SYNTHESIS AND REACTIONS OF SULFINIMINES

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DECLARATIONS

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

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ABSTRACT

A large majority of drugs and drug candidates incorporate amine functionality and these include important compounds such as morphine, quinine and nicotine. N-Sulfinyl-imines (sulfinimines) are a versatile class of intermediates in organic synthesis particularly for the preparation of amines and amine derivatives. We herein report an efficient and cost effective one-pot synthesis of sulfinimines in enantiopure form (>99.8% ee) and in relatively high yields.

In our investigations, we developed the scheme that involves the use of 1,2,3-oxathiazolidine-2-oxide derived from (1R, 2S)-(-)-norephedrine as a chiral auxiliary. Opening of the 1,2,3-oxathiazolidine-2-oxide with a mesityl Grignard reagent followed by treatment of the crude mixture with lithium hexamethyldisilasane afforded the mestyl sulfinamide in 72% yield and 76% recovery of the chiral auxiliary.

As an extension to this scheme, when the crude reaction mixture obtained after addition of the lithium hexamethyldisilasane was treated with 1.1 equivalents of an aldehyde and three (3) equivalents of $Ti(OEt)_4$ afforded the corresponding mesityl sulfinimines in high yields (>30 – 60%) and excellent enantiomeric excess (>99.8%). This to our knowledge is the first ever 3-step, one-pot syntheses of enantiopure sulfinimines using chiral aminoalcohol derived 1,2,3-oxathiazolidine-2-oxide as a chiral auxiliary.

The mesitylsulfinamide thus produced was utilised in a novel free radical cyclisation reaction to yield mesitylsulfinyl protected enantiopure aminoindane in 68% yield.

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ABBREVIATIONS

Å	angstrom
Ac	acetyl
AIBN	2,2'-azobiisobutyronitrile
aq.	aqueous
Ar	aryl
atm.	atmospheres
β	beta
BBN	borabicyclo[3.3.1]nonane
Bn	benzyl
BOC	butoxycarbonyl
b.p	boiling point
br	broad
Bu	butyl
conc.	concentrated
cm	centimetre
Cyc	cyclohexyl
d	doublet
DCM	dichloromethane
δ	chemical shift in parts per million
dd	doublet of doublets
de	diastereomeric excess
DIBAL-H	diisobutylaluminium hydride
DMAP	dimethylamino pyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
El	electron impact
Et	ethyl
equiv.	equivalent
h	hour(s)
HMDS	hexamethyldisilazide

HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
^{i}Pr	isopropyl
IR	infra red
J	coupling constant in NMR spectroscopy
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazane
m	multiplet
M	molarity of solution
mCPBA	meta-chloroperoxybenzoic acid
m.p.	melting point
m/z	mass to charge ratio
Me	methyl
min	minutes
Ms	methanesulfonyl
MS	molecular sieves
n	normal
$NaHCO_3$	Sodium bicarbonate
NaHMDS	sodium hexamethyldisilazane
Na_2SO_4	sodium sulfate
NCS	*N*-chlorosuccinimide
NMR	nuclear magnetic resonance
n.O.e	nuclear Overhauser enhancement
p	para
Ph	phenyl
PMP	para-methoxyphenol
ppm	parts per million
PPTS	pyridinium para-toluenesulfonate
py	pyridine
q	quartet
Red-Al	Sodium bis(2-methoxyethoxy)aluminum dihydride
ref.	reference
r.t	room temperature

s	singlet
sat.	saturated
t	triplet
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TLC	thin layer chromatography
TMEDA	*N*, *N*, *N', N'*-tetramethylethylenediamine
TMS	trimethylsilyl
Ts	toluenesulfonyl
THF	tetrahydrofuran

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1.0 Introduction

A large majority of drugs and drug candidates incorporate amine functionality; greater than 75% according to some reports.[1] Amines include important compounds such as morphine, quinine, nicotine and pseudoephedrine hydrochloride, (Figure **1**). Despite their widespread abundance, efficient methods for the asymmetric syntheses of amines are often difficult and not widely available for the many structural classes of amines.

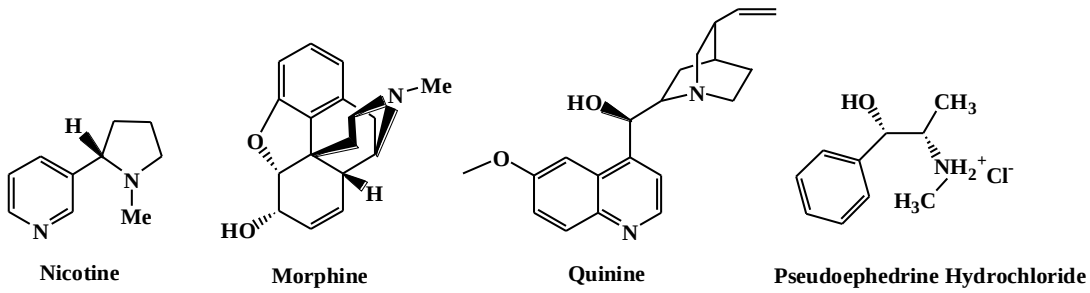
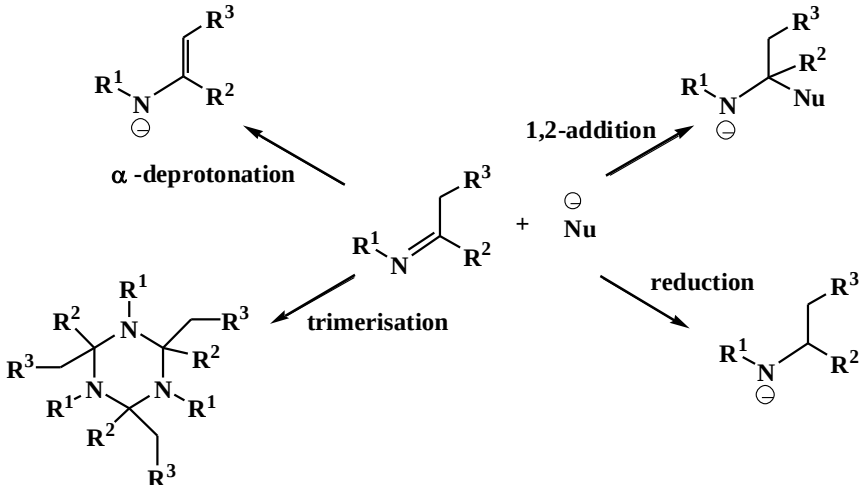


Figure 1 – Some biologically active compounds with amine functionality

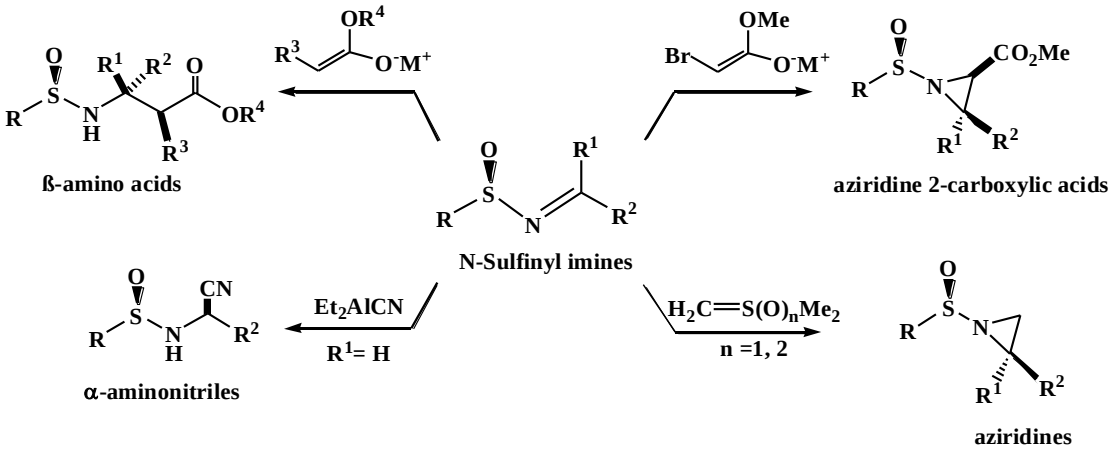
One of the most versatile procedures used to generate amines is the 1,2-addition of nucleophiles to imines. Imines are readily accessible by the condensation reaction of aldehydes and ketones with primary amines and amine derivatives. However, imines are poor electrophiles (compared to aldehydes and other carbonyl compounds) and when reacted with basic carbanion nucleophiles, are susceptible to competition between 1,2 addition, abstraction of acidic α-protons forming an aza-enolate or the formation of reductive coupling products (Scheme **1**). Nitrogen substitution is required to prevent oligomerisation of imines[2] and many imines are also hydrolytically unstable. Therefore, there are many challenges in the use and handling of imines as precursors to amines. Chemists have therefore exploited *N*-substituted imines and used this *N*-substitution to control reactivity.



Scheme 1 – Possible reactions of imines

A good *N*-substituent must offer an easy route to stable imines and also activate the imine for the addition of a wide range of nucleophiles. Such a substituent should ideally also be a chiral directing group, be inexpensive to synthesize or purchase and easy to cleave under mild conditions to afford the amine compound.[3] Some of the *N*-substituents that have been used include the toluenesulfonyl (-Ts) the diphenylphosphine (-Dpp) and the *para*-methoxyphenyl (–PMP) groups. Though these have been used widely as protecting groups, they have however provided several challenges to the synthetic chemist. The –Ts[3b,c] and –PMP[3d] groups, for instance, have proved quite difficult to remove without the use of strongly acidic or reductive reagents and whilst it is relatively more easy to remove the –Dpp group, this renders *N*-Dpp protected substrates less stable and prone to hydrolysis.[3e]

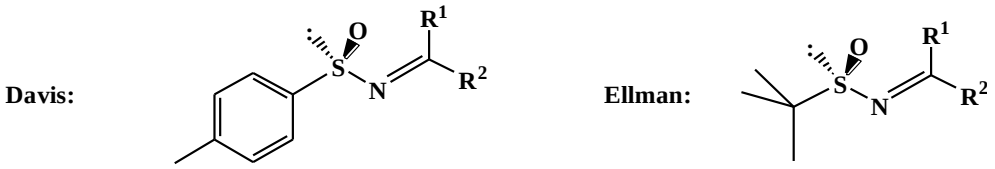
A group of *N*-substituents that satisfy all of these criteria and provide a very general approach for the synthesis of a broad range of amine-containing compounds[3] are the sulfinyl protecting groups. *N*-Sulfinyl imines (sulfinimines) are a versatile class of intermediates in organic synthesis particularly for the preparation of amines and amine derivatives (Scheme **2**).[3a,4]



Scheme 2 – Some synthetic uses of sulfinimines

Sulfinyl imines are stable and isolable compounds. The sulfinyl group also activates the imine, and the configurationally stable stereocenter at sulfur can provide diastereofacial selectivity for nucleophilic addition. Moreover, the sulfinyl group is readily cleaved by brief treatment with acid.[4]

The most common types of sulfinimine are by far the *p*-toluenesulfinyl imines and the *tert*-butanesulfinyl imines. Whilst the *p*-toluenesulfinyl imines were pioneered by Davis and co-workers[4a,e] in their syntheses, the *tert*-butanesulfinyl imines have been championed by Ellman and his co-workers,[4b,c,d] (Figure **2**).

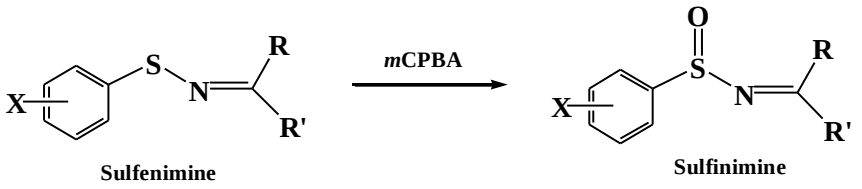


R^1 = H, alkyl, aryl
R^2 = alkyl, aryl

Figure 2 – Davis' and Ellman's sulfinimines

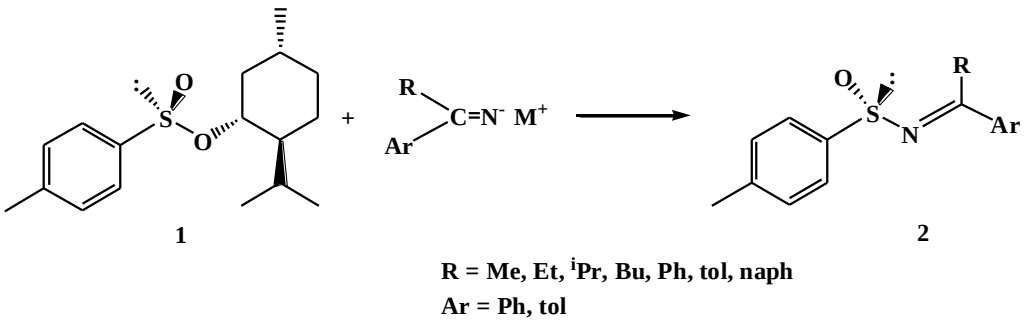
1.1 Syntheses of Sulfinimines

The synthesis of sulfinimines has attracted a lot of attention in recent times. The first examples of sulfinimines were prepared by Davis *et al*.[5a] He reported the syntheses of *N*-arylsulfinimines in racemic form by oxidation of their corresponding *N*-arylsulfenimines[6] with *m*CPBA (Scheme **3**).



Scheme 3 – Oxidation of sulfenimines with *m*CPBA

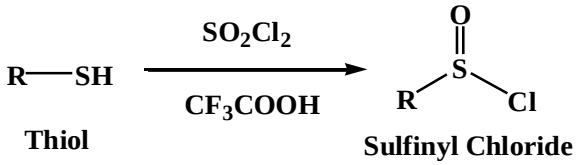
The first enantiomerically pure sulfinimines were synthesized by Cinquini *et al.*,[7] by the reaction of metal ketimines with the Andersen reagent, (1*R*,2*S*,5*R*)-(-)-menthyl (*S*)-*p*-toluenesulfinate[8] (Scheme **4**). The Andersen reagent (**1**) was the most widely used chiral auxiliary of its time for introducing the sulfinyl group and had previously been used for the synthesis of sulfoxides. Its advantage lies in its commercial availability in both enantiomeric forms and can also be prepared on kilogram scales from (+)- and (-)-menthol.



Scheme 4 – Iminolysis of the Andersen reagent using metal amides

The use of the Andersen reagent and related sulfinates are a major route towards sulfinimines therefore it is appropriate that the syntheses of such chiral auxiliaries are

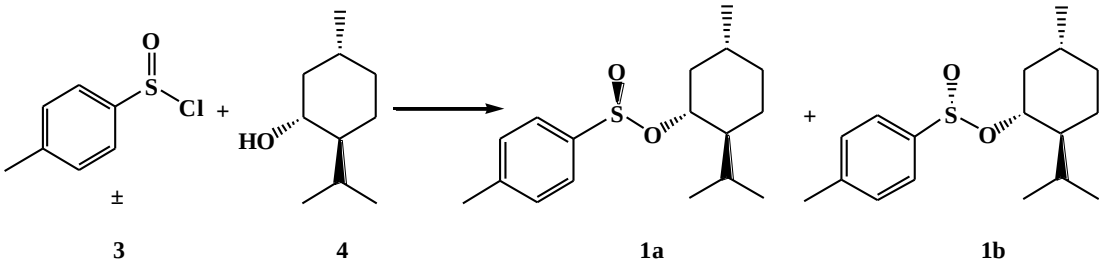
mentioned as part of this discussion. Most of these sulfinates are derivatives of sulfinyl chlorides. The earliest synthesis of sulfinyl chlorides involves the oxidative chlorination of sulfenyl derivatives of thiols with peracetic acids, prepared by reacting acetic acids with hydrogen peroxide.[9] Douglas and co-workers[10] were, however, first to report this procedure using chlorine gas as the chlorinating agent but this procedure has since been modified,[9c,11,12] replacing chlorine gas with sulfuryl chloride (Scheme **5**). These methods are however plagued by long reaction times[12b] and are not stereoselective.



Scheme 5 – Oxidation of thiols to sulfinyl chloride

Sulfinyl chlorides are usually not purified before use since purification by distillation, the preferred method, may lead to either decomposition or explosion.[13] Sulfinyl chlorides have been reported to decompose completely within hours when stored at room temperature and to produce a noticeable darkening within weeks even when stored at –30 °C.[9] In order to prevent loss of the compound, sulfinyl chlorides are usually reacted immediately to either the sulfinamide or the sulfinate ester, which are much more stable. All the above mentioned schemes, however, yield racemic sulfinyl chlorides.

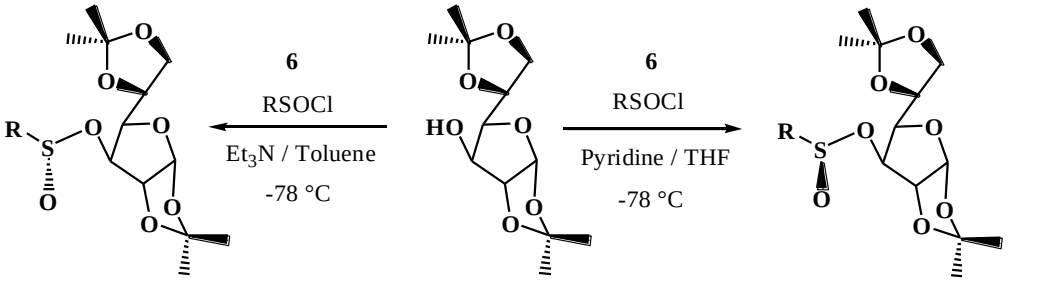
In order to resolve racemic mixtures of sulfinyl chlorides, Andersen[8] developed a method based on reacting the sulfinyl chlorides with an enantiomerically pure chiral alcohol, (-)-menthol, to form the sulfinate esters as a pair of easily separable diastereomers (Scheme **6**).



3 **4** **1a** **1b**

Scheme 6 – Resolution of racemic *p*-toluenesulfinyl chloride

The advantage of Andersen's method is that only one of the diastereomers is crystalline. However, the resolved sulfinate esters were found to be epimerically unstable at the sulfur in acidic medium.[14] Fernandez *et al*.[15] reported that diacetone-D-glucose (DAG), a chiral alcohol, was found to react with sulfinyl chlorides in the presence of a tertiary amine to form their corresponding sulfinates. The advantage of the DAG method over Andersen's method is that the configuration at sulfur is influenced by the choice of amine hence it is possible to produce one enantiomerically pure form of the sulfinate (**7a** and **7b**) by using the appropriate base (Scheme **7**).



(S,S)-Sulfinate **Diacetone-D-glucose** **(R,S)-Sulfinate**

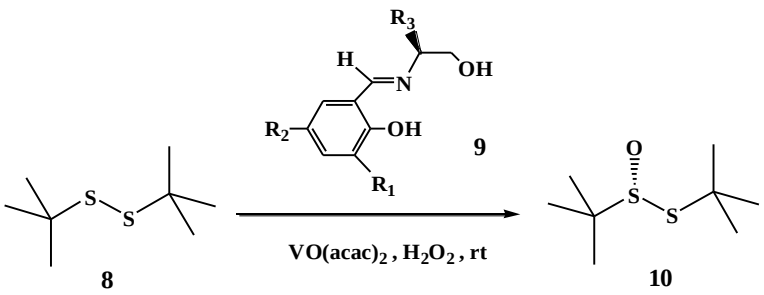
7b **5** **7a**

Scheme 7 – Selective resolution using diacetone-D-glucose (DAG)

The above methods are, however, not without problems: the need for chromatographic separation of the diastereomerically enriched mixture of high molecular weight DAG-sulfinates makes this method unsuitable for large scale production.[16] Other reported

diastereomeric sulfinyl intermediates are expensive to produce and also require chromatographic separation of high molecular weight chiral intermediates.[17]

In order to avoid the use of high molecular weight chiral auxiliaries and the associated problems involving cost and purification, Ellman and co-workers[16] published the first example of the catalytic asymmetric oxidation of a disulfide with high yield and enantiomeric excesses, using hydrogen peroxide as a stoichiometric oxidant in the presence of catalytic amounts of Schiff base-vanadium complexes **9** (Scheme **8**).



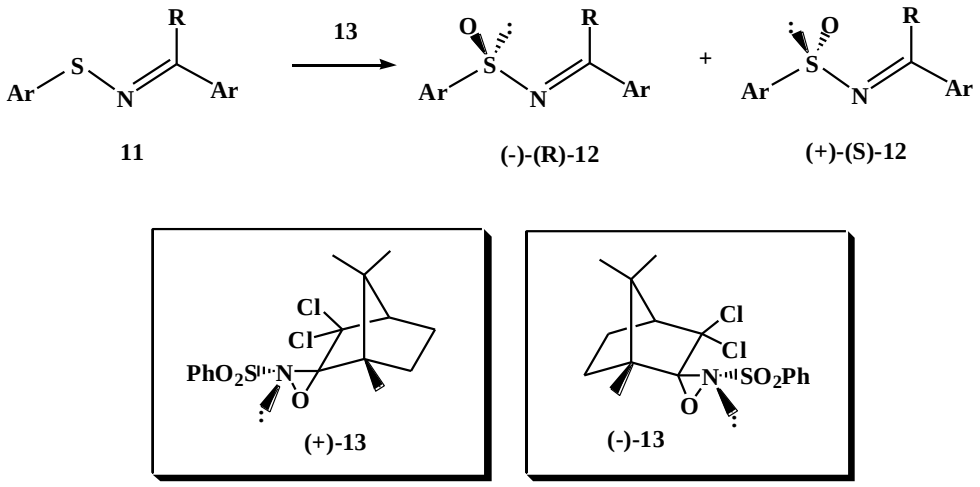
Scheme 8 – Asymmetric oxidation of *tert*-butyldisulfide

Catalytic asymmetric oxidation at the sulfur appears more attractive since it offers high selectivities and low catalyst loadings using relatively inexpensive and clean reagents. *Tert*-butyl *tert*-butanethiosulfinate (**10**), which is the most widely studied product of this catalytic asymmetric oxidation method, can then be further transformed to sulfinimines or their precursors.

Whilst there are many routes to sulfinimines, the various methods can be grouped into three main classes namely oxidation, iminolysis and condensation. We will look at these in succession.

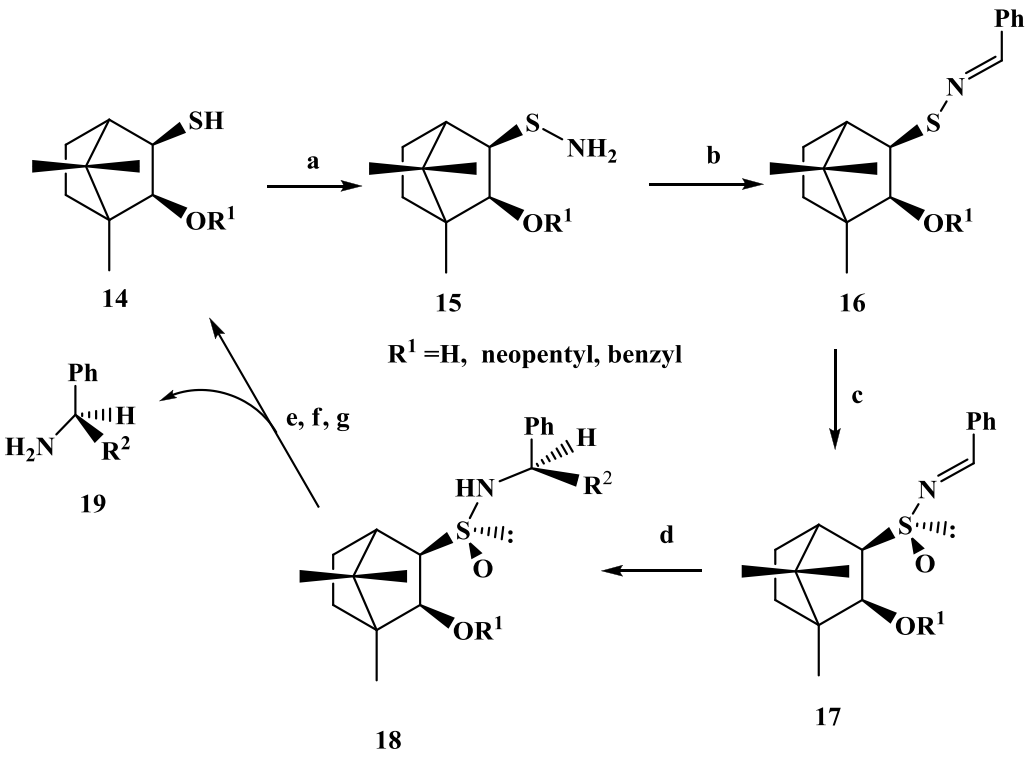
1.1.1 Oxidation

The first asymmetric oxidation of sulfenimines to chiral enantiopure sulfinimines was reported by Davis. This methodology involves the asymmetric oxidation of the sulfenimines (**11**) with stoichiometric amounts of the chiral oxidant *N*-(phenylsulfonyl)(3,3-dichlorocamphoryl)oxaziridine (**13**)[18] in tetrachloromethane. The sulfinimines (**12**) were isolated by flash chromatography with 85-95% yield and 88-90% enantiomeric excesses (ee). Crystallization from *n*-hexane improved the ee's to >97% (Scheme **9**).



Scheme 9 – First asymmetric oxidation of sulfenimines

Other methods of oxidation of sulfenimines have been reported, including one by Yang and co-workers[19] which utilised mercapto chiral auxiliaries derived from camphor (Scheme **10**). The stereoselective oxidations of sulfenimines **16** were carried out either with *m*-chloroperbenzoic acid (*m*CPBA) in dichloromethane or magnesium monoperoxyphthalic acid (MMPP) in methanol. Both procedures gave very good yields of the chiral sulfinimines **18,** but *m*CPBA gave relatively better diastereoselectivities.



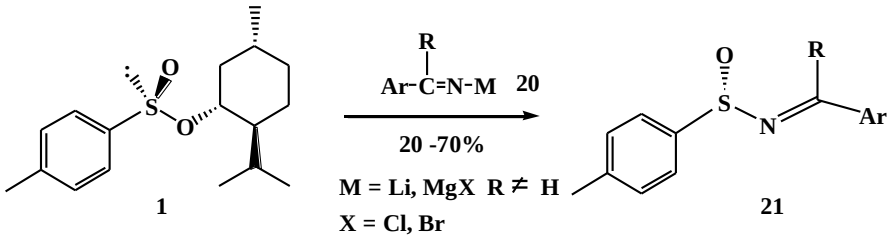
(a) NCS, NH_3, CH_2Cl_2, -33 °C; (b) PhCHO, CH_2Cl_2, -33 °C; (c) oxidants: *m*CPBA or MMPP; (d) alkyl metal reagent R^2M; (e) HCl, MeOH; (f) Zn, $TiCl_4$; (g) $LiAlH_4$,THF

Scheme 10 – Asymmetric synthesis of sulfinimines using mercapto chiral auxiliaries

1.1.2 Iminolysis

Since Cinquini *et al.*[7] reported the first enantiomerically pure sulfinimines by the reaction of metal ketimines (**20**) with the Andersen reagent (**1**), (*1R,2S,5R*)-(-)-menthyl (*S*)-*p*-toluenesulfinate[8] (Scheme **11**), there has been a lot of interest in this procedure.[20] The method is based on generating the metal ketimines by addition of Grignard or organolithium reagents to nitriles. The procedure is therefore limited by the availability of the appropriate nitriles. It was found that this method works for only aromatic nitriles, which imply that the scheme can not be used to synthesise aliphatic sulfinimines. Another disadvantage was that it could only be used to produce sulfinyl ketimines but not aldimines. In order to produce sulfinyl aldimines, Davis[21] treated the Andersen reagent (**1**)

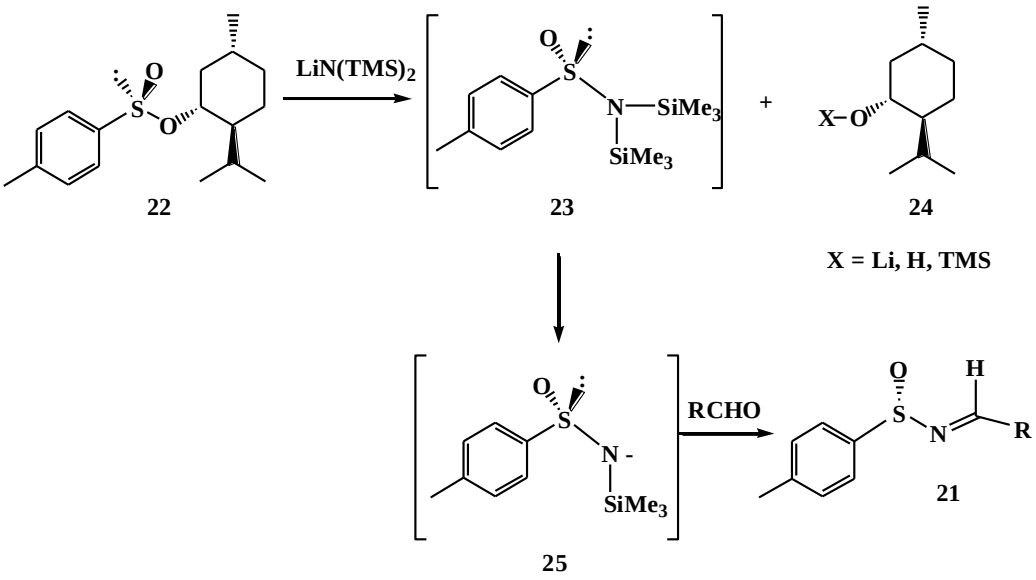
with DIBAL-H-reduced benzonitrile but no sulfinimine was detected. Further tests revealed that the aldiminoaluminium species was formed but may not have been nucleophilic enough to attack the Andersen's reagent. This problem was addressed by addition of one equivalent of methyllithium to the DIBAL-H-reduced nitriles, which formed the corresponding aluminate complexes. Treatment of the aluminate complexes generated with Andersen's reagent gave the desired aldimines in 33-56% optimised yield. This process however did not work well for aliphatic nitriles: the best result obtained for an aliphatic nitrile was just 3%!!



Scheme 11 – Typical iminolysis of Andersen's reagent with metal amides

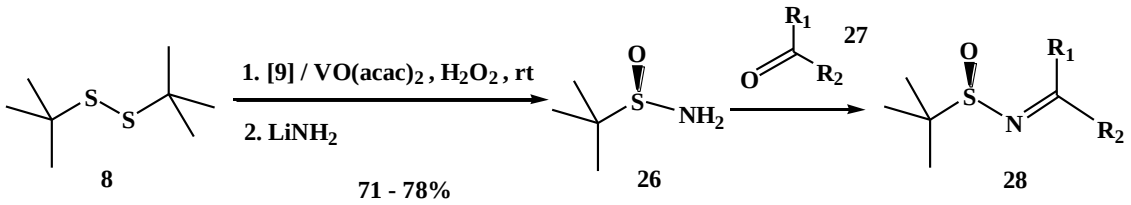
1.1.3 Condensation

One of the most simple methods for the formation of sulfinimines involves the condensation of a primary sulfinamide with a carbonyl compound to afford the corresponding sulfinimine. The first synthesis of enantiomerically pure sulfinimine using this protocol was reported by Davis *et al.*[22] He reported that treatment of (+)-(*S*)-*p*-toluenesulfinamide **23**, derived from reacting Andersen's reagent with LiHMDS, with *p*-nitrobenzaldehyde and CsF gave the corresponding sulfinimine [(*S*)-(+)-*N*-(*p*-nitrobenzylidene)-*p*-toluenesulfinamide] in 95% yield (Scheme **12**) and more than 95% diastereomeric excess (de). This procedure was, however, not universally applicable to all aldehydes and different fluoride additives are required for different aldehydes.



Scheme 12 – First reported condensation of sulfinamides with aldehydes

Ellman and co-workers continued their extensive work into the synthesis of enantiopure sulfinamides. They reported the large scale preparation of *tert*-butanesulfinamide **26** in enantiopure form in two steps and in 71% overall yield from the very inexpensive *tert*-butyl disulfide **8** starting material.[23] The *tert*-butanesulfinamide **26** formed can then be condensed with aldehydes or ketones to form the corresponding sulfinimines **28**, (Scheme **13**).



Scheme 13 – Synthesis and condensation of *tert*-butanesulfinamide with carbonyl compounds

Branchaud[24] had reported that treatment of a carbonyl compound with a primary sulfenamide, in the presence of $MgSO_4$ as a drying agent and pyridinium *p*-toluenesulfonate (PPTS) as a catalyst, was found to be a universal practical preparation of sulfenimines. Armed with this information and the enantiopure *tert*-butanesulfinamide,

Ellman and co-workers reported the adoption of Branchaud's protocol to synthesize sulfinimines derived from of all kinds of carbonyl compounds[25] using different types of dehydrating agents. The presence of a drying agent in the reaction mixture appears to be the significant driving factor in the protocol. As a condensation reaction, the dehydrating agent tends to help drive the reaction forward. This was evident in the fact that the stronger the dehydrating agent, the more robust the protocol. Davis *et al*.[26] subsequently reported successful condensation of *p*-toluenesulfinamide with aldehydes and ketones using molecular sieves as well as $Ti(OEt)_4$ as water scavengers.

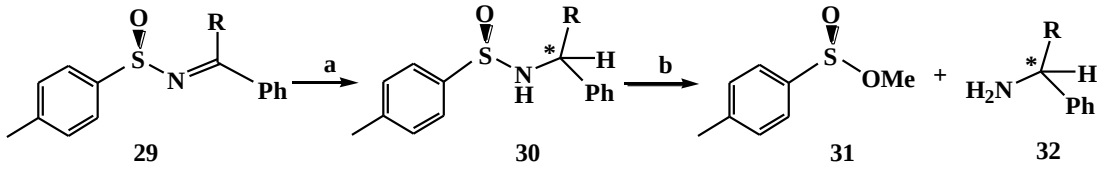
1.2 Reactions of Sulfinimines

1.2.1 Syntheses of amines

After Cinquini *et al.*[7] reported the first synthesis of enantiomerically pure sulfinimines, the way was paved for exploitation of sulfinimines as intermediates in the synthesis of a wide range of substrates and the investigation of the possibility of induction of the chirality of the sulfur onto the resulting product.

1.2.1.1 Hydride reduction

Following on from their work on the synthesis of chiral *p*-tolylsulfinimines, Cinquini *et al.*[27] reported arguably the first synthesis of chiral amines by reduction of the corresponding chiral sulfinimine. They reported that the chiral sulfinimines were reduced in high yield (80-85%) by lithium aluminium hydride to afford the sulfinamides **30** with diastereomeric ratios ranging from 4:1 to 9:1 for the sulfinimines examined as evaluated by ^{1}H-NMR spectroscopy (Scheme **14**). The sulfinamides thus produced were deprotected by acid methanolysis using Mikolajczyk's method[28] to give the optically active amines **32** in 57-80% yield.



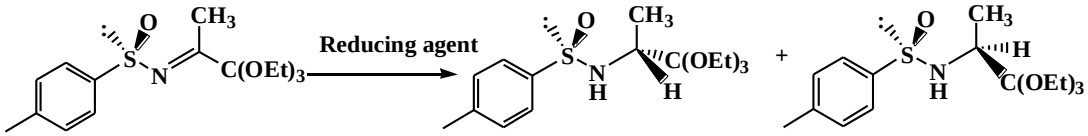
Scheme 14 – Metal hydride reduction of *p*-toluenesulfinimines and their deprotection

Further investigations showed that the use of alkoxy-lithium aluminium hydrides in the reduction of sulfinimines **29** generally resulted in a small but significant increase in the stereoselectivity from a maximum of 90:10 with lithium aluminium hydride up to 96:4 with dimenthyloxy lithium aluminium hydride.[29]

Hua and co-workers[30] followed with a report on the stereoselective reduction of *N*-tolylsulfinimines derived from acetophenone and butylphenylketone with

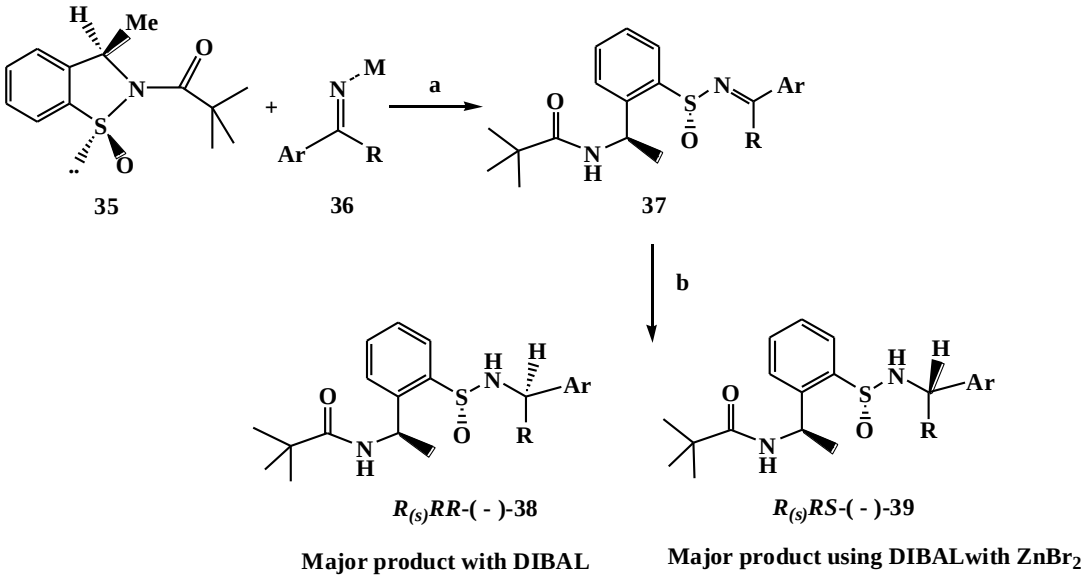
diisobutylaluminium hydride in THF at -30 °C for 1 h, which gave the (*R*)-sulfinamides in 92-96% yield and diastereoselectivities of 94:6 and 96:4 for the two sulfinyl ketimines investigated. The diastereomers were easily separated by column chromatography using silica gel, and the separate sulfinamides were then hydrolyzed with 2 equivalents of CF_3CO_2H in methanol at 25 °C for 3 hours to give 100% optically pure amines.[30]

However, in a later investigation on the reduction of sulfinimine **33**, derived from triethylorthoacetate,[31] Hua and co-workers reported the use of lithium aluminium hydride or diisobutylaluminium hydride as reducing agents afforded mixtures of diastereomers as products, whereas the use of 9-borabicyclo[3.3. l]nonane (9-BBN) yielded exclusively the *R*-diastereomer in 95% yield when reacted with the sulfinimine **33** in THF at 0° C, (Scheme **15**). Thus the type of substrate can affect the diastereoselectivity in the reduction step, which can be overcome with the choice of reducing agent.



Scheme 15 – Hua's oxidation of *p*-toluenesulfinimines using 9-BBN

In 1996, Wills and co-workers[32] reported the results of their research into the use of several types of reducing agents on 2-[1-(*tert*-butylcarbony1amino)ethyl] sulfinyl ketimines **37** (Scheme **16**). The highest selectivity was obtained using diisobutylaluminium hydride (DIBAL) in THF at -23 °C yielding $R_{(S)}RR$-(-)-**38** as the predominant isomer. More significantly, they reported that treatment of the sulfinyl ketimines **37** with 1 equivalent of zinc(II) bromide at room temperature, followed by two equivalents of DIBAL, resulted in the formation of the diastereomeric products $R_{(S)}RR$-(-)-**38** and $R_{(S)}RS$-(-)-**39**. The selectivity of this reduction procedure, compared to the DIBAL reduction, was completely reversed yielding $R_{(S)}RS$-(-)-**39** as the predominant isomer, as determined by HPLC and high field ^{1}H NMR analysis. This protocol was, however, found not to be universal as the same reversal is not observed in the reactions of analogues lacking an amide side chain.

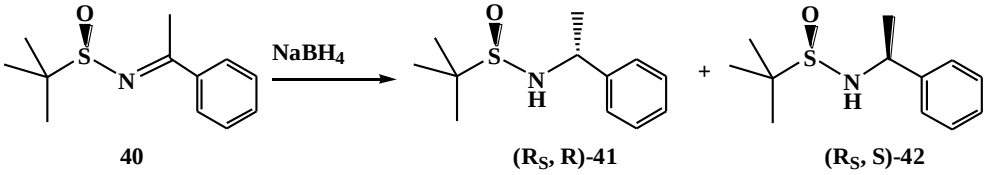


(a) THF, - 78 °C (b) Reducing agent

Scheme 16 – Wills' selective reduction of 2-[1-(*tert*-butylcarbony1amino)ethyl]sulfinyl ketimines

Although the asymmetric reduction of sulfinyl imines has subsequently been explored, the small number of sulfinyl ketimines that were synthetically accessible limited these studies. Moreover, reducing agents such as DIBAL, $LiAlH_4$ and 9-BBN that provide the highest stereoselectivities with sulfinimines are not compatible with a variety of functionalities, such as nitriles, esters, or certain alkenes. Ellman and co-workers[33] had previously reported the condensation of *tert*-butanesulfinamide with a wide variety of aldehydes and ketones in the presence of $Ti(OEt)_4$ to form the corresponding aldimines and ketimines respectively. The resulting *tert*-butanesulfinyl ketimines were reduced *in situ* with $NaBH_4$ to afford *tert*-butanesulfinyl-protected amines (Scheme **17**). The $Ti(OEt)_4$ was initially used as a water scavenger and catalyst for the imine condensation, but as a Lewis acid, it was observed to provide higher reduction rates and diastereoselectivities. For instance, when the classical reduction reaction was performed at -48 °C without $Ti(OEt)_4$, the yield was 83% and gave a diastereomeric ratio of 92:8, while in the presence of $Ti(OEt)_4$ and the same conditions, the sulfinamide **41** was isolated in 97% yield with a diastereomeric ratio of 96:4. Since there was $Ti(OEt)_4$ in the reaction mixture from the condensation reaction, it was possible to carry out the whole procedure in one-pot. The main advantage of the method was its generality, in that not only aromatic but also aliphatic acyclic ketones can be reductively

aminated in good yields and with high diastereoselectivities. In addition, the procedure is compatible with functionalities such as nitriles and double bonds conjugated to the imine.



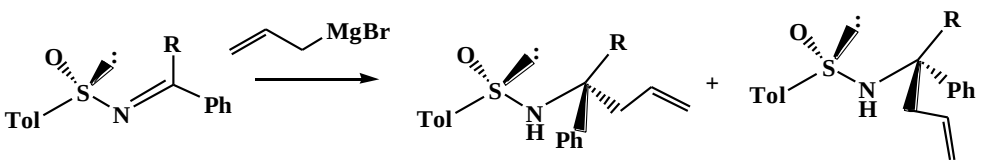
40 **(R_S, R)-41** **(R_S, S)-42**

Scheme 17 – Reduction of *tert*-butanesulfinyl ketimines

Asymmetric reduction of sulfinimines to yield amines has a lot of advantages. Firstly, for many synthetic targets a ketone precursor is more readily accessible than the aldehyde and Grignard precursors. Secondly, the sulfinyl group activates the imine C=N bond towards the 1,2-addition of mild reducing agents and this allows the synthesis of amines with functionalities that are incompatible with Grignard reagents.

1.2.1.2 Reactions with organometallic compounds

Hua and co-workers[34] reported that when *p*-toluenesulfinyl ketimines **43** derived from Andersen's reagent are treated with allylmagnesium bromide, the sulfinimines undergo stereoselective 1,2 addition with the Grignard reagent to afford the corresponding α-branched sulfinamides **44** and **45** in 84-98% yield and from 91:9 to 100% de. The sulfinamides are easily deprotected by acid methanolysis to give their corresponding amines.



43

43a: R = Me
43b: R = *n*-Bu

44

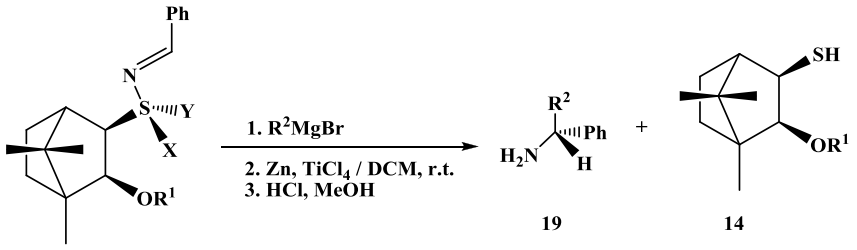
44a: 98%
44b: 84%

45

45a: 0%
45b: 8%

Scheme 18 – Reaction of sulfinimines to form α-branched amines

Yang and co-workers, working on their camphor-based mercapto chiral aldimine auxiliaries, reported the results of the asymmetric addition reactions of organolithium and Grignard reagents to the sulfinimines in THF. They observed the general correspondence of higher diastereoselectivities (70% to >98%) with decrease in size of the nucleophiles of the Grignard reagent used. For instance, allyl, *iso*-propyl and *n*-butylmagnesium bromides gave diastereomeric excesses of 98%, 88% and 82% respectively (Table **1**). The organolithium reagent, *n*-butyllithium which was reacted with the same aldimine substrate **18a** gave a maximum diastereomeric excess of 50%, (Table **1**).[19]



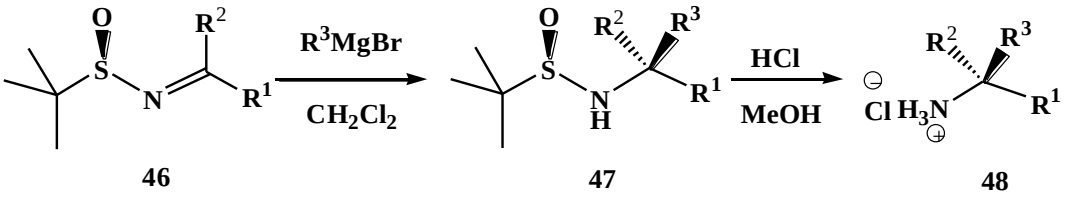
18a X= : , Y= O , R^1 = neopentyl
18b X = : , Y= O , R^1 = benzyl

Entry	Substrate	Nucleophile	Yield %	% de (*S* config)
1	**18a**	allylMgBr	96	>98
2		MeMgI	96	>97
3		EtMgI	92	70
4		*n*-BuMgBr	96	82
5		*n*-BuLi	60	50
6		*i*-PrMgBr	83	88
7		*t*-BuMgBr	60	>98
8	**18b**	allylMgBr	84	>98
9		MeMgI	84	>98
10		EtMgI	54	30
11		*n*-BuMgBr	71	70
12		*n*-BuLi	90	20
13		*t*-BuMgBr	50	>98

Table 1 - Yang's amine synthesis

Moreau *et al.* reported that *p*-toluenesulfinyl protected amines were prepared in good yields by treatment of *p*-toluenesulfinyl aldimines, derived from Andersen's reagent, with 2 equivalents of benzyl magnesium chloride solution in toluene at -30 °C.[35] Yields of 55-76% were obtained and the diastereomeric excesses ranged from 60-94% after recrystallisation of the product. Ellman and co-workers followed with a report on the addition of Grignard reagents to *tert*-butanesulfinyl aldimines.[36] They reported a near quantitative yield of the *tert*-butanesulfinamides in all but one of the examples and diastereomeric ratios of 89:11 to 97:3. The sulfinamides can then be easily cleaved by acid

methanolysis to afford the α-branched amines in excellent yields (88-97%) and, more significantly, high diastereoselectivities. It was found that the highest diastereoselectivities were obtained when CH_2Cl_2 was used as solvent (Scheme **19**). However when phenylmagnesium bromide was added to the *N*-sulfinylketimines **46** under the same conditions mentioned previously for 1,2-additions to *N*-sulfinyl aldimines, a 2:3 mixture of (*R*,*R*)-**47** and (*R*,*S*)-**47** was obtained in 21% yield.[36]

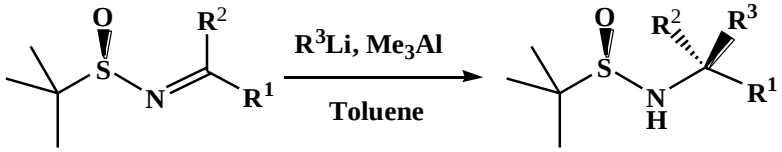


46 **47** **48**

Scheme 19 - Reaction of sulfinimines to form α, α-dibranched amines

Phenyllithium in toluene was found to be considerably more reactive, affording **47** in 65% yield with a diastereomeric ratio of 94:6.[36] This was, however, found not to be a universal protocol for 1,2-additions of organolithium reagents to *N*-sulfinylketimines, since other attempts with other substrates gave poor yields and diastereoselectivities.

This led Ellman and co-workers to explore the use of Lewis acids to enhance the product yield. Lewis acids such as $Al(O\text{-}i\text{-}Pr)_3$, trialkylaluminiums, $BF_3\text{-}Et_2O$, and Et_2Zn were investigated, and it was found that trialkylaluminiums like Me_3Al had the most effect on the 1,2-additions. The yield was increased from a range of 26-67% to 61-100% and the diastereomeric ratio was increased from a minimum of 63:37 to a minimum of 89:11 when Me_3Al was used as an additive during the addition (Table **2**). Significantly, this reaction favoured the diastereoisomer opposite to that obtained when Grignard reagents are used. The sulfinamides can then be easily cleaved by acid methanolysis to afford the α,α -dibranched amines.[36]



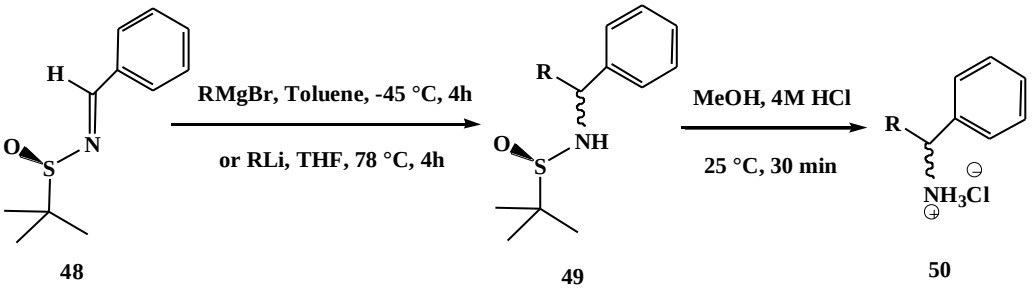
46 **47**

					Product			
Entry	**Reactant**	**R^1**	**R^2**	**R^3**	**Me_3Al equiv.**	**config.**	**Yield (%)**	**dr**
1	**46a**	Me	*i*-Pr	Ph	0	**(*R*)-47a**	65	94/6
2	**46a**	Me	*i*-Pr	Ph	1.1	**(*R*)-47a**	93	97/3
3	**46b**	Me	Ph	Bu	0	**(*S*)-47b**	26	99/1
4	**46b**	Me	Ph	Bu	1.1	**(*S*)-47b**	86	98/2
5	**46c**	Me	Bu	Bu	0	**(*R*)-47b**	67	63/37
6	**46c**	Me	Bu	Ph	1.1	**(*R*)-47b**	93	89/11
7	**46d**	Bu	Ph	Me	1.1	**(*R*)-47b**	quant	99/1
8	**46a**	Me	*i*-Pr	Bu	1.1	**(*S*)-47c**	61	99/1
9	**46e**	Bu	*i*-Pr	Me	0	**(*R*)-47c**	54	82/18
10	**46e**	Me	*i*-Pr	Me	1.1	**(*R*)-47c**	82	91/9

Table 2 – Me_3Al mediated 1,2-Additions of organolithiums to *N*-sulfinyl ketimines[36]

Ellman *et al.*[37], continuing with their work on the 1,2-additions of organolithiums to aldimines, published the results of his extensive work into the synthesis of amines by 1,2-additions of organometallic reagents to *tert*-butylsulfinyl aldimines and ketimines. The results were similar to what had been reported earlier[36] but in addition, they reported that phenylmagnesium bromide, prepared by metathesis of $MgBr_2$ and PhLi in Et_2O was nearly as effective as commercially available PhMgBr, giving the desired sulfinamide in 88% yield and 94:6 diastereomeric ratios.

Plobeck and Powell[38] later reported that certain aryl Grignard reagents, particularly para-substituted phenyl Grignard reagents, gave better yields and stereoselectivities when added to *N-tert*-butylsulfinylarylaldimines compared to the addition of phenyllithium and phenylmagnesium bromide (Table **3**). There was switchover of diastereofacial selectivity in the addition between PhMgBr and PhLi in all cases except one. The diastereomeric ratio of the sulfinamides could be improved by chromatography or recrystallisation. For instance, the diastereomeric ratio in one case (Entry 1) was increased from 86:14 to >99:1 by two recrystallisations (Table **3**).

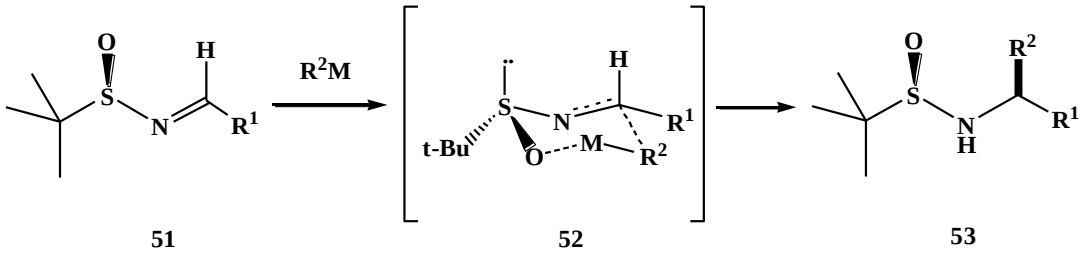


48 **49** **50**

			Sulfinylamide 49		Amine 50	
Entry	**R**	**M**	**Yield (%)**	**dr**	**Absolute config.**	**Yield (%)**
1	1-Naphthyl	MgBr	88 (62)	86:14(99.5:0.5)	*S*	94
2		Li	84	8:92	*R*	94
3	4-Cl-Phenyl	MgBr	86	88:12	*S*	97
4		Li	78	27:73	*R*	94
5	4-Br-Phenyl	MgBr	89	85:15	*S*	80
6		Li	85	13:87	*R*	88
7	4-CF_3-Phenyl	MgBr	85	80:20	*S*	71
8		Li	92	8:92	*R*	75
9	4-Me_2N-Phenyl	MgBr	N.r	-	-	-
10		Li	64	50:50	-	-
11	3-Furanyl	MgBr	76	97:3	*S*	81
12		Li	64	29:71	*R*	74

Table 3 – Plobeck's addition of organometallic reagents to *N-tert*-butanesulfinimines

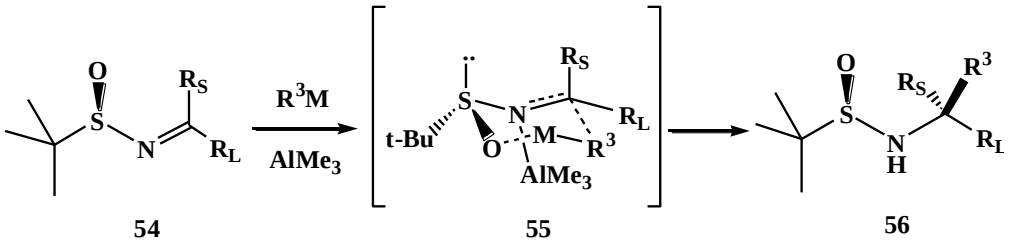
The stereochemistry of the products can be rationalised using a six-membered transition state with a chair conformation. In this transition state, (Scheme **20**) the bulky *tert*-butyl group of the sulfinimine occupies the less hindered equatorial position resulting in preferential attack from the same face for all additions. This transition state is consistent with the observed asymmetric induction for all of the reactions performed and is consistent with the observed solvent effects. The non-coordinating solvent, CH_2Cl_2, provides the highest selectivities, while more strongly coordinating solvents like Et_2O and especially THF are likely to interfere with the formation of the proposed six-membered ring transition state resulting in reduced selectivities.[37]



Scheme 20 – Explanation of the stereochemical outcome of 1,2-addition

The transition state shown in Scheme **21** is consistent with all of the experimental data for the Me_3Al mediated 1,2-additions of organolithiums to sulfinimines **54** due to the following reasons:[37]

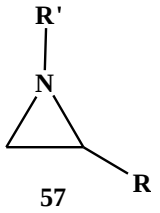
- Since lithium tetraalkylaluminiums do not transfer an alkyl group to **54**, then the 1,2-additions of organolithiums to sulfinimine **54** in the presence of Me_3Al appears to occur faster than aluminate formation.
- The substantial effect of Me_3Al on the yields and diastereocontrol supports the formation of a reactive sulfinimine-Me_3Al complex.
- The solvent effects further support a sulfinimine-Me_3Al complex, since coordinating ethereal solvents have been found to result in dramatically reduced yields and selectivities.
- The six-membered transition state model correctly predicts the product stereochemistry for all the compounds whose configurations could be determined.



