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Sulfur(IV)-Mediated Carbon-Carbon Bond Formation

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Finally, I extend my greatest thanks to my family and friends from outside of university, who have provided tremendous support and much needed distraction throughout my PhD.

Abstract

This thesis details the development of methods for and application of the synthesis of carbon-carbon bonds using organic sulfur(IV) chemistry. More specifically, the formation of $C(sp^2)$-$C(sp^3)$ and $C(sp^3)$-$C(sp^3)$ bonds is explored in detail. The necessity for this research stems from a correlation between a high proportion of sp^3-centres in drug candidates, and their success in clinical trials. By facilitating the synthesis of drug candidates with higher fractions of sp^3-hybridised carbon atoms, it is hoped that the rate of candidates proceeding through clinical trials may increase.

The first topic addressed is the ligand coupling reactions of sulfoxides. In such reactions, the treatment of appropriately substituted sulfoxides with organometallic reagents forms $C(sp^2)$-$C(sp^3)$ coupling products *via* σ-sulfurane intermediates. These reactions have the ability to excel where transition metal-catalysed cross-couplings fail; in the coupling of electron-deficient (hetero)aromatic groups and alkyl groups. Very few reports have been published detailing the scope and utility of this reaction.

The application of this methodology to the synthesis of diarylmethanes is explored in detail. Diarylmethanes are designated as privileged structures for the presence of these moieties in a vast array of diversely functional drug products. Investigation of the scope of the ligand coupling reaction allows for the elucidation of (hetero)aromatic moieties which can undergo this reaction. The depth of analysis in which the scope of benzylic substituents is studied allowed for the elucidation of previously unreported trends, which have been assigned to steric and electronic characteristics of the σ-sulfurane intermediates. This knowledge gained is applied to the synthesis of both enantiomerically enriched diarylmethanes and well-known drug products.

Further exploration of the scope of ligand coupling reactions focusses on the coupling of α-functionalised alkyl groups. Remarkable success is found in this completely unexplored area. Benzylic ethers, carbamates and halides are synthesised through a combination of inter-molecular and intra-molecular ligand coupling reactions. It is proposed that these reactions would be suitable for use in the synthesis of natural products to prove their utility.

A newly-discovered sulfoxide homologation is detailed, which occurs upon reaction of sulfenate by-products with the aforementioned benzylic halides, both synthesised

by a ligand coupling reaction. This is particularly interesting since a similar homologated sulfoxide is found in the substructure of omeprazole, a blockbuster proton pump inhibitor.

The second topic addressed is the synthesis of (±)-TAN1251A. The envisaged route proceeds through a novel palladium-catalysed [3+2] cycloaddition of sulfinimines, forming methylene pyrrolidines. Previous work focussed on the use of this methodology to produce a diamine, mono-protected as a sulfonamide. A key aspect of the research presented in this thesis is the formation of the C ring of the spiro-fused 1,4-diazabicyclo[3.2.1]octane moiety. Initial investigations focus on the synthesis of a pyruvic acid fragment to react with the aforementioned diamine. This concept is developed into the use of pyruvic acid synthetic equivalents: azlactones. A late stage intermediate is produced, however formation of the C ring from this intermediate is not observed. Synthesis is hampered by the deprotection of the sulfonamide, which forms several by-products under the strongly acidic conditions required.

A revised retrosynthesis proposes that early deprotection of the diamine sulfonamide would prevent complications. The use of a simplified fragment to facilitate C ring formation is devised, comprising of an α-haloketone. Synthesis of the unprotected diamine is accelerated by serendipity, where a reductive amination also effects the elimination of a sulfinyl group. Formation of an α-haloketone fragment is found to be troublesome, however synthesis *via* the natural product chavicol provides the required functionality. A wide variety of conditions are examined to effect the combination of these fragments. While coupling of the fragments is successful in providing another late-stage intermediate of (±)-TAN1251A, formation of the desired C ring is not achieved. Finally, the potential to effect an enantioselective synthesis of (±)-TAN1251A is confirmed using a chiral sulfinamide to direct diastereoselective ketone reduction.

Abbreviations

ψ	Pseudorotation
Ac	Acetyl
Boc	*t*-Butoxycarbonyl
Bn	Benzyl
Bt	Benzotriazole
Bus	*t*-Butylsulfonyl
Cb	*N,N*-diisopropylaminocarbonyl
COSY	Correlation spectroscopy
CDI	Carbonyldiimidazole
CPME	Cyclopentyl methyl ether
CSA	Camphorsulfonic acid
Cy	Cyclohexyl
DCC	*N,N*'-Dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
dec.	Decomposes
DIBAL-H	Diisobutylaluminium hydride
DICHED	1,2-Dicyclohexyl-1,2-ethanediol
dioxane	1,4-Dioxane
DIPEA	*N,N*-Diisopropylethylamine
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	*N,N*-Dimethylformamide
DMP	Dess-Martin periodinane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone
DMSO	Dimethylsulfoxide
DPEphos	(Oxydi-2,1-phenylene)bis(diphenylphosphine)
DPPA	Diphenylphosphoryl azide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
ee	Enantiomeric excess
es	Enantioselectivity
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
HMDS	Hexamethyldisilamide
HMPA	Hexamethylphosphoramide
HRMS	High resolution mass spectrometry

Hz	Hertz
L	Ligand
LDA	Lithium diisopropylamide
M	Metal
Ms, mesyl	Methanesulfonyl
***m*CPBA**	3-Chloroperoxybenzoic acid
Ms	Methane sulfonyl
MS	Molecular sieves
NBS	*N*-bromosuccinimide
NMM	*N*-Methylmorpholine
NMO	*N*-Methylmorpholine-*N*-oxide
Nu	Nucleophile
Pg	Protecting group
Pin	Pinacol ester
Piv	Pivaloyl
PMB	*para*-Methoxybenzyl
PPTS	Pyridinium *para*-toluenesulfonate
Py/py	Pyridyl/pyridine
Red-Al®	Sodium bis(2-methoxyethoxy)aluminumhydride
rt	Room temperature
sat.	Saturated
TBAF	Tetrabutylammonium fluoride
TBDPS	*t*-Butyldiphenylsilyl
TBS	*t*-Butyldimethylsilyl
TBHP	*t*-Butyl hydroperoxide
TCA	Trichloroacetic acid
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
TLC	Thin layer chromatography
THF	Tetrahydrofuran
TMEDA	N,N,N',N'-Tetramethylethane-1,2-diamine
TMM	Trimethylenemethane
TMS	Trimethylsilyl
Tol	Tolyl
TPAP	Tetrapropylammonium perruthenate
Troc	2,2,2-Trichloroethyl carbonate
Ts, tosyl	*para*-Toluenesulfonyl
XRD	X-Ray diffraction

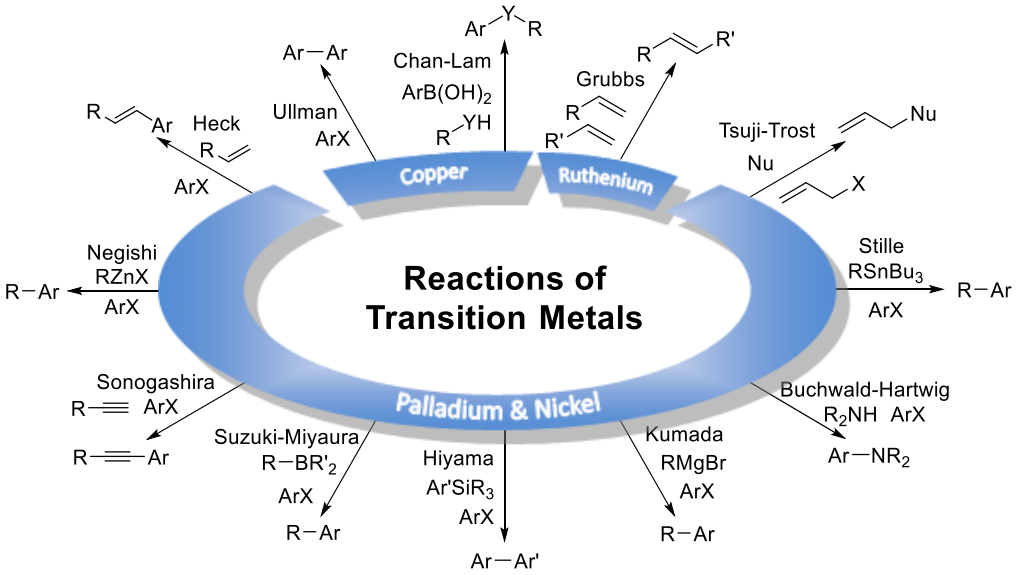
Chapter 1: Introduction

The increasing complexity of treatment of constantly evolving diseases is forming an impending problem for healthcare services globally. The World Health Organisation recognises the challenge imposed by antimicrobial resistance, which includes bacterial infection, parasites, viruses and fungi, as "an increasingly serious threat to global public health that requires action across all government sectors and society".[1] In order to treat such diseases, novel medicines must be produced which are more efficient, more specific and, hence, more effective.

Despite huge effort from pharmaceutical companies, the number of drugs obtaining market authorisation each year has decreased dramatically over the last decade. This decline is causing the costs for pharmaceutical companies to get one new drug to market to rapidly increase. One recent estimate puts the cost to develop and gain market approval for a drug at around $2.6 billion.[2–4] The reasons for this decline in the number of drugs reaching the market are complex, however attrition rates within phase II clinical trials have been widely accepted as a key factor in this figure.[5] Comparison of the causes for attrition of drugs in phase II trials highlights decreasing efficacy and safety of drug candidates as large and growing issues.[6] In order to understand the reasons for this decline in efficacy we must study the interaction of drug molecules with the human body and assess what we, as synthetic organic chemists, can do to rectify this.

A relatively small range of amino acid units are combined within the human body to form a huge variety of intricate and functionally diverse three-dimensional proteins.[7] The net result of protein intricacy is efficient action on very specific substrates, whether that may be a chemical transformation or a binding interaction. Interacting with such precise proteins in this manner to rebuff disease has very recently been achieved using biological medicines. These are elaborate and sometimes bespoke technologies, employing engineered biological molecules such as monoclonal antibodies.[8,9]

It has been suggested that within the small-molecule drug development process, a tendency has developed to use facile, robust chemistry to alter functionality in hit to lead optimisations.[10] One can envisage rapid diversification of molecules using chemistries such as the transition metal-catalysed cross-coupling methodologies which won the 2010 Nobel Prize in Chemistry (Scheme 1.1).



Scheme 1.1: Overview of transition metal-catalysed reactions

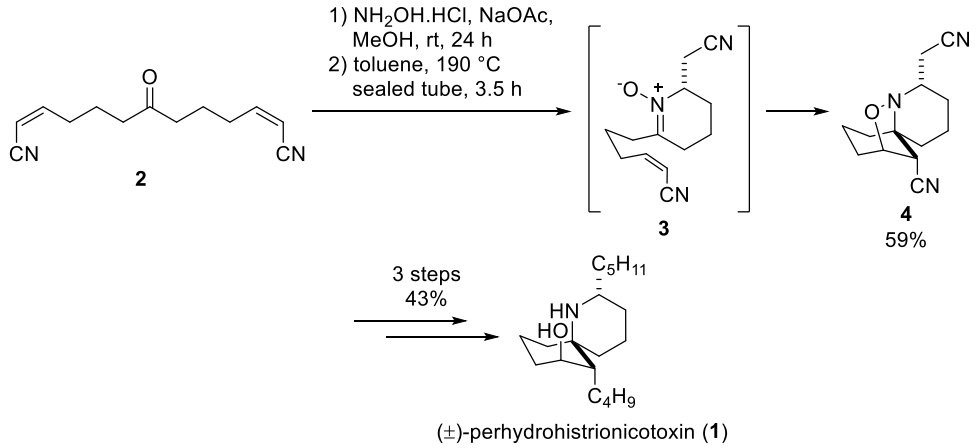
Such chemistries are much more amenable to the coupling of two sp^2-hybridised centres, leading to sp^2-rich final compounds. By the nature of sp^2-hybridised atoms, these molecules may exhibit large areas of two dimensional chemical structure through default rather than design.

In order to devise novel and competitive medicines formed of small organic molecules, we must produce drug candidates which match the inherent intricacies of proteins to the best of our ability. This can only be achieved by exploring the full area of chemical space, and by escaping any bias towards highly sp^2-rich molecules. It is natural to imagine that the three-dimensional active site of a protein will form the highest affinity and most specific interactions with an appropriately designed three-dimensional molecules. It can be easily inferred that such molecules require high amounts of sp^3-hybridisation within them.

Lovering *et al.* have performed statistical analysis on the fraction of sp^3 hybridised carbons (Fsp^3) in drug candidates.[11] Their study shows that the Fsp^3 of marketed drugs is 31% higher than the Fsp^3 for compounds entering phase I trials, suggesting that compounds with higher Fsp^3 values are more likely to pass clinical trials.

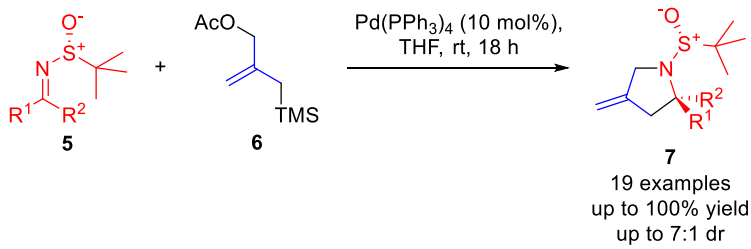
In order to address the bias towards sp^2-rich drug candidates, a large amount of research has been performed into developing sp^2-sp^3 and sp^3-sp^3 cross-coupling reactions.[12–14] While simple transition metal catalyst systems are often very useful, these difficult couplings can require the use of elaborate catalyst/ligand systems

which can be undesirable due to commercial availability and cost.[15] The Stockman group has set a precedent of combining simple, cheap and commercially available reagents to provide intricate, high-value and sp^3-rich products in an operationally facile manner. A seminal example of this is their synthesis of (±)-perhydrohistrionicotoxin (**1**), whereby ketodinitrile **2** is reacted with hydroxylamine (Scheme 1.2).[16] Oxime formation and Michael addition affords nitrone **3**. Intramolecular nitrone/olefin cyclisation produces tricyclic isoxazolidine **4** in a good yield.



*Scheme 1.2: A two-directional synthesis of (±)-perhydrohistrionicotoxin (**1**)*[16]

The Stockman group has also substantially contributed to the development of sulfur(IV) methodology.[17–23] In one recent example it was shown that sulfinimines **5** can be reacted with Trost's trimethylenemethane (TMM) reagent **6** in the presence of a simple palladium catalyst to form diastereomerically enriched methylene pyrrolidines **7** (Scheme 1.3).[18,24] Linking these two chemistries is the relatively facile formation of complex compounds with high sp^3 content; desirable characteristics for drug candidates.



*Scheme 1.3: Diastereoselective cycloaddition of t-butylsulfinimines **5** with TMM reagent **6***[18]

This thesis aims to detail the development of research in two key areas which are related through the chemistry of sulfur(IV). Specifically, the induction of carbon-carbon bond formation will be addressed, producing compounds with high Fsp^3. The first of these areas will study the ligand coupling reactions of sulfoxides and

their use in the synthesis of drug products. Secondly, application of the aforementioned palladium-catalysed [3+2] cyclisation to the synthesis of a series of biologically active natural products will be examined.

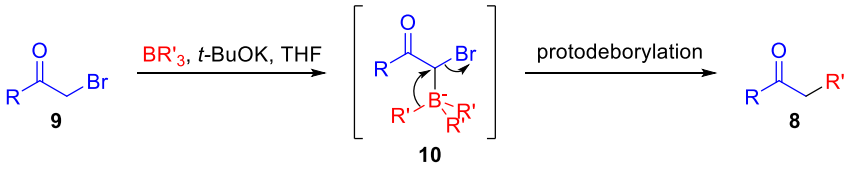
Chapter 2: Ligand coupling reactions of sulfoxides

2.1 Introduction

Herein, a comprehensive review of chemistries related to the carbon-carbon bond forming reactions mediated by p-block elements will be reviewed. A particular emphasis will be placed upon ligand coupling reactions, which are relevant to the aims of this thesis. Transition metal-catalysed reactions of the p-block elements will not be covered.

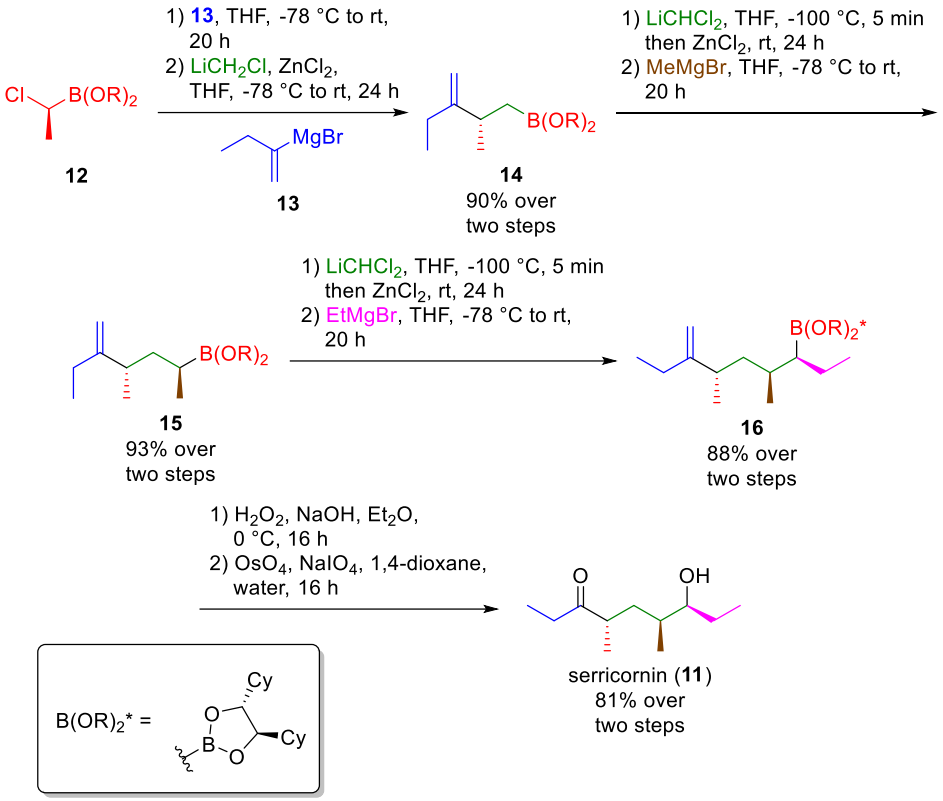
2.1.1 Boron

In seminal reports, Brown *et al.* demonstrated that α-alkyl ketones **8** could be formed from α-bromoketones **9** by employing a 1,2-migration of an intermediate boronate **10** (Scheme 2.1).[25,26] This process was found to be wide in scope and was able to proceed with retention of stereochemistry under certain conditions.[27,28]



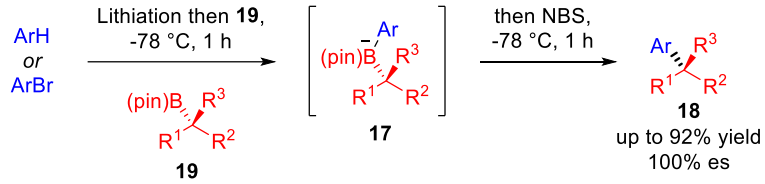
*Scheme 2.1: α-Alkylation of ketones **8** with boranes*[25,26]

Development of this chemistry found that employing more stable boronic acid esters rather than boranes is preferable. Similar methodologies have been used in several natural product syntheses.[29] To exemplify this, Matteson and co-workers employed sequential homologations and 1,2-boronate rearrangements in the synthesis of serricornin (**11**). Chiral 1,2-dicyclohexyl-1,2-ethanediol (DICHED) boronic esters were incorporated to direct stereoselectivity (Scheme 2.2).[30,31]



*Scheme 2.2: Asymmetric synthesis of serricornin (**11**)*[30]

Following initial results presented by Suzuki, the group of Aggarwal used NBS to enable an enantiospecific 1,2-boronate rearrangement on enantiomerically enriched boronate pinacol esters **17** (Scheme 2.3). A variety of electron-rich aromatic groups formed sp^2-sp^3 coupling products **18** in excellent enantioselectivity.[32,33]



*Scheme 2.3 - Enantiospecific sp^2 –sp^3 coupling of secondary and tertiary boronic esters **19***[32]

2.1.2 Hypervalency

Compounds of second row elements and below have more than one non-zero oxidation state available. The chemistry of such p-block elements has gained much interest in recent years for their ability to perform chemistry usually associated with the d-block elements. Defined concisely by Musher in 1969, hypervalency had already been exploited by many researchers.[34]

> *"We classify as 'hypervalent' molecules and ions all those molecules and ions formed by elements in Groups V-VIII of the periodic table in any of*

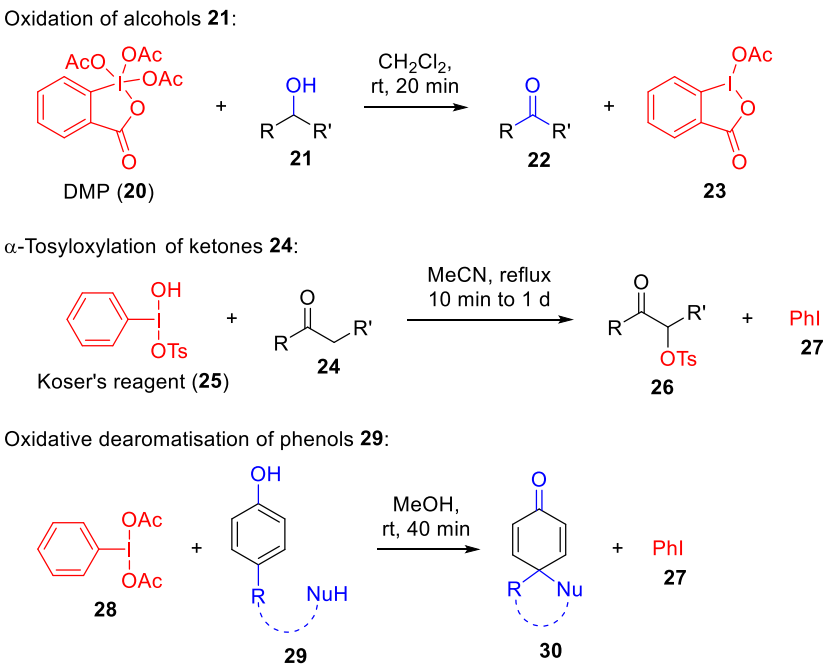
their valences other than their lowest stable chemical valence of 3, 2, 1 and 0 respectively."

I. J. Musher[34]

While many hypervalent species are stable to air, moisture and temperature, the oxidation or reduction of hypervalent atoms to different oxidation states can provide significant enthalpic driving force for reactions. This energy has been exploited by many chemists to perform both oxidative and reductive chemical transformations.

2.1.3 Iodine

Hypervalent compounds of iodine have found widespread use within the synthetic community for performing oxidative transformations (Scheme 2.4). Iodine(V) reagent Dess-Martin periodinane (DMP, **20**) is frequently used in the oxidation of alcohols **21** to aldehydes and ketones **22**.[35] The α-oxysulfonylation of ketones **24** can be performed in one step using iodine(III) compound Koser's reagent (**25**).[36] Another iodine(III) reagent, $PhI(OAc)_2$ (**28**), is used in a variety of oxidative transformations, with the oxidative dearomatisation of phenols **29** to spirocyclic dienones **30** being a particularly common example.[37–39]

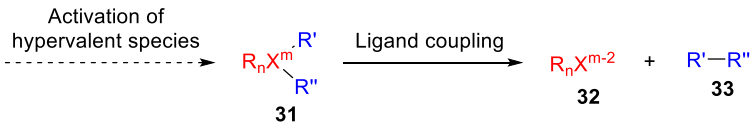


*Scheme 2.4: **Oxidative transformations of common hypervalent iodine reagents with typical conditions***[35–39]

2.1.3.2 Ligand coupling reactions of organoiodine compounds

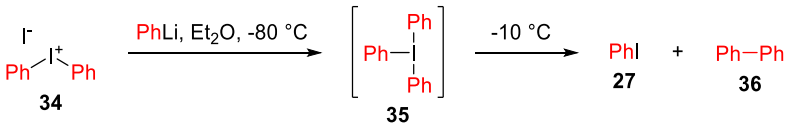
Reductive extrusion of two ligands from a hypervalent p-block element **31** is denoted as a ligand coupling reaction (Scheme 2.5). Such reactions form carbon-carbon and

carbon-heteroatom bonds, and have been reported to occur with a number of central p-block elements: bismuth, iodine, lead, phosphorus, selenium, silicon, sulfur, tellurium and thallium.[40,41] Since carbon-heteroatom ligand coupling reactions are beyond the scope of this thesis, and have been reviewed elsewhere, this review will focus on carbon-carbon bond forming reactions.[40]



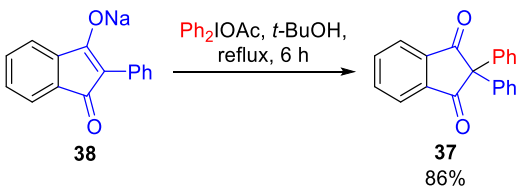
Scheme 2.5: General depiction of ligand coupling reactions

While early reports describe the formation of ligand coupling products from iodonium salts,[42,43] Wittig first proposed the formation of a metastable iodane intermediate **35** in such reactions. The low temperature reaction of diphenyliodonium iodide (**34**) with phenyllithium formed triphenyliodane (**35**, Scheme 2.6).[44] Warming the reaction mixture to -10 °C caused decomposition of iodane **35**, forming iodobenzene (**27**) and biphenyl (**36**).



*Scheme 2.6: Decomposition of triphenyliodane (**35**), forming biphenyl (**36**) and iodobenzene (**27**)*[44]

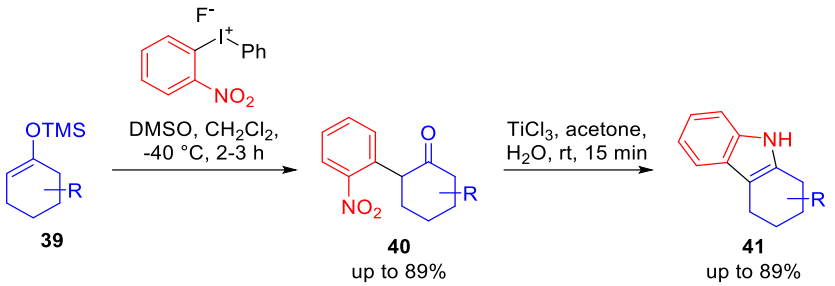
A seminal report from Beringer describes the treatment of diaryliodonium salts with enolates of 1,3-indandiones, causing arylation of the enolate to produce compounds such as diaryl 1,3-indanone **37** (Scheme 2.7).[45] This reaction is proposed to proceed through a ligand coupling reaction from an iodane rather than a radical process. Indeed, radical traps such as 1,1-diphenylethene inhibit the radical decomposition of iodanes; improving yields of ligand coupling products.[46,47] Malonates have also been shown to undergo similar ligand coupling reactions with diaryliodonium triflates.[48]



*Scheme 2.7: Ligand coupling through iodanes – arylation of 1,3-indandione **38***[45]

Silyl enol ethers have been used to produce a wide range of α-phenylketones under more mild conditions.[49] The group of Rawal has developed the ligand coupling of silyl enol ethers **39** with diaryliodonium fluorides to provide a range of nitroarenes **40** and indoles **41**, following reduction with $TiCl_3$ (Scheme 2.8). Presumably the selective

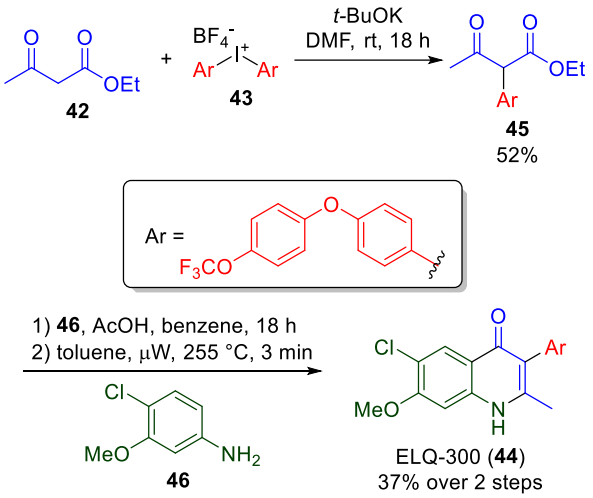
nitroaryl-coupling of the iodane is due to the electron-deficient *ortho*-nitroarene being more amenable to ligand coupling than the phenyl group.[50]



39 **40** up to 89% **41** up to 89%

*Scheme 2.8: Synthesis of indoles **41** from the reduction of ortho-nitroaryl ligand coupling products **40**[50]*

The coupling of β-keto esters **42** with diaryliodonium salts **43** has been used in conjunction with the Conrad–Limpach reaction to synthesise a range of 3-aryl-4(1*H*)-quinolones including the anti-malaria drug candidate ELQ-300 (**44**, Scheme 2.9).[51]

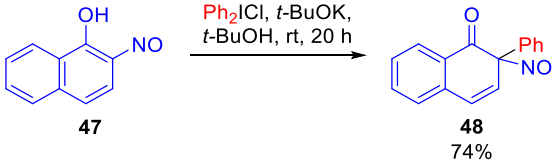


42 **43** **45** 52%

46 ELQ-300 (**44**) 37% over 2 steps

*Scheme 2.9: Synthesis of ELQ-300 (**44**) using ligand coupling and Conrad-Limpach reaction[51]*

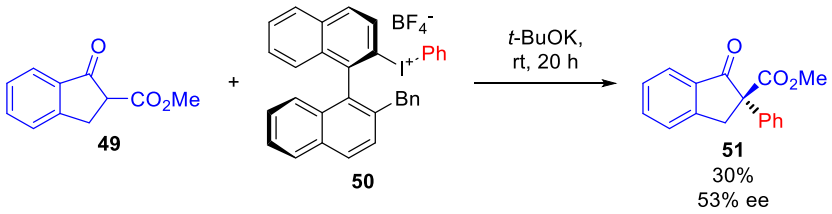
Diphenyliodonium chloride has been found to induce dearomatisation of phenol **47** and provide α-aryl ketone **48** in a good yield (Scheme 2.10).[52]



47 **48** 74%

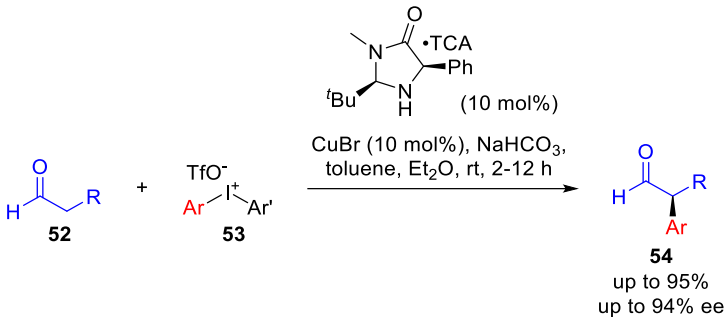
*Scheme 2.10: Ligand coupling reaction of diphenyl iodonium chloride with phenol **47**[52]*

The ligand coupling reactions of iodine(III) species to form enantiomerically enriched α-aryl carbonyl compounds have been developed by a number of groups. Reaction of chiral binapthyl iodonium salt **50** with indanone **49** produces arylated β-ketoester **51** in 53% enantiomeric excess (Scheme 2.11).[53]



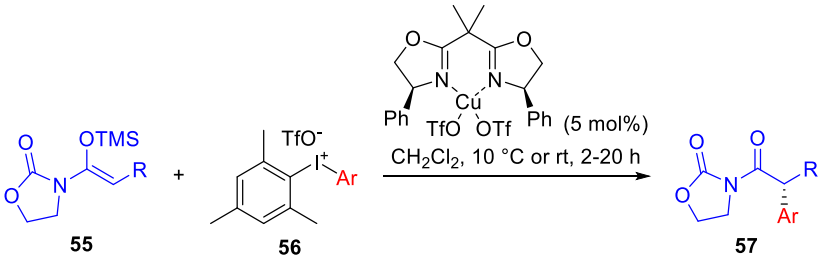
*Scheme 2.11: Chiral binapthyliodane **50** used for the asymmetric arylation of indanone **49***[53]

MacMillan has performed the α-arylation of aldehydes **52** using diaryliodonium salts **53** and a copper(I) source. A chiral amine ligand is used to provide highly enantiomerically enriched α-aryl aldehydes **54** (Scheme 2.12).[54]



*Scheme 2.12: Copper(I)-catalysed enantioselective α-arylation of aldehydes **52***[54]

Gaunt has used a similar chiral copper(II)-bisoxazoline catalyst in the α-arylation of silylketenimides **55**, derived from *N*-acyloxazolidinones, with mesitylaryliodonium triflates **56** (Scheme 2.13).[55] A wide range of α-arylated products **57** were produced in excellent yields and enantiomeric excesses.

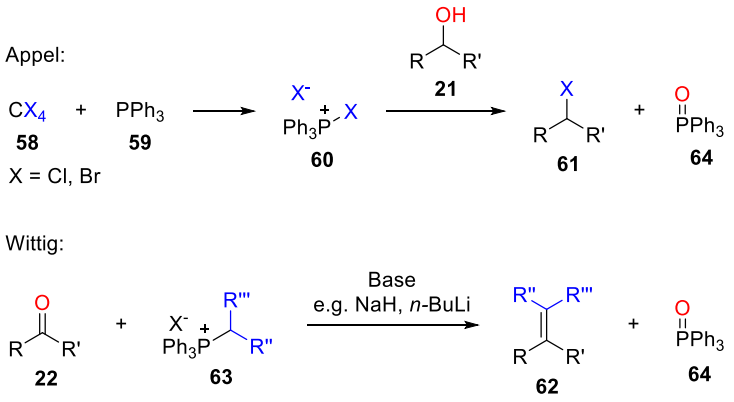


*Scheme 2.13: Copper(II)-bisoxazoline-catalysed α-arylation of silylketenimides **55** with mesitylaryliodonium triflates **56***[55]

2.1.4 Phosphorus

The chemistry of organophosphorus compounds has also gained much widespread use (Scheme 2.14). One example is the Appel reaction, which traditionally proceeds by the reaction of carbon tetrahalides **58** with triphenylphosphine (**59**), forming a hypervalent phosphonium halide **60**. Reaction with alcohols **21** forms alkyl halides **61**. The Wittig reaction transforms carbonyl compounds **22** into olefins **62** using alkyl phosphonium salts **63**.[56] The formation of stable phosphorus(V) oxides, such as

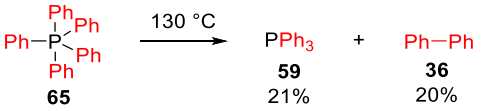
triphenylphosphine oxide (**64**), in stoichiometric amounts is a recurring trend in these chemistries.



*Scheme 2.14: **Common reactions of hypervalent phosphorus reagents***

2.1.4.2 Ligand coupling reactions of organophosphorus compounds

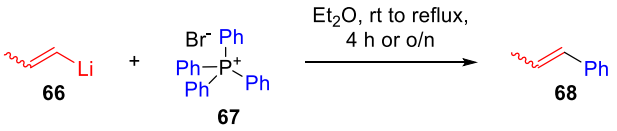
Ligand coupling reactions of organophosphorus compounds have been studied in much less detail than those of iodine. The first report of a ligand coupling reaction of an organophosphorus compound was disseminated by Wittig (Scheme 2.15). Thermal decomposition of pentaphenylphosphorane (**65**) yielded almost equimolar amounts of triphenylphosphine (**59**) and biphenyl (**36**).[57]



*Scheme 2.15: **Thermal decomposition of pentaphenylphosphorane (65), yielding triphenylphosphine (59) and biphenyl (36)**[57]*

The reaction of geometrically enriched 1-propenyllithium **66** with phosphonium salt **67** have been shown to form styrenes **68** with almost complete retention of geometry about the alkene (Table 2.1).[58]

*Table 2.1: Retention of alkene geometry in the coupling of geometrically enriched 1-propenyllithium **66** with triphenylphosphonium bromide (**67**)*[58]

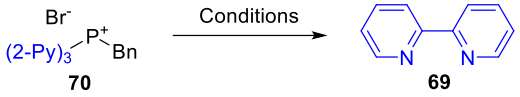


1-Propenyllithium (66)		**1-Propenylbenzene (68)**		
cis	*trans*	*cis*	*trans*	Yield (%)
0	100	0	100	25
97	3	96	4	9

Oae obtained 2,2'-bipyridine (**69**) from the exposure of phosphonium salt **70** or phosphine oxide **71** to neutral or acidic aqueous solutions (Table 2.2, Table 2.3).[59]

While ligand coupling proceeds smoothly at room temperature for phosphonium salt **70**, no detectable 2,2'-bipyridine (**69**) was obtained in comparable reactions of phosphine oxides **71**. Refluxing conditions were required to induce reaction in these cases.

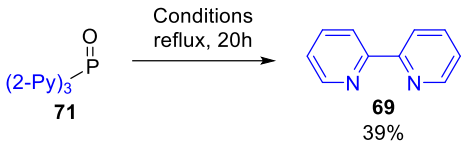
*Table 2.2: Formation of 2,2'-bipyridine (**69**) from phosphonium salts **70** under neutral and acidic conditions*[59]



70 **69**

Conditions	Yield 69 (%)
H_2O, 60 °C, 2.5 h	47
0.2 M HCl, rt, 0.5 h	64
0.2 M HCl, reflux, 10 h	73

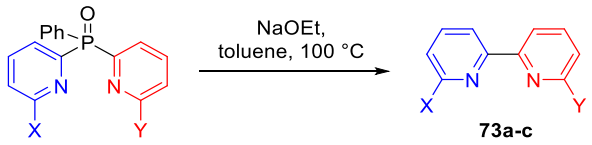
*Table 2.3: Formation of 2,2'-bipyridine (**69**) from phosphine oxides **71** under neutral and acidic conditions*[59]



71 **69** 39%

Conditions	Yield 69 (%)
H_2O	50
0.2 M HCl	80
AcOH	35

Newkome found that treatment of di(2-pyridyl)phosphine oxides **72** with sodium ethoxide forms 2,2'-bipyridines **73** (Scheme 2.16).[60] Crossover experiments provide support for an intramolecular mechanism, which they proposed proceeds through a phosphorane intermediate as suggested previously. The specificity for both 2-pyridyl groups coupling over the phenyl group shows a preference for ligand coupling reactions to occur between electron-deficient species.



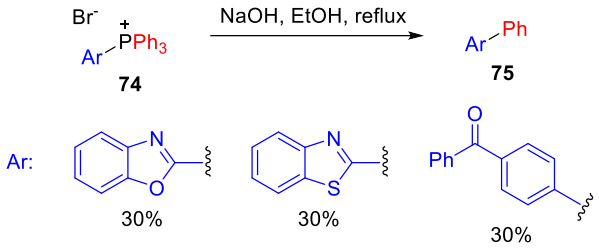
72a: X = H, Y = Br
72b: X = Y = Br
72c: X = Y = Cl

73a-c
50-60%

*Scheme 2.16: Formation of 2,2'-bipyridines **73a-c** from phosphine oxides **72a-c***[60]

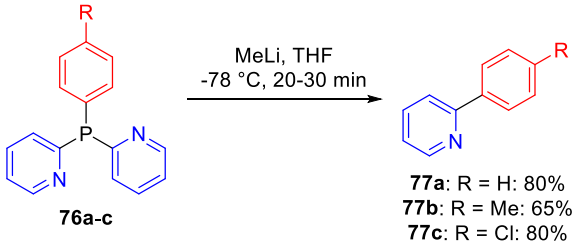
Allen has shown that aryl-phenyl ligand coupling can be achieved through the alkaline hydrolysis of phosphonium salts **74** (Scheme 2.17).[61] While phosphonium salts **74** are

only functionalised with one electron-deficient (hetero)aromatic substituent, the selective coupling of these groups suggests that they are more amenable to ligand coupling than phenyl groups.



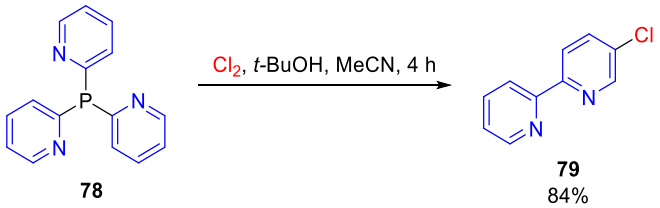
*Scheme 2.17: Alkaline hydrolysis of (hetero)aryl phosphonium salts **74***[61]

The scope of aryl-aryl couplings was enhanced by Oae, by reacting triarylphosphines **76a-c** with methyllithium at -78 °C to form biaryls **77a-c** (Scheme 2.18).[62] It is interesting to note that aryl-2-pyridyl coupling was seen preferentially over 2-pyridyl-2'-pyridyl coupling.



*Scheme 2.18: Low temperature aryl-2-pyridyl coupling of triarylphosphines **76a-c***[62]

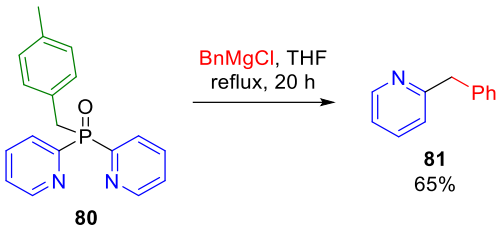
Reaction of triarylphosphines and triarylphosphine oxides with electrophiles can provide diaryl ligand coupling products with functionalisation at the 5-position of one of the aryl rings (Scheme 2.19).[63] The reaction of phosphine **78** with chlorine produces chlorobipyridine **79** in 84% yield. Similar results have been found with bromine, diazonium salts, sulfenyl chlorides, selenyl chlorides and sulfinyl chlorides.[64,65]



*Scheme 2.19: Chlorinated biaryl **79** formed from the reaction of phosphine **78** with elemental chlorine*[63]

The group of Oae further developed this chemistry by performing an sp^2-sp^3 cross-coupling with phosphine oxide **80** and benzylic Grignard reagents; forming 2-benzylpyridine (**81**) (Scheme 2.20).[66] It is thought that the selectivity observed between the 4-methylbenzyl group (green) and the benzyl group (red) can be

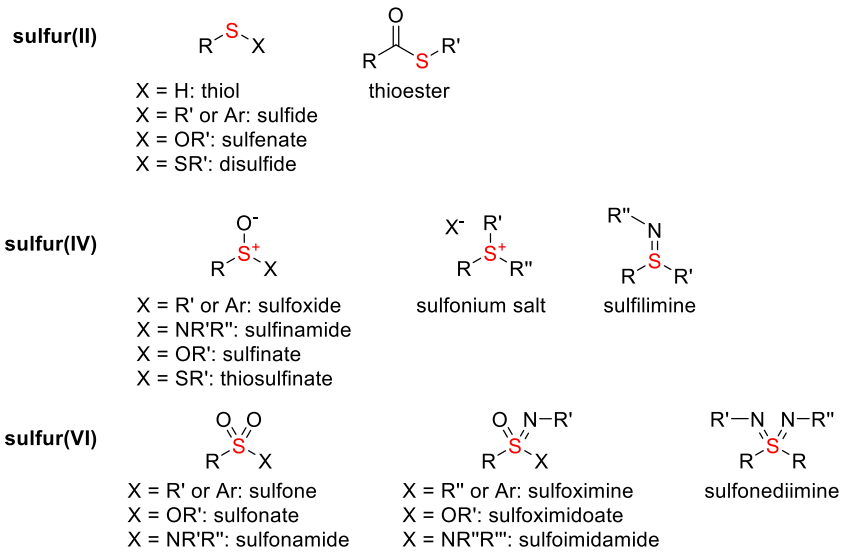
reasoned from the conformation and ligand coupling mechanism of the intermediate λ_5-phosphane.



*Scheme 2.20: Formation of 2-benzylpyridine (**81**) from phosphine oxide **80**[66]*

2.1.5 Sulfur

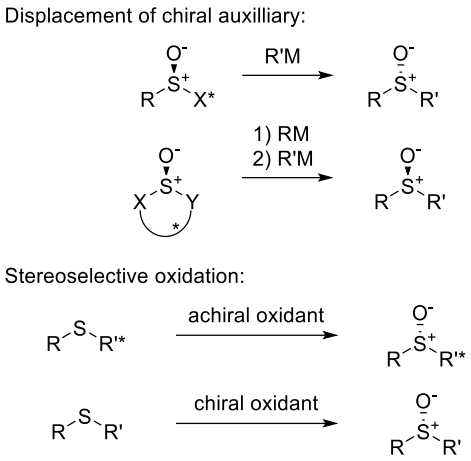
Organosulfur compounds have long been studied for their curious range of reactivities in different oxidation states. As such, a wide range of sulfur compounds may be synthesised (Scheme 2.21). While sulfur(II) compounds are achiral, sulfur(IV) and sulfur(VI) compounds are chiral when appropriately substituted, with a lone pair making sulfur(IV) compounds usually tetrahedral.



Scheme 2.21: Common organosulfur compounds containing oxygen and nitrogen

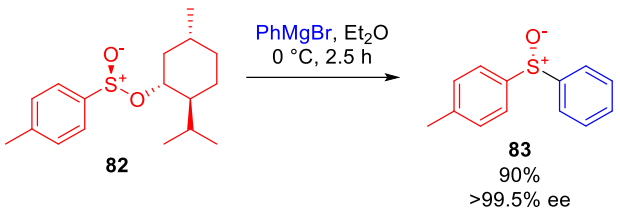
2.1.5.2 Synthesis of enantiomerically enriched sulfoxides

Synthesis of chiral sulfoxides can be performed by two primary methods (Scheme 2.22): the use of a chiral auxiliary which is displaced by nucleophiles, or the asymmetric oxidation of sulfides. Chiral auxiliaries may be monodentate, such as sulfinate esters, or bidentate for example 1,2,3-oxathiazolidine-2-oxides. On the other hand, stereoselective oxidation may be directed by either a chiral substrate or a chiral oxidant, and can be performed by either chemical or enzymatic means.[67]



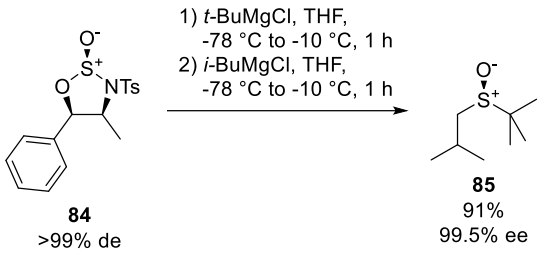
Scheme 2.22: Key methods for the synthesis of chiral sulfoxides

The synthesis of chiral sulfoxides by displacement of a chiral auxiliary was pioneered by Andersen, who formed sulfinate esters of menthol, which are resolvable by crystallisation (Scheme 2.23).[68–72] Reaction of menthol sulfinate esters **82** with Grignard reagents affords enantiomerically pure sulfoxides **83** through nucleophilic substitution of the sulfinyl centre.



*Scheme 2.23: Andersen synthesis of enantiomerically enriched sulfoxide **83** from menthol sulfinate ester **82**[70]*

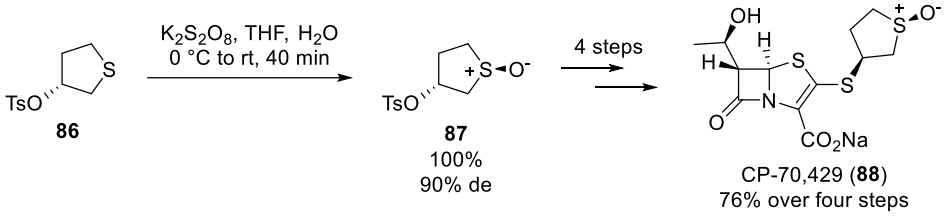
Bidentate chiral sulfinyl transfer reagents have also been used in the synthesis of enantiomerically enriched sulfoxides. These reagents are frequently derived from chiral pools, and can be reacted sequentially with two organometallic reagents to afford chiral sulfinyl-containing compounds such as sulfoxides and sulfinamides. Norephedrine derived *N*-sulfonyl-1,2,3-oxa-thiazolidine-2-oxide **84**, developed by Senanayake, is one of several reagents used for this purpose (Scheme 2.24).[17,23,72,73]



*Scheme 2.24: Synthesis of enantiomerically pure sulfoxides using sulfinyl transfer reagent **84**[74]*

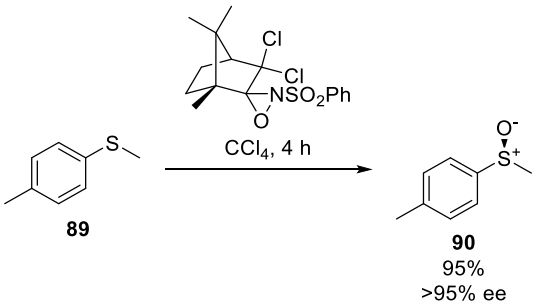
Diastereoselective oxidation of sulfides to sulfoxides has been performed on many substrates. Proximal hydrogen bonding moieties can significantly increase the

diastereomeric excess of such an oxidation. Diastereoselective oxidation of *O*-tosyl sulfide **86** to sulfoxide **87** was used in the synthesis of antibacterial penem CP-70,429 (**88**, Scheme 2.25).[75,76]



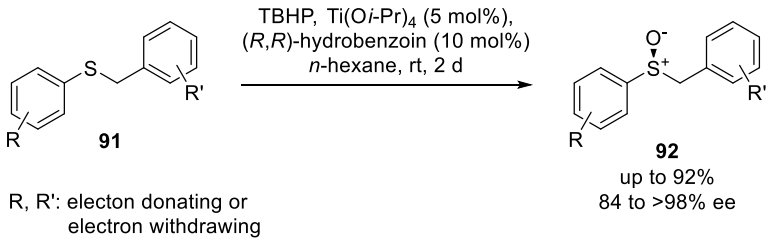
*Scheme 2.25: Diastereoselective oxidation of O-tosyl sulfide **86** using potassium persulfate*[75,76]

Chiral complexes of iron, titanium, vanadium and manganese as well as chiral peracids and oxaziridines have been investigated as enantioselective oxidants of sulfides.[67,77] Camphor-derived oxaziridines, developed by Davis, are excellent examples of stoichiometric oxidants, with the *geminal* dichloride essential to achieving high enantiomeric excesses (Scheme 2.26).[78]



*Scheme 2.26: Highly enantioselective oxidation of sulfide **89** using Davis' oxaziridine*[78]

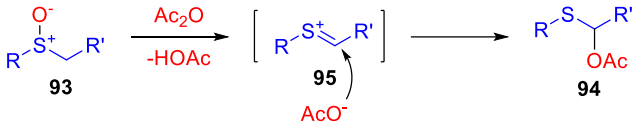
While the oxidation of aryl methyl sulfides remains widely investigated, the oxidation of aryl benzyl sulfides **91** has gained recent attention, as obtaining high enantiomeric excess with these substrates is typically more challenging. The use of a titanium/hydrobenzoin catalyst system to synthesise enantiomerically enriched aryl benzyl sulfoxides **92** was found to be highly enantioselective by the group of Cardellicchio (Scheme 2.27).[79]



*Scheme 2.27: Titanium/hydrobenzoin-catalysed enantioselective oxidation of aryl benzyl sulfides **91***[79]

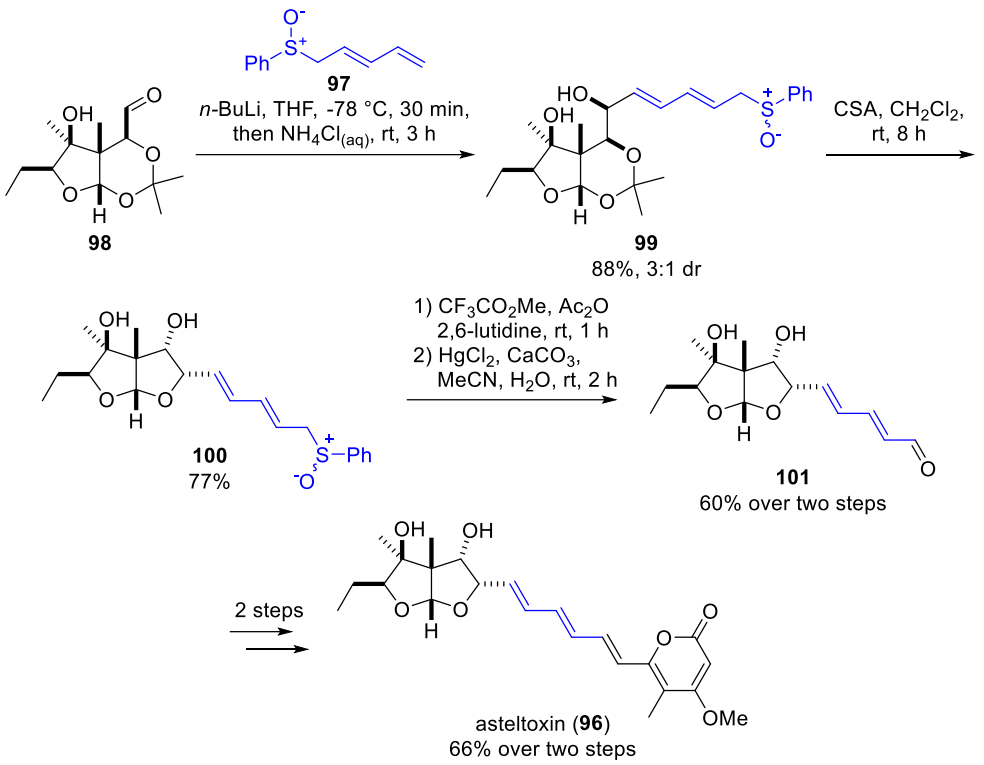
2.1.5.3 The Pummerer rearrangement

Arguably the most widely recognised reaction of organosulfur(IV) reagents, the Pummerer rearrangement transforms sulfoxides **93** containing at least one α-hydrogen into α-acyloxy thioethers **94** (Scheme 2.28).[80] Activation of the sulfoxide **93** forms a thionium intermediate **95**, which is attacked by nucleophiles, typically acetate, to form α-functionalised sulfides **94**. This field has developed substantially since its discovery, and since several comprehensive reviews are available on this subject, only a brief overview will be given here.[81–84]



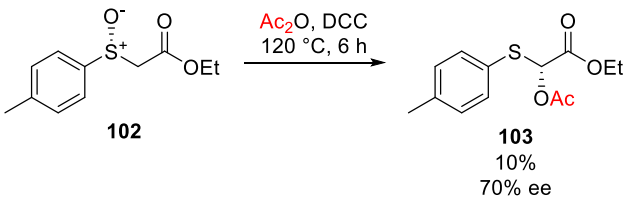
*Scheme 2.28: The Pummerer rearrangement of sulfoxides **93***[80]

The use of sulfoxides in natural product syntheses is frequently followed by the Pummerer rearrangement to functionalise the α-carbon. Schreiber's synthesis of asteltoxin (**96**) employs the anion of pentadienyl sulfoxide **97**, first used by Corey as a synthetic equivalent to the anion of the corresponding dienyl aldehyde.[85] Reaction with aldehyde **98** forms alcohol **99** (Scheme 2.29).[86] Exposure to camphor sulfonic acid (CSA) induced rearrangement to bis(tetrahydrofuran) **100**. Pummerer rearrangement and mercuric chloride-mediated hydrolysis of the resulting α-acyloxy thioether affords aldehyde **101**, which was converted to aseltoxin (**96**) in two further steps.



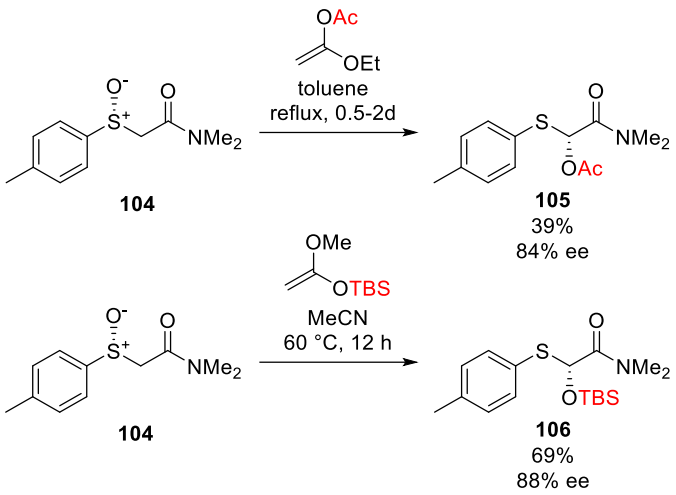
*Scheme 2.29: Synthesis of asteltoxin (**96**) using the Pummerer rearrangement*[86]

The chirality of sulfoxides has inspired many researchers to investigate their stereoselective reactions. On the study of Pummerer rearrangements which retain the stereochemical information of enantiomerically pure sulfoxides, enantiomeric excesses were initially poor.[87] The group of Oae found that the use of *N*,*N*′-dicyclohexylcarbodiimide (DCC) to scavenge acetic acid formed, prevents product racemisation. Subjection of sulfoxide **102** to these conditions yields α-acyloxy thioether **103** in 70% enantiomeric excess (Scheme 2.30).[88] Key to Pummerer rearrangements which retain stereochemical integrity is the close association of acetate with the intermediate thionium ion, preventing loss of stereochemical information.



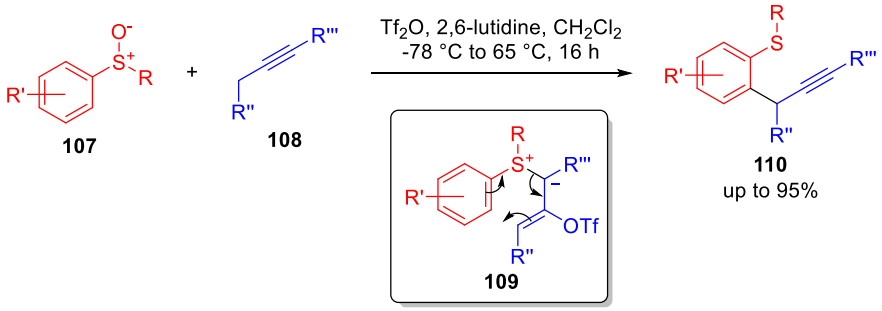
*Scheme 2.30: Synthesis of enantiomerically enriched α-acetoxy sulfide **103** with DCC*[88]

Investigating alternatives to anhydrides in the Pummerer rearrangement, the group of Kita has showed that the reaction of vinylic acetals with enantiomerically enriched sulfoxide **104** produces α-acetoxy sulfide **105** and α-silyloxy sulfide **106** in enantiomeric excesses of 88% and 84% respectively (Scheme 2.31).[89,90]



*Scheme 2.31: Synthesis of enantiomerically enriched α-oxy sulfides **105-106** using vinyl acetals*[89,90]

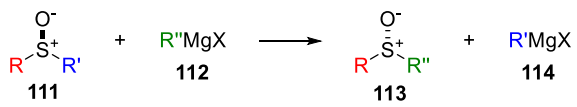
More recent developments in the Pummerer rearrangement have been described by the group of Procter.[84] The combination aryl sulfoxides **107** with triflic anhydride initiates a Pummerer rearrangement, which is "interrupted" by the nucleophilic attack of an alkyne **108** on the thionium intermediate (Scheme 2.32).[91] 2,6-Lutidine induces the formation of allylic sulfonium ylide **109**, which undergoes thio-Claisen rearrangement to form arylated alkynes **110**. Overall, the reaction is a metal-free CH-CH-type cross-coupling, which produces $C(sp^2)$-$C(sp^3)$ coupling products.



*Scheme 2.32: Interrupted Pummerer/thio-Claisen rearrangements of aryl sulfoxides **107***[91]

2.1.5.4 Magnesium-sulfoxide exchange

Magnesium-sulfoxide exchange has been used to great effect within the synthetic community. In these reactions, a sulfoxide **111** is reacted with a Grignard reagent **112** to yield a new sulfoxide **113** and a new Grignard reagent **114** (Scheme 2.33). This has been used in both the synthesis of enantiomerically enriched sulfoxides and novel Grignard reagents.

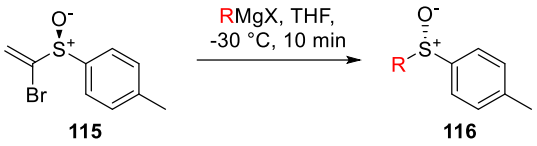


Scheme 2.33: Magnesium-sulfoxide exchange

2.1.5.4.2 Synthesis of chiral sulfoxides

Naso found that the reaction of enantiomerically pure 1-bromovinyl sulfoxide **115** with Grignard reagents at low temperatures produces a range of aryl and vinyl sulfoxides (Table 2.4). Good to very good yields and excellent enantiomeric excesses of sulfoxides **116** were produced following inversion at the sulfinyl centre.[92]

*Table 2.4: Synthesis of enantiomerically enriched sulfoxides **116** by magnesium-sulfoxide exchange*[92]

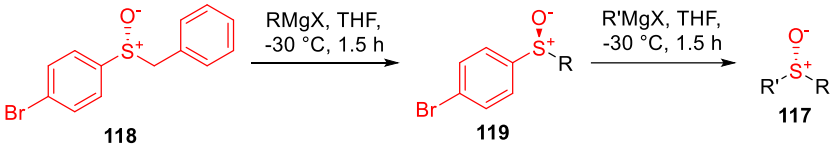


115 **116**

R	Yield 116 (%)	ee (%)
Ph	77	100
n-Bu	81	99
n-Pr	79	100
i-Pr	86	100
Et	73	98

The same group developed on this chemistry to synthesise enantiomerically enriched dialkyl sulfoxides **117** by performing sequential addition of alkyl Grignard reagents to (*R*)-benzyl-4-bromophenyl sulfoxide (**118**, Table 2.5).[93] The first substitution with a Grignard reagent selectively removes the benzyl group, while the second removes the 4-bromophenyl group.

*Table 2.5: Synthesis of enantiomerically pure dialkylsulfoxides **113** by magnesium-sulfoxide exchange*[93]



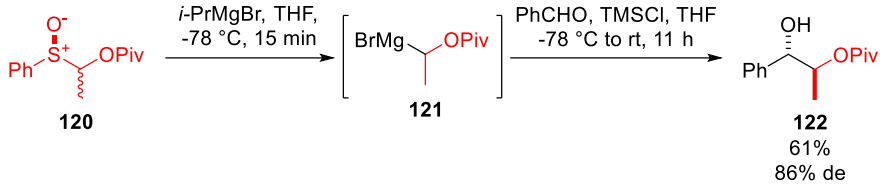
118 >98% ee **119** **117**

R	R'	Yield 117 (%)	ee (%)
n-pentyl	*n*-dodecyl	62	>98
n-dodecyl	*n*-pentyl	69	>98
n-dodecyl	*i*-Pr	91	>98

2.1.5.4.3 Synthesis of novel Grignard reagents

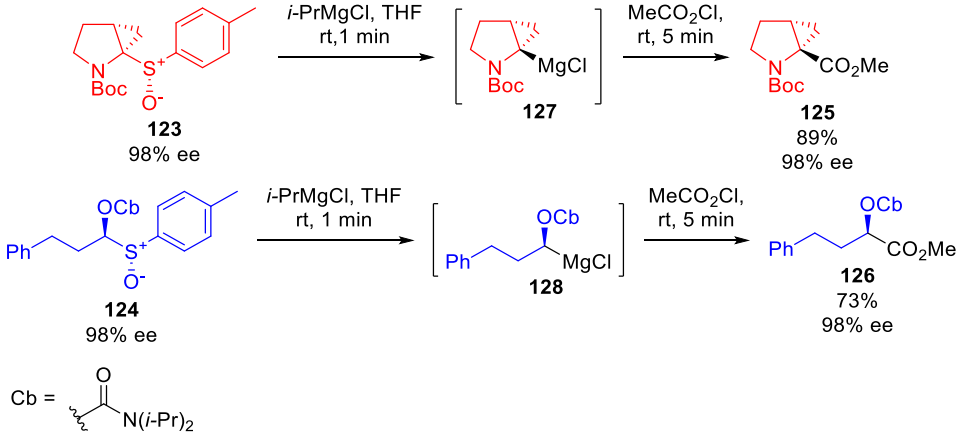
Sulfoxides have been used widely in the synthesis of novel and enantiomerically enriched magnesium carbenoids. In the synthesis of α-oxy-Grignard reagents, Knochel found that the treatment of pivaloyl sulfoxide **120** with *i*-PrMgBr affords racemic

pivaloyl Grignard reagent **121** (Scheme 2.34).[94] Condensation with benzaldehyde affords diastereomerically enriched alcohol **122**.



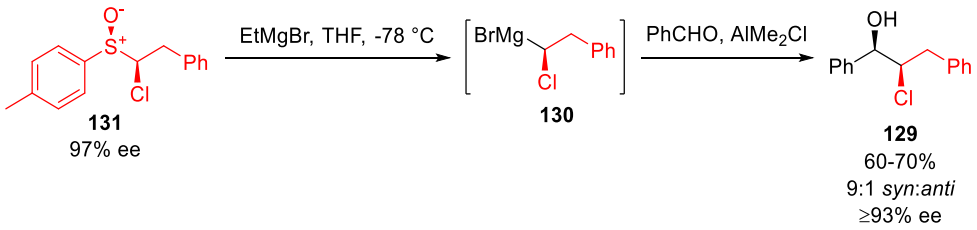
*Scheme 2.34: Synthesis of pivaloyl Grignard reagent **121** using magnesium-sulfoxide exchange*[94]

O'Brien built on this work by performing magnesium-sulfoxide exchange reactions on enantiomerically enriched α-amino sulfoxide **123** and α-oxy sulfoxide **124** (Scheme 2.35).[95] Electrophilic trapping of the corresponding Grignard reagents with methyl chloroformate affords ester **125** and ester **126** with no apparent degradation of enantiomeric excess.



*Scheme 2.35: Synthesis of α-amino Grignard reagent **127** and α-oxy Grignard reagent **128** by magnesium-sulfoxide exchange*[95]

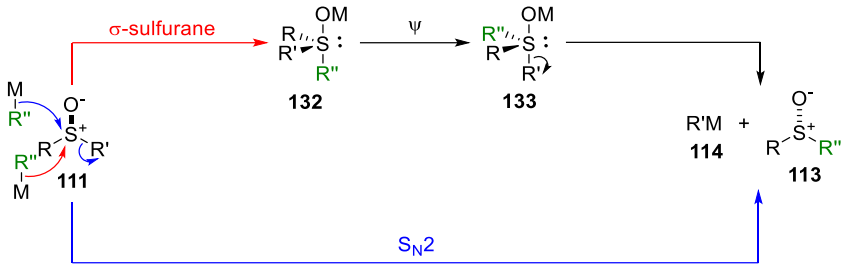
α-Halo Grignard reagents may be formed in a similar manner from appropriately substituted sulfoxides. Chlorohydrin **129** was formed in excellent enantiomeric excess following the reaction of Grignard reagent **130** with benzaldehyde (Scheme 2.36).[96,97]



*Scheme 2.36: Formation of α-halo Grignard reagent **130** by magnesium-sulfoxide exchange*[96]

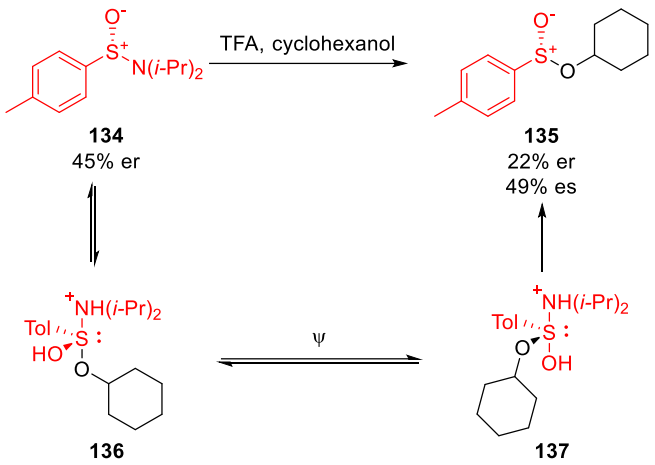
Such metal-sulfoxide exchange reactions (also referred to as ligand exchange, *vide infra*: Table 2.7) have, to the best of our knowledge, received scant mechanistic investigation. While it is difficult to entirely rule out an S_N2 mechanism, it is generally accepted that addition of the organometallic reagent to the sulfoxide **111** forms an

intermediate σ-sulfurane **132** (Scheme 2.37). Pseudorotation (ψ) forms σ-sulfurane **133**, with a new conformation, before a new organometallic reagent **114** is eliminated.[98–100]



Scheme 2.37: Plausible mechanisms for metal-sulfoxide exchange[98]

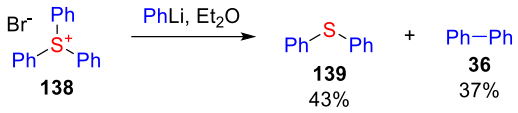
Evidence to support a mechanism which proceeds through a σ-sulfurane intermediate is provided by the observation that sulfinyl stereochemistry is retained in the acid-catalysed alcoholysis of sulfinamide **134** (Scheme 2.38). Mikołajczyk *et al*. report that exposure of sulfinamide **134** to TFA in cyclohexanol forms sulfinate ester **135** with 75% retention of stereochemistry.[100] This transformation would not be possible by an S_N2 mechanism. They propose that σ-sulfurane **136** is formed from the attack of cyclohexanol on the protonated sulfinamide. σ-Sulfurane **136** is proposed to be unstable due to the steric interaction of the axial oxy-cyclohexyl ligand and the equatorial 4-tolyl ligand. Pseudorotation by the Berry mechanism (*vide infra*: Scheme 2.51) is suggested to afford σ-sulfurane **137**, which is lower in energy than σ-sulfurane **136** as the bulky substituents are in more spacious equatorial positions. Elimination of diisopropylamine is also possible from this σ-sulfurane conformation as it is in an axial position, affording sulfinate ester **135** in 75% enantioselectivity (es).



*Scheme 2.38: Retention of stereochemistry in the alcoholysis of sulfinamide **134***[100]

2.1.5.5 *Ligand coupling reactions of sulfur compounds*

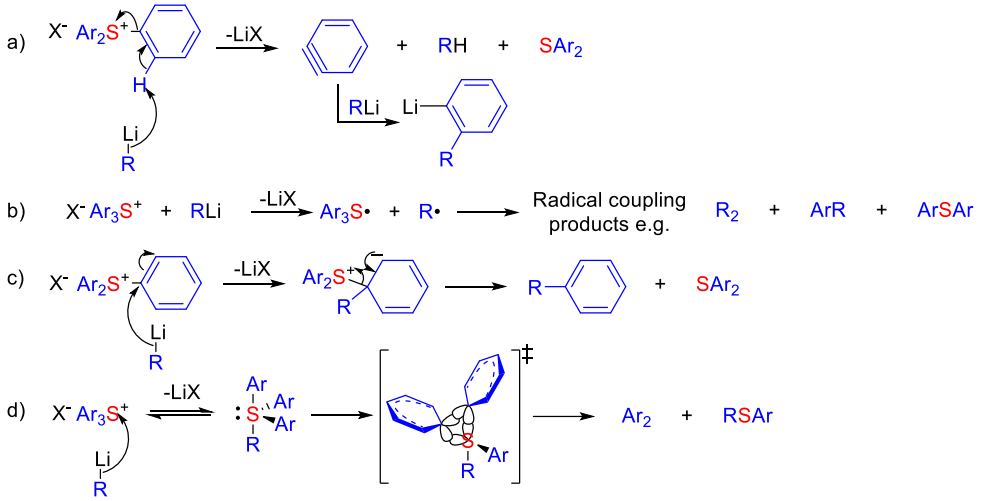
The first ligand coupling reactions involving organosulfur compounds were performed from triarylsulfonium salts. In 1952 Wittig reported that the reaction of triphenylsulfonium bromide (**138**) with phenyllithium affords diphenylsulfide (**139**) and biphenyl (**36**, Scheme 2.39).[101] It was proposed that this reaction proceeds through a 4-valent intermediate, similar to those which Wittig had seen with selenium and tellurium, however no evidence was forthcoming beyond this analogy.



*Scheme 2.39: Wittig and Fritz's synthesis of biphenyl (**36**) from triphenylsulfonium bromide (**134**)*[101]

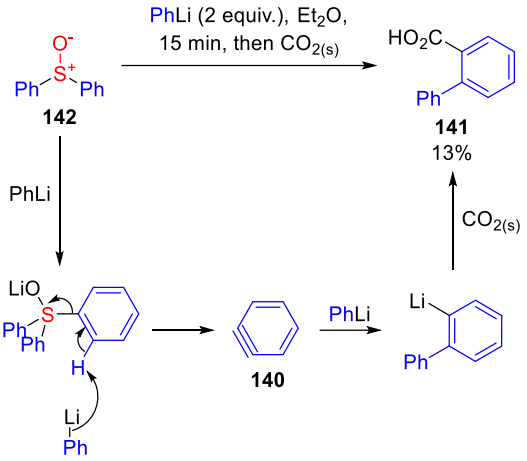
2.1.5.5.2 Mechanistic studies

Mechanistic investigation of this carbon-carbon bond forming transformation of sulfur(IV) compounds has been undertaken by a number of groups.[102–112] Investigations focussed on four potential mechanisms (Scheme 2.40): an aryne intermediate (a), radical mechanism (b), aromatic substitution (c) and the formation of a σ-sulfurane intermediate followed by ligand coupling (d).



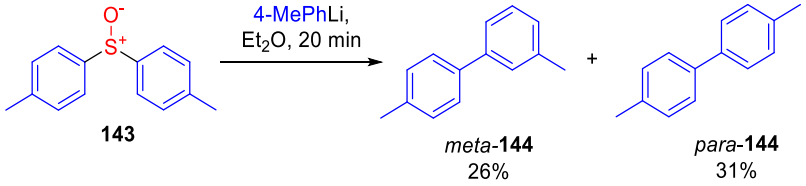
Scheme 2.40: Potential mechanisms for biaryl formation from aryl sulfonium salts[103]

Andersen and coworkers proposed that benzyne (**140**) is an intermediate in the formation of biaryls from triarylsulfonium salts.[113–115] The isolation of small quantities of *ortho*-carboxybiphenyl **141** from the reaction of phenyllithium with diphenylsulfoxide (**142**), which was quenched with carbon dioxide, provides evidence to support benzyne intermediate **140** (Scheme 2.41).[115]



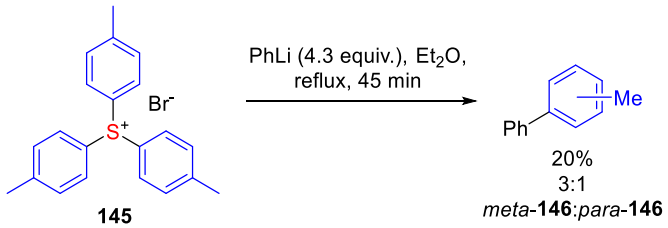
*Scheme 2.41: Evidence for the presence of benzyne (**140**) in the reaction of diphenylsulfoxide (**142**) with phenyllithium*[115]

The group of Andersen also showed that the reaction of *para*-tolylsulfoxide (**143**) with *para*-tolyllithium forms *meta,para'*-bitolyl (*meta*-**144**) and *para,para'*-bitolyl (*para*-**144**) in a 1.2:1 ratio; further supporting a benzyne intermediate (Scheme 2.42).[114]



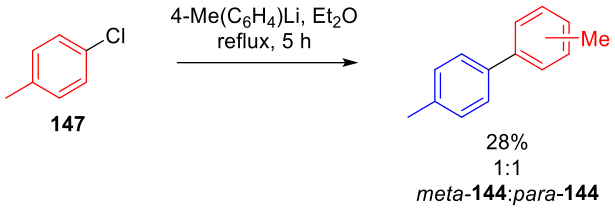
*Scheme 2.42: Formation of m,p'-bitolyl (meta-**144**) providing evidence for a benzyne intermediate*[114]

A similar result was obtained by Oae from the reaction of tri-(*para*-tolyl)sulfonium bromide (**145**) with phenyllithium, producing a mixture of *meta*- and *para*- regioisomers of phenyltoluene (**146**, Scheme 2.43).[116]



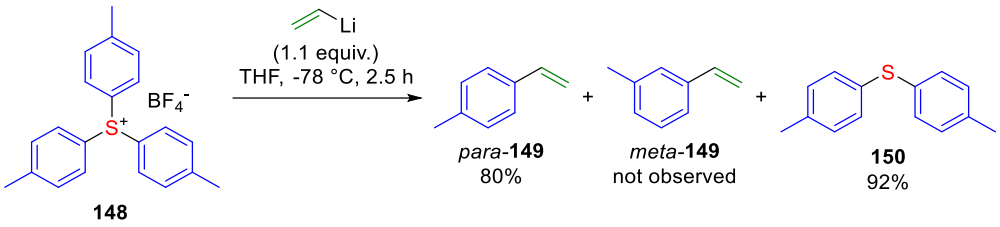
Scheme 2.43: Oae's evidence for a benzyne intermediate[116]

Independent control experiments in which the required benzyne intermediate was reacted with *para*-tolyllithium yielded a 1:1 ratio of *meta*- to *para*-substituted methylbitolyl (Scheme 2.44).[117] The discrepancy between this result and that of Oae (*vide supra*: Scheme 2.43) suggests that reaction *via* a benzyne intermediate is not the only mechanism active in Oae's example.



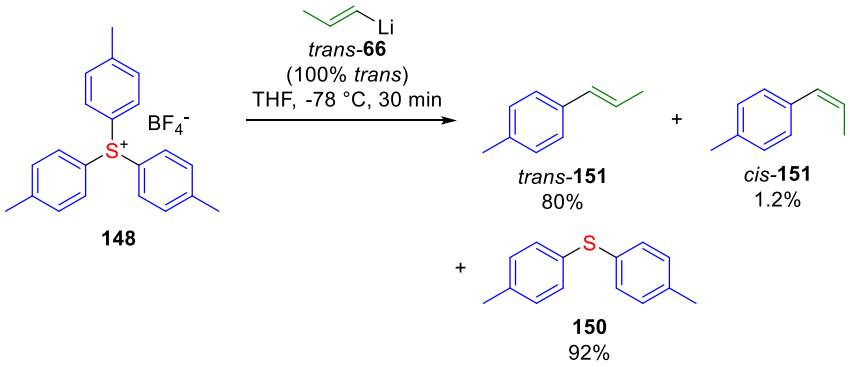
*Scheme 2.44: Reaction of para-tolyllithium with 4-chlorotoluene (**147**)*[117]

The temperature dependence of these reactions was discerned by Trost, who undertook a similar investigation at -78 °C, rather than at room temperature or reflux as by Andersen and Oae (Scheme 2.45, *vide supra*: Scheme 2.41, Scheme 2.42 and Scheme 2.43).[104] The reaction of a tri(*para*-tolyl)sulfonium salt **148** with vinyllithium forms only *para*-methylstyrene (*para*-**149**), while *meta*-methylstyrene (*meta*-**149**) was not observed. It is important to note that an 80% yield of *para*-methylstyrene (*para*-**149**) is obtained with only 1.1 equivalents of vinyl lithium. This would not be possible *via* a benzyne mechanism, where at least two equivalents of organometallic reagent are required to obtain yields above 50%.[103]



Scheme 2.45: Trost's evidence against a benzyne mechanism[104]

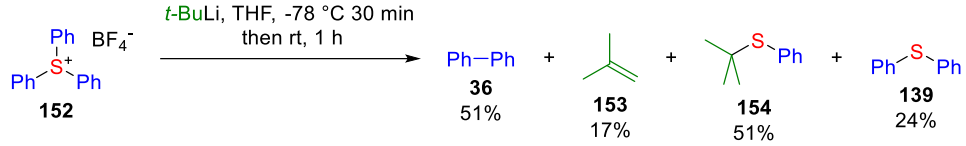
Trost also provides evidence against a radical mechanism at low temperatures by using geometrically pure substituted vinyllithium **66** (Scheme 2.46).[103] The formation of only traces of *cis*-propenylbenzene (*cis*-**151**) suggests that either the radical mechanism is slow compared to another mechanism, or that isomerisation is occurring through instability of the vinyl-group in another step of the mechanism.



Scheme 2.46: Evidence against a dominant radical mechanism[103]

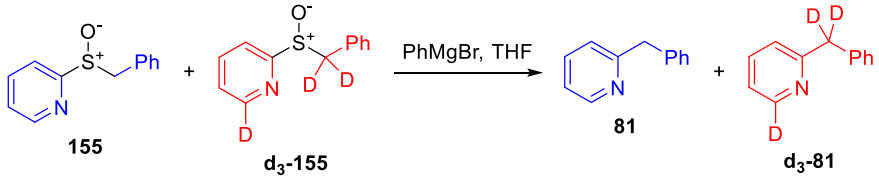
It has been suggested that when alkyllithium species are used, both radical and nucleophilic substitution mechanisms would produce significant amounts of

alkylbenzenes, especially when *t*-butyllithium is used (Scheme 2.47). However, in the reaction of triphenylsulfonium salt **152** with either *t*- or *n*-butyllithium, no butylbenzenes are formed.[103]



Scheme 2.47: Trost's evidence against radical and nucleophilic substitution mechanisms[103]

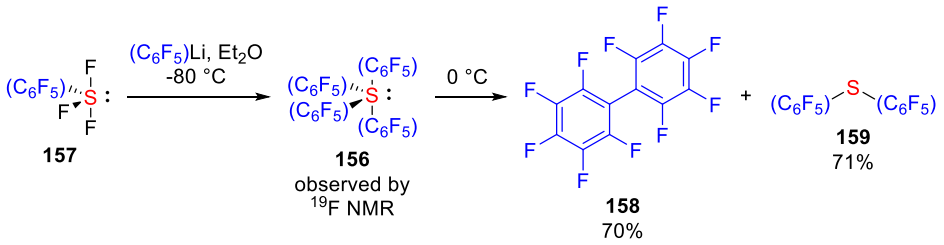
Evidence against an intermolecular or fragmenting reaction mechanism was provided by Oae, who performed crossover experiments in the ligand coupling of benzyl-2-pyridyl sulfoxides **155** (Scheme 2.48).[118] The exclusive formation of diarylmethane **81** and diarylmethane **d_3-81** shows that this reaction either proceeds by a unimolecular mechanism or a mechanism where any fragments are short-lived and remain in a tight solvent cage when not directly bonded.



Scheme 2.48: Crossover experiments performed by Oae[118]

2.1.5.5.3 Characterisation, bonding and reactivity of σ-sulfuranes

The first characterisation of a tetraarylsulfurane came in 1971 from the group of Sheppard.[112] Low temperature ^{19}F NMR spectroscopy was used to characterise tetrakis(pentafluorophenyl)sulfurane (**156**), produced in the reaction of pentafluorophenyllithium with perfluorosulfurane **157** (Scheme 2.49). Decomposition of σ-sulfurane **156** was observed upon warming to 0 °C, forming ligand coupling products decafluorobiphenyl (**158**) and bis(pentafluorophenyl)sulfide (**159**). More recently tetraphenylsulfurane has been characterised by similar methods by Furukawa *et al.*, which also decomposes to form ligand coupling products.[119]



Scheme 2.49: The first characterisation of a tetraarylsulfurane[112]

Although tetraarylsulfuranes seem to be unstable at room temperature, some σ-sulfuranes are stable at room temperature (Figure 2.1).[120,121] Highly electronegative substituents are required to stabilise the hypervalent sulfur centre.[122,123] Martin sulfurane (**160**) is commercially available and widely used for the dehydration of alcohols.

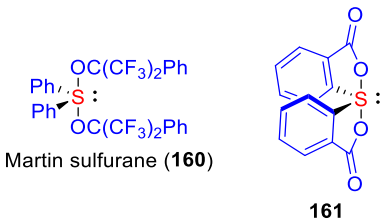


Figure 2.1: Examples of σ-sulfuranes which are stable at room temperature[120,121]

2.1.5.5.4 Theoretical studies on σ-sulfuranes

Sulfur tetrafluoride (SF_4) is a colourless gas which releases HF on exposure to wawter. That said, it is stable at room temperature. The structure of SF_4 has been calculated as distorted trigonal bipyramidal, which bares close resemblance to the early microwave structure assigned by Tolles and Gwinn (Figure 2.2).[124,125]

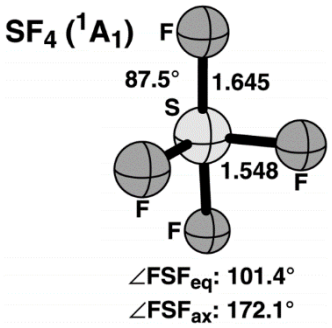


Figure 2.2: RCCSD(T)/AVQZ level calculation of SF_4 structure. Bond lengths are in Å. Figure adapted from primary literature[124]

Ab initio studies have shown that d-orbital contribution within bond hybridisation of hypervalent species can be largely ruled out; only significantly impacting in backbonding.[126,127] The σ-sulfurane intermediate is sp^2-hybridised, with the p_z orbital occupying the axial plane and three orthogonal sp^2-orbitals bonding to the equatorial substituents. The bonding model most accepted at the time of writing was initially proposed by Rundle and Pimentel, whereby three atoms share four electrons in the axial plane (3c-4e, Scheme 2.50 and Figure 2.3).[128–130] Depictions of this bonding model suggest that at no time are both axial ligands bonded to the sulfur p_z orbital, however the tight nature of this rapid conversion prevents complete dissociation of either axial ligand.

