Novel Synthetic Methods for the Preparation of Nitrogen Containing Sulfur(VI) Functionalities

A Thesis Submitted by

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Declarations

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Abstract

The adoption of unusual functional groups into medicinal and agrochemical research programmes provides enhanced coverage of both chemical and intellectual property space. In this regard, sulfoximines and sulfonimidamides, the mono-aza analogues of sulfones and sulfonamides respectively are receiving considerable attention as bioisosteres in drug design. However, restrictive synthetic methods have, in part, limited the utility of these motifs in the life sciences. In this thesis, the development of synthetic methodology towards accessing these nitrogen containing sulfur(VI) functionalities is described.

Initially, a procedure for the gram scale preparation of enantioenriched sulfoximines from sulfoxides is described. This methodology builds upon previous NH transfer work, with a focus on how this can be applied in a safe and robust manner on larger scales. Next, thiols are explored as substrates under NH and O transfer conditions and are subsequently shown to be suitable precursors to sulfonimidates or primary sulfonamides depending on the reaction conditions.

Further extension of this NH and O transfer methodology to sulfenamides allows access to sulfonimidamides in just two straightforward steps from commercially available starting materials. This methodology is applicable to late stage functionalisation reactions as well as in the preparation of an aza-analogue of a marketed drug. Novel λ^6-sulfanenitrile species are identified as intermediates in the NH and O transfer, shedding further light onto the mechanism of these reactions.

Finally, sulfinamide salts are isolated for the first time and are shown to be effective precursors to sulfonimidoyl fluorides, giving rise to the first facile route toward enantioenriched sulfonimidamides through a sulfur fluoride exchange (SuFEx) reaction.

A summary of specific conclusions and future work can be found in the penultimate section. Experimental details and data for all compounds synthesised during this research can be found in the final section.

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Abbreviations

ADMET	Absorption, distribution, metabolism, excretion and toxicity
API	Active pharmaceutical ingredient
aq.	Aqueous
ATR	Ataxia telangiectasia mutated and RAD3-related protein
BCS	Biopharmaceutical classification system
Boc	*tert*-Butyloxycarbonyl
BSO	L-Buthionine sulfoximine
CDI	1,1'-Carbonyldiimidazole
DBU	1,8-Diazabicyclo [5.4.0]undec-7-ene
DCE	Dichloroethane
DOS	Diversity orientated synthesis
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMSO	Dimethyl sufoxide
ee	Enantiomeric excess
er	Enantiomeric ratio
EPA	United States Environmental Protection Agency
equiv	Equivalents
FBDD	Fragment based drug discovery
Fsp^3	Fraction sp^3
GSK	GlaxoSmithKline
h	Hour
HBA	Hydrogen bond acceptors
HBCat	Catecholborane
HBD	Hydrogen bond donors

HPLC	High-performance liquid chromatography
HRMS	High Resolution Mass Spectrometry
HTS	High-throughput screening
HVIR	Hypervalent iodine reagent
IR	Infrared
*m*CPBA	*meta*-Chloroperoxybenzoic acid
mp	Melting point
MSH	*O*-Mesitylene sulfonyl hydroxylamine
MSO	L-Methionine sulfoximine
MW	Molecular weight
NMR	Nuclear magnetic resonance spectroscopy
NCS	*N*-Chlorosuccinimide
Ns	Nosyl
ppm	Parts per million
Pht	Phthalimide
Ro5	Rule of five
sat.	Saturated
SuFEx	Sulfur fluoride exchange reactions
Ses	2-(Trimethylsilyl)ethanesulfonyl
TBD	Triazabicyclodecene
TBDPS	*tert*-Butyldiphenylsilyl
TFA	Trifluoroacetic acid
TFE	Trifluoroethanol
THP	Tetrahydropyran
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl

Troc	2,2,2-Trichloroethoxycarbonyl
Ts	Tosyl
TSPA	Total polar surface area
VMAR	Vinylogous Mukaiyama aldol reaction
USA	United States of America

1. Introduction

1.1 The Role of Organic Synthesis in Drug Discovery

Whilst it is widely accepted that the roots of literature and the modern arts can be traced back to Ancient Greece, it is less clear cut for modern science.[1] In fact the birth of organic chemistry is widely believed to have happened many years later, in the 18th century.[2] However, it was only at the end of the 19th century, scarcely over a hundred years ago, when 'modern' organic chemistry was ushered in alongside the advent of the pharmaceutical and dye industries.[3] Indeed, it is a testament to society in recent times that chemistry problems for undergraduate students written less than a hundred years ago are scarcely relevant today.[4] Despite the massive amount of knowledge acquired over the past century in organic synthesis and the consequent societal advancements made, great challenges remain, with healthcare being as crucial as ever. In this regard, the pharmaceutical industry holds some of the most important answers to this complex issue.

1.1.1 Attrition in the Drug Discovery Pipeline

Organic synthesis underpins a lot of the current drug discovery process but continues to be a rate-limiting factor toward accessing new active pharmaceutical ingredients (API's).[5] In-particular, the lack of synthetic methods to construct increasingly complex molecules in a practical manner has been singled out as one of the main areas where further research is required. Whilst molecular complexity is subjective, it has been attempted to be quantified by considering the number of stereogenic centres; rings; synthetic steps required and the molecular weight (MW) of a molecule, with an increase in these variables correlating with an increase in molecular complexity.[6] As the average molecular complexity of compounds entering development rises year on year, the onus is on academia to develop new synthetic methods which can help toward the construction of these compounds.[7]

It is an unfortunate reality that developing a new drug is an extremely time consuming and costly endeavour. On average the process takes around thirteen years from inception, with a 2016 estimate putting the cost of bringing a new drug to market at a staggering $2.56 billion.[8,9] A key driver for this ever increasing price tag is the failure rate (attrition) of drug compounds passing through clinical trials. As approximately 70% of total costs are incurred during clinical trials and with just 11.8% of compounds entering clinical trials being successful and reaching the market, it becomes apparent how drug discovery costs can be so high.[9] However, it is interesting to note that seemingly small decreases in attrition rates can make a huge difference to the overall cost of developing a new drug. For instance, a 16% decrease in phase II attrition, would result in a 25% decrease to the overall cost of a drug.[10] Therefore, examining and

addressing the root cause of this attrition during the clinical phases of development is one practical way that efficiency can be increased in the pharmaceutical industry, with the hope that the benefits of this are passed onto the end user.

There are a multitude of reasons why a compound may fail during clinical trials and it can also be due to any combination of these. Some of the most common causes of failure of terminated compounds include safety (toxicology and clinical safety), pharmacokinetics/bioavailability, and efficacy. Interestingly, there has been a large change in how the proportion of each of the above three factors contribute to the downfall of a compound over time (Figure 1.1).[11,12]

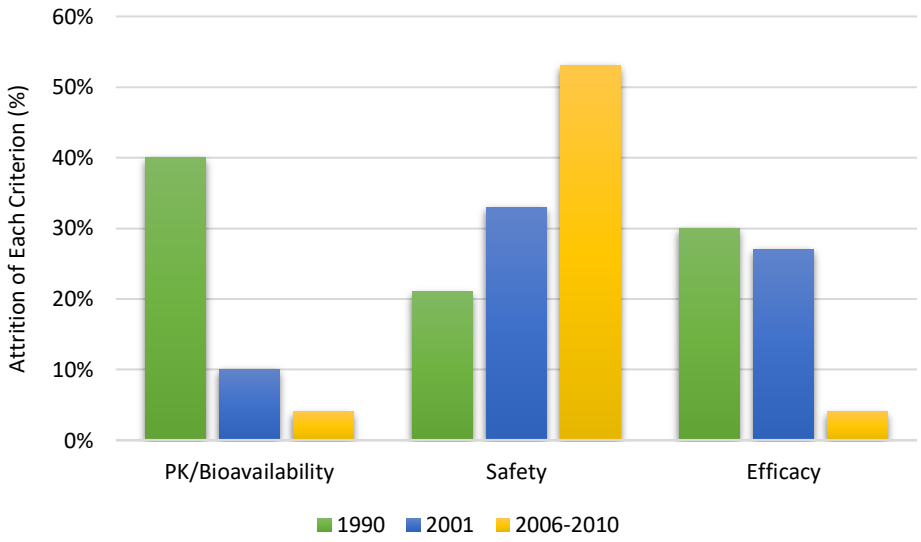


Figure 1.1: Reasons for attrition in clinical trials during three different time periods.

There has been a sharp decline in the number of compounds failing due to pharmacokinetics/bioavailability from ~40% in 1990 to just 4% in 2006-2010. However, safety, namely toxicology, has been responsible for an increasing amount of failures during clinical trials (53%). A 2014 review by AstraZeneca found that over half of the compounds that failed during clinical trials due to their safety profile had compound-related issues compared to target-related.[13] It is therefore possible that more astute control over the physicochemical properties of a compound could lead to reduced attrition rates.

1.1.2 Properties of Drug Candidates

1.1.2.1 Physicochemical Property Guidelines

An analysis of some key physicochemical properties of approved drugs reveal that they tend to preferentially occupy a small range of values.[14] This led to compounds that fall within this range being described as drug-like. Consequently, medicinal chemists have attempted to put limits on some of these parameters to guide their drug discovery efforts. For example, in 1997, Lipinski and co-workers reported on the “rule of 5” (Ro5) which identified four physicochemical

properties common to the 90th percentile of drugs and candidate drugs reaching phase II clinical trials. Poor absorption or permeation was found to be more likely when compounds had molecular weight > 500 Da, hydrogen bond donors (HBD) > 5, hydrogen bond acceptors (HBA) > 10 and the calculated logarithm of the 1-octanol/water partition coefficient (cLogP) > 5.[15] Whilst the Ro5 is intended to be used as a guideline for oral absorption, it is often (mis)used as a definition of drug like space.[16] Since this seminal report, more tightly defined "rules" have been generated which take into account toxicological risk rather than the compound not being orally absorbed. This includes the GlaxoSmithKline (GSK) 4/400 rule which indicates that compounds with a cLogP < 4 and a MW < 400 have a more favourable absorption, distribution, metabolism, excretion and toxicity (ADMET) profile.[17] In addition, the Pfizer 3/75 rule suggests that compounds with a cLogP < 3 and a total polar surface area (TPSA) > 75 Å^2 gave a six-fold reduction in the prevalence of *in vivo* toxicity compared to compounds with cLogP > 3 and TPSA < 75 Å^2.[18] However, doubts over the reliability of these guidelines have been cast in recent times, with larger and more diverse data sets showing no meaningful link between physicochemical properties and compounds that progress into Phase I compared to failing in preclinical toxicology studies.[11]

Whilst the above guidelines are useful for generating libraries at the start point of a drug discovery campaign, it is clear that putting defined limits on physicochemical properties can lead to missed opportunities, as evidenced by the fact that four out of the top ten selling drugs in the US in 2010 broke the 3/75 rule.[19] Nevertheless, control of physicochemical properties during compound optimisation is highly beneficial in identifying a candidate of drug quality.[11]

1.1.2.2 Desirable Physicochemical Properties

In vitro potency is typically the key parameter used in the lead optimisation stage to select candidates for full preclinical evaluation and can typically be increased with added lipophilicity and molecular weight.[20] However, using these two parameters to increase potency results in compounds becoming too large and lipophilic. This addiction to "molecular obesity" can be detrimental to the future of the compound as a drug candidate.[16] Corroborating this, data from GSK shows that up to 15 ADMET parameters that are routinely analysed by medicinal chemists deteriorate with either increasing MW, cLogP or both.[17] The high lipophilicity of a compound is also associated with its ability to be active against many targets (i.e. promiscuity) which as a result leads to pharmacologically based toxicology.[21]

Another worrying trend is the low solubility of drug candidates, with 75% displaying low solubility as defined by belonging to Biopharmaceutical Classification System (BCS) classes II and IV.[22] Compounds with insufficient solubility have a higher risk of attrition and therefore lead to higher costs in drug development.[23] It is well known that the increased lipophilicity of

a compound has a marked decrease on its solubility.[24] Other important factors include the fraction sp^3 (Fsp^3) which is defined by the number of sp^3 hybridised carbons/total carbon count, and the number of chiral centres in a compound. It has been demonstrated that there is a significant correlation between both increasing saturation and increasing presence of chiral centres as compounds progress through clinical testing, which could be attributed to their typically increased solubility.[25]

Whilst it is possible to overcome certain barriers presented by the ADMET of a drug candidate by methods such as formulation.[26] It is clearly more favourable to construct potent compounds with low MW and lipophilicity which contain multiple stereocentres and a high amount of 3D character to give the best chance of preventing issues with their ADMET profile arising later down the line. This presents medicinal chemists with a considerable challenge, however, the development of new technologies and synthetic methodologies has helped this goal become more attainable.

1.1.2.3 Strategies to Control Physicochemical Properties

Fragment based drug discovery (FBDD) is one such method that has been touted to help medicinal chemists synthesise leaner and more complex drug candidates. FBDD has two main advantages over traditional high-throughput screening (HTS) which has been the dominant method of generating hits in medicinal chemistry programmes for the last twenty years. The first is a significantly larger amount of chemical space can be sampled with fragments and the second is that the hits obtained are typically higher quality and more atom efficient.[27] In this regard, by reducing the number of pharmacophoric elements in the initial lead, only the necessary interactions can be built into the compound as it is optimised.[16] This therefore has the potential to deliver smaller and less lipophilic drugs. As of January 2020, FBDD is responsible for the delivery of three drugs to the market.[28]

The quality of the initial hits from FBDD is highly dependent on the diversity of the compound libraries that are used for screening and up until recently these libraries have consisted of predominantly flat heterocycle motifs. For example, a previously reported analysis of 18,534 organic fragments from the ZINC database showed that 75% of conventional fragments have either linear (1D) or planar shape (2D).[29] This is due to the fact that some of the most commonly used reactions in medicinal chemistry are amide bond formations and Suzuki–Miyaura couplings which lead to an increase in the sp^2 character of a compound.[30] To maximise the potential of techniques such as FBDD or even HTS, compound libraries need to better cover chemical space by containing more 3D structures.

In 2009 AstraZeneca launched a “strategic reagent initiative” as one potential answer to this problem whereby the synthesis of novel chemical building blocks is carried out in-house to

help diversify library collections.[31] Another approach to synthesise chemically diverse compound collections involves the use of diversity–oriented synthesis (DOS) whereby a common intermediate can be exploited in order to synthesise chemically diverse compound collections to rapidly cover chemical space.[29] Another such strategy to increase Fsp^3 and alter the shape of a compound is through the introduction of saturated bioisosteres of aromatic rings such as benzene.[32]

To this end, bioisosteres are an attractive solution to diversify compound collections. The development and application of bioisosteres has long been used in medicinal chemistry to address a number of aspects associated with the design and development of drug candidates.[33] The term “bioisostere” was introduced by Harris Friedman in 1950 to describe functionalities which were more alike in biological rather than physical properties.[34] Typically, they are used to bring about a structural change to a compound which could be beneficial or unfavourable depending on context. For instance they have been utilised to increase potency, improve physicochemical properties, reduce or redirect metabolism and acquire novel intellectual property.[33] A well-known example of this is the replacement of a C–H bond for a C–F bond which can potentially block a metabolic site on the compound or favour a particular conformation.[35] Bioisosteres continue to be discovered for a variety of commonly used functional groups in medicinal chemistry, for instance, oxetanes have emerged as replacement groups for *gem*-dimethyl and carbonyl groups with more applications for these cyclic ethers actively being researched.[36]

The implementation of bioisosteres into drug candidates is just one possible strategy medicinal chemists can use to address challenges which are associated with physicochemical properties in drug discovery. The discovery of new bioisosteres which could address particularly troublesome physicochemical properties such as poor solubility, high lipophilicity and low 3D character are therefore sought after and would positively expand the medicinal chemist’s “toolbox”. This, in tandem with other efforts made across the pharmaceutical industry can help reduce attrition in the drug discovery pipeline and lead to more available medicines.

1.2 Sulfonimidamides and Sulfoximines as Desirable Motifs

1.2.1 Intrinsic Properties of Sulfonimidamides and Sulfoximines

Sulfonimidamides and sulfoximines are hexavalent sulfur compounds which both contain a formal S=O and S=N double bond. In the case of sulfoximines the sulfur centre has single bonds to two carbon-linked substituents, whereas in sulfonimidamides the sulfur centre has single bonds to a carbon and a nitrogen-linked substituents (Figure 1.2).

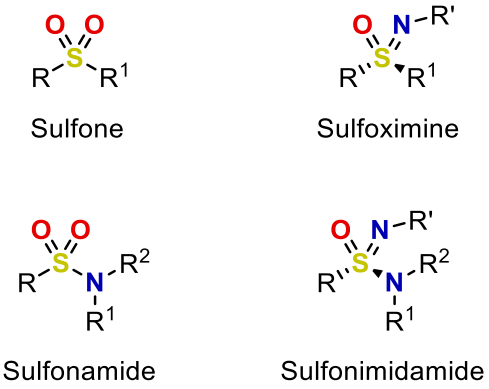


Figure 1.2: Structure of various sulfur(VI) functionalities.

In general, sulfoximines and sulfonimidamides are chemically and configurationally stable compounds.[37,38] Sulfoximines and sulfonimidamides are isoelectronic with sulfones and sulfonamides respectively but the introduction of the nitrogen atom creates the possibility of asymmetry and an additional point for structural diversity (i.e. substituent R'). When comparing a representative sulfone to its aza-analogue, the sulfoximine has a larger bond angle between the two heteroatoms than the sulfone, giving it an increased distortion from a regular tetrahedral geometry. In addition, there is a slight increase in the S=N bond length when compared to the S=O bond of a sulfone, in line with the increased atomic radius of the nitrogen atom (Table 1.1).[39,40] When R' = H this is commonly referred to as the "free" NH sulfoximine or sulfonimidamide, this position can be readily functionalised due to the relative acidity of the NH proton ($pK_a \approx 24$ for sulfoximines). When R' ≠ H, the acidity of the protons α to the sulfur centre on the R group are strongly dependant on the nature of the R' group. For instance, the

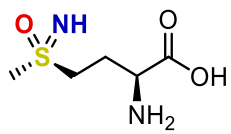
Entry	Compound	d(S=O) [Å]	d(S=N) [Å]	d(S-C) [Å]	C-S-C θ [°]	O-S-X θ [°]
1		1.46	1.53	1.76	103.5	120.4 X = NH
2		1.45	-	1.76	103.9	116.7 X = O

Table 1.1: Bond angles and lengths in sulfoximines and sulfones.[39,40]

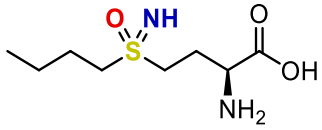
measured $pK_a \approx 25$ if R' = Ts or $pK_a = 33$ if R' = Me for sulfoximines in DMSO. The analogous protons in a sulfone fall in this range of values with a $pK_a \approx 29$.[41] The mildly basic nitrogen atom in these compounds allows for co-ordination to metal ions or formation of salts with mineral acids.[42,43] With the heteroatoms surrounding the sulfur centre being HBA's, in the case of when R' = H the functionality has dual hydrogen bond donor/acceptor capabilities. The unique combination of these properties has led to sulfoximines and more recently sulfonimidamides being increasingly used in the life sciences.

1.2.2 Applications of Sulfoximines in Synthesis

In 1946 it was established that dogs fed a diet rich with "agenized" flour were subject to canine hysteria and eventual death.[44] This was of great concern since it was estimated that 90% of the flour milled in England was agenized, a process which uses nitrogen trichloride to improve the baking properties of the flour. The toxic factor was eventually identified as the sulfoximine of the amino acid methionine (MSO).[45] The same substance was later found to be produced naturally by *Cnestis palala*, a plant of the Connaraceae family, species of which are known to be toxic.[46] It was later revealed that MSO's mode of action was as a transition state inhibitor of glutamine synthetase and γ-glutamylcysteine.[47] Increasing the length of the alkyl chain was shown to increase the specificity for γ-glutamylcysteine synthetase over glutamine



L-Methionine (*S*)-Sulfoximine



L-Buthionine Sulfoximine

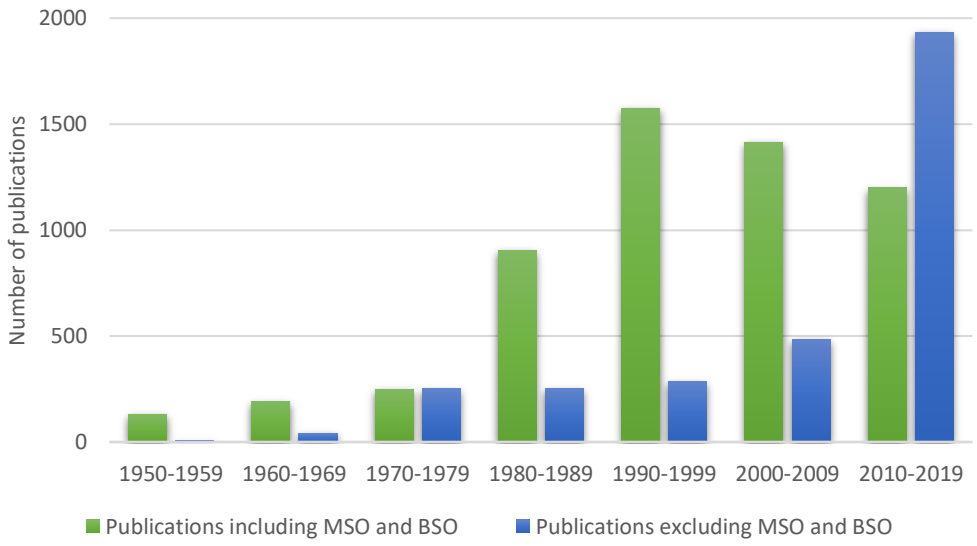
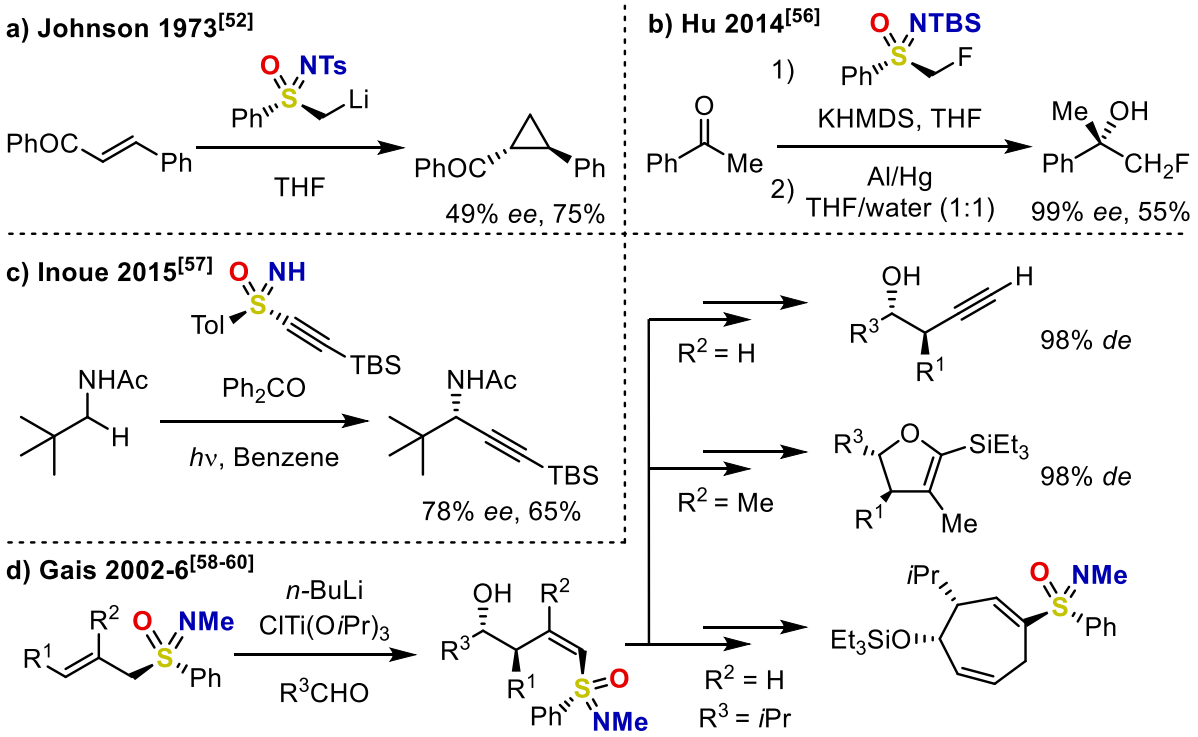


Figure 1.3: Bioactive sulfoximines MSO and BSO and their prevalence in publications related to sulfoximines in the time between 1950-2019.

synthetase and consequently L-buthionine sulfoximine (BSO) has been evaluated in conjunction with chemotherapy agents in Phase I clinical trials.[48,49] Whilst BSO was found to be clinically safe and caused significant tumour shrinkage, further studies are still required. MSO and BSO have dominated the sulfoximine literature since their inception, however, there has been a shift toward finding new applications for sulfoximines with just 38% of sulfoximine containing publications including MSO and BSO in the past decade (Figure 1.3). Due to the research efforts of Johnson and co-workers in the 1970s, sulfoximines began to be recognised as useful motifs outside of the applications of MSO and BSO.[50] The relative acidity of the α-protons to the sulfur centre enable it to act as a nucleophile when deprotonated, whilst the overall electron-withdrawing nature of the moiety allow it to act as an electrophile.[37] This coupled with the fact they have the potential to be enantiomerically pure has led them to be described as "chiral chemical chameleons".[51] The inherent chirality of the sulfoximine motif combined with different HBA properties compared to sulfones has led to their use as directing groups in C–H activation and in asymmetric reactions, which can broadly be split into the sulfoximine acting as a chiral auxiliary or as a chiral ligand.

1.2.2.1 Chiral Auxiliaries

The first report of asymmetry being induced by a sulfoximine based chiral auxiliary was by Johnson and co-workers in 1973 (Scheme 1.1a).[52] Since then, sulfoximines have been increasingly used in this arena, with some important examples of these shown below.[53–55] Hu and co-workers have described how a monofluorinated enantiopure sulfoximine allows for the



Scheme 1.1: Examples of sulfoximines acting as chiral auxiliaries.

generation of highly enantioenriched monofluoromethyl alcohols after desulfoximination (Scheme 1.1b).[56] Inoue and co-workers have shown that sulfoximines can be used as traceless chiral auxiliaries in promoting an enantioselective alkynylation of N-substituted C(sp^3)–H bonds (Scheme 1.1c).[57] Finally, Gais and co-workers have shown that a variety of systems can be accessed after an initial asymmetric reaction with a titanium sulfoximine complex (Scheme 1.1d).[58–60]

1.2.2.2 Chiral Ligands

Difficulties in recycling the sulfoximine auxiliary and the multiple synthetic steps required for their preparation in high *ee* has led to their use as ligands to be a more attractive and subsequently more active area of research. The first report on this topic, the use of β-hydroxysulfoximines **1** in nickel-catalysed conjugate additions to chalcones, was described by Bolm and co-workers in the early 1990's.[61] Thereafter, chiral sulfoximine based ligands have been utilised in a variety of transformations, with examples of the ligands used and their applications shown below (Figure 1.4).[55,62,63] After Bolm's seminal example, C_2-symmetric bissulfoximines were found to effect the same transformations in higher *ee* **2**,[64] with phosphorylated sulfoximines offering some of the best *ee* in allylic substitutions to date **3** and **4**.[65,66] C_2-symmetric bissulfoximines **5** with an aromatic backbone have been shown to be effective ligands in Cu(II) catalysed Diels–Alder and hetero Diels–Alder reactions.[67,68] Ligand **6** has seen widespread use including in Mukaiyama aldol reactions, vinylogous Mukaiyama aldol reactions (VMARs) and most recently in asymmetric halogenations.[69–72] Hydrogenation

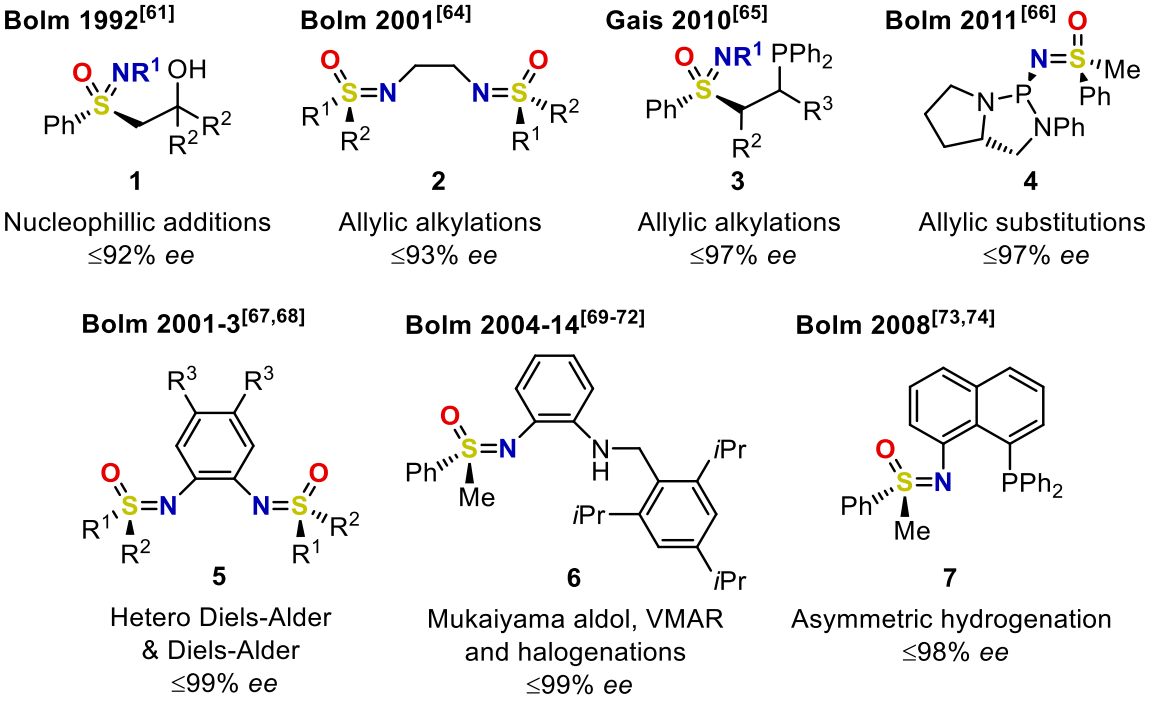


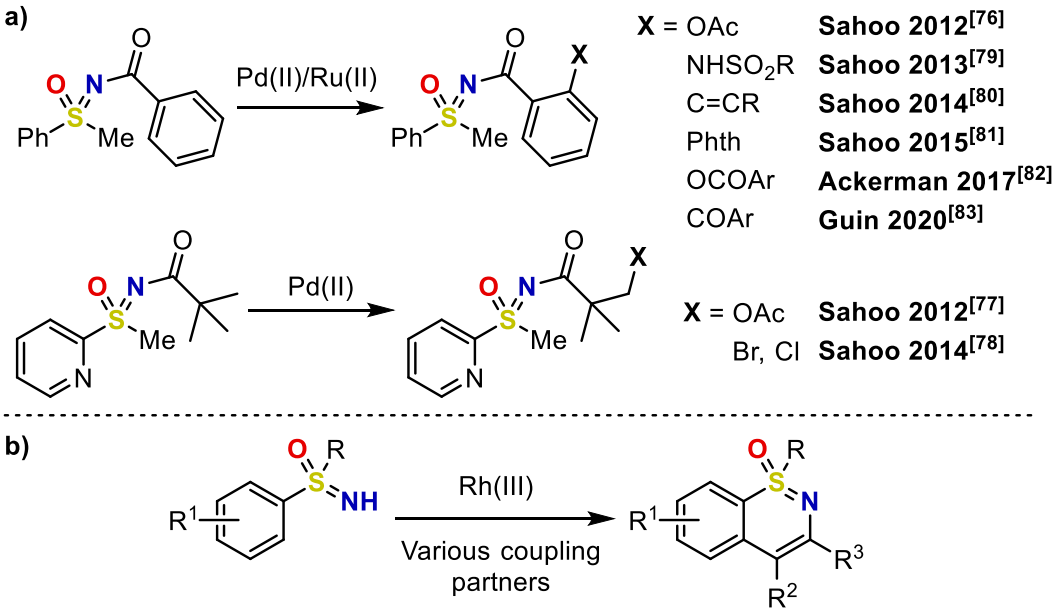
Figure 1.4: Examples of sulfoximines acting as chiral ligands.

reactions are the last major area of interest for sulfoximine based ligands, with ligand **7** promoting hydrogenations of α,β-unsaturated ketones and quinolines under Ir catalysis.[73,74]

1.2.2.3 Directing Groups

Outside of these two main applications of sulfoximines in organic synthesis, they have begun to find increasing use as directing groups in the field of C–H activation.[75] Sahoo and co-workers reported the first use of sulfoximines acting as directing groups in a Pd-catalysed acetoxylation on C(sp^2)–H and later the same year C(sp^3)–H systems.[76,77] Acyl sulfoximine directing groups have been shown to introduce halides,[78] sulfonamides,[79] alkenyls,[80] phthalimides,[81] esters,[82] and acyl groups to C–H bonds (Scheme 1.2a).[83] In all cases the sulfoximine directing group can be cleaved from the resulting products and recovered.

Research combining the directing group ability and reactivity of NH sulfoximines has shown that sulfoximines directly bound to the aromatic ring can afford 1,2-benzothiazines and related heterocyclic compounds via C–H/N–H functionalisation.[84] Three different protocols to access 1,2-benzothiazines have been reported by Bolm and co-workers, using alkynes, α-diazocarbonyl compounds, and allyl methyl carbonates as coupling partners under Rh(III)-catalysis.[85–87] Cramer and co-workers have further developed this methodology by showing that it is possible to perform enantioselectively with α-diazocarbonyl compounds and have used this to kinetically resolve racemic sulfoximines.[88,89] Other notable examples include Glorius and co-workers use of α-MsO/TsO ketones and Lee and co-workers use of pyridotriazole and 3-diazoindolin-2-imines as coupling partners all under Rh(III)-catalysis to form 1,2-benzothiazines (Scheme 1.2b).[90–92]



Scheme 1.2: The potential of sulfoximines as directing groups for C–H activation.

1.2.3 Applications of Sulfonimidamides in Synthesis

Sulfonimidamides have a briefer history when compared to sulfoximines, which in part is due to their relatively recent discovery (although there was an isolated report before Levchenko's research project began in the 1960's) and their lack of uptake until the past five years (Figure 1.5).[93] Nevertheless, their potential has started to be realised with similar applications to sulfoximines found, however, the presence of the extra nitrogen has led to their use as nitrene sources for a variety of reactions.

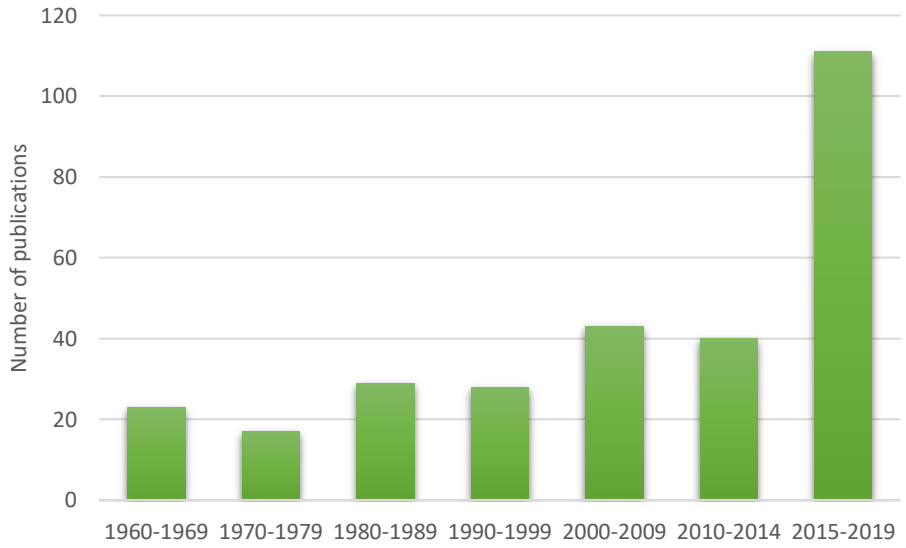


Figure 1.5: Publications containing a sulfonimidamide from the 1960's to date according to SciFinder.

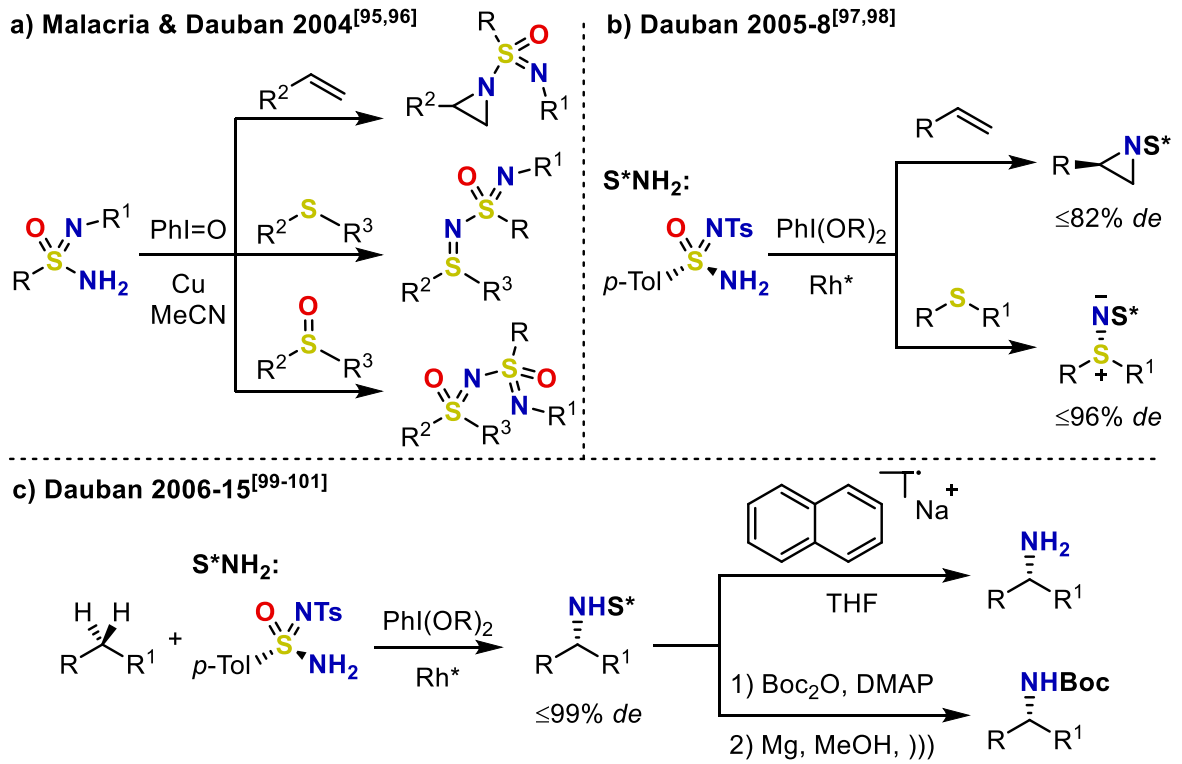
1.2.3.1 Chiral Nitrene Precursors

Iminoiodanes are iodine(III) reagents with a formal double bond to nitrogen, often as part of a sulfonamide and are established as powerful aminating reagents in organic synthesis by acting as nitrene precursors.[94] The corresponding sulfonimidamide versions of these reagents therefore offer similar opportunities, however, with the potential to be chiral.

The first report on the use of sulfonimidamides as nitrene transfer reagents was made, almost simultaneously, by the groups of Malacria and Dauban in 2004, protected aziridines, sulfilimines and sulfoximines could all be accessed from the corresponding precursors under nitrene transfer conditions (Scheme 1.3a).[95,96] Dauban and co-workers have further expanded this chemistry, by using an enantiomerically pure sulfonimidamide, complemented by a chiral Rh(II) catalyst to afford aziridines and sulfilimines diastereoselectively (Scheme 1.3b).[97,98]

Potentially the most powerful reactivity of these sulfonimidamide nitrenes is their ability to stereoselectively aminate C–H bonds in hydrocarbons. Dauban initially showed in 2006 that these sulfonimidamide reagents can install a protected amine diastereoselectively onto benzylic, allylic and alkane substrates (Scheme 1.3c).[99] In more recent years the same group

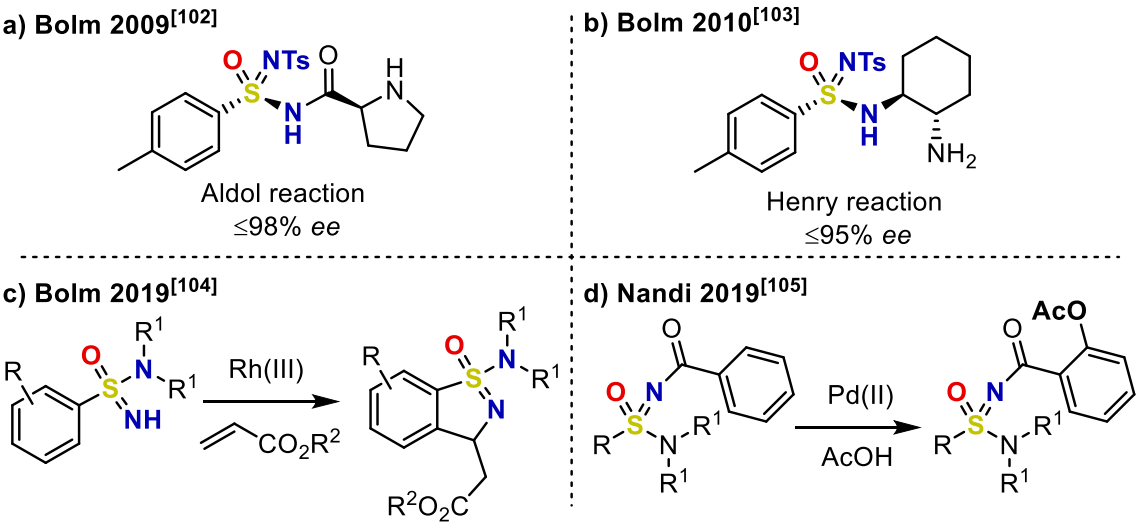
has shown that this transformation is possible on more functionalised substrates such as hypervalent iodine reagents and this allows for subsequent one-pot cross-couplings to afford highly functionalised, optically pure amines.[100] The sulfonimidamide group can be removed under reductive conditions to yield the primary amine or under different conditions, the Boc protected amine without epimerisation of the carbon centre (Scheme 1.3c).[99,101]



Scheme 1.3: Reactivity of sulfonimidamide nitrenes with different substrates.

1.2.3.2 Emerging Applications

Sulfonimidamides clearly possess similar advantageous properties as sulfoximines for asymmetric reactions and have begun to be exploited for similar transformations. In 2009 Bolm and co-workers showed that enantioenriched sulfonimidamides could be used as organocatalysts in an aldol reaction to generate the corresponding products in high enantioselectivities (Scheme 1.4a).[102] A year later the same group reported on the first sulfonimidamide based ligand in asymmetric catalysis in an enantioselective Henry reaction (Scheme 1.4b).[103] Recently, their use as directing groups in C–H activation has been exemplified by installing acetate groups or to construct 3D heterocycles (Scheme 1.4c & d).[104,105]



Scheme 1.4: Emerging applications of sulfonimidamides.

1.2.4 Sulfonimidamides and Sulfoximines in Medicinal Chemistry

Whilst sulfoximines and sulfonimidamides have been recognised for their synthetic utility, they have also found applications in electronics and materials chemistry.[106,107] Highly fluorinated motifs are of particular importance in this aspect and have shown promise in liquid crystal displays or in Li-ion cells as superacids.[108,109] However, potentially the most promising applications of these sulfur moieties is their use in medicinal chemistry.[38,110–113]

1.2.4.1 History of Bioactive Sulfoximines

Despite the discovery of sulfoximines deriving from their potent biological activity, the sulfoximine motif has seen limited uptake in medicinal chemistry programmes until recently. Satzinger and Stoss at Gödecke pioneered the use of the sulfoximine group in medicinal chemistry in the search for new antiasthmatic agents in 1970.[114] Whilst sulfoxifen displayed convincing clinical studies, it was terminated by the company before it was ready for the market. There have been several other examples of bioactive sulfoximines since sulfoxifen, however, the pan-CDK inhibitor project at Bayer Pharma AG produced the first sulfoximine clinical candidate for many years.[110] In 2009 the initial sulfonamide containing clinical candidate ZK 304709 failed in Phase I with lack of aqueous solubility being the primary cause.[115] A follow up programme in 2013 identified the sulfoximine containing compound roniciclib as having equivalent or improved potency, increased selectivity and a 22-fold increase in solubility compared to ZK 304709.[116] Roniciclib had excellent pharmacokinetics in humans in Phase I trials but it was revealed in 2018 that Phase II studies were terminated due to a safety signal.[117] Nevertheless, the project aroused a significant interest in sulfoximines at Bayer Pharma AG, leading to two additional clinical candidates. At a similar time, AstraZeneca reported on a sulfone containing series of compounds which were inhibitors of ataxia

telangiectasia mutated and RAD3-related (ATR) protein kinase.[118] However, the lead compound AZ20 was deemed to be of insufficient quality to undergo further development due to its low aqueous solubility and high risk of drug-drug interactions. Swapping out the sulfone moiety for a sulfoximine dramatically improved the physicochemical properties of the molecule and as a consequence the evaluation of ceralasertib in Phase I/II studies is ongoing (Figure 1.6).[119,120]

Outside of medicinal chemistry, sulfoximines have also seen application in the agrochemistry industry as a novel structural class of insecticide. Sulfoxaflor was approved for use on sap feeding insects by the EPA for applications in the USA in 2013 (Figure 1.6).[121] However, it was later withdrawn due to concerns over the potential hazards to bees.[122] Nevertheless, sulfoximines are likely to have further application in both medicinal and agrochemistry settings as evidenced by several recent reports.[123–125]

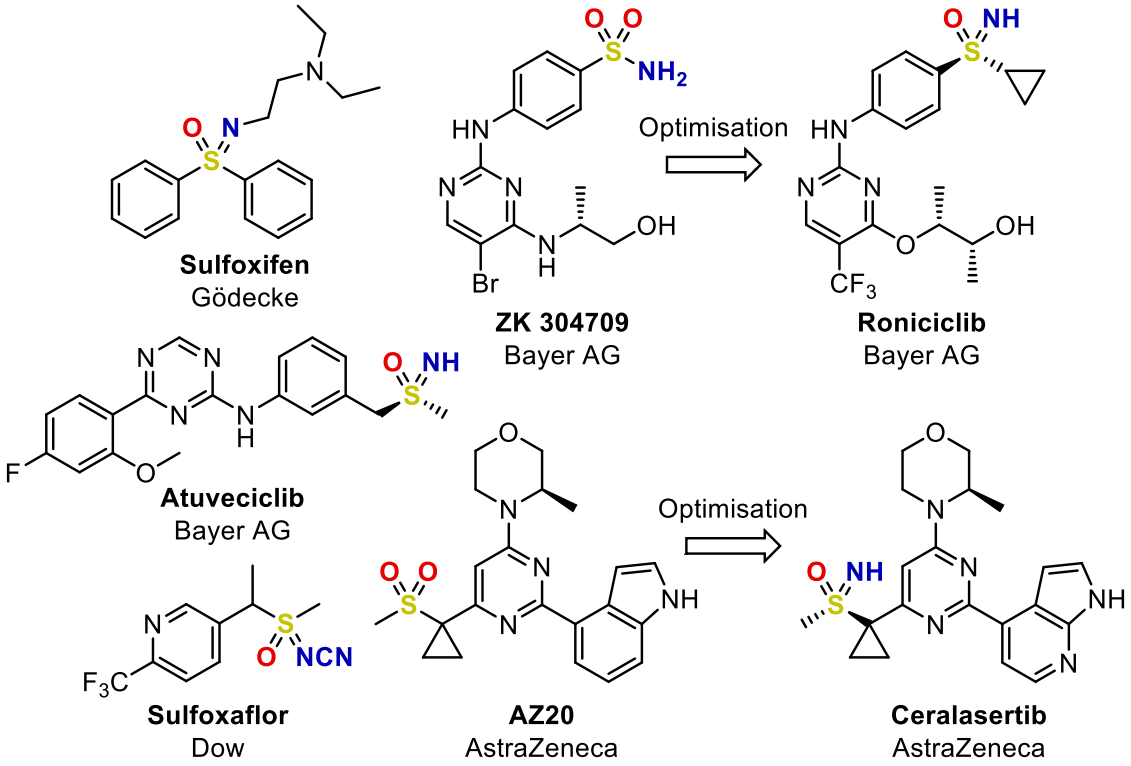


Figure 1.6: Structures of various bioactive sulfoximine containing compounds.

1.2.4.2 History of Bioactive Sulfonimidamides

The interest in sulfonimidamides in medicinal and agrochemistry was very modest up until around 2012, with a significant increase in the number of patents and publications for this application thereafter.[38] Although there have been numerous reports of bioactive sulfonimidamides, there has yet to be a clinical candidate disclosed.[111] The majority of the applications of sulfonimidamides in this context have been as bioisosteric replacements for sulfonamide groups. Some notable examples include the sulfonimidamide analogue of

Tasisulam, which shows comparable properties to Tasisulam (an antitumor agent that failed in Phase II), however, potentially without the toxic side effects.[126] Another example of where the sulfonimidamide analogue offered beneficial properties to the parent sulfonamide is in the case of marketed drug celecoxib where increased stability was observed (Figure 1.7).[127]

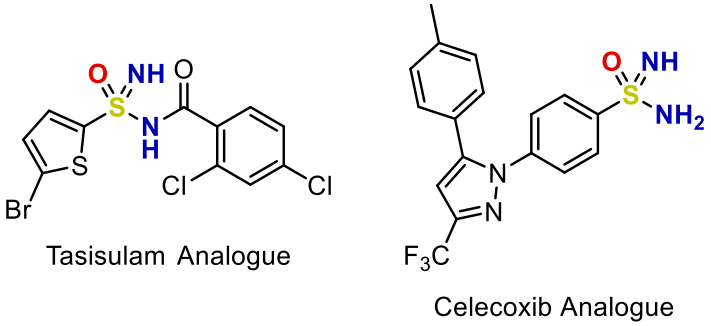


Figure 1.7: Bioactive examples of sulfonimidamides.

1.2.4.3 Sulfoximines and Sulfonimidamides as Bioisosteres

Sulfone and sulfonamide functionalities are highly prevalent in marketed drugs and so the evaluation of these aza analogues with their oxygen counterparts is of particular interest.[128]

In this regard, sulfoximines and sulfonimidamides have been shown to act as bioisosteres of sulfones and sulfonamides respectively.[129] In addition, a matched molecular pair analysis showed that physicochemical properties such as solubility, lipophilicity, plasma protein binding, permeability and metabolic stability are generally improved when compared against their oxygen counterparts (Figure 1.8a).[130]

The unique combination of properties these motifs possess has led to their evaluation as bioisosteres for a variety of other functional groups as well. For example, sulfoximines have been used to strategically replace a range of functionalities including alcohol, amidine, amine and sulfonamide moieties.[110,131] Sulfonimidamides on the other hand are less well explored but offer similar potential, for example their ability to act as carboxylic acid bioisosteres with tuneable pK_a via introduction of an acyl group has been reported (Figure 1.8b).[132,133] Overall, studies on these aza-analogues groups have concluded that there is no intrinsic flaw with these functionalities and that they are a valuable addition to the medicinal chemists toolbox.[131,134]

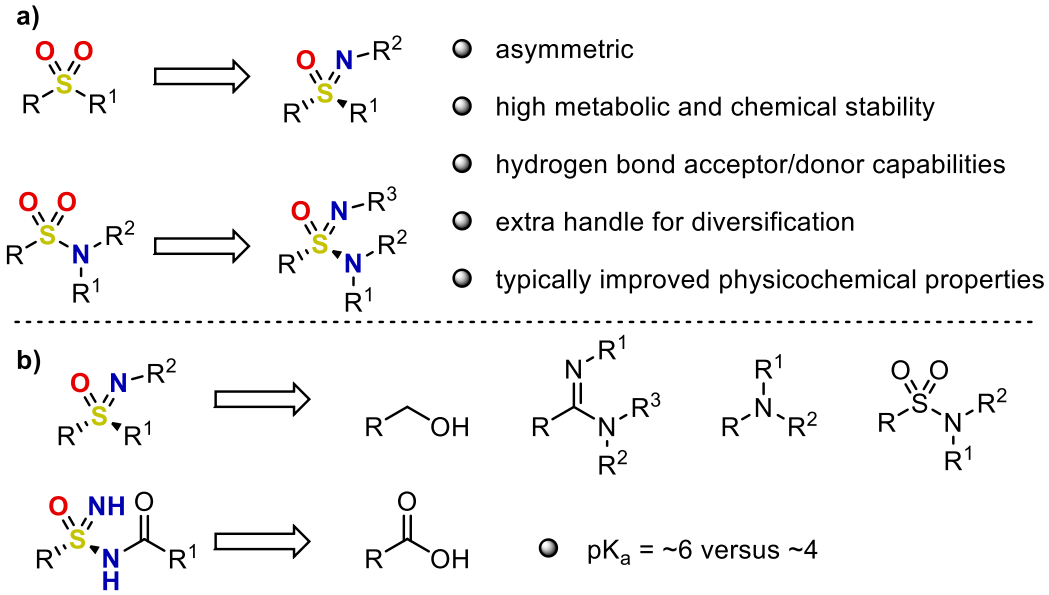


Figure 1.8: Sulfoximines and sulfonimidamides as bioisosteres.

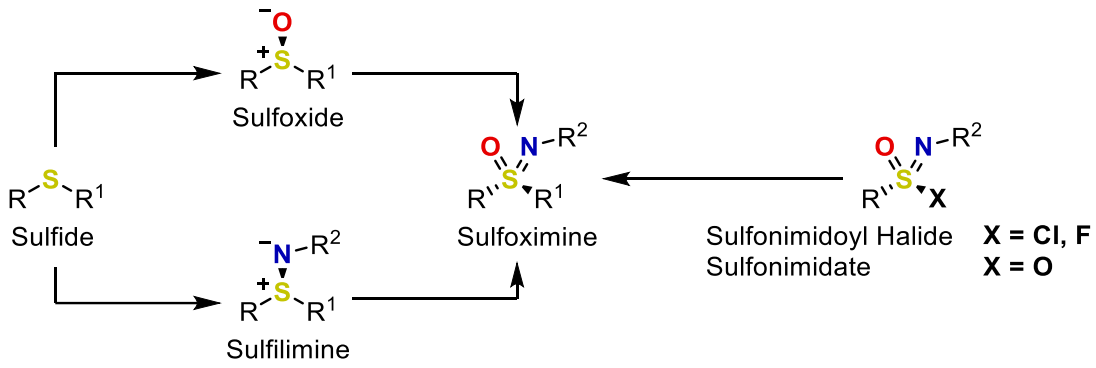
1.3 Synthetic Methods to Access Sulfonimidamides and Sulfoximines

The range of applications for sulfoximines and sulfonimidamides makes it clear that simple synthetic methods to access these functional groups are of considerable importance. Indeed, the lack of safe and scalable synthetic methods to access them is likely the main reason why these motifs have only seen limited success until now.[135–137]

1.3.1 Preparation of Sulfoximines

The majority of sulfoximine forming reactions begin with the sulfide in place and in a two-step procedure perform an oxidation and imination in either order. Most methods to form sulfoximines from sulfides perform the oxidation step first and then introduce the nitrogen group second, instead of performing an initial imination leading to a sulfilimine. The main reason is the relative stability of these substrates to oxidation and therefore the requirement of strong oxidants such as potassium permanganate to synthesise the sulfoximine. In addition, certain sulfilimines can have stability concerns (Scheme 1.5).[138]

Another route is centred around S–C bond-forming methodologies, commonly this involves the displacement of a leaving group on a preformed sulfur(VI) centre by a carbon based nucleophile to form a new S–C bond. Popular starting materials for this include sulfonimidoyl halides as well as sulfonimidates, however, sulfinamides have recently been used to this end as well (Scheme 1.5).



Scheme 1.5: General routes for sulfoximine synthesis.

Methods starting from sulfides can broadly be split into two categories, those which are transition metal free and those which are transition metal catalysed.