Scheme 21 - Explanation of the stereochemical outcome of 1,2-addition mediated by a Lewis acid

1.2.2 Syntheses of aziridines

Aziridines (or ethylene imines) are the smallest nitrogen-containing heterocycle. These three-membered ring systems are made up of a core of one amine group and two carbon atoms complete the ring. The rings may have various degrees of substitution on the carbon atoms as well as the nitrogen (Figure **3**).



57

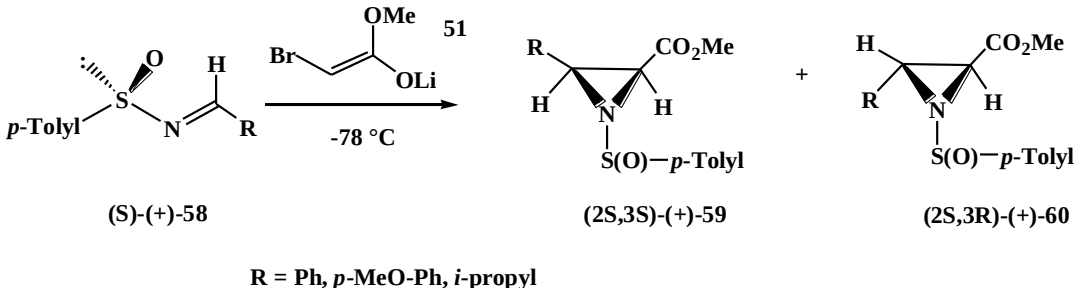
R, R' = alkyl or aryl

Figure 3 – Basic structure of an aziridine

Aziridines (**57**) have been synthetic targets as well as useful building blocks in synthesis since Gabriel's discovery in 1888.[39] The ring strain of aziridines, about 26.7 kcal/mol for the parent unsubstituted aziridine,[40] is thought to make the ring susceptible to a number of reactions. These reactions may either lead to an expansion in the size of the ring or even an opening of the ring in order to relieve the ring strain. Aziridines have recently attracted much interest because of their use as versatile intermediates in the syntheses of compounds like pyrrolizidines,[41] amaryllidacceae alkaloids,[42] other alkaloids[43] and other biologically active compounds.[44,45] Various methods have been employed in the syntheses of aziridines and because aziridines are similar in structure to cyclopropanes and epoxides, their syntheses tend to mimic the synthesis of cyclopropanes[46] and epoxides.[47] These methods include nitrogen transfer to olefins,[48] transition metal-catalysed nitrene transfer to olefins[49] and carbene transfer to imines.[50] We will however concentrate on the use of chiral sulfinimines as precursors to aziridines.

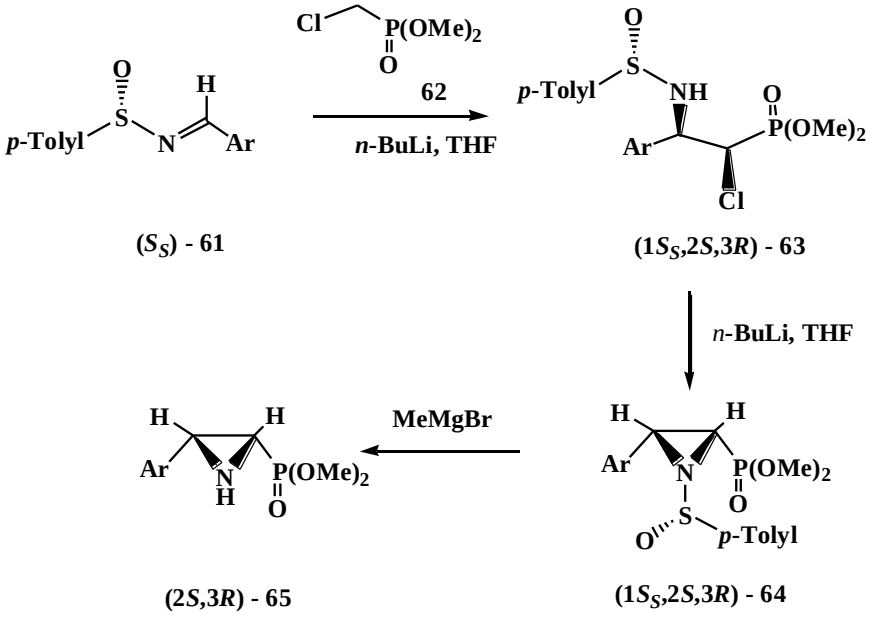
The aza-Darzen's reaction was adapted by Davis *et al.*[51] for the synthesis of chiral aziridine-2-carboxylic acids using sulfinimine precursors. The original process involved adding the lithium enolate of methyl-2-bromoacetate to a series of *p*-toluenesulfinyl protected imines (Scheme **22**) at -78 °C, which, after an aqueous work-up, resulted in the formation of the aziridine-2-carboxylic acids **59** and **60** in good yields (up to 77%) and

excellent *cis/trans* ratio (up to 99:1). In all cases, the *cis*-aziridine was formed nearly exclusively.



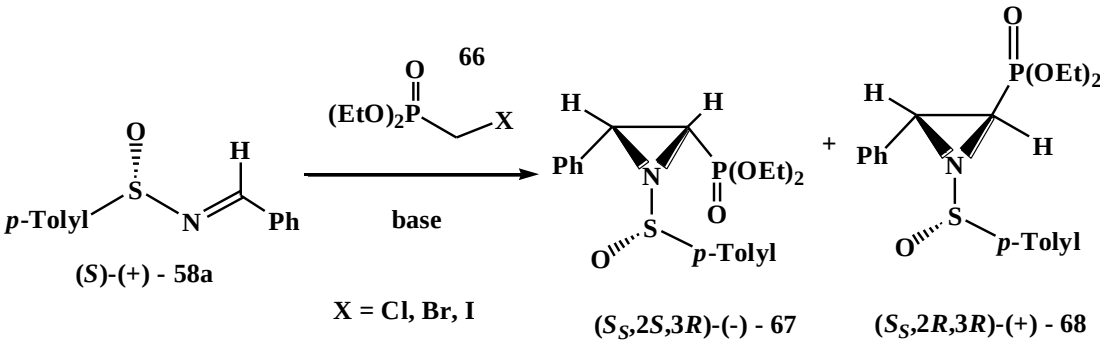
Scheme 22 – Aza-Darzen's aziridination

Davis and co-workers[52] reported a further modification of the aza-Darzen's reaction to prepare enantiopure aziridine-2-phosphonates (Scheme **23**). When this protocol was applied to the lithium anion of diethyl chloromethylphosphonate, no aziridine was found, but the α-chloro-β-amino adducts (S_S,1*S*,2*R*)-(+)-**63** and its (S_S,l*R*,2*R*)-(+) diastereomer were produced in high yield in a 59:41 ratio which were then isolated by flash chromatography. The aziridination was, however, achieved by the treatment of the α-chloro-β-amino adducts with NaH, which readily afforded aziridines (S_S,2*S*,3*R*)-(-)-**64** in 76% yield (Scheme **23**). The exclusive (*R*)-absolute induction at C-2 in the aziridine **64** was opposite to that found in the analogous carboxylic ester.[51]



Scheme 23 – Synthesis of aziridine-2-phosphonates

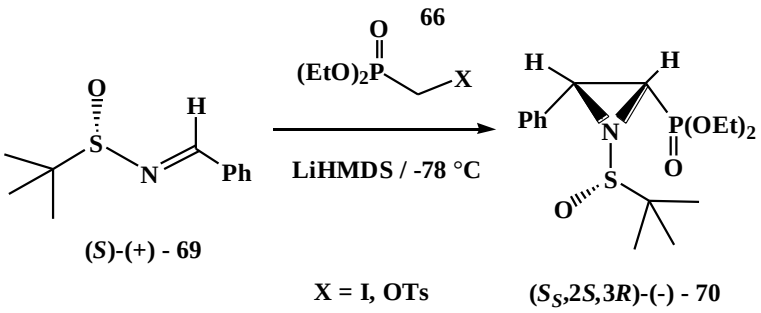
Davis and co-workers continued their work on the preparation of *N*-sulfinylaziridine 2-carboxylates by reporting further results of their work with α-haloenolates in the aza-Darzen's reaction.[53] Davis reported that the use of the potassium enolate reduced the diastereoselectivity significantly compared to the sodium and lithium enolates whilst reduced reaction times tended to increase yields. The attempt at one pot synthesis of the aziridines was not very successful as they resulted in a marked decrease in de's but the yields were slightly better. The same method was used by Davis and co-workers to synthesise enantiopure *N*-sulfinylaziridine-2-phosphonates, which were utilized as highly functionalised chiral building blocks in highly stereoselective asymmetric syntheses of α-aminophosphonates and α-methyl-α-aminophosphonates.[54] The same protocol explored for the synthesis of *N*-sulfinyl aziridine-2-phosphonates was employed in a one-pot synthesis (Scheme **24**).[55] Davis reported that treating a mixture of two equivalents of the halomethylphosphonate **66** and 1 equivalent of the sulfinimine **58a** with the appropriate base at -78 °C, and quenching the reaction mixture with aqueous saturated NH_4Cl at that temperature before warming to room temperature, gave the aziridines without any α-halo-*α*-amino adduct. It however proved to be exceedingly tedious to separate the aziridine isomers and repetitive chromatographic separation was required which resulted in poor yields. It was found that when the reaction was stopped at the α-halo-*α*-amino adduct intermediate stage, the two isomers can be more easily separated, and the enantiopure α-halo-*α*-amino adducts were then cyclised to the corresponding aziridines separately.



Scheme 24 – Synthesis of aziridine-2-phosphonates

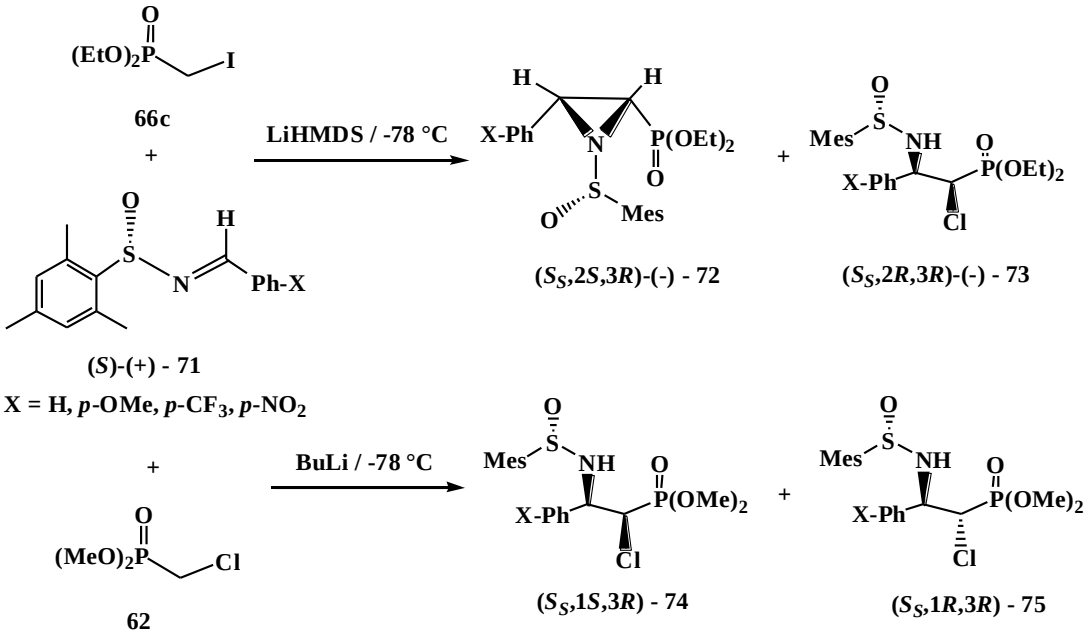
The influence of the sulfinyl auxiliary on the diastereoselectivity of α-aminophosphonates was investigated by aziridination of diethyl iodo- or tosylphosphonates **66c** or **66d** and (*S*)-(+)-*N*-*tert*-butanesulfinimine **69**, using the previously developed protocol (Scheme **25**).

Importantly, the aziridine (-)-**70** was formed directly as a single isomer, in 82 and 32% isolated yields, respectively.[55]



Scheme 25 – Synthesis of aziridine-2-phosphonates using *N*-*tert*-butanesulfinimine

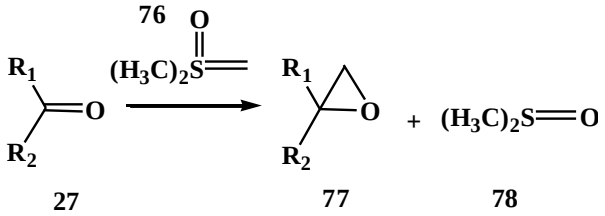
With Senanayake's discovery of a novel protocol for the asymmetric synthesis of diversely substituted sulfinamides, using aminoindanol-derived *endo*-(-)-1,2,3-oxathiazolidine-2-oxide,[56] the stage was set for the exploitation of the method for the synthesis of diversely substituted sulfinimines. In addition to the *p*-tolyl and *t*-butyl sulfinimines already utilised in the synthesis of aziridines by the aza-Darzen's method, Davis and co-workers employed the 2,4,6-trimethylphenylsulfinyl (mesityl) group in the synthesis of *N*-sulfinyl aziridine 2-phosphonates.[57] The procedure involves treating the *N*-(2,4,6-trimethylphenylsulfinyl) imines (*S*)-(+)-**71** and diethyl iodomethylphosphonate **66c** with two equivalents of LiHMDS at -78 °C (Scheme **26**). Importantly, only sulfinimines having the 4-methoxyphenyl and phenyl groups afforded the aziridines (S_S,*2S*,*3R*)-(-)-**65** as single diastereoisomers in one pot and in 75-78% isolated yield, whilst aryl sulfinimines containing electron-withdrawing groups gave complex mixtures of *α*-amino-α-chloro phosphonates **66a** albeit with improved diastereomeric ratios compared to the *N*-(*p*-toluenesulfinyl) auxiliary.[57] The deprotection of the *N*-mesitylsulfinylaziridines was found to proceed using methyl magnesium bromide to give the free N-H aziridines in good yields.



Scheme 26 – Synthesis of aziridine-2-phosphonates using mesitylsulfinimines 71

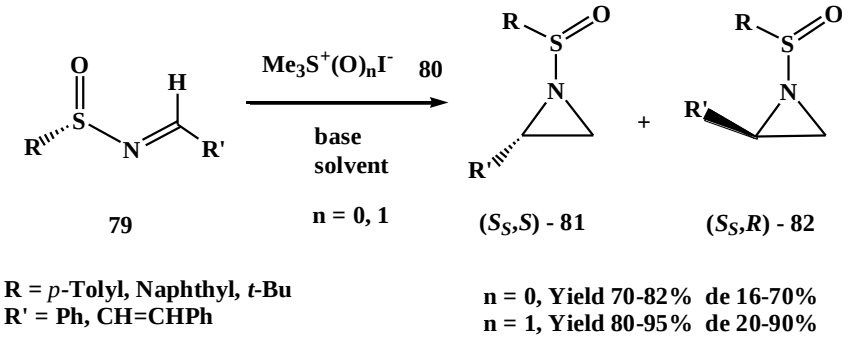
Davis and Deng recently reported a procedure for the synthesis of methyl-2-chloroaziridine-2-carboxylates which are precursors for the synthesis of the first examples of enantiopure 2-substituted 2H-azirine 3-carboxylates.[58]

In 1962, Corey and Chaykovsky[59] reported that treatment of ketones and aldehydes with dimethyloxosulfonium methylide yielded the corresponding epoxides in very high yields (Scheme **27**). They went on to report the use of dimethylsulfonium methylide also as a methylene transfer agent,[60] giving epoxides in comparable yields to those obtained for dimethyloxosulfonium methylide. The most interesting report was that both ylides are good nucleophiles that function to transfer methylene not only to carbonyl C=O bonds but also to other electrophilic unsaturated linkages like C=N, C=S, and in certain cases C=C.[61] This method however has largely been employed only for the syntheses of epoxides and cyclopropanes.



Scheme 27 - Corey–Chaykovsky epoxidation

In 1995, Ruano *et al.*[62] reported a modification of the Corey–Chaykovsky methylene-transfer reaction to produce aziridines. It was found that reaction of activated dimethylsulfonium methylide with chiral non-racemic p-toluenesulfinyl imines furnished the chiral aziridines in good yield (Scheme **28**).



Scheme 28 – Ruano's aziridination using the Corey-Chaykovsky method

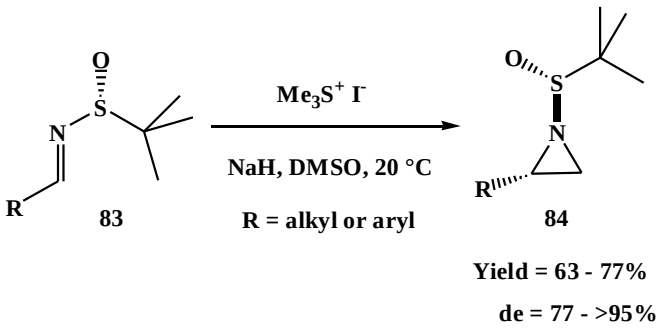
Davis and co-workers[63] as well as Ruano and co-workers[64] independently reported the use of dimethyloxosulfonium methylide instead of dimethylsulfonium methylide in synthesising aziridines using the same reported modification of the classic Corey–Chaykovsky methylene-transfer reaction. The results revealed that the use of dimethyloxosulfonium methylide gave aziridines of predominantly (*S*) configuration at the aziridine carbon whilst dimethylsulfonium methylide afforded aziridines of inverted stereochemistry compared to the former. Ruano and co-workers[65] subsequently reported that aziridinations of the sulfinimines using dimethyloxosulfonium methylide gave relatively higher yields and diastereoselectivities compared to those using dimethylsulfonium methylide under identical conditions but the reaction times for the dimethyloxosulfonium methylide were considerably longer. Significantly, the best stereo-directing group was the *tert*-butyl group (64-90% de) compared to the *p*-tosyl (16-46% de) and naphthyl groups (54-66% de).

The proposed mechanism to justify the observed rates and stereochemistry of the products is similar to that proposed for reactions of the ylides with the aldehydic carbonyl group.[66] According to this mechanism, the reactions with dimethylsulfonium methylide occur under kinetic control, whereas those of the dimethyloxosulfonium methylide are subjected to thermodynamic control. The diastereomeric ratio obtained from dimethylsulfonium

methylide must therefore be controlled by the relative rates of its attack on the diastereotopic faces of the C=N bond of the *N*-sulfinylimines, whereas that obtained from dimethyloxosulfonium methylide must be related to the thermodynamic stability of the diastereomeric addition products.[65]

There has been a flurry of reports on the modified Corey–Chaykovsky reaction to synthesise aziridines using a wide range of sulfur ylides. Dai and co-workers[67] have reported extensively on the use of dimethylsulfonium allylide to synthesize vinyl aziridines using the modified Corey-Chaykovsky protocol, albeit with sulfonyl imines rather than sulfinyl imines.

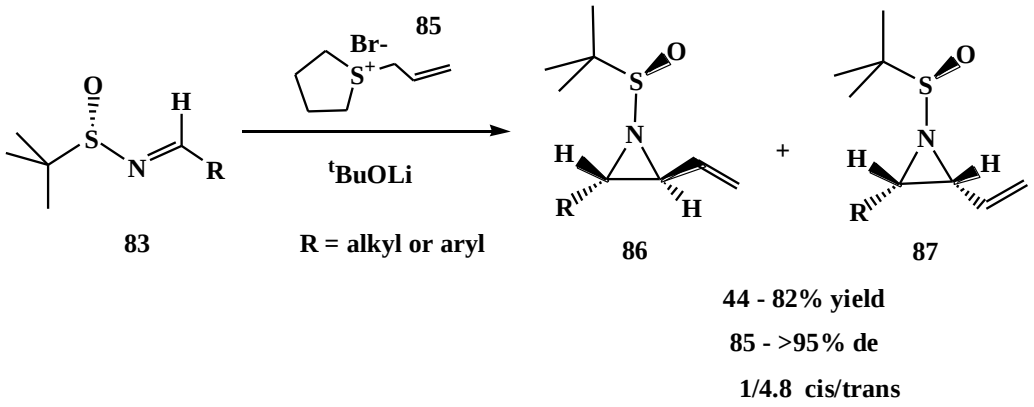
Stockman and co-workers reported the results of their work on the reaction of dimethylsulfonium methylide with a range of aromatic, heterocyclic and aliphatic *tert*-butylsulfinyl imines to form the corresponding aziridines in 63–84% yield and 77–95% diastereomeric excesses[68] (Scheme **29**). These results confirm the report by Ruano and co-workers[65] about the excellent stereo-directing and activating properties of the *tert*-butylsulfinyl group in the synthesis of aziridines using the modified Corey-Chaykovsky reaction.



Scheme 29 – Stockman *et al.*'s use of the Corey-Chaykovsky protocol to synthesise methylaziridines

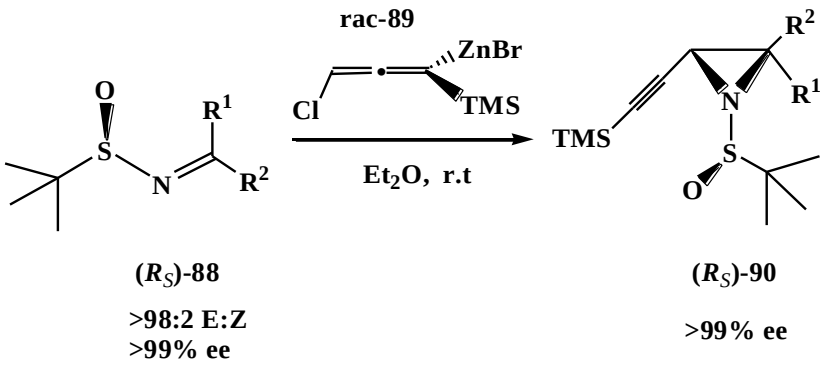
Stockman and co-workers, following on from their earlier work on the synthesis of vinyl aziridines,[69] reported the results of their work into utilising enantiopure *N*-*tert*-butylsulfinyl imines and ylides derived from *S*-allyl tetrahydrothiophenium bromide to synthesise vinyl aziridines[70] (Scheme **30**). Optimal conditions for the aziridination reaction involve the use of lithium *tert*-butoxide to deprotonate the sulfur salt in THF at room temperature. The

reaction gave high yields (44-82%) of the aziridines (**86** and **87**) and excellent diastereoselectivities (85- >95%).



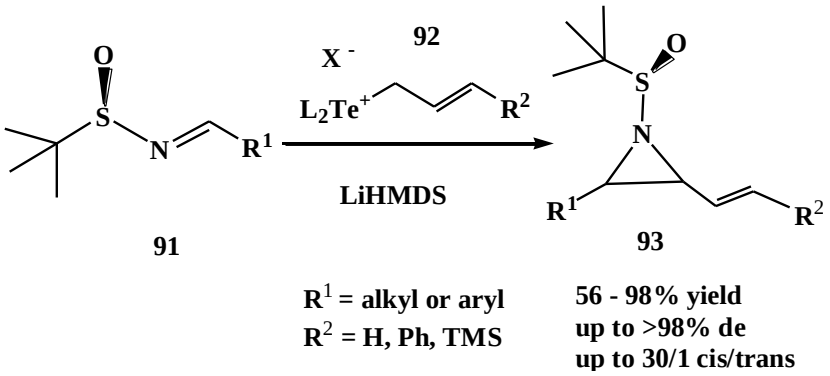
Scheme 30 – Asymmetric synthesis of vinyl aziridines using allyl tetrahydrothiophenium ylide

An interesting scheme reported by Chemla and Ferreira[71] involved the synthesis of enantiopure *trans*-ethynyl *N*-*tert*-butanesulfinylaziridines (R_S)-**90** by reaction of enantiopure aldimines and ketimines **88** with racemic allenylzinc species **89** (Scheme **31**). Good yields (50-87%) and excellent *trans*:*cis* ratio (up to 94:6) were obtained using a large excess of racemic allenylzinc **89**. The aziridines were isolated as diastereomerically (>98:2 dr) and enantiomerically (>99% ee) pure compounds after silica gel chromatography.[71]



Scheme 31 – Asymmetric synthesis of trans-ethynyl aziridines using racemic allenylzinc

Another interesting adaptation of the Corey-Chaykovsky reaction was reported by Dai and co-workers[72] involving the synthesis of optically active *cis*-2-substituted vinylaziridines by the reaction of *N*-*tert*-butylsulfinyl imines with telluronium ylides. The reaction gave the aziridines in good to excellent yields (55-85%) and excellent diastereoselectivity, up to 98% in most cases (Scheme **32**).

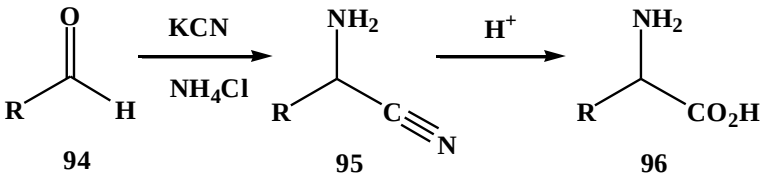


Scheme 32 – Synthesis of vinyl aziridines using telluronium ylides

1.2.3 Syntheses of amino acids

Amino acids are a very important group of compounds that act both as building blocks of proteins and as intermediates in metabolism. Proteins catalyze almost all metabolism within living cells and regulate virtually all cellular processes. The amino acid sequence is known to play an important role in the folding and hence structure of a protein. With only 20 amino acids known to occur naturally, the synthesis of amino acids constitutes a major area of research that can yield an invaluable library of amino acids and hence new proteins and enzymes that may hold the key to yet unsolved chemical and biological catalytic mysteries.

The first known synthesis of amino acids was by Adolph Strecker in 1850.[73] Strecker reported that when an aldehyde was condensed with ammonium chloride in the presence of potassium cyanide, an α-aminonitrile was obtained which can be subsequently hydrolyzed to give the desired amino-acid in high yield. The use of ketones instead of aldehydes gives substituted α,α-dibranched amino acids whist the use of primary amines affords the *N*-substituted amino acids.[74]

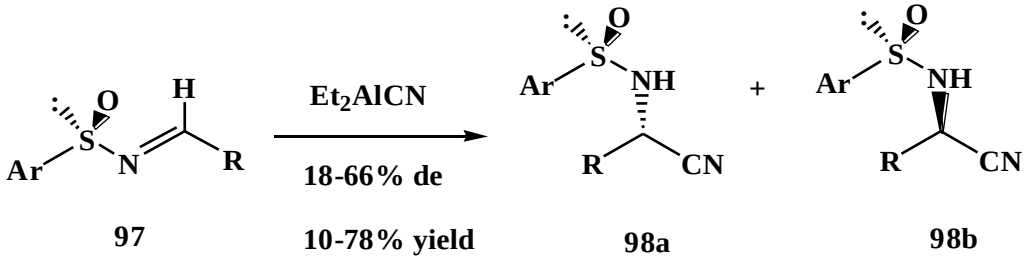


R = alkyl or aryl

Scheme 33 – Strecker's amino acid syntheses

The use of a chiral *N*-auxiliary was hoped to impart chirality to the newly formed stereogenic centre within the product. To this end, many chiral auxiliaries had been employed in an effort to obtain enantiomerically pure amino acids. These include 5-amino-4-phenyl-1,3-dioxanes,[75] 1-amino-tetra-*O*-pivaloyl-β-D-galactopyranose[76] and α-phenylglycinol[77] auxiliaries. Though very useful in the synthesis of amino acids, these methods however have had limited successes because of the poor de's and problem with the removal of the chiral auxiliaries.[77]

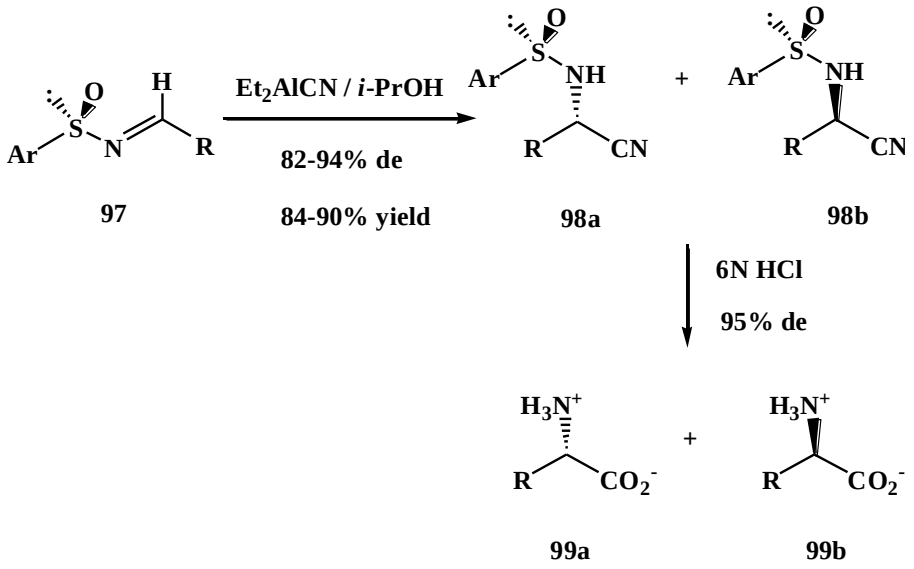
Davis and co-workers were the first to attempt the asymmetric synthesis of amino acids using chiral sulfinimines in a modification of the Strecker synthesis. They postulated that addition of cyanide sources to sulfinimines could to give α-aminonitriles which, upon hydrolysis, would give α-amino acids. In the event, cyanide sources such as KCN and CuCN failed to add to the *N*-(benzylidene)-*p*-toluenesulfinamide under various conditions whilst the use of TMSCN only gave 9-20% of the expected α-aminonitrile.[78] Reaction of a series of sulfinimines having the *p*-toluenesulfinyl and *N*-2-methoxy-1-naphtylsulfinyl auxiliaries with diethylaluminium cyanide, however, afforded a mixture of corresponding diastereoisomers **98** in poor to good yields (<10 - 78%), but the diastereoselectivities were only modest (18–66%). These diastereomers were however easily separable by silica gel chromatography. Treatment of the enatiopure α-aminonitrile **98** with 6N HCl simultaneously removed the sulfinyl group and hydrolyzed the nitrile, affording the α-amino acids **99** in 67-81% yield with enantiomeric excesses of >95% and without epimerization, thus eliminating one of the problems with the classic Strecker synthesis.



97 **98a** **98b**

Scheme 34 – First asymmetric amino acid synthesis using modified Strecker protocol

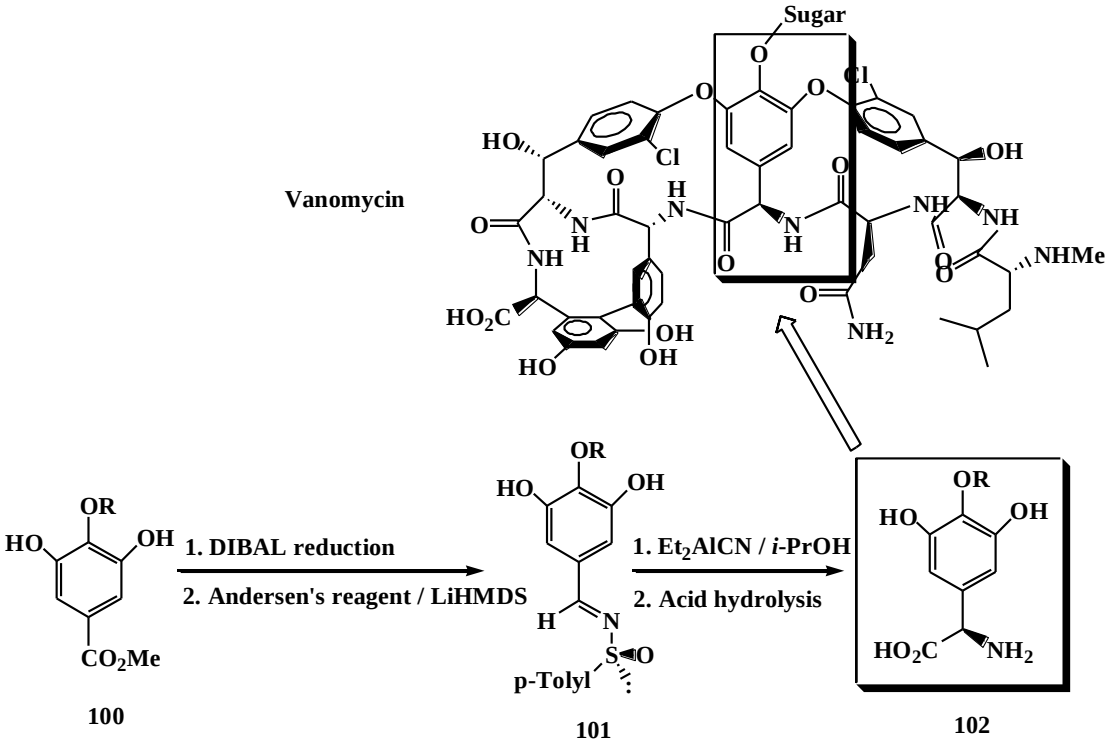
Significantly, it was observed that treatment of Et_2AlCN with isopropyl alcohol (*i*-PrOH) prior to addition to the sulfinimine resulted in a dramatic improvement in the diastereoselectivity (de) to 82–94%.[79] The enhanced de's were attributed to the reduced Lewis acidity of Et(O-*i*-Pr)AlCN as against that of Et_2AlCN which makes it more selective. Diastereomerically pure **98** (> 96% de) were obtained by crystallization of the aminonitriles in 80-90% yield and the corresponding enantiomerically pure amino acids were obtained in >95% yield by heating by heating the diastereomerically pure α-aminonitriles at reflux with 6N HCl followed by purification on an ion exchange resin (Scheme **35**).



Scheme 35 – Improved sulfinimine mediated asymmetric Strecker amino acid syntheses

Davis and co-workers applied the modified Strecker synthesis to the synthesis of the central core amino acid of vancomycin, which was the drug of choice, and increasingly of last resort, for the treatment of infections of methicillin-resistant *Staphylococcus aureus* (MRSA) and other Gram-positive organisms. Its unique structure and the emergence of vancomycin-resistant microbes have made it an important synthetic target. The synthesis of derivatives of **102** (Scheme 36) such as (*R*)-(4-methoxy-3,5-dihydroxyphenyl)glycine had previously been reported. Boger, using Sharpless asymmetric dihydroxylation, prepared the *N*-Boc derivative of **102** in 12-13 steps and 94% ee[80] whilst Zhu employed a Strecker-type synthesis with (*S*)-phenylglycinol as the chiral auxiliary which involved 13-14 steps and afforded the *N*-Troc derivative of **102** in 80% ee.[81] Other more efficient protocols have subsequently been reported which involved about 8-15 synthetic steps.[82]

Davis and Fanelli however utilised the sulfinimine Strecker methodology in a highly efficient four-step synthesis of (*R*)-**102** and its derivatives (Scheme **36**).[83] This was achieved by the addition of EtAl(O-*i*-Pr)-CN to the 3,4,5-trimethoxy and 3,5-diisopropoxy-4-methoxy sulfinimines **100a** and **100b** respectively to afford the corresponding α-amino nitriles **101a** and **101b** in good yield and excellent diastereoselectivities (92-96% de). Acid hydrolysis afforded the (*R*)-**102** in >97% ee and 40% overall yield (Scheme 36).



Scheme 36 – Synthesis of the core amino acid of Vanomycin

Strategically placed fluorine has been shown to enhance biological activity and availability[84] and the synthesis of non-racemic *α*-fluoro-α-amino acids (**103**, Figure **4**) has been accomplished by Davis and co workers.[85] The sulfinimine-mediated Strecker methodology has also been used by Davis *et al*.[86] to synthesize (*2S,6S*)-diaminopimelic acid (DAP) (**104**, Figure **4**) and *meso*-(*2S,2R*)-diaminopimelic acid (*meso*-DAP) (**105**, Figure **4**) which are essential for the growth of bacteria and plants. Furthermore, *meso*-DAP is a cross-linking unit of the cell wall peptidoglycan of most Gram-negative and some Gram-positive bacteria and therefore partly responsible for cell wall integrity.[87] In addition, *α*-hydroxy-α-amino acids (**106**, **107** and **108**), which are an important class of amino acids that include threonine, serine, and *α*-hydroxyproline, have also been synthesised using the Davis-Strecker approach.[88]

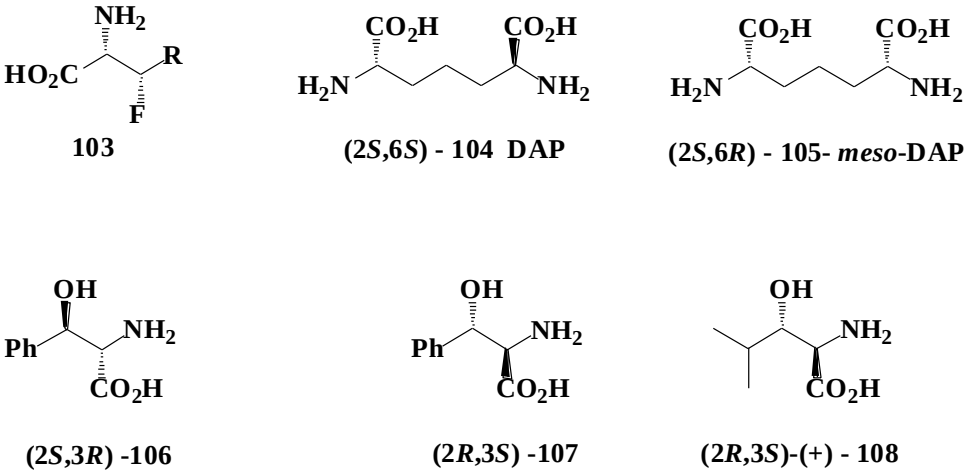
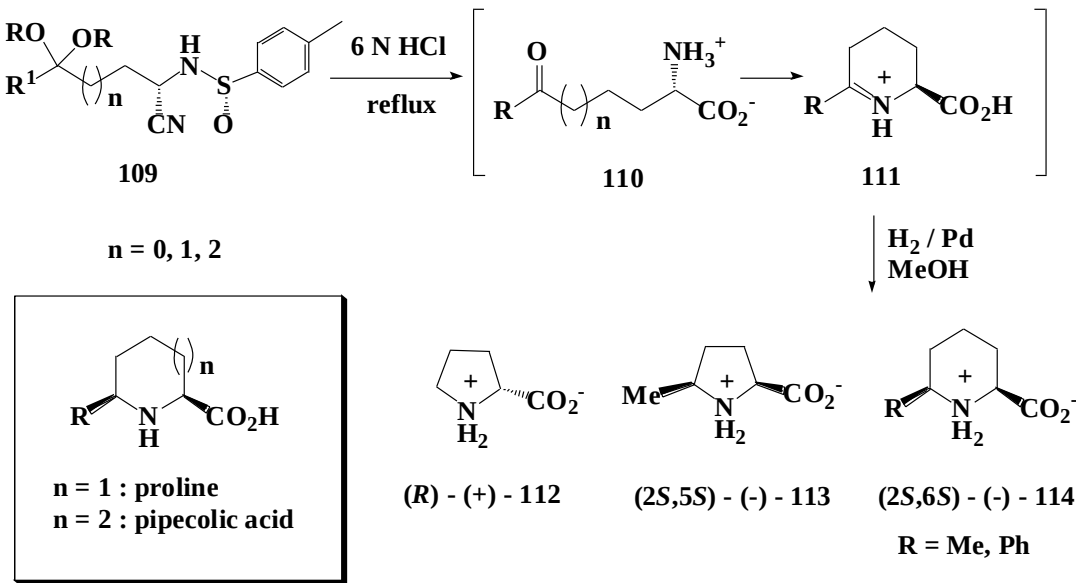


Figure 4 – Some amino acids synthesised using the asymmetric Strecker synthesis

The *tert*-butylsulfinimines have also been employed with great success in the sulfinimine-mediated asymmetric Strecker protocol by Davis[89] and Cordi.[90] Another interesting use of the sulfinimine-mediated asymmetric Strecker protocol was in the syntheses of cyclic amino acids, including proline and pipecolic acid (homoproline) and their derivatives, using masked oxo-sulfinimines.[91] These cyclic amino acids are known to confer rigidity on a protein and this influences cell recognition events.[92]

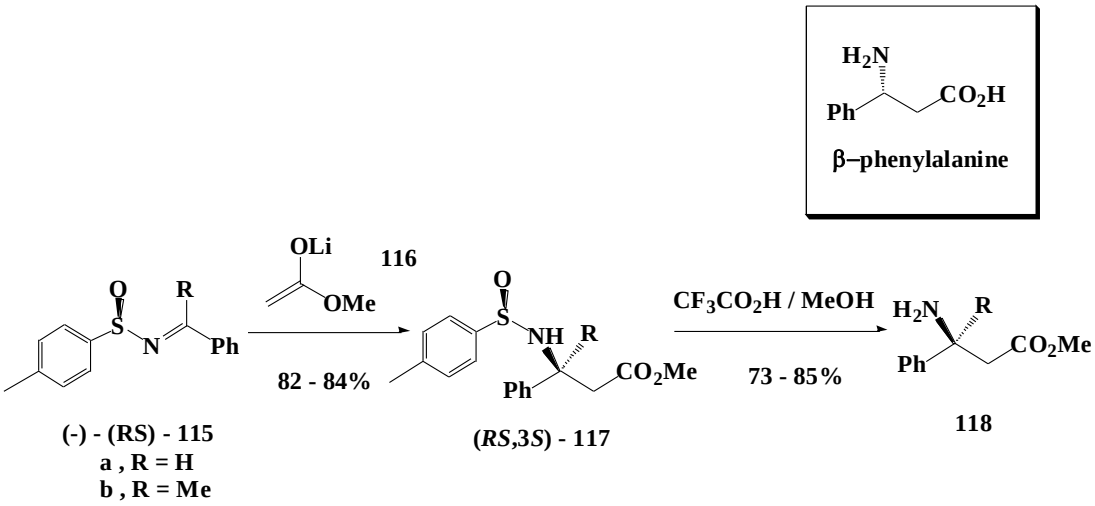


Scheme 37 – Asymmetric syntheses of cyclic amino acids

The masked oxo-sulfinimines were synthesised by condensation of the *p*-tolylsulfinamides derived from Andersen's reagent and the masked oxo-aldehydes using well established protocols.[21] The masked oxo-sulfinimines obtained were subjected to the usual asymmetric Strecker protocol to obtain the masked oxo-α-amino nitriles (**109**) in 74-95% yield and 74-93% de. The most important stage in the synthesis occurs when the diastereomerically pure amino nitriles **109** were subjected to hydrolysis which accomplishes five operations in a single pot (Scheme **37**). Hydrolysis with 6N HCl removes the *N*-toluenesulfinyl auxiliary with concomitant conversion of the nitrile to the acid and deprotects the oxo group to give the oxo-α-amino acid **110**, which then cyclises to give the iminium ion **111**. The crude iminium salt **112** was isolated and dissolved in MeOH before being hydrogenated using hydrogen and palladium over carbon. The cyclic amino acids were isolated using an ion-exchange column to obtain the corresponding cyclic amino acids **112**-**114** in 48-95% yield and 93-98% ee (Scheme **37**).[91]

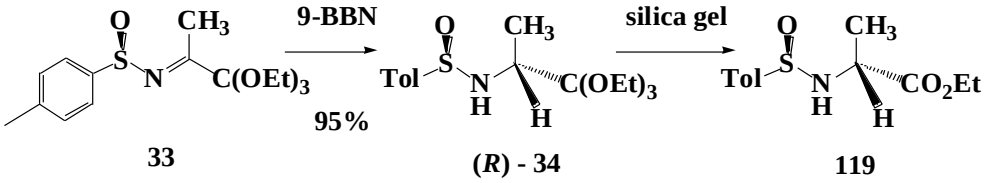
Hou and co-workers reported that the fluoride anion served as a promotor to initiate the addition of silicon reagents, such as allyltrimethylsilane, TMSCN, and $TMSN_3$, to imines in excellent yields.[93] Most importantly, they found that in the presence of the fluoride anion, TMSCN is also successfully added to the C=N bond of sulfinimines when there is a hydrogen atom at the α-position of the C=N bond.[93]

Though the sulfinimine-mediated asymmetric Strecker protocol is a very popular and versatile means of synthesising amino acids, other methods have also been utilised to convert sulfinimines to amino acids. These include the addition of enolates to chiral sulfinimines. Thus, addition of 1.5 equivalents of LDA to the same equivalent of methyl acetate, by Davis and co-workers,[94] and subsequent addition of the enolate generated to enantiopure sulfinimines **115** gave sulfinamides **117a** and **117b** in 74% and 90% isolated yields respectively. Significantly, hydrolysis with TFA occurred without epimerization to afford the β-aminoesters **118a** and **118b** in 73 and 85% yields respectively (Scheme **38**).[94] This new protocol was again used by Davis and co workers[95] to synthesise β-phenylalanine (Scheme **38**), which is an important constituent of the antitumor cyclic peptide astins A-C[96] and is a precursor of the C-13 side chain of taxol[94] in >98% ee.



Scheme 38 - Scheme 38 - Davis and co-workers' synthesis of *β*-phenylalanine

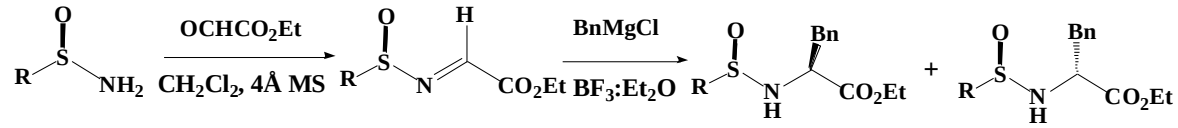
A new method for the synthesis of α-amino acids from sulfinimines was reported by Hua and co-workers, in which reduction of chiral *N*-[1-(triethoxymethyl)ethylidene] sulfinimine **33** with 9- borabicyclo[3.3.1] nonane (9-BBN), gave the sulfinamide ***R*-(34)** exclusively in 95% yield[31] (Scheme **39**). Hydrolysis of the ortho ester ***R*-(34)** on a silica gel column overnight gave a quantitative yield of the ester **119** (Scheme **39**), which was readily converted to the corresponding amino acid.



Scheme 39 – Hua's α-amino acid synthesis

Davis and co-workers also reported the use of glyoxylate derived sulfinimine to synthesise α-amino acids.[97] The sulfinimines were prepared by 4Å molecular sieve (MS) mediated condensation[26] of (*S*)-(+)-*p*-toluenesulfinamide (**120**) or (*R*)-(+)-*tert*-butanesulfinamide (**121**) with ethyl glyoxylate (Scheme **40**). BnMgCl was found to add regioselectively at the imino carbon to give (S_S,*2R*)-**124** and (S_S,2*S*)-**125** in 56% combined yield and 82:18 diastereomeric ratio. However, these diastereomers were found not to be separable by chromatography, coupled with other competition reactions such as oligomerisation. The

use of Lewis acids was explored as a means of overcoming these problems. It was found, however, that pre-complexation of (*S*)-**122** with 2 equivalents of $BF_3 \cdot OEt_2$ significantly reduced oligomerisation, but the yield (31%) and diastereoselectivity (63:37) were markedly reduced. With the *tert*-butanesulfinyl imine (*R*)-**123** however, addition of 2 equivalents of $BF_3 \cdot OEt_2$ improved the yield of the desired sulfinamide from 23% to 70% isolated yield and the diastereoselectivity was also increased from 90:10 to 94:6. The use of 2 equivalents of BnMgCl was also found necessary for optimal yield and diastereoselectivity.[97]



Scheme 40 – Amino acid synthesis from glyoxylate-derived sulfinimines

1.3 Nakadomarin A

Nakadomarin A was first isolated from the marine sponge *Amphimedon* sp. (SS-264) collected off the Kerama Islands in Okinawa, Japan.[98] When the structure was elucidated, it was found to be made up of a novel furan-containing hexacyclic alkaloid consisting of an unprecedented 8/5/5/5/15/6 ring system. The structure contains three different heterocyclic rings and is flanked with fused 8-membered and bridging 15-membered rings. The tetracyclic core also contains 4 stereogenic carbons including an all-carbon stereocenter.[99]

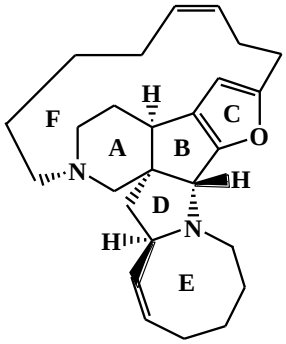


Figure 5 – (-)-Nakadomarin A

Nakadomarin A was isolated together with some manzamine alkaloids[98] and it appears to be biosynthetically related to the manzamines[100] and ircinals.[101] Nakadomarin A, just like the closely related manzamine alkaloids, has remarkable biological activity. It has exhibited cytotoxicity against marine lymphoma L1210 cells (IC50 1.3 μg/mL) and inhibitory activity against cyclin dependent kinase 4 (IC50 9.9 μg/mL). Nakadomarin A has also showed antimicrobial activity against the fungus *Trichophyton mentagrophytes* (MIC 23 μg/mL) and the Gram-positive bacterium *Corynebacterium xerosis* (MIC 11 μg/mL).[98]

These biological activities and the low natural availability (1.8×10^{-3} % of the wet weight of the sponge) have prompted chemists to explore ways of synthesizing nakadomarin A. Its complex structure however poses a formidable synthetic challenge. Kobayashi has postulated that ircinal is a common intermediate in the biosynthesis of both nakadomarin A[102] and the manzamines[101] (Figure **6**).[102]

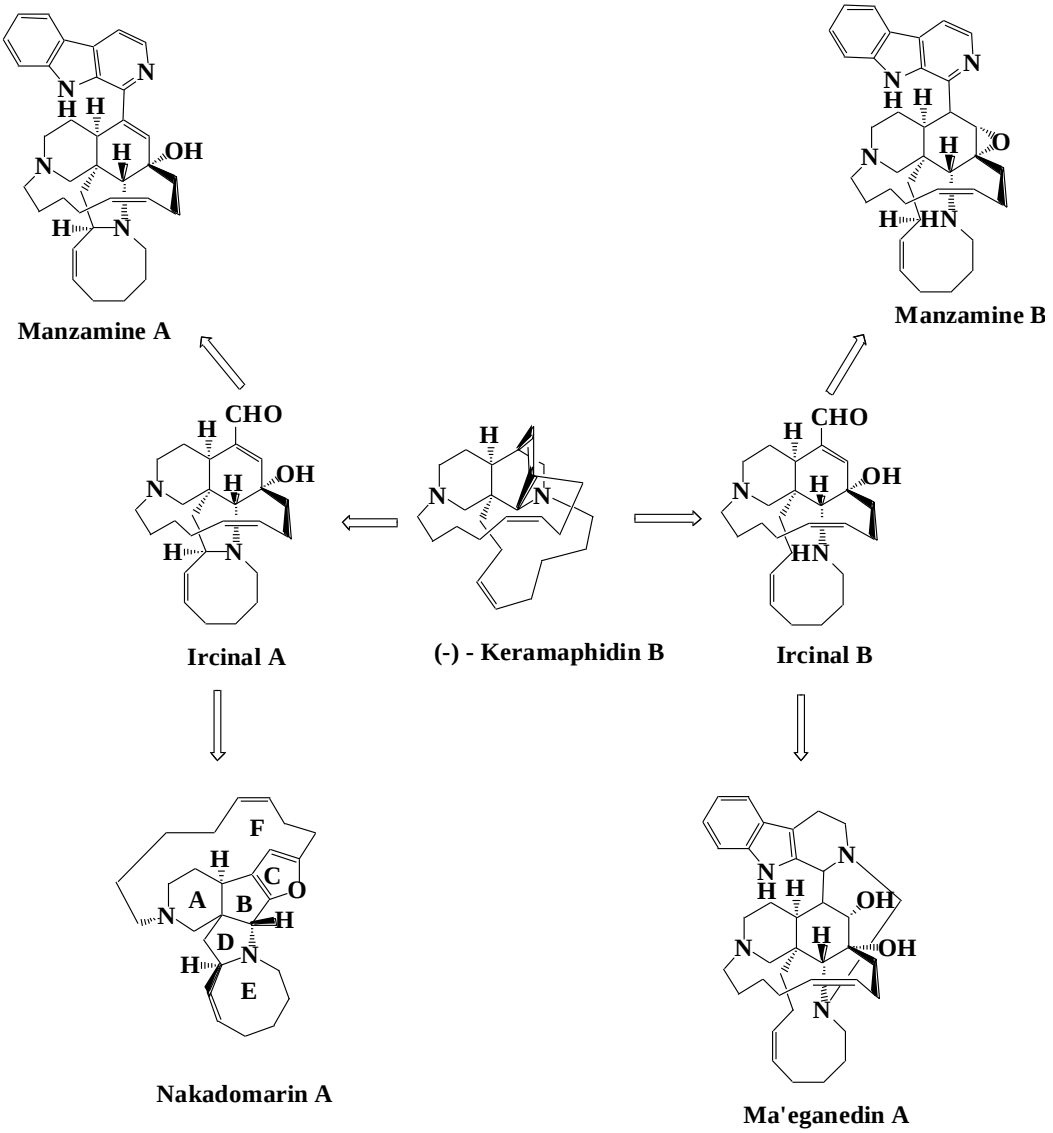
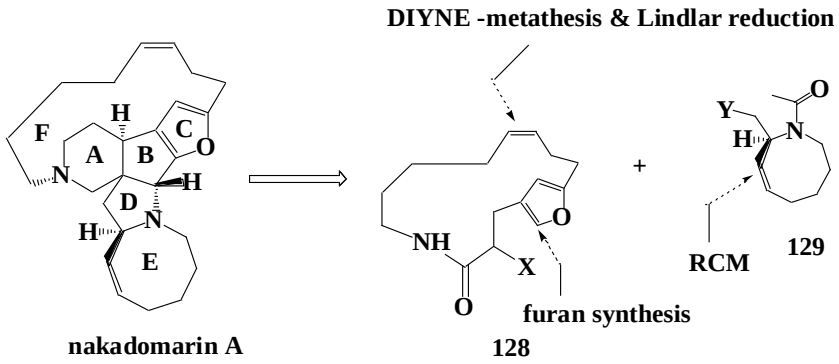


Figure 6 – Possible biosynthetic transformations of the Manzamine family

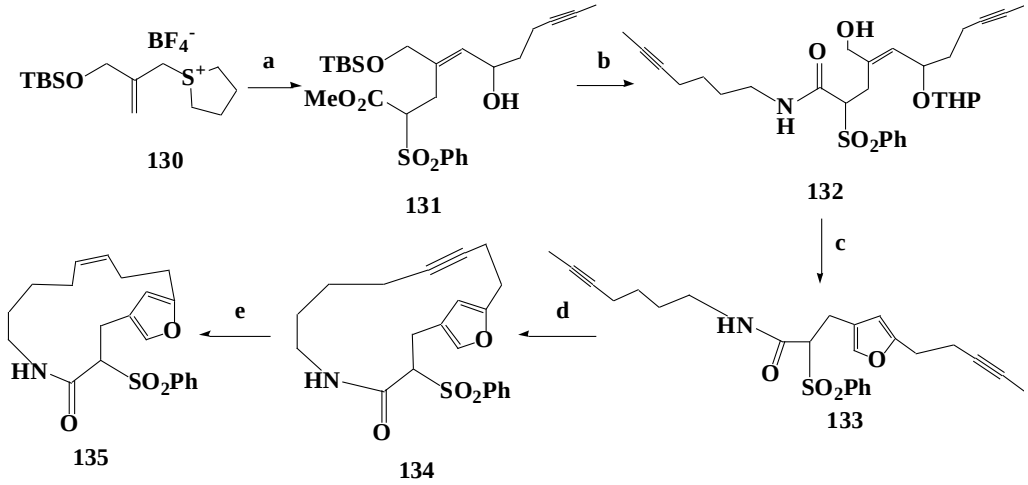
FÜRSTNER'S APPROACH

Most attempts to synthesize nakadomarin A have focused on the stereoselective construction of the ABCD central core which involves a reactive furan ring, before assembling the EF rings. A disconnection was proposed by Fürstner and co-workers, however, based on elaborating the most challenging structural features early on in the synthesis to ensure that the requisite chiral centers are established long before the latter stages of the synthesis.[103] The challenging aspects include the 15-membered ring with a (*Z*)-configured double bond **128**, the strained hexahydroazocine moiety **129**, and the furan sub-unit (Scheme **41**). These motifs would then have strategically placed functionalities that would facilitate the coupling of the sub-units after their synthesis.