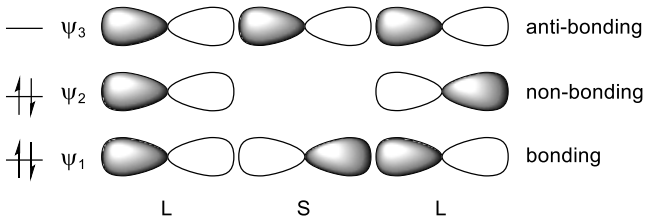
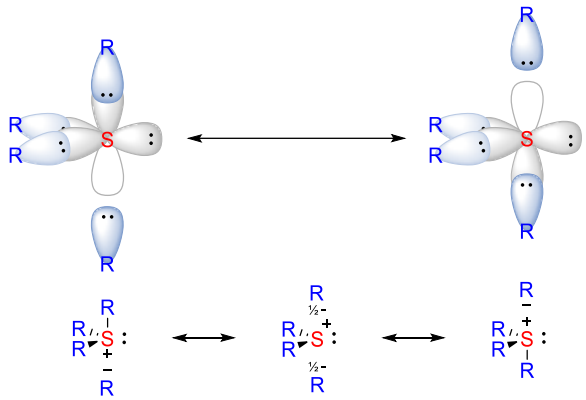


Figure 2.3: Molecular orbital representation of the 3c-4e bonding model within σ-sulfuranes

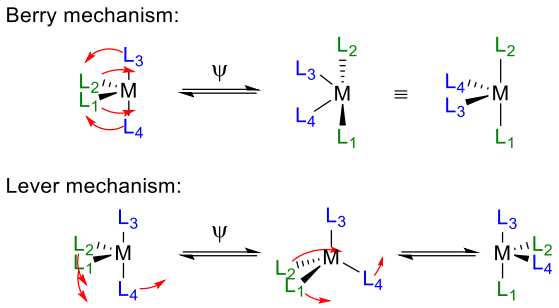


Scheme 2.50: Illustration of the 3c-4e bonding model of σ-sulfuranes

More recently a number of groups have made enhancements to this theory, but the basic conclusions of the model remain valid. Woon has reported that a recoupled pair bonding model is predominant sulfur fluorides such as SF_4. This better represents the stability of some sulfur fluorides and their excited states, however this makes little difference in the case of σ-sulfurane SF_4.[124,131,132] Such bonding models are stabilised by electronegative substituents, explaining why SF_4 is more stable than tetraarylsulfuranes.[133]

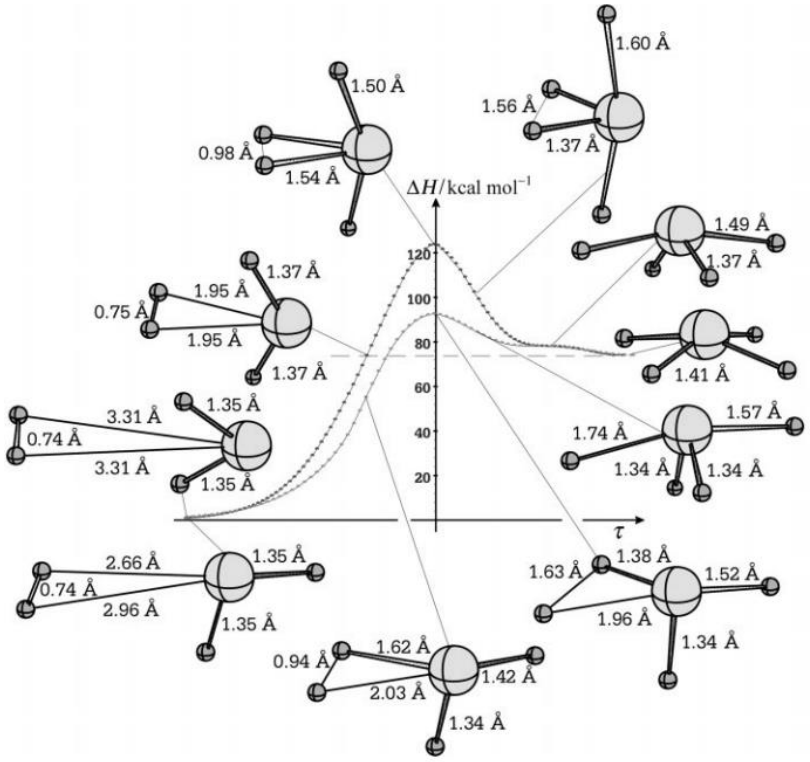
Axial and equatorial positions of σ-sulfuranes have significantly different electronic and steric properties due to the electronics and geometry of the sulfur centre. Bulky substituents of the σ-sulfurane favour the less sterically encumbered equatorial positions due to the *ca*. 120° bond angles around the equatorial plane of the sulfur atom. More electronegative groups prefer to adopt axial positions to bond with the less electronegative p orbital of the σ-sulfurane (Bent's rule).[134]

Pseudorotation of σ-sulfuranes may occur before their decomposition; altering the conformation of ligands around the central atom. Two processes are responsible for this on four-coordinate species; the Berry and the lever pseudorotation mechanisms (Scheme 2.51).[135–137] While calculations suggest that the Berry mechanism is lower in energy, the lever mechanism can provide access to certain topomers which the Berry mechanism cannot.



Scheme 2.51: Berry and lever mechanisms of pseudorotation[135–137]

Reductive extrusion of substituents from σ-sulfuranes has most frequently been studied using the decomposition of sulfurane, SH_4, to hydrogen and hydrogen sulfide as a model. A number of recent studies have assigned a C_1 transition state in preference to a C_{2v} transition state (Scheme 2.52).[123,138,139] This asymmetric extrusion occurs by primary elongation of an axial S-H bond, followed by the elongation of the equatorial S-H bond with concurrent shortening of the H-H bond. *Ab initio* calculations estimate the energy of SH_4 to be between 80 kcal/mol and 98 kcal/mol higher than $SH_2 + H_2$, exhibiting the enthalpic gains of ligand coupling processes.[123,138,139]

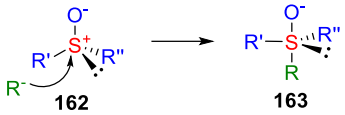


Scheme 2.52: Intrinsic reaction coordinates of the C_{2v} path (upper) and the C_1 path (lower) for the reaction $SH_2 + H_2 \rightarrow SH_4$ at the B3LYP/6-31+G(d) level of theory. Figure adapted from primary literature[123]

2.1.5.5.5 Experimental studies on the ligand coupling of sulfoxides

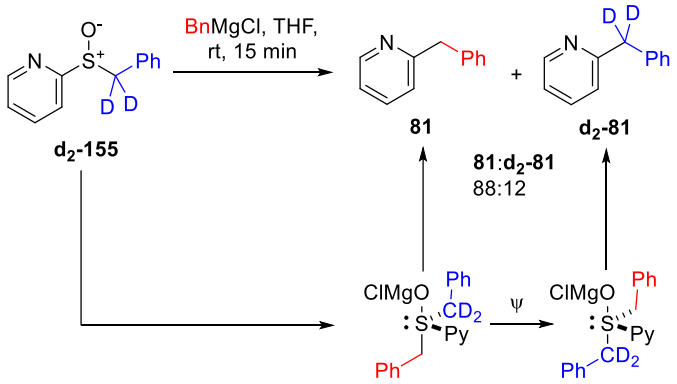
Nucleophilic attack of an organometallic reagent on a sulfoxide **162** occurs by attack on the sulfinyl centre opposite to the most electronegative substituent (Scheme

2.53).[100,140] Hence, a σ-sulfurane **163**, of distorted trigonal bipyramidal geometry, is formed with what was the organometallic reagent and the most electronegative substituent in the axial positions.



*Scheme 2.53: Formation of σ-sulfuranes **163** from sulfoxides **162***

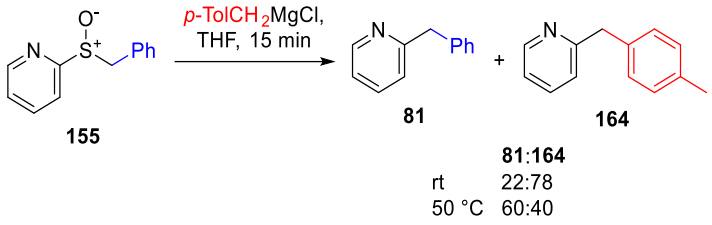
Evidence for the attack of the organometallic reagent opposite to the most electronegative substituent is provided by the reaction of d_2-benzyl-2-pyridylsulfoxide **d_2-155** with benzylmagnesium chloride. Much larger amounts of the non-labelled diarylmethane **81** than deuterated diarylmethane **d_2-81** were isolated (Scheme 2.54).[140] Since σ-sulfuranes are unstable, short-lived intermediates, they will most likely form kinetic products. Therefore, it can be inferred that this result shows that the ligand provided by the Grignard reagent is initially situated in the correct, axial, position to undergo ligand coupling. In this example, pseudorotation to place the deuterated benzylic ligand in an axial position can occur but is slower than ligand coupling.



*Scheme 2.54: Evidence to suggest the trajectory of attack of BnMgCl on sulfoxide **d_2-155***[140]

Oae also performed the reaction of benzyl-2-pyridylsulfoxide **155** with *para*-methylbenzylmagnesium chloride (Scheme 2.55). This reaction produces a high ratio of *para*-methylbenzyl-2-pyridine (**164**) to benzyl-2-pyridine (**81**) at room temperature, as may be expected from the previous discussion.[140] However, increasing the reaction temperature to 50 °C shifts the product ratio in favour of benzyl-2-pyridine (**81**). This suggests that an increase of temperature increases the relative rate of pseudorotation compared to that of ligand coupling. This also shows that the benzyl ligand prefers to undergo ligand coupling compared to the *para*-methylbenzyl ligand. This may be due to the slightly more electron-rich

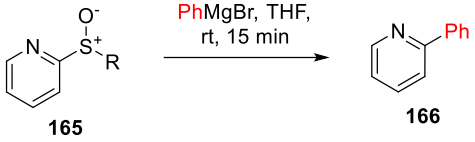
para-methylbenzyl ligand being less stable in the electropositive axial σ-sulfurane position than the benzyl ligand. Hence, the *para*-methylbenzyl ligand is less available in the axial position to undergo ligand coupling.



Scheme 2.55: Increasing relative rate of pseudorotation at higher temperatures[140]

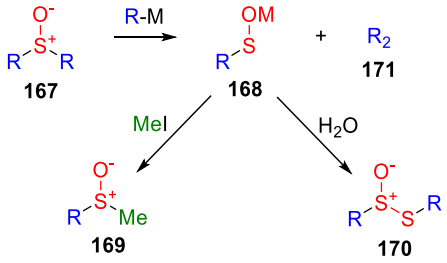
The group of Oae showed that the nature of the σ-sulfurane substituent that is not involved in the ligand coupling reaction is important. In the reaction of 2-pyridylalkylsulfoxides **165** with phenylmagnesium bromide, a dramatic trend is apparent when the alkyl group is changed (Table 2.6).[141] Higher substitution on the α-carbon provides much improved yields of 2-phenylpyridine (**166**). Presumably, the more sterically encumbered *t*-butyl group prefers to occupy a more spacious equatorial position on the σ-sulfurane. This provides stability for the σ-sulfurane configuration which can undergo ligand coupling and may retard pseudorotation, providing higher yields of the desired ligand coupling product.

Table 2.6: Effect of alkyl substituent on yield of ligand coupling[141]



R	Yield 166 (%)
Me	9
Et	6
i-Pr	17
t-Bu	85

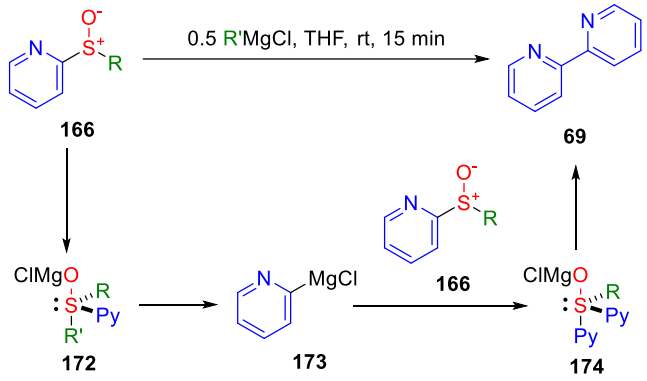
As opposed to sulfonium salts, which generate sulfide byproducts, sulfoxides **167** generate an equivalent of corresponding metal sulfenates **168** upon ligand coupling (Scheme 2.56). Quenching the reactions with MeI generates methylsulfoxides **169**, while quenching with water induces dimerization of the metal sulfenates **168**, generating thiosulfinates **170**.[118] The Stockman group has reported that thiosulfinates **170** disproportionate to form disulfoxides and disulfides at elevated temperatures.[142]



Scheme 2.56: Byproducts formed from quenching of ligand coupling reactions[118]

In the ligand coupling reactions of 2-pyridyl sulfoxides **166**, the main competing pathway forms 2,2'-bipyridine (**69**). Following generation of a σ-sulfurane **172** which is not susceptible to ligand coupling, a 2-pyridylmagnesium halide **173** can be formed (Table 2.7). This process has been described previously as magnesium-sulfoxide exchange, but in the field of ligand coupling reactions it is known as ligand exchange (*vide supra*: Section 2.1.5.4).[143] The 2-pyridylmagnesium halide **173** can react with the remaining substrate **166** to undergo ligand coupling which produces 2,2'-bipyridine (**69**). However, when the same substrate, sulfoxide **166**, is reacted with benzylmagnesium bromide, ligand coupling occurs and no 2,2'-bipyridine (**69**) is formed as ligand coupling is effective.

Table 2.7: Formation of 2,2'-bipyridine from ligand exchange reactions[143]

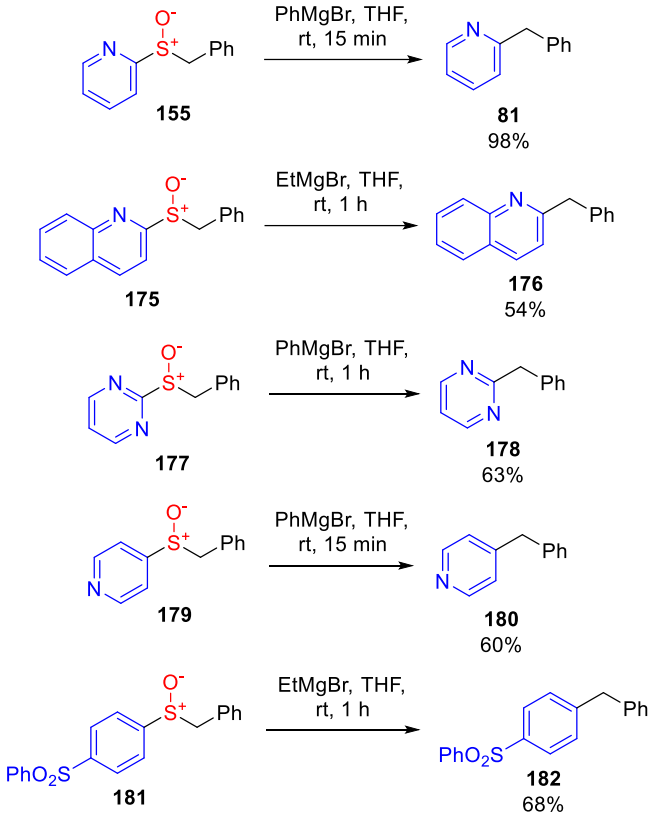


R	R'	Yield 69 (%)
Me	Me	73
Me	Et	63
Me	Ph	79
Ph	Et	71
Et	Et	55
Me	Bn (1 equiv.)	0

2.1.5.5.6 Prior scope of the ligand coupling of sulfoxides

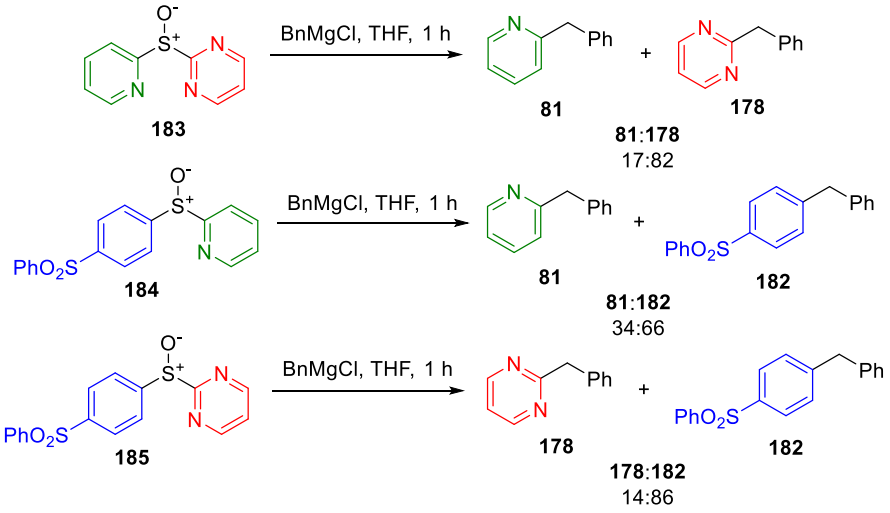
The group of Oae has briefly explored the scope of ligand coupling of (hetero)aryl sulfoxides. Sulfoxides bearing 2-pyridyl, 2-quinolinyl, 2-pyrimidyl, 4-pyridyl or 4-sulfonylphenyl aromatic rings can achieve ligand coupling reactions when exposed

to Grignard reagents (Scheme 2.57).[141,144,145] 3-Pyridylsulfoxides do not undergo ligand coupling under these conditions, suggesting that electron deficiency of the aryl ring is required.



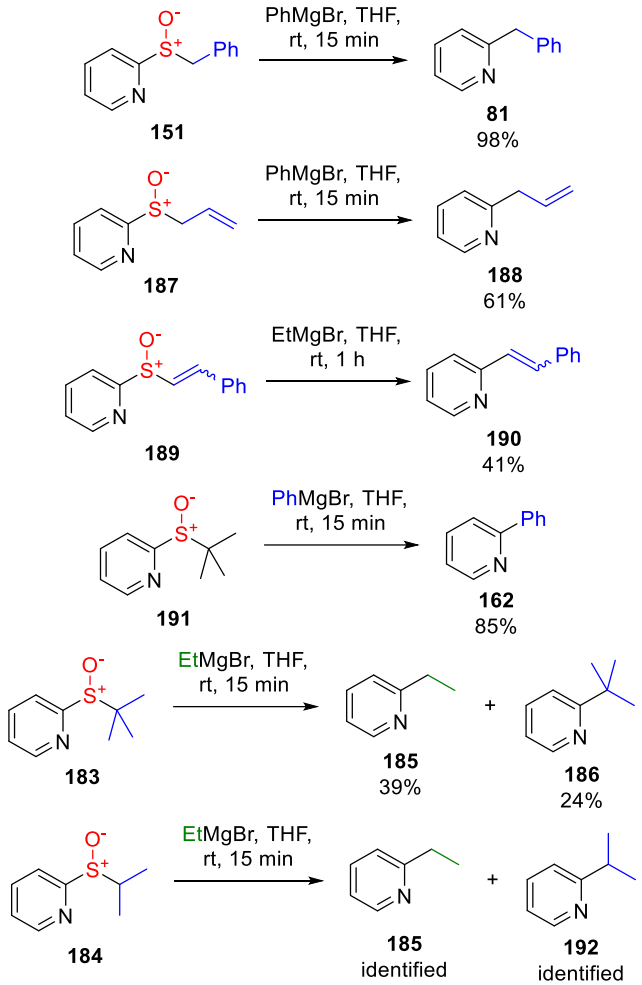
Scheme 2.57: Ligand coupling yields for various (hetero)aromatic benzyl sulfoxides[144,145]

Competition reactions of di(hetero)aryl sulfoxides with benzylmagnesium chloride show the following trend for coupling reactivity: 4-(benzenesulfonyl)phenyl > 2-pyrimidyl > 2-pyridyl (Scheme 2.58).[145]



Scheme 2.58: Competition reactions of di(hetero)arylsulfoxides[145]

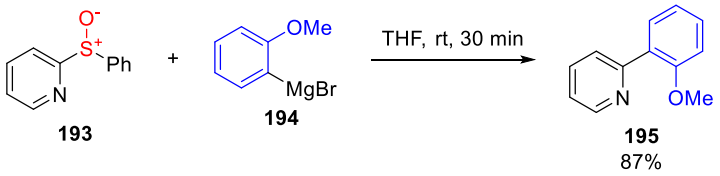
In addition to benzyl groups, allyl, vinyl, aryl and alkyl moieties can undergo ligand coupling reactions (Scheme 2.59).[143,146] To the best of our knowledge, the reaction of *t*-butyl sulfoxide **183** and *i*-propyl sulfoxide **184** with EtMgBr are the only two examples of alkyl-pyridyl ligand coupling, apart from benzyl. For alkyl groups to undergo ligand coupling it seems that an unstable, electron rich, σ-sulfurane is required as bulky *t*-butyl sulfoxide **183** produces higher yields than *i*-propyl sulfoxide **184**. It is interesting to note that 2-ethylpyridine (**185**) is formed in a higher yield than 2-*t*-butylpyridine (**186**). This is presumably due to the sterically encumbered *t*-butyl group preferring to occupy an equatorial position where it cannot undergo ligand coupling. This will be compounded by the fact that the ethyl ligand initially occupies the axial position, where it can undergo ligand coupling.



Scheme 2.59: Ligand coupling yields for various 2-pyridylsulfoxides[141,143,146]

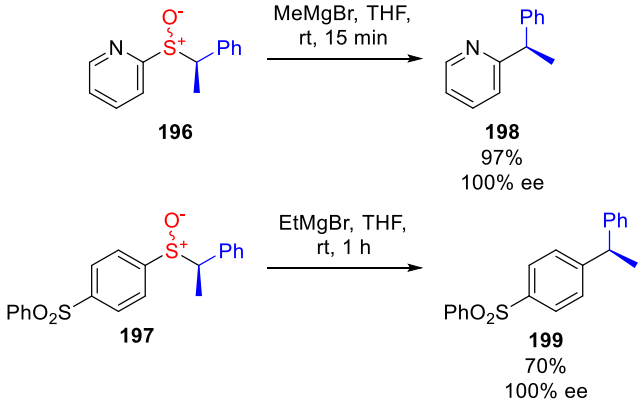
The ligand coupling of sulfoxide **193** with 2-methoxyphenylmagnesium bromide (**194**) was performed by Furukawa *et al.*, affording (2-methoxyphenyl)-2-pyridine (**195**) in a very good yield (Scheme 2.60).[147] Since the 2-methoxyphenyl ligand is both more electron-rich and more sterically encumbered than the phenyl ligand, it is surprising

that the 2-methoxyphenyl ligand remains in the axial position to undergo ligand coupling. One might expect pseudorotation to occur, placing the 2-methoxyphenyl ligand in a more suited equatorial position. Presumably, the initial position of the 2-methoxyphenyl ligand in the axial position aids its ligand coupling. It may also be that more electron-rich ligands are more able to undergo ligand coupling when they are in an axial position.



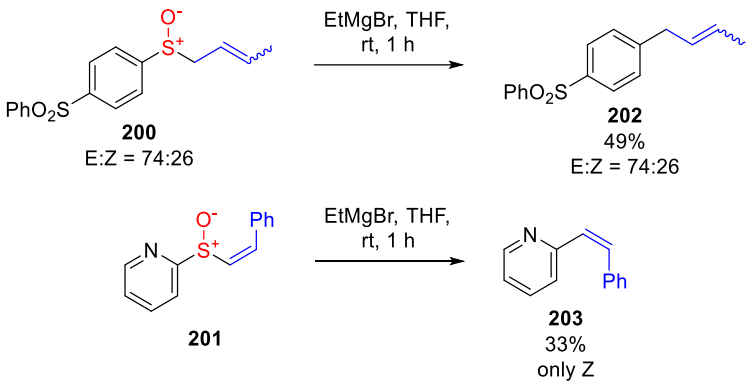
*Scheme 2.60: **Synthesis of (2-methoxyphenyl)-2-pyridine (52) by ligand coupling**[147]*

Arguably the most synthetically interesting aspect of this reaction is that any stereochemical information on the α-carbon of the sulfoxide is retained in the product. This was exhibited by the group of Oae in two examples (Scheme 2.61).[118] Since the retention of stereochemistry was observed with both 2-pyridyl sulfoxide **196** and 4-sulfonylphenyl sulfoxide **197**, retention due to any coordination with the 2-pyridyl ring can be ruled out.



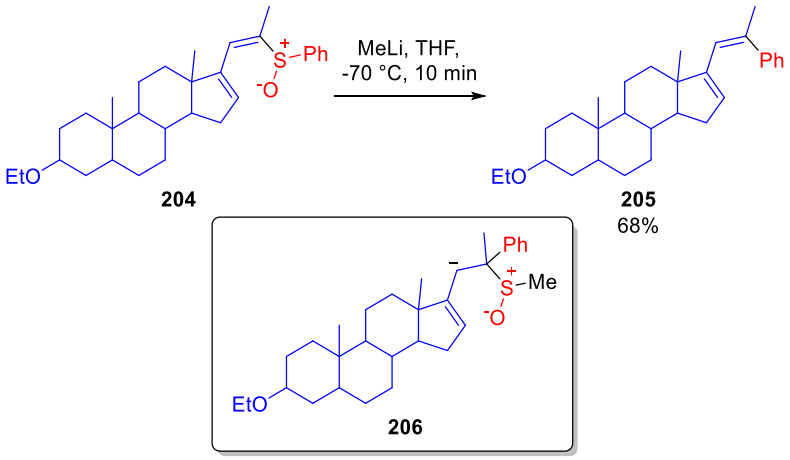
*Scheme 2.61: **Retention of benzylic stereochemistry during ligand coupling**[118]*

The group of Oae have also found that the couplings of allyl sulfoxide **200** and vinyl sulfoxide **201** proceeds with complete preservation of the geometry around the olefin (Scheme 2.62).[146]



Scheme 2.62: Ligand coupling of aryl groups with allyl and vinyl groups[146]

The reaction of phenyl sulfoxide **204** with methyllithium was found to provide styrene **205**. The report by Neef *et al*. does not describe the reaction as occurring through a ligand coupling reaction. Instead, the reaction is described as occurring through initial σ-sulfurane formation, followed by a 1,2-migration of the phenyl ring which forms allylic anion **206**. Elimination of methyl sulfenate was proposed to form styrene **205**. Based on the previously discussed retention of stereochemical information in the ligand coupling reaction, the regioselectivity seen in the formation of styrene **205** suggests that a ligand coupling mechanism is plausible (Scheme 2.63).[148]



*Scheme 2.63: Potential ligand coupling of dienylphenyl sulfoxide **204***[148]

2.2 Aims of this work

Transition metal catalysis has been developed for the formation of carbon-carbon bonds in recent decades. Vast amounts of research are devoted to the study of traditional transition metal-catalysed cross-coupling reactions, while some fundamental issues still limit their utility. The first key issue is that it remains problematic to form enantiomerically enriched $C(sp^3)$-$C(sp^3)$ and $C(sp^2)$-$C(sp^3)$ bonds. Typical complications which arise in this area include β-hydride elimination and racemisation of stereochemistry. These issues are typically addressed by developing complex ligand systems to induce stereochemistry and prevent β-hydride elimination.[149–156] Secondly, the coupling of electron-deficient organometallic reagents is widely known to be susceptible to low yields due to protodemetallation.[157,158] Many cross-coupling reactions which incorporate electron-deficient arenes focus on avoiding the use of such electron-deficient arene organometallic reagents.[159–165]

To the best of our knowledge, the enantioselective coupling of electron-deficient arenes with alkyl moieties using transition-metal catalysis has never been reported. It has been shown that the ligand coupling reactions of species such as sulfoxides can be used to synthesise such bonds in apparent ease (*vide supra*: Section 2.1.5.5.6). The limited amount of literature, especially of recent years, devoted to the study of this phenomenon is, however, perplexing. While the mechanism of ligand coupling reactions of organosulfur compounds has been explored thoroughly, the scope of such reactions remains vastly underexplored. As a result, the early studies of pioneers such as Oae and Trost have become buried in the literature.

It is therefore aimed to revitalise the field of ligand coupling reactions using sulfoxides, primarily by thoroughly exploring and expanding the scope of these reactions. An emphasis will be placed upon the areas in which traditional transition metal-catalysed cross-coupling is troublesome. This will include the formation of $C(sp^2)$-$C(sp^3)$ bonds, exploration of the (hetero)aromatic species and alkyl groups which will undergo ligand coupling as well as the effect of different organometallic reagents which mediate ligand coupling reactions.

2.3 Synthesis of diarylmethanes

Diarylmethanes are named as privileged structures for their prevalence in a number of compounds with wide-ranging biological activities.[166,167] Notable examples include podophyllotoxin (**207**, Figure 2.4), a tubulin polymerisation inhibitor and lonafarnib (**208**), a farnesyltransferase inhibitor. Histamine H1 receptor antagonists **209a**-**209b** are used in the treatment of hayfever, with chlorphenamine (**209b**) being sold as its maleate salt by GSK as an "over the counter" medication branded as Piriton®. Sertraline (**210**) and citalopram (**211**) are antidepressants and selective serotonin reuptake inhibitors (SSRIs). Three brands of sertraline (**210**) and five brands of citalopram (**211**) are found in the "Top 200 Pharmaceutical Products by US Prescription in 2012" list, compiled by the group of Njarðarson.[168] As such, syntheses of these moieties are much sought after.

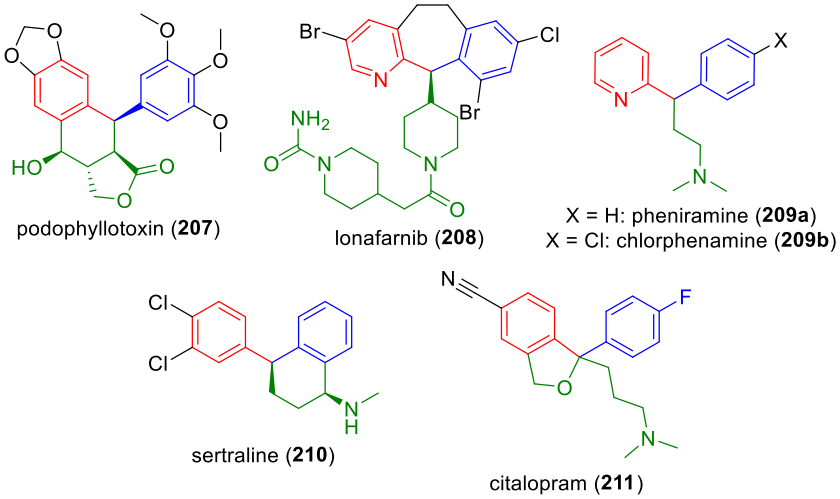
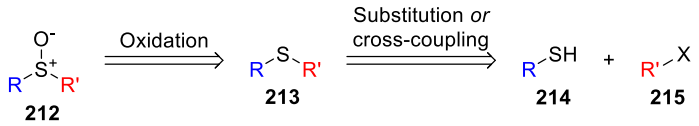


Figure 2.4: Structures of common diarylmethanes

2.3.1.2 Synthesis of sulfoxides for examination

In order to probe the limitations of the reaction, it was proposed that a range of sulfoxides **212** would be synthesised (Scheme 2.64). Racemic sulfoxides **212** can be synthesised by oxidation of the corresponding sulfides **213**, which in turn can be synthesised by substitution or cross-coupling of thiols **214** with halides **215**.

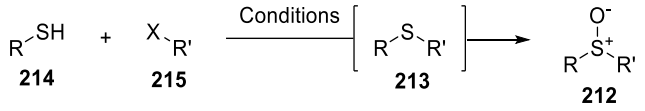


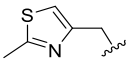
*Scheme 2.64: **Proposed synthetic route to racemic sulfoxides 212***

A range of commercially available thiols **214** were used to synthesise sulfides **213aa**-**bn** by either alkylation or arylation (Table 2.8). Oxidation of sulfides **213aa**-**bn**

was performed, in all cases, using one equivalent of *m*CPBA, providing sulfoxides **212aa**-**bn** in generally good to excellent yields over two steps.

Table 2.8**: Yields for the synthesis of benzyl-2-pyridylsulfoxides **108aa-bn

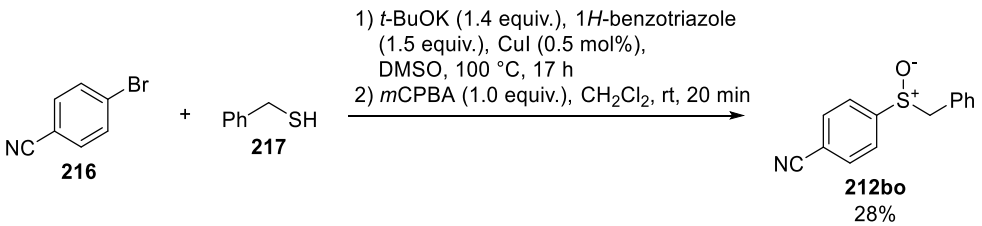


Entry	R	R'	X	Conditions	Product	Yield 212 (%)
1	Bn	2-Py	Cl	a, g	**212aa**	89
2	CH_2Mes	2-Py	Cl	a, g	**212ab**	73
3	2-Py	CH_2(2-Me(C_6H_4))	Cl	b, g	**212ac**	97
4	CH_2(3-Me(C_6H_4))	2-Py	Cl	a, g	**212ad**	87
5	2-Py	CH_2(4-Me(C_6H_4))	Cl	b, g	**212ae**	80
6	CH_2(4-F(C_6H_4))	2-Py	Cl	a, g	**212af**	64
7	CH_2(2-Cl(C_6H_4))	2-Py	Cl	a, g	**212ag**	60
8	2-Py	CH_2(3-Cl(C_6H_4))	Cl	b, g	**212ah**	56
9	2-Py	CH_2(4-Cl(C_6H_4))	Cl	b, g	**212ai**	97
10	2-Py	CH_2(4-Br(C_6H_4))	Br	c, g	**212aj**	76
11	2-Py	CH_2(2-CF_3(C_6H_4))	Cl	b, g	**212ak**	96
12	CH_2(3-CF_3(C_6H_4))	2-Py	Cl	a, g	**212al**	52
13	2-Py	CH_2(4-CF_3(C_6H_4))	Cl	b, g	**212am**	97
14	2-Py	CH_2(3-MeO(C_6H_4))	Cl	b, g	**212an**	96
15	CH_2(4-MeO(C_6H_4))	2-Py	Cl	a, g	**212ao**	81
16	2-Py		Cl	b, g	**212ap**	90
17	CH_2(2-furyl)	2-Py	Cl	a, g	**212aq**	81
18	2-Py	CH_2(2-Py)	Cl	b, g	**212ar**	92
19	2-Py	CH_2(3-Py)	Cl	b, g	**212as**	84
20	2-Py	CH_2(4-Py)	Cl	b, g	**212at**	34
21	2-Py	CH_2(Cy)	Br	b, g	**212au**	82
22	4-Py	CH(CH_3)Ph	OH	d, g	**212av**	19
24*	2-benzothiazolyl	CH(CH_3)Ph	OH	d, g	**212ax**	64
25*	2-benzimidazolyl	Bn†	Br	e, g	**212ay**	53
26		CH(CH_3)Ph†	Br	b, g	**212az**	82

27	2-imidazolyl	Bn†	Br	b, g	**212ba**	46
28*		CH(CH_3)Ph‡	Br	e, f, g	**212bb**	51
29*		PMB†	Cl	e, g	**212bc**	32
30	2-thienyl	Bn	Br	b, g	**212bd**	92
31	4-F(C_6H_4)	CH(CH_3)Ph	Br	b, g	**212be**	93
32	4-CF_3(C_6H_4)	Bn	Br	b, g	**212bf**	78
33		CH(CH_3)Ph	Br	b, g	**212bg**	81
34	3-CF_3(C_6H_4)	Bn	Br	b, g	**212bh**	78
35*		CH(CH_3)Ph	Br	e, g	**212bi**	71
36	2-CF_3(C_6H_4)	Bn	Br	b, g	**212bj**	88
37*		CH(CH_3)Ph	Br	b, g	**212bk**	88
38*	4-NO_2(C_6H_4)	Bn	Br	e, g	**212bl**	92
39	Bn	Me	I	b, g	**212bm**	53
40	2-Py	Me	I	e, g	**212bn**	70

*Notes: *) work performed by Mindaugas Šiaučiulis; †) N(Ar) protected as this group also; ‡) N(Ar) protected with a methyl group. Reagents and conditions*: a) *2-chloropyridine (1.0 equiv.), benzylic mercaptan (1.1 to 1.5 equiv.), t-BuOK (1.1 to 2.0 equiv.), THF, 40 °C, 18 to 42 h; b) 2-mercaptopyridine (1.0 to 1.2 equiv.), benzylic halide (1.0 to 2.0 equiv.), NaOEt (1.2 to 2.2 equiv.), EtOH, rt, 2.5 h to 4 d; c) 2-mercaptopyridine (1.0 equiv.), 4-bromobenzylbromide (1.0 equiv.), K_2CO_3 (1.2 equiv.), MeCN, rt, 22 h; d) thiol (1.0 equiv.), 1-phenylethanol (1.5 equiv.), DMF (1.7 equiv.), $(COCl)_2$ (1.5 equiv.), NEt_3 (3.0 equiv.), THF, 0 °C to rt, 22 h; e) thiol (1.0 equiv.), either 1-(bromoethyl)benzene, BnBr, PMBCl or MeI (1.1 to 1.2 equiv.), t-BuOK (1.2 equiv.), EtOH, rt, 1 h to 5 h; f) MeI (1.1 equiv.), NaH (1.1 equiv.), DMF, 0 °C to rt, o/n; g) mCPBA (1.0 equiv.), CH_2Cl_2, 0 °C or rt, 15 min to 2 h.*

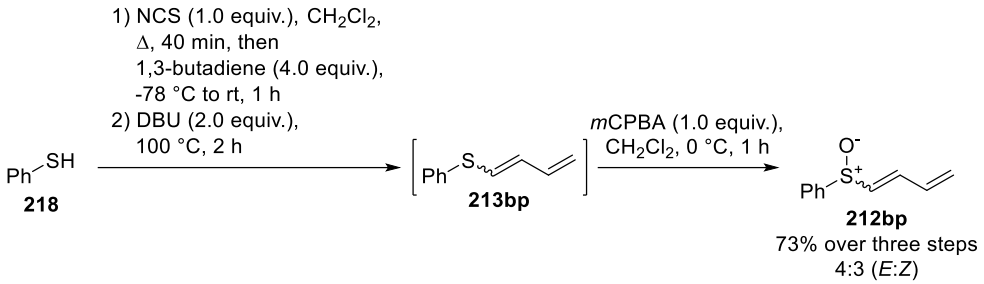
Synthesis of 4-cyanophenyl sulfoxide **212bo** was performed using literature conditions to couple 4-bromobenzonitrile (**216**) with benzyl mercaptan (**217**) under copper(I) catalysis.[169] Subsequent oxidation of the corresponding sulfide afforded 4-cyanophenyl sulfoxide **212bo** in a 28% yield over two steps.



*Scheme 2.65: Synthesis of 4-cyanophenyl sulfoxide **212bo**. Work performed by Mindaugas Šiaučiulis*

It was also proposed that dienes would be investigated in place of (hetero)arenes, drawing on precedent from Neef *et al.* (*vide supra*: Scheme 2.63).[148] As such, known dienyl sulfide **213bp** was synthesised by the chlorination and substitution of thiophenol (**218**), followed by alkaline elimination of HCl (Scheme 2.66). Oxidation, as

before, afforded seperable dienyl sulfoxides ***E*-212bp** and ***Z*-212bp** in a ratio of 4:3 respectively.



*Scheme 2.66: Synthesis of dienyl sulfoxides **E-212bp** and **Z-212bp***

2.3.1.3 Optimisation of the Grignard reagent

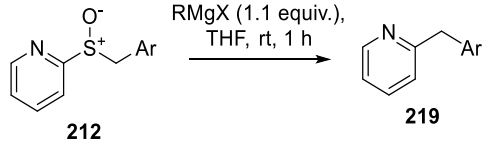
Reports from the group of Oae suggest that the yield of ligand coupling can change dramatically based on the non-coupling group (*vide supra*: Table 2.6). With a range of substrates in hand, optimisation of the Grignard reagent was performed (Table 2.9). It was decided that selected benzyl-2-pyridyl sulfoxides would be used for this investigation due to the precedence of ligand coupling with these molecules (*vide supra*: Section 2.1.5.5.6).

2-Methyl-4-((pyridin-2-ylsulfinyl)methyl)thiazole (**212ap**) was chosen for this study for its simple ^{1}H NMR spectrum, making identification of products facile. 2,4,6-Trimethylbenzyl sulfoxide **212ab** and 2-methylbenzyl sulfoxide **212ac** were chosen to study sterically demanding substrates, while 4-(trifluoromethyl)benzyl sulfoxide **212am** was chosen to represent electron deficient benzylic groups.

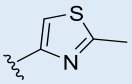
Gratifyingly, thiazole-containing sulfoxide **212ap** formed an impressive 73% yield of diarylmethane **219ap** when exposed to *t*-butylmagnesium chloride (entry 3). Methyl and phenyl Grignard reagents provided diarylmethane **219ap** in slightly lower yields of 57% and 60% respectively (entries 1 and 2). Mesitylmagnesium bromide formed only a small quantity of ligand coupling product (entry 4). It was proposed that this low yield was due to the steric bulk of mesityl Grignard reagent rendering it unable to attack the sulfinyl centre. This postulation was corroborated by the presence of large amounts of starting material **212ap** in the crude ^{1}H NMR. Sterically demanding 2,4,6-trimethylbenzyl substrate **212ab** provided an excellent yield (90%) of corresponding diarylmethane **219ab** upon exposure to phenylmagnesium bromide (entry 6). Methylmagnesium bromide and *t*-butylmagnesium chloride produced

slightly lower yields of 76% and 79% respectively with the same substrate **212ab** (entries 5 and 9). Cyclohexylmagnesium bromide generated slightly lower yields of diarylmethane **219ab** (entry 8). 2-Methylbenzyl sulfoxide **212ac** formed a very good yield of diarylmethane **219ac** with phenyl, cyclohexyl and *t*-butyl Grignard reagents (entries 10-12). In the reaction of 4-(trifluoromethyl)benzyl sulfoxide **212am** with Grignard reagents, it was found that methylmagnesium bromide performed favourably compared to *t*-butylmagnesium bromide (entries **14** and **15**).

Table 2.9: Screening of substrates with Grignard reagents



212 **219**

Entry	Ar	RMgX	Product	Yield 219 (%)
1		MeMgBr	**219ap**	57
2		PhMgBr		60
3		*t*-BuMgCl		73
4		MesMgBr		6
5	Mes	MeMgBr	**219ab**	76
6		PhMgBr		90
7		cyclohexylMgCl		62
8		*t*-BuMgCl		79
9	2-Me(C_6H_4)	MeMgBr	**219ac**	73
10		PhMgBr		88
11		cyclohexylMgBr		87
12		*t*-BuMgCl		84
13		MesMgBr		7
14	4-CF_3(C_6H_4)	MeMgBr	**219am**	63
15		*t*-BuMgCl		40

It can be seen that no single Grignard reagent examined provides the best yields of all diarylmethanes **219** from the sulfoxides **212** studied. It was therefore decided that two or three Grignard reagents would be chosen from those examined to simplify the selection process for those wanting to perform this ligand coupling reaction. *t*-Butylmagnesium chloride was chosen as it provided either best or very close to best yields with three out of the four substrates chosen. However, the use of

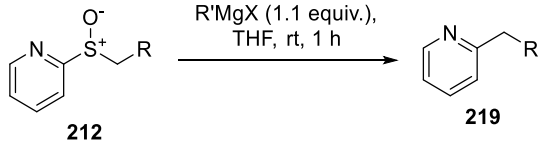
t-butylmagnesium chloride with electron-deficient 4-(trifluoromethylbenzyl) sulfoxide **212am** provided poor yields of corresponding diarylmethane **219am**. Despite not being as effective with three out of four substrates, methylmagnesium bromide was included in the condensed optimisation to accommodate for electron-deficient substrates.

2.3.2 Scope of the benzyl arene

Having chosen Grignard reagents to use in future studies, the extent to which substitution of the benzyl arene can be tolerated by the ligand coupling reaction was examined next. As stated above, it was decided that these ligand coupling reactions would be performed using both methylmagnesium bromide and *t*-butylmagnesium chloride.

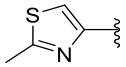
Gratifyingly, yields of diarylmethanes **219aa-au** over 60% were obtained for more than three quarters of substrates (Table 2.10). Further examination of the yields shows that diarylmethanes **219aa-au** can be formed in up to 98% yield using this methodology (entry 4). Unfunctionalised diarylmethanes **219aa-ae** were synthesised in good to excellent yields (entries 1-5). The formation of aryl halides **219af-aj** illustrates the potential for further functionalisation of products by, for example, halogen-metal exchange or transition metal-catalysed cross-coupling (entries 6-10). Both electron-rich and electron deficient aryl substitutions were well tolerated under these reaction conditions (entries 11-15). Diheteroarylmethanes **219ap-at** were synthesised in some impressive yields (up to 81%), demonstrating the versatility of this reaction (entries 16-20). Expectedly, cyclohexane-containing sulfoxide **212au** produced no desired ligand coupling product **219au** (entry 21). Presumably this shows that there is an electronic requirement, which the benzylic group fulfils, in order to undergo ligand coupling, and that removal of the arene prevents ligand coupling processes.

*Table 2.10: Reaction of 2-pyridyl sulfoxides **212aa-au** with MeMgBr and t-BuMgCl*



212 219

Entry	R	Product	Yield 219 (%) MeMgBr	Yield 219 (%) *t*-BuMgCl
1	Ph	**219aa**	56	**70**
2	Mes	**219ab**	76	**79**

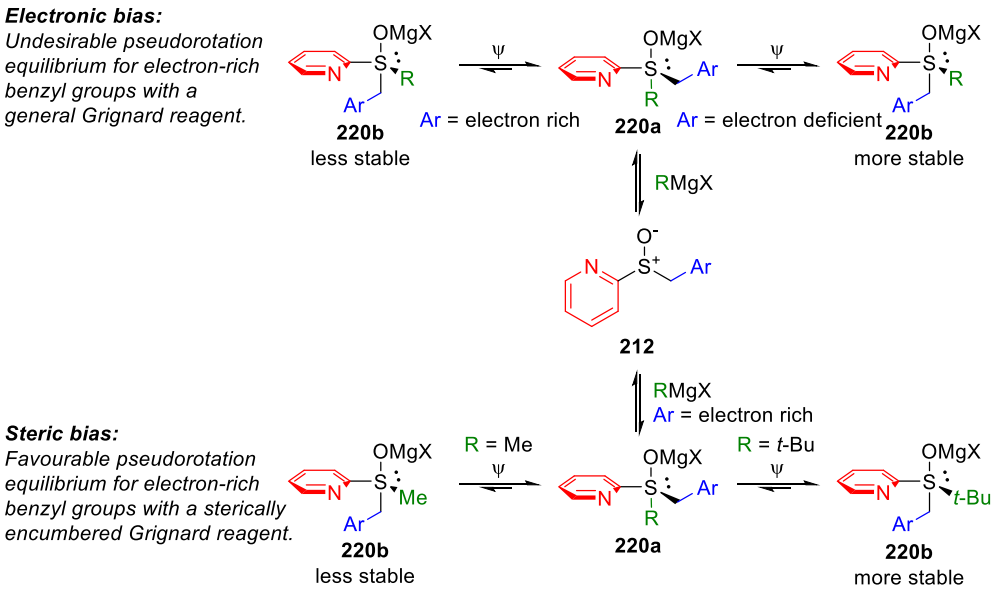
3	2-Me(C_6H_4)	**219ac**	73	**84**
4	3-Me(C_6H_4)	**219ad**	54	**98**
5	4-Me(C_6H_4)	**219ae**	65	**85**
6	4-F(C_6H_4)	**219af**	71	**79**
7	2-Cl(C_6H_4)	**219ag**	**77**	71
8	3-Cl(C_6H_4)	**219ah**	67	**68**
9	4-Cl(C_6H_4)	**219ai**	**84**	81
10	4-Br(C_6H_4)	**219aj**	67	**71**
11	2-CF_3(C_6H_4)	**219ak**	**47**	29
12	3-CF_3(C_6H_4)	**219al**	**58**	38
13	4-CF_3(C_6H_4)	**219am**	**63**	40
14	3-MeO(C_6H_4)	**219an**	66	**88**
15	4-MeO(C_6H_4)	**219ao**	38	**89**
16		**219ap**	57	**73**
17	2-Furyl	**219aq**	**74**	67
18	2-Py	**219ar**	13	**81**
19	3-Py	**219as**	**72**	**72**
20	4-Py	**219at**	**26**	13
21	Cy	**219au**	0	-

The results confirm that neither Grignard reagent examined provides optimal yields with all substrates. Comparison of the electronic nature of each arene with yield of diarylmethane **219** produced shows that electron rich benzylic groups favour ligand coupling using *t*-butylmagnesium chloride (entries 1-5, 14 and 15). Electron deficient benzylic groups generate higher yields of diarylmethanes **219** with methylmagnesium bromide (entries 8-10 and 11-13). This information may allow for the prediction of whether MeMgBr and *t*-BuMgCl will provide highest yields if the electronic nature of a substrate is clear.

Explanation of this trend may be found in studying the σ-sulfurane intermediate of the ligand coupling reaction. As stated previously (*vide supra*: Section 2.1.5.5.5), the attack of a Grignard reagent on a benzyl-2-pyridyl sulfoxide **212** will form a σ-sulfurane **220a** where the nucleophile will initially adopt an axial position (Scheme 2.67, top). A pseudorotation (ψ) is required to bring the benzylic ligand into an axial

position, to form σ-sulfurane **220b** which has the correct geometry to undergo a ligand coupling reaction. In the case of electron-deficient benzyl ligands, this pseudorotation is favourable as the more electronegative ligand prefers to be in a more electropositive axial position (electronic bias, top-right). Hence, for electron-deficient benzyl ligands, less bulky Grignard reagents, such as methylmagnesium bromide, are preferable to enhance the steric accessibility of the sulfoxide.

For electron-rich arenes, however, the required pseudorotation is unfavourable as the more electropositive ligand prefers to bond to the more electronegative equatorial positions around the σ-sulfurane (electronic bias, top-left). A bulky *t*-butyl ligand counteracts this by requiring a more spacious equatorial position, forcing the benzyl ligand into an axial position where it can undergo ligand coupling (steric bias, bottom). In summary, *t*-butylmagnesium chloride is thought to overcome the detrimental electronic bias of electron-rich benzyl groups by introducing a competitive steric bias on σ-sulfurane intermediates.



Scheme 2.67: Electronic and steric biases affecting the pseudorotation equilibria of σ-sulfurane intermediates

2.3.3 Scope of the (hetero)aromatic group

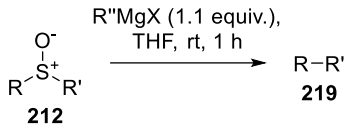
Efforts were directed towards determining the scope of ligand coupling of benzyl sulfoxides with regards to the (hetero)arene, in the synthesis of diarylmethanes (Table 2.11). Reaction of 2-pyridylsulfoxide **212aa** and 4-pyridylsulfoxide **212av** with Grignard reagents was successful, forming diarylmethanes **219aa** and **219av** in 70% and 40% yield respectively (entries 1 and 2). This compares well with similar examples

from the group of Oae (*vide supra*: Scheme 2.57). No formation of desired diarylmethane **219aw** was noted in the reaction of 2-benzothiazolyl sulfoxide **212aw** with MeMgBr (entry 3). Exposure of benzothiazole **212ax**, which is only different from sulfoxide **212aw** due to the methylated benzylic position, to MeMgBr produced a trace of, what was tentatively assigned as, diarylmethane **219ax** by ^{1}H NMR analysis (entry 4). Interestingly, benzimidazole sulfoxides **212ay** and **212az** exhibited the same trend, with larger amounts of methylated diarylmethane **219az** formed in comparable reactions (entries 5 and 6). 2-Imidazolyl sulfoxides **212ba-bc** were also subjected to ligand coupling conditions (entries 7 to 9). While no desired diarylmethane **219ba** or diarylmethane **219bb** were formed, electron-rich PMB sulfoxide **212bc** formed a trace of the corresponding diarylmethane **219bc** by ^{1}H NMR and HRMS. It may be inferred from these results that more electron-rich benzylic groups, either with benzylic methylation or electron-rich arenes, are more amenable to ligand coupling. Unfortunately, thiophene sulfoxide **212bd** formed no ligand coupling product **219bd** (entry 10). Reaction of 4-fluorophenyl sulfoxide **212be** with MeMgBr afforded no ligand coupling products (entry 11). Trifluoromethylphenyl sulfoxides **212bf**-**bk** reacted more favourably (entries 12-18). Again, methylation of the benzylic centre produced higher amounts of ligand coupling product (entries 12 and 13). An increase in yield of 4-(trifluoromethyl)phenyl diarylmethane **219bg** was noted when MeMgBr was used than to when *t*-BuMgCl was used (entries 13 and 14). This was attributed to the increased steric bulk around the sulfinyl centre preventing attack of the bulkier Grignard reagent. While reaction of 2- and 4-(trifluoromethyl)phenyl sulfoxides **212bg** and **212bk** with MeMgBr produced diarylmethanes **219bg** and **219bk**, 3-(trifluoromethyl)phenyl sulfoxide **212bi** did not form any ligand couling product **219bi** (entries 14, 16 and 18). This observation provides evidence to support the development of a formal negative charge on the (hetero)arene during the ligand coupling process, since this would be more stabilised by arenes which are electron-deficient at the *ipso*-position. This could be construed as the benzylic ligand coupling with the (hetero)arene by an S_NAr-like mechanism.

The exposure of 4-nitrophenyl sulfoxide **212bl** to Grignard reagents was performed at low temperature to prevent undesired nucleophilic addition commonly observed with nitroaromatics (entry 19).[170] Despite a number of attempts, nitro diarylmethane **219bl** was never observed (entries 20-21). Gratifyingly, 4-benzonitrile sulfoxide **212bo** underwent ligand coupling reaction in a 33% yield on exposure to MeMgBr (entry 22).

Low yields were usually accompanied by recovered starting material or isolated by-products such as ligand exchange or homocoupling products (*vide supra*: Scheme 2.56)

Table 2.11**: Ligand coupling reactions of (hetero)aryl benzyl sulfoxides **212aa** and **212av-bn



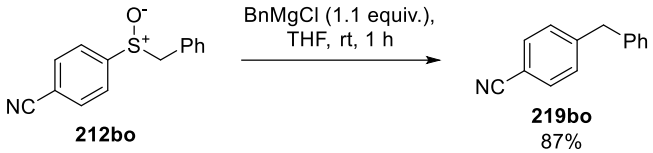
Entry	R	R'	R''MgX	Product	Yield 219 (%)
1	2-Py	Bn	*t*-BuMgCl	**219aa**	70
2	4-Py	$CH(CH_3)Ph$	MgMgBr	**219av**	40
4[a]	2-benzothiazolyl	$CH(CH_3)Ph$	MeMgBr	**219ax**	Trace
5[a]	2-benzimidazolyl	Bn[b]	MeMgBr	**219ay**	Trace
6		$CH(CH_3)Ph$[b]	MeMgBr	**219az**	36
7	2-imidazolyl	Bn[b]	*t*-BuMgCl	**219ba**	0
8[a]		$CH(CH_3)Ph$[c]	MeMgBr	**219bb**	0
9[a]		PMB[b]	MeMgBr	**219bc**	Trace
10	2-thienyl	Bn	*t*-BuMgCl	**219bd**	0
11	4-$F(C_6H_4)$	$CH(CH_3)Ph$	MeMgBr	**219be**	0
12	4-$CF_3(C_6H_4)$	Bn	*t*-BuMgCl	**219bf**	0
13		$CH(CH_3)Ph$	*t*-BuMgCl	**219bg**	Trace
14			MeMgBr		36
15	3-$CF_3(C_6H_4)$	Bn	*t*-BuMgCl	**219bh**	0
16[a]		$CH(CH_3)Ph$	MeMgBr	**219bi**	0
17	2-$CF_3(C_6H_4)$	Bn	*t*-BuMgCl	**219bj**	0
18[a]		$CH(CH_3)Ph$	MeMgBr	**219bk**	15
19[a]	4-$NO_2(C_6H_4)$	Bn	*t*-BuMgCl[d]	**219bl**	0
20[a]			MeMgBr[e]		0
21[a]			MeMgBr[d]		0
22[a]	4-$CN(C_6H_4)$	Bn	MeMgBr[f]	**219bo**	33

Notes: a) work performed by *Mindaugas Šiaučiulis; b) N(Ar) protected as this group also; c) N(Ar) protected with a methyl group; d) reaction performed at -40 °C;* e) *reaction performed at 0 °C; f) reaction performed at -20 °C.*

2.3.3.2 Formation of diarylmethanes by cross-coupling

Examining the potential to perform cross-coupling reactions, 4-benzonitrile sulfoxide **212bo** was reacted with BnMgCl providing diarylmethane **219bo** in an 87% yield

(Scheme 2.68). This is a significant improvement on the previous yield of diarylmethane **219bo**, when MeMgBr was used (33%, *vide supra*: Table 2.11, entry 22). Presumably, the higher availability of benzyl ligands around the σ-sulfurane facilitates the ligand coupling reaction. Furthermore, the initial conformation of the σ-sulfurane will have a benzyl ligand in the axial position, so pseudorotation is not required before ligand coupling can occur. This is reminiscent of the observations of Oae, where it was found that a higher yield of ligand coupling product was produced with the Grignard reagent than with the second ligand on the sulfoxide (*vide supra*: Section 2.1.5.5.5).



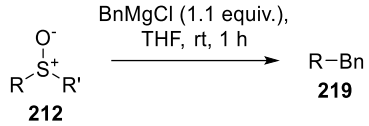
212bo

219bo
87%

*Scheme 2.68: Enhanced ligand coupling of 4-benzonitrile sulfoxide **212bo**. Work performed by Mindaugas Šiaučiulis*

Pure cross-coupling reactions were also examined (Table 2.12). Methyl-2-pyridyl sulfoxide (**212bn**) formed diarylmethane **219aa** in 71% yield upon reaction with BnMgCl (entry 1). This yield is significantly higher than the yield achieved by with benzyl-2-pyridyl sulfoxide and MeMgBr (56%), which is curious since the three organic ligands around the sulfoxide are the same (*vide supra*: Table 2.10, entry 1). Presumably the higher cross-coupling yield is due to the initial positioning of the benzyl ligand in the axial position; the correct conformation for ligand coupling to occur. Dienyl sulfoxides ***E*-212bp** and ***Z*-212bp** were exposed to BnMgCl, providing the desired ligand coupling products in low yield (entries 2 and 3). Gratifyingly, retention of alkene geometry was noted in analysis by ^{1}H NMR. This suggests that there is not a long-lived formal negative charge developing on the diene, since this would have caused isomerisation. The absence of olefinic peaks, save those of the products, in crude ^{1}H NMR spectra suggested that ligand exchange was forming butadiene anion, which was protonated and removed *in vacuo* upon workup. This may explain the low yields of products ***E*-219bp** and ***Z*-219bp**. In the case of commercially available ethyl-4-benzoyl sulfoxide **212bq**, exposure to benzylmagnesium bromide at room temperature afforded a 43% yield of diarylmethane **219bq**, while a 20% higher yield was obtained when the reaction was performed at 0 °C (entries 4 and 5). This could be due to the suppression of alkylation of the ester or the retardation of pseudorotation, since pseudorotation would form a σ-sulfurane conformation prohibitive of ligand coupling.

Table 2.12**: Cross-ligand coupling reactions of sulfoxides **212bn, 212bo-bq



Entry	R	R'	Product	Yield 219 (%) / dr[a]
1	2-Py	Me	**219aa**	71
2[b]	*E*-butadienyl	Ph	***E*-219bp**	8 / >95:5
3[b]	*Z*-butadienyl	Ph	***Z*-219bp**	6 / 94:6
4[c]	4-(EtO_2C)(C_6H_4)	Me	**219bq**	43
5[c,d]				63

Notes: a) dr determined by integration of olefinic protons in 1H NMR spectrum; b) dr of starting material >95:5; c) work performed by Mindaugas Šiaučiulis; d) reaction performed at 0 °C.

The cross-coupling reactions of (hetero)aryl organometallic reagents with benzyl sulfoxide **212bm** to form diarylmethanes was studied next (Table 2.13). 2-Pyridylmagnesium bromide was initially synthesised by reacting 2-bromopyridine with magnesium and stoichiometric amounts of 1,2-dibromoethane (entries 1 and 2).[171] Reaction with benzyl methyl sulfoxide (**212bm**) at -40 °C produced a low yield of diarylmethane **219aa** (entry 1). Attempting to optimise this reaction, the same Grignard reagent was reacted with sulfoxide **212bm** at room temperature, however similar amounts of product were observed by ^{1}H NMR (entry 2). The formation of this Grignard reagent was found to be capricious, giving concentrations between 0.2 M and 0.05 M. Synthesis of the Grignard reagent was therefore attempted by magnesium-halogen exchange with *i*-propylmagnesium chloride in an attempt to form the reagent in a more controllable manner.[172] Reaction with benzyl methyl sulfoxide (**212bm**) was attempted at room temperature, however diarylmethane **219aa** was not observed by crude ^{1}H NMR (entry 3). Lithium chloride was added in an attempt to break Grignard dimers, as devised by the group of Knochel,[173,174] however the crude ^{1}H NMR spectrum showed no formation diarylmethane **219aa** (entry 4). With the hypothesis that the low yield was as a result of slow pseudorotation, the reaction was performed at 40 °C to 50 °C to effect the learnings of Oae (*vide supra*: Scheme 2.55). Again, no trace of desired diarylmethane **219aa** was observed by ^{1}H NMR (entry 5).

It was envisaged that nitrophenyl Grignard reagents could be used in a similar manner to effect ligand coupling; allowing for the formation of nitro-containing diarylmethanes **219** which were unable to be synthesised in previous efforts (*vide*

supra: Table 2.11). Knochel has previously described the preparation of such reagents.[175] The synthesis of 2-nitrophenylmagnesium chloride was performed by exposing 2-nitroiodobenzene to phenylmagnesium chloride (entry 6). Unfortunately, no desired diarylmethane **219bq** was observed by ^{1}H NMR.

Large amounts of remaining starting material **212bm** were observed in the post-reaction analysis of all of these reactions. It is suggested that the electron-deficient Grignard reagents used are either too stable to react with sulfoxide **212bm**, or that deprotonation of the benzyl group is a faster, competitive reaction pathway.

*Table 2.13: Use of (hetero)aryl Grignard reagents to form diarylmethanes **219**. Work performed by Mindaugas Šiaučiulis*



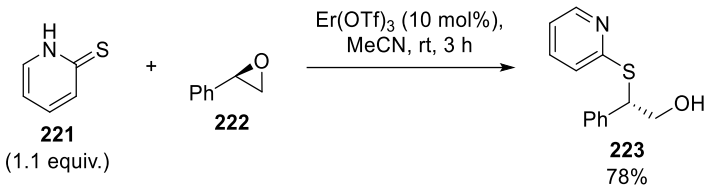
212bm **219**

Entry	Conditions (equiv.)	(Het)ArMgX	Product	Yield 219 (%)
1	2-bromopyridine (1.0), Mg (2.0), 1,2-dibromoethane (1.0), THF, rt, 1 h, then **212bm** (1.0), THF, -40 °C, 1 h	2-PyMgBr	**219aa**	9
2	2-bromopyridine (1.0), Mg (2.0), 1,2-dibromoethane (1.0), THF, rt, 1 h, then **212bm** (1.0), THF, -40 °C, 1 h	2-PyMgBr	**219aa**	10[a]
3	2-bromopyridine (1.0), *i*-PrMgBr (1.1), THF, rt, 1 h, then **212bm** (1.0), THF, rt, 2.5 h	2-PyMgBr	**219aa**	-
4	2-bromopyridine (1.0), *i*-PrMgBr (1.1), THF, rt, 1 h, then LiCl (2.0), rt, 1 h, then **212bm** (1.0), THF, rt, 2.5 h	2-PyMgBr	**219aa**	-
5	2-bromopyridine (1.0), *i*-PrMgBr (1.1), THF, rt, 1 h, then **212bm** (1.0), THF, 40 °C to 50 °C, 3.5 h	2-PyMgBr	**219aa**	-
6	2-nitrobenzene (1.0), PhMgCl (1.1), THF, -40 °C, 30 min, then **212bm** (1.2), -40 °C to rt, 5 h	2-$NO_2(C_6H_4)$MgCl	**219bq**	-

Notes: a) conversion calculated by analysis of the crude ^{1}H NMR spectrum.

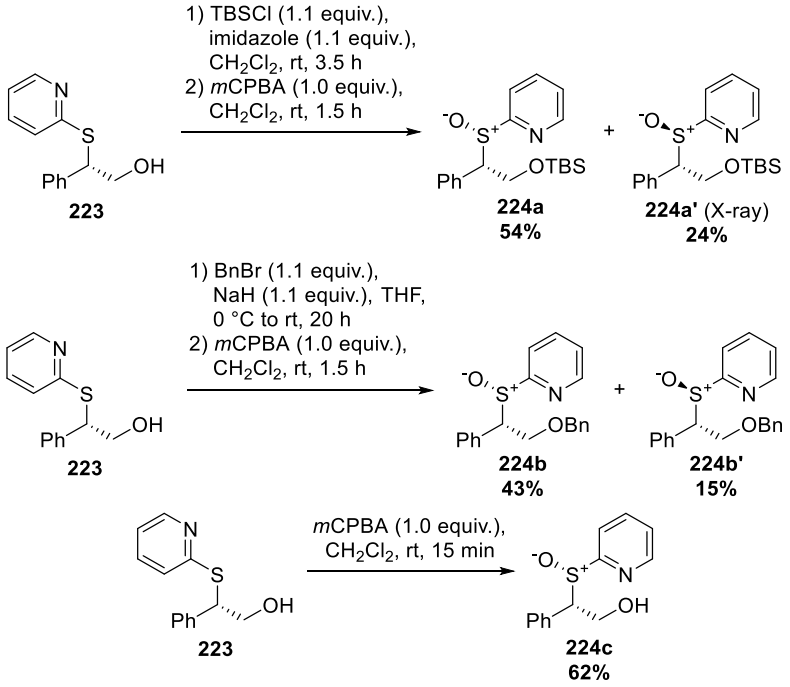
2.3.3.3 Synthesis of enantiomerically enriched diarylmethanes

The effect of substitution of the benzylic moiety upon this reaction was studied next. 2-Mercaptopyridine (**221**) was used to perform a regioselective attack upon (*R*)-styrene oxide (**222**, Scheme 2.69). Good regioselectivity was obtained using catalytic erbium(III) triflate, as devised by Nardi, forming alcohol **223** in good yield.[176]



*Scheme 2.69: Synthesis of pyridyl alcohol **223** from (R)-styrene oxide (**222**)*

In order to provide a range of substrates for examination, alcohol **223** was subjected to a number of conditions to form derivatives (Scheme 2.70). Protection of alcohol **223** as either the corresponding benzyl ether or TBS ether, and subsequent oxidation provided sulfoxides **224a** and **224b**. The diastereomers of each sulfoxide were separable by careful column chromatography (Scheme 2.70). The oxidation of alcohol **223** was also performed and, while a mixture of diastereomers was observed by crude ^{1}H NMR, chromatography afforded only one pure diastereomer of sulfoxide **224c**. The stereocentres of each diastereomer were fully assigned using a combination of single-crystal X-ray crystallography of crystalline products together with comparison of ^{1}H NMR chemical shifts of the benzylic proton to assign non-crystalline substrates (Figure 2.5).



*Scheme 2.70: Protection and oxidation of pyridyl alcohol **223***

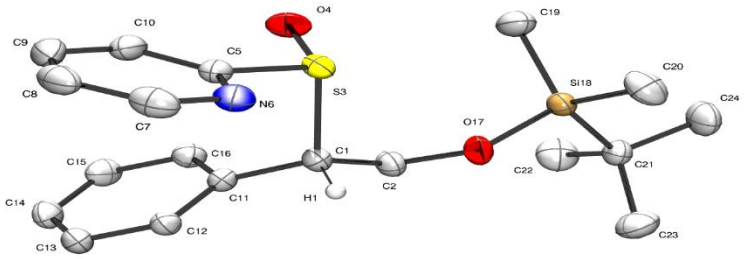
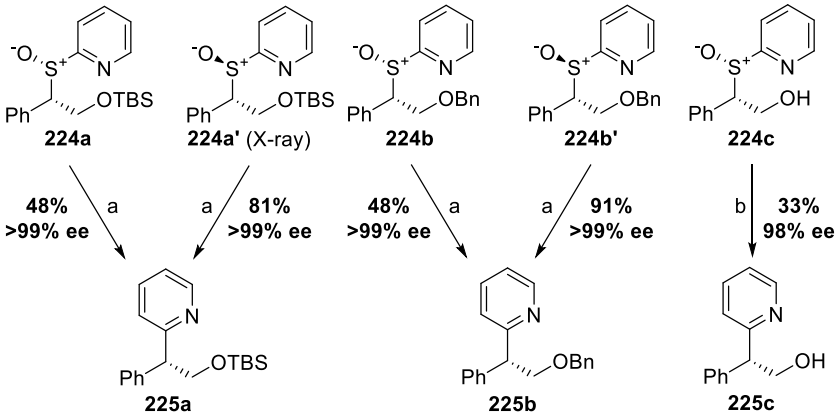


*Figure 2.5: Single crystal XRD structure of sulfoxide **224a'***

Subjection of sulfoxides **224** to MeMgBr successfully provided all desired diarylmethanes **225**, exemplifying the tolerance to substitution of this reaction (Scheme 2.71). The enantiomeric excess of each product was determined using chiral HPLC. A slightly lower enantiomeric excess was seen for the synthesis of alcohol **225c**, however in all cases enantiomeric excess was greater than 98%. These results, achieved with no optimisation, demonstrate the remarkable performance of this methodology in stereoretentive couplings.



*Scheme 2.71: **Ligand coupling reactions of enantiomerically pure sulfoxides 224**. Reagents and conditions: a) MeMgBr (1.1 equiv.), THF, rt, 1h; b) MeMgBr (2.2 equiv.), THF, rt, 1h.*

Higher yields of diarylmethanes were produced by substrates with (*R*)-sulfinyl centres, which is attributed to steric differences between each diastereomer. This proposal is corroborated by the analysis of the structures of (*S*)-sulfoxide **224a** and (*R*)-sulfoxide **224'** (Figure 2.6). The 2-pyridyl group restricts nucleophilic attack from one side of the sulfinyl centre of each sulfoxide. The phenyl group of the (*S*)-sulfinyl diastereomer **224a** obstructs the attack of the Grignard reagent from the other side of the sulfinyl centre, while (*R*)-sulfinyl diastereomer **224a'** has more room for nucleophilic attack around the sulfinyl centre.

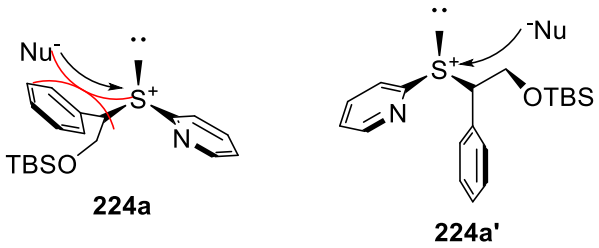
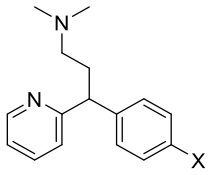


*Figure 2.6: Proposed energy-minimised structures of (S)-sulfoxide **224a** and (R)-sulfoxide **224a'** viewed from opposite to the sulfinyl oxygen (the sulfinyl oxygen has been omitted for clarity)*

2.4 Synthesis of histamine H1 antagonists

Pheniramine (**209a** Figure 2.7) and chlorphenamine (**209b**) are histamine H1 antagonists, marketed as antihistamines as the corresponding maleate salts. Despite usually being marketed as racemates, only the dextrorotatory (*S*)-isomers are biologically active, making stereoselective synthesis preferable. Most notably, chlorphenamine maleate is sold in the UK by GSK under the brand name Piriton®. Efforts were directed towards the synthesis of histamine H1 antagonists **209**, which bear the 2-benzylpyridine substructure, as a proof of the utility of this ligand coupling methodology.

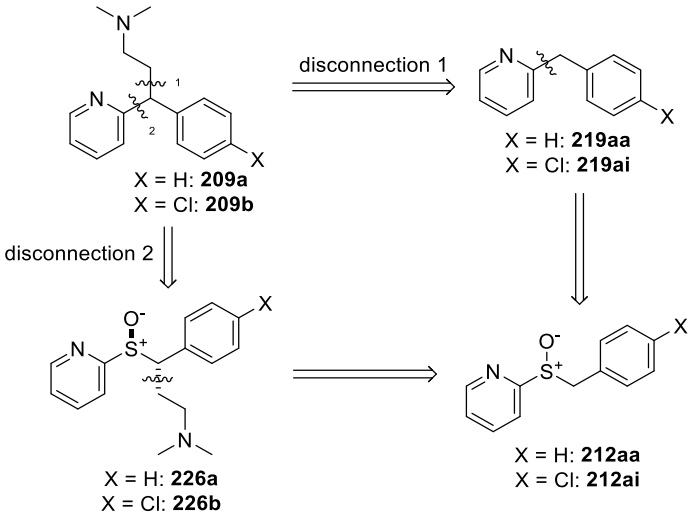


X = H: pheniramine (**209a**)
X = Cl: chlorphenamine (**209b**)

Figure 2.7**: Structure of diarylmethane histamine H1 antagonists **209

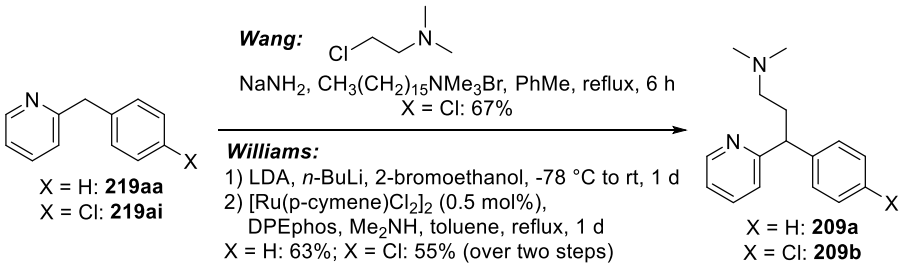
2.4.2 Retrosynthetic analysis

Retrosynthetic analysis led to the consideration of two routes for the synthesis of histamine H1 antagonists **209** (Scheme 2.72). Disconnection of the dimethylaminoethane sidechain (disconnection 1) would give the ligand coupling products benzyl-2-pyridylsulfoxides **212aa** and **212ai**, the synthesis of which has already been mentioned (*vide supra*: Table 2.10). It was hypothesised that disconnection of the pyridyl-benzyl bond (disconnection 2) may allow an enantiomerically enriched sulfoxide to be used as a directing group to effect a diastereoselective alkylation, enabling synthesis of the enantiomerically enriched drug products.



*Scheme 2.72: **Retrosynthetic analysis of histamine H1 antagonists 209***

The alkylation of 2-(4-chlorobenzyl)pyridine (**219ai**) to form chlorphenamine (**209b**) has been performed by two groups. Workers from Guangxi University used a phase transfer-catalysed alkylation, while Williams employed a ruthenium-catalysed hydrogen borrowing amination (Scheme 2.73).[177,178] Williams also used his methodology to synthesise pheniramine (**209a**), and this marks the syntheses of 2-(4-chlorobenzyl)pyridine (**219ai**) and 2-benzylpyridine (**219aa**), as formal syntheses of pheniramine (**209a**) and chlorphenamine (**209b**, *vide supra*: Table 2.10).



*Scheme 2.73: **Previous syntheses of histamine H1 antagonists 209 from diarylmethanes 219**. Notes: DPEphos = bis(2-diphenylphosphinophenyl)ether*[177,178]

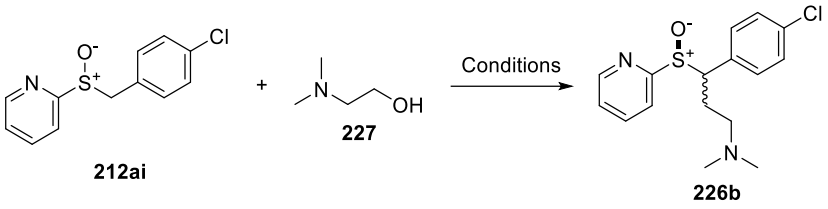
2.4.3 Synthesis by sulfoxide alkylation

Since racemic sulfoxide **212ai** was available in reasonable quantities from previous studies, its alkylation at the benzylic position was examined using different electrophiles. The electrophiles were chosen for their assumed utility in the synthesis of histamine H1 antagonists **209**.

A one-pot mesylation and alkylation of 2-(dimethylamino)ethanol (**227**) was attempted initially (Table 2.14). Hence, sulfonylation of alcohol **227** was performed before the corresponding methane sulfonate was combined with sulfoxide **212ai**,

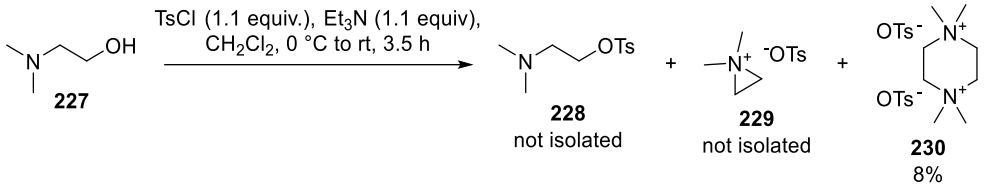
which had been deprotonated with LDA. The reaction was performed in THF and CH_2Cl_2, however only sulfoxide **212ai** was observed by mass spectrometry in both cases (entries 1 and 2 respectively).

Table 2.14: Attempts at an in-situ mesylation/alkylation strategy



Entry	Conditions (equiv.)	Comments
1	**227** (1.2), MsCl (1.2), NEt_3 (1.4), THF, rt, 40 min then (**212ai** (1.0), LDA (1.2), THF, 0 °C to rt, 30 min), rt, 20 h	No formation of **226b** observed by HRMS
2	**212ai** (1.0), LDA (1.2), CH_2Cl_2, 0 °C, 20 min, then (**227** (2.0), MsCl (2.0), NEt_3 (2.2), CH_2Cl_2, 0 °C to rt, 25 min) then, rt, 19 h	No formation of **226b** observed by HRMS

It was believed that the formation of the sulfonate may be the issue with the reaction. An attempt was therefore made to isolate tosylate **228** (Scheme 2.74). Unfortunately, tosylate **228** was not isolated, while a low yield of a compound which was initially assigned as ammonium tosylate salt **229** was obtained. Analysis by single crystal X-ray diffraction analysis showed that the correct structure was in fact dimeric diammonium ditosylate **230** (Figure 2.8).



*Scheme 2.74: **Attempted tosylation of 2-(dimethylamino)ethanol (227)***

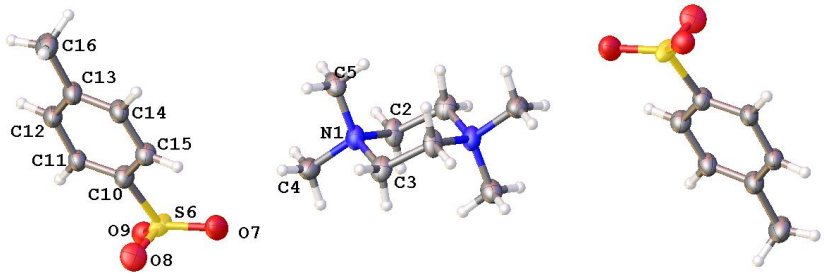
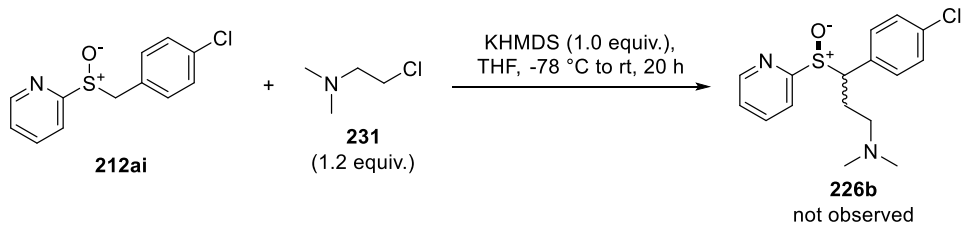


*Figure 2.8: Single crystal X-ray diffraction crystallography structure of diammonium ditosylate **230***

In an attempt to mimic the alkylation approach of Wang, 1-chloro-2-(dimethylamino)ethane (**231**) was prepared by the basic hydrolysis of its hydrochloride salt, which was purified by distillation.[179] Deprotonation of sulfoxide

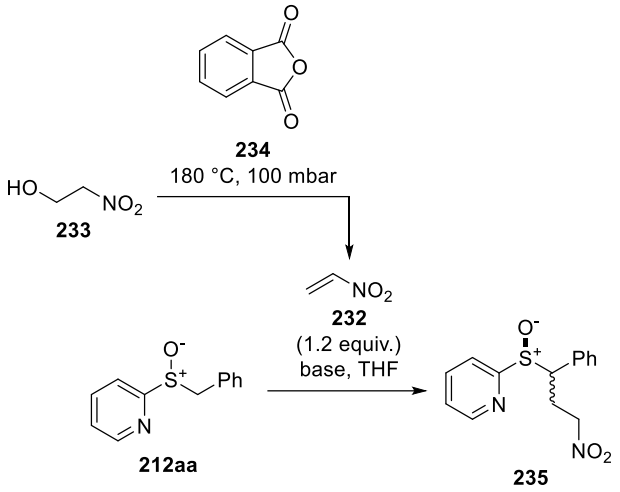
212ai with KHMDS followed by reaction with the alkyl chloride was performed, however only sulfoxide **212ai** was observed by mass spectrometry (Scheme 2.75).



*Scheme 2.75: Alkylation of sulfoxide **212ai** using 2-(dimethylamino)ethylchloride (**231**)*

It was perceived that alkyl chloride **231** was too-poor a nucleophile to be reactive, and that the aryl-chloride moiety may cause undesirable complications due to halogen-metal exchange. A revised synthetic plan was saught *via* the alkylation of 2-benzylpyridine (**212aa**). The use of nitroethylene (**232**), synthesised by the distillative dehydration of 2-nitroethanol (**233**) using phthalic anhydride (**234**), was investigated (Table 2.15).[180] Deprotonation of sulfoxide **212aa** with LDA and exposure to nitroethylene (**232**) provided 8% of desired product (entry 1). Proposing that the alkylation was not complete within the 5 minutes allowed, the deprotonation time was increased to 30 min, however no formation of nitro sulfoxide **235** was observed (entry 2). Large quantities of remaining sulfoxide **212aa** were observed in the crude ^{1}H NMR. It was proposed that different bases may aid deprotonation. The use of sodium hydride showed no effervescence, suggesting that deprotonation was not occurring, and no conversion of sulfoxide **212aa** was seen (entry 3). Exposure of sulfoxide **212aa** to potassium hydride produced effervescence and a colour change of the solution from colourless to orange, suggesting that deprotonation was occurring. Addition of nitroethylene (**232**), however showed no formation of product even when left overnight (entries 4 and 5).

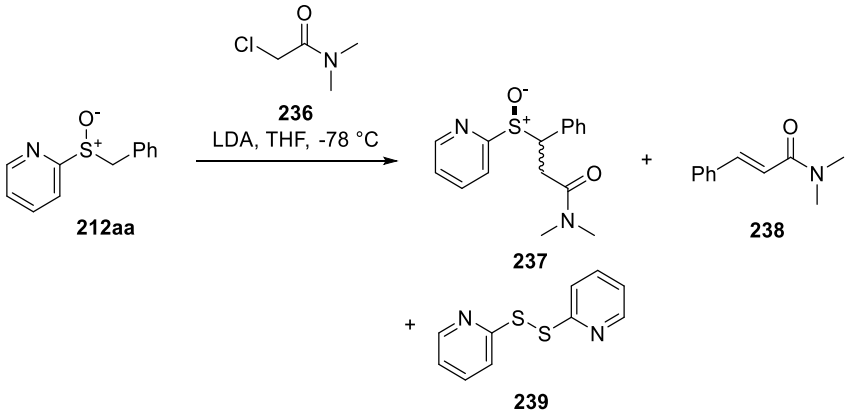
*Table 2.15: Alkylation of sulfoxide **212aa** using nitroethylene (**232**)*



		Deprotonation		Alkylation		
Entry	**Base (equiv.)**	**Time**	**Temp. (°C)**	**Time**	**Temp. (°C)**	**Yield 235 (%)**
1	LDA (1.1)	5 min	0	5 h	0 °C	8
2	LDA (1.1)	30 min	-78	18 h	-78 to rt	0
3	NaH (1.2)	18 h	rt	4 h	-78	0
4	KH (1.6)	3 h	rt	3 h	-78 to rt	0
5	KH (1.4)	40 min	rt	16 h	rt	0

Exploring the use of more reactive electrophiles to obtain H1 antagonists, sulfoxide **212aa** was reacted with α-chloroamide **236**, in an attempt to form alkylated sulfoxide **237** (Table 2.16). Sulfoxide **212aa** was deprotonated with LDA before adding α-chloroamide **236**, yielding styrene **238** and disulfide **239** in equimolar amounts (entry 1). It was proposed that a lower reaction concentration and increasing the equivalents of α-chloroamide **236** would increase the control of the reaction. On performing reactions at several temperatures, it was found that the lower concentration of the reaction significantly inhibited reaction (entries 2-4). In these cases, large amounts of sulfoxide **212aa** was observed by crude ^{1}H NMR and HRMS.

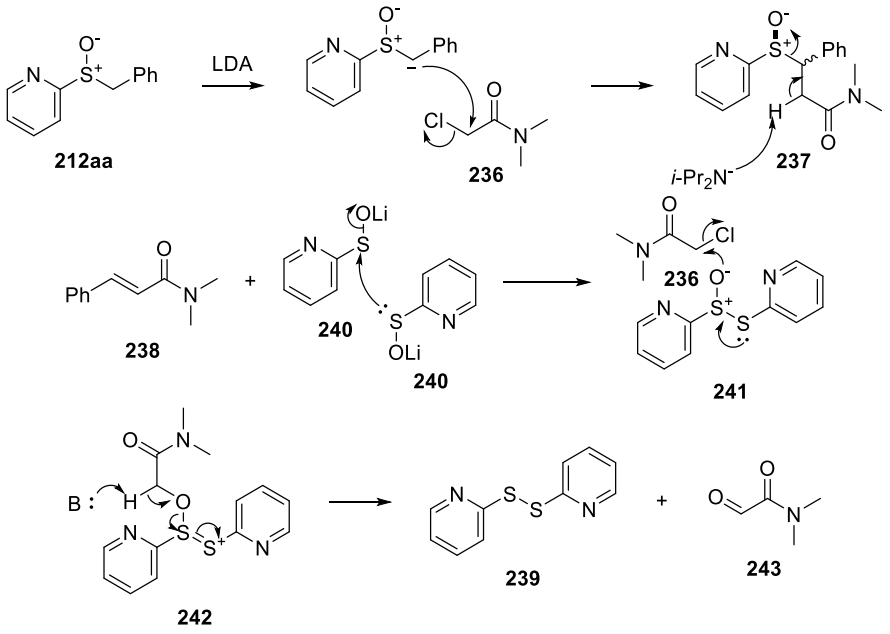
*Table 2.16: Alkylation of sulfoxide **212aa** with α-chlorodimethylacetamide (**236**)*



Entry	Conditions (equiv.)	Yield 238 (%)	Yield 239 (%)
1	LDA (1.1), THF (0.1 M) -78 °C, 30 min, then **236** (1.2), -78 °C to rt, 3 h	42	44
2[a]	LDA (1.1), THF (0.01 M) 0 °C, 35 min, then **236** (10), -78 °C, 1 h	-	-
3	LDA (1.1), THF (0.01 M) 0 °C, 30 min, then **236** (10), -78 °C, 2.5 h	-	-
4	LDA (1.1), THF (0.01 M) 0 °C, 45 min, then **236** (10), 0 °C, 2.5 h	-	-

*Notes: a) reverse addition: sulfoxide **212aa** solution added to chloroamide **236** solution.*

Pondering a mechanism for this process, the presence of the phenyl and amide moieties in styrene **238** suggested the decomposition of the desired alkylated product **237** (Scheme 2.76). It is proposed that after the successful alkylation, desired product **237** is deprotonated by lithium diisopropylamide, forming styrene **238** from the elimination of lithium sulfenate **240**. Dimerisation of lithium sulfenate **240** would form thiosulfinate **241**, which it is thought could be reduced to disulfide **239** by reaction with α-chloroamide **236**.

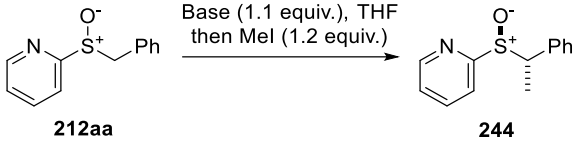


*Scheme 2.76: **Proposed mechanism for the formation of styrene 238 and disulfide 239***

It was decided that a more fundamental approach to the investigation of the diastereoselective alkylation of benzylic sulfoxides **212** should be taken. Deprotonation of benzyl sulfoxide **212aa**, followed by alkylation with iodomethane was studied (Table 2.17). Conversion of sulfoxide **212aa** and the diastereomeric ratio of alkylated sulfoxide **244** were determined by integration of the benzylic protons in ^{1}H NMR spectra.