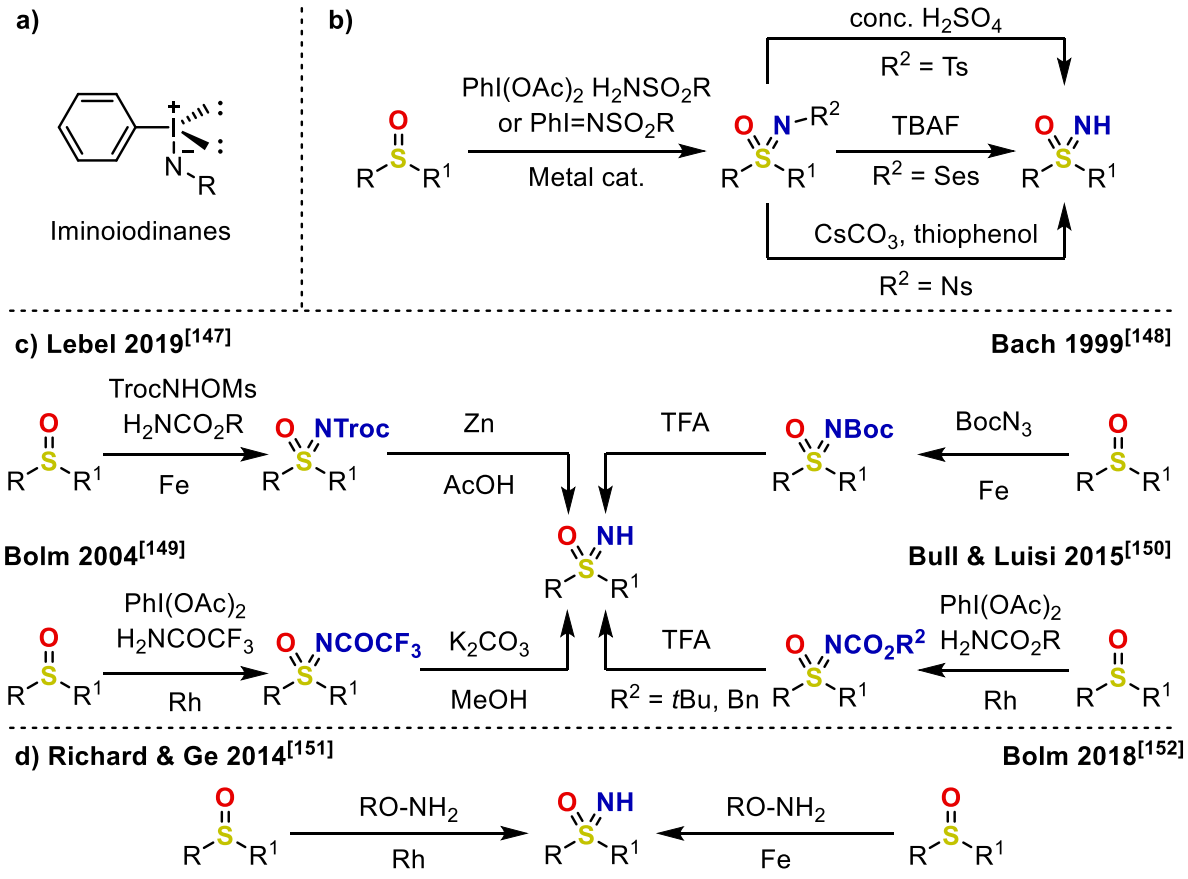
1.3.1.1 Transition Metal Catalysed Methods

In 1991 Evans and co-workers described the use of iminoiodinanes for the formation of aziridines under copper catalysed conditions.[139] This pioneering paper drew a lot of attention to these nitrene precursors in organic synthesis.[94] In these iodine(III) species the iodine is bound to the aryl ring via a σ-bond while the nitrogen-linked ligand is bonded by a formal double

bond considered to be a two centre-four electron bond leading to the iodine centre adopting a bent geometry corresponding to the AX_2E_2 type (Scheme 1.6a).

The use of iminoiodinanes to synthesise protected sulfoximines directly was first shown in 1998 using CuOTf as catalyst.[140] A variety of other metal catalysts such as manganese,[141] ruthenium,[142] silver[143] and iron[144] have also been shown to suitably stabilise the generated nitrene species which facilitates the transfer to the sulfur atom. Further developments showed that iminoiodanes could be formed *in situ*, with a suitable iodine(III) reagent and sulfonamide.[145] The drawback to these methods are that they afford the corresponding sulfonyl protected sulfoximine which is often non-trivial to deprotect in order to yield the more synthetically useful free NH (Scheme 1.6b).[37,146]

Alternative functionalities, which are easier to remove from the sulfoximine nitrogen have been examined for their transfer to sulfur centres. Other strategies to access *N*-protected sulfoximines include the iron catalysed transfer of a NTroc group in batch or flow conditions[147] and the use of $BocN_3$ to afford the NBoc protected sulfoximines under iron-mediated conditions.[148] In both of these cases, the corresponding carbamate protecting group was shown to be removeable, however, the simple conditions required for the removal of the Boc group and it's ubiquity in organic synthesis make it an attractive option. Bolm and co-workers



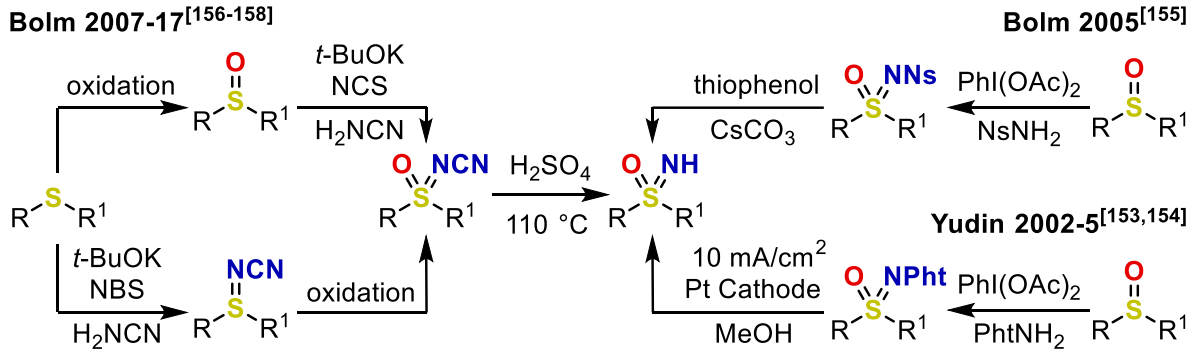
Scheme 1.6: Transition metal catalysed methods towards free NH sulfoximines from sulfoxides.

showed in 2004 under iodine(III) mediated conditions with a rhodium catalyst that the trifluoroacetamide group could be transferred to either sulfides or sulfoxides, leading to NH sulfoximines after an *in situ* deprotection.[149] In 2015 Bull, Luisi and co-workers extended Bolm's rhodium catalysed conditions to include the transfer of carbamate groups, knowing that these are easily removable and recognising the desirability of this class of protecting group in organic synthesis (Scheme 1.6c).[150]

Methods which synthesise the free NH sulfoximine directly are clearly desirable and at present there are two methods available that can transfer NH directly under transition metal catalysis to sulfoxides. This includes Richards and Ge's rhodium catalysed process and Bolm's iron catalysed NH transfer. In both cases, the hydroxylamine aminating reagent has concerns associated with its stability (Scheme 1.6d).[151,152]

1.3.1.2 Transition Metal Free Methods

Issues can arise from the use of transition metals in the preparation of pharmaceutical products and can be expensive on a large scale. Therefore, several methods to access sulfoximines have been reported in order to access them more sustainably. Alternative transition metal free routes which afford protected sulfoximines have been developed, including the iodine(III) mediated transfer of $NsNH_2$ and $PhtNH_2$ groups to sulfoxides[153–155] and the generation of *N*-cyanosulfoximines through the use of an electrophilic halide source.[156–158] However, in all cases a discrete deprotection step is necessary to access the synthetically valuable free NH sulfoximine (Scheme 1.7).



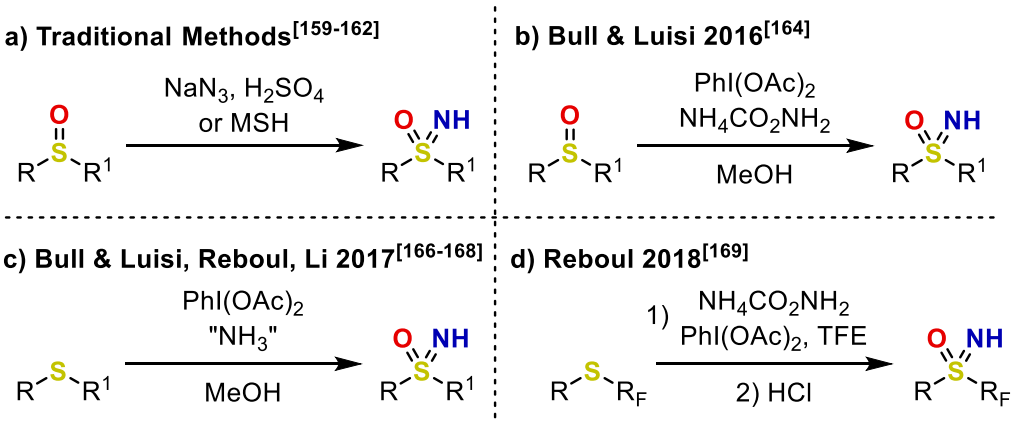
Scheme 1.7: Transition metal free methods towards free NH sulfoximines.

After their discovery in the 1940's the conventional method to synthesise sulfoximines was through the use of hydrazoic acid with a sulfoxide to yield the free NH sulfoximine.[159] This method has seen widespread use for many years, including a recent example under flow conditions.[160] Only in the past decade is it being phased out completely, despite reports of an explosion using these conditions reported as early as 1970.[161] Aside from the obvious safety concerns, this method is not suitable for the synthesis of branched alkyl sulfoximines and

causes racemisation of enantioenriched sulfoxide starting materials. The use of *O*-mesitylene sulfonyl hydroxylamine (MSH) as an aminating agent has been shown to circumvent these issues, however, MSH is not without safety concerns either (Scheme 1.8a).[162,163]

In 2016 Bull, Luisi and co-workers explored the use of carbamate salts as nitrogen sources for the formation of NH sulfoximines, expecting decarboxylation to occur either before or after the N-transfer.[135] The use of ammonium carbamate as a cheap and easy to handle nitrogen source was found to afford NH sulfoximines, surprisingly, under metal free conditions.[164] This serendipitous discovery was the first report of a safe, transition metal free protocol for the direct synthesis of NH sulfoximines (Scheme 1.8b). The NH transfer methodology is tolerant of a range of sulfoxide starting materials, affording the corresponding NH sulfoximines in high yield. The NH transfer occurs stereospecifically with retention of the sulfur configuration allowing access to highly enantioenriched sulfoximines. A robustness screen further indicated the compatibility of this protocol with various functionalities, showing alkene, alkyne, amine, phenol, ester, aldehyde, and nitrile functionalities are all tolerated.[165] The main two drawbacks of this methodology include the lack of tolerability of electron rich heterocycles such as indoles and the low yields obtained for electron poor sulfoximines, owing to the reduced nucleophilicity of the sulfoxide.

In 2017 Bull, Luisi and co-workers, as well as two other groups independently at a similar time, examined sulfides as substrates under the previously developed NH transfer conditions to sulfoxides.[164] The expected sulfilimine products were not observed and instead the corresponding sulfoximines were obtained in high yield in a chemoselective one-pot NH and O transfer (Scheme 1.8c).[166–168] Considering that most preparations of sulfoximines are based on two step oxidation/imination strategies from sulfides, this methodology offers a considerable advance. The functional group compatibility is largely the same as in the case of the NH transfer to sulfoxides, however, the sulfoximine products are afforded as racemates, with no



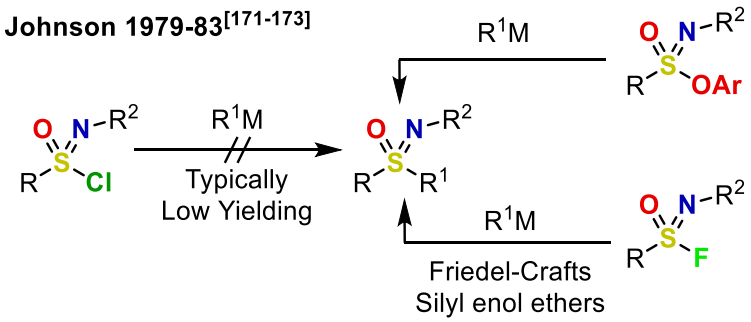
Scheme 1.8: Transition metal free methods to access sulfoximines directly.

enantioselective variants currently known. The scope of this NH and O transfer was further expanded in 2018 by Reboul and co-workers to include the synthesis of perfluoroalkylated sulfoximines.[169] The key change was the use of trifluoroethanol (TFE) as the solvent instead of methanol, however this method requires an *in situ* deprotection of the acylated sulfoximine intermediate using hydrochloric acid (Scheme 1.8d). A more environmentally friendly set of conditions has been developed by Zheng, Xu and co-workers in 2020 whereby the use of a surfactant allows the reaction to be carried out on water, with diacetoxytrifluoro iodobenzene found to be the optimal oxidant under these conditions.[170]

1.3.1.3 C–S Bond Forming Strategies

Although powerful methods to transform sulfides directly into sulfoximines have been developed, these require a pre-installed sulfur centre. Having different options for synthesis helps overcome issues associated with a particular route. In this light, S–C bond forming methods allow for a different approach to access sulfoximines. Sulfonimidates and sulfonimidoyl halides both present an electrophilic sulfur centre which have shown promise in S–C bond forming strategies.

Johnson and co-workers were the first to extensively examine these electrophilic sulfur species for this purpose. Originally sulfonimidoyl chlorides were studied, however, it was found that when these reacted with organometallic reagents, it typically resulted in reductions to sulfinamides or afforded the sulfoximine in low yield.[171] The same group later showed sulfonimidates were more useful for this purpose, affording sulfoximines in good yields when reacting with organolithium reagents.[172] Conversion of sulfonimidoyl chlorides to their more stable fluoride counterparts led to improved reactivity with organometallic reagents as well as showing good reactivity in Friedel-Crafts reactions and with silyl enol ethers to produce a variety of sulfoximines.[173] These pioneering studies were usually limited to single examples or a very limited scope, so in recent years this chemistry has been further examined (Scheme 1.9).

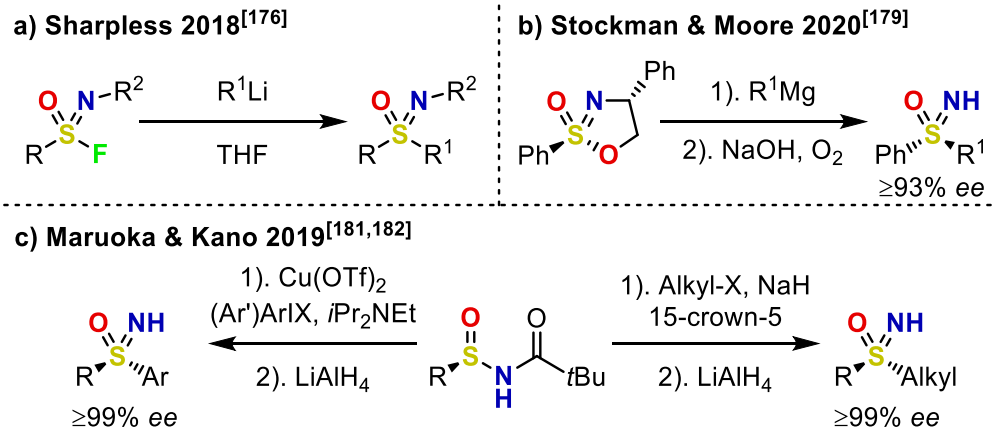


Scheme 1.9: Pioneering studies on S–C bond forming reactions to reach sulfoximines.

Whilst there have been some isolated reports on the use of sulfonimidoyl chlorides as effective precursors to sulfoximines,[174] sulfonimidoyl fluorides provide better opportunities due to their increased stability.[175] As part of the growing area of sulfur-fluoride exchange reactions (SuFEx) Sharpless and co-workers have examined sulfonimidoyl fluorides as versatile hubs for the synthesis of sulfoximines, sulfonimidates and sulfonimidamides although their formation via this route requires the handling of gaseous SOF_4 and pyrophoric reagents (Scheme 1.10a).[176]

In 2018, Stockman, Moore and co-workers further examined sulfonimidates for their potential to form sulfoximines when reacting with Grignard reagents, based on Reggelin and co-workers initial study.[177,178] The same group went on to further exploit the reaction between cyclic sulfonimidates and Grignard reagents for the asymmetric synthesis of NH sulfoximines (Scheme 1.10b).[179,180]

An alternative strategy for the asymmetric synthesis of sulfoximines has been disclosed by Maruoka, Kano and co-workers starting from commercially available enantioenriched sulfinamides. Using a base and either a copper catalyst and diaryliodonium salt or an alkyl iodide and crown ether, enantiopure sulfoximines can be obtained from secondary sulfinamides.[181,182] This methodology goes some way to addressing the need of a general approach to synthesise enantioenriched sulfoximines, however, the main drawbacks are the limited scope of the R group and the harsh reagents required to access the free NH-sulfoximine products (Scheme 1.10c).

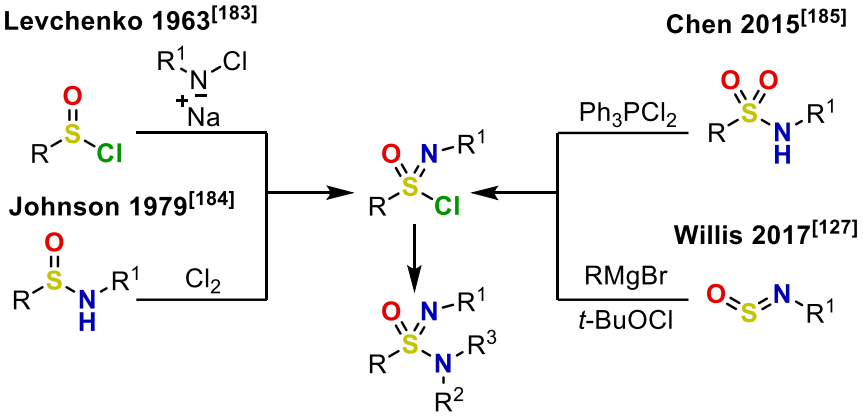


Scheme 1.10: S–C bond forming reactions to reach sulfoximines.

1.3.2 Preparation of Sulfonimidamides

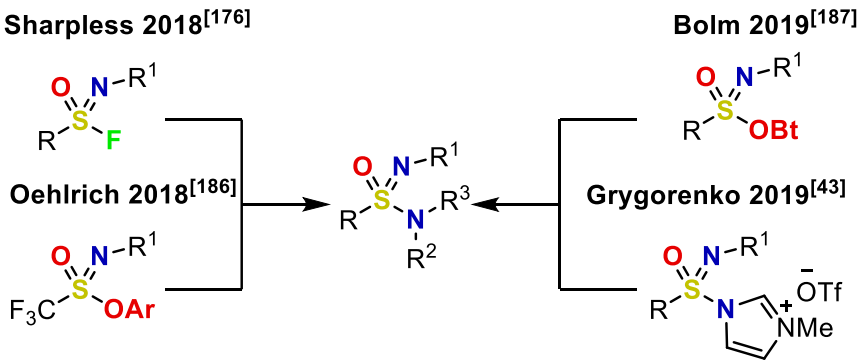
Most methods to prepare sulfonimidamides have been through S–N bond forming reactions. Typically, this involves the addition of an amine into a sulfonimidoyl halide species, although more recent methods have utilised sulfinamides and even sulfoximines as the electrophilic sulfur species.[106]

Levchenko and co-workers seminal route to sulfonimidamides involved an oxidative imination of sulfinyl chlorides with chloramine-T followed by reaction with an amine.[183] Johnson and co-workers refined this route by making it easier to access the corresponding sulfonimidoyl chlorides, through oxidative chlorination of sulfinamides.[184] Modern synthetic methods have also exploited sulfonimidoyl chloride intermediates including Chen and co-workers route from sulfonamides or Willis and co-workers use of sulfinylamines as a linchpin reagent (Scheme 1.11).[127,185]



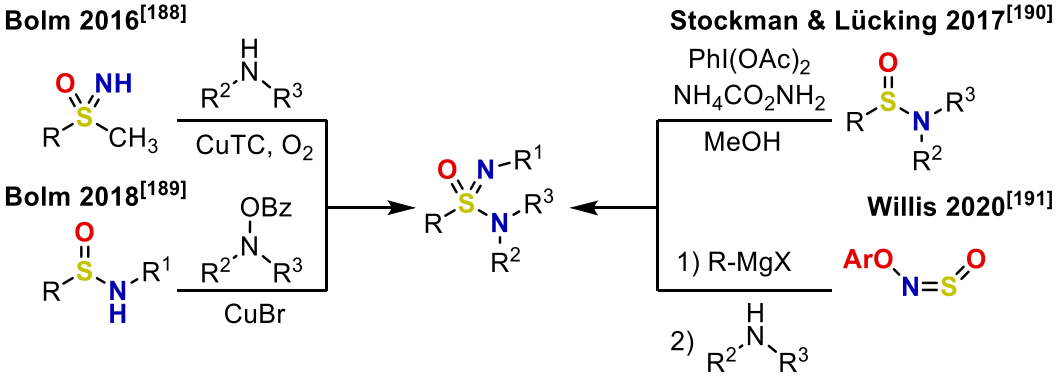
Scheme 1.11: Methods to reach sulfonimidamides through sulfonimidoyl chlorides.

However, as previously discussed, sulfonimidoyl chlorides suffer from their lack of stability and so Johnson and co-workers introduced sulfonimidoyl fluorides as more stable alternatives which display similar reactivity.[173] Sharpless and co-workers showed that these were suitable precursors to sulfonimidamides, however, just a small substrate scope was shown and deprotonated amines were typically used as nucleophiles.[176] Sulfonimidates have also been used as sulfonimidamide precursors including Oehlrich and co-workers tetrafluorophenyl sulfonimidate ester for the synthesis of trifluoromethyl sulfonimidamides[186] and Bolm and co-workers use of *O*-benzotriazolyl esters to access a wider range of sulfonimidamides.[187] Grygorenko and co-workers have recently shown that sulfonimidoyl imidazole salts are also suitable precursors to sulfonimidamides (Scheme 1.12).[43]



Scheme 1.12: Alternatives to sulfonimidoyl chlorides as electrophilic sulfonimidamide precursors.

Nucleophilic attack of an amine on an electrophilic sulfur(VI) centre is the predominant method used for the synthesis of sulfonimidamides. There are just a few alternative methods including a radical based process described by Bolm and co-workers who used methyl sulfoximines as sulfonimidamide precursors.[188] The same group later described a copper catalysed cross coupling between sulfinamides and *O*-benzoyl hydroxylamines to yield sulfonimidamides.[189] Drawing inspiration from Bull, Luisi and co-workers previous report on the NH transfer to sulfoxides,[164] Stockman, Lücking and co-workers have shown sulfinamides are also suitable substrates under analogous NH transfer conditions yielding the corresponding free NH sulfonimidamide products.[190] More recently, Willis and co-workers have described the use of a novel sulfinylhydroxylamine (BiPhONSO) which can act as a sulfinyl nitrene precursor, allowing access to sulfonimidamides or sulfoximines (Scheme 1.13).[191]

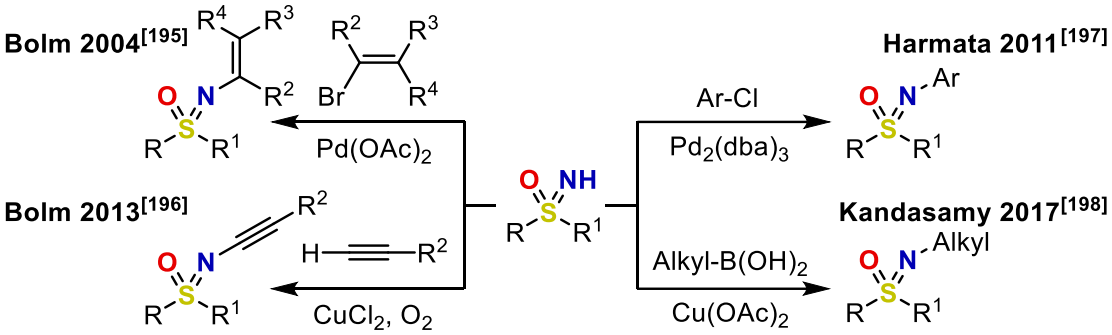


Scheme 1.13: Alternative precursors to sulfonimidamides.

1.3.3 Functionalisation of Sulfoximines and Sulfonimidamides

Synthetic methods to reach sulfoximines or sulfonimidamides centre around accessing the free NH derivatives as isosteres of their corresponding oxygen analogues. However, with the introduction of the nitrogen atom it allows for the exploration of another exit vector. As such many methods have been developed to functionalise the imine nitrogen of these compounds.[84,134] The NH proton of sulfoximines has a $pK_a \approx 24$ in DMSO,[41] allowing for deprotonation at this site which can then react with certain electrophiles, for example alkylhalides in alkylation reactions.[192] Radical based reactions are also possible on this centre and can be used to install trifluoromethyl or nitrile groups.[193,194] Probably the most well exploited avenue of functionalisation of these compounds is through transition metal catalysed cross-coupling reactions with various electrophilic partners.[84] The majority of these reactions have been carried out on sulfoximines, however, in 2018 Stockman, Lücking and co-workers showed that the sulfonimidamide imine nitrogen displays very similar reactivity and a plethora of manipulations that had been exemplified on sulfoximines were also shown to be compatible with sulfonimidamides.[134] Some representative examples of transition metal catalysed transformations are shown below, including alkenylations,[195] alkynylations,[196] arylations[197]

and alkylations[198] (Scheme 1.14). Most of the NH transformations are restricted to palladium or copper catalysts and so the use of more diverse and abundant metals remains a key challenge in this area.



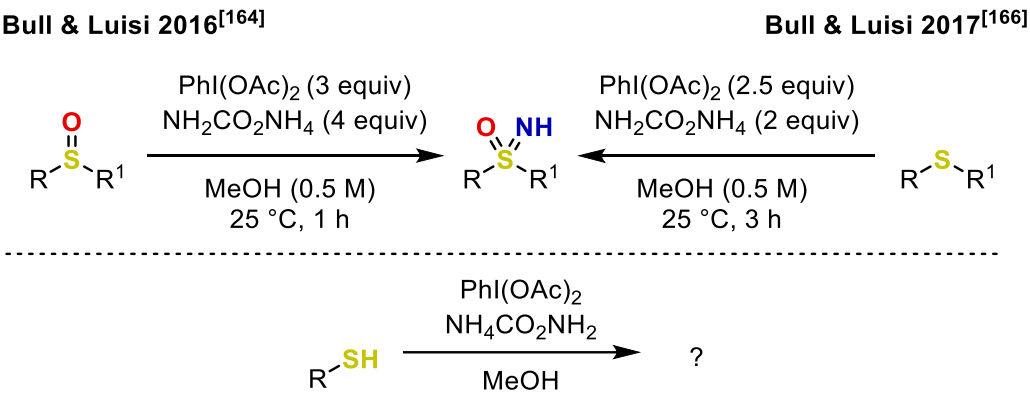
Scheme 1.14: NH Functionalisation of sulfoximines.

1.4 Project Aims

The research in this thesis is concerned with the further development of methodologies to access nitrogen containing sulfur(VI) functionalities, primarily through extending the aforementioned NH (and O) transfer methodology that has previously been exemplified on sulfoxide,[164] sulfide[166–168] and sulfinamide[190] substrates to yield the corresponding sulfoximine or sulfonimidamide products. These sulfone and sulfonamide aza-analogues can offer favourable physicochemical properties over their oxygen containing counterparts. Their lack of uptake in medicinal chemistry and beyond is likely due to historically limited synthetic methods which were often either unsafe, inconvenient or expensive. This work aimed to address these issues by examining different precursors and alternative bond forming reactions for their preparation.

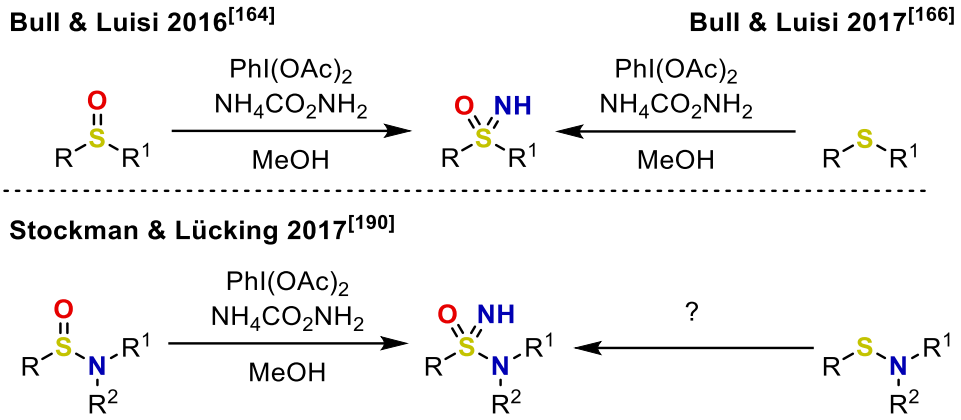
To demonstrate the introduction of modern synthetic methods towards enantioenriched sulfoximines, a representative NH transfer reaction to an enantioenriched sulfoxide would be investigated. In developing a procedure for the generation of multi-grams of this material it was hoped to draw further attention to the safe, convenient and inexpensive methods that are now available for their synthesis (Section 2.1).

To further extend the NH and O transfer methodology, thiols were to be examined as substrates. Under these conditions it was envisaged that useful nitrogen containing sulfur(VI) species could be formed (Scheme 1.15, Section 2.2).



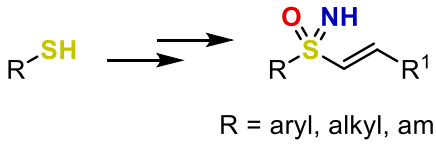
Scheme 1.15: Extending the NH and O transfer methodology to thiols.

As well as thiols, sulfenamides were to be examined under NH and O transfer conditions. After Stockman and co-workers extension of the NH transfer methodology to sulfinamides to form sulfonimidamides,[190] it was theorised that sulfenamides would also allow access to sulfonimidamides in a similar manner to sulfides acting as sulfoximine precursors (Scheme 1.16, Section 2.3).[166]



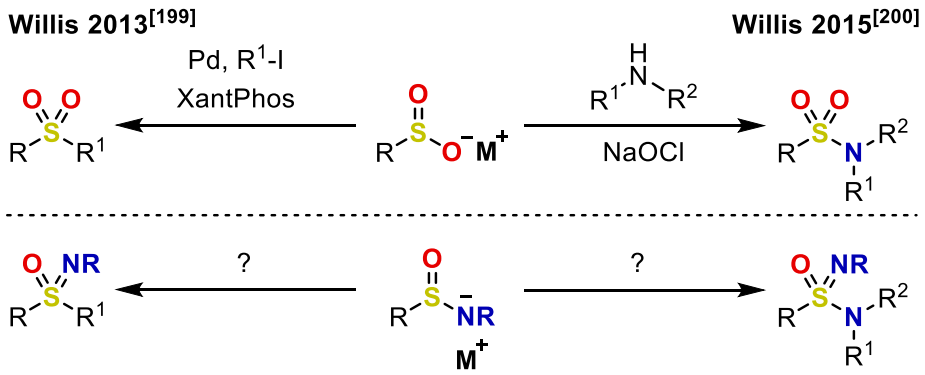
Scheme 1.16: Sulfenamides as possible precursors to sulfonimidamides.

The synthesis of vinyl sulfoximines and sulfonimidamides was then targeted, hoping to utilise the newly developed NH and O transfer methodologies which make their synthesis more straightforward than previous routes. Vinyl sulfones and sulfonamides have been shown to have applications as protein-targeted covalent probes and it was hoped the corresponding aza-analogues would exhibit similar reactivity for the synthesis of future covalent probes (Scheme 1.17, Section 2.4).



Scheme 1.17: New synthetic routes toward vinyl sulfoximines and sulfonimidamides.

Whilst the developed NH and O transfer methodology allows straightforward access to sulfoximines and sulfonimidamides, it has some drawbacks with the most pertinent being the lack of direct applicability to library synthesis. More useful therefore would be a general method to access sulfoximines or sulfonimidamides via S–C or S–N bond formation respectively. Whilst a variety of S–N bond forming reactions exist for sulfonimidamides there has been no general route for their enantioselective synthesis and so this was another key aim. Sulfinate



Scheme 1.18: Sulfinamide salts as aza analogues of sulfinate salts.

salts have been demonstrated as bench stable building blocks for the synthesis of sulfones and sulfonamides.[199,200] It was postulated that the corresponding aza-analogues, namely sulfinamides salts, would exhibit similar behaviour and therefore allow access to both sulfoximines and sulfonimidamides (Scheme 1.18, Section 2.5).

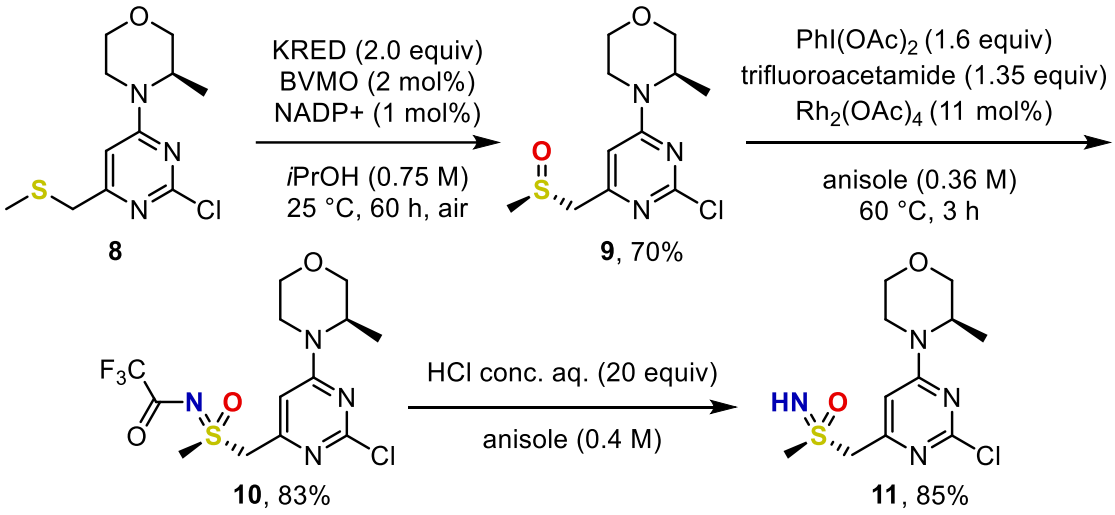
2. Results and Discussion

2.1 Sulfoxide to Sulfoximine Multigram Synthesis

2.1.1 The Importance of Enantioenriched Sulfoximines

Synthetic methods for the generation of enantioenriched compounds is of great importance, especially in the pharmaceutical and agrochemical industries where the efficacy of the biological agent can be highly dependent on the enantiomer administered.[201] The most infamous example of the biological effect that two different enantiomers possess is in the case of the medication thalidomide. The medication (to prevent morning sickness) was initially sold as a racemate, however it was later discovered that the (–)-*S*-enantiomer is a teratogen which caused birth defects in thousands of children in the 1960's.[202] The thalidomide scandal caused widespread reform in the approval mechanism of new medicines and led to a renewed focus upon enantioselective methods in organic synthesis.

It is therefore unsurprising that most of the disclosed clinical candidates which contain a sulfoximine moiety are single enantiomers (and diastereomers). One such example of this is the previously discussed ATR inhibitor ceralasertib developed by AstraZeneca. Details and discussion of the multi-kilo manufacturing process of ceralasertib was published in 2019 by the process chemists responsible at AstraZeneca.[120] The scale-up route was kept the same as the medicinal chemistry route with improved conditions found for each step. The installation of the enantioenriched sulfoximine moiety was an important challenge in the multi-kilo synthesis of ceralasertib and the key steps in the plant scale route to install the sulfoximine are shown below (Scheme 2.1).



Scheme 2.1: Plant scale route to Ceralsertib.

With sulfide **8** in place, an enantioselective oxidation mediated by a Baeyer−Villiger monooxygenase (BVMO) enzyme afforded the desired diastereomer in 70% yield and >99% dr.[203] With the stereochemistry now set on the sulfur atom, Bolm's rhodium-catalysed imination was then carried out to transfer trifluoroacetamide to sulfoxide **9** to afford the protected sulfoximine **10** with complete retention of stereochemistry.[149] A deprotection step with conc. HCl is then required to access the free NH sulfoximine **11**, which remains in place for the rest of the route toward ceralasertib.

The example of ceralasertib highlights the need for simple and inexpensive methods for the preparation of NH sulfoximines. Considerable savings could be made if the route from sulfide **8** to sulfoximine **11** contained fewer synthetic steps and didn't require precious metal catalysts. Such was the demand in finding another route from **9** to **11** hydrazoic acid generated *in situ* in flow was used to effect this transformation and whilst this afforded **11** in a 77% yield, the chirality at the sulfur was not retained.[160] Therefore the route reverted back to using Bolm's methodology, which on plant scale requires 1.3 kg of $Rh_2(OAc)_4$ per 88 kg of **9**.

The methodology developed by Bull, Luisi and co-workers on the transition metal-free direct NH (and O) transfer to sulfoxides or sulfides can allow for shorter overall synthetic routes to free NH sulfoximines as removal of a protecting group is not required. In addition, the simple set of conditions means each run is inexpensive when compared to transition metal catalysed protocols. Because of this, various groups have begun implementing this methodology in their own research programmes when constructing sulfoximine containing compounds for various

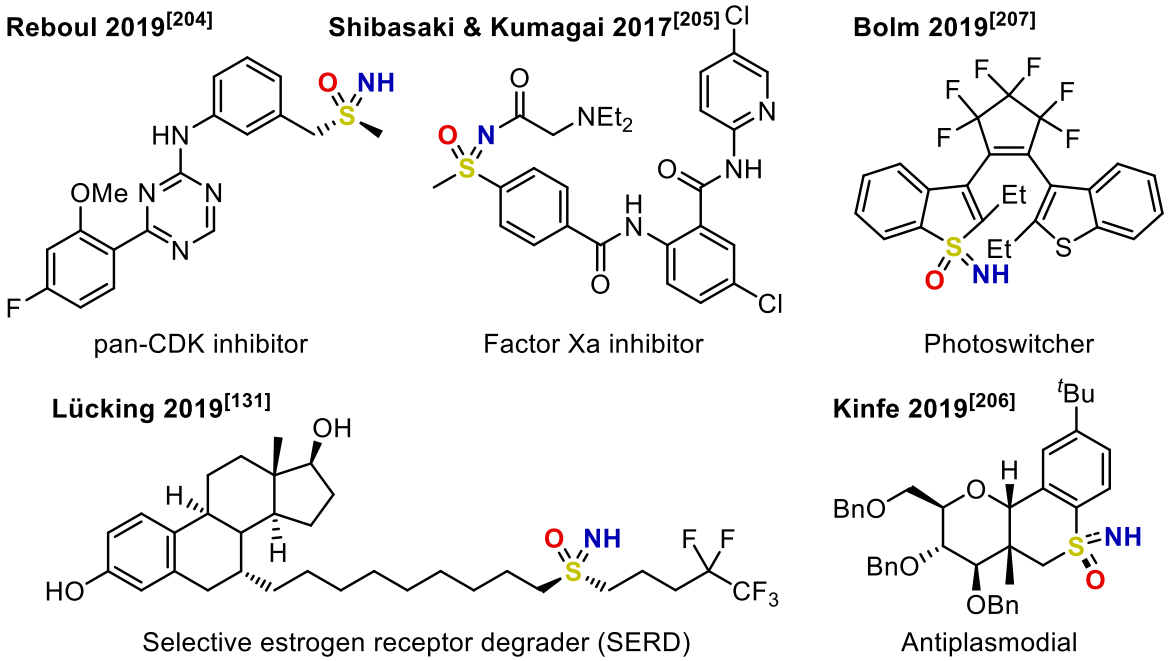


Figure 2.1: Sulfoximines synthesised using Bull & Luisi's NH (and O) transfer protocols.

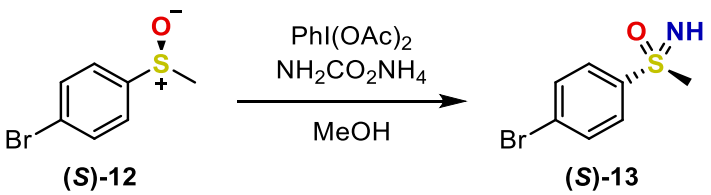
applications. Examples include a range of bioactive molecules published by various research groups including those of Reboul,[204] Shibasaki & Kumagai,[205] Kinfe[206] and Lücking,[131] as well as a dithienylethene-type photoswitcher reported by Bolm and co-workers (Figure 2.1).[207]

2.1.2 Project Aims

The above NH (and O) transfer methodologies have received considerable attention, however, there are no reports of performing either transformation on multigram scales. The scale up of a reaction is an integral part in the manufacture of, for example, new API's where kilograms of materials are typically required. Unfortunately, the scaling up of reactions in batch comes with a myriad of problems such as accurate control of the reaction time, mixing during additions and the possibility of runaway reactions.[208] Therefore, the aim of this work was to develop a protocol for the generation of sulfoximines from sulfoxides on multigram scales.

Whilst the one-pot NH and O transfer to sulfides[166] is a highly convenient method for the preparation of sulfoximines, to date there are no enantioselective variants of this transformation, affording only racemic mixtures. Therefore, due to the high array of enantioselective methods available for the oxidation of sulfides[209] and considering the NH transfer to sulfoxides proceeds stereospecifically with retention of stereochemistry[164] it was envisaged that this methodology could be one pragmatic way of synthesising enantioenriched sulfoximines on scale.

The model substrate for the optimisation of the gram scale synthesis of sulfoximines was chosen as sulfoxide **(*S*)-12**. The aryl-alkyl system is a frequently seen combination (Figure 1.6), with the aryl bromide functionality offering an extra handle for diversification in, for example, cross-coupling reactions. In addition to this, the mildly electron withdrawing nature of the *p*-Br substituent[210] makes it a slightly more challenging system to optimise for. It was also noted that the multigram synthesis of **(*S*)-12** had already been reported by Jackson and co-workers in 2009 based on their initial conditions found in 2005.[211,212] The target therefore became the gram scale synthesis of sulfoximine **(*S*)-13** from sulfoxide **(*S*)-12** (Scheme 2.2).



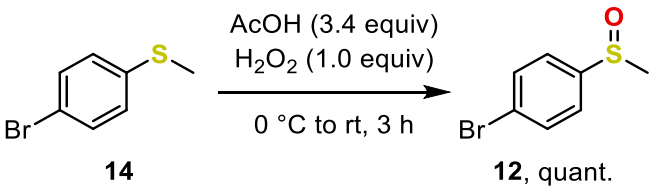
(*S*)-12 **(*S*)-13**

Scheme 2.2: The intended multigram synthesis of targeted sulfoximine **(*S*)-13**.

2.1.3 Reaction Optimisation

*2.1.3.1 Racemic Synthesis of Sulfoxide **12***

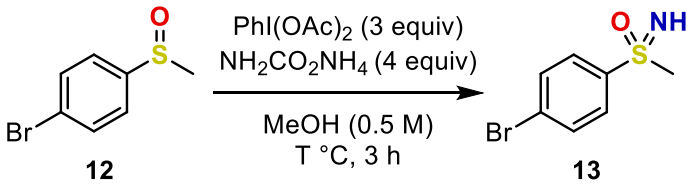
Optimisation of the multigram synthesis of **(*S*)-13** was carried out on the less synthetically valuable racemic starting material **12**. Sulfoxide **12** could be easily prepared from the commercially available sulfide **14** via a hydrogen peroxide mediated oxidation adapted from conditions published by Golchoubian and co-workers (Scheme 2.3).[213]



Scheme 2.3: Synthesis of 16.5 g of sulfoxide **12**. Reaction(s) on a 75 mmol scale.

2.1.3.2 Order of Addition of Reagents

With a route affording multigrams of starting material **12**, attention turned to the optimisation of the NH transfer to afford sulfoximine **13**. In-keeping with the original publication, the equivalents of reagents was kept the same but ascertaining the best order of addition for this on a larger scale was the first priority. The order of addition was analysed in the original paper and it was found that adding the solvent last afforded marginally higher yields of the sulfoximine than adding either the oxidant or ammonia source last, with yields being substantially lower when adding the sulfoxide last.[164] However, adding solvent last on large scales is unfavourable due to the lack of control over the reaction and the possibility of thermal runaways. Therefore, the decision was made to add the solvent into the reaction vessel first, followed by the starting material. Evaluation of which order to add the bis(acetoxy)iodobenzene



Entry	Final Reagent Added	T (ºC)	Conversion (%) [a]
1	$PhI(OAc)_2$	25	98
2	$NH_2CO_2NH_4$	25	98
3	$NH_2CO_2NH_4$	0 to 25	98

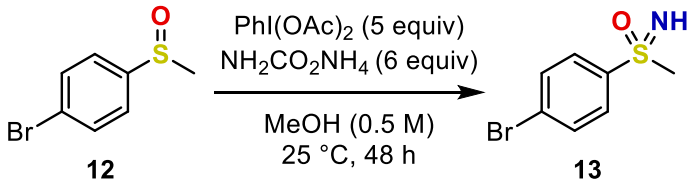
Table 2.1: Order of addition tests for the synthesis of sulfoximine **13**. Reactions on 10 mmol scale.
[a] Conversion determined by the ratio of **12**:**13** by ^{1}H NMR spectroscopy.

or ammonium carbamate was then carried out (Table 2.1). In both cases the ratio between the sulfoxide and sulfoximine product was 1:50 and so with the order of addition having seemingly no effect on the reaction profile, the reagents could be added by what was deemed the safest order. The largest safety concern with this reaction is the exotherm generated from decarboxylation of the ammonium carbamate. This decarboxylation event is mediated by the acetic acid which is generated *in situ* from the bis(acetoxy)iodobenzene. With this in mind, it was deemed easier to control the decarboxylation when adding the ammonium carbamate last. In this protocol, the solvent, starting material and bis(acetoxy)iodobenzene could be added as single portions whereas a portion wise addition of the ammonium carbamate allows for as much gas and heat generation as the operator deems safe on the scale the reaction is being carried out on.

To try to slow the decarboxylation, the ammonium carbamate was added last at 0 °C in an ice bath, before being warmed to 25 °C in a water bath. In this case, no decarboxylation was observed at 0 °C, meaning during warming to 25 °C, with all of the ammonium carbamate in solution, an uncontrolled decarboxylation began. Despite this, the product profile remained the same as in previous cases with a very high conversion to the desired sulfoximine **13** observed (Table 2.1, entry 3).

2.1.3.3 Maximising Conversion to the Product

With a procedure in place for the order of addition of the reagents, attention turned to trying to increase the conversion of the staring material to product. If ~100% conversion could be attained, purification of the reaction mixture would be trivial as the only other component of the crude aside from the product and starting material is the iodobenzene generated from the oxidant. In order to try and increase the conversion further, the reaction time was extended to

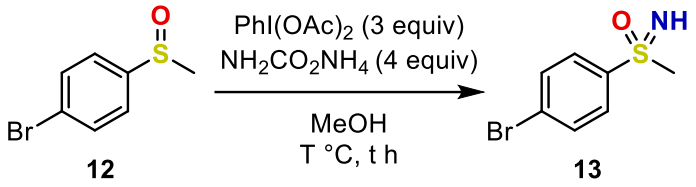


Entry	Total $PhI(OAc)_2$ (equiv)	Total $NH_2CO_2NH_4$ (equiv)	Time (h)	Conversion (%) [a]
1	2.1	2	1	84
2	3	4	24	98
3	5	6	48	98

Table 2.2: Multiple additions of reagents over a 48 h period for the synthesis of sulfoximine **13**. Reactions on 13 mmol scale. [a] Conversion determined by the ratio of **12**:**13** by ^{1}H NMR spectroscopy.

48 h, with further equivalents of reagents added at regular time intervals (Table 2.2). Initially, adding less equivalents of oxidant and ammonia source led to a reduced conversion when compared to the standard equivalents (Table 2.2, entry 1). Adding more reagents to bring the total added in line with the standard equivalents and leaving the reaction for 24 h led to a 98% conversion. With additional time and equivalents making no difference to the conversion of the reaction (Table 2.2, entries 2 & 3).

The final attempt to increase the conversion of the reaction led to the examination of the concentration and temperature of the reaction (Table 2.3). Running at increased or decreased concentrations again led to stalling of the reaction (Table 2.3, entries 1 to 3) and heating the reaction mixture to reflux made no difference to the conversion of the sulfoxide to sulfoximine (Table 2.3, entry 4).



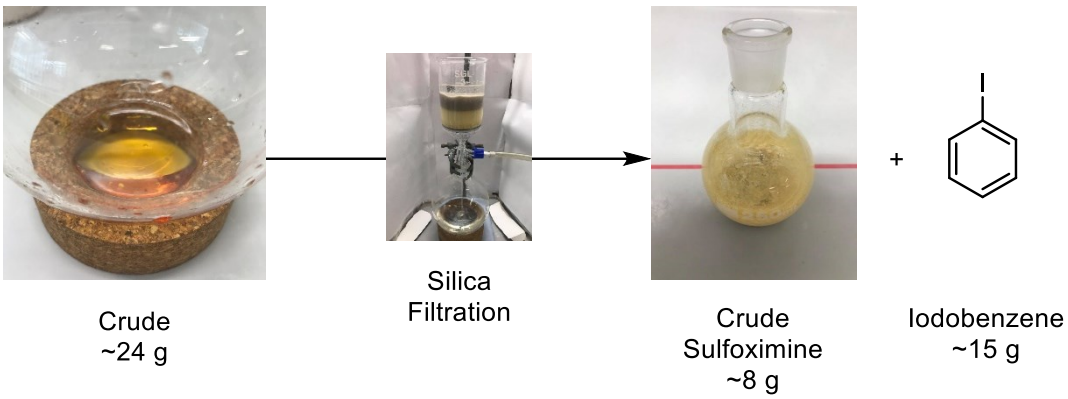
Entry	Concentration (M)	T (°C)	Time (h)	Conversion (%) [a]
1	0.4	25	1	96
2	0.6	25	1	96
3	0.7	25	1	97
4	0.4	70	24	96

Table 2.3: Different solvent concentrations tested for the synthesis of sulfoximine **13**. Reactions on 5 mmol scale. [a] Conversion determined by the ratio of **12**:**13** by ^{1}H NMR spectroscopy.

2.1.3.4 Finding Purification Conditions

With the conversion of the starting material to product seemingly being limited to ~97%, different purification methods then focussed upon accessing the pure sulfoximine **13**. An initial aqueous work up to remove any salts derived from the acetic acid and ammonia in solution afforded a mixture of iodobenzene, sulfoximine **13** and sulfoxide **12** after drying, filtering and concentrating. Attempts at conventional column chromatography purification were successful in isolating the desired sulfoximine **13**, however, due to the similar polarities of the starting material and product, a long stationary phase was required alongside large amounts of solvent. Column chromatography on a large scale is also undesirable and is often avoided where possible, hence, finding alternative methods to purify the crude mixture was a priority. Due to the highly non-polar nature of iodobenzene compared to the sulfoximine/sulfoxide mixture, it was envisaged that it could easily be removed by a silica plug. Loading the crude mixture onto

a ~5 cm bed of silica followed by washing with hexane then ethyl acetate allowed for the removal of iodobenzene in the hexane wash and isolation of the sulfoxide/sulfoximine mixture in the ethyl acetate wash (Scheme 2.3).



Scheme 2.3: Silica filtration to remove iodobenzene from the crude.

With a route toward accessing >95% pure sulfoximine **13**, efforts then turned to removing any residual starting material as the only remaining impurity. The next aim was to measure any solubility differences between sulfoxide **12** and sulfoximine **13** with the hope of finding conditions for recrystallisation. Solvents such as acetone, ethanol, water, heptane and acetonitrile showed either complete dissolution or none at all of the sulfoxide and sulfoximine at the concentrations shown. However, ethyl acetate showed partial solubility of both compounds **12** and **13** at room temperature in five volumes of solvent whilst complete dissolution at reflux indicating this may be a suitable solvent for recrystallisation. Examining

Entry	Solvent	Compound	5 volumes of solvent [a]			10 volumes of solvent [a]		
			22 °C	40 °C	Reflux	22 °C	40 °C	Reflux
1	ethyl acetate	**12**						
2		**13**						
3	20% ethyl acetate in heptane	**12**						
4		**13**						
5	50% ethyl acetate in heptane	**12**						
6		**13**						

Table 2.4: Solubility screen of compounds **12** and **13** in different concentrations of ethyl acetate. Red boxes correspond to no observable dissolution, orange corresponds to partial dissolution and green corresponds to complete dissolution. [a] 1 volume of solvent corresponds to 1 mL per gram of material.

the two-solvent system of heptane and ethyl acetate at different ratios indicated that compounds **12** and **13** had clear and exploitable differences in their solubilities in ethyl acetate/heptane mixtures (Table 2.4). With sulfoxide **12** showing increased solubility in ethyl acetate compared to sulfoximine **13** it was postulated that by recrystallisation in a two-solvent system of ethyl acetate in heptane that the majority of sulfoxide **12** would remain in the filtrate, leaving the pure sulfoximine **13** in the precipitate.

The next aim was to find the best ratio of ethyl acetate and heptane for the recrystallisation solvent (Table 2.5). In general, high purity of product (as determined by the ratio of the starting material to product) could be obtained to the detriment of the mass recovery of the precipitate and therefore yield of the reaction. It was found that 60% ethyl acetate in heptane offered the best compromise between high purity and high mass recovery (Table 2.5, entry 3).

Entry	Ethyl acetate in heptane	Mass recovery (%)		Purity (%) [a]	
		Precipitate	Filtrate	Precipitate	Filtrate
1	40%	70	24	99.9	91
2	50%	88	6	99.4	71
3	60%	92	4	99.0	56
4	70%	82	16	99.7	83

Table 2.5: Recrystallisation of 500 mg of 98.2% pure sulfoximine **13** in various solvent systems and the corresponding mass recoveries and purities of the precipitate and filtrate. In all cases the minimum amount of solvent was added until complete dissolution of the solid at 85 °C the solution was then allowed to cool to room temperature over 2 h before being left for a further 16 h. *a* Purity determined by the ratio of **12**:**13** by ^{1}H NMR spectroscopy.

With 60% ethyl acetate in heptane taken as the optimum solvent system for recrystallisation, the next objective was ascertaining the exact quantity of solvent required in order to obtain sulfoximine **13** in high yields and purity from 5.5 g of mixed material (Table 2.6). Unfortunately, on this scale it was found that upon adding ethyl acetate the solvent would induce melting of the solid and form one miscible layer. This behaviour made it very difficult to determine accurately how much solvent would be needed to perform an effective recrystallisation. Using two different volumes of 60% ethyl acetate in heptane, followed by the addition of heptane until the mixture became turbid led to two very similar mass recoveries in the precipitate and filtrate (Table 2.6, entries 1 & 2). In both cases, the precipitate from the recrystallisation had very similar purities to the starting material and significant mass was lost in the filtrate. A final attempt at recrystallisation was made with 35% ethyl acetate in heptane in case a reduced

Entry	Ethyl acetate in heptane	Mass recovery (%)		Solvent volume (mL)	
		Precipitate	Filtrate	Ethyl acetate in heptane	Heptane
1	60%	82	15	11	3
2	60%	83	13	7.5	2
3	35%	77	20	30	0

Table 2.6: Recrystallisation of 5.5 g of 97% pure sulfoximine **13** in various solvent systems and the corresponding mass recoveries and volume of solvent used. In all cases the minimum amount of solvent was added until complete dissolution of the solid at 85 °C, followed by heptane (if applicable) until turbid, then heating to 90 °C to make the solution clear, before being cooled to room temperature over 2 h then being left for a further 16 h.

polarity would have a more favourable outcome, however, the mass recovery was even lower in this case (Table 2.6, entry 3). With recrystallisation proving to be an ineffective method for purification of sulfoximine **13**, the differences in solubility of the sulfoxide **12** and sulfoximine **13** were sought to be exploited through a trituration process. Knowing that sulfoxide **12** has increased solubility in ethyl acetate compared to sulfoximine **13** (Table 2.4), it was postulated that by adding dilute ethyl acetate in heptane to the mixture that the solvent would selectively dissolve the starting material over the product leaving the purified product after filtration. Pleasingly, this was the case, with the initial test with 10 volumes of 20% ethyl acetate in heptane increasing the purity of the sulfoximine **13**. However, a significant amount of mass was still being lost in the filtrate and the purity of the filtrate was reasonably high with respect to the sulfoximine **13**. Reducing the polarity of the solvent to 10% ethyl acetate in heptane led to improved mass recovery and purity of the sulfoximine **13** in the precipitate, which was increased further by reducing the solvent polarity to 5% ethyl acetate in heptane (Table 2.7).

