SYNTHESIS, REACTIONS AND APPLICATIONS OF CHIRAL FIVE-MEMBERED RING HETEROCYCLES

by

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Thesis presented for the degree of
DOCTOR OF PHILOSOPHY

University of St. Andrews October 1992

To Stephanie and my parents

Declaration

I, Shaun Terrance Einar Mesher, hereby certify that this thesis has been composed by myself, it is a record of my own work and has not been accepted in partial or complete fulfilment of any other degree or professional qualification.

Signed Date 15th October 1992

I was admitted to the Faculty of Science of the University of St. Andrews under Ordinance General No. 12 on October 1st 1989 and as a candidate for the degree of Ph.D. on October 1st 1990.

Signed Date 15th October 1992

I hereby certify that the candidate has fulfilled the conditions of the Resolution and Regulations appropriate to the Degree of Ph.D.

Signature of supervisor. Date 15th Oct 1992

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Lecture Courses

The following is a statement of the courses attended during the period of research; Organic Research Seminars (3 years attendance); Asymmetric Synthesis, Dr. R. A. Aitken; Lanthanides, Actinides and Nuclear Reactions, Dr. D. T. Richens; Spectroscopy, Dr. R. K. Mackie; Alicyclic Chemistry, Dr. F. G. Riddell; Photochemistry, Dr. J. A. Crayston; Pharmaceutical Chemistry, Dr. R. A. Aitken and Dr. A. R. Butler; Unusual Oxides and Sulphides of carbon, Dr. R. A. Aitken; Case Studies in Mechanistic Chemistry, Dr. A. R. Butler; Industrial Chemistry, Dr. C. Glidewell and Dr. D. M. Smith; Advanced NMR, Dr. F. G. Riddell; Advanced Topics in Bioinorganic Chemistry, Dr. D. T. Richens

Acknowledgements

I would like to thank Dr. Alan Aitken for his excellent supervision and guidance, and all the hard work it took to get me here.

Thanks are also due to all past and present colleagues of Lab 434 for their help and friendship. The staff and post grads who give the Chemistry department character and to the technical staff (especially Melanja) who run it.

Thank you to Stephanie and Wendy for the typing.

Finally, I thank the University of St. Andrews for financial support.

ABSTRACT

A series of chiral 2,4-disubstituted 2-thiazolines have been prepared and successfully oxidised to the corresponding 1,1-dioxides using the newly discovered oxidising system: $KMnO_4$ under phase-transfer conditions in the presence of 1 eq. benzoic acid. The dioxides were found to be extremely susceptible to hydrolysis which prevented their isolation with a 2-methyl substituent. With a 2-phenyl group the compounds were fully characterised but attempted 5-alkylation failed due to hydrolysis.

The thermal decomposition of this ring system has been examined for the first time and found to proceed by three-way cleavage to give SO_2, benzonitrile and an alkene.

In an attempt to suppress this pathway, the preparation of chiral thiazolidine 1,1-dioxides was attempted. Reduction of the 2-thiazolines using Al/Hg led to reductive dimerisation analogous to the Pinacol Reduction to give novel bis-thiazolidines, but with a 2-t-butyl subtituent the thiazolidine was obtained and readily oxidised. A second series of substituted thiazolidine 1,1-dioxides was obtained from *R*-cysteine.

Pyrolysis of these compounds, again not previously investigated, led to complete ring fragmentation to give SO_2, an alkene and fragments derived from an imine.

A series of chiral thiazolidin-2-one 1,1-dioxides has been obtained by oxidation of the corresponding thiazolidine-2-thiones, most conveniently using the $KMnO_4$ / $PhCO_2H$ / PTC conditions, and their pyrolysis examined in detail for the first time. The major process is three-way fragmentation to give SO_2, an alkene and an isocyanate. A novel minor pathway has been discovered which leads to thiazolines and thiazoles by rearrangement and loss of CO_2 and H_2O.

A variety of proline-derived chiral bicyclic iminium salts have been prepared and evaluated as reagents for kinetic resolution of secondary alcohols. Enantiomeric excess in the range 6-25% has been achieved and the information gained should allow design of more selective analogues in the future. Attempts to prepare a diphenyl substituted iminium salt led to a novel fragmentation reaction to give an acyclic product for which a mechanism is proposed.

Finally ^{33}S NMR spectra have been obtained using an MSL 500 instrument for a total of 25 compounds, many of them from previously unstudied compound classes and this has effectively extended the range of broad line-widths for which useful spectra can be obtained.

CONTENTS

INTRODUCTION

F. Preparation of 3-acetyl-4-(*R*)-methoxycarbonyl-2-substituted thiazolidines

DISCUSSION

INTRODUCTION

A. 5-Membered Nitrogen Containing Heterocycles in Asymmetric Induction

In the last two decades the area of asymmetric synthesis has seen a dramatic increase in the number of methods available to produce chiral non-racemic materials in high enantiometric purity. An increasing number of these methods use what is termed a "chiral auxiliary" to produce a new stereogenic centre within a prochiral material. These auxiliaries are derived from the pool of naturally occurring chiral compounds such as alkaloids, carbohydrates, and amino acids.

The consequence of binding the auxiliary ionically or covalently is to induce diastereotopicity within the molecule. Efficient control during the stereodifferentiating step, from the auxiliary to the new asymmetric centre, ensures that one diastereomer predominates over the other possible stereoisomers. Several methods then allow the non-destructive, efficient removal of the auxiliary to provide the enantiomerically enriched product.

Due to the large scope of this area, this review will only focus on chiral compounds incorporating a nitrogen-containing 5-membered heterocycle. Their use as chiral auxiliaries, reagents, catalysts and co-catalysts will be discussed.

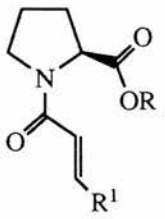
1. Pyrrolidines

The majority of pyrrolidine chiral auxiliaries are derived from the naturally occurring amino acid (*S*)-proline and these are employed in a wide variety of reactions.

1.1 Cycloaddition Reactions

With a chiral auxiliary attached to the diene, dienophile or Lewis acid catalyst, the broad scope of the cycloaddition reaction can be applied to the production of a large variety of optically active compounds.

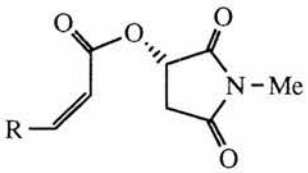
Lewis acid catalysed Diels-Alder reactions between *N*-acryloyl-[1] and *N*-crotonoyl-(*S*)-proline benzyl and allyl esters[2] **1** and a variety of dienes, gave the cycloadducts in excellent yields, with 97% endo selectivity and high



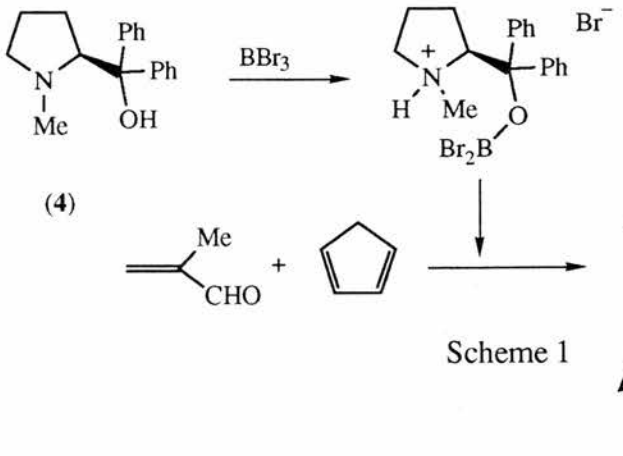
(**1**) R=CH_2Ph, allyl
R^1=Me, H

(**2**) R=CO_2Me, CH_2OMe or CH_2OCH_2OMe

enantiomeric excess (e.e.). The choice of Lewis acid affects the outcome: titanium (IV) chloride or tin (IV) chloride give the (*R*) cycloadduct, whereas $EtAlCl_2$, BF_3 or $ZnCl_4$ give the (*S*) configuration. Chiral acylamides **2** undergo asymmetric Diels-Alder reactions with cyclopentadiene to give the adducts with excellent diastereomeric excess (d.e.) (67-98%) and up to 92% endo selectivity.[3] Asymmetric Diels-Alder reactions of enoates **3** derived



(**3**) R=H, Me or Br

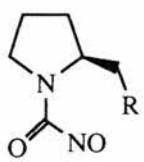


(**4**)

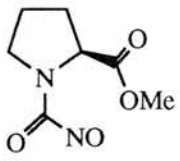
Scheme 1

from (*S*)-*N*-methyl-2-hydroxysuccinimide react with cyclohexadienes and cyclopentadienes in the presence of $TiCl_4$ with excellent diastereoselectivity (94-98% d.e.).[4] The diphenyl substituted (*S*)-prolinol compound **4** was used to catalyse Diels-Alder cyclisations in the presense of boron tribromide producing the adducts in greater than 99:1 for the exo adduct and in 97% e.e. Scheme 1.[5]

Heteroatom Diels-Alder reactions involving acylnitroso derivatives of (*S*)-proline **5-9**[6] give the 1,2-oxazine cycloadducts in 80-90% yield with d.e.s up to >98%. The acylnitroso dienophiles **10** R=Me[7] or R=CH_2OMe,[8] were



(**5**) R=OH
(**6**) R=OMe
(**7**) R=NHPh



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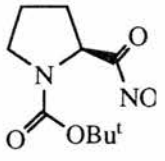
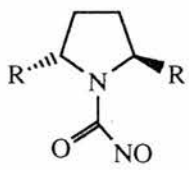


(**9**)

similarly reacted with a variety of dienes to afford the cycloadducts in excellent yields and d.e.s up to >98%. Reaction of the enimine precursor **11** with **10** R=CH_2OMe gives the adduct **12**, reduction and hydrolysis of which gives enantiomerically pure α-amino acids in good yields.[9] Chiral four



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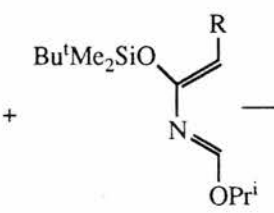

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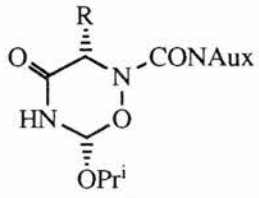
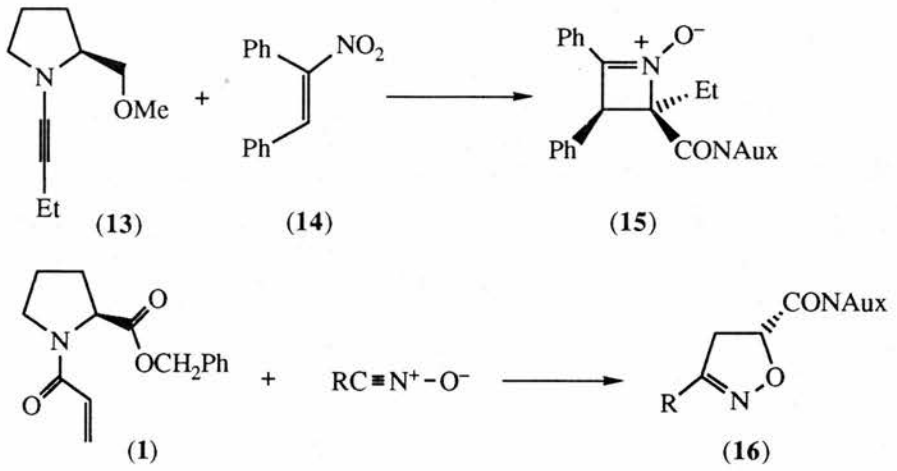


(**12**)

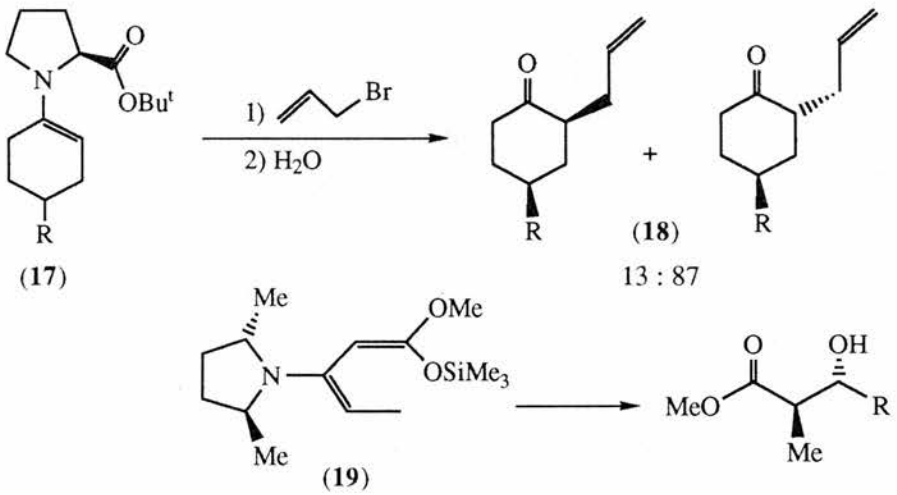
membered cyclic nitrones **15** were synthesised in 51% yield and 46% d.e.[10] from the [4+2] cycloaddition of nitroalkene **14** with ynamine **13** followed by rearrangement. 1,3-Dipolar cycloaddition between **1** R^1=H, R=$PhCH_2$ and

nitrile oxides gave the isoxazolines[11] **16** in excellent yields but poor d.e. (3:1, *S:R*).

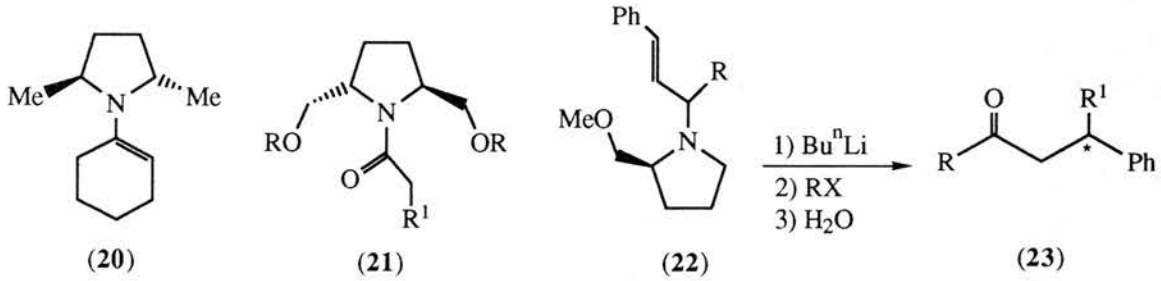


1.2 Alkylation Reactions

The reaction of enamine **17** with allyl bromide provides, after hydrolysis, **18** as a mixture of cis and trans diastereomers and 16-20% yield.[12] Condensation of enamine **19** with an acid chloride followed by L-selectride reduction affords a cyclic lactone, periodic acid degradation of this followed by reaction with diazomethane, produces the β-hydroxy ester in 94-97% e.e.[13]



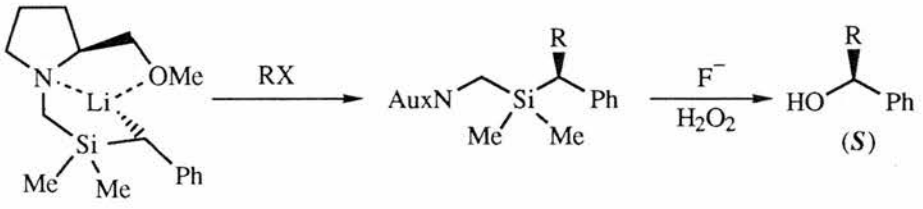
Alkylation of the enamine **20** provides the α-substituted cyclohexanones in 80% e.e.[14] and alkylation of the enolate of **21** affords, after hydrolysis, α-amino acids in excellent yields (81-97%) and e.e.s between 95 and 97%.[15]



(**20**) (**21**) (**22**) (**23**)

Asymmetric alkylation of the homoenolate equivalent **22** R=H[16] with alkyl halides provides the β-substituted aldehydes **23** in yields between 2 and 90% and e.e.s of 22-87%, with the e.e. strongly dependant on the solvent used but not the size of the alkylating reagent. For R=alkyl the corresponding β-substituted 3-phenylketones[17] are produced in 40-95% yield and 11-77% e.e. with the configuration of the asymmetric centre depending heavily on the size of the alkylating reagent, the solvent, temperature and the counter ion.

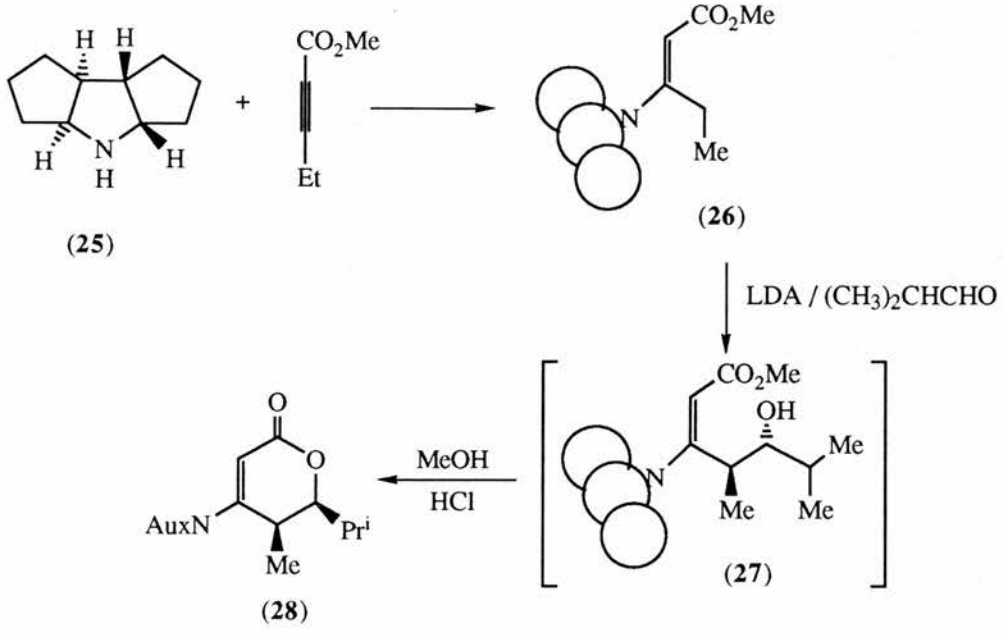
Enantioselective alkylation of **24** gave the arylcarbinols,[18] after removal of the auxiliary in excellent yields (80-90%) and e.e.s greater than 99%. The



(**24**)

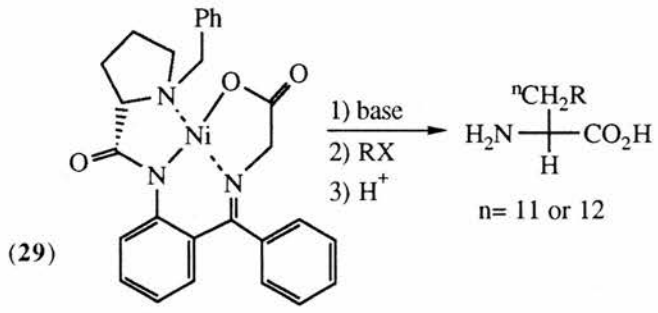
benzyl moiety in **24** can be replaced by an allyl group to produce homoallylic alcohols but the e.e. then drops to 50%.[19] Asymmetric induction was observed[20] when the tricyclic amine **25** was reacted with an ynoate to provide

the enoate **26**, which was then treated with base and isobutyraldehyde to

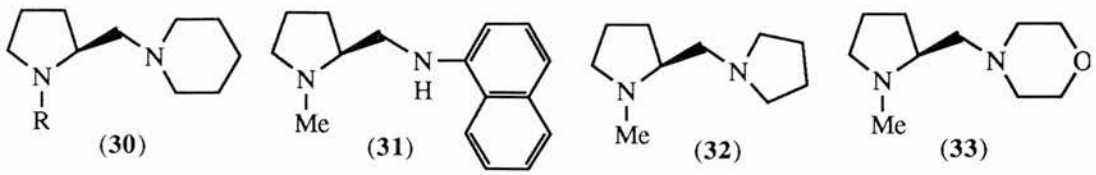


afford the *anti* aldol product **27**. Under the reaction conditions **27** cyclises spontaneously to give the lactone **28** in 95% e.e.

Formation of the glycine or alanine chiral nickel complex **29** followed by: proton abstraction by a base, attack of an electrophile and hydrolysis afforded novel[21, 22] and radiolabelled[23] α-amino acids with 80-90% e.e.

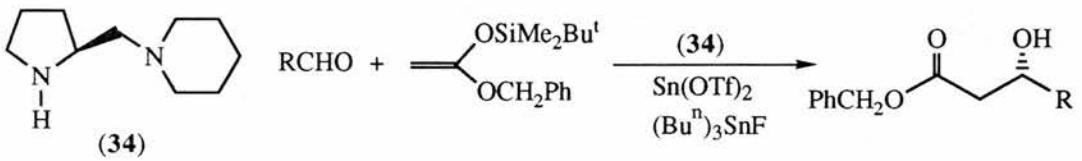


Tin (II) complexes of **30-33** bring about aldol reactions to give *syn* products with greater than 99% e.e.[24] An Aldol type reaction between achiral ketene silyl acetals and achiral aldehydes in the presence of a chiral diamine



(30) (31) (32) (33)

34 coordinated to tin(II)triflate gives α-hydroxy compounds in good yields (51-76%) and 89- >98% e.e.[25]



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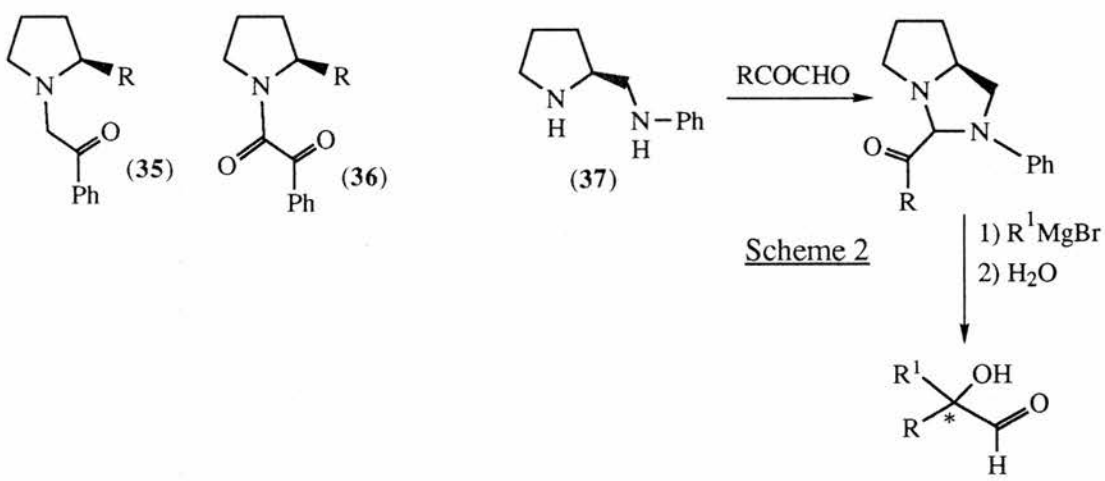
1.3 Addition of Organometallic Reagents to CO

Diastereoselective alkylation of α-amino ketones **35** R=CH_2OMe with organometallics gave the (*S*)-substituted alcohols when magnesium or zinc were used and (*R*) isomers when lithium was used, with 25-100% e.e.[26] Allylation of (*S*)-proline α-keto amides **36** R=CO_2Me or CO_2Pr^i in the presence of a Lewis acid[27] and alkylation of **36** R= CH_2OMe using Grignard



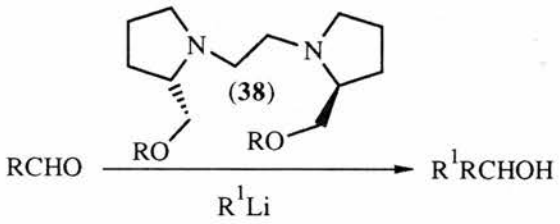
(35) (36) (37)

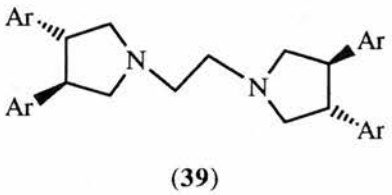
Scheme 2

reagents,[28] gives the tertiary homoallylic alcohols and α-substituted α-hydroxycarboxylic acids in good yields with e.e.s up to 98% and 81%

respectively. Condensation of keto-aldehydes with **37** to give the bicyclic aminal followed by alkylation affords α-hydroxy α-substituted aldehydes in 67-82% yield and 94-96% e.e., Scheme 2.[29]

The diamine **38** used in the presence of an aldehyde and alkyl lithium or magnesium reagents, provides the alkylated secondary alcohols in 20-95%

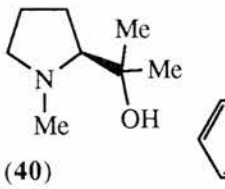




(39)

e.e.s and good yields[30] and **38** in the presence of benzaldehyde and Bu^nLi[31] gives (*R*)-1-phenyl-1-pentanol in 4-36% e.e. The C_2-symmetrical diamine **39**, complexes alkyl magnesium bromides, which react with aldehydes to give the secondary alcohols in 40-75% e.e. and 68-96% yield.[32] Tin (II) triflate complexes of chiral diamine ligand **30** R=Me have been used in the alkylation of aldehydes to give homoallylic alcohols in 52-84% e.e.[33]

Alkyl and arylaldehydes react with dialkyl zinc reagents in the presence of a chiral catalyst **4** or **40-49** to give optically active secondary alcohols in excellent yields. The e.e.s vary depending on the catalyst from a minimum of 34-60% for **40**[34] and **41**,[35] to a maximum of 80-100% for **4**,[36] **42**,[37] **43** and



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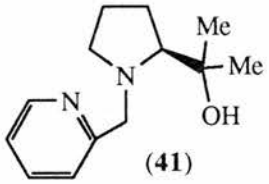

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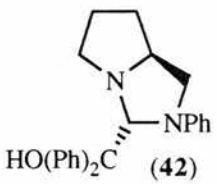

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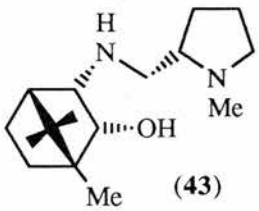

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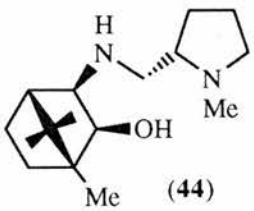

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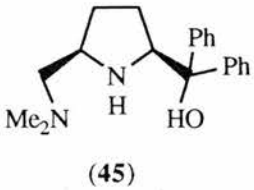

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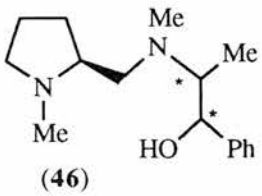

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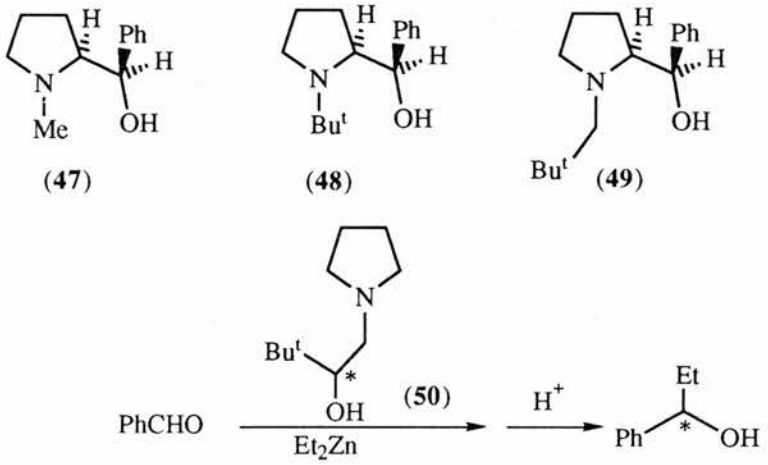
44,[38] **45**,[39] **46**,[40] and **47** to **49**.[41] Also the configuration of the alcohol depends on the catalyst, whereas **40**, **41**, **43** and **47-49** give the (*R*) isomer, **4**, **42** and **44-46** give the (*S*) configuration in excellent chemical yields. The amino alcohol **49** has also been used to synthesise (*R*)-fluorine containing and deuterio alcohols with very high e.e.[41]



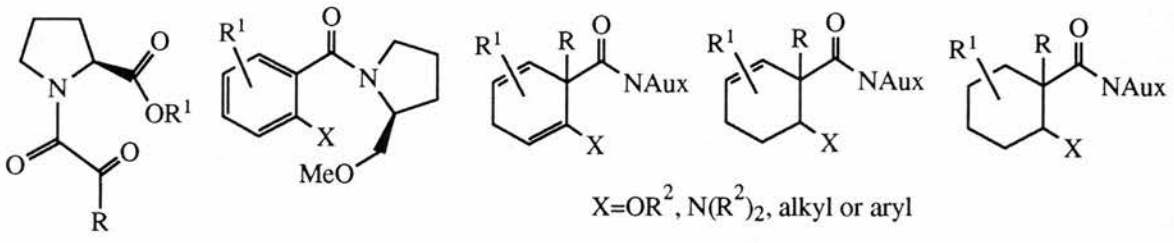
Scheme 3

Sterically constrained tertiary β-amino alcohols **50** catalyse the ethylation of benzaldehyde in good yields but with poor e.e.s (4-20%)[42], Scheme 3.

1.4 Reductions

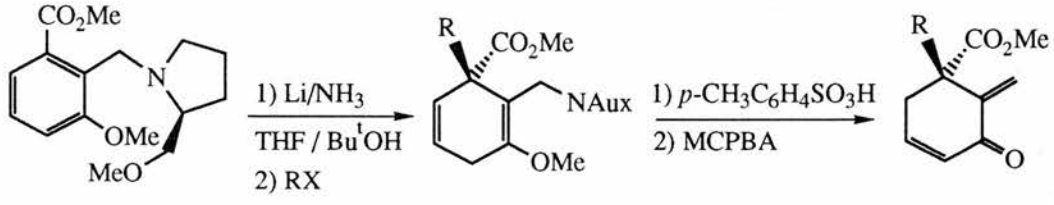
Reduction of (*S*)-α-ketoamide **36** R=CO_2Me with $LiBH_4$ affords (*S*)-α-hydroxyacids while with DIBAL, the (*R*)-isomers are formed in good yields with e.e.s in each case greater than 80%.[43] Reduction of (*S*)-α-ketoamide **51** sodium borohydride using a mixed hydroxylic and non-hydroxylic solvent provided the (*S*)-α-hydroxyacids in up to 69% e.e. and high yields.[44] Chiral

cyclohexadiene, cyclohexene and cyclohexane rings **53**[45] can be synthesised in



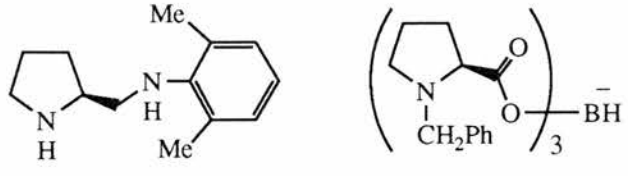
(**51**) (**52**) (**53**)

excellent e.e., >99% and good overall yield from a Birch reduction / alkylation of chiral 2-(alkoxy, amino, alkyl and aryl) benzoic acids **52**.[46]



(**54**) (**55**)

Birch reduction of **54** and alkylation of the resulting enolate gives **55** after removal of the auxiliary in yields of 50-90% and a diastereoisomer ratio (d.r.) >20:1.[47, 48]



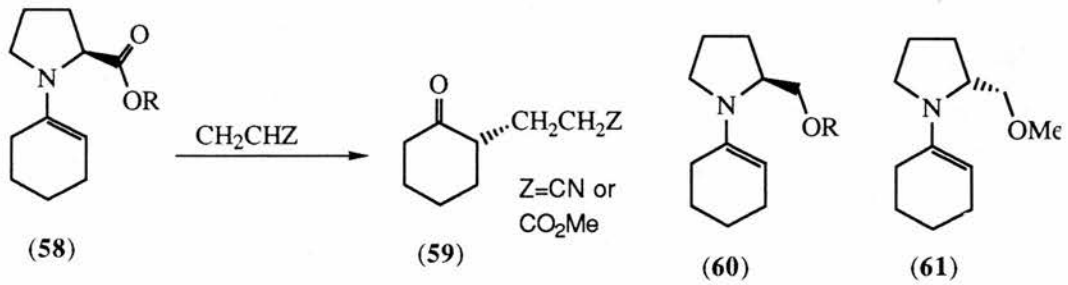
(**56**) (**57**)

Coordination of the chiral diamine **56** to lithium aluminium hydride gave a reagent which reduced propiophenone to 1-phenyl-1-propanol in 90% yield and 96% e.e.[49] Reduction of imines with the borohydride complex **57** afforded the (*S*)-amines in 88-90% yield and 70-86% enatiomeric excess.[50]

1.5 Conjugate Addition

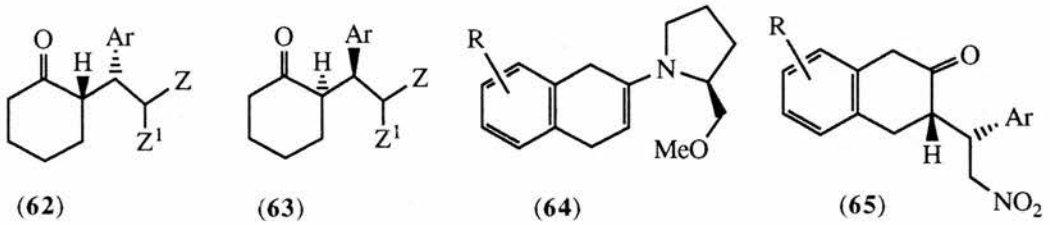
Addition to a double bond can be achieved asymmetrically if the attached chiral auxiliary can significantly influence the incoming nucleophile.

Asymmetric Michael additions using cyclohexanone (*S*)-proline enamines **58** R=Me, Et or Bu^t [51] produced **59** in 34-59% e.e. and poor yields.



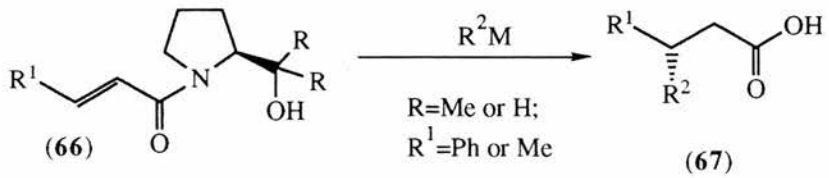
(58) (59) (60) (61)

Michael addition of **60** R=Me and **61** similarly give **62** and **63** respectively (Z=H, Z^1=NO_2 or Z=Z^1=CO_2R) in excellent yields of 56-81%, with e.e.s of



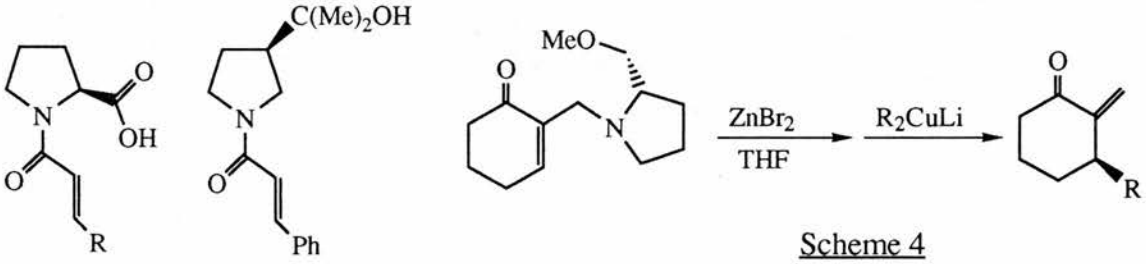
(62) (63) (64) (65)

>90%.[52, 53] Michael addition to enamines **64**, derived from β-tetralones and 2-(methoxymethyl)pyrrolidine, affords after hydrolysis of the auxiliary, **65** in moderate yield and 75-95% e.e.[54]



(66) (67)

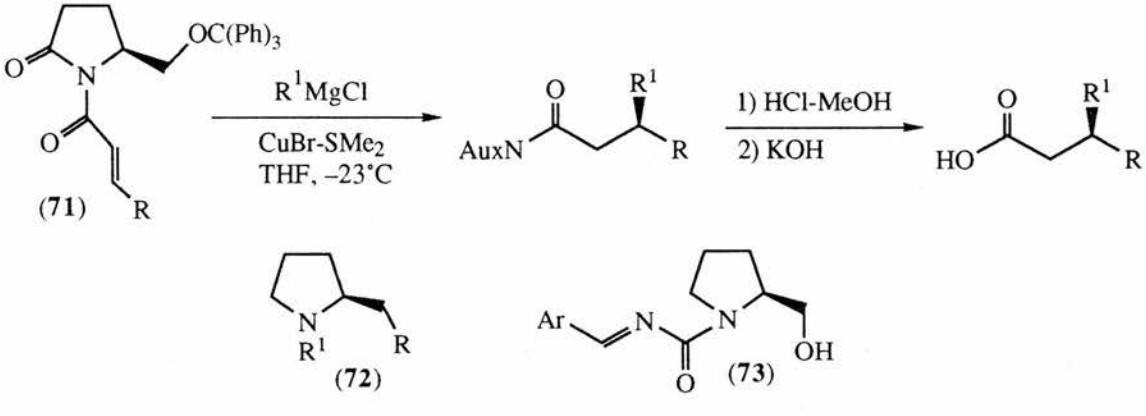
Asymmetric conjugate addition to **66** using organolithium / magnesium reagents gives after hydrolysis, the 3-substituted carboxylic acids **67** in 13-81% yield and 4-100% e.e.[55] It was found that the addition of tertiary amines to the reaction mixture increases the diastereoselectivities to >95% in some cases. Conjugate addition of metal alkyls to **68** and **69** also produced β-substituted carboxylic acids[56] in good yields with e.e.s between 50-88%, and



(68) (69) (70)

Scheme 4

70 similarly gave 3-substituted-2-exo-methylene cyclohexanones in 90% e.e. and 50% yields[57], Scheme 4. Conjugate addition reactions between **71** and Grignard reagents in the presence of CuBr-SMe_2 gave after removal of the auxiliary, β,β-disubstituted carboxylic acids with high e.e.s, 77-97% and excellent yields, 75-91%.[58] Conjugate addition reactions between chiral

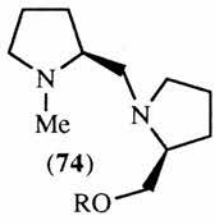


(71) (72) (73)

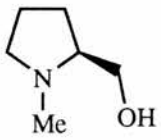
organo-cuprates (containing **72** and a transferable alkyl ligand) and prochiral α,β-unsaturated ketones afforded the adducts in yields between 30 and 95%. When R^1=H and R=OMe, SPh, SMe, OLi or pyrrolidine the e.e.s varied from

41-83%,[59] when R[1]=H and R=O-CH_2OMe, the e.e.s were up to 56%[60] and when R=OH and R[1]=H or Me, the e.e.s were up to 41%.[61] Ethylation of **73** with diethylzinc was achieved in high yields and in 86-100% d.e.[62]

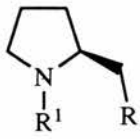
Alkylation using chiral metal bases with transferable ligands was achieved by using **74** R=Me chelated to methyl lithium, which alkylates di-*p*-tolylsulphine Ar_2CSO, to give the methyl sulphoxide derivative $Ar_2CHS(O)Me$ in 55% e.e.[63] Methyl cuprates with chiral ligands **75** and **76** have been used to methylate chalcone in 80% yield[64, 65] and up to 88% and 65% e.e.



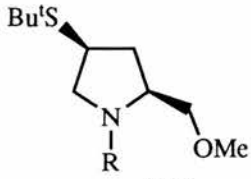
(**74**)



(**75**)



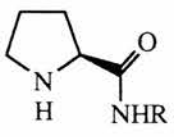
(**76**) R=CH_2OH, R^1=CO_2Bu^t
R=OH, R^1=H
R=OH, R^1=CO_2Bu^t
R=CH_2OH, R^1=Me



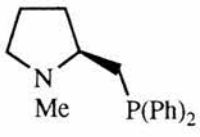
(**77**)

respectively. Methyl cuprate complexes of **77** react with chalcone to afford (*S*)-1,3-diphenylbutan-1-one in 75% e.e. and 95% yield.[66, 67] Complexes of **30-33** have also been used in Michael type addition reactions with 70% e.e. for the products[68] and the asymmetric synthesis of glycerol derivatives with up to 84% e.e.[69]

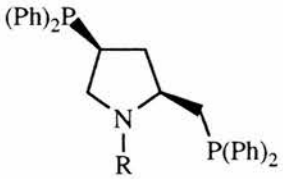
Catalytic Michael addition reactions using nickel complexes of **78** give the adducts in up to 61% e.e.[70] Conjugate addition of isopropylmagnesium



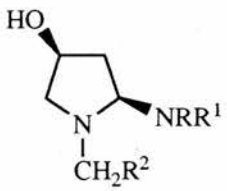
(**78**)



(**79**)



(**80**)

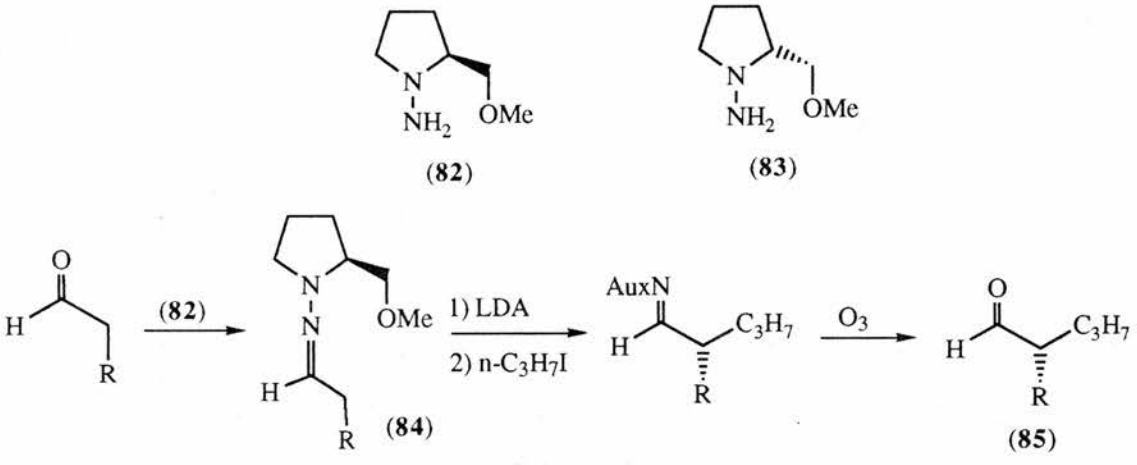


(**81**) R=H or Me;
R^1=Py, C_6H_{11} or Napth;
R^2=Me or Bu^t

chloride to 2-cyclohexen-1-one in the presence of chiral zinc complexes of **37**, **74** R=H, **79** or **80** R=H, provide 3-isopropylcyclohexanone in very poor e.e. (0-22%) but with good yields[71] and **81** catalyses the asymmetric addition of thiols to 2-cycloalken-1-ones with e.e.s up to 88% and good chemical yields.[72]

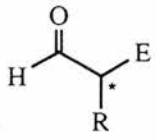
1.6 Reactions of Chiral Hydrazones

The chiral auxiliaries (*S*)- or (*R*)-1-amino-2-methoxymethylpyrrolidine, (SAMP) **82** or (RAMP) **83** are versatile tools in the formation of carbon-carbon or carbon-oxygen bonds and the wide variety of reactions they can be used for have been reviewed by Enders.[73] Predictable configuration of the new asymmetric centre is achieved using either the SAMP or RAMP auxiliary which allows the synthesis of either the (*S*) or (*R*) isomer. The (SAMP) or (RAMP)-hydrazones, formed by the condensation of **82** or **83** with a ketone

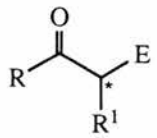


Scheme 5

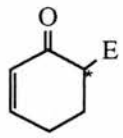
or an aldehyde **84** (Scheme 5), are deprotonated with a base to give the azaenolates which undergo a plethora of stereoselective reactions[74]: α-Mono and α,α'-bis alkylation of aldehydes, ketones, α-ketoesters[75] and symmetrical ketones[76] give **85-89** and α-and / or β-substituted primary amines **90** and **91**,



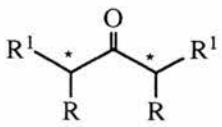
(**85**) e.e.>90%



(**86**) e.e.≥90%
Yield=74-93%

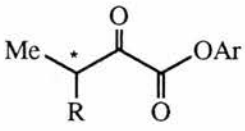


(**87**) e.e. 60-99%

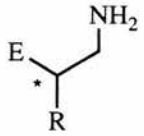


(**88**) d.e.>98%

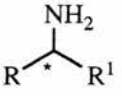
diastereo and enantioselective aldol reactions giving **92** and **93**, diastereo and



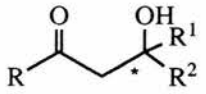
(**89**) e.e. 85->95%
yield=39-67%



(**90**) e.e.>95%

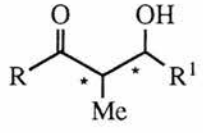


(**91**) e.e. 76->90%
Yield=41-73%

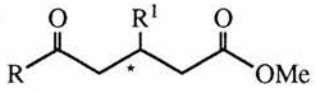


(**92**) e.e.=100%
(cryst.)

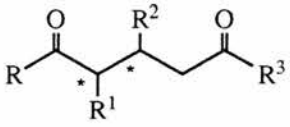
enantioselective Michael additions to form substituted keto esters **94**,[77, 78] **95** and **96**; formation of lactones **97**, octahydroquinolinediones **98**,[79] various heterocycles and α-alkyl lactams; hydroxylation to give α-alkoxy aldehydes /



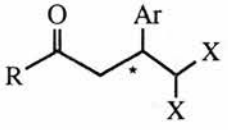
(**93**) e.e.=100%
(cryst.), syn



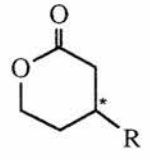
(**94**) e.e.>96-100%
Yield=45-62%



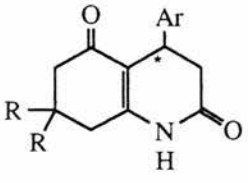
(**95**) e.e.90-100%,
anti



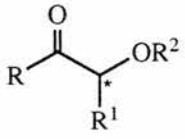
(**96**) e.e.≥95%
yield=50-82%



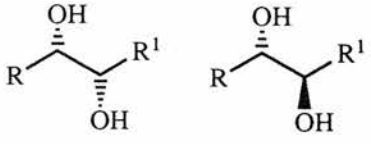
(**97**) e.e.>95%



(**98**) e.e.>98%
yield=50-60%

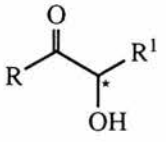


(**99**) e.e. 89->96%
Yield=50-70%



(**100**) cis/trans e.e. 95-98%
Yield=14-58%

ketones **99**,[80] the diols **100**[81] and hydroxyketones **101**[82] and the synthesis of α,α'-disubstituted spiroacetals **102**.[83] Ozonolysis or acid hydrolysis cleaves the auxiliary from the target compound producing the products in excellent e.e., and moderate to good yields.



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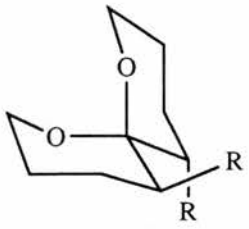
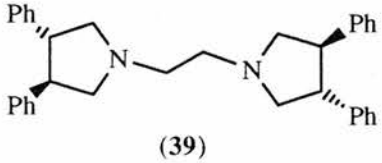


(102) e.e. 15-100%
yield=15-68%

1.7 Oxidations

The diamine **39** (Ar=Ph) and osmium tetroxide can be used for the cis dihydroxylation of alkenes with the optimum conditions at –110°C to afford the diols in 85% yield and 97% e.e.[84, 85] Likewise the oxidation of alkenes with osmium tetroxide and **74** R=Me, give the *syn* diols with e.e.s of 75-90% and chemical yields of 56-87%.[86] *N,N*'-dialkyl-2,2'-bipyrrolidines **103** have been used in the asymmetric osmylation of di- and mono-substituted alkenes to provide the (*S,S*) diols (R=pentyl or neohexyl) in yields from 79-99% and e.e.s of 80-100%.[87]



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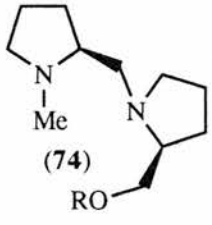

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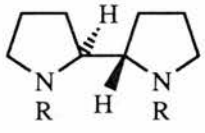
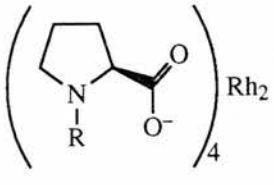


(103)

1.8 Carbenes and Nitrenes

The intramolecular carbene addition of **105** gave **106** in 80% yield and 33%



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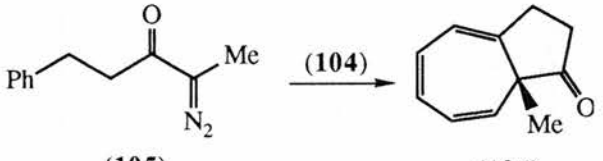
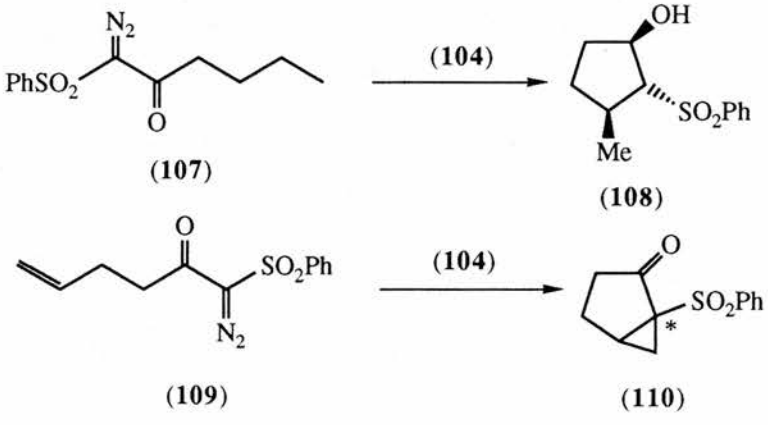
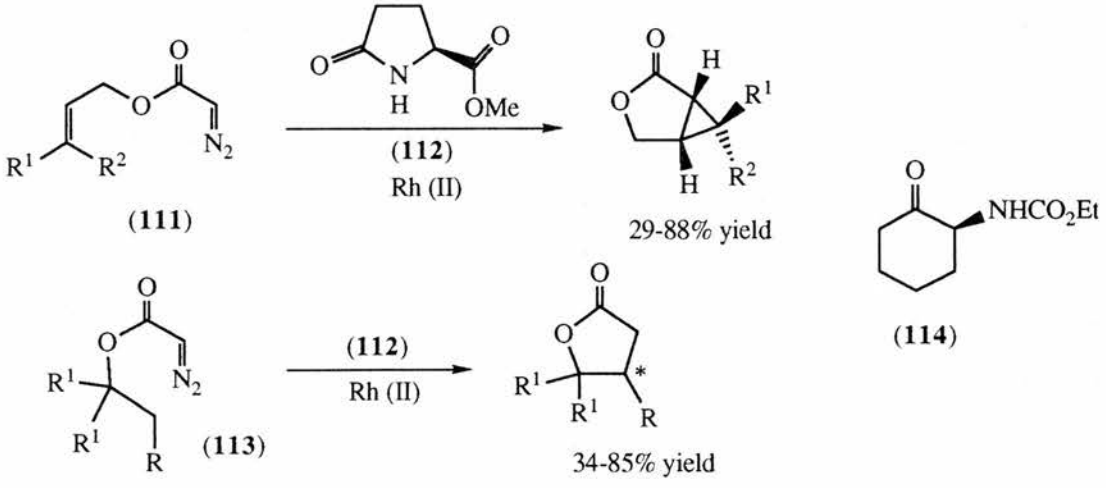


(105) (104) (106)

e.e., when carried out using the rhodium (II) catalyst **104**. Intramolecular cyclisation reactions involving a catalytic amount of **104** were used to prepare the alcohol **108** from the diazo compound **107**, by intramolecular CH insertion followed by reduction of the C=O group, in 60% e.e. after



recrystallisation and the cyclopropane **110** from the unsaturated diazo compound **109** in 12% e.e.[88] Catalytic cyclopropanation can also be achieved in high e.e. (up to 94%) via the intramolecular cyclisation of alkenyldiazoacetates **111**, using a dirhodium (II) tetrakis complex of **112**.



Results show that higher enantioselectivity was achieved when (*Z*) alkenes were used.[89] This catalyst was also used in the intramolecular carbon-

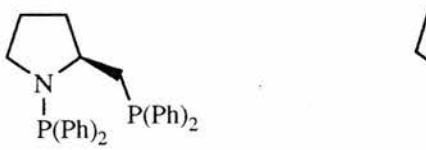
hydrogen insertion reaction starting from **113** to give the γ-lactones in up to 91% e.e.[90]

Ethyl azidoformate reacts with **58** R=Bu^t or **60** R=$SiMe_3$ or Me upon photolysis, to provide (*S*)-**114** in moderate yields with e.e.s ranging from 3-77%. The opposite configuration (*R*)-**114** can be produced by reacting the same substrates, with (ethoxycarbonyl)nitrene produced by α-elimination.[91]

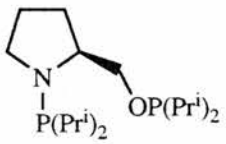
1.9 Catalytic Hydrogenation

Asymmetric catalytic hydrogenation of prochiral compounds containing a carbon-nitrogen, carbon-carbon and carbon-oxygen double bonds can be achieved by the presence of a chiral ligand transition metal complex in excellent e.e.s.

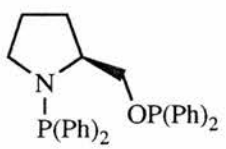
(*S*)-Proline derived ligands **115**, **116**,[92] **117**,[93] **118**[94] and **119**[95] have been successfully employed for the enantioselective rhodium-catalysed



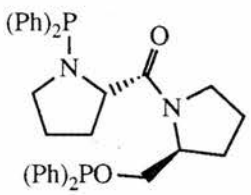
(**115**)



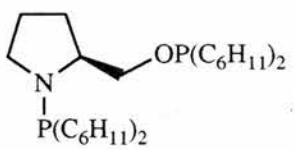
(**116**)



(**117**)



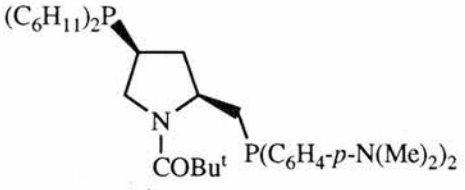
(**118**)



(**119**)

hydrogenation of ketones, α-ketoamides and alkenes with e.e.s ranging from 0-93%. Carbon-nitrogen double bond reduction has been carried out with an iridium complex of **80**[96] and with a rhodium complex of **120**.[97] Hydrogenation of carbon-carbon bonds is catalysed in excellent chemical yield, by rhodium complexes of: **120** to give saturated products in 93% e.e.,

121-124 with e.e.s of 9-92%,[92] **80** R=CO_2Bu^t or R=H with e.e.s from 2-91%,[98] **80** R=$COBu^t$, H or CO_2Bu^t with e.e.s up to 93%,[99] **80** R=CONHPh or



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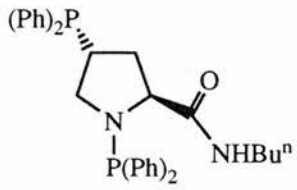

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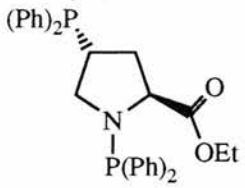

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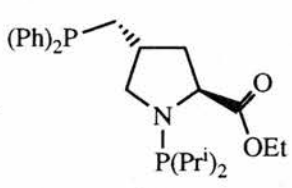

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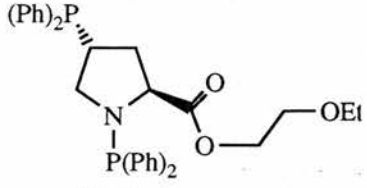
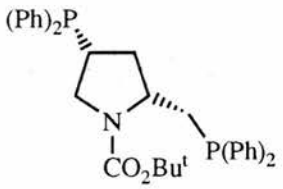


(124)

CO_2Bu^t and **125** with e.e.s up to 98%,[100] **126** with up to 99% e.e.,[101] **127** in high e.e.,[102] **128**, R=2-MeO-, 3-MeO- or 4-MeO-C_6H_4 in 98% e.e.,[103] **128**



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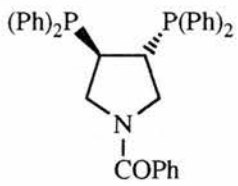

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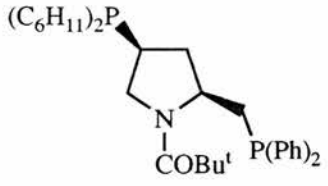

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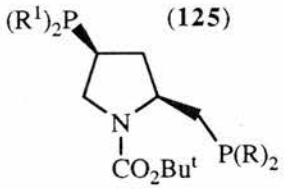

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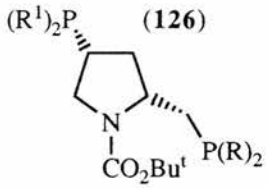

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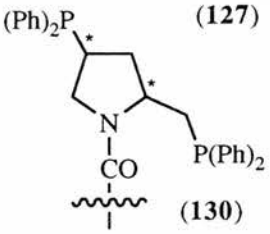
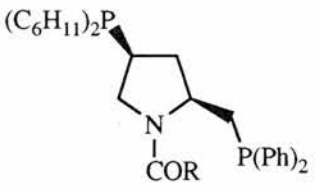


(130)

R^1=R=4,3,5-$MeOMe_2C_6H_2$ in 58-99% e.e.,[104] **128** R=Ph, R^1=4-Me_2N-C_6H_4 and **129** with e.e.s between 85 and 98%[105] and polymer supported **130** with (*R,R*) or (*S,S*) isomers, in 33-91% e.e.[106] Hydrogenation of carbon-oxygen double bonds is catalysed by rhodium complexes of: **131** with e.e.s ranging up to 97%,[107] **132** with e.e.s of 2-77%,[108] **133** with e.e.s between 68-91%[109] and **120** in high e.e.[97]

(*S*)-Proline derived amide **78** complexes copper and acts as a catalyst for the hydrogenation of enamides in up to 99% e.e.[110]



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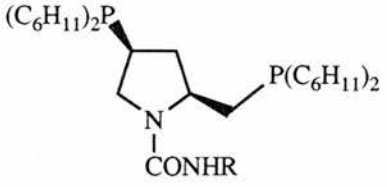

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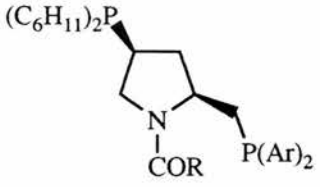
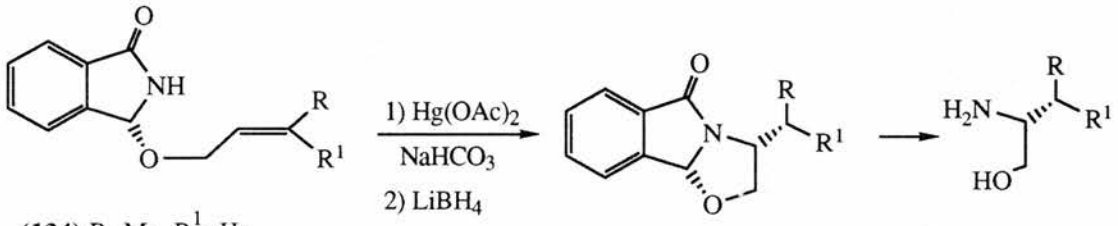


(133)

1.10 Miscellaneous Reactions

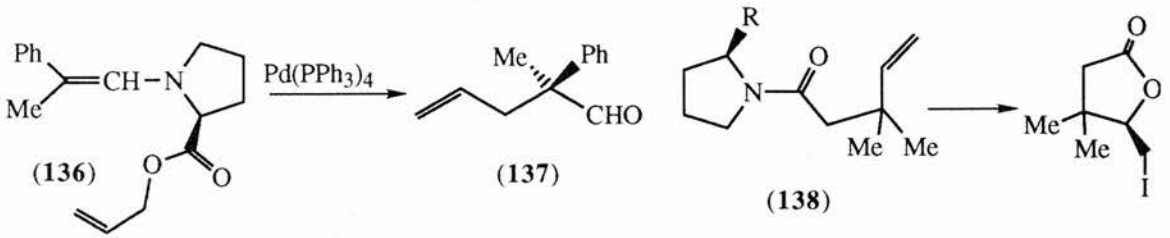
1,3-Stereo induction is observed when unsaturated amidals **134** undergo amidomercuration to give **135** with endo face selectivity greater than 99:1. Removal of the auxiliary produces the amino alcohol in 98% e.e.[111]



(134) R=Me, R^1=H;
R=H, R^1=Pr^n;R=H, R^1=Ph;
R=Ph, R^1=H.

(135)

Treatment of the chiral enamine **136** with tetrakis (triphenylphosphine)-palladium produced the corresponding aldehyde **137** in poor yields (41%) but



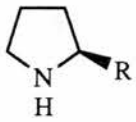
(136)

(137)

(138)

in 90% e.e.[112] 1,6-Asymmetric induction was observed in the iodolactonisation of γ,δ-unsaturated amides **138**.[113]

Optically active dialkyl phenyl phosphates **140**[114] and both enantiomers of trialkyl phosphates **141**[115] were prepared, starting from chlorophenyl



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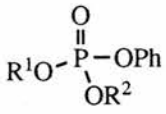

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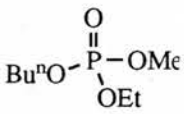
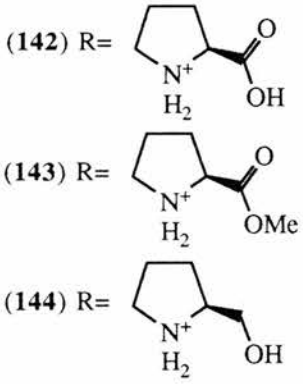


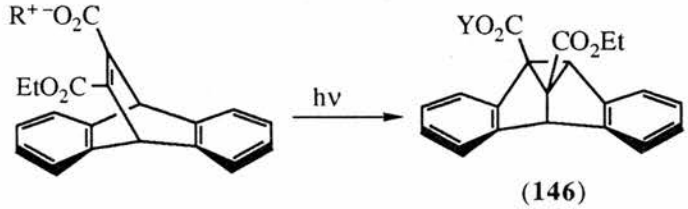
(141)

phosphoramidates of **139** R=CO_2Et, and bis (2,4-dichlorophenyl)phosphoramidates of **139** R=$C(Me)_2OMe$ in high yields with e.e.s >97% and 87-92% respectively.