Scheme 41 – Fürstner's disconnection of nakadomarin A

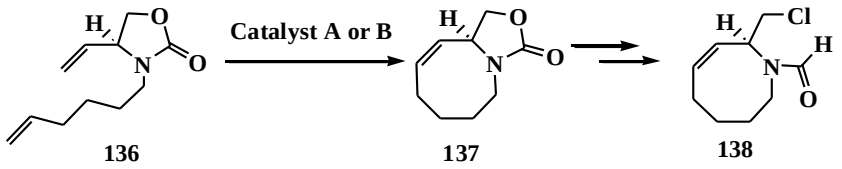
The synthesis started with sulfonium salt **130**, which was obtained from commercially available 3-chloro-2-chloromethyl-1-propene[104] and continued through an elaborate scheme involving the construction of the furan ring with the necessary substitutions and diyne functionality **131**. The diyne **131** was subjected to diyne RCM metathesis to give the desired cycloalkyne **134** in 90% yield followed by Lindlar reduction to offer the (*Z*)-alkene **135** which is an equivalent of **128** in 97% yield (Scheme **42).** [103]



[a] i) ^{t}BuLi, 4-hexynal; 71% ii) methy(phenylsulfonyl)acetate, Pd(PPh$_3$)$_4$; 81%. [b] i) DHP, HCl; 89% ii) TBAF, NH$_4$F; 81% iii) 1-amino-5-heptyne, NaCN; 96%. [c] i) MnO$_2$ ii) aq. HCl; 96%. [d] (^{t}BuO)$_3$W≡CCMe$_3$; 90%. [d] Lindlar reduction; 97%

Scheme 42 - Synthesis of the 15-membered ring segment of nakadomarin A

The hexahydroazocine segment **129** was prepared using a literature procedure[105] via conventional RCM of diene **136** but using different ruthenium-based catalysts. The bicyclo[6.3.0]undecene **137** thus formed was readily converted into the chloride **138** (Scheme **43**).[103]



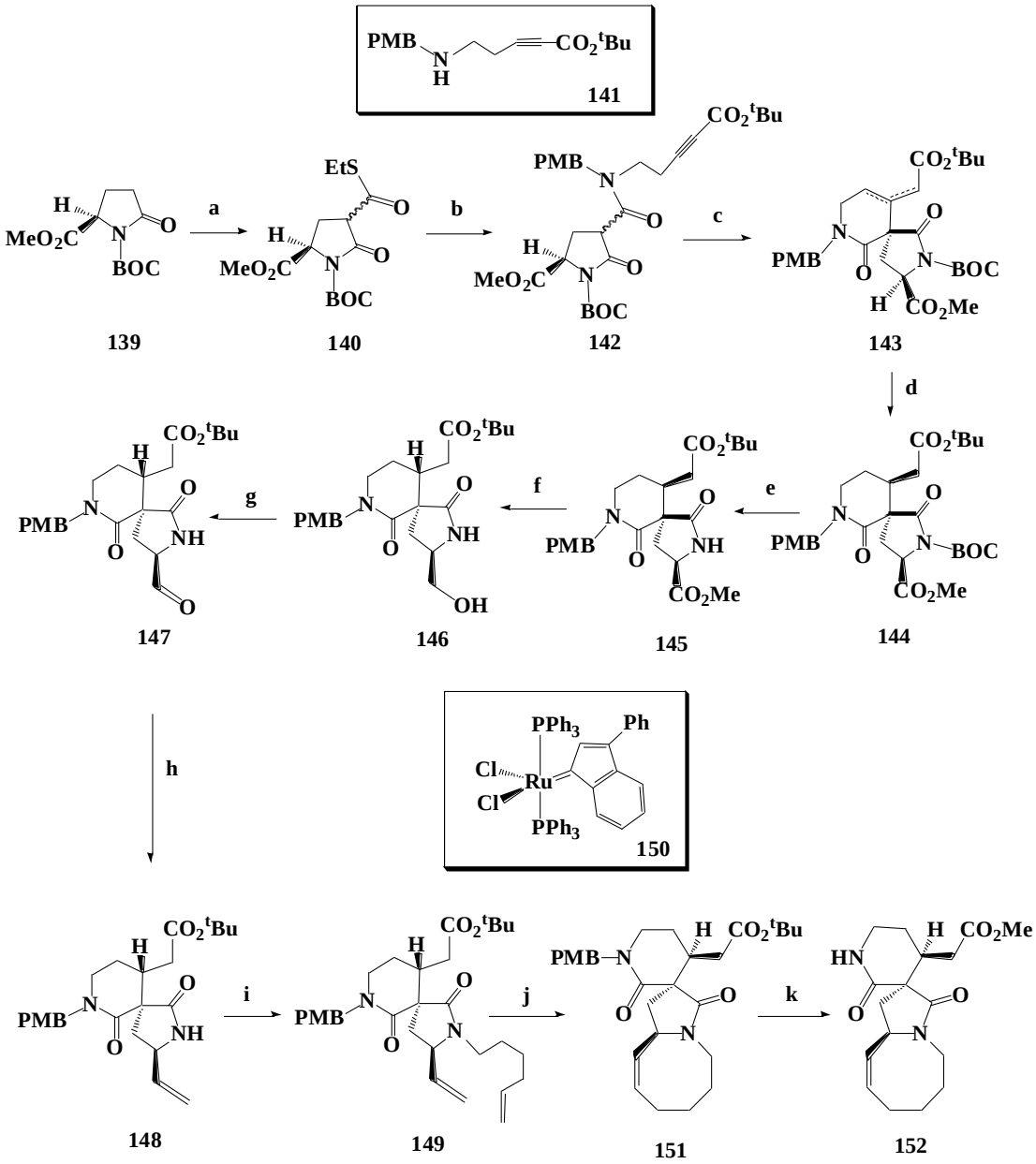
136 **137** **138**

A = $(PCy_3)_2Cl_2Ru$=CHPh (10%), 76% B = (p-cymene)$(PCy_3)RuCl_2$ / hν (10%), 72%

Scheme 43- Synthesis of the hexahydroazocine segment of nakadomarin A

Fürstner and co-workers followed later with synthesis of the fully functional ADE-ring system of nakadomarin A in which the quaternary centre was set with the correct absolute stereochemistry using Michael reaction to construct the AD rings and the E ring was formed by ring closing metathesis (RCM).[106] Starting with the methyl ester of (R)-(-)-pyroglutamic acid, the Michael substrate and the subsequent cyclisation product **152** were obtained by the protocol reported by Brands (Scheme 44).[107]

Brands and co-workers had first reported this novel and efficient approach to the pyrrolo[2, 3-i]isoquinoline (ABC) subunit of manzamines based on an intramolecular Michael reaction.[107] In the event, enantiomerically pure methyl ester of pyroglutamic acid was protected with the BOC group to give **139.** The lithium enolate of **139** was quenched with ethyl thiochloroformate to give the addition product **140** in 96% isolated yield. Treatment of a mixture of **140** and the acetylenic amino ester **141**, prepared using a standard Corey-Fuchs protocol[108] starting from propanolamine, with an equivalent of silver triflate in the presence of DIPEA as an acid scavenger gave **142** in 73% yield. Heating **142** with excess DIPEA in acetonitrile led to an intramolecular Michael reaction and gave **143**. This was followed by hydrogenation over palladium on charcoal in methanol to give the requisite bicyclic **144** with complete stereocontrol in 80% yield over the two steps (Scheme **44**).[106]



[a] i) 2eq LiHMDS, THF ii) CICOSEt, 96%. [b] 141, AgOTf, DIPEA, MeCN, 73%. [c] DIPEA, MeCN, reflux. [d] H_2 (1 atm), Pd/C, MeOH, 80% (over two steps). [e] $Mg(ClO_4)_2$ (25 mol%), CH_3CN, 50 °C, 99%. [f] $LiBH_4$, THF, r.t., 82%. [g] Dess -Martin periodinane, H_2O (1 equiv), CH_2Cl_2 , r.t., 78%. [h] CH_2I_2 , $Ti(OiPr)_4$, Zn, THF, r.t., 84%. [i] NaH, DMF, 0 °C, then 6-iodo-1-hexene, r.t., 88%. [j] Catalyst 150 (5 mol%), CH_2Cl_2 , reflux, 98%. [k] i) CF_3COOH, reflux; ii) Me_3SiCHN_2 , toluene/MeOH 3.5:1, 85%.

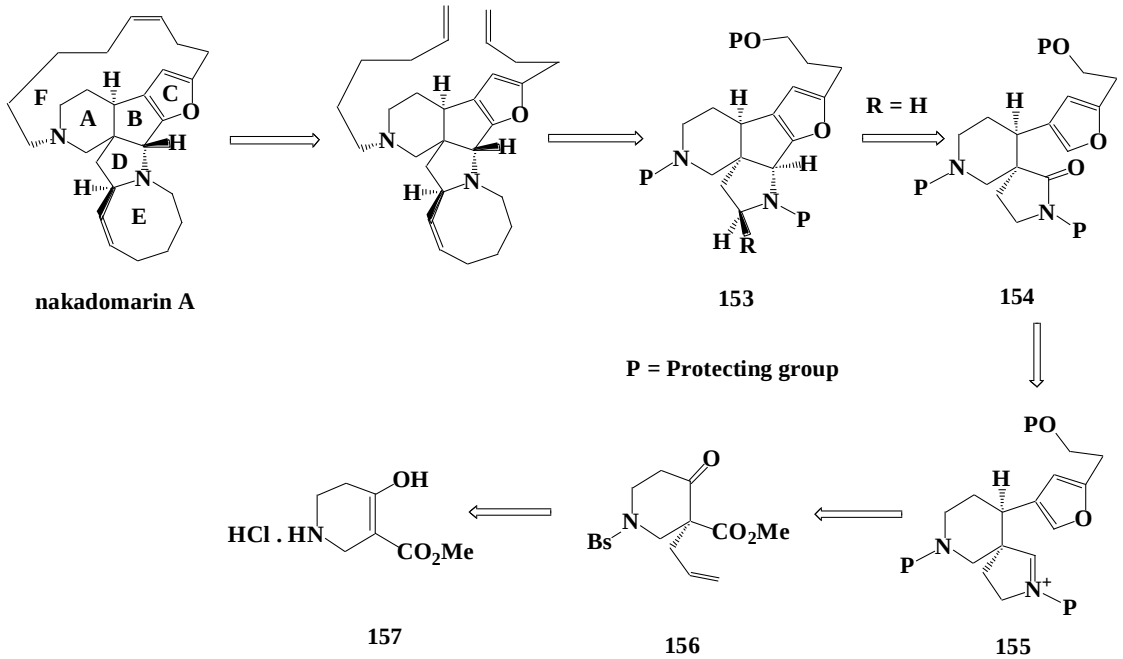
Scheme 44 – Fürstner's synthesis of the ADE ring motif of nakadomarin A

The BOC group of **144** (Scheme 44) was removed and the methyl ester of the bicyclic product **145** was selectively reduced with $LiBH_4$ to obtain **146**. The subsequent alcohol was then oxidised with Dess-Martin periodinane to obtain the aldehyde **147** which was then converted to the alkene **148** utilising the Takai-Nozaki protocol,[109] which involves using CH_2I_2 as the methylene source with $Ti(O\text{-}i\text{-}Pr)_4$ and activated zinc dust (Scheme **44**).

The alkene **148** was subsequently N-alkylated with 6-iodo-1-hexene to give the diene **149** which provides the required substrate for cyclisation to the eight-membered ring by RCM. The key RCM transformation proceeded nearly quantitatively when a dilute solution of the diene **149** in CH_2Cl_2 was heated to reflux in the presence of 5 mol% of the Grubbs-type phenylindenylidene catalyst (**150**) for 18 hours to afford the ADE motif **151** in 85% yield.[106] The PMB group was then removed with TFA which also led to removal of the *tert*-butyl group of the ester, exposing the carboxylic acid group, hence the carboxylic acid group was re-protected as the methyl ester **152**.

NISHIDA'S APPROACH

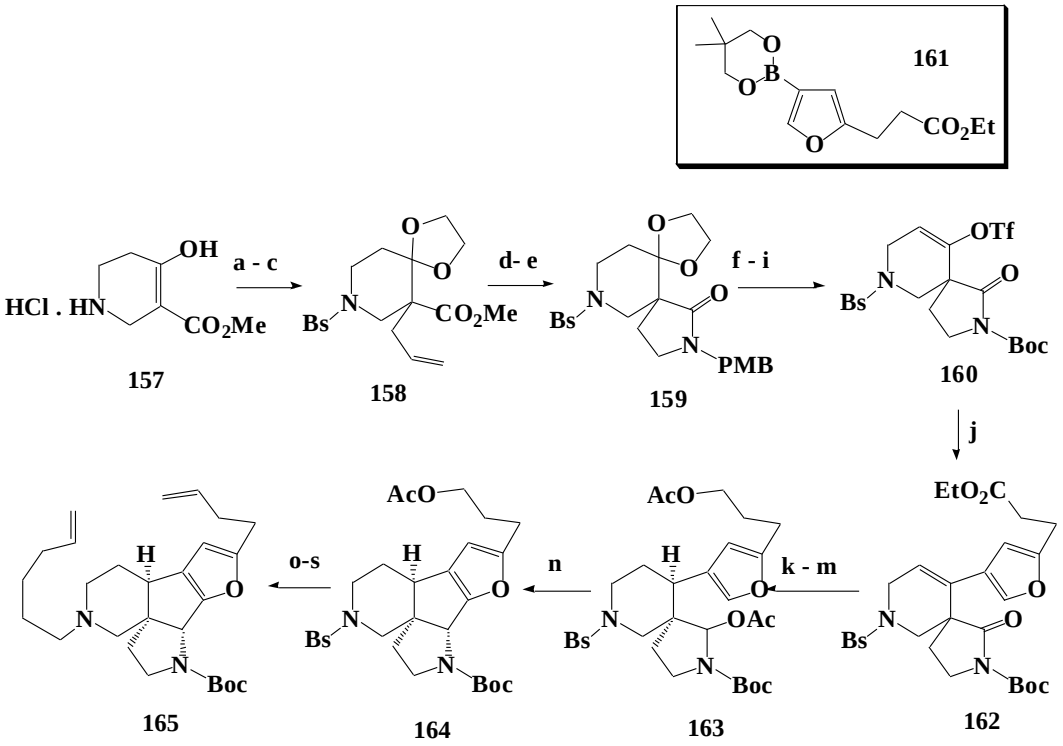
The synthesis of the ABCD ring system of nakadomarin A was reported by Nishida and Nakagawa using a retrosynthetic approach involving intramolecular cyclisation of a spiro-γ-lactam bearing a substituted furan ring (Scheme **45)**,[110] which was further simplified to commercially available methyl 4-oxo-3-piperidinecarboxylate hydrochloride **153**.



Scheme 45 – Nishida's disconnection of nakadomarin A

The synthesis of the spiro-γ-lactam bearing a substituted furan ring **162** was achieved in 10 steps from 4-oxo-3-piperidinecarboxylate hydrochloride **157** (Scheme **45**). The intramolecular cyclisation was achieved by DIBAL reduction of the spiro-lactam, acetylation followed by treatment with *p*-toluenesulfonic acid[111] to obtain the tetracyclic core of nakadomarin A.

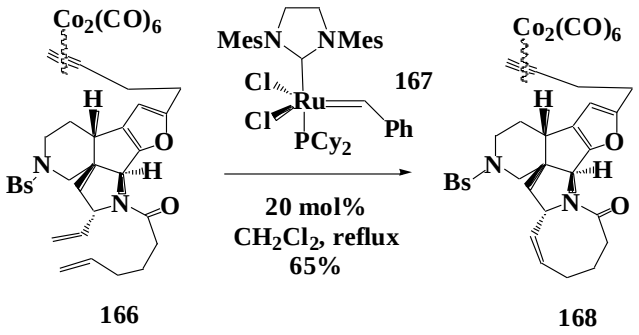
Attempted hydrogenation of the alkenic cyclisation product however was not selective and led to over-reduction, destroying the important furan moiety. This was overcome by hydrogenation of **162** prior to DIBAL reduction and cyclisation to **163**.[110] They also reported that if the furan ring of the boronic ester used to achieve the coupling of the spiro-lactam to the furan ring has the appropriate substitution, then it is possible to further achieve the installation of the F-ring of nakadomarin after synthesis of the core ABCD ring.



(a) $PhSO_2Cl$, $NaHCO_3$; (b) allyl bromide, K_2CO_3; (c) ethylene glycol, pTsOH; (d) OsO_4, $NaIO_4$, aq. THF; (e) PMB–NH_2, MeOH, AcOH, rt, 1 h, then $NaBH_3CN$, reflux, 2 h; (f) CAN, aq. MeCN, rt; (g) 70% $HClO_4$,CH_2Cl_2; (h) Boc_2O, Et_3N, DMAP;(i) $LiN(TMS)_2$, THF, -65°C, then $PhNTf_2$, 3°C; (j) 161, $Pd(PPh_3)_4$, LiCl, DME, aq. Na_2CO_3, 80°C, 7 h; (k) H_2, 10% Pd-C; (l) DIBAL, toluene, -65°C to rt; (m) Ac_2O, pyridine; (n) pTsOH, CH_2Cl_2; (o) 1N NaOH, rt, MeOH;(p) Dess–Martin oxid. rt, CH_2Cl_2; (q) $Ph_3P=CH_2$, THF–toluene; (r) Na, anthracene, DME, -65°C; (s) $TsO(CH_2)_4CH=CH_2$,iPr_2NEt, THF

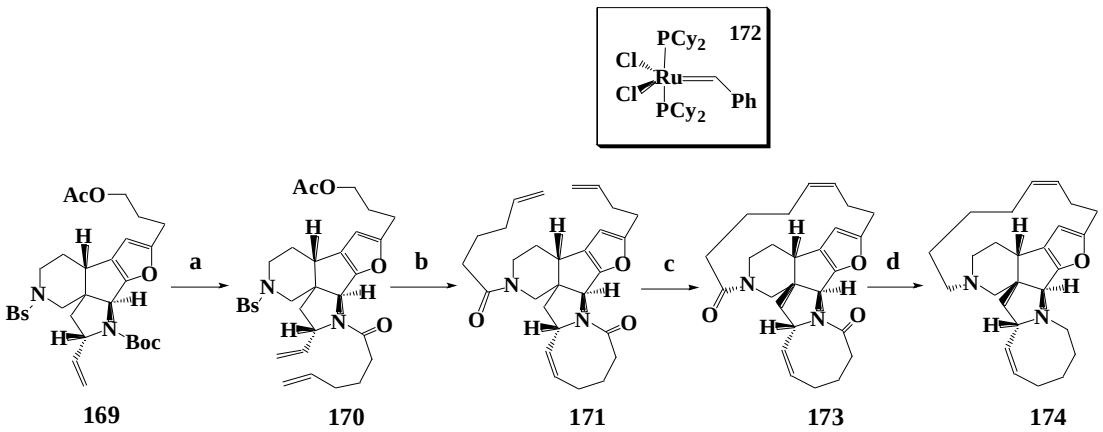
Scheme 46 – Nishida's synthesis of the ABCD core of nakadomarin A

Nishida and co-workers were able to perform an alkene RCM on **166**, an *N*-alkylated analogue of **165**.[113] This was done in the presence of a protected alkyne to obtain the E-ring of nakadomarin A and afforded the ABCDE pentacyclic structure **168** (Scheme **47**).



Scheme 47 – RCM of the ABCD core in the presence of a protected terminal alkyne

Having successfully constructed the ABCDE ring system of nakadomarin A, Nishida and co-workers attempted the first total synthesis of nakadomarin A[114] utilising methodology developed from their earlier model studies.[111-113] The significant difference was the introduction of an alkenic group with the right stereochemistry earlier on in the synthesis therefore the group appears beta to the nitrogen of the D-ring at the latter stages of the synthesis to facilitate the proposed RCM that would complete the E-ring (Scheme **48**).

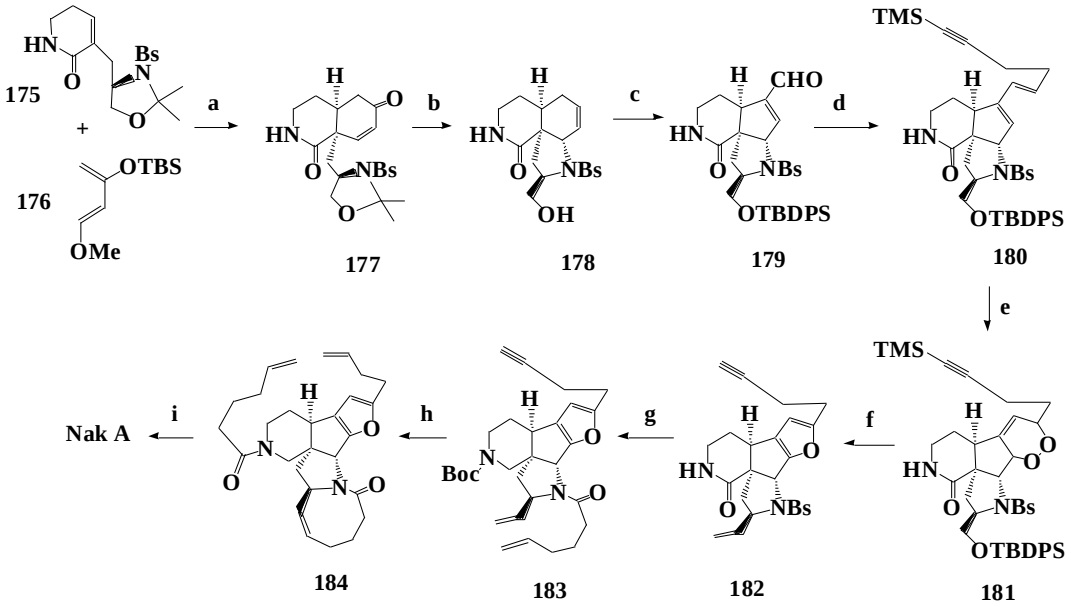


[a] i) TFA, CH_2Cl_2; ii) 5-hexenoic acid, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (WSC) . HCl, HOBt, 73% (4 steps) [b] i) 163 (20 mol %), CH_2Cl_2, 2 mM, 50 °C, 1.5 h; ii) 2 N NaOH, MeOH, rt, 1.5 h, 64% (2 steps); iii) Dess-Martin periodinane, 80%; iv) $Ph_3Pd{=}CH_2$, 72% v) Na, naphthalene; vi) 5-hexenoic acid, WSC.HCl, HOBt, 77% (2 steps) [c] 172 (15 mol %), CH_2Cl_2, 0.5 mM, 50 °C, 24 h, 26% (24Z), 44% (24E); [d] Red-Al, toluene, reflux, 86%

Scheme 48 – Nishida's synthesis of (+)-nakadomarin A

The nitrogen of the D-ring of **169** was deprotected and *N*-alkylated with 5-hexenoic acid to give the diene **170**, which was subjected to an alkene RCM to complete the E-ring in 73% yield. The C-ring substituent was then transformed to the required alkene group and the A-ring was also *N*-alkylated with 5-hexenoic acid to give the diene **171** which was then subjected to alkene RCM to complete the F-ring and yield **173** in 70% yield.[114] Selective reduction of both carbonyl functionalities of the amides of **173** gave **174** in 86% yield and completed the total synthesis. Unfortunately, the reaction yielded a mixture of the *Z* and *E* geometric isomers in a 2:3 ratio respectively. Disappointingly, results showed that the synthesis accomplished the first total synthesis of (+)-nakadomarin A, the non-natural enantiomer and not the expected (-)-nakadomarin A.[114]

In order to achieve the synthesis of (-)-nakadomarin A, Nishida and co-workers adopted a new strategy that involved the hydroisoquinoline **177**, obtained by a Diels–Alder reaction and having the required stereochemistry of the A-ring proton.[115] The D- ring was then constructed having the necessary substituent group that could be converted later on to obtain the alkene group required for RCM that would lead to the E-ring (**178**). The six-membered B ring was cleaved by ozonolysis to give an unstable bisaldehyde, which was recyclised to a five-membered ring by aldol condensation with *N*-methylanilinium trifluoroacetate to give the unsaturated aldehyde **179**. Wittig olefination of aldehyde **179** selectively gave the *Z* olefin **180**, which was converted to endoperoxide **181** by singlet oxygen.[115] The C-ring was synthesised by reaction of **181** with potassium tert-butoxide followed by treatment with strong HCl to yield the furan **182**.[116] Boc-protection of the -NH group of the A-ring, followed by removal of the Bs group and *N*-alkylation with 5-hexenoyl chloride gave the diene **183**, and set the stage for the RCM to the E-ring. The alkyne was, however, first protected as a dicobalt complex prior to treatment with the Grubbs catalyst as previously reported.[113] Successful cyclisation of the E-ring by RCM was followed by removal of the Boc group and *N*-alkylation with 5-hexenoyl chloride, whilst the terminal alkyne was also deprotected and reduced to the corresponding alkene **184**, setting the stage for the RCM, which was achieved using the Grubbs' catalyst **172**. The synthesis was completed by selectively reducing both carbonyl groups of the amides with Red-Al to afford (-)-nakadomarin A (Scheme **49**).[115]



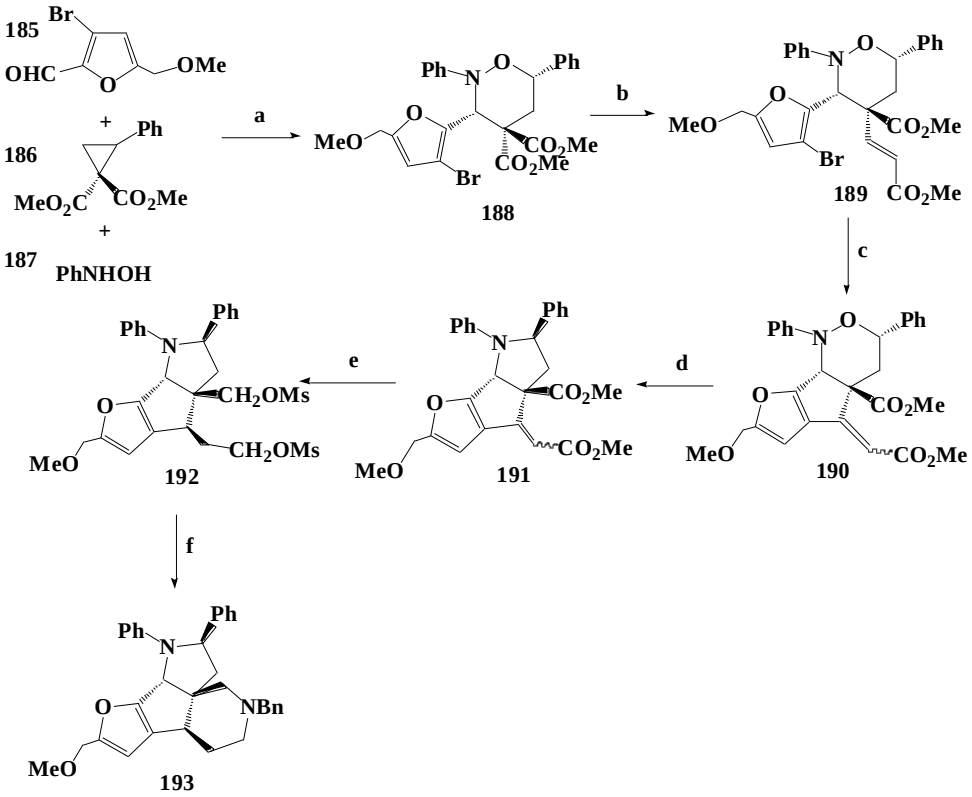
[a] neat, 180 °C, 1 h; then TFA, CH_2Cl_2, room temperature, 52% (diastereomer 35%). [b] i) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, CH_2Cl_2 /MeOH, -78 °C, 98% (d.r.=2:1); ii) HCl (6 N), benzene, reflux, 1 h, 70%; [c] i) TBDPSCl, imidazole; ii) Na/anthracene, DME, -65 C, 74% (two steps); iii) O_3, CH_2Cl_2, -78 C; then Me_2S, room temperature; iv) *N*-methylanilinium trifluoroacetate, THF, reflux, 75% (two steps); [d] $IPh_3PCH_2CH_2CH_2CCTMS$, NaH, THF, -78 °C - RT, 76%; [e] O_2, halogen lamp, Rose Bengal, CH_2Cl_2 /MeOH, 0 °C, quant. (14a/14b=1.2:1) [f] i) *t*BuOK, THF, -78 °C; then HCl (6 N), room temperature, 88% (from 14a), *t*BuOK, THF, -30 °C, then HCl (6 N), room temperature, 69% (from 14b); ii) Dess–Martin oxidation, 90%; iii) $TMSCH_2MgCl$, Et_2O, room temperature, 83% (d.r.=2:1); iv) $BF_3 \cdot Et_2O$, CH_2Cl_2, room temperature; v) K_2CO_3, MeOH, 81% (two steps); [g] i) Boc_2O, DMAP, Et_3N, CH_2Cl_2, 93%; ii) DIBAH, toluene, -78 °C; iii) Et_3SiH, $BF_3 \cdot Et_2O$, CH_2Cl_2, -78 °C, 84% (two steps); iv) Na/naphthalene, DME, -65 °C; v) 5-hexenoyl chloride, Et_3N, CH_2Cl_2, 92% (two steps); [h] i) $Co_2(CO)_8$, CH_2Cl_2, 91%; ii) Grubbs catalyst 167 (25 mol%), CH_2Cl_2 (to 1.0 mm) reflux, 1.5 h, 83%; iii) nBu_3SnH, benzene, 65 °C, 75%;iv) TFA, CH_2Cl_2 ; v) 5-hexenoylchl oride, Et_3N, CH_2Cl_2, 92% (two steps); [h] i) Grubbs catalyst 172 (20 mol%), CH_2Cl_2 (to 0.5 mm), reflux, 24 h, Z isomer 26%, E isomer 46%; ii) Red-Al, toluene, reflux, 92%.

Scheme 49 – Asymmetric synthesis of (-)-nakadomarin A by Nshida and co-workers

KERR'S APPROACH

Young and Kerr reported the synthesis of the tetracyclic core of nakadomarin A[117] using a synthesis of pyrrolidine rings by a formal homo [3 + 2] dipolar cycloaddition of nitrones with cyclopropanes with excellent diastereoselectivity.[118] It involves the cleavage of the *N-O* bond of the tetrahydrooxazine intermediate, conversion of the resultant hydroxyl functionality to a leaving group, and the subsequent ring closure to yield the pyrrolidine ring.[119] The first step involves the three-component coupling of phenylhydroxylamine **187**, furfural **185**, and cyclopropane **186** to produce the adduct **188** in 74% yield (Scheme **50**).[120] Selective DIBAL reduction of the equatorial ester of **188** to the aldehyde followed by Horner-Emmons olefination produced the enoate **189**, which underwent Heck

cyclisation to **190**. Cleavage of the *N-O* bond and recyclisation to the pyrrolidine afforded the tricyclic compound **191**. Reduction of the enoate double bond with nickel boride yielded the saturated diester followed by reduction of the diester to the diol and preparation of the dimesylate to obtain **192**. The synthesis of the piperidine ring was achieved by double mesylate displacement with benzylamine to give the tetracycle **193**. This model thus provided a protocol for the synthesis of the tetracyclic core of nakadomarin A and onward to the natural product.[117]

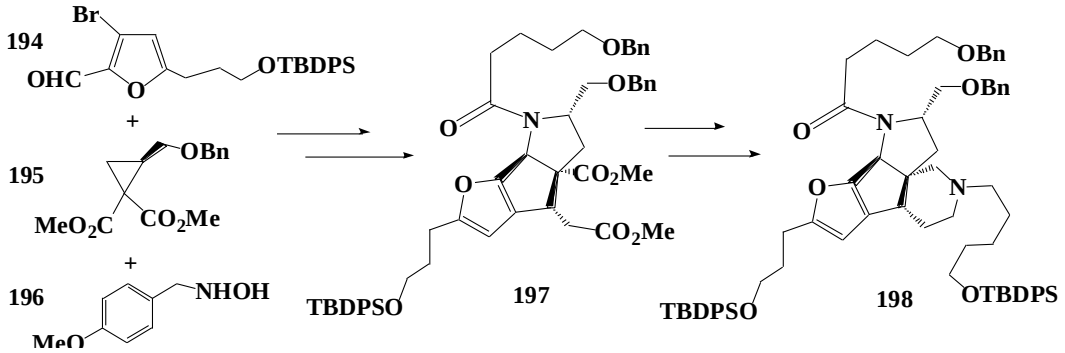


[a] 10 mol% $Yb(OTf)_3$, 4Å MS / toluene /rt, 74%. [b] i) DIBAL, CH_2CL_2, -78 °C, 95%; ii) $(MeO)_2P(O)CH_2CO_2Me$, t-BuOK / THF / rt, 73%. [c] $Pd(PPh_3)_4$ / $AgSO_4$, Et_3N / DMF, 78%. [d] i) H2, Pd/C, MeOH; ii) MsCl/ Et_3N/CH_2Cl_2, 66% (2 steps). [e] i) $NiCl_2/NaBH_4$, MeOH, -40 °C, 66%; ii) $LiAlH_4$/ THF/ 0 °C, 70%; iii) MsCl, Et_3N/ DMAP, CH_2Cl_2 -78°C, 95%. [f] $BnNH_2$, THF/EtOH, reflux, 95%

Scheme 50 - Young and Kerr's synthesis of the tetracyclic core of nakadomarin A

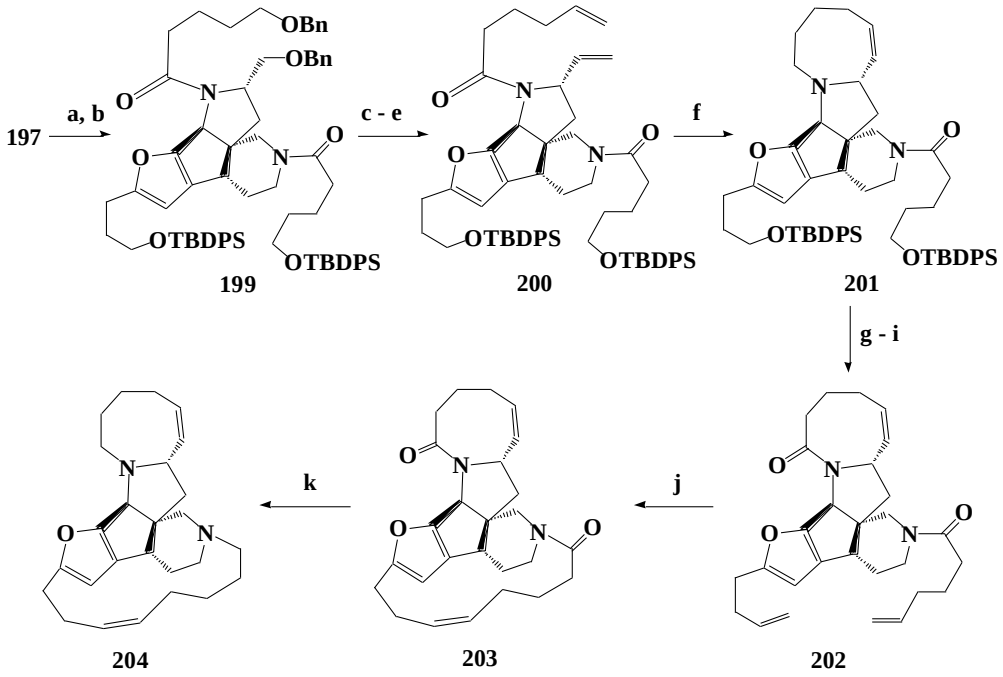
Armed with this information, Young and Kerr synthesised the pyrrolidine **197** as previously[117] and progressed this onward to the tetracycle **198** with an aim to completing the synthesis of the natural product (Scheme **51**).[121] However, the nakadomarin A was produced as a mixture of stereoisomers with the inseparable *E*-isomer after RCM of the alkenic intermediate that formed the F-ring**.** Analysis of the structure showed that in contrast, Nishida's substrate **184** introduces an amide into the 15-membered macrocycle

that likely decreases the flexibility of the metathesis product, allowing for separation of the *E* and *Z*-isomers by standard silica flash column chromatography.



Scheme 51 - Kerr's *N*-alkylation of the tetracyclic products

In order to circumvent this problem, the tricyclic **197** was treated with ethanolic ammonia and the resulting secondary amine acylated with 5-*tert*-butyldiphenylsiloxy-*n*-pentanoyl chloride to produce the bisamide **199**. Bisdebenzylation, oxidation, and Wittig olefination produced metathesis substrate **200**. Azocine **203** was prepared by treatment of diene **200** with Grubbs' second generation metathesis catalyst **167**. Removal of the silyl groups, oxidation to the bisaldehyde and olefination produced the diene **202** which set the stage for another RCM. Treatment of **202** with Grubbs' first generation catalyst **172** gave the desired *cis*-cycloalkene **203** along with the undesired trans-isomer. Reduction of the amido carbonyls with Red-Al gave *ent*-(+)-nakadomarin A **204** in 20% yield over three steps (Scheme **52**).[121]



(a) NH_3, EtOH/THF (10:1), reflux; (b) $ClC(O)(CH_2)_4OTBDPS$, NEt_3, CH_2Cl_2, 0 °C to room temperature, 77% (two steps); (c) BCl_3, CH_2Cl_2, -78 °C to -50 °C to -78 °C, 71%; (d) IBX, DMSO, room temperature; (e) t-BuOK, $MePPh_3Br$, THF/toluene, room temperature, 30-45% (two steps); (f) 20 mol % 167, CH_2Cl_2 (0.7 mM), reflux, 84%; (g) MeOH, AcCl, room temperature; (h) Dess-Martin periodinane, CH_2Cl_2, 0 °C to room temperature, 70% (two steps); (i) t-BuOK, $MePPh_3Br$, THF/toluene, room temperature; (j) 30 mol % 172, CH_2Cl_2 (0.2 mM), reflux, 28% *E*-isomer (two steps), yield for *Z*-isomer given after reduction; (k) Red-Al, toluene, reflux (20%, three steps).

Scheme 52 – Kerr's total synthesis of (+)-nakadomarin A

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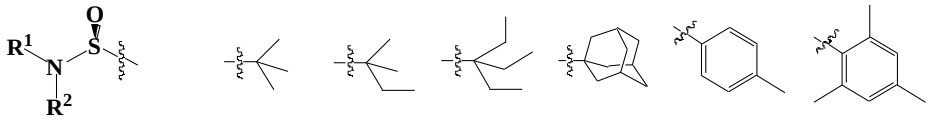
2.0 Results and Discussion

2.1 Towards the syntheses of sulfinimines

There are many *N*-alkyl and *N*-aryl sulfinyl protecting groups which have been widely used in synthesis including the *tert*-butyl, tolyl and mesityl groups (Figure **7**).[1]



205 **R^1, R^2 = H, alkyl, aryl**

Figure 7 - Alkyl and aryl groups used with the sulfinyl protecting group

Our group's interest in chiral sulfinimines stems from previous work in the group on the transformation of chiral *tert*-butylsulfinimines into aziridines.[2] The *tert*-butylsulfinyl group was found to be a good directing group for use towards aziridination, offering good yields and excellent diastereoselectivities. This promising method however had its drawbacks as further unpublished work in the group showed that:

- The *tert*-butylsulfinyl protecting group proved to be fairly difficult to remove without ring opening of the aziridine.
- Routes to the *tert*-butylsulfinamide, required for the synthesis of *tert*-butylsulfinimines, are fairly costly in terms of reagents and tedious in terms of practical deliberations.

Davis, however, reported that *N*-arylsulfinyl protecting groups are fairly easy to remove from aziridines using MeMgBr or MeLi.[3] Various arylsulfinyl groups were tested and the mesitylsulfinyl group was reported to be the best offering almost quantitative yields and similar directing group ability to the *tert*-butylsulfinyl group. However, the drawbacks of Davis' reported method are:

- Mesitylsulfinyl reagents are relatively expensive.
- The routes to the mesitylsulfinyl group are lengthy.[3b]

We therefore set out to address some of the key issues involved with the synthesis of the promising mesitylsulfinimines. Our aims for the project included:

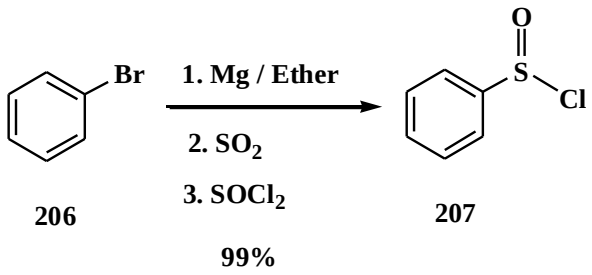
- To find a short and relatively inexpensive route to aryl sulfinimines.
- Investigate a wide range of aldehydes with the aim of establishing the scope of the methodology.
- Investigate the use of an ylide approach to vinyl aziridines which should give us a great flexibility in the range of vinyl aziridines available.
- Employ parallel synthesis techniques to speed the process of substrate screening.

Our primary aim at this stage was to find a short and relatively inexpensive route to arylsulfinyl groups especially mesitylsulfinyl groups, which would provide an easy entrance to mesitylsulfinamides and subsequently mesitylsulfinimines.

2.1.1 Synthesis from Sulfinyl Chlorides

Sulfinyl chlorides are versatile substrates in the preparation of sulfinyl derivatives such as sulfinates, sulfinamides and sulfoxides. The most commonly used methods for their preparation are based on the oxidation of their sulfenyl precursors.[4,5] As mentioned previously in this report, Prinzbach and Netscher[6] reported a relatively simple method of converting thiols to their corresponding sulfinyl chlorides, which can be readily converted to their corresponding sulfinamides. We initially explored this procedure but it was limited by lack of availability of the appropriate thiols for our proposed synthesis and we therefore gave up on the procedure.

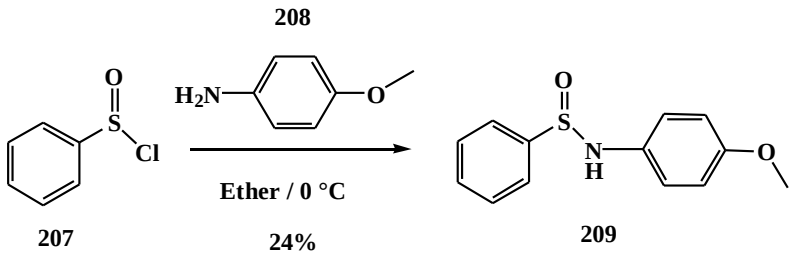
We found a procedure that involved the one-pot synthesis of sulfinyl chlorides from Grignard reagents reported by Ellman and co-workers.[7] This procedure afforded the simplest route to the sulfinyl chloride and involved adding the Grignard reagent to condensed sulfur dioxide to form the sulfinate, which was then converted to the sulfinyl chloride by addition of thionyl chloride (Scheme **53**). Using this procedure, we were able to produce benzenesulfinyl chloride as adjudged by ^{1}H-NMR and ^{13}C-NMR.



Scheme 53 – Preparation of racemic benzenesulfinyl chloride

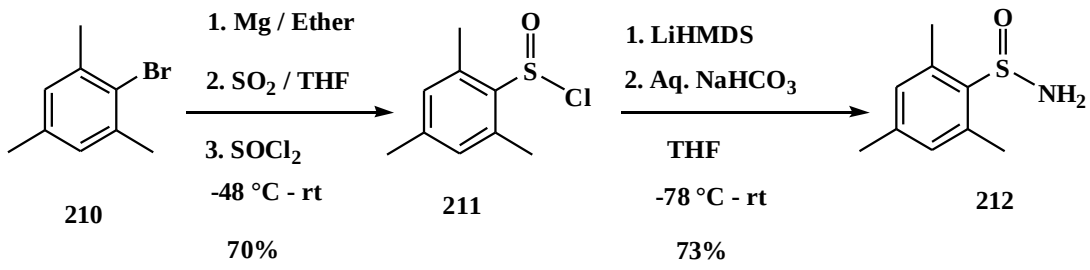
We could not use mass spectroscopy results to positively prove the synthesis of the sulfinyl chloride because it was very sensitive, but we were however fortunate to find literature in which benzenesulfinyl chloride was reacted with a number of arylamines to form the corresponding sulfinamides and this enabled the sulfinyl chlorides to be positively identified.[8]

When benzenesulfinyl chloride (**207)** was reacted with two equivalents of *p*-anisidine **208** in ether at 0 °C (Scheme **54**), purple crystals of the benzenesulfinamide **209** were obtained and after recystallisation from pentane, the melting point was found to be 129 °C, similar to that reported.[8] Our ^{1}H-NMR and ^{13}C-NMR analysis of the product was also positive and this was further confirmed by the mass spectrometry results.



Scheme 54 – Reaction of benzenesulfinyl chloride with *p*-anisidine

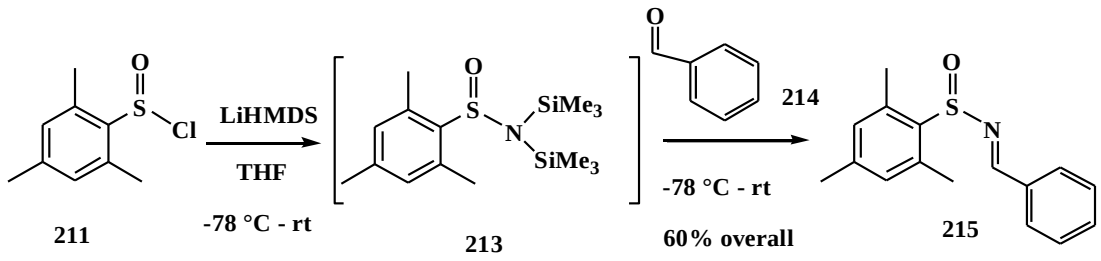
This encouraged us to attempt the synthesis of mesitylsulfinyl chloride **211** which would offer us a route to mesityl sulfinimines. This was accomplished by converting 2-bromomesitylene to its corresponding Grignard reagent and adding it to condensed sulfur dioxide and adding thionyl chloride to the reaction mixture (Scheme **55**). From our previous experiences with sulfinyl chlorides and from available research, we decided against attempting any purification of the crude mixture. Though to the best of our knowledge, there was no precedence of adding metal amides to sulfinyl chlorides, we envisaged that such a reaction is plausible due to the fact that sulfinates have been reported to react with LiHMDS to yield the corresponding sulfinamides.[9]



Scheme 55 – Preparation of mesityl sulfinamide 212

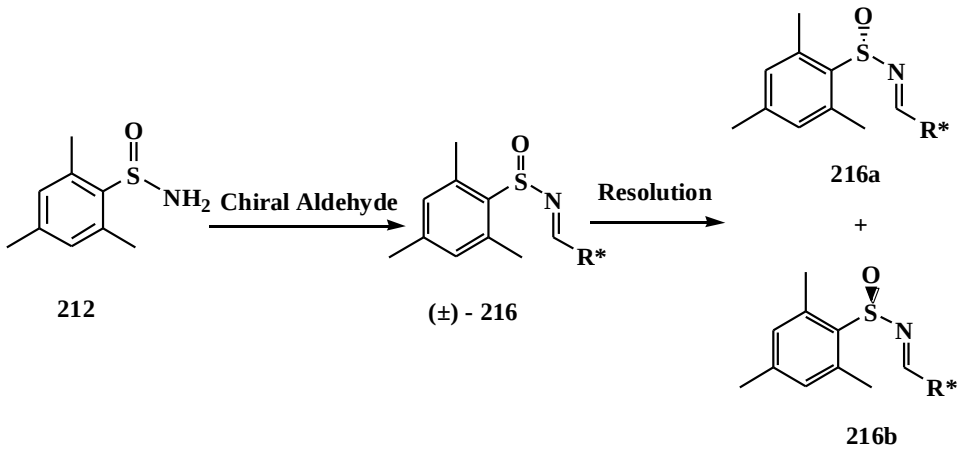
We obtained the mesitylsulfinamide **212** by first reacting sulfinyl chloride **211** with LiHMDS at –78 °C, quenching with saturated aqueous NH_4Cl solution and purification by column chromatography to afford **212** in 73% yield (Scheme **55**). The main advantage of this procedure was that the whole process from the condensation of sulfur dioxide to the addition of LiHMDS was a one-pot procedure but its disadvantage was that the sulfinamide thus produced was racemic. We were therefore faced with finding a way of resolving the sulfinamide before it would be useful in any future asymmetric synthesis.

Davis and co-workers reported a one-pot procedure,[9] which involves conversion of sulfinates to sulfinamides and the subsequent condensation of the sulfinamide with an aldehyde. We were able to subsequently obtain the sulfinimine **215** in 60% yield, by successfully adopting this method (Scheme **56**).



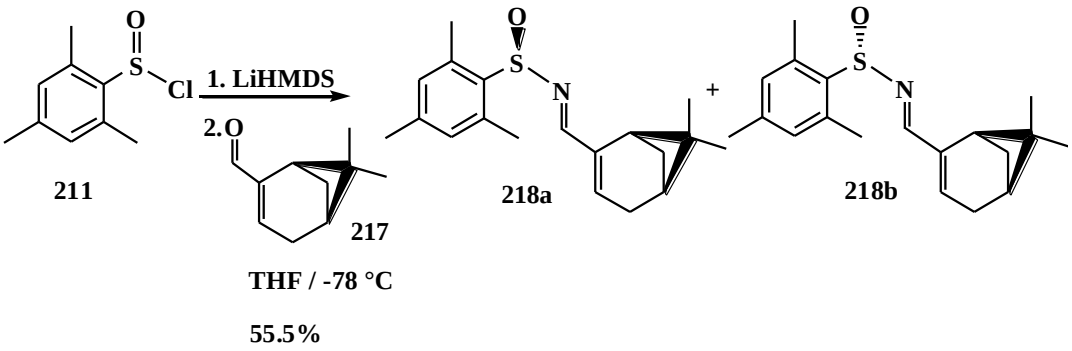
Scheme 56 – One pot synthesis of mesitylsulfinimines from mesitylsulfinyl chloride

This success meant that we were able to obtain our sulfinimine in a one-pot reaction beginning with the condensation of the sulfur dioxide. Having successfully established this protocol for obtaining mesityl sulfinimines, we turned our attention to finding ways of obtaining enantiopure sulfinimines. We postulated that resolution could be achieved by reacting the racemate **212** with an enantiopure chiral aldehyde to form the corresponding sulfinimines (Scheme **57**). This would yield a mixture of diastereoisomers and hopefully, they can be separated based on their physical properties, and then hydrolysed to yield the enantiopure sulfinamides.



Scheme 57 – Resolution of the racemic mesitylsulfinamide

Our first attempt involved the use of (-)-myrtenal as the chiral aldehyde mainly due to its availability in our laboratory and also its bulky nature (Scheme **58**).



Scheme 58 – Preparation of myrtenal derived sulfinimine

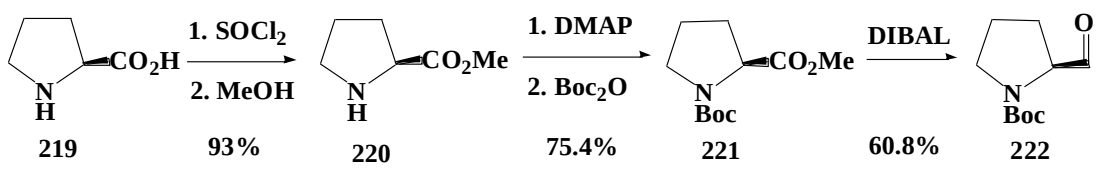
The mesitylsulfinyl chloride (**211**) was reacted with LiHMDS at –78 °C, and allowed to warm to room temperature over several hours until the reaction was completed as determined by TLC. Myrtenal **217** was then added and the mixture stirred until completion as determined by TLC. The ^{1}H-NMR of the product obtained after purification by column chromatography showed the presence of two diastereomeric sulfinimines **218a** and **218b** in a 1:1 ratio. The TLC also showed two overlapping spots.

This good result was, however, tempered by the fact that it proved practically impossible to clearly separate the diastereomeric mixture by column chromatography or selective crystallisation. We were therefore forced to abandon the use of this aldehyde after several

failed resolution attempts and the mixture was obtained in 55% combined yield. We thought that since the chiral centre in myrtenal was not adjacent to the imine functionality in the corresponding sulfinimine, this might account for the lack of selectivity in terms of their physical properties. We therefore decided to use a different chiral aldehyde which would form a sulfinimine that has the two chiral centers in the molecule very close to each other and this we hoped would boost their diasteroeselectivities and hence afford a means of separation.

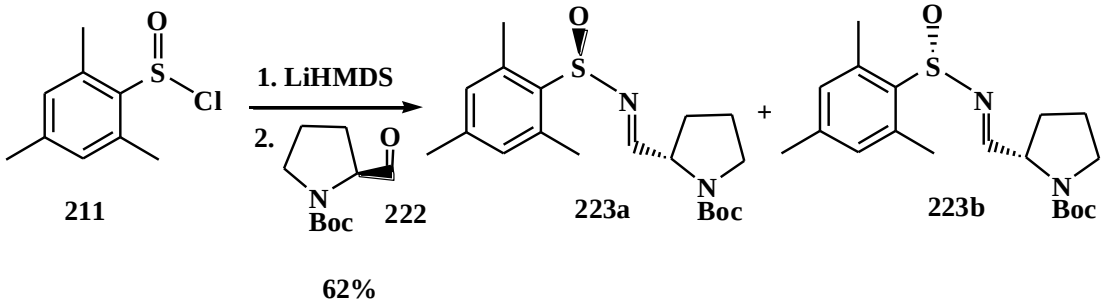
We therefore set out to find another chiral aldehyde. It was postulated that the corresponding aldehyde of *N*-protected *L*-proline would be a good candidate for such an attempt, and its bulky nature would hopefully offer another enhancement to the physical properties of the sulfinimines that would be formed, and hence boost our chances of separating them.