Performing both deprotonation and alkylation at or below -60 °C provided only low to modest conversion and dr (entries 1, 2, 6 and 8). Both conversion and dr improved substantially when the additions were performed at -78 °C before the reaction mixture was immediately allowed to warm to room temperature (entry 3), however dr was still modest. Deprotonation and alkylation at -40 °C followed by allowing the reaction mixture to warm to room temperature provided excellent conversion and modest dr (entry 12). Room temperature alkylation with double the quantity of LDA provided complete consumption of the substrate, but poor dr and the ^{1}H NMR showed significant amounts of by-products (entry 5). A one hour deprotonation time degraded both dr (entry 4) and conversion (entries 1, 10 and 14), compared to a deprotonation time to five minutes (entries 2, 11 and 15). This could suggest that diastereoselective deprotonation of the sulfoxide occurs under kinetic control. Modest dr and very good conversion was seen with a deprotonation time of only 30 seconds (entry 12). The use of LiTMP provided comparable results to LDA (entries 11 and 16).

*Table 2.17: Optimisation of the methylation of benzyl sulfoxide **212aa***



212aa **244**

		Deprotonation		Alkylation			
Entry	**Base**	**Temp. (°C)**	**Time**	**Temp. (°C)**	**Time**	**Conversion 244 (%)[a]**	**dr[a] (erythro:threo)**
1	LDA	-78	1 h	-78	1 h	23	1:1.2
2	LDA	-78	5 min	-78	1 h	28	1:1.3
3[b]	LDA	-78 to rt	0.5 h	-78 to rt	1.5 h	98	1:2.6
4	LDA	-78 to rt	1 h	-78 to rt	1 h	80	1:1.8
5[c]	LDA	-78 to rt	0.5 h	rt	1.3 h	100[d]	1:1.5
6	LDA	-78	5 min	-78 to -60	1 h	55	1:2.2
7	LDA	-78	5 min	-78 to -40	1 h	88	1:2.1
8	LDA	-60	5 min	-60	1 h	36	1:1.4
9	LDA	-60	5 min	-60 to 0	1 h	73	1:1.8
10	LDA	-40	1 h	-40	1 h	65	1:2.6
11	LDA	-40	5 min	-40	1 h	80	1:2.4
12	LDA	-40	30 s	-40	1 h	83	1:2.0
13	LDA	-40	5 min	-40 to 0	1 h	95	1:2.0
14	LDA	0	1 h	0	1 h	82	1:1.8
15	LDA	0	5 min	0	1 h	96	1:1.9
16	LiTMP	-40	5 min	-40	1 h	88	1:2.4

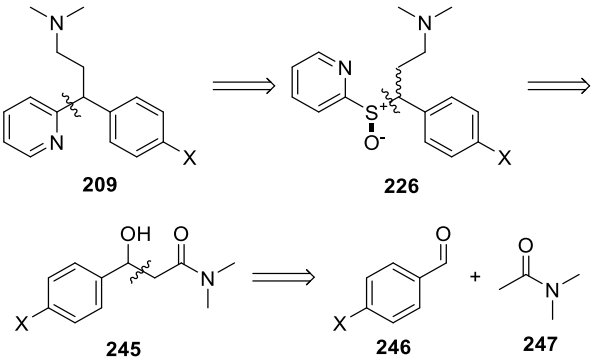
Notes: a) determined by integration of benzylic protons in ^{1}H NMR. Assignment based on literature precedent;[181] b) MeI (5 equiv.), LDA (1.2 equiv.) used; c) MeI (7.0 equiv.), LDA (2.4 equiv.) used; d) significant decomposition observed by ^{1}H NMR.

In summary, the diastereoselective alkylation of benzyl sulfoxide **212aa** provides only modest diastereoselectivity. Furthermore, alkylation has only been achieved with strong electrophiles such as iodomethane and α-chloroamides, neither of which were able to produce the required functionality.

2.4.4 Retrosynthetic analysis *via* aldol adducts

Reanalysis of sulfoxide **226**, required to produce histamine 1H antagonists **209**, led to consideration of the disconnection of the 2-pyridylsulfinyl group (Scheme 2.77). It was envisaged that sulfoxide **226** could be synthesised through the substitution of benzylic

alcohol **245**, which could be formed by aldol reaction of benzaldehydes **246** with DMA (**247**).

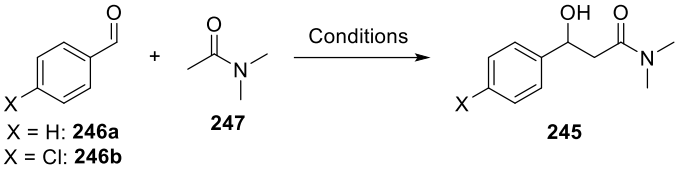


*Scheme 2.77: **Retrosynthetic analysis of histamine H1 antagonists 209 to aldol adducts 245***

2.4.5 Synthesis using aldol adducts

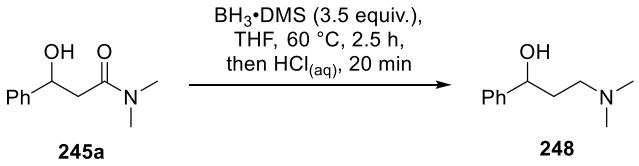
Synthesis of alcohol **245b** was attempted by deprotonation of DMA (**247**) with LDA, followed by reaction with 4-chlorobenzaldehyde (**246b**), however alcohol **245b** was not observed by analysis of the crude reaction mixture (Table 2.18, entry 1). Anhydrous $CeCl_3$ was employed to form the cerium enolate of DMA (**247**), as similar substrates are reported to provide near-quantitative yields, however again no formation of alcohol **245b** was observed (entry 2).[182] Considering that the aryl chloride was complicating the reaction, the aldol condensation of the cerium enolate of DMA (**247**) with benzaldehyde (**246a**) was attempted. Gratefully, alcohol **245a** was isolated in a yield which correlated well with literature reports (entry 3).[182]

*Table 2.18: Aldol reaction of benzaldehydes **246** with DMA (**247**)*



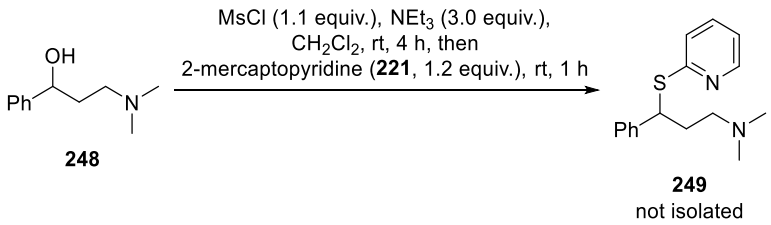
Entry	X	Conditions (equiv.)	Yield 245 (%)
1	Cl	**247** (2.0), LDA (2.1), THF, -78 °C to rt, 15 min, then **246b** (1.0), -78 °C to rt, o/n	0
2	Cl	**247** (2.0), LDA (2.2), THF, -78 °C to rt, 1 h, $CeCl_3$ (2.1), -78 °C, 1 h, then **246b** (1.0), -78 °C to rt, 2 h	0
3	H	**247** (2.0), LDA (2.2), THF, -78 °C 30 min, then $CeCl_3$ (2.1), -78 °C, 45 min then **246a** (1.0), -78 °C to rt, o/n	89

Borane reduction of the amide proceeded smoothly, providing amine **248** in an excellent yield (92%) after an acidic workup to hydrolyse the borane adduct (Scheme 2.78).



*Scheme 2.78: Borane reduction of amide **245a***

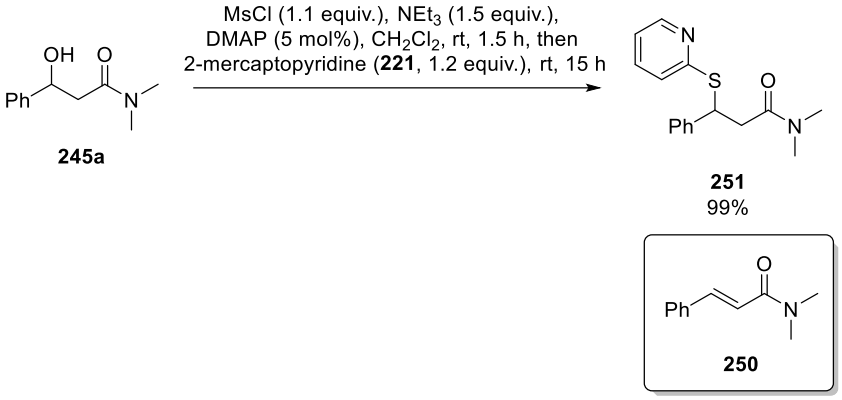
Substitution of alcohol **248** was attempted using a one-pot mesylation and substitution strategy (Scheme 2.79). ^{1}H NMR of the reaction mixture following mesylation showed an upfield shift of the benzylic proton, suggesting that mesylation was successful. Addition of 2-mercaptopyridine (**221**) provided a complex mixture of products, with only a small amount of what was tentatively assigned as sulfide **249** observed by crude ^{1}H NMR. The appearance of olefinic peaks in the ^{1}H NMR suggests that elimination processes were occuring.



*Scheme 2.79: Mesylation and substitution of alcohol **248***

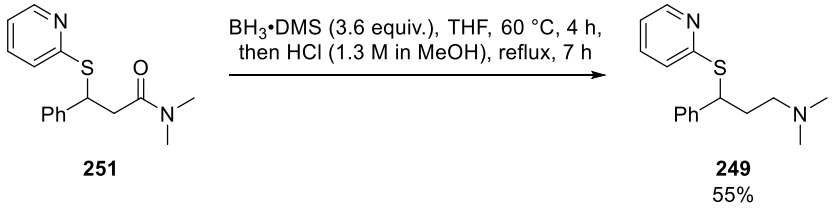
Proposing that the substitution was complicated by the tertiary amine, amide **245a** was subjected to the substitution conditions (Scheme 2.80). The sulfonate ester intermediate was found to be unstable to analysis by TLC, so ^{1}H NMR was used to

ensure complete conversion of alcohol **245a** prior to the addition of 2-mercaptopyridine (**221**). Complete sulfonylation was found to require less than 1 h, while the formation of styrene **250**, from the elimination of the mesylate, was observed when 2-mercaptopyridine (**221**) was not added until 20 h. Gratifyingly, following the addition of 2-mercaptopyridine (**221**) the reaction proceeded smoothly to provide sulfide **251** in an almost quantitative yield.



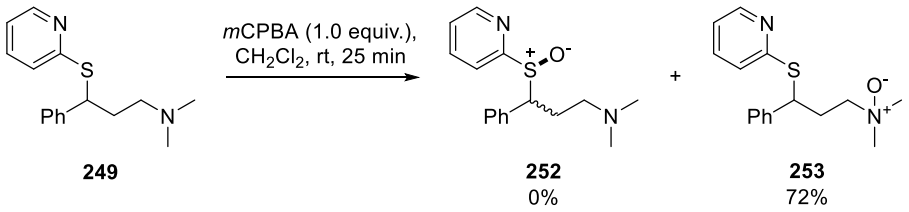
*Scheme 2.80: Mesylation and substitution of alcohol **245a***

With sulfide **251** in hand, reduction of the amide moiety using borane proceeded well (Scheme 2.81). Methanolic HCl was used to decompose borane adducts.



*Scheme 2.81: Borane reduction of amide **251** to amine **249***

Oxidation of sulfide **249** was performed using *m*CPBA (Scheme 2.82). The formation of sulfoxide **252** was supported by incorporation of oxygen into the molecule, seen by mass spectrometry. ^{1}H NMR showed no significant chemical shift difference between the 2-pyridyl peaks of the isolated product (Figure 2.9, red trace) and sulfide **249** (blue trace), which would be expected if *S*-oxidation had occurred. By contrast, the *N*-methyl peaks of the isolated product appear diastereotopic and shifted downfield by ca. 1 ppm relative to those of sulfide **249**. These observations suggest that *N*-oxidation of the tertiary amine was preferential over *S*-oxidation, producing *N*-oxide **253**.



*Scheme 2.82: Oxidation of sulfide **249***

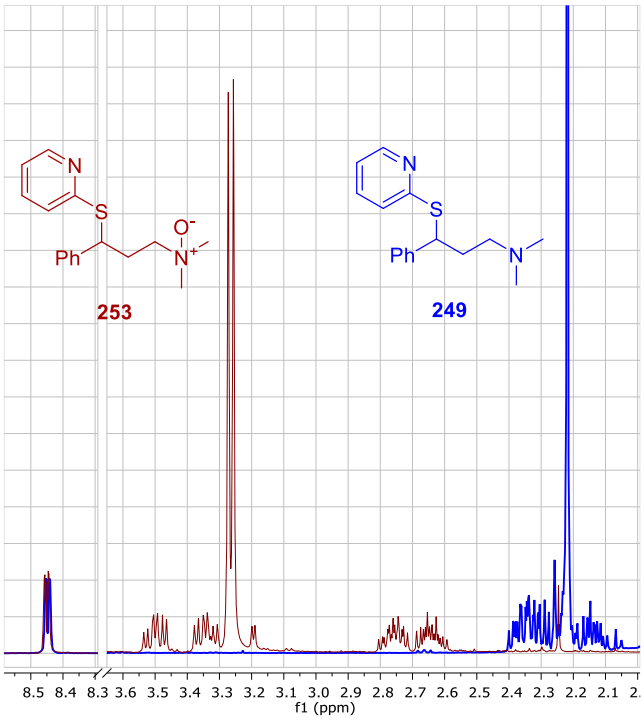
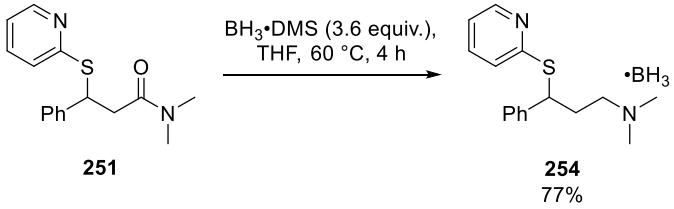


*Figure 2.9: Overlaid ^{1}H NMR spectra of amine **249** (blue trace) and N-oxide **253** (red trace)*

It was clear that a modification of the route was required to enable *S*-oxidation. The oxidation of amide **251** was considered, however the decomposition of amide sulfoxide **237** seen before (*vide supra:* Scheme 2.76) suggested that the oxidation of sulfide **251** would be fruitless. Instead, it was proposed that keeping the amine protected as its borane adduct would allow *S*-oxidation product to form. Isolation of borane complex **254** was performed by reducing amide **251** with borane, using a neutral workup (Scheme 2.83). Fortunately, borane adduct **254** was found to be stable to purification by column chromatography.

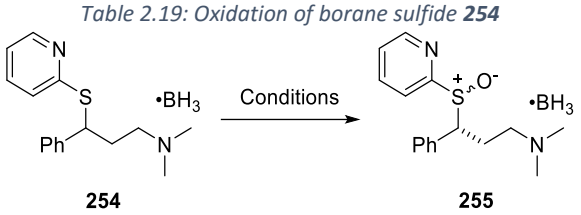


*Scheme 2.83: Synthesis of borane adduct **254***

Oxidation of borane adduct **254** to sulfoxide **255** was troublesome (Table 2.19). Using usual conditions of *m*CPBA in CH_2Cl_2, significant amounts of decomposition of the

borane complex was seen, and *S*-oxidation yield was only modest (entry 1). Pyridine was added to prevent decomposition of the borane adduct by modulating the acidity of the reaction mixture, however no oxidation was observed (entry 2). The use of sodium periodate in methanol provided no discerable oxidation of sulfide **254**, while the borane adduct was hydrolysed (entries 3 and 4).

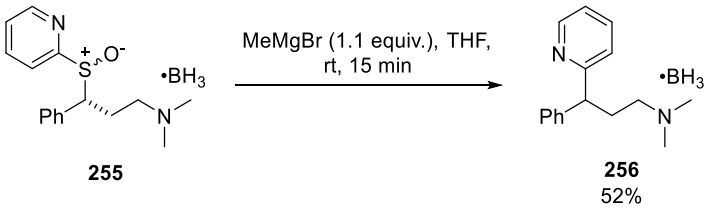
*Table 2.19: Oxidation of borane sulfide **254***



254 **255**

Entry	Conditions (equiv.)	Yield 255 (%)	dr
1	*m*CPBA (1.0), CH_2Cl_2, rt, 30 min	47	1:2.4
2	*m*CPBA (1.0), pyridine (2.0), CH_2Cl_2, rt, 1 h	-	-
3	$NaIO_4$ (1.0), MeOH, H_2O, rt, 24 h	-	-
4	$NaIO_4$ (1.0), MeOH, 40 °C, 3 h	-	-

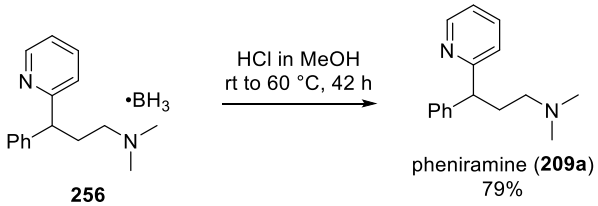
Sulfoxide **255** was subjected to MeMgBr in order to induce ligand coupling, which formed the borane adduct of pheniramine (**256**) in a 52% yield (Scheme 2.84). While no by-products of the reaction were isolated, analysis by TLC showed the complete disappearance of sulfoxide **255**, suggesting that other reactions, such as ligand exchange, were lowering the yield of diarylmethane **256**.



255 **256**
52%

*Scheme 2.84: Ligand coupling of sulfoxides **255***

Deborylation of amine **256** was achieved using methanolic HCl. Slow conversion was noted at room temperature after 18 h, so the reaction mixture was heated to 60 °C, affording pheniramine (**209a**) in 79% yield (Scheme 2.85).

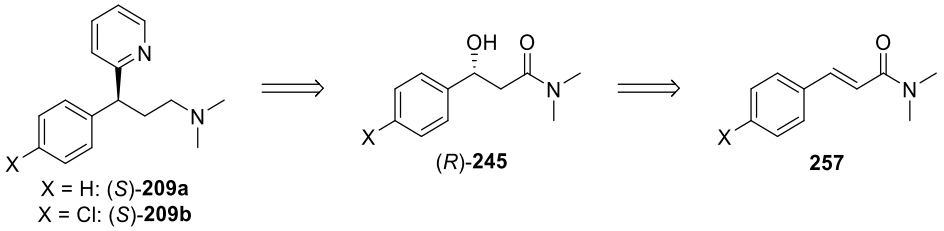


256 pheniramine (**209a**)
79%

*Scheme 2.85: Formation of pheniramine (**209a**)*

2.4.6 Enantioselective synthesis by asymmetric hydroboration

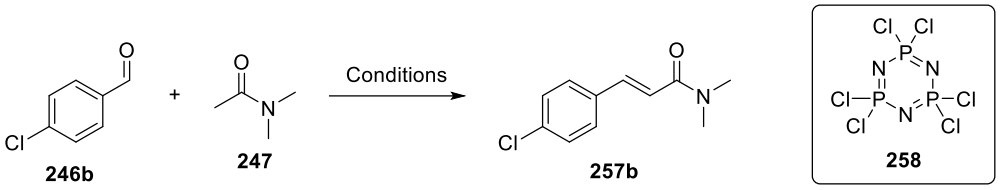
It was envisaged that an enantioselective synthesis of histamine 1H antagonists (*S*)-**209** could be performed from enantiomerically enriched alcohols (*R*)-**245** (Scheme 2.86). Synthesis of alcohols (*R*)-**245** could be achieved through a metal-catalysed hydroboration and oxidation of the corresponding styrenes **257**.



*Scheme 2.86: **Retrosynthetic analysis of enantiomerically enriched histamine 1H antagonists (S)-209***

The synthesis of styrene **257b** was undertaken by the aldol condensation of DMA (**247**) with 4-chlorobenzaldehyde (**246b**, Table 2.20). Basic conditions failed to induce reaction (entry 1). The use of substoichiometric amounts of phosphonitrilic chloride trimer (**258**) with a catalytic amount of sulfuric acid produced styrene **257b** in a reasonable yield (entry 2). Deterioration of yield was noted upon scale-up (entry 3).

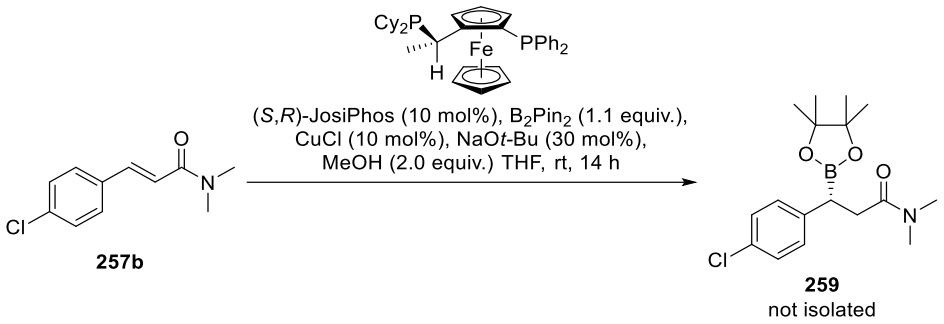
*Table 2.20: Synthesis of styrene **257b***



Entry	Conditions (equiv.)	Yield 257b (%)
1	**247** (1.0), NaOH (10 mol%), EtOH, 80 °C, 17 h	0
2[a]	**247** (11), **258** (10 mol%), H_2SO_4 (10 mol%), 120 °C, 19 h	63
3[b]	**247** (11), **258** (10 mol%), H_2SO_4 (10 mol%), 120 °C, 21 h	38

a) performed on 1 mmol scale; b) performed on 12 mmol scale.

Hydroboration of styrene **257b** was explored, employing copper(I)-catalysed conditions from the group of Yun.[183] Product was observed by crude mass spectrometry, however low conversion (ca. 30%) was noted by crude ^{1}H NMR.[184] Unfortunately, efforts to isolate pinacol ester **259** using silica gel chromatography provided no product (Scheme 2.87).



*Scheme 2.87: **Copper(I)-catalysed hydroboration of styrene 257b***

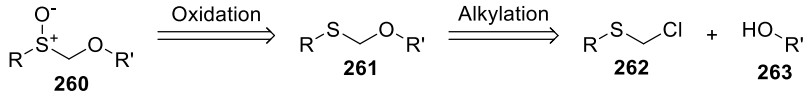
In conclusion, the use of diastereoselective functionalisation of sulfoxides towards the synthesis of histamine H1 antagonists **209** was explored, however limited yields and diastereoselectivities were found. Synthesis *via* an aldol adduct provided pheniramine (**209a**) in a 13% yield over 6 steps. A brief exploration into the elaboration of this chemistry to provide an enantioselective synthesis of pheniramine (**209a**) was also conducted.

2.5 Synthesis of benzylic ethers

It was hoped that the scope of this reaction could be expanded beyond the synthesis of diarylmethanes. It was suggested that other functionalities, other than benzylic groups, may be able to undergo ligand coupling reactions.

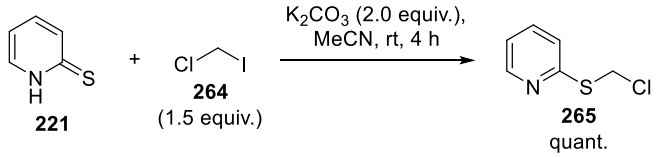
2.5.1 Synthesis of α-alkoxy sulfoxides

A range of α-alkoxy sulfoxides **260** was imagined to be accessible from thioacetals **261**, which could be formed by the reaction of chloromethylsulfides **262** with alcohols **263** (Scheme 2.88).



*Scheme 2.88: **Planned synthetic route to α-alkoxysulfoxides 260***

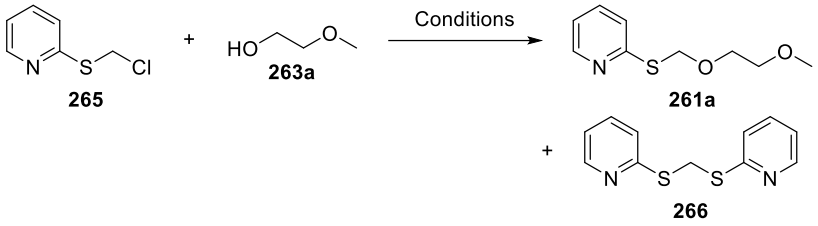
2-Mercaptopyridine (**221**) was reacted with chloroiodomethane (**264**), producing chloromethyl sulfide **265** in a quantitative yield (Scheme 2.89).



*Scheme 2.89: **Synthesis of chloromethylsulfide 265***

Reaction of chloromethylsulfide **265** with 2-methoxyethanol (**262a**) provided thioacetal **260a** in a low yield (16%, Table 2.21, entry 1). Visable decomposition of the substrate was noted upon addition of the base, the final reagent. The order of addition of reagents was therefore modified to sulfide **265** being added to a solution of the other reagents, which produced a significant improvement in yield (40%, entry 2). Increasing the equivalents of base and performing the reaction in neat 2-methoxyethanol (**262a**) provided no significant increase in yield (entries 3 and 4). The use of both stronger and weaker bases was fruitless (entries 5 and 6).

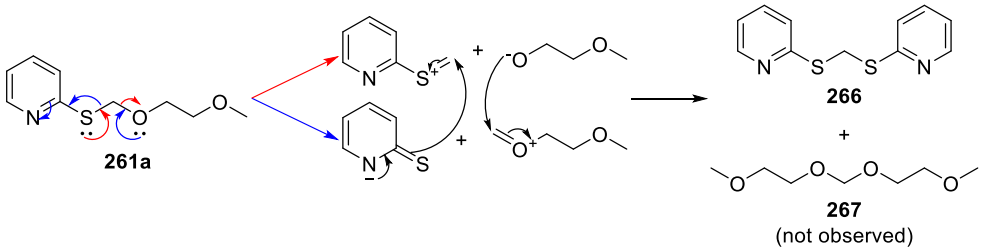
*Table 2.21: Synthesis of thioacetal **261a***



Entry	Conditions (equiv.)	Yield 261a (%)	Yield 266 (%)
1	**263a** (10), KO*t*-Bu (1.5), NaI (1.1), MeCN, rt, 17 h	16	66
2	**263a** (10), KO*t*-Bu (1.5), NaI (1.1), MeCN, rt, 16 h	40	36
3	**263a** (10), KO*t*-Bu (5.0), NaI (1.1), MeCN, rt, 18 h	37	58
4	**263a** (neat), KO*t*-Bu (1.5), rt, 18 h	46	24
5	**263a** (10), K_2CO_3 (1.5), NaI (1.1), MeCN, rt, 16 h	0	n/d[a]
6	**263a** (10), NaH (1.5), NaI (1.1), DMF, rt, 17 h	29	45

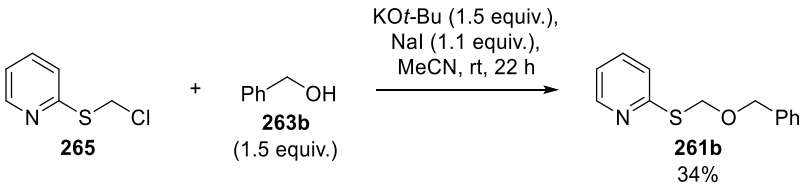
a*) not determined*

Dithioacetal by-product **266** was produced in useful yields (up to 66%). Postulation of a mechanism for the formation of dithioacetal **266** led to the consideration of decomposition of desired thioacetal **261a** (Scheme 2.90). Recombination of the pyridyl fragments, as depicted, would form dithioacetal **266**. It is proposed that acetal **267** may also be produced from the recombination of the ether-containing fragments, however no evidence for the formation of this was found.



*Scheme 2.90: Proposed formation of dithioacetal **266** by decomposition of thioacetal **261a***

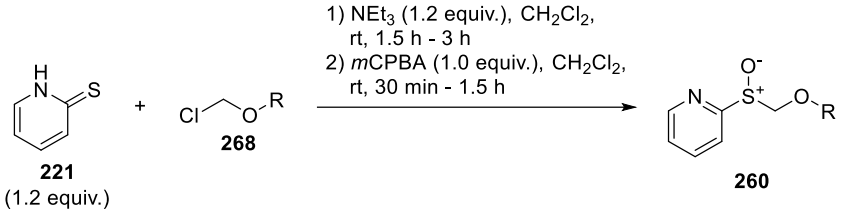
Reaction of chloromethylsulfide **265** with benzyl alcohol (**263b**) similarly produced a low yield of desired thioacetal **261b**. This suggests that this route to thioacetals **261** is generally poor, and not poor for only 2-methoxyethanol (**263a**, Scheme 2.91).



*Scheme 2.91: Synthesis of thioacetal **261b** from chloromethylsulfide **265***

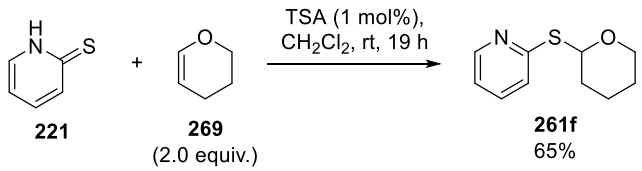
It was decided that the approach to the required thioacetals **261** would be changed due to the low yields produced. The alkylation of 2-mercaptopyridine (**221**) with a range of chloromethylethers **268** was proposed. This approach was far more successful, producing a range of thioacetals **261** from commercially available chloromethylethers **268** (Table 2.22). Oxidation with *m*CPBA afforded the required α-alkoxy sulfoxides **260** in up to 84% yield over two steps. The efficiency of this route compared to the previous route is demonstrated by the very good yield of sulfoxide **260a** over two steps (entry 1). It should be noted that both thioacetals **261** and the corresponding sulfoxides **260** require storage at -20 °C to prevent decomposition.

*Table 2.22: Synthesis of ethereal ligand coupling substrates **260***



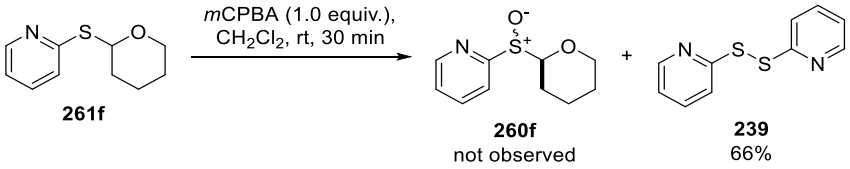
Entry	R	Product	Yield 260 (%)
1	$MeO(CH_2)_2$	**260a**	81
2	Bn	**260b**	38
3	$Cl(CH_2)_2$	**260c**	82
4	$TMS(CH_2)_2$	**260d**	84
5	4-$Cl(C_6H_4)$	**260e**	65

Efforts were directed towards the synthesis of ethers with functionality on the methylene unit of the thioacetyl. Synthesis of thioacetal **261f** was performed by the acid-catalysed alkylation of 2-mercaptopyridine (**221**), as in a THP ether synthesis (Scheme 2.92).



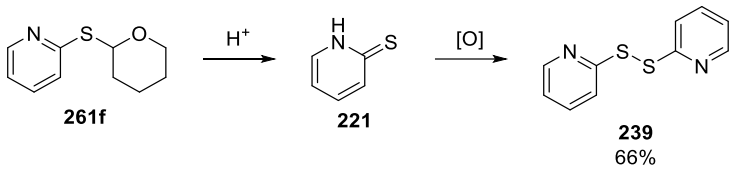
*Scheme 2.92: Synthesis of THP thioether **261f***

Oxidation of thioacetal **261f** provided large amounts of disulfide **239** (Scheme 2.93). No formation of desired sulfoxide **260f** was observed by either mass spectrometry or ^{1}H NMR.



*Scheme 2.93: **Oxidation of thioacetal 261f***

Presumably, the acidic oxidation conditions hydrolysed thioacetal **261f**, forming 2-mercaptopyridine (**221**, Scheme 2.94). This may have been subsequently oxidised to disulfide **239** by *m*CPBA.

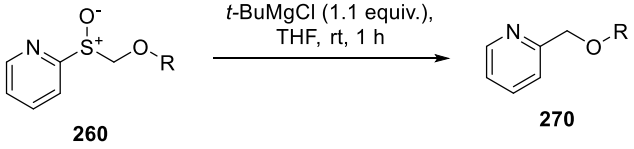


*Scheme 2.94: **Proposed pathway for the formation of disulfide 239***

2.5.2 Ligand coupling reactions of α-alkoxy sulfoxides

Subjection of the substrates to *t*-butylmagnesium chloride in THF successfully induced ligand coupling in all substrates **260a-e** (Table 2.23). Very good yields of benzylic ethers **270** were obtained of the benzyl, chloroethyl and 4-chlorophenyl substrates (entries 2, 3 and 5), while fair yields were obtained of methoxyethyl and TMS ethyl substrates (entries 1 and 4). The ability to retain functionality such as aryl and alkyl chlorides as well as TMS groups exemplifies the synthetic utility of this reaction.

*Table 2.23: Ligand coupling of ethereal sulfoxides **259a-e***



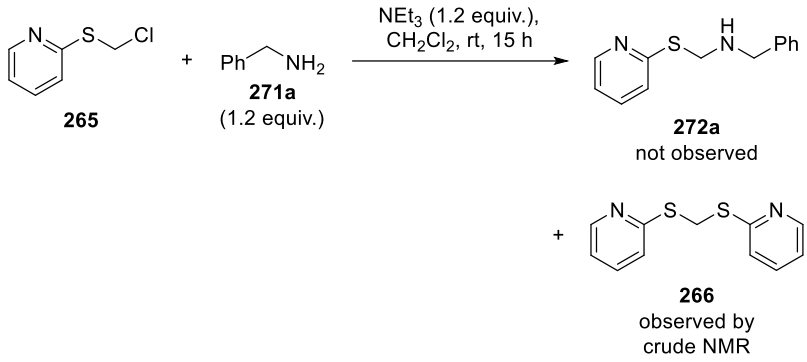
Entry	R	Product	Yield 270 (%)
1	$MeO(CH_2)_2$	**270a**	64
2	Bn	**270b**	87
3	$Cl(CH_2)_2$	**270c**	87
4	$TMS(CH_2)_2$	**270d**	54
5	4-$Cl(C_6H_4)$	**270e**	84

2.6 Synthesis of benzylic amines and their derivatives

Due to the success observed with benzyl and α-alkoxy sulfoxides, it was envisaged that ligand coupling reactions may be able to occur with α-amino sulfoxides.

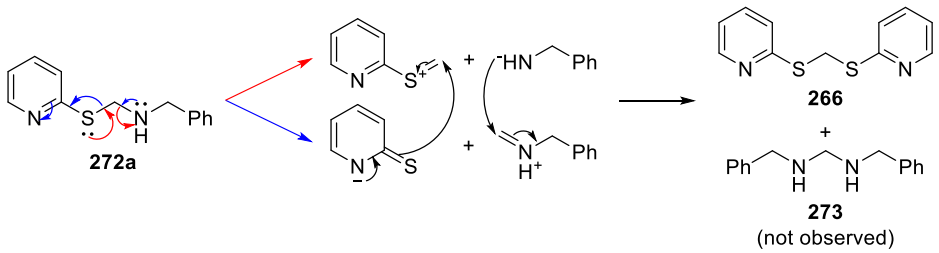
2.6.1 Synthesis of α-amino sulfoxides

The synthesis of α-amino sulfides and sulfoxides has been reported as problematic by the group of O'Brien.[185] It was envisaged that thioaminals may be synthesised from chloromethyl sulfides, as was seen with thioacetals (*vide supra*: Table 2.21). Exposure of chloromethyl sulfide **265** to benzylamine (**271a**) afforded dithioacetal **266** exclusively, as noted by crude ^{1}H NMR (Scheme 2.95).



*Scheme 2.95: **Attempted synthesis of N-benzyl thioaminal 272a***

It was proposed that dithioacetal **266** was being formed by a similar mechanism as depicted in the synthesis of thioacetals **261**, whereby desired *N*-benzyl thioaminal **272a** was forming but subsequently decomposing (Scheme 2.96). It was suggested that reducing the electron-richness of the aminal nitrogen would prevent decomposition of the thioaminal.

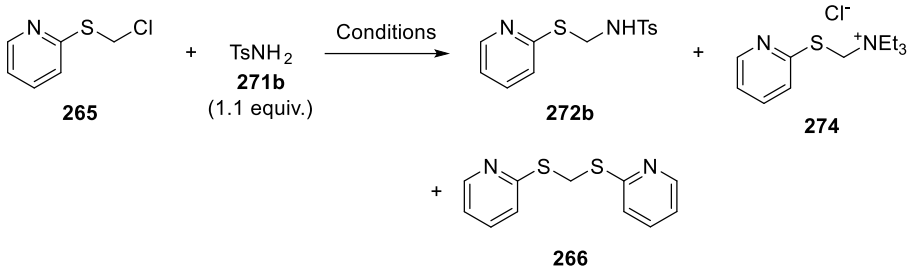


*Scheme 2.96: **Proposed decomposition of N-benzyl thioaminal 272a***

Hence, the synthesis of *N*-tosyl thioaminal **272b** was attempted (Table 2.24). Initial investigations using triethylamine as a base, as before, showed that 80% conversion to triethylamine adduct **274** by ^{1}H NMR (entry 1). This suggests that tosylamide (**271b**) is less nucleophilic than triethylamine, and is not nucleophilic enough to displace the ammonium salt formed. To prevent competitive substitution by triethylamine, a

non-nucleophilic base was used instead. Potassium carbonate in CH_2Cl_2, afforded no desired product **272b** in analysis by mass spectrometry (entry 2). Analysis of the crude reaction mixture by ^{1}H NMR showed a mixture of chlorosulfide **265** and dithioacetal **266**. The observation that the tosylamide (**271b**) was sparingly soluble led to the hypothesis that a more polar solvent may aid this reaction. However, the use of DMF as solvent for the reaction showed complete conversion of chlorosulfide **265** to dithioacetal **266** by crude ^{1}H NMR (entry 3).

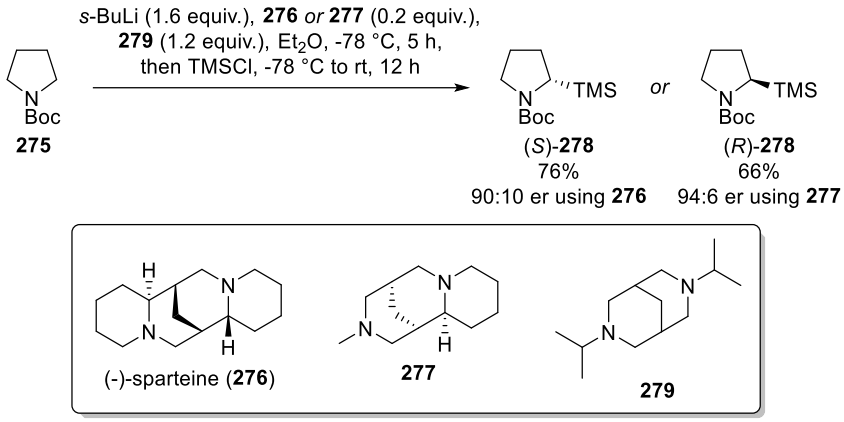
*Table 2.24: Attempted synthesis of N-tosyl thioaminal **272b***



Entry	Conditions (equiv.)	Notes
1	NEt_3 (1.2), CH_2Cl_2, rt, 18 h	Triethylamine adduct **274** observed in 80% conversion by crude ^{1}H NMR
2	K_2CO_3 (1.2), CH_2Cl_2, rt, 15 h	Complex mixture, predominantly chlorosulfide **265** and dithioacetal **266**, by crude ^{1}H NMR
3	K_2CO_3 (1.2), DMF, rt, 15 h	Full conversion to dithioacetal **266** observed by crude ^{1}H NMR

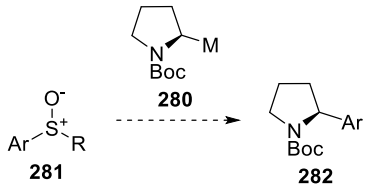
2.6.2 Cross-coupling with α-amino organometallic reagents

The group of O'Brien has developed the formation of α-amino organometallic reagents from *N*-Boc heterocycles, such as pyrrolidine **275** (Scheme 2.97).[186] An interesting aspect of this chemistry is that the use of sub-stoichiometric amounts of chiral diamines, such as (-)-spartine (**276**) or diamine **277**, can produce stoichiometric amounts of an enantiomerically enriched organolithium reagent. These can be quenched with electrophiles to provide enantiomerically enriched products, such as silanes (*R*)-**278** or (*S*)-**278**.



*Scheme 2.97: Enantioselective deprotonation and silylation of N-Boc pyrrolidine (**275**) by the group of O'Brien*[186]

Since issues had been encountered in the synthesis of α-amino sulfoxides, the use of α-aminoorganometallic reagents **280** as nucleophiles in the ligand coupling reaction was envisaged (Scheme 2.98). It was proposed that exposure of an α-aminoorganometallic reagent **280** to an appropriately substituted sulfoxide **281** may induce a cross-coupling reaction in a similar manner as was seen with benzylic Grignard reagents (*vide supra*: Section 2.3). This could produce enantiomerically enriched aryl heterocycles **282**.



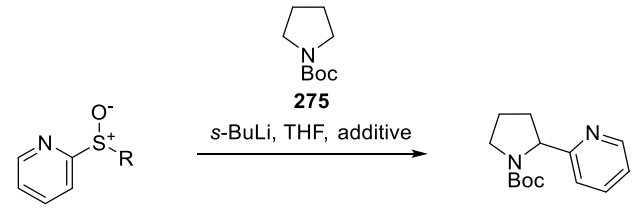
*Scheme 2.98: Proposed route to enantiomerically enriched benzylic carbamates **282***

N-Boc pyrrolidine (**275**) was examined to test the proposed cross-coupling reaction (Table 2.25). Encouragingly, aryl pyrrolidine **282a** was obtained in 44% yield on the first attempt, where 2.0 equivalents of methyl sulfoxide **212bn** were used relative to pyrrolidine **275** (entry 1). 1.4 Equivalents of methyl sulfoxide **212bn** were isolated from the reaction mixture, suggesting that this reactant was not being consumed efficiently. It was decided that the reaction would benefit from optimisation of the conditions. Reversal of the stoichiometry of the reaction reduced the yield of aryl pyrrolidine **282a**, however it was believed that the use of 1.0 equivalents of sulfoxide **212bn** would be preferential for this methodology (entry 2). Large amounts of sulfoxide **212bn** (0.6 equiv.) were isolated again. An equimolar amount of *s*-BuLi relative to *N*-Boc pyrrolidine (**275**) produced a similar yield (entry 3). This result provides evidence against the deprotonation of sulfoxide **212bn** by excess *s*-BuLi as a competitive reaction pathway. The addition of sulfoxide **212bn** as a solution in THF

was attempted in order to provide better control of the reaction, however a complex mixture of products was formed (entry 4). An alternative protocol for the preparation of such organolithium reagents from the group of O'Brien, where deprotonation was performed over 5 h in the presence of TMEDA, provided a lower conversion of aryl pyrrolidine **282a** (12%, entry 5).[187]

It was proposed that deprotonation of methyl sulfoxide **212bn** by the α-aminoorganolithium reagent **280a** might be impeding the reaction. To prevent such side-reactions, methyl sulfoxide **212bn** was substituted for commercially available phenyl sulfoxide **281a**. The observed conversion of aryl pyrrolidine **282a** was lower, with some unidentified by-products observed by HRMS (entry 6). Another protocol, devised by the group of Beak, where deprotonation was performed at -78 °C over 2 h, did not significantly increase conversion of desired product **282a** (entry 7).[188]

*Table 2.25: Ligand coupling of N-Boc organolithium reagent **280a** with 2-pyridyl sulfoxides **281***



R = Me: **212bn**
R = Ph: **281a**

282a

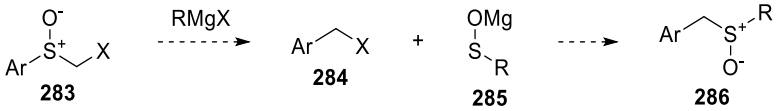
Entry	R	equiv. 275	equiv. s-BuLi	Temp (°C)	Time	additive (equiv.)	Yield 282a (%)
1	Me	0.5	0.7	-30	5 min	-	44
2	Me	1.8	2.5	-30	5 min	-	36
3	Me	1.8	1.8	-30	5 min	-	30
4[a]	Me	1.8	1.8	-30	5 min	-	36[b,c]
5[d]	Me	1.3	1.3	-78	5 h	TMEDA (1.3)	12[b]
6	Ph	1.8	1.8	-30	5 min	-	24[b,c]
7	Ph	0.5	0.6	-78	2 h	TMEDA (1.0)	26[b]

*a) sulfoxide **281a** added as a 0.2M solution in THF; b) conversion by integration of 2-pyridyl peaks in ^{1}H NMR; c) complex mixture of products; d) Et_2O used instead of THF.*

2.7 Homologation of α-halo sulfoxides

Despite the clear synthetic utility of ligand coupling reactions, stoichiometric amounts of sulfenate-derived by-products are created, which have been introduced before (*vide supra*: Scheme 2.56). It was thought that the reaction could be made more atom economical by using the known chemistry of sulfenates to incorporate these by-products in a second, tandem reaction.

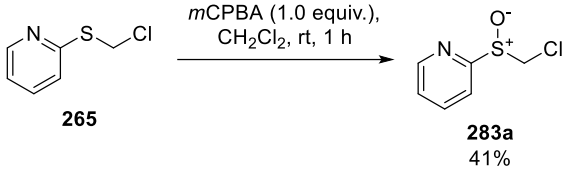
It was proposed that ligands with α-halogens may be able to undergo ligand coupling reactions as has been seen with α-oxy, α-amino and α-phenyl (benzyl) ligands (Scheme 2.99). Assuming successful ligand coupling reaction of an α-halo sulfoxide **283**, a benzylic halide **284** and a magnesium sulfenate **285** would be formed which could react further to form homologated sulfoxides **286**.



*Scheme 2.99: **Proposed route to homologated sulfoxides 286***

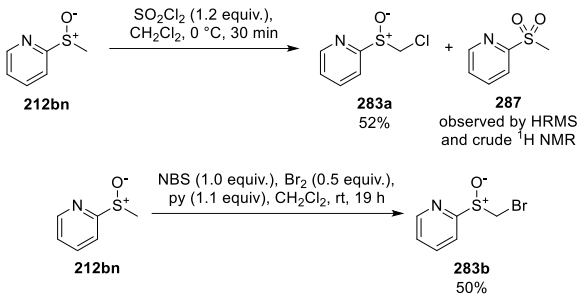
2.7.2 Synthesis of α-halo sulfoxides

As such, the synthesis of halomethyl sulfoxide substrates was undertaken. The oxidation of chloromethyl sulfide **265**, in hand from earlier studies (*vide supra*: Scheme 2.89), formed chloromethyl sulfoxide **283a** in 41% yield (Scheme 2.100).



*Scheme 2.100: **Synthesis of chloromethyl sulfoxide 283a by oxidation of sulfide 265***

Owing to the relatively low yield of α-chloro sulfoxide **283a** formed, the literature was examined for conditions to effect the α-halogenation of sulfoxides. Chlorination of methyl sulfoxide **212bn** was performed using sulfuryl chloride (Scheme 2.101).[189] In this reaction, methyl sulfone **287** was identified as a major by-product by crude ^{1}H NMR and mass spectrometry. Synthesis of bromomethyl sulfoxide **283b** was undertaken by exposing methyl sulfoxide **212bn** to NBS and bromine in the presence of pyridine.[190]

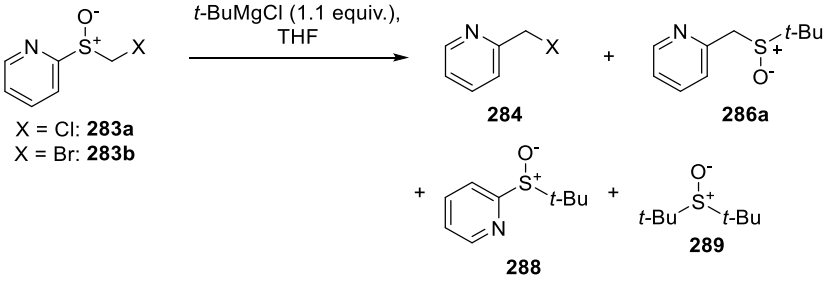


*Scheme 2.101: Synthesis of halomethyl sulfoxides **283a-b** by α-halogenation. Work performed by Mindaugas Šiaučiulis*

2.7.3 Homologative ligand coupling reactions

α-Chloromethyl sulfoxide **283a** and α-bromomethyl sulfoxide **283b** were subjected to *t*-butylmagnesium chloride to induce ligand coupling (Table 2.26). Initial reaction with α-chloromethyl sulfoxide **283a** afforded homologated sulfoxide **286a** in a modest yield (38%), along with small quantities of ligand exchange by-products **288** and **289** (9% and 7% respectively, entry 3). While 2-chloromethylpyridine (**284a**) was observed by crude ^{1}H NMR, it was never isolated (probably due to volatility). Optimisation of the homologation reaction was performed by determining conversion from crude ^{1}H NMR spectra. It was found that low temperatures decrease the rate of conversion of benzyl chloride **284a** to homologated sulfoxide **286a** (entries 1 and 2). Significant amounts of starting material **283a** remained after 1 h when the reaction was performed at -20 °C. Increasing the reaction temperature to 40 °C made no significant change to the conversion of either homologated sulfoxide **286a** or benzyl chloride **284a** compared to those recorded at room temperature (entries 3 and 4). A 5 min reaction time produced homologated product **286a** in a similar conversion to a similar 1 h reaction, suggesting that both ligand coupling and alkylation of the sulfenate intermediate are both rapid (entries 3 and 5). Extended reaction times caused a slight decrease in conversion, presumably due to decomposition of homologated sulfoxide **286a** (entry 6). Higher conversion was observed when bromomethyl sulfoxide **283b** was reacted at 0 °C (entry 7). A similar reaction performed at room temperature produced conversions of homologated product **286a** similar to that for chloride **283a** (entries 8 and 3). Both reactions performed with bromomethyl sulfoxide **286b** produced complex mixtures of products. It is thought that the increased electrophilicity of α-bromo sulfoxide **286b** may lead to more by-products from bromide substitution.

Table 2.26: Homogative ligand coupling reaction

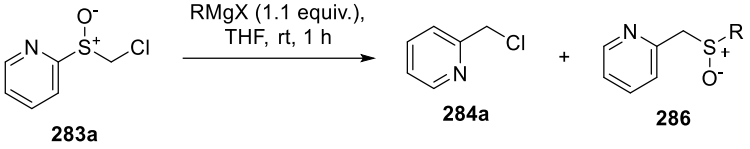


Entry	X	Temperature (°C)	Time	Conversion 284 (%)[a]	Conversion 286a (%)[a]
1[b]	Cl	-20	1 h	40	6[c]
2[b]	Cl	0	1 h	53	19
3	Cl	rt	1 h	41[e]	41 (38)[d]
4[b]	Cl	40	1 h	45	34
5[b]	Cl	rt	5 min	55	40
6[b]	Cl	rt	5.5 h	53	30
7[b]	Br	0	1 h	0	44
8[b]	Br	rt	1 h	0	32

a) conversion determined by analysis of ^{1}H NMR specta; b) work performed by Mindaugas Šiaučiulis; c) 47% remaining starting material; d) isolated yield; e) average of two results

To determine whether the Grignard reagent significantly affected the yield of homologated product **286**, chloromethylsulfoxide **283a** was subjected to a range of Grignard reagents (Table 2.27). Homologated products **286** were identified by characteristic diastereotopic benzylic protons seen in the crude ^{1}H NMR at around 4.1 ppm. Unfortunately, conversion to homologated products **286** when using Grignard reagents other than *t*-butylmagnesium chloride were poor (entries 2-4). Interestingly, conversion of chloride **284a** was more respectible with the other Grignard reagents, especially in the case of *i*-propenylmagnesium bromide (69%, entry 2).

*Table 2.27: Reaction of chloromethylsulfoxide **283a** with Grignard reagents*



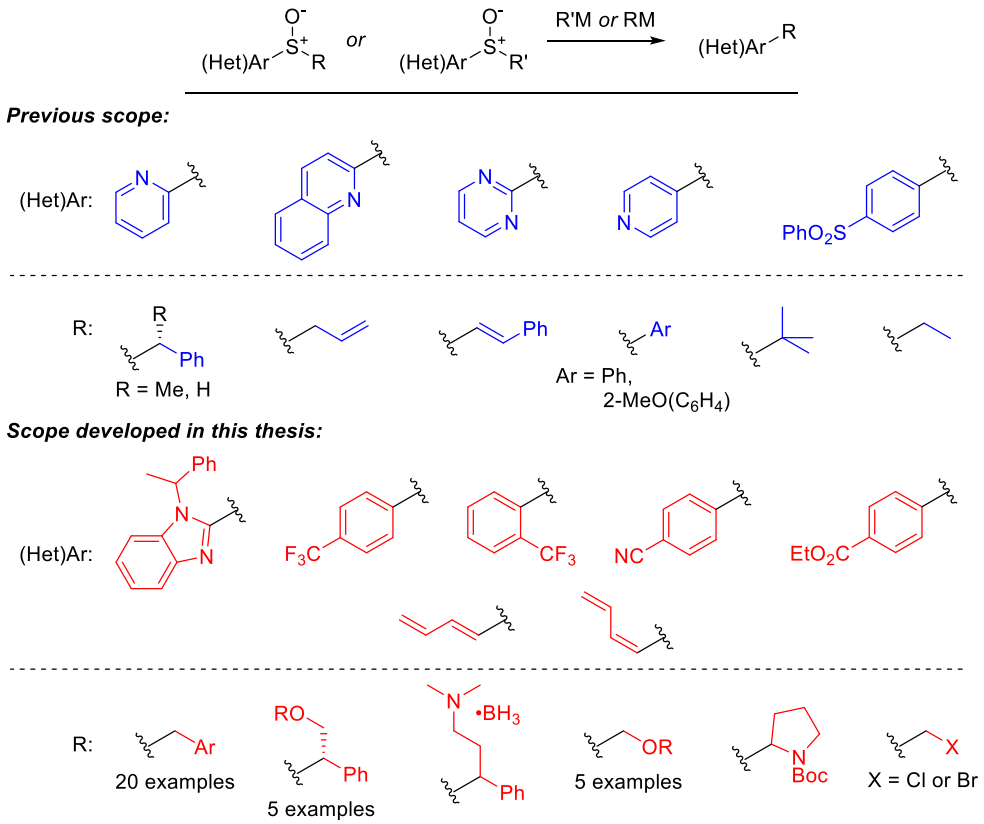
Entry	RMgX	Desired product	Conversion 284a (%)[a]	Conversion 286 (%)[a]
1	*t*-BuMgCl	**286a**	41[c]	41 (38)[b]
2[d]	*i*-propenylMgBr	**286b**	69	6
3[d]	PhMgBr	**286c**	30	0
4[d]	EtMgBr	**286d**	47	19

Notes: a) conversion determined by analysis of ^{1}H NMR specta; b) isolated yield; c) average of two results; d) work performed by Mindaugas Šiaučiulis

From the conversions recorded it can be seen that there is a significant mass loss in many cases. This is attributed to ligand exchange products as seen before (*vide supra*: Table 2.26). The absence of characteristic peaks for ligand exchange products in ^{1}H NMR spectra unfortunately prevented the determination of conversion.

2.8 Conclusions and future work

From the research presented in this chapter, it is clear that the ligand coupling reactions of sulfoxides has been developed far beyond the point previously represented in the literature (Scheme 2.102). Initial investigation into the Grignard reagent used to perform the intra-molecular ligand coupling of benzyl-2-pyridyl sulfoxides found that no Grignard reagent provides optimal yields with all substrates. It was discovered that MeMgBr and *t*-BuMgCl could be used to produce a wide variety of diarylmethanes in high yields. Having only two Grignard reagents to choose from simplifies the optimisation process for those wishing to apply this chemistry. The fact that no Grignard reagent examined provided optimal yields with all substrates was exhibited by an interesting trend, which was unveiled upon exploration of substitution of the benzylic (hetero)aromatic group. Electron-rich benzylic ligands formed higher yields of diarylmethanes with *t*-BuMgCl, and electron-deficient benzylic ligands formed higher yields with MeMgBr. This trend was assigned to steric and electronic effects upon the pseudorotation equilibria of σ-sulfurane intermediates.



Scheme 2.102: Summary of the scope of the ligand coupling reaction of sulfoxides

Aryl substitution tolerated on the benzylic ligand includes electron-rich, electron-deficient and sterically encumbered functionality. It was also shown that diarylmethanes can be synthesised containing aryl-halogens, providing scope for

derivatisation of products, and heteroaromatics, exhibiting the orthogonality of the ligand coupling reaction.

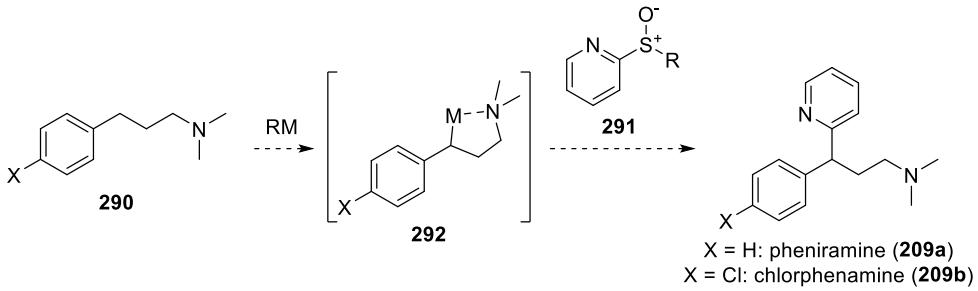
Examination of the (hetero)aromatic substituent of the ligand coupling reaction found that, further to the previous scope of the reaction, benzimidazolyl, (trifluoromethyl)phenyl, cyanophenyl and alkyl benzoyl groups undergo ligand coupling to form diarylmethanes. Interestingly, low yields of ligand coupling products were isolated between two dienes and a benzylic ligand, which proceeded with retention of alkene geometry in both cases.

Diarylmethanes were synthesised by both inter-molecular (cross-coupling) and intra-molecular ligand coupling reactions. It was found that yields could be improved by performing ligand coupling reactions in an inter-molecular fashion, while the ability to rapidly access a wider range of compounds compared to when using intra-molecular reactions is clear. Introducing the benzylic substituent as a Grignard reagent is effective, however only poor yields were obtained when 2-pyridyl and 2-nitrophenyl Grignard reagents were reacted with benzyl sulfoxides.

The synthesis and ligand coupling reactions of benzyl sulfoxides, which were functionalised at the α-carbon, was studied. Diastereoselective alkylation to form such sulfoxides was investigated but requires further development since conversions to alkylated products and corresponding diastereomeric ratios were poor. α-Functionalised benzyl sulfoxides were effectively synthesised by the alkylation of thiols, followed by oxidation. This method was employed in the synthesis of a range of β-functionalised benzyl sulfoxides which were enantiomerically enriched at the α-centre. Reaction with a Grignard reagent produced the corresponding diarylmethanes with almost complete stereoselectivity, further exhibiting the tolerance of this reaction to α-chirality. Separation of sulfoxide diastereomers allowed for the gathering of useful information regarding the yields obtained from the ligand coupling reaction of each. It was found that one diastereromer provides around twice the yield of ligand coupling product compared to the other.

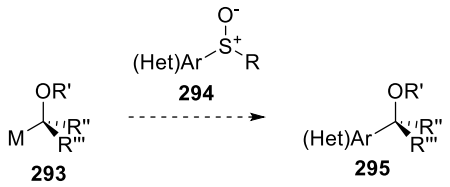
In order to demonstrate the utility of ligand coupling reactions, the synthesis of histamine H1 antagonists was investigated. The synthesis of the substrate required to produce pheniramine (**209a**) provided two main difficulties, however these were negotiated and ligand coupling delivered the desired drug product. Another route to histamine 1H antagonists **209** could be by a cross-coupling approach (Scheme 2.103).

Deprotonation of 3-phenyl-*N*,*N*-dimethylpropylamines **290** and reaction with 2-pyridyl sulfoxides **291** could provide histamine 1H antagonists **209** directly. Such a route would avoid troublesome substrate synthesis.



*Scheme 2.103: **Proposed cross-coupling route to histamine 1H antagonists 209***

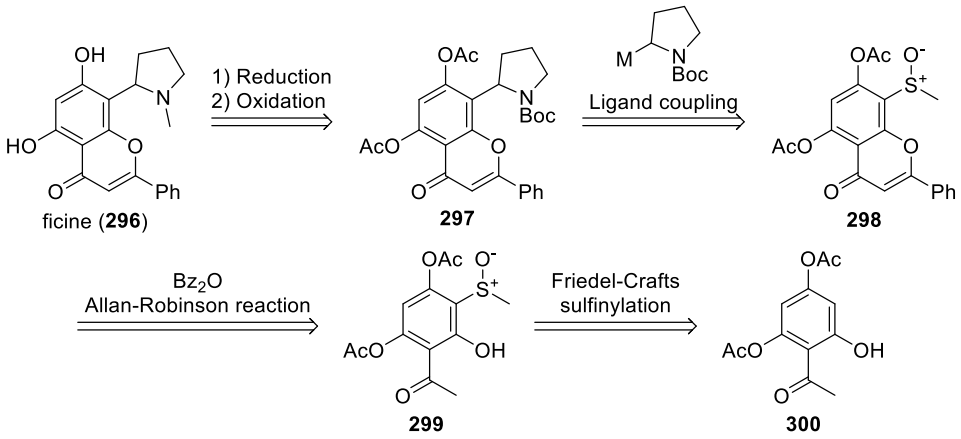
The scope of the ligand coupling reaction was also extended past the synthesis of diarylmethanes. α-Alkoxy sulfoxides produced some very good yields of benzylic ethers. It was found that substrates were unstable to prolonged storage at room temperature, and the introduction of functionality at the thioacetal methylene meant that oxidation yielded decomposition in one case. Therefore, it is proposed that this area of the methodology could also benefit from being developed into a cross-coupling protocol (Scheme 2.104). With precedence set in the synthesis of diarylmethanes by cross-coupling reactions, enantiomerically enriched α-oxy organolithium reagents **293** could be reacted with appropriate sulfoxides **294** provide enantiomerically enriched benzylic ethers **295**.[191]



*Scheme 2.104: **Proposed synthesis of enantiomerically enriched benzylic ethers 295***

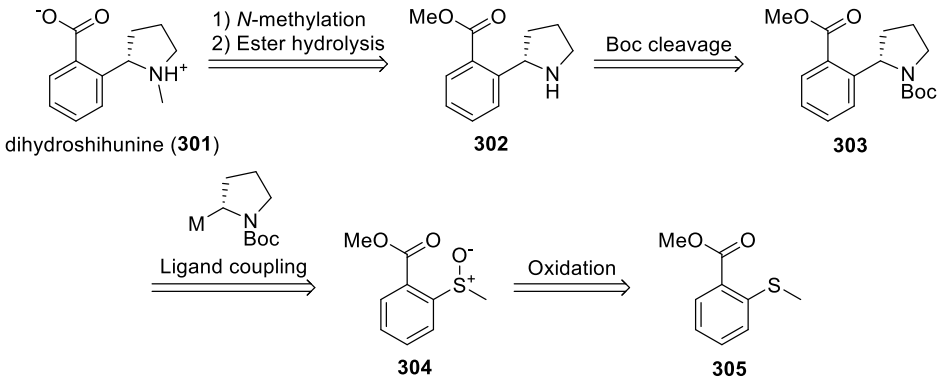
Synthesis of α-amino sulfoxides proved more troublesome than α-oxy sulfoxides, which corroborates literature reports.[185] To circumvent the synthesis of these substrates, the cross-coupling of 2-pyridyl sulfoxides with an α-amino organometallic reagent was investigated. The desired cross-coupling product was isolated in up to 44% yield, showing that the troublesome synthesis of unstable α-amino sulfoxides is not necessary. Further optimisation of this reaction would enhance its utility. In particular, it is proposed that the organolithium species used ia not a soft enough nucleophile to perform the reaction. The use of similar Grignard reagents or organocopper species may yield more effective ligand coupling product.

Following extended optimisation of this reaction, its use in the synthesis of natural products may be investigated. Ficine (**296**) is a highly active kinase-inhibiting natural product, isolated from *Ficus pantoniana* (Scheme 2.105).[192,193] It is envisaged that ficine (**296**) could be synthesised from *N*-Boc pyrrolidine **297** by global reduction with a reagent such as DIBAL-H, followed by re-oxidation to the ketone. Protection of the phenols as acetyl esters, together with the fused pyran-4-one functionality should render the ring electron-deficient enough to undergo ligand coupling. It is proposed that the pyrrolidine moiety could therefore be installed using a ligand coupling reaction under the optimised conditions from methyl sulfoxide **298**. Disconnection of pyran-4-one **298** by an Allan-Robinson reaction unveils its potential synthesis from acetophenone **299**. Finally, the sulfinyl moiety would be installed by a Friedel-Crafts sulfinylation from commercially available acetophenone **300**.[194]



*Scheme 2.105: **Retrosynthetic analysis of ficine (296)***

In order to exploit the full potential of the ligand coupling reaction, it is proposed that an enantioselective synthesis could be effected using a similar method (Scheme 2.106). Dihydroshihunine (**301**) was isolated from *Banisteriopsis caapi,* and its (*S*)-stereocentre was characterised by Kawanishi *et al*.[195] Dihydroshihunine (**301**) could be synthesised by the *N*-methylation and ester hydrolysis of pyrrolidine **302**. Envisaging the required functionality for a ligand coupling reaction, *N*-Boc-pyrrolidine **303** could be hydrolysed to form pyrrolidine **302**. Ligand coupling reaction of methyl sulfoxide **304** would install the pyrrolidine ring. A chiral ligand for the organometallic reagent would provide the desired enantiomeric excess. Methyl sulfoxide **304** would be readily synthesised by the oxidation of commercially available methyl sulfide **305**.

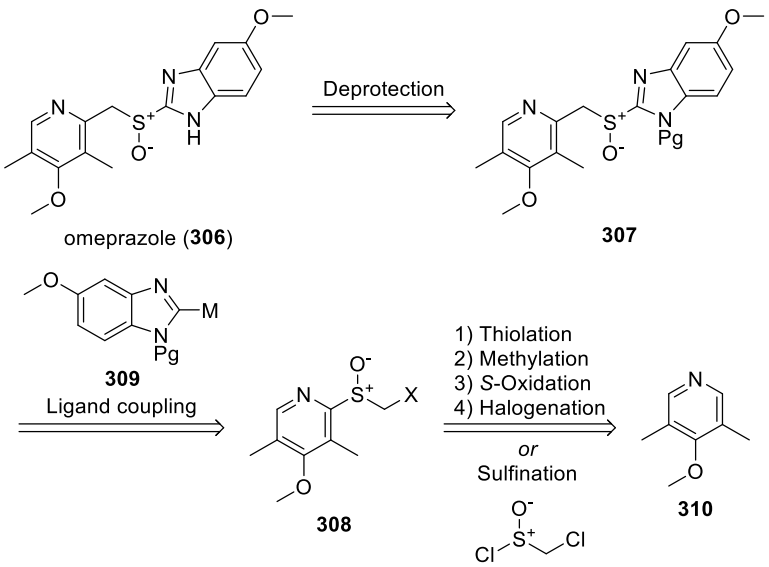


*Scheme 2.106: **Proposed retrosynthesis of dihydroshihunine (301)***

Exploring the coupling of other α-functionalised sulfoxides, it was found that α-halo sulfoxides undergo efficient ligand coupling reactions to produce benzylic halides. Furthermore, it was observed that in some cases the benzylic halide was able to alkylate the sulfenate by-product of the ligand coupling reaction, generating homologated sulfoxides. This previously completely unexplored reaction sequence is an interesting development in the field of ligand coupling reactions, and provides excellent atom economy.

Further-adding to the synthetic utility of this reaction is the presence of similar homologated sulfoxides in drug products. One example is omeprazole (**306**), a proton pump inhibitor which was developed by Astra AB (now AstraZeneca, Scheme 2.107). Omeprazole (**306**) was reported as the third highest-grossing generic medicine in the United States of America in 2011, with sales of $2.59 billion, and is included in the WHO list of essential medicines.[196,197]

It may be envisaged that a protected form of omeprazole **307** may be synthesised by the ligand coupling reaction of a halomethyl sulfoxide **308** with a deprotonated protected benzimidazole **309**. Halomethyl sulfoxide **308** could be synthesised from commercially available pyridine **310**, either by four well-precidented steps or by direct sulfination using commercially available chloromethyl sulfinyl chloride.[198]

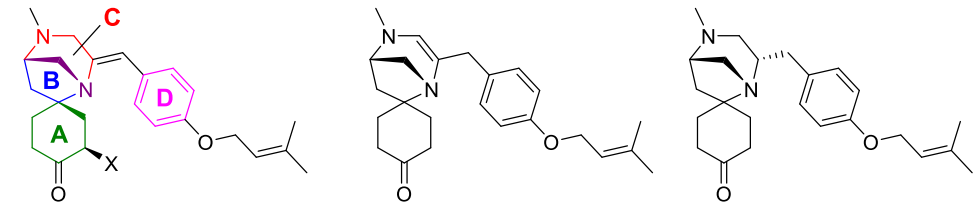


*Scheme 2.107: **Proposed synthesis of omeprazole (306)***

Chapter 3: Synthesis of TAN-1251 alkaloids

It has previously been noted that compounds with higher fractions of sp^3-hybridised carbon atoms more likely to excel as drug candidates within clinical trials. The ability to use a new methodology in the production of compounds with high fractions of sp^3-hybridised carbon atoms in a chemo- and stereoselective manner is therefore highly desirable. Natural products provide compelling targets for the application of novel methodology, and are particularly attractive when the desired natural product or products are biologically active.

Takeda Chemical Industries, Japan, reported the isolation of TAN-1251A, B, C and D (**311a-d**) from a broth of *Penicillium thomii* RA-89 in 1991 (Figure 3.1).[199,200] TAN-1251A (**311a**) and TAN-1251B (**311b**) have an antagonistic ED_{50} of 8.0 nM and 1.3 nM respectively against acetylcholine-induced contraction of isolated Guinea pig ileum. Furthermore, acute toxicity studies show no adverse effects in mice at doses of 100 mg kg^{-1}. These compounds are therefore proposed to be promising candidates for mydriatic, anti-spasmodic or anti-ulcer therapies.[199]



X = H: (-)-TAN-1251A (**311a**)
X = OH: (+)-TAN-1251B (**311b**)

(+)-TAN-1251C (**311c**)

(+)-TAN-1251D (**311d**)

*Figure 3.1: The TAN-1251 alkaloids (**311a-d**)*[200]

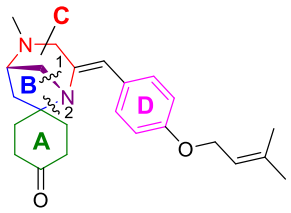
The TAN-1251 alkaloids (**311a-d**) all possess a cyclohexanone (ring A) which is spiro-fused with a 1,4-diazabicyclo[3.2.1]octane ring system (rings B and C) with pendant (4-prenyloxy)benzyl (ring D) and groups. They vary in unsaturation around the C ring, and (+)-TAN-1251B (**311b**) bares a chiral α-hydroxy ketone on the A ring.

3.2 Previous syntheses of the TAN-1251 alkaloids

The biological activity and intricate structure exhibited by the TAN-1251 alkaloids (**311a-d**) has attracted the attention of synthetic organic chemists to deliver fast routes to these compounds. Here follows a review of the synthetic efforts towards the TAN1251 alkaloids (**311a**-**d**). The syntheses are divided based upon the order in which the ABC ring system is synthesised.

3.2.1 ABC approach

The cyclohexanone A ring is frequently used, in a protected form, as the starting material to synthesise TAN-1251 alkaloids (**311a-d**). Most syntheses therefore concentrate efforts on the synthesis of the 1,4-diazabicyclo[3.2.1]octane B and C rings. Synthesis of the B ring has previously focussed on the formation of C-N bonds to the bridgehead nitrogen (Figure 3.2: bond 1 and bond 2). These were synthesised either by amide formation (bond 1), or oxidative phenolic coupling (bond 2).

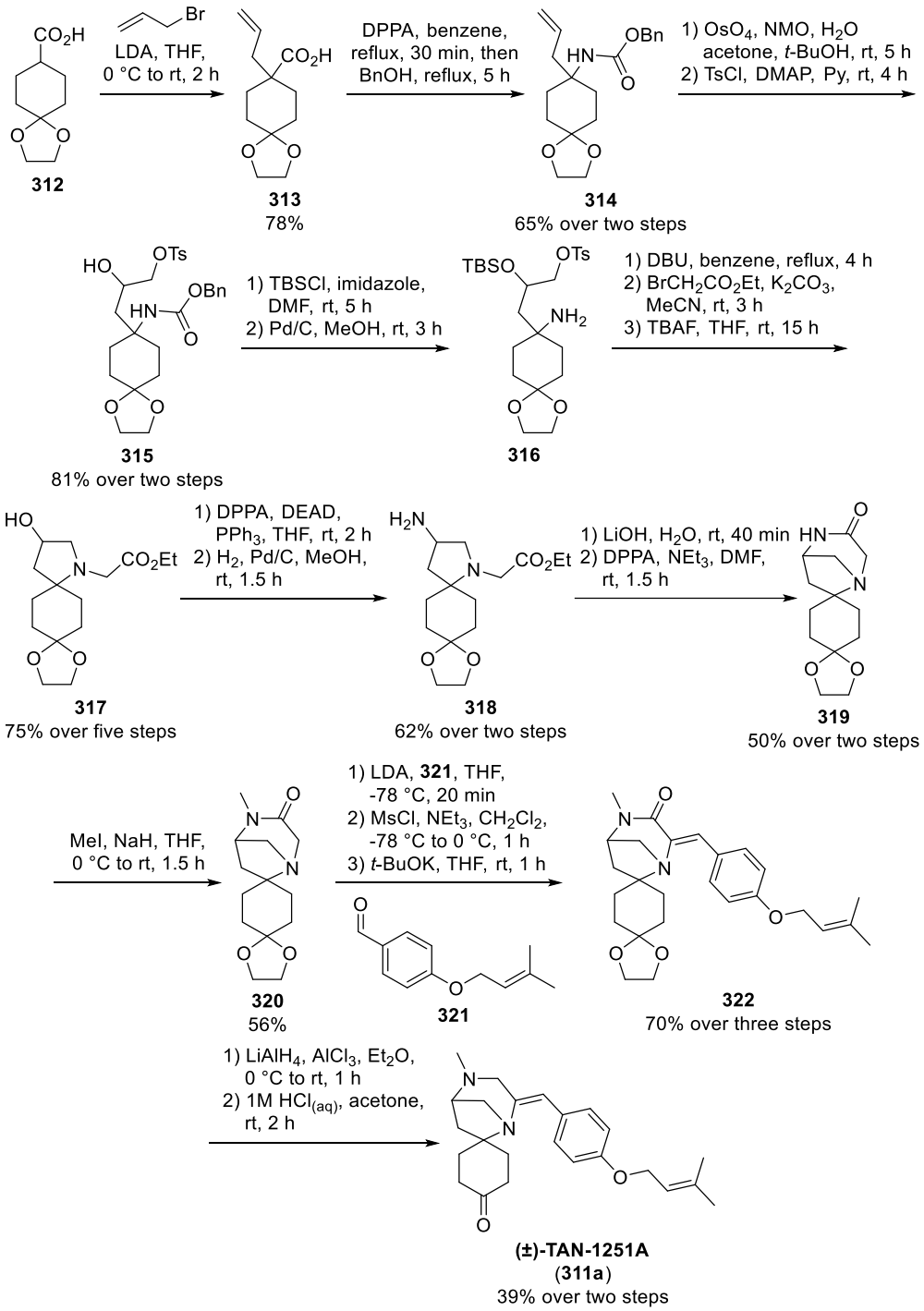


(-)-TAN1251A (**311a**)

Figure 3.2: Routes to the B ring following synthesis of the A ring

The first published synthesis of a TAN-1251 alkaloid (**311a-d**) was by Kawahara and coworkers in 1998. Robust methodology was employed to perform a racemic synthesis of (±)-TAN-1251A (**311a**), in an ABC fashion (Scheme 3.1).[201,202] α-Alkylation of carboxylic acid **312** with allyl bromide affords acid **313**. Diphenylphosphoryl azide (DPPA) was used to perform a Curtius rearrangement, and trapping of the isocyanate intermediate with benzyl alcohol gave carbamate **314**.[203] Dihydroxylation of the olefin, followed by selective sulfonylation of the primary alcohol provides tosylate **315**. Silyl protection of the secondary alcohol and reductive cleavage of the carbamate affords amine **316**. Subjection to refluxing basic conditions caused an S_N2-like substitution of the tosylate, forming the B ring. Alkylation of the secondary amine and deprotection of the silyl-protected alcohol produced alcohol **317** in good yield. Alcohol **317** was converted to amine **318** by reduction of the corresponding azide. The C ring was formed by basic hydrolysis of ester **318** followed by activation of the carboxylic acid with DPPA, which allowed for the *in situ* formation of lactam **319**. *N*-methylation affords methyl lactam **320**. An aldol reaction with aldehyde **321**,

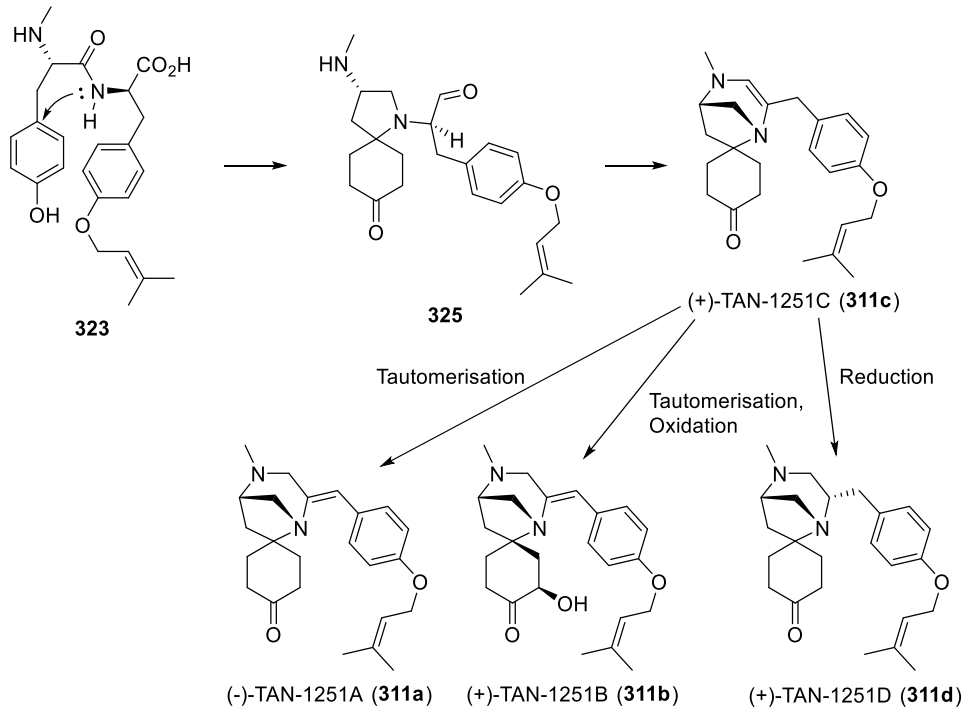
mesylation and elimination incorporated the D ring, affording α,β-unsaturated lactam **322**. The synthesis of (±)-TAN-1251A (**311a**) was completed by amide reduction and deprotection of dioxolane **322**, resulting in a total synthesis yielding 1.0% over 22 steps.



*Scheme 3.1: Kawahara synthesis of (±)-TAN-1251A (**311a**)*[201,202]

Snider published a biomimetic total synthesis of all four TAN-1251 alkaloids (**311a-d**), which marks the first total syntheses of TAN-1251B, C and D (**311c-d**).[200] They propose that the biosynthesis of the TAN-1251 alkaloids takes place from a dipeptide **323**,

derived from two molecules of L-tyrosine (**324**), which undergoes *ipso*-cyclisation and reduction to form the 5,6-spirocycle **325** (Scheme 3.2). Intramolecular condensation of amino aldehyde **325** is proposed to form TAN-1251C (**311c**), which can be converted into other TAN-1251 alkaloids (**311a**, **311b** and **311d**) by isomerisation, oxidation and/or reduction.

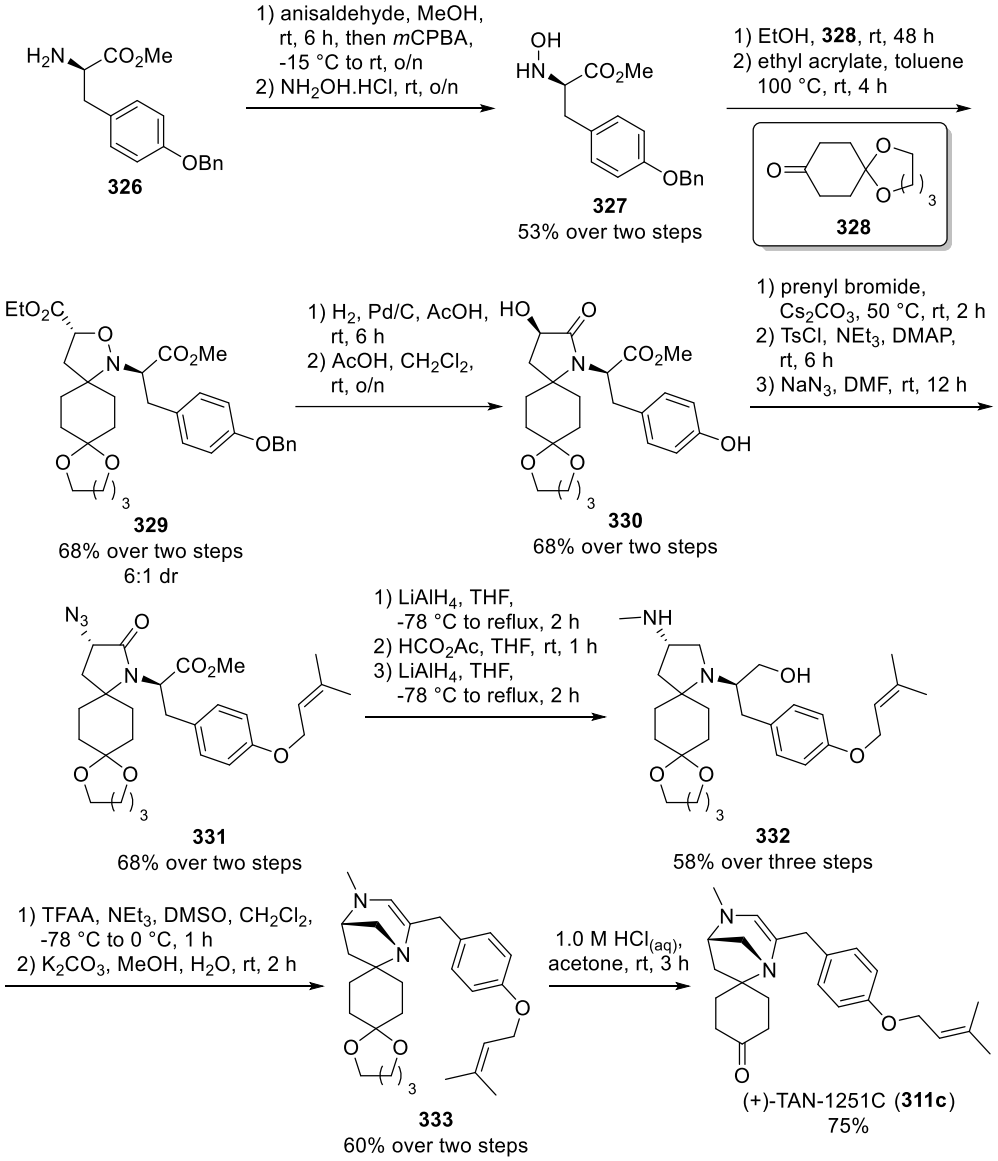


*Scheme 3.2: **Snider's proposed biosynthesis of (+)-TAN-1251C (311c)**[200]*

The total synthesis of (+)-TAN-1251C (**311c**) by Snider *et al.* is biomimetic; utilising the stereochemistry of a derivative of L-tyrosine to provide the required stereochemistry for an enantioselective route. Furthermore, a late-stage intermediate of (+)-TAN-1251C (**311c**) is used to produce the other TAN1251 alkaloids (**311a**, **311b** and **311d**), as in the proposed biosynthesis.

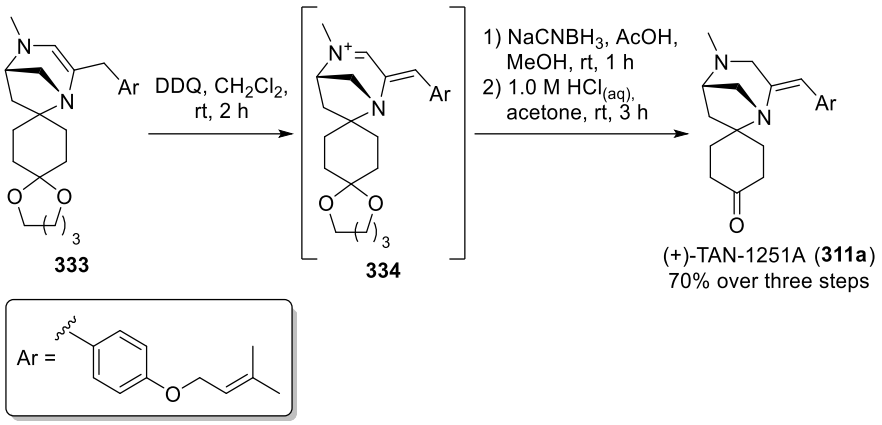
Oxidation of *O*-benzyltyrosine methyl ester (**326**) using conditions from the group of Grundke produces hydroxylamine **327** (Scheme 3.3).[200,204] Nitrone formation with ketone **328**, followed by [3+2] cycloaddition with ethyl acrylate affords isoxazolidine **329** in a diastereomeric ratio of 6:1. Simultaneous reduction of the isoxazolidine N-O bond and benzyl deprotection followed by subjection to acetic acid synthesises lactam **330** in a good yield. Prenylation of the phenol, tosylation of the hydroxyl group and substitution using sodium azide delivers azide **331**. Lithium aluminium hydride reduces the ester, azide and lactam, before formylation and reduction gives methylamine **332**. Oxidation of primary alcohol **332** using trifluoroacetic anhydride

and triethylamine in DMSO affords the corresponding aldehyde, and intramolecular cyclisation by attack of the methyl amine gave enamine **333**. Hydrolysis of ketal **333** in acidic acetone yields (+)-TAN-1251C (**311c**).



