Advances in the Application of *N*-Sulfinyl Auxiliaries to the Synthesis of Pyrrolidines and α-Amino Acid Derivatives

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Abstract

Pyrrolidines are widely prevalent in pharmaceuticals, catalysis and agrochemicals. The (3+2) cycloaddition of azomethine ylides with alkenes is one of the most powerful methods for pyrrolidine synthesis. This reaction creates 2 σ-bonds and up to 4 new stereocentres in one reaction. Methods for the stereoselective synthesis of pyrrolidines which possess functionality in the 2- and 5-positions have been extensively developed; however, methods for the stereoselective synthesis of pyrrolidines without substituents in the 2- and 5-position are sparse.

We investigated the synthesis of pyrrolidines *via* the (3+2) cycloaddition of *N*-sulfinyl azomethine ylides and electron-deficient alkenes with the aim of controlling the stereochemistry in the 3- and 4-positions. We synthesised (*S*)-2-methyl-*N*,*N*-bis((trimethylsilyl)methyl)propane-2-sulfinamide and subjected this to photoredox catalysis and discovered this generates sulfinyl radical by lysis of the nitrogen-sulfur bond. The sulfinyl radical added to the alkene yielding a sulfoxide product.

We were successful in forming azomethine ylides *via* acid catalysis of suitable *N*-sulfinyl precursors. These reacted with electron-deficient alkenes to provide access to *N*-sufinyl pyrrolidines. This reaction did not lead to stereochemical control in the 3- and 4- positions of the pyrrolidines. This was due to racemisation of the auxiliary under the reaction conditions giving a 1:1 mixture of diastereomers.

During our efforts to improve the yields of the reactions towards pyrrolidines, serendipitously, we discovered a 1,3-migration reaction of *N*-sulfinyl-α-aminoesters to sulfinyl amines. This discovery has so far led to an efficient synthesis of both enantiomers of *tert*-leucine ethyl ester, racemic 1-adamantyl glycine and racemic cyclohexyl glycine and has potential to lead to the synthesis of many unnatural α-amino acids. Initial mechanistic considerations and studies point to this being a radical chain mechanism.

Acknowledgements

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Contents

I Introduction 8

The Case for Saturated Heterocycles 8
Pyrrolidine Prevalence 9
Pyrrolidine Synthesis 10
Azomethine Ylide Basics 10
Metal Chelation Strategies 14
Organocatalysis 22
Chiral Auxiliary Strategies 28
Sulfinamides 32
Synthesis of *tert*-butanesulfinamide 33
Applications of Chiral Sulfinamides in Synthesis 34
Classic Mode of Reactivity 34
Different Transition States 35
Scope of Organometallic Reagents 36
Radical Additions to Sulfinimines 37
Sulfinamides in Asymmetric Heterocycle Synthesis 39
α-Amino Acid Synthesis 42
Introduction to α-Amino Acid Synthesis 42
Disconnection A: Introduction to the Strecker Synthesis 44
Disconnection B: α-Amination by displacement of α-halides 49
Disconnection C: Reduction of Imines 51
Disconnection D: Installing R-Groups 53
Applications and Synthesis of Select Unnatural α-Amino Acids 58

II Aims and Objectives 62

III Results and Discussion 63

1. Photoredox Attempts at *N*-Sulfinyl AMY Generation 63
Introduction to Photoredox Catalysis 63
Precedent for AMY Generation from Photoredox Catalysis 66
Synthesis of analogous *N*-sulfinyl AMY Precursor 66
Attempts towards One-Pot bis-addition 67
Two-step attempts towards model substrate 69
Determining the Oxidation Potential of the Model Substrate: 71

Photoredox Reaction Set-up 72
Catalyst Screening 73
Proposed Photoredox Mechanism 76
2. Acid Catalysed AMY Generation 79
Precedent for Acid Catalysed AMY generation 79
Synthesis of analogous *N*-Sulfinyl Precursor 80
Screening Acid Catalysts 81
Solvent Selection 83
Further Optimisation 84
Altering Dipolarophiles 88
Varying Sulfinamide Substituent 89
Varying Equivalents of AMY Precursor 91
Assessing Diastereoselectivity of chiral *N*-sulfinyl AMYs 92
Synthesis of Racemic *N*-Sulfinyl AMY precursor in Pursuit of Racemic Standard 94
N-Benzyl versus N-Sulfinyl Energy Levels 98
Syn- versus *Anti*-selectivity 99
3. 1,3-Migrations in *N*-Alkylsulfinyl Iminoacetates 102
Attempts Towards Carbonyl Stabilised AMYs 102
Stereochemistry and Mechanism 105
Sulfinamide Syntheses for Application in 1,3-Migration Reactions 109
Synthesis of ethyl-2-(sulfinyl)imino)acetates 114
AIBN Initiated 1,3-Rearrangements 116
General Method from alkenes 117
Investigating Electron Withdrawing Groups 119
Expansion of Substrate Scope without Initiators 120
1,3 Migration Mechanistic Study 121
General Conclusion 123
IV Experimental 125
References 162

Abbreviations

9-BBN - 9-Borabicyclo[3.3.1]nonane

Å - Ångstrom

acac - acetylacetonate

AIBN - 2,2'-Azobis(2-methylpropionitrile)

AMY - Azomethine Ylide

Boc -tert-Butyloxycarbonyl

Boc_2O - tert-Butyloxycarbonyl Anhydride

BOX - bisoxazoline

bpz - bipyrazine

bs - broad singlet

COD - 1,5-cycloctadiene

d - doublet

DABCO - 1,4-diazabicyclo[2.2.2]octane

DBU - 1,8-diazabicyclo[5.4.0]undec-7-ene

DCA - 9,10-dicyanoanthracene

DCM - dichloromethane

DCN - 1,4-dicyanonapthalene

DFT - Density Functional Theory

DIPEA - *N,N*-Diisopropylethylamine

DMF - *N,N*-dimethylformamide

DMS - Dimethyl Sulfide

DMSO - Dimethyl Sulfoxide

DNBA - 3,5-dinitrobenzoic acid

dr - diastereomeric ratio

DTBM - di-*Tert*-butyl-4-methoxyphenyl

E - Cell potential

e^- - electron

EDTA - Ethylenediaminetetraacetic Acid

ee - enantiomeric excess

eq - equivalents

ESI - Electrospray Ionisation

EWG - Electron Withdrawing Group

F - Faraday's Constant

FDA - Food and Drug Administration

FTIR - Fourier-transform infrared spectroscopy

h - Hours

HE - Hanztsch Ester

HOMO - Highest Occupied Molecular Orbital

HRMS - High Resolution Mass Spectrometry

hv - Energy (photons)

KO^tBu - potassium *tert*-butoxide

LA - Lewis Acid

LDA - lithium diisopropylamine

LED - Light Emitting Diode

LiHMDS - lithium bis(trimethylsilyl)amide

LUMO - Lowest Unoccupied Molecular Orbital

M - Molarity

m/z - mass/charge

Mes - Mesityl

mins - Minutes

MOM - methyl methoxy

MS - Molecular Sieves

NAD - Nicotinamide adenine dinucleotide

NADH - Reduced Nicotinamide adenine dinucleotide

NCS - *N*-Chloro Succinimide

NMP - *N*-methyl Pyrrolidine

NMR - Nuclear Magnetic Resonance

PC - Photocatalyst

PEA - Phenyl Ethylamine

PMP - *para*-methoxy phenyl

ppm - Parts Per Million

p-Tol - *para*-Tolyl

q - quartet

Quant. - Quantitative

R_f - Distance travelled by component/ distance travelled by solvent front

RNA - Ribonucleic Acid

RT - Room Temperature

s - singlet

SCE - Standard Calomel Electrode

t - triplet

TFA - Trifluoroacetic acid

THF - tetrahydrofuran

TLC - Thin Layer Chromatography

TMG - 1,1,3,3,-tetramethylguanidine

TMS - trimethylsilane

z - Number of electrons

ΔE - Energy Difference

ΔG - Gibb's free energy

ν_{max} - wavelength

I Introduction

The Case for Saturated Heterocycles

Over the past few decades, human therapeutic chemical entities have become more diverse such as the use of monoclonal antibodies[1] and RNA[2]. However, small-molecule pharmaceuticals remain the largest class, making up 64% of the new approvals by the FDA in 2018.[3] The well-known publications "Escape from flatland" in 2009[4] and "Escape from flatland 2" in 2013[5] both analysed various properties of compounds from the discovery to drug approval stage. Some of the key findings were that the higher complexity, which can be quantified by the Fsp^3 (number of sp^3 hybridised carbons/total carbon count), the more likely a compound is to gain approval as a drug; and, a higher number of stereocentres in a compound increases the likelihood a compound will be approved. To this end, many research groups, including the Stockman group, have been investigating new ways of incorporating less explored functional groups to increase complexity and introduce chiral centres rapidly and robustly.

Pyrrolidine Prevalence

Extensively found in pharmaceuticals, insecticides, natural products and catalysts, pyrrolidines are extremely important and prevalent heterocycles (**Figure 1**). Vosaroxin (**1**) is currently under stage III clinical trials for the treatment of acute myelogenous leukaemia[6] and the NK_3 antagonist (**2**)[7], as well as the MC4R agonist (**3**), highlight 2,5-disubstitued pyrrolidine drug candidates.[8] Diaryl prolinol ether (**4**) exemplifies a powerful class of organocatalysts used in asymmetric enamine and iminium catalysis.[9] The pyrrolidine ring can also be found as a constituent of larger fused and bridged heterocyclic systems such as in the opioid agonist eseroline (**5**) or cocaine (**6**) respectively. Methodologies for pyrrolidine synthesis are plentiful and diverse and an extensive review would cover many volumes. For this reason, the attention of this introduction will be focused on the chemistry of azomethine ylides.

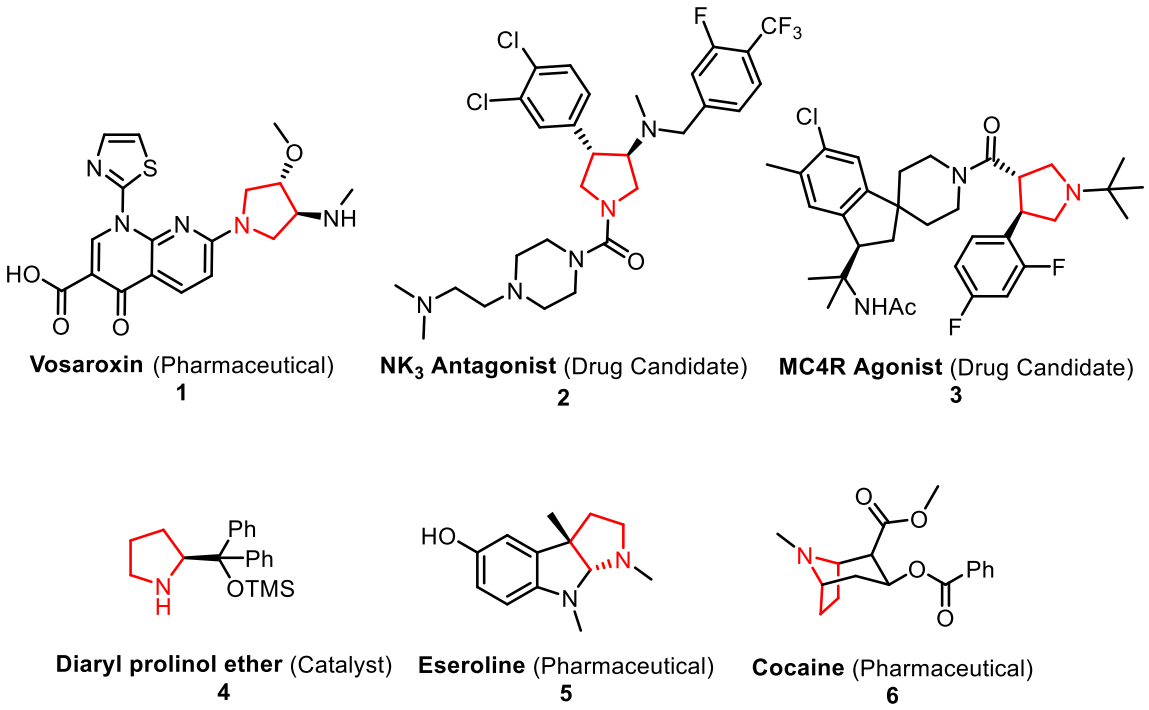
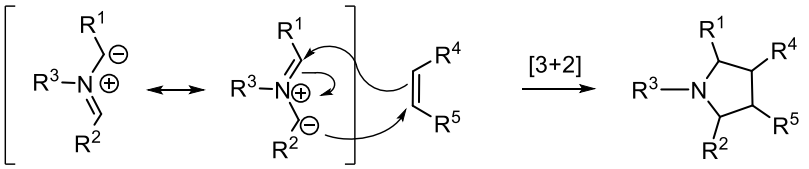


Figure 1: Useful pyrrolidine containing molecules with the pyrrolidine ring highlighted in red

Pyrrolidine Synthesis

Azomethine Ylide Basics

One of the more powerful methods for constructing pyrrolidine rings is the (3+2) cycloaddition of an azomethine ylide (AMY) with an alkene (**Scheme 1**). The reaction creates 2 σ-bonds and up to 4 new stereocentres. AMYs are short-lived intermediates, generated from appropriate precursors and can be drawn as two resonance forms.



Scheme 1: General reaction scheme for the (3+2) cycloaddition of an AMY with an alkene

AMYs are 1,3-dipoles and possess two carbons and one nitrogen in a C-N-C configuration. All three atoms are sp^2 hybridised and therefore possess a p-orbital each. Across the three p-orbitals are 4-shared electrons making the azomethine electron rich which, through using frontier molecular orbital theory, explains their affinity for electron poor alkenes (**Figure 2**).

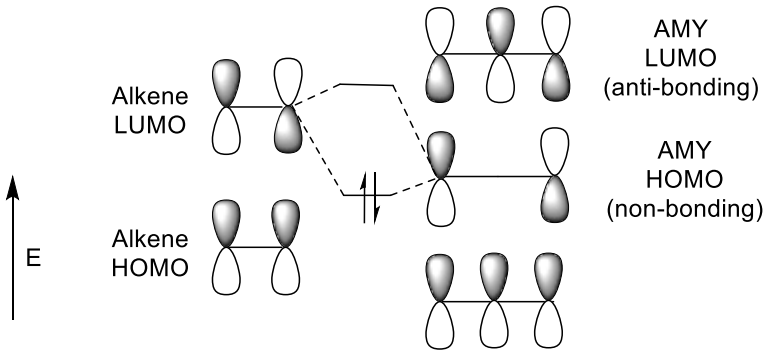


Figure 2: Frontier Molecular Orbital Diagram illustrating the main interaction between an alkene and an AMY

According to the Woodward-Hoffman rules the reaction is symmetry allowed through the primary interaction of the alkene LUMO and the AMY HOMO as both are anti-symmetric. Lowering the LUMO

of the alkene by electron withdrawing groups increases orbital overlap with the AMY HOMO, decreasing the reaction energy barrier.[10]

AMYs can be classed as stabilised and non-stabilised, with stabilised possessing electron withdrawing groups on one of the AMY's carbons. AMYs possessing alkyl or no substituents are classed as non-stabilised (**Figure 3**).

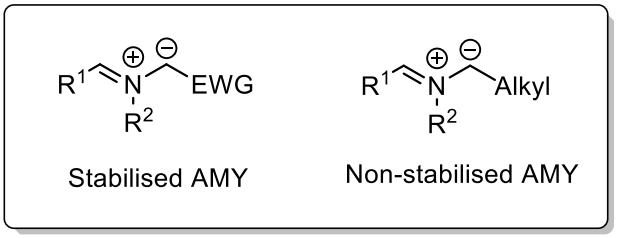


Figure 3: AMYs classed by stabilisation of the charges

The conjugation of the π-system within an AMY prevents rotation around the C-N bonds therefore AMYs can possess one of 3 configurations or "shapes" (**Figure 4**). The "shape" of an AMY will have implications in the relative stereochemistry within the pyrrolidine products. W- and U-shaped AMYs will afford pyrrolidines with the 2- and 5- substituents with a *syn*-relationship whereas Z-shaped AMYs will afford pyrrolidines with 2- and 5-substituents with an *anti*-relationship.

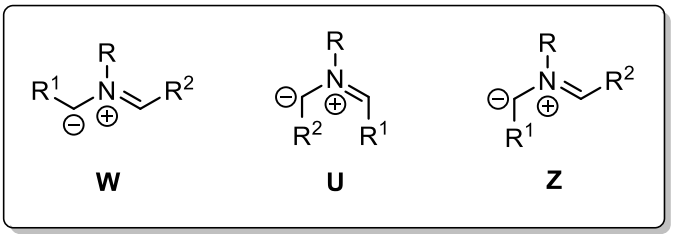


Figure 4: The possible "shapes" of AMYs possessing substituents

Cycloaddition reactions can be considered as progressing through two transition states (**Figure 5**). The *endo*-transition state can be described as when the substituents of an alkene overlap the AMY and the *exo*-transitions state is when the substituents face away from the AMY. Whether a cycloaddition proceeds through the *endo*- or *exo*-transition state is decided by a number of factors including sterics, secondary orbital interactions and solvent polarity.[11]

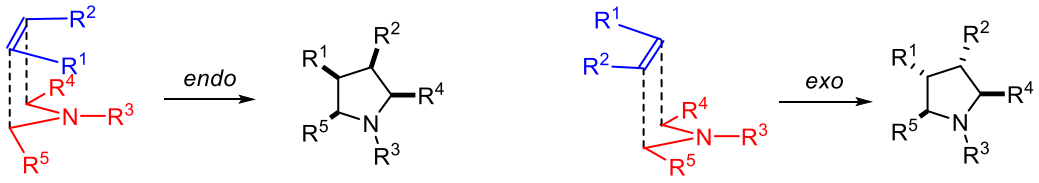
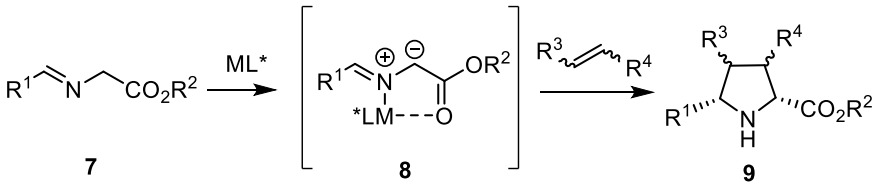


Figure 5: *endo*- and *exo*-transitions states of an alkene reacting with an AMY

The final consideration for the reaction of AMYs with alkenes is enantioselectivity or diastereoselectivity when there are multiple enantiomeric or diastereomeric pyrrolidine products possible. Strategies which aim to control these outcomes which will now be discussed in detail.

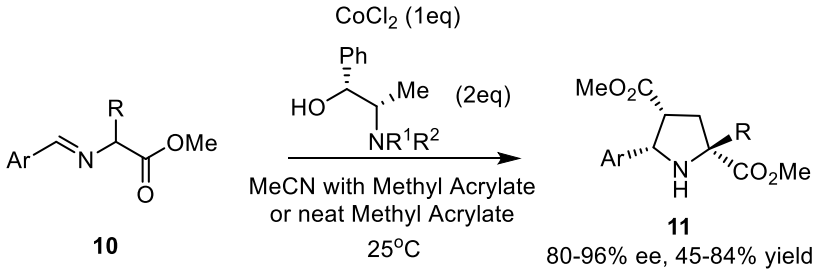
Metal Chelation Strategies

Chiral ligand-metal complexes have been widely applied in the synthesis of chiral pyrrolidines. The classic mode of action (**Scheme 2**) involves a 5-membered metallocycle AMY **8** forming between the nitrogen and oxygen of an α-iminoester (**7**) and a chiral ligand-metal complex. (3+2) Cycloaddition of AMY **8** with alkenes then affords the corresponding pyrrolidine **9**.



Scheme 2: Mode of asymmetric induction of (3+2) cycloadditions of AMYs using chiral ligand-metal complexes

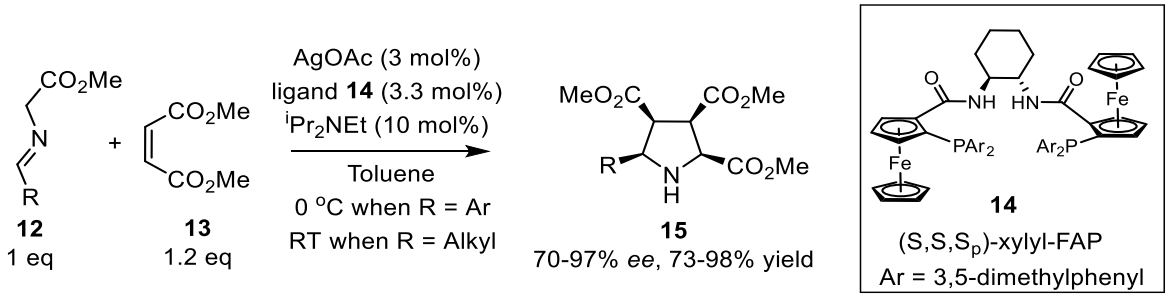
Grigg and co-workers were the first to publish an example of the chiral ligand-metal strategy in 1991 (**Scheme 3**).[12] The AMY precursors were α-iminoesters **10** and the procedure was stoichiometric with respect to cobalt(II) chloride and ephedrine. 5-Aryl pyrrolidines **11** were afforded in good to excellent yields from reaction with the dipolarophile, methyl acrylate. The reaction strongly favoured *endo*-selective products.



Scheme 3: First example of asymmetric (3+2) cycloaddition of an AMY using the chiral ligand-metal complex strategy

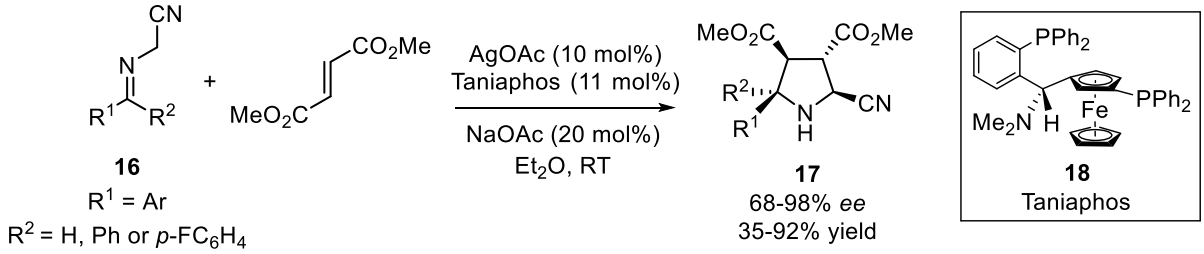
Based on the seminal work by Grigg, two research groups, Zhang and Jørgensen, simultaneously and independently, reported catalytic chiral ligand-metal complex methodologies for the synthesis of

pyrrolidines from α-iminoesters *via* (3+2) cycloadditions of AMYs with electron-deficient olefins. The methodology from Zhang [13] and co-workers (**Scheme 4**) used silver(I) acetate and the expensive chiral ligand (*S*, *S*, S_p)-xylyl-FAP (**14**). Methyl α-iminoesters **12** reacted with diethyl maleate **13** to afford the tetra-substituted pyrrolidines **15.** This reaction was completely *endo*-selective and offered excellent enantioselectivities. Imines with aryl groups gave the best results while alkyl substituents required extended reaction times; 48 hours as opposed to 7 hours for aryl groups.



Scheme 4: Zhang's catalytic protocol for the asymmetric catalytic synthesis of pyrrolidines from α-iminoesters.[13]

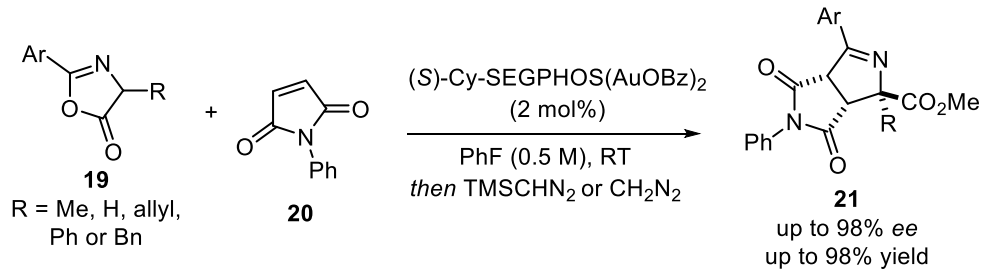
The protocol from the Jørgensen group utilised similar α-iminoesters, all of which possess aryl groups on the imine.[14] This protocol uses $Zn(OTf)_2$ as the metal salt and (*S*)-*tert*-Bu-BOX as the chiral ligand which afforded yields of 76-95% and *ee*s of 68-94% when the reaction was conducted with electron deficient olefins.



Scheme 5: α-iminonitriles as AMY precursors

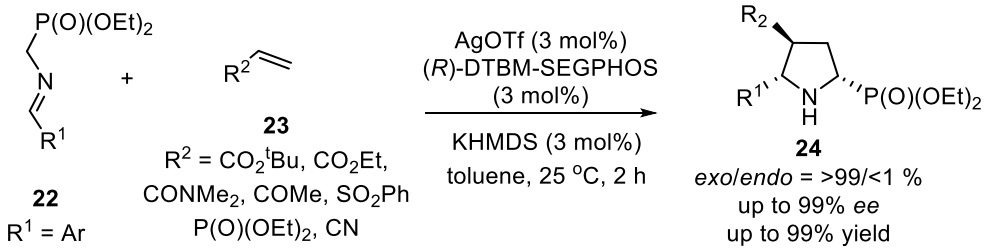
Carretero and co-workers have extended the AMY precursors to α-iminonitriles **16** providing a route to 5-nitrile pyrrolidines **17** (**Scheme 5**) again using silver(I) acetate but using Taniaphos (**18**) as the

ligand .[15] The 2-position was found to tolerate only aryl and heteroaryl groups with electron deficient rings working best. This reaction was completely *endo*-selective. The *exo*-products were achieved by Toste and co-workers through the use of azlactones (**19**) or münchnones, a class of mesoionic compounds which can act as AMYs. The (*S*)-Cy-SEGPHOS(AuOBz)$_2$ chiral ligand-metal complex was preformed and controlled the reaction of the formed AMYs with *N*-phenyl maleamide (**20**) to give fused pyrrolidine derivatives **21** in excellent yields and excellent ees for most examples.



Scheme 6: Azlactones as AMY precursors

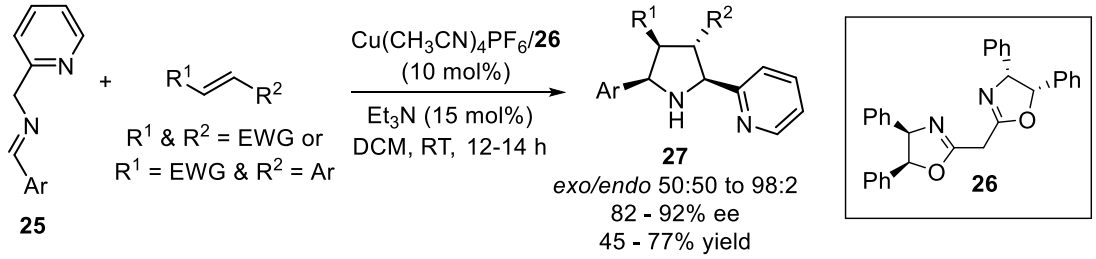
5-Phosphonate substituted pyrrolidines (**24**) were synthesised by Kobayashi and co-workers (**Scheme 7**) from the α-iminophosphonates (**22**).[16] The pKa of the α-proton of the α-iminophosphonate is much higher than previous examples, resulting in the need for a stronger base, KHMDS. This methodology also provided access to the *exo*-products in excellent yields and *ee*s. A variety of dipolarophiles (**23**) were shown to be compatible in this reaction resulting in good scope for 3-position substitution.



Scheme 7: α-iminophosphonates as AMY precursors

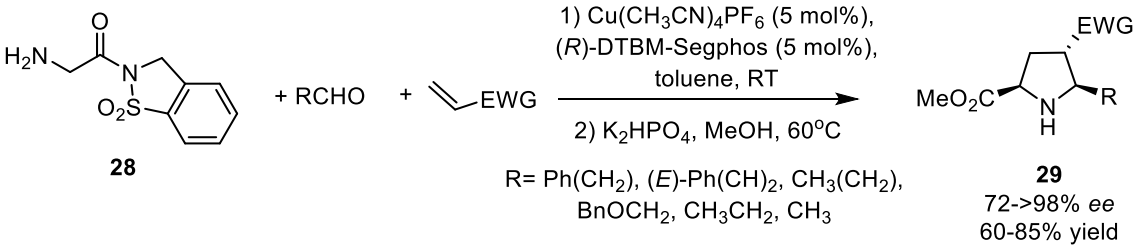
Tetrakis(acetonitrile)copper(I) hexafluorophosphate and bisoxazoline **26** were shown to extend the AMY precursors to include *N*-(2-pyridylmethyl)imines (**25**) which give 2-pyridyl pyrrolidines (**27**) (**Scheme 8**).[17] Yields were slightly lower than previous examples and the *endo/exo* ratio was on

average much lower but the *exo*-products did predominate. 3-Pyridyl and 4-pyridylmethyl imines did not yield the desired pyrrolidines demonstrating the important role of the metallocycle AMY intermediate. Carretero and co-workers later expanded on this work to include 9 more heteroaryls being incorporated into the 5-position.[18]



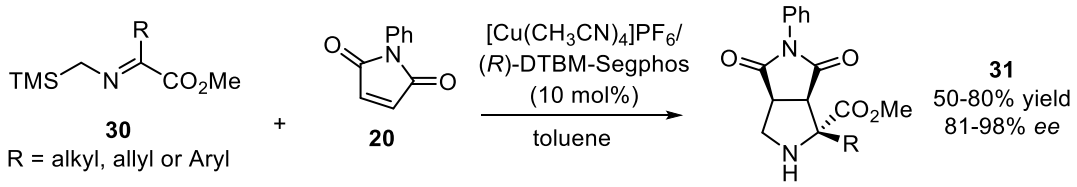
Scheme 8: *N*-(2-Pyridylmethyl)imines as AMY precursors

Early methods for the metal chelation strategy were largely limited to α-iminoesters derived from non-enolisable aldehydes such as aryl and α,β-unsaturated aldehydes due to their higher stability i.e. inability to tautomerise. More recent studies have expanded the scope to include 2-alkyl substituted pyrrolidines and 2-unsubstituted pyrrolidines. Kobayashi and co-workers developed a methodology which provided access to AMYs bearing aliphatic groups. These AMYs react with dipolarophiles to pyrrolidines with aliphatic groups in the 2-position. The conditions found to work best were silver bis(trimethylsilyl) amide and (*R*)-DTBM-SEGPHOS in diethyl ether at 0 °C.[16] Garner and co-workers published a second solution and a larger variation of the original metal chelation strategy by employing a multi-component strategy. AMYs from enolisable aldehydes are afforded from the *in-situ* generation of α-iminoesters from glycyl sultams (**28**) (**Scheme 9**). The glycyl sultam group activates the α-position of the imine providing access to the metalated AMYs. Tetrakis(acetonitrile)copper(I) hexafluorophosphate and the use of (*R*)-DTBM- SEPGPHOS was found to be an excellent catalytic system, yielding *exo*-selectivity >99:1 for most examples of 5-alkyl pyrrolidines (**29**).[19]



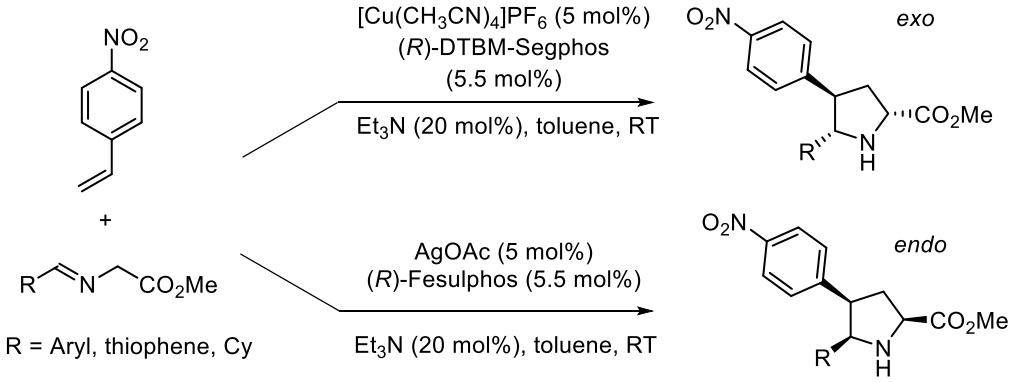
Scheme 9: Glycyl sultams as activating groups within AMY precursors

The synthesis of enantioenriched 5-unsubstituted pyrrolidines (**31**) was achieved by Carretero and co-workers in 2012 through the use of α-silylimines (**30**) (**Scheme 10**).[20] A number of dipolarophiles were used including N- phenyl maleamide (**20**) and vinyl sulfonates. The sulfonates were then shown to be removable either through use of a sodium-mercury amalgam or DMAP to give pyrrolidines with no substituents in the 5- and 4-positions.



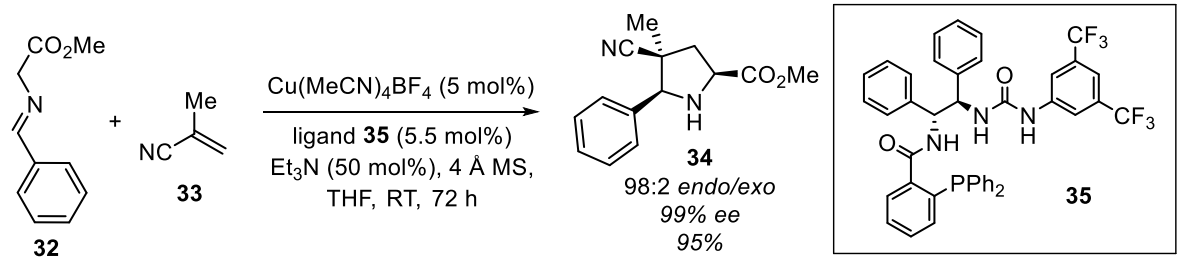
Scheme 10: α-silylimines as AMY precursors to afford 5-unsubstituted pyrrolidines

Copper(I) and silver(I) are the most common metals for the metal chelation strategy. *Exo/endo*-selectivity can often be switched by switching from one metal to the other exemplified by Carretero and co-workers in 2016 on their work which extended dipolarophiles to alkenyl arenes (**Scheme 11**).[21]



Scheme 11: *Exo/endo* tunability through switching of Cu(I) and Ag(I)

In general, most dipolarophiles with one or more electron withdrawing groups show good reactivity and afford pyrrolidines with good *ee*s. However, one dipolarophile which was found not to give good selectivity is methacrylonitrile (**33**). The ligands discussed in the previous examples of the metal-chelation strategy have used sterics to control stereochemistry. In 2019, Zhang and co-workers used sterics *and* electronics to control stereochemical outcome in the (3+2) cycloaddition of AMYs chelated by the copper and urea ligand **35** complex. This provided access to 3-methyl-3-nitrile pyrrolidines **34** from reaction of α-iminoester **32** with methacrylonitrile (**33**) (**Scheme 12**).[22]



Scheme 12: Controlling stereochemistry when methacrylonitrole is used as dipolarophile using a chiral urea-derivative ligand

The lowest energy transition state (**Figure 6**) involves proton donation from the urea moiety to the nitrogen atom of the nitrile group, fixing the dipolarophiles orientation during the cycloaddition. All possible transition states were studied using DFT calculations which correlated to the observed products.

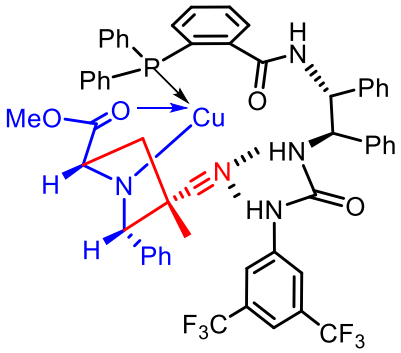
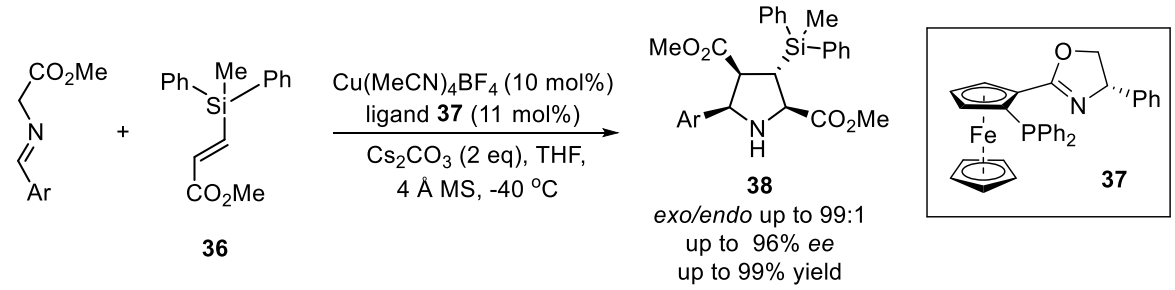


Figure 6: Zhang's urea derived ligand (black) transition state during AMY (blue) (3+2) cycloaddition with methacrylonitrile (red)

The chiral metal-ligand catalyst strategy works well for the synthesis of pyrrolidines with a carboxylate and some other lone-pair donor groups in the 2-position. However, this is also a drawback for this methodology as it does not allow for the synthesis of pyrrolidines without functionality in the 2-position.

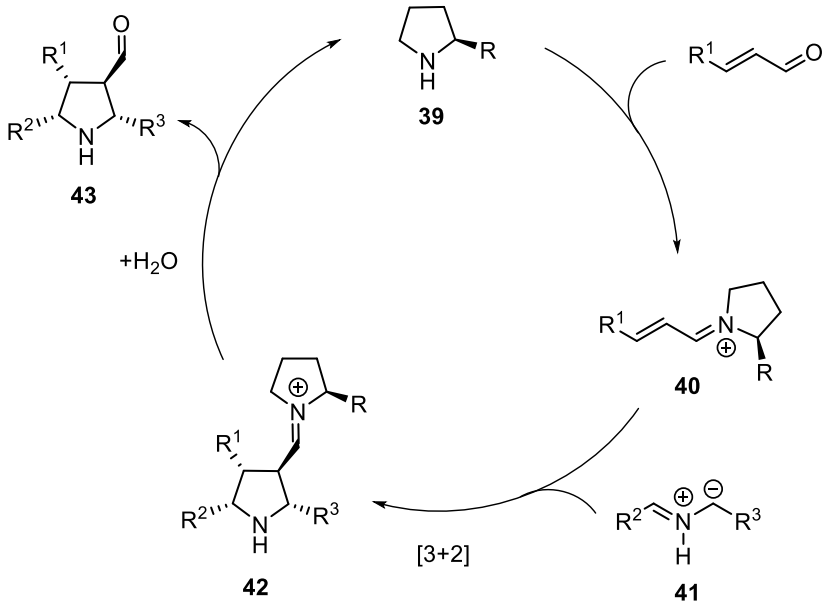
The scope of compatible dipolarophiles is vast and has recently been reviewed for the chiral metal-ligand strategy.[23] One advance worth discussing is the use of β-silyl acrylates as dipolarophiles. The silyl group can be readily converted into a hydroxy-group providing access to 3-hydroxy pyrrolidines, a common functionality in natural products.[24] Installing a hydroxy group in this position is difficult because enol ethers are not suitable for the (3+2) cycloaddition of AMY due to being electron rich. Deng and co-workers showed tetrakis(acetonitrile) copper(I) tetrafluoroborate and ferrocene ligand **37** is an efficient catalytic system for the enantioselective synthesis of pyrrolidines **38** bearing a silyl group in the 3-position from β-silyl acrylates **36** (**Scheme 13**).[25] Further modifications led to poly-hydroxylated pyrrolidines.



Scheme 13: synthesis of 3-silyl pyrrolidines from β-silyl acrylates

Organocatalysis

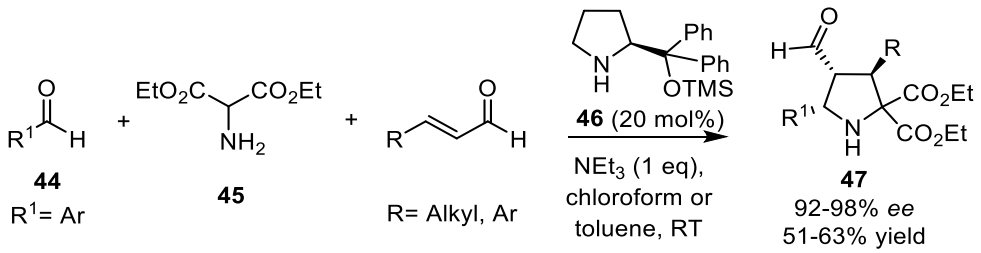
The approaches available for asymmetric organocatalytic (3+2) cycloadditions of AMYs are much more varied than their metal-catalysed counterparts. They have been extensively reviewed in recent publications.[23,26] The first approach to be outlined is the application of chiral secondary amines **39**. The general mechanism is illustrated (**Scheme 14**). AMYs are electron-rich dipoles and as a result, have a high-energy HOMO. Their reactivity with dipolarophiles is governed by the interaction with the LUMO on the dipolarophile as this results in the most efficient frontier molecular orbital overlap. Chiral secondary amines catalyse the (3+2) cyloaddition of AMYs with dipolarophiles by forming an iminium ion **40** with an α,β-unsaturated aldehyde, thereby lowering the energy of the LUMO. This provides enhanced efficiency in overlap between the HOMO of the dipole (in this case an AMY **41**) and the newly lowered LUMO of the dipolarophile in **40**. The cycloaddition product **42** then undergoes hydrolysis to release the catalysts and 4- or 3-formyl pyrrolidines **43**.



Scheme 14: General mechanism of chiral iminium ion activation of (3+2) cycloaddition of AMYs with α,β-unsaturated aldehydes.

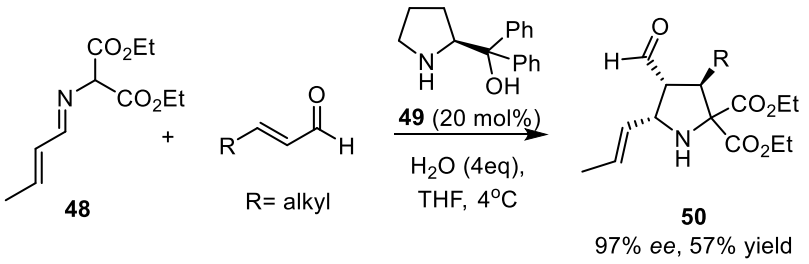
The first example of asymmetric iminium activation in (3+2) cycloadditions was reported in 2007 by Johannes and co-workers in the 1,3-cycloaddition of nitrones to α,β-unsaturated aldehydes using (*S*)-

diphenylprolinol trimethylsilyl ether.[27] Later in the same year Vicario[28] and Córdova[29] (**Scheme 15**) independently applied this strategy to the asymmetric synthesis of 4-formyl pyrrolidines from AMYs generated *in situ* from aldehydes **44** and amino malonates **45** in a three-component reaction to give highly functionalised pyrroldines **47** in moderate yields and excellent enantioselectivity controlled by the secondary amine catalyst **46**. Typically the catalyst loading for secondary amine catalysis is much higher than the metal chelation strategy; in this example, 20 mol% of **46** was required.



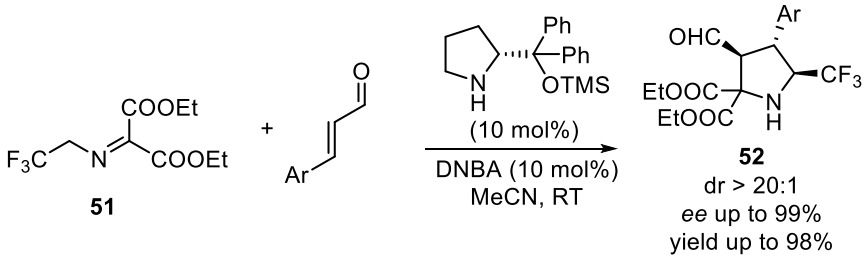
Scheme 15: Example from the Córdova research group of diarylprolinol silyl ethers as asymmetric organocatalysts in the (3+2) cycloaddition of azomethine ylides

In a recent study by Cossío and co-workers, 5-alkenyl pyrrolidine derivatives **50** were synthesised from imine **48** using the secondary amine **49** bearing a free hydroxyl group (**Scheme 16**).[30] Computational studies indicated that the asymmetric pyrrolidine synthesis *via* chiral secondary amine catalysts derived from proline may not be pericyclic as first believed but instead proceed through a Michael/Mannich mechanism. This work also allowed access to 5-formyl substituted pyrrolidines by ozonolysis of the 5-alkenyl cyclisation products. Unfortunately, the reaction did not proceed well when aldehydes bearing β-aryl substituents were used, limiting the products to alkyl groups in the 3-position.



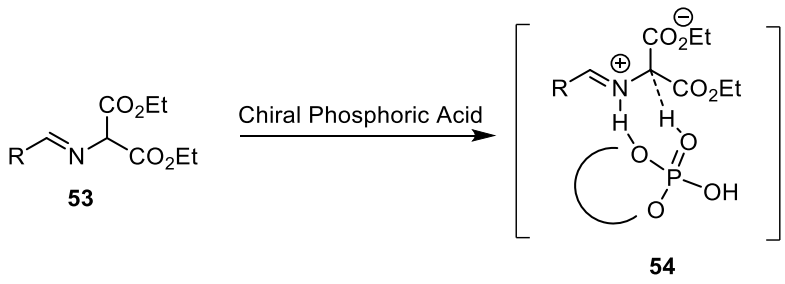
Scheme 16: Example of the synthesis of a 5-alkenyl pyrrolidine derivative via diarylprolinol catalysis.

Using α-cyanoglycine esters as AMY precursors allows the synthesis of 2-cyano-2-ester-substittued pyrrolidines.[31] 5-Trifluoromethyl pyrrolidines (**52**) were synthesised by Wang and co-workers in 2019 using the secondary amine catalysis methodology from imine **51** (**Scheme 17**).[32] Addition of DNBA (3,5-dinitrobenzoic acid) when compared to benzoic acid as an additive decreased the reaction time from 31h to 3h in the optimisation. Again, only aryl groups were tolerated in the β-position of the aldehyde.