L-proline was esterified by reacting with methanol and thionyl chloride at 0 °C to afford the methyl ester **220** as a colourless oil in 93% yield after silica gel column chromatography. The methyl ester **220** was then *N*-protected with the *tert*-butyloxycarbonyl (BOC) group by reaction with di-*tert*-butyl dicarbonate (BOC-anhydride) in diethyl ether at 0 °C to offer the *N*-BOC protected ester **221** in 75% yield. The ester functionality of **221** was then reduced with DIBAL in toluene at -78 °C. The reaction was quenched with 10 mL of methanol and warmed to -40 °C and stirred with Rochelle's salt for two hours to turbidity and break-up the emulsion formed. The two phases obtained were separated, and the aqueous layer was extracted with ethyl acetate and concentrated in under reduced pressure. The residue was purified by silica gel column chromatography to obtain the corresponding aldehyde **222** in **61**% yield (Scheme **59**).



Scheme 59 – Preparation of *L*-proline derived *N*-protected aldehyde

As previously, the mesitylsulfinyl chloride **(211**) in THF at -78 °C was reacted with LiHMDS and warmed to room warm to room temperature over several hours until the reaction was completed as determined by TLC, followed by addition of the aldehyde **222** and the mixture was then stirred until completion. Satisfyingly, we were able to obtain a 62% yield of the two diastereomeric sulfinimines **223a** and **223b** in a 1:1 ratio (Scheme **60**) as adjudged by ^{1}H-NMR.



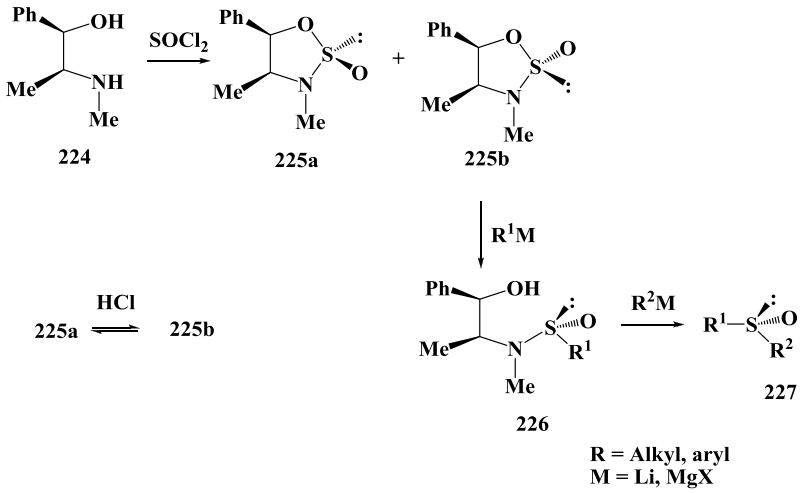
Scheme 60 – Resolution with *N*-BOC protected aldehyde from *L*-proline

Unfortunately however, our attempt to separate the diastereomeric mixture of sulfinimines **221a** and **221b** by column chromatography or selective crystallisation was again unsuccessful.

Whilst the resolution method using chiral aldehydes appeared to be a relatively simple solution, we decided that to continue a search for a suitable aldehyde was not a fruitful use of time and thus we changed tactics to asymmetric synthesis. We were hampered from pursuing this “resolution” further by the relatively expensive cost of chiral aldehydes and the fact that up to 50% of the product may not be of any use in further synthesis.

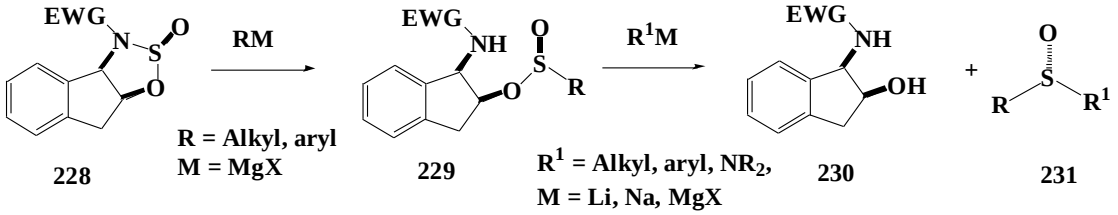
2.1.2 Synthesis from amino alcohols

Wudl and Lee[10] reported the synthesis of 1,2,3-oxathiazolidine-2-oxide derived from (-)-ephedrine during an investigation on the synthesis of optically active sulfoxides in 1973. The scheme involved synthesis of the 1,2,3-oxathiazolidine-2-oxide **225** by treating (-)-ephedrine with thionyl chloride and an appropriate base to close the acyclic structure of the substrate. This was followed by selectively cleaving the more reactive S-O bond of the 1,2,3-oxathiazolidine-2-oxide with carbon nucleophiles to produce acyclic sulfonamide derivatives **226** which are then reacted with another carbon nucleophile to the give the optically active sulfoxides **227** (Scheme **61**).



Scheme 61 – Wudl and Lee's synthesis of chiral sulfoxides

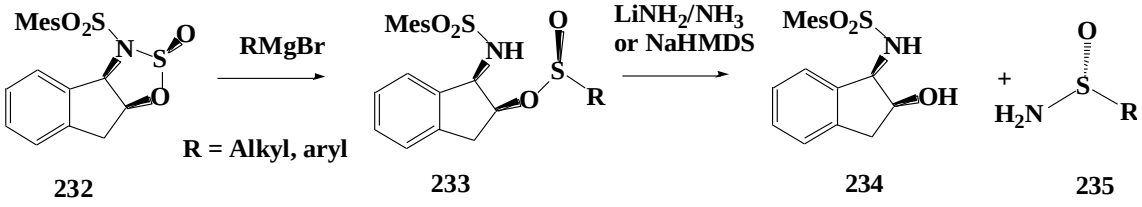
Wudl and Lee's work, however, had its drawbacks which include low yields and enantioselectivities, as well as the fact that it was relatively difficult to cleave the S-N bond of the acyclic sulfonamide derivatives formed after the addition of the first nucleophile. Since then only a few others[11] have used this work. However in 2002, Senanayake and co-workers[12] reported a modification of the Wudl and Lee procedure using (1*R*,2*S*)-*N*-tosyl-aminoindanol instead of (-)-ephedrine and altering the order of cleavage of the 1,2,3-oxathiazolidine-2-oxide, thus selectively cleaving the S-N bond first instead of the S-O bond in the presence of appropriate nucleophiles leading to formation of a "sulfinate-like" intermediate **229** (Scheme **62**).



Scheme 62 - Selective reactivities of nucleophiles with 1,2,3-oxathiazolidine-2-oxide

The reversal of the order of cleavage was accomplished by activation of the nitrogen of the 1,2,3-oxathiazolidine-2-oxide **228** with an appropriate electron-withdrawing substituent which leads to a considerable weakening of the S-N bond relative to the S-O bond, hence the reversal of the order of cleavage. This overcame one of the major problems associated with the Wudl scheme since the S-O bonds of sulfinates are far more easily cleaved than their corresponding S-N bonds of sulfonamides.

The synthesis of the S-O transfer agent **232** was carried out as follows: (1*R*,2*S*)-aminoindanol was *N*-protected with mesitylsulfonyl group, and the corresponding (1*R*,2*S*)-1-*N*-tosyl-aminoindanol that resulted was treated with 1.5 equiv of thionyl chloride, followed by a slow addition of 2.5 equiv of TEA at -45 °C over several hours. Quenching the reaction with an aqueous solution of sodium bicarbonate at -45 °C provided a clean 75:25 diastereomeric mixture of *endo*/*exo*-**232** with yields in excess of 98%. When the *endo*-**232** in THF at -78 °C was treated with *tert*-butylmagnesium bromide solution, it significantly lead to cleavage of the S-N bond in the presence of the S-O bond of **232** to give (1*R*,2*S*,*R*)-**233** sulfinate ester in >95% yield as a stable and crystalline solid (Scheme **63**).

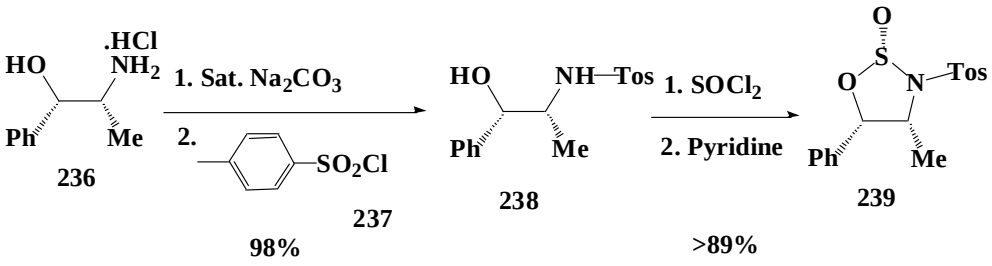


Scheme 63 – Use of 1,2,3-oxathiazolidine-2-oxide in the synthesis of sulfinamides

Exposure of the sulfinate **233** to lithium amide in liquid ammonia or sodium hexamethydisilasane (NaHMDS) solution at -78 °C in THF led to cleavage of the S-O bond in an S_N2 fashion with inversion of configuration at the S atom to afford of (*R*)-*tert*-buanesulfinamide **235** (R = ^{t}Bu) in more than 90% yield and 99.5% ee with an excellent recovery of the chiral auxiliary **234** (>96%). This procedure was successfully applied to a wide range of Grignard reagents affording the corresponding sulfinamides in 72-93% yield and 90-99.8% ee.

Other advantages of Senanayake's method over the Wudl and Lee's scheme include the higher yields, which were nearly quantitative, the products were highly enantiopure and the overall process was also highly reproducible on kilogram scale for the asymmetric production of diversely substituted sulfinamides and sulfoxides with regeneration of the chiral auxiliary.

As we began to find ways of adopting this procedure to our objectives, Senanayake and co-workers[12] reported the use norephedrine instead of aminoindanol in a similar scheme, but this time in the synthesis of chiral sulfoxides. This was very important for us in terms of cost, as commercial norephedrine is up to three times cheaper than aminoindanol and the 1,2,3-oxathiazolidine-2-oxide is formed exclusively as one diastereomer. We were successfully able to use this procedure to produce the 1,2,3-oxathiazolidine-2-oxide in excellent 90% yield and exclusive enantioselectivity and diastereoselectivity (Scheme **64**).

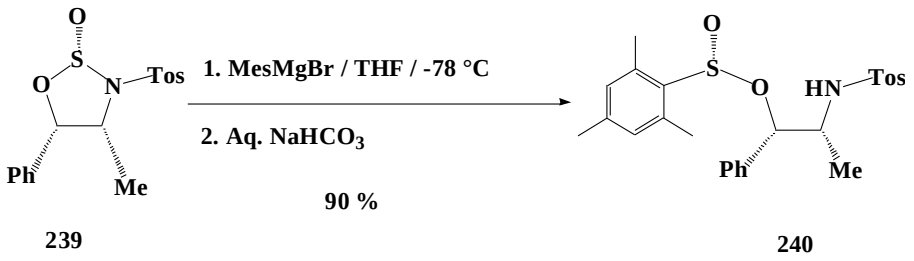


Scheme 64 – Synthesis of norephedrine derived 1,2,3-oxathiazolidine-2-oxide

The synthesis of the *N*-tosylnorephedrine was accomplished in >98% yield by reaction of commercially available (1*R*,2*S*)-norephedrine with *p*-toluenesulfonyl chloride in ethyl acetate and saturated sodium carbonate solution. It is possible to obtain the product as

white crystalline plates after recrystallisation from hexane. The 1,2,3-oxathiazolidine-2-oxide **239** was obtained in >89% yield as a white solid by treating a THF solution of the *N*-tosyl-norephdrine **238** with thionyl chloride at -78 °C under argon and followed by a drop-wise addition of a THF solution of anhydrous pyridine over a three hour period and stirring the reaction mixture at -78 °C until completion of the reaction as determined by TLC. The reaction was quenched at -78 °C with aqueous sodium bicarbonate and extracting the aqueous layer with ethyl acetate. The reaction is very clean and does not require any tedious purification procedure apart from recrystallisation from the mother liquor obtained after quenching the reaction and extraction with ethyl acetate. Although only one isomer was detectable, it was thought that a series of recrystallisations enhanced the enantiopurity of the product. The product **239** was thus obtained as white crystalline plates.

With the 1,2,3-oxathiazolidine-2-oxide **239** in hand, we were able to cleanly cleave the S-N bond by reaction with mesitylmagnesium bromide solution in THF at -78 °C and stirred at that temperature for 2 hours. Quenching of the reaction with aqueous sodium bicarbonate solution and purification by column chromatography afforded the mesityl sulfinate of *N*-tosylnorephdrine **240** in 90% yield and as a single diastereomer (Scheme **65**).

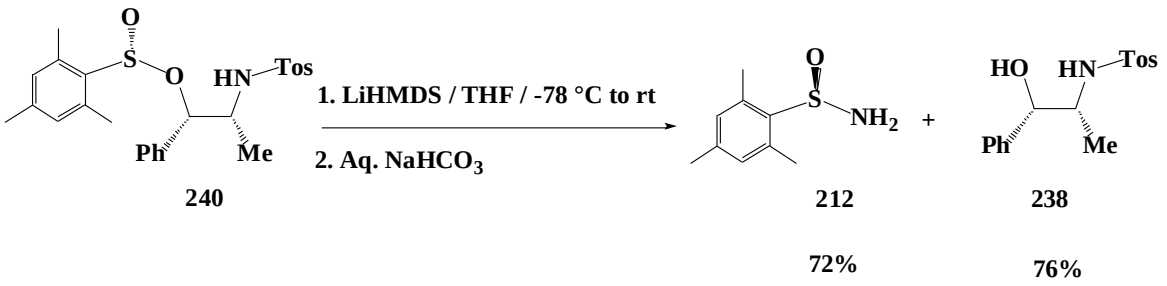


239 **240**

Scheme 65 – Opening of 1,2,3-oxathiazolidine-2-oxide 239 with a Grignard reagent

Senanayake and co-workers had not treated the (1*R*, 2*S*)-(-)-norephedrine derived sulfinate **240** with lithium amide in liquid ammonia to produce sulfinamides,[13] although we thought that this procedure was entirely possible since this had been applied successfully to the aminoindane derived sulfinate.[12] From the experiences of other members of the group involving the condensation of liquid ammonia we thought of other ways of substituting this procedure may be possible and advantageous. There are several examples of cleavage of the S-O bonds of sulfinates with lithium hexamethydisilasane (LiHMDS) solution to yield sulfinamides.[14] We subsequently reacted **240** with LiHMDS solution in THF at -78 °C and

allowed the reaction to warm slowly to room temperature. The reaction was monitored by TLC until completion and quenched with aqueous sodium bicarbonate solution. Purification by column chromatography gave enantiopure mesitylsulfinamide **212** in 72% yield and 99.8% ee as judged by chiral HPLC using the racemate of **212** as a reference. The *N*-tosylnorephedrine was also recovered in 76% yield (Scheme **66**).



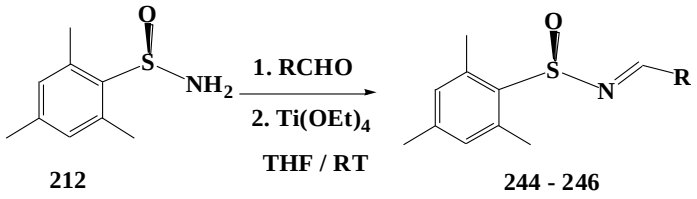
240 **212** **238**

72% **76%**

Scheme 66 – Preparation of enantiopure Sulfinamide 212 from the sulfinate 240

Having successfully obtained the mesitylsulfinamide, we then turned our attention to the synthesis of mesitylsulfinimines. In the preparation of sulfinimines, excess $CuSO_4$ is typically used as a Lewis acid catalyst and water scavenger for aldehyde precursors, while $Ti(OEt)_4$ is the reagent of choice for ketones and for less reactive substrates.[15] With enantiopure (*R*)-(-)-2,4,6-trimethylphenylsulfinamide (**212)** in hand, we set out to explore the scope of its reaction by condensing it with a series of aldehydes **241-243** (Scheme **67**).

In the process, the mesitylsulfinamide (**212**), was reacted with the aldehydes in THF at room temperature using three equivalents of $Ti(OEt)_4$ as dessicant. The isolated yields were very impressive, ranging from 86-95% according to our estimates which are quite conservative since it was usually based on the yields after several purifications. Table **4** is a summary of the yields obtained and the aldehydes used as well as their enantiomeric purities as determined by chiral HPLC analysis.



212 244 - 246

Scheme 67 – Condensation of mesityl sulfinamide 212 with aldehydes

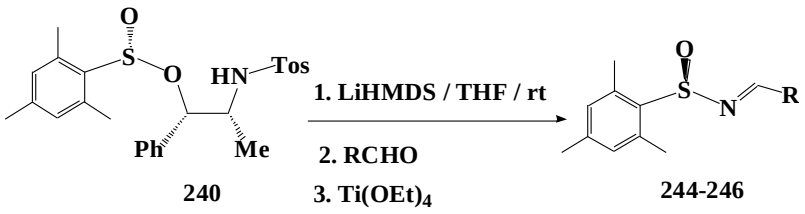
Entry	*Substrate*	*Product*	*Yield*	*ee*
1	**241**	**244**	>95%	99.8%
2	**242**	**245**	>95%	99.8%
3	**243**	**246**	86%	99.8%

Table 4 – Condensation of mesityl sulfinamide 212 with aldehydes

As mentioned previously, the enantiomeric purities were determined by chiral HPLC analysis of the sulfinimines. The selectivity of the sulfinimines is dependent on that of the sulfinamide **212** since the condensation reactions with the aldehydes yields exclusively the *trans*-sulfinimines. As a confirmation that the sulfinimines thus produced remained enantiomerically pure, the racemate **215** was used as a reference to verify the purity of the sulfinimine **246**. The enantiomeric purity of the sulfinimine **246** was thus adjudged to be 99.8% using chiral HPLC and this proved that there was no loss of enantiomeric purity during the condensation reactions and thus we judged that there was no need to synthesise racemates of the other sulfinimines as references for determination of their enantiomeric purities.

As reported earlier in our use of Grignard reagents towards sulfinimines, we were able to adopt a one-pot procedure,[14] which involves conversion of sulfinates to sulfinamides and

the consequent condensation of the sulfinamide with an aldehyde to form the required sulfinimines. Armed with this knowledge, we first treated the sulfinate **240** with lithium bis(trimethylsilyl)amide (LiHMDS) at -78 °C and allowed to warm to room temperature and the reaction monitored until completion, after which 1.1 equivalents of benzaldehyde was added with three equivalents of $Ti(OEt)_4$ (Scheme **68**). After completion of the reaction, as monitored by TLC, water was added and the mixture filtered through celite before the filtrate was extracted with ethyl acetate. It was gratifying to note that after purification by column chromatography, the benzylidene sulfinimine **246** was isolated in 60% yield and without any change in the enantiomeric purity as compared to the step-wise process.



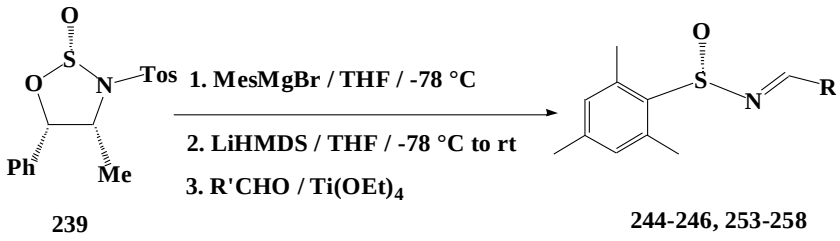
Scheme 68 – One-pot synthesis of mesityl sulfinimines 244 - 246 from the sulfinate 240

We explored the use of this new one-pot procedure on other aldehydes in order to test its scope and reproducibility and we are happy to say that the yields obtained were excellent (Table **5**) and comparable to that obtained if the step-wise process was employed. These results were very encouraging as they also showed no loss of enantiomeric purity and the recovery of the chiral auxiliary was 74% which was comparable to the 76% obtained from the single step used to produce the enantiopure sulfinamide **212** from **240** whilst saving a reaction step and the time and work involved with purification.

Entry	*Substrate*	*Product*	*Yield*	*ee*
1	**241**	**244**	76%	99.8%
2	**242**	**245**	74%	99.8%
3	**243**	**246**	60%	99.8%

Table 5 - One-pot synthesis of mesityl sulfinimines from the sulfinate 238

Having successfully established the methodology of the one-pot synthesis of enantiopure sulfinimines **244-246** from the sulfinate **240**, we then set our attention to extending the scope of the scheme. We envisaged that it is possible to synthesise the sulfinamide **212** in one-pot starting from the 1,2,3-oxathiazolidine-2-oxide **239**. If this step was successfully achieved, then it would be entirely possible as well to condense the crude sulfinamide with an aldehyde to obtain the corresponding mesitylsulfinimines. This would comprise a four-component coupling and offer a very direct method for the synthesis of chiral sulfinimines (Scheme **69**).



Scheme 69 – One-pot synthesis of mesityl sulfinimines from the 1,2,3-oxathiazolidine-2-oxide 239

Entry	*Substrate*	*Product*	*Yield*	*ee*
1	**241**	**244**	46%	99.8%
2	**242**	**245**	60%	99.8%
3	**243**	**246**	54%	99.8%
4	**247**	**253**	50%	99.8%
5	**248**	**254**	36%	99.8%
6	**249**	**255**	57%	99.8%
7	**250**	**256**	30%	99.8%
8	**251**	**257**	44%	99.8%
9	**252**	**258**	44%	99.8%

Table 6 – Results of the novel one-pot, three-step synthesis of sulfinimines from 239

In developing the process, the 1,2,3-oxathiazolidine-2-oxide **239** was treated with the mesitylmagnesium bromide solution at -78 °C under an argon atmosphere and the reaction stirred at that temperature for about one hour and monitored for completion by TLC. After completion, a solution of LiHMDS was added to the mixture in the same pot. The reaction was allowed to warm to room temperature and monitored for completion by TLC. On completion, one equivalent of the aldehyde and 3 equivalents of $Ti(OEt)_4$, the desiccant, were added (Scheme **69**). The reaction was quenched with aqueous sodium bicarbonate solution on completion and purification was done by silica gel column chromatography to obtain the enantiopure sulfinimines.

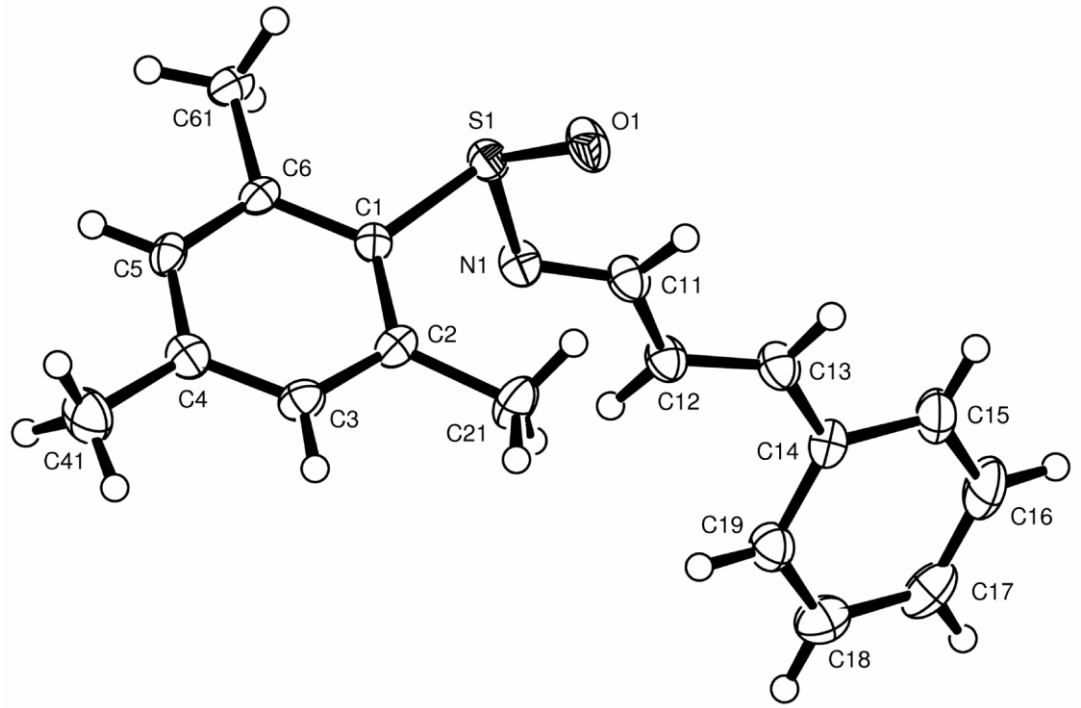


Figure 7 – Crystal structure of sulfinimine 255

It was gratifying to know that that the protocol was universal for all the aldehydes examined and afforded the corresponding mesityl sulfinimines in yields ranging from 30-60% with enantiomeric purities >99.8% as judged by chiral HPLC. Table **6** is a summary of the reaction yields and the aldehyde substrates employed. The alkyl mesityl sulfinimines

244 and **245** were oils and the remaining aryl mesityl sulfinimines (**246**, **253**-**258**) were solids. Sulfinimines **254**, **255** and **258** were yellow crystalline solids. The assigned stereochemistry of the products were confirmed by X-ray of the crystal structure of sulfinimine **255** (Figure **7**).

The yields quoted were not optimised but are, however, impressive and significantly higher than what would have been expected if the syntheses were carried out as multi-step reaction rather than a one-pot reaction. For instance, the cyclohexyl sulfinimine was obtained in 60.1% yield (Table **3**, entry 2) which is higher compared to an overall yield of 48.1% that was obtained in the multi-step synthesis.

It was noted that more electron deficient aldehydes (Table **6**, entries 5 and 7) gave the lowest yields (35.5% and 30% respectively) and this may reflect on the reactivity of these towards hydrolysis. Undoubtedly, the yields could be improved if optimisation had been attempted since this would reduce possible aldol reactions of the aldehyde caused by excess LiHMDS and other addition products from excess Grignard reagent.

Sulfinimines obtained from aliphatic substrates (Table **6**, entries 1 and 2) were found to be colourless viscous oils at ambient conditions whilst those of aromatic and heteroaromatic substrates were generally solids at ambient conditions (Table **6**, entries 3, 4, 5, 6, 7, 8 and 9). The *p*-nitrophenyl- (entry 5), cinnamyl- (entry 6) and 2-naphthyl- (entry 9) were found to be yellow crystalline solids whilst the phenyl- (entry 3), *p*-methoxy- (entry 4), 2-pyridinyl- (entry 7) and 2-furanyl- (entry 8) mesitylsulfinimines were found to be generally white.

The X-ray crystal structure of sulfinimine **255** indicated that it has the *E*-geometry (Figure **7**) and it was reasonable to assume that all the sulfinimines (**244-246, 253-258)** have a similar geometry.[14,16] The preferences for the *E*-geometry was explained by fact that the bulky R and mesitylsulfinyl groups are in the thermodynamically most stable configuration where there are the fewest nonbonded steric interactions. The high preference for (*E*)-sulfinimines could also have arisen from a syn elimination of Me_3SiOLi as is required of the Peterson olefination.[17]

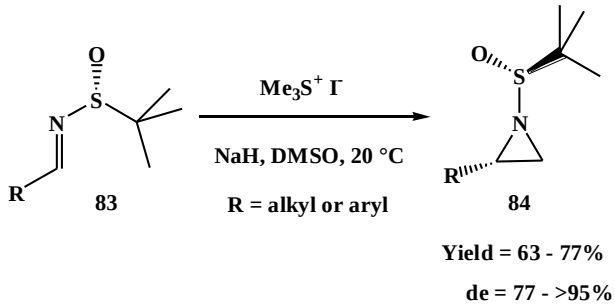
2.2 Attempted Aziridinations

Our interest in aziridines stems from previous work within the group that found a convenient and highly efficient procedure that utilises the Corey-Chaykovsky method to synthesise chiral aziridines from enantiopure sulfinimines.

Ruano and co-workers[18] reported the reaction of chiral non-racemic *p*-tolylsulfinimines with activated dimethylsulfonium methylide to furnish chiral aziridines. Although Ruano investigated a wide range of conditions in order to establish the optimal conditions for the the aziridinations, only a single sulfinimine was used in the report. The report however established that for aziridinations with dimethylsulfonium methylide, the best results were obtained when the reaction was carried out in DMSO at room temperature using sodium hydride as base to generate the ylide. This afforded the aziridine in 79% yield and 36:64 diastereomeric ratio.

Ruano later reported more results of their work on the asymmetric Corey-Chaykovsky protocol,[19] but significantly, the work compared the influence of the substituent at the sulfinyl sulfur on the yields and stereoselectivities of aziridinations. In general, an increase in the steric hindrance of this substituent always led to an increase in diastereoselectivity, thus the stereoselectivity of the reaction was improved from 20% with the *p*-tolyl auxiliary to 54% with the naphthyl auxiliary and up to 70% with the *t*-butyl auxiliary. This report thus established the *t*-butyl sulfinyl auxiliary as an excellent stereo-directing group for aziridinations using dimethylsulfonium methylide in the asymmetric Corey-Chaykovsky protocol. The report, however, used only a small range of sulfinimines

Work within our research group by Stockman and co-workers[20] reported the results of their extensive work into the scope and methodology of the asymmetric Corey-Chaykovsky protocol using dimethylsulfonium methylide and *tert*-butylsulfinyl imines. The optimum conditions for aziridination was confirmed to involve the generation of the dimethylsulfonium methylide by treating trimethylsulfonium iodide with sodium hydride in anhydrous DMSO at room temperature and subsequent slow addition of a solution of the *t*-butyl sulfinyl imine (Scheme **30**).

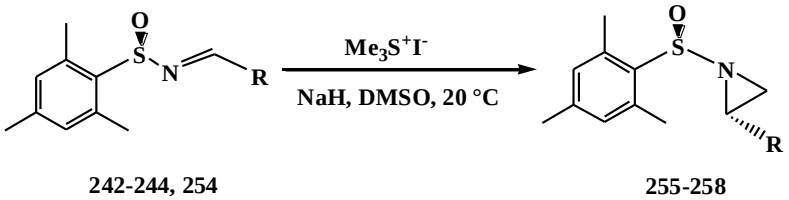


Scheme 29 – Stockman *et al.*'s use of the Corey-Chaykovsky protocol to synthesise aziridines

The significant differences between the Stockman's report and Ruano's were the wider range of sulfinimines employed by Stockman and co-workers and the drastically reduced reaction times: Stockman's aziridinations were usually complete within 5 hours whilst Ruano's method took days to complete. The ease of the work-up also makes Stockman's protocol a method of choice for preparation of aziridines using trimethylsulfonium iodide.

With a wide range of enantiopure sulfinimines in hand, we turned our attention to investigating the scope of the modified Corey-Chaykovsky protocol, developed previously within the group, with mesityl sulfinimines, which it was hoped would be more amenable to *N*-deprotection than the previously synthesised *N*-*tert*-butylsulfinyl aziridines.

We therefore used examples of primary and secondary alkyl and aromatic mesitylsulfinimines to test the scope of the aziridination methodology (Scheme **70**) using the mesitylsulfinyl auxiliary and to compare the results to those obtained using the *tert*-butylsulfinyl auxiliary. The results of our findings are described in Table **7**.



Scheme 70 – Syntheses of methylaziridines using enantiopure mesitylsulfinimines

Entry	*Substrate*	*Product*	*Yield*	**d.e**
1	**244**	**259**	93%	60%
2	**245**	**260**	66%	67%
3	**246**	**261**	95%	63%
4	**258**	**262**	50%	60%

Table 7 – Aziridinations using mesitylsulfinimines in the modified Corey-Chaykovsky protocol

Using the previously optimised procedure, aziridinations were carried out using trimethylsulfonium iodide and sodium hydride in anhydrous DMSO at room temperature to generate the dimethylsulfonium methylide and a solution of the mesitylsulfinyl imine was subsequently added slowly to the solution of the ylide. In general, the aziridinations proceeded in good to excellent yields (50-95%). The lowest yield obtained for the naphthyl imine (Table **7**, entry 4) could be attributed to the threshold setting of the UV detector used for the Biotage flash chromatography; the others where purified by manual column chromatography.

The diastereomeric ratios were determined through inspection and comparison of the integrals of the associated aziridine peaks of the ^{1}H-NMR of the 2 possible diatereomers of the crude products. The de's obtained were moderate 60-67%, with the cyclohexyl imine (Table **7**, entry 2) affording the highest diastereoselectivity, a result which was consistent

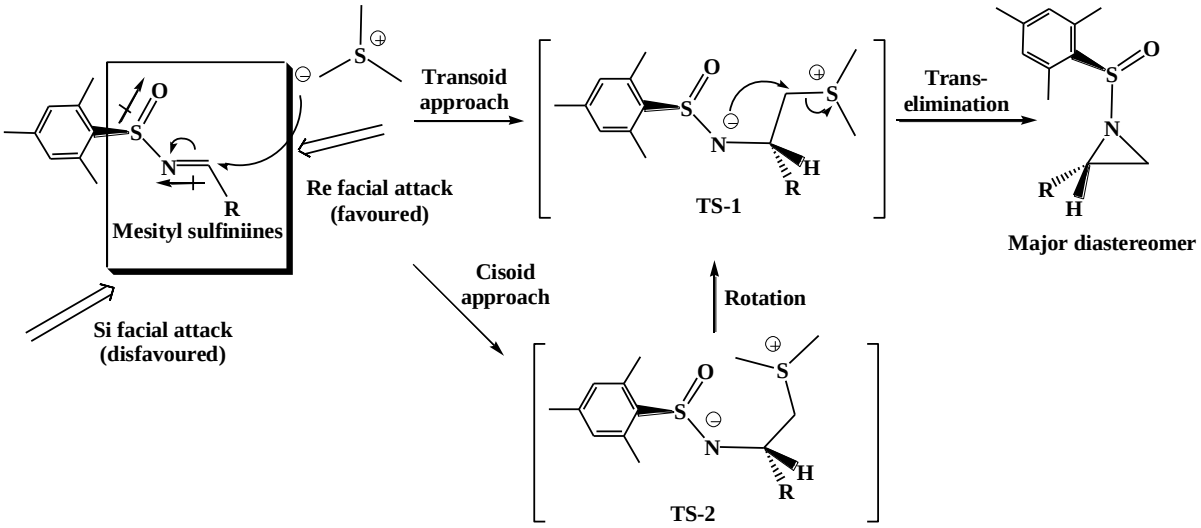
with the earlier report within the group[20] that the cyclohexyl imine of the *tert*-butyl auxiliary also gave the highest de of >95%.

In all substrates examined for the aziridination, the major diastereomer observed was adjudged to have the (*S*)-stereochemistry at C-2. This inference was based on previous work within the Stockman group[20] and the mechanistic rationale for the observed stereochemistry as outlined by Aggarwal *et al.* in their computational studies.[21]

In establishing a mechanism that explains the observed stereochemical outcome for the aziridination of sulfinimines with sulfur ylides, Aggarwal *et al.*[21] postulated that the addition of the ylides to double bonds including an imine bond is dictated by steric factors of the various groups on both faces of the prochiral imine group. If we adopt the transition state proposed by Yamamoto *et al.*,[22] then the imines are locked in an *E*-conformation, with the steric bulk of the chiral mesityl group introducing a high level of diastereofacial selectivity into the addition reaction (Scheme **71**).

Addition of the dimethylsulfonium methylide to the mesityl sulfinimines can occur by two possible mechanisms: a Re facial attack or a Si facial attack. Addition from the Re face is more favoured sterically and the ylide can approach the Re face either in a *trans* or *cis* fashion which leads to formation of **TS-1** and **TS-2** respectively. *Trans*-elimination of dimethyl sulfide occurs successfully in **TS-1** to give the (*R, 2S*)-aziridine as the major product but **TS-2** needs to undergo rotation to **TS-1** before anti-elimination to form the (*R, 2S*)-isomer (Scheme **71**). Si attack however, is unfavoured sterically because of the chiral mesitylsulfinyl group which is pointing out of the plane in the Si face. This makes it more difficult for a successful attack on the imine from the Si face compared to an attack from the more favoured Re face and therefore the (*R, 2R*)-isomer is formed as the minor product compared to the (*R, 2S*)-isomer which is formed as a major product.

Work within the Stockman group[20] on the aziridination reactions of *tert*-butylsulfinimines led to the isolation of a wide range aziridines. *N*-[*Tert*-butyl-(R_S)-sulfinyl]-2-(*S*)-(phenyl-*E*-vinyl)-aziridine was isolated as one of the major isomers and its absolute stereochemistry was confirmed by X-ray crystallography (Figure **8**).



Scheme 71 – Origin of stereochemistry in the addition dimethylsulfonium methylide to mesityl sulfinimines

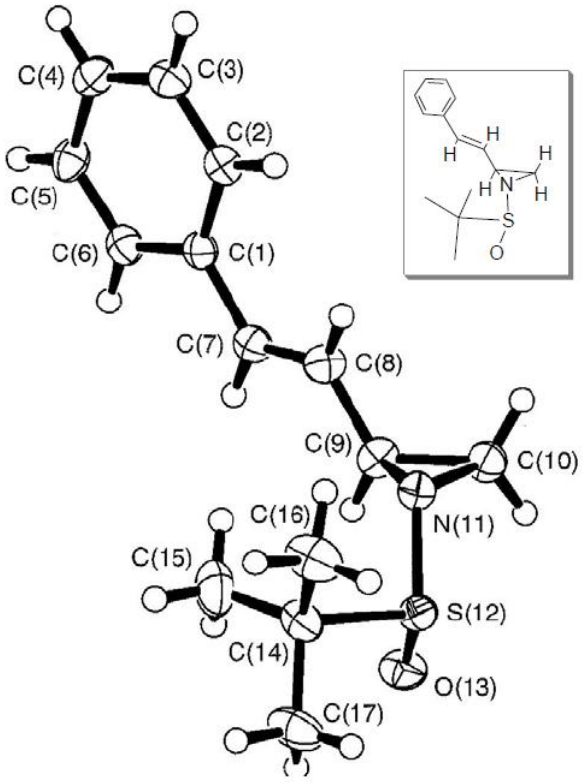


Figure 8 – Crystal structure of *N*-[*Tert*-butyl-(R_S)-sulfinyl]-2-(*S*)-(phenyl-*E*-vinyl)-aziridine

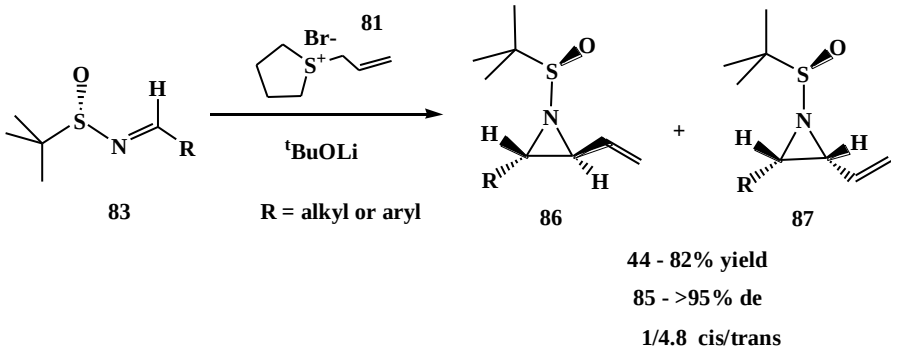
The X-ray crystal structure (Figure **8**) shows that N-S bond is *trans* to the C(9)-C(8) bond but most significantly, the structure has an *S* absolute configuration at C(9). This observation is consistent with the proposed mechanisms of aziridination.[20-22]

Using this evidence, by analogy, we propose that the absolute configuration at C2 of the major product isolated in our aziridination process using mesitylsulfinimines is *S*. Unfortunately attempts to confirm this by X-ray were hampered by the fact that it was practically impossible to separate the diastereomers of the *N*-mesityl aziridines by column chromatography and therefore all the ^{1}H-NMR and ^{13}C-NMR characterisation of our aziridine products was carried out on the mixture of the diastereomers. The ^{1}H-NMR and ^{13}C-NMR data provided are therefore only those of the major diastereomers, which are easily determined from the spectra.

Although aziridination reactions of mesityl sulfinimines gave high yields, this was found to be tempered by the poorer diastereoselectivities obtained compared to those of the *tert*-butyl auxiliary. We therefore turned our attention to the use of allyl sulfur ylides, which with their increased bulk, may give comparable or superior diastereoselectivities to those previously obtained with the *tert*-butyl sulfinimines.

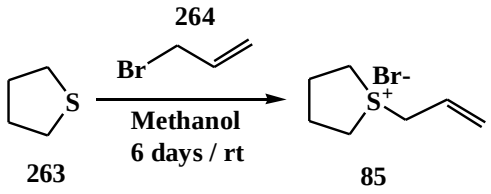
This method had been pioneered by Hou and Dai[23] and involved the addition of ylides of allylsulfonium salts to substituted imines to afford the corresponding vinyl aziridines. Others[24] have also exploited this method to synthesise variously substituted vinyl aziridines and to extend the scope of the protocol.

Earlier work within our research group[25a] on the synthesis of vinyl aziridines utilising sulfonyl imines extended the scope of the aziridination process. This report was followed by the results of their work into utilising enantiopure *N*-*tert*-butylsulfinyl imines and allylsulfonium ylides to synthesise vinyl aziridines[25b] (Scheme **72**). Optimal conditions for the aziridination reaction were reported to involve the use of lithium *tert*-butoxide to deprotonate *S*-allyl tetrahydrothiophenium bromide salt in THF at room temperature. The reaction gave high yields (44-82%) of the aziridines (**86** and **87**) and excellent diastereoselectivities (85- >95%).



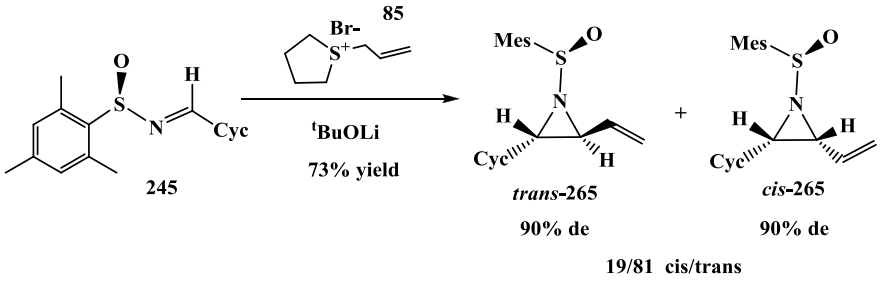
Scheme 72 – Asymmetric synthesis of vinyl aziridines using allyl tetrahydrothiophenium ylide

One important starting material required for the aziridination was the *S*-allyl tetrahydrothiophenium bromide salt. Synthesis of the *S*-allyl tetrahydrothiophenium bromide salt was achieved by stirring tetrahydrothiophene with allyl bromide in methanol at room temperature for 6 days. Removal of the methanol *in vacuo* followed by trituration of the residue with diethyl ether afforded the *S*-allyl tetrahydrothiophenium bromide salt as an off-white crystalline solid in 91% yield (Scheme **73**).[20b]



Scheme 73 – Synthesis of the *S*-allyl tetrahydrothiophenium bromide salt

Armed with the *S*-allyl tetrahydrothiophenium bromide salt, we decided to investigate the scope of the aziridination using cyclohexyl-substituted mesitylsulfinimine **245** in the modified Corey-Chaykovsky protocol reported by Stockman and co-workers[25] to synthesise the corresponding vinyl aziridine. In the event, a solution of the lithium *tert*-butoxide was added drop-wise to a mixture of the *S*-allyl tetrahydrothiophenium bromide salt and the mesitylsulfinimine **245** in THF at room temperature. The mixture was then stirred for about 10 minutes and the progress monitored by TLC. The reaction was completed in 30 minutes. The product was purified by silica gel column chromatography after an aqueous work-up (Scheme **74**).



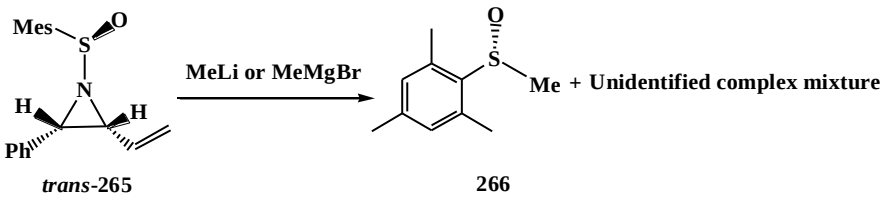
Scheme 74 – Synthesis of the cyclohexyl vinylaziridine

The cyclohexyl-substituted vinyl aziridine was isolated in 73% overall yield with a *cis*/*trans* ratio of 19:81. The de of both *cis* and *trans* aziridines was judged to be in excess of 90%, by analysis of the ^{1}H-NMR of the crude reaction product after work-up. The cyclohexyl-substituted vinyl aziridine obtained using the *tert*-butylsulfinyl auxiliary was reported in 78% yield and a *cis*/*trans* ratio of 17:83 with a de of >95%.[25] These results show a similarity in the selectivities of the *tert*-butylsulfinyl and the mesitylsulfinyl auxiliaries for vinyl aziridinations, though the results are slightly in favour of the *tert*-butylsulfinyl auxiliary.

We were able to separate the *cis* and *trans* aziridines by column chromatography however, it was again impossible to separate the diastereomers by column chromatography and therefore all the ^{1}H-NMR and ^{13}C-NMR characterisation of the aziridine products was done using the crude mixture of the diastereomers. The de of the *trans* was found to be in excess of 90% as the integrals for the other diastereomer (epimeric at C2 and C3) could not be detected in the ^{1}H-NMR. The ^{1}H-NMR and ^{13}C-NMR data provided are therefore only the discernible peaks of the major diastereomers as those for the minor diastereomers are not clearly discernible.

With these encouraging results in hand, our next focus was to attempt the deprotection of the vinyl aziridine **265**. This step was very important to our overall aims in that, the deprotected aziridine would provide us access to *N*-alkylated aziridines with a view to attempting an aza-Wittig ring-expanding rearrangement and other useful reactions of vinyl aziridines. Davis had reported that the addition of MeMgBr or MeLi to sulfinyl aziridine 2-phosphonates and monosubstituted aziridines led to the removal of the sulfinyl auxiliary to afford the *–NH* aziridines in good yields.[3]

Armed with this information, we set out to attempt the deprotection of the vinyl aziridine **265**, firstly by treating it with MeLi at -78 °C. After several attempts, we were unable to isolate any *–NH* aziridine. We again tried the deprotection, this time with MeMgBr.[3a,b] Once again, we were not able to isolate any aziridine product, however, in both instances, we were able to obtain the sulfoxide **266** with a complex mixture of side products which we were unable to characterise (Scheme **75**).



***trans*-265** **266**

Scheme 75 – Attempted deprotection of the vinylaziridine 265

The reported methods of deprotection[3] were not carried out on any vinylaziridines however, it was reported that the presence of activating substituents on the aziridine ring increases the propensity for ring opening of the aziridine whilst the presence of a deactivating group like the carboxylate group increase the stability of the ring towards nucleophilic attack. The vinyl substituent on the aziridine **265** should ideally act as a deactivating group, however, the vinyl group itself is thought to be susceptible to nucleophilic attack and this could expose the aziridine ring to other reactions that could lead to the destruction of the aziridine ring.

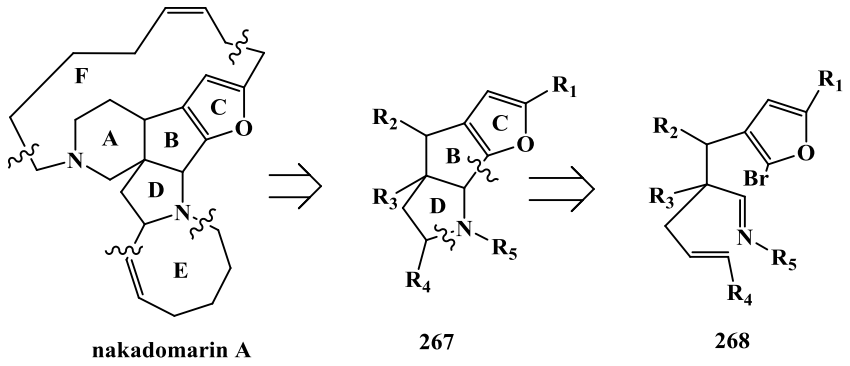
Thus, having shown that mesityl sulfinimines are able to undergo Corey-Chaykovsky type aziridinations (albeit with lower diastereoselectivity than the corresponding *tert*-butyl sulfinimines), our attention turned to investigating other unexplored reactivity of sulfinimines – their use in radical chemistry. The next section will discuss our investigations in this area and a model study using this chemistry aimed at the synthesis of nakadomarin A.

3 Model studies towards the BCD ring of Nakadomarin A

3.1.1 Retrosynthesis of nakadomarin A

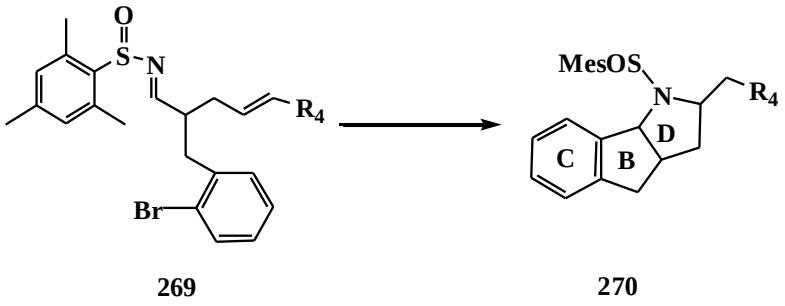
Nakadomarin A is an intriguing molecule whose structure contains many compelling challenges for the synthetic chemist (see introduction). In our attempt to synthesize the BCD ring of nakadomarin A, we suggested a retrosynthetic path that will involve readily available starting materials and significantly incorporate a sulfinimine as one of the key intermediates (Scheme **76**). Our key retrosynthetic step would be the tandem cyclisation of the B and D rings from the precursor **268**. We decided to use the potentially more easily accessed model system **269** that could be used to explore an intramolecular radical cyclisation to afford the BCD model system **270**. The main aim of this study was primarily to determine the feasibility of such a procedure, and the stereoselectivity can then be tuned to match that of nakadomarin A after successful cyclisation.

Retrosynthesis:



nakadomarin A 267 268

Model Study:



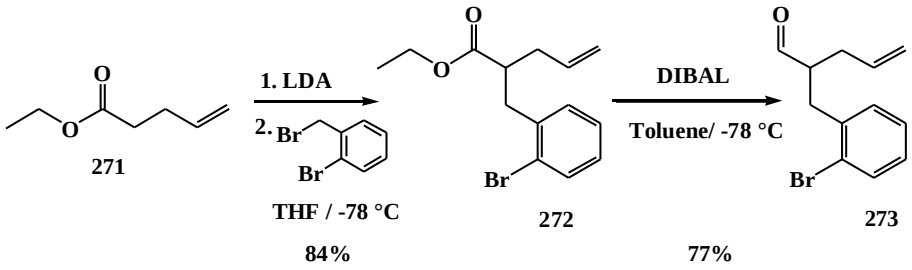
269 270

Scheme 76 – Proposed retrosynthesis and model study of the BCD ring of nakadomarin A

We thus turned our attention to finding the suitable chemical transformation. We anticipated a possible cyclisation to start from the furan ring and onto the imine carbon and would continue onto the imine nitrogen which will then attack the olefinic group to complete the cyclisation. Such a reaction would proceed through either a free radical reaction or by an anionic reaction initiated by lithium-halogen exchange on the furan ring. Due to the limited availability and relative expense of furan containing reagents or substrates, we decided to replace the furan ring with a benzene ring for the model study.

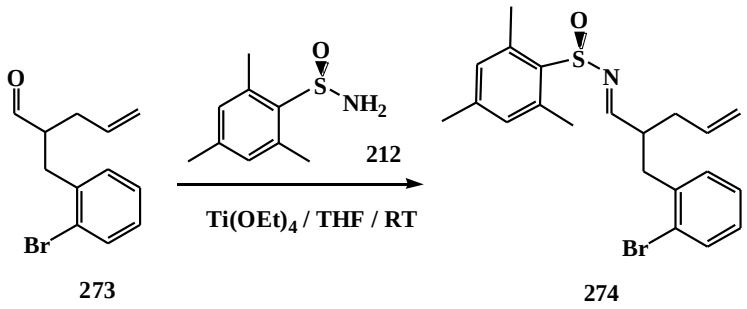
3.1.2 Serendipitous synthesis of aminoindanyl sulfinamides

We found the synthetic precursor of **269** to be commercially available ethyl-4-pentenoate **271**, which we were able to successfully alkylate with 2-bromophenyl bromide by first adding the ester to LDA, generated *in situ* by adding *n*-BuLi to *N,N*-diisopropylamine in THF, at -78 C and then adding a solution of the bromide. This afforded the alkylated product **272** in 84% yield after purification by column chromatography. The product **273** was subsequently obtained by reduction of a solution of the ester **272** in toluene with DIBAL at -78 C to the corresponding aldehyde. The reaction was quenched with 10 mL of methanol and warmed to -40 °C and stirred with Rochelle's salt for two hours to turbidity and break-up the emulsion formed. The two phases obtained were separated and the aqueous layer was extracted with ethyl acetate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain the aldehyde **273** in 77% yield (Scheme **77**).



Scheme 77 – Alkylation of 271 and subsequent reduction of the ester functionality

The aldehyde **273** was then condensed with mesitylsulfinamide **212** using $Ti(OEt)_4$ as water scavenger and promoter to afford the sulfinimine **274** in 80% yield as a 1:1 mixture of diastereomers (Scheme **78**).[26] Disappointingly, try as we did, we were not successful in separating the diastereomers of the sulfinimine **274** and we therefore decided to use the diasteroemric mixture in our onward synthesis.



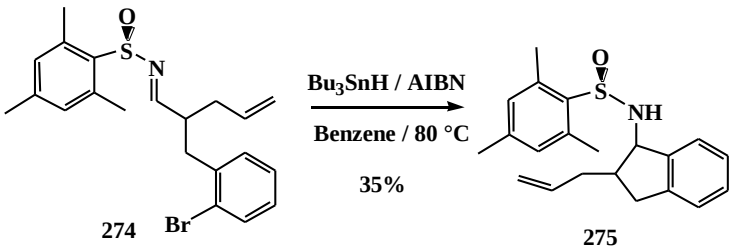
Scheme 78 – Condensation of the aldehyde 273 with mesitylsulfinamide

As mentioned earlier, we had envisaged in our retrosynthesis a radical or anion generated at the furan ring (now benzene ring) in the place of the halogen (bromine) and this would then trigger the concerted reaction. After careful analysis, we opted to explore the free radical route, mainly because of uncertainty about what the addition of an organolithium reagent, in order to generate an anion, would result in since organolithium reagents are known to add to the C=N bond of sulfinamides in a 1,2-fashion to give the corresponding sulfinamide.[26] There are examples of free radical cyclisation reactions in literature involving imines[27] but to the best of our knowledge, we are aware of only one involving sulfinimines.[28] Such a successful cyclisation would therefore also be novel.