*Scheme 3.3: **Snider synthesis of (+)-TAN-1251C (311c)**[200]*

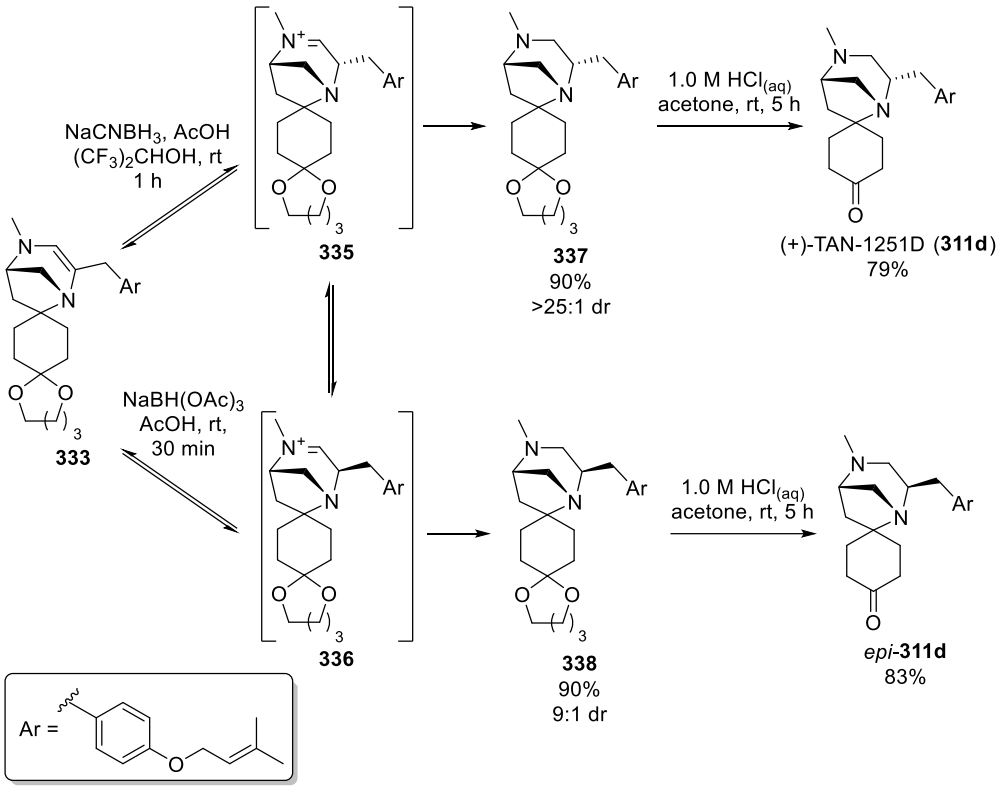
Enamine **333** was used in the synthesis of the remaining TAN-1251 alkaloids (**311a**, **311b** and **311d**) by the same group. Oxidation of the benzylic position of enamine **333** using DDQ affords α,β-unsaturated iminium ion **334** (Scheme 3.4). Sodium cyanoborohydride was used to effect 1,2-reduction. Hydrolysis completed the total synthesis of (-)-TAN-1251A (**311a**) in 17 steps and 4.1% overall yield; the highest yielding and joint second shortest synthesis of (-)-TAN-1251A (**311a**).



*Scheme 3.4: Snider's synthesis of (-)-TAN-1251A (**311a**) from enamine **333***[200]

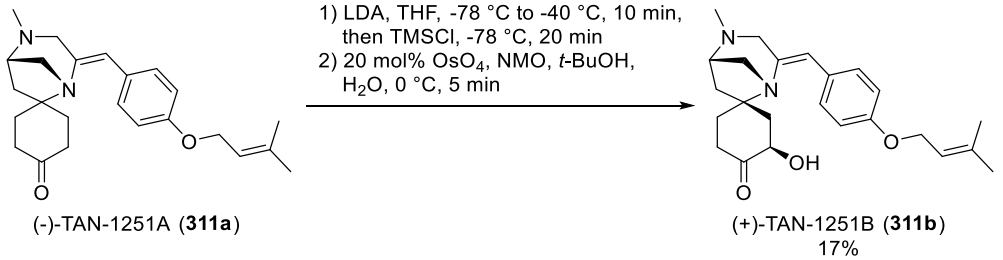
Snider *et al.* also developed the diastereoselective reduction of enamine **333** to form (+)-TAN-1251D (**311d**, Scheme 3.5).[200] Solvent polarity and choice of reducing agent were found to be very important to keep the reaction under kinetic control and hence obtain a high diastereoselectivity for this reaction. More polar solvents ($(CF_3)_2CHOH > CF_3CH_2OH > MeOH$) were shown to give higher diasteroselectivity. The group rationalised that polar solvents stabilise kinetically stable iminium ion **335**, and therefore retard the conversion of iminium ion **335** to undesired but thermodynamically more stable iminium ion **336**. Sodium cyanoborohydride was chosen over sodium triacetoxyborohydride to effect rapid reduction of kinetically more stable iminium ion **335**, thereby preventing degradation of stereochemistry. Hence, under the optimised conditions of sodium cyanoborohydride in hexafluoroisopropanol, the group can obtain diamine **337** in greater than 25:1 diastereomeric ratio. Exposure to acidic acetone affords (+)-TAN-1251D (**311d**) in a 71% yield from enamine **333**.

Treatment of enamine **333** with sodium triacetoxyborohydride in acetic acid forms diamine **338**, an epimer of diamine **337**, in a 9:1 diastereomeric ratio. Acetal hydrolysis provides *epi*-(+)-TAN-1251D (*epi*-**311d**) in a 75% yield from enamine **333**.



*Scheme 3.5: Snider's synthesis of (+)-TAN-1251D (**311d**) from enamine **333**[200]*

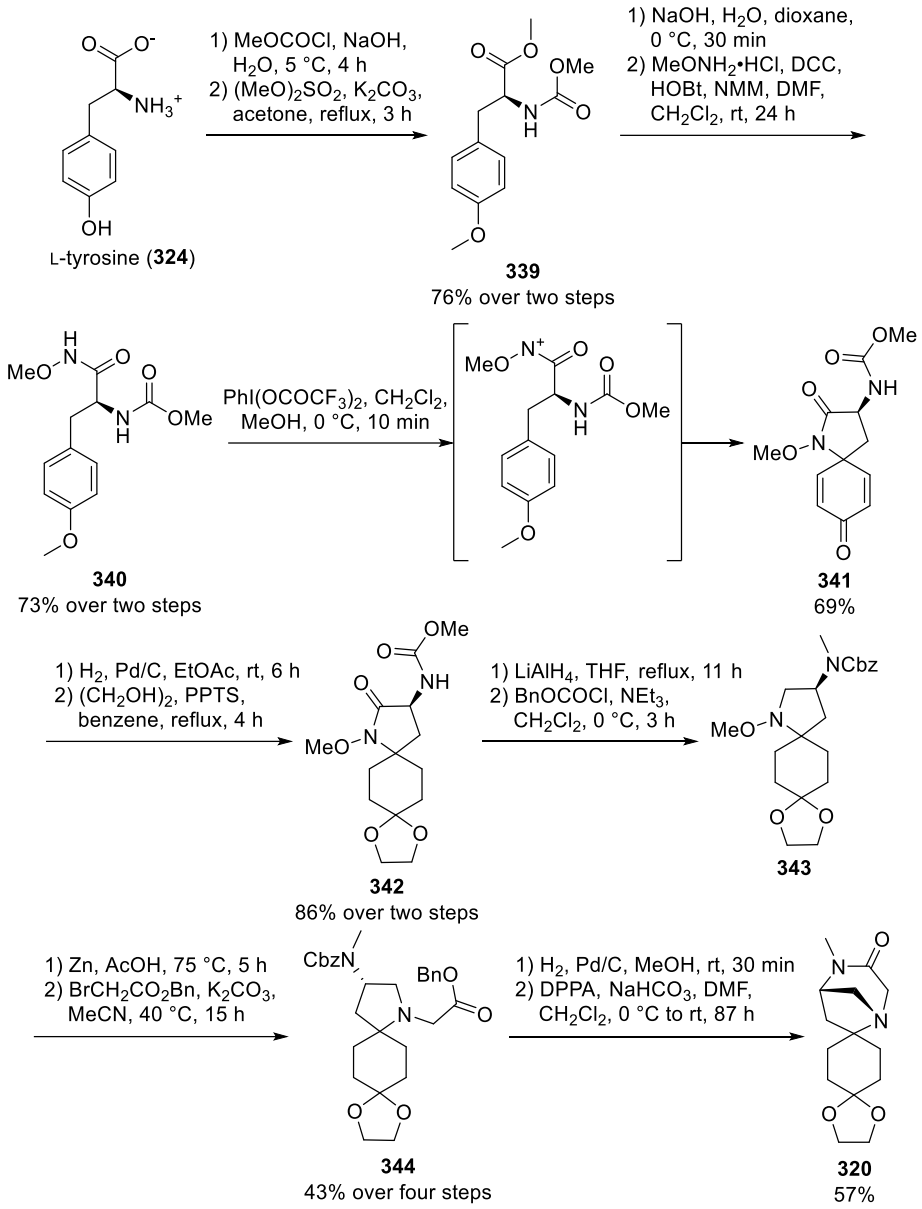
Oxidation of (-)-TAN-1251A (**311a**) to (+)-TAN-1251B (**311b**) proved troublesome for the group of Snider. Initial attempts at the oxidation using various oxaziridines or *m*CPBA affords incorrect epimers and oxidation of different functionalities. Oxidation of a crude mixture of TMS-enol ethers of (-)-TAN-1251A (**311a**) using OsO_4/NMO gives 39% of a mixture of 4 epimers in an 8:7 ratio of (+)-TAN-1251B (**311b**) to all other epimers (Scheme 3.6). Preparatory TLC followed by HPLC using a Chiralpak® AD column is required to separate (+)-TAN-1251B (**311b**) from all of the other epimers, affording (+)-TAN-1251B (**311b**) in a 17% yield from (-)-TAN-1251A (**311a**).



*Scheme 3.6: Snider's synthesis of (+)-TAN1251B (**311b**)*[200]

The formal synthesis of (-)-TAN1251A (**311a**) by the group of Wardrop proceeds *via* a key iodine(III)-mediated dearomatising phenolic oxidation to form the central 5,6-spirocentre (Scheme 3.7).[205] In a similar manner to that of Snider *et al.,* this synthesis starts from L-tyrosine (**324**), which was triply protected as the methyl

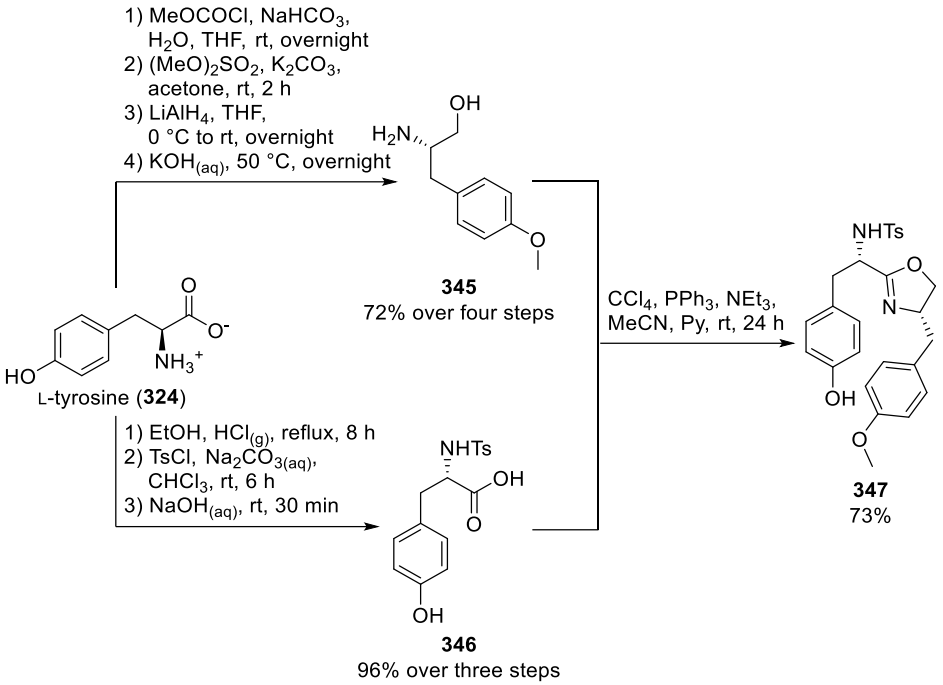
carbamate, anisole and methyl ester **339**. Hydrolysis of methyl ester **339** followed by DCC/HOBt coupling of the corresponding acid with methoxylamine affords the *N*-methoxylamide **340**. In the key step of this synthesis, iodine(III)-mediated activation of *N*-methoxylamide **340** forms the corresponding *N*-methoxyl-*N*-acylnitrenium ion. As such, Friedel-Crafts-type attack by the aryl ring is facilitated, forming the dimethoxy ketal which is hydrolysed *in situ* to afford dienone **341**. Double 1,4-reduction of ketone **341**, followed by protection as the dioxolane affords acetal **342**. Double reduction of carbamate **342** and Cbz protection of the methylamine provides carbamate **343**. Chemoselective reduction of the hydroxylamine was performed using acidic zinc, before alkylation of the pyrrolidine nitrogen affords ester **344**. Hydrogenation was employed to remove the Cbz group and benzyl ester, and allowed for DPPA-mediated lactamisation to form Kawahara's intermediate **320** (*vide supra:* Scheme 3.1). This marks the joint-shortest synthesis of (-)-TAN-1251A (**311a**) by longest linear sequence, at 17 steps.



*Scheme 3.7: Wardrop's formal synthesis of (-)-TAN-1251A (**311a**)*[205]

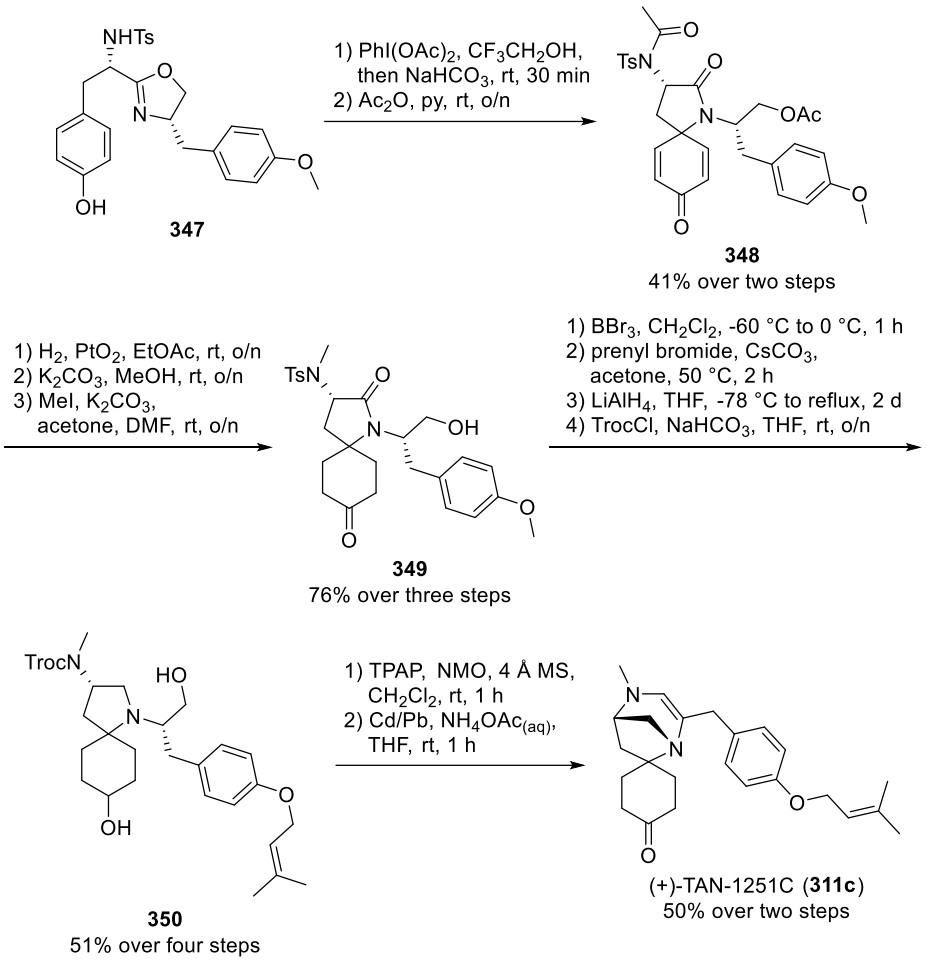
Ciufolini's synthesis of (-)-TAN-1251C (**311c**) takes a bifurcating approach from L-tyrosine (**324**) (Scheme 3.8).[206] Recombination of the derived fragments is followed by a key iodine(III)-mediated phenolic oxidation to form the A-B ring spirocentre.

One portion of L-tyrosine (**324**) was *N*-protected as the methyl carbamate, before the phenol and carboxylic acid were both methylated. The resulting ester was reduced to the corresponding alcohol, and basic hydrolysis of the carbamate affords amino alcohol **345**. Another portion of L-tyrosine (**324**) was subjected to esterification, *N*-tosylation and hydrolysis to give carboxylic acid **346** in an excellent 93% yield over three steps. Reunion of amino alcohol **345** with carboxylic acid **346**, undertaken using the Vorbrüggen modification of the Appel reaction, forms oxazoline **347**.[207]



*Scheme 3.8: Initial steps of Ciufolini's 2001 total synthesis of (-)-TAN-1251C (**311c**)* [206]

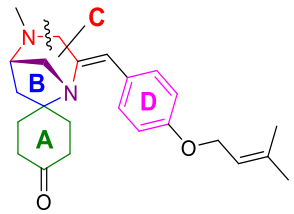
Iodine(III)-mediated phenolic oxidation of oxazoline **347** caused formation of the B ring (Scheme 3.9). Acetyl-protection of the primary alcohol was required to prevent undesired Michael attack on the cyclohexanone moiety, and also acetylated the sulfonamide to afford dienone **348**. Reduction of dienone **348** to the corresponding ketone was investigated, however palladium and rhodium-based catalysts caused extensive aromatisation through cleavage of the spirocentre C-N bond. Platinum on carbon and Raney nickel both over-reduced the ketone moiety to its corresponding alcohol. Adam's catalyst (platinum(IV) dioxide), was found to effect selective hydrogenation of dienone **348**, formed the corresponding ketone in 96% yield. Hydrolysis of both acetyl groups followed by *N*-methylation affords methyl sulfonamide **349**. Methyl ether deprotection of phenol **349** was followed by subjection to prenyl bromide; introducing the required prenyl group. Reduction of the sulfonamide, amide and ketone by lithium aluminium hydride, and Troc protection produced carbamate **350**. Dual oxidation of diol **350** was performed with TPAP/NMO. Subjection of the corresponding aldehyde to Cd/Pb couple efficiently deprotected the Troc group and induced cyclisation to form the C ring and hence (+)-TAN-1251C (**311c**). This is the shortest synthesis of TAN-1251C (**311c**) to date, at 16 steps for the longest linear sequence, and in a reasonable overall yield of 4.0%.



*Scheme 3.9: Final steps of Ciufolini's 2001 total synthesis of (+)-TAN-1251C (**311c**)*[206]

3.2.2 ACB approach

Honda and coworkers have reported the synthesis of TAN-1251A, C and D (**311a**, **311c** and **311d**) using ACB approaches.[208,209] These syntheses form the C ring through formation of amides of the methylated nitrogen (Figure 3.3). Iodine(III)-mediated oxidative cyclisations of the corresponding phenol are used to synthesise the B rings in a similar manner to Wardrop and Ciufolini's ABC approaches (*vide supra*: Scheme 3.7, Scheme 3.8 and Scheme 3.9).

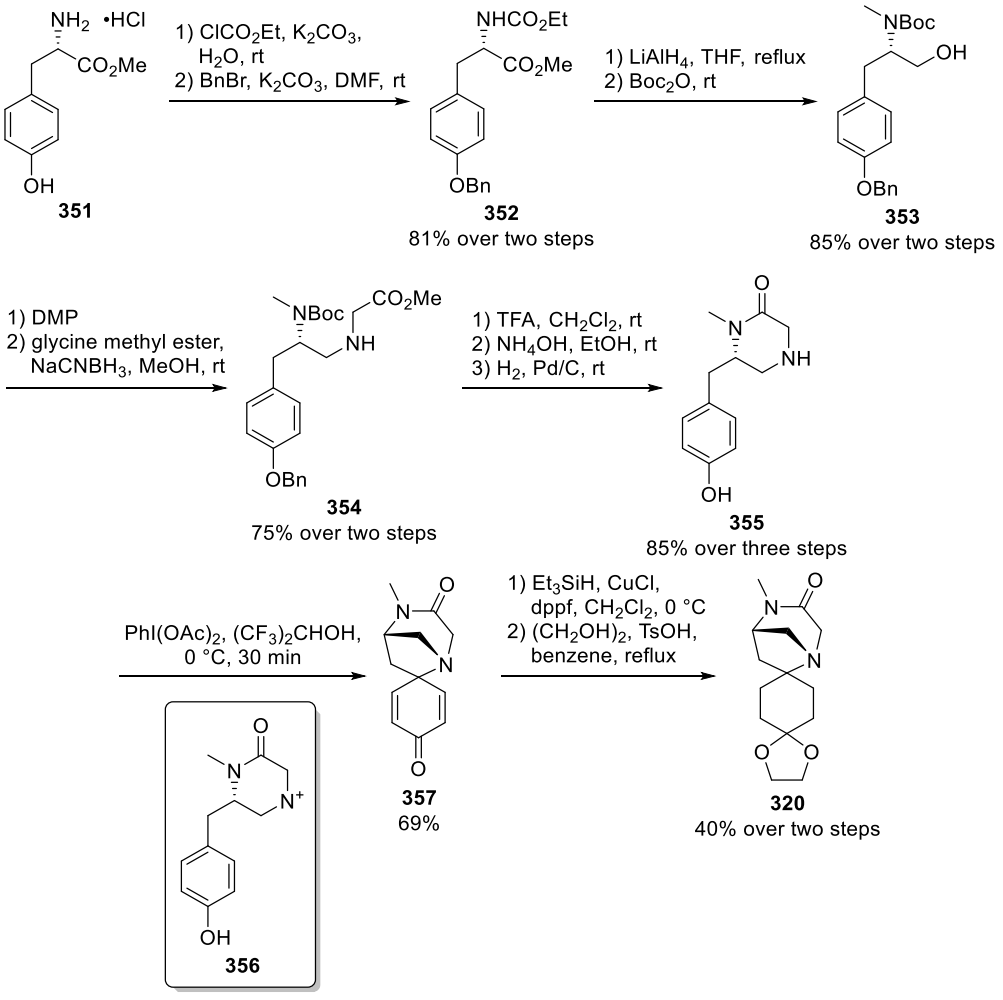


(-)-TAN1251A (**311a**)

Figure 3.3: Routes to the C ring following synthesis of the A ring

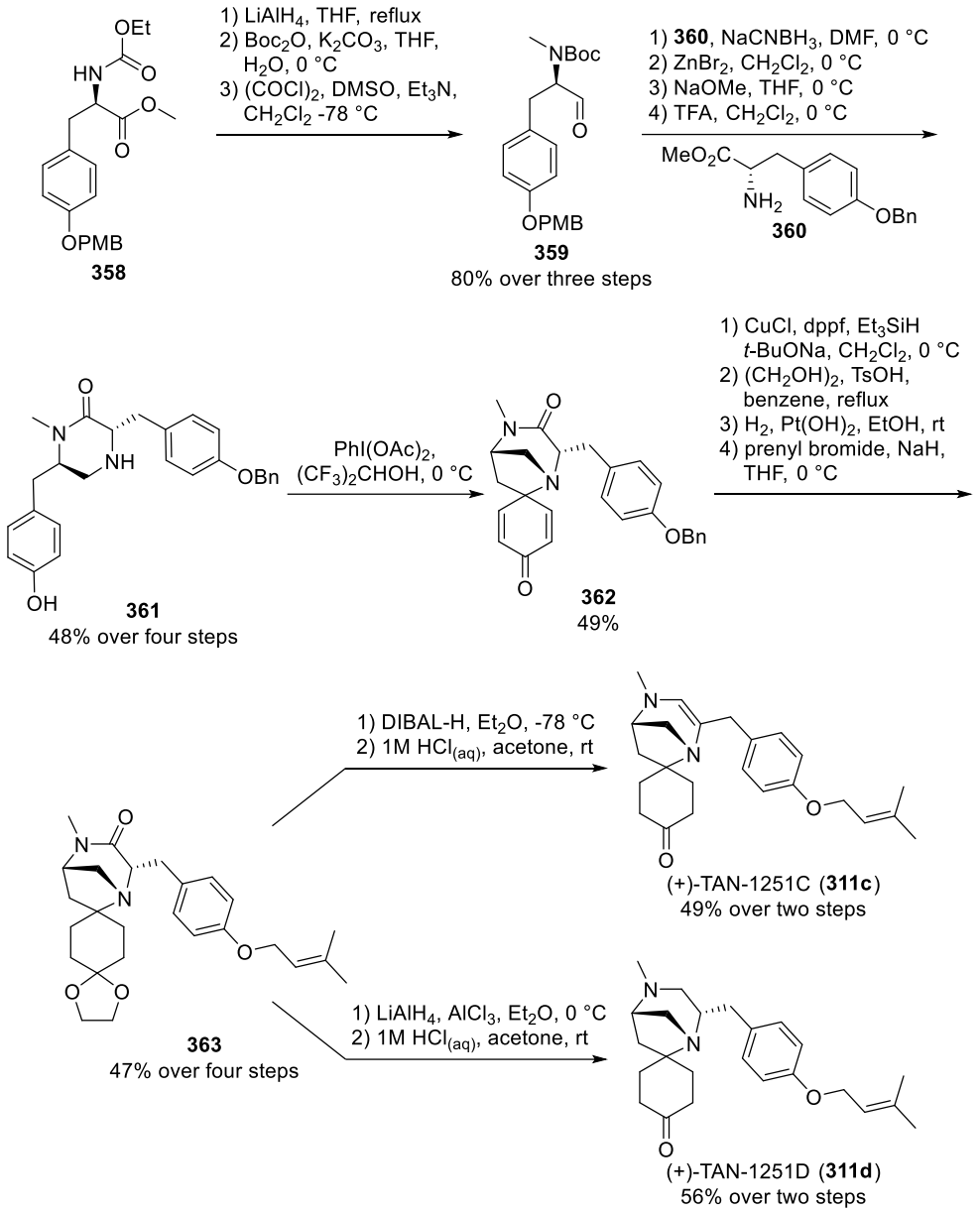
In their formal synthesis of (-)-TAN-1251A (**311a**), the group of Honda started from L-tyrosine methyl ester hydrochloride (**351**, Scheme 3.10).[208] Amine protection as the

ethyl carbamate and benzyl protection of the phenol gave ether **352**. Reduction of ester **352** using lithium aluminium hydride also reduced the carbamate to the corresponding methyl amine. Boc-protection of the methyl amine provides carbamate **353**. Dess-Martin oxidation of primary alcohol **353** to the corresponding aldehyde and subsequent reductive amination with glycine methyl ester gave amine **354**. Boc deprotection allowed for an ammonium hydroxide-mediated lactam formation to produce the C ring. Hydrogenation of the benzyl ether affords phenol **355**. The key spirocyclisation step to form the B ring was initially attempted using *N*-chlorosuccinimide and silver oxide to form the aminylium ion **356**, however no desired product **357** was formed. Instead, reaction of phenol **355** with bis(acetoxy)iodobenzene in hexafluoroisopropanol produced dienone **357** in a 69% yield. Mild double 1,4-reduction of dienone **357** was performed using copper hydride (generated *in situ* from CuCl and Et_3SiH). Acetal protection of the ketone gives Kawahara's intermediate **320** (*vide supra:* Scheme 3.1*)*.



*Scheme 3.10: **Honda's 2002 formal synthesis of (-)-TAN1251A (311a)**[208]*

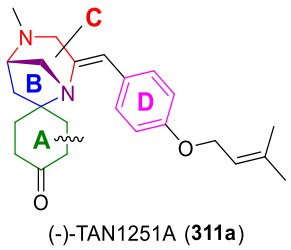
The group of Honda has also synthesised (-)-TAN-1251C (**311c**) and (+)-TAN-2351D (**311d**), using using two L-tyrosine (**324**) derivatives to provide the required stereochemistry, in a similar manner to Ciufolini and co-workers (Scheme 3.11, *vide supra*: Scheme 3.8).[209] Triple-protected L-tyrosine **358**, was exposed to lithium aluminium hydride, effecting reduction of the ester to the corresponding alcohol and the carbamate to the methyl amine. Boc protection of the methyl amine and Swern oxidation of the alcohol gave aldehyde **359**. Reductive amination was used to couple this fragment with *O*-benzyl-L-tyrosine methyl ester (**360**). Subjection to $ZnBr_2$ provides chemoselective removal of the Boc protecting group. Lactam formation to produce the C ring was achieved under alkaline conditions, before acid-mediated PMB deprotection affords phenol **361** in a 48% yield over four steps. Aromatic oxidation, as in their previous synthesis, successfully formed the required A/B ring spirocentre of dienone **362**. Double 1,4-reduction of dienone **362** and protection of the resultant ketone affords the corresponding dioxirane, as before (*vide supra*: Scheme 3.10). Hydrogenation was employed to cleave the benzyl ether, which was replaced by a prenyl group to give prenyl phenyl ether **363**. Partial reduction of lactam **363** using DIBAL-H, followed by hydrolysis provides (+)-TAN1251C (**311c**). (+)-TAN1251D (**311d**) was formed from the same intermediate, lactam **363**, by full reduction with lithium aluminium hydride followed by hydrolysis.



*Scheme 3.11: Honda's 2004 synthesis of (+)-TAN1251C (**311c**) and (+)-TAN1251D (**311d**)*[209]

3.2.3 BAC approach

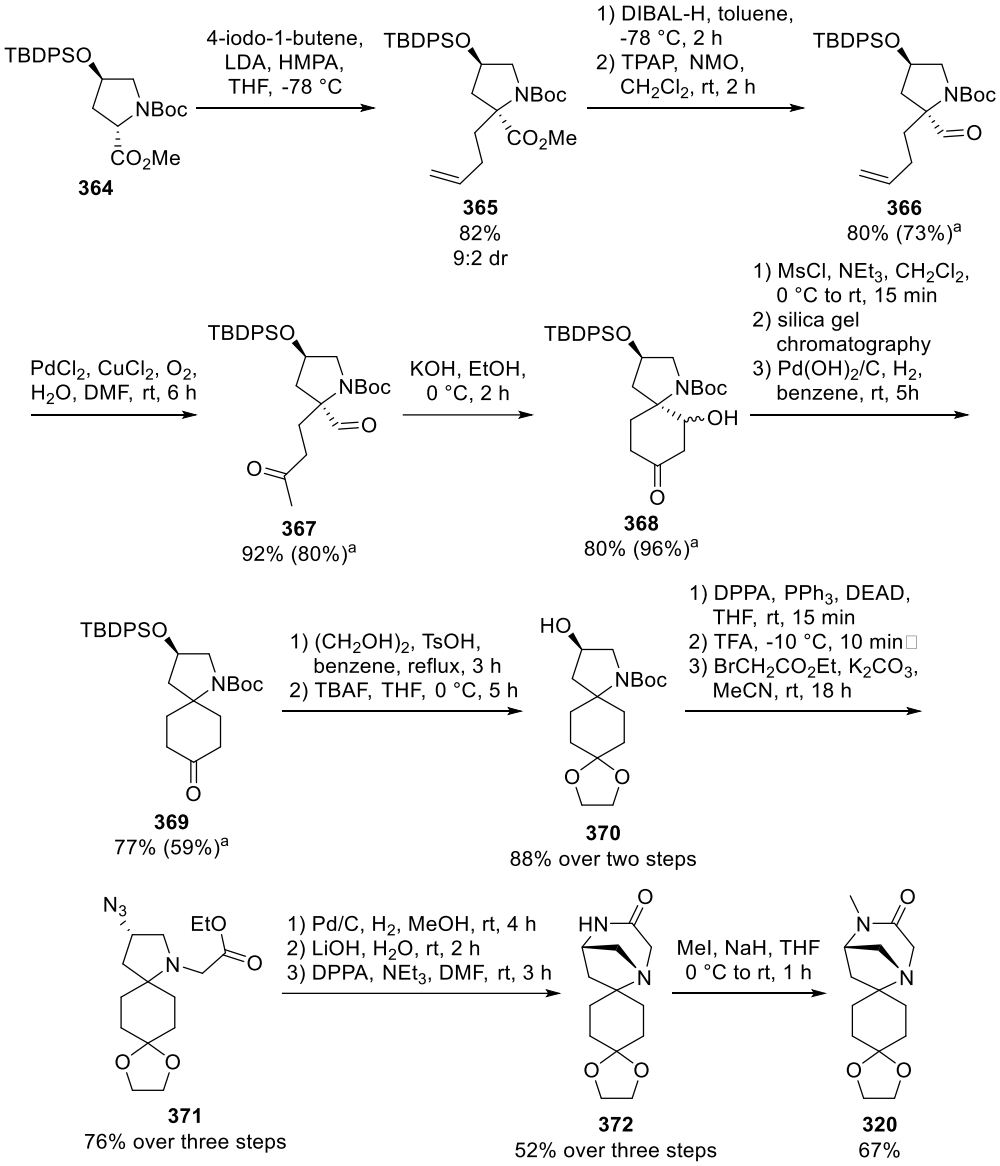
Syntheses employing BAC routes to the TAN-1251 alkaloids (**311a-d**) have focussed on the use of chiral pyrrolidines, as a ready-formed B-ring, followed by synthesis of the A ring using aldol condensations to form the bond depicted in Figure 3.4.



(-)-TAN1251A (**311a**)

Figure 3.4: Routes to the C ring following synthesis of the B ring

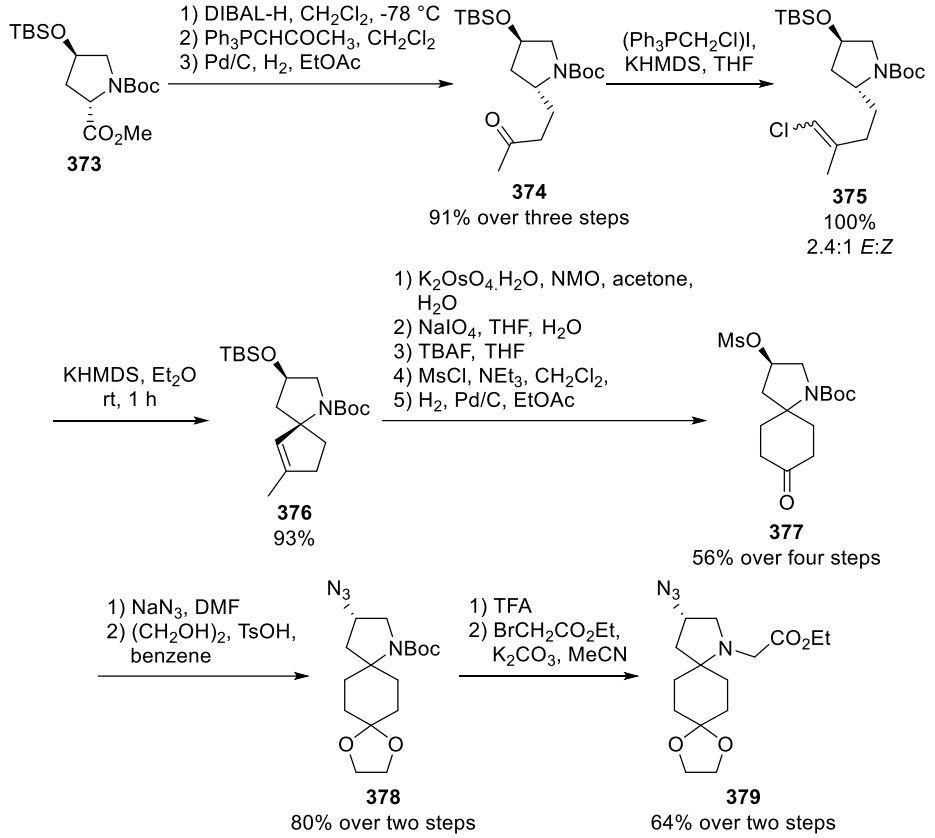
Nagumo and Kawahara improved on their previous synthesis of (±)-TAN-1251A (**311a**, *vide supra*: Scheme 3.1) by using 4-hydroxy-L-proline-derrived chiral pool **364** to access (-)-TAN1251A (**311a**) (Scheme 3.12).[210] α-Alkylation of ester **364** formed ester **365**. Chemoselective DIBAL-H reduction formed the corresponding alcohol, before oxidation gave aldehyde **366**. Wacker oxidation formed ketone **367** in an excellent 92% yield. Hydroxide-mediated aldol reaction formed the A ring of cyclohexanone **368** in an 80% yield. Mesylation and elimination (effected during column chromatography) followed by a selective 1,4-reduction was employed to remove the redundant hydroxyl group, forming ketone **369**. Ketal protection of ketone **369** was performed before fluoride-mediated deprotection of the silyl ether affords alcohol **370**. Mitsunobu reaction of secondary alcohol **370** introduced the azide, and Boc-deprotection followed by *N*-alkylation with ethyl bromoacetate gives ester **371**. Reduction of azide **188** and hydrolysis of the ester gave the corresponding amino acid, before DPPA is employed to form the B ring as lactam **372**. Methylation of the amide using iodomethane forms Kawahara's intermediate **320** (*vide supra:* Scheme 3.1); completing the formal synthesis of (-)-TAN1251A (**311a**).



*Scheme 3.12: Formal synthesis of (-)-TAN-1251A (**311a**) from proline-derived chiral pool **364**.*[210] *Notes: a) yield for diastereomer.*

The Hayes group's formal synthesis of (-)-TAN1251A (**311a**) shows a similar approach to the Nagumo and Kawahara group synthesis, in that the A ring is formed by aldol reaction (Scheme 3.13, *vide supra:* Scheme 3.12).[211] Selective DIBAL-H reduction of triple-protected hydroxyproline **373** is used to form the corresponding aldehyde. Wittig reaction and 1,4-reduction by hydrogenation affords ketone **374**. A second Wittig reaction forms vinyl chloride **375**. Deprotonation of the olefinic proton produces the vinyl carbene, which performs a C-H insertion α to the carbamate nitrogen; forming [5,5]-spirocycle **376**. Two-step oxidative cleavage of olefin **376** followed by silyl deprotection also effects aldol reaction to form the A ring. Di-mesylation and selective hydrogenation of the A ring mesylate provides ketone **377** in a similar manner to Nagumo, Kawahara and co-workers (*vide supra:* Scheme 3.12).

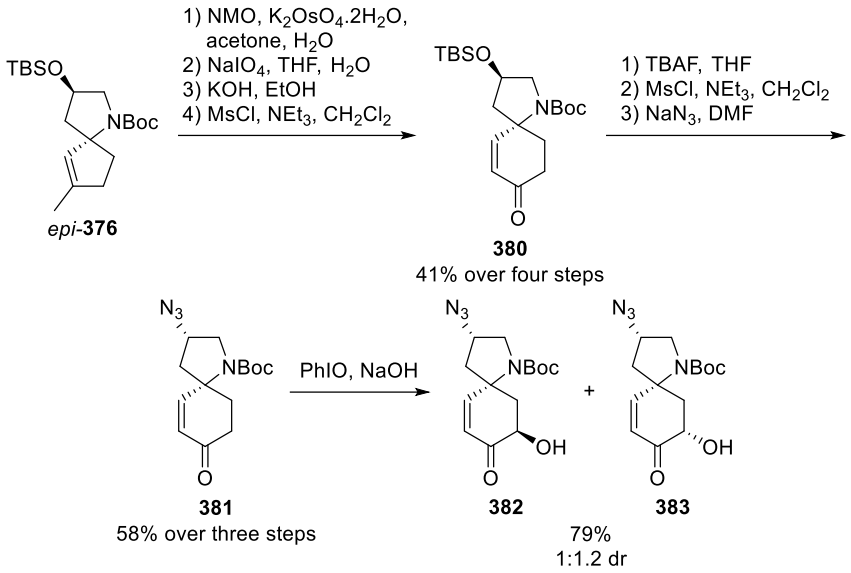
Nucleophilic inversion of the pyrrolidine mesylate stereocentre by sodium azide is followed by protection of the ketone to afford dioxolane **378**. Deprotection of the carbamate and *N*-alkylation with ethyl bromoacetate gives Kawahara's intermediate **379** (*vide supra:* Scheme 3.1).



*Scheme 3.13: Hayes's 2004 formal synthesis of (-)-TAN-1251A (**311a**)*[211]

Further research by the Hayes group has led to a partial synthesis of (+)-TAN-1251B (**311b**) which, to date, has only been fully synthesised by Snider *et al.* (Scheme 3.14).[212] The key step of this synthesis is the partially selective α-oxidation of the A ring ketone. [5,5]-Spirocycle *epi*-**376** was subjected to oxidative cleavage of the olefin, and elimination of the redundant hydroxyl group to afford ketone **380**. The resulting olefin was not reduced, as in the Hayes group synthesis of (-)-TAN1251A (**311a**). Silyl deprotection, and mesylation of the newly formed alcohol allows for a substitution to afford azide **381**. α-Oxidation of ketone **381** by iodosobenzene yields α-hydroxyketones **382** and **383** in a very good yield (79%) and a 1:1.2 diastereomeric ratio respectively. Two undesired epimers, which are formed in the synthesis of (+)-TAN1251B (**311b**) by Snider *et al.* (*vide supra*: Scheme 3.6), are prevented from forming by the residing olefin; protecting one side of the cyclohexane ring from oxidation. The minor diastereomer, α-hydroxyketone **382**, has the required

stereochemistry for the synthesis of (+)-TAN1251B (**311b**), and is closely related to intermediates seen in the Hayes group's synthesis of (-)-TAN-1251A (**311a**, *vide supra:* Scheme 3.13).

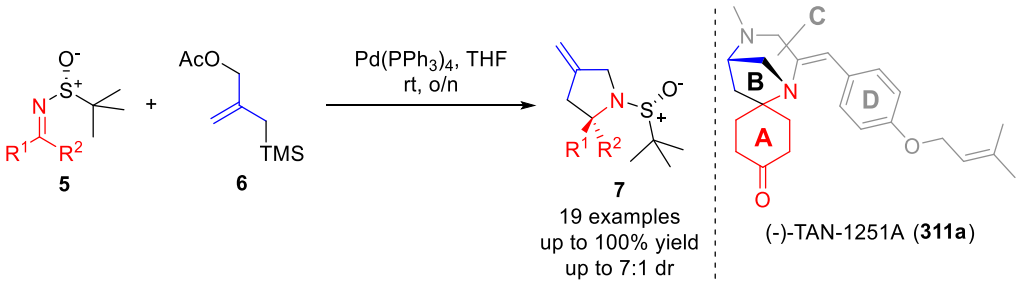


*Scheme 3.14: Efforts towards the synthesis of (+)-TAN-1251B (**311b**) by the Hayes group*[212]

3.3 Retrosynthetic analysis of (±)-TAN-1251A

Having studied the previous syntheses of TAN-1251 alkaloids (**311a-d**), it was proposed that a more expedient, elegant and scalable synthesis of (±)-TAN-1251A (**311a**) could be effected using an ABC approach. Previous ABC approaches required between 4 and 10 steps to form the B ring (Snider and Kawahara, *vide supra:* Scheme 3.3 and Scheme 3.1 respectively). It was envisaged that a more rapid synthesis of the B ring could be performed in only two steps by utilising a novel [3+2] cycloaddition developed within the Stockman Group.[18,213]

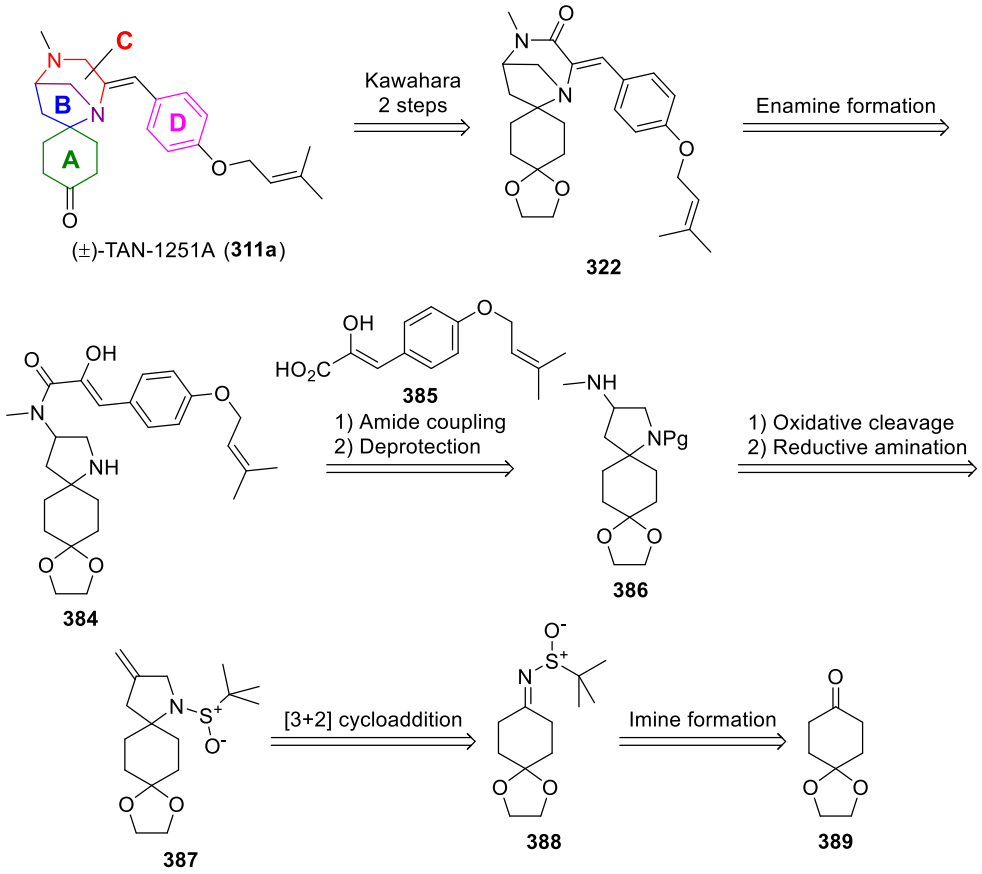
Previous research within the Stockman group has shown that sulfinimines **5** can be transformed into methylene pyrrolidines **7** in one operationally simple step (Scheme 3.15). The methylene moiety provides a handle to introduce functionality in the correct position of the pyrrolidine ring, as depicted. The reaction is performed under palladium catalysis, using Trost's TMM reagent (**6**). No heating or cooling is required, and the desired products are formed in up to 100% chemical yield and in high diastereomeric ratios. While successful with sulfinimines formed from either aldehydes or ketones, highest diastereomeric excesses were produced with sulfinyl aldimines.



*Scheme 3.15: **Palladium-catalysed formation of diastereomerically enriched methylene pyrrolidines 7 from sulfinimines 5 and Trost's TMM reagent (6)**[18]*

A retrosynthesis was envisaged from Kawahara's intermediate **322**, used in the synthesis of (±)-TAN-1251A (**311a**, Scheme 3.16, *vide supra:* Scheme 3.1). Formation of the C ring of Kawahara's intermediate **322** was proposed to be possible using an intramolecular condensation of the amine and enol of compound **384**. Amide **384** could be produced by the coupling of arylpyruvic acid **385** with mono-protected diamine **386**. Synthesis of diamine **386** would be undertaken by performing oxidative cleavage and reductive amination of methylene pyrrolidine **387**. The key step in this synthesis is the transformation of sulfinimine **388** into methylene pyrrolidine **387**.[18] Such a route will therefore join only a few syntheses which form the central 5,6-spirocentre using chemistries not involving iodine(III) reagents. The retrosynthesis

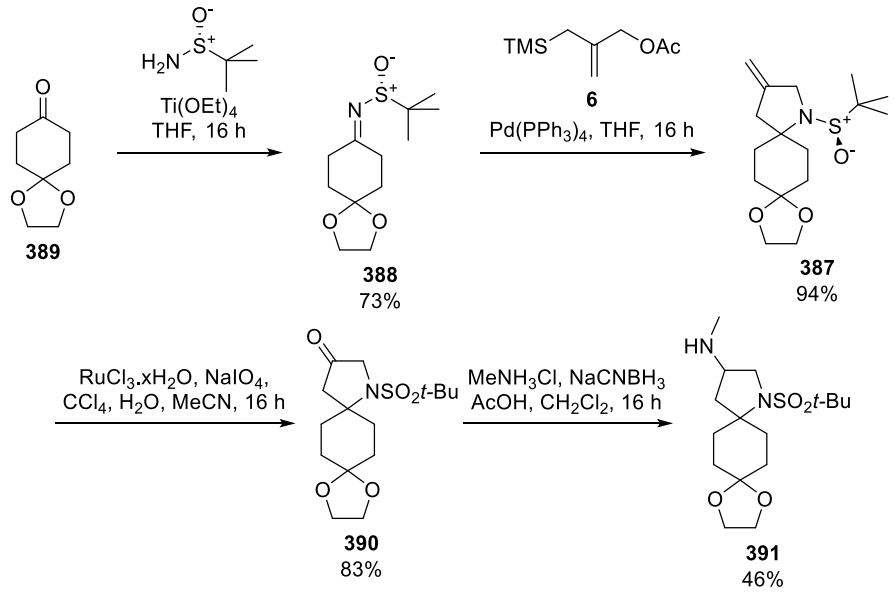
shown suggests that a formal synthesis of (±)-TAN-1251A (**311a**) could be undertaken in just 9 steps.



*Scheme 3.16: Retrosynthetic analysis of (±)-TAN-1251A (**311a**)*

3.4 Previous efforts towards the synthesis of (±)-TAN-1251A

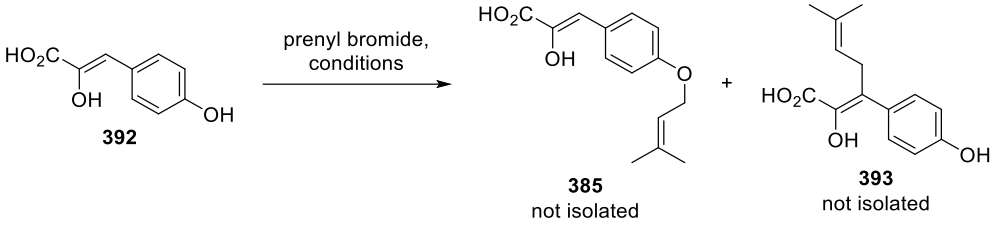
Prior work towards the synthesis of (±)-TAN-1251A (**311a**) within the Stockman group was undertaken by George Procopiou (Scheme 3.17).[213] Synthesis of sulfinimine **388** proceeded in good yield under conditions from the group of Ellman.[214] Palladium-catalysed [3+2] cycloaddition gave methylene-pyrrolidine **387** in 94% yield. Oxidative cleavage of the *exo*-methylene **387** was successful, however oxidation of the sulfinyl group was also observed; forming *t*-butyl sulfonamide **390**.[215] Sulfinyl oxidation was unfortunate since sulfur centre's chirality, which could have been used to produce an enantioselective synthesis, was removed. Reductive amination with methylamine hydrochloride provided racemic amine **391** in a modest yield of 46%.



*Scheme 3.17: **Synthesis of amine 391**. Work performed by George Procopiou*[213]

Efforts were also made towards the synthesis of an pyruvic acid fragment **385** by the prenylation of 4-hydroxyphenylpyruvic acid (**392**, Table 3.1).[213] A wide range of conditions were used to effect alkylation of the phenol, however a complex mixture of products was generally observed. In two cases (entries 3 and 8) mono-alkylation was observed, however benzylic alkylation product **393** was assigned as the major product.

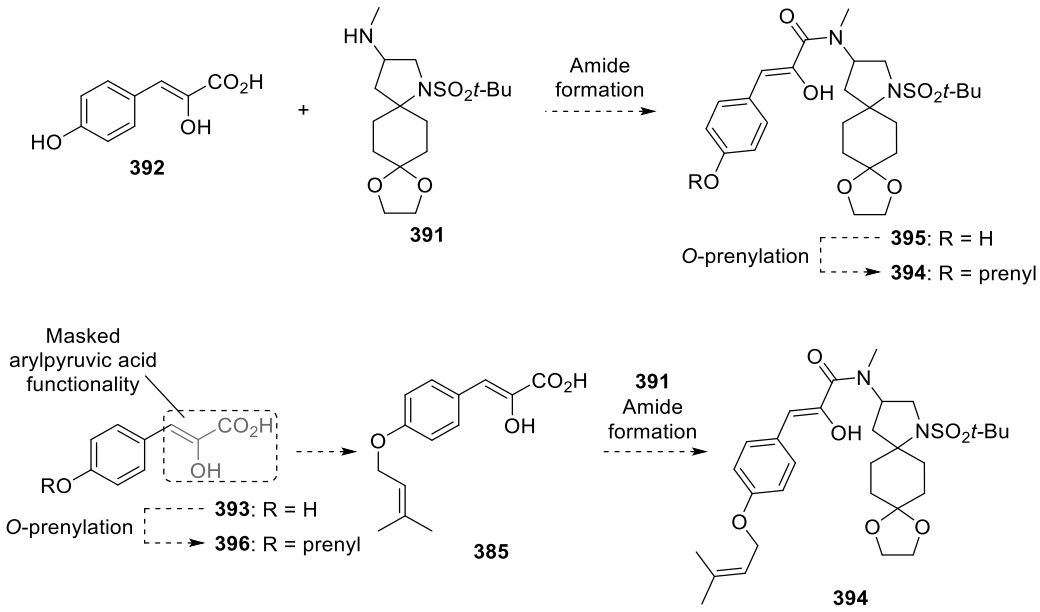
*Table 3.1: Attempts at the phenol-alkylation of 4-hydroxyphenylpyruvic acid (**392**)*[213]



Entry	Conditions	Comment
1	K_2CO_3, DMF, rt	aldol-type self condensation
2	K_2CO_3, MeCN, 0 °C	complex mixture
3	K_2CO_3, THF, -78 °C	alkylation observed at benzylic centre
4	Cs_2CO_3, THF, rt then reflux	complex mixture
5	Cs_2CO_3, THF, rt then reflux	complex mixture
6	NaH, THF, rt	complex mixture
7	NaH, THF, 0 °C	complex mixture
8	*n*-BuLi, THF, -78 °C	alkylation observed at benzylic centre
9	KHMDS, THF, -78 °C	complex mixture
10	Na_2CO_3, MeOH, -78 °C	complex mixture

3.5 Aims of this work

It was proposed that the aforementioned retrosynthesis of (±)-TAN1251A (**311a**) remained sound. Previous synthetic efforts have provided amine fragment **391**, however the synthesis of pyruvic acid fragment **385** remained unsolved. It was therefore aimed that the synthesis of a pyruvic acid fragment would be further investigated. Since attempts at phenol prenylation in the presence of pyruvic acid functionality had proved to be fruitless, a different approach was required (Scheme 3.18). It was thought that this could be possible through the coupling of pyruvic acid **392** with amine **391** prior to prenylation. Alternatively, a more complex synthesis of the fragment may be necessary, where the prenyl group is incorporated into a masked pyruvic acid **393**, which is either a protected pyruvic acid or a pyruvic acid precursor. Subsequent deprotection or synthesis of the pyruvic acid functionality would enable amide coupling with amine **391** to provide amide **394**.



*Scheme 3.18: Proposed route to amide **394***

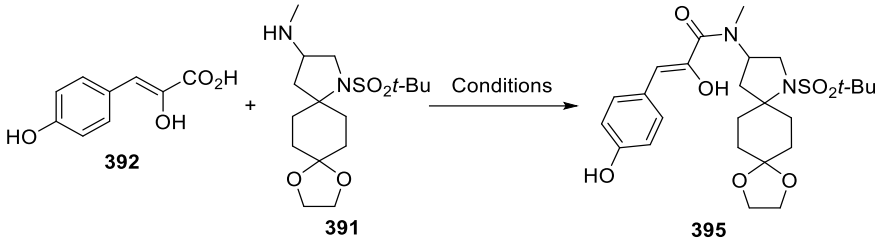
With amide **394** in hand, it was aimed that deprotection of the sulfonamide and intra-molecular condensation of the enol moiety with the piperidine nitrogen, to form the C ring, would be examined.

3.6 Synthesis and use of pyruvic acids in the synthesis of (±)-TAN1251A

3.6.1 Amide coupling of 4-hydroxyphenylpyruvic acid

The coupling of amine **391** and 4-hydroxyphenylpyruvic acid (**392**) was attempted (Table 3.2). Initially attempting the coupling using DCC, no product was observed by HRMS (entry 1). Coupling was observed by HRMS when HATU was used, however attempts to isolate amide **395** either by silica (entry 2) or C18-silica (entry 3) chromatography were unsuccessful.

*Table 3.2: Attempted synthesis of amide **395***

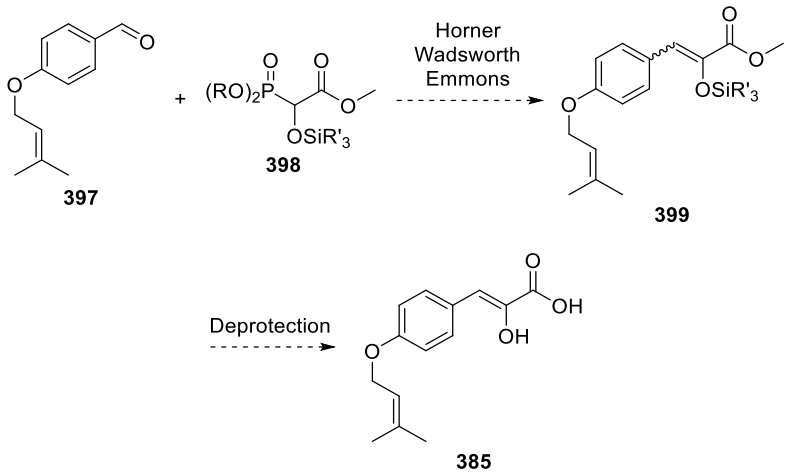


Entry	Conditions (equiv.)	Comment
1	**391** (1.0), **392** (1.0), DCC (1.0), DIPEA (2.1), CH_2Cl_2, THF, rt, 18 h	no amide **395** observed by HRMS
2	**391** (1.0), **392** (1.5), HATU (1.5), DIPEA (3.0), DMF, 0 °C to rt, 18 h	amide **395** identified by HRMS, however isolation was unsuccessful by silica gel chromatography
3	**391** (1.0), **392** (1.5), HATU (1.5), DIPEA (3.0), DMF, 0 °C to rt, 18 h	amide **395** identified by HRMS, however isolation was unsuccessful by manual C18-silica gel chromatography

It was thought that the difficulty seen in chromatographic purification was due to the two acidic sites on amide **395**: the phenol and enol moieties. It was proposed that the prenylation of the phenol prior to a coupling would aid chromatographic purification.

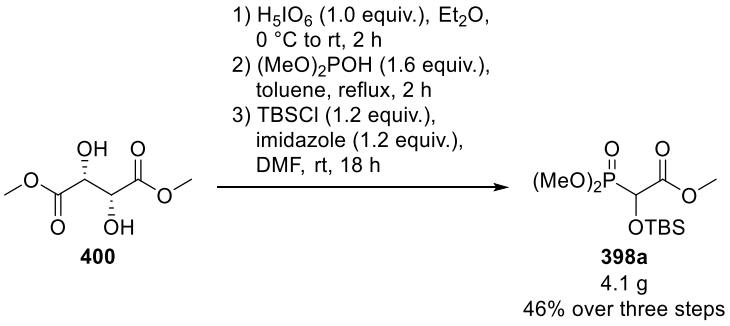
3.6.2 Arylpyruvic acid functionality *via* a silyl enol ether

Literature precedent from Nakamura suggested that prenyl aldehyde **397** could be reacted with an appropriate phosphonate ester **398** to form silyl enol ether **399** (Scheme 3.19).[216] It was thought that ester hydrolysis and removal of the silyl protecting group could generate required arylpyruvic acid **385**. Hence, synthesis of a suitable phosphonate ester **398** and prenyl aldehyde **397** was required.



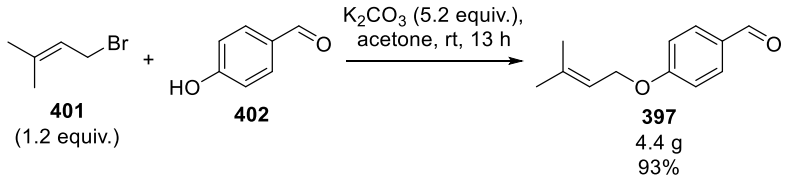
*Scheme 3.19: Proposed route to arylpyruvic acid **385** via a silyl enol ether **399***

Phosphonate ester **398a** was chosen as it has been previously been isolated by Nakamura (Scheme 3.20).[216] As such, synthesis was successfully completed in three steps from dimethyl-L-tartrate (**400**), to produce 4.1 g of phosphonate ester **398a**.[216]



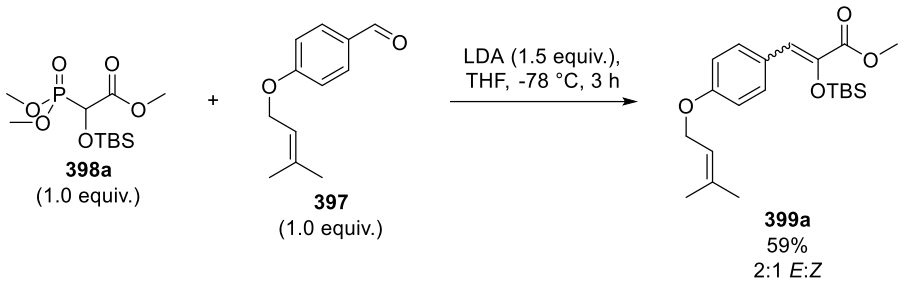
*Scheme 3.20: Synthesis of phosphonate ester **398a**[216]*

Synthesis of prenyl benzaldehyde **397** has been reported in several TAN-1251 alkaloid syntheses (*vide supra:* Section 3.2). A procedure from the group of Venkateswarlu was followed to obtain 4.4 g of prenyl aldehyde **397** in a 93% yield (Scheme 3.21).[217]



*Scheme 3.21: Synthesis of prenyl aldehyde **397***

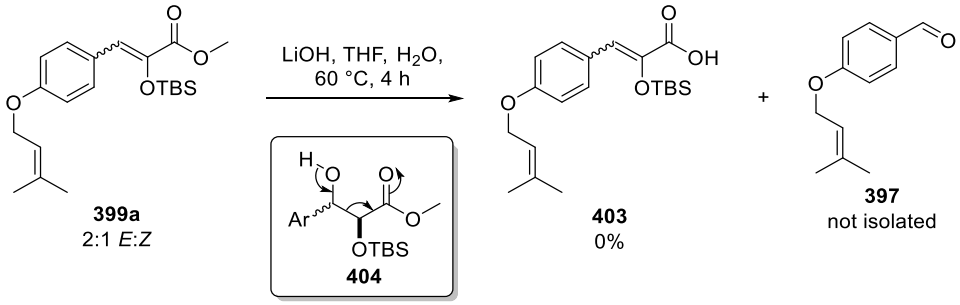
The reaction of prenyl aldehyde **397** with phosphonate ester **398a** under Horner-Wadsworth-Emmons conditions provided silyl enol ether **399a** as a 2:1 (*E*:*Z*) ratio of geometric isomers, which were not separated.



*Scheme 3.22: Horner-Wadsworth-Emmons reaction of phosphonate ester **398a** to form silyl enol ether **399a***

The hydrolysis of ester **399a** was attempted using lithium hydroxide in order to provide desired prenyl pyruvate fragment **403** (Scheme 3.23). Following acidification and extraction of the reaction mixture, the only product identified by ^{1}H NMR and HRMS was aldehyde **397**.

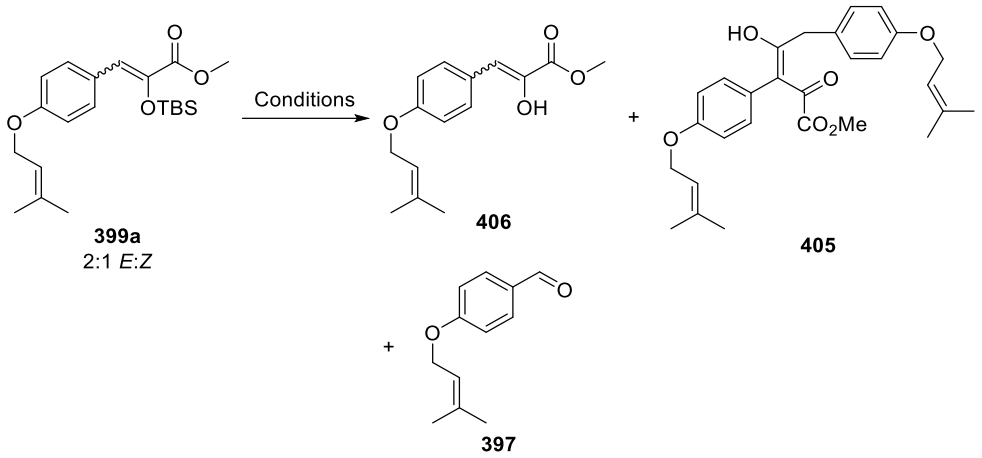
It was proposed that a 1,4-addition of hydroxide to the α,β-unsaturated ester forms alcohol **404**, which can undergo a retro-aldol reaction to form aldehyde **397**. Silyl-deprotection of ester **399a** prior to ester hydrolysis would make the benzylic position less electrophilic, and therefore could prevent decomposition by a 1,4-addition of hydroxide. As such, the deprotection of silyl enol ether **399a** by exposure to fluoride was envisaged.



*Scheme 3.23: Attempted deprotection of pyruvic acid precursor **399a***

Treatment of silyl enol ether **399a** with TBAF formed of a small amount of aldehyde **397** (16%) and larger amounts of what was tentatively assigned by ^{1}H NMR and HRMS as condensation product **405** (64%, Table 3.3, entry 1). While the silyl group was being removed, it was thought that water in the TBAF was causing decomposition of desired methyl pyruvate **406**. To counteract this suspected hydrolysis, anhydrous HF·pyridine was employed as a anhydrous fluoride source (entry 2). While desired methyl pyruvate **406** was identified by ^{1}H NMR and HRMS, it was found to be inseparable from aldehyde **397**. It could be possible that methyl pyruvate **406** was decomposing to aldehyde **397**, however this was not studied.

*Table 3.3: TBS deprotection of silyl enol ether **399a***



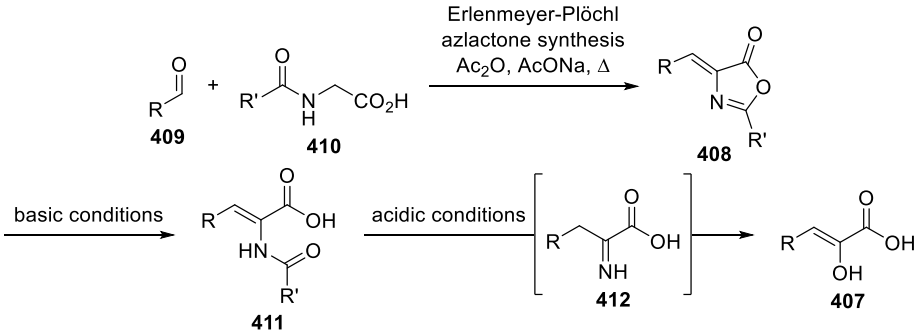
Entry	Conditions (equiv.)	Yield 406 (%)	Yield 405 (%)	Yield 397 (%)
1	TBAF (1.1), THF, rt, 30 min	0	64	16
2	HF·pyridine, pyridine, THF, rt, 1 h	45[a]	0	24[a]

*Notes: a) Conversion calculated based on ratio of aromatic peaks in the ^{1}H NMR spectrum of a mixure of **397** and **406**.*

Owing to the apparent inability to isolate methyl pyruvate **406**, it was deemed necessary to investigate the synthesis of arylpyruvic acid **385** by alternative means.

3.6.3 Arylpyruvic acid functionality *via* an azlactone

Synthesis of pyruvic acids **407** may also be performed through the hydrolysis of azlactones **408** (Scheme 3.24). The Erlenmeyer-Plöchl azlactone synthesis converts aldehydes **409** into azlactones **408** by a series of dehydration reactions with *N*-acylglycines **410**.[218–222] Hydrolysis of an azlactone **408** to form a pyruvic acid **407** is typically undertaken using basic conditions, to form an enamide **411**, followed by acidic conditions, to cleave the amide bond and hydrolyse imine **412**.

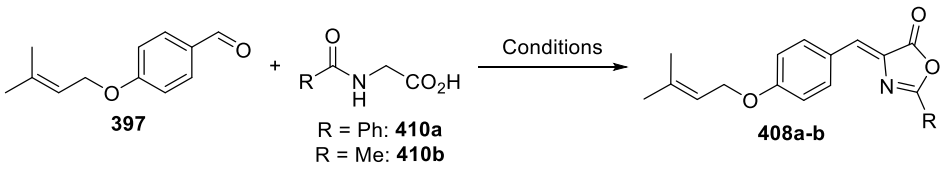


*Scheme 3.24: Synthesis of pyruvic acids **407** via azlactones **408**[218–222]*

With prenyl aldehyde **397** in hand (*vide supra:* Scheme 3.21), the synthesis of azlactones **408a-b** was investigated using *N*-benzoyl glycine (**410a**) and

N-acetylglycine (**410b**, Table 3.4). Synthesis of azlactone **408a** was achieved in a 29% yield using equimolar amounts of aldehyde **397** and acid **410a** with acetic anhydride and sodium acetate (entry 1).[223] The same conditions were employed with *N*-acetylglycine (**410b**) in order to synthesise azlactone **408b**. Unfortunately, azlactone **408b** was inseperable from aldehyde **397** by column chromatography (entries 2 and 3). Hence, to produce pure azlactone **408a**, full conversion of aldehyde **397** was required. This was achieved by using 2 equivalents of both *N*-acetylglycine (**410b**) and sodium acetate (entries 4 and 5) to give azlactone **408b** in an average yield of 46%. The use of microwave conditions with silica gel was not successful (entry 6).[224] This was attributed to the recorded temperature rising rapidly above the safety limit of the apparatus since heat transfer within the vessel was inefficient, and hence the reaction was not heated sufficiently.

*Table 3.4: Synthesis of azlactones **408a-b***

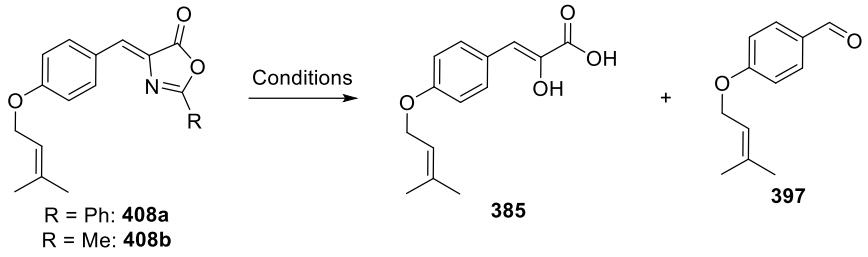


Entry	Conditions (equiv.)	R	Product	Yield 408 (%)	Comments
1	Ac_2O (3.0), AcONa (1.0), **410a** (1.0), **397** (1.0), 95 °C, 3 h	Ph	**408a**	29	
2	Ac_2O (10), AcONa (1.0), **410b** (1.0), **397** (1.0), 100 °C, 23 h	Me	**408b**	-[a]	1:0.6 ratio of **408b**:**397** by crude ^{1}H NMR
3	Ac_2O (3.0), AcONa (1.1), **410b** (1.1), **397** (1.0), 100 °C, 26 h	Me	**408b**	45[b]	1:0.3 ratio of **408b**:**397** by ^{1}H NMR
5	Ac_2O (3.0), AcONa (2.0), **410b** (2.0), **397** (1.0), 100 °C, 20 h	Me	**408b**	42	no aldehyde **397** seen by HRMS or ^{1}H NMR
6	Ac_2O (3.0), AcONa (2.0), **410b** (2.0), **397** (1.0), 100 °C, 16 h	Me	**408b**	49	no aldehyde **397** seen by HRMS or ^{1}H NMR
4	Ac_2O (3.2), AcONa (1.0), **410b** (1.0), **397** (1.0), silica gel (0.5 g/mmol), 120 °C, µW, 3 min then 250 °C, µW, 2 x 3 min	Me	**408b**	-[a]	complex mixture of products seen by HRMS and ^{1}H NMR

Notes: a) not isolated; b) calculated based on purity by ^{1}H NMR.

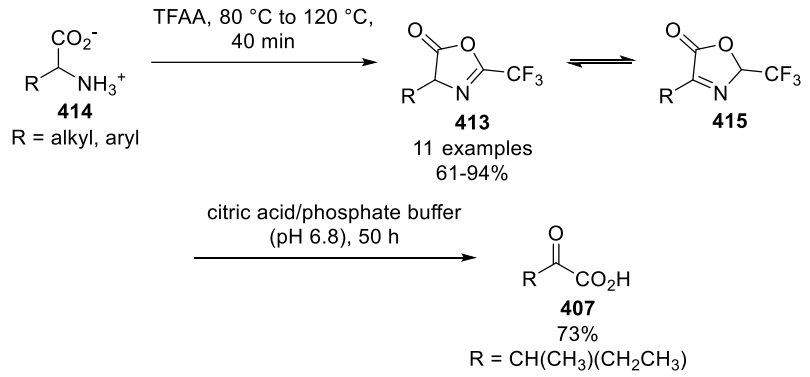
Hydrolysis of phenyl azlactone **408a** and methyl azlactone **408b** was attempted to form arylpyruvic acid **385** (Table 3.5). Initial attempts were made with phenyl azlactone **408a**, which was refluxed in aqueous sodium hydroxide before acidification and extraction (entry 1).[223] Formation of aldehyde **397** was observed by HRMS during the course of the reaction. Sodium bisulfite was used, as in the literature procedure, to remove aldehyde **397** from the reaction mixture. However, following acidification a low mass recovery was noted and a complex mixture of products was observed by ^{1}H NMR. Repeating the same procedure without using sodium bisulfite produced only traces of aldehyde **397** by ^{1}H NMR (entry 2). While pyruvic acid **385** was observed by HRMS, analysis by ^{1}H NMR showed only traces of what was tentatively assigned as pyruvic acid **385**, with large amounts of a product with only aryl-peaks. Proposing that the basic hydrolysis was causing decomposition of the pyruvic acid, azlactone **408a** was heated under reflux in 1 M HCl (entry 3). Unfortunately, no conversion of azlactone **408a** was observed. It was thought that methyl azlactone **408b**, would be easier to hydrolyse than phenyl azlactone **408a** due to decreased conjugation of the azlactone. Hence, the hydrolysis of methyl azlactone **408b** to arylpyruvic acid **385** was attempted. Following another literature procedure for the hydrolysis of azlactones, methyl azlactone **408b** was subjected to basic conditions followed by heated acidic conditions(entry 4).[225] Unfortunately, a complex mixture of products was observed by both ^{1}H NMR and HRMS. A hydrolysis protocol developed by Douglas and Gulland, which employs barium hydroxide, was also followed, however no desired arylpyruvic acid **385** was observed by HRMS (entry 5).[226]

*Table 3.5: Attempted hydrolysis of azlactones **408a-b***



Entry	R	Conditions (equiv.)	Comments
1	Ph	20% $NaOH_{(aq)}$, 110 °C, 2 h then $NaHSO_3$, filter, then 10% $HCl_{(aq)}$, extraction	Formation of aldehyde **397** observed by HRMS during reaciton. Low mass recovery
2	Ph	20% $NaOH_{(aq)}$, 110 °C, 3 h, then $HCl_{(aq)}$, pH 3, extraction	Product observed by HRMS. Complex mixture by ^{1}H NMR
3	Ph	1.0M $HCl_{(aq)}$, 110 °C, 13 h	Starting material recovered
4	Me	1 M $NaOH_{(aq)}$, 90 °C, 20 min, then $HCl_{(aq)}$ pH 2, 100 °C, 20 h	Complex mixture of products
5	Me	$Ba(OH)_2$ (12), EtOH:H_2O (9:1), 105 °C, 20 h	No product **385** observed by HRMS

Looking to facilitate azlactone hydrolysis, the strategy of Weygand *et al.* was explored (Scheme 3.25). They synthesised a range of trifluoromethyl azlactones **413**, which could be hydrolysed under neutral conditions, to synthesise a range of pyruvic acids **407**.[227]

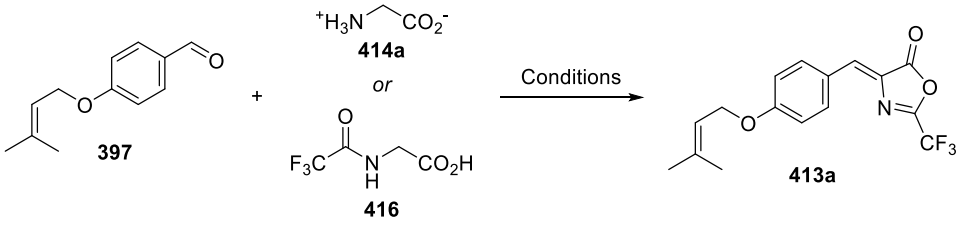


*Scheme 3.25: Weygand approach to pyruvic acids **407** via trifluoromethyl oxazolones **413**[227]*

It was hoped that the treatment of glycine with trifluoroacetic anhydride (TFAA) in the presence of aldehyde **397** would *N*-trifluoroacetyl-protect glyine (**414a**) before forming azlactone **413a** (Table 3.6). Performing the reaction, no product was observed by either ^{1}H NMR or HRMS (entry 1). Following addition of the TFAA, it was observed that the reaction mixture turned black and a significant exotherm was noted. It was proposed that hydrolysis of TFAA formed TFA, which was decomposing something in the reaction mixture. Sodium trifluoroacetate was added to reduce the acidity of the reaction mixture and prevent this decomposition, however similar results were

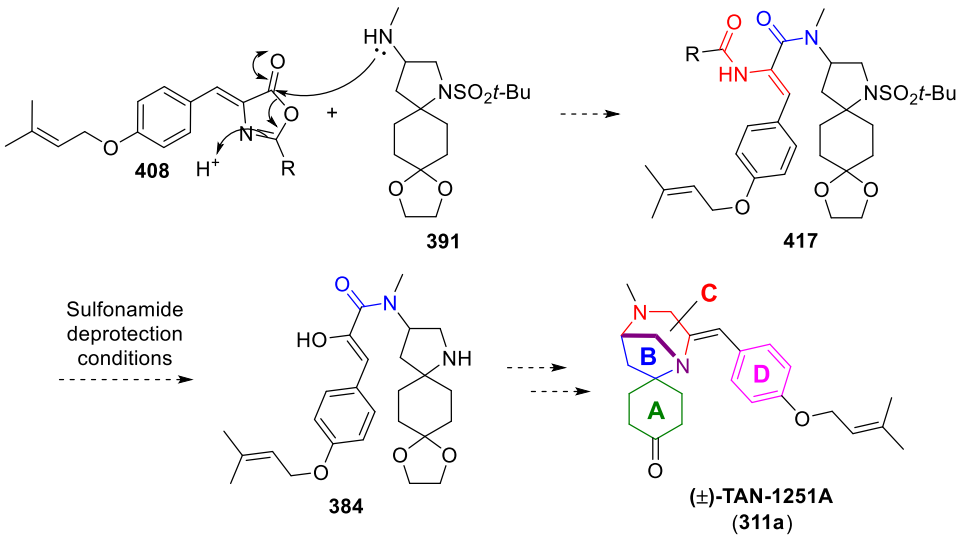
observed (entry 2). Postulating that the prior trifluoroacetylation of glycine would aid azlactone formation, *N*-trifluoroacetylglycine **416** was treated with acetic anhydride and sodium acetate in the presence of aldehyde **397** (entry 3). Unfortunately, no desired azlactone **413a** was observed by HRMS.

*Table 3.6: Attempted synthesis of trifluoromethyl azlactone **413a***



Entry	Conditions (equiv.)
1	TFAA (3.0), **414a** (2.0), **397** (1.0), 100 °C, 1 h
2	TFAA (5.0), CF_3CO_2Na (2.0), **414a** (2.0), **397** (1.0), 100 °C, 21 h
3	Ac_2O (3.0), AcONa (2.0), **416** (2.0), **397** (1.0), 100 °C, 21 h

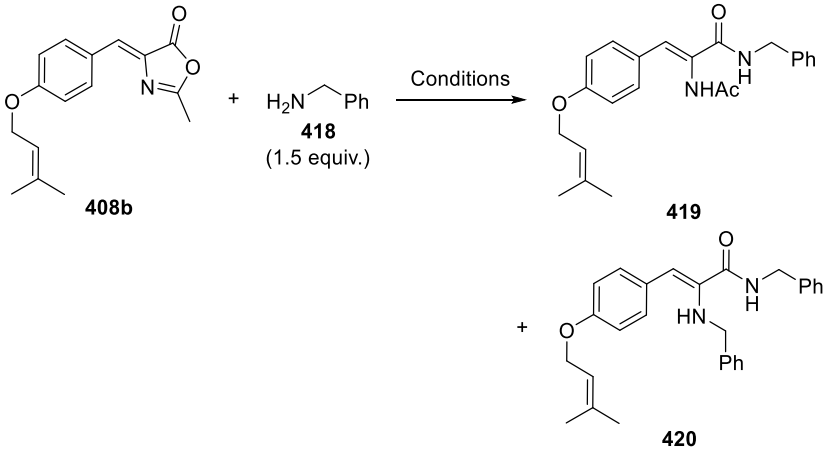
It was concluded the hydrolysis of azlactones was incompatible with the synthesis of arylpyruvic acid **385**. Further investigation into known reactivities of azlactones allowed for the hypothesis of a nucleophilic attack of amine **391** on an azlactone **408** (Scheme 3.26). Such a reaction would form amide **417**, with the required amide bond (blue). It was hoped that the acidic conditions required to deprotect the sulfonamide would also cleave the enamide moiety (red) rather than the central amide (blue, *vide infra*: Scheme 3.27).



*Scheme 3.26: Proposed formation of amide **417** from azlactone **408** and amine **391***

The model reaction of azlactone **408b** with benzylamine (**418**) as a substitute for amine **391** was attempted to test the potential for this route (Table 3.7). Performing the reaction in refluxing toluene, isolation of amide **419** in a 21% yield exhibited potential for the genuine reaction to work (entry 1). A peak which was tentatively assigned as enamine **420** was observed by HRMS analysis of the crude reaction mixture. This provides evidence to support the proposed approach, suggesting that the C ring could be formed from condensation of the enamide with a proximal amine. It was thought that the addition of a mild base may aid the reaction by facilitating proton transfer and hence producing a higher chemical yield. The addition of potassium carbonate produced a small increase in yield of amide **419**, with enamine **420** again being observed by HRMS (entry 2).

*Table 3.7: Model coupling of azlactone **408a** with benzylamine (**418**)*

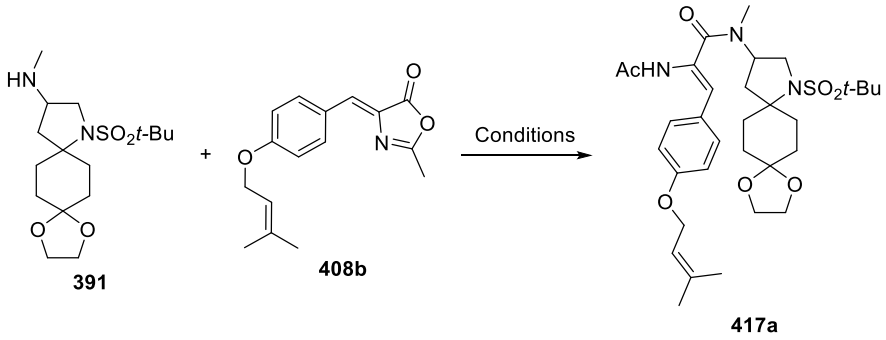


Entry	Conditions (equiv.)	Yield 419 (%)	Comments
1	$BnNH_2$ (1.5), toluene, 115 °C, 16 h	21	enamine **420** observed by HRMS but not isolated
2	$BnNH_2$ (1.5), K_2CO_3 (2.0) toluene, 115 °C, 16 h	25	enamine **420** observed by HRMS but not isolated

Having produced encouraging results in the model system, investigation was directed at the coupling of amine **391** with azlactone **408b** to produce amide **417a** (Table 3.8). The conditions adapted from the model study afforded no observable product by HRMS or TLC following heating under microwave irradiation at 120 °C for 1 hour (entry 1). Proposing that the insolublity of potassium carbonate in toluene was inhibiting its basic action, triethylamine was added and the reaction was subjected to the same heating conditions. Following workup and chromatography, amide **417a** was isolated in a 25% yield. The use of DME instead of toluene was tested to see whether a more polar solvent would increase yield (entry 2). After one hour under microwave irradiation, an 11% yield of amide **417a** was isolated. To determine whether the

azlactone could be activated by the presence of an acid, camphorsulfonic acid (CSA) was added (entry 3). Unfortunately, no conversion of azlactone **408b** was observed, presumably as amine **391** was protonated, and therefore made unreactive, by the acidic conditions. Reaction of the fragments in chloroform for 2 days provided amide **417a** in 39% yield (entry 4).[228] A similar yield was obtained in ethanol with catalytic amounts of acetic acid (entry 5).[229] The best yield of amide **417a** was obtained in acetonitrile; conditions from Yampolsky and co-workers (entry 6).[230] Amide **417a** was obtained in a 67% yield at room temperature. It was proposed that heating the reaction may increase yield of amide **417a**. When the same reaction was performed at 90 °C, only a slight increase in yield of amide **417a** was observed (69%, entry 7).

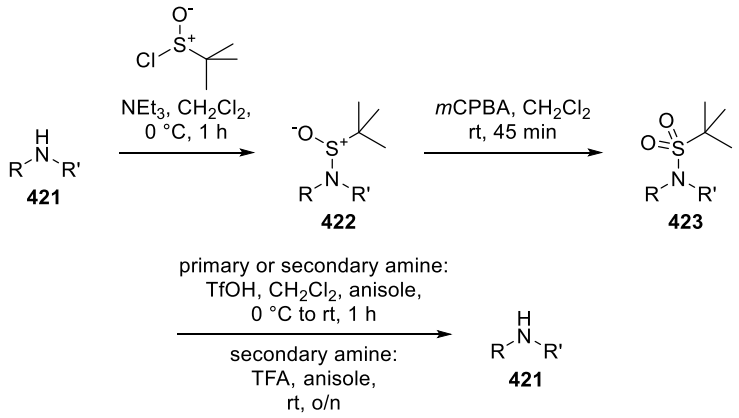
*Table 3.8: Amide coupling to form enamide **417a***



Entry	Conditions (equiv.)	Yield 417a (%)
1	K_2CO_3 (2.0), toluene, 120 °C, µW, 1 h, then NEt_3 (2.0), 120 °C, µW, 1 h	25
2	K_2CO_3 (2.0), DME, 120 °C, µW, 1 h	11
3	CSA (0.2), DME, 120 °C, µW, 1 h	-
4	$CHCl_3$, rt, 2 d	39
5	AcOH (1 drop), EtOH, 85 °C, µW, 11 h	40
6	MeCN, rt, 24 h	67
7	MeCN, 90 °C, 22 h	69

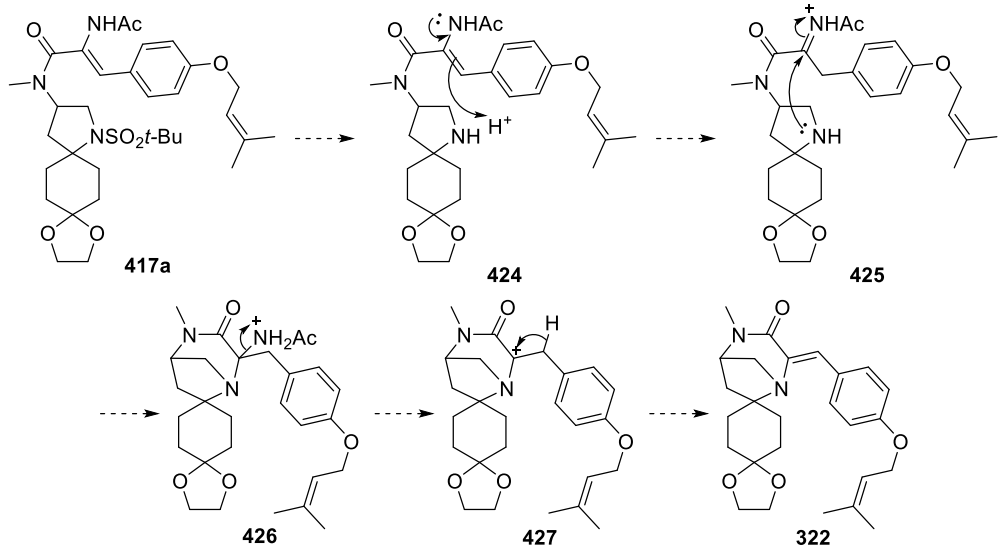
Having amide **417a** in hand, deprotection of the *t*-butyl sulfonamide was examined. These moieties were first reported for their use as amine protecting groups by the group of Weinreb, and have been called Bus groups (Scheme 3.27).[215] Amines **421** are protected as sulfinimines **422**, before oxidation using *m*CPBA affords *t*-butylsulfonamides **423**. The deprotection of primary and secondary *t*-butylsulfonamides **423** can be achieved with triflic acid and anisole in CH_2Cl_2.