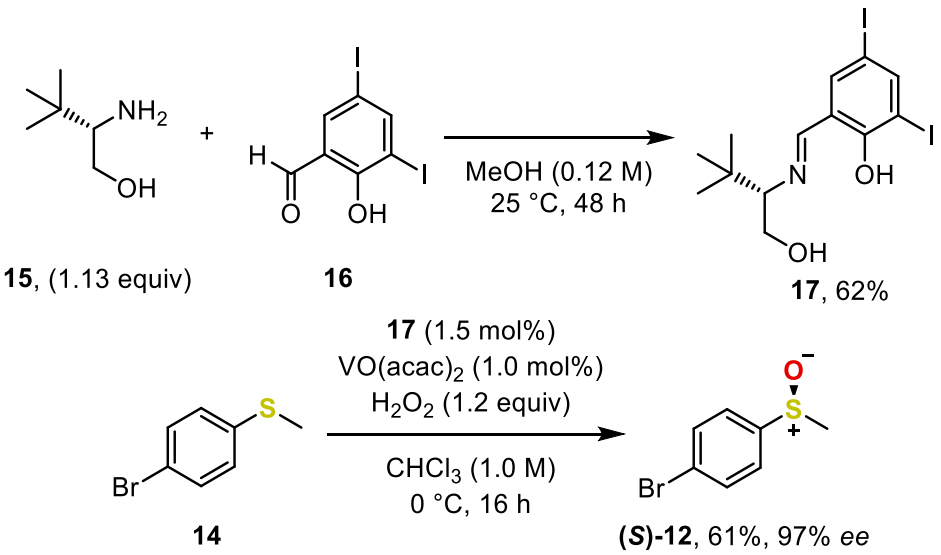
Entry	Ethyl acetate in heptane	Mass recovery (%)		Purity (%) [a]	
		Precipitate	Filtrate	Precipitate	Filtrate
1	20%	85	13	96.8	81
2	10%	89	9	97.9	71
3	5%	91	7	97.8	64

Table 2.7: Trituration of 2.5 g of 95.5% pure sulfoximine **13**, in various solvent systems and the corresponding mass recoveries and purities of the precipitate and filtrate. Trituration carried out by stirring at 500 rpm for 20 minutes, followed by filtration and collection of the precipitate. In all cases 10 volumes of solvent was used corresponding to 10 mL per gram of material. [a] Purity determined by the ratio of **12**:**13** by ^{1}H NMR spectroscopy.

2.1.4 Enantioenriched Procedure

*2.1.4.1 Accessing Sulfoxide **(S)-12***

Having established a method for the purification of sulfoximine **13** via trituration, Attention turned toward accessing the enantioenriched sulfoxide starting material **(*S*)-12** to exemplify this methodology for the preparation of enantioenriched sulfoximine **(*S*)-13**. To access sulfoxide **(*S*)-12** the *Organic Syntheses* procedure from Jackson and co-workers was followed based on their initial study on the vanadium catalysed oxidation of alkyl-aryl sulfides.[211,212] Initially, the synthesis of chiral Schiff base **17** was carried out via imine formation of a commercially available amine **15** and aldehyde **16** to generate the required ligand in good yield (Scheme 2.4). In order to generate enough of the sulfoxide **(*S*)-12** for these studies, the reaction from the *Organic Syntheses* procedure was carried out twice. However, to ensure a uniform *ee* across the two batches, they were combined before the final purification step. After recrystallisation, 16.1 g of sulfoxide **(*S*)-12** was accessed in 97% *ee* and 61% yield (Scheme 2.4).

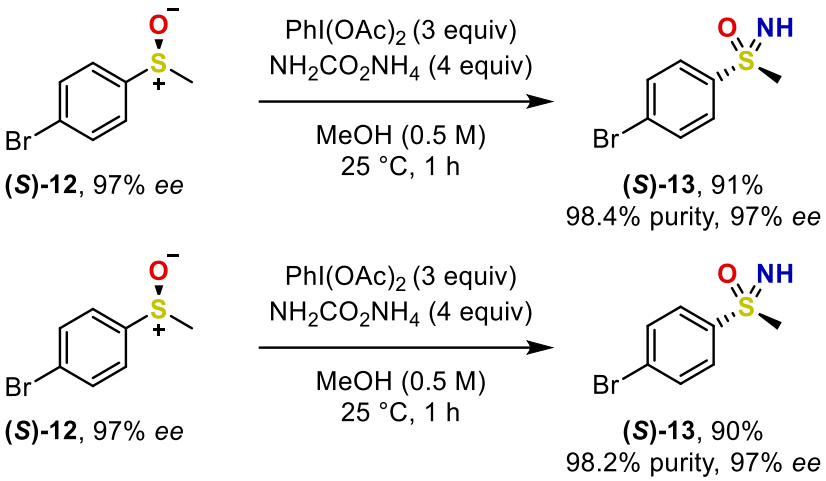


Scheme 2.4: The synthesis of chiral ligand **17** and its use in the enantioselective oxidation of sulfide **14** for the preparation of sulfoxide **(*S*)-12**. Synthesis of **17** on a 2.7 mmol scale. Synthesis of **(*S*)-12** on a 60 mmol scale, repeated and the batches combined before recrystallisation to give 16.1 g of **(*S*)-12**.

*2.1.4.2 Accessing Sulfoximine **(S)-13***

After developing a procedure for the synthesis of sulfoximine **13**, it was applied to its enantioenriched derivative **(*S*)-13**. The reaction was run twice to ensure the repeatability of the procedure and performed on a 35 mmol scale which corresponds to ~8 g of sulfoxide **(*S*)-12**. A highly detailed procedure was documented for the synthesis of **(*S*)-13** which can be read in section 4.2.1. By following this procedure which includes the addition of ammonium carbamate last, a silica filtration to remove the iodobenzene and a trituration to remove any remaining

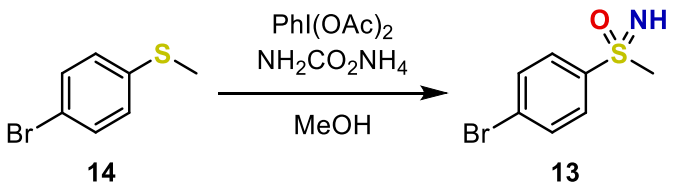
starting material, 7.44 g of enantioenriched sulfoximine **(*S*)-13** could be accessed with complete retention of *ee* in a 91% yield and a purity of 98.4%. A repeat of this reaction afforded 7.35 g of **(*S*)-13** with complete retention of *ee* in a 90% yield and a purity of 98.2% (Scheme 2.5).



Scheme 2.5: Development of a procedure for the multigram synthesis of enantioenriched sulfoximine **(*S*)-13** via NH transfer to sulfoxide **(*S*)-12**. Synthesis of **(*S*)-13** on a 35 mmol scale. Purity calculated by ^{1}H NMR spectroscopy with respect to 1,3,5-trimethoxybenzene as an internal standard.

2.1.5 Conclusions

A method for the preparation of enantioenriched sulfoximine **(*S*)-13** based upon Bull, Luisi and co-workers initial report on the NH transfer to sulfoxides has been developed.[164] In this work, a procedure has been established for carrying out this reaction to form multigrams of material, which is becoming increasingly important.[125] Whilst the trituration step in the procedure is likely substrate specific, other aspects of the procedure, including the order of addition studies and silica plug filtration is broadly applicable. Future work includes extending this methodology to encompass the NH and O transfer to sulfides to allow for the preparation of multi-grams of racemic sulfoximines, based upon Bull, Luisi and co-workers initial work (Scheme 2.6).[166]



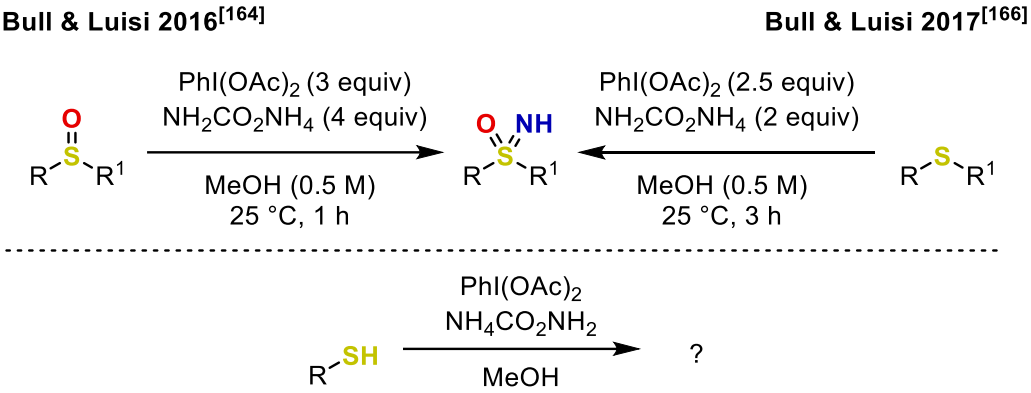
Scheme 2.6: Future work toward the multigram synthesis of sulfoximine **13** from sulfide **14**.

2.2 Synthesis of Sulfonimidates and Primary Sulfonamides from Thiols

A concise account of the work presented here has been published in *Organic Letters*.[214]

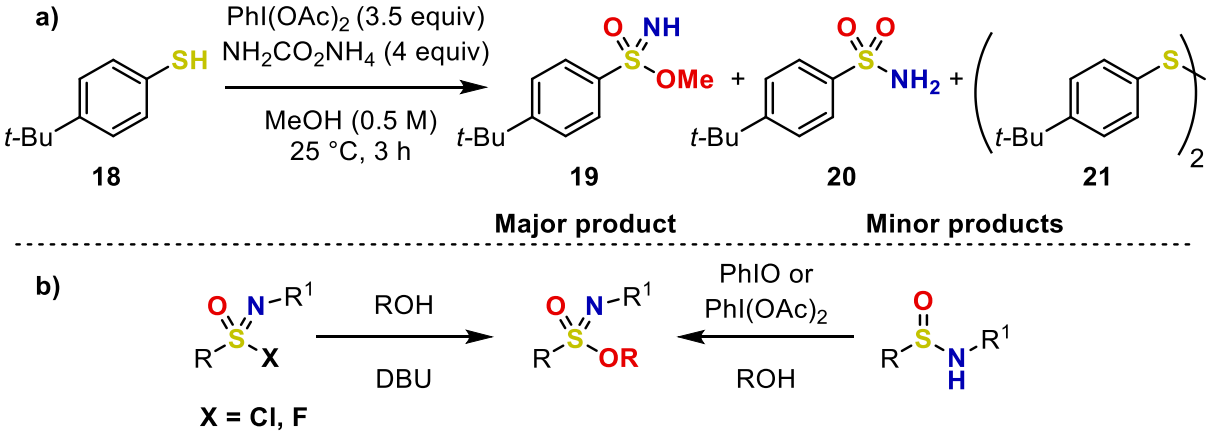
2.2.1 Optimisation of the NH and O Transfer to Thiols

The Bull and Luisi groups prior work on the on the NH (and O) transfer to sulfoxides and sulfides to synthesise sulfoximines inspired the examination of thiols under analogous conditions (Scheme 2.7). The majority of the following work (section 2.2.1) on the optimisation of this reaction was carried out by Dr Sahra St John-Campbell, Michelle Afonso and Gala Ogalla Estévez.



Scheme 2.7: Thiols as previously unexplored substrates under NH and O transfer conditions.

Initially, thiol **18** was subjected to preliminary NH and O transfer conditions using 3.5 equivalents of bis(acetoxy)iodobenzene and 4 equivalents of ammonium carbamate in methanol at room temperature. This afforded sulfonimidate **19** as the major product, alongside sulfonamide **20** and disulfide **21** (Scheme 2.8a). Optimising this transformation to be able to form sulfonimidates from thiols in high yield was a key objective as this functional group is traditionally made from sulfonimidoyl halides[172,176,215] or sulfinamides[178,216,217] which can

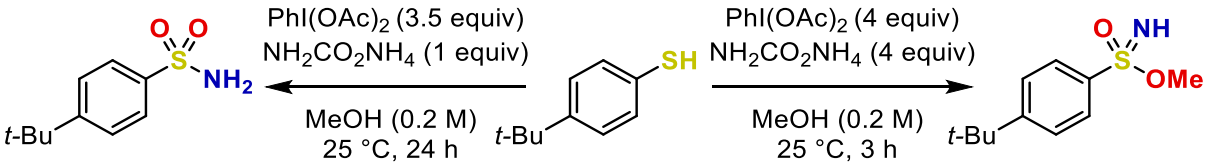


Scheme 2.8: Initial product distribution from the NH and O transfer to thiols and traditional methods to synthesise sulfonimidates from sulfonimidoyl halides or sulfinamides.

require multiple synthetic steps to access (Scheme 2.8b). Sulfonimidates are useful building blocks to form sulfoximines and sulfonimidamides through their reactivity at the sulfur centre by displacement of the alkoxide as discussed previously in section 1.3.1.3. They are also used in material science for their ability to self-polymerise at elevated temperatures[218,219] and due to the readily functionalised stereogenic sulfur centre, sulfonimidates can also act as chiral templates for asymmetric synthesis.[180]

To try and increase the yield of the desired sulfonimidate **19** different reagent equivalents, order of additions and reaction temperatures and times were all tested. Increasing the equivalents of bis(acetoxy)iodobenzene from 3.5 to 4 removed any remaining disulfide and gave the best yield of **19**. However, preventing the formation of sulfonamide **20** proved difficult and under all the conditions tested, it was always formed in small amounts. In addition, purification via silica flash chromatography failed to afford sulfonimidate **19** due to coelution with sulfonamide **20**. Due to concerns about the stability of sulfonimidate **19** on silica and to try and improve its separation, a variety of stationary phases were examined.[220] Fortunately, sulfonamide **20** was retained on neutral alumina and column chromatography using this stationary phase allowed for the isolation of clean sulfonimidate **19** in 65% yield (Scheme 2.9).

Sulfonamides are currently the most prevalent sulfur containing functional group in approved drugs.[221] As synthetic methods to synthesise primary sulfonamides from thiols are limited.[222–224] it was deemed important to find a separate set of NH and O transfer conditions to favour the formation of the sulfonamide. Pleasingly, it was identified that when decreasing the equivalents of ammonium carbamate from 4 to 1, sulfonamide **20** was formed as the major product. Furthermore, extending the reaction time from 3 h to 24 h allowed for the isolation of sulfonamide **20** in 80% yield after silica chromatography (Scheme 2.9).



20, 80% **18** **19**, 65%

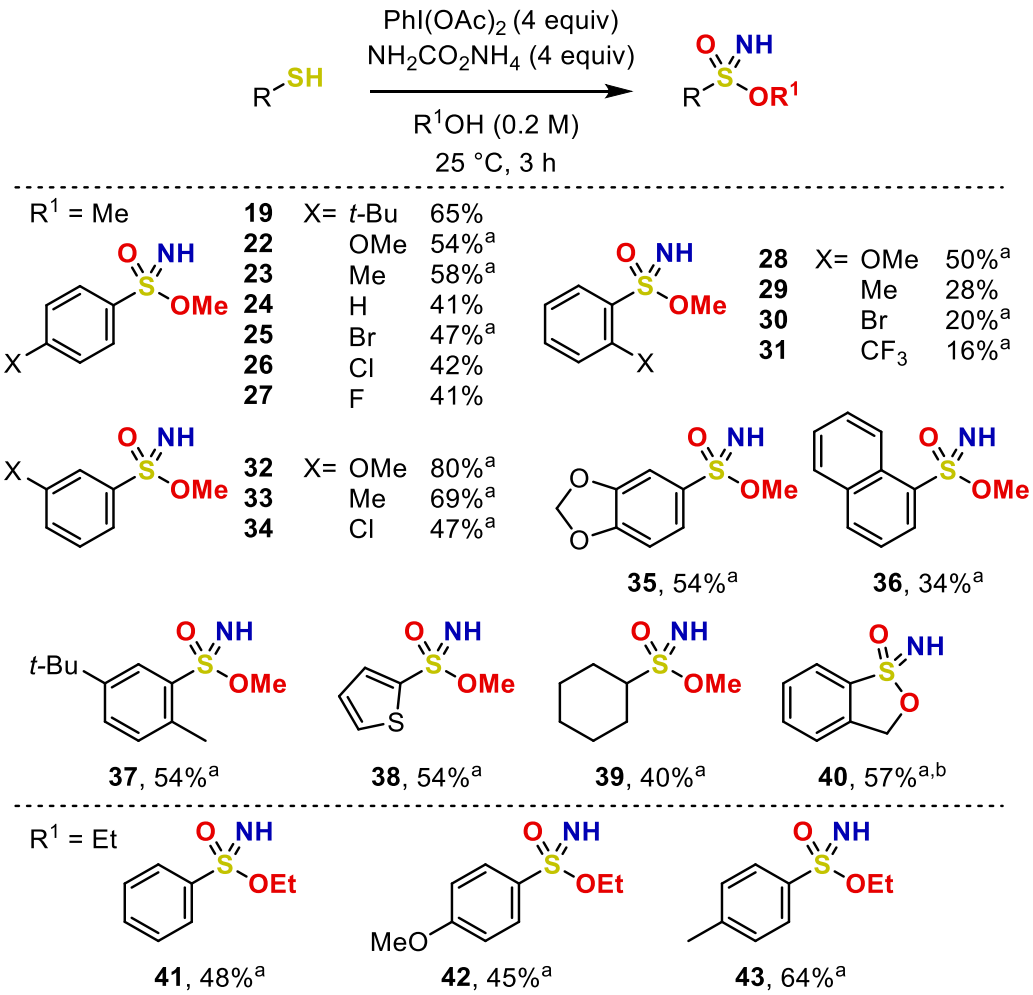
Scheme 2.9: Optimised conditions for the NH and O transfer to thiol **18** to selectively synthesise either sulfonimidate **19** or sulfonamide **20**. Optimisation first examined by Michelle Afonso and then finalised by Gala Ogalla Estévez.

2.2.2 Scope of the NH and O Transfer to Thiols

With complimentary conditions to selectively synthesise either sulfonamides or sulfonimidates from thiols in hand, the scope of these transformations was explored to identify which functionalities can be tolerated under the reaction conditions.

2.2.2.1 Sulfonimidate Scope

Sulfonimidates were first examined, which could be synthesised directly from a number of commercially available thiols (Scheme 2.10). A variety of electron donating and electron withdrawing substituents in the *para*-position of the phenyl ring were successful **19**, **22-27**, with electron donating substituents generally affording the sulfonimidate in a higher yield. This effect is more pronounced in the *ortho*-substituted examples **28-31** but the yields are somewhat reduced due to the increased steric bulk around the sulfur atom. Comparatively higher yields are obtained for the *meta*-substituted examples **32-34**. Multi-substituted thiols also afforded the desired sulfonimidate **35-37**. The methodology could also be applied to thiophene containing example **38**, and cyclohexane thiol **39**. Interestingly, 2-mercaptobenzyl-alcohol afforded cyclic sulfonimidate **40** with intramolecular ring closure being preferred over intermolecular attack from the solvent. Switching the reaction solvent to ethanol afforded the corresponding ethyl sulfonimidates **41-43**, offering a simple method to vary the R^1 group on

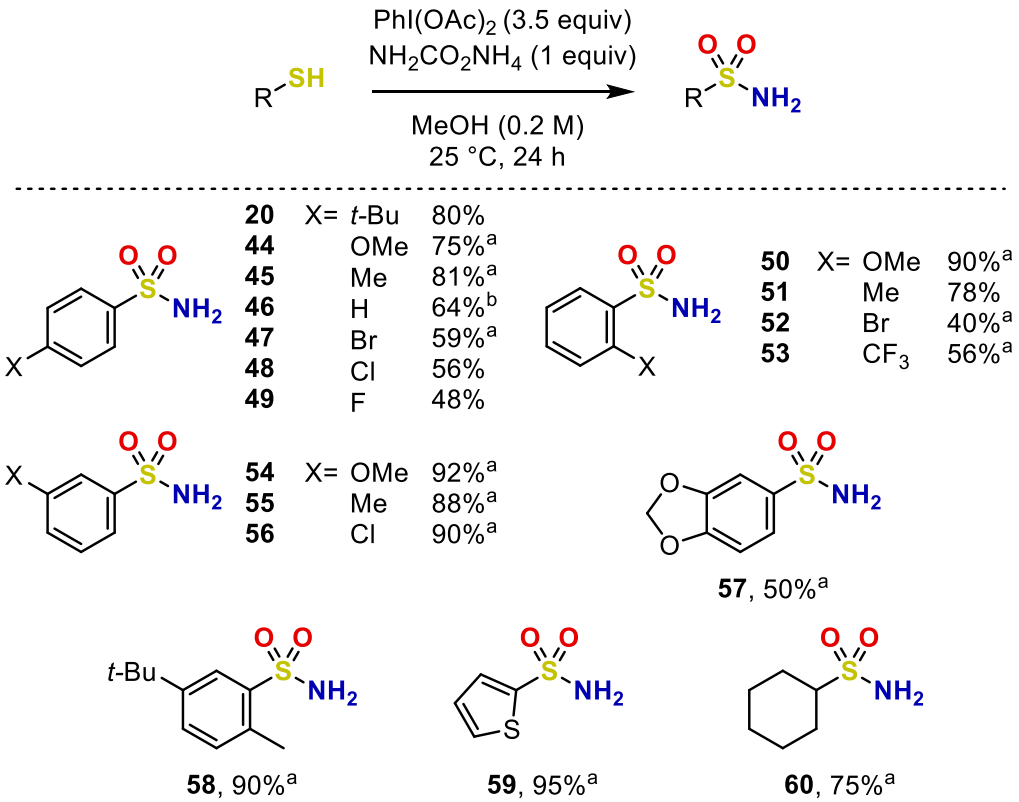


Scheme 2.10: Scope of the sulfonimidate synthesis varying the R group and using different alcohol solvents to vary the R^1 group. Reactions conducted on a 0.5 mmol scale. [a] Reactions performed by Dr Arianna Tota or Dr Sahra St John-Campbell. [b] Reaction conducted on a 2.5 mmol scale.

the sulfonimidate. This methodology allowed access to a variety of NH-sulfonimidates from typically commercially available starting materials and avoids the multi-step preparation of sulfonimidoyl halides and sulfinamides.

2.2.2.2 Sulfonamide Scope

A similar set of thiols were used to investigate the scope of sulfonamide synthesis from thiols (Scheme 2.11). Compared to the sulfonimidate scope, higher yields were obtained across the board for the highly selective sulfonamide formation. This is likely due to sulfonamide being formed as a minor product under the sulfonimidate conditions, which is then removed through a neutral alumina column. As in the case of sulfonimidate synthesis, the yields of the sulfonamide products were dependant on the electronics of the system, with more electron rich thiols affording generally higher yields of the sulfonamide. As well as *ortho*, *meta* and *para*-substituted aromatics, polysubstituted examples, a thiophene and alkyl system all afforded the corresponding sulfonamides in good to excellent yields.

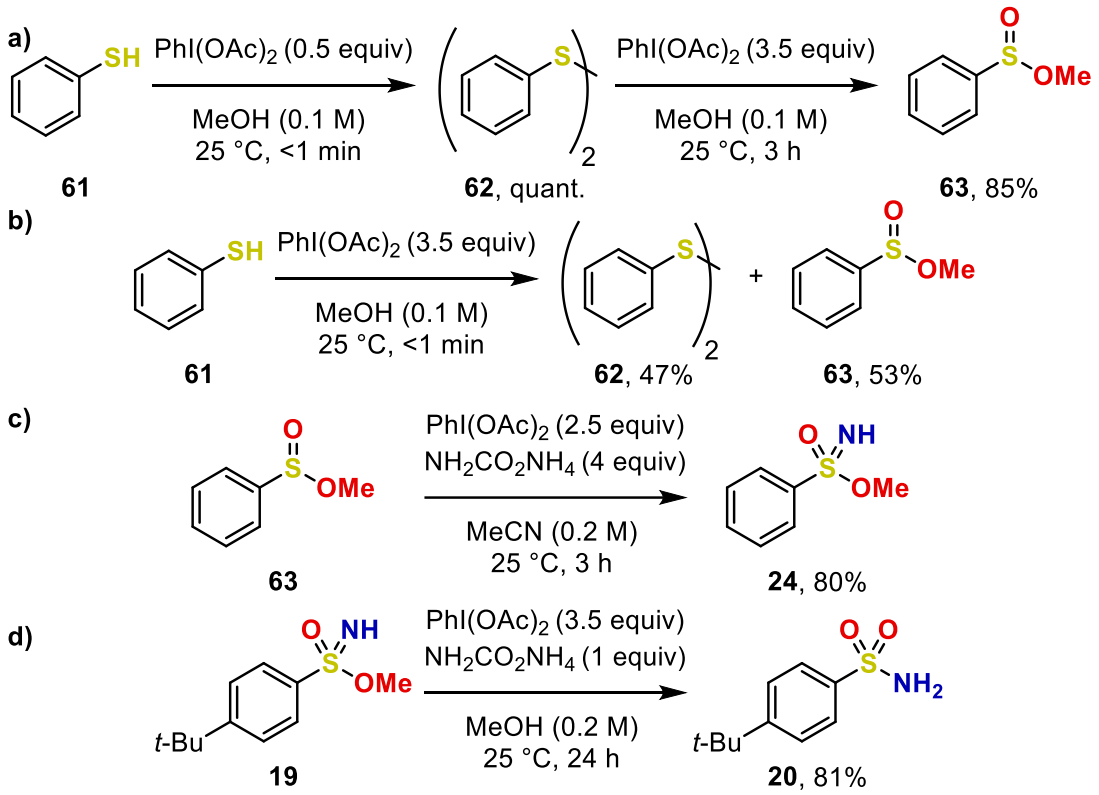


Scheme 2.11: Scope of the sulfonamide synthesis varying the R group. Reactions conducted on a 0.5 mmol scale. [a] Reactions performed by Dr Arianna Tota or Dr Sahra St John-Campbell. [b] Reaction conducted on a 1.0 mmol scale.

2.2.3 Order of Events in the NH and O Transfer to Thiols

2.2.3.1 Control Reactions

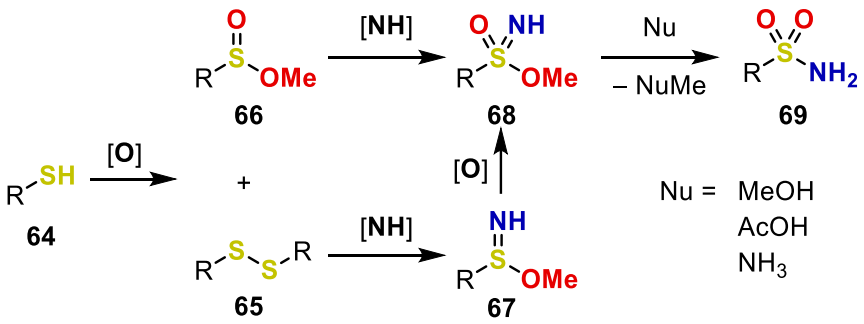
To provide insight into the reaction mechanism and to ascertain the order of events, a series of control experiments were carried out. The majority of the following work (section 2.2.3) on the control reactions was carried out by Dr Arianna Tota. It has previously been shown that thiols can be oxidised to the corresponding disulfides upon treatment of bis(acetoxy)iodobenzene in alcohol solvents.[225] This was also found to be the case in this study, affording a quantitative amount of disulfide with just 0.5 equiv of bis(acetoxy)iodobenzene in under a minute (Scheme 2.12a). When taking the same disulfide **62** and treating it with further bis(acetoxy)iodobenzene in methanol, the sulfinate ester **63** was formed in high yield (Scheme 2.12a). Treatment of thiol **61** with 3.5 equivalents of oxidant directly afforded an equal mixture of disulfide and sulfinate ester after a minute (Scheme 2.12b). Sulfonimidate **24** could be formed in high yield from sulfinate ester **63** in acetonitrile, suggesting one possible route toward sulfonimidates (Scheme 2.12c). Sulfonimidate **19** was shown to be an immediate precursor to sulfonamide **20** under the reaction conditions (Scheme 2.12d), corroborating proposals from Maricich and co-workers on the ability of sulfonimidates to act as alkylating agents, forming sulfonamides.[226]



Scheme 2.12: Control reactions for the NH and O transfer to thiols, giving insight into the reaction sequence. Reactions conducted on a 0.5 mmol scale. Reactions a-c performed by Dr Arianna Tota.

2.2.3.2 Reaction Sequence

Due to the very rapid formation of disulfides and sulfinate esters from thiols in the presence of 3.5 equivalents of oxidant, it is likely this is the first step in the reaction sequence. NH transfer to the sulfinate ester **66** likely constitutes a major pathway to the sulfonimidate, which can then convert to the sulfonamide **69** under more acidic conditions and extended reaction times through attack of a nucleophile. GCMS analysis could not detect any other intermediates, aside from a putatively assigned sulfinimidate species deriving from cyclohexane thiol. Although at the time there had been only sporadic reports of sulfinimidates in the literature, recent methodology from Luisi and co-workers have shown they are stable compounds and can be accessed from sulfenamides.[227] Therefore, an alternative pathway from the disulfide could also be operating in tandem, with NH transfer to the disulfide forming a sulfinimidate **67**, which could then be further oxidised to the sulfonimidate **68** (Scheme 2.13). This mechanistic sequence is corroborated by a recent report from Morandi and co-workers on the NH and O transfer to thiols to form sulfinamides.[228]



Scheme 2.13: Possible reaction sequence to generate sulfonimidates and sulfonamides.

2.2.4 Conclusions

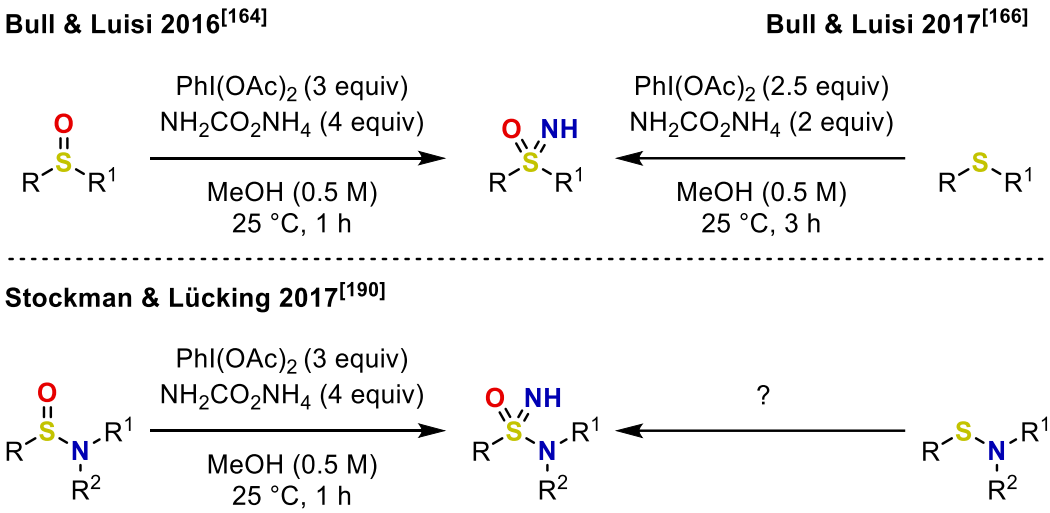
Two NH and O transfer reactions have been developed from thiols, affording either sulfonimidates or sulfonamides in good to high yields using ammonium carbamate as an ammonia source and bis(acetoxy)iodobenzene as the oxidant. Under both sets of conditions, a broad scope was demonstrated for the synthesis of sulfonimidates or sulfonamides. The synthesis of sulfonamides requires comparatively longer reaction times and lower concentrations of ammonia in order to convert the sulfonimidate to the sulfonamide through displacement of the alkyl on the alkoxy group. Preliminary mechanistic work indicates a possible reaction pathway toward sulfonamides from thiols, however, further studies would be needed to elucidate more intermediate species and the mechanistic aspects of the nitrogen and oxygen transfer processes under these conditions.

2.3 Synthesis of Sulfonimidamides from Sulfenamides

A concise account of the work presented here has been published in *Angewandte Chemie*.[229]

2.3.1 Project Aims

Bull, Luisi and co-workers previous work on the synthesis of sulfoximines from both sulfoxides and sulfides has allowed for the convenient, metal-free preparation of sulfoximines.[164,166] In 2017, Stockman, Lücking and co-workers extended this methodology, showing sulfinamides are also suitable precursors for NH transfer, affording sulfonimidamides.[190] This project aimed to explore the potential for sulfenamides to act as suitable substrates for NH and O transfer in order to access sulfonimidamides (Scheme 2.14).



Scheme 2.14: NH and O transfer methodologies to sulfoximines and sulfonimidamides.

As previously discussed in section 1.3.2, the synthesis of sulfonimidamides has traditionally been carried out through the attack of an amine on a sulfonimidoyl chloride. Alternatives to sulfonimidoyl chlorides have recently been established, including sulfonimidoyl fluorides and sulfonimidates. However, these precursors often require multiple synthetic steps to access and although recent developments from sulfinamides or sulfinylhydroxylamines as a linchpin reagent goes someway to addressing this, these methods have different associated drawbacks. These include the use of highly reactive species which require very low temperatures for their safe handling such as sulfuryl chloride or Grignard reagents. With this in mind, sulfenamides are useful precursors to sulfonimidamides as they are relatively simple to make in one-step from commercially available starting materials. Therefore, developing a simple set of conditions to allow access to sulfonimidamides from sulfenamides, would have considerable value.

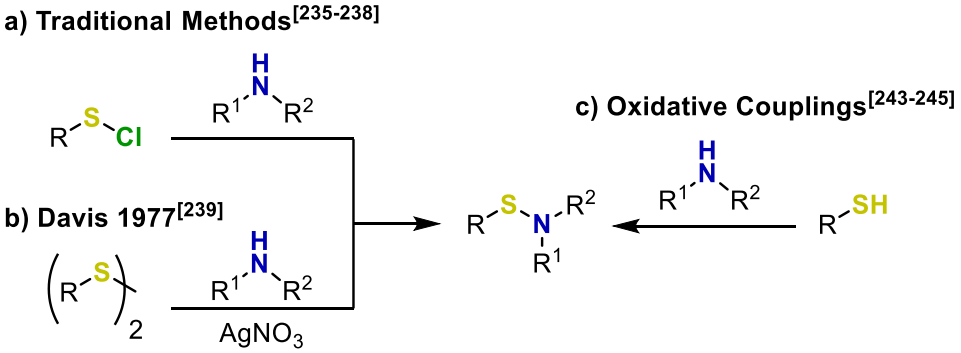
2.3.2 Preparation of Sulfenamides

2.3.2.1 Prior Literature

Sulfenamides have been shown to have interesting biological activity including applications as antifungals and antibiotics due to their high reactivity with cysteine residues.[230–232] They are also essential for the modern rubber industry as vulcanisation agents.[233] Despite this, only limited methods are available for their synthesis.[234]

The first method by which they were prepared was reported by Zincke and co-workers in the early 1900's and is carried out via the reaction of an amine with a sulfenyl chloride[235] and this route continues to be the most popular method for their preparation despite the typically highly unstable nature of the sulfenyl chloride starting materials (Scheme 2.15a).[236] Modern developments have allowed for the *in situ* preparation of sulfenyl chlorides from thiols or disulfides through the use of alternative electrophilic chlorinating agents, such as NCS, to bypass the use of traditional Cl_2 gas.[237,238] An alternative route for the synthesis of sulfenamides, is the reaction of amines and disulfides under silver nitrate mediated conditions (Scheme 2.15b). However, due to the poor atom economy involved this route was not initially pursued.[239]

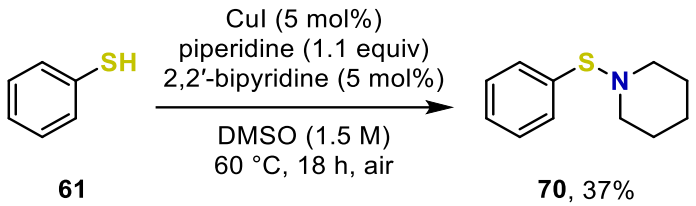
Instead, recent reviews on S–N bond formation reactions highlighted a range of new methodologies which seemed desirable.[240–242] The most attractive of these being the oxidative coupling between thiols and amines. These S–N bond forming methodologies have the promise of being more atom efficient, on top of negating the need for harsh reagents and the isolation of sulfenyl chlorides. Of particular note was Taniguchi's copper catalysed sulfenamide formation by dehydrocoupling of thiols with amines.[243] At the start of this project, this was one of the only general methods to access sulfenamides from thiols and amines, although there have been other, more recent advances (Scheme 2.15c).[225,244,245]



Scheme 2.15: Strategies for sulfenamide synthesis from sulfenyl chlorides, disulfides or thiols.

2.3.2.2 Initial Tests

Taniguchi's coupling of thiols and amines were first examined to prepare sulfenamides (Scheme 2.16).[243] Under these copper-catalysed conditions the corresponding sulfenamide **70** was accessed in 37% yield from thiophenol **61** and piperidine, selected as the model substrates.



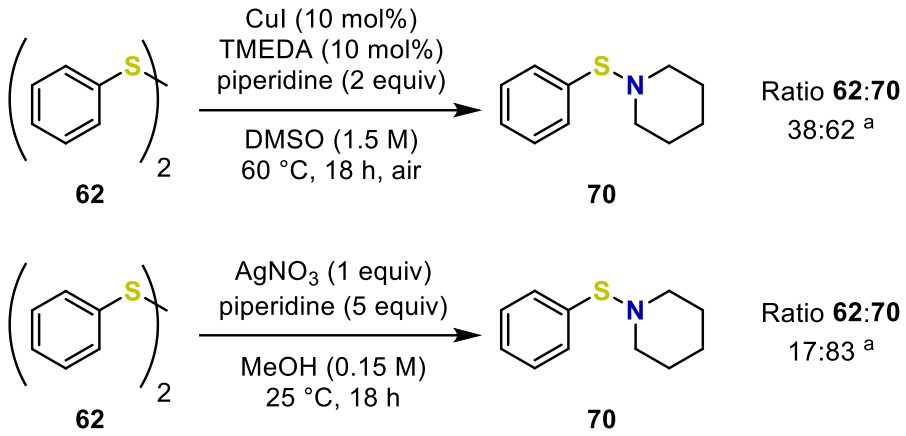
61 **70**, 37%

Scheme 2.16: Synthesis of sulfenamide **70** under copper catalysed conditions. Reaction on a 0.5 mmol scale.

As two purifications via flash column chromatography were required in order to isolate sulfenamide **70** cleanly it is probable the yield could be increased further from 37% as it had been reported that sulfenamides are unstable to silica.[246] Whilst the use of an eluent containing 2% triethylamine was used with the hope of minimising losses, inevitably some of **70** degraded. In order to provide enough material for further testing the reaction was scaled up to a 2.5 mmol scale, however, just a 15% conversion to the product was observed. The remainder of the material obtained in the reaction was diphenyl disulfide **62** derived from oxidation of thiophenol. Therefore, alternative methods were investigated that would be more suitable to larger scale.

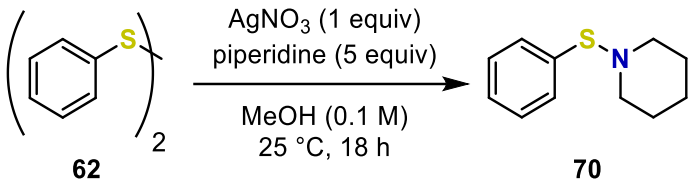
2.3.2.3 Optimisation of Sulfenamide Synthesis

With a lack of alternative methods from thiols and amines, routes from diphenyl disulfide **62** were examined, hoping that by starting at this higher oxidation state sulfenamide formation may be encouraged. In-particular two routes were tested, one from Taniguchi on related copper-catalysed conditions and another being the aforementioned silver nitrate mediated conditions from Davis and co-workers (Scheme 2.17).[239,247] Under these literature conditions, sulfenamide **70** was the major product in both cases when analysing the crude reaction mixture. However, the conditions from Davis and co-workers afforded the highest conversion to sulfenamide **70** and so further examination was carried out to see if full conversion to sulfenamide could be encouraged (Table 2.8).



Scheme 2.17: Synthesis of sulfenamide **70** under literature conditions.[239,247] Reactions on a 2.5 mmol scale. [a] Ratio of the crude determined by ^{1}H NMR spectroscopy after an aqueous work up.

Reducing the reaction scale to 0.2 mmol resulted in the ratio between the disulfide **62** and sulfenamide **70** in the crude reaction mixture to reach almost 50:50 (Table 2.8, entry 1). Since the initial reaction was carried out in a flask open to the air, tests were carried out to determine whether performing the reaction under an inert atmosphere or in a flame dried flask would make a difference to conversion of the reaction (Table 2.8, entries 2 & 3). Knowing that light can induce silver oxide formation, a reaction was also performed in the dark in the hope it would increase the conversion of the reaction (Table 2.8, entry 4). In all these cases, there

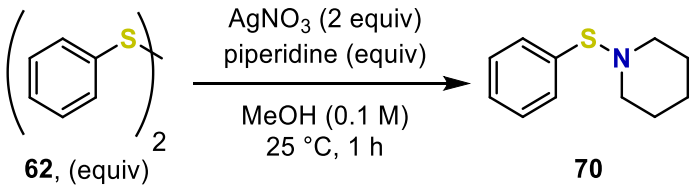


Entry	Variable	Ratio (%) [a]	
		62	**70**
1	-	51	49
2	Ar atm	54	46
3	Ar atm & flame dried flask	54	46
4	No light	53	47
5	1.2 equiv of $AgNO_3$	23	77
6 [b]	2.0 equiv of $AgNO_3$	0	100

Table 2.8: Changes to the standard reaction conditions and their effect on the ratio between **62** and **70** after an aqueous work up. Reactions on a 0.2 mmol scale. [a] Ratio of the crude determined by ^{1}H NMR spectroscopy. [b] Reaction time = 1 h.

was no significant effect on the ratio between the disulfide **62** and sulfenamide **70** (Table 2.8, entries 2 to 4). Pleasingly, increasing the equivalents of silver nitrate in the reaction caused the reaction conversion to rise dramatically after first increasing it to 1.2 equivalents, then 2 equivalents (Table 2.8, entries 5 & 6). In addition, 100% conversion was observed after just an hour with 2 equivalents of silver nitrate, shortening the rection time considerably.

With the reaction now at full conversion, the next objective was to explore how the equivalents of amine and disulfide may lead to a change in product distribution. Initial exploration was carried out by fixing the equivalents of the disulfide at 1 and observing how the yield changes with respect to decreasing the equivalents of amine (Table 2.9). Since 5 equivalents seemed like an excessive amount and would be wasteful, especially if a bespoke amine is used on larger scales, this was reduced to 3 equivalents of amine and this afforded the corresponding sulfenamide **70** in an 88% yield (Table 2.9, entry 1). Reducing the equivalents further to 1 predictably reduced the yield of the sulfenamide **70** (Table 2.9, entries 2 to 4). Using an excess of disulfide with respect to the amine, which would be useful for situations where the amine was the more valuable component, the yield for sulfenamide **70** stayed constant ~25% even when using 3 equivalents of disulfide (Table 2.9, entries 5 to 7).

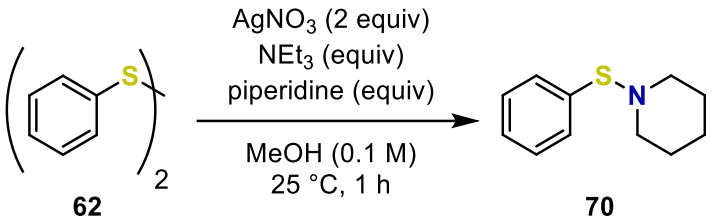


62, (equiv) **70**

Entry	Disulfide **62** (equiv)	Piperidine (equiv)	Yield [a]	
			62	**70**
1	1	3	88%	0%
2	1	2	80%	4%
3	1	1.33	64%	31%
4	1	1	31%	-
5	1.33	1	26%	-
6	2	1	19%	-
7	3	1	25%	-

Table 2.9: Changes to the equivalents of the disulfide **62** and piperidine and their effect on the NMR yield of **70** after an aqueous work up. Reactions on a 0.2 mmol scale. [a] Yields calculated by ^{1}H NMR spectroscopy with respect to 1,3,5-trimethoxybenzene as an internal standard.

Further studies on the sulfenamide formation of model substrate **70** was carried out later when revisiting this transformation for the synthesis of vinyl sulfonimidamides in section 2.4. It was postulated that the yield of the reaction was so dependent on the amine equivalents due to the nitric acid that is formed *in situ* which can presumably degrade the sulfenamide products. This explains why an excess of amine is required to achieve good yields. Instead of the excess amine being used as sacrificial base, triethylamine was added in equimolar amounts to the silver nitrate (Table 2.10). The yield for sulfenamide **70** was dramatically increased with the addition of triethylamine when the amine and disulfide are used in close to equimolar amounts (Table 2.10, entry 1 and 2). In fact, using triethylamine allowed for the disulfide to be used in excess very effectively, which is useful for particularly precious amines (Table 2.10, entry 3).

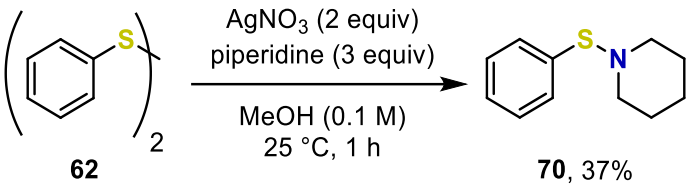


62 **70**

Entry	Disulfide **62** (equiv)	Piperidine (equiv)	Yield [a]	
			70	**70** [b]
1	1	1.33	64%	77%
2	1	1	31%	65%
3	1.33	1	26%	91%

Table 2.10: Changes to the equivalents of the disulfide **62** and piperidine and their effect on the NMR yield of **70** after an aqueous work up. Reactions on a 0.2 mmol scale. [a] Yields calculated by ^{1}H NMR spectroscopy with respect to 1,3,5-trimethoxybenzene as an internal standard. [b] 2 equiv of NEt_3 added to the reaction mixture.

With three equivalents of amine affording the highest NMR yields of sulfenamide **70** in the initial study, the next objective was to test the current purification protocol to access the pure sulfenamide by obtaining an isolated yield. The work-up procedure includes an initial filtration, in order to remove any insoluble silver mercaptide, followed by removal of methanol *in vacuo* and an aqueous work up, extracting with diethyl ether (×3). After drying using Na_2SO_4, filtering and removing any solvent, further purification was carried out via conventional flash column chromatography using a silica stationary phase. By following this route, isolation of the sulfenamide in a 37% yield on a 2.5 mmol scale could be achieved (Scheme 2.18).



62 **70**, 37%

Scheme 2.18: Isolation of sulfenamide **70** to test its purification. Reaction on a 2.5 mmol scale.

The large disparity between the NMR yield and the isolated yield was attributed to the instability of the sulfenamide toward the silica stationary phase. Therefore, a stationary phase test was performed to examine the stability of sulfenamide **70** to a variety of commonly used stationary phases (Figure 2.2).[220] A sample of sulfenamide **70** was prepared as above before being dissolved in CH_2Cl_2 and then subjected to the below stationary phases (Figure 2.2 b-h). To replicate a purification procedure each portion was added to a slurry of stationary phase in eluent and stirred for 30 mins. After this time the stationary phase was filtered and washed with CH_2Cl_2. After removal of the solvent, the sample was analysed by ^{1}H NMR, affording the above results. The recovery of sulfenamide **70** was dramatically influenced by different stationary phases, with silica, as expected, showing widespread degradation. All other stationary phases tested showed degradation of sulfenamide **70** to some extent, however,

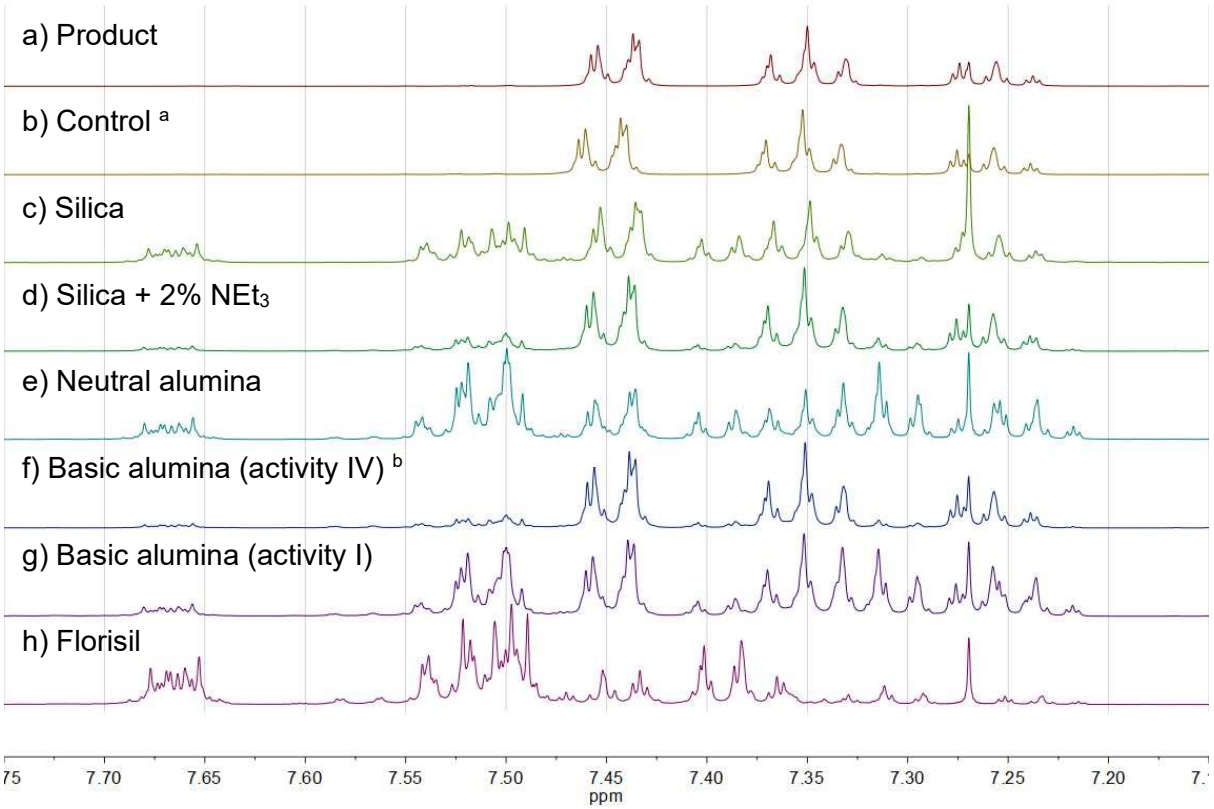
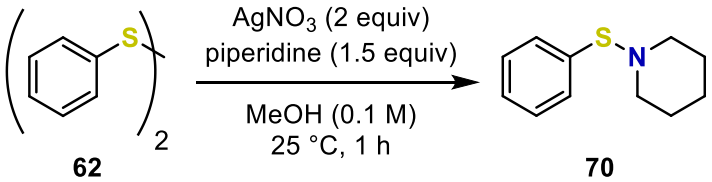


Figure 2.2: Selected section of ^{1}H NMR indicating the stability of sulfenamide **70** to stationary phases. [a] Sample of sulfenamide **70** stirred in pentane for 30 mins. [b] Basic alumina (activity IV) prepared by addition of water (10% w/w) to basic alumina (activity I).

base-doped silica (2% triethylamine) and basic alumina (activity IV) clearly returned sulfenamide **70** in the best purities. To quantify which stationary phase is the most benign in this case the above steps were repeated with an internal standard which showed basic alumina (activity IV) returned 47% of sulfenamide **70** and base-doped silica returned 23% of sulfenamide **70**. Therefore, basic alumina (activity IV) was decided to be the stationary phase of choice to purify the sulfenamides. The non-polar nature of sulfenamide **70** allowed for the straightforward separation from any (non disulfide) impurities, simply by filtering the crude through a plug of basic alumina (activity IV) which was hoped would also limit any degradation of the sulfenamide on the stationary phase due to the shorter contact time than full length column chromatography.

Whilst 3 equivalents of amine afforded the desired sulfenamide **70** in the highest yield, using such a large excess of amine could be detrimental, especially when using amines which are particularly expensive. Therefore, it was decided to use 1.5 equivalents of amine and these conditions were used to explore the robustness of the purification procedure. To test whether any of sulfenamide **70** was lost using the new purification procedure, an internal standard was added to the reaction mixture and NMR analysis conducted at various steps in the purification (Table 2.11). Pleasingly, the yield of the sulfenamide by ^{1}H NMR was within error of the internal standard throughout all steps in the purification affording clean sulfenamide **70** in a 60% yield. With a more reliable set of conditions found for the purification of sulfenamides, the next objective was to explore the applicability of the sulfenamide formation reaction across a range of substrates.



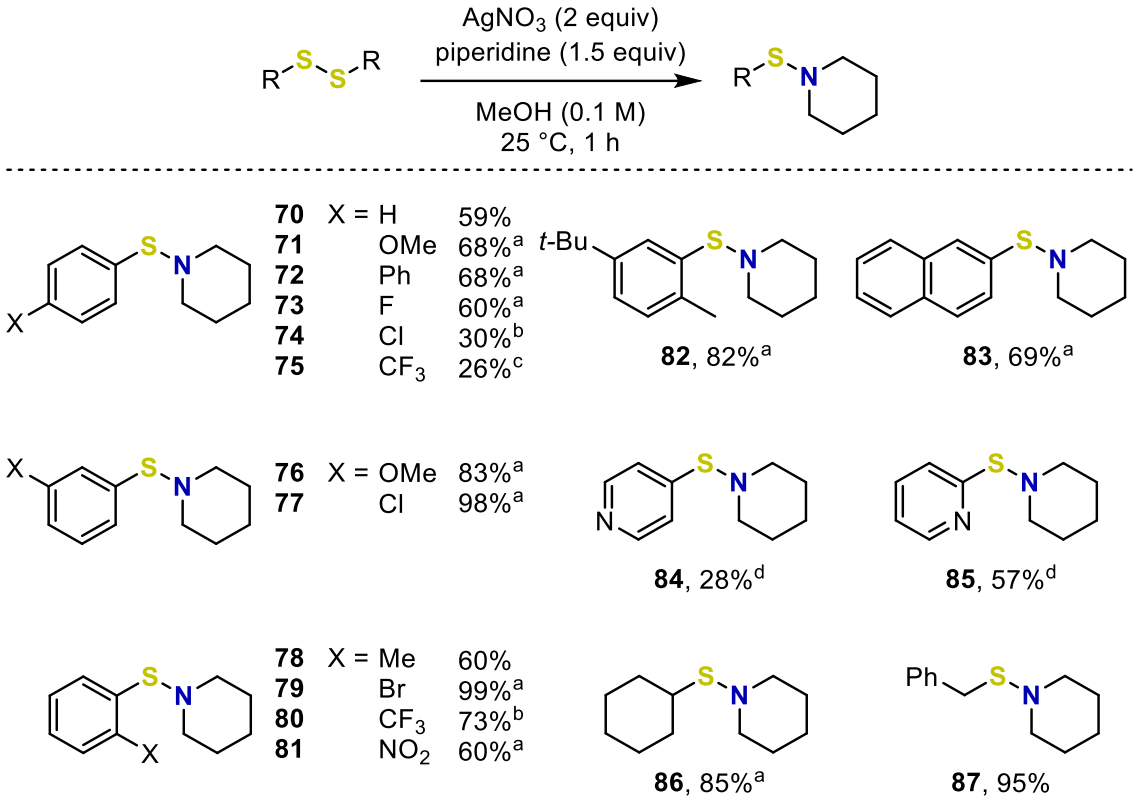
62 **70**

Entry	Purification step	Yield **70** [a]
1	After filtering off silver mercaptide	63%
2	After aqueous work up	61%
3	After filtering through basic alumina (activity IV)	60%

Table 2.11: NMR yield of sulfenamide **70** after different steps in the purification procedure. Reaction on a 1.6 mmol scale. [a] Yields calculated by ^{1}H NMR spectroscopy with respect to 1,3,5-trimethoxybenzene as an internal standard.

2.3.2.4 Scope of Transformation

Having decided on the optimal reaction conditions, exploration of the scope of the sulfenamide synthesis was carried out by first varying the disulfide and reacting with piperidine (Scheme 2.19). This work (Section 2.3.2.4) was conducted in collaboration with Prof. Renzo Luisi's group at the University of Bari, with Dr Arianna Tota and Marco Colella performing some of the following scope examples.