Photolysis of the carboxylic acid salts **142-145** in the solid state gave **146** after esterification of the acid with e.e.s from 14-80% and yields from 65-100%.[116]

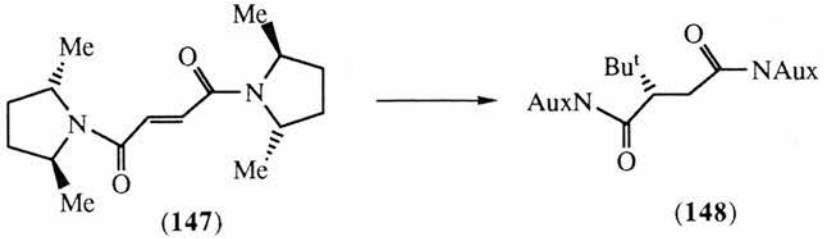


(142) R=
(143) R=
(144) R=
(145) R= HN^+-Strychnine



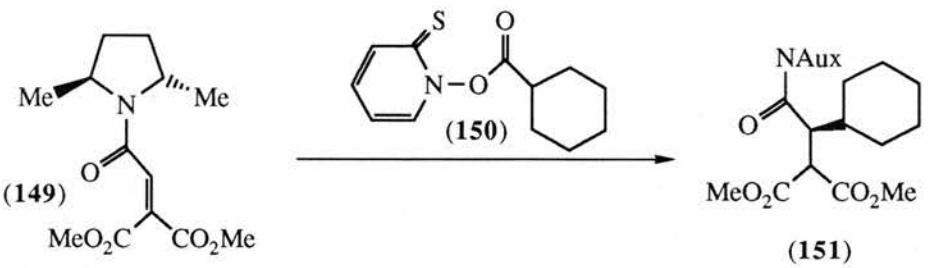
(146)

Stereoselectivity with alkyl radicals has been achieved by the addition of

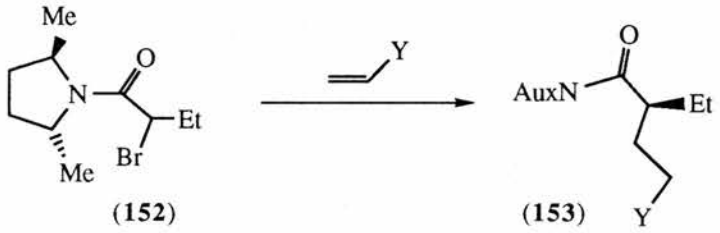


(147) **(148)**

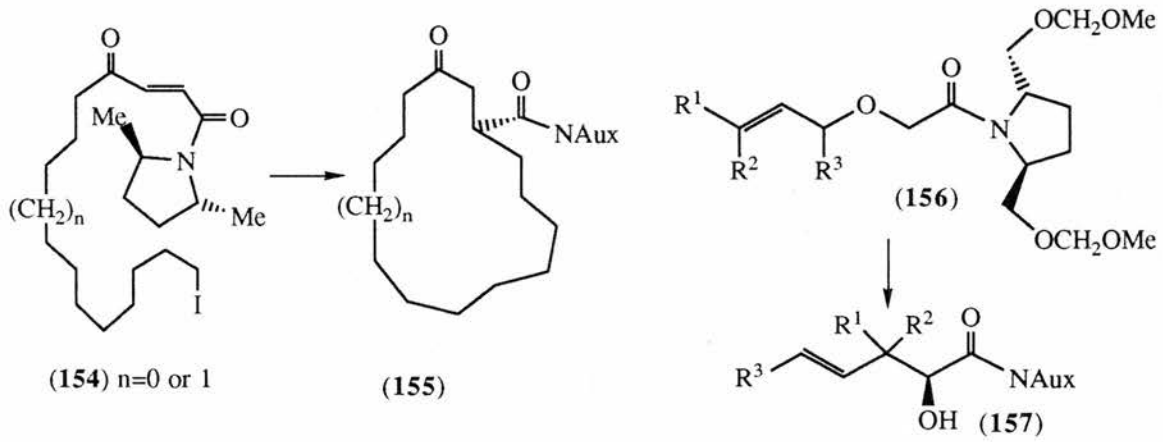
a t-butyl radical[117, 118] to **147** to give the adduct **148** in 60% yield and an 80:1 d.r. Low temperature cyclohexyl radical addition to **149** under



photolysis conditions using a Barton ester **150**, gives the (*S*) isomer **151** in greater than 25:1 d.r. and 90% yield.[119] Radicals generated from **152** gave



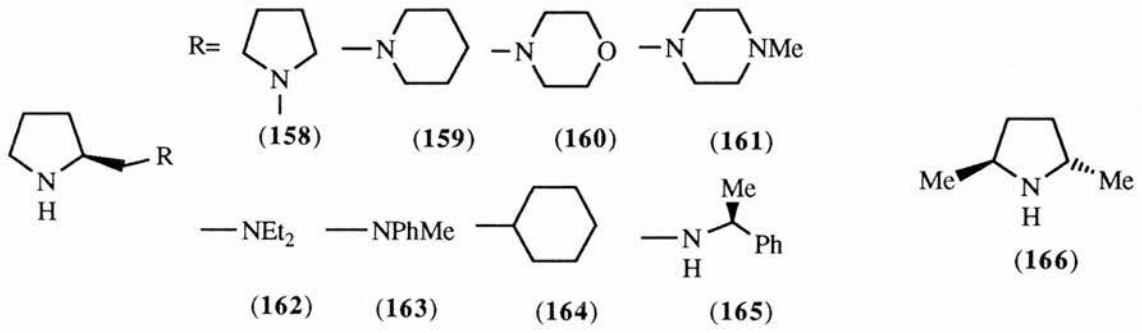
the addition products **153** in moderate yield and good selectivity (25:1 at room temperature / 36:1 at –24°C) for the (*S*)-isomer,[120] and radical



macrocyclisation of **154** gave **155** with good diastereoselectivity (14:1, *R*:*S*) and moderate yields.[121]

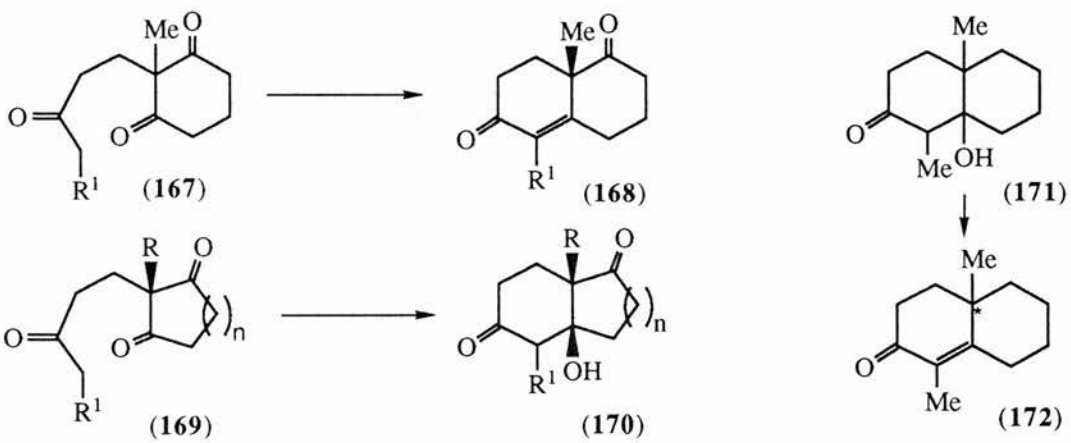
An asymmetric Wittig rearrangement of the amido ester **156**, gave the α-hydroxyamide **157** in the presence of a base with high d.e.s, 33-96%.[122]

Asymmetric isomerisation of symmetrical epoxides to allylic alcohols was carried out by chiral lithium amide bases derived from **30**,[123] **158-165**[124] and **166**[125] in good yield (up to 78%) and with good e.e., 47-92%.



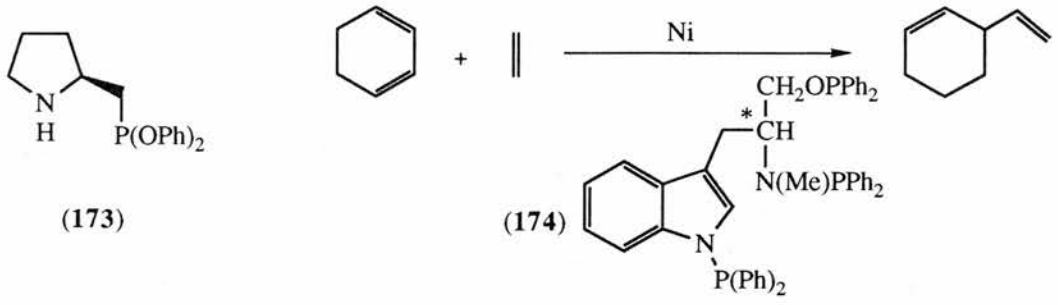
Using chiral epoxides and bases from **158** and **160**, allylic alcohols were obtained in 65-92% yield and 26-90% e.e.[126]

Asymmetric cyclisation of triketones **167** and **169** using a catalytic amount of (*S*)-proline afforded bicyclic enone **168** (R^1=H in 43% yield and 100% e.e.[127] and when R^1=Me in 43-60% yield and 23-33% e.e.[128]) and **170**



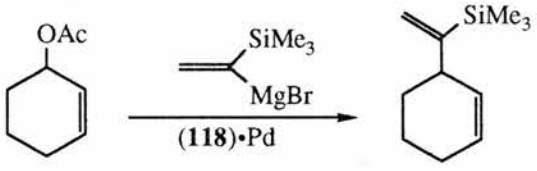
in 71-100% yield and 93-100% e.e. respectively.[129, 130] (*S*)-Proline also brings about kinetic resolution when it catalyses the dehydration of racemic **171** to provide **172** in moderate e.e. but very poor yields.[131]

The (*S*)-proline derived amide **78** complexes copper and acts as a catalyst for the allylic acetoxylation of alkenes in 30% e.e.[132]

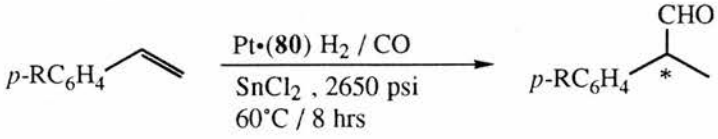


Pyrrolidines **115** and **173** have been used in asymmetric hydrosilylation of acetophenone in 4-42% e.e.[92] Although a nickel complex of **115** shows poor enantioselectivity in the catalysed hydrovinylation of 1,3-cyclohexadienes, this reaction was achieved in up to 92% e.e. with a nickel complex of **174**.[92]

A platinum complex of **118** in the presence of carbon monoxide and hydrogen, catalyses the hydroformylation of styrene in 48% e.e. and 70%



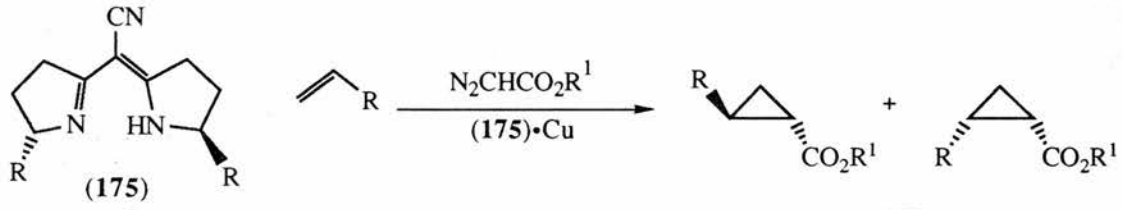
conversation,[133] whereas **118** complexed with palladium, catalyses the reaction of cyclohexenyl acetate to give 3-(1-trimethylsilyl vinyl)cyclohexene in high yields but with rather moderate enantioselectivity, 33%.[134] Platinum



complexes of **80** R=CO_2Bu^t catalyse the hydroformylation of a variety of prochiral alkenes in 14-87% yield and in e.e. of 58-98%.[135]

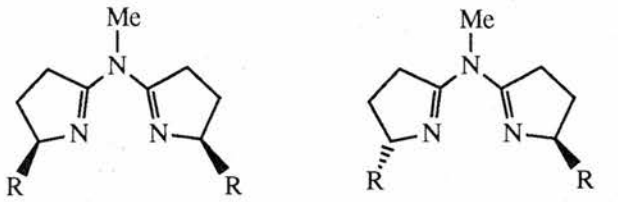
2. Semicorrins

Efficient enantioselective synthesis of chiral cyclopropanes **176**, from a variety of alkenes and diazo alkyl / aryl acetates was achieved in the presence



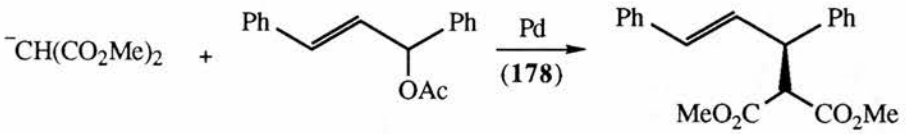
(176)

of a catalytic amount of a copper complex of **175**. With **175**, R=CMe_2OH e.e.s were found to be between 68-97%.[102] Cis / trans ratios of (4:1) and e.e.s of 20-85% were obtained for **175**, R=CO_2Me, $CH_2OSiMe_2Bu^t$ or CMe_2OH.[136, 137] These reports also noted that if R^1 on the diazo ester was changed to *d*-menthyl or *l*-menthyl the cis ratio would increase to (82:18) with e.e.s rising to 90-99%.[138] Changing to the aza-semicorrins **177**, R=CMe_2OSiMe_3 or $CMe_2OSiMe_2Bu^t$ or **178** afforded the cyclopropanes in



good chemical yields with e.e.s between 43-99% and again high e.e.s were observed with the diazo *d*-menthyl ester. Ligand **178** in the presence of palladium also catalyses allylic nucleophilic substitution of **179** to afford **180**

in 32-99% yield and 73-95% e.e.[139] Chiral cobalt complexes of semicorrin **175**, R=$CH_2OSiMe_2Bu^t$, CH_2OEt or CMe_2OH catalyse the reduction of α,β-unsaturated prochiral esters and amides with sodium borohydride in 73-94%

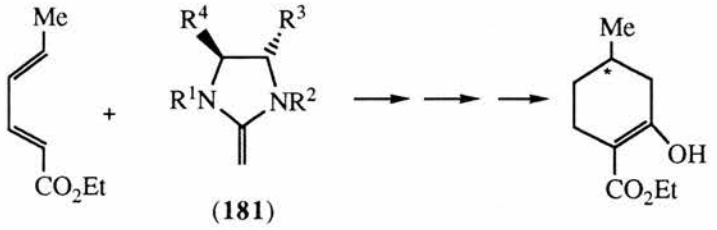


(179) **(180)**

e.e. and up to 97% yields, with the (*E*) isomer giving the (*R*) configuration only and the (*Z*) isomer giving the (*S*) configuration.[140]

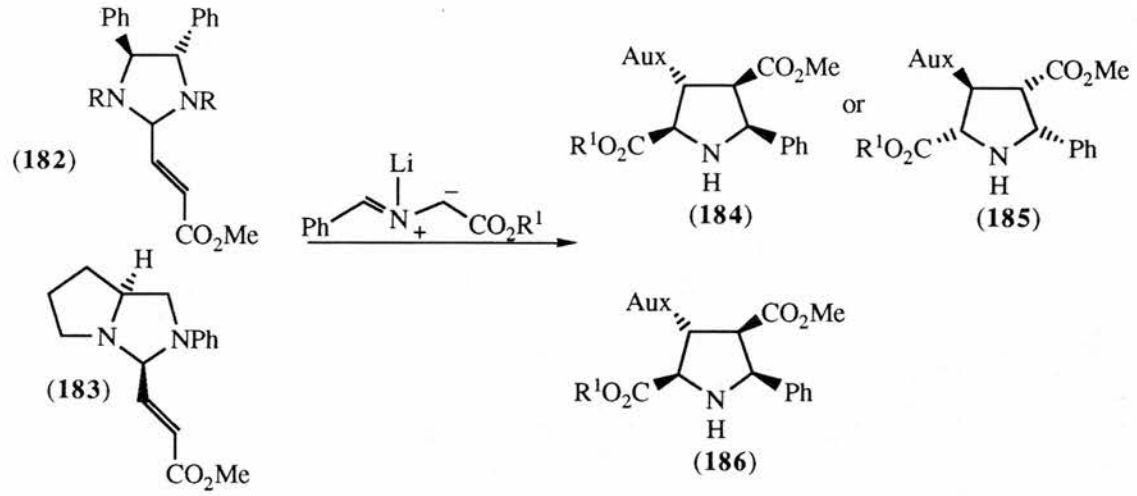
3. Imidazolidines

Optically active cyclohexenes were prepared via the inverse Diels-Alder reaction of 2,4-hexadienoate with a variety of imidazolidines **181** at room

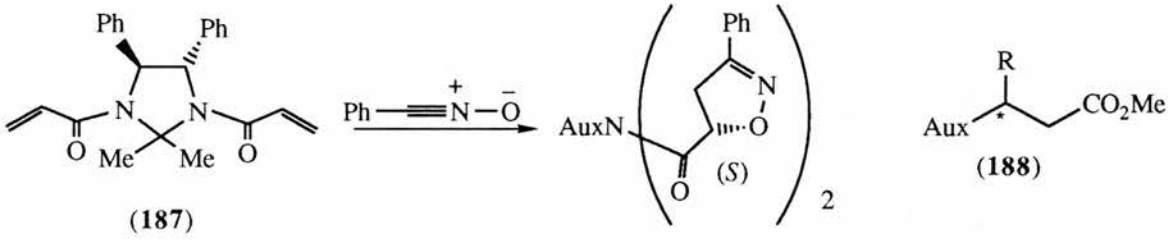


(181)

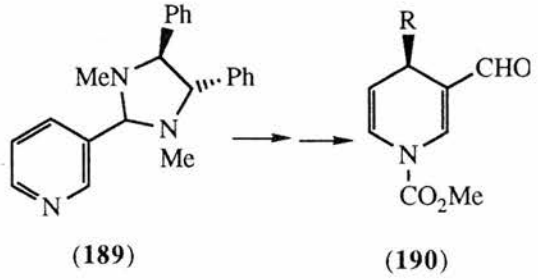
temperature, acid hydrolysis of the auxiliary and reduction of the ketone providing the alcohol in 35-60% yield and 3-46% e.e.[141] 1,3-Dipolar cycloaddition between *N*-metallated azomethine ylides and α,β-unsaturated esters attached to chiral controllers **182** or **183** afford the adducts **184** or **185**[142] and **186**[143] in 82% yields and as one single diastereomer. For $R^1=Bu^t$ and R=phenyl, **184** is obtained exclusively whereas if R^1=Me and R=Me, only **185** is obtained. Chiral isoxazolines in up to 91% e.e. are formed in the



dipolar cycloaddition of the acrylamide derivative **187** and benzonitrile oxide.[144]

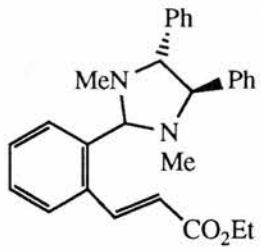


Conjugate addition reactions using **183** and cuprate reagents gives the adducts **188** in 38-83% yield and 35-93% e.e.[145] Dialkyl cuprates react with the chiral aminal **189** to give after acylation and acid hydrolysis, substituted



tetrahydropyridines **190** in 90% yields and 95% e.e.[146] Conjugate addition reactions using dialkyl copper reagents and the imidazolidines **191** and **192**

showed very high diastereoselectivity.[147] The enoate **191** gave **193** in 57% yield and 78% e.e. and **192** provided **193** in 80-90% yield and 90-96% e.e.



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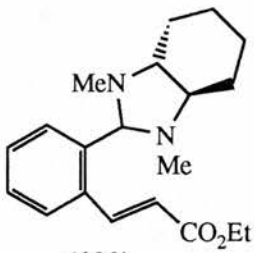

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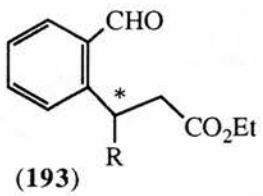

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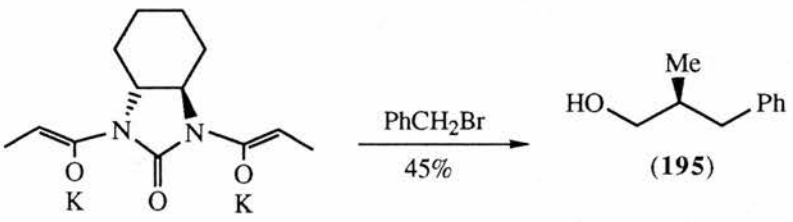
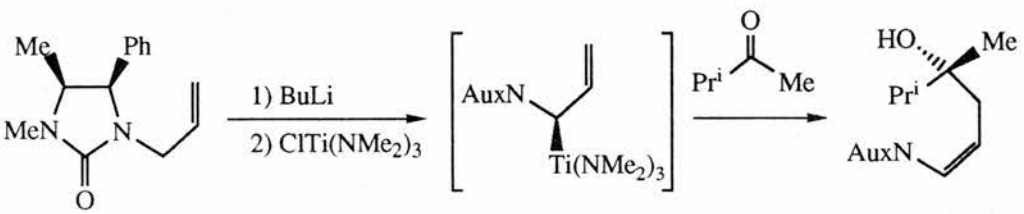
Asymmetric alkylation of the bis-enolate **194** with alkyl halides gives after reductive removal of the auxiliary, **195** in 93% e.e.[148]



(194) **(195)**

Allylic carbamates **196** undergo diastereoselective lithiation and titanation to produce after addition of a ketone, the tertiary alcohol **197** in 96% d.e.[149]

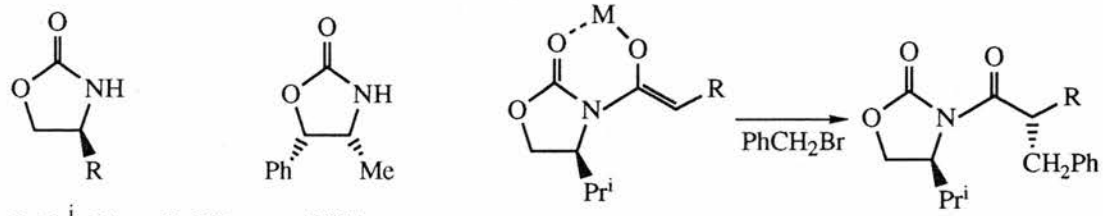


(196) **(197)**

4. Oxazole and Isoxazole Systems

4.1 Oxazolidinones

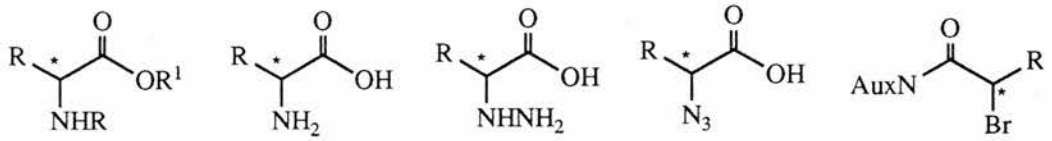
Oxazolidin-2-ones have been used extensively as chiral auxiliaries in the alkylation of metal enolates, where chelation and steric factors play an integral part in the diastereofacial selection in the addition to an electrophile.[150] Due to the nature of the products (diastereomers) the compounds are easily obtained in pure form by chromotography or crystallisation and non-destructive removal of the auxiliary gives pure enantiomers usually in very high yields. The *N*-acyl derivatives of **198** or **199**, derived respectively from amino acids and norephedrine, are metalated and reacted with an electrophile to give the desired products **200** in high yields and almost enantiomerically



(**198**) R=Pr^i, Ph or $PhCH_2$ (**199**)

(**200**) 92% yield and >98% d.e.

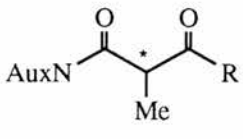
pure.[151] Use of **198** as opposed to **199** also controls the desired stereoselectivity at the new stereocentre affording either (*R*) or (*S*)



(**201**) (**202**) (**203**) (**204**) (**205**)

enantiomers. Use of a nitrogen electrophile has given access to a variety of α-amino acids **201**[151] and **202**, α-hydrazino acids **203**[152, 153] and α-azido acids

204[154] all in high yields and in 97- >99% e.e. Bromination to give **205**,[155]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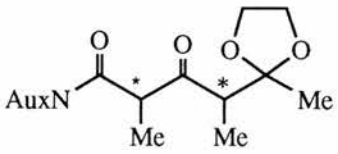
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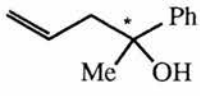
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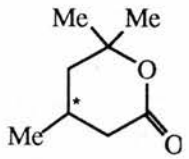
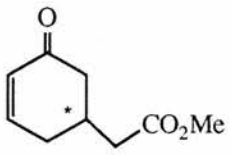

(209)

acylation to give **206**[156] and addition reactions to give products **207**,[157] **208**,[158] **209**,[159] and **210**[160] all proceed in high yields with predictably high e.e.s. Bulky aryl carboxylic acids **211**,[161] cyclopropanes **212**,[162] and the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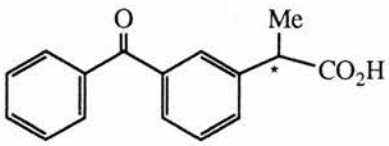
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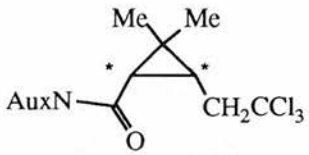
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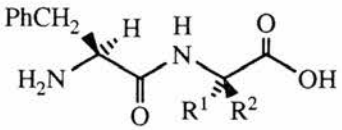
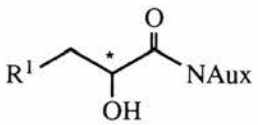

(213) >99% d.e.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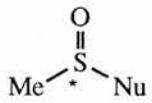
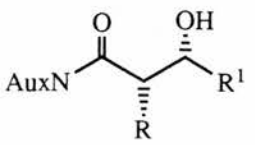
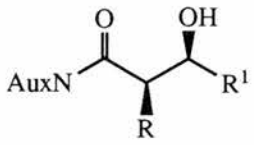

(215)

dipeptides **213**[163] have all been synthesised in good yields and e.e.s, the latter by bis alkylation. The chiral imide enolates can also be oxygenated to give **214**[164] and chiral organosulphur compounds **215** have been made in high enantiomeric purity,[165] by chromatograpy of the diastereomeric *N*-sulphinyl oxazolidinones which are then reacted with a wide variety of nucleophiles.

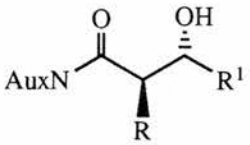
In the aldol reaction the choice of auxiliary and Lewis acid can determine the type of adduct obtained. A boron enolate derived from **198** added to an aldehyde gives *syn 1* products only,[166, 167] whereas the corresponding titanium enolate gave only *syn 2* products.[168] *Syn 2* adducts are also obtained with the boron enolate derived from **199**[167, 169] and with the



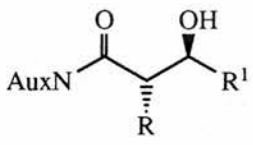
Syn 1



Syn 2

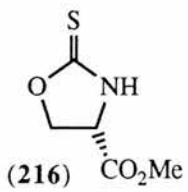


Anti 1



Anti 2

chiral auxiliary **216** in 96-99% e.e. and high yields.[170] Aldol reactions



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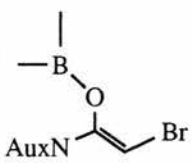

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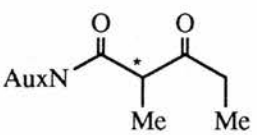
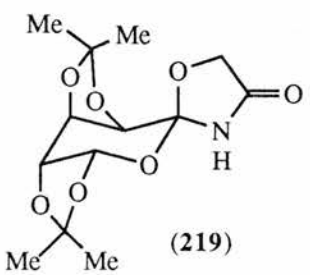


(218)

between **217** and an aldehyde give *syn 1* or *2* type adducts, depending on the auxiliary, **198** or **199**. The halogen can then be substituted by a S_N2 type mechanism to afford *anti 1* or *anti 2* products.[171] Aldol reactions on β-keto imides **218** provide the *anti 2* adducts in 78% yield.[172] Recently the oxazolidinone **219** derived from galactose, was acylated with propionyl chloride and then underwent an aldol condensation with benzaldehyde in the presence of n-butyllithium to provide the *syn 1* adduct **220** in 88% d.e.[173]



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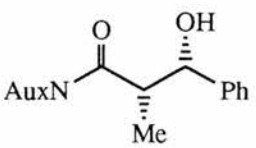
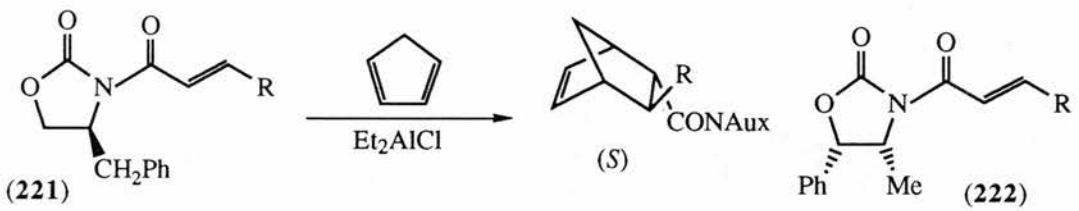


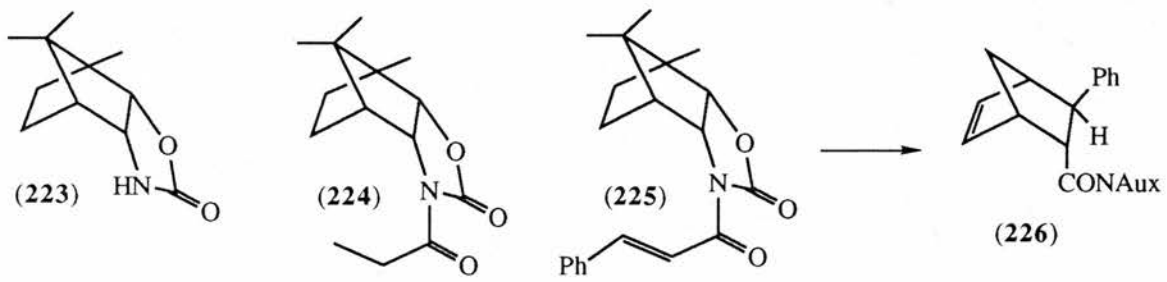
(220)

α,β-Unsaturated carboximides **221** undergo efficient Diels-Alder cycloadditions to give the endo (*S*)-adducts in greater than 98% enantiomeric

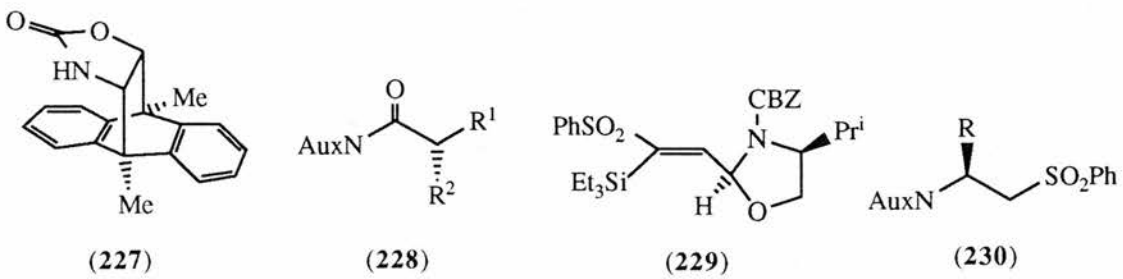
purity and up to 99% yield,[174] and use of **222** gives the (*R*) endo adduct in high e.e. and yield.[175, 176]



The oxazolidinone **223** derived from [(1*S*)-endo]-(–)-borneol has recently been shown to be a versitile chiral auxilary in a number of asymmetric transformations. Alkylation of the lithium enolate of **224** with various alkyl



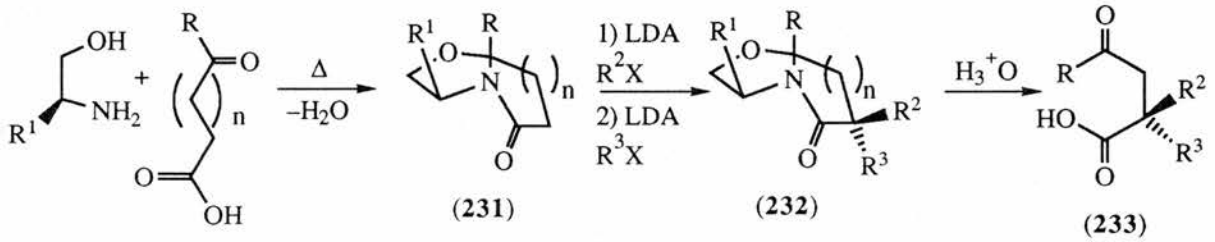
halides provided the alkylated products in 6-99% yields and 82- >99% d.e. The boron chelated enolate of **224** undergoes efficent aldol condensation to give only the *syn 2* adducts in high yields and Et_2AlCl catalysed Diels-Alder reactions between **225** and cyclopentadiene provide the cycloadducts **226** in 92% yield and 99% d.e.[177]



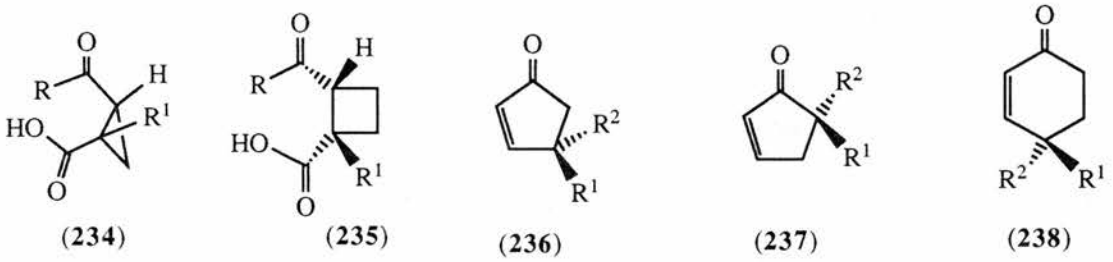
Alkylation of the *N*-acyl enolate of **227** gives the α-substituted product **228** in greater than 500:1 stereoselectivity,[178] and conjugate addition to **229** proceeds in 40% yields to give **230**.[179]

4.2 Oxazolidines

Condensation of a γ- or δ-ketoacid with an enantiomerically pure amino alcohol gives the bicyclic lactams **231** which have been used for a wide variety of asymmetric transformations.[180] Generation of the enolate and alkylation is repeated twice to give a newly generated asymmetric quaternary

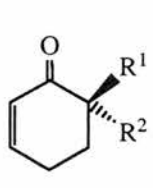


carbon centre **232**. The absolute configuration of the new stereocentre can be reversed by changing the order of addition of the alkyl halides due to a predominantly endo attack by the electrophile. This method and reaction of



the corresponding α,β-unsaturated lactams allows the synthesis of: 2,2-dialkyl ketoacids **233**, cyclopropanes **234**, cyclobutanes **235**, cyclopentenones **236** and **237**, cyclohexenones **238** and **239**, indanones **240**, naphthalenones **241**, 3,3-disubstituted dihydronaphthalenes **242**, hydrinden-2-ones **243**,[181] 2-

substituted pyrrolidine **244**, 2,3-disubstituted pyrrolidines **245**,[182] and 5-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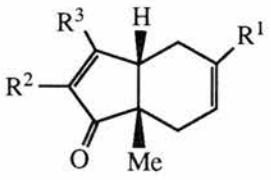
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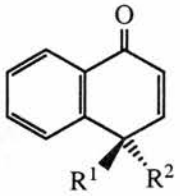
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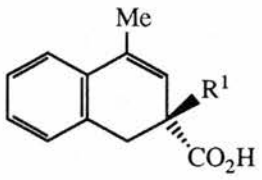
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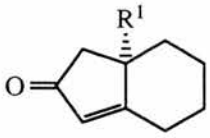
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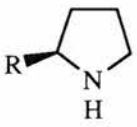
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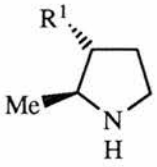
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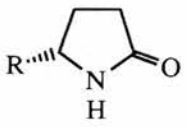
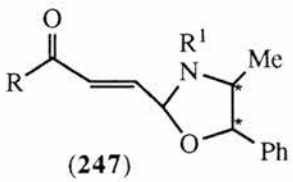

(246)

substituted pyrrolidin-2-ones **246** all in good to excellent yields with predictably high e.e.

Oxazolidines **247** derived from fumaraldehyde-bisdimethylacetal and *N*-protected (1*R*, 2*S*) or (1*S*, 2*R*) norephedrine undergo: conjugate addition reactions with cuprate reagents to produce in 90-99% e.e. **248**[183, 184, 185] and **249**,[186] efficient epoxidation to give **250**[187, 188] in >98% e.e., cyclopropanation to give **251** in 60% yield,[189] and osmylation giving the diol **252**, whereas potassium permanganate gives the diol **253** in 60-95% yield and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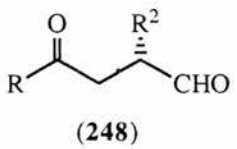
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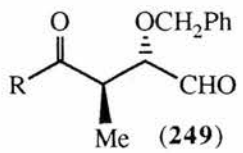
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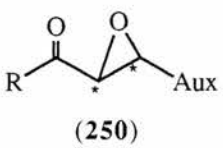
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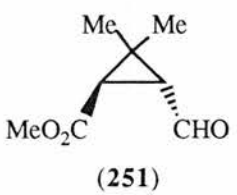
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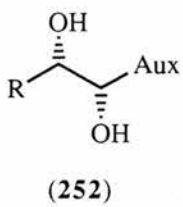
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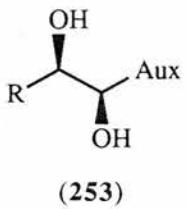
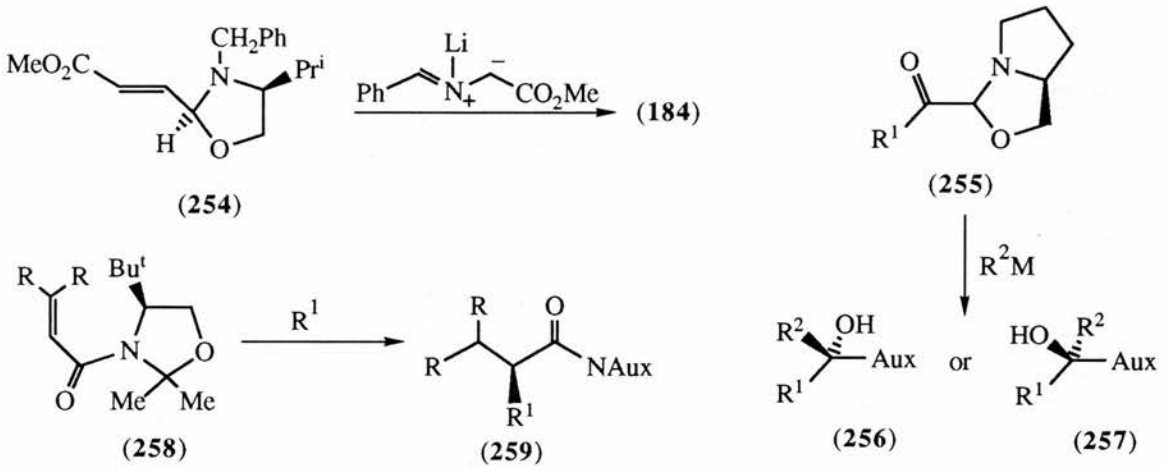

(253)

45-60% d.e.[190] Cycloaddition of **254** with *N*-metallated azomethine ylides affords **184** as one isomer in 82-100% yields.[191] Diastereoselectivity can be

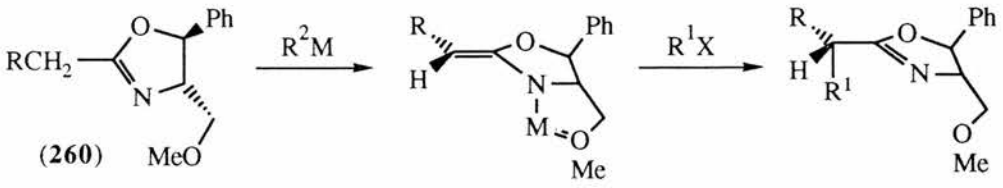
controlled in the addition of organo magnesium or titanium reagents to **255** to give **256** in 98% d.e. whereas addition of organo lithium reagents gives **257** in 80% d.e.[192]



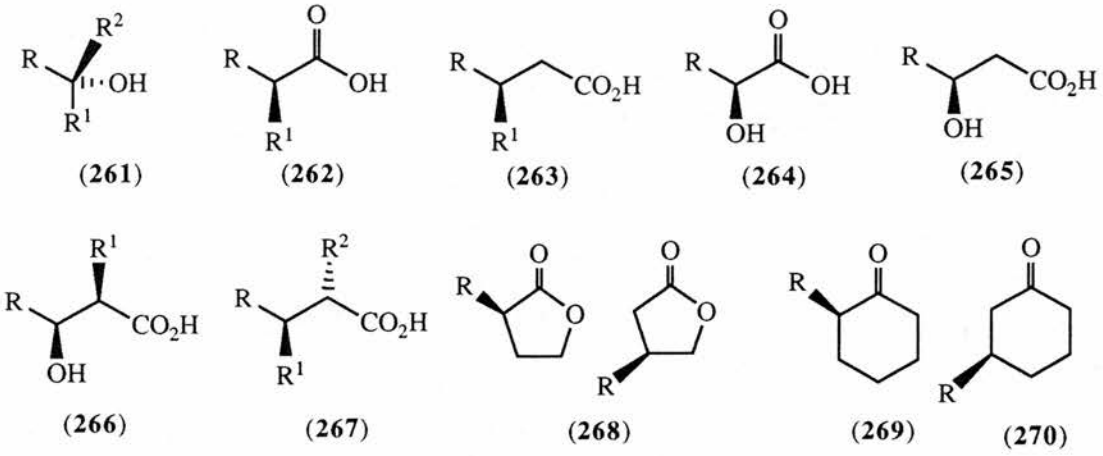
Stereoselective radical addition (on the least substituted alkene carbon) to **258**, gives **259** in greater than 80:1 diastereoselectivity.[193]

4.3 2-Oxazolines

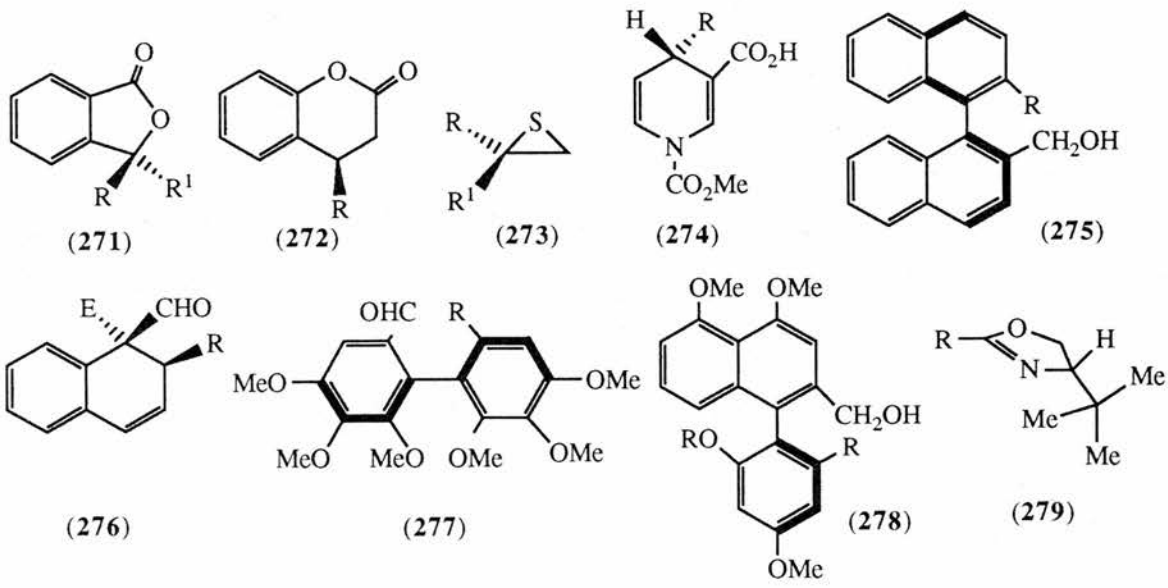
The synthesis of **260** from (1*S*, 2*R*)-1-phenyl-2-amino-1,3-propanediol and an imino or ortho ester gives a very versatile carbon-carbon bond forming auxiliary. Formation of the chelated *Z*-metal azaenolate renders one diastereotopic face "open" to the attacking electrophile, resulting in the significant enhancement of one diastereoisomer over the other. The asymmetric induction[194, 195] demonstrated by this reaction and the conjugate



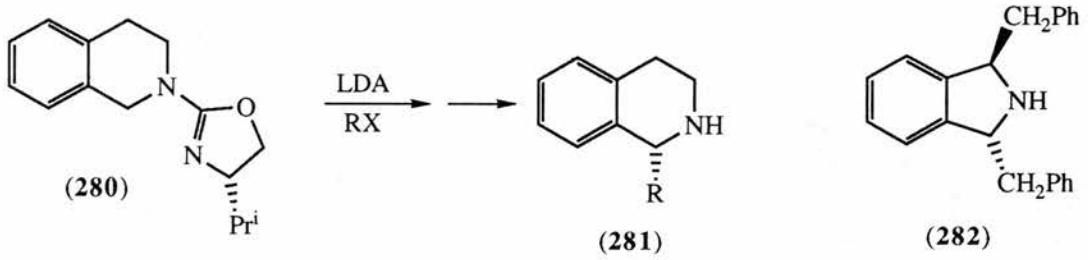
addition to metal chelated vinyl oxazolines,[196] has been used to synthesise chiral tertiary alcohols **261**, substituted carboxylic acids **262-267**, substituted cyclic lactones and cyclohexanones **268-272**, thiiranes **273**, dihydropyridines



274,[197] binaphthyls **275**, dihydronaphthalenes **276**,[198, 199, 200] chiral biaryls **277**,[201, 202, 203] and **278**, all in good yields with high to excellent e.e.s. Recently,[204, 205] a new chiral controller **279** made from (*S*)-t-leucinol has shown excellent diastereofacial results in the synthesis of **263** and **276** with e.e. >93% and >99% respectively, due solely to the steric effect imposed by the t-butyl group.

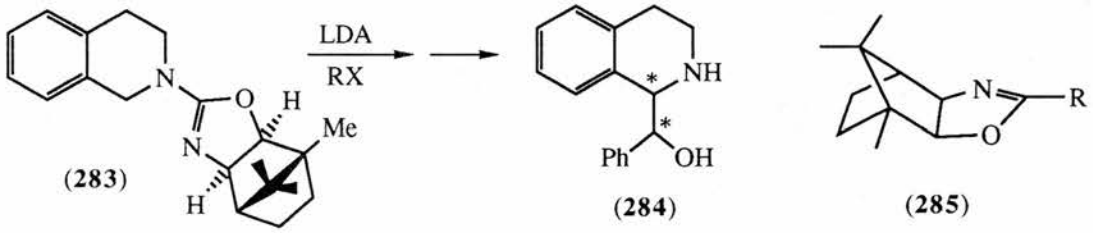


Alkylation of tetrahydroisoquinolyloxazoline **280** is carried out with predictable stereoselectivity to give **281** with yields of 84-90% and e.e.s



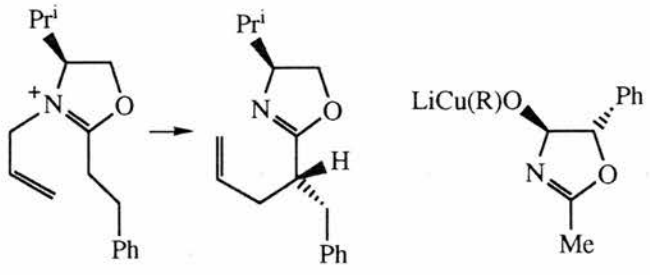
(280) (281) (282)

>90%.[206, 207, 208] The same chiral auxiliary has been used to synthesise (*R,R*)-1,3-dibenzylisoindoline **282**[209] in 42% overall yield. A variety of oxazolines were prepared[210] to optimise the reaction of **280-281** including the use of **283** to give **284** in 50% overall yield and crude d.e. of 80%, rising to 100%



(283) (284) (285)

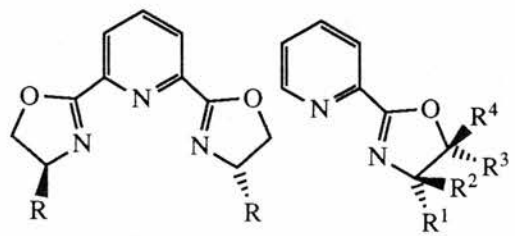
after recrystallisation.[211] The novel camphor based oxazoline **285** had earlier been used to synthesise α-hydroxy carboxylic acids **264** in 56-88% e.e.[212] and α,β-unsaturated derivatives of **285** undergo asymmetric Diels-Alder reactions after activation by TFAA with various dienes to give the adducts with greater than 90% d.e. and 20-76% yield.[213, 214] Aza Claisen rearrangement of **286** in



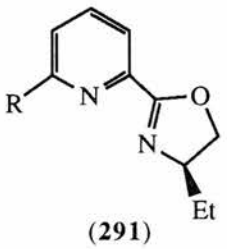
(286) (287) (288)

the presence of Bu^{n}Li gives **287** in 13-88% yield and 82-97% d.e.[215] and conjugate addition to enones with chiral cuprate reagent **288** provides the adduct **270** in 10% e.e.[216]

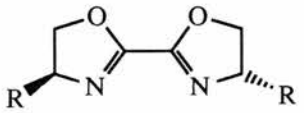
Catalytic asymmetric hydrosilylation of prochiral ketones with diphenylsilane and rhodium complexes of **289**,[217] **290**,[218] **291**[219] and **292**[220] provide after hydrolysis, secondary alcohols in 60-90% yields and 27-95% e.e. A copper complex of **290** monophenylates symmetrical diols in 26-93%



(**289**) R=Pr^i, Bu^t or Bu^s (**290**)

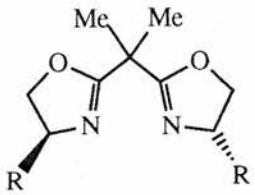


(**291**)

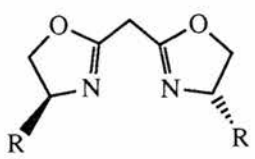


(**292**) R=Pr^i, $PhCH_2$, Ph, Bu^t, CMe_2OH or CH(Me)Et

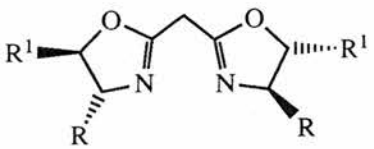
yields and up to 50.4% e.e.[221] Bisoxazolines **292** are efficient C_2-symmetric co-catalysts for: hydrogenation of ketones in the presence of iridium, to afford secondary alcohols in up to 94% yields and 91% e.e.; allylic



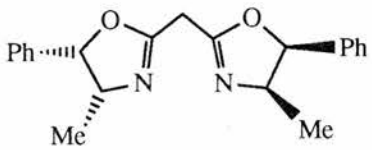
(**293**) R=Pr^i or Bu^t



(**294**) R=Pr^i, Ph, $PhCH_2$ or Bu^t



(**295**) R^1=Ph, R=Me; R^1=H, R=CH_2OH; R^1=H, R=Et



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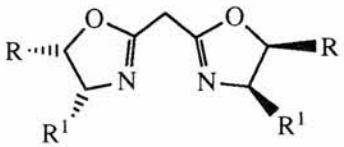
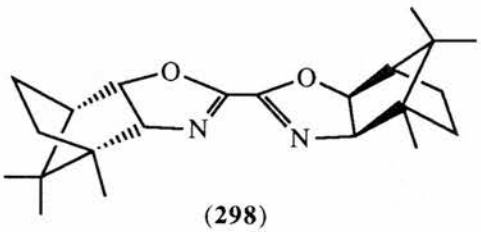


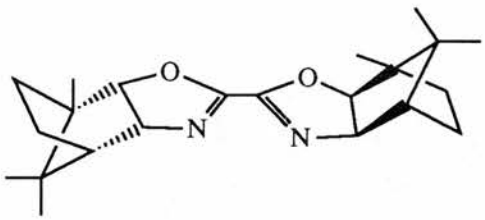
(**297**) R^1=Et, R=Bu^t; R^1=R=Ph

nucleophilic substitution of **179** in the presence of palladium, to give **180** in high yields and 77% e.e.; and cyclopropanation of styrene in the presence of

copper to give the trans cyclopropane **176** in up to 96% e.e.[222] Copper complexes of **292-294**,[223] **295**[224] and **296-299**[225] produce high

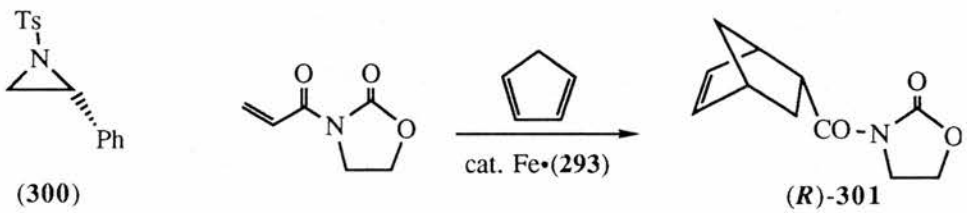


(**298**)



(**299**)

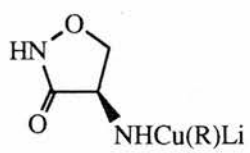
enantioselectivity (up to 98%) in the cyclopropanation of prochiral alkenes with a variety of diazoesters to give the cis cyclopropanes in high yields. Optically active aziridine **300** is produced from styrene and Ph-I=NTs in the presence of copper triflate and **293** R=Bu^t in 61% e.e.[223] Iron complexes of **293**, R=Ph catalyse the Diels-Alder reaction shown to give **301** with 99% endoselectivity and 93:7 enantioselectivity for the (*R*) isomer.[226]



(**300**) (***R***)-**301**

4.4 Isoxazolidinones

Poor enantioselectivity (10%) was observed when the chiral organocuprate reagent, **302** underwent conjugate additions to enones.[216]

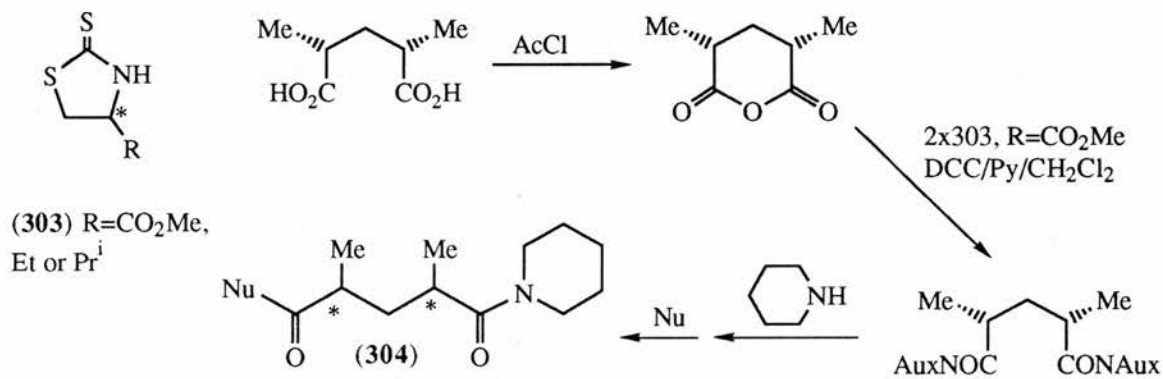


(**302**)

5. Thiazole and Isothiazole Systems

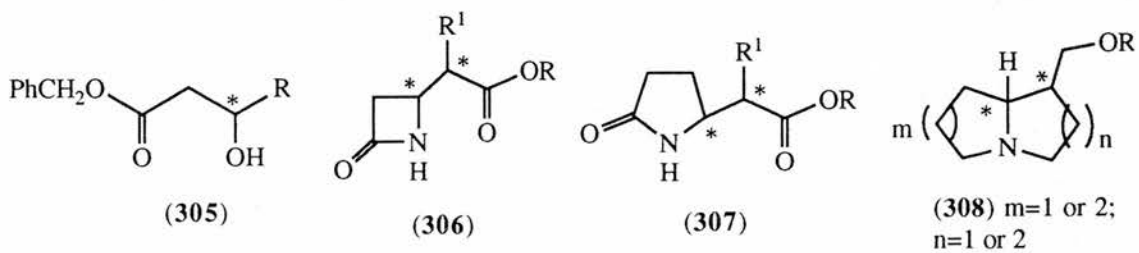
5.1 Thiazolidinethiones and Thiazolidines

Optically pure α-amino acid derived amino alcohols and carbon disulphide condense to give the thiazolidinethione **303** which displays excellent asymmetric induction when the *N*-acyl derivates are reacted with tin triflate



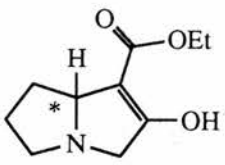
Scheme 6

and alkylated to produce a wide variety of chiral compounds.[227] The auxiliary **303** has been used in the synthesis of: **304** from meso dicarboxylic acids in 79-98% yield and 100% e.e. after purification (Scheme 6), the preparation of β-hydroxy esters **305**, β-lactams **306**, substituted pyrrolidinones **307**,[228] pyrrolizidines,



indolizidines and quinolizidines **308** in high yields with d.e.s >90%. Pyrrolizidines **309**,[229] disubstituted pyrrolidinones **310**[230] and butenolides

311[231] are all similarly prepared in high yields with up to 99% e.e. and cyclic lactone **312** bearing 3 asymmetric centres was synthesised in 5-32% yield as a



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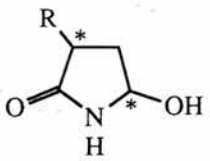

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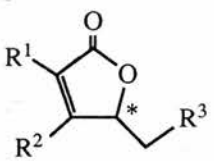

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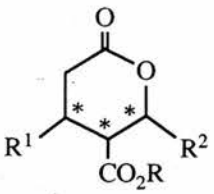
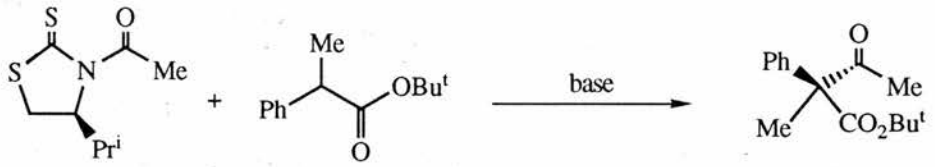


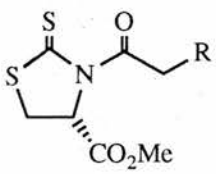
(312)

single isomer.[232] Claisen condensation reactions were carried out by reacting



(313) (314)

the enolate of **313** with an ester to provide **314** in 77% yield and 96% e.e.[233] and aldol reactions between thiazolidinethione **315** and a number of aldehydes give the *syn 2* product **316** only, with greater than 96% e.e. and 60-95% yields.[170, 234, 235]



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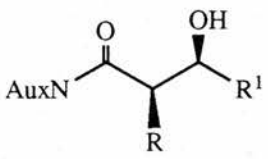

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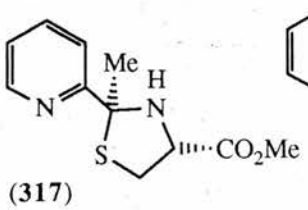

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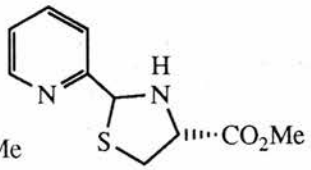
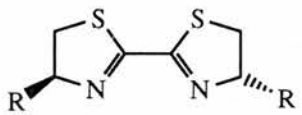


(318)

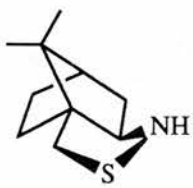
Prochiral ketones are hydrosilylated catalytically using a rhodium complex of **317** or **318** to afford the secondary alcohols with greater than 80% e.e. after hydrolysis.[236]

5.2 2-Thiazolines

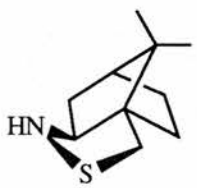
The C_2 symmetric bithiazolines **319** catalyse the hydrosilylation of acetophenone to give (*R*)-1-phenylethanol in good yield with e.e.s up to 84%.[220]



(**319**) R=Pr^i or $PhCH_2$



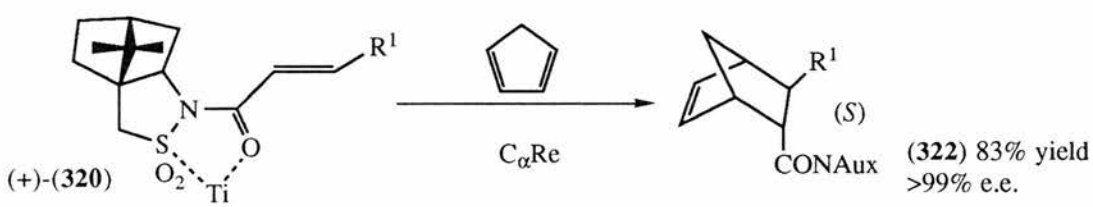
(**320**)



(**321**)

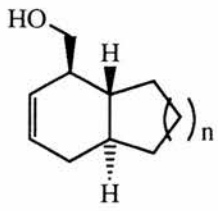
5.3 Isothiazolidine S,S-Dioxides

The rigid nature of the camphor derived sultams **320** (+) and **321** (–) bestows excellent diastereotopic face selectivity on the *N*-acylated sultams as shown in the Diels-Alder reaction to give **322**. To reverse the sense of asymmetric induction the (–) camphor sultam can be used with equally good results. Due

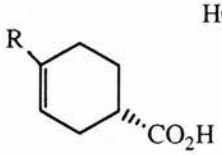


to the high crystallinity of the diastereomeric products, >99% e.e. is routinely achieved in the majority of synthetic operations with the recovery of more than 90% of the auxiliary.[237, 238]

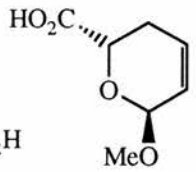
The sultams were initially conceived as dienophile auxiliaries and readily undergo inter and intramolecular Diels Alder reactions, to give **323**



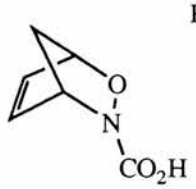
(**323**) n=1 or 2



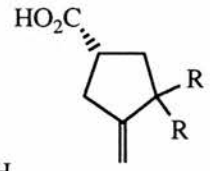
(**324**)



(**325**)

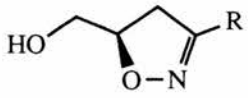


(**326**)



(**327**)

and **324**, [4+2] heterocycloadditions to give **325**[239, 240] and **326**,[241] [3+2] cycloaddition to give **327**[242] and [3+2] heterocycloadditions to give **328**,[243, 244, 245] and **329**[246] in good to excellent yields with a single stereoisomer after



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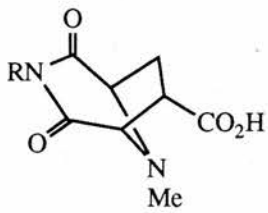
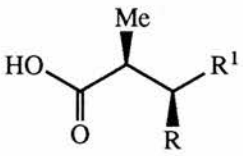


(**329**)



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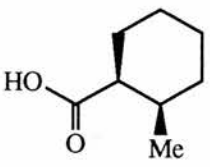
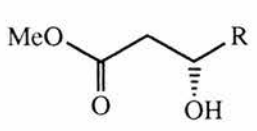


(**331**)

purification.