Secondary *t*-butylsulfonamides **423** can also be deprotected using less acidic conditions: anisole in TFA.



*Scheme 3.27: General conditions for the protection and deprotection of amines **421** as t-butylsulfonamides **423***[215]

It was hoped that, following deprotection of *t*-butylsulfonamide **417a**, the acidic conditions would facilitate the tautomerisation of enamide **424** to acetyl iminium ion **425** (Scheme 3.28). A 6-*exo*-trig cyclisation of the pyrrolidine nitrogen onto the acyl iminium ion could then form C ring of the 1,4-diazabicyclo[3.2.1]octane system. Elimination of acetamide from aminal **426** could form enamine **322**.

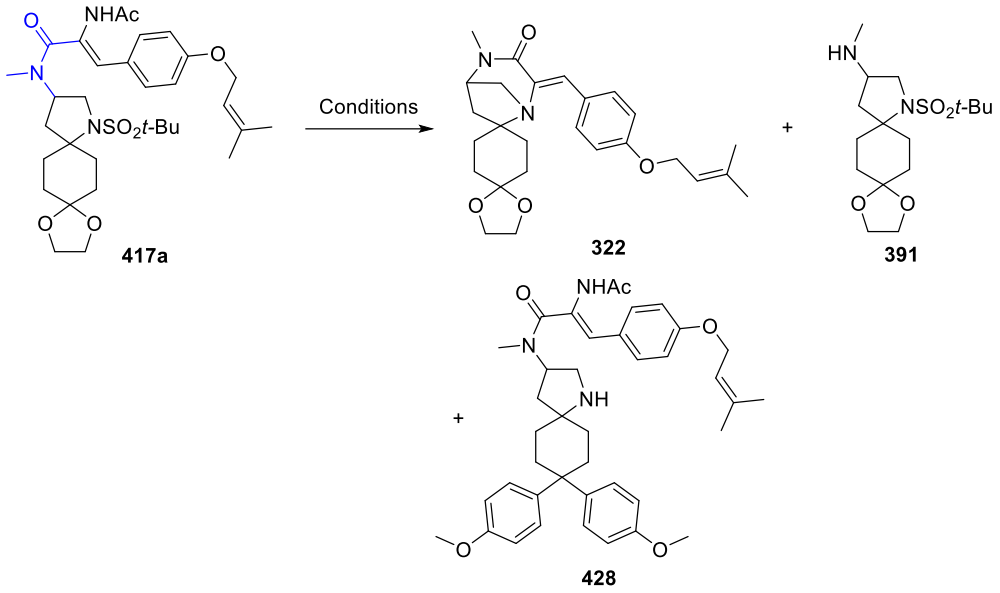


*Scheme 3.28: Proposed strategy towards tricyclic intermediate **322***

Deprotection of sulfonamide **417a** was attempted with the aim of providing tricyclic intermediate **322**. (Table 3.9). Following exposure of sulfonamide **417a** to triflic acid and anisole, analysis by ^{1}H NMR showed neither *t*-butyl peaks nor characteristic prenyl peaks (entry 1). It was inferred that deprotection of both the sulfonamide and prenyl group were occurring, and no desired product **322** was observed by HRMS. It was proposed that the prenyl group was being deprotected by hydrolysis due to traces

of water, either in the reaction mixture or during the quench of the reaction with aqueous sodium hydroxide solution. Attempting to prevent this hydrolysis, both anisole and CH_2Cl_2 were dried by distillation (CaH) and triflic acid was added as a solution in anhydrous CH_2Cl_2 to facilitate handling (entry 2). Furthermore, to prevent introduction of water before the reaction mixture was fully quenched, the quench was carefully performed with anhydrous potassium carbonate. Aqueous sodium hydroxide was only added when the reaction mixture had cooled to room temperature and was homogenous in appearance. Under these rigorously dry conditions, deprotection of the prenyl group was prevented and sulfonamide deprotection was noted. The formation of diarylmethane **428** was however observed in significant amounts by ^{1}H NMR and HRMS. It was thought that conditions commonly used in the deprotection of sulfinamides may be more effective. The use of anhydrous HCl in CPME produced amine **391**, observed by both ^{1}H NMR and HRMS (entry 3). This suggests that the acidic conditions caused the hydrolysis of the central amide of compound **417a** (blue).

*Table 3.9: Attempts at sulfonyl-deprotection of amide **417a***

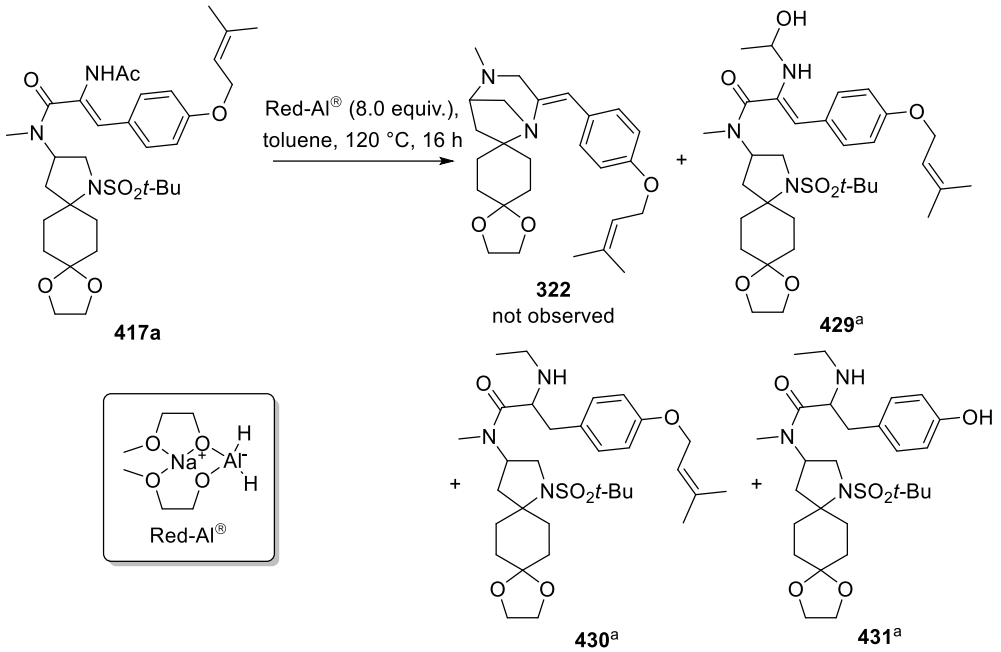


Entry	Conditions (equiv.)	Notes
1	TfOH (ca. 3.0), anisole (20), CH_2Cl_2, 0 °C, 40 min, then quench with NaOH (1.0 M)	^{1}H NMR shows no *t*-butyl group, however no prenyl group either. No product **322** identified by HRMS
2	TfOH (0.2 M in CH_2Cl_2, 6.0), anisole (20), CH_2Cl_2, 0 °C, 1 h, then quench with $K_2CO_{3(s)}$	Complex mixture observed by HRMS, including diarylmethane **428.** No desired product **322** observed. Complete removal of prenyl group noted by ^{1}H NMR
3	HCl (2 M in CPME, 1.0), CH_2Cl_2, rt, 1.5 h	Amide **391**, but no product **322** observed by HRMS

While the deprotection of sulfonamide **417a** was observed under acidic conditions, competing side reactions such as the diarylation of the dioxolane and deprotection of the prenyl group led to the belief that this was going to be a troublesome reaction to optimise for the given substrate.

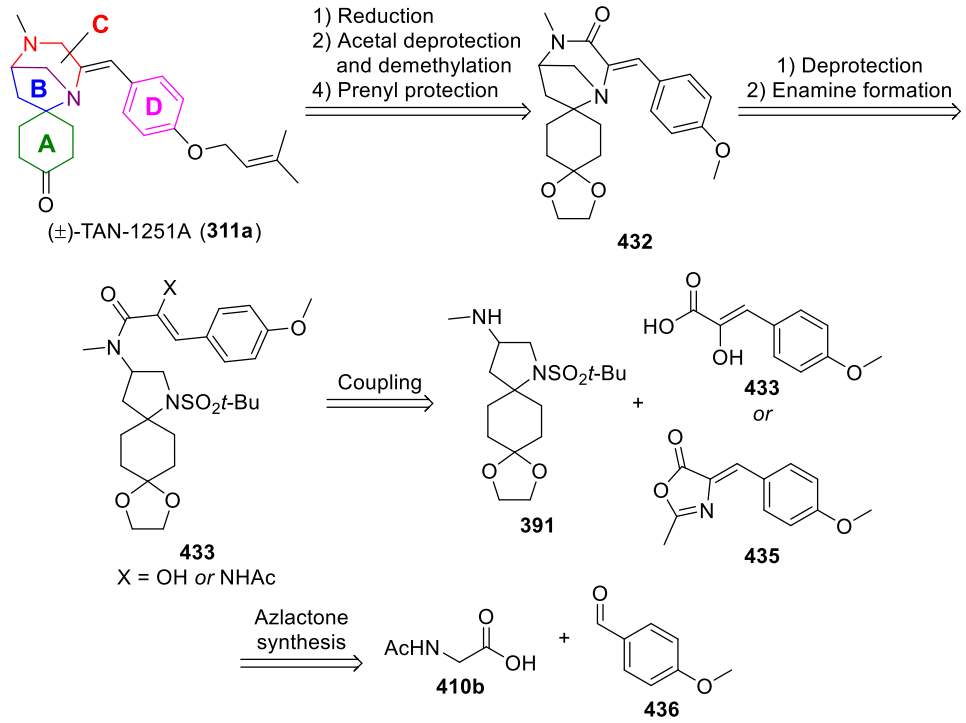
Seeking better results using established reductive methods to deprotect sulfonamide **417a**, the use of sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al®) was explored (Scheme 3.29).[231] Exposure of sulfonamide **417a** to Red-Al® initially produced effervescence. Analysis by HRMS prior to heating of the reaction mixture showed the formation of a mixture of hemiaminal **429** and amine **430**. Reduction was attributed to the acetamide due to its greater steric availability and higher degree of electrophilicity compared to the central α,β-unsaturated amide. Proceeding to heat the reaction mixture under reflux, HRMS indicated that sulfonamide deprotection was

not occurring. Deprotection of the prenyl group was noted, with HRMS indicating the formation of phenol **431** (Scheme 3.29).



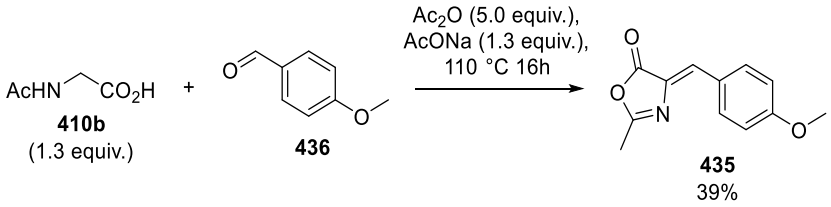
Scheme 3.29: Attempted reductive sulfonamide deprotection. Notes: a) tentatively assigned by HRMS

Due to a lack of material to continue current studies, it was proposed that more material should be brought through. The opportunity was taken to revise the current synthetic route based upon the learnings already presented (Scheme 3.30). It was proposed that a protected phenol would prevent the issues encountered with instability of the prenyl group. It was hoped that a methyl-protected phenol would provide the required stability throughout the synthesis. Furthermore, late-stage reduction and deprotection of the methyl ether **432** may conveniently also deprotect the acetal. Phenol prenylation could provide the functionality required for a total synthesis of (±)-TAN-1251A (**311a**). Amide **433** would be synthesised from arylpyruvic acid **434**, which has been previously isolated from the hydrolysis of azlactone **435**,[232] and amine **391**. The direct coupling of amine **391** with azlactone **435** could also be explored if necessary. Hence, the synthesis of azlactone **435** was required to be used in the synthesis of amide **433**.



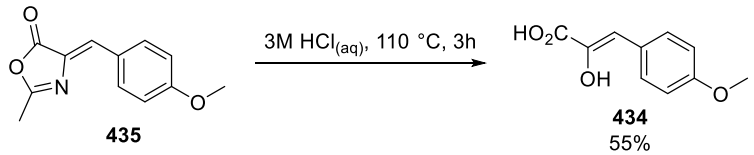
*Scheme 3.30: **Revised retrosynthetic analysis of (±)-TAN-1251A (311a)***

The synthesis of azlactone **435** from *para*-anisaldehyde (**436**) was performed using previously described conditions (Scheme 3.31, *vide supra:* Section 3.6.3).



*Scheme 3.31: **Synthesis of O-methyl azlactone 435***

Hydrolysis of azlactone **435** to arylpyruvic acid **434** was performed under acidic conditions (Scheme 3.32).[232] Crystallisation of the product from the reaction mixture, followed by filtration and trituration (1:1 EtOAc:MeOH) afforded analytically pure pyruvic acid **434**.

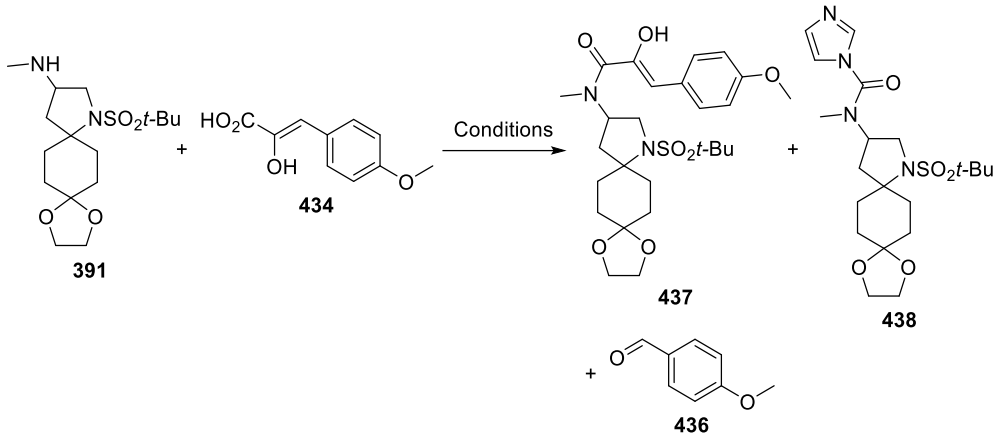


*Scheme 3.32: **Synthesis of 4-methoxyphenylpyruvic acid 434***

The coupling of pyruvic acid **434** with amine **391** to form amide **437** was attempted (Table 3.10). Use of CDI as a coupling reagent only showed formation of urea **438**, suggesting that pyruvic acid **434** is insufficiently nucleophilic (entry 1). Employing HATU, small amounts of aldehyde **436** were isolated, presumably due to the basic

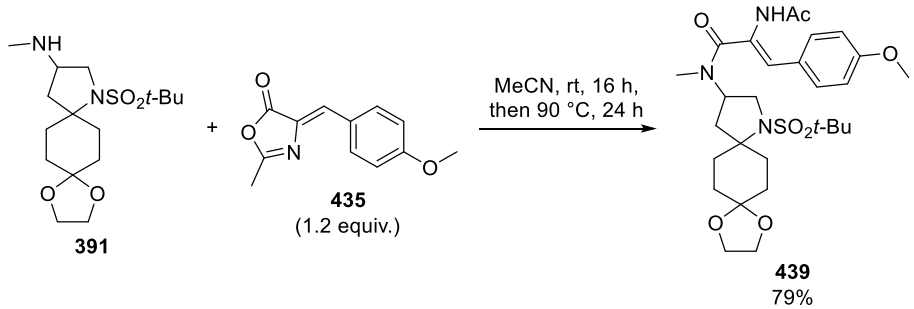
decomposition of pyruvic acid **434**, and again no desired amide **437** was observed by HRMS (entry 2).

*Table 3.10: Amide coupling of amine **391** with pyruvic acid **434***



Entry	Conditions (equiv.)	Comments
1	**434** (1.0), CDI (2.0), THF, 70 °C , 1 h then **391** (2.5), 50 °C, 22 h	No desired product **437** observed by HRMS. Only urea **438** and amine **391** observed by HRMS.
2	**391** (1.2), **434** (1.0), HATU (1.2), DIPEA (3.0), DMF, rt, 20 h	No desired product **437** observed by HRMS. Aldehyde **436** isolated in 11% yield.

Proceeding to attempt the coupling of the amine **391** with azlactone **434**, previously optimised conditions provided amide **439** in a 79% yield (Scheme 3.33, *vide supra*: Table 3.8).

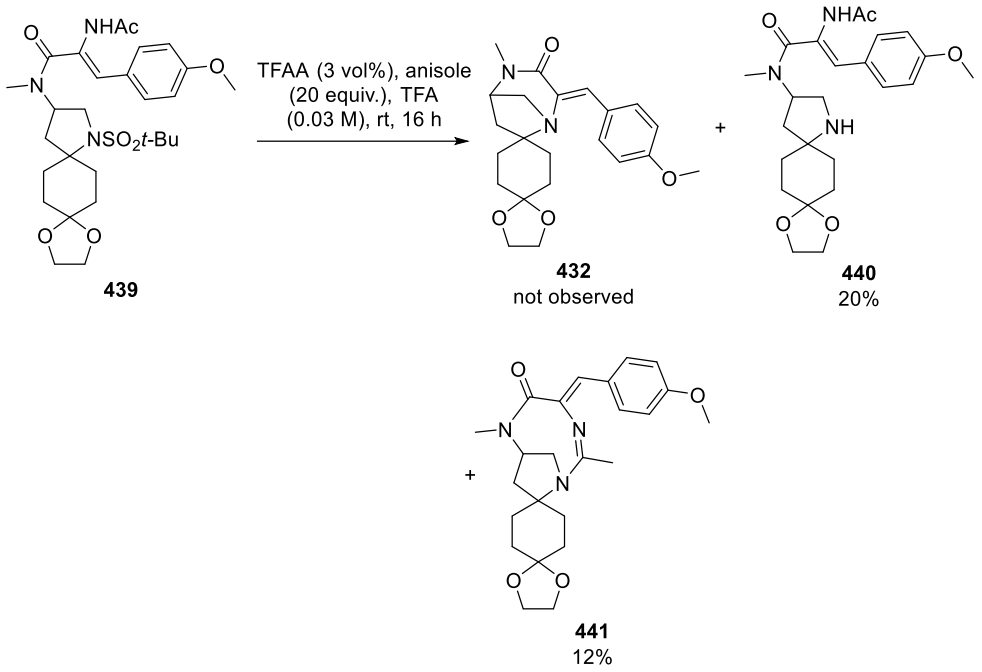


*Scheme 3.33: Formation of amide **439** from azlactone **435***

With amide **439** in hand, attention was directed towards its sulfonamide deprotection in order to form enamine **432** (Scheme 3.34). Since the use of triflic acid in the deprotection of a similar sulfonamide **417a** formed a number of by-products (*vide supra:* Table 3.9), the use of TFA and anisole was investigated (*vide supra:* Scheme 3.27). Building on experiences using triflic acid, it was realised that dry conditions

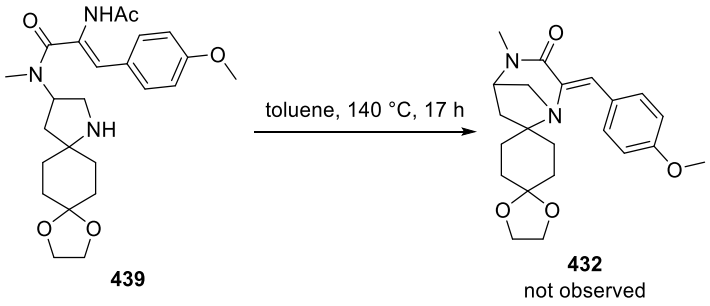
would be preferable to prevent undesired side reactions. It was envisaged that small amounts of TFAA would dry the TFA prior to the required reaction.

On exposure of sulfonamide **439** to the TFA with TFAA, amine **440** was isolated in a 20% yield, showing that desulfonylation was occurring. No desired lactam **432** was observed by HRMS. It would appear that while the deprotection is effective, the tautomerisation and cyclisation to form the desired product do not occur under these reaction conditions. Small amounts of byproduct **441** containing an interesting 1,3,6-triazabicyclo[5.2.1]decane core were isolated and tentatively assigned by HRMS and ^{1}H NMR. Presumably this was formed from the cyclisation and dehydration of amine **440** with excess TFAA. When this reaction was repeated to bring through material, no desulfonylated products were observed by HRMS, showing the capricious nature of this reaction.



*Scheme 3.34: **Desulfonylation of sulfonamide 439***

The desired cyclisation of amine **440** to form the C ring was addressed. It was thought that due to the acidic conditions of the reaction mixture required to deprotect the sulfonamide, the amine was protonating and being rendered unreactive. Hence, amine **440** was heated under reflux in toluene (Scheme 3.35). Unfortunately, after removal of the reaction solvent, analysis by HRMS and ^{1}H NMR showed no desired lactam **431**.

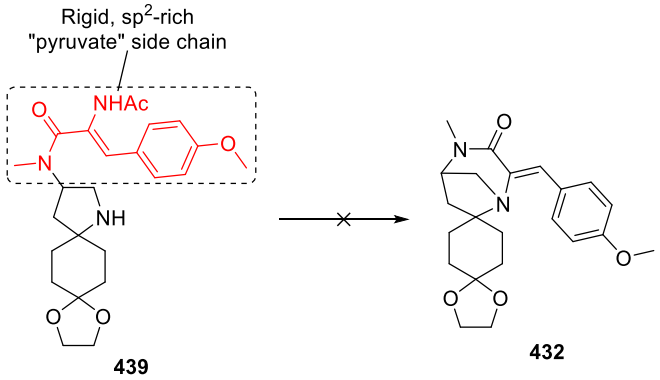


439 **432** not observed

*Scheme 3.35: **Attempted intramolecular condensation of amine 439***

3.7 The use of haloketones towards the synthesis of (±)-TAN-1251A

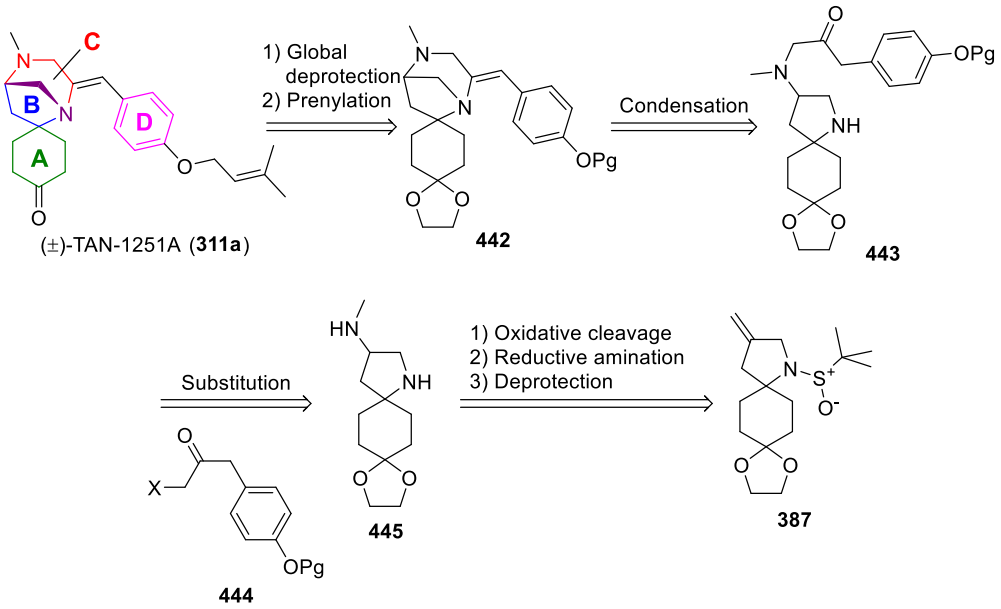
Having explored the use of pyruvic acids and their synthetic equivalents in the synthesis of (±)-TAN-1251A (**311a**), it was found that formation of the C ring was difficult. It was proposed that restriction in rotation caused by the sp^2-hybridised centres on the "pyruvate" side chain were preventing the interaction of the amine and the enamide of amide **439** required to form lactam **432** (Scheme 3.36).



*Scheme 3.36: "Pyruvate" side chain illustrated on amide **439***

Envisioning a similar, yet simplified, approach to (±)-TAN-1251A (**311a**), a more flexible and stronger electrophile, compared to the enamide used previously, was sought (Scheme 3.37). Removing the unnecessary amide carbonyl from previously envisaged enamine **432**, it was proposed that enamine **442** could be formed from the intra-molecular condensation of amino ketone **443**. The coupling of an α-haloketone **444** with amine **445** would form required amino ketone **443**. The use of α-halo acid chlorides, epoxides and cyclic sulfates were all considered but disregarded as condensation would form a matched and unmatched pair of diastereomers; producing a maximum yield of 50% in the formation of the C ring.

Early removal of the pyrrolidine nitrogen protecting group was postulated to prevent later complications with deprotection, when acid-labile functionalities would be present. The selective substitution of the α-haloketone **444** by the pendant methyl amine, as opposed to the pyrrolidine nitrogen, is required. It was proposed that the congested cyclohexanone spirocentre next to the pyrrolidine nitrogen would hinder nucleophilic attack by this this group, affording the correct amino ketone **443**. A phenol protecting group which requires orthogonal deprotection conditions would be convenient for this synthesis, as before. It was therefore proposed that both methyl and silyl ethers would be investigated to perform this role.

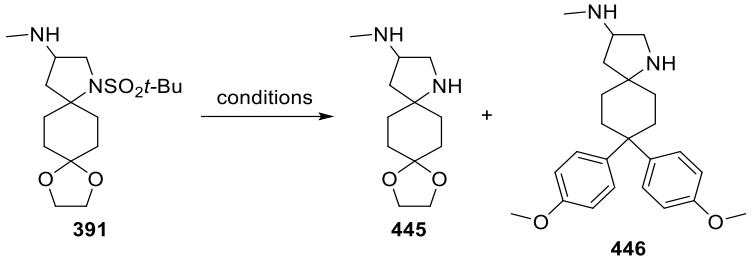


*Scheme 3.37: **Retrosynthetic analysis of (±)-TAN-1251A (311a)***

3.7.1 Synthesis of un-protected diamine

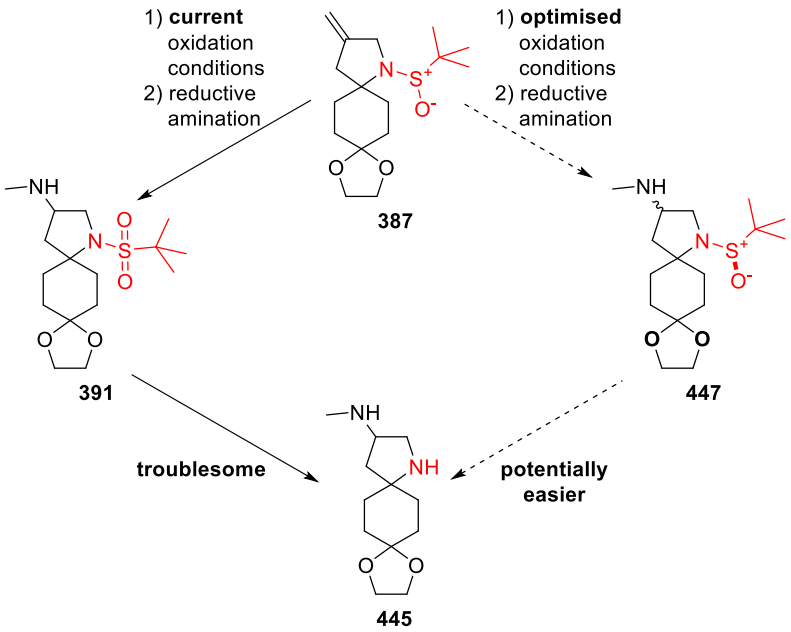
Having sulfonamide **387** in hand from previous synthetic efforts, its deprotection to afford diamine **445** was attempted (Table 3.11). Following exposure to triflic acid and acid/base extraction, a product which had encorporated two *para*-methoxyphenyl moieties was identified by ^{1}H NMR (entry 1). The disappearance of the dioxolane protons in the ^{1}H NMR spectrum and correlation to HRMS analysis suggested that diarylmethane **446** had been formed, similar to diarylmethane **427** observed previously (*vide supra*: Table 3.9). Using TFA for less acidic conditions it was found that a large amount of acetal deprotection was occurring, while sulfonyl deprotection was slow (entry 2). As before, premixing TFA and anisole with TFAA prior to reaction prevented complete hydrolysis of the dioxirane, however sulfonyl deprotection was poor.

*Table 3.11: Deprotection of amine **391***



Entry	Conditions (equiv.)	Comments
1	TfOH (6.0), anisole (20), CH_2Cl_2 (0.03 M), 0 °C to rt, 2 h	Only diarylmethane **446** (34%) isolated.
2	anisole (20), TFA (0.03 M), rt, 17 h	Sulfinyl deprotection and complete acetal deprotection observed by HRMS.
3	TFAA (2 vol%), anisole (20), TFA (0.03 M), rt, 19 h	diamine **445** observed by HRMS. Mainly sulfonamide **391** by ^{1}H NMR. Partial acetyl deprotection observed

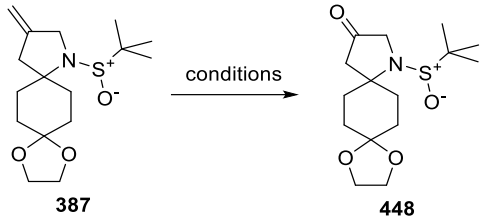
It was reasoned that optimisation of sulfonyl deprotection would be complex due to the limited number of conditions known to effect deprotection of *t*-butylsulfonamides and competing acetal decomposition. It was proposed that the deprotection of sulfinamide **447** to form diamine **445** may be more facile (Scheme 3.38). The current oxidation protocol, using ruthenium tetroxide, oxidises sulfinamide **387** to the corresponding sulfonamide, which is more difficult to deprotect (*vide supra*: Scheme 3.17). In order to synthesise sulfinamide **447**, the conditions of the oxidative cleavage of sulfinamide **387** required optimisation to retain the sulfur oxidation state.



*Scheme 3.38: Proposed strategy to form diamine **445***

As such, the dihydroxylation and oxidative cleavage of methylene pyrrolidine **387** was explored (Table 3.12). Osmium tetroxide was investigated due to literature precedent suggesting that it performs dihydroxylation of olefins without oxidising sulfinyl groups.[233,234] This is presumably due to its lower reduction potential compared to ruthenium tetroxide. [234–237] A one-pot dihydroxylation and oxidative cleavage was initially attempted, providing a good 70% yield of ketone **448** (entry 1).[233] A two-step dihydroxylation followed by oxidative cleavage protocol formed ketone **448** in a higher yield (86%, entry 2). Investigating the catalyst loading, higher yields of ketone **448** were isolated using 5 mol% OsO_4 (entry 3) than when using 20 mol% OsO_4 (entry 2). The reaction was amenable to scale up from 0.1 mmol to 2.9 mmol scale providing analytically pure material in 95% yield without the need for column chromatography (entry 3). Substituting the organic solvent for THF did not produce as high yields of ketone **448** compared to acetone (entries 3 and 4). It should be noted that in no case was sulfinyl oxidation observed by HRMS.

*Table 3.12: Dihydroxylation and oxidative cleavage of methylene pyrrolidine **387***



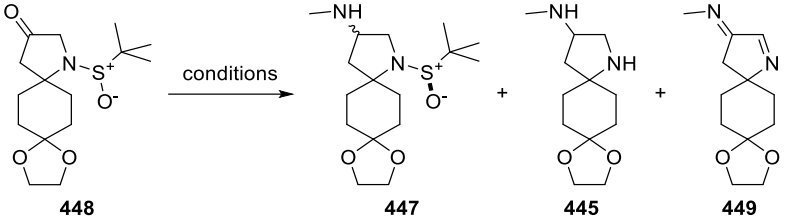
387 **448**

Entry	Conditions (equiv.)	Scale (mmol)	Yield 448 (%)
1	OsO_4 (5 mol%), $NaIO_4$ (3.0), acetone:H_2O (0.3 M, 3:1), rt, 17 h	0.10	70
2	1) OsO_4 (20 mol%), NMO (2.5), acetone:H_2O (0.3 M, 3:1), rt, 22 h; 2) $NaIO_4$ (2.5), acetone:H_2O (0.06 M, 3.5:1), rt, 22 h	0.10	86
3	1) OsO_4 (5 mol%), NMO (2.5), acetone:H_2O (0.2 M, 3:1), rt, 4 h; 2) $NaIO_4$ (2.5), acetone:H_2O (0.05 M, 3:1), rt, 6 h	2.9	95
4	1) OsO_4 (5 mol%), NMO (1.8), THF:H_2O (0.3 M, 6:1), rt, 22 h; 2) $NaIO_4$ (1.1), acetone:H_2O (0.06 M, 3.5:1), rt, 17 h	0.10	79

Having ketone **448** in hand and in reasonable quantities, reductive amination with methylamine was investigated (Table 3.13). In the optimisation of this transformation, ^{1}H NMR was used to calculate percent conversion to products. Previous conditions

produced only traces of desired amine **447** (entry 1, *vide supra*: Scheme 3.17).[213] Changing the solvent to methylene chloride similarly provided only low conversion to amine **447** (27%, entry 2), while using methanol provided no product (entry 3). A two-step reductive amination procedure using methylamine in chloroform, prepared from stirring aqueous methylamine with sodium hydroxide under chloroform, was performed (entry 4).[238] Reduction of what was presumed to be the methyl imine of ketone **448** and methylamine afforded large amounts of de-sulfinyl diamine **445** as determined by ^{1}H NMR and HRMS (entry 4). It was initially thought that the HCl formed from titanium(IV) chloride was deprotecting the sulfinamide, however changing the Lewis acid to titanium(IV) ethoxide produced similar results (entry 5). In the absence of a Lewis acid, the use of more mild reducing agents produced a new product, which was tentatively assigned as diimine **449** by ^{1}H NMR and HRMS (entries 6 and 7). Scale up of the reaction by approximately 10 times showed that yields of the diamine **445** were capricious (entry 8). Purification of diamine **445** was performed by chromatography using a Biotage KP-NH pre-packed cartridge column to prevent diamine **445** streaking on standard silica gel.

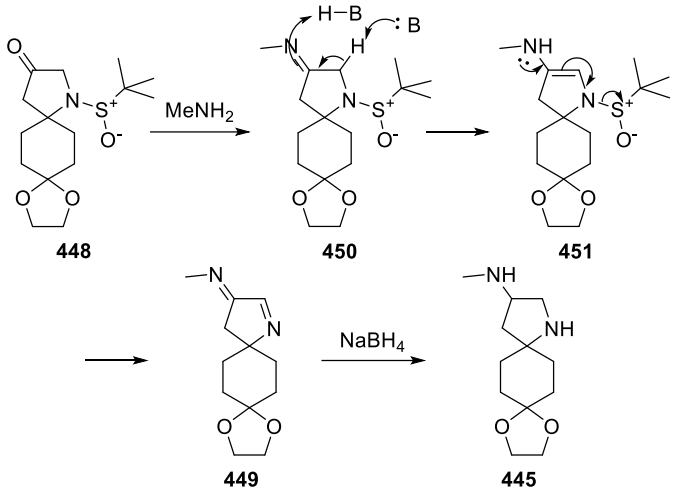
*Table 3.13: Reductive amination of ketone **448** with methylamine*



Entry	Conditions (equiv.)	Conversion 447/445/449 (%)[a]	Comments
1	$MeNH_3Cl$ (10), $NaBH_3CN$ (5.0), AcOH (1 drop), CH_2Cl_2, MeOH, rt, 24 h	trace/0/0	Complex mixture of products
2	$MeNH_3Cl$ (10), $NaBH_3CN$ (5.0), AcOH (1 drop), CH_2Cl_2, rt, 22 h	27/0/0[b]	Complex mixture of products
3	$MeNH_3Cl$ (10), $NaBH_3CN$ (1.5), AcOH (1 drop), MeOH, rt, 4 h	0/0/0	Starting material isolated
4	$MeNH_2$ (sat. in $CHCl_3$), $TiCl_4$ (0.7), $CHCl_3$, 80 °C, 1 h then $NaBH_4$ (2.7), MeOH, rt, 1 h	0/74/0	
5	$MeNH_2$ (sat. in $CHCl_3$), $Ti(OEt)_4$ (0.7), $CHCl_3$, 80 °C, 1 h then $NaBH_4$ (2.7), MeOH, rt, 2.5 h	7/74/0	
6	$MeNH_2$ (sat. in $CHCl_3$), $NaBH_3CN$ (1.5), AcOH (1 drop), CH_2Cl_2, rt, 16 h	18/0/37	complex mixture of products
7	$MeNH_2$ (sat. in $CHCl_3$), $NaBH(OAc)_3$ (1.5), AcOH (1 drop), CH_2Cl_2, rt, 16 h	0/0/83	
8	$MeNH_2$ (sat. in $CHCl_3$), $Ti(OEt)_4$ (0.7), $CHCl_3$, 80 °C, 2 h then $NaBH_4$ (2.7), MeOH, rt, 35 min	23/43/0 (11/43/0)[b]	

Notes: a) determined by comparison of integration of diagnostic peaks to the sum of all dioxolane peaks; b) isolated yield

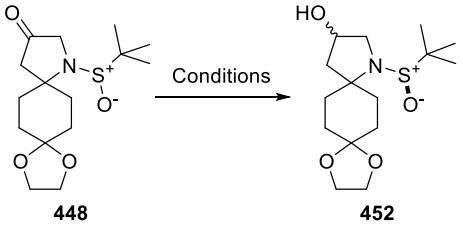
The serendipitous sulfinyl deprotection was seen as convenient since it removes the need to perform an extra step to carry out this operation. Hypothesising about a mechanism for this process, the initial formation of imine **450** was envisaged. Tautomerisation to form enamine **451**, followed by elimination of *t*-butyl sulfenate would generate diimine **449**; identified by ^{1}H NMR and HRMS (Scheme 3.39). Conjugation between the two imines enhances the stability of the π-system of diimine **449**. As such, only the stronger reducing agent, sodium borohydride, could reduce this species to form diamine **445**.



*Scheme 3.39: **Proposed mechanism to the formation of dimine 449 and diamine 445***

Such a mechanism would not allow for the synthesis of an enantiomerically enriched amine **445**. Therefore, as an aside, it was envisaged that a diastereoselective reduction of ketone **448** to alcohol **452** could be used in an enantioselective synthesis of (-)-TAN2151A (**311a**). Initially, $NaBH_4$ provided alcohol **452** in only modest diastereoselectivity (Table 3.14, entry 1). Using the more sterically encumbering L-selectride® in an attempt to maximise diastereoselectivity, alcohol **452** was formed in a reasonable 4.6:1 dr (entry 2). In both cases, diastereomeric ratio was determined by integration of the proton assigned as α-to the alcohol, which was tentatively assigned by COSY NMR.

*Table 3.14: Diastereoselective reduction of ketone **448***

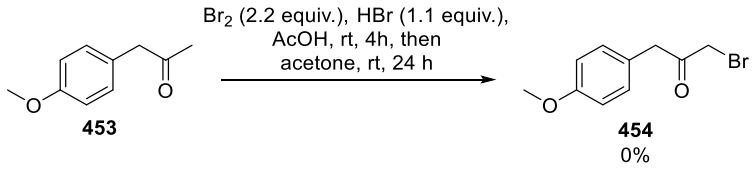


Entry	Conditions (equiv.)	Diastereomeric ratio 452
1	$NaBH_4$ (2.7), MeOH, rt, 3 h	1.7:1
2	L-selectride® (2.0), THF, -78 °C to rt, 18 h	4.6:1

3.7.2 Synthesis of an α-haloketone

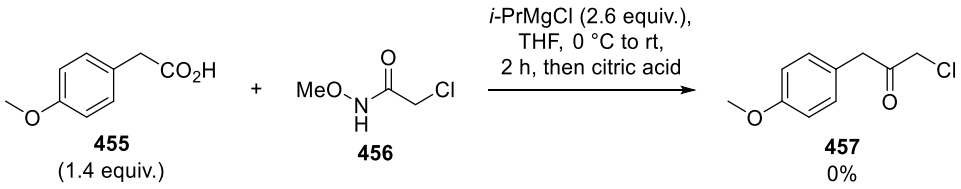
With diamine **445** in hand, attention was turned to the synthesis of an α-haloketone **444** (*vide supra*: Scheme 3.37). Known conditions were investigated in an effort to synthesise α-haloketones with appropriate functionality in a concise manner. As such, the dibromination/selective monodebromination conditions from the group of Chi were performed on phenylacetone **453**. Unfortunately, no α-bromoketone **454** was

observed by ^{1}H NMR, where similar literature compounds were used for comparison (Scheme 3.40).[239]



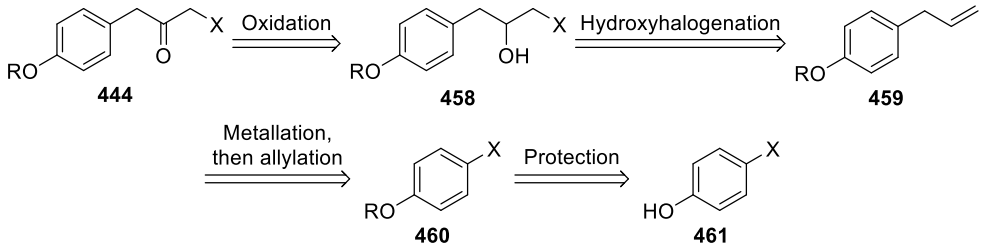
*Scheme 3.40: Dibromination/selective debromination used towards the synthesis of α-bromoketone **454***

The synthesis of α-chloroketones has also been achieved from phenylacetic acids by Zacuto *et al*. Benzylic acylation of the phenylacetic acid (**455**) with α-chloro Weinrub amide **456** provides α-chloroketones (Scheme 3.41). Again, no α-haloketone **457** was observed in either ^{1}H NMR or HRMS analysis of the reaction product.[240]



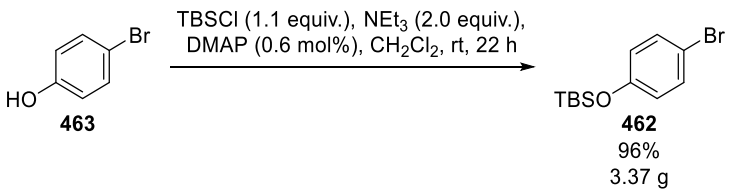
*Scheme 3.41: Attempted syntheses of α-haloketones **457***

Finding no success using concise literature conditions, it was decided that more usual means to approach the synthesis of this fragment should be investigated. It was proposed that an α-haloketone **444** could be formed by oxidation of the corresponding alcohol **458** (Scheme 3.42). Hydroxyhalogenation was envisaged to synthesise halohydrin **458** from allylic arene **459**. The allyl group could be installed by metalation and alkylation of a protected halophenol **460**.



*Scheme 3.42: Retrosynthetic analysis of an α-haloketone **444** using hydroxyhalogenation*

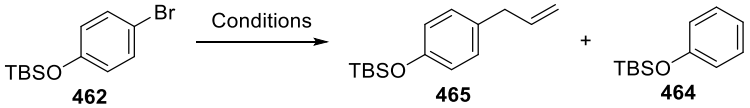
Synthesis initiated with the synthesis of *O*-TBS phenol **462** in an excellent 96% yield under standard conditions from 4-bromophenol (**463**, Scheme 3.43).



*Scheme 3.43: Synthesis of O-TBS phenol **462***

The allylation of bromoarene **462** by metalation followed by quenching with allyl bromide was examined (Table 3.15). Formation of the corresponding Grignard reagent and subsequent addition of allyl bromide was attempted, however only small amounts of product were isolated (entry 1). Lithium/halogen exchange was explored, and control experiments showed full conversion to debromoarene **464**. Exposure to *n*-BuLi, followed by allyl bromide afforded only traces of allylated product **465** by ^{1}H NMR (entry 2). The amount of remaining bromide suggested that a stronger organolithium reagent was required to effect full metalation. The use of *t*-BuLi provided no traces of the desired allylated product **465** (entry 3). Analysis of the ^{1}H NMR spectrum showed higher amounts of remaining starting material **462** and debromoalkene **464**. Attempts to optimise the reaction by transmettalating to copper(I) in DMPU were not effective (entry 4), while exclusion of DMPU provided 20% conversion to desired product **465** in what was otherwise a complex ^{1}H NMR spectrum (entry 5). Use of TMEDA to stabilise the intermediate organolithium species provided no conversion to allylic arene **465** by ^{1}H NMR (entry 6).

*Table 3.15: Allylation of aryl bromide **462***

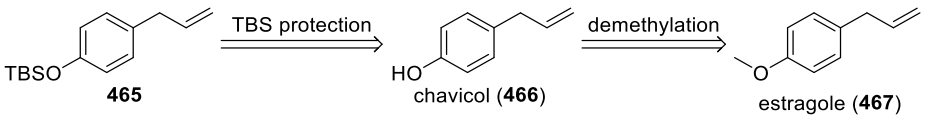


Entry	Conditions (equiv.)	Conversion 465 (%)	Notes
1	Mg (1.1), I_2, THF, 80 °C, 17 h then allyl bromide, 7 h	28 (6)[a]	61% remaining bromide **462**
2	*n*-BuLi (1.1), THF, -78 °C, 20 min then allyl bromide, 15 h	trace	40% remaining bromide **462**
3	*t*-BuLi (2.2), THF, -78 °C, 10 min then allyl bromide, 2 h	-	53% remaining bromide **462** 47% debromoarene **464**
4	*n*-BuLi (1.2), CuBr.DMS (1.1), THF:DMPU (1:1), -20 °C, 1.5 h then allyl bromide, -78 °C to rt, 16 h	-	remaining bromide **462**
5	*n*-BuLi (1.1), CuBr.DMS (1.2), THF, -78 °C, 40 min, then allyl bromide, 15 h	20	complex mixture of products
6	*n*-BuLi (1.1), TMEDA (1.2), THF, -78 °C, 20 min then allyl bromide, 15 h	-	20% remaining bromide **462**

Notes: a) Yield calculated from the purity of isolated product by ^{1}H NMR

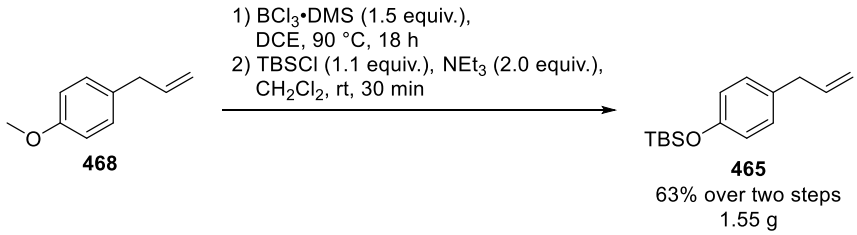
It was proposed that the TBS protecting group may be being deprotonated by the metallated arene, protonating the arene and preventing the desired allylation. With

the allylation of bromoarene **462** proving troublesome, a different strategy was sought for the synthesis of allylic arene **459**. It was proposed that the order of synthesis could be reversed to install the allyl group before the phenol protecting group (Scheme 3.44). Allylic arene **465** could be synthesised by the TBS protection of chavicol (**466**). Exploration of the literature showed that it is possible to form chavicol (**466**) by demethylation of commercially available estragole (**467**), a commercially available chemical and the major component of basil oil.[241,242]



*Scheme 3.44: **Revised strategy for the synthesis of allylic arene 465***

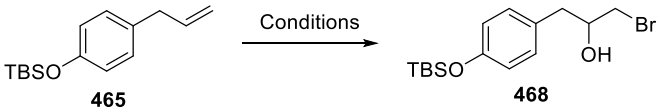
Conditions from the group of Denton were used to cleave the methyl ether of estragole (**467**, Scheme 3.45).[242] TBS-protection of the crude chavicol (**466**) afforded required silyl ether **465** in a 63% yield over two steps.



*Scheme 3.45: **Synthesis of TBS ether 465***

Formation of bromohydrin **468** from allylic arene **465** was investigated using literature conditions (Table 3.16).[243,244] Reaction with NBS in aqueous DMSO afforded only 19% of desired alcohol **468** (entry 1). Catalytic amounts of ammonium acetate and using aqueous acetone as solvent afforded the desired alcohol **468** in a 40% yield, which was sufficient for this stage of the investigation (entry 2). Complex mixtures of other products were observed under both conditions by crude ^{1}H NMR.

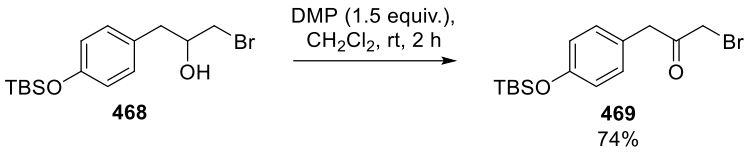
*Table 3.16: Synthesis of bromohydrin **468***



Entry	Conditions (equiv.)	Yield 468 (%)	Notes
1	NBS (1.1), DMSO, H_2O, 0 °C to rt, 6 h	19[a]	trace SM, complex mixture of other products
2	NBS (1.1), NH_4OAc (10 mol%), H_2O, acetone, rt, 15 min	40	20% remaining SM, complex mixture of other products

Notes: a) conversion by crude ^{1}H NMR

Oxidation of bromohydrin **468** to generate required α-bromoketone **469** was performed with DMP. Ketone **469** was isolated in a 74% yield following column chromatography (Scheme 3.46).

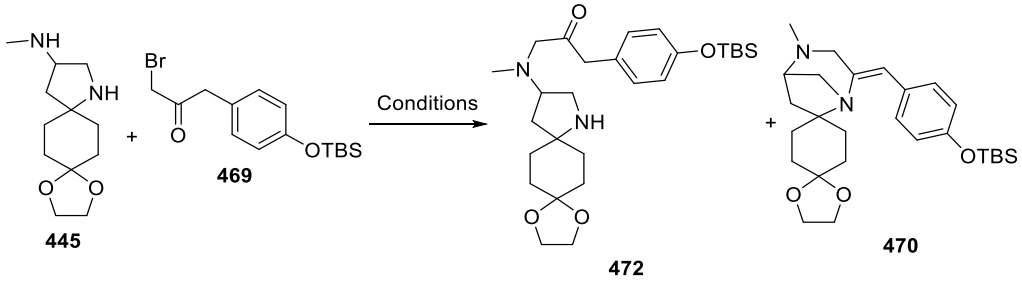


*Scheme 3.46: **Oxidation of bromohydrin 468***

3.7.3 Formation of the C ring using α-halocarbonyl compounds

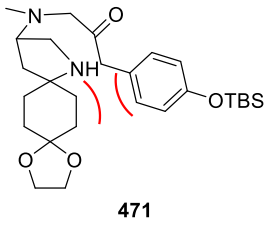
Having both diamine **445** and α-bromoketone **469** in hand, investigation focussed on coupling the two fragments to form enamine **470** (Table 3.17). While combination of the fragments in acetonitrile showed formation of amine **471** by HRMS, analysis by ^{1}H NMR was inconclusive with at least four sets of aromatic protons (entry 1). Attempting to induce intramolecular condensation to form enamine **470**, the crude sample was heated in deuterated chloroform (entry 2). Unfortunately, no further change in the ^{1}H NMR spectrum was observed. Proposing that the amine **471** was protonated and unable to react further, a basic workup was performed, however while significant shifts were observed by ^{1}H NMR, no expected styrene protons were observed to show formation of enamine **470** (entry 3). In an attempt to force the dehydration of amine **471** it was mixed with titanium(IV) ethoxide, however still no enamine **470** was observed by ^{1}H NMR or HRMS even after heating (entries 4 and 5). Exposure to scandium(III) triflate similarly produced no product (entry 7). Addition of trimethylsilyl triflate caused instant decomposition of the reaction mixture (entry 8).

*Table 3.17: Attempted synthesis of enamine **470***



Entry	Conditions (equiv.)	Remarks
1	MeCN, CH_2Cl_2 rt, 15 h	complete formation of amine **471** by HRMS, complex mixture by ^{1}H NMR
2	1) as entry 1 2) $CDCl_3$, 60 °C, 2 h	no change from entry 1
3	1) as entry 2 2) workup (K_2CO_3)	no change in HRMS, no formation of styrene **470** seen, shifts in ^{1}H NMR
4	1) as entry 3 2) $Ti(OEt)_4$ (1.0), $CDCl_3$, rt, 17 h	no change in HRMS, no formation of styrene **470** seen, shifts in ^{1}H NMR
5	1) as entry 4 2) 80 °C, 6 h	no change in HRMS, no formation of styrene **470** seen, shifts in ^{1}H NMR
6	1) as entry 5 2) workup (H_2O)	no change in HRMS, no formation of styrene **470** observed by ^{1}H NMR
7	1) as entry 6 2) $Sc(OTf)_3$ (0.5), $CDCl_3$, sonication, rt, 1 h	no change in HRMS, no formation of styrene **470** observed by ^{1}H NMR
8	1) as entry 6 2) TMSOTf (1.0), $CDCl_3$, rt	decomposition observed visually as well as by HRMS and ^{1}H NMR

It was proposed that the intra-molecular condensation of amine **471** was being inhibited by the steric interaction between the aromatic D ring and the cyclohexane A ring (Scheme 3.47).

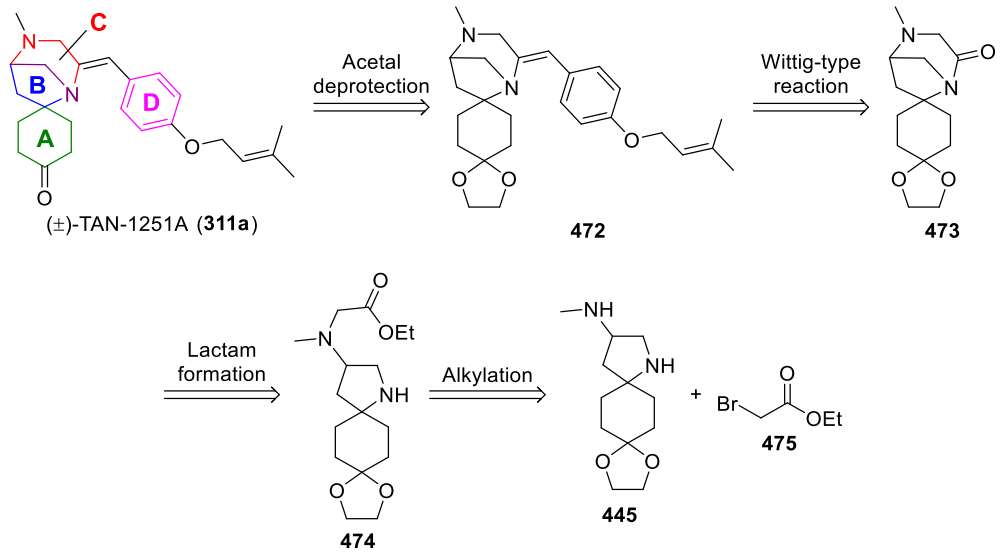


471

*Scheme 3.47: Proposed steric clash inhibiting the condensation of amine **471***

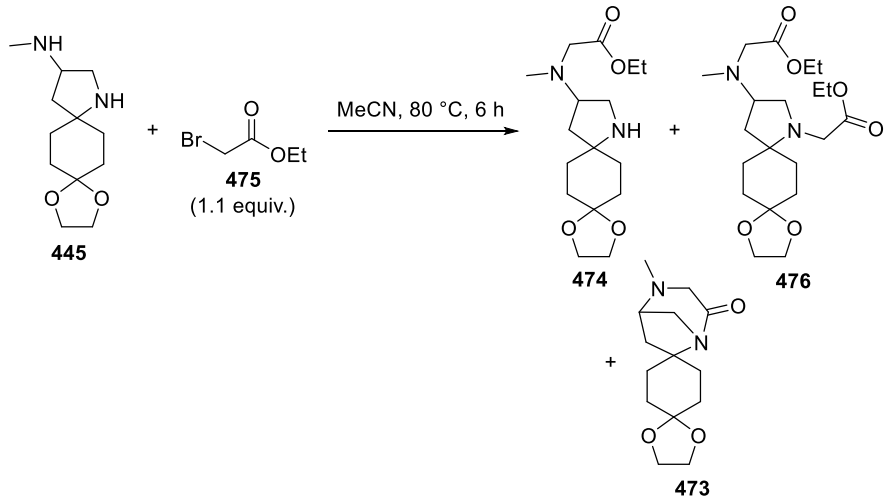
To remove any steric inhibition caused by the D ring, a simplification of the system was deemed necessary. It was thought that (±)-TAN-1251A (**311a**) could be formed from acetal **472** (Scheme 3.48). This could in turn be formed by a Wittig-type olefination from lactam **473**. While it may be unusual to see an amide performing a Wittig-type olefination, it was proposed that the bridgehead position of the amide

nitrogen would render its lone pair out of conjugation with the C-O π* orbital. This will make this species more electronically similar to a ketone than an amide. Opening the C ring of lactam **473**, it was envisaged that α-aminoester **474** could be formed from the reaction of ethyl bromoacetate (**475**) with amine **445**.



*Scheme 3.48: Retrosynthetic analysis of (±)-TAN-1251A (**311a**)*

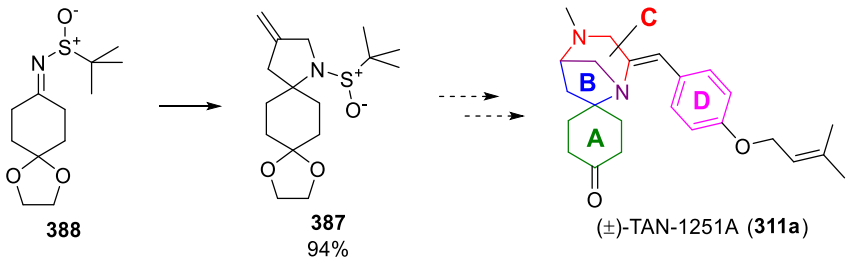
The required alkylation of diamine **445** with ethyl bromoacetate (**475**) was performed in acetonitrile since these conditions had been shown to work well previously (Scheme 3.49, *vide supra*: Scheme 3.33). Complete consumption of amine **445**, with formation of amine **474** and traces of dialkylated product **476** was observed after 45 minutes at 80 °C by HRMS. However, proceeding to heat the reaction for a further 5 hours, no formation of lactam **473** was observed by HRMS. The formation of diester **476** shows that the conformation of the molecule allows for alkylation of the spirocyclic amine by strong external electrophiles.



*Scheme 3.49: Reaction of diamine **445** with ethyl bromoacetate (**475**)*

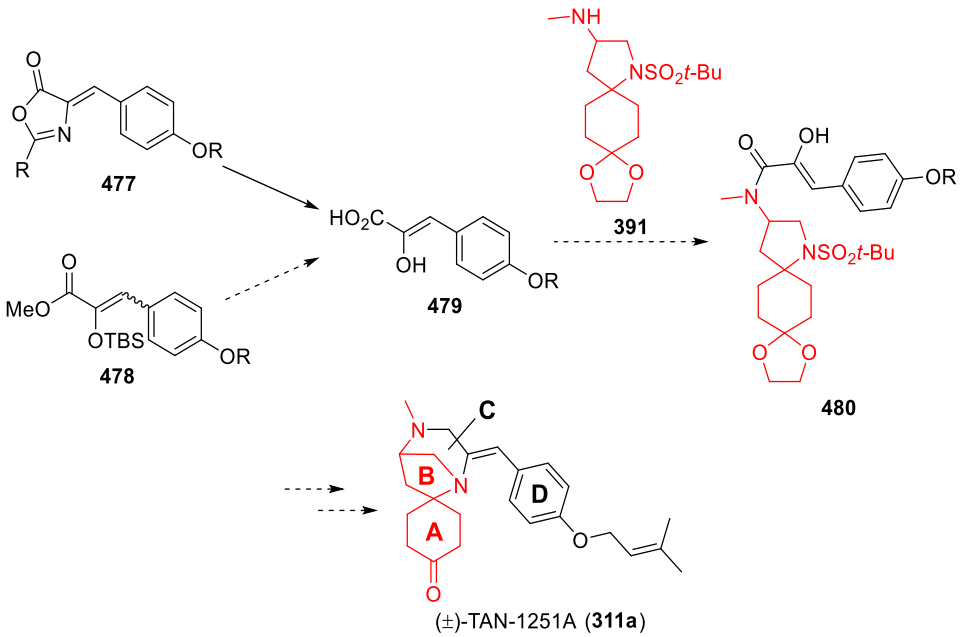
3.8 Conclusions and future work

A significant amount of work has been devoted to the synthesis of (±)-TAN-1251 (**311a**) from methylene pyrrolidine **387**, synthesised using a novel palladium-catalysed [3+2] cycloaddition (Scheme 3.50).



Scheme 3.50: Synthetic overview

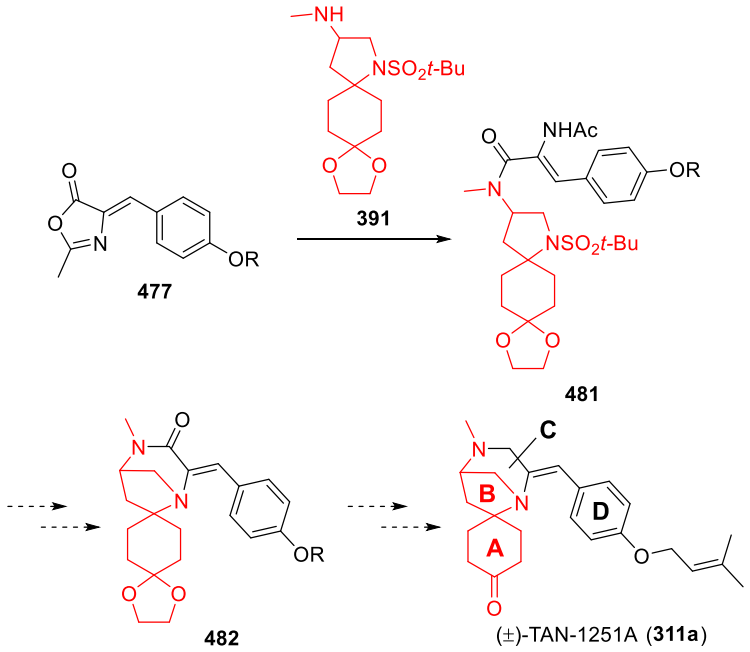
Initial efforts explored the synthesis and use of arylpyruvic acid fragments (Scheme 3.51). In particular, azlactones **477** and silyl enol ether **478** were investigated as precursors to arylpyruvic acids **479**. Issues were encountered in the synthesis of the arylpyruvic acids **479**, finding susceptibility to decomposition during hydrolysis of their precursors. Methoxyarylpyruvic acid **479** (R = Me) was successfully synthesised from an azlactone **477** (R = Me). However, unfortunately, its coupling with amine **391** was unsuccessful, and so alternative routes were sought.



*Scheme 3.51: The synthesis and use of arylpyruvic acids **479** towards the synthesis of (±)-TAN-1251 (**311a**)*

Coupling issues were overcome by the direct combination of azlactones **477** with amine **391** to provide a range of amides **481** for examination (Scheme 3.52). Competitive deprotection of prenylated phenol **481** (R = prenyl) during required

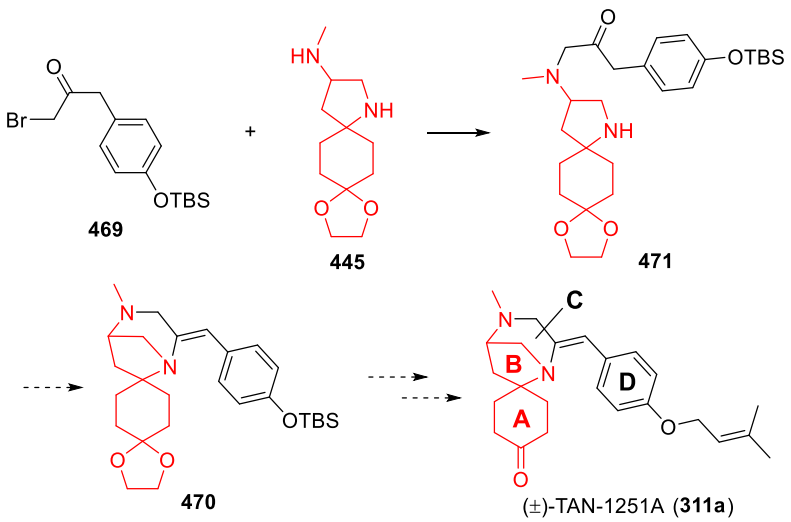
deprotection of the sulfonamide was encountered, leading to a revision of the synthetic plan. Anisole **481** (R = Me) was synthesised in an attempt to produce a more robust substrate. While sulfonamide deprotection of anisole **481** (R = Me) was achieved, significant arylation of the acetal was also observed. Unfortunately, attempts to force the formation the C ring from the desulfonylated amine were not successful. It was considered that the pyrrolidine nitrogen was too sterically encumbered to undergo the desired cyclisation to form enamine **482** due to the proximal cyclohexanone spirocentre.



*Scheme 3.52: Couplings between azlactones **477** and amine **391** used in the synthesis of (±)-TAN-1251 (**311a**)*

Reconsidering the synthesis, it was decided that far simpler substrates should be explored (Scheme 3.53). The unnecessary sulfonamide and enamide functional groups, which require deprotection, were removed from the redesigned synthesis. Futhermore, removal of unnecessary sp^2 hybridisation from the "pyruvate" side chain was proposed to make the side chain more flexible. It was hoped that this would allow the molecule to adopt the required conformation to form the C ring.

The synthesis of diamine **445** was achieved using a short and serendipitous route from known methylene pyrrolidine **387**. After some troublesome synthesis, α-bromoketone **469** was derived from estragole (**467**). While combination of the fragments was observed, formation of the C ring was not. It was proposed that an unfavourable steric interaction between the phenol D ring and the cyclohexanone A ring was hampering the reaction.



*Scheme 3.53: Simplification of the synthetic route towards (±)-TAN-1251 (**311a**)*

Investigating whether removal of the sterically demanding D ring would aid the formation of the C ring, ethyl bromoacetate (**475**) was used in place of α-bromoketone **469**. Despite again observing the coupling of the two fragments, no sign of the C ring forming was seen.

The desired cyclisations to form the C ring share a common *exo-trig* cyclisation of the pyrrolidine nitrogen. It was proposed that the sterically encumbered cyclohexane spirocentre proximal to the pyrrolidine nitrogen prevents this required intramolecular cyclisation (Figure 3.5).

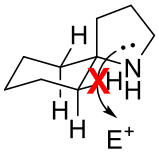
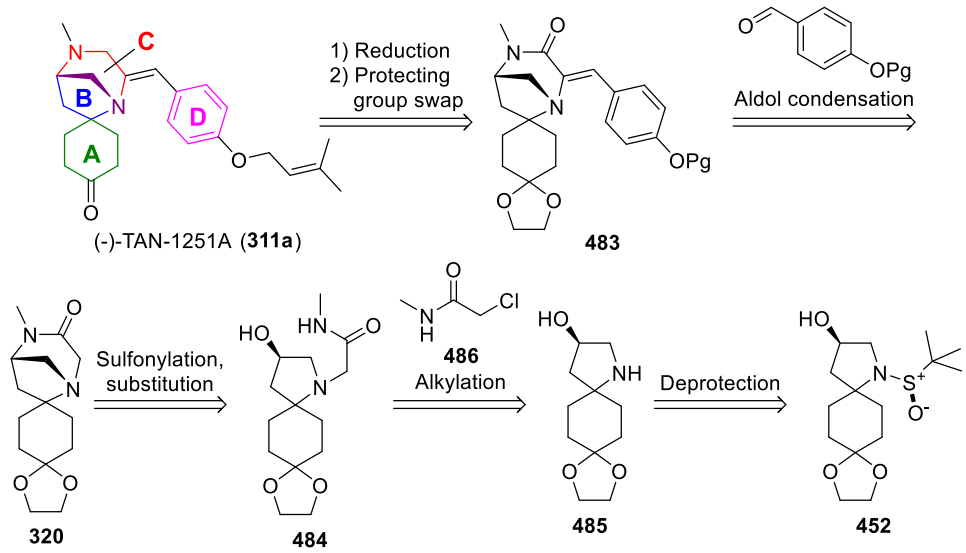


Figure 3.5: Structure of the sterically congested 1-azaspiro[4.5]decane core

An alternative synthesis could focus on the formation of this troublesome bond prior to forming the C ring, rather than attempting to perform both operations in the same step. An enantioselective retrosynthesis of (-)TAN-1251A (**311a**) could take such an approach (Scheme 3.54). The use of a protected phenol **483** would prevent troublesome reduction and acetal hydrolysis in the presence of the prenyl group. Envisaging the synthesis of Kawahara's intermediate **320** by intra-molecular displacement of alcohol **484**, C-N cleavage reveals that this could be synthesised from amino alcohol **485** and α-chloroamide **486**. Finally, the deprotection of sulfinamide **452** would be required. Sulfinamide **452** has already synthesised in a diastereoselective manner (*vide supra*: Table 3.14).



*Scheme 3.54: **Revised retrosynthesis of (-)-TAN-1251A (311a)***

Chapter 4: Summary

Firstly, this thesis explored the field of ligand coupling reactions of sulfoxides, with a wealth of discoveries made in the scope of the formation of $C(sp^2)$-$C(sp^3)$ bonds. Sulfoxides have been shown to mediate the coupling of many (hetero)aromatic groups with alkyl groups functionalised at the α-position with either (hetero)aromatic groups, ethers, carbamates or halogens.

This chemistry has been applied to the synthesis of drug products, as well as the synthesis of enantiomerically enriched products; exhibiting the utility of this reaction. Such wide-ranging cross-couplings with electron-deficient (hetero)aromatic groups are unheard of in the field of transition metal-catalysed cross-couplings. It is hoped that this chemistry can be developed yet further in the future, and be widely applied to the synthesis of drug products as well as natural products.

Secondly, the synthesis of (±)-TAN1251A was investigated. A novel palladium-catalysed [3+2] cycloaddition of sulfinimines, which forms both a $C(sp^3)$-$C(sp^3)$ bond and a C-N bond, had previously been used to provide a diamine, mono-protected as a sulfonamide. Research initially focussed on the synthesis of pyruvic acid fragments and synthetic equivalents, especially azlactones, to couple with the diamine. Despite difficulties being encountered in the formation and use of this fragment, as well as in the sulfonamide deprotection, a late stage intermediate of (±)-TAN1251A was formed. Unfortunately, the required cyclisation to form the C ring was not successful.

Using knowledge gained from the shortcomings of these previous investigations, a revised synthetic route was planned which utilised an α-haloketone, and early deprotection of the sulfonamide to prevent later complications. While the desired late stage intermediate was generated, formation of the C ring was not successful. The potential for elaboration of such a route to yield an enantioselective synthesis of (-)-TAN1251A was confirmed by performing a diastereoselective ketone reduction. Using this knowledge, a new route to the synthesis of (-)-TAN1251A has been devised. The novel [3+2] cycloaddition is still utilised, however the formation of the C ring is approached in a more traditional manner to provide a total synthesis of (-)-TAN1251A.

This thesis has documented the author's investigation into the formation of both $C(sp^2)$-$C(sp^3)$ bonds and $C(sp^3)$-$C(sp^3)$ bonds using the chemistry of sulfur(IV). The

application of these chemistries to the synthesis of drug products, enantiomerically enriched products and natural products shows the potential for these methods in the wider chemical community and industry. It is hoped that these results will facilitate the synthesis of drug products with higher Fsp^3 values, which may lower attrition rates of drug candidates through clinical trials.

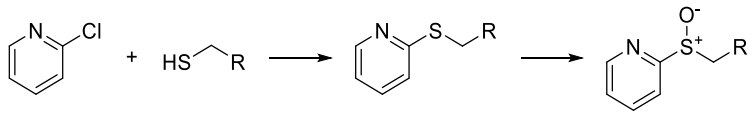
Chapter 5: Experimental data

5.1 General Experimental Procedures

Unless otherwise stated, all reagents were purchased from commercial sources and used without additional purification. NaOEt was freshly prepared from sodium and absolute ethanol. THF was freshly distilled under argon from the sodium/benzophenone. All other anhydrous solvents were purchased or obtained from in house solvent purification towers. Petroleum ether means the petroleum fraction b.p. 40 - 60 °C. Water was deionised prior to use. All air or moisture-sensitive reactions were conducted in flame-dried glassware under an atmosphere of argon or nitrogen. Brine is a saturated aqueous solution of sodium chloride. Unless otherwise stated, all reactions were performed at rt. TLCs were performed on Merck silica gel 60 F_{254} and visualised by UV lamp. Column chromatography was performed on silica gel Fluka 60.

NMR spectra were recorded using either a Bruker DPX300, Bruker DPX400, Bruker AV400, Bruker AV(III)400, Bruker AV(III)400HD or Bruker AV500 spectrometer. Chemical shifts are quoted in ppm and are referenced to solvent. Coupling constant values (*J*) are corrected and are given in Hertz (Hz). Infrared spectra were recorded using a Bruker Tensor 27 FTIR spectrometer. High resolution mass spectra were recorded using a Bruker MicroTOF spectrometer. Melting points were taken using Stuart Scientific SMP3 melting point apparatus.

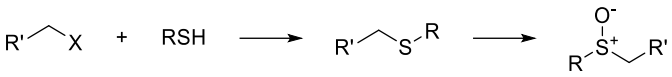
5.1.1 General procedure A: Sulfoxides *via* S_NAr reactions



To a solution of the appropriate thiol (1.1 equiv.) in THF (5 mL) was added KO*t*-Bu (1.1 equiv.). The reaction mixture was stirred for 20 min before 2-chloropyridine (1.0 equiv.) was added and the reaction mixture was heated to 40 °C. When no 2-chloropyridine remained (TLC) the reaction mixture was cooled to rt before adding water (5 mL/mmol 2-chloropyridine) and brine (5 mL/mmol) and extracting with EtOAc (3 x 10 mL/mmol) and the combined organic layers were washed with water (5 mL/mmol) and then brine (5 mL/mmol), before drying ($MgSO_4$) and concentrating *in vacuo* to give the crude sulfide. The sulfide was then dissolved in CH_2Cl_2 (10 mL/mmol) before adding *m*CPBA (70-77 wt% with water and 3-chlorobenzoic

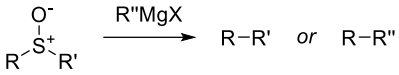
acid, 1.0 equiv.). After 15 min NaOH (3 mL, 0.5 M in water) was added. The organic layers were separated, and the aqueous layer was washed with CH_2Cl_2 (2 x 30 mL). The combined organic layers were dried ($MgSO_4$) before concentrating *in vacuo* and column chromatography afforded pure sulfoxide.

5.1.2 General procedure B: Sulfoxides *via* S_N2 reactions



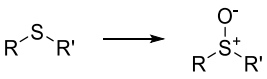
To a solution of the appropriate thiol (1.2 equiv.) in solvent (5 mL/mmol) was added base (1.2 equiv., or 2.2 equiv. if a hydrochloride salt of the chloride was used) and the reaction mixture was stirred for 10 min before the electrophile was added. When no electrophile remained (TLC) water-soluble solvents were removed *in vacuo* and water (30 mL) was added. The aqueous layer was washed with EtOAc or CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo* to afford crude sulfide. To a solution of the crude sulfide in CH_2Cl_2 (10 mL/mmol) was added *m*CPBA (70-77 wt% with water and 3-chlorobenzoic acid, 1 equiv.). After 15 min NaOH (10 mL, 0.5 M in distilled water) was added, the organic layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried ($MgSO_4$) before concentrating *in vacuo* and column chromatography afforded pure sulfoxide.

5.1.3 General procedure C: Ligand coupling of sulfoxides



To a solution of the sulfoxide (1.0 equiv.) in THF (10 mL/mmol) was added Grigard reagent (1.1 equiv.) dropwise. The reaction mixture was stirred for 15 min before cautiously adding water (20 mL/mmol) and extracting with CH_2Cl_2 (3 x 40 mL/mmol). The combined organic layers were dried ($MgSO_4$) before concentrating *in vacuo* and column chromatography afforded pure product.

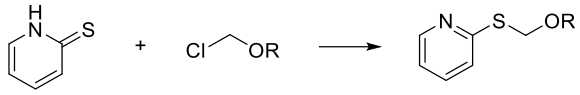
5.1.4 General procedure D: Oxidation of sulfides to sulfoxides



To a solution of sulfide (1.0 equiv.) in CH_2Cl_2 (10 mL/mmol) was added *m*CPBA (70-77 wt% with water and 3-chlorobenzoic acid, 1.0 equiv). After 15 min NaOH (0.5 M in water, 20 mL/mmol) was added. The organic layers were separated, and the

aqueous layer was washed with CH_2Cl_2 (2 x 40 mL/mmol). The combined organic layers were dried ($MgSO_4$) before concentrating *in vacuo* and column chromatography afforded pure sulfoxide.

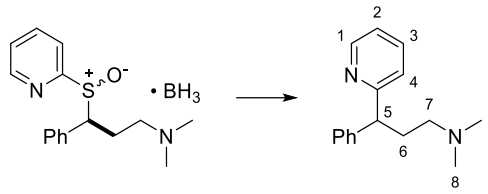
5.1.5 General procedure E: Alkylation of sulfides



To a solution of 2-mercaptopyridine (1.2 equiv.) in CH_2Cl_2 (10 mL/mmol) was added Et_3N (1.2 equiv.) and chloromethyl ether (1.0 equiv.). After 1.5 h to 22 h at room temperature the reaction mixture was concentrated onto silica gel *in vacuo*, and column chromatography afforded pure thioacetal.

5.2 Compounds from Chapter 2

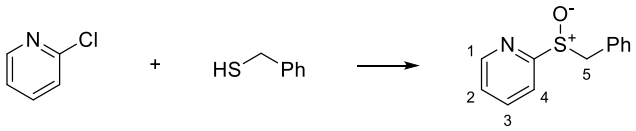
Pheniramine (209a)[178,245]



General procedure C: N,N-dimethyl-3-phenyl-3-(pyridin-2-ylsulfinyl)propan-1-amine borane adduct (**255**, 35 mg, 0.12 mmol), THF (1.2 mL) and MeMgBr (3.0 M in Et_2O, 0.05 mL, 0.13 mmol) followed by borane cleavage using HCl (1.3 M in MeOH, 2.0 mL) afforded *title compound* (12 mg, 42%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 8.56 (1H, ddd, *J* 4.9, 1.9 and 0.9, 1-H), 7.55 (1H, ddd, *J* 7.7, 7.6 and 1.9, 3-H), 7.37-7.33 (2H, m, Ph-H x 2), 7.31-7.25 (2H, m, Ph-H x 2), 7.21-7.14 (2H, m, 4-H and Ph-H), 7.08 (1H, ddd, *J* 7.6, 4.9 and 1.2, 2-H), 4.14 (1H, t, *J* 7.3, 5-H) 2.49-2.36 (1H, m, 6-H), 2.30-2.17 (3H, m, 6-H and 7-H x 2), 2.20 (6H, s, 8-H_3 x 2); δ_C (100 MHz, $CDCl_3$) 163.8 (C), 149.4 (CH), 143.8 (C), 136.5 (CH), 128.6 (CH), 128.1 (CH), 126.5 (CH), 122.9 (CH), 121.4 (CH), 58.0 (CH_2), 51.5 (CH), 45.6 (CH_3), 33.0 (CH_2); **HRMS** (ESI+) *m/z* calculated for calculated for $[C_{16}H_{21}N_2]^+$: 241.1699, found 241.1706. Data agrees with literature.

2-(Benzylsulfinyl)pyridine (212aa)

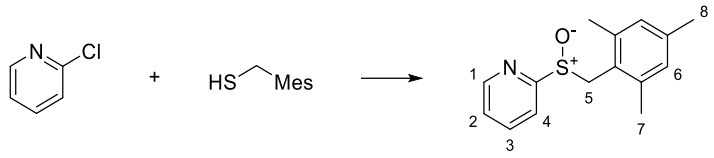


General procedure A: 2-chloropyridine (0.94 mL, 10 mmol), benzyl mercaptan (1.3 mL, 11 mmol), KO*t*-Bu (1.2 g, 11 mmol), THF (50 mL), *m*CPBA (282 mg, 1.1 mmol) and CH_2Cl_2 (11 mL) (11% of crude sulfide used in oxidation) gave *title compound* (221 mg, 89%) as a colourless solid.

M.p. 86-89 °C; δ_H (400 MHz, $CDCl_3$) 8.70 (1H, d, *J* 4.7, 1-H), 7.81 (1H, ddd, *J* 7.8, 7.6 and 1.7, 3-H), 7.63 (1H, dd, *J* 7.8 and 1.1, 4-H), 7.38 (1H, ddd, *J* 7.6, 4.7 and 1.1, 2-H) 7.31-7.23 (3H, m, Ph-H x 3), 7.06-7.02 (2H, m, Ph-H x 2), 4.40 (1H, d, *J* 13.1, 5-H), 4.09 (1H, d, *J* 13.1, 5-H); δ_C (100 MHz, $CDCl_3$) 163.8 (C), 149.4 (CH), 137.7 (CH), 130.4 (CH), 129.4 (C), 128.4 (CH), 128.2 (CH), 124.7 (CH), 120.7 (CH), 60.0 (CH_2); **IR** ($CHCl_3$)/cm^{-1}

3057, 3004, 2462, 1578, 1563, 1497, 1453, 1424, 1242, 1085, 1038; **HRMS** (ESI) *m/z* calculated for $[C_{12}H_{11}NNaOS]^+$: 240.0459, found 240.0453.

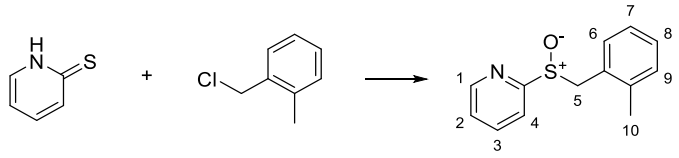
2-((2,4,6-Trimethylbenzyl)sulfinyl)pyridine (212ab)



General procedure A: 2,4,6-trimethylbenzyl mercaptan (2.5 g, 15 mmol), 2-chloropyridine (0.94 mL, 10 mmol), KO*t*-Bu (2.2 g, 20 mmol), THF (50 mL), *m*CPBA (2.4 g, 9.8 mmol) and CH_2Cl_2 (100 mL) (98% of crude sulfide used in oxidation) gave *title compound* (1.86 g, 73%) as a colourless solid.

M.p. 84-86 °C; **δ_H** (400 MHz, $CDCl_3$) 8.68 (1H, d*, J* 4.7, 1-H), 8.03 (1H, d*, J* 7.8, 4-H), 7.96 (1H, dd*, J* 7.8 and 7.4, 3-H), 7.42 (1H, dd*, J* 7.4 and 4.7, 2-H), 6.93 (2H, s, 6-H x 2), 4.42 (1H, d*, J* 13.2, 5-H), 4.29 (1H, d*, J* 13.2, 5-H), 2.37 (6H, s, 7-H_3 x 2), 2.31 (3H, s, 8-H_3); **δ_C** (100 MHz, $CDCl_3$) 165.6 (C), 149.6 (CH), 138.5 (C), 137.9 (CH), 137.9 (C), 129.4 (CH), 125.1 (C), 124.7 (CH), 119.8 (CH), 56.9 (CH_2), 21.0 (CH_3), 20.6 (CH_3); **IR** (ATR)/cm^{-1} 3090, 2971, 2913, 1613, 1573, 1560, 1453, 1419, 1375, 1051, 1032, 992, 849, 758; **HRMS** (ESI+) *m/z* calculated for $[C_{15}H_{17}NNaOS]^+$: 282.0929, found 282.0924.

2-((2-Methylbenzyl)sulfinyl)pyridine (212ac)

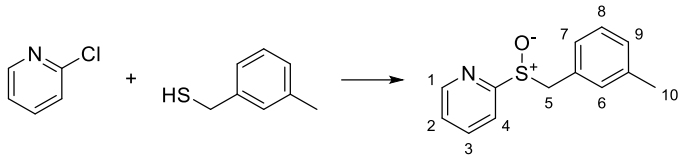


General procedure B: 2-methylbenzyl chloride (1.3 mL, 10 mmol), 2-mercaptopyridine (**221**, 1.3 g, 12 mmol), EtOH (50 mL), NaOEt (4.5 mL, 12 mmol), *m*CPBA (2.4 g, 9.6 mmol) and CH_2Cl_2 (100 mL) (96% of crude sulfide used in oxidation) gave *title compound* (2.20 g, 97%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 8.63 (1H, ddd*, J* 4.6, 1.6 and 0.8, 1-H), 7.85 (1H, dd*, J* 7.6 and 7.6, 3-H), 7.79 (1H, d*, J* 7.6, 4-H), 7.37-7.32 (1H, m, 2-H), 7.23-7.16 (2H, m, (6-H, 7-H, 8-H or 9-H) x 2), 7.09 (1H, dd*, J* 7.3 and 7.0, 6-H, 7-H, 8-H or 9-H), 6.99 (1H, d*, J* 7.3, 6-H, 7-H, 8-H or 9-H), 4.51 (1H, d*, J* 13.1, 5-H), 4.06 (1H, d*, J* 13.1, 5-H), 2.35 (3H, s, 10-H_3); **δ_C** (100 MHz, $CDCl_3$) 164.4 (C), 149.5 (CH), 137.9 (C), 137.8 (CH), 131.4 (CH), 130.5 (CH), 128.6 (C), 128.5 (CH), 126.0 (CH), 124.8 (CH), 120.3 (CH), 58.9 (CH_2), 19.8 (CH_3); **IR**

($CHCl_3$)/cm^{-1} 3001, 2929, 2462, 1578, 1563, 1495, 1453, 1424, 1242, 1095, 1038, 992, 877; **HRMS** (ESI+) *m/z* calculated for $[C_{13}H_{13}NNaOS]^+$: 254.0616, found 254.0608.

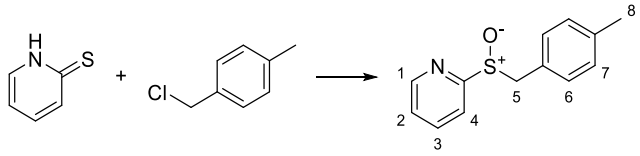
2-((3-Methylbenzyl)sulfinyl)pyridine (212ad)



General procedure A: 3-methylbenzyl mercaptan (970 mg, 7.0 mmol), 2-chloropyridine (550 µL, 5.8 mmol), KO*t*-Bu (780 mg, 7.0 mmol), THF (35 mL), *m*CPBA (1.4 g, 5.7 mmol) and CH_2Cl_2 (55 mL) (97% of crude sulfide used in oxidation) gave *title compound* (1.16 g, 87%) as a pale yellow oil.