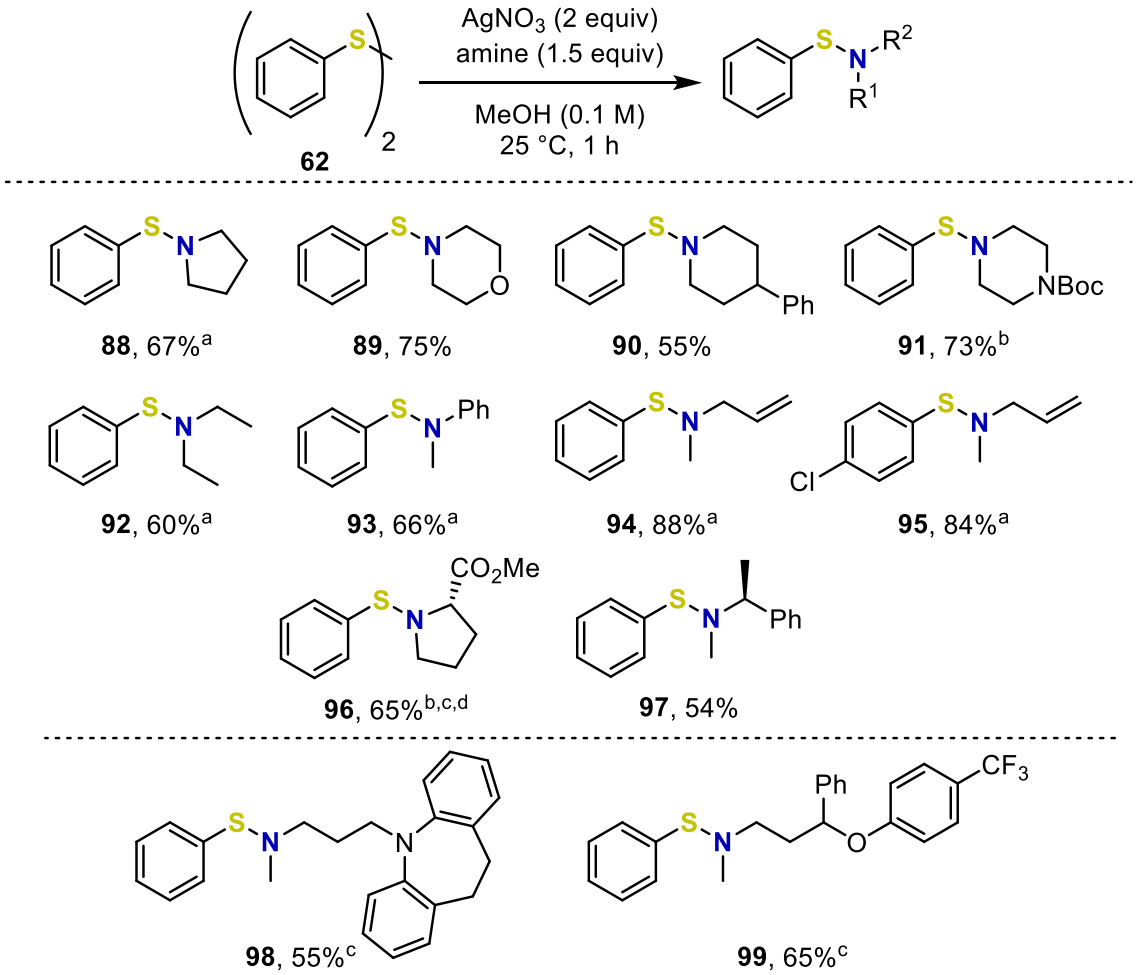


Scheme 2.19: Scope of the sulfenamide synthesis varying the R group of the disulfide. Reactions conducted on a 0.7–2.1 mmol scale, typically 2.0 mmol. [a] Reactions performed by Dr Arianna Tota or Marco Colella. [b] Mixture obtained after the reaction was re-subjected to the reaction conditions. [c] An additional 2 equivalents of piperidine and silver nitrate was added after 4 h, total reaction time 18 h, purified by distillation. [d] Purified by flash column chromatography with a silica stationary phase.

Examination of a range of disulfides with different electron rich and electron donating substituents in the *ortho*, *meta* and *para* position of the aromatic ring **70**-**81** was carried out and pleasingly all substrates were found to be successful in this case. No obvious trends could be drawn aside from typically increased yields for electron poor disulfides, which is particularly true for the *ortho* substituted series **78**-**81**. Other successful substrates include the di-substituted example **82** and napthyl derivative **83**. Pyridyl containing examples could also be synthesised and interestingly in these cases the sulfenamide could be readily purified by conventional flash column chromatography with a silica stationary phase **84**-**85**. Pleasingly alkyl and benzylic sulfenamides could also be formed under this methodology **86**-**87**. In some

cases, disulfide starting material was still present after the reaction and to remove any remaining starting material the mixture could be re-subjected to the reaction conditions, or additional equivalents of amine and silver nitrate could be added during the reaction. Where disulfide still remained, additional purification was carried out by distillation.

Next, the amine portion of the reaction was examined with diphenyl disulfide as the coupling partner for the formation of various sulfenamides (Scheme 2.20). A range of cyclic as well as acyclic amines could be used to afford the corresponding sulfenamides in good yields **88**-**92**. An aniline derivative as well as an allylic amine also worked well, including with a *para*-chloro substituent on the disulfide **93**-**95**. Enantiomerically pure amines could be used and they showed no loss of *ee* at the chiral centre on the amine **96**-**97**. To exemplify the methodology further two amine containing drugs, desipramine and fluoxetine, could be used to form the corresponding sulfenamides **98**-**99**. Again, in some cases, starting material was present in the

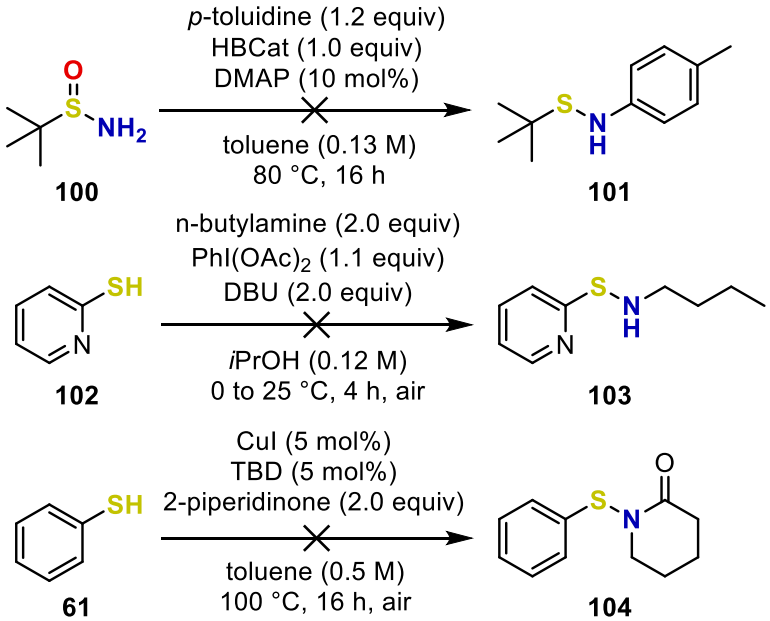


Scheme 2.20: Scope of the sulfenamide synthesis varying the R group of the amine. Reactions conducted on a 0.7–2.1 mmol scale, typically 2.0 mmol. [a] Reactions performed by Dr Arianna Tota or Marco Colella. [b] Additional silver nitrate/amine equivalents added with extended rection times. [c] HCl salt of amine used, triethylamine added as base. [d] Extra purification by distillation carried out.

reaction mixture and this could be removed upon addition of more amine/silver nitrate or by further purification by distillation. In the cases where the amines were used as hydrochloride salts, triethylamine was added in equimolar amount to neutralise any acid.

2.3.2.5 Unsuccessful Substrates

Whilst a reasonably diverse library of sulfenamides could be synthesised using the above method, there were some notable substrates that didn't work. In-particular, primary amines such as *n*-butylamine and *tert*-butylamine were unsuccessful, in both cases resulting in complex mixtures. This was attributed to the reduced nucleophilicity of these amines compared to secondary examples and so alternative methods to access these types of sulfenamides were examined (Scheme 2.21). Conditions involving the reduction of sulfinamides to sulfenamides[248] as well as a hypervalent iodine mediated oxidation of thiols were tested,[225] however, unfortunately in both of these cases the literature conditions also failed to yield the desired products. Inspired by a copper catalysed process between amides and thiols, acyl sulfenamides also posed as interesting targets. However, once again no product was recovered from the reaction.[249]



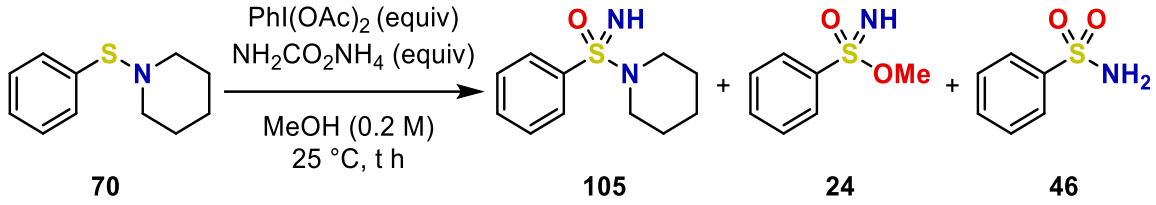
Scheme 2.21: Unsuccessful reactions toward accessing secondary and acyl sulfenamide substrates. Reactions conducted on a 0.5 mmol scale.

2.3.3 Optimisation of NH and O Transfer to Sulfenamides

2.3.3.1 Initial NH and O Transfer Conditions Screen

With a library of sulfenamides now available for further functionalisation, the next goal was to assess their suitability as NH and O transfer precursors, to afford sulfonimidamides. To do this, sulfenamide **70** was first subjected to previously successful NH and O transfer conditions to

sulfides and sulfoxides (Table 2.12).[164,166] Pleasingly, the desired sulfonimidamide product **105** was formed in moderate yield, however, sulfonimidate **24** and sulfonamide **46** were also formed as significant by-products (Table 2.12, entry 1). Investigations began on varying the equivalents of the oxidant and ammonium carbamate which found that decreasing the equivalents of both down to 2.5 and 2 respectively made no noticeable effect on the product distribution (Table 2.12, entries 2 to 4). Reducing the equivalents further only resulted in either reduced yields or return of starting material (Table 2.12, entries 5 & 6). Extending the reaction time from 1 to 18 h, only aided in the conversion of sulfonimidate **24** to sulfonamide **46** (Table 2.12, entry 7). Having ascertained the optimum equivalents of oxidant and ammonia source to effect NH and O transfer (Table 2.12, entry 4), preventing the formation of the side products **24** and **46** was the next aim. The S–N bond is known to be acid labile in sulfenamides and it was hypothesised that the formation of the by-products were due to the formation of thiophenol in solution, which have been previously shown to afford sulfonimidates or sulfonamides under related NH and O transfer conditions.[214]



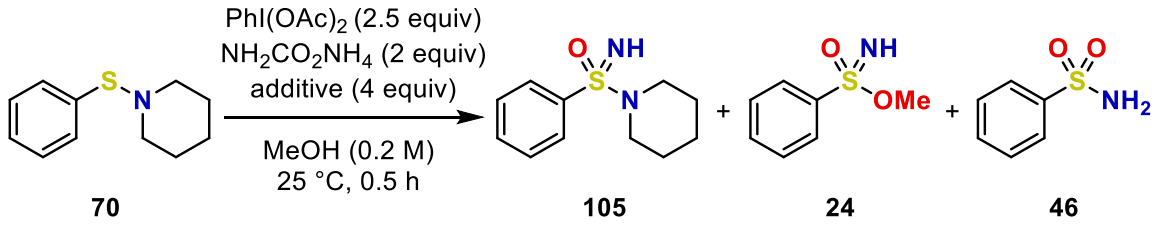
70 **105** **24** **46**

Entry	$NH_2CO_2NH_4$ (equiv)	$PhI(OAc)_2$ (equiv)	Time (h)	Yield (%) [a]				
				70	**105**	**24**	**46**	Total
1	4	3	3	0	**56**	11	6	73
2	4	2.5	3	0	**58**	15	3	76
3	3	2.5	3	0	**77**	14	3	94
4	2	2.5	1	0	**59**	12	5	76
5	2	2.0	0.5	6	**48**	14	15	83
6	1	2.5	0.5	0	**30**	18	3	51
7	2	2.5	18	0	**58**	9	17	84

Table 2.12: Product distribution from initial NH and O transfer conditions to sulfenamide **70**. Reactions on a 0.1 mmol scale. [a] Yields calculated by ^{1}H NMR spectroscopy with respect to 1,3,5-trimethoxybenzene as an internal standard.

2.3.3.2 Base Additive Screen

Next, the reaction was performed in alternative solvents such as acetonitrile and toluene which have shown to be suitable for this type of transformation previously, but these only afforded complex mixtures with return of starting material. Therefore, the effect that various bases would have on the reaction was examined, hoping to quench any excess protons in solution deriving from the bis(acetoxy)iodobenzene (Table 2.13). Magnesium oxide which has previously been shown to be compatible under related conditions had no effect on the product distribution (Table 2.13, entry 1).[150] The addition of potassium carbamate and triethylamine seemed to decrease the reaction conversion, whilst having no real effect on the by-product distribution (Table 2.13, entries 2 & 3). Limited success was initially seen when using sodium hydroxide, with an increased formation of the desired product **105** whilst much reducing the formation of the acid derived side products, however, when repeating this reaction, the product distribution was much more in-line with what had been observed in tests with other bases (Table 2.13, entries 4 & 5).



70 **105** **24** **46**

Entry	Additive	Yield (%) [a]				
		70	**105**	**24**	**46**	Total
1	MgO	0	**62**	8	11	81
2	K_2CO_3	21	**36**	3	8	68
3	NEt_3	30	**47**	18	14	109
4	NaOH	0	**86**	5	8	99
5	NaOH	18	**44**	12	12	86

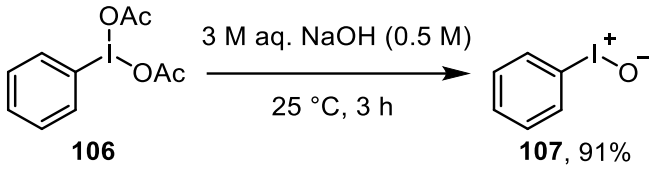
Table 2.13: Product distribution when adding different bases under NH and O transfer conditions to sulfenamide **70**. Reactions on a 0.1 mmol scale. [a] Yields calculated by ^{1}H NMR spectroscopy with respect to 1,3,5-trimethoxybenzene as an internal standard.

2.3.3.3 Iodosylbenzene as an Alternative Oxidant

The initial result observed with sodium hydroxide corroborated the proposal that the acidity of the reaction mixture can have an effect on the product distribution of the reaction, however, adding a base was perhaps not the best means to mediate this. As release of acetic acid into

the reaction mixture from the bis(acetoxy)iodobenzene was deemed to be the issue, the use of an alternative hypervalent iodine reagent (HVIR) was considered. Iodosylbenzene, known to dissolve in alcohol solvents to release water instead of acetic acid, has previously been shown to be able to mediate the synthesis of sulfonimidates from sulfinamides.[216] Therefore, it was postulated that it would also be an effective oxidant in this transformation and allow for the mediation of the acidity of the reaction.

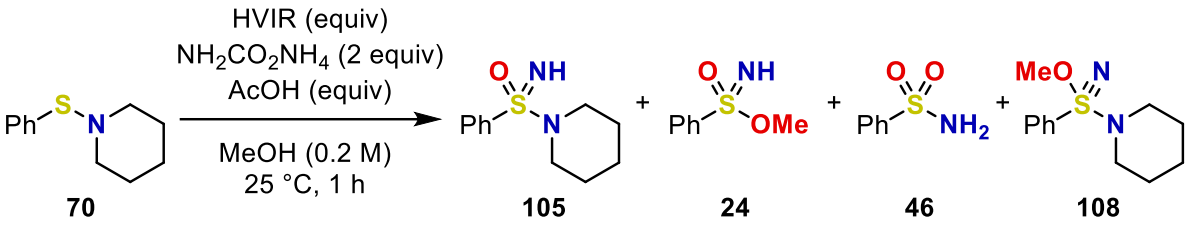
In order to access iodosylbenzene, treatment of bis(acetoxy)iodobenzene **106** with aqueous 3 M sodium hydroxide afforded **107** according to Dauban, Dodd and co-workers prior report (Scheme 2.22).[250]



106 **107**, 91%

Scheme 2.22: Synthesis of iodosylbenzene **107** from bis(acetoxy)iodobenzene **106**. Reaction(s) conducted on a 10 mmol scale.

The product distribution was examined when utilising iodosylbenzene with different equivalents of acetic acid (Table 2.14). When adding in 5 equivalents of acetic acid alongside 2.5 equivalents of iodosylbenzene it was found that the product distribution was essentially the same as when using 2.5 equivalents of bis(acetoxy)iodobenzene (Table 2.14, entries 1 & 2). However, when not adding in any acetic acid a new compound **108** was formed as the major product (Table 2.14, entry 3). This new species was only identified later in the optimisation process as an unprecedented alkoxy-amino-λ^6-sulfanenitrile (see section 2.3.6 for further discussion on this class of compounds). Pleasingly, upon addition of either 0.5 or 1 equivalents of acetic acid, this novel species would convert into the desired sulfonimidamide **105** with minimum formation of by-products **24** and **46** (Table 2.14, entries 4 & 5).

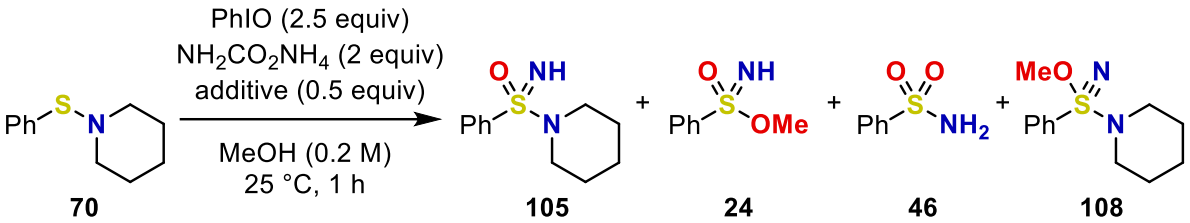


Entry	$PhI(OAc)_2$ (equiv)	PhIO (equiv)	AcOH (equiv)	Yield (%) [a]				
				105	**24**	**46**	**108**	Total
1	2.5	-	-	**65**	15	3	0	83
2	-	2.5	5	**51**	11	8	0	70
3	-	2.5	0	**11**	2	3	47	63
4	-	2.5	1	**52**	5	3	0	60
5	-	2.0	0.5	**63**	3	4	trace	70

Table 2.14: Product distribution when altering the HVIR to effect NH and O transfer to sulfenamide **70**. Reactions on a 0.1 mmol scale. [a] Yields calculated by ^{1}H NMR spectroscopy with respect to 1,3,5-trimethoxybenzene as an internal standard.

2.3.3.4 Acid Additive Screen

With the ability to change the acid additive of the reaction, the effect of different acids on the product distribution of the NH and O transfer was examined (Table 2.15). Initially, 0.5 equivalents of the additive were used but this led to incomplete conversion of the alkoxy-amino-λ^6-sulfanenitrile **108** to the sulfonimidamide **105** in many cases. The use of formic acid led to a very similar product profile as acetic acid (Table 2.15, entries 1 & 2). Interestingly, worse conversions were seen with other carboxylic acids such as pivalic acid, benzoic acid and trifluoracetic acid (Table 2.15, entries 3 to 5). *p*-Toluenesulfonic acid, perhaps due to its higher acidity, led to a slight increase in the amount of the thiol derived by-products **24** and **46** (Table 2.15, entry 6). Whilst it was interesting to see that other acids were able to facilitate sulfonimidamide formation, it was clear that no real improvement on the formation of sulfonimidate **24** or sulfonamide **46** could be made by simply switching the acid additive. Therefore, acetic acid was carried through to the other optimisation steps for easier comparison to previous results.

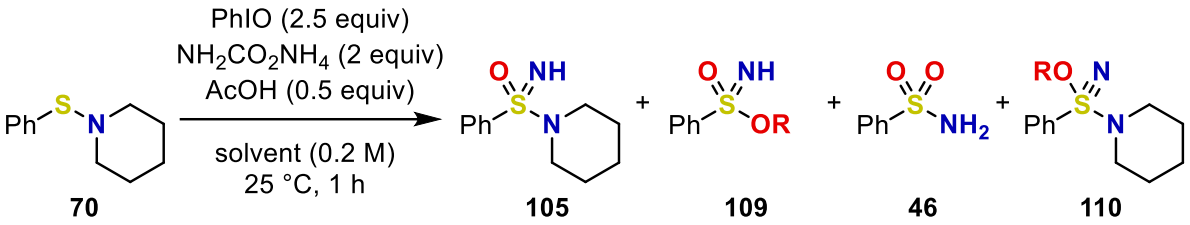


Entry	Additive	Yield (%) [a]				
		105	**24**	**46**	**108**	Total
1	AcOH	**63**	3	4	trace	70
2	HCO_2H	**64**	1	3	trace	68
3	PivOH	**26**	1	4	65	96
4	$PhCO_2H$	**35**	3	5	55	98
5	TFA	**25**	2	5	55	87
6	TsOH	**35**	4	7	42	88

Table 2.15: Product distribution when altering the acid additive to effect NH and O transfer to sulfenamide **70**. Reactions on a 0.1 mmol scale. [a] Yields calculated by ^{1}H NMR spectroscopy with respect to 1,3,5-trimethoxybenzene as an internal standard.

2.3.3.5 Solvent Screen

Alcohol solvents were then screened to see whether they would have an effect on the stability of the sulfenamide and to further increase the yield of sulfonimidamide **105** by preventing unproductive pathways in the reaction mechanism (Table 2.16). When using ethanol as the solvent it was found that the formation of thiol derived by-products **109** and **46** fell slightly but a significant amount of the alkoxy-amino-λ^6-sulfanenitrile **110** remained in the reaction mixture, in this case with an ethoxy group attached to the sulfur centre (Table 2.16, entry 2). It was interesting to see that different variants of these types of species could be synthesised simply by changing the alcohol solvent, something which was later exploited to synthesise a small library of these types of compound (Section 2.3.6.3). Upon changing the solvent to more sterically hindered and more nucleophilic alcohols such as isopropanol and *tert*-butanol the yield of sulfonimidamide **105** increased, in-line with reduced formation of any by-products (Table 2.16, entries 3 & 4). In the case of ethylene glycol, the reaction mainly returned starting material and more acidic alcohols such as trifluoroethanol and hexafluoroisopropanol seemed to cause widespread degradation of the starting material (Table 2.16, entries 5 to 7). The results using isopropanol and *tert*-butanol were similarly positive but given the difficult handling properties of *tert*-butanol, isopropanol was chosen as the reaction solvent going forward.

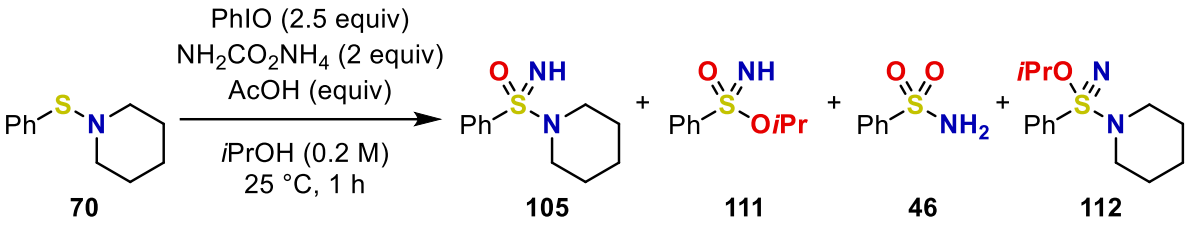


Entry	Solvent	Yield (%) [a]					
		70	**105**	**109**	**46**	**110**	Total
1	MeOH	0	**63**	3	4	trace	70
2	EtOH	0	**55**	1	2	18	76
3	*i*PrOH	0	**79**	1	2	0	82
4	*t*-BuOH [b]	0	**76**	1	1	0	78
5	$(CH_2OH)_2$	47	**4**	1	1	0	53
6	TFE	2	**22**	8	4	0	36
7	HFIP	0	**5**	8	0	0	13

Table 2.16: Product distribution when altering the solvent to effect NH and O transfer to sulfenamide **70**. OR group in **109** and **110** derived from the solvent. Reactions on a 0.1 mmol scale. [a] Yields calculated by ^{1}H NMR spectroscopy with respect to 1,3,5-trimethoxybenzene as an internal standard. [b] Reaction carried out at 30 °C.

2.3.3.6 Acid Equivalents Comparison

In the final part of the optimisation process, an examination on the optimal equivalents of acetic acid was carried out in order to convert all of the alkoxy-amino-λ^6-sulfanenitrile to the sulfonimidamide. Whilst 0.5 equivalents had been adequate on a 0.1 mmol scale, this corresponded to just 5.7 µL of acetic acid which has a high degree of error. Therefore, the scale was doubled and various stock solutions of acetic acid in isopropanol were prepared to reduce any error in the measurement of the acetic acid equivalents. Examination of the product profiles when varying the equivalents of acetic acid from 0 to 1.0 was then carried out (Table 2.17). The formation of by-products **111** and **46** derived from the acid instability of the sulfenamide were kept essentially the same across all entries. However, as expected, when more acetic acid was added an increased conversion of the alkoxy-amino-λ^6-sulfanenitrile **112** to the sulfonimidamide **105** was seen. Under these revised conditions, it was found that 1.0 equivalent of acetic acid was required to ensure complete conversion and therefore maximise the yield of the desired product **105** (Table 2.17, entry 5).

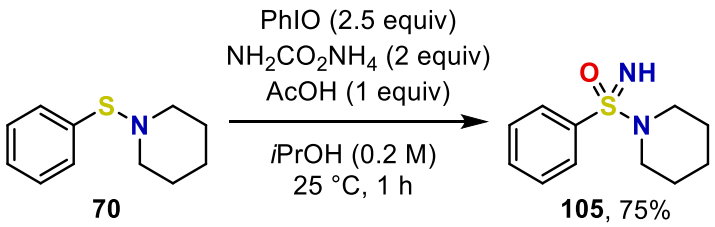


Entry	AcOH (equiv)	Yield (%) [a]				
		105	**111**	**46**	**112**	Total
1	0	**27**	1	1	53	82
2	0.3	**53**	1	1	23	78
3	0.5	**72**	1	1	9	83
4	0.7	**85**	1	1	2	89
5	1.0	**90**	2	1	0	93

Table 2.17: Product distribution when altering the equivalents of acetic acid to effect NH and O transfer to sulfenamide **70**. Reactions on a 0.2 mmol scale. Equivalents of acetic acid calculated by using stock solutions of acetic acid in isopropanol. [a] Yields calculated by ^{1}H NMR spectroscopy with respect to 1,3,5-trimethoxybenzene as an internal standard.

*2.3.3.7 Isolation of Sulfonimidamide **105***

With a high *in situ* yield of sulfonimidamide **105** obtained through the addition of 1 equivalent of acetic acid, these conditions were then repeated on a 0.5 mmol scale to compare how the yields obtained through ^{1}H NMR compared to the isolated yield. The purification process involves a simple aqueous work up and extraction with CH_2Cl_2 followed by purification by flash column chromatography. It was decided that neutral alumina would be used as the stationary phase for the isolation sulfonimidamides due to its ability to retain any sulfonamide which might be formed under the reaction conditions, as discovered in section 2.2.[214] Pleasingly, under the optimised NH and O transfer conditions, the isolation of sulfonimidamide **105** could be achieved in 75% yield (Scheme 2.23).



Scheme 2.23: Optimised NH and O transfer conditions to sulfenamide **70** to access sulfonimidamide **105**. Reaction conducted on a 0.5 mmol scale.

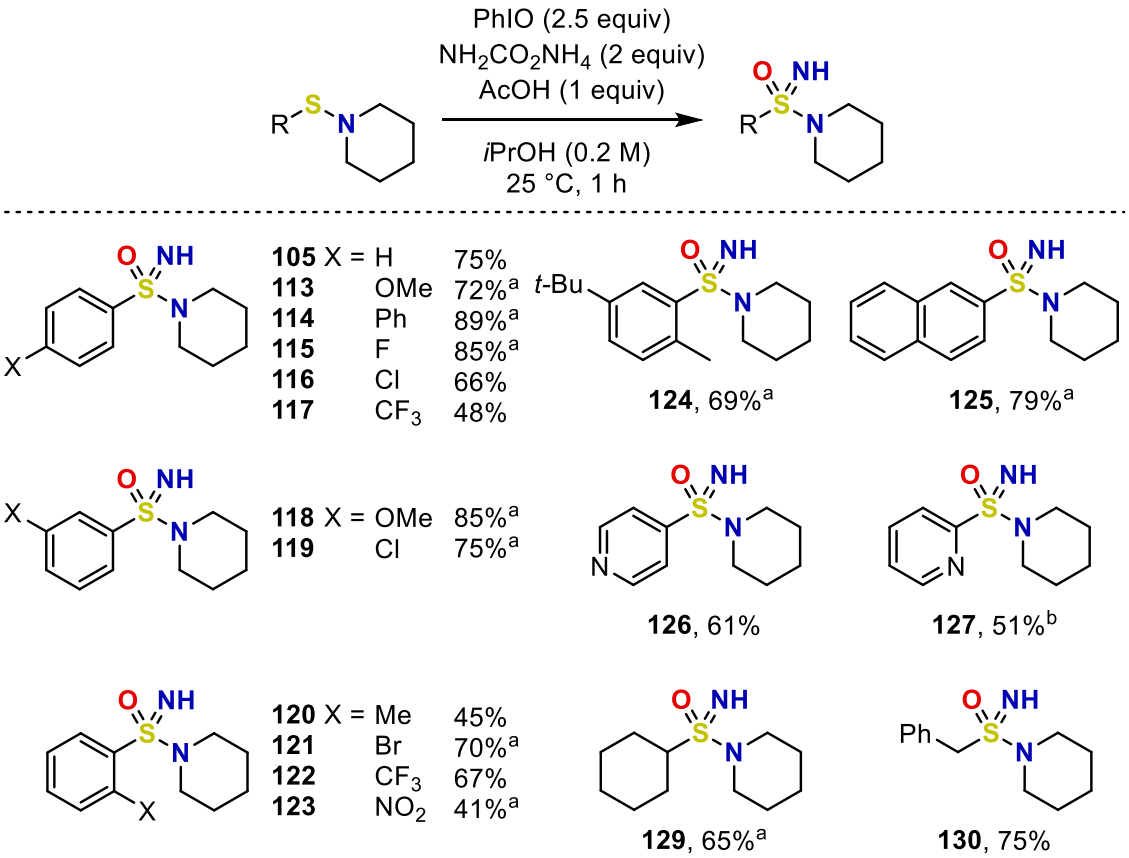
2.3.4 Scope of NH and O Transfer to Sulfenamides

Having found conditions for the synthesis of sulfonimidamide **105** from sulfenamide **70** in high yield, the scope of this transformation was then explored to ascertain the limits of reactivity.

2.3.4.1 Varying the Sulfur Substituent

Exploration of the scope of this transformation began by varying the R group attached to the sulfenamides (Scheme 2.24). This work (section 2.3.4) was conducted in collaboration with Prof. Renzo Luisi's group at the University of Bari, with Dr Arianna Tota and Marco Colella performing some of the following scope examples.

Pleasingly, all the sulfenamides synthesised in scheme 2.19 were amenable to this transformation, affording the corresponding the sulfonimidamide in good to high yield in all cases. A variety of mono-substituted aromatics containing electron withdrawing and donating groups were compatible with this reaction, irrespective of the position of the substituent (i.e. *ortho*-, *meta*- or *para*-) providing sulfonimidamides **105**, **113**-**125**. Generally, yields were dependant on the electron density on the sulfur atom, with more electron rich examples

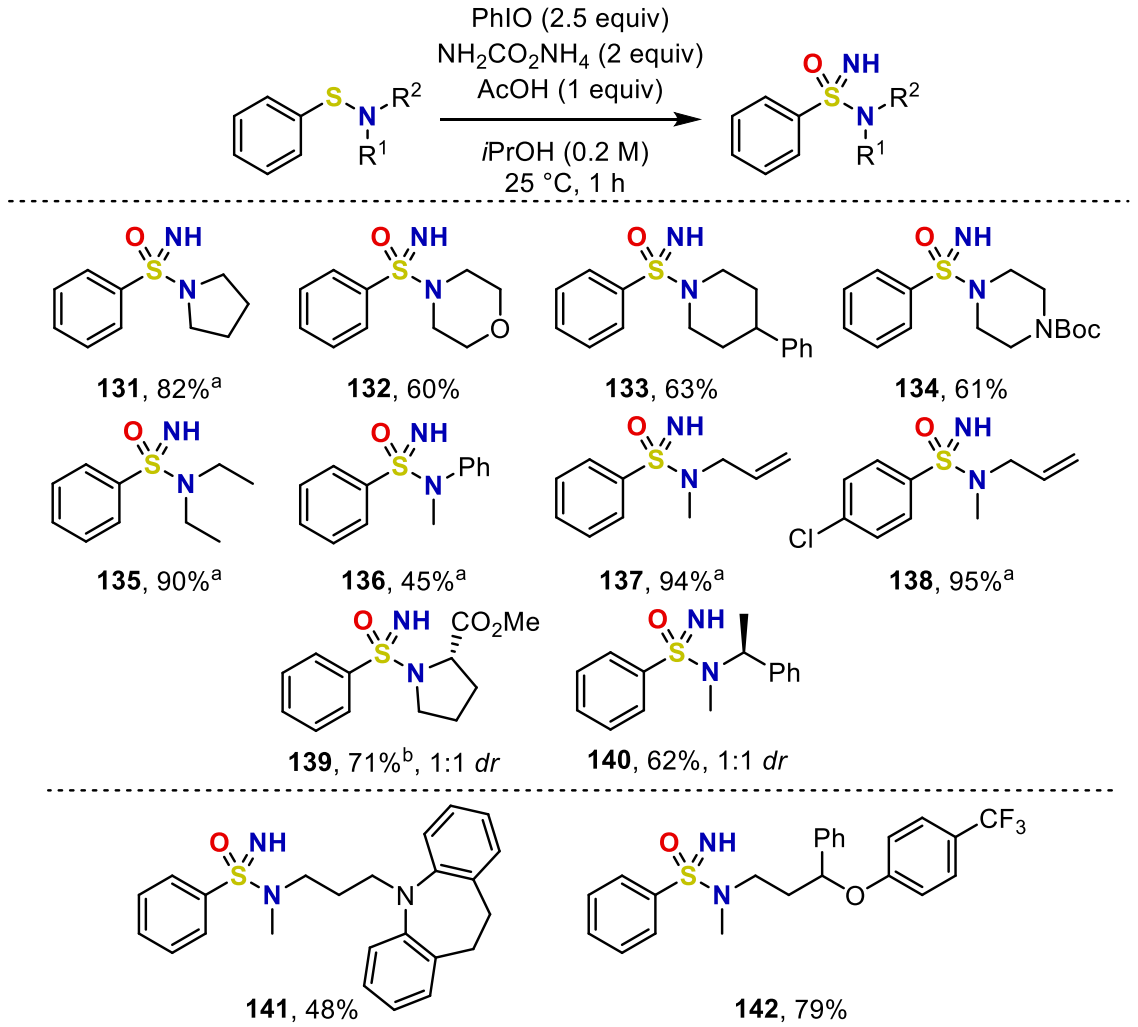


Scheme 2.24: Scope of the sulfonimidamide synthesis varying the R group of the sulfenamide. Reactions conducted on a 0.4–1.2 mmol scale, typically 0.5 mmol. [a] Reactions performed by Dr Arianna Tota or Marco Colella. [b] A 14% yield of the corresponding *N*-acylated product of **127** was obtained compound **128**.

affording the sulfonimidamide in higher yields. Pyridine containing examples **126** and **127** afforded the sulfonimidamide in good yields as well as alkyl and benzylic examples **129** and **130**. Interestingly, the corresponding *N*-acylated sulfonimidamide product of **127** was also obtained as a side product in a 14% yield under the reaction conditions to form **128**.

2.3.4.2 Varying the Amino Moiety

The scope of the amine portion of the sulfenamides was then examined (Scheme 2.25). Again, all the sulfenamides synthesised in scheme 2.20 were suitable sulfonimidamide precursors. A variety of cyclic amines and acyclic amines could be used successfully **131**-**135**. Aniline derived example **136** was also a suitable substrate and the highest yields were obtained in the allyl examples **137** and **138**. Enantiomerically pure amines could first be used in the sulfenamide synthesis, followed by NH and O transfer to yield the corresponding sulfonimidamide **139** and **140**. In both of these cases, the sulfonimidamide was afforded as a

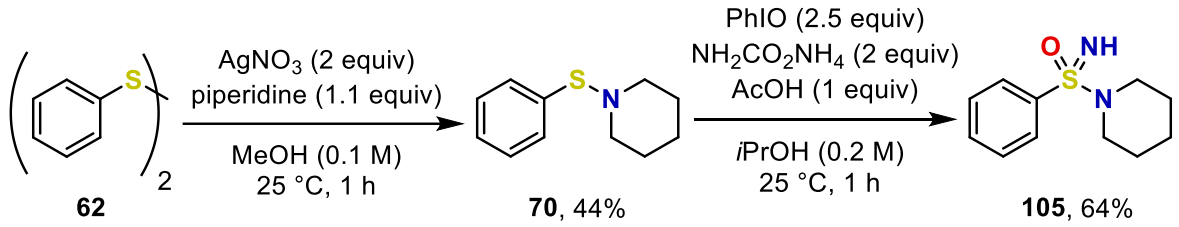


Scheme 2.25: Scope of the sulfonimidamide synthesis varying the R^1 and R^2 group of the sulfenamide. Reactions conducted on a 0.4–1.2 mmol scale, typically 0.5 mmol. [a] Reactions performed by Dr Arianna Tota or Marco Colella. [b] Purified on a silica stationary phase.

1:1 mixture of diastereomers, with no loss of *ee* observed at the chiral centre. Interestingly, compound **139** required purification on a silica stationary phase, instead of neutral alumina which was typically used, to prevent the formation of a ring closure product, see section 2.3.4.5 for more details. Amine containing drugs desipramine and fluoxetine were amenable to this NH and O transfer methodology, illustrating the potential of the method for late stage functionalisation in the synthesis of **141** and **142**.

*2.3.4.3 Gram Scale Synthesis of Sulfonimidamide **105***

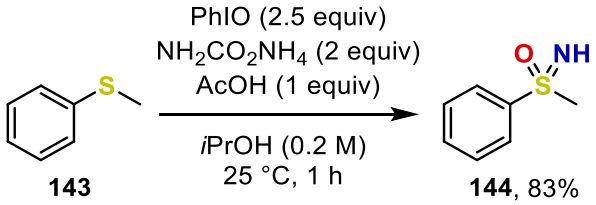
To demonstrate how this methodology can be amenable for larger scales, a gram scale synthesis of sulfonimidamide **105** from commercially available disulfide **62** was conducted (Scheme 2.26). Using just 1.1 equivalents of piperidine, sulfenamide **70** could be accessed in a 44% yield. The reduced equivalents of piperidine was used to display how costs could be reduced on scale, especially if the amine was particularly precious. NH and O transfer then allowed for the synthesis of 1.3 g of sulfonimidamide **105** in a 64% yield. The ~10% drop in yield on this scale is not necessarily attributed to issues of scaling up, but more the reduced purity of the sulfenamide **70** starting material due to the low equivalents of piperidine used.



Scheme 2.26: Synthesis of 1.3 g of sulfonimidamide **105**. Initial sulfenamide formation conducted on a 24 mmol scale.

*2.3.4.4 Applying Conditions to Sulfide **143***

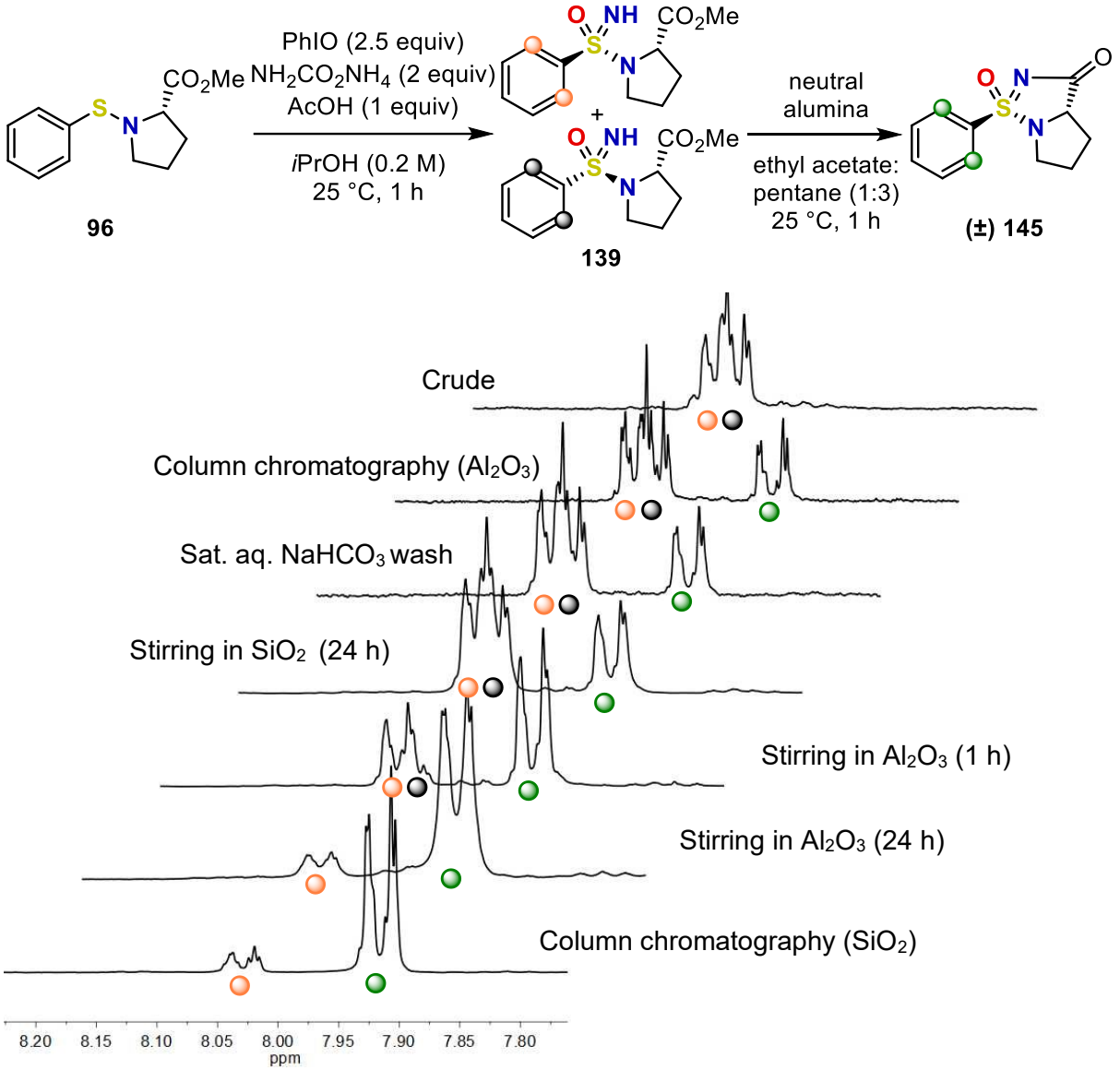
The evaluation of these newly developed NH and O transfer conditions with those previously found for the synthesis of sulfoximines was then carried out. Sulfide **143** was treated under these milder conditions accessing sulfoximine **144** in a 83% yield, providing a useful alternative to previously found conditions for acid sensitive substrates (Scheme 2.27).[166]



Scheme 2.27: Synthesis of sulfoximine **144** under newly found NH and O transfer conditions. Reaction conducted on a 0.5 mmol scale.

*2.3.4.5 Ring Closure of Sulfonimidamide **139***

Following the general procedure for the synthesis of sulfonimidamide **139**, it was found that despite the ^{1}H NMR of the crude displaying a 1:1 mixture of the two diastereomers, upon isolation via flash column chromatography on neutral alumina an unequal amount of the two diastereomers were isolated and a new product was also observed **145**. This product proved stable to a saturated aqueous $NaHCO_3$ wash as well as stirring the mixture in SiO_2 with an EtOAc:pentane (3:1) eluent. However, when stirring in alumina preferential conversion of one diastereomer to **145** was seen after an hour and when left for extended periods both diastereomers showed near complete conversion to ring closed sulfonimidamide **145** as a single diastereomer, presumably through gradual epimerisation of the methyl ester of **139**. Product **145** was further purified by column chromatography (SiO_2) (Scheme 2.28).



Scheme 2.28: Conversion of diastereomeric mixture **139** to ring closed sulfonimidamide **145**.

The relative configuration of **145** was confirmed by NOE experiments. Weak correlation was observed between the *ortho*-protons of the phenyl ring and those on the opposite face of the pyrrolidine ring to the carbonyl. The same diastereomer of a similar compound (tolyl instead of phenyl) was recently reported by Sandström and co-workers. In their report they obtained a crystal structure to confirm the absolute configuration. The ^{1}H NMR of compound **145** maps well onto their reported ^{1}H NMR of the related sulfonimidamide, corroborating our proposal.[251]

2.3.5 Probenecid Analogue

*2.3.5.1 Accessing Intermediate **151***

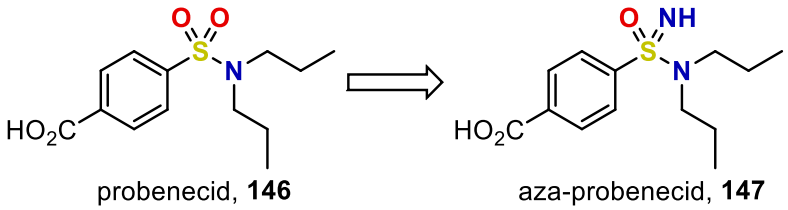
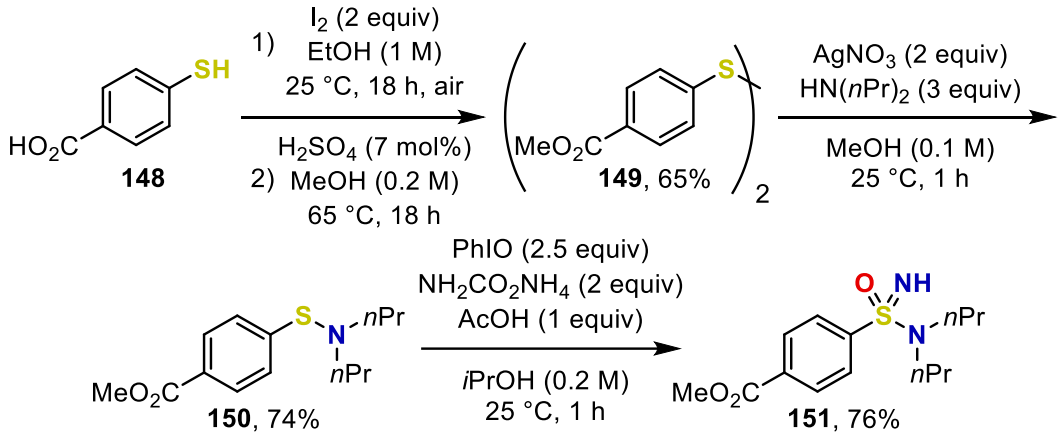


Figure 2.3: Structure of probenecid and its aza-analogue.

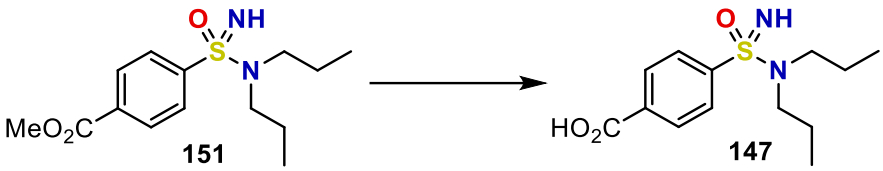
To further illustrate the potential of this methodology for the preparation of drug-like compounds, the synthesis of an aza-analogue of a drug currently on the market was targeted. To this end, probenecid **146** was identified which is a sulfonamide containing drug currently used for the treatment of gout (Figure 2.3).[252] In order to access the sulfonimidamide derivative, thiol **148** was obtained from a commercial vendor. Then, by using literature conditions, synthesis of the corresponding disulfide and protection of the carboxylic acid as the methyl ester in a single telescoped process to access **149** was carried out.[253] Application of the standard sulfenamide formation conditions allowed access to **150** which upon subjection to the standard NH and O transfer conditions yielded sulfonimidamide **151** in high yield (Scheme 2.29).



Scheme 2.29: Synthesis of sulfonimidamide **151** from commercially available thiol **148**, exemplifying the developed NH and O transfer methodology. Initial reaction on a 6.5 mmol scale.

*2.3.5.2 Deprotection of Intermediate **151***

In order to access the direct aza-analogue of probenecid, deprotection conditions of the methyl ester were required (Table 2.18). Initial attempts under basic conditions were unsuccessful, yielding a complex mixture of products, likely due to hydroxide attack at the sulfur centre cleaving the S–N bond (Table 2.18, entry 1). Attempts at using TMSI, which has previously been shown to be able to deprotect sulfonimidamide containing esters only proved to silylate the nitrogen of the sulfonimidamide starting material and not affect the methyl ester presumably due to its comparatively higher nucleophilicity compared to the ester (Table 2.18, entry 2).[251] However, when switching to acidic conditions (1:1 TFA:H_2O) the methyl ester was hydrolysed, without formation of side products, with the remaining 15% being starting material (Table 2.18, entry 3). Under these conditions, aza-probenecid **147** could be isolated in an 80% yield.

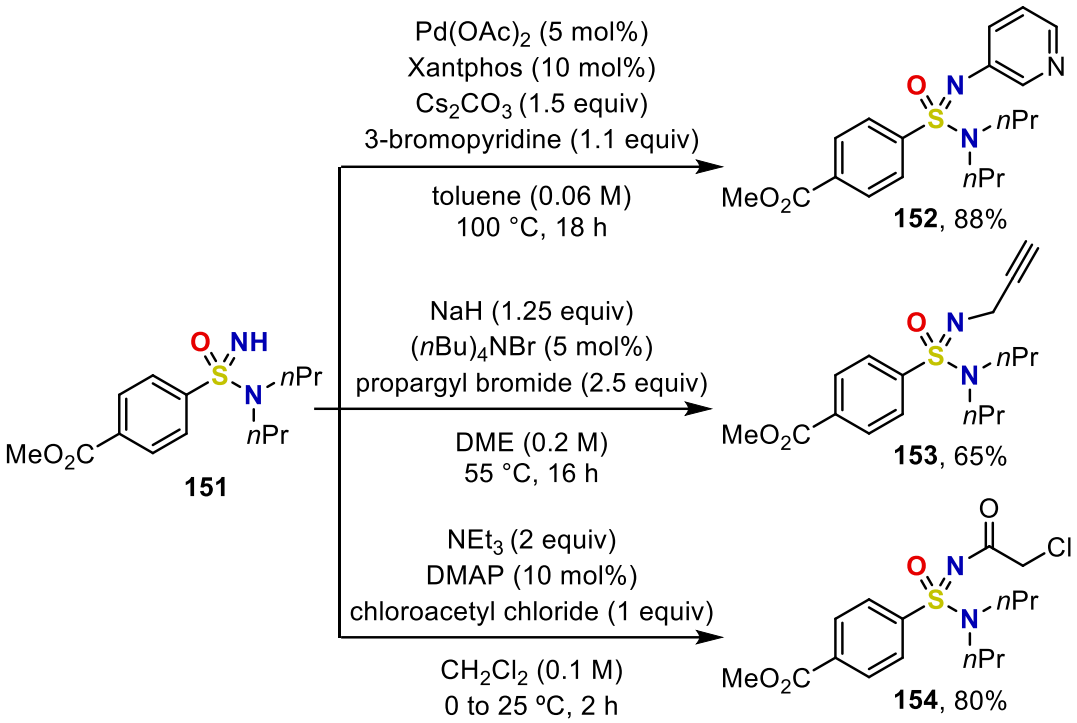


Entry	Reagent	Conditions	Observation
1	LiOH (1.1 equiv)	MeOH, 65 °C, 24 h	Complex degradation
2	TMSI (5 equiv)	MeCN, 85 °C, 24 h	*N*-Silylation of starting material
3	TFA:H_2O (1:1 v/v, 0.2 M)	90 °C, 24 h	85% conversion to product [a]

Table 2.18: Deprotection of methyl ester **151** to afford the direct aza-analogue of probenecid **147**. Reactions on a 0.1 mmol scale. [a] aza-probenecid accessed in an 80% isolated yield.

*2.3.5.3 N-Functionalisation of Intermediate **151***

To display the potential of the sulfonimidamide group to explore broader chemical space than their oxygen analogues, *N*-functionalisation of intermediate **151** was undertaken (Scheme 2.30). A palladium catalysed cross-coupling enabled the formation of the *N*-pyridyl derivative **152** under conditions described by Stockman, Lücking and co-workers.[134] Alkylation conditions with propargyl bromide[192] allowed access to **153** and acylation with chloroacetyl chloride afforded **154**, installing functionalities which have interest in click chemistry or as covalent probes respectively.



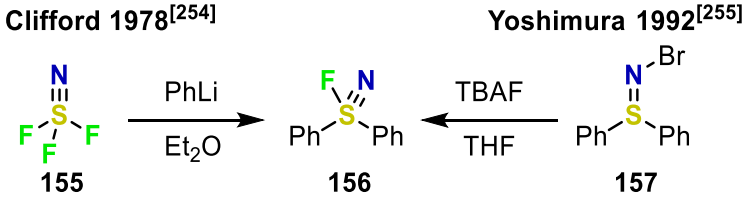
Scheme 2.30: *N*-Functionalisation reactions of intermediate **151** to explore broader chemical space. Reactions performed on a 0.1 mmol scale.

2.3.6 Chemistry of Alkoxy-amino-λ^6-sulfanenitriles

Acid free conditions in the NH and O transfer to sulfenamides gave rise to intriguing alkoxy-amino-λ^6-sulfanenitrile structures. By making a small library of this class of compound it was hoped their chemistry and reactivity could be explored further. There have been no prior reports of this functional group in the literature, however, there have been reports of related λ^6-sulfanenitrile structures and comparing the chemistry of these with the alkoxy-amino-λ^6-sulfanenitriles isolated in this study became a key aim.

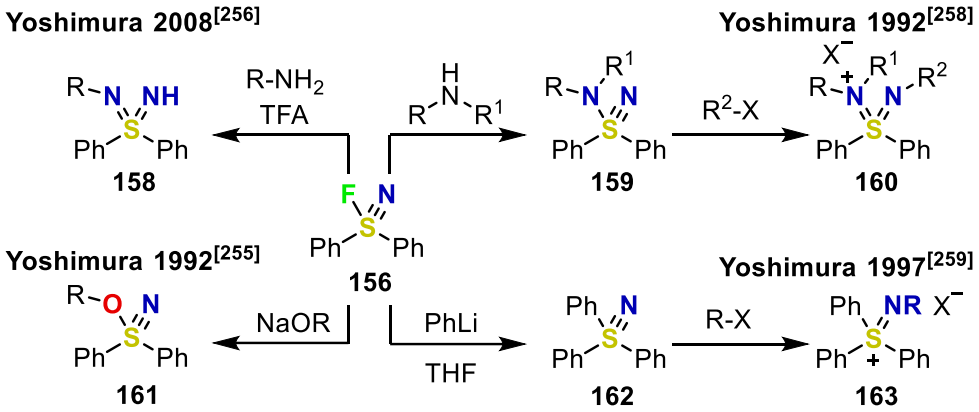
2.3.6.1 Prior Reports of λ^6-sulfanenitriles

The first organic compounds containing an S≡N bond were reported by Clifford and co-workers in the 1970's who synthesised fluoro-λ^6-sulfanenitriles through the addition of phenyl lithium to trifluorothiazyne (NSF_3).[254] Yoshimura and co-workers developed an alternative route toward these useful compounds in the early 1990's from bromosulfilimines (Scheme 2.31).[255]



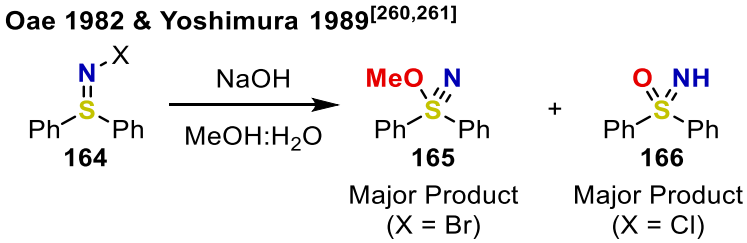
Scheme 2.31: Synthetic routes toward fluoro-λ^6-sulfanenitriles.

Fluoro-λ^6-sulfanenitriles are interesting as precursors to a range of other sulfur-nitrogen bonded species through nucleophilic attack on the sulfur centre and loss of fluoride. A variety of nitrogen, oxygen and carbon-based nucleophiles have been shown to be reactive with these compounds (Scheme 2.32). The use of primary amines as nucleophiles affords sulfondiimines[256] and this has more recently been extended by Bolm and co-workers who have shown sulfilimines can be converted to sulfondiimines directly via a halo-λ^6-sulfanenitrile intermediate.[257] Secondary amines can be used to afford sulfondiimines salts after reaction with an alkyl halide[258] and related salts can also be accessed after the reaction of phenyl lithium.[259] Most pertinently to this work, however, is the reaction of alkoxides with fluoro-λ^6-sulfanenitriles which affords alkoxy-λ^6-sulfanenitriles.[255]



Scheme 2.32: Reactivity of fluoro-λ^6-sulfanenitriles with different nucleophiles.