Another consideration in the use of free radical chemistry was whether the reaction could be photo or thermally induced. Because of the complexities involved with photo initiation of free radicals and the unavailability and or lack of access to such equipment, we opted to use thermal initiation of our proposed reaction. There are a lot of examples of the use of tributyltin hydride (Bu_3SnH) as a source of radical and AIBN as a thermal radical initiator[29] so we opted to use these mainly due to their ready availability. The most widely reported methods involve using Bu_3SnH and about 1.0 equivalents to as low as 0.1 equivalents of AIBN in benzene and the mixture heated at reflux. From our literature survey, we found that such reactions were usually conducted in low dilutions and it was

also sometimes appropriate to remove all traces of gases such as oxygen and nitrogen dissolved in the solution as these may interfere with the reaction. Solutions of the reaction mixtures are therefore degassed by bubbling a steady flow of dry argon through the solution prior to heating to reflux under an atmosphere of argon.[30]

In the event, we added 1.2 equivalents of Bu_3SnH and 2.0 equivalents of AIBN to the sulfinimine **274** and added enough benzene to make a 0.2 molar solution with respect to the sulfinimine **274**. The flask was set up for heating at reflux but the solution was first degassed with argon for 20 minutes after which the solution was kept under argon and heated at reflux at 80 °C (Scheme **80**). After 45 minutes, the reaction was monitored by TLC and it was observed that all of the sulfinimine **274** starting material had been consumed and the TLC did not change after an hour. The reflux was stopped and the mixture cooled to room temperature and evaporated *in vacuo*. A crude sample of the mixture was taken and run on the LCMS and significantly showed a substantial peak around the required mass. After column chromatography, the major product was isolated in 35% yield (Scheme **79**).



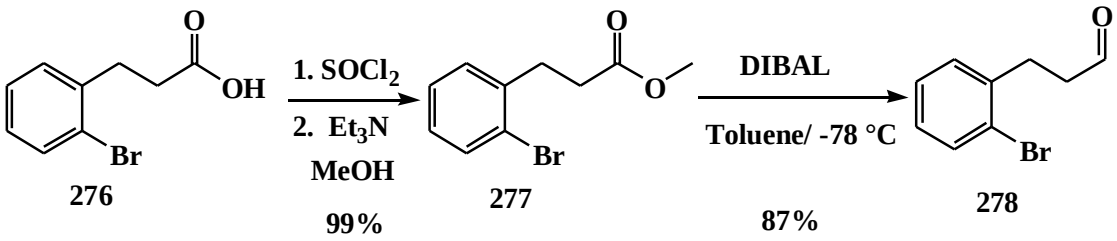
Scheme 79 – Free radical intramolecular cyclisation of the sulfinimine 274

From the ^{1}H-NMR however, it was evident that some olefinic group was still present in the product but significantly, the imine proton had disappeared and there were significant shifts in the position of the other proton peaks relative to those of the starting material. After careful analysis of the other data, it became clear that the reaction did occur but not entirely as expected. Instead of two concerted cyclisations, only the first one occurred and that accounted for the presence of the olefinic group in the ^{1}H-NMR spectra. The reaction may have stopped after the first stage which is the successful attack of the radical, formed on the benzene ring in place of the bromine atom, on the imine carbon. The radical that

was subsequently generated on the now sulfinamide nitrogen then failed to attack the olefinic group and this resulted in the amino indanyl sulfinamide product **275**. The rationale behind these deductions is explained later in this chapter.

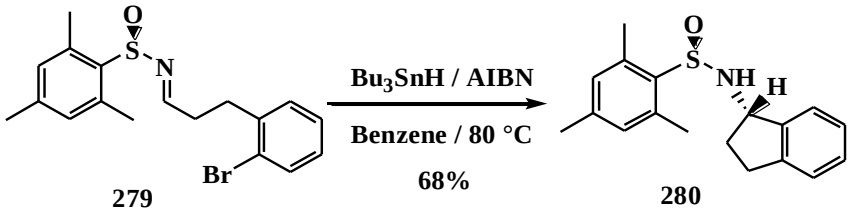
These are just two of the possibilities, but our concern at this stage was to confirm that the proposed structure of the product was right and that such a result would be reproducible. To confirm this, we decided to repeat the same reaction with a similar substrate that lacks the allyl side-chain and hopefully that would yield amino indanyl sulfinamide, which can be deprotected to give amino indane. The spectral data can then be compared with those of commercially available amino indane.

In the process, commercially available 3-(2-bromophenyl)propanoic acid **276** was esterified with methanol in 99% yield and the corresponding methyl-3-(2-bromophenyl)propanoate **277** was reduced with DIBAL followed by Rochelle's salt work-up to afford the aldehyde **278** in 87% yield. The aldehyde was readily condensed with the mesityl sulfinamide **212** using $Ti(OEt)_4$, as a water scavenger as reported previously in the other condensations, to afford the sulfinimine **279** in 81% yield (Scheme **80**).



Scheme 80 – Synthesis of the aldehyde 278 from 3-(2-bromophenyl)propanoic acid 272

For the free radical reaction, the same conditions were used as previously. A solution of all the reagents in benzene was degassed with dry argon and heated at reflux under argon for 45 minutes. After the TLC showed the consumption of all the sulfinimine **279**, the heating was stopped and the mixture concentrated *in vacuo*. Purification of the product by column chromatography gave **280** in 68% isolated yield as a yellow oil (Scheme **81**). It was very gratifying to see the LCMS results gave the expected mass ion and the structure was confirmed by ^{1}H-NMR and ^{13}C-NMR.



Scheme 81 - Free radical intramolecular cyclisation of the sulfinimine 279

The main problem with the above reaction and the previous one was the persistence of tin residues even after several purifications by column chromatography, and this appears on the NMR spectra. We were able to significantly reduce these residues by using a 10% KF in silica gel for the column chromatography.[33] Purification was further enhanced by first stirring the crude mixture with a concentrated solution of KF for an hour and then extracting with DCM.[34] The organic extracts can then be concentrated and the residue further purified by column chromatography using 10% KF in silica gel. Importantly, the product was obtained as white crystalline needles instead of the yellow oil obtained without the KF purification. Significantly, the reaction was found to yield a single diastereomer; the other was not detected either by H-NMR or chiral HPLC. We were able to confirm the structure and stereochemistry of the compound using X-ray crystallography which showed that the compound is made up of a chain of molecules held together by strong hydrogen bonding (Figure **9**).

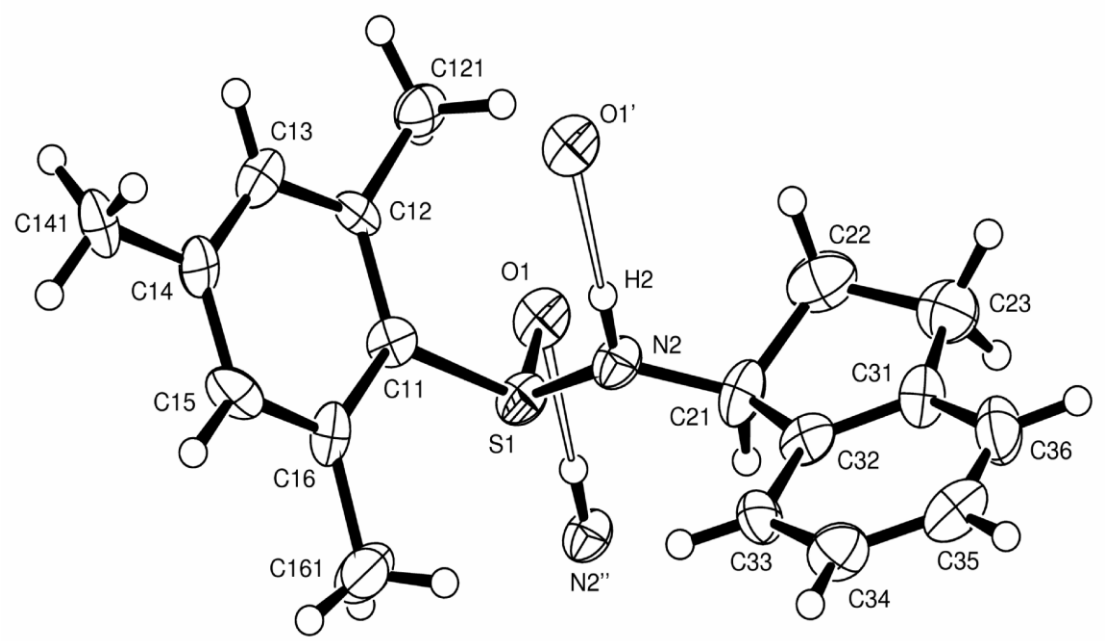
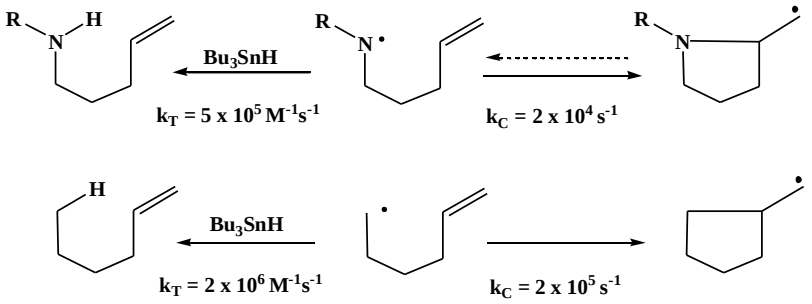


Figure 9 – Crystal structure of mesitylsulfinyl amino indane 280

With the exact stereochemistry of the product **280** confirmed from the X-ray crystal structure, we turned our attention to finding the reasons for observing only mono-cyclisation in the case the attempted double cyclisation of **274**. The factors may include the presence of excess tributyltin in the reaction mixture that may have readily reacted with the nitrogen radical formed after the first cyclisation step to form an amine, or the proposed onward reaction of the nitrogen radical with the olefinic group, which would yield a primary radical, did not occur because of the relative stability of primary radical product compared to the amine intermediate. We inferred from the literature[31,32] and from our results that the inability of the tandem double cyclisation reaction to proceed as proposed could be due to a number of factors:

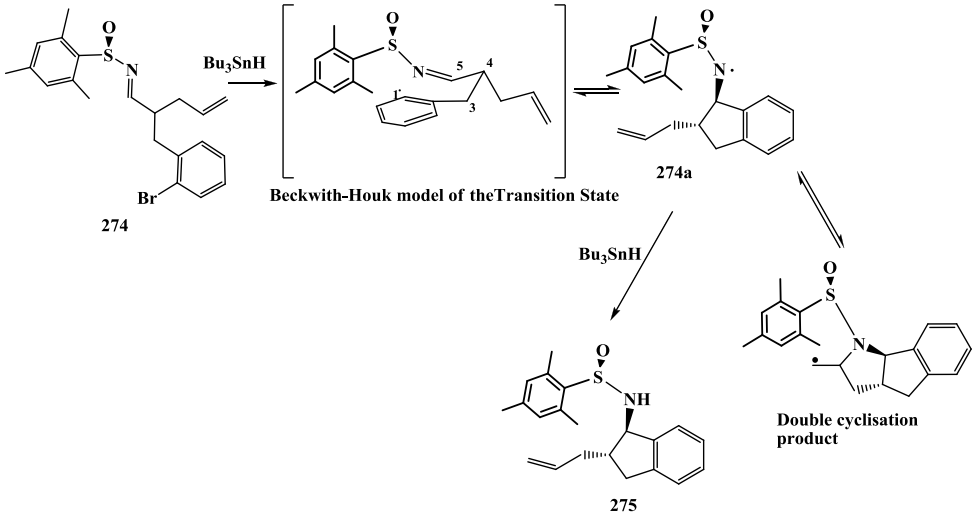
- The relative instability of nitrogen centred radicals: The rate constant of cyclisation (k_C) of a secondary nitrogen centred radicals with an alkenyl group to give a primary radical is about 10 times slower than an analogous carbon centred radical (Scheme **82)**[31] and the cyclisation reaction of the nitrogen centred radicals is also reversible. The rate constant of termination (k_T) of the same secondary nitrogen centred radicals with tributyltin hydride is however 25 times faster than the rate constant of cyclisation for the same substrate.[31]



Scheme 82- Absolute rate constants of Nitrogen and Carbon centred radicals

This means that if there is competition between a second cyclisation of our substrate **274** and termination of the radical **274a** by tributyltin hydride, the reversible nature of the proposed cyclisation, and its lower rate constant compared with that of the termination reaction with tributyltin hydride, meant that the second cyclisation step was unlikely to be achieved under the conditions of our reaction.

- Beckwith-Houk Model: The Beckwith-Houk predictive model[32] for stereocontrol in 5-hexenyl radical cyclisations suggests that the most favourable first cyclisation of our starting material **274** would yield the 5-*exo* nitrogen-centred radical intermediate, but most importantly, the nitrogen radical is predicted to be *trans* with the allyl group. This could be explained by assuming a chair-like conformation in the aryl radical cyclisation transition state (Scheme **83**).



Scheme 83 – Proposed mechanism of cyclisation of 274 to form 275

The allyl group adopts the most thermodynamically favourable pseudo-equatorial orientation at position 4 of the chair-like transition state. Substitutions at position 4, according to the model, coupled with allylic strain which in our model is the imine functionality, ensures an exclusive 1,2-*trans* selectivity in the product. The aryl carbons at positions 1 and 2 in our transition state model also offer extra rigidity to the system and thereby increases the selectivity of the reaction.

This model could also be used to explain why it appears that only one isomer was observed from the ^{1}H-NMR though the starting material was made up of a mixture of diastereomers. The most thermodynamically stable conformation of the transition state is when the allyl group is in an equatorial position, a conformation which would be significantly more favourable than when the allyl group is at an axial position (which the other diasteroisomer would require to cyclise), as this would lead to a 2,4–diaxial steric repulsion. This latter conformation would therefore be a least likely transition state and in our opinion, the diastereomer which is more likely to adopt such a conformation in its transition state would not produce any cyclisation product. This would account for the relatively low yield of this reaction compared to the reaction of **279** to give **280** (Scheme **83**) because the conformation of **279** in the transition state would not have the same steric factors to contend with.

- If the allyl group is *trans* to the nitrogen-centred radical in **274a**, the product of the free radical cyclisation of our transition state model, then the conformation of the **274a** would be thermodynamically unfavourable for a second cyclisation to proceed. This would explain why the reaction did not proceed as envisaged to give a double cyclisation product.

Our stereochemical assignment of **275** was based the following:

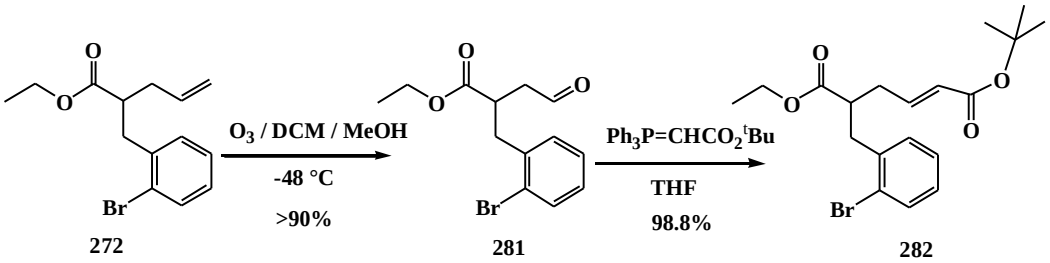
i. The known stereochemistry at position 1 of **280** from its crystal structure which shows that the amine nitrogen is pointing up the plane and that gives an *R* configuration. This configuration is also consistent with our proposed mechanism for the reaction which shows the imine hydrogen at position 5 of the chair-like conformation pointing down the plane in an axial like fashion. This accounts for

the hydrogen at position 1 of the product pointing down the plane and the amine nitrogen pointing up the plane in the product after the free radical cyclisation.

ii. Similarly, the equatorial position of the allyl group in the transition state implies that it points down the plane in the product after the free radical cyclisation. This means that the allyl group and the amine group are *trans* to each other in the final product. A coupling constant of 8 Hz was observed between the proton next to the sulfinamine and the proton on the allyl-bearing carbon of the ring, also lending credence to a *trans* relationship, although it is notoriously difficult to use NMR to assign stereochemistry on five-membered rings.

With the structure postulated, we turned our attention to our earlier attempt to perform a double cyclisation. In order to achieve this, we tried to address one of the suspected reasons for the expected double cyclisation reaction not going to completion.

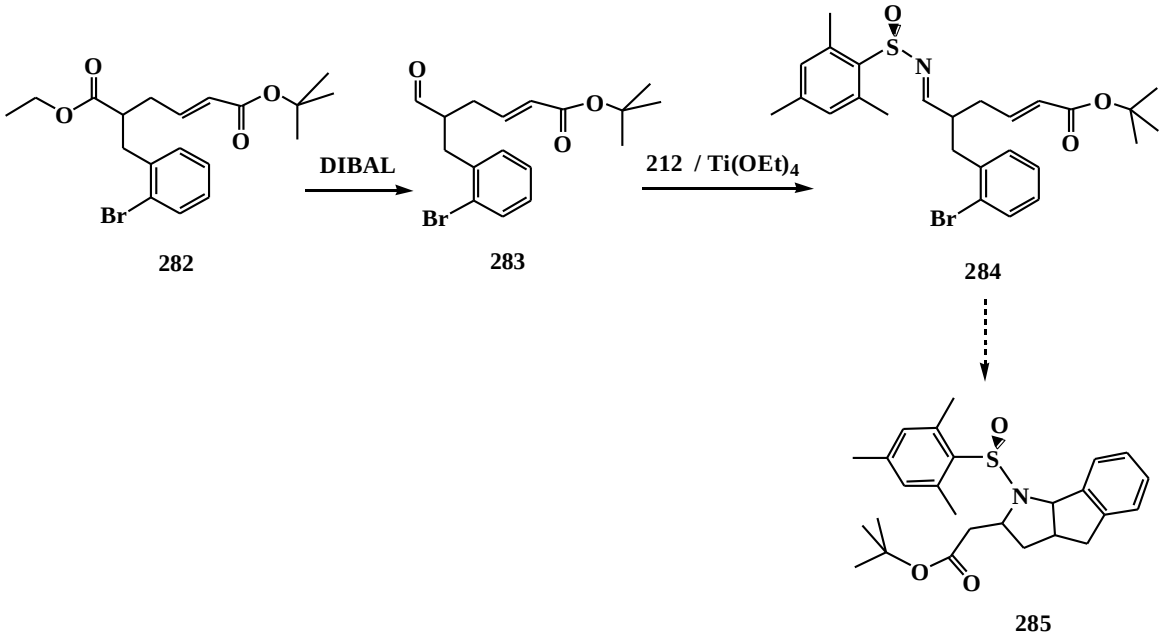
Our approach to this was to modify the structure of the sulfinimine **274** to include a group next to the olefinic group that would stabilise the free radical formed after the cyclisation. This would also mean that the radical formed after attack on the olefin would be a secondary radical which is relatively more stable. We proposed that if a group like an ester group was conjugated with the olefinic group, this would encourage the process. We therefore modified the earlier scheme (Scheme **77**) instead of redesigning the entire scheme. In the event, the olefin **272** was subjected to ozonolysis by bubbling ozone through a DCM/methanol solution of the olefin **272** until the solution turned blue and persisted. This was followed by a reductive work-up with dimethyl sulfide and purification by silica gel column chromatography to give the aldehyde **281** in >90% yield. The aldehyde **281** readily underwent Wittig olefination with commercially available (*tert*-butoxycarbonylmethylene)-triphenylphosphorane in THF to afford the diester **282** in 99% yield (Scheme **84**).



Scheme 84 – Synthesis of the diester 282 via ozonolysis and Wittig olefination

We set out to selectively reduce the ethyl ester to give us access to the aldehyde **283** (Scheme **85**). We hypothesised that the relatively bulky nature of the *tert*-butyl group, compared to the ethyl group, would render the *tert*-butyl ester less susceptible to reduction. This would enable selective reduction of the ethyl ester in the presence of the *tert*-butyl ester. It was also thought that milder reducing agents would be more discriminating and would therefore offer more selectivity.

We first attempted the reduction of **282** using one equivalent of DIBAL in toluene at -78 °C. After several hours of stirring at that temperature, the TLC showed only a little new spot for a possible product compared to that of the starting material. This did not change when the reaction was warmed to -48 °C for several hours. The reaction was stopped and after work up and purification, the aldehyde **283** was obtained in 6% yield.



Scheme 85 – Attempts to achieve the double cyclisation

Having attempted the DIBAL reduction several times without any improvement in the yields, we therefore turned our attention to utilising other reducing agents that may offer better yields.[35] Aqueous LiOH, bis(tributyltin) oxide and lithium tri-*tert*-butylaluminium hydride were all utilised in an attempt to selectively reduce the ethyl ester to no avail.

Reducing agent	**Yield**
DIBAL	6%
LiOH	Trace
Bis(tributyltin) oxide	Trace
Lithium tri-*tert*-butylaluminium hydride	Trace

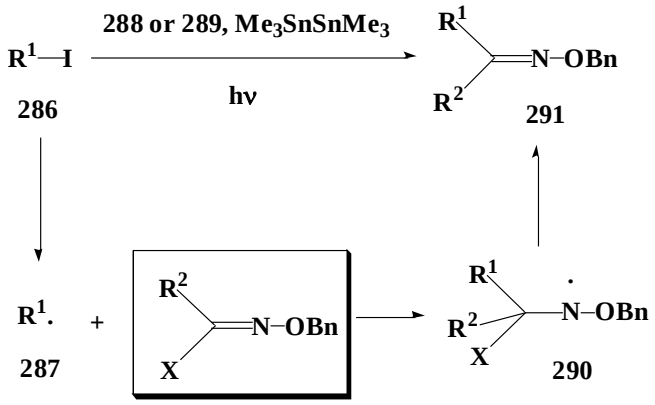
Table 8 – Attempted reduction of 282

After these unsuccessful attempts at selectively reducing the ethyl ester, we decided to rethink our scheme again and modify the synthetic strategy.

3.1.3 Use of radical acceptors in the free radical cyclisation

After the setback of not being able to selectively reduce the ethyl ester of **282** in the presence of the *tert*-butyl ester, we turned our attention to finding a route that would avoid the need for the reduction step. After careful consideration of our previous work and reported research work by other workers into radical chemistry, we decided to utilise **272** again as a substrate but in this instance, to employ a radical acceptor that would hopefully react with the primary radical that would be possibly formed on double cyclisation of **272**. This would then hopefully encourage the forward reaction.

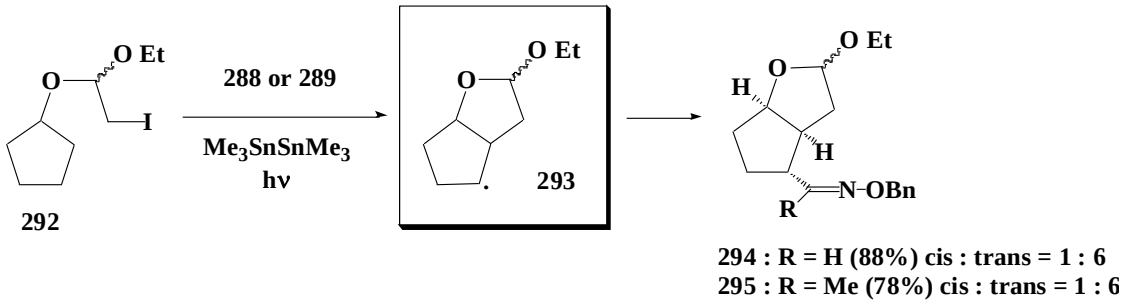
Radical acceptors have been widely used in radical chemistry reactions but our interest was drawn to one that had been utilised in a reaction similar to the one we have proposed. Kim and co-workers reported a novel radical-mediated acylation reaction based on the use of thiol esters as radical acceptors.[36] The concept was based on the fact that alkyl radicals undergo facile additions to C=N bonds of oxime ethers and hydrazones.[36] They found that irradiating a mixture of an alkyl or aryl halide, a phenylsulfonyl oxime ether and bis(trialkyl)tin with light of 300 nm led to formation of the alkyl or aryl radical of the halide which undergoes addition to the C=N bond of the phenylsulfonyl oxime ether and subsequent β-exclusion of a phenyl thio radical which reacts with bis(trialkyl)tin to propagate the chain (Scheme **86**) .



288 : R^2 = H, X = SO_2Ph
289 : R^2 = Me, X = SO_2Ph

Scheme 86 – Kim's radical-mediated acylation reaction with oxime ethers

Encouraged by the success of this acylation approach, they studied the feasibility of the cyclization-acylation sequence, which cannot be achieved using conventional synthetic methods (Scheme **87**). When a mixture of the halide **292**, $Me_3SnSnMe_3$ (1.2 equiv), the oxime ether **288** (2.0 equiv), and acetone (5 equiv) in benzene (0.3M in the iodide) was irradiated at 300 nm for 4 h, the cyclisation-addition product **294** was isolated in 88% yield.



292

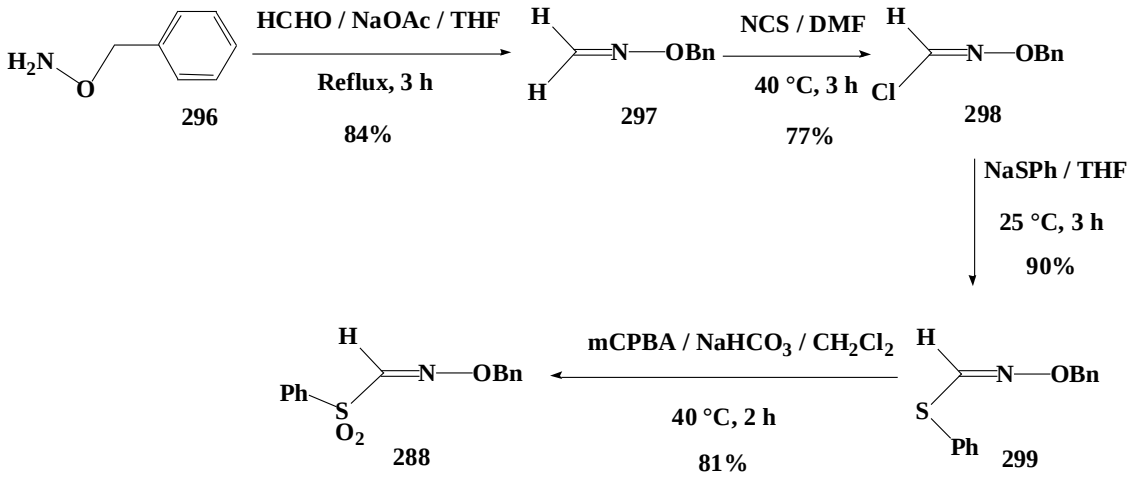
294 : R = H (88%) cis : trans = 1 : 6
295 : R = Me (78%) cis : trans = 1 : 6

Scheme 87 – Kim's cyclization-acylation reaction

Thermal initiation with AIBN was also investigated with **292** and **288**. However, the reaction was incomplete even after 12 h, and the yield was considerably lower (40%). For our work, such a yield is proof that thermal initiation is feasible and very encouraging. More significantly, Kim and co workers reported the results of their studies into a sequential inter- and intramolecular acylation approach leading to cyclic oximes and hence cyclic ketones. He reported that whereas the earlier acylation scheme works for alkyl iodides, for aryl iodides, the standard radical conditions of Bu_3SnH/AIBN are required.[38]

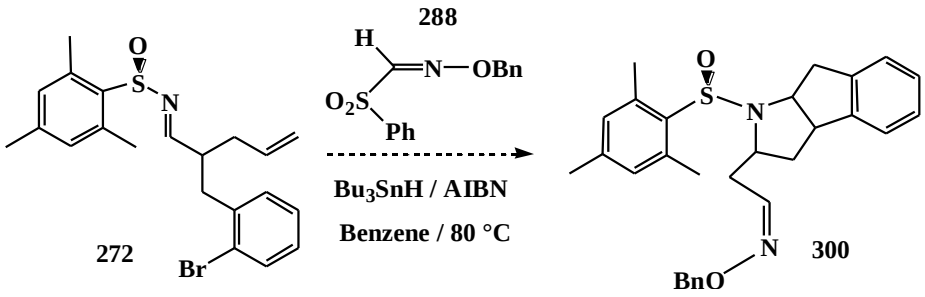
Armed with this information, we set out to employ this scheme. Our first step was to obtain the oxime ether **288** that would serve as the radical acceptor. Thus *O*-benzylhydroxylamine **296** was heated to reflux with formaldehyde to afford *O*-benzylformaldoxime **297** in 84% yield. The *O*-benzylformaldoxime **297** was heated with NCS in DMF at 40 °C to afford the *O*-benzylformohydroximoylchloride **298** in 77% yield. Reaction of the *O*-benzylformohydroximoylchloride **298** with sodium thiophenolate in THF at room temperature gave *S*-phenyl-*N*-(benzyloxy)-thioformidate **299** in 90% yield. The *O*-benzyl-α-(phenylsulfonyl)formaldoxime **288** was obtained by oxidation of the *S*-phenyl-*N*-

(benzyloxy)thioformidate **299** with *m*CPBA in DCM initially at 0 °C and then warming the mixture to 40 °C. This afforded the *O*-benzyl-α-(phenylsulfonyl)formaldoxime **288** in 81% yield (Scheme **88**).[39]



Scheme 88 – Synthesis of the oxime ether O-benzyl-α-(phenylsulfonyl)-formaldoxime 288

Having successfully obtained the necessary oxime ether **288**, we set out to explore the feasibility of utilising Kim's cyclization-acylation reaction[36] in our attempt to achieve the double cyclisation of the sulfinamides **272**, (Scheme **89**).



Scheme 89 – Attempted cyclization-acylation reaction

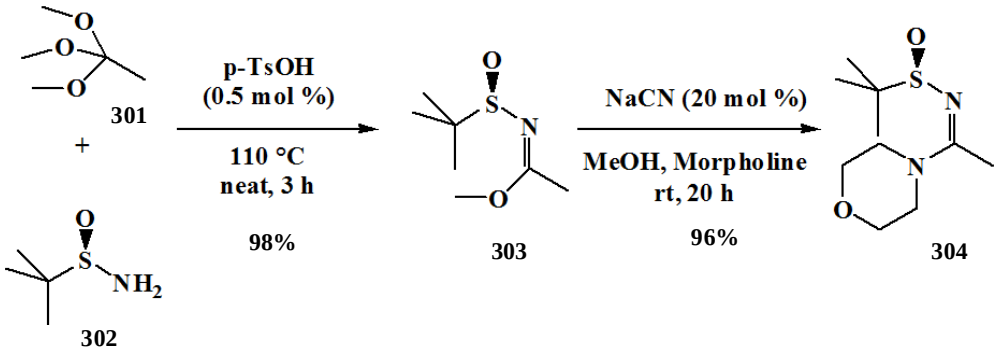
The sulfinimine **272** was treated with the *O*-benzyl-α-(phenylsulfonyl)formaldoxime **288** utilising the thermal initiation process reported.[37] After several attempts, we were not able

to isolate any cyclisation or acylation product. It appears that some of the starting material is consumed during the reaction, however, this does not lead to any identifiable product.

3.1.4 Asymmetric synthesis of substrates for free radical cyclisation

Whilst exploring ways of achieving the double cyclisation, we were simultaneously working on ways of synthesising the intermediate **272** in enantiomerically enriched form to enable us to easily determine the stereoselectivities at the various chiral centres.

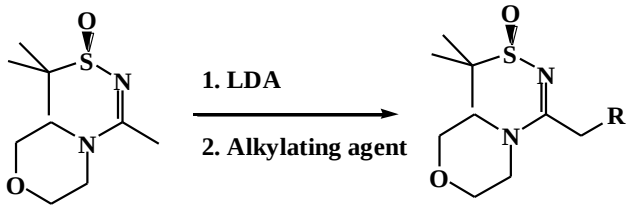
Ellman and co-workers reported the use of a sulfinamide derivative to carry out asymmetric alkylations.[40] It was reported that the amidine **304** underwent stereoselective alkylation when treated with KHMDS in THF at –78 °C followed by an alkyl or aryl halide.



Scheme 90 – Ellman's synthesis of the amidate 304

Armed with this information and *t*-butylsulfinamide, which was readily available in our laboratory from previous work carried out in the group, we were able to produce **303** by heating the orthoester **301** to reflux with *tert*-butylsulfinamide **302** at 110 °C for 3 hours in the presence of a catalytic amount of *p*-toluenesulfonic acid. After completion, the mixture was concentrated and purified by column chromatography to afford **303** in 98% yield as colourless oil. The amidate **303** was stirred with morpholine in methanol and a catalytic amount of sodium cyanide for 20 hours at room temperature, after which the reaction was quenched with aqueous KOH and the mixture was extracted with dichloromethane. The organic extracts were concentrated *in vacuo* and purified by silica gel column chromatography to afford **304** in 96% yield as a white solid, (Scheme **90**). With **304** in

hand, we were able to explore alkylations with a range of alkylating agents, to yield products that had previously not been reported, (Scheme **91**).[39]



304 **307 - 308**

Scheme 91 – Alkylations using the amidate 304

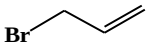
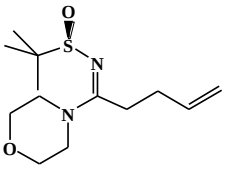
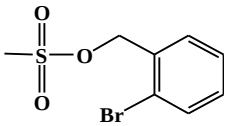
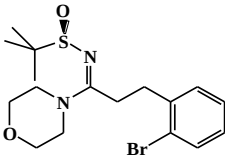
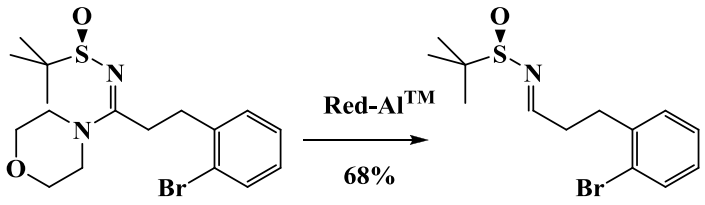
Entry	Alkylating agent	Product	Yield
1	**305** 	**307** 	60%
2	**306** 	**308** 	97%

Table 9 - Alkylations using the amidate 304

The alkylations were carried out by treating the amidine **304** with LDA, produced *in situ* by adding n-butyllithium to diisopropylamine in THF at 0 C. A solution of the amidine **304** was then added slowly to the LDA solution at –78 °C and the mixture stirred for 45 minutes at that temperature after which a solution of the electrophile was added slowly. After completion, the reaction was quenched with acetic acid in THF at –78 °C and followed by a saturated solution of sodium bicarbonate. The mixture was extracted with ethyl acetate, concentrated *in vacuo* and purified by silica gel column chromatography to afford the alkylation products (Table **9**).

The amidine product **307** was obtained in 60% yield on alkylation with allyl bromide after silica gel column chromatography, followed by recrystallisation of the product. For the synthesis of amidine **308,** methylsulfonium protected 2-bromobenzyl alcohol **306** was used instead of 2-bromobenzyl bromide. This was due to the fact that 2-bromobenzyl bromide is extremely lachrymatory and therefore caused problems with handling. The other reasons were the ready availability of the 2-bromobenzyl alcohol and methylsulfonium chloride in our laboratory and the cheaper cost of synthesising methylsulfonium protected 2-bromobenzyl alcohol **306** and the time to be saved rather than ordering 2-bromobenzyl bromide. The amidine **308** was obtained in 97% yield using the same synthetic and purification protocols outlined above. The successful synthesis of **308** alerted us to the fact that it can be used as an alternative route to aminoindane due to its similarity in structure with the sulfinimine **279**. We also discovered that amidines can be easily reduced to their corresponding sulfinimines on reaction with Red-Al™.[40]

Thus, a solution of Red-Al™ was added to a solution of the aldimine **308** in THF at –42 °C and the mixture was stirred at that temperature and monitored by TLC for completion. The reaction was quenched with saturated solution of potassium carbonate and extracted with ethyl acetate. The organic extracts were concentrated and the residue purified by silica gel column chromatography to afford **309** in 68% yield as a colourless viscous oil (Scheme **92**).

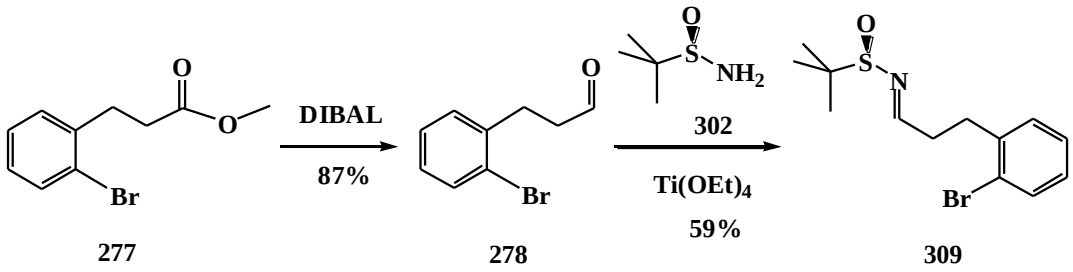


308 **309**

Scheme 92 – Reduction of the amidate 304 to the sulfinimine 305

Alternatively, we were able to synthesise **309** by reducing the ester **277** with DIBAL at –78 °C to afford the aldehyde **278** in 87% yield after purification and condensing with *t*-butanesulfinamide **302** in the presence of $Ti(OEt)_4$ as a water scavenger/promoter. The reaction was quenched as usual by addition of water and filtration through celite and

extraction of the filtrate with ethyl acetate. Concentration of the organic extracts and purification by silica gel column chromatography afforded a colourless viscous oil in 59% yield. It was gratifying to note that all the physical data obtained were consistent with those obtained for **309** using Scheme **93** and we can therefore conclude that the colourless oil obtained by this scheme is in fact compound **309**.



277 **278** **309**

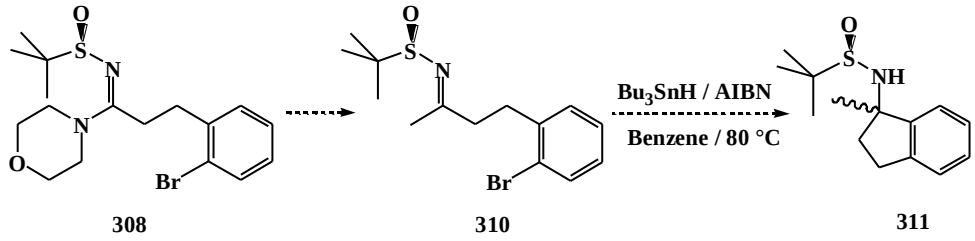
Scheme 93 – Alternative synthesis of the sulfinimine 305

Disappointingly, we were not able to try out the reaction to form the aminoindanyl sulfinamide before the end of our term of research. A successful reaction of **309** would have served as a comparison of the scope and selectivities of the two sulfinyl groups on the novel free radical reaction.

3.1.5 Future work

The other schemes that we proposed but were not able to implement include:

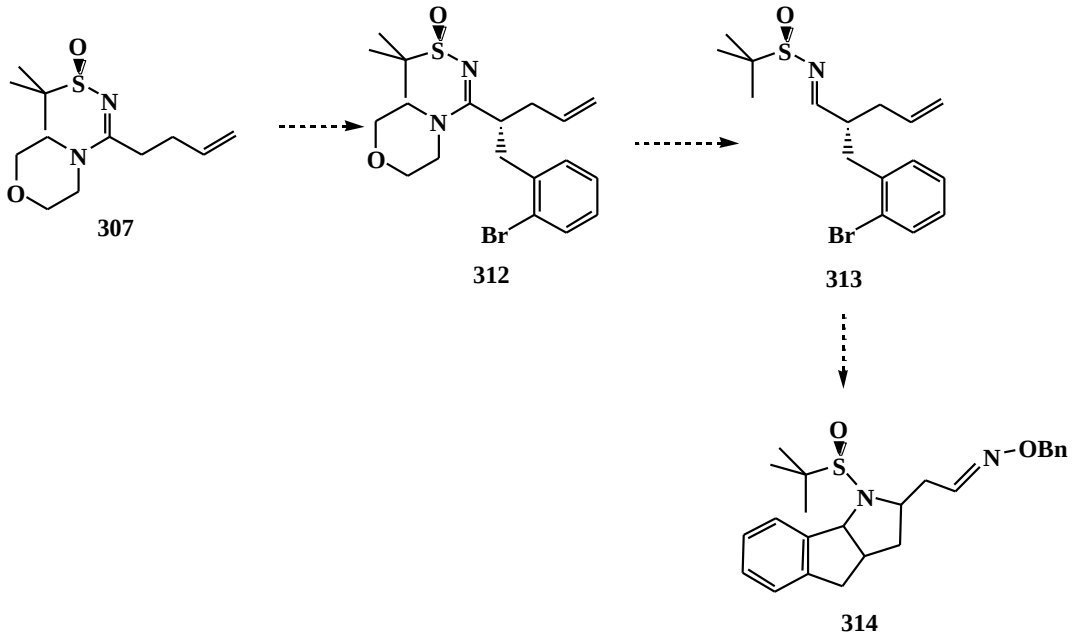
- Synthesis and cyclisation of the ketimine **310** (Scheme **94**)



308 **310** **311**

Scheme 94 – Proposed synthesis of the ketimine 310 and its cyclistion

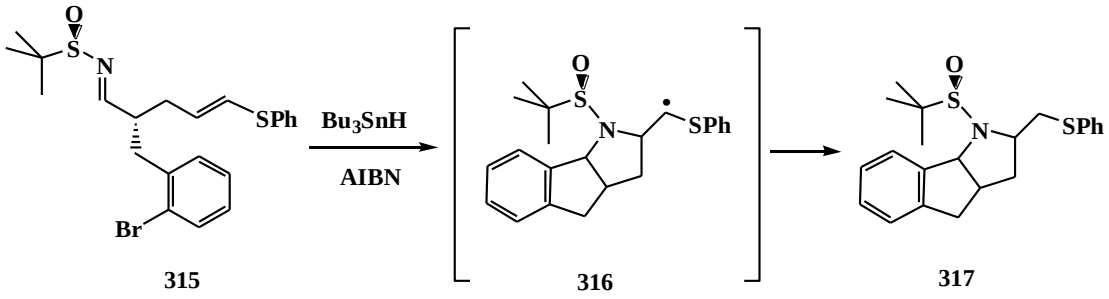
- Asymmetric alkylation of **307** to give the alkylation product **312** which could be reduced to enantiopure **313**, a very useful model substrate for the asymmetric synthesis of the BCD ring of nakadomarin A once we have been able to achieve the elusive double cyclisation (Scheme **95**).



307 **312** **313** **314**

Scheme 95 - Proposed asymmetric alkylation to synthesise 314

- Alternatively, we could investigate electron-rich alkenes in order that the electrophilic *N*-radical might react. Sulfinimine **315** would also be able to stabilise the secondary radical formed with an adjacent sulfide group (Scheme **96**).



315 **316** **317**

Scheme 96 – Proposed use of sulphide substitution as a stabilising group for the 2° radical

3.2 References

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3.0 Experimental

General Procedures

Unless otherwise stated, all chemicals were obtained from commercial sources and used without further purification. The nitrogen and argon used were oxygen and moisture free. The petroleum ether used is light petroleum ether, (b.p. 40-60 °C), THF was freshly distilled from sodium, and DCM was also distilled from sodium. Organic layers were dried over magnesium sulfate or anhydrous sodium sulfate. Temperatures quoted in the reaction conditions are the temperature of the reaction mixtures and not the cooling or heating baths.

Thin layer chromatography was carried out on Whatman glass backed silica gel 60 F254 coated plates or Merck aluminium backed aluminium oxide 60 F254 coated plates. Visualisation was performed through a range of standard procedures including UV, vanillin, potassium permanganate and phosphomolybdic acid.

Column chromatography was performed at ambient temperature using Merck silica gel 60 (0.063-0.200 mm) or BDH neutral or variously deactivated aluminium oxide. Solvent ratios are detailed as v/v.

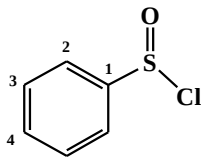
^{1}H-NMR spectra were recorded at 400 MHz on a Varian 400 Lambda spectrometer. Signals are quoted in ppm with tetramethylsilane as an internal reference. ^{13}C-NMR spectra were recorded at 100.6 MHz on the same spectrometer. The solvents and operating frequency are indicated for each set of data, with coupling constant *J* values given in Hertz.

Infrared spectra were recorded on a Perkin-Elmer 1720X FT-IR spectrophotometer as neat films or nujol mulls for solid materials.

Melting points are uncorrected and were recorded using a Stuart Scientific SMP1 melting point apparatus. Low resolution mass spectra, El (low resolution electron impact); ES (low resolution electrospray); CI(chemical ionisation); and High resolution mass spectrometry were obtained *via* the EPSRC National Mass Spectroscopy Service Centre at the University of Wales, Swansea.

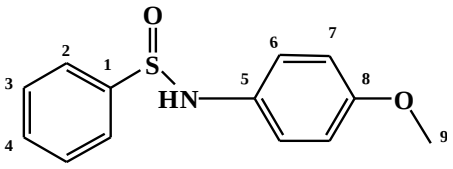
3.1 Attempted synthesis and resolution of sulfinimines via sulfinyl chlorides

Benzenesulfinyl chloride (207) [1]



Sulfur dioxide (~2 mL) was condensed into a dry 50 mL flask kept over an acetonitrile-carbon dioxide bath at –48 °C and under an argon atmosphere. Dry THF (2 mL) was added and stirred. A 3M solution of phenylmagnesium bromide (4 mL, 12 mmol) was added drop-wise over a 30-minute period resulting in a slurry and the mixture stirred for 1 hour at –48 °C and then allowed to reach room temperature slowly until the mixture was homogenous. The mixture was then put over an ice-bath and thionyl chloride (0.95 mL, 13.10 mmol) was added drop-wise (30 minutes) the mixture was allowed to reach room temperature overnight. The mixture was diluted with pentane (50 mL) and filtered through celite on a medium frit. The residue was washed with pentane (3 x 10 mL). Evaporation of the solvent afforded **207** (0.93 g, 99%) as a bright orange oil. δ_H (400MHz, $CDCl_3$) 7.71-7.7.75 (1H, m, 4-H), 7.58-7.63 (2H, m, 2-H), 7.42-7.53 (2H, m, 3-H).

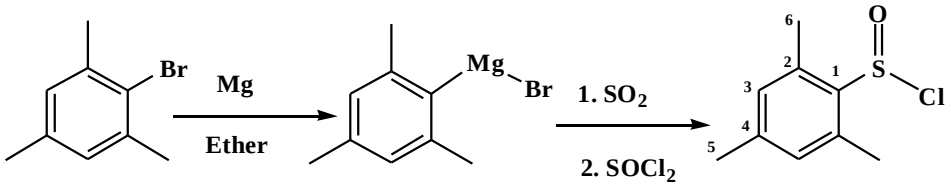
Benzenesulfinic acid (4-methoxyphenyl)-amide (209)[1]



To a stirred solution of p-anisidine (0.63 g, 3.98 mmol) in diethyl ether (5 mL) was added a solution of **207** (0.40 g, 2.49 mmol) in diethyl ether (5 mL) at 0 °C and the mixture stirred for 12 hours. The mixture was filtered and the residue washed with water (2 x 2 mL) and the remaining residue added to the filtrate. Evaporation of the solvent and recrystallisation from pentane afforded **209** (0.12 g, 24%) as purple crystals. Mpt. 129 °C, (Lit. Mpt. 132

°C)[1]; δ_H (400MHz, $CDCl_3$) 7.77-7.78 (2H, m, 2-H), 7.51-7.52 (3H, m, 3-H and 4-H), 7.01-7.04 (2H, m, 7-H) 6.80-6.83 (2H, m, 6-H); MS (EI/CI): m/z 122 (100%), 247 (62%, $[M]^+$); HRMS calculated for $C_{13}H_{13}NNaO_2S$: 270.0559 $[M+Na]^+$, Found: 270.0559.

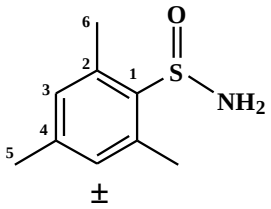
2,4,6-Trimethylbenzenesulfinyl chloride (211)[2]



210 **211**

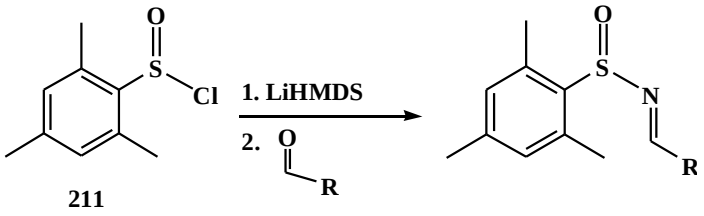
To oven dried magnesium turnings (1.30 g, 54.17 mmol) in a round-bottomed flask kept under argon and fitted with a reflux condenser was added a single crystal of iodine and a few drops of dry diethyl ether added just to wet the magnesium turnings. The mixture was then heated to reflux and a few drops of 2-bromomesitylene added and heated at reflux for 1 hour. More diethyl ether (10 mL) and the rest of the 2-bromomesitylene (8.0 mL, mmol) were added drop-wise. The mixture was then heated at reflux for 18 hours. Sulfur dioxide (~8 mL) was condensed into a dry 500 mL flask kept over an acetonitrile-carbon dioxide bath at –48 °C and under an argon atmosphere. Dry THF (5 mL) was added and stirred. All of the mesitylmagnesium bromide formed was added drop-wise over a 30-minute period forming a slurry and the mixture stirred for 1 hour at –48 °C and then allowed to reach room temperature slowly until the mixture was homogenous. The mixture was then put over an ice-bath and thionyl chloride (4.0 mL, 13.1 mmol) was added drop-wise (30 minutes) the mixture was allowed to reach room temperature overnight. The mixture was diluted with pentane (50 mL) and filtered through celite on a medium frit. The residue was washed with pentane (3 x 10 mL). Evaporation of the solvent afforded **211** (7.40 g, 70%) as a bright orange oil. δ_H (400MHz, $CDCl_3$) 6.82 (2H, s, 3-H), 2.24 (3H, s, 5-H_3), 2.19 (6H, s, 6-H_3); δ_C (100MHz, $CDCl_3$) 143.4, 139.5, 131.7, 129.1, 21.6, 21.3.

2,4,6-Trimethylphenylsulfinamide (212)[3]



In a 100 mL one-neck, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed **211** (0.51 g, 2.49 mmol) in THF (40 mL). The reaction mixture was cooled to -78 °C, and LiHMDS (1.0 M solution in THF, 3.49 mmol) was added drop-wise via syringe. The reaction was warmed to room temperature, stirred for 1 h, and monitored for the disappearance of **211** by TLC. The reaction mixture was quenched with saturated NH_4Cl (30 mL), an additional 10 mL of water was added, and the mixture was extracted with ethyl acetate (3 X 15 mL). The organic phase was dried ($MgSO_4$) and concentrated. Column chromatography gave a solid that was crystallized with *n*-hexane to give **212** (1.05 g, 73%) as colourless crystals. Mpt. 103 - 109 °C (Lit. Mpt. 115-116 °C[5]); IR (neat) 3277, 3101, 2963, 1600, 1449, 1018 cm^{-1}; δ_H (400MHz, $CDCl_3$) 6.85 (2H, s, 3-H), 4.40 (2H, br s, $-NH_2$), 2.58 (6H, s, 6-H_3), 2.27 (3H, s, 5-H_3); δ_C (100MHz, $CDCl_3$) 140.9, 138.9, 136.3, 131.0, 20.9, 19.1; MS (EI/CI): m/z 184 (69%, $[M+H]^+$), 167 (100%); HRMS calculated for $C_9H_{14}NOS$: 184.0790 $[M+H]^+$, Found: 184.0790.

General procedure A for the one-pot synthesis of mesitylsulfinyl imines[6]

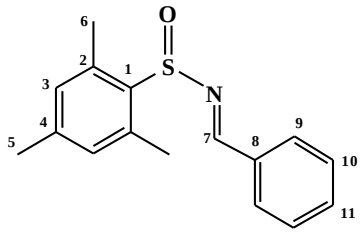


211

To a stirred solution of **211** (1 equiv) in THF under a N_2 atmosphere and cooled to -78 °C was added drop-wise via syringe LiHMDS (1.0 M solution in THF, 1.5 equiv). The reaction was warmed to room temperature, stirred for 1 h, and monitored for the disappearance of **211** by TLC. The aldehyde (1.1 equiv) was added and the mixture stirred

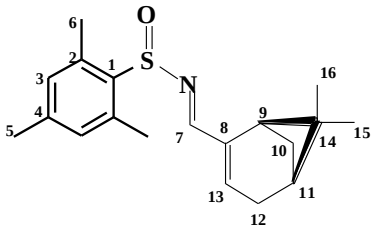
under a N_2 atmosphere at ambient temperatures. Conversion was monitored by TLC after the reaction mixture was quenched with saturated NH_4Cl (30 mL), and the mixture was extracted with ethyl acetate (3 X 20 mL). The combined organic phases were washed with brine (20 mL) and water (20 mL) and dried over $MgSO_4$. Concentration of the organic layer and purification by column chromatography gives a solid that was crystallized with *n*-hexane to give the sulfinyl imines.

***N*-(Benzylidene)-2,4,6-trimethylphenylsulfinamide (215)**



Prepared using General Procedure A with **211** (0.51 g, 2.49 mmol), LiHMDS (3.75 mmol) and benzaldehyde (0.29 g, 2.74 mmol). Isolated as colourless needles (0.41 g, 60%); Mpt. 79 – 83 °C; IR (nujol) 3050, 1607, 1576, 1461 cm^{-1}; δ_H (400MHz, $CDCl_3$) 2.28 (3H, s, 5-H_3), 2.50 (6H, s, 6-H_3), 6.88 (2H, s, 3-H), 7.46-7.47 (3H, m, 10-H, 11-H), 7.84-7.86 (2H, m, 9-H), 8.83 (1H, s, 7-H); δ_C (100MHz, $CDCl_3$) 162.0, 142.1, 138.8, 135.7, 134.2, 132.9, 131.2, 129.9, 129.3, 21.5, 19.3; MS (EI/CI): m/z 271 (26%, M), 167 (83%), 77 (100%); HRMS calculated for $C_{16}H_{17}NOS$: 271.1025 [M^+], Found: 271.1028.

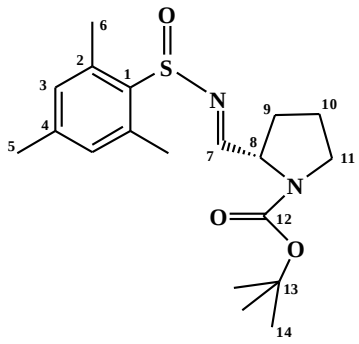
***N*-[6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-ylmethylene)-2,4,6-trimethylphenylsulfinamide (218)**



Prepared General Procedure A with **211** (0.60 g, 2.96 mmol), LiHMDS (2.96 mmol) and (-)-myrtenal (0.29 g, 1.93 mmol). Isolated as dark yellow/orange oil (0.33 g, 56%) as an inseperable 1:1 mixture of diastereomers.