δ_H (400 MHz, $CDCl_3$) 8.68 (1H, dd*, J* 4.7, 1.5 and 1.1, 1-H), 7.81 (1H, ddd*, J* 7.8, 7.5 and 1.5, 3-H), 7.66 (1H, dd*, J* 7.8, 1.1 and 1.0, 4-H), 7.36 (1H, ddd*, J* 7.5, 4.7 and 1.0, 2-H), 7.14 (1H, dd*, J* 7.8 and 7.5, 8-H), 7.09 (1H, d*, J* 7.5, 9-H), 6.86 (1H, s, 6-H), 6.85 (1H, d*, J* 7.8, 7-H), 4.35 (1H, d*, J* 13.1, 5-H), 4.02 (1H, d*, J* 13.1, 5-H), 2.27 (3H, s, 10-H_3); **δ_C** (100 MHz, $CDCl_3$) 164.0 (C), 149.4 (CH), 138.1 (C), 137.7 (CH), 131.1 (CH), 129.4 (C), 129.0 (CH), 128.3 (CH), 127.4 (CH), 124.6 (CH), 120.6 (CH), 60.4 (CH_2), 21.3 (CH_3); **IR** ($CHCl_3$)/cm^{-1} 3056, 3005, 2925, 2463, 1608, 1578, 1563, 1488, 1453, 1424, 1092, 1038, 993; **HRMS** (ESI+) *m/z* calculated for $[C_{13}H_{13}NNaOS]^+$: 254.0616, found 254.0613.

2-((4-Methylbenzyl)sulfinyl)pyridine (212ae)[246]

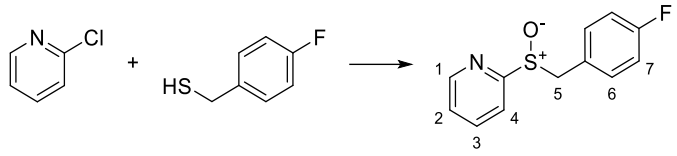


General procedure B: 4-methylbenzyl chloride (1.3 mL, 10 mmol), 2-mercaptopyridine (**221**, 1.3 g, 12 mmol), NaOEt (4.5 mL, 12 mmol), EtOH (50 mL), *m*CPBA (2.6 g, 10.0 mmol) and CH_2Cl_2 (100 mL) gave *title compound* (1.84 g, 80%) as a colourless solid.

M.p. 48-52 °C; **δ_H** (400 MHz, $CDCl_3$) 8.63 (1H, d, *J* 4.8, 1-H), 7.75 (1H, ddd*, J* 7.7, 7.7 and 1.4, 3-H), 7.60 (1H, d*, J* 7.7, 4-H), 7.34-7.29 (1H, m, 2-H), 7.01 (2H, d*, J* 7.7, 6-H x 2 or 7-H x 2), 6.88 (2H, d*, J* 7.7, 6-H x 2 or 7-H x 2), 4.31 (1H, d*, J* 13.1, 5-H), 4.01 (1H, d*, J* 13.1, 5-H), 2.26 (3H, s, 8-H_3); **δ_C** (100 MHz, $CDCl_3$) 163.9 (C), 149.3 (CH), 138.0 (C), 137.7 (CH), 130.2 (CH), 129.1 (CH), 126.2 (C), 124.6 (CH), 120.6 (CH), 59.8 (CH_2), 21.2 (CH_3); **IR** (ATR)/cm^{-1} 3048, 2924, 1578, 1560, 1578, 1560, 1515, 1450, 1422, 1105,

1046, 1035, 990, 821, 774; **HRMS** (ESI+) *m/z* calculated for $[C_{13}H_{13}NNaOS]^+$: 254.0616, found 254.0601. Data agrees with literature.

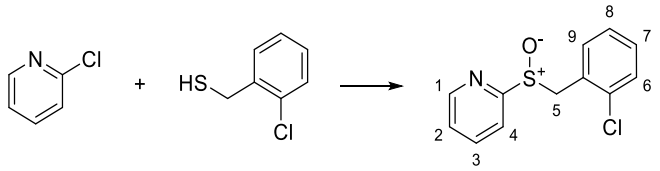
2-((4-Fluorobenzyl)sulfinyl)pyridine (212af)



General procedure A: 2-chloropyridine (0.58 mL, 700 mg, 6.1 mmol), 4-fluorobenzylmercaptan (1.0 g, 7.3 mmol), KO*t*-Bu (820 mg, 7.3 mmol), THF (35 mL), *m*CPBA (980 mg, 4.0 mmol) and CH_2Cl_2 (40 mL) (65% of crude sulfide used in oxidation) gave *title compound* (880 mg, 64%) as a pale yellow solid.

M.p. 77-80 °C; δ_H (400 MHz, $CDCl_3$) 8.65 (1H, ddd, *J* 4.7, 1.7 and 0.9, 1-H), 7.77 (1H, ddd, *J* 7.8, 7.7 and 1.7, 3-H), 7.55 (1H, ddd, *J* 7.8, 1.1 and 0.9, 4-H), 7.33 (1H, ddd, *J* 7.7, 4.7 and 1.1, 2-H), 7.00-6.88 (4H, m, 6-H x 2 and 7-H x 2), 4.32 (1H, d, *J* 13.3, 5-H), 4.07 (1H, d, *J* 13.3, 5-H); δ_C (100 MHz, $CDCl_3$) 163.6 (C), 162.9 (C, d, *J* 247), 149.4 (CH), 137.8 (CH), 132.0 (CH, d, *J* 8), 125.1 (C, d, *J* 3), 124.7 (CH), 120.8 (CH), 115.4 (CH, d, *J* 22), 58.8 (CH_2); δ_F (377 MHz, $CDCl_3$) -113.6 (tt, *J* 8.6 and 5.5); **IR** (ATR)/cm^{-1} 1604, 1578, 1562, 1511, 1452, 1424, 1159, 1093, 1048, 1038, 838; **HRMS** (ESI+) *m/z* calculated for $[C_{12}H_{10}FNNaOS]^+$:258.0365, found 258.0362.

2-((2-Chlorobenzyl)sulfinyl)pyridine (212ag)

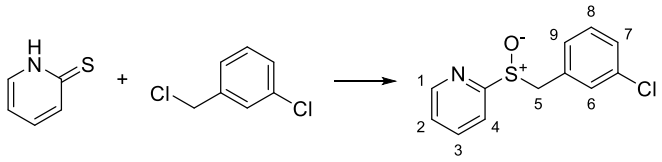


General procedure A: 2-chloropyridine (0.94 mL, 10 mmol), 2-chlorobenzylmercaptan (1.0 mL, 11 mmol), KO*t*-Bu (1.2 g, 11 mmol), THF (50 mL), *m*CPBA (310 mg, 1.3 mmol) and CH_2Cl_2 (13 mL) (18% of crude sulfide used in oxidation) gave *title compound* (2.20 g, 60%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 8.64 (1H, ddd*, J* 4.8, 1.8 and 1.0, 1-H), 7.84 (1H, ddd*, J* 7.8, 7.6 and 1.8, 3-H), 7.73 (1H, ddd*, J* 7.8, 1.2 and 1.0, 4-H), 7.37 (1H, ddd*, J* 7.6, 4.8 and 1.2, 2-H), 7.33 (1H, d*, J* 7.8, 6-H or 9-H), 7.26-7.17 (3H, m*,* (6-H or 9-H), 7-H and 8-H), 4.61 (1H, d*, J* 13.0, 5-H) 4.15 (1H, d*, J* 13.0, 5-H); δ_C (100 MHz, $CDCl_3$) 164.0 (C), 149.7 (CH), 137.9 (CH), 135.1 (C), 132.8 (CH), 129.8 (CH), 129.7 (CH), 128.1 (C), 126.8 (CH), 125.0 (CH), 120.3 (CH), 58.3 (CH_2); **IR** ($CHCl_3$)/cm^{-1} 3057, 3007, 1578, 1563, 1475, 1452, 1424,

1085, 1055, 1038, 992, 868; **HRMS** (ESI+) *m/z* calculated for $[C_{12}H_{10}ClNNaOS]^+$: 274.0069, found 274.0051.

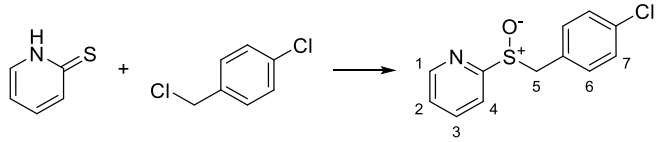
2-((3-Chlorolbenzyl)sulfinyl)pyridine (212ah)



General procedure B: 3-chlorobenzylchloride (1.3 mL, 10 mmol), 2-mercaptopyridine (**221**, 1.3 g, 12 mmol), NaOEt (4.5 mL, 12 mmol), EtOH (50 mL), *m*CPBA (2.4 g, 9.9 mmol) and CH_2Cl_2 (100 mL) (99% of crude sulfide used in oxidation) gave *title compound* (1.39 g, 56%) as a colourless solid.

M.p. 75-78 °C; δ_H (400 MHz, $CDCl_3$) 8.65 (1H, ddd, *J* 4.8, 1.7 and 1.0, 1-H), 7.78 (1H, dd, *J* 7.8 and 7.7, 1.7, 3-H), 7.58 (1H, d, *J* 7.8, 1.3 and 1.0, 4-H), 7.34 (1H, ddd, *J* 7.7, 4.8 and 1.3, 2-H), 7.21 (1H, d, *J* 8.1, 7-H), 7.14 (1H, dd, *J* 8.1 and 7.8, 8-H), 6.91 (1H, d, *J* 7.8, 9-H), 6.90 (1H, s, 6-H), 4.33 (1H, d, *J* 13.2, 5-H), 4.04 (1H, d, *J* 13.2, 5-H); δ_C (100 MHz, $CDCl_3$) 163.5 (C), 149.5 (CH), 137.8 (CH), 134.1 (C), 131.3 (C), 130.2 (CH), 129.5 (CH), 128.5 (CH), 128.3 (CH), 124.8 (CH), 120.7 (CH), 59.2 (CH_2); **IR** (ATR)/cm^{-1} 3047, 1597, 1576, 1559, 1476, 1451, 1424, 1119, 1081, 1075, 1046, 1036, 998, 990, 895, 876, 802, 777, 702; **HRMS** (ESI+) *m/z* calculated for $[C_{12}H_{10}ClNNaOS]^+$: 274.0069, found 274.0059.

2-((4-Chlorobenzyl)sulfinyl)pyridine (212ai)[247]

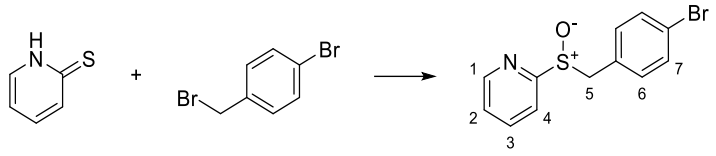


General procedure B: 4-chlorobenzylchloride (1.3 mL, 10 mmol), 2-mercaptopyridine (**221**, 1.3 g, 12 mmol), NaOEt (4.5 mL, 12 mmol), EtOH (50 mL), *m*CPBA (2.4 g, 9.7 mmol) and CH_2Cl_2 (100 mL) (98% of crude sulfide used in oxidation) gave *title compound* (2.39 g, 97%) as a colourless solid.

M.p. 78-82 °C; δ_H (400 MHz, $CDCl_3$) 8.67 (1H, ddd, *J* 4.9, 1.8 and 1.1, 1-H), 7.80 (1H, dd, *J* 7.9 and 7.7, 1.8, 3-H), 7.58 (1H, ddd, *J* 7.9, 1.3 and 1.1, 4-H), 7.33 (1H, ddd, *J* 7.6, 4.7 and 1.3, 2-H), 7.16 (2H, d, *J* 8.3, 6-H), 6.89 (2H, d, *J* 8.3, 7-H), 4.34 (1H, d, *J* 13.2, 5-H), 4.06 (1H, d, *J* 13.2, 5-H); δ_C (100 MHz, $CDCl_3$) 163.4 (C), 149.4 (CH), 137.8 (CH), 134.4 (C), 131.6 (CH), 128.5 (CH), 127.7 (C), 124.8 (CH), 120.8 (CH), 58.7 (CH_2); **HRMS**

(ESI+) *m/z* calculated for $[C_{12}H_{10}ClNNaOS]^+$: 274.0069, found 274.0061. Data agrees with literature.

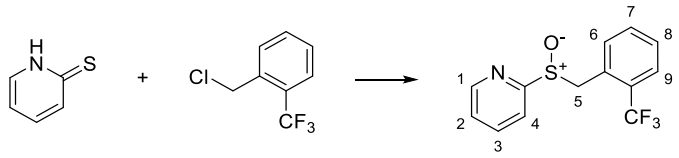
2-((4-Bromobenzyl)sulfinyl)pyridine (212aj)



To a solution of 2-mercaptopyridine (**221**, 390 mg, 3.5 mmol) in MeCN (35 mL) was added K_2CO_3 (580 mg, 4.2 mmol) and 4-bromobenzyl bromide (880 mg, 3.5 mmol). After 22 h water (40 mL) was added and this was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give the crude sulfide. To a solution of the crude sulfide (3.5 mmol) in CH_2Cl_2 (35 mL) was added *m*CPBA (77 wt%, 790 mg, 3.5 mmol). After 30 min NaOH (1 M in water, 10 mL) was added, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic phases were dried ($MgSO_4$) and column chromatography (50-60% EtOAc/petroleum ether) gave *title compound* (780 mg, 76%) as a colourless solid.

M.p. 86-88 °C; **δ_H** (400 MHz, $CDCl_3$) 8.66 (1H, ddd, *J* 4.7, 1.7 and 1.0, 1-H), 7.80 (1H, ddd, *J* 7.8, 7.6 and 1.7, 3-H), 7.58 (1H, ddd, *J* 7.8, 1.2 and 1.0, 4-H), 7.35 (1H, ddd, *J* 7.6, 4.7 and 1.2, 2-H), 7.34 (2H, d, *J* 8.4, 7-H x 2), 6.85 (2H, d, *J* 8.4, 6-H x 2), 4.31 (1H, d, *J* 13.2, 5-H), 4.04 (1H, d, *J* 13.2, 5-H); **δ_C** (100 MHz, $CDCl_3$) 163.4 (C), 149.5 (CH), 137.9 (CH), 132.0 (CH), 131.5 (CH), 128.3 (C), 124.8 (CH), 122.7 (C), 120.9 (CH), 58.9 (CH_2); **IR** (ATR)/cm^{-1} 3007, 1578, 1488, 1453, 1424, 1098, 1072, 1049, 1013, 821; **HRMS** (ESI+) *m/z* calculated for $[C_{12}H_{10}BrNNaOS]^+$: 317.9559, found 317.9571. **CHN** calculated for $C_{12}H_{10}BrNOS$: C 48.66, H 3.40, N 4.73 found: C 48.65, H 3.19, N 4.65.

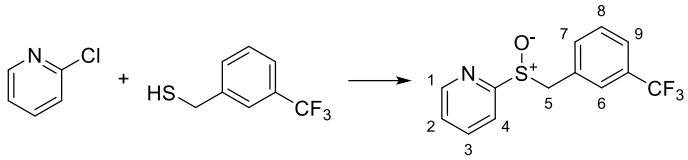
2-((2-(Trifluoromethyl)benzyl)sulfinyl)pyridine (212ak)



General procedure B: 2-(trifluoromethyl)benzylchloride (1.5 mL, 10 mmol), 2-mercaptopyridine (**221**, 1.30 g, 12 mmol), NaOEt (4.5 mL, 12 mmol), EtOH (50 mL), *m*CPBA (2.40 g, 9.7 mmol) and CH_2Cl_2 (100 mL) (97% of crude sulfide used in oxidation) gave *title compound* (2.71 g, 96%) as a colourless solid.

M.p. 84-87 °C; **δ_H** (400 MHz, $CDCl_3$) 8.67 (1H, ddd, *J* 4.7, 1.4 and 1.3, 1-H), 7.95-7.90 (2H, m, 3-H and (6-H or 9-H)), 7.70 (1H, d, *J* 7.8, 4-H), 7.56-7.37 (4H, m, 2-H, (6-H or 9-H), 7-H and 8-H), 4.70 (1H, d, *J* 13.3, 5-H), 4.08 (1H, d, *J* 13.3, 5-H); **δ_C** (100 MHz, $CDCl_3$) 164.5 (C), 149.9 (CH), 138.1 (CH), 133.5 (CH), 132.0 (CH), 129.5 (C, q, *J* 30.0), 129.2 (C, q, *J* 1.5), 128.6 (CH), 126.6 (CH, q, *J* 5.52), 125.1 (CH), 124.1 (C, q, *J* 274.0), 120.0 (CH), 58.9 (CH_2); **IR** (ATR)/cm^{-1}, 3057, 3002, 2461, 1730, 1608, 1578, 1563, 1499, 1453, 1424, 1316, 1299, 1180, 1126, 1038, 992, 957, 881; **HRMS** (ESI+) *m/z* calculated for $[C_{13}H_{10}F_3NNaOS]^+$: 308.0333, found 308.0266.

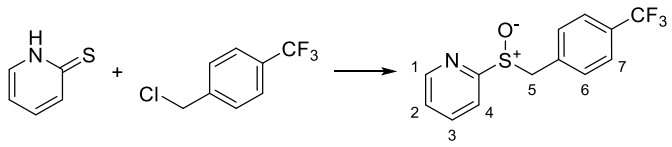
2-((3-(Trifluoromethyl)benzyl)sulfinyl)pyridine (212al)



General procedure A: 2-chloropyridine (0.39 mL, 4.2 mmol), 3-(trifluoromethyl)benzylmercaptan (960 mg, 5.0 mmol), KO*t*-Bu (560 mg, 5.0 mmol), THF (25 mL), *m*CPBA (550 mg, 2.2 mmol) and CH_2Cl_2 (25 mL) (92% of crude sulfide used in oxidation) gave *title compound* (575 mg, 52%) as a colourless solid.

M.p. 63-65 °C; **δ_H** (400 MHz, $CDCl_3$) 8.69 (1H, ddd, *J* 4.7, 1.6 and 0.9, 1-H), 7.76 (1H, ddd, *J* 7.8, 7.7 and 1.6, 3-H), 7.51 (1H, d, *J* 7.5, 9-H), 7.50 (1H, ddd, *J* 7.8, 1.1 and 0.9, 4-H) 7.40 (1H, dd, *J* 7.5 and 7.5, 8-H), 7.37 (1H, ddd, *J* 7.7, 4.7 and 1.1, 2-H), 7.31 (1H, d, *J* 7.5, 7-H), 7.00 (1H, s, 6-H), 4.41 (1H, d, *J* 13.2, 5-H), 4.15 (1H, d, *J* 13.2, 5-H); **δ_C** (101 MHz, $CDCl_3$) 163.1 (C), 149.4 (CH), 137.7 (CH), 133.9 (CH), 130.5 (C, q, *J* 32.4), 130.0 (C), 128.6 (CH), 126.7 (CH, q, *J* 3.8), 124.9 (CH, q, *J* 3.6), 124.8 (CH), 123.8 (C, q, *J* 272.2), 120.7 (CH), 58.8 (CH_2); **δ_F** (377 MHz, $CDCl_3$) 62.74 (s); **IR** (ATR)/cm^{-1} 2974, 1578, 1451, 1424, 1332, 1158, 1116, 1044, 1036; **HRMS** (ESI+) *m/z* calculated for $[C_{13}H_{10}F_3NNaOS]^+$: 308.0333, found 308.0318.

2-((4-(Trifluoromethyl)benzyl)sulfinyl)pyridine (212am)

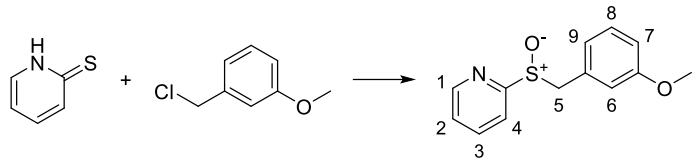


General procedure B: 4-(trifluoromethyl)benzylchloride (1.10 g, 5.72 mmol), 2-mercaptopyridine (**221**, 760 mg, 6.9 mmol), NaOEt (2.6 mL, 6.9 mmol), EtOH

(30 mL), *m*CPBA (1.40 g, 5.5 mmol) and CH_2Cl_2 (55 mL) (96% of crude sulfide used in oxidation) gave *title compound* (1.57 g, 97%) as a colourless solid.

M.p. 126-129 °C; δ_H (400 MHz, $CDCl_3$) 8.69 (1H, ddd, *J* 4.7, 1.7 and 0.9, 1-H), 7.80 (1H, ddd, *J* 8.7, 7.7 and 1.7, 3-H), 7.58 (1H, ddd, *J* 7.8, 1.1 and 0.9, 4-H), 7.49 (2H, d, *J* 8.0, 7-H x 2), 7.38 (1H, ddd, *J* 7.7, 4.7 and 1.1, 2-H), 7.12 (2H, d, *J* 8.0, 6-H x 2), 4.43 (1H, d, *J* 13.1, 5-H), 4.15 (1H, d, *J* 13.1, 5-H); δ_C (101 MHz, $CDCl_3$) 163.2 (C), 149.4 (CH), 137.8 (CH), 133.3 (C), 130.6 (CH), 130.3 (C, q, *J* 32.6), 125.1 (CH, q, *J* 3.7), 124.8 (CH), 124.0 (C, q, *J* 272.2), 120.7 (CH), 58.9 (CH_2); δ_F (377 MHz, $CDCl_3$) -62.69 (s); **IR** (ATR)/cm^{-1} 2971, 1575, 1424, 1328, 1125, 1105, 1068, 1037; **HRMS** (ESI+) *m/z*, calculated for $[C_{13}H_{10}F_3NNaOS]^+$: 308.0333, found 308.0324.

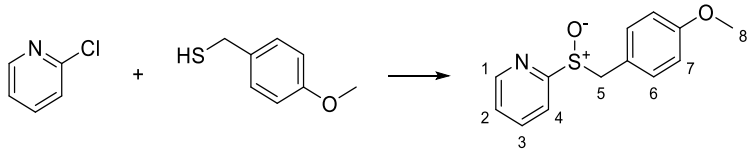
2-((3-Methoxybenzyl)sulfinyl)pyridine (212an)



General procedure B: 3-methoxybenzyl chloride (1.5 mL, 10 mmol), 2-metcaptopyridine (**221**, 1.2 g, 11 mmol), NaOEt (2.7 M in EtOH, 3.9 mL, 11 mmol), EtOH (50 mL), *m*CPBA (77 wt%, 2.3 g, 10 mmol) and CH_2Cl_2 (100 mL) gave *title compound* (2.36 g, 96%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 8.66 (1H, ddd, *J* 4.7, 1.6 and 0.8, 1-H), 7.80 (1H, ddd, *J* 7.8, 7.6 and 1.2, 3-H), 7.66 (1H, d, *J* 7.8, 1.1 and 0.9, 4-H), 7.35 (1H, dd, *J* 7.6, 4.7 and 1.1, 2-H), 7.14 (1H, dd, *J* 8.1 and 7.7, 8-H), 6.80 (1H, ddd, *J* 8.1, 1.8 and 1.4, 9-H), 6.63 (1H, ddd, *J* 7.7, 1.6 and 1.4, 7-H), 6.56 (1H, dd, *J* 1.8 and 1.6, 6-H), 4.34 (1H, d, *J* 13.1), 4.02 (1H, d, *J* 13.1), 3.70 (3H, s); δ_C (100 MHz, $CDCl_3$) 163.9 (C), 159.5 (C), 149.4 (CH), 137.8 (CH), 130.9 (C), 129.4 (CH), 124.7 (CH), 122.8 (CH), 120.7 (CH), 115.4 (CH), 114.4 (CH), 60.3 (CH_2), 55.3 (CH_3); **IR** (ATR)/cm^{-1} 3010, 1731, 1601, 1579, 1491, 1454, 1424, 1268, 1168, 1155, 1086, 1048, 994, 876; **HRMS** (ESI+) *m/z* calculated for $[C_{13}H_{13}NNaO_2S]^+$: 270.0565, found 270.0561.

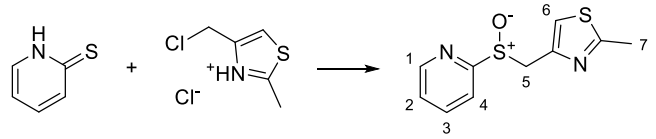
2-((4-Methoxybenzyl)sulfinyl)pyridine (212ao)



General procedure A: 2-chloropyridine (0.94 mL, 10 mmol), 4-methoxybenzylmercaptan (1.5 mL, 11 mmol), KO*t*-Bu (1.2 g, 11 mmol), THF (50 mL), *m*CPBA (290 mg, 1.2 mmol) and CH_2Cl_2 (12 mL) (12% of crude sulfide used in oxidation) gave *title compound* (243 mg, 81%) as a colourless solid.

M.p. 93-95 °C; **δ_H** (400 MHz, $CDCl_3$) 8.66 (1H, dd*, J* 4.7 and 1.6, 1-H), 7.78 (1H, ddd*, J* 7.8, 7.6 and 1.6, 3-H), 7.59 (1H, d*, J* 7.8, 4-H), 7.34 (1H, dd*, J* 7.6 and 4.7, 2-H), 6.91 (2H, d*, J* 8.7, 6-H x 2), 6.75 (2H, d*, J* 8.7, 7-H x 2), 4.31 (1H, d*, J* 13.3, 5-H), 4.02 (1H, d*, J* 13.3, 5-H), 3.76 (3H, s, 8-H_3); **δ_C** (100 MHz, $CDCl_3$) 163.9 (C), 159.7 (C), 149.4 (CH), 137.8 (CH), 131.6 (CH), 124.7 (CH), 121.2 (C), 120.8 (CH), 113.9 (CH), 59.3 (CH_3), 55.2 (CH_3); **IR** (ATR)/cm^{-1} 2971, 2926, 1609, 1575, 1560, 1510, 1448, 1420, 1301, 1248, 1180, 1046, 1035, 991, 830, 821, 773; **HRMS** (ESI+) *m/z* calculated for $[C_{13}H_{13}NNaO_2S]^+$: 270.0565, found 270.0546.

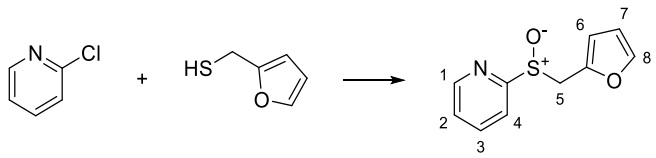
2-Methyl-4-((pyridin-2-ylsulfinyl)methyl)thiazole (212ap)



General procedure B: 2-mercaptopyridine (**221**, 870 mg, 7.8 mmol), 4-chloromethyl-2-methylthiazole hydrochloride (1.2 g, 6.5 mmol), NaOEt (5.4 mL, 14 mmol), EtOH (30 mL), *m*CPBA (1.6 g, 6.3 mmol) and CH_2Cl_2 (65 mL) (98% of crude sulfide used in oxidation) gave *title compound* (1.37 g, 90%) as a colourless gum.

δ_H (400 MHz, $CDCl_3$) 8.70 (1H, ddd, *J* 4.7, 1.7 and 0.9, 1-H), 7.88 (1H, ddd, *J* 7.8, 7.6 and 1.7, 3-H), 7.79 (1H, ddd, *J* 7.8, 1.1 and 0.9, 4-H), 7.40 (1H, ddd, *J* 7.6, 4.7 and 1.1, 2-H), 7.05 (1H, s, 6-H), 4.53 (1H, d, *J* 13.4, 5-H), 4.26 (1H, d, *J* 13.4, 5-H), 2.64 (3H, s, 7-H_3) **δ_C** (100 MHz, $CDCl_3$) 165.8 (C), 163.8 (C), 149.5 (CH), 144.4 (C), 137.6 (C), 124.6 (CH), 120.1 (CH), 118.6 (CH), 56.0 (CH_2), 19.0 (CH_3); **IR** ($CHCl_3$)/cm^{-1} 3002, 2464, 1578, 1563, 1516, 1452, 1424, 1321, 1187, 1143, 1049; **HRMS** (ESI+) *m/z* calculated for $[C_{10}H_{11}N_2OS_2]^+$: 239.0307, found 239.0309.

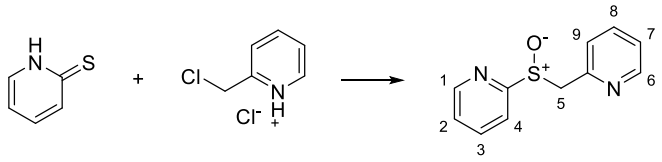
2-((Furan-2-ylmethyl)sulfinyl)pyridine (212aq)



General procedure A: 2-chloropyridine (0.94 mL, 10 mmol), furfurylmercaptan (1.1 mL, 11 mmol), KO*t*-Bu (1.2 g, 11 mmol), THF (50 mL), *m*CPBA (320 mg, 1.3 mmol) and CH_2Cl_2 (13 mL) (36% of crude sulfide used in oxidation) gave *title compound* (240 mg, 90%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 8.64 (1H, ddd*, J* 4.8, 1.7 and 0.9, 1-H), 7.84 (1H, ddd*, J* 7.8, 7.6 and 1.7, 3-H), 7.74 (1H, ddd*, J* 7.8, 1.1 and 0.9, 4-H), 7.36 (1H, dd*, J* 7.6, 4.8 and 1.1, 2-H), 7.26 (1H, d*, J* 1.9, 8-H), 6.27 (1H, dd*, J* 3.2 and 1.9, 7-H), 6.16 (1H, d*, J* 3.2, 6-H), 4.40 (1H, d*, J* 14.1, 5-H), 4.17 (1H, d*, J* 14.1, 5-H); **δ_C** (100 MHz, $CDCl_3$) 163.9 (C), 149.6 (CH), 143.9 (C), 143.6 (CH), 137.9 (CH), 124.8 (CH), 120.4 (CH), 111.6 (CH), 111.0 (CH), 53.4 (CH_2); **IR** ($CHCl_3$)/cm^{-1} 3007, 1578, 1563, 1499, 1453, 1425, 1151, 1127, 1113, 1086, 1071, 1049, 1039, 1013, 992, 936; **HRMS** (ESI+) *m/z* calculated for $[C_{10}H_9NNaO_2S]^+$:230.0252, found 230.0240.

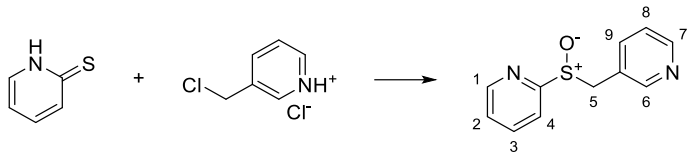
2-((Pyridin-2-ylmethyl)sulfinyl)pyridine (212ar)



General procedure B: 2-mercaptopyridine (**221**, 1.3 g, 12 mmol), 2-picolyl chloride hydrochloride (1.6 mg, 10 mmol), NaOEt (8.2 mL, 22 mmol), EtOH (50 mL), *m*CPBA (2.4 g, 9.8 mmol) and CH_2Cl_2 (100 mL) (98% of crude sulfide used in oxidation) gave *title compound* (2.02 g, 92%) as a colourless solid.

M.p. 73-75 °C; δ_H (400 MHz, $CDCl_3$) 8.67 (1H, ddd, *J* 4.7, 1.7 and 1.0, 1-H), 8.48 (1H, ddd, *J* 4.9, 1.8 and 1.0, 6-H), 7.82 (1H, ddd, *J* 7.8, 7.6 and 1.7, 3-H), 7.71 (1H, dd, *J* 7.8, 1.1 and 1.0, 4-H), 7.63 (1H, 7.7, 7.6 and 1.8, 8-H), 7.36 (1H, ddd, *J* 7.6, 4.7 and 1.1, 2-H), 7.23 (1H, 7.7, 1.4 and 1.0, 9-H), 7.19 (1H, ddd, *J* 7.7, 4.9 and 1.18, 7-H), 4.53 (1H, d*, J* 13.0, 5-H), 4.23 (1H, d*, J* 13.0, 5-H); **δ_C** (100 MHz, $CDCl_3$) 163.8 (C), 150.6 (C), 149.8 (CH), 149.6 (CH), 137.7 (CH), 136.3 (CH), 125.3 (CH), 124.7 (CH), 122.8 (CH), 120.1 (CH), 62.2 (CH_2); **IR** (ATR)/cm^{-1} 3090, 3048, 1594, 1576, 1560, 1469, 1451, 1437, 1423, 1395, 1087, 1046, 1037, 993, 764, 748; **HRMS** (ESI+) *m/z* calculated for $[C_{11}H_{11}N_2OS]^+$: 219.0587, found 219.0593.

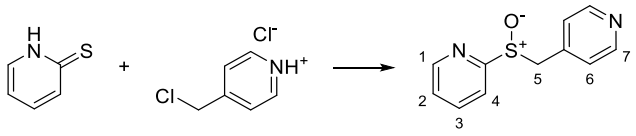
2-((Pyridin-3-ylmethyl)sulfinyl)pyridine (212as)



General procedure B: 2-mercaptopyridine (**221**, 1.3 g, 12 mmol), 3-picolyl chloride hydrochloride (1.6 g, 10 mmol), NaOEt (8.2 mL, 22 mmol), EtOH (50 mL), *m*CPBA (2.3 g, 9.5 mmol) and CH_2Cl_2 (100 mL) (95% of crude sulfide used in oxidation) gave *title compound* (1.79 g, 84%) as a colourless solid.

M.p. 108-112 °C; **δ_H** (400 MHz, $CDCl_3$) 8.64 (1H, d*, J* 4.7, 1-H), 8.43 (1H, d*, J* 4.8, 7-H), 7.98 (1H, d*, J* 1.6, 6-H), 7.73 (1H, dd*, J* 7.8 and 7.6, 3-H), 7.46 (1H, d*, J* 7.8, 4-H), 7.40 (1H, dd, 7.8 and 1.6, 9-H), 7.29 (1H, dd*, J* 7.6 and 4.7, 2-H), 7.15 (1H, dd*, J* 7.8 and 4.8, 8-H), 4.31 (1H, d*, J* 13.4, 5-H), 4.08 (1H, d*, J* 13.4, 5-H); **δ_C** (100 MHz, $CDCl_3$) 162.7 (C), 150.5 (CH), 149.4 (CH), 149.1 (CH), 137.6 (CH x 2), 124.9 (C), 124.7 (CH), 122.8 (CH), 120.6 (CH), 55.9 (CH_2); **IR** (ATR)/cm^{-1} 3057, 2966, 2927, 1577, 1562, 1480, 1448, 1425, 1217, 1143, 1098, 1045, 1034, 1029, 991, 880, 807, 776, 712; **HRMS** (ESI+) *m/z*, calculated for $[C_{11}H_{11}N_2OS]^+$: 219.0587, found 219.0593.

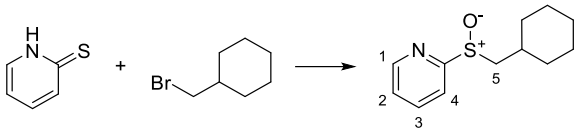
2-((Pyridin-4-ylmethyl)sulfinyl)pyridine (212at)



General procedure B: 2-mercaptopyridine (**221**, 1.3 g, 12 mmol), 4-picolyl chloride hydrochloride (1.6 g, 10 mmol), NaOEt (8.2 mL, 22 mmol), EtOH (50 mL), *m*CPBA (1.1 g, 4.4 mmol) and CH_2Cl_2 (45 mL) (96% of crude sulfide used in oxidation) gave *title compound* (701 mg, 34%) as a pale orange solid.

M.p. 106-110 °C; **δ_H** (400 MHz, $CDCl_3$) 8.66 (1H, ddd*, J* 4.7, 1.7 and 0.9, 1-H), 8.43 (2H, dd*, J* 4.4 and 1.6, 7-H x 2), 7.77 (1H, ddd*, J* 7.8, 7.7 and 1.7, 3-H), 7.54 (1H, ddd, 7.8, 1.1 and 0.9, 4-H), 7.35 (1H, ddd*, J* 7.7, 4.7 and 1.1, 2-H), 6.88 (2H, dd*, J* 4.4 and 1.6, 6-H x 2), 4.33 (1H, d*, J* 13.1, 5-H), 4.06 (1H, d*, J* 13.1, 5-H); **δ_C** (100 MHz, $CDCl_3$) 162.8, 149.5, 149.4, 138.0, 137.8, 125.0, 124.9, 120.6, 58.0; **IR** (ATR)/cm^{-1} 3026, 2908, 1599, 1579, 1559, 1455, 1425, 1046, 1037, 992, 779; **HRMS** (ESI+) *m/z* calculated for $[C_{11}H_{11}N_2OS]^+$: 219.0587, found 219.0597.

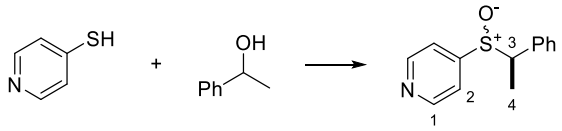
2-((Cyclohexylmethyl)sulfinyl)pyridine (212au)



Performed by general procedure A: (bromomethyl)cyclohexane (1.4 mL, 10 mmol), 2-mercaptopyridine (**221**, 1.3 g, 12 mmol), NaOEt (4.5 mL, 12 mmol), and EtOH (50 mL), *m*CPBA (2.0 g, 8.2 mmol) and CH_2Cl_2 (80 mL) (98% of crude sulfide used for oxidation) gave *title compound* (1.79 g, 82%) as a pale yellow oil.

δ_H (400 MHz, $CDCl_3$) 8.58 (1H, d, *J* 4.8, 1-H), 7.99 (1H, dd, *J* 7.8 and 1.2, 4-H), 7.90 (1H, ddd, *J* 7.8, 7.6 and 1.7, 3-H), 7.33 (1H, ddd, *J* 7.6, 4.8 and 1.2, 2-H), 2.89 (1H, ddd, *J* 13.1, 9.5 and 1.6, 5-H), 2.71 (1H, ddd, *J* 13.1, 4.5 and 1.6, 5-H), 2.19-1.96 (2H, m, Cy-H x 2), 1.79-1.58 (4H, m, Cy-H x 4), 1.37-0.99 (5H, m, Cy-H x 5); **δ_C** (100 MHz, $CDCl_3$) 165.8 (C), 149.5 (CH), 138.0 (CH), 124.4 (CH), 119.6 (CH), 63.4 (CH_2), 33.4 (CH), 32.9 (CH_2), 32.1 (CH_2), 26.0 (CH_2), 25.9 (CH_2), 25.6 (CH_2); **IR** ($CHCl_3$)/cm^{-1} 2999, 2929, 2856, 1578, 1564, 1451, 1424, 1085, 1031, 993; **HRMS** (ESI) *m/z* calculated for $[C_{13}H_{13}NNaO_2S]^+$: 224.1104, found 224.1105.

4-((1-Phenylethyl)sulfinyl)pyridine (212av)

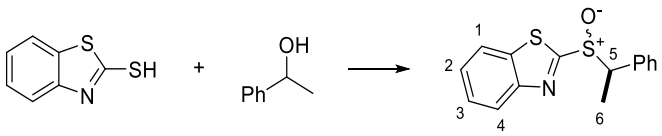


A solution of DMF (120 µL, 1.7 mmol) in CH_2Cl_2 (3 mL) was cooled to 0 °C before charging $(COCl)_2$ (130 µL, 1.5 mmol) and stirring at 0 °C for 30 min; until effervescence stopped. The reaction mixture was concentrated *in vacuo* at rt before adding THF (15 mL) and cooling the mixture to 0 °C. 1-Phenylethanol (170 µL, 1.5 mmol), Et_3N (420 µL, 3.0 mmol) and 4-metcaptopyridine (110 mg, 1.0 mmol) were added and the reaction mixture was allowed to warm to rt and was stirred for 22 h. Brine (10 mL) was added and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) before concentrating *in vacuo*. Column chromatography (40% EtOAc/petroleum ether) gave 4-((1-phenylethyl)thio)pyridine (47 mg, 22%) as a pale yellow oil.

Performed by general procedure D: 4-((1-phenylethyl)thio)pyridine (45 mg, 0.21 mmol), CH_2Cl_2 (3 mL) and *m*CPBA (77 wt%, 47 mg, 0.21 mmol) gave *title compound* (42 mg, 87%, 0.3:0.7 mixture of diastereomers) as a colourless solid.

δ_H (400 MHz, $CDCl_3$) 8.59 (1.4 H, d, *J* 4.5, 1-H x 1.4), 8.55 (0.6H, d, *J* 4.5, 1-H x 0.6), 7.34-7.22 (3H, m, Ph-H x 3), 7.10 (1.4H, d, *J* 4.5, 2-H x 1.4), 7.05-7.02 (1.4H, m, Ph-H x 1.4), 6.98-6.94 (1.2H, m, 2-H x 0.6 and Ph-H x 0.6), 4.12 (0.3H, q, *J* 7.2, 3-H x 0.3), 3.81 (0.7H, q, *J* 7.1, 3-H x 0.7), 1.72 (2.1H, d, *J* 7.1, 4-H x 2.1), 1.64 (0.9H, d, *J* 7.2, 4-H x 0.9); δ_C (100 MHz, $CDCl_3$) 152.6 (C), 151.0 (C), 149.8 (CH), 149.5 (CH), 134.8 (C), 132.9 (C) 129.0 (CH), 128.9 (CH), 128.8 (CH), 128.7 (2 x CH), 128.4 (CH), 119.4 (CH), 119.2 (CH), 67.4 (CH), 64.1 (CH), 14.4 (CH_3), 12.0 (CH_3); **IR** ($CHCl_3$)/cm^{-1} 1602, 1454, 1404, 1099, 1081, 1047; **HRMS** (ESI+) *m/z* calculated for $[C_{13}H_{13}NNaOS]^+$: 254.0610, found 254.0608.

2-((1-Phenylethyl)sulfinyl)benzo[d]thiazole (212ax)



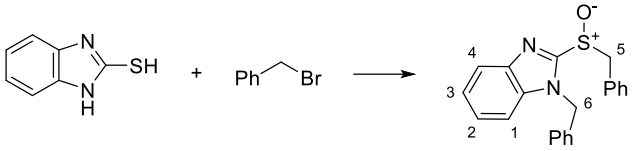
A solution of DMF (110 µL, 1.4 mmol) in CH_2Cl_2 (3 mL) was cooled to 0 °C before charging $(COCl)_2$ (110 µL, 1.2 mmol) and stirring at 0 °C for 5 min; until effervescence stopped. The reaction mixture was concentrated *in vacuo* at rt before adding THF (10 mL) and cooling the mixture to 0 °C. 1-Phenylethanol (140 µL, 1.2 mmol), Et_3N (0.35 mL, 2.5 mmol) and 2-mercaptobenzothiazole (140 mg, 0.83 mmol) were added and the reaction mixture was allowed to warm to rt and was stirred for 4 h. Water (10 mL) and brine (10 mL) was added and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) before concentrating *in vacuo*. Column chromatography (3% EtOAc/petroleum ether) gave 2-((1-phenylethyl)thio)benzo[d]thiazole as a pale yellow oil (144 mg, 60%).

General procedure B using 2-((1-phenylethyl)thio)benzo[d]thiazole (78 mg, 0.29 mmol) and *m*CPBA (77 wt%, 65 mg, 0.29 mmol) in CH_2Cl_2 (3 mL). The crude product was purified by column chomatography (5-20% EtOAc/petroleum ether) to give *title compound* (83 mg, 64%, 3:1 ratio of diastereomers) as a yellow solid.

Major diastereomer: δ_H (400 MHz, $CDCl_3$) 8.07 (1H, ddd, *J* 8.3, 1.2 and 0.7, 1-H or 4-H), 7.96 (1H, ddd, *J* 8.2, 1.3 and 0.7, 1-H or 4-H), 7.56 (1H, ddd, *J* 8.3, 7.2 and 1.3, 2-H or 3-H), 7.48 (1H, ddd, *J* 8.2, 7.2 and 1.2, 2-H or 3-H), 7.35-7.28 (5H, m, Ph-H x 5), 4.46 (1H, q, *J* 7.1, 5-H), 1.68 (3H, d, *J* 7.1, 6-H_3); δ_C (101 MHz, $CDCl_3$) 176.7 (C), 154.0 (C), 136.2 (C), 135.4 (C), 129.0 (CH), 128.9 (CH), 128.9 (CH), 127.0 (CH), 126.2 (CH), 124.1 (CH), 122.3 (CH), 66.8 (CH), 11.9 (CH_3); **IR** (ATR)/cm^{-1} 2927, 1555, 1493, 1470, 1453,

1424, 1370, 1312, 1064; **HRMS** (ESI+) *m/z* calculated for $[C_{15}H_{13}NOS_2Na]^+$: 310.0331, found 310.0338.

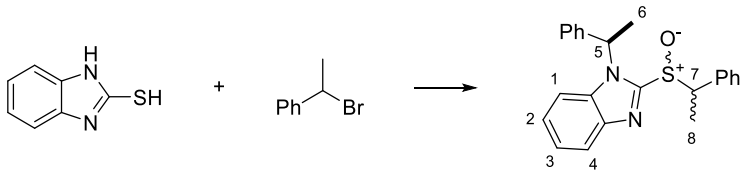
1-Benzyl-2-(benzylsulfinyl)-1H-benzo[d]imidazole (212ay)



Work performed by Mindaugas Šiaučiulis. General procedure B using 1-benzyl-2-(benzylthio)-1H-benzo[d]imidazole (330 mg, 1.00 mmol), *m*CPBA (224 mg, 77 wt%, 1.00 mmol) in CH_2Cl_2 (10 mL) afforded title compound (310 mg, 90%) as a pale yellow solid.

δ_H (400 MHz, $CDCl_3$) 7.90 (1 H, dd, *J* 8.6, 1.0, 1-H or 4-H), 7.35 (1H, ddd, *J* 7.6, 7.1 and 1.3, 2-H or 3-H), 7.34-7.21 (8H, m, Ph-H x 6, 2-H or 3-H and 1-H or 4-H), 7.16-7.13 (2H, m, Ph-H x 2), 7.03-6.99 (2H, m, Ph-H x 2), 5.48 (1H, d, *J* 16.0, 6-H), 5.20 (1H, d, *J* 16.0, 6-H), 4.67 (1H, d, *J* 12.7, 5-H), 4.50 (1H, d, *J* 12.7, 5-H); **δ_C** (400 MHz, $CDCl_3$) 150.9 (C), 142.5 (C), 136.2 (C), 135.7 (C), 130.8 (CH), 129.1 (C), 129.0 (CH), 128.9 (CH), 128.8 (CH), 128.2 (CH), 127.0 (CH), 124.9 (CH), 123.7 (CH), 121.1 (CH), 110.9 (CH), 60.7 (CH_2), 47.5 (CH_2); **IR** ($CHCl_3$)/cm^{-1} 3037, 3010, 1603, 1497, 1431, 1424, 1230, 1212, 1202, 1056; **HRMS** (ESI+) *m/z* calculated for $[C_{21}H_{18}N_2SONa]^+$: 369.1032, found 369.1036.

1-(1-Phenylethyl)-2-((1-phenylethyl)sulfinyl)-1H-benzo[d]imidazole (212az)



To a solution of 2-mercaptobenzimidazole (300 mg, 2.0 mmol) in EtOH (10 mL) was added NaOEt (21 wt% in EtOH, 1.9 mL, 5.0 mmol) and 1-bromoethylbenzene (540 µL, 4.0 mmol) and this was stirred for 2 h before being heated under reflux for 2 h. The reaction mixture was allowed to cool to rt and 1-bromoethylbenzene (140 µL, 1.0 mmol) was added and the reaction mixture was heated under reflux for 2 h. Brine (10 mL) was added before removing the organic solvent *in vacuo*. This was extracted with EtOAc (3 x 15 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (10% EtOAc/petroleum ether) gave

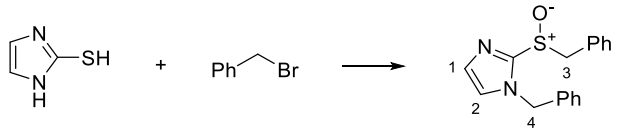
1-(1-phenylethyl)-2-((1-phenylethyl)thio)-1H-benzo[d]imidazole as a colourless oil (410 mg, 57%, 1.4:1.6 mixture of diastereomers).

General procedure D: 2-((1-phenylethyl)thio)-1H-benzo[d]imidazole (350 mg, 1.0 mmol), CH_2Cl_2 (10 mL) and *m*CPBA (220 mg, 1.0 mmol) gave *title compound* (384 mg, quant., 0.5:1.0 ratio of mixture of diastereomers 1 (less polar, colourless oil, 0.2:0.8 ratio of two diastereomers) to mixture of diastereomers 2 (more polar, colourless oil, 0.5:0.5 ratio of two diastereomers).

Mixture of diastereomers 1: δ_H (400 MHz, $CDCl_3$) 8.13 (0.2H, dd, *J* 1.9 and 1.6 4-H x 0.2), 8.03 (0.2H, ddd, *J* 7.9, 1.6 and 1.2, 3-H x 0.2), 7.88 (0.8H, dd, *J* 8.4 and 8.4, 3-H x 0.8), 7.60 (0.2 H, ddd, *J* 8.0, 1.9 and 1.2, 1-H x 0.2), 7.44 (0.2 H, dd, *J* 8.0 and 7.9, 2-H x 0.2), 7.37-7.24 (9.2H, m, 1-H x 0.8, 2-H x 0.8, 4-H x 0.8 and Ph-H x 6.8) 7.21 (1H, m, Ph-H), 7.17-7.44 (0.8H, m, Ph-H x 0.8), 7.04-7.00 (0.4 H, m, Ph-H x 0.4), 6.98-6.92 (1H, m, Ph-H), 6.58 (1H, q, *J* 7.1, 5-H), 4.86 (1H, app. dq, *J* 7.3 and 4.3, 7-H), 1.89 (1.2H, d, *J* 7.1, 6-H x 1.2), 1.84 (1.8H, d, *J* 7.3, 8-H x 1.8), 1.74 (1.2H, d, *J* 7.3, 8-H x 1.2), 1.46 (1.8H, d, *J* 7.1, 6-H x 1.8); δ_C (100 MHz, $CDCl_3$) 150.2 (C), 149.9 (C), 139.4 (C), 139.0 (C), 135.2 (C), 135.1 (C), 134.7 (C), 134.4 (C), 134.3 (C), 133.4 (CH), 131.8 (C), 130.3 (CH), 129.3 (CH), 129.3 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.3 (CH), 127.8 (CH), 127.8 (CH), 126.5 (CH x 2) 124.2 (CH), 124.0 (CH), 123.3 (CH), 123.3 (CH), 121.1 (CH), 120.9 (CH), 113.4 (CH), 113.1 (CH), 65.1 (CH), 64.6 (CH), 53.9 (CH), 53.3 (CH), 18.9 (CH_3), 18.1 (CH_3), 15.6 (CH_3), 14.9 (CH_3); **IR** ($CHCl_3$)/cm^{-1} 3009, 1703, 1496, 1454, 1433, 1264, 909; **HRMS** (ESI+) *m/z* calculated for $[C_{23}H_{23}N_2OS]^+$: 375.1526, found 375.1527.

Mixture of diastereomers 2: δ_H (400 MHz, $CDCl_3$) 7.88 (1H, ddd, *J* 8.2, 3.0 and 1.0, 4-H), 7.38-7.12 (11H, m, 2-H, 3-H, Ph-H x 9), 6.93 (0.5H, ddd, *J* 8.3, 1.0 and 0.9 1-H x 0.5), 6.85 (0.5H, ddd, *J* 8.4, 1.0 and 0.9, 1-H x 0.5), 6.62 (1H, dd, *J* 8.3 and 1.2, Ph-H), 6.18 (0.5H, q, *J* 7.1, 5-H x 0.5), 5.97 (0.5H, q, *J* 7.1, 5-H x 0.5), 5.28 (0.5H, q, *J* 7.2, 7-H x 0.5), 5.15 (0.5H, q, *J* 7.2, 7-H x 0.5), 1.95 (3H, d, *J* 7.2, 8-H_3), 1.89 (1.5H, d, *J* 7.1, 6-H x 1.5), 1.32 (1.5H, d, *J* 7.1, 6-H x 1.5); δ_C (100 MHz, $CDCl_3$) 152.9 (C), 152.2 (C), 143.3 (C), 143.2 (C), 138.6 (C), 138.4 (C), 135.0 (C), 134.8 (C), 133.7 (C), 133.6 (C), 129.2 (CH), 129.1 (CH x 2), 129.0 (CH), 128.9 (CH), 128.8 (CH), 128.8 (CH), 128.7 (CH), 128.1 (CH), 127.9 (CH), 126.3 (CH x 2), 124.3 (CH), 124.2 (CH), 123.3 (CH), 123.2 (CH), 121.4 (CH x 2), 113.0 (CH), 112.9 (CH), 64.8 (CH), 64.0 (CH), 54.4 (CH), 54.1 (CH), 18.7 (CH_3), 18.0 (CH_3), 15.7 (CH_3), 15.3 (CH_3); **IR** ($CHCl_3$)/cm^{-1} 3009, 1704, 1495, 1454, 1432, 1257, 909; **HRMS** (ESI+) *m/z* calculated for $[C_{23}H_{23}N_2OS]^+$: 375.1526, found 375.1528.

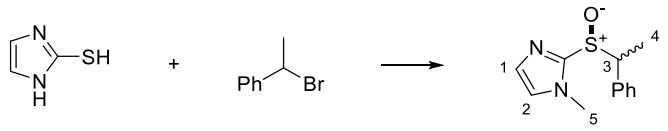
1-Benzyl-2-(benzylsulfinyl)-1H-imidazole (212ba)



General procedure B: 2-mercaptoimidazole (510 mg, 5.1 mmol), BnBr (1.2 mL, 9.7 mmol), NaOEt (2.7 M in EtOH, 3.8 mL, 10.1 mmol) and EtOH (25 mL) afforded sulfide (900 mg). Sulfide (860 mg) *m*CPBA (77 wt%, 690 mg, 3.1 mmol) and CH_2Cl_2 (30 mL) and column chromatography (30-50% EtOAc/petroleum ether) afforded *title compound* (700 mg, 48%) as a colourless solid.

M.p. 90-93 °C; δ_H (400 MHz, $CDCl_3$) 7.42-7.25 (7H, m, 2-H and Ph-H x 6), 7.16 (2H, d, *J* 6.5, Ph-H x 2), 6.98 (2H, dd, *J* 6.5 and 3.0, Ph-H x 2), 6.88 (1H, d, *J* 1.0, 1-H), 5.19 (1H, d, *J* 15.1, 4-H), 4.84 (1H, d, *J* 15.1, 4-H), 4.68 (1H, d, *J* 12.5, 3-H), 4.45 (1H, d, *J* 12.5, 3-H); δ_C (100 MHz, $CDCl_3$) 144.2 (C), 135.4 (C), 130.8 (CH), 130.3 (CH), 129.3 (C), 129.0 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 127.7 (CH), 123.5 (CH), 60.2 (CH_2), 49.9 (CH_2); **IR** (ATR)/cm^{-1} 3094, 3062, 3033, 2974, 2929, 1496, 1454, 1430, 1265, 1036, 913, 900, 798, 771, 714, 702, 495, 481, 463; **HRMS** (ESI+) *m/z* calculated for $[C_{17}H_{17}N_2OS]^+$: 297.1056, found 297.1056.

1-Methyl-2-((1-phenylethyl)sulfinyl)-1H-imidazole (212bb)

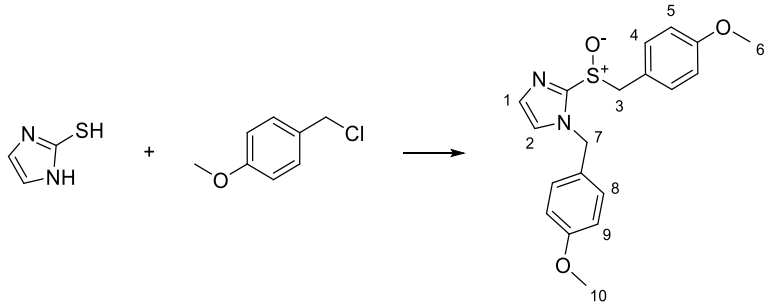


Work performed by Mindaugas Šiaučiulis. To a solution of 2-((1-phenylethyl)thio)-1H-imidazole (150 mg, 0.74 mmol) in DMF (10 mL) was added NaH (19 mg, 60 wt% in mineral oil, 0.81 mmol) at 0°C and stirred for 10 min. To the resulting solution was added iodomethane (50 µL, 0.81 mmol) and stirred overnight. The reaction was quenched with MeOH (1 mL) and brine (10 mL). This mixture was extracted with CH_2Cl_2 (2 x 15 mL) and the combined organic layers were washed with brine (5 x 20 mL). The organic layer was dried ($MgSO_4$), and concentrated *in vacuo* to give 1-methyl-2-((1-phenylethyl)thio)-1H-imidazole (113 mg, 71%) as a yellow oil.

General procedure B using 1-methyl-2-((1-phenylethyl)thio)-1H-imidazole (109 mg, 0.500 mmol) and *m*CPBA (112 mg, 77 wt%, 0.50 mmol) in CH_2Cl_2 (5 mL) afforded title compound (107 mg, 91% as a 0.7:0.3 ratio of diastereomers) as a yellow solid.

δ_H (300 MHz, $CDCl_3$) 7.35-7.21 (3 H, m, Ph-H x 3), 7.18 (0.7 H, d, *J* 1.1, 2-H x 0.7), 7.16 (0.3 H, d, *J* 1.2, 2-H x 0.3), 7.07-6.98 (2 H, m, Ph-H x 2), 6.77 (0.7 H, d, *J* 1.1, 1-H x 0.7), 6.72 (0.3 H, d, *J* 1.1, 1-H x 0.3), 4.65 (0.7 H, q, *J* 7.2, 3-H x 0.7), 4.34 (0.3 H, q, *J* 7.3, 3-H x 0.3), 3.17 (2.1 H, s, 5-H x 2.1), 3.03 (0.9 H, s, 5-H x 0.9), 1.83 (2.1 H, d, *J* 7.3, 4-H x 2.1), 1.80 (0.9 H, d, *J* 7.3, 4-H x 0.9); **δ_C** (101 MHz, $CDCl_3$, major diastereomer) 143.6 (C), 134.9 (C), 130.3 (CH), 128.9 (CH), 128.7 (CH), 128.4 (CH), 124.2 (CH), 65.2 (CH), 32.9 (CH_3), 14.5 (CH_3); **IR** ($CHCl_3$)/cm^{-1} 3117, 3065, 29933, 2872, 1475, 1465, 1413, 1278, 1052, 915; **HRMS** (ESI+) *m/z* calculated for $[C_{12}H_{14}N_2OSNa]^+$: 257.0719, found 257.0726.

1-(4-Methoxybenzyl)-2-((4-methoxybenzyl)sulfinyl)-1H-imidazole (212bc)



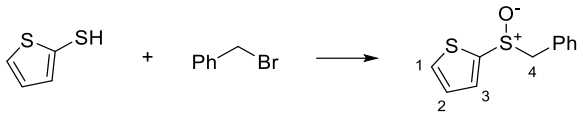
Work performed by Mindaugas Šiaučiulis. General procedure A using 2-mercaptoimidazole (200 mg, 2.00 mmol), 4-methoxybenzyl chloride (600 µL, 4.40 mmol), and KO*t*-Bu (560 mg, 5.0 mmol) in EtOH (10 mL). Crude product was purified by column chromatography (EtOAc/petroleum ether 30-60%) to afford 1-(4-methoxybenzyl)-2-((4-methoxybenzyl)thio)-1H-imidazole (185 mg, 27%) as a yellow oil.

General procedure B using 1-(4-methoxybenzyl)-2-((4-methoxybenzyl)thio)-1H-imidazole (180 mg, 0.530 mmol) and *m*CPBA (120 mg, 77 wt%, 0.530 mmol) in CH_2Cl_2 (5 mL). The crude product was purified by column chromatography to afford *title compound* (125 mg, 0.350 mmol, 66%) as a pale yellow solid.

M.p. 95 °C (decomp.); **δ_H** (300 MHz, $CDCl_3$) 7.22 (1 H, d, *J* 1.2, 2-H), 7.09-7.00 (2 H, m, (4, 5, 8, 9)-H x 2), 6.96-6.68 (7 H, m, 1-H and (4, 5, 8, 9)-H x 6), 5.10 (1 H, d, *J* 14.9, 7-H), 4.82 (1 H, d, *J* 14.9, 7-H), 4.64 (1 H, d, *J* 12.5, 3-H), 4.39 (1 H, d, *J* 12.5, 3-H), 3.79 (3 H, s, 6-H_3 or 10-H_3), 3.77 (3 H, s, 6-H_3 or 10-H_3); **δ_C** (101 MHz, $CDCl_3$) 160.0 (C), 159.7 (C), 144.3 (C), 132.0 (CH), 130.4 (CH), 129.3 (CH), 127.5 (C), 123.2 (CH), 121.0 (C), 114.4 (CH), 114.3 (CH), 59.5 (CH_2), 55.4 (CH_3 x 2), 49.5 (CH_2); **IR** (ATR)/cm^{-1} 3008, 2962, 2653,

2839, 1161, 1513, 1463, 1303, 1251, 1178, 1035; **HRMS** (ESI+) *m/z* calculated for $[C_{19}H_{21}N_2O_3S]^+$: 357.1267, found 357.1276

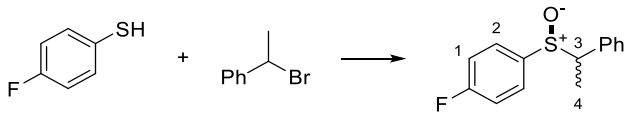
2-(Benzylsulfinyl)thiophene (212bd)



General procedure B: 2-mercaptothiophene (0.40 mL, 4.3 mmol), BnBr (0.49 mL, 4.1 mmol), NaOEt (2.7 M in EtOH, 1.6 mL, 4.3 mmol) and EtOH (22 mL) afforded sulfide (924 mg). Sulfide (903 mg), *m*CPBA (980 mg, 4.4 mmol) and CH_2Cl_2 (50 mL) and column chromatography (10-30% EtOAc/petroleum ether) afforded *title compound* (840 mg, 92%) as a colourless solid.

M.p. 60-63 °C; δ_H (400 MHz, $CDCl_3$) 7.65 (1H, dd, *J* 5.0 and 1.3, 1-H), 7.36-7.28 (3H, m, Ph-H x 3), 7.15 (1H, dd, *J* 3.7 and 1.3, 3-H), 7.12 (2H, m, Ph-H x 2), 7.06 (1H, dd, *J* 5.0 and 3.7, 2-H), 4.39 (1H, d, *J* 12.4, 4-H), 4.18 (1H, d, *J* 12.4, 4-H); δ_C (101 MHz, $CDCl_3$) 145.0 (C), 131.2 (CH), 130.3 (CH), 129.8 (CH), 129.3 (C), 128.8 (CH), 128.6 (CH), 127.3 (CH), 65.2 (CH_2); **IR** (ATR)/cm^{-1} 3081, 3028, 2912, 1493, 1453, 1403, 1232, 1089, 1070, 1030, 764, 731, 695; **HRMS** (ESI+) *m/z* calculated for $[C_{11}H_{10}NaOS_2]^+$: 245.0065, found 245.0064.

1-Fluoro-4-((1-phenylethyl)sulfinyl)benzene (212be)

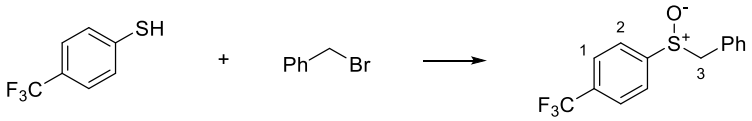


To a solution of 4-fluorothiophenol (229 µL, 2.0 mmol) in EtOH (10 mL) was added NaOEt (21 wt% in EtOH, 1.49 mL, 4.0 mmol) and this was stirred for 2 h before adding (1-bromoethyl)benzene (299 µL, 2.2 mmol). After 17 h water (5 mL) was added and the organic solvents were removed *in vacuo*. This was extracted with EtOAc (3 x 15 mL) and the combined organic layers were dried ($MgSO_4$) before concentrating *in vacuo* to give (4-fluorophenyl)(1-phenylethyl)sulfane (478 mg, quant.) as a colourless oil.

General procedure D: (4-fluorophenyl)(1-phenylethyl)sulfane (200 mg, 0.9 mmol), CH_2Cl_2 (10 mL) and *m*CPBA (193 mg, 0.9 mmol) gave *title compound* (198 mg, 93%, 0.6:0.4 ratio of diastereomers) as a colourless solid.

δ_H (400 MHz, $CDCl_3$), 7.34-7.19 (5H, m, 1-H x 2, Ph-H x 3), 7.11-6.97 (4H, m, 2-H x 2, Ph-H x 2), 4.06 (0.4H, q, *J* 7.1, 3-H x 0.4), 3.80 (0.6H, q, *J* 7.2, 3-H x 0.6), 1.74 (1.8H, d, *J* 7.2, 4-H x 1.8), 1.61 (1.2H, d, *J* 7.1, 4-H x 1.2); δ_C (100 MHz, $CDCl_3$) 164.5 (C x 2, d, *J* 251.2), 137.5 (C, d, *J* 3.1), 135.7 (C, d, *J* 3.1), 135.2 (C), 133.7 (C), 129.0 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 127.5 (CH, d, *J* 8.7), 127.4 (CH, d, *J* 8.9), 115.9 (C, d, *J* 22.6), 115.8 (C, d, *J* 22.4), 67.7 (CH), 64.4 (CH), 14.6 (CH_3), 11.9 (CH_3); δ_F (377 MHz, $CDCl_3$) -108.49 (0.6 F, tt, *J* 8.4 and 5.2), -108.72 (0.6 F, tt, *J* 8.3 and 5.3); **IR** ($CHCl_3$)/cm^{-1} 3004, 1591, 1493, 1454, 1240, 1153, 1083, 1036, 835; **HRMS** (ESI+) *m/z* calculated for $[C_{14}H_{14}FOS]^+$: 249.0744, found 249.0739.

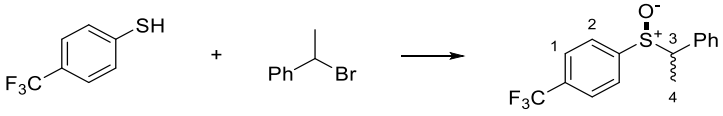
1-(Benzylsulfinyl)-4-(trifluoromethyl)benzene (212bf)



General procedure B: 4-(trifluoromethyl)benzenethiol (1.0 mL, 7.3 mmol), BnBr (0.79 mL, 6.6 mmol), NaOEt (2.7 M in EtOH, 2.6 mL, 7.0 mmol) and EtOH (30 mL) afforded sulfide (1.79 g). Sulfide (1.72 g, 6.42 mmol), *m*CPBA (77 wt%, 1.44 g, 6.4 mmol) and CH_2Cl_2 (65 mL) and column chromatography (10-25% EtOAc/petroleum ether) afforded *title compound* (1.48 g, 82%) as a colourless solid.

M.p. 161-164 °C; δ_H (400 MHz, $CDCl_3$) 7.70 (2H, d, *J* 8.2, 1-H x 2), 7.49 (2H, d, *J* 8.2, 2-H x 2), 7.36-7.27 (3H, m, Ph-H x 3), 7.00 (2H, d, *J* 6.7, Ph-H x 2), 4.14 (1H, d, *J* 12.7, 3-H), 4.06 (1H, d, *J* 12.7, 3-H); δ_C (100 MHz, $CDCl_3$) 147.3 (C), 133.24 (C, q, *J* 33.8), 130.5 (CH), 128.7 (CH), 128.7 (CH), 128.5 (C), 125.9 (CH, q, *J* 3.7), 125.0 (CH), 123.6 (C, q, *J* 272.7), 63.5; δ_F (377 MHz, $CDCl_3$) -62.81 (3F, s); **IR** (ATR)/cm^{-1} 3036, 2969, 2918, 1602, 1492, 1399, 1319, 1167, 1153, 1112, 1059, 1037, 1011, 832, 765, 696, 594; **HRMS** (ESI+) *m/z* calculated for $[C_{14}H_{11}F_3NaOS]^+$: 307.0375, found 307.0374.

1-((1-Phenylethyl)sulfinyl)-4-(trifluoromethyl)benzene (212bg)

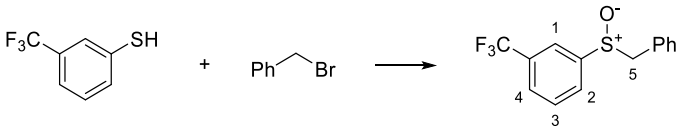


General procedure B: 4-(trifluoromethyl)thiophenol (240 µL, 2.0 mmol), (1-bromoethyl)benzene (300 µL, 2.2 mmol), EtOH (10 mL) and NaOEt (21 wt% in EtOH, 1.5 mL, 4.0 mmol) gave crude sulfide (451 mg) as a colourless oil. Crude sulfide

(1.90 g, 6.60 mmol), CH_2Cl_2 (70 mL) and *m*CPBA (1.5 g, 0.60 mmol) gave *title compound* (1.60 g, 65%, 0.3:0.7 ratio of diastereomers) as a colourless solid.

δ_H (400 MHz, $CDCl_3$) 7.62 (1.4H, d, *J* 8.1, 1-H x 1.4), 7.59 (0.6H, d, *J* 8.1, 1-H x 0.6), 7.37-7.24 (4.4H, m, Ph-H x 4.4), 7.20 (0.6H, d, *J* 8.1, 2-H x 0.6), 7.03 (1.4H, m, 2-H x 1.4), 6.98 (0.6H, m, Ph-H x 0.6), 4.13 (0.3 H, q, *J* 7.2, 3-H x 0.3), 3.83 (0.7H, q, *J* 7.1, 3-H x 0.7), 1.75 (2.1H, d, *J* 7.1, 4-H x 2.1), 1.65 (0.9H, d, *J* 7.2, 4-H x 0.9); δ_C (100 MHz, $CDCl_3$) 146.6 (C), 144.9 (C), 134.9 (C), 133.2 (C), 133.0 (C, q, *J* 32.7), 132.9 (C, q, *J* 32.7), 128.7 (CH x 3), 128.6 (CH), 128.6 (CH), 128.3 (CH), 125.6 (CH), 125.4 (CH, q, *J* 3.8), 125.4 (CH), 125.2 (CH, q, *J* 3.6), 123.6 (C, q, *J* 272.6), 123.5 (C, q, *J* 272.6), 67.5 (CH), 64.4 (CH), 14.3 (CH_3), 11.9 (CH_3); δ_F (377 MHz, $CDCl_3$) 62.81 (0.9F, s), 62.83 (2.1F, s); **IR** (ATR)/cm^{-1} 3008, 2934, 1607, 1495, 1454, 1402, 1324, 1173, 1137, 1061, 834; **HRMS** (ESI+) *m/z* calculated for $[C_{15}H_{13}F_3NaOS]^+$: 321.0537, found 321.0530.

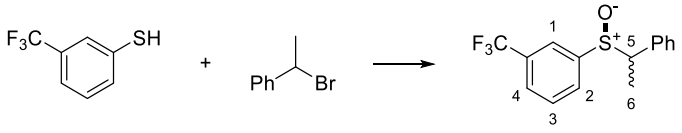
1-(Benzylsulfinyl)-3-(trifluoromethyl)benzene (212bh)



General procedure B: 3-(trifluoromethyl)thiophenol (510 mg, 2.9 mmol), BnBr (0.32 mL, 2.7 mmol), NaOEt (2.7 M in EtOH, 1.1 mL, 2.9 mmol) and EtOH (14 mL) afforded sulfide (740 mg). Sulfide (720 mg, 2.7 mmol), *m*CPBA (77 wt%, 600 mg, 2.7 mmol), and CH_2Cl_2 (25 mL) followed by column chromatography afforded *title compound* (602 mg, 81%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 7.71 (1H, d, *J* 6.9, 2-H or 4-H), 7.58-7.52 (2H, m, 2-H or 4-H, 3-H), 7.51 (1H, s, 1-H), 7.31 (1H, t, *J* 7.4, Ph-H), 7.25 (2H, dd, *J* 7.4 and 7.2, Ph-H x 2), 6.94 (2H, d, *J* 7.2, Ph-H x 2), 4.13 (1H, d, *J* 12.6, 5-H), 4.01 (1H, d, *J* 12.6, 5-H); δ_C (100 MHz, $CDCl_3$) 144.3 (C), 131.5 (C, q, *J* 33.3), 130.4 (CH), 129.5 (CH), 128.7 (CH x 2), 128.4 (C), 128.0 (CH, q, *J* 3.7), 127.8 (CH), 123.5 (C, q, *J* 272.8), 121.8 (CH, q, *J* 3.9), 63.6 (CH_2); δ_F (377 MHz, $CDCl_3$) -62.84 (3F, s); **IR** (ATR)/cm^{-1} 3085, 3038, 2971, 2920, 1493, 1420, 1319, 1275, 1157, 1119, 1098, 1080, 1064, 1039, 799, 762, 693, 483, 489; **HRMS** (ESI+) *m/z* calculated for $[C_{14}H_{11}F_3NaOS]^+$: 307.0375, found 307.0373.

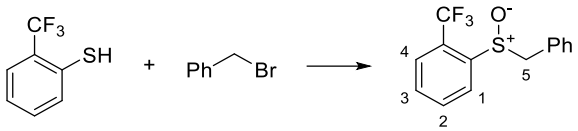
1-((1-Phenylethyl)sulfinyl)-3-(trifluoromethyl)benzene (212bi)



Work performed by Mindaugas Šiaučiulis. General procedure B: 3-(trifluoromethyl)thiophenol (0.27 mL, 2.0 mmol), (1-bromoethyl)benzene (0.31 mL, 2.2 mmol), EtOH (11 mL) and KO*t*-Bu (280 mg, 2.5 mmol) gave crude sulfide (580 mg). Crude sulfide (580 mg), CH_2Cl_2 (20 mL) and *m*CPBA (460 mg, 2.0 mmol) gave *title compound* (430 mg, 71%, 0.7:0.3 ratio of diastereomers) as a pale yellow oil.

δ_H (300 MHz, $CDCl_3$) 7.68-7.61 (1H, m, 2-H or 4-H), 7.51-7.39 (1.7H, m, 2-H or 4-H and Ph-H x 0.7), 7.35-7.16 (4.3H, m, 1-H, 3-H and Ph-H x 2.3), 6.99-6.89 (2H, m, Ph-H x 2), 4.11 (0.3H, q, *J* 7.1, 5-H x 0.3), 3.79 (0.7H, q, *J* 7.2, 5-H x 0.7), 1.74 (2.1H, d, *J* 7.1, 6-H x 2.1), 1.63 (0.9 H, d, *J* 7.1, 6-H x 0.9); δ_C (101 MHz, $CDCl_3$, major diastereomer) 143.7 (C), 134.7 (C), 131.1 (C, q, *J* 33.1), 129.1 (CH), 128.8 (CH), 128.7 (CH x 2), 128.2 (CH), 127.8 (CH, q, *J* 3.56), 123.4 (C, q, *J* 272.9), 122.2 (CH, q, *J* 3.8), 67.9 (CH), 14.6 (CH_3); δ_F (377 MHz, $CDCl_3$) -62.83 (2.1F, s), -62.87 (0.9F, s); **IR** (ATR)/cm^{-1} 3032, 3021, 3012, 1731, 1604, 1495, 1454, 1325, 1275, 1227, 1175, 1137, 1097; **HRMS** (ESI+) *m/z* calculated for $[C_{15}H_{13}F_3NaOS]^+$: 321.0537, found 321.0535.

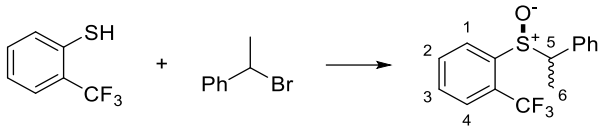
1-(Benzylsulfinyl)-2-(trifluoromethyl)benzene (212bj)



General procedure B: 2-(trifluoromethyl)thiophenol (1.0 mL, 7.6 mmol), BnBr (0.86 mL, 7.2 mmol), NaOEt (2.7 M in EtOH, 2.8 mL, 7.6 mmol) and EtOH (30 mL) afforded sulfide (1.97 g). Sulfide (1.91 g), *m*CPBA (77 wt%, 1.60 g, 7.1 mmol) and CH_2Cl_2 (70 mL) followed by column chromatography (10-20% EtOAc/petroleum ether) afforded *title compound* (1.81 g, 91%) as a pale yellow oil.

δ_H (400 MHz, $CDCl_3$) 7.81 (1H, d, *J* 7.3, 1-H or 4-H), 7.75 (1H, d, *J* 7.1, 1-H or 4-H), 7.64 (1H, dd, *J* 7.5 and 7.1, 2-H or 3-H), 7.60 (1H, dd, *J* 7.5 and 7.3, 2-H or 3-H), 7.36-7.28 (3H, m, Ph-H x 3), 7.10 (2H, d, *J* 6.5, Ph-H x 2), 4.24 (1H, d, *J* 13.1, 5-H), 3.87 (1H, d, *J* 13.1, 5-H); δ_C (100 MHz, $CDCl_3$) 142.9 (C), 132.7 (CH), 131.1 (CH), 130.6 (CH), 129.4 (C), 128.6 (CH), 128.6 (CH), 126.9 (C, q, *J* 32.9), 126.4 (CH, q, *J* 5.2), 126.1 (CH), 123.7 (C, q, *J* 274.4), 62.9 (CH_2); δ_F (377 MHz, $CDCl_3$) -57.09 (3F, s); **IR** ($CHCl_3$)/cm^{-1} 3068, 1595, 1497, 1455, 1439, 1315, 1262, 1180, 1136, 1086, 1056, 1028; **HRMS** (ESI+) *m/z* calculated for $[C_{14}H_{11}F_3NaOS]^+$: 307.0380, found 307.0376

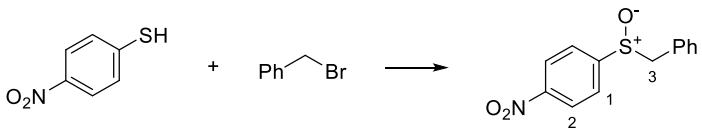
1-((1-Phenylethyl)sulfinyl)-2-(trifluoromethyl)benzene (212bk)



Work performed by Mindaugas Šiaučiulis. General procedure B: 2-(trifluoromethyl)thiophenol (0.27 mL, 2.0 mmol), (1-bromoethyl)benzene (0.31 mL, 2.2 mmol), EtOH (10 mL) and KO*t*-Bu (280 mg, 2.5 mmol) gave crude sulfide (580 mg). Crude sulfide (580 mg), CH_2Cl_2 (20 mL) and *m*CPBA (460 mg, 2.0 mmol) gave *title compound* (537 mg, 88%, one diastereomer) as a colourless solid.

M.p. 68-70 °C; δ_H (400 MHz, $CDCl_3$) 8.20 (1H, dddd, *J* 7.8, 1.3, 0.6 and 0.5, 1-H), 7.80 (1H, dddd, *J* 7.9, 7.5, 1.3 and 0.7, 3-H), 7.72 (1H, ddd, *J* 7.9, 1.2 and 0.6, 4-H), 7.63 (1H, ddd, *J* 7.8, 7.5 and 1.2 and 1.1, 2-H), 7.40-7.27 (5H, m, Ph-H x 5), 4.00 (1H, q, *J* 7.1, 5-H), 1.47 (3H, d, *J* 7.1, 6-H_3); δ_C (101 MHz, $CDCl_3$) 142.6 (C), 137.4 (C), 132.7 (CH), 131.3 (CH), 129.1 (CH), 128.8 (CH), 128.7 (CH), 127.6 (C, q, *J* 32.7), 127.0 (CH, q, *J* 5.2), 126.9 (CH), 123.9 (C, q, *J* 274.9), 64.5, 10.1; δ_F (377 MHz, $CDCl_3$) -56.7 (3F, s); **IR** (ATR)/cm^{-1} 3017, 1314, 1219, 1179, 1135, 1086, 1028, 774.; **HRMS** (ESI+) *m/z* calculated for $[C_{15}H_{13}F_3NaOS]^+$: 321.0537, found 321.0539.

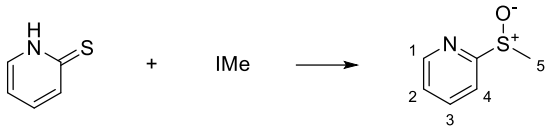
1-(Benzylsulfinyl)-4-nitrobenzene (212bl)[248]



Work performed by Mindaugas Šiaučiulis. General procedure B: 4-nitrothiophenol (160 mg, 2.0 mmol), EtOH (10 mL), KO*t*-Bu (270 mg, 2.4 mmol) and BnBr (0.26 mL, 2.2 mmol) afforded crude benzyl(4-nitrophenyl)sulfane (490 mg). Crude benzyl(4-nitrophenyl)sulfane (490 mg, 2.0 mmol), *m*CPBA (470 mg, 77 wt%, 2.1 mmol) in CH_2Cl_2 (20 mL) afforded title compound (480 mg, 93%) as a pale yellow solid.

M.p. 164-168 °C; δ_H (300 MHz, $CDCl_3$) 8.26 (2H, d, *J* 8.9, 2-H x 2), 7.49 (2H, d, *J* 8.9, 1-H x 2), 7.34-7.18 (3H, m, Ph-H x 3), 6.96 (2H, dd, *J* 8.0 and 1.4, Ph-H x 2), 4.15 (1H, d, *J* 12.7, 3-H), 4.07 (1H, d, *J* 12.7, 3-H); **IR** (ATR)/cm^{-1} 3096, 2962, 2910, 1600, 1579, 1521, 1340, 1312, 1286, 1080, 1032, 1008. Data agrees with literature.

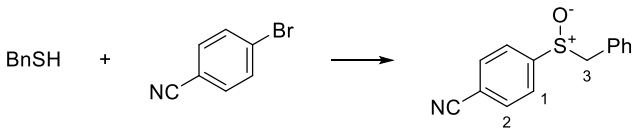
2-(Methylsulfinyl)pyridine (212bn)



General procedure B: 2-mercaptopyridine (**221**, 500 mg, 4.5 mmol), iodomethane (0.34 mL, 5.4 mmol), Et_3N (0.75 mL, 5.4 mmol) and CH_2Cl_2 (45 mL) afforded 2-(methylthio)pyridine (480 mg, 85%) as a pale orange oil. 2-(Methylthio)pyridine (470 mg, 3.8 mmol), *m*CPBA (930 mg, 4.1 mmol) and CH_2Cl_2 (40 mL) afforded *title compound* (530 mg, 100%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 8.62 (1H, ddd, *J* 4.8, 1.7 and 1.0, 1-H), 8.03 (1H, ddd, *J* 7.8, 1.2 and 1.0, 4-H), 7.95 (1H, ddd, *J* 7.8, 7.6 and 1.7, 3-H), 7.38 (1H, ddd, *J* 7.6, 4.8 and 1.2, 2-H), 2.85 (3H, s, 5-H_3); δ_C (100 MHz, $CDCl_3$) 166.1 (C), 149.7 (CH), 138.3 (CH), 124.7 (CH), 119.4 (CH), 41.4 (CH_3); **IR** ($CHCl_3$)/cm^{-1} 3007, 1578, 1453, 1424, 1086, 1038, 956; **HRMS** (ESI+) *m/z* calculated for $[C_6H_7NNaOS]^+$: 164.0141, found 164.0142.

4-(Benzylsulfinyl)benzonitrile (212bo)



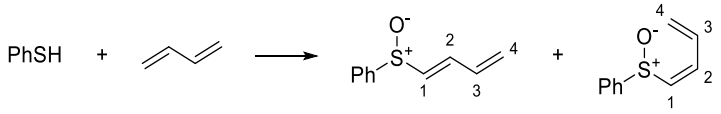
Work performed by Mindaugas Šiaučiulis. Procedure adapted from a literature method.[169] A solution of benzyl mercaptan (**217**, 0.37 mL, 3.2 mmol), 4-bromobenzonitrile (**216**, 550 mg, 3.0 mmol), 1H-benzotriazole (4 mg, 0.03 mmol), and CuI (3 mg, 0.02 mmol) in anhydrous DMSO (4 mL) was stirred for 10 min and then KO*t*-Bu (470 mg, 4.2 mmol) was added. The reaction mixture was then heated at 100 °C for 16 h. The reaction mixture was diluted with water (30 mL) extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with water (4 x 20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Column chromatography (3-40% EtOAc/petroleum ether) afforded *title compound* 4-(benzylthio)benzonitrile[249] (270 mg, 39%) as a yellow solid.

General procedure D: 4-(benzylthio)benzonitrile (260 mg, 1.2 mmol), CH_2Cl_2 (10 mL) and *m*CPBA (260 mg, 1.2 mmol) gave *title compound* (200 mg, 71%) as a pale yellow solid.

M.p. 149-151 °C; δ_H (400 MHz, $CDCl_3$) 7.68 (2H, d, *J* 8.4, 2-H x 2), 7.42 (2H, d, *J* 8.4, 1-H x 2), 7.34-7.23 (3H, m, Ph-H x 3), 6.94 (2H, d, *J* 6.7, Ph-H x 2), 4.11 (1H, d, *J* 12.7, 3-H),

4.04 (1H, d, *J* 12.7, 3-H); δ_C (100 MHz, $CDCl_3$) 148.6 (C), 132.5 (CH), 130.4 (CH), 128.9 (CH), 128.8 (CH), 128.1 (C), 125.3 (CH), 117.9 (C), 115.0 (C), 63.3 (CH_2); **IR** (ATR)/cm^{-1} 3029, 2921, 2851, 2239, 1487, 1454, 1079, 1040, 1019, 841, 762; **HRMS** (ESI+) *m/z* calculated for $[C_{14}H_{12}NOS]^+$: 242.0634, found 242.0628.

(E)-(Buta-1,3-dien-1-ylsulfinyl)benzene (E-212bp) and (Z)-(buta-1,3-dien-1-ylsulfinyl)benzene (Z-212bp)[250,251]



To a suspension of *N*-chlorosuccinimide (680 mg, 5.1 mmol) in CH_2Cl_2 (5 mL) was added thiophenol (**218**, 50 µL, 0.50 mmol) and was heated gently until the orange colour disappeared before cooling to 0°C and charging thiophenol (0.46 mL, 4.5 mmol). The reaction mixture was allowed to warm up to rt for 30 min before cooling to -78°C and butadiene (6.7 mL, 20 mmol) was added. The reaction mixture was allowed to warm to rt and was concentrated *in vacuo* before adding chloroform (2.5 mL) and stirring overnight. The resulting suspension was filtered, the filtrate was concentrated *in vacuo* to afford crude (2-chlorobut-3-en-1-yl)(phenyl)sulfane (990 mg).

To 1,8-diazabicycloundec-7-ene (1.5 mL, 10 mmol) at was added (2-chlorobut-3-en-1-yl)(phenyl)sulfane (990 mg, 5.0 mmol) at 100 °C. After 20 min the reaction mixture was cooled to rt, diluted with HCl (0.5 M in water, 25 mL), and this was extracted with Et_2O (25 mL). The ethereal layer was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give buta-1,3-dien-1-yl(phenyl)sulfane (**213bp**, 260 mg, 1.6 mmol, 33%) as a pale yellow oil.