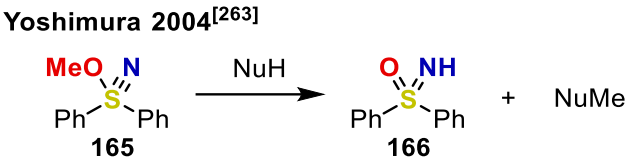
Alkoxy-λ^6-sulfanenitriles are the carbon-based analogues of alkoxy-amino-λ^6-sulfanenitriles and have been known since their first preparation in 1989 by Yoshimura and co-workers.[260] Their serendipitous discovery occurred through the treatment of bromosulfilimines with an aqueous solution of sodium hydroxide. Whilst the treatment of chlorosulfilimines with aqueous sodium hydroxide had been shown to afford sulfoximines previously,[261] under analogous conditions with bromosulfilimines alkoxy-λ^6-sulfanenitriles are formed as the major product with the sulfoximine as a by-product (Scheme 2.33).



Scheme 2.33: First formation of alkoxy-λ^6-sulfanenitriles from bromosulfilimines.

Through this route from bromosulfilimines, it was not possible to isolate the alkoxy-λ^6-sulfanenitrile **165** cleanly and instead facile conversion to sulfoximine **166** was seen

when attempting to purify these mixtures with flash column chromatography. However, an improved set of conditions from fluoro-λ^6-sulfanenitriles developed by Yoshimura and co-workers in 1998 resulted in their isolation for the first time.[262] The inherent instability of alkoxy-λ^6-sulfanenitriles to acidic and basic conditions and even at elevated temperatures has been exploited in the context of them being powerful alkylating agents to a range of nucleophiles including thiols, amines and carboxylates (Scheme 2.34).[263]



Scheme 2.34: Alkoxy-λ^6-sulfanenitrile **165** as an alkylating agent to various nucleophiles.

More recently, alkoxy-λ^6-sulfanenitrile **167** has been identified as an intermediate in the NH and O transfer to sulfides under conditions reported by Reboul and co-workers in 2017 for the synthesis of sulfoximines.[167] The related alkoxy-amino-λ^6-sulfanenitriles that have been identified in this study represent a new class of λ^6-sulfanenitrile that have been fully characterised alongside small amounts of the corresponding sulfonimidamide (Figure 2.4).

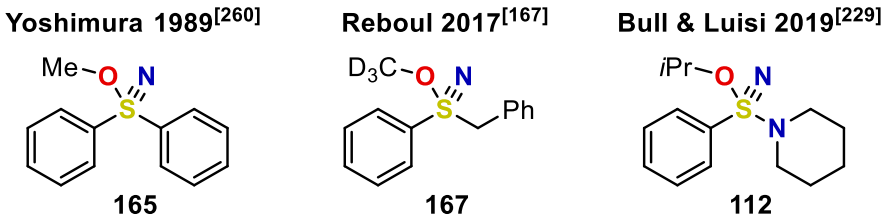


Figure 2.4: Prior reports of alkoxy-λ^6-sulfanenitriles and alkoxy-amino-λ^6-sulfanenitrile **112** identified in this study.

2.3.6.2 S≡N Bonding Evidence

The S≡N triple bond is a particularly unusual species, seldom seen in organic chemistry literature. Therefore, comparison of the spectroscopic data of alkoxy-amino-λ^6-sulfanenitriles with similar species containing an S≡N bond was considered a valuable approach to gaining further understanding of this particular λ^6-sulfanenitrile species. A comparison of the absorption of ν_{SN} and where possible the bond length of various compounds containing an S≡N and S=N bond as determined by X-ray structures is shown below (Table 2.19).[264–266] The ν_{SN} of sulfonimidamides usually appears slightly higher than that of sulfoximines, likely due to the more electronegative nitrogen *versus* carbon atom attached to the sulfur centre. This trend is also observed with the alkoxy-amino-λ^6-sulfanenitriles isolated in this study compared to the alkoxy-λ^6-sulfanenitriles in Yoshimura and co-workers study (Table 2.19, entries 1 to 4).[262] In both of these cases, the λ^6-sulfanenitrile species have a ν_{SN} absorption ~100 cm^{-1} higher than

the corresponding sulfoximine or sulfonimidamide, indicating the increased bond order associated with these compounds. The alkoxy-amino-λ^6-sulfanenitriles in this study exhibit quite a high ν_{SN} absorption compared to isolated λ^6-sulfanenitriles with other substitution patterns, in line with the reduced electron density on the sulfur atom (Table 2.19, entries 5 to 8). Further spectroscopic confirmation of the S≡N bond was achieved through using DFT calculations of the ν_{SN} absorption in λ^6-sulfanenitriles **112** and **165** (Table 2.19, entries 3 & 4).

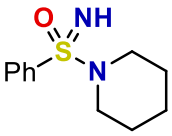
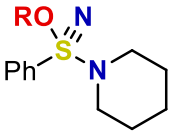
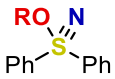
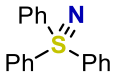
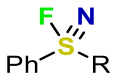
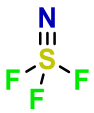
Entry	Compound	IR absorption ν_{SN} (cm^{-1})	SN bond length (Å)
1		**1257**[229]	**1.499**[190]
2		**1222**[164] a	**1.528**[40] b
3		**1349-1363**[229] (calculated **1368**) c	-
4		**1327-1335**[262] (calculated **1332**) d	**1.441**[262] e
5		**1267**[259]	**1.462**[259]
6		**1285-1298**[258]	-
7		**1361**[255] a	**1.444**[264] f
8		**1524**[265]	**1.415**[266]

Table 2.19: Analysis of IR absorption frequency and bond length of the SN bond in various compounds. [a] R = Ph. [b] R = Me. [c] R = *i*Pr, experimentally observed value = 1363. [d] R = Me, experimentally observed value = 1331.[262] [f] R = *p*-nitrophenyl.

Further clarity on the bonding and orbital contributions in these S≡N species was established based on, models proposed by Mews, Parsons and co-workers in 2008, specifically for trifluorothiazyne **155**.[266] Model A requires participation of d-orbitals and model B cannot be justified under experimental observations and hence a more accurate representation of the S≡N bond is shown in model C. With the concept of negative hyperconjugation, the interaction

of the nonbonding orbitals on the nitrogen with the antibonding orbitals on the sulfur, the issues with model A and B are overcome (Figure 2.35).

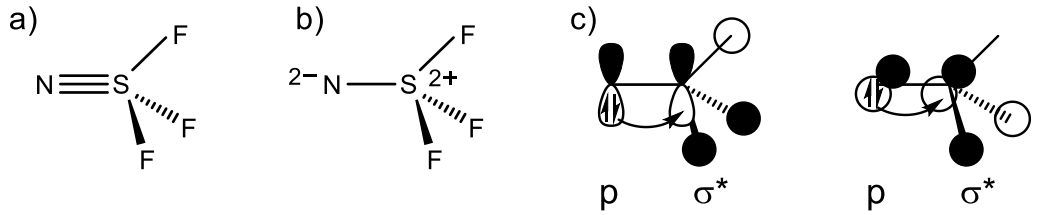
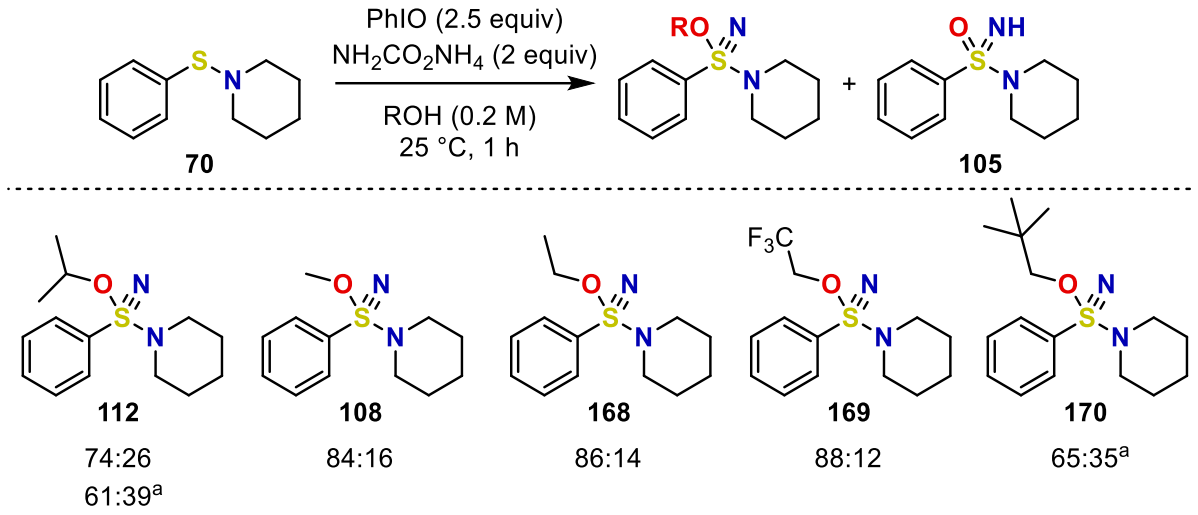


Figure 2.35: Three different models for the bonding in trifluorothiazyne **155**. With model C fitting experimental findings and *ab initio* calculations.[266]

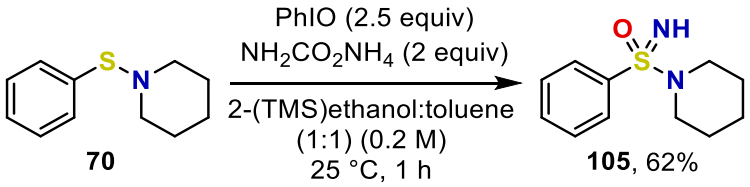
2.3.6.3 Synthesis of Alkoxy-amino-λ⁶-sulfanenitriles

There were many similarities between the observations reported by Yoshimura on alkoxy-λ⁶-sulfanenitriles and the alkoxy-amino-λ⁶-sulfanenitriles in this study. For instance, after their synthesis from sulfenamides under acid free conditions, attempts at removing any sulfonimidamide that had formed in the reaction were unsuccessful as purification via flash chromatography instead converted all of the alkoxy-amino-λ⁶-sulfanenitriles to the sulfonimidamide on each stationary phase tested.[220] Therefore, the alkoxy-amino-λ⁶-sulfanenitriles in this study were isolated as mixtures with a small amount of sulfonimidamide present in each case. Switching the alcohol solvent allowed trivial access to a range of different λ⁶-sulfanenitrile structures (Scheme 2.36). Interestingly, the ratio between the λ⁶-sulfanenitrile and sulfonimidamide differed depending on which alcohol was used and this was broadly in-line with the nucleophilicity of the solvent, with more electron-rich alcohols affording an increased amount of the λ⁶-sulfanenitrile relative to the sulfonimidamide. Solid alcohols could also be used such as neopentyl alcohol when dissolved in an equimolar amount of toluene, in this case a reduced amount of λ⁶-sulfanenitrile is formed presumably due to the decreased concentration of the alcohol relative to sulfenamide **70**. When phenol or *p*-methoxyphenol were used as the reaction solvent, the starting material was returned with no reaction taking place.



Scheme 2.36: Synthesis of alkoxy-amino-λ^6-sulfanenitriles under acid free NH and O transfer conditions. Compounds **108**, **112** and **168-170** are afforded as mixtures with the corresponding sulfonimidamide **105**. Reactions performed on a 0.15 mmol scale. [a] Solvent a 1:1 mixture of the alcohol and toluene.

Using a labile alcohol, it was postulated sulfonimidamide **105** could be accessed directly in the absence of an acid. It was hoped by using 2-trimethylsilylethanol as the solvent for the reaction an unstable intermediate would be formed allowing conversion to the sulfonimidamide through silyl promoted elimination. This was indeed the case, with the ratio between the λ^6-sulfanenitrile relative to the sulfonimidamide being substantially reduced (15:85), allowing for the isolation of sulfonimidamide **105** in a 62% yield after purification via column chromatography (Scheme 2.37).

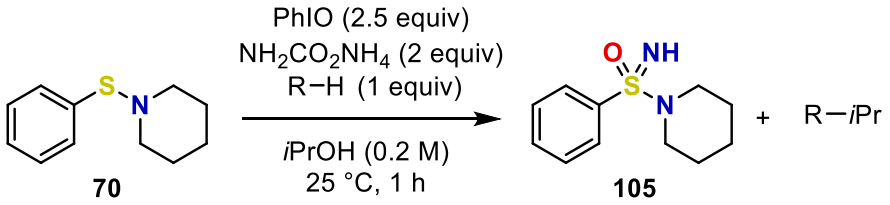


Scheme 2.37: Synthesis of sulfonimidamide **105** under acid free conditions.

2.3.6.4 Reactivity of Alkoxy-amino-λ^6-sulfanenitriles

The main role of the acetic acid under the standard reaction conditions to form sulfonimidamides is to break down the intermediate alkoxy-amino-λ^6-sulfanenitriles. After drawing comparisons to Yoshimura and co-workers' study on related of amino-λ^6-sulfanenitriles[263] it was postulated that this process involved alkylation of the conjugate base. To test this theory, attempts were made to identify isopropyl acetate under the standard reaction conditions. However, due to its low boiling point, it could only be detected later by *in situ* ^{1}H NMR studies. Instead, in the knowledge that other acids can effect this transformation (section 2.3.3.4), benzoic acid and *p*-toluenesulfonic acid were used as

possible alternatives which would form less volatile alkylated species (Table 2.20). Pleasingly, isopropyl benzoate was detected in a 48% yield in the crude mixture. This is presumed to form through protonation of the S≡N bond followed by attack of the conjugate base (Table 2.20, entry 2). In the case of *p*-toluenesulfonic acid, a reduced yield of **105** was observed, however, it seemed to have been solely derived from attack of the sulfonate anion on the isopropyl group (Table 2.20, entry 3).

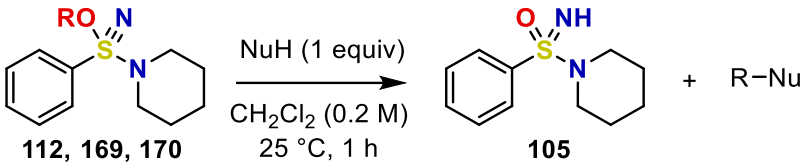


Entry	R-H	Yield (%) [a]	
		105	R–*i*Pr
1	AcOH	90	- [b]
2	$PhCO_2H$	89	48
3	*p*TsOH	30 [c]	29

Table 2.20: Attempted detection of alkylated species from the break down of alkoxy-amino-λ^6-sulfanenitrile **112** with different acids. Reactions on a 0.2 mmol scale. [a] Yields calculated by ^{1}H NMR spectroscopy with respect to 1,3,5-trimethoxybenzene as an internal standard. [b] Only observed during *in situ* ^{1}H NMR studies. [c] Remaining staring material decomposed.

To further understand the reactivity of these alkoxy-amino-λ^6-sulfanenitriles, they were treated with various nucleophiles in dichloromethane at room temperature (Table 2.21). The following reactions were performed on mixtures of the λ^6-sulfanenitrile:sulfonimidamide with the yields taking into account the already present sulfonimidamide in the reaction. Subjecting model alkoxy-amino-λ^6-sulfanenitrile **112** to benzoic acid led to a quantitative yield of the sulfonimidamide **105** alongside a 93% yield of the corresponding alkylated conjugate base (Table 2.21, entry 1). Thiophenol and phenol were both shown to be suitable reagents to effect this transformation as well, with the yield of the corresponding alkylated product reducing in line with the reduced acidity of the nucleophiles (Table 2.21, entry 2 & 3). Importantly, when sodium acetate or methyl iodide were used the starting λ^6-sulfanenitrile was returned, with no alkylation observed, confirming the requirement to have an acid present to break down the alkoxy-amino-λ^6-sulfanenitriles (Table 2.21, entry 4 and 5). Interesting λ^6-sulfanenitriles such as **169** could be used to transfer the 2,2,2-trifluoroethyl group to thiophenol, which may be hard to introduce through other means (Table 2.21, entry 6). The highly sterically hindered neopentyl

group could be transferred to benzoic acid and thiophenol, displaying the ability of these alkoxy-amino-λ^6-sulfanenitriles to act as alkylating agents (Table 2.21, entry 7 to 9).



112, 169, 170 **105**

Entry	R	Nu-H	Yield (%) [a,b]	
			105	R-Nu
1		$PhCO_2H$	quant	93
2		PhSH	92	84
3	*i*Pr	PhOH	quant	63
4		AcONa [c]	0	0
5		MeI [d]	0	0
6	CF_3CH_2	PhSH	74	75
7		$PhCO_2H$	69	63
8	$(CH_3)_3CCH_2$	PhSH	34	26
9		PhSH [e]	42	38

Table 2.21: Reactivity of alkoxy-amino-λ^6-sulfanenitriles with various nucleophiles. Reactions on a 0.1 mmol scale. [a] Yields calculated by ^{1}H NMR spectroscopy with respect to 1,3,5-trimethoxybenzene as an internal standard. [b] The amount of **105** corresponds to the amount of **105** formed in the reaction after subtraction of that already present in the mixture deriving from the synthesis of the alkoxy-amino-λ^6-sulfanenitrile (26% with **112**, 12% with **169** and 35% with **170**). [c] *i*PrOH used as a co-solvent to solubilise AcONa (1:1). [d] 2 equivalents of MeI used. [e] Reaction time extended to 72 h.

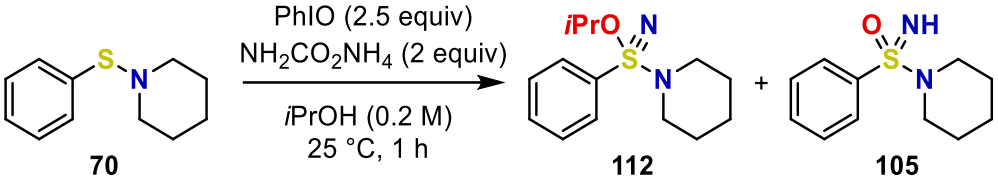
2.3.7 Mechanistic Proposals

Having isolated and explored the reactivity of the intermediate alkoxy-amino-λ^6-sulfanenitriles it is clear that at least one source of the oxygen atom in the sulfonimidamide products originates from the solvent. However, tests were carried out to determine whether there are other sources of oxygen in the final products aside from the solvent.

2.3.7.1 Oxygen Incorporation from Water

It was postulated that if the alcohol solvent could add into an intermediate species, then so could any water that is present in the reaction. In order to test this hypothesis, various water doping experiments were carried out under the standard reaction conditions. First the effect of

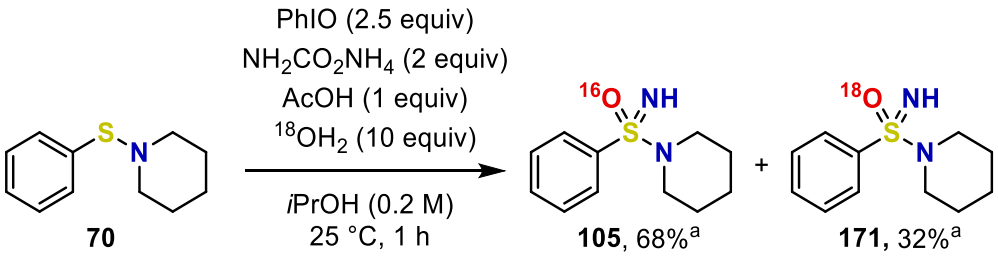
adding in 5 equivalents was examined in terms of how the λ⁶-sulfanenitrile:sulfonimidamide ratio would change (Table 2.22). Under the standard conditions in the absence of acid a roughly 3:1 ratio between the λ⁶-sulfanenitrile and sulfonimidamide in the product distribution is seen (Table 2.22, entry 1). This ratio remains essentially unchanged after addition of water to the mixture and extraction with dichloromethane and this indicates that λ⁶-sulfanenitrile **112** is stable to water (Table 2.22, entry 2). However, when adding in five equivalents of water at the beginning of the reaction, this changed the product ratio to 3:2 (Table 2.22, entry 3).



Entry	Variable	Ratio (%) [a]	
		112	**105**
1	-	74	26
2	Aqueous Workup	73	27
3	H_2O (5 equiv)	60	40

Table 2.22: Effect of water on the product distribution under acid free NH and O transfer conditions. Reactions on a 0.15 mmol scale. [a] Determined by the integral of **112**:**105** by ^{1}H NMR spectroscopy.

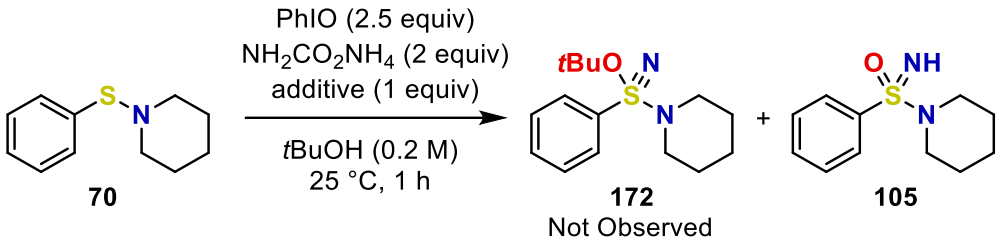
In order to attribute the increase in sulfonimidamide formation to incorporation of water and no other effects, the standard reaction conditions were altered by adding 10 equivalents of ^{18}O labelled water (Scheme 2.38). After isolating the sulfonimidamide, HRMS analysis showed that roughly a third of the product consisted of the ^{18}O isotope *versus* the ^{16}O isotope. This indicated that water, alongside the solvent, are possible sources of oxygen in the sulfonimidamide products.



Scheme 2.38: Synthesis of ^{18}O labelled sulfonimidamide **171**. Reaction performed on a 0.15 mmol scale. [a] Ratio determined by the peak heights of **105**:**171** in HRMS.

2.3.7.2 Oxygen Incorporation from Carboxylate

Attempts at using *t*BuOH as the reaction solvent under acid free conditions, did not yield the expected λ^6-sulfanenitrile product **172** (Table 2.23). Instead, starting material was returned, alongside a small amount of product **105** (Table 2.23, entry 1). However, when adding 1 equivalent of acetic acid, this significantly changed the product distribution, affording sulfonimidamide **105** as the major product (Table 2.23, entry 2). It was postulated that this was due to the acetate assisting in the solubilisation of the iodosylbenzene, which was poor in *t*BuOH. Although, when using sodium acetate as an additive it was found that essentially the same product distribution was seen (Table 2.23, entry 3). As it was known that sodium acetate cannot break down the intermediate λ^6-sulfanenitrile **112** (Table 2.21), this suggested that the acetate had a crucial role in the formation of sulfonimidamide **105** under the below conditions, perhaps through oxygen transfer.



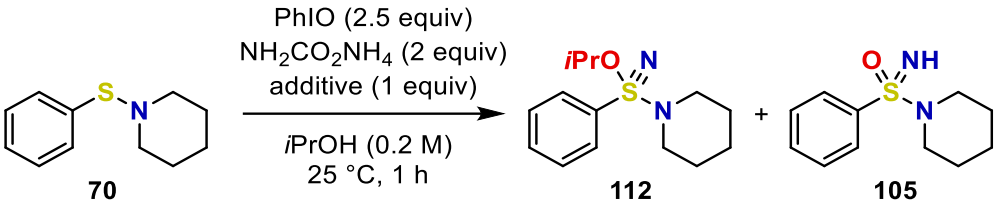
70 **172** Not Observed **105**

Entry	Additive	Ratio (%) [a]		
		70	**172**	**105**
1	-	82	0	18
2	AcOH	12	0	88
3	AcONa	18	0	82

Table 2.23: Effect of additives on the product distribution under NH and O transfer conditions in *t*BuOH. Reactions on a 0.15 mmol scale. [a] Determined by the integral of **70**:**105** by ^{1}H NMR spectroscopy.

To investigate the role of the carboxylate further, control reactions were performed with different carboxylate salts (Table 2.24). When using sodium acetate in place of acetic acid under the standard reaction conditions, sulfonimidamide **105** was formed in high yield (Table 2.24, entry 1). λ^6-Sulfanenitrile **112** was also detected which is expected to be stable under the reaction conditions, given that sodium acetate is not able to break down these species, but only in low yield. In order to check that the sodium counterion is not facilitating the break down of λ^6-sulfanenitrile **112** the reaction was performed with tetrabutylammonium acetate and essentially the same product profile was observed (Table 2.24, entry 2). These results suggested a third pathway whereby through attack of the carboxylate on the sulfur centre an

acetoxy-amino-λ^6-sulfanenitrile could be formed which breaks down under the reaction conditions to form sulfonimidamide **105**. This explains the increased conversion to the sulfonimidamide and the reduced formation of the λ^6-sulfanenitrile **112**, as the acetate is in competition with the solvent. Additionally, when using sodium benzoate, a reduced amount of the sulfonimidamide **105** was formed, whilst an increased amount of λ^6-sulfanenitrile **112** was formed through attack of the solvent (Table 2.24, entry 3). This was rationalised by considering the reduced nucleophilicity and increased steric bulk of the benzoate compared to the acetate.

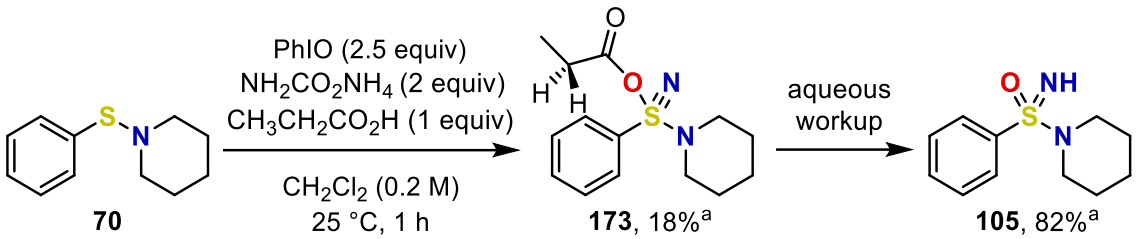


70 **112** **105**

Entry	Additive	Ratio (%) [a]		
		70	**112**	**105**
1	AcONa	10	9	73
2	$AcONBu_4$	13	7	74
3	$PhCO_2Na$	12	55	36

Table 2.24: Effect of carboxylate salts on the product distribution under NH and O transfer conditions in *i*PrOH. Reactions on a 0.15 mmol scale. [a] Yields calculated by ^{1}H NMR spectroscopy with respect to 1,3,5-trimethoxybenzene as an internal standard.

The next aim was to try and detect this fleeting acyloxy-amino-λ^6-sulfanenitrile species. To achieve this, the solvent was changed to dichloromethane as it was assumed the normal *i*PrOH solvent would facilitate its break down. In addition, the use of propanoic acid instead of acetic acid was considered with the expectation that this species would be easier to detect through ^{1}H NMR spectroscopy given that it should exhibit diastereotopic protons α to the carbonyl group instead of the expected singlet when using acetic acid. Pleasingly, under these conditions the acyl-amino-λ^6-sulfanenitrile **173** could be detected in 18% yield after evaporation of the solvent. When performing an aqueous work up on this mixture, all of the acyloxy-amino-λ^6-sulfanenitrile species **173** broke down, affording sulfonimidamide **105** in an 82% yield from sulfenamide **70** (Scheme 2.39).

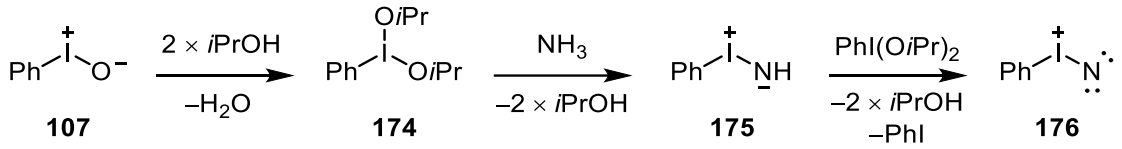


Scheme 2.39: Detection of acyl-amino-λ^6-sulfanenitrile toward the synthesis of sulfonimidamide **105**. Reaction performed on a 0.15 mmol scale. [a] Yields calculated by ^{1}H NMR spectroscopy with respect to 1,3,5-trimethoxybenzene as an internal standard.

*2.3.7.3 Formation of Iodonitrene **176***

The first step in the reaction mechanism was expected to be a solubilisation of the polymeric iodosylbenzene in the isopropanol solvent. Reactions on hypervalent iodine centres are akin to more traditional transition metal chemistry and display ligand exchange, reductive elimination and ligand coupling.[267] Iodosylbenzene is essentially insoluble in non-nucleophilic organic solvents or in water, but is readily dissolved in methanol to form iodobenzene dimethoxide, PhI(OMe)$_2$ formed through a ligand exchange reaction on the iodine centre.[268] Electrospray ionization mass spectrometry has been used to try to further identify the species that are present in methanolic solutions of iodosylbenzene and whilst the major peak corresponded to [PhIOMe]$^+$, dimeric species are also present.[269,270] It is likely that when iodosylbenzene is added to isopropanol, a similar process occurs forming iodobenzene diisopropoxide, PhI(O*i*Pr)$_2$ **174** as the major component (Scheme 2.40).

Prior studies on the NH transfer to sulfoxides by Bull, Luisi and co-workers have shown that under related conditions the role of the ammonium carbamate is to act as a convenient source of ammonia in solution through decarboxylation. In fact, other ammonia sources were shown to afford the corresponding sulfoximines just as efficiently, including ammonium acetate or ammonia in methanol solution.[164] The ammonia in solution is then expected to undergo a ligand exchange with the iodobenzene diisopropoxide, forming iminoiodane **175** (Scheme 2.40). Known iminoiodanes are iodine(III) reagents which typically require a strongly electron-withdrawing group such as a sulfonamide to stabilise the negative charge on the nitrogen atom.[94] An iminoiodinane derived from ammonia is therefore expected to be unstable and short-lived. Previous attempts at detecting this species through ^{1}H NMR studies have been unsuccessful, presumably due to its fleeting nature. However, it has been observed in ^{15}N labelled flow HRMS experiments when mixing bis(acetoxy)iodobenzene with ammonium acetate in methanol.[164]



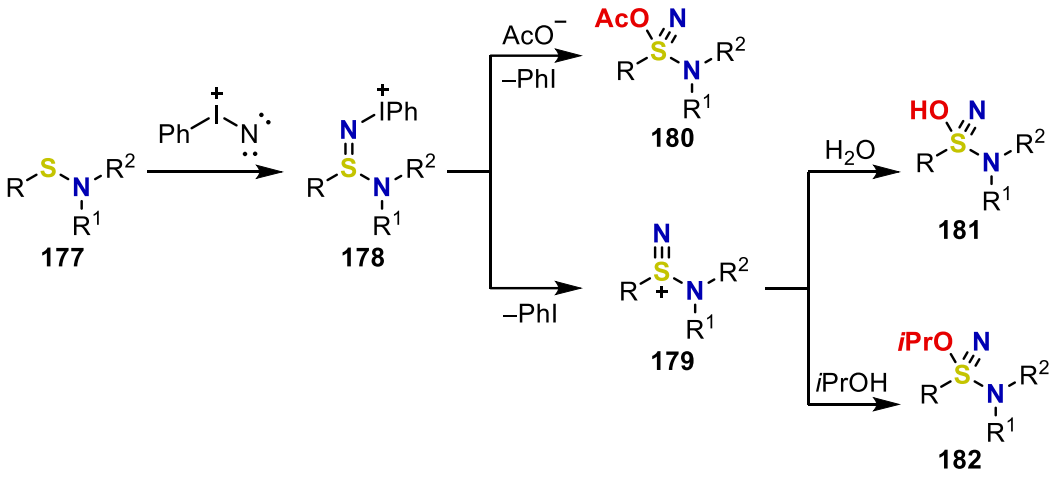
Scheme 2.40: Mechanistic proposal for the formation of iodonitrene **176**.

Iodonitrene **176** has been detected through similar ^{15}N labelled flow HRMS experiments and is seemingly less prevalent than iminoiodane **175** in solution. These studies were conducted on bis(acetoxy)iodobenzene as the starting material, but since this is known to dissolve in methanol to form similar species to iodosylbenzene, it is believed that iodonitrene **176** is also the active nitrogen transfer reagent under these conditions.[270]

*2.3.7.4 Formation of λ⁶-sulfanenitrile Intermediates **180-181***

From the isolation of various λ^6-sulfanenitriles it is apparent that the nitrogen atom is transferred to the sulfenamide before the oxygen atom, indicating that after the formation of iodonitrene **176**, this species reacts with the sulfenamide to generate intermediate **178**. This sulfinamidine intermediate, with an excellent leaving group on the imine nitrogen, is well poised for a nucleophilic attack on the sulfur centre (Scheme 2.41).

Intermediate **178** is similar to the halosulfilimines that Yoshimura has previously shown can be used for the synthesis of alkoxy-λ^6-sulfanenitriles or sulfoximines (Scheme 2.33).[260] Kinetic analysis on those systems indicated that nucleophilic attack on the sulfur centre could proceed via an SN1 mechanism forming a cationic λ^6-sulfanenitrile species before nucleophilic attack or an SN2 mechanism whereby the loss of the leaving group on the imine nitrogen occurs at the same time as nucleophilic attack.[271] An SN2 mechanism was shown to be likely with charged nucleophiles such as alkoxides, whereas an SN1 mechanism was more probable with a neutral nucleophile such as the alcohol solvent. In addition, the rate constant for the SN1 pathway was larger when utilising iodosulfilimines *versus* bromo- or chloro derivatives. Considering this, it is possible that the attack of the solvent and water in this system proceeds via an SN1 mechanism and the attack of the acetate proceeds via an SN2 mechanism, forming a variety of λ^6-sulfanenitrile intermediates **180**-**182** which have differing levels of stability (Scheme 2.41).



Scheme 2.41: Mechanistic proposal for the formation of λ^6-sulfanenitrile intermediates **180**-**182**.

*2.3.7.5 Formation of Sulfonimidamides **184***

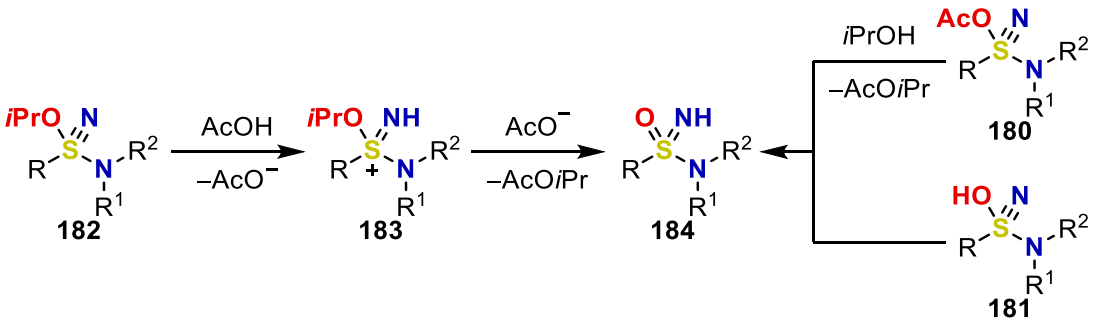
λ^6-Sulfanenitriles derived from intermediate **178** break down through attack of different nucleophiles to afford sulfonimidamide **184**. Importantly, all intermediate λ^6-sulfanenitrile species go on to form the desired sulfonimidamides under the reaction conditions, conferring the high observed chemoselectivity (Scheme 2.42).

Acyl-amino-λ^6-sulfanenitrile **180** can only be observed when the reaction is carried out in a non-nucleophilic solvent, suggesting they are rapidly broken down through the action of the alcohol solvent, forming isopropyl acetate. However, it is possible that these intermediates can act as acylating agents to other nucleophiles in solution, including the imine nitrogen of the sulfonimidamide, which is one possible route for the formation of acylated pyridyl sulfonimidamide **128** (Scheme 2.42). This pathway is more troublesome when using a less nucleophilic solvent such as trifluoroethanol, or acetonitrile for example.[167,169]

It is likely that hydroxy-amino-λ^6-sulfanenitrile **181** instantly tautomerises in solution to the more stable sulfonimidamide **184**.

Alkoxy-amino-λ^6-sulfanenitriles **182** are stable under acid free conditions and require an acid to be broken down to form the desired sulfonimidamide **184**. Acetic acid was the reagent of choice under these conditions, but less acidic species such as thiophenol and phenol were also capable of inducing their break down. According to kinetic analysis conducted on the thiol and acid mediated break down of alkoxy-λ^6-sulfanenitriles, a two-step mechanism is proposed for the acetic acid promoted break down of alkoxy-amino-λ^6-sulfanenitriles **182** to sulfonimidamides **184** (Scheme 2.42).[272,273] The measured pK_{aH} of amino-λ^6-sulfanenitriles is ~7[258] and so alkoxy-amino-λ^6-sulfanenitrile **182** is likely slightly lower, making it a good match for acetic acid. An initial protonation of the λ^6-sulfanenitrile nitrogen then allows for attack on

the alkyl group via an SN1 or SN2 mechanism depending on the nature of the alkyl group, affording the sulfonimidamide **184** and isopropyl acetate. In addition, the isotope effect was measured, indicating attack of the nucleophile being the rate determining step.[273]



Scheme 2.42: Mechanistic proposal for the formation of sulfonimidamides **184**.

It is currently unclear how much each pathway contributes to the overall synthesis of sulfonimidamide **184**, but it is likely that the water incorporation pathway contributes the least to the overall amount of sulfonimidamide that is formed. In the ^{18}O labelling studies with 10 equivalents of water added, this only contributed to roughly a third of the sulfonimidamide product, however, water released from the iodosylbenzene and any water not omitted from the glassware or solvent would clearly contribute to the ^{16}O labelled product. In addition, when performing the reaction in the absence of acid and comparing the ratios of λ^6-sulfanenitrile:sulfonimidamide, in theory the only competing pathway with λ^6-sulfanenitrile formation is through incorporation of water forming sulfonimidamide. Evidently in the cases observed in this study, incorporation of solvent is much more favourable than water under those conditions. It is less clear whether incorporation of acetate or solvent is more prevalent. However, the sheer abundance of the solvent *versus* the acetate as well as the absence of *N*-acyl products, which are significant by-products in trifluoroethanol under related conditions for the synthesis of sulfoximines,[169] indicates that solvent incorporation is the major pathway toward sulfonimidamide synthesis.

These mechanistic studies are corroborated by other proposals for the synthesis of sulfoximines from both sulfoxides and sulfides.[135,164,166,167,169,274]

2.3.8 Conclusions

A convenient procedure for the synthesis of NH-sulfonimidamides from sulfenamides has been developed. Utilising prior knowledge of NH and O transfer chemistry to sulfur centres, conditions have been found to be applicable to acid sensitive sulfenamides. Using iodosylbenzene, the acidity of the reaction can be easily controlled by adding in 1 equivalent of acetic acid. When no external acid is added, it is possible to isolate novel

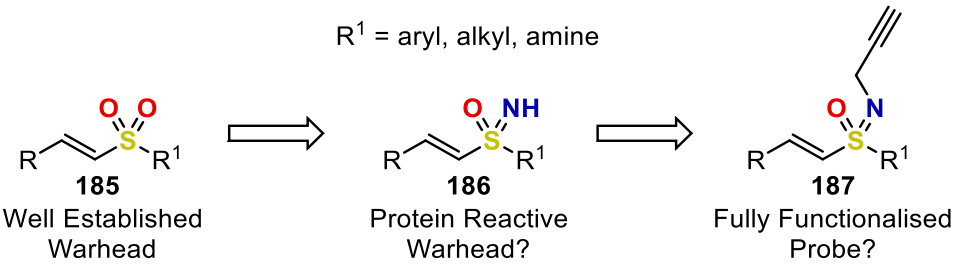
alkoxy-amino-λ^6-sulfanenitriles. These species have been shown to be powerful alkylating agents to a range of acidic nucleophiles, transferring alkyl groups which may have been hard to implement using other means. The detection of λ^6-sulfanenitrile intermediates provides unique insight into the reaction mechanism of these NH and O transfer reactions and indicates the solvent, acetate and water are all possible sources of the oxygen in the final products. The developed methodology has a high tolerance for different functionalities and is very time and cost efficient in the construction of sulfonimidamide scaffolds. It is possible to be used for late-stage functionalisation as evidenced by the incorporation of a sulfonimidamide into antidepressants fluoxetine and desipramine. This route toward sulfonimidamides has also been used for the synthesis of an aza-analogue of sulfonamide containing drug probenecid. The utility of the nitrogen in sulfonimidamides has also been exemplified through various N-functionalisation's on aza-probenecid.

Drawbacks of this methodology include the varied results obtained through the reaction of secondary sulfenamide substrates and the reduced yield obtained from electron poor substrates. In addition, substrates which contain an electron rich heterocycle have been shown to be incompatible with these NH and O transfer conditions previously, presumably due to their reactivity with the electrophilic iodonitrene.[164] These remain key challenges with this NH and O transfer chemistry and although Reboul and co-workers have shown that trifluoroethanol can be used to enhance the reactivity of electron poor sulfide systems, this leads to other issues such as formation of *N*-acyl products.[169]

2.4 Accessing New Reactive Warheads for Drug Discovery

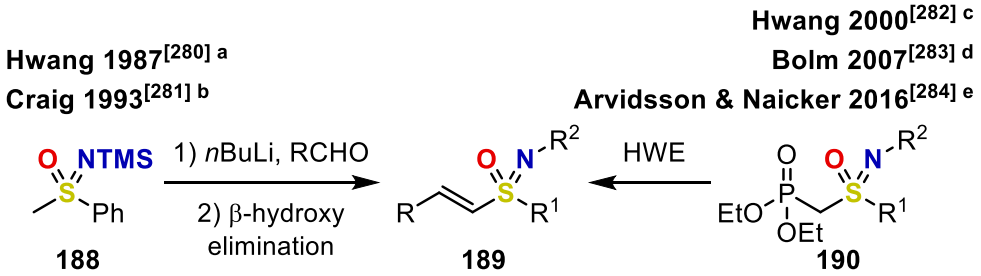
2.4.1 Project Aims

Vinyl sulfones and sulfonamides are well established electrophiles and have been well used as reactive warheads in protein-targeted covalent probes for many years.[275,276] However, new and bespoke warheads which have different protein selectivity and reactivity profiles are of vital importance for future covalent probes.[277,278] Therefore, it was postulated that vinyl sulfoximines and sulfonimidamides could offer unique and potentially useful reactivity profiles as warheads in future covalent probes. These aza-analogues offer different hydrogen bonding architectures as well as an extra handle for diversification on the nitrogen for installation of chemical biology functionalities such as alkynes, allowing for the generation of fully functionalised probes (Scheme 2.43).[279]



Scheme 2.43: Potentially valuable warheads and probes based on sulfoximines or sulfonimidamides.

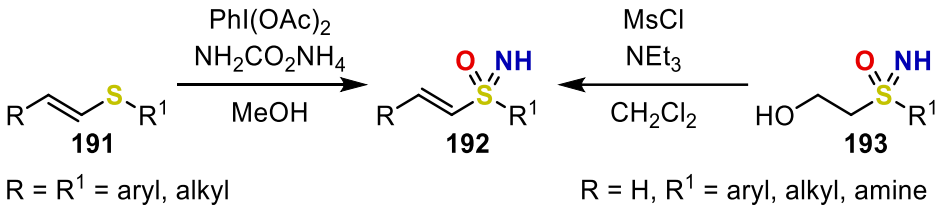
The two main approaches that have been used to access vinyl sulfoximines previously include carbonyl addition followed by β-hydroxy activation/elimination[280,281] and Horner-Wadsworth-Emmons (HWE) olefination.[282–284] Whilst these routes demonstrate the stability of vinyl sulfoximines, they have clear limitations. They require long synthetic sequences, including various protecting group manipulations and the imination step typically involves the use of either hydrazoic acid or MSH, which as previously discussed have various safety concerns associated with their use (Scheme 2.44). Vinyl sulfonimidamides on the other hand are essentially unknown aside from two recent examples,[191] which is a reflection on the historically limited synthetic methods available for their synthesis.



Scheme 2.44: Previous methods to access vinyl sulfoximines. [a] Elimination with CDI. [b] Elimination with MeOCOCl. [c] R^1 = Ar, R^2 = TMS. [d] R^1 = Me, R^2 = TBDPS. [e] R^1 = Ar, R^2 = H.

With the introduction of new and facile NH and O transfer methodology from sulfides or sulfenamides respectively, there is the potential for shorter and safer routes towards vinyl sulfoximines and sulfonimidamides.[166,229]

Two main routes to these potential warheads were envisaged to allow for the synthesis of either terminal or substituted derivatives. The first involves a metal catalysed alkyne hydrothiolation to afford vinyl sulfides which could then undergo direct oxidation/imination to afford substituted vinyl sulfoximines. The other route drew inspiration from the β-hydroxy activation/elimination approaches that were previously discussed[280,281] and utilised a mesylation strategy to activate the β-hydroxy group to afford terminal vinyl sulfoximines or sulfonimidamides (Scheme 2.45).

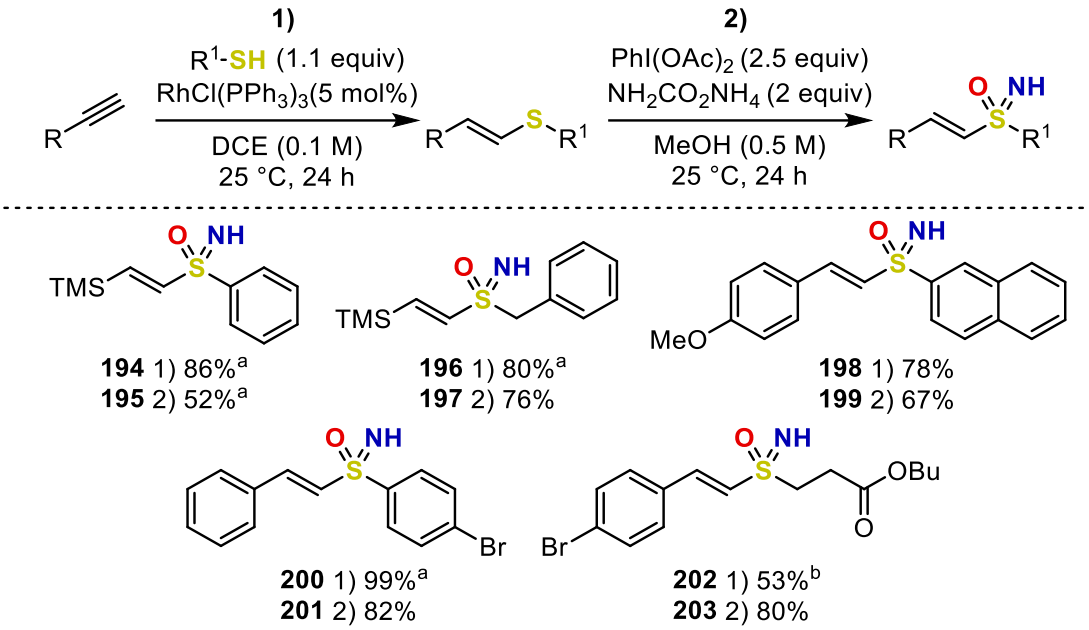


Scheme 2.45: Proposed routes toward vinyl sulfoximines and sulfonimidamides.

2.4.2 Hydrothiolation of Alkynes

There are a variety of methods available for the synthesis of either branched,[285,286] linear *E*-vinyl sulfides[287,288] or linear *Z*-vinyl sulfides[289] in high regio- and stereoselectivity. In this study, linear *E*-vinyl sulfides were targeted and both of the aforementioned methodologies for these products utilise Wilkinson's catalyst ($RhCl(PPh_3)_3$) to mediate the alkyne hydrothiolation. Due to the more extensive thiol scope described by Love and co-workers, using dichloroethane (DCE) as the reaction solvent, these conditions were used for the synthesis of a variety of vinyl sulfides for further functionalisation.[288] This work (Section 2.4) was conducted in collaboration with Prof. Alan Armstrong's group at Imperial College London, with Dr Gregory Craven, Stephanie Greed, Alex McDermott and Ruth Tweedy performing some of the following scope examples.

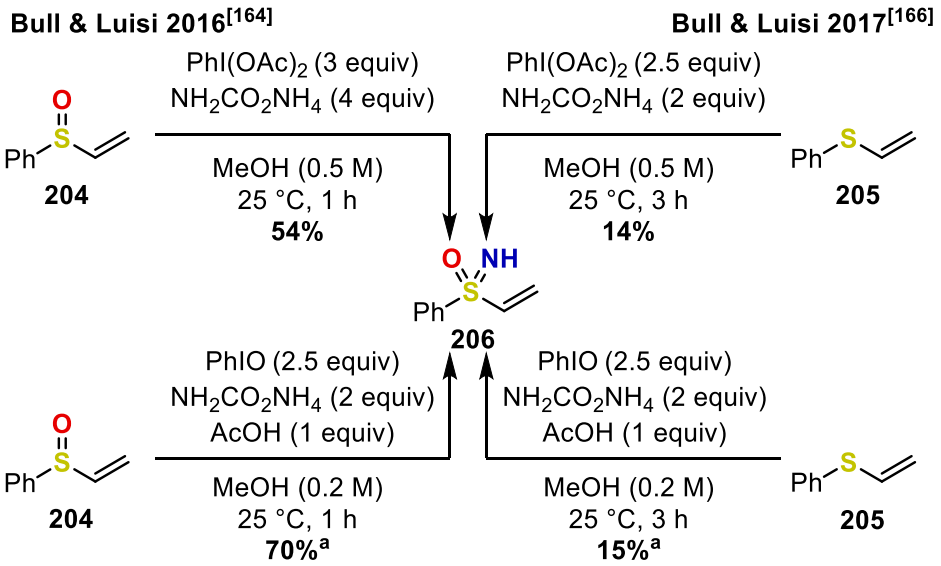
A variety of *E*-vinyl sulfides were accessed using various silyl, aryl and alkyl alkynes in conjunction with different alkyl and aryl thiols. The corresponding *E*-vinyl sulfoximines could then be synthesised through NH and O transfer methodology (Scheme 2.46).[166] The incorporation of aryl bromides, esters and amines allows for further elaboration of these scaffolds. The TMS protected alkenes that are present in **195** and **197** also offer the possibility to access terminal vinyl sulfoximines. The hydrothiolation reaction to access sulfide **202** required heating to reflux and a higher catalyst loading as just trace amount of product was formed under the standard reaction conditions.



Scheme 2.46: Synthesis of vinyl sulfoximines through hydrothiolation of alkynes to form vinyl sulfides followed by one-pot NH and O transfer. Initial reactions performed on a 1.0-2.0 mmol scale. [a] Reactions performed by either Dr Gregory Craven or Stephanie Greed. [b] 10 mol% of $RhCl(PPh_3)_3$ used as well as heating to 65 °C.

2.4.3 β-Hydroxy Activation/Elimination

In previous NH and O transfer studies, it was shown that terminal vinyl sulfoximines can only be isolated in moderate or low yield, depending on the starting material (Scheme 2.47).[164,166] This reduced yield has been attributed to acid catalysed polymerisation which was hoped to



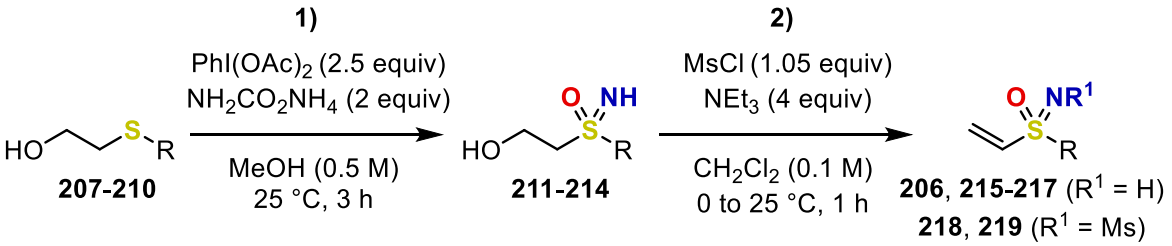
Scheme 2.47: Comparing prior routes toward vinyl sulfoximine **206** to milder NH and O transfer conditions.[229] Reactions performed on a 0.2 mmol scale. [a] Yields calculated by ^1H NMR spectroscopy with respect to 1,3,5-trimethoxybenzene as an internal standard.

be nullified through the use of milder NH and O transfer conditions.[229] Whilst improvements in the yield was seen from vinyl sulfoxide **203**, the yield from sulfide **205** remained essentially the same. Deterred by the limited availability of terminal vinyl sulfoxides or sulfinamides, the introduction of the NH and O groups to the sulfur centre therefore had to occur before the vinyl group was in place which required a different approach.

As β-hydroxy activation/elimination is an established approach to terminal vinyl sulfoximines, it was hoped that prior routes could be improved upon with modern NH and O transfer methods. Namely, with the β-hydroxy group in place, it was envisaged that a NH and O transfer could occur, followed by a chemoselective mesylation step which would convert the β-hydroxy group to an effective leaving group to induce the triethylamine mediated elimination.

2.4.3.1 Synthesis of Sulfoximines

This route was applied to four different β-hydroxy sulfides which themselves could be obtained from commercial vendors. In all cases, the NH and O transfer to these substrates proceeded



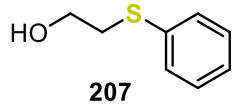
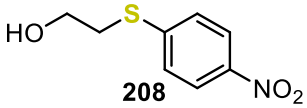
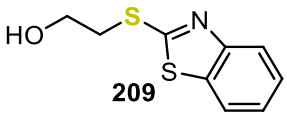
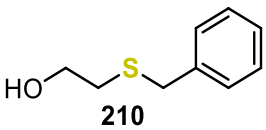
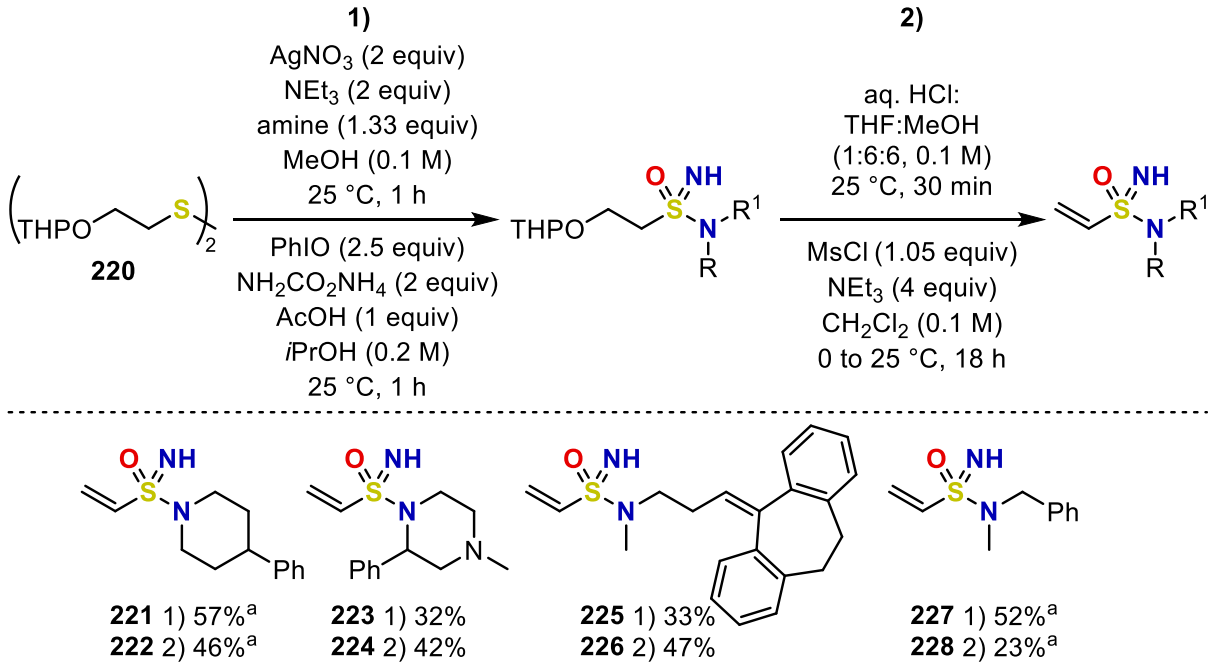
Entry	Sulfide	Yield (%)		
		211-214	**206**, **215-217**	**218**, **219**
1	 **207**	73	50	6
2	 **208**	87[a]	52[a]	-
3	 **209**	54	39	-
4	 **210**	91[a]	35[a]	29[a]

Table 2.25: Synthesis of terminal vinyl sulfoximines via alcohol elimination. Initial reactions performed on a 1.0-2.0 mmol scale. [a] Reactions performed by either Stephanie Greed or Ruth Tweedy.

in high yield, including benzothiazole substrate **209** in order to yield a variety of β-hydroxy sulfoximines **211**-**214** (Table 2.25). Treating alcohols **211**-**214** to a slight excess of methane sulfonyl chloride allowed access to a variety of vinyl NH sulfoximine substrates **206**, **215**-**217** bearing aromatic, heteroaromatic or benzyl substituents. Although good chemoselectivity was generally observed, in some cases it was also possible to isolate the corresponding mesylated vinyl sulfoximines **218**, **219**. These are anticipated to be more electrophilic than their corresponding NH counterparts and may represent an interesting class of warhead in their own right.

