 3:5 (Figure 2.10, bottom spectrum).

In the Lewis acid experiment, after 5 minutes a new product was formed. Mass spectrometry identified a single product with a *m/z* of 328 and the ^{1}H NMR spectrum did not resemble any of the three known compounds of the previous reaction (Figure 2.11). The *m/z* of the new product was 84 mass units higher than the starting material. These observations were attributed to an addition of deuterated benzene under the reaction conditions, *via* an electrophilic aromatic substitution-like mechanism, which would afford either **323** or **324**.

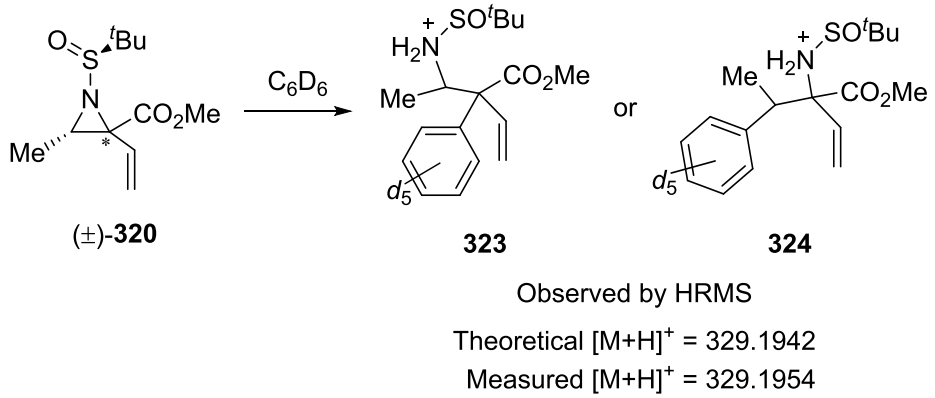
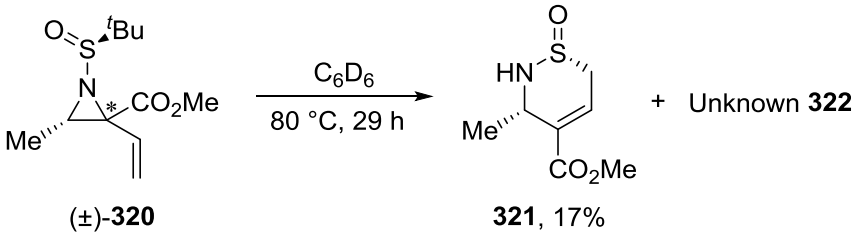


Figure 2.11. Proposed additions of d_6-benzene into aziridine (±)-**320**.

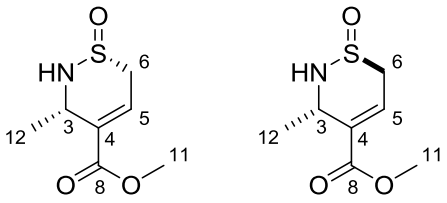
To determine the identity of unknown **322**, a sample of aziridine (±)-**320** was heated in deuterated benzene at 80 °C for 29 h (Scheme 2.19).



Scheme 2.19. Isolation of the unknown **322**.

It was postulated that unknown **322** could be the other diastereoisomer of sulfinamide **321**. Following careful chromatography, the two products were successfully separated and by comparison of the analytical data the identity of unknown **322** was tentatively assigned as the other diastereoisomer (Table 2.9).

Table 2.9. Comparison of the NMR data of sulfinamide **321** and proposed **322**.



321 **322**

Entry	Proton	Sulfinamide **321** (ppm)	**322** (ppm)	Δ (ppm)
1	3	4.03-3.92	4.40-4.27	0.36
2	5	6.58	6.59-6.48	0.04
3	6	2.88-2.70	2.66-2.52	0.20
4	11	3.33	3.30	0.03
5	12	1.71	1.09	0.62

Entry	Carbon	Sulfinamide **321** (ppm)	**322** (ppm)	Δ (ppm)
1	3	46.8	42.7	4.1
2	4	132.9	133.3	0.4
3	5	128.0	127.7	0.3
4	6	48.4	48.1	0.3
5	8	165.3	165.4	0.1
6	11	51.4	51.3	0.1
7	12	24.4	20.8	3.6

A large change in the environments of the protons at the 3 position, 6 position and 12 position were observed (Table 2.9, entry 1, 3 and 5, respectively). For example, the chemical shifts of the methyl group (proton 12) of sulfinamide **321** and the proposed **322** exhibit a $\Delta\ \delta_H$ of 0.62 ppm (Table 2.9, entry 5). Protons 5 and 11 had an almost identical chemical shifts which may be expected if **322** was indeed the other diastereisomer of **321** (Table 2.9, entry 2 and 4, respectively).

Furthermore, the chemical shifts of the carbons of both molecules compare very favourable to each other (Table 2.9). The only notable shifts were those of carbon 3 and carbon 12 which each exhibited a $\Delta\ \delta_C$ of approximately 4.0 ppm (Table 2.9, entry 1 and 7, respectively).

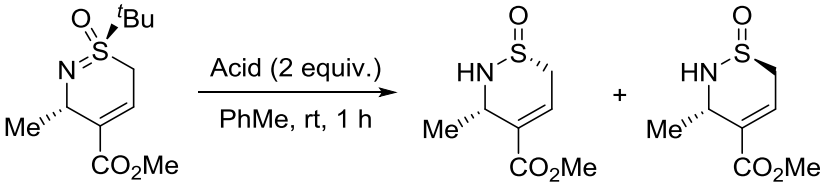
In conclusion, the evidence from the NMR data along with the identical *m/z* provided by mass spectrometry analysis and very similar infrared spectra, were indicative of diastereoisomers with inversion of stereochemistry at the sulfur centre or at the carbon centre alpha to the nitrogen.

In addition, the reaction temperature for the aziridine (±)-**305** rearrangement and sulfoximine **264** elimination was screened in 10 degree intervals from 30 to 100 degrees by Dr. Ryan Liffey.[128] The naphthyl example of aziridine (±)-**305** was stirred in toluene at each temperature – in triplicate – and the yield determined using an internal standard. We concluded that 50 degrees was the best compromise of reaction time versus degradation.

2.2.3 Chemical Study – Brønsted Acids

The next avenue in our investigations into the elimination of the *tert*-butyl group was the use of Brønsted acids. After much experimentation with the number of equivalents of trifluoroacetic acid (0.1-2 equivalents), the number of equivalents appeared to only have an effect on the reaction time. Sulfoximine **166** was treated with each acid in toluene at room temperature and the results are shown in Table 2.10 and are displayed in Figure 2.12.

Table 2.10. Acid screen for the de-*tert*-butylation of sulfoximine **166**.



166 **321** **322**

Entry	Acid	pK_a	**166** (%)	**321** (%)	**322** (%)
1	acetic acid (AA)	4.8	89.7	5.7	-
2	benzoic acid (BA)	4.2	92.9	6.6	-
3	4-nitrobenzoic acid (4-NBA)	3.4	83.6	6.1	-
4	*ortho*-phosphoric acid (o-PA)	2.1	12.3	46.6	-
5	dichloroacetic acid (DCA)	1.3	-	67.2	9.8
6	camphorsulfonic acid (CSA)	1.2	-	56.3	10.7
7	trichloroacetic acid (TCA)	0.7	-	67.1	11.4
8	trifluoroacetic acid (TFA)	-0.2	14.6	60.9	7.9
9	hydrochloric acid (HCl)	-8.0	-	22.9	2.7

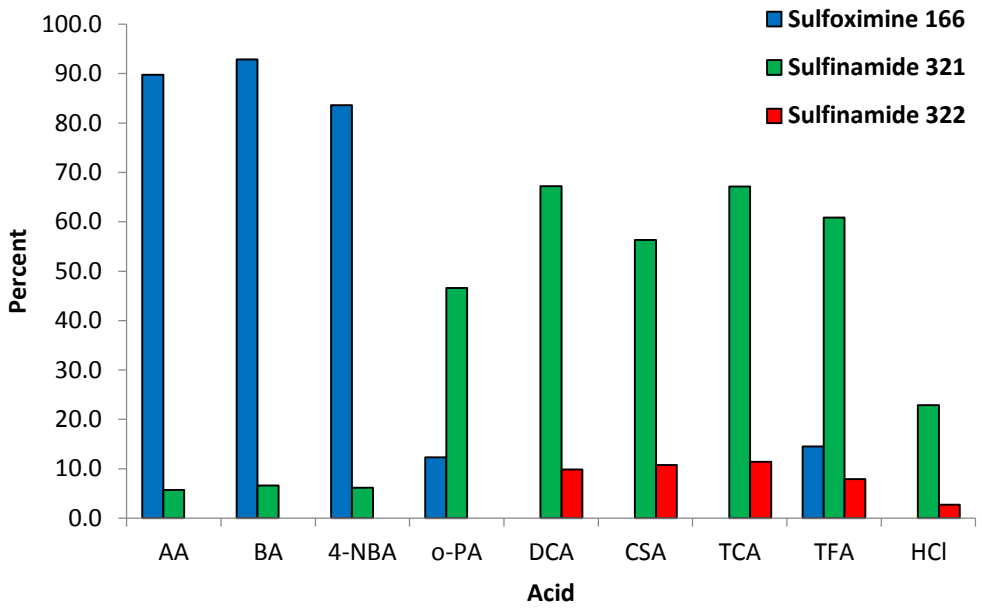
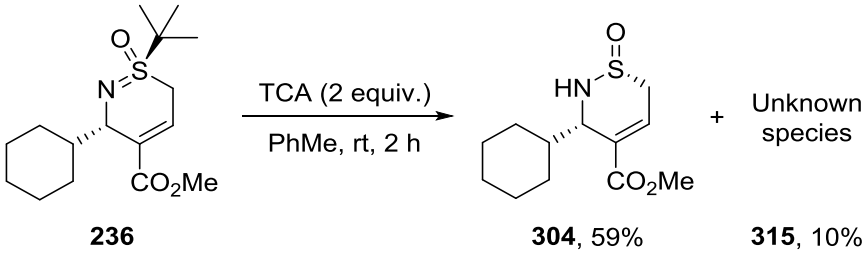


Figure 2.12. Isolation of known compounds from the acid screen.

Organic acids with a pK_a value between 3.4 and 4.8 afforded low conversion of **166** to **321** (Table 2.10, entries 1-3). Phosphoric acid was the only acid that appeared to afford only **321** (Table 2.10, entry 4). However, when this experiment was repeated with a 3 h reaction time, a ratio of **321** and **322** of 5:3 was obtained. The stronger organic acids afforded significant levels of **322** (Table 2.10, entries 5-8). Surprisingly, after 1 h the reaction with trifluoroacetic acid still contained unreacted sulfoximine **166** (Table 2.10, entry 8). Moreover, the same result was obtained on replicate. For comparison, when a strong mineral acid such as hydrochloric acid was used, very high levels of degradation were observed (Table 2.10, entry 9). It should be noted that mass recovery was significantly higher in reactions where **166** was the major product (Table 2.10, entries 1-3). This was attributed to difficulty extracting **321** from the aqueous phase during the work-up.

In order to unequivocally assign the relative stereochemistry of what was tentatively assigned as the other diastereoisomer of **321**, it was imperative that we obtained a crystal structure. As discussed earlier, the experiments with the cyclohexyl sulfoximine **236** also gave a mixture of products (Table 2.8). Therefore, employing 2 equivalents of trichloroacetic acid in toluene at room temperature, full consumption of **236** was observed within 2 h (Scheme 2.20). The ratios of the diastereoisomers was 92:8 in the crude ^{1}H NMR spectrum. Meticulous chromatography afforded **304** in 59% yield and **315** in 10% yield, which corresponds to an isolated 86:14 *dr*.



236 **304**, 59% **315**, 10%

Scheme 2.20. Isolation of unknown **315**.

With sufficiently pure **315** in hand, the X-ray crystal structure shown in Figure 2.13 was obtained. The crystal structure confirmed our hypothesis that unknown species **322** (R = methyl) and **315** (R = cyclohexyl) were indeed the other diastereomers **321** and **304** respectively – with the opposite stereochemistry at the sulfur stereocentre.

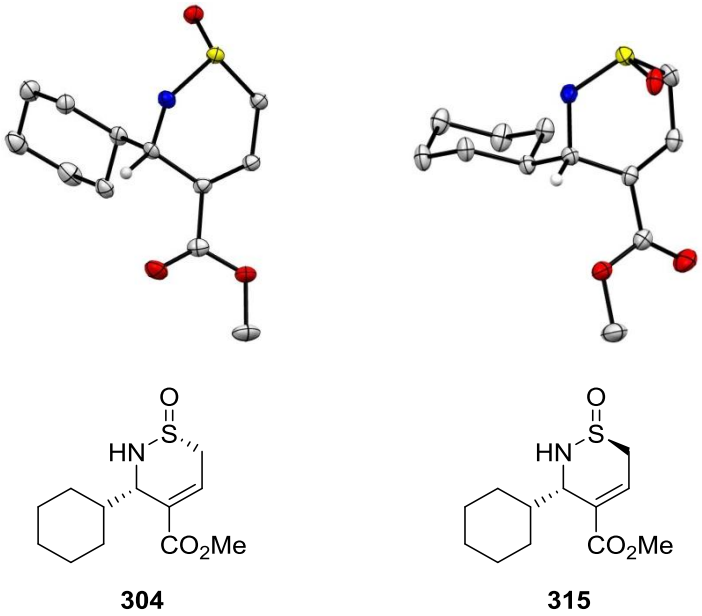
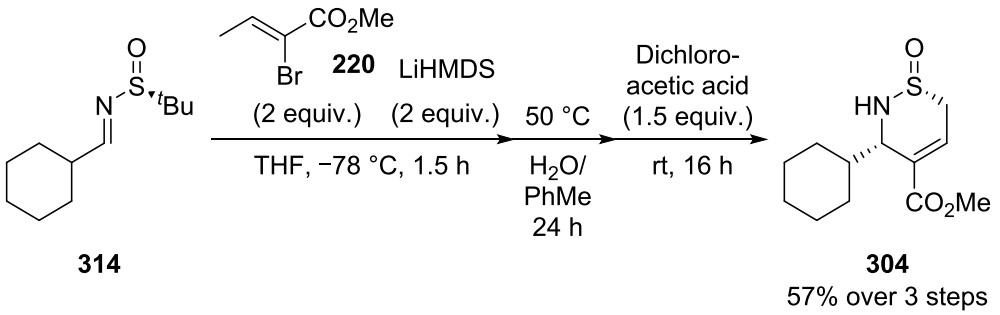


Figure 2.13. Crystal structures of sulfinamide **304** and sulfinamide **315**.

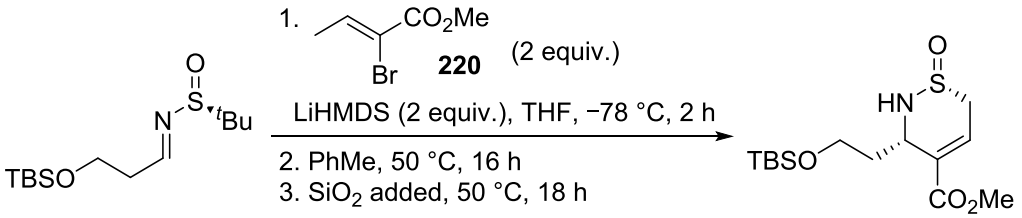
In order to demonstrate the potential of using an acid to de-*tert*-butylate the sulfoximines (**264**), dichloroacetic acid was employed in a one-pot reaction to afford **304** (Scheme 2.21). Pleasingly, when R^1 = cyclohexyl, sulfinamide **304** was obtained in 57% yield over 3 steps. The rationale behind using dichloroacetic acid was that it was the mildest acid that achieved full conversion. After each reaction the crude product was used in the next step without purification. Sulfinamide **304** was observed in the crude ^{1}H NMR spectrum in a 92:8 *dr*. In this case, minor diastereoisomer **315** was not isolated.



314 **304**
57% over 3 steps

Scheme 2.21. One-pot preparation of **304** using dichloroacetic acid.

It was found that the *tert*-butyl sulfoximines **264** were not stable on silica gel. Thus, despite there being no literature precedent for the use of silica gel in this fashion, the application of silica gel as a de-*tert*-butylation agent was explored. Sulfinimine **324** was subjected to a telescoped three-step procedure, with a work-up only after the aziridination, which afforded **325** in a modest 36% yield (Scheme 2.22). It was postulated that the acidic reaction conditions led to deprotection of the alcohol thereby lowering the yield.



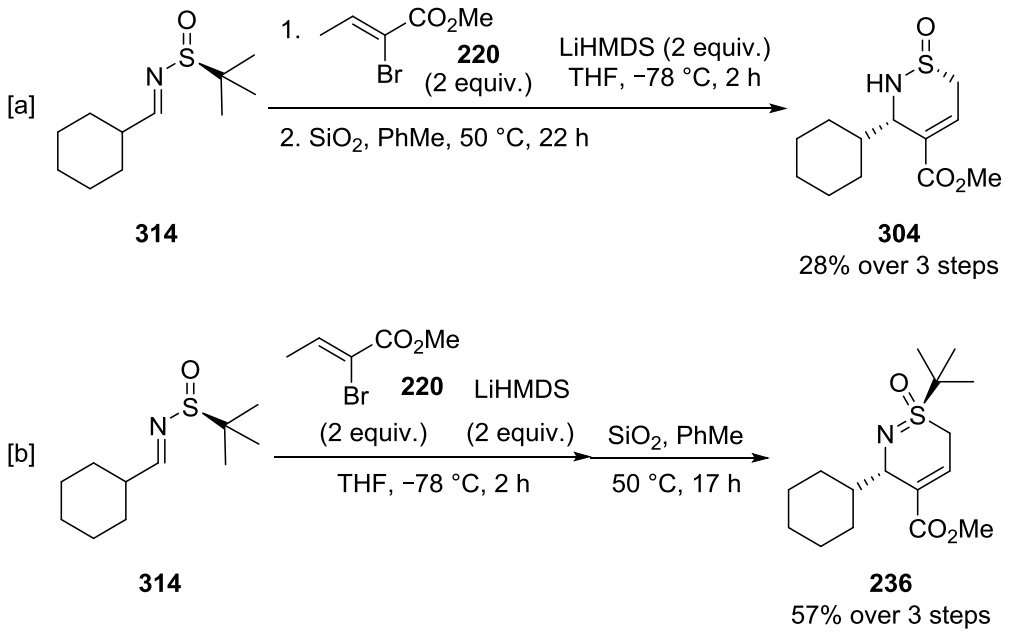
324 **325**
36% over 3 steps

Scheme 2.22. One-pot preparation of sulfinamide **325** using silica gel.

After much experimentation combining reaction steps, the second and third generations of the method gave very mixed results (Scheme 2.23). These iterations took the form of a two-step telescoped procedure and a one-pot procedure represented by reaction [a] and [b], respectively. In the two-step procedure a work-up was performed after the aziridination. Whereas in the

one-pot procedure, silica gel was used with a dual purpose: to quench the aziridination and to act as the de-*tert*-butylating agent.

Pleasingly, the two-step procedure gave sulfinamide **304**, albeit in 28% over 3 steps and with the same 92:8 *dr* in the crude ^{1}H NMR (Scheme 2.23, reaction [a]). In stark contrast, the one-pot procedure gave sulfoximine **236** in a 57% yield over 3 steps. This result was analogous to the intentional one-pot preparation of sulfoximine **236** in Scheme 2.16.[120] The one-pot reaction with silica gel was replicated using sulfinimine **324** and sulfinamide **325** was isolated in an identical 57% yield.



Scheme 2.23. Telescoped two-step preparation of sulfinamide **304** and unexpected one-pot preparation of sulfoximine **236**.

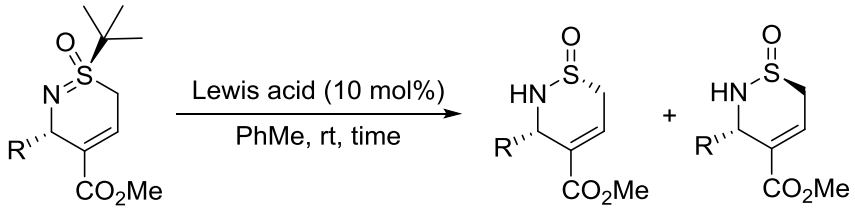
Lastly, it was postulated if a solid-supported acid resin could be used to achieve the elimination. Using **236**, Amberlyst® 15 resin gave a 93:7 mixture of diastereoisomers of **304** and **315**.

2.2.4 Chemical Study – Lewis Acids

Elucidation of the structure of sulfinamide **315** and **322** was very pleasing, however, we were not satisfied with the moderate product recovery (Table 2.10) and the consistent *dr* (Figure 2.9) afforded by the previous studies. Not deterred by the result with boron trifluoride (Figure 2.11), we believed metal Lewis acids were our best approach as metal ions (such as Ni^{2+}, Cu^{2+} and Zn^{2+}) have been used to acidify amide hydrogens by coordination through the amide terminus of amino acid residues in peptides.[132–134] Based on this literature, it is conceivable that a metal ion could coordinate with the oxygen and nitrogen of sulfoximine **264** thereby making the sulfur more electropositive (Scheme 2.17). This facilitates the elimination of isobutene from **316** and forms either a formal bond or interaction with the metal (**317**). Once the heteroatom-metal bond is exchanged for a nitrogen-hydrogen bond, hence making the process catalytic, product **265** is afforded.

The Lewis acid promoted de-*tert*-butylation of **264** was investigated using 10 mol% of the Lewis acid in toluene at room temperature (Table 2.11).

Table 2.11. De-*tert*-butylation induced by Lewis acids.



264 **265** **326**

Entry	R	Lewis acid	Time	**264**[a]	**265**[a]	**326**[a]	Comments[b]
1	$TBSO(CH_2)_2$-	$Ti(O^iPr)_4$	24 h	-	-	-	No reaction
2	$TBSO(CH_2)_2$-	BF_3	5 h	-	-	-	Two compounds
3	$TBSO(CH_2)_2$-	$SnCl_4$	6 h	-	-	-	Two compounds
4	cyclohexyl	$Cu(OTf)_2$	24 h	0	0	0	Complex mixture
5	cyclohexyl	$MgBr_2.OEt_2$	24 h	17	31	2	
6	cyclohexyl	$NiCl_2$	24 h	70	14	0	
7	cyclohexyl	$Zn(OAc)_2$	24 h	88	6	0	
8	cyclohexyl	$Zn(SO_4)_2$	24 h	80	10	0	
9	cyclohexyl	$ZnCl_2$	24 h	25	54	1	
10	cyclohexyl	$Zn(ClO_4)_2.6H_2O$	24 h	0	79	8	
11	cyclohexyl	$Zn(OTf)_2$	24 h	0	77	5	
12[c]	cyclohexenyl	$Zn(OTf)_2$	24 h	0	94	0	
13[c]	cyclohexenyl	$In(OTf)_3$	24 h	-	-	-	Complex mixture
14[c]	cyclohexenyl	$Yb(OTf)_3$	24 h	-	-	-	Complex mixture
15[c]	cyclohexenyl	$Er(OTf)_3$	24 h	-	-	-	SM remained

[a] NMR yield. [b] Based on TLC and/or NMR analysis. [c] Performed by Dr. Ryan Liffey.

Titanium(IV) isopropoxide did not facilitate elimination of the *tert*-butyl group (Table 2.11, entry 1). In experiments with the TBS-protected substrate and boron trifluoride and tin(IV) chloride, a second compound related to the product was observed (Table 2.11, entries 2 and 3). Unfortunately, the ^1H NMR peaks of the second compound were so similar to the desired product that it was not possible to elucidate yields for the reactions. It was postulated that the counter ions of the Lewis acids were forming their respective

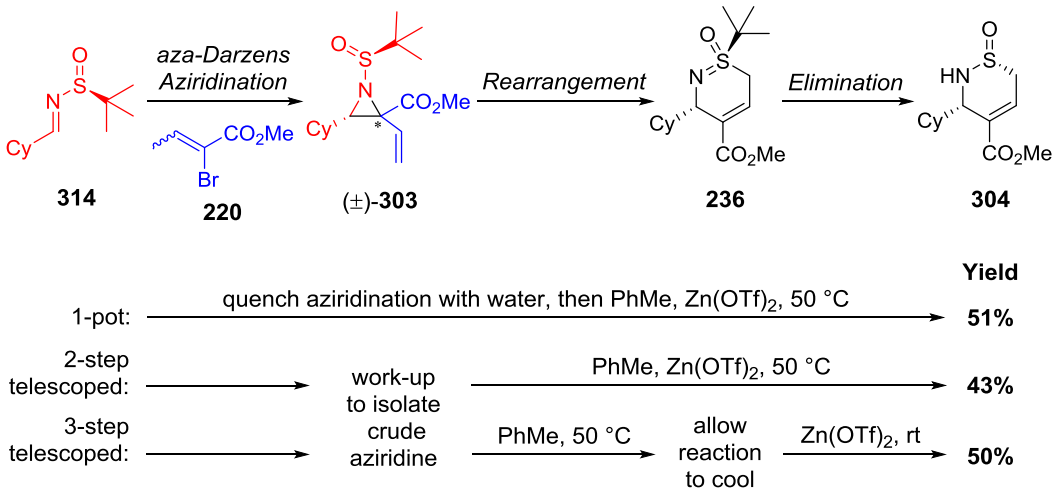
protonated acids, which led to deprotection of the *tert*-butyldimethylsilyl group of **325**.

The product of the reaction with copper(II) triflate did not correspond to **304** or **315**, whereas magnesium(II) bromide afforded a mixture of products (Table 2.11, entries 4 and 5). Nickel(II) chloride, zinc(II) acetate, zinc(II) sulfate and zinc(II) chloride achieved only slow elimination of the *tert*-butyl group after 24 h (Table 2.11, entries 6-9). The best results were obtained with zinc(II) perchlorate and zinc(II) triflate (Table 2.11, entries 10 and 11). The reactions with indium(III) triflate and ytterbium(III) triflate gave complex mixtures (Table 2.11, entries 13 and 14), whereas erbium(III) triflate did not fully consume the starting material after 24 h (Table 2.11, entry 15). Due to the inherent hazards surrounding perchlorate, it was decided that zinc(II) triflate would be used as the Lewis acid. The reaction with zinc(II) triflate was repeated and was complete in only 2 hours.

Unfortunately, the formation of **315** appeared unavoidable for the cyclohexyl substrate. Resubmitting sulfinamide **304** to the conditions of 10 mol% zinc(II) triflate in toluene at room temperature did not lead to a change in the *dr* after 24 hours. Moreover, heating sulfinamide **304** at elevated temperatures of 70 °C led to no change in *dr* and heating at 90 °C only led to degradation of the starting material.

2.2.5 Finalising the Procedure

With a method for de-*tert*-butylation in hand, there were a number of considerations to be made to decide whether a one-pot, two-step or three-step protocol would be employed (Scheme 2.24). Firstly, as we had already discovered, the major diastereoisomer of aziridine **303** underwent facile rearrangement to sulfoximine **236** prior to chromatography.[120] Consequently, it seemed logical to telescope the aziridination into the rearrangement. In contrast, the minor diastereoisomer of aziridine **303** required heating to accelerate its rearrangement. As described previously in the thermal study, a reaction temperature of 50 degrees was identified as the best compromise. Secondly, *tert*-butyl sulfoximine **236** was not stable on silica gel. Again, it seemed logical to telescope the rearrangement of the sulfoximine into the elimination. Finally, throughout this investigation the thermal elimination of the *tert*-butyl group of **236** had been capricious, even at 50 degrees. Thus, zinc(II) triflate was employed to achieve full elimination.



Scheme 2.24. Comparison of the procedures to obtain sulfinamide **304**.

The one-pot, two-step and three-step procedures are shown above in Scheme 2.24. In the one-pot procedure, the *aza*-Darzens aziridination was quenched with water and then diluted with toluene before zinc(II) triflate was added. The resulting biphasic mixture was then heated to 50 degrees and the progress of the reaction was monitored by ^{1}H NMR spectroscopy. When the reaction was deemed complete then an aqueous work-up was performed before purification by column chromatography. In the two-step procedure, an aqueous work-up was performed after the *aza*-Darzens aziridination to obtain the crude aziridine (±)-**303**, which was analysed by ^{1}H NMR spectroscopy. The crude aziridine (±)-**303** was then heated to 50 degrees in toluene with zinc(II) triflate and monitored by ^{1}H NMR spectroscopy. In the three-step procedure, the same operation was performed on the crude aziridine (±)-**303**, before it was dissolved in toluene and then heated to 50 degrees. When aziridine (±)-**303** was consumed as judged by ^{1}H NMR spectroscopic analysis, the reaction was allowed to cool to room temperature before zinc(II) triflate was added and then stirred until any remaining sulfoximine **236** was eliminated. As an aqueous work-up had been performed earlier in the two- and three-step procedures, the reaction mixture was concentrated before purification by column chromatography.

Overall, there was a negligible difference in the yields from the 3 protocols. When R = cyclohexyl, the yields of **304** for the one-pot, two-step and three step procedures were 51%, 43% and 50%, respectively. The discrepancy in the two-step was most likely attributed to loss during purification. Therefore, operational and analytical simplicity had bigger influences on the decision.

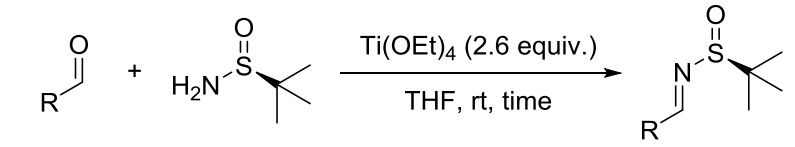
In the one-pot procedure, a large excess of toluene was required to solvent swap the aziridine from the tetrahydrofuran. For example, for every mmol of starting material, 63 mL of a 5:1:10 mixture of tetrahydrofuran, water and toluene was required. Moreover, the concern over the water solubility of the sulfinamides meant it was desirable to perform the work-up on the aziridine. Another advantage of performing the work-up, after the *aza*-Darzens aziridination, was the removal of any impurities within the aziridine's characteristic alkene region of the ^{1}H NMR spectrum. Lastly, the elimination of the *tert*-butyl group using zinc(II) triflate was facile, therefore the [2,3]-sigmatropic rearrangement was the rate limiting step of this methodology – thereby making the three-step procedure unnecessary.

In conclusion, it was decided that the two-step protocol would be used, primarily because of the improved ease by which the reaction could be monitored by ^{1}H NMR spectroscopy.

2.2.6 Scope

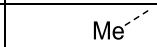
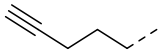
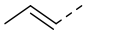
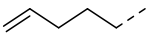
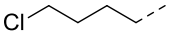
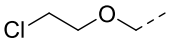
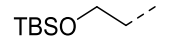
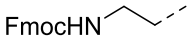
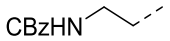
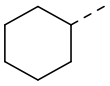
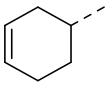
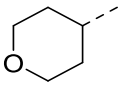
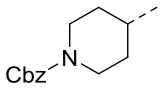
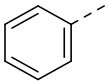
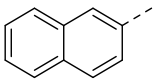
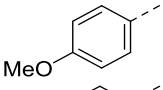
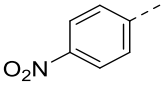
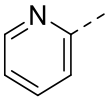
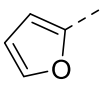
Using the same sulfinimine condensation conditions, *tert*-butyl sulfinimines **120**, **121**, **123**, **125**, **126**, **314**, **324**, **327**-**341** were obtained in 41-92% yield (Table 2.12).[46,135] Substrates with a wide range of functional groups that included alkyl, unsaturation, halide, protected hetereoatoms, heterocyclic systems and aromatic rings were prepared.

Table 2.12. Scope of the *tert*-butyl sulfinimine condensation.



1.3 equiv. (*S*)-**7**

120, 121, 123, 125, 126
314, 324, 327-341

Entry	R	Time (h)	Compound	Yield (%)
1		17	**327**	41
2[a]		-	**328**	67
3		26	**329**	85
4		18	**330**	70
5		22	**331**	82
6		16	**332**	37
7		22	**324**	83
8		24	**333**	71
9		4	**334**	54
10[a]		-	**335**	59
11		21	**336**	87
12		29	**314**	93
13[a]		-	**337**	78
14		48	**338**	73
15		24	**339**	76
16		18	**120**	99
17[a]		-	**340**	72
18		4	**121**	86
19		18	**341**	88
20		94	**123**	31
21[a]		-	**125**	78
22			**126**	92

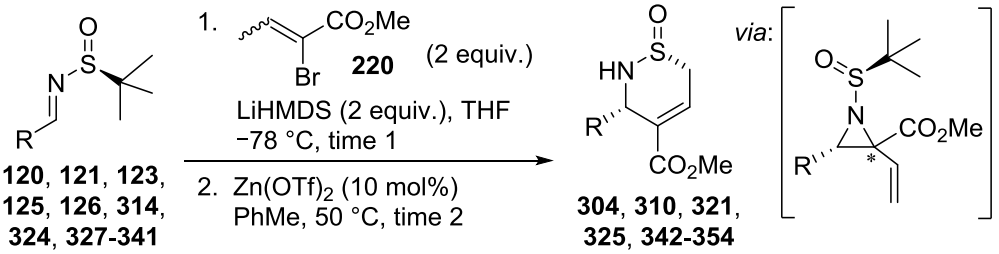
[a] Performed by Dr. Ryan Liffey.

Again, in agreement with the literature, all examples were prepared exclusively as the *E*-isomer. Reaction completion was monitored by thin layer chromatography. It should be noted that the reaction times were not necessarily as long as those shown below. For convenience these reactions were generally set-up at the end of the working day and thus left overnight.

With sulfinimines (**120**, **121**, **123**, **125**, **126**, **314**, **324**, **327**-**341**) in hand, the scope of the two-step telescoped preparation of chiral cyclic sulfinamides was investigated (Table 2.13).

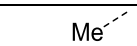
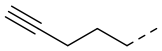
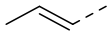
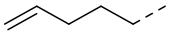
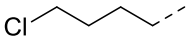
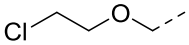
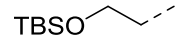
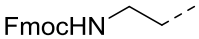
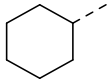
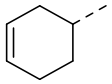
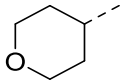
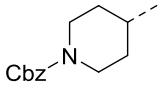
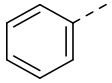
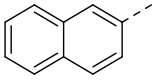
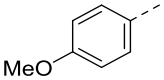
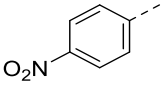
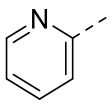
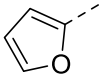
Initially, the *aza*-Darzens aziridination was monitored by thin layer chromatography, later in the project LC-MS was used in tandem due to its more representative quantification of the reaction completion (Table 2.13, column 3). In general, the aziridination was complete within 1-2 h. The [2,3]-sigmatropic rearrangement/elimination was monitored by ^{1}H NMR spectroscopy. This step was complete in 15-24 h for mono-substituted substrates and, in general, within 39-47 h for di-substituted substrates (Table 2.13, column 4). Similar to what we observed during our previous work with mesityl aziridines,[52] it was postulated that the increased steric bulk of the di-substituted substrate would decrease the rate of the aziridine rearrangement. Good to excellent yields (35-68%) were obtained over 3 steps for mono-substituted substrates, which represents 70-88% yield per step (Table 2.13, entries 1-9). Higher yields of 48-91% were afforded for di-substituted substrates, which equates to excellent yields of 78-97% per step. Due to the systematic approach of a scope investigation, the small increase in yields was

Table 2.13. Scope of the telescoped two-step sulfinamide methodology.



120, **121**, **123**, **125**, **126**, **314**, **324**, **327-341**

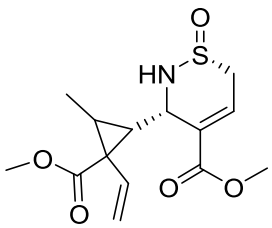
304, **310**, **321**, **325**, **342-354**

Entry	R	Time 1 (h)[a]	Time 2 (h)[b]	Compound	Yield (%)
1		1	17	**321**	48 (95:5 *dr*)[c]
2[d]		N/A	N/A	**342**	63
3[e]		1	19	–	0
4		1	20	**343**	55
5		1.25	24	**344**	35
6		1	16	**345**	68
7		2	15	**325**	44
8		2	21	**346**	58
9		2	21	**347**	61
10[d]		N/A	N/A	**348**	48
11		1	47	**349**	49
12		2	41	**304**	91 (93:7 *dr*)[c]
13[d]		N/A	N/A	**350**	66
14		1	41	**351**	76
15		2	39	**352**	62
16		1	47	**310**	38
17[d]		N/A	N/A	**353**	43
18[e]		1	-	–	0
19		1	28	**354**	35
20[f]		3	-	–	0
21[d,f]		-	-	–	0
22[f]		-	-	–	0

[a] monitored by TLC and/or LC-MS. [b] monitored by ^{1}H NMR. [c] isolated dr. [d] performed by Dr. Ryan Liffey. [e] aziridine observed by TLC and/or LC-MS. [f] aziridine not observed. N/A = data not available

attributed to procedural familiarity. The major limitation of this methodology was aromatic and heteroaromatic substrates (Table 2.13, entries 16-21). Moderate yields of 38% and 43% were obtained for Table 2.13, entries 16 and 17). The electron-donating aryl aziridine collapsed back to the starting sulfinimine, observed by LC-MS (Table 2.13, entry 18). In contrast, the electron-withdrawing example gave a 35% yield (Table 2.13, entry 19). The pyridyl and furfuryl substrates did not form the aziridine, although the pyridyl example was taken forward into the rearrangement/elimination step to confirm this observation and, as expected, no sulfoximine was observed (Table 2.13, entries 20 and 21). Finally, the aziridination was unsuccessful with a tri-substituted alkyl substrate (Table 2.13, entry 22).

The methodology has excellent functional group tolerance, which includes: alkyls; terminal unsaturation (alkyne and alkene); halogens; ethers and silyl ethers; carbamates (Fmoc and CBz); and alkyl heterocycles. However, when the alkene was conjugated to the sulfinimine (Table 2.13, entry 3), the ^{1}H NMR of the purified product was a cyclic sulfinamide species **355** that also contained a terminal alkene and methyl ester (Figure 2.14). It is conceivable that the conjugation with the sulfinimine activated this alkene to preferential reaction with the lithium enolate, prior to the desired *aza*-Darzens aziridination.



355

Figure 2.14. Proposed cyclopropane byproduct.

Of the 17 successful examples, 15 gave the product as a single diastereomer. The two examples that did not were methyl, in an isolated 95:5 *dr*, and cyclohexyl, in an isolated 93:7 *dr* (Table 2.13, entries 1 and 12 respectively). It was not possible to determine the diastereomeric ratio in the crude ^{1}H NMR spectra. Due to the capricious nature of the purification of the cyclic sulfinamides, it was not uncommon to observe the elution of the other diastereisomer before the first diastereisomer had fully eluted.

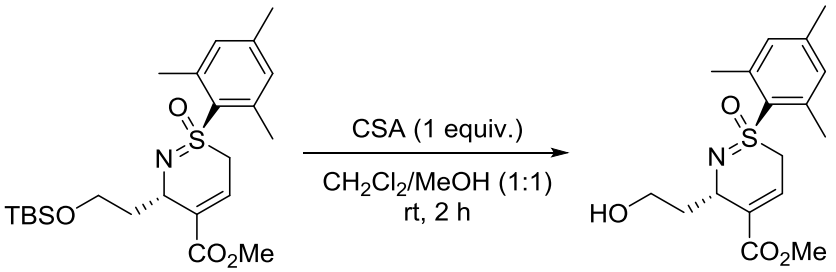
2.3 Further Reactivity of Cyclic Sulfoximines and Sulfinamides

From the outset of any investigation into a new methodology there is always the intention to demonstrate its application, be it towards a natural product or simply to expand the field of that particular area. This research project has produced a variety of cyclic sulfoximines and cyclic sulfinamides from which we believed there was the potential to access a wide range of small molecules. If these small molecules could be accessed following simple transformations then this would greatly increase the value of the methodology previously presented. Herein, we report the first attempts to discover these simple transformations.

2.3.1 Intramolecular Lactone Formation

As the earlier research has shown, the stability of *tert*-butyl sulfoximines **264** under even mild conditions (40 °C) was poor. Therefore, the mesityl sulfoximines **262** were chosen as a more suitable substrate as they have been shown to be stable under acidic/basic conditions or when heated to 70 °C.

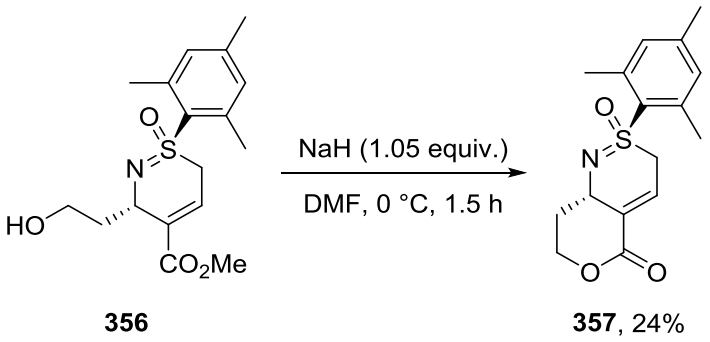
As part of our investigations into conjugate additions into the enoate of the sulfoximines **262** and sulfinamides **264**, the lactonisation of alcohol **356** was an early target. The Stockman group's conditions of stoichiometric camphorsulfonic acid in 1:1 dichloromethane/methanol at room temperature afforded **356** following column chromatography in 68% yield (Scheme 2.25).[60]



290 **356**, 68%

Scheme 2.25. Deprotection of *tert*-butyldimethylsilyl moiety.

Deprotonation of alcohol **356** with sodium hydride at 0 °C in dimethylformamide afforded lactone **357** in only 24% yield (Scheme 2.26). Thin layer chromatography showed complete consumption of **356** therefore the poor yield was attributed to degradation/byproduct formation and loss during purification. Formation of lactone **357** with triethylamine in deuterated chloroform was monitored by ^{1}H NMR spectroscopy, however, the transformation was very slow (>5 days) even with heating at 40 °C.

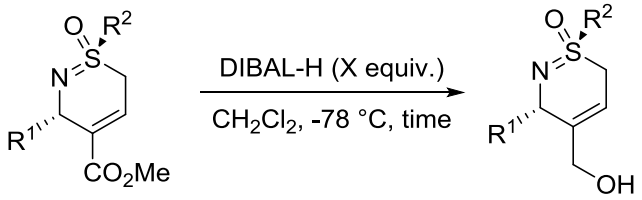


Scheme 2.26. Intramolecular cyclisation of **356** to form lactone **357**.

2.3.2 Ester Reduction

Reduction of the α,β-unsaturated ester was achieved using excess diisobutylaluminium hydride solution in dichloromethane at –78 °C for 1-2 h (Table 2.14).