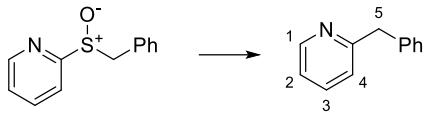
General procedure D: buta-1,3-dien-1-yl(phenyl)sulfane (**213bp**, 260 mg, 1.6 mmol), *m*CPBA (380 mg, 77 wt%, 1.7 mmol) and CH_2Cl_2 (15 mL) afforded (*E*)-(buta-1,3-dien-1-ylsulfinyl)benzene (***E*-212bp**, 62 mg, 22%) as a pale yellow oil and (*Z*)-(buta-1,3-dien-1-ylsulfinyl)benzene (***Z*-212bp**, 61 mg, 22%) as a pale yellow oil.

(*E*)-(buta-1,3-dien-1-ylsulfinyl)benzene (***E*-212bp**): δ_H (400 MHz, $CDCl_3$) 7.66-7.60 (2H, m, Ph-H x 2), 7.54-7.45 (3H, m, Ph-H x 3), 6.99 (1H, dd, *J* 15.1, 10.5, 2-H), 6.41 (1H, ddd, *J* 16.7, 10.5 and 10.0, 3-H), 6.37 (1H, d, *J* 15.1, 1-H), 5.56 (1 H, d, *J* 16.7, 4-H), 5.43 (1H, d, *J* 10.0, 4-H); δ_C (101 MHz, $CDCl_3$) 143.9 (C), 137.7 (CH), 136.7 (CH), 133.4 (CH), 131.3 (CH), 129.6 (CH), 124.8 (CH), 124.3 (CH_2); **IR** ($CHCl_3$)/cm^{-1} 3067, 3000, 1584,

1477, 1444, 1244, 1084, 1038, 1000, 951, 926; **HRMS** (ESI+) *m/z* calculated for $[C_{10}H_{11}OS]^+$: 179.0525, found 179.0530. Data agrees with literature.

(*Z*)-(buta-1,3-dien-1-ylsulfinyl)benzene (***Z*-212bp**): δ_H (400 MHz, $CDCl_3$) 7.62-7.58 (2H, m, Ph-H x 2), 7.53-7.43 (3H, m, Ph-H x 3), 7.19 (1 H, ddd, *J* 16.7, 11.1 and 10.1, 3-H), 6.62 (1 H, dd, *J* 11.1 and 9.7, 2-H), 6.19 (1H, dd, *J* 9.7 and 2.1, 1-H), 5.57 (1H, d, *J* 16.7, 4-H), 5.55 (1H, dd, *J* 10.1 and 2.1, 4-H); δ_C (101 MHz, $CDCl_3$) 144.2 (C), 138.5 (CH), 136.4 (CH), 130.9 (CH), 130.8 (CH), 129.5 (CH), 125.7 (CH_2), 124.2 (CH); **IR** ($CHCl_3$)/cm^{-1} 3067, 1574, 1444, 1068, 1034, 930, 660; **HRMS** (ESI+) *m/z* calculated for $[C_{10}H_{11}OS]^+$: 179.0525, found 179.0527. Data agrees with literature.

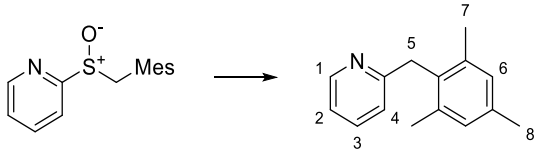
2-Benzylpyridine (219aa)[159,252]



General procedure C: 2-(benzylsulfinyl)pyridine (**212aa**, 96 mg, 0.44 mmol) *t*-BuMgCl (0.48 mL, 0.48 mmol) and THF (4.4 mL) gave *title compound* (52 mg, 70%) as a pale yellow oil.

δ_H (400 MHz, $CDCl_3$) 8.58 (1H, dd*, J* 5.2 and 1.9, 1-H), 7.60 (1H, ddd*, J* 7.7, 7.7 and 1.9, 3-H), 7.37-7.23 (5H, m, 2-H, 4-H and Ph-H x 3), 7.16-7.12 (2H, m, Ph-H x 2), 4.20 (2H, s, 5-H_2); δ_C (100 MHz, $CDCl_3$) 161.1 (C), 149.4 (CH), 139.6 (C), 136.6 (CH), 129.1 (CH), 128.7 (CH), 126.5 (CH), 123.2 (CH), 121.3 (CH), 44.8 (CH_2); **IR** ($CHCl_3$)/cm^{-1} 3007, 2979, 2917, 1743, 1688, 1602, 1578, 1510, 1462, 1385, 1310, 1248, 1160, 991, 833; **HRMS** (ESI+) *m/z* calculated for $[C_{12}H_{12}N]^+$: 170.0964, found 170.0963. Data agrees with literature.

2-(2,4,6-Trimethylbenzyl)pyridine (219ab)[253]

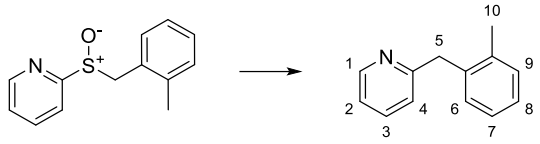


General procedure C: 2-((2,4,6-trimethylbenzyl)sulfinyl)pyridine (**212ab**, 98 mg, 0.38 mmol), *t*-BuMgCl (0.42 mL, 0.42 mmol) and THF (3.8 mL) gave *title compound* (64 mg, 79%) as a pale yellow oil.

δ_H (400 MHz, $CDCl_3$) 8.56 (1H, ddd*, J* 4.9, 1.8 and 0.9, 1-H), 7.50 (1H, ddd*, J* 7.8, 7.6 and 1.8, 3-H), 7.09 (1H, ddd*, J* 7.6, 4.9 and 1.1 2-H), 6.93 (2H, s, 6-H x 2), 6.76 (1H, ddd*, J*

7.8, 1.1 and 0.9, 4-H), 4.23 (2H, s, 5-H_2), 2.32 (3H, s, 8-H_3), 2.25 (6H, s, 7-H_3 x 2); **δ_C** (100 MHz, $CDCl_3$) 160.7 (C), 149.3 (CH), 137.3 (C), 136.6 (CH), 136.1 (C), 132.7 (C), 129.1 (CH), 121.4 (CH), 121.0 (CH), 37.9 (CH_2), 20.9 (CH_3), 20.2 (CH_3); **HRMS** (ESI+) *m/z* calculated for $[C_{15}H_{18}N]^+$: 212.1434, found 212.1429. Data agrees with literature.

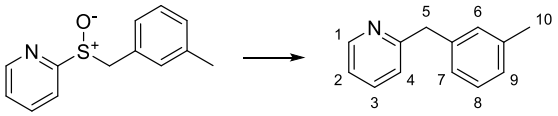
2-(2-Methylbenzyl)pyridine (219ac)[159]



General procedure C: 2-((2-methylbenzyl)sulfinyl)pyridine (**212ac**, 84 mg, 0.36 mmol), *t*-BuMgCl (0.40 mL, 0.40 mmol) and THF (3.6 mL) gave *title compound* (55 mg, 84%) as a pale yellow oil.

δ_H (400 MHz, $CDCl_3$) 8.56 (1H, dd*, J* 4.9, 1.8 and 1.0, 1-H), 7.53 (1H, ddd*, J* 7.8, 7.6 and 1.8, 3-H), 7.20-7.14 (4H, m, (6-9)-H x 4), 7.10 (1H, dd*, J* 7.6, 4.9 and 1.2, 2-H), 6.96 (1H, ddd*, J* 7.8, 1.2 and 1.0, 4-H), 4.19 (2H, s, 5-H_2), 2.25 (3H, s, 10-H_3); **δ_C** (100 MHz, $CDCl_3$) 160.8 (C), 149.4 (CH), 137.6 (C), 136.9 (C), 136.5 (CH), 130.5 (CH), 130.3 (CH), 126.9 (CH), 126.2 (CH), 122.8 (CH), 121.2 (CH), 42.5 (CH_2), 19.8 (CH_3); **HRMS** (ESI+) *m/z* calculated for $[C_{12}H_{14}N]^+$: 184.1121, found 184.1115. Data agrees with literature.

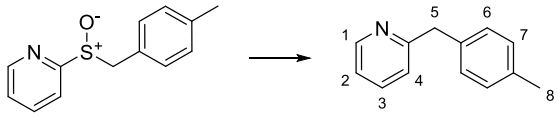
2-(3-Methylbenzyl)pyridine (219ad)[254]



General procedure C: 2-((3-methylbenzyl)sulfinyl)pyridine (**212ad**, 100 mg, 0.45 mmol), *t*-BuMgCl (0.49 mL, 0.49 mmol) and THF (4.5 mL) gave *title compound* (81 mg, 98%) as a pale yellow oil.

δ_H (400 MHz, $CDCl_3$) 8.56 (1H, ddd*, J* 4.8, 1.7 and 1.1, 1-H), 7.56 (1H, ddd*, J* 7.7, 7.6 and 1.7, 3-H), 7.20 (1H, dd*, J* 7.6 and 7.5, 8-H), 7.14-7.01 (5H, m, 2-H, 4-H, 6-H, 7-H and 9-H), 4.13 (2H, s, 5-H_2), 2.32 (3H, s, 10-H_3); **δ_C** (100 MHz, $CDCl_3$) 161.2 (C), 149.4 (CH), 139.5 (C), 138.3 (C), 136.6 (CH), 130.0 (CH), 128.6 (CH), 127.2 (CH), 126.2 (CH), 123.2 (CH), 121.3 (CH), 44.8 (CH_2), 21.4 (CH_3); **δ_F** (377 MHz, $CDCl_3$) -63.13 (s); **IR** ($CHCl_3$)/cm^{-1} 3060, 3006, 2960, 2484, 1607, 1593, 1570, 1476, 1435, 1171, 1148, 1095, 1051, 998, 885, 635, 621; **HRMS** (ESI+) *m/z* calculated for $[C_{12}H_{14}N]^+$: 184.1113, found 184.1115. Data agrees with literature.

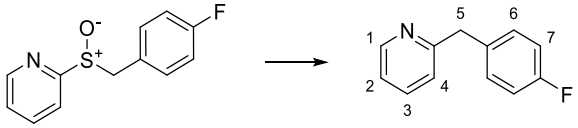
2-(4-Methylbenzyl)pyridine (219ae)[252]



General procedure C: 2-((4-methylbenzyl)sulfinyl)pyridine (**3e**, 94 mg, 0.41 mmol), *t*BuMgCl (0.45 mL, 0.45 mmol) and THF (4.1 mL) gave *title compound* (64 mg, 85%) as a pale yellow oil.

δ_H (400 MHz, $CDCl_3$) 8.55 (1H, ddd*, J* 4.9, 1.9 and 1.0, 1-H), 7.55 (1H, ddd*, J* 7.7, 7.6 and 1.9, 3-H), 7.17 (2H, d*, J* 8.1, 6-H x 2 or 7-H x 2), 7.12 (2H, d*, J* 8.1, 6-H x 2 or 7-H x 2), 7.14-7.10 (2H, m, 2-H and 4-H), 4.16 (2H, s, 5-H_2), 2.35 (3H, s, 8-H_3); δ_C (100 MHz, $CDCl_3$) 161.4 (C), 149.4 (CH), 136.5 (CH), 136.5 (C), 135.9 (C), 129.3 (CH), 129.1 (CH), 123.1 (CH), 121.2 (CH), 44.3 (CH_2), 21.1 (CH_3); **HRMS** (ESI+) *m/z* calculated for $[C_{12}H_{14}N]^+$: 184.1113, found 184.1104. Data agrees with literature.

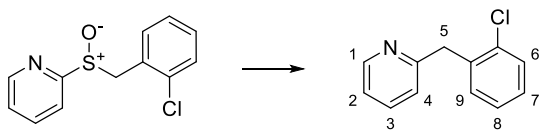
2-(4-Fluorobenzyl)pyridine (219af)[255]



General procedure C: 2-((4-fluorobenzyl)sulfinyl)pyridine (**212af**, 94 mg, 0.40 mmol), *t*-BuMgCl (0.44 mL, 0.44 mmol) and THF (4.0 mL) gave *title compound* (60 mg, 79%) as a pale yellow oil.

δ_H (400 MHz, $CDCl_3$) 8.54 (1H, ddd, *J* 4.9, 1.9 and 0.9, 1-H), 7.58 (1H, ddd, *J* 7.7, 7.6 and 1.9, 3-H), 7.21 (2H, dd, *J* 8.6 and 5.0, 6-H x 2), 7.12 (1H, ddd, *J* 7.6, 4.9 and 1.2, 2-H), 7.09 (1H, dd, *J* 7.7 and 1.1, 4-H), 6.98 (2H, dd, *J* 8.7 and 8.6, 7-H), 4.12 (2H, s, 5-H_2); δ_C (100 MHz, $CDCl_3$) 161.8 (C, d, *J* 221.2), 160.4 (C), 149.3 (CH), 136.8 (CH), 135.1 (C, d, *J* 3.0), 130.5 (CH, d, *J* 7.9), 123.1 (CH), 121.4 (CH), 115.4 (CH, d, *J* 21.0), 43.7 (CH_2); δ_F (377 MHz, $CDCl_3$) -116.87 (1F, tt, *J* 8.7 and 5.0); **HRMS** (ESI+) *m/z* calculated for $[C_{12}H_{11}FN]^+$: 188.0870, found 188.0880. Data agrees with literature.

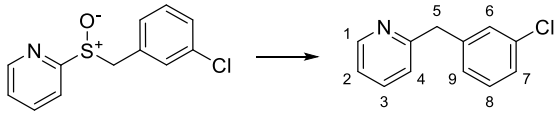
2-(2-Chlorobenzyl)pyridine (219ag)



General procedure C: 2-((2-chlorobenzyl)sulfinyl)pyridine (**212ag**, 280 mg, 1.1 mmol), MeMgBr (0.73 mL, 2.2 mmol) and THF (11 mL) gave *title compound* (173 mg, 77%) as a pale yellow oil.

δ_H (400 MHz, $CDCl_3$) 8.55 (1H, dd*, J* 4.8, 1.8 and 0.9 1-H), 7.57 (1H, ddd*, J* 7.9, 7.5 and 1.8, 3-H), 7.40 (1H, dd*, J* 7.3 and 2.0, 6-H or 9-H), 7.27 (1H, dd*, J* 7.1 and 2.1, 6-H or 9-H), 7.21 (1H, ddd*, J* 7.3, 7.3 and 2.1, 7-H or 8-H), 7.18 (1H, ddd*, J* 7.3, 7.1 and 2.0, 7-H or 8-H), 7.11 (1H, dd*, J* 7.5 and 4.8 and 1.1, 2-H), 7.09 (1H, ddd*, J* 7.9, 1.1 and 0.9, 4-H), 4.30 (2H, s, 5-H_2); **δ_C** (100 MHz, $CDCl_3$) 159.6 (C), 149.5 (CH), 137.2 (C), 136.6 (CH), 134.3 (C), 131.6 (CH), 129.7 (CH), 128.1 (CH), 127.1 (CH), 123.2 (CH), 121.5 (CH), 42.1 (CH_2); **IR** ($CHCl_3$)/cm^{-1} 3072, 3011, 2966, 1593, 1571, 1474, 1435, 1149, 1126, 1091, 1052, 1039, 997, 612; **HRMS** (ESI+) *m/z* calculated for $[C_{12}H_{11}ClN]^+$: 204.0575, found 204.0574.

2-(3-Chlorobenzyl)pyridine (219ah)[255]



General procedure C: 2-((3-chlorobenzyl)sulfinyl)pyridine (**212ah**, 650 mg, 2.6 mmol), MeMgBr (1.7 mL, 5.2 mmol) and THF (26 mL) gave *title compound* (436 mg, 67%) as a pale yellow oil.

δ_H (400 MHz, $CDCl_3$) 8.55 (1H, ddd*, J* 4.7, 1.8 and 1.0, 1-H), 7.61 (1H, ddd*, J* 7.7, 7.6 and 1.0, 3-H), 7.26-7.07 (6H, m, 2-H, 4-H, and (6-9)-H x 4), 4.12 (2H, s, 5-H_2); **δ_C** (100 MHz, $CDCl_3$) 160.2 (C), 149.6 (CH), 141.6 (C), 136.8 (CH), 134.4 (C), 129.9 (CH), 129.3 (CH), 127.4 (CH), 126.7 (CH), 123.2 (CH), 121.6 (CH), 44.3 (CH_2); **HRMS** (ESI+) *m/z* calculated for $[C_{12}H_{11}ClN]^+$: 204.0575, found 204.0566. Data agrees with literature.

2-(4-Chlorobenzyl)pyridine (219ai)[256]

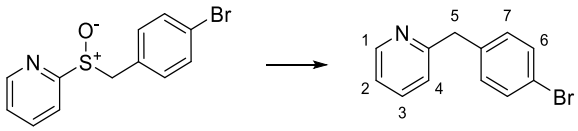


General procedure C: 2-((4-chlorobenzyl)sulfinyl)pyridine (**212ai**, 660 mg, 2.6 mmol), MeMgBr (1.8 mL, 5.3 mmol) and THF (26 mL) gave *title compound* (454 mg, 84%) as a pale yellow oil.

δ_H (400 MHz, $CDCl_3$) 8.56 (1H, ddd*, J* 4.9, 1.8 and 0.9, 1-H), 7.59 (1H, ddd*, J* 7.7, 7.6 and 1.8, 3-H), 7.27 (2H, d*, J* 8.6, 6-H x 2 or 7-H x 2), 7.20 (2H, d*, J* 8.6, 6-H x 2 or 7-H x 2)

7.13 (1H, ddd, *J* 7.6, 4.9 and 1.1, 2-H), 7.10 (1H, ddd, *J* 7.7, 1.1 and 0.9, 4-H), 4.13 (2H, s, 5-H_2); δ_C (100 MHz, $CDCl_3$) 160.4 (C), 149.5 (CH), 138.1 (C), 136.7 (CH), 132.2 (C), 130.5 (CH), 128.7 (CH), 123.1 (CH), 121.5 (CH), 44.0 (CH_2); **IR** ($CHCl_3$)/cm^{-1} 3140, 2965, 2485, 1590, 1571, 1492, 1475, 1435, 1408, 1149, 1092, 1051, 1017, 998, 848; **HRMS** (ESI+) *m/z* calculated for $[C_{12}H_{11}ClN]^+$: 204.0575, found 204.0553. Data agrees with literature.

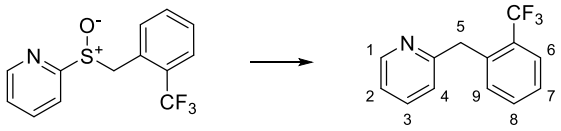
2-(4-Bromobenzyl)pyridine (219aj)[255]



General procedure C: 2-((4-bromobenzyl)sulfinyl)pyridine (**212aj**, 94 mg, 0.32 mmol), *t*-BuMgCl (0.86 M in THF, 0.41 mL, 0.35 mmol) and THF (3.2 mL) gave *title compound* (56 mg, 71%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 8.55 (1H, ddd, *J* 4.9, 1.9 and 1.1, 1-H), 7.59 (1H, ddd, *J* 7.7, 7.6 and 1.9, 3-H), 7.42 (2H, d, *J* 8.4, 6-H x 2), 7.16-7.11 (1H, m, 2-H), 7.14 (2H, d, *J* 8.4, 7-H x 2), 7.09 (1H, ddd, *J* 7.7, 1.3 and 1.1, 4-H), 4.10 (2H, s, 5-H_2); δ_C (100 MHz, $CDCl_3$) 160.4 (C), 149.6 (CH), 138.6 (C), 136.8 (CH), 131.8 (CH), 131.0 (CH), 123.2 (CH), 121.6 (CH), 120.5 (C), 44.2 (CH_2); **IR** ($CHCl_3$)/cm^{-1} 2965, 1596, 1570, 1488, 1435, 1405, 1071, 1013, 846; **HRMS** (ESI+) *m/z* calculated for $[C_{12}H_{11}BrN]^+$: 248.0060, found 248.0065. Data agrees with literature.

2-(2-(Trifluoromethyl)benzyl)pyridine (219ak)

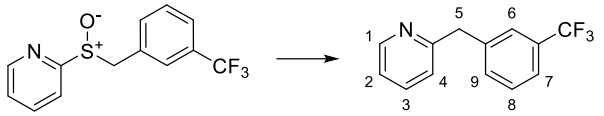


General procedure C: 2-((2-(trifluoromethyl)benzyl)sulfinyl)pyridine (**212ak**, 820 mg, 2.9 mmol), MeMgBr (1.9 mL, 5.8 mmol) and THF (29 mL) gave *title compound* (322 mg, 47%) as a pale yellow oil.

δ_H (400 MHz, $CDCl_3$) 8.57 (1H, ddd, *J* 4.9, 1.7 and 0.8, 1-H), 7.67 (1H, d, *J* 7.7, 6-H), 7.57 (1H, ddd, *J* 7.7, 7.6 and 1.7, 3-H), 7.46 (1H, dd, *J* 7.6 and 7.5, 8-H), 7.36-7.29 (2H, m, 7-H and 4-H), 7.13 (1H, ddd, *J* 7.7 and 4.9 and 1.1, 2-H), 7.02 (1H, d, *J* 7.8, 9-H), 4.37 (2H, s, 5-H_2); δ_C (100 MHz, $CDCl_3$) 160.0 (C), 149.4 (CH), 137.9 (C, q, *J* 1.5), 136.7 (CH), 132.2 (CH), 132.0 (CH, q, *J* 1.0), 128.8 (C, q, *J* 29.8), 126.7 (CH), 126.0 (CH, q, *J* 5.7), 124.5 (C, q, *J* 273.9), 123.4 (CH), 121.5 (CH), 40.7 (CH_2, q, *J* 1.8); **IR** ($CHCl_3$)/cm^{-1} 3074,

2970, 2484, 1609, 1593, 1571, 1498, 1476, 1457, 1434, 1315, 1158, 1126, 1061, 1038, 997, 957, 655, 617; **HRMS** (ESI+) *m/z* calculated for $[C_{13}H_{11}F_3N]^+$: 238.0838, found 238.0823. Data agrees with literature.

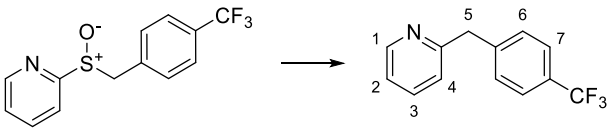
2-(3-(Trifluoromethyl)benzyl)pyridine (219al)[161,257]



General procedure C: 2-((3-(trifluoromethyl)benzyl)sulfinyl)pyridine (**212al**, 270 mg, 1.0 mmol), MeMgBr (0.68 mL, 2.0 mmol) and THF (10 mL) gave *title compound* (131 mg, 58%) as a pale yellow oil.

δ_H (400 MHz, $CDCl_3$) 8.56 (1H, ddd, *J* 5.0, 1.8 and 0.9, 1-H), 7.62 (1H, ddd, *J* 7.7, 7.7 and 1.8, 3-H), 7.55 (1H, s, 6-H), 7.52-7.38 (3H, m, (7-9)-H x 3), 7.19-7.11 (2H, m, 2-H and 4-H), 4.22 (2H, s, 5-H_2); **δ_C** (100 MHz, $CDCl_3$) 160.0 (C), 149.7 (CH), 140.5 (C), 136.9 (CH), 132.6 (CH, q, *J* 1.1), 131.0 (C, q, *J* 32.1), 129.1 (CH), 125.9 (CH, q, *J* 3.8), 124.3 (C, q, *J* 272.3), 123.4 (CH, q, *J* 3.8), 123.3 (CH), 121.7 (CH), 44.4 (CH_2); **δ_F** (377 MHz, $CDCl_3$) -62.56 (s); **HRMS** (ESI+) *m/z*, calculated for $[C_{13}H_{11}F_3N]^+$: 238.0838, found 238.0845. Data agrees with literature.

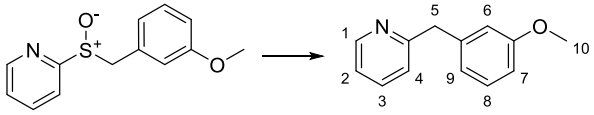
2-(4-(Trifluoromethyl)benzyl)pyridine (219am)[159]



General procedure C: 2-((4-(trifluoromethyl)benzyl)sulfinyl)pyridine (**212am**, 610 mg, 2.1 mmol), MeMgBr (1.5 mL, 4.5 mmol) and THF (23 mL) gave *title compound* (321 mg, 63%) as a pale yellow oil.

δ_H (400 MHz, $CDCl_3$) 8.56 (1H, d, *J* 4.9, 1.9 and 1.0, 1-H), 7.60 (1H, ddd, *J* 7.8, 7.7 and 1.9, 3-H), 7.55 (2H, d, *J* 8.1, 7-H x 2), 7.37 (2H, d, *J* 8.1, 6-H x 2), 7.16-7.10 (2H, m, 2-H and 4-H), 4.20 (2H, s, 5-H_2); **δ_C** (126 MHz, $CDCl_3$) 159.9 (C), 149.7 (CH), 143.6 (C, q, *J* 1.2), 136.9 (CH), 129.5 (CH), 128.9 (C, q, *J* 32.4), 125.6 (CH, q, *J* 3.8), 124.2 (C, q, *J* 272.2), 123.3 (CH), 121.7 (CH), 44.4 (CH_2); **δ_F** (377 MHz, $CDCl_3$) -63.13 (s); **HRMS** (ESI+) *m/z*, calculated for $[C_{13}H_{11}F_3N]^+$: 238.0838, found 238.0851. Data agrees with literature.

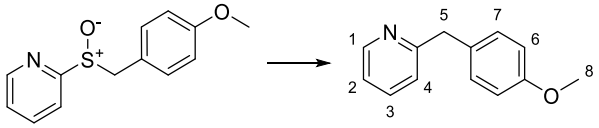
2-(3-Methoxybenzyl)pyridine (219an)[258]



General procedure C: 2-((3-methoxybenzyl)sulfinyl)pyridine (**212an**, 120 mg, 0.47 mmol), *t*-BuMgCl (0.52 mL, 0.52 mmol) and THF (4.7 mL) gave *title compound* (83 mg, 88%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 8.58 (1H, dd, *J* 5.6 and 1.6, 1-H), 7.61 (1H, ddd, *J* 7.7, 7.7 and 1.9, 3-H), 7.25 (1H, dd, *J* 8.0 and 7.6, 8-H), 7.17-7.13 (2H, m, 2-H and 9-H), 6.86 (1H, ddd, *J* 7.6, 1.56 and 0.88 4-H), 6.81 (1H, t, *J* 2.1, 6-H), 6.76 (1H, ds, *J* 8.0, 2.4, 7-H), 4.17 (2H, s, 5-H_2), 3.80 (3H, s, 10-H_3); δ_C (100 MHz, $CDCl_3$) 160.9 (C), 159.9 (C), 149.4 (CH), 141.1 (C), 136.7 (CH), 129.7 (CH), 123.3 (CH), 121.6 (CH), 121.4 (CH), 114.9 (CH), 111.9 (CH), 55.3 (CH_3), 44.8 (CH_2); **IR** ($CHCl_3$)/cm^{-1} 3011, 2961, 1593, 1489, 1476, 1435, 1259, 1151, 1051, 997; **HRMS** (ESI+) *m/z* calculated for $[C_{13}H_{14}NO]^+$: 200.1070, found 200.1075. Data agrees with literature.

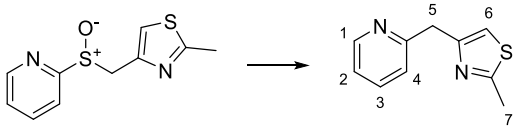
2-(4-Methoxybenzyl)pyridine (219ao)[159]



General procedure C: 2-((4-methoxybenzyl)sulfinyl)pyridine (**212ao**, 100 mg, 0.41 mmol), *t*-BuMgCl (0.45 mL, 0.45 mmol) and THF (4.1 mL) gave *title compound* (72 mg, 89%) as a yellow oil. Data agrees with literature.

δ_H (400 MHz, $CDCl_3$) 8.57 (1H, dd*, J* 5.7 and 1.8, 1-H), 7.59 (1H, ddd*, J* 7.7, 7.7 and 1.8, 3-H), 7.21 (2H, d*, J* 8.7, 7-H x 2), 7.15-7.10 (2H, m, 2-H and 4-H), 6.88 (2H, d*, J* 8.7, 6-H x 2), 4.13 (2H, s, 5-H_2), 3.80 (3H, s, 8-H_3); δ_C (100 MHz, $CDCl_3$) 161.5 (C), 158.3 (C), 149.4 (CH), 136.6 (CH), 131.7 (C), 130.2 (CH), 123.1 (CH), 121.2 (CH), 114.1 (CH), 55.3 (CH_3), 43.9 (CH_2); **IR** ($CHCl_3$)/cm^{-1} 3008, 2959, 2838, 2485, 1611, 1592, 1571, 1512, 1475, 1465, 1436, 1301, 1248, 1178, 1108, 1036, 997, 842, 605; **HRMS** (ESI+) *m/z* calculated for $[C_{13}H_{14}NO]^+$: 200.1070, found 200.1072.

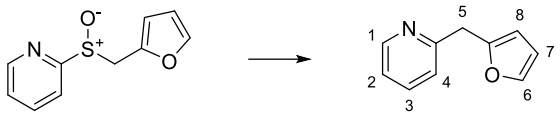
2-Methyl-4-(pyridin-2-ylmethyl)thiazole (219ap)



General procedure C: 2-methyl-4-((pyridin-2-ylsulfinyl)methyl)thiazole (**212ap**, 80 mg, 0.34 mmol), *t*-BuMgCl (0.37 mL, 0.37 mmol) and THF (3.4 mL) gave *title compound* (46 mg, 73%) as a pale yellow oil.

δ_H (400 MHz, $CDCl_3$) 8.54 (1H, ddd, *J* 4.9, 1.7 and 0.9, 1-H), 7.59 (1H, ddd, *J* 7.7, 7.6 and 1.7, 3-H), 7.26 (1H, dd, *J* 7.7 and 0.9, 4-H), 7.15 (1H, dd, *J* 7.6 and 4.9, 2-H), 6.81 (1H, s, 6-H), 4.28 (2H, s, 5-H_2), 2.70 (3H, s, 7-H_3); **δ_C** (100 MHz, $CDCl_3$) 166.0 (C), 159.1 (C), 153.8 (C), 149.3 (CH), 136.9 (CH), 123.6 (CH), 121.6 (CH), 114.5 (CH), 40.2 (CH_2), 19.2 (CH_3); **IR** ($CHCl_3$)/cm^{-1} 2973, 2480, 1591, 1572, 1523, 1476, 1435, 1185, 1051, 998, 863; **HRMS** (ESI+) *m/z*, calculated for $[C_{10}H_{11}N_2S]^+$: 191.0637, found 191.0643.

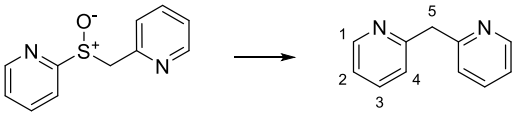
2-(Furan-2-ylmethyl)pyridine (219aq)[259]



General procedure C: 2-((furan-2-ylmethyl)sulfinyl)pyridine (**212aq**, 210 mg, 1.0 mmol), MeMgBr (0.68 mL, 2.0 mmol) and THF (10 mL) gave *title compound* (121 mg, 74%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 8.54 (1H, ddd, *J* 4.9, 1.8 and 1.0, 1-H), 7.60 (1H, ddd, *J* 7.8, 7.6 and 1.8, 3-H), 7.34 (1H, dd, *J* 1.9 and 0.8, 6-H), 7.17 (1H, ddd, *J* 7.8, 1.1 and 1.0, 4-H), 7.12 (1H, ddd, *J* 7.6, 4.9 and 1.1, 2-H), 6.31 (1H, dd, *J* 3.2 and 1.9, 7-H), 6.12 (1H, dd, *J* 3.2 and 0.8, 8-H), 4.17 (2H, s, 5-H_2); **δ_C** (100 MHz, $CDCl_3$) 158.3 (C), 152.9 (C), 149.5 (CH), 141.9 (CH), 136.7 (CH), 123.0 (CH), 121.7 (CH), 110.5 (CH), 107.0 (CH), 37.4 (CH_2); **IR** ($CHCl_3$)/cm^{-1} 2970, 1669, 1594, 1572, 1506, 1477, 1436, 1148, 1092, 1073, 1051, 1011, 998, 939, 885; **HRMS** (ESI+) *m/z* calculated for $[C_{10}H_{10}NO]^+$: 160.0757, found 160.0758. Data agrees with literature.

Di(pyridin-2-yl)methane (219ar)[260]

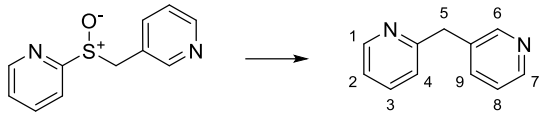


General procedure C: 2-((pyridin-2-ylmethyl)sulfinyl)pyridine (**212ar**, 97 mg, 0.44 mmol), *t*-BuMgCl (0.49 mL, 0.49 mmol) and THF (0.44 mL) gave *title compound* (60 mg, 81%) as a pale yellow oil.

δ_H (500 MHz, $CDCl_3$) 8.51 (2H, ddd, *J* 4.9, 1.8 and 0.9, 1-H x 2), 7.55 (2H, ddd, *J* 7.8, 7.6 and 1.8, 3-H x 2), 7.24 (2H, ddd, *J* 7.8, 0.9 and 1.0, 4-H x 2), 7.10 (2H, ddd, *J* 7.6, 4.9

and 1.0, 2-H x 2), 4.33 (2H, s, 5-H x 2); **δ_C** (125 MHz, $CDCl_3$) 159.5 (C), 149.5 (CH), 136.6 (CH), 123.6 (CH), 121.5 (CH), 47.3 (CH_2); **HRMS** (ESI+) *m/z* calculated for $[C_{11}H_{11}N_2]^+$: 171.0917, found 171.0916. Data agrees with literature.

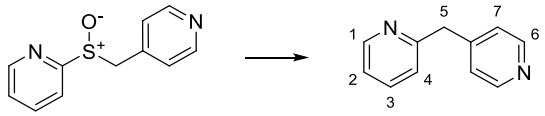
2-(Pyridin-3-ylmethyl)pyridine (219as)[161]



General procedure C: 2-((pyridin-3-ylmethyl)sulfinyl)pyridine (**212as**, 100 mg, 0.48 mmol), *t*-BuMgCl (0.53 mL, 0.53 mmol) and THF (4.8 mL) gave *title compound* (59 mg, 72%) as a pale yellow oil.

δ_H (400 MHz, $CDCl_3$) 8.55-8.52 (2H, m, 1-H and 6-H), 8.49 (1H, dd*, J* 4.8 and 1.7, 7-H), 7.59 (1H, dd*, J* 7.7 and 1.7, 9-H), 7.57 (1H, ddd*, J* 7.8, 4.8, and 1.1, 2-H or 8-H), 7.20 (1H, ddd*, J* 7.7, 4.8 and 0.8, 2-H or 8-H), 7.14-7.09 (2H, m, 3-H and 4-H), 4.13 (2H, s); **δ_C** (100 MHz, $CDCl_3$) 159.8 (C), 150.4 (CH), 149.7 (CH), 148.0 (CH), 136.8 (CH), 136.6 (CH), 135.1 (C), 123.6 (CH), 123.2 (CH), 121.7 (CH), 41.8 (CH_2); **IR** ($CHCl_3$)/cm^{-1} 3087, 3061, 2969, 2484, 1593, 1577, 1477, 1435, 1426, 1150, 1103, 1051, 1029, 997, 843, 637, 618; **HRMS** (ESI+) *m/z* calculated for $[C_{11}H_{11}N_2]^+$: 171.0917, found 171.0917. Data agrees with literature.

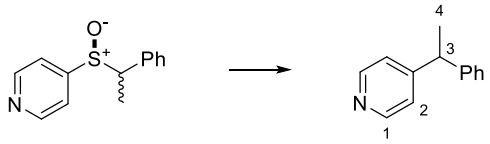
2-(Pyridin-4-ylmethyl)pyridine (219at)[261]



General procedure C: 2-((pyridin-4-ylmethyl)sulfinyl)pyridine (**212at**, 290 mg, 1.4 mmol), *t*-BuMgCl (0.90 mL, 2.7 mmol) and THF (14 mL) gave *title compound* (60.0 mg, 26%) as a pale yellow oil.

δ_H (400 MHz, $CDCl_3$) 8.58 (1H, ddd*, J* 4.8, 1.7 and 0.9, 1-H), 8.52 (2H, d*, J* 4.5, 6-H x 2), 7.63 (1H, ddd*, J* 7.7, 7.7 and 1.7, 3-H), 7.21-7.14 (4H, m, 2-H, 4-H and 7-H x 2), 4.15 (2H, s, 5-H_2); **δ_C** (100 MHz, $CDCl_3$) 159.0 (C), 150.0 (CH), 149.8 (CH), 148.4 (C), 136.9 (CH), 124.4 (CH), 123.4 (CH), 121.9 (CH), 44.0 (CH_2); **IR** ($CHCl_3$)/cm^{-1} 3383, 1673, 1591, 1581, 1436, 1411, 1309, 1290, 994, 801, 747; **HRMS** (ESI+) *m/z*, calculated for $[C_{11}H_{11}N_2]^+$: 171.0917, found 171.0920. Data agrees with literature.

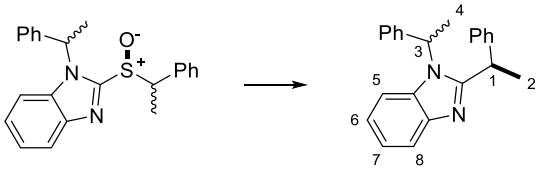
4-(1-Phenylethyl)pyridine (219av)[262]



Performed by general procedure C: 4-((1-phenylethyl)sulfinyl)pyridine (**212av**, 34 mg, 0.15 mmol), THF (1.5 mL) and MeMgBr (2.3 M in Et_2O, 62 µL, 0.15 mmol) gave *title compound* (11 mg, 40%) as a pale yellow oil.

δ_H (400 MHz, $CDCl_3$) 8.52 (2H, d, *J* 5.9, 1-H x 2), 7.37-7.32 (2H, m, Ph-H x 2), 7.28-7.20 (3H, m, Ph-H x 3), 7.16 (2H, d, *J* 5.9, 2-H x 2), 4.15 (1H, q, *J* 7.2, 3-H), 1.67 (3H, d, *J* 7.2, 4-H_3). **IR** ($CHCl_3$)/cm^{-1} 2975, 2483, 1598, 1494, 1453, 1416, 1241, 1028, 997, 830; **HRMS** (ESI+) *m/z* calculated for $[C_{13}H_{14}N]^+$: 184.1121, found 184.1128. Data agrees with literature.

1,2-Bis(1-phenylethyl)-1H-benzo[d]imidazole (219az)



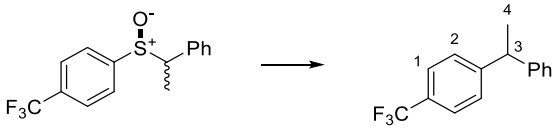
General procedure C: 1-(1-phenylethyl)-2-((1-phenylethyl)sulfinyl)-1*H*-benzo[*d*]imidazole (**212az**, 320 mg, 0.9 mmol), MeMgBr (0.30 mL, 0.9 mmol) and THF (9 mL) gave *title compound* (100 mg, 36%) as a 1.1:1.0 ratio of diastereomer 1 (less polar, colourless oil) to diastereomer 2 (more polar, colourless oil).

Diastereomer 1: δ_H (400 MHz, $CDCl_3$) 7.91 (1H, d*, J* 8.2, 5-H), 7.37-7.25 (8H, m, Ph-H x 8), 7.22 (1H, ddd*, J* 8.2, 7.3 and 1.1, 7-H), 7.19-7.15 (2H, m, Ph-H x 2) 7.04 (1H, ddd*, J* 8.2, 7.3 and 0.9, 6-H), 6.91 (1H, dd*, J* 8.2 and 0.9, 8-H), 5.69 (1H, q*, J* 7.0, 3-H), 4.49 (1H, q*, J* 7.0, 1-H), 1.97 (3H, d*, J* 7.0, 4-H_3), 1.40 (3H, d*, J* 7.0, 2-H_3); δ_C (100 MHz, $CDCl_3$) 156.6 (C), 143.3 (C), 142.9 (C), 139.7 (C), 133.7 (C), 129.0 (CH), 128.8 (CH), 127.6 (CH), 127.4 (CH), 127.0 (CH), 126.2 (CH), 122.1 (CH), 121.7 (CH), 119.8 (CH), 112.2 (CH), 53.2 (CH), 39.4 (CH), 22.3 (CH_3), 17.2 (CH_3); **IR** ($CHCl_3$)/cm^{-1} 2986, 2482, 1603, 1498, 1457, 1399; **HRMS** (ESI+) *m/z* calculated for $[C_{23}H_{23}N_2]^+$: 327.1856, found 327.1859.

Diastereomer 2: δ_H (400 MHz, $CDCl_3$) 7.84 (1H, ddd*, J* 8.2, 0.97 and 0.97, 5-H), 7.33-7.23 (4H, m, Ph-H x 4), 7.21-7.10 (5H, m, 7-H and Ph-H x 4), 6.97 (1H, ddd*, J* 8.2, 7.3 and 1.0, 6-H), 6.79-6.76 (2H, ddd, *J* 7.4, 2.1 and 1.0, Ph-H x 2), 6.74 (1H, ddd*, J* 8.3, 1.0 and 0.9, 8-H), 5.74 (1H, q*, J* 7.1, 3-H), 4.41 (1H, q*, J* 7.1, 1-H), 1.91 (3H, d*, J* 7.1,

4-H_3), 1.82 (3H, d, *J* 7.1, 2-H_3); δ_C (100 MHz, $CDCl_3$) 156.7 (C), 143.3 (C), 143.0 (C), 138.9 (C), 133.9 (C), 129.1 (CH), 128.5 (CH), 127.6 (CH), 127.6 (CH), 127.1 (CH), 126.6 (CH), 122.1 (CH), 121.7 (CH), 119.8 (CH), 111.9 (CH), 52.8 (CH), 39.4 (CH), 22.1 (CH_3), 18.4 (CH_3); **IR** ($CHCl_3$)/cm^{-1} 2982, 2484, 1603, 1497, 1457, 1397; **HRMS** (ESI+) *m/z* calculated for $[C_{23}H_{23}N_2]^+$: 327.1856, found 327.1858.

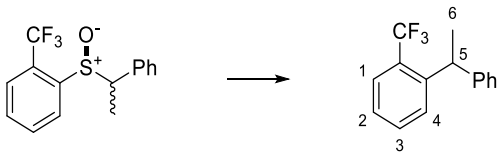
1-(1-Phenylethyl)-4-(trifluoromethyl)benzene (219bg)[263]



General procedure C: 1-((1-phenylethyl)sulfinyl)-4-(trifluoromethyl)benzene (**212bg**, 480 mg, 1.6 mmol), MeMgBr (0.59 mL, 1.8 mmol) and THF (11 mL) gave *title compound* (154 mg, 38%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 7.57 (2H, d, *J* 7.0, 1-H x 2), 7.39-7.32 (4H, m, Ph-H x 4), 7.28-7.23 (3H, m, 2-H x 2 and Ph-H), 4.25 (1H, q, *J* 7.2, 3-H), 1.70 (3H, q, *J* 7.2, 4-H); δ_C (100 MHz, $CDCl_3$) 150.6 (C, q, *J* 1.1), 145.4 (C), 128.5 (C, q, *J* 32.4), 128.0 (CH), 128.6 (CH), 127.7 (CH), 126.4 (CH), 125.3 (CH, q, *J* 3.8), 124.3 (C, q, *J* 271.8), 44.8 (CH), 21.8 (CH_3); **HRMS** (EI) *m/z* calculated for $[C_{15}H_{13}F_3Na]^+$: 250.0969, found 250.0973. Data agrees with literature.

1-(1-Phenylethyl)-2-(trifluoromethyl)benzene (219bk)



Work performed by Mindaugas Šiaučiulis. General procedure C: 1-((1-phenylethyl)sulfinyl)-3-(trifluoromethyl)benzene (**212bk**, 110 mg, 0.35 mmol), MeMgBr (0.30 mL, 0.88 mmol) and THF (5 mL) gave *title compound* (13 mg, 15%) as a colourless oil.

δ_H (300 MHz, $CDCl_3$) 7.64 (1H, dd, *J* 7.8 and 1.4, 1-H), 7.42 (1H, ddd, *J* 7.8, 7.7 and 1.3, 2-H), 7.34-7.17 (7H, m, 3-H, 4-H and Ph-H x 5), 4.65 (1H, q, *J* 7.1, 5-H), 1.65 (3H, d, *J* 7.1, 6-H_3); δ_C (100 MHz, $CDCl_3$) 146.3 (C), 145.1 (C), 132.1 (CH), 130.0 (CH), 128.5 (CH), 127.9 (C, q, *J* 29.3), 127.8 (CH), 126.3 (CH), 126.0 (CH), 125.7 (CH, q, *J* 5.9), 124.9 (C, q, *J* 273.7), 39.5 (CH), 22.2 (CH_3); δ_F (376 MHz, $CDCl_3$) -58.42 (1F, s); **IR** ($CHCl_3$)/cm^{-1} 3017,

2977, 1607, 1494, 1452, 1313, 1230, 1209, 1160, 1124, 1035; **HRMS** (EI+) *m/z* calculated for $[C_{15}H_{13}F_3]$:250.0969, found 250.0971.

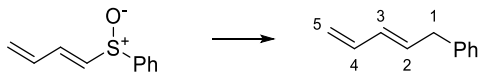
4-Benzylbenzonitrile (219bo)[263]



Work performed by Mindaugas Šiaučiulis. General procedure C: 4-(benzylsulfinyl)benzonitrile (**212bo**, 37 mg, 0.15 mmol), BnMgCl (1.9 M in THF, 90 µL, 0.17 mmol) and THF (1.5 mL) afforded *title compound* (26 mg, 86%) as a pale yellow oil.

δ_H (400 MHz, $CDCl_3$) 7.57 (2H, d, *J* 8.2, 1-H x 2), 7.34-7.22 (5H, m, 2-H x 2 and Ph-H x 3), 7.16 (2H, m, Ph-H x 2), 4.04 (2H, s, 3-H_2); δ_C (100 MHz, $CDCl_3$) 146.9 (C), 139.5 (C), 132.4 (CH), 129.8 (CH), 129.1 (CH), 128.9 (CH), 126.8 (CH), 119.1 (C), 110.2 (C), 42.1 (CH_2); **IR** ($CHCl_3$)/cm^{-1} 3066, 3009, 2926, 2854, 2230, 1604, 1508, 1496, 1454, 1415, 909; **HRMS** (ESI+) *m/z* calculated for $[C_{14}H_{11}NNa]^+$: 216.0784, found 216.0782. Data agrees with literature.

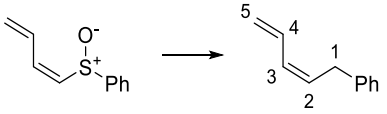
(E)-Penta-2,4-dien-1-ylbenzene (E-219bp)[264,265]



General procedure C using (*E*)-(buta-1,3-dien-1-ylsulfinyl)benzene (***E*-212bp**, 53 mg, 0.30 mmol) and BnMgCl (0.17 mL, 1.9 M in THF, 0.33 mmol) and THF (2.5 mL) afford *title compound* (7.8 mg, 8%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 7.33-7.14 (5H, m, Ph-H x 5), 6.34 (1H, dt, *J* 17.0, 10.4 and 10.2, 4-H), 6.11 (1H, dd, *J* 14.9 and 10.4, 3-H), 5.85 (1H, dt, *J* 14.9 and 6.9, 2-H), 5.14 (1H, dd, *J* 17.0 and 1.6, 5-H), 5.01 (1H, dd, *J* 10.2 and 1.7, 5-H), 3.43 (2H, d, *J* 6.9, 1-H_2); δ_C (100 MHz, $CDCl_3$) 140.2 (C), 137.1 (CH), 133.6 (CH), 132.2 (CH), 128.7 (CH), 128.6 (CH), 126.3 (CH), 115.9 (CH_2), 39.1 (CH_2); **IR** ($CHCl_3$)/cm^{-1} 3087, 2927, 2855, 1650, 1603, 1494, 1453, 1007, 953, 906; **HRMS** (EI) *m/z* calculated for $[C_{11}H_{12}]^+$: 144.0934, found 144.0934. Data agrees with literature.

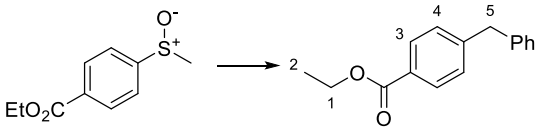
(Z)-Penta-2,4-dien-1-ylbenzene (Z-219bp)[265]



General procedure C using (*Z*)-(buta-1,3-dien-1-ylsulfinyl)benzene (***Z*-212bp**, 47 mg, 0.26 mmol), BnMgCl (0.15 mL, 1.9 M in THF, 0.29 mmol) and THF (2.5 mL) afforded *title compound* (2.5 mg, 6%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 7.33-7.25 (2H, m, Ph-H x 2), 7.23-7.17 (3H, m, Ph-H x 3), 6.77 (1H, dddd, *J* 16.8, 10.9, 10.1 and 1.1, 4-H), 6.14 (1H, ddd, *J* 10.9, 10.4 and 1.6, 3-H), 5.63 (1H, dtdd, *J* 10.4, 7.8, 2.2, 1.1, 2-H), 5.29 (1H, dd, *J* 16.8 and 2.1, 5-H), 5.18 (1H, ddd, *J* 10.1, 2.2 and 2.1, 5-H), 3.55 (1H, dd, *J* 7.8 and 1.6, 1-H_2); **δ_C** (101 MHz, $CDCl_3$) 140.6 (C), 132.1 (CH), 130.7 (CH), 130.1 (CH), 128.6 (CH), 128.5 (CH), 126.2 (CH), 118.2 (CH_2), 34.1 (CH_2); **IR** ($CHCl_3$)/cm^{-1} 3086, 2927, 2855, 1495, 1454, 1433, 1000, 912; **HRMS** (ESI+) *m/z* calculated for $[C_{11}H_{12}]^+$: 144.0936, found 1440934. Data agrees with literature.

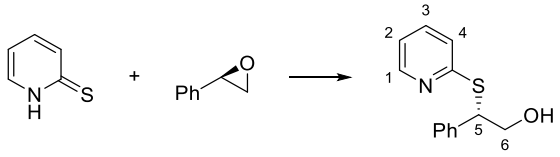
Ethyl 4-benzylbenzoate (219bq)[266]



Work performed by Mindaugas Šiaučiulis. General procedure C using ethyl 4-(methylsulfinyl)benzoate (**212bq**, 42 mg, 0.20 mmol), BnMgCl (120 µL, 1.9 M in THF, 0.22 mmol) and THF (2 mL) at 0°C afforded *title compound* (30 mg, 0.125 mmol, 63%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 7.98 (2H, d, *J* 8.2, 3-H x 2), 7.35-7.14 (7H, m, 4-H x 2 and Ph-H x 5), 4.38 (2H, q, *J* 7.1, 1-H_2), 4.05 (2H, s, 5-H_2), 1.40 (3H, t, *J* 7.1, 2-H_3); **δ_C** (101 MHz, $CDCl_3$) 166.7 (C), 146.5 (C), 140.3 (C), 129.9 (CH), 129.1 (CH), 128.7 (CH), 128.6 (C), 126.5 (CH), 61.0 (CH_2), 42.1 (CH_2), 14.5 (CH_3). **IR** ($CHCl_3$)/cm^{-1} 3006, 2986, 2930, 2908, 1712, 1611, 1602, 1509, 1465, 1417, 1369, 1282, 1180, 1108, 1022, 856; **HRMS** (ESI+) *m/z* calculated for $[C_{16}H_{17}O_2]^+$: 241.1223, found 241.1216. Data agrees with literature.

(S)-2-Phenyl-2-(pyridin-2-ylthio)ethan-1-ol (223)[267]

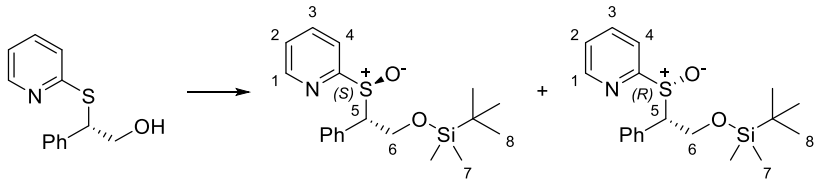


To a solution of (*R*)-styrene oxide (**222**, 1.2 g, 1.1 mL, 10 mmol) in MeCN (20 mL) was added 2-mercaptopyridine (**221**, 1.2 g, 11 mmol) and $Er(OTf)_3$ (0.60 g, 1.0 mmol). After 3 hours the reaction was concentrated *in vacuo* and column chromatography

(10-30% EtOAc/petroleum ether) gave *title compound* (1.79 g, 78%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 8.42 (1H, d*, J* 5.1, 1-H), 7.52 (1H, ddd*, J* 7.5, 7.5 and 1.5, 3-H), 7.39-7.24 (6H, m, 4-H and Ph-H x 5), 7.06 (1H, dd*, J* 7.5 and 5.1, 2-H), 4.97 (1H, dd*, J* 8.0 and 5.4, 5-H), 4.17 (1H, dd*, J* 11.3 and 5.4, 6-H), 4.14 (1H, dd*, J* 11.3 and 8.0, 6-H); **δ_C** (100 MHz, $CDCl_3$) 158.9 (C), 149.1 (CH), 138.8 (C), 136.8 (CH), 129.0 (CH), 128.0 (CH), 127.9 (CH), 123.3 (CH), 120.4 (CH), 68.4 (CH), 52.8 (CH_2); **HRMS** (ESI+) *m/z*, calculated for $[C_{13}H_{14}NOS]^+$: 232.0791, found 232.0791. Data agrees with literature.

2-((S)-((S)-2-((t-Butyldimethylsilyl)oxy)-1-phenylethyl)sulfinyl)pyridine (224) and 2-((R)-((S)-2-((t-butyldimethylsilyl)oxy)-1-phenylethyl)sulfinyl)pyridine (224a')



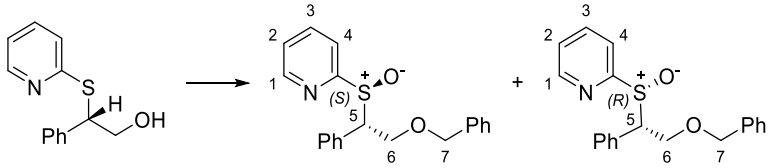
A mixture of imidazole (180 mg, 2.6 mmol) and TBSCl (390 mg, 2.6 mmol) and 2-phenyl-2-(pyridin-2-ylthio)ethan-1-ol (**223**, 500 mg, 2.2 mmol) in CH_2Cl_2 (2.5 mL) was stirred for 3.5 h before water (5 mL) was added. Following extraction of the aqueous layer with CH_2Cl_2 (3 x 5 mL), the combined organic layers were dried ($MgSO_4$) to give sulfide (740 mg) as a colourless oil. General procedure D: Sulfide (110 mg, 0.31 mmol), CH_2Cl_2 (3 mL) and *m*CPBA (75 mg, 0.31 mmol) gave *title compound* (111 mg, 99%) as a 2.1:1 ratio of to **224a** (more polar, as a colourless oil) to **224a'** (less polar, as a colourless solid,).

224a: **δ_H** (400 MHz, $CDCl_3$) 8.60 (1H, ddd*, J* 4.7, 1.7 and 0.9, 1-H), 7.76 (1H, ddd*, J* 7.8, 7.6 and 1.7, 3-H), 7.67 (1H, ddd*, J* 7.8, 1.1 and 0.9, 4-H), 7.31 (1H, ddd*, J* 7.6, 4.7 and 1.1, 2-H), 7.30-7.21 (5H, m, Ph-H x 5), 4.37 (1H, dd*, J* 10.1 and 6.1, 6-H), 4.33 (1H, dd, 6.1 and 4.6, 5-H), 4.21 (1H, dd*, J* 10.1 and 4.6, 6-H), 0.81 (9H, s, 8-H_3 x 3), -0.04 (3H, s, 7-H_3), -0.04 (3H, s, 7-H_3); **δ_C** (100 MHz, $CDCl_3$) 163.7 (C), 149.4 (CH), 137.3 (CH), 134.2 (C), 129.1 (CH), 128.5 (CH), 128.3 (CH), 124.6 (CH), 121.2 (CH), 71.3 (CH), 60.2 (CH_2), 25.9 (CH_3), 18.3 (C), -5.5 (CH_3), -5.6 (CH_2); **IR** ($CHCl_3$)/cm^{-1} 3003, 2957, 2930, 2858, 1602, 1453, 1423, 1257, 1107, 1038, 837; **HRMS** (ESI+) *m/z*, calculated for $[C_{19}H_{18}NO_2SSi]^+$: 362.1605, found 362.1591. **$[\alpha]^{21}{}_D$** = 335.36 (c 0.090, $CHCl_3$)

224a': **M.p.** = 88-90 °C; **δ_H** (400 MHz, $CDCl_3$) 8.60 (1H, ddd*, J* 4.6, 1.3 and 0.6, 1-H), 7.50 (1H, ddd*, J* 7.7, 7.7 and 1.7, 3-H), 7.23-7.11 (3H, m, 2-H, 4-H and Ph-H) 7.09-7.05 (2H,

m, Ph-H x 2), 6.86-6.81 (2H, m, Ph-H x 2), 4.54 (1H, dd, *J* 10.4 and 10.6, 6-H), 4.21 (1H, dd, *J* 10.4 and 5.2, 6-H), 4.12 (1H, dd, *J* 10.6 and 5.2, 5-H), 0.99 (9H, s, 8-H_3 x 3), 0.21 (3H, s, 7-H_3), 0.17 (3H, s, 7-H_3); **δ_C** (100 MHz, $CDCl_3$) 164.0 (C), 148.9 (CH), 137.1 (CH), 131.1 (C), 128.9 (CH), 128.1 (CH), 127.8 (CH), 123.9 (CH), 120.9 (CH), 71.1 (CH), 61.5 (CH_2), 26.0 (CH_3), 18.4 (C), -5.3 (CH_3), -5.4 (CH_3); **IR** ($CHCl_3$)/cm^{-1} 2952, 2929, 2856, 1422, 1254, 1104, 1051, 1039, 832, 771, 701; **HRMS** (ESI+) *m/z*, calculated for $[C_{19}H_{18}NO_2SSi]^+$: 362.1605, found 362.1598; **$[\alpha]^{21}_D$** = 65.40 (c 0.150, $CHCl_3$).

2-((S)-((S)-2-(Benzyloxy)-1-phenylethyl)sulfinyl)pyridine (224b) and 2-((R)-((S)-2-(benzyloxy)-1-phenylethyl)sulfinyl)pyridine (224b')



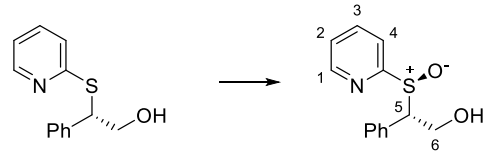
To a solution of (2*S*)-2-phenyl-2-(pyridin-2-ylsulfinyl)ethan-1-ol (**223**, 240 mg, 1.0 mmol) in THF (10 mL) at 0 °C was added NaH (60 wt% in mineral oil, 45 mg, 1.1 mmol) and this was allowed to warm to rt over 30 min. Benzyl bromide (0.13 mL, 1.1 mmol) was then added and the reaction mixture was allowed to stir overnight. Water (10 mL) was added and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) before concentrating *in vacuo*. Column chromatography (2-8% EtOAc/petroleum ether) afforded the pure sulfide (213 mg, 64%). General procedure D: sulfide (210 mg, 0.64 mmol), *m*CPBA (77 wt%, 140 mg, 0.64 mmol) and CH_2Cl_2 (6 mL) gave *title compound* (214 mg, 99%) as a 2.2:1 ratio of **224b** (colourless oil) to **224b'** (colourless oil).

224b: **δ_H** (400 MHz, $CDCl_3$) 8.59 (1H, ddd, *J* 4.5, 1.5 and 0.9, 1-H), 7.69 (1H, ddd, *J* 7.9, 7.8 and 1.5, 3-H), 7.66-7.62 (1H, m, 4-H), 7.31-7.22 (9H, m, 2-H and Ph-H x 8), 7.09 (2H, dd, *J* 7.4 and 2.0, Ph-H x 2), 4.52 (1H, dd, *J* 7.1 and 5.4, 5-H), 4.39 (2H, s, 7-H_2), 4.24 (1H, dd, *J* 10.6 and 7.1, 6-H), 3.99 (1H, dd, *J* 10.6 and 5.4, 6-H); **δ_C** (100 MHz, $CDCl_3$) 163.5 (C), 149.4 (CH), 137.7 (C), 137.3 (CH), 134.0 (C), 129.0 (CH), 128.8 (CH), 128.6 (CH), 128.3 (CH), 127.7 (CH), 127.7 (CH), 124.5 (CH), 121.1 (CH), 73.0 (CH_2), 68.3 (CH), 66.2 (CH_2); **IR** ($CHCl_3$)/cm^{-1} 3069, 3011, 1578, 1562, 1497, 1453, 1423, 1103, 1038; **HRMS** (ESI+) *m/z* calculated for $[C_{20}H_{19}NNaO_2S]^+$: 360.1029, found 360.1036; **$[\alpha]^{21}_D$** = 21.68 (c 0.410, $CHCl_3$).

224b': **δ_H** (400 MHz, $CDCl_3$) 8.59 (1H, ddd, *J* 4.1, 1.6 and 1.5, 1-H), 7.51 (1H, ddd, *J* 7.6, 7.6 and 1.6, 3-H), 7.43-7.33 (4H, m, Ph-H x 4), 7.32-7.27 (1H, m, Ph-H), 7.20-7.11 (3H,

m, 2-H, 4-H and Ph-H), 7.05 (2H, dd, *J* 7.4 and 7.3, Ph-H x 2), 6.79 (2H, d, *J* 7.1, Ph-H x 2), 4.77 (1H, d, *J* 12.0, 7-H), 4.68 (1H, d, *J* 12.0, 7-H), 4.37 (1H, dd, *J* 10.1 and 8.1, 6-H), 4.34 (1H, dd, *J* 10.1 and 3.2, 6-H), 3.99 (1H, dd, *J* 8.1 and 3.2, 5-H); δ_C (100 MHz, $CDCl_3$) 163.5 (C), 149.1 (CH), 137.8 (C), 137.2 (CH), 130.7 (C), 129.0 (CH), 128.6 (CH), 128.3 (CH), 127.9 (CH), 127.9 (CH), 127.9 (CH), 124.2 (CH), 121.0 (CH), 73.7 (CH_2), 68.5 (CH), 67.9 (CH_2); **HRMS** (ESI+) *m/z* calculated for $[C_{20}H_{19}NNaO_2S]^+$: 360.1029, found 360.1026. **IR** ($CHCl_3$)/cm^{-1} 3069, 3011, 1578, 1562, 1497, 1453, 1423, 1103, 1038; $[\alpha]^{21}_D$ = 287.94 (c 0.570, $CHCl_3$).

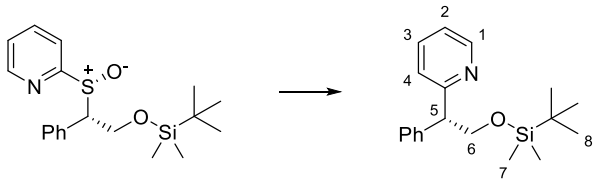
(S)-2-Phenyl-2-((S)-pyridin-2-ylsulfinyl)ethan-1-ol (224c)



General procedure D: (*S*)-2-phenyl-2-(pyridin-2-ylthio)ethan-1-ol (**223**, 190 mg, 0.83 mmol), *m*CPBA (77 wt%, 210 mg, 0.83 mmol) and CH_2Cl_2 (8 mL) gave *title compound* (128 mg, 62%, one diastereomer) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 8.66 (1H, ddd, *J* 4.8, 1.7 and 1.0, 1-H), 7.87 (1H, ddd, *J* 7.8, 7.6 and 1.7, 3-H), 7.76 (1H, ddd, *J* 7.8, 1.1 and 1.0, 4-H), 7.41 (1H, ddd, *J* 7.6, 4.8 and 1.1, 2-H), 7.37-7.32 (3H, m, Ph-H x 3), 7.31-7.26 (2H, m, Ph-H x 2), 4.46 (1H, dd, *J* 15.2 and 7.4, 6-H), 4.46 (1H, dd, *J* 7.4 and 7.4, 5-H), 4.23 (1H, dd, *J* 15.2 and 7.4, 6-H), 3.15 (1H, br s, O-H); δ_C (100 MHz, $CDCl_3$) 163.2 (C), 149.8 (CH), 137.9 (CH), 133.3 (C), 129.1 (CH), 129.0 (CH), 128.8 (CH), 125.2 (CH), 121.1 (CH), 68.4 (CH), 52.8 (CH_2); **IR** ($CHCl_3$)/cm^{-1} 3462, 3011, 1582, 1559, 1454, 1417, 1126, 1049; **HRMS** (ESI+) *m/z* calculated for $[C_{13}H_{13}NNaO_2S]^+$: 270.0559, found 270.0556; $[\alpha]^{21}_D$ = 70.83 (c 0.110, $CHCl_3$).

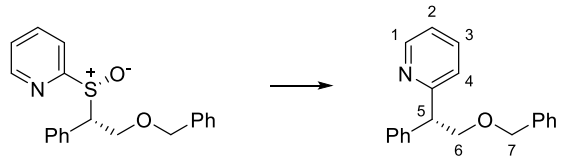
(R)-2-(2-((t-Butyldimethylsilyl)oxy)-1-phenylethyl)pyridine (225a)



General procedure C: 2-((*R*)-((*S*)-2-((*t*-butyldimethylsilyl)oxy)-1-phenylethyl)sulfinyl)pyridine (**224a'**, 53 mg, 0.15 mmol), MeMgBr (3.0 M in Et_2O, 54 µL, 1.9 mmol) and THF (1.5 mL) gave *title compound* (38 mg, 81% yield, >99.5% ee) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 8.59 (1H, ddd, *J* 4.9, 1.9 and 0.9, 1-H), 7.57 (1H, ddd, *J* 7.6, 7.6 and 1.9, 3-H), 7.38-7.34 (2H, m, Ph-H x 2), 7.31-7.25 (2H, m, Ph-H x 2), 7.22-7.17 (2H, m, 4-H and Ph-H), 7.11 (1H, ddd, *J* 7.6, 4.9 and 1.1, 2-H), 4.40 (1H, dd, *J* 9.6 and 7.2, 6-H), 4.27 (1H, dd, *J* 7.2 and 6.4, 5-H), 4.16 (1H, dd, *J* 9.6 and 6.4, 6-H), 0.77 (9H, s, 8-H_3 x 3), -0.10 (6H, s, 7-H_3 x 2); **δ_C** (100 MHz, $CDCl_3$), 161.9 (C), 149.2 (CH), 141.5 (C), 136.3 (CH), 128.8 (CH), 128.4 (CH), 126.7 (CH), 124.1 (CH), 121.5 (CH), 66.7 (CH_2), 56.1 (CH), 25.8 (CH_3), 18.2 (C), -5.5 (CH_3), -5.5 (CH_3); **IR** ($CHCl_3$)/cm^{-1} 2956, 2930, 2857, 1593, 1472, 1434, 1256, 1110, 838; **HRMS** (ESI+) *m/z*, calculated for $[C_{19}H_{18}NOSi]^+$: 314.1935, found 314.1927; **$[\alpha]^{21}_D$** = -48.69 (c 0.510, $CHCl_3$); ee was determined by HPLC with an DAICEL CHIRALPAK® ID HPLC column (4.6 mm × 250 mm, 5 µm) (TBME/n-hexane = 3/97, λ = 254 nm, 1 mL/min, 20 °C) t_R (major enantiomer) = 9.769 min, t_R (minor enantiomer) = 8.477 min, ee >99.5%.

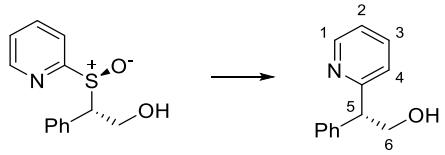
(R)-2-(2-(Benzyloxy)-1-phenylethyl)pyridine (225b)



General procedure C: 2-(((S)-2-(benzyloxy)-1-phenylethyl)sulfinyl)pyridine (**224b'**, 14 mg, 0.042 mmol), MeMgBr (2.0 M in Et_2O, 23 µL, 0.045 mmol) and THF (4.1 mL) gave *title compound* (63 mg, 91%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$); 8.58 (1H, ddd, *J* 4.9, 1.9 and 0.9, 1-H), 7.58 (1H, ddd, *J* 7.7, 7.6 and 1.9, 3-H), 7.40-7.16 (11H, m, 4-H and Ph-H x 10), 7.12 (1H, ddd, *J* 7.6, 4.9 and 1.1, 2-H), 4.56 (1H, d, *J* 12.3, 7-H), 4.52 (1H, d, *J* 12.3, 7-H), 4.44 (1H, dd, *J* 7.5 and 7.0, 5-H), 4.29 (1H, dd, *J* 9.4 and 7.7, 6-H), 4.04 (1H, dd, *J* 9.4 and 7.0, 6-H); **δ_C** (100 MHz, $CDCl_3$) 161.6 (C), 149.4 (CH), 141.2 (C), 138.5 (C), 136.5 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 127.7 (CH), 127.6 (CH), 126.9 (CH), 123.7 (CH), 121.7 (CH), 73.3 (CH_2), 73.2 (CH_2), 53.8 (CH); **IR** ($CHCl_3$)/cm^{-1} 3066, 3011, 2963, 2865, 1716, 1592, 1495, 1474, 1453, 1434, 1316, 1276, 1177, 1117, 1097, 1073, 1027; **HRMS** (ESI+) *m/z* calculated for $[C_{20}H_{20}NO]^+$: 290.1539, found 290.1535. **$[\alpha]^{21}_D$** = -58.57 (c 0.620, $CHCl_3$); ee was determined by HPLC with an DAICEL CHIRALPAK® AS-H HPLC column (4.6 mm × 250 mm, 5 µm) (2-propanol/n-hexane = 10/90, λ = 254 nm, 1 mL/min, 20 °C) t_R (major enantiomer) = 6.418 min, t_R (minor enantiomer) = 6.042 min, ee = 99%.

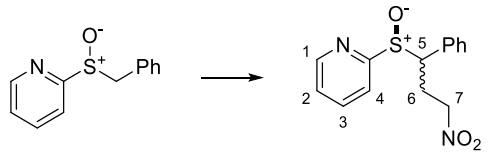
(R)-2-Phenyl-2-(pyridin-2-yl)ethan-1-ol (225c)



General procedure C: (*S*)-2-phenyl-2-((*S*)-pyridin-2-ylsulfinyl)ethan-1-ol (**224c**, 71 mg, 0.29 mmol), MeMgBr (3.0M in Et_2O, 0.21 mL, 0.64 mmol) and THF (2.9 mL) gave *title compound* (19 mg, 33%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 8.60 (1H, ddd, *J* 5.1, 1.9 and 0.9, 1-H), 7.64 (1H, ddd, *J* 7.8, 7.7 and 1.9, 3-H), 7.35 (2H, m, Ph-H x 2), 7.31-7.21 (4H, m, 2-H and Ph-H x 3), 7.06 (1H, d, *J* 7.8, 4-H), 4.37 (1H, dd, *J* 15.0 and 8.3, 6-H), 4.37 (1H, dd, *J* 8.3 and 8.2, 5-H), 4.12 (1H, dd, *J* 15.0 and 8.2, 6-H); δ_C (100 MHz, $CDCl_3$) 163.1 (C), 148.2 (CH), 140.9 (C), 137.2 (CH), 128.8 (CH x 2), 127.2 (CH), 124.6 (CH), 121.9 (CH), 66.7 (CH_2), 53.8 (CH); **IR** ($CHCl_3$)/cm^{-1} 3353, 3011, 1595, 1569, 1494, 1474, 1434, 1098, 1057, 1026; **HRMS** (ESI+) *m/z* calculated for $[C_{13}H_{14}NO]^+$: 200.1070, found 200.1071. $\mathbf{[\alpha]^{21}_D}$ = 70.83 (c 0.110, $CHCl_3$); ee was determined by HPLC with an DAICEL CHIRALPAK® ID HPLC column (4.6 mm × 250 mm, 5 μm) ((EtOH/TBME)/n-hexane = (1/99)/60, λ = 254 nm, 1 mL/min, 20 °C) t_R (major enantiomer) = 11.253 min, t_R (minor enantiomer) = 13.940 min, ee = 98%.

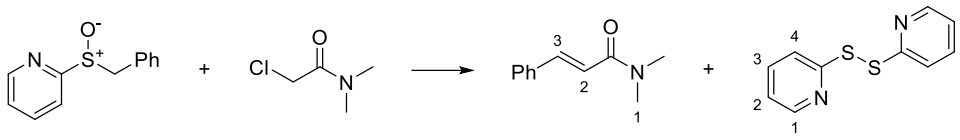
2-((3-Nitro-1-phenylpropyl)sulfinyl)pyridine (235)



To a solution of 2-(benzylsulfinyl)pyridine (**212aa**, 110 mg, 0.48 mmol) in THF (5 mL) at 0 °C was added LDA (freshly prepared from diisopropylamine (75 μL, 0.53 mmol), nBuLi (1.2M in hexanes, 0.44 mL, 0.53 mmol) and THF (2 mL)), and after 5 minutes was added nitroethylene (0.23 mL, 0.53 mmol, freshly prepared from 2-nitroethanol and phthalic anhydride).[180] After 2 h was added nitroethylene (0.23 mL, 0.53 mmol), before stirring for 3 h. Water (5 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL) before the combined organic layers were dried ($MgSO_4$) and concentrated. Column chromatography afforded *title compound* (13 mg, 8%) as a pale orange gum.

δ_H (400 MHz, $CDCl_3$) 8.60 (1H, ddd, *J* 4.7, 1.7 and 0.9, 1-H), 7.54 (1H, ddd, *J* 7.7, 7.6 and 1.7, 3-H), 7.23 (1H, ddd, *J* 7.6, 4.7 and 1.2, 2-H), 7.20-7.08 (4H, m, 4-H and Ph-H x 3), 6.80 (2H, m, Ph-H x 2), 4.54 (1H, dt, *J* 13.9 and 6.1, 7-H), 4.38 (1H, ddd, 13.9, 8.3 and 6.1, 7-H), 4.17 (1H, dd, *J* 10.7 and 6.0, 5-H), 3.12 (1H, dddd, *J* 14.6, 8.3, 6.1 and 6.0, 6-H), 2.88 (1H, ddt, *J* 14.6, 10.7 and 6.1, 6-H); δ_C (100 MHz, $CDCl_3$) 162.6 (C), 149.2 (CH), 137.5 (CH), 130.7 (C), 128.8 (CH x 2), 128.2 (CH), 127.1 (C), 124.7 (CH), 120.7 (CH), 72.8, 64.6, 28.1; **IR** ($CHCl_3$)/cm^{-1} 3057, 2933, 2853, 1649, 1604, 1574, 1540, 1448, 1417, 1314, 1153, 1111, 1025, 759, 694; **HRMS** (ESI+) *m/z* calculated for $[C_{14}H_{14}N_2NaO_3S]^+$: 313.0617, found 313.0612.

***N,N-Dimethylcinnamamide (238)*[268] *and 1,2-di(pyridin-2-yl)disulfane (239)*[269]**



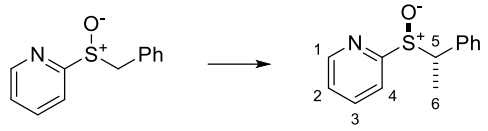
To a solution of 2-(benzylsulfinyl)pyridine (**212aa**, 91 mg, 0.42 mmol) in THF (3 mL) ad -78 °C was added LDA (freshly prepared from diisopropylamine (65 µL, 0.46 mmol), nBuLi (1.2M in hexanes, 0.38 mL, 0.46 mmol) and THF (1 mL)), and after 30 minutes was added 2-chloro-*N*,*N*-dimethylacetamide (**236**, 52 µL, 0.50 mmol). The reaction mixture was stirred for 1.5 h before being allowed to warm to rt, and it was stirred for another 1 h and water (5 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated. Column chromatography (40-70% EtOAc/petroleum ether) afforded *N*,*N*-dimethylcinnamamide (**238**, 31 mg, 42%) as a colourless solid and 1,2-di(pyridin-2-yl)disulfane (**239**, 21 mg, 44%) as a colourless solid.

N,*N*-Dimethylcinnamamide (**238**): δ_H (400 MHz, $CDCl_3$) 7.67 (1H, d, *J* 15.4, 3-H), 7.53 (2H, dd, *J* 7.7 and 1.9, Ph-H x 2), 7.40-7.32 (3H, m, Ph-H x 3), 6.89 (1H, d, *J* 15.4, 2-H), 3.18 (3H, s, 1-H_3), 3.07 (3H, s, 1-H_3); δ_C (101 MHz, $CDCl_3$) 166.8 (C), 142.5 (CH), 135.5 (C), 129.7 (CH), 128.9 (CH), 127.9 (CH), 117.6 (CH), 37.6 (CH_3), 36.1 (CH_3); **HRMS** (ESI+) *m/z* calculated for $[C_{11}H_{14}NO]^+$:176.1070, found 176.1079. Data agrees with literature.

1,2-Di(pyridin-2-yl)disulfane (**239**): δ_H (400 MHz, $CDCl_3$) 8.47 (2H, ddd, *J* 4.8, 1.4 and 1.3, 1-H x 2), 7.65-7.57 (4H, m, 3-H x 2 and 4-H x 2), 7.11 (2H, ddd, *J* 6.3, 4.8 and 2.2, 2-H x 2); δ_C (101 MHz, $CDCl_3$) 159.1 (C), 149.7 (CH), 137.5 (CH), 121.2 (CH), 119.8 (CH);

HRMS (ESI+) *m/z* calculated for $[C_{10}H_9N_2S_2]^+$: 221.0216, found 221.0202. Data agrees with literature.

2-((1-Phenylethyl)sulfinyl)pyridine (244)

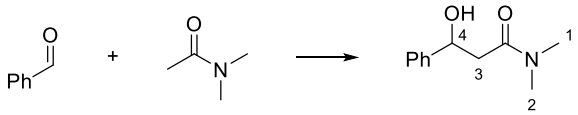


To a solution of 2-(benzylsulfinyl)pyridine (**212aa**, 220 mg, 1.0 mmol) in THF (4 mL) at -40 °C was added added LDA (0.5 M in THF, 2.2 mL, 1.1 mmol) and after 5 min was added iodomethane (75 μL, 1.2 mmol). After 1 h MeOH (0.5 mL), water (5 mL) and brine (5 mL) were added sequentially and the reaction mixture was extracted with CH_2Cl_2 (3 x 15 mL) before the combined organic layers were dried ($MgSO_4$) and concentrated to afford crude *title compound* (dr = 1:2.3 erythro:threo). Column chromatography (20-40% EtOAc/petroleum ether) afforded *title compound* (160 mg, 67%) as a mixture of diastereomers.

Major diastereomer: δ_H (400 MHz, $CDCl_3$) 8.61 (1H, ddd, *J* 4.7, 1.7 and 1.0, 1-H), 7.56 (1H, ddd, *J* 7.8, 7.7 and 1.7, 3-H), 7.33-7.30 (1H, m, Ph-H), 7.23 (1H, ddd, *J* 7.7, 4.7 and 1.1, 2-H), 7.18 (1H, ddd, *J* 7.8, 1.1 and 1.0, 4-H), 7.15-7.06 (2H, m, Ph-H x 2), 6.83-6.79 (2H, m, Ph-H x 2) 4.19 (1H, q, *J* 7.4, 5-H), 1.88 (3H, d, *J* 7.4, 6-H_3); δ_C (101 MHz, $CDCl_3$) 163.8 (C), 149.0 (CH), 137.3 (CH), 134.2 (C), 128.5 (CH), 128.0 (CH), 127.8 (CH), 124.4 (CH), 120.6 (CH), 63.0 (CH), 16.2 (CH_3); **HRMS** (ESI+) *m/z* calculated for $[C_{13}H_{13}NNaOS]^+$: 254.0610, found 254.0612.

Minor diastereomer: δ_H (400 MHz, $CDCl_3$) 8.63 (1H, ddd, *J* 4.8, 1.7 and 1.0, 1-H), 7.83 (1H, ddd, *J* 7.7, 7.6 and 1.7, 3-H), 7.75 (1H, ddd, *J* 7.7, 1.2 and 1.0, 4-H), 7.35 (1H, ddd, *J* 7.6, 4.8 and 1.2, 2-H), 7.33-7.28 (6H, m, 2-H and Ph-H x 5); 4.29 (1H, q, *J* 7.2, 5-H), 1.43 (3H, d, *J* 7.2, 6-H_3); δ_C (101 MHz, $CDCl_3$) 163.5 (C), 149.6 (CH), 137.6 (CH), 136.9 (C), 130.4 (CH), 128.7 (CH), 128.4 (CH), 124.7 (CH), 121.2 (CH), 63.5 (CH), 11.2(CH_3); **HRMS** (ESI+) *m/z* calculated for $[C_{13}H_{13}NNaOS]^+$: 254.0610, found 254.0613.

3-Hydroxy-N,N-dimethyl-3-phenylpropanamide (245a)[270]

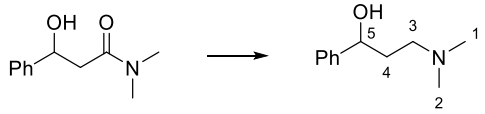


$CeCl_3.7H_2O$ (1.4 g, 3.6 mmol) was heated *in vacuo* (1-10 mbar) at 100 °C for 2 h and at 150 °C for a further 2 h to provide anhydrous $CeCl_3$ as a fine powder. In a separate

flask a solution of LDA (0.5M in THF, 7.6 mL, 3.8 mmol, freshly prepared) in THF (2 mL) at -78 °C was treated with dimethylacetamide (**247**, 0.32 mL, 3.4 mmol) and stirred for 30 min. To a slurry of the anhydrous $CeCl_3$ in THF (8 mL) was added the lithium enolate solution, and this was stirred for 45 min before cooling to -78 °C and adding a solution of benzaldehyde (**246a**, 0.18 mL, 1.7 mmol) in THF (2 mL). After stirring for 16 h LCMS analysis showed complete conversion of benzaldehyde and H_2O (5 mL) and KH_2PO_4 (*ca*. 2 g) was added. Following extraction with CH_2Cl_2 (4 x 50 mL) the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (40% EtOAc/petroleum ether to 50% EtOAc/10 MeOH/petroleum ether) afforded pure *title compound* (296 mg, 89%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 7.42-7.32 (4H, m, Ph-H x 4), 7.31-7.25 (1H, m, Ph-H), 5.14 (1H, dd, *J* 9.4 and 3.0, 4-H), 2.98 (3H, s, 1-H_3 or 2-H_3), 2.94 (3H, s, 1-H_3 or 2-H_3), 2.69 (1H, dd, *J* 16.5 and 3.0, 3-H), 2.61 (1H, dd, *J* 16.5 and 9.4, 3-H); **HRMS** (ESI+) *m/z* calculated for $[C_{11}H_{15}NNaO_2]^+$: 216.0995, found 216.1005. Data agrees with literature.

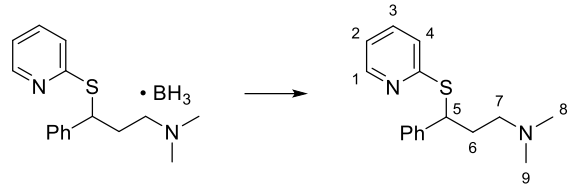
3-(Dimethylamino)-1-phenylpropan-1-ol (248)[271]



To a solution of 3-hydroxy-N,N-dimethyl-3-phenylpropanamide (**245a**, 50 mg, 0.26 mmol) in THF (2.5 mL) was added BH_3.DMS (2.0 M in THF, 0.46 mL, 0.92 mmol). The vessel was sealed and heated to 60 °C. After 2.5 h, HCl (1.0 M aqueous solution, 1.5 mL) was added and this was stirred for 20 min and then basified with NaOH (1.0 M aqueous solution) to >pH 10 and extracted with EtOAC (3 x 20 mL). The combined organic layers were dried ($MgSO_4$), concentrated and column chromatography (30-40% EtOAc/petroleum ether) afforded *title compound* (43 mg, 92%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 7.40-7.34 (4H, m, Ph-H x 4), 7.33-7.28 (1H, m, Ph-H), 4.73 (1H, dd, *J* 7.0 and 5.9, 5-H), 2.99 (1H, ddd, *J* 12.6, 9.3 and 6.9, 3-H), 2.82 (1H, ddd, *J* 12.6, 9.1 and 7.4, 3-H), 2.59 (3H, s, 1-H_3 or 2-H_3), 2.55 (3H, s, 1-H_3 or 2-H_3), 2.22-2.14 (2H, m, 4-H_2); δ_C (101 MHz, $CDCl_3$) 143.8 (C), 128.9 (CH), 128.2 (CH), 125.8 (CH), 72.9 (CH), 61.8 (CH_2), 52.2 (CH_3), 51.4 (CH_3), 33.4 (CH_2); **HRMS** (ESI+) *m/z* calculated for $[C_{11}H_{18}NO]^+$: 180.1383, found 180.1390. Data agrees with literature.

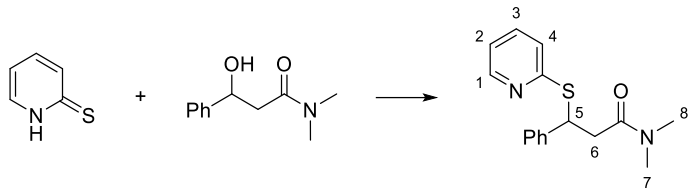
N,N-Dimethyl-3-phenyl-3-(pyridin-2-ylthio)propan-1-amine (249)



N,N-dimethyl-3-phenyl-3-(pyridin-2-ylthio)propan-1-amine - borane complex (**254**, 25 mg, 0.092 mmol) was treated with HCl (1.3 M in MeOH, 2 mL) and was stirred for 2.5 h before heating to reflux for 4 h, until complete conversion was observed by HRMS. H_2O (10 mL) was added before the solution was basified with K_2CO_3 (ca. 1 g) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (40% EtOAc/petroleum ether to 5% Et_3N/EtOAc) afforded *title compound* (17 mg, 68%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 8.42 (1H, ddd, *J* 4.9, 1.9 and 1.0, 1-H), 7.44-7.38 (3H, m, 3-H and Ph-H x 2), 7.32-7.26 (2H, m, Ph-H x 2), 7.23-7.19 (1H, m, Ph-H), 7.09 (1H, ddd, *J* 8.1, 1.1 and 1.0, 4-H), 6.94 (1H, ddd, *J* 7.4, 4.9 and 1.1, 2-H), 5.01 (1H, dd, *J* 8.9 and 5.8, 5-H), 2.38-2.02 (4H, m, 6-H x 2 and 7-H x 2), 2.19 (6H, s, 8-H_3 and 9-H_3); δ_C (100 MHz, $CDCl_3$) 158.9 (C), 149.6 (CH), 142.2 (C), 136.1 (CH), 128.6 (CH), 128.0 (CH), 127.2 (CH), 122.9 (CH), 119.8 (CH), 57.5 (CH_2), 46.8 (CH), 45.7 (CH_3 x 2), 34.7 (CH_2); **IR** ($CHCl_3$)/cm^{-1} 3050, 2978, 2949, 2863, 2824, 2777, 1578, 1558, 1454, 1417, 1123, 1044; **HRMS** (ESI+) *m/z* calculated for $[C_{16}H_{21}N_2S]^+$: 273.1420, found 273.1419.