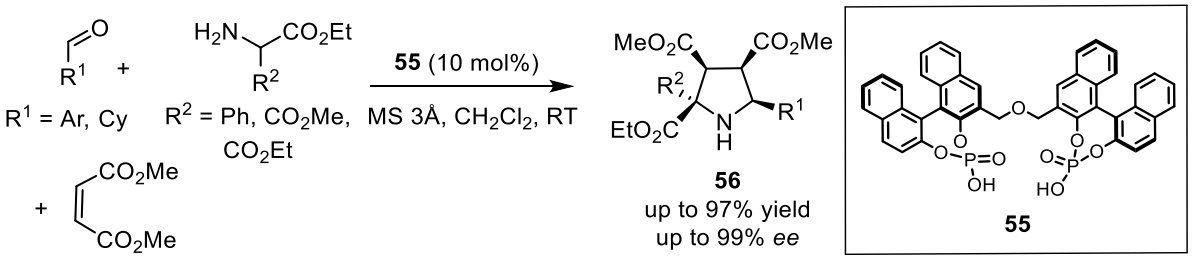
Scheme 17: Synthesis of 5-trifluoromethyl pyrrolidines

A second approach to asymmetric organocatalysts is the use of chiral Brønsted acids, with chiral phosphoric acids most commonly being employed. These catalysts act on the AMY by hydrogen bonding with α-iminomalonates **53** due to their ability to undergo prototropy to AMYs. This forms a chelated AMY in a chiral environment **54** (**Scheme 18**).



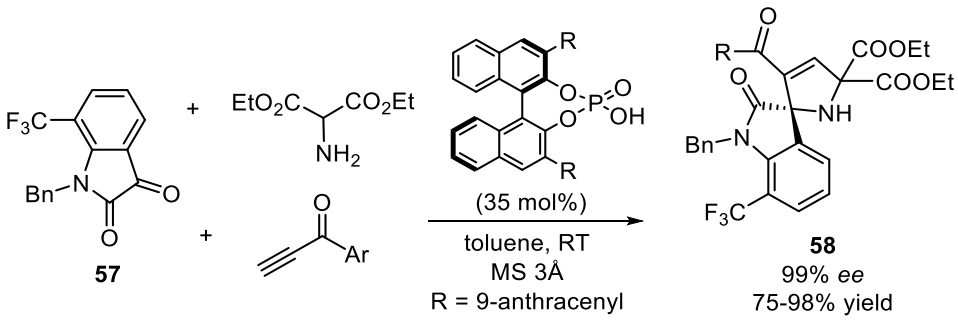
Scheme 18: Chiral Phosphoric facilitating prototropy of α-iminomalonates to chiral AMYs

The first study was published in 2008 by Gong and co-workers who found that chiral phosphoric acid **55** gave the best results when screening seven chiral phosphoric acid catalysts for the synthesis of highly substituted pyrrolidines **56**. [33] Seventeen aldehydes were employed, sixteen of which possessed aryl groups in the β-position and the remaining example being cyclohexyl.



Scheme 19: First example of asymmetric synthesis of pyrrolidines using a chiral phosphoric acid catalyst

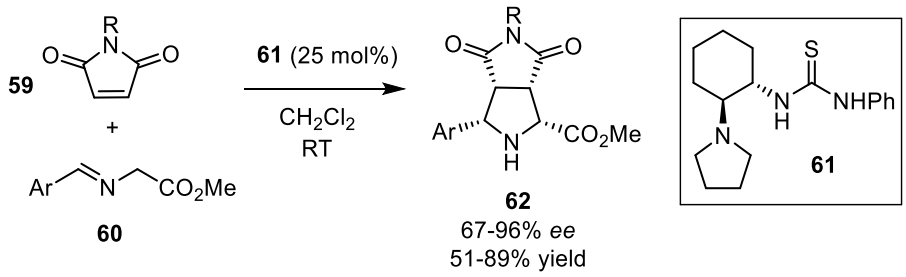
Dipolarophile reaction partners have since been widely expanded to include allenoates,[34] isoindolines[35] and alkynes,[36] all of which involve the *in situ* generation of the AMY from aminomalonates and aldehydes. The source of AMY has also been expanded to include α-keto esters[37] and isatins **57** which give spirocyclic products **58**[38] (**Scheme 20**).



Scheme 20: Isatin derived azomethine ylides as reaction partners in chiral phosphoric acid catalysed (3+2) cycloadditions

Of notable importance in the above iminium catalysed and the phosphoric acid catalysed approach is that most examples require two electron-withdrawing substituents in the α-position of the AMY resulting in their incorporation in the product.

A third approach to the asymmetric organocatalysis of (3+2) cycloadditions for pyrrolidines is the use of thiourea derivatives (**Scheme 21**). These approaches only require one electron withdrawing group on the AMY instead of two as required in the previous organocatalytic methodologies. The mode of action is likely similar to that of chiral phosphoric acids, i.e. hydrogen bonding of the catalyst to the α-imino ester/AMY provides a transition state which favours (3+2) on one prochiral face of the AMY over the other. Xu, Wang and co-workers demonstrated thiourea derivative **61** asymmetrically induced (3+2) cycloaddition AMYs from α-imino esters **60** and maleimides **59** to afford the corresponding pyrrolidines **62**.

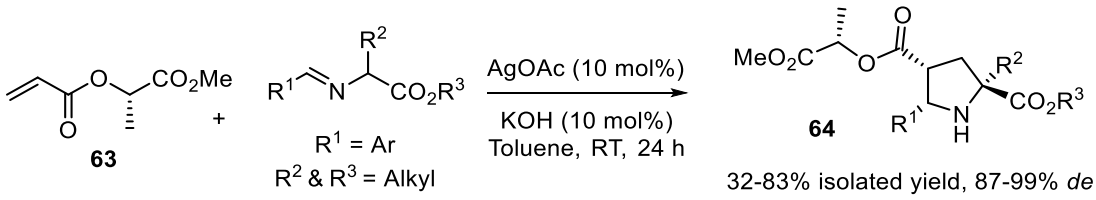


Scheme 21: Thiourea derivatives acting as an asymmetric catalyst in azomethine ylide (3+2) cyloadditions

Thiourea examples have been used for the synthesis of 4-nitro substituted pyrrolidines but the methodology is limited to α-imino esters possessing *ortho*-phenols. A thiourea catalysed reaction also provided access to polysubstituted chromeno[4,3-b] pyrrolidine derivatives through a cascade process.[39]

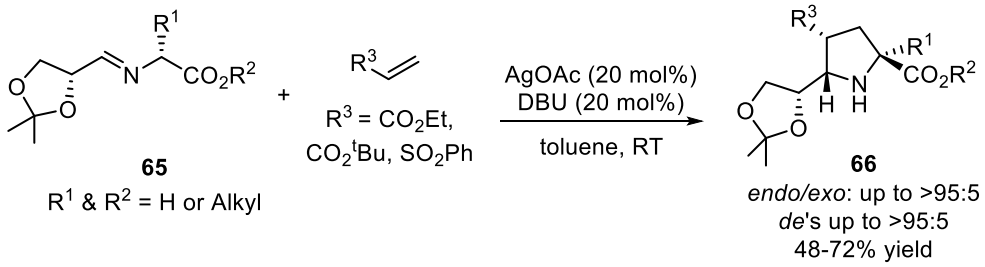
Chiral Auxiliary Strategies

Chiral auxiliaries have been employed as elements of the dipolaropile and the AMY. Beginning with the dipolarophile, Cossío and co-workers showed by incorporating an element of chirality into the alkoxy chain of an acrylate (**63**) , the regio- and diastereoslectivity of the (3+2) cycloaddition could be controlled to give pyrrolidines (**64**) (**Scheme 22**).[40] This work was applied in the synthesis of Hepatitis C RNA-polymerase inhibitors.



Scheme 22: Chiral acrylates as reaction partners to delivery diastereoselectivity in pyrrolidine synthesis.

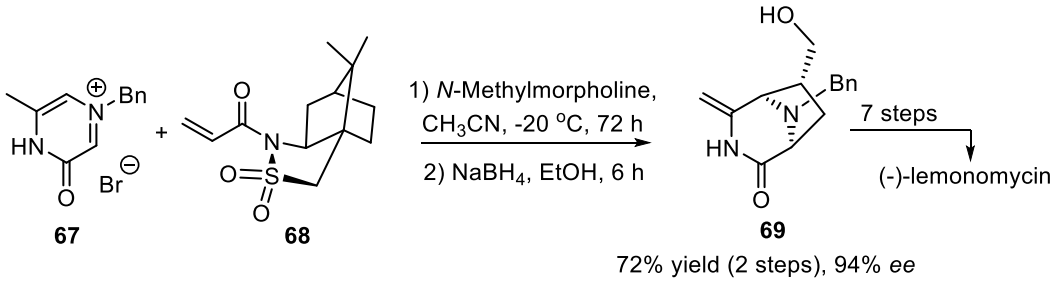
Badorrey and co-workers also used a metal-chiral auxiliary strategy, However this time they embedded the chiral auxiliary in the α-iminoester AMY precursor **65** (**Scheme 23**).[41] The yields of the pyrrolidine products **66** were moderate to good but the work also demonstrated the possibility to switch between *endo*- and *exo*-selectivity. Silver(I) acetate gave *endo*-products whereas Copper(I) acetate gave *exo*-products. The *de*s for most examples were good and the 5-acetal products could be deprotected to afford 1,2-diols which could then undergo oxidative cleavage with sodium periodate to afford 5-formyl pyrroldines.



Scheme 23: Metal catalysed pyrrolidine synthesis from AMY precursors with chiral auxiliaries

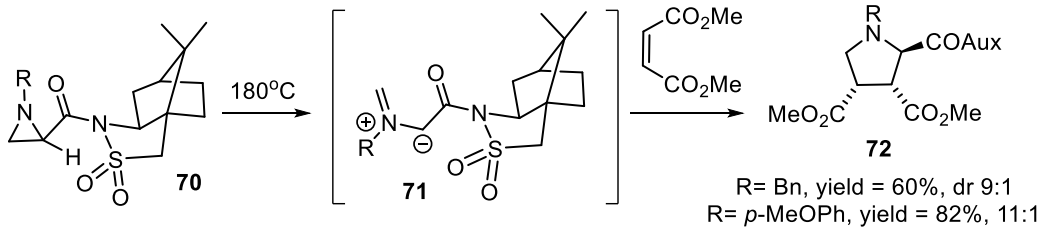
The use of chiral auxiliaries also allows preparation of enantiomerically enriched pyrrolidines *via* AMYs which do not involve a metallocycle being formed.

Stoltz and co-workers reported a similar use of chiral dipolarophiles in 2003, in this instance using an Oppolzer derived sultam acrylamide **68**. The *in-situ* generation of an AMY from the salt **67** resulted in the formation of bridged pyrrolidine **69** which was the key intermediate towards the synthesis of (-)-lemonomycin (**Scheme 24**).[42] It is notable that as this method does not require the use of a metal, the starting materials do not require a carbonyl group in the α-position to the AMY nitrogen providing access to pyrrolidines without a carbonyl group in the 2-position.



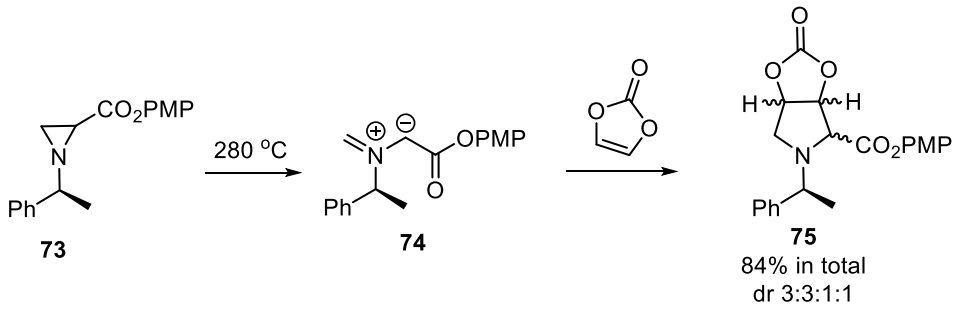
Scheme 24: Chiral sultam acrylamide acting as a dipolarophile to form a key pyrrolidine in the synthesis of (-)-lemonomycin

Oppolzer's camphor sultam has also been used as a chiral auxiliary on a carbon atom which is involved in the π-system of the AMY. Garner and co-workers first synthesised aziridine **70** which underwent the well-documented thermal reverse electrocyclization to form AMY **71**. These intermediates then took part in the (3+2) cycloaddition reactions to give pyrrolidines **72** in good yields and good diastereoselectivity (**Scheme 25**).[43] The selectivity was rationalised by the exclusive formation of the *Z*-AMY and the *endo*- transition state being favoured.



Scheme 25: Oppolzer's sultam as a chiral auxiliary on an AMY

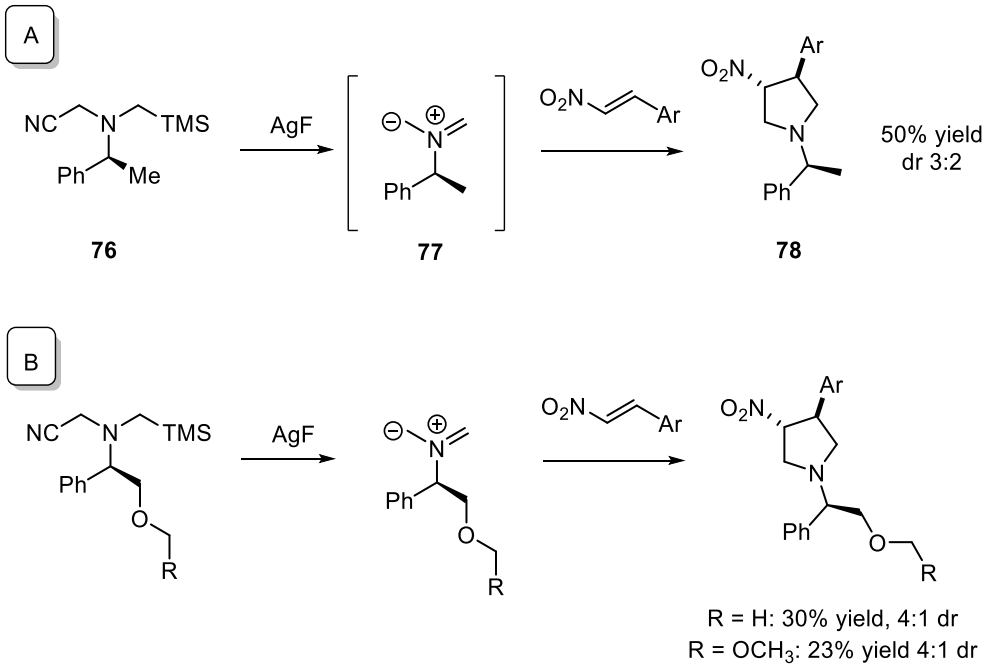
Chiral auxiliaries can also be placed on the nitrogen of the AMY. Takano and co-workers synthesised aziridine **73** which also underwent reverse electrocyclization to form AMY **74** and subsequent (3+2) cycloaddition with maleic anhydride to give pyrroldines **75** (**Scheme 26**).[44] The reaction gave a mixture of diastereomeric products in a ratio of 3:3:1:1 demonstrating poor selectivity for this strategy.



Scheme 26: AMY bearing chiral auxiliary on the nitrogen atom

Another example of poor diastereoselectivity in the nitrogen auxiliary bearing strategy was reported by Padwa and co-workers (**Scheme 27**).[45] This strategy also highlights an entirely alternative method for generating AMYs. Instead of the metal mediated formation and the aziridine opening methods described above, this method uses an *N*-cyanomethyl-*N*-silylmethyl amine (**76**) which undergoes a fragmentation in the presence of silver fluoride to form the AMY (**77**) *in-situ*. The (*S*)-1-phenylethan-1-amine derivative **76** gave diastereoselectivity of 3:2 in a 50% yield when synthesising pyrrolidine **78** (**Scheme 27 A**). By increasing the size of the auxiliary to a longer ether chain (**Scheme 27 B**), the diastereoselectivity of the reaction increased to 4:1 but this was detrimental to the yield. The diastereomeric ratio also plateaued at the methoxy methyl derivative as increasing the size again to

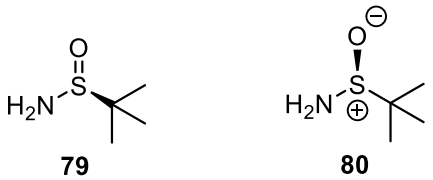
the methoxymethoxymethyl derivative produced the same diastereomeric ratio but with another decrease in the yield of the desired pyrrolidine.



Scheme 27: Fragmentation of cyanomethylamines to form an AMY bearing a chiral auxiliary

Sulfinamides

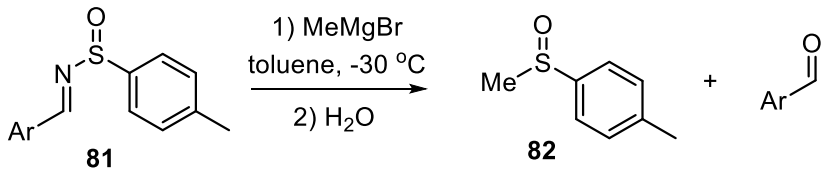
Sulfinamides have found application as chiral equivalents of ammonia. The most frequently utilised is *tert*-butanesulfinamide (**Figure 7**), colloquially known as Ellman's sulfinamide due to Prof. Jonathan Ellman's extensive work on the synthesis and application of the molecule.[46] Sulfinamides can be depicted as two resonance forms (**79** and **80**), the electron lone pair is usually omitted in illustrations and the stereochemical information is depicted on the S-C bond for resonance form **79** and the S-O bond for resonance form **80**. The illustration method used in this thesis will be that used for **79**.



79 **80**

Figure 7: Two methods of depicting *tert*-butane sulfinamide

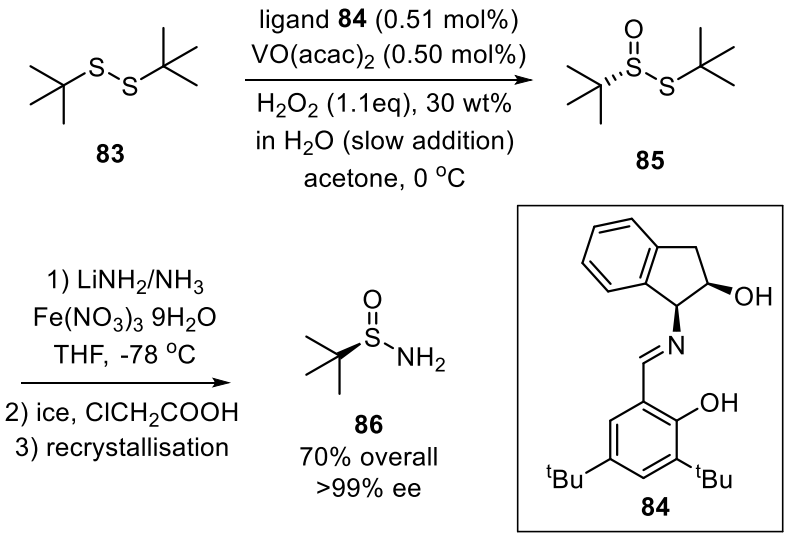
Two other chiral sulfinamides have found frequent application as chiral ammonia equivalents, *para*-tolylsulfinamide and mesitylsulfinamide. However, *tert*-butanesulfinamide has been found to have superior properties in many situations. One example of the undesirable reactivity of *para*-tolylsulfinimines is when adding the more reactive alkyl Grignard reagents to sulfinimines **81** (**Scheme 28**).[47] These more reactive Grignard reagents will add solely onto the sulfur, lysing the sulfur-nitrogen bond, giving sulfoxide **82** as the product.



81 **82**

Scheme 28: Addition of alkyl Grignard reagents to *para*-tolylsulfinimines

Synthesis of *tert*-butanesulfinamide



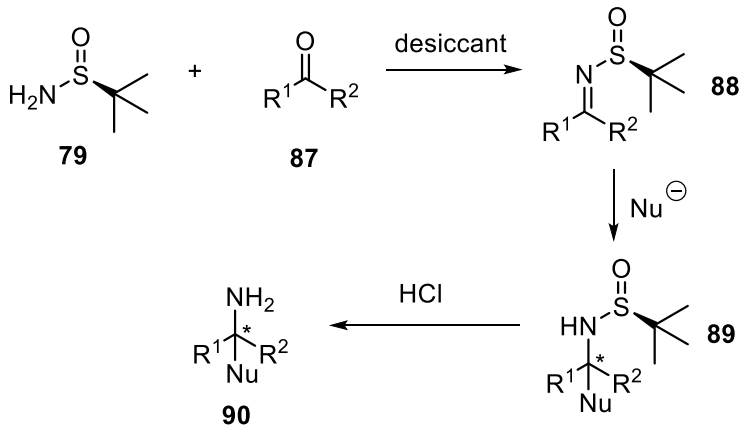
Scheme 29: The optimised methodology for the synthesis of enantiomerically pure *tert*-butanesulfinamide

Ellman and co-workers published the first catalytic synthesis of *tert*-butanesulfinamide in 1997.[48] But, the route suffered from lack of scalability due to issues surrounding the use of a biphasic system. An improved catalytic system (**Scheme 29**) reported by Weix and Ellman overcame these drawbacks.[49] The use of acetone as the solvent was key to the improved scalability as this created a monophasic reaction mixture. The two-step synthesis first involves an asymmetric oxidation of *tert*-butyl disulphide (**83**) to intermediate **85** using vanadium acetylacetonate and ligand **84.** As well as using a first-row transition metal, the starting material, *tert*-butyl disulfide (**83**), is a waste product from the oil and gas industry and the oxidant, hydrogen peroxide whose only by-product is water, boosts the "green" credentials of this step. A nucleophilic substitution reaction is then performed by lithium amide on intermediate **85** which gives crude *tert*-butanesulfinamide which after purification by recrystallisation gives **86** in 70% yield and >99% *ee*. The process has been scaled-up to over tonne scale and is used by a number of companies.[50] Both enantiomers are commercially available.

Applications of Chiral Sulfinamides in Synthesis

Classic Mode of Reactivity

The general method for the preparation (**Scheme 30**) of chiral amines from *tert*-butanesulfinamide (**79**) involves its condensation onto an aldehyde or ketone **87** in the presence of a desiccant to give the aldimine or ketimine **88** respectively. Nucleophilic addition across the sulfinimine affords the sulfinimide **89** in diastereomeric excess which can then be hydrolysed under acidic conditions to afford the desired amine **90**.

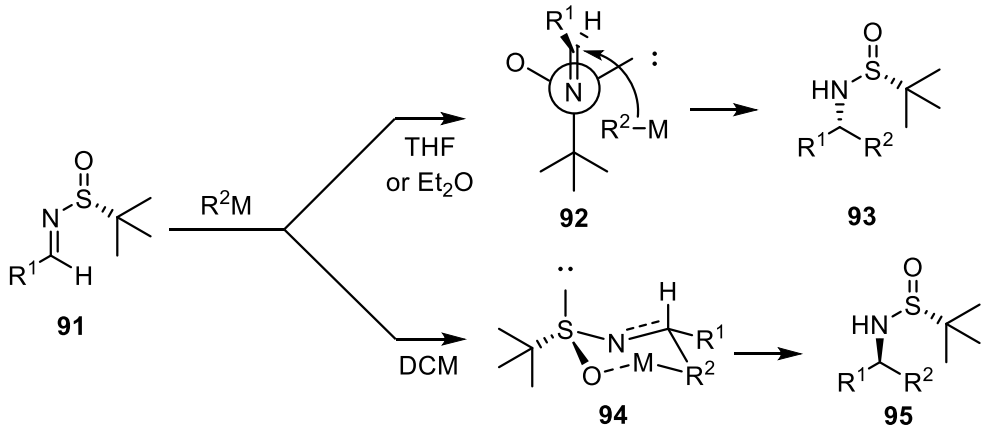


Scheme 30: General scheme for synthesis of chiral amines from *tert*-butanesulfinamide

Chiral sulfinamides have been used as chiral ammonia equivalents in the enantioselectivity synthesis of α-amino acids, β-amino acids, δ-amino acids, amino alcohols, 1-2-amino sulfides, aziridines and β-hydroxy-α-methylene esters, piperidines and pyrrolidines.[50]

Different Transition States

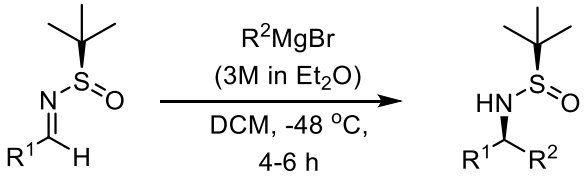
The stereochemical outcome is dependent on the solvent employed (**Scheme 31**).[51] Coordinating solvents such as THF and diethyl ether interrupt metal chelation to the substrate and give rise to an open transition state (**92**) whereas DCM allows formation of a 6-membered transition state (**94**) from coordination of the metal from the organometallic reagent and the oxygen from the sulfinimine. This allows for tuning of the stereochemical outcome of the reaction based on the solvent. Ethereal solvents provide access to products **93** and DCM provides access to products **95** when beginning from (*R*)-*tert*-butyl sulfinimines **91**.



Scheme 31: Open transition state (**92**) and closed transition state (**94**) when adding organometallic reagents to aldimines

Scope of Organometallic Reagents

Ellman and co-workers published extensively on the addition of organolithium and Grignard reagents into *N*-*tert*-butyl sulfinyl aldimines and ketimines.[52] Branched organometallic reagents, eg. ^{t}BuMgBr, ^{t}BuLi and ^{i}PrMgBr, usually give poor yields in addition reactions to imines.[53] This is also the case when adding to sulfinimines. Of notable absence in this work was the use of *tert*-butyllithium or *tert*-butylmagnesium halides and the lowest yield for this work was that of the addition *iso*-propylmagnesium bromide into *N*-sulfinyl aldimine **91** to give **96** (R^1 = Ph, R^2 = ^{i}Pr) in 29%. This highlights the difficulties with branched organometallic reagents in these reactions. The addition of *iso*-propylmagnesium bromide (R^2 = ^{i}Pr) into *N*-sulfinyl alkyl aldimines (R^1 = Et) did proceed smoothly with yields typically above 90% and linear alkyl organometallic reagents and aromatic organometallic reagents generally work well in this methodology (**Table 1**).



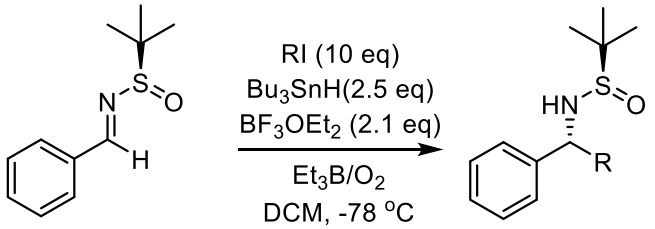
91 **96**

R^1	R^2	Yield	dr
Ph	Me	96	97:3
Ph	Et	98	92:8
Ph	^{i}Pr	29	97:3
Ph	vinyl	79	94:6
Et	Me	96	93:7
Et	^{i}Pr	97	98:2
^{i}Pr	Me	97	98:2
^{i}Pr	Ph	98	89:11

Table 1: Select examples of Grignard addition into *N*-*tert*-butyl sulfinyl imines

Radical Additions to Sulfinimines

The incompatibility of branched organometallic reagents, especially *tert*-butyllithium and *tert*-butyl Grignard reagents in addition reactions to tert-butyl sulfinyl imines **91** has been somewhat overcome by the application of radical additions by Alonso an co-workers (**Table 2**).[54] Notably, this reaction progresses through the open transition state **92** previously discussed, giving the opposite stereochemical outcome to organometallic 1,2-additions in DCM. Beginning from *N*-sulfinyl aldimine **97**, this protocol furnishes the desired sulfinamides **98** in good to excellent yield and all reactions proceeded with excellent diastereoslectivity. Although this work achieved the addition of branched and linear alkyl groups to *N-tert* butyl sulfinyl aldimines, the method is extremely inefficient using 10 equivalents of alkyl halide and the extremely neurotoxic tributyl tin hydride in 2.5 equivalents. The by-products from tin reagents are extremely hard to remove and therefor makes methodologies containing these tin chain carriers inappropriate for the synthesis of pharmaceuticals.[55]



97 **98**

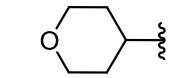
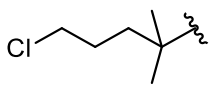
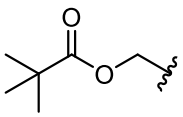
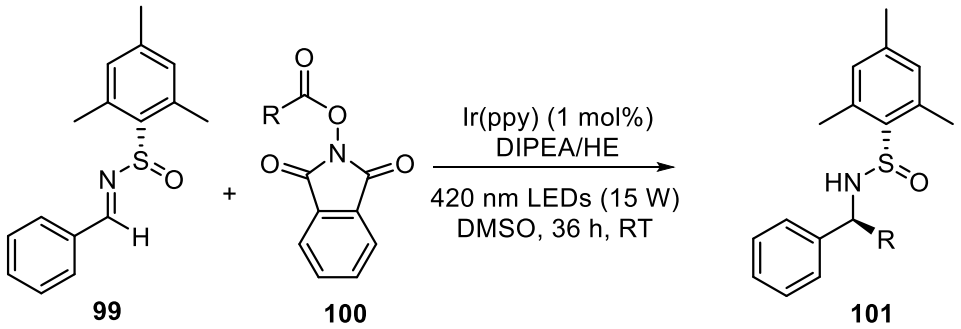
R	Yield (%)	dr
Et	60	>98:2
Iso-propyl	91	>98:2
Cyclohexyl	90	>98:2
Tert-butyl	75	>98:2
	65	>98:2
	50	>98:2
	32	>98:2

Table 2: Alkyl halides used as radical precursors in addition reaction to *N-tert*-butyl sulfinyl imines

Alemán and co-workers extended radical additions to sulfinimines **99** to radicals generated by photoredox catalysis from *N*-hydroxy phthalimide esters **100** (**Table 3**).[56] Photoexcitation of the Iridium catalyst allows donation of an electron from the catalyst to the *N*-hydroxy phthalimide ester substrates. This results in fragmentation and the release of the R-group radical which then undergoes stereoselective addition to the sulfinimine. Hydrogen extraction from the Hanztsch ester affords the sulfinimide products **101**. Four examples were reported all of which gave excellent drs above 98:2 however yields were more modest with *tert*-butyl and *n*-butyl giving yields of 36% and 41% respectively. The aryl group could also be altered to include substituted phenyl groups and 2-pyridine and 2-thiophene.



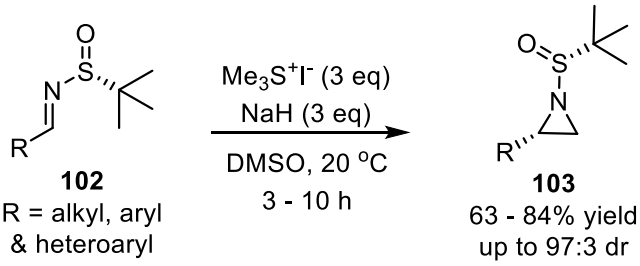
99 **100** **101**

R	Yield (%)	dr
^{i}Pr	79	>98:2
Cyclohexyl	74	>98:2
^{t}Bu	36	>98:2
^{n}Bu	41	>98:2

Table 3: Photoredox mediated radical addition to sulfinimines

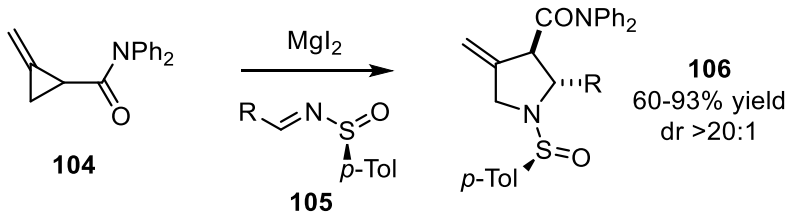
Sulfinamides in Asymmetric Heterocycle Synthesis

The *N*-sulfinyl chiral auxiliaries have also been applied to the synthesis of heterocycles. The synthesis of chiral aziridines from chiral sulfinimines is possible by a variety of routes[46] but the most broadly applicable synthesis is reaction with ylides (**Scheme 32**). Garcia Ruano and co-workers first reported the reaction[57] and the substrate scope was later greatly expanded by the Stockman Group.[58] This method is applicable to a wide variety of *N*-sulfinyl aldimines **102** including, alkyl, aryl and heteroaryls to give the corresponding aziridines **103**. Khiar and co-workers indicated it is possible to switch the diastereoselectivity by switching the (dimethylsulfaniumyl)methanide for (dimethyloxosulfaniumyl)methanide although surprisingly, no yields were given for the reaction.[59]



Scheme 32: Corey-Chaykovsky reaction for the asymmetric aziridine synthesis

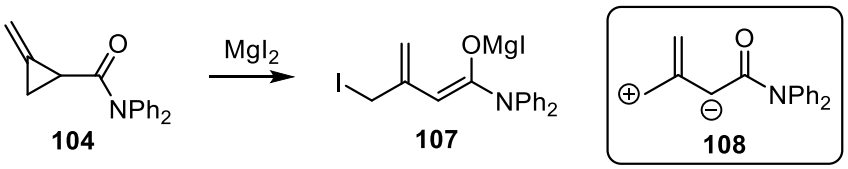
N-Sulfinyl auxiliaries have also been applied to the asymmetric synthesis of pyrrolidines although not through the previously mentioned (3+2) cycloadditions. Lautens and co-workers reported the formal (3+2) cycloaddition of a *N*-*para*-tolyl sulfinimine **105** with an allyl precursor **104** (**Scheme 33**).[60]



Scheme 33: Sulfinamimine performing a formal (3+2) cycloaddition to give pyrroldines

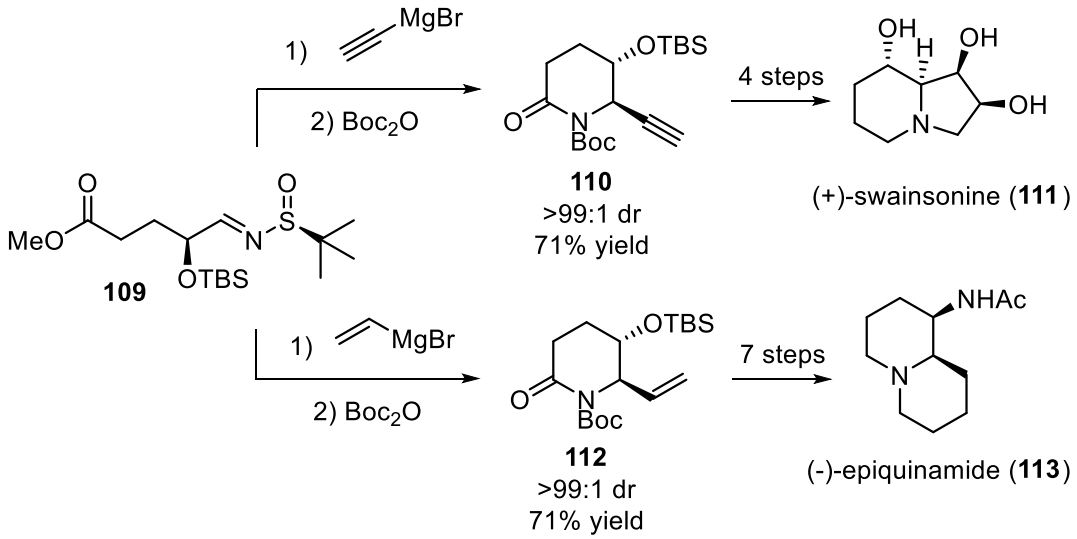
Pyrrolidines **106** were synthesised in excellent yields and with excellent diastereoselectvities when allyl and aromatic imines were used. Unfortunately, alkyl imines were unsuccessful reactions partners

for this methodology. The reaction progresses first through intermediate **107** which is generated *in-situ* and acts as a trimethylmethylene **108** equivalent (**Scheme 34**). This intermediate undergoes and enolate 1,2-addition on the imine and the resulting nitrogen anion undergoes a nucleophilic substitution on the C-I bond closing the ring.



Scheme 34: allyl precursor acting as TMM equivalent

Gautun and co-workers applied chiral *N*-sulfinyl α-imino esters in the Diels-alder reaction with dienes[61] which produced piperidines with yields up to 76% and diastereomeric ratios up to 99:1. This demonstrates the ability of chiral sulfinamides to control stereochemistry in concerted and step-wise cycloadditions. Further applications of the *N*-sulfinyl auxiliary in the synthesis of piperidines via a step-wise ring formation, similar to that of Lautens work on pyrrolidine synthesis, is the divergent synthesis to natural products (+)-swainsonine (**111**) and (-)-epiquinamide (**113**) (**Scheme 35**).[62] From the α-siloxy-*N*-sulfinyl aldimine **109**, ethynylmagnesium bromide adds selectively followed by ring closing to give piperidine **110** in excellent diastereomeric ratio. 4 further steps afforded (+)-swainsonine (**111**) in 16.8% overall yield. Similarly, addition of vinylmagnesium bromide and subsequent ring closing affords piperidine **112** with the same yield. Further modifications provided access to (-)-epiquinamide (**113**).



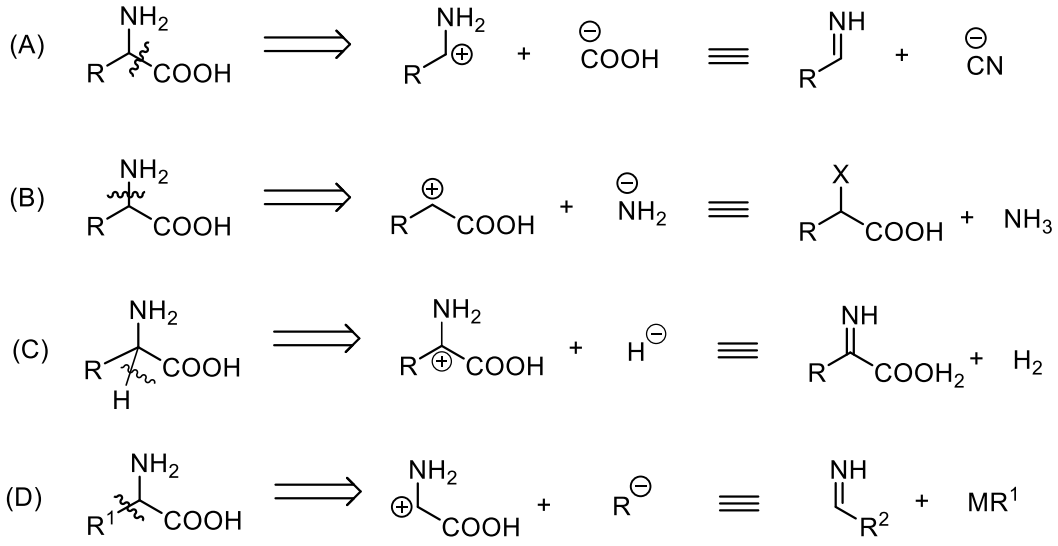
Scheme 35: Synthesis of (+)-swainsonine and (-)-epiquinamide from a common *N*-sulfinyl aldimine

α-Amino Acid Synthesis

Introduction to α-Amino Acid Synthesis

α-Amino acids are some of the most important building blocks for the chemical and biological sciences. Although there are only 20 natural α-amino acids found in humans, the number of α-amino acids found in the whole animal kingdom, plants and microorganisms runs into hundreds.[63] This does not include the synthetic α-amino acids that have been synthesised and applied by mankind in areas such as pharmaceuticals.

When installing the stereocentre in α-amino acid synthesis, the approaches can be grouped into categories with respect to the disconnection being made according to retrosynthesis. There are four categories when using this logic (**Scheme 36**). Disconnection A involves the installation of the carboxylic acid group in the stereocentre forming reaction. The synthons produced in this disconnection equate to a cyanide ion and an imine, commonly known as the Strecker reaction.



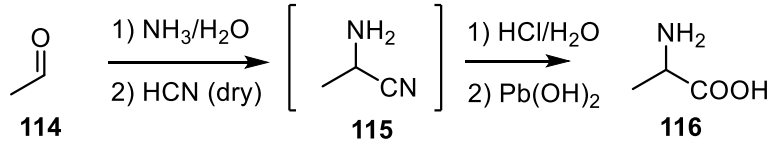
Scheme 36: The four disconnections available when categorising amino acid synthesis through retrosynthesis

Disconnection B installs the nitrogen in the stereocentre forming reaction. The synthons created form this disconnection equate to ammonia or an ammonia equivalent and an α-halo carboxylic acid or α-

halo carboxylic acid equivalent. Disconnection C installs the hydrogen in the stereocentre forming step. This equates to a hydrogen and an imine derivative. Disconnection D installs the R-group in the stereocentre forming reaction. These synthons equate to an organometallic reagent adding into an imine but can, less commonly, be viewed as one-electron variant ie. the R-group radical adding into an imine. We will now briefly review these four approaches.

Disconnection A: Introduction to the Strecker Synthesis

The first synthesis of an α-amino acid was reported by Adolf Strecker in 1850.[64,65] This discovery was serendipitous, as Strecker had been attempting to synthesise lactic acid but instead obtained alanine (**116**) (**Scheme 37**). Acetaldehyde (**114**) is first condensed with ammonia to form the imine followed by addition of the nitrile to give an α-amino nitrile **115**. Acid hydrolysis of the nitrile group yields the amino acid.



114 **115** **116**

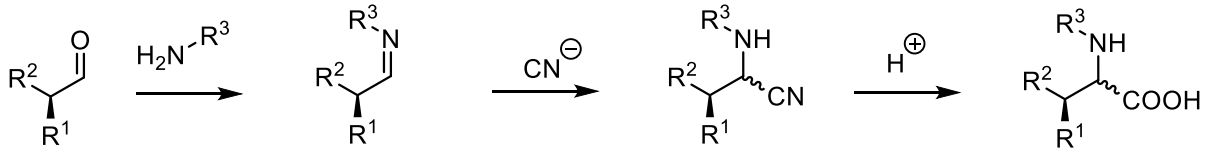
Scheme 37: The first synthesis of an amino acid

This method was used in 1864 with only slight variations by Hermann Strecker, Adolf Strecker's brother, for the synthesis of leucine.[66] Jay and Curtius applied the method to the synthesis of glycine[67] and the Strecker synthesis was then used by Lipp to synthesise valine[68], Ehrlich to synthesise isoleucine[69] and Tiemann to make phenylalanine.[70] The main variation in these later examples being the use of the less toxic alkali earth metal cyanide salts. These early examples were all performed with no control of stereochemistry and therefor produced racemic mixtures.

Since these seminal contributions, the Strecker reaction has become widely studied with vast numbers of asymmetric examples being reported; from natural amino acids, non-natural amino acids and biologically active molecules which have been extensively reviewed.[71] We would like to introduce the main methods of asymmetric induction in Strecker Reaction and give examples of each method.

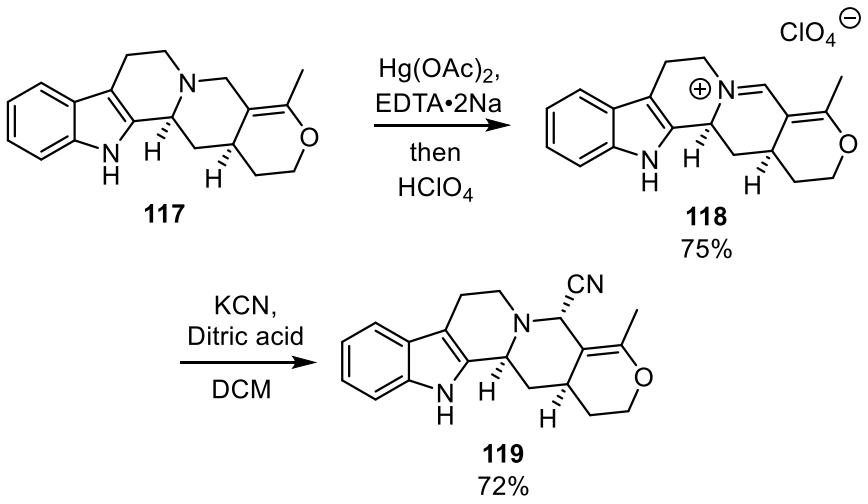
Diastereoselective Strecker from Chiral Non-racemic Imines

The general method of asymmetric induction by the diastereoselective Strecker from chiral non-racemic imines is outlined in **Scheme 38**. In this method, aldehydes or ketones possessing a chiral centre, usually in the α-position are condensed with an amine to form the imine. The imine is then attacked by a cyanide source and the chiral centre/s in the molecule of the imine control the face of attack resulting in diastereoselective synthesis of the α-amino nitrile. The nitrile is then hydrolysed to give the α-amino acid.



Scheme 38: General method for the diastereoselective Strecker Synthesis

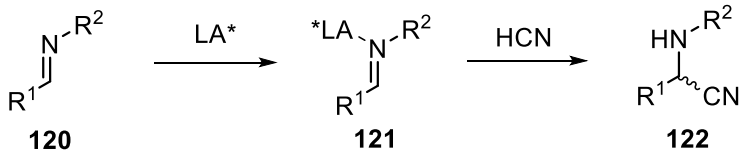
Iminium ions also work well for this methodology. Husson and co-workers used the diastereoselective Strecker to install a new chiral centre in the synthesis of the skeleton of deoxypumiloside (**Scheme 39**).[72] Amine **117** was oxidised to the perchlorate iminium salt **118**. The adjacent stereocentres induce curvature in the molecule making reverse side attack preferential, affording the α-amino nitrile **119**.



Scheme 39: Synthesis of intermediate towards skeleton of deoxypumiloside *via* Strecker reaction

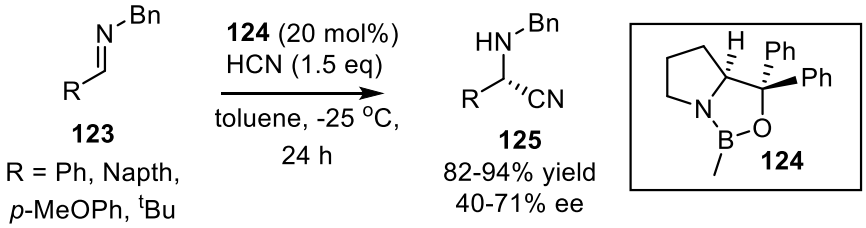
Catalytic Strecker Reactions

The general mode of reactivity for the catalytic Strecker is coordination of a Lewis acid to the imine substrate **120** (**Scheme 40**). Examples of organic Lewis acids and metal Lewis acids have been reported. In the case of the organic Lewis acids, the organic molecule will be chiral. In the case of metal catalysed examples, a chiral ligand will be employed. Complex **121** is therefore chiral and one face of the imine is attacked preferentially by the cyanide ion, resulting in enantioselective synthesis of α-amino nitriles **122**.