Other reactions include: addition of organo copper or magnesium reagents to conjugated *N*-enoyl sultams to produce **330** and **331** in 56-83% yields,[247, 248] the synthesis of α-amino acids via amination of the sultam enolates[249] or alkylation of glycinate equivalents[250, 251] in high chemical yields and greater than 99% e.e. High yielding aldol reactions to give *syn 1* and *syn 2* products via the tin or boron enolates respectively,[252] *anti 2* aldols via the silyl enolates with zinc or titanium promoted addition of aromatic or aliphatic aldehydes[253] and aldol type reactions to give the β-hydroxy ester **332** have been reported.[254] Osmylation of the α,β-unsaturated *N*-acyl sultams give cis



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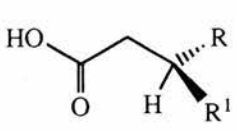

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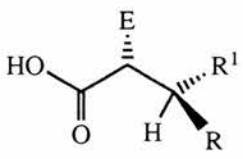
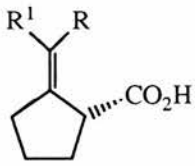


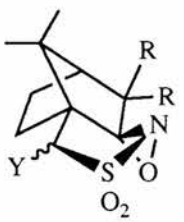
(**334**)



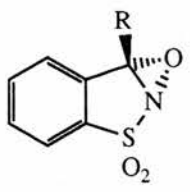
(**335**)

diols in high yield, hydrogenation of prochiral *N*-alkenoylsultams gives the carboxylic acids **333** in 92-100% yield and hydride or conjugate addition / enolate trapping gives **334** in high yields. High levels of induction are also seen in radical addition, cyclisation and annulation reactions with achiral alkenes and alkynes to give **335.**[255]

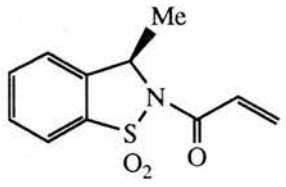
The development of a method to oxidise structurally diverse non-functionalised substrates with high stereoselective control has been realised by the use of the (+)- (or (–)) camphorylsulphoryl oxaziridine **336**.[256] Enantioselective oxidation[257] of prochiral metal enolates with e.e.s of more than 95%,[258, 259] sulphides and selenides to their oxides with e.e.s from 3-72%, epoxidation of nonfunctionalised trans alkenes and hydroxylation of enolates with very high stereoinduction[260] are achieved by **336**. In an attempt to improve enantioselectivity, the saccharin derived oxiziridine **337** was synthesised but lacked the well-defined regions which are topologically dissimilar (as in **336**), and failed to give improved asymmetric induction.[261]



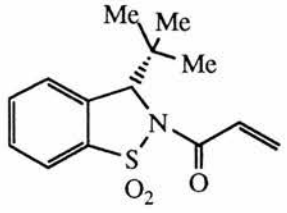
(+)-(**336**) R=H, Cl or OMe; Y=H,CH_2Ph, $CH_2C_6H_4OMe$-*p* or $CH_2C_6H_4CF_3$-*p*



(**337**)



(**338**)



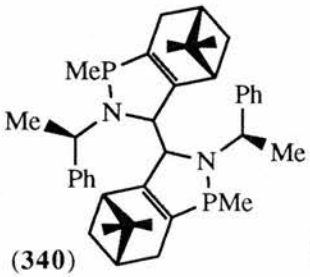
(**339**)

In an effort to avoid some of the inherent problems of **320** and **321**, the saccharin derived N-enoyl sultams **338** and **339** were designed and these undergo efficient Diels-Alder reactions with very high endo / exo ratios of more than 99:1 to give the adduct in 83% yield and >99% d.e.[262] 1,3-Dipolar cycloaddition with **338** afforded **328** in 66-87% yield[263] and alkylation and

aldol reactions to give *syn 1*, *syn 2* and *anti 2* type products in 80-94% yield, have shown this to be a very versatile auxiliary.[264]

6. Isoazaphospholidines

The bis-isoazaphospholidine **340** has been successfully employed as a catalyst in the codimerisation of alkenes to give the methoxynapthtyl butene **341** in 83% e.e. and 72% yield.[265]



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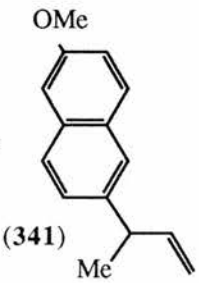

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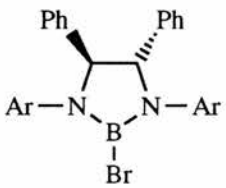

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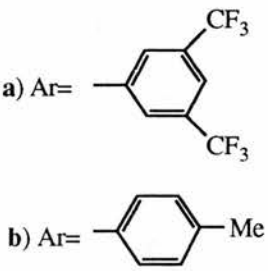
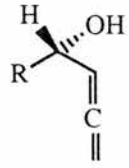


7. 5-Membered Heterocycles Containing N or O and B or P

7.1 Diazaborolidines

The chiral bromoboranes **342a** and **b** are versatile auxiliaries for: amination of enolates to give β-amino acids,[266] addition reactions to aldehydes giving **343** and **344**,[267] and highly diastereoselective Ireland-Clasien rearrangments of achiral allylic esters to give (*R*,*S*) **345** or (*S*,*S*) **346** depending on the base (Et_3N or Pr^i_2NEt) or solvent (toluene or CH_2Cl_2) used.[268] Aldol reactions



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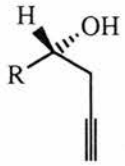

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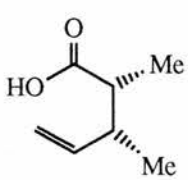

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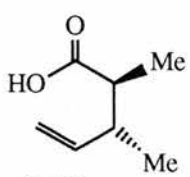

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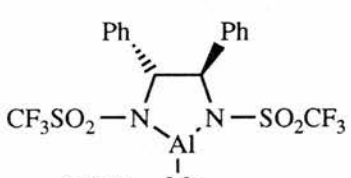
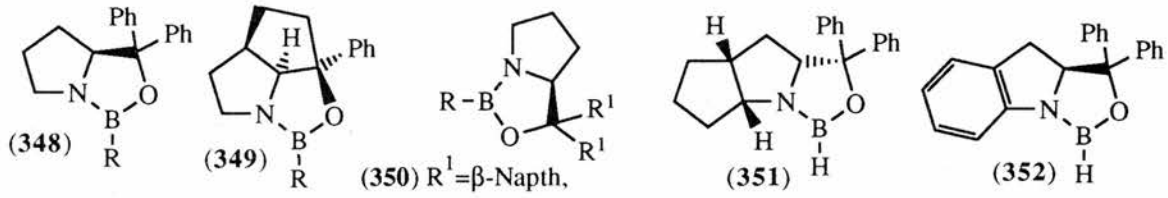


(347)

using **342a** can give either *anti 2* or *syn 1* products, again depending on the base used, Et_3N or Pr^i_2NEt respectively[269, 270] and Diels-Alder reactions involving the chiral Lewis acid **347** provide cycloadducts with high endoselectivity.[271] All of these reactions gave excellent yields with the crude e.e. greater than 90% and were subsequently recrystallised to give the pure enantiomer.

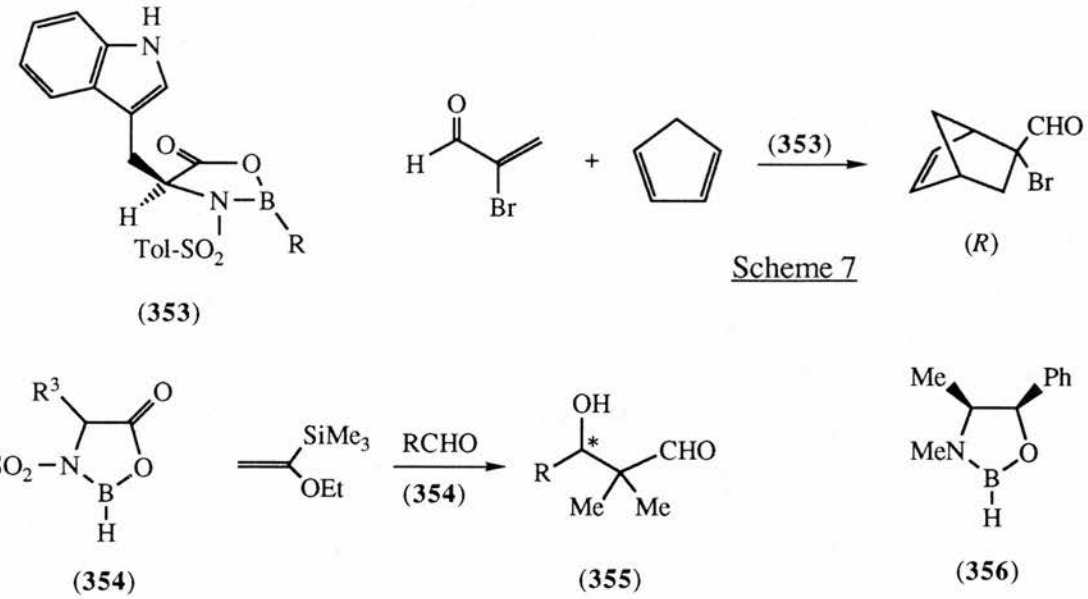
7.2 Oxazaborolidines

Catalytic borane reduction of achiral ketones R_SCOR_L where R_L is larger than R_S occurs with predictability and high enantioselectivity using the catalysts **348-352**. Oxazaborolidine **348** gives secondary alcohols in 93-100% e.e.,[272] bicyclic oxazaborolidine **349** gave (*R*)-1-phenylethanol in 97.5% e.e.[273] and



350 gives chiral alcohols in 82-98% e.e.[274] The tricyclic **351** gives poor e.e.s of 48-61%[275] but the tricyclic **352** produces the secondary alcohols in 79-93% e.e.[276] and good to excellent yields are achieved using all the oxazaborolidine catalysts.

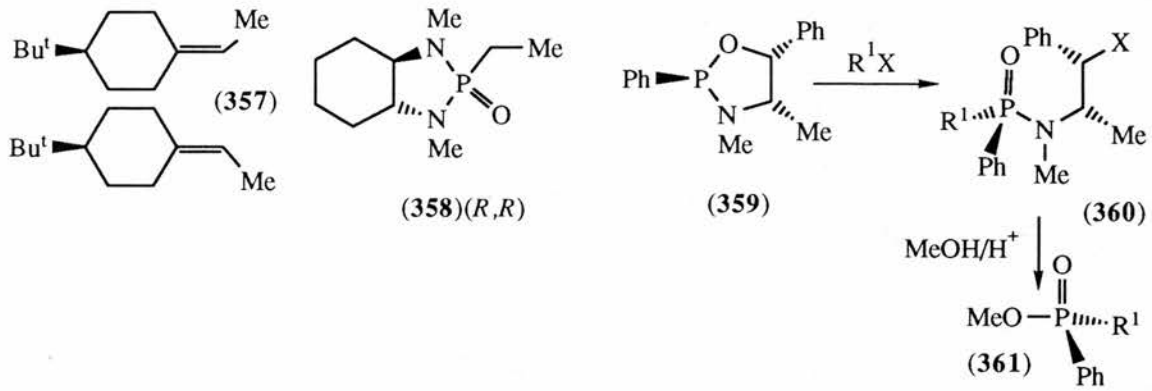
Diels-Alder addition of 2-bromoacrolein with cyclopentadiene produces the (*R*) exo adduct in good yields and in 92% stereoselectivity (exo / endo) using the (*S*)-tryptophan derived oxazaborolidine **353** to coordinate the



dienophile (Scheme 7).[277, 278] Efficient enantioselective cycloadditions between various dienes and dienophiles were also catalysed by **354** to give the adducts in up to 86% e.e.[279, 280, 281] Silyl ketene acetals undergo efficient stereoselective aldol reactions with a variety of aldehydes using the borane compound **354** to afford **355** in 77-85% yields and 45-98% e.e.[282] and **356** was used as a catalyst for addition of diethylzinc to aromatic and aliphatic aldehydes to give the chiral alcohols in 85% yield and 93-96% and 32% e.e. respectively.[283]

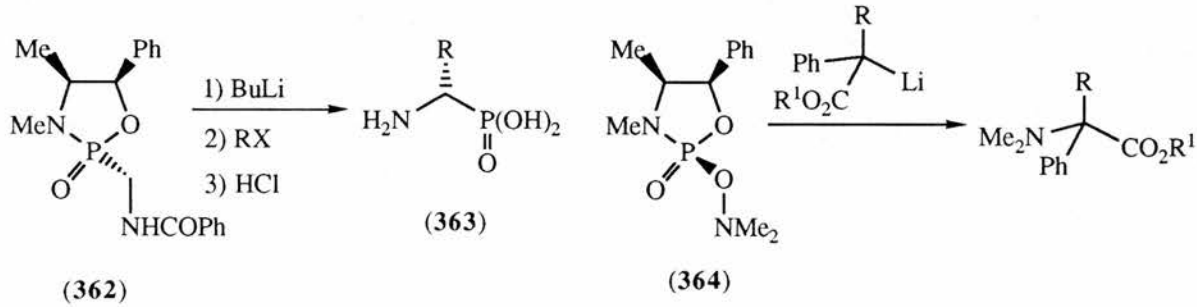
7.3 Diazaphospholidines

Asymmetric Wittig-Horner type olefination of 4-t-butyl cyclohexanone gave (*R*) or (*S*) **357** using the bicyclic (*R*,*R*) or (*S*,*S*) phosphonate **358** in 90% e.e.[284]

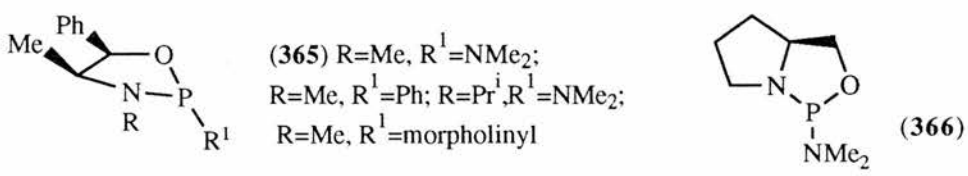


7.4 Oxazaphospholidines

The oxazaphospholidine **359** reacts with alkyl halides to give the phosphinamide **360**, acid methanolysis of which gives (*R*)-methyl phenylphosphinate **361** in 96% e.e.[285] Alkylation of **362** gives 1-aminoalkylphosphonic acid **363** in 83-98% e.e. and 67-92% yield,[286] and electrophilic amination of enolates with **364** gives the phenylglycine

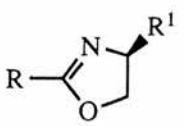


derivatives in 50-62% yield and 8-23% e.e. Conjugate addition of organocopper reagents in the presence of **365** or **366**, to cyclohexenone provides the chiral cyclohexanones in >90% and 62% yield and up to 75% and 23% e.e., respectively.[287]



B. Programme of Research

As described in section A of this introduction, chiral oxazolines **367** have been among the most useful of all auxiliaries for asymmetric synthesis, largely due to the extensive work of the Meyers group (A 4.3). The corresponding achiral thiazolines **368** have been used in the synthesis of aldehydes



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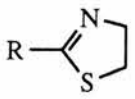

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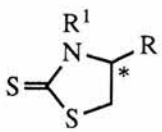
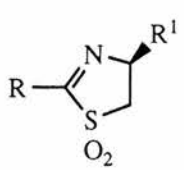


(369)

but the chiral equivalents have not been examined. The amino acid derived thiazolidine thiones **369** have also proved to be valuable chiral auxiliaries (A5.1). In all these studies however the heterocycle has simply been destroyed after serving its function as a directing group.

Our objective at the beginning of this work was to use the heterocycles more constructively by introducing additional functionality, hopefully with high diastereoselectivity, before conversion to acyclic or ring-contracted products. Specifically, oxidation of a chiral derivative of **368** to the little known thiazoline S,S-dioxides **370** followed by deprotonation and alkylation at the 5-postion seemed likely to give **371** which could provide a new



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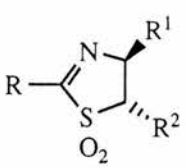

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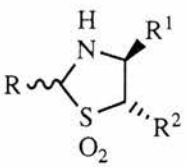

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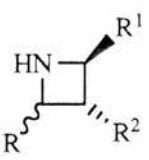


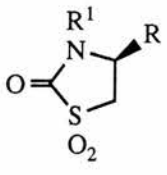
(373)

synthesis of specifically *E*-alkenes upon the expected thermal extrusion of RCN and SO_2. Reduction of **371** to **372** might result in subsequent extrusion

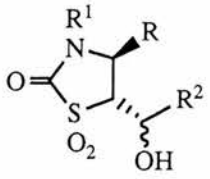
of only SO_2 to give versatile chiral azetidines with three contiguous stereocentres **373**.

Previous work in this laboratory had shown however that it was very difficult to obtain the S,S-dioxides **370**[288] and further work on this using new oxidants seemed worthwhile. The outcome of thermolysis of both **371** and **372** was also of considerable interest since neither reaction had been examined before.

Oxidation of **369** to the thiazolidinone S,S-dioxides **374** was also of particular interest since 5-alkylation with an aldehyde would give **375** which



(374)



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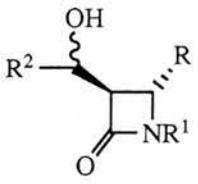

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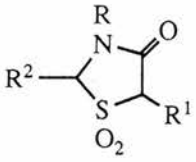
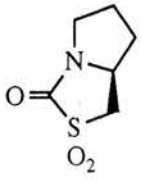


(377)

could potentially extrude SO_2 to give β-lactams **376** of the thienamycin type. Although the the isomeric thiazolidine-4-one S,S-dioxides **377** have indeed been shown to afford β-lactams thermally or photochemically, a preliminary pyrolysis study of **374** had shown complete fragmentation to occur giving R^1NCO, SO_2 and $RCHCH_2$.[288] This was only done for a single example ($R=R^1=CH_2Ph$) however and further detailed study of other examples seemed worthwhile. In particular it seemed possible that tethering the R and R^1 groups together, as in example **378** derived from *S*-proline, might suppress the complete fragmentation and afford the desired β-lactams.



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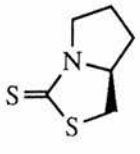

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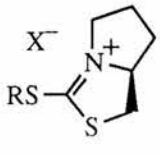


(380)

Consideration of the novel precursor to **378**, compound **379** suggested an additional area for study; the iminium salts such as **380** readily derived by treatment with an alkyl halide might be useful as reagents for kinetic resolution since one enantiomer of a racemic nucleophilic compound might well attack **380** much more readily than the other. The development of such readily available heterocycles as reagents for kinetic resolution was a particularly attractive goal since there are few such custom-designed reagents known at present.

EXPERIMENTAL

A. Symbols and Abbreviations

mmol	millimoles
M	mol dm^{-3}
hr,min	hours, minutes
GC-MS	gas chromatography-mass spectrometry
TLC	thin layer chromatography
NMR	nuclear magnetic resonance
δ	chemical shift in ppm
J	spin-spin coupling constant in Hz
s,d,t,q,m	singlet, doublet, triplet, quartet, multiplet
ν_{max}	infrared absorbtion frequency in cm^{-1}
MS	mass spectroscopy
m/z	mass to charge ratio
M^+	mass of molecular ion
FVP	flash vacuum pyrolysis
RT	room temperature
m.p.	melting point
b.p.	boiling point
eq.	equivalent
e.e.	enantiomeric excess
d.e.	diastereomeric excess
THF	tetrahydrofuran
DMF	dimethylformamide
PTC	phase transfer catalysis
HPLC	high performance liquid chromatograpy

B Instrumentation and General Techniques

1. N.M.R. Spectroscopy

a) ^{1}H NMR

Routine spectra were obtained at 60 MHz on a Varian EM-360 spectrometer and 200 MHz on a Varian Gemini 200. Spectra of new compounds and variable temperature spectra were obtained at 300 MHz on a Bruker AM-300 spectrometer operated by the author and Mrs M Smith . Chiral shift reagent spectra were also obtained at 300 MHz on a Bruker AM-300 spectrometer operated by the author.

b) ^{13}C NMR

Routine spectra were obtained at 50 MHz on a Varian Gemini 200 and spectra of new compounds were obtained at 75 MHz on a Bruker AM-300 spectrometer operated by the author and Mrs M Smith .

c) ^{33}S NMR

Spectra were obtained at 38 MHz on a Bruker MSL-500 spectrometer operated by Drs. F.G. Riddell and S. Arumugam.

All ^{1}H and ^{13}C spectra were obtained from solutions in deuteriochloroform, except when stated otherwise, ^{33}S spectra were obtained from saturated solutions in water, chloroform or the neat liquid and chemical shifts are expressed in parts per million to high frequency of tetramethylsilane for ^{1}H and ^{13}C and to high frequency of sodium sulphate for ^{33}S.

2. Infrared Spectroscopy

Spectra were obtained on a Perkin-Elmer 1420 ratio recording spectrophotometer or Perkin-Elmer 1710 Fourier transform spectrophotometer. Solids were run as nujol mulls and liquids as thin films using matched sodium chloride cells. Spectra were calibrated with the polystyrene peak at 1603 cm^{-1}.

3. Mass Spectrometry

Mass spectra were obtained on a Finnigan Incos 50 mass spectrometer and low resolution and high resolution measurements were obtained on an AEI MS50 instrument, both operated by Mr C Millar.

4. Gas Chromatography-Mass Spectrometry

Gas chromatography-mass spectrometry studies were carried out on a Hewlett-Packard 5890A gas chromatograph coupled to a Finnigan Incos mass spectrometer operated by Mr C Miller.

5. Elemental Analysis

Microanalyses for carbon, hydrogen and nitrogen were carried out on a Carlo-Erba 1106 elemental analyser operated by Mrs S Smith.

6. Melting points

Routine melting points were determined using an Electrothermal melting point apparatus while melting points of new compounds were determined on a Reichert hot-stage microscope. All melting points are uncorrected.

7. Thin Layer Chromatography

This was carried out using 0.2 mm layers of silica (Merck, Kieselgel $60F_{254}$) on aluminium sheets. The components were observed under ultraviolet light.

8. Preparative Thin Layer Chromatography

This was carried out using 1.0 mm layers of silica (Merck, Kieselgel 60-80 mesh), containing 0.5% Woelm fluorescent green indicator, on glass plates. After locating the components with ultraviolet light, the bands were scraped off and the products removed from the support by soaking in dichloromethane for 3h.

9. Column Chromatography

This was carried out using Fisons silica gel for chromatography (60-120 mesh).

10. Drying and Evaporation of Organic Solutions

Organic solutions were dried by standing over anhydrous magnesium sulphate and were evaporated under reduced pressure on a Büchi rotary evaporator.

11. Drying and Purification of Solvents

Commercially available solvents were used without further purification unless otherwise indicated. Dry ether and dry toluene were prepared by the addition of sodium wire. Dry THF was prepared by preliminary drying with sodium wire and then distilling from potassium benzophenone ketyl. Dry DMF was prepared by shaking with activated alumina, filtration and distillation under nitrogen at reduced pressure; collecting the fraction b.p. 40°C / 10 torr, and stored over molecular sieves. "Pet ether" refers to light petroleum, the redistilled 40-60°C boiling fraction being used for chromatography.

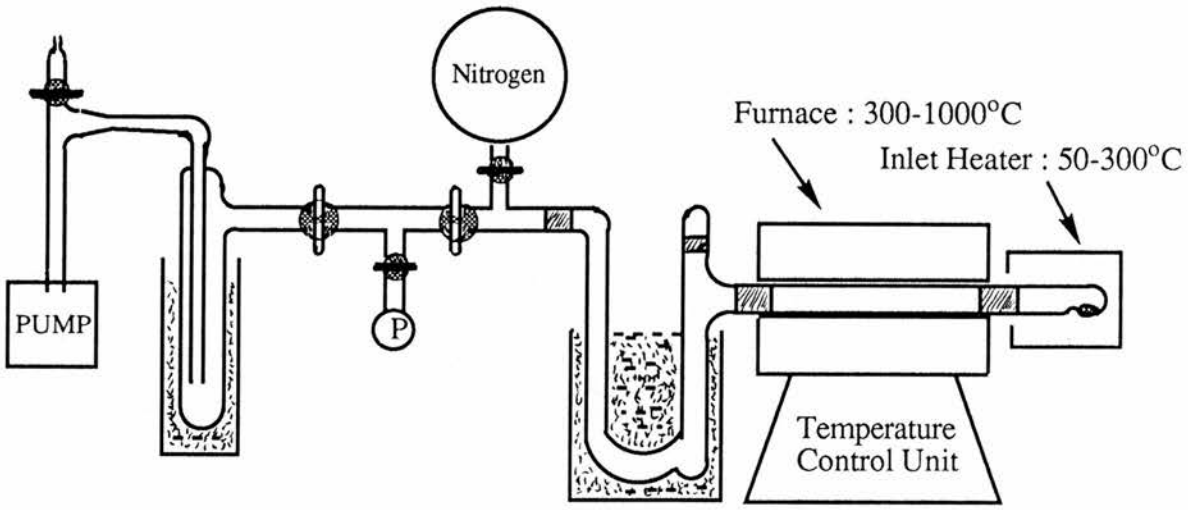
12. Photochemical Reactions

The lamp used was a 400W medium pressure, water cooled mercury lamp supplied by Applied Photophysics Ltd, London. Small scale reactions could be performed by attaching a quartz tube containing the reaction mixture to the side of the reactor well.

13. Flash Vacuum Pyrolysis

The apparatus used was based on the design of W D Crow, Australian National University. A similar set up is illustrated in a recent monograph by Brown.[289]

The essential features of the apparatus are shown below. The sample was volatilised from a horizontal inlet tube, heated *via* an external



heat source, through a 30 × 2.5 cm silica tube. This was heated at temperatures in the range of 550-900°C by a Carbolite Eurotherm Tube Furnace MTF-12/38A, the temperature being measured by a Pt/Pt-13% Rh thermocouple situated at the centre of the furnace. The non-volatile products were collected at the furnace exit and the volatile products collected in a U-shaped trap cooled in liquid nitrogen. The whole system was maintained at a pressure of 10^{-2}-10^{-3} torr by an Edwards Model E2M5 high capacity rotary oil pump, the pressure being measured on a Pirani gauge situated between the trap and the pump. Under these conditions the contact time in the hot zone was estimated to be in the range 1-10 ms.

The pyrolysis conditions are quoted as follows: "(weight of material volatilised, furnace temperature, average pressure during the pyrolysis, inlet temperature)".

After the pyrolysis the system was isolated from the pump and filled with nitrogen gas. The products were then dissolved out of the trap with deuteriochloroform and analysed directly by NMR. For small scale experiments yields were determined by adding an accurately weighed quantity of a solvent such as CH_2Cl_2 and comparing integrals.

14 Optical Rotation

Optical rotation measurements were performed with an Optical Activity AA-1000 polarimeter operating at 589 nm using a 5 ml solution cell with a 10 cm path length or a 1 ml solution cell with a 20 cm path length.

15. Chiral Lanthanide NMR Shift Reagents

The experiments were carried out at both 200 and 300 MHz on standard NMR samples using *tris* [3-(heptafluoropropylhydroxy--methylene)-(+)-camphorato]europium (III).

The enantiomerically enriched samples were run after the racemic analogues had been used to optimise the experimental conditions in each case.

C. Preparation and Reactions of (*R*)- and (*S*)-2-phenyl-4-substituted 2-thiazoline 1,1-dioxides

1. Preparation of (*R*)- and (*S*)-2-benzoylamino alcohols

a) Preparation of (*S*)-2-amino-3-methylbutan-1-ol (*S*-valinol, **392**)

Based on a procedure by Meyers,[290] *S*-valine was added slowly to a stirred suspension of lithium aluminium hydride (14.3 g, 376 mmol) in dry THF (500 ml) under N_2, then the reaction was heated under reflux for 120 hr. After cooling the reaction to 0°C, finely ground sodium sulphate decahydrate (37.1 g, 121 mmol) was added and the solution stirred for an additional 15 min. The reaction was filtered and the salts washed with boiling isopropanol (500 ml). Evaporation afforded an orange oil which was kugelrohr distilled to afford (*S*)-2-amino-3-methylbutan-1-ol (**392**)(17.61 g, 68%) as a colourless solid, b.p. 60°C / 0.05 torr (lit.[291] 55-57°C / 2 torr).

b) Preparation of (*R*)-2-benzoylaminobutan-1-ol (**390** R=Et)

A procedure by Ireland[292] was modified as follows; a solution of (*R*)-2-aminobutan-1-ol (**392**)(30.13 g, 338 mmol) and triethylamine (34.1 g, 375 mmol) in CH_2Cl_2 (150 ml) was stirred at RT, while a solution of benzoyl chloride (47.4 g, 39.2 ml, 338 mmol) in CH_2Cl_2 (150 ml) was added dropwise. After stirring for 20 hr, the solution was washed with water (x 2), 2M hydrochloric acid and water, dried and evaporated to yield a white solid. This was recrystallised from hexane / ethyl acetate to afford (*R*)-2-benzoylaminobutan-1-ol (**390** R=Et)(58.7 g, 90%) as colourless crystals, m.p. 92-93°C (lit.[288] 93-94°C).

c) Preparation of (*S*)-2-benzoylamino-3-methylbutan-1-ol (**390** R=Pr^i)

The procedure of *b*) starting from (*S*)-2-amino-3-methylbutan-1-ol (5.0 g, 48.5 mmol) and recrystallisation of the residue from hexane / ethyl acetate

afforded (*S*)-2-benzoylamino-3-methylbutan-1-ol (**390** R=Pr^i)(4.81 g, 48%) as colourless crystals, m.p. 100-101°C (lit.[288] 107-108°C).

2. Preparation of (*R*)- and (*S*)-2-phenyl-4-substituted 2-thiazolines

a) Preparation of (*R*)-4-ethyl-2-phenyl-2-thiazoline (**389**)

To a suspension of (*R*)-2-benzoylaminobutan-1-ol (**390** R=Et)(9.34 g, 48.4 mmol) in CH_2Cl_2 (250 ml), was added phosphorous pentasulphide (18.03 g, 81.1 mmol). After the mixture had been heated under reflux with stirring for 22 hr, it was filtered and the filtrate washed with 2M sodium hydroxide (2 x 100 ml) and water. The solution was then dried and evaporated to yield a yellow oil. Kugelrohr distillation afforded (*R*)-4-ethyl-2-phenyl-2-thiazoline (**389**)(7.24 g, 78%) as a pale yellow oil, b.p. 120°C / 0.05 torr (lit.[288] 92-93°C / 0.4 torr).

b) Preparation of (*S*)-4-isopropyl-2-phenyl-2-thiazoline (**388**)

The procedure of *a*) starting from (*S*)-2-benzoylamino-3-methylbutan-1-ol (**390** R=Pr^i)(4.8 g, 23 mmol), followed by kugelrohr distillation of the product afforded (*S*)-4-isopropyl-2-phenyl-2-thiazoline (**388**)(4.01 g, 85%) as a clear oil, b.p. 125°C / 0.2 torr (lit.[288] 176°C / 1.3 torr).

c) Preparation of (*S*)-4-benzyl-2-phenyl-2-thiazoline (**387**)

The procedure of *a*) starting from previously prepared[288] (*S*)-2-benzoylamino-3-phenylpropan-1-ol (**390** R=CH_2Ph)(12.34 g, 48.4 mmol), followed by kugelrohr distillation of the product afforded (*S*)-4-benzyl-2-phenyl-2-thiazoline (**387**)(10.5 g, 86%) as a yellow oil, b.p. 160°C / 0.05 torr (lit.[288] 220°C / 0.1 torr).

3. Oxidation of (*R*)- and (*S*)-2-phenyl-4-substituted 2-thiazolines

a) Preparation of (*R*)-4-ethyl-2-phenyl-2-thiazoline 1,1-dioxide (**400**)

A solution of (*R*)-4-ethyl-2-phenyl-2-thiazoline (**389**)(1.0 g, 5.24 mmol), benzoic acid (0.64 g, 5.24 mmol) and benzyltriethylammonium chloride (0.2 g, 0.88 mmol) in CH_2Cl_2 (50 ml) was stirred vigorously for 15 hr at RT, in the presence of potassium permanganate (1.66 g, 10.48 mmol) and water (100 ml). Sodium metabisulphite was then added until the colour of the solution changed from dark brown to beige. The solution was filtered through celite, the organic layer separated and the aqueous layer extracted with CH_2Cl_2. The combined organic extracts were washed with aqueous hydrazine dihydrochloride (1M), saturated aqueous sodium carbonate and brine, dried and evaporated to yield a clear oil, which crystallised on standing to afford (*R*)-4-ethyl-2-phenyl-2-thiazoline 1,1-dioxide (**400**)(1.05 g, 90%) as a colourless solid, m.p. 69-70°C; $[\alpha]_D^{20}$ +11.25° (c=1.04, CH_2Cl_2); (Found: C, 58.5; H, 6.2; N, 6.2; m/z 223.0650. $C_{11}H_{13}NO_2S$ requires C, 59.2; H, 5.9; N, 6.3%; m/z 223.0667); ν_{max} (nujol) 3300, 1630, 1460, 1300 and 1140 (SO_2), 1000, 780 and 700 cm^{-1}; δ_H (300 MHz) 8.1 (2H, m), 7.5 (3H, m), 4.37 (1H, m), 3.41 (1H, half of AB pattern of d, J_{AB} 13.4, J_{AX} 7.2 Hz), 2.92 (1H, half of AB pattern of d, J_{AB} 13.4 , J_{BX} 5.7 Hz), 1.97-1.75 (2H, m) and 1.1 (3H, t, J 8 Hz); δ_C (75 MHz) 161.5 (4^{ry}), 132.7 (CH), 129.1 (2 CH), 128.2 (2 CH), 126.3 (4^{ry}), 62.8 (CH), 50.9 (CH_2), 29.1 (CH_2) and 10.0 (CH_3); δ_S (38.4 MHz) +36.6 ($W_{1/2}$ 200 Hz); m/z 223 (M^+, 1%), 177 (5), 159 (65), 130 (13), 122 (5), 117 (5), 104 (100) and 77 (70).

Attempted recrystallisation of (*R*)-4-ethyl-2-phenyl-2-thiazoline 1,1-dioxide afforded 2-benzoylaminobutane-1-sulphonic acid (**410** R=Et, n=3) and 2-benzoylaminobutane-1-sulphinic (**410** R=Et, n=2); δ_H (300 MHz, CD_3SOCD_3) 11.1 (1H, br s), 8.4 (1H, br s), 7.95 (2H, m), 7.55 (3H, m), 4.4 (1H, m), 3.15 (1H, half of AB pattern of d, J_{AB} 16.5 Hz, J_{AX} 8.2 Hz), 3.0 (1H,

half of AB pattern of d, J_{AB} 16.5 , J_{BX} 5.1 Hz) 1.95 (1H, m), 1.75 (1H, m) and 1.00 (3H, t, J 9 Hz); δ_C (75 MHz, CD_3SOCD_3) 165.85 (CO), 135.15 (4^{ry}), 131.1 (CH), 128.3 (2 CH), 127.2 (2 CH), 54.4 (CH_2), 48.3 (CH), 26.6 (CH_2) and 10.3 (CH_3); m/z 241 (M^+, 1%), 239 (20), 210 (20), 146 (50), 122 (55), 105 (100) and 77 (80).

b) Preparation of (*S*)-4-isopropyl-2-phenyl-2-thiazoline 1,1-dioxide (**399**)

The procedure as in *a*) starting from (*S*)-4-isopropyl-2-phenyl-2-thiazoline (**388**)(1.14 g, 5.24 mmol) gave an oil which crystallised on standing to afford (*S*)-4-isopropyl-2-phenyl-2-thiazoline 1,1-dioxide (**399**)(1.06 g, 85%) as a colourless solid, m.p. 78-80°C; $[\alpha]_D^{20}$ +10.4° (c=1.02, CH_2Cl_2); (Found: m/z 237.0827. $C_{12}H_{15}NO_2S$ requires m/z 237.0823); ν_{max} (nujol) 3000-2900, 1620, 1460, 1310 and 1130 (SO_2), 770 and 690 cm^{-1}; δ_H (300 MHz) 8.1 (2H, m), 7.5 (3H, m), 4.25 (1H, m), 3.34 (1H, half of AB pattern of d, J_{AB} 13.52 , J_{AX} 7.3 Hz), 2.96 (1H, half of AB pattern of d, J_{AB} 13.52, J_{BX} 6.6 Hz), 2.1 (1H, m), 1.08 (3H, d, J 6.77 Hz) and 1.00 (3H, d, J 6.75 Hz); δ_C (75 MHz) 161.3 (4^{ry}), 132.5 (CH), 128.8 (2 CH), 128.0 (2 CH), 126.2 (4^{ry}), 66.8 (CH), 48.8 (CH_2), 33.1 (CH), 18.4 (CH_3) and 18.0 (CH_3); m/z 237 (M^+, 5%), 172 (60), 157 (20), 145 (15), 129 (30), 116 (20) and 103 (100).

Attempted recrystallisation of (*S*)-4-isopropyl-2-phenyl-2-thiazoline 1,1-dioxide provided 2-benzoylamino-3-methylbutane-1-sulphonic acid (**410** R=Pr^i, n=3) and 2-benzoylamino-3-methylbutane-1-sulphinic acid (**410** R=Pr^i, n=2); δ_C (75 MHz, CD_3SOCD_3) 166.6 (CO), 134.7 (4^{ry}), 130.97 (CH), 128.1 (2 CH), 127.2 (2 CH), 63.0 (CH_2), 54.2 (CH), 32.5 (CH), 18.45 (CH_3) and 17.8 (CH_3).

c) Preparation of (*S*)-4-benzyl-2-phenyl-2-thiazoline 1,1-dioxide (**398**)

The procedure as in *a*) starting from (*S*)-4-benzyl-2-phenyl-2-thiazoline (**387**)(1.33 g, 5.24 mmol), afforded (*S*)-4-benzyl-2-phenyl-2-thiazoline 1,1-

dioxide (**398**)(1.39 g, 93%) as a yellow oil; $[\alpha]_D^{20}$ –0.375° (c=1.6, CH_2Cl_2); (Found: C, 67.8; H, 5.2; N, 4.9. $C_{16}H_{15}NO_2S$ requires C, 67.3; H, 5.3; N, 4.9%); ν_{max} (neat) 3060, 3020, 1630, 1500, 1455, 1315 and 1140 (SO_2), 775, 750 and 700 cm^{-1}; δ_H (300 MHz) 8.11 (2H, m), 7.6-7.2 (8H, m), 4.7 (1H, m), 3.37 (1H, half of AB pattern of d, J_{AB} 13.8, J_{AX} 5.5 Hz), 3.23 (1H, half of AB pattern of d, J_{AB} 13.6, J_{AX} 7.1 Hz), 2.95 (1H, half of AB pattern of d, J_{AB} 13.6, J_{BX} 5.8 Hz), 2.90 (1H, half of AB pattern of d, J_{AB} 13.8, J_{BX} 8.8 Hz); δ_C (75 MHz) 162.2 (4^{ry}), 136.2 (4^{ry}), 132.8 (CH), 129.3 (2 CH), 129.1 (2 CH), 128.8 (2 CH), 128.2 (2 CH), 127.2 (CH), 126.3 (4^{ry}), 62.7 (CH), 50.6 (CH_2) and 41.7 (CH_2); δ_S (23 MHz) +1.28 ($W_{1/2}$ 263 Hz); m/z 145 (M^+–140, 5%), 128 (5), 117 (100), 103 (15), 91 (30) and 77 (10).

Attempted recrystallisation of (*S*)-4-benzyl-2-phenyl-2-thiazoline 1,1-dioxide produced 2-benzoylamino-3-phenylpropane-1-sulphonic acid (**409**) and 2-benzoylamino-3-phenylpropane-1-sulphinic acid (**408**); (Found: C, 63.1; H, 5.6; N, 4.6. $C_{16}H_{17}NO_3S$ requires C, 63.3; H, 5.6; N, 4.6%); δ_H (300 MHz, CD_3SOCD_3) 8.6 (1H, m), 7.75 (2H, m), 7.5 (3H, m), 7.35 (5H, m), 5.5 (1H, br s), 4.5 (1H, m), 3.15-2.75 (4H, m); δ_C (75 MHz, CD_3SOCD_3) 165.66 (CO), 137.9 (4^{ry}), 134.3 (4^{ry}), 131.1 (CH), 129.2 (2 CH), 128.2 (4 CH), 127.1 (2 CH), 126.2 (CH), 62.4 (CH_2), 46.0 (CH) and 40.0 (CH_2).

4. FVP of (*R*)- and (*S*)-2-phenyl-4-substituted 2-thiazoline 1,1-dioxides

a) Flash vacuum pyrolysis of (*R*)-4-ethyl-2-phenyl-2-thiazoline 1,1-dioxide (**400**)

The FVP of (*R*)-4-ethyl-2-phenyl-2-thiazoline 1,1-dioxide (**400**)(213 mg, 600°C, $1.0x10^{-3}$ torr, inlet 50-60°C), gave a yellow oil in the cold trap and a white solid at the furnace exit. The ^{13}C and ^1H NMR spectra of the solid showed it to be the starting material (trace) and ^{13}C and ^1H NMR analysis of the oil showed two compounds; but-1-ene (78%) and benzonitrile (93.7%).

b) Flash vacuum pyrolysis of (*S*)-4-isopropyl-2-phenyl-2-thiazoline 1,1-dioxide (**399**)

The FVP of (*S*)-4-isopropyl-2-phenyl-2-thiazoline 1,1-dioxide (**399**)(212.9 mg, 600°C, 1.0×10^{-3} torr, inlet 50-60°C), gave a yellow oil which was analysed by ^{13}C and ^{1}H NMR and shown to contain two compounds; 3-methylbut-1-ene (68%) and benzonitrile (82.6%).

c) Flash vacuum pyrolysis of (*S*)-4-benzyl-2-phenyl-2-thiazoline 1,1-dioxide (**398**)

The FVP of (*S*)-4-benzyl-2-phenyl-2-thiazoline 1,1-dioxide (**398**)(236.6 mg, 600°C, 4.0×10^{-3} torr, inlet 60-70°C), gave a yellow oil which was analysed by ^{13}C and ^{1}H NMR and shown to contain three compounds; allyl benzene (>90%), benzonitrile (>90%) and the starting sulphone (3.6%).

5. Attempted photolysis of (*R*)- and (*S*)-2-phenyl-4-substituted 2-thiazoline 1,1-dioxides

a) Attempted photolysis of (*R*)-4-ethyl-2-phenyl-2-thiazoline 1,1-dioxide (**400**)

A few milligrams of (*R*)-4-ethyl-2-phenyl-2-thiazoline 1,1-dioxide (**400**) was placed in a dry NMR tube, dissolved in d_6-acetone / TMS and irradiated. After 48 hr a white solid had precipitated out of solution. NMR analysis of the solid identified two compounds 2-benzoylaminobutane-1-sulphinic acid (**410** R=Et, n=2) and 2-benzoylaminobutane-1-sulphonic acid (**410** R=Et, n=3).

b) Attempted photolysis of (*S*)-4-benzyl-2-phenyl-2-thiazoline 1,1-dioxide (**398**)

The procedure of *a*) using (*S*)-4-benzyl-2-phenyl-2-thiazoline 1,1-dioxide (**398**) gave a solid whose NMR analysis identified two compounds 2-benzoylamino-3-phenylpropane-1-sulphinic acid (**408**) and 2-benzoylamino-3-phenylpropane-1-sulphonic acid (**409**).

c) Attempted photolysis of (*S*)-4-isopropyl-2-phenyl-2-thiazoline 1,1-dioxide (**399**)

A solution of (*S*)-4-isopropyl-2-phenyl-2-thiazoline 1,1-dioxide (**399**)(0.17 g, 0.7 mmol) and CH_2Cl_2 (5 ml) was placed in a dry quartz tube, under N_2 and irradiated for 3 hr. Evaporation of the solvent gave a white solid which was shown to be the starting material.

6. Reduction of (*R*)- and (*S*)-2-phenyl-4-substituted 2-thiazolines

a) Preparation of 2,2'-bi[(*R*)-4-ethyl-2-phenylthiazolidine] (**422**)

Following a procedure by Meyers,[293] 1/2 inch squares of aluminium foil (1.3 g) were roughed with sand paper and then etched with 5% potassium hydroxide solution until hydrogen was evolved. The solution was decanted, the foil rinsed with water and then covered with a 0.5% mercuric chloride solution for 2 mins. The mercuric chloride solution was decanted away and the foil rinsed with water, decanted and covered again with a 0.5% mercuric chloride solution for 2 mins. Finally, the mercuric chloride solution was decanted away and the foil rinsed with water, ethanol and ether. To the treated foil (*R*)-4-ethyl-2-phenyl-2-thiazoline (**389**)(1.0 g, 5.24 mmol) and ether (shaken with water, 75 ml) was added and the solution heated under reflux for 4 hr. The mixture was filtered, dried with potassium carbonate and evaporated to yield a yellow oil. Preparative TLC (ether / pet. ether (1:1)) afforded 2,2'-bi[(*R*)-4-ethyl-2-phenylthiazolidine] (**422**)(as a mixture of stereoisomers, 0.99 g, 98%) as a pale yellow oil, (Found: m/z 384.1688.

$C_{22}H_{28}N_2S_2$ requires m/z 384.1694); ν_{max} (neat) 3230 and 3150 (NH), 2900, 1420, 1230, 1130, 875, 700 and 670 cm^{-1}; δ_C (75 MHz) 143.7 (4^{ry}), 143.5 (4^{ry}), 142.9 (4^{ry}), 142.8 (4^{ry}), 129.1 to 125.8 (40 CH), 94.8 (4^{ry}), 93.7 (4^{ry}), 91.1 (2 4^{ry}), 68.1 (CH), 65.7 (CH), 65.6 (CH), 65.5 (CH), 41.4 (CH_2), 41.0 (CH_2), 40.9 (CH_2), 40.4 (CH_2), 27.9 (CH_2), 27.1 (CH_2), 26.9 (CH_2), 26.5 (CH_2), 11.8 (CH_3), 11.3 (2 CH_3) and 10.7 (CH_3); m/z 384 (M^+, 5%), 222 (5), 192 (100), 162 (10), 104 (40), 77 (25) and 55 (20).

b) Preparation of 2,2'-bi[(*S*)-4-benzyl-2-phenylthiazolidine] (**421**)

Following the procedure from *a*) (*S*)-4-benzyl-2-phenyl-2-thiazoline (**387**)(1.33 g, 5.24 mmol) was reacted to give after work up, 2,2'-bi[(*S*)-4-benzyl-2-phenylthiazolidine] (**421**)(as a mixture of stereoisomers, 1.0 g, 76%) as a clear oil, ν_{max} (neat) 3300 and 3230 (NH), 3040, 2930, 1500, 1460, 915, 740 and 700 cm^{-1}; δ_C (75 MHz) 143.9 (4^{ry}), 143.3 (4^{ry}), 142.8 (4^{ry}), 139.5 (4^{ry}), 138.4 (4^{ry}), 138.1 (4^{ry}) , 129.7 to 126.2 (60 CH), 94.8 (4^{ry}), 93.7 (4^{ry}), 90.6 (4^{ry}), 67.3 (CH), 64.8 (CH), 64.1 (CH), 41.2 (CH_2), 41.0 (CH_2), 40.7 (CH_2), 40.4 (CH_2), 40.1 (CH_2) and 40.0 (CH_2); m/z 508 (M^+, 2%), 254 (100), 164 (100), 117 (60), 106 (50) and 91 (35).

D. Preparation of (*R*)- and (*S*)-2-methyl-4-substituted 2-thiazoline 1,1-dioxides

1. Preparation of (*R*)- and (*S*)-2-methyl-4-substituted 2-oxazolines

a) Preparation of ethyl iminoacetate hydrochloride (**397**)

The title compound was prepared using the method by Dox,[294] to afford ethyl iminoacetate hydrochloride (**397**)(66.54 g, 74%) as colourless crystals, m.p. 99-101°C (lit.[294] m.p. 107-108°C).

b) Preparation of 2-(*S*)-amino-3-phenylpropan-1-ol (*S*-phenylalaninol, **391**)

The method was based on a procedure by Meyers.[295] A solution of sodium borohydride (75.7 g, 200 mmol) in 50% aqueous ethanol (750 ml) was stirred at 0°C while a solution of 2-(*S*)-amino-3-phenylpropanoic acid methyl ester hydrochloride (86.6 g, 401 mmol) in 50% aqueous ethanol (750 ml) was added dropwise. After heating under reflux for 146 hr, the ethanol was evaporated off and sodium hydroxide 2M (300 ml) was added to the aqueous layer. The aqueous layer was extracted with ethyl acetate (150 ml x 5) and the combined organic layers dried and evaporated to afford 2-(*S*)-amino-3-phenylpropan-1-ol (**391**)(42.3 g, 70%) as colourless crystals, m.p. 88-89°C (lit.[295] 89-91°C).

c) Preparation of (*R*)-4-ethyl-2-methyl-2-oxazoline

Danger: The product from this reaction was found, unexpectedly to be toxic, exposure to the vapour causing severe headaches and vertigo.

Following a procedure by Meyers,[296] CH_2Cl_2 (400 ml) and ethyl iminoacetate hydrochloride (**397**)(29 g, 235 mmol) were stirred together and cooled down to 0°C. A solution of (*R*)-2-aminobutan-1-ol (**393**)(14.89 g, 167 mmol) in CH_2Cl_2 (150 ml) was added and the reaction allowed to warm up to RT and stir for 76 hr. The solution was washed with water and the aqueous layer extracted with CH_2Cl_2, the combined organic extracts were dried and evaporated to yield a yellow oil. Kugelrohr distillation of the product afforded (*R*)-4-ethyl-2-methyl-2-oxazoline (9.86 g, 52%) as a colourless oil, b.p. 70°C / 14 torr; $[\alpha]_D^{20}$ +25.5° (c=7.7, CH_2Cl_2); (Found: m/z 113.0834. $C_6H_{11}NO$ requires m/z 113.0841); ν_{max} (neat) 2980, 1740, 1675, 1390, 1270, 1230, 985 and 900 cm^{-1}; δ_H (300 MHz) 4.28 (1H, half of AB pattern of d, J_{AB} 8.0, J_{AX} 9.3 Hz), 3.95 (1H, m), 3.82 (1H, half of AB pattern of d, J_{AB} 8.0, J_{BX}

8.0 Hz), 1.94 (3H, d, J 1.3 Hz), 1.66-1.44 (2H, m) and 0.95 (3H, t, J 7 Hz); δ_C (75 MHz) 164.35 (4^{ry}), 72.23 (CH_2), 67.89 (CH), 28.85 (CH_2), 13.82 (CH_3) and 10.12 (CH_3); m/z 113 (M^+, 55%), 84 (100), 68 (75), 56 (80) and 43 (80).

d) Preparation of (*S*)-4-benzyl-2-methyl-2-oxazoline

The procedure of *c)* starting from (*S*)-2-amino-3-phenylpropan-1-ol (**391**)(14.52 g, 117.5 mmol), afforded after kugelrohr distillation (*S*)-4-benzyl-2-methyl-2-oxazoline (10.98 g, 75%) as a pale yellow oil, b.p. 125°C / 0.6 torr (lit.[288] 96°C / 0.02 torr).

2. Preparation of (*R*)- and (*S*)-2-methyl-4-substituted 2-thiazolines

a) Preparation of (*R*)-4-ethyl-2-methyl-2-thiazoline (**396**)

To a suspension of phosphorus pentasulphide (20.05 g, 90.5 mmol) in CH_2Cl_2 (200 ml), (*R*)-4-ethyl-2-methyl-2-oxazoline (6.2 g, 54.5 mmol) was added and the mixture heated under reflux for 138 hr with stirring. The resulting suspension was filtered and the filtrate washed with 2M sodium hydroxide (x 3) and water. The organic layer was then dried and evaporated in a cold bath to give an oil which was kugelrohr distilled to afford (*R*)-4-ethyl-2-methyl-2-thiazoline (**396**)(2.25 g, 32%) as a yellow oil, b.p. 85°C / 14 torr; $[\alpha]_D^{20}$ +99.9° (c=1.3, CH_2Cl_2); (Found: m/z 129.0619. $C_6H_{11}NS$ requires m/z 129.0612); ν_{max} (neat) 2980, 2920, 2860, 1635, 1460, 1435, 1370 and 1155 cm^{-1}; δ_H (300 MHz) 4.34 (1H, m), 3.38 (1H, half of AB pattern of d, J_{AB} 10.8, J_{AX} 8.5 Hz), 2.98 (1H, half of AB pattern of d, J_{AB} 10.8, J_{BX} 8.4 Hz), 2.20 (3H, d, J 1.7 Hz), 1.81 (1H, m), 1.64 (1H, m) and 1.02 (3H, t, J 7 Hz); δ_C (75 MHz) 165.1 (4^{ry}), 79.0 (CH), 38.8 (CH_2), 28.1 (CH_2), 20.3 (CH_3) and 11.0 (CH_3); m/z 129 (M^+, 70%), 100 (50), 88 (80), 68 (50), 60 (60) and 55 (100).

b) Preparation of (*S*)-4-benzyl-2-methyl-2-thiazoline (**394**)

The procedure of *a*) starting from (*S*)-4-benzyl-2-methyl-2-oxazoline (9.53 g, 54.5 mmol), followed by kugelrohr distillation of the product afforded (*S*)-4-benzyl-2-methyl-2-thiazoline (**394**)(6.76 g, 65%) as a pale yellow oil, b.p. 155°C / 0.2 torr (lit.[288] 233°C / 2 torr).

3. Attempted preparation of (*S*)-2-methyl-4-substituted 2-thiazoline 1,1-dioxides

a) Oxidation of (*S*)-4-isopropyl-2-methyl-2-thiazoline (**395**)

A solution of (*S*)-4-isopropyl-2-methyl-2-thiazoline (**395**)(0.75 g, 5.24 mmol)(previously prepared[288]), benzoic acid (0.64 g, 5.24 mmol) and benzyltriethylammonium chloride (0.2 g, 0.88 mmol) in CH_2Cl_2 (50 ml) was stirred vigorously for 5 hr at RT, in the presence of potassium permanganate (1.66 g, 10.48 mmol) and water (100 ml). For work up see C. 3. *a*. Evaporation of the dried solution gave (< 10 mg) of a yellow oil, which quickly decomposed to give organic insoluble products.

b) Oxidation of (*S*)-4-benzyl-2-methyl-2-thiazoline (**394**)

The procedure of *a*) starting from (*S*)-4-benzyl-2-methyl-2-thiazoline (**394**)(1.0 g, 5.24 mmol), gave upon evaporation of the dried solution (25 mg) of a white solid, which was insoluble in organic solvents.

E. Preparation and Pyrolysis of 3-acetyl-4-(*S*)-benzyl-2-t-butylthiazolidine 1,1-dioxide

1. Preparation of 2-(*S*)-trimethylacetylamino-3-phenylpropan-1-ol (423)

A procedure by Ireland[292] was modified as follows, a solution of (*S*)-2-amino-3-phenylpropan-1-ol (**391**)(20.0 g, 132 mmol) and triethylamine (14.8

g, 147 mmol) in CH_2Cl_2 (100 ml) was stirred at RT, while a solution of trimethylacetyl chloride (15.9 g, 16.25 ml, 132 mmol) in CH_2Cl_2 (50 ml) was added dropwise. After stirring 20 hr, the solution was washed with water (x 2), 2M hydrochloric acid and water, dried and evaporated to yield a white solid. Recrystallisation of the residue from hexane / ethyl acetate afforded 2-(*S*)-trimethylacetylamino-3-phenylpropan-1-ol (**423**)(21.46 g, 69%), as pale yellow crystals, m.p. 72-73°C (lit.[288] 75-76°C).

2. Preparation of 4-(*S*)-benzyl-2-t-butyl-2-thiazoline (424)

To a suspension of phosphorus pentasulphide (6.55 g, 24.7 mmol) in CH_2Cl_2 (100 ml), (*S*)-2-trimethylacetylamino-3-phenylpropan-1-ol (**423**)(4.36 g, 18.6 mmol) was added and the mixture heated under reflux for 138 hr with stirring. The resulting suspension was filtered and the filtrate washed with 2M sodium hydroxide (x 3) and water. The organic layer was then dried and evaporated to give an orange oil. Kugelrohr distillation afforded 4-(*S*)-benzyl-2-t-butyl-2-thiazoline (**424**)(3.67 g, 65%) as an orange oil, b.p. 155°C / 0.5 torr (lit.[288] 172°C / 1 torr).

3. Preparation of 4-(*S*)-benzyl-2-t-butylthiazolidine (425)

Aluminium amalgam was prepared according to the procedure outlined in C. 6. *a*. A solution of 4-(*S*)-benzyl-2-t-butyl-2-thiazoline (**424**)(1.22 g, 5.24 mmol) in ether (shaken with water, 75 ml) was added to the amalgam and heated under reflux for 6 hr, to give after work up (see C. 6. *a*) an oil (1.38 g). Column chromatography of this using silica and ether (R_F=0.71) afforded 4-(*S*)-benzyl-2-t-butylthiazolidine (**425**)(0.99 g, 80%) as a colourless oil in 50% d.e., b.p. 196°C / 0.9 torr; (Found: m/z 235.1390. $C_{14}H_{21}NS$ requires m/z 235.1395); ν_{max} (neat) 3300 (NH), 2970, 1600, 1500, 1480, 1460, 1370, 1185, 1120, 750 and 700 cm^{-1}; δ_H (300 MHz) major diastereomer 7.3-7.1 (5H, m), 4.45 (1H, s), 3.3 (1H, m), 3.15 (1H, half of AB pattern of d, J_{AB} 12,

J_{AX} 6 Hz), 2.7 (1H, half of AB pattern of d, J_{AB} 12, J_{BX} 8 Hz), 2.8 (1H, half of AB pattern of d, J_{AB} 10, J_{AX} 5 Hz), 2.3 (1H, half of AB pattern of d, J_{AB} 10, J_{BX} 10 Hz), 1.45 (1H, br s) and 1.0 (9H, s); δ_C (75 MHz) major diastereomer 137.7 (4^{ry}), 128.6 (2 CH), 128.0 (2 CH), 126.0 (CH), 81.1 (CH), 65.8 (CH), 39.6 (CH_2), 38.4 (CH_2), 33.5 (4^{ry}) and 26.5 (3 CH_3); δ_C minor diastereomer 138.9 (4^{ry}), 128.7 (2 CH), 127.9 (2 CH), 125.8 (CH), 79.8 (CH), 65.2 (CH), 38.9 (CH_2), 38.2 (CH_2), 34.7 (4^{ry}) and 26.6 (3 CH_3); m/z 235 (M^+, 5%), 234 (10), 220 (30), 178 (80), 142 (60), 117 (70), 86 (100), 57 (55) and 41 (60).

4. Preparation of 3-acetyl-4-(*S*)-benzyl-2-t-butylthiazolidine (426)

A mixture of acetic anhydride (4 ml) and (*S*)-4-benzyl-2-t-butylthiazolidine (**425**)(2.2 g, 9.4 mmol) was heated under reflux for 20 min. The reaction was allowed to cool, water (40 ml) was added and the solution heated to boiling and cooled again. The mixture was extracted with CH_2Cl_2 and the extract washed with saturated aqueous sodium carbonate and water. Drying and evaporation afforded 3-acetyl-4-(*S*)-benzyl-2-t-butylthiazolidine (**426**)(2.11 g, 81%) as a colourless solid in 93% d.e., m.p. 75-92°C; (Found: C, 69.2; H, 8.5; N, 5.0. $C_{16}H_{23}NOS$ requires C, 69.3; H, 8.4; N, 5.1%); ν_{max} (nujol) 1735, 1650 (CO), 1385, 1310, 1050, 895, 750 and 700 cm^{-1}; δ_H (300 MHz, 50°C) 7.25 (5H, m), 5.4-5.2 (1H, br s), 4.5 (1H, br s), 3.4 (1H, br s), 2.9 (2H, m), 2.8 (1H, br s), 2.25 (3H, s) and 1.1 (9H, s); δ_C (75 MHz, 50°C) 171.7 (CO), 138.3 (4^{ry}), 129.0 (2 CH), 128.8 (2 CH), 126.9 (CH), 74.1 (CH), 65.6 (CH), 42.3 (CH_2), 39.0 (4^{ry}), 36.2 (CH_2), 27.9 (3 CH_3) and 23.7 (CH_3); m/z 277 (M^+, 1%), 233 (70), 220 (80), 178 (70), 142 (100), 117 (65) and 92 (30).

5. Preparation of 3-acetyl-4-(*S*)-benzyl-2-t-butylthiazolidine 1,1-dioxide (427)

A solution of 3-acetyl-4-(*S*)-benzyl-2-t-butylthiazolidine (**426**)(1.45 g, 5.24 mmol), benzoic acid (0.64 g, 5.24 mmol) and benzyltriethylammonium chloride (0.2 g, 0.88 mmol) in CH_2Cl_2 (50 ml) was stirred vigorously for 15 hr at RT, in the presence of potassium permanganate (1.66 g, 10.48 mmol) and water (100 ml). For work up see C. 3. a. Evaporation of the solution afforded 3-acetyl-4-(*S*)-benzyl-2-t-butylthiazolidine 1,1-dioxide (**427**)(1.45 g, 90%) as colourless crystals in >99% d.e., m.p. 140-145°C; (Found: C, 61.85; H, 7.65; N, 4.5. $C_{16}H_{23}NO_3S$ requires C, 62.1; H, 7.5; N, 4.5%); ν_{max} (nujol) 1735, 1665 (CO), 1375, 1315, 1265, 1150, 1110, 750 and 700 cm^{-1}; δ_H (300 MHz, 50°C) 7.35-7.2 (5H, m), 4.8 (1H, br s), 4.65 (1H, br s), 3.5 (1H, m), 3.05 (2H, m), 2.8 (1H, m), 2.25 (3H, s) and 1.3 (9H, s); δ_C (75 MHz, 50°C) 172.9 (CO), 136.0 (4^{ry}), 129.2 (2 CH), 128.8 (2 CH), 127.5 (CH), 80.8 (CH), 56.5 (CH), 52.4 (CH_2), 42.4 (CH_2), 35.8 (4^{ry}), 27.3 (3 CH_3) and 22.5 (CH_3); m/z 309 (M^+, 5%), 245 (30), 218 (70), 128 (100), 118 (85), 112 (95), 86 (25) and 43 (50).

6. FVP of 3-acetyl-4-(*S*)-benzyl-2-t-butylthiazolidine 1,1-dioxide (427)

The FVP of 3-acetyl-4-(*S*)-benzyl-2-t-butylthiazolidine 1,1-dioxide (**427**)(183.2 mg, 600°C, 6.0×10^{-3} torr, inlet 50-60°C), gave a yellow oil at the furnace exit and a yellow oil in the cold trap. The ^{13}C and ^{1}H NMR spectra of the oil from the furnace exit showed the presence of two compounds; allyl benzene (3.2%) and trimethylacetaldehyde (1%). The ^{13}C and ^{1}H NMR spectra of the oil from the trap showed three compounds; allyl benzene (40%), trimethylacetonitrile (9%) and trimethylacetaldehyde (6.4%). GC-MS of the oil from the trap showed bibenzyl (7%), 2-t-butylthiazole (5.7%) and 1-phenyl-1-propyne (4.7%).