Table 2.14. Ester reduction of sulfoximines **233**, **290** and **311**.



233: R^1 = Ph, R^2 = ^{t}Bu
311: R^1 = TBSO, R^2 = ^{t}Bu
290: R^1 = TBSO, R^2 = Mes

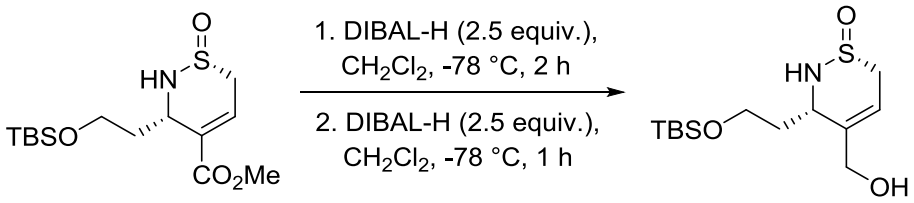
358: R^1 = Ph, R^2 = ^{t}Bu
359: R^1 = TBSO, R^2 = ^{t}Bu
360: R^1 = TBSO, R^2 = Mes

Entry	Substrate	Scale (mmol)	X	time (h)	Yield (%)	Product
1	**233**	0.10	2.5	1	77	**358**
2	**311**	0.08	2.5	1.25	65	**359**
3	**290**	0.66	3.5	2	68	**360**

The reduction proceeded well for all substrates with short reaction times. Pleasingly, examples containing *tert*-butyl (Table 2.14, entries 1 and 2) and mesityl (Table 2.14, entry 3) were tolerated and isolated in good yield. It

should be noted that the example with the TBS-protected alcohol and R^2 = mesityl (Table 2.14, entry 3) used another equivalent of diisobutylaluminium hydride. The longer reaction time was attributed to the quality of the diisobutylaluminium hydride solution (Table 2.14, entries 2 and 3, respectively).

For comparison, the reduction of sulfinamide **325** to **361** was attempted, although, it did not proceed as smoothly. Nevertheless, after two treatments with diisobutylaluminium hydride at –78 °C, complete consumption of the starting material was achieved (Scheme 2.27). In contrast, reduction of sulfinamide **321** (R = methyl) was observed after 1 h, however, the product was too water soluble and hence partitioned into the aqueous layer and could not be re-extracted. Overall, too few examples of cyclic sulfinamides and cyclic sulfoximines were investigated and therefore no conclusions about the ester reduction scope can be made.



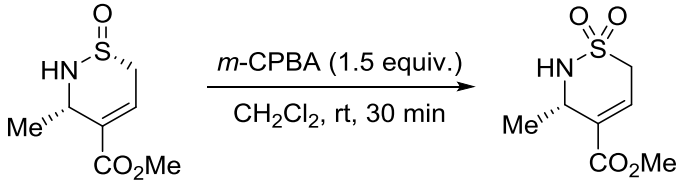
325 **361**, 51%

Scheme 2.27. Ester reduction of sulfinamide **325**.

Attempts to reduce the ester with lithium aluminium hydride or lithium borohydride gave complex mixtures. Mass spectrometry analysis of the lithium borohydride reaction contained the complete reduction product – without the alkene.

2.3.3 Oxidation of Cyclic Sulfinamides

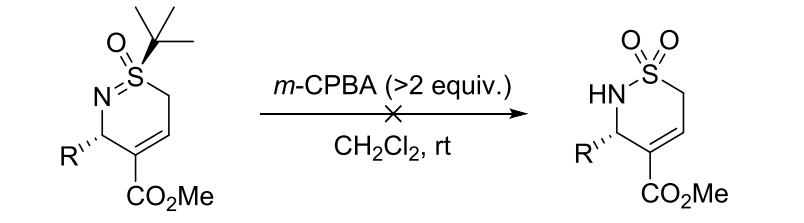
Cyclic sulfinamides are readily oxidised to cyclic sulfonamides, or sultams, using *meta*-chloroperoxybenzoic acid. Indeed, sultam **362** was obtained in an excellent 85% yield without further purification (Scheme 2.28).



321 **362**, 85%

Scheme 2.28. Oxidation of sulfinamide **321** to sultam **362**.

Sultam synthesis is more well known in the literature in comparison to cyclic sulfinamide synthesis.[136] Therefore, the transformation of sulfoximines **233** and **311** into their respective sultams in one-pot would demonstrate their versatility. As shown previously, sulfoximine **166** was converted into sulfinamide **321** using weak to moderately strong acids (Table 2.10). It was postulated that stirring the sulfoximine with at least two equivalents of *meta*-chloroperoxybenzoic acid would afford the respective sultam (Scheme 2.29). Unfortunately, both reactions showed complete degradation of the starting materials.



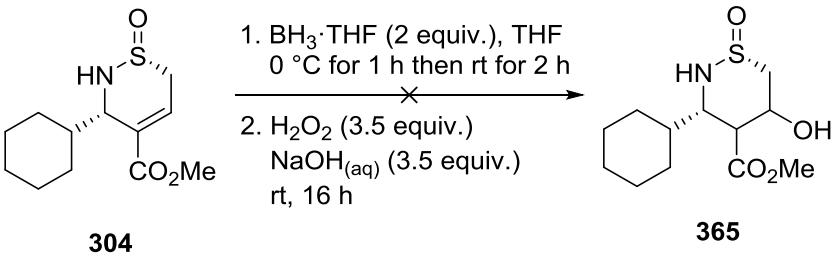
233: R = Ph
311: R = TBSO

363: R = Ph
364: R = TBSO

Scheme 2.29. Attempted one-pot preparation of sultams **363** and **364**.

2.3.4 Attempted Hydroboration of Cyclic Sulfinamide

It was highly desirable to functionalise at the 4-position of the enoate region. Using standard conditions, the hydroboration of sulfinamide **304** to **365** was investigated (Scheme 2.30). ^{1}H NMR analysis of the enoate region in the crude reaction mixture determined that, relative to only each other, there was: 29% unreacted starting material **304**, 48% of the other diastereoisomer **323** of the starting material and 23% of a new species. Mass spectrometry analysis of the crude product identified only the starting material **304** and its diastereoisomer **323**. In addition, analysis of the aqueous layer by mass spectrometry identified the ester hydrolysis product of the starting material **304**.



304 **365**

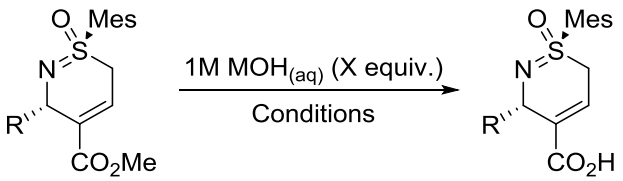
Scheme 2.30. Attempted hydroboration of sulfinamide **304**.

Under these reaction conditions the highest level of diastereoisomer **323** was observed. Therefore, an in depth investigation to try and replicate this result was undertaken. However, repetition of the above conditions and subsequent changes to every permutation of the reaction conditions, which included using each reagent separately, were unsuccessful.

2.3.5 Hydrolysis of the Ester of Cyclic Sulfoximines

The α,β-unsaturated ester of the cyclic sulfoximines and cyclic sulfinamides is the key functional group in order to access a wider range of higher value materials. Therefore, it was highly desirable that a protocol for their hydrolysis be identified. The prominent method in the literature used a source of hydroxide. Two procedures that used lithium hydroxide were investigated: the first was widely used within the Stockman group; the second was from the literature and was chosen because the substrate, the methyl ester of angelic acid, had a similar substitution pattern around the sulfoximines.[137] The results from these experiments are shown below in Table 2.15.

Table 2.15. Investigation into the hydrolysis of the ester.

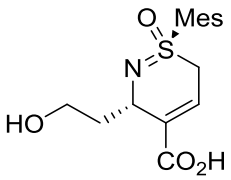


262 **366**

Entry	R	M	X	Conditions	Analysis
1	TBSO	Li	1.1	MeOH/H_2O (1:1) reflux, 4 h	Only product peak by MS
2[a]	TBSO	Li	1.0	MeOH/H_2O (1:1) reflux, 5 h	Not complete after 5 h by MS
3	TBSO	Li	1.05	THF, 60 °C, 48 h	Very low conversion by MS
4[a]	TBSO	Li	1.1[b]	THF, reflux, 24 h	No reaction after 3 h by MS. Very low conversion after 7 h by MS
5[a]	Me	Li	1.1[c]	THF, reflux, 54 h	Complete by LC-MS
6[a]	Me	Na	3.5	THF, rt, 24 h	Complete by LC-MS

[a] Crude analysed by ^{1}H NMR in MeOD. [b] Water added after 3 h. Additional 1M $LiOH_{(aq)}$ (2 equiv.) added after 7 h. [c] Additional 1M $LiOH_{(aq)}$ (1.1 equiv.) added after 30 h.

Hydrolysis of the sulfoximine proceeded very smoothly by mass spectrometry (Table 2.15, entry 1). However, after following the acidic aqueous work-up described, after multiple extractions, no product was isolated. Mass spectrometry analysis of the aqueous layer identified the fully deprotected **367**, which suggested the TBS group was cleaved during the acidification with 3 M hydrochloric acid (Figure 2.15).

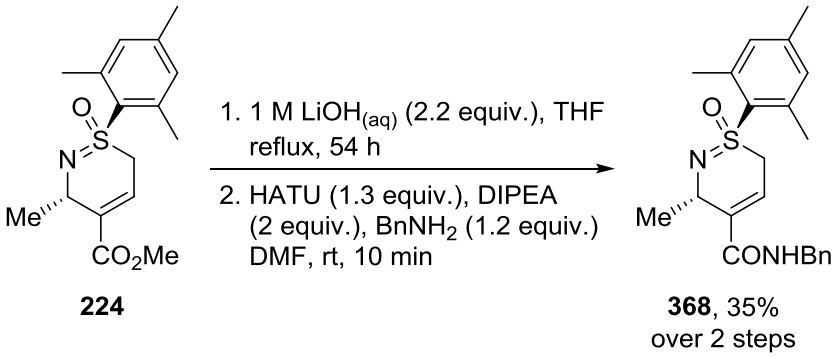


367

Figure 2.15. Fully deprotected sulfoximine **367**.

Unfortunately, the reaction proved capricious and in all repeat reactions the complete hydrolysis of the ester could not be replicated (Table 2.15, entry 2). The procedure commonly used within the Stockman group gave poor conversion (Table 2.15, entry 3). This procedure was repeated at reflux but only after the addition of another 2 equivalents of lithium hydroxide, after 7 h, was complete hydrolysis observed (Table 2.15, entry 4). These conditions proved more ineffective when R = methyl with a 54 h reaction time (Table 2.15, entry 5). Nevertheless, the crude product was tested in a small scale HATU-amide coupling with benzylamine and following column chromatography afforded amide **368** in 35% yield over 2 steps (Scheme 2.31). The best conditions were obtained using excess aqueous sodium hydroxide solution in tetrahydrofuran at room temperature (Table 2.15, entry 6). It

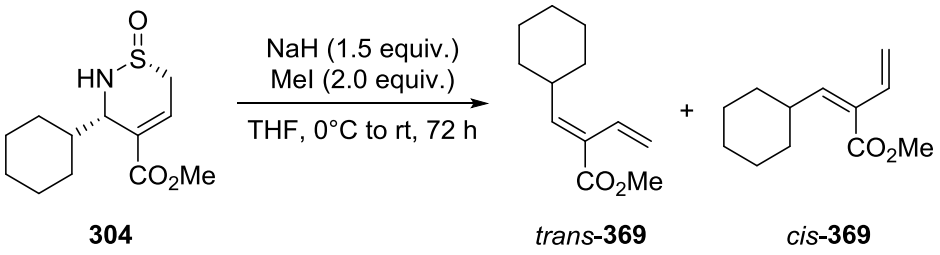
should be noted that these reactions were performed on approximately 0.08 mmol scale.



Scheme 2.31. Two step preparation of amide **368**.

2.3.6 Alkylation of Cyclic Sulfinamides

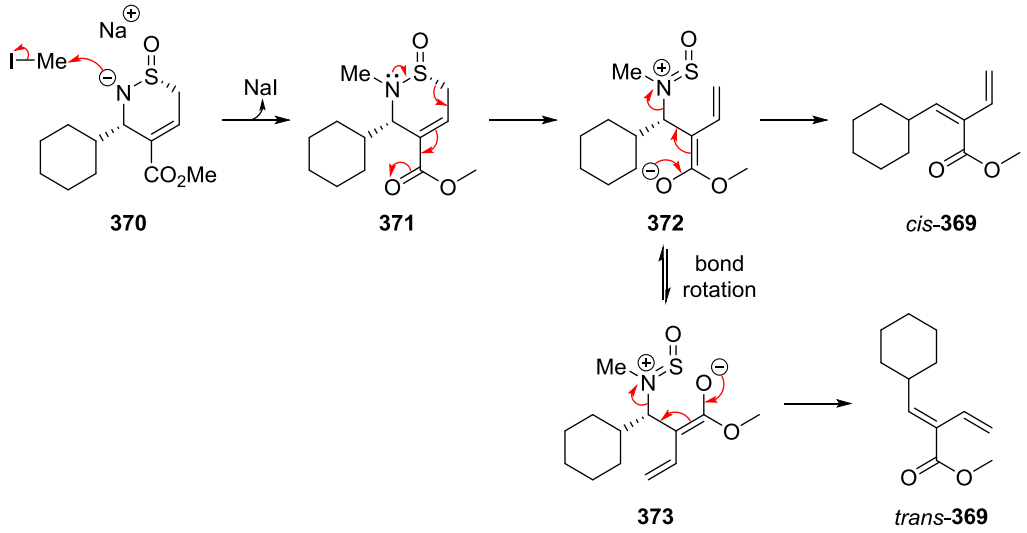
Methylation of the nitrogen in sulfinamide **304** was attempted using standard conditions of methyl iodide and sodium hydride in tetrahydrofuran from 0 °C to room temperature (Scheme 2.32).



Scheme 2.32. Proposed degradation products following methylation of **304**.

Surprisingly, the ^{1}H NMR spectrum of the crude product contained a 1:1 mixture of two products. After comparison with the literature, the first product was identified as diene *trans*-**369**.[131] It is then conceivable that the second product, which had signals in the same regions of the ^{1}H and ^{13}C NMR spectrums, was the *cis*-isomer of diene **369**. Initially, it was proposed that a retro-Diels-Alder-type reaction afforded diene **369**. However, as these

reactions are concerted, a single isomer of diene **369** would have been expected. It was postulated that following the desired methylation of **370**, **371** may have undergone a step-wise degradation to afford a racemic mixture of *cis*-**369** and *trans*-**369** dienes (Scheme 2.33).

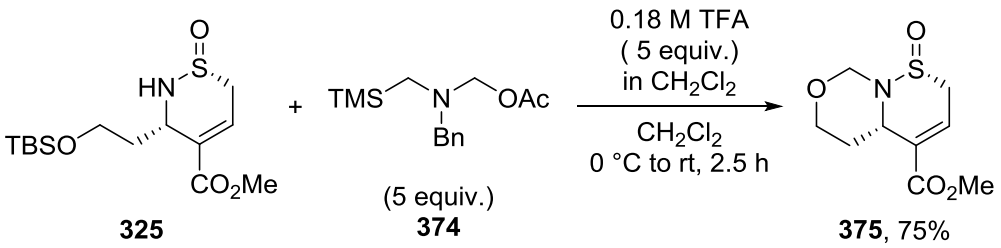


Scheme 2.33. Proposed decomposition of **369**.

Interestingly, when potassium hydroxide was used instead of sodium hydride, an approximate 3:1 ratio of *trans*-**369** and *cis*-**369** was observed – albeit with a significantly lower recovery of the crude material.

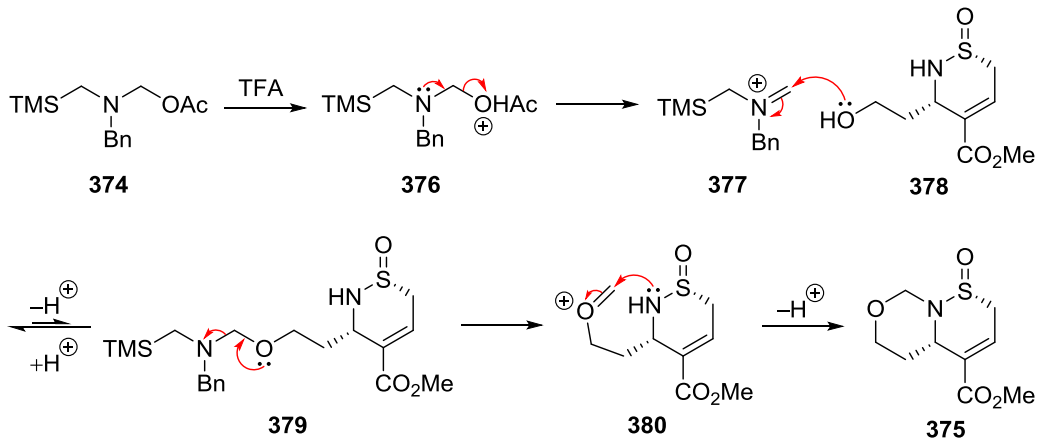
2.3.7 Addition of Azomethine Ylides

Lastly, the attempted addition of a nitrogen-based 1,3-dipole, formed from **374** with trifluoroacetic acid, led to the fascinating, serendipitous discovery of an unusual cyclisation of **325** (Scheme 2.34).[138]



Scheme 2.34. Serendipitous cyclisation of **325** to afford bicycle **375**.

We propose that under the reaction conditions trifluoroacetic acid protonates **374** to give **376**, which subsequently eliminates acetic acid to afford **377** (Scheme 2.35). We then propose that **378**, formed by deprotection of the alcohol protecting group in **325**, reacts with **377** to form the hemiaminal-type species **379**. We believe this process would be reversible as the lone pair on the nitrogen is more available to push back into the nitrogen-carbon bond and thus breaking the newly formed carbon-oxygen bond. Nevertheless, should the sequence of arrows lead to the formation of the highly electrophilic species **380**, then ring closing would be achieved by the addition of the nitrogen of the cyclic sulfinamide to afford bicycle **375** in an excellent 75% yield.

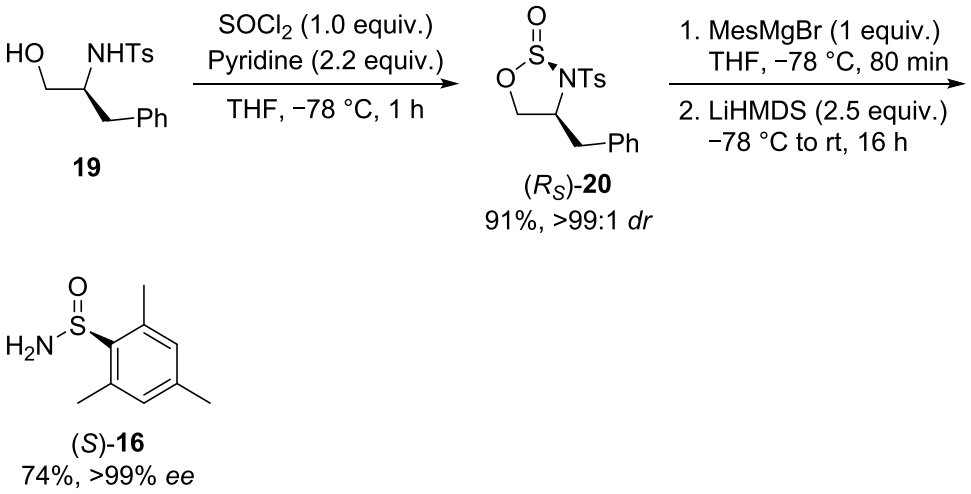


Scheme 2.35. Proposed mechanism for the cyclisation to afford **375**.

2.4 Conclusions

During the course of this work two areas of research around cyclic sulfoximines were completed. Along the way existing methodologies have been evaluated and in some cases improved upon. Both research areas used the [3,3]-sigmatropic rearrangement of 2-vinylaziridines methodology published by the Stockman group in 2016.[120]

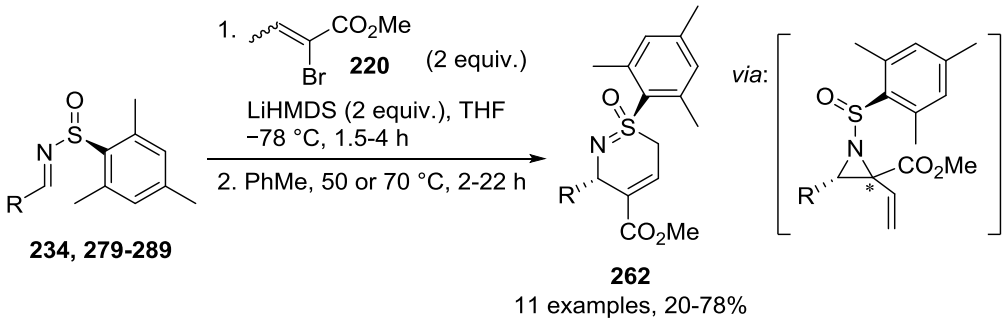
The first concerned the expansion of the scope of the *NH*-3-pyrrolines **263** methodology. The Stockman group's synthesis of chiral template (R_S)-**20**, which had previously been prepared in 77% yield using ISOLUTE® CN cartridges, was optimised to 91% yield in >99:1 *dr* on a 66 mmol scale following filtration through a silica plug (Scheme 2.36). The preparation of mesityl sulfinamide (*S*)-**16** was completed from (R_S)-**20** in 74% yield as a single enantiomer.



Scheme 2.36. Improved synthesis of (R_S)-**20** and preparation of (*S*)-**16**.

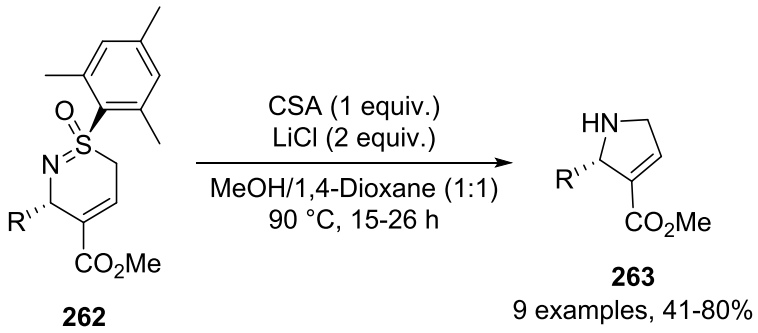
With (*S*)-**16** in hand, Ellman's sulfinimine condensation conditions were employed in the synthesis of 12 mesityl sulfinimines **234**, **279**-**289** in 41%-92%

yield.[46,135] The sulfinimines **234**, **279**-**289** were then used to demonstrate the scope of the [3,3]-sigmatropic rearrangement methodology, which included 5 new examples (Scheme 2.37).



Scheme 2.37. One-pot synthesis of cyclic sulfoximines **262**.

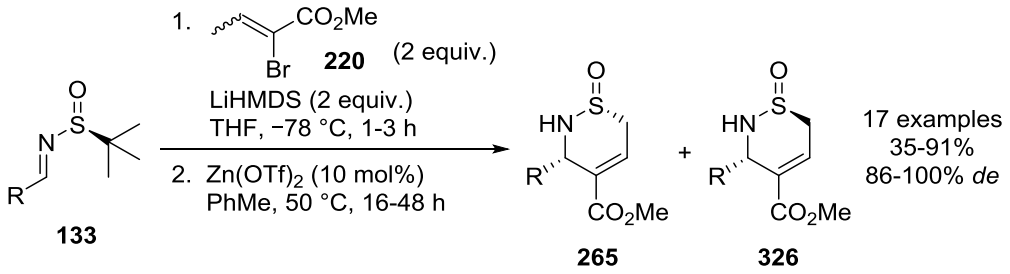
The 11 sulfoximines were then submitted to the Stockman group's ring contraction conditions to afford 9 pyrrolines in 41-80% yield (Scheme 2.38).



Scheme 2.38. Expanded scope of the ring contraction of **263**.

The second was the design of a methodology to prepare chiral cyclic sulfinamides **265** from readily accessible *tert*-butyl sulfinimines **133** (Scheme 2.39). A two-step telescoped protocol was developed, which employed a catalytic Lewis acid, to prepare 17 examples of cyclic sulfinamides **265** in 35-91% yield. Of the 17 examples, 15 were obtained as a single diastereoisomer.

The identity of the other diastereoisomer **326** was elucidated by X-ray crystallography.



Scheme 2.39. Two-step telescoped synthesis of cyclic sulfinamides **265**.

Finally, regarding the further functionalisation of the cyclic sulfoximine **223** and cyclic sulfinamide **265** products, there were preliminary results in the areas of: lactone formation, ester reduction, sulfinamide oxidation, alkene hydroboration, ester hydrolysis and sulfinamide alkylation.

2.5 Future Work

The cyclic sulfinamides project is more or less complete and we believe we have a reproducible procedure with a wide substrate scope. Ideally, we would like to know definitively what the mechanism of the de-*tert*-butylation is, however, we do not know what approach is required to elucidate this answer. Secondly, if it wasn't for two of the seventeen examples that didn't afford a single diastereoisomer, then we could have stated unequivocally that the reaction was completely diastereoselective. Again however, we do not have a hypothesis for this occurrence or an approach to elucidate this answer also.

Similarly, the cyclic sulfoximine to 3-pyrroline project is nearing completion. Ideally, the substrate could be larger but the overall value this would add is

minimal. Besides, combined with the two formal syntheses of pyrrolizidine alkaloids by previous members of the group, this project does not require further investigation.

The third project has the most scope for expansion. We envisage that the cyclic sulfinamides **265** have potential as small cores in drug discovery. They have ideal properties as a starting point in drug discovery: molecular weight between 190 and 330 (if the protecting groups are not included); 4 hydrogen bond acceptors (2 apiece in the sulfinamide and ester groups), 1 hydrogen bond donor (2 if the R group at the 3-position has an alcohol or amine).

Another idea we had was the application of cyclic sulfinamide **381** as an α-glucose analogue if we could functionalise the alkene of the en-oate region *via* an oxa-Michael-type reaction (Figure 2.16). There may be potential for these very interesting molecules and further investigation along these lines would be very interesting indeed.

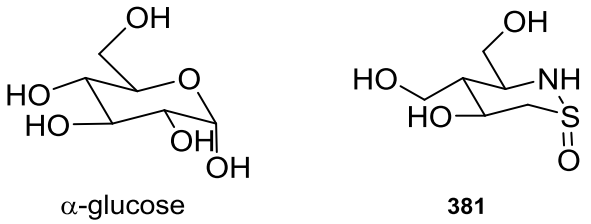


Figure 2.16. Cyclic sulfinamide **381** as an α-glucose analogue.

Finally, the serendipitous isolation of bicycle **375** allows access to an expected but nonetheless fascinating possibility of further investigating the potential of this cyclisation on other substrates.

3. Experimental

3.1 General Procedures

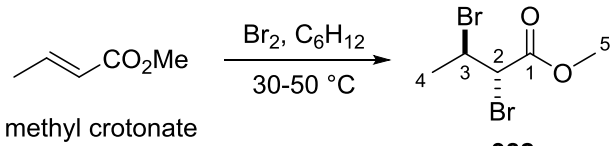
All reagents were purchased from commercial sources and used without additional purification. Tetrahydrofuran was freshly distilled under argon from the sodium benzophenone ketyl radical. All other anhydrous solvents were purchased or obtained from in house solvent purification towers. All reactions were conducted in flame-dried glassware and, when anhydrous solvents are specified, were conducted under an inert atmosphere of argon. Petroleum ether refers to the fraction in the boiling range 40-60 °C. Brine is a saturated aqueous solution of sodium chloride in distilled water. Water is deionised. Solvent evaporation was performed under reduced pressure using a rotary evaporator with a water bath temperature of 40 °C unless stated otherwise.

Thin layer chromatography was performed on Merck silica gel 60 F_{254} and visualised by UV lamp and then aqueous alkaline potassium permanganate, vanillin in ethanol or phosphomolybdic acid hydrate in ethanol. Column chromatography was performed on silica gel Fluka 60. Proton and ^{13}C NMR spectral data were recorded using Bruker AV400, Bruker AV(III)400, Bruker AV(III)400HD and Bruker DPX400 spectrometers. Chemical shifts in ^{1}H NMR are quoted in ppm in reference to either chloroform (7.26 ppm), benzene (7.16 ppm), water (4.79 ppm) or referenced to residual reaction solvents if the residual chloroform peak was obscured by other peaks in that region. Chemical shifts in ^{13}C NMR are quoted in ppm in reference to deuterated chloroform (central line of the 1:1:1 triplet as 77.16 ppm). Coupling constant (*J*) values are given in Hertz. Infrared spectral data in chloroform were

recorded using a Perkin-Elmer 1600 FTIR spectrometer. Infrared spectral data in methanol were recorded using a Bruker Alpha Platinum-ATR spectrometer. Optical rotation data was recorded using an ADP440 polarimeter. Mass spectrometry data was recorded using the open-access Bruker MicroTOF spectrometer in electrospray ionisation mode.

The names of compounds were generated using Cambridgesoft ChemDraw® software. The numbering system is different to that used by Cambridgesoft ChemDraw® software.

Methyl *anti*-2,3-dibromobutanoate (382)



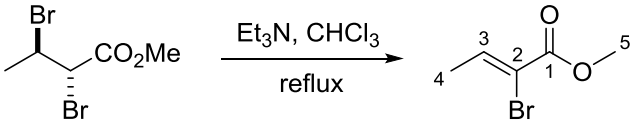
methyl crotonate

382

Bromine (20 mL, 390 mmol) was added to methyl crotonate (39.4 mL, 372 mmol) in cyclohexane (372 mL). The resulting solution was stirred at 30 °C for 1 h, 40 °C for 1 h and then 50 °C for 1 h. Allowed to cool to room temperature before a saturated solution of sodium bisulfite (150 mL) was added. The layers were separated and then the aqueous layer was extracted with diethyl ether (50 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and then concentrated *in vacuo* to afford **382** (91.3 g, 95%) as a colourless oil without further purification.

δ_H (400 MHz, $CDCl_3$) 4.44 (1H, dq, *J* = 11.0, 6.4 Hz, H-3), 4.36 (1H, d, *J* = 11.0 Hz, H-2), 3.82 (3H, s, H-5), 1.89 (3H, d, *J* = 6.4 Hz, H-4); **δ_c** (101 MHz, $CDCl_3$) 168.5 (C1), 53.4 (C5), 49.4 (C2), 45.7 (C3), 24.0 (C4). Data consistent with literature.[139]

Methyl (*Z*)-2-bromobut-2-enoate (220)[140]



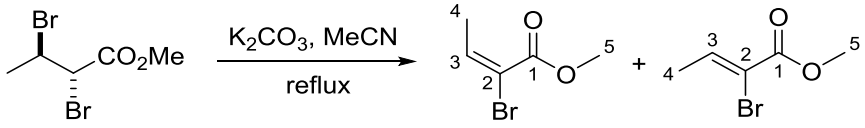
382 ***Z*-220**

Triethylamine (25.9 mL, 186 mmol) was added to methyl *trans*-2,3-dibromobutanoate **382** (9.86 mL, 92.9 mmol) in chloroform (93 mL). The resulting solution was heated to reflux and stirred overnight. Aqueous 2 M

HCl (93 mL) was added and the biphasic mixture was stirred for 2 h. The layers were separated and then the aqueous layer was extracted with ethyl acetate (50 mL x2). The combined organic extracts were dried over anhydrous magnesium sulfate and then concentrated *in vacuo* to afford the crude product as a brown oil. Purification through a plug of silica gel (eluting with ethyl acetate) afforded **220** (9.37 g, 56%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 7.38 (1H, q, *J* = 6.9 Hz, H-3), 3.82 (3H, s, H-5), 1.94 (3H, d, *J* = 6.9 Hz, H-4); **δ_c** (101 MHz, $CDCl_3$) 163.1 (C1), 141.8 (C3), 117.3 (C2), 53.3 (C5), 18.0 (C4); **GC/MS**: t_R = 6.80 min, *m/z* 178 (M^+). Data consistent with literature.[141]

Methyl (*E*)-2-bromobut-2-enoate and methyl (*Z*)-2-bromobut-2-enoate (220)

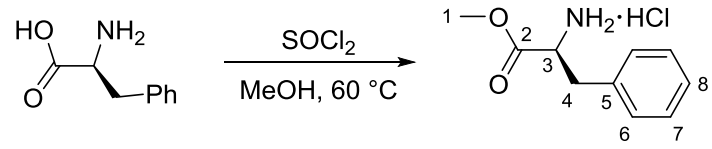


382 **E-220** **Z-220**

Potassium carbonate (72.8 g, 527 mmol) was added to methyl *trans*-2,3-dibromobutanoate **382** (91.3 g, 351 mmol) in acetonitrile (351 mL). The resulting slurry was heated to reflux and stirred overnight. The mixture was allowed to cool to room temperature before being filtered through Celite® and washed with acetonitrile (100 mL x2). The organic extract was dried over anhydrous magnesium sulfate and then concentrated *in vacuo* to afford **220** (52.9 g, 84%, as a 7.7:1 mixture of *E*/*Z* isomers) as an orange oil without further purification.

δ_H (400 MHz, $CDCl_3$) *trans*: 7.38 (1H, q, *J* = 6.9 Hz, H-3), 3.82 (3H, s, H-5), 1.94 (3H, d, *J* = 6.9 Hz, H-4). *cis*: 6.77 (1H, q, *J* = 7.5 Hz, H-3), 3.81 (3H, s, H-5), 2.04 (3H, d, *J* = 7.5 Hz, H-4); **δ_c** (101 MHz, $CDCl_3$) *trans*: 163.1 (C1), 141.8 (C3), 117.3 (C2), 53.3 (C5), 18.0 (C4). *cis*: 163.5 (C1), 144.2 (C3), 111.5 (C2), 52.9 (C5), 17.6 (C4); **GC/MS**: t_R = 6.80 min, *m/z* 178 (M^+). Data consistent with literature.[142]

Methyl (*S*)-phenylalaninate hydrochloride (269)

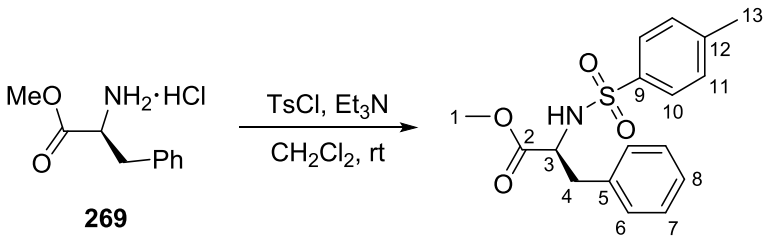


L-phenylalanine **269**

Thionyl chloride (17.6 mL, 242 mmol) was added carefully to a slurry of L-phenylalanine (20.0 g, 121 mmol) in methanol (200 mL) at 0 °C and then heated to reflux and stirred overnight. The reaction mixture was concentrated *in vacuo* to give the crude product (34.6 g) as a yellow amorphous solid. Purified by recrystallisation from methanol/diethyl ether (1:5) to afford **269** (23.5 g, 90%) as a white solid.

δ_H (400 MHz, D_2O) 7.45-7.34 (3H, m, H-7 and H-8), 7.30-7.23 (2H, m, H-6), 4.40 (1H, dd, *J* = 7.6, 5.8 Hz, H-3), 3.81 (3H, s, H-1), 3.32 (1H, dd, *J* = 14.5, 5.8 Hz, H-4a), 3.21 (1H, dd, *J* = 14.5, 7.6 Hz, H-4b); **δ_c** (101 MHz, D_2O) 170.0 (C2), 133.7 (C5), 129.4 (C6), 129.3 (C7), 128.1 (C8), 54.1 (C3), 53.5 (C1), 35.5 (C4); ***m/z*** (ESI+) 180 ($[M+H]^+$, 100%); **HRMS** calculated for $[C_{10}H_{14}NO_2]^+$ $(M+H)^+$ 180.1019, found 180.1031. Data consistent with the literature.[143]

Methyl *N*-tosyl (*S*)-phenylalaninate (270)



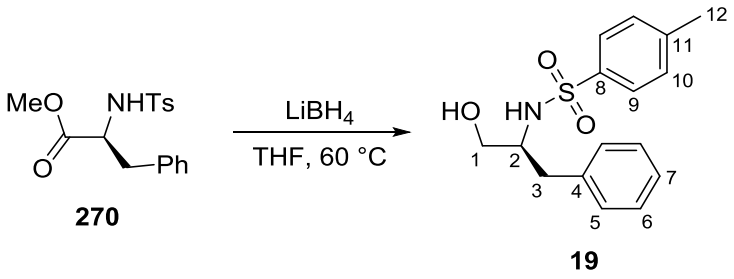
269 **270**

Triethylamine (12.4 mL, 89.2 mmol) was added to a slurry of methyl (*S*)-phenylalaninate hydrochloride **269** (7.99 g, 37.0 mmol) in dichloromethane (200 mL) at room temperature. The solution was cooled to 0 °C before *p*-toluenesulfonyl chloride (10.2 g, 53.5 mmol) was added portionwise. The resulting mixture was allowed to warm to room temperature and then stirred overnight. Water (120 mL) was added and then the layers were separated. The aqueous layer was extracted with ethyl acetate (25 mL x2). The combined organics were washed with brine (120 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give the crude product (16.1 g) as a yellow amorphous solid. Purified by column chromatography over silica gel (eluting with 1:4 ethyl acetate/petroleum ether) afforded **270** (11.0 g, 89%) as an off-white amorphous solid.

δ_H (400 MHz, $CDCl_3$) 7.68–7.60 (2H, m, H-10), 7.27–7.21 (5H, m, H-6, H-7 and H-8), 7.11–7.04 (2H, m, H-11), 5.04 (1H, d, *J* = 9.1 Hz, NH), 4.21 (1H, dt, *J* = 9.1, 6.0 Hz, H-3), 3.49 (3H, s, H-1), 3.03 (2H, d, *J* = 6.0 Hz, H-4), 2.41 (3H, s, H-13); **δ_c** (101 MHz, $CDCl_3$) 171.4 (C2), 143.7 (C12), 136.8 (C9), 135.1 (C5), 129.7 (C11), 129.5 (C6), 128.7 (C7), 127.4 (C8), 127.3 (C10), 56.7 (C3), 52.5 (C1), 39.5 (C4), 21.7 (C13); ***m/z*** (ESI+) 356 ($[M+Na]^+$, 97%); **HRMS** calculated for

$[C_{17}H_{19}NNaO_4S]^+$ $(M+Na)^+$ 356.0927, found 356.0927. Data consistent with the literature.[144]

_N_-Tosyl (_S_)-phenylalaninol (19)



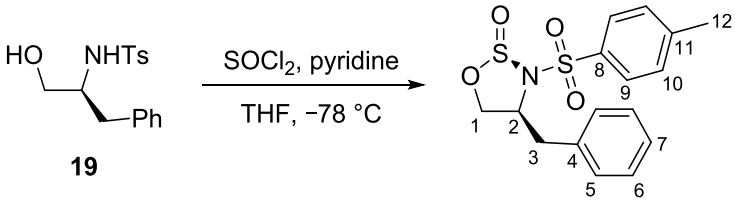
270 **19**

Lithium borohydride (4.82 g, 221 mmol) was carefully added to a solution of methyl *N*-tosyl (*S*)-phenylalaninate **270** (33.5 g, 101 mmol) in tetrahydrofuran (335 mL) at 0 °C. The mixture was heated to 60 °C and stirred for 1 h. Quenched very slowly with water (450 mL) and then ethyl acetate (335 mL) was added. The phases were split and then the aqueous layer was extracted with ethyl acetate (56 mL x2). The combined organics were washed with brine (111 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give the crude product (30.0 g) as a yellow oil that crystallised on prolonged standing. Purification by column chromatography over silica gel (eluting with 1:3 then 1:1 ethyl acetate/petroleum ether) afforded **19** (27.4 g, 89%) as a white amorphous solid.

δ_H (400 MHz, $CDCl_3$) 7.64–7.55 (2H, m, H-9), 7.24–7.19 (2H, m, H-10), 7.19–7.15 (3H, m, H-6 and H-7), 7.03–6.90 (2H, m, H-5), 4.99 (1H, d, *J* = 7.2 Hz, NH), 3.64 (1H, dd, *J* = 11.2, 3.9 Hz, H-1a), 3.53 (1H, dd, *J* = 11.2, 4.8 Hz, H-1b), 3.51-3.38 (1H, m, H-2), 2.78 (1H, dd, *J* = 13.8, 7.0 Hz, H-3a), 2.67 (1H, dd, *J* = 13.8, 7.2 Hz, H-3b), 2.41 (3H, s, H-12), 2.26 (1H, br s, OH); **δ_C** (101 MHz, $CDCl_3$) 143.5

(C11), 137.0 (C8), 136.9 (C4), 129.8 (C10), 129.3 (C5), 128.8 (C6), 127.1 (C9), 126.8 (C7), 64.2 (C1), 56.8 (C2), 37.9 (C3), 21.7 (C12); ***m/z*** (ESI+) 328 ($[M+Na]^+$, 100%); **HRMS** calculated for $[C_{16}H_{19}NNaO_3S]$ ($M+Na^+$) 328.0978, found 328.0976. Data consistent with the literature.[145]

(2*R*,4*S*)-4-Benzyl-3-tosyl-1,2,3-oxathiazolidine 2-oxide (20)

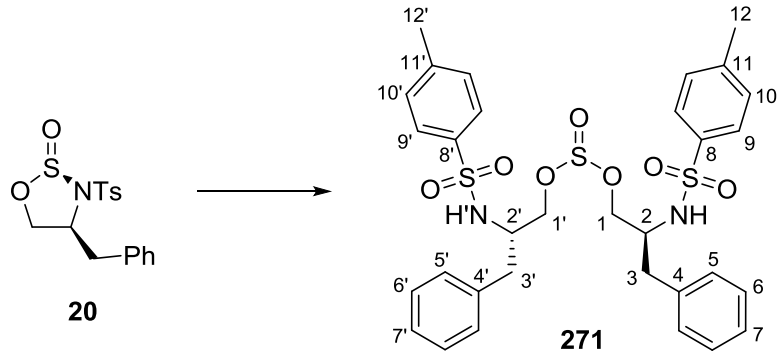


19 **20**

To a 3-neck round-bottom flask equipped with a dropping funnel and thermometer, *N*-tosyl (*S*)-phenylalaninol **19** (20.0 g, 65.5 mmol) was dissolved in anhydrous tetrahydrofuran (600 mL) and degassed with N_2 for 15 min. The solution was cooled to –78 °C before thionyl chloride (4.75 mL, 65.5 mmol) was added dropwise *via* the dropping funnel. Anhydrous pyridine (11.7 mL, 144 mmol) in anhydrous tetrahydrofuran (80 mL) was added dropwise *via* the dropping funnel over 15-20 min. The resulting mixture was stirred at –78 °C for 2 h and then allowed to warm to –20 °C. At –20 °C the cold mixture was filtered through a pad of silica gel, washed with dichloromethane (100 mL) and then concentrated *in vacuo* at room temperature to give the crude product (22.80 g) as a white amorphous solid. Purified by filtration through a small plug of silica gel (eluting with 100% dichloromethane) to afford **20** (21.0 g, 91%, >99:1 *dr* determined from its ^{1}H NMR spectrum) as a white amorphous solid.