Data for mixture: IR (neat) 2918, 1737, 1677, 1566, 1082 cm^{-1}; δ_H (400MHz, $CDCl_3$) 8.38 and 8.35 (1H, s, 7-H), 6.82 (2H, s, 3-H), 6.42-6.46 (1H, m, 13-H), 2.94-2.97 (1H, m, 9-H), 2.52-2.59 (2H, m, 12-H_2), 2.44 and 2.42 (6H, s, 6-H_3), 2.26 (3H, s, 5-H_3), 2.13-2.16 (1H, m, 11-H), 1.12 (H, d *J* = 9.2, 10-H*H*), 1.06 (1H, d, *J* = 9.2, 10*H*H), 0.79 (3H, s, 16-H_3), 0.72 (3H, s, 15-H_3); δ_C (100MHz, $CDCl_3$) 162.3 and 161.7, 147.4, 141.7, 141.5, 141.1, 138.7, 131.0, 40.9, 40.2, 37.9, 33.2, 31.4, 26.0, 21.3, 21.3, 19.1; MS (EI/CI): m/z 315 (9%, M^+), 167 (71%), 139 (100%), 105 (100%); HRMS calculated for $C_{19}H_{26}NOS$: 316.1730 $[M+H]^+$, Found: 316.1726

***N*-(2-Pyrrolidine-1-carboxylic acid tert-butyl ester)-2,4,6-trimethylphenylsulfinamide (223)**

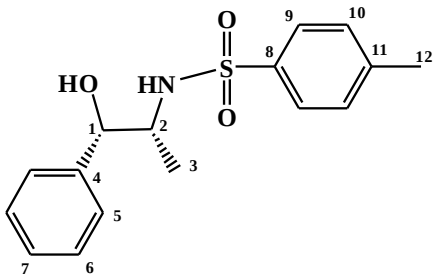


Prepared General Procedure A with **211** (1.23 g, 6.21 mmol), LiHMDS (6.30 mmol) and the aldehyde **222**[6] (1.24 g, 6.21 mmol). Isolated as a colourless viscous oil (1.40 g, 62%) as an inseperable 1:1 mixture of diastereomers.

Data for mixture: IR (neat) 2973, 1693, 1390, 1089 cm^{-1}; δ_H (400MHz, $CDCl_3$) 8.17 and 8.09 (1H, d, *J*=4.2, 7-H), 6.81 (2H, s, 3-H), 4.46-4.60 (1H, m, 8-H), 3.37-3.54 (2H, m, 11-H_2), 2.43 (6H, s, 6-H_3), 2.25 (3H, s, 5-H_3), 1.79-1.90 (2H, m, 9-H_2), 1.39 and 1.35 (9H, s, 14-H_3), 0.80-0.89 (2H, m, 10-H_2); δ_C (100MHz, $CDCl_3$) 167.4 and 1.67.1 (C=N), 157.8 and 157.2 (C=O), 138.4, 131.1, 131.1, 80.4, 60.9, 47.0 and 46.7, 30.5, 29.9, 28.6, 23.8, 21.3, 19.1; MS (EI/CI): m/z 365 (45%, $[M+H]^+$), 214 (100%), 199 (92%); HRMS calculated for $C_{19}H_{29}N_2O_3S$: 365.1893 $[M+H]^+$, Found: 365.1895

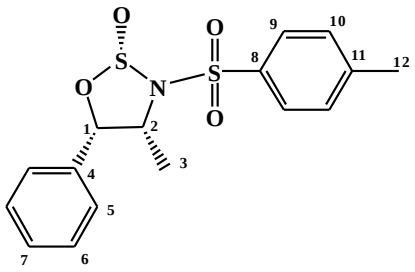
3.2 Synthesis of enantiopure sulfinimines using *N*-tosyl norephedrine

_N_-(2-Hydroxy-1-methyl-2-phenylethyl)-4-methylbenzenesulfonamide (238)[3,4]



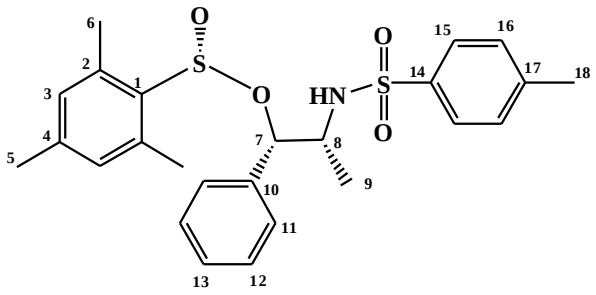
To (1*S*, 2*R*)-(-)-norephedrine hydrochloride (4.00 g, 21.3 mmol) and *p*-toluenesulfonyl chloride (4.06 g, 21.3 mmol) in a 250 mL round bottom flask equipped with a magnetic stirrer was added sodium carbonate (5.65 g, 53.3 mmol). Water (50 mL) and ethyl acetate (50 mL) were added and the reaction was stirred at room temperature overnight. The two layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 20 mL) and the combined organic layer washed with brine (30 mL) and water (30 mL) and dried over $MgSO_4$. Evaporation of the solvent and recrystallisation from hexane afforded **238** (6.37 g, 98%) as colourless crystalline plates. Mpt. 83.0-84.1 °C (Lit. Mpt. for (1*R*, 2*S*)-**238:** 103-105 °C[4b]) ; IR (neat) 3500, 3328, 3032, 2974, 1600, 1350, 1151, 696 cm^{-1}; δ_H (400MHz, $CDCl_3$) 7.75-7.77 (2H, m, 9-H), 7.23-7.32 (7H, m, 5-H, 6-H, 7-H, 10-H), 5.0 (1H, d, *J* = 8.6, NH), 4.78 (1H, d, *J* = 2.7, 1-H), 3.53-3.58 (1H, dqd, *J* = 8.6, 6.8, 2.7, 2-H), 2.75 (1H, b, OH), 2.41 (3H, s, 12-H_3), 0.82 (3H, d, *J* = 6.8, 3-H_3); δ_C (100MHz, $CDCl_3$) 143.6, 140.3, 137.9, 129.9, 128.4, 127.8, 127.1, 126.2, 75.9, 54.8, 21.4, 14.7; MS (EI/CI): m/z 323 (80%, $[M+NH_4]^+$), 189 (100%), 152 (77%); HRMS calculated for $C_{16}H_{23}N_2O_3S$: 323.1424 $[M+NH_4]^+$, Found: 323.1426

(*R*)-4-Methyl-5-phenyl-3-(toluene-4-sulfonyl)-[1,2,3]oxathiazolidine-2-oxide (239)[3,4]



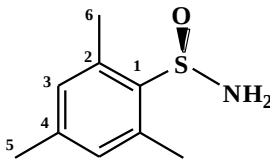
A 2-neck 250 mL round-bottom flask fitted with an addition funnel and equipped with a magnetic stirrer and argon inlet was charged with **238** (10.34 g, 33.9 mmol) and THF (60 mL). After the reaction mixture was chilled to -78 °C, thionyl chloride (5.64 g, 47.4 mmol) was added slowly *via* a syringe in one portion, followed by slow addition of pyridine (6.7 g, 0.84 mol) in THF (30 mL) over a 3-4 h period. After the addition was completed, the reaction mixture was stirred for 30 min, warmed to –45 °C with stirring, and the reaction was monitored by TLC analysis. Once the reaction was completed, the reaction was quenched with saturated $NaHCO_3$ aqueous solution (30 mL), and the mixture was diluted with ethyl acetate (40 mL) and warmed to ambient temperature with stirring. The phases were allowed to separate and the aqueous phase was removed. The organic phase was washed with brine (20 mL), dried, and evaporated to dryness to afford a white to off white crystalline product. Crystallization of the crude product from ethyl acetate/hexane gave **239** (10.83 g, 91%) as colourless crystalline plates. Mpt. 125.9-126.8 °C (No Lit. Mpt. available); IR (neat) 2980, 1594, 1349, 1197, 1162 cm^{-1}; δ_H (400MHz, $CDCl_3$) 7.49-7.52 (2H, m, 9-H), 6.91-7.01 (7H, m, 5-H, 6-H, 7-H, 10-H), 5.21 (1H, d, *J* = 5.5, 1-H), 3.79-3.88 (1H, qd *J* = 6.9, 5.5, 2-H), 2.08 (3H, s, 12-H_3), 0.47 (3H, d, *J* = 6.9, 3-H_3). δ_C (100MHz, $CDCl_3$) 145.3, 136.6, 133.4, 130.4, 129.2, 128.9, 127.7, 126.4, 92.1, 57.1, 21.5, 16.6; MS (EI/CI): m/z 369 (100%, $[M+NH_4]^+$), 288 (47%), 134 (49%); HRMS calculated for $C_{16}H_{21}N_2O_4S_2$: 369.0937 $[M+NH_4]^+$, Found: 369.0940

2,4,6-Trimethylbenzenesulfinic acid 1-phenyl-2-(toluene-4-sulfonylamino)-propyl ester (240)[4]



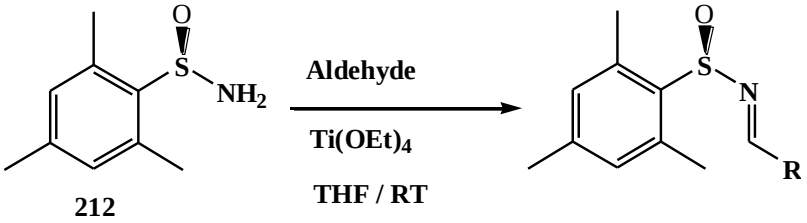
A 2-neck 100 mL round-bottom flask fitted with a stirring bar and argon inlet, was charged with **239** (4.89 g, 13.90 mmol) and THF (20 ml). The mixture was stirred at ambient temperature to give a solution, and cooled to –78 °C, followed by addition of MesMgBr (20 mL, 0.8 M in Ether) slowly *via* a syringe. After stirring at –78 °C for 1 h, the reaction mixture was warmed to –45 °C and the reaction was monitored by TLC analysis. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (10 mL) and diluted with ethyl acetate (20 mL). The aqueous phase was extracted with ethyl acetate (10 mL). The organic phases were combined and washed with brine (20 mL) and water (10 mL), dried over Na_2SO_4, and concentrated to afford **240** (5.95 g, 91%) as a white "sticky" solid. Found: IR (neat) 3247, 2980, 1330, 1089 cm^{-1}; δ_H (400MHz, $CDCl_3$) 7.75-7.86 (2H, m), 7.24-7.35 (5H, m), 6.99-7.01 (2H, m), 6.85 (2H, s, 3-H), 5.63 (1H, d, J=9.4, NH), 5.04 (1H, d, *J* = 2.5, 7-H) 3.70-3.74 (1H, dqd, *J* = 9.4, 6.9, 2.5, 8-H), 2.48 (6H, s, 6-H3), 2.42 (3H, s, 18-H3), 2.29 (3H, s, 1-H3), 1.00 (3H, d, J=6.9, 9-H3); δ_C (100MHz, $CDCl_3$) 143.6, 142.7, 138.5, 138.0, 137.8, 137.6, 131.0, 130.0, 128.7, 128.4, 127.4, 126.0, 85.0, 60.6, 54.6, 21.8, 21.4, 21.3, 19.3, 15.3, 14.4; MS (EI/CI): m/z 489 (8%, $[M+NH_4]^+$), 472 (4%, $[M+H]^+$), 288 (100%), 189 (61%), 152 (86%); HRMS calculated for $C_{25}H_{31}N_2O_4S_2$: 489.1876 $[M+NH_4]^+$, Found: 489.1875

(*R*)-(-)-2,4,6-Trimethylphenylsulfinamide (212)[3,5]



In a 100 mL one-neck, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed **240** (0.43 g, 0.91 mmol) in THF (20 mL). The reaction mixture was cooled to -78 °C, and LiHMDS (1.0 M solution in THF, 1.22 mmol) was added drop-wise via syringe. The reaction was warmed to room temperature, stirred for 1 h, and monitored for the disappearance of **240** by TLC. The reaction mixture was quenched with saturated NH_4Cl (30 mL), an additional 10 mL of water was added, and the mixture was extracted with ethyl acetate (3 X 15 mL). The organic phase was dried ($MgSO_4$) and concentrated. Column chromatography gives a solid that was crystallized with *n*-hexane to give **212** (0.12 g, 72%) of colourless needles. Mpt. 93.5-95.6 °C [Lit. Mpt. for opposite enantiomer: 115-116 °C (Toluene), 125-126 °C (Ethyl acetate)][5]; $[\alpha]^{25}_{D}$ –161.2 (*c* 0.5, $CHCl_3$) [Lit. for opposite enantiomer: $[\alpha]^{20}_{D}$ +177.8 (*c* 0.5, $CHCl_3$)][5]; IR (neat) 3277, 3101, 2963, 1600, 1449, 1018 cm^{-1}; δ_H (400MHz, $CDCl_3$) 6.85 (2H, s, 3-H), 4.40 (2H, b, $-NH_2$), 2.58 (6H, s, 6-H_3), 2.27 (3H, s, 5-H_3); δ_C (100MHz, $CDCl_3$) 140.5, 139.0, 136.2, 130.7, 20.8, 19.1; MS (EI/CI): m/z 184 (69%, $[M+H]^+$), 167 (100%); HRMS calculated for $C_9H_{14}NOS$: 184.0790 $[M+H]^+$, Found: 184.0790.

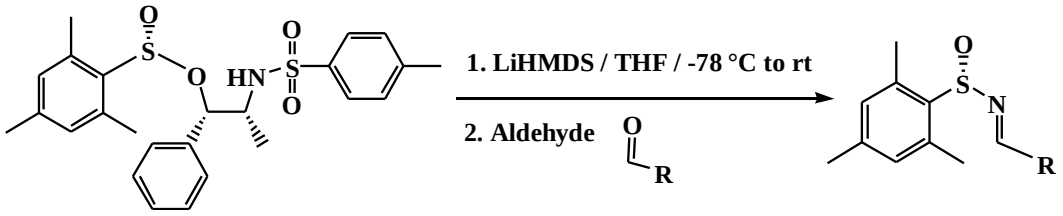
General procedure B for the condensation of aldehydes with mesitylsulfinamide 212[6,7]



212

A solution of **212** (1 equiv), $Ti(OEt)_4$ (3 equiv) and aldehyde (1.1 equiv) in THF was stirred under a N_2 atmosphere at ambient temperatures. Conversion was monitored by TLC after which the mixture was poured into an equal volume of brine while rapidly stirring. The resulting suspension was filtered through a plug of celite, and the filter cake was washed with EtOAc. The filtrate was transferred to a separatory funnel where the organic layer was washed with brine. The brine layer was extracted once with a small volume of EtOAc, and the combined organic portions were dried (Na_2SO_4), filtered, and concentrated. The sulfinyl imines were purified by silica gel chromatography

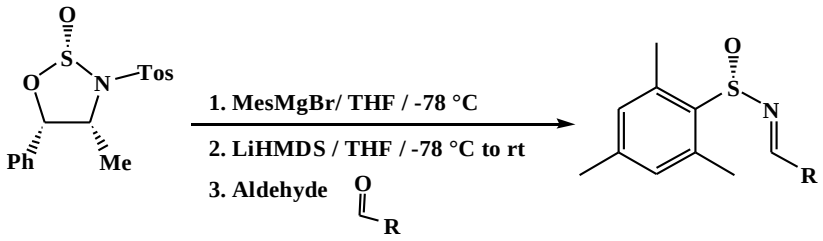
General procedure C for the one-pot synthesis of mesitylsulfinyl imines from 2,4,6-trimethylbenzenesulfinic acid 1-phenyl-2-(toluene-4-sulfonylamino)propyl ester (240)



A solution of LiHMDS in THF (2 equiv) was added drop-wise via syringe to a solution of the sulfinate **240** at -78 °C and the reaction mixture was warmed to room temperature. The reaction was stirred at room temperature for 1 hour and monitored for completion by TLC. The aldehyde (1.1 equiv) and $Ti(OEt)_4$ (3 equiv) were then added to the reaction mixture and stirred at room temperature. Conversion was monitored by TLC after which the

mixture was quenched with a saturated solution of $NaHCO_3$ with rapid stirring. The resulting suspension was filtered through a plug of celite, and the filter cake was washed with ethyl acetate. The filtrate was transferred to a separatory funnel and the phases separated. The organic layer was then washed with brine and the combined aqueous layer was extracted once with ethyl acetate. The combined organic portions were dried sodium sulfate (Na_2SO_4), filtered and concentrated. The sulfinyl imines were purified by silica gel chromatography.

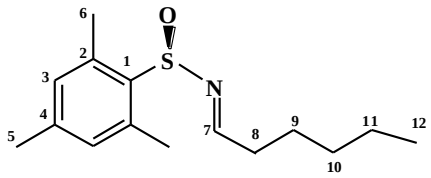
General Procedure D for the one-pot synthesis of mesitylsulfinyl imines from (*R*)-4-methyl-5-phenyl-3-(toluene-4-sulfonyl)-[1,2,3]oxathiazolidine 2-oxide (239)



In a 100 mL one-neck, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed **239** (1 equiv.) in THF (40 mL). The reaction mixture was cooled to -78 °C, followed by addition of MesMgBr (1.15 equivalents in ether) slowly *via* a syringe. After the addition, the reaction was stirred at –78 °C for 1 h and the reaction mixture was warmed to –45 °C and monitored by TLC analysis. After completion, a solution of LiHMDS in THF (2 equiv) was added drop-wise via syringe and the reaction mixture was warmed to room temperature. The reaction was stirred at room temperature for 1 hour and monitored for completion by TLC. The aldehyde (1.1 equiv) and $Ti(OEt)_4$ (3 equiv) were then added to the reaction mixture and stirred at room temperature. Conversion was monitored by TLC after which the mixture was quenched with a saturated solution of $NaHCO_3$ with rapid stirring. The resulting suspension was filtered through a plug of celite, and the filter cake was washed with ethyl acetate. The filtrate was transferred to a separatory funnel and the phases separated. The organic layer was then washed with brine and the combined aqueous layer was extracted once with ethyl acetate. The combined organic portions were dried Na_2SO_4, filtered and concentrated. The sulfinyl imines were purified by silica gel chromatography.

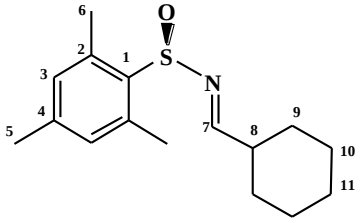
The yields for all the sulfinimines quoted below are based on General Procedure D:

(*R*)-*N*-Hexylidene-2,4,6-trimethylphenylsulfinamide (244)



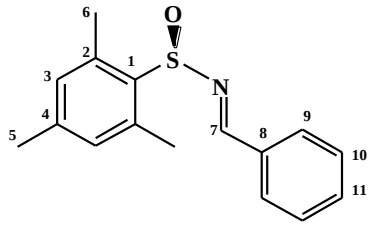
Product obtained as a viscous colourless oil (0.53 g, 46% yield). $[\alpha]^{25}_{D}$ –239.6 (*c* 0.52, $CHCl_3$); IR (neat) 2954, 2926, 1732, 1617, 1087, 619 cm^{-1}; δ_H (400MHz, $CDCl_3$) 8.22 (1H, t, *J*=5.1, 7-H), 6.77 (2H, s, 3-H), 2.42-2.47 (2H, m, 8-H_2), 2.38 (6H, s, 6-H_3), 2.19 (3H, s, 5-H_3), 1.51-1.57 (2H, m, 9-H_2), 1.15-1.30 (4H, m, 10-H_2 and 11-H_2), 0.84 (3H, t, *J* = 8, 12-H_3); δ_C (100MHz, $CDCl_3$) 168.5, 141.8, 138.4, 135.3, 131.0, 36.1, 31.6, 25.6, 22.6, 21.3, 19.0, 14.1; MS (EI/CI): m/z 265 (8%, M^+), 143 (91%), 157 (100%), 91 (91%); HRMS calculated for $C_{15}H_{24}NOS$: 266.1573 $[M+H]^+$, Found: 266.1575

(*R*)-*N*-(Cyclohexylmethylene)-2,4,6-trimethylphenylsulfinamide (245)



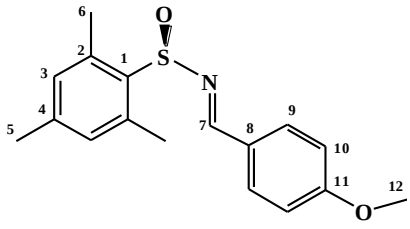
Product obtained as a pale yellow viscous oil (0.72 g, 60% yield). $[\alpha]^{25}_{D}$ –237.9 (*c* 0.52, $CHCl_3$); IR (neat) 2925, 2855, 1595, 1449, 1431, 1092 cm^{-1}; δ_H (400MHz, $CDCl_3$) 8.15 (1H, d, *J* = 5.2, 7-H), 6.81 (2H, s, 3-H), 2.42 (6H, s, 6-H_3), 2.24 (3H, s, 5-H_3), 2.18-2.23 (1H, m, 8-H), 1.49-1.84 (2H, m), 1.13-1.41 (4H, m, 10-H_2), 0.82-0.87 (2H, m, 11-H_2); δ_C (100MHz, $CDCl_3$) 171.4, 141.6, 138.4, 135.4, 130.9, 43.0, 21.2, 25.7, 25.2, 20.9, 18.6; MS (EI/CI): m/z 277 (8%, M^+), 167 (90%), 139 (100%), 105 (92%), 91 (69%); HRMS calculated for $C_{16}H_{24}NOS$: 278.1573 $[M+H]^+$, Found: 278.1577

(*R*)-*N*-(Benzylidene)-2,4,6-trimethylphenylsulfinamide (246)



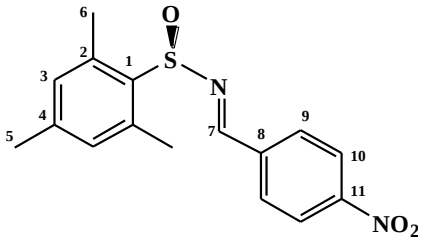
Product obtained as colourless crystalline plates (0.87 g, 54% yield). Mpt. 94.4-95.6 ºC; $[\alpha]^{25}_{D}$ –150.7 (*c* 0.52, $CHCl_3$); IR (neat) 2981, 2879, 1602, 1572, 1448 cm^{-1}; δ_H (400MHz, $CDCl_3$) 8.82 (1H, s, 7-H), 7.83-7.85 (2H, m, 9-H), 7.46-7.47 (3H, m, 10-H, 11-H), 6.85 (2H, s, 3-H), 2.49 (6H, s, 6-H_3), 2.27 (3H, s, 5-H_3); δ_C (100MHz, $CDCl_3$) 161.9, 141.9, 138.7, 135.6, 134.1, 132.7, 131.1, 129.8, 129.1, 21.3, 19.1; MS (EI/CI): m/z 271 (26%, M), 167 (83%), 77 (100%); HRMS calculated for $C_{16}H_{17}NOS$: 271.1025 [M^+], Found: 271.1028.

(*R*)-*N*-(4-Methoxybenzylidene)-2,4,6-trimethylbenzenesulfinamide (253)



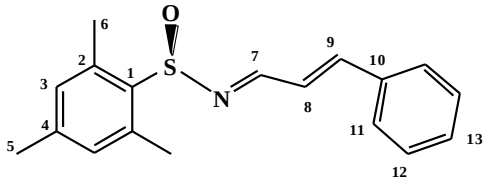
Product obtained as off-white cubes (0.54 g, 50% yield). Mpt. 84.3-86.1 ºC; $[\alpha]^{25}_{D}$ –86.7 (*c* 0.5, $CHCl_3$); IR (neat) 2964, 2931, 3863, 1597, 1563, 1420, 1247, 1081 cm^{-1}; δ_H (400MHz, $CDCl_3$) 8.75 (1H, s, 7-H), 7.79-7.81 (2H, m, 10-H), 6.94-6.97 (2H, m, 9-H), 6.85 (2H, s, 3-H), 3.86 (3H, s, 12-H_3), 2.50 (6H, s, 6-H_3), 2.28 (3H, s, 5-H_3); δ_C (100MHz, $CDCl_3$) 163.1, 160.8, 141.6, 138.5, 135.8, 131.5, 130.8, 127.1, 114.3, 55.5, 21.1, 18.9; MS (EI/CI): m/z 302 (44%, $[M+H]^+$), 136 (81%), 52 (100%); HRMS calculated for $C_{17}H_{19}NO_2S$: 302.1209 $[M+H]^+$, Found: 302.1211

(*R*)-*N*-(4-Nitrobenzylidene)-2,4,6-trimethylbenzenesulfinamide (254)



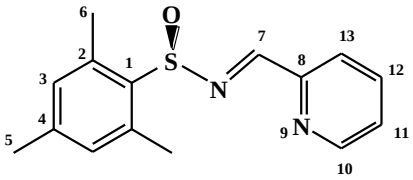
Product obtained as yellow crystalline needles (0.29 g, 36% yield). Mpt. 146.2-147.0 ºC; $[\alpha]^{25}_{D}$ –43.1 (*c* 0.5, $CHCl_3$); IR (neat) 3110, 2993, 1737, 1582, 1516, 1088, 1078 cm^{-1}; δ_H (400MHz, $CDCl_3$) 8.91 (1H, s, 7-H), 8.29-8.33 (2H, m, 10-H), 8.00-8.04 (2H, m, 9-H), 6.88 (2H, s, 3-H), 3.86 (3H, s, 12-H_3), 2.50 (6H, s, 6-H_3), 2.30 (3H, s, 5-H_3); δ_C (100MHz, $CDCl_3$) 159.3, 149.9, 142.5, 138.9, 138.5, 134.5, 131.0, 130.2, 124.2, 21.1, 18.9; MS (EI/CI): m/z 317 (3%, $[M+H]^+$), 287 (6%), 136 (20%), 155 (100%); HRMS calculated for $C_{16}H_{17}N_2O_3S$: 317.0954 $[M+H]^+$, Found: 317.0949

(*R*)-*N*-(3-Phenylallylidene)-2,4,6-trimethylphenylsulfinamide (255)



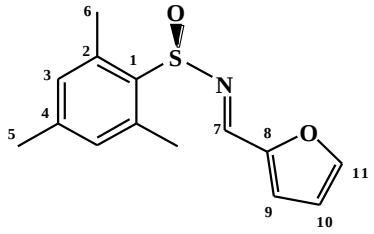
Product obtained as yellow crystalline plates (0.51 g, 57% yield). Mpt. 104.7-106.2 ºC; $[\alpha]^{25}_{D}$ –401.7 (*c* 0.53, $CHCl_3$); IR (neat) 2976, 1827, 1623, 1598, 1566, 1448, 1071, 995, 753 cm^{-1}; δ_H (400MHz, $CDCl_3$) 8.53 (1H, d, *J* = 9.2, 7-H), 7.44-7.47 (2H, m, Ar-H), 7.31-7.38 (2H, m, Ar-H), 7.18-7.19 (1H, m, Ar-H), 7.16 (1H, dd, *J* = 9.2, 6.7, 8-H), 7.05 (1H, d, *J* = 6.7, 9-H), 6.79 (2H, s, 3-H), 2.42 (6H, s, 6-H_3), 2.20 (3H, s, 5-H_3); δ_C (100MHz, $CDCl_3$) 162.6, 146.5, 141.8, 138.4, 135.0, 131.0, 130.4, 129.1, 128.6, 128.0, 125.5, 21.0, 18.7; MS (EI/CI): m/z 297 (10%, M^+), 249 (27%), 167 (55%), 105 (100%), 91 (70%); HRMS calculated for $C_{18}H_{20}NOS$: 298.1260 $[M+H]^+$, Found: 298.1261

(*R*)-*N*-(Pyridin-2-ylmethylene)-2,4,6-trimethylbenzenesulfiamide (256)



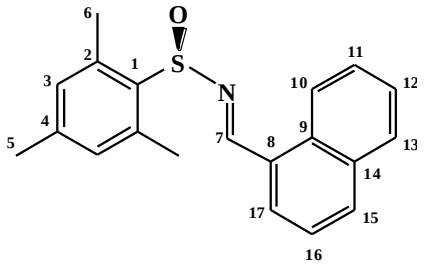
Product obtained as off-white cubes (0.10 g, 30% yield). Mpt. 86.3-88.1 ºC; $[\alpha]^{25}_{D}$ –151.9 (*c* 0.51, $CHCl_3$); IR (neat) 2958, 1600, 1464, 1087 cm^{-1}; δ_H (400MHz, $CDCl_3$) 8.94 (1H, s, 7-H), 8.74-8.76 (1H, m, 10-H), 7.98-8.00 (1H, m, 13-H), 7.79-7.81 (1H, m, 11-H) 7.38-7.41 (1H, m, 12-H), 6.86 (2H, s, 3-H), 2.51 (6H, s, 6-H_3), 2.28 (3H, s, 5-H_3); δ_C (100MHz, $CDCl_3$) 162.2, 152.3, 150.2, 141.9, 138.6, 136.8, 134.9, 130.9, 126.0, 123.7, 20.4, 18.9; MS (EI/CI): m/z 272 (3%, M^+), 139 (20%), 105 (66%), 91 (65%), 78 (100%); HRMS calculated for $C_{15}H_{17}N_2OS$: 273.1056 $[M+H]^+$, Found: 273.1055

(*R*)-*N*-(Furan-2-ylmethylene)-2,4,6-trimethylbenzenesulfinamide (257)



Product obtained as white "wool-like" solid (0.34 g, 44% yield). Mpt. 102.2-103.3 ºC; $[\alpha]^{25}_{D}$ –127.1 (*c* 0.52, $CHCl_3$); IR (neat) 3128, 2971, 1737, 1604, 1546, 1473, 1076, 791, 763 cm^{-1}; δ_H (400MHz, $CDCl_3$) 8.64 (1H, s, 7-H), 7.62-7.63 (1H, m, 11-H), 7.04-7.05 (1H, m, 9-H), 6.84 (2H, s, 3-H), 6.56-6.57 (2H, m, 10-H), 2.49 (6H, s, 6-H_3), 2.27 (3H, s, 5-H_3); δ_C (100MHz, $CDCl_3$) 150.5, 148.8, 147.1, 141.8, 138.6, 135.1, 130.9, 119.0, 112.6, 21.1, 18.9; MS (EI/CI): m/z 261 (9%, M^+), 213 (46%), 167 (50%), 139 (73%), 105 (100%); HRMS calculated for $C_{14}H_{16}NO_2S$: 262.0896 $[M+H]^+$, Found: 262.0893

(*R*)-*N*-(Naphthalen-1-ylmethylene)-2,4,6-trimethylbenzenesulfiamide (258)



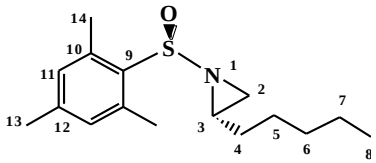
Product obtained as yellow crystalline cubes (0.82 g, 44% yield). Mpt. 121.7-122.0 ºC; $[\alpha]^{25}_{D}$ –120.0 (*c* 0.54, $CHCl_3$); IR (neat) 2964, 2360, 1594, 1567, 1081 cm^{-1}; δ_H (400MHz, $CDCl_3$) 9.49 (1H, s, 7-H), 8.90-8.92 (1H, d *J*= 8.4, 17-H), 8.05 (1H, d, *J*= 7.1, 15-H), 7.98 (1H, d, *J*= 8.2, 10-H), 7.88 (1H, dd, *J*= 8.4, 7.1, 16-H), 7.52-7.61 (3H, m, 11-H, 12-H, 13-H), 6.86 (2H, s, 3-H), 2.56 (6H, s, 6-H_3), 2.27 (3H, s, 5-H_3); δ_C (100MHz, $CDCl_3$) 161.0, 141.7, 138.5, 135.7, 133.9, 133.2, 131.4, 131.2, 130.9, 129.4, 128.8, 128.0, 126.5, 125.2, 124.1, 20.9, 18.8; MS (EI/CI): m/z 322 (14%, $[M+H]^+$), 171 (40%), 156 (100%); HRMS calculated for $C_{20}H_{20}NOS$: 322.126 [M+H], Found: 322.126

3.3 Synthesis of aziridines

General procedure E for the preparation of mono-substituted mesitylsulfinyl aziridines[8,9,10]

NaH (60% in mineral oil, 3 equivalents) was washed with pentane (2 x 5 mL) under argon and the pentane was removed by use of a syringe after the NaH had settled. To the pre-washed NaH was added DMSO (5 mL) and trimethysulfonium iodide (3 equivalents) was added in small portions. The slurry was stirred at room temperature under argon until the solution became clear after which the mesitylsulfinimine (1 equivalent) was added drop-wise as a solution in DMSO (3 mL). The reaction was stirred at room temperature and monitored for completion by TLC. After completion, ice-cold saturated brine was added on completion and then filtered through a short pad of celite. The filtrate was extracted with ethyl acetate (3 x 20 mL) and concentrated in vacuo. The residue was redissolved in hexane-diethyl ether solution (1:1, 20 mL) and washed with water (20 mL) and the organic layer dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography using activity 4 alumina to give the sulfiny aziridines.

2-Pentyl-1-(2,4,6-trimethylbenzenesulfinyl)aziridine (259)

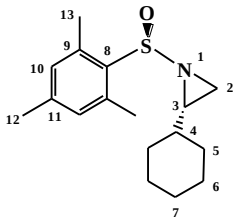


Imine **244** (0.45 g, 1.70 mmol) was reacted using general procedure E to give the product as a colourless oil (0.44 g, 93%) as an inseperable 4:1 mixture of diastereomers (major diastereomer **259a** shown),

Data for major diastereomer 259a: IR (neat) 3691, 2959, 2254, 1602, 1086 cm^{-1}; δ_H (400MHz, $CDCl_3$) 6.86 (2H, s, 11-H), 2.68-2.73 (1H, m, 3-H), 2.62 (6H, s, 14-H_3), 2.31 (3H, s, 13-H_3), 2.20 (1H, d, J = 6.8, 2-H_a), 1.90 (1H, d, J = 4.4, 2-H_b), 1.12 – 1.59 (8H, m), 0.83 (3H, m, 8-H_3); δ_C (100MHz, $CDCl_3$) 138.2, 130.4, 130.0, 128.2, 38.1, 21.5, 32.5,

32.4, 25.1, 29.8, 23.1, 14.0, 14.1; MS (EI/CI): m/z 289 (50%), 302 (100%, $[M+H]^+$); HRMS calculated for $C_{16}H_{25}NNaOS$: 302.1549 [M+Na], Found: 302.1546

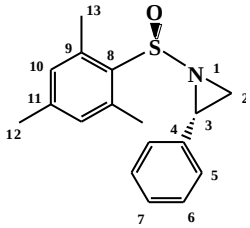
2-Cyclohexyl-1-(2,4,6-trimethylbenzenesulfinyl)aziridine (260)



Imine **245** (0.53 g, 1.91 mmol) was reacted using general procedure E to give the product as a colourless oil (0.37 g, 66%) as an inseperable 5:1 mixture of diastereomers (major diastereomer **260a** shown),

Data for major diastereomer 260a: IR (neat) 3691, 2929, 2254, 1602, 1084 cm^{-1}; δ_H (400MHz, $CDCl_3$) 6.86 (2H, s, 10-H), 2.63 (6H, s, 13-H_3), 2.49-2.52 (1H, m, 3-H), 2.31 (3H, s, 12-H_3), 2.16 (1H, d, J = 6.8, 2-H_a), 1.90 (1H, d, J = 5.2, 2-H_b), 1.60-1.66 (1H, m, 4-H), 1.05-1.26 (6H, m), 0.81-0.96 (4H, m); δ_C (100MHz, $CDCl_3$) 136.3, 130.2, 129.5, 128.4, 38.1, 21.5, 32.9, 32.7, 31.4, 29.8, 23.1, 22.6; MS (EI/CI): m/z 314 (100%, $[M+Na]^+$), 291 (23%, M^+); HRMS calculated for $C_{17}H_{25}NNaOS$: 314.1549 [M+Na], Found: 314.1535

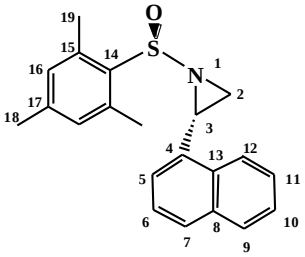
2-Phenyl-1-(2,4,6-trimethylbenzenesulfinyl)aziridine (261)



Imine **246** (0.35 g, 1.29 mmol) was reacted using general procedure E to give the product as a colourless oil (0.35 g, 95%) as an inseperable 9:2 mixture of diastereomers (major diastereomer **261a** shown),

Data for major diastereomer 261a: IR (neat) 2926, 1498, 1087, 908 cm^{-1}; δ_H (400MHz, $CDCl_3$) 7.12-7.30 (5H, m, Ar), 6.83 (2H, s, 10-H), 3.86 (1H, dd, *J* = 4.8, 6.8, 3-H), 2.62 (1H, d, *J* = 4.8, 2-H_a), 2.60 (6H, s, 13-H_3), 2.30 (1H, d, *J* = 6.8, 2-H_b), 2.28 (3H, s, 12-H_3); δ_C (100MHz, $CDCl_3$) 136.8, 130.1, 130.0, 128.1, 127.5, 127.3, 125.9, 125.6, 32.7, 31.4, 28.9, 18.0; MS (EI/CI): m/z 286 (54%, $[M+H]^+$), 120 (100%); HRMS calculated for $C_{17}H_{20}NOS$: 286.1260 [M+H], Found: 286.1262

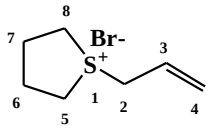
2-Naphthalen-1-yl-1-(2,4,6-trimethylbenzenesulfinyl)aziridine (262)



Imine **258** (0.20 g, 0.62 mmol) was reacted using general procedure E to give the product as a colourless oil (0.10 g, 50%) as an inseperable 8:1 mixture of diastereomers (major diastereomer **262a** shown),

Data for major diastereomer 262a: IR (neat) 3979, 1596, 1089 cm^{-1}; δ_H (400MHz, $CDCl_3$) 8.22 (1H, d, Ar), 7.85 (1H, d, Ar-H), 7.72 (1H, d, Ar-H), 7.51 (2H, m, Ar-H), 7.23 (1H, m, Ar-H), 7.12 (1H, d, Ar-H), 6.83 (2H, s, 16-H), 4.38 (1H, dd, *J* = 4.0, 4.0, 3-H), 2.75 (1H, d, *J* = 4.0, 2-H_a), 2.61 (6H, s, 19-H_3), 2.27 (3H, s, 18-H_3), 2.21 (1H, d, *J* = 4.0, 2-H_b); δ_C (100MHz, $CDCl_3$) 136.8, 133.3, 133.1, 132.6, 130.1, 130.0, 128.1, 127.5, 127.3, 125.9, 125.6, 128.5, 127.8, 126.4, 32.7, 31.4, 28.9, 18.0; MS (EI/CI): m/z 358 (100%, $[M+Na]^+$); HRMS calculated for $C_{21}H_{21}NNaOS$: 358.1236 [M+Na], Found: 358.1222

S-Allyltetrahydrothiophenium bromide[9] (85)

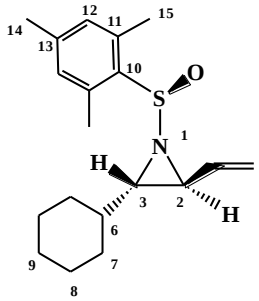


To a solution of allyl bromide, (14.3 ml, 19.9 g, 165 mmol) in anhydrous methanol (100 ml), under an atmosphere of nitrogen at 0 °C was added tetrahydrothiophene (14.6 ml, 14.6 g, 165 mmol) dropwise over a period of 10 minutes. The mixture was then stirred over 6 days, with the progress of the reaction monitored by TLC, (1:1 pet. ether / EtOAc). Once complete, the methanol was removed under reduced pressure, yielding a yellow oil, (19.4 g, 91 %). The oil was triturated with Et_2O, to yield an off white solid. Washing with anhydrous toluene afforded *S*-allyl tetrahydrothiophenium bromide, 264, (19.2 g, 90 %), as a white crystalline powder. IR (thin film)/cm^{-1} 2940, 2360, 2198, 1634, 1420, 1255, 920; δ_H (400MHz, $CDCl_3$) 5.8-5.65 (1H, ddt, *J* = 16.8, 10, 7.2, H-3), 5.59 (1H, d, *J* = 16.8, H-4), 5.37 (1H, d, *J* = 10, H-4), 4.26 (1H, d, *J* = 7.2, 2-H_2), 3.67-3.62 (2H, m, 5 or 8-H_2), 3.49-3.45 (2H, m, 5 or 8-H_2), 2.82-2.21 (4H, m, 6-H_2, 7-H_2); δ_C (100MHz, $CDCl_3$) 127.42, 125.36 , 45.17, 43.39, 29.21.

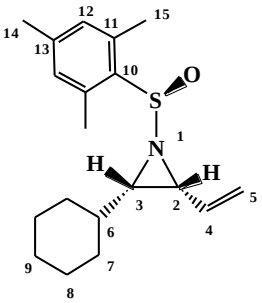
2-Cyclohexyl-1-(2,4,6-trimethylbenzenesulfinyl)-3-vinylaziridine (265)

A solution of the *S*-allyltetrahydrothiophenium bromide, (0.31, 1.50 mmol), in anhydrous tetrahydrofuran, (5 mL), was stirred at room temperature under an atmosphere of argon. After 10 minutes, a solution of the mesitylsulfinyl imine **260** (0.28 g, 1.00 mmol), in anhydrous tetrahydrofuran, (5 mL), was added to the reaction mixture. The cloudy dispersion was then stirred for a further 20 minutes. At this stage the lithium *tert*-butoxide, (1.5 mL, 1.0 M, 1.50 mmol), was added, portion-wise, to the reaction mixture, resulting in a significant colour change. Once the reaction was complete, ice-cold brine, (15 mL), was added, and the biphasic reaction was stirred rapidly for 10 minutes. The resulting cloudy mixture was then filtered through a pad of celite, the product extracted into diethyl ether, washed with brine and dried over sodium sulfate. The organic fraction was concentrated *in vacuo* to yield a crude mixture containing the aziridine which was isolated by column

chromatography to afford **265** (0.23 g, 73%) as a colourless oil[11] and an inseperable mixture of diastereomers (cis/trans ratio of 4:1 and a de of 90% for both diastereomers).



***trans*-265** (data for major *trans* distereomer): δ_H (400MHz, $CDCl_3$) 6.81 (2H, s, 12-H), 5.91 (1H, ddd, *J* = 16.0, 8.0, 4.0, 4-H), 5.45 (1H, d, *J* = 16.0, 5-H_a), 5.35 (1H, d, *J* = 8.0, 5-H_b), 2.93 (1H, dd, *J* = 4.0, 2-H), 2.64 (6H, s, 15-H_3), 2.25 (3H, s, 14-H_3), 2.08 (1H, dd, *J* = 8.0, 4.0 3-H); 1.53 (4H, m, *cyclohexyl*-H_2,), 1.05 (4H, m, *cyclohexyl*-H_2), 0.83 (2H, m, *cyclohexyl*-H_2), 0.56 (1H, m, 6-H); δ_C (100MHz, $CDCl_3$) 141.7, 138.8, 137.2, 132.7, 130.6, 121.3, 60.3, 49.1, 47.6, 39.2, 29.8, 25.9, 21.0, 19.5; (EI/CI): m/z 318 (32%, $[M+H]^+$), 154 (100%), 152 (87%); HRMS calculated for $C_{19}H_{28}NOS$: 318.1886 [M+H], Found: 318.1884.

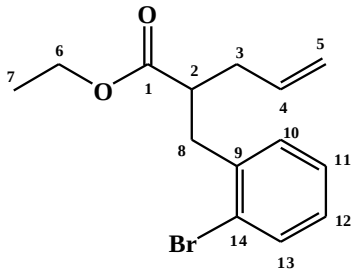


A small amount of *cis* diastereomer was isolated, with just enough to carry out a 1H NMR: ***cis*-265** (data for major cis diastereomer): δ_H (400MHz, $CDCl_3$) 6.79 (2H, s, 12-H), 5.78 (1H, ddd, *J* = 12.0, 8.0, 4.0, 4-H), 5.41 (1H, d, *J* = 12.0, 5-H_a), 5.24 (1H, d, *J* = 8.0, 5-H_b), 2.97 (1H, dd, *J* = 4.0, 2-H), 2.58 (1H, dd, *J* = 4.0, 3-H), 2.54 (6H, s, 15-H_3), 2.24 (3H, s, 14-H_3), 1.66 (4H, m, *cyclohexyl*-H_2), 1.17 (7H, m, *cyclohexyl*-H_2, 6-H), 0.83 (2H, m, *cyclohexyl*-H_2);

3.4 Syntheses and free radical reactions of sulfinimine derivatives

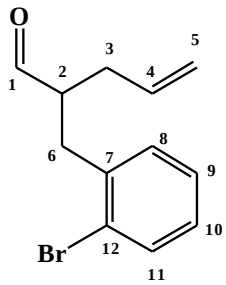
3.4.1 Serendipitous synthesis of aminoindanyl sulfinamides

Ethyl-2-(2-bromobenzyl)-pent-4-enoate (272)



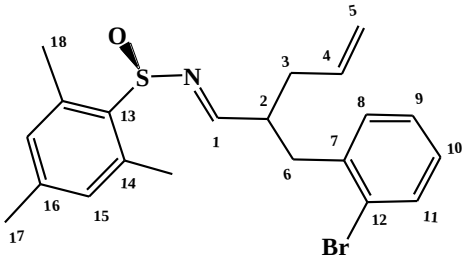
To a THF solution of diisopropylamine (0.66 mL, 4.68 mmol) at 0 ºC under argon was added n-BuLi (1.6 M in hexanes), (2.88 mL, 4.60 mmol) dropwise over 10 minutes. After the addition, the solution was stirred at room temperature for 20 minutes and then cooled to –78 ºC. Ethyl-4-penpentenoate (0.50 g, 3.90 mmol), in dry THF (5 mL), was then added slowly dropwise and the mixture stirred at –78 ºC for 1 hour. 2-Bromobenzyl bromide (1.17 g, 4.68 mmol), in dry THF (5 mL), was added slowly dropwise and the mixture stirred at –78 ºC for 1 hour and then monitored by TLC. After completion, the reaction was warmed gently to room temperature and quenched with brine (10 mL). The mixture was transferred into a separatory funnel, extracted with ethyl acetate and dried over Na_2SO_4. Evaporation of the solvent and purification by column chromatography (Ethyl acetate/ Petroleum ether: 1/30) afforded the title compound (0.98 g, 84 %) as a pale yellow oil. IR (neat) 3075, 2977, 2926, 1729, 1471, 1440, 916, 748 cm^{-1}; δ_H (400MHz, $CDCl_3$) 7.05-7.54 (4H, m, Ar-H), 5.74-5.84 (1H, dddd, *J* = 6.8, 4.0, 3.2, 4-H), 5.04-5.13 (2H, dd, *J* = 6.6, 4.0, 5-H), 4.00-4.08 (2H, m, 6-H_2), 2.86-3.04 (3H, m, 2-H, 8-H_2) 2.27-2.47 (2H, m, 3-H_2) 1.09-1.18 (3H, t, *J* = 7.0, 7-H_3); δ_C (100MHz, $CDCl_3$) 174.9, 138.9, 135.2, 133.1, 131.5, 128.4, 127.5, 124.9, 117.5, 60.5, 45.4, 38.2, 36.7, 14.4; MS (EI/CI): m/z 314 (100%, $[M+NH_4^+]$), 297 (8%, M^+), 236 (25%); HRMS calculated for $C_{14}H_{21}{}^{79}BrO_2$: 314.0750 $[M+NH_4]^+$, Found: 314.0749

2-(2-Bromobenzyl)-pent-4-enal (273)



To a solution of ethyl-2-(2-bromobenzyl)-pent-4-enoate (**272**) (2.81 g, 9.45 mmol) in dry toluene (15 mL) at –78 ºC was added DIBAL (1.0 M solution in toluene, 10.24 mL, 10.24 mmol) in a trickle along the side of the flask over 30 minutes period and the solution stirred at that temperature for 3 hours and monitored by TLC. After completion, methanol (10 mL) was added and the solution warmed to –30 ºC. This was then poured into a vigorously stirred Rochelle's salt (1.2M sodium potassium tartrate solution) and stirred at room temperature for 2 hours. The organic layer was separated, the aqueous layer extracted with ethyl acetate and the combined organic layer dried over Na_2SO_4. Purification by column chromatography (ethyl acetate/ petroleum ether: 1/15) afforded the title compound (1.85 g, 77 %) as a colourless oil. IR (neat) 1728, 1470, 1440 cm^{-1}; δ_H (400MHz, $CDCl_3$) 9.71 (1H, s, 1-H), 7.05-7.56 (4H, m, Ar-H), 5.74-5.84 (1H, dddd, *J* = 6.8, 4.0, 3.2, 4-H), 5.04-5.13 (2H, dd, *J* = 6.6, 4.0, 5-H), 3.11-3.15 (1H, m, 2-H), 2.82-3.04 (2H, m, 6-H_2) 2.28-2.48 (2H, m, 3-H_2); δ_C (100MHz, $CDCl_3$) 174.9, 138.9, 135.2, 133.1, 131.5, 128.4, 127.5, 124.9, 117.5, 60.5, 45.4, 14.4; MS (CI): m/z 271 (100%, $[M+NH_4^+]$), 230 (20%), 171 (30%); HRMS calculated for $C_{12}H_{13}{}^{79}BrO$: 271.0750 $[M+NH_4]^+$, Found: 271.0749

***N*-[2-(2-Bromobenzyl)-pent-4-enylidene]-2,4,6-trimethylbenzenesulfinamide (274)**



To a stirred solution 2-(2-bromo-benzyl)-pent-4-enal (**273**) (1.38 g, 5.46 mmol) in dry THF under argon was added $Ti(OEt)_4$ (3.73 g, 3.43 mL, 16.37 mmol) and the reaction was stirred for 10 minutes. The sulfinamide, 2,4,6-trimethylphenylsulfinamide **(212),** (1.00 g, 5.46 mmol) was then added and the mixture stirred overnight and monitored by TLC. After completion, water (10 mL) was added to the mixture, which was then and filtered through celite. The organic layer was separated, the aqueous layer was extracted with ethyl acetate and the combined organic layers dried over Na_2SO_4. Evaporation of the solvent and purification by column chromatography (ethyl acetate/ petroleum ether: 1/15) afforded the title compound (1.84 g, 80 %) as a yellow semi solid and inseparable 1:1 mixture of diastereomers.