2.4.3.2 Synthesis of Sulfonimidamides

It was postulated that an analogous β-hydroxy activation/elimination route could be utilised to access terminal vinyl sulfonimidamides when combined with the NH and O transfer methodology to sulfenamides.[229] Due to a lack commercial availability, the β-hydroxy sulfenamides that were required for these targets first needed to be synthesised. To implement the desired side chain on the sulfenamide, disulfide **220** was first formed through THP protection before reaction with a sulfenamide. With refined conditions for the synthesis of sulfenamides using triethylamine, a selection of THP protected sulfenamides could be accessed which were telescoped directly into the NH and O transfer reaction to afford the THP protected sulfonimidamides in good yield across the two steps (Scheme 2.48). A simple deprotection of the THP group mediated by hydrochloric acid then afforded the alcohol. This in turn, could be mesylated and eliminated *in situ* to afford the corresponding vinyl



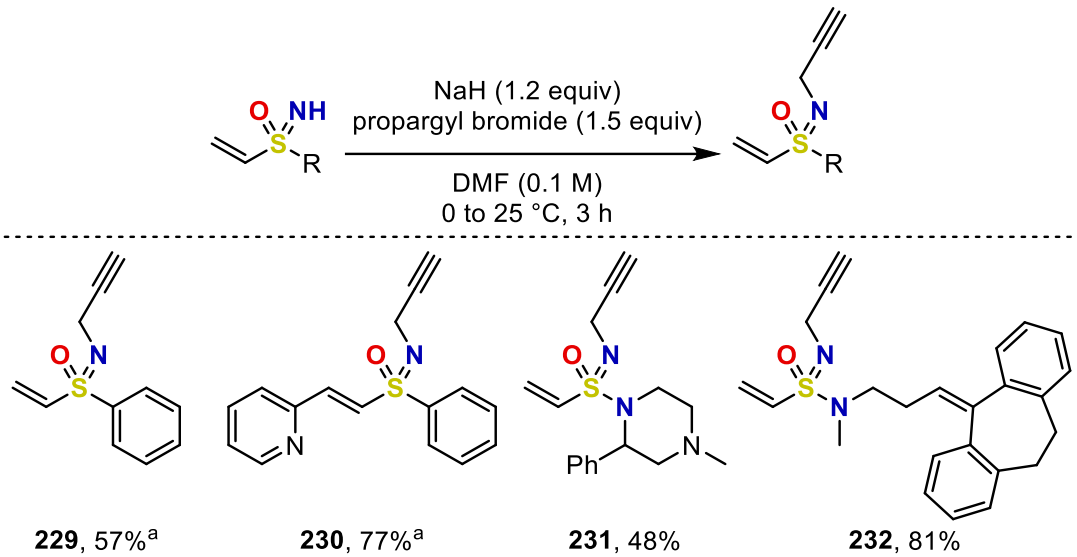
Scheme 2.48: Synthesis of terminal vinyl sulfonimidamides via alcohol elimination. Initial reactions performed on a 2.5 mmol scale. [a] Reactions performed by Gregory Craven.

sulfonimidamides. This simple and general route was applied to a variety of amines including nortriptyline, demonstrating the compatibility of this methodology with bioactive compounds.

2.4.4 *N*-Propargylation of Vinyl Sulfoximines and Sulfonimidamides

Click chemistry has become an extremely powerful tool for bioconjugation reactions which are useful for a variety of chemical biology experiments.[290] The gold standard reaction in this field is the copper(I)-catalysed cycloaddition of terminal alkynes and azides to form 1,2,3-triazoles due to its reliability, specificity, and biocompatibility.[291] However, many of the traditional types of covalent warheads do not offer a convenient handle for alkyne incorporation.[278] Therefore the incorporation of an alkyne handle to access a fully functionalised probe can be synthetically challenging.[292] Sulfoximines and sulfonimidamides offer a convenient handle from the imine nitrogen to incorporate a propargyl group in order to potentially access a fully functionalised probe in a straight forward manner.

To install a propargyl group into the newly developed warheads, conditions were adapted from the *N*-functionalisation of aza-probenecid (Section 2.3.5.3).[192] It was found that the phase transfer catalyst was not necessary in these cases to access propargylated sulfoximines and sulfonimidamides (Scheme 2.49). Terminal and substituted vinyl sulfoximines were successful in generating the desired *N*-functionalised sulfoximines as were two terminal vinyl sulfonimidamides affording **229**-**232**, showing the ability of these warheads to yield fully functionalised probes for chemical biology applications.



Scheme 2.49: *N*-Propargylation of vinyl sulfoximines and sulfonimidamides. Reactions performed on a 0.2 mmol scale. [a] Reactions performed by Alex McDermott.

2.4.5 Conclusions

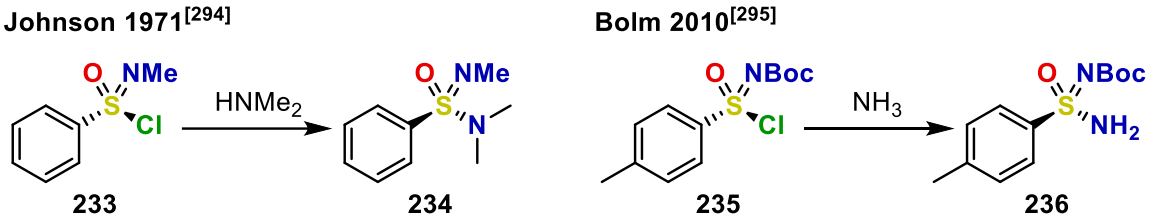
Two different routes have been developed for the synthesis of vinyl sulfoximines and sulfonimidamides. An initial hydrothiolation of alkynes affords substituted vinyl sulfides which can then be transformed into the corresponding sulfoximines with recently developed NH and O transfer methodology. The other route builds upon prior work on a β-hydroxy activation/elimination strategy to access terminal vinyl sulfoximines. However, this work improves on the literature precedent through the shortening of the synthetic sequence through the absence of protecting groups and a simpler oxidation/imination strategy. This route is also amenable to the synthesis of vinyl sulfonimidamides, of which there are very few examples. Propargylation of these newly developed warheads allows access to a novel class of fully functionalised probes for chemical biology.

2.5 Synthesis of Sulfonimidamides from Sulfonimidoyl Fluorides

A concise account of the work presented here has been published in *Chemistry A European Journal*.[293]

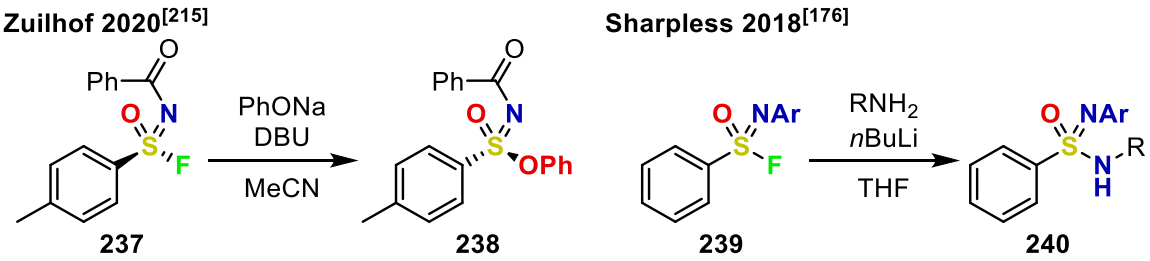
2.5.1 Project Aims

A broad array of methods for the preparation of sulfonimidamides are now available, having increased dramatically in the past few years (Section 1.3.2). However, there remains no general means of accessing enantioenriched derivatives, although two single examples have been reported from sulfonimidoyl chlorides (Scheme 2.50).[294,295]



Scheme 2.50: Only prior examples of enantioenriched sulfonimidamides.

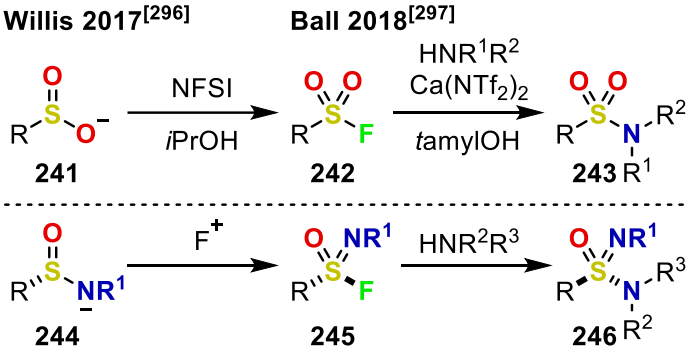
As previously discussed, sulfonimidoyl chlorides have stability concerns associated with them, but sulfonimidoyl fluorides on the other hand are much more stable and present useful opportunities in this arena.[175] The first enantioenriched sulfonimidoyl fluorides have been reported recently by Zuilhof and co-workers, prepared by separation of the enantiomers by chiral HPLC.[215] This study generated sulfonimidoyl fluorides and treated them with phenols to form sulfonimidates. This study illustrated both the configurational stability of the starting materials and that full retention of the *ee* was possible when reacting sulfonimidoyl fluorides with sodium phenolate (Scheme 2.51). In addition, Sharpless and co-workers have demonstrated that sulfonimidoyl fluorides can react with amines to form sulfonimidamides, however, there were just four examples and prior deprotonation of the amine with *n*BuLi was carried out in most cases (Scheme 2.51).[176]



Scheme 2.51: Recent precedent on the reactivity of sulfonimidoyl fluorides.

Building on these studies, it was hoped that the preparation of enantioenriched sulfonimidamides could be achieved through an enantioretentive reaction of neutral amines

with enantioenriched sulfonimidoyl fluorides. The preparation of sulfonimidoyl fluorides was targeted through fluorination of a novel sulfinamide salt species, drawing analogy to sulfinate salts which have been demonstrated to be effective precursors to sulfonamides via a sulfonyl fluoride intermediate (Scheme 2.52).[296,297]



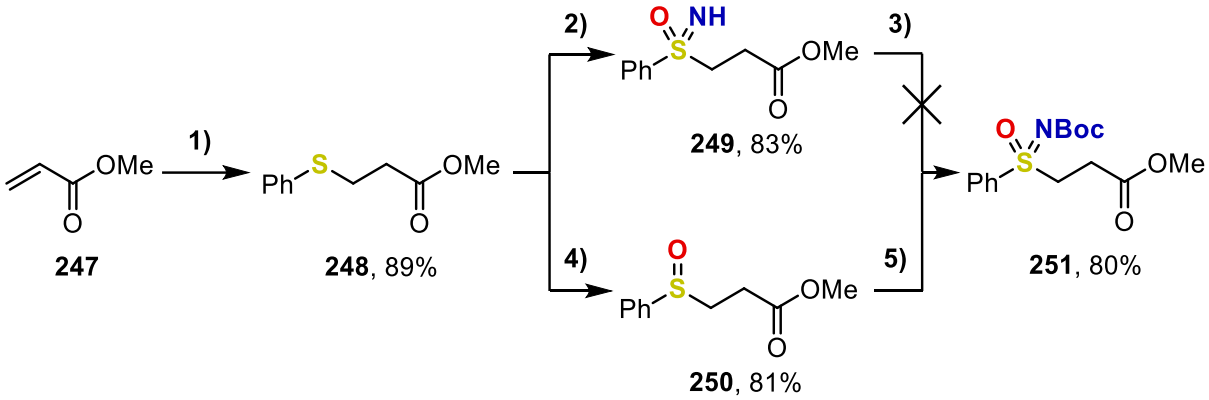
Scheme 2.52: Formation of sulfonamides from sulfinate salts and the planned analogous route from sulfinamide salts to form sulfonimidamides in an enantioselective fashion.

2.5.2 Accessing Sulfinamide Salts

At the time sulfinamide salts had not been reported in the literature before aside from being postulated as intermediates in allylic sulfinamide synthesis.[298] However, during the course of this study, further cases of sulfinamide salts as intermediates in synthesis were reported.[181,182,189] Thereby their isolation was a key milestone on this project and it was envisaged that sulfinamide salts could be prepared from the elimination of methyl acrylate from an NBoc sulfoximine, again drawing analogy to sulfinate salts.[299] The NBoc group was expected to be sufficiently electron withdrawing to allow for their isolation.

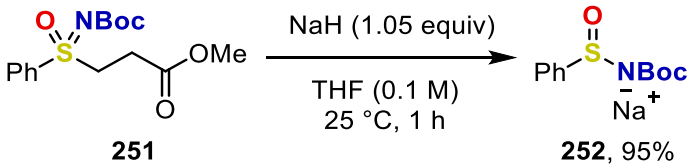
*2.5.2.1 Synthesis of Phenyl Sulfinamide Salt **252***

The first sulfinamide salt target became phenyl derivative **252** with the initial reaction toward this compound involving the 1,4 addition of thiophenol into methyl acrylate based on Ranu and co-workers conditions.[300] With the desired R group installed on the sulfur and the necessary methyl propionate group on the other side for elimination, the required oxygen and NBoc group could be introduced to the sulfur atom. The first route which was trialled for the synthesis of NBoc sulfoximine **251** involved the NH and O transfer to sulfide **248**[166] followed by Boc protection of the free NH sulfoximine based on Bolm and co-workers conditions.[301] However, since sodium hydride couldn't be used in this case for fear of competing deprotonation α to the ester, triethylamine was used but could not mediate this reaction, instead returning starting material. Therefore, another route was trialled which first oxidised sulfide **248** to sulfoxide **250** under the action of *m*CPBA, followed by NBoc transfer[150] and, pleasingly, in this case desired sulfoximine **251** could be accessed with >80% yield achieved in each step (Scheme 2.53).



Scheme 2.53: Routes to *N*Boc protected sulfoximine **251**. 1) PhSH (1 equiv), NaOAc (0.15 equiv), THF:H_2O (1:1, 0.3 M), 25 °C, 18 h, 15.0 mmol scale. 2) $PhI(OAc)_2$ (2.5 equiv), $NH_2CO_2NH_4$ (2 equiv), MeOH (0.3 M), 25 °C, 3 h, 1.0 mmol scale, 3) Boc_2O (1.1 equiv), NEt_3 (1.1 equiv), CH_2Cl_2 (0.1 M), 25 °C, 18 h, 0.83 mmol scale. 4) *m*CPBA (1.05 equiv), CH_2Cl_2 (0.15 M), 0 to 25 °C, 5 h, 13.2 mmol scale. 5) *t*Bu carbamate (1.5 equiv), $Rh_2(OAc)_4$ (2.5 mol%), $PhI(OAc)_2$ (1.5 equiv), MgO (4 equiv), CH_2Cl_2 (0.1 M), 40 °C, 18 h, 0.44 mmol scale.

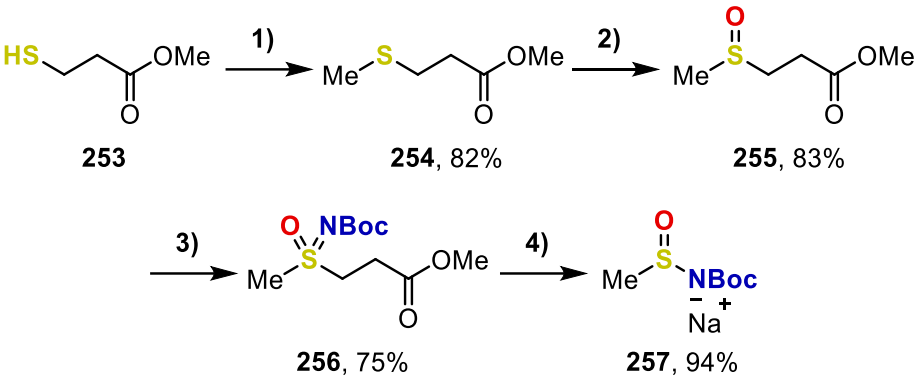
With a route through to sulfoximine **251** established the crucial elimination step was tested in order to access sulfinamide salt **252**. Treating sulfoximine **251** with sodium hydride in tetrahydrofuran caused precipitation of a white solid which upon filtration could be isolated and was identified as sulfinamide salt **252**. Just under a gram of this species could be isolated in a near quantitative yield as a white powder. Sulfinamide salt **252** was stable to long term storage in the freezer but was sensitive to protonation either with silica gel or upon addition of methanol (Scheme 2.54).



Scheme 2.54: Accessing sulfinamide salt **252** through sodium hydride mediated elimination of sulfoximine **251**. Reaction performed on a 3.4 mmol scale.

*2.5.2.2 Synthesis of Methyl Sulfinamide Salt **257***

With the phenyl sulfinamide salt available, attention turned to its methyl derivative in order to access a different substituent on the sulfur atom (Scheme 2.55). In this case, a thioalkylation strategy was implemented to access sulfide **254** before following the previously established route involving oxidation, NBoc transfer and elimination. High yields were obtained across all steps and the methyl sulfinamide salt **257** made a useful addition to the already synthesised phenyl sulfinamide salt **252** in order to further explore the reactivity of this novel species.

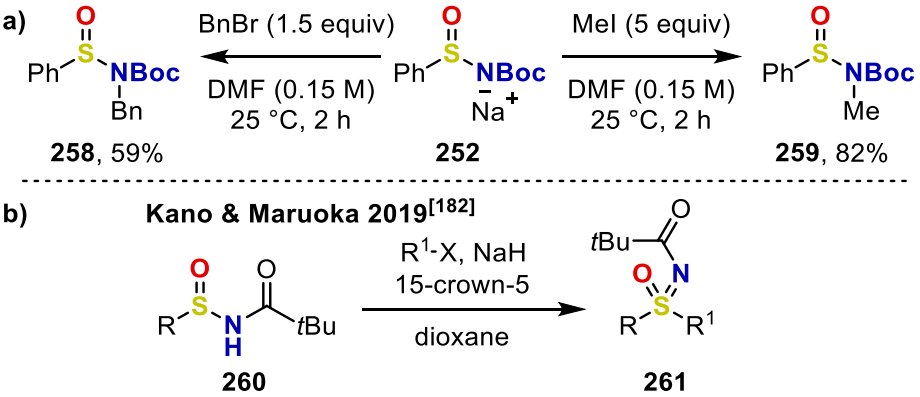


Scheme 2.55: Route toward methyl sulfinamide salt **257**. 1) MeI (2 equiv), K_2CO_3 (1.2 equiv), acetone (0.2 M), 25 °C, 24 h, 10 mmol scale. 2) *m*CPBA (1.05 equiv), CH_2Cl_2 (0.2 M), 25 °C, 1 h, 5.1 mmol scale. 3) *t*Bu carbamate (1.5 equiv), $Rh_2(OAc)_4$ (2.5 mol%), $PhI(OAc)_2$ (1.5 equiv), MgO (4 equiv), CH_2Cl_2 (0.1 M), 40 °C, 18 h, 2.38 mmol scale. 4) NaH (1.05 equiv), THF (0.1 M), 25 °C, 1 h, 1.5 mmol scale.

2.5.3 Preliminary Assessment of Sulfinamide Salt Reactivity

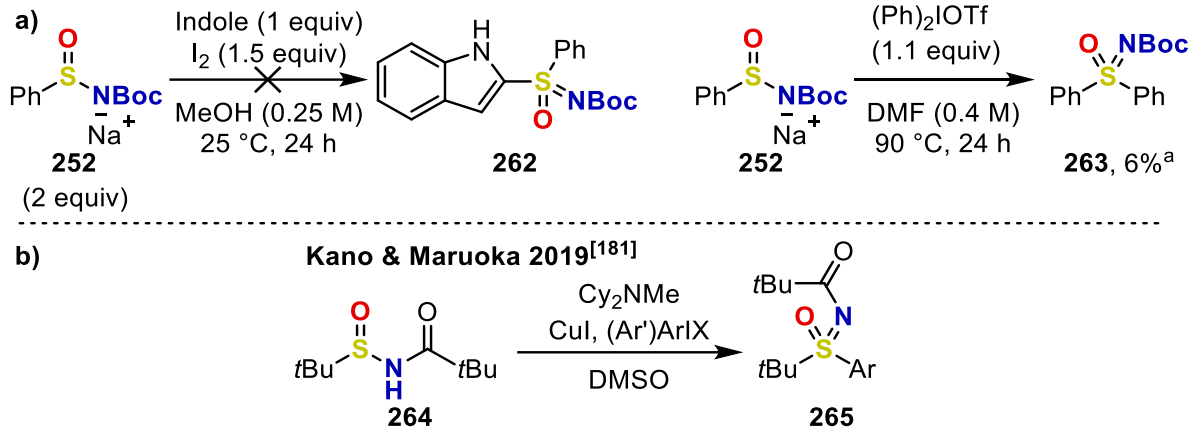
2.5.3.1 Alkylation Conditions

With two different sulfinamide salts available, their chemical reactivity was then assessed under alkylation conditions to form sulfoximines. The nucleophilic sulfinamide salts were initially reacted with alkyl halides in DMF to examine which atom would be alkylated (Scheme 2.56a). Unfortunately, *S*-alkylation was not observed which would form sulfoximines and instead alkylation occurred on the nitrogen atom to form substituted sulfinamides. These results are in agreement with a more recent report from Kano, Maruoka and co-workers on the alkylation of sulfinamide salts formed *in situ* who also saw no appreciable alkylation on the sulfur with a Boc protecting group. Instead, a pivaloyl protecting group was required on the nitrogen alongside a crown ether in dioxane as the solvent to achieve good *S*-selectivity (Scheme 2.56b).[182]



Scheme 2.56: Synthesis of sulfinamides from sulfinamide salt **252** and conditions for *S*-selectivity from Kano, Maruoka and co-workers. Reactions performed on a 0.2 mmol scale.

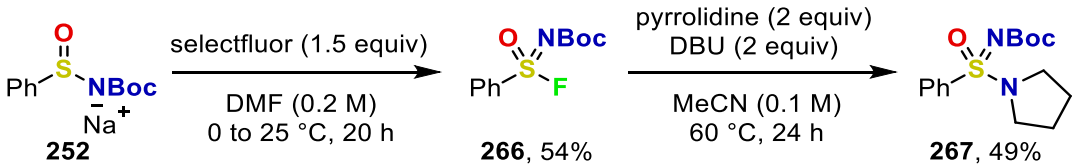
With simple electrophiles not affording the desired sulfoximine products, alternative arylation conditions were used which had been exemplified for the synthesis of sulfones from sulfinate salts (Scheme 2.57a).[302,303] Using indoles in what is understood to operate under a radical based mechanism failed to afford any of the desired sulfoximine product, instead likely just forming halogenated indole. When using a diaryliodonium salt as an electrophile, a small amount of the desired sulfoximine was observed in a 6% ^{1}H NMR yield but this result was not pursued further. Later, Kano, Maruoka and co-workers reported on the arylation of sulfinamide salts under copper catalysed conditions using diaryliodonium salts (Scheme 2.57b).[181]



Scheme 2.57: Arylation conditions for sulfinamide salt **252** and arylation conditions to form sulfoximines from Kano, Maruoka and co-workers. Reactions performed on a 0.2 mmol scale. [a] Yield calculated by ^{1}H NMR spectroscopy with respect to 1,3,5-trimethoxybenzene as an internal standard.

2.5.3.2 Accessing Sulfonimidamides

After various alkylation/arylation conditions were tested unsuccessfully to form sulfoximines from sulfinamide salt **252**, fluorination conditions were tested using Selectfluor which is a powerful electrophilic source of fluorine.[304] Pleasingly, under the preliminary conditions tested, sulfonimidoyl fluoride **266** could be isolated in a good yield (Scheme 2.58). The sulfonimidoyl fluoride **266** was then subjected to Sharpless and co-workers conditions for sulfonimidamide synthesis with pyrrolidine and the desired sulfonimidamide product **267** was formed in a good yield.[176]

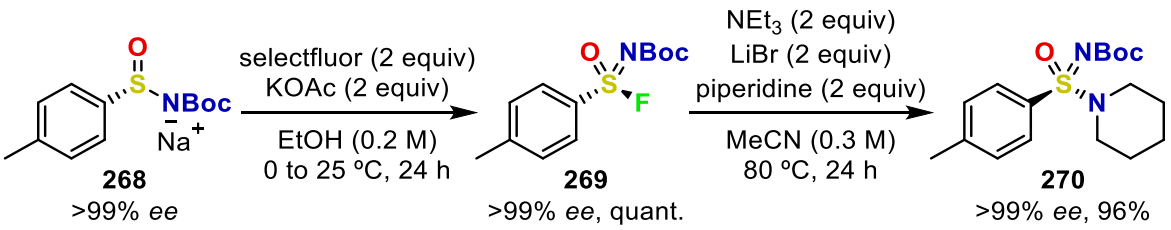


Scheme 2.58: Synthesis of sulfonimidamide **267** from sulfonimidoyl fluoride intermediate **266**. Reactions performed on 0.15 and 0.08 mmol scale respectively.

2.5.4 Optimisation of Sulfonimidamide Synthesis

Whilst the route from sulfinamide salt **252** for the synthesis of sulfonimidamides was very promising, major challenges were required to be overcome including increasing the yield of both fluorination and amine coupling steps and adapting this methodology to be amenable for the synthesis of enantioenriched substrates. Further optimisation of this reaction was carried out by Stephanie Greed and Dr Fahima Idiris.

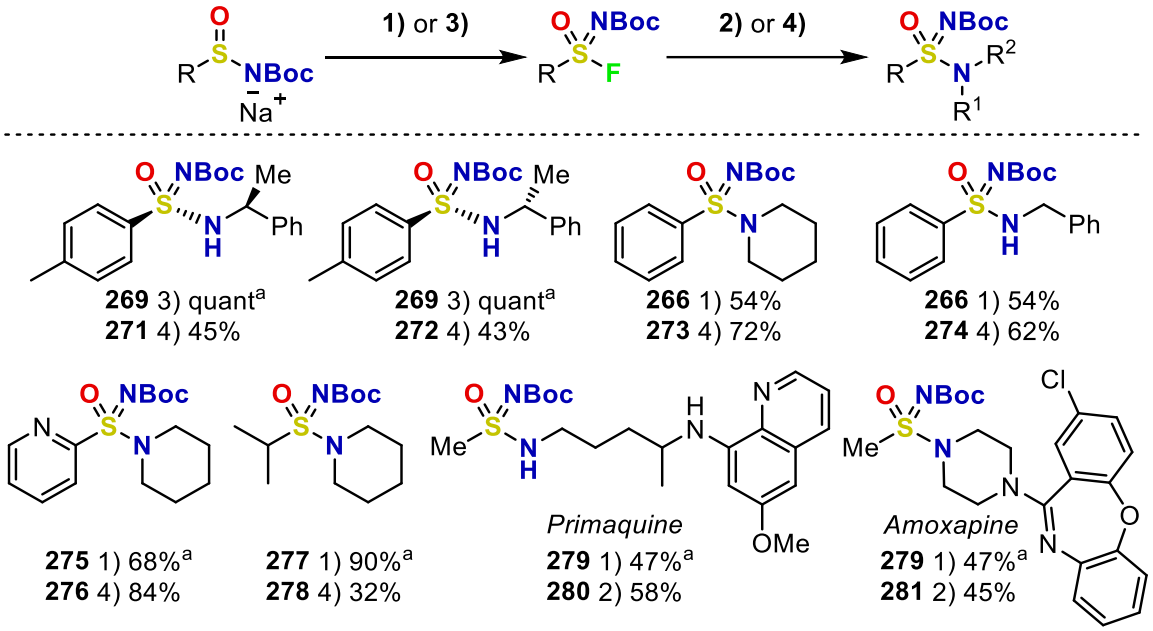
The key findings in the optimisation process were that the yield of sulfonimidoyl fluoride could be improved by not purifying it through flash column chromatography as it was shown to be unstable to silica. In addition, the yield of the sulfonimidamide formation could be increased further when using triethylamine as a base instead of DBU. However, when starting with >99% *ee* sulfinamide salt **268** these conditions were not applicable for the formation of enantioenriched sulfonimidamides. The loss in *ee* was hypothesised to occur from degenerate attack of fluoride ions in solution on the sulfonimidoyl fluoride centre, causing racemisation. Fluoride ion trapping strategies were explored which led to the optimised conditions below (Scheme 2.59). Ethanol was used as the solvent in the fluorination step to reduce the nucleophilicity of the fluoride and lithium bromide was used as a fluoride scavenger in the amine coupling step, allowing for complete preservation of the *ee* in the sulfonimidamide product **270**.



Scheme 2.59: Optimised sulfonimidamide synthesis from sulfinamide salt **252**, preserving the *ee* of the starting material in very high yield. Reactions performed on a 0.25 mmol scale. Optimisation and above reactions carried out by Stephanie Greed and Dr Fahima Idiris.

2.5.5 Scope of Sulfonimidamide Synthesis

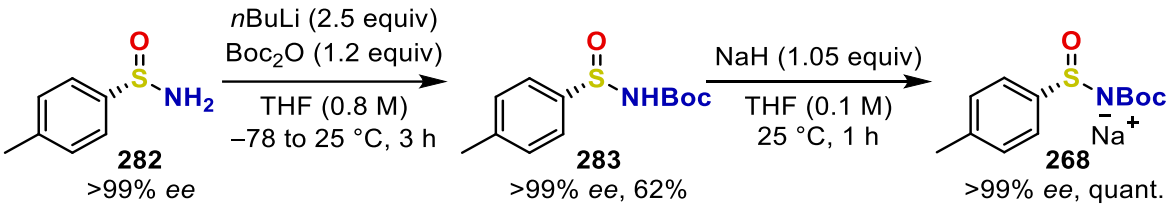
The scope of this transformation was primarily explored by Stephanie Greed. A variety of primary and secondary amines could be used with complete enantiospecificity to afford a range of enantioenriched *p*-tolyl sulfonimidamides. Interestingly, single diastereomers could be formed when enantioenriched amines were used (Scheme 2.60). Alternative sulfinamide salts could be accessed and applied in this methodology including phenyl, pyridyl, *i*Pr and methyl examples. The methyl sulfinamide salt allows for the addition of a small polar moiety which is particularly interesting for the late stage functionalisation of different amine containing drugs such as primaquine and amoxapine.



Scheme 2.60: Selected examples in the scope of the sulfonimidamide synthesis. 1) selectfluor (1.5 equiv), DMF (0.2 M), 0 to 25 °C, 18 h, 2.5 mmol scale. 2) amine (2.0 equiv), NEt_3 (2.0 equiv), THF (0.3 M), 80 °C, 24 h, 0.25 mmol scale. 3) selectfluor (2.0 equiv), KOAc (2.0 equiv), ethanol (0.2 M), 0 to 25 °C, 24 h, 1.0 mmol scale. 4) amine (2.0 equiv), NEt_3 (2.0 equiv), LiBr (2.0 equiv), MeCN (0.3 M), 80 °C, 24 h, 0.25 mmol scale. [a] Reactions carried out by Stephanie Greed

2.5.6 A General Approach to Enantioenriched Sulfonimidamides

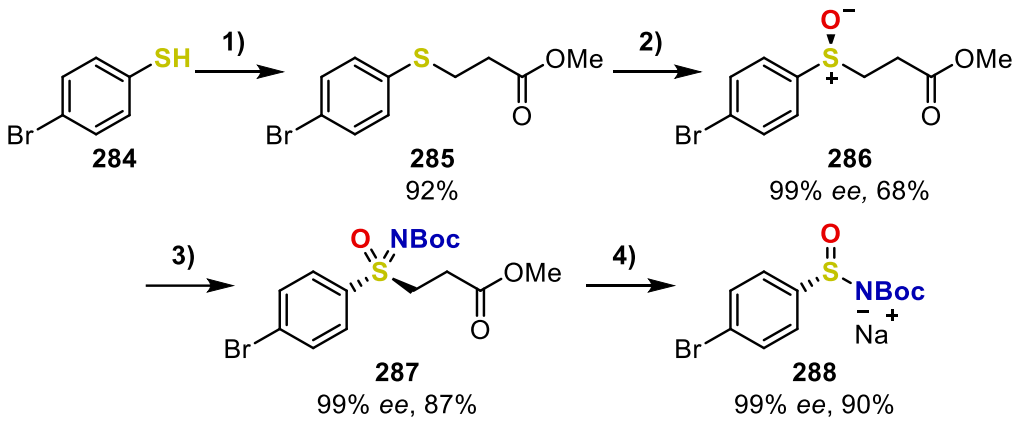
The enantioenriched *p*-tolyl sulfinamide salt **268** could be accessed from commercially available enantioenriched primary sulfinamide **282** through an initial Boc protection[295] followed by deprotonation with sodium hydride. This reaction sequence was optimised and carried out by Stephanie Greed (Scheme 2.61).



Scheme 2.61: Synthesis of enantioenriched sulfinamide salt **268** from commercially available **282**.

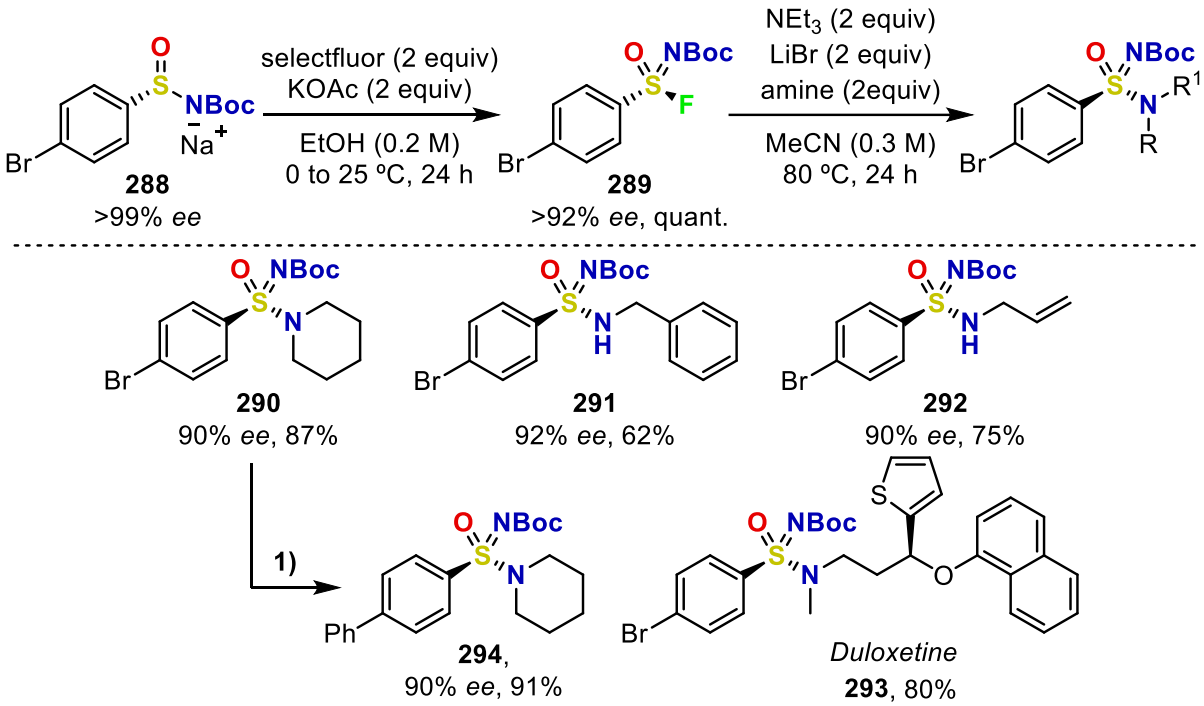
Whilst this route is highly convenient for the synthesis of enantioenriched *p*-tolyl sulfonimidamides, there is currently only a very small library of enantioenriched primary sulfinamide salts which are available from commercial vendors. Therefore, to demonstrate a general approach toward accessing enantioenriched aryl sulfonimidamides, enantioenriched sulfinamide salt **288** was targeted. It was postulated that the current route toward novel sulfinamide salts could be adapted to involve an enantioselective oxidation of the sulfide to sulfoxide as there are a variety of known methods for this type of transformation.[209] To test

this theory, sulfide **285** could be accessed under standard 1,4-addition conditions and then enantioselective oxidation conditions developed by Jackson and co-workers were trialled with great success yielding enantioenriched sulfoxide **286** in a good yield and very high *ee*.[211,212] With the sulfoxide in place, NBoc transfer and elimination using 5 M sodium hydroxide in methanol yielded sulfinamide salt **288** with complete retention of *ee* across both steps (Scheme 2.62).



Scheme 2.62: Synthesis of enantioenriched sulfinamide salt **288**. 1) methyl acrylate (1.1 equiv), NaOAc (0.15 equiv), THF:H_2O (1:1, 0.3 M), 25 °C, 18 h, 20 mmol scale. 2) $VO(acac)_2$ (1 mol%), (*S*,*E*)-2-(((1-hydroxy-3,3-dimethylbutan-2-yl)imino)methyl)-4,6-diiodophenol (1.5 mol%), H_2O_2 (1.2 equiv), $CHCl_3$ (1.0 M), 0 °C, 72 h, 6.0 mmol scale. 3) *t*Bu carbamate (1.5 equiv), $Rh_2(OAc)_4$ (2.5 mol%), $PhI(OAc)_2$ (1.5 equiv), MgO (4 equiv), CH_2Cl_2 (0.1 M), 40 °C, 18 h, 4.1 mmol scale. 4) 5 M NaOH in MeOH (1.05 equiv), CH_2Cl_2 (0.1 M), 25 °C, 1 h, 3.4 mmol scale.

With enantioenriched sulfinamide salt **288** in hand, this was then subjected to the fluorination and amine coupling conditions (Scheme 2.63). The fluorination step saw a slight drop in *ee* to 92% but there was complete retention in the sulfonimidamide products after the amine coupling step. A selection of different primary and secondary amines could be used to afford highly enantioenriched products and the single enantiomer drug duloxetine could be used, affording **293** as a single diastereomer. The *p*-Br functionality was shown to serve as a useful handle in the sulfonimidamide products for additional functionalisation when subjected to standard Suzuki-Miyuara cross-coupling conditions.[133]



Scheme 2.63: Synthesis of enantioenriched *p*-Br sulfonimidamides. Fluorination carried out on 1.2 mmol scale. Amine coupling carried out on 0.2 mmol scale. 1) $PhB(OH)_2$ (1.5 equiv), K_2CO_3 (2.0 equiv), $Pd(dtbpf)Cl_2$, (10 mol%), $MeCN:H_2O$ (1:1, 0.2 M), 80 °C, 2 h, 0.1 mmol scale.

2.5.7 Conclusions

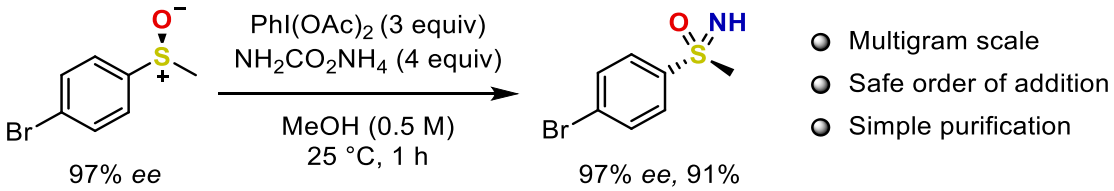
Novel sulfinamide salts have been isolated for the first time and have been shown to be easy to handle, bench-stable solids which can serve as useful building blocks toward interesting sulfur(VI) functionalities. Their reactivity with electrophilic sources of fluorine gives rise to sulfonimidoyl fluorides which are stable precursors to sulfonimidamides via a SuFEx reaction. These conditions allow for the first facile route toward enantioenriched sulfonimidamides. A diverse library of sulfinamides salts were synthesised including alkyl examples which show promise in late stage functionalisation reactions. A variety of primary and secondary amines could be utilised, giving rise to a diverse library of sulfonimidamide containing compounds in high yield and *ee*.

3. Conclusions and Future Work

3.1 Summary of Chapter 2

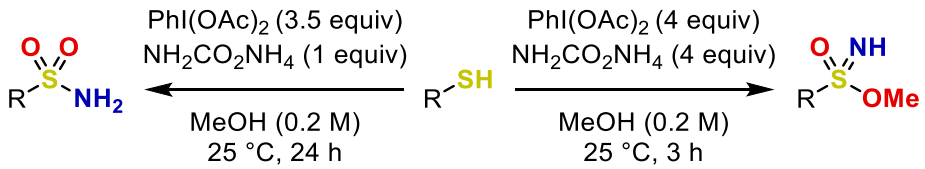
Sulfoximines and sulfonimidamides are valuable motifs in the life sciences as they have been shown to induce often favourable physicochemical properties on compounds of interest when compared to their corresponding oxygen counterparts. Therefore, there is significant demand for synthetic methods which allows improved access to these sulfur(VI) functional groups. The research in this thesis attempts to address some of this unmet need through development of facile and simple routes for their preparation.

In Chapter 2.1, a detailed procedure was developed for the gram scale synthesis of a highly enantioenriched sulfoximine. This methodology is an expansion of previous NH transfer work to sulfoxides but with a focus on producing larger quantities of material. It is hoped that the procedure developed and the various order of addition/purification experiments that have been conducted provide a stepping-stone to those who wish to conduct this reaction on increased scales, something which is deemed to become increasingly important as sulfoximines and sulfonimidamides are incorporated into drug candidates with increasing frequency (Scheme 3.1).



Scheme 3.1: Summary of work conducted in Chapter 2.1.

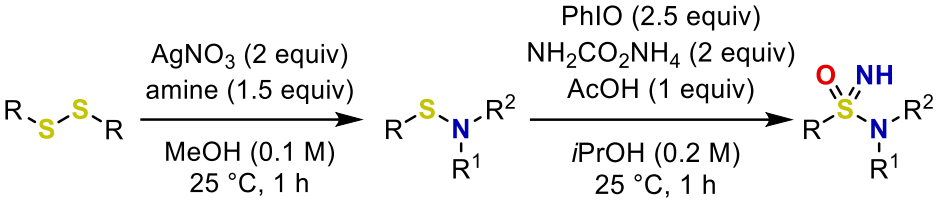
In Chapter 2.2, thiols were examined as substrates under NH and O transfer conditions leading to the development of conditions for the synthesis of sulfonimidates. It was found that by extending the reaction time and decreasing the equivalents of ammonium carbamate, primary sulfonamides were the major product, through conversion of the sulfonimidate intermediate (Scheme 3.2).



Scheme 3.2: Summary of methodology developed in Chapter 2.2.

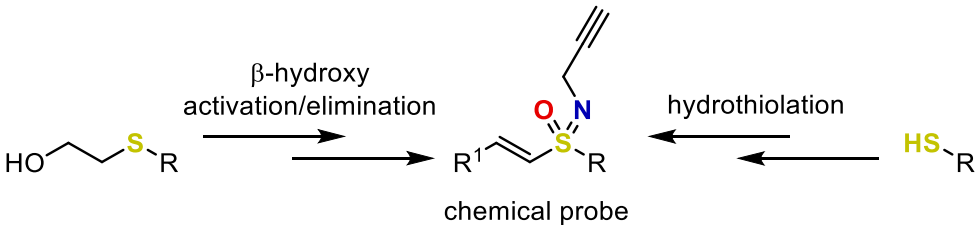
In Chapter 2.3, a procedure for the synthesis of sulfenamides was developed based upon the addition of an amine to a disulfide under silver nitrate mediated conditions. Sulfenamides were then shown to be effective precursors to sulfonimidamides under NH and O transfer conditions.

The instability of the starting materials toward acid led to the development of more neutral conditions through the use of iodosylbenzene as the hypervalent iodine reagent. However, the addition of 1 equivalent of acetic acid was required to break down intermediate λ^6-sulfanenitrile species to form the desired sulfonimidamide products. The novel alkoxy-amino-λ^6-sulfanenitrile species isolated in this study for the first time provide unique insight into this and other NH and O transfer mechanisms. Overall a variety of sulfonimidamide containing compounds can be accessed via this simple methodology in high yield. The route is amenable to late stage functionalisation approaches and the synthesis of medicinally relevant compounds as demonstrated through the preparation of aza-probenecid (Scheme 3.3).



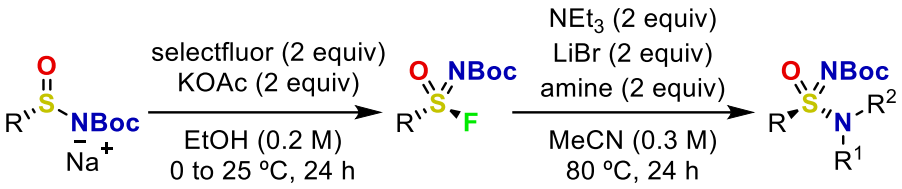
Scheme 3.3: Summary of methodology developed in Chapter 2.3.

In Chapter 2.4, previously developed NH and O transfer methods for the formation of sulfoximines and sulfonimidamides were applied towards the synthesis of their vinyl counterparts. Overall, two approaches were taken, one involving a β-hydroxy activation/elimination strategy and the other utilising the hydrothiolation of alkynes. These routes are amenable for the rapid formation of a new electrophilic warhead which may have application in covalent drug discovery. The extra handle for functionalisation that the imine nitrogen provides allows for the installation of propargyl groups, enabling the formation of fully functionalised probes (Scheme 3.4).



Scheme 3.4: Summary of methodology developed in Chapter 2.4.

In Chapter 2.5, an alternative route toward sulfonimidamides was demonstrated, avoiding the previously developed NH and O transfer methodology. Initially, sulfinamide salts were isolated for the first time and their reactivity to form sulfonimidoyl fluorides was demonstrated. Through a SuFEx reaction, sulfonimidoyl fluorides provide access to sulfonimidamides. This route was shown to be amenable to accessing enantioenriched derivatives, providing the first facile route for their synthesis (Scheme 3.5).



Scheme 3.5: Summary of methodology developed in Chapter 2.5.

3.2 Future Work

3.2.1 Improvements to the NH and O Transfer

The NH and O transfer methodology that has been developed in the group for the synthesis of sulfoximines and sulfonimidamides is a highly convenient protocol in terms of the simplicity of the setup, the lack of expensive reagents including the absence of a metal catalyst and the ability it provides to quickly build up complex products from simple starting materials. However, there are also a variety of general drawbacks to this protocol which have been touched upon previously.

3.2.1.1 Altering the Iodonitrene Reactivity

Some of these drawbacks are due to the inherent reactivity of the iodonitrene generated *in situ* which is the active aminating reagent, such as the incompatibility of these methodologies with electron rich heterocycles including indoles,[164] or the reduced yields that are obtained in the case of electron poor substrates. One possible method of modulating the iodonitrene reactivity would be to alter the phenyl substituent on the iodine centre by adding electron withdrawing or donating groups. Another method of modulating the iodonitrene reactivity includes changing the reaction solvent and this has been exemplified by Reboul and co-workers by showing that trifluoroethanol enhances the yields obtained for sulfoximines from electron poor sulfides.[169] Further studies are required to examine the role of the solvent in these systems and whether this can be used in conjunction with a specific HVIR to further increase the yield of electron poor substrates.

3.2.1.2 Making the Transformation More Environmentally Friendly

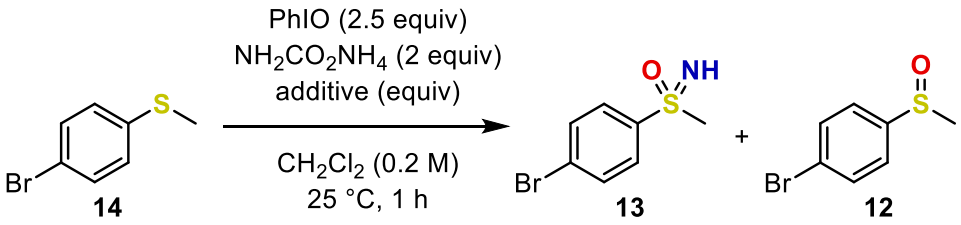
Whilst in general the current NH and O transfer conditions are reasonably 'green', there is definite scope to make this transformation more environmentally benign. The alcohol solvent is one area that the reaction could be improved and by using a solvent selection guide,[305] changing to a higher molecular weight alcohol solvent such as *n*BuOH would hopefully have little impact on the yield in the reaction, whilst making the reaction much 'greener'. A recent report by Xu, Zhen and co-workers have developed this further by showing that sulfoximines can be synthesised from sulfides under these NH and O transfer conditions in water with a surfactant.[170] In addition, they demonstrate how the iodoarene can be recycled through a heptane extraction in the aqueous work up of the reaction. This can then be regenerated into the HVIR through a separate oxidation step. This could be improved further, however, by an *in situ* regeneration of the HVIR, potentially allowing for the reaction to be catalytic with regard to the iodoarene. Catalytic cycles involving HVIR have been known since 2005 and the challenge in using a catalytic amount of iodoarene would be to find a stoichiometric oxidant

which would not oxidise the sulfur centre to facilitate unproductive pathways.[306] However, conditions have been found for the oxidation of sulfides to sulfoxides using catalytic HVIRs so these would be a good place to begin an investigation.[307]

3.2.1.3 Developing an Enantioselective Process

With the plethora of methods that are now available for the synthesis of sulfoximines and sulfonimidamides, attention is increasingly turning to stereoselective methods for their preparation.[136] Whilst the NH transfer methodology allows access to enantioenriched products (although this hasn't yet been proven for sulfonimidamides) this relies on enantioenriched starting materials which can be hard to access, particularly for sulfinamides. Therefore, there is significant interest in developing an NH and O transfer procedure which generates enantioenriched products from both sulfides and sulfenamides. Whilst there is a good understanding of the current mechanism in the NH and O transfer to these substrates, it is currently unclear what the stereodetermining step is in the reaction pathway. This is dependent on whether the attack of the nucleophile on (in the case of sulfenamides) the sulfinamidine intermediate **178** is an SN1 or SN2 type process and as proposed in this work, it is a mixture of both, further complicating matters (Scheme 2.41). If an SN1 pathway is dominant as is expected then it is plausible that by using a chiral alcohol or acid, then some enantioselectivity could be observed in the final products. Preliminary results showed that no enantioinduction was obtained when using a small library of chiral acids/alcohols in dichloromethane with sulfide **14** and iodosylbenzene as the oxidant (Table 3.1). Interestingly, when Boc-L-valine was used as an additive this afforded an increased yield of **13** in comparison to acetic acid (Table 3.1, entries 3 and 6). When screening other solvents including acetonitrile and toluene, almost analogous product profiles were obtained as in the case of CH_2Cl_2, including 50:50 enantiomeric ratios.

Whilst these results are very much preliminary, they suggest that it may be difficult to influence the enantiomeric ratio by using a chiral additive alone. This suggests that a SN2 type mechanism may be more prevalent than expected. If this is the case then a chiral HVIR could be used to influence the *ee* of the products, since the stereodetermining step would be attack of the iodonitrene on the sulfur centre. The use of chiral HVIRs in other transformations has been shown to be an effective way of introducing *ee* in the products and could be applied in the NH and O transfer methodology.[267]



Entry	Additive (equiv)	Yield [a]				er
		14	**13**	**12**	Total	
1	-	23	58	9	90	-
2	AcOH (1.5)	15	90	1	106	-
3	AcOH (5)	66	34	0	100	-
4	L-(+)-tartaric acid (1.5)	70	25	3	98	50:50
5	D-(−)-mandelic acid (1.5)	41	40	7	88	50:50
6	Boc-Val-OH (1.5)	2	95	0	97	50:50
7	*i*PrOH (1.5)	13	68	9	90	-
8	(−)-menthol (1.5)	29	58	7	97	50:50

Table 3.1: The effect of different additives on the yield and er of sulfoximine **13**. Reactions performed on a 0.2 mmol scale. [a] Yield calculated by ^{1}H NMR spectroscopy with respect to 1,3,5-trimethoxybenzene as an internal standard.

3.2.1.4 Exploring Other Nucleophiles

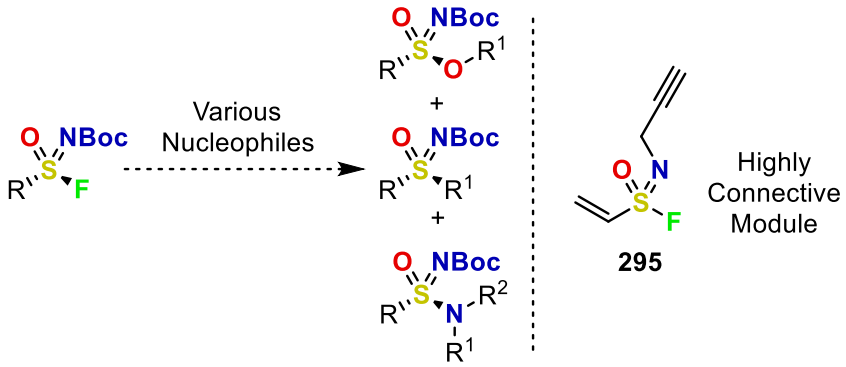
Whilst the premise of this work has been concerned with the synthesis of nitrogen containing sulfur(VI) functionalities. It is certainly plausible that other nucleophiles (aside from sulfur based systems) would be reactive with the *in situ* generated iodonitrene. This has recently been demonstrated by Reboul and co-workers who have shown that diazirines can be formed from amino acids under related NH and O transfer conditions.[308] This is also an on-going area of research within the Bull and Luisi groups, who have recently published on the synthesis of hydrazinium salts from tertiary amines.[309] Other interesting nucleophiles which warrant further research are alkenes for the synthesis of aziridines and enol ethers for an α-amination reaction.

3.2.2 Sulfonimidoyl Fluorides Reactivity

The main utility of sulfinamide salts in this work has been their subjection to fluorination conditions for the preparation of sulfonimidoyl fluorides which have been demonstrated to be effective precursors to sulfonimidamides. However, their reactivity with other nucleophiles such

as Grignard reagents, alkyl/aryl lithium's and other anionic species such as deprotonated amides, ketones or alcohols would all yield interesting products, enhancing coverage of chemical space related to these sulfur(VI) derivatives and this is an active area of research within the Bull group.

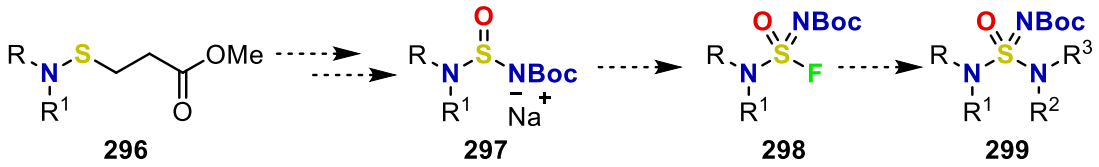
In addition, the potential of SuFEx reactivity is beginning to be realised in 'click' chemistry for application in the area of chemical biology.[310–312] Sulfonimidoyl fluorides therefore present interesting opportunities for the synthesis of chemical probes and covalent drugs.[313] The synthesis of alkenylsulfonimidoyl fluorides is therefore of interest considering the utility of the oxygen counterparts, particularly as the nitrogen offers an additional handle to incorporate a propargyl group for example.[314,315] The synthesis of ethenesulfonimidoyl fluoride **295** would be a break through in this regard, containing three highly reactive orthogonal functionalities (Scheme 3.6).



Scheme 3.6: Sulfonimidoyl fluorides giving access to new sulfur(VI) chemical space and ethenesulfonimidoyl fluoride **295** as a new connective hub in the life sciences.

3.2.3 Synthesis of Aza-sulfinamide Salts

Sulfinamide salts have the ability to either be reactive themselves under arylation or alkylation conditions, or form sulfonimidoyl fluorides which have the potential to be reactive to a variety of nucleophiles. Whilst this allows access to a diverse amount of chemical space, one of the R groups on the sulfur atom is limited early on in the synthesis and is required to be carbon based. It is therefore interesting to explore the aza-analogues of sulfinamide salts such as **297** where the carbon-based group would instead be amine derived. If these are able to be formed and follow the same general reactivity as sulfinamide salts then highly under represented and under explored compound classes could be accessed such as imidosulfuric diamides **299**, which have recently been synthesised for the first time.[43] In addition, sulfuramidimidoyl fluorides **298** could be accessed, which have been recently identified as interesting compounds in SuFEx chemistry due to their weak reactivity with proteins, meaning they can be highly selective warheads (Scheme 3.7).[316]



Scheme 3.7: Aza-sulfinamide salts giving rise to under explored compound classes.

3.2.4 Next Generation Sulfonimidoyl Donors

Sulfonimidoyl fluorides offer a relatively simple means toward accessing enantioenriched sulfonimidamides and potentially other sulfur(VI) derivatives too. However, these are typically difficult to handle oils which will gradually degrade when on the bench. Sulfinamide salts are therefore a preferred building block but these require further manipulation before giving rise to, for example, sulfonimidamides. In addition, due to the nature of the fluoride leaving group, elevated temperatures are required for their reactivity with neutral amines, meaning extra precautions are required to prevent against sulfonimidoyl fluoride racemisation.