Scheme 40: General method of catalytic induction in the Strecker reaction

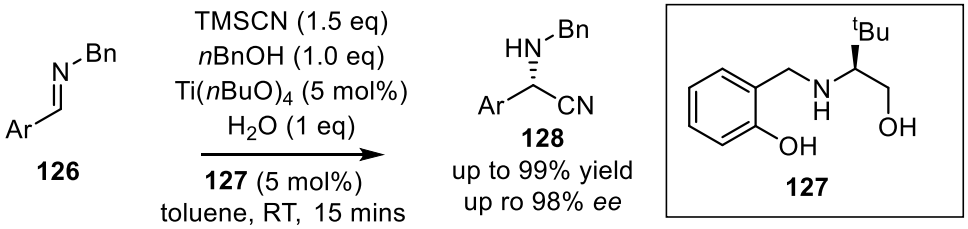
Chiral oxazaborolidines (**124**) which were developed by Corey for the asymmetric reduction of ketones and asymmetric Diels-Alder reactions[73] have been applied to the asymmetric Strecker reaction by Berkessel and co-workers (**Scheme 41**).[74] Benzyl imines (**123**) were reacted with oxazaborolidine **124** and hydrogen cyanide at -25 °C. The reaction gave the α-amino nitriles **125** in good yield but moderate enantioselectivity. Moreover, the substrate scope for the reaction was extremely limited but exemplifies organocatalysis applied to the asymmetric Strecker reaction.



Scheme 41: Oxazaborolidines as enantionselective catalysts in the Strecker Reaction

Metal catalysed examples are vast in number.[71] One of the "greener" examples was reported by Chai and co-workers in 2010 (**Scheme 42**)[75] and was later performed in flow through a solid supported

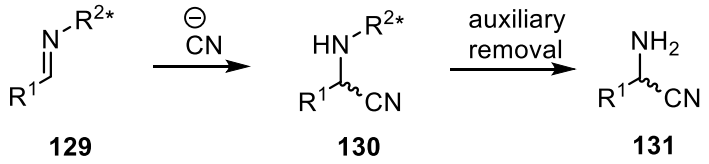
catalyst.[76] The reaction benefits from the use of earth-abundant titanium metal catalyst, readily available ligand **127** and easily progressing at room temperature with a reaction duration of 15 minutes. Benzyl protected imines (**126**) were converted to the corresponding α-amino nitriles **128** in excellent yields and enantioselectivities, however, only aryl derivatives were reported.



Scheme 42: Titanium catalysed asymmetric Strecker reaction

Chiral Auxiliary Controlled Asymmetric Strecker Reactions

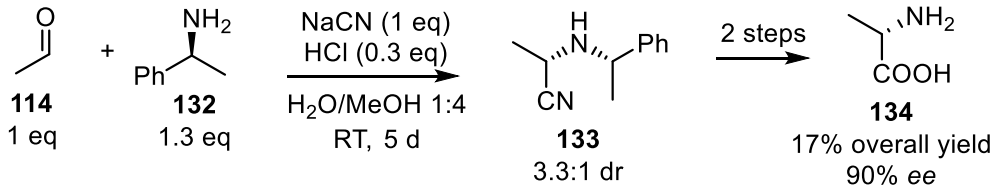
The general method for chiral auxiliary controlled asymmetric Strecker reactions (**Scheme 43**) begins with the synthesis of an imine (**129**) bearing a chiral auxiliary on the nitrogen atom. A cyanide ion source then adds selectively to one face of the imine to form α-amino nitriles **130** and then in a separate or telescoped step, the auxiliary is removed to yield the α-amino nitrile **131**. This extra auxiliary removal step can be viewed as a drawback in this approach.



Scheme 43: General Scheme for auxiliary controlled asymmetric Strecker

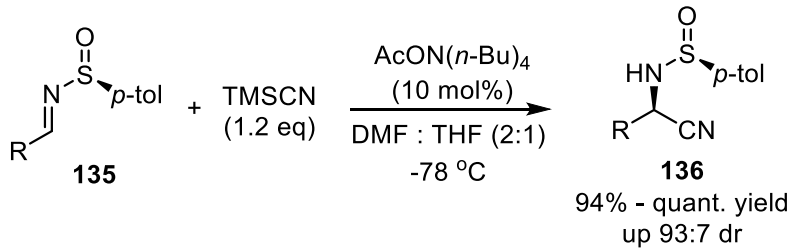
The first asymmetric Strecker reaction reported employed a chiral auxiliary (**Scheme 44**) .[77] Harada and co-workers used (*S*)-phenylethylamine (PEA) (**132**) as the source of chirality which underwent *in-situ* condensation with acetaldehyde (**114**) and was subsequently attacked by the cyanide source, sodium cyanide, to give α-amino nitrile **133** with a diastereomeric ratio of 3.3:1. The nitrile group was hydrolysed to the carboxylic acid and the protecting group was removed by standard hydrogenation

conditions to afford (*S*)-alanine (**134**) in low 17% overall yield but in good enantiomeric excess of 90%. PEA has also been used in various examples since this first report.



Scheme 44: The first asymmetric Strecker reaction

Mukaiyama and co-workers reported one of the many examples of *N-para*-tolyl sulfininimines **135** in chiral auxiliary controlled Strecker reactions (**Scheme 45**).[78] Trimethylsilyl cyanide, as in many of the asymmetric Strecker reactions involving *N*-sulfinyl auxiliaries, acts as the cyanide ion source with 10 mol% of tetra-*N*-butylammonium acetate. The α-amino nitrile product **136** is then hydrolysed to give the corresponding amino acid.



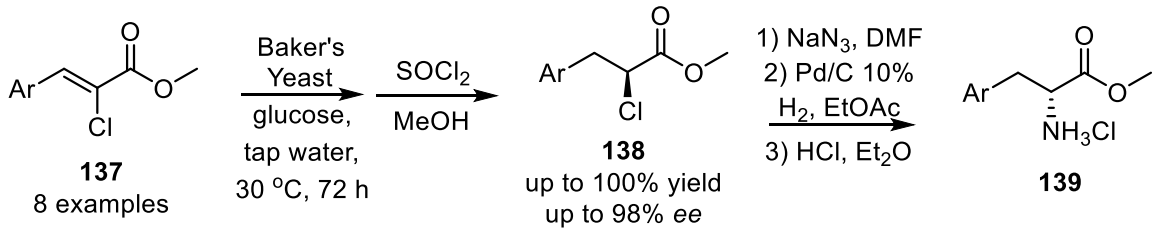
Scheme 45: Chiral sulfinamides as auxiliaries in the asymmetric Strecker reaction

N-Tert-butyl sulfinyl imines have also been employed as the chiral auxiliary in the asymmetric Strecker reaction. Lu and co-workers used this approach to synthesis of α-trifluoromethylated α-amino acids.[79]

Disconnection B: α-Amination by displacement of α-halides

α-Amination is perhaps the least employed method for α-amino acid synthesis. The stereocentre is usually in place by a previous transformation and the amination step simply inverts the stereocentre to produce the desired α-amino acid derivative. We will therefor include the method used to introduce the stereocentre in our discussion.

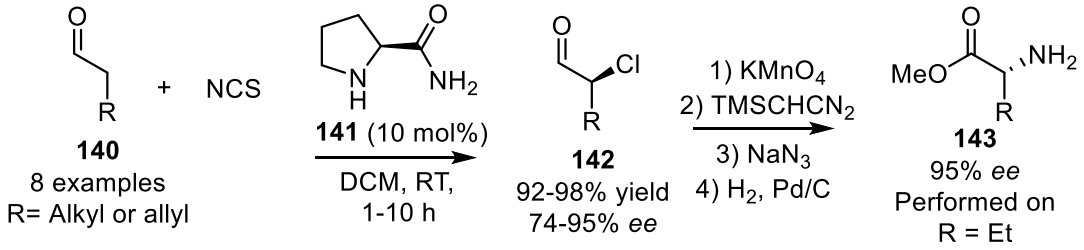
Parmeggiani and co-workers achieved the synthesis of phenylalanine derivatives (**139**) *via* an asymmetric reduction of α-halo-β-arylacrylates (**137**) to give chiral α-halo-esters (**138**) (**Scheme 46**). These esters were treated with sodium azide in *N,N*-dimethyl formamide which inverts the stereocentre followed by hydrogenation to give the desired amino acid derivatives. The asymmetric reduction was achieved using Baker's yeast and these conditions also transformed the ester into the carboxylic acid which had to be reinstalled using thionyl chloride and methanol for the following steps to be successful.



Scheme 46: Synthesis of phenylalanine derivatives by asymmetric hydrogenation and α-amination

Jørgensen and co-workers reported the asymmetric chlorination of aldehydes employing chiral secondary amine catalysts.[80] The α-chloro-aldehydes were then converted to the corresponding amino acids (**Scheme 47**). Secondary enamine catalysis is a heavily studied area[81] and the synthesis of α-amino acids via this approach is just one of many transformations which can be resultant from this approach. The mechanism of these reactions begins with the formation of an enamine between the aldehyde **140** and chiral secondary amine catalyst **141**. This intermediate then performs a facial selective chlorination providing access to an α-chloro imine which undergoes hydrolysis to provide the α-chloro aldehydes **142**. Only one substrate was then subjected to a four-step sequence to provide

the methyl ester amino acid derivative **143**. Oxidation to the carboxylic acid by potassium permanganate followed by methylation by the common methylating agent trimethylsilyldiazomethane gave the methyl ester. The chlorine group was then displaced by sodium azide, inverting the stereochemistry, and the azide was converted to the amine by hydrogenation. Only alkyl and allyl groups were reported which compliments the work previously discussed (**Scheme 46**) which solely reported aryl groups.



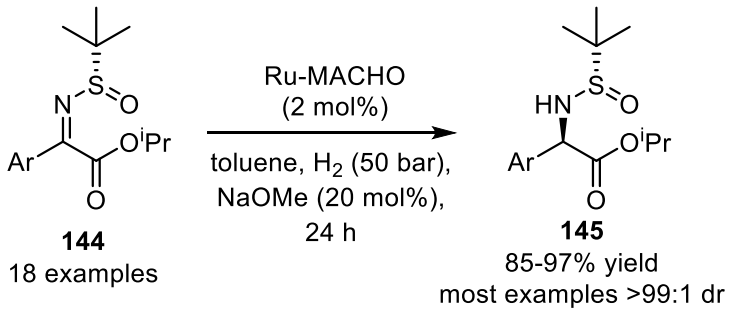
Scheme 47: Asymmetric synthesis of amino acids via α-chlorination then amination

Disconnection C: Reduction of Imines

The asymmetric reduction of imines to amino acid derivatives is achieved by either hydrogenation (ligand or auxiliary controlled) or the use of a reducing agent (auxiliary controlled).

Hydrogenation in the Asymmetric Synthesis of Amino Acids

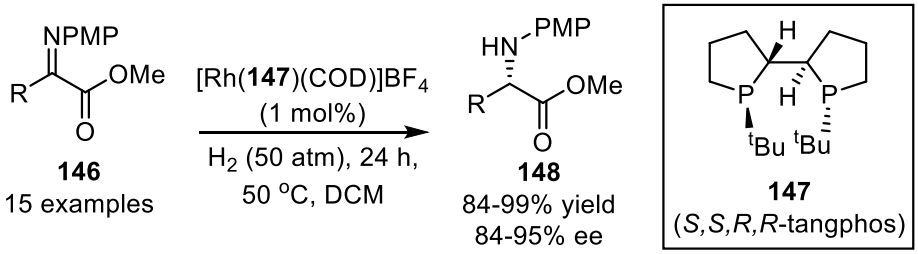
Tang and co-workers reported the auxiliary controlled hydrogenation of ketimines **144** for the synthesis of amino acid derivatives **145** (**Scheme 48**).[82] The *N*-*tert*-butyl sulfinyl auxiliary performed well with most examples giving diastereomeric ratios above 99:1. Treating the sulfinamide products **145** with methanolic hydrochloric acid will remove the auxiliary to give the corresponding amino acid derivatives. The authors found that reducing the pressure from 50 bar to 30 bar resulted in lower yields and diastereoselectivity demonstrating that high pressures are necessary for the desired reactivity.



Scheme 48: Auxiliary controlled hydrogenation for the synthesis of amino acid derivatives

Ligand controlled asymmetric hydrogenation of imines towards amino acids derivatives **148** is also possible (**Scheme 49**). Zhang and co-workers demonstrated that *para*-methoxy phenyl (PMP) protected imines **146** undergo asymmetric hydrogenation with a rhodium and ligand **147** to give the corresponding amines in excellent yields and excellent enantioselectivities. However, the use of high

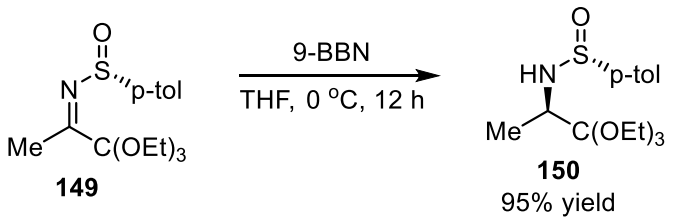
pressures of hydrogen were also necessary for the success of the protocol. The only non-aryl substituent to successfully undergo the transformation was cyclohexyl.



Scheme 49: Ligand controlled hydrogenation to amino acid derivatives

Reducing Agents in the Asymmetric Synthesis of Amino Acids

Methods which use metal or metalloid hydride sources are less developed than the hydrogenation counterparts. Hua and co-workers also used *N*-sulfinyl ketimines for the synthesis of amino acid derivatives **150** (**Scheme 50**).[83] The reducing agent in this instance was 9-BBN, a hydride reducing agent, avoiding the use of high pressure hydrogen, however, the carboxylic acid was masked as an ortho ester and the only substrate reported was the alanine precursor **149**.

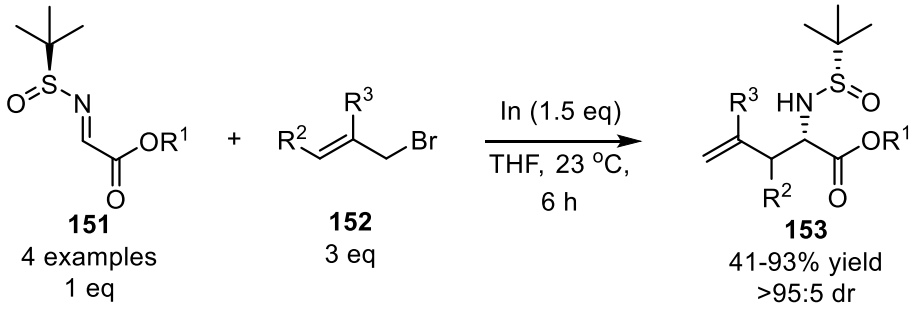


Scheme 50: Reduction of *N*-sulfinyl imines with 9-Borabicyclo[3.3.1]nonane (9-BBN)

Disconnection D: Installing R-Groups

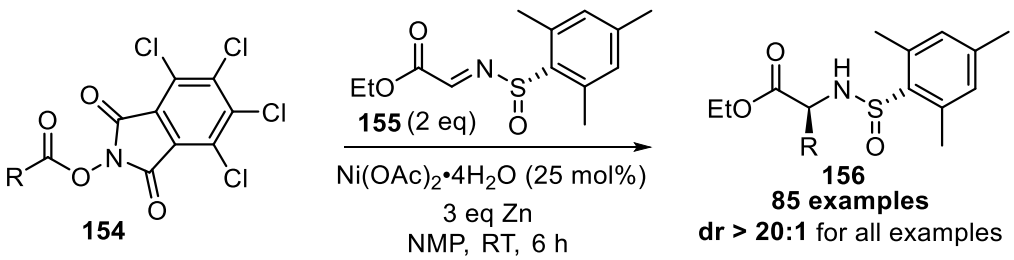
Radical 1,2-Additions

Yus and co-workers described the indium mediated radical 1,2-addition of allyl bromides **152** to α-iminoesters **151** (**Scheme 51**).[84] The reaction provided access to the unnatural allyl amino acid derivatives **153** which would be converted into the amino acids by treating the products with acid.



Scheme 51: Indium mediated allylation of α-iminoesters

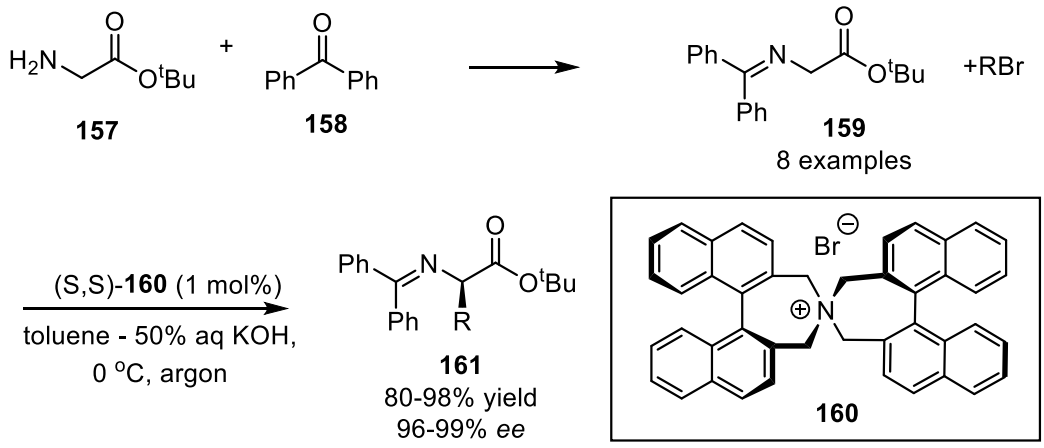
Baran and co-workers reported the application of redox active esters **154** for the synthesis of α-amino acid derivatives **156** (**Scheme 52**).[85] The redox active esters can be synthesised from the corresponding carboxylic acids making them easily prepared. Zinc acts as a one-electron reductant, releasing the R-groups as radicals which undergo addition into the *N*-mesityl sulfinyl imine **155**. Acid hydrolysis of sulfinamides **156** produces the corresponding α-amino acid. The reaction showed excellent compatibility with primary, secondary and tertiary radicals and the diastereomeric ratios were greater than 20:1 for all examples. The examples described included some extremely "exotic" unnatural amino acid derivatives.



Scheme 52: Radical addition to *N*-sulfinyl aldimines for the synthesis of amino acids

Alkylation of Glycine Derivatives

Phase transfer catalysis for the synthesis of amino acids is an extensive area, many examples of this mode of reactivity exist and they have been extensively reviewed.[63] The method is exemplified by Maruoka and co-workers use of chiral ammonium bromide catalyst **160** for the alkylation of glycine derivatives **161** (**Scheme 53**).[86] Glycine (**157**) and benzophenone (**158**) are first condensed to form imine **159**. This lowers the pKa of the α-protons, allowing them to be removed by medium strength bases, in this case, potassium hydroxide, which forms an enolate. These ionic species then have a higher affinity for the ionic catalyst which places the substrate in a chiral environment, inducing enantioselectivity when the enolate reacts with the alkyl bromide. This example allowed access to propargylic, alkyl, allyl and benzyl derivatives in high enantioselectivity and yield.

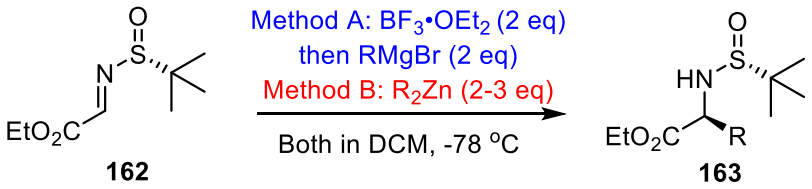


Scheme 53: Phase transfer catalysis for enantioselective alkylation of glycine

Nucleophilic 1,2-additions

David and co-workers reported the first successful protocol of Grignard and dialkyl zinc reagents additions to glyoxylate sulfinimines **162** (**Table 4**) to give α-*N*-sulfinyl amino esters **163** which undergo acid hydrolysis to the corresponding amino acids.[87] Glyoxylate sulfinimines **162** undergo significant reaction at the sulfur instead of the desired imine carbon resulting in low yields when performed in the absence of $BF_3 \bullet Et_2O$. Davis found that $BF_3 \bullet Et_2O$ improved yields and also improved diastereoselectivity. The ethyl and methyl Grignard reagents were shown to give significant reduction

of the imine bond, resulting in low yields. To overcome this, a second method was developed which employed dialkylzinc reagents for installing these substituents.

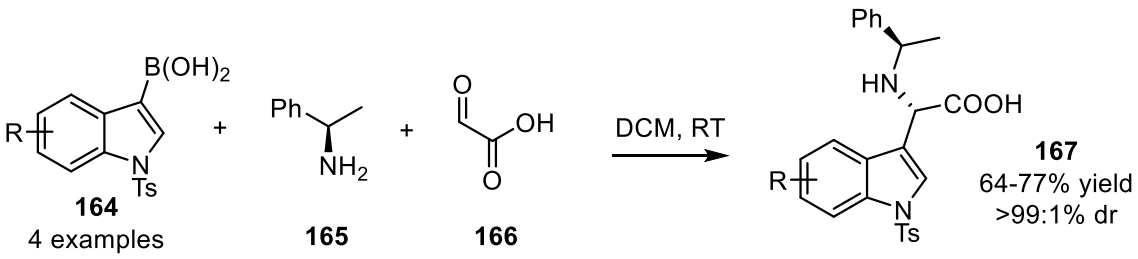


162 **163**

R	Method	Yield (%)	dr
Bn	A	70	94:6
Ph	A	70	84:16
Et	B	88	>99:1
Me	B	43	92:8

Table 4: First successful organometallic additions to glyoxylate sulfinimines towards the synthesis of amino acids

Jiang and co-workers described the auxiliary controlled stereoselective synthesis of indole substituted amino acids in excellent diastereomeric ratios employing a three-component Petasis reaction (**Scheme 54**).[88] The auxiliary used was (*R*)-α-methylbenzylamine (**165**) which condenses with glyoxylic acid (**166**) to form a chiral imine. The indolyl boronic acids **164** then undergo 1,2-addition to form the amino acid derivatives **167** in good yields and excellent diastereomeric ratios.

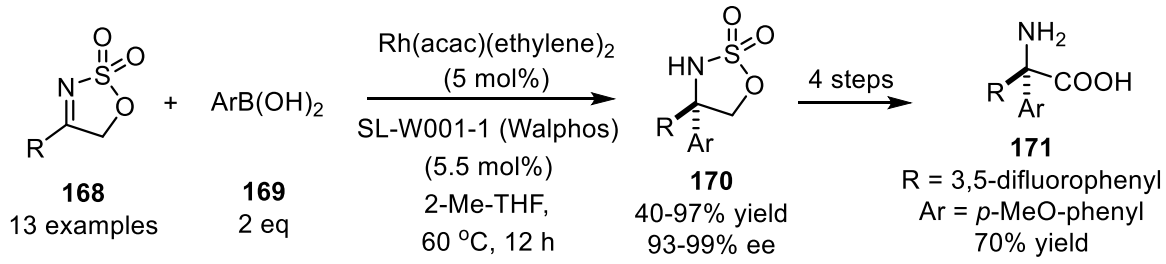


164 4 examples **165** **166**

Scheme 54: Petasis reaction for stereoselective synthesis of 3-indole substituted amino acids

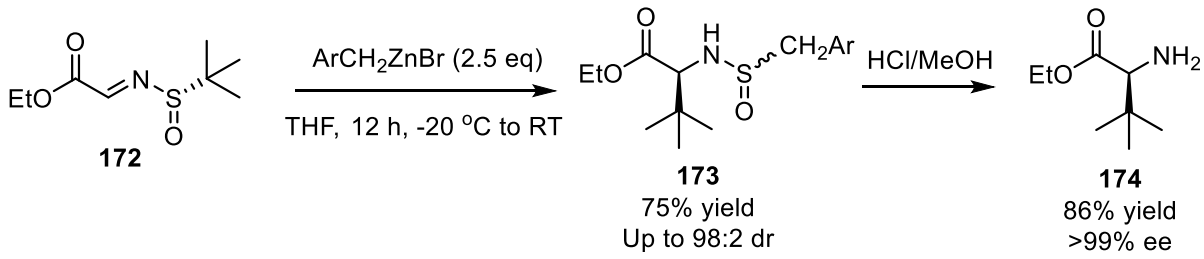
It is important to note that the same type of reactivity was examined by Naskar and co-workers with chiral sulfinamides as the nitrogen component but these gave 1:1 ratios of diastereomers.[89]

Merck published a chiral ligand controlled synthesis of unnatural tertiary amino acid derivatives from the addition of aryl boronic acids **169** to cyclic ketimines **168** (**Scheme 55**).[90] The protocol uses the di-phosphine ligand Walphos and a rhodium(I) salt as the catalytic system which provides the desired products in excellent enantioselectivities. Yields were high when the R-group in the starting material was aryl but dropped slightly when the R-group was alkyl (as low as 40% for R = Et). The protocol suffers from the requirement of 4 steps from the sulfamate products **170** to remove the sulfone group and provide access to the amino acids **171**.



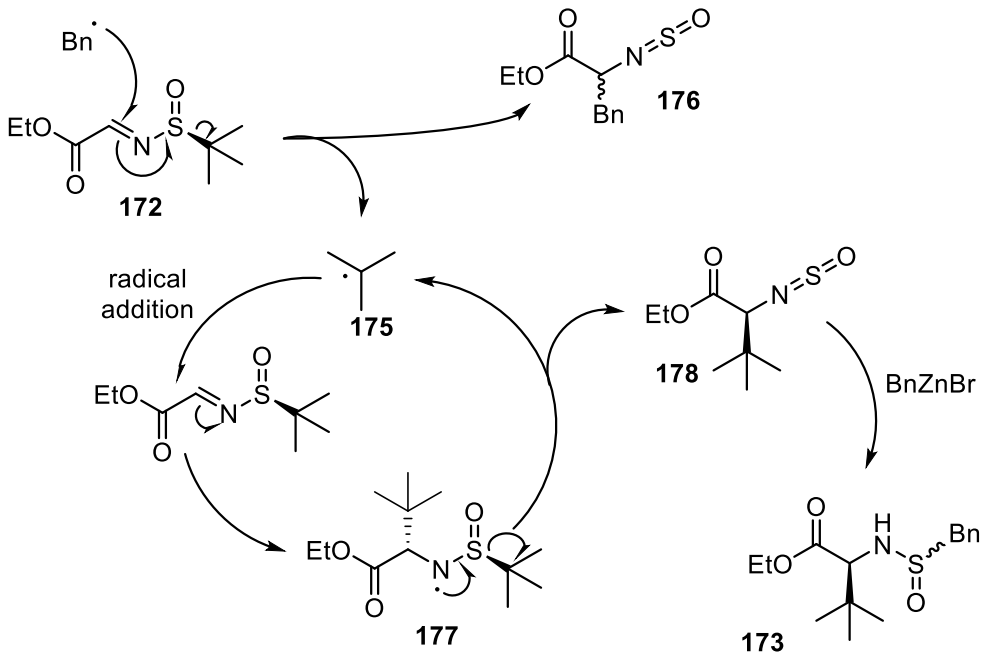
Scheme 55: Rh(I) catalysed 1,2-addition of aryl boronic acids to cyclic sulfamates

Wei and co-workers described a migration and addition reaction of glyoxylate *tert*-butyl sulfinimines **172** (**Scheme 56**).[91] The *tert*-butyl of the sulfinyl group migrates onto the carbon of the imine and the benzyl zinc bromide adds to the sulfur to give sulfinamide **173**. The creation of the chiral centre in the α-position of the ester was enantioselective and the reaction overall was diatereoselective with most organozinc reagents employed resulting in good drs for **173**. The sulfinyl group could be removed easily to give access to *tert*-Leucine ethyl ester (**174**) in good yield and excellent enantiomeric excess.



Scheme 56: Migration and addition during Grignard addition to glyoxylate sulfinimines

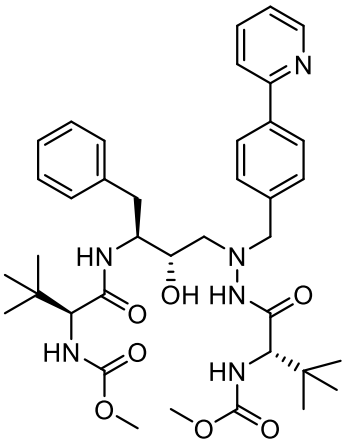
The proposed mechanism (**Scheme 57**) involves the creation of a benzyl radical from the benzyl zinc bromide. This adds to sulfinimine **172** to form side product **176** in small quantities and a *tert*-butyl radical **175**. This *tert*-butyl radical reacts with a second equivalent of **172** creating chain propagation. *Tert*-butyl radicals continue to be ejected and add to the sulfinimine **172** consuming all the starting material forming radical **177** which eliminates to sulfinyl amine **178**. **178** reacts with benzyl zinc bromide which forms the final product **173**.



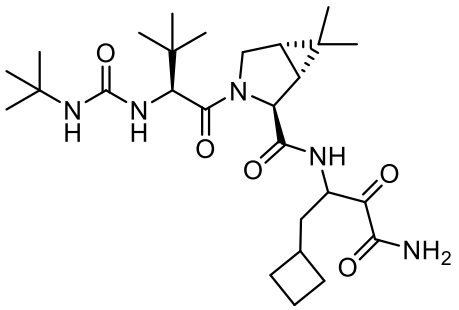
Scheme 57: Mechanism for the Migration-Addition of *tert*-butyl glyoxylate sulfinimines

***Tert*-leucine applications**

Tert-leucine is a valuable chemical required in a number of scientific areas. It is so important that it has entire reviews dedicated to its synthesis and applications.[92] One of the most important areas is the use of *tert*-leucine in oligomeric peptide pharmaceuticals such as Atazanavir, a treated for HIV/AIDS, and Boceprevir, a treatment for Hepatitus C. The most prevalent enantiomer of *tert*-leucine in peptide drugs is the (*S*)-enantiomer or L-*tert*-leucine. *Tert*-leucine's utility is derived from its large hydrophobic side-chain, instilling useful properties in drug molecules.[93,94]



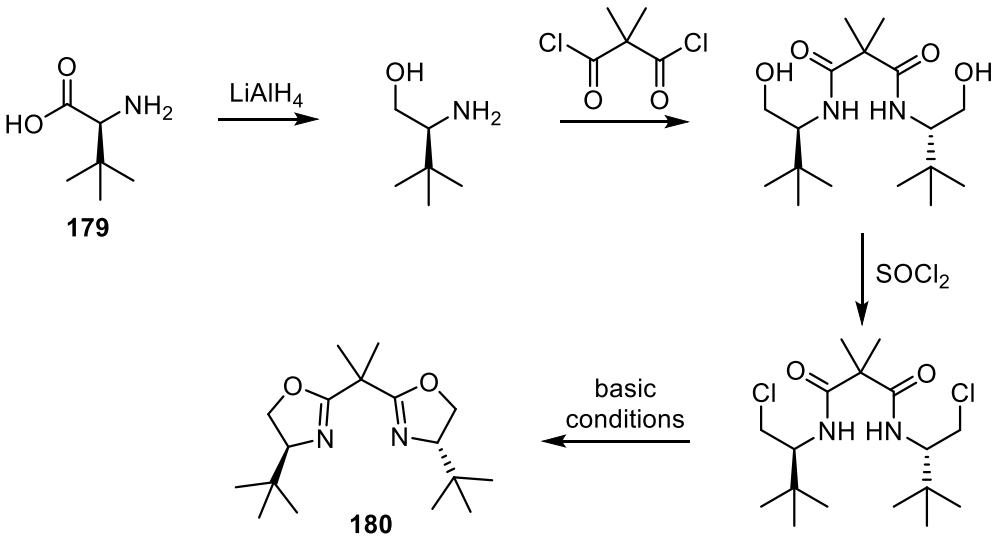
Atazanavir
(HIV/AIDS treatment)



Boceprevir
(Hepatitus C treatment)

Figure 8: Two anti-viral peptide pharmaceuticals containing (*S*)-tert-leucine

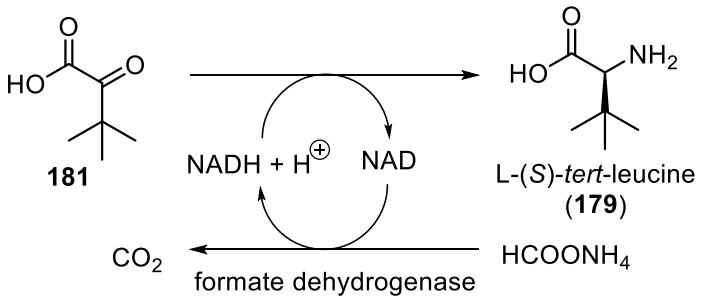
The same bulky and hydrophobic properties of tert-leucine have made is a valuable intermediate towards a number of chiral ligands. BOX ligands are a class of ligands of which the tert-butyl derivative is extremely useful and has been applied to a wide range of reactions including asymmetric Diels-Alder and asymmetric cyclopropanations.[95] The synthesis of (*R*,*R*)-2,2'-isopropylidenebis(4-tert-butyl-2-oxazoline) (**180**) can be achieved in a number of ways, and all of these begin with *tert*-leucine (**179**). One of these syntheses is outlined in **Scheme 58**.



Scheme 58: Synthesis of (*R,R*)-2,2'-isopropylidenebis(4-*tert*-butyl-2-oxazoline)

Synthesis of *tert*-leucine

L-(*S*)-*tert*-leucine (**179**) is manufactured from trimethylpyruvic acid (**181**) on an industrial scale by Evonik.[96] The process is enzymatic using leucine dehydrogenase isolated from *B. cereus* with formate dehydrogenase (FDH) from *Candida boidinii* for the regeneration of cofactor. The reaction gives conversion rates of 93% and enantiomeric excess of 99% but the process is expensive due to costs associated with enzyme isolation and co-factor addition.



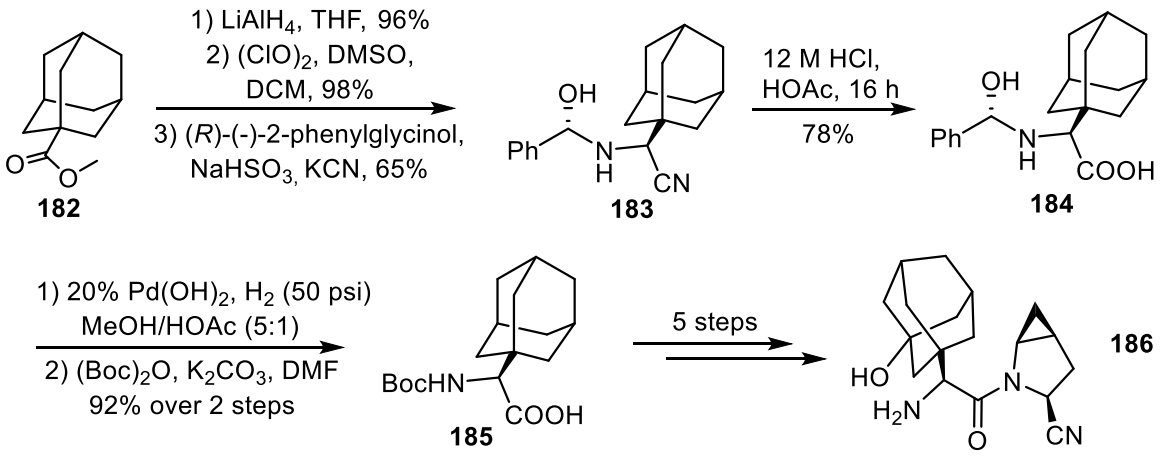
Scheme 59: Enzymatic synthesis of L-(*S*)-*tert*-leucine

An equivalent D-(*R*)-selective dehydrogenase is not known.[97] Evonik have an alternative process for D-(*R*)-tert-leucine which involves the use of a D-hydantoinase enzyme but this produces the N-carbamoyl product and the protecting group must be removed by treatment with HNO_2. Hummel and

co-workers described the synthesis of D-(*R*)-tert-leucine by performing an oxidative resolution on a racemic mixture of *tert*-leucine using the same leucine dehydrogenase as Evonik employ for the synthesis of L-(*S*)-*tert*-leucine and an NADH oxidase enzyme.

1-Adamantyl Glycine Applications

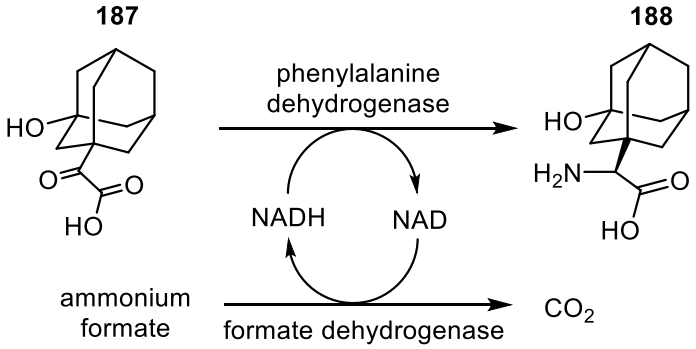
1-Adamnatyl glycine is also a bulky hydrophobic moiety which finds application in medicinal chemistry.[94] One example of a pharmaceutical is Saxagliptin (**186**) which contains the 1-adamantyl glycine (**185**) core and is an intermediate on the route to Saxagliptin. Bristol Myers Squibb published the first synthesis of Saxagliptin[98] which began with methyl-adamantane-1-carboxylate (**182**). This underwent a reduction to the alcohol, re-oxidation to the aldehyde and condensation with the expensive chiral auxiliary (*R*)-2-phenyl-glycinol and then Strecker conditions to give the α-amino nitrile **183** (**Scheme 60**). Acid hydrolysis gave α-amino acid **184** followed by removal of the auxiliary and Boc-protection to give Boc-protected 1-adamantyl glycine (**185**). 5 further transformations give Saxagliptin (**186**).



Scheme 60: First synthesis of Saxagliptin

This multi-step synthesis was later replaced by a much more concise method by Bristol Myers Squibb. From keto acid **187,** which had the 3-hydroxy group already in place, it was found that a phenylalanine dehydrogenase successfully synthesised the desired 3-hydroxy-1-adamantyl glycine (**188**) (**Scheme**

61). This new method removed the need for the expensive chiral auxiliary (*R*)-2-phenyl-glycinol and the highly toxic Strecker conditions as well as removing 4 steps overall.

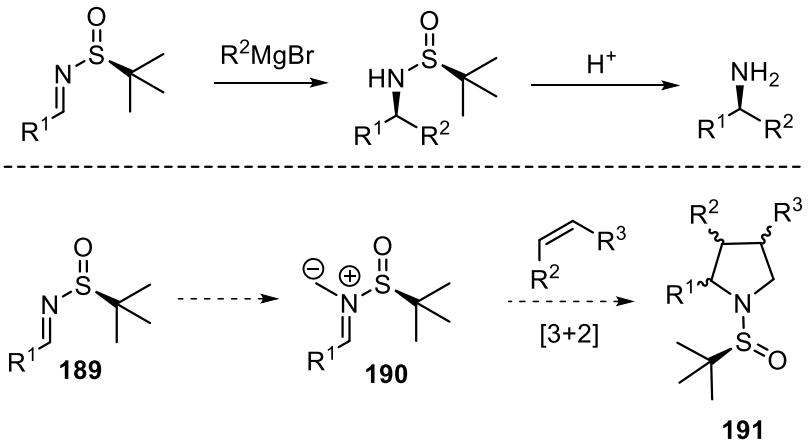


Scheme 61: Enzymatic route to 3-hydroxy-1-adamantyl glycine

II Aims and Objectives

The primary aim of the work described in this thesis was the asymmetric synthesis of 3,4-substitued pyrrolidines by a cheap broadly applicable protocol. The absence of precious metals and expensive complex ligands were viewed as important factors when proposing methodologies due to the cost, customising required when switching between substrates, as outlined in the introduction, and the contemporary focus on sustainability.

We took inspiration from the work on AMYs bearing chiral auxiliaries discussed previously (**page 30**) as well as the Stockman group's previous work on chiral sulfur functional groups, specifically chiral sulfinimines and sulfinamides. The classic mode (**Scheme 62**) of asymmetric induction to prepare chiral amines *via* Grignard addition to chiral sulfinimines is made possible by the rigidity of sulfinimines due to strongly opposing dipoles which we hoped to utilise. This led us to propose a novel reactive intermediate (**190**); an AMY bearing a chiral *N*-sulfinyl group, with the aim of reacting these *N*-sulfinyl AMYs with olefins in a (3+2) cycloaddition to afford pyrrolidines (**191**). Structurally, this intermediate is sulfinimine **189** with the addition of a $^{-}CH_2$ group but this intermediate is unlikely accessible from sulfinimine **189**. Alternatively, we aimed to investigate various methods for the generation of *N*-sulfinyl AMYs through well-established protocols for AMY generation.



Scheme 62: Top: Classic mode of chiral amine synthesis via sulfinimine. Bottom: Proposed sulfinimine structure adaptation to give chiral *N*-sulfinyl AMY

III Results and Discussion

1. Photoredox Attempts at *N*-Sulfinyl AMY Generation

Introduction to Photoredox Catalysis

The field of photoredox chemistry has recently expanded to give a vast array of novel modes of reactivity.[99] Photoredox catalysis can either reduce or oxidise a substrate to begin a reaction sequence. Reduction of a substrate begins by photo-excitation of a photo-catalyst (**Figure 9**), becoming a stronger reducing species through placing an electron in a high energy orbital. Donation of this electron results in reduction of the substrate and oxidation of the catalyst.

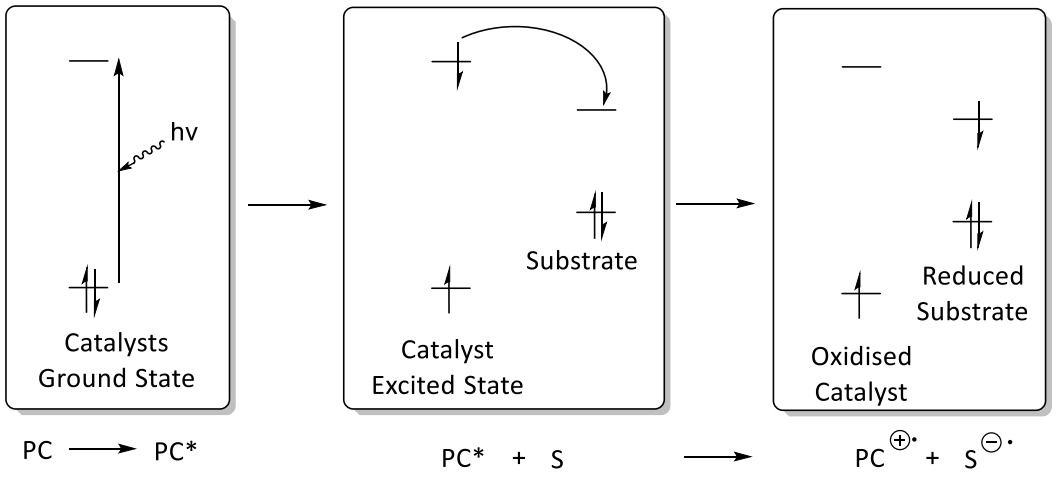


Figure 9: Mechanism of a photoredox catalyst (PC) reducing a substrate (S)

Conversely, at the same time a photo-excitation promotes an electron to a high-energy oribital, a hole is produced in the photoredox catalyst. The photocatalyst can accept an electron into this hole from a substrate therefore oxidising the substrate (**Figure 10**).

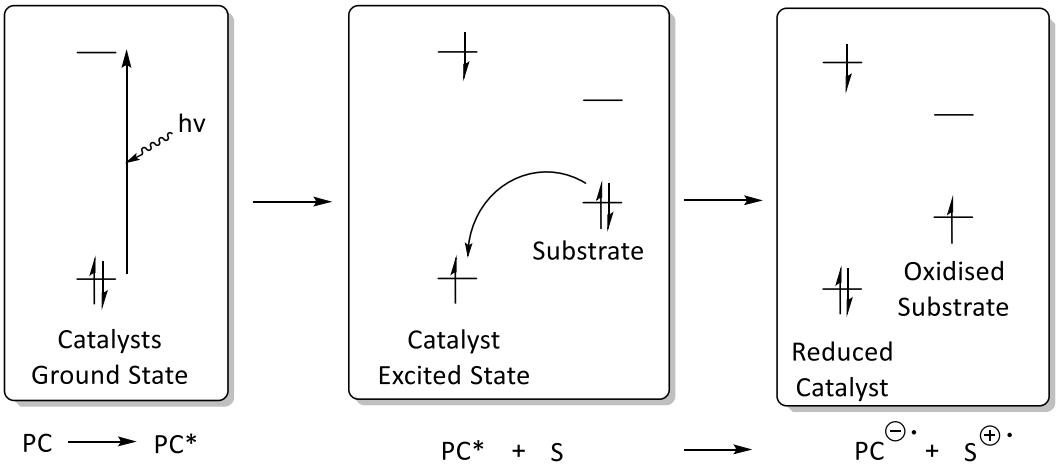


Figure 10: Mechanism of a photoredox catalyst oxidising a substrate

The tendency of a substrate to be either oxidised or reduced can be deduced by obtaining its oxidation/reduction potential by cyclic voltammetry. This then allows selection of an appropriate photoredox catalyst by comparing the oxidation/reduction potential of the photocatalyst in the photoexcited state.