δ_H (400 MHz, $CDCl_3$) 7.89–7.75 (2H, m, H-9), 7.41–7.33 (2H, m, H-10), 7.33–7.20 (3H, m, H-6 and H-7), 7.15–7.06 (2H, m, H-5), 4.82 (1H, app. t, *J* = 9.1 Hz, H-1a), 4.40 (1H, dd, *J* = 9.1, 6.5 Hz, H-1b), 3.91 (1H, dddd, *J* = 10.6, 9.1, 6.5, 4.2 Hz, H-2), 3.38 (1H, dd, *J* = 13.5, 4.2 Hz, H-3a), 2.75 (1H, dd, *J* = 13.5, 10.6 Hz, H-3b), 2.46 (3H, s, H-12); **δ_c** (101 MHz, $CDCl_3$) 145.2 (C11), 136.0 (C4), 135.4 (C8), 130.3 (C10), 129.0 (C6), 128.8 (C5), 127.6 (C9), 127.4 (C7), 77.8 (C1), 60.5 (C2), 39.2 (C3), 21.7 (C12); ***m/z*** (ESI+) 374 ($[M+Na]^+$, 100%); **HRMS** calculated for $[C_{16}H_{17}NNaO_4S_2]$ ($M+Na^+$) 374.0491, found 374.0491. Data consistent with the literature.[21]

Bis-((*S*)-2-((4-methylphenyl)sulfonamido)-3-phenylpropyl) sulfite (271)

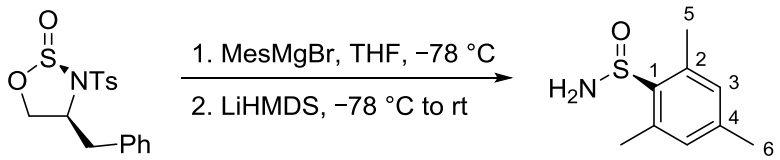


A sample of (2*R*,4*S*)-4-Benzyl-3-tosyl-1,2,3-oxathiazolidine 2-oxide **20** (1.00 g) that was stored for 2 years was re-purified by column chromatography over silica gel (eluting with 1:9, 1:4 then 3:7 ethyl acetate/cyclohexane) to afford **271** (150 mg) as a colourless oil.

$[\alpha]_D^{17}$ –45 (*c* 1.00, $CHCl_3$); **υ_{max}** (cm^{-1}) 3278 (NH), 3029, 2951, 2925, 1325, 1154, 1091, 981, 664; **δ_H** (400 MHz, $CDCl_3$) 7.66–7.55 (4H, m, H-9 and H-9'), 7.25–7.13 (10H, m, H-6, H-6', H-7, H-7', H-10 and H-10'), 7.05–6.98 (4H, m, H-5 and H-5'), 5.51 (1H, d, *J* = 7.7 Hz, NH), 5.44 (1H, d, *J* = 8.2 Hz, NH'), 4.16 (1H, m,

H-1a'), 4.14 (1H, m, H-1a), 3.99 (1H, dd, *J* = 10.3, 3.4 Hz, H-1b'), 3.95 (1H, dd, *J* = 10.6, 4.0 Hz, H-1b), 3.78–3.70 (1H, m, H-2'), 3.70–3.62 (1H, m, H-2), 2.83 (2H, ddd, *J* = 15.6, 13.9, 7.3 Hz, H-3a and H-3a'), 2.72 (2H, ddd, *J* = 13.9, 7.5, 2.2 Hz, H-3b and H-3b'), 2.41 (6H, s, H-12 and H-12'); $\boldsymbol{\delta_c}$ (101 MHz, $CDCl_3$) 143.4 (C11 or C11'), 143.4 (C11 or C11'), 137.3 (C8 or C8'), 137.3 (C8 or C8'), 136.4 (C4 or C4'), 136.3 (C4 or C4'), 129.8 (C10 and C10'), 129.3 (C5 or C5'), 129.2 (C5 or C5'), 128.8 (C6 or C6'), 128.8 (C6 or C6'), 127.0 (C7 and C7'), 126.9 (C9 or C9'), 126.9 (C9 or C9'), 64.8 (C1), 63.6 (C1'), 54.6 (C2 or C2'), 54.5 (C2 or C2'), 37.9 (C3 and C3'), 21.6 (C12 and C12'); ***m/z*** (ESI+) 679 ($[M+Na]^+$, 97%); **HRMS** calculated for $[C_{32}H_{36}N_2NaO_7S_3]^+$ $(M+Na)^+$ 679.1577, found 679.1541.

(*S*)-2,4,6-Trimethylbenzenesulfinamide (16)



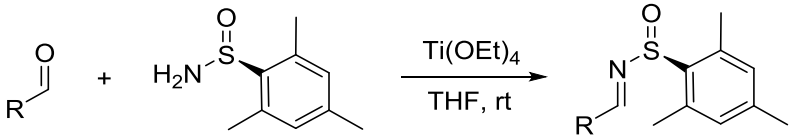
20 **16**

To a solution of (2*R*,4*S*)-4-benzyl-3-tosyl-1,2,3-oxathiazolidine 2-oxide **20** (6.58 g, 18.7 mmol) in anhydrous tetrahydrofuran (66 mL) at –78 °C was added a 1.0 M solution of 2-mesitylmagnesium bromide in diethyl ether (18.7 mL, 18.7 mmol). The solution was stirred for 80 min at –78 °C before a 1.0 M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran/ethyl benzene (46.8 mL, 46.8 mmol) was added. The resulting mixture was allowed to warm to room temperature and then stirred overnight. Quenched with a saturated aqueous solution of ammonium chloride (50 mL). The aqueous layer was extracted with ethyl acetate (15 mL x2). The combined organics were washed with brine

(20 mL), dried over anhydrous magnesium sulfate and then concentrated *in vacuo* to give the crude product as an orange oil. Purification by column chromatography over silica gel (eluting with 1:1 ethyl acetate/petroleum ether then 1:0 ethyl acetate) afforded **16** (2.54 g, 74%, 99:1 *er*) as an off-white amorphous solid.

CSP-HPLC: Chiralcel OD, 4.6 × 250 mm, 10 μm; 9:1 (Hexane/^{i}PrOH), 1.0 mL min^{-1}, 250 nm; (*S*)-**16**, r_t = 19.7 min, (*R*)-**16**, r_t = 28.3 min; υ_{max} ($CHCl_3$)/cm 2955, 2931, 2857, 1717, 1437, 1277, 1256, 1186, 1152, 1094; δ_H (400 MHz, $CDCl_3$) 6.87 (2H, s, H-3), 4.40 (2H, br s, NH_2), 2.60 (6H, s, H-5), 2.28 (3H, s, H-6); δ_c (101 MHz, $CDCl_3$) 140.9 (C4), 139.0 (C1), 136.3 (C2), 131.0 (C3), 21.1 (C5), 19.4 (C5); ***m/z*** (ESI+) 206 ([M+Na]$^+$, 100%); **HRMS** calculated for [$C_9H_{13}NNaOS$] (M+Na$^+$) 206.0610, found 206.0623. Data consistent with the literature.[19]

3.2 General procedure for the preparation of *N*-[mesityl-(*S*)-sulfinyl]-aldimines 234, 279-289.[46]

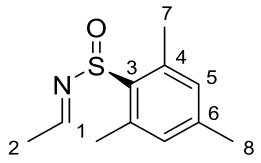


(*S*)-**16** **234**, **279-289**

A solution of titanium(IV) ethoxide (2.94-43.7 mmol, 2.6 equivalents) and the corresponding aldehyde (1.47-21.8 mmol, 1.3 equivalents) in tetrahydrofuran (9.0-134 mL) were stirred at room temperature for 30 min. A solution of (*S*)-2,4,6-trimethylbenzenesulfinamide **16** (1.13-16.8 mmol, 1.0 equivalent) in tetrahydrofuran (2.3-34 mL) was added and the reaction was stirred at room temperature until the sulfinamide was consumed. Brine (5.7-84 mL) was

added and the resulting slurry was stirred vigorously for 10 min before being filtered through a pad of Celite®. The layers were separated and then the aqueous layer was extracted with ethyl acetate (2.3-34 mL x3). The combined organic extracts were washed with 20% w/v brine (2.3-34 mL), dried over anhydrous sodium sulfate and then concentrated *in vacuo*.

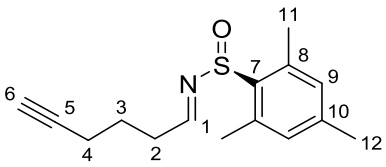
_N_-[Mesityl-(_S_)-sulfinyl]-acetaldimine (279)



The general procedure was followed using acetaldehyde (0.51 mL, 9.16 mmol) and afforded the crude product (1.38 mg) as an orange oil. Purification by column chromatography over silica gel (eluting with 1:9 to 3:7 ethyl acetate/cyclohexane) afforded **279** (559 mg, 41%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 8.32 (1H, q, *J* = 5.1 Hz, H-1), 6.84 (2H, s, H-5), 2.46 (6H, s, H-7), 2.27 (3H, s, H-8), 2.25 (3H, d, *J* = 5.1 Hz, H-2); **δ_c** (101 MHz, $CDCl_3$) 164.4 (C1), 141.8 (C6), 138.3 (C4), 135.2 (C3), 131.0 (C5), 22.3 (C2), 21.2 (C8), 18.9 (C7); ***m/z*** (ESI+) 232 ($[M+Na]^+$, 18%); **HRMS** calculated for $[C_{11}H_{15}NNaOS]^+$ $(M+Na)^+$ 232.0767, found 232.0758. Data consistent with the literature.[60]

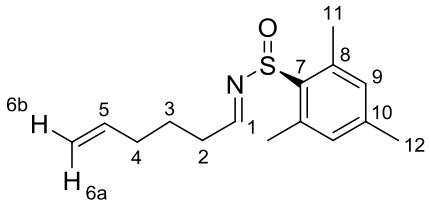
***N*-[Mesityl-(*S*)-sulfinyl]-5-hexynealdimine (280)**



The general procedure was followed using 5-hexynal (852 mg, 8.86 mmol) and afforded the crude product (1.83 g) as a yellow oil. Purification by column chromatography over silica gel (eluting with 3:97 to 9:91 ethyl acetate/petroleum ether) afforded **280** (1.21 g, 68%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 8.32 (1H, t, *J* = 4.6 Hz, H-1), 6.84 (2H, s, H-9), 2.69–2.63 (2H, m, H-2), 2.45 (6H, s, H-11), 2.30–2.24 (2H, m, H-4), 2.27 (3H, s, H-12), 1.98 (1H, t, *J* = 2.6 Hz, H-6), 1.92–1.80 (2H, m, H-3); **δ_c** (101 MHz, $CDCl_3$) 167.1 (C1), 141.8 (C10), 138.3 (C8), 135.2 (C7), 131.0 (C9), 83.3 (C5), 69.5 (C6), 34.8 (C2), 24.3 (C3), 21.2 (C12), 18.9 (C11), 18.1 (C4); ***m/z*** (ESI+) 284 ($[M+Na]^+$, 42%); **HRMS** calculated for $[C_{15}H_{19}NNaOS]^+$ $(M+Na)^+$ 284.1080, found 284.1079. Data consistent with the literature.[60]

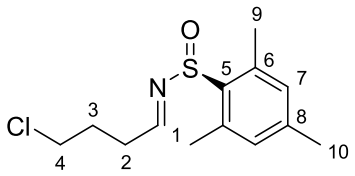
***N*-[Mesityl-(*S*)-sulfinyl]-5-hexenealdimine (281)**



The general procedure was followed using 5-hexenal (720 mg, 7.31 mmol) and afforded the crude product (1.91 g) as a yellow oil. Purification by column chromatography over silica gel (eluting with 3:97 ethyl acetate/cyclohexane) afforded **281** (831 mg, 56%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 8.30 (1H, t, *J* = 5.0 Hz, H-1), 6.84 (2H, s, H-9), 5.77 (1H, ddt, *J* = 17.0, 10.2, 6.7 Hz, H-5), 5.08–4.94 (2H, m, H-6), 2.57–2.51 (2H, m, H-2), 2.45 (6H, s, H-11), 2.27 (3H, s, H-12), 2.16–2.09 (2H, m, H-4), 1.77–1.68 (2H, m, H-3); **δ_c** (101 MHz, $CDCl_3$) 167.9 (C1), 141.7 (C10), 138.3 (C8), 137.7 (C5), 135.2 (C7), 131.0 (C9), 115.6 (C6), 35.4 (C2), 33.3 (C4), 24.9 (C3), 21.2 (C12), 18.9 (C11); ***m/z*** (ESI+) 286 ($[M+Na]^+$, 25%); **HRMS** calculated for $[C_{15}H_{21}NNaOS]^+$ $(M+Na)^+$ 286.1236, found 286.1237. Data consistent with the literature.[60]

***N*-[Mesityl-(*S*)-sulfinyl]-4-chlorobutylaldimine (282)**

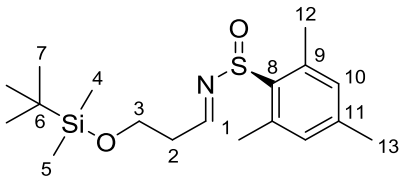


The general procedure was followed using 4-chlorobutanal (900 mg, 8.45 mmol) and afforded the crude product (2.46 g) as a yellow oil. Purification by column chromatography over silica gel (eluting with 3:97 then 1:19 then 1:9 ethyl acetate/cyclohexane) afforded **282** (1.17 g, 66%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 8.33 (1H, t, *J* = 4.3 Hz, H-1), 6.85 (2H, s, H-7), 3.58 (2H, app. td, *J* = 6.7, 0.8 Hz, H-4), 2.71 (2H, tdd, *J* = 7.1, 4.3, 1.6 Hz, H-2), 2.45 (6H, s, H-9), 2.27 (3H, s, H-10), 2.12 (2H, quin, *J* = 6.7 Hz, H-3); **δ_c** (101 MHz, $CDCl_3$) 166.4 (C1), 141.9 (C8), 138.3 (C6), 135.1 (C5), 131.0 (C7), 44.1 (C4), 33.1 (C2), 28.2 (C3), 21.2 (C10), 18.9 (C9); ***m/z*** (ESI+) 294 ($[M+Na]^+$, 59%); **HRMS**

calculated for $[C_{13}H_{18}ClNNaOS]^+$ $(M+Na)^+$ 294.0690, found 294.0692. Data consistent with the literature.[60]

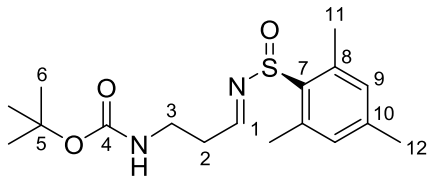
_N_-[Mesityl-(_S_)-sulfinyl]-3-(_tert_-butyldimethylsilyloxy)propylaldimine (283)



The general procedure was followed using 3-(*tert*-butyldimethylsilyloxy)propanal (4.11 g, 21.8 mmol) and afforded the crude product (4.73 g) as a yellow oil. Purification by column chromatography over silica gel (eluting with 1:15 to 1:6 ethyl acetate/petroleum ether) afforded **283** (3.03 g, 78%) as a yellow oil.

$[\alpha]_D^{23}$ +61 (*c* 0.02, $CHCl_3$); **υ_{max}** (cm^{-1}) ($CHCl_3$) 3007, 2957, 2931, 2885, 2858, 1621, 1602, 1471, 1257, 1098; **δ_H** (400 MHz, $CDCl_3$) 8.35 (1H, t, *J* = 4.9 Hz, H-1), 6.84 (2H, s, H-10), 3.96-3.89 (2H, m, H-3), 2.73 (2H, td, *J* = 6.1, 4.9 Hz, H-2), 2.46 (6H, s, H-12), 2.27 (3H, s, H-13), 0.87 (9H, s, H-7), 0.04 (3H, s, H-4 or H-5), 0.03 (3H, s, H-4 or H-5); **δ_c** (101 MHz, $CDCl_3$) 166.6 (C1), 141.8 (C11), 138.4 (C9), 135.2 (C8), 131.0 (C10), 59.8 (C3), 39.4 (C2), 26.0 (C7), 21.2 (C13), 18.9 (C12), 18.4 (C6), -5.3 (C4 and C5); ***m/z*** (ESI+) 376 ($[M+Na]^+$, 100%); **HRMS** calculated for $[C_{18}H_{31}NNaO_2SSi]^+$ $(M+Na)^+$ 376.1737, found 376.1741.

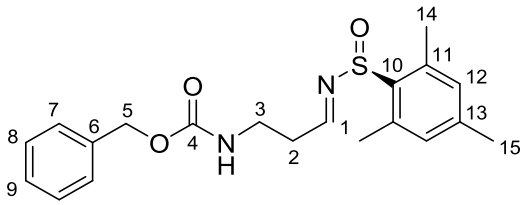
***N*-[Mesityl-(*S*)-sulfinyl]-3-(*tert*-butoxycarbonylamino)propylaldimine (284)**



The general procedure was followed using 3-(*tert*-butoxycarbonylamino)propanal (1.20 g, 6.93 mmol) and afforded the crude product (2.28 g) as a yellow oil. Purification by column chromatography over silica gel (eluting with 1:4 to 2:3 ethyl acetate/cyclohexane) afforded **284** (1.11 g, 62%) as a colourless oil.

$[\alpha]_D^{20}$ +155 (*c* 0.54, $CHCl_3$); **υ_{max}** (cm^{-1}) (neat) 3343 (NH), 2976, 2932, 1694 (C=O), 1618, 1506, 1366, 1271, 1248, 1165, 1080, 731; **δ_H** (400 MHz, $CDCl_3$) 8.32 (1H, t, *J* = 3.9 Hz, H-1), 6.84 (2H, s, H-9), 4.80 (1H, br s, NH), 3.48–3.38 (2H, m, H-3), 2.82–2.65 (2H, m, H-2), 2.44 (6H, s, H-11), 2.27 (3H, s, H-12), 1.41 (9H, s, H-6); **δ_c** (101 MHz, $CDCl_3$) 165.8 (C1), 155.8 (C4), 141.9 (C10), 138.3 (C8), 135.1 (C7), 131.0 (C9), 79.5 (C5), 36.6 (C3), 36.3 (C2), 28.5 (C6), 21.2 (C12), 18.8 (C11); ***m/z*** (ESI+) 339 ($[M+H]^+$, 100%); **HRMS** calculated for $[C_{17}H_{27}N_2O_3S]^+$ $(M+H)^+$ 339.1737, found 339.1737.

***N*-[Mesityl-(*S*)-sulfinyl]-3-(benzyloxycarbonylamino)propylaldimine (285)**

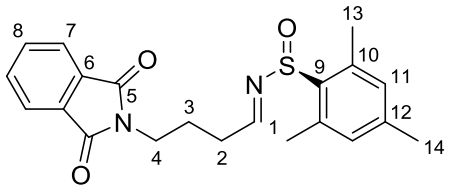


The general procedure was followed using 3-(benzyloxycarbonylamino) propanal (305 mg, 1.47 mmol) and afforded the crude product (559 mg) as a

yellow oil. Purification by column chromatography over silica gel (eluting with 1:3 to 1:1 ethyl acetate/cyclohexane) afforded **285** (288 mg, 68%) as a colourless oil.

$[\alpha]_D^{20}$ +168 (*c* 0.5, $CHCl_3$); **υ_{max}** (cm^{-1}) (neat) 3329 (NH), 3063, 3032, 2955, 1697 (C=O), 1618, 1520, 1454, 1244, 1215, 1140, 1078, 1026, 735; **δ_H** (400 MHz, $CDCl_3$) 8.34 (1H, t, *J* = 3.7 Hz, H-1), 7.39–7.29 (5H, m, H-7, H-8 and H-9), 6.82 (2H, s, H-12), 5.15–5.01 (3H, m, H-8 and NH), 3.58–3.47 (2H, m, H-3), 2.84–2.68 (2H, m, H-2), 2.43 (6H, s, H-14), 2.26 (3H, s, H-15); **δ_c** (101 MHz, $CDCl_3$) 165.7 (C1), 156.3 (C4), 141.9 (C13), 138.3 (C11), 136.5 (C6), 135.1 (C10), 131.0 (C12), 128.6 (C8), 128.3 (C7), 128.2 (C9), 66.9 (C5), 37.0 (C3), 36.1 (C2), 21.2 (C15), 18.8 (C14); ***m/z*** (ESI+) 373 ($[M+H]^+$, 82%); **HRMS** calculated for $[C_{20}H_{25}N_2O_3S]^+$ $(M+H)^+$ 373.1580, found 373.1577.

_N_-[Mesityl-(_S_)-sulfinyl]-4-(1,3-dioxoisoindolin-2-yl)butylaldimine (286)

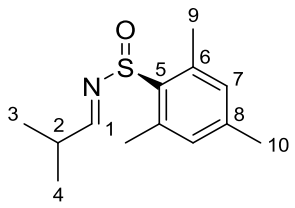


The general procedure was followed using 4-(1,3-dioxoisoindolin-2-yl)butanal (1.21 g, 5.57 mmol) and afforded the crude product (2.14 g) as a yellow oil. Purification by column chromatography over silica gel (eluting with 1:9, 15:85, 1:4, 1:3 then 3:7 ethyl acetate/petroleum ether) afforded **286** (1.08 g, 66%) as a white amorphous solid.

$[\alpha]_D^{24}$ +181 (*c* 1.00, $CHCl_3$); **υ_{max}** (cm^{-1}) 3024, 2931, 2875, 1771 (C=O imide), 1706, 1618, 1601, 1395, 1372, 1086, 1036, 719; **δ_H** (400 MHz, $CDCl_3$) 8.30 (1H,

t, *J* = 4.4 Hz, H-1), 7.81 (2H, app. dd, *J* = 5.5, 3.0 Hz, H-7), 7.69 (2H, app. dd, *J* = 5.5, 3.0 Hz, H-8), 6.81 (2H, s, H-11), 3.74 (2H, t, *J* = 7.0 Hz, H-4), 2.62–2.55 (2H, m, H-2), 2.42 (6H, s, H-13), 2.24 (3H, s, H-14), 2.06–1.96 (2H, m, H-3); δ_c (101 MHz, $CDCl_3$) 168.4 (C5), 166.3 (C1), 141.7 (C12), 138.3 (C10), 135.1 (C9), 134.1 (C8), 132.1 (C6), 130.9 (C11), 123.4 (C7), 37.4 (C4), 33.4 (C2), 24.5 (C3), 21.2 (C14), 18.8 (C13); ***m/z*** (ESI+) 383 ($[M+H]^+$, 100%); **HRMS** calculated for $[C_{21}H_{23}N_2O_3S]^+$ $(M+H)^+$ 383.1424, found 383.1428.

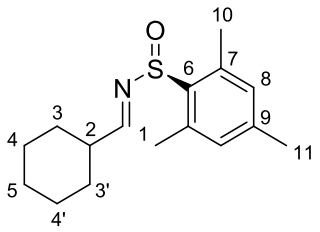
_N_-[Mesityl-(_S_)-sulfinyl]-isobutylaldimine (287)



The general procedure was followed using isobutyraldehyde (0.65 mL, 7.09 mmol) and afforded the crude product (1.34 g) as a yellow oil. Purification by column chromatography over silica gel (eluting with 1:99, 2:98, 4:96 then 6:94 ethyl acetate/petroleum ether) afforded **287** (1.14 g, 88%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 8.19 (1H, d, *J* = 5.2 Hz, H-1), 6.84 (2H, s, H-7), 2.74 (1H, heptd, *J* = 6.9, 5.2 Hz, H-2), 2.45 (6H, s, H-9), 2.27 (3H, s, H-10), 1.17 (3H, d, *J* = 6.9 Hz, H-3 or H-4), 1.16 (3H, d, *J* = 6.9 Hz, H-3 or H-4); δ_c (101 MHz, $CDCl_3$) 172.3 (C1), 141.7 (C8), 138.4 (C6), 135.4 (C5), 131.0 (C7), 34.9 (C2), 21.2 (C10), 19.1 (C3 or C4), 19.0 (C3 or C4), 18.9 (C9); ***m/z*** (ESI+) 260 ($[M+Na]^+$, 100%); **HRMS** calculated for $[C_{13}H_{19}NNaOS]^+$ $(M+Na)^+$ 260.1080, found 260.1075. Data consistent with literature.[146]

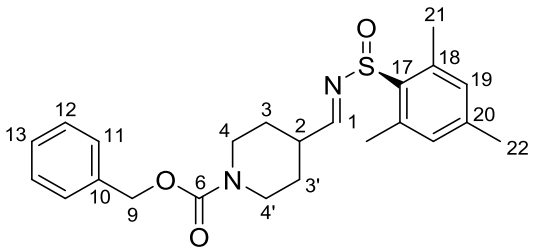
***N*-[Mesityl-(*S*)-sulfinyl]-cyclohexylaldimine (288)**



The general procedure was followed using cyclohexanecarboxaldehyde (0.86 mL, 7.09 mmol) and afforded the crude product (1.87 g) as a yellow oil. Purification by column chromatography over silica gel (eluting with 3:97 to 15:85 ethyl acetate/petroleum ether) afforded **288** (1.39 g, 92%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 8.17 (1H, d, *J* = 5.3 Hz, H-1), 6.83 (2H, s, H-8), 2.55–2.40 (1H, m, H-2), 2.45 (6H, s, H-10), 2.27 (3H, s, H-11), 1.92–1.82 (2H, m, H-3_{eq} and H-$3'_{eq}$), 1.81–1.72 (2H, m, H-4_{eq} and H-$4'_{eq}$), 1.71–1.65 (1H, m, H-5_{eq}), 1.41–1.19 (5H, m, H-3_{ax}, H-$3'_{ax}$, H-4_{ax}, H-$4'_{ax}$ and H-5_{ax}); **δ_c** (101 MHz, $CDCl_3$) 171.3 (C1), 141.7 (C9), 138.4 (C7), 135.4 (C6), 131.0 (C8), 44.2 (C2), 29.4 (C3 or C3'), 29.4 (C3 or C3'), 25.9 (C5), 25.4 (C4 or C4'), 25.4 (C4 or C4'), 21.2 (C11), 18.9 (C10); ***m/z*** (ESI+) 300 ($[M+Na]^+$, 23%); **HRMS** calculated for $[C_{16}H_{23}NNaOS]^+$ $(M+Na)^+$ 300.1393, found 300.1393. Data consistent with literature.[60]

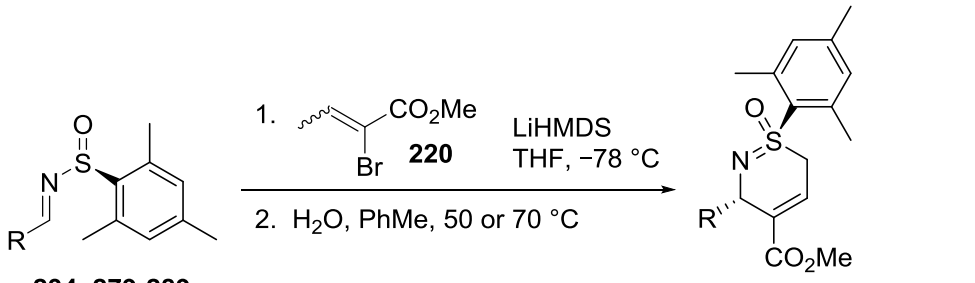
***N*-[Mesityl-(*S*)-sulfinyl]-4-(benzyloxycarbonylpiperidine)aldimine (289)**



The general procedure was followed using 4-formyl-*N*-benzyloxycarbonyl-piperidine (1.76 g, 7.09 mmol) and afforded the crude product (2.70 g) as a yellow oil. Purification by column chromatography over silica gel (eluting with 1:9 to 2:3 ethyl acetate/petroleum ether) afforded **289** (1.60 g, 71%) as a colourless oil.

$[\alpha]_D^{25}$ +88 (*c* 1.00, $CHCl_3$); **υ_{max}** (cm^{-1}) 2929, 2858, 1693 (C=O), 1427, 1219, 1081, 698; **δ_H** (400 MHz, $CDCl_3$) 8.23 (1H, d, *J* = 4.5 Hz, H-1), 7.39–7.35 (5H, m, H-8, H-9 and H-10), 6.87 (2H, s, H-13), 5.14 (2H, s, H-6), 4.28–4.10 (2H, m, H-4_{eq} and H-$4'_{eq}$), 3.01–2.88 (2H, m, H-4_{ax} and H-$4'_{ax}$), 2.74–2.63 (1H, m, H-2), 2.46 (6H, s, H-15), 2.30 (3H, s, H-16), 1.94–1.85 (2H, m, H-3_{eq} and H-$3'_{eq}$), 1.64–1.53 (2H, m, H-3_{ax} and H-$3'_{ax}$); **δ_c** (101 MHz, $CDCl_3$) 168.9 (C1), 155.3 (C5), 141.9 (C14), 138.3 (C12), 136.8 (C7), 135.0 (C11), 131.0 (C13), 128.6 (C9), 128.1 (C10), 128.0 (C8), 67.3 (C6), 43.4 (C4 or C4'), 43.4 (C4 or C4'), 42.0 (C2), 28.3 (C3 and C3'), 21.2 (C16), 18.9 (C15); ***m/z*** (ESI+) 435 ($[M+Na]^+$, 100%); **HRMS** calculated for $[C_{23}H_{28}N_2NaO_3S]^+$ $(M+Na)^+$ 435.1713, found 435.1713.

3.3 General procedure for the preparation of methyl (1*S*,3*S*)-1-mesityl-3,6-dihydro-1λ^6,2-thiazine-4-carboxylate 1-oxides 224, 226, 228, 230-232, 290-294.[60]

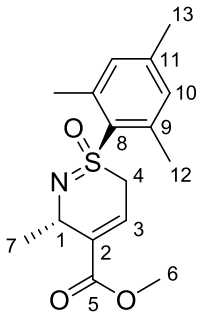


234, **279-289**

224, **226**, **228**, **230-232**, **290-294**

To a solution of methyl 2-bromo-2-butenoate **220** (2.00-7.22 mmol, 2 equivalents) in anhydrous tetrahydrofuran (8.0-28.9 mL) at –78 °C was added a 1.0 M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (2.00-7.22 mmol, 2 equivalents). The solution was stirred at –78 °C for a 20 min before the *N*-[mesityl-(*S*)-sulfinyl]-aldimine **234**, **279**-**289** (1.00-3.61 mmol, 1 equivalent) in anhydrous tetrahydrofuran (2-7.22 mL) was added. The resulting mixture was stirred at –78 °C until the sulfinimine was consumed. The cold solution was then poured into brine (5-18 mL) and stirred for 10 min. The layers were separated and then the aqueous layer was extracted with ethyl acetate (5-18 mL x3). The organic extracts were combined, dried over anhydrous magnesium sulfate and then concentrated *in vacuo* to afford the crude aziridine. The crude aziridine was redissolved in toluene (10-36 mL) and then the solution was stirred at 50 °C or 70 °C until the aziridine was consumed by ^{1}H NMR monitoring. The reaction mixture was allowed to cool to room temperature and then concentrated *in vacuo*.

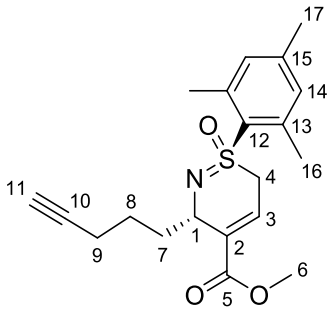
Methyl (1*S*,3*S*)-1-mesityl-3-methyl-3,6-dihydro-1λ^6,2-thiazine-4-carboxylate 1-oxide (224)



The general procedure was followed at 70 °C using *N*-[mesityl-(*S*)-sulfinyl]-acetaldimine **279** (755 mg, 3.61 mmol) and afforded the crude product (1.41 g) as a yellow oil. Purification by column chromatography over silica gel (eluting with 1:9 to 3:7 ethyl acetate/cyclohexane) afforded **224** (628 mg, 57%) as a yellow amorphous solid.

δ_H (400 MHz, $CDCl_3$) 7.05–6.97 (1H, m, H-3), 6.93 (2H, s, H-10), 4.74–4.65 (1H, m, H-1), 4.05 (1H, ddd, *J* = 18.9, 4.8, 2.7 Hz, H-4a), 3.82 (3H, s, H-6), 3.73 (1H, ddd, *J* = 18.9, 3.7, 1.8 Hz, H-4b), 2.61 (6H, s, H-12), 2.28 (3H, s, H-13), 1.55 (3H, d, *J* = 6.8 Hz, H-7); **δ_c** (101 MHz, $CDCl_3$) 166.0 (C5), 142.8 (C11), 140.3 (C9), 137.2 (C2), 133.9 (C8), 132.7 (C10), 129.0 (C3), 52.2 (C6), 51.9 (C1), 49.3 (C4), 25.4 (C7), 22.8 (C12), 21.0 (C13); ***m/z*** (ESI+) 308 ($[M+H]^+$, 100%); **HRMS** calculated for $[C_{16}H_{22}NO_3S]^+$ $(M+H)^+$ 308.1315, found 308.1322. Data consistent with the literature.[60]

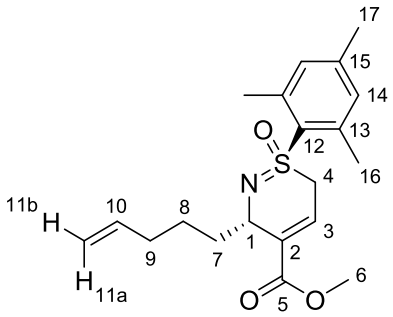
Methyl (1*S*,3*S*)-1-mesityl-3-(pent-4-yn-1-yl)-3,6-dihydro-1λ^6,2-thiazine-4-carboxylate 1-oxide (232)



The general procedure was followed at 50 °C using *N*-[mesityl-(*S*)-sulfinyl]-5-hexynealdimine **280** (261 mg, 1.00 mmol) and afforded the crude product (418 mg) as an orange oil. Purification by column chromatography over silica gel (eluting with 1:9 and then 15:85 ethyl acetate/petroleum ether) afforded **232** (202 mg, 56%) as a yellow amorphous solid.

δ_H (400 MHz, $CDCl_3$) 7.02 (1H, dd, *J* = 5.2, 3.3 Hz, H-3), 6.92 (2H, s, H-14), 4.65–4.56 (1H, m, H-1), 4.08 (1H, ddd, *J* = 19.0, 5.2, 2.4 Hz, H-4a), 3.81 (3H, s, H-6), 3.69 (1H, ddd, *J* = 19.0, 3.3, 1.8 Hz, H-4b), 2.58 (6H, s, H-16), 2.32–2.18 (2H, m, H-9), 2.26 (3H, s, H-17), 2.02–1.92 (2H, m, H-7a and H-8a), 1.91 (1H, t, *J* = 2.6 Hz, H-11), 1.84–1.70 (2H, m, H-7b and H-8b); **δ_c** (101 MHz, $CDCl_3$) 166.0 (C5), 142.8 (C15), 140.2 (C13), 136.6 (C2), 134.3 (C12), 132.7 (C14), 129.7 (C3), 84.8 (C10), 68.2 (C11), 55.8 (C1), 52.2 (C6), 49.7 (C4), 37.8 (C7), 25.5 (C8), 22.7 (C16), 21.0 (C17), 18.3 (C9); ***m/z*** (ESI+) 360 ($[M+H]^+$, 100%); **HRMS** calculated for $[C_{20}H_{26}NO_3S]^+$ $(M+H)^+$ 360.1628, found 360.1628. Data consistent with the literature.[60]

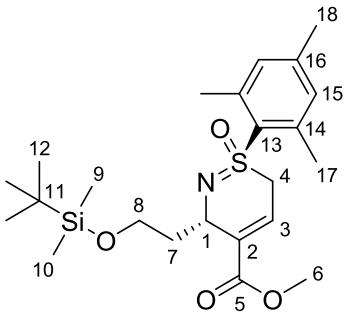
Methyl (1*S*,3*S*)-1-mesityl-3-(pent-4-en-1-yl)-3,6-dihydro-1λ^6,2-thiazine-4-carboxylate 1-oxide (231)



The general procedure was followed at 50 °C using *N*-[mesityl-(*S*)-sulfinyl]-5-hexenealdimine **281** (263 mg, 1.00 mmol) and afforded the crude product (496 mg) as an orange oil. Purification by column chromatography over silica gel (eluting with 3:97, 1:19, 8:92 then 11:89 ethyl acetate/cyclohexane) afforded **231** (155 mg, 43%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 7.00 (1H, dd, *J* = 5.3, 3.3 Hz, H-3), 6.91 (2H, s, H-14), 5.82 (1H, ddt, *J* = 17.1, 10.2, 6.6 Hz, H-10), 5.00 (1H, ddd, *J* = 17.1, 3.6, 1.5 Hz, H-11a), 4.91 (1H, ddt, *J* = 10.2, 2.2, 1.5 Hz, H-11b), 4.66–4.56 (1H, m, H-1), 4.09 (1H, ddd, *J* = 19.0, 5.3, 2.4 Hz, H-4a), 3.80 (3H, s, H-6), 3.68 (1H, ddd, *J* = 19.0, 3.3, 1.8 Hz, H-4b), 2.58 (6H, s, H-16), 2.26 (3H, s, H-17), 2.16–2.06 (2H, m, H-9), 1.88–1.75 (2H, m, H-7a and H-8a), 1.73–1.60 (2H, m, H-7b and H-8b); **δ_c** (101 MHz, $CDCl_3$) 166.1 (C5), 142.7 (C15), 140.2 (C13), 139.1 (C10), 136.9 (C2), 134.5 (C12), 132.7 (C14), 129.5 (C3), 114.3 (C11), 56.3 (C1), 52.2 (C6), 49.8 (C4), 38.3 (C7), 33.6 (C9), 25.7 (C8), 22.7 (C16), 21.0 (C17); ***m/z*** (ESI+) 362 ($[M+H]^+$, 100%); **HRMS** calculated for $[C_{20}H_{28}NO_3S]^+$ $(M+H)^+$ 362.1784, found 362.1787. Data consistent with the literature.[60]

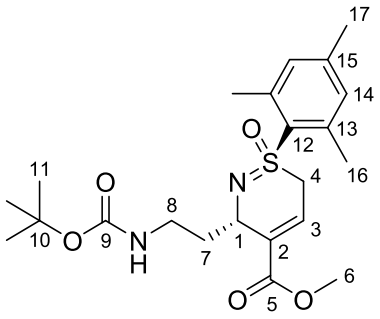
Methyl (1*S*,3*S*)-1-mesityl-3-(2-*tert*-butyldimethylsilyloxyethyl)-3,6-dihydro-1λ^6,2-thiazine-4-carboxylate 1-oxide (290)



The general procedure was followed at 50 °C using *N*-[mesityl-(*S*)-sulfinyl]-3-(*tert*-butyldimethylsilyloxy)propylaldimine **283** (354 mg, 1.00 mmol) and afforded the crude product (490 mg) as an yellow oil. Purification by column chromatography over silica gel (eluting with 3:97, 6:94, 9:91 and then 12:88 ethyl acetate/petroleum ether) afforded **290** (235 mg, 52%) as a yellow oil.

$[\alpha]_D^{22}$ +86 (*c* 0.5, $CHCl_3$); **υ_{max}** (cm^{-1}) ($CHCl_3$) 2955, 2931, 2885, 2857, 1717 (C=O), 1648 (C=C), 1603, 1472, 1438, 1277, 1256, 1186, 1152, 1094, 1036; **δ_H** (400 MHz, $CDCl_3$) 7.02 (1H, dd, *J* = 5.1, 3.4 Hz, H-3), 6.92 (2H, s, H-15), 4.72 (1H, app. ddt, *J* = 10.3, 3.7, 2.1 Hz, H-1), 4.08 (1H, ddd, *J* = 18.9, 5.1, 2.5 Hz, H-4a), 4.03–3.88 (2H, m, H-8), 3.80 (3H, s, H-6), 3.70 (1H, ddd, *J* = 18.9, 3.4, 1.8 Hz, H-4b), 2.59 (6H, s, H-17), 2.27 (3H, s, H-18), 2.09–2.00 (1H, m, H-7a), 1.92 (1H, dddd, *J* = 13.0, 10.3, 7.3, 4.8 Hz, H-7b), 0.89 (9H, s, H-12), 0.06 (6H, s, H-9 and H-10); **δ_c** (101 MHz, $CDCl_3$) 166.0 (C5), 142.7 (C16), 140.2 (C14), 136.7 (C2), 134.4 (C13), 132.7 (C15), 129.5 (C3), 61.0 (C8), 53.4 (C1), 52.2 (C6), 49.6 (C4), 41.8 (C7), 26.2 (C12), 22.7 (C17), 21.0 (C18), 18.5 (C11), -5.0 (C9 or C10), -5.1 (C9 or C10); ***m/z*** (ESI+) 452 ($[M+H]^+$, 100%); **HRMS** calculated for $[C_{23}H_{38}NO_4SSi]^+$ $(M+H)^+$ 452.2285, found 452.2298.

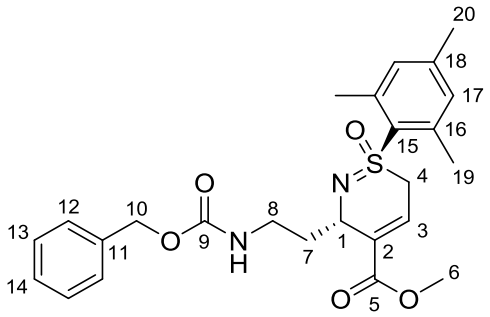
Methyl (1*S*,3*S*)-1-mesityl-3-(2-*tert*-butoxycarbonylaminoethyl)-3,6-dihydro-1λ^6,2-thiazine-4-carboxylate 1-oxide (291)



The general procedure was followed at 70 °C using *N*-[mesityl-(*S*)-sulfinyl]-3-(*tert*-butoxycarbonylamino)propylaldimine **284** (339 mg, 1.00 mmol) and afforded the crude product (451 mg) as an orange oil. Purification by column chromatography over silica gel (eluting with 1:9, 1:4, 3:7 then 2:3 ethyl acetate/cyclohexane) afforded **291** (88 mg, 20%) as a yellow oil.