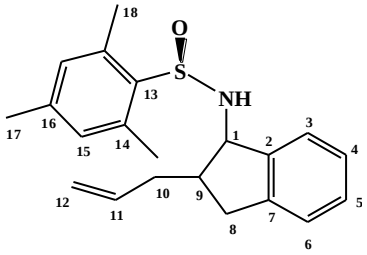
274a: IR (neat) 2924, 1729, 1089, 1025, 907, 732 cm^{-1}; δ_H (400MHz, $CDCl_3$) 8.26 (1H, d *J*= 5.4, 1-H), 7.01-7.54 (4H, m, Ar-H), 6.81 (2H, s, 12-H), 5.74-5.84 (1H, dddd, *J* = 6.8, 4.0, 3.2, 4-H), 5.04-5.13 (2H, dd, *J* = 6.6, 4.0, 5-H), 3.02-3.17 (2H, m, 3-H_2), 3.94-2.99 (1H, m, 2-H), 2.38 (6H, s, 18- H_3), 2.30-2.47 (2H, m, 6-H_2), 2.28 (3H, s, 17- H_3) δ_C (100MHz, $CDCl_3$) 169.8, 141.6, 138.5, 138.3, 135.0, 134.7, 133.1, 131.7, 130.8, 128.2, 127.4, 124.8, 117.9, 45.0, 37.7, 36.4, 21.1, 18.8; MS (EI/CI): m/z 418 (10%, M^+), 317 (10%), 249 (20%), 167 (100%); HRMS calculated for $C_{21}H_{24}{}^{79}BrNNaOS$ $[M+Na]^+$: 440.0654, Found: 440.0651

274b:

IR (neat) 2924, 1729, 1089, 1025, 907, 732 cm^{-1}; δ_H (400MHz, $CDCl_3$) 8.23 (1H, d *J*= 5.4, 1-H), 7.01-7.54 (4H, m, Ar-H), 6.81 (2H, s, 12-H), 5.73-5.84 5.74-5.84 (1H, dddd, *J* = 6.8, 4.0, 3.2, 4-H), 5.04-5.13 (2H, dd, *J* = 6.6, 4.0, 5-H), 3.02-3.17 (2H, m, 3-H_2), 3.94-2.99 (1H, m, 2-H), 2.35 (6H, s, 18- H_3), 2.30-2.47 (2H, m, 6-H_2), 2.27 (3H, s, 17- H_3) δ_C (100MHz, $CDCl_3$) 169.1, 141.5, 138.4, 138.2, 135.0, 134.6, 132.9, 131.5, 130.7, 128.0,

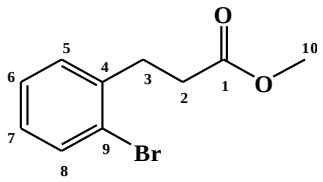
127.2, 124.7, 117.8, 44.7, 37.5, 36.3, 21.1, 18.8; MS (EI/CI): m/z 418 (10%, M^+), 317 (10%), 249 (20%), 167 (100%); HRMS calculated for $C_{21}H_{24}{}^{79}BrNNaOS$ $[M+Na]^+$: 440.0654, Found: 440.0651

***N*-(2-Allylindan-1-yl)-2,4,6-trimethylbenzenesulfinamide (275)**



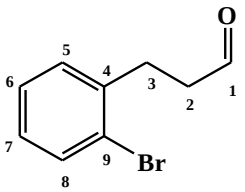
A dry benzene solution of the sulfinimine *N*-[2-(2-bromo-benzyl)-pent-4-enylidene]-2,4,6-trimethyl-benzenesulfinamide **274** (0.10 g, 0.24 mmol, 0.2M), tributyltin hydride (0.09 g, 0.29 mmol) and azodiisobutyronitrile AIBN (0.08 g, 0.50mmol) was degassed by bubbling argon through for 20 minutes. The solution was then refluxed at 85 ºC until all sulfinimine has been consumed as monitored by TLC. The solution was allowed to cool to room temperature and the benzene evaporated under vacuum. The residue was re-dissolved in diethyl ether and a saturated solution of sodium fluoride was added and the mixture stirred vigorously for 1 hour. The mixture was then filtered through a short pad of celite and the organic layer separated. The aqueous layer was extracted with ether and the combined organic layer was dried over Na_2SO_4. Evaporation of the solvent and purification by column chromatography (DCM) afforded the title compound (0.12 g, 36%) as a brown oil. δ_H (400MHz, $CDCl_3$) 7.16-7.43 (4H, m, Ar-H), 6.86 (2H, s, 15-H), 5.69-5.80 (1H, m, 11-H), 5.05-5.08 (2H, m, 12-H), 4.54-4.60 (1H, dd, *J* = 9.2, 8, 1-H), 4.38-4.40 (1H, d, *J* = 9.2 N-H), 3.02-3.08 (1H, m, 8a-H), 2.49-2.63 (4H, m, 8b-H, 9-H, 10-H_2), 2.60 (6H, s, 18-H_3), 2.28 (3H, s, 17-H_3); δ_C (100MHz, $CDCl_3$) 144.0, 142.6, 141.1, 138.7, 137.3, 137.1, 131.4, 128.7, 127.4, 125.7,125.3, 117.1, 66.9, 50.0, 36.9, 30.3, 21.6, 20.4; MS (EI): m/z 339 (10%, M^+), 317 (5%), 249 (100%), 130 (80%); HRMS calculated for $C_{21}H_{25}NNaOS$ $[M+Na]^+$: 362.0281, Found: 362.0778

Methyl-3-(2-bromophenyl)propionoate (277)



To a solution of 3-(2-bromophenyl)propionic acid (4.01 g, 17.50mmol) in methanol (10 mL) at 0 ºC was added thionyl chloride (2.19 g, 1.34 mL, 18.37 mmol) dropwise. The mixture was then stirred at 0 ºC for 30 minutes and triethylamine (1.86 g, 2.56 mL, 18.87 mmol) was added dropwise and stirred for 30 minutes at that temperature. The mixture was then allowed to warm to room temperature and stirred for a further 1 hour. The solvent was evaporated and the residue filtered and washed with diethyl ether. The filtrate was concentrated and the residue purified by column chromatography (ethyl acetate/ petroleum ether: 1/5) to afford the title compound (4.21 g, 99 %) as a colourless viscous oil. IR (neat) 3057, 1733, 749 cm^{-1}, δ_H (400MHz, $CDCl_3$) 7.06-7.54 (4H, m, Ar-H), 3.68 (3H, s, 10-H_3), 4.10-4.15 (2H, t, 2-H_2), 3.05-3.09 (2H, t, 3-H_2); δ_C (100MHz, $CDCl_3$) 173.1, 139.7, 132.9, 130.5, 128.1, 127.6, 124.4, 51.7, 33.9, 31.4; MS (EI/CI): m/z 260 (26%, $[M+NH_4^+]$), 182 (83%), 150 (19%); HRMS calculated for $C_{10}H_{15}{}^{79}BrNO_2$ $[M+NH_4]^+$: 260.0281, Found: 260.0778

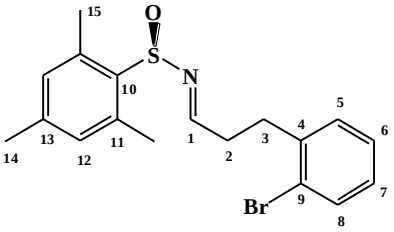
3-(2-Bromophenyl)propionaldehyde (278)



To a solution of methyl-3-(2-bromo-phenyl)-propionoate **277** (3.03 g, 12.46 mmol) in dry toluene (25 mL) at –78 ºC was added DIBAL (1M solution in toluene, 13.71 mL, 13.71 mmol)) in a trickle along the side of the flask over 30mins period and the solution stirred at that temperature for 3 hours and monitored by TLC. After completion, methanol (10 mL) was added and the solution warmed to –30 ºC. This was then poured into a vigorously stirred Rochelle's salt (1.2M sodium potassium tartrate solution) and stirred at room temperature for 2 hours. The organic layer was separated, the aqueous layer extracted with

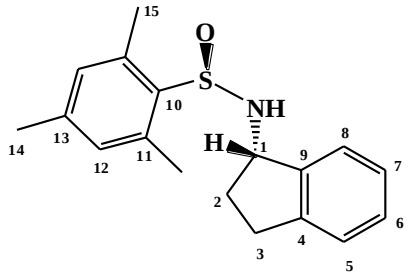
ethyl acetate and the combined organic layer dried over Na_2SO_4. Purification by column chromatography (ethyl acetate/ petroleum ether: 1/5) afforded the title compound (2.30 g, 87 %) as a colourless oil. IR (neat) 1721, 1470, 748; δ_H (400MHz, $CDCl_3$) 9.84 (1H, s, 1-H), 7.06-7.55 (4H, m, Ar-H), 2.79-2.83 (2H, t, *J* = 7.1, 2-H_2), 2.64-2.68 (2H, t, *J* = 7.1, 3-H_2); δ_C (100MHz, $CDCl_3$) 201.0, 133.9, 133.2, 130.8, 128.4, 127.9, 124.5, 43.9, 28.9; MS (EI/CI): m/z 213 (7%, M^+), 149 (100%), 77 (15%); HRMS calculated for $C_9H_9{}^{79}BrOS$: 212.9762 $[M+H]^+$, Found: 212.9756

(*R*)-*N*-[3-(2-Bromophenyl)propylidene]-2,4,6-trimethylbenzenesulfinamide (279)



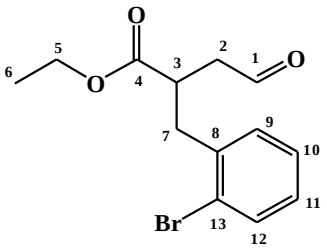
To a stirred solution of 3-(2-bromophenyl)propionaldehyde **(278)** (2.30 g, 10.80 mmol) in dry THF (20 mL) under argon was added the $Ti(OEt)_4$ (7.39 g, 6.79 mL, 32.40 mmol) and the reaction was stirred for 5-10 minutes. (R)-2,4,6-trimethylphenylsulfinamide **212** (1.98 g, 10.80 mmol) was then added and the mixture stirred overnight and monitored by TLC. After completion, water was added to the mixture and the filtered through celite. The organic layer was separated, the aqueous layer extracted with ethyl acetate and the combined organic layer dried over Na_2SO_4. Evaporation of the solvent and purification by column chromatography (hexane/ dichloromethane: 2/1) afforded the title compound (3.31 g, 81 %) as a white solid. $[\alpha]^{25}{}_D$ –201.0 (*c* 0.5, $CHCl_3$); IR (neat) 2929, 1617, 1438, 1095 cm^{-1}; δ_H (400MHz, $CDCl_3$) 8.35-8.37 (1H, t, *J = 4.0*, 1-H), 7.04-7.54 (4H, m, Ar-H), 6.84 (2H, s, 12-H), 3.04-3.09 (2H, dd, *J* = 7.3, 4.0, 2-H_2), 2.78-2.89 (2H, t, J = 7.3, 3-H_2) 2.43 (6H, s, 15- H_3), 2.28 (3H, s, 14- H_3); δ_C (100MHz, $CDCl_3$) 166.6, 141.7, 139.6, 138.3, 135.0, 132.9, 130.8, 130.5, 128.1, 127.6, 124.3, 35.8, 31.9, 28.7, 21.1; MS (EI/CI) m/z 378 (12%, $[M+H]^+$), 214 (73%), 132(100%); HRMS calculated for $C_{18}H_{21}{}^{79}BrNOS$: 378.0522 $[M+H]^+$, Found: 378.0527

***N*-(Indan-1-yl)-2,4,6-trimethylbenzenesulfinamide (280)**



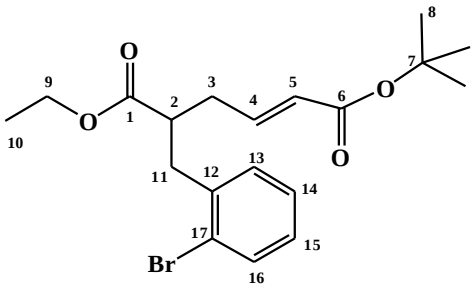
A dry benzene solution of *N*-[3-(2-bromophenyl)propylidene]-2,4,6-trimethyl-benzenesulfinamide **279** (0.61 g, 1.60 mmol, 0.2M), tributyltin hydride (0.56 g, 0.52 mL, 1.92 mmol) and azodiisobutyronitrile AIBN (0.53 g, 3.2 mmol) was degassed by bubbling argon through for 20 minutes. The solution was refluxed at 85 ºC until all sulfininimine has been consumed as monitored by TLC. The solution was allowed to cool to room temperature and the benzene evaporated under vacuum. The residue was re-dissolved in ether and a saturated solution of sodium fluoride was added and the mixture stirred vigorously for 1 hour. The mixture was then filtered through a short pad of celite and the organic layer separated. The aqueous layer was extracted with ether and the combined organic layer was dried over Na_2SO_4. Evaporation of the solvent and purification by column chromatography (dichloromethane) afforded the title compound (0.33 g, 68 %) as colourless crystalline needles. $[\alpha]^{25}_{D}$ –103.9 (*c* 0.52, $CHCl_3$); IR (neat) 3159, 2924, 1042, 845, 743 cm^{-1}; δ_H (400MHz, $CDCl_3$) 7.17-7.36 (4H, m, Ar-H), 6.86 (2H, s, 12-H), 4.91 (1H, ddd, *J* = 9.6, 7.6, 4.3, 1-H), 4.35 (1H, d, *J* = 9.6 N-H), 2.95-3.02 (1H, m, 3-Ha), 2.81-2.91 (1H, m, 2-Ha), 2.65-2.73 (1H, m, 3-Hb) 2.59 (6H, s, 15- H_3), 2.28 (3H, s, 14- H_3), 1.94-2.01 (1H, m, 2-Hb); δ_C (100MHz, $CDCl_3$) 143.5, 143.0, 140.5, 138.3, 136.4, 130.8, 128.1, 126.6, 124.8, 124.6, 62.1, 36.9, 30.3, 21.0, 19.6; MS (CI): m/z 322 (100%, $[M+Na]^+$), 300 (24%, $[M+H]^+$), 167 (80); HRMS calculated for $C_{18}H_{21}NNaOS$: 322.1236 $[M+Na]^+$, Found: 322.1232. X-ray data in appendix II

Ethyl-2-(2-bromobenzyl)-4-oxo-butanoate (281)



A stream of ozone was bubbled through a solution of **272** (0.53 g, 1.79 mmol) in DCM (20 mL) and methanol (10 mL) at –78 ºC until the solution turned blue and the colour persisted. The mixture was stirred at that temperature for a further 10 minutes, then argon was bubbled through until the solution turned colourless. The reaction was warmed to –42 ºC and dimethyl sulfide (0.65 mL, 0.55 g, 8.83 mmol) was added dropwise. The mixture was stirred for a further 10 minutes and allowed to warm to room temperature and monitored by TLC. Evaporation of the solvent and purification by column chromatography (ethyl acetate/ petroleum ether: 1/5) afforded the title compound (0.53 g, 99%) as a pale yellow oil: IR (neat) 2980, 1723, 1180, 752 cm^{-1}; δ_H (400MHz, $CDCl_3$) 9.71 (1H, s, 1-H), 7.07-7.54 (4H, m, Ar-H), 4.04-4.15 (2H, m, 5-H_2), 3.16-3.34 (2H, m, 2-H_2), 2.86-2.93 (2H, m, 2-H, 7-H_2) 2.51-2.60 (H, m, 3-H) 1.09-1.18 (3H, t, J = 6.3, 6-H_3); δ_C (100MHz, $CDCl_3$) 199.9, 173.8, 137.8, 133.1, 131.3, 128.5, 127.5, 124.7, 60.9, 44.6, 39.4, 37.7, 14.1; MS (CI): m/z 317 (40%, $[M+Na]^+$), 249 (100%); HRMS calculated for $C_{13}H_{15}{}^{79}BrNaO_3$: 321.0097 $[M+H]^+$, Found: 321.0090

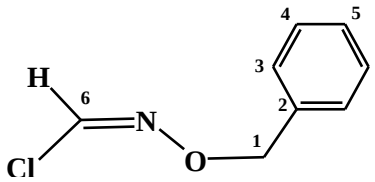
1-*Tert*-butyl-6-ethyl-5-(2-bromobenzyl)-hex-2-enedioate (282)



A solution of the aldehyde **272** (1.06 g, 3.54 mmol) in THF (10 mL) was added dropwise to a stirred solution of *tert*-butoxycarbonylmethylene)triphenylphosphorane (1.33 g, 3.54 mmol) in THF (25 mL) at room temperature and under argon. The reaction was stirred at

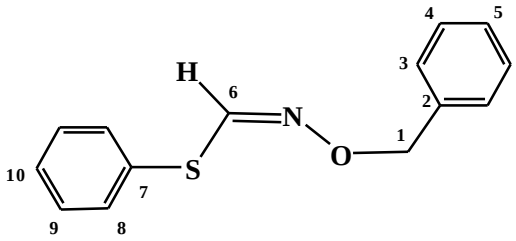
room temperature for 2 hours and monitored by TLC. After completion, the mixture was concentrated and purified by column chromatography (ethyl acetate/ petroleum ether: 1/5) to afford the title compound (1.39 g, 99 %) as a colourless viscous oil. IR (neat) 2976, 1720, 1712, 1145, 1025 cm^{-1}; δ_H (400MHz, $CDCl_3$) 6.99-7.47 (4H, m, Ar-H), 6.68-6.76 (1H, m, 4-H), 5.69-5.73 (H, d, 5-H), 3.92-4.08 (2H, m, 9-H_2), 2.85-3.00 (3H, m, 2-H, 3-H_2) 2.29-2.52 (2H, m, 11-H_2) 1.39 (9H, s, 8-H_3), 1.05-1.07 (3H, t, J = 3.6 10-H_3); δ_C (100MHz, $CDCl_3$) 174.3, 165.7, 143.9, 138.3, 133.1, 131.4, 128.6, 127.6, 125.4, 124.9, 80.5, 60.8, 44.8, 38.4, 34.6, 28.3, 14.3; MS (EI/CI): m/z 414 (100%, $[M+NH_4^+]$), 358 (50%), 336 (23%); HRMS calculated for $C_{19}H_{26}{}^{79}BrO_4$: 397.1009 $[M+H]^+$, Found: 397.1010

_O_-Benzylformohydroximoylchloride (298)[11]



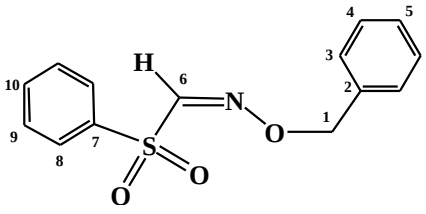
To a solution of *O*-benzylformaldoxime (0.98 g, 7.4 mmol) in DMF (20 mL) was added *N*-chlorosuccinamide (1.09 g, 8.14 mmol). The reaction mixture was heated for 3 hours at 40 °C, diluted with ether (50 mL), and washed with aqueous 10% HCl (2 x 20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane: 1/50) to afford the *O*-benzyl-formohydroximoylchloride (0.85 g, 77%) as a colourless liquid. δ_H (400MHz, $CDCl_3$) 7.75-7.40 (5H, m, Ar-H), 6.95 (1H, s, 6-H), 5.19 (2H, s, 1-H_2); δ_C (100MHz, $CDCl_3$) 136.6, 128.4, 128.2, 124.6, 77.1. Data matched literature.[11a]

S-Phenyl-*N*-(benzyloxy)-thioformidate (299)[11]



The sodium salt of thiophenol was prepared by adding a solution of thiophenol (0.83 g, 0.77 mL, 7.54 mmol) to sodium hydride (0.18 g, 7.54 mmol) in THF (10 mL) at room temperature. The slurry was stirred for 30 minutes and then added to a solution of *O*-benzyl-formohydroximoylchloride (3.178 g, 18.74 mmol) in THF (30 mL). The reaction was stirred for 3 hours at room temperature, diluted with diethyl ether (40 mL) and washed with aqueous $NaHCO_3$ (2 x 20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate/hexane: 1/20) to give *S*-phenyl-*N*-(benzyloxy)thioformidate (4.01 g, 90%) as a white solid. Mpt. 38-39 °C (Lit. Mpt. 38-39 °C); IR (neat) 3024, 2933, 1564, 1452, 1266, 1210, 1021 cm^{-1}; δ_H (400MHz, $CDCl_3$) 7.25-7.55 (11H, m), 5.23 (2H, s, 1-H_2); δ_C (100MHz, $CDCl_3$) 146.2, 137.5, 132.5, 131.7, 129.5, 128.7, 128.4, 128.0, 76.6; HRMS calculated for $C_{14}H_{13}NOS$: 243.0718 (M^+), Found 243.0713. Data matched literature.[11a]

O-Benzyl-α-(phenylsulfonyl)formaldoxime (288)[11a]

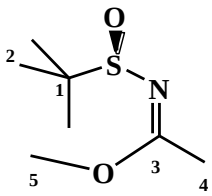


To a solution of *S*-phenyl-*N*-(benzyloxy)-thioformidate (4.88 g, 20.0 mmol) in CH_2Cl_2 (25 mL) was added $NaHCO_3$ (3.37 g, 40.1) and mCPBA (7.61 g, 44.1 mmol) at 0 °C. After being stirred for 1 hour, the reaction was heated for 1 hour at 40 °C, diluted with CH_2Cl_2 (20 mL) and washed with aqueous $NaHCO_3$ (2 x 20 mL), aqueous Na_2SO_3 (20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* and the residue was purified by silica gel column chromatography (ethyl

acetate/hexane : 1/7) to give *O*-benzyl-α-(phenylsulfonyl)formaldoxime (4.48 g, 88%) as a white solid. Mpt 51-52 °C (Lit. Mpt. 51-52 °C); IR (neat) 3045, 1563, 1449, 1317, 1150 cm^{-1}; δ_H (400MHz, $CDCl_3$) 6.95-7.95 (11H, m), 5.10 (2H, s, 1-H_2); δ_C (100MHz, $CDCl_3$) 143.8, 139.3, 135.3, 134.3, 129.2, 128.9, 128.5, 128.4, 128.2, 78.8; HRMS calculated for $C_{14}H_{13}NO_3S$: 275.0616 (M^+), Found 275.0629. Data matched literature.[11a]

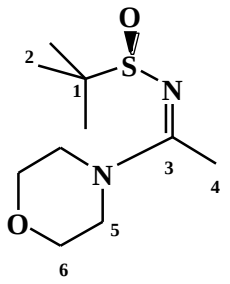
3.4.2 Attempted asymmetric syntheses of cyclisation substrates

(*R*)-Methyl-(*tert*-butanesulfinyl)imidate (303)[12]



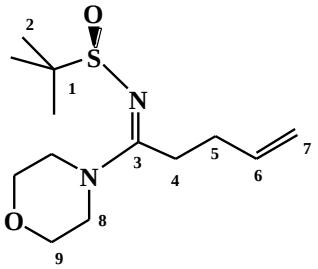
To a 100 mL round bottomed flask charged with *tert*-butanesulfinamide (4.67 g, 38.51 mmol) was added trimethyl orthoformate (38.51 mL, 36.81 g, 306 mmol) and *p*-toluenesulfonic acid (1.0 mg, 0.001 mmol). The mixture was brought to reflux and the resulting solution was stirred for 3 h and monitored for completion by TLC. After completion, the volatile materials were removed in vacuo and 25 mL of diethyl ether was added. The mixture was filtered, concentrated and purified by silica gel column chromatography (hexanes:EtOAc 9:1) to afford the title compound (6.04 g, 89%) as a colourless oil. $[\alpha]^{25}_D$ –177.4° (*c* 1.0, $CHCl_3$) (Lit. $[\alpha]^{23}_D$ –122°)[12]; IR (neat) 1611, 1245, 1082 cm^{-1}; δ_H (400MHz, $CDCl_3$) 7.80 (s, 1H), 3.78 (s, 3H), 1.18 (s, 9H); δ_C (100MHz, $CDCl_3$) 160.6, 56.5, 55.0, 22.2. Data matched literature.[12]

(*R*)-2-Methylpropane-2-sulfinic acid-(1-morpholin-4-ylethylidene)amide (304)[12]



To the imidate **301** (1.26 g, 7.10 mmol) with NaCN (0.06 g, 1.4 mmol) in morpholine (11.35 mL) was added MeOH (2.8 mL, MeOH/morpholine 1:4 v/v). The nitrogen inlet was removed from the flask sealed with a septa, and the reaction mixture was stirred at room temperature for 20 h. A 1.0 M solution of KOH was then added and the mixture was extracted three times with CH_2Cl_2. The combined organic portions were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was isolated by silica gel chromatography to afford the amidine product **304** (1.48 g, 90%) as a white solid: Mpt 39-42 °C (Lit. Mpt. 39-42 °C[12]); IR (neat) 1539 cm^{-1}; δ_H (400MHz, $CDCl_3$) 3.50-3.70 (8H, m, 5-H_2, 6-H_2), 2.31 (3H, s, 4-H_3), 1.14 (9H, s, 2-H_3); δ_C (100MHz, $CDCl_3$) 167.1, 116.3, , 66.3, , 54.9, 45.2, 22.0; HRMS calculated for ($C_{10}H_{21}N_2O_2S$) $[M+H]^+$, 233.1324, Found 233.1323. Data matched literature.[12]

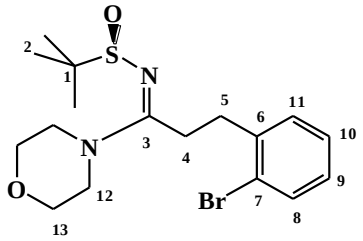
(*R*)-2-Methylpropane-2-sulfinic acid-(1-morpholin-4-ylpent-4-enylidene)amide (307)



To a solution of LDA (1.8 M in THF, 2.0 mL, 3.60 mmol) was added THF (10 mL) and the solution was cooled to -78 °C. The amidine **304** (0.56 g, 2.39 mmol) in THF (5 mL) was added dropwise. After the addition, the solution was stirred for 45 min at -78 °C, then allyl bromide (0.35 g, 0.25 mL, 2.87 mmol) in THF (2 mL) was added to the solution and stirring was continued at -78 °C for 3 h. After completion of the reaction, 2N AcOH in THF (6.0 mL, 11.95 mmol) was cooled to -78 °C and added to the reaction mixture with

stirring, followed by a saturated aqueous solution of $NaHCO_3$. The organic layer was collected and the aqueous layer was extracted twice with EtOAc. The combined organic portions were dried over Na_2SO_4, filtered and concentrated. Column chromatography (5:4:1 hexanes/EtOAc/NEt_3) of the crude material afforded **307** (0.64 g, 99%) as colourless crystalline needles. $[\alpha]^{25}_D$ –85.1(*c* 0.52, $CHCl_3$); IR (neat) 2962, 1530, 1047 cm^{-1}; δ_H (400MHz, $CDCl_3$) 5.78-5.86 (1H, m, 6-H), 5.04-5.11 (2H, m, 7-H), 3.40-3.76 (8H, m, 8-H_2, 9-H_2), 2.78-2.91 (2H, m, 5-H_2) 2.34-2.47 (1H, m, 4-H_b), 2.19-2.29 (1H, m, 4-H_a), 1.14 (9H, s, 2-H_3); δ_C (100MHz, $CDCl_3$) 170.5, 136.1, 116.1, 66.7, 55.2, 31.6, 29.7, 22.6; MS (EI/CI): m/z 273 (34%, $[M+H]^+$), 169 (16%), 105 (11%), 88 (100%); HRMS calculated for $C_{13}H_{25}{}^{79}BrN_2O_2S$: 273.1631 $[M+H]^+$, Found: 273.1632

(*R*)-2-Methylpropane-2-sulfinic acid-[3-(2-bromo-phenyl)-1-morpholin-4-ylpropylidene]amide (308)

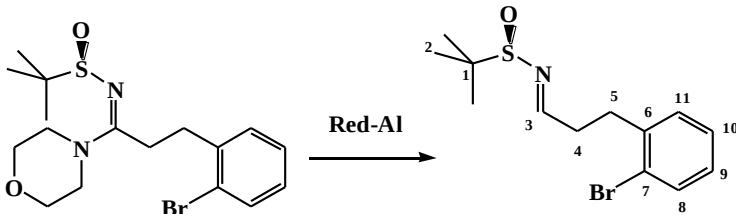


To a solution of LDA (1.8 M in THF, 0.54 mL, 0.97 mmol) was added THF (10 mL) and the solution was cooled to -78 °C. The amidine **304** (0.20 g, 0.88 mmol) in THF (5 mL) was added dropwise. After the addition, the solution was stirred for 45 min at -78 °C, then methanesulfonic acid 2-bromo-benzyl ester **306** (0.26 g, 0.25 mL, 0.97 mmol) in THF (2 mL) was added to the solution and stirring was continued at -78 °C for 3 h. After completion of the reaction, 2N AcOH in THF (1.34 mL, 2.68 mmol) was cooled to -78 °C and added to the reaction mixture with stirring, followed by a saturated aqueous solution of $NaHCO_3$. The organic layer was collected and the aqueous layer was extracted twice with EtOAc. The combined organic portions were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography (5:4:1 hexanes/EtOAc/NEt_3) of the crude residue afforded the amidine **308** (0.35 g, 98%) as a brownish crystaline solid. $[\alpha]^{25}_D$ –66.6 (*c* 0.47, $CHCl_3$); IR (neat) 2948, 1520, 1042 cm^{-1}; δ_H (400MHz, $CDCl_3$) 7.45 (1H, d, *J* = 7.9, 8-H), 7.35 (1H, d, *J* = 7.5, 11-H), 7.19-7.7.23 (1H, m, 9-H), 7.02-7.06 (1H, m, 10-H), 3.40-3.80 (8H, m, 12-H_2, 13-H_2), 2.94-3.11 (4H, m, 4-H_2, 5-H_2) 1.14 (9H, s, 2-H_3); δ_C (100MHz,

$CDCl_3$) 170.1, 139.4, 132.9, 131.6, 128.8, 128.3, 124.1, 66.7, 55.2, 34.2, 29.7, 22.4; MS (EI/CI): m/z 401 (13%, $[M+H]^+$), 178 (46%), 149 (76%), 129 (100%), 105 (60%); HRMS calculated for $C_{17}H_{27}{}^{79}BrN_2O_2S$: 401.0893 $[M+H]^+$, Found: 401.0890

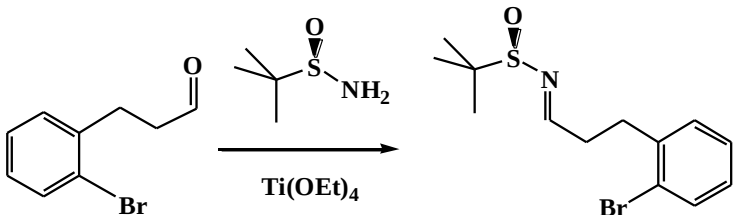
(*R*)-2-Methylpropane-2-sulfinic acid [3-(2-bromo-phenyl)propylidene]amide

Method A: Conversion of Amidine 308 to Aldimine 309 with Red-Al.



To a solution of **308 (**0.20 g, 0.50 mmol) in THF (10 mL) was slowly added a solution of Red-Al (3.5 M, 0.72 mL, 2.5 mmol) in toluene at -40 °C, and the resulting mixture was stirred for 20 h. The reaction was then quenched by addition of a saturated aqueous solution of K_2CO_3 and the reaction mixture was diluted with EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (2x10 mL). The combined organic portions were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (9:1 hexanes/EtOAc) to afford the title compound (0.11 g, 68%) as a colourless viscous oil. $[\alpha]^{25}_D$ –145.5 (*c* 0.58, $CHCl_3$); IR (neat) 2958, 1736, 1620, 1083, 749 cm^{-1}; δ_H (400MHz, $CDCl_3$) 8.11-8.13 (1H, t, *J* = 4.1, 3-H), 7.52 (1H, d, *J* = 7.9, 8-H), 7.19-7.23 (2H, m, 9-H, 10-H), 7.04-7.08 (1H, m, 11-H), 3.05-3.08 (2H, t, *J* = 7.7, 5-H_2), 2.82-2.87 (2H, dd, *J* = 7.7, 4.1, 4-H_2), 1.15 (9H, s, 2-H_3); δ_C (100MHz, $CDCl_3$) 168.35, 139.9, 133.2, 130.6, 128.3, 127.8, 124.6, 56.9, 36.2, 32.1, 22.5; MS (EI/CI): m/z 316 (20%, $[M+H]^+$), 214 (84%), 149 (15%), 132 (100%); HRMS calculated for $C_{13}H_{19}{}^{79}BrNOS$: 316.0365 $[M+H]^+$, Found: 316.0368

Method B: Synthesis by condensation of 278 with *tert*-butanesulfinamide 302



To a stirred solution of 3-(2-Bromo-phenyl)propionaldehyde **274** (1.25 g, 5.87 mmol) in dry THF (20 mL) under argon was added the $Ti(OEt)_4$ (4.02 g, 3.69 mL, 17.61 mmol) and stirred for 5-10 minutes. *Tert*-butanesulfinamide **298** (0.71 g, 5.87 mmol) was then added and the mixture stirred overnight and monitored by TLC. After completion, water was added to the mixture and the filtered through celite. The organic layer was separated, the aqueous layer extracted with ethyl acetate and the combined organic layer dried over Na_2SO_4. Evaporation of the solvent and purification by column chromatography (Hexane/ dichloromethane: 2/1) afforded the title compound in 59% yield.

3.5 References

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4.0 Appendices

4.1 Appendix I- Crystal structure analysis of enantiopure Mesitylsulfinamide **255**

Crystal and structure refinement data for Mes-SO-N=CH-CH=CH-Ph

Identification code	leonids1
Empirical formula	C18 H19 N O S
Formula weight	297.4
Crystal system	Orthorhombic
Space group	P $2_12_12_1$ (no.19)
Unit cell dimensions	a = 6.9225(4) Å α = 90 ° b = 7.9322(5) Å β = 90 ° c = 29.0251(18) Å γ = 90 °
Volume	1593.79(17) $Å^3$
No. of formula units, Z	4
Calculated density	1.239 Mg/m^3
F(000)	632
Absorption coefficient	0.202 mm^{-1}
Temperature	140(1) K
Wavelength	0.71073 Å
Crystal colour, shape	pale yellow plate
Crystal size	0.68 x 0.44 x 0.18 mm
Crystal mounting	on a glass fibre, in oil, fixed in cold N_2 stream
On the diffractometer:	
Theta range for data collection	3.8 to 27.5 °
Limiting indices	-8<=h<=8, -10<=k<=10, -37<=l<=37
Completeness to theta = 27.5	99.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.023 and 0.982
Reflections collected (not including absences)	21403
No. of unique reflections	3643 [R(int) for equivalents = 0.037]
No. of 'observed' reflections ($I > 2\sigma_I$)	3533
Structure determined by:	direct methods, in SHELXS

Refinement:	Full-matrix least-squares on F^2, in SHELXL
Data / restraints / parameters	3643 / 0 / 193
Goodness-of-fit on F2	1.139
Final R indices ('observed' data)	R1 = 0.033, wR2 = 0.079
Final R indices (all data)	R1 = 0.035, wR2 = 0.080
Reflections weighted: $w = [\sigma^2(Fo^2)+(0.0412P)^2+0.26P]^{-1}$ where $P=(Fo^2+2Fc^2)/3$	
Absolute structure parameter	0.03(6)
Largest diff. peak and hole	0.31 and -0.19 e.Å^{-3}
Location of largest difference peak	close to C(1)

Table 1. Atomic coordinates (x 10^5) and equivalent isotropic displacement parameters ($Å^2$ x 10^4). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor. E.s.ds are in parentheses.

	x	y	z	U(eq)
C(1)	10481(21)	40283(18)	46643(5)	184(3)
C(2)	11035(22)	57978(18)	46918(5)	228(3)
C(21)	11298(27)	69214(21)	42757(6)	333(4)
C(3)	11912(23)	65170(19)	51275(5)	256(3)
C(4)	12496(22)	55561(21)	55266(5)	251(3)
C(41)	13197(29)	63728(26)	59952(6)	382(4)
C(5)	12192(20)	38136(19)	54872(5)	215(3)
C(6)	11138(18)	30164(18)	50597(5)	190(3)
C(61)	11062(23)	11115(18)	50451(5)	243(3)
S(1)	8144(5)	29387(5)	41266.0(12)	236.4(10)
O(1)	-7552(17)	37179(17)	38506(4)	328(3)
N(1)	30213(18)	34868(17)	39176(4)	244(3)
C(11)	30982(23)	38771(21)	34926(5)	256(3)
C(12)	49192(23)	42631(21)	32706(5)	257(3)
C(13)	50303(24)	44999(21)	28159(6)	276(3)
C(14)	67611(23)	49187(21)	25514(5)	257(3)
C(15)	68094(29)	45891(25)	20812(6)	352(4)
C(16)	84315(32)	49674(27)	18216(6)	414(5)
C(17)	99974(30)	57248(25)	20230(7)	398(4)
C(18)	99734(29)	60816(23)	24901(7)	360(4)
C(19)	83760(25)	56717(22)	27538(6)	300(3)

Table 2. Molecular dimensions. Bond lengths are in Ångstroms, angles in degrees. E.s.ds are in parentheses.

C(1)-S(1)	1.7914(14)	S(1)-N(1)	1.7003(13)
C(1)-C(2)	1.406(2)	N(1)-C(11)	1.273(2)
C(1)-C(6)	1.4011(19)	C(11)-C(12)	1.448(2)
C(2)-C(21)	1.501(2)	C(12)-C(13)	1.335(2)
C(2)-C(3)	1.389(2)	C(13)-C(14)	1.461(2)
C(3)-C(4)	1.387(2)	C(14)-C(15)	1.390(2)
C(4)-C(41)	1.507(2)	C(14)-C(19)	1.397(2)
C(4)-C(5)	1.387(2)	C(15)-C(16)	1.385(3)
C(5)-C(6)	1.395(2)	C(16)-C(17)	1.370(3)
C(6)-C(61)	1.5116(19)	C(17)-C(18)	1.385(3)
S(1)-O(1)	1.4848(12)	C(18)-C(19)	1.384(3)
C(2)-C(1)-S(1)	122.24(11)	N(1)-S(1)-C(1)	96.11(7)
C(6)-C(1)-S(1)	116.11(10)	O(1)-S(1)-N(1)	111.01(7)
C(6)-C(1)-C(2)	121.62(13)	C(11)-N(1)-S(1)	116.46(11)
C(3)-C(2)-C(1)	117.58(13)	N(1)-C(11)-C(12)	121.26(14)
C(1)-C(2)-C(21)	123.17(14)	C(13)-C(12)-C(11)	121.30(14)
C(3)-C(2)-C(21)	119.23(14)	C(12)-C(13)-C(14)	126.75(15)
C(4)-C(3)-C(2)	122.41(14)	C(15)-C(14)-C(13)	119.52(15)
C(3)-C(4)-C(41)	121.22(15)	C(19)-C(14)-C(13)	122.17(14)
C(5)-C(4)-C(3)	118.57(14)	C(15)-C(14)-C(19)	118.30(15)
C(5)-C(4)-C(41)	120.21(15)	C(16)-C(15)-C(14)	120.86(17)
C(4)-C(5)-C(6)	121.73(13)	C(17)-C(16)-C(15)	120.27(17)
C(5)-C(6)-C(1)	118.08(13)	C(16)-C(17)-C(18)	119.85(17)
C(1)-C(6)-C(61)	123.35(13)	C(19)-C(18)-C(17)	120.21(19)
C(5)-C(6)-C(61)	118.57(13)	C(18)-C(19)-C(14)	120.48(16)
O(1)-S(1)-C(1)	109.60(7)		

Table 3. Anisotropic displacement parameters ($Å^2$ x 10^4) for the expression:

$$\exp\{-2\pi^2(h^2a^{*2}U_{11} + \ldots + 2hka^*b^*U_{12})\}$$

E.s.ds are in parentheses.

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C(1)	150(7)	217(7)	185(6)	7(5)	7(5)	8(5)
C(2)	208(7)	216(7)	262(7)	51(6)	27(6)	14(6)
C(21)	435(10)	252(7)	313(8)	96(6)	24(7)	41(8)
C(3)	290(8)	191(6)	288(8)	-2(6)	29(6)	6(6)
C(4)	201(7)	309(8)	243(7)	-22(6)	24(6)	2(6)
C(41)	421(10)	458(10)	266(8)	-82(7)	37(7)	-16(9)
C(5)	158(7)	285(7)	203(7)	72(6)	16(5)	-6(6)
C(6)	118(6)	204(6)	247(7)	51(6)	19(5)	3(6)
C(61)	210(8)	203(7)	317(8)	49(6)	4(6)	-6(6)
S(1)	212(2)	289(2)	208(2)	-11.4(15)	8.0(14)	-6.5(15)
O(1)	184(5)	550(7)	249(5)	6(5)	-36(5)	-26(5)
N(1)	190(6)	322(7)	221(6)	-18(5)	19(5)	21(5)
C(11)	206(7)	321(8)	241(7)	-13(6)	-15(6)	7(6)
C(12)	205(7)	329(8)	237(7)	-4(6)	-16(6)	8(7)
C(13)	228(7)	350(9)	250(7)	-3(6)	-32(6)	9(7)
C(14)	274(8)	288(8)	208(7)	41(6)	10(6)	31(7)
C(15)	395(10)	439(10)	223(8)	49(7)	-19(7)	-25(8)
C(16)	546(12)	481(10)	215(8)	60(8)	101(8)	19(10)
C(17)	414(10)	376(10)	406(10)	116(8)	177(8)	18(9)
C(18)	305(8)	348(9)	428(9)	35(8)	37(8)	-30(7)
C(19)	302(8)	339(8)	259(8)	-6(7)	16(7)	-7(7)

Table 4. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3). All hydrogen atoms were included in idealised positions with U(iso)'s set at 1.2*U(eq) or, for the methyl groups, 1.5*U(eq) of the parent carbon atom.

	x	y	z	U(iso)
H(21A)	180	6540	4058	50
H(21B)	2386	6886	4136	50
H(21C)	840	8057	4367	50
H(3)	1212	7686	5153	31
H(41A)	1437	7572	5960	57
H(41B)	2412	5950	6163	57
H(41C)	155	6117	6161	57
H(5)	1270	3160	5753	26
H(61A)	1157	676	5354	37
H(61B)	2210	722	4875	37
H(61C)	-53	727	4897	37
H(11)	1964	3915	3321	31
H(12)	6033	4348	3448	31
H(13)	3887	4387	2650	33
H(15)	5739	4108	1939	42
H(16)	8458	4706	1509	50
H(17)	11074	5999	1847	48
H(18)	11034	6598	2627	43
H(19)	8377	5899	3068	36

Table 5. Torsion angles, in degrees. E.s.ds are in parentheses.

C(6)-C(1)-S(1)-O(1)	131.14(11)
C(2)-C(1)-S(1)-O(1)	-46.97(14)
C(6)-C(1)-S(1)-N(1)	-113.97(11)
C(2)-C(1)-S(1)-N(1)	67.92(13)
O(1)-S(1)-N(1)-C(11)	-25.66(14)
C(1)-S(1)-N(1)-C(11)	-139.39(13)
S(1)-N(1)-C(11)-C(12)	-176.13(12)
N(1)-C(11)-C(12)-C(13)	172.92(17)
C(11)-C(12)-C(13)-C(14)	179.01(16)
C(12)-C(13)-C(14)-C(15)	158.92(18)
C(12)-C(13)-C(14)-C(19)	-22.2(3)

Crystal structure analysis of Mes-SO-N=CH-CH=CH-Ph, Compound **255**

Crystal data: **$C_{18}H_{19}NOS$, M = 297.4. Orthorhombic, space group $P2_12_12_1$ (no. 19), a = 6.9225(4), b = 7.9322(5), c = 29.0251(18) Å, V = 1593.79(17) Å^3. Z = 4, Dc = 1.239 g cm^{-3}, F(000) = 632, T = 140(1) K, μ(Mo-Kα) = 2.0 cm^{-1}, λ(Mo-Kα) = 0.71069 Å.**

Crystals are pale yellow plates. One, *ca* 0.68 x 0.44 x 0.18 mm, was mounted in oil on a glass fibre and fixed in the cold nitrogen stream on an Oxford Diffraction Xcalibur-3 CCD diffractometer equipped with Mo-Kα radiation and graphite monochromator. Intensity data were measured by thin-slice ω- and φ-scans. Total no. of reflections recorded, to θ_{max} = 27.5°, was 21403 of which 3643 were unique (Rint = 0.037); 3533 were 'observed' with $I > 2\sigma_I$.

Data were processed using the CrysAlis-CCD and -RED (1) programs. The structure was determined by the direct methods routines in the SHELXS program (2A) and refined by full-matrix least-squares methods, on F^2's, in SHELXL (2B). The non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were included in idealised positions and their Uiso values were set to ride on the Ueq values of the parent carbon atoms. At the conclusion of the refinement, wR_2 = 0.080 and R_1 = 0.035 (2B) for all 3643 reflections weighted $w = [\sigma^2(F_o^2) + (0.0412P)^2 + 0.26P]^{-1}$ with $P = (F_o^2 + 2F_c^2)/3$; for the 'observed' data only, R_1 = 0.033. The absolute structure is that shown in the Figure, with the Flack x parameter = 0.03(6).

In the final difference map, the highest peak (*ca* 0.31 eÅ^{-3}) was close to C(1).

Scattering factors for neutral atoms were taken from reference (3). Computer programs used in this analysis have been noted above, and were run through WinGX (4) on a Dell Precision 370 PC at the University of East Anglia.

References

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(4) L. J. Farrugia, *J. Appl. Cryst.*, (1999) **32**, 837-838 .

Legends for Figures

Figure 1. **View of a molecule of Mes-SO-N=CH-CH=CH-Ph, indicating the atom numbering scheme. Thermal ellipsoids are drawn at the 50% probability level.**

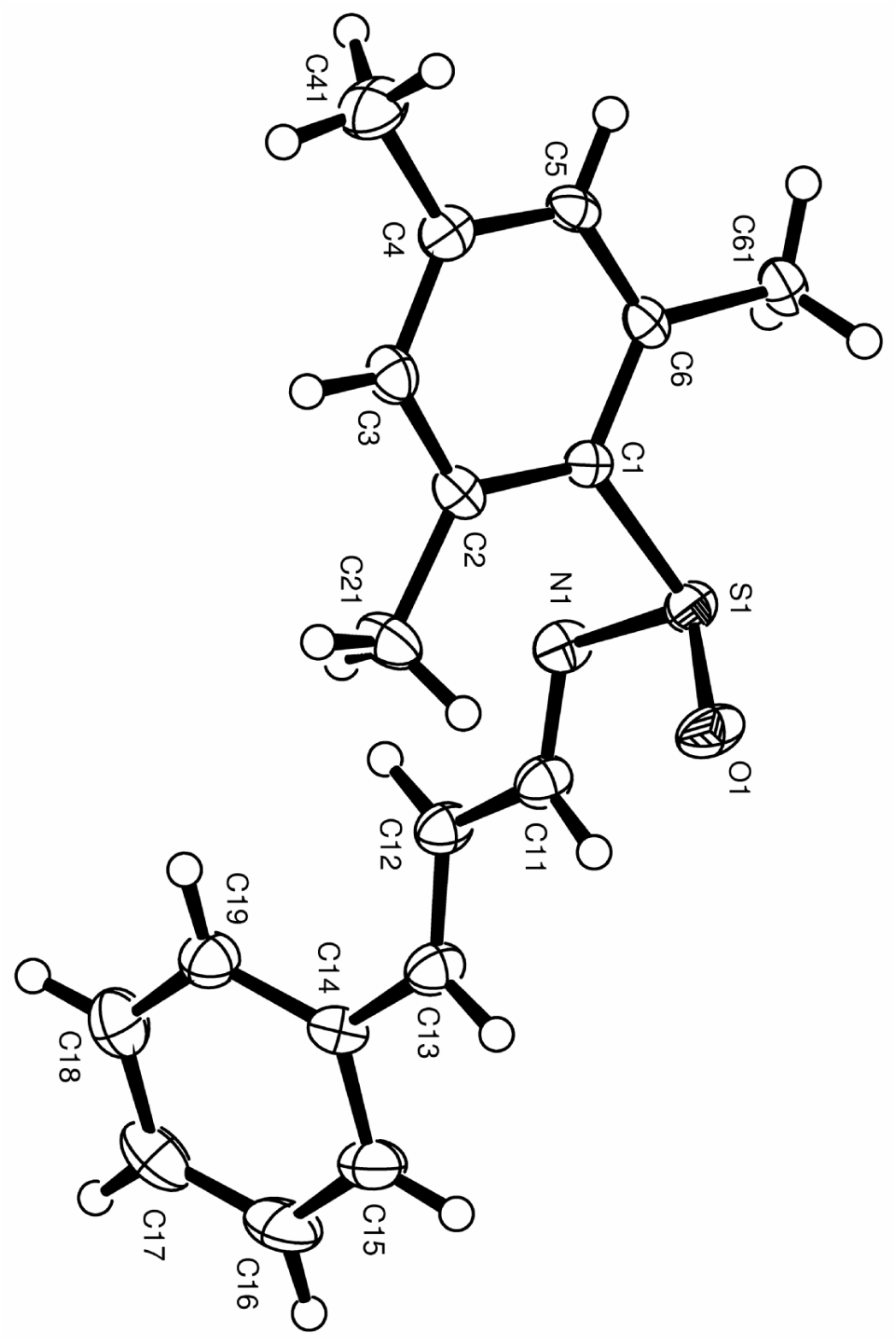

C41
C5
C61
C4
C6
C3
C1
C2
C21
N1
S1
O1
C12
C11
C19
C14
C13
C18
C15
C17
C16

FIGURE 1

4.2 Appendix II - Crystal structure analysis of *N*-Mesityl aminoindane **280**

Crystal and structure refinement data for Mes-SO-NH-indane

Identification code	leonids2
Elemental formula	C18 H21 N O S
Formula weight	299.4
Crystal system	Monoclinic
Space group	$P2_1$ (no. 4)
Unit cell dimensions	a = 4.6233(6) Å α = 90 ° b = 22.347(2) Å β = 110.426(14)° c = 8.3179(13) Å γ = 90 °
Volume	805.34(18) $Å^3$
No. of formula units, Z	2
Calculated density	1.235 Mg/m^3
F(000)	320
Absorption coefficient	0.200 mm^{-1}
Temperature	140(1) K
Wavelength	0.71073 Å
Crystal colour, shape	colourless needle
Crystal size	0.48 x 0.06 x 0.03 mm
Crystal mounting	on a glass fibre, in oil, fixed in cold N_2 stream
On the diffractometer:	
Theta range for data collection	4.5 to 21.2 °
Limiting indices	-4<=h<=4, -22<=k<=22, -8<=l<=8
Completeness to theta = 21.25	99.4 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.025 and 0.956
Reflections collected (not including absences)	5775
No. of unique reflections	1772 [R(int) for equivalents = 0.156]
No. of 'observed' reflections	($I > 2\sigma_I$) 931
Structure determined by:	direct methods, in SHELXS

Refinement:	Full-matrix least-squares on F^2, in SHELXL
Data / restraints / parameters	1772 / 2 / 196
Goodness-of-fit on F^2	0.710
Final R indices ('observed' data)	R1 = 0.052, wR2 = 0.045
Final R indices (all data)	R1 = 0.120, wR2 = 0.055
Reflections weighted: $w = \sigma^{-2}(Fo^2)$	
Absolute structure parameter	0.12(13)
Largest diff. peak and hole	0.22 and -0.21 e.Å^{-3}
Location of largest difference peak	near N(2)

Table 1. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor. E.s.ds are in parentheses.

	x	y	z	U(eq)
O(1)	-139(10)	4505(2)	5210(7)	36(2)
S(1)	2477(4)	4300.2(9)	6738(3)	29.9(6)
C(11)	5076(14)	4912(4)	7605(11)	23(2)
C(12)	5532(16)	5376(4)	6587(11)	22(2)
C(13)	7736(18)	5807(3)	7363(13)	30(3)
C(14)	9470(18)	5784(4)	9096(12)	28(2)
C(15)	8929(16)	5325(4)	10066(11)	34(2)
C(16)	6753(16)	4884(4)	9367(12)	29(2)
C(121)	3895(15)	5426(4)	4703(11)	33(2)
C(141)	11985(15)	6238(3)	9872(10)	39(2)
C(161)	6260(15)	4398(5)	10496(10)	50(3)
N(2)	5022(12)	3907(3)	6188(9)	30(2)
C(21)	4050(17)	3327(4)	5413(12)	37(3)
C(22)	3029(17)	3309(4)	3444(11)	48(3)
C(23)	3817(17)	2672(4)	3014(11)	46(3)
C(31)	6348(16)	2482(4)	4616(11)	30(2)
C(32)	6510(17)	2853(4)	5933(13)	30(2)
C(33)	8771(19)	2782(4)	7566(12)	32(2)
C(34)	10753(16)	2297(4)	7773(12)	41(2)
C(35)	10536(20)	1912(4)	6443(14)	42(3)
C(36)	8338(19)	2005(4)	4833(13)	45(3)

Table 2. Molecular dimensions. Bond lengths are in Ångstroms, angles in degrees. E.s.ds are in parentheses.

O(1)-S(1)	1.488(5)	N(2)-H(2)	0.80(2)
S(1)-C(11)	1.796(8)	N(2)-C(21)	1.447(9)
S(1)-N(2)	1.656(6)	C(21)-C(22)	1.539(10)
C(11)-C(12)	1.401(9)	C(21)-C(32)	1.503(10)
C(11)-C(16)	1.400(10)	C(22)-C(23)	1.541(9)
C(12)-C(121)	1.488(10)	C(23)-C(31)	1.496(10)
C(12)-C(13)	1.386(10)	C(31)-C(32)	1.355(10)
C(13)-C(14)	1.384(11)	C(31)-C(36)	1.379(10)
C(14)-C(141)	1.508(10)	C(32)-C(33)	1.404(10)
C(14)-C(15)	1.381(10)	C(33)-C(34)	1.391(10)
C(15)-C(16)	1.383(9)	C(34)-C(35)	1.377(10)
C(16)-C(161)	1.504(10)	C(35)-C(36)	1.385(12)
O(1)-S(1)-C(11)	109.9(4)	C(21)-N(2)-S(1)	117.3(5)
O(1)-S(1)-N(2)	111.8(3)	C(21)-N(2)-H(2)	117(5)
N(2)-S(1)-C(11)	94.3(3)	N(2)-C(21)-C(22)	115.5(8)
C(12)-C(11)-S(1)	122.8(6)	N(2)-C(21)-C(32)	114.6(7)
C(16)-C(11)-S(1)	115.8(7)	C(32)-C(21)-C(22)	102.0(8)
C(16)-C(11)-C(12)	121.4(7)	C(21)-C(22)-C(23)	105.2(7)
C(11)-C(12)-C(121)	124.3(7)	C(31)-C(23)-C(22)	103.3(7)
C(13)-C(12)-C(11)	118.3(8)	C(32)-C(31)-C(23)	110.6(7)
C(13)-C(12)-C(121)	117.4(9)	C(36)-C(31)-C(23)	127.9(9)
C(14)-C(13)-C(12)	121.6(9)	C(32)-C(31)-C(36)	121.4(8)
C(13)-C(14)-C(141)	120.0(9)	C(31)-C(32)-C(21)	112.1(8)
C(15)-C(14)-C(13)	118.6(9)	C(33)-C(32)-C(21)	126.2(9)
C(15)-C(14)-C(141)	121.3(8)	C(31)-C(32)-C(33)	121.7(8)
C(14)-C(15)-C(16)	122.5(8)	C(34)-C(33)-C(32)	116.3(9)
C(15)-C(16)-C(11)	117.6(8)	C(35)-C(34)-C(33)	121.8(8)
C(11)-C(16)-C(161)	122.5(8)	C(34)-C(35)-C(36)	120.4(9)
C(15)-C(16)-C(161)	119.9(8)	C(31)-C(36)-C(35)	118.2(9)
S(1)-N(2)-H(2)	114(5)		

Hydrogen bond dimensions

D-H...A	D-H	H...A	D...A	<(D-H...A)
N(2)-H(2)...O(1′)	**0.80(2)**	**2.17(6)**	**2.953(9)**	**165(6)**

Symmetry operation:
′ : 1+x, y, z

Table 3. Anisotropic displacement parameters ($Å^2$ x 10^3) for the expression:

$$\exp\{-2\pi^2(h^2a^{*2}U_{11} + \ldots + 2hka^*b^*U_{12})\}$$

E.s.ds are in parentheses.

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	22(3)	38(4)	43(4)	1(3)	6(3)	-2(2)
S(1)	22.9(12)	28.0(14)	40.0(16)	1.6(16)	12.5(12)	-1.6(13)
C(11)	8(4)	30(6)	26(7)	3(5)	-2(4)	1(4)
C(12)	19(5)	31(6)	16(6)	3(6)	6(5)	11(4)
C(13)	20(6)	23(6)	50(9)	-1(6)	15(6)	0(4)
C(14)	24(6)	24(6)	36(8)	-6(6)	9(5)	12(4)
C(15)	34(6)	45(7)	17(6)	10(6)	1(5)	20(5)
C(16)	20(5)	23(5)	37(7)	-7(5)	1(5)	3(4)
C(121)	33(5)	27(6)	41(7)	5(6)	17(5)	7(4)
C(141)	42(5)	42(7)	29(6)	-17(5)	7(4)	0(4)
C(161)	61(5)	31(6)	54(8)	6(6)	15(5)	-8(5)
N(2)	24(4)	28(5)	40(5)	-1(4)	12(3)	-8(3)
C(21)	32(6)	24(6)	54(8)	-5(6)	13(5)	2(4)
C(22)	38(6)	48(7)	52(8)	14(7)	8(5)	-1(5)
C(23)	40(6)	52(7)	46(8)	-1(6)	13(5)	-9(5)
C(31)	17(5)	30(6)	39(7)	-7(5)	7(5)	2(4)
C(32)	16(6)	33(7)	37(7)	3(6)	5(5)	-8(5)
C(33)	38(6)	31(7)	32(7)	-3(5)	17(5)	6(5)
C(34)	38(6)	40(7)	38(7)	11(6)	4(5)	9(5)
C(35)	29(6)	33(7)	65(9)	11(7)	15(6)	2(5)
C(36)	49(6)	42(7)	54(8)	-19(6)	30(6)	-10(5)

Table 4. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3). The amino hydrogen atom was located in a difference map; the N(2)-H(2) bond length was restrained. All other hydrogen atoms were included in idealised positions with U(iso)'s set at 1.2*U(eq) or, for the methyl groups, 1.5*U(eq) of the parent carbon atom.

	x	y	z	U(iso)
H(13)	8056	6119	6704	36
H(15)	10071	5312	11233	41
H(12A)	4354	5081	4145	49
H(12B)	4564	5781	4284	49
H(12C)	1710	5447	4464	49
H(14A)	12478	6249	11092	59
H(14B)	11289	6626	9396	59
H(14C)	13790	6128	9621	59
H(16A)	7576	4467	11661	75
H(16B)	6745	4017	10120	75
H(16C)	4143	4399	10427	75
H(2)	6067(124)	4104(23)	5799(78)	36
H(21)	2318	3191	5741	45
H(22A)	4133	3606	3033	58
H(22B)	831	3384	2925	58
H(23A)	2046	2409	2760	56
H(23B)	4518	2676	2042	56
H(33)	8934	3045	8460	39
H(34)	12267	2231	8839	49
H(35)	11875	1588	6626	51
H(36)	8207	1751	3923	54

Table 5. Torsion angles, in degrees. E.s.ds are in parentheses.

O(1)-S(1)-C(11)-C(16)	152.1(5)
N(2)-S(1)-C(11)-C(16)	-92.9(6)
O(1)-S(1)-C(11)-C(12)	-30.8(7)
N(2)-S(1)-C(11)-C(12)	84.2(6)
O(1)-S(1)-N(2)-C(21)	-68.0(7)
C(11)-S(1)-N(2)-C(21)	178.6(7)
S(1)-N(2)-C(21)-C(32)	-142.7(7)
S(1)-N(2)-C(21)-C(22)	99.1(8)
N(2)-C(21)-C(22)-C(23)	150.1(6)
C(32)-C(21)-C(22)-C(23)	25.1(8)
C(21)-C(22)-C(23)-C(31)	-24.4(8)
C(22)-C(23)-C(31)-C(32)	14.3(9)
C(22)-C(23)-C(31)-C(36)	-165.6(8)
N(2)-C(21)-C(32)-C(31)	-143.0(7)
C(22)-C(21)-C(32)-C(31)	-17.4(10)
N(2)-C(21)-C(32)-C(33)	36.9(13)
C(22)-C(21)-C(32)-C(33)	162.4(8)

Crystal structure analysis of Mes-SO-NH-indane **280**

Crystal data: $C_{18}H_{21}NOS$, M = 299.4. Monoclinic, space group $P2_1$ (no. 4), a = 4.6233(6), b = 22.347(2), c = 8.3179(13) Å, β = 110.426(14) °, V = 805.34(18) $Å^3$. Z = 2, Dc = 1.235 g cm^{-3}, F(000) = 320, T = 140(1) K, μ(Mo-Kα) = 2.0 cm^{-1}, λ(Mo-Kα) = 0.71069 Å.

Crystals are colourless needles. One was cut down to *ca* 0.48 x 0.06 x 0.03 mm, mounted in oil on a glass fibre and fixed in the cold nitrogen stream on an Oxford Diffraction Xcalibur-3 CCD diffractometer equipped with Mo-Kα radiation and graphite monochromator. Intensity data were measured by thin-slice ω- and φ-scans. Total no. of reflections recorded, to θ_{max} = 21.25°, was 5775 of which 1772 were unique (Rint = 0.156); 931 were 'observed' with $I > 2\sigma_I$.