The following electrochemical half-equations can be used to determine whether an excited photoredox catalyst (cat*) could potentially efficiently oxidise a substrate (sub):

$$(1)\quad cat^{*} + e^{-} \rightarrow cat^{-\cdot} \quad E_{1/2}^{red} = x$$

$$(2)\quad sub^{+\cdot} + e^{-} \rightarrow sub \quad E_{1/2}^{ox} = y$$

Equation (1) describes the transformation an excited photoredox catalyst would undergo when oxidizing a substrate and its reduction potential quoted versus a standard electrode. This number is usually negative for a molecule in its ground state. Equation (2) describes the reverse transformation a substrate undergoes when being oxidised in a photoredox reaction. Counterintuitively, the potential is referred to as an oxidation potential even though a reduction is depicted. When referring to the oxidation potential of a species, we are therefore referring to the potential associated with the reduction of the resultant cation ($sub^{+\cdot}$). This number is usually positive as moving from a cationic radical to a neutral species is most often thermodynamically favourable. To calculate the cell potential

for the reaction we therefore need to reverse equation (2) to give the reaction which *actually* occurs to give equation (3). The potential for this equation is multiplied by -1 as the transformation is now moving in the opposite direction.

$$(3) \quad sub \rightarrow sub^{+\cdot} + e^{-} \qquad E_{1/2}^{ox} = -y$$

By combing equation (1) with equation (3) we can deduce the cell potential of the overall transformation and therefore deduce whether the described transformation is thermodynamically favourable:

$$cat^{*} + sub \rightarrow cat^{-\cdot} + sub^{+\cdot} \qquad E^{cell} = x - y$$

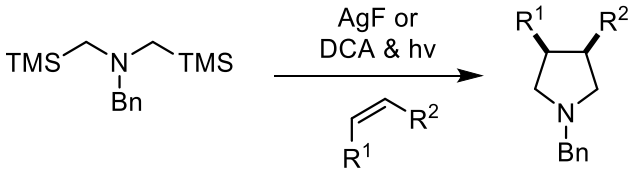
If x - y results in a positive number this equates to a thermodynamically favourable transformation as described by the Nernst equation:

$$\Delta G = -zFE$$

Where ΔG is the Gibb's free energy, z is the number of electron's in the process, F is Faraday's constant and E is the cell potential. As the Nernst equation shows, a positive cell potential results in a negative Gibbs's free energy and therefore a thermodynamically favourable process.

Precedent for AMY Generation from Photoredox Catalysis

Pandey and co-workers reported a method of generating AMYs by bis-desilylation of substrate **192** beginning with a single electron oxidation of the substrate.[100] Two oxidation methods were employed, the first is the use of silver fluoride as a chemical oxidant and the second being photoredox catalysis by either dicyanonapthalene (DCN) irradiated with ultra-violet light or 9,10-dicyanoanthracene (DCA) irradiated with visible light. This generates *N*-benzyl AMYs which underwent (3+2) cycloaddition with electron deficient olefins to give pyrrolidines **193** (**Scheme 63**).

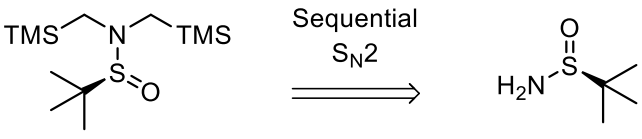


192 **193**

Scheme 63: Formation of AMYs and participation in (3+2) cycloadditions to pyrrolidines[100]

Synthesis of analogous *N*-sulfinyl AMY Precursor

The analogous *N*-sulfinyl AMY precursor **194** could potentially be accessed from the cheap commercially available (*S*)-2-methyl-2-propanesulfinamide (**79**) (**Scheme 64**) by performing a sequential addition of two methyltrimethylsilane groups either in one pot or in two separate reactions.

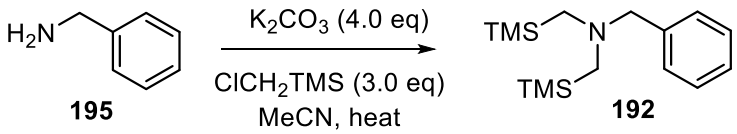


194 **79**

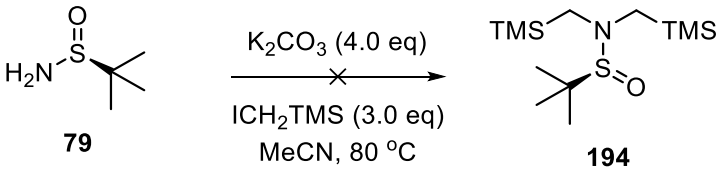
Scheme 64: Retrosynthesis of model substrate **194** to commerically available (*S*)-2-methyl-2-propanesulfinamide (**79**)

Attempts towards One-Pot bis-addition

The conditions used by Pandey and co-workers[100] to prepare the *N*-benzyl AMY precursor **192** from benzylamine (**195**) (**Scheme 65**) were first investigated with one alteration, switching chloromethyl trimethylsilane for iodomethyl trimethylsilane. The conditions were found only to return starting material (**Scheme 66**). Temperature and yield were not provided in the original publication.

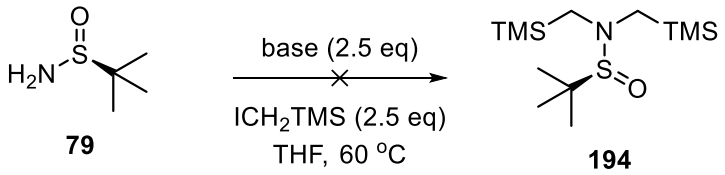


Scheme 65: Synthesis of *N*-benzyl AMY precursor



Scheme 66: Conditions from *N*-benzyl AMY precursor applied to (*S*)-2-methyl-2-propanesulfinamide

A number of nitrogen bases were screened in the reaction of (*S*)-2-methyl-2-propanesulfinamide (**79**) with iodomethyltrimethylsilane (**Table 5**). Triethylamine, DABCO and TMG all returned starting material with none of the desired product **194**.



Base	Yield
Et_3N	-
DABCO	-
TMG	-

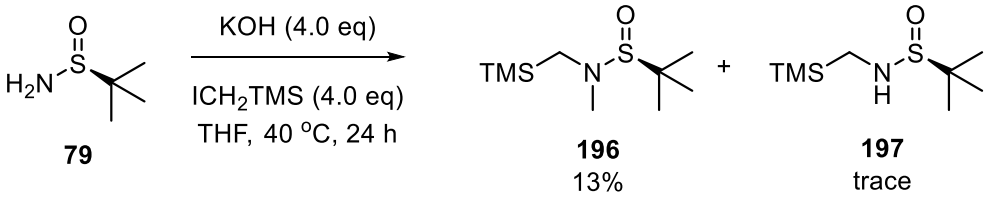
Table 5: Screening of nitrogen bases for the bis-nucleophilic substitution of iodomethyl trimethylsilane with (*S*)-2-methyl-2-propanesulfinamide

The failure to prepare model substrate **194** from the above methods is likely due to the lowered nucleophilicity of the (*S*)-2-methyl-2-propanesulfinamide (**79**) nitrogen in comparison to benzylamine. It was therefore rationalised that by using a stronger base may lead to product formation by first forming the anion of (*S*)-2-methyl-2-propanesulfinamide (**79**) which can then react with the electrophile.

The alkylation of sulfinamides had been achieved by Zeng and co-workers using potassium hydroxide as the base and methyl iodide as the alkylating agent[101] so we set out to investigate the analogous reaction for the synthesis of substrate **194**.

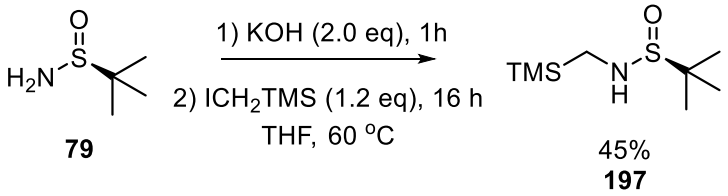
Two-step attempts towards model substrate

Replacing the base with potassium hydroxide (pK_a = 15.7) and stirring at 40 °C in THF did not give any of the desired bis-methyltrimethylsilane product but afforded a trace amount of mono-methyltrimethylsilane product **197** and unexpectedly 13% of the mono-methyltrimethylsilane-mono-methyl product **196** (**Scheme 67**). This unexpected product presumably is derived by reaction of **197** with a second equivalent of iodomethyltrimethylsilane followed by subsequent removal of the TMS group by hydroxide.



Scheme 67: Increasing strength of base for (*S*)-2-methyl-2-propanesulfinamide deprotonation

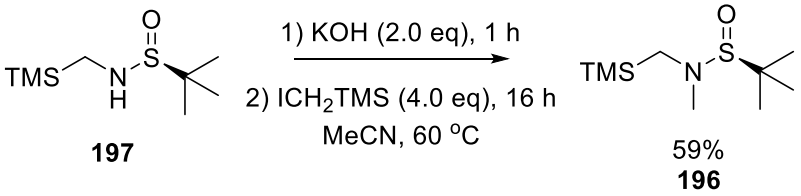
Based on this result it was decided to attempt to install the two methyltrimethylsilane groups onto the nitrogen in separate reactions. The first step was made possible by reducing the number of equivalents of both potassium hydroxide and iodomethyltrimethylsilane (**Scheme 68**) which afforded the desired mono-methyltrimethylsilane adduct **197** in 45% yield.



Scheme 68: Attempt at synthesising mono-adduct **197**

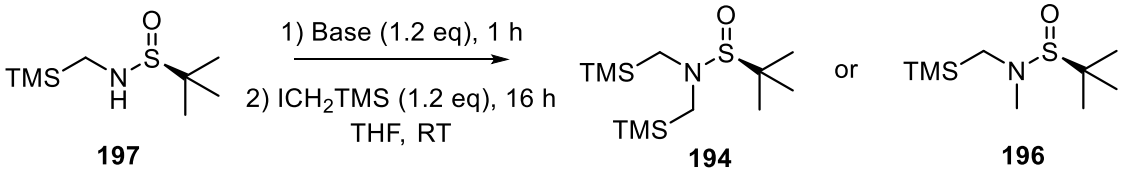
From **197,** we attempted to add the second methyltrimethylsilane retaining potassium hydroxide but this also gave the methyl adduct **196** in 59% yield (**Scheme 69**). This presumably occurs through **194** forming in the reaction mixture which then undergoes loss of a TMS group through reaction with

potassium hydroxide. The observation that only one TMS group reacts is indicative that **194** is much more prone to react in this manner than **196**. This higher reactivity could be attributed to steric crowding in **194** making the TMS groups more reactive than in **196** where there is less steric bulk around the nitrogen.



Scheme 69: Attempt towards addition of second methyltrimethylsilane group

It was rationalised that the second addition may be possible by employing a non-nucleophilic bases to avoid TMS removal. Potassium *tert*-butoxide also gave the methyl addition product **196** (**Table 6**, **Entry 1**) and suspecting this was due to oxygen's silylphilicity, non-nucleophilic nitrogen bases were next employed. LiHMDS (**Entry 2**) and LDA (**Entry 3**) gave the desired product **194** in 18% and 21% respectively. Although these yields were poor, it was deemed acceptable as the hypothesis could now be tested.



Entry	Base	Yield **194** (%)	Yield **196** (%)
1	KO^{t}Bu	-	35
2	LiHMDS	18	-
3	LDA	21	-

Table 6: Screening non-nucleophilic bases

Determining the Oxidation Potential of the Model Substrate:

Before model substrate **194** could be subjected to any reaction conditions, it was necessary to determine the oxidation potential for appropriate photoredox catalyst selection. In DCM and with a standard calomel electrode at a scan rate of 0.1 Vs^{-1} the oxidation potential of **194** was found to be +1.25 V (**Figure 11**). Moreover, the voltammogram shows an irreversible oxidation due to the absence of a reduction peak. It is possible the shape of the voltammogram is indicative of an EC process, which is an electrochemical process followed by a chemical process.[102] This agrees with the desired mechanism.

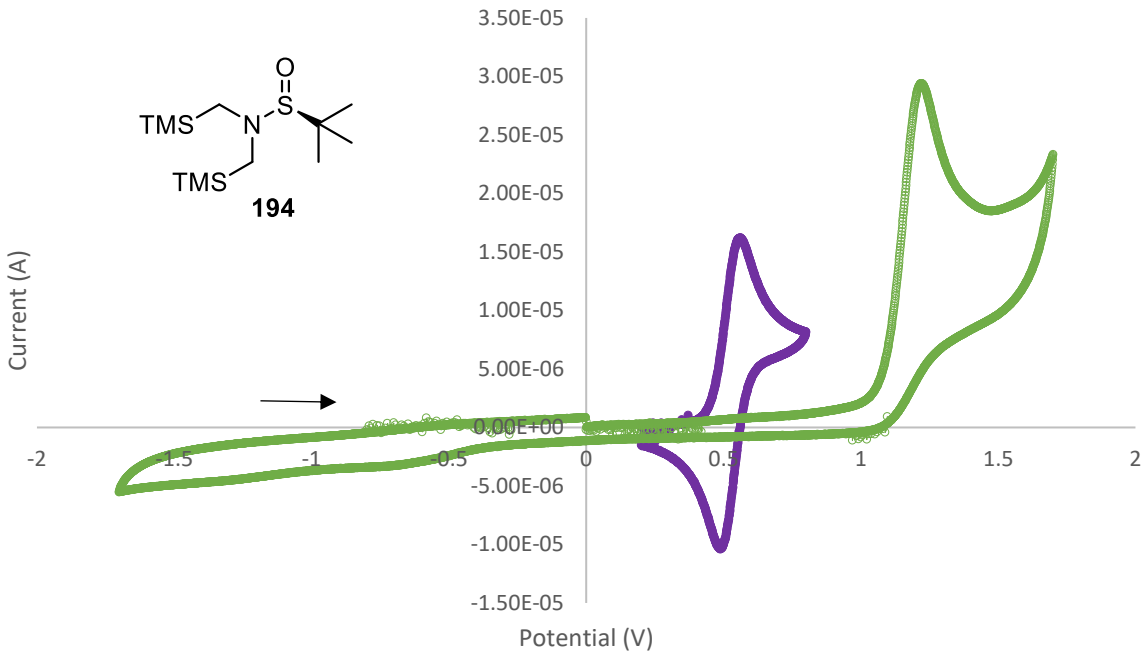


Figure 11: Cyclic Voltammogram in DCM of AMY precursor **194** (green) with ferrocene (purple) as the standard ($E^{ox}_{1/2}$ = +0.53 V). Standard Calomel Electrode used as a reference electrode. Scan rate of 0.1 Vs^{-1}

An oxidation potential of +1.25 V significantly limits the reaction parameters which are available for screening. Acetonitrile was selected due to its high oxidation potential (approx. +3 V vs SCE)[103] and four photoredox catalysts were selected for screening due to their sufficiently high oxidising potential (**Figure 12**).

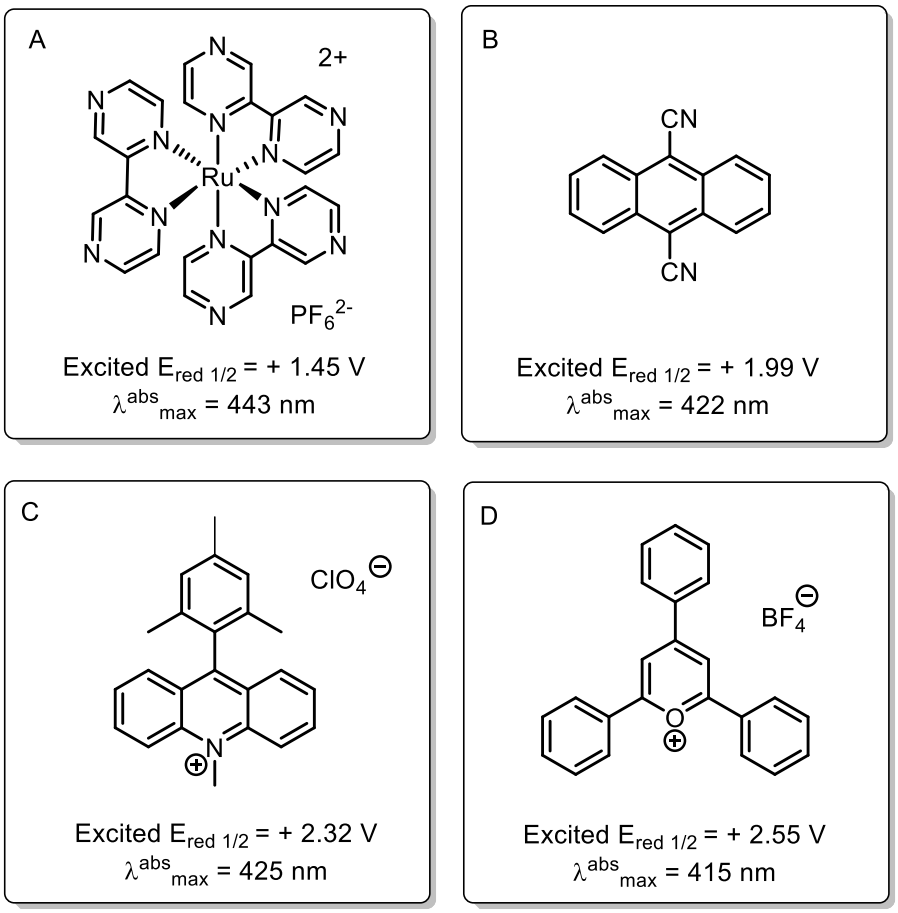
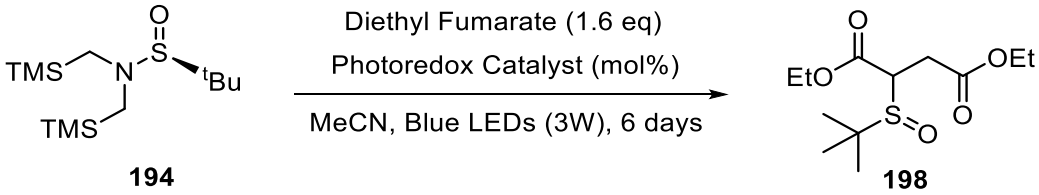


Figure 12: Available photoredox catalysts with excited state reduction potentials (vs SCE) above +1.25. A) $[Ru(bpz)_3][PF_6]$; B) 9,10-dicyanoanthracene (DCA); C) 9-Mesityl-10-methylacridinium perchlorate ($Mes\text{-}Acr^+$); D) 2,4,6-Triphenylpyrylium tetrafluoroborate (TPT^+)

Photoredox Reaction Set-up

The solvent (acetonitrile), model substrate **194** (AMY precursor), diethyl fumarate (dipolarophile) and the photoredox catalysts were placed in a vial then sparged for 30 minutes with nitrogen. The contents were then stirred and illuminated with a 3W blue LED bulb as the photoredox catalysts employed have absorbances (λ^{abs}_{max}) which are in the blue region of the spectrum. The reaction vials were covered with a case which was lined with tinfoil. The reactions were monitored by thin layer chromatography and when consumption of **194** was complete, the solvent was removed, and the product was purified by column chromatography on silica or the yield was calculated by quantitative NMR.

Catalyst Screening



Photoredox Catalyst	Mol%	Yield (%)
$[Ru(bpz)_3]^{2+}$	2	28[a]
DCA	10	61[b]
Mes-Acr$^+$	10	43[b]
TPT$^+$	10	76[b]

Table 7: Catalyst screening experiments. [a] Isolated yield. [b] NMR yield. pyrazine as internal standard.

AMY generation and trapping with a dipolarophile was attempted with the appropriate photoredox catalysts (**Table 7**). The reaction conditions did not produce the desired pyrrolidines but instead possibly produced a sulfoxide addition product **198** in low to good yields. **198** was purified by column chromatography by isolating a single spot, however, after removal of solvent under reduced pressure some of the product had decomposed to give a second spot by TLC. The second spot was found to be diethyl fumarate indicating **198** is unstable and decomposes. This results in the samples which underwent NMR analysis containing diethyl fumarate but as this spectrum is known, we are still able to report the NMR data for **198** (**Figure 15**). H^b, H^c and H^d are easily visible. H^a overlaps with the quartet of diethyl fumarate at δ = 4.26 and H^e, H^f and H^g are present and overlap with the triplet of diethyl fumarate at δ = 1.32. The data from ^{1}H NMR spectrsoscopy, ^{13}C NMR spectroscopy and mass spectrometry were consistent with two possible products, sulfoxide **198** and sulfenate ester **199** (**Figure 13**). The calculated m/z for the sodium adduct of **198** and **199** = 301.1086 $[M+Na]^+$ and a mass peak of 301.1088 was detected.

Figure 13: Possible products based on NMR spectroscopy and mass spectrometry data

Similar examples for both possible structures were found in the literature and their structures compared (**Figure 14**). Sulfoxide **198** possesses a proton in the α-position of an ester and a sulfoxide group, similar to **200**.[104] Diethyl tartrate (**201**) possesses a proton in the α-position of an ester and an oxygen atom, similar to the other possible structure of the product **199**.[105]

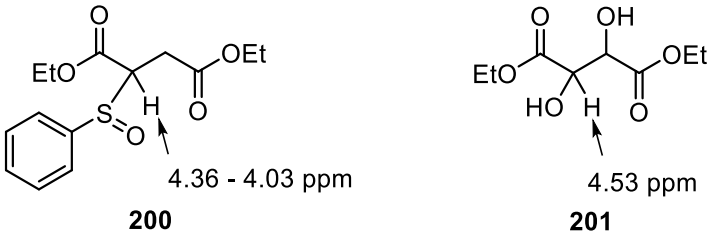


Figure 14: Compounds with comparable structures to the possible products

Based on these examples is was determined the product was more likely to be sulfoxide **198** due to the chemical shift of the α-proton in the product at 4.00 ppm (**Figure 15**).

There is the possibility of producing 4 stereoisomers in this reaction (**Figure 16**). Our proposed mechanism involves the cleavage of the C-S bond to form sulfinyl radicals (**Scheme 70**). Homolytic cleavage of the C-S bond in sulfoxides has been shown to lead to the racemisation of sulfinyl radicals and we therefore do not believe any enantiomeric excess is retained in the products.[106] Only one product spot was visible by TLC and this product has ^{1}H NMR and ^{13}C NMR spectra consistent with one set of diastereomers ie. no splitting of signals. This indicates a very diastereoselective reaction and the product **198** is a racemic mixture of **198a** and **198d** or a racemic mixture of **198b** and **198c**.

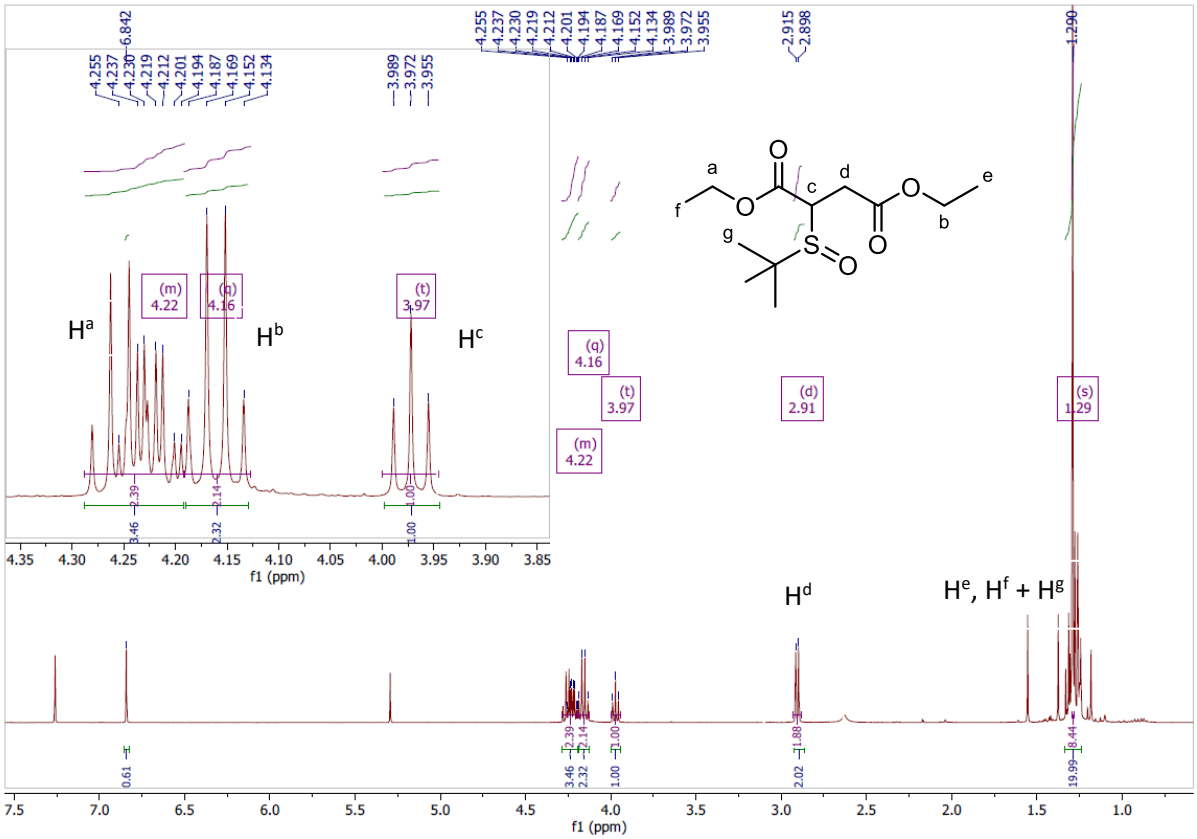


Figure 15: ^{1}NMR spectrum of product **198**

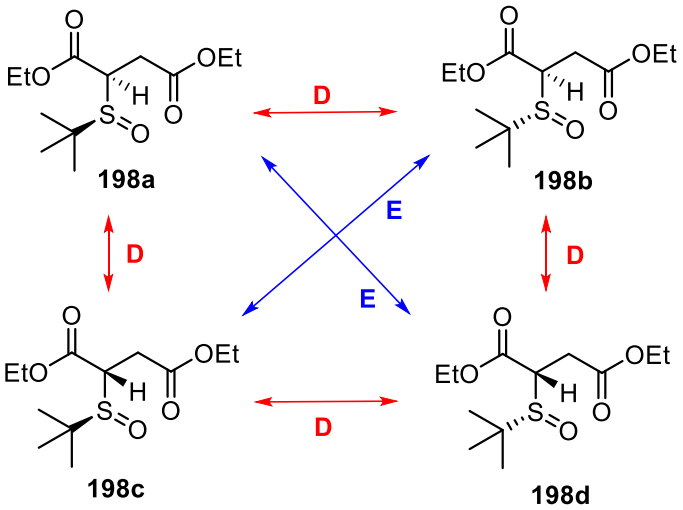
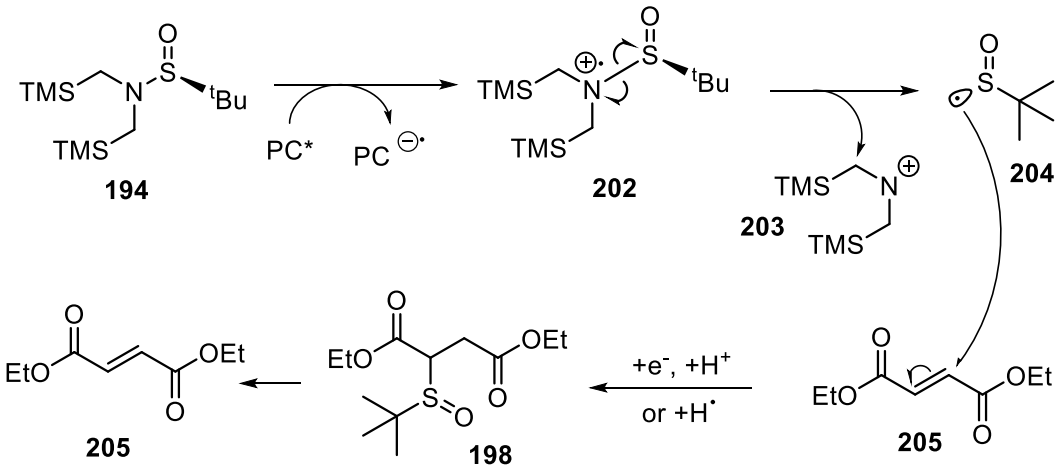


Figure 16: Possible stereoisomers of **198. D** denotes stereoisomers which are diastereomers of each other. **E** denotes enantiomers.

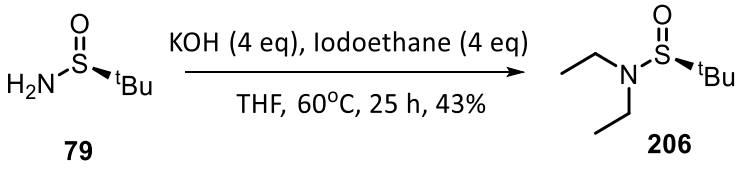
Proposed Photoredox Mechanism



Scheme 70: Proposed mechanism for the formation of a sulfoxide

Scheme 70 depicts a possible mechanism for the formation of **198**. The first step is the one electron oxidation of **194** by the excited photoredox catalyst to give the radical cationic species **202**. Instead of the desired loss of a TMS cation, the nitrogen-sulfur bond undergoes homolytic cleavage to give an unusual nitrogen cation **203** and sulfinyl radical **204**. This is perhaps made possible by the double β-cation stabilisation through hyperconjugation of the TMS groups. Radical addition to the diethyl fumarate (**205**) followed by either a one electron reduction and proton capture or homolytic hydrogen abstraction leads to the product **198** which then decomposes back to **205** over time.

It was rationalised that, if the role of the TMS groups outlined in the mechanism (**Scheme 70**) is correct, then a substrate without these TMS groups would prevent the homolytic cleavage of the nitrogen-sulfur bond. Also, if the TMS groups were stabilising positive charges on the nitrogen, their removal should make the first single electron oxidation more difficult ie. the oxidation potential of the molecule would be higher. To investigate this hypothesis, we synthesised **206** from Ellman's sulfinamide **79** in a single step (**Scheme 71**)



Scheme 71: Synthesis of (*S*)-*N,N*-diethyl-2-methylpropane-2-sulfinamide

The cyclic voltammogram for molecule **206** was obtained and the oxidation potential was found to be +1.5V (vs SCE in DCM) (**Figure 17**), significantly higher than the bis-TMS analogue **194** which is consistent with the hypothesis that the silicon atoms are making the resultant nitrogen radical cationic species more stable.

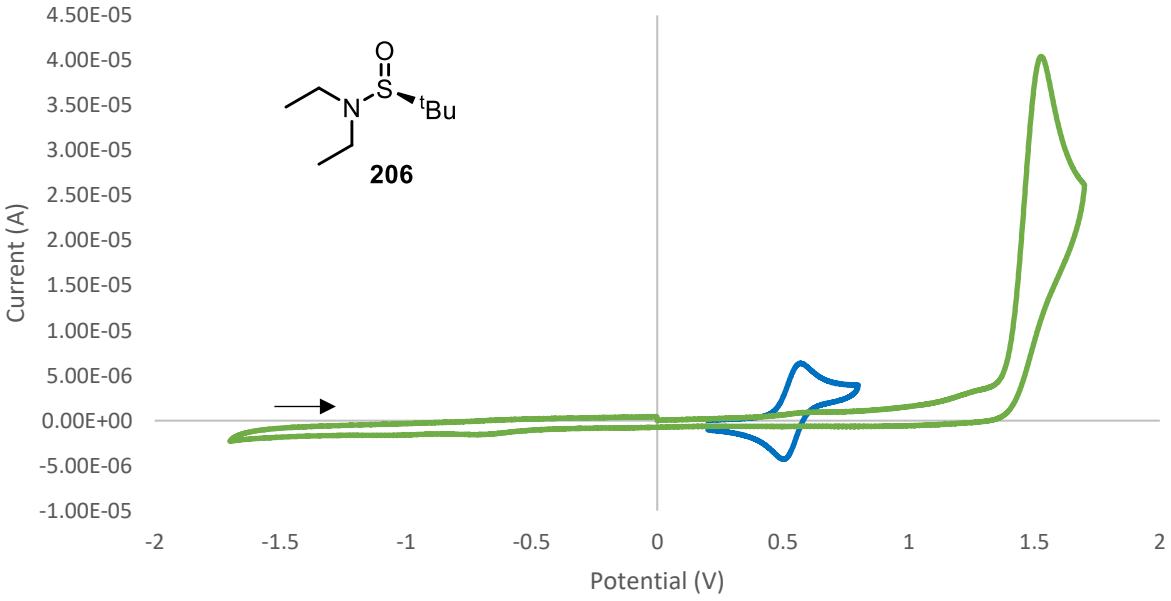


Figure 17: Cyclic voltammogram in DCM of (*S*)-*N,N*-diethyl-2-methylpropane-2-sulfinamide (**206**) with a scan rate of 0.1 Vs^{-1} (green) with ferrocene (blue) as a standard.

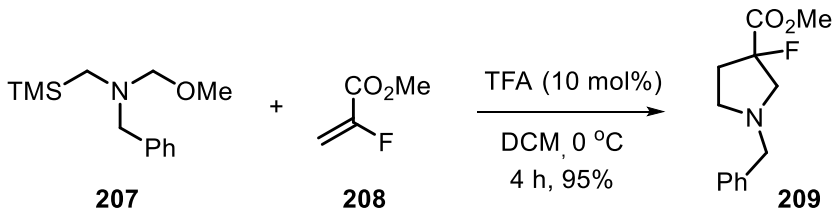
Sulfinamide **206** was then subjected to the same reaction conditions as in **Table 7** with the same photoredox catalysts apart from $[Ru(bpz)_3][PF_6]$ as this would not be a strong enough oxidant. No addition product **198** was found from these reactions, only starting material was returned, indicating the TMS groups in sulfinamide **194** facilitate the cleavage of the nitrogen-sulfur bond.

These experiments indicate that generation of AMYs from the precursor **194** is not possible due to the homolytic cleavage of the nitrogen-sulfur bond. Alternative routes to generating AMYs containing chiral sulfinyl groups were therefore pursued.

2. Acid Catalysed AMY Generation

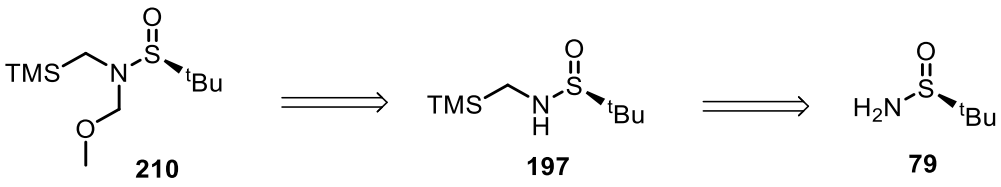
Precedent for Acid Catalysed AMY generation

N-(Methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (**207**) is a common reagent for the generation of AMYs which can undergo (3+2) cycloaddition reactions with dipolarophiles such as **208** to give pyrrolidine products **209** (**Scheme 72**).[107] The AMY reacts with a diverse range of electron-poor alkenes and alkynes but is non-chiral therefore gives racemic mixtures with pro-chiral dipolarophiles. Trifluoroacetic acid acts as a catalyst to fragment precursor **207** into AMYs *in-situ*.



Scheme 72: *N*-(Methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine as an AMY precursor for pyrrolidine synthesis

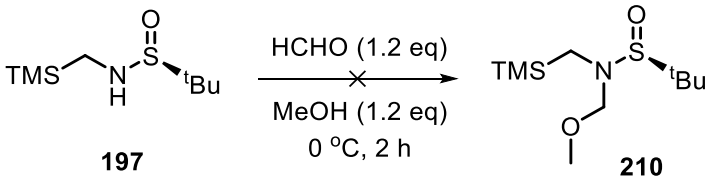
The first goal was to synthesise the analogous *N*-sulfinyl AMY precursor (**210**) from *(S)*-2-methyl-2-propanesulfinamide (**79**). The first step for the synthesis of *N*-methyltrimethylsilane derivative (**197**) had already been achieved in the previous project (pg. 68) so attention moved towards installation of the methyl methoxy group.



Scheme 73: Retrosynthesis of analogous *N*-sulfinyl AMY precursor

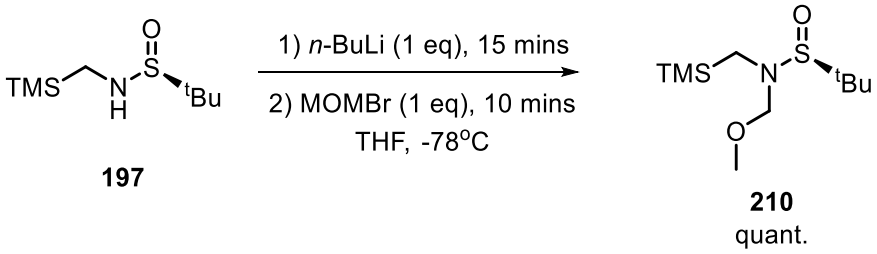
Synthesis of analogous *N*-Sulfinyl Precursor

The reagent *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (**207**) is synthesised from *N*-(trimethylsilylmethyl)benzylamine by reacting with formaldehyde and methanol.[108] The same reaction was attempted on the analogous molecule **197** but the reaction only returned starting material (**Scheme 74**), most likely as a result of the lowered nucleophilicity of the nitrogen due to the presence of the electron withdrawing sulfinyl group.



Scheme 74: Attempt at installing methyl methoxy residue towards AMY precursor **210**

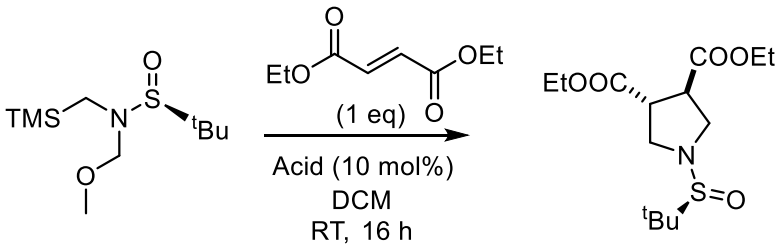
The solution for getting intermediate **197** to act as a nucleophile was the use of a strong base. In a 2-step sequence, *n*-BuLi deprotonates **197** followed by addition of bromomethyl methyl ether at -78 °C (**Scheme 75**). The product **210** is formed in quantitative yields and does not require further purification. The reaction was also attempted with chloromethyl methyl ether. This formed the product but in much lower yield and a complex mixture was formed, which would have required purification.



Scheme 75: Synthesis of *N*-sulfinyl AMY precursor for acid catalysis

Screening Acid Catalysts

With AMY precursor **210** in hand, acids were screened to find a suitable catalyst. Due to the potential acid sensitivity of the *N*-sulfinyl group, attention was first focused on finding a Lewis acid which could potentially minimise sulfinyl removal. The dipolarophile selected was diethyl fumarate as the two electron withdrawing groups should result in high reactivity with any AMY generated. The Lewis acid experiments failed to afford any of the desired pyrrolidine. The metal Lewis Acid afforded only starting material (**Table 8**, **Entries 1-3**) and boron trifluoride etherate (**Entry 4**) gave no product and decomposed the starting material. When the Brønsted acid TFA was used, pyrroldine **211** was isolated in an 8% yield with a 1:1 ratio of diastereoisomers (**Entry 5**) determined by ^{1}H and ^{13}C NMR. The strong protic acids, fluoroboric and triflic acid (**Entries 6 & 7**), gave no product and decomposed the starting material.



210 **211**

Entry	Acid	Yield (%)
1	$Zn(OTf)_2$	0
2	$Sc(OTf)_2$	0
3	$Yb(OTf)_3$	0
4	$BF_3 \cdot OEt_2$	0
5	TFA	8 (1:1 dr)
6	$HBF_4 \cdot OEt_2$	0
7	CF_3SO_3H	0

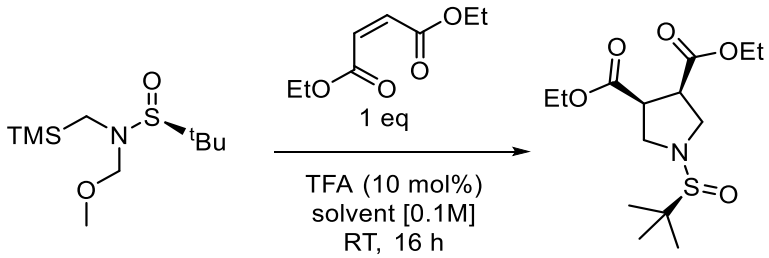
Table 8: Acid Catalyst Screening for AMY generation

The mixture of diastereoisomers (**Entry 5**) made NMR analysis complicated so the dipolarophile reacting partner was switched to diethyl maleate as only one diastereoisomer would now be possible, simplifying analysis.

When switching from diethyl fumarate to diethyl maleate, the NMR spectra of the products **211** and **212** are different, most notably **211** possesses two singlets in a number of key carbon atoms because of the presence of diastereomers, whereas **211** does not. This gave us confidence that the (3+2) cycloaddition was progressing in a concerted manner as the *E*-alkene of diethyl fumarate appears to give an *anti*- configuration of the ethyl ester groups in **211** and the Z-alkene of diethyl maleate appears to give *syn*-configuration of the ethyl ester groups of **212**.

Solvent Selection

Switching the dipolarophile from diethyl fumarate to diethyl maleate gave an improved yield of **212** at 21% (**Table 9, Entry 1**) likely as a result of the increased strain present in (*Z*)-alkenes. Chloroform-*d* and acetonitrile gave a lower yield of 10% and 11% (**Entry 2, Entry 3**) whereas toluene and protic solvents methanol and trifluoroethanol all gave none of the desired product (**Entry 4, Entry 5 & Entry 6**). Switching to ethereal solvents led to improvements in yield. Diethyl ether (**Entry 7**) gave 17% of the desired pyrrolidine **212** and THF (**Entry 8**) gave the second highest yield at 35% but 1,4-dioxane was the best solvent investigated (**Entry 9**) with a yield of 41%. Attempts to improve the yield by adding desiccants sodium sulfate (**Entry 10**) and 4 Å molecular sieves (**Entry 11**) gave no improvement.

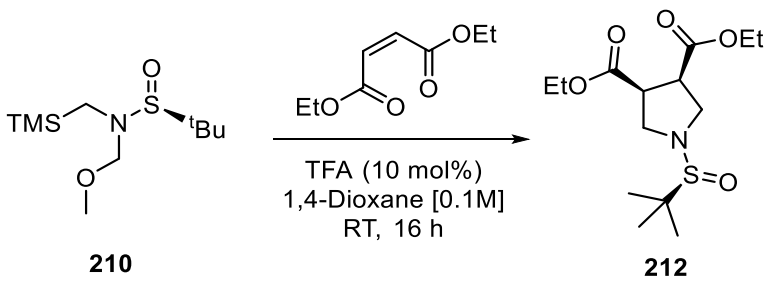


210 **212**

Entry	Solvent	Yield
1	DCM[a]	21
2	Chloroform-*d*	10
3	Acetonitrile	11
4	Toluene	0
5	Methanol	0
6	Trifluoroethanol	0
7	Diethyl Ether	17
8	THF	35
9	1,4-dioxane	41
10	1,4-dioxane[b]	42
11	1,4-dioxane[c]	40

Table 9: NMR yields for solvent screen for the synthesis of *N*-sulfinyl pyrrolidine **212.** Pyrazine used as internal standard. [a] Isolated yield [b] sodium sulfate added [c] 4 Å molecular sieves

Further Optimisation

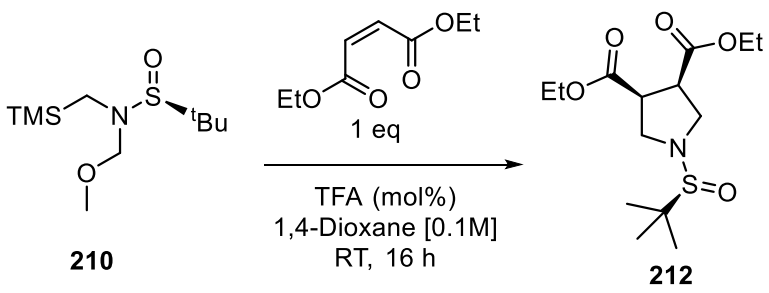


210 **212**

Entry	Diethyl Maleate Equivalents	Yield (%)
1	1	41
2	2	38
3	5	46

Table 10: NMR yields of pyrroldine from variation in the equivalents of dipolarophile, diethyl maleate. Pyrazine used as the internal standard.

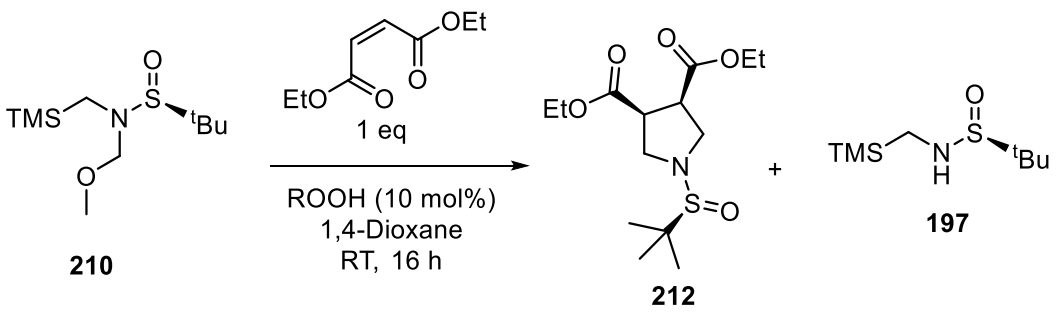
The equivalents of dipolarophile were varied, first to 2 equivalents (**Table 10**, **Entry 2**) and then to 5 equivalents (**Entry 3**). These experiments gave similar results at 38% and 46% yield respectively. If the reaction yield was being limited by the efficiency of the (3+2) cycloaddition step, an increase in concentration of dipolarophile would likely increase the number of collisions between AMY and dipolarophile and would therefore increase the net number of successful collisions resulting in a higher yield. The observation that increasing the amount of dipolarophile does not increase yield is perhaps indicating the (3+2) cycloaddition step is not the limiting factor in this reaction and that the generation of the AMY from the precursor **210** is the main factor limiting the yield.



Entry	TFA mol%	Yield (%)
1*	5	0
2	10	41
3	20	25

Table 11 : NMR yields from variation in the concentration of TFA. Pyrazine used as the internal standard*Reaction extended to 7 days

Variation in the concentration of TFA away from 10 mol% was detrimental to the yield. 5 mol% TFA (**Table 11**, **Entry 1**) surprisingly gave no product and, doubling the amount of TFA to 20 mol% (**Entry 3**) decreased the yield to 25%.