$[\alpha]_D^{23}$ +50 (*c* 1.00, $CHCl_3$); **υ_{max}** (cm^{-1}) 3383 (NH), 2974, 2950, 2931, 1705 (C=O), 1648 (C=C), 1508, 1218, 1244, 1163 – did not observe a second distinctive C=O band; **δ_H** (400 MHz, $CDCl_3$) 7.05 (1H, dd, *J* = 5.0, 3.4 Hz, H-3), 6.94 (2H, s, H-14), 5.30 (1H, br s, NH), 4.70–4.61 (1H, m, H-1), 4.15–4.07 (1H, m, H-4a), 3.81 (3H, s, H-6), 3.72 (1H, ddd, *J* = 19.1, 3.5, 1.8 Hz, H-4b), 3.56–3.42 (1H, m, H-8a), 3.42–3.31 (1H, m, H-8b), 2.59 (6H, s, H-16), 2.28 (3H, s, H-17), 2.17–2.07 (1H, m, H-7a), 1.81–1.71 (1H, m, H-7b), 1.42 (9H, s, H-11); **δ_c** (101 MHz, $CDCl_3$) 165.8 (C5), 156.2 (C9), 143.0 (C15), 140.2 (C13), 136.1 (C2), 133.9 (C12), 132.8 (C14), 129.8 (C3), 78.7 (C10), 54.9 (C1), 52.4 (C6), 49.7 (C4), 38.7 (C8), 37.8 (C7), 28.6 (C11), 22.7 (C16), 21.0 (C17); ***m/z*** (ESI+) 437 ($[M+H]^+$, 100%); **HRMS** calculated for $[C_{22}H_{33}N_2O_5S]^+$ $(M+H)^+$ 437.2105, found 437.2112.

Methyl (1*S*,3*S*)-1-mesityl-3-(2-benzyloxycarbonylaminoethyl)-3,6-dihydro-1λ^6,2-thiazine-4-carboxylate 1-oxide (292)

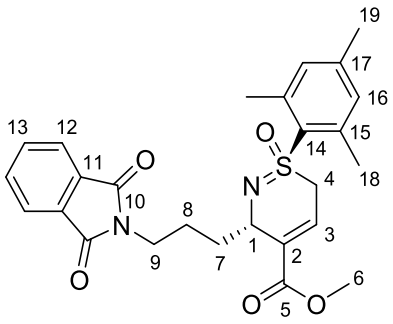


The general procedure was followed at 50 °C using *N*-[mesityl-(*S*)-sulfinyl]-3-(benzyloxycarbonylamino)propylaldimine **285** (373 mg, 1.00 mmol) and afforded the crude product (567 mg) as an orange oil. Purification by column chromatography over silica gel (eluting with 1:9, 1:4, 3:7 then 2:3 ethyl acetate/cyclohexane) afforded **292** (161 mg, 34%) as a colourless oil.

[α]$_D^{23}$ +82 (*c* 1.00, $CHCl_3$); **υ$_{max}$** (cm^{-1}) 3362 (NH), 3031, 2949, 1709 (C=O), 1648 (C=C), 1518, 1453, 1437, 1240, 1220, 1034, 738, 696; **δ$_H$** (400 MHz, $CDCl_3$) 7.42–7.29 (5H, m, H-12, H-13 and H-14), 7.07 (1H, dd, *J* = 5.0, 3.4 Hz, H-3), 6.95 (2H, s, H-17), 5.61 (1H, t, *J* = 5.7 Hz, NH), 5.18–5.06 (2H, m, H-10), 4.74–4.60 (1H, m, H-1), 4.11 (1H, ddd, *J* = 19.1, 5.1, 2.5 Hz, H-4a), 3.81 (3H, s, H-6), 3.74 (1H, ddd, *J* = 19.1, 3.5, 1.8 Hz, H-4b), 3.65–3.54 (1H, m, H-8a), 3.53–3.44 (1H, m, H-8b), 2.59 (6H, s, H-19), 2.30 (3H, s, H-20), 2.23–2.11 (1H, m, H-7a), 1.88–1.78 (1H, m, H-7b); **δ$_c$** (101 MHz, $CDCl_3$) 165.7 (C5), 156.5 (C9), 143.0 (C18), 140.2 (C16), 137.1 (C11), 135.9 (C2), 133.7 (C15), 132.8 (C17), 129.8 (C3), 128.5 (C13 or C14), 128.0 (C12), 127.9 (C13 or C14), 66.4 (C10), 54.8 (C1), 52.3 (C6), 49.5 (C4), 39.2 (C8), 37.7 (C7), 22.6 (C19), 21.0 (C20); ***m/z*** (ESI+) 471

([M+H]$^+$, 100%); **HRMS** calculated for $[C_{25}H_{31}N_2O_5S]^+$ $(M+H)^+$ 471.1948, found 471.1958.

Methyl (1S,3S)-3-(3-(1,3-dioxoisoindolin-2-yl)propyl)-1-mesityl-3,6-dihydro-1λ^6,2-thiazine-4-carboxylate 1-oxide (293)

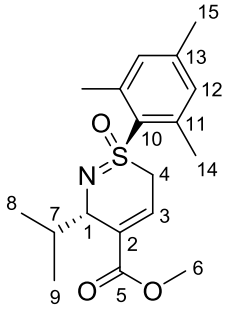


The general procedure was followed at 50 °C using *N*-[mesityl-(*S*)-sulfinyl]-4-(1,3-dioxoisoindolin-2-yl)butylaldimine **286** (383 mg, 1.00 mmol) and afforded the crude product (807 mg) as a yellow oil. Purification by column chromatography over silica gel (eluting with 15:85, 1:4, 1:3 then 3:7 ethyl acetate/cyclohexane) afforded **293** (193 mg, 40%) as a white solid.

$[\alpha]_D^{23}$ +94 (*c* 1.00, $CHCl_3$); **υ_{max}** (cm^{-1}) 2935, 2857, 1770 (C=O imide), 1706 (C=O ester), 1646 (C=C), 1602, 1396, 721; **δ_H** (400 MHz, $CDCl_3$) 7.80 (2H, dd, *J* = 5.5, 3.0 Hz, H-12), 7.66 (2H, dd, *J* = 5.5, 3.0 Hz, H-13), 7.00 (1H, dd, *J* = 5.2, 3.3 Hz, H-3), 6.89 (2H, s, H-16), 4.63–4.54 (1H, m, H-1), 4.05 (1H, ddd, *J* = 18.9, 5.2, 2.4 Hz, H-4a), 3.81-3.63 (2H, m, H-9), 3.74 (3H, s, H-6), 3.63 (1H, ddd, *J* = 18.9, 3.4, 1.7 Hz, H-4b), 2.53 (6H, s, H-18), 2.25 (3H, s, H-19), 2.23–2.14 (1H, m, H-8a), 1.93–1.84 (2H, m, H-7a and H-8b)), 1.76–1.66 (1H, m, H-7b); **δ_c** (101 MHz, $CDCl_3$) 168.6 (C10), 165.9 (C5), 142.7 (C17), 140.1 (C15), 136.4 (C2), 134.2 (C14), 133.7 (C13), 132.6 (C16), 132.4 (C11), 130.0 (C3), 123.1 (C12), 55.8 (C1),

52.2 (C6), 49.7 (C4), 38.0 (C9), 35.8 (C7), 25.6 (C8), 22.6 (C18), 21.0 (C19); ***m/z*** (ESI+) 481 ($[M+H]^+$, 100%); **HRMS** calculated for $[C_{26}H_{29}N_2O_5S]^+$ $(M+H)^+$ 481.1792, found 481.1789.

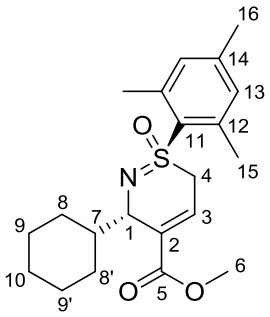
Methyl (1*S*,3*S*)-1-mesityl-3-isopropyl-3,6-dihydro-1λ^6,2-thiazine-4-carboxylate 1-oxide (226)



The general procedure was followed at 50 °C using *N*-[mesityl-(*S*)-sulfinyl]-isobutylaldimine **287** (237 mg, 1.00 mmol) and afforded the crude product (414 mg) as a yellow oil. Purification by column chromatography over silica gel (eluting with 3:97, 6:94, 1:9 then 15:85 ethyl acetate/cyclohexane) afforded **226** (205 mg, 61%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 6.98 (1H, dd, *J* = 6.1, 2.9 Hz, H-3), 6.89 (2H, s, H-12), 4.62 (1H, dt, *J* = 5.9, 2.2 Hz, H-1), 4.10 (1H, ddd, *J* = 18.7, 6.1, 2.2 Hz, H-4a), 3.79 (3H, s, H-6), 3.59 (1H, dt, *J* = 18.7, 2.5 Hz, H-4b), 2.57 (6H, s, H-14), 2.25 (3H, s, H-15), 2.15–1.98 (1H, app. oct, *J* = 6.7 Hz, H-7), 1.02 (3H, d, *J* = 6.7 Hz, H-8 or H-9), 1.02 (3H, d, *J* = 6.7 Hz, H-8 or H-9); **δ_c** (101 MHz, $CDCl_3$) 166.6 (C5), 142.4 (C13), 140.0 (C11), 136.8 (C2), 136.0 (C10), 132.7 (C12), 130.0 (C3), 63.1 (C1), 52.3 (C6), 50.0 (C4), 35.1 (C7), 22.9 (C14), 20.9 (C15), 20.4 (C8 or C9), 18.3 (C8 or C9); ***m/z*** (ESI+) 336 ($[M+H]^+$, 100%); **HRMS** calculated for $[C_{18}H_{26}NO_3S]^+$ $(M+H)^+$ 336.1628, found 336.1635. Data consistent with the literature.[60]

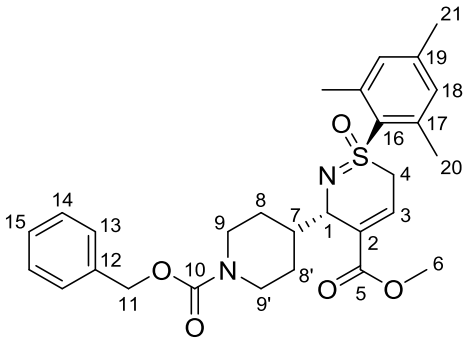
Methyl (1*S*,3*S*)-1-mesityl-3-cyclohexyl-3,6-dihydro-1λ^6,2-thiazine-4-carboxylate 1-oxide (228)



The general procedure was followed at 70 °C using *N*-[mesityl-(*S*)-sulfinyl]-cyclohexylaldimine **288** (277 mg, 1.00 mmol) and afforded the crude product (507 mg) as an orange oil. Purification by column chromatography over silica gel (eluting with 1:24, 7:93 then 1:9 ethyl acetate/cyclohexane) afforded **228** (206 mg, 55%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 6.97 (1H, dd, *J* = 6.3, 2.6 Hz, H-3), 6.89 (3H, s, H-13), 4.64 (1H, app. dt, *J* = 6.3, 2.0 Hz, H-1), 4.11 (1H, ddd, *J* = 18.5, 6.3, 2.0 Hz, H-4a), 3.80 (3H, s, H-6), 3.59 (1H, app. dt, *J* = 18.5, 2.6 Hz, H-4b), 2.57 (6H, s, H-15), 2.25 (3H, s, H-16), 1.95–1.87 (1H, m, H-8_{eq} or H-$8'_{eq}$), 1.79–1.65 (3H, m, H-7, H-9_{eq} and H-$9'_{eq}$), 1.64–1.54 (2H, m, H-8_{eq} or H-$8'_{eq}$ and H-10_{eq}), 1.39-1.28 (1H, m, H-8_{ax} or H-$8'_{ax}$), 1.28–1.16 (4H, m, H-8_{ax} or H-$8'_{ax}$, H-9_{ax}, H-$9'_{ax}$ and H-10_{ax}); **δ_c** (101 MHz, $CDCl_3$) 166.7 (C5), 142.5 (C14), 140.1 (C12), 136.9 (C2), 136.0 (C11), 132.7 (C13), 130.0 (C3), 62.5 (C1), 52.3 (C6), 50.1 (C4), 45.4 (C7), 30.8 (C8 or C8'), 28.7 (C8 or C8'), 26.6 (C9 or C9'), 26.5 (C9 or C9'), 26.4 (C10), 23.0 (C15), 20.9 (C16); ***m/z*** (ESI+) 376 ($[M+H]^+$, 100%); **HRMS** calculated for $[C_{21}H_{30}NO_3S]^+$ $(M+H)^+$ 376.1941, found 376.1942. Data consistent with the literature.[60]

Methyl (1*S*,3*S*)-1-mesityl-3-(1-benzyloxycarbonylpiperidin-4-yl)-3,6-dihydro-1λ^6,2-thiazine-4-carboxylate 1-oxide (294)

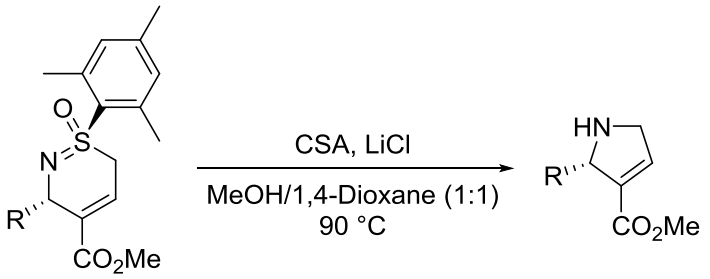


The general procedure was followed at 50 °C using *N*-[mesityl-(*S*)-sulfinyl]-4-(benzyloxycarbonylpiperidine)aldimine **289** (413 mg, 1.00 mmol) and afforded the crude product (734 mg) as an orange oil. Purification by column chromatography over silica gel (eluting with 15:85, 1:4, 1:3 then 3:7 ethyl acetate/cyclohexane) afforded **294** (216 mg, 42%) as a yellow oil.

$[\alpha]_D^{24}$ +99 (*c* 0.80, $CHCl_3$); **υ_{max}** (cm^{-1}) 2938, 2856, 1694 (C=O), 1434, 1272, 1251, 1219, 1124, 1078, 1034; **δ_H** (400 MHz, $CDCl_3$) 7.38–7.27 (5H, m, H-13, H-14 and H-15), 7.04 (1H, dd, *J* = 6.1, 2.8 Hz, H-3), 6.91 (2H, s, H-18), 5.11 (2H, s, H-11), 4.65 (1H, app. dt, *J* = 7.2, 1.9 Hz, H-1), 4.32–4.09 (3H, m, H-4a, H-9_{eq} and H-$9'_{eq}$), 3.81 (3H, s, H-6), 3.67–3.60 (1H, m, H-4b), 2.70 (2H, m, H-9_{ax} and H-$9'_{ax}$), 2.56 (6H, s, H-20), 2.26 (3H, s, H-21), 2.04–1.95 (1H, m, H-8_{eq} or H-$8'_{eq}$), 1.91–1.81 (1H, m, H-7), 1.57–1.44 (3H, m, H-8_{ax}, H-$8'_{ax}$ and H-8_{eq} or H-$8'_{eq}$); **δ_C** (101 MHz, $CDCl_3$) 166.5 (C5), 155.3 (C10), 142.7 (C19), 140.1 (C17), 137.1 (C12), 136.1 (C2), 135.1 (C16), 132.7 (C18), 130.9 (C3), 128.5 (C14), 127.9 (C15), 127.9 (C13), 67.0 (C11), 61.1 (C1), 52.4 (C6), 50.2 (C4), 44.3 (C9 or C9'), 44.1 (C9 or C9'), 44.0 (C7), 29.6 (C8 or C8'), 28.3 (C8 or C8'), 22.9 (C20), 21.0

(C21); ***m/z*** (ESI+) 511 ($[M+H]^+$, 100%); **HRMS** calculated for $[C_{28}H_{35}N_2O_5S]^+$ $(M+H)^+$ 511.2261, found 511.2268.

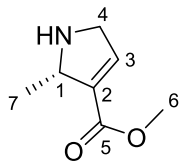
3.4 General procedure for the preparation of methyl (*S*)-2,5-dihydro-1*H*-pyrrole-3-carboxylates 266, 278, 296-302.[60]



224, **226**, **228**, **230-232**, **290-294** **266**, **278**, **296-302**

To a solution of methyl 1-mesityl-3,6-dihydro-1λ^6,2-thiazine-4-carboxylate 1-oxide **224**, **226**, **228**, **230**-**232**, **290**-**294** (0.106-0.325 mmol, 1 equivalent) in a 1:1 mixture of methanol/1,4-dioxane (1.06-3.25 mL) was added lithium chloride (0.212-0.650 mmol, 2 equivalents) and camphorsulfonic acid (0.106-0.325 mmol, 1 equivalent). The mixture was stirred vigorously at 90 °C. The resulting solution was allowed to cool to room temperature before being loaded onto a pre-packed Biotage Isolute® SCX-2 cartridge that was primed with methanol. The cartridge was then flushed with 2 cartridge volumes of methanol. The product was eluted with 1.0 M ammonia in methanol solution (2.12-6.50 mmol, 20 equivalents) and then 2 cartridge volumes of methanol. The resulting organic solution was concentrated *in vacuo*.

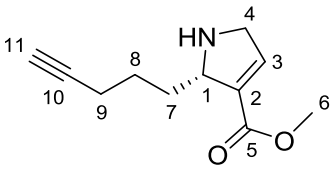
Methyl (*S*)-2-methyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (278)



The general procedure was followed using methyl (1*S*,3*S*)-1-mesityl-3-methyl-3,6-dihydro-1λ^6,2-thiazine-4-carboxylate 1-oxide **224** (100 mg, 0.325 mmol) and afforded **278** (32 mg, 68%) as an orange oil.

$[\alpha]_D^{26}$ +43 (*c* 0.95, $CHCl_3$); **υ_{max}** (cm^{-1}) 3379 (NH), 2954, 1721 (C=O), 1646 (C=C), 1439, 1266, 1246, 1203; **δ_H** (400 MHz, $CDCl_3$) 6.78 (1H, dd, *J* = 4.0, 2.2 Hz, H-3), 4.53–4.42 (1H, m, H-1), 4.10 (1H, ddd, *J* = 17.4, 4.0, 2.1 Hz, H-4a), 3.98 (1H, app. dt, *J* = 17.4, 2.2 Hz, H-4b), 3.77 (3H, s, H-6), 1.47 (3H, d, *J* = 6.6 Hz, H-7); **δ_c** (101 MHz, $CDCl_3$) 163.3 (C5), 138.5 (C3), 137.8 (C2), 60.1 (C1), 52.0 (C4), 51.9 (C6), 20.0 (C7); ***m/z*** (ESI+) 142 ($[M+H]^+$, 43%); **HRMS** calculated for $[C_7H_{12}NO_2]^+$ $(M+H)^+$ 142.0863, found 142.0867.

Methyl (*S*)-2-(pent-4-yn-1-yl)-2,5-dihydro-1*H*-pyrrole-3-carboxylate (296)

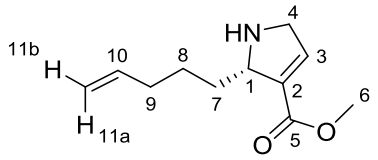


The general procedure was followed using methyl (1*S*,3*S*)-1-mesityl-3-(pent-4-yn-1-yl)-3,6-dihydro-1λ^6,2-thiazine-4-carboxylate 1-oxide **232** (56 mg, 0.156 mmol) and afforded **296** (23 mg, 77%) as an orange oil.

$[\alpha]_D^{26}$ +20 (*c* 1.00, $CHCl_3$); **υ_{max}** (cm^{-1}) 3285 (C≡CH), 2949, 2863, 2115 (C≡C), 1719 (C=O), 1636 (C=C), 1436, 1240, 1200, 1117, 638; **δ_H** (400 MHz, $CDCl_3$)

6.85 (1H, app. q, *J* = 2.0 Hz, H-3), 4.30–4.21 (1H, m, H-1), 3.96–3.83 (2H, m, H-4), 3.76 (3H, s, H-6), 2.26–2.20 (2H, m, H-9), 1.99–1.89 (1H, m, H-7a), 1.96 (1H, t, *J* = 2.6 Hz, H-11), 1.69–1.55 (3H, m, H-7b and H-8); δ_c (101 MHz, $CDCl_3$) 164.2 (C5), 141.4 (C3), 137.4 (C2), 84.4 (C10), 68.6 (C11), 63.9 (C1), 53.4 (C4), 51.6 (C6), 34.1 (C7), 25.1 (C8), 18.6 (C9); ***m/z*** (ESI+) 194 ($[M+H]^+$, 100%); **HRMS** calculated for $[C_{11}H_{16}NO_2]^+$ $(M+H)^+$ 194.1176, found 194.1178.

Methyl (*S*)-2-(pent-4-en-1-yl)-2,5-dihydro-1*H*-pyrrole-3-carboxylate (297)

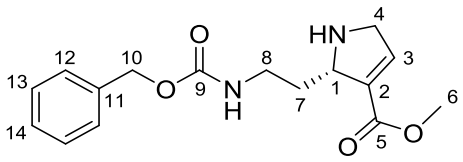


The general procedure was followed using methyl (1*S*,3*S*)-1-mesityl-3-(pent-4-en-1-yl)-3,6-dihydro-1λ^6,2-thiazine-4-carboxylate 1-oxide **231** (60 mg, 0.166 mmol) and afforded **297** (23 mg, 72%) as a yellow oil.

$\mathbf{[\alpha]_D^{24}}$ +24 (*c* 1.00, $CHCl_3$); υ_{max} (cm^{-1}) 3339 (NH), 3075 (C=CH_2), 2928, 2855, 1716 (C=O), 1639 (C=C), 1436, 1237, 1097, 911; δ_H (400 MHz, $CDCl_3$) 6.81 (1H, app. q, *J* = 2.1 Hz, H-3), 5.79 (1H, ddt, *J* = 17.0, 10.2, 6.7 Hz, H-10), 4.99 (1H, ddd, *J* = 17.0, 3.6, 1.6 Hz, H-11a), 4.93 (1H, ddt, *J* = 10.2, 2.1, 1.2 Hz, H-11b), 4.26–4.19 (1H, m, H-1), 3.91 (1H, ddd, *J* = 17.5, 4.6, 2.1 Hz, H-4a), 3.84 (1H, ddd, *J* = 17.5, 2.8, 2.6 Hz, H-4b), 3.74 (3H, s, H-6), 2.12–2.02 (2H, m, H-9), 1.88–1.77 (1H, m, H-7a), 1.54–1.40 (3H, m, H-8 and H-7b); δ_c (101 MHz, $CDCl_3$) 164.2 (C5), 140.9 (C3), 138.8 (C10), 137.6 (C2), 114.7 (C11), 64.2 (C1), 53.2 (C4), 51.6 (C6), 34.3 (C7), 33.8 (C9), 25.4 (C8); ***m/z*** (ESI+) 196 ($[M+H]^+$, 100%);

HRMS calculated for $[C_{11}H_{18}NO_2]^+$ $(M+H)^+$ 196.1332, found 196.1335. Data consistent with the literature.[60]

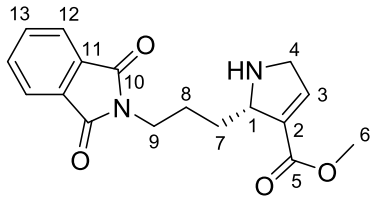
Methyl (*S*)-2-(2-benzyloxycarbonylaminoethyl)-2,5-dihydro-1*H*-pyrrole-3-carboxylate (298)



The general procedure was followed using methyl (1*S*,3*S*)-1-mesityl-3-(2-benzyloxycarbonylaminoethyl)-3,6-dihydro-1λ^6,2-thiazine-4-carboxylate 1-oxide **292** (50 mg, 0.106 mmol) and afforded **298** (26 mg, 80%) as a yellow oil.

$[\alpha]_D^{23}$ –5 (*c* 1.00, $CHCl_3$); **υ_{max}** (cm^{-1}) 3330 (NH), 3015, 2952, 1703 (C=O), 1636 (C=C), 1239, 1216, 745, 697, 665; **δ_H** (400 MHz, $CDCl_3$) 7.36–7.29 (5H, m, H-12, H-13 and H-14), 6.83 (1H, app. q, *J* = 2.0 Hz, H-3), 5.99 (1H, br s, NH), 5.11–5.04 (2H, m, H-10), 4.38–4.28 (1H, m, H-1), 3.92–3.82 (2H, m, H-4), 3.73 (3H, s, H-6), 3.43–3.35 (1H, m, H-8a), 3.31–3.23 (1H, m, H-8b), 2.08–1.96 (1H, m, H-7a), 1.73–1.59 (1H, m, H-7b); **δ_c** (101 MHz, $CDCl_3$) 164.0 (C5), 156.7 (C9), 141.6 (C3), 137.0 (C2), 136.9 (C11), 128.6 (C13 or C14), 128.2 (C12), 128.1 (C13 or C14), 66.6 (C10), 63.1 (C1), 53.0 (C4), 51.8 (C6), 39.1 (C8), 33.5 (C7); ***m/z*** (ESI+) 305 ($[M+H]^+$, 100%); **HRMS** calculated for $[C_{16}H_{21}N_2O_4]^+$ $(M+H)^+$ 305.1496, found 305.1500.

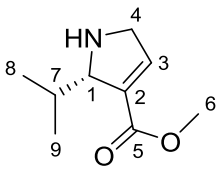
Methyl (S)-2-(3-(1,3-dioxoisoindolin-2-yl)propyl)-2,5-dihydro-1*H*-pyrrole-3-carboxylate (299)



The general procedure was followed using methyl (1S,3S)-3-(3-(1,3-di oxoisoindolin-2-yl)propyl)-1-mesityl-3,6-dihydro-1λ^6,2-thiazine-4-carboxylate 1-oxide **293** (70 mg, 0.146 mmol) and afforded **299** (28 mg, 61%) as a yellow oil.

$[\alpha]_D^{23}$ +26 (*c* 1.00, $CHCl_3$); **υ_{max}** (cm^{-1}) 3351 (NH), 3018, 2949, 2857, 1770 (C=O imide), 1704 (C=O ester), 1650 (C=C), 1630, 1396, 748, 719; **δ_H** (400 MHz, $CDCl_3$) 7.81 (2H, app. dd, *J* = 5.4, 3.0 Hz, H-12 and H-12'), 7.68 (2H, app. dd, *J* = 5.5, 3.0 Hz, H-13 and H-13'), 6.81 (1H, app. q, *J* = 2.0 Hz, H-3), 4.28–4.22 (1H, m, H-1), 3.88–3.83 (2H, m, H-4), 3.72–3.67 (2H, m, H-9), 3.70 (3H, s, H-6), 1.93–1.80 (1H, m, H-7a), 1.82–1.68 (2H, m, H-8), 1.58–1.48 (1H, m, H-7b); **δ_c** (101 MHz, $CDCl_3$) 168.5 (C10), 164.1 (C5), 141.4 (C3), 137.1 (C2), 134.0 (C13), 132.2 (C11), 123.3 (C12), 63.8 (C1), 53.2 (C4), 51.7 (C6), 38.0 (C9), 32.0 (C7), 25.2 (C8); ***m/z*** (ESI+) 315 ($[M+H]^+$, 100%); **HRMS** calculated for $[C_{17}H_{19}N_2O_4]^+$ $(M+H)^+$ 315.1339, found 315.1349.

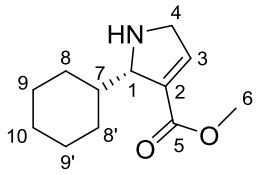
Methyl (*S*)-2-isopropyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (300)



The general procedure was followed using methyl (1*S*,3*S*)-1-mesityl-3-isopropyl-3,6-dihydro-1λ^6,2-thiazine-4-carboxylate 1-oxide **226** (45 mg, 0.134 mmol) and afforded **300** (9.4 mg, 41%) as a yellow oil.

[α]$_D^{23}$ +47 (*c* 0.30, $CHCl_3$); **υ$_{max}$** (cm^{-1}) 3360 (NH), 2956, 2931, 2875, 1714 (C=O), 1651 (C=C), 1437, 1243, 1214, 752; **δ$_H$** (400 MHz, $CDCl_3$) 6.85 (1H, app. q, *J* = 2.0 Hz, H-3), 4.29–4.23 (1H, m, H-1), 3.97–3.85 (2H, m, H-4), 3.75 (3H, s, H-6), 2.22 (1H, pd, *J* = 6.9, 2.8 Hz, H-7), 1.01 (3H, d, *J* = 6.9 Hz, H-8 or H-9), 0.78 (3H, d, *J* = 6.9 Hz, H-8 or H-9); **δ$_C$** (101 MHz, $CDCl_3$) 164.3 (C5), 141.0 (C3), 136.4 (C2), 69.5 (C1), 54.0 (C4), 51.7 (C6), 30.8 (C7), 20.4 (C8 or C9), 15.3 (C8 or C9); ***m/z*** (ESI+) 170 ($[M+H]^+$, 100%); **HRMS** calculated for $[C_9H_{16}NO_2]^+$ $(M+H)^+$ 170.1176, found 170.1177.

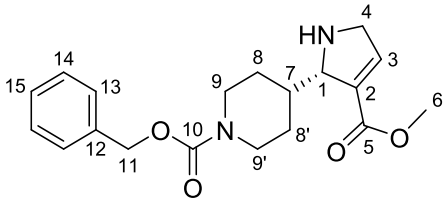
Methyl (*S*)-2-cyclohexyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (301)



The general procedure was followed using methyl (1*S*,3*S*)-1-mesityl-3-cyclohexyl-3,6-dihydro-1λ^6,2-thiazine-4-carboxylate 1-oxide **228** (70 mg, 0.186 mmol) and afforded **301** (22 mg, 57%) as a yellow oil.

$[\alpha]_D^{25}$ +25 (*c* 0.55, $CHCl_3$); **υ_{max}** (cm^{-1}) 3344 (NH), 2926, 2852, 1710 (C=O), 1636 (C=C), 1439, 1240, 1022; **δ_H** (400 MHz, $CDCl_3$) 6.82 (1H, dd, *J* = 3.9, 2.0 Hz, H-3), 4.25–4.18 (1H, m, H-1), 3.95–3.83 (2H, m, H-4), 3.74 (3H, s, H-6), 1.88–1.80 (1H, m, H-7), 1.77–1.69 (2H, m, H-8_{eq} or H-$8'_{eq}$ and H-9_{eq} or H-$9'_{eq}$), 1.65–1.58 (2H, m, H-8_{eq} or H-$8'_{eq}$ and H-9_{eq} or H-$9'_{eq}$), 1.47–1.41 (1H, m, H-10_{eq}), 1.33–1.22 (2H, m, H-8_{ax} and H-$8'_{ax}$), 1.21–1.03 (3H, m, H-9_{ax}, H-$9'_{ax}$ and H-10_{ax}); **δ_c** (101 MHz, $CDCl_3$) 164.2 (C5), 140.7 (C3), 135.9 (C2), 69.2 (C1), 53.9 (C4), 51.7 (C6), 41.0 (C7), 30.9 (C8 or C8'), 26.7 (C8 or C8'), 26.4 (C9 or C9'), 26.2 (C9 or C9'), 25.9 (C10); ***m/z*** (ESI+) 210 ($[M+H]^+$, 100%); **HRMS** calculated for $[C_{12}H_{20}NO_2]^+$ $(M+H)^+$ 210.1489, found 210.1486.

Methyl (*S*)-2-(1-benzyloxycarbonylpiperidin-4-yl)-2,5-dihydro-1*H*-pyrrole-3-carboxylate (302)

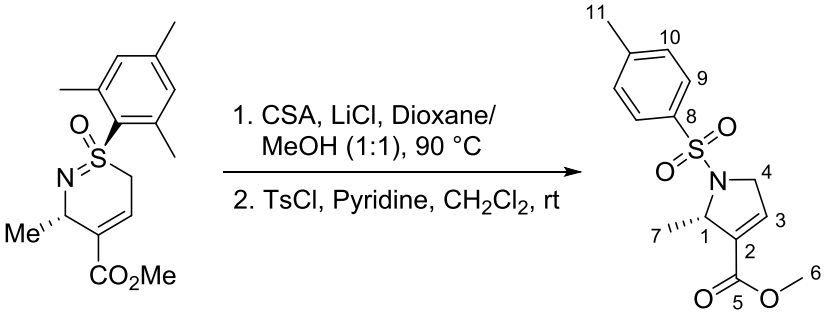


The general procedure was followed using methyl (1*S*,3*S*)-1-mesityl-3-(1-benzyloxycarbonylpiperidin-4-yl)-3,6-dihydro-1λ^6,2-thiazine-4-carboxylate 1-oxide **294** (120 mg, 0.235 mmol) and afforded **302** (43 mg, 53%) as a yellow oil.

$[\alpha]_D^{25}$ +10 (*c* 0.82, $CHCl_3$); **υ_{max}** (cm^{-1}) 3368 (NH), 2940, 2854, 1683 (C=O), 1638 (C=C), 1434, 1222, 1104, 1025; **δ_H** (400 MHz, $CDCl_3$) 7.37–7.26 (5H, m, H-13, H-14 and H-15), 6.87 (1H, app. q, *J* = 2.0 Hz, H-3), 5.14–5.04 (2H, m, H-11), 4.31–4.11 (3H, m, H-1, H-9_{eq} and H-$9'_{eq}$), 3.88 (1H, ddd, *J* = 17.9, 2.4 Hz, H-4a), 3.80–

3.71 (1H, m, H-4b), 3.74 (3H, m, H-6), 2.81–2.61 (2H, m, H-9_{ax} and H-$9'_{ax}$), 2.03–1.93 (1H, m, H-7), 1.57–1.42 (2H, m, H-8 or H-8'), 1.40–1.26 (2H, m, H-8 or H-8'); $\boldsymbol{\delta_c}$ (101 MHz, $CDCl_3$) 164.3 (C5), 155.3 (C10), 142.3 (C3), 137.0 (C12), 135.4 (C2), 128.5 (C14), 127.9 (C15), 127.9 (C13), 68.0 (C1), 67.0 (C11), 54.3 (C4), 51.7 (C6), 44.4 (C9 or C9'), 44.1 (C9 or C9'), 39.7 (C7), 29.7 (C8 or C8'), 25.0 (C8 or C8'); ***m/z*** (ESI+) 345 ($[M+H]^+$, 100%); **HRMS** calculated for $[C_{19}H_{25}N_2O_4]^+$ $(M+H)^+$ 345.1809, found 345.1812.

Methyl (*S*)-2-methyl-1-tosyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (273)

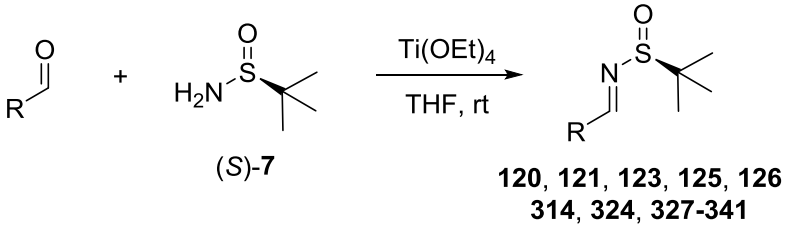


To a solution of methyl (1*S*,3*S*)-1-mesityl-3-methyl-3,6-dihydro-1λ^6,2-thiazine-4-carboxylate 1-oxide **224** (100 mg, 0.325 mmol) in a 1:1 mixture of 1,4-dioxane/methanol (3.26 mL) was added lithium chloride (28 mg, 0.651 mmol) and camphorsulfonic acid (76 mg, 0.325 mmol). The mixture was stirred vigorously at 90 °C. The resulting solution was allowed to cool to room temperature and then concentrated *in vacuo* to afford the crude pyrroline (231 mg) as an orange oil. A portion of methyl (*S*)-2-methyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate **278** (115 mg) was dissolved in dichloromethane (1.63 mL) and pyridine (55 µL, 0.683 mmol) and then *p*-toluenesulfonyl chloride (68 mg, 0.358 mmol) was added. The resulting solution was stirred at room

temperature for 19 h. To achieve full consumption of starting material, *p*-toluenesulfonyl chloride (31 mg, 0.163 mmol) and pyridine (28 µL, 0.358 mmol) were added and stirred at room temperature for another 1.5 h. Ethyl acetate (3.30 mL) was added and then the organic layer was washed with water (2 mL), 1 M HCl (2 mL), saturated aqueous solution of sodium bicarbonate (2 mL), brine (2 mL) then dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude product (99 mg) as an orange oil. Purification by column chromatography over silica gel (eluting with 1:9 to 3:7 ethyl acetate/cyclohexane) afforded **273** (25 mg, 48% over two steps) as a yellow oil.

$[\alpha]_D^{21}$ +68 (*c* 0.5, $CHCl_3$); **υ_{max}** (cm^{-1}) 2979, 2952, 2872, 1720 (C=O), 1644 (C=C), 1269, 1160 (S=O), 1090, 1068, 1016, 665, 607, 550; **δ_H** (400 MHz, $CDCl_3$) 7.74–7.68 (2H, m, H-9), 7.34–7.27 (2H, m, H-10), 6.54 (1H, dd, *J* = 4.0, 2.1 Hz, H-3), 4.76–4.65 (1H, m, H-1), 4.31 (1H, ddd, *J* = 17.5, 5.4, 2.0 Hz, H-4a), 4.20 (1H, dt, *J* = 17.5, 2.4 Hz, H-4b), 3.72 (3H, s, H-6), 2.42 (3H, s, H-12), 1.54 (3H, d, *J* = 6.3 Hz, H-7); **δ_c** (101 MHz, $CDCl_3$) 162.8 (C5), 143.8 (C11), 136.5 (C2), 135.7 (C3), 134.7 (C8), 130.0 (C10), 127.5 (C9), 62.3 (C1), 54.7 (C4), 52.0 (C6), 22.3 (C7), 21.7 (C12); ***m/z*** (ESI+) 318 ($[M+Na]^+$, 100%); **HRMS** calculated for $[C_{14}H_{17}NNaO_4S]^+$ $(M+Na)^+$ 318.0770, found 318.0781.

3.5 General procedure for the preparation of *N*-[*tert*-butyl-(*S*)-sulfinyl]-aldimines 120, 121, 123, 125, 126, 314, 324, 327-341.[46]

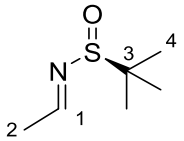


(*S*)-**7**

120, **121**, **123**, **125**, **126**
314, **324**, **327-341**

A solution of titanium(IV) ethoxide (2.14-87.4 mmol, 2.6 equivalents) and the corresponding aldehyde (1.07-43.7 mmol, 1.3 equivalents) in tetrahydrofuran (6.6-269 mL) were stirred at room temperature for 30 min. A solution of (*S*)-*tert*-butyl-sulfinamide (*S*)-**7** (0.82-33.6 mmol, 1.0 equivalent) in tetrahydrofuran (1.6-67 mL) was added and the reaction was stirred until the sulfinamide was consumed. Brine (4-168 mL) was added and the resulting slurry was stirred vigorously for 5 min before being filtered through a pad of Celite®. The layers were separated and then the aqueous layer was extracted with ethyl acetate (2-67 mL x3). The combined organic extracts were washed with 20% w/v brine (2-67 mL), dried over anhydrous magnesium sulfate and then concentrated *in vacuo*.

_N_-[*tert*-Butyl-(*S*)-sulfinyl]-acetaldimine (327)

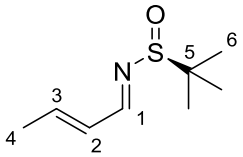


The general procedure was followed using acetaldehyde (1.20 mL, 21.5 mmol) and afforded the crude product (1.83 g) as a yellow oil. Purification by

column chromatography over silica gel (eluting with 1:4 to 3:7 ethyl acetate/cyclohexane) afforded **327** (789 mg, 32%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 8.07 (1H, q, *J* = 5.1 Hz, H-1), 2.22 (3H, d, *J* = 5.1 Hz, H-2), 1.18 (9H, s, H-4); **δ_c** (101 MHz, $CDCl_3$) 166.1 (C1), 56.6 (C3), 22.5 (C2), 22.4 (C4); ***m/z*** (ESI+) 148 ($[M+H]^+$, 29%); **HRMS** calculated for $[C_6H_{14}NOS]^+$ $(M+H)^+$ 148.0791, found 148.0793. Data consistent with literature.[147]

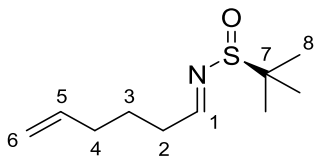
***N*-[*tert*-Butyl-(*S*)-sulfinyl]-but-2-en-1-ylaldimine (329)**



The general procedure was followed using crotonaldehyde (0.44 mL, 5.36 mmol) and afforded the crude product (678 mg) as a yellow oil. Purification by column chromatography over silica gel (eluting with 0:1 to 2:3 ethyl acetate/cyclohexane) afforded **329** (609 mg, 85%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 8.16 (1H, d, *J* = 9.1 Hz, H-1), 6.55 (1H, dq, *J* = 15.3, 6.6 Hz, H-3), 6.43 (1H, ddd, *J* = 15.3, 9.1, 1.3 Hz, H-2), 1.96 (3H, dd, *J* = 6.6, 1.3 Hz, H-4), 1.19 (9H, s, H-6); **δ_c** (101 MHz, $CDCl_3$) 164.1 (C1), 146.7 (C3), 130.4 (C2), 57.3 (C5), 22.6 (C6), 19.0 (C4); ***m/z*** (ESI+) 196 ($[M+Na]^+$, 100%); **HRMS** calculated for $[C_8H_{15}NNaOS]^+$ $(M+Na)^+$ 196.0767, found 196.0768. Data consistent with literature.[148]

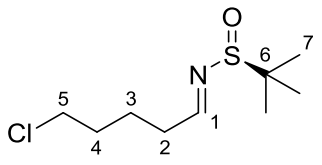
***N*-[*tert*-Butyl-(*S*)-sulfinyl]-5-hexenaldimine (330)**



The general procedure was followed using 5-hexenal (296 mg, 3.02 mmol) and afforded the crude product (453 mg) as a yellow oil. Purification by column chromatography over silica gel (eluting with 1:4 to 1:1 ethyl acetate/petroleum ether) afforded **330** (326 mg, 70%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 8.06 (1H, t, *J* = 4.6 Hz, H-1), 5.78 (1H, ddt, *J* = 16.9, 10.2, 6.7 Hz, H-5), 5.07–4.95 (2H, m, H-6), 2.52 (2H, td, *J* = 7.4, 4.6 Hz, H-2), 2.17–2.07 (2H, m, H-4), 1.72 (2H, p, *J* = 7.4 Hz, H-3), 1.18 (9H, s, H-8); **δ_c** (101 MHz, $CDCl_3$) 169.5 (C1), 137.8 (C5), 115.5 (C6), 56.6 (C7), 35.5 (C2), 33.2 (C4), 24.8 (C3), 22.5 (C8); ***m/z*** (ESI+) 224 ($[M+Na]^+$, 100%); **HRMS** calculated for $[C_{10}H_{19}NNaOS]^+$ $(M+Na)^+$ 224.1080, found 224.1076. Data consistent with literature.[149]

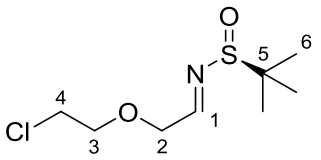
***N*-[*tert*-Butyl-(*S*)-sulfinyl]-5-chloropentanaldimine (331)**



The general procedure was followed using 5-chloropentanal (980 mg, 8.13 mmol) and afforded the crude product (1.89 g) as a colourless oil. Purification by column chromatography over silica gel (eluting with 1:4 ethyl acetate/cyclohexane) afforded **331** (1.14 g, 82%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 8.08 (1H, t, *J* = 4.4 Hz, H-1), 3.56 (2H, t, *J* = 6.1 Hz, H-5), 2.56 (2H, td, *J* = 7.0, 4.4 Hz, H-2), 1.90–1.76 (4H, m, H- 3 and H-4), 1.19 (9H, s, H-7); **δ_c** (101 MHz, $CDCl_3$) 168.9 (C1), 56.7 (C6), 44.6 (C5), 35.4 (C2), 32.0 (C4), 22.8 (C3), 22.5 (C7); ***m/z*** (ESI+) 224 ($[M+H]^+$, 53%); **HRMS** calculated for $[C_9H_{19}ClNOS]^+$ $(M+H)^+$ 224.0870, found 224.0870. Data consistent with literature.[150]

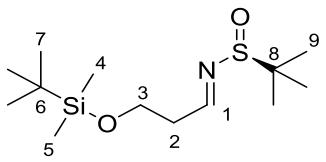
***N*-[*tert*-Butyl-(*S*)-sulfinyl]-(2-chloroethoxy)ethylaldimine (332)**



The general procedure was followed using 2-(2-chloroethoxy)ethanal (897 mg, 7.32 mmol) and afforded the crude product (1.60 g) as a colourless oil. Purification by column chromatography over silica gel (eluting with 1:4 to 3:7 ethyl acetate/cyclohexane) afforded **332** (468 mg, 37%) as a colourless oil.