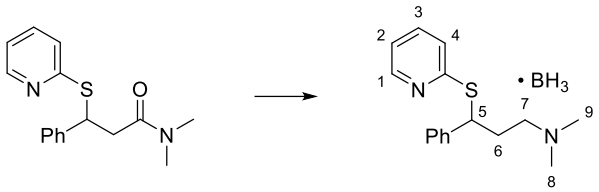
N,N-Dimethyl-3-phenyl-3-(pyridin-2-ylthio)propanamide (251)



To a solution of 3-hydroxy-N,N-dimethyl-3-phenylpropanamide[182] (**245a**, 400 mg, 2.1 mmol) in CH_2Cl_2 (20 mL) was added Et_3N (0.43 mL, 3.1 mmol), MsCl (0.18 mL, 2.3 mmol) and DMAP (13 mg, 0.10 mmol). After 1 h complete conversion of the alcohol was noted by ^1H NMR and 2-mercaptopyridine (270 mg, 2.5 mmol) and Et_3N (0.43 mL, 3.1 mmol) was added. After stirring for 15 h, K_2CO_3 (sat. aq., 50 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). Column chromatography (40-60% EtOAc/petroleum ether) afforded *title compound* (585 mg, 99%) as a pale yellow oil.

δ_H (400 MHz, $CDCl_3$) 8.43 (1H, ddd, *J* 4.9, 1.9 and 1.0, 1-H), 7.50-7.46 (2H, m, Ph-H x 2), 7.44 (1H, ddd, *J* 8.1, 7.4 and 1.9, 3-H), 7.31-7.26 (2H, m, Ph-H x 2), 7.23-7.18 (1H, m, Ph-H), 7.13 (1H, ddd, *J* 8.1, 1.1 and 1.0, 4-H), 6.96 (1H, ddd, *J* 7.4, 4.9 and 1.1, 2-H), 5.47 (1H, dd, *J* 8.9 and 5.7, 5-H), 3.20 (1H, dd, *J* 15.5 and 5.7, 6-H), 3.06 (1H, dd, *J* 15.5 and 8.9, 6-H), 2.97 (3H, s, 7-H_3 or 8-H_3), 2.85 (3H, s, 7-H_3 or 8-H_3); δ_C (100 MHz, $CDCl_3$) 170.1 (C), 158.6 (C), 149.7 (CH), 141.3 (C), 136.2 (CH), 128.6 (CH), 128.0 (CH), 127.5 (CH), 122.5 (CH), 119.9 (CH), 45.3 (CH), 40.3 (CH_2), 37.4 (CH_3), 35.6 (CH_3); **IR** ($CHCl_3$)/cm^{-1} 3008, 1639, 1578, 1495, 1453, 1417, 1123 cm^{-1}; **HRMS** (ESI+) *m/z* calculated for $[C_{16}H_{19}N_2OS]^+$: 287.1213, found 287.1205.

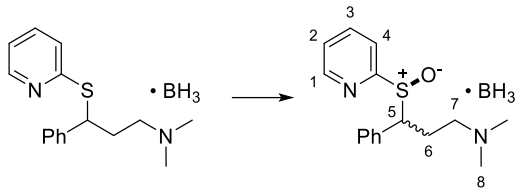
N,N-Dimethyl-3-phenyl-3-(pyridin-2-ylthio)propan-1-amine borane complex (254)



To a solution of N,N-dimethyl-3-phenyl-3-(pyridin-2-ylthio)propanamide (**251**, 140 mg, 0.47 mmol) in THF (5 mL) was added BH_3·DMS (2.0 M in THF, 0.83 mL, 1.7 mmol), and this was heated at 60 °C for 4 h. The reaction mixture was cooled to rt and NaOH (1.0 M in H_2O, 5 mL) was added cautiously before brine (50 mL) was added. This was extracted with CH_2Cl_2 (3 x 50 mL), and the combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* before column chromatography (40% EtOAc/petroleum ether to 60% EtOAc and 5% Et_3N/petroleum ether) afforded *title compound* (100 mg, 77%) as a pale yellow solid.

Mp: 97-99 °C; δ_H (270 MHz, $CDCl_3$) 8.44 (1H, ddd, *J* 5.0, 1.9 and 0.9, 1-H), 7.45 (1H, ddd, *J* 7.9, 7.5 and 1.9, 3-H), 7.42-7.37 (2H, m, Ph-H x 2), 7.35-7.29 (2H, m, Ph-H x 2), 7.27-7.22 (1H, m, Ph-H), 7.11 (1H, ddd, *J* 7.9, 1.1 and 1.0, 4-H), 6.99 (1H, ddd, *J* 7.5, 5.0 and 1.1, 2-H), 4.97 (1H, dd, *J* 8.6 and 6.4, 5-H), 2.92 (1H, dd, *J* 12.2 and 4.7, 6-H), 2.73 (1H, dd, *J* 12.2 and 4.9, 6-H), 2.62-2.39 (2H, m, 7-H x 2), 2.55 (3H, s, 8-H_3 or 9-H_3), 2.53 (3H, s, 8-H_3 or 9-H_3); δ_C (101 MHz, $CDCl_3$) 158.0 (C), 149.6 (CH), 141.0 (C), 136.3 (CH), 128.9 (CH), 127.8 (CH), 127.8 (CH), 123.0 (CH), 120.1 (CH), 62.7 (CH), 51.9 (CH_3), 51.3 (CH_3), 46.4 (CH_2), 30.9 (CH_2); δ_B (128 MHz, $CDCl_3$, {^{1}H}) -9.9; **HRMS** (ESI+) *m/z* calculated for $[C_{16}H_{24}BN_2S]^+$:287.1748, found 287.1735; **IR** ($CHCl_3$)/cm^{-1} 3043, 3008, 2375, 2275, 1578, 1557, 1454, 1417, 1168, 1123, 1025, 986, 876; **CHN** calculated for $C_{16}H_{23}BN_2S$: C 67.14, H 8.10, N 9.79 found: C 66.88, H 8.18, N 9.53.

N,N-Dimethyl-3-phenyl-3-(pyridin-2-ylsulfinyl)propan-1-amine borane adduct (255)

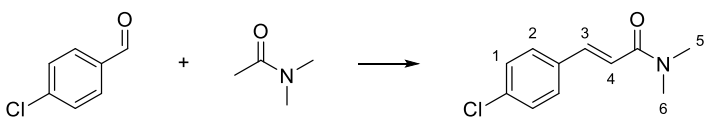


General procedure D: N,N-dimethyl-3-phenyl-3-(pyridin-2-ylthio)propan-1-amine borane complex (**254**, 24 mg, 0.084 mmol), *m*CPBA (77 wt%, 19 mg, 0.084 mmol) and CH_2Cl_2 (3 mL) gave *title compound* (12 mg, 47%) as a colourless gum.

Major diastereomer: δ_H (400 MHz, $CDCl_3$) 8.64 (1H, ddd, *J* 4.7, 1.8 and 1.0, 1-H), 7.81 (1H, ddd, *J* 7.8, 7.7 and 1.8, 3-H), 7.64 (1H, ddd, *J* 7.8, 1.1 and 1.0, 4-H), 7.37 (1H, ddd, *J* 7.7, 4.7 and 1.1, 2-H), 7.33-7.29 (3H, m, Ph-H x 3), 7.20-7.15 (2H, m, Ph-H x 2), 4.10 (1H, dd, *J* 10.2 and 4.6, 5-H), 2.70-2.51 (3H, m, 6-H and 7-H x 2), 2.49 (3H, s, 8-H_3), 2.48 (3H, s, 8-H_3), 2.40-2.29 (1H, m, 6-H); δ_C (100 MHz, $CDCl_3$) 162.6 (C), 149.9 (CH), 137.7 (CH), 133.7 (C), 129.1 (CH), 129.0 (CH), 128.8 (CH), 125.3 (CH), 121.6 (CH), 67.1 (CH), 62.0 (CH_2), 51.6 (CH_3), 51.6 (CH_3), 21.8 (CH_2); δ_B (128 MHz, $CDCl_3$, {^{1}H}) -9.67 (1B, s); **IR** ($CHCl_3$)/cm^{-1} 3085, 3067, 3007, 2957, 2934, 2855, 2376, 2275, 1578, 1562, 1477, 1424, 1168, 1038; **HRMS** (ESI+) *m/z* calculated for $[C_{16}H_{24}BN_2OS]^+$: 303.1697, found 303.1695.

Minor diastereomer: δ_H (400 MHz, $CDCl_3$) 8.61 (1H, ddd, *J* 4.7, 1.7 and 0.9, 1-H), 7.54 (1H, ddd, *J* 7.8, 7.7 and 1.7, 3-H), 7.23 (1H, ddd, *J* 7.6, 4.7 and 1.2, 2-H), 7.17-7.07 (4H, m, 4-H, Ph-H x 3), 6.80-6.76 (2H, m, Ph-H x 2), 3.99 (1H, dd, *J* 9.7 and 5.9, 5-H), 3.04-2.93 (1H, m, 7-H), 2.89-2.79 (1H, m), 2.75-2.67 (2H, m, 6-H), 2.63 (3H, s, 8-H_3), 2.60 (3H, s, 8-H_3); δ_C (100 MHz, $CDCl_3$) 162.8 (C), 149.2 (CH), 137.5 (CH), 131.4 (C), 128.7 (CH), 128.5 (CH), 128.1 (CH), 124.6 (CH), 120.8 (CH), 66.1 (CH), 62.0 (CH_2), 51.8 (CH_3), 51.6 (CH_3), 25.2 (CH_2); δ_B (128 MHz, $CDCl_3$, {^{1}H}) -9.96 (1B, s); **IR** ($CHCl_3$)/cm^{-1} 3062, 3011, 3005, 2929, 2855, 2375, 2274, 1579, 1542, 1453, 1424, 1168, 1038; **HRMS** (ESI+) *m/z* calculated for $[C_{16}H_{24}BN_2OS]^+$: 303.1697, found 303.1698.

(E)-3-(4-Chlorophenyl)-N,N-dimethylacrylamide (257b)[272]

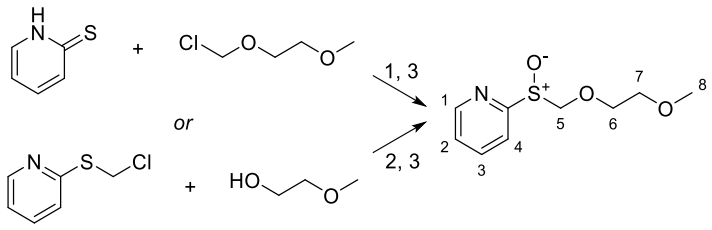


To a solution of phosphonitrilic chloride trimer (**258**, 35 mg, 0.10 mmol) in dimethylacetamide (**247**, 1.0 mL, 11 mmol) was added H_2SO_4 (98%, 1 drop from a 21

guage needle) and this was stirred for 1 h before 4-chlorobenzaldehyde (**246b**, 141 mg, 1.0 mmol) was added, and the reaction mixture was heated at 120 °C for 19 h. The reaction mixture was poured onto water (20 mL) and diluted with EtOAc (20 mL) before the organic phase was washed with water (4 x 20 mL) and was dried ($MgSO_4$), filtered, concentrated and subjected to column chromatography (40-60% EtOAc/petroleum ether) to provide *title compound* (132 mg, 63%) as a colourless solid.

δ_H (400 MHz, $CDCl_3$) 7.61 (1H, d, *J* 15.4, 3-H), 7.45 (2H, d, *J* 8.5, 1-H x 2 or 2-H x 2), 7.34 (2H, d, *J* 8.5, 1-H x 2 or 2-H x 2), 6.86 (1H, d, *J* 15.4, 4-H), 3.17 (3H, s, 5-H_3 or 6-H_3), 3.07 (3H, s, 5-H_3 or 6-H_3); δ_C (101 MHz, $CDCl_3$) 166.5 (C), 141.1 (CH), 135.5 (CH), 134.0 (CH), 129.2 (CH), 118.1 (CH), 37.6 (CH_3), 36.1 (CH_3); **HRMS** (ESI+) *m/z* calculated for $[C_{11}H_{13}ClNO]^+$: 210.0680, found 210.0688. Data agrees with literature.

2-(((2-Methoxyethoxy)methyl)sulfinyl)pyridine (259a)



1) To a solution of KO*t*-Bu (140 mg, 1.3 mmol) in 2-methoxyethanol (**262a**, 8.5 mL) was added 2-((chloromethyl)thio)pyridine (**265**, 0.1 mL, 0.85 mmol) and this was stirred for 18 h before the reaction mixture was charged with EtOAc (20 mL) and washed with H_2O (3 x 20 mL) before the organic layer was dried ($MgSO_4$), filtered and evaporated. Column chromatography (20% EtOAc/petroleum ether) afforded 2-(((2-methoxyethoxy)methyl)thio)pyridine (**260a**, 77 mg, 46%) as a colourless oil.

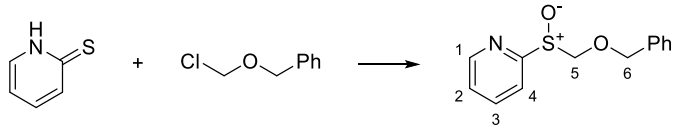
2) General procedure E: 2-mercaptopyridine (**221**, 200 mg, 1.8 mmol), 2-methoxyethoxymethyl chloride (**268a**, 0.17 mL, 1.5 mmol), Et_3N (0.25 mL, 1.8 mmol) and CH_2Cl_2 (18 mL) afforded 2-(((2-methoxyethoxy)methyl)thio)pyridine (**260a**, 290 mg, 98%) as a colourless oil.

3) General procedure D: 2-(((2-methoxyethoxy)methyl)thio)pyridine (**260a**, 41 mg, 0.21 mmol), *m*CPBA (46 mg, 0.21 mmol) and CH_2Cl_2 (2 mL) afforded *title compound* (40 mg, 89%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 8.63 (1H, ddd, *J* 4.7, 1.7 and 0.9, 1-H), 8.02 (1H, ddd, *J* 7.7, 1.1 and 0.9, 4-H), 7.94 (1H, ddd, *J* 7.7, 7.5 and 1.7, 3-H), 7.38 (1H, ddd, *J* 7.5, 4.7 and 1.1, 2-H),

4.97 (1H, d, *J* 10.7, 5-H), 4.68 (1H, d, *J* 10.7, 5-H), 4.07 (1H, dt, *J* 11.1 and 4.3, 6-H), 4.02 (1H, dt, *J* 11.1 and 4.7, 6-H), 3.58 (2H, t, *J* 4.7 and 4.3, 7-H_2), 3.36 (3H, s, 8-H_3); δ_C (100 MHz, $CDCl_3$) 162.4 (C), 149.8 (CH), 138.1 (CH), 124.8 (CH), 120.9 (CH), 92.2 (CH_2), 73.0 (CH_2), 91.7 (CH_2), 59.2 (CH_3); **IR** ($CHCl_3$)/cm^{-1} 3053, 2991, 1712, 1575, 1561, 1448, 1419, 1418, 1116, 1085, 1045, 989; **HRMS** (ESI+) *m/z* calculated for $[C_9H_{14}NO_3S]^+$: 216.0689, found 216.0694.

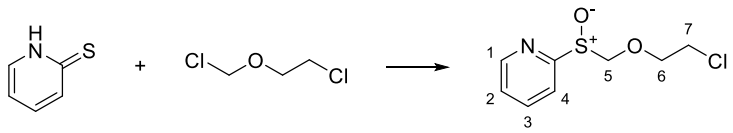
2-(((Benzyloxy)methyl)sulfinyl)pyridine (259b)



General procedure E: 2-mercaptopyridine (**221**, 200 mg, 1.8 mmol), benzyl chloromethyl ether (**268b**, 75 wt% purity, 0.28 mL, 1.5 mmol), Et_3N (0.25 mL, 1.8 mmol) and CH_2Cl_2 (18 mL) afforded 2-(((benzyloxy)methyl)thio)pyridine (**260b**, 350 mg, 100%) as a colourless oil. General procedure D: 2-(((benzyloxy)methyl)thio)pyridine (**260b**, 340 mg, 1.5 mmol), *m*CPBA (252 mg, 1.5 mmol) and CH_2Cl_2 (15 mL) afforded *title compound* (260 mg, 69%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 8.62 (1H, ddd, *J* 4.7, 1.7 and 1.0, 1-H), 8.05 (1H, ddd, *J* 7.8, 1.1 and 1.0, 4-H), 7.95 (1H, ddd, *J* 7.8, 7.7 and 1.7, 3-H), 7.40-7.27 (6H, m, 2-H and Ph-H x 5), 4.96 (1H, d, *J* 11.9, 6-H), 4.94 (1H, d, *J* 10.6, 5-H), 4.89 (1H, d, *J* 11.9, 6-H), 4.66 (1H, d, *J* 10.6, 5-H); δ_C (100 MHz, $CDCl_3$) 162.4 (C), 149.8 (CH), 138.1 (CH), 136.5 (C), 128.7 (CH), 128.4 (CH), 128.2 (CH), 124.8 (CH), 121.0 (CH), 90.6 (CH_2), 75.2 (CH_2); **HRMS** (ESI+) *m/z* calculated for $[C_{13}H_{14}NO_2S]^+$: 248.0740, found 248.0740; **IR** ($CHCl_3$)/cm^{-1} 3008, 1578, 1563, 1454, 1424, 1133, 1102, 1037 cm^{-1}.

2-(((2-Chloroethoxy)methyl)sulfinyl)pyridine (259c)

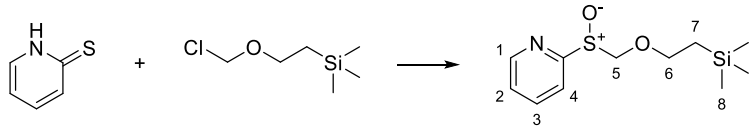


General procedure E: 2-mercaptopyridine (**221**, 200 mg, 1.8 mmol), 2-chloroethyl chloromethyl ether (**268c**, 0.16 mL, 1.5 mmol), Et_3N (0.25 mL, 1.8 mmol) and CH_2Cl_2 (18 mL) afforded 2-(((2-chloroethoxy)methyl)thio)pyridine (**260c**, 290 mg, 94%) as a colourless oil. General procedure D: 2-(((2-chloroethoxy)methyl)thio)pyridine (**260c**,

200 mg, 1.0 mmol), *m*CPBA (220 mg, 1.0 mmol) and CH_2Cl_2 (10 mL) afforded *title compound* (190 mg, 87%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 8.63 (1H, ddd, *J* 4.8, 1.7 and 1.0, 1-H), 8.02 (1H, ddd, *J* 7.8, 1.2 and 1.0, 4-H), 7.95 (1H, ddd, *J* 7.8, 7.5 and 1.7, 3-H), 7.39 (1H, ddd, *J* 7.5, 4.8 and 1.2, 2-H), 4.97 (1H, d, *J* 10.8, 5-H), 4.70 (1H, d, *J* 10.8, 5-H), 4.18 (1H, ddd, *J* 11.1, 5.6 and 5.5, 6-H), 4.09 (1H, ddd, *J* 11.1, 6.0 and 5.3, 6-H), 3.65 (2H, m, 7-H_2); δ_C (100 MHz, $CDCl_3$) 162.0 (C), 149.8 (CH), 138.2 (CH), 124.9 (CH), 121.0 (CH), 91.6 (CH_2), 73.8 (CH_2), 42.6 (CH_2); **HRMS** (ESI+) *m/z* calculated for $[C_8H_{11}ClNO_2S]^+$: 220.0194, found 220.0195; **IR** ($CHCl_3$)/cm^{-1} 3009, 1666, 1575, 1541, 1453, 1425, 1113, 1037 cm^{-1}.

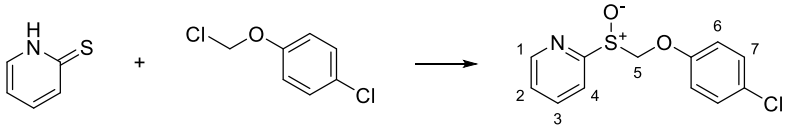
2-(((2-(Trimethylsilyl)ethoxy)methyl)sulfinyl)pyridine (259d)



General procedure E: 2-mercaptopyridine (**221**, 200 mg, 1.8 mmol), 2-(trimethylsilyl)ethoxymethyl chloride (**268d**, 90 wt% purity, 0.30 mL, 1.5 mmol), Et_3N (0.25 mL, 1.8 mmol), CH_2Cl_2 (18 mL) and column chromatography (5% EtOAc/petroleum ether) afforded 2-(((2-(trimethylsilyl)ethoxy)methyl)thio)pyridine (**260d**, 360 mg, 100%) as a colourless oil. General procedure D: 2-(((2-(trimethylsilyl)ethoxy)methyl)thio)pyridine (**260d**, 290 mg, 1.2 mmol), *m*CPBA (270 mg, 1.2 mmol) and CH_2Cl_2 (12 mL) afforded *title compound* (170 mg, 57%) as a colourless oil.

δ_H (500 MHz, $CDCl_3$) 8.63 (1H, ddd, *J* 4.8, 1.7 and 1.0, 1-H), 8.03 (1H, ddd, *J* 7.8, 1.2 and 1.0, 4-H), 7.94 (1H, ddd, *J* 7.8, 7.6 and 1.7, 3-H), 7.38 (1H, ddd, *J* 7.6, 4.8 and 1.2, 2-H), 4.87 (1H, d, *J* 10.5, 5-H), 4.60 (1H, d, *J* 10.5, 5-H), 4.01-3.95 (1H, m, 6-H), 3.89-3.84 (1H, m, 6-H), 1.00 (2H, dd, *J* 8.9 and 7.9, 7-H_2), 0.00 (9H, s, 8-H_3x3); δ_C (125 MHz, $CDCl_3$) 162.7(C), 149.7 (CH), 138.1 (CH), 124.7 (CH), 120.9 (CH), 92.0 (CH_2), 71.5 (CH_2), 18.4 (CH_2), -1.3 (CH_3); **HRMS** (ESI+) *m/z* calculated for $[C_{11}H_{20}NO_2SSi]^+$: 258.0979, found 258.0984; **IR** ($CHCl_3$)/cm^{-1} 3008, 2957, 2897, 1577, 1449, 1421, 1251, 1104, 1035, 860, 838 cm^{-1}.

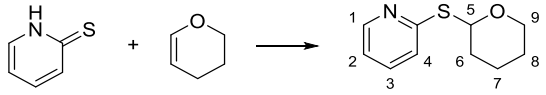
2-(((4-Chlorophenoxy)methyl)sulfinyl)pyridine (259e)



General procedure E: 2-mercaptopyridine (**221**, 200 mg, 1.8 mmol), α,4-dichloroanisole (**268e**, 270 mg, 1.5 mmol), Et_3N (0.25 mL, 1.8 mmol) and CH_2Cl_2 (18 mL) afforded 2-(((4-chlorophenoxy)methyl)thio)pyridine (**260e**, 280 mg, 74%) as a colourless solid. General procedure D: 2-(((4-chlorophenoxy)methyl)thio)pyridine (**260e**, 270 mg, 1.0 mmol), *m*CPBA (230 mg, 1.0 mmol), CH_2Cl_2 (10 mL) and column chromatography (40-50% EtOAc/petroleum ether) afforded *title compound* (260 mg, 88%) as a colourless solid.

Mp: 58-61 °C; δ_H (400 MHz, $CDCl_3$) 8.66 (1H, ddd, *J* 4.8, 1.7 and 1.0, 1-H), 8.05 (1H, ddd, *J* 7.8, 1.1 and 1.0, 4-H), 7.97 (1H, ddd, *J* 7.8, 7.6 and 1.7, 3-H), 7.42 (1H, ddd, *J* 7.6, 4.8 and 1.1, 2-H), 7.26 (2H, d, *J* 9.0, 6-H x 2 or 7-H x 2), 7.04 (2H, d, *J* 9.0, 6-H x 2 or 7-H x 2), 5.44 (1H, d, *J* 10.6, 5-H), 5.08 (1H, d, *J* 10.6, 5-H); δ_C (100 MHz, $CDCl_3$) 161.8 (C), 156.4 (C), 149.9 (CH), 138.3 (CH), 129.7 (CH), 128.1 (C), 125.1 (CH), 121.1 (CH), 117.6 (CH), 88.8 (CH_2); **HRMS** (ESI+) *m/z* calculated for $[C_{12}H_{10}ClNNaO_2S]^+$: 290.0013, found 290.0012; **IR** ($CHCl_3$)/cm^{-1} 3009, 1579, 1562, 1490, 1453, 1425, 1172, 1091, 1063, 1038, 826 cm^{-1}.

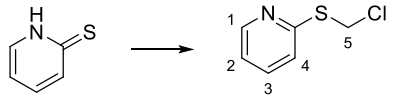
2-((Tetrahydro-2H-pyran-2-yl)thio)pyridine (260f)[273]



To a solution of 2-mercaptopyridine (**221**, 500 mg, 4.5 mmol) in CH_2Cl_2 (40 mL) was added 3,4-dihydro-*2H*-pyran (**269**, 0.82 mL, 9.0 mmol) and TSA.H_2O (9 mg, 0.05 mmol) and this was stirred for 19 h before it was dried onto silica gel, and column chromatography (10% EtOAc/petroleum ether) afforded *title compound* (570 mg, 65%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 8.45 (1H, ddd, *J* 4.9, 1.9 and 1.1, 1-H), 7.52 (1H, ddd, *J* 8.0, 7.7 and 1.9, 3-H), 7.30 (1H, ddd, *J* 8.0, 1.1 and 1.1, 4-H), 7.02 (1H, ddd, *J* 7.7, 4.9 and 1.1, 2-H), 5.94 (1H, dd, *J* 5.5 and 4.1, 5-H), 4.11 (1H, ddd, *J* 11.7, 6.9 and 4.7, 9-H), 3.67 (1H, ddd, *J* 11.7, 4.8 and 4.7, 9-H), 2.11 (1H, dddd, *J* 13.3, 8.68, 4.2 and 4.1, 6-H), 1.96-1.79 (2H, m, 6-H and 8-H), 1.76-1.60 (3H, m, 7-H_2 and 8-H); **IR** ($CHCl_3$)/cm^{-1} 3053, 2946, 2855, 1579, 1561, 1454, 1418, 1124, 1103, 1077, 1037, 1006, 988; **HRMS** (ESI+) *m/z* calculated for $[C_{10}H_{13}NNaOS]^+$: 218.0610, found 218.0615. Data agrees with literature.

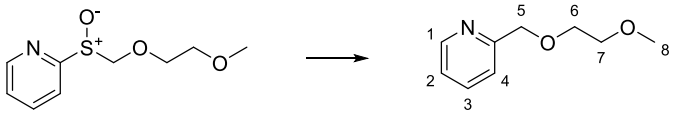
2-((Chloromethyl)thio)pyridine (265)[274]



To a solution of 2-mercaptopyridine (**221**, 560 mg, 5.0 mmol) in MeCN (50 mL) was added K_2CO_3 (1.4 g, 10 mmol) and chloroiodomethane (**264**, 0.55 mL, 7.5 mmol) and after 14 h water (100 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated to afford *title compound* (830 mg, quant.) as a brown oil.

δ_H (270 MHz, $CDCl_3$) 8.54 (1H, ddd, *J* 4.9, 1.9 and 1.0, 1-H), 7.58 (1H, ddd, *J* 8.0, 7.4 and 1.9, 3-H), 7.26 (1H, ddd, *J* 8.0, 1.1 and 1.0, 4-H), 7.10 (1H, ddd, *J* 7.4, 4.9 and 1.1, 2-H), 5.38 (2H, s, 5-H_2); δ_C (101 MHz, $CDCl_3$) 154.9 (C), 150.0 (CH), 136.8 (CH), 123.1 (CH), 121.0 (CH), 45.5 (CH_2); **IR** ($CHCl_3$)/cm^{-1} 304, 296, 1578, 1561, 1455, 1419, 1123; **HRMS** (ESI+) *m/z* calculated for $[C_6H_7ClNS]^+$: 159.9982, found 159.9979. Data agrees with literature.

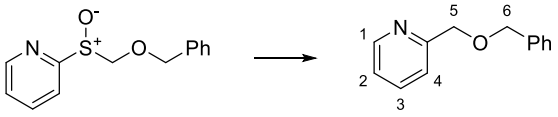
2-((2-Methoxyethoxy)methyl)pyridine (270a)



General procedure C: 2-(((2-methoxyethoxy)methyl)sulfinyl)pyridine (**259a**, 32 mg, 0.15 mmol), *t*-BuMgCl (0.86 M in THF, 0.19 mL, 0.16 mmol), THF (1.5 mL) and column chromatography (40-100% EtOAc/petroleum ether) afforded *title compound* (16 mg, 64%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 8.54 (1H, dd, *J* 4.9 and 1.8, 1-H), 7.69 (1H, ddd, *J* 7.7, 7.6 and 1.8, 3-H), 7.48 (1H, d, *J* 7.7, 4-H), 7.18 (1H, dd, *J* 7.6 and 4.9, 2-H), 4.69 (2H, s, 5-H_2), 3.74-3.71 (2H, m, 6-H_2), 3.63-3.60 (2H, m, 7-H_2), 3.40 (3H, s, 8-H_3); δ_C (100 MHz, $CDCl_3$) 158.6 (C), 149.2 (CH), 136.8 (CH), 122.5 (CH), 121.6 (CH), 74.3 (CH_2), 71.9 (CH_2), 70.1 (CH_2), 59.1 (CH_3); **IR** ($CHCl_3$)/cm^{-1} 3061, 2960, 2928, 2856, 1728, 1494, 1364, 1308, 1246, 1124, 971; **HRMS** (ESI+) *m/z* calculated for $[C_9H_{14}NO_2]^+$: 168.1019, found 168.1022.

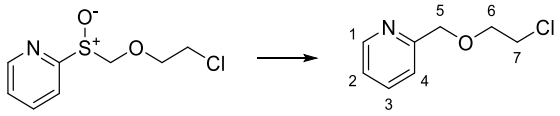
2-((Benzyloxy)methyl)pyridine (270b)



General procedure C: 2-(((benzyloxy)methyl)sulfinyl)pyridine (**259b**, 58 mg, 0.23 mmol), *t*-BuMgCl (0.86 M in THF, 0.30 mL, 0.26 mmol), THF (2.3 mL) and column chromatography (20-30% EtOAc/petroleum ether) afforded *title compound* (40 mg, 87%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 8.56 (1H, ddd, *J* 4.6, 1.8 and 0.8, 1-H), 7.70 (1H, ddd, *J* 7.7, 7.6 and 1.8, 3-H), 7.50 (1H, ddd, *J* 7.7, 0.8 and 0.7, 4-H), 7.42-7.27 (5H, m, Ph-H x 5), 7.19 (1H, ddd, *J* 7.6, 4.6 and 0.7, 2-H), 4.70 (2H, s, 6-H_2), 4.66 (2H, s, 5-H_2); δ_C (100 MHz, $CDCl_3$) 158.7 (C), 149.2 (CH), 138.1 (C), 136.8 (CH), 128.6 (CH), 128.0 (CH), 127.9 (CH), 122.5 (CH), 121.6 (CH), 73.2 (CH_2), 73.1 (CH_2); **HRMS** (ESI+) *m/z* calculated for $[C_{13}H_{14}NO]^+$: 200.1070, found 200.1077; **IR** ($CHCl_3$)/cm^{-1} 2966, 2865, 1731, 1595, 1477, 1454, 1436, 1357, 1245, 1108, 1077 cm^{-1}.

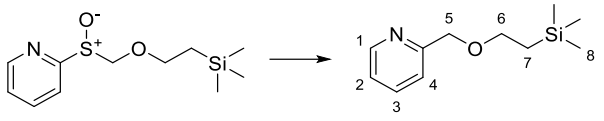
2-((2-Chloroethoxy)methyl)pyridine (270c)



General procedure C: 2-(((2-chloroethoxy)methyl)sulfinyl)pyridine (**259c**, 55 mg, 0.25 mmol), *t*-BuMgCl (0.86 M in THF, 0.32 mL, 0.28 mmol), THF (2.5 mL) and column chromatography (30-50% EtOAc/petroleum ether) afforded *title compound* (37 mg, 87%) as a pale yellow oil.

δ_H (400 MHz, $CDCl_3$) 8.55 (1H, ddd, *J* 4.9, 1.4 and 1.2, 1-H), 7.71 (1H, ddd, *J* 7.8, 7.7 and 1.4, 3-H), 7.48 (1H, ddd, *J* 7.8, 1.2 and 1.1, 4-H), 7.20 (1H, ddd, *J* 7.7, 4.9 and 1.1, 2-H), 4.71 (2H, s, 5-H_2), 3.84 (2H, t, *J* 5.7, 6-H_2 or 7-H_2), 3.70 (2H, t, *J* 5.7, 6-H_2 or 7-H_2); δ_C (100 MHz, $CDCl_3$) 158.1 (C), 149.3 (CH), 136.9 (CH), 122.7 (CH), 121.6 (CH), 74.2 (CH_2), 71.0 (CH_2), 43.0 (CH_2); **HRMS** (ESI+) *m/z* calculated for $[C_8H_{11}ClNO]^+$: 172.0524, found 172.0529; **IR** ($CHCl_3$)/cm^{-1} 3009, 2964, 2860, 2130, 1593, 1478, 1436, 1359, 1271, 1120, 1034 cm^{-1}.

2-((2-(Trimethylsilyl)ethoxy)methyl)pyridine (270d)

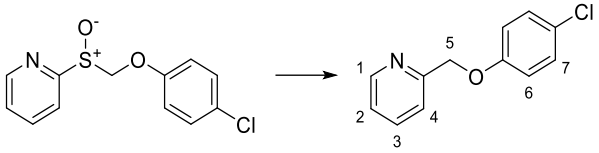


General procedure C: 2-(((2-(trimethylsilyl)ethoxy)methyl)sulfinyl)pyridine (**259d**, 57 mg, 0.22 mmol), *t*-BuMgCl (0.86 M in THF, 0.28 mL, 0.24 mmol), THF (2.2 mL) and

column chromatography (10-30% EtOAc/petroleum ether) provided *title compound* (25 mg, 54%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 8.54 (1H, ddd, *J* 4.9, 1.8 and 1.0, 1-H), 7.69 (1H, ddd, *J* 7.8, 7.7 and 1.8, 3-H), 7.44 (1H, ddd, *J* 7.8, 1.1 and 1.0, 4-H), 7.17 (1H, ddd, *J* 7.7, 4.9 and 1.1, 2-H), 4.61 (2H, s, 5-H_2), 3.66 (2H, t, *J* 8.3, 6-H_2), 1.04 (2H, t, *J* 8.3, 7-H_2), 0.02 (9H, s, 8-H_3x3); δ_C (100 MHz, $CDCl_3$) 159.0 (C), 149.0 (CH), 136.6 (CH), 122.2 (CH), 121.3 (CH), 73.3 (CH_2), 69.4 (CH_2), 18.3 (CH_2), -1.34 (CH_3); **HRMS** (ESI+) *m/z* calculated for $[C_{11}H_{20}NOSi]^+$: 210.1309, found 210.1313; **IR** ($CHCl_3$)/cm^{-1} 3073, 3007, 2957, 2926, 2897, 2864, 1593, 1573, 1477, 1436, 1355, 1250, 1107, 1082, 861, 838 cm^{-1}.

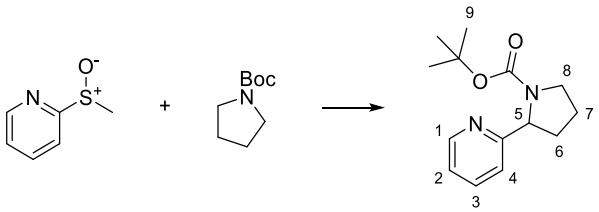
2-((4-Chlorophenoxy)methyl)pyridine (270e)



General procedure C: 2-(((4-chlorophenoxy)methyl)sulfinyl)pyridine (**259e**, 74 mg, 0.28 mmol), *t*-BuMgCl (0.86 M in THF, 0.35 mL, 0.30 mmol), THF (2.8 mL) and column chromatography (20-40% EtOAc/petroleum ether) afforded *title compound* (52 mg, 84%) as a colourless solid.

Mp: 75-77 °C; δ_H (400 MHz, $CDCl_3$) 8.60 (1H, ddd, *J* 5.0, 1.3 and 1.3, 1-H), 7.71 (1H, ddd, *J* 7.8, 7.7 and 1.8, 3-H), 4.49 (1H, dd, *J* 7.8 and 1.3, 4-H), 7.25-7.21 (3H, m, 2-H and 6-H x 2), 6.91 (2H, d, *J* 8.9. 7-H x 2), 5.18 (2H, s, 5-H_2); δ_C (100 MHz, $CDCl_3$) 157.1 (C), 157.0 (C), 149.5 (CH), 137.0 (CH), 129.6 (CH), 129.5 (CH), 126.2 (C), 122.9 (CH), 121.5 (CH), 116.3 (CH), 71.1 (CH_2); **IR** ($CHCl_3$)/cm^{-1} 3009, 2974, 1596, 1492, 1437, 1282, 1171, 1094, 1050, 825; **HRMS** (ESI+) *m/z* calculated for $[C_{12}H_{11}ClNO]^+$: 220.0524, found 220.0527;

t-Butyl 2-(pyridin-2-yl)pyrrolidine-1-carboxylate (282a)



To a solution of *N*-Boc-pyrrolidine (**275**, 35 µL, 0.20 mmol) in THF (1.4 mL) at -30 °C was added *s*-BuLi (0.25 mL, 0.28 mmol) and after 5 min 2-(methylsulfinyl)pyridine (**212bn**, 48 µL, 0.40 mmol). After 30 min the reaction mixture was allowed to warm to rt and was stirred for 30 min before adding water (5 mL) and extracting with CH_2Cl_2 (3

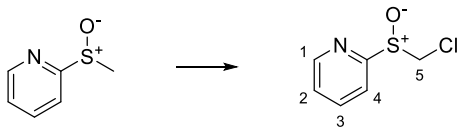
x 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated and column chromatography (40-100% EtOAc/petroleum ether) afforded *title compound* (22 mg, 44%) as a colourless oil.

Data reported as a 0.6:0.4 ratio of rotamers. δ_H (270 MHz, $CDCl_3$) 8.56-8.51 (1H, m, 1-H), 7.65 (1H, ddd, *J* 7.7, 7.7 and 1.8, 3-H), 7.23-7.12 (2H, m, 2-H and 4-H), 5.05-4.97 (0.4H, m, 5-H x 0.4), 4.92-4.84 (0.6H, m, 5-H x 0.6), 3.68-3.48 (2H, m, 8-H_2), 2.46-2.26 (1H, m, 6-H), 2.09-1.93 (1H, m, 6-H), 1.93-1.83 (2H, m, 7-H_2), 1.45 (3.6H, s, 9-H x 3.6), 1.19 (5.4H, s, 9-H x 5.4); δ_C (100 MHz, $CDCl_3$) 163.8 (C), 149.3 (C), 149.0 (CH), 136.3 (CH), 121.6 (CH), 119.6 (CH), 79.3 (C), 62.9 (CH), 47.1 (CH_2), 34.36 (CH_2), 28.2 (CH_3), 23.2 (CH_2); **IR** ($CHCl_3$)/cm^{-1} 2979, 2879, 1686, 1593, 1476, 1435, 1402, 1162, 1121; **HRMS** (ESI+) *m/z* calculated for $[C_9H_{13}N_2]^+$: 149.1073, found 149.1075.

2-((Chloromethyl)sulfinyl)pyridine (283a)



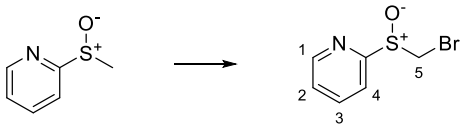
General procedure D: 2-((chloromethyl)thio)pyridine (**265**, 64 mg, 0.40 mmol), *m*CPBA (99 mg, 0.4 mmol) and CH_2Cl_2 (4 mL) afforded *title compound* (29 mg, 41%) as a colourless oil.



Work performed by Mindaugas Šiaučiulis. To a solution of 2-(methylsulfinyl)pyridine (**212bn**, 420 mg, 3.0 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added SO_2Cl_2 (0.29 mL, 3.6 mmol) and this was stirred for 30 min before the reaction mixture was washed with NaOH (0.5 M in water, 2 x 20 mL). The organic phase was dried ($MgSO_4$) and concentrated and column chromatography (30% IPA/petroleum ether) afforded *title compound* (275 mg, 52%) as a pale yellow oil.

δ_H (400 MHz, $CDCl_3$) 8.64 (1H, ddd, *J* 4.8, 1.6 and 0.9, 1-H), 8.01 (1H, ddd, *J* 7.9, 1.6 and 0.9, 4-H), 7.97 (1H, ddd, *J* 7.9, 7.0 and 1.6, 3-H), 7.44 (1H, ddd, *J* 7.0, 4.8 and 1.6, 2-H), 4.85 (1H, d, *J* 11.2, 5-H), 4.65 (1H, d, *J* 11.2, 5-H); δ_C (100 MHz, $CDCl_3$) 161.3 (C), 150.0 (CH), 138.1 (CH), 125.5 (CH), 121.8 (CH), 60.6 (CH_2); **IR** (ATR)/cm^{-1} 3014, 2950, 1577, 1559, 1448, 1420, 1383, 1283, 1234, 1146, 1085, 1053, 1033, 991; **HRMS** (ESI+) *m/z* calculated for $[C_6H_6ClNNaOS]^+$: 197.9751, found 197.9752.

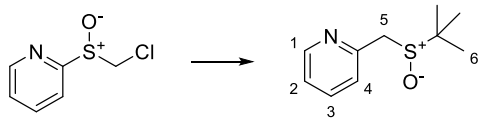
2-((bromomethyl)sulfinyl)pyridine (283b)



Work performed by Mindaugas Šiaučiulis. To a solution of 2-(methylsulfinyl)pyridine (**212bn**, 440 mg, 3.1 mmol) in CH_2Cl_2 (5 mL) was added N-bromosuccinimide (550 mg, 3.1 mmol), pyridine (520 µL, 6.5 mmol), and bromine (80 µL, 1.6 mmol) and reaction mixture was heated at 35 °C. After 72 h the reaction mixture was quenched with sodium sulfite (sat. aq., 25 mL) and this was extracted with $CHCl_3$ (3 x 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated and column chromatography (60% EtOAc/petroleum ether) afforded *title compound* (256 mg, 37%) as an off-white solid.

M.p. 70-74 °C; δ_H (400 MHz, $CDCl_3$) 8.64 (1 H, dt, *J* 4.7, 1.3, 1-H), 8.03 – 7.90 (2 H, m, 3-H and 4-H), 7.44 (1 H, ddd, *J* 6.8, 4.7, 2.2, 2-H), 4.74 (1 H, d, *J* 10.7, 5-H), 4.59 (1 H, d, *J* 10.7, 5-H'); δ_C (101 MHz, $CDCl_3$) 161.82, 149.85, 137.89, 125.33, 121.62, 48.61; **IR** (ATR)/cm^{-1} 3000, 2924, 1723, 1577, 1449, 1420, 1367, 1208, 1128, 1083, 1047, 990; **HRMS** (ESI+) *m/z* calculated for $[C_6H_6BrNNaOS]^+$: 241.9246, found 241.9246.

2-((t-Butylsulfinyl)methyl)pyridine (286a)

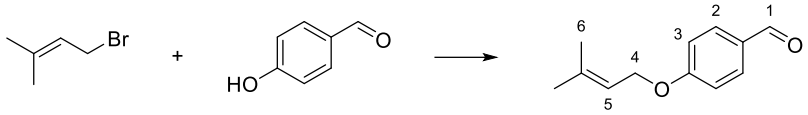


General procedure C: 2-((chloromethyl)sulfinyl)pyridine (**283a**, 19 mg, 0.11 mmol), *t*-BuMgCl (0.87 in THF, 0.14 mL, 0.12 mmol), THF (1.1 mL) and column chromatography (40% EtOAc/petroleum ether to 3% MeOH/EtOAc) afforded *title compound* (8 mg, 38%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 8.60 (1H, ddd, *J* 4.9, 1.8, and 1.0, 1-H), 7.69 (1H, ddd, *J* 7.7, 7.6 and 1.8, 3-H), 7.42 (1H, ddd, *J* 7.7, 1.1 and 1.0, 4-H), 7.23 (1H, ddd, *J* 7.6, 4.9 and 1.1, 2-H), 4.04 (1H, d, *J* 12.5, 5-H), 3.78 (1H, d, *J* 12.5, 5-H), 1.34 (9H, s, 6-H_3x3); δ_C (100 MHz, $CDCl_3$) 152.9 (C), 150.1 (CH), 137.0 (CH), 125.5 (CH), 123.0 (CH), 55.2 (CH_2), 54.1 (C), 23.2 (CH_3); **IR** ($CHCl_3$)/cm^{-1} 3060, 2982, 2870, 1592, 1473, 1436, 1367, 1084, 1033; **HRMS** (ESI+) *m/z* calculated for $[C_{10}H_{16}NOS]^+$: 198.0947, found 198.0959.

5.3 Compounds from Chapter 3

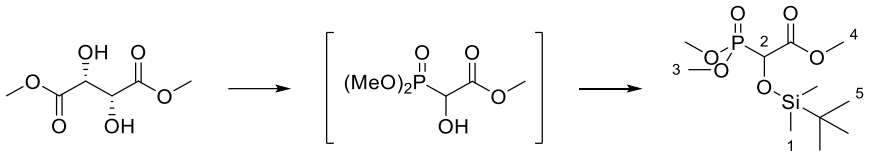
3-Methylbut-2-en-1-yl)oxy)benzaldehyde (397)[217]



To a mixture of 4-hydroxybenzaldehyde (**402**, 3.1 g, 25 mmol) and K_2CO_3 (17 g, 130 mmol) in acetone (50 mL) was added prenyl bromide (**401**, 3.5 mL, 30 mmol). The reaction mixture was stirred at for 13 h before being filtered. The filtrate was evaporated *in vacuo* and the resulting oil was purified by column chromatography (10% EtOAc/petroleum ether) to give *title compound* (4.43 g, 93%) as colourless needles.

δ_H (400 MHz, $CDCl_3$) 9.88 (1H, s, 1-H), 7.82 (2H, d, *J* 8.7, 2-H x 2), 7.00 (2H, d, *J* 8.7, 3-H x 2), 5.49 (1H, t, *J* 6.8, 5-H), 4.60 (2H, d, *J* 6.8, 4-H), 1.81 (3H, s, 6-H_3), 1.76 (3H, s, 6-H_3); δ_C (100 MHz, $CDCl_3$) 191.0 (CH), 164.1 (C), 139.3 (C), 132.1 (CH), 130.0 (CH), 118.9 (CH), 115.1 (C), 65.3 (CH_2), 26.0 (CH_3), 18.4 (CH_3); **IR** (ATR)/cm^{-1} 2982, 2938, 2745, 1688, 1601, 1578, 1509, 1249, 1161, 989; **HRMS** (ESI+) *m/z* calculated for $[C_{12}H_{14}NaO_2]^+$: 213.0886, found 213.0889. Data agrees with literature.

Methyl 2-((t-butyldimethylsilyl)oxy)-2-(dimethoxyphosphoryl)acetate (398a)[275]

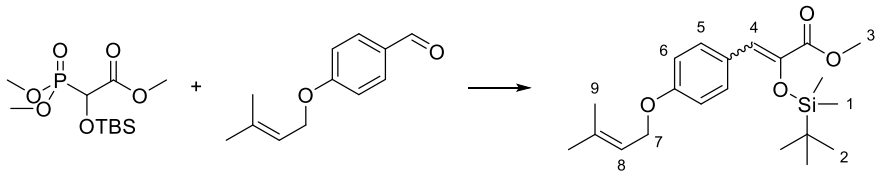


To a suspension of dimethyl-L-tartrate (**400**, 5.0 g, 28 mmol) in Et_2O (30 mL) at 0 °C was added H_6IO_5 (6.4 g, 28 mmol) and after 25 min it was allowed to warm to rt and was stirred for a further 75 min. The colourless precipitate was removed by cannula filtration in to a 3-necked round-bottomed-flask fitted with Dean-Stark trap and a condenser, before being concentrated to a colourless oil *in vacuo*. Dimethylphosphite (4.3 mL, 46 mmol) was charged to the oil before adding toluene (30 mL) and heating the resulting solution to reflux for 2 h. Concentration *in vacuo* followed by filtration through silica with EtOAc gave crude methyl 2-(dimethoxyphosphoryl)-2-hydroxyacetate (6.2 g) as a pale yellow oil. To a solution of the crude methyl 2-(dimethoxyphosphoryl)-2-hydroxyacetate (5.6 g) in DMF (30 mL) was charged TBSCl (5.1 g, 34 mmol), and imidazole (2.3 g, 34 mmol) before

being stirred for 18 h. Water (300 mL) and Et_2O (200 mL) were charged. The aqueous phase was extracted with EtOAc (200 mL) before the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (60% EtOAc/petroleum ether) gave *title compound* (4.06 g, 46%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 4.84 (1H, d, *J* 18.1, 2-H), 3.85 (3H, d, *J* 10.7, 3-H_3), 3.83 (3H, d, *J* 10.7, 3-H_3) 3.81 (3H, d, *J* 0.5, 4-H_3), 0.92 (9H, s, 5-H_3 x 3), 0.12 (3H, s, 1-H_3), 0.11 (3H, s, 1-H_3); δ_C (100 MHz, $CDCl_3$) 169.1 (d, *J* 2.7, C), 70.6 (d, *J* 162.4, CH), 54.3 (d, *J* 6.8, CH_3), 52.9 (CH_3), 25.7 (CH_3), 18.5 (C), -5.25 (CH_3), -5.39 (CH_3); δ_P (162 MHz, $CDCl_3$) 17.93 (dsept, *J* 18.1 and 10.7); **IR** ($CHCl_3$)/cm^{-1} 2958, 2932, 2887, 2859, 1755, 1464, 1438, 1260, 1139, 1040, 841; **HRMS** (ESI+) *m/z* calculated for $[C_{11}H_{26}O_6PSi]^+$: 313.1231, found 313.1241. Data agrees with literature.

Methyl 2-((t-butyldimethylsilyl)oxy)-3-(4-((3-methylbut-2-en-1-yl)oxy)phenyl)acrylate (399a)

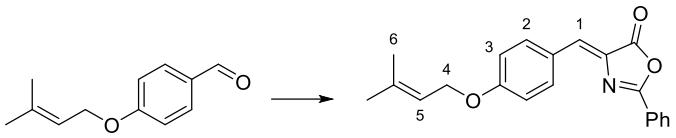


A solution of methyl 2-((*t*-butyldimethylsilyl)oxy)-2-(dimethoxyphosphoryl)acetate (**398a**, 650 mg, 2.1 mmol) in THF (4 mL) was cooled to -78 °C before being charged with lithium diisopropylamide (1.5 M in cyclohexane, 2.1 mL, 3.1 mmol) dropwise. The resulting mixture was stirred at -78 °C for 30 min before a solution of 4-((3-methylbut-2-en-1-yl)oxy)benzaldehyde (**397**, 400 mg, 2.1 mmol) in THF (2 mL) was charged, and washed in to the flask with THF (2 mL). The resulting mixture was allowed to warm to rt. After 2.5 h the reaction mixture was quenched with sat. aq. NH_4Cl (10 mL), water (1 mL) and EtOAc (10 mL). The organic layer was washed with water (2 x 10 mL) and sat. aq. NH_4Cl (2 x 10 mL) before being dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (5% to 10% EtOAc/petroleum ether) gave *title compound* (462 mg, 59%, 0.6:0.4 ratio of *E*:*Z* isomers) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 7.67 (0.6H, d, *J* 8.8, 5-H x 0.6), 7.24 (1.4H, d, *J* 8.6, 5-H x 1.4), 6.90 (0.6H, d, *J* 8.8, 6-H x 0.6), 6.87 (1.4H, d, *J* 8.6, 6-H x 1.4), 6.85 (0.3H, s, 4-H), 6.42 (0.6H, s, 4-H), 5.52 (1H, t, *J* 6.8, 8-H), 4.55 (0.6H, d, *J* 6.8, 7-H x 0.6), 4.53 (1.4H, d, *J* 6.8, 7-H_2 x 1.4), 3.83 (1.2H, s, 3-H x 1.2), 3.71 (1.8H, s, 3-H x 1.8), 1.83 (3H, s, 9-H_3), 1.78 (1.2H, s, 9-H x 1.2), 1.77 (1.8H, s, 9-H x 1.8), 1.01 (5.4H, s, 2-H_3 x 5.4), 0.99 (3.6H, s, 2-H_3 x 3.6), 0.24 (3.6H, s, 1-H_3 x 3.6), 0.17 (2.4H, s, 1-H_3 x 2.4); δ_C (100 MHz, $CDCl_3$) 166.2 (C),

165.6 (C), 158.8 (C), 158.2 (C), 140.5 (C), 138.8 (C), 138.4 (C), 138.3 (C), 131.4 (CH), 130.1 (CH), 126.7 (C), 126.6 (C), 121.2 (CH), 119.6 (CH), 119.5 (CH), 119.2 (CH), 114.3 (CH), 114.2 (C), 64.8 (CH_2), 64.7 (CH_2), 52.0 (CH_3), 51.6 (CH_3), 25.9 (CH_3), 25.8, (CH_3), 25.6 (CH_3), 18.6 (CH_3), 18.3 (CH_3), 18.2 (CH_3), 18.2 (CH_3), -3.88 (CH_3), -4.78 (CH_3); **IR** (ATR)/cm^{-1} 2953, 2932, 2860, 1719, 1606, 1509, 1437, 1242, 1177, 996, 839; **HRMS** (ESI+) *m/z* calculated for $[C_{21}H_{32}NaO_4Si]^+$: 399.1962, found 399.1958.

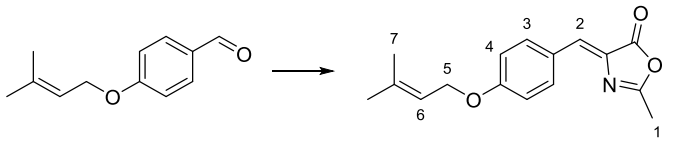
(Z)-4-(4-((3-Methylbut-2-en-1-yl)oxy)benzylidene)-2-phenyloxazol-5(4H)-one (408a)



To a mixture of 4-((3-methylbut-2-en-1-yl)oxy)benzaldehyde (**397**, 95 mg, 0.50 mmol), AcONa (41 mg, 0.5 mmol) and *N*-benzoylglycine (**410a**, 89 mg, 0.5 mmol) in a sealed tube was charged acetic anhydride (140 µL, 1.5 mmol) and heated to 95 °C for 3 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ (3 mL), and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried ($MgSO_4$) before concentrating *in vacuo*. Column chromatography (1% to 10% EtOAc/petroleum ether) gave *title compound* (51 mg, 31%) as a yellow solid.

δ_H (400 MHz, $CDCl_3$) 8.21-8.16 (4H, m, 2-H x 2 and Ph-H x 2), 7.60 (1H, app. t*, J* 7.4, Ph-H), 7.53 (2H, app. t*, J* 7.4, Ph-H x 2) 7.23 (1H, s, 1-H), 7.01 (2H, d*, J* 8.9, 3-H x 2), 5.51 (1H, t*, J* 6.8, 5-H), 4.60 (2H, d*, J* 6.8, 4-H_2), 1.82 (3H, s, 6-H_3), 1.78 (3H, s, 6-H_3); δ_C (101 MHz, $CDCl_3$) 168.2 (C), 162.6 (C), 161.8 (C), 139.1 (C), 134.7 (CH), 133.1 (CH), 132.2 (CH), 131.2 (CH) 129.1 (C), 128.3 (CH), 126.6 (C), 126.1 (C), 119.2 (CH), 115.4 (CH), 115.2 (CH), 65.2 (CH_2), 26.0 (CH_3), 18.4 (CH_3); **IR** (ATR)/cm^{-1} 3011, 2938, 1789, 1654, 1599, 1509, 1251, 1160, 986; **HRMS** (ESI+) *m/z* calculated for $[C_{21}H_{20}NO_3]^+$: 334.1438, found 334.1428.

2-Methyl-4-(4-((3-methylbut-2-en-1-yl)oxy)benzylidene)oxazol-5(4H)-one (408b)

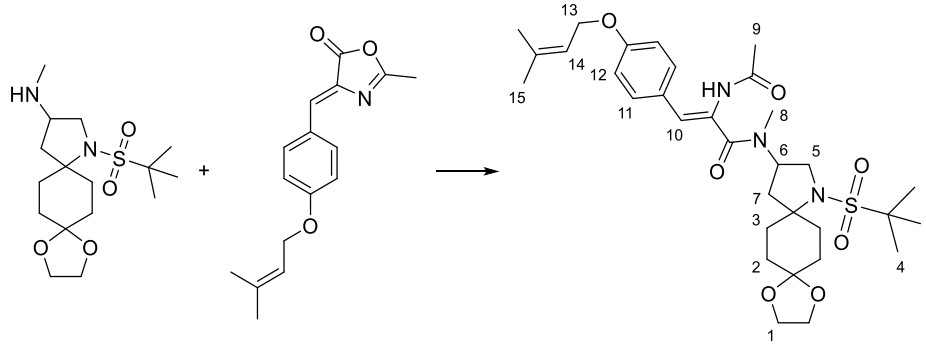


To a mixture of 4-((3-methylbut-2-en-1-yl)oxy)benzaldehyde (**397**, 260 mg, 1.4 mmol), AcONa (230 mg, 2.8 mmol) and *N*-acetylglycine (**410b**, 320 mg, 2.8 mmol)

in a sealed tube was charged acetic anhydride (390 µL, 4.1 mmol) and heated to 100 °C for 24 h. This was immediately purified by column chromatography (5% to 10% EtOAc/petroleum ether) to give *title compound* (154.8 mg, 42%) as a yellow solid.

δ_H (400 MHz, $CDCl_3$) 8.07 (2H, d*, J* 8.6, 3-H x 2), 7.13 (1H, s, 2-H), 6.98 (2H, d*, J* 8.6, 4-H x 2), 5.51 (1H, t*, J* 6.7, 6-H), 4.60 (2H, d*, J* 6.7, 5-H_2), 2.41 (3H, s, 1-H_3), 1.83 (3H, s, 7-H_3), 1.79 (3H, s, 7-H_3); δ_C (100 MHz, $CDCl_3$) 168.2 (C), 164.8 (C), 161.5 (C), 138.9 (C), 134.3 (CH), 131.6 (CH), 130.3 (C), 126.0 (C), 119.0 (CH), 115.1 (CH), 65.0 (CH_2), 25.8 (CH_3), 18.3 (CH_3), 15.6 (CH_3); **IR** (ATR)/cm^{-1} 3011, 1800, 1658, 1592, 1510, 1249, 1159, 995; **HRMS** (ESI+) *m/z* calculated for $[C_{16}H_{18}NO_3]^+$: 272.1281, found 272.1274.

2-Acetamido-N-(9-(t-butylsulfonyl)-1,4-dioxa-9-azadispiro[4.2.4^8.2^5] tetradecan-11-yl)-N-methyl-3-(4-((3-methylbut-2-en-1-yl)oxy)phenyl)acrylamide (417a)

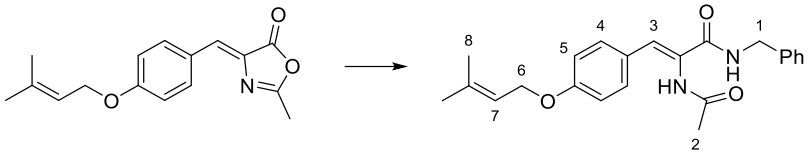


A solution of *N*-methyl-9-(2-methylpropane-2-sulfonyl)-1,4-dioxa-9-azadispiro[4.2.4^8.2^5] tetradecan-11-amine (**391**, 180 mg, 0.53 mmol) and 2-methyl-4-(4-((3-methylbut-2-en-1-yl)oxy)benzylidene)oxazol-5(4H)-one (**408b**, 130 mg, 0.48 mmol) in MeCN (2.5 mL) in a sealed tube was heated at 90 °C for 92 h before the solvent was removed *in vacuo*. Column chromatography (5% Et_3N/Et_2O to 60% EtOAc + 5% Et_3N /Et_2O) gave *title compound* (204 mg, 69%) as a colourless solid.

m.p. = 235-237 °C; δ_H (400 MHz, $CDCl_3$) 7.32 (2H, d*, J* 8.7, 11-H x 2), 6.95 (2H, d*, J* 8.7, 12-H x 2), 5.77 (1H, br s, 10-H), 5.52 (1H, t*, J* 6.7, 14-H) 4.99-4.90 (1H, m, 6-H), 4.56 (2H, d*, J* 6.7, 13-H_2) 4.02-3.83 (5H, m, 1-H_2 x 2 and 5-H), 3.40 (1H, m, 5-H), 3.14-2.81 (4H, m, 3-H and 8-H_3), 2.56 (1H, dd*, J* 12.8 and 8.5, 7-H), 2.13 (3H, s, 9-H_3), 1.94-1.85 (1H, m, 7-H), 1.84 (3H, s, 15-H_3), 1.79 (3H, s, 15-H_3), 1.82-1.54 (7H, m, 3-H x 3 and 2-H x 4), 1.41 (9H, s, 4-H_3 x 3); δ_C (100 MHz, $CDCl_3$) 169.8 (C), 169.0 (C), 158.9 (C), 138.7 (C), 130.0 (CH), 128.4 (C), 125.8 (C), 119.3 (CH), 118.7 (CH), 115.1 (CH), 107.6 (C), 69.1 (C), 64.9 (CH_2), 64.5 (CH_2), 64.4 (CH_2), 61.6 (C), 55.1 (CH), 51.0 (CH_2), 37.6 (CH_2), 34.4 (CH_2), 33.0 (CH_2), 30.3 (CH_3), 25.9 (CH_3), 25.1 (CH_3), 22.9 (CH_3), 18.3 (CH_3); **IR**

(ATR)/cm^{-1} 2974, 2933, 2880, 1684, 1604, 1500, 1296, 1241, 1176, 1109, 1103, 942, 892, 651, 572, 514; **HRMS** (ESI+) *m/z* calculated for $[C_{32}H_{48}N_3O_7S]^+$: 618.3207, found 618.3215.

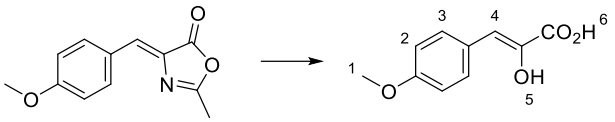
2-Acetamido-N-benzyl-3-(4-((3-methylbut-2-en-1-yl)oxy)phenyl) acrylamide (419)



A mixture of 4-(4-((3-methylbut-2-en-1-yl)oxy)benzylidene)-2-phenyloxazol-5(4H)-one (**408b**, 20 mg, 0.074 mmol), K_2CO_3 (21 mg, 0.15 mmol) and benzylamine (**418**, 12 µL, 0.11 mmol) in toluene (0.2 mL) in a microwave tube was capped and heated to 115 °C for 16 h. The reaction mixture was concentrated *in vacuo*, before column chromatography (5-100% EtOAc/petroleum ether) gave *title compound* (6.7 mg, 25%) as a yellow/brown gum.

δ_H (400 MHz, $CDCl_3$) 8.14 (2H, d*, J* 8.9, 4-H x 2), 7.40-7.31 (3H, m, Ph-H x 3), 7.28-7.23 (2H, m, Ph-H x 2), 7.18 (1H, s, 3-H), 6.98 (2H, d*, J* 8.9, 5-H x 2), 5.52 (1H, t*, J* 6.7, 7-H), 4.86 (2H, s, 1-H_2), 4.60 (2H, d*, J* 6.7, 6-H_2), 2.28 (3H, s, 2-H_3), 1.83 (3H, s, 8-H_3), 1.79 (3H, s, 8-H_3); δ_C (100 MHz, $CDCl_3$) 170.7 (C), 161.0 (C), 160.8 (C), 138.7 (C), 136.6 (C), 136.3 (C), 134.1 (CH), 128.9 (CH), 128.0 (CH), 127.9 (CH), 127.0 (C) and 127.0 (CH), 119.3 (CH), 115.0 (CH), 64.9 (CH_2), 43.9 (CH_2), 25.8 (CH_3), 18.3 (CH_3), 16.1 (CH_3); **IR** (ATR)/cm^{-1} 2931, 1701, 1643, 1599, 1509, 1248, 1175, 1137; **HRMS** (ESI+) *m/z* calculated for $[C_{21}H_{20}NO_3]^+$: 379.2016, found 379.1996.

2-Hydroxy-3-(4-methoxyphenyl)acrylic acid (434)[232]

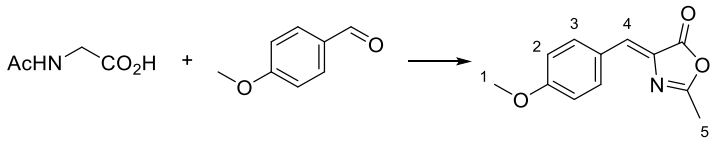


A suspension of 4-(4-methoxybenzylidene)-2-methyloxazol-5(*4H*)-one (**435**, 350 mg, 1.6 mmol) in HCl (3M in water, 5 mL) was heated at 110 °C for 3 h before cooling to rt and leaving to stand at rt overnight. Filtration and trituration of the residue (EtOAc:MeOH 1:1, 2 mL) afforded *title compound* (170 mg, 55%) as a pale brown solid.

δ_H (400 MHz, MeOD) 7.74 (2H, d, *J* 8.9, 3-H x 2), 6.91 (2H, d, *J* 8.9, 2-H x 2), 6.48 (1H, s, 4-H x 2), 3.82 (3H, s, 1-H_3); δ_H (400 MHz, d^6-DMSO) 13.01 (1H, br s, 6-H), 8.95 (1H, br s, 5-H), 7.71 (2H, d, *J* 8.9, 3-H x 2), 6.92 (2H, d, *J* 8.9, 2-H x 2), 6.37 (1H, s, 4-H), 3.76

(3-H, s, 1-H_3); δ_C (101 MHz, d^6-DMSO) 166.5 (C), 158.4 (C), 140.0 (C), 130.7 (CH), 127.5 (C), 113.8 (CH), 109.8 (CH), 22.1 (CH_3); **HRMS** (ESI+) *m/z* calculated for $[C_{10}H_9O_4]^-$: 193.0506, found 193.0507. Data agrees with literature.

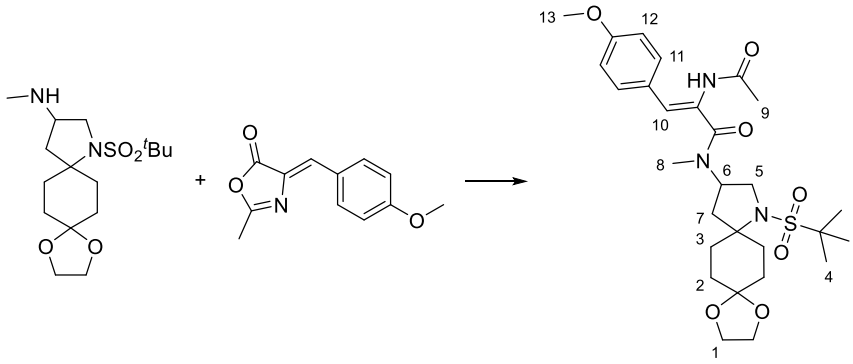
4-(4-Methoxybenzylidene)-2-methyloxazol-5(4H)-one (435)[276]



To a mixture of 4-methoxybenzaldehyde (**436**, 0.89 mL, 7.4 mmol), *N*-acetylglycine (**410b**, 1.1 g, 9.6 mmol) and NaOAc (780 mg, 9.6 mmol) was added acetic anhydride (3.5 mL, 37 mmol) and this was heated to 110 °C for 16 h. Ice (ca. 25 mL) was added under rapid stirring and the mixture was allowed to warm to rt before filtration afforded a brown solid residue. Column chromatography of the residue (10% EtOAc/petroleum ether) afforded *title compound* (815 mg, 51%) as a pale yellow solid.

δ_H (400 MHz, $CDCl_3$) 8.06 (2H, d, *J* 8.8, 3-H x 2), 7.11 (1H, s, 4-H), 6.96 (2H, d, *J* 8.8, 2-H x 2), 3.87 (3H, s, 1-H_3), 2.39 (3H, s, 5-H_3); δ_C (100 MHz, $CDCl_3$) 168.2 (C), 164.9 (C), 162.1 (C), 134.3 (CH), 131.5 (CH), 130.4 (C), 126.2 (C), 114.5 (CH), 55.4 (CH_3), 15.6 (CH_3); **HRMS** (ESI+) *m/z* calculated for $[C_{12}H_{12}NO_3]^+$:218.0812, found 218.0819. Data agrees with literature.

2-Acetamido-N-(9-(t-butylsulfonyl)-1,4-dioxa-9-azadispiro[4.2.48.25]tetradecan-11-yl)-3-(4-methoxyphenyl)-N-methylacrylamide (439)

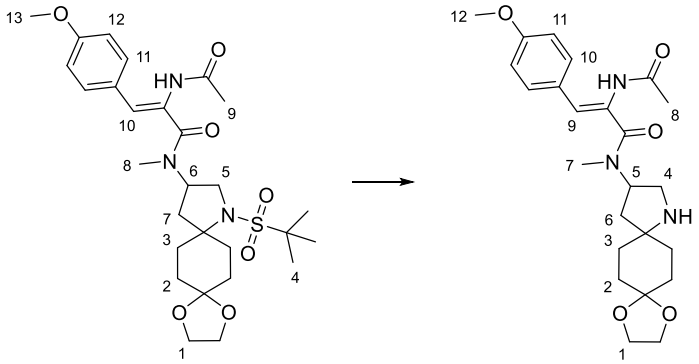


To a mixture of 4-(4-methoxybenzylidene)-2-methyloxazol-5(*4H*)-one (**435**, 120 mg, 0.55 mmol) and 9-(*t*-butylsulfonyl)-*N*-methyl-1,4-dioxa-9-azadispiro[4.2.48.25]tetradecan-11-amine (**391**, 160 mg, 0.46 mmol) was added MeCN (1.0 mL) and the mixture was stirred for 16 h before heating at 90 °C for 24 h

before being cooled to rt. Filtration of the reaction mixture and washing of the residue with petroleum ether afforded *title compound* (205 mg, 79%) as a colourless solid.

M.p. 226-229 °C; δ_H (400 MHz, $CDCl_3$) 8.23 (1H, br s, N-H), 7.30 (2H, d, *J* 8.8, 11-H x 2), 6.91 (2H, d, *J* 8.8, 12-H x 2), 5.72 (1H, br s, 10-H), 4.95 (1H, m, 6-H), 3.98-3.80 (5H, m, 1-H_2 x 2 and 5-H), 3.84 (3H, s, 13-H_3), 3.37 (1H, dd, *J* 10.6 and 7.7, 5-H), 2.93 (3H, br s, 8-H_3), 2.84 (1H, td, *J* 13.5 and 4.0, 3-H), 2.52 (1H, dd, *J* 12.8 and 8.5, 7-H), 2.10 (3H, s, 9-H_3), 1.86 (1H, dd, *J* 12.8 and 9.8, 7-H), 1.80-1.50 (5H, m, 2-H x 2 and 3-H x 3), 1.77 (1H, dd, *J* 12.3 and 2.7, 2-H), 1.60 (1H, td, *J* 13.5 and 4.2, 2-H), 1.38 (9H, s, 4-H_3 x 3); δ_H (400 MHz, 343 K, d_6-DMSO) 9.52 (1H, br s, N-H), 7.48 (2H, d, *J* 8.9, 12-H x 2), 6.96 (2H, d, *J* 8.9, 11-H x 2), 6.11 (1H, s, 10-H), 4.82 (1H, m, 6-H), 3.89-3.81 (4H, m, 1-H_2 x 2), 3.80 (3H, s, 13-H_3), 3.69 (1H, dd, *J* 10.0 and 8.2, 5-H), 3.31 (1H, dd, *J* 10.0 and 8.4, 5-H), 2.89 (3H, br s, 8-H_3), 2.62 (1H, m, 3-H), 2.48-2.41 (2H, m, 2-H and 7-H), 1.98 (3H, s, 9-H_3), 1.98-1.90 (1H, m, 7-H), 1.73-1.48 (7H, m, 2-H x 3 and 3-H x 3), 1.32 (9H, s, 4-H_3 x 3); δ_C (126 MHz, D_6-DMSO) 170.0 (C), 169.6 (C) 159.4 (C), 130.9 (CH), 128.9 (C) 127.0 (C), 120.4 (CH) 114.5 (CH), 107.5 (C), 68.9 (C), 64.1 (CH_2), 61.3 (C), 55.7 (CH_3), 50.7 (CH_2), 37.1 (CH_2), 36.6 (CH), 33.8 (CH_2), 32.7 (CH_2), 32.6 (CH_2), 31.3 (CH_2), 29.48 (CH_3), 25.1 (CH_3), 22.7 (CH_3); **IR** (ATR)/cm^{-1} 3292, 2978, 2943, 2882, 1687, 1617, 1500, 1293, 1254, 1111, 1008, 943, 895, 657, 574; **HRMS** (ESI+) *m/z* calculated for $[C_{28}H_{41}N_3NaO_7S]^+$: 586.2557, found 586.2568.

2-Acetamido-N-(1,4-dioxa-9-azadispiro[4.2.48.25]tetradecan-11-yl)-3-(4-methoxyphenyl)-N-methylacrylamide (440)

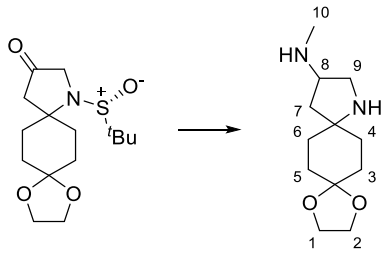


A solution of anisole (0.31 mL, 2.8 mmol) and TFAA (0.13 mL) in TFA (4.3 mL) was stirred for 30 min before adding 2-acetamido-*N*-(9-(t-butylsulfonyl)-1,4-dioxa-9-azadispiro[4.2.48.25]tetradecan-11-yl)-3-(4-methoxyphenyl)-*N*-methylacrylamide (**439**, 79 mg, 0.14 mmol). After 16 h, K_2CO_3 (ca. 1 g) was added cautiously and stirred thoroughly before adding K_2CO_3 (sat. aq., 5 mL) and water (ca. 10 mL) to dissolve remaining inorganic solids. This was extracted with CH_2Cl_2 (2 x 15 mL) and the

combined organic layers were dried ($MgSO_4$) before column chromatography afforded *title compound* (13 mg, 20%) as a pale orange oil.

δ_H (400 MHz, $CDCl_3$) 8.67 (1H, br s, AcN-H), 7.39 (2H, d, J 8.8, 10-H x 2), 6.91 (2H, d, J 8.8, 11-H x 2), 5.94 (1H, br s, 9-H), 4.54 (1H, br s, N-H), 3.90 (4H, s, 1-H_2 x 2), 3.82 (3H, s, 12-H_3), 3.56 (3H, br s, 7-H_3), 3.18 (1H, br s, 5-H), 2.27-2.16 (1H, m, 4-H), 2.13 (3H, s, 8-H_3), 2.08-1.97 (1H, m, 4-H), 1.85-1.73 (1H, m, 6-H), 1.67-1.53 (1H, m, 6-H), 1.43-1.22 (8H, m, 2-H_2 x 2 and 3-H_2 x 2); δ_C (partial, 101 MHz, $CDCl_3$) 159.8 (C), 130.5 (CH), 120.2 (CH), 114.5 (CH), 64.5 (CH_2), 55.5 (CH_3), 38.1 (CH, HMQC), 33.0 (CH_2, HMQC) 31.6 (CH_2, HMQC), 29.8 (CH_2), 22.9 (CH_3); HRMS calculated for $[C_{24}H_{34}N_3O_5]^+$: 444.2493, found 444.2497.

N-Methyl-1,4-dioxa-9-azadispiro[4.2.48.25]tetradecan-11-amine (445)

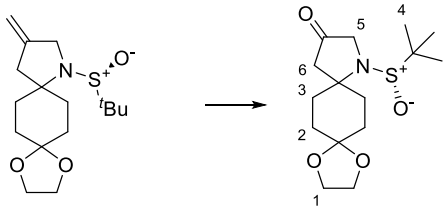


To a suspension of NaOH (5.5 g) in $CHCl_3$ (7 mL) was added $MeNH_2$ (40 wt% in water, 4.8 mL) with vigorous stirring until effervescence ceased. To a solution of (*S*)-9-(*t*-butylsulfinyl)-1,4-dioxa-9-azadispiro[4.2.48.25]tetradecan-11-one (**448**, 250 mg, 0.81 mmol) in $CHCl_3$ (21 mL) was added the organic supernatant of the methylamine solution (4.0 mL) and this was added to a solution of $Ti(OEt)_4$ (0.12 mL, 0.56 mmol) in $CHCl_3$ (3 mL). After stirring at rt for 1 h, the reaction mixture was heated at 80 °C for 1.5 h before cooling to rt and filtering *in vacuo* and concentrating *in vacuo*. To a solution of the residue in anhydrous MeOH (40 mL) was added $NaBH_4$ (83 mg, 2.2 mmol). After 30 min the reaction mixture was concentrated *in vacuo* and NaOH (0.2M in water, 25 mL) was added and this was extracted with CH_2Cl_2 (3 x 30 mL) before the combined organic phases were dried ($MgSO_4$) and concentrated. Column chromatography (50-100% EtOAc/petroleum ether, Biotage KP-NH 28g cartridge), provided *title compound* (79 mg, 43%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 3.93 (4H, m, 1-H_2 and 2-H_2), 3.16 (1H, dddd, *J* 7.5, 5.7, 5.5 and 5.2, 8-H), 3.07 (1H, dd, *J* 11.2 and 5.7, 9-H), 2.76 (1H, dd, *J* 11.2 and 5.2, 9-H), 2.38 (3H, s, 10-H_3), 1.95 (1H, dd, *J* 13.0 and 7.5, 7-H), 1.82-1.52 (8H, m, 3-H_2, 4-H_2, 5-H_2 and 6-H_2),

1.33 (1H, dd, *J* 13.0 and 5.5, 7-H); δ_C (100 MHz, $CDCl_3$) 108.7 (C), 64.4 (CH_2), 64.3 (CH_2), 61.5 (CH), 60.6 (C), 51.8 (CH_2), 44.4 (CH_2), 35.5 (CH_2), 35.3 (CH_2), 32.4 (CH_2), 32.2 (CH_2); **IR** ($CHCl_3$)/cm^{-1} 3606, 2951, 1446, 1372, 1104, 1035, 889; **HRMS** (ESI+) *m/z* calculated for $[C_{12}H_{23}N_2O_2]^+$: 227.1754, found 227.1755.

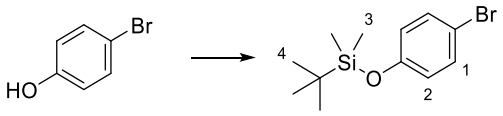
(S)-9-(t-Butylsulfinyl)-1,4-dioxa-9-azadispiro[4.2.48.25]tetradecan-11-one (448)



To a solution of (*S*)-9-(*t*-butylsulfinyl)-11-methylene-1,4-dioxa-9-azadispiro[4.2.48.25]tetradecane (**387**, 920 mg, 2.9 mmol) and NMO (860 mg, 7.4 mmol) in acetone (9.0 mL) and water (3.0 mL) was added OsO_4 (4 wt% in water, 0.93 mL, 0.15 mmol) and this was stirred for 4 h before adding $Na_2S_2O_3$ (sat. aq., 20 mL) and extracting the solution with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine (10 mL) before being dried ($MgSO_4$), filtered and concentrated. The residue was dissolved in acetone (41 mL) and water (13 mL) and $NaIO_4$ (1.55 g, 7.3 mmol) was added. After 6 h the reaction mixture was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated to provide *title compound* (870 mg, 95%) as a colourless solid.

M.p. 110-115 °C; δ_H (400 MHz, $CDCl_3$) 4.10 (1H, d, *J* 18.5, 5-H), 4.02-3.91 (4H, m, 1-H_2 x 2), 3.30 (1H, d, *J* 18.5, 5-H), 2.68 (1H, d, *J* 17.4, 6-H), 2.33 (1H, d, *J* 17.4, 6-H), 2.30 (1H, tdd, *J* 13.3, 3.9 and 1.1, 2-H or 3-H), 2.15 (1H, td, *J* 12.8 and 4.1, 2-H or 3-H), 1.92-1.51 (6H, m, (2-H and 3-H) x 6), 1.24 (9H, s, 4-H_3 x 3); δ_C (100 MHz, $CDCl_3$) 211.0 (C), 107.5 (C), 66.3 (C), 64.6 (CH_2), 64.5 (CH_2), 57.9 (C), 47.9 (CH_2), 47.6 (CH_2), 36.2 (CH_2), 32.8 (CH_2), 32.2 (CH_2), 30.8 (CH_2), 24.1 (CH_3); **IR** (ATR) cm^{-1} 1758, 1103, 1060, 1035, 989, 936, 841, 487; **HRMS** (ESI+) *m/z* calculated for $[C_{15}H_{25}NNaO_4S]^+$: 338.1396, found 338.1407; $[\alpha]^{22}_D$ = 91.33 (c 0.230, $CHCl_3$).

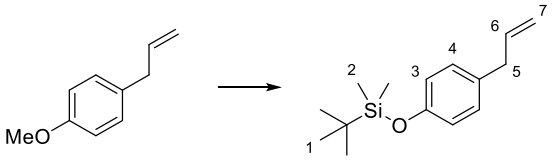
(4-Bromophenoxy)(t-butyl)dimethylsilane (462)[277]



To a solution of 4-bromophenol (**463**, 2.0 g, 12 mmol) in CH_2Cl_2 (50 mL) was added TBSCl (1.8 g, 12 mmol), Et_3N (3.3 mL, 24 mmol) and DMAP (9 mg, 0.07 mmol) before stirring for 3 h and adding TBSCl (170 mg, 1.2 mmol), and stirring for 4 h and adding TBSCl (1.0 g, 6.6 mmol). The reaction mixture was stirred for 16 h before NaOH (1.0 M in water, 15 mL) was added and the mixture was separated and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. Trituration (Et_2O) and column chromatography (petroleum ether) afforded *title compound* (3.37 g, 96%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 7.32 (2H, d, *J* 8.6, 1-H x 2), 6.71 (2H, d, *J* 8.6, 3-H x 2), 0.97 (9H, s, 4-H_3 x 3), 0.18 (6H, s, 3-H_3 x 2); δ_C (101 MHz, $CDCl_3$) 155.0 (C), 132.4 (CH), 122.0 (CH), 113.7 (C), 25.8 (CH_3), 18.3 (C), -4.3 (CH_3); **HRMS** (EI) *m/z* calculated for $[C_{12}H_{19}OSiBr]^+$: 286.0383, found 286.0387. Data agrees with literature.

(4-Allylphenoxy)(t-butyl)dimethylsilane (465)[278]

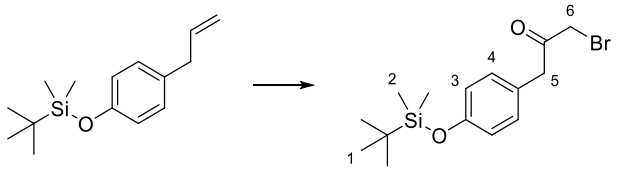


To a solution of 4-allyl anisole (**468**, 1.5 mL, 10 mmol) in DCE (45 mL) was added BCl_3.DMS (2.7 g, 15 mmol) and this was heated under reflux for 18 h, when it was cooled to rt, water (45 mL) was added and the resulting mixture was stirred vigerously for 15 min. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 40 mL) before the combined organic phases were dried ($MgSO_4$), filtered through a plug of silica gel and concentrated. To a solution of the residue in CH_2Cl_2 (100 mL) was added TBSCl (2.5 g, 16.5 mmol) and Et_3N (4.2 mL, 30 mmol). After 2 d, NaOH (1.0 M in water, 40 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL) before the combined organic phases were dried ($MgSO_4$) and concentrated. Column chromatography (petroleum ether) gave *title compound* (1.55 g, 63%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 7.03 (2H, d, *J* 8.6, 4-H x 2), 6.76 (2H, d, *J* 8.6, 4-H x 2), 5.95 (1H, ddt, *J* 15.7, 10.6 and 6.7, 7-H), 5.05 (1H, ddt, *J* 15.7, 1.9 and 1.6, *cis*-7-H), 5.04 (1H, ddt, *J* 10.6, 1.9 and 1.4, *trans*-7-H), 3.32 (2H, ddd, *J* 6.7, 1.6 and 1.4, 5-H_2), 0.98 (9H, s, 1-H_3 x 3), 0.18 (6H, s, 2-H_3 x 2); δ_C (100 MHz, $CDCl_3$) 154.0 (C), 138.1 (CH), 132.8 (C), 129.6 (CH), 120.1 (CH), 115.5 (CH_2), 39.6 (CH_2), 25.9 (CH_3), 18.4 (C), -4.3 (CH_3); **IR** ($CHCl_3$)/cm^{-1}

3081, 2958, 2931, 2898, 2859, 1608, 1509, 1472, 1257, 916, 841; **HRMS** (ESI+) *m/z* calculated for $[C_{15}H_{24}OSi]^+$: 248.15909, found 248.1585. Data agrees with literature.

1-Bromo-3-(4-((t-butyldimethylsilyl)oxy)phenyl)propan-2-one (469)



To a solution of (4-allylphenoxy)(*t*-butyl)dimethylsilane (**465**, 100 mg, 0.40 mmol) in acetone (1.6 mL) was added NH_4OAc (3 mg, 0.04 mmol) and NBS (79 mg, 0.44 mmol) before adding water (0.4 mL). After 15 min, water (5 mL) was added and this was extracted with CH_2Cl_2 (3 x 10 mL) before the combined organic phases were dried ($MgSO_4$) and concentrated. Column chromatography (10% EtOAc/petroleum ether) gave 1-bromo-3-(4-((*t*-butyldimethylsilyl)oxy)phenyl)propan-2-ol (**468**, 55 mg, 40%) as a colourless oil. To a solution of 1-bromo-3-(4-((*t*-butyldimethylsilyl)oxy)phenyl)propan-2-ol (**468**, 44 mg, 0.13 mmol) in CH_2Cl_2 (1.5 mL) was added Dess-Martin periodinane (83 mg, 0.20 mmol). After 2 h $Na_2S_2O_3$ (sat. aq., 5 mL) was added and this was extracted with CH_2Cl_2 (3 x 15 mL) before the combined organic phases were dried ($MgSO_4$) and concentrated. Column chromatography (5% EtOAc/petroleum ether) gave *title compound* (33 mg, 74%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 7.08 (2H, d, *J* 8.6, 4-H x 2), 6.81 (2H, d, *J* 8.6, 3-H x 2), 3.90 (2H, s, 6-H_2), 3.86 (2H, s, 5-H_2), 0.98 (9H, s, 1-H_3 x 3), 0.19 (6H, s, 2-H_3 x 2); δ_C (100 MHz, $CDCl_3$) 199.9 (C), 155.2 (C), 130.6 (CH), 125.8 (C), 120.7 (CH), 46.2 (CH_2), 33.6 (CH_2), 25.8 (CH_3), 18.3 (C), -4.3 (CH_3); **IR** ($CHCl_3$)/cm^{-1} 2958, 2932, 2888, 2859, 1715, 1604, 1510, 1266, 912, 842; **HRMS** (ESI+) *m/z* calculated for $[C_{15}H_{23}BrNaO_2Si]^+$: 365.0543, found 365.0534.

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