Data were processed using the CrysAlis-CCD and -RED (1) programs. The structure was determined by the direct methods routines in the SHELXS program (2A) and refined by full-matrix least-squares methods, on F^2's, in SHELXL (2B). The non-hydrogen atoms were refined with anisotropic thermal parameters. The amino hydrogen atom was located in a difference map and was refined with a restrained N-H bond length; the other hydrogen atoms were included in idealised positions and their Uiso values were set to ride on the Ueq values of the parent carbon atoms. At the conclusion of the refinement, wR_2 = 0.055 and R_1 = 0.120 (2B) for all 1772 reflections weighted $w = \sigma^{-2}(F_o^2)$; for the 'observed' data only, R_1 = 0.052. The Flack parameter, x, is 0.12(13); the correct absolute configuration is shown in the Figure.

In the final difference map, the highest peak (*ca* 0.22 $eÅ^{-3}$) was close to N(2).

Scattering factors for neutral atoms were taken from reference (3). Computer programs used in this analysis have been noted above, and were run through WinGX (4) on a Dell Precision 370 PC at the University of East Anglia.

References

(5) Programs CrysAlis-CCD and -RED, Oxford Diffraction Ltd., Abingdon, UK (2005).

(6) G. M. Sheldrick, SHELX-97 - Programs for crystal structure determination (SHELXS) and refinement (SHELXL), University of Göttingen, Germany (1997).

(7) *'International Tables for X-ray Crystallography'*, Kluwer Academic Publishers, Dordrecht (1992). Vol. C, pp. 500, 219 and 193.

(8) L. J. Farrugia, *J. Appl. Cryst.*, (1999) **32**, 837-838 .

Legends for Figures

Figure 2. View of a molecule of Mes-SO-NH-indane, indicating the atom numbering scheme. Thermal ellipsoids are drawn at the 50% probability level.

Notes on the structure

There is an N-H…O hydrogen bond which links molecules in chains parallel to the *a* axis. Both S(1) and N(2) show their three bonds in a tetrahedral arrangement in which the fourth site is vacant.

The shape of the five-membered ring is constrained to an envelope form, with C(22) as the flap atom.

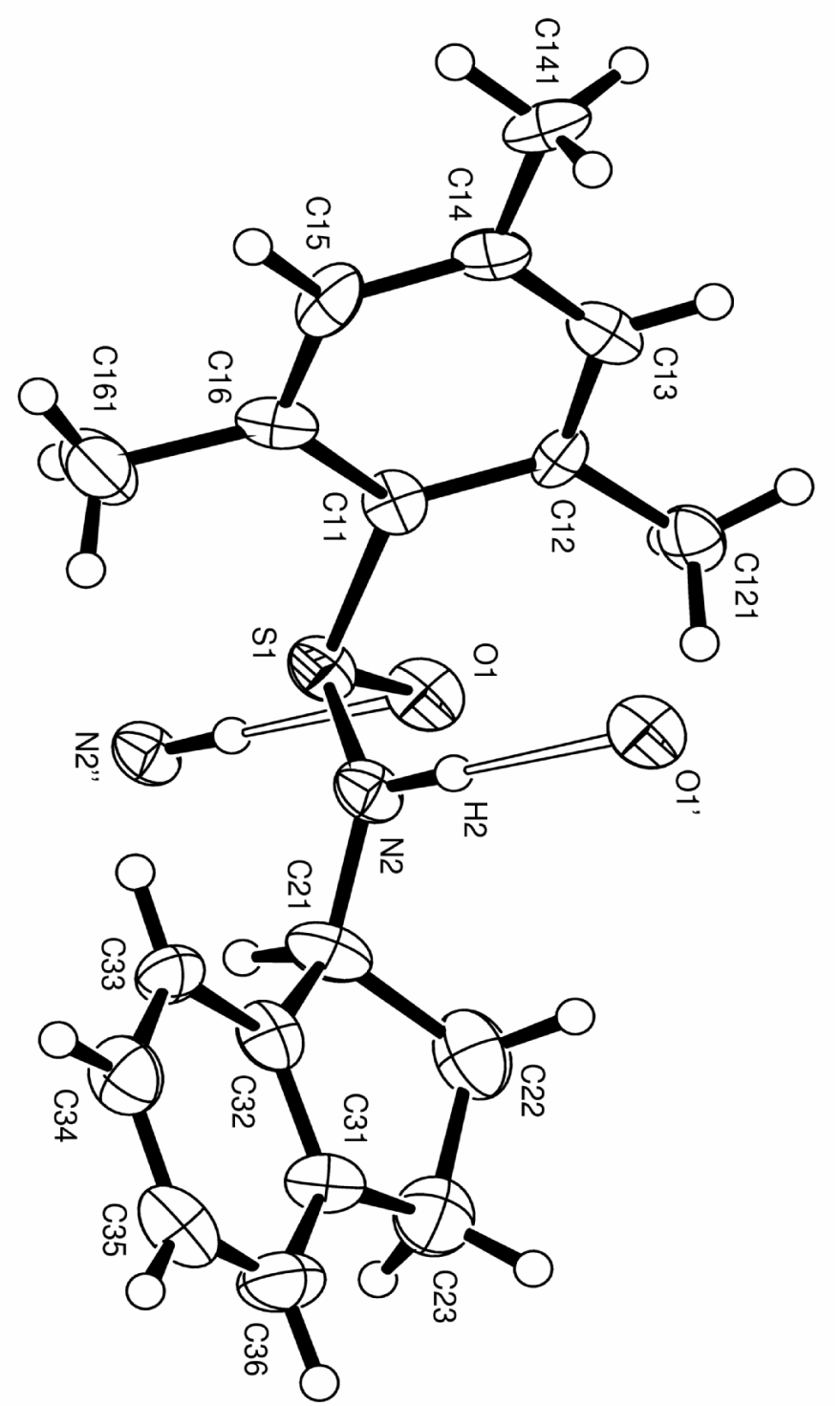

C141
C14
C15
C13
C161
C16
C11
C12
C121
S1
O1
N2"
O1'
H2
N2
C21
C33
C22
C34
C32
C31
C35
C23
C36

FIGURE 2

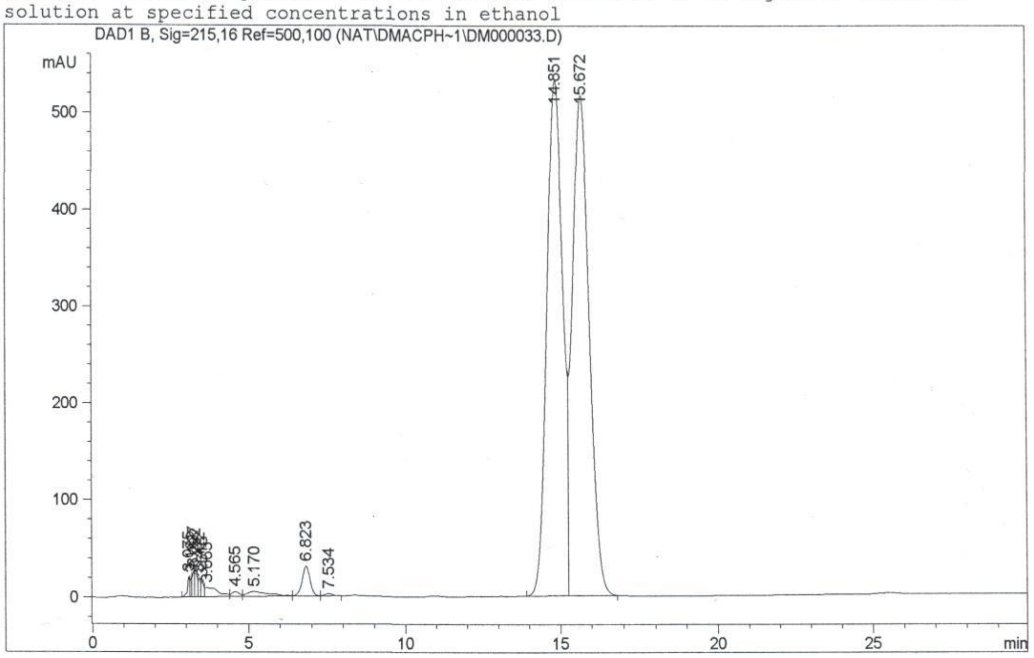
4.3 Chiral HPLC Data of the Sulfinimines

Racemic 2,4,6-Trimethylphenylsulfinamide (212)

Data File C:\HPCHEM\1\DATA\NAT\DMACPH~1\DM000033.D Sample Name: LKSN 082

LKSN 082

```
==========================================================================
Injection Date  : 22/09/2005 15:21:22 PM        Seq. Line :   3
Sample Name     : LKSN 082                       Location : Vial 3
Acq. Operator   : Natasha Spearing                   Inj :   1
Acq. Instrument : Chiral Instrument 1          Inj Volume : 20 µl
Method          : C:\HPCHEM\1\METHODS\NAT\DMACPHER.M
Last changed    : 22/09/2005 14:28:29 PM by Natasha Spearing
Chiralcel OD ( 250mm x 4.6mm; 10 um particle size ); Serial Number: OD00CE-EH032;
Heptane : Absolute Ethanol (90:10 v/v pump-mixed): Isocratic for 30.0 minutes at 1.0
mLmin-1: Ambient temperature; U.V. Absorbance at 215nm; 20 uL injection volume of
solution at specified concentrations in ethanol
```




```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 B, Sig=215,16 Ref=500,100
```

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.075	BV	0.0747	109.17654	20.98005	0.2741
2	3.161	VV	0.0503	69.96139	20.24506	0.1756
3	3.227	VV	0.0651	123.88072	26.25237	0.3110
4	3.282	VV	0.0815	151.77097	24.09593	0.3810
5	3.422	VV	0.0682	96.77873	20.10016	0.2430
6	3.515	VV	0.0852	94.50813	15.94005	0.2373
7	3.663	VV	0.3669	293.00308	9.85267	0.7356
8	4.565	VV	0.2644	90.89041	5.29090	0.2282
9	5.170	VV	0.6638	275.72076	5.30995	0.6922
10	6.823	VB	0.2652	544.23608	30.94167	1.3663
11	7.534	BB	0.2634	44.28992	2.49190	0.1112
12	14.851	BV	0.5393	1.88422e4	531.88989	47.3019

Appendices

Data File C:\HPCHEM\1\DATA\NAT\DMACPH~1\DM000033.D Sample Name: LKSN 082

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
13	15.672	VB	0.5714	1.90976e4	516.49030	47.9429

Totals : 3.98340e4 1229.88089

Results obtained with enhanced integrator!

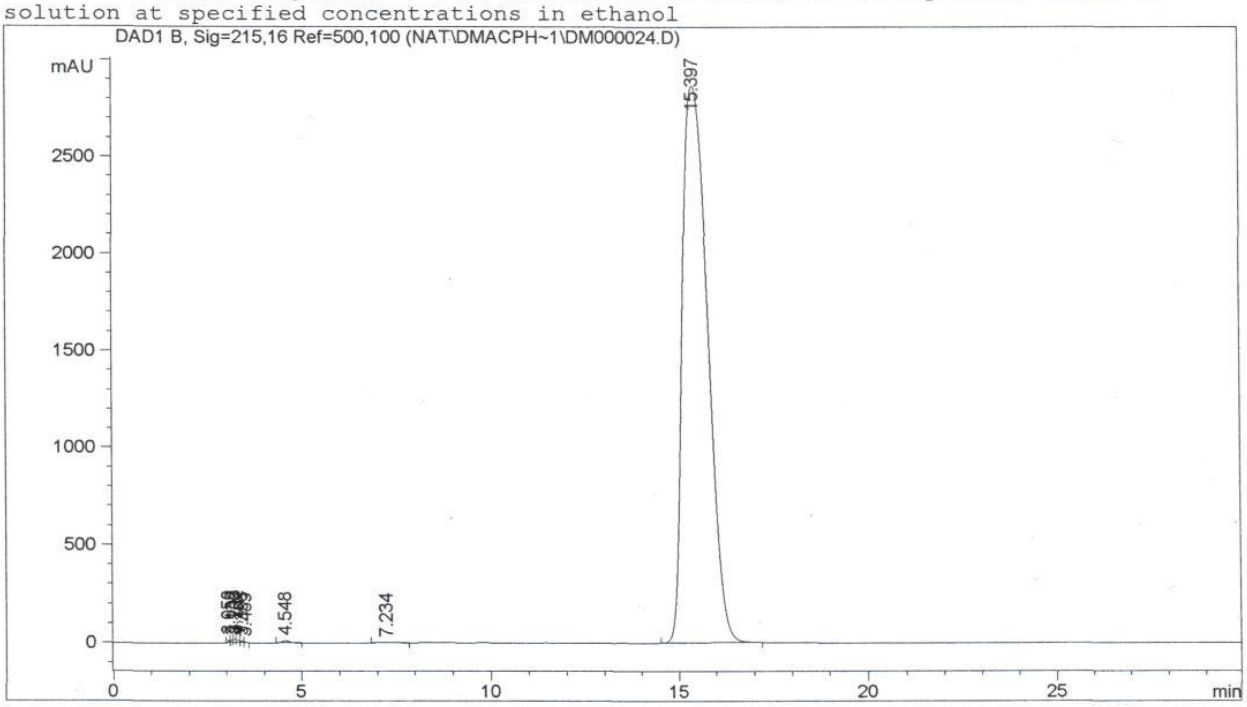
*** End of Report ***

Enantiopure (*R*)-(-)-2,4,6-Trimethylphenylsulfinamide (212)

Data File C:\HPCHEM\1\DATA\NAT\DMACPH~1\DM000024.D Sample Name: LKSN 124

LKSN 124

```
==========================================================================
Injection Date  : 20/09/2005 16:23:10 PM        Seq. Line :   4
Sample Name     : LKSN 124                       Location : Vial 6
Acq. Operator   : Natasha Spearing                   Inj :   1
Acq. Instrument : Chiral Instrument 1          Inj Volume : 20 µl
Acq. Method     : C:\HPCHEM\1\METHODS\NAT\DMACPHER.M
Last changed    : 20/09/2005 16:24:23 PM by Natasha Spearing
                  (modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\NAT\DMACPHER.M
Last changed    : 20/09/2005 12:06:12 PM by Natasha Spearing
Chiralcel OD ( 250mm x 4.6mm; 10 um particle size ); Serial Number: OD00CE-EH032;
Heptane : Absolute Ethanol (90:10 v/v pump-mixed): Isocratic for 10.0 minutes at 1.0
mLmin-1: Ambient temperature; U.V. Absorbance at 215nm; 20 uL injection volume of
solution at specified concentrations in ethanol
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 B, Sig=215,16 Ref=500,100
```

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.050	BV	0.0581	61.15326	16.16907	0.0454
2	3.138	VV	0.0512	50.95538	14.41545	0.0378
3	3.203	VV	0.0631	82.43724	18.83075	0.0612
4	3.262	VV	0.0881	94.81188	16.72343	0.0704
5	3.398	VV	0.0718	54.53350	11.39259	0.0405
6	3.489	VB	0.0618	25.84429	6.30390	0.0192
7	4.548	BP	0.2264	161.60530	11.75190	0.1199
8	7.234	PP	0.3582	66.91713	2.84700	0.0497
9	15.397	BB	0.7636	1.34171e5	2869.05664	99.5561

Racemic *N*-(Benzylidene)-2,4,6-trimethylphenylsulfinamide (215)

Data File C:\HPCHEM\1\DATA\NAT\DMACPH~1\DM000011.D Sample Name: DM105787-086

DM105787-086

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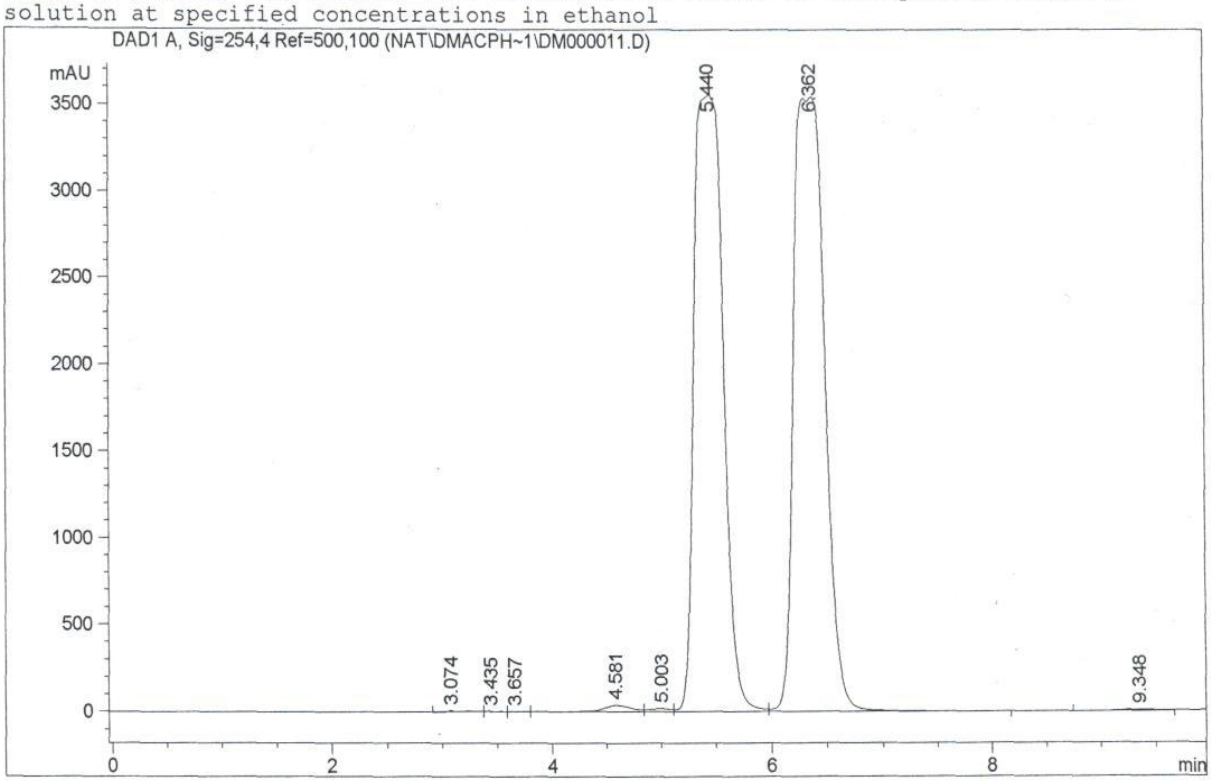
Injection Date  : 20/09/2005 12:40:32 PM        Seq. Line :   3
Sample Name     : DM105787-086                   Location : Vial 3
Acq. Operator   : Natasha Spearing                   Inj :   1
Acq. Instrument : Chiral Instrument 1          Inj Volume : 20 µl
Method          : C:\HPCHEM\1\METHODS\NAT\DMACPHER.M
Last changed    : 20/09/2005 12:06:12 PM by Natasha Spearing
Chiralcel OD ( 250mm x 4.6mm; 10 um particle size ); Serial Number: OD00CE-EH032;
Heptane : Absolute Ethanol (90:10 v/v pump-mixed): Isocratic for 10.0 minutes at 1.0
mLmin-1: Ambient temperature; U.V. Absorbance at 215nm; 20 uL injection volume of
solution at specified concentrations in ethanol
```




```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=500,100
```

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.074	BV	0.1331	93.39517	9.30183	0.0689
2	3.435	VV	0.1084	47.19327	5.71344	0.0348
3	3.657	VV	0.1384	36.89099	3.63575	0.0272
4	4.581	VV	0.3131	836.21991	39.80110	0.6169
5	5.003	VV	0.2064	289.05289	20.76019	0.2133
6	5.440	VV	0.2983	6.52553e4	3553.12842	48.1426
7	6.362	VB	0.3105	6.86710e4	3537.54224	50.6625
8	9.348	BV	0.4776	316.90533	9.89574	0.2338
Totals :				1.35546e5	7179.77871	

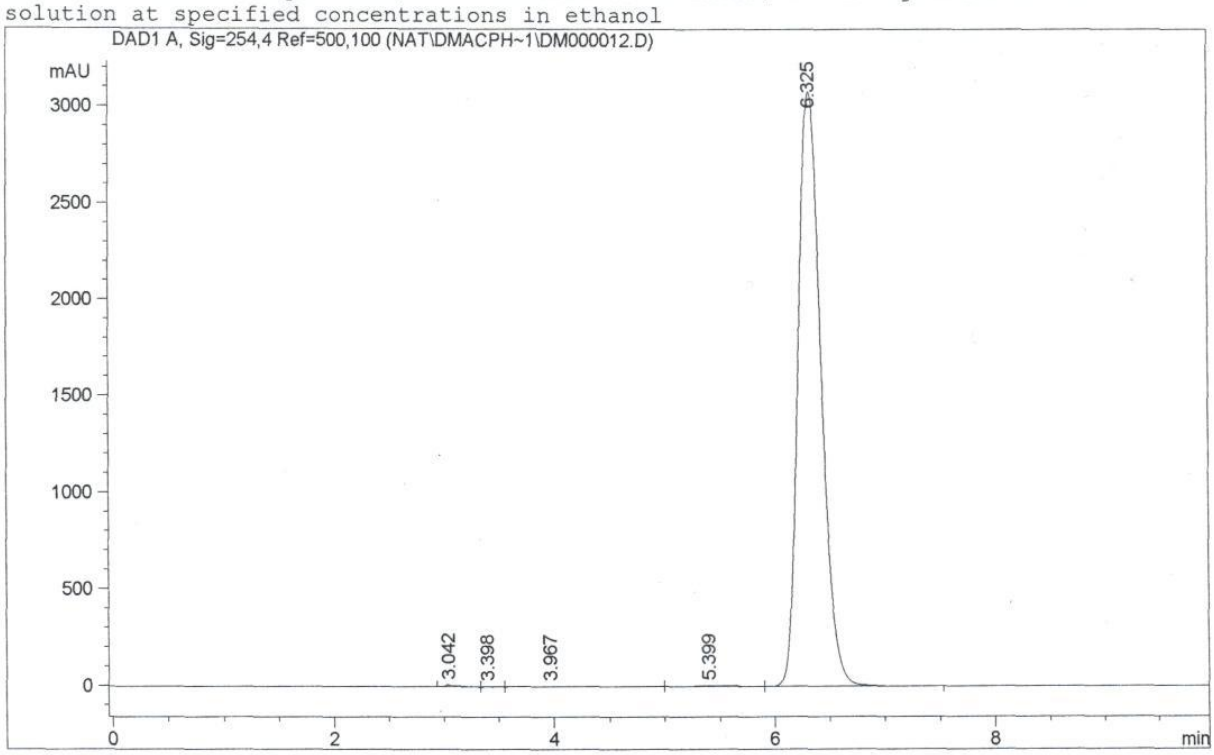
```
 Results obtained with enhanced integrator!
```

Enantiopure (*R*)-*N*-(Benzylidene)-2,4,6-trimethylphenylsulfinamide (246)

Data File C:\HPCHEM\1\DATA\NAT\DMACPH~1\DM000012.D Sample Name: DM105787-128

DM105787-128

```
==========================================================================
Injection Date  : 20/09/2005 12:52:07 PM        Seq. Line :   4
Sample Name     : DM105787-128                   Location : Vial 4
Acq. Operator   : Natasha Spearing                  Inj :   1
Acq. Instrument : Chiral Instrument 1          Inj Volume : 20 µl
Method          : C:\HPCHEM\1\METHODS\NAT\DMACPHER.M
Last changed    : 20/09/2005 12:56:55 PM by Natasha Spearing
                  (modified after loading)
Chiralcel OD ( 250mm x 4.6mm; 10 um particle size ); Serial Number: OD00CE-EH032;
Heptane : Absolute Ethanol (90:10 v/v pump-mixed): Isocratic for 10.0 minutes at 1.0
mLmin-1: Ambient temperature; U.V. Absorbance at 215nm; 20 uL injection volume of
solution at specified concentrations in ethanol
```




```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=500,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   3.042 BP    0.1278   93.05873   10.06836   0.2060
   2   3.398 VV    0.0835   23.52213    3.83568   0.0521
   3   3.967 VV    0.8163  191.92770    3.19748   0.4248
   4   5.399 VV    0.3940  163.85170    5.46243   0.3627
   5   6.325 VB    0.2252 4.47041e4  3083.24097  98.9544

Totals :                   4.51765e4  3105.80492

 Results obtained with enhanced integrator!
==========================================================================
                          *** End of Report ***

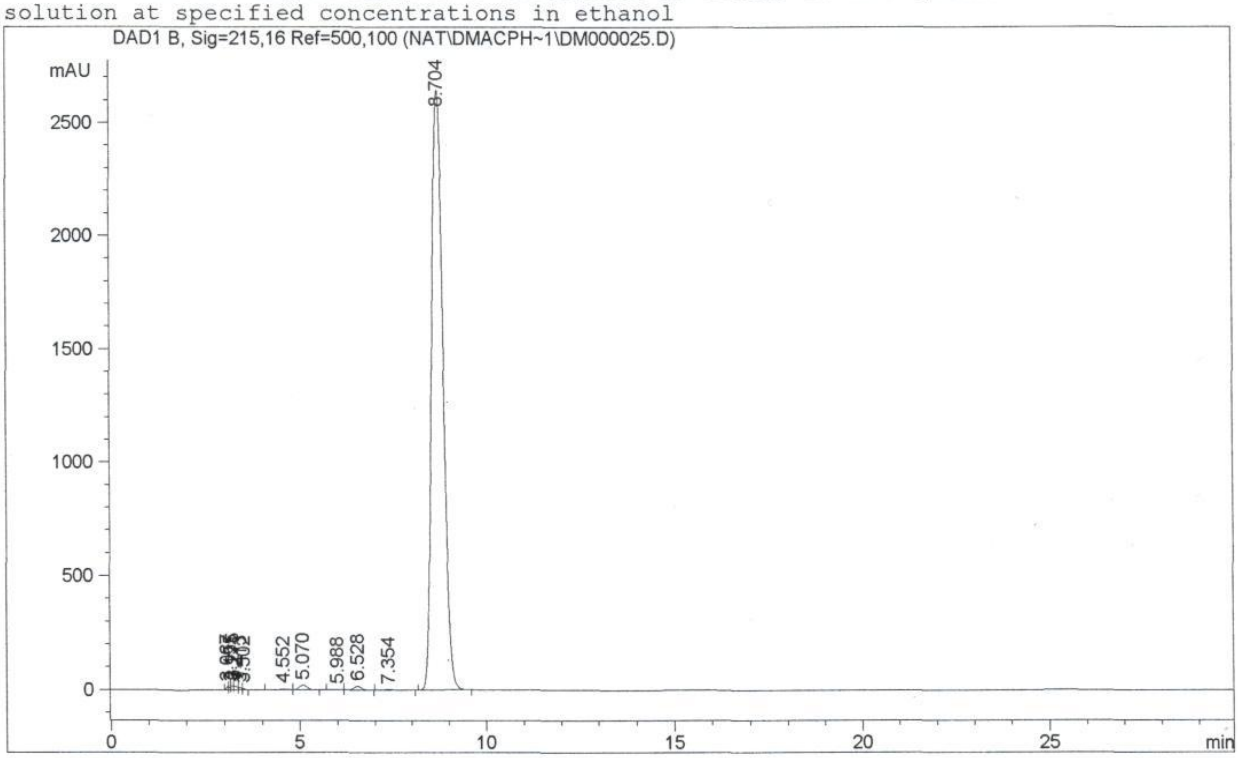
Chiral Instrument 1 20/09/2005 13:26:18 PM Natasha Spearing          Page 1 of 1
```

Enantiopure (*R*)-*N*-(4-Methoxy-benzylidene)-2,4,6-trimethylbenzenesulfinamide (253)

Data File C:\HPCHEM\1\DATA\NAT\DMACPH~1\DM000025.D Sample Name: LKSN 130

LKSN 130

```
==========================================================================
Injection Date  : 20/09/2005 16:54:46 PM        Seq. Line :   5
Sample Name     : LKSN 130                       Location : Vial 7
Acq. Operator   : Natasha Spearing                   Inj :   1
Acq. Instrument : Chiral Instrument 1          Inj Volume : 20 µl
Acq. Method     : C:\HPCHEM\1\METHODS\NAT\DMACPHER.M
Last changed    : 20/09/2005 16:24:23 PM by Natasha Spearing
                  (modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\NAT\DMACPHER.M
Last changed    : 21/09/2005 09:14:48 PM by Natasha Spearing
                  (modified after loading)
Chiralcel OD ( 250mm x 4.6mm; 10 um particle size ); Serial Number: OD00CE-EH032;
Heptane : Absolute Ethanol (90:10 v/v pump-mixed): Isocratic for 30.0 minutes at 1.0
mLmin-1: Ambient temperature; U.V. Absorbance at 215nm; 20 uL injection volume of
solution at specified concentrations in ethanol
```




```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 B, Sig=215,16 Ref=500,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   3.067 BV    0.0558   58.26881   15.53679   0.1018
   2   3.155 VV    0.0484   46.46766   14.13370   0.0812
   3   3.215 VV    0.0601   80.59958   18.78307   0.1408
   4   3.271 VV    0.0784  102.03325   16.90448   0.1782
   5   3.413 VV    0.0677   50.60021   10.99731   0.0884
   6   3.502 VB    0.0639   26.51969    6.45837   0.0463
   7   4.552 BV    0.3143   87.31805    4.10280   0.1525
   8   5.070 VB    0.2488  328.27826   20.95293   0.5734
```

Data File C:\HPCHEM\1\DATA\NAT\DMACPH~1\DM000025.D Sample Name: LKSN 130

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
9	5.988	PV	0.2453	29.06371	1.79088	0.0508
10	6.528	VB	0.2380	273.50125	17.53604	0.4777
11	7.354	BP	0.3235	65.85223	2.98405	0.1150
12	8.704	BB	0.3394	5.60993e4	2645.97583	97.9938
Totals :				5.72479e4	2776.15625	

Results obtained with enhanced integrator!

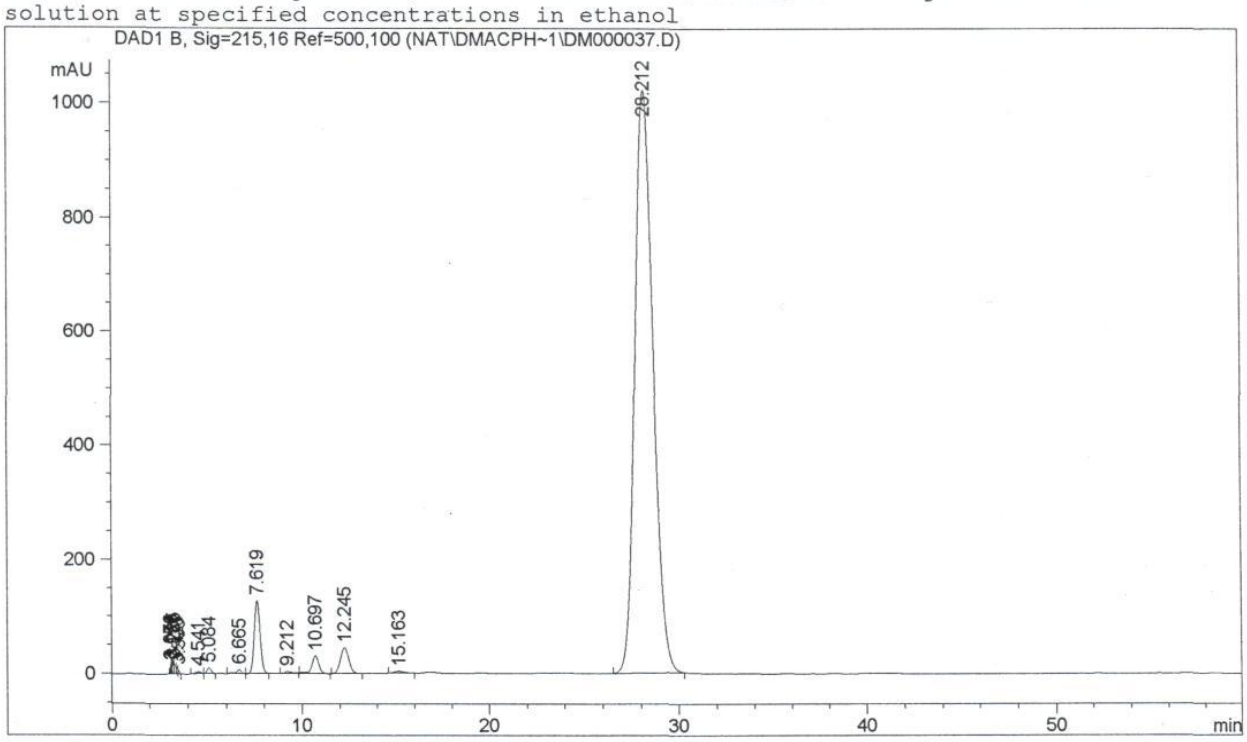
*** End of Report ***

Enantiopure (*R*)-*N*-(4-Nitro-benzylidene)-2,4,6-Trimethyl-benzenesulfinamide (254)

Data File C:\HPCHEM\1\DATA\NAT\DMACPH~1\DM000037.D Sample Name: LKSN 131

LKSN 131

```
==========================================================================
Injection Date  : 23/09/2005 13:36:46 PM        Seq. Line :   3
Sample Name     : LKSN 131                       Location : Vial 3
Acq. Operator   : Natasha Spearing                   Inj :   1
Acq. Instrument : Chiral Instrument 1          Inj Volume : 20 µl
Method          : C:\HPCHEM\1\METHODS\NAT\DMACPHER.M
Last changed    : 23/09/2005 11:31:48 PM by Natasha Spearing
Chiralcel OD ( 250mm x 4.6mm; 10 um particle size ); Serial Number: OD00CE-EH032;
Heptane : Absolute Ethanol (90:10 v/v pump-mixed): Isocratic for 60.0 minutes at 1.0
mLmin-1: Ambient temperature; U.V. Absorbance at 215nm; 20 uL injection volume of
solution at specified concentrations in ethanol
```




```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 B, Sig=215,16 Ref=500,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]       [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   3.078 BV    0.0566   61.08874   15.96691   0.0823
   2   3.158 VV    0.0504   49.79113   14.36552   0.0671
   3   3.225 VV    0.0644   82.00939   18.26977   0.1105
   4   3.286 VV    0.0924   99.06641   16.41345   0.1335
   5   3.423 VV    0.0655   53.01199   12.01764   0.0714
   6   3.508 VB    0.0662   27.69871    6.43153   0.0373
   7   4.541 BV    0.2772   71.95879    3.63167   0.0970
   8   5.084 VP    0.2453  156.26079   10.16793   0.2106
   9   6.665 BP    0.2847  146.10118    7.32365   0.1969
  10   7.619 VB    0.3402 2734.37842  127.49986   3.6850
  11   9.212 PB    0.4027  107.66621    3.64418   0.1451
  12  10.697 BP    0.4081  835.66223   31.03489   1.1262
```

Data File C:\HPCHEM\1\DATA\NAT\DMACPH~1\DM000037.D Sample Name: LKSN 131

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
13	12.245	BB	0.4815	1411.16089	45.04797	1.9017
14	15.163	BB	0.5280	132.24115	3.12297	0.1782
15	28.212	BB	1.0469	6.82358e4	1022.06000	91.9572
Totals :				7.42039e4	1336.99795	

Results obtained with enhanced integrator!

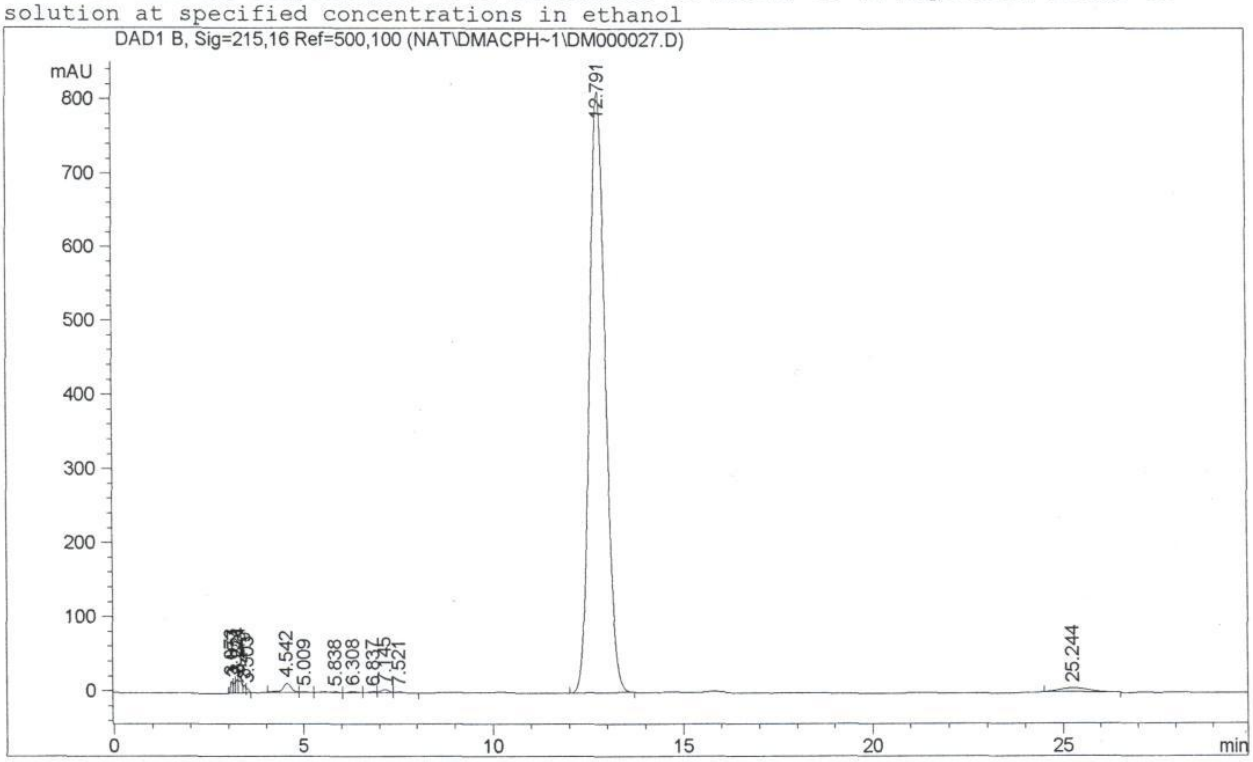
*** End of Report ***

Enantiopure (R)-*N*-(3-Phenyl-allylidene)-2,4,6-trimethylphenylsulfinamide (255)

Data File C:\HPCHEM\1\DATA\NAT\DMACPH~1\DM000027.D Sample Name: LKSN 132

LKSN 132

```
==========================================================================
Injection Date  : 20/09/2005 17:57:56 PM        Seq. Line :   7
Sample Name     : LKSN 132                       Location : Vial 9
Acq. Operator   : Natasha Spearing                   Inj :   1
Acq. Instrument : Chiral Instrument 1          Inj Volume : 20 µl
Acq. Method     : C:\HPCHEM\1\METHODS\NAT\DMACPHER.M
Last changed    : 20/09/2005 16:24:23 PM by Natasha Spearing
                  (modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\NAT\DMACPHER.M
Last changed    : 21/09/2005 09:14:48 PM by Natasha Spearing
                  (modified after loading)
Chiralcel OD ( 250mm x 4.6mm; 10 um particle size ); Serial Number: OD00CE-EH032;
Heptane : Absolute Ethanol (90:10 v/v pump-mixed): Isocratic for 30.0 minutes at 1.0
mLmin-1: Ambient temperature; U.V. Absorbance at 215nm; 20 uL injection volume of
solution at specified concentrations in ethanol
```




```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 B, Sig=215,16 Ref=500,100

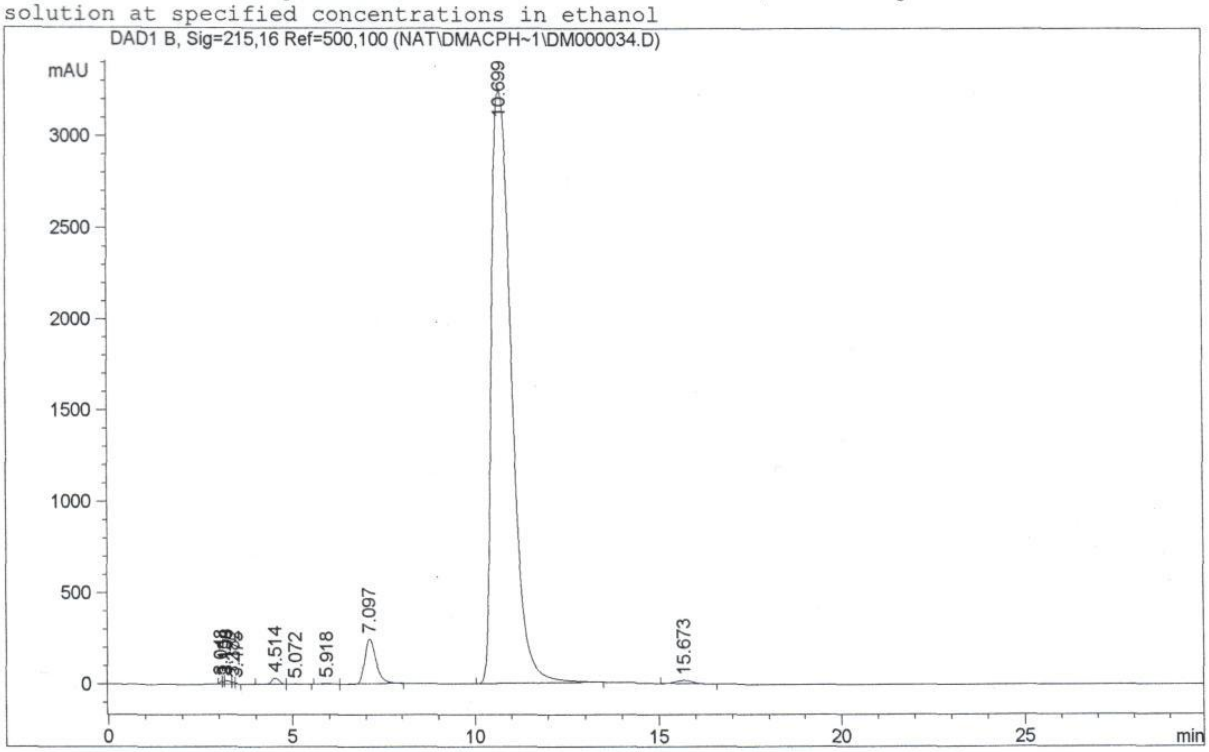
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   3.073 BV    0.0586   63.09836   16.50107   0.2563
   2   3.157 VV    0.0507   48.62708   14.26875   0.1975
   3   3.221 VV    0.0609   80.40047   18.41603   0.3265
   4   3.274 VV    0.0798  102.06499   16.58719   0.4145
   5   3.419 VV    0.0626   48.90206   11.27085   0.1986
   6   3.503 VP    0.0624   26.72419    6.18510   0.1085
   7   4.542 BV    0.2551  205.03711   12.13396   0.8328
   8   5.009 VP    0.2116   18.78312    1.35583   0.0763
```

(*R*)-*N*-(Pyridin-2-ylmethylene)-2,4,6-Trimethyl-benzenesulfiamide (256)

Data File C:\HPCHEM\1\DATA\NAT\DMACPH~1\DM000034.D Sample Name: LKSN 133

LKSN 124

```
==================================================================
Injection Date  : 22/09/2005 15:52:58 PM        Seq. Line :   4
Sample Name     : LKSN 133                       Location : Vial 4
Acq. Operator   : Natasha Spearing                   Inj :   1
Acq. Instrument : Chiral Instrument 1          Inj Volume : 20 µl
Method          : C:\HPCHEM\1\METHODS\NAT\DMACPHER.M
Last changed    : 22/09/2005 15:54:43 PM by Natasha Spearing
                  (modified after loading)
Chiralcel OD ( 250mm x 4.6mm; 10 um particle size ); Serial Number: OD00CE-EH032;
Heptane : Absolute Ethanol (90:10 v/v pump-mixed): Isocratic for 30.0 minutes at 1.0
mLmin-1: Ambient temperature; U.V. Absorbance at 215nm; 20 uL injection volume of
solution at specified concentrations in ethanol
```




```
==================================================================
                        Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 B, Sig=215,16 Ref=500,100
```

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.048	BV	0.0563	65.10513	17.16381	0.0502
2	3.134	VV	0.0496	51.76289	15.24646	0.0399
3	3.198	VV	0.1222	184.66887	19.55913	0.1423
4	3.382	VV	0.0608	48.61473	11.62967	0.0375
5	3.475	VB	0.0627	28.18320	7.04120	0.0217
6	4.514	BV	0.2360	496.57269	33.68171	0.3828
7	5.072	VB	0.2719	45.86577	2.59942	0.0354
8	5.918	BP	0.2768	87.17562	4.82562	0.0672
9	7.097	VB	0.3314	5403.75781	246.85020	4.1652
10	10.699	PB	0.5289	1.22706e5	3247.20435	94.5803
11	15.673	PP	0.5094	619.61029	18.56426	0.4776

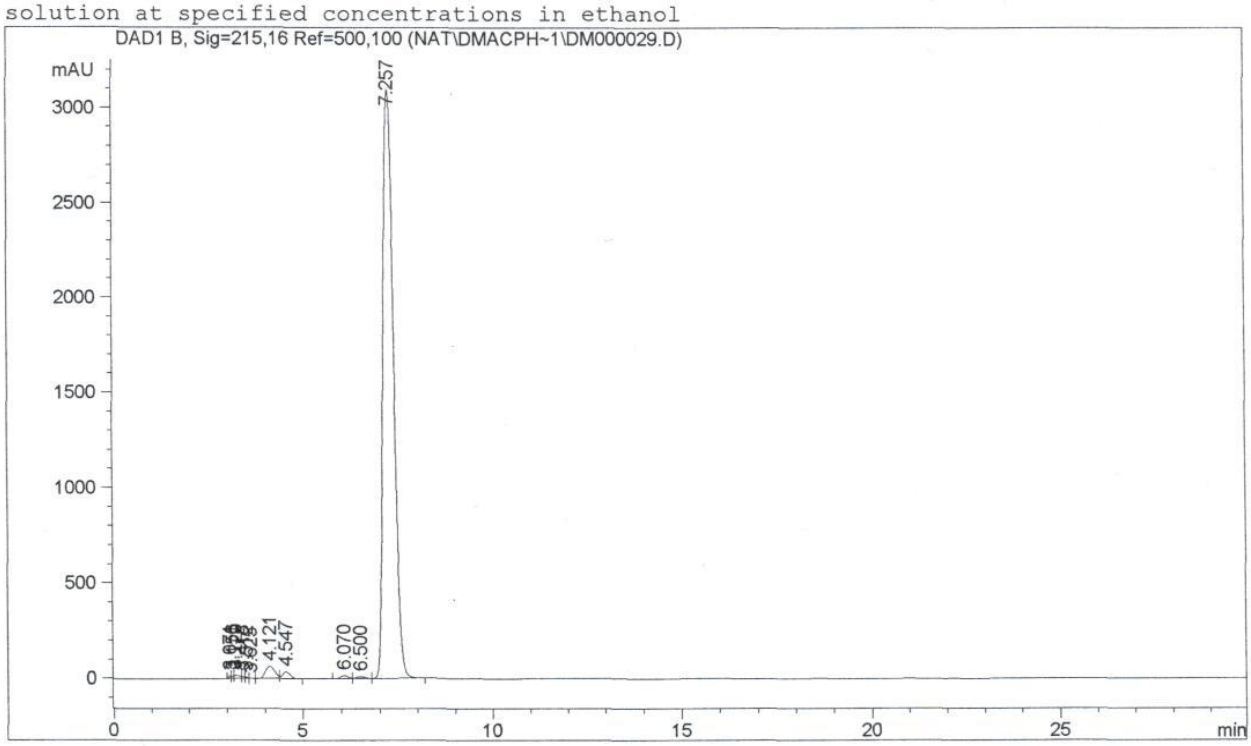
Enantiopure (*R*)-*N*-(Furan-2-ylmethylene)-2,4,6-Trimethyl-benzenesulfinamide (257)

Data File C:\HPCHEM\1\DATA\NAT\DMACPH~1\DM000029.D Sample Name: LKSN 134

LKSN 134

```
================================================================================
Injection Date  : 20/09/2005 19:01:08 PM        Seq. Line :   9
Sample Name     : LKSN 134                      Location : Vial 11
Acq. Operator   : Natasha Spearing                  Inj :   1
Acq. Instrument : Chiral Instrument 1          Inj Volume : 20 µl
Acq. Method     : C:\HPCHEM\1\METHODS\NAT\DMACPHER.M
Last changed    : 20/09/2005 16:24:23 PM by Natasha Spearing
                  (modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\NAT\DMACPHER.M
Last changed    : 21/09/2005 09:14:48 PM by Natasha Spearing
                  (modified after loading)
```

Chiralcel OD (250mm x 4.6mm; 10 um particle size); Serial Number: OD00CE-EH032; Heptane : Absolute Ethanol (90:10 v/v pump-mixed): Isocratic for 30.0 minutes at 1.0 mLmin-1: Ambient temperature; U.V. Absorbance at 215nm; 20 uL injection volume of solution at specified concentrations in ethanol




```
================================================================================
                          Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 B, Sig=215,16 Ref=500,100
```

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.071	PV	0.0529	56.10013	16.00167	0.0906
2	3.156	VV	0.0522	52.21455	14.44756	0.0843
3	3.229	VV	0.1387	186.87425	19.01185	0.3018
4	3.418	VV	0.0750	62.99859	12.46780	0.1017
5	3.512	VV	0.0596	35.09841	8.59418	0.0567
6	3.625	VP	0.0964	10.72843	1.77710	0.0173
7	4.121	VV	0.2824	1120.12476	63.94560	1.8087
8	4.547	VP	0.2319	515.48920	36.25929	0.8324

Data File C:\HPCHEM\1\DATA\NAT\DMACPH~1\DM000029.D Sample Name: LKSN 134

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
9	6.070	PV	0.2144	242.82866	17.23460	0.3921
10	6.500	VV	0.2372	167.70461	10.79604	0.2708
11	7.257	VP	0.3101	5.94789e4	3096.72314	96.0436
Totals :				6.19290e4	3297.25885	

Results obtained with enhanced integrator!

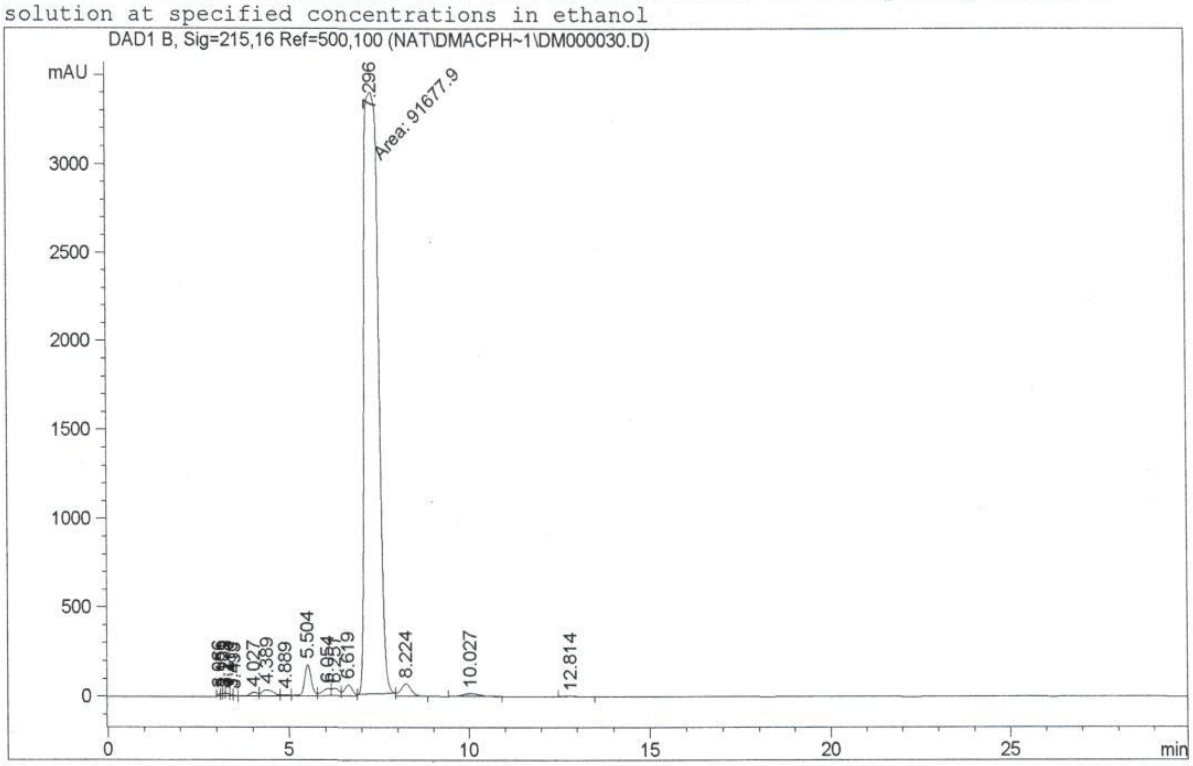
*** End of Report ***

Enantiopure (*R*)-*N*-(Naphthalen-1-ylmethylene)-2,4,6-trimethylbenzenesulfiamide (258)

Data File C:\HPCHEM\1\DATA\NAT\DMACPH~1\DM000030.D Sample Name: LKSN 146

LKSN 146

```
==========================================================================
Injection Date  : 20/09/2005 19:32:43 PM        Seq. Line :  10
Sample Name     : LKSN 146                       Location : Vial 12
Acq. Operator   : Natasha Spearing                   Inj :   1
Acq. Instrument : Chiral Instrument 1          Inj Volume : 20 µl
Acq. Method     : C:\HPCHEM\1\METHODS\NAT\DMACPHER.M
Last changed    : 20/09/2005 16:24:23 PM by Natasha Spearing
                  (modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\NAT\DMACPHER.M
Last changed    : 21/09/2005 13:25:02 PM by Natasha Spearing
                  (modified after loading)
Chiralcel OD ( 250mm x 4.6mm; 10 um particle size ); Serial Number: OD00CE-EH032;
Heptane : Absolute Ethanol (90:10 v/v pump-mixed): Isocratic for 10.0 minutes at 1.0
mLmin-1: Ambient temperature; U.V. Absorbance at 215nm; 20 uL injection volume of
solution at specified concentrations in ethanol
```




```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 B, Sig=215,16 Ref=500,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   3.066 BV    0.0562   58.98287   15.55693   0.0590
   2   3.151 VV    0.0469   43.91937   13.95908   0.0439
   3   3.209 VV    0.0622   77.65858   18.06438   0.0777
   4   3.273 VV    0.0947  103.25805   16.57148   0.1033
   5   3.410 VV    0.0685   53.51652   11.45830   0.0536
   6   3.493 VV    0.0667   30.50165    6.50565   0.0305
   7   4.027 VV    0.2665  347.40225   20.84057   0.3476
   8   4.389 VV    0.3632  795.07062   35.24461   0.7956
```

Data File C:\HPCHEM\1\DATA\NAT\DMACPH~1\DM000030.D Sample Name: LKSN 146

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
9	4.889	VV	0.2476	121.22910	7.30590	0.1213
10	5.504	VV	0.2002	2314.62207	177.47920	2.3162
11	6.054	VV	0.2408	688.93011	41.26636	0.6894
12	6.251	VV	0.2134	608.70630	41.91736	0.6091
13	6.619	VV	0.2308	1007.36591	65.74499	1.0080
14	7.296	MM	0.4508	9.16779e4	3389.48950	91.7388
15	8.224	VB	0.3044	1414.30054	69.79139	1.4152
16	10.027	BB	0.4852	542.66254	16.87232	0.5430
17	12.814	BP	0.3423	47.58058	1.76611	0.0476
Totals :				9.99336e4	3949.83414	

Results obtained with enhanced integrator!

*** End of Report ***