$[\alpha]_D^{20}$ +235 (*c* 0.5, $CHCl_3$); **υ_{max}** (cm^{-1}) (neat) 2963, 2928, 2903, 2868, 1736, 1634, 1456, 1364, 1128, 1078, 1016, 667, 583; **δ_H** (400 MHz, $CDCl_3$) 8.09 (1H, t, *J* = 3.1 Hz, H-1), 4.53–4.39 (2H, m, H-2), 3.82 (2H, t, *J* = 5.8 Hz, H-3), 3.66 (2H, t, *J* = 5.8 Hz, H-4), 1.21 (9H, s, H-6); **δ_c** (101 MHz, $CDCl_3$) 166.3 (C1), 72.7 (C2), 71.6 (C3), 57.2 (C5), 42.7 (C4), 22.5 (C6); ***m/z*** (ESI+) 226 ($[M+H]^+$, 100%); **HRMS** calculated for $[C_8H_{17}ClNO_2S]^+$ $(M+H)^+$ 226.0663, found 226.0665.

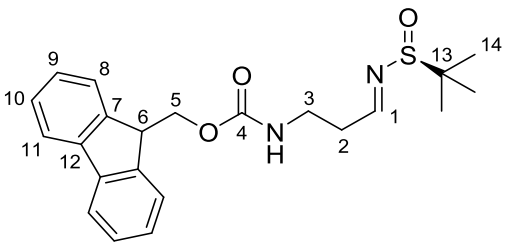
***N*-[*tert*-Butyl-(*S*)-sulfinyl]-3-(*tert*-butyldimethylsilyloxy)propylaldimine (324)**



The general procedure was followed using 3-(*tert*-butyldimethylsilyloxy)propanal (8.23 g, 43.7 mmol) and afforded the crude product (9.50 g) as a yellow oil. Purification by column chromatography over silica gel (eluting with 1:3 ethyl acetate/petroleum ether) afforded **324** (8.16 g, 83%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 8.09 (1H, t, *J* = 4.7 Hz, H-1), 3.95-3.90 (2H, m, H-3), 2.75-2.69 (2H, m, H-2), 1.19 (9H, s, H-9), 0.87 (9H, s, H-7), 0.05 (3H, s, H-4 or H-5), 0.05 (3H, s, H-4 or H-5); **δ_c** (101 MHz, $CDCl_3$) 168.0 (C1), 59.7 (C3), 56.7 (C8), 39.6 (C2), 26.0 (C7), 22.5 (C9), 18.4 (C6), -5.2 (C4 and C5); ***m/z*** (ESI+) 292 ($[M+H]^+$, 100%); **HRMS** calculated for $[C_{13}H_{30}NO_2SSi]^+$ $(M+H)^+$ 292.1761, found 292.1772. Data consistent with literature.[151]

***N*-[*tert*-Butyl-(*S*)-sulfinyl]-3-(fluorenylmethyloxycarbonylamino)propyl-aldimine (333)**

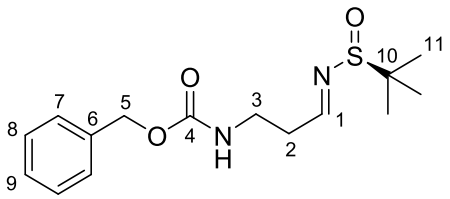


The general procedure was followed using 3-(fluorenylmethyloxycarbonyl amino)propanal (665 mg, 2.25 mmol) and afforded the crude product (815

mg) as a colourless oil. Purification by column chromatography over silica gel (eluting with 1:9 to 2:3 ethyl acetate/cyclohexane) afforded **333** (492 mg, 71%) as a colourless oil.

$[\alpha]_D^{20}$ +106 (*c* 0.77, $CHCl_3$); **υ_{max}** (cm^{-1}) (neat) 3321 (NH), 3065, 2959, 2899, 1701 (C=O), 1622, 1530, 1449, 1244, 1142, 1065, 1020, 758, 727; **δ_H** (400 MHz, $CDCl_3$) 8.13 (1H, t, *J* = 3.5 Hz, H-1), 7.76 (2H, d, *J* = 7.5 Hz, H-11), 7.57 (2H, d, *J* = 7.5 Hz, H-8), 7.40 (2H, t, *J* = 7.5 Hz, H-10), 7.31 (2H, t, *J* = 7.5 Hz, H-9), 5.12 (1H, br s, NH), 4.41 (2H, d, *J* = 6.9 Hz, H-5), 4.20 (1H, t, *J* = 6.9 Hz, H-6), 3.68–3.45 (2H, m, H-3), 2.89–2.63 (2H, m, H-2), 1.20 (9H, s, H-14); **δ_c** (101 MHz, $CDCl_3$) 167.5 (C1), 156.4 (C4), 144.0 (C7), 141.5 (C12), 127.9 (C10), 127.2 (C9), 125.1 (C8), 120.1 (C11), 66.8 (C5), 56.9 (C13), 47.4 (C6), 37.1 (C3), 36.3 (C2), 22.5 (C14); ***m/z*** (ESI+) 467 ($[M+C_3H_5N_2]^+$, 100%); **HRMS** calculated for $[C_{25}H_{31}N_4O_3S]^+$ $(M+C_3H_5N_2)^+$ 467.2111, found 467.2112.

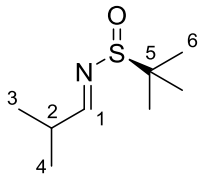
***N*-[*tert*-Butyl-(*S*)-sulfinyl]-3-(benzyloxycarbonylamino)propylaldimine (334)**



The general procedure was followed using 3-(benzyloxycarbonylamino) propanal (1.31 g, 6.32 mmol) and afforded the crude product (2.09 g) as a yellow oil. Purification by column chromatography over silica gel (eluting with 1:9 to 1:1 ethyl acetate/cyclohexane) afforded **334** (815 mg, 54%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$8.09 (1H, t, *J* = 3.6 Hz, H-1), 7.38–7.27 (5H, m, H-7, H-8 and H-9), 5.47–5.17 (1H, m, NH), 5.08 (2H, s, H-5), 3.63–3.41 (2H, m, H-3), 2.83–2.63 (2H, m, H-2), 1.17 (9H, s, H-11); **δ_c** (101 MHz, $CDCl_3$) 167.4 (C1), 156.3 (C4), 136.5 (C6), 128.6 (C8), 128.2 (C9), 128.2 (C7), 66.8 (C5), 56.8 (C10), 37.1 (C3), 36.3 (C2), 22.4 (C11); ***m/z*** (ESI+) 379 ($[M+C_3H_5N_2]^+$, 100%); **HRMS** calculated for $[C_{18}H_{27}N_4O_3S]^+$ $(M+C_3H_5N_2)^+$ 379.1806, found 379.1798. Data consistent with literature.[152]

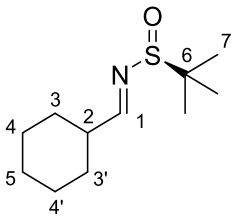
_N_-[_tert_-Butyl-(_S_)-sulfinyl]-2-methylpropylaldimine (336)



The general procedure was followed using isobutyraldehyde (0.98 mL, 10.7 mmol) and afforded the crude product (1.52 g) as a colourless oil. Purification by column chromatography over silica gel (eluting with 0:1 to 1:2 ethyl acetate/cyclohexane) afforded **336** (1.26 g, 87%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 7.98 (1H, d, *J* = 4.3 Hz, H-1), 2.78–2.63 (1H, m, H-2), 1.18 (9H, s, H-6), 1.17–1.14 (6H, m, H-3 and H-4); **δ_c** (101 MHz, $CDCl_3$) 173.7 (C1), 56.6 (C5), 35.0 (C2), 22.4 (C6), 19.0 (C3 and C4); ***m/z*** (ESI+) 198 ($[M+Na]^+$, 100%); **HRMS** calculated for $[C_8H_{17}NNaOS]^+$ $(M+Na)^+$ 198.0923, found 198.0925. Data consistent with literature.[153]

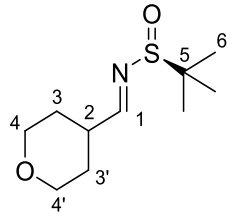
***N*-[*tert*-Butyl-(*S*)-sulfinyl]-cyclohexylaldimine (314)**



The general procedure was followed using cyclohexanecarboxaldehyde (3.90 mL, 32.2 mmol) and afforded the crude product (5.73 g) as a yellow oil. Purification by column chromatography over silica gel (eluting with 1:19 to 1:9 ethyl acetate/petroleum ether) afforded **314** (4.94 g, 93%) as a colourless oil that became a colourless amorphous solid on standing.

δ_H (400 MHz, $CDCl_3$) 7.95 (1H, d, *J* = 4.6 Hz, H-1), 2.54–2.36 (1H, m, H-2), 1.93–1.82 (2H, m, H-3_{eq} and H-$3'_{eq}$), 1.82–1.73 (2H, m, H-4_{eq} and H-$4'_{eq}$), 1.71–1.63 (1H, m, H-5_{eq}), 1.37–1.27 (4H, m, H-3_{ax}, H-$3'_{ax}$, H-4_{ax} and H-$4'_{ax}$), 1.26–1.20 (1H, m, H-5_{ax}), 1.17 (9H, s, H-7); **δ_c** (101 MHz, $CDCl_3$) 172.9 (C1), 56.6 (C6), 44.1 (C2), 29.4 (C3 and C3'), 26.0 (C5), 25.5 (C4 or C4'), 25.5 (C4 or C4'), 22.4 (C7); ***m/z*** (ESI+) 238 ($[M+Na]^+$, 100%); **HRMS** calculated for $[C_{11}H_{21}NNaOS]^+$ $(M+Na)^+$ 238.1236, found 238.1248. Data consistent with literature.[154]

***N*-[*tert*-Butyl-(*S*)-sulfinyl]-4-(tetrahydropyran)aldimine (338)**

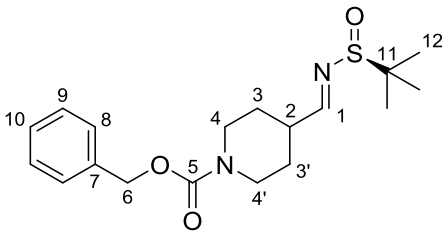


The general procedure was followed using tetrahydro-*2H*-pyran-4-carbaldehyde (1.22 g, 10.7 mmol) and afforded the crude product (1.83 g) as a

yellow oil. Purification by column chromatography over silica gel (eluting with 1:4 to 1:1 ethyl acetate/petroleum ether) afforded **338** (1.31 g, 73%) as a white amorphous solid.

$[\alpha]_D^{25}$ **+**229 (*c* 1.00, $CHCl_3$) **υ_{max}** (cm^{-1}) 2953, 2926, 2843, 1619, 1082; **δ_H** (400 MHz, $CDCl_3$) 7.98 (1H, d, *J* = 4.0 Hz, H-1), 3.98 (2H, dt, *J* = 11.4, 3.6 Hz, H-4_{eq} and H-$4'_{eq}$), 3.47 (2H, app. td, *J* = 11.4, 2.4 Hz, H-4_{ax} and H-$4'_{ax}$), 2.69 (1H, app. tq, *J* = 11.4, 4.0 Hz, H-2), 1.86–1.77 (2H, m, H-3_{eq} and H-$3'_{eq}$), 1.75–1.61 (2H, m, H-3_{ax} and H-$3'_{ax}$), 1.17 (9H, s, H-6); **δ_c** (101 MHz, $CDCl_3$) 170.8 (C1), 67.2 (C4 or C4'), 67.2 (C4 or C4'), 56.7 (C5), 41.1 (C2), 29.2 (C3 or C3'), 29.0 (C3 or C3'), 22.4 (C6); ***m/z*** (ESI+) 240 ($[M+Na]^+$, 100%); **HRMS** calculated for $[C_{10}H_{19}NNaO_2S]^+$ $(M+Na)^+$ 240.1029, found 240.1029. Compound is known in the literature, however, only a mass spectrometry datum was reported.[155]

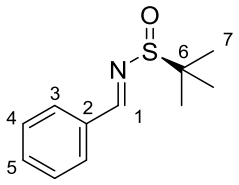
***N*-[*tert*-Butyl-(*S*)-sulfinyl]-4-(benzyloxycarbonylpiperidine)aldimine (339)**



The general procedure was followed using 4-formyl-*N*-benzyloxycarbonyl-piperidine (804 mg, 3.25 mmol) and afforded the crude product (1.09 g) as a colourless oil. Purification by column chromatography over silica gel (eluting with 1:4 to 1:1 ethyl acetate/cyclohexane) afforded **339** (666 mg, 76%) as a colourless oil.

$[\alpha]_D^{20}$ +112 (*c* 0.5, $CHCl_3$); **υ_{max}** (cm^{-1}) (neat) 3319, 3067, 2957, 2899, 1701, 1622, 1526, 1449, 1244, 1065, 1020, 758, 727; **δ_H** (400 MHz, $CDCl_3$) 8.00 (1H, d, *J* = 3.8 Hz, H-1), 7.39–7.28 (5H, m, H-8, H-9 and H-10), 5.13 (2H, s, H-6), 4.16 (2H, m, H-4_{eq} and H-$4'_{eq}$), 2.97 (2H, app. t, *J* = 12.5 Hz, H-4_{ax} and H-$4'_{ax}$), 2.64 (1H, m, H-2), 1.91 (2H, m, H-3_{eq} and H-$3'_{eq}$), 1.64–1.48 (2H, m, H-3_{ax} and H-$3'_{ax}$), 1.18 (9H, s, H-12); **δ_c** (101 MHz, $CDCl_3$) 170.6 (C1), 155.3 (C5), 136.9 (C7), 128.6 (C9), 128.2 (C10), 128.1 (C8), 67.3 (C6), 56.8 (C11), 43.5 (C4 or C4'), 43.4 (C4 or C4'), 42.0 (C2), 28.5 (C3 or C3'), 28.3 (C3 or C3'), 22.5 (C12); ***m/z*** (ESI+) 419 ($[M+C_3H_5N_2]^+$, 100%); **HRMS** calculated for $[C_{21}H_{31}N_4O_3S]^+$ $(M+C_3H_5N_2)^+$ 419.2111, found 419.2117. Compound is known in the literature, however, no data were reported.[156]

_N_-[_tert_-Butyl-(_S_)-sulfinyl]-benzaldimine (120)

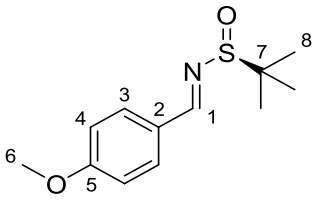


The general procedure was followed using benzaldehyde (1.09 mL, 10.7 mmol) and afforded the crude product (1.96 g) as a yellow oil. Purification by column chromatography over silica gel (eluting with 1:39 to 2:3 ethyl acetate/petroleum ether) afforded **120** (1.71 g, 99%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 8.58 (1H, s, H-1), 7.89-7.81 (2H, m, H-3), 7.55-7.42 (3H, m, H-4 and H-5), 1.26 (9H, s, H-7); 162.9 (C1), 134.2 (C2), 132.5 (C5), 129.5 (C3), 129.0 (C4), 57.9 (C6), 22.7 (C7); ***m/z*** (ESI+) 210 ($[M+H]^+$, 14%); **HRMS**

calculated for $[C_{11}H_{16}NOS]^+$ $(M+H)^+$ 210.0947, found 210.0956. Data consistent with literature.[154]

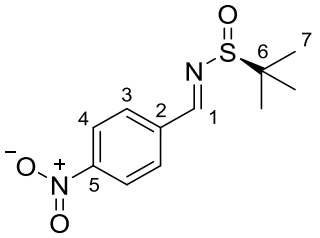
_N_-[_tert_-Butyl-(_S_)-sulfinyl]-4-methoxybenzaldimine (121)



The general procedure was followed using *p*-anisaldehyde (0.65 mL, 5.36 mmol) and afforded the crude product (1.35 g) as a yellow amorphous solid. Purification by column chromatography over silica gel (eluting with 1:9 to 1:1 ethyl acetate/petroleum ether) afforded **121** (851 mg, 86%) as a yellow amorphous solid.

δ_H (400 MHz, $CDCl_3$) 8.51 (1H, s, H-1), 7.87–7.72 (2H, m, H-3), 7.04–6.89 (2H, m, H-4), 3.87 (3H, s, H-6), 1.25 (9H, s, H-8); **δ_c** (101 MHz, $CDCl_3$) 163.1 (C5), 161.8 (C1), 131.3 (C3), 127.3 (C2), 114.3 (C4), 57.6 (C7), 55.5 (C6), 22.6 (C8); ***m/z*** (ESI+) 262 ($[M+Na]^+$, 100%); **HRMS** calculated for $[C_{12}H_{17}NNaO_2S]$ $(M+Na^+)$ 262.0872, found 262.0874. Data consistent with literature.[154]

_N_-[_tert_-Butyl-(_S_)-sulfinyl]-4-nitrobenzaldimine (341)

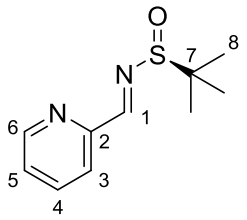


The general procedure was followed using 4-nitrobenzaldehyde (780 mg, 6.44 mmol) and afforded the crude product (1.23 g) as a yellow amorphous solid.

Purification by column chromatography over silica gel (eluting with 1:9 to 1:1 ethyl acetate/petroleum ether) afforded **341** (1.11 g, 88%) as a yellow amorphous solid.

δ_H (400 MHz, $CDCl_3$) 8.67 (1H, s, H-1), 8.33 (2H, d, *J* = 8.8 Hz, H-4), 8.02 (2H, d, *J* = 8.8 Hz, H-3), 1.29 (9H, s, H-7); **δ_c** (101 MHz, $CDCl_3$) 160.8 (C1), 150.0 (C5), 139.0 (C2), 130.2 (C3), 124.4 (C4), 58.6 (C6), 22.8 (C7); ***m/z*** (ESI+) 277 ($[M+Na]^+$, 24%); **HRMS** calculated for $[C_{11}H_{14}N_2NaO_3S]^+$ $(M+Na)^+$ 277.0617, found 277.0632. Data consistent with literature.[157]

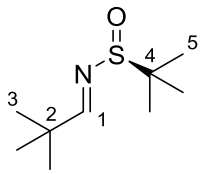
_N_-[_tert_-Butyl-(_S_)-sulfinyl]-2-pyridylaldimine (123)



The general procedure was followed using 2-pyridine carboxaldehyde (0.51 mL, 5.36 mmol) and afforded the crude product (479 mg) as an orange oil. Purification by column chromatography over silica gel (eluting with 1:3 ethyl acetate/petroleum ether) afforded **123** (267 mg, 31%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 8.78–8.73 (1H, m, H-6), 8.71 (1H, s, H-1), 8.03 (1H, d, *J* = 7.8 Hz, H-3), 7.83 (1H, app. td, *J* = 7.8, 1.7 Hz, H-4), 7.41 (1H, app. ddd, *J* = 7.5, 4.8, 1.2 Hz, H-5), 1.29 (9H, s, H-8); **δ_c** (101 MHz, $CDCl_3$) 163.8 (C1), 152.6 (C2), 150.3 (C6), 136.9 (C4), 126.0 (C5), 123.2 (C3), 58.2 (C7), 22.8 (C8); ***m/z*** (ESI+) 233 ($[M+Na]^+$, 100%); **HRMS** calculated for $[C_{10}H_{14}N_2NaOS]^+$ $(M+Na)^+$ 233.0719, found 233.0725. Data consistent with literature.[158]

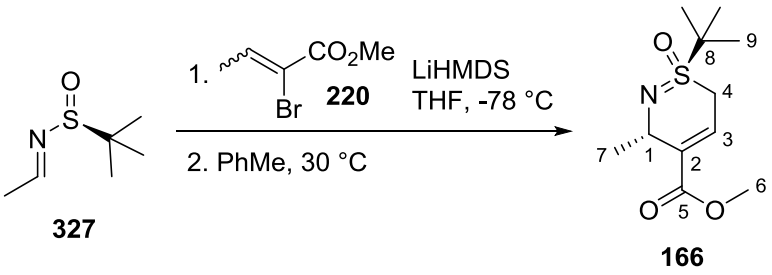
***N*-[*tert*-Butyl-(*S*)-sulfinyl]-2,2-dimethylpropylaldimine (126)**



The general procedure was followed using pivaldehyde (0.12 mL, 1.07 mmol) and afforded **126** (180 mg, 89%) as a yellow oil without further purification.

δ_H (400 MHz, $CDCl_3$) 7.92–7.88 (1H, m, H-1), 1.16 (9H, s, H-5), 1.14 (9H, s, H-3); δ_c (101 MHz, $CDCl_3$) 175.8 (C1), 56.6 (C4), 38.1 (C2), 26.8 (C3), 22.4 (C5); ***m/z*** (ESI+) 212 ($[M+Na]^+$, 100%); **HRMS** calculated for $[C_9H_{19}NNaOS]^+$ $(M+Na)^+$ 212.1080, found 212.1082. Data consistent with literature.[147]

Methyl (1*S*,3*S*)-1-(*tert*-butyl)-3-methyl-3,6-dihydro-1λ^6,2-thiazine-4-carboxylate 1-oxide (166)

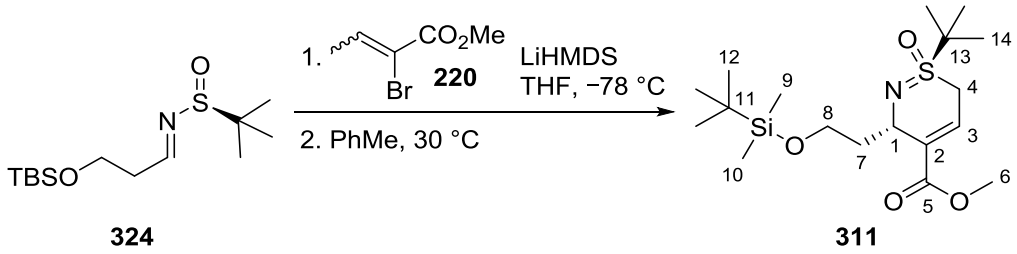


To a solution of methyl 2-bromo-2-butenoate **220** (3.24 mL, 27.2 mmol) in anhydrous tetrahydrofuran (250 mL) at –78 °C was added a 1.0 M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (27.2 mL, 27.2 mmol). The solution was stirred at –78 °C for a 20 min before *N*-[*tert*-butyl-(*S*)-sulfinyl]-acetaldimine **327** (2.00 g, 13.6 mmol) in anhydrous tetrahydrofuran (22 mL) was added. The resulting mixture was stirred at –78 °C for 4 h before the cold solution was poured into brine (100 mL) and stirred for 10 min. The layers

were separated and then the aqueous layer was extracted with ethyl acetate (30 mL x3). The organic extracts were combined, dried over anhydrous magnesium sulfate and then concentrated *in vacuo* to afford the crude product as an orange oil which was then dissolved in toluene (68 mL) and heated to 30 °C for 9 days. The resulting solution was concentrated *in vacuo* at 30 °C to afford the crude product (4.14 g) as an orange oil. Purification by column chromatography over silica gel (eluting 1:1 to 1:0 ethyl acetate/ petroleum ether) afforded **166** (1.69 g, 51% over two steps) as a yellow amorphous solid.

δ_H (400 MHz, $CDCl_3$) 6.93 (1H, dd, *J* = 4.9, 3.8 Hz, H-3), 4.56 (1H, m, H-1), 3.94 (1H, ddd, *J* = 18.1, 4.9, 2.6 Hz, H-4a), 3.76 (3H, s, H-6), 3.26 (1H, ddd, *J* = 18.1, 3.8, 1.6 Hz, H-4b), 1.44 (3H, d, *J* = 6.8 Hz, H-7), 1.39 (9H, s, H-9); **δ_c** (101 MHz, $CDCl_3$) 165.8 (C5), 138.8 (C2), 128.2 (C3), 60.1 (C8), 52.2 (C6), 51.8 (C1), 39.7 (C4), 24.6 (C7), 23.7 (C9); ***m/z*** (ESI+) 268 ($[M+Na]^+$, 28%); **HRMS** calculated for $[C_{11}H_{19}NNaO_3S]^+$ $(M+Na)^+$ 268.0978, found 268.0982. Data consistent with literature.[60]

Methyl (1*S*,3*S*)-1-(*tert*-butyl)-3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3,6-dihydro-1λ^6,2-thiazine-4-carboxylate 1-oxide (311)

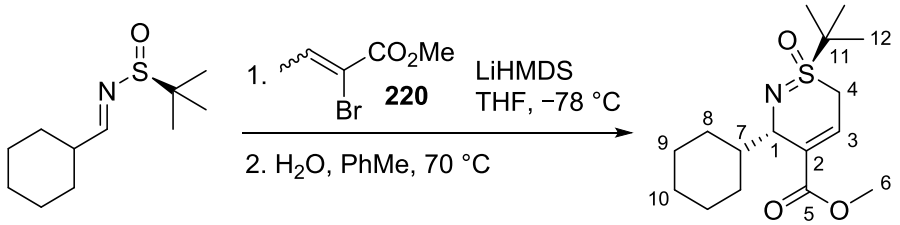


324 **311**

To a solution of methyl 2-bromo-2-butenoate **220** (0.82 mL, 6.86 mmol) in anhydrous tetrahydrofuran (55 mL) at –78 °C was added a 1.0 M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (6.86 mL, 6.86 mmol). The solution was stirred at –78 °C for a 20 min before *N*-[*tert*-butyl-(*S*)-sulfinyl]-3-(*tert*-butyldimethylsilyloxy)propyl aldimine **324** (1.00 g, 3.43 mmol) in anhydrous tetrahydrofuran (14 mL) was added. The resulting mixture was stirred at –78 °C for 1 h before the cold solution was poured into brine (64 mL) and stirred for 10 min. The layers were separated and then the aqueous layer was extracted with ethyl acetate (15 mL x3). The organic extracts were combined, dried over anhydrous magnesium sulfate and then concentrated *in vacuo* to afford the crude aziridine as an orange oil (2.39 g). Purification by column chromatography over silica gel (eluting with 1:19 to 1:3 ethyl acetate/petroleum ether) to afford the aziridine as a yellow oil (0.88 g) of which a portion (711 mg, 1.95 mmol) was dissolved in toluene (20 mL) and heated to 30 °C for 70 h. The resulting solution was concentrated *in vacuo* at 30 °C to afford the crude product (809 mg) as an orange oil. Purification by column chromatography over silica gel (eluting with 1:19 to 1:3 ethyl acetate /petroleum ether) afforded **311** (271 mg, 25% over two steps) as a yellow oil.

$[\alpha]_D^{25}$ +20 (*c* 0.5, $CHCl_3$); **υ_{max}** (cm^{-1}) (MeOH) 2953, 2929, 2856, 1717 (C=O), 1646 (C=C), 1276, 1249, 1204, 1084, 1064, 834, 776; **δ_H** (400 MHz, $CDCl_3$) 6.94 (1H, dd, *J* = 5.0, 3.7 Hz, H-3), 4.65–4.55 (1H, m, H-1), 3.98–3.83 (3H, m, H-4a and H-8), 3.75 (3H, s, H-6), 3.23 (1H, ddd, *J* = 18.1, 3.8, 1.7 Hz, H-4b), 1.96 (1H, dddd, *J* = 13.2, 8.1, 7.1, 3.7 Hz, H-7a), 1.77 (1H, dddd, *J* = 13.2, 10.5, 6.2, 4.5 Hz, H-7b), 1.39 (9H, s, H-14), 0.88 (9H, s, H-12), 0.05 (3H, s, H-9 or H-10), 0.04 (3H, s, H-9 or H-10); **δ_c** (101 MHz, $CDCl_3$) 166.0 (C5), 138.4 (C2), 128.8 (C3), 60.6 (C8), 60.0 (C13), 53.1 (C1), 52.1 (C6), 40.9 (C7), 39.8 (C4), 26.1 (C12), 23.7 (C14), 18.5 (C11), -5.1 (C9 or C10), -5.2 (C9 or C10); ***m/z*** (ESI+) 390 ($[M+H]^+$, 34%); **HRMS** calculated for $[C_{18}H_{36}NO_4SSi]^+$ $(M+H)^+$ 390.2129, found 390.2132.

Methyl (1*S*,3*S*)-1-(*tert*-butyl)-3-cyclohexyl-3,6-dihydro-1λ^6,2-thiazine-4-carboxylate 1-oxide (236)



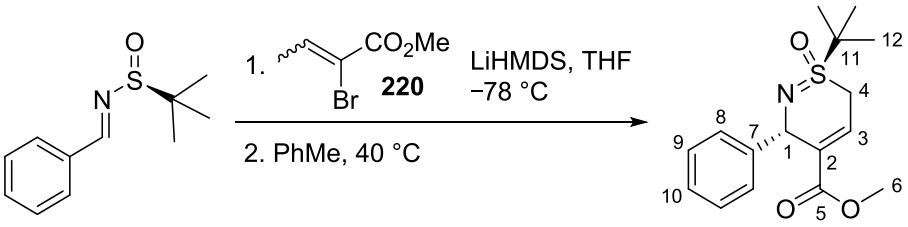
314 **236**

To a solution of methyl 2-bromo-2-butenoate **220** (1.66 mL, 13.9 mmol) in anhydrous tetrahydrofuran (111 mL) at –78 °C was added a 1.0 M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (13.9 mL, 13.9 mmol). The solution was stirred at –78 °C for a 20 min before *N*-[*tert*-butyl-(*S*)-sulfinyl]-cyclohexylaldimine **314** (1.50 g, 6.97 mmol) in anhydrous tetrahydrofuran (28 mL) was added. The resulting mixture was stirred at –78 °C for 3 h. Water (28 mL) and toluene (278 mL) were added and the resulting biphasic mixture was

heated at 70 °C for 22 h. The resulting mixture was concentrated *in vacuo* to afford the crude product (4.74 g) as a yellow solid. Purification by column chromatography over silica gel (eluting with 1:9 to 1:1 ethyl acetate/petroleum ether) afforded **236** (1.88 g, 86% over two steps) as a pale yellow solid.

υ_{max} (cm^{-1}) (MeOH) 2923, 2851, 1714 (C=O), 1644 (C=C), 1267, 1200, 1148, 1073, 867; **δ_H** (400 MHz, $CDCl_3$) 6.96 (1H, dd, *J* = 6.8, 2.7 Hz, H-3), 4.53 (1H, app. dt, *J* = 7.0, 1.6 Hz, H-1), 4.09 (1H, ddd, *J* = 18.3, 6.8, 1.4 Hz, H-4a), 3.77 (3H, s, H-6), 3.13 (1H, ddd, *J* = 18.2, 2.6, 2.0 Hz, H-4b), 1.98–1.89 (1H, m, H-8_{eq} or H-$8'_{eq}$), 1.77–1.67 (2H, m, H-9_{eq} or H-$9'_{eq}$ and H-10_{eq}), 1.62–1.50 (3H, m, H-7, H-8_{eq} or H-$8'_{eq}$ and H-9_{eq} or H-$9'_{eq}$), 1.36 (9H, s, H-12), 1.28–1.11 (5H, m, H-8_{ax}, H-$8'_{ax}$, H-9_{ax}, H-$9'_{ax}$ and H-10_{ax}); **δ_c** (101 MHz, $CDCl_3$) 166.5 (C5), 139.7 (C2), 129.9 (C3), 62.9 (C1), 61.0 (C11), 52.2 (C6), 45.3 (C7), 40.7 (C4), 30.8 (C8 or C8'), 29.0 (C8 or C8'), 26.5 (C9 or C9'), 26.4 (C9 or C9'), 26.3 (C10), 23.9 (C12); ***m/z*** (ESI+) 336 ($[M+Na]^+$, 55%); **HRMS** calculated for $[C_{16}H_{27}NNaO_3S]^+$ $(M+Na)^+$ 336.1604, found 336.1616. Data consistent with literature.[121]

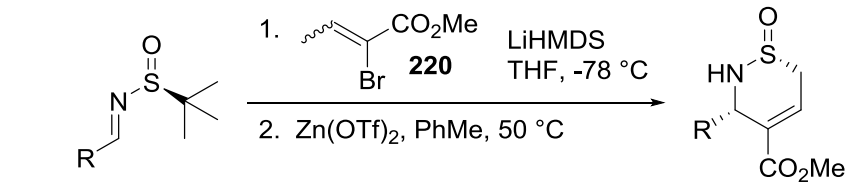
Methyl (1*S*,3*S*)-1-(*tert*-butyl)-3-phenyl-3,6-dihydro-1λ^6,2-thiazine-4-carboxylate 1-oxide (233)



To a solution of methyl 2-bromo-2-butenoate **220** (1.14 mL, 9.57 mmol) in anhydrous tetrahydrofuran (85 mL) at –78 °C was added a 1.0 M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (9.57 mL, 9.57 mmol). The solution was stirred at –78 °C for a 20 min before *N*-[*tert*-butyl-(*S*)-sulfinyl]-benzaldimine **120** (1.00 g, 4.78 mmol) in anhydrous tetrahydrofuran (11 mL) was added. The resulting mixture was stirred at –78 °C for 1 h before the cold solution was poured into brine (60 mL) and stirred for 10 min. The layers were separated and then the aqueous layer was extracted with ethyl acetate (15 mL x3). The organic extracts were combined, dried over anhydrous magnesium sulfate and then concentrated *in vacuo* to afford the crude product as an orange oil which was then dissolved in toluene (48 mL) and heated to 40 °C for 7 days. The resulting solution was concentrated *in vacuo* to afford the crude product (1.71 g) as an orange oil. Purification by column chromatography over silica gel (eluting with 1:4 to 1:1 ethyl acetate/petroleum ether) afforded **233** (325 mg, 22% over two steps) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 7.48–7.42 (2H, m, H-8), 7.32–7.25 (2H, m, H-9), 7.23–7.17 (1H, m, H-10), 7.12 (1H, dd, *J* = 5.1, 4.0 Hz, H-3), 5.74 (1H, app. t, *J* = 2.3 Hz, H-1), 4.06 (1H, ddd, *J* = 17.9, 5.1, 2.6 Hz, H-4a), 3.69 (3H, s, H-6), 3.33 (1H, ddd, *J* = 17.9, 4.0, 1.8 Hz, H-4b), 1.43 (9H, s, H-12); **δ_c** (101 MHz, $CDCl_3$) 165.8 (C5), 142.5 (C7), 137.3 (C2), 129.2 (C3), 128.4 (C9), 127.6 (C8), 127.1 (C10), 60.8 (C11), 60.0 (C1), 52.2 (C6), 39.9 (C4), 23.8 (C12); ***m/z*** (ESI+) 330 ($[M+Na]^+$, 58%); **HRMS** calculated for $[C_{16}H_{21}NNaO_3S]^+$ $(M+Na)^+$ 330.1134, found 330.1136. Data consistent with literature.[60]

3.6 General procedure for the preparation of methyl (1*R*,3*S*)-3,6-dihydro-2*H*-1,2-thiazine-4-carboxylate 1-oxides 304, 310, 321, 325, 342-354



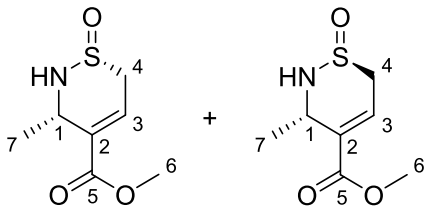
120, **121**, **123**, **125**, **126** **314**, **324**, **327-341**

304, **310**, **321** **325**, **342-354**

To a solution of methyl 2-bromo-2-butenoate **220** (1.00-2.00 mmol) in anhydrous tetrahydrofuran (4.0-8.0 mL) at –78 °C was added a 1.0 M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (1.00-2.00 mmol). The solution was stirred at –78 °C for 20 minutes before a solution of *N*-*tert*-butyl-(*S*)-sulfinimine **120**, **121**, **123**, **125**, **126**, **314**, **324**, **327**-**341** (0.50-1.00 mmol) in anhydrous tetrahydrofuran (1.0-2.0 mL) was added. The resulting mixture was stirred at –78 °C until the sulfinimine was consumed. The cold solution was then poured into brine (2.5-5 mL) and stirred for 10 min. The layers were

separated and then the aqueous layer was extracted with ethyl acetate (2.5-5 mL x3). The organic extracts were combined, dried over anhydrous sodium sulfate and then concentrated *in vacuo* to afford the crude aziridine. Zinc trifluoromethanesulfonate (0.05-0.10 mmol) was added to a solution of the crude aziridine in toluene (5-10 mL) and then the mixture was stirred at 50 °C until the aziridine was consumed by ^{1}H NMR monitoring. The reaction mixture was allowed to cool to room temperature and then concentrated *in vacuo*.

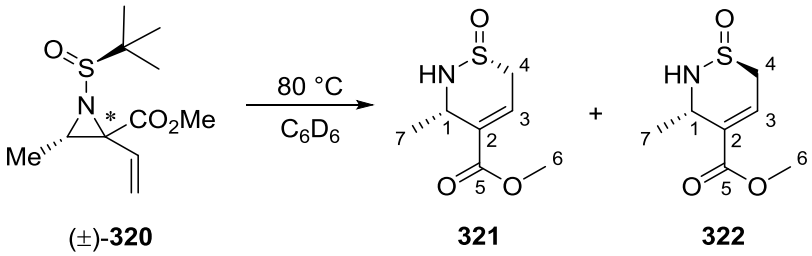
Methyl (1*R*,3*S*)-3-methyl-3,6-dihydro-2*H*-1,2-thiazine-4-carboxylate 1-oxide (321) and methyl (1*S*,3*S*)-3-methyl-3,6-dihydro-2*H*-1,2-thiazine-4-carboxylate 1-oxide (322)



321 **322**

Preparation 1: The general procedure was followed using *N*-[*tert*-butyl-(*S*)-sulfinyl]-acetaldimine **327** (147 mg, 1.00 mmol) and afforded the crude product (389 mg) as an orange oil. Purification by column chromatography over silica gel (eluting with 3:7 to 1:0 ethyl acetate/cyclohexane) afforded a mixture of **321** and **322** (**321**:**322** = 95:5 *dr*, 91 mg, 48%) as a pale yellow amorphous solid.

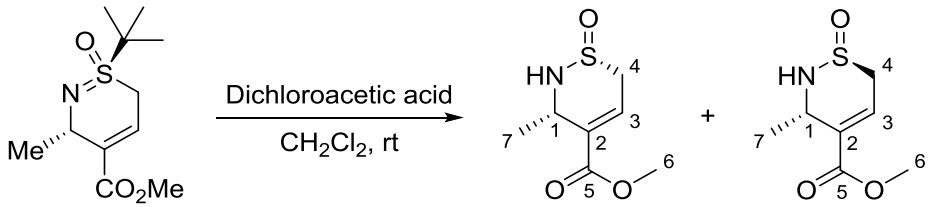
Preparation 2:



(±)-**320** **321** **322**

A solution of aziridine (±)-**320** (~50:50 mixture of diastereoisomers) (30 mg, 0.122 mmol) in deuterated benzene (0.5 mL) was heated to 80 °C for 29 h. The resulting mixture was concentrated *in vacuo* to afford the crude product as an orange oil. Purification by column chromatography over silica gel (eluting with ethyl acetate) afforded **321** (4 mg, 17%) as a pale yellow amorphous solid and **322** (6 mg, 26%) as a pale yellow amorphous solid.

Preparation 3:



166 **321** **322**

Dichloroacetic acid (0.27 mL, 3.26 mmol) was added to a solution of methyl (1*S*,3*S*)-1-(*tert*-butyl)-3-methyl-3,6-dihydro-1λ^6,2-thiazine-4-carboxylate 1-oxide **166** (400 mg, 1.63 mmol) in dichloromethane (16 mL) and stirred at room temperature for 1 h before it was quenched with a saturated aqueous solution of sodium bicarbonate (5 mL). The layers were separated and then the aqueous layer was extracted with dichloromethane (5 mL x2). The organic extracts were combined, dried over anhydrous magnesium sulfate and then

concentrated *in vacuo* to afford the crude product (189 mg) as a brown amorphous solid. Purification by column chromatography over silica gel (eluting with 1:1 to 1:0 ethyl acetate/petroleum ether) afforded **321** (166 mg, 54%) as a pale yellow amorphous solid and a mixture of **321** and **322** (**321**:**322** = 3:7 mixture of isomers, 25 mg, 8%) as a pale yellow amorphous solid.