F. Preparation of 3-acetyl-4-(*R*)-methoxycarbonyl-2-substituted thiazolidine 1,1-dioxides

1. Preparation of 4-(*R*)-carboxy-2-substituted thiazolidines

The three procedures that follow are based on a method by Ratner and Clarke.[297]

a) Preparation of 4-(*R*)-carboxy-2-ethylthiazolidine (**429**)

To a solution of *R*-cysteine (10 g, 82.5 mmol) in water (200 ml), a solution of propionaldehyde (5.74 g, 7.14 ml, 99 mmol) in ethanol (200 ml) was added and the mixture stirred for 24 hr. The solution was evaporated to give a solid which was recrystallised from ethanol and water with cooling (4°C), to afford 4-(*R*)-carboxy-2-ethylthiazolidine (**429**)(11.04 g, 84%) as a colourless powder, m.p. 154-155°C (lit.[298] 160-161°C).

b) Preparation of 4-(*R*)-carboxy-2-isopropylthiazolidine (**430**)

To a solution of *R*-cysteine (10 g, 82.5 mmol) in water (200 ml), a solution of isobutyraldehyde (7.14 g, 9 ml, 99 mmol) in ethanol (200 ml) was added, the mixture stirred for 5 hr and then cooled to 4°C and left overnight. The product was filtered off to afford 4-(*R*)-carboxy-2-isopropylthiazolidine (**430**)(9.51 g, 66%) as colourless crystals, m.p. 173-174°C (lit.[299] 180-182°C).

c) Preparation of 4-(*R*)-carboxy-2-phenylthiazolidine (**431**)

To a solution of *R*-cysteine (10 g, 82.5 mmol) in water (200 ml), a solution of benzaldehyde (10.5 g, 99 mmol) in ethanol (200 ml) was added and the mixture stirred for 16 hr. The solid was filtered off and washed with cold water, cold ethanol and ether. Drying afforded 4-(*R*)-carboxy-2-phenylthiazolidine (**431**)(16.64 g, 96%) as a colourless powder, m.p. 154-155°C (lit.[300] 159-160°C).

2. Preparation of 4-(*R*)-methoxycarbonyl-2-substituted thiazolidines

a) Preparation of 4-(*R*)-methoxycarbonyl-thiazolidine (**432**)

The procedure was based on a method by Ratner and Clarke.[297] Thionyl chloride (8.9 g, 5.5 ml, 75.0 mmol) was added dropwise to a cooled solution (–20°C) of 4-(*R*)-carboxythiazolidine (**428**)(14.7 g, 0.1 mol) in methanol (150 ml). The mixture was stirred at –20°C for 30 min and then allowed to warm up to RT and stirred for another 6 hr. The solvent was evaporated to afford the crude hydrochloride salt, which was then dissolved in water (5 ml) and covered with ether (50 ml). Anhydrous potassium carbonate was then added slowly to excess, the ether layer decanted off and the solid mass extracted with ether (x 3). The combined ether layers were then dried and evaporated to afford a colourless oil. Kugelrohr distillation yielded 4-(*R*)-methoxycarbonylthiazolidine (**432**)(11.65 g, 79%) as a colourless oil, b.p. 165°C / 10 torr (lit.[297] 75°C / 1.0 torr).

b) Preparation of 2-ethyl-4-(*R*)-methoxycarbonylthiazolidine (**433**)

The procedure of *a*) starting from 4-(*R*)-carboxy-2-ethylthiazolidine (**429**)(5.0 g, 31 mmol), followed by kugelrohr distillation yielded 2-ethyl-4-(*R*)-methoxycarbonylthiazolidine (**433**)(3.18 g, 58%) as a colourless oil in 34% d.e., b.p. 112°C / 0.2 torr $[\alpha]_D^{20}$ –109° (c=1.55, CH_2Cl_2) (lit.[301] $[\alpha]_D^{20}$ –114° (CH_2Cl_2)).

c) Preparation of 2-isopropyl-4-(*R*)-methoxycarbonylthiazolidine (**434**)

The procedure of *a*) starting from 4-(*R*)-carboxy-2-isopropylthiazolidine (**430**)(8.75 g, 50 mmol), followed by kugelrohr distillation yielded 2-isopropyl-4-(*R*)-methoxycarbonylthiazolidine (**434**)(6.28 g, 66%) as a colourless oil in 38% d.e., b.p. 105°C / 0.2 torr; (Found: m/z

189.0843. $C_8H_{15}NO_2S$ requires m/z 189.0823); ν_{max} (neat) 3280 (NH), 2980, 1740 (CO), 1435, 1340, 1270, 1200, 1165 and 820 cm^{-1}; δ_H (300 MHz) major diastereomer 4.35 (1H, d, J 7.7 Hz), 3.85 (1H, m), 3.8 (3H, s), 3.3 (1H, half of AB pattern of d, J_{AB} 10.3, J_{AX} 7.7), 2.75 (1H, half of AB pattern of d, J_{AB} 10.3, J_{BX} 10.3Hz), 2.3 (1H, br s), 2.0 (1H, m), 1.15 (3H, d, J 8.5) and 1.1 (3H, d, J 8.5); δ_H minor diastereomer 4.45 (1H, d, J 8.5 Hz), 4.15 (1H, t, J 7 Hz), 3.75 (3H, s), 3.2 (1H, half of AB pattern of d, J_{AB} 11, J_{AX} 7.3), 3.0 (1H, half of AB pattern of d, J_{AB} 11, J_{BX} 7.7), 2.3 (1H, br s), 1.8 (1H, m), 1.05 (3H, d, J 6.8) and 1.0 (3H, d, J 6.8); δ_C (75 MHz) major diastereomer 171.7 (CO), 78.0 (CH), 65.4 (CH), 52.4 (CH_3), 37.5 (CH_2), 33.6 (CH), 20.7 (CH_3) and 20.3 (CH_3); δ_C minor diastereomer 172.2 (CO), 76.8 (CH), 64.3 (CH), 52.4 (CH_3), 37.3 (CH_2), 35.1 (CH), 20.5 (CH_3) and 19.7 (CH_3); m/z 189 (M^+, 10%), 146 (100), 130 (30), 86 (90) and 55 (40).

d) Preparation of 4-(*R*)-methoxycarbonyl-2-phenylthiazolidine (**435**)

The procedure of *a*) starting from 4-(*R*)-carboxy-2-phenylthiazolidine (**431**)(10.45 g, 50 mmol), followed by kugelrohr distillation provided 4-(*R*)-methoxycarbonyl-2-phenylthiazolidine (**435**)(4.32 g, 39%) as a colourless oil in 24% d.e., b.p. 185°C / 0.25 torr (lit.[302] b.p. 154-155°C / 1.5 torr).

3. Preparation of 3-acetyl-4-(*R*)-methoxycarbonyl-2-substituted thiazolidines

a) Preparation of 3-acetyl-4-(*R*)-methoxycarbonylthiazolidine (**436**)

A solution of acetic anhydride (6.4 ml) and 4-(*R*)-methoxycarbonylthiazolidine (**432**)(4.0 g, 27.2 mmol) was heated under reflux for 20 min. The mixture was allowed to cool, water (40 ml) was added and the solution heated to boiling and then cooled again. The mixture was extracted with CH_2Cl_2 and the extract washed with saturated aqueous sodium carbonate and water. Drying and evaporation afforded an oil which was

kugelrohr distilled yielding 3-acetyl-4-(*R*)-methoxycarbonylthiazolidine (**436**)(5.15 g, >99%) as a colourless oil, b.p. 160°C / 0.2 torr (lit.[302] 152°C / 0.5 torr).

b) Preparation of 3-acetyl-2-ethyl-4-(*R*)-methoxycarbonylthiazolidine (**437**)

The procedure of *a*) starting from 2-ethyl-4-(*R*)-methoxycarbonylthiazolidine (**433**)(3.18 g, 18 mmol), followed by kugelrohr distillation yielded 3-acetyl-2-ethyl-4-(*R*)-methoxycarbonylthiazolidine (**437**)(3.45 g, 89%) as a colourless oil in 26% d.e., b.p. 180°C / 0.8 torr; (Found: m/z 217.0783. $C_9H_{15}NO_3S$ requires m/z 217.0773); ν_{max} (neat) 2960, 1750 (CO), 1650 (CO), 1400, 1350, 1200 and 1175 cm^{-1}; δ_H (300 MHz) major diastereomer 5.0-4.8 (2H, m), 3.75 (3H, s), 3.5-3.3 (2H, m), 2.2 (3H, s), 2.0 (1H, m), 1.8 (1H, m) and 1.05 (3H, t, J 7 Hz); δ_H minor diastereomer 5.3 (1H, dd, J 4, 11.4Hz), 4.8 (1H, m), 3.85 (3H, s), 3.5-3.3 (2H, m), 2.15 (1H, m), 2.1 (3H, s), 1.55 (1H, m) and 0.9 (3H, t, J 7 Hz); δ_C (75 MHz) major diastereomer 171.1 (CO), 168.1 (CO), 67.3 (CH), 62.1 (CH), 52.5 (CH_3), 31.6 (CH_2), 30.7 (CH_2), 22.0 (CH_3) and 11.4 (CH_3); δ_C minor diastereomer 170.9 (CO), 168.6 (CO), 66.1 (CH), 63.1 (CH), 52.9 (CH_3), 33.2 (CH_2), 29.2 (CH_2), 23.0 (CH_3) and 11.2 (CH_3); m/z 217 (M^+, 55%), 188 (60), 158 (40), 146 (95), 131 (75), 116 (75), 98 (45), 86 (80), 68 (50), 59 (85) and 43 (100).

c) Preparation of 3-acetyl-2-isopropyl-4-(*R*)-methoxycarbonylthiazolidine (**438**)

The procedure of *a*) starting from 2-isopropyl-4-(*R*)-methoxycarbonylthiazolidine (**434**)(5.0 g, 26 mmol), followed by kugelrohr distillation yielded 3-acetyl-2-isopropyl-4-(*R*)-methoxycarbonylthiazolidine (**438**)(5.85 g, 97%) as a colourless oil in 28% d.e., b.p. 193°C / 0.4 torr;

(Found: C, 52.1; H, 7.4; N, 6.1; m/z 231.0934. $C_{10}H_{17}NO_3S$ requires C, 51.9; H, 7.4; N, 6.1%; m/z 231.0929); ν_{max} (neat) 2960, 1750 (CO), 1650 (CO), 1390, 1200, 1170 and 1010 cm^{-1}; δ_H (300 MHz) major diastereomer 5.0 (1H, t, J 8.5 Hz), 4.75 (1H, d, J 8.5 Hz), 3.75 (3H, s), 3.3 (2H, m), 2.2 (3H, s), 2.05 (1H, m) and 1.1 (6H, d, J 7 Hz); δ_H minor diastereomer 5.3 (1H, d, J 8.5 Hz), 4.8 (1H, t, J 8 Hz), 3.8 (3H, s), 3.4 (2H, m), 2.1 (3H, s), 2.05 (1H, m) and 1.0 (6H, d, J 7 Hz); δ_C (75 MHz) major diastereomer 171.6 (CO), 169.2 (CO), 72.1 (CH), 62.2 (CH), 52.4 (CH_3), 35.2 (CH), 31.9 (CH_2), 22.5 (CH_3), 20.2 (CH_3) and 19.1 (CH_3); δ_C minor diastereomer 171.1 (CO), 169.6 (CO), 70.4 (CH), 63.3 (CH), 52.8 (CH_3), 34.2 (CH), 33.3 (CH_2), 22.8 (CH_3), 19.9 (CH_3) and 19.1 (CH_3); m/z 231 (M^+, 20%), 188 (75), 172 (15), 146 (100), 130 (40), 86 (80), 59 (60) and 43 (100).

d) Preparation of 3-acetyl-4-(*R*)-methoxycarbonyl-2-phenylthiazolidine (**439**)

A solution of acetic anhydride (4 ml) and 4-(*R*)-methoxycarbonyl-2-phenylthiazolidine (**435**)(3.8 g, 17 mmol) was heated under reflux for 20 min. The mixture was allowed to cool, water (40 ml) was added and the solution heated to boiling and cooled again. Crystallisation upon cooling, followed by filtration and drying of the solid afforded 3-acetyl-4-(*R*)-methoxycarbonyl-2-phenylthiazolidine (**439**)(4.39 g, 98%) as colourless crystals in 76% d.e., m.p. 120-122°C; (Found: C, 58.5; H, 5.8; N, 5.3. $C_{13}H_{15}NO_3S$ requires C, 58.8; H, 5.7; N, 5.3%); ν_{max} (nujol) 1750 (CO), 1640 (CO), 1350, 1200, 1180 and 730 cm^{-1}; δ_H (300 MHz) 7.65 (2H, m), 7.35 (3H, m), 6.05 (1H, s), 4.95 (1H, t), 3.8 (3H, s), 3.25 (2H, m) and 1.9 (3H, s); δ_C (75 MHz) 170.5 (CO), 170.0 (CO), 140.6 (4^{ry}), 128.8 (2 CH), 128.3 (CH), 126.3 (2 CH), 66.6 (CH), 64.4 (CH), 52.6 (CH_3), 32.0 (CH_2) and 22.7 (CH_3); m/z 265 (M^+, 3%), 222 (35), 179 (50), 164 (45), 146 (20) and 43 (100).

4. Preparation of 3-acetyl-4-(*R*)-methoxycarbonyl-2-substituted thiazolidine 1,1-dioxides

a) Preparation of 3-acetyl-4-(*R*)-methoxycarbonylthiazolidine 1,1-dioxide (**440**)

A solution of 3-acetyl-4-(*R*)-methoxycarbonylthiazolidine (**436**)(1.88 g, 10.48 mmol), benzoic acid (1.28 g, 10.48 mmol) and benzyltriethylammonium chloride (0.4 g, 1.76 mmol) in CH_2Cl_2 (100 ml) was stirred vigorously for 15 hr at RT, in the presence of potassium permanganate (3.32 g, 21 mmol) and water (200 ml). For work up see C. 3. a. Evaporation of the solution afforded 3-acetyl-4-(*R*)-methoxycarbonylthiazolidine 1,1-dioxide (**440**)(1.17 g, 50%) as a colourless oil which crystallised on standing, m.p. 75-76°C (lit.[302] b.p. 170 / 0.5 torr).

b) Preparation of 3-acetyl-2-ethyl-4-(*R*)-methoxycarbonylthiazolidine 1,1-dioxide (**441**)

The method of *a*) starting from 3-acetyl-2-ethyl-4-(*R*)-methoxycarbonylthiazolidine (**437**)(2.27 g, 10.48 mmol), followed by evaporation of the solution afforded 3-acetyl-2-ethyl-4-(*R*)-methoxycarbonylthiazolidine 1,1-dioxide (**441**)(2.35 g, 90%) as colourless crystals in 32% d.e., m.p. 72-103°C; (Found: C, 43.4; H, 5.9; N, 5.6. $C_9H_{15}NO_5S$ requires C, 43.4; H, 6.1; N, 5.6%); ν_{max} (nujol) 3480, 3300, 1745 (CO), 1660 (CO), 1320-1170, 1110, 1005, 940, 875 and 820 cm^{-1}; δ_H (300 MHz) major diastereomer 5.3 (1H, t, J 8 Hz), 4.55 (1H, t, J 7 Hz), 3.75 (3H, s), 3.6 (1H, half of AB pattern of d, J_{AB} 13, J_{AX} 10.6 Hz), 3.4 (1H, half of AB pattern of d, J_{AB} 13, J_{BX} 8.1), 2.2 (3H, s), 1.8 (2H, m) and 1.2 (3H, t, J 7 Hz); δ_H minor diastereomer 5.1-4.9 (2H, m), 3.85 (3H, s), 3.7-3.5 (2H, m), 2.2 (3H, s), 2.1-1.95 (2H, m) and 1.1 (3H, t, J 7 Hz); δ_C (75 MHz) major diastereomer 170.0 (CO), 169.4 (CO), 74.5 (CH), 53.2 (CH), 52.8 (CH_3), 47.7

(CH_2), 25.5 (CH_2), 22.1 (CH_3) and 10.1 (CH_3); δ_C minor diastereomer 171.1 (CO), 170.3 (CO), 72.0 (CH), 55.2 (CH), 53.7 (CH_3), 49.4 (CH_2), 23.9 (CH_2), 21.2 (CH_3) and 9.9 (CH_3); m/z 185 (M^+-SO_2, 10%), 143 (75), 84 (95), 55 (40) and 43 (100).

c) Preparation of 3-acetyl-2-isopropyl-4-(*R*)-methoxycarbonylthiazolidine 1,1-dioxide (**442**)

The method of *a*) starting from 3-acetyl-2-isopropyl-4-(*R*)-methoxycarbonylthiazolidine (**438**)(2.42 g, 10.48 mmol), followed by evaporation of the solution afforded 3-acetyl-2-isopropyl-4-(*R*)-methoxycarbonyl thiazolidine 1,1-dioxide (**442**)(2.81 g, 100%) as colourless crystals in 18% d.e., m.p. 76-79°C; (Found: C, 45.4; H, 6.35; N, 5.2. $C_{10}H_{17}NO_5S$ requires C, 45.6; H, 6.5; N, 5.3%); ν_{max} (nujol) 1750 (CO), 1660 (CO), 1380, 1310, 1150, 1120, 890 and 810 cm^{-1}; δ_H (300 MHz) major diastereomer 5.3 (1H, t, J 9 Hz), 4.35 (1H, d, J 9.4 Hz), 3.8 (3H, s), 3.7-3.4 (2H, m), 2.25 (3H, s), 2.1 (1H, m), 1.3 (3H, d, J 7.7 Hz) and 1.2 (3H, d, J 7.7 Hz); δ_H minor diastereomer 5.05 (1H, t, J 8 Hz), 4.9 (1H, d, J 8.5 Hz), 3.85 (3H, s), 3.7-3.4 (2H, m), 2.25 (3H, s), 2.1 (1H, m), 1.2 (3H, d, J 7.7 Hz) and 1.0 (3H, d, J 7.7 Hz); δ_C (75 MHz) major diastereomer 170.8 (CO), 169.2 (CO), 78.7 (CH), 53.1 (CH), 52.7 (CH_3), 47.4 (CH_2), 31.1 (CH), 22.4 (CH_3), 19.2 (CH_3) and 19.1 (CH_3); δ_C minor diastereomer 171.1 (CO), 169.2 (CO), 75.4 (CH), 55.1 (CH), 53.6 (CH_3), 48.9 (CH_2), 30.4 (CH), 21.2 (CH_3), 19.2 (CH_3) and 18.8 (CH_3); δ_S (38.4 MHz) +18.7 ($W_{1/2}$ 400 Hz); m/z 263 (M^+, 0.5%), 199 (15), 184 (30), 157 (70), 98 (85), 87 (60), 55 (80) and 43 (100).

d) Preparation of 3-acetyl-4-(*R*)-methoxycarbonyl-2-phenylthiazolidine 1,1-dioxide (**443**)

The method of *a*) starting from 3-acetyl-4-(*R*)-methoxycarbonyl-2-phenylthiazolidine (**439**)(2.77 g, 10.48 mmol), followed by evaporation of the

solution afforded 3-acetyl-4-(*R*)-methoxycarbonyl-2-phenylthiazolidine 1,1-dioxide (**443**)(2.88 g, 93%) as colourless crystals in 70% d.e., m.p. 211-215°C (sublimes); (Found: C, 52.4; H, 5.0; N, 4.6. $C_{13}H_{15}NO_5S$ requires C, 52.5; H, 5.1; N, 4.7%); ν_{max} (nujol) 1760 (CO), 1660 (CO), 1380, 1350, 1210, 1145, 1005 and 700 cm^{-1}; δ_H (300 MHz) 7.75 (2H, m), 7.5 (3H, m), 5.5 (1H, s), 4.95 (1H, dd, J 7, 8.6 Hz), 3.9 (3H, s), 3.6 (1H, half of AB pattern of d, J_{AB} 11, J_{AX} 7.7 Hz), 3.35 (1H, half of AB pattern of d, J_{AB} 11, J_{BX} 9.4) and 2.0 (3H, s); δ_C (75 MHz, CD_3SOCD_3) 170.5 (CO), 168.9 (CO), 132.1 (4^{ry}), 129.4 (CH), 128.7 (2 CH), 128.0 (2 CH), 75.3 (CH), 54.1 (CH), 52.7 (CH_3), 47.9 (CH_2) and 22.2 (CH_3); m/z 297 (M^+, 5%), 233 (60), 190 (100), 174 (70), 132 (100), 130 (100), 104 (100), 89 (90), 77 (85) and 43 (100).

5. FVP of 3-acetyl-4-(*R*)-methoxycarbonyl-2-substituted thiazolidine 1,1-dioxides

a) Flash vacuum pyrolysis of 3-acetyl-4-(*R*)-methoxycarbonylthiazolidine 1,1-dioxide (**440**)

The FVP of 3-acetyl-4-(*R*)-methoxycarbonylthiazolidine 1,1-dioxide (**440**)(101.6 mg, 700°C, $1.0x10^{-3}$ torr, inlet 50-60°C), gave an orange oil which was analysed by ^{13}C and ^1H NMR and five compounds were identified; the starting compound (10%), methyl acrylate (20%), acetic acid (10%), methanol (10%) and acetamide (10%).

b) Flash vacuum pyrolysis of 3-acetyl-2-ethyl-4-(*R*)-methoxycarbonyl thiazolidine 1,1-dioxide (**441**)

The FVP of 3-acetyl-2-ethyl-4-(*R*)-methoxycarbonylthiazolidine 1,1-dioxide (**441**)(256.5 mg, 600°C, $1.0x10^{-3}$ torr, inlet 50-60°C), gave a yellow oil at the furnace exit and a yellow oil in the cold trap. The ^{13}C and ^1H NMR of the material from the furnace exit showed mainly the starting compound (10%) and ^{13}C and ^1H NMR spectra of the material from the trap showed the

presence of three compounds; methyl acrylate (16.6%), acetic acid (47%) and methanol (33%).

c) Flash vacuum pyrolysis of 3-acetyl-2-isopropyl-4-(*R*)-methoxycarbonyl thiazolidine 1,1-dioxide (**442**)

The FVP of 3-acetyl-2-isopropyl-4-(*R*)-methoxycarbonylthiazolidine 1,1-dioxide (**442**)(151.6 mg, 700°C, 1.0×10^{-3} torr, inlet 40°C), gave a dark brown oil which was analysed by ^{13}C and ^{1}H NMR and four compounds were identified; methyl acrylate (28%), acetic acid (60%), methanol (30%) and acetamide (<0.5%).

d) Flash vacuum pyrolysis of 3-acetyl-4-(*R*)-methoxycarbonyl-2-phenyl thiazolidine 1,1-dioxide (**443**)

The FVP of 3-acetyl-4-(*R*)-methoxycarbonyl-2-phenylthiazolidine 1,1-dioxide (**443**)(19.5 mg, 700°C, 1.0×10^{-3} torr, inlet 70-100°C), gave a black oil which was analysed by ^{13}C and ^{1}H NMR and four compounds were identified; methyl acrylate (47%), acetic acid (73%), methanol (41%), and benzaldehyde (16.8%). GC-MS identified one additional compound; benzonitrile (18.4%).

G. Preparation of 1,3-dithiolan-2-one

a) Preparation of 1,3-dithiolane-2-thione (**402**)

The title compound was prepared by the method of Culvenor *et al.*,[303] using ethylene oxide and carbon disulphide in the presence of potassium hydroxide to afford after recrystallisation 1,3-dithiolane-2-thione (**402**)(3.93 g, 58%) as yellow crystals, m.p. 30-32°C (lit. m.p. 36-37°C).

b) Preparation of 1,3-dithiolane-2-one (**403**)

A solution of 1,3-dithiolane-2-thione (**402**)(1.0 g, 7.35 mmol), benzoic acid (0.9 g, 7.35 mmol) and benzyltriethylammonium chloride (0.27 g, 1.2 mmol) in CH_2Cl_2 (50 ml) was stirred vigorously for 3 hr at RT, in the presence of potassium permanganate (3.48 g, 22.05 mmol) and water (100 ml). After workup (see C. 3. a.), kugelrohr distillation of the residue afforded 1,3-dithiolan-2-one (**403**)(0.60 g, 70%) as a pale yellow oil which slowly crystallised, b.p. 95 / 1.0 torr and m.p. 32-33°C (lit.[304] b.p. 90-92°C / 4 torr and m.p. 35°C).

H. Preparation of (*R*)- and (*S*)-3,4-disubstituted thiazolidine-2-one 1,1-dioxides

1. Preparation of (*S*)-2-hydroxymethylpyrrolidine (*S*-prolinol, 460)

Following a procedure by Enders,[305] a suspension of lithium aluminium hydride (11.0 g, 290 mmol) in dry THF (400 ml), was stirred under N_2. The solution was then heated to reflux, the heat switched off and *S*-proline (20 g, 173.7 mmol) added slowly to maintain refluxing conditions. After addition of *S*-proline, the reaction was again heated to reflux for a further 1 hr and 45 min. The heat was turned off, and a solution of potassium hydroxide (4.76 g) dissolved in water (20 ml) slowly added to the THF solution, then the mixture was heated under reflux for an additional 15 min. The reaction mixture was filtered while hot and the salts washed with boiling isopropanol (250 ml). Evaporation of the combined filtrate afforded (*S*)-2-hydroxymethylpyrrolidine (**460**)(17.2 g, 97%).

2. Preparation of (*R*)- and (*S*)-2-benzylideneamino alcohols

a) Preparation of (*R*)-2-benzylideneaminobutan-1-ol (**457** R=Et)

A procedure by Freifelder[306] was modified as follows; benzaldehyde (24.4 g, 230 mmol) was added to a stirred solution of (*R*)-2-aminobutan-1-ol (**393**)(19.58 g, 220 mmol) in toluene (250 ml). Heating under reflux for 1 hr using a Dean-Stark separator followed by evaporation, yielded a white solid which was recrystallised from hexane to afford (*R*)-2-benzylideneaminobutan-1-ol (**457** R=Et)(30.14 g, 77%) as colourless needles, m.p. 57-58°C; $[\alpha]_D^{20}$ +37.8° (c=1.0, CH_2Cl_2); (Found: C, 74.6; H, 8.8; N, 7.9. $C_{11}H_{15}NO$ requires C, 74.5; H, 8.5; N, 7.9 %); $\nu_{max.}$ (nujol) 3280 (OH), 1645 (CN) 1060, 1000, 780 and 705 cm^{-1}; δ_H (300 MHz) 8.2 (1H, s), 7.65 (2H, m), 7.35 (3H, m), 3.7 (2H, m), 3.15 (1H, m), 2.9 (1H, br s), 1.6 (2H, m), and 0.85 (3H, t); δ_C (75 MHz) 162.0 (CH), 135.8 (4^{ry}), 130.7 (CH), 128.5 (2 CH), 128.3 (2 CH), 74.7 (CH), 66.0 (CH_2), 25.0 (CH_2), and 10.7 (CH_3); m/z 177 (M^+, 15%), 176 (50), 146 (100), 132 (25), 118 (30), 104 (50), 91 (85), 77 (35) and 41 (60).

b) Preparation of (*S*)-2-benzylideneamino-3-methylbutan-1-ol (**457** R=Pr^i)

Using the procedure of *a*), but starting from 2-(*S*)-amino-3-methylbutan-1-ol (**392**)(14.6 g, 142 mmol), afforded after recrystallisation of the residue from hexane, (*S*)-2-benzylideneamino-3-methylbutan-1-ol (457 R=Pr^i)(21.1 g, 77%) as colourless crystals, m.p. 70-71°C (lit.[288] 71-72°C).

3. Preparation of (*R*)- and (*S*)-2-benzylamino alcohols

a) Preparation of (*R*)-2-benzylaminobutan-1-ol (**458** R=Et)

In the presence of hydrogen gas (12 l, 0.54 mol) a solution of (*R*)-2-benzylideneaminobutan-1-ol (**457** R=Et)(92.1 g, 0.52 mol) and 5% palladium / charcoal catalyst (3.0 g) in ethyl acetate (500 ml) was stirred vigorously at RT for 24 hr. The solution was then filtered though celite and evaporated to afford a waxy solid. Recrystallisation of this residue from hexane yielded

(*R*)-2-benzylaminobutan-1-ol (**458** R=Et)(71.6 g, 77%) as a colourless solid, m.p. 74-75°C; $[\alpha]_D^{20}$ –28.5° (c=1.0, CH_2Cl_2); (Found: C, 73.4; H, 9.6; N, 7.7. $C_{11}H_{17}NO$ requires C, 73.7; H, 9.6; N, 7.8%); ν_{max} (nujol) 3400-3000 (OH), 3280 (NH), 1060, 865, 745 and 700 cm^{-1}; δ_H (300 MHz) 7.3 (4H, m), 7.2 (1H, m), 3.8 and 3.62 (2H, AB pattern J_{AB} 13.7 Hz), 3.6 (1H, half of AB pattern of d, J_{AB} 10.3, J_{AX} 4.3Hz), 3.35 (1H, half of AB pattern of d, J_{AB} 10.3, J_{BX} 6 Hz), 2.6 (1H, m), 2.4 (2H, br s), 1.5 (2H, m) and 0.9 (3H, t); δ_C (75 MHz) 140.3 (4^{ry}), 128.5 (2 CH), 128.1 (2 CH), 127.1 (CH), 62.6 (CH_2), 59.8 (CH), 51.0 (CH_2), 24.2 (CH_2) and 10.4 (CH_3); m/z 179 (M^+, 1%), 148 (100), 106 (55), 91(100), 77(50), 65(75) and 56(70).

b) Preparation of (*S*)-2-benzylamino-3-methylbutan-1-ol (**458** R=Pr^i)

Using the procedure of *a*), but starting from (*S*)-2-benzylideneamino-3-methylbutan-1-ol (**457** R=Pr^i)(21.57 g, 0.113 mol), followed by kugelrohr distillation of the residue yielded (*S*)-benzylamino-3-methylbutan-1-ol (**458** R=Pr^i)(17.5 g, 80.3%) as a clear oil, b.p. 106-108°C / 2 torr (lit.[288] 103-107°C / 0.4 torr).

4. Preparation of (*R*)- and (*S*)-3,4-disubstituted thiazolidine-2-thiones

a) Preparation of (*R*)-3-benzyl-4-ethylthiazolidine-2-thione (**459** R=Et)

A procedure by Roth[307] was modified as follows; (*R*)-2-benzylaminobutan-1-ol (**458** R=Et)(8.0 g, 45 mmol), 2M sodium hydroxide (150 ml) and carbon disulphide (9.8 ml, 12.4 g, 163.1 mmol) were stirred together at RT for 20 hr. A further portion of carbon disulphide (5.0 ml, 6.3 g, 83 mmol) was added and the solution stirred for an additional 4 hr. The solution was extracted with CH_2Cl_2 and the organic layer washed with water, dried and evaporated to afford an orange residue. Recrystallisation from hexane / ethyl acetate (2:1), yielded (*R*)-3-benzyl-4-ethylthiazolidine-2-thione

(**459** R=Et)(7.7 g, 72%) as colourless crystals, m.p. 61-62°C; $[\alpha]_D^{20}$ +91.3° (c=1.0, CH_2Cl_2); (Found: C, 60.7; H, 6.1; N, 5.9. $C_{12}H_{15}NS_2$ requires C, 60.7; H, 6.4; N, 5.9%); $\nu_{max.}$ (nujol) 3060, 3040, 1475-1425, 1225, 1175, 1025 (CS), 760 and 700 cm^{-1}; δ_H (300 MHz) 7.3 (5H, m), 5.75 and 4.25 (2H, AB pattern, J_{AB} 17.1 Hz), 4.0 (1H, m), 3.35 (1H, half of AB pattern of d, J_{AB} 10.3, J_{AX} 7.7 Hz), 2.95 (1H, half of AB pattern of d, J_{AB} 10.3, J_{BX} 5.1 Hz), 1.65 (2H, m), and 0.9 (3H, t); δ_C (75 MHz) 197.0 (CS), 135.2 (4^{ry}), 128.8 (2 CH), 127.9 (CH), 127.7 (2 CH), 67.7 (CH), 50.1 (CH_2), 31.7 (CH_2), 24.1 (CH_2), and 9.2 (CH_3); m/z 237 (M^+, 15%), 148 (100), 132 (5), 121 (10), 104 (5), 91 (70), and 65 (25).

b) Preparation of (*S*)-3-benzyl-4-isopropylthiazolidine-2-thione (**459** R=Pr^i)

The same procedure as in *a*) starting from (*S*)-benzylamino-3-methylbutan-1-ol (**458** R=Pr^i)(20 g, 103.6 mmol), followed by recrystallisation of the product from hexane with a few drops of ethyl acetate and cooling (–20°C), afforded (*S*)-3-benzyl-4-isopropylthiazolidine-2-thione (**459** R=Pr^i)(9.17 g, 36%) as colourless crystals, m.p. 76-77°C (lit.[288] 77-78°C).

c) Preparation of (*S*)-3-thia-1-azabicyclo[3.3.0]octane-2-thione (**379**)

The same procedure as in *a*) starting from (*S*)-2-hydroxymethylpyrrolidine (**460**)(17.8 g, 175 mmol), with recrystallisation of the product from ethanol, yielded (*S*)-3-thia-1-azabicyclo[3.3.0]octane-2-thione (**379**)(13.6 g, 49%) as colourless crystals, m.p. 130-131°C; $[\alpha]_D^{20}$ –159.8° (c=1.0, CH_2Cl_2); (Found: C, 45.1; H, 5.5; N, 8.78. $C_6H_9NS_2$ requires C, 45.2; H, 5.7; N, 8.8%); ν_{max} (nujol) 1360, 1340, 1245, 1210, 1180, 1055, 1030 (CS), 940 and 850 cm^{-1}; δ_H (300 MHz) 4.65 (1H, m), 3.6 (1H, m), 3.45 (1H, m), 3.35 (2H, dd, J 1.6, 7.3 Hz), 2.5-2.3 (2H, m), 2.2 (1H,

m) and 1.8 (1H, m); δ_C (75 MHz) 191.1 (CS), 71.9 (CH), 46.3 (CH_2), 35.8 (CH_2), 31.4 (CH_2), and 28.8 (CH_2); m/z 159 (M^+, 70%), 126 (5), 118 (10), 85 (30), 72 (25), 67 (50), 45 (35) and 41 (100).

5. Preparation of (*R*)- and (*S*)-3,4-disubstituted thiazolidin-2-ones

a) Preparation of (*R*)-3-benzyl-4-ethylthiazolidin-2-one (**465** R=Et)

A solution of (*R*)-3-benzyl-4-ethylthiazolidine-2-thione (**459** R=Et)(1.24 g, 5.24 mmol), benzoic acid (0.64 g, 5.24 mmol) and benzyltriethylammonium bromide (0.23 g, 0.86 mmol) in CH_2Cl_2 (50 ml) was stirred vigorously for 3 hr at RT, in the presence of potassium permanganate (2.48 g, 15.72 mmol) and water (100 ml). Workup (see C. 3. *a*) gave a yellow oil which was kugelrohr distilled to afford (*R*)-3-benzyl-4-ethylthiazolidin-2-one (**465** R=Et)(0.88 g, 76%) as pale green oil, b.p. 215°C / 0.7 torr; $[\alpha]_D^{20}$ –26.1° (c=1.07, CH_2Cl_2); (Found: C, 65.6; H, 7.0; N, 6.6; m/z 221.0859. $C_{12}H_{15}NOS$ requires C, 65.1; H, 6.8; N, 6.3%; m/z 221.0874); ν_{max} (neat) 2970-2940, 1670 (CO), 1460, 1410, 1230, and 710 cm^{-1}; δ_H (300 MHz) 7.3 (5H, m), 4.9 and 4.0 (2H, AB pattern, J 15.2 Hz), 3.55 (1H, m), 3.25 (1H, half of AB pattern of d, J_{AB} 11, J_{AX} 7.7 Hz), 2.9 (1H, half of AB pattern of d, J_{AB} 11, J_{BX} 6 Hz), 1.75-1.5 (2H, m), and 0.87 (3H, t, J 7.4 Hz); δ_C (75 MHz) 171.9 (CO), 136.3 (4^{ry}), 128.6 (2 CH), 127.7 (2 CH), 127.5 (CH), 59.1 (CH), 46.3 (CH_2), 29.9 (CH_2), 24.4 (CH_2), and 8.6 (CH_3); m/z 221 (M^+, 90%), 192 (85), 165 (20), 122 (25), 104 (70), 91 (100) and 65 (80).

b) Preparation of (*S*)-3-benzyl-4-isopropylthiazolidin-2-one (**465** R=Pr^i)

The same procedure as in *a*) starting from (*S*)-3-benzyl-4-isopropylthiazolidine-2-thione (**459** R=Pr^i)(1.32 g, 5.24 mmol), afforded after kugelrohr distillation (*S*)-3-benzyl-4-isopropylthiazolidin-2-one (**465**

R=Pr^{i})(1.2 g, 43%) as a pale yellow solid, m.p. 33-35°C b.p. 185°C / 0.7 torr; $[\alpha]_D^{20}$ +34.0° (c=1.02, CH_2Cl_2); (Found: m/z 235.1026. $C_{13}H_{17}NOS$ requires m/z 235.1031); ν_{max} (neat) 3025, 2964, 1723, 1664 (CO), 1455, 1435, 1260, 1215, and 705 cm^{-1}; δ_H (300 MHz) 7.25 (5H, m), 5.1 and 3.9 (2H, AB pattern, J 17 Hz), 3.55 (1H, m), 3.1 (1H, half of AB pattern of d, J_{AB} 13, J_{AX} 9.5 Hz), 3.0 (1H, half of AB pattern of d, J_{AB} 13, J_{BX} 7 Hz), 2.2 (1H, m), 0.9 (3H, d, J 8.6 Hz) and 0.85 (3H, d, J 8.6 Hz); δ_C (75 MHz) 172.9 (CO), 135.9 (4^{ry}), 128.7 (2 CH), 128.0 (2 CH), 127.7 (CH), 62 (CH), 46.6 (CH_2), 28.1 (CH), 24.9 (CH_2), 18.2 (CH_3) and 14.5 (CH_3); m/z 235 (M^+, 15%), 192 (45), 176 (5), 133 (10), 105 (5), 91 (100) and 77 (5).

c) Preparation of (*S*)-3,4-dibenzylthiazolidin-2-one (**465** R=CH_2Ph)

The same procedure as in *a*) starting from (*S*)-3,4-dibenzylthiazolidine-2-thione (**459** R=CH_2Ph)(1.57 g, 5.24 mmol), afforded after kugelrohr distillation (*S*)-3,4-dibenzylthiazolidin-2-one (**465** R=CH_2Ph)(0.66 g, 45%) as an orange oil, b.p. 225°C./ 0.3 torr (lit.[288] m.p. 70-71°C).

d) Preparation of (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide (**468**)

Based on a procedure by Roussel,[308] a solution of (*S*)-3-thia-1-azabicyclo[3.3.0]octane-2-thione (**379**)(4.0 g, 25 mmol), acetone (110 ml), and methyl iodide (15.6 ml, 35.5 g, 250 mmol) was stirred for 16 hr at RT. The resulting precipitate was filtered off and washed with ether. The filtrate was concentrated and a second crop of the product filtered off and washed with ether. The solids were combined to yield (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide (**468**)(6.74 g, 90%) as a pale yellow powder, m.p. 111-112°C; $[\alpha]_D^{20}$ –256.5° (c= 1.66, CH_2Cl_2); (Found: C, 27.8; H, 3.9; N, 4.6. $C_7H_{12}INS_2$ requires C, 27.9; H, 4.0; N, 4.7%); ν_{max} (nujol) 1555 (C-N), 1300, 1200, 1170, (C-S) and 950 cm^{-1}; δ_H (300 MHz) 5.2

(1H, m), 3.87 (2H, m), 3.7 (1H, m), 3.55 (1H, m), 2.75 (3H, s), 2.45 (2H, m), and 2.2 (2H, m); δ_C (75 MHz) 186.8 (4^{ry}), 77.5 (CH), 49.3 (CH_2), 38.5 (CH_2), 29.5 (CH_2), 29.4 (CH_2), and 19.8 (CH_3); m/z 159 (M^+–MeI, 30%), 126 (5), 118 (10), 85 (30), 82 (10) and 67 (50).

e) Preparation of (*S*)-3-thia-1-azabicyclo[3.3.0]octan-2-one (**469**)

Based on a procedure by Roussel,[308] (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide (**468**)(22.58 g, 75 mmol), was added to a solution of sodium methoxide (75 mmol) in methanol (200 ml), and stirred for 16 hr at RT. Water (400 ml) was added and the mixture extracted with CH_2Cl_2. The combined organic layers were washed with water, dried and evaporated to yield a yellow solid. Recrystallisation of the residue from ether / ethyl acetate with cooling (–20°C), afforded (*S*)-3-thia-1-azabicyclo[3.3.0]octan-2-one (**469**)(8.37 g, 78%) as colourless crystals, m.p. 70-71°C; $[\alpha]_D^{20}$ –35.4° (c=1.0, CH_2Cl_2); (Found: C 50.1; H 6.3; N 9.6. C_6H_9NOS requires C 50.3; H 6.3; N 9.8%); ν_{max} (nujol) 3320, 1700 (CO), 1385, 930 and 890 cm^{-1}; δ_H (300 MHz) 4.25 (1H, m), 3.55 (1H, m), 3.4 (1H, half of AB pattern of d, J_{AB} 12, J_{AX} 8.6Hz), 3.25 (1H, half of AB pattern of d, J_{AB} 12, J_{BX} 10.3 Hz), 3.2 (1H, m), 2.3-2.0 (3H, m), and 1.6 (1H, m); δ_C (75 MHz) 169.8 (CO), 63.0 (CH), 43.3 (CH_2), 33.2 (CH_2), 30.8 (CH_2), and 27.2 (CH_2); m/z 143 (M^+, 30%), 114 (5), 85 (5), 80 (5), 74 (20), 70 (30) and 55 (100).

6. Preparation of (*R*)- and (*S*)-3,4-disubstituted thiazolidin-2-one 1,1-dioxides

a) Preparation of (*R*)-3-benzyl-4-ethylthiazolidin-2-one 1,1-dioxide (**455**)

i) A solution of (*R*)-3-benzyl-4-ethylthiazolidin-2-one (**465** R=Et)(1.16 g, 5.24 mmol), benzoic acid (0.64 g, 5.24 mmol) and benzyltriethylammonium bromide (0.23 g, 0.86 mmol) in CH_2Cl_2 (50 ml) was stirred vigorously for 3

hr at RT, in the presence of potassium permanganate (1.66 g, 10.48 mmol) and water (100 ml). For work up see C. 3. a. Evaporation gave a yellow solid which was recrystallised from ether / CH_2Cl_2 to afford (*R*)-3-benzyl-4-ethylthiazolidin-2-one 1,1-dioxide (**455**)(0.95 g, 72%) as colourless crystals, m.p. 102-103°C; $[\alpha]_D^{20}$ +47° (c=0.1, CH_2Cl_2); (Found: C, 56.75; H, 6.0; N, 5.5. $C_{12}H_{15}NO_3S$ requires C, 56.9; H, 6.0; N, 5.5%); ν_{max} (nujol) 3420, 1710 (CO), 1320 and 1140 (SO_2), 940, 850, 755 and 700 cm^{-1}; δ_H (300 MHz) 7.4 (4H, m), 7.25 (1H,m), 5.1 and 4.2 (2H, AB pattern, J 15.4 Hz), 3.7 (1H, m), 3.35 (1H, half of AB pattern of d, J_{AB} 13.7, J_{AX} 7.7 Hz), 3.15 (1H, half of AB pattern of d, J_{AB} 13.7, J_{BX} 4.3 Hz), 1.95 (1H, m), 1.85 (1H, m), and 0.9 (3H, t, 7.7 Hz). δ_C (75 MHz) 159.8 (CO), 133.4 (4^{ry}), 129.3 (2 CH), 128.8 (CH), 128.2 (2 CH), 51.3 (CH), 47.2 (2 CH_2), 24.6 (CH_2) and 8.7 (CH_3); m/z 189 (M^+–SO_2, 2%), 161 (2), 133 (50), 105 (30), 91 (100) and 77 (10).

ii) A solution of (*R*)-3-benzyl-4-ethylthiazolidine-2-thione (**459** R=Et)(1.24 g, 5.24 mmol), benzoic acid (0.64 g, 5.24 mmol) and benzyltriethylammonium bromide (0.23 g, 0.86 mmol) in CH_2Cl_2 (50 ml) was stirred vigorously for 15 hr at RT, in the presence of potassium permanganate (4.14 g, 26.2 mmol) and water (100 ml). For work up see C. 3. a. Recrystallisation of the residue from ether / CH_2Cl_2 afforded (*R*)-3-benzyl-4-ethylthiazolidin-2-one 1,1-dioxide (**455**)(0.95 g, 72%) as colourless crystals, m.p. 102-103°C, identical to that obtained above.

iii) Based on a procedure by Gaul,[309] a solution of (*R*)-3-benzyl-4-ethylthiazolidine-2-thione (**459** R=Et)(5.92 g, 25 mmol) and acetic acid (150 ml), was stirred and heated to 75°C. This was followed by dropwise addition of peroxyacetic acid (32%, 30 g, 125 mmol) over a period of 30 min. After an additional 30 min, hot filtration of the solution through a celite pad yielded a clear solution, which was again heated to 75°C. After a total of 2.5 hr the solution was allowed to cool to RT and then concentrated to 50 ml. Water (20 ml) was added and the solution heated to 100°C. Crystals precipitated upon

cooling and the product was recrystallised from ether / CH_2Cl_2 to afford (*R*)-3-benzyl-4-ethylthiazolidin-2-one 1,1-dioxide (**455**)(1.71 g, 27%) as pale yellow crystals, m.p. 102-103°C, identical to that obtained above.

b) Preparation of (*S*)-3-benzyl-4-isopropylthiazolidin-2-one 1,1-dioxide (**456**)

The above procedure (H. *6. a iii*) was followed using (*S*)-3-benzyl-4-isopropylthiazolidine-2-thione (**459** R=Pr^i)(6.28 g, 25 mmol). The solution was allowed to cool and then concentrated to 25 ml. Water (200 ml) was then added and the solution extracted with CH_2Cl_2. The combined organic layers were washed with saturated aqueous sodium carbonate (x 2) and water, dried and evaporated to yield a brown oil. Recrystallisation of the residue from ether / CH_2Cl_2 with cooling (–20°C) afforded (*S*)-3-benzyl-4-isopropylthiazolidin-2-one 1,1-dioxide (**456**)(2.18 g, 33%) as pale yellow needles, m.p. 114-115°C; $[\alpha]_D^{20}$ –39.6° (c= 1.02, CH_2Cl_2); (Found: C, 58.4; H, 6.4; N, 5.2. $C_{13}H_{17}NO_3S$ requires C, 58.4; H, 6.4; N, 5.2%); ν_{max} (nujol) 3420, 1720 (CO), 1325 and 1135 (SO_2), 760, 740 and 700 cm^{-1}; δ_H (300 MHz) 7.3-7.2 (5H, m), 5.1 and 4.2 (2H, AB pattern, J 15 Hz), 3.75 (1H, m), 3.25 (1H, half of AB pattern of d, J_{AB} 14, J_{AX} 8 Hz), 3.1 (1H, half of AB pattern of d, J_{AB} 14, J_{BX} 5.8 Hz), 2.4(1H, m) 0.89 (3H, d, J 7 Hz) and 0.85 (3H, d, J 7 Hz); δ_C (75 MHz) 160.7 (CO), 133.4 (4^{ry}), 129.2 (2 CH), 128.7 (CH), 128.2 (2 CH), 54.5 (CH), 47.1 (CH_2), 42.7 (CH_2), 27.4 (CH), 18.2 (CH_3) and 13.9 (CH_3); m/z 203 (M^+–SO_2, 15%), 160 (10), 133 (90), 105 (30), 91 (100) and 77 (5).

c) Preparation of (*S*)-3,4-dibenzylthiazolidin-2-one 1,1-dioxide (**453**)

i) The procedure and workup from H. 6 *.a. iii*) was used with (*S*)-3,4-dibenzylthiazolidine-2-thione (**459** R=CH_2Ph)(7.5 g, 25 mmol) to afford crystals upon cooling. The product was recrystallised from ether / CH_2Cl_2

with cooling (–20°C), to afford (*S*)-3,4-dibenzylthiazolidin-2-one 1,1-dioxide (**453**)(1.25 g, 16%) as colourless needles, m.p. 157-158°C (lit.[288] 143-144°C).

ii) A solution of (*S*)-3,4-dibenzylthiazolidine-2-thione (**459** R=CH_2Ph)(1.57 g, 5.24 mmol), benzoic acid (0.64 g, 5.24 mmol) and benzyltriethylammonium bromide (0.23 g, 0.86 mmol) in CH_2Cl_2 (75 ml) was stirred vigorously at RT, in the presence of potassium permanganate (2.48 g, 15.72 mmol) and water (150 ml). After stirring for 3 hours, additional benzoic acid (0.64 g, 5.24 mmol) and potassium permanganate (1.66 g, 10.44 mmol) was added and the mixture stirred for another 15 hr. Workup (see C. 3. a.) yielded a colourless solid. Recrystallisation of this from ether / CH_2Cl_2 with cooling (–20°C), afforded (*S*)-3,4-dibenzylthiazolidin-2-one 1,1-dioxide (**453**)(1.1 g, 67%) as colourless needles, m.p. 157-158°C, identical to the product obtained above.

d) Preparation of (*S*)-3-thia-1-azabicyclo[3.3.0]octan-2-one 3,3-dioxide (**378**)

i) A solution of (*S*)-3-thia-1-azabicyclo[3.3.0]octan-2-one (**469**)(1.5 g, 10.48 mmol), benzoic acid (1.28 g, 10.48 mmol) and benzyltriethylammonium bromide (0.46 g, 1.72 mmol) in CH_2Cl_2 (100 ml) was stirred vigorously for 15 hr at RT, in the presence of potassium permanganate (3.32 g, 20.96 mmol) and water (200 ml). Workup (see C. 3. a.), yielded a colourless solid. Recrystallisation from ether / CH_2Cl_2 afforded (*S*)-3-thia-1-azabicyclo[3.3.0]octan-2-one 3,3-dioxide (**378**)(1.27 g, 70%) as colourless crystals, m.p. 175-176°C; $[\alpha]_D^{20}$ +30.7° (c=0.104, DMSO); (Found: C, 41.1; H, 5.2; N, 7.95. $C_6H_9NO_3S$ requires C, 41.1; H, 5.2; N, 8.0%); ν_{max} (nujol) 3440, 1740 (CO), 1320 and 1130 (SO_2) and 1160 cm^{-1}; δ_H(CD_2Cl_2, 300 MHz) 3.95 (1H, m), 3.8(1H, dd, J 12.8, 5.5 Hz), 3.55 (2H, m), 3.1 (1H, dd, J.12.8, 9.3 Hz), 2.39 (1H, m), 2.2 (1H, m), 2.02 (1H, m) and 1.55 (1H, qd,

J 12, 8 Hz); δ_C (75 MHz) 157.7 (CO), 53.7 (CH_2), 52.6 (CH), 43.8 (CH_2), 32.3 (CH_2), and 23.4 (CH_2); m/z 111 (M^+-SO_2, 25%), 82 (10), 68 (80), 67 (100), 55 (70) and 53 (55).

ii) Following a procedure by Gaul,[309] a solution of (*S*)-3-thia-1-azabicyclo[3.3.0]octan-2-one (**469**)(7.15 g, 50 mmol) and acetic acid (50 ml), was stirred and heated to 75°C. This was followed by dropwise addition of peroxyacetic acid (32%, 23.77 g, 0.1 mol) over a period of 12 hr. After a total of 24 hr, THF (10-20 ml) was added to the hot solution until crystals precipitated, the mixture was then left overnight at 4°C. The solution was filtered to afford (*S*)-3-thia-1-azabicyclo[3.3.0]octan-2-one 3,3-dioxide (**378**)(3.22 g, 37%) as colourless needles, m.p. 175-176°C, identical to the product above.

Concentration of the solution and the addition of THF, precipitated a white solid, which was filtered off to afford (*S*)-pyrrolidine-2-methanesulphonic acid (**466**)(1.97 g, 24%) as a colourless powder, m.p. 260°C (dec.); $[\alpha]_D^{20}$ +31.2° (c=1.0, H_2O); (Found: C, 36.0; H, 6.6; N, 8.2. $C_5H_{11}NO_3S$ requires C, 36.4; H, 6.7; N, 8.5); ν_{max} (nujol) 2900-2400, 1377, 1172 and 1045 cm^{-1}; δ_H (CD_3SOCD_3, 300 MHz) 8.9 (1H, br s), 8.4 (1H, br s), 3.75 (1H, m), 3.15 (2H, m), 2.9 (1H, m), 2.87 (1H, d, J 1.9 Hz), 2.1 (1H, m), 1.9 (1H, m), 1.8 (1H, m) and 1.6 (1H, m); δ_C (CD_3SOCD_3, 75 MHz) 56.5 (CH), 51.8 (CH_2), 44.8 (CH_2), 29.8 (CH_2), and 22.7 (CH_2); m/z 165 (M^+, 5%), 157 (5), 122 (5), 111 (10), 97 (10), 84 (55) and 44 (90).

7. FVP of (*R*)- and (*S*)-3,4-disubstituted thiazolidin-2-one 1,1-dioxides

a) Flash vacuum pyrolysis of (*R*)-3-benzyl-4-ethylthiazolidin-2-one 1,1-dioxide (**455**)

The FVP of (*R*)-3-benzyl-4-ethylthiazolidin-2-one 1,1-dioxide (**455**)(0.10 g, 650°C, $1.0x10^{-3}$ torr, inlet 80°C), gave a yellow oil. The ^{13}C

and ^{1}H NMR spectra showed nine compounds to be present; Bibenzyl (6.7%), dibenzylurea (16.1%), but-1-ene (8.6%), 4-ethyl-2-phenyl-2-thiazoline (3.2%), 2-phenylthiazole (2.2%), toluene (2.7%), propanal (1.5%), benzaldehyde (1.2%) and *N*-benzylidenebenzylamine (3.3%). GC-MS analysis also showed benzonitrile (18.9%) to be present.

b) Flash vacuum pyrolysis of (*S*)-3-benzyl-4-isopropylthiazolidin-2-one 1,1-dioxide (**456**)

The pyrolysis of (*S*)-3-benzyl-4-isopropylthiazolidin-2-one 1,1-dioxide (**456**)(102.7 mg, 650°C, $1.0x10^{-3}$ torr, inlet 80-100°C) afforded a yellow oil in the cold trap. The ^{13}C and ^{1}H NMR spectra showed nine compounds to be present; bibenzyl (3.4%), dibenzylurea (5%), 3-methylbut-1-ene (5.5%), 4-isopropyl-2-phenyl-2-thiazoline (2.2%), 2-phenylthiazole (2.15%), benzaldehyde (0.9%), 2-methylpropanal (9.5%), toluene (1.2%) and *N*-benzylidenebenzylamine (7.4%). GC-MS analysis of the oil identified two additional products; benzonitrile (7.7%) and 4-isopropyl-2-phenylthiazole (1.5%).

c) Flash vacuum pyrolysis of (*S*)-3,4-dibenzylthiazolidin-2-one 1,1-dioxide (**453**)

The pyrolysis of (*S*)-3,4-dibenzylthiazolidin-2-one 1,1-dioxide (**453**)(117.9 mg, 650°C, $2.0x10^{-3}$ torr , inlet 70-90°C) afforded a yellow oil at the furnace exit and in the cold trap. The ^{13}C and ^{1}H NMR spectra showed the oil to contain seven products: bibenzyl (12%), dibenzylurea (7.5%), allyl benzene (17.9%), benzaldehyde (4.1%), 2-phenylthiazole (7.5%), 4-benzyl-2-phenyl-2-thiazoline (3.1%) and toluene (5.6%). GC-MS analysis of the oil identified one additional compound; benzonitrile (7.4%).

d) Flash vacuum pyrolysis of (*S*)-3-thia-1-azabicyclo[3.3.0]octan-2-one 3,3-dioxide (**378**)

The pyrolysis of (*S*)-3-thia-1-azabicyclo[3.3.0]octan-2-one 3,3-dioxide (**378**)(121.5 mg, 600°C, 1.0×10^{-3} torr, inlet 90-110°C) afforded a yellow oil in the cold trap. The ^{13}C and ^{1}H NMR spectra showed a number of compounds to be present, but identification proved inconclusive (see discussion).

8. FVP product synthesis for (*R*)- and (*S*)-3,4-disubstituted thiazolidin-2-one 1,1-dioxides

a) Preparation of thiobenzamidoacetaldehyde dimethyl acetal (**499**)

Based on a procedure by Lawson and Searle,[310] *S*-(thiobenzoyl)thioglycolic acid (19.08 g, 90 mmol), sodium hydroxide (3.6 g, 90 mmol) and water (100 ml) were added together. The solution was stirred for 10 min at RT, then aminoacetaldehyde dimethyl acetal (10 g, 10.36 ml, 95 mmol) was added and the solution stirred until the colour changed from red to orange (10 min). The solid was filtered off, washed with water and recrystallised from ethyl acetate to afford thiobenzamidoacetaldehyde dimethyl acetal (**499**)(17.52 g, 87%) as orange crystals, m.p. 77-78°C; (Found: C, 58.6; H, 6.8; N, 6.2. $C_{11}H_{15}NO_2S$ requires C, 58.6; H, 6.7; N, 6.2%); ν_{max} (nujol) 3325 (NH), 1380, 1340, 1325, 1300, 1220, 1120, 1050, 990, 785 and 700 cm^{-1}; δ_H (300 MHz) 7.85 (1H, br s), 7.6 (2H, m), 7.4 (3H, m), 4.65 (1H, t, J 7 Hz), 4.0 (2H, t, J 7.5 Hz), and 3.45 (6H, s); δ_C (75 MHz) 199.6 (CS), 141.6 (4^{ry}), 131.1 (CH), 128.4 (2 CH), 126.7 (2 CH), 101.4 (CH), 54.7 (2 CH_3) and 47.9 (CH_2); m/z 225 (M^+, 15%), 194 (10), 160 (10), 121 (55), 88 (100) and 77 (30).

b) Preparation of 2-phenylthiazole (**500**)

Based on the procedure by Lawson and Searle,[310] polyphosphoric acid (40 ml) was heated to 180°C and thiobenzamidoacetaldehyde dimethyl acetal (**499**)(12 g, 52 mmol) was added slowly to the stirred solution. After 1 hr the solution was cooled, diluted with water and made alkaline with sodium hydroxide (pH 8.0). The aqueous solution was extracted with ether and evaporated to afford a brown oil. Kugelrohr distillation yielded 2-phenylthiazole (**500**)(2.1 g, 25%) as a colourless oil b.p. 160°C / 1.0 torr (lit.[310] 267-9°C); δ_H (300 MHz) 7.95 (2H, m), 7.8 (1H, d, J 3.2 Hz), 7.35 (3H, m) and 7.25 (1H, d, J 3.3 Hz); δ_C (75 MHz) 168.2 (4^{ry}), 143.6 (CH), 133.5 (4^{ry}), 129.9 (CH), 128.9 (2 CH), 126.5 (2 CH) and 118.7 (CH).

c) Preparation of 3-methylbut-1-ene

The FVP of isoamylacetate (2.5 g, 19 mmol, 750°C, 7.0×10^{-3} torr, inlet 0°C) afforded 3-methylbut-1-ene (0.2 g, 15%), δ_H (300 MHz) 5.85 (1H, m), 4.9 (2H, m), 2.3 (1H, m) and 1.0 (6H, d, J 8 Hz); δ_C (75 MHz) 146.0 (CH), 111.1 (CH_2), 32.0 (CH) and 22.0 (2 CH_3).

d) Preparation of *N*-benzylidenebenzylamine

The procedure by Freifelder[306] was modified as follows; benzaldehyde (5.43 g, 51.2 mmol) was added to a stirred solution of benzylamine (5.48 g, 51.2 mmol) in toluene (150 ml). Heating under reflux for 1 hr using a Dean-Stark separator followed by evaporation of the solution, afforded a yellow oil which was kugelrohr distilled to yield *N*-benzylidenebenzylamine (9.0 g, 90%) as a colourless oil, b.p. 175°C / 0.5 torr (lit.[311] b.p. 200-202 / 10-20 torr); δ_H (200 MHz) 8.25 (1H, s), 7.7 (2H, m), 7.35-7.1 (8H, m) and 4.7 (2H, s); δ_C (50 MHz) 162.6 (CH), 140.1 (4^{ry}), 136.9 (4^{ry}), 131.4 (CH), 129.3 (2 CH), 129.2 (2 CH), 129.0 (2 CH), 128.7 (2 CH), 127.7 (CH) and 65.6 (CH_2).

e) Flash vacuum pyrolysis of benzylisocyanate

The FVP of benzylisocyanate (0.2 g, 650°C, $1.0x10^{-3}$ torr,inlet 0°C, inert packing in the furnace tube) produced no change in the starting compound. Upon standing overnight the liquid solidified to afford dibenzylurea (0.18 g, 99%), δ_C (75 MHz, CD_3SOCD_3) 158.1 (CO), 140.7 (2 4^{ry}), 128.1 (4 CH), 126.9 (4 CH), 126.5 (2 CH) and 42.9 (2 CH_2); δ_H (300 MHz) 7.4-7.1 (10H, m), 6.5 (2H, br s) and 4.25 (4H, d, J 4 Hz).

f) Preparation of 4-ethyl-2-phenylthiazole (**505**)

Based on a method by Asinger, Thiel and Schroder,[312] (*R*)-4-ethyl-2-phenyl-2-thiazoline (**389**)(1.99 g, 10.44 mmol) and elemental sulphur (0.67 g, 20.96 mmol) were mixed together and heated to 200-210°C for 30 min. The reaction was placed under vacuum (water pump) and left heating at 200°C for an additional 2 hr. The solution was cooled and diluted with ether (20 ml), filtered, concentrated and diluted with ether (20 ml) again. Filtration and evaporation afforded an oil which was kugelrohr distilled to yield 4-ethyl-2-phenylthiazole (**505**)(1.6 g, 81%) as a red oil, b.p. 165°C / 1.0 torr; (Found: C, 69.7; H, 5.8; N, 7.6; m/z 189.0620. $C_{11}H_{11}NS$ requires C, 69.8; H, 5.9; N, 7.4; m/z 189.0612); ν_{max} (neat) 1520, 1500, 1460, 1440, 770 and 700 cm^{-1}; δ_H (300 MHz) 7.9 (2H, m), 7.4 (3H, m), 6.8 (1H, s), 2.9 (2H, q) and 1.3 (3H, t, J 7 Hz); δ_C (75 MHz) 167.5 (4^{ry}), 160.1 (4^{ry}), 133.9 (4^{ry}), 129.7 (CH), 128.8 (2 CH), 126.4 (2 CH), 112.1 (CH), 25.0 (CH_2) and 13.4 (CH_3); m/z 189 (M^+, 90%), 188 (100), 174 (50), 161 (25), 121 (35), 104 (60), 85 (80), 77 (70) and 71 (90).

g) Preparation of 4-isopropyl-2-phenylthiazole (**504**)

The procedure of *f)* starting from (*S*)-4-isopropyl-2-phenyl-2-thiazoline (**388**)(2.14 g, 10.44 mmol), followed by kugelrohr distillation yielded 4-isopropyl-2-phenylthiazole (**504**)(1.14 g, 54%) as a yellow oil, b.p. 125°C /

0.1 torr; (Found: m/z 203.0763. $C_{12}H_{13}NS$ requires m/z 203.0769); ν_{max} (neat) 1513, 1499, 1458, 1002, 764 and 689 cm^{-1}; δ_H (300 MHz) 8.0 (2H, m), 7.4 (3H, m), 6.85 (1H, s), 3.15 (1H, m) and 1.4 (6H, d, J 8 Hz); δ_C (75 MHz) 167.3 (4^{ry}), 164.8 (4^{ry}), 134.0 (4^{ry}), 129.7 (CH), 128.8 (2 CH), 126.5 (2 CH), 110.9 (CH), 31.1 (CH) and 22.4 (2 CH_3); m/z 203 (M^+, 80%), 188 (80), 104 (80), 85 (80), 77 (90) and 45 (100).

h) Preparation of 4-benzyl-2-phenylthiazole (**503**)

The procedure of *f*) starting from (*S*)-4-benzyl-2-phenyl-2-thiazoline (**387**)(2.66 g, 10.44 mmol), followed by kugelrohr distillation yielded 4-benzyl-2-phenylthiazole (**503**)(1.39 g, 53%) as a yellow oil, b.p. 250°C / 4.0 torr; (Found: m/z 251.0778. $C_{16}H_{13}NS$ requires m/z 251.0769); ν_{max} (neat) 1520, 1500, 1460, 1440, 775, 730 and 705 cm^{-1}; δ_H (300 MHz) 7.9 (2H, m), 7.35 (8H, m), 6.7 (1H, s) and 4.2 (2H, s); δ_C (75 MHz) 167.5 (4^{ry}), 157.5 (4^{ry}), 139.0 (4^{ry}), 133.9 (4^{ry}), 129.8 (CH), 129.1 (2 CH), 128.8 (2 CH), 128.5 (2 CH), 126.5 (2 CH), 126.4 (CH), 114.3 (CH) and 38.0 (CH_2); m/z 251 (M^+, 60%), 147 (45), 122 (35), 115 (45), 104 (15) and 77 (15).

i) Preparation of 3,4-dihydro-5-methyl-2*H*-pyrrole (**498**)

The title compound was prepared using the method of Lindblom *et al.*[313] An ethereal solution of methyllithium (1.4 M, 37.5 ml, 50 mmol) was cooled to –20°C and a solution of *N*-vinylpyrrolidin-2-one (5.0 g, 45 mmol) dissolved in ether (50 ml) was added dropwise over a period of 2 min. The mixture was stirred for a further 2 min at –20°C and then 1M hydrochloric acid (70 ml) was added and the mixture stirred for an additional 2 min. The organic layer was separated and extracted with dilute hydrochloric acid, the combined aqueous layers were washed with ether and then treated with sodium hydroxide until pH 10. The imine was extracted with CH_2Cl_2 and the extracts combined, dried, evaporated and kugelrohr distilled to afford 3,4-dihydro-5-

methyl-2*H*-pyrrole (**498**)(1.83 g, 49%) as a colourless oil, b.p. 50°C / 14 torr (lit.[313] b.p. 103-105°C); δ_C (75 MHz) 174.7 (4ry), 61.1 (CH_2), 38.7 (CH_2), 23.0 (CH_2) and 19.7 (CH_3).