Therefore, an alternative leaving group which would be more readily cleaved and would not cause racemisation once it left the sulfur would be desirable. To this end, imidazole salts offer an attractive solution as they have been demonstrated to form bench stable solids which are facile leaving groups that do not readily undergo nucleophilic attack of the sulfur centre. Grygorenko and co-workers have recently demonstrated the power that these reagents can have as sulfonimidoyl donors, although only demonstrated this on a single example.[43] What would be more powerful is two orthogonal leaving groups on the sulfur centre and this has been described for the corresponding oxygen analogues for the synthesis of a variety of sulfonyl compounds by Sharpless and co-workers.[317] If the corresponding aza analogue of **301** could be synthesised, this would allow access to unprecedented sulfur(VI) chemical space, especially if the two enantiomers were available as salts from commercial vendors (Figure 3.1).

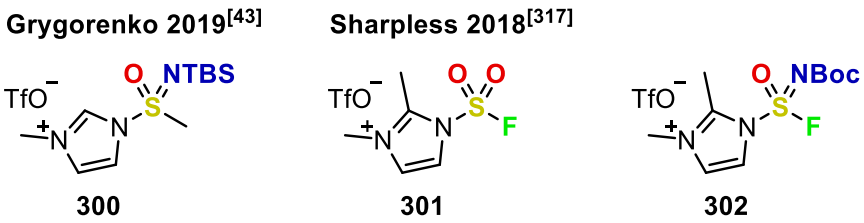


Figure 3.1: Imidazole salts as facile leaving groups on sulfur hubs and **302** as a gateway to unprecedented sulfur(VI) chemical space.

4. Experimental

4.1 General Experimental Considerations

All non-aqueous reactions were run under an inert atmosphere (argon) with flame-dried glassware, using standard techniques (unless otherwise stated). Anhydrous solvents were obtained by filtration through drying columns (THF, CH_2Cl_2, DMF, MeCN, EtOH and toluene) or used as supplied.

Flash chromatography was performed using 230–400 mesh silica, with the indicated solvent system according to standard techniques. Analytical thin-layer chromatography (TLC) was performed on precoated, glassbacked silica gel plates. Visualization of the developed chromatogram was performed by UV absorbance (254 nm) and stained with aqueous potassium permanganate solution or a ninhydrin solution in ethanol.

Nuclear magnetic resonance spectra were recorded on 400 MHz spectrometers. The frequency used to record the NMR spectra is given in each assignment and spectrum (^{1}H NMR at 400 MHz; ^{13}C NMR at 101 MHz; ^{19}F NMR at 377 MHz). Chemical shifts for ^{1}H NMR spectra are recorded in parts per million with the residual protic solvent resonance as the internal standard ($^{13}CDCl_3$, δ = 7.27 ppm, D_2O, δ = 4.79 ppm, $(CD_3)_2SO$, δ = 2.50 ppm, CD_3OD, δ = 3.31, $(CD_3)_2CO$, δ = 2.05 ppm). Data is reported as follows: chemical shift (multiplicity [s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintet, m = multiplet and br = broad], coupling constant (in Hz), integration and assignment). ^{13}C NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in parts per million with the residual protic solvent resonance as the internal standard ($^{13}CDCl_3$, δ = 77.0 ppm, $(^{13}CD_3)_2SO$, δ = 39.5 ppm, $^{13}CD_3OD$, δ = 49.0, $(^{13}CD_3)_2CO$, δ = 29.8 ppm). ^{19}F NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in parts per million referenced to the standard monofluorobenzene: $\delta = -113.5$ ppm. Assignments of ^{1}H and ^{13}C spectra were based upon the analysis of δ_H and *J* values, as well as DEPT, COSY and HSQC experiments where appropriate.

IR spectra were recorded as solids or neat liquids on an Agilent Cary 630 FTIR spectrometer and are reported in wavenumbers (cm^{-1}) to the nearest integer.

High-resolution mass spectrometry (HRMS) analyses were performed using electrospray ion source (ESI). This was performed using a Waters LCT Premier equipped with an ESI source operated in positive ion mode. The software used was MassLynx 4.1. This software does not account for the electron and all the calibrations/references are calculated accordingly, i.e. $[M+H]^+$ is detected and the mass is calibrated to output [M+H]. In the cases where this software is used the HRMS is reported as [M+H].

All melting points were determined in open glass capillaries and are uncorrected.

Reagents: Commercial reagents were used as supplied or purified by standard techniques where necessary.

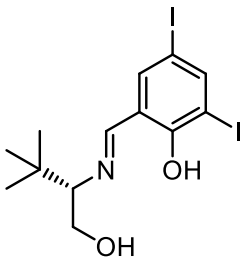
Observed optical rotation (α') was measured at the indicated temperature (T °C) and were converted to the corresponding specific rotations $[\alpha]^{T}_{D}$ in deg cm^2 g^{-1} , concentration (c) in g per 100 mL.

HPLC analyses were carried out on an Agilent 1260 Infinity Series system, employing Daicel Chiracel columns.

4.2 Experimental Details and Characterisation Data

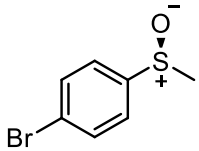
4.2.1 Sulfoxide to Sulfoximine Multigram Synthesis

(*S*,*E*)-2-(((1-Hydroxy-3,3-dimethylbutan-2-yl)imino)methyl)-4,6-diiodophenol (17)



Prepared according to a literature procedure.[211] 3,5-Diiodosalicylaldehyde (1.00 g, 2.66 mmol, 1.0 equiv) was added to a solution of (L)-(+)-*tert*-leucinol (350 mg, 3.0 mmol, 1.13 equiv) in MeOH (15 mL, 0.17 M) at 25 °C and stirred for 48 h. The solvent was removed under reduced pressure and the crude product dissolved in 5 mL of EtOH at 80 °C. Recrystallisation occurs at 3 °C for 20 h. The crystals were filtered and washed with ice-cold EtOH (3 × 2 mL), and then dried under vacuum to afford ligand **17** as a yellow solid (864 mg, 69%). R_f = 0.31 (30% EtOAc in hexane); mp = 165–167 °C. IR (film)/cm^{-1} 2963, 1736, 1636, 1479, 1438, 1215, 1148, 1051, 868; ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.80 (s, 1H, N=CH), 8.05 (s, 1H, Ar-OH), 7.93 (d, *J* = 2.2 Hz, 1H, Ar-H), 7.46 (d, *J* = 2.2 Hz, 1H, Ar-H), 4.02 (dd, *J* = 11.7, 2.7 Hz, 1H, C*H*$_a$H$_b$OH), 3.90 (s, 1H, CH$_2$O*H*), 3.68 (dd, *J* = 11.4, 9.6 Hz, 1H, CH$_a$*H*$_b$OH), 3.14 (dd, *J* = 9.5, 2.5 Hz, 1H, NCH), 1.01 (s, 9H, 3 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4 (N=CH), 164.6 (Ar-C_q), 149.8 (Ar-C), 141.0 (Ar-C), 117.1 (Ar-C_q), 92.5 (Ar-C_q), 78.2 (NCH), 76.0 (Ar-C_q), 61.9 (CH_2OH), 32.9 (*C*$(CH)_3$), 26.9 (3 × CH_3). Analytical data (NMR, mp, IR) in agreement with those reported in the literature.[211]

(*S*)-(–)-*p*-Bromophenyl methyl sulfoxide ((*S*)-12)

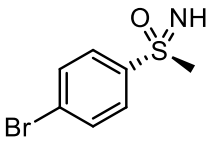


Prepared according to a literature procedure.[211,212] A solution of $VO(acac)_2$ (159 mg, 0.60 mmol, 1 mol%) in $CHCl_3$ (15 mL) was added dropwise to a solution of (*S*,*E*)-2-(((1-hydroxy-3,3-dimethylbutan-2-yl)imino)methyl)-4,6-diiodophenol (426 mg, 0.90 mmol, 1.5 mol%) in $CHCl_3$ (15 mL) at 25 °C and stirred for 30 min. *p*-Bromophenyl methyl sulfide **14** (12.19 g, 60 mmol, 1.0 equiv) and $CHCl_3$ (30 mL) were added and the reaction mixture cooled to 0 °C. H_2O_2 (30% in H_2O, 7.4 mL, 7.2 mmol, 1.2 equiv) was added dropwise and the mixture left to vigorously stir at 0 °C for 16 h. Sat. aq. $Na_2S_2O_3$ (30 mL) was added and the aqueous mixture was extracted with $CHCl_3$ (3 × 100 mL) and washed with brine (100 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (40% EtOAc in pentane) afforded the crude sulfoxide. This procedure was repeated and the two batches combined before being recrystallised from hot ethyl acetate:heptane (20:80, 150 mL). Recrystallization occurred as the solution sat at room temperature (16 h, 25 °C). The crystals were filtered and washed with heptane (3 × 20 mL), and then dried under vacuum to afford sulfoxide **(*S*)-12** as a white solid (16.12 g, 61%, 97%

ee). R_f 0.14 (40% EtOAc in pentane). mp = 74–76 °C. IR (film)/cm^{-1} 3071, 3004, 1573, 1468, 1386, 1084, 1032, 1006, 957, 827, 719, 678. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.62 (m, 2H, 2 × Ar-H), 7.56–7.48 (m, 2H, 2 × Ar-H), 2.72 (s, 3H, SCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8 (Ar-C_q), 132.5 (2 × Ar-C), 125.4 (Ar-C_q), 125.1 (2 × Ar-C), 44.0 (SCH_3). $[\alpha]^{23}_D$ = –95 (c 1.8, acetone). HPLC conditions: Chiralpak IE column, 90:10 *n*hexane:*i*PrOH, flow rate: 1 mL min^{-1}, 35 °C, UV detection wavelength: 250 nm, **(*S*)-12** retention time: 25 min. Analytical data (NMR, mp, IR) in agreement with those reported in the literature.[211]

Procedure for preparing the racemic starting material (**12**): To a solution of *p*-bromophenyl methyl sulfide **14** (15.3 g, 75 mmol, 1.0 equiv) in acetic acid (15.0 mL, 253 mmol, 3.4 equiv) was added H_2O_2 (30% in H_2O, 7.7 mL, 75 mmol, 1.0 equiv) at 0 °C and allowed to warm to room temperature. After 2 h the reaction was quenched at 0 °C with aq. 1 M NaOH (150 mL) and the aqueous mixture was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent removed under reduced pressure to afford sulfoxide **12** (16.4 g, quant.) as a white solid with characterisation data in accordance with the above. HPLC conditions: Chiralpak IE column, 90:10 *n*hexane:*i*PrOH, flow rate: 1 mL min^{-1}, 35 °C, UV detection wavelength: 250 nm, **12** retention times: 25 & 27 min.

(*S*)-(4-Bromophenyl)(imino)(methyl)-λ^6-sulfanone ((*S*)-13)



In air, a 250 mL one-necked round-bottomed flask (24/40), was equipped with a Teflon coated oval-shaped magnetic stirrer bar (32 mm × 15 mm), suspended in a water bath at 25 °C and charged with MeOH (70 mL). Stirring of 500 rpm was initiated. (*S*)-(–)-*p*-Bromophenyl methyl sulfoxide **((*S*)-12)** (7.67 g, 35.0 mmol, 1.0 equiv) followed by bis(acetoxyiodo)benzene (33.8 g, 105 mmol, 3.0 equiv) were added to the flask as single portions via powder funnel. Ammonium carbamate (10.9 g, 140 mmol, 4.0 equiv) was then added gradually to the suspension in roughly ten equal portions over a period of ten minutes allowing for controlled decarboxylation. The reaction mixture was stirred at 25 °C for 1 h, during which time the reaction mixture turned from colourless to yellow and reaction progress can be monitored by TLC. The organic solvent was evaporated under reduced pressure (25 °C, 35 mmHg) to give a yellow slurry which was diluted with deionized H_2O (150 mL) and transferred to a 500 mL separatory funnel, rinsing with CH_2Cl_2 (3 × 50 mL). The layers were separated, and the aqueous mixture is washed with CH_2Cl_2 (2 × 100 mL). The combined organic fractions were dried over anhydrous Na_2SO_4 (ca. 100 g). The solution was filtered through a 7 cm medium-porosity sintered-glass funnel and the Na_2SO_4 washed with CH_2Cl_2 (150 mL) into a 1-L round-bottomed flask. The organic solvent was evaporated under reduced pressure (25 °C, 250 mmHg) to give the crude product as a brown oil (ca. 37 g) The crude reaction mixture was then charged via Pasteur pipette onto the

top of a silica pad (50 g SiO_2) in a 7 cm medium-porosity sintered-glass funnel rinsing with CH_2Cl_2 (2 mL). The iodobenzene was then eluted by flushing the silica pad with 500 mL of hexane:EtOAc 9:1 (v/v) into a 1-L round-bottomed flask. The sulfoxide and sulfoximine were then eluted using EtOAc (1 L) into two 1-L round-bottomed flasks. The organic solvent was then evaporated under reduced pressure (25 °C, 60 mmHg) and the resulting brown solid transferred into a 250 mL one necked round-bottomed flask rinsing with EtOAc (3 × 5 mL). The solvent was then removed under reduced pressure (25 °C, 60-20 mmHg) to afford the product as a brown solid (ca. 8.1 g). Further purification was carried out by adding 80 mL of hexane:EtOAc 19:1 (v/v) to the product and stirring for 20 minutes at 500 rpm with a Teflon coated oval-shaped magnetic stirrer bar (32 mm × 15 mm) in a water bath at 25 °C. The mixture was then filtered under vacuum using an 8 cm Büchner funnel with a Whatman #1 filter paper. Hexane (150 mL) was then added to the flask to transfer any residual solid as well as wash the precipitate. The precipitate was then transferred to a 100 mL one necked round-bottomed flask and then placed under high vacuum (21 °C, 0.11 mmHg) for 16 h to remove any residual solvent to yield sulfoximine **((*S*)-13)** as a pale brown solid (7.44 g, 91%, 97% *ee*). R_f 0.19 (40% acetone in hexane). mp = 102–104 °C. IR (film)/cm^{-1} 3273, 3302, 3083, 2962, 1569, 1374, 1215, 1088, 1062, 1017, 939. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91–7.83 (m, 2H, 2 × Ar-H), 7.73–7.65 (m, 2H, 2 × Ar-H), 3.10 (s, 3H, SCH_3), 2.72 (s, 1H, NH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.6 (Ar-C_q), 132.5 (2 × Ar-C), 129.3 (2 × Ar-C), 128.3 (Ar-C_q), 46.2 (SCH_3). $[\alpha]^{23}_D$ = +15 (c = 0.93, $CHCl_3$). (lit.[318] $[\alpha]^{25}_D$ = +17.8 (c = 0.93, $CHCl_3$)). HPLC conditions: Chiralpak IE column, 90:10 *n*hexane:*i*PrOH, flow rate: 1 mL min^{-1}, 35 °C, UV detection wavelength: 254 nm, **((*S*)-13)** retention time: 25 min. Analytical data (^{1}H, ^{13}C NMR and IR) in agreement with those reported in the literature.[151]

Racemic material could be accessed using the analogous procedure on racemic starting material **12**. HPLC conditions: Chiralpak IE column, 90:10 *n*hexane:*i*PrOH, flow rate: 1 mL min^{-1}, 35 °C, UV detection wavelength: 254 nm, **13** retention times: 25 & 26 min.

4.2.2 Synthesis of Sulfonimidates and Primary Sulfonamides from Thiols

4.2.2.1 General Procedures

General procedure A for the synthesis of sulfonimidates:

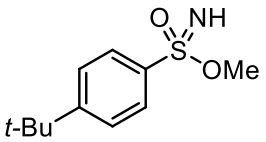
Ammonium carbamate (156 mg, 2.0 mmol, 4 equiv) and bis(acetoxy)iodobenzene (644 mg, 2.0 mmol, 4 equiv) were added to a solution of thiol (0.50 mmol, 1 equiv) in MeOH (2.5 mL, 0.2 M) at 25 °C and stirred for 3 h. The solvent was removed under reduced pressure. Purification by flash column chromatography (neutral Al_2O_3, 20-35% EtOAc in pentane) afforded the title sulfonimidates.

General procedure B for the synthesis of sulfonamides:

Ammonium carbamate (39 mg, 0.5 mmol, 1 equiv) and bis(acetoxy)iodobenzene (564 mg, 1.75 mmol, 3.5 equiv) were added to a solution of thiol (0.50 mmol, 1 equiv) in MeOH (2.5 mL, 0.2 M) at 25 °C and stirred for 24 h. The solvent was removed under reduced pressure. Purification by flash column chromatography (SiO_2, 20-35% EtOAc in pentane) afforded the title sulfonamides.

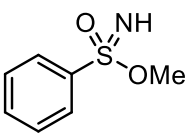
4.2.2.2 Synthesis of Sulfonimidates

Methyl 4-(*tert*-butyl)benzenesulfonimidate (19)



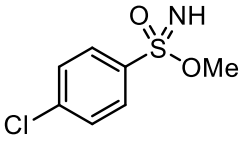
General procedure A was followed using 4-*tert*-butylthiophenol **18** (83 mg, 0.5.0 mmol) to afford sulfonimidate **19** as a white solid (69 mg, 65%). R_f 0.34 (25% EtOAc in pentane). mp = 31–33 °C. IR (film)/cm^{-1} 3283, 2960, 1594, 1277, 1150, 994, 963, 755. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95–7.88 (m, 2H, 2 × Ar-H), 7.56–7.49 (m, 2H, 2 × Ar-H), 3.63 (s, 3H, OCH_3), 3.24 (bs, 1H, NH), 1.33 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.9 (Ar-C_q), 133.8 (Ar-C_q), 127.5 (2 × Ar-C), 125.9 (2 × Ar-C), 55.4 (OCH_3), 35.1 (Ar-*C*$(CH_3)_3$), 31.0 ($C(CH_3)_3$). HRMS (ESI) *m/z* Calcd for $C_{11}H_{18}NO_2S$ [M+H]: 228.1058; Found: 228.1052.

Methyl benzenesulfonimidate (24)



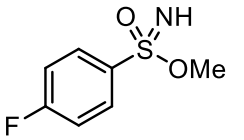
General procedure A was followed using thiophenol **61** (55 mg, 0.50 mmol) to afford sulfonimidate **24** as a colourless oil (29 mg, 50%). R_f 0.14 (25% EtOAc in pentane). IR (film)/cm^{-1} 3274, 2948, 1478, 1446, 1272, 1147, 955, 733. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04–7.99 (m, 2H, Ar-H), 7.65–7.59 (m, 1H, Ar-H), 7.59–7.49 (m, 2H, Ar-H), 3.65 (s, 3H, OCH_3), 3.26 (bs, 1H, NH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.9 (Ar-C_q), 133.1 (Ar-C), 128.9 (2 × Ar-C), 127.7 (2 × Ar-C), 55.6 (OCH_3). HRMS (ESI) *m/z* Calcd for $C_7H_{10}NO_2S$ [M+H]: 172.0432; Found: 172.0428.

Methyl 4-chlorobenzenesulfonimidate (26)



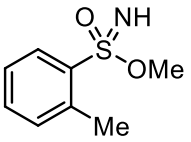
General procedure A was followed using 4-chlorothiophenol (72 mg, 0.50 mmol) to afford sulfonimidate **26** as a colourless oil (39 mg, 42%). R_f 0.29 (25% EtOAc in pentane). IR (film)/cm^{-1} 3288, 2948, 1582, 1474, 1395, 1269, 1088, 964, 757. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98–7.92 (m, 2H, 2 × Ar-H), 7.53–7.47 (m, 2H, 2 × Ar-H), 3.65 (s, 3H, OCH_3), 3.30 (bs, 1H, NH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.7 (Ar-C_q), 135.5 (Ar-C_q), 129.22 (2 × Ar-C), 129.18 (2 ×Ar-C), 55.6 (OCH_3). HRMS (ESI) *m/z* Calcd for $C_7H_9NO_2SCl$ [M+H]: 206.0043; Found: 206.0043.

Methyl 4-fluorobenzenesulfonimidate (27)



General procedure A was followed using 4-fluorothiophenol (64 mg, 0.50 mmol) to afford sulfonimidate **27** as a yellow solid (15 mg, 41%). R_f 0.22 (25% EtOAc in pentane). mp = 43–45 °C. IR (film)/cm^{-1} 3281, 3074, 2952, 1589, 1494, 1270, 1153, 956, 714. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07–8.00 (m, 2H, 2 × Ar-H), 7.25–7.18 (m, 2H, 2 × Ar-H), 3.66 (s, 3H, OCH_3), 3.25 (bs, 1H, NH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.4 (d, $^1J_{C\text{-}F}$ = 255.6 Hz, Ar-CF), 133.0 (d, $^4J_{C\text{-}F}$ = 2.4 Hz, Ar-C_q), 130.5 (d, $^3J_{C\text{-}F}$ = 9.5 Hz, 2 × Ar-C), 116.2 (d, $^2J_{C\text{-}F}$ = 22.7 Hz, 2 × Ar-C), 55.6 (OCH_3). ^{19}F NMR (377 MHz, $CDCl_3$) δ –104.6 (Ar-F). HRMS (ESI) *m/z* Calcd for $C_7H_9NO_2SF$ [M+H]: 190.0338; Found: 190.0333.

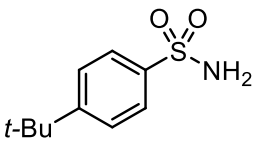
Methyl 2-methylbenzenesulfonimidate (29)



General procedure A was followed using 2-methylthiophenol (62 mg, 0.50 mmol) to afford sulfonimidate **29** as a colourless oil (26 mg, 28%). R_f 0.31 (25% EtOAc in pentane). IR (film)/cm^{-1} 3285, 3062, 2947, 1456, 1268, 1151, 963, 722. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.4, 1H, Ar-H), 7.51–7.44 (m, 1H, Ar-H), 7.36–7.29 (m, 2H, 2 × Ar-H), 3.64 (s, 3H, OCH_3), 3.34 (bs, 1H, NH), 2.70 (s, 3H, Ar-CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.0 (Ar-C_q), 135.4 (Ar-C_q), 133.0 (Ar-C), 132.6 (Ar-C), 129.7 (Ar-C), 125.9 (Ar-C), 55.1 (OCH_3), 20.4 (Ar-CH_3). HRMS (ESI) *m/z* Calcd for $C_8H_{12}NO_2S$ [M+H]: 186.0589; Found: 186.0583.

4.2.2.3 Synthesis of Sulfonamides

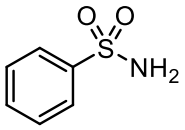
4-(*tert*-Butyl)benzenesulfonamide (20)



General procedure B was followed using 4-*tert*-butylthiophenol **18** (83 mg, 0.50 mmol) to afford sulfonamide **20** as a white solid (85 mg, 80%). R_f 0.33 (25% EtOAc in pentane). mp = 130–132 °C. IR (film)/cm^{-1} 3357, 3262, 2963, 1567, 1397, 1326, 1161, 1091, 830. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88–7.83 (m, 2H, 2 × Ar-H), 7.53–7.48 (m, 2H, 2 × Ar-H), 5.32 (bs, 2H, NH_2), 1.33 (s, 9H, $C(CH_3)_3$). ^{13}C NMR

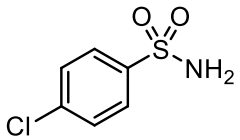
(101 MHz, $CDCl_3$) δ 156.4 (Ar-C_q), 139.0 (Ar-C_q), 126.2 (2 × Ar-C), 126.0 (2 × Ar-C), 35.1 (Ar-*C*$(CH_3)_3$), 31.0 (C(*C*$H_3)_3$). Analytical data (mp, IR, NMR) in agreement with those reported in the literature.[319,320]

Benzenesulfonamide (46)



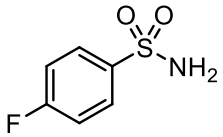
General procedure B was followed using thiophenol **61** (55 mg, 0.50 mmol) to afford sulfonamide **46** as a white solid (32 mg, 40%). R_f 0.14 (25% EtOAc in pentane). mp = 150–153 °C. IR (film)/cm^{-1} 3320, 3070, 2922, 2503, 2397, 1479, 1447, 1327, 1310, 1150, 1087, 841, 754. ^{1}H NMR (400 MHz, CD_3OD) δ 7.94–7.88 (m, 2H, 2 × Ar-H), 7.62–7.50 (m, 3H, 3 × Ar-H), 4.90 (bs, 2H, NH_2). ^{13}C NMR (101 MHz, CD_3OD) δ 145.0 (Ar-C_q), 133.2 (Ar-C), 130.0 (2 × Ar-C), 127.0 (2 × Ar-C). Analytical data (mp, IR) in agreement with those reported in the literature.[321,322]

4-Chlorobenzenesulfonamide (48)



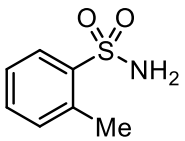
General procedure B was followed using 4-chlorothiophenol (72 mg, 0.50 mmol) to afford sulfonamide **48** as a white solid (55 mg, 56%). R_f 0.25 (25% EtOAc in pentane). mp = 141–143 °C. IR (film)/cm^{-1} 3277, 3090, 2497, 2353, 2327, 1584, 1474, 1318, 1145, 1086, 819. ^{1}H NMR (400 MHz, CD_3OD) δ 7.92–7.84 (m, 2H, 2 × Ar-H), 7.58–7.49 (m, 2H, 2 × Ar-H), 4.82 (bs, 2H, NH_2). ^{13}C NMR (101 MHz, CD_3OD) δ 143.7 (Ar-C_q), 139.2 (Ar-C_q), 130.1 (2 × Ar-C), 128.8 (2 × Ar-C). Analytical data (mp, IR) in agreement with those reported in the literature.[322,323]

4-Fluorobenzenesulfonamide (49)



General procedure B was followed using 4-fluorothiophenol (64 mg, 0.50 mmol) to afford sulfonamide **49** as a white solid (42 mg, 48%). R_f 0.24 (25% EtOAc in pentane). mp = 120–122 °C. IR (film)/cm^{-1} 3314, 3109, 2516, 2411, 1587, 1493, 1225, 1321, 1145, 836. ^{1}H NMR (400 MHz, CD_3OD) δ 8.02–7.87 (m, 2H, 2 × Ar-H), 7.33–7.20 (m, 2H, 2 × Ar-H), 4.90 (bs, 2H, NH_2). ^{13}C NMR (101 MHz, CD_3OD) δ 164.0 (d, $^1J_{C\text{-}F}$ = 251.4 Hz, Ar-CF_q), 139.3 (d, $^4J_{C\text{-}F}$ = 3.2 Hz, FAr-C_q), 128.0 (d, $^3J_{C\text{-}F}$ = 9.3 Hz, 2 × FAr-C), 114.9 (d, $^2J_{C\text{-}F}$ = 22.6 Hz, 2 × FAr-C). ^{19}F NMR (377 MHz, CD_3OD) δ –109.4 (Ar-F). Analytical data (mp, IR) in agreement with those reported in the literature.[320,324]

2-Methylbenzenesulfonamide (51)



General procedure B was followed using 2-methylthiophenol (62 mg, 0.50 mmol) to afford sulfonamide **51** as a white solid (67 mg, 78%). R_f 0.27 (25% EtOAc in pentane). mp = 153–154 °C. IR (film)/cm^{-1} 3373, 3253, 3098, 2601, 1559, 1309, 1148. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.84 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.48 (td, *J*

= 7.7, 7.3, 1.4 Hz, 1H, Ar-H), 7.42–7.31 (m, 2H, 2 × Ar-H), 3.36 (bs, 2H, NH_2), 2.58 (s, 3H, Ar-CH_3).^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 142.1 (Ar-C_q), 135.9 (Ar-C_q), 132.2 (Ar-C), 131.9 (Ar-C), 127.0 (Ar-C), 126.1 (Ar-C), 19.9 (Ar-CH_3). Analytical data (mp, IR, NMR) in agreement with those reported in the literature.[223,322,325]

4.2.3 Synthesis of Sulfonimidamides through NH and O transfer

4.2.3.1 General Procedures

General procedure C for the synthesis of sulfenamides from disulfides and amines:
Procedure adapted from Davis and co-workers.[239] Amine (4.0 mmol, 1.5 equiv) and silver nitrate (679 mg, 4.0 mmol, 2.0 equiv) were added to a solution of disulfide (2.0 mmol, 1.0 equiv) in MeOH (20 mL, 0.1 M) at 25 °C, under air, and stirred for 1 h. The reaction mixture was filtered and washed with MeOH (2 × 50 mL). The filtrate solvent was removed under reduced pressure. H_2O (75 mL) was added to the crude mixture and the aqueous mixture extracted with CH_2Cl_2 (3 × 75 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent removed under reduced pressure. Purification by filtration through a basic alumina (activity IV) plug (2 cm thick) with 1% Et_2O in pentane (300 mL) afforded the corresponding sulfenamide.

General procedure D for the synthesis of sulfonimidamides by NH and O transfer to sulfenamides:
Iodosylbenzene (2.5 equiv), ammonium carbamate (2.0 equiv) and acetic acid (1.0 equiv) were added to a solution of sulfenamide (1.0 equiv) in *i*PrOH (0.2 M) at 25 °C and stirred for 1 h. The solvent was then removed under reduced pressure and to the crude sat. aq. $NaHCO_3$ (20 mL) was added. The aqueous mixture was then extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were dried (Na_2SO_4), filtered and the solvent removed under reduced pressure. Purification by flash column chromatography (neutral Al_2O_3) as described for each entry afforded the corresponding sulfonimidamide.

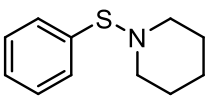
General procedure E for the synthesis of alkoxy-amino-λ^6-sulfanenitriles:
Iodosylbenzene (83 mg, 0.45 mmol, 2.5 equiv) and ammonium carbamate (23 mg, 0.30 mmol, 2.0 equiv) were added to a solution of sulfenamide **70** (29 mg, 0.15 mmol, 1.0 equiv) in an alcohol solvent (0.2 M) at 25 °C and stirred for 1 h. The solvent was then removed under reduced pressure and to the crude H_2O (20 mL) was added. The aqueous mixture was then extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were dried (Na_2SO_4), filtered and the solvent removed under reduced pressure.

General procedure F reactivity of alkoxy-amino-λ^6-sulfanenitriles with different nucleophiles:

The nucleophile (~0.10 mmol, 1.0 equiv) was added to a mixture of alkoxy-amino-λ^6-sulfanenitrile:**105** (~0.10 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL, 0.2 M) at 25 °C and stirred for 1 h or the time specified. The solvent was then removed under reduced pressure. Analysis of ^{1}H NMR with an internal standard indicated the yield of different alkylated nucleophiles.

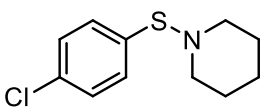
4.2.3.2 Synthesis of Sulfenamides

1-(Phenylthio)piperidine (70)



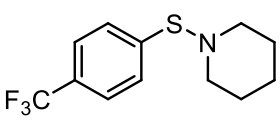
General procedure C was followed using piperidine (296 μL, 3.0 mmol) and 1,2-diphenyldisulfane (436 mg, 2.0 mmol) afforded sulfenamide **70** (228 mg, 59%) as a colourless oil. R_f 0.14 (100% pentane). IR (film)/cm^{-1} 3057, 2932, 2849, 2817, 1584, 1475, 1465, 1438, 1217, 1101, 1023, 916. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.43 (m, 2H, 2 × Ar-H), 7.40–7.33 (m, 2H, 2 × Ar-H), 7.30–7.24 (m, 1H, Ar-H), 3.01–2.93 (m, 4H, 2 × NCH_2), 1.67 (p, *J* = 5.8 Hz, 4H, 2 × NCH_2CH_2), 1.43–1.34 (m, 2H, $N(CH_2)_2CH_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.4 (Ar-C_q), 129.3 (2 × Ar-C), 128.5 (Ar-C), 127.0 (2 × Ar-C), 57.6 (2 × NCH_2), 27.3 (2 × NCH_2CH_2), 23.1 ($N(CH_2)_2CH_2$). Analytical data (NMR, IR) in agreement with those reported in the literature.[243]

1-((4-Chlorophenyl)thio)piperidine (74)



General procedure C was followed using piperidine (296 μL, 3.0 mmol) and 1,2-bis(4-chlorophenyl)disulfane (574 mg, 2.0 mmol) to afford a mixture of disulfide and sulfenamide. This was then resubjected to general procedure C (aside from additional disulfide) once more to afford sulfenamide **74** as a colourless oil (135 mg, 30%). R_f 0.27 (100% pentane). IR (film)/cm^{-1} 2935, 2817, 1472, 1451, 1389, 1217, 1092, 1009, 921, 812. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.34 (m, 2H, 2 × Ar-H), 7.34–7.29 (m, 2H, 2 × Ar-H), 2.94 (dd, *J* = 6.4, 5.4 Hz, 4H, 2 × NCH_2), 1.64 (p, *J* = 5.7 Hz, 4H, 2 × NCH_2CH_2), 1.42–1.34 (m, 2H, $N(CH_2)_2CH_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.2 (Ar-C_q), 132.9 (Ar-C_q), 130.2 (2 × Ar-C), 128.7 (2 × Ar-C), 57.7 (2 × NCH_2), 27.3 (2 × NCH_2CH_2), 23.1 ($N(CH_2)_2CH_2$). Analytical data (NMR, IR) in agreement with those reported in the literature.[326]

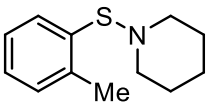
1-((4-(Trifluoromethyl)phenyl)thio)piperidine (75)



General procedure C was followed using piperidine (296 μL, 3.0 mmol) and 1,2-bis(4-(trifluoromethyl)phenyl)disulfane (709 mg, 2.0 mmol). After 4 h, an additional equiv of piperidine and silver nitrate were added

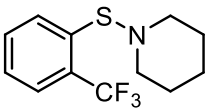
and the reaction mixture was left for a further 18 h to afford a mixture of disulfide and sulfenamide. Additional purification was carried out by distillation (130 °C, 1.4 mbar) to afford sulfenamide **75** as a colourless oil (136 mg, 26%). R_f 0.35 (100% pentane). IR (film)/cm^{-1} 2936, 2922, 1604, 1321, 1159, 1103, 918, 823, 700. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.53 (m, 2H, 2 × Ar-H), 7.44–7.40 (m, 2H, 2 × Ar-H), 3.07–3.01 (m, 4H, 2 × NCH_2), 1.69 (p, *J* = 5.5 Hz, 4H, 2 × NCH_2CH_2), 1.52–1.45 (m, 2H, $N(CH_2)_2CH_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.4 (Ar-C_q), 127.4 (q, $^2J_{C\text{-}F}$ = 32.2 Hz, Ar-C_q), 125.5 (q, $^3J_{C\text{-}F}$ = 3.7 Hz, 2 × Ar-C), 124.3 (2 × Ar-C), 124.3 (q, $^1J_{C\text{-}F}$ = 271.0 Hz, Ar-CF_3), 57.7 (2 × NCH_2), 27.3 (2 × NCH_2CH_2), 23.2 ($N(CH_2)_2CH_2$). ^{19}F NMR (377 MHz, $CDCl_3$) δ –62.27. HRMS (ESI) *m/z*: Calcd for $C_{12}H_{15}NSF_3$ [M+H]: 262.0877; Found: 262.0871.

1-(*o*-Tolylthio)piperidine (78)



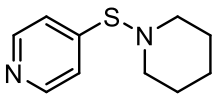
General procedure C was followed using piperidine (296 μL, 3.0 mmol) and 1,2-di-*o*-tolyldisulfane (493 mg, 2.0 mmol) to afford sulfenamide **78** as a yellow oil (249 mg, 60%). R_f 0.29 (100% pentane). IR (film)/cm^{-1} 3061, 2933, 2850, 2816, 1589, 1463, 1217, 1035, 920, 745, 681. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 7.8, 1.3 Hz, 1H, Ar-H), 7.23–7.19 (m, 1H, Ar-H), 7.16–7.06 (m, 2H, 2 × Ar-H), 3.06–2.96 (m, 4H, 2 × NCH_2), 2.27 (s, 3H, Ar-CH_3), 1.74–1.63 (m, 4H, 2 × NCH_2CH_2), 1.50–1.40 (m, 2H, $N(CH_2)_2CH_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.9 (Ar-C_q), 134.2 (Ar-C_q), 130.1 (Ar-C), 126.1 (Ar-C), 125.9 (Ar-C), 125.5 (Ar-C), 57.7 (2 × NCH_2), 27.4 (2 × NCH_2CH_2), 23.3 ($N(CH_2)_2CH_2$), 19.3 (Ar-CH_3). Analytical data (NMR, IR) in agreement with those reported in the literature.[326]

1-((2-(Trifluoromethyl)phenyl)thio)piperidine (80)



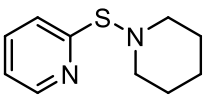
General procedure C was followed using piperidine (296 μL, 3.0 mmol) and 1,2-bis(2-(trifluoromethyl)phenyl)disulfane (709 mg, 2.0 mmol) to afford a mixture of disulfide and sulfenamide. This was then resubjected to general procedure C (aside from additional disulfide) once more to afford sulfenamide **80** as a yellow oil (383 mg, 73%). R_f 0.71 (100% pentane). IR (film)/cm^{-1} 2937, 2852, 2823, 1594, 1442, 1312, 1250, 1172, 1123, 1032, 762. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.59 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.51 (t, *J* = 7.5 Hz, 1H, Ar-H), 7.19 (t, *J* = 7.6 Hz, 1H, Ar-H), 3.13–3.03 (m, 4H, 2 × NCH_2), 1.70 (p, *J* = 5.8 Hz, 4H, 2 × NCH_2CH_2), 1.56–1.47 (m, 2H, 2 × $N(CH_2)_2CH_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.5 (Ar-C_q), 131.6 (Ar-C), 126.6 (q, $^3J_{C\text{-}F}$ = 5.4 Hz, Ar-C), 125.0 (Ar-C), 124.4 (Ar-C), 124.0 (q, $^1J_{C\text{-}F}$ = 274.0 Hz, Ar-CF_3), 124.0 (q, $^2J_{C\text{-}F}$ = 32.8 Hz, Ar-C_q) 57.6 (2 × NCH_2), 27.3 (2 × NCH_2CH_2), 23.3 ($N(CH_2)_2CH_2$). ^{19}F NMR (376 MHz, $CDCl_3$) δ –61.17. HRMS (ESI) *m/z*: Calcd for $C_{12}H_{15}NF_3S$ [M+H]: 262.0877; Found: 262.0873.

4-(Piperidin-1-ylthio)pyridine (84)



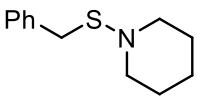
General procedure C was followed using piperidine (296 μL, 3.0 mmol) and 1,2-di(pyridin-4-yl)disulfane (441 mg, 2.0 mmol). The product was purified by column chromatography (SiO_2, 30% Et_2O in pentane) to afford sulfenamide **84** as a pale green oil (110 mg, 28%). R_f 0.20 (30% Et_2O in pentane). IR (film)/cm^{-1} 2933, 2847, 2821, 1572, 1476, 1405, 1215, 1099, 1036, 917, 805, 708. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45–8.36 (m, 2H, 2 × Ar-H), 7.23–7.19 (m, 2H, 2 × Ar-H), 3.10–3.03 (m, 4H, 2 × NCH_2), 1.72–1.68 (m, 4H, 2 × NCH_2CH_2), 1.56–1.47 (m, 2H, $N(CH_2)_2CH_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.5 (Ar-C_q), 149.1 (2 × Ar-C), 116.9 (2 × Ar-C), 57.5 (2 × NCH_2), 27.2 (2 × NCH_2CH_2), 23.2 ($N(CH_2)_2CH_2$). Analytical data (NMR, IR) in agreement with those reported in the literature.[225]

2-(Piperidin-1-ylthio)pyridine (85)



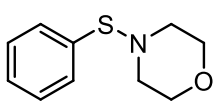
General procedure C was followed using piperidine (296 μL, 3.0 mmol) and 1,2-di(pyridin-2-yl)disulfane (441 mg, 2.0 mmol). The product was purified by column chromatography (SiO_2, 10% Et_2O in pentane) to afford sulfenamide **85** as a colourless oil (220 mg, 57%). R_f 0.24 (10% Et_2O in pentane). IR (film)/cm^{-1} 3041, 2933, 2847, 1572, 1446, 1416, 1125, 1039, 756. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H, Ar-H), 7.60 (ddd, *J* = 8.1, 7.3, 1.8 Hz, 1H, Ar-H), 7.49 (dt, *J* = 8.1, 1.1 Hz, 1H, Ar-H), 6.95 (ddd, *J* = 7.3, 4.8, 1.2 Hz, 1H, Ar-H), 3.21–3.13 (m, 4H, 2 × NCH_2), 1.72–1.66 (m, 4H, 2 × NCH_2CH_2), 1.57–1.46 (m, 2H, $N(CH_2)_2CH_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5 (Ar-C_q), 149.3 (Ar-C), 136.4 (Ar-C), 119.0 (Ar-C), 118.0 (Ar-C), 57.6 (2 × NCH_2), 27.4 (2 × NCH_2CH_2), 23.3 ($N(CH_2)_2CH_2$). Analytical data (NMR, IR) in agreement with those reported in the literature.[225]

1-(Benzylthio)piperidine (87)



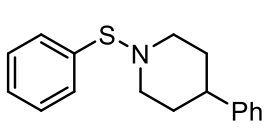
General procedure C was followed using piperidine (296 μL, 3.0 mmol) and 1,2-dibenzyldisulfane (493 mg, 2.0 mmol) to afford sulfenamide **87** as a colourless crystalline solid (394 mg, 95%). R_f 0.20 (100% pentane). mp = 33–34 °C. IR (film)/cm^{-1} 3026, 2929, 2847, 2803, 1602, 1494, 1449, 1218, 1103, 1036, 764, 697. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.28 (m, 4H, 4 × Ar-H), 7.26–7.20 (m, 1H, Ar-H), 3.95 (s, 2H, $ArCH_2$), 3.00–2.95 (m, 4H, 2 × NCH_2), 1.59–1.54 (m, 4H, 2 × NCH_2CH_2), 1.41–1.32 (m, 2H, $N(CH_2)_2CH_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.8 (Ar-C_q), 129.3 (2 × Ar-C), 128.4 (2 × Ar-C), 126.6 (Ar-C), 57.8 (2 × NCH_2), 36.2 ($ArCH_2$), 27.2 (2 × NCH_2CH_2), 23.1 ($N(CH_2)_2CH_2$). Analytical data (mp) in agreement with those reported in the literature.[327]

4-(Phenylthio)morpholine (89)



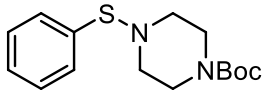
General procedure C was followed using 1,2-diphenyldisulfane (437 mg, 2.0 mmol) and morpholine (259 μL, 3.0 mmol) to afford sulfenamide **89** as a colourless oil (292 mg, 75%). R_f 0.10 (100% pentane). IR (film)/cm^{-1} 3055, 2956, 2851, 1449, 1255, 1111, 930, 739, 690. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.45 (m, 2H, 2 × Ar-H), 7.40–7.35 (m, 2H, 2 × Ar-H), 7.33–7.28 (m, 1H, Ar-H), 3.76–3.70 (m, 4H, 2 × OCH_2), 3.01–2.93 (m, 4H, 2 × NCH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.6 (Ar-C_q), 130.5 (2 × Ar-C), 128.7 (Ar-C), 127.9 (2 × Ar-C), 67.7 (2 × OCH_2), 56.1 (2 × NCH_2). Analytical data (NMR, IR) in agreement with those reported in the literature.[328]

4-Phenyl-1-(phenylthio)piperidine (90)



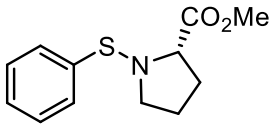
General procedure C was followed using 1,2-diphenyldisulfane (437 mg, 2.0 mmol) and 4-phenylpiperidine (484 mg, 3.0 mmol) to afford sulfenamide **90** as a glassy solid (295 mg, 55%). R_f 0.10 (100% pentane). mp = 44–46 °C. IR (film)/cm^{-1} 3056, 3026, 2873, 2814, 1580,1476, 1438, 1241, 924, 738, 697. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.46 (m, 2H, 2 × Ar-H), 7.42–7.35 (m, 2H, 2 × Ar-H), 7.33–7.27 (m, 3H, 3 × Ar-H), 7.24–7.18 (m, 3H, 3 × Ar-H), 3.35 (m, 2H, 2 × NCH_aH$_b$), 2.88 (td, *J* = 11.8, 2.8 Hz, 2H, 2 × NCH$_a$$H_b$), 2.42 (tt, *J* = 12.0, 3.9 Hz, 1H, ArC-H), 1.92 (qd, 12.0, 3.8 Hz, 2H, 2 × $NCH_2C$$H_aH_b$), 1.86–1.78 (m, 2H, 2 × $NCH_2CH_a$$H_b$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.9 (Ar-C_q), 135.7 (Ar-C_q), 130.0 (2 × Ar-C), 128.6 (Ar-C), 128.4 (2 × Ar-C), 127.4 (2 × Ar-C), 126.8 (2 × Ar-C), 126.2 (Ar-C), 57.3 (2 × NCH_2), 41.3 (Bn-C), 34.7 (2 × NCH_2CH_2). Analytical data (mp) in agreement with those reported in the literature.[231]

***tert*-Butyl 4-(phenylthio)piperazine-1-carboxylate (91)**



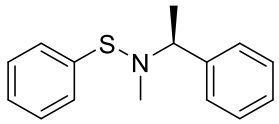
General procedure C was followed using 1,2-diphenyldisulfane (437 mg, 2.0 mmol) and 1-boc-piperazine (559 mg, 3.0 mmol). After an initial 2 h reaction time, an additional equiv of silver nitrate was added and stirred for another 2 h to afford sulfenamide **91** as a white solid (428 mg, 73%). R_f 0.14 (100% pentane). mp = 87–89 °C. IR (film)/cm^{-1} 3071, 2941, 1677, 1423, 1364, 1248, 1129, 756, 686. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.45 (m, 2H, 2 × Ar-H), 7.37 (t, *J* = 7.3 Hz, 2H, 2 × Ar-H), 7.32–7.27 (m, 1H, Ar-H), 3.48–3.45 (m, 4H, 2 × $BocNCH_2$), 2.93–2.90 (m, 4H, 2 × $SNCH_2$), 1.43 (s, 9H, 3 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.5 (C=O), 134.4 (Ar-C_q), 130.8 (2 × Ar-C), 128.7 (Ar-C), 128.0 (2 × Ar-C), 79.8 ($C_q(CH_3)_3$), 55.7 (2 × $SNCH_2$), 44.5 (2 × $BocNCH_2$), 28.4 $(CH_3)_3$. HRMS (ESI) *m/z*: Calcd for $C_{15}H_{23}N_2O_2S$ [M+H]: 295.1480; Found: 295.1490.

Methyl (phenylthio)-*L*-prolinate (96)



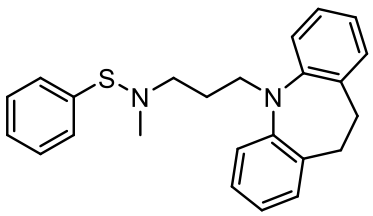
General procedure C was followed using 1,2-diphenyldisulfane (437 mg, 2.0 mmol), triethylamine (416 μL, 3.0 mmol, 1.5 equiv) and L-proline methyl ester hydrochloride (479 mg, 3.0 mmol). After an initial 2 h reaction time, an additional equiv of silver nitrate was added and stirred for another 2 h to afford a mixture of sulfenamide and disulfide. Additional purification was carried out by distillation (175 °C, 1.2 mbar) to afford sulfenamide **96** as a yellow oil (307 mg, 65%). R_f 0.15 (5% Et_2O in pentane). IR (film)/cm^{-1} 3056, 2952, 2870, 1737, 1580, 1476, 1438, 1203, 1170, 738, 693. ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.28 (m, 4H, 4 × Ar-H), 7.20–7.15 (m, 1H, Ar-H), 3.91 (dd, *J* = 8.6, 4.1 Hz, 1H, $NCHCO_2Me$), 3.72 (s, 3H, OCH_3), 3.52–3.44 (m, 1H, NCH_aH_b), 3.23 (m, 1H, NCH_aH_b), 2.29–2.19 (m, 1H, $N(CHCO_2Me)CH_aH_b$), 2.09–1.99 (m, 2H, $NCH_2CH_aH_b$ and $N(CHCO_2Me)CH_aH_b$), 1.96–1.87 (m, 1H, $NCH_2CH_aH_b$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3 (C=O), 139.7 (Ar-C_q), 128.8 (2 × Ar-C), 125.9 (Ar-C), 125.2 (2 × Ar-C), 66.7 ($NCHCO_2Me$), 56.0 (NCH_2), 52.0 (OCH_3), 31.0 ($N(CHCO_2Me)CH_2$), 25.0 (NCH_2CH_2). HRMS (ESI) *m/z*: Calcd for $C_{12}H_{16}NO_2S$ [M+H]: 238.0902; Found: 238.0909.

(*S*)-*N*-Methyl-*S*-phenyl-*N*-(1-phenylethyl)thiohydroxylamine (97)



General procedure C was followed using 1,2-diphenyldisulfane (437 mg, 2.0 mmol) and (*S*)-*N*-methyl-1-phenylethan-1-amine (437 μL, 3.0 mmol) to afford sulfenamide **97** as a colourless oil (261 mg, 54%). R_f 0.38 (100% pentane). IR (film)/cm^{-1} 3060, 3026, 2974, 2862, 2795, 1580, 1476, 1438, 1148, 1025, 738, 700. ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.30 (m, 9H, 9 × Ar-H), 7.23–7.17 (m, 1H, Ar-H), 4.20 (q, *J* = 6.8 Hz, 1H, $CHCH_3$), 2.82 (s, 3H NCH_3), 1.61 (d, *J* = 6.8 Hz, 3H $CHCH_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.2 (Ar-C_q), 141.7 (Ar-C_q), 2 × 128.6 (Ar-C), 2 × 128.3 (Ar-C), 2 × 127.2 (Ar-C), 2 × 125.3 (Ar-C), 2 × 124.3 (Ar-C), 65.8 ($CHCH_3$), 44.5 (NCH_3), 20.4 ($CHCH_3$). HRMS (ESI) *m/z*: Calcd for $C_{15}H_{18}NS$ [M+H]: 244.1160; Found: 244.1152.

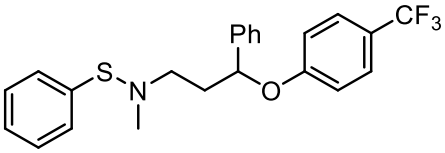
***N*-(3-(10,11-Dihydro-5*H*-dibenzo[*b*,*f*]azepin-5-yl)propyl)-*N*-methyl-*S*-phenylthiohydroxylamine (98)**



General procedure C was followed using 1,2-diphenyldisulfane (437 mg, 2.0 mmol), triethylamine (346 μL, 2.5 mmol, 1.25 equiv) and desipramine hydrochloride (757 mg, 2.5 mmol, 1.25 equiv) to afford sulfenamide **98** as a brown oil (409 mg, 55%). R_f 0.16 (100% pentane). IR (film)/cm^{-1} 3056, 2918, 2837, 1577, 1472, 1439, 1226, 738, 686. ^1H NMR (400 MHz, $CDCl_3$) δ 7.55–7.49 (m, 2H, 2 × Ar-H), 7.35–7.30 (m, 2H, 2 × Ar-H), 7.25–7.21 (m, 1H, Ar-H), 7.17–7.07 (m, 6H, 6 × Ar-H), 6.93 (td, *J* = 7.3,

1.5 Hz, 2H, 2 × Ar-H), 3.81 (t, *J* = 6.7 Hz, 2H, $(Ar)_2NCH_2$), 3.14 (s, 4H, $(Ar\text{-}CH_2)_2$), 2.87 (t, *J* = 6.8 Hz, 2H, $SN(CH_3)CH_2$), 2.74 (s, 3H, NCH_3), 1.91 (p, *J* = 6.8 Hz, 2H, $(CH_2)_2CH_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.3 ($Ar\text{-}C_q$), 134.2 (Ar-C), 129.8 (2 × Ar-C), 129.1 (2 × Ar-C), 128.6 (2 × Ar-C), 127.5 (Ar-C), 127.2 (2 × $Ar\text{-}C_q$), 126.8 (2 × $Ar\text{-}C_q$), 126.3 (2 × Ar-C), 122.4 (2 × Ar-C), 120.0 (2 × Ar-C), 57.1 ($SN(CH_3)CH_2$), 48.2 ($(Ar)_2NCH_2$), 46.9 (NCH_3), 32.2 ($(Ar\text{-}CH_2)_2$), 26.7 $(CH_2)_2CH_2$). HRMS (ESI) *m/z*: Calcd for $C_{24}H_{27}N_2S$ [M+H]: 375.1895; Found: 375.1894.

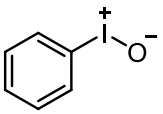
_N_-Methyl-_S_-phenyl-_N_-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)thiohydroxylamine (99)



General procedure C was followed using 1,2-diphenyldisulfane (437 mg, 2.0 mmol), triethylamine (346 μL, 2.5 mmol, 1.25 equiv) and fluoxetine hydrochloride (865 mg, 2.5 mmol, 1.25 equiv) to afford sulfenamide **99** as a pink oil (539 mg, 65%). R_f 0.37 (100% pentane). IR (film)/cm^{-1} 3064, 2929, 2947, 2803, 1613, 1517, 1323, 1245, 1159, 1111, 834, 738, 697. ^1H NMR (400 MHz, $CDCl_3$) δ 7.47–7.42 (m, 2H, 2 × Ar-H), 7.40–7.29 (m, 9H, 9 × Ar-H), 7.27–7.24 (m, 1H, Ar-H), 6.93–6.87 (m, 2H, 2 × Ar-H), 5.31 (dd, *J* = 8.4, 4.8 Hz, 1H, OC*H*Ar), 3.04 (ddd, *J* = 12.8, 7.5, 6.5 Hz, 1H, NC*H*H), 2.92 (ddd, J = 12.6, 6.8, 5.5 Hz, 1H, NCH*H*), 2.85 (s, 3H, NCH_3), 2.38–2.16 (m, 2H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.7 ($Ar\text{-}C_q$), 141.1 ($Ar\text{-}C_q$), 136.9 ($Ar\text{-}C_q$), 128.8 (2 × Ar-C), 128.8 (2 × Ar-C), 128.7 (2 × Ar-C), 127.8 (Ar-C), 127.1 (Ar-C), 126.7 (q, $^3J_{C\text{-}F}$ = 4.0 Hz, 2 × Ar-C), 125.8 (2 × Ar-C), 124.4 (q, $^1J_{C\text{-}F}$ = 272.2 Hz, CF_3), 122.7 (q, $^2J_{C\text{-}F}$ = 32.6 Hz, Ar-C), 115.7 (2 × Ar-C), 77.8 (O*C*HAr), 54.8 (NCH_2), 47.6 (NCH_3), 37.1 (CH_2). ^{19}F NMR (377 MHz, $CDCl_3$) δ -61.52 (CF_3). HRMS (ESI) *m/z*: Calcd for $C_{23}H_{23}NOSF_3$ [M+H]: 418.1452; Found: 418.1454.