Methyl (1*R*,3*S*)-3-methyl-3,6-dihydro-2*H*-1,2-thiazine-4-carboxylate 1-oxide (321)

$[\alpha]_D^{25}$ –116 (*c* 0.55, $CHCl_3$); **υ_{max}** (cm^{-1}) (MeOH) 3204 (NH), 2980, 2952, 2905, 1713 (C=O), 1657 (C=C), 1437, 1274, 1245, 1086, 1049 (S=O), 747; **δ_H** (400 MHz, $CDCl_3$) 7.00 (1H, ddd, *J* = 5.8, 2.9, 1.7 Hz, H-3), 4.49 (1H, br s, NH), 4.25–4.15 (1H, m, H-1), 3.80 (3H, s, H-6), 3.68–3.56 (1H, m, H-4a), 3.36 (1H, dddd, *J* = 18.0, 5.8, 1.9, 1.2 Hz, H-4b), 1.65 (3H, d, *J* = 6.9 Hz, H-7); **δ_c** (101 MHz, $CDCl_3$) 165.3 (C5), 132.7 (C2), 127.3 (C3), 52.2 (C6), 48.5 (C4), 46.7 (C1), 24.5 (C7); ***m/z*** (ESI+) 190 ($[M+H]^+$, 100%); **HRMS** calculated for $[C_7H_{12}NO_3S]^+$ $(M+H)^+$ 190.0532, found 190.0532.

Additional NMR data:

δ_H (400 MHz, C_6D_6) 6.58 (1H, ddd, *J* = 5.2, 3.3, 1.7 Hz, H-3), 4.41 (1H, br s, NH), 4.03–3.92 (1H, m, H-1), 3.33 (3H, s, H-6), 2.88–2.70 (2H, m, H-4), 1.71 (3H, d, *J* = 6.8 Hz, H-7); **δ_c** (101 MHz, C_6D_6) 165.3 (C5), 132.9 (C2), 128.0 (C3), 51.4 (C6), 48.4 (C4), 46.8 (C1), 24.4 (C7).

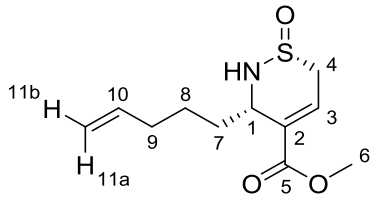
Methyl (1*S*,3*S*)-3-methyl-3,6-dihydro-2*H*-1,2-thiazine-4-carboxylate 1-oxide (322)

$[\alpha]_D^{29}$ +73 (*c* 0.27, $CHCl_3$); **υ_{max}** (cm^{-1}) (MeOH) 3192 (NH), 2952, 2927, 2852, 1713 (C=O), 1650 (C=C), 1436, 1362, 1274, 1243, 1033; **δ_H** (400 MHz, C_6D_6) 6.59-6.48 (1H, m, H-3), 4.40–4.27 (1H, m, H-1), 3.45 (1H, m, NH), 3.30 (3H, s, H-6), 2.66–2.52 (2H, m, H-4), 1.09 (3H, d, *J* = 6.6 Hz, H-7); **δ_c** (101 MHz, C_6D_6) 165.4 (C5), 133.3 (C2), 127.7 (C3), 51.3 (C6), 48.1 (C4), 42.7 (C1), 20.8 (C7); ***m/z*** (ESI+) 212 ($[M+Na]^+$, 30%); **HRMS** calculated for $[C_7H_{11}NNaO_3S]^+$ $(M+Na)^+$ 212.0352, found 212.0327.

Additional NMR data:

δ_H (400 MHz, $CDCl_3$) 6.94 (1H, ddd, *J* = 7.2, 2.6, 1.2 Hz, H-3), 4.54–4.41 (1H, m, H-1), 4.25 (1H, br s, NH), 3.78 (3H, s, H-6), 3.48 (1H, ddd, *J* = 16.7, 4.5, 2.6 Hz, H-4a), 3.36 (1H, ddt, *J* = 16.7, 7.2, 2.4 Hz, H-4b), 1.40 (3H, d, *J* = 6.6 Hz, H-7).

Methyl (1*R*,3*S*)-3-(pentyl-4-ene)-3,6-dihydro-2*H*-1,2-thiazine-4-carboxylate 1-oxide (343)

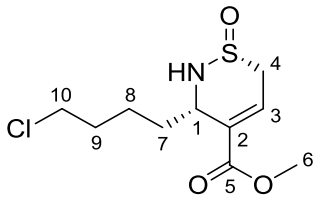


The general procedure was followed using *N*-[*tert*-butyl-(*S*)-sulfinyl]-5-hexenaldimine **330** (201 mg, 1.00 mmol) and afforded the crude product (423 mg) as a brown oil. Purification by column chromatography over silica gel

(eluting with 2:3 to 1:0 ethyl acetate/cyclohexane) afforded **343** (134 mg, 55%) as a pale yellow amorphous solid.

$[\alpha]_D^{22}$ –156 (*c* 0.83, $CHCl_3$); **υ_{max}** (cm^{-1}) (MeOH) 3213 (NH), 2951, 2924, 2856, 1712 (C=O), 1656 (C=C), 1640 (C=C), 1435, 1241, 1038, 911; **δ_H** (400 MHz, $CDCl_3$) 6.99 (1H, ddd, *J* = 5.1, 3.4, 1.5 Hz, H-3), 5.83 (1H, ddt, *J* = 17.0, 10.2, 6.6 Hz, H-10), 5.03 (1H, ddd, *J* = 17.0, 3.4, 1.6 Hz, H-11a), 5.00–4.95 (1H, m, H-11b), 4.87–4.77 (1H, m, NH), 4.10–4.00 (1H, m, H-1), 3.80 (3H, s, H-6), 3.72 (1H, dt, *J* = 18.2, 3.4 Hz, H-4a), 3.33 (1H, ddt, *J* = 18.2, 5.1, 1.3 Hz, H-4b), 2.19–2.06 (3H, m, H-7a and H-9), 1.85–1.69 (2H, m, H-7b and H-8a), 1.59–1.44 (1H, m, H-8b); **δ_c** (101 MHz, $CDCl_3$) 165.5 (C5), 138.4 (C10), 132.8 (C2), 127.9 (C3), 114.9 (C11), 52.2 (C6), 51.0 (C1), 49.1 (C4), 35.7 (C7), 33.2 (C9), 26.3 (C8); ***m/z*** (ESI+) 266 ($[M+Na]^+$, 82%); **HRMS** calculated for $[C_{11}H_{17}NNaO_3S]^+$ $(M+Na)^+$ 266.0821, found 266.0826.

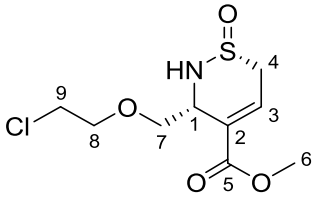
Methyl (1*R*,3*S*)-3-(4-chlorobutyl)-3,6-dihydro-2*H*-1,2-thiazine-4-carboxylate 1-oxide (344)



The general procedure was followed using *N*-[*tert*-Butyl-(*S*)-sulfinyl]-5-chloropentanaldimine **331** (224 mg, 1.00 mmol) and afforded the crude product (446 mg) as an orange oil. Purification by column chromatography over silica gel (eluting with 3:7 to 1:0 ethyl acetate/cyclohexane) afforded **344** (94 mg, 35%) as a yellow amorphous solid.

$[\alpha]_D^{20}$ –129 (*c* 0.27, $CHCl_3$); **υ_{max}** (cm^{-1}) (MeOH) 3271 (NH), 2955, 2868, 1715 (C=O), 1657 (C=C), 1439, 1277, 1246, 1229, 1167, 1032, 638; **δ_H** (400 MHz, $CDCl_3$) 6.99 (1H, ddd, *J* = 5.1, 3.4, 1.2 Hz, H-3), 4.81 (1H, br s, NH), 4.08–3.97 (1H, m, H-1), 3.79 (3H, s, H-6), 3.72 (1H, ddd, *J* = 18.3, 3.4 Hz, H-4a), 3.62–3.50 (2H, m, H-10), 3.31 (1H, dddd, *J* = 18.3, 5.1, 1.4 Hz, H-4b), 2.21–2.06 (1H, m, H-7a), 1.86–1.70 (4H, m, H-7b, H-8a and H-9), 1.66–1.54 (1H, m, H-8b); **δ_c** (101 MHz, $CDCl_3$) 165.4 (C5), 132.6 (C2), 128.2 (C3), 52.3 (C6), 50.9 (C1), 49.2 (C4), 45.0 (C10), 35.4 (C7), 32.0 (C9), 24.3 (C8); ***m/z*** (ESI+) 334 ($[M+C_3H_5N_2]^+$, 40%); **HRMS** calculated for $[C_{13}H_{21}ClN_3O_3S]^+$ $(M+C_3H_5N_2)^+$ 334.0987, found 334.1004.

Methyl (1*R*,3*R*)-3-((2-chloroethoxy)methyl)-3,6-dihydro-2*H*-1,2-thiazine-4-carboxylate 1-oxide (345)

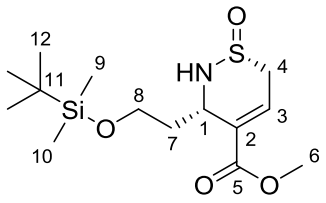


The general procedure was followed using *N*-[*tert*-Butyl-(*S*)-sulfinyl]-(2-chloroethoxy)ethylaldimine **332** (226 mg, 1.00 mmol) and afforded the crude product (494 mg) as an orange oil. Purification by column chromatography over silica gel (eluting with 3:7 to 1:0 ethyl acetate/cyclohexane) afforded **345** (182 mg, 68%) as an off-white amorphous solid.

$[\alpha]_D^{20}$ –174 (*c* 0.49, $CHCl_3$); **υ_{max}** (cm^{-1}) (MeOH) 3300 (NH), 2955, 2922, 2911, 1713 (C=O), 1657 (C=C), 1437, 1364, 1244, 1227, 1113, 1030, 916, 743, 638; **δ_H** (400 MHz, $CDCl_3$) 7.12 (1H, dt, *J* = 5.4, 2.4 Hz, H-3), 5.35 (1H, br s, NH), 4.32–4.16 (1H, m, H-1), 3.96 (1H, dd, *J* = 9.6 Hz, H-7a), 3.90–3.75 (3H, m, H-7b

and H-8), 3.81 (3H, s, H-6), 3.76–3.60 (3H, m, H-4a and H-9), 3.42 (1H, dd, *J* = 18.1, 5.4 Hz, H-4b); δ_c (101 MHz, $CDCl_3$) 165.0 (C5), 130.2 (C3), 127.9 (C2), 73.2 (C7), 71.1 (C8), 52.4 (C6), 50.7 (C1), 48.5 (C4), 43.3 (C9); ***m/z*** (ESI+) 336 ($[M+C_3H_5N_2]^+$, 37%); **HRMS** calculated for $[C_{12}H_{19}ClN_3O_4S]^+$ $(M+C_3H_5N_2)^+$ 336.0779, found 336.0779.

Methyl (1*R*,3*S*)-3-(2-*tert*-butyldimethylsilyloxyethyl)-3,6-dihydro-2*H*-1,2-thiazine-4-carboxylate 1-oxide (325)

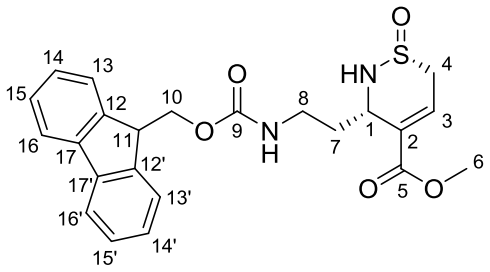


The general procedure was followed using *N*-[*tert*-butyl-(*S*)-sulfinyl]-3-(*tert*-butyldimethylsilyloxy)propylaldimine **324** (200 mg, 0.69 mmol) and afforded the crude product (354 mg) as a yellow oil. Purification by column chromatography over silica gel (eluting with 1:4 to 1:0 ethyl acetate/cyclohexane) afforded **325** (100 mg, 44%) as a pale yellow amorphous solid.

$\mathbf{[\alpha]_D^{25}}$ –136 (*c* 0.5, $CHCl_3$); υ_{max} (cm^{-1}) (MeOH) 3228 (NH), 2952, 2929, 2885, 2856, 1717 (C=O), 1657 (C=C), 1471, 1463, 1436, 1390, 1361, 1248 (S=O), 1081, 1059, 1043, 835, 777; δ_H (400 MHz, $CDCl_3$) 7.02 (1H, dt, *J* = 4.7, 2.9 Hz, H-3), 5.40 (1H, br s, NH), 4.28–4.17 (1H, m, H-1), 3.97 (1H, ddd, *J* = 10.8, 6.4, 4.2 Hz, H-8a), 3.87 (1H, ddd, *J* = 10.8, 7.4, 4.3 Hz, H-8b), 3.79 (3H, s, H-6), 3.58 (1H, dt, *J* = 17.9, 2.9 Hz, H-4a), 3.39–3.31 (1H, m, H-4b), 2.35 (1H, dddd, *J* = 14.0, 10.3, 7.4, 4.2 Hz, H-7a), 1.95 (1H, dddd, *J* = 14.0, 6.7, 4.3, 2.6 Hz, H-7b),

0.93 (9H, s, H-12), 0.10 (6H, s, H-9 and H-10); δ_c (101 MHz, $CDCl_3$) 165.4 (C5), 132.1 (C2), 127.8 (C3), 62.5 (C8), 52.2 (C6), 50.1 (C1), 48.4 (C4), 37.3 (C7), 26.0 (C12), 18.3 (C11), -5.3 (C9 or C10), -5.4 (C9 or C10); ***m/z*** (ESI+) 334 ($[M+H]^+$, 100%); **HRMS** calculated for $[C_{14}H_{28}NO_4SSi]^+$ $(M+H)^+$ 334.1503, found 334.1511.

Methyl (1*R*,3*S*)-3-(fluorenylmethyloxycarbonylaminoethyl)-3,6-dihydro-2*H*-1,2-thiazine-4-carboxylate 1-oxide (346)

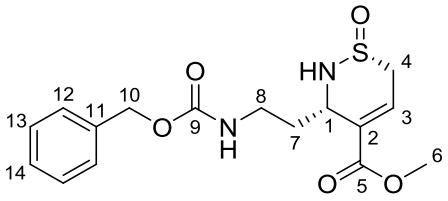


The general procedure was followed using *N*-[*tert*-butyl-(*S*)-sulfinyl]-3-(fluorenylmethyloxycarbonylamino)propylaldimine **333** (200 mg, 0.50 mmol) and afforded the crude product (389 mg) as a yellow oil. Purification by column chromatography over silica gel (eluting with 3:7 to 1:0 ethyl acetate/cyclohexane) afforded **346** (129 mg, 58%) as an off-white amorphous solid.

$[\alpha]_D^{20}$ –82 (*c* 0.5, $CHCl_3$); υ_{max} (cm^{-1}) (MeOH) 3291 (NH), 3061, 3042, 2951, 2901, 1713 (C=O), 1659 (C=C), 1531, 1450, 1256, 1169, 1034, 760, 741; δ_H (400 MHz, $CDCl_3$) 7.76 (1H, d, *J* = 7.5 Hz, H-16 or H-16'), 7.75 (1H, d, *J* = 7.6 Hz, H-16 or H-16'), 7.59 (2H, d, *J* = 7.3 Hz, H-13 and H-13'), 7.40 (1H, dd, *J* = 7.5, 7.3 Hz, H-15 or H-15'), 7.38 (1H, dd, *J* = 7.6, 7.3 Hz, H-15 or H-15'), 7.31 (1H, t, *J* = 7.3 Hz, H-14 or H-14'), 7.28 (1H, t, *J* = 7.3 Hz, H-14 or H-14'), 7.11–6.93 (1H,

m, H-3), 6.20 (1H, br s, NH), 5.24–5.02 (1H, m, NH), 4.48 (1H, dd, *J* = 10.7, 6.8 Hz, H-10a), 4.40 (1H, dd, *J* = 10.7, 6.8 Hz, H-10b), 4.21 (1H, t, *J* = 6.8 Hz, H-11), 4.03–3.90 (1H, m, H-1), 3.85–3.71 (1H, m, H-8a), 3.79 (3H, s, H-6), 3.66 (1H, ddd, *J* = 18.4, 3.2 Hz, H-4a), 3.31 (1H, dd, *J* = 18.4, 5.4 Hz, H-4b), 3.20 (1H, dd, *J* = 14.5, 4.4 Hz, H-8b), 2.31–2.16 (1H, m, H-7a), 1.96–1.83 (1H, m, H-7b); **δ_C** (101 MHz, $CDCl_3$) 165.4 (C5), 158.1 (C9), 143.9 (C12 or C12'), 143.8 (C12 or C12'), 141.5 (C17 or C17'), 141.5 (C17 or C17'), 131.8 (C2), 128.9 (C3), 127.9 (C15 or C15'), 127.9 (C15 or C15'), 127.2 (C14 or C14'), 127.2 (C14 or C14'), 125.2 (C13 or C13'), 125.1 (C13 or C13'), 120.2 (C16 or C16'), 120.1 (C16 or C16'), 67.0 (C10), 52.2 (C6), 49.0 (C4), 47.4 (C11), 46.9 (C1), 38.0 (C8), 36.7 (C7); ***m/z*** (ESI+) 509 ($[M+C_3H_5N_2]^+$, 27%); **HRMS** calculated for $[C_{26}H_{29}N_4O_5S]^+$ $(M+C_3H_5N_2)^+$ 509.1853, found 509.1861.

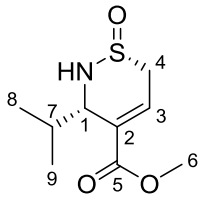
Methyl (1*R*,3*S*)-3-(benzyloxycarbonylaminoethyl)-3,6-dihydro-2*H*-1,2-thiazine-4-carboxylate 1-oxide (347)



The general procedure was followed using *N*-[*tert*-butyl-(*S*)-sulfinyl]-3-(benzyloxycarbonylamino)propylaldimine **334** (200 mg, 0.64 mmol) and afforded the crude product (384 mg) as a yellow oil. Purification by column chromatography over silica gel (eluting with 3:7 to 1:0 ethyl acetate/cyclohexane) afforded **347** (139 mg, 61%) as a yellow oil.

$[\alpha]_D^{20}$ –111 (*c* 0.36, $CHCl_3$); **υ_{max}** (cm^{-1}) (MeOH) 3298 (NH), 3067, 3034, 2953, 2835, 1699 (C=O), 1659 (C=C), 1530, 1437, 1246, 1022, 739, 696, 638; **δ_H** (400 MHz, $CDCl_3$) 7.39–7.27 (5H, m, H-12, H-13 and H-14), 7.08-6.93 (1H, m, H-3), 6.27 (1H, br s, NH), 5.21 (1H, dd, *J* = 8.5, 4.9 Hz, NH), 5.14 (1H, d, *J* = 12.3 Hz, H-10a), 5.06 (1H, d, *J* = 12.3 Hz, H-10b), 4.10–4.00 (1H, m, H-1), 3.85-3.71 (1H, m, H-8a), 3.77 (3H, s, H-6), 3.66 (1H, dt, *J* = 18.4, 3.2 Hz, H-4a), 3.30 (1H, dd, *J* = 18.4, 5.4 Hz, H-4b), 3.20 (1H, app. dq, *J* = 14.3, 4.4 Hz, H-8b), 2.23 (1H, ddt, *J* = 14.9, 11.9, 3.5 Hz, H-7a), 1.91 (1H, m, H-7b); **δ_c** (101 MHz, $CDCl_3$) 165.4 (C5), 158.1 (C9), 136.4 (C11), 131.9 (C2), 128.9 (C3), 128.7 (C13), 128.3 (C14), 128.1 (C12), 67.2 (C10), 52.2 (C6), 48.9 (C4), 47.0 (C1), 38.0 (C8), 36.7 (C7); ***m/z*** (ESI+) 421 ($[M+C_3H_5N_2]^+$, 100%); **HRMS** calculated for $[C_{19}H_{25}N_4O_5S]^+$ $(M+C_3H_5N_2)^+$ 421.1540, found 421.1549.

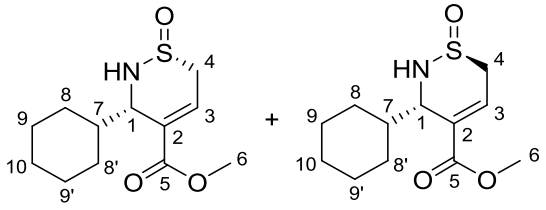
Methyl (1*R*,3*S*)-3-isopropyl-3,6-dihydro-2*H*-1,2-thiazine-4-carboxylate 1-oxide (349)



The general procedure was followed using *N*-[*tert*-butyl-(*S*)-sulfinyl]-2-methylpropylaldimine **336** (175 mg, 1.00 mmol) and afforded the crude product (371 mg) as a brown oil. Purification by column chromatography over silica gel (eluting with 3:7 to 1:0 ethyl acetate/cyclohexane) afforded **349** (106 mg, 49%) as a pale yellow amorphous solid.

$[\alpha]_D^{22}$ –112 (*c* 0.75, $CHCl_3$); **υ_{max}** (cm^{-1}) (MeOH) 3208 (NH), 2957, 2871, 1712 (C=O), 1649 (C=C), 1435, 1386, 1364, 1278, 1242, 1040; **δ_H** (400 MHz, $CDCl_3$) 6.91 (1H, dd, *J* = 5.6, 4.0 Hz, H-3), 4.74 (1H, d, *J* = 3.8 Hz, NH), 4.11–4.05 (1H, m, H-1), 4.00 (1H, ddd, *J* = 17.9, 5.6, 2.1 Hz, H-4a), 3.78 (3H, s, H-6), 3.18 (1H, ddd, *J* = 17.9, 4.0, 1.3 Hz, H-4b), 2.33 (1H, dhept, *J* = 8.3, 6.8 Hz, H-7), 1.09 (3H, d, *J* = 6.8 Hz, H-8 or H-9), 0.89 (3H, d, *J* = 6.8 Hz, H-8 or H-9); **δ_c** (101 MHz, $CDCl_3$) 166.1 (C5), 135.7 (C2), 129.7 (C3), 58.4 (C1), 52.3 (C6), 50.7 (C4), 32.7 (C7), 20.3 (C8 or C9), 19.6 (C8 or C9); ***m/z*** (ESI+) 240 ($[M+Na]^+$, 100%); **HRMS** calculated for $[C_9H_{15}NNaO_3S]^+$ $(M+Na)^+$ 240.0665, found 240.0666.

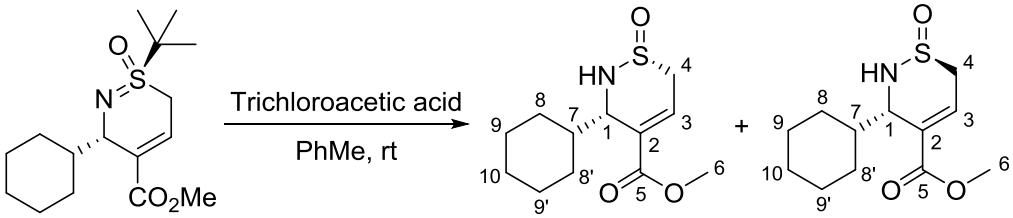
Methyl (1*R*,3*S*)-3-cyclohexyl-3,6-dihydro-2*H*-1,2-thiazine-4-carboxylate 1-oxide (304) and methyl (1*S*,3*S*)-3-cyclohexyl-3,6-dihydro-2*H*-1,2-thiazine-4-carboxylate 1-oxide (315)



304 **315**

Preparation 1: The general procedure was followed using *N*-[*tert*-butyl-(*S*)-sulfinyl]-cyclohexylaldimine **314** (215 mg, 1.00 mmol) and afforded the crude product (590 mg) as an orange solid. Purification by column chromatography over silica gel (eluting with 2:3 to 1:0 ethyl acetate/cyclohexane) afforded **304** (132 mg, 52%) as a pale yellow amorphous solid and a mixture of **304** and **315** (**304**:**315** = 10:1.8 mixture of isomers, 102 mg, 39%) as a pale yellow amorphous solid.

Preparation 2:



Trichloroacetic acid (0.32 mL, 3.19 mmol) was added to a solution of methyl (1*S*,3*S*)-1-(*tert*-butyl)-3-cyclohexyl-3,6-dihydro-1λ^6,2-thiazine-4-carboxylate 1-oxide **236** (500 mg, 1.60 mmol) in toluene (16 mL) and stirred at room temperature for 2 h before it was quenched with a saturated aqueous solution of sodium bicarbonate (5 mL). The layers were separated and then the aqueous layer was extracted with ethyl acetate (5 mL x3). The organic extracts were combined, dried over anhydrous magnesium sulfate and then concentrated *in vacuo* to afford the crude product (650 mg) as an orange amorphous solid. Purification by column chromatography over silica gel (eluting with 2:3 to 7:3 then 1:0 ethyl acetate/cyclohexane) afforded **304** (243 mg, 59%) as a pale yellow amorphous solid and **315** (39 mg, 10%) as a pale yellow amorphous solid.

Methyl (1*R*,3*S*)-3-cyclohexyl-3,6-dihydro-2*H*-1,2-thiazine-4-carboxylate 1-oxide (304)

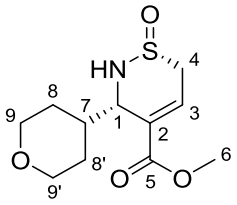
$[\alpha]_D^{22}$ –78 (*c* 1.15, $CHCl_3$); **υ_{max}** (cm^{-1}) (MeOH) 3246 (NH), 2939, 2921, 2848, 1709 (C=O), 1648 (C=C), 1436, 1265, 1231, 1042; **δ_H** (400 MHz, $CDCl_3$) 6.92 (1H, dd, *J* = 5.9, 3.8 Hz, H-3), 4.61 (1H, br d, *J* = 4.4 Hz, NH), 4.17–4.09 (1H, m, H-1), 4.05 (1H, ddd, *J* = 17.9, 5.9, 1.9 Hz, H-4a), 3.79 (3H, s, H-6), 3.19 (1H, ddd,

J = 17.9, 3.8, 1.2 Hz, H-4b), 2.15–2.06 (1H, m, H-8_{eq} or H-$8'_{eq}$), 2.05–1.95 (1H, m, H-7), 1.79–1.59 (3H, m, H-9_{eq}, H-$9'_{eq}$ and H-10_{eq}), 1.52–1.43 (1H, m, H-8_{eq} or H-$8'_{eq}$), 1.31–1.00 (5H, m, H-8_{ax}, H-$8'_{ax}$, H-9_{ax}, H-$9'_{ax}$ and H-10_{ax}); **δ_C** (101 MHz, $CDCl_3$) 166.2 (C5), 136.1 (C2), 129.9 (C3), 57.7 (C1), 52.3 (C6), 50.8 (C4), 42.3 (C7), 30.9 (C8 or C8'), 29.9 (C8 or C8'), 26.3 (C9 or C9'), 26.2 (C9 or C9'), 25.9 (C10); ***m/z*** (ESI+) 280 ($[M+Na]^+$, 27%); **HRMS** calculated for $[C_{12}H_{19}NNaO_3S]^+$ $(M+Na)^+$ 280.0978, found 280.0976.

Methyl (1*S*,3*S*)-3-cyclohexyl-3,6-dihydro-2*H*-1,2-thiazine-4-carboxylate 1-oxide (315)

$[\alpha]_D^{13}$ +35 (*c* 0.5, $CHCl_3$); **υ_{max}** (cm^{-1}) 3221 (NH), 2925, 2852, 1714 (C=O), 1650 (C=C), 1268, 1242, 1042, 1007; **δ_H** (400 MHz, $CDCl_3$) 7.05 (1H, dd, *J* = 7.8, 2.6 Hz, H-3), 4.43–4.26 (2H, m, H-1 and NH), 3.78 (3H, s, H-6), 3.44 (1H, ddt, *J* = 16.0, 7.8, 2.2 Hz, H-4a), 3.30 (1H, ddd, *J* = 16.0, 3.9, 2.6 Hz, H-4b), 1.95–1.88 (1H, m, H-7), 1.83–1.77 (1H, m, H-8_{eq} or H-$8'_{eq}$), 1.73–1.64 (3H, m, H-8_{eq} or H-$8'_{eq}$, H-9_{eq} and H-$9'_{eq}$), 1.46–1.39 (1H, m, H-10_{eq}), 1.34–1.29 (1H, m, H-8_{ax} or H-$8'_{ax}$), 1.20–1.06 (4H, m, H-8_{ax} or H-$8'_{ax}$, H-9_{ax}, H-$9'_{ax}$ and H-10_{ax}); **δ_C** (101 MHz, $CDCl_3$) 165.6 (C5), 132.1 (C2), 128.2 (C3), 52.8 (C1), 52.2 (C6), 48.3 (C4), 41.3 (C7), 30.0 (C8 or C8'), 26.7 (C8 or C8'), 26.4 (C9 or C9'), 26.2 (C9 or C9'), 25.5 (C10); ***m/z*** (ESI+) 280 ($[M+Na]^+$, 100%); **HRMS** calculated for $[C_{12}H_{19}NNaO_3S]^+$ $(M+Na)^+$ 280.0978, found 280.0979.

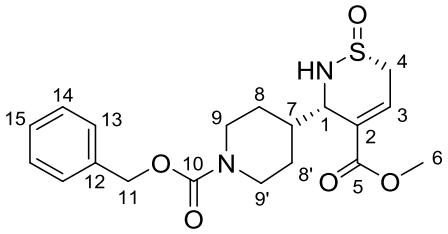
Methyl (1R,3S)-3-(tetrahydro-2H-pyran-4-yl)-3,6-dihydro-2H-1,2-thiazine-4-carboxylate 1-oxide (351)



The general procedure was followed using *N*-[*tert*-butyl-(*S*)-sulfinyl]-4-(tetrahydropyran)aldimine **338** (217 mg, 1.00 mmol) and afforded the crude product (425 mg) as an orange oil. Purification by column chromatography over silica gel (eluting with 2:3 to 1:0 ethyl acetate/cyclohexane) afforded **351** (196 mg, 76%) as a pale yellow amorphous solid.

$[\alpha]_D^{22}$ –75 (*c* 1.00, $CHCl_3$); **υ_{max}** (cm^{-1}) (MeOH) 3247, 3227 (NH), 2951, 2847, 1708 (C=O), 1650 (C=C), 1437, 1266, 1241, 1086, 1031, 985; **δ_H** (400 MHz, $CDCl_3$) 6.95 (1H, dd, *J* = 5.9, 3.6 Hz, H-3), 4.91 (1H, br d, *J* = 4.5 Hz, NH), 4.17–4.05 (2H, m, H-1 and H-4a), 3.97 (1H, ddd, *J* = 11.5, 5.2, 1.5 Hz, H-9_{eq} or H-$9'_{eq}$), 3.89 (1H, ddd, *J* = 11.4, 4.8, 1.6 Hz, H-9_{eq} or H-$9'_{eq}$), 3.78 (3H, s, H-6), 3.37 (1H, td, *J* = 11.9, 2.3 Hz, H-9_{ax} or H-$9'_{ax}$), 3.25 (1H, td, *J* = 11.7, 2.4 Hz, H-9_{ax} or H-$9'_{ax}$), 3.18 (1H, ddd, *J* = 18.1, 3.6, 1.0 Hz, H-4b), 2.32–2.19 (1H, m, H-7), 2.07–2.00 (1H, m, H-8_{eq} or H-$8'_{eq}$), 1.51–1.35 (2H, m, H-8_{eq} or H-$8'_{eq}$ and H-8_{ax} or H-$8'_{ax}$), 1.34–1.26 (1H, m, H-8_{ax} or H-$8'_{ax}$); **δ_c** (101 MHz, $CDCl_3$) 166.0 (C5), 135.4 (C2), 130.6 (C3), 67.9 (C9 or C9'), 67.5 (C9 or C9'), 57.0 (C1), 52.4 (C6), 51.0 (C4), 40.2 (C7), 30.9 (C8 or C8'), 30.3 (C8 or C8'); ***m/z*** (ESI+) 282 ($[M+Na]^+$, 56%); **HRMS** calculated for $[C_{11}H_{17}NNaO_4S]^+$ $(M+Na)^+$ 282.0770, found 282.0766.

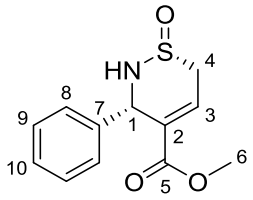
Methyl (1*R*,3*S*)-3-(1-(benzyloxycarbonyl)piperidin-4-yl)-3,6-dihydro-2*H*-1,2-thiazine-4-carboxylate 1-oxide (352)



The general procedure was followed using *N*-[*tert*-Butyl-(*S*)-sulfinyl]-4-(benzyloxycarbonylpiperidine)aldimine **339** (351 mg, 1.00 mmol) and afforded the crude product (629 mg) as an orange oil. Purification by column chromatography over silica gel (eluting with 3:7 to 1:0 ethyl acetate/cyclohexane) afforded **352** (245 mg, 62%) as a yellow amorphous solid.

$[\alpha]_D^{20}$ –43 (*c* 0.73, $CHCl_3$); **υ_{max}** (cm^{-1}) (MeOH) 3277 (NH), 2951, 2936, 2926, 2859, 1694 (C=O and C=C), 1439, 1273, 1254, 1221, 1032, 641; **δ_H** (400 MHz, $CDCl_3$) 7.38–7.27 (5H, m, H-13, H-14 and H-15), 6.96 (1H, dd, *J* = 5.7, 3.7 Hz, H-3), 5.18 (1H, br s, NH), 5.09 (2H, s, H-11), 4.29–4.03 (4H, m, H-1, H-4a, H-9_{eq} and H-$9'_{eq}$), 3.78 (3H, s, H-6), 3.22 (1H, dd, *J* = 18.4, 3.5 Hz, H-4b), 2.81–2.57 (2H, m, H-9_{ax} and H-$9'_{ax}$), 2.25–2.12 (1H, m, H-7), 2.12–2.04 (1H, m, H-8_{eq} or H-$8'_{eq}$), 1.46–1.23 (3H, m, H-8_{eq} or H-$8'_{eq}$, H-8_{ax} and H-$8'_{ax}$); **δ_c** (101 MHz, $CDCl_3$) 165.8 (C5), 155.3 (C10), 136.9 (C12), 135.0 (C2), 130.6 (C3), 128.6 (C14), 128.0 (C15), 127.9 (C13), 67.1 (C11), 56.5 (C1), 52.5 (C6), 50.5 (C4), 44.0 (C9 or C9'), 43.9 (C9 or C9'), 40.9 (C7), 29.8 (C8 or C8'), 29.1 (C8 or C8'); ***m/z*** (ESI+) 461 ($[M+C_3H_5N_2]^+$, 100%); **HRMS** calculated for $[C_{22}H_{29}N_4O_5S]^+$ $(M+C_3H_5N_2)^+$ 461.1853, found 461.1863.

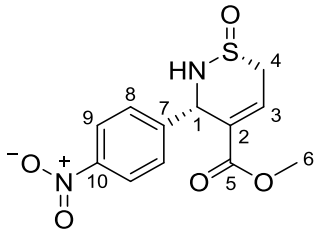
Methyl (1*R*,3*S*)-3-phenyl-3,6-dihydro-2*H*-1,2-thiazine-4-carboxylate 1-oxide (310)



The general procedure was followed using *N*-[*tert*-butyl-(*S*)-sulfinyl]-benzaldimine **120** (147 mg, 1.00 mmol) and afforded the crude product (389 mg) as an orange oil. Purification by column chromatography over silica gel (eluting with 3:7 to 1:0 ethyl acetate/cyclohexane) afforded **310** (96 mg, 38%) as a pale yellow amorphous solid.

$[\alpha]_D^{25}$ –69 (*c* 1.00, $CHCl_3$); **υ_{max}** (cm^{-1}) (MeOH) 3205 (NH), 3061, 3062, 2953, 1719 (C=O), 1659 (C=C), 1437, 1293, 1252, 1113, 1043, 700; **δ_H** (400 MHz, $CDCl_3$) 7.52–7.45 (2H, m, H-8), 7.33–7.27 (2H, m, H-9), 7.26–7.19 (1H, m, H-10), 7.14 (1H, dt, *J* = 6.5, 2.6 Hz, H-3), 5.08–5.02 (1H, m, H-1), 4.94–4.87 (1H, m, NH), 3.60 (3H, s, H-6), 3.58 (1H, m, H-4a) 3.42 (1H, ddt, *J* = 17.3, 6.5, 1.7 Hz, H-4b); **δ_c** (101 MHz, MeOD) 165.1, 141.0, 131.6, 128.8, 128.5, 128.3, 127.8, 55.0, 52.0, 48.2; ***m/z*** (ESI+) 274 ($[M+Na]^+$, 100%); **HRMS** calculated for $[C_{12}H_{13}NNaO_3S]^+$ $(M+Na)^+$ 274.0508, found 274.0512.

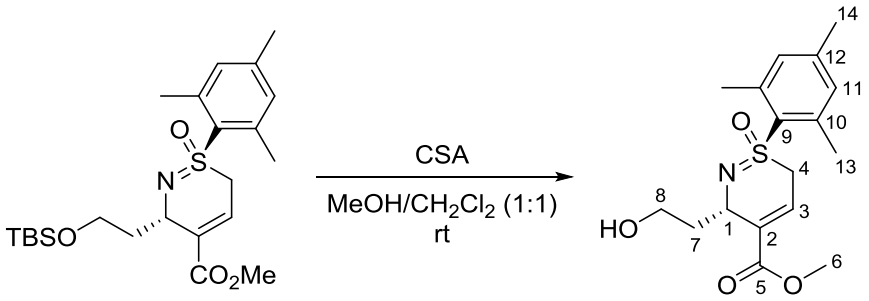
Methyl (1*R*,3*S*)-3-(4-nitrophenyl)-3,6-dihydro-2*H*-1,2-thiazine-4-carboxylate 1-oxide (354)



The general procedure was followed using *N*-[*tert*-butyl-(*S*)-sulfinyl]-acetaldimine **341** (147 mg, 1.00 mmol) and afforded the crude product (389 mg) as an orange oil. Purification by column chromatography over silica gel (eluting with 3:7 to 1:0 ethyl acetate/cyclohexane) afforded **355** (103 mg, 35%) as a pale yellow amorphous solid.

$[\alpha]_D^{26}$ –66 (*c* 1.00, MeCN); **υ_{max}** (cm^{-1}) (MeOH) 3219 (NH), 2954, 2926, 2853, 1720 (C=O), 1660 (C=C), 1520, 1348, 1294, 1253, 1044; **δ_H** (400 MHz, $CDCl_3$) 8.23–8.15 (2H, m, H-9), 7.79–7.72 (2H, m, H-8), 7.30 (1H, dt, *J* = 6.4, 2.4 Hz, H-3), 5.25–5.17 (1H, m, H-1), 4.73 (1H, br s, NH), 3.74–3.67 (1H, m, H-4a), 3.67 (3H, s, H-6), 3.56 (1H, dddd, *J* = 17.5, 6.4, 2.0, 1.2 Hz, H-4b); **δ_c** (101 MHz, $CDCl_3$) 164.7 (C5), 148.1 (C7), 147.4 (C10), 130.2 (C2), 130.1 (C8), 129.6 (C3), 123.9 (C9), 54.1 (C1), 52.4 (C6), 48.4 (C4); ***m/z*** (ESI+) 319 ($[M+Na]^+$, 42%); **HRMS** calculated for $[C_{12}H_{12}N_2NaO_5S]^+$ $(M+Na)^+$ 319.0359, found 319.0354.

Methyl (1*S*,3*S*)-3-(2-hydroxyethyl)-1-mesityl-3,6-dihydro-1λ^6,2-thiazine-4-carboxylate 1-oxide (356)[60]



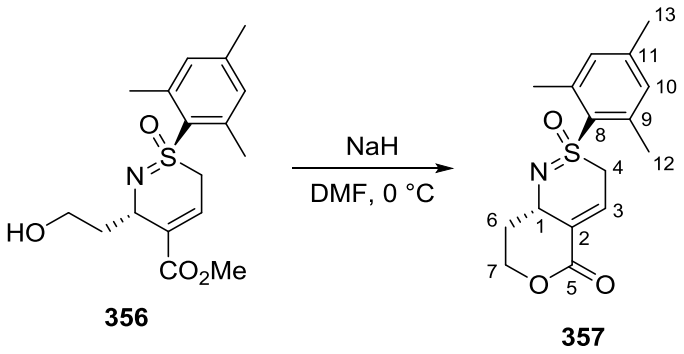
290 **356**

To a solution of methyl (1*S*,3*S*)-1-mesityl-3-(2-*tert*-butyldimethylsilyloxyethyl)-3,6-dihydro-1λ^6,2-thiazine-4-carboxylate 1-oxide **290** (560 mg, 1.24 mmol) in methanol (6.2 mL) and dichloromethane (6.2 mL) was added camphorsulfonic acid (288 mg, 1.24 mmol). The resulting solution was stirred at room temperature for 2 h before it was quenched with a saturated aqueous solution of sodium bicarbonate (10 mL) and stirred for 5 min. The layers were separated and then the aqueous layer was extracted with ethyl acetate (10 mL) and dichloromethane (10 mL x2). The organic extracts were combined, dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude product (480 mg) as a yellow oil. Purification by column chromatography over silica gel (eluting with ethyl acetate) afforded **356** (284 mg, 68%) as a yellow oil.

$[\alpha]_D^{22}$ +286 (*c* 0.5, $CHCl_3$); **υ_{max}** (cm^{-1}) ($CHCl_3$) 3006, 2955, 1717 (C=O), 1650 (C=C), 1603, 1438, 1278, 1246, 1147, 1066, 1037; **δ_H** (400 MHz, $CDCl_3$) 7.09–7.02 (1H, m, H-3), 6.94 (2H, s, H-11), 4.82–4.72 (1H, m, H1), 4.08 (1H, ddd, *J* = 18.8, 4.9, 2.7 Hz, H-4a), 4.01–3.89 (2H, m, H-8), 3.82 (3H, s, H-6), 3.75 (1H,

ddd, *J* = 18.9, 3.6, 1.9 Hz, H-4b), 2.60 (6H, s, H-13), 2.28 (3H, s, H-14), 2.15–2.02 (1H, m, H-7a), 1.95 (1H, dddd, *J* = 13.8, 10.4, 6.7, 4.9 Hz, H-7b); δ_c (101 MHz, $CDCl_3$) 165.9 (C5), 143.1 (C12), 140.3 (C10), 135.9 (C2), 133.8 (C9), 132.8 (C11), 129.4 (C3), 61.8 (C8), 55.1 (C1), 52.4 (C6), 49.3 (C4), 40.5 (C7), 22.8 (C13), 21.0 (C14); ***m/z*** (ESI+) 338 ($[M+H]^+$, 100%); **HRMS** calculated for $[C_{17}H_{24}NO_4S]^+$ $(M+H)^+$ 338.1421, found 338.1417.