9. Attempted photolysis of (*R*)- and (*S*)-3,4-disubstituted thiazolidin-2-one 1,1-dioxides

a) Attempted photolysis of (*S*)-3-thia-1-azabicyclo[3.3.0]octan-2-one 3,3-dioxide (**378**)

A few milligrams of (*S*)-3-thia-1-azabicyclo[3.3.0]octan-2-one 3,3-dioxide (**378**) was placed in a dry NMR tube, dissolved in d_6-acetone / TMS and irradiated for 4.5 hr. Analysis of the solution by NMR showed no change in the starting material and the photolysis reaction was allowed to continue. After a further 10 days of irradiation there was still no change in the starting material.

b) Attempted photolysis of (*R*)-3-benzyl-4-ethylthiazolidin-2-one 1,1-dioxide (**455**)

The procedure of *a*) starting with (*R*)-3-benzyl-4-ethylthiazolidin-2-one 1,1-dioxide (**455**), resulted after 10 days of irradiation, in no change in the starting material.

c) Attempted photolysis of (*S*)-3,4-dibenzylthiazolidin-2-one 1,1-dioxide (**453**)

The procedure of *a*) starting with (*S*)-3,4-dibenzylthiazolidin-2-one 1,1-dioxide (**453**) led after 24 hr, to a small orange crystal appearing and after 10 days no further change resulted. The majority of the starting material was found to have remained unchanged and the orange crystal was found to be 2-benzylamino-3-phenyl-1-propanesulphonic acid (**481**); (Found: C, 61.7; H, 6.4; N, 4.5. $C_{16}H_{19}NO_3S$ requires C, 62.9; H, 6.3; N, 4.6. $C_{16}H_{19}NO_3S$•0.4

H_2O requires C, 61.5; H, 6.4; N, 4.5%); δ_C (CD_3SOCD_3, 75 MHz) 136.0 (4^{ry}), 132 (4^{ry}), 129.5 (2 CH), 129.3 (2 CH), 129.0 (CH), 128.8 (2 CH), 128.6 (2 CH), 127.0 (CH), 56.5 (CH), 48.8 (CH_2), 47.5 (CH_2) and 35.2 (CH_2). Other spectroscopic properties (^1H NMR, IR, MS) in agreement with previous work.[288]

d) Attempted photolysis of *i)* (*S*)-3-thia-1-azabicyclo[3.3.0]octan-2-one 3,3-dioxide (**378**), *ii)* (*R*)-3-benzyl-4-ethylthiazolidin-2-one 1,1-dioxide (**455**) and *iii)* (*S*)-3,4-dibenzylthiazolidin-2-one 1,1-dioxide (**453**) in acetonitrile

Using a method used by Sousa,[314] the thiazolidin-2-one 1,1-dioxides (50 mg) were dissolved in a solution of *t*-butanol / acetonitrile (4.5 ml, 6:1 v/v) and irradiated for 53 hr. Analysis by NMR showed no change in the starting material, in each case.

e) Attempted photolysis of *i)* (*S*)-3-thia-1-azabicyclo[3.3.0]octan-2-one 3,3-dioxide (**378**), *ii)* (*R*)-3-benzyl-4-ethylthiazolidin-2-one 1,1-dioxide (**455**), *iii)* (*S*)-3-benzyl-4-isopropylthiazolidin-2-one 1,1-dioxide (**456**) and *iv)* (*S*)-3,4-dibenzylthiazolidin-2-one 1,1-dioxide (**453**) in the presence of acetophenone

The thiazolidin-2-one-1,1-dioxides (0.10 g), CH_2Cl_2 (5 ml) and one drop of acetophenone were added to a quartz tube under N_2 and the solutions irradiated for 24 hr and then evaporated.

i) Starting from (*S*)-3-thia-1-azabicyclo[3.3.0]octan-2-one 3,3-dioxide (**378**), NMR analysis of the residue showed no change from the starting material after 24 hr. The sample was irradiated for a further 7 days and a black residue precipitated out of solution. The solution was decanted off the residue and then evaporated to afford a brown solid (71 mg) which was

identified as the starting material. The black residue was shown by NMR to be (*S*)-pyrrolidine-2-methanesulphonic acid (**466**).

ii) Starting from (*R*)-3-benzyl-4-ethylthiazolidin-2-one 1,1-dioxide (**455**), NMR analysis of the residue showed the starting material and <5% of a new compound. The sample was irradiated for a further 7 days and a black residue precipitated out of solution. The solution was decanted off the residue and then evaporated to afford a brown solid (70.1 mg) which was identified as the starting material. Identification of the black residue has proved inconclusive.

iii) Starting from (*S*)-3-benzyl-4-isopropylthiazolidin-2-one 1,1-dioxide (**456**), NMR analysis of the residue showed no change from the starting material. The sample was irradiated for a further 7 days and a brown residue precipitated out of solution. The solution was decanted off the residue and then evaporated to afford a brown solid (90 mg) which was identified as the starting material. Identification of the black residue has proved inconclusive.

iv) Starting from (*S*)-3,4-dibenzylthiazolidin-2-one 1,1-dioxide (**453**), NMR analysis of the residue showed the starting material and <5% of 2-benzylamino-3-phenyl-1-propanesulphonic acid (**481**). The sample was irradiated for a further 7 days and a brown residue precipitated out of solution. The solution was decanted off the residue and then evaporated to afford a brown solid (81.3 mg) which was identified as the starting material. The brown residue was shown to be 2-benzylamino-3-phenyl-1-propanesulphonic acid (**481**).

I. Kinetic resolution of secondary alcohols

1. Preparation of (±)-alkoxides

a) Preparation of sodium 1-phenylethoxide, sodium 1-phenyl-1-propoxide, sodium 1-phenyl-2-propoxide and sodium 3,3-dimethyl-2-butoxide

Under a N_2 atmosphere the alcohol (13.3 mmol) and sodium metal (1.15 g, 50 mmol) were added to dry toluene (15 ml) and heated under reflux for 8 hr. The solution was allowed to cool, the excess sodium was removed and the solution used immediately.

b) Potassium 1-phenylethoxide

Using the same conditions as above but with potassium metal, potassium 1-phenylethoxide was prepared and used immediately.

c) Preparation of lithium 1-phenylethoxide

A solution of toluene and 1-phenylethanol was cooled to –78°C under N_2 and n-butyl lithium in hexane (1.05 eq.) was added slowly. The solution was used immediately.

2. Preparation of (*S*)-2,2-dialkoxy-3-thia-1-azabicyclo[3.3.0] octanes

a) Preparation of (*S*)-2,2-dimethoxy-3-thia-1-azabicyclo[3.3.0]octane (**470**)

Following a procedure by Roussel,[308] (*S*)-2-methylthio-3-thia-1λ⁴-azabicyclo[3.3.0]oct-1-enium iodide (**468**) (see H. 5. *d*) (7.53 g, 25 mmol), was added to a solution of sodium methoxide (100 mmol) in methanol (250 ml) and the mixture stirred for 16 hr at RT. Water (400 ml) was added and the medium extracted with CH_2Cl_2. The combined organic layers were dried and the solvent evaporated to yield a yellow oil. Kugelrohr distillation afforded (*S*)-2,2-dimethoxy-3-thia-1-azabicyclo[3.3.0]octane (**470**)(3.09 g, 65%) as a yellow oil, b.p. 160-170°C with a small amount (*S*)-3-thia-1-azabicyclo[3.3.0]octane-2-one present; ν_{max} (neat) 3500-3400, 2960, 1700, 1450, 1390, 1200-1150, 1080, 1050 and 915 cm^{-1}; δ_H (300 MHz) 3.85 (1H, m), 3.45 (3H, s), 3.35 (3H, s), 3.2-3.0 (2H, m), 3.0-2.8 (2H, m), 2.2 (1H, m),

1.9 (2H, m) and 1.65 (1H, m); δ_C (75 MHz) 131.7 (4^{ry}), 66.3 (CH), 53.3 (CH_3), 50.6 (CH_3), 47.0 (CH_2), 37.8 (CH_2), 30.7 (CH_2) and 23.6 (CH_2); m/z 189 (M^+, 10%), 174 (15), 158 (20), 142 (15), 128 (80), 82 (30) and 42 (100).

b) Preparation of (*S*)-2,2-diethoxy-3-thia-1-azabicyclo[3.3.0]octane (**511**)

The procedure of *a*) using a solution of sodium ethoxide (100 mmol) in ethanol (250 ml), afforded after evaporation an oil containing two compounds; (*S*)-3-thia-1-azabicyclo[3.3.0]octane-2-one (**469**) (minor) and (*S*)-2,2-diethoxy-3-thia-1-azabicyclo[3.3.0]octane (**511**) (major) (5.4 g) as a yellow oil; δ_C (75 MHz) 130.9 (4^{ry}), 66.2(CH), 61.6 (CH_2), 59.1 (CH_2), 47.3 (CH_2), 38.0 (CH_2), 30.9 (CH_2), 23.5 (CH_2), 15.0 (CH_3) and 14.96 (CH_3).

c) Preparation of (*S*)-2,2-di(1-phenylethoxy)-3-thia-1-azabicyclo[3.3.0] octane (**512**)

The procedure of *a*) using a solution of sodium 1-phenylethoxide (100 mmol) in CH_2Cl_2 (250 ml), gave a crude mixture shown by ^{13}C NMR to contain (*S*)-3-thia-1-azabicyclo[3.3.0]octane-2-one (**469**) and (*S*)-2,2-di(1-phenylethoxy)-3-thia-1-azabicyclo[3.3.0]octane (**512**); δ_C (75 MHz) 133.0 (4^{ry}), 128.6-124.5 (12 CH), 69.954 (CH), 69.907 (CH), 47.62 (CH), 38.95 (CH_2), 29.98 (CH_2), 25.29 (2 CH_3), 24.84 (CH_2) and 15.99 (CH_2).

d) Preparation of (*S*)-2,2-di(1-phenylethoxy)-3-thia-1-azabicyclo[3.3.0] octane (**512**) in acetonitrile

To a solution of sodium 1-phenylethoxide (100 mmol) in acetonitrile (50 ml), (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide (**468**)(7.53 g, 25 mmol) was added and the reaction was stirred for 3 hr at RT. Pet ether was added and the reaction filtered to afford a solid. The 1-phenylethanol from the solid was purified according to I. 7. *a*) and the $[\alpha]_D^{20}$ was found to be zero. The filtrate was evaporated to afford a crude amber oil

(9.85 g) which GC-MS showed to contain (*S*)-2,2-di(1-phenylethoxy)-3-thia-1-azabicyclo[3.3.0] octane (**512**), 1-phenylethanol and a small amount of (*S*)-3-thia-1-azabicyclo[3.3.0]octane-2-one (**469**).

3. Preparation of α-substituted (*S*)-hydroxymethylpyrrolidines

a) Preparation of (*S*)-2-(diphenylhydroxymethyl)pyrrolidine (**525**)

Following a procedure Mathre *et al.*,[315] a suspension (*S*)-proline (57.5 g, 0.5 mol) in dry THF (600 ml) was cooled to 15°C and stirred vigorously. A solution of trichloromethyl chloroformate (59.35 g, 36.2 ml, 0.3 mol) in toluene (300 ml) was added dropwise to the cooled mixture over a period of 1 hr and after complete addition the solution was heated to 40°C for 2 hr and then cooled to 15°C. While maintaining the temperature at 15°C the solution was concentrated to 100 ml and then redissolved in dry THF (600 ml). Cooling the solution further to 0°C, dry triethylamine (53 g, 0.53 mol) was added slowly and the reaction stirred for 1 hr. The solution was filtered and the solid washed with dry THF (3x100 ml). The filtrate was then added dropwise to a solution of phenylmagnesium chloride (1.5 mol) in dry THF (750 ml) cooled to –15°C, over a period of 1 hr.. After addition, the reaction was stirred for 3 hr at –15°C and a further 1 hr at 0°C and then quenched in a cooled (0°C) solution of 2M H_2SO_4 (1.0 l, 2.0 mol). The mixture was stirred for 1 hr, filtered and the solid washed with THF (3x500 ml), the filtrate was then concentrated to 1 l, cooled (0-5°C) for 16 hr and filtered. The resulting solid was washed with water (2x100 ml), ethyl acetate (3x175 ml) and dried under vacuum to afford the sulphate salt (49.84 g). The sulphate salt (30.2 g, 50 mmol) was then added to a solution of THF (100 ml) and 2M sodium hydroxide (100 ml) and stirred at RT until all the solid had dissolved. The mixture was then diluted with toluene (400 ml), filtered and the organic layer separated and washed with water. Evaporation of the solvent afforded an oil which crystallised on standing. Recrystallisation from hexane gave (*S*)-2-

(diphenylhydroxymethyl)pyrrolidine (**525**)(21.62 g, 85%) as pale yellow crystals, m.p. 72-73°C and $[\alpha]_D^{20}$ –39.3 (c=0.73, MeOH) (lit.[315] m.p. 79-79.5°C and $[\alpha]_D^{24}$ –58.8 (c=3.0, MeOH)).

b) Preparation of (*S*)-2-(2-hydroxy-2-propyl)pyrrolidine (**530**)

The above procedure was used with (*S*)-proline (23.8, 0.25 mol) and methylmagnesium iodide (750 mmol), to afford (*S*)-2-(2-hydroxy-2-propyl)pyrrolidine (**530**)(1.3 g, 4%) as a colourless semi solid, b.p. 109°C / 0.6 torr and $[\alpha]_D^{20}$ –31° (c=0.78, CH_3OH) (lit.[316] $[\alpha]_D^{18}$ –93.4° (c=2.987, CH_3OH)).

c) Preparation of 2-(*S*)-[(*R*)-α-hydroxybenzyl]pyrrolidine (**526**)

Following a method by Soai,[317] (*S*)-proline (23 g, 0.2 mol) was added to a cooled (0°C) suspension of phosphorus pentachloride (41.66 g, 0.2 mol) in CH_2Cl_2 (600 ml) and stirred for 12 hr, allowing the solution to warm up to RT. The solvent was evaporated and the residue dried under vacuum at RT (2 torr) for 5 hr. Dry benzene (600 ml) and aluminium chloride (80.0 g, 0.6 mol) were then added to the residue and the mixture heated under reflux for 12 hr. After cooling to RT the mixture was quenched with an ice cooled 1M HCl (300 ml) solution and then the aqueous phase separated and washed with ethyl acetate. With continued agitation the aqueous layer was neutralised with sodium carbonate, until a thick solid precipitated out of solution. The resulting viscous mixture was first extracted with CH_2Cl_2 (3 x) and then filtered. The filter cake was then thoroughly washed with CH_2Cl_2. The extracts were combined with the filtrate, washed with water and dried for 1 hr. The dried organic layer was concentrated (400 ml), methanolic hydrogen chloride (300 ml) was added and the resulting red solution evaporated to give a dark red oil. The residue was weighed and redissolved in ethanol (200 ml), which was then cooled to 0°C. Sodium borohydride (3 eq.) was slowly added

to the stirred solution over a period of 1 hr with warming of the mixture to RT. After 16 hr, the mixture was quenched with 3M HCl and concentrated to remove the ethanol. The aqueous layer was washed with ethyl acetate and then made alkaline with solid sodium hydroxide. The alkaline solution was extracted with CH_2Cl_2 which was dried and evaporated to yield a brown oil which was kugelrohr distilled to provided 2-(*S*)-[(*R*)-α-hydroxybenzyl]pyrrolidine (**526**)(13.8 g, 39 %) as a yellow oil, b.p. 190°C / 2 torr and 89.2% d.e. (lit.[317] b.p. 170°C / 3 torr and 92% d.e.).

4. Preparation of bicyclic carbamates

a) Preparation of (*S*)-3-oxa-1-azabicyclo[3.3.0]octan-2-one (**520**)

Based on a method by Kaneko,[318] (*S*)-prolinol (**460**)(5.0 g, 50 mmol) was dissolved in a mixture of water (85 ml) and 40% aqueous potassium hydroxide (12.5 ml) and cooled to –5°C. A solution of phosgene in toluene (1.93 M, 6.53 g, 34.2 ml, 66 mmol) was added concurrently with a solution of 40% aqueous potassium hydroxide (25 ml) over a period of 15 min and the resulting mixture allowed to warm up to RT. After 16 hr the reaction was extracted with CH_2Cl_2 and the combined organic layers washed with water and dried. Evaporation and kugelrohr distillation afforded (*S*)-3-oxa-1-azabicyclo[3.3.0]octan-2-one (**520**)(3.33 g, 52%) as clear oil, b.p. 165°C / 0.2 torr; $[\alpha]_D^{20}$ –34.3° (c=1.06, CH_2Cl_2); (Found: C, 55.9; H, 7.2; N, 11.3; m/z 127.0629. $C_6H_9NO_2$ requires C, 56.7; H, 7.1; N, 11.0%; m/z 127.0633); ν_{max} (neat) 3480-3370, 1750 (CO), 1400, 1230, 1080, 1050, 990 and 780cm^{-1}; δ_H (300 MHz) 4.52 (1H, half AB pattern of d, J_{AB} 8.9, J_{AX} 7.9 Hz), 4.18 (1H, half AB pattern of d, J_{AB} 8.9, J_{BX} 3.5), 3.92 (1H, m), 3.61 (1H, m), 3.18 (1H, m), 2.14-1.86 (3H, m) and 1.48 (1H, m); δ_C (75 MHz) 161.73 (CO), 67.85 (CH_2), 59.45 (CH), 45.8 (CH_2), 30.7 (CH_2) and 25.7 (CH_2); m/z 127 (M^+, 60%), 99 (40), 97 (50), 90 (70), 69 (70) and 55 (100).

b) Preparation of (*S*)-3-oxa-1-azabicyclo[3.3.0]octane-2-thione (**521**)

Based on a method by Sharma,[319] a stirred solution of triethylamine (10.12 g, 14 ml, 0.1 mol) and (*S*)-prolinol (**460**)(5.0 g, 50 mmol) in CH_2Cl_2 (250 ml), was cooled down to 0°C and a solution of thiophosgene (7.59 g, 5.03 ml, 66 mmol) in CH_2Cl_2 (100 ml) was added dropwise. The solution was allowed to warm up to RT and stirred overnight. The mixture was then washed with water (2 x) and 0.5 M sodium hydroxide, dried and evaporated to afford a black oil (6.49 g). Column chromatography of this on alumina using ether as the eluant gave a yellow semi solid which was recrystallised from ethanol with cooling (–20°C) overnight to afford (*S*)-3-oxa-1-azabicyclo[3.3.0]octane-2-thione (**521**)(3.11 g, 43%) as colourless crystals, m.p. 58-59°C; $[\alpha]_D^{20}$ +69° (c=1.02, CH_2Cl_2); (Found: C, 50.3; H, 6.4; N, 9.8. C_6H_9NOS requires C, 50.3; H, 6.3; N, 9.8%); ν_{max} (nujol) 2980-2860, 1510-1450, 1350, 1250, 1140 (CS), 740 and 650 cm^{-1}; δ_H (300 MHz) 4.78 (1H, m), 4.35-4.24 (2H, m), 3.83 (1H, m), 3.46 (1H, m), 2.29-2.08 (3H, m) and 1.60 (1H, m); δ_C (75 MHz) 189.5 (CS), 73.2 (CH_2), 63.1 (CH), 47.5 (CH_2), 30.8 (CH_2) and 26.6 (CH_2); m/z 143 (M^+, 100%), 83 (40), 68 (45), 55 (80) and 41 (65).

c) Preparation of (*S*)-4,4-diphenyl-3-oxa-1-azabicyclo[3.3.0]octane-2-thione (**529**)

The procedure of *b*) starting from 2-(*S*)-(diphenylhydroxymethyl)pyrrolidine (**525**)(12.65 g, 50 mmol), gave a black oil (14.04 g) which upon column chromatography on alumina using ether as the eluant gave a dark orange oil. This was crystallised from acetonitrile to afford (*S*)-4,4-diphenyl-3-oxa-1-azabicyclo[3.3.0]octane-2-thione (**529**)(7.51 g, 51%) as yellow crystals, m.p. 110-111°C; $[\alpha]_D^{20}$ –44.6° (c=0.936, CH_2Cl_2); (Found: C, 73.3; H, 5.4; N, 4.7. $C_{18}H_{17}NOS$ requires C, 73.2; H, 5.8; N, 4.7%); ν_{max} (nujol) 1742, 1673, 1365, 1328, 1286, 1254, 1173, 920, 895,

795, 761 and 698 cm^{-1}; δ_H (300 MHz) 7.5-7.2 (10H, m), 4.87 (1H, dd, J 10.4, 5.8 Hz), 3.8 (1H, m), 3.5 (1H, m), 2.1 (2H, m), 1.9 (1H, m) and 1.2 (1H, m); δ_C (75 MHz) 187.2 (CS), 141.8 (4^{ry}), 139.4 (4^{ry}), 128.6 (2 CH), 128 56 (CH), 128.5 (2 CH), 128.0 (CH), 126.2 (2 CH), 126.0 (2 CH), 93.1 (4^{ry}), 72.2 (CH), 47.4 (CH_2), 28.7 (CH_2) and 26.6 (CH_2); m/z 295 (M^+, 45%), 234 (20), 198 (100), 165 (55), 113 (15) and 77 (15).

d) Preparation of (*S*)-3-thia-1-azabicyclo[3.3.0]octane-2-thione (**379**)

To a suspension of phosphorus pentasulphide (2.44 g, 11 mmol) and CH_2Cl_2 (30 ml), (*S*)-3-thia-1-azabicyclo[3.3.0]octan-2-one (**469**)(1.65 g, 11.5 mol) was added and the solution heated under reflux for 20 hr. The solution was filtered and washed with 2M sodium hydroxide (x2) and water, dried and evaporated to afford (*S*)-3-thia-1-azabicyclo[3.3.0]octane-2-thione (**379**)(1.63 g, 90%) as a colourless powder, identical to that prepared in H. 4. *c*).

e) Preparation of (4*R*,5*S*)-4-phenyl-3-thia-1-azabicyclo[3.3.0]octane-2-thione (**545**)

The procedure from H. 4. *a*. was modified as follows; 2-(*S*)-[(*R*)-α-hydroxybenzyl]pyrrolidine (**526**)(2.0 g, 11.3 mmol), 2M sodium hydroxide (50 ml) and carbon disulphide (2.8 g, 2.2 ml, 37 mmol) were stirred together at RT for one week. The solution was extracted with CH_2Cl_2 and the combined organic layer washed with water, dried and evaporated to afford a yellow residue. Kugelrohr distillation (b.p. 200°C / 0.05 torr) provided a yellow solid, which was recrystallised from ethanol to give (4*R*,5*S*)-4-phenyl-3-thia-1-azabicyclo[3.3.0]octane-2-thione (**545**)(0.64 g, 24%) as brown crystals in 100% d.e., m.p. 113-114°C; $[\alpha]_D^{20}$ –23.4° (c=1.06, CH_2Cl_2); (Found: C, 61.2; H, 5.7; N, 6.0. $C_{12}H_{13}NS_2$ requires C, 61.2; H, 5.6; N, 6.0%); ν_{max} (nujol) 1735, 1480, 1305, 1210, 1155, 1040, 950 and 700 cm^{-1}; δ_H (300 MHz) 7.49-7.35 (5H, m), 5.02 (1H, d, J 11.5 Hz), 4.68 (1H, m), 3.71

(1H, m), 3.57 (1H, m), 2.42 (1H, m), 2.29 (1H, m), 2.08 (1H, m) and 1.87 (1H, m); δ_C (75 MHz) 190.6 (CS), 134.7 (4^{ry}), 129.1 (2 CH), 128 7 (CH), 128.0 (2 CH), 77.9 (CH), 57.9 (CH), 46.8 (CH_2), 30.3 (CH_2) and 28.4 (CH_2); m/z 235 (M^+, 100%), 166 (20), 158 (20), 143 (10), 117 (20), 91 (25), 85 (30) and 77 (10).

i) Large scale preparation of (4*R*,5*S*)-4-phenyl-3-thia-1-azabicyclo [3.3.0]octane-2-thione (**545**)

The experiment was repeated using 2-(*S*)-[(*R*)-α-hydroxybenzyl]pyrrolidine (**526**)(29.1 g, 164 mmol), carbon disulphide (32.4 ml, 0.54 mol) in 2M aqueous sodium hydroxide (400 ml). After 2 days an oil (~3.0 g) was isolated using the same method as above and used immediately (see below 5. *f. i.*).

f) Preparation of (4*R*,5*S*)-4-phenyl-3-thia-1-azabicyclo[3.3.0]octan-2-one

The procedure from C. 3. *a*) was used with crude (4*R*,5*S*)-4-phenyl-3-thia-1-azabicyclo[3.3.0]octane-2-thione (**545**)(1.06 g, 4.5 mmol)(of ~70%d.e.), benzoic acid (0.53 g, 4.5 mmol), benzyltriethylammonium bromide (0.17 g, 0.74 mmol), CH_2Cl_2 (50 ml), potassium permanganate (2.13 g, 13.5 mmol) and water (100 ml) which were stirred together for 3 hr at RT. The usual workup and evaporation produced an orange oil which was kugelrohr distilled to yield (4*R*,5*S*)-4-phenyl-3-thia-1-azabicyclo[3.3.0]octan-2-one (0.45 g, 46%) as an orange oil in 68% d.e., b.p. 230°C at 0.05 torr; (Found: m/z 219.0725. $C_{12}H_{13}NOS$ requires m/z 219.0718); ν_{max} (neat) 2980, 2890, 1685, 1460, 1390, 790 and 700 cm^{-1}; δ_H (300 MHz) 7.47-7.30 (5H, m), 4.8 (1H, d J 9.5 Hz), 4.25 (1H, m), 3.6 (1H, m), 3.25 (1H, m), 2.3-1.9 (3H, m) and 1.65 (1H, m); δ_C (75 MHz) 168.5 (CO), 137.1 (4^{ry}), 128.9 (2 CH), 128 4 (CH), 127.8 (2 CH), 70.5 (CH), 55.6 (CH), 43.5 (CH_2), 29.8 (CH_2)

and 27.2 (CH_2); m/z 219 (M^+, 30%), 122 (60), 105 (100), 77 (80), 70 (100) and 43 (70).

g) Attempted preparation of (*S*)-4,4-diphenyl-3-thia-1-azabicyclo[3.3.0] octane-2-thione (**528**)

i) A solution of carbon disulphide (1.8 ml, 30 mmol), 2-(*S*)-(diphenylhydroxymethyl)pyrrolidine (**525**)(2.0 g, 7.9 mmol), sodium hydroxide (25 g) and water (25 ml) was stirred for 24 hr at RT. The solution was filtered and the solid washed slowly with 2M hydrochloric acid and then CH_2Cl_2. The organic layer was separated, washed with water, dried and evaporated to yield (*S*)-4,4-diphenyl-3-oxa-1-azabicyclo[3.3.0]octane-2-thione (**529**)(0.38 g, 16%), identical to that obtained in I. 4. *c*.

ii) Using a method by Piper,[320] 2-(*S*)-(diphenylhydroxymethyl)pyrrolidine (**525**)(4.27 g, 16.9 mmol), carbon disulphide (5.13 g, 4.05 ml, 67.5 mmol), dry DMF (50 ml) and potassium carbonate (4.7 g, 34 mmol) were stirred together for 24 hr, with heating under reflux. The mixture was poured into water (150 ml), extracted with CH_2Cl_2 and the combined organic layers were washed with 1M hydrochloric acid, water (3 x), dried and then evaporated to afford an orange oil (4.13 g). Column chromatography of the orange oil on silica using ether as the eluant gave a colourless oil which was crystallised from ethyl acetate / ether with cooling (0°C) to afford colourless crystals (1.9 g). NMR shows the presence of two compounds in a 2:1 ratio, (*S*)-4,4-diphenyl-3-oxa-1-azabicyclo[3.3.0]octane-2-thione (**529**) and possibly (*S*)-4,4-diphenyl-3-thia-1-azabicyclo[3.3.0]octane-2-thione (**528**); δ_C (75 MHz) 190.6 (CS), 140.9 (4^{ry}), 140.7 (4^{ry}), 128.9-126.0 (10 CH), 77.5 (CH), 68.6 (4^{ry}), 46.7 (CH_2), 27.9 (CH_2) and 27.6 (CH_2).

iii) (*S*)-4,4-diphenyl-3-oxa-1-azabicyclo[3.3.0]octane-2-thione (**529**)(2 g, 6.78 mmol) was dissolved in CH_2Cl_2 (25 ml) and phosphorus pentasulphide (2.44 g, 11 mmol) was added to the solution and the mixture heated under

reflux for 24 hr. The solution was filtered and the organic layer washed with 2M sodium hydroxide (2x), water and dried. Evaporation gave a red oil which was identified by MS to be the starting material.

5. Preparation of bicyclic carbamate salts

a) Preparation of triethyloxonium tetrafluoroborate

The title compound was prepared in good yield by the method of Meerwein,[321] as colourless crystals and stored under ether.

b) Preparation of (*S*)-2-ethoxy-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium tetrafluoroborate (**513**)

Based on another method by Meerwein,[322] (*S*)-3-thia-1-azabicyclo[3.3.0]octane-2-one (**469**)(7.15 g, 50 mmol) was added to a solution of triethyloxonium fluoroborate (11.4 g, 60 mmol) in CH_2Cl_2 (40 ml) and heated under reflux for 3 hr. After cooling, ether (50 ml) and water (5 drops) were added to the reaction and an oil precipitated out of solution. The solution was decanted off and the oil washed with ether (2 x), redissolved in CH_2Cl_2 and dried. Evaporation produced (*S*)-2-ethoxy-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium tetrafluoroborate (**513**)(9.8 g, 76%) as a yellow oil; ν_{max} (neat) 3200-3100, 2980, 1630, 1450, 1410, 1380, 1335, 1100-1000, 840 and 820 cm^{-1}; δ_H (200 MHz) 4.9 (1H, m), 4.7 (1H, m), 4.55 (1H, m), 3.85 (3H, m), 3.55 (1H, m), 2.6-2.2 (3H, m), 2.0 (1H, m) and 1.55 (3H, t, J 6.5 Hz); δ_C (50 MHz) 177.6 (4^{ry}), 77.1 (CH_2), 69.5 (CH), 45.6 (CH_2), 36.5 (CH_2), 29.4 (CH_2), 28.3 (CH_2) and 14.4 (CH_3); m/z 143 (M^+–$EtBF_4$, 100%), 115 (15), 74 (20), 70 (30), 55 (65) and 41 (65). NMR shows a small amount of the starting material present.

c) Preparation of (*S*)-2-ethylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium tetrafluoroborate (**514**)

The method of *b*) starting from (*S*)-3-thia-1-azabicyclo[3.3.0]octane-2-thione (**379**)(4.0 g, 25 mmol), followed by evaporation yielded (*S*)-2-ethylthio-3-thia-1λ⁴-azabicyclo[3.3.0]oct-1-enium tetrafluoroborate (**514**)(3.9 g, 57%) as an amber oil; ν_{max} (neat) 3620, 3550, 2975, 2880, 1635, 1560, 1450, 1100-1000 and 860 cm^{-1}; δ_H (200 MHz) 5.1 (1H, m), 3.8 (2H, m), 3.7 (2H, m), 3.35 (2H, q, J 8 Hz), 2.6 (2H, m), 2.35 (1H, m), 2.1 (1H, m) and 1.5 (3H, t, J 7.4 Hz); δ_C (50 MHz) 185.6 (4ry), 76.9 (CH), 48.3 (CH_2), 36.6 (CH_2), 31.4 (CH_2), 29.2 (CH_2), 29.1 (CH_2) and 14.3 (CH_3); m/z 159 (M^+–$EtBF_4$, 100%), 85 (20), 67 (30), 41 (60) and 27 (45). NMR shows a small amount of the starting material present.

d) Preparation of (*S*)-2-ethoxy-3-oxa-1λ⁴-azabicyclo[3.3.0]oct-1-enium tetrafluoroborate (**522**)

The method of *b*) starting from (*S*)-3-oxa-1-azabicyclo[3.3.0]octane-2-one (**520**)(2.54 g, 20 mmol), followed by evaporation yielded (*S*)-2-ethoxy-3-oxa-1λ⁴-azabicyclo[3.3.0]oct-1-enium tetrafluoroborate (**522**)(4.27 g, 88%) as a yellow oil; ν_{max} (neat) 3500, 1650, 1530, 1460, 1100-1020, 845 and 730 cm^{-1}; δ_H (200 MHz) 5.25 (1H, m), 4.95 (1H, m), 4.85-4.6 (3H, m), 3.8 (1H, m), 3.45 (1H, m), 2.45 (1H, m), 2.3-2.0 (3H, m) and 1.5 (3H, t, J 7 Hz); δ_C (75 MHz) 163.6 (4ry), 78.0 (CH_2), 74.0 (CH_2), 63.2 (CH), 44.8 (CH_2), 29.3 (CH_2), 27.1 (CH_2) and 14.1 (CH_3); m/z 156 (M^+–BF_4, 5%), 142 (100), 127 (15), 98 (30), 70 (95) and 55 (50). NMR shows a small amount of the starting material present.

e) Preparation of (*S*)-2-methylthio-3-oxa-1λ⁴-azabicyclo[3.3.0]oct-1-enium iodide (**523**)

A solution of (*S*)-3-oxa-1-azabicyclo[3.3.0]octane-2-thione (**521**)(2.0 g, 14 mmol), AR acetone (50 ml) and methyl iodide (8.72 ml, 19.88 g, 140 mmol) was stirred for 24 hr at RT. Ether (50 ml) was added and the mixture

filtered to afford a small amount of the title compound (0.25 g) (contaminated with an unknown compound) as a colourless powder. The filtrate was evaporated and the resulting oil shown to contain two compounds by ^{13}C NMR. A minor unknown compound and (*S*)-2-methylthio-3-oxa-1λ⁴-azabicyclo[3.3.0]oct-1-enium iodide (**523**)(3.70 g, 74%) as an orange oil; δ_H (300 MHz) 4.15 (1H, m), 3.5 (3H, m), 3.35 (1H, m), 2.35 (3H, s) and 2.15-1.85 (4H, m); δ_C (75 MHz) 166.6 (4ry), 59.1 (CH), 47.1 (CH_2), 30.7 (CH_2), 23.4 (CH_2), 12.6 (CH_3) and 9.68 (CH_2); m/z 159 (M^+ –I, 100%), 126 (40), 118 (45), 85 (85), 67 (100) and 55 (90).

f) Preparation of (4*R*,5*S*)-2-methylthio-4-phenyl-3-thia-1λ⁴-azabicyclo [3.3.0]oct-1-enium iodide (**546**)

A solution of (4*R*,5*S*)-4-phenyl-3-thia-1-azabicyclo[3.3.0]octane-2-thione (**545**) of ~70% d.e. (1.23 g, 5.24 mmol), AR acetone (25 ml) and methyl iodide (3.25 ml, 7.4 g, 52.4 mmol) was stirred for 16 hr at RT. The solid was then filtered off and washed with ether to afford (4*R*,5*S*)-2-methylthio-4-phenyl-3-thia-1λ⁴-azabicyclo[3.3.0]oct-1-enium iodide (**546**) (1.68 g, 85%) as a yellow powder in 78% d.e., m.p. 104-106°C; (Found: C, 41.4; H, 4.1; N, 3.7. $C_{13}H_{16}INS_2$ requires C, 41.4; H, 4.3; N, 3.7%); ν_{max} (nujol) 1740, 1565, 1390, 1160, 1040, 780 and 700 cm^{-1}; δ_H (300 MHz) 7.62 (2H, m), 7.40 (3H, m), 6.19 (1H, d J 13.2 Hz), 5.5 (1H, m), 4.06 (1H, m), 3.85 (1H, m), 2.93 (3H, s), 2.73-2.54 (3H, m) and 2.14 (1H, m); δ_C (75 MHz) 187.1 (4ry), 131.2 (4ry), 129.9 (CH), 129.5 (2 CH), 128.7 (2 CH), 82.2 (CH), 60.5 (CH), 50.1 (CH_2), 29.3 (CH_2), 27.9 (CH_2) and 19.6 (CH_3); m/z 235 (M^+ –MeI, 100%), 166 (45), 131 (30), 117 (50), 90 (60) and 85 (70).

i) Using the same procedure as above, the oil (~3.0 g) from the large scale preparation 4. *e. i.* (above), provided (4*S*,5*S*)-2-methylthio-4-phenyl-3-thia-1λ⁴-azabicyclo [3.3.0]oct-1-enium iodide (**547**)(0.88 g) as a yellow powder in >95% d.e.; δ_H (300 MHz) 7.45 (2H, m), 7.3 (3H, m), 6.0 (1H, m), 5.7 (1H, d

J 8.6 Hz), 3.7-3.5 (2H, m), 3.0 (3H, s), 2.4 (1H, m), 2.1 (1H, m) and 1.8-1.7 (2H, m).

g) Attempted preparation of (*S*)-2-methylthio-4,4-diphenyl-3-oxa-1λ⁴-azabicyclo [3.3.0]oct-1-enium iodide (**533**)

A solution of (*S*)-4,4-diphenyl-3-oxa-1-azabicyclo[3.3.0]octane-2-thione (**529**)(4.14 g, 14 mmol), AR acetone (50 ml) and methyl iodide (8.72 ml, 19.88 g, 140 mmol) was stirred for 24 hr at RT. Ether (50 ml) was added and the reaction stirred an additional 1 hr. The solution was then evaporated to yield a black oil (6.45 g) which was redissolved in CH_2Cl_2, washed with sodium metabisulphite (2 x), water and dried. Evaporation afforded a brown solid which was recrystallised from hexane / ethanol to gave 5-(methylthiocarbonylamino)-1,1-diphenylpentan-2-one (**534**)(1.65 g, 36%) as colourless crystals, m.p. 88-89°C; (Found: C, 69.7; H, 6.65; N, 4.3. $C_{19}H_{21}NO_2S$ requires C, 69.7; H, 6.5; N, 4.3%); ν_{max} (nujol) 3340 (NH), 1715 (CO), 1650 (CO), 1510, 1260, 1210, 1055, 850 and 700 cm^{-1}; δ_H (300 MHz) 7.3-7.15 (10H, m), 5.95 (1H, br s), 5.1 (1H, s), 3.15 (2H, q, J 8 Hz), 2.55 (2H, t, J 8 Hz), 2.25 (3H, s) and 1.7 (2H, m); δ_C (75 MHz) 208.18 (CO), 167.79 (CO), 138.16 (2 4ry), 128.86 (4 CH), 128.64 (4 CH), 127.19 (2 CH), 64.05 (CH), 40.56 (CH_2), 39.76 (CH_2), 23.68 (CH_2) and 12.23 (CH_3); m/z 309 (M^+–18, 40%), 262 (10), 234 (40), 206 (15), 182 (50), 105 (100) and 77 (65).

h) Preparation of (*S*)-2-benzylthio-3-thia-1λ⁴-azabicyclo[3.3.0]oct-1-enium bromide (**519**)

Based on a procedure by Roussel,[308] a solution of (*S*)-3-thia-1-azabicyclo[3.3.0]octane-2-thione (**379**)(4.0 g, 25 mmol), acetone (110 ml), and benzyl bromide (30 ml, 42.75 g, 250 mmol) was stirred for 16 hr at RT. The resulting precipitate was filtered off and washed with ether. The filtrate was concentrated and a second crop filtered off and washed with ether. The

solids were combined to yield (*S*)-2-benzylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium bromide (**519**)(6.37 g, 77%) as a pale yellow powder; δ_H (200 MHz) 7.55-7.3 (5H, m), 5.3 (1H, m), 4.8 and 4.6 (2H, AB pattern, J_{AB} 19 Hz), 4.05 (2H, m), 3.85 (1H, m), 3.7 (1H, m), 2.6 (1H, m) and 2.35 (2H, m); δ_C (75 MHz) 185.4 (4^{ry}), 132.4 (4^{ry}), 129.5 (2 CH), 129.2 (2 CH), 129.0 (CH), 76.7 (CH), 49.1 (CH_2), 41.2 (CH_2), 38.4 (CH_2), 29.5 (CH_2), and 29.3 (CH_2). The product was contaminated with 15-25% of (*S*)-3-thia-1-azabicyclo[3.3.0]octane-2-thione (**379**).

6. The attempted authentic synthesis of 5-(methylthiocarbonyl--amino)-1,1-diphenylpentan-2-one (534)

a) Preparation of 1,1-diphenyl-5-hydroxypentan-2-one (**538**)

Using the method of Bunce,[323] a solution of γ-butyrolactone (3.44 g, 40 mmol) and dry THF (100 ml) was stirred at RT. Another solution of dry THF (150 ml), diphenylmethane (13.5 g, 80 mmol) and 2M n-butyllithium (41 ml, 82 mmol) was prepared in a dropping funnel over 20 min. The lithiated solution was added dropwise over a period of 20 min and then the mixture was heated to reflux for 10 min. The mixture was allowed to cool and was quenched with aqueous ammonium chloride. The solution was diluted with ether (200 ml) and the organic layer separated and washed with water, brine and dried. Evaporation provided a yellow oil which was kugelrohr distilled to separate the unreacted diphenylmethane, which was collected and 1,1-diphenyl-5-hydroxypentan-2-one (**538**)(7.59 g, 80%) which was left behind. ^{1}H NMR analysis matches literature values.

b) Preparation of 5-bromo-1,1-diphenylpentan-2-one (**539**)

To a stirred solution of 1,1-diphenyl-5-hydroxypentan-2-one (**538**)(1.5 g, 6.36 mmol) in CH_2Cl_2 (25 ml), phosphoros tribromide (1.72 g, 0.6 ml, 6.36 mmol) dissolved in CH_2Cl_2 (20 ml) was added dropwise. After 3 hr at

RT the solution was washed with water, brine, dried and evaporated to give 5-bromo-1,1-diphenylpentan-2-one (**539**)(1.84 g, 91%) as a dark brown oil; δ_H (300 MHz) 7.3-7.10 (10H, m), 5.1 (1H, s), 3.25 (2H, t, J 8 Hz), 2.65 (2H, t, J 8 Hz) and 2.05 (2H, m); δ_C (75 MHz) 207.2 (CO), 138.2 (2 4ry), 128.8 (4 CH), 128 6 (4 CH), 127.2 (2 CH), 64.1 (CH), 40.6 (CH_2), 33.0 (CH_2) and 26.7 (CH_2); m/z 318 (^{81}Br-M$^+$, 5%), 316 (^{79}Br-M$^+$, 5), 236 (30), 180 (30), 167 (100), 152 (70), 105 (65), 77 (50) and 41 (80).

c) Preparation of *S*-methyl thiocarbamate

A solution of methylthiocyanate, water and hydrogen chloride gas was mixed together according to the procedure of Yamamoto[324] and after two days the title compound was isolated as yellow crystals (9.47 g, 61%).

d) Attempted preparation of 5-(methylthiocarbonylamino)-1,1-diphenyl--pentan-2-one (**534**)

A solution of 5-bromo-1,1-diphenylpentan-2-one (**539**)(1.7 g, 5.4 mmol) dissolved in dry DMF (10 ml) was added dropwise to a stirred solution of dry DMF (20 ml), sodium hydride (0.139 g, 5.8 mmol) and *S*-methyl thiocarbamate (0.53 g, 5.8 mmol) at RT and the reaction left overnight. The solution was washed with water (x 4), dried and evaporated to gave a black oil. NMR analysis showed a large percentage of the starting material present and an unknown which was not consistent with the desired product.

e) Preparation of 5-azido-1,1-diphenylpentan-2-one (**540**)

Using a procedure by Carrie,[325] sodium azide (0.62 g, 9.54 mmol) was added to a stirred solution of 5-bromo-1,1-diphenylpentan-2-one (**539**)(2 g, 6.36 mmol) in DMF (25 ml). After 18 hr at RT the reaction was poured into water and extracted with ether. The organic phase was then washed with water (x 4) and dried. The solvent was evaporated to afford 5-azido-1,1-

diphenylpentan-2-one (**540**)(1.7 g, 96%) as a black oil; ν_{max} (neat) 2097 (N_3), 1718 (CO), 1495, 1453, 1286, 1100, 747 and 702 cm^{-1}; δ_H (300 MHz) 7.3-7.1 (10H, m), 5.05 (1H, s), 3.1 (2H, t, J 7 Hz), 2.55 (2H, t, J 7 Hz) and 1.75 (2H, m); δ_C (75 MHz) 207.2 (CO), 138.2 (2 4ry), 128.9 (4 CH), 128.7 (4 CH), 127.2 (2 CH), 64.1 (CH), 50.1 (CH_2), 39.3 (CH_2) and 23.1 (CH_2).

f) Attempted preparation of 5-amino-1,1-diphenylpentan-2-one (**541**)

Continuing the procedure from above, the azide (**540**) was used immediately and redissolved in THF (25 ml) and triphenylphosphine (1.67 g, 6.36 mmol) was added. Water (0.17 g, 9.54 mmol) was added after a few min and the reaction stirred for 12 hr at RT. The solution was evaporated and the residue redissolved in toluene. The toluene solution was extracted with 6M HCl (x 3) and the combined aqueous layers made alkaline with solid sodium hydroxide. The aqueous phase was extracted with ether, the combined ether fractions were washed with brine, dried and evaporated to afford a yellow oil. Kugelrohr distillation gave a product which appeared to be 3,3-diphenylpiperidin-2-one (**542**)(0.45 g, 28%) as a yellow oil, b.p. 170°C / 0.01 torr (lit.[326] m.p. 190°C); ν_{max} (neat) 3381 (NH), 3026, 1636 (CO), 1495, 1448, 1310, 1177, 1030 and 701 cm^{-1}; δ_H (300 MHz) 7.85-7.25 (11H, m), 3.9 (2H, t, J 7 Hz), 2.5 (2H, t, J 7 Hz) and 2.05 (2H, m); δ_C (75 MHz) 181.3 (CO), 143.7 (2 4ry), 128.1 (4 CH), 127 7 (4 CH), 127.4 (2 CH), 80.0 (4ry), 59.4 (CH_2), 35.0 (CH_2) and 24.3 (CH_2); m/z 251 (M^+, 15%), 182 (40), 105 (100), 91 (30), 77 (60) and 51 (25).

g) Preparation of 2-oxo-1,1-diphenylpentane-5-ammonium trifluoroacetate (**543**)

A procedure by Evans[151] was used to hydrogenate 5-azido-1,1-diphenylpentan-2-one (**540**)(5.32 g, 19.08 mmol) in a solution of methanol (100 ml), trifluoroacetic acid (6.53 g, 4.4 ml, 57.24 mmol) and 5% palladium

on charcoal catalyst. Under hydrogen gas at atmospheric pressure the reaction was complete after 12 hr at RT. The solution was filtered using a celite pad and evaporated to give crude 2-oxo-1,1-diphenylpentane-5-ammonium trifluoroacetate (**543**)(6.8 g, 100%) as a black semi solid; δ_H (300 MHz) 7.5-7.0 (13H, m), 5.05 (1H, s), 4.05 (2H, m), 3.05 (2H, m) and 2.2 (2H, m); δ_C (75 MHz) 196.7 (CO), 160.6 (CO, q, J_{CCF} 38.9 Hz), 134.9 (2 4ry), 129.7 (4 CH), 129.0 (2 CH), 128.8 (4 CH), 115.6 (CF_3, q, J_{CF} 288 Hz), 54.3 (CH), 54.1 (CH_2), 36.9 (CH_2) and 20.1 (CH_2).

h) Attempted preparation of 5-((methylthio)thiocarbonylamino)-1,1-diphenylpentan-2-one (**544**)

A solution of potassium hydroxide (0.56 g, 10 mmol), 50% aqueous ethanol (40 ml), 2-oxo-1,1-diphenylpentan-5-ammonium trifluoroacetate (**543**)(1.79 g, 5 mmol) and carbon disulphide (0.36 ml, 6 mmol) was stirred for 1 hr at RT. Iodomethane (0.85 g, 0.37 ml, 6 mmol) was then added to the reaction and the solution stirred for an additional 4hr. The reaction was extracted with CH_2Cl_2 and the organic layers washed with water and dried. Evaporation afforded a black residue which was analysed by ^{13}C and ^1H NMR and found to contain a number of unknown compounds. The disappearance of the CH proton suggested that none of the desired product had been prepared.

7. Reaction of (*S*)-2-methylthio-3-thia-1λ⁴-azabicyclo[3.3.0]oct-1-enium iodide (468) with 2 eq. (±)-alkoxides

a) Sodium 1-phenylethoxide in CH_2Cl_2

A solution of (*S*)-2-methylthio-3-thia-1λ⁴-azabicyclo[3.3.0]oct-1-enium iodide (**468**)(7.53 g, 25 mmol) in CH_2Cl_2 (100 ml) was added to dry 1-phenylethoxide (50 mmol) and the mixture stirred at RT for 24 hr. Hexane (100 ml) was poured in and the solution filtered to give a yellow solid (5.32 g). The solid was added to a solution of water and CH_2Cl_2, the organic phase

was separated and the aqueous phase extracted with CH_2Cl_2. The combined organic layers were washed with water, dried and evaporated to give an amber oil. Column chromatography on silica with hexane / ether (1:1) as the eluant gave 1-phenylethanol (R_F=0.38) as the major fraction, $[\alpha]_D^{20}$ –12.04° (c=0.947, hexane) 29.2% e.e. The filtrate was washed with water, dried and evaporated to afford a yellow oil. Analysis by NMR showed three compounds: (*S*)-3-thia-1-azabicyclo[3.3.0]octan-2-one (**469**), 1-phenylethanol and methyl 1-phenylethyl sulphide.

b) Lithium 1-phenylethoxide

A solution of lithium 1-phenylethoxide (20 mmol) in toluene (20 ml) was reacted with (*S*)-2-methylthio-3-thia-1λ⁴-azabicyclo[3.3.0]oct-1-enium iodide (**468**)(3.01 g, 10 mmol) at –78°C. After stirring for 16 hr and allowing the reaction to warm up to RT, pet ether was added and the solution filtered to give a solid. From the solid, 1-phenylethanol (2.34 g, 19 mmol) was isolated (see above). The filtrate was analysed by ^{13}C NMR and was shown to contain no starting material and none of the expected products.

In a second experiment a solution of lithium 1-phenylethoxide (20 mmol) in toluene (20 ml) was allowed to warm up to RT, (*S*)-2-methylthio-3-thia-1λ⁴-azabicyclo[3.3.0]oct-1-enium iodide (**468**)(3.01 g, 10 mmol) was added and the reaction stirred for 16 hr. The solid was isolated in the usual way and 1-phenylethanol (1.77 g, 14.5 mmol), $[\alpha]_D^{20}$ –5.1° (c=0.83, CH_2Cl_2) was obtained. The filtrate was analysed by ^{13}C NMR and was shown to contain the starting salt, (*S*)-3-thia-1-azabicyclo[3.3.0]octan-2-one (**469**) and 1-phenylethanol.

c) Potassium 1-phenylethoxide

A solution of potassium 1-phenylethoxide (20 mmol) in toluene (20 ml) was reacted with (*S*)-2-methylthio-3-thia-1λ⁴-azabicyclo[3.3.0]oct-1-enium

iodide (**468**)(3.01 g, 10 mmol) at RT. After stirring for 16 hr, pet ether was added and the solution filtered to give a solid. From the solid, 1-phenylethanol (0.6 g, 9.4% e.e.) $[\alpha]_D^{20}$ –3.86° (c=1.45, hexane) was isolated in the usual way. The filtrate was analysed by ^{13}C NMR and was shown to contain three compounds: (*S*)-3-thia-1-azabicyclo[3.3.0]octan-2-one (**469**), 1-phenylethanol and methyl 1-phenylethyl sulphide.

d) Sodium 1-phenylethoxide, sodium 1-phenyl-1-propoxide, sodium 1-phenyl-2-propoxide and sodium 3,3-dimethyl-2-butoxide in toluene

A solution of (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide (**468**)(2.0 g, 6.65 mmol) and the prepared alkoxide (13.3 mmol) in toluene (15 ml) was stirred together at RT for 16 hr. Water was added to the reaction and the organic phase, separated, dried and evaporated to give a yellow oil.

Starting from sodium 1-phenylethoxide, kugelrohr distillation of the crude oil afforded a mixture (*S*)-1-phenylethanol (18% e.e.) and methyl 1-phenylethyl sulphide (0.46 g) as a colourless oil, b.p. 108-150°C / 15 torr. Further distillation, 150°C / 1 torr gave a mixture of all three expected products, (*S*)-3-thia-1-azabicyclo[3.3.0]octan-2-one (**469**), 1-phenylethanol and methyl 1-phenylethyl sulphide.

Starting from sodium 1-phenyl-1-propoxide, kugelrohr distillation of the crude oil afforded a mixture (*S*)-1-phenyl-1-propanol (12% e.e.) and methyl 1-phenylpropyl sulphide (0.55 g) as a colourless oil, b.p. 100-150°C / 15 torr.

Starting from sodium 1-phenyl-2-propoxide, kugelrohr distillation of the crude oil afforded a mixture of 1-phenyl-2-propanol (6% e.e.) and methyl 1-phenyl-2-propyl sulphide (1.19 g) as a colourless oil, b.p. 110-150°C / 15 torr.

Starting from sodium 3,3-dimethyl-2-butoxide, kugelrohr distillation of the crude oil afforded toluene and 3,3-dimethyl-2-butanol (0.5% e.e.) as a colourless oil, b.p.70-130°C / 15 torr.

e) Recovery of the thione (**379**)

Using the crude residue left after distillation from the reaction with sodium 1-phenyl-1-propoxide, the oil was redissolved in CH_2Cl_2 (25 ml) and phosphorus pentasulphide (2.44 g, 11 mmol) was added to the solution and the reaction heated under reflux for 24 hr. The solution was filtered and the organic layer washed with 2M sodium hydroxide (2 x), water and dried. Evaporation of the solvent gave an orange solid which was recrystallised from ethanol to afford (*S*)-3-thia-1-azabicyclo[3.3.0]octane-2-thione (**379**)(0.28 g, 26%) as orange crystals.

f) Determination of enantiomeric excess

The e.e.s were determined by two methods: ^{1}H NMR analysis of the oils in the presence of tris[3-(heptafluoropropyl-hydroxymethylene)-(+)-camphorato] europium(III), and esterification of the alcohols using (–)-(*R*)-O-methylmandelic acid, following a procedure by Trost.[327] (–)-(*R*)-O-methylmandelic acid was prepared according to the procedure by Reeve,[328] to afford (–)-(*R*)-O-methylmandelic acid (3.37 g, 20%) as colourless crystals, m.p. 63-65°C and $[\alpha]_D^{22}$ –152.6° (c=1.60, H_2O) (lit.[329] m.p. 65-67°C and $[\alpha]_D^{22}$ –161.9° (c=1.66, H_2O)).

8. Reaction of (*S*)-2-benzylthio-3-thia-1λ^4-azabicyclo[3.3.0] oct-1-enium bromide (519) with sodium (±)-1-phenylethoxide

A solution of (*S*)-2-benzylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium bromide (**519**)(8.05 g, 25 mmol) and the prepared alkoxide (50 mmol) in toluene (50 ml) was stirred together at RT for 16 hr. Water was added to the

reaction and the organic phase separated, washed with water, dried and evaporated to give a crude yellow oil (14 g). The oil was analysed by NMR and GC-MS and found to contain a number of compounds including (*S*)-3-thia-1-azabicyclo[3.3.0]octane-2-one(**469**), 1-phenylethanol and benzyl 1-phenylethyl sulphide. Column chromatography of the yellow oil on silica using hexane / ether (1:1) as the eluant gave 4 fractions. Fractions: one (R_F=0.85) contained benzyl 1-phenylethyl sulphide and benzylthiol (3.02 g). Two was an unidentifiable mixture. Three (R_F 0.3) afforded (*S*)-1-phenylethanol (2.7 g, 88%) $[\alpha]_D^{20}$ –11.3° (c=3.3, hexane), 27.5% e.e. and four, eluted with CH_2Cl_2 gave (*S*)-3-thia-1-azabicyclo[3.3.0]octan-2-one (**469**)(0.41 g, 12%).

9. Reaction of (*S*)-2-ethoxy-3-thia-1λ⁴-azabicyclo[3.3.0]oct-1-enium tetrafluoroborate (513) with sodium (±)-1-phenylethoxide

A solution of (*S*)-2-ethoxy-3-thia-1λ⁴-azabicyclo[3.3.0]oct-1-enium tetrafluoroborate (**513**)(6.48 g, 25 mmol) and the prepared alkoxide (50 mmol) in toluene (50 ml) was stirred together at RT for 24 hr. Pet ether (150 ml) was added to the reaction and the solution filtered, concentrated (25 ml) and pet ether added again to precipitate the alkoxide. The solution was filtered, the filtrate removed and the solid washed with water and CH_2Cl_2. The organic phase was separated, the aqueous phase extracted with CH_2Cl_2 (2 x) and the combined organic layers dried and evaporated to afford (*S*)-1-phenylethanol (40 mg) as a colourless oil, $[\alpha]_D^{20}$ –10.5° (c=0.609, hexane), 25% e.e.

The filtrate was evaporated to afford an orange oil (12.65 g) which was shown by NMR and GC-MS to contain two major products; 1-phenylethanol and possibly (*S*)-2-ethoxy-2-(1-phenylethoxy)-3-thia-1-azabicyclo[3.3.0]

octane (**524**), m/z 293 (M^+, 5%), 188 (10), 142 (100), 105 (30), 98 (20), 70 (60) and 29 (40).

10. Reaction of (*S*)-2-ethoxy-3-oxa-1λ⁴-azabicyclo[3.3.0]oct-1-enium tetrafluoroborate (522) with sodium (±)-1-phenylethoxide

A solution of (*S*)-2-ethoxy-3-oxa-1λ⁴-azabicyclo[3.3.0]oct-1-enium tetrafluoroborate (**522**)(3.16 g, 13.3 mmol) and the prepared alkoxide (26.6 mmol) in toluene (25 ml) was stirred together at RT for 24 hr. Pet ether (50 ml) was added to the reaction and the solution filtered, the filtrate was washed with water, dried and evaporated to afford an orange oil (4.48 g), which was shown by NMR to contain 1-phenylethanol and possibly (*S*)-2-ethoxy-2-(1-phenylethoxy)-3-oxa-1-azabicyclo[3.3.0]octane (**524**) in the form of diastereomers.

11. Reaction of (*S*)-2-methylthio-3-oxa-1λ⁴-azabicyclo[3.3.0] oct-1-enium iodide (523) with sodium (±)-1-phenylethoxide

A solution of (*S*)-2-methylthio-3-oxa-1λ⁴-azabicyclo[3.3.0]oct-1-enium iodide (**523**)(3.80 g, 13.3 mmol) and the alkoxide (26.6 mmol) in toluene (25 ml) was stirred together at RT for 16 hr. Pet ether (50 ml) was added to the reaction and the solution filtered, the filtrate was evaporated to afford a yellow oil (3.74 g). The filter cake was washed with water and extracted with CH_2Cl_2, dried and evaporated to give a yellow oil (1.28 g). ^1H NMR analysis shows 1-phenylethanol e.e. 0%, determined by chiral shift experiment and possibly methyl 1-phenylethyl sulphide. ^{13}C NMR analysis of the filtrate showed 1-phenylethanol and an unknown in the form of a diastereomer.

12. Reaction of (4*S*,5*S*)-2-methylthio-4-phenyl-3-thia-1λ⁴-azabicyclo [3.3.0]oct-1-enium iodide (547) with sodium (±)-1-phenylethoxide and sodium (±)-1-phenyl-1-propoxide

A solution of (4*S*,5*S*)-2-methylthio-4-phenyl-3-thia-1λ⁴-azabicyclo [3.3.0]oct-1-enium iodide (**547**)(0.4 g, 1.06 mmol) and the prepared alkoxide (2.12 mmol) in toluene (5 ml) was stirred together at RT for 16 hr. Water was added to the reaction and the organic phase, separated, dried and evaporated to give a yellow oil.