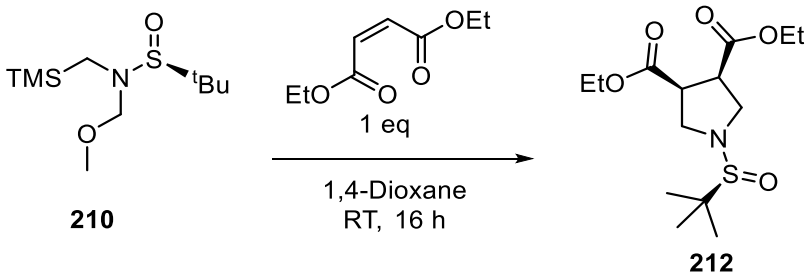


Entry	R	Yield (%) of 212	Yield (%) of 197
1	CF_3	41	0
2	CH_3	0	0
3	CHF_2	0	58

Table 12: Investigating the effect of acidity of the carboxylic acid on yield

The drastic difference in yield when varying the TFA loading lead to an investigation into altering the carboxylic acid catalyst. Acetic Acid (**Table 12**, **Entry 2**) yielded no product but did return the starting material, suggesting the pKa is not high enough to protonate the precursor **210**. Difluoroacetic acid provided no desired product **212** or starting material **210**, however 2-methyl-*N*-((trimethylsilyl)methyl)propane-2-sulfinamide (**197**) was found to be the main product with 58% yield. These experiments demonstrate the necessity of TFA as the catalyst.

The discovery that TFA was the only one of these three carboxylic acids to successful perform the desired reaction led us to query if the reaction had a very narrow pKa range that would successfully lead to the AMY being formed and that TFA fell into this range or did the trifluoroacetate ion have a more involved role other than a non-participant counter ion. In order to investigate the effect of the trifluoroacetate ion, we doped our reaction various quantities of dried sodium trifluoroacetate. Our previously optimised conditions (**Table 13**, **Entry 1**) had given a 41% yield of desired pyrrolidine. Adding 20 mol% and 40 mol% of sodium trifluoroacetate (**Entry 2 & Entry 4**) gave comparable results at 35% and 36% respectively. Removing the TFA and retaining 40 mol% sodium trifluoroacetate (**Entry 4**), resulted in none of the desired product. These results indicate it is the pKa of TFA which results in the desired activity and the trifluoroacetate ion plays little, if any role.

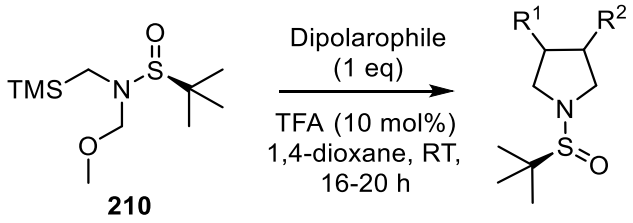


Entry	TFA (mol%)	$NaOOCCF_3$ (mol%)	Yield (%)
1	10	0	41
2	10	20	35
3	10	40	36
4	0	40	0

Table 13: NMR yields from adding various quantities of sodium trifluoroacetate to optimised reaction conditions. Pyrazine used as the internal standard.

Altering Dipolarophiles

We investigated different dipolarophiles with the aim of increasing the scope of *N*-sulfinyl pyrrolidines (**Table 14**). We first investigated norbornene (**Entry 1**) due to the ring strain present in the double bond as this may increase reactivity with the AMY but this reaction did not lead to any of the desired product. We turned to maleic anhydride (**Entry 2**) as this is more electron poor than diethyl maleate and therefor possesses a lower LUMO, increasing reactivity with the AMY but this also led to none of the desired product. The last dipolarophile we investigated was phenyl vinyl sulfone (**Entry 3**). This reaction gave a trace of product according to mass spectrometry but attempts to purify and isolate the sample failed.



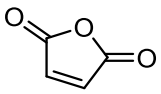
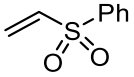
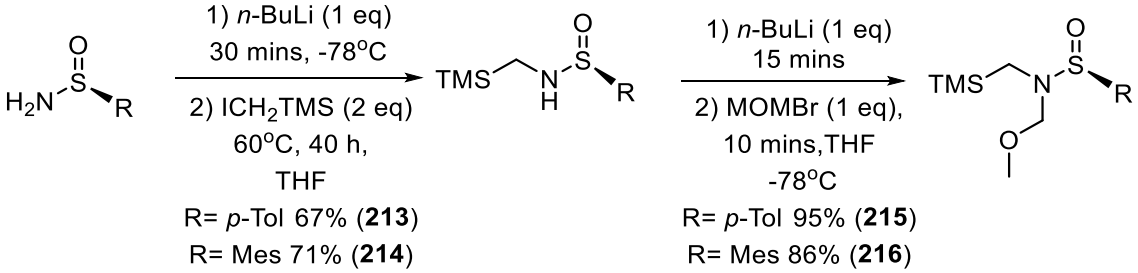
Entry	Dipolarophile	Yield (%)
1		0
2		0
3		Trace

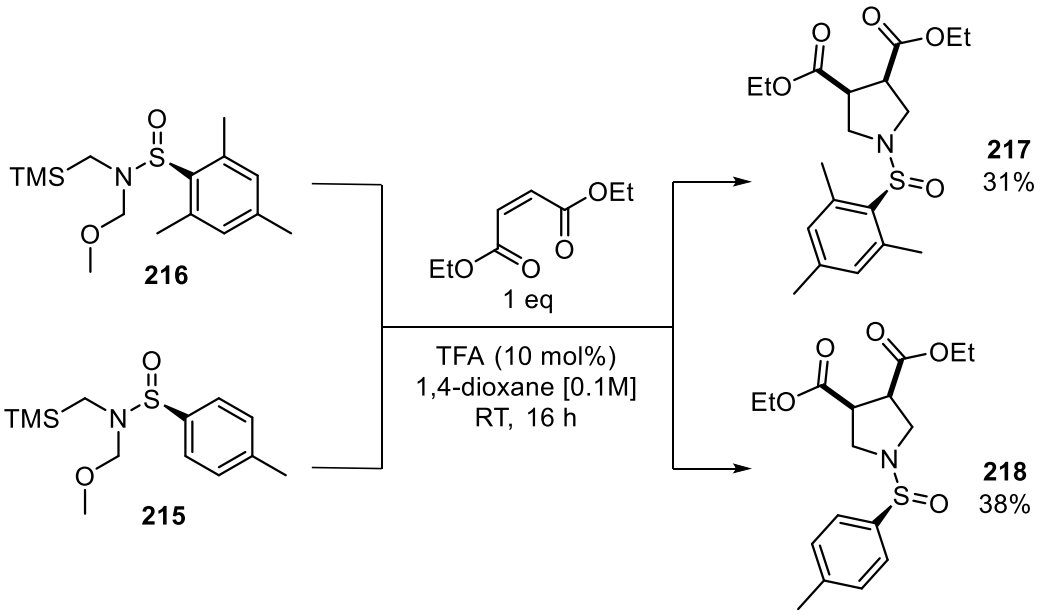
Table 14: Reacting AMY precursor **212** with various dipolarophiles

Varying Sulfinamide Substituent

When considering the causes of the low yield we wondered if **212** could be undergoing de-*tert*-butylation before forming the AMY as this would be a non-productive pathway. Reaction conditions are known where *tert*-butyl sulfinimines give no desired product but mesityl and *para*-tolyl sulfinimines work well under the same conditions.[85] We investigated both (**Scheme 76**), first synthesising the AMY precursors. We further optimised the conditions for the first step of the AMY precursor synthesis. From the corresponding sulfinamides, deprotonation with *n*-BuLi followed by addition of iodomethyl trimethylsilane afforded the desired intermediates **213** & **214** in good yield for both substituents. The extended reaction duration and heating was crucial in improving the yield for this step. For example, when running the same reaction for 22 hours at room temperature, less than 10% of the desired product **213** was detected by quantitative NMR. The installation of the MOM-group went smoothly for both examples to give AMY precursors **215** & **216** in 95% and 86% respectively.



Scheme 76: Synthesis of mesityl and *para*-tolyl AMY precursor

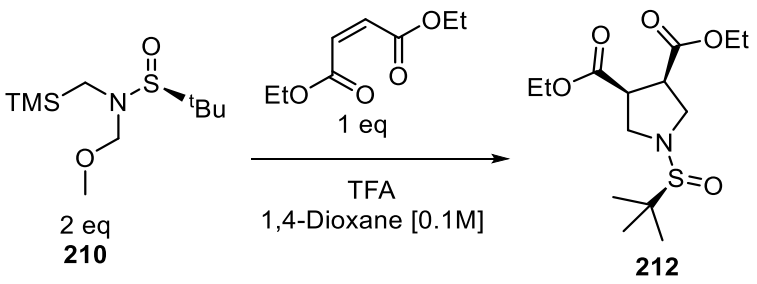


Scheme 77: Application of optimised conditions on mesityl and *para*-tolyl substituted AMY precursors

The mesityl AMY precursor **216** when subjected to the reaction conditions gave the corresponding pyrrolidine **217** in a lower yield of 31% (**Scheme 77**). The *para*-tolyl precursor **215** also gave a lower yield of pyrrolidine **218** at 38%. This unfortunately did not produce higher yields but this does show that the reaction works for a number of AMY precursors which can be synthesised from commercially available chiral sulfinamides.

For all of the reactions discussed in the acid catalysed methodology thus far, complete consumption of the AMY precursors was observed and unreacted alkene is found in the reaction mixture. This indicates that the AMY precursor does not efficiently form the AMY and is destroyed, or alternatively, or simultaneously, when the AMY is formed, rather than performing the desired (3+2) cycloaddition, an alternative quenching pathway occurs. Whatever the mechanism, for all AMY precursors, one equivalent of AMY precursor gives 30-40% of AMY successful in performing the desired (3+2) cycloaddition. We rationalised by changing the limiting reagent to the alkene and increasing the equivalents of AMY precursor we could increase the equivalents of AMYs formed which then go on to perform successful (3+2) cycloadditions.

Varying Equivalents of AMY Precursor



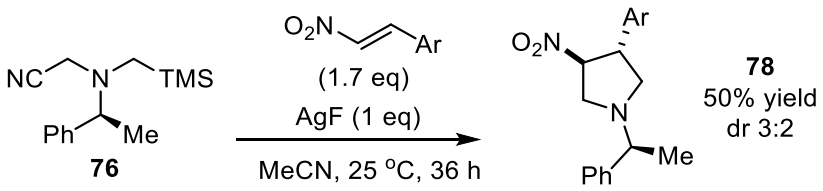
Entry	Temperature (°C)	TFA (mol%)	Time (h)	Yield (%)
1	r.t.	20	16	50*
2	r.t.	20	40	31
3	r.t.	20 + 20	16 +24 (40)	65
4	40	20	2	66

Table 15: NMR yields from experiments increasing AMY precursor equivalents to 2 *based on conversion of alkene. Pyrazine used as the internal standard.

Changing the equivalents of AMY precursor to 2 (**Table 15, Entry 1**) resulted in a small increase in yield to 50%, however the crude reaction mixture contained approximately 66% of unreacted AMY precursor **210** and 50% of the diethyl maleate indicating further increases may be possible. We increased the time for the reaction in the hope of observing higher consumption of the AMY precursor **212** (**Entry 2**). We did see complete consumption over this time period but a slight drop in yield was observed. It was proposed the TFA catalyst was dying over the long reaction duration and the AMY precursor was being consumed via a separate non-productive pathway. We therefore conducted two experiments. The first was adding a second portion of 20 mol% of TFA at 16 hours to replace dying catalyst (**Entry 3**) and the second was raising the temperature to 40 °C (**Entry 4**) to lower reaction durations. Both reactions gave improved yields of **212** of 65% and 66% respectively and the reaction time when conducted at 40 °C was lowered to 2 hours. With this further optimised reaction yield and reaction duration, we decided it was now appropriate to test the diastereoselectivity of the reaction.

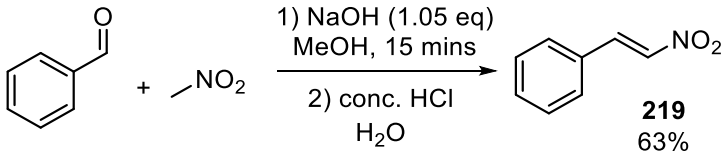
Assessing Diastereoselectivity of chiral *N*-sulfinyl AMYs

As discussed previously (page 30), *N*-(1-phenylethyl)-AMY precursor **76** fragments to give the *N*-(1-phenylethyl)-AMY (**Scheme 78**).[45] The *N*-sulfinyl AMY compared to AMY formed from **76** only differs in the auxiliary. We therefore decided to use the same dipolarophile so direct comparison can be made between the two methods.



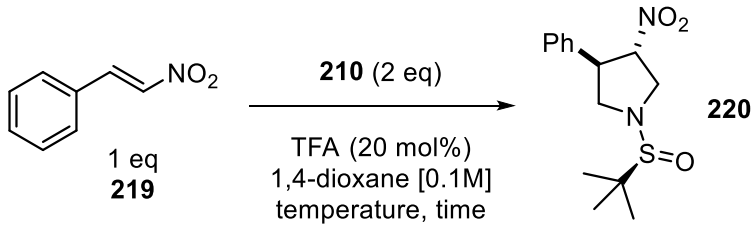
Scheme 78: Chiral benzyl auxiliaries in AMY (3+2) cycloaddition

β-Nitro styrene was first synthesised by performing an Henry reaction on benzaldehyde with nitromethane (**Scheme 79**).[109] The crude addition product was then dripped slowly into HCl solution which resulted in the elimination of water to give the product, β-Nitro styrene (**219**), in a 63% yield.



Scheme 79: β-Nitro styrene synthesis

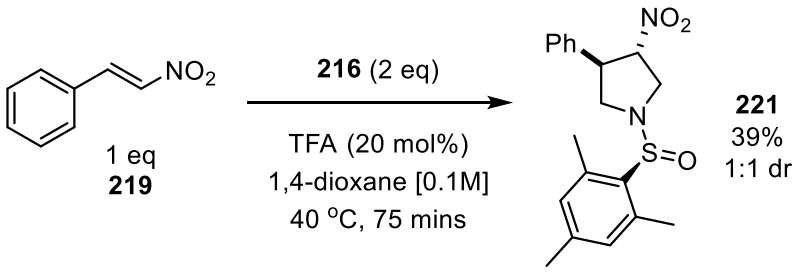
β-Nitro styrene was then subjected to the optimised reaction conditions (**Table 16, Entry 1**). Not only did this see a dramatic drop in yield to 25% when switching the dipolarophile to β-nitro styrene, the reaction did not achieve any diastereoselectivity in the synthesis of pyrrolidine **220**. We lowered the reaction temperature to room temperature (20 °C) (**Entry 2**) with the aim of promoting one product over the other. These conditions only produced a trace of product **220** based on the crude reaction mixture ^{1}H NMR spectrum. No product was isolated after purification and we were therefore unable to obtain a diastereomeric ratio.



Entry	Temperature (°C)	Time (h)	Yield (%)	dr
1	40	2	25	1:1
2	20	16	trace	-

Table 16: Assessing Diastereoselectivity of AMY precursor **210**

We also investigated the diastereoslectivity of the mesityl derivative **221**. Subjected to the optimised reaction conditions, this gave the desired pyrrolidine in 39% and a diastereomeric ratio of 1:1 (**Scheme 80**). Purification was extremely difficult as the product co-eluted with the sulfinamide **197** which was a major side-product. Eventually, an eluent of 5% ethyl acetate in toluene was found to separate the two compounds.

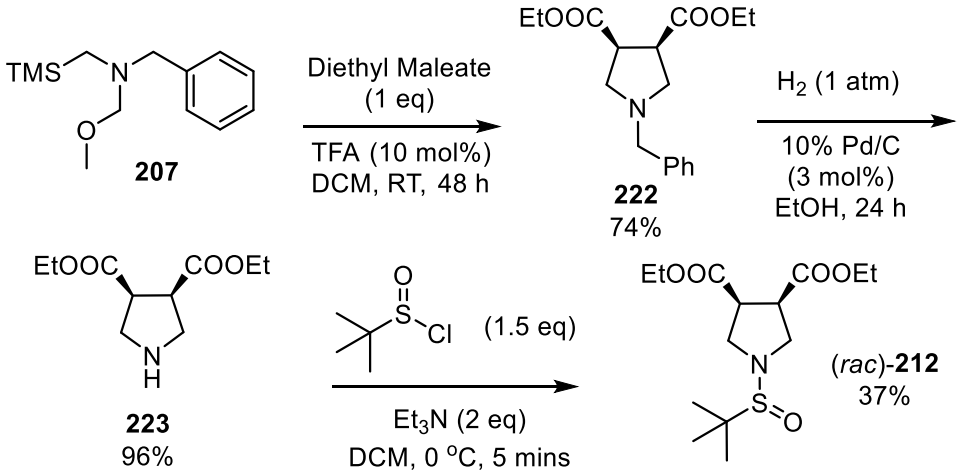


Scheme 80: Assessing diastereoselectivity of AMY precursor **216**

The lack of diastereomeric excess was extremely disappointing. AMY precursor **76** from the literature (**Scheme 78**) gave a diastereomeric ratio of 3:2 and the auxiliaries we had investigated were also large and we therefore expected to see at least some selectivity . We now began to question our assumption that the sulfinyl centre was retaining its chirality through the reaction. Up until this point we did not have access to chiral HPLC so sought help from outside our lab.

Synthesis of Racemic *N*-Sulfinyl AMY precursor in Pursuit of Racemic Standard

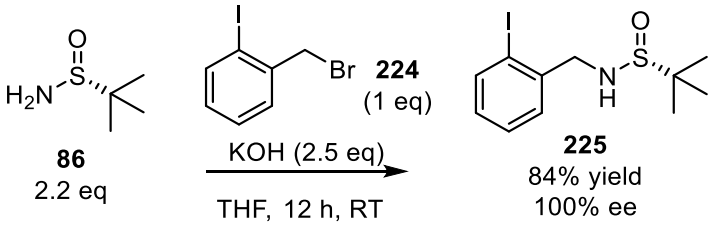
We required a sample of racemic **212** to act as a standard in chiral HPLC. *N*-(Methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (**207**) underwent (3+2) cycloaddition with diethyl maleate in DCM with 10 mol% TFA to give pyrrolidine **222** in 74% yield. Removal of the benzyl protecting group with standard hydrogenation conditions gave pyrrolidine **223** in 96% yield.[110] Racemic **212** was synthesised in 37% by substitution of **223** with tert-butyl sulfinyl chloride. This could now be used as a standard to perform chiral HPLC and investigate whether AMY precursor **210** formed AMYs which retain their stereochemistry undergoing (3+2) cycloadditions.



Scheme 81: Synthesis of racemic **212**

We then separated the two enantiomers of (*rac*)-**212** on a chiral HPLC column and compared to the trace to that of what we thought was (*S)*-**212**. To our surprise, both samples were a 1:1 mixture of enantiomers (See Appendix 1). We believe that the racemisation is happening during the (3+2) reaction and not in the starting material preparation. This is due to previous publications which have performed similar alkylations on sulfinamides and these reactions returned products with 100% enantiomeric excess (**Scheme 82**). From **86**, Qingle and co-workers performed a deprotonation with potassium hydroxide in the presence of alkyl bromide **224**. This yielded the alkylated sulfinamide **225** in 84% and complete stereo-retention.[101] Moreover, our sample of **210** prepared from enantiomerically pure (*S*)-*tert*-butanesulfinamide gave an optical rotation of $[\alpha]_D^{20}$ = + 15.1 providing

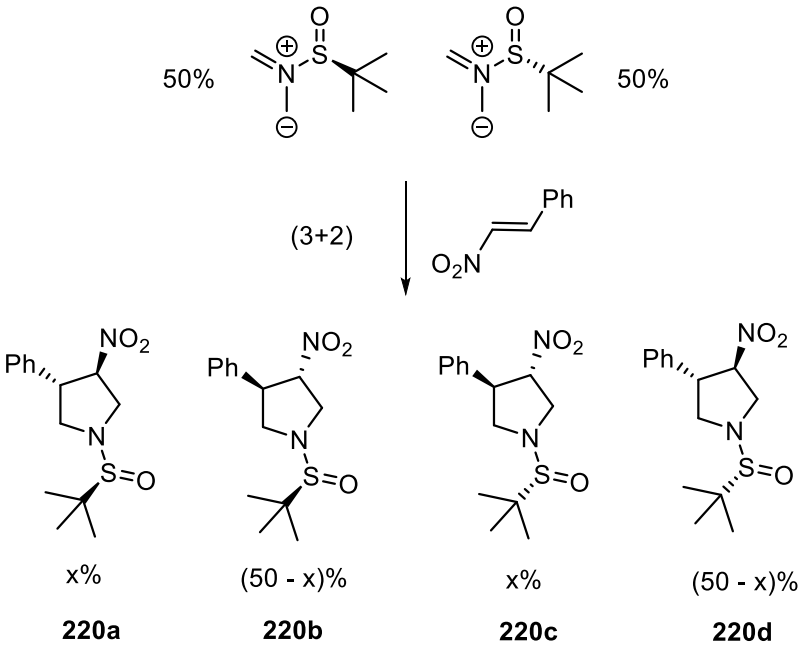
strong evidence that the starting material **210** was not racemic in reaction where we observed 50:50 mixtures by NMR analysis.



Scheme 82: Qingle and co-workers stereo-retentive alkylation of sulfinamides

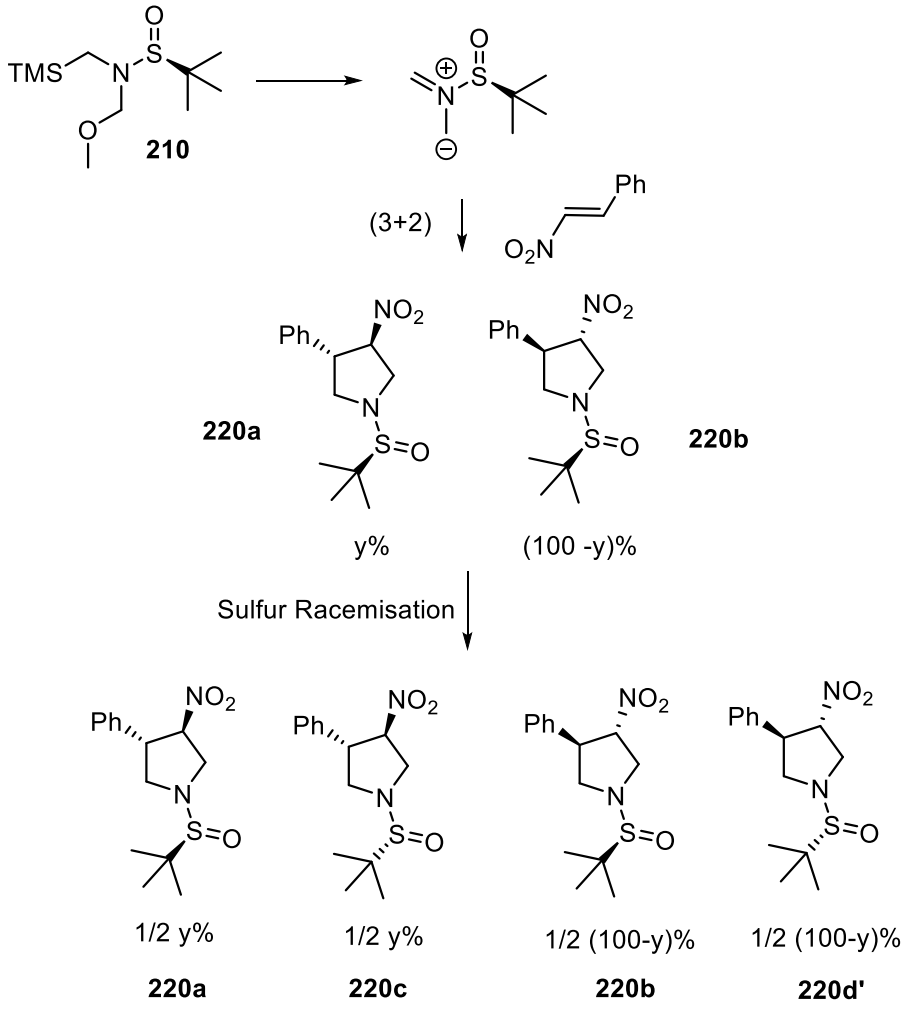
We can definitively say that at some point in the reaction the sulfur atom is racemising as the chiral HPLC separation of **212** (**Table 15**) showed a 50:50 mixture. We have not obtained enough information to draw conclusions on the diastereoselectivity of the (3+2) cycloaddition of *N*-sulfinyl AMYs from **210**, **215** and **216**. However, it is still possible that the (3+2) cycloaddition *N*-sulfinyl AMYs from **210**, **215** and **216** could be highly diastereoselective but the racemisation of the sulfur atom complicates the analysis. We can eliminate one possible scenario (**Scheme 83**) by analysing the observed 50:50 mixture by NMR. A second possible mechanism (**Scheme 84**) could mean that we have a diastereoselective reaction but the racemisation of the sulfur atom is hiding this diastereoselectivity. It is also possible that the sulfur atom is racemising and the (3+2) cycloaddition is not diastereoselective.

We can eliminate the possibility that the sulfur atom is racemised before (3+2) cycloaddition and that the subsequent (3+2) cycloaddition is diastereoselective. We will use the example in **Table 16** as a demonstration. **Scheme 83** depicts the racemic mixture of AMYs which would result if the sulfur atom racemised before the (3+2) cycloaddition. The possible products **220a** and **220c**, are enantiomers and would therefore have the same NMR spectra. **220b** and **220d** are enantiomers and would also have the same NMR spectra but different to **220a** and **220c**. If the (3+2) cycloaddition is diastereoselective then there would not be an equal amount of **220a** and **220b** ie. x ≠ 25. The same is true for **220c** and **220d**, if the (3+2) cycloaddition is diastereoselective there would not be an equal amount of these two products. We would expect the amount of **220a** and **220c** to be the same and the amounts of **220b** and **220d** to be the same. In a scenario where racemisation at sulfur occurs first followed by a diastereoselective (3+2) cycloaddition (x ≠ 25) we would therefore not see a 50:50 mixture by NMR. **220a** and **220c** would comprise of (x + x)% and **220b** and **220d** would comprise of ((50-x)+(50-x))% and if x ≠ 25 then the ratio of **220a** & **220c** : **220b** & **220d** (the distinct pairs by NMR) could not be the observed 50:50 mixture by NMR analysis.



Scheme 83: Scenario in which the sulfur atom racemises followed by a diastereoselective (3+2) cycloaddition.

It is possible that the racemisation at the sulfur atom occurs after the (3+2) cycloaddition and the (3+2) cycloaddition is diastereoselective (**Scheme 84**). If the enantiomeric purity of the sulfur atom is maintained when forming the AMY from **210** and this reacts with the dipolarophile diastereoselectively, this would result in a mixture of **220a** and **220b** where y ≠ 50. Subsequent racemisation of the sulfur atom would result in the ratios illustrated. **220a** and **220b** are enantiomers and they would have the same NMR spectra and their percentage would be 1/2y + ½(100-y) which equals 50%. The same is true for **220c** and **220d** but their spectra would be different to **220a** and **220b**, hence a 50:50 mixture visible by NMR analysis. Future work could establish if this is the scenario which is occurring by removing the sulfinyl group and subjecting the resultant N-H pyrrolidines to chiral HPLC.



Scheme 84: Second Possible mechanism resulting in 50:50 mixture by ^{1}H NMR.

N-Benzyl versus N-Sulfinyl Energy Levels

One possible explanation for the lower yields of *N*-sulfinyl AMYS compared to *N*-benzyl AMYs is the relative energy levels (**Figure 18**). The main orbital interaction in a (3+2) cycloaddition of an AMY with a dipolarophile is between the HOMO of the AMY and the LUMO of the dipolarophile. The electron donating benzyl group raises the energy of the HOMO creating better overlap with the LUMO of the dipolarophile. The electron withdrawing sulfinyl group will lower the energy of the HOMO meaning less efficient overlap with the LUMO of the dipolarophile resulting in a less facile reaction and therefore lower yields.

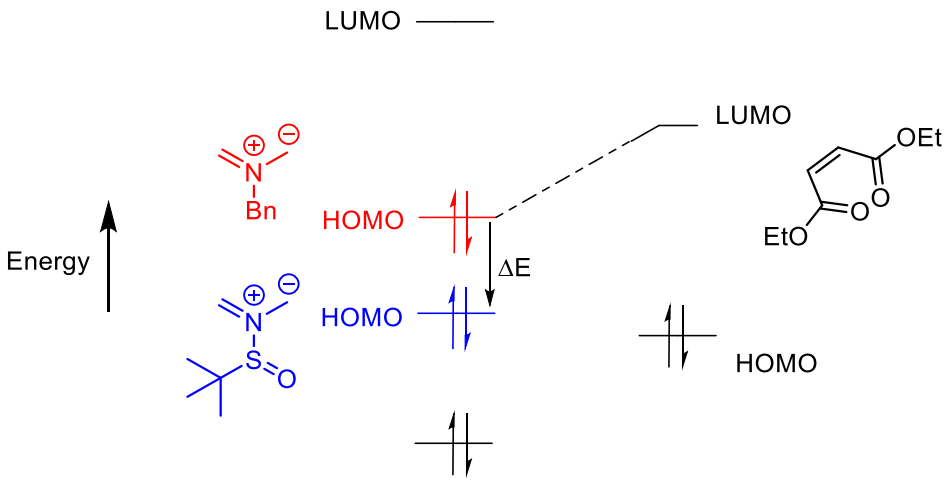
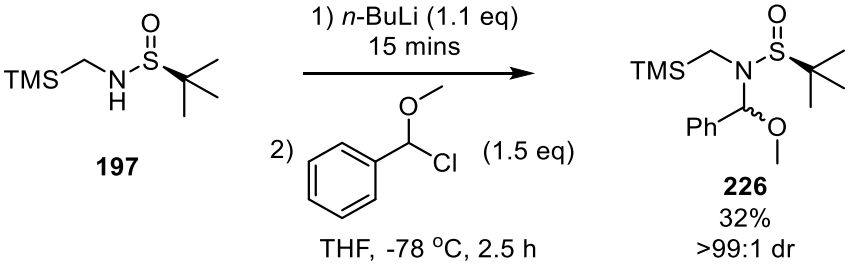


Figure 18: Relative Energy levels of *N*-benzyl AMY versus *N*-sulfinyl AMYs

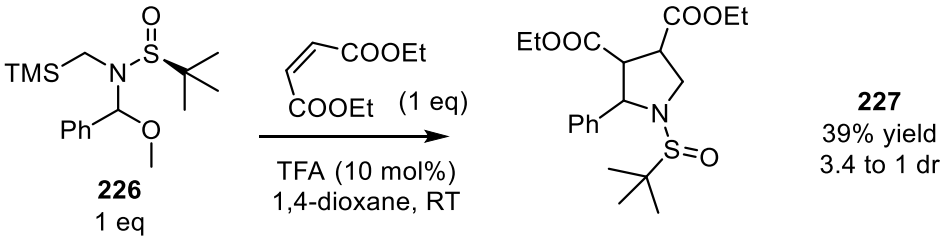
Syn- versus *Anti*-selectivity

Prior to the improved optimisation through increasing the equivalents of AMY precursor (**Table 15**), we had attempted to assess the diastereoselectivity of *N*-sulfinyl AMYs for the 2-position of pyrrolidines. To this end, we synthesised AMY precursor **226** by deprotonation of **197** with *n*BuLi and then adding 1-chloro-1-methoxy toluene as the electrophile which gave the desired product in 32% yield after purification on alumina (**Scheme 85**). Only one diastereomer of **226** was isolated and the crude ^{1}H NMR does not appear to show a second diastereomer, indicating that this reaction is highly diastereoselective. **226** would form the AMY with an appendant phenyl group which after undergoing a (3+2) cycloaddition would afford the 2-phenyl-*N*-sulfinyl pyrrolidines.



Scheme 85: Synthesis of 2-phenyl AMY precursor

We then performed the (3+2) cycloaddition reaction with one equivalent of AMY precursor **226** on one equivalent of diethyl maleate (**Scheme 86**). We believe that this reaction afforded the pyrrolidine **227** in a diatereomeric ratio of 3.4 to 1 and an overall yield of 39% as evident from the mass spectrometry (396.1845 $[M+H]^{+}$) and the crude ^{1}H NMR spectra. However, column chromatography on silica did not the separate the two compounds and full assignment was not possible. Due to the difficulties in assigning relative stereochemistry on 5-memebered heterocycles, we were unable to determine which of the products was the *syn*-product or the *anti*-product, however a ratio of 3.4 to 1 shows that the reaction is quite selective.[111] Future work would focus on isolating each product and obtaining crystal structures to determine absolute stereochemistry.



Scheme 86: Assessing diastereoselectivity of *N*-sulfinyl AMYs for the synthesis of 2-substituted pyrroldidines

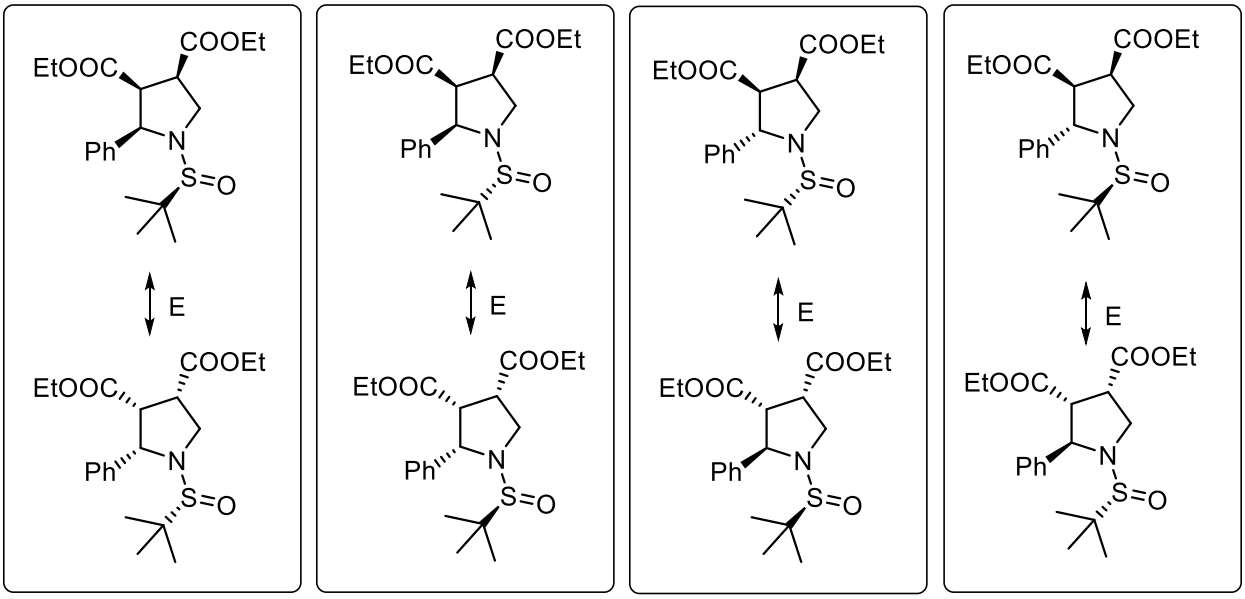


Figure 19: All possible products from phenyl substituted AMY precursors

All possible products from this phenyl substituted AMY precursor have been depicted (**Figure 19**) with the pairs of enantiomers drawn. Fortunately, we were able to pick out the benzylic protons and the coupling constants between the benzylic protons and the 3-positions, which were 7.7 Hz and 7.1 Hz **Figure 20**. This ^{1}H NMR analysis shows that only two of these pairs are present in a 3.4 to 1 ratio (we are assuming pairs due to the earlier discovery that the sulfinyl group racemises). However, we are unable to determine which of these products are present.

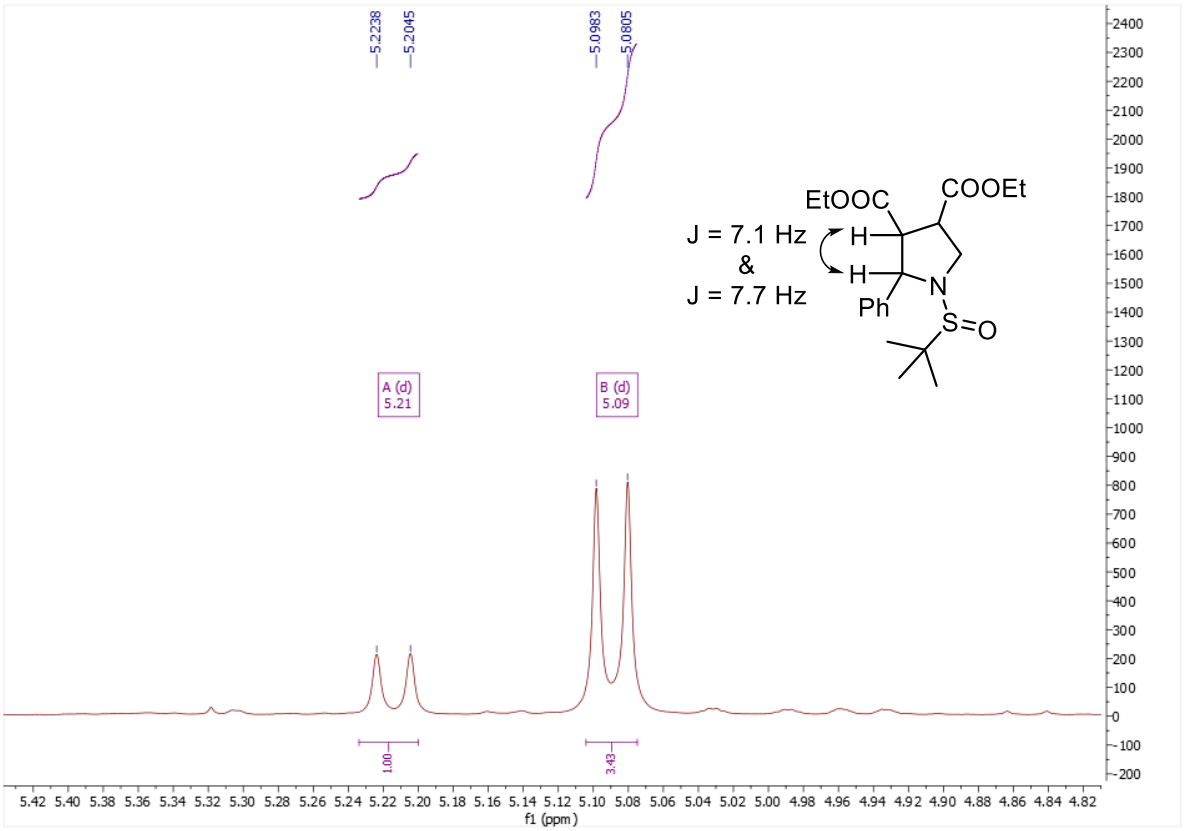
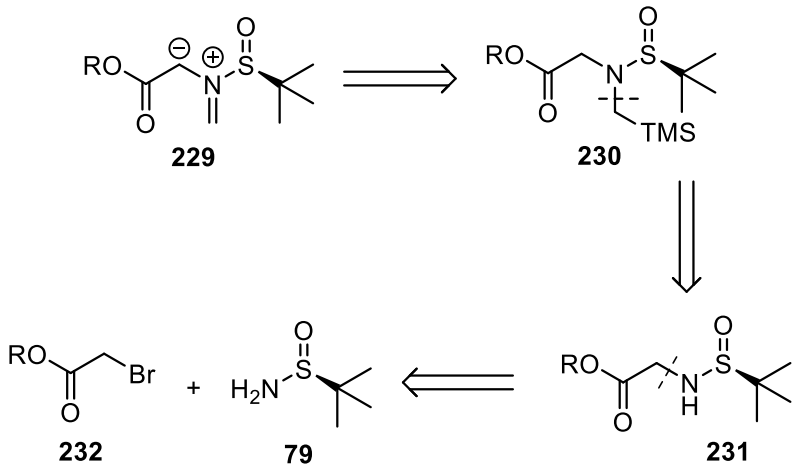


Figure 20: Analysis of Crude ^{1}H NMR of **227** showing ratio of benzylic protons

3. 1,3-Migrations in *N*-Alkylsulfinyl Iminoacetates

Attempts Towards Carbonyl Stabilised AMYs

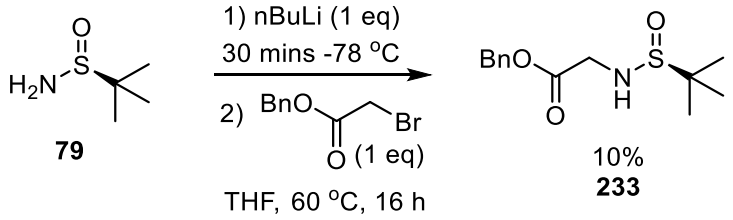
During the course of our efforts to improve yields in the (3+2) cycloaddition of *N*-sulfinyl AMYs we decided to investigate stabilising groups on the AMY. The most widely applied stabilising group on AMYs is the α-ester. We therefore set out to incorporate this into the AMY to give **229** which could be formed from AMY precursor **230** whose retrosynthesis is described in **Scheme 87**. **230** could be accessed from installing the methyltrimethylsilane group onto **231** *via* a nucleophilic substitution reaction and which itself is accessible from, also by a nucleophilic substitution reaction of *tert*-butane sulfinamide (**79**) and a 2-bromo acetate derivative **232**.



Scheme 87: Retrosynthesis for stabilised AMYs **229** via sequential S_N2 reactions

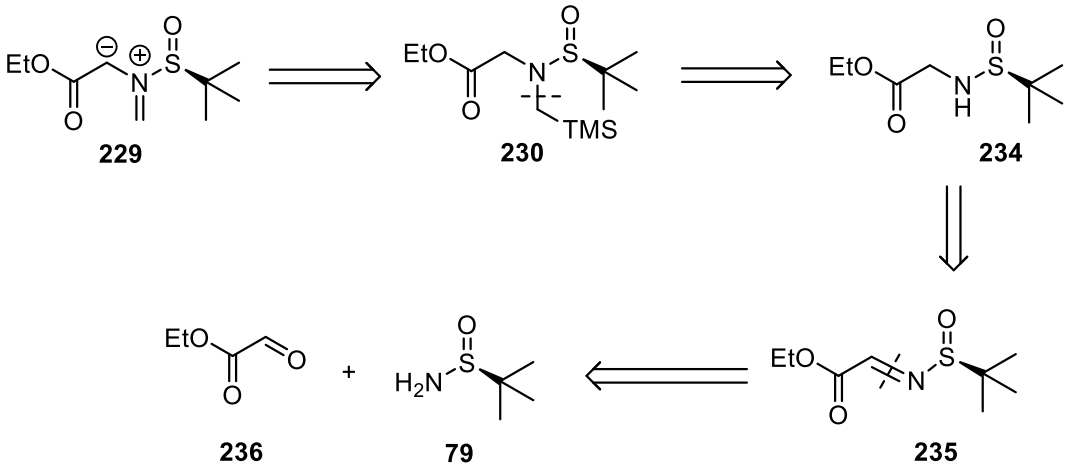
We repurposed the chemistry we had developed in previous work (**Scheme 76**) for the installation of the methyltrimethylsilane group to give **213** and **214**. The first step remained the same, deprotonation of (*S*)-t*ert*-butane sulfinamide (**79**) with nBuLi. The electrophile was then replaced with benzyl 2-bromoacetate (**232**) and the reaction duration and temperature were retained. The reaction gave the desired product **233** but the yield was unsatisafactory at 10% (**Scheme 88**).

It is possible that this reduction in yield, when compared to the previous example, is due to competitive substitution on the ester group.



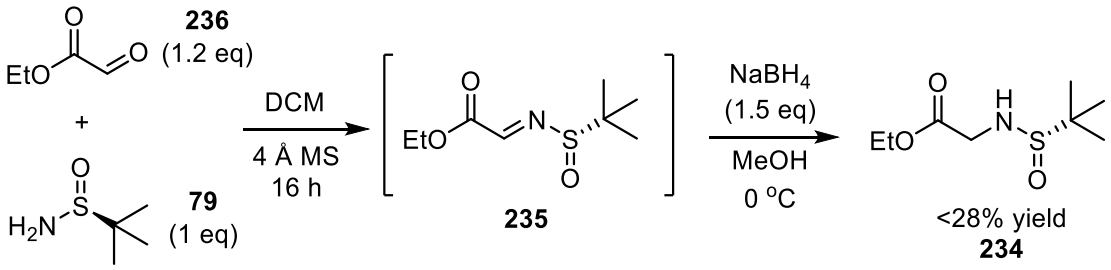
Scheme 88: S_N2 attempt at installing ester moiety

Due to the low yield of the first step we altered the retrosynthesis to remove the first S_N2 reaction and replace it with more established sulfinamide condensation chemistry. The revised retrosynthesis is described in **Scheme 89**. Stabilised AMY **229** is the same, as well as the precursor **230**. The AMY precursor would be accessed by an S_N2 reaction on ethyl (*S*)-(*tert*-butylsulfinyl)glycinate (**234**). **234** Would be synthesised by a reduction of *N*-*tert*-butylsulfinyl iminoacetate (**235**) and the synthesis of **235** is a known literature preparation, a condensation between ethyl glyoxalate (**236**) and (*S*)-*tert*-butane sulfinamide (**79**).[91]



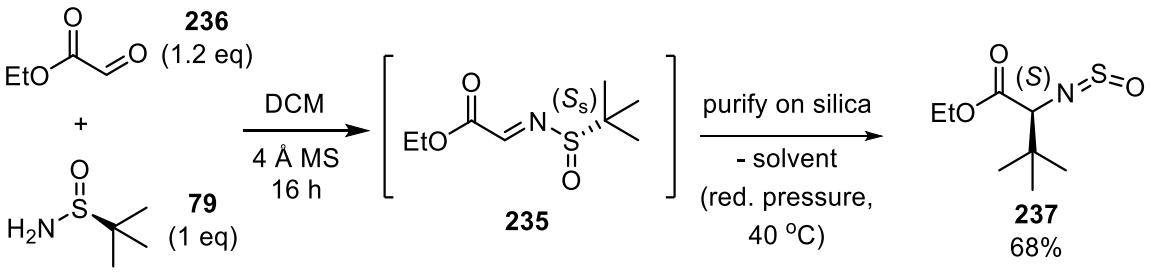
Scheme 89: Retrosynthesis of ester-stabilised AMY

We first performed the condensation of ethyl glyoxylate **236** and **79** followed by a telescoped reduction with sodium borohydride of imine **235** in the hope of avoiding purification by chromatography. This gave the desired glycinate **234**. However, the isolated yield was low at 28% and the purification was difficult failing to give a clean sample. It was therefore decided to purify *N*-sulfinyl imine **235** before performing the reduction in the hope of an improved yield and more importantly, obtaining a pure sample of **234**.