(2*S*,8a*S*)-2-Mesityl-3,7,8,8a-tetrahydro-5*H*-2λ^4-pyrano[4,3-*c*][1,2]thiazin-5-one 2-oxide (357)

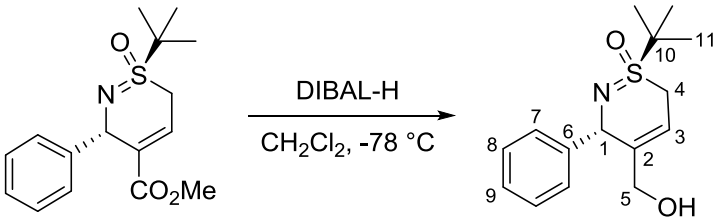


To a solution of methyl (1*S*,3*S*)-3-(2-hydroxyethyl)-1-mesityl-3,6-dihydro-1λ^6,2-thiazine-4-carboxylate 1-oxide **356** (97 mg, 0.29 mmol) in *N*,*N*-dimethylformamide (2.9 mL) at 0 °C was added sodium hydride (60% dispersion in mineral oil) (12.1 mg, 0.30 mmol). The resulting mixture was stirred at 0 °C for 1.5 h before it was quenched with brine (2.9 mL) and then ethyl acetate (3 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 mL x3). The combined organic extracts were washed with 20% w/v brine (3 mL x3), dried over anhydrous magnesium sulfate and then concentrated *in vacuo* to afford the crude product (81 mg) as a brown oil. Purification by column chromatography over

silica gel (eluting with 1:4 to 1:1 ethyl acetate/cyclohexane) afforded **357** (21 mg, 24%) as a yellow oil.

$[\alpha]_D^{22}$ +64 (*c* 1.2, $CHCl_3$); **υ_{max}** (cm^{-1}) ($CHCl_3$) 3688, 3608, 3011, 2983, 1716 (C=O), 1636 (C=C), 1602, 1401, 1267, 1248, 1159, 1094, 1046; **δ_H** (400 MHz, $CDCl_3$) 7.30 (1H, app. dt, *J* = 7.5, 2.7 Hz, H-3), 7.00 (2H, s, H-10), 4.50 (1H, ddd, *J* = 11.5, 4.8, 2.5 Hz, H-7a), 4.45–4.34 (2H, m, H-1 and H-7b), 3.99 (1H, ddd, *J* = 15.7, 7.5, 1.6 Hz, H-4a), 3.68 (1H, ddd, *J* = 15.6, 5.5, 2.5 Hz, H-4b), 2.64 (6H, s, H-12), 2.40 (1H, ddt, *J* = 13.8, 5.1, 2.7 Hz, H-6a), 2.31 (3H, s, H-13), 2.21 (1H, dtd, *J* = 13.8, 12.0, 4.8 Hz, H-6b); **δ_c** (101 MHz, $CDCl_3$) 164.5 (C5), 143.7 (C11), 141.1 (C9), 133.4 (C8), 133.2 (C10), 131.9 (C2), 130.0 (C3), 67.6 (C7), 53.3 (C1), 49.1 (C4), 34.6 (C6), 23.4 (C12), 21.1 (C13); ***m/z*** (ESI+) 306 ($[M+H]^+$, 100%); **HRMS** calculated for $[C_{16}H_{20}NO_3S]^+$ $(M+H)^+$ 306.1158, found 306.1159.

(1*S*,3*S*)-1-(*tert*-Butyl)-4-(hydroxymethyl)-3-phenyl-3,6-dihydro-1λ^6,2-thiazine 1-oxide (358)



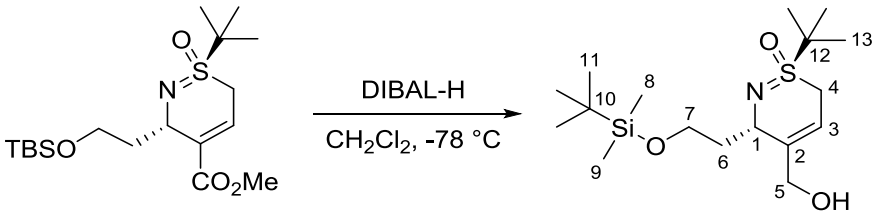
233 **358**

To a solution of methyl (1*S*,3*S*)-1-(*tert*-butyl)-3-phenyl-3,6-dihydro-1λ^6,2-thiazine-4-carboxylate 1-oxide **233** (30 mg, 0.098 mmol) in dichloromethane (1.0 mL) at –78 °C was added a 1.0 M solution of DIBAL-H in dichloromethane (0.24 mL, 0.24 mmol) dropwise. The resulting solution was stirred at –78 °C for 1 h before a saturated aqueous solution of Rochelle's salt (2 mL) was

added and the resulting mixture stirred vigorously for at least 1 h. The layers were separated and then the aqueous layer was extracted with dichloromethane (3 mL x2). The organic extracts were combined, dried over anhydrous magnesium sulfate and then concentrated *in vacuo* at 30 °C to afford **358** (21 mg, 77%) as a yellow oil without further purification.

$[\alpha]_D^{25}$ –49 (*c* 0.9, $CHCl_3$); **υ_{max}** (cm^{-1}) (MeOH) 3364 (OH), 2924, 2871, 1644 (C=C), 1454, 1269, 1204, 1099, 1025, 880, 760, 700; **δ_H** (400 MHz, $CDCl_3$) 7.49–7.43 (2H, m, H-7), 7.34–7.24 (2H, m, H-8), 7.24–7.18 (1H, m, H-9), 6.01–5.92 (1H, m, H-3), 5.13–5.00 (1H, m, H-1), 3.94–3.85 (1H, m, H-5a), 3.84–3.75 (2H, m, H-4a and H-5b), 3.40–3.31 (1H, m, H-4b), 1.44 (9H, s, H-11); **δ_c** (101 MHz, $CDCl_3$) 142.9 (C6), 142.8 (C2), 128.6 (C8), 128.2 (C7), 127.3 (C9), 112.3 (C3), 64.8 (C5), 61.6 (C1), 59.9 (C10), 38.8 (C4), 23.8 (C11); ***m/z*** (ESI+) 302 ($[M+Na]^+$, 28%); **HRMS** calculated for $[C_{15}H_{21}NNaO_2S]^+$ $(M+Na)^+$ 302.1185, found 302.1193.

(1*S*,3*S*)-1-(*tert*-Butyl)-3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-(hydroxy-methyl)-3,6-dihydro-1λ^6,2-thiazine 1-oxide (359)



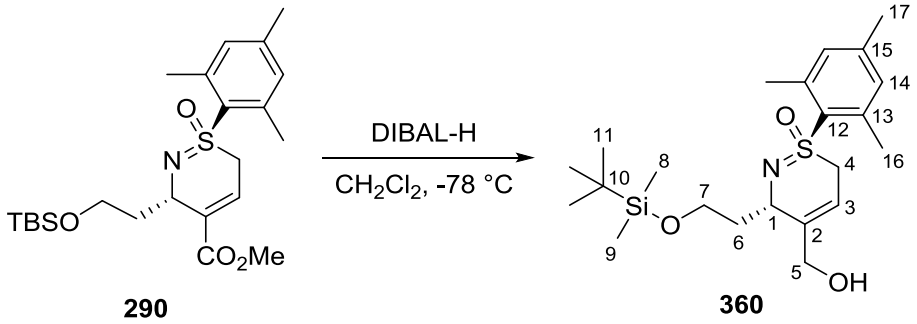
311 **359**

To a solution of methyl (1*S*,3*S*)-1-(*tert*-butyl)-3-(2-*tert*-butyldimethylsilyloxy ethyl)-3,6-dihydro-1λ^6,2-thiazine-4-carboxylate 1-oxide **311** (30 mg, 0.077 mmol) in dichloromethane (0.8 mL) at –78 °C was added a 1.0 M solution of

DIBAL-H in toluene (0.19 mL, 0.19 mmol) dropwise. The resulting solution was stirred at –78 °C for 1.25 h before a saturated aqueous solution of Rochelle's salt (1 mL) was added and the resulting mixture stirred vigorously for at least 1 h. The layers were separated and then the aqueous layer was extracted with ethyl acetate (3 mL x3). The organic extracts were combined, wash with brine (2 mL), dried over anhydrous magnesium sulfate and then concentrated *in vacuo* at 30 °C to afford the crude product (24 mg) as a yellow oil. Purification by column chromatography over silica gel (eluting with 2:3 to 4:1 ethyl acetate /petroleum ether) afforded **359** (18 mg, 65%) as a colourless oil.

$[\alpha]_D^{27}$ +18 (*c* 0.8, $CHCl_3$); **υ_{max}** (cm^{-1}) (MeOH) 3395 (OH), 2953, 2927, 2855, 1461, 1252, 1200, 1153, 1094, 1078, 1006, 838, 775; **δ_H** (400 MHz, $CDCl_3$) 5.86–5.77 (1H, m, H-3), 4.19–4.10 (3H, m, H-1 and H-5), 3.98–3.75 (3H, m, H-4a and H-7), 3.20–3.09 (1H, m, H-4b), 1.94–1.82 (2H, m, H-6), 1.40 (9H, s, H-13), 0.89 (9H, s, H-11), 0.07 (3H, s, H-8 or H-9), 0.06 (3H, s, H-8 or H-9); **δ_c** (101 MHz, $CDCl_3$) 145.1 (C2), 112.8 (C3), 65.2 (C5), 60.8 (C7), 59.6 (C12), 54.2 (C1), 40.2 (C6), 39.3 (C4), 26.1 (C11), 23.7 (C13), 18.5 (C10), -5.1 (C8 or C9), -5.2 (C8 or C9); ***m/z*** (ESI+) 362 ($[M+H]^+$, 53%); **HRMS** calculated for $[C_{17}H_{36}NO_3SSi]^+$ $(M+H)^+$ 362.2180, found 362.2190.

(1*S*,3*S*)-3-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-4-(hydroxymethyl)-1-mesityl-3,6-dihydro-1,2-thiazine 1-oxide (360)



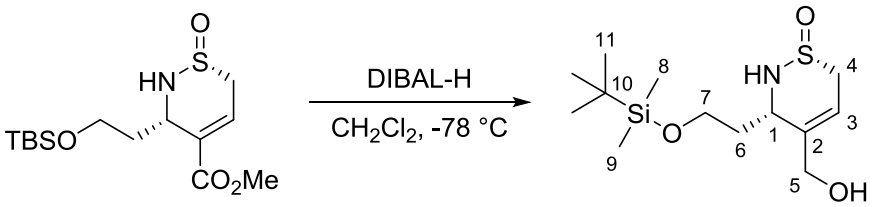
290 **360**

To a solution of methyl (1*S*,3*S*)-1-mesityl-3-(2-*tert*-butyldimethylsilyloxyethyl)-3,6-dihydro-1λ^6,2-thiazine-4-carboxylate 1-oxide **290** (300 mg, 0.66 mmol) in dichloromethane (6.6 mL) at –78 °C was added a 1.0 M solution of DIBAL-H in dichloromethane (2.32 mL, 2.32 mmol) dropwise. The resulting solution was stirred at –78 °C for 2 h before a saturated aqueous solution of Rochelle's salt (6.6 mL) was added and the resulting mixture stirred vigorously for at least 1 h. The layers were separated and then the aqueous layer was extracted with dichloromethane (10 mL x2). The organic extracts were combined, dried over anhydrous magnesium sulfate and then concentrated *in vacuo* to afford the crude product (276 mg) as a yellow oil. Purification by column chromatography over silica gel (eluting with 2:3 to 4:1 ethyl acetate/petroleum ether) afforded **360** (191 mg, 68%) as a yellow oil which solidified on standing.

$[\alpha]_D^{25}$ +56 (*c* 0.5, $CHCl_3$); **υ_{max}** (cm^{-1}) (MeOH) 3356 (OH), 2952, 2927, 2855, 1638 (C=C), 1602, 1563, 1461, 1252, 1207, 1156, 1093, 834, 775; **δ_H** (400 MHz, $CDCl_3$) 6.91 (2H, s, H-14), 5.85–5.79 (1H, m, H-3), 4.28–4.21 (1H, m, H-1), 4.21–4.16 (2H, m, H-5), 4.00–3.87 (3H, m, H-4a and H-7), 3.59–3.50 (1H, m, H-4b),

2.61 (6H, s, H-16), 2.26 (3H, s, H-17), 2.02–1.89 (2H, m, H-6), 0.89 (9H, s, H-11), 0.07 (6H, s, H-8 and H-9); δ_c (101 MHz, $CDCl_3$) 143.7 (C2), 142.4 (C15), 140.2 (C13), 134.8 (C12), 132.6 (C14), 113.3 (C3), 65.2 (C5), 61.1 (C7), 54.5 (C1), 49.0 (C4), 40.9 (C6), 26.1 (C11), 22.7 (C16), 21.0 (C17), 18.4 (C10), -5.1 (C8 or C9), -5.2 (C8 or C9); ***m/z*** (ESI+) 424 ($[M+H]^+$, 100%); **HRMS** calculated for $[C_{22}H_{38}NO_3SSi]^+$ $(M+H)^+$ 424.2336, found 424.2334.

(1*R*,3*S*)-3-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-4-(hydroxymethyl)-3,6-dihydro-2*H*-1,2-thiazine 1-oxide (361)



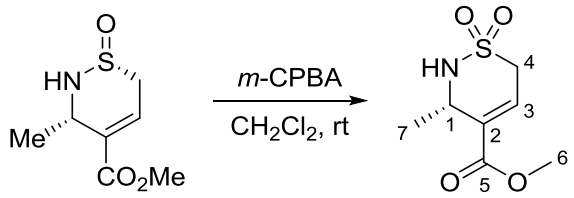
325 **361**

To a solution of methyl (1*R*,3*S*)-3-(2-*tert*-butyldimethylsilyloxyethyl)-3,6-dihydro-2*H*-1,2-thiazine-4-carboxylate 1-oxide **325** (30 mg, 0.09 mmol) in dichloromethane (0.9 mL) at –78 °C, a 1.0 M solution of DIBAL-H in dichloromethane (0.22 mL, 0.22 mmol) was added dropwise. The resulting solution was stirred at –78 °C for 2 h before a saturated aqueous solution of Rochelle's salt (2 mL) was added and the resulting mixture stirred vigorously for at least 1 h. The layers were separated and then the aqueous layer was extracted with dichloromethane (2 mL x2). The organic extracts were combined, dried over anhydrous magnesium sulfate and then concentrated *in vacuo* to afford the crude product (31 mg) as a colourless oil. The crude NMR contained a 2:1 ratio of product/starting material. The crude material was dissolved in dichloromethane (0.9 mL) cooled to –78 °C before the addition of

a 1.0 M solution of DIBAL-H in dichloromethane (0.22 mL, 0.22 mmol) dropwise. The resulting solution was stirred at –78 °C for 1 h. The same work-up procedure was followed to afford the crude product (23 mg) as a colourless oil. Purification by column chromatography over silica gel (eluting with 1:19 methanol/dichloromethane) afforded **361** (14 mg, 51%) as a colourless oil.

$[\alpha]_D^{29}$ –115 (*c* 0.7, $CHCl_3$); **υ_{max}** (cm^{-1}) (MeOH) 3283 (OH), 2952, 2927, 2883, 2855, 1471, 1463, 1406, 1388, 1360, 1252, 1079, 1032, 1006, 832, 775; **δ_H** (400 MHz, $CDCl_3$) 5.86–5.79 (1H, m, H-3), 5.36 (1H, br s, NH), 4.31–4.20 (1H, m, H-5a), 4.20–4.09 (1H, m, H-5b), 4.01–3.92 (2H, m, H-1 and H-7a), 3.89–3.81 (1H, m, H-7b), 3.49–3.39 (1H, m, H-4a), 3.26–3.16 (1H, m, H-4b), 2.30–2.17 (1H, m, H-6a), 2.01–1.90 (1H, m, H-6b), 0.91 (9H, s, H-11), 0.10 (3H, s, H-8 or H-9), 0.09 (3H, s, H-8 or H-9); **δ_c** (101 MHz, $CDCl_3$) 139.2 (C2), 112.5 (C3), 65.4 (C5), 62.2 (C7), 51.0 (C1), 48.0 (C4), 36.7 (C6), 26.0 (C11), 18.3 (C10), -5.3 (C8 or C9), -5.3 (C8 or C9); ***m/z*** (ESI+) 306 ($[M+H]^+$, 100%); **HRMS** calculated for $[C_{13}H_{28}NO_3SSi]^+$ $(M+H)^+$ 306.1554, found 306.1559.

Methyl (*S*)-3-methyl-3,6-dihydro-2*H*-1,2-thiazine-4-carboxylate 1,1-dioxide (362)



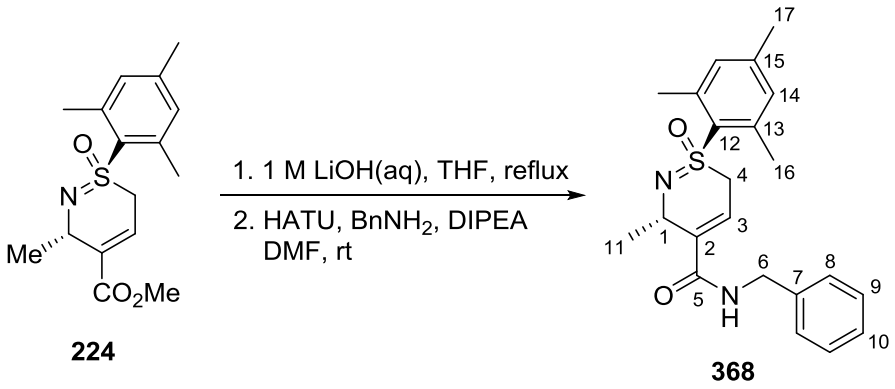
321 **362**

To a solution of methyl (1*R*,3*S*)-3-methyl-3,6-dihydro-2*H*-1,2-thiazine-4-carboxylate 1-oxide **321** (50 mg, 0.26 mmol) in dichloromethane (2 mL) was added *m*-CPBA (89 mg, 0.40 mmol) as a solution in dichloromethane (0.6 mL). The resulting solution was stirred at room temperature for 30 min before it was quenched with a saturated aqueous solution of sodium bicarbonate (1.5 mL). The layers were separated and then the aqueous layer was extracted with dichloromethane (2 mL x2). The organic extracts were combined, dried over anhydrous magnesium sulfate and then concentrated *in vacuo* to afford **362** (46 mg, 85%) as an orange oil (which solidified on standing) without further purification.

$[\alpha]_D^{25}$ –24 (*c* 0.75, $CHCl_3$); **υ_{max}** (cm^{-1}) (MeOH) 3263 (NH), 2956, 1714 (C=O), 1650 (C=C), 1436, 1332, 1301 (S=O), 1247, 1158, 1138 (S=O), 1051, 1020, 749; **δ_H** (400 MHz, $CDCl_3$) 6.85 (1H, ddd, *J* = 5.2, 4.1, 1.3 Hz, H-3), 4.84 (1H, s, NH), 4.59–4.42 (1H, m, H-1), 3.87–3.72 (2H, m, H-4), 3.77 (3H, s, H-6), 1.50 (3H, d, *J* = 6.9 Hz, H-7); **δ_c** (101 MHz, $CDCl_3$) 165.3 (C5), 133.6 (C2), 129.7 (C3), 52.9 (C1), 52.4 (C6), 47.7 (C4), 19.9 (C7); ***m/z*** (ESI+) 228 ($[M+Na]^+$, 92%); **HRMS** calculated for $[C_7H_{11}NNaO_4S]^+$ $(M+Na)^+$ 228.0301, found 228.0309; ***m/z*** (ESI-)

204 ([M-H]$^-$, 100%); **HRMS** calculated for $[C_7H_{10}NO_4S]^-$ (M-H)$^-$ 204.0336, found 204.0335.

(1S,3S)-N-benzyl-1-mesityl-3-methyl-3,6-dihydro-1λ^6,2-thiazine-4-carboxamide 1-oxide (368)

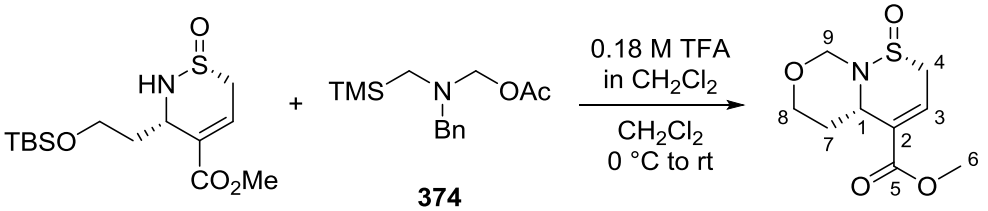


To a solution of methyl (1*S*,3*S*)-1-mesityl-3-methyl-3,6-dihydro-1λ^6,2-thiazine-4-carboxylate 1-oxide **224** (30 mg, 0.10 mmol) in tetrahydrofuran (1 mL) was added 1.0 M solution of lithium hydroxide in water (107 µL, 0.11 mmol). The solution was heated to reflux and stirred for 54 h. The reaction mixture was concentrated *in vacuo* to afford the crude product (34 mg) as an orange oil, which was then dissolved in dimethylformamide (1 mL) before benzylamine (13 µL, 0.12 mmol) and diisopropylethylamine (34 µL, 0.20 mmol) were added. A solution of HATU (48 mg, 0.13 mmol) in dimethylformamide (0.5 mL) was added at room temperature and the resulting mixture was stirred for 10 min. Quenched with saturated aqueous sodium bicarbonate solution (2 mL) and then ethyl acetate (3 mL) added. The layers were separated and then the organic layer was washed with 20% w/v brine (3 mL x3), brine (3 mL), dried over anhydrous magnesium sulfate and then concentrated *in vacuo* to afford the crude product (51 mg) as an orange oil. Purification by column

chromatography over silica gel (eluting with 1:4, 3:7, 2:3, 1:1 and then 3:2 ethyl acetate/cyclohexane) afforded **368** (13 mg, 35%) as a yellow oil.

$[\alpha]_D^{17}$ +94 (*c* 1.00, $CHCl_3$); **υ_{max}** (cm^{-1}) 3308 (NH), 3030, 2967, 2924, 2855, 1661 (C=O amide), 1630 (C=C), 1603, 1530, 1218, 1162, 846, 697; **δ_H** (400 MHz, $CDCl_3$) 7.35–7.28 (5H, m, H-8, H-9 and H-10), 6.93 (2H, s, H-14), 6.40 (1H, app. t, *J* = 4.0 Hz, H-3), 6.21 (1H, t, *J* = 5.8 Hz, NH), 4.80–4.70 (1H, m, H-1), 4.58–4.48 (2H, m, H-6), 3.92 (1H, dt, *J* = 17.8, 3.6 Hz, H-4a), 3.62 (1H, ddd, *J* = 17.8, 4.2, 1.9 Hz, H-4b), 2.62 (6H, s, H-16), 2.28 (3H, s, H-17), 1.51 (3H, d, *J* = 7.0 Hz, H-11); **δ_c** (101 MHz, $CDCl_3$) 167.6 (C5), 143.0 (C15), 142.4 (C2), 140.5 (C13), 138.1 (C7), 133.4 (C12), 132.8 (C14), 129.0 (C9), 128.0 (C8), 127.8 (C10), 120.3 (C3), 51.9 (C1), 47.8 (C4), 44.0 (C6), 24.9 (C11), 22.8 (C16), 21.0 (C17); ***m/z*** (ESI+) 383 ($[M+H]^+$, 100%); **HRMS** calculated for $[C_{22}H_{27}N_2O_2S]^+$ $(M+H)^+$ 383.1788, found 383.1793.

Methyl (1*R*,4a*S*)-2,4a,5,6-tetrahydro-8*H*-[1,2]thiazino[2,3-*c*][1,3]oxazine-4-carboxylate 1-oxide (375)



325 **374** **375**

At 0 °C, a 0.18 M solution of trifluoroacetic acid (60 µL, 0.75 mmol) in dichloromethane (4.2 mL) was added to a solution of methyl (1*R*,3*S*)-3-(2-*tert*-butyldimethylsilyloxyethyl)-3,6-dihydro-2*H*-1,2-thiazine-4-carboxylate 1-oxide **325** (50 mg, 0.15 mmol) and amine **374** (178 mg, 0.75 mmol) in

dichloromethane (1.5 mL). The resulting mixture was allowed to warm to room temperature and then stirred for 2.5 h before it was quenched with a saturated aqueous sodium bicarbonate solution (1.5 mL). The layers were separated and then the aqueous layer was extracted with dichloromethane (2 mL x2). The organic extracts were combined, dried over anhydrous magnesium sulfate and then concentrated *in vacuo* to afford the crude product (441 mg) as a yellow oil. Purification by column chromatography over silica gel (eluting with ethyl acetate) afforded **375** (26 mg, 75%) as a yellow oil.

$[\alpha]_D^{25}$ –111 (*c* 1.15, $CHCl_3$); **υ_{max}** (cm^{-1}) (MeOH) 2954, 2925, 2852, 1709 (C=O), 1656 (C=C), 1435, 1389, 1325, 1277, 1243, 1171, 1093, 1063, 1029, 988, 619; **δ_H** (400 MHz, $CDCl_3$) 7.04 (1H, ddd, *J* = 6.2, 2.9, 2.2 Hz, H-3), 5.13 (1H, d, *J* = 11.4 Hz, H-9a), 4.74 (1H, d, *J* = 11.4 Hz, H-9b), 4.26–4.20 (2H, m, H-1 and H-8a), 3.88 (1H, td, *J* = 12.1, 2.6 Hz, H-8b), 3.80 (3H, s, H-6), 3.56 (1H, ddd, *J* = 17.3, 3.7, 2.9 Hz, H-4a), 3.49 (1H, ddd, *J* = 17.3, 6.2, 1.6 Hz, H-4b), 2.42 (1H, qd, *J* = 12.4, 4.8 Hz, H-7a), 1.93–1.88 (1H, m, H-7b); **δ_c** (101 MHz, $CDCl_3$) 164.9 (C5), 131.2 (C2), 127.4 (C3), 85.1 (C9), 67.7 (C8), 54.6 (C1), 52.3 (C6), 50.0 (C4), 30.9 (C7); ***m/z*** (ESI+) 254 ($[M+Na]^+$, 100%); **HRMS** calculated for $[C_9H_{13}NNaO_4S]^+$ $(M+Na)^+$ 254.0457, found 254.0467.

4. References

1 H. Gilman and H. L. Morris, *J. Am. Chem. Soc.*, 1926, **48**, 2399–2404.

2 E. U. Jonsson, C. C. Bacon and C. R. Johnson, *J. Am. Chem. Soc.*, 1971, **93**, 5306–5308.

3 C. R. Johnson, E. U. Jonsson and C. C. Bacon, *J. Org. Chem.*, 1979, **44**, 2055–2061.

4 C. R. Johnson and A. Wambsgans, *J. Org. Chem.*, 1979, **44**, 2278–2280.

5 M. T. Robak, M. A. Herbage and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 3600–3740.

6 A. V. Reddy, S. U. Bhaskara Rao, G. L. Narasimha and P. K. Dubey, *Synth. Commun.*, 2009, **39**, 1451–1456.

7 X. Su, W. Zhou, Y. Li and J. Zhang, *Angew. Chem. Int. Ed.*, 2015, **54**, 6874–6877.

8 C. Wang, X. Wu, L. Zhou and J. Sun, *Eur. J. Chem.*, 2008, **14**, 8789–92.

9 J. G. Tillett, in *Sulphinic Acids, Esters and Derivatives*, John Wiley & Sons, Inc., Chichester, UK, 1990, pp. 603–622.

10 M. Harmata and P. Zheng, *Org. Lett.*, 2007, **9**, 5251–5253.

11 G. Liu, D. A. Cogan and J. A. Ellman, *J. Am. Chem. Soc.*, 1997, **119**, 9913–9914.

12 D. J. . Weix, J. A. . Ellman, X. . Wang and D. P. Curran, *Org. Synth.*, 2005, **82**, 157.

13 D. A. Cogan, G. Liu, K. Kim, B. J. Backes and J. A. Ellman, *J. Am. Chem. Soc.*, 1998, **120**, 8011–8019.

14 K. K. Andersen, *Tetrahedron Lett.*, 1962, **3**, 93–95.

15 S. Colonna, R. Giovini and F. Montanari, *Chem. Commun.*, 1968, 865.

16 A. Nudelman and D. J. Cram, *J. Am. Chem. Soc.*, 1968, **90**, 3869–3870.

17 F. A. Davis, R. E. Reddy, J. M. Szewczyk and P. S. Portonovo, *Tetrahedron Lett.*, 1993, **34**, 6229–6232.

18 F. A. Davis, Y. Zhang, Y. Andemichael, T. Fang, D. L. Fanelli and H. Zhang, *J. Org. Chem.*, 1999, **64**, 1403–1406.

19 Z. Han, D. Krishnamurthy, P. Grover, Q. K. Fang and C. H. Senanayake, *J. Am. Chem. Soc.*, 2002, **124**, 7880–7881.

20 Z. Han, D. Krishnamurthy, P. Grover, Q. K. Fang, X. Su, H. S. Wilkinson, Z.-H. Lu, D. Magiera and C. H. Senanayake, *Tetrahedron*, 2005, **61**, 6386–6408.

21 C. Roe, H. Hobbs and R. A. Stockman, *Chem. - A Eur. J.*, 2011, **17**, 2704–2708.

22 Y. Zhang, S. Chitale, N. Goyal, G. Li, Z. S. Han, S. Shen, S. Ma, N. Grinberg, H. Lee, B. Z. Lu and C. H. Senanayake, *J. Org. Chem.*, 2012, **77**, 690–695.

23 C. Bolm, O. Simić and M. Martin, *Synlett*, 2001, 1878–1880.

24 S. Gaillard, C. Papamicaël, G. Dupas, F. Marsais and V. Levacher,

Tetrahedron, 2005, **61**, 8138–8147.

25 M. Harmata and B. F. Herron, *Tetrahedron*, 1991, **47**, 8855–8862.

26 O. Wichterle and J. Roček, *Collect. Czechoslov. Chem. Commun.*, 1954, **19**, 282–297.

27 G. Kresze, A. Maschke, R. Albrecht, K. Bederke, H. P. Patzschke, H. Smalla and A. Trede, *Angew. Chem. Int. Ed. English*, 1962, **1**, 89–98.

28 Y. A. Arbuzov, *Russ. Chem. Rev.*, 1964, **33**, 407–424.

29 B. J. Wagner, J. T. Doi and W. K. Musker, *J. Org. Chem.*, 1990, **55**, 4156–4162.

30 J. T. Doi and W. K. Musker, *J. Org. Chem.*, 1985, **50**, 1–4.

31 J. Coulomb, V. Certal, L. Fensterbank, E. Lacôte and M. Malacria, *Angew. Chem.*, 2006, **118**, 649–653.

32 B. Nguyen, E. J. Emmett and M. C. Willis, *J. Am. Chem. Soc.*, 2010, **132**, 16372–16373.

33 H. Konishi, H. Tanaka and K. Manabe, *Org. Lett.*, 2017, **19**, 1578–1581.

34 S. I. Bell and S. M. Weinreb, *Tetrahedron Lett.*, 1988, **29**, 4233–4236.

35 M. Wills, R. J. Butlin, I. D. Linneya and R. W. Gibson, *J. Chem. Soc. Perkin Trans. 1*, 1991, **36**, 3383.

36 F. A. Davis, J. Qu, V. Srirajan, R. Joseph and D. D. Titus, *Heterocycles*, 2002, **58**, 251.

37 J. Coulomb, V. Certal, M.-H. Larraufie, C. Ollivier, J.-P. Corbet, G. Mignani, L. Fensterbank, E. Lacôte and M. Malacria, *Chem. - A Eur. J.*, 2009, **15**, 10225–10232.

38 W. Ye, L. Zhang, C. Ni, J. Rong and J. Hu, *Chem. Commun.*, 2014, **50**, 10596–10599.

39 J. A. Fernández-Salas, M. M. Rodríguez-Fernández, M. C. Maestro and J. L. García-Ruano, *Chem. Commun.*, 2014, **50**, 6046–6048.

40 D. A. Cogan, G. Liu and J. Ellman, *Tetrahedron*, 1999, **55**, 8883–8904.

41 E. S. Levchenko and A. V. Kirsanov, *Zh. Obs. Khim.*, 1960, **30**, 1553.

42 O. G. Mancheño and C. Bolm, *Beilstein J. Org. Chem.*, 2007, **3**, 25.

43 S. P. Fritz, A. Mumtaz, M. Yar, E. M. McGarrigle and V. K. Aggarwal, *Eur. J. Org. Chem.*, 2011, 3156–3164.

44 A. Prakash, M. Dibakar, K. Selvakumar, K. Ruckmani and M. Sivakumar, *Tetrahedron Lett.*, 2011, **52**, 5625–5628.

45 X. Sun, X. Tu, C. Dai, X. Zhang, B. Zhang and Q. Zeng, *J. Org. Chem.*, 2012, **77**, 4454–4459.

46 G. Liu, D. A. Cogan, T. D. Owens, T. P. Tang and J. A. Ellman, *J. Org. Chem.*, 1999, **64**, 1278–1284.

47 D. A. Cogan and J. A. Ellman, *J. Am. Chem. Soc.*, 1999, **121**, 268–269.

48 J. A. Deyrup, *J. Org. Chem.*, 1969, **34**, 2724–2727.

49 F. A. Davis, P. Zhou and G. V. Reddy, *J. Org. Chem.*, 1994, **59**, 3243–3245.

50 F. A. Davis, H. Liu, P. Zhou, T. Fang, G. V. Reddy and Y. Zhang, *J. Org. Chem.*, 1999, **64**, 7559–7567.

51 T. M. Solá, I. Churcher, W. Lewis and R. A. Stockman, *Org. Biomol. Chem.*, 2011, **9**, 5034.

52 T. Moragas, I. Churcher, W. Lewis and R. A. Stockman, *Org. Lett.*, 2014, **16**, 6290–6293.

53 R. E. Ireland, P. Wipf and J. D. Armstrong, *J. Org. Chem.*, 1991, **56**, 650–657.

54 P. Dinér, A. Sadhukhan and B. Blomkvist, *ChemCatChem*, 2014, **6**, 3063–3066.

55 Zhiyan Huang, A. Hongshan Lai and Y. Qin, *J. Org. Chem.*, 2007, **72**, 1373–1378.

56 Q. Wen, L. Zhang, J. Xiong and Q. Zeng, *European J. Org. Chem.*, 2016, 5360–5364.

57 P. D. Kennewell and J. B. Taylor, *Chem. Soc. Rev.*, 1975, **4**, 189.

58 P. D. Kennewell and J. B. Taylor, *Chem. Soc. Rev.*, 1980, **9**, 477.

59 H. R. Bentley, E. E. McDermott and J. K. Whitehead, *Nature*, 1950, **165**, 150–151.

60 T. M. Solà, PhD Thesis, The University of Nottingham, 2013.

61 C. R. Johnson, E. R. Janiga and M. Haake, *J. Am. Chem. Soc.*, 1968, **90**, 3890–3891.

62 C. R. Johnson and G. F. Katekar, *J. Am. Chem. Soc.*, 1970, **92**, 5753–5754.

63 C. R. Johnson, *Acc. Chem. Res.*, 1973, **6**, 341–347.

64 M. Reggelin and C. Zur, *Synthesis (Stuttg).*, 2000, 1–64.

65 C. Bolm, M. Felder and J. Muller, *Synlett*, 1992, 439–441.

66 H. Okamura and C. Bolm, *Chem. Lett.*, 2004, **33**, 482–487.

67 S.-M. Lu and C. Bolm, *Adv. Synth. Catal.*, 2008, **350**, 1101–1105.

68 O. G. Mancheño, J. Dallimore, A. Plant and C. Bolm, *Adv. Synth. Catal.*, 2010, **352**, 309–316.

69 U. Lücking, *Angew. Chem. Int. Ed.*, 2013, **52**, 9399–9408.

70 G. Siemeister, U. Lücking, A. M. Wengner, P. Lienau, W. Steinke, C. Schatz, D. Mumberg and K. Ziegelbauer, *Mol. Cancer Ther.*, 2012, **11**, 2265–73.

71 H. Oberhammer and W. Zeil, *Naturforsch*, 1970, **25a**, 845.

72 M. Goehring, *Q. Rev. Chem. Soc.*, 1956, **10**, 437.

73 H. R. Bentley, E. E. McDermott and J. K. Whitehead, *Nature*, 1950, **165**, 735–735.

74 V. Bizet, C. M. M. Hendriks and C. Bolm, *Chem. Soc. Rev.*, 2015, **44**, 3378–3390.

75 J. Bull, L. Degennaro and R. Luisi, *Synlett*, 2017, **28**, 2525–2538.

76 E. Mellanby, *Br. Med. J.*, 1946, **2**, 885–887.

77 T. Moran, *Lancet*, 1947, **250**, 289–291.

78 H. R. Bentley, E. E. McDermott, J. Pace, J. K. Whitehead and T. Moran, *Nature*, 1949, **163**, 675–676.

79 H. R. Bentley, E. E. Mcdermott and J. K. Whitehead, *Proc. R. Soc. London. Ser. B, Biol. Sci.*, 1951, **138**, 265–72.

80 C. R. Johnson and E. R. Janiga, *J. Am. Chem. Soc.*, 1973, **95**, 7692–7700.

81 F. Misani, T. W. Fair and L. Reiner, *J. Am. Chem. Soc.*, 1951, **73**, 459–461.

82 C. R. Johnson and C. W. Schroeck, *J. Am. Chem. Soc.*, 1973, **95**, 7418–7423.

83 C. R. Johnson, R. A. Kirchhoff and H. G. Corkins, *J. Org. Chem.*, 1974, **39**, 2458–2459.

84 Y. Tamura, K. Sumoto, J. Minamikawa and M. Ikeda, *Tetrahedron Lett.*, 1972, **13**, 4137–4140.

85 L. A. Carpino, *J. Am. Chem. Soc.*, 1960, **82**, 3133–3135.

86 J. Mendiola, J. A. Rincón, C. Mateos, J. F. Soriano, O. de Frutos, J. K. Niemeier and E. M. Davis, *Org. Process Res. Dev.*, 2009, **13**, 263–267.

87 D. R. Rayner, D. M. Von Schriltz, J. Day and D. J. Cram, *J. Am. Chem. Soc.*, 1968, **90**, 2721–2723.

88 G. Y. Cho and C. Bolm, *Tetrahedron Lett.*, 2005, **46**, 8007–8008.

89 L. B. Krasnova, R. M. Hili, O. V. Chernoloz and A. K. Yudin, *Arkivoc*, 2005, **4**, 26.

90 C. A. Dannenberg, L. Fritze, F. Krauskopf and C. Bolm, *Org. Biomol. Chem.*, 2017, **15**, 1086–1090.

91 O. G. Mancheño, O. Bistri and C. Bolm, *Org. Lett.*, 2007, **9**, 3809–3811.

92 H. Kwart and A. A. Kahn, *J. Am. Chem. Soc.*, 1967, **89**, 1950–1951.

93 D. Carr, T. P. Seden and R. W. Turner, *Tetrahedron Lett.*, 1969, **10**, 477–478.

94 C. R. Johnson, R. A. Kirchhoff, R. J. Reischer and G. F. Katekar, *J. Am. Chem. Soc.*, 1973, **95**, 4287–4291.

95 J. F. K. Müller and P. Vogt, *Tetrahedron Lett.*, 1998, **39**, 4805–4806.

96 E. Lacôte, M. Amatore, L. Fensterbank and M. Malacria, *Synlett*, 2002, 116–118.

97 T. Bach and C. Korber, *Tetrahedron Lett.*, 1998, **39**, 5015–5016.

98 O. G. Mancheño and C. Bolm, *Org. Lett.*, 2006, **8**, 2349–2352.

99 O. G. Mancheño, J. Dallimore, A. Plant and C. Bolm, *Org. Lett.*, 2009, **11**,

2429–2432.

100 H. Okamura and C. Bolm, *Org. Lett.*, 2004, **6**, 1305–1307.

101 M. Zenzola, R. Doran, R. Luisi and J. A. Bull, *J. Org. Chem.*, 2015, **80**, 6391–6399.

102 H. R. Bentley and J. K. Whitehead, *J. Chem. Soc.*, 1950, **0**, 2081–2082.

103 P. K. Claus, W. Rieder, P. Hofbauer and E. Vilsmaier, *Tetrahedron*, 1975, **31**, 505–510.

104 S.-L. Huang and D. Swern, *J. Org. Chem.*, 1979, **44**, 2510–2513.

105 C. R. Johnson and R. A. Kirchhoff, *J. Org. Chem.*, 1979, **44**, 2280–2280.

106 J. Wang, M. Frings and C. Bolm, *Angew. Chem. Int. Ed.*, 2013, **52**, 8661–8665.

107 H. Takada, M. Oda, A. Oyamada, K. Ohe and S. Uemura, *Chirality*, 2000, **12**, 299–312.

108 Y. Miyake, H. Takada, K. Ohe and S. Uemura, *J. Chem. Soc. Perkin Trans. 1*, 1998, 2373–2376.

109 C. Ohta and T. Katsuki, *Tetrahedron Lett.*, 2001, **42**, 3885–3888.

110 Y. Tamura, T. Uchida and T. Katsuki, *Tetrahedron Lett.*, 2003, **44**, 3301–3303.

111 R. W. Heintzelman, R. B. Bailey and D. Swern, *J. Org. Chem.*, 1976, **41**, 2207–2209.

112 Y. Chen and J. Gibson, *RSC Adv.*, 2015, **5**, 4171–4174.

113 C. R. Johnson, E. U. Jonsson and A. Wambsgans, *J. Org. Chem.*, 1979, **44**, 2061–2065.

114 P. Stoss and G. Satzinger, *Angew. Chem. Int. Ed. English*, 1971, **10**, 76–76.

115 P. Stoss and G. Satzinger, *Chem. Ber.*, 1972, **105**, 2575–2583.

116 C. R. Johnson, G. F. Katekar, R. F. Huxol and E. R. Janiga, *J. Am. Chem. Soc.*, 1971, **93**, 3771–3773.

117 M. Harmata and E. O. Schlemper, *Tetrahedron Lett.*, 1987, **28**, 5997–6000.

118 M. Harmata, R. J. Claassen and C. L. Barnes, *J. Org. Chem.*, 1991, **56**, 5059–5062.

119 M. Harmata and N. Pavri, *Angew. Chem. Int. Ed.*, 1999, **38**, 2419–2421.

120 T. Moragas, R. M. Liffey, D. Regentová, J.-P. S. Ward, J. Dutton, W. Lewis, I. Churcher, L. Walton, J. A. Souto and R. A. Stockman, *Angew. Chem. Int. Ed.*, 2016, **55**, 10047–10051.

121 D. Regentová, PhD Thesis, The University of Nottingham, 2013.

122 H. R. Bentley, E. E. McDermott, T. Moran, J. Pace and J. K. Whitehead, *Proc. R. Soc. Ser. B-Biological Sci.*, 1950, **137**, 402–417.