Starting from sodium 1-phenylethoxide, kugelrohr distillation of the crude oil afforded (*S*)-1-phenylethanol (6% e.e.) as a colourless oil, b.p. 105-115°C / 15 torr.

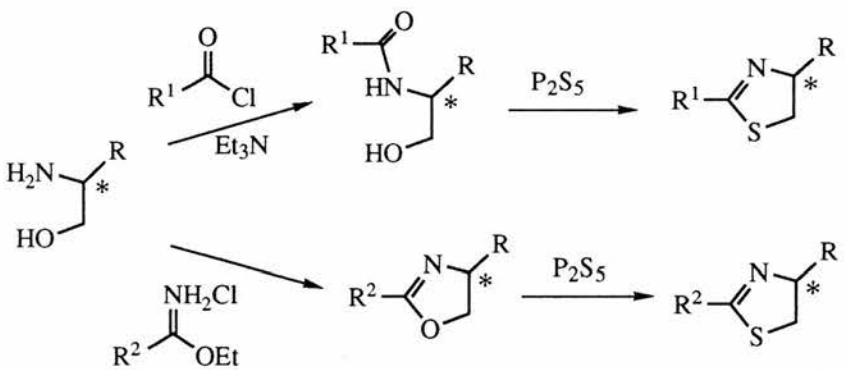
Starting from sodium 1-phenyl-1-propoxide, kugelrohr distillation of the crude oil afforded (*S*)-1-phenyl-1-propanol (8% e.e.) as a colourless oil, b.p. 115-130°C / 15 torr.

DISCUSSION

A. Preparation of (*R*) and (*S*)-2,4-disubstituted 2-thiazoline 1,1-dioxides

1. Background

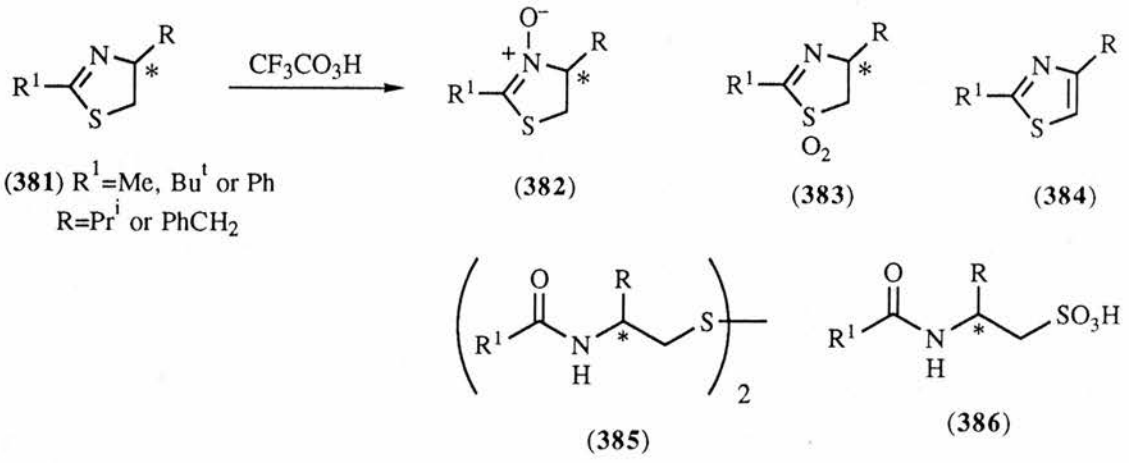
Preparation of the chiral 2-thiazolines has been described by Armstrong.[288] The reaction of an acyl chloride or an alkoxyimidate salt with an amino alcohol produces acylamino alcohols or 2-alkyloxazolines. Either of these can be reacted with P_2S_5 to afford the desired 2-substituted 2-thiazolines as shown in Scheme 8.



Scheme 8

The oxidation of five membered rings containing N and S may proceed in various ways and we have recently reviewed this area.[330] The behaviour of the 2-thiazolines towards oxidation was studied in detail by Armstrong and a number of interesting conclusions were reached. Oxidation of **381** using peroxytrifluoroacetic acid generated *in situ* or N_2O_4 provided the previously unknown 2-thiazoline 3-oxides **382**, with the main evidence for these compounds coming from the ^{13}C and ^{1}H NMR spectra. Numerous attempts were made to oxidise the ring sulphur and produce the sulphones **383**, but the majority of these methods resulted in failure. A total of 21 different

experiments using 10 different agents for the oxidation of **381** gave one or

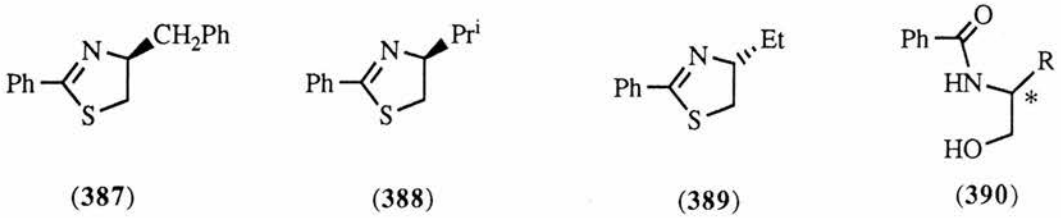


more of the products **383-386**. In the three cases in which Armstrong obtained the sulphones **383**; the yield was below 5% for R=Pr^i, R^1=Ph, the sulphone was characterised only by ^{1}H NMR where R=CH_2Ph and R^1=Ph and was inseparable from **386** and the spectroscopic data for R=Et and R^1=Ph was subsequently found wrong.

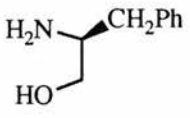
As described in the Programme of Research, the goal in oxidising **381** was to obtain **383** in high yields and this would then allow metallation of the C-5 position. The incoming electrophile would be influenced by the R group on the C-4 position, giving a new asymmetric centre at the C-5 position.

2. Preparation of 2,4-disubstituted 2-thiazolines

The synthesis of thiazolines **387-389** and **394-396** was achieved using the



procedures outlined by Armstrong[288] and shown in Scheme 8. 2-Phenyl-2-thiazolines **387** and **388** were synthesised by the reaction of an amino alcohol **391** or **392**, with benzoyl chloride in the presence of Et_3N to give **390**. The



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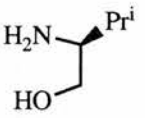

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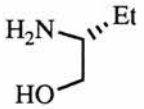
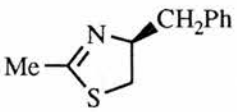


(393)

amino alcohols **391** and **392** were prepared by the reduction of (*S*)-phenylalanine and (*S*)-valine using well known methods. The thiazoline **389** was prepared starting from commercially available (*R*)-2-amino-1-butanol **393**. The benzoylamino alcohol **390** undergoes a ring closure reaction with P_2S_5 to give the desired thiazolines. The Pinner synthesis was used to prepare ethyl iminoacetate hydrochloride **397** which was reacted with amino alcohol **391** or **393** to provide the oxazolines and these were then reacted with P_2S_5 to afford the thiazolines **394** and **396** (a sample of **395** was available from the work of Armstrong). All the thiazolines prepared gave spectroscopic data matching that previously obtained.[288]



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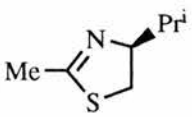

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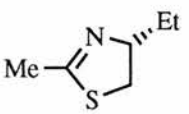

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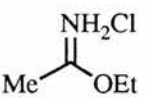
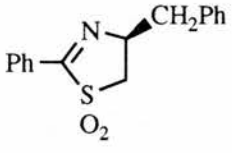


(397)

3. Oxidation of 2,4-disubstituted 2-thiazolines

The successful oxidation of **387-389** was carried out using $KMnO_4$ / benzoic acid and PTC conditions, a new oxidising system discovered quite serendipitously in the course of this work. Thus oxidation of a pure sample of **387** with $KMnO_4$ alone under PTC conditions was found to result in clean

dehydrogenation to the corresponding thiazole **503** in agreement with the previous work.[288] However on one occasion an impure sample of **387** was used, and this led to exclusive formation of the sulphone **398**. Examination of the starting material showed it to be contaminated with benzoic acid most likely carried through from the initial reaction of **391** with benzoyl chloride.



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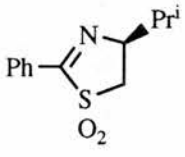

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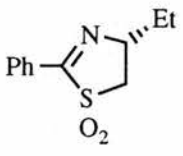
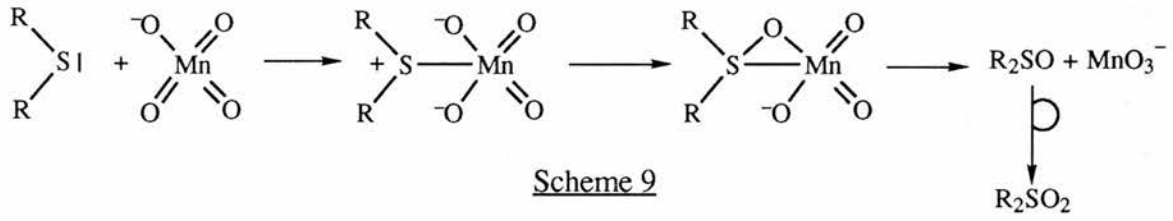


(400)

Potassium permanganate has been widely used for the oxidation of organosulphur compounds, both in homogeneous media, principally acetic acid, and under PTC conditions.[331]

The role of an acid (both benzoic and acetic acid have been used successfully and presumably any acid will work) in the selective oxidation of thiazolines **387-389** is still unclear. Potassium permanganate in the presense of acetic acid (5-10% quantities) has been used to oxidise dialkyl or diaryl sulphides and sulphoxides to their respective sulphones.[331] The reaction of thiazolines (**387** and **389**) in the absence of benzoic acid give a 1:1 ratio of the starting material and the thiazole. Reaction of thiazoline **387** with a catalytic amount of benzoic acid present afforded the starting material, the sulphone **398** and the thiazole **503** in a 2.5:1:1 ratio and reaction of thiazoline **389** with peroxybenzoic acid under PTC conditions supplied ring opened products observed by Armstrong[288] and a small quantity of the thiazole **505**. Work by Ross[332] in this laboratory has found that 2 or 3 equivalents of benzoic acid does not change the outcome of the reactions and the sulphones are produced as usual.

According to Lee[333] the mechanism for oxidation of sulphides under basic conditions is outlined in Scheme 9. An unshared pair of electrons on the sulphur, attacks the metal centre and binds to the empty d-orbital of the



Scheme 9

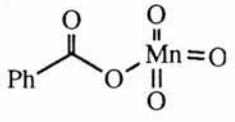
$$3RSR + 4KMnO_4 + 2H_2O \longrightarrow 4MnO_2 + 3RSO_2R + 4KOH$$

$$3RSR + 4KMnO_4 + 3PhCO_2H \longrightarrow 3RSO_2R + 4MnO_2 + 3PhCO_2K + KOH + H_2O$$

Figure 1

manganese, the slow transfer of an oxygen to sulphur gives the sulphoxide, repetition of the procedure affords the sulphone. For the normal stoichiometric equation (Figure 1), 4 potassium hydroxides are formed for every 3 sulphones. If 1 eq. of benzoic acid is added, the majority of the potassium hydroxide is mopped up therefore making the reaction less alkaline. From these observations it would appear that the oxidation of **387-389** to sulphone **398**, **399** or **400** and the thiazolidine-2-thiones to their respective sulphones (see Section E) requires a specific pH and the addition of 1 eq. of benzoic acid to the reaction accomplishes this task.

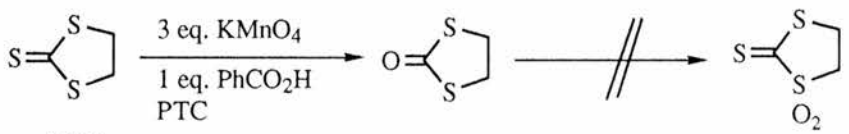
The formation of sulphones as opposed to thiazoles also suggests that a different oxidising species is involved in the presence of benzoic acid and cannot simply be due to a pH effect as is the case for the thiazolidine-2-thione oxidation (see Section E). It is suggested that this might be a benzoic /



(401)

manganic anhydride species such as **401** although this is largly speculation and requires further work to confirm it. The more obvious explanation that the permanganate reacts with the acid to generate perbenzoic acid *in situ* was ruled out by oxidation of **387** with preformed perbenzoic acid which gave the ring-opened products **385** and **386** accompanied by some thiazole **384**.

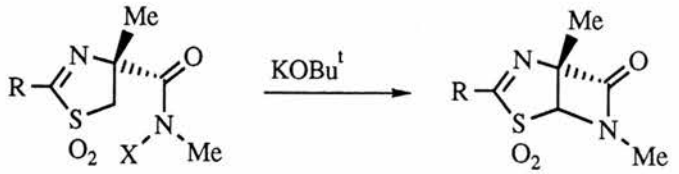
This reagent system has also proved useful for a wide variety of organosulphur compounds. As an example, reaction of 1,3-dithiolane-2-thione **402** with 3 eq. of $KMnO_4$, 1 eq. of benzoic acid and PTC conditions



(402) (403)

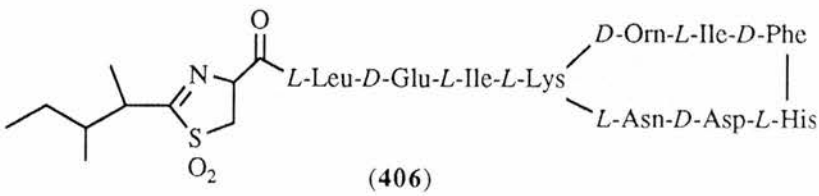
provides 1,3-dithiolan-2-one **403** in 70% yields. Using the above procedure further oxidation with an additional 2 eq. of $KMnO_4$, gave only the starting material, presumably due to the deactivation of the ring sulphurs by the CO double bond. Other workers in this laboratory have successfully applied the reagent system to many other systems.[332, 334]

These sulphones **398-400** were therefore readily prepared using this new method of oxidation and were obtained analytically pure directly from the convenient workup procedure. There are few previous reports of 2-thiazoline 1,1-dioxides. Scott obtained the highly substituted example **404** in



(**404**) X=$O_3SC_6H_4$-*p*-NO_2
R=C_6H_4-*p*-OMe

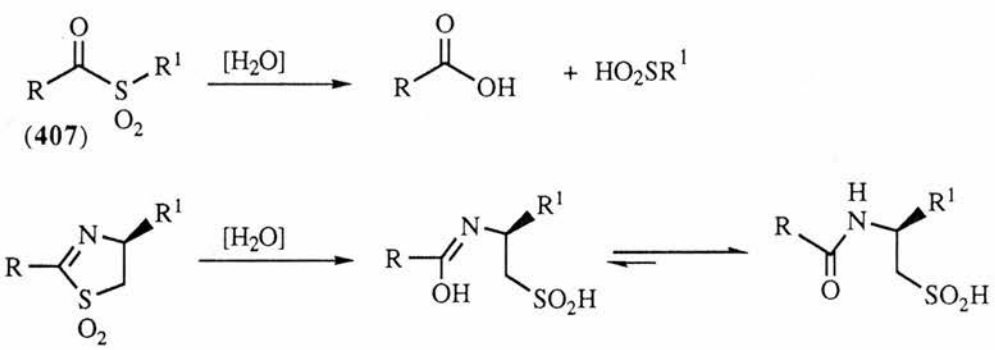
(**405**)



(**406**)

1976 by MCPBA oxidation of the corresponding thiazoline but this was used immediately for cyclisation to **405**.[335] A thiazoline dioxide moeity has also been generated in the complex bacitracin A structure **406** by oxidation of the corresponding thiazoline with $KMnO_4$.[336] Apart from these two examples the sulphones obtained here are to the best of our knowledge the first representatives of this compound class.

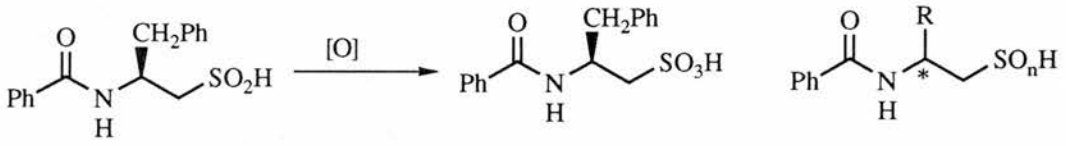
The three sulphones were found to be extremely susceptible to hydrolysis. This finding is not really surprising since they are effectively cyclic α-iminosulphones and therefore bear a close resemblance to the α-ketosulphones **407**, a little known class of compounds which were only



(**407**)

recently obtained by Schank[337] and also found to be extremely susceptible to hydrolysis in an analogous way. Thus, initial attempts to recrystallise **398**, afforded the sulphinic acid **408** which slowly disproportionates or oxidises in

air to give the sulphonic acid **409**. The main evidence for these acids comes from the correct elemental analysis of **408** and at a later date the ^{13}C NMR



(408) **(409)** **(410)**

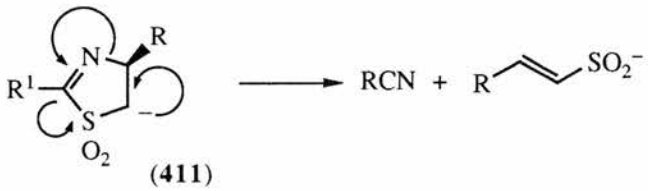
spectrum revealing the presence of a small amount of **409**, (the sulphonic acids **409** and **410** n=3, R=Pr^i or Et were fully characterised by Armstrong). Based on the assignment of the sulphinic acid ^{13}C shifts in the spectrum of **408** and the known sulphonic acid shifts of **410** n=3, R=Et or Pr^i, the ^{13}C spectra of the hydrolysed sulphones **399** and **400** were found to contain varying amounts of their respective sulphinic and sulphonic acids. This assumes that the ^{13}C shifts in the sulphinic acids **410** n=2, R=Et or Pr^i, are similar in nature to those of **408**. These observations go some way to explaining the formation of acylaminosulphonic acid **386** and acylaminodisulphides **385** in many of the previous oxidation attempts. It is likely that the desired sulphones **383** were formed in these cases but were hydrolysed to the sulphinic acids under the conditions used. These would then disproportionate to give **385** and **386**. It is a testament to the excellent selective properties of the PTC system that no hydrolysis was observed here even when the products are formed in the presence of water.

This hydrolysis process was found to be even faster in the oxidation of 2-methyl-2-thiazolines **394-396**, and the resulting sulphones were found to degrade either during the workup of the reaction mixture or during the reaction itself and only the hydrolysis products were obtained

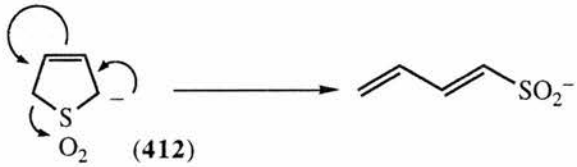
4. Attempted alkylation of the 2-thiazoline 1,1-dioxides

In an effort to alkylate the C-5 position of the thiazoline sulphones, **400** was chosen as a representative and reacted with a lithium base. Deprotonation with LDA was followed by the addition of methyl iodide to the reaction mixture. The reaction was then quenched and ^{13}C and ^{1}H NMR revealed the major compound present to be unchanged **400**. Quenching the reaction with D_2O and subsequent NMR analysis revealed that no deuterium was incorporated into the sulphone therefore a stronger base was required to deprotonate the C-5 position of the sulphone. Another experiment using Bu^nLi and TMEDA as a complexing agent and D_2O quenching again afforded the sulphone **400** unchanged. These results would indicate that a stronger base then Bu^nLi is required to achieve the alkylation of the C-5 position but due to the results obtained in the FVP of sulphones **398-400**, this line of experimentation was abandoned.

It is interesting to note that even if deprotonation had been achieved there is the possibility of cycloreversion in the resulting anion **411** to give the

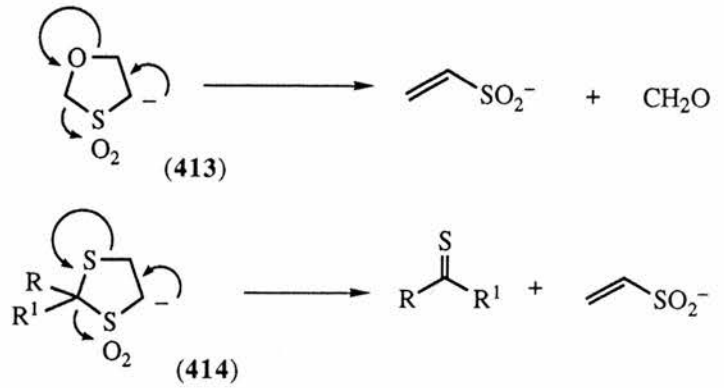


(411)



(412)

nitrile and vinyl sulphinate anion as shown. This is well known for the carbocyclic analogue **412**[338] and the O and S analogues **413**[339] and **414**.[340]



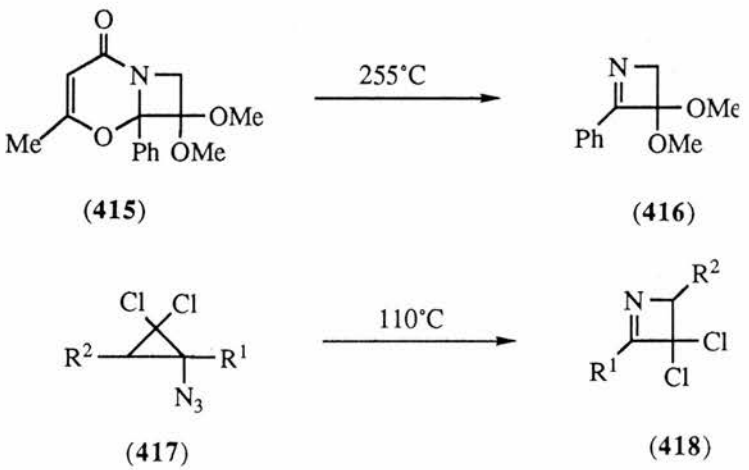
(413)

(414)

B. FVP and photolysis of the 2-thiazoline 1,1-dioxides

1. Background

1-Azetines are thermally labile and reactive compounds and their stability greatly depends on the presence of substitutents which can act as stabilising groups.[341] These are often electronegative groups which pull electron density from the π bond and are frequently attached to the C-2 or N position. Pyrolysis conditions have been used to prepare 1-azetines, as illustrated

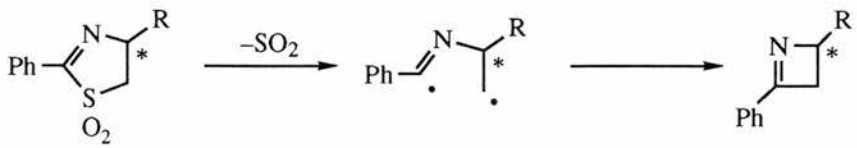


(415) (416)

(417) (418)

in the synthesis of 1-azetine **416** in 57% yield which involves the pyrolysis of **415**[342] at 255°C. Thermal rearrangement of the azide **417** also leads to the formation of 1-azetine **418**.[343]

The pyrolysis of the 2-thiazoline 1,1-dioxide ring systems has no

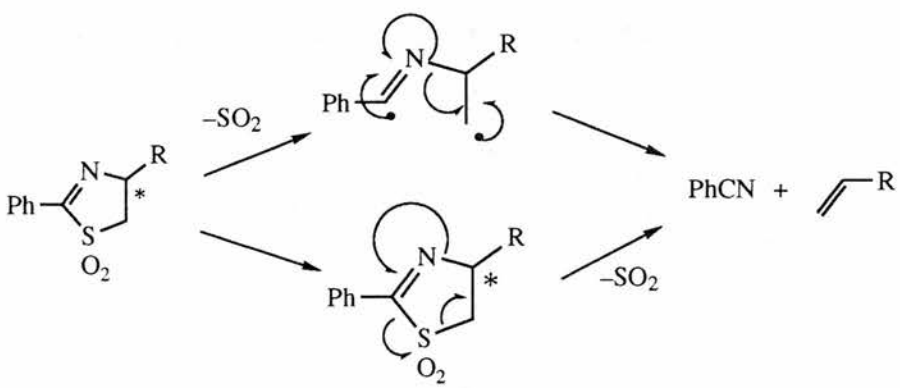


Scheme 10

literature precedent and the results while not unexpected were not predictable. With the extrusion of SO_2, it was hoped that the diradical intermediate would ring close to give the 1-azetines (Scheme 10).

2. Pyrolysis results

The FVP of the sulphones **398-400** at 600°C resulted in extrusion of SO_2 coupled to a diradical or concerted fragmentation mechanism to afford benzonitrile and the terminal alkene in yields approaching 100% (Scheme 11).



Scheme 11

3. Photolysis results

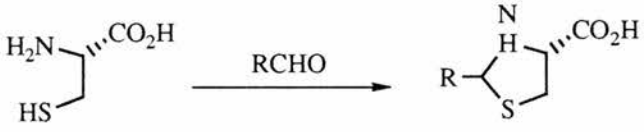
Photochemical extrusion of SO_2 from the sulphones **398-400** was examined using CH_2Cl_2 or acetone as solvents. By using the 2-phenyl moiety on the

thiazoline ring as a photoactivating group photolysis in CH_2Cl_2 resulted in no change in the sulphone. Reaction in d_6-acetone provided the sulphinic and sulphonic acids in small quantities presumably due to residual water in the NMR solvent. Using AR acetone, photolysis of **398** for 48 hours provided a yellow oil in which no starting material was found. GC-MS analysis showed 8 unidentified compounds to be present with the largest peak having m/e 98 and ^{13}C NMR analysis showed 6 carbonyl shifts. The long reaction time needed to produce a change in the sulphone **398** resulted in the total fragmentation of the ring with possible reactions involving acetone accounting for the large number of carbonyls observed in the ^{13}C NMR.

C. Preparation of 2,3,4-trisubstituted thiazolidine 1,1-dioxides

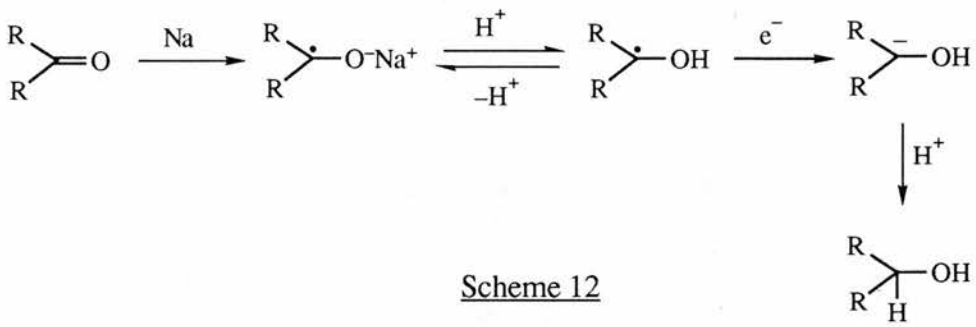
1. Background

As will be described in Section E the synthesis of thiazolidine-2-thiones can be accomplished by the reaction of CS_2 and an amino alcohol. A simpler method to chiral thiazolidines was reported by Schubert[344] which involves the



condensation of various aldehydes with (*R*)-cysteine to provide the thiazolidine carboxylic acids. Another example for the preparation of the thiazolidine ring system is the metal reduction of thiazolines in the presence of a proton donor.[293] The mechanism although not investigated in detail is analogous to the metal reduction of ketones[345] carried out with sodium metal in an alcohol, Scheme 12. One electron is added to the ketone to give the radical anion

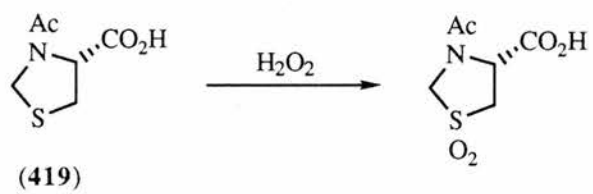
which is protonated to give a carbon radical, this is subsequently reduced to a



Scheme 12

carbanion by another one electron addition and protonation affords the alcohol. The preparation of trisubstituted thiazolidines was carried out using both of these methods.

Oxidation of these ring systems has been known since the late 1930's when Ratner[297] oxidised **419** up to the sulphone with H_2O_2. The use of $KMnO_4$, benzoic acid and PTC conditions, although not previously investigated was expected to give excellent results.



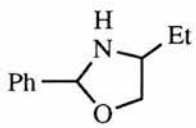
(**419**)

2. Preparation of thiazolidines from the reduction of thiazolines

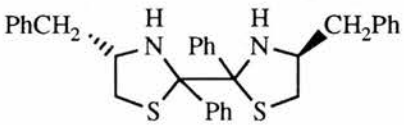
The reduction of the CN double bond in sulphones **398** and **400** was attempted initially as this would provide a direct route to compounds ready for FVP. Aluminium amalgam in wet ether was the general and efficient procedure used by Meyers[293] to obtain a variety of thiazolidines with greater than 95% conversion. Using the above method, the thiazoline 1,1-dioxides **398** and **400** remained unchanged. Using H_2 / Pd or stronger reducing metals such as sodium amalgam in wet ether also provided the same result.

Presumably the electron withdrawing properties of the SO_2 moiety pulls electron density away from the CN double bond thereby making it unreactive.

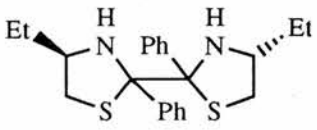
Using sodium amalgam in ethanol (a better proton source), the sulphone **398** appeared to fragment with GC-MS analysis identifying 8 compounds, with the largest being *N*-benzylidenebenzylamine. The second largest peak was identified as the oxazolidine **420** and the thiazoline **389** was also present.



(420)

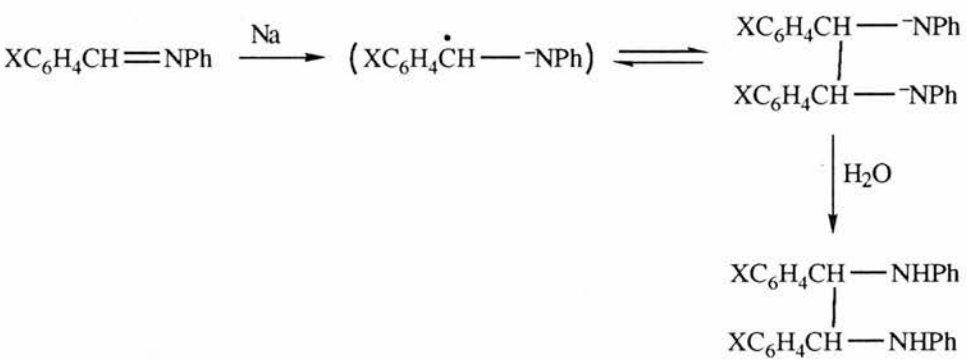


(421)

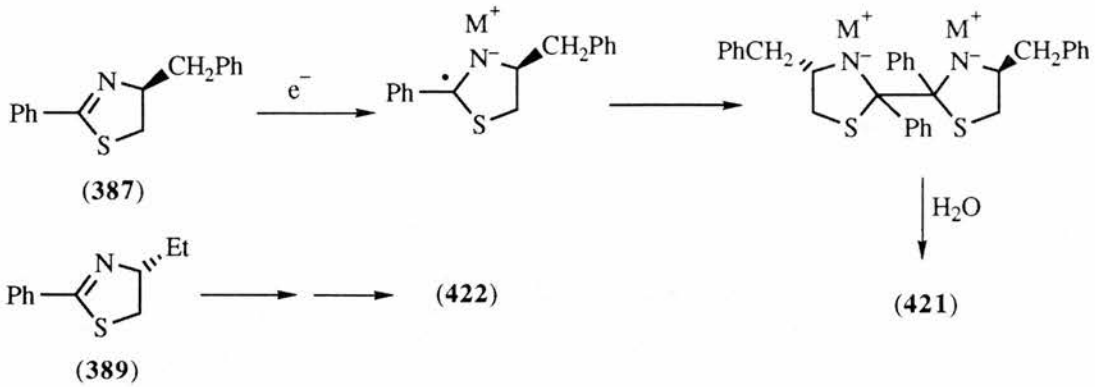


(422)

Since the sulphones were unreactive under most conditions the unoxidised thiazolines **387** and **389** were reduced with Al / Hg in wet ether to produce the dimers **421** and **422**. Reductive dimerisation of imines by alkali

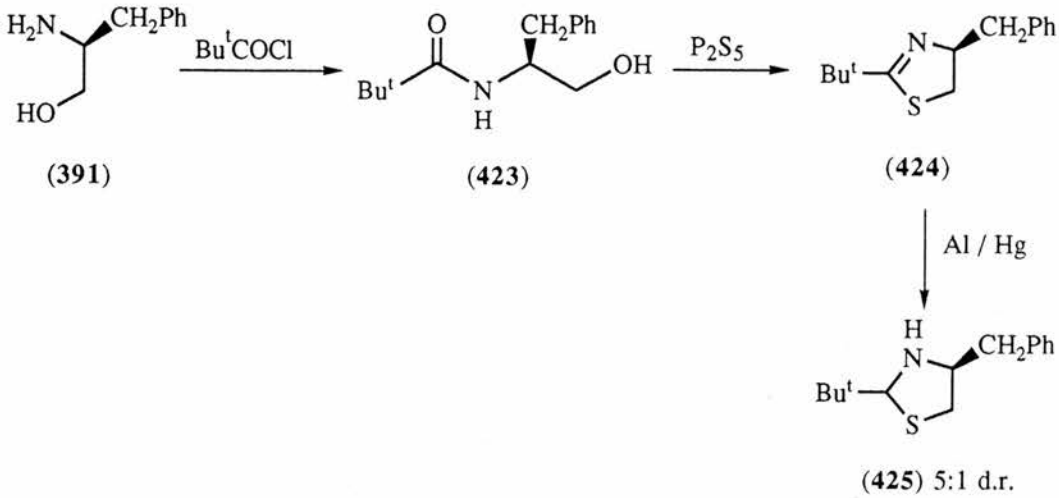


metals has been suggested[346] to proceed by the mechanism outlined above. Electron donating substitutents (X) were found to destabilise the radical anion and inhibit dimerisation whereas electron withdrawing substitutents had the opposite effect. One electron donation to **387** would give the radical anion which is stabilised by the electron withdrawing 2-phenyl group and would favour dimerisation. Water present in the ether donates 2 protons to give the observed product **421** and the same scheme can be used to explain **422**.



Evidence for the identity of **421** and **422** comes from the MS, which showed the presence of M^+ peaks at 508 and 384 with their respective base peaks equal to half their mass. ^{13}C NMR analysis was extremely complicated with the majority of carbons registering 3 or 4 chemical shifts, this reflected the fact that with 2 fixed stereocentres and two new stereogenic centres, 4 distereomers (*SRRS*), (*SSRS*), (*SRSS*) and (*SSSS*) as in the case of **421**, were possible.

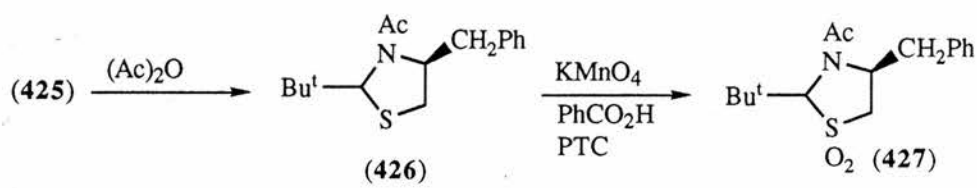
In an attempt to suppress the reductive dimerisation and obtain simple thiazolidines, choice of a bulkier 2-substituent was tried. Replacing the 2-phenyl moiety by a t-butyl group allowed the successful reduction of the imine bond with aluminium amalgam, to gave the thiazolidine **425**. The thiazoline **424** was prepared from trimethylacetyl chloride and the amino alcohol **391** to give the amido alcohol **423**. Ring closure using P_2S_5 as previously described, gives the thiazoline **424**. ^1H NMR showed **425** to be present as 2 diastereomers in roughly a 5:1 ratio but an NOE experiment on the major diastereomer failed to show any long range proton coupling between C(2)-H and C(4)-H and therefore the absolute configuration of the major isomer remains unknown at this time.



(391) (423) (424)

(425) 5:1 d.r.

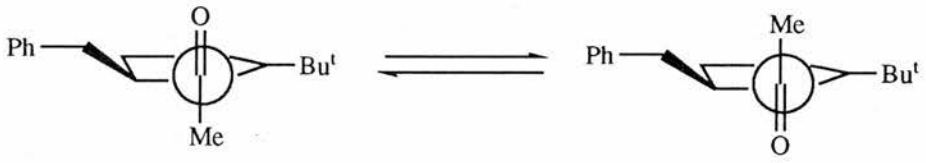
Oxidation of **425** using MCPBA in CH_2Cl_2 gave only an intractable mixture in which GC-MS analysis identified 10 compounds. As will be seen later in the oxidation of thiazolidine-2-thiones (Section E), protection of the nitrogen was necessary in order to ensure complete oxidation to the sulphone with no side reactions. The ring nitrogen in the thiazolidine **425** was therefore acetylated with acetic anhydride to afford **426** in 92% d.e. after crystallisation. Oxidation using $KMnO_4$ / benzoic acid and PTC conditions provided the crystalline sulphone **427** essentially as a pure stereoisomer. The successive diastereomeric enrichment on going from **425** to **426** to **427** is notable but in fact not unusual for crystalline compounds.



(426) (427)

NMR analysis of **426** and **427** revealed a number of broad peaks in both the ^{13}C and ^{1}H spectra. This indicated the existence of a dynamic process in which the conformers of **426** and **427** are exchanging at a rate comparable to the NMR time scale. A slow rate of exchange and therefore a large free energy of activation ($\Delta G^{\ddagger}$) for the interconversion between conformers A and

B, will be observed as two different species in the NMR spectrum. As seen in the NMR spectra of the thiazolidine carboxylic acids in the next Section, a fast rate of exchange and therefore a small $\Delta G^{\ddagger}$ for the interconversion of A and B, will be shown as an averaged spectrum in which the mean values for conformers A and B are plotted as one species.



A Scheme 13 **B**

A variable temperature NMR experiment was conducted on **426** and **427** with temperatures ranging from 233 K to 323 K to calculate the approximate free energy of activation ($\Delta G^{\ddagger}$) for each compound in the conversion from A to B. The labels, A and B in (Scheme 13) have been arbitrarily assigned. Cooling the sample to 233 K slowed the rate of interconversion down enough to observe the two conformers and from the ^{13}C and ^{1}H spectra of **426** and **427** at 233 K it can be observed that the population of conformers is unequal (i.e. the position of the equilibrium favours A or B) and from the intensity of these signals in the ^{1}H NMR spectrum the free energy (ΔG) of this process can be calculated.[347]

At low temperature the ^{1}H NMR spectrum of **426** shows the methyl signal and the t-butyl signal split into two. As the sample gradually warms up the two split signals merge into two broad singlets and finally sharpen up to give one signal for the methyl group and one for the t-butyl group. The temperature at which the two signals merge into one is called the coalescence point. Using the temperature at the coalescence point and the difference in chemical shift from the low temperature split signal, the free energy of activation for the interconversion of A and B can be calculated (see Table 1).

The low temperature ^{13}C spectrum of **426** shows 9 carbons split in two, with the $\Delta G^{\ddagger}$ calculated in the same manner as above, see Table 1.

Table 1.

Free energy of activation for thiazolidine 426.

^{1}H NMR	Peak type	T_C K	$\Delta G^{\ddagger}$ kJmol^{-1}	ΔG kJmol^{-1}
	CH_3	278	59.5	0.79
	Bu^t	288	62.1	0.79
^{13}C NMR	CO	293	62.4	
	4ry	303	61.2	
	CH	298	61.9	
	CH	313	61.1	
	CH	293	64.7	
	CH_2	303	61.9	
	4ry	303	61.1	
	CH_2	278	59.9	
	CH_3	298	62.5	

The ^{1}H NMR low temperature spectrum of **427** shows two main split signals due to the methyl and t-butyl group and the ^{13}C low temperature spectrum shown in Figure 2, displays 10 split signals. The coalescence of the split signals from the methyl peak in the ^{1}H spectrum and two carbons from the ^{13}C spectrum are shown in Figure 3. The ^{1}H and ^{13}C signals exist in two states at 233 K and as energy was added to the system they merge at the coalescence temperatures, 298 K, 303 K and 288 K respectively and sharpen into one averaged signal. The free energy of activation for thiazolidine S,S-dioxide **427** is listed in Table 2.

Low temperature ^{13}C NMR of 3-acetyl-4-(*S*)-benzyl -2-t-butylthiazolidine 1,1-dioxide (427)

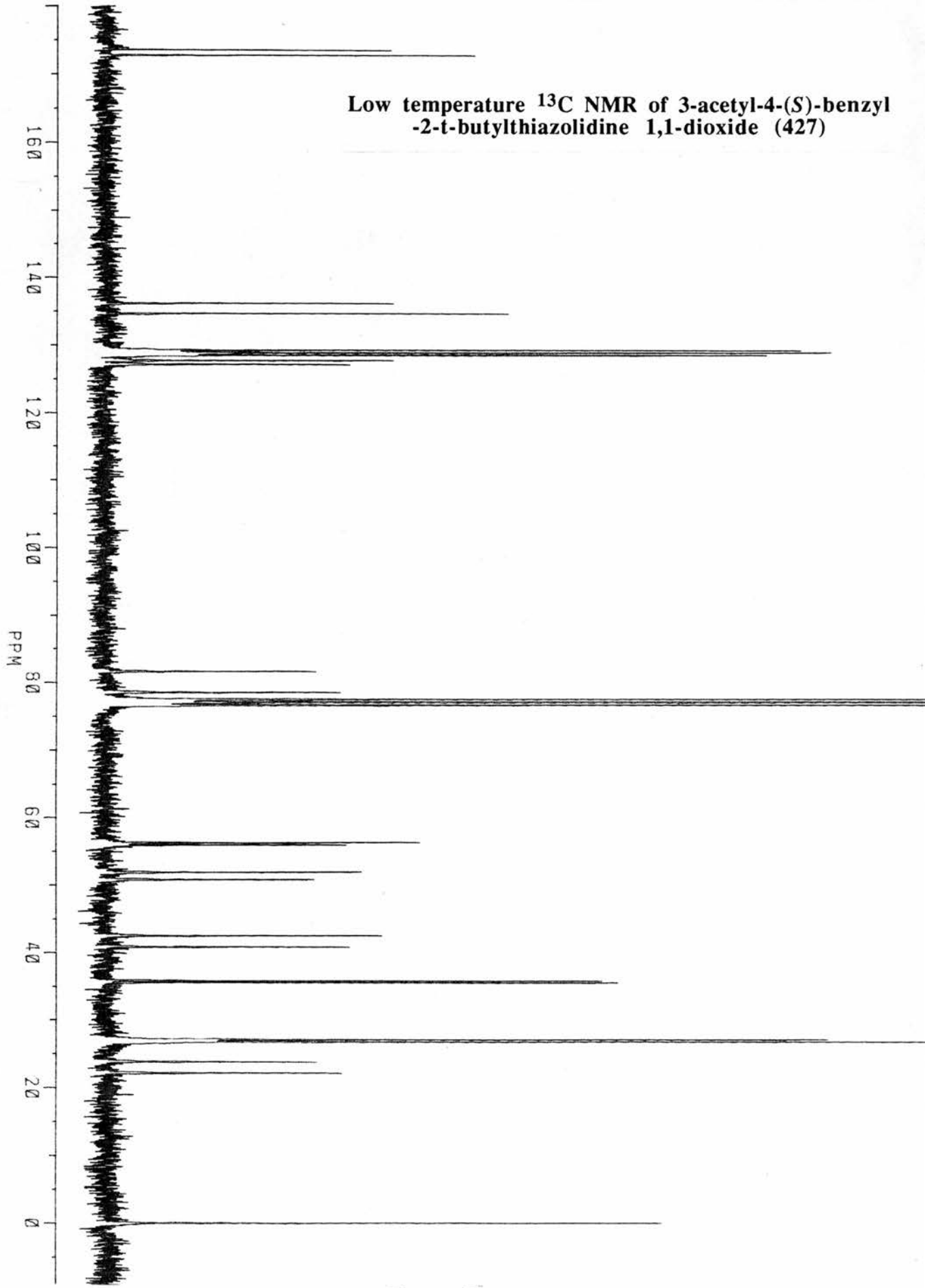


Figure 2

Variable temperature ^{1}H and ^{13}C NMR examples of (427)

Figure 3

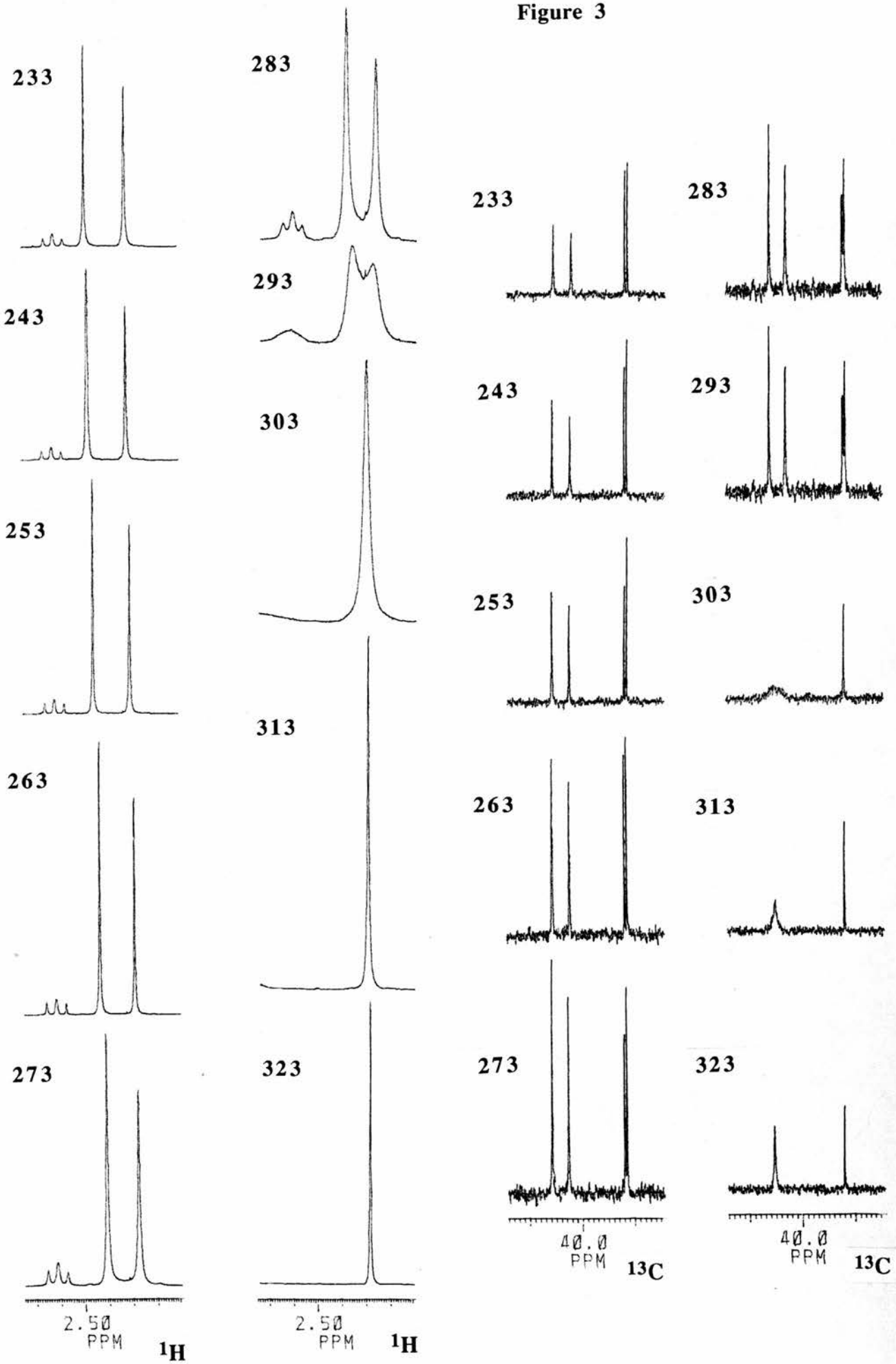


Table 2.

Free energy of activation for thiazolidine S,S-dioxide 427.

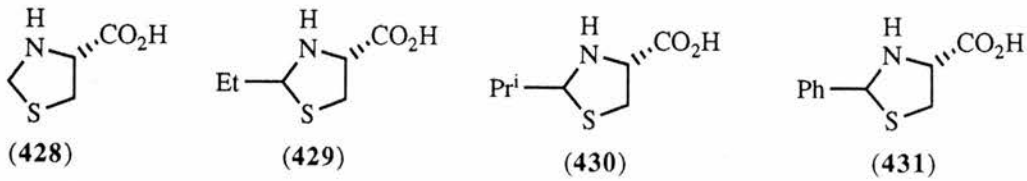
	Peak type	T_C K	$\Delta G^{\ddagger}$ kJmol^{-1}	ΔG kJmol^{-1}
^{1}H NMR	CH_3	298	61.3	0.39
	Bu^t	293	62.4	0.39
^{13}C NMR	CO	298	60.9	
	4ry	298	59.3	
	CH	298	61.7	
	CH	313	60.4	
	CH	288	60.8	
	CH_2	303	61.2	
	CH_2	303	60.1	
	4ry	288	61.5	
	CH_3	288	61.0	
	CH_3	303	60.1	

Comparision of the averaged $\Delta G^{\ddagger}_{AV}$ for each compound; **426** $\Delta G^{\ddagger}_{AV}$=61.7 kJmol^{-1} and **427** $\Delta G^{\ddagger}_{AV}$ =60.9 kJmol^{-1} shows that the free energy of activation for the interconversion between conformers is approximately the same for both molecules and the free energy barrier to rotation (ΔG) in **426** ΔG=790 Jmol^{-1} was found to be almost twice that of **427** ΔG=390 Jmol^{-1}.

3. Preparation of thiazolidine 1,1-dioxides from (*R*)-cysteine

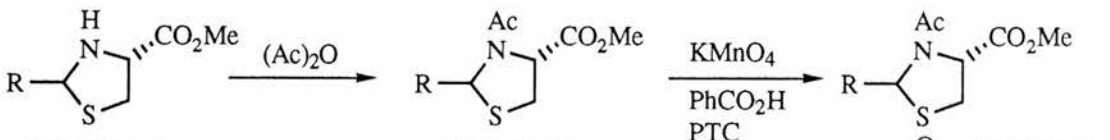
Well established methods were used to prepare the sulphones derived from the basic thiazolidine rings systems **428-431**. The preparation of **429-431** (**428**

is commercially available) was achieved by the condensation of (*R*)-cysteine



(428) (429) (430) (431)

with propionaldehyde, isobutyraldehyde and benzaldehyde, respectively. The thiazolidine carboxylic acids were then converted into their respective methyl esters **432-435**, the ring nitrogen was acetylated with acetic anhydride to give



(**432**) R=H
(**433**) R=Et
(**434**) R=Pr^i
(**435**) R=Ph

(**436**) R=H
(**437**) R=Et
(**438**) R=Pr^i
(**439**) R=Ph

(**440**) R=H
(**441**) R=Et
(**442**) R=Pr^i
(**443**) R=Ph

the trisubstituted thiazolidines **436-439** and finally oxidation with $KMnO_4$ / benzoic acid under PTC conditions provided the sulphones **440-443**. The formation of the sulphones was confirmed by spectroscopic analysis. Infrared absorptions of the SO_2 moiety were observed between 1350-1310 and 1170-1145 cm^{-1} which matched expected values, and the ^{13}C NMR signal for the ring CH_2 adjacent to the oxidised sulphur experienced a 15 ppm chemical shift to higher frequency, relative to the unoxidised sulphur, also matching observations in the thiazolidine-2-thione oxidations to be described in Section E.

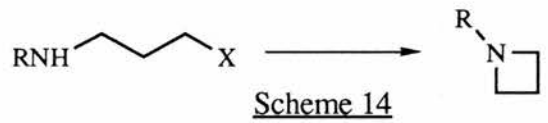
A slight broadening of the lines in the ^1H and ^{13}C NMR spectra was observed for sulphones **440** to **443**, again indicative of a dynamic process involving the interconversion of conformers around the amide bond. An extra set of shifts representing the other conformer was seen in the RT NMR

spectra of **440** and **441** indicating a slow interconversion rate and therefore a large $\Delta G^{\ddagger}$, but this was not determined quantitatively.

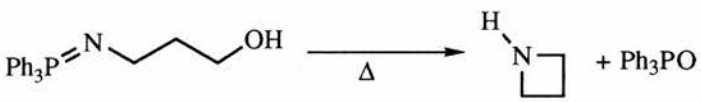
D. FVP of trisubstituted thiazolidine 1,1-dioxides

1. Background

The most general approach to the synthesis of the azetidine ring is the cyclisation of a 3-substituted propylamine where X is either a halide or a sulphonate, Scheme 14.[341] Cyclisation using pyrolysis conditions was used to

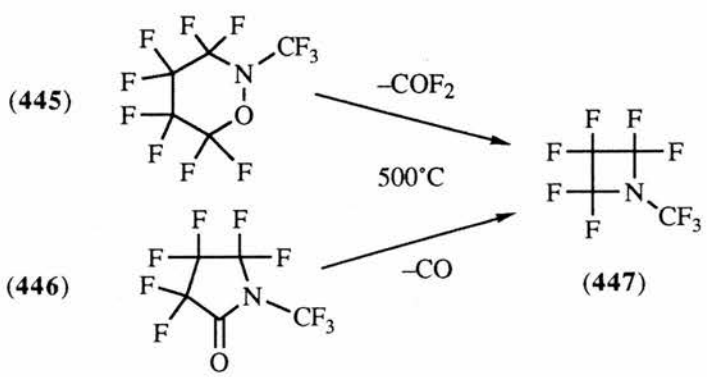


Scheme 14

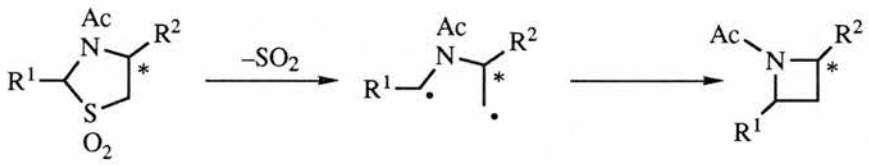


(444)

cyclise the ylide **444** to afford the azetidine in 33% yield[348] and thermolysis of **445** or **446** with the loss of carbonyl difluoride or carbon monoxide affords the polyfluoro azetidine **447**.[349]



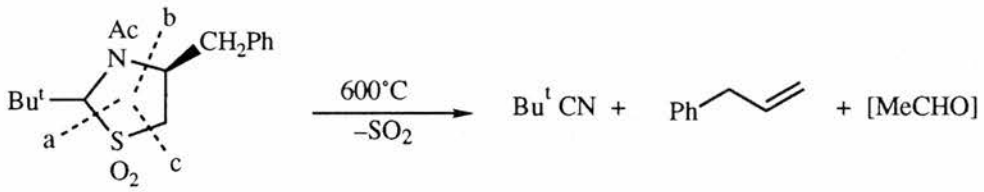
The FVP of sulphones **427** and **440-443** was considered a viable method to obtain optically active azetidines, Scheme 15. Extrusion of SO_2 would give the diradical which could ring close to give the optically active azetidine with possible racemisation at the R^1 group. As with the thiazoline dioxides of Section B, the pyrolytic behaviour of this heterocyclic system has not previously been examined.



Scheme 15

2. Pyrolysis results

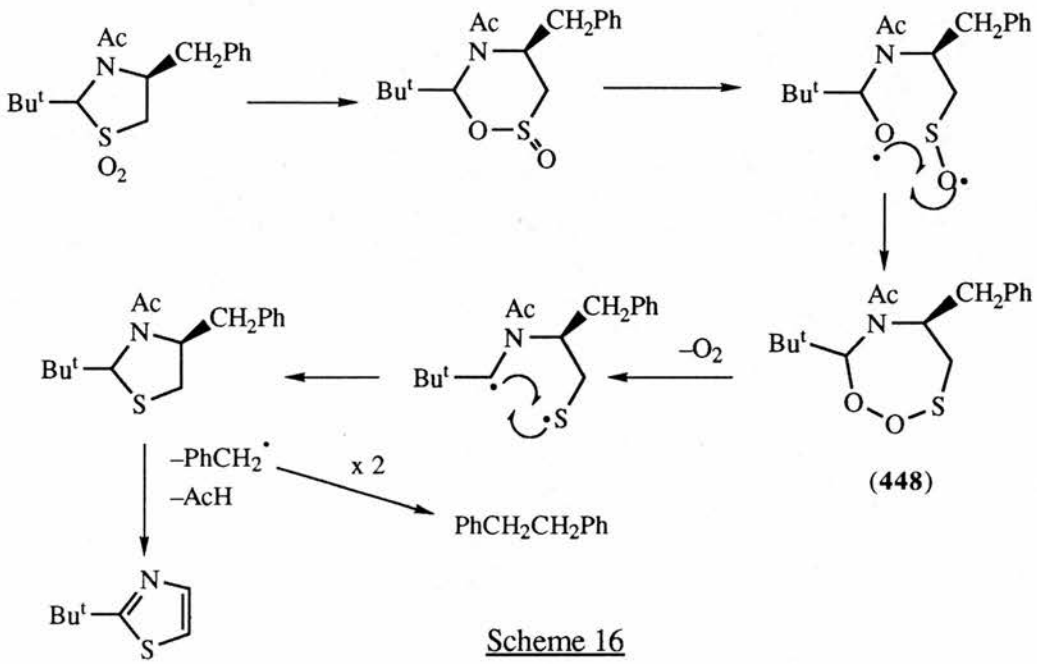
The FVP of **427** at 600°C results in fragmentation of the thiazolidine ring at positions a, b and c to give primarily allyl benzene. Loss of the acetyl group



(**427**)

provides trimethylacetonitrile, with the presence of bibenzyl, 1-phenyl-1-propyne, pivalaldehyde and 2-t-butylthiazole also indicated in varying amounts from GC-MS, ^{13}C and ^{1}H NMR analysis. The thiazole was identified by GC-MS only, although in significant quantities (5.7%) and 3 peaks in the GC-MS trace remained unidentified. A speculative mechanism for the formation of the thiazole is based on the extrusion of oxygen (Scheme 16). Ring expansion to give the sulphinate ester, is followed by cleavage of the S-O bond and the

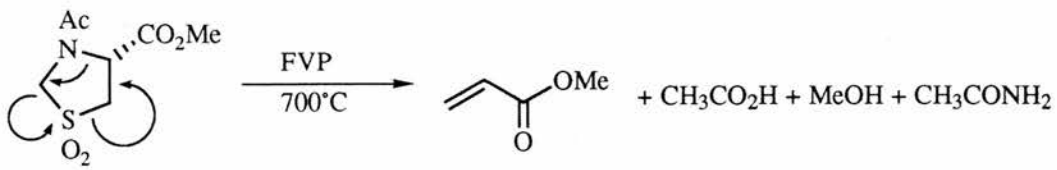
reformation of the oxygen-oxygen bond giving **448**. Loss of molecular oxygen followed by a benzyl radical and acetaldehyde provides 2-t-



Scheme 16

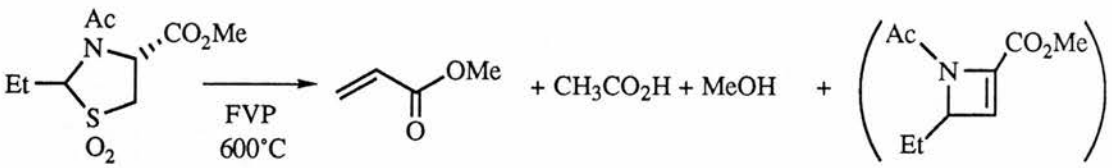
butylthiazole. The bibenzyl found is consistent with this but no trace of acetaldehyde could be found, perhaps due to its loss by evaporation.

The FVP of sulphone **440** at 700°C also fragments the molecule in the usual way to give methyl acrylate, acetic acid, methanol and acetamide, all clearly identifiable from the ^{13}C and ^{1}H NMR spectra. Acetic acid and acetamide are presumed to be derived from hydrolysis of the methyleneimine but if any formaldehyde was formed it was lost by evaporation or possibly reduced to methanol. Alternatively the methanol could arise by elimination from methyl acrylate.



(440)

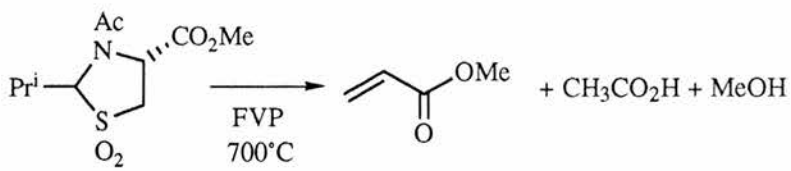
From the pyrolysis of **441** at 600°C, acetic acid, methyl acrylate and methanol were identified by ^{1}H NMR. GC-MS analysis gave a very clean trace with 4 major compounds present, the largest being m/z 183. This



(441) **(449)**

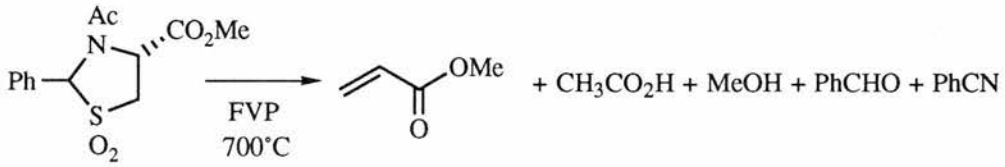
corresponds to a loss of 66 from the original sulphone **441** which would correspond to the 2-azetine **449**. Isolation of this was attempted on preparative TLC but GC-MS of the isolated compound now showed more than 10 compounds to be present, with none of the parent compound left.

FVP of **442** at 700°C, followed the same general pattern, with complete fragmentation being the dominant process observed. ^{1}H NMR identified methyl acrylate, acetic acid and methanol as the major products and GC-MS identified isobutyraldehyde, isobutyronitrile and methyl acetate.



(442)

Thermolysis of **443** at 700°C, gave a very clean ^{1}H NMR spectrum consisting of methyl acrylate, acetic acid, methanol and benzaldehyde with GC-MS identifying benzonitrile.

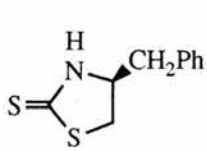


(443)

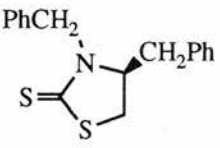
E. Preparation of (*R*) and (*S*)-thiazolidin-2-one 1,1-dioxides

1. Background

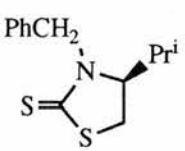
The preparation of thiazolidine-2-thiones involves the condensation of carbon disulphide and an amino alcohol.[350] Previous work in this laboratory by Armstrong[288] outlined the direct synthesis of **450** to **452** starting from the amino alcohols (*S*)-phenylalanine and (*S*)-valine.