Scheme 90: Attempts at telescoping condensation and reduction to glycinate **234**

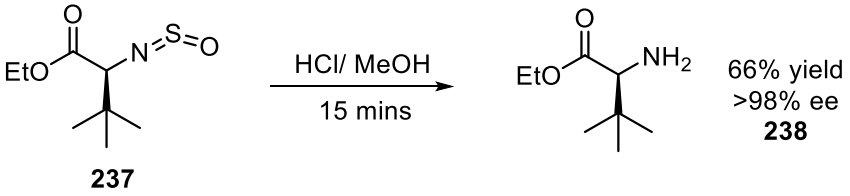
The condensation was performed as described in the literature[91] and the mass obtained after purification by column chromatography equates to a yield of 68%. The imine is clearly visible in the ^{1}H NMR spectra. The crude product and the R_f value of the isolated fractions after column chromatography are the same as the product in the crude mixture before column chromatography. The imine is therefore still present after purification, however, after removing the solvent under reduced pressure at 40 °C, imine **235** is no longer present on TLC chromatography. The NMR analysis confirmed that imine **235** has completely rearranged to give *N*-sulfinyl amine **237** (**Scheme 91**)**.**



Scheme 91: 1,3-Migration of *tert*-butyl group

Acid catalysed methanolysis is a reliable method of sulfinyl-protecting group removal and when applied to sulfinyl amine **237** yields the corresponding amine, (*S*)-tert-leucine ethyl ester (**238**), in 68%

yield and >98% enantiomeric excess (**Scheme 92**) (See Appendix 2). Further evidence of the structure of **237** was found in the crude reaction mixture as dimethyl sulfite was detected in the ^{1}H NMR spectra ($CDCl_3$, δ 3.64 ppm, s). Hydrolysis of the ester would allow access to (*S*)-*tert*-leucine, an extremely valuable and important chemical with applications in ligand synthesis and protein synthesis. By switching (*S*)-*tert*-butane sulfinamide for (*R*)-*tert*-butane sulfinamide the (*R*)-tert-leucine ethyl ester was also synthesised in comparable yields and comparable enantiomeric excess.



Scheme 92: Removal of sulfinyl group to give (*S*)-*tert*-leucine ethyl ester

Stereochemistry and Mechanism

It is possible to rationalise the likely mechanism by considering the stereochemical relationship between starting materials and products and through chemical logic. The main considerations are, is the reaction concerted, ionic or radical? In the case of the latter two possibilities, is the reaction inter- or intramolecular? Relevant to all of the mechanisms considered is the configuration adopted by *N*-sulfinyl aldimines due to the favourable interaction between the sulfinyl oxygen and the imine hydrogen (**Figure 21**).[112]

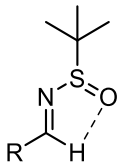
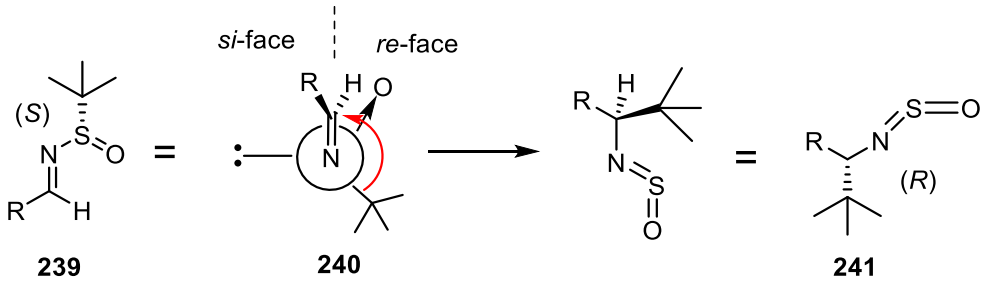


Figure 21: Configuration adopted by *N*-sulfinyl aldimines

The first mechanism we will consider is the concerted mechanism (**Scheme 93**). Beginning with *N*-sulfinyl aldimine **239,** the transition state would be **240** due to the favourable interaction between in the oxygen atom of the sulfinyl and the hydrogen atom of the imine. A concerted mechanism would

see the *tert*-butyl group move across the *re*-face and onto the imine carbon, depicted by the curly arrow in red. This would result in the new carbon stereocentre created being (*R*) (**241**), the opposite of what is observed in the products. Moreover, movement of the *tert*-butyl group would require overlap between the S-C σ-bond and the N-C π*-orbital which appears to be impossible given the rigidity of the imine bond. For these reasons it was deemed that a concerted mechanism is extremely unlikely.



Scheme 93: Possible concerted mechanism

When considering ionic mechanisms (**Figure 22**), only one ionic breakage of the sulfur-carbon bond makes chemical logic. Breaking the bond to give **242** and **243** places a carbocation in the α-position of a carbonyl and a *tert*-butyl anion, an extremely reactive species making the splitting of the bond in this fashion extremely unlikely. Breaking the sulfur-carbon bond ionically to give **244** and **245** is much more likely.

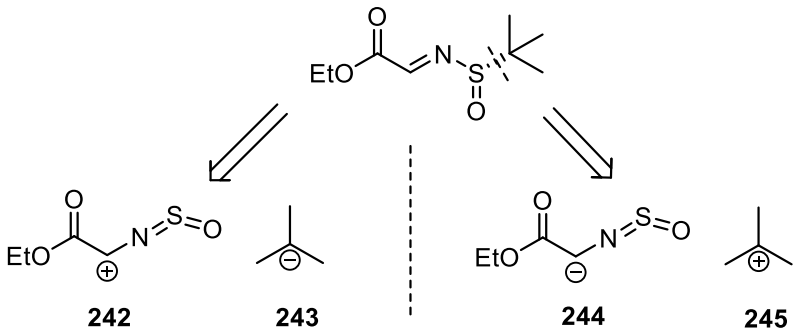


Figure 22: Possible Ionic lysis of the S-C bond

However, species **244** can be drawn as resonance form **246** and the true nature of the species is likely to be closer to **246** than **244.** In this mechanistic scenario, the stereochemical information would have been lost due to the formation of a sp^2 carbon. When **245** and **246** recombined to give the product, a racemic mixture would be resultant. As we see >98% ee in our reaction, this cannot be the mechanism occurring.

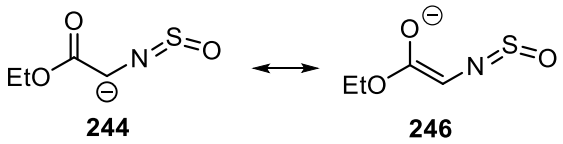
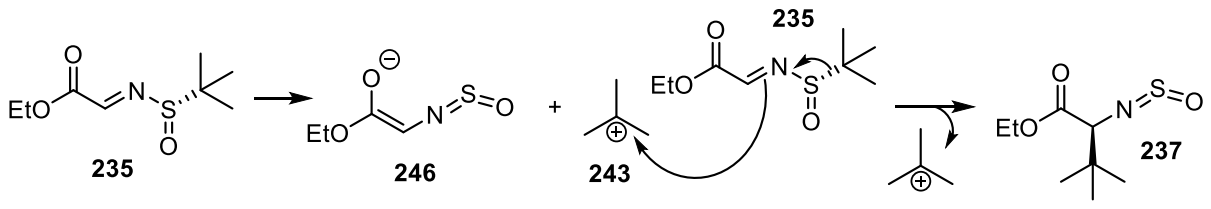


Figure 23: The two resonance forms of the anionic species

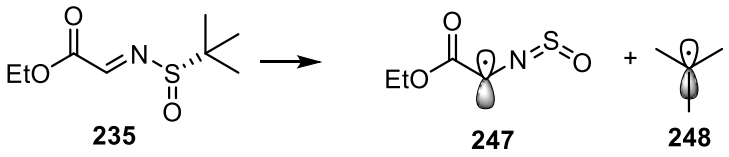
An intermolecular mechanism (chain mechanism) would possibly allow retention of the stereochemical information (**Scheme 94**). Imine **235** would break into *tert*-butyl cation **243** and the anionic species **246**. **243** would then go on to react with a second equivalent of imine **235** to give the product and release the *tert*-butyl cation again, propagating the reaction. The last step of this mechanism is when this argument begins to seem unlikely. The last step involves a carbocation attacking a carbon atom which possesses a partially positively charge due to the polarisation of the imine bond and these species would therefore electronically repel each other, making this intermolecular ionic mechanism unlikely.



Scheme 94: Ionic chain mechanism

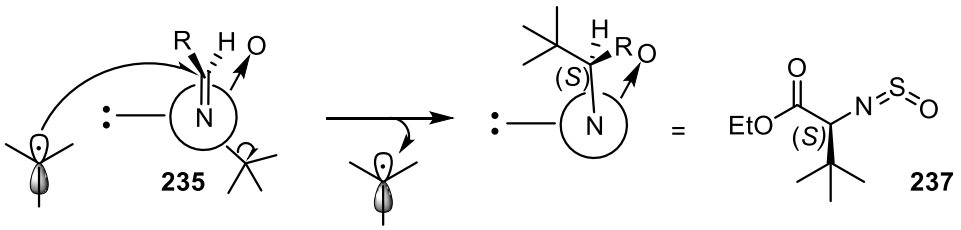
The third possible mode of bond breakage is a radical homolysis of the sulfur-carbon bond (**Scheme 95**). Both radicals formed are stabilised, **247** possesses a radical in the α-position of a carbonyl and the *tert*-butyl radical (**248**) is stabilised by hyperconjugation with the C-H σ-bonds. When considering

intra-molecular and inter-molecular, intramolecular radical reactions have the same problem as the previously discounted ionic intramolecular mechanism. Radicals easily interconvert and the stereochemical information would been lost if the reaction was a radical homolyses followed by a recombination.



Scheme 95: Radical breakage of the S-C bond

This leaves the radical chain mechanism for consideration (**Scheme 96**). The open transition state is the acting transition state for 1,2-radical additions to *N*-sulfinyl imines.[85] **235** is depicted as a Newman projection with the *tert*-butyl radical adding to the *N*-sulfinyl imine carbon, releasing the *tert*-butyl on the sulfur therefore propagating the mechanism. This would result in a new (*S*)-carbon chiral centre and the outcome we observe when using (*S*)-**235** is in fact (*S*)-**237.**



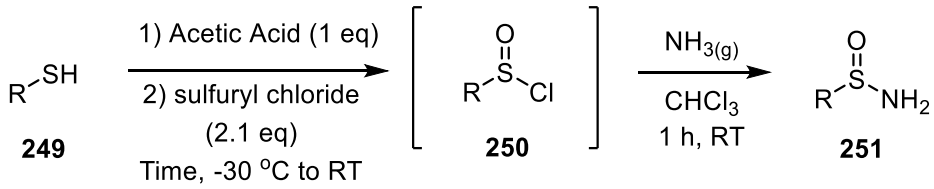
Scheme 96: Radical chain, open transition state mechanism

This mechanism is similar to that reported by Wei and co-workers (**Scheme 56**) which contains the same propagation step but it is initiated by the organozinc reagent. At this point, we do not have a suggestion for the initiation of the reaction (**Scheme 91**) backed by experimental observation.

This incredible serendipitous discovery directed a lot of attention into investigating whether different groups would migrate and whether different electron withdrawing groups could be employed.

Sulfinamide Syntheses for Application in 1,3-Migration Reactions

Previous projects in the Stockman group had used a general method for the synthesis of sulfinyl chlorides which we attempted to apply to the substrates we required.[113] Beginning from thiols **249,** reacting with 1 equivalent of acetic acid and 2.1 equivalents of sulfuryl chloride at -30 °C gave access to the benzyl and cyclohexyl sulfinyl chlorides **250** in 3 hours (**Table 17**). 1-Adamantylthiol did not react under these conditions to afford the corresponding sulfinyl chloride and only the starting material was observed by TLC. The benzyl and cyclohexyl sulfinyl chloride intermediates **250** were not isolated but were dissolved in chloroform and ammonia was bubbled through the solution for 30 minutes which afforded the corresponding sulfinamides **251** in 35% and 58% yield respectively.



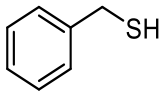
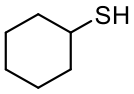
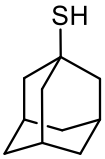
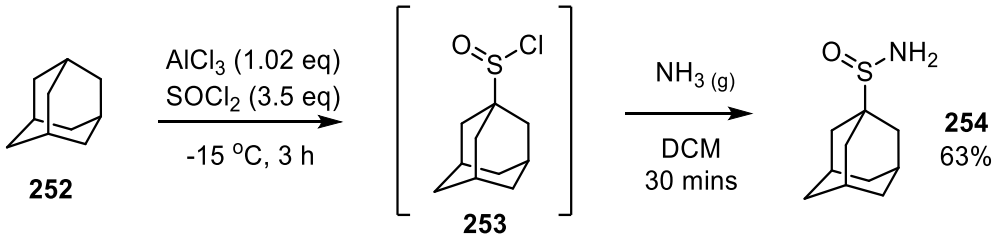
R	Time	Yield 251 (%)
	3	35
	3	58
	24	0

Table 17: Converting thiols to sulfinamides *via* sulfinyl chlorides

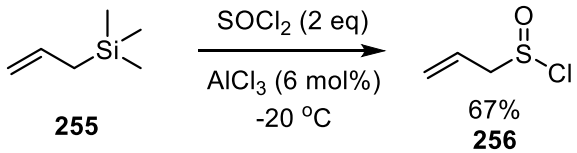
We were extremely interested in the 1-adamantyl sulfinamide substrate as this would also produce a tertiary migrating group. We searched the literature and found a preparation of 1-adamantyl sulfinyl chloride from adamantane which we thought could be converted into the corresponding sulfinamide using the conditions used for the previous examples.[114] Adamantane (**252**) was successfully converted

into sulfinyl chloride **253** using this method (**Scheme 97**). Dissolving **253** in DCM and bubbling ammonia through at room temperature subsequently yielded the desired 1-adamantyl sulfinamide (**254**) in 63% yield. Notably, there is no way of monitoring the progress of the first step of the preparation. We therefore had to experiment with duration and found lowering the duration of the first step to 2 hours resulted in a lower yield of 46% of the sulfinamide **254**.



Scheme 97: Synthesis of 1-adamantyl sulfinamide

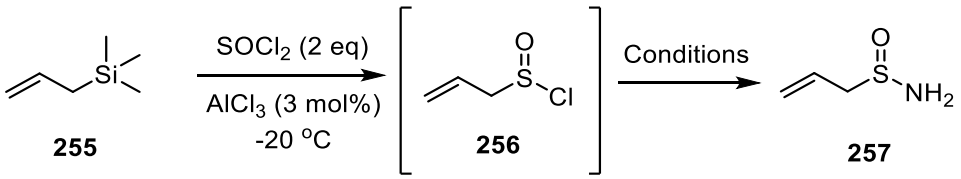
The lower molecular weight targets that we wished to pursue, allyl sulfinamide and cyclopropyl sulfinamide, could possibly be made from the corresponding thiols but these thiols cause extreme stench and it was deemed prudent to investigate other syntheses. It is also important to mention that to the best of our knowledge, no synthesis of these two molecules has been reported before. The synthesis of allyl sulfinyl chloride **256** from allyl trimethylsilane (**255**) is a robust reaction (**Scheme 98**) which had been previously performed in our lab.[115] We rationalised it would be possible to convert sulfinyl chloride **255** into the corresponding sulfinamide by a simple substitution with ammonia or an ammonia equivalent.



Scheme 98: Synthesis of allyl sulfinyl chloride from allyl trimethylsilane

Conversion from **255** to **256** was deemed to have worked well from the crude ^{1}H NMR and taken into the next reactions without purification. The first conditions investigated (**Table 18**, **Entry 1**) were taken

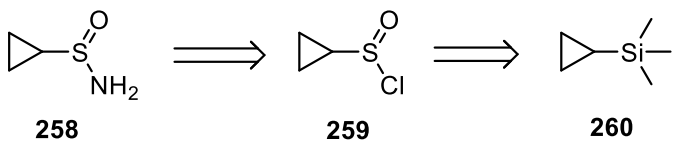
from the previous successful conversions from sulfinyl chlorides to sulfinamides. These conditions did not yield the desired product but completely consumed the starting material. We hypothesised that the double bond was moving to come into conjugation with the sulfinyl group, which could be made possible due to the relative acidity of the proton in the α-position of the sulfur. We then hypothesised that ammonia was adding twice as it was in excess, once into the sulfinyl chloride and one 1,4 addition to the newly rearranged double bond. We therefore attempted more controlled conditions (**Entry 2**). One equivalent of LiHMDS at low temperature was added to added to the sulfinyl chloride (**256**). This also did not yield the desired product **257** and consumed the starting material to give an unidentified mixture of products. Notably there were no alkene peaks in the crude NMR which shows its removal.



Entry	Conditions	Yield (%)
1	$NH_{3\,(g)}$, DCM	0
2	LiHMDS (1 eq), THF, -40 °C	0

Table 18: Conditions attempted for conversion of allyl sulfinyl chloride to allyl sulfinamide

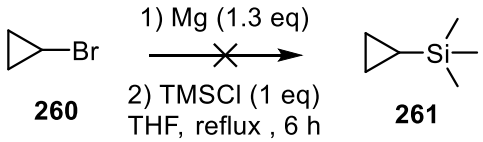
In the interest of time we decided to try and progress in other areas and abandoned the synthesis of allyl sulfinamide **257**. We next attempted to synthesise cyclopropyl sulfinamide (**258**) *via* cyclopropyl sulfinyl chloride (**259**) from cyclopropyl trimethylsilane **260** (**Scheme 99**).



Scheme 99: Retrosynthesis of cyclopropyl sulfinamide

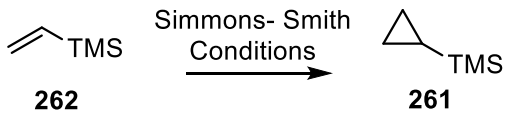
This synthesis would avoid the requirement to synthesise the corresponding cyclopropyl thiol and would be an improved synthesis of cyclopropyl sulfinyl chloride **259**, avoiding the stench of cyclopropyl

thiol.[116] We first attempted the synthesis of **260** from commercially available cyclopropyl iodide **261** (**Scheme 100**). Preparing the Grignard was assumed to be successful due to the heat evolved and the consumption of the magnesium turnings. Unfortunately, cyclopropyl trimethylsilane **261** could not be seen by mass spectrometry due to its low molecular weight and nothing was observed by TLC due to either the low molecular weight meaning **261** evaporated off the TLC plate or perhaps due to the lack of oxidizable or reactive atoms resulting in no spots being observed in either a potassium permanganate of vanillin dip. Despite the lack of evidence of product formation, the crude mixture was distilled, but no product was recovered from the reaction.



Scheme 100: Preparing cyclopropyl Grignard reagent for reaction with chlorotrimethylsilane

We proposed an alternative route to **261**, which was conversion of vinyl trimethylsilane (**262**) to the desired product by Simmons-Smith conditions. The first conditions attempted (**Table 19**, **Entry 1**), employed diethyl zinc as the zinc source.[117] Again, we were unable to detect the product by mass spectrometry or TLC and decided to distil the crude mixture but no product was obtained. A modification was also attempted (**Entry 2**) which used zinc in place of diethyl zinc but again no product was found after distillation.



262 **261**

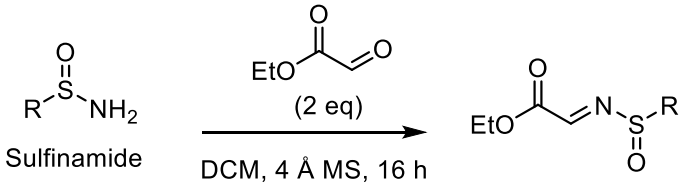
Entry	Conditions	Yield (%)
1	Diethyl Zinc (1 eq) I_2CH_2 (1.5 eq) Toluene, 60 °C	0
2	Zn (2.6 eq) Cu(I)Cl (2.6 eq) I_2CH_2 (1.3 eq) Et_2O, reflux	0

Table 19: Simmons Smith Reactions on vinyl trimethylsilane

We decided to abandon the synthesis of cyclopropyl sulfinamide **258** and investigate whether we could synthesise imino acetates from the sulfinamides we had synthesised.

Synthesis of ethyl-2-(sulfinyl)imino)acetates

1-Adamantyl sulfinamide (**254**), cyclohexyl sulfinamide (**263**) and benzyl sulfinamide (**264**) were condensed onto ethyl glyoxylate to give the corresponding imines in good yields. Only one (*E*)/(*Z*) isomer was observed for each sulfinamide which we assume is the (*E*)-isomer due to the known favourable interaction between the aldimine hydrogen and the sulfinyl oxygen (**Figure 21**).



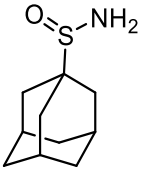
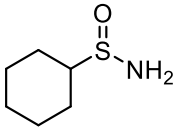
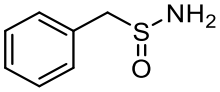
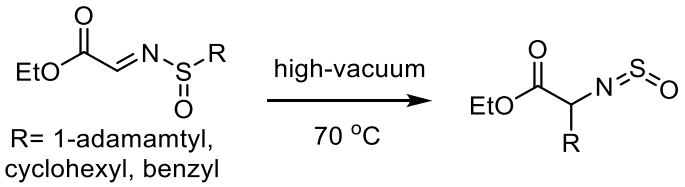
Sulfinamide	Yield (%)
 **254**	72
 **263**	65
 **264**	57

Table 20: Condensation of ethyl glyoxylate and various sulfinamides

265, **266** and **267** were purified but none of the substrates rearranged to give the analogous products as observed in **Scheme 91**. We hoped by increasing the magnitude of the conditions we could push **265**, **266** and **267** to arrange to the corresponding sulfinyl amines. To this end, we placed the samples under high vacuum on a Schlenk line while heating the sample to 70 °C.



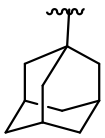
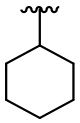
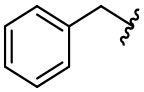
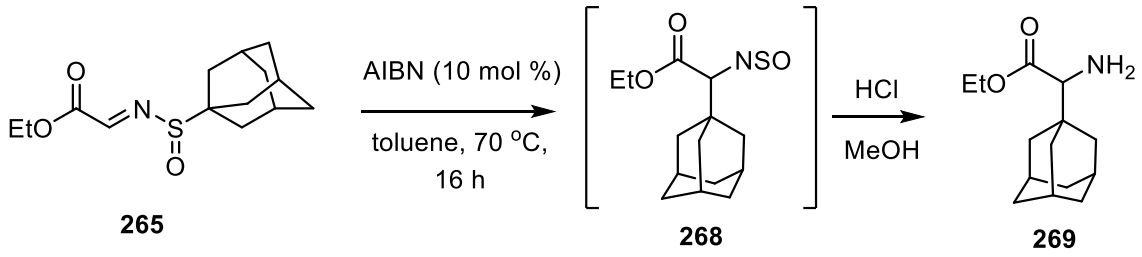
R	Yield
 **265**	0
 **266**	trace
 **267**	0

Table 21: Attempts at rearranging ethyl-2-(sulfinyl)imino)acetates to sulfinyl amines

The 1-adamantyl derivative **265** and the benzyl derivative **267** did not result in any rearrangement under these conditions, however the cyclohexyl derivative **266** did show what appears to be a trace of product by the emergence of a doublet at 5.15 ppm in the ^{1}H NMR spectra which would correspond to the proton in the α-position to the nitrogen. This result does not correspond with the expected stability of the respective radicals. We would expect the 1-adamantyl radical to be more stable that the cyclohexyl on account of them being tertiary and secondary respectively and comparing to the established radical stability scale where stability of alkyl radicals is, tertiary > secondary > primary.[118] The creation of a tertiary radical would be more thermodynamically favourable than a secondary and ejection of the 1-adamantyl would therefore be expected to be more facile than the cyclohexyl.

AIBN Initiated 1,3-Rearrangements

We hypothesised that the 1,3 rearrangements which had not progressed by the removal of oxygen by high vacuum and elevated temperature (**Table 21**) could be initiated by a chemical initiator. **265** was placed in a Schlenk flask with 10 mol% AIBN in toluene and the oxygen was removed by freeze-pump-thaw cycles (**Scheme 101**). Starting material **265** was completely consumed in the reaction but due to the perceived complications involved with purification of the sulfinyl amine **268,** we did not attempt isolation, but we reacted the crude mixture with HCl to remove the sulfinyl group. After column chromatography we isolated the 1-adamantyl glycine ethyl ester **269** in 29% yield.



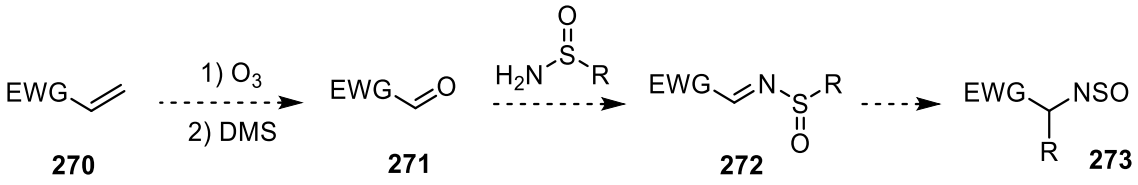
265 **268** **269**

Scheme 101: Synthesis of 1-adamantyl glycine ethyl ester

We attempted the same reaction on the cyclohexyl analogue **266**. The reaction consumed the starting material but gave an extremely complicated reaction mixture (9 spots by TLC) and there was no evidence of the sulfinyl amine by mass spectrometry or ^{1}H NMR spectrum**.** The result in **Scheme 101** further strengthened our argument that the mechanism was in fact the radical chain mechanism we had proposed in **Scheme 96**.

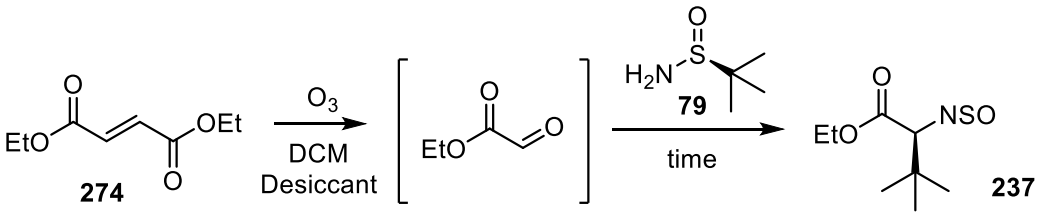
General Method from alkenes

We were interested in varying the electron withdrawing group in the substrates. We hoped to develop a general method, beginning from available alkenes (**270**) (**Scheme 102**). Ozonolysis followed by quenching with dimethyl sulfide would give the corresponding aldehydes **271.** We believed this intermediate would be unstable and would therefore aim to avoid isolation by condensing the crude reaction mixture with sulfinamides to give sulfinimines **272** which would then undergo rearrangement to give sulfinyl amines **272**.



Scheme 102: Proposed methodology for alternating electron withdrawing group

We undertook a short optimisation on diethyl fumarate (**274**) with the main aim of finding an alternative desiccant due to difficulties we encountered when removing molecular sieves. We began with molecular sieves and 1 equivalent (**Table 22, Entry 1**) and 1.5 equivalents of diethyl fumarate (**Entry 2**). Ozonolysis followed by condensation with *tert*-butyl sulfinamide (**79**) gave the desired product **237** in 66% and 78% respectively.



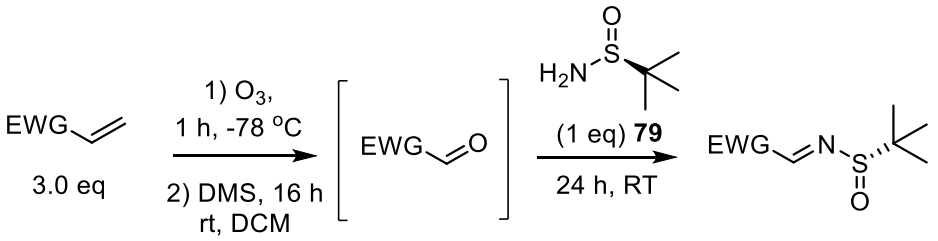
Entry	Diethyl Fumarate (Eq)	Desiccant	Time (h)	Yield (%)
1	1	4 Å MS	48	66
2	1.5	4 Å MS	48	78
3	1.5	silica	48	28
4	1.5	$MgSO_4$	48	59

Table 22: Optimisation of telescoping ozonolysis and condensation

We then investigated silica and $MgSO_4$ as these would be much easier to remove from the reaction mixture. Silica (**Entry 3**) gave a significantly reduced yield of 28% and $MgSO_4$ (**Entry 4**) gave a reduced yield of 59% but can still be considered as acceptable and should be an option if this chemistry is scaled-up. However, when exploring the scope of this chemistry we opted to stay with molecular sieves as this gave the best results. The entries above all showed the sulfinyl imine in the crude ^1H NMR spectra but rearranged to the sulfinyl amine (**237**) after purification and removal of solvent under reduced pressure and 40 °C.

Investigating Electron Withdrawing Groups

We then investigated different electron withdrawing groups by subjecting them to the optimised conditions established above. Phenyl vinyl sulfoxide (**Table 23**, **Entry 1**) was ozonised and then condensed with *tert*-butyl sulfinamide (**79**).



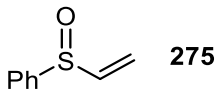
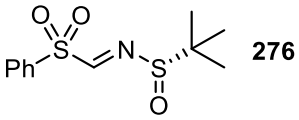
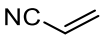
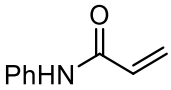
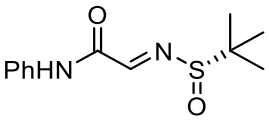
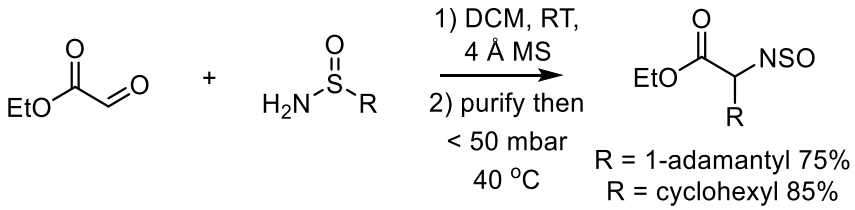
Entry	Alkene	Product	Yield (%)
1	 **275**	 **276**	trace
2	 **277**	No Product	0
3	 **278**	 **279**	14

Table 23: Alkenes possessing electron withdrawing groups undergoing ozonolysis and condensation with *tert*-butane sulfinamide

From phenyl vinyl sulfoxide (**275**) the sulfoxide seemed to have oxidised to the sulfone from the ozonolysis. The only product detected was the sulfone **276** and was only visible by mass spectrometry but no sample could be isolated. Acrylonitrile (**277**) (**Entry 2**) when put through the same conditions did not yield any product. Phenyl acrylamide (**278**) (**Entry 3**) successfully gave the imine analogue (**279**) in 14% yield but after purification did not rearrange to give the sulfinyl amine. These experiments show that telescoping the reaction for different electron withdrawing alkenes does not work well. An alternative method of preparing the sulfinyl imines bearing alternative electron withdrawing groups would be required.

Expansion of Substrate Scope without Initiators

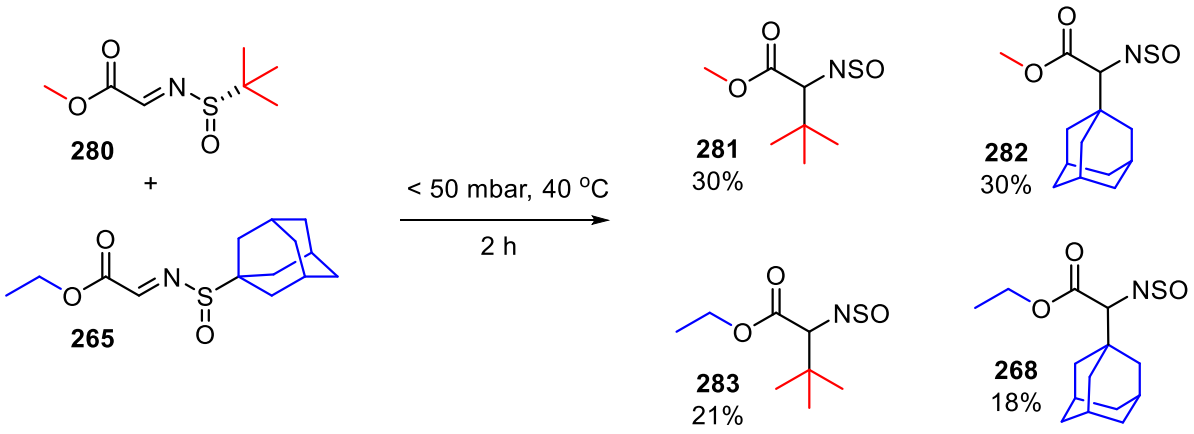
Within our group, Oliver Goodrich later discovered that the 1-adamantyl sulfinyl imine **265** and cyclohexyl sulfinyl imine **266** can be rearranged to give sulfinyl amines when purified by column chromatography. A lower polarity eluent was the important change (10 % ethyl acetate in petrol compared to 20% ethyl acetate in petrol being used previously) which was then placed under reduced pressure for 2 hours and 40 °C (**Scheme 103**). This was achieved on a rotary evaporator.



Scheme 103: Work performed in group on various sulfinamide substrates

1,3 Migration Mechanistic Study

The expansion of the substrate scope opened opportunities to investigate the mechanism of the 1,3 migration. We had previously rationalised that the reaction was a radical chain mechanism (**Scheme 96**). We separately synthesised sulfinyl imine **280** and **265**. We purified them and before removing the solvent we combined them in a single round bottomed flask. The solvent was removed at 50 mbar and 40 °C. If the mechanism is intramolecular, we would expect to see only the two homo-products **281** and **268**. We knew from the isolation of **283** and **268** in previous experiments that the protons in the α-position of the nitrogen had chemical shifts of 4.93 ppm and 4.81 ppm respectively. In the crude ^{1}H NMR we would therefore expect to see two singlets around these chemical shifts and if the reaction was intramolecular, we would not see **283** at 4.93 ppm as this would be an intermolecular product. If the reaction was intermolecular, we would see 4 singlets in this region and both **283** and **268** would be visible.



Scheme 104: 1,3 Migration crossover experiment

We did find 4 peaks in this region of the ^{1}H NMR spectra, 4.97 ppm, 4.93 ppm (**283**), 4.85 ppm and 4.81 ppm (**268**), which integrated to a ratio of 1 to 0.71 to 1 to 0.61 respectively. Assuming the two unidentified products are **281** and **282**, we can attribute these to be 30% each of the mixture.

In mass spectrometry, the sulfinyl imines lose the sulfinyl group and appear as the NH_3^+ adducts. When running mass spectrometry of the mixture of **281**, **282**, **283**, and **268** we would therefore expect to see the adducts depicted in (**Figure 24**). We did see all four of these adducts in relatively equal intensity. The result of this experiment is extremely strong evidence that the reaction is an intermolecular mechanism.

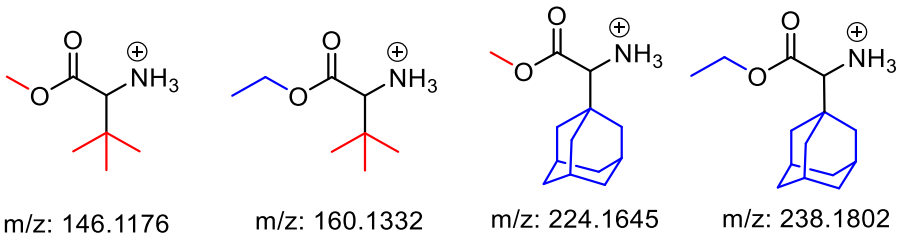


Figure 24: amino acid ethyl ester ions expected in mass spectrometry

Experiments which attempt to establish how this reaction is initiated have not yet been carried out and should be conducted. Future work should be performed to establish which groups will migrate in this reaction as the discovery that cyclohexyl groups migrate suggests that a wide range of α-amino acids with secondary R-groups could be synthesised. It would be possible to perform these reactions which begin from the enantiomerically pure α-iminoesters in order to assess the stereoselectivity of these different R-groups.

General Conclusion

Photoredox attempts at generating AMYs from (*S*)-2-methyl-*N*,*N*-bis((trimethylsilyl)methyl)propane-2-sulfinamide (**194**) did not achieve the desired results. Oxidation by the photocatalyst led to formation of a *tert*-butyl sulfinyl radical which underwent radical addition to the dipolarophile (diethyl fumarate) to give the unstable sulfoxide product **198**. The high oxidation potential of **194** required the use of highly oxidising photoredox catalysts which limited the investigable conditions to acetonitrile as the solvent as this is the only solvent that would not be oxidised.

Acid catalysed attempts successfully led to the synthesis of five new pyrrolidines in moderate to good yields which possessed *N*-sulfinyl moieties. This demonstrates AMYs possessing *N*-sulfinyl groups can be formed and react in the desired (3+2) cycloaddition although less efficiently that the electron rich *N*-benzyl analogue. This reaction appears to be concerted as NMR analysis showed different products resulting from (3+2) cycloaddition reaction with the (*E*)- and (*Z*)-alkenes, diethyl fumarate and diethyl maleate. Through the work we conducted, our hypothesis that *N*-sulfinyl groups could control the stereochemistry in the 3- and 4-positions of pyrrolidines was not be proven or disproven. The method for AMY generation (catalytic TFA in 1,4-dioxane) led to racemisation of the sulfinyl group resulting in an apparent 1:1 mixture by NMR analysis. We demonstrated this does not necessarily mean that the (3+2) cycloaddition reaction is not diastereoselective. To prove whether this a diastereoselective reaction a method of generating *N*-sulfinyl AMYs without racemisation of the sulfur would need to be discovered, or, removal of the *N*-sulfinyl groups from the products would need to be performed and then chiral HPLC performed to assess the enantiomeric excess of the resultant pyrrolidine.

Through our attempts to increase yields of our (3+2) cycloaddition reactions, we synthesised (*S*)- and (*R*)-ethyl (*E*)-2-((*tert*-butylsulfinyl)imino)acetate (**235**) with the aim of synthesising *N*-sulfinyl AMYs bearing carbonyl stabilising groups. We discovered that **235** rearranges to give the sulfinyl amine **237**, probably though a radical chain mechanism. We confirmed *via* a crossover experiment that the reaction is intermolecular, however a satisfactory explanation of initiation has not yet been

established. The sulfinyl amines underwent acid catalysed methanolysis to give both *tert*-leucine ethyl esters enantiomers in good yields. The reaction proceeds with complete retention of stereochemistry with the (*R*)-α-imino ester giving the (*R*)-*tert*-leucine ethyl ester and *vice versa*. Work later carried out in the group extended this reaction to 1-adamantyl and cyclohexyl derivatives.

IV Experimental

Reagents were purchased from a chemical supplier and used without further purification unless specified. Diethyl maleate and acetic acid were distilled under an argon atmosphere and stored over 4Å molecular sieves. TLCs were performed on silica gel on aluminium unless otherwise stated and were visualised using potassium permanganate dip or vanillin dip. Experiments carried out under an argon atmosphere unless otherwise stated.

Dry THF, toluene and diethyl ether were obtained by passing over an alumina column. Dry DCM, DMF, 1,4-Dioxane, DMSO, Ethyl Acetate and Acetonitrile were purchased from Acros.

Silica column chromatography was performed on silica gel (40-63µm). Alumina column chromatography was performed on neutral aluminium (pore size 58 Å) purchased from Sigma Aldrich. Solvents were purchased from a chemical supplier. 40-60°C Petrol was used where petrol is specified as a solvent.

^{1}H NMR spectra were carried out in $CDCl_3$ or CD_3OD on a Bruker 400 MHz spectrometer. ^{1}H NMR shifts (δ) were reported in ppm with the shift of $CDCl_3$ (δ = 7.26) or CD_3OD (δ = 3.31) as the internal standard. ^{13}C NMR were reported in ppm with the shift of the central peak of $CDCl_3$ (δ = 77.16) or CD_3OD (δ = 49.00) as the internal standard. Mass spectrums were obtained from Bruker MicroTOF spectrometer. IR spectra were recorded on a Perkin Elmer 1600 FTIR spectrometer.

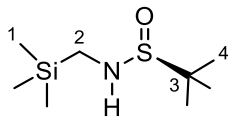
Quantitative NMR yields were obatined by combing a sample of known mass from the crude product with a sample of known mass in pyrazine, dissolved in $CDCl_3$ and submitted for ^{1}H NMR analysis then calculated using the following formula:

$$Yield = 100\left(\frac{4pnt}{rmL}\right)$$

Where ‘p’ equals the number of moles of pyrazine added the NMR sample, ‘n’ equals the number of protons in the ^{1}H NMR spectra the selected peak corresponds to in the product, ‘t’ equals the total

mass of the crude sample, ‘r’ equals the ratio of the pyrazine peak (δ = 8.58) to the selected peak in the product, ‘m’ equals the mass of sample taken from the crude product and ‘L’ equals the moles of limiting reagent.

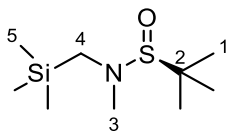
(*S*)-2-Methyl-*N*-((trimethylsilyl)methyl)propane-2-sulfinamide (197)



(*S*)-2-Methylpropane-2-sulfinamide (1.0 g, 8.0 mmol), potassium hydroxide (0.9 g, 16 mmol) and dry THF (80 mL) were combined under argon. The solution was stirred and heated to 60 °C for 1 hour. Iodomethyltrimethylsilane (1.5 mL, 10 mmol) was added dropwise and allowed to stir at 60 °C for 15 minutes. The THF was removed under reduced pressure and the crude material was washed with water (200 mL) which was extracted with EtOAc (3 x 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford a yellow oil (0.87 g). The crude product was purified by column chromatography (40 % EtOAc in petrol) to afford the title compound as a pale-yellow oil (0.42 g, 2.0 mmol, 37%).

$[\alpha]_D^{20}$ = +12.3 (c = 1.01, $CHCl_3$); **R_f** = 0.37 (50% EtOAc in petrol); **ν_{max}** (cm^{-1}) = 3218, 2955, 1248, 1056, 838, 696; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.83 (1H, d, *J*=9.1 Hz, N-H), 2.70 (1H, d, *J*=13.8 Hz, H-2), 2.41 (1H, dd, *J*=13.8, 9.1 Hz, H-2), 1.19 (9H, s, H-4), 0.06 (9H, s, H-1). **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 56.0 (C-3), 34.8 (C-2), 23.0 (C-4), -2.4 (C-1). **HRMS** (ESI) calculated m/z for $C_8H_{21}NNaOSSi$ = 230.1011 $[M+Na]^+$; found 230.1005.

(*S*)-*N*,2-Dimethyl-*N*-((trimethylsilyl)methyl)propane-2-sulfinamide (196)

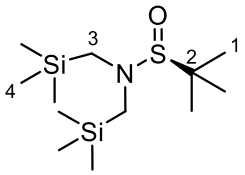


Potassium hydroxide (0.27 g, 4.8 mmol), acetonitrile (24 mL) and **197** (0.46 g, 2.4 mmol) were combined under argon. The solution was stirred at room temperature for 1 hour followed by addition of iodomethyltrimethylsilane (1.43mL, 9.6 mmol) by syringe pump (0.5 mL/h) over approximately 3

hours. The solution was stirred for 14 hours then the solvent was removed. The mother liquor was transferred to a separating funnel and washed with water (100 mL) and extracted with DCM (5 x 15 mL). The combined organic layers were dried (Na_2SO_4) then the solvent was removed to afford crude product as a brown oil (0.43 g). The compound was purified by column chromatography (30% ethyl acetate in petrol) to afford a yellow oil (314 mg, 1.42 mmol, 59%).

R_f = 0.35 in 50% ethyl acetate/petrol; **ν_{max}** = 2954, 1249, 1073, 840, 704; **^{1}H NMR** ($CDCl_3$, 400 MHz), δ 2.64 (3H, s, H-3), 2.63 – 2.43 (2H, m, H-4), 1.16 (9H, s, H-1), 0.10 (9H, s, H-5); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 58.6 (C-2), 44.9 (C-4), 37.8 (C-3), 23.8 (C-1), -0.9 (C-5). **HRMS** (ESI) m/z calculated for $C_9H_{23}NNaOSSi$ = 244.1167 $[M+Na]^+$; found 244.1158.

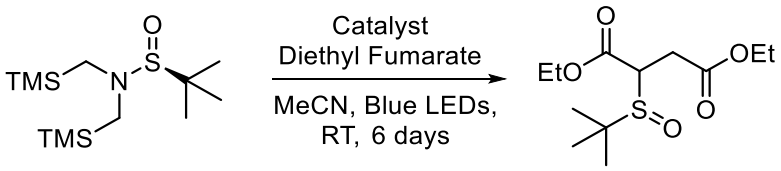
(*S*)-2-Methyl-*N,N*-bis((trimethylsilyl)methyl)propane-2-sulfinamide (194)



197 (0.60 g, 3.0 mmol) was placed under argon and dissolved in dry THF (30 mL). The solution was cooled to 0 °C then LiHMDS in THF (1.7 mL of a 2.1 M solution, 3.6 mmol) was added dropwise. The mixture was stirred at 0 °C for 30 minutes the allowed to warm to room temperature for 15 minutes. Iodomethyltrimethylsilane (0.54 mL, 3.6 mmol) was added and the mixture was warmed to 40 °C and allowed to stir for 18 hours. THF was removed under reduced pressure and the remaining liquor was diluted with ethyl acetate (100 mL) and saturated $NaHCO_{3\,(aq)}$ solution (300 mL). The organic layer was removed, and the aqueous layer extracted with ethyl acetate (2 x 100 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure to afford a yellow oil (352 mg). The crude product was purified by column chromatography (10-15% EtOAc in petrol) to afford the title compound as a pale-yellow oil (200 mg, 23%).

R_f = 0.52 (50% EtOAc in petrol); **ν_{max}** (cm^{-1}) = 2953, 1248, 1074, 835; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.65 – 2.42 (4H, m, H-3), 1.20 (9H, s, H-1), 0.12 (18H, s, H-4); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 58.6 (C-2), 41.3 (C-3), 24.4 (C-1), -0.7 (C-4); **HRMS** (ESI) m/z calculated for $C_{12}H_{32}NOSSi_2$ =294.1743 $[M+H]^+$; found 294.1734.