123 C. Moessner and C. Bolm, *Angew. Chem. Int. Ed.*, 2005, **44**, 7564–7567.

124 D. Xiao and X. Zhang, *Angew. Chem. Int. Ed.*, 2001, **40**, 3425–3428.

125 GB Pat., WO2011/154737 (A1), 2011.

126 CA Pat., CA2739739, 2016.

127 https://www.sigmaaldrich.com-date accessed 24/09.

128 R. M. Liffey, PhD Thesis, University of Nottingham, 2017.

129 T. Hudlicky, G. Sinai-zingde and G. Seoane, *Synth. Commun.*, 1987, **17**, 1155–1163.

130 *Http://www.biotage.com/product-page/isolute-scx-2*, 2018-01-11.

131 S. Ceccarelli, U. Piarulli and C. Gennari, *J. Org. Chem.*, 2000, **65**, 6254–6256.

132 B. A. F. Le Bailly, L. Byrne and J. Clayden, *Angew. Chem. Int. Ed.*, 2016, **55**, 2132–2136.

133 H. Sigel, *Angew. Chem. Int. Ed. Eng.*, 1968, **7**, 137–138.

134 H. Sigel and B. Martin, *Chem. Rev*, 1982, **82**, 385–426.

135 F. A. Davis, T. Ramachandar and Y. Wu, *J. Org. Chem.*, 2003, **68**, 6894–6898.

136 V. A. Rassadin, D. S. Grosheva, A. A. Tomashevskii and V. V. Sokolov, *Chem. Heterocycl. Compd.*, 2013, **49**, 39–65.

137 K. C. Nicolaou, M. Nevalainen, M. Zak, S. Bulat, M. Bella and B. S. Safina, *Angew. Chem. Int. Ed.*, 2003, **42**, 3418–3424.

138 N. Spiccia, J. Basutto, P. Jokisz, L. S.-M. Wong, A. G. Meyer, A. B. Holmes, J. M. White and J. H. Ryan, *Org. Lett.*, 2011, **13**, 486–489.

139 I. O. O. Korhonen, M. Pitkänen and J. N. J. Korvola, *Tetrahedron*, 1982, **38**, 2837–2841.

140 J. M. Fevig, R. W. Marquis and L. E. Overman, *J. Am. Chem. Soc.*, 1991, **113**, 5085–5086.

141 E. Brenna, F. G. Gatti, A. Manfredi, D. Monti and F. Parmeggiani, *Org. Process Res. Dev.*, 2012, **16**, 262–268.

142 P. E. Maligres, G. R. Humphrey, J.-F. Marcoux, M. C. Hillier, D. Zhao, S. Krska and E. J. J. Grabowski, *Org. Process Res. Dev.*, 2009, **13**, 525–534.

143 T. Hvidt, W. A. Szarek and D. B. Maclean, *Can. J. Chem.*, 1988, **66**, 779–782.

144 W.-R. Li and H.-H. Chou, *Synthesis (Stuttg).*, 2000, 84–90.

145 L. A. Gandon, A. G. Russell, T. Güveli, A. E. Brodwolf, B. M. Kariuki, N. Spencer and J. S. Snaith, *J. Org. Chem.*, 2006, **71**, 5198–5207.

146 A. Viso, R. Fernández de la Pradilla and M. Ureña, *Tetrahedron*, 2009, **65**, 3757–3766.

147 K. W. Kells and J. M. Chong, *Org. Lett.*, 2003, **5**, 4215–4218.

148 J. P. McMahon and J. A. Ellman, *Org. Lett.*, 2005, **7**, 5393–5396.

149 L. Ye, W. He and L. Zhang, *Angew. Chem. Int. Ed.*, 2011, **50**, 3236–3239.

150 V. Arnaud, F. Franck, A. Pérez-Luna and F. Chemla, *Org. Lett.*, 2007, **9**, 4705–4708.

151 J. L. H. Madsen, C. U. Hjørringgaard, B. S. Vad, D. Otzen and T. Skrydstrup, *Chem. - A Eur. J.*, 2016, **22**, 8358–8367.

152 D. R. Fandrick, C. S. Johnson, K. R. Fandrick, J. T. Reeves, Z. Tan, H. Lee, J. J. Song, N. K. Yee and C. H. Senanayake, *Org. Lett.*, 2010, **12**, 748–751.

153 K. W. Kells and J. M. Chong, *Org. Lett.*, 2003, **5**, 4215–4218.

154 Y. Bolshan and R. A. Batey, *Org. Lett.*, 2005, **7**, 1481–1484.

155 US Pat., WO2011/026904 (A1), 2011.

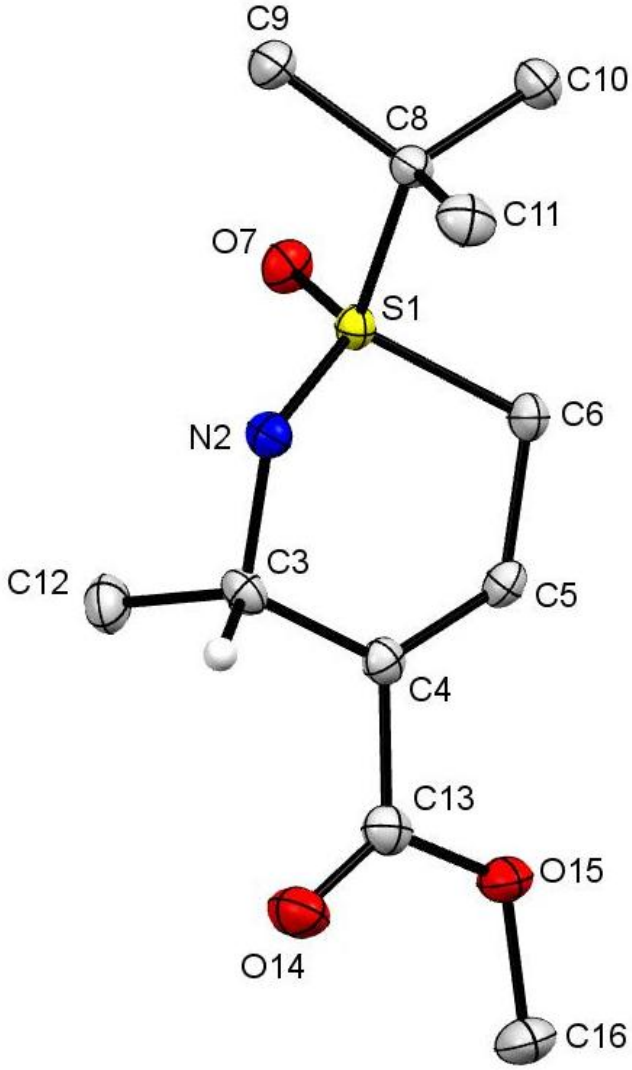
156 US Pat., US2016/213664 (A1), 2016.

157 T. A. Boebel and J. F. Hartwig, *Tetrahedron*, 2008, **64**, 6824–6830.

158 S. Srinath, S. Ramu, S. Elavarasan, D. Paradesi, R. M. Kumar, K. Ilango and B. Baskar, *Mol. Catal.*, 2017, **443**, 294–300.

5. Appendix – X-ray Crystal Structure Data

Methyl (1*S*,3*S*)-1-(*tert*-butyl)-3-methyl-3,6-dihydro-1λ^6,2-thiazine-4-carboxylate 1-oxide (166)

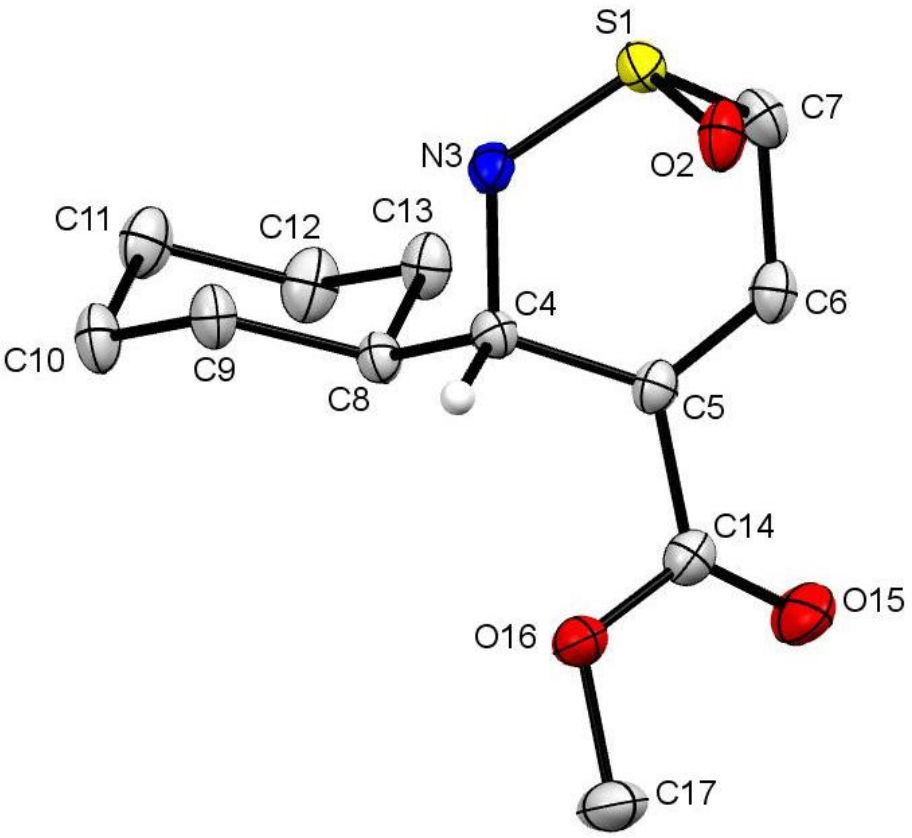


Selected hydrogens of the molecule have been omitted for clarity.

CCDC No. = 1484615

$C_{11}H_{19}NO_3S$ Mw = 245.33; T = 120(10) K; λ = 1.54184 Å; Orthorhombic; *P* 2_1 2_1 2_1 space group; a = 6.1762(5) Å, b = 9.8315(8) Å, c = 20.5884(16) Å; α = 90°, β = 90°, γ = 90°; V = 1250.16(18) Å^3; Z = 4; D = 1.303 Mg/m^3; R = 0.0317 (all data), wR = 0.0789, GoF = 1.097.

Methyl (1*S*,3*S*)-3-cyclohexyl-3,6-dihydro-2*H*-1,2-thiazine-4-carboxylate 1-oxide (323)



Selected hydrogens of the molecule have been omitted for clarity.

$C_{12}H_{19}NO_3S$ Mw = 257.34; T = 120 K; λ = 1.54184 Å; Orthorhombic; *P* 2_1 2_1 2_1 space group; a = 8.22387(15) Å, b = 10.16241(18) Å, c = 15.4066(3) Å; α = 90°, β = 90°, γ = 90°; V = 1287.59(4) $Å^3$; Z = 4; D = 1.328 Mg/m^3; R = 0.0301, wR = 0.0809, GoF = 1.118.

Rearrangements

International Edition: DOI: 10.1002/anie.201604188
German Edition: DOI: 10.1002/ange.201604188

Sigmatropic Rearrangement of Vinyl Aziridines: Expedient Synthesis of Cyclic Sulfoximines from Chiral Sulfinimines

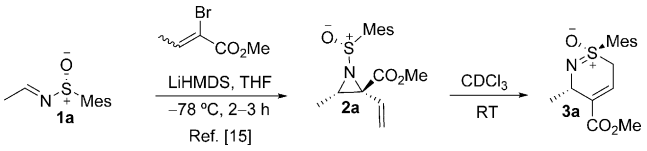
*Toni Moragas, Ryan M. Liffey, Dominika Regentová, Jon-Paul S. Ward, Justine Dutton, William Lewis, Ian Churcher, Lesley Walton, José A. Souto, and Robert A. Stockman**

Abstract: *A novel rearrangement of 2-vinyl aziridine 2-carboxylates to unusual chiral cyclic sulfoximines is described herein. The method allows the synthesis of substituted cyclic sulfoximines in high yields with complete stereocontrol, and tolerates a wide substrate scope. A one-pot process starting directly from sulfinimines provides access to complex chiral sulfoximines in only two steps from commercially available aldehydes. A mechanistic hypothesis and synthetic application in the formal synthesis of trachelanthamidine, by transformation of a cyclic sulfoximine into a pyrroline, is also disclosed.*

Since the first isolation of sulfoximines by Bentley and co-workers in 1950[1] these sulfur-containing compounds have found applications in functional-group transformations and asymmetric synthesis,[2] drug development,[3] crop treatment,[4] and insect control.[5] Largely ignored in medicinal chemistry for around 50 years, the sulfoximine group has recently been the object of significant new interest.[3] Sulfoximines are three-dimensional motifs with three points of attachment in orthogonal vectors,[6] and functionalisation at the nitrogen and carbon centers α to the sulfur atom is versatile and facile.[7–9]

Despite the promising biological activity showed by the few previously synthesised cyclic sulfoximines,[3] methods describing the synthesis of these compounds are scarce and mainly involve the multistep synthesis of linear sulfoximines[10,11] and subsequent cyclizations.[12] Furthermore, they generally describe benzofused cyclic sulfoximines. This limitation is found in the recent work reported by Hu et al. where a very elegant one-step synthesis of cyclic sulfoximines was achieved, starting from enantiomerically pure sulfinimines, by cycloaddition with benzynes.[13] Herein we describe a simple and versatile method for the synthesis of nonfused six-membered cyclic sulfoximines with complete diastereocontrol and a wide substrate range.

Building on our prior work in the area of aza-Darzens-type aziridinations of chiral *tert*-butanesulfinimines[14] and *S*-mesitylsulfinimines,[15] we were drawn to the potential use of 2-bromobut-2-enoic acid methyl ester as a potential partner for an aza-Darzens-type aziridination of chiral sulfinimines. The products, trisubstituted vinyl aziridine 2-carboxylates, would be potentially versatile intermediates for asymmetric synthesis.[16] Thus, we investigated the aza-Darzens reaction of the acetaldehyde-derived S-mesitylsulfinimine **1a** using LiHMDS as base in THF at −78 °C (Scheme 1). Pleasingly,



Scheme 1. Unprecedented rearrangement of aziridines leading to sulfoximines. HMDS = hexamethyldisilazide, Mes = 2,4,6-trimethylphenyl, THF = tetrahydrofuran.

we found excellent conversion into the vinyl aziridine **2a**. However, upon standing in deuterochloroform, we observed that this vinyl aziridine underwent a rearrangement to afford a new compound. After purification and extensive characterization we found that the isolated product corresponds to the cyclic sulfoximine **3a** wherein chiral information is retained.

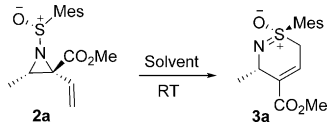
Herein, we present our findings on the substrate scope of this novel rearrangement and offer a mechanistic hypothesis for this interesting transformation.

Intrigued by the observed rearrangement, we wanted to explore the influence of solvent and temperature on the sulfoximine formation (Table 1). No clear correlation was found between the nature of solvent and the reaction performance, and best results obtained when $CDCl_3$, $[D_6]$DMSO, MeOD, and C_6D_6 were used as a solvent. C_6D_6 was the selected solvent to study the influence of temperature on the described rearrangement. In a very straightforward manner we determined that an increase in temperature clearly improves the yield of the reaction, thus leading to the desired compound in 80 and 92% yield when the solution was heated at 40 and 70 °C, respectively.

Initially, reaction conditions performed at 40 °C were chosen for the purpose of scope determination (Table 2). Several aziridines were synthesised following our previously reported method,[15] and they were subsequently submitted to

[*] Dr. T. Moragas, R. M. Liffey, Dr. D. Regentová, J.-P. S. Ward, J. Dutton, Dr. W. Lewis, Dr. J. A. Souto, Prof. R. A. Stockman
School of Chemistry, University of Nottingham
University Park, Nottingham, NG7 2RD (UK)
E-mail: robert.stockman@nottingham.ac.uk
Prof. I. Churcher
GlaxoSmithKline Medicines Research Centre
Gunnels Wood Road, Stevenage, SG1 2NY (UK)
Dr. L. Walton
Lilly (UK)
Erl Wood Manor, Windlesham, GU20 6PH (UK)
Dr. J. A. Souto
Departamento de Química Orgánica, Universidade de Vigo
36310 Vigo (Spain)
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under http://dx.doi.org/10.1002/anie.201604188.

Table 1: Optimisation of reaction conditions.



2a 3a

Entry	Solvent	Yield [%][a]	Entry	Solvent	Yield [%][a]
1	$CDCl_3$	50	6	$[D_7]$DMF	12
2	$[D_6]$DMSO	57	7	C_6D_6	50
3	$[D_6]Et_2O$	22	8	C_6D_6	80[b]
4	CD_3OD	50	9	C_6D_6	92[c]
5	CD_3CN	15	10	cyclohexene	60[b,d]

[a] Yield determined by NMR spectroscopy. [b] 40 °C. [c] 70 °C. [d] Yield of isolated product. DMF = *N*,*N*-dimethylformamide. DMSO = dimethylsulfoxide.

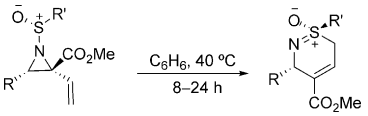
the rearrangement reaction conditions. The rearrangement reaction showed broad scope for substitution at the 3-position of the vinylaziridine. The rearrangement seemed tolerant of sterically hindered alkylaziridines, which transformed into the corresponding sulfoximines in good yields (entries 2 and 3). The reaction also performed well in the presence of saturated carbocycles (entries 4 and 5). Unsaturation and silylethers were also tolerated under the reaction conditions, thus affording sulfoximines in good yields (entries 6–8)

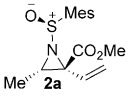
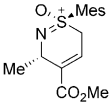
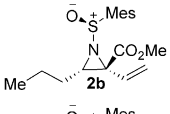
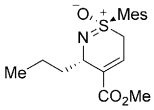
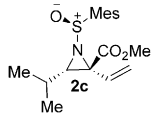
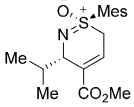
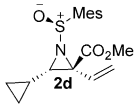
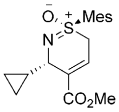
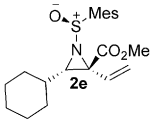
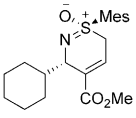
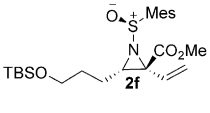
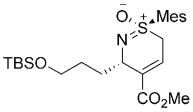
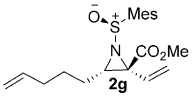
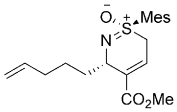
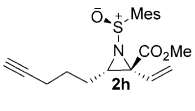
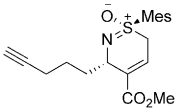
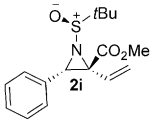
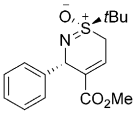
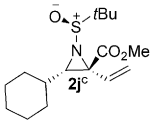
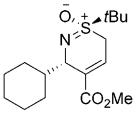
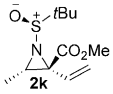
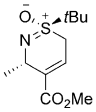
We were pleased to find that suitable crystals for X-ray analysis were isolated for sulfoximine **3b** (Figure 1), **3i** and **3k** from which unambiguous confirmation of the structure and configuration of the formed heterocycle was obtained (see the Supporting Information for further details).

In the case of aziridine **2j** (Table 2, entry 10), we noted that the two diastereomeric aziridines formed from the corresponding sulfinimine rearranged to the same cyclic sulfoximine **3j**. We therefore decided to investigate whether the rate of rearrangement of these diastereomers was different. The rearrangement reactions of (*E*)-**2j** and (*Z*)-**2j** were monitored by ^{1}H NMR spectroscopy.[17] The rearrangement of (*E*)-**2j** was found to be around three times faster than the corresponding *Z* isomer. Presuming a concerted rearrangement,[18] we attribute this difference in rate to the increased steric bulk around the mesityl group for the *Z*-isomer (Scheme 2). As the reaction works in a wide range of solvents, including polar and nonpolar, as well as in nucleophilic solvents like methanol, this gives further evidence of a concerted rearrangement. De Kimpe and co-workers previously disclosed a related rearrangement wherein a 2-aryl, 2-vinyl aziridine heterolyses, thus yielding a transient allyl cation, and in that case the products formed are pyrrolines.[19] Similarly Njardarson and co-workers have reported on the copper-catalyzed transformation of vinyl azidirines to pyrrolines.[20] In our case it can be postulated that the ester functionality activates the alkene such that a sigmatropic rearrangement is possible. We believe that homolysis is not involved, as we saw no signs of radical trapping when carrying out reactions in the presence of radical traps or in cyclohexene as solvent (see the Supporting Information).

Although efficient for the preparation of mesityl sulfoximines, our procedure revealed low reactivity for *tert*-butylsulfoximines. In an effort to develop a more efficient process we envisaged a one-pot protocol. Thus, after the formation of aziridine was deemed complete, as determined by TLC, excess base in the reaction was quenched by addition of water, and benzene was added to the reaction mixture before heating. Pleasingly, the telescoped procedure resulted in good

Table 2: Sulfoximine synthesis from vinyl aziridines **2**.



Entry	2[a]	3	Yield [%]
1			3a 80
2			3b 82
3			3c 93
4			3d 68
5			3e 77
6			3f 88
7			3g 97
8			3h 79
9			3i 16[b]
10			3j 10[b]
11			3k 45[b]

[a] Yield of product isolated after purification. Scale: 0.5 mmol. [b] 70 °C. [c] 1.2:1 *trans*/*cis*. TBS = *tert*-butyldimethylsilyl.

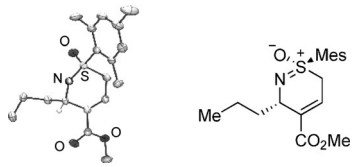
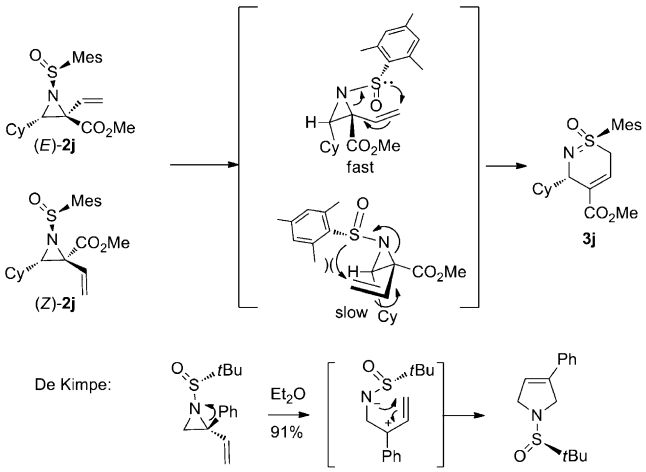


Figure 1. X-Ray structure of sulfoximine **3b** (CCDC 1484617). Thermal elipsoids shown at 50% probability.



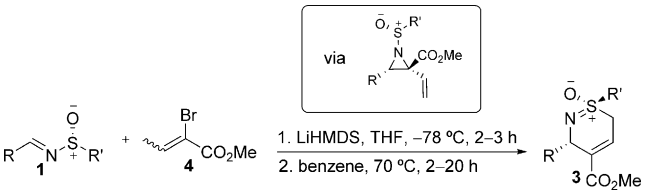
Scheme 2. Proposed mechanistic pathway, and comparison to De Kimpe's rearrangement.

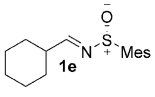
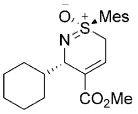
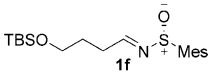
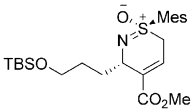
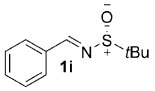
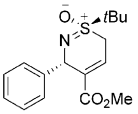
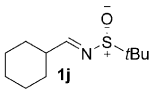
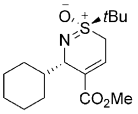
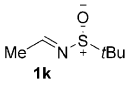
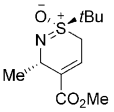
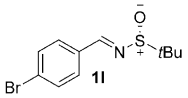
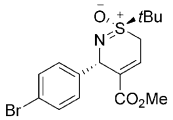
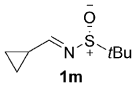
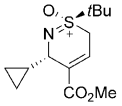
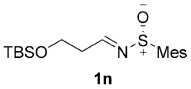
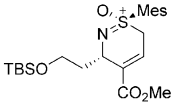
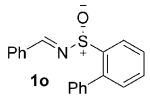
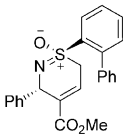
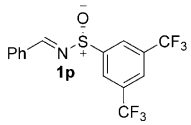
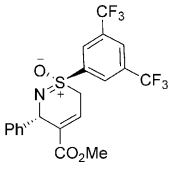
yields. In general they surpassed the yields of the two-step procedure[21] (Table 3). The sulfoximine **3e** was isolated in 49% yield following the one-pot procedure compared to the 33% overall yield observed for the two-step method.[22] Furthermore, the less reactive *tert*-butylsulfinimines (entries 3–7) were efficiently converted into the corresponding sulfoximines using this new protocol, although it was noted that these products were prone to thermal elimination of the *tert*-buyl group (this process was also noted by Hu and co-workers[13] in their cyclic sulfoximines). We also found that the method is compatible with less common sulfinimines such as biphenyl- or 3,5-bistrifluoromethylphenyl sulfinimine, which can be conveniently synthesised in one step from the parent aldehyde[14c] (entries 9 and 10). In all cases, the cyclic sulfoximines were isolated as single diastereomers.

Whilst exploring the reactivity of the new cyclic sulfoximines, we discovered that these compounds, themselves the product of a ring-expansion, upon treatment with camphorsulfonic acid (CSA) and LiCl in 1,4-dioxane/MeOH at reflux, undergo ring contraction to yield pyrrolines. Reacting the sulfoximine **3f** under these reaction conditions yielded pyrroline **5** in 80% yield (Scheme 3).[23] We believe this reaction proceeds by N-protonation, followed by an S_N2 ring opening of the sulfoximine[24a] and ring closure onto the alkyl chloride and chloride-induced deprotection of the amine.[24b]

To exemplify the utility of these two novel ring transformations, we proceeded to carry out a formal synthesis of the pyrrolizidine alkaloid trachelanthamidine[25] (Scheme 4). The synthesis started with a monoprotection of 1,4-butanediol (**6**) with TBSCl in an 85% yield, followed by Swern oxidation

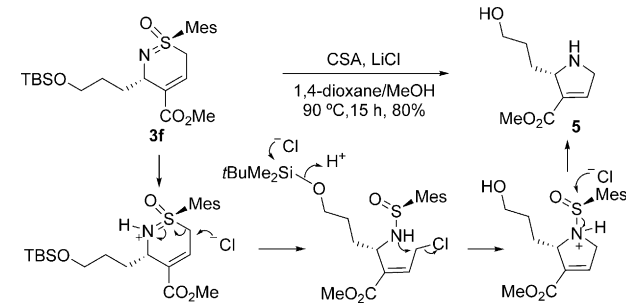
Table 3: One-pot preparation of the sulfoximines **3**.



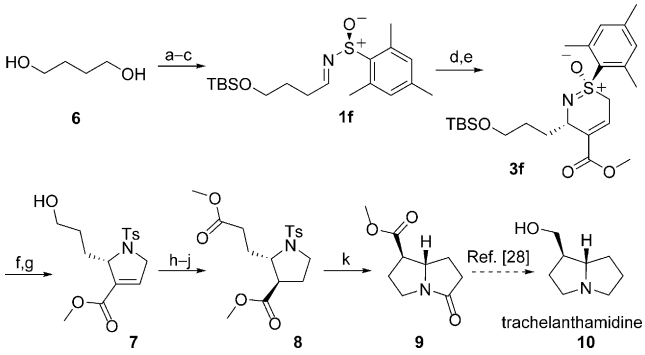
Entry	**1**[a]	**3**	Yield [%]
1	 **1e**		**3e** 49
2	 **1f**		**3f** 60
3	 **1i**		**3i** 22[b]
4	 **1j**		**3j** 74
5	 **1k**		**3k** 51[b]
6	 **1l**		**3l** 23
7	 **1m**		**3m** 48
8	 **1n**		**3n** 60
9	 **1o**		**3o** 37
10	 **1p**		**3p** 26

[a] Yield of product isolated after purification. [b] Reaction in toluene for 7 days.

and condensation of the corresponding aldehyde with mesitylsulfinamide under Ellman's conditions to form the sulfin-



Scheme 3. Ring-contraction of sulfoximine to pyrroline.



Scheme 4. Formal synthesis of trachelanthamidine. Reagents and conditions: a) TBSCl, NaH, THF, RT, 19 h (93%); b) DMSO, NEt_3, $(COCl)_2$, CH_2Cl_2, 19 h; c) (*S*)-mesitylsulfinamide, $Ti(OEt)_4$, THF, RT, 20 h (69% over 2 steps); d) methyl 2-bromo-2-butenoate, LiHMDS, THF, −78 °C, 3 h; e) H_2O, benzene, 40 °C to 70 °C, 19 h (60% over two steps); f) CSA, LiCl, MeOH/1,4-dioxane 1:1, 90 °C, 18 h; g) NEt_3, TsCl, CH_2Cl_2, 0 °C to RT, 30 min. (44% over two steps); h) Pd/C, H_2, MeOH, RT, 96 h (59%); i) PDC, DMF, RT, 18 h; j) $SOCl_2$, MeOH, 0 °C to reflux, 18 h (78% over two steps); k) Mg, MeOH, RT. to reflux, 7 h (65%). PDC = pyridiniumdichromate, Ts = 4-toluenesulfonyl.

imine **1f** in 69% yield over two steps.[26] With **1f** in hand, **3f** was obtained by the previously described two-step, one-pot process. The aza-Darzens reaction with methyl 2 bromo-2-butenoate generated the desired aziridine, which upon heating yields **3f** as a single enantiomer in a 60% yield over two steps. Ring contraction of **3f** with CSA and lithium chloride yielded the desired pyrroline, which upon N-tosylation at 0 °C gave the pyrroline **7** in 44% over two steps[27] (Kamimura et al. had previously reported the synthesis of a *tert*-butyl ester in their synthesis of trachelanthamidine).[28] Selective hydrogenation using the reaction conditions of Kamimura gave excellent selectivity, a 92:8 diastereomeric ratio as observed by ^{1}H NMR spectroscopy, however, the yield was moderate. To complete the formal synthesis of trachelanthamidine, the alcohol was exposed to PDC,[29] thus producing the corresponding carboxylic acid followed by esterification with methanol to give the diester **8** in a 78% yield over two steps: At this stage our synthesis intercepts that of Kamimura et al.[28a] The N-tosyl protecting group of **8** was removed with Mg in MeOH,[30] and subsequent cyclisation between the deprotected amine and the ester in the C2 side-chain gave the desired pyrrolizidinone **9** in 65% yield.[28a] Several groups have previously converted **9** into trachelanthamidine, and thus this represents a formal synthesis.[31]

In summary, we have developed a methodology for the synthesis of chiral cyclic sulfoximines starting from simple sulfinimines. The reaction can be either performed by isolation of the aziridine intermediate and subsequent thermal rearrangement (two step protocol) or in a one-pot fashion, the latter allowing for the isolation of the desired heterocycle without the need of manipulating otherwise relatively unstable aziridine intermediates. We have also demonstrated the formal synthesis of the biologically active natural product trachelanthamidine in an overall yield of 5%.

Acknowledgements

The authors wish to thank Dr. Thomas E. Storr for preparing the X-ray figures and GlaxoSmithKline (TM, JD), Xunta de Galicia (JAS), Lilly (JPSW) and EPSRC (DR, JAS, RAS, EP/015078) for funding.

Keywords: heterocycles · rearrangements · small ring compounds · sulfur · synthetic methods

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 10047–10051
Angew. Chem. **2016**, *128*, 10201–10205

[1] H. R. Bentley, E. E. McDermott, J. Pace, J. K. Whitehead, T. Moran, *Nature* **1950**, *165*, 150.
[2] a) C. R. Johnson, *Acc. Chem. Res.* **1973**, *6*, 341; b) C. R. Johnson in *Comprehensive Organic Chemistry, Vol. 3* (Eds.: D. H. Barton, W. D. Ollis), Pergamon Press, Oxford, **1979**, pp. 223–232; c) C. R. Johnson, *Aldrichimica Acta* **1985**, *18*, 3; d) C. R. Johnson, M. R. Barbachyn, N. A. Meanwell, C. J. Stark, J. R. Zeller, *Phosphorus Sulfur Relat. Elem.* **1985**, *24*, 531; e) S. G. Pyne, *Sulfur Rep.* **1992**, *12*, 57; f) M. Mikołajczyk, J. Drabowicz, P. Kiełbasiński, *Chiral Sulfur Reagents: Applications in Asymmetric Synthesis and Stereoselective Synthesis*, CRC Press, Boca Raton, **1997**; g) S. G. Pyne, *Sulfur Rep.* **1999**, *21*, 281; h) H.-J. Gais in *Asymmetric Synthesis with Chemical and Biological Methods* (Eds.: D. Enders, K.-E. Jaeger), Wiley-VCH, Weinheim, **2007**, pp. 75–115; i) H.-J. Gais, *Heteroat. Chem.* **2007**, *18*, 472; j) M. Harmata, *e-EROS Encyclopedia of Reagents for Organic Synthesis*, Wiley, New York, **2007**; k) C. Bolm in *Asymmetric Synthesis with Chemical and Biological Methods* (Eds.: D. Enders, K.-E. Jaeger), Wiley-VCH, Weinheim, **2007**, pp. 149–176; l) C. Worch, A. C. Mayer, C. Bolm in *Organosulfur Chemistry in Asymmetric Synthesis* (Eds.: T. Toru, C. Bolm), Wiley-VCH, Weinheim, **2008**, pp. 209–232; m) M. Frings, I. Thomé, C. Bolm, *Beilstein J. Org. Chem.* **2012**, *8*, 1443.
[3] U. Lücking, *Angew. Chem. Int. Ed.* **2013**, *52*, 9399; *Angew. Chem.* **2013**, *125*, 9570, and references therein.
[4] A. Plant, J. E. Boehmer, A. L. Peace, US 20050228027.
[5] Y. Zhu, R. B. Rogers, J. X. Huang, US 20050228027.
[6] M. Reggelin, C. Zur, *Synthesis* **2000**, 1.
[7] a) C. Bolm, J. P. Hildebrand, *Tetrahedron Lett.* **1998**, *39*, 5731; b) E. J. Corey, A. Venkatestwarl, *J. Am. Chem. Soc.* **1972**, *94*, 6190; c) K. J. Hwang, *J. Org. Chem.* **1986**, *51*, 99; d) C. R. Johnson, C. W. Schroeck, J. R. Shanklin, *J. Am. Chem. Soc.* **1973**, *95*, 7424; e) H. W. Roesky, F. Schrumpf, M. Z. Noltemeyer, *Z. Naturforsch. B* **1989**, *44*, 35; f) I. Leichtweis, H. W. Roesky, M. Z. Noltemeyer, H. G. Z. Schmidt, *Z. Naturforsch. B* **1991**, *46*, 425.
[8] W. L. Mock, J. T. Tsay, *J. Am. Chem. Soc.* **1989**, *111*, 4467.

[9] a) E. J. Corey, T. H. Lowry, *Tetrahedron Lett.* **1962**, *3*, 515; b) E. J. Corey, T. H. Lowry, *Tetrahedron Lett.* **1965**, *6*, 793; c) E. J. Corey, T. H. Lowry, *Tetrahedron Lett.* **1965**, *6*, 803; d) D. J. Cram, R. D. Trepka, P. S. Janiak, *J. Am. Chem. Soc.* **1966**, *88*, 2749.

[10] a) H. R. Bentley, J. K. Whitehead, *J. Chem. Soc.* **1952**, 1572; b) C. R. Johnson, M. Haake, C. W. Schroeck, *J. Am. Chem. Soc.* **1970**, *92*, 6594; c) P. Stoss, G. Satzinger, *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 76; *Angew. Chem.* **1971**, *83*, 83; d) R. H. Rynbrandt, D. P. Balgoyen, *J. Org. Chem.* **1978**, *43*, 1824; e) H. Kwart, A. A. Kahn, *J. Am. Chem. Soc.* **1967**, *89*, 1950; R. Tanaka, K. Yamabe, *J. Chem. Soc. Chem. Commun.* **1983**, 329.

[11] a) C. R. Johnson, E. U. Jonsson, A. Wanbsgans, *J. Org. Chem.* **1979**, *44*, 2061; b) C. R. Johnson, A. Wanbsgans, *J. Org. Chem.* **1979**, *44*, 2278; c) E. U. Jonsson, C. C. Bacon, C. R. Johnson, *J. Am. Chem. Soc.* **1971**, *93*, 5306; d) C. R. Johnson, K. G. Bis, J. H. Cantillo, N. A. Meanwell, *J. Org. Chem.* **1983**, *48*, 1; e) M. Harmata, *Tetrahedron Lett.* **1989**, *30*, 437.

[12] a) T. R. Williams, D. J. Cram, *J. Org. Chem.* **1973**, *38*, 20; b) K. Schaffner-Sabba, H. Tomaselli, B. Henrici, H. B. Renfroe, *J. Org. Chem.* **1977**, *42*, 952; c) C. Bolm, H. Villar, *Synthesis* **2005**, 1421, and references therein; d) M. Harmata, S. K. Ghosh, *Org. Lett.* **2001**, *3*, 3321; e) M. Harmata, X. Hong, *Synlett* **2007**, 0969; f) M. Harmata, N. L. Calkins, R. G. Baughman, C. L. Barnes, *J. Org. Chem.* **2006**, *71*, 3650; g) L. Wang, D. L. Priebbenow, X. Y. Chen, F.-F. Pan, C. Bolm, *Eur. J. Org. Chem.* **2015**, 3338; h) M. Zenzola, R. Doran, L. Degennaro, R. Luisi, J. A. Bull, *Angew. Chem. Int. Ed.* **2016**, *55*, 7203; i) H. Wang, M. Frings, C. Bolm, *Org. Lett.* **2016**, *18*, 2431.

[13] W. Ye, L. Zhang, C. Ni, J. Rong, J. Hu, *Chem. Commun.* **2014**, *50*, 10596.

[14] a) C. Roe, T. Moragas-Solá, L. Sasraku-Neequye, H. Hobbs, I. Churcher, D. MacPherson, R. A. Stockman, *Chem. Commun.* **2011**, *47*, 7491; b) T. Moragas-Solá, I. Churcher, R. A. Stockman, *Org. Biomol. Chem.* **2011**, *9*, 5034; c) C. Roe, H. Hobbs, R. A. Stockman, *Chem. Eur. J.* **2011**, *17*, 2704.

[15] T. Moragas, W. Lewis, I. Churcher, R. A. Stockman, *Org. Lett.* **2014**, *16*, 6290.

[16] W. McCoull, F. A. Davis, *Synthesis* **2000**, 1347.

[17] See supporting information for further details.

[18] A low-yielding thermal rearrangement of *S*-allyl sulfoximines to allylic sulfinamides (the reverse of our case) with retention of configuration at sulfur has been previously reported: H.-J. Gais, M. Scommoda, D. Lenz, *Tetrahedron Lett.* **1994**, *35*, 7361; although theoretical calculations suggest that this rearrangement has a large barrier and is not general: M. Harmata, R. Glaser, G. S. Chen, *Tetrahedron Lett.* **1995**, *36*, 9145.

[19] E. Leemans, F. Colpaert, S. Mangelinkx, S. De Brabendere, B. Denolf, N. De Kimpe, *Synlett* **2011**, 674.

[20] a) D. J. Mack, J. T. Njardarson, *Chem. Sci.* **2012**, *3*, 3321; b) M. Brichacek, M. Navarro Villalobos, A. Plichta, J. T. Njardarson, *Org. Lett.* **2011**, *13*, 1110; c) M. Brichacek, J. T. Njardarson, *Org. Lett.* **2008**, *10*, 5023; d) M. Brichacek, J. T. Njardarson, *Org. Biomol. Chem.* **2009**, *7*, 1761; e) E. A. Ilardi, J. T. Njardarson, *J. Org. Chem.* **2013**, *78*, 9533.

[21] For comparative purposes isolated yields of synthesised aziridines have been described in the supporting information.

[22] The desired compound was obtained together with small amounts of the corresponding 1,2-disulfoxide. This transformation has been previously reported by us. J. A. Souto, W. Lewis, R. A. Stockman, *Chem. Commun.* **2014**, *50*, 12630.

[23] See supporting information for a proposed mechanism for this transformation.

[24] a) For reports on the related *C*–S bond cleavage of allylic aminosulfoxonium species by nucleophiles see: S. K. Tiwari, A. Schneider, S. Koepp, H.-J. Gais, *Tetrahedron Lett.* **2004**, *45*, 8343; S. Koep, H.-J. Gais, G. Raabe, *J. Am. Chem. Soc.* **2003**, *125*, 13243; S. H. Tiwari, H.-J. Gais, A. Lindenmaier, G. S. Babu, G. Raabe, L. R. Reddy, F. Köhler, M. Günter, S. Koep, V. B. R. Iska, *J. Am. Chem. Soc.* **2006**, *128*, 7360; b) Deprotection of *tert*-butyl sulfoximines and derivatives under thermal conditions have been previously reported. F. A. Davis, J. Qu, V. Srirajan, R. Joseph, D. D. Titus, *Heterocycles* **2002**, *58*, 251.

[25] G. P. Menschikov, *Zh. Obshch. Khim.* **1946**, *16*, 1311.

[26] a) J. A. Ellman, D. A. Cogan, T. P. Tang, G. Liu, T. D. Owens, *J. Org. Chem.* **1999**, *64*, 1278; b) M. T. Robak, M. A. Herbage, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 3600.

[27] A. G. Myers, B. A. Lanman, *Org. Lett.* **2004**, *6*, 1045.

[28] a) A. Kamimura, A. Ishikawa, F. Noguchi, *J. Org. Chem.* **2010**, *75*, 3578; b) V. Declerck, H. Allouchi, J. Martinez, F. Lamaty, *J. Org. Chem.* **2007**, *72*, 1518.

[29] E. J. Corey, G. Schmidt, *Tetrahedron Lett.* **1979**, 399.

[30] L. C. Pattenden, H. Adams, S. A. Smith, J. P. A. Harrity, *Tetrahedron* **2008**, *64*, 2951.

[31] a) K. Neuenschwarder, *Tetrahedron Lett.* **1980**, *21*, 3841; b) J. P. Celerier, M. Haddad, D. Jacoby, G. Lhommet, *Tetrahedron Lett.* **1987**, *28*, 6597; c) X. L. M. Despinoy, H. McNab, *Org. Biomol. Chem.* **2009**, *7*, 4502.

Received: April 29, 2016
Revised: June 13, 2016
Published online: July 13, 2016