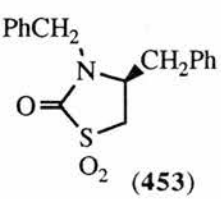
(450)



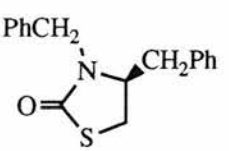
(451)



(452)



(453)

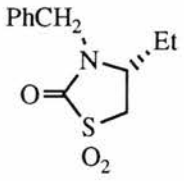


(454)

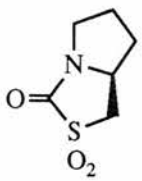
The oxidation of **450** was found to lead to ring opened products, but this could be prevented by protection of the nitrogen with a benzyl group. Oxidation of **451** using a variety of oxidants and conditions proceeded in very low yields, affording **453** and **454** plus a number of unidentified compounds. Notably $KMnO_4$ in a 50% aqueous acetic acid solution gave **453** in 5% yield and **454** in 4.5%.

2. Synthesis of (*R*) and (*S*)-thiazolidine-2-thiones

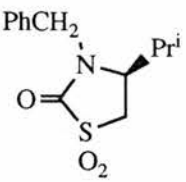
The synthesis of **453** (for further studies) and the previously unknown compounds **455**, **378** and **456** began with preparation of the corresponding



(455)

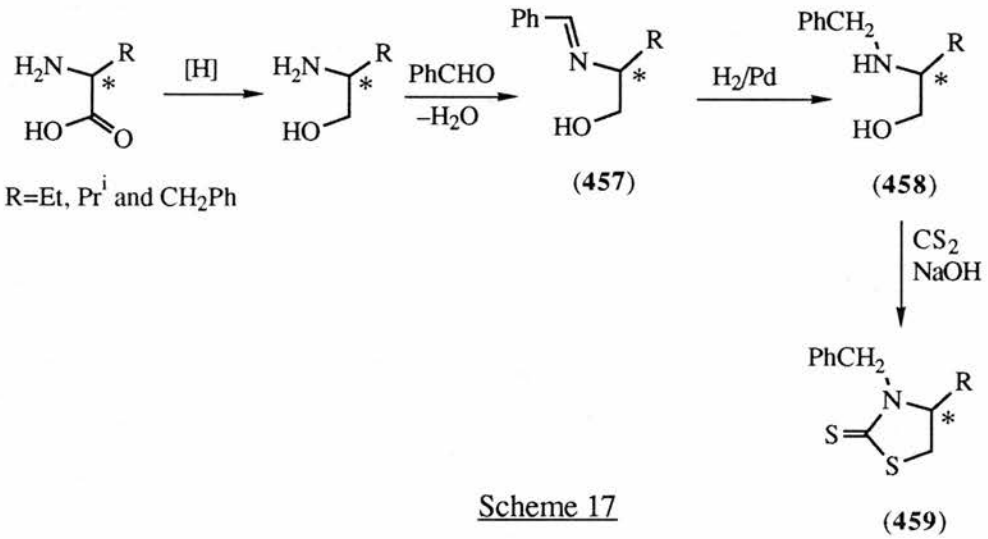


(378)



(456)

thiazolidine-2-thiones **459** and **379** which was carried out according to the methods outlined by Armstrong,[288] and shown in Scheme 17.



R=Et, Pr^i and CH_2Ph

(457)

(458)

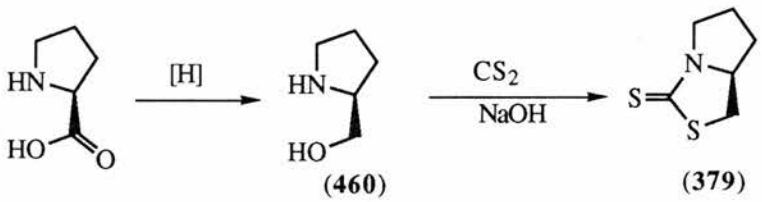
(459)

Scheme 17

The amino alcohols **391-393** (discussed in Section A) were condensed with benzaldehyde, with azeotropic removal of water to give the imines **457**, reduction of which, with hydrogen in the presence of a palladium on charcoal catalyst provided the *N*-benzylamino alcohols **458**. Condensation of **458** with carbon disulphide afforded the thiazolidine-2-thione ring system **459**, with its characteristic thiocarbonyl ^{13}C NMR shift around 197 ppm. Two well-defined AB systems are also visible in the ^1H NMR spectra of **459**. Mutually coupled protons on the *N*-methylene give rise to a simple AB pattern with a coupling constant around 16-17 Hz and a well defined chemical shift difference of about 1.8 ppm due in part to the conformationally locked protons of the *N*-methylene and the anisotropic effect of the thiocarbonyl group. An ABX pattern is observed for C-5 H in which the diastereotopic geminal protons are

coupled with the higher frequency C-4 proton and have a chemical shift difference of 0.1-0.4 ppm.

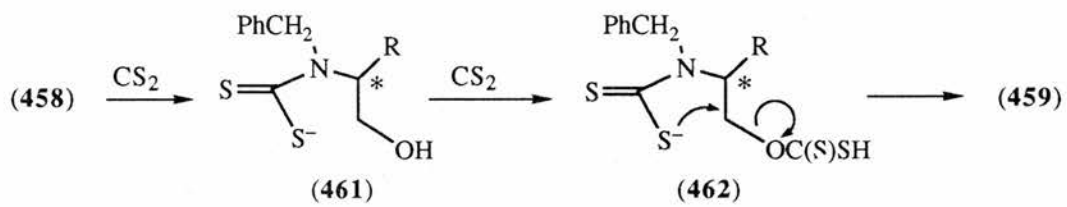
The preparation of the bicyclic thiazolidine-2-thione **379** was performed similarly. (*S*)-Proline was reduced with $LiAlH_4$ and condensation



(460) **(379)**

of **460** with carbon disulphide furnished the bicyclic product **379**. The spectroscopic characteristics of **379** include the thiocarbonyl ^{13}C NMR shift of 191 ppm and a very complicated ^{1}H NMR spectrum due to the complex proton couplings of the bicyclic system. The proton-proton COSY spectra of all the bicyclic systems were carried out to assign the protons unambiguously and are shown later in Table 3 (page 156).

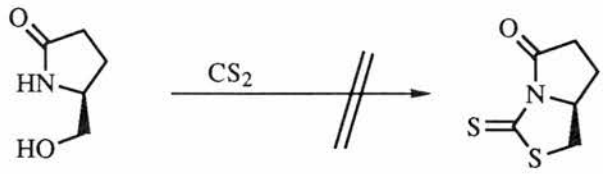
Mechanistically carbon disulphide reacts with **458** to give the dithiocarbamate **461**, addition of another carbon disulphide gives the



(461) **(462)**

dithiocarbamate / xanthate ester **462** and nucleophilic attack by S^- leads to ring closure and the observed products.[351, 352]

In an effort to introduce additional functionality into the bicyclic dithiocarbamates, **463** derived from pyroglutamic acid, failed to react with carbon disulphide to give **464**, presumably due to the weak nucleophilic character of what is now an amide nitrogen.

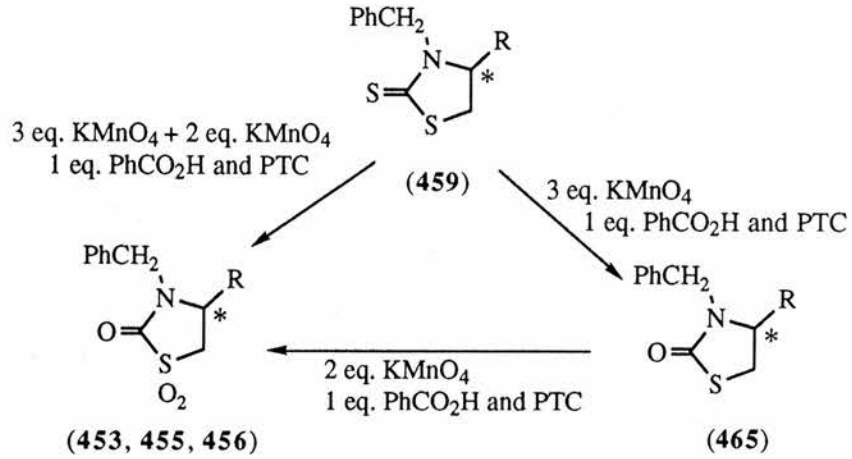


(463) (464)

3. Oxidation of (*R*) and (*S*)-thiazolidine-2-thiones

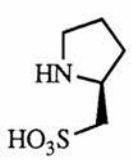
In 1961 Gaul[309] reported the oxidation of 3-substituted thiazolidine-2-thiones in up to 90% yield using peracetic acid, and the same method applied to **459** R=Et, Pr^i or $PhCH_2$ furnished **453**, **455** and **456** in yields between 16-30%. Using the new method developed in the course of this work and described in Section A, the sulphones **453** and **455** were obtained by $KMnO_4$ oxidation in a phase transfer system containing 1 eq. of benzoic acid, in improved yields of ~70%.

As mentioned above 50% acetic acid afforded very poor yields of the desired thiazolidine sulphones and indeed without benzoic acid present in the PTC system, **459** reacts only partially to gave **465** in 40% yield and further oxidation to give the sulphone was not observed. Using 3 eq. of $KMnO_4$, 1 eq. of benzoic acid and PTC conditions the thiazolidines **459** are oxidised to give the thiazolidin-2-ones **465** which can be isolated at this point. Further addition of $KMnO_4$ affords the sulphones **453** and **455** in high yields. As demonstrated by Gaul[309] the first step in the oxidation of thiazolidine-2-thiones is the exchange of the exocyclic sulphur for oxygen. With the presence of sulphur poisoning any remaining $KMnO_4$ and therefore further oxidation, the thiazolidin-2-ones **465** can be isolated in up to 76% yield.

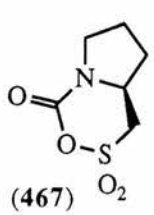


The distinctive characteristics of the thiazolidin-2-ones **465** include a ^{13}C NMR carbonyl shift of 172 ppm which is down from 197 ppm (in **459**). A smaller (1 ppm and 0-0.3 ppm) chemical shift difference was observed for the AB pattern of the *N*-methylene protons with coupling constants of 15-17 Hz, and in the ABX systems respectively. The carbonyl shows a typical thiocarbamate infrared stretch at 1650-1670 cm^{-1}.

Specific attributes of the sulphones (**453**, **455** and **456**) include a further decrease in ^{13}C NMR frequency for the carbonyl to 160 ppm and a significant increase in frequency for the C-5 carbon by about 17 ppm in comparison to thiazolidin-2-ones **465**. These differences are due primarily to the increased electron widthdrawing effect of the sulphone moiety. The AB and ABX patterns are present and very similar to the thiazolidin-2-ones **465**. Infrared absorptions of 1720 cm^{-1} for the carbonyl and 1320 and 1135 cm^{-1} for the sulphone group match reported literature values.[309]

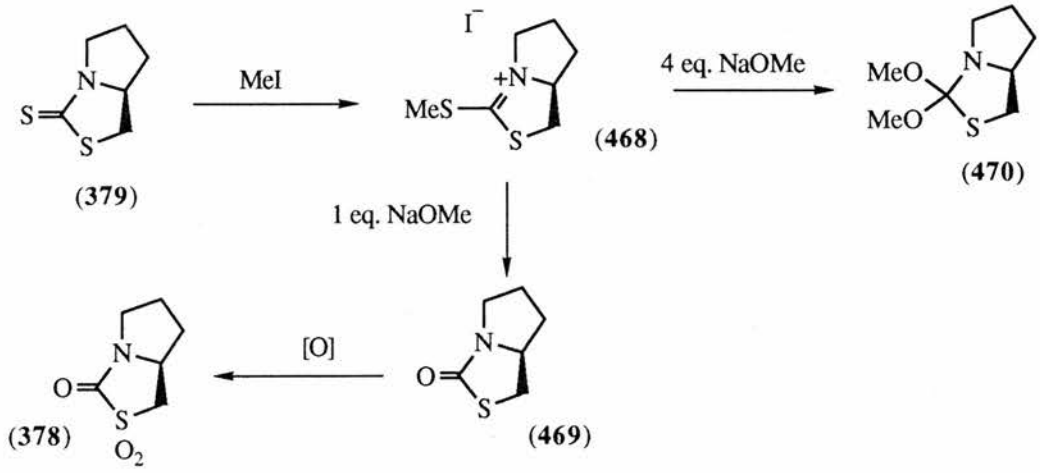


(466)



(467)

Initial attempts to oxidise **379**, using a number of reagents lead to the isolation of **466** in high yields. The isolation of the sulphone **378** proved difficult due to the presence of elemental sulphur, its low solubility in organic solvents and its facile ability to over oxidise. An experiment was conducted in which **379** was oxidised by peroxyacetic acid (5 eq.) in acetic acid at 75°C (following the exact procedure by Gaul[309]) with aliquots taken at 3, 8 and 24 hr. The aliquots were analysed by ^{13}C NMR and the results were as follows: After 3 hours **379** and **469** were absent and **378** was present in equal amounts to an unknown compound with a carbonyl peak at 165 ppm, thought at the time to be the sulphoxide. After 8 hours the signals due to the sulphone **378** had diminished and the unknown had grown in intensity. After 24 hours the sulphone had all been converted to the unknown. Attempted isolation of the unknown failed and only afforded compound **466**, which led us to believe that the unknown was a mixed anhydride **467**[353] which, with the addition of water could easily hydrolyse with decarboxylation of the carbamic acid to give **466**.



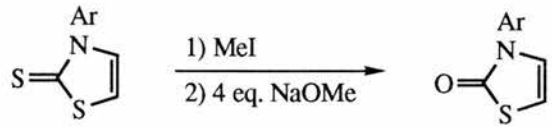
Scheme 18

It therefore seemed necessary to eliminate the exocyclic sulphur first and then oxidise **469** with 2 eq. of a oxidising agent, see Scheme 18. The

removal of exocyclic sulphur can be accomplished by a number of methods Br_2 / AcOH[354], H_2O_2 in alkali[355] and HgO / AcOH.[356]

As described above the use of 3 eq. $KMnO_4$ and 1 eq. benzoic acid under PTC conditions fails in this instance to fully convert **379** to **469**, because the solvents involved gel into a very viscous emulsion which makes agitation impossible.

Formation of the thiazolidin-2-one **469** was realised by an electrophilic addition reaction employing methyl iodide and the thiazolidine-2-thione **379** to give the iminium salt **468**. Treatment of **468** with 1 eq. of sodium methoxide affords **469** in very respectable yields. This method was based on



(471) **(472)**

a literature report of conversion of 3-arylthiazolinethiones **471** to the corresponding thiazolinones **472** using 4 eq. of sodium methoxide.[308] Under these conditions **468** reacted to give the orthothiocarbamate **470**, which will be discussed in Section G. The orthothiocarbamate **470** was essentially stable to distillation at 170°C but slight decomposition to the thiazolidin-2-one **469** was observed.

The unique spectroscopic features of these bicyclic compounds are as follows: The characteristics of **468** in the ^{13}C NMR are the iminium carbon shift at 187 ppm and the appearance of a methyl signal at 20 ppm. The ^{13}C NMR shift for the carbonyl of **469** at 170 ppm, was similar to those obtained for the other thiazolidin-2-ones **465**. For both **468** and **469** the ^{1}H NMR spectra were analysed in detail and the results are shown in Table 3. The orthothiocarbamate **470** was identified by ^{1}H and ^{13}C NMR which showed two different O-methyl signals separated by 0.1 ppm in the proton and 2.5 ppm in

the carbon spectrum. Finally the quarternary carbon in **470**, surrounded by four heteroatoms has been shifted to lower frequencies in comparison to **468** and **469**, to 132 ppm, a very high value for an sp^3 carbon atom.

The oxidation of **469** was accomplished using two methods. The first method using 2 eq. of peroxyacetic acid, afforded **378** in 37% yield and **466** in 24% yield. The second method using 2 eq. of $KMnO_4$, 1 eq. of benzoic acid and PTC conditions, gave **378** in 70% yield. ^{13}C NMR data for the bicyclic sulphone **378** closely resembled that of the other sulphones **453**, **455** and **456** with a carbonyl shift at 158 ppm and the C-5 carbon shifted to higher frequencies by roughly 20 ppm from the C-5 carbon in **469**. Infrared absorption for the carbonyl and SO_2 also resembled those previously mentioned and the complex ^1H coupling of **378** is shown by the 2D NMR spectrum on the next page, with the results in Table 3.

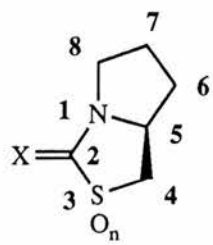


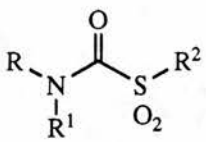
Table 3

Proton Shift data (ppm) from 2D NMR experiments

Compound	C-4	C-5	C-6	C-7	C-8	Me
379	3.35	4.65	2.2, 1.8	2.5-2.3	3.6, 3.45	
468	3.9, 3.85	5.2	2.2	2.45	3.7, 3.55	2.75
469	3.4, 3.25	4.25	2.05-1.6	2.3-2.1	3.55, 3.2	
378	3.8, 3.1	3.95	2.3, 1.55	2.2-2.02	3.55	

In contrast to the thiazoline dioxides described in Section A, the thiazolidin-2-one dioxides prepared here were not readily hydrolysed. This is

consistent with the previous finding by Barton *et al.*[357] that acyclic carbamoyl sulphones **473** did not hydrolyse easily in contrast to α-ketosulphones. The presence of the extra heteroatom evidently deactivates the system considerably.

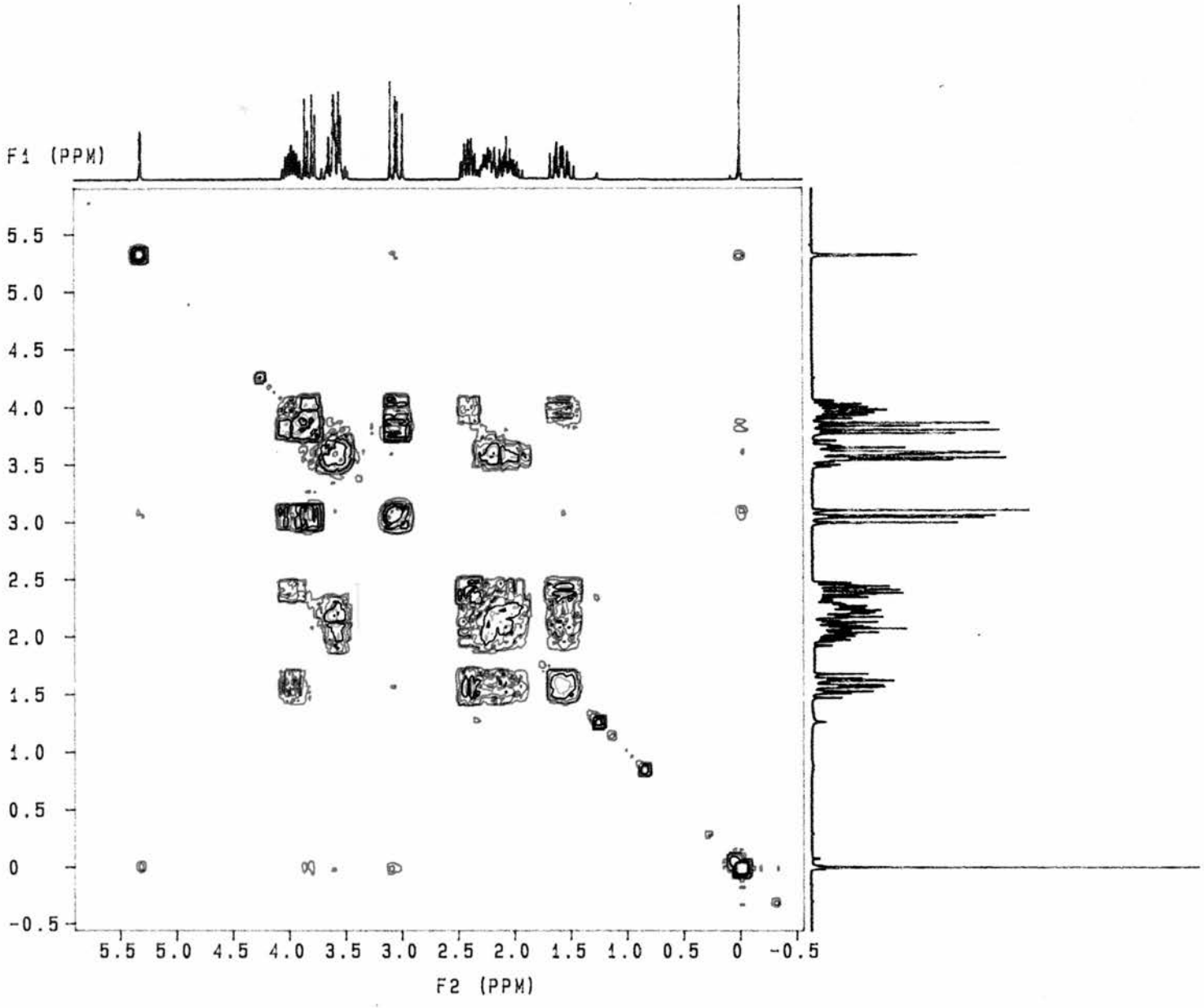


(473)

2D NMR of (*S*)-3-thia-1-azabicyclo [3.3.0]octan-2-one 3,3-dioxide (378)

EXP4 PULSE SEQUENCE: COSY
DATE 12-14-90
SOLVENT CDCL3
FILE COSY

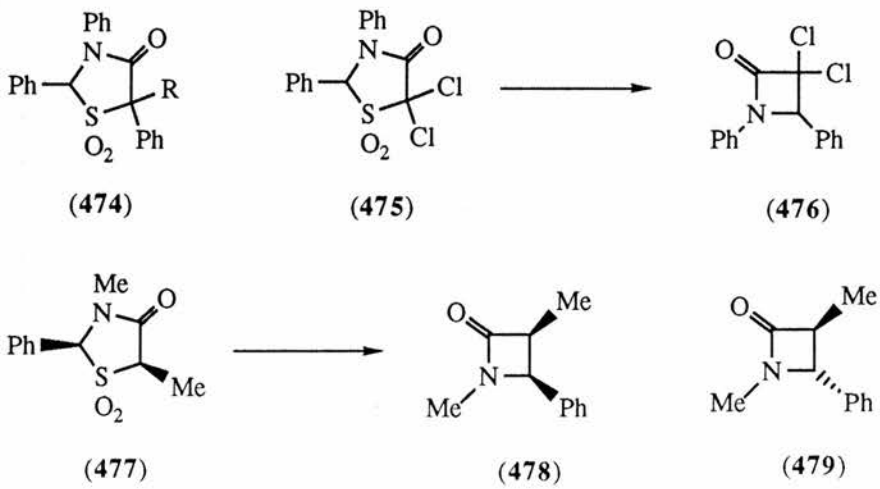
COSY PULSE SEQUENCE
OBSERVE PROTON
FREQUENCY 199.975 MHZ
1D SPECTRAL WIDTH (F2) 1291.8 HZ
2D SPECTRAL WIDTH (F1) 1291.8 HZ
ACQ. TIME 0.198 SEC
RELAXATION DELAY 1.0 SEC
PULSE WIDTH 90 DEGREES
FIRST PULSE 90 DEGREES
AMBIENT TEMPERATURE
NO. REPETITIONS 16
NO. INCREMENTS 128
DATA PROCESSING
PSEUDO-ECHO SHAPED
FT SIZE 512 X 512
TOTAL TIME 47.9 MINUTES



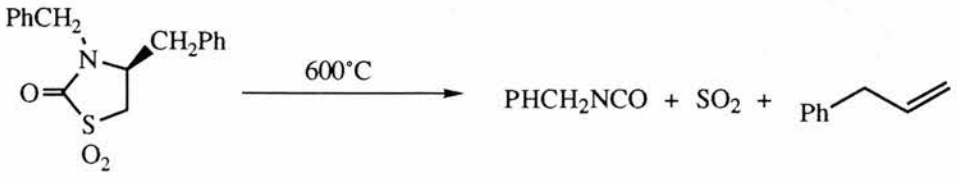
F. Pyrolysis and photolysis of (*R*) and (*S*)-thiazolidin-2-one 1,1-dioxides

1. Background

With the synthesis of **378**, **453**, **455** and **456** the extrusion of SO_2 could be investigated. Under thermal or photochemical conditions the loss of SO_2 in similar ring systems has produced a variety of β-lactams. Kagan[358] has reported the synthesis of β-lactams by a thermal or photochemical reaction involving **474**. The heating of **475** affords high yields of β lactam **476**,[359] and Sousa[314] addressed the problem of obtaining optically active β-lactams

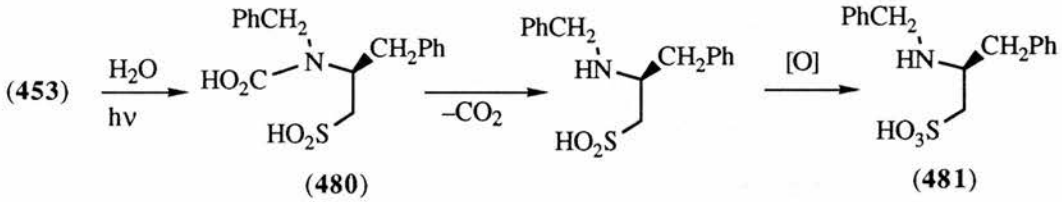


478 and **479** from the extrusion of SO_2 from **477**. Armstrong,[288] however found in a preliminary study that the FVP of sulphone **453** at 600°C gave benzylisocyanate, allylbenzene and SO_2 as main products. The steric hindrance between the two benzyl groups was thought to be the driving force behind the fragmentation. The use of smaller alkyl groups or a bridging group between the N-3 and C-4 positions might lessen the strain and allow the formation of β-lactams.



(453)

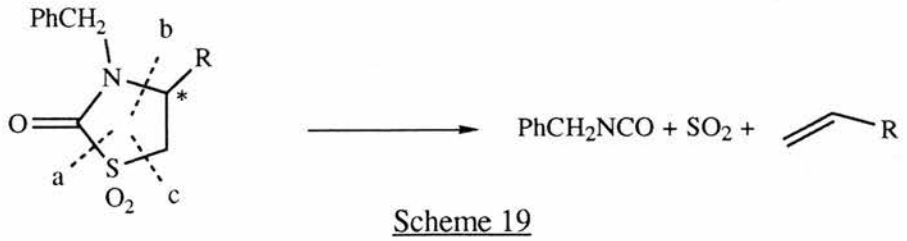
Under photochemical conditions Armstrong found that the majority of sulphone **453** remained unchanged, only after 2-7 days did a minute crystal appear in the quartz tube. NMR, MS and elemental analysis has shown this



crystal to be the aminosulphonic acid **481** formed by the hydrolysis of **453** to give the carbamic-sulphinic acid **480**, followed by decarboxylation and oxidation or disproportionation to give the sulphonic acid **481**.

2. FVP of (*R*) and (*S*)-thiazolidin-2-one 1-1-dioxides

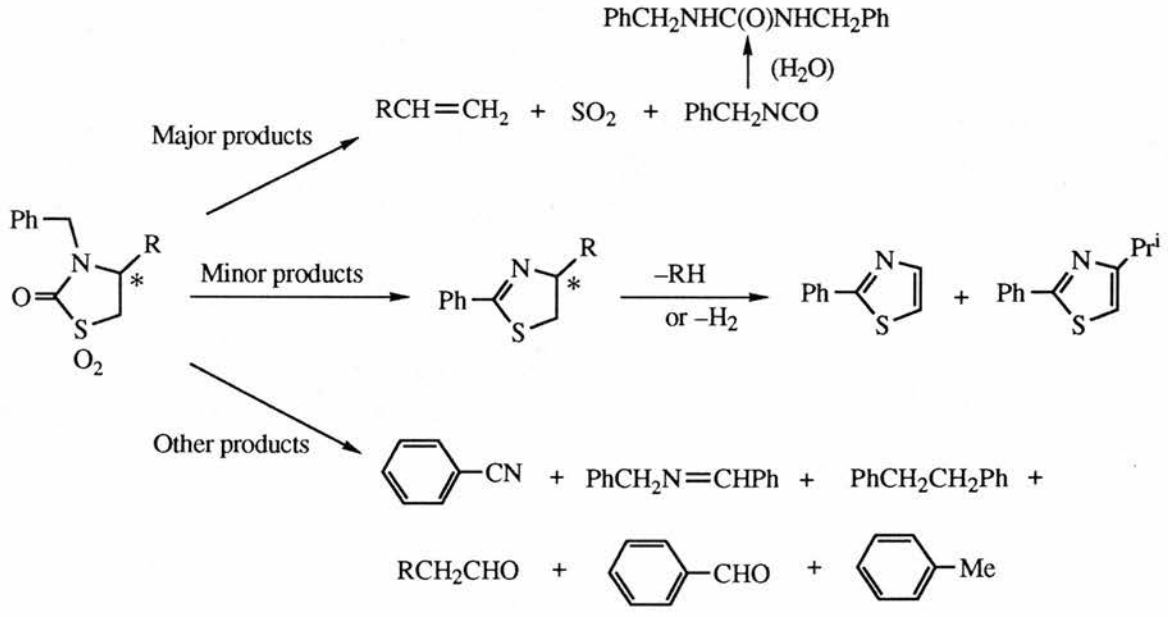
Pyrolysis of sulphones **453**, **455** and **456** resulted mainly in the complete fragmentation shown in Scheme 19 to give benzyl isocyanate, identified as the hydrolysis product dibenzylurea, a terminal alkene and SO_2. However closer



Scheme 19

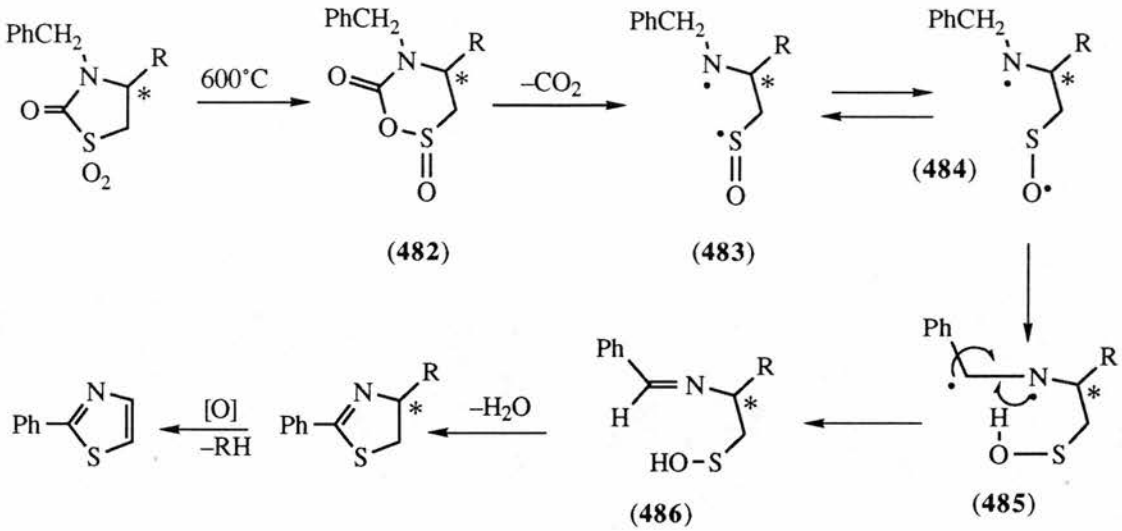
(453, 455, 456)

examination (Scheme 20) of the products revealed the presence of additional minor products. The presence of bibenzyl and toluene, pointed to loss of the *N*-benzyl group as a benzyl radical and benzonitrile may be derived from benzyl isocyanate. The presence of benzaldehyde and aldehydes (RCH_2CHO)



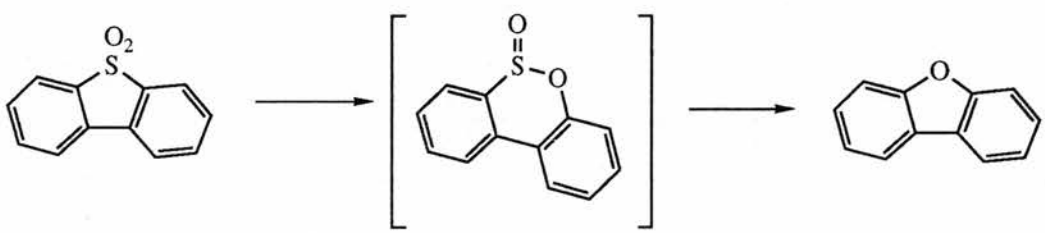
Scheme 20

and *N*-benzylidenebenzylamine (found only in the pyrolysates of sulphones **455** and **456**) points to further complex decomposition pathways. Most interesting however was the formation of small but significant yields of thiazolines and thiazoles. In all three cases a minor pathway led to 2-phenyl-4-substituted-2-thiazoline, 2-phenylthiazole and in the case of sulphone **456**, 2-phenyl-4-isopropylthiazole. These products can be accounted for (Scheme 21) by initial ring expansion to give the carbamic-sulphinic anhydride **482** which loses CO_2 to give the diradicals **483-484**. Abstraction of the benzylic H by the sulphenoxyl radical, leads to formation of the imine **486** which dehydrates to afford the observed products. The thiazoline can then be further dehydrogenated with loss of RH to give the thiazole while 2-phenyl-4-isopropylthiazole is formed by the oxidative elimination of hydrogen.



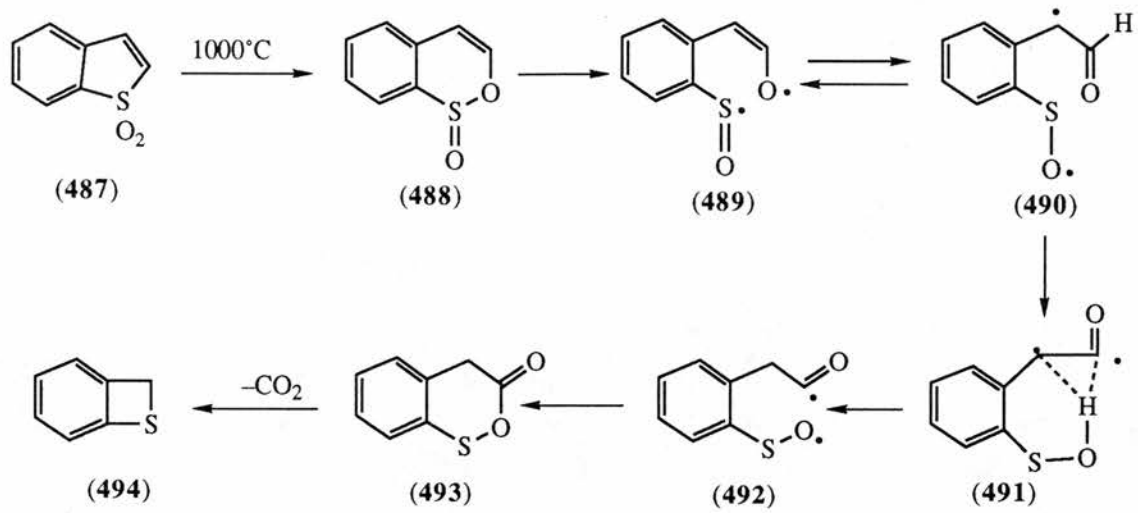
Scheme 21

This reaction has some similarity to the formation of benzothiete **494** from benzo[b]thiophene 1,1-dioxide **487** shown in Scheme 23. Previous work had shown that the pyrolysis of dibenzothiophene dioxide proceeded via a



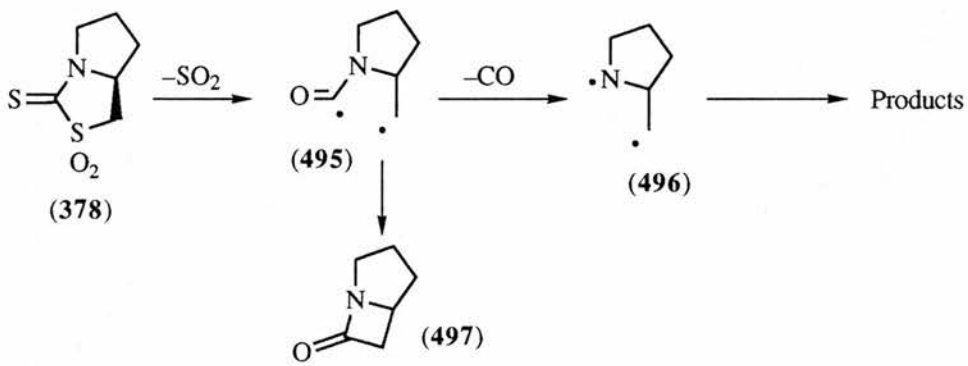
Scheme 22

sulphone-sulphite rearrangement as shown in Scheme 22.[360] van Tilborg[361] proposed that the pyrolysis of **487** proceeded along the same lines to give **488**. Rupture of the S-O bond affords the diradicals **489-490** which undergoes a 1,2-hydrogen shift **491** via the neighbouring sulphenoxyl radical, to give **492**. Intramolecular recombination and loss of CO_2 produces the benzothiete **494**.



Scheme 23

It was expected that sulphone **378** would lose SO_2 to give the diradical



495, which could recombine to give the β-lactam **497** or lose CO to give another diradical **496** which could rearrange to give one or more of the expected products in Figure 4.

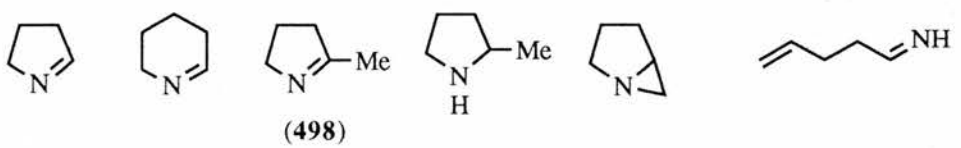
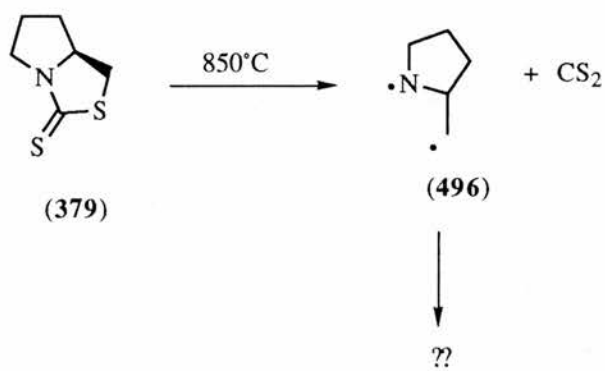


Figure 4

Pyrolysis of **378** at 500-600°C afforded a number of compounds, but none of the β-lactam **497** was observed. GC-MS analysis showed 4

compounds with the largest peak having m/e 84 ($C_5H_{10}N$). ^{13}C NMR analysis identified two terminal alkene shifts and two carbonyl amide or imine shifts at 160 ppm. When the ^{13}C NMR shifts obtained from the pyrolysis were matched against the known shifts from the compounds in Figure 4, a number of similarities were highlighted but no exact matches occurred. Therefore diradicals **495** and **496** must have a number of other reaction pathways available to them.

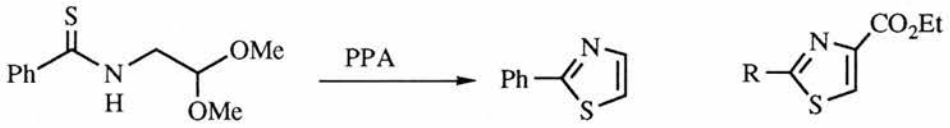
In an attempt to further understand these fragmentation pathways the thiazolidinethione **379** was pyrolysed at 850°C. The predicted loss of carbon



disulphide was observed, leaving the diradical **496** to rearrange into two compounds according to ^{13}C NMR and GC-MS analysis. Unfortunately, these two unknown compounds were different from any of the compounds obtained in the earlier pyrolysis of **378**, presumably due to the higher temperatures involved. GC-MS analysis exhibited two peaks with the largest having m/e 83 (C_5H_9N). Obviously the pyrolyses of **378** and **379** closely resemble each other but identification of the main products has remained frustratingly elusive.

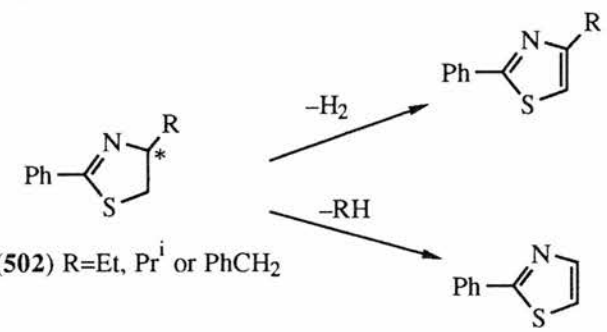
3. FVP: Authentic product synthesis

The FVP of sulphones **453**, **455** and **456** produced a number of compounds which needed verification against their authentic samples. These included the three new rearrangement products, 2-phenyl-4-substituted-2-thiazoline, 2-phenyl-4-isopropylthiazole and 2-phenylthiazole. The thiazolines were already known (see Section A) and were verified against Armstrong's reported NMR values.[288] The 2-phenylthiazole **500** was synthesised by the acid catalysed cyclization of thiobenzamidoacetaldehyde dimethyl acetal[310] **499**.



(**499**) (**500**) (**501**)

In the FVP, the oxidation appears to occur via two different reaction pathways, with either the loss of hydrogen or RH (Scheme 24). Meyers[362] has

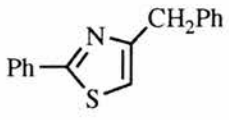


(**502**) R=Et, Pr^i or $PhCH_2$

Scheme 24

synthesised 4-substituted-2-phenylthiazoles **501** from the corresponding thiazolines by a method involving nickel peroxide in methylcyclohexane, but under these conditions the thiazolines **502** were found to be unreactive. Presumably, the elimination of hydrogen was facilitated by the presence of an

electron withdrawing group at the C-4 position which weakens the C-H bond and promotes oxidation. Armstrong's reported use of $KMnO_4$ and PTC



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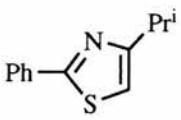

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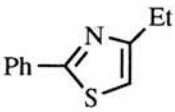
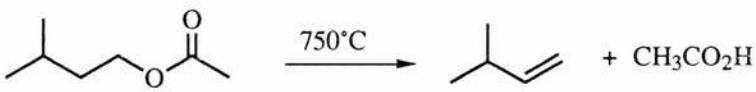


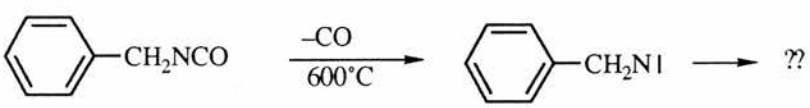
(505)

conditions converted only 50% of the thiazolines to the thiazoles and separation of the mixture was difficult. The oxidative elimination of hydrogen was achieved[312] by mixing the thiazolines with sulphur in a 1:3 ratio and heating under vacuum to 200°C for 2 hours, with 100% conversion. Only thiazole **504** was found by GC-MS in the pyrolysate of sulphone **456**; **503** and **505** were not formed from **453** and **455**.

From the pyrolysis of sulphone **456**, 3-methyl-1-butene was generated and the authentic sample was used to verify the ^1H and ^{13}C values. This was prepared by the FVP of iso-amyl acetate at 750°C.[363]



A number of compounds were thought to arise from the further reaction of benzyl isocyanate during the pyrolysis of the sulphone. With the formation of benzyl isocyanate in the furnace, loss of CO would give the



nitrene which could account for a number of observed products. However the FVP of benzyl isocyanate carried out at 600°C, produced only the starting material. The reaction of benzyl isocyanate observed in our case was the

rapid hydrolysis in the NMR sample to produce the observed product dibenzylurea.

Finally, the condensation of benzylamine with benzaldehyde, afforded an authentic sample of *N*-benzylidenebenzylamine which was identified from the pyrolysates of sulphones **455** and **456**. The origin of this product in the pyrolyses remains unclear.

When the computer library linked to the GC-MS failed to recognise any of the compounds obtained in the pyrolysis of **378** and **379**, a literature search was conducted to find the ^{13}C and ^{1}H NMR values for the most possible products (see Figure 4). No ^{13}C NMR data was listed for 3,4-dihydro-5-methyl-2*H*-pyrrole **498** and its synthesis from *N*-vinylpyrrolidine was carried out according to the method by Lindblom.[313] The synthesis of its tautomer **506** was attempted but the presence of a hydrogen on an enamine is unfavourable and only the imine was isolated.

(498) **(506)**

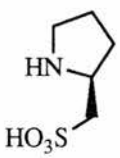
4. Photolysis of (*R*) and (*S*)-thiazolidin-2-one 1,1-dioxides

Acetone and acetophenone are used as sensitisers in photochemical reactions and assist in the transfer energy to the reacting molecule. The molecules themselves can also contain photosensitising groups which transfer energy directly to the compound. The sulphones **453**, **455** and **456** possess a *N*-benzyl group which should also act as a photosensitising group.

The photochemical reaction carried out by Armstrong[288] was in acetone and sulphone **453** was to all intents and purposes unreactive under these conditions. Sulphones **378** and **455** were reacted under the same conditions

but remained unchanged. Sousa extruded SO_2 from **477** under photochemical conditions using *t*-butanol and acetonitrile as the solvent, relying on the phenyl group to act as the photosensitiser.[314] Under these conditions sulphones **453**, **455** and unsurprisingly **378** all remained unreacted.

The photolysis of sulphones **378**, **453**, **455** and **456** using 5 drops acetophenone in CH_2Cl_2 afforded after 7 days a black tar in 10-30% yields, deposited on the sides of the quartz tube which was soluble only in protic solvents. The remaining sulphone (70-90%) was recovered unchanged. ^{13}C NMR analysis of the black tar identified compound **466** from the photolysis of **378**, compound **481** from the photolysis of **453** and the products from the photolysis of **455** and **456** are also suspected to be the sulphonic acids **507** and **508**.



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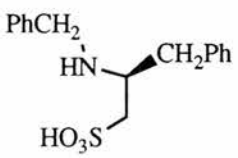
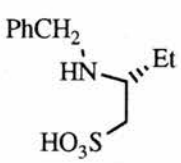
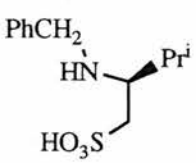


(481)



(507)



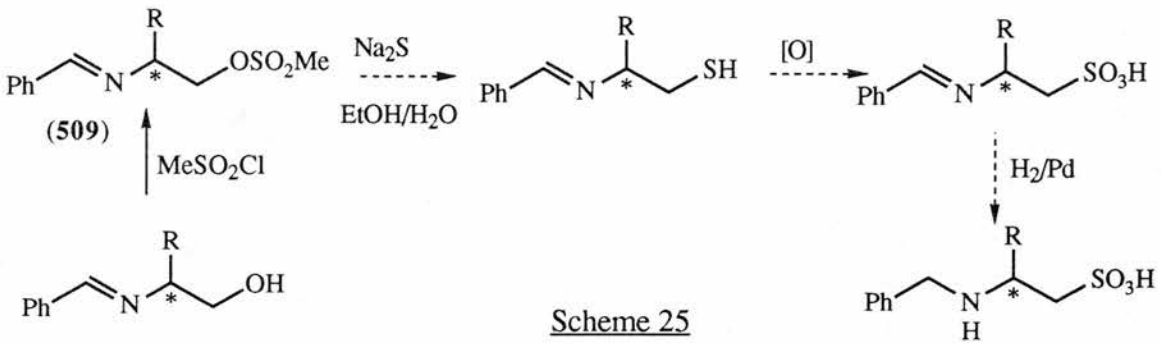
(508)

Thus although the thiazolidin-2-one dioxides are less easily hydrolysed than the thiazoline dioxides the failure of SO_2 extrusion leads to the same result. Slow hydrolysis of the sulphone over a period of days continues until the water has been consumed, at which point the remaining sulphone is inert to the reaction conditions.

5. Photolysis: Authentic product synthesis

The attempted synthesis of the suspected sulphonic acids **507** and **508** followed Scheme 25. Mesylation of the imino alcohol **457** R=Et or Pr^i would

gave **509** which was then reacted with sodium sulphide. Oxidation of the resulting thiol and reduction of the imine would provide the sulphonic acids.



Scheme 25

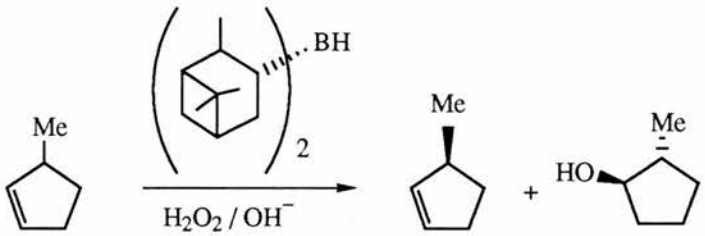
Problems occurred with the S_N2 reaction of HS^- on **509**, in which a number of compounds were isolated. NMR analysis of the reaction mixture revealed the absence of the imine carbon, so it appeared as if the ^-SH was attacking the imine carbon rather than displacing the mesylate group. Reduction of the imine **509** to remove the reactivity of that bond afforded another mixture of compounds presumably because the newly formed amine was now reactive in the presence of the mesylate. A more carefully thought out method to synthesise the sulphonic acids, which takes into account the two reactive centres, will have to be found in order to carry out this preparation.

G. Kinetic resolution using bicyclic iminium salts

1. Background

Kinetic resolution is an enantioselective process in which one enantiomer in a racemic mixture reacts preferentially over the other. It occurs when the rate constants for each enantiomer to form products differ, in a reaction involving a chiral catalyst or chiral reagent. An example is the stoichiometric asymmetric hydroboration of racemic 3-methyl cyclopentene[364] in which the

(*S*) enantiomer is less reactive and is recovered at the end of the reaction in 30% e.e. The (*R*) enantiomer having the more favourable conformation to



Scheme 26

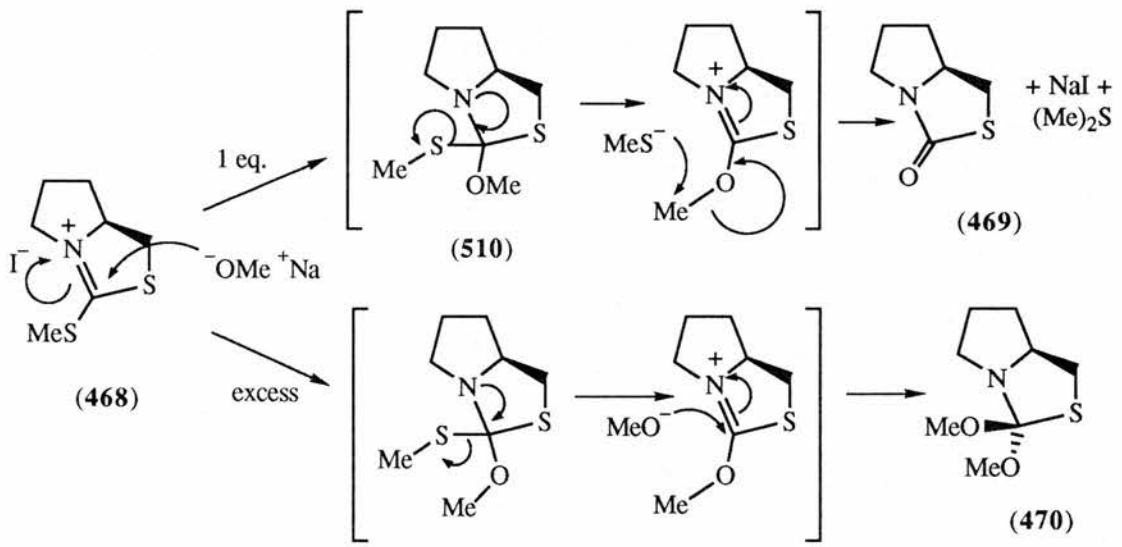
react with the chiral reagent, is consumed faster to produce the optically enriched alcohol Scheme 26. A number of other examples involving chiral reagents, catalysts and enzymes have been reviewed recently by Kagan.[365]

In a perfect situation a racemic mixture would react with one enantiomer being completely transformed into the product and the other enantiomer remaining completely unchanged. If the reagent was chiral and 2 equivalents of a racemic substrate was used, kinetic resolution would be observed with 50% of the substrate remaining unchanged and 50% reacting, ideally.

In the reaction of the iminium salt **468** to the thiazolidinone **469**, one equivalent of sodium methoxide was used to carry out the transformation, to provide **469** and dimethyl sulphide as the by-product. The formation of the sulphide is consistent with unpublished results by Roussel *et. al.*[366] If 2 equivalents of a racemic secondary sodium alkoxide were used, one enantiomer might react preferentially and give optically active sulphides and the other might remain unreacted. Isolation from the reaction mixture could potentially provide an easy access to optically active alcohols and sulphides which would otherwise be very difficult to obtain by conventional synthesis.

2. Initial results

The key reaction to consider is the transformation of **468** to **469**. As mentioned briefly in Section E a large excess of base changes the reaction pathway in favour of **470**. The proposed mechanism (Scheme 27) postulates

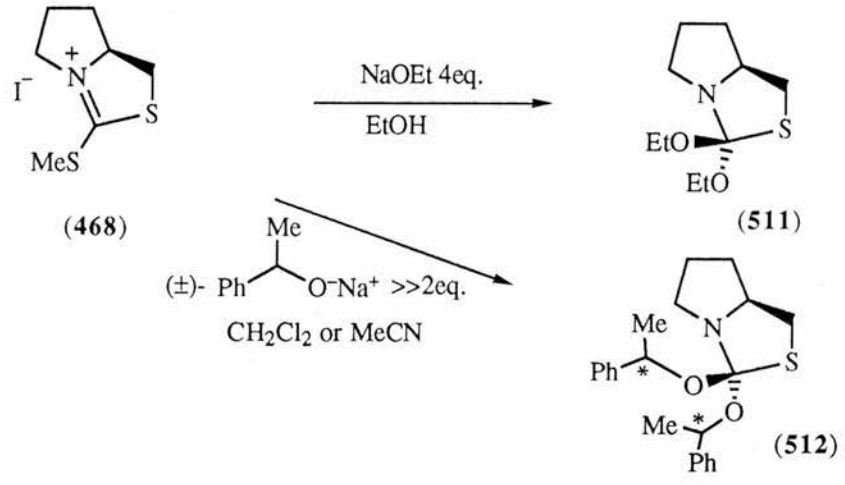


Scheme 27

that with 1 eq. of base nucleophilic addition of the base to the iminium salt gives the transition state **510**. Breakdown of the transition state intermediate occurs as shown to give the observed product **469**. With excess base, nucleophilic substitution dominates giving **470** in high yields.

Using a large excess of sodium ethoxide or sodium 1-phenylethoxide in CH_2Cl_2 the orthothiocarbamates **511** and **512** were also prepared and identified by NMR only, since any type of purification resulted in the breakdown of the ortho esters. Of great importance was the presence of only one diastereomer in the ^{13}C NMR spectrum of **512**, indicating that **468** does show considerable selectivity in its reaction with chiral alkoxides. The ^{13}C NMR shift of the quaternary carbon in **511** and **512** was 130 and 133 ppm respectively, which was in good agreement with the value for **470**. The

formation of **512** was also carried out in acetonitrile with identification of



the ortho ester by GC-MS, which showed the main component to have m/z 369. Most significantly in this reaction, the recovered alcohol was shown to be racemic by optical rotation measurements, implying that the salt **468** first selects one enantiomer and then the opposite one to give a single stereoisomer of the product.

These results indicate that the chiral iminium salt **468** shows high enantioselectivity in the presence of a large excess of a racemic alkoxide but would it display the same enantioselectivity with 2 eq.?

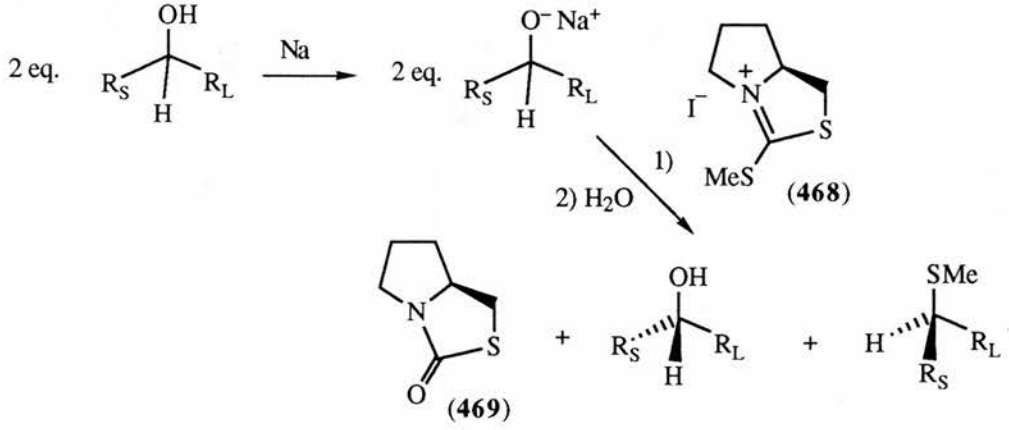
3. Reaction of the iminium salt (468) with 2 eq of alkoxide

In 1934 Fisher[367] reported that in the preparation of secondary sodium alkoxides, decomposition of the alkoxide was directly related to the darkening in colour of the solution. A loss of efficiency as condensing agents was noticed if the alkoxide solution was exposed to the atmosphere for any length of time accompanying a darkening of colour.

A rapid colour change in the above reaction **468->469** was noticed when the alkoxide was isolated in its solid form and dissolved in another

solvent chosen for that reaction (CH_2Cl_2 and acetonitrile). To avoid this problem toluene was chosen as the solvent in which the alkoxide was formed under N_2 and the reaction with the iminium salt took place.

Addition of exactly 2 eq. of a racemic secondary sodium alkoxide to 1 eq. of the iminium salt **468** (see Scheme 28) in toluene provided the



Scheme 28

thiazolidinone **469**, an optically active alcohol (see Table 4) and the (presumably) optically active sulphide.

Table 4.

Kinetic resolution of secondary alcohols.

Entry	Alcohol	e.e.%	Configuration
1	PhCH(Me)OH	18	*S*
2	PhCH(Et)OH	12	*S*
3	$PhCH_2CH(Me)OH$	6	*R*
4	$Bu^tCH(Me)OH$	0.5	n.a.

Initial isolation of the alcohol involved the addition of a nonpolar solvent to precipitate the alkoxide, filtration and hydrolysis of the alkoxide to give the alcohol, usually needing column chromatography to purify it. This

however, did not remove all of the alkoxide from the mother liquor and when attempted distillation of the sulphide was preformed a large number of unknown compounds were present as shown by the subsequent GC-MS and ^{13}C NMR analysis of the mother liquor. The sulphides unfortunately were never isolated in their pure state and were always contaminated with one or two unknown compounds.

This problem was overcome by the hydrolysis of the alkoxide at the end of the reaction, subsequent distillation removing the alcohol, contaminated with some of the sulphide. Analysis of the remaining mother liquor revealed the presence of the thiazolidinone **469**, the sulphide and a small amount of alcohol. The important point is that the mother liquor was stable and could be manipulated in various ways to achieve the desired separation of the three products. Future work involving column chromatography of the mother liquor should allow isolation of each product and would be an important step forward.

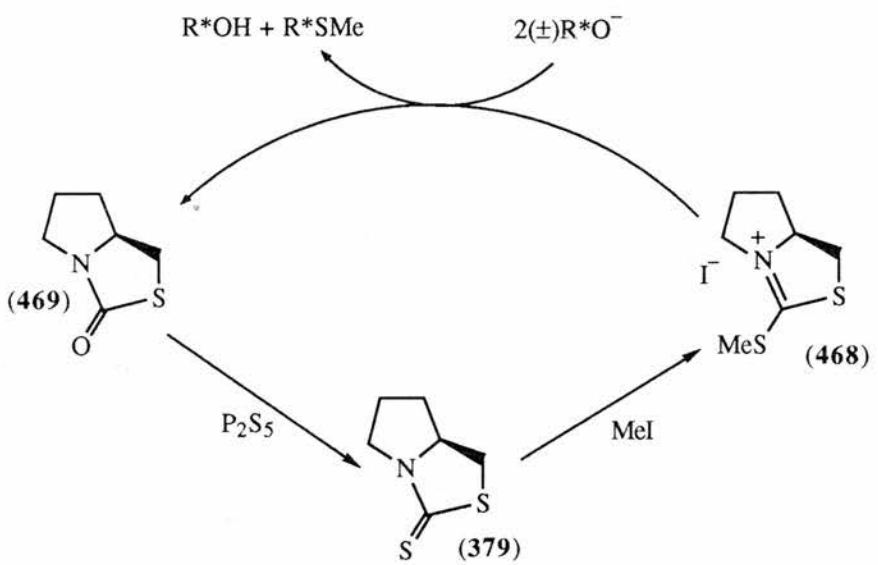
Initial results with the purified alcohol gave optional rotation measurements indicating up to 30% e.e. but in the presence of a chiral shift reagent the alcohols isolated by distillation and contaminated with the sulphides, gave the e.e. values listed in Table 4. The anomalous results are entries 3 and 4; Entry 3 can be explained by the presence of a methyl and a methylene group, which are attached to the reacting centre of the alcohol. Due to the similarity in size of these two groups, the chiral iminium salt can not distinguish between the two enantiomers and this leads to the low e.e. and the reversed configuration observed in the experiment. Entry 4 is perhaps more difficult to explain but it appears as if an aryl group attached to the alcohol is essential for efficient kinetic resolution using the iminium salt **468**.

Other attempts at measuring the e.e.'s had little or no success. Injection of 3,5 dinitrobenzoic acid esters of the alcohols onto a chiral HPLC column, failed to give the necessary base line separation for accurate e.e.

determination. Kinetic resolution was responsible for the incomplete reaction of the alcohols with (*R*)-α-methoxy-α-(trifluromethyl)phenylacetyl chloride probably due to the steric hindrance of the secondary alcohols. The last method used was the formation of (*R*)-*O*-methylmandelate esters, employing (*R*)-*O*-methylmandelic acid, DCC and the alcohol. In this case complete reaction of the alcohols took place but the diastereomers, formed from the distilled alcohols (with some sulphide present) give cluttered ^{1}H NMR spectra. The diastereomeric splittings were therefore not always clear cut. The e.e.s obtained by this method closely resembled those obtained by the shift reagent except for entry 2. For entry 1, 18% e.e.; 2, 16% e.e. and 3, 6% e.e.

4. Recycling the thiazolidinone 469

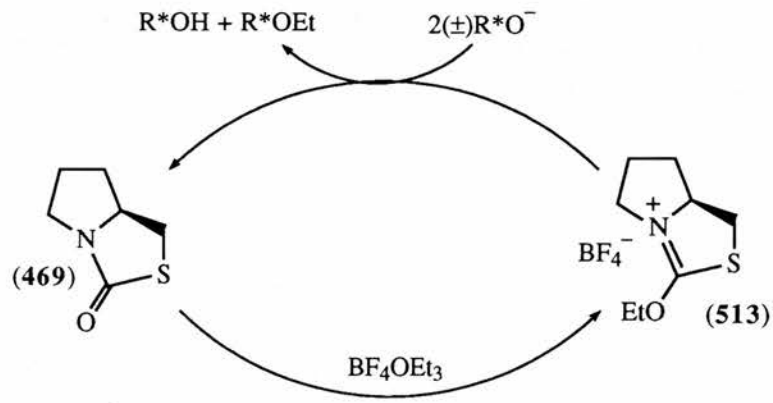
The reusability of a chiral reagent is an important consideration in the development of any successful enantioselective process. To recycle the thiazolidinone **469** it must first be transformed back into an iminium salt.