Diethyl 2-(*tert*-butylsulfinyl)succinate (198)



198

General method: Diethyl fumarate (0.19 g, 1.09 mmol), Catalyst and **194** (0.20 g, 0.68 mmol) were taken up in MeCN (5.4 mL) under N_2 in a scintillation vial. The mixture was degassed with N_2 for 30 mins then the mixture was illuminated with 3W blue LED bulb for 6 days.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.29 – 4.19 (m, 2H, H-6 or H-9), 4.16 (q, *J* = 7.2 Hz, 2H, H-6 or H-9), 3.97 (t, *J* = 6.8 Hz, 1H, H-3), 2.91 (d, *J* = 6.8 Hz, 2H, H-4), 1.29 (m, 15H, H-1, H-7 & H10); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.13 (C-5 or C-8), 169.34 (C-5 or C-8), 62.13 (C-6 or C-9), 61.26 (C-6 or C-9), 56.43 (C-2), 54.50 (C-3), 29.32 (C-4), 22.68 (C-1), 14.12 (C-7 or C-10), 14.02 (C-7 or C-10); **HRMS** (ESI) m/z calculated for $C_{12}H_{22}NaO_5S$ = 301.1086 $[M+Na]^+$, found 301.1088.

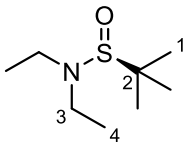
Experiment 198A: General procedure followed using Tris(2,2'-bipyrazine)ruthenium bis(hexafluorophosphate) (12 mg, 0.014 mmol, 2 mol%) as the catalyst. The crude reaction mixture was concentrated onto silica and purified by column chromatography on silica (20% EtOAc in petrol) to afford the title compound as a yellow oil (52 mg, 0.19 mmol, 28%). Isolated as 0.3:1 mixture of diethyl fumarate to title compound.

Experiment 198B: General procedure followed using Dicyanoanthracene (16 mg, 0.07 mmol, 10 mol%) as the catalyst. The solvent was removed *in vacuo* and the yield of the title compound was calculated by quantitative NMR analysis as described in the general experimental (61% yield).

Experiment 198C: General procedure followed using 9-mesityl-10-methyl acridium tetrafluoroborate. (7.0 mg, 0.07 mmol, 10 mol%) as the catalyst. The solvent was removed *in vacuo* and the yield of the title compound was calculated by quantitative NMR analysis as described in the general experimental (43% yield).

Experiment 198D: General procedure followed using 2,4,6-triphenylpyrylium tetrefluoroborate (7.0 mg, 0.07 mmol, 10 mol%) as the catalyst. The solvent was removed *in vacuo* and the yield of the title compound was calculated by quantitative NMR analysis as described in the general experimental (76% yield).

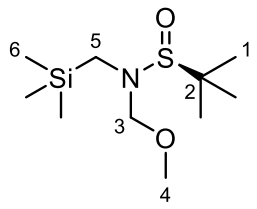
(*S*)-*N,N*-Diethyl-2-ethylpropane-2-sulfinamide (206)



(*S*)-2-Methylpropane-2-sulfinamide (1.0 g, 8.2 mmol), dry THF (80 mL) and KOH (1.9 g, 33 mmol) were combined under argon. The mixture was heated to 60 °C and stirred for 15 minutes followed by the addition of iodoethane (2.7 mL, 33 mmol). The reaction mixture was stirred at 60 °C for 25 hours followed by removal of the THF under reduced pressure. The resultant mixture was washed with water (300 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure, affording crude product which was purified by column chromatography (50% EtOAc in petrol) affording the title compound as a yellow oil (620 mg, 3.5 mmol, 43%).

R_f = 0.47 (50 % EtOAc in petrol); **ν_{max}** (cm^{-1}) = 2971, 2867, 1455, 1379, 1359, 1168, 1069, 1003, 886, 785, 644, 591; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 3.13 (2H, m, H-3), 2.93 (2H, m, H-3), 1.18 – 1.05 (15H, m, H-1 & H-4); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 57.4 (C-2), 41.8 (C-3), 23.3 (C-1), 14.1 (C-4). **HRMS** (ESI) m/z calculated for $C_8H_{19}NNaOS$ =200.1085 $[M+Na]^+$; found 200.1085.

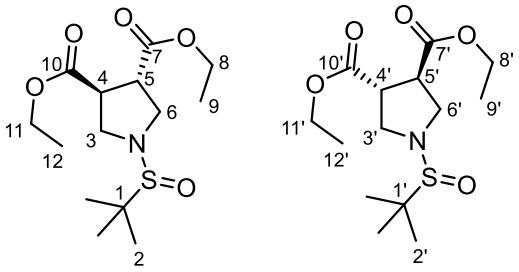
(*S*)-*N*-(Methoxymethyl)-2-methyl-*N*-((trimethylsilyl)methyl)propane-2-sulfinamide (210)



197 (100 mg, 0.48 mmol)) was dissolved in THF (4.8 mL). The solution was cooled to -78 °C under argon followed by dropwise addition of *n*-BuLi (0.22 mL of a 2.2 M solution in hexanes, 0.48 mmol) and the solution was stirred for 10 minutes followed by the dropwise addition of bromomethyl methyl ether (0.036 mL, 0.48 mmol). The solution was stirred for 15 minutes then quenched with saturated $NaHCO_{3\,(aq)}$ solution (100 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over Na_2SO_4 followed by the removal of the solvents to afford a colourless oil (120 mg, 99%) which was used without further purification.

$[\alpha]_D^{20}$ = + 15.1 (c = 1.01, $CHCl_3$); **R_f** = 0.68 (50% EtOAc in petrol; **ν_{max}** (cm^{-1}) = 2953, 1455, 1360, 1249, 1074, 848; **^{1}H NMR** (CD_3OD, 400 MHz) δ 4.52 (2H, s, H-3), 3.31 (3H, s, H-4), 2.60 (2H, s, H-5), 1.21 (9H, s, H-1), 0.16 (9H, s, H-6); **^{13}C NMR** (CD_3OD, 101 MHz) δ 84.6 (C-3), 59.7 (C-4), 55.6 (C-2), 35.3 (C-5), 23.4 (C-1), -1.2 (C-6); **HRMS** (ESI) calculated for $C_{10}H_{25}NNaO_2SSi$ = 274.1273 $[M+Na]^+$; found 274.1270.

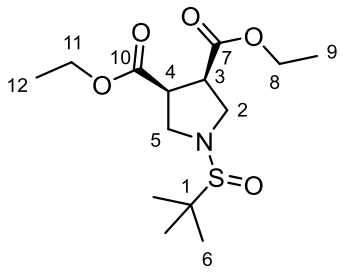
Diethyl (3*S*,4*S*)-1-(*tert*-butylsulfinyl)pyrrolidine-3,4-dicarboxylate and diethyl (3*R*,4*R*)-1-(*tert*-butylsulfinyl)pyrrolidine-3,4-dicarboxylate (211)



1,4-Dioxane (4 mL), diethyl fumarate (0.05 mL, 0.4 mmol) and **210** (100 mg, 0.4 mmol) were combined under argon, followed by the addition of trifluoracetic acid (4 µL, 0.04 mmol). The mixture was stirred for 18 hours at room temperature and the reaction was determined to be complete by TLC. The reaction was quenched with saturated $Na_2CO_{3\,(aq)}$ solution (50 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed to give the crude product as a yellow oil which was purified by column chromatography (EtOAc/Petrol 1:4) to afford the title compound as a colourless oil (10 mg, 8%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 (ap. qdd, *J* = 7.1, 1.8, 0.8 Hz, 4H, H-11, H-8, H-11' & H-8'), 3.85 – 3.77 (m, 1H, H-3, H-6, H-3' or H-6'), 3.70 – 3.63 (m, 1H, H-3, H-6, H-3' or H-6'), 3.52 – 3.44 (m, 1H, H-3, H-6, H-3' or H-6'), 3.42 – 3.36 (m, 1H, H-4, H-5, H-4' or H-5'), 3.33 (m, 2H, H-4, H-5, H-4' or H-5' & H-3, H-6, H-3' or H-6'), 1.26 (t, *J* = 7.1 Hz, 6H, H-9, H-12, H-9' & H-12'), 1.16 (s, 4.5H), 1.15 (s, 4.5 H, H-2 & H-2'); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.9 (C-10, C-7, C-10' & C-7'), 61.5 (C-11 & C-8 or C-11 & C-11' or C-8 & C-11' or C-8 & C-8'), 61.5 (C-11 & C-8 or C-11 & C-11' or C-8 & C-11' or C-8 & C-8'), 58.0 (C-1 or C-1'), 57.9 (C-1 or C-1'), 50.6 (C-6 & C-3 or C-6 & C-6' or C-3 & C-6' or C-3 & C-3'), 50.2 (C-6 & C-3 or C-6 & C-6' or C-3 & C-6' or C-3 & C-3'), 47.1 (C-5 & C-4 or C-5 & C-5' or C-4 & C-5' or C-4 & C-4'), 46.6 (C-5 & C-4 or C-5 & C-5' or C-4 & C-5' or C-4 & C-4'), 24.2 (C-2 or C-2'), 23.3 (C-2 or C-2'), 14.3 (C-12 & C-9 or C-12 & C-12' or C-9 & C-12' or C-9 & C-9'), 14.3 (C-12 & C-9 or C-12 & C-12' or C-9 & C-12' or C-9 & C-9'); **HRMS** (ESI) calculated for $C_{14}H_{25}NNaO_5S$ = 342.1351 $[M+Na]^+$; found 342.1362.

Diethyl (3*S*,4*R*)-1-(*tert*-butylsulfinyl)pyrrolidine-3,4-dicarboxylate (212)



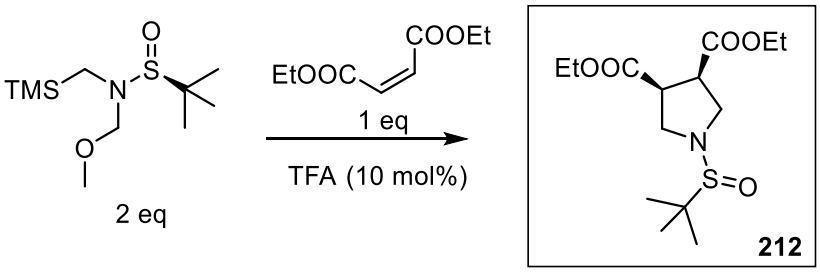
Method 1: 1,4-Dioxane (4 mL), diethyl maleate (0.05 mL, 0.4 mmol) and **210** (100 mg, 0.4 mmol) were combined under argon, followed by the addition of trifluoracetic acid (4 µL, 0.04 mmol). The mixture was stirred for 18 hours at room temperature and the reaction was determined to be complete by TLC. The reaction was quenched with saturated $Na_2CO_{3\,(aq)}$ solution (50 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed to give the crude product as a yellow oil which was purified by column chromatography (EtOAc/Petrol 1:4) to afford the title compound as a colourless oil (47 mg, 41%).

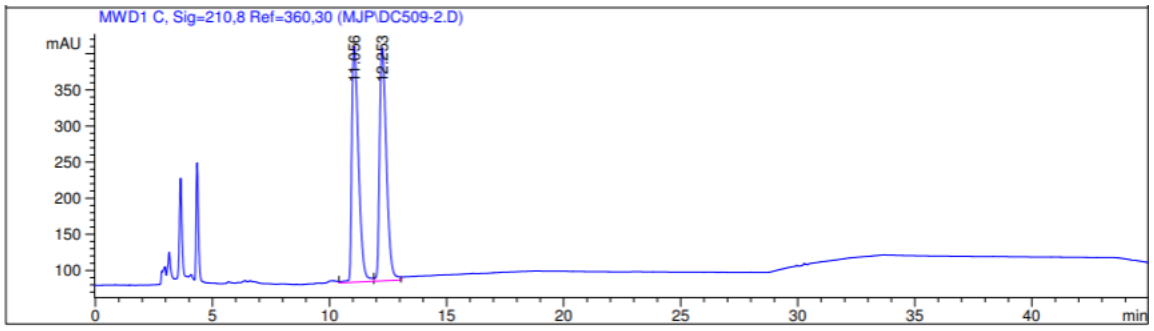
Method 2: 1,4-Dioxane (4 mL), diethyl maleate (0.05 mL, 0.4 mmol) and **210** (200 mg, 0.8 mmol) were combined under argon, followed by the addition of trifluoracetic acid (8 µL, 0.08 mmol). The mixture was stirred for 2 hours 40 °C and the reaction was determined to be complete by TLC. The reaction was quenched with saturated $Na_2CO_{3\,(aq)}$ solution (50 mL) and extracted with EtOAc (3 x 15 mL). An NMR yield of the title compound was calculated following the procedure described in the general experimental (66%).

Method 3: Triethylamine (95 mg, 0.94 mmol), *tert*-butylsulfinyl chloride (98 mg, 0.70 mmol) and DCM (4.7 mL) were combined under argon and cooled to 0 °C. **223** (100 mg, 0.47 mmol) was added and the mixture was stirred for 5 mins. The crude mixture was diluted with sat. $NaHCO_3$ solution (aq) (30 mL) and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (EtOAc/Petrol 1:4) to afford the title compound as a colourless oil (56 mg, 37%).

R_f = 0.52 (50% EtOAc in petrol, appears red in vanillin); **ν_{max}** (cm^{-1}) = 2978, 1733, 1372, 1199, 1180, 1058, 1035, 921, 731; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 4.19 – 4.10 (4H, m, H-8 & H-11), 3.90 (1H, dd, *J*=10.8, 8.1 Hz, H-5), 3.76 (1H, dd, *J*=11.1, 5.6 Hz, H-2), 3.58 (1H, dd, *J*=11.1, 7.1 Hz, H-2), 3.34 (1H, dd, *J*=10.8, 6.8 Hz, H-5), 3.28 – 3.16 (2H, m, H-3 & H-4), 1.25 (6H, t, *J*=7.2, H-9 & H-12), 1.17 (9H, s, H-6); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 171.5 (C-7), 171.5 (C-10) 61.2 (C-8), 61.2 (C-11) 58.0 (C-1), 53.7 (C-5) 46.3 (C-4 & C-3), 46.0 (C-2), 23.3 (C-6) , 14.2 (C-9 & C-12); **HRMS** (ESI) calculated for $C_{14}H_{25}NNaO_5S$ = 342.1351 $[M+Na]^+$; found 342.1362.

Chiral HPLC data for Method 2:



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

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000


Signal 1: MWD1 B, Sig=254,16 Ref=360,30

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  11.059 BB    0.3273   90.85839    4.21813  52.5325
   2  12.252 BB    0.3064   82.09803    4.01814  47.4675
```

Column Conditions:

Column - Chiralcel OJ-H (4.6 mm x 250 mm)

Isocratic conditions - *iso*-Hexane/ IPA

Flow rate - 1.00 mL / min

Monitored - 210 nM (8 nm bw) and 254nm (16 nm bw)

Time (min)	*Iso*-hexane (%)	IPA (%)
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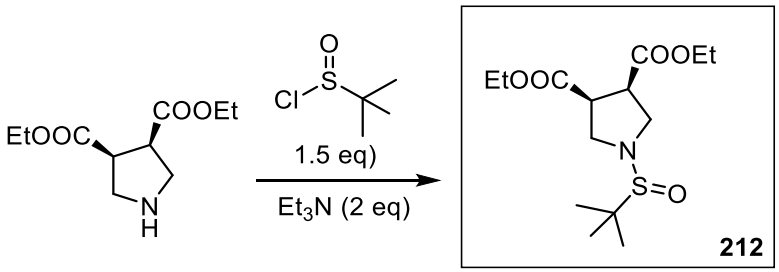
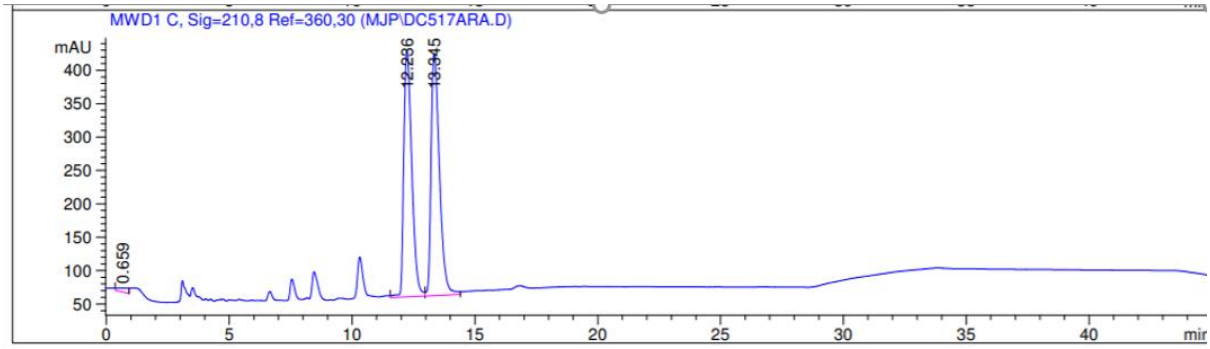
5	95	5
15	90	10
25	90	10
30	75	25
40	75	25
45	95	5

Chiral HPLC data for method 3:



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=====================================================================
                      Area Percent Report
=====================================================================
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   0.659 BV    0.3957  190.63879    5.88880   1.1152
   2  12.236 VV    0.3588 8367.22461  368.67584  48.9483
   3  13.345 VB    0.3652 8536.13867  361.93619  49.9365
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Column Conditions:

Column - Chiralcel OJ-H (4.6 mm x 250 mm)

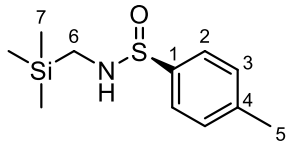
Isocratic conditions - *iso*-Hexane/ IPA

Flow rate - 1.00 mL / min

Monitored - 210 nM (8 nm bw) and 254nm (16 nm bw)

Time (min)	*Iso*-hexane (%)	IPA (%)
0	95	5
5	95	5
15	90	10
25	90	10
30	75	25
40	75	25
45	95	5

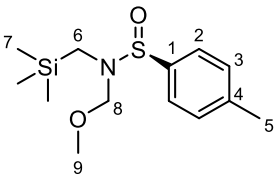
(*S*)-4-Methyl-*N*-((trimethylsilyl)methyl)benzenesulfinamide (213)



(*S*)-*p*-Toluenesulfinamide (1.3 g, 8.3 mmol) was dissolved in dry THF (83 mL). The mixture was cooled to -78 °C followed by dropwise addition of *n*-BuLi (3.8 mL of a 2.2M solution in hexanes, 8.3 mmol). The solution was stirred for 1 hour followed by dropwise addition of (iodomethyl)trimethylsilane (2.4 mL, 16 mmol). The solution was warmed to room temperature then heated to 60 °C and stirred for 40 hours. The mixture was quenched with saturated $NaHCO_{3\,(aq)}$ solution (250 mL) and diluted with water (250 mL). The aqueous mixture was extracted with EtOAc (3 × 100 mL) and the combined organic layers were washed with brine (100 mL) then dried (Na_2SO_4). The solvent was removed under reduced pressure to afford the crude product (2.5 g) which was purified by column chromatography (20% EtOAc in petrol) to give the title compound as a white solid (1.1 g, 67%).

R_f = 0.46 (50% EtOAc in petrol); **ν_{max}** (cm^{-1}) = 3226, 2952, 1488, 1453, 1422, 1249, 1056, 842, 808, 702, 549, 449; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.58 – 7.51 (2H, m, H-3), 7.33 – 7.28 (2H, m, H-2), 3.76 (1H, bs, N-H), 2.42 (3H, s, H-5), 2.52 (1H, d, *J*=13.8 Hz, H-6), 1.94 (1H, d, *J*=13.8 Hz, H-6), 0.03 (9H, s, H-7); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 141.2 (C-1), 140.7 (C-4), 129.6 (C-2), 126.4 (C-3), 27.3 (C-6), 21.5 (C-5), -2.7 (C-7). **HRMS** (ESI) calculated for $C_{11}H_{20}NOSSi$ = 242.1035 $[M+H]^+$; found 242.1045.

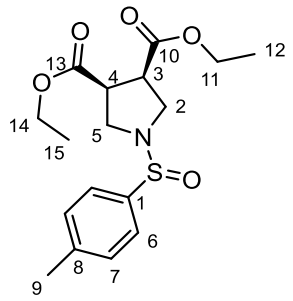
(*S*)-*N*-(Methoxymethyl)-2-methyl-*N*-((trimethylsilyl)toluenesulfinamide (215)



213 (1.0 g, 4.1 mmol) was dissolved in dry THF (41 mL) under argon. The solution was cooled to -78 °C followed by dropwise addition of *n*-BuLi (1.9 mL of a 2.2M solution in hexanes, 4.1 mmol). The solution was stirred for 10 minutes followed by the dropwise addition of bromomethyl methyl ether (0.30 mL, 1.1 mmol). The solution was stirred for 15 minutes then quenched with saturated $NaHCO_{3\,(aq)}$ solution (150 mL) and extracted with EtOAc (3 × 70 mL). The combined organic layers were washed with brine (100 mL) then dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded the product as a colourless oil (1.13g, 4.0 mmol, 95%) which was used without further purification.

$\boldsymbol{\nu_{max}}$ (cm^{-1}) = 2953, 1676, 1491, 1322, 1248, 1142, 1086, 844, 707; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.51 (2H, m, H-3), 7.30 – 7.25 (2H, m, H-2), 4.70 – 4.58 (2H, m, H-8), 3.34 (3H, s, H-9), 2.50 (1H, d, *J*=14.9, Hz, H-6), 2.39 (3H, s, H-5), 2.18 (1H, d, *J*=14.9 Hz, H-6), -0.05 (9H, s, H-7); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 141.3 (C-1), 141.1 (C-4), 129.6 (C-2), 126.2 (C-3), 85.2 (C-8), 55.8 (C-9), 32.3 (C-6), 21.5 (C-5), -1.6 (C-7). **HRMS** (ESI) calculated for $C_{13}H_{23}NNaO_2SSi$ = 308.1116 $[M+Na]^+$; found 308.1119.

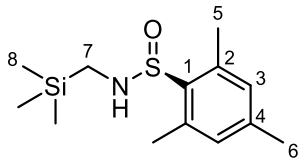
Diethyl (3*S*,4*R*)-1-(*p*-tolylsulfinyl)pyrrolidine-3,4-dicarboxylate (218)



Dry 1,4-dioxane (3.5 mL), diethyl maleate (0.050 mL, 0.40 mmol) and **215** (100 mg, 0.35 mmol) were combined followed by the addition of trifluoracetic acid (2.7 µL, 0.035 mmol). The mixture was stirred for 24 hours then quenched with saturated $NaHCO_{3\,(aq)}$ solution (100 mL) then extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (50 mL) then dried (Na_2SO_4). The solvent was removed under reduced pressure to give the crude product as a yellow oil which was purified by column chromatography (20% EtOAc in petrol) to afford the title compound as a colourless oil (57 mg, 46%).

$\boldsymbol{\nu_{max}}$ (cm^{-1}) = 2920, 1733, 1396, 1204, 1031, 1009, 815, 682, 568; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.53 (2H, d, *J*=8.1 Hz, H-7), 7.29 (2H, d, *J*=8.1 Hz, H-6), 4.19 – 4.06 (4H, m, H-11 & H14), 3.81 (1H, dd, *J*=10.9, 6.8 Hz, H-5), 3.71 (1H, dd, *J*=10.9, 7.5 Hz, H-5), 3.60 (1H, dd, *J*=10.7, 7.9 Hz, H-2), 3.38 – 3.23 (2H, m, H-3 & H-4), 3.10 (1H, dd, *J*=10.9, 6.2 Hz, H-2), 2.40 (3H, s, H-9), 1.27 – 1.21 (6H, m, H-12 & H-15); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 171.5 (C-10), 171.2 (C-13), 141.4 (C-1), 140.8 (C-8), 129.8 (C-6), 126.0 (C-7), 61.2 (C-11), 61.2 (C-14), 51.1 (C-5) , 46.5 (C-3), 46.05 (C-4), 45.81 (C-2), 21.48 (C-9), 14.23 (C-12), 14.20 (C-15); **HRMS** (ESI) m/z calculated for $C_{17}H_{24}NO_5SS$ =354.1375 $[M+H]^+$; found 354.1399.

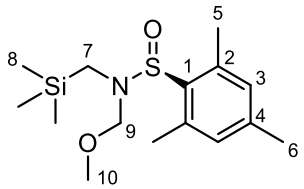
(*S*)-2,4,6-Trimethyl-*N*-((trimethylsilyl)methyl)benzenesulfinamide (214)



(*S*)-2,4,6-Trimethylbenzenesulfinamide (1.0 g, 5.5 mmol) and THF (55 mL) were combined. The solution was cooled to -78 °C and *n*-BuLi (2.4 mL of a 2.2M solution in hexanes, 5.5 mmol) was added dropwise then allowed to stir for 30 minutes. Iodomethyltrimethylsilane (2.3 g, 11 mmol) was added in one portion. The solution was warmed to room temperature before heating at 60 °C and stirring for 24 hours. Saturated $NaHCO_{3\ (aq)}$ solution (100 mL) and water (100 mL) were added followed by extraction with ethyl acetate (3 x 70 mL). The combined organic layers were washed with brine then dried (Na_2SO_4) followed by removal of the solvent to give the crude product as a yellow oil (1.49 g). The product was purified by column chromatography (30% ethyl acetate in petrol) to give the title compound as a yellow-tinged oil (1.05 g, 3.88 mmol, 71%).

$\boldsymbol{\nu_{max}}$ (cm^{-1}) = 3217, 2950, 1449, 1252, 1067, 853; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.84 (s, 2H, H-3), 3.74 (t, *J* = 6.5 Hz, 1H, N-H), 2.58-2.53 (m, 8H, H-5 & H-7), 2.28 (s, 3H, H-6), 0.05 (s, 9H, H-8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.6 (C-1, C-2 or C-4), 137.3 (C-1, C-2 or C-4), 137.1 (C-1, C-2 or C-4), 130.9 (C-3), 32.4 (C-7), 21.1 (C-6), 19.7 (C-5), -2.7 (C-8); **HRMS** (ESI) m/z calculated for $C_{13}H_{24}NOSSi$ = 270.1342 $[M+H]^+$; found 270.1351.

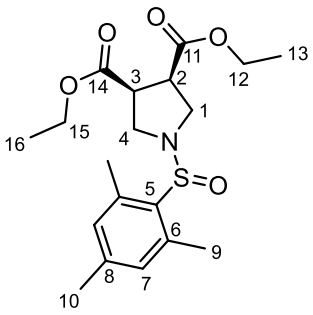
(*S*)-*N*-(Methoxymethyl)-2,4,6-trimethyl-*N*-((trimethylsilyl)methyl)benzenesulfinamide (216)



214 (1.0 g, 3.7 mmol) was dissolved in THF (37 mL). The mixture was cooled to -78°C followed by dropwise addition of *n*-BuLi (1.6 mL of a 2.2M solution in hexanes, 3.7 mmol). The solution was stirred for 10 minutes followed by the dropwise addition of bromomethyl methyl ether (0.30 mL, 3.7 mmol). The solution was stirred for 15 minutess then quenched with saturated $NaHCO_{3\,(aq)}$ solution (150 mL) and extracted with ethyl acetate (3 × 70 mL). The combined organic layers were washed with brine (100 mL) then dried (Na_2SO_4) Removal of the solvent afforded a colourless oil (1.0 g). The crude product was purified on an alumina column (10% ethyl acetate in petrol) to give the title compound as a colourless oil (1.0 g, 3.19 mmol, 86%).

R_f = 0.75 (50% EtOAc in petrol); **ν_{max}** (cm^{-1}) = 2953, 1602, 1452, 1248, 1091, 1045, 732, 687, 620, 440; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.83 (s, 2H, H-3), 4.69 – 4.55 (m, 2H, H-9), 3.30 (s, 3H, H-10), 2.78 – 2.53 (m, 2H, H-7), 2.51 (s, 6H, H-5), 2.28 (s, 3H, H-6) -0.09 (s, 9H, H-8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.6 (C-1, C-2 or C-4), 138.2 (C-1, C-2 or C-4), 135.4 (C-1, C-2 or C-4), 131.3 (C-3), 85.3 (C-9), 56.0 (C-10), 34.1 (C-7), 21.1 (C-6), 19.9 (C-5), -1.7 (C-8); **HRMS** (ESI) m/z calculated for $C_{15}H_{27}N^{35}ClO_2SSi$ = 348.1126 $[M+^{35}Cl]^-$; found 348.1092.

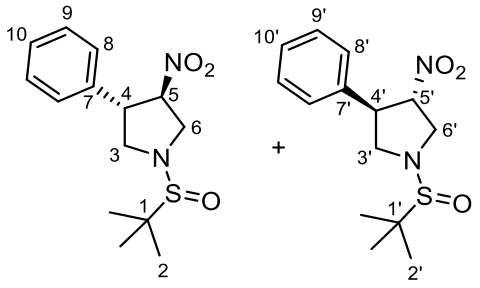
Diethyl (3*S*,4*R*)-1-(mesitylsulfinyl)pyrrolidine-3,4-dicarboxylate (217)



Dry 1,4-dioxane (3.2 mL), diethyl maleate (55 mg, 0.32 mmol) and **216** (100 mg, 0.32 mmol) were combined, followed by the addition of trifluoracetic acid (2.5 µL, 0.032 mmol). The mixture was stirred for 18 hours and was determined to be complete by TLC. The reaction was quenched with saturated $NaHCO_{3\,(aq)}$ (50 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extractions were dried (Na_2SO_4) and the solvent was removed to give the crude product as a yellow oil which was purified by column chromatography (20% EtOAc in petrol) to afford the title compound as a colourless oil (38 mg, 31%).

R_f = 0.13 (20% EtOAc in Petrol); **ν_{max}** (cm^{-1}) = 2980, 2932, 1733, 1465, 1373, 1200, 1086, 1013, 729; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.80 (s, 2H, H-7), 4.12-4.08 (m, H-15 & H-12), 3.84 – 3.74 (m, 2H, H-1 or H-4), 3.68 – 3.61 (m, 1H, H-1 or H-4), 3.36 – 3.29 (m, 2H, H-2 & H-3), 3.28 – 3.22 (m, 1H, H-1 or H-4), 2.48 (s, 6H, H-9), 2.26 (s, 3H, H-10), 1.19 (m, 6H, H-16 & H-13); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.3 (C-11 or C-14), 171.1 (C-11 or C-14), 140.4 (C-5), 137.7 (C-6 or C-8), 134.4 (C-6 or C-8), 131.1 (C-7), 61.1 (C-12 or C-15), 61.0 (C-12 or C-15), 50.1 (C-4 or C-1), 47.1 (C-4 or C-1), 46.0 (C-2 or C3), 45.9 (C-2 or C-3), 20.9 (C-10), 19.5 (C-9), 14.1 (C-13 or C-16), 14.0 (C-13 or C-16); **HRMS** (ESI) calculated for $C_{19}H_{27}NNaO_5S$ = 404.1508 $[M+Na]^+$; found 404.1506.

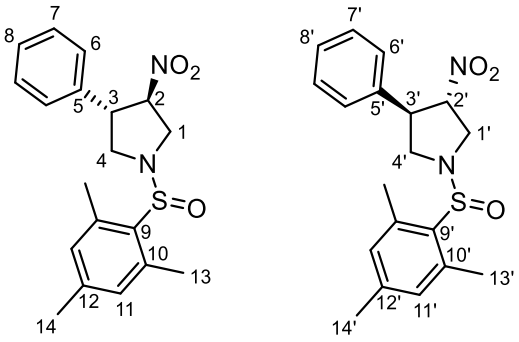
(3*S*,4*R*)-1-(*tert*-Butylsulfinyl)-3-nitro-4-phenylpyrrolidine and (3*R*,4*S*)-1-(*tert*-butylsulfinyl)-3-nitro-4-phenylpyrrolidine (220)



1,4-Dioxane (4 mL), β-nitro styrene (0.06 g, 0.4 mmol), **210** (0.20g, 0.8 mmol) and TFA (6 µL, 0.08 mmol) were combined under argon. The mixture was heated to 40 °C for 2 hours then quenched with saturated $NaHCO_{3\,(aq)}$ solution (30 mL) then extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL) then dried over Na_2SO_4. The solvent was removed under reduced pressure to give the crude product which was purified by column chromatography (15% EtOAc in petrol) to afford the title compound as a colourless oil and a 1:1 inseparable mixture of diastereoisomers (30 mg, 0.1 mmol 25%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.26 (m, 5H, H-8, H8', H-9, H-9', H-10, H-10'), 5.12 – 4.96 (m, 1H, H-5 & H-5'), 4.23 – 3.94 (m, 3H, H-3 & H-4 or H-6, & H-3' & H-4' or H-6'), 3.91 – 3.66 (m, 2H, H-3 or H-6 & H-3' or H-6'), 1.24 (s, 4.5H, H-2 or H-2'), 1.23 (s, 4.5H, H-2 or H-2'); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.6 (C-7 or C-7'), 137.4 (C-7 or C-7'), 129.3, 129.3, 128.3, 128.2, 127.6, 127.4 (C-8, C-8', C-9, C9', C-10, C-10'), 90.0 (C-5 or C-5'), 89.9 (C-5 or C-5'), 58.4 (C-1 or C-1'), 58.2 (C-1 or C-1'), 55.2 (C-3 or C-6 or C-3' or C-6'), 53.0 (C-3 or C-6 or C-3' or C-6'), 52.1 (C-3 or C-6 or C-3' or C-6'), 50.4 (C-4 or C-4'), 50.3 (C-3 or C-6 or C-3' or C-6'), 49.4 (C-4 or C-4'), 23.3 (C-2 or C-2'), 23.2 (C-2 or C-2'); **HRMS** (ESI) calculated for $C_{14}H_{20}N_2NaO_3S$ = 319.1092 $[M+Na]^+$; found 319.1095.

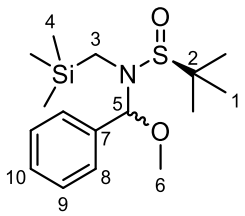
(3*R*,4*S*)-1-(Mesitylsulfinyl)-3-nitro-4-phenylpyrrolidine and (3*S*,4*R*)-1-(mesitylsulfinyl)-3-nitro-4-phenylpyrrolidine (221)



1,4-Dioxane (3.4 mL), β-nitro styrene (0.025 g, 0.17 mmol), **216** (0.105g, 0.34 mmol) and TFA (3 µL, 0.04 mmol) were combined under argon. The mixture was heated to 40 °C for 75 minutes then quenched with saturated $NaHCO_{3\,(aq)}$ solution (30 mL) then extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL) then dried over Na_2SO_4. The solvent was removed under reduced pressure to give the crude product which was purified by column chromatography (5% EtOAc in toluene) to afford the title compound as a colourless oil and a 1:1 inseparable mixture of diastereoisomers (24 mg, 0.067 mmol, 39%).

R_f = 0.14 (10 EtOAc in petrol); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.24 (m, 10H, H-6, H-6', H-7, H-7', H-8 & H-8'), 6.86 (s, 2H, H-11 or H-11'), 6.85 (s, 2H, H-11 or H-11'), 5.06-4.99 (m, 2H, H-2 & H-2'), 4.18 – 3.97 (m, 5H, H-3 & H-3' & H-1, H-1', H-4 or H-4'), 3.89 (dd, *J* = 11.3, 7.5 Hz, 1H, H-1 or H-1' or H-4 or H-4'), 3.66 – 3.48 (m, 4H, H-1 or H-1' or H-4 or H-4'), 2.55 (s, 6H, H-13 or H-13'), 2.52 (s, 6H, H-13 or H-13'), 2.29 (s, 3H, H-14 or H-14'), 2.29 (s, 3H, H-14 or H-14'); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.2 (C-9 or C-9'), 141.1 (C-9 or C-9'), 138.2, 138.1, 138.1, 138.0 (C-10, C-12, C-10' & C-12'), 133.9 (C-5), 133.9 (C-5'), 131.5 (C-11 or C-11'), 131.4 (C-11 or C-11'), 129.4, 129.2, 128.4, 128.3, 127.5, 127.4 (C-6, C-7, C-8, C-6', C-7', C-8'), 90.2 (C-2 or C-2'), 90.0 (C-2 or C-2'), 53.5, 51.7, 51.3, 49.7, 49.5, 49.1 (C-1, C-1', C-3, C-3', C-4, C-4'), 21.1 (C-14 & C-14'), 19.7 (C-13 & C-13'); **HRMS** (ESI) calculated for $C_{19}H_{22}N_2NaO_3S$ = 381.1249 $[M+Na]^+$; found 381.1249.

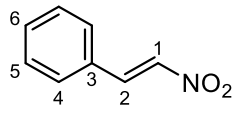
(2-((*S*)-tert-butylsulfinyl)-3-methoxy-3-phenylpropyl)trimethylsilane (226)



197 (0.40 mg, 1.9 mmol) and THF (20 mL) were combined and cooled to -78 °C under argon. *n*-BuLi (1.0 mL of a 2.2M solution in hexanes, 2.1 mmol) was added dropwise and allowed to stir for 15 minutes. 1-Chloro-1-methoxy toluene (0.11 g, 2.9 mmol) was added in one portion and stirred at -78 °C for 2.5 hours. The reaction was quenched with pH 7 phosphate buffer solution (100 mL) and extracted with DCM (3 x 50 mL). The combined organic layers were washed with brine then dried (Na_2SO_4) followed by removal of the solvent to afford crude product. The crude product was purified by column chromatography with an eluent of 5% EtOAc in petrol and on silica which was first washed with triethylamine solution (2.5 vol% in petrol). The title compound was obtained in one diastereomer as a colourless oil (201 mg, 0.62 mmol, 32%).

R_f = 0.49 (20% EtOAc in petrol); **ν_{max}** (cm^{-1}) = 2953, 2827, 1693, 1420, 1248, 1149, 1071, 841, 761; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 (m, 5H, H-7, H-8, H-9 & H-10), 5.56 (s, 1H, H-5), 3.39 (s, 3H, H-6), 2.54 – 2.35 (m, 2H, H-3), 1.28 (s, 9H, H-4), -0.09 (s, 9H, H-1); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.7 (C-7), 128.3 (C-8, C-9 or C-10), 128.2 (C-8, C-9 or C-10), 127.8 (C-8, C-9 or C-10), 88.8(C-5), 59.5 (C-2), 56.0 (C-6), 33.3 (C-3), 23.6 (C-1), -0.7 (C-4); **HRMS** (ESI) calculated for $C_{16}H_{29}NNaO_2SSi$ = 350.1586 $[M+Na]^+$; found 350.1578.

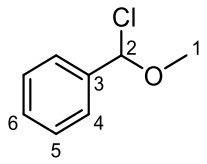
β-nitro styrene



Methanol (7.0 mL), benzaldehyde (2.0 g, 18.8 mmol) and nitromethane (1.15 g, 18.8 mmol) were combined and cooled to 0 °C. A methanolic solution of NaOH (0.79 g (19.7 mmol) in 4.0 mL) was added dropwise and a precipitate appeared. Methanol was added until stirring resumed then left for 15 minutes. Water was added until the solution became transparent then the solution was dripped slowly into a beaker containing conc. HCL (7 mL) and water (10 mL) resulting in the formation of a yellow solid which was then filtered off and washed with water. The solid was dried under high vacuum at 50 °C to afford the title compound as a yellow solid (1.77 g, 11.9 mmol, 63%) and was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 13.7 Hz, 1H, H-1), 7.64 – 7.42 (m, 6H, H-2, H-3, H-4, H-5 & H-6). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.2 (C-1), 137.3, 132.3, 130.2, 129.5, 129.3 (C-2, C-3, C-4, C-5, C-6). **Data agree with literature.**[119]

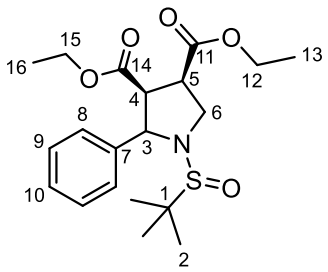
1-Chloro-1-methoxy toluene



$Yb(OTf)_3$ (3.1 mg, 0.005 mmol) and benzaldehyde dimethyl acetal (3.14 mL, 21.0 mmol) were dissolved in dry DCM (9.0 mL). The reaction flask was placed in a water bath (to maintain internal temperature at RT) and acetyl chloride (1.60 mL, 22.0 mmol) was added slowly then allowed to stir for 72 hours. The solvent was removed and the crude mixture was distilled under reduced pressure (8 mbar, 66-68 °C) to give the title compound as a colourless oil (1.40 g, 9 mmol, 43%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.51 (m, 2H, H-4, H-5 or H-6), 7.45 – 7.35 (m, 3H, H-4, H-5 or H-6), 6.52 (s, 1H, H-2), 3.74 (s, 3H, H-1), **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.8 (C-3), 129.9, 128.6, 125.9 (C-4, C-5 & C-6), 99.8 (C-2), 58.3 (C-1). **Data agree with literature.**[120]

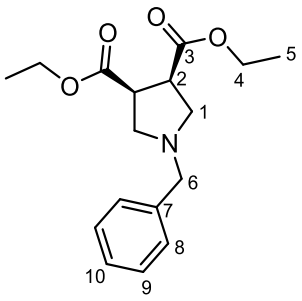
Diethyl 1-(tert-butylsulfinyl)-2-phenylpyrrolidine-3,4-dicarboxylate (227)



226 (100 mg, 0.31 mmol), Diethyl maleate (45 mg, 0.31 mmol) and 1,4-dioxane (3.1 mL) were combined under argon then TFA was added (2.4 µL, 0.031 mmol) and the mixture was stirred at RT for 18 h. The reaction was quenched with sat. $NaHCO_{3\ (aq)}$ solution (25 mL), extracted with DCM (3 x 15 mL) then the combined organic fractions were dried over Na_2SO_4. The crude product was purified by column chromatography on silica (20% EtOAc in petrol) to give the title compound in a 3.4 : 1 mixture of diastereomers as a yellow oil (49 mg, 0.12 mmol, 39% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 6.5H, H-7, H-8, H-9 & H-10), 5.49 (d, *J* = 9.5 Hz, 1H, H-3), 5.07 (d, *J* = 7.2 Hz, 0.3H, H-3), 4.27 – 4.04 (m, 5.2H, H-12 & H-15), 3.83 – 3.69 (m, 2.6H, H-4 & H-5 or H-6), 3.63 – 3.53 (m, 2.6H, H-4 & H-5 or H-6), 3.31 – 3.18 (m, 1.3H, H-4 or H-5 or H-6), 1.20 (m, 5.3H, H-2 & H-16 or H-2 & H-13), 0.98 (s, 9H, H-2), 0.81 (t, *J* = 7.1 Hz, 2.6H, H-13 or H-16); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.3, 171.1, 171.0, 170.2, 142.2, 139.4, 128.9, 128.3, 128.1, 127.7, 127.5, 126.7, 62.9, 61.6, 61.1, 60.9, 60.6, 59.4, 58.1, 58.0, 57.8, 55.2, 52.2, 49.0, 43.8, 22.9, 22.9, 14.2, 13.6; **HRMS** (ESI) calculated m/z for $C_{20}H_{30}NO_5S$ = 396.1845 $[M+H]^+$; found 396.1859.

Diethyl (3*S*,4*R*)-1-benzylpyrrolidine-3,4-dicarboxylate (222)

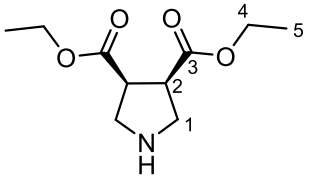


DCM (42 mL), diethyl maleate (0.72 g, 4.2 mmol) and *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (1.0 g, 4.2 mmol) were combined under argon. Trifluoroacetic acid (48 mg, 0.42 mmol) were added and heat evolution was observed. The mixture was stirred for 48 hours under room temperature then quenched with sat. $NaHCO_{3\,(aq)}$ solution (50 mL). The organic layer was separated and the aqueous layer washed twice with DCM (2 x 30 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed to give the crude product as a yellow oil. Purification was performed by column chromatography (15-20% EtOAc in petrol) to give the title compound as a colourless oil (0.92 g, 3.01 mmol, 72%).

R_f = 0.22 (20% EtOAc in petrol); **ν_{max}** (cm^{-1}) = 2980, 2811, 1732, 1371, 1192, 1029, 740, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 – 7.21 (m, 5H, H-8, H-9 & H-10), 4.11 (q, *J* = 7.1 Hz, 4H, H-4), 3.66 (s, 2H, H-6), 3.34 – 3.24 (m, 2H, H-2), 3.21 – 3.10 (m, 2H, H-1), 2.78 – 2.68 (m, 2H, H-1), 1.23 (t, *J* = 7.2 Hz, 6H, H-5);

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7 (C-3), 138.7 (H-7, H-8, H9 or H-10), 128.8 (H-7, H-8, H9 or H-10), 128.5 (H-7, H-8, H9 or H-10), 127.3 (H-7, H-8, H9 or H-10), 60.8 (C-4), 60.1 (C-6), 56.3 (C-1), 45.5 (C-2), 14.2 (C-5); **HRMS** (ESI) calculated m/z for $C_{17}H_{24}NO_4$ = 306.1705 $[M+H]^+$; found 306.1716.

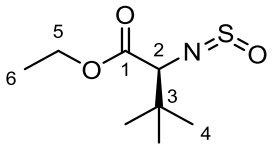
Diethyl (3*S*,4*R*)-pyrrolidine-3,4-dicarboxylate (223)



Ethanol (16.4 mL), 10% Pd/C (50 mg, 0.047 mmol) and **222** (500 mg) were added to a round bottomed flask. The flask was placed under vacuum then filled with hydrogen three times. The mixture was then stirred under hydrogen for 24 hours. The mixture was filtered through celite and washed with EtOAc (80 mL) then the solvent was removed to afford the title compound which was used without further purification as a yellow tinged oil (340 mg, 1.58 mmol, 96%).

R_f = 0.3 (5% MeOH in DCM); **ν_{max}** (cm^{-1}) = 3322, 2981, 2939, 2904, 1726, 1372, 1189, 1033, 859; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.12 (q, *J* = 7.1 Hz, 4H, H-4), 3.39 – 3.32 (m, 2H, H-1), 3.23 – 3.16 (m, 2H, H-2), 3.11 (ddd, *J* = 11.7, 5.4, 1.9 Hz, 2H, H-1), 2.03 – 1.88 (m, 1H, N-H), 1.25 (t, *J* = 7.1 Hz, 6H, H-5); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.1 (C-3), 60.9 (C-4), 50.9 (C-1), 47.9 (C-2), 14.3 (C-5); **HRMS** (ESI) calculated for $C_{10}H_{18}NO_4$ = 216.1236 $[M+H]^+$; found 216.1250.

Ethyl (*S*)-3,3-dimethyl-2-((oxo-sulfaneylidene)amino)butanoate (237)



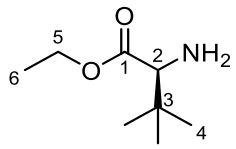
Method 1: To a round bottomed flask which was dried under vacuum and placed under argon was added 4 ÅMS, diethyl fumarate (0.43 g, 2.5 mmol) and DCM (17 mL). Ozone was then bubbled through

the flask while stirring at -78 °C for one hour. The solution was purged of the blue colour by an oxygen flow followed by addition of dimethyl sulfide (0.25 mL, 3.3 mmol) and allowed to warm to room temperature and stir for 16 hours. (S)-2-Methylpropane-2-sulfinamide (0.2 g, 1.7 mmol) was added and allowed to stir for 48 hours. The mixture was filtered through a celite plug and rinsed with DCM followed by the removal of the solvent to afford the crude mixture which was purified by column chromatography to give ethyl (*S,E*)-2-((tert-butylsulfinyl)imino)acetate. The sample was placed under reduced pressure at 40 °C for 2 hours and the sample rearranged to afford the title compound as a colourless liquid (265 mg, 78%).

Method 2: To a round bottomed flask which was dried under vacuum and placed under argon was added 4 ÅMS, ethyl glyoxylate (50 wt% in toluene) (2.0 mL, 9.9 mmol), (S)-2-Methylpropane-2-sulfinamide (1.0 g, 8.3 mmol) and DCM (42 mL). The mixture was heated to 50 °C for 5 minutes then allowed to cool to RT and stirred for 48 h. The mixture was filtered through celite and washed through with DCM (50 mL) then concentrated under reduced pressure to afford the crude product. The crude product was purified by column chromatography on silica (20% EtOAc in petrol) to afford ethyl (*S,E*)-2-((tert-butylsulfinyl)imino)acetate which when concentrated under reduced pressure, rearranged to afford the title compound as a yellow oil (1.16 g, 5.64 mmol, 66%).

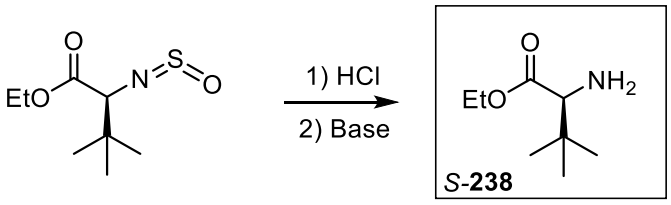
$\boldsymbol{\nu_{max}}$ (cm^{-1}) = 2967, 1736, 1368, 1244, 1204, 1156, 1023; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.93 (s, 1H, H-2), 4.23 (q, *J* = 7.1 Hz, 2H, H-5), 1.30 (t, *J* = 7.1 Hz, 3H, H-6), 1.05 (s, 9H, H-4); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.1 (C-1), 69.7 (C-2), 61.7 (C-5), 35.8 (C-3), 26.7 (C-4), 14.3 (C-6); **HRMS** (ESI) m/z calculated for $C_8H_{18}NO_2$ = 160.1338 $[M\text{-}SO+H]^+$ (title compound fragments in mass spectrometer to eject SO to form the NH_3^+); found 160.1334.

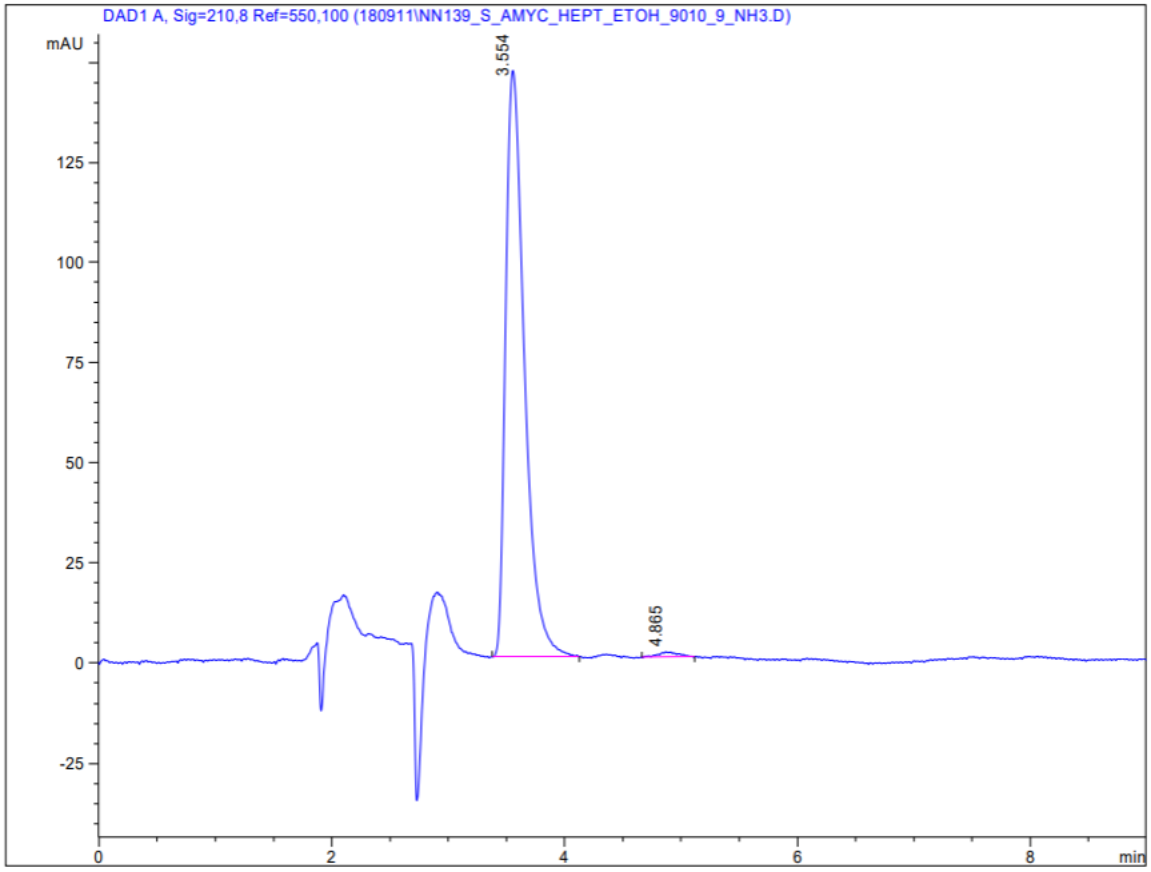
(*S*)-*Tert*-Leucine Ethyl Ester (238)



237 (400 mg, 1.95 mmol) was stirred in 1M methanolic HCl solution (5 mL) for 15 minutes then basified with saturated Na_2CO_3 solution. The solution was then extracted with DCM (3 x 5 mL) and the combined organic layers were dried (Na_2SO_4) to afford the crude product as a colourless oil. Column chromatography was performed (3% methanol in DCM) to afford the title compound as a colourless oil (203 mg, 1.29 mmol, 66%).

$[\alpha]_D^{22}$ +31.8 (c = 0.64, $CHCl_3$, literature value = +47.1 (c = 1.20, $CHCl_3$)[121]); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.17 (q, *J* = 7.1, 2H, H-5), 3.13 (s, 1H, H-1), 1.46 (s, 2H, N-H), 1.28 (t, *J* = 7.1 Hz, 3H, H-6), 0.96 (s, 9H, H-4); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.1 (C-1), 63.6 (C-2), 60.5 (C-5), 34.5 (C-3), 26.5 (C-4), 14.4 (C-6); **HRMS** (ESI) calculated for $C_8H_{18}NO_2$ = 160.1332 $[M+H]^+$; found 160.1345. Data agree with literature.[122]





#	Meas. R	Height	Width	Area	Area %	Symmetr
1	3.554	146.498	0.187	1.641e3	99.067	0.594
2	4.865	1.310	0.197	15.462	0.933	0.593

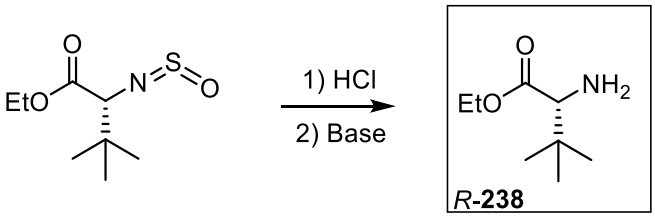
Column Conditions:

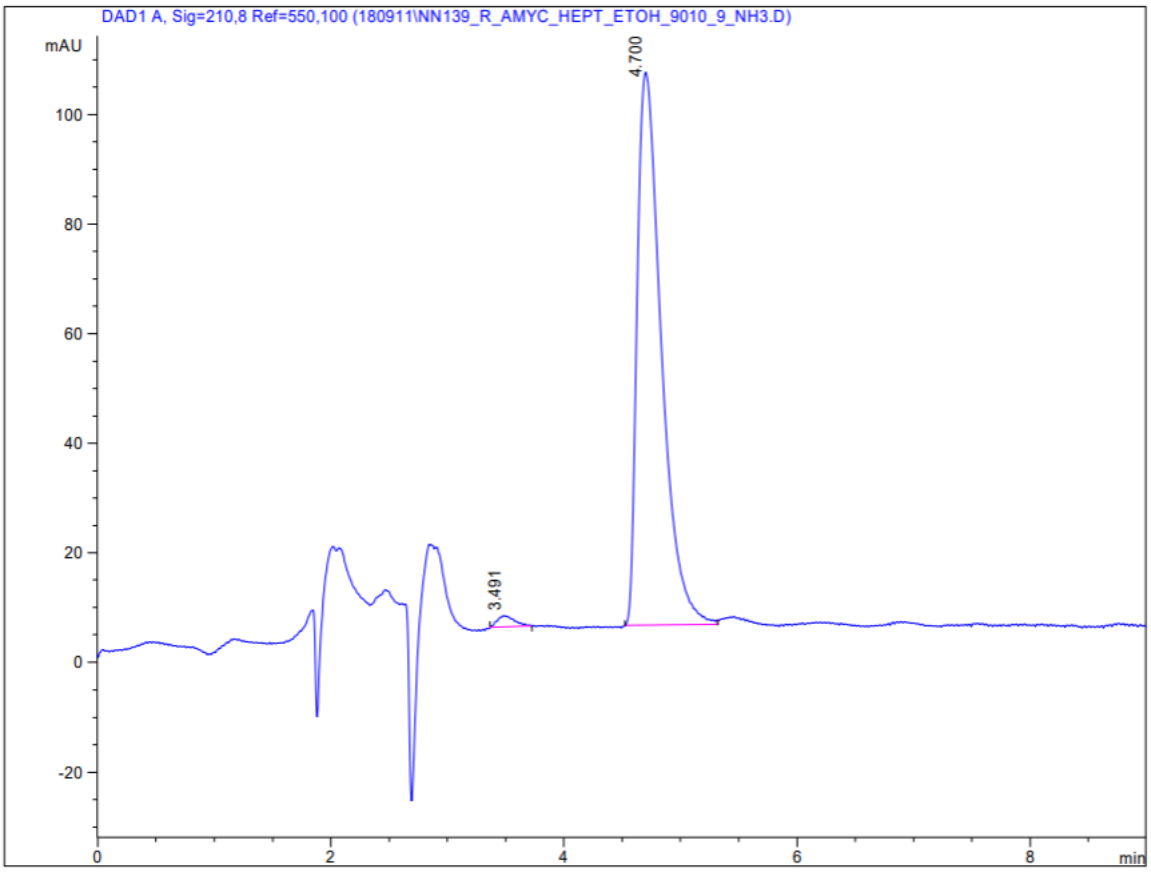
Column - Amy-C (4.6 mm x 150 mm, 5 µm)

Isocratic Conditions - 90:10 Heptane/EtOH (0.2% v/v NH3)

Flow Rate - 1 mL/min

Monitored - 210 nm





#	Meas. R	Height	Width	Area	Area %	Symmetr
1	3.491	2.082	0.171	21.422	1.451	0.759
2	4.700	101.024	0.240	1.455e3	98.549	0.522

Column Conditions:

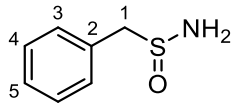
Column - Amy-C (4.6 mm x 150 mm, 5 µm)

Isocratic Conditions - 90:10 Heptane/EtOH (0.2% v/v NH3)

Flow Rate - 1 mL/min

Monitored - 210 nm

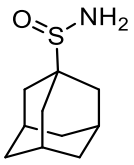
Benzyl Sulfinamide (264)



To a dried round bottomed flask under argon was added acetic acid (0.47 mL, 8.1 mmol), benzyl thiol (0.94 mL, 8.1 mmol) and sulfuryl chloride (0.2 mL, 3.4 mmol) dropwise. The mixture was cooled to -40 °C and additional sulfuryl chloride (1.2 mL, 14 mmol) was added dropwise over 30 minutes then the mixture was allowed to stir at -40 °C for 3 hours. The solution was warmed to room temperature and allowed to stir for 2 hours followed by the removal of all volatiles to give crude benzyl sulfinyl chloride which was confirmed by ^{1}H NMR. The crude sulfinyl chloride was dissolved in DCM (81 mL) and ammonia was bubbled through the solution for 30 minutes. The mixture was washed with water (200 mL) and the organic layer was removed. The aqueous was washed with DCM (2 x 50 mL) and the organic layers were combined and dried (Na_2SO_4). The solvent was removed to give crude product as a yellow solid which was purified by column chromatography with EtOAc as the eluent to give the title compound as a white solid (442 mg, 2.8 mmol, 35%).

R_f = 0.47 (100% EtOAc); **ν_{max}** (cm^{-1}) = 3236, 3061, 3029, 2924, 1574, 1493, 1454, 1417, 1183, 993, 774, 726, 697, 601, 475, 440; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 – 7.28 (m, 5H, H-3, H-4 & H-5), 4.07 – 3.80 (m, 4H, H-1 & NH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 131.1 (C-3 or C-4), 128.9 (C-3 or C-4), 128.6 (C-2 or C-5), 128.1 (C-2 or C-5), 61.8 (C-1); **HRMS** (ESI) m/z calculated for C_7H_9NNaSO = 178.0303 $[M+Na]^+$; found 178.0303. Compound not previously reported.

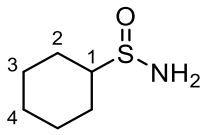
Adamantane-1-sulfinamide (254)



To a dried round bottomed flask under argon was added aluminium chloride (2.0 g, 15 mmol) and the flask was cooled to -15 °C. Thionyl chloride (10 mL, 51 mmol) was added portion wise forming a colourless solution. Adamantane (2.0 g, 15 mmol) was added portion wise over 1 hour and the solution was then stirred at -15 °C for an additional 1.5 hours. The volatiles were removed by placed under reduced pressure and the resultant residue was dissolved in DCM (100 mL) followed by bubbling ammonia gas through the solution for 30 minutes. The resultant emulsion was washed with water (200 mL) and the aqueous was extracted DCM (2 x 50 mL). The combined organic layers were washed with brine and dried (Na_2SO_4) followed by removal of the solvent under reduced pressure to afford the crude product as a yellow solid. The product was purified by column chromatography to give the title compound as a white solid (1.35 g, 6.77 mmol, 46%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (s, 2H), 2.21 – 2.14 (m, 3H), 1.94 – 1.66 (m, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 57.2, 36.6, 34.4, 28.7; **HRMS** (ESI) m/z calculated for $C_{10}H_{17}NNaSO$ = 222.0929 $[M+Na]^+$; found 222.0920. **Data agrees with literature.**[123]

Cyclohexane Sulfinamide (263)

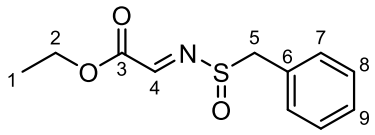


To a dried round bottomed flask under argon was added acetic acid (0.34 mL, 5.9 mmol), Cyclohexane thiol (0.69 g, 5.9 mmol) and sulfuryl chloride (0.2 mL, 3.4 mmol) dropwise. The mixture was cooled to -40 °C and additional sulfuryl chloride (0.81 mL, 9.1 mmol) was added dropwise over 30 mins then the mixture was stirred at -40 °C for 3 hours. The solution was warmed to room temperature and allowed to stir for 2 hours followed by the removal of all volatiles to give crude cyclohexane sulfinyl chloride

which was confirmed by ^{1}H NMR. The crude sulfinyl chloride was dissolved in DCM (59 mL) and ammonia was bubbled through the solution for 30 mins. The mixture was washed with water (200 mL) and the organic layer was removed. The aqueous was washed with DCM (2 x 50 mL) and the organic layers were combined and dried (Na_2SO_4). The solvent was removed to give crude product as a yellow solid which was purified by column chromatography with EtOAc as the eluent to give the title compound as a white solid (390 mg, 2.7 mmol, 46%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (s, 2H, NH_2), 2.47 (tt, *J* = 11.3, 3.7 Hz, 1H, H-1), 2.06 – 2.02 (m, 2H), 1.91 – 1.87 (m, 2H), 1.76 – 1.65 (m, 1H), 1.55 – 1.13 (m, 5H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 63.8 (C-1), 25.9, 25.7, 25.5, 25.3, 25.2; **HRMS** (ESI) m/z calculated for $C_6H_{13}NNaSO$ = 170.0616 $[M+Na]^+$; found 170.0615. **Data agrees with literature.**[124]

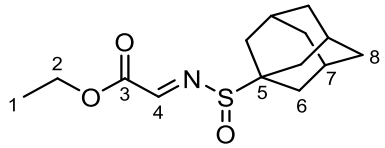
Ethyl (*E*)-2-((benzylsulfinyl)imino)acetate (267)



264 (260 mg, 1.7 mmol) was added to a dried flask under argon with 4 Å molecular sieves. A solution of ethyl glyoxylate (3.3 mmol) in DCM (16.5 mL) was added and solution was stirred for 16 hours at 21 °C. The solution was filtered through celite and washed with DCM followed by the removal of the solvent under reduced pressure to give the crude product as a yellow oil. The crude product was purified by column chromatography with an eluent of 15% ethyl acetate in petrol to give the title compound a s a colourless liquid (227 mg, 0.95 mmol, 57%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H, H-4), 7.41 – 7.15 (m, 5H, H-7, H-8 & H-9), 4.36 (q, *J* = 7.2 Hz, 2H, H-2), 4.28 (d, *J* = 13.0 Hz, 1H, H-5), 3.99 (d, *J* = 13.0 Hz, 1H, H-5), 1.36 (t, *J* = 7.2 Hz, 3H, H-1); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.9 (C-3), 155.2 (C-4), 131.2 (C-6), 128.8 (C-7, C-8 or C-9), 128.5 (C-7, C-8 or C-9), 127.0 (C-7, C-8 or C-9), 62.6 (C-2), 60.3 (C-5), 14.1 (C-1); **HRMS** (ESI) m/z calculated for $C_{11}H_{13}NNaSO_3$ = 262.0514 $[M+Na]^+$; found 262.0509.

Ethyl (*E*)-2-(((-adamantan-1-yl)sulfinyl)imino)acetate (265)

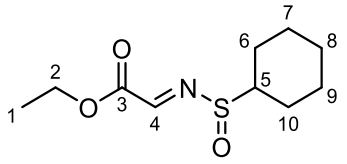


A solution of ethyl glyoxylate (0.37 g, 3.3 mmol) in DCM (16.5 mL) was added to a dried round bottomed flask under argon containing **254** (0.33 g, 1.7 mmol) and 4Å molecular sieves. The solution was stirred for 18 hours then filtered through celite and washed with DCM. The solvent was removed

to afford a yellow oil which was purified by column chromatography (15% ethyl acetate in petrol) to afford the title compound as a white solid (0.37 g, 1.3 mmol, 79%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 2.4 Hz, 1H, H-4), 4.38 (qd, *J* = 7.2, 2.4 Hz, 2H, H-2), 2.19 – 2.13 (m, 3H, H-7), 2.02 – 1.90 (m, 3H, H-6 or H-8), 1.85 – 1.65 (m, 9H, H-6 or H-8), 1.38 (t, *J* = 7.2, 3H, H-1); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.2 (C-3), 155.5 (C-4), 62.5 (C-2), 61.4 (C-5), 36.3 (C-6 or C-8), 35.1 (C-6 or C-8), 29.0 (C-7), 14.2 (C-1); **HRMS** (ESI) calculated for $C_{14}H_{21}NNaO_3S$ = 306.1140 $[M+Na]^+$; found 306.1125.

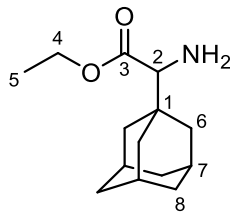
Ethyl (*E*)-2-((cyclohexylsulfinyl)imino)acetate (266)



A solution of ethyl glyoxylate (0.37 g, 3.3 mmol) in DCM (16.5 mL) was added to a dried round bottomed flask under argon containing **263** (0.24 g, 1.7 mmol) and 4Å molecular sieves. The solution was stirred for 18 hours then filtered through celite and washed with DCM. The solvent was removed to afford a yellow oil which was purified by column chromatography (15% ethyl acetate in petrol) to afford the title compound as a colourless oil (0.248 g, 1.07 mmol, 65%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 2.86 (tt, *J* = 11.9, 3.7 Hz, 1H), 2.19 – 2.10 (m, 1H), 1.96 – 1.84 (m, 2H), 1.79 – 1.65 (m, 2H), 1.55 – 1.44 (m, 2H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.35 – 1.18 (m, 3H), **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.2, 155.1, 62.7, 62.2, 26.3, 25.7, 25.5, 25.3, 23.0, 14.2. **HRMS** (ESI) calculated for $C_{10}H_{17}NNaO_3S$ = 254.0827; found 254.0835.

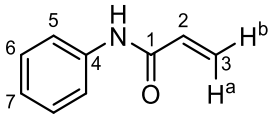
Ethyl 2-(adamantan-1-yl)-2-aminoacetate (269)



To a Schlenk flask was added ethyl (*E*)-2-(((-adamantan-1-yl)sulfinyl)imino)acetate (100 mg, 0.35 mmol), AIBN (6.0 mg, 0.035 mmol) and toluene (3.50 mL). The mixture was degassed and placed under argon *via* five freeze-pump-thaw cycles then heated at 70 °C for 16 hours. The solvent was removed under reduced pressure followed by addition of 1M HCl solution (5 mL). The solution was washed with ethyl acetate (1 x 3 mL) and neutralised with saturated $Na_2CO_{3\ (aq)}$ solution resulting in a white precipitate. The aqueous layer was then washed with ethyl acetate (3 x 3 mL) and the combined organic layers were dried (Na_2SO_4). The solvent was removed under reduced pressure to give the crude product as a colourless liquid. Purification by column chromatography was performed (40% EtOAc in petrol) to give the title compound as a colourless oil (24 mg, 0.1mmol, 29%).

R_f = 0.18 in 40% ethyl acetate in petrol; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 4.17 (q, *J* = 7.1 Hz, 2H, H-4), 2.98 (s, 1H, H-2), 1.99 (m, 3H, H-7), 1.79 – 1.59 (m, 9H, H-6 or H-8), 1.56 – 1.45 (m, 5H, H-6 & NH_2), 1.30 – 1.26 (t, *J* = 7.1 Hz, m, 3H, H-5); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.6 (C-3), 64.4 (C-2), 60.4 (C-4), 38.6 (C-6 or C-8), 37.1 (C-6 or C-8), 36.2 (C-1), 28.5 (C-7), 14.5 (C-5); **HRMS** (ESI) calculated for $C_{14}H_{24}NO_2$ = 238.1807 $[M+H]^+$; found 238.1810.

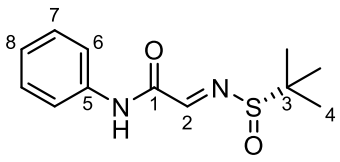
_N_-Phenylacrylamide (278)



Water (5 mL), acetone (20 mL), K_2CO_3 (2.8 g, 20 mmol) and aniline (0.91 mL, 10 mL) were combined then cooled to 0 °C. Acryloyl chloride (1.1 mL, 20 mmol) was added dropwise and the mixture was stirred for 1 hour. The mixture was filtered and the filtrate was concentrated under reduced pressure then dissolved in water (20 mL) and extracted with DCM (3 x 20 mL). The combined organic layers were combined then dried (Na_2SO_4). A single crystal of BHT was added and the solvent was removed by bubbling air through the solution to afford the crude product as an off white solid. The compound was purified by column chromatography (15-30% EtOAc in petrol) and the solvent was removed by bubbling air through the solution after adding a single BHT crystal to afford the title compound as a white solid (1.37 g, 93%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (s, 1H, N-H), 7.70 – 7.63 (m, 2H, H-5 or H-6), 7.36 – 7.29 (m, 2H, H-5 or H-6), 7.11 – 7.03 (m, 1H, H-7), 6.44 (dd, *J* = 17.0, 10.1 Hz, 1H, H-2), 6.25 (dd, *J* = 17.0, 2.1 Hz, 1H, H-3a), 5.75 (dd, *J* = 10.1, 2.1 Hz, 1H, H-3b); **^{13}C NMR** (101 MHz, DMSO) δ 163.1 (C-1), 139.0, 131.9, 128.7, 126.8, 123.5, 119.3 (C-2, C-3, C-4, C-5, C-6 & C-7). Agrees with literature.[125]

(*S,E*)-2-((Tert-butylsulfinyl)imino)-*N*-phenylacetamide (279)



N-Phenyl acrylamide (300 mg, 2.04 mmol) was dissolved in DCM (10 mL) and cooled to -78 °C then placed under ozone for 45 minutes. The reaction was judged to be complete by the formation of a blue solution. Dimethyl sulfide was added, and the solution was allowed to warm to room temperature and stirred for 16 hours. The solvent was removed under reduced pressure then washed

with water (50 mL) and extracted with diethyl ether (20 mL) then the combined organic fractions were dried (Na_2SO_4). The solvent was removed to afford a crude intermediate (130 mg). The crude intermediate was placed under an argon atmosphere, dissolved in DCM (9 mL) then 4Å molecular sieves (5 g) and (*S*)-2-methyl-2-propanesulfinamide (109 mg, 0.9 mmol) were added. The solution was stirred at room temperature for 16 hours and the mixture was filtered through celite followed by removal of the solvent under reduced pressure to afford an oil (249 mg). The oil was purified by column chromatography (20% EtOAc in petrol) to afford the title compound as a colourless oil (33 mg, 0.13 mmol, 14%).

R_f = 0.67 in 50% EtOAc in petrol; **ν_{max}** (cm^{-1}) = 3223, 2954, 2927, 1601, 1438, 1248, 1074, 1050, 1031, 844, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.56 (s, 1H, N-H), 8.04 (s, 1H, H-2), 7.73 – 7.57 (m, 2H, H-6 or H-7), 7.44 – 7.30 (m, 2H, H-6 or H-7), 7.21 – 7.15 (m, 1H, H-8), 1.30 (s, 9H, H-4); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.3(C-1), 158.4 (C-2), 136.7 (C-5), 129.4 (C-6 or C-7), 125.4 (C-8), 119.9 (C-6 or C-7), 59.0 (C-3), 22.9 (C-4); **HRMS** (ESI) calculated for $C_{12}H_{16}N_2NaO_2S$ = 275.0830 $[M+Na]^+$; found 275.0828.

References

1 S. Singh, N. K. Kumar, P. Dwiwedi, J. Charan, R. Kaur, P. Sidhu and V. K. Chugh, *Curr. Clin. Pharmacol.*, 2018, **13**, 85–99.

2 J. Lieberman, *Nat. Struct. Mol. Biol.*, 2018, 25, 357–364.

3 A. Mullard, *Nat. Rev. Drug Discov.*, 2019, **18**, 85–89.

4 F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752–6756.

5 F. Lovering, *Medchemcomm*, 2013, **4**, 515–519.

6 V. Sedov and R. K. Stuart, *Ther. Adv. Hematol.*, 2017, **8**, 185–195.

7 H. Ratni, T. M. Ballard, C. Bissantz, T. Hoffmann, P. Jablonski, F. Knoflach, H. Knust, P. Malherbe, M. Nettekoven, A. Patiny-Adam, C. Riemer, M. Schmitt and W. Spooren, *Bioorganic Med. Chem. Lett.*, 2010, **20**, 6735–6738.

8 S. He, Z. Ye, P. H. Dobbelaar, I. K. Sebhat, L. Guo, J. Liu, T. Jian, Y. Lai, C. L. Franklin, R. K. Bakshi, J. P. Dellureficio, Q. Hong, N. N. Tsou, R. G. Ball, D. E. Cashen, W. J. Martin, D. H. Weinberg, T. MacNeil, R. Tang, C. Tamvakopoulos, Q. Peng, R. R. Miller, R. A. Stearns, H. Y. Chen, A. S. Chen, A. M. Strack, T. M. Fong, D. E. MacIntyre, M. J. Wyvratt and R. P. Nargund, *Bioorganic Med. Chem. Lett.*, 2010, **20**, 2106–2110.

9 K. L. Jensen, G. Dickmeiss, H. Jiang, L. Albrecht and K. A. Jørgensen, *Acc. Chem. Res.*, 2012, **45**, 248–264.

10 J. Friedrichs, M. LüßMann and I. Frank, *ChemPhysChem*, 2010, **11**, 3339–3342.

11 J. Sauer, *Angew. Chemie Int. Ed. English*, 1967, **6**, 16–33.

12 P. Allway and R. Grigg, *Tetrahedron Lett.*, 1991, **32**, 5817–5820.

13 J. M. Longmire, B. Wang and X. Zhang, *J. Am. Chem. Soc.*, 2002, **124**, 13400–13401.

14 A. S. Gothelf, K. V. Gothelf, R. G. Hazell and K. A. Joørgensen, *Angew. Chemie - Int. Ed.*, 2002, **41**, 4236–4238.

15 R. Robles-Machín, I. Alonso, J. Adrio and J. C. Carretero, *Chem. - A Eur. J.*, 2010, **16**, 5286–5291.

16 Y. Yamashita, T. Imaizumi and S. Kobayashi, *Angew. Chemie - Int. Ed.*, 2011, **50**, 4893–4896.

17 S. Padilla, R. Tejero, J. Adrio and J. C. Carretero, *Org. Lett.*, 2010, **12**, 5608–5611.

18 A. Pascual-Escudero, M. González-Esguevillas, S. Padilla, J. Adrio and J. C. Carretero, *Org. Lett.*, 2014, **16**, 2228–2231.

19 R. Joseph, C. Murray and P. Garner, *Org. Lett.*, 2014, **16**, 1550–1553.

20 J. Hernández-Toribio, S. Padilla, J. Adrio and J. C. Carretero, *Angew. Chemie Int. Ed.*, 2012, **51**, 8854–8858.

21 A. Pascual-Escudero, A. de Cózar, F. P. Cossío, J. Adrio and J. C. Carretero, *Angew. Chemie Int. Ed.*, 2016, **55**, 15334–15338.

22 Y. Xiong, Z. Du, H. Chen, Z. Yang, Q. Tan, C. Zhang, L. Zhu, Y. Lan and M. Zhang, *J. Am. Chem. Soc.*, 2019, **141**, 961–971.

23 J. Adrio and J. C. Carretero, *Chem. Commun.*, 2014, **50**, 12434–12446.

24 B. M. Trost, D. B. Horne and M. J. Woltering, *Chem. - A Eur. J.*, 2006, **12**, 6607–6620.

25 F. Tian, F. S. He, H. Deng, W. L. Yang and W. P. Deng, *Org. Lett.*, 2018, **20**, 3838–3842.

26 T. Hashimoto and K. Maruoka, *Chem. Rev.*, 2015, **115**, 5366–5412.

27 S. S. Chow, M. Nevalainen, C. A. Evans and C. W. Johannes, *Tetrahedron Lett.*, 2007, **48**, 277–280.

28 J. L. Vicario, S. Reboredo, D. Badía and L. Carrillo, *Angew. Chemie Int. Ed.*, 2007, **46**, 5168–5170.

29 I. Ibrahem, R. Rios, J. Vesely and A. Córdova, *Tetrahedron Lett.*, 2007, **48**, 6252–6257.

30 S. Reboredo, E. Reyes, J. L. Vicario, D. Badía, L. Carrillo, A. de Cózar and F. P. Cossío, *Chem. - A Eur. J.*, 2012, **18**, 7179–7188.

31 S. Lin, L. Deiana, G.-L. Zhao, J. Sun and A. Córdova, *Angew. Chemie Int. Ed.*, 2011, **50**, 7624–7630.

32 Z. Dong, Y. Zhu, B. Li, C. Wang, W. Yan, K. Wang and R. Wang, *J. Org. Chem.*, 2017, **82**, 3482–3490.

33 X.-H. Chen, W.-Q. Zhang and L.-Z. Gong, *J. Am. Chem. Soc.*, 2008, **130**, 5652–5653.

34 J. Yu, W.-J. Chen and L.-Z. Gong, *Org. Lett.*, 2010, **12**, 4050–4053.

35 C. Wang, X. H. Chen, S. M. Zhou and L. Z. Gong, *Chem. Commun.*, 2010, **46**, 1275–1277.

36 F. Shi, S. W. Luo, Z. L. Tao, L. He, J. Yu, S. J. Tu and L. Z. Gong, *Org. Lett.*, 2011, **13**, 4680–4683.

37 C. Guo, J. Song and L. Z. Gong, *Org. Lett.*, 2013, **15**, 2676–2679.

38 F. Shi, R. Y. Zhu, X. Liang and S. J. Tu, *Adv. Synth. Catal.*, 2013, **355**, 2447–2458.

39 L. Tian, G. Q. Xu, Y. H. Li, Y. M. Liang and P. F. Xu, *Chem. Commun.*, 2014, **50**, 2428–2430.

40 C. Nájera, M. D. G. Retamosa, J. M. Sansano, A. De Cózar and F. P. Cossío, *European J. Org. Chem.*, 2007, 5038–5049.

41 J. A. Gálvez, M. D. Díaz-De-Villegas, M. Alías and R. Badorrey, *J. Org. Chem.*, 2013, **78**, 11404–11413.

42 E. R. Ashley, E. G. Cruz and B. M. Stoltz, *J. Am. Chem. Soc.*, 2003, **125**, 15000–15001.

43 P. Garner and O. Dogan, *J. Org. Chem.*, 1994, **59**, 4–6.

44 S. Takano, M. Moriya and K. Ogasawara, *Tetrahedron: Asymmetry*, 1992, **3**, 681–684.

45 A. Padwa, Y.-Y. Chen, U. Chiacchio and W. Dent, *Tetrahedron*, 1985, **41**, 3529–3535.

46 M. T. Robak, M. A. Herbage and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 3600–3740.

47 P. Moreau, M. Essiz, J. Y. Mérour and D. Bouzard, *Tetrahedron Asymmetry*, 1997, **8**, 591–598.

48 G. Liu, D. A. Cogan and J. A. Ellman, *J. Am. Chem. Soc.*, 1997, **119**, 9913–9914.

49 D. J. Weix and J. A. Ellman, *Org. Lett.*, 2003, **5**, 1317–1320.

50 M. T. Robak, M. A. Herbage and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 3600–3740.

51 N. Plobeck and D. Powell, *Tetrahedron: Asymmetry*, 2002, **13**, 303–310.

52 K. Chandra Babu, R. Buchi Reddy, K. Mukkanti, G. Madhusudhan and P. Srinivasulu, *J. Chem. Pharm. Res.*, 2012, **4**, 4988–4994.

53 C. J. Moody, P. T. Gallagher, A. P. Lightfoot and A. M. Z. Slawin, *J. Org. Chem.*, 1999, **64**, 4419–4425.

54 J. A. Fernández-Salas, M. C. Maestro, M. M. Rodríguez-Fernández, J. L. García-Ruano and I. Alonso, *Org. Lett.*, 2013, **15**, 1658–1661.

55 P. A. Baguley and J. C. Walton, *Angew. Chemie Int. Ed.*, 1998, **37**, 3072–3082.

56 A. F. Garrido-Castro, H. Choubane, M. Daaou, M. C. Maestro and J. Alemán, *Chem. Commun.*, 2017, **53**, 7764–7767.

57 J. García Ruano, I. Fernández, M. del Prado Catalina and A. A. Cruz, *Tetrahedron: Asymmetry*, 1996, **7**, 3407–3414.

58 D. Morton, D. Pearson, R. A. Field and R. A. Stockman, *Synlett*, 2003, 1985–1988.

59 I. Fernández, V. Valdivia, B. Gori, F. Alcudia, E. Álvarez and N. Khiar, *Org. Lett.*, 2005, **7**, 1307–1310.

60 M. E. Scott and M. Lautens, *J. Org. Chem.*, 2008, **73**, 8154–8162.

61 T. Andreassen, M. Lorentzen, L.-K. Hansen and O. R. Gautun, *Tetrahedron*, 2009, **65**, 2806–2817.

62 C. M. Si, Z. Y. Mao, H. Q. Dong, Z. T. Du, B. G. Wei and G. Q. Lin, *J. Org. Chem.*, 2015, **80**, 5824–5833.

63 K. Maruoka and T. Ooi, *Chem. Rev.*, 2003, **103**, 3013–3028.

64 A. Strecker, *Justus Liebigs Ann. Chem.*, 1850, **75**, 27–45.

65 A. Strecker, *Justus Liebigs Ann. Chem.*, 1854, **91**, 349–351.

66 H. Strecker, *Justus Liebigs Ann. Chem.*, 1864, **130**, 217–223.

67 R. Jay and T. Curtius, *Berichte der Dtsch. Chem. Gesellschaft*, 1894, **27**, 59–62.

68 A. Lipp, *Justus Liebig's Ann. der Chemie*, 1880, **205**, 1–32.

69 F. Ehrlich, *Berichte der Dtsch. Chem. Gesellschaft*, 1907, **40**, 2538–2562.

70 F. Tiemann, *Berichte der Dtsch. Chem. Gesellschaft*, 1880, **13**, 381–385.

71 J. Wang, X. Liu and X. Feng, *Chem. Rev.*, 2011, **111**, 6947–6983.

72 O. P. Thomas, A. Zaparucha and H. P. Husson, *European J. Org. Chem.*, 2002, **2002**, 157–162.

73 E. J. Corey, R. K. Bakshi and S. Shibata, *J. Am. Chem. Soc.*, 1987, **109**, 5551–5553.

74 A. Berkessel, S. Mukherjee and J. Lex, *Synlett*, 2006, 41–44.

75 A. M. Seayad, B. Ramalingam, K. Yoshinaga, T. Nagata and C. L. L. Chai, *Org. Lett.*, 2010, **12**, 264–267.

76 A. M. Seayad, B. Ramalingam, C. L. L. Chai, C. Li, M. V. Garland and K. Yoshinaga, *Chem. - A Eur. J.*, 2012, **18**, 5693–5700.

77 K. Harada, *Nature*, 1963, **200**, 1201.

78 E. Takahashi, H. Fujisawa, T. Yanai and T. Mukaiyama, *Chem. Lett.*, 2005, **34**, 604–605.

79 H. Wang, X. Zhao, Y. Li and L. Lu, *Org. Lett.*, 2006, **8**, 1379–1381.

80 N. Halland, A. Braunton, S. Bachmann, M. Marigo and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2004, **126**, 4790–4791.

81 S. Mukherjee, J. W. Yang, S. Hoffmann and B. List, *Chem. Rev.*, 2007, 107, 5471–5569.

82 Q. Wei, F. Zhang, X. Zhao, C. Wang, J. Xiao and W. Tang, *Org. Biomol. Chem.*, 2017, **15**, 5468–5471.

83 D. H. Hua, N. Lagneau, H. Wang and J. Chen, *Tetrahedron: Asymmetry*, 1995, **6**, 349–352.

84 E. Maciá, F. Foubelo and M. Yus, *Tetrahedron*, 2016, **72**, 6001–6010.

85 S. Ni, A. F. Garrido-Castro, R. R. Merchant, J. N. de Gruyter, D. C. Schmitt, J. J. Mousseau, G. M. Gallego, S. Yang, M. R. Collins, J. X. Qiao, K. S. Yeung, D. R. Langley, M. A. Poss, P. M. Scola, T. Qin and P. S. Baran, *Angew. Chemie - Int. Ed.*, 2018, **57**, 14560–14565.

86 T. Ooi, M. Kameda and K. Maruoka, *J. Am. Chem. Soc.*, 2003, **125**, 5139–5151.

87 F. A. Davis and W. McCoull, *J. Org. Chem.*, 1999, **64**, 3396–3397.

88 B. Jiang, C. G. Yang and X. H. Gu, *Tetrahedron Lett.*, 2001, **42**, 2545–2547.

89 D. Naskar, A. Roy, W. L. Seibel and D. E. Portlock, *Tetrahedron Lett.*, 2003, **44**, 8865–8868.

90 J. Kong, M. McLaughlin, K. Belyk and R. Mondschein, *Org. Lett.*, 2015, **17**, 5520–5523.

91 W. Huang, J. L. Ye, W. Zheng, H. Q. Dong and B. G. Wei, *J. Org. Chem.*, 2013, **78**, 11229–11237.

92 A. S. Bommarius, M. Schwarm, K. Stingl, M. Kottenhahn, K. Huthmacher and K. Drauz, *Tetrahedron: Asymmetry*, 1995, **6**, 2851–2888.

93 A. S. Bommarius, M. Schwarm, K. Stingl, M. Kottenhahn, K. Huthmacher and K. Drauz, *Tetrahedron: Asymmetry*, 1995, **6**, 2851–2888.

94 D. Meister, S. M. Taimoory and J. F. Trant, *Pept. Sci.*, 2018, **111**, e24058.

95 G. Desimoni, G. Faita and K. A. Jørgensen, *Chem. Rev.*, 2006, **106**, 3561–3651.

96 Y.-P. Xue, C.-H. Cao and Y.-G. Zheng, *Chem. Soc. Rev.*, 2018, **47**, 1516–1561.

97 W. Hummel, M. Kuzu and B. Geueke, *Org. Lett.*, 2003, **5**, 3649–3650.

98 D. J. Augeri, J. A. Robl, D. A. Betebenner, D. R. Magnin, A. Khanna, J. G. Robertson, A. Wang, L. M. Simpkins, P. Taunk, Q. Huang, S. P. Han, B. Abboa-Offei, M. Cap, L. Xin, L. Tao, E. Tozzo, G. E. Welzel, D. M. Egan, J. Marcinkeviciene, S. Y. Chang, S. A. Biller, M. S. Kirby, R. A. Parker and L. G. Hamann, *J. Med. Chem.*, 2005, **48**, 5025–5037.

99 C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322–5363.

100 G. Pandey, G. Lakshmaiah and G. Kumaraswamy, *J. Chem. Soc. Chem. Commun.*, 1992, 1313–1314.

101 X. Lv, Q. Xiang and Q. Zeng, *Org. Prep. Proced. Int.*, 2014, **46**, 164–175.

102 N. Elgrishi, K. J. Rountree, B. D. McCarthy, E. S. Rountree, T. T. Eisenhart and J. L. Dempsey, *J. Chem. Educ.*, 2018, **95**, 197–206.

103 M. D. Arning and S. D. Minteer, in *Handbook of Electrochemistry*, Elsevier, 2007, pp. 813–827.

104 S. Wu, X. Lei, E. Fan and Z. Sun, *Org. Lett.*, 2018, **20**, 522–525.

105 W. Thaharn, T. Bootwicha, D. Soorukram, C. Kuhakarn, S. Prabpai, P. Kongsaeree, P. Tuchinda, V. Reutrakul and M. Pohmakotr, *J. Org. Chem.*, 2012, **77**, 8465–8479.

106 Y. Guo and W. S. Jenks, *J. Org. Chem.*, 1997, **62**, 857–864.

107 V. S. Yarmolchuk, P. K. Mykhailiuk and I. V. Komarov, *Tetrahedron Lett.*, 2011, **52**, 1300–1302.

108 J. Shi, J. S. Stover, L. R. Whitby, P. K. Vogt and D. L. Boger, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 6038–6041.

109 S. P. Midya, J. Rana, T. Abraham, B. Aswin and E. Balaraman, *Chem. Commun.*, 2017, **53**, 6760–6763.

110 Y. Morimoto, Y. Terao and K. Achiwa, *Chem. Pharm. Bull.*, 1987, **35**, 2266–2271.

111 B. Mikhova, S. L. Spassov, K. Popandova, V. Dryanska, C. Ivanov, H. Duddeck and M. Kaiser, *J. Mol. Struct.*, 1987, **161**, 231–235.

112 E. A. Salter, D. C. Forbes and A. Wierzbicki, *Int. J. Quantum Chem.*, 2012, **112**, 509–518.

113 P. M. Matos, W. Lewis, J. C. Moore and R. A. Stockman, *Org. Lett.*, 2018, **20**, 3674–3677.

114 H. Stetter, M. Krause and W.-D. Last, *Angew. Chemie*, 1968, **80**, 970–971.

115 J. Bai, B. K. Zambroń and P. Vogel, *Org. Lett.*, 2014, **16**, 604–607.

116 E. Block, A. Schwan and D. A. Dixon, *J. Am. Chem. Soc.*, 1992, **114**, 3492–3499.

117 J. Furukawa, N. Kawabata and J. Nishimura, *Tetrahedron*, 1968, **24**, 53–58.

118 F. De Vleeschouwer, V. Van Speybroeck, M. Waroquier, P. Geerlings and F. De Proft, *J. Org. Chem.*, 2008, **73**, 9109–9120.

119 J. A. Burkhard, B. H. Tchitchanov and E. M. Carreira, *Angew. Chemie - Int. Ed.*, 2011, **50**, 5379–5382.

120 A. Berkessel, S. Das, D. Pekel and J.-M. Neudörfl, *Angew. Chemie Int. Ed.*, 2014, **53**, 11660–11664.

121 J. L. M. Matos, S. Vásquez-Céspedes, J. Gu, T. Oguma and R. A. Shenvi, *J. Am. Chem. Soc.*, , DOI:10.1021/jacs.8b11699.

122 M. D. Broadhurst and D. J. Cram, *J. Am. Chem. Soc.*, 1974, 96, 581–583.

123 Z. Han, D. Krishnamurthy, P. Grover, Q. K. Fang and C. H. Senanayake, *J. Am. Chem. Soc.*, 2002, **124**, 7880–7881.

124 F. Xue, F. Wang, J. Liu, J. Di, Q. Liao, H. Lu, M. Zhu, L. He, H. He, D. Zhang, H. Song, X.-Y. Liu and Y. Qin, *Angew. Chemie Int. Ed.*, 2018, **57**, 6667–6671.

125 S. Chanthamath, S. Takaki, K. Shibatomi and S. Iwasa, *Angew. Chemie - Int. Ed.*, 2013, **52**, 5818–5821.