Scheme 29

Two methods were available, one involving the exchange of exocyclic oxygen for sulphur with P_2S_5 to give the thiazolidinethione **379** which could then be converted to the original iminium salt **468**, Scheme 29.

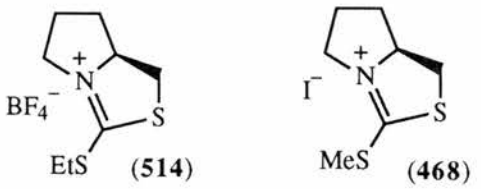
Alternatively **469** could be used as the basis of the resolution procedure by formation of the iminium salt **513**. If this reacted analogously to **468** with alkoxides it would produce a chiral alcohol and a chiral ethyl ether as shown



Scheme 30

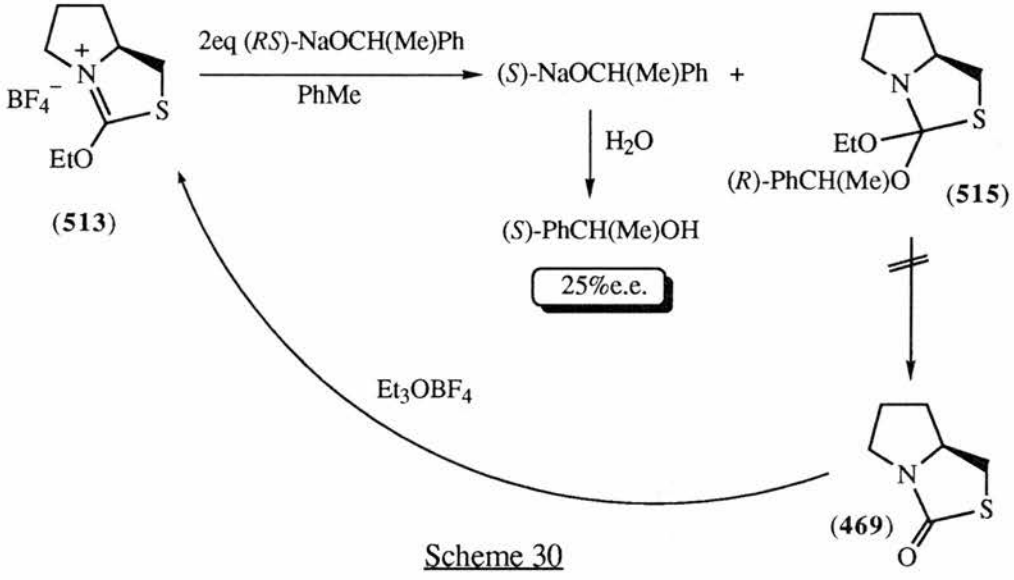
in Scheme 30. The direct conversion to the iminium salt **513** appeared to be the easiest solution and its synthesis was carried out by reacting **469** with triethyloxonium fluoroborate. The electrophilic addition resulted in an oil which was analysed by ^{13}C NMR and found to contain a quaternary carbon (no carbonyl absorption in the infrared) at 178 ppm, shifted to higher frequencies in comparison to the carbonyl in **469** and in the correct region for imine carbons. Also found in the ^{13}C NMR was the expected ethyl group.

The fluoroborate salt **514** was also synthesised, from **379** and triethyloxonium fluoroborate, but was never used in any kinetic resolution experiments. Comparison of ^{13}C NMR shifts for the quaternary carbons from



514 and **468** showed a difference of 1 ppm.

The iminium salt **513** was then reacted with 2 eq. of 1-phenylethoxide to afford (after filtration of the alkoxide and hydrolysis) (*S*)-1-phenylethanol in 25% e.e. from optical rotation measurements, see Scheme 31.

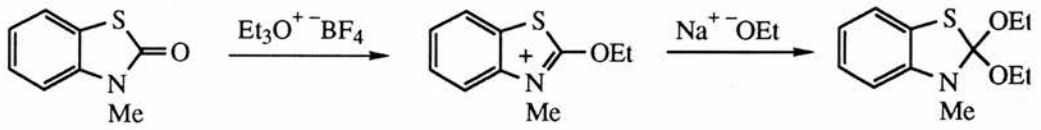


Scheme 30

GC-MS analysis of the remaining mother liquor identified the orthothiocarbamate **515** m/z 273 as the largest peak, 1-phenylethanol and a small amount of the thiazolidinone **469**. GC-MS also identified significant quantities of toluene, ethylbenzene, styrene and acetophenone all compounds associated with the presence of soluble sodium 1-phenylethoxide and the numerous degradation reaction pathways available to it.

The stability of the orthothiocarbamate **515** inhibits the regeneration of the thiazolidinone **469** and therefore prevents the use of **513** as chiral reagent in the kinetic resolution of racemic alcohols. This result is not really unexpected since, although both the orthodithiocarbamate **510** and the

orthothiocarbamates **470** and **515** are compounds of a type little studied before,[368] a good precedent for the stability of the latter is provided by the early work of Meerwein.[369] Thus reaction of **516** with Et_3OBF_4 followed by NaOEt gave the stable orthothiocarbamate **517** which showed no tendency to eliminate Et_2O to regenerate **516**.



(516) **(517)**

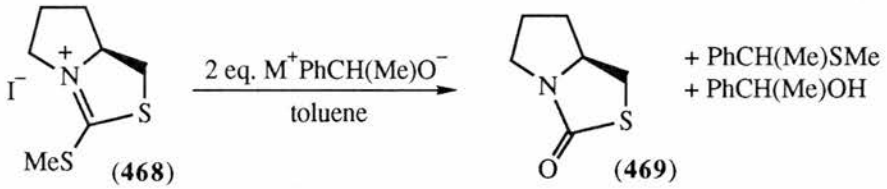
The use of P_2S_5 to regenerate the thiazolidinethione was then the only alternative. An experiment involving pure thiazolidinone **469** and 1 eq. of P_2S_5 provided the thiazolidinethione **379** in 90% yield. Using the mother liquor from experiment I. 7. *d*, in which the alkoxide was completely hydrolysed and the alcohol and sulphide were removed by distillation, and reacting it with 2 eq. of P_2S_5 afforded **379** in 28% yield. ^{13}C NMR analysis of the resulting oil showed **379** and **469** to be present in equal amounts.

5. Counter cation effects

Changing the cation could possibly have an effect on the reactivity of the alkoxide, with the possibility of increasing the enantioselectivity of the reaction.

Formation of lithium 1-phenylethoxide in toluene and reaction with the iminium salt **468** at RT and at –78°C produced, after filtration 73% and 96% of the unreacted lithium alkoxide. Preparation of potassium 1-phenylethoxide and reaction with **468** at RT provided the thiazolidinone **469**, the sulphide and the isolated alcohol in 9% e.e. measured by optical rotation. The lack

of reaction using lithium may be due to the increased solubility of the lithium

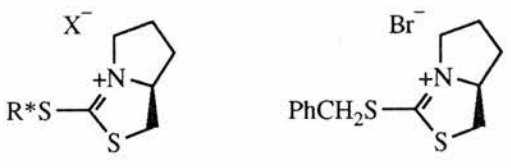


M	e.e. of alcohol
Li	-
Na	18
K	9

salt in the organic solvent (toluene + 8 ml of hexane) coupled to a decrease in solubility for the iminium salt **468** (especially at -78°C), which would slow down the reaction rate. The reduced e.e. for the potassium alkoxide could possibly be due to an increase in the rate of reaction and therefore decreased selectivity by the iminium salt.

6. Use of other *S*-substituted iminium salts for kinetic resolution

The reaction of various racemic alkyl bromides and iodides with **379** was seen as a possible route to obtain *S*-substituted iminium salts **518**. Using only 2 eq. of a racemic alkyl halide could also lead to the preferential reaction of one enantiomer. Unfortunately **379** was unreactive in the presence of these

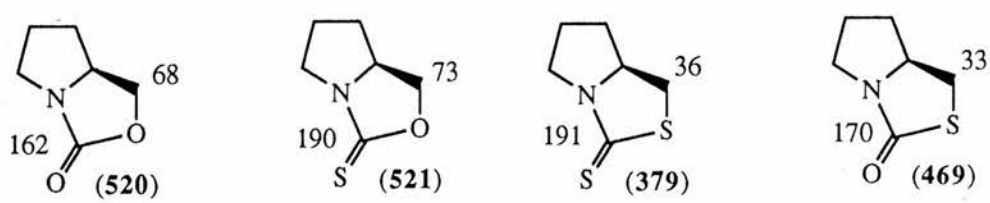


secondary alkyl halides, and even benzyl bromide only went to ~75% completion to give **519** and **379** as an inseparable mixture.

The crude iminium salt **519** was reacted again with 10 eq. benzyl bromide to give a powder which contained only a small percentage of the starting material **379**. Reaction of **519** with 2 eq. of sodium (±) 1-phenylethoxide provided (*S*)-1-phenylethanol in 27.5% e.e. measured by optical rotation. The e.e. values obtained by optical rotation for the benzyl iminium salt **519** and the methyl iminium salt **468** (up to 30% e.e.) are similar and it would appear that substitution on the exocyclic sulphur has little effect on the efficiency of the kinetic resolution process.

7. Formation of iminium salts from oxazolidinones and oxazolidinethiones

The oxazolidinone **520** was prepared from a literature[318] procedure involving phosgene and (*S*)-prolinol and the oxazolidinethione **521** was similarly synthesised from (*S*)-prolinol and thiophosgene. The physical characteristics of these molecules showed the ^{13}C NMR signals for the C-4 carbon, shifted to higher frequencies by more than 30 ppm in comparison of the values for **469**

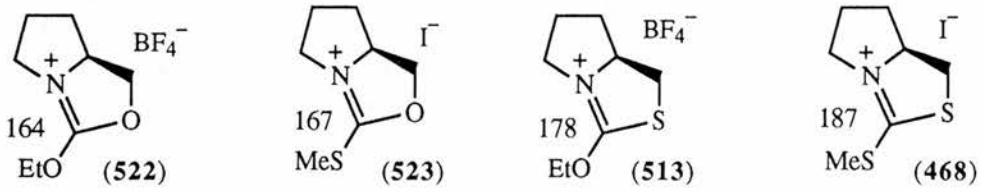


Values in ppm

and **379**. Another major difference was between the carbonyls of **469** and **520**, replacement of the ring sulphur by oxygen causes a decrease in frequency from 170 to 162 ppm but in the case of **379** and **521** the difference between the carbonyls, 191 to 190 ppm was not as noticeable. As in the case

of the other bicyclic systems **379**, **468** and **378** the ^{1}H NMR spectra of **520** and **521** were very complex.

Formation of the iminium salts **522** and **523** was carried out using the previously discussed reagents, triethyloxonium fluoroborate and methyl iodide, respectively. In comparison to their ring sulphur analogues the formation of the two salts **522** and **523** was not qualitatively as clean with the

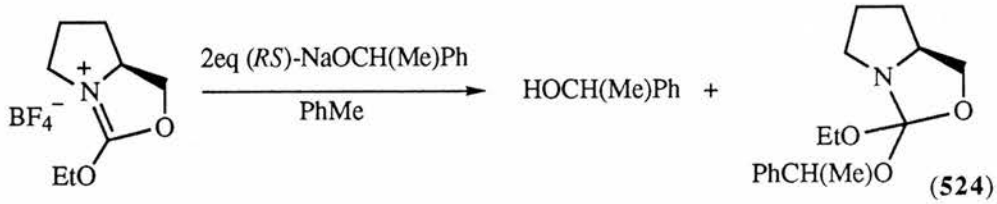


Values in ppm

presence of **520** plus an unknown compound in the oil of **522** and a small amount of an unknown material in the solid and oil of **523**. The ^{13}C NMR values for the imine carbons of **522** and **533** have been shifted to a lower frequency by 15 and 20 ppm in comparison their sulphur analogues **513** and **468**.

8. Attempted use of oxazolidine-derived iminium salts for kinetic resolution

The iminium salt **522** was added to 2 eq. of sodium 1-phenylethoxide in toluene with the expectation of obtaining the ortho ester **524**. Hydrolysis of



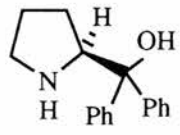
the reaction mixture and ^{13}C NMR analysis revealed the presence of 1-phenylethanol and signals which could represent compound **524**. This time however, in contrast to the formation of **512** the majority of the signals were doubled indicating two diastereomers were present, probably due to a random selection of the alkoxides by the iminium salt. GC-MS analysis however failed to verify the presence of **524** and gave a trace containing 8 peaks, the largest corresponding to 1-phenylethanol and one identified as the oxazolidinone **520**.

The reaction of **523** with 2 eq of sodium 1-phenylethoxide was altogether different and probably resembles the pathways involved in the reaction of **529 –> 534**. After 24 hr some of the alcohol was obtained by filtration and was found to be racemic by chiral shift experiment. ^{13}C NMR analysis of the mother liquor gave an extraordinarily clean spectrum with only 1-phenylethanol and an unknown. This unknown had double peaks for the majority of its carbons and is therefore likely to be a diastereomeric pair. The spectrum contained one CH at 73 ppm, 4 CH_2's at 91, 49, 32 and 22 ppm, 2 CH_3 below 25 ppm and one or two quaternary carbons. The problem of assigning a structure to this unknown rests with the explanation of the CH_2 at 91 ppm. GC-MS analysis gave 9 peaks, 3 of them larger than the rest with m/z 122, 157 and 105. M/z 122 was identified as 1-phenylethanol and m/z 105 as an ethylbenzene fragment, occuring at roughly 8 minutes on the GC-MS trace. Low resolution MS only revealed the presence of 1-phenylethanol. Obviously the unknown product was too fragile for the GC-MS and high concentrations of the alcohol in the sample mask the unknown compound in the MS analysis.

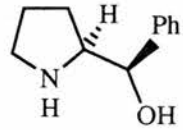
H. Preparation of more selective substituted iminium salts for kinetic resolution

1. Background

Corey's use of the oxazaborolidines as described in the introduction (A. 7.1) to achieve reductions with very high enantioselectivity, suggested a promising new direction for this work. By incorporating additional bulky groups into the iminium salts, the increase in steric bulk on the faces of the molecule should restrict the access of the approaching alkoxide.



(525)



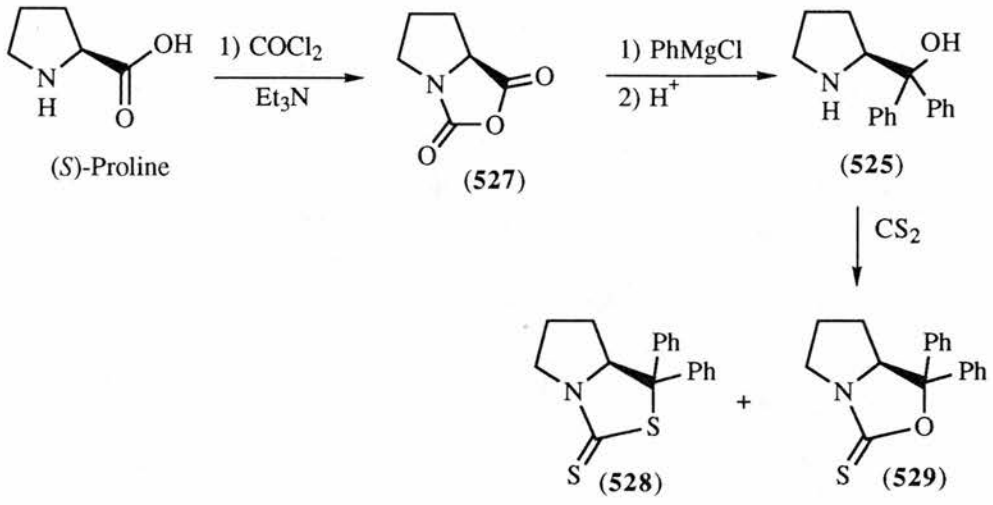
(526)

With this in mind the phenyl substituted amino alcohols **525** and **526** were prepared using known methods and reaction with carbon disulphide and methyl iodide was expected to provide the substituted iminium salts.

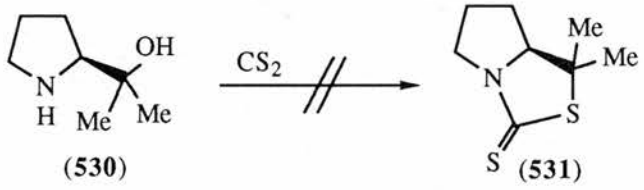
2. Attempted preparation of diphenyl substituted iminium salts

The preparation developed by Mathre[315] was used to synthesise the amino alcohol **525**. By reacting (*S*)-proline with phosgene to give the *N*-carboxyanhydride **527**, followed by a Grignard addition using phenylmagnesium chloride diphenylprolinol derivative **525**, was prepared. Condensation with carbon disulphide using concentrated base failed to give the thiazolidinethione **528** in adequate yields, with the product usually contaminated with the oxazolidinethione **529**. Initially the steric bulk of the

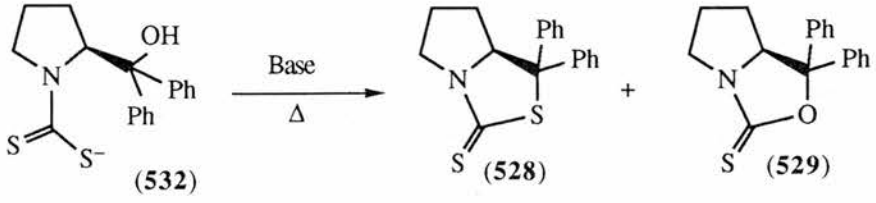
phenyl groups was thought to be responsible for the lack of cyclisation with



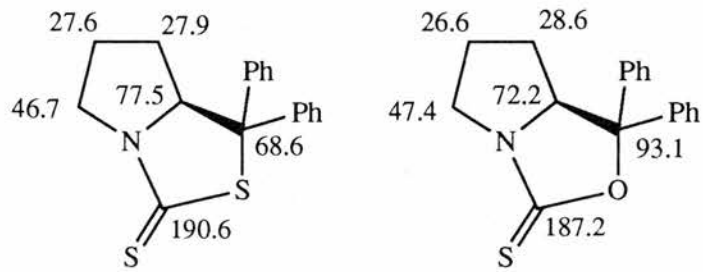
CS_2, so the α,α-dimethyl amino alcohol **530** was prepared again using the method by Mathre. Although the yields were very poor in the synthesis of



530, enough was obtained to reacted with CS_2 in an attempt to prepare **531**. Again, **530** failed to react with CS_2 confirming previous observations[351, 352] that tertiary alcohols in general show no reactivity towards CS_2. The dithiocarbamate **532** was probably formed in each case but only with forcing conditions did any sort of cyclisation take place. Clearly the attachment of the second CS_2 to the OH group necessary for formation of **528** did not occur to any great extent and **529** was formed as an alternative product.



Evidence for the structure of **528** and **529** comes from the GC-MS showing two peaks with m/z 311 and m/z 295 and the ^{13}C NMR data as shown in Figure 5. The ^{13}C NMR data from the authentic synthesis of **529** (see below), matches that found in the mixed samples with the extra signals then assigned to the thiazolidinethione **528**. The thiocarbonyls from **528** and **529** have ^{13}C shifts very similar to **379** but the most remarkable difference comes in the ^{13}C shifts of the C-4 carbon which shifts to higher frequency (25 ppm

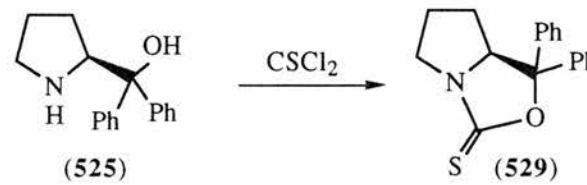


(528) **(529)**

Figure 5. ^{13}C NMR (ppm)

higher) when sulphur is replaced by the more electronegative oxygen. The C-6 and C-7 assignments are uncertain in both compounds.

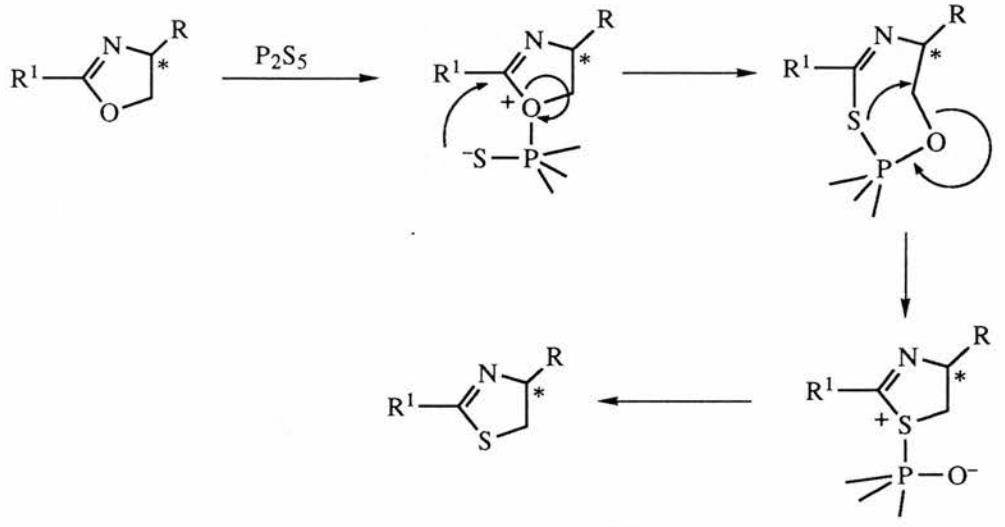
The successful synthesis of **529** involved reaction of **525** with thiophosgene using a procedure by Sharma.[319] The conversion of **529** to **528**



(525) **(529)**

would then allow the synthesis of the corresponding iminium salt. This was attempted by a method detailed extensively by Armstrong (see Scheme 32), which involved exchanging the ring oxygen in **529** for sulphur, using P_2S_5. Armstrong postulated that the driving force behind the exchange was the high

affinity of phosphorus for oxygen and a decrease in ring strain with the incorporation of the larger sulphur atom. Application of this procedure to oxazolidinethione **529**, however, gave no reaction, a result attributed to the steric hindrance experienced by P_2S_5 as it approached the two phenyl groups.

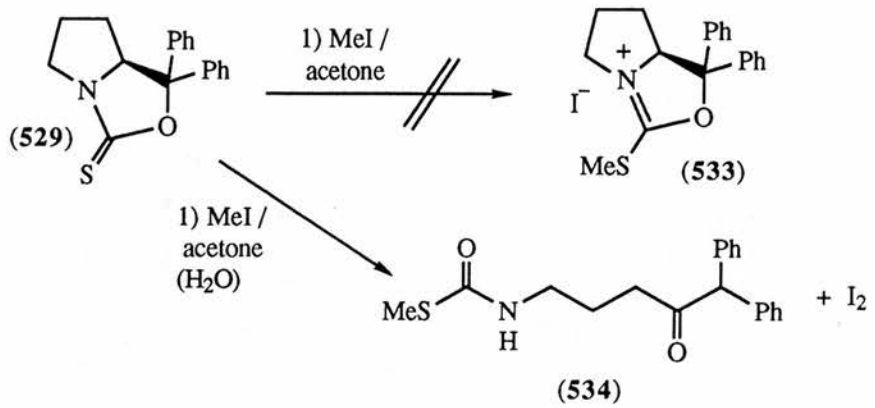


Scheme 32

Following the failure to prepare **528**, it was considered worthwhile preparing and evaluating the iminium salt derived from **529** for kinetic resolution, even though the corresponding non phenyl-substituted salts **522** and **523** had not been useful as described in Section G. 8.

The preparation of **533** was expected to proceed easily using the established reaction with methyl iodide in acetone. However, unlike all the previous cases, no salt precipitated out even after 24 hr. Since addition of ether in an attempt to precipitate the salt had no apparent affect after 1 hr, the solution was evaporated to afford a black tar, in which GC-MS analysis identified two major peaks, m/z 254 and m/z 309. The peak at 254 corresponded to molecular iodine, but the species responsible for the peak at 309 remains unknown. After removal of the iodine ^{13}C NMR identified 2 carbonyl carbons at 208 ppm and 168 ppm. The peak at 208 is likely to be due to a ketone as it is too low for a thione and the peak at 168 is likely to be

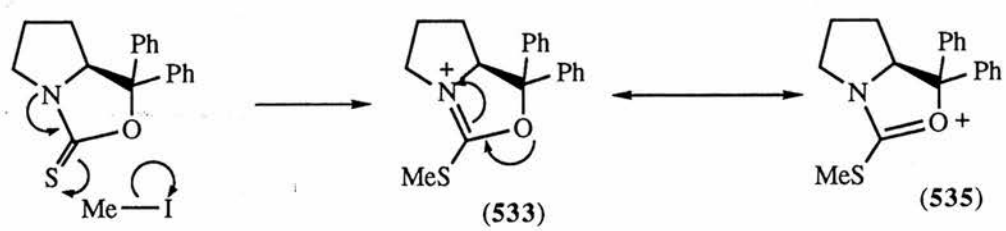
due to an amide, as it would be much higher if it was a thioamide. Along with



Scheme 33

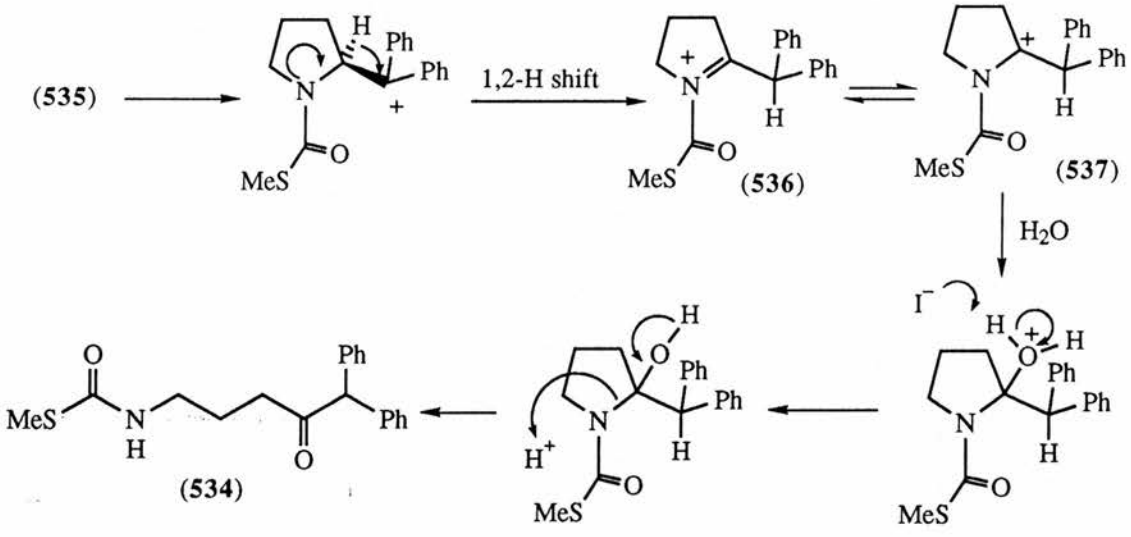
the two carbonyls were one CH, $3CH_2$'s and a CH_3 plus the two phenyl groups which had identical shifts, meaning the molecule was now achiral. Lassaigne's test indicated the presence of a nitrogen and a sulphur but no halogens and ^1H NMR verified the presence of 1 CH, 3 CH's, a CH_3, 2 phenyl groups (10 CH's) and a NH proton, 21 protons all together. Elemental analysis verified the molecular formula of $C_{19}H_{21}NO_2S$ and 2D ^1H-^1H and ^1H-^{13}C COSY NMR indicated that the most likely structure was that of **534** with a molecular weight of 327.

The proposed mechanism behind the transformation (Scheme 34) begins with the electrophilic addition of CH_3 to the sulphur to give the iminium salt



Scheme 34

533 which may have a significant contribution from the oxonium salt tautomeric form **535**. Due to the ring strain involved in the oxonium salt coupled to the presence of a potential neighbouring cation stabilised carbon, an irreversible ring opening occurs. The lone pair on the nitrogen initiates a 1,2-hydrogen shift to provide the iminium ion **536** which is in equilibrium with its contributing form **537**. Iminium ions are known[370] to undergo rapid hydrolysis with cleavage of the C-N double bond and by this mechanism the observed product **534** is formed.

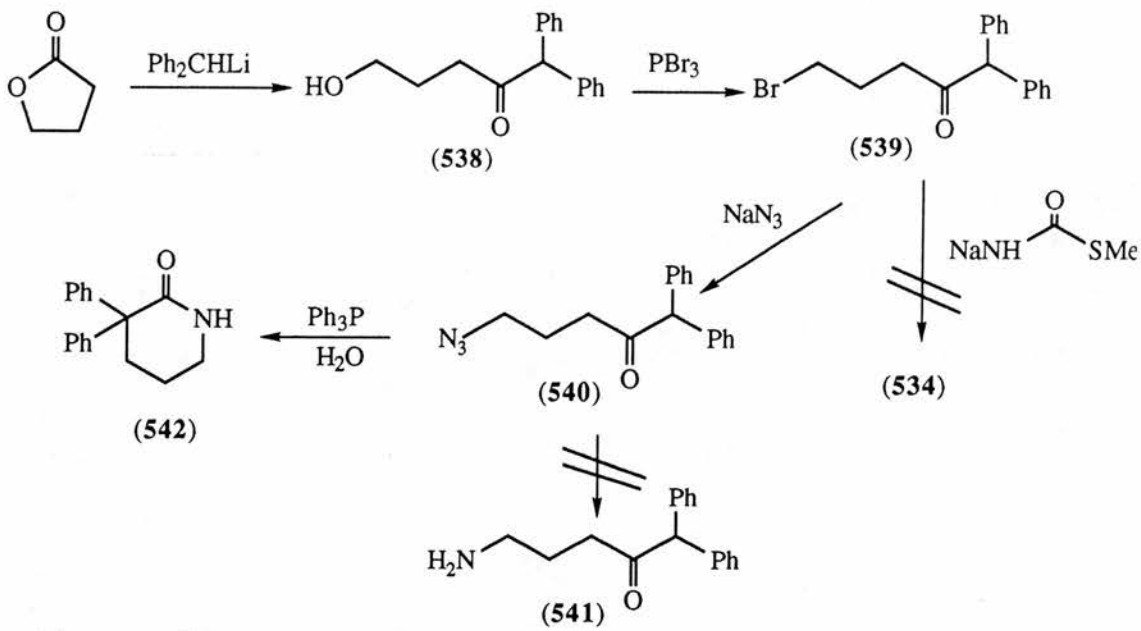


Scheme 34 cont.

The synthesis of an authentic sample **534** was attempted via two different pathways, Scheme 35. γ-Butyrolactone was reacted with the anion derived from diphenylmethane, to give the diphenylketone **538** whose properties agreed with reported values.[323] Nucleophilic substitution of the hydroxy function with PBr_3 gave **539** which was verified by MS, having a double peak at M^+ 316 and 318, characteristic of a bromide containing molecule.

The first pathway involved the reaction of **539** with the anion of *S*-methyl thiocarbamate. *S*-methyl thiocarbamate was synthesised by a literature

procedure which takes methyl thiocyanide, water and hydrogen chloride gas



Scheme 35

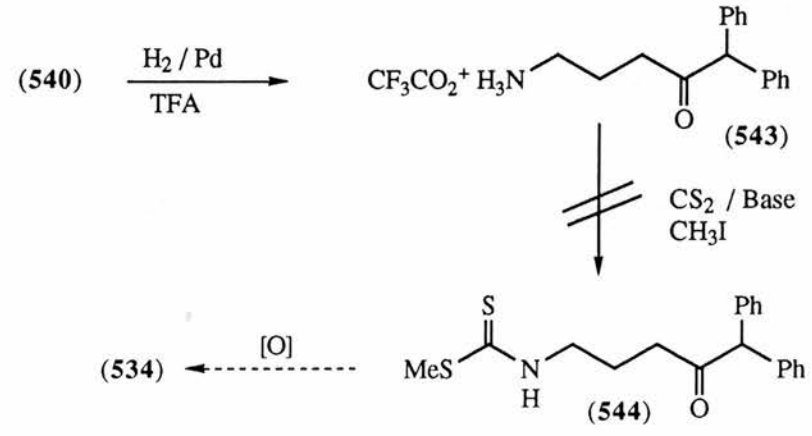
and allows the reaction to "age" for two days.[324] The anion was generated with sodium hydride and reacted with **539**. Analysis by ^{13}C NMR identified unreacted **539** and an unknown compound which was not **534**.

The second pathway involved the nucleophilic substitution of bromide by an azide anion to give **540** with its very characteristic infrared absorptions at 2100 cm^{-1}. The idea behind the synthesis of **540** was to generate the primary amine **541** which could then be reacted with CS_2 and methyl iodide to give **544**, which upon oxidation using $KMnO_4$ / benzoic acid and PTC conditions would give **534**.

The first method used to generate the amine was to react the azide with triphenylphosphine and water.[325] Analysis of the product appeared to indicate that it was the piperidinone **542** but the compound was obtained as an oil, whereas the literature reports on this compound describe it as a solid, m.p. 190°C.[371] The ^{13}C NMR spectrum of **542** showed two quaternary carbon shifts at 181 and 80 ppm, aromatic carbons and 3 CH_2's. MS analysis shows

m/z 251 which matches the proposed structure and the ^1H NMR spectrum does not appear to show any NH proton shift, but this could be within the aromatic range as six-ring cyclic amides are known to have high frequency shifts. The mechanism responsible for the formation of the 6 membered piperidine **542** is still under consideration.

Another method to produce the amine **541** was reduction of the azide using H_2 / Pd in the presence of trifluoroacetic acid.[151] This gave the trifluoroacetate salt **543** as identified by the presence of the ^{13}C-^{19}F coupling, J_{CF}=288 Hz and J_{CCF}=38.9 Hz which is very close to the coupling observed in trifluoroacetic acid. Unfortunately the reaction of **543** with CS_2 and exactly 2

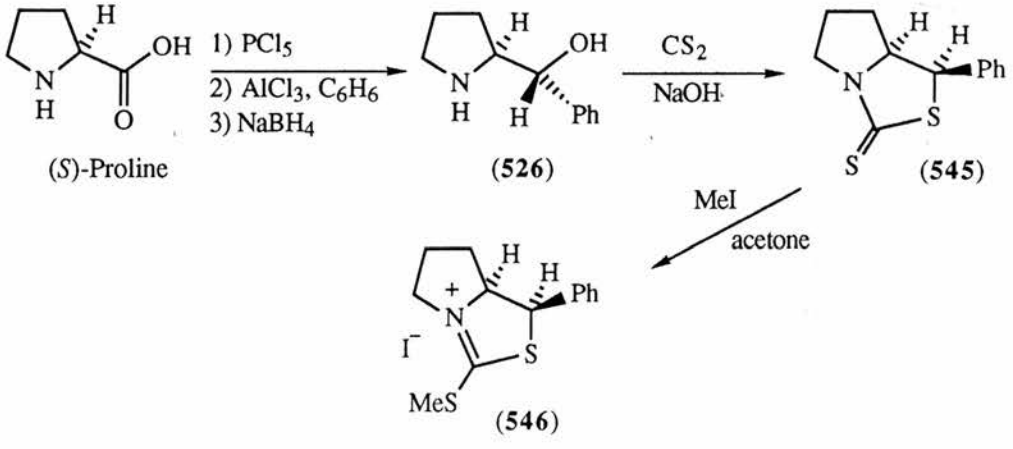


Scheme 35 cont.

eq. of base in the presence of methyl iodide failed. GC-MS analysis of the resulting oil showed 13 peaks with the largest having m/z 236. The most likely problem was the presence of the acidic proton on the C-1 carbon which is α to the ketone, making it equally if not more reactive than the amine functionality. The presence of numerous functional groups in **534** makes its synthesis more difficult than it first appeared.

3. Preparation and use of monophenyl-substituted iminium salts

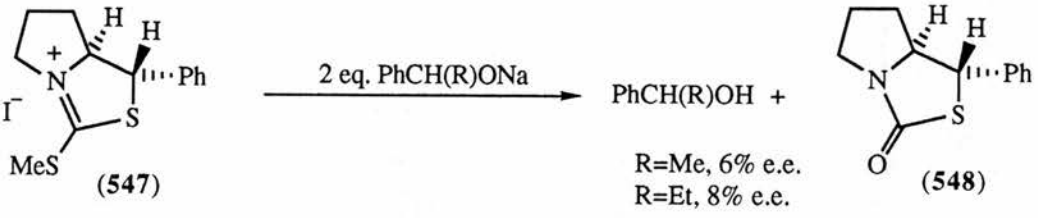
The amino alcohol **526** was prepared by a Friedel-Crafts acylation with (*S*)-proline of benzene in 89% e.e. followed by borohydride reduction.[317] It was then condensed with CS_2 under alkaline conditions to give the thiazolidinethione **545** in roughly 100% e.e. after recrystallisation. The ^1H NMR has very complex coupling but the C-4 proton is easily identifiable as a doublet J=11.5 Hz. The ^{13}C NMR shifts are almost identical to those found in **528** except that the C-4 carbon is shifted to a lower frequency by 10 ppm to 58 ppm.



Electrophilic addition with methyl iodide proceeded smoothly to give the iminium salt **546** which was identified by the appearance of a methyl group in the NMR spectra. The ^{13}C NMR shift for the imine carbon of 187 ppm closely matches the iminium shift of **468**.

The above procedure was repeated on a larger scale but during this synthesis the diastereomer **547** was isolated and identified by ^1H NMR. Subsequent reaction of **547** with racemic sodium 1-phenylethoxide and sodium 1-phenyl-1-propoxide in toluene afforded after hydrolysis of the alkoxides, the respective alcohols in 6% and 8% e.e. These low values are reminiscent of a report by Soai in which the addition of diethylzinc to

benzaldehyde was catalysed by **48** in up to 100% e.e. The opposite



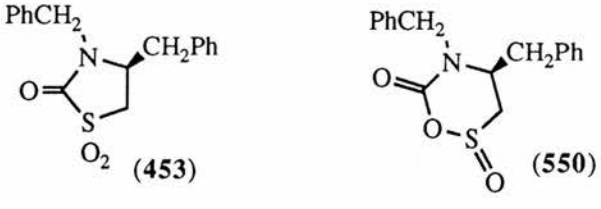
diastereomer **549** was found to provide 1-phenyl-1-propanol in 3-31% e.e.[41] and so **546** seems a promising chiral reagent for further study.

(48) **(549)**

I. ^{33}S NMR studies

1. Background

In previous work in this laboratory,[288] the thiazolidinone dioxide **453** was prepared but the predominant loss of SO in its chemical ionisation mass spectrum suggested that the compound obtained might actually have the



isomeric structure **550**. This type of ring expansion is not uncommon in sulphone chemistry and indeed similar processes have been postulated earlier in this thesis (page 160-162). A report by Trost[372] had described the use of

^{33}S NMR to solve just such a problem in a related acyclic system. In the case of **453** a sharp signal was observed on the AM300 instrument, effectively ruling out the alternative structure **550** which was expected to have a signal too broad to be observed.[288]

As a result of the work described earlier in this thesis a number of novel organosulphur compounds were available and so we decided to investigate the application of the more powerful MSL 500 solid state NMR instrument to ^{33}S NMR.

2. Previous work

With a natural abundance of 0.76%, a nuclear spin of 3/2, a moderate quadrupolar moment and a small magnetogyric ratio, ^{33}S can be 10 to 1000 times less sensitive then the ^{13}C nucleus depending largely on the electric field gradient (efg). In highly symmetrical electronic environments such as SO_4^{2-}, the efg is low resulting in small line widths and high sensitivity. Highly asymmetric charge distribution which exists in RSR and RC(S)R type molecules, leads to a high efg and concomitant broad lines. Line widths can vary from 0.03 Hz to greater than 5 kHz and can also be influenced (to a lesser extent) by the concentration of sulphur in the sample, the viscosity of the sample and the temperature. Line widths are important since with a chemical shift range of over 1000 ppm, very broad lines can lead to large errors in assignment of the ^{33}S shifts. In a recent review[373] an NMR data table was compiled with all the known chemical shifts of sulphur containing compounds. These shifts are shown by compound type and compiled by the author in Figure 6.

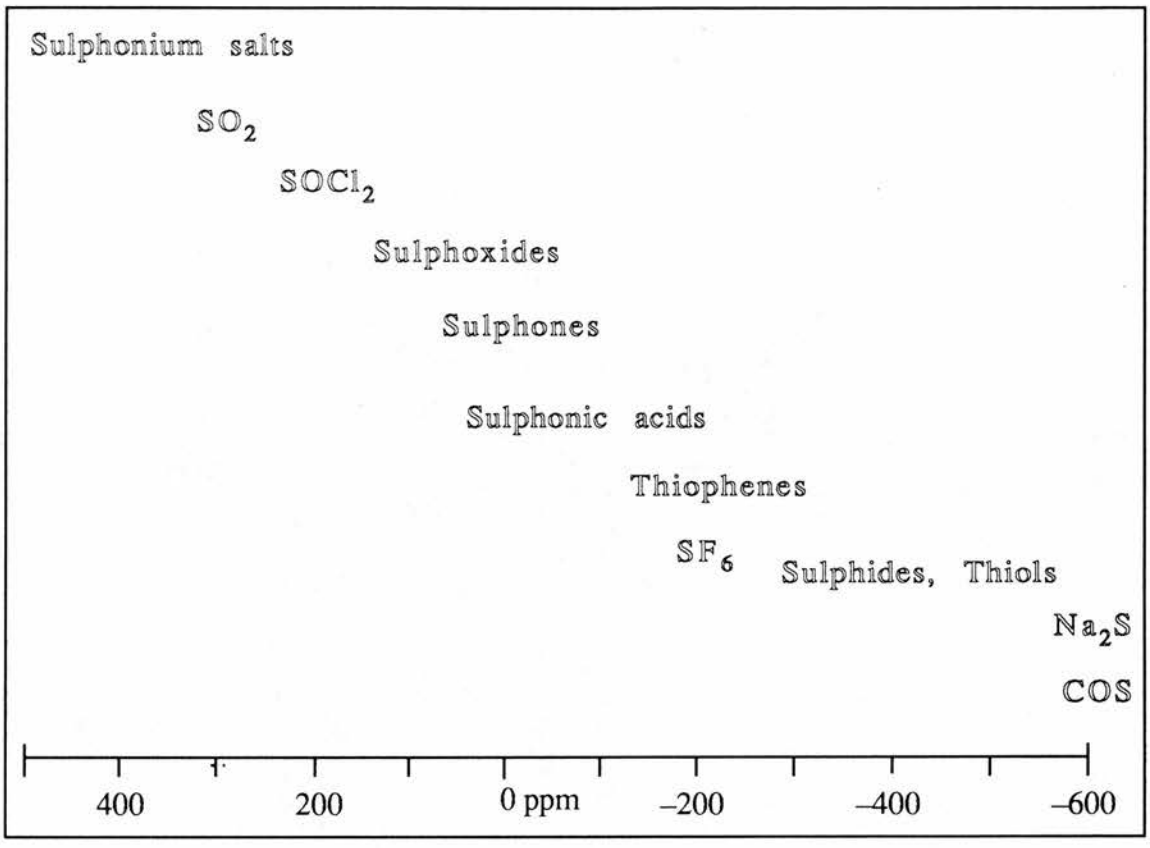
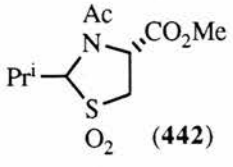


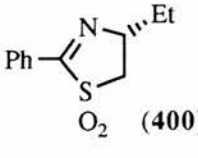
Figure 6

3. Results

The 25 new results listed in Table 5 were run on the MSL 500 using commercially available samples except for **400** and **442** which were prepared as described earlier in this thesis and entries 16, 17[374] and 24[375] which were prepared by literature methods.



(442)



(400)

Table 5

^{33}NMR shift values and line widths

Entry	Compound	δ_S (ppm)	$W_{1/2}$ (Hz)
1.	PhNCS	–569 ± 100	23000
2.	PhSMe	–390	19800
3.	$PhCH_2SH$	–379	6540
4.	MeSCN	–369	4480
5.	PhSH	–332	7031
6.	EtSSEt	–297	10644
7.	2-methylthiazole	–57	4200
8.	$PhSO_2NH_2$	–25	977
9.	$K_2S_2O_8$	–23	3000
10.	$PhSO_2H$	–19	610
11.	*p*-Me-$C_6H_4SO_2N(Me)NO_2$	–18	5000
12.	$PhSO_2Na$	-12	640
13.	*p*-Me-$C_6H_4SO_2NHNH_2$	–7	2300
14.	$HOCH_2SO_2Na$	–5	500
15.	$PhSO_2Cl$	–0.1	6800
16.	$PhSO_2F$	+4	6300
17.	$EtSO_2F$	+17	1980
18.	**442**	+18.7	460
19.	$PhCH_2SO_2Cl$	+22.5	5600
20.	$EtSO_2Cl$	+23	1980
21.	$PhCH_2SO_2F$	+25	5100
22.	**400**	+36.6	220
23.	3-methylisothiazole	+51	7700
24.	EtSOCl	+217	6200
25.	PhNSO	+251	6600

Using the increased power of the MSL 500 has allowed the observation of signals from organosulphur compounds with line widths up to 23 kHz, entry 1. A few of the results differ substantially from those reported previously using inferior instruments for example; EtSSEt was reported to have a shift of –499 ppm in 1972[376] but the much improved spectrum obtained here gave a value of –297 ppm (entry 6).

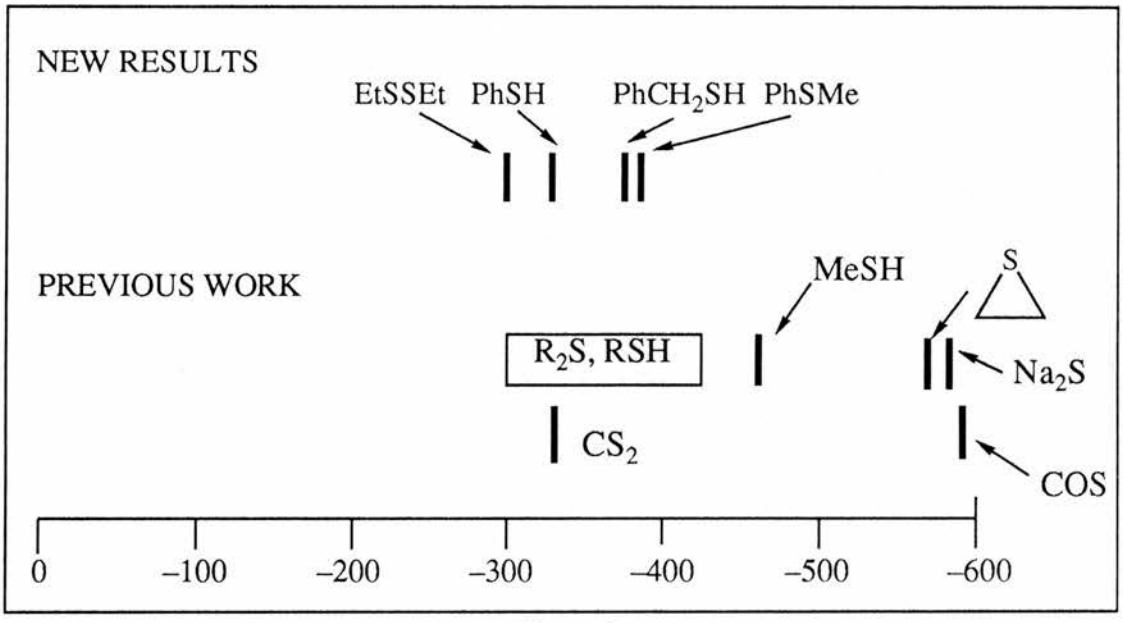


Figure 7

As shown in Figure 7, sulphides, disulphides and thiols give some of the lowest known chemical shift values for sulphur containing molecules. The line widths can vary dramatically and both ends of the spectrum are represented in Figure 7: Carbon disulphide with a line width of 350 Hz to phenyl methyl sulphide and a line width of 20 kHz. There is good agreement between the four new results, which include the first thiophenol and the first arylalkyl sulphide to be observed, and previous reports.[377]

The investigation of sulphonyl and sulphinyl halides represents the first time these type of compounds have been examined by ^{33}S NMR, Figure 8.

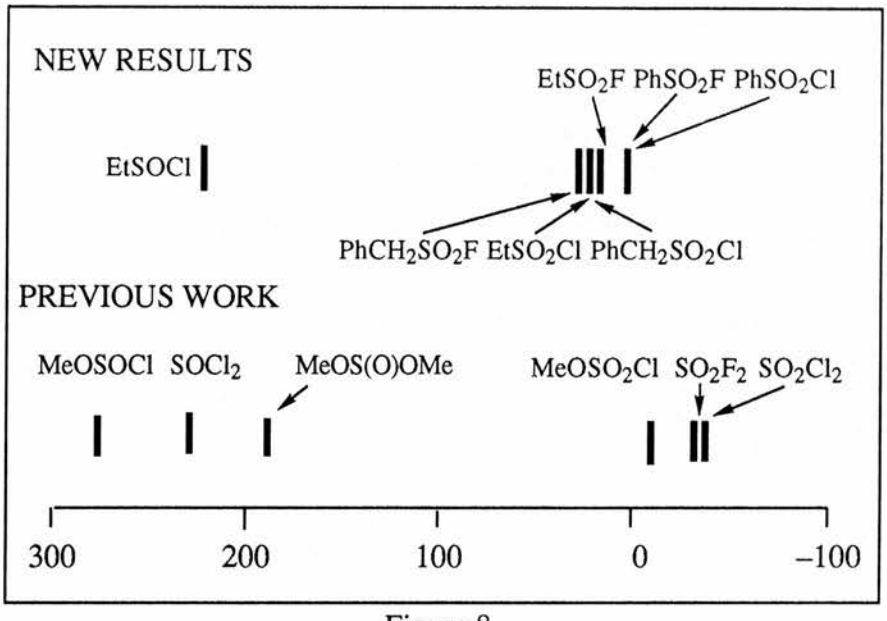


Figure 8

The shifts of the sulphonyl halides which are all between 0 and 25 ppm, due to the increasing electropositive nature of the sulphur atom are consistent with each other, with line widths varying between 2-6 kHz. Ethane sulphinyl chloride (entry 24) shows a dramatic shift to higher frequency in comparison to the sulphonyl halides and the value compares favourably with those for thionyl chloride and methoxysulphinyl chloride.[378]

A few compounds investigated in the past 20 years were unobservable under conditions dictated by the power of the spectrometer. One example is provided by the thioamides listed in entries 11 and 13, whose shifts compare well to benzenesulphonamide, entry 8. *N*-sulphinyl aniline with a shift of +251 ppm and a line width of 6.6 kHz, is the first reported compound of its type and correlates closely with similar molecules, particularly SO_2 (δ_S +375).

Sulphones possess a very symmetrical electronic environment around the sulphur, hence a low efg and therefore small line widths. The vast

majority of publications[372, 379] deal solely with sulphones because of the ease with which quality spectra can be obtained. On the MSL 500 for example a

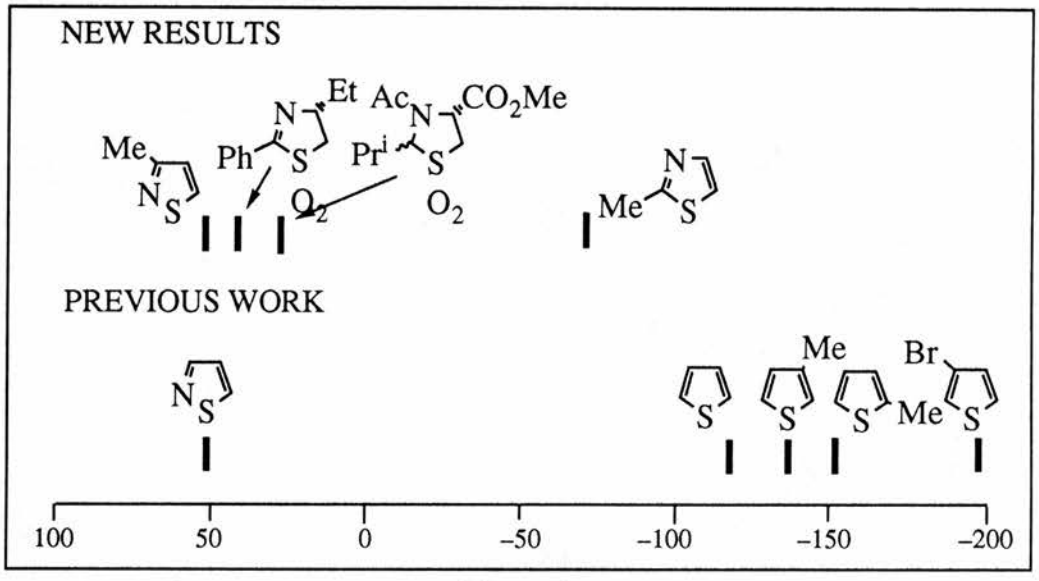
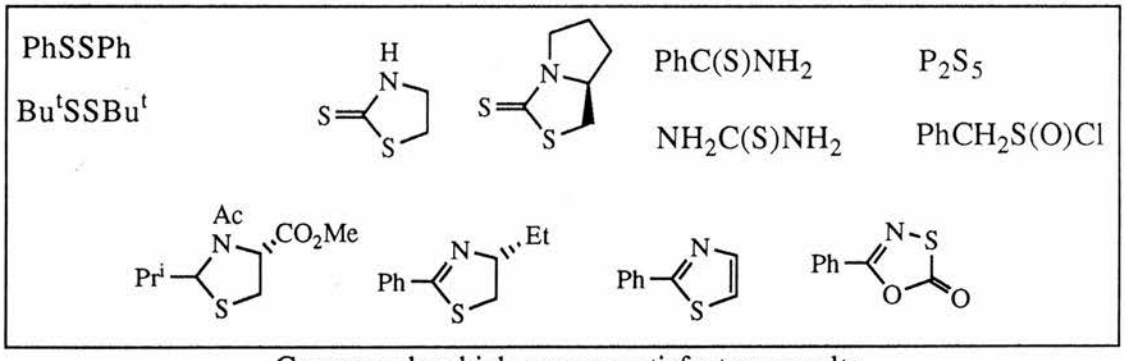


Figure 9

spectrum of **400** was obtained in under 2 min. Sulphur containing heterocycles with an oxidation state other than (VI) have been largely ignored due to their broad line widths. In Figure 9 four new results are presented but a large majority of the heterocycles gave unsatisfactory results (Figure 10).



Compounds which gave unsatisfactory results

Figure 10

The selection of compounds (Figure 10) that did not give satisfactory results can be explained by a number of reasons. Although the disulphides

have two sulphur atoms per molecule they have a higher molecular weight and are very viscous in comparison to entry 6. Heating the disulphides could possibly improve line widths enough to obtain the ^{33}S spectra. The thiocarbonyl compounds all possessed highly disordered charge distribution around the CS π bond, hence the resulting very broad lines (eg entry 1) in which determination of a chemical shift was almost impossible. In the case of ring sulphur, the compounds examined usually possessed high molecular weights and this affects the molecular tumbling constant (related to temperature, viscosity and concentration) and therefore very broad lines were observed.

Two spectra have been included which show the different nature of sulphur and how it influences the spectrum obtained, Figures 11 & 12. Thiophenol (Figure 11) has a high efg, therefore a line width of 6540 Hz (this sample was zeroed to carbon disulphide which has a shift of –332 with respect to sodium sulphate, hence the discrepancy between Figure 11 and Table 5; entry 5). *p*-Toluenesulphonyl hydrazine on the other hand has a lower efg and Figure 12 shows a somewhat sharper line (2300 Hz).

Figure 11. Thiophenol

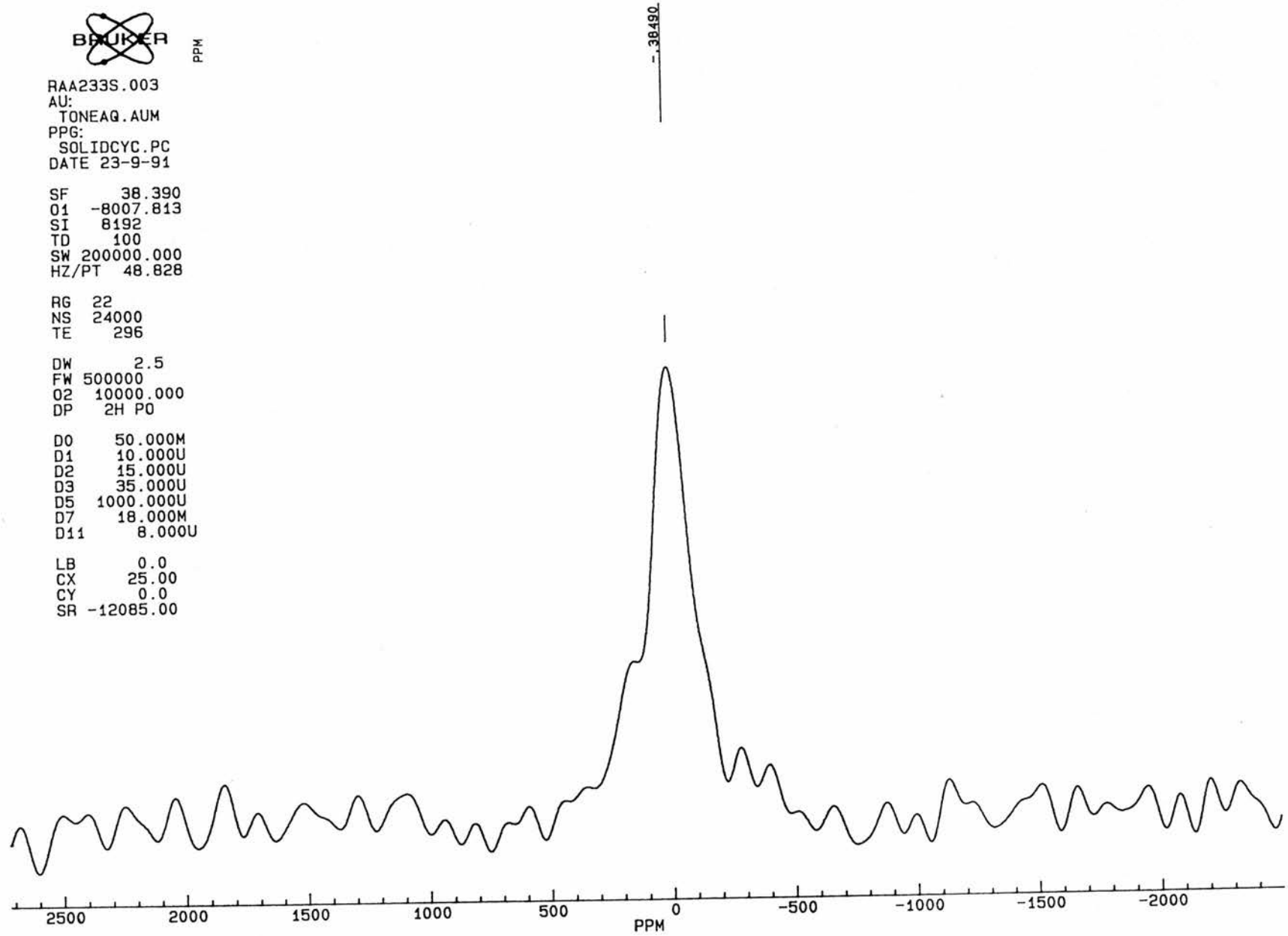
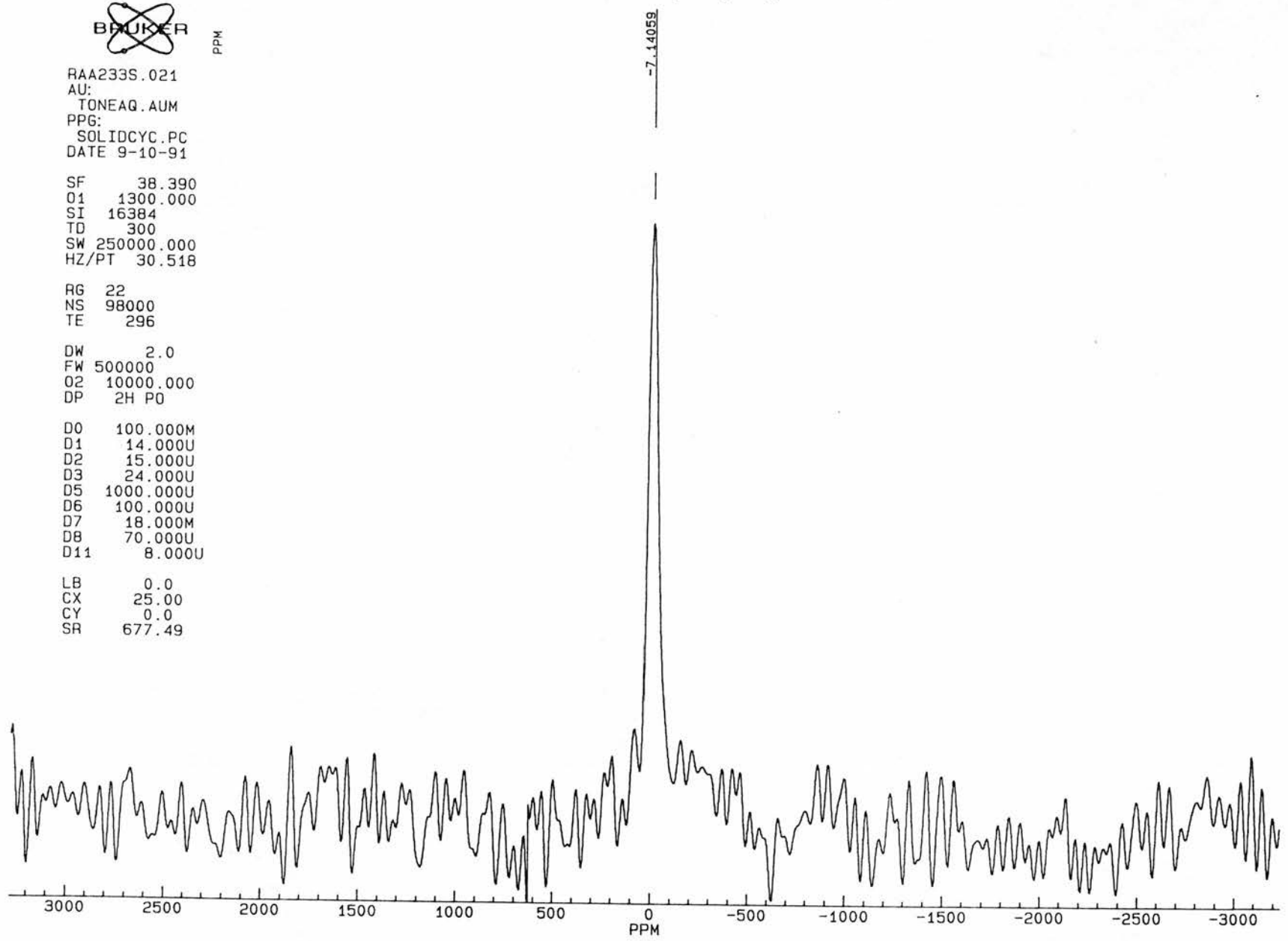


Figure 12. ***p*-Toluenesulphonyl hydrazine**



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