4.2.3.3 Synthesis of Sulfonimidamides

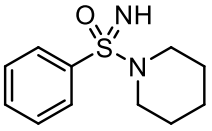
Iodosylbenzene (107)



Procedure adapted from Malcolmson and co-workers.[329] Bis(acetoxy)iodobenzene (3.22 g, 10.0 mmol, 1.0 equiv) was added portion wise to a solution of 3 M aq. NaOH (20 mL) at 25 °C and stirred for 1 h. H_2O (20 mL) was added to the suspension which was stirred for an additional 1 h. The suspension was then filtered to collect the yellow precipitate, which was washed with H_2O (100 mL) and $CHCl_3$ (100 mL). Excess solvent was then removed under reduced pressure to afford iodosylbenzene as a yellow solid (2.00 g, 91%). mp = 209–211 °C (decomposition, lit. = 210 °C). IR (film)/cm^{-1} 3038, 1566, 1433, 1302, 1152, 995, 731, 688. ^1H NMR data recorded in CD_3OD correspond to dimethoxy(phenyl)-λ^3-iodane; in the absence of a coordinating solvent iodosylbenzene is an insoluble polymeric material. ^1H NMR (400 MHz, CD_3OD) δ 8.12–8.01 (m, 2H, 2 × Ar-H), 7.67–

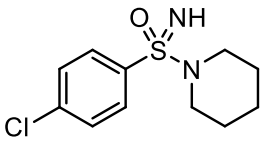
7.57 (m, 3H, 3 × Ar-H).^{13}C NMR data could not been collected due to the poor solubility of iodosylbenzene. Analytical data (^{1}H NMR, mp, IR) in agreement with those reported in the literature.[330,331]

1-(Phenylsulfonimidoyl)piperidine (105)



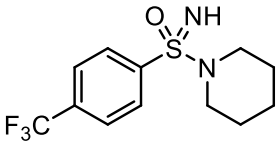
General procedure D was followed using sulfenamide **70** (97 mg, 0.50 mmol). Purification by flash column chromatography (neutral Al_2O_3, 30% EtOAc in pentane) afforded sulfonimidamide **105** as a white solid (84 mg, 75%). R_f 0.20 (20% EtOAc in pentane). mp = 105–106. IR (film)/cm^{-1} 3234, 2949, 2858, 2838, 1470, 1446, 1257 (S=N), 977, 907, 763, 721. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94–7.84 (m, 2H, 2 × Ar-H), 7.62–7.46 (m, 3H, 3 × Ar-H), 2.99 (t, *J* = 5.5 Hz, 4H, 2 × NCH_2), 2.48 (bs, 1H, NH), 1.62 (p, *J* = 5.9 Hz, 4H, 2 × NCH_2CH_2), 1.45–1.32 (m, 2H, $N(CH_2)_2CH_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.3 (Ar-C_q), 132.1 (Ar-C), 128.6 (2 × Ar-C), 127.9 (2 × Ar-C), 47.9 (2 × NCH_2), 25.6 (2 × NCH_2CH_2), 23.6 ($N(CH_2)_2CH_2$). Analytical data (NMR, mp and IR) in agreement with those reported in the literature.[318]

1-(4-Chlorophenylsulfonimidoyl)piperidine (116)



General procedure D was followed using sulfenamide **74** (114 mg, 0.50 mmol). Purification by flash column chromatography (neutral Al_2O_3, 25% EtOAc in pentane) afforded sulfonimidamide **116** as a white solid (85 mg, 66%). R_f 0.22 (25% EtOAc in pentane). mp = 76–77. IR (film)/cm^{-1} 3277, 2938, 2852, 1581, 1475, 1452, 1255 (S=N), 1088, 917, 835, 751, 697. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86–7.79 (m, 2H, 2 × Ar-H), 7.51–7.45 (m, 2H, 2 × Ar-H), 2.98 (dd, *J* = 6.4, 5.4 Hz, 4H, 2 × NCH_2), 2.47 (bs, 1H, NH), 1.62 (p, *J* = 5.8 Hz, 4H, 2 × NCH_2CH_2), 1.42–1.37 (m, 2H, $N(CH_2)_2CH_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.6 (Ar-C_q), 134.8 (Ar-C_q), 129.4 (2 × Ar-C), 128.9 (2 × Ar-C), 47.9 (2 × NCH_2), 25.6 (2 × NCH_2CH_2), 23.6 ($N(CH_2)_2CH_2$). Analytical data (NMR, mp and IR) in agreement with those reported in the literature.[318]

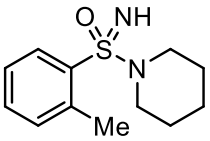
1-(4-(Trifluoromethyl)phenylsulfonimidoyl)piperidine (117)



General procedure D was followed using sulfenamide **75** (131 mg, 0.50 mmol). Purification by flash column chromatography (neutral Al_2O_3, 20% EtOAc in pentane) afforded sulfonimidamide **117** as a white solid (70 mg, 48%). R_f 0.61 (30% EtOAc in pentane). mp = 115–117 °C. IR (film)/cm^{-1} 3283, 2940, 2863, 1607, 1402, 1321, 1260 (S=N), 1129, 1064, 919, 642. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05–7.99 (m, 2H, 2 × Ar-H), 7.80–7.76 (m, 2H, 2 × Ar-H), 3.06–2.97 (dd, *J* = 6.3, 5.3 Hz, 4H, 2 × NCH_2), 2.55 (bs, 1H, NH), 1.63 (p, *J* = 5.5, 4H, 2 × NCH_2CH_2), 1.46–1.37 (m, 2H, $N(CH_2)_2CH_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.3 (Ar-C_q), 133.8 (q, $^{2}J_{C\text{-}F}$ = 32.8 Hz, Ar-C_q),

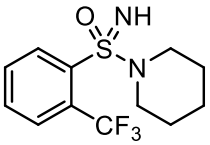
128.4 (2 × Ar-C), 125.8 (q, $^{3}J_{C\text{-}F}$ = 3.6 Hz, 2 × Ar-C), 123.4 (q, $^{1}J_{C\text{-}F}$ = 272.2 Hz, Ar-CF_3), 47.9 (2 × NCH_2), 25.6 (2 × NCH_2CH_2), 23.5 ($N(CH_2)_2CH_2$). ^{19}F NMR (377 MHz, $CDCl_3$) δ –63.0. HRMS (ESI) *m/z*: Calcd for $C_{12}H_{16}N_2OSF_3$ [M+H]: 293.0935; Found: 293.0948.

1-(2-Methylphenylsulfonimidoyl)piperidine (120)



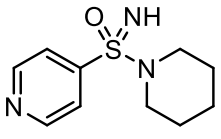
General procedure D was followed using sulfenamide **78** (104 mg, 0.50 mmol). Purification by flash column chromatography (neutral Al_2O_3, 20% EtOAc in pentane) afforded sulfonimidamide **120** as a colourless oil (53 mg, 45%). R_f 0.41 (30% EtOAc in pentane). IR (film)/cm^{-1} 3274, 2936, 2851, 1469, 1239 (S=N), 1106, 917, 761, 712. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (m, 1H, Ar-H), 7.41 (td, *J* = 7.5, 1.5 Hz, 1H, Ar-H), 7.31–7.26 (m, 2H, 2 × Ar-H), 3.16 (m, 4H, 2 × NCH_2), 2.71 (s, 3H, Ar-CH_3), 2.60 (bs, 1H, NH), 1.61 (m, 4H, 2 × NCH_2CH_2), 1.51 (m, 4H, $N(CH_2)_2CH_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.0 (Ar-C_q), 137.8 (Ar-C_q), 132.9 (Ar-C), 132.0 (Ar-C), 129.7 (Ar-C), 125.7 (Ar-C), 46.6 (2 × NCH_2), 25.8 (2 × NCH_2CH_2), 23.9 ($N(CH_2)_2CH_2$), 21.1 (Ar-CH_3). HRMS (ESI) *m/z*: Calcd for $C_{12}H_{19}N_2OS$ [M+H]: 239.1218; Found: 239.1217.

1-(2-(Trifluoromethyl)phenylsulfonimidoyl)piperidine (122)



General procedure D was followed using sulfenamide **80** (131 mg, 0.50 mmol). Purification by flash column chromatography (neutral Al_2O_3, 30% EtOAc in pentane) afforded sulfonimidamide **122** as a yellow oil (97 mg, 67%). R_f 0.08 (25% EtOAc in pentane). IR (film)/cm^{-1} 3287, 2941, 2855, 1443, 1305, 1264 (S=N), 1151, 117, 1031, 933, 773, 712. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 7.6, 1.7 Hz, 1H, Ar-H), 7.87 (dd, *J* = 7.4, 1.8 Hz, 1H, Ar-H), 7.71–7.60 (m, 2H, 2 × Ar-H), 3.25 (m, 4H, 2 × NCH_2), 2.87 (bs, 1H, NH), 1.71–1.59 (m, 4H, 2 × NCH_2CH_2), 1.55 (m, 2H, $N(CH_2)_2CH_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.8 (Ar-C_q), 132.0 (Ar-C), 131.8 (Ar-C), 131.2 (Ar-C), 128.5 (q, $^{3}J_{C\text{-}F}$ = 6.8 Hz, Ar-C_q), 127.8 (q, $^{2}J_{C\text{-}F}$ = 32.9 Hz, Ar-C_q), 122.8 (q, $^{1}J_{C\text{-}F}$ = 273.7 Hz, Ar-CF_3), 46.8 (2 × NCH_2), 25.7 (2 × NCH_2CH_2), 23.9 ($N(CH_2)_2CH_2$). ^{19}F NMR (376 MHz, $CDCl_3$) δ –56.4. HRMS (ESI) *m/z*: Calcd for $C_{12}H_{16}N_2OF_3S$ [M+H]: 293.0935; Found: 293.0943.

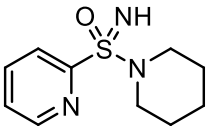
4-(Piperidine-1-sulfonimidoyl)pyridine (126)



General procedure D was followed using sulfenamide **84** (97 mg, 0.50 mmol). Purification by flash column chromatography (neutral Al_2O_3, 100% EtOAc) afforded sulfonimidamide **126** as a yellow solid (68 mg, 61%). R_f 0.19 (100% EtOAc). mp = 109–111 °C. IR (film)/cm^{-1} 3250, 2937, 2829, 1573, 1446, 1402, 1267 (S=N), 1207, 1140, 1044, 988, 909, 727, 686. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85–8.81 (m, 2H, 2 × Ar-H), 7.75–7.70 (m, 2H, 2 × Ar-H), 3.05–2.99 (m, 4H, 2 × NCH_2), 2.57 (s, 1H, NH), 1.66–1.60 (m, 4H, 2 × NCH_2CH_2), 1.45–1.37 (m, 2H, $N(CH_2)_2CH_2$). ^{13}C NMR (101 MHz,

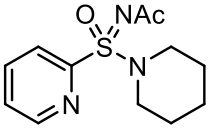
$CDCl_3$) δ 150.7 (Ar-C), 144.8 (Ar-C_q), 121.2 (Ar-C), 47.9 (2 × NCH_2), 25.6 (2 × NCH_2CH_2), 23.5 ($N(CH_2)_2CH_2$). HRMS (ESI) *m/z*: Calcd for $C_{10}H_{16}N_3OS$ [M+H]: 226.1014; Found: 226.1023.

2-(Piperidine-1-sulfonimidoyl)pyridine (127)



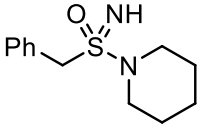
General procedure D was followed using sulfenamide **85** (97 mg, 0.50 mmol). Purification by flash column chromatography (neutral Al_2O_3, 55% EtOAc in pentane) afforded NH sulfonimidamide **127** as a colourless oil (57 mg, 51%) and acylated sulfonimidamide **128** as a white solid (19 mg, 14%). Analytical data for NH sulfonimidamide **127**: R_f 0.18 (55% EtOAc in pentane). IR (film)/cm^{-1} 3276, 2937, 2851, 1572, 1450, 1256 (S=N), 1156, 1096, 1043, 988, 920, 734, 689. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (ddd, *J* = 4.7, 1.8, 0.9 Hz, 1H, Ar-H), 8.04 (dt, *J* = 7.9, 1.1 Hz, 1H, Ar-H), 7.87 (td, *J* = 7.8, 1.8 Hz, 1H, Ar-H), 7.45 (ddd, *J* = 7.6, 4.7, 1.1 Hz, 1H, Ar-H), 3.30–3.20 (m, 4H, 2 × NCH_2), 2.82 (s, 1H, NH), 1.60 (p, *J* = 5.6 Hz, 4H, 2 × NCH_2CH_2), 1.47–1.40 (m, 2H, $N(CH_2)_2CH_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.9 (Ar-C_q), 149.5 (Ar-C), 137.6 (Ar-C), 126.0 (Ar-C), 122.9 (Ar-C), 48.0 (2 × NCH_2), 25.8 (2 × NCH_2CH_2), 23.8 ($N(CH_2)_2CH_2$). Analytical data (NMR and IR) in agreement with those reported in the literature.[190]

***N*-(Oxo(piperidin-1-yl)(pyridin-2-yl)-λ^6-sulfaneylidene)acetamide (128)**



Prepared according to the above procedure for NH sulfonimidamide **127**. Acylated sulfonimidamide **128** afforded as a white solid (19 mg, 14%). R_f 0.23 (55% EtOAc in pentane). mp = 105–107 °C. IR (film)/cm^{-1} 2940, 2855, 1648, 1576, 1449, 1364, 1245 (S=N), 1058, 935, 846. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (ddd, *J* = 4.7, 1.8, 0.9 Hz, 1H, Ar-H), 8.11 (dt, *J* = 7.9, 1.0 Hz, 1H, Ar-H), 7.92 (td, *J* = 7.8, 1.7 Hz, 1H, Ar-H), 7.48 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H, Ar-H), 3.44–3.27 (m, 4H, 2 × NCH_2), 2.14 (s, 3H, CH_3), 1.69–1.60 (m, 4H, 2 × NCH_2CH_2), 1.55–1.49 (m, 2H, $N(CH_2)_2CH_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.0 (C=O), 156.6 (Ar-C_q), 149.7 (Ar-C), 137.8 (Ar-C), 126.4 (Ar-C), 124.4 (Ar-C), 47.1 (2 × NCH_2), 27.0 (CH_3), 25.4 (2 × NCH_2CH_2), 23.7 ($N(CH_2)_2CH_2$). HRMS (ESI) *m/z*: Calcd for $C_{12}H_{18}N_3O_2S$ [M+H]: 268.1120; Found: 268.1125.

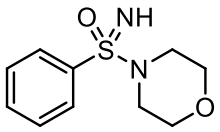
1-(*S*-benzylsulfonimidoyl)piperidine (130)



General procedure D was followed using sulfenamide **87** (104 mg, 0.50 mmol). Purification by flash column chromatography (neutral Al_2O_3, 30% EtOAc in pentane) afforded sulfonimidamide **130** as a white solid (89 mg, 75%). R_f 0.14 (30% EtOAc in pentane). mp = 153–155 °C. IR (film)/cm^{-1} 3276, 3063, 2937, 2847, 1495, 1453, 1252 (S=N), 1211, 1151, 1077, 1047, 921, 771, 723, 697. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.29 (m, 5H, 5 × Ar-H), 4.24 (d, *J* = 13.4 Hz, 1H, SC*H*HAr), 4.20 (d, *J* = 13.6 Hz, 1H, SCH*H*Ar), 3.22–3.10 (m, 4H, 2 × NCH_2), 2.12 (s, 1H, NH), 1.61–1.45 (m, 6H, 2 ×

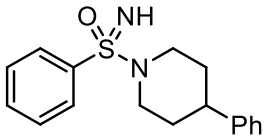
NCH_2CH_2 and $N(CH_2)_2CH_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.0 (2 × Ar-C), 129.5 (Ar-C_q), 128.6 (2 × Ar-C), 128.5 (Ar-C), 56.8 ($ArCH_2$), 47.6 (2 × NCH_2), 26.2 (2 × NCH_2CH_2), 23.9 ($N(CH_2)_2CH_2$). HRMS (ESI) *m/z*: Calcd for $C_{12}H_{19}N_2OS$ [M+H]: 239.1218; Found: 239.1209.

4-(Phenylsulfonimidoyl)morpholine (132)



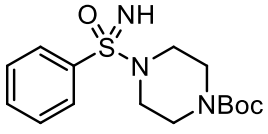
General procedure D was followed using sulfenamide **89** (98 mg, 0.50 mmol). Purification by flash column chromatography (neutral Al_2O_3, 35% EtOAc in pentane) afforded sulfonimidamide **132** as a white solid (68 mg, 60%). R_f 0.18 (35% EtOAc in pentane). mp = 104–106 °C. IR (film)/cm^{-1} 3271, 2967. 2856. 1446, 1255 (S=N), 1111, 928, 725, 690. ^1H NMR (400 MHz, $CDCl_3$) δ 7.91–7.86 (m, 2H, 2 × Ar-H), 7.63–7.57 (m, 1H, Ar-H), 7.56–7.51 (m, 2H, 2 × Ar-H), 3.78–3.67 (m, 4H, 2 × OCH_2), 3.06–2.95 (m, 4H, 2 × NCH_2), 2.56 (bs, 1H, NH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.1 (Ar-C_q), 132.6 (Ar-C), 128.8 (2 × Ar-C), 128.1 (2 × Ar-C), 66.4 (2 × OCH_2), 47.1 (2 × NCH_2). Analytical data (NMR, mp and IR) in agreement with those reported in the literature.[318,331]

4-Phenyl-1-(phenylsulfonimidoyl)piperidine (133)



General procedure D was followed using sulfenamide **90** (135 mg, 0.50 mmol). Purification by flash column chromatography (neutral Al_2O_3, 30% EtOAc in pentane) afforded sulfonimidamide **133** as an orange solid (94 mg, 63%). R_f 0.20 (30% EtOAc in pentane). mp = 112–114 °C. IR (film)/cm^{-1} 3317, 3071, 2941, 2832, 1677, 1423, 1364, 1252 (S=N), 1133, 913, 756, 690. ^1H NMR (400 MHz, $CDCl_3$) δ 7.96–7.90 (m, 2H, 2 × Ar-H), 7.64–7.51 (m, 3H, 3 × Ar-H), 7.32–7.27 (m, 2H, 2 × Ar-H), 7.25–7.18 (m, 1H, Ar-H), 7.18–7.12 (m, 2H, 2 × Ar-H), 4.09–4.03 (m, 2H, 2 × NCH_aH_b), 2.55 (bs, 1H, NH), 2.39 (tt, *J* = 12.0, 4.0 Hz, 1H, Bn-H), 2.28 (tdd, *J* = 11.8, 5.6, 2.8 Hz, 2H, 2 × NCH_aH_b), 1.94–1.75 (m, 4H, 2 × NCH_2CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.0 (Ar-C_q), 136.1 (Ar-C_q), 132.3 (Ar-C), 128.7 (2 × Ar-C), 128.5 (2 × Ar-C), 128.0 (2 × Ar-C), 126.7 (2 × Ar-C), 126.5 (Ar-C), 48.1 (NCH_2), 47.6 (NCH_2), 41.9 (Bn-C), 33.1 (NCH_2CH_2), 32.9 (NCH_2CH_2). HRMS (ESI) *m/z*: Calcd for $C_{17}H_{21}N_2OS$ [M+H]: 301.1375; Found: 301.1384.

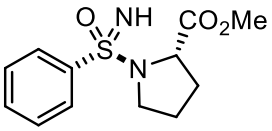
***tert*-Butyl 4-(phenylsulfonimidoyl)piperazine-1-carboxylate (134)**



General procedure D was followed using sulfenamide **91** (147 mg, 0.50 mmol). Purification by flash column chromatography (neutral Al_2O_3, 50% EtOAc in pentane) afforded sulfonimidamide **134** as a white solid (99 mg, 61%). R_f 0.12 (50% EtOAc in pentane). mp = 141–143 °C. IR (film)/cm^{-1} 3265, 2922, 1692, 1416, 1244 (S=N), 1121, 909, 723, 685. ^1H NMR (400 MHz, $CDCl_3$) δ 7.90–7.85 (m, 2H, 2 × Ar-H), 7.62–7.56 (m, 1H, Ar-H), 7.56–7.50 (m, 2H, 2 × Ar-H), 3.49–3.46 (m, 4H, 2 × $BocNCH_2$), 2.99–2.96 (m, 4H, 2 × $SNCH_2$), 2.57 (bs, 1H, NH), 1.40 (s, 9H, 3 × CH_3). ^{13}C

NMR (101 MHz, $CDCl_3$) δ 154.2 (C=O), 135.4 (Ar-C_q), 132.6 (Ar-C), 128.9 (2 × Ar-C), 128.0 (2 × Ar-C), 80.2 ($C_q(CH_3)_3$), 46.8 (2 × $SNCH_2$), 43.3 (2 × $BocNCH_2$), 28.3 $(CH_3)_3$. Analytical data (NMR, mp and IR) in agreement with those reported in the literature.[190]

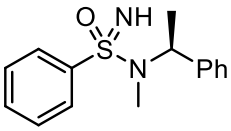
Methyl (phenylsulfonimidoyl)-*L*-prolinate (139)



General procedure D was followed using sulfenamide **96** (119 mg, 0.50 mmol). Purification by flash column chromatography (SiO_2, 35% EtOAc in pentane) afforded sulfonimidamide **139** as a separable mixture of diastereomers (1:1) **139a** and **139b** as a white solid (95 mg, 71%). **139a**: R_f 0.19 (35% EtOAc in pentane). mp = 122–124 °C. IR (film)/cm^{-1} 3295, 2952, 2877, 1740, 1446, 1263 (S=N), 1207, 1136, 1013, 756, 693. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02–7.95 (m, 2H, 2 × Ar-H), 7.62–7.56 (m, 1H, Ar-H), 7.55–7.50 (m, 2H, 2 × Ar-H), 4.12 (dd, *J* = 8.1, 4.1 Hz, 1H, $NCHCO_2Me$), 3.74 (s, 3H, OCH_3), 3.63–3.49 (m, 1H, NCH_aH_b), 3.27–3.21 (m, 1H, NCH_aH_b), 2.92 (s, 1H, NH), 2.00–1.93 (m, 1H, $N(CHCO_2Me)CH_aH_b$), 1.91–1.80 (m, 2H, $N(CH_2)CH_aH_b$), 1.65–1.56 (m, 1H, $N(CHCO_2Me)CH_aH_b$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3 (C=O), 137.3 (Ar-C_q), 132.4 (Ar-C), 128.9 (2 × Ar-C), 127.6 (2 × Ar-C), 60.8 ($NCHCO_2Me$), 52.4 (OCH_3), 49.7 (NCH_2), 30.7 ($N(CHCO_2Me)CH_2$), 24.6 (NCH_2CH_2). HRMS (ESI) *m/z*: Calcd for $C_{12}H_{17}N_2O_3S$ [M+H]: 269.0960; Found: 269.0964. HPLC conditions: Chiralpak IA column, 97:3 *n*hexane:*i*PrOH, flow rate: 1 mL min^{-1}, 35 °C, UV detection wavelength: 250 nm, **139a** retention time: 91 min. **139b**: R_f 0.09 (35% EtOAc in pentane). mp = 107–109 °C. IR (film)/cm^{-1} 3291, 2952, 2877, 1744, 1446, 1263, 1207, 1136, 1014, 756, 693. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04–7.97 (m, 2H, 2 × Ar-H), 7.61–7.55 (m, 1H, Ar-H), 7.55–7.49 (m, 2H, 2 × Ar-H), 4.24–4.21 (m, 1H, $NCHCO_2Me$), 3.75 (s, 3H, OCH_3), 3.53–3.47 (m, 1H, NCH_aH_b), 3.29–3.19 (m, 1H, NCH_aH_b), 2.93 (s, 1H, NH), 1.98–1.87 (m, 3H, $N(CHCO_2Me)CH_aH_b$ and $N(CH_2)CH_aH_b$), 1.67–1.58 (m, 1H, $N(CHCO_2Me)CH_aH_b$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3 (C=O), 138.2 (Ar-C_q), 132.4 (Ar-C), 128.9 (2 × Ar-C), 127.6 (2 × Ar-C), 61.1 ($NCHCO_2Me$), 52.4 (OCH_3), 49.0 (NCH_2), 30.9 ($N(CHCO_2Me)CH_2$), 24.7 (NCH_2CH_2). HRMS (ESI) *m/z*: Calcd for $C_{12}H_{17}N_2O_3S$ [M+H]: 269.0960; Found: 269.0964. HPLC conditions: Chiralpak IA column, 97:3 *n*hexane:*i*PrOH, flow rate: 1 mL min^{-1}, 35 °C, UV detection wavelength: 250 nm, **139b** retention time: 105 min.

By using the enantiomer of the amine, synthesis of the enantiomeric pairs for proof of *ee* retention was carried out. Diastereomers **139c** and **139d** were afforded as a separable mixture (1:1) with characterisation data in accordance with the above. HPLC conditions: Chiralpak IA column, 97:3 *n*hexane:*i*PrOH, flow rate: 1 mL min^{-1}, 35 °C, UV detection wavelength: 250 nm, **139c** and **139d** retention time: 75 and 81 min.

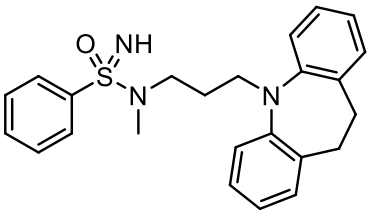
***N*-Methyl-*N*-((*S*)-1-phenylethyl)benzenesulfonimidamide (140)**



General procedure D was followed using sulfenamide **97** (122 mg, 0.50 mmol). Purification by flash column chromatography (neutral Al_2O_3, 30% EtOAc in pentane) afforded sulfonimidamide **140** as an inseparable mixture of diastereomers (1:1) **140a** and **140b** as a colourless oil (85 mg, 62%). R_f 0.20 (30% EtOAc in pentane). IR (film)/cm^{-1} 3280, 3063, 2978, 1446, 1256 (S=N), 976, 909, 755, 719. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05–7.97 (m, 4H, 4 × Ar-H_{a+b}), 7.62–7.49 (m, 6H, 6 × Ar-H_{a+b}), 7.36–7.24 (m, 10H, 10 × Ar-H_{a+b}), 5.48–5.39 (m, 2H, C$H_{a+b}$$CH_3$), 2.68 (s, 3H, NC($H_{a/b}$)$_3$), 2.63 (s, 3H, NC($H_{a/b}$)$_3$), 1.23 (d, *J* = 7.0 Hz, 3H, CHC($H_{a/b}$)$_3$), 1.21 (d, *J* = 7.1 Hz, 3H, CHC($H_{a/b}$)$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.8 (Ar-$C_{(a/b)q}$), 140.6 (Ar-$C_{(a/b)q}$), 2 × 140.5 (Ar-$C_{a/b}$), 132.0 (Ar-$C_{a/b}$), 132.0 (Ar-$C_{a/b}$), 2 × 128.9 (Ar-$C_{a/b}$), 2 × 128.4 (Ar-$C_{a/b}$), 2 × 128.3 (Ar-$C_{a/b}$), 2 × 127.4 (Ar-$C_{a/b}$), 2 × 127.3 (Ar-$C_{a/b}$), 2 × 127.3 (Ar-$C_{a/b}$), 2 × 127.2 (Ar-$C_{a/b}$), 2 × 127.2 (Ar-$C_{a/b}$), 2 × 126.8 (Ar-$C_{a/b}$), 55.5 ($C_{a/b}$HCH_3), 55.0 ($C_{a/b}$HCH_3), 29.4 (NC($H_{a/b}$)$_3$), 29.3 (NC($H_{a/b}$)$_3$), 15.9 (CH$C_{a/b}$$H_3$), 14.6 (CH$C_{a/b}$$H_3$). HRMS (ESI) *m/z*: Calcd for $C_{15}H_{19}N_2OS$ [M+H]: 275.1218; Found: 275.1227. Chiralpak IA column, 93:7 *n*hexane:*i*PrOH, flow rate: 1 mL min^{-1}, 35 °C, UV detection wavelength: 250 nm, **140a** and **140b** retention time: 24 and 28 min.

By using the enantiomer of the amine, synthesis of the enantiomeric pairs for proof of *ee* retention was carried out. Diastereomers **140c** and **140d** were afforded as an inseparable mixture (1:1) with characterisation data in accordance with the above. Chiralpak IA column, 93:7 *n*hexane:*i*PrOH, flow rate: 1 mL min^{-1}, 35 °C, UV detection wavelength: 250 nm, **140c** and **140d** retention time: 22 and 27 min.

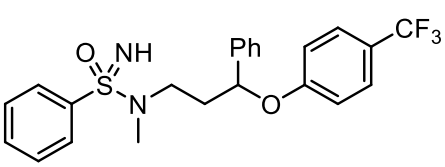
***N*-(3-(10,11-Dihydro-5*H*-dibenzo[*b,f*]azepin-5-yl)propyl)-*N*-methylbenzenesulfonimidamide (141)**



General procedure D was followed using sulfenamide **98** (187 mg, 0.50 mmol). Purification by flash column chromatography (neutral Al_2O_3, 25% EtOAc in pentane) afforded sulfonimidamide **141** as a brown solid (98 mg, 48%). R_f 0.13 (25% EtOAc in pentane). mp = 113–115 °C. IR (film)/cm^{-1} 3302, 2922, 1595, 1446, 1237 (S=N), 1066, 902, 757, 716. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.4 Hz, 2H, 2 × Ar-H), 7.57–7.45 (m, 3H, 3 × Ar-H), 7.20–7.04 (m, 6H, 6 × Ar-H), 6.95 (t, *J* = 7.3 Hz, 2H, 2 × Ar-H), 3.81 (t, *J* = 6.5 Hz, 2H, (Ar)$_2$NCH_2), 3.32–3.13 (m, 5H, (Ar-CH_2)$_2$ + SN(CH_3)C$H_a$$H_b$), 2.90 (dt, *J* = 13.3, 6.7 Hz, 1H, SN(CH_3)C$H_a$$H_b$), 2.63 (s, 3H, NC$H_3$), 2.35 (s, 1H, NH), 1.81–1.69 (m, 2H, (CH_2)$_2$CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.9 (Ar-C_q), 137.2 (Ar-C_q), 134.2 (Ar-C_q), 132.0 (Ar-C), 129.9 (2 × Ar-C), 128.7 (2 × Ar-C), 127.5 (2 × Ar-C), 126.4 (2 × Ar-C), 122.6 (2 × Ar-C), 119.8 (2 × Ar-C), 48.8 (SN(CH_3)CH_2), 47.4 ((Ar)$_2$NCH_2), 35.7

(NCH_3), 32.1 (Ar-CH_2)$_2$), 26.1 (CH_2)$_2$$CH_2$). HRMS (ESI) *m/z*: Calcd for $C_{24}H_{28}N_3OS$ [M+H]: 406.1953; Found: 406.1950.

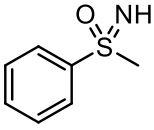
_N_-Methyl-_N_-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)benzenesulfonimidamide (142)



General procedure D was followed using sulfenamide **99** (209 mg, 0.50 mmol). Purification by flash column chromatography (neutral Al_2O_3, 30% EtOAc in pentane) afforded sulfonimidamide **142** as an inseparable mixture of diastereomers (1:1) **142a** and **142b** as a colourless oil (176 mg, 79%). R_f 0.29 (30% EtOAc in pentane). IR (film)/cm^{-1} 3321, 3068, 2930, 1613, 1517, 1446 1326, 1252 (S=N), 1111, 1069. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95–7.88 (m, 4H, 4 × Ar-H$_{a+b}$), 7.61–7.49 (m, 6H, 6 × Ar-H$_{a+b}$), 7.49–7.43 (m, 4H, 4 × Ar-H$_{a+b}$), 7.40–7.30 (m, 10H, 10 × Ar-H$_{a+b}$), 6.97–6.89 (m, 4H, 4 × Ar-H$_{a+b}$), 5.32 (dd, *J* = 9.1, 3.8 Hz, 1H, OCH$_a$Ar), 5.26 (dd, *J* = 8.7, 4.2 Hz, 1H, OCH$_b$Ar), 3.54 (ddd, *J* = 13.3, 8.4, 6.6 Hz, 1H, NC*H*H$_a$), 3.32 (dt, *J* = 13.4, 7.4 Hz, 1H, NC*H*H$_b$), 3.18 (ddd, *J* = 13.4, 8.1, 5.3 Hz, 1H, NCH*H*$_b$), 3.01 (ddd, *J* = 13.3, 6.9, 4.6 Hz, 1H, NCH*H*$_a$), 2.79–2.71 (s, 6H, NCH$_{3(a+b)}$), 2.48 (s, 1H, NH$_{a/b}$), 2.33 (s, 1H, NH$_{a/b}$), 2.29–2.13 (m, 2H, CH$_{2b}$), 2.13–2.00 (m, 2H, CH$_{2a}$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3 (2 × Ar-C$_{q(a+b)}$), 140.6 (Ar-C$_{q(a/b)}$), 140.5 (Ar-C$_{q(a/b)}$), 137.4 (Ar-C$_{q(a/b)}$), 137.0 (Ar-C$_{q(a/b)}$), 132.29 (Ar-C$_{a/b}$), 132.26 (Ar-C$_{a/b}$), 128.92 (4 × Ar-C$_{a/b}$), 128.89 (4 × Ar-C$_{a/b}$), 128.14 (Ar-C$_{a/b}$), 128.07 (Ar-C$_{a/b}$), 127.69 (2 × Ar-C$_{a/b}$), 127.65 (2 × Ar-C$_{a/b}$), 126.92 (q, $^3J_{C\text{-}F}$ = 3.5 Hz, 2 × Ar-C$_{a/b}$), 126.81 (q, $^3J_{C\text{-}F}$ = 3.8 Hz, 2 × Ar-C$_{a/b}$), 125.9 (2 × Ar-C$_{a/b}$), 125.8 (2 × Ar-C$_{a/b}$), 124.40 (q, $^1J_{C\text{-}F}$ = 271.1 Hz, CF$_{3(a+b)}$), 124.36 (q, $^1J_{C\text{-}F}$ = 271.0 Hz, CF$_{3(a/b)}$), 123.00 (q, $^2J_{C\text{-}F}$ = 32.5 Hz, Ar-C$_{q(a/b)}$), 122.96 (q, $^2J_{C\text{-}F}$ = 32.8 Hz, Ar-C$_{q(a/b)}$), 115.9 (2 × Ar-C$_{(a/b)}$), 115.8 (2 × Ar-C$_{(a/b)}$), 77.8 (O*C*H$_b$Ar), 77.3 (O*C*H$_a$Ar), 47.8 (N*C*H$_{2b}$), 47.7 (N*C*H$_{2a}$), 37.4 (*C*H$_{2a}$), 37.3 (*C*H$_{2b}$), 36.3 (N*C*H$_{3(a/b)}$), 36.1 (N*C*H$_{3(a/b)}$). ^{19}F NMR (377 MHz, $CDCl_3$) δ -61.58 (CF$_{3(a/b)}$), -61.59 (CF$_{3(a/b)}$). HRMS (ESI) *m/z*: Calcd for $C_{23}H_{24}N_2O_2SF_3$ [M+H]: 449.1511; Found: 449.1507.

*4.2.3.4 Synthesis of Sulfoximine **144***

Imino(methyl)(phenyl)-λ^6-sulfanone (144)

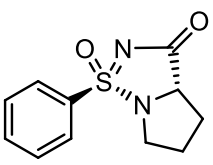


General procedure D was followed using sulfide **143** (62 mg, 0.50 mmol). Purification by flash column chromatography (SiO_2, 100% EtOAc in pentane) afforded sulfoximine **144** as a yellow oil (64 mg, 83%). R_f 0.22 (100% EtOAc). IR (film)/cm^{-1} 3269, 2926, 1446, 1218 (S=N), 1095, 991, 741, 689. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05–7.99 (m, 2H, 2 × Ar-H), 7.66–7.60 (m, 1H, Ar-H), 7.59–7.53 (m, 2H, 2 × Ar-H), 3.12 (s, 3H, SCH_3), 2.25 (s, 1H, NH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5 (Ar-C$_q$), 133.0 (Ar-C), 129.3

(2 × Ar-C), 127.7 (2 × Ar-C), 46.1 (SCH_3). Analytical data (NMR and IR) in agreement with those reported in the literature.[332]

*4.2.3.5 Synthesis of Ring Closed Product **145***

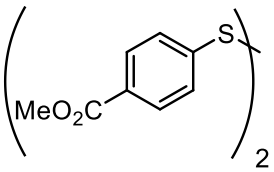
(1*R*,3a*S*)-1-Phenyl-3a,4,5,6-tetrahydro-3*H*-1λ^4-pyrrolo[1,2-*b*][1,2,5]thiadiazol-3-one 1-oxide (145)



Neutral Al_2O_3 (10 g) was added to a solution of sulfonimidamide **139a** (10 mg, 0.04 mmol) in EtOAc:hexane (1:1, 1 mL, 0.04 M) at 25 °C and stirred for 5 h. The reaction mixture was filtered and washed with EtOAc (100 mL). The filtrate solvent was removed under reduced pressure. Purification by flash column chromatography (SiO_2, 55% EtOAc in hexane) afforded **145** as a colourless oil (7 mg, 74%). R_f 0.18 (50% EtOAc in pentane). IR (film)/cm^{-1} 2956, 1700, 1446, 1259 (S=N), 122, 1163, 1103, 1010, 756, 686. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93–7.86 (m, 2H, 2 × Ar-H), 7.73–7.65 (m, 1H, Ar-H), 7.63–7.56 (m, 2H, 2 × Ar-H), 4.41 (dd, *J* = 8.4, 6.1 Hz, 1H, $NCHCO_2Me$), 4.04 (ddd, *J* = 11.5, 6.2, 4.9 Hz, 1H, NCH_aH_b), 3.08 (ddd, *J* = 11.8, 8.1, 7.0 Hz, 1H, NCH_aH_b), 2.35–2.19 (m, 2H, $N(CHCO_2Me)CH_2$), 2.07–1.98 (m, 2H, $N(CH_2)CH_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.7 (C=O), 138.4 (Ar-C_q), 134.2 (Ar-C), 129.4 (2 × Ar-C), 127.4 (2 × Ar-C), 70.3 ($NCHCO_2Me$), 47.9 (NCH_2), 29.8 ($N(CHCO_2Me)CH_2$), 27.3 (NCH_2CH_2). HRMS (ESI) *m/z*: Calcd for $C_{11}H_{13}N_2O_2S$ [M+H]: 237.0698; Found: 237.0708. NOE analysis confirmed the relative stereochemistry of **145**.

4.2.3.6 Synthesis and N-Functionalisation of aza-Probenecid

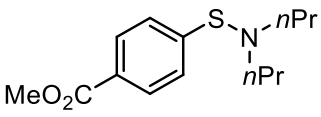
Dimethyl 4,4'-disulfanediyldibenzoate (149)



Procedure adapted from Labar, Jubault and co-workers.[253] I_2 (3.29 g, 13.0 mmol, 2 equiv) was added to a solution of 4-mercaptobenzoic acid (1.0 g, 6.5 mmol, 1 equiv) in EtOH (6.5 mL) at 25 °C, under air, and stirred for 18 h. The reaction mixture was filtered and washed with EtOH (3 × 75 mL). The precipitate was collected and dried under reduced pressure to afford 4,4'-disulfanediyldibenzoic acid which was used without further purification. Conc. H_2SO_4 (1 mL) was added to a solution of 4,4'-disulfanediyldibenzoic acid (845 mg, 2.80 mmol, 1 equiv) in MeOH (15 mL, 0.2 M) at room temperature, heated to 65 °C and stirred for 18 h. The reaction mixture was filtered and washed with MeOH (3 × 75 mL). The filtrate solvent was removed under reduced pressure and purification by flash column chromatography (SiO_2, 20% EtOAc in pentane) afforded disulfide **149** as a white solid (705 mg, 65%). R_f 0.55 (30% EtOAc in pentane). mp = 125–126 °C. IR (film)/cm^{-1} 3410, 2996, 2948, 1710, 1587, 1431, 1394, 1274, 1107, 1010, 749. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.6 Hz, 4H, 4 × Ar-H), 7.55 (d, *J* =

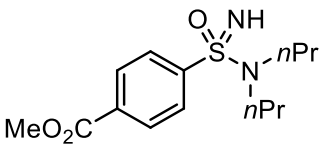
8.3 Hz, 4H, 4 × Ar-H), 3.92 (s, 6H, 2 × OCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4 (C=O), 142.1 (2 × Ar-C_q), 130.3 (4 × Ar-C), 128.8 (2 × Ar-C_q), 125.9 (4 × Ar-C), 52.2 (2 × OCH_3). Analytical data (NMR, mp and IR) in agreement with those reported in the literature.[253,333]

Methyl 4-((dipropylamino)thio)benzoate (150)



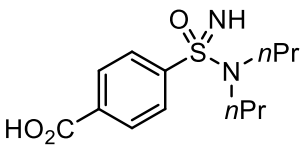
General procedure C was followed using disulfide **149** (669 mg, 2.0 mmol) and dipropylamine (416 µL, 3.0 mmol). Further purification was carried out by distillation (160 °C, 1.3 mbar) to afford sulfenamide **150** as a colourless oil (334 mg, 63%). R_f 0.30 (5% Et_2O in pentane). IR (film)/cm^{-1} 2959, 2874, 1714, 1591, 1431, 1271, 1103, 984, 760. ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.6 Hz, 2H, 2 × Ar-H), 7.29 (d, *J* = 8.6 Hz, 2H, 2 × Ar-H), 3.90 (s, 3H, OCH_3), 3.02–2.97 (m, 4H, 2 × NCH_2), 1.66–1.59 (m, 4H, 2 × NCH_2CH_2), 0.89 (t, *J* = 7.4 Hz, 6H, 2 × $N(CH_2)_2CH_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0 (C=O), 150.5 (Ar-C_q), 129.7 (2 × Ar-C), 121.8 (2 × Ar-C), 120.3 (Ar-C_q), 60.6 (2 × NCH_2), 51.9 (OCH_3), 21.8 (2 × NCH_2CH_2), 11.4 (2 × $N(CH_2)_2CH_3$). HRMS (ESI) *m/z*: Calcd for $C_{14}H_{22}NO_2S$ [M+H]: 268.1371; Found: 268.1367.

Methyl 4-(*N*,*N*-dipropylsulfamidimidoyl)benzoate (151)



General procedure D was followed using sulfenamide **150** (135 mg, 0.50 mmol). Purification by flash column chromatography (neutral Al_2O_3, 30% EtOAc in pentane) afforded sulfonimidamide **151** as a white solid (105 mg, 70%). R_f 0.15 (30% EtOAc in pentane). mp = 68–70 °C. IR (film)/cm^{-1} 3295, 2963, 2873, 1722, 1599, 1435, 1252 (S=N), 1103, 976, 864, 767, 730, 697. ^1H NMR (400 MHz, $CDCl_3$) δ 8.17–8.10 (m, 2H, 2 × Ar-H), 8.04–7.96 (m, 2H, 2 × Ar-H), 3.95 (s, 3H, OCH_3), 3.24–2.98 (m, 4H, 2 × NCH_2), 2.52 (s, 1H, NH), 1.60–1.40 (m, 4H, 2 × NCH_2CH_2), 0.86 (t, *J* = 7.4 Hz, 6H, 2 × $N(CH_2)_2CH_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.9 (C=O), 144.6 (Ar-C_q), 133.0 (Ar-C_q), 130.0 (Ar-C), 127.2 (Ar-C), 52.5 (OCH_3), 50.8 (2 × NCH_2), 22.3 (2 × NCH_2CH_2), 11.2 (2 × $N(CH_2)_2CH_3$). HRMS (ESI) *m/z*: Calcd for $C_{14}H_{23}N_2O_3S$ [M+H]: 299.1429; Found: 299.1434.

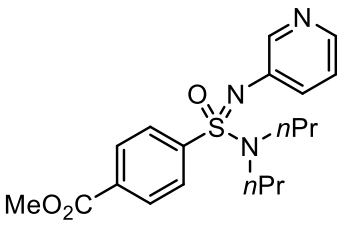
4-(*N*,*N*-Dipropylsulfamidimidoyl)benzoic acid (147)



Sulfonimidamide **151** (42 mg, 0.14 mmol) was added to a stirred solution of TFA:H_2O (700 µL, 1:1, 0.2 M) at room temperature, heated to 90 °C and stirred for 24 h. H_2O (30 mL) was then added and the aqueous mixture extracted with EtOAc (3 × 30 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent removed under reduced pressure. Purification by flash column chromatography (SiO_2, 2 to 5% MeOH in CH_2Cl_2) afforded aza-probenecid **147** as a white solid (32 mg, 80%). R_f 0.22 (5% MeOH in CH_2Cl_2). mp = 132–134 °C. IR (film)/cm^{-1} 3272,

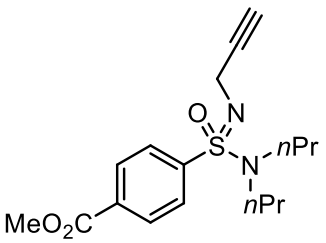
2963, 2873, 1692, 1423, 1289, 1263 (S=N), 1114, 984, 726. ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 8.22 (d, *J* = 8.1 Hz, 2H, 2 × Ar-H), 8.11 (d, *J* = 8.2 Hz, 2H, 2 × Ar-H), 7.58 (bs, 2H, OH and NH), 3.23-3.11 (m, 4H, 2 × NCH_2), 1.59-1.54 (m, 4H, 2 × NCH_2CH_2), 0.88 (t, *J* = 7.4 Hz, 6H, 2 × $N(CH_2)_2CH_3$). ^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ 166.3 (C=O), 145.7 (Ar-C_q), 133.8 (Ar-C_q), 130.4 (Ar-C), 127.9 (Ar-C), 51.2 (2 × NCH_2), 22.7 (2 × NCH_2CH_2), 11.1 (2 × $N(CH_2)_2CH_3$). HRMS (ESI) *m/z*: Calcd for $C_{13}H_{21}N_2O_3S$ [M+H]: 285.1273; Found: 285.1280.

Methyl 4-(*N*,*N*-dipropyl-*N′*-(pyridin-3-yl)sulfamidimidoyl)benzoate (152)



Procedure adapted from Stockman, Lücking and co-workers.[134] 3-Bromopyridine (10.6 μL, 0.11 mmol, 1.1 equiv), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 5 mol%), Xantphos (5.8 mg, 0.01 mmol, 10 mol%) and Cs_2CO_3 (49 mg, 0.15 mmol, 1.5 equiv) were added to a solution of sulfonimidamide **151** (30 mg, 0.10 mmol, 1 equiv) in toluene (1.5 mL, 0.06 M) at room temperature, heated to 100 °C and stirred for 18 h. The mixture was then cooled, diluted with Et_2O (25 mL) and filtered through a pad of celite and washed with Et_2O (50 mL). The filtrate solvent was removed under reduced pressure and purification by flash column chromatography (SiO_2, 50% EtOAc in pentane) afforded **152** as a colourless oil (33 mg, 88%). R_f 0.25 (50% EtOAc in pentane). IR (film)/cm^{-1} 2963, 2873, 1725, 1561, 1476, 1275 (S=N), 1230, 1185, 1096, 1014, 976, 805, 764, 708. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (dd, *J* = 2.7, 0.7 Hz, 1H, Ar-H), 8.21 (dd, *J* = 4.7, 1.5 Hz, 1H, Ar-H), 8.19–8.16 (m, 2H, 2 × Ar-H), 8.11–8.07 (m, 2H, 2 × Ar-H), 7.55 (ddd, *J* = 8.2, 2.7, 1.5 Hz, 1H, Ar-H), 7.15 (ddd, *J* = 8.2, 4.7, 0.8 Hz, 1H, Ar-H), 3.96 (s, 3H, OCH_3), 3.10 (ddd, *J* = 9.0, 6.5, 2.3 Hz, 4H, 2 × NCH_2), 1.50–1.28 (m, 4H, 2 × NCH_2CH_2), 0.73 (t, *J* = 7.4 Hz, 6H, 2 × $N(CH_2)_2CH_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7 (C=O), 145.6 (Ar-C_q), 143.9 (Ar-C_q), 143.0 (Ar-C_q), 140.5 (Ar-C), 133.4 (Ar-C), 130.2 (2 × Ar-C), 130.0 (Ar-C), 127.2 (2 × Ar-C), 123.4 (Ar-C), 52.6 (OCH_3), 50.2 (2 × NCH_2), 21.5 (2 × NCH_2CH_2), 11.2 (2 × $N(CH_2)_2CH_3$). HRMS (ESI) *m/z*: Calcd for $C_{19}H_{26}N_3O_3S$ [M+H]: 376.1695; Found: 376.1688.

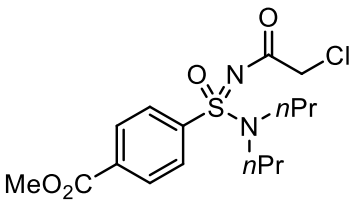
Methyl 4-(*N′*-(prop-2-yn-1-yl)-*N*,*N*-dipropylsulfamidimidoyl)benzoate (153)



Procedure adapted from Johnson and co-workers.[192] NaH (5.0 mg, 0.13 mmol, 1.25 equiv) was added to a solution of sulfonimidamide **151** (30 mg, 0.10 mmol, 1 equiv) in dimethoxyethane (0.5 mL, 0.2 M) at 25 °C and stirred for 15 minutes. Propargyl bromide (27 μL, 0.25 mmol, 2.5 equiv) and tetra-n-butylammonium bromide (1.6 mg, 0.005 mmol, 5 mol%) were then added and the reaction left for an additional 18 h. H_2O (25 mL) was added and the aqueous mixture was then extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were dried (Na_2SO_4), filtered and the solvent removed under

reduced pressure. Purification by flash column chromatography (SiO_2, 15% Et_2O in pentane) afforded **153** as a colourless oil (22 mg, 65%). R_f 0.27 (20% Et_2O in pentane). IR (film)/cm^{-1} 3280, 2967, 2877, 1729, 1397, 1278 (S=N), 1148, 1111, 980, 872, 767, 693. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14–8.11 (m, 2H, 2 × Ar-H), 8.01–7.99 (m, 2H, 2 × Ar-H), 3.97 (d, *J* = 2.5 Hz, 2H, NC*H*$_2$C≡CH), 3.95 (s, 3H, OCH_3), 3.12–3.08 (m, 4H, 2 × NCH_2), 2.24 (t, *J* = 2.5 Hz, 1H, RC≡C*H*), 1.51–1.43 (m, 4H, 2 × NCH_2CH_2), 0.86 (t, *J* = 7.4 Hz, 6H, 2 × $N(CH_2)_2CH_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.9 (C=O), 143.8 (Ar-C_q), 133.0 (Ar-C_q), 130.0 (2 × Ar-C), 127.2 (2 × Ar-C), 82.9 (R*C*≡CH), 70.0 (RC≡*C*H), 52.5 (OCH_3), 50.0 (2 × NCH_2), 31.0 (N*C*H$_2$C≡CH), 21.7 (2 × N*C*H$_2$CH$_2$), 11.3 (2 × $N(CH_2)_2CH_3$). HRMS (ESI) *m/z*: Calcd for $C_{17}H_{25}N_2O_3S$ [M+H]: 337.1586; Found: 337.1582.

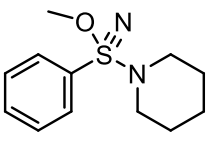
Methyl 4-(*N'*-(2-chloroacetyl)-*N*,*N*-dipropylsulfamidimidoyl)benzoate (154)



Chloroacetyl chloride (8.0 μL, 0.10 mmol, 1.0 equiv), DMAP (1.2 mg, 0.01 mmol, 10 mol%) and triethylamine (28 μL, 0.20 mmol, 2 equiv) was added to a solution of sulfonimidamide **151** (30 mg, 0.10 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL, 0.1 M) at 0 °C, warmed to room temperature and stirred for 2 h. H_2O (25 mL) was then added and the aqueous mixture was then extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were dried (Na_2SO_4), filtered and the solvent removed under reduced pressure. Purification by flash column chromatography (SiO_2, 20% EtOAc in pentane) afforded **154** as a colourless oil (30 mg, 80%). R_f 0.30 (20% EtOAc in pentane). IR (film)/cm^{-1} 2967, 2877, 1729, 1673, 1438, 1282 (S=N), 1197, 1092, 1014, 865, 764. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21–8.16 (m, 2H, 2 × Ar-H), 8.02–7.98 (m, 2H, 2 × Ar-H), 4.09 (d, *J* = 14.2 Hz, 1H, C*H*HCl), 4.09 (d, *J* = 14.2 Hz, 1H, CH*H*Cl), 3.97 (s, 3H, OCH_3), 3.34–3.25 (m, 2H, 2 × NC*H*H), 3.13 (ddd, *J* = 14.2, 8.6, 6.8 Hz, 2H, 2 × NCH*H*), 1.65–1.51 (m, 4H, 2 × NCH_2CH_2), 0.85 (t, *J* = 7.4 Hz, 6H, 2 × $N(CH_2)_2CH_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1 (C=O), 165.5 (C=O), 143.0 (Ar-C_q), 134.2 (Ar-C_q), 130.3 (2 × Ar-C), 127.6 (2 × Ar-C), 52.7 (OCH_3), 49.6 (2 × NCH_2), 46.0 (CH_2Cl), 21.7 (2 × N*C*H$_2$CH$_2$), 11.1 (2 × $N(CH_2)_2CH_3$). HRMS (ESI) *m/z*: Calcd for $C_{16}H_{24}N_2O_4SCl$ [M+H]: 375.1145; Found: 375.1142.

4.2.3.7 Synthesis of Alkoxy-amino-λ^6-sulfanenitriles

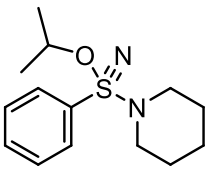
1-[Methoxy(nitrilo)phenyl-λ^6-sulfanyl]piperidine (108)



General procedure E was followed using MeOH to afford λ^6-sulfanenitrile **108** as a brown oil. **108** characterised as a mixture with the corresponding sulfonimidamide (84:16). R_f 0.50 (10% MeOH in CH_2Cl_2). IR (film)/cm^{-1} 3060, 2937, 2847, 1446, 1356 (S≡N), 1263, 1166, 1051, 984, 916, 719. ^{1}H NMR (400 MHz, $CDCl_3$)

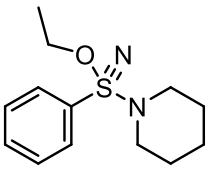
δ 7.86–7.80 (m, 2H, 2 × Ar-H), 7.51–7.41 (m, 3H, 3 × Ar-H), 3.74 (s, 3H, OCH_3), 3.08 (h, *J* = 6.7 Hz, 4H, 2 × NCH_2), 1.60–1.55 (m, 4H, 2 × NCH_2CH_2), 1.50–1.46 (q, *J* = 5.7 Hz, 2H, $N(CH_2)_2CH_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.4 (Ar-C_q), 131.6 (Ar-C), 128.7 (2 × Ar-C), 127.3 (2 × Ar-C), 47.5 (OCH_3), 46.4 (2 × NCH_2), 25.6 (2 × NCH_2CH_2), 24.0 ($N(CH_2)_2CH_2$). HRMS (ESI) *m/z*: Calcd for $C_{12}H_{19}N_2OS$ [M+H]: 239.1218; Found: 239.1229.

1-[Nitrilo(phenyl)[propan-2-yl)oxy]-λ⁶-sulfanyl]piperidine (112)



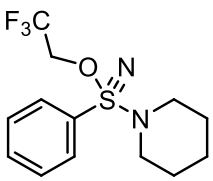
General procedure E was followed using *i*PrOH to afford λ⁶-sulfanenitrile **112** as a brown oil. **112** characterised as a mixture with the corresponding sulfonimidamide (74:26). R_f 0.11 (5:4:1 CH_2Cl_2:EtOAc:MeOH). IR (film)/cm^{-1} 3398, 2936, 2852, 1445, 1363 (S≡N), 1253, 1102, 907, 831, 722, 691. ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 8.0, 1.7 Hz, 2H, 2 × Ar-H), 7.54–7.42 (m, 3H, 3 × Ar-H), 5.13 (hept, *J* = 6.3 Hz, 1H, $CH(CH_3)_2$), 3.09–3.04 (m, 4H, 2 × NCH_2), 1.64–1.55 (m, 4H, 2 × NCH_2CH_2), 1.55–1.45 (m, 2H, $N(CH_2)_2CH_2$), 1.41 (d, *J* = 6.3 Hz, 3H, CH_3), 1.28 (d, *J* = 6.3 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.9 (Ar-C_q), 131.3 (Ar-C), 128.6 (2 × Ar-C), 127.3 (2 × Ar-C), 67.7 ($CH(CH_3)_2$), 46.3 (2 × NCH_2), 25.6 (2 × NCH_2CH_2), 24.1($N(CH_2)_2CH_2$), 23.4 (CH_3), 23.3 (CH_3). HRMS (ESI) *m/z*: Calcd for $C_{14}H_{22}N_2OS$ [M+H]: 267.1526; Found: 267.1534.

1-[Ethoxy(nitrilo)phenyl-λ⁶-sulfanyl]piperidine (168)



General procedure E was followed using EtOH to afford λ⁶-sulfanenitrile **168** as a brown oil. **168** Characterised as a mixture with the corresponding sulfonimidamide (86:14). R_f 0.46 (10% MeOH in CH_2Cl_2). IR (film)/cm^{-1} 3060, 2974, 2937, 2851, 1472, 1379, 1349 (S≡N), 1259, 1085, 1013, 879, 715. ^1H NMR (400 MHz, $CDCl_3$) δ 7.88–7.82 (m, 2H, 2 × Ar-H), 7.49–7.42 (m, 3H, 3 × Ar-H), 4.26–4.10 (m, 2H, OCH_2) 3.13–3.02 (m, 4H, 2 × NCH_2), 1.58 (p, *J* = 5.5 Hz, 4H, 2 × NCH_2CH_2), 1.51–1.43 (m, 2H, $N(CH_2)_2CH_2$), 1.35 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.0 (Ar-C_q), 131.5 (Ar-C), 128.7 (2 × Ar-C), 127.3 (2 × Ar-C), 58.9 (OCH_2), 46.4 (2 × NCH_2), 25.6 (2 × NCH_2CH_2), 24.1 ($N(CH_2)_2CH_2$), 15.3 (OCH_2CH_3). HRMS (ESI) *m/z*: Calcd for $C_{13}H_{21}N_2OS$ [M+H]: 253.1375; Found: 253.1384.

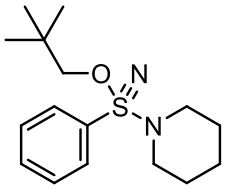
1-[Nitrilo(phenyl)[2,2,2-trifluoroethoxy]- λ⁶-sulfanyl]piperidine (169)



General procedure E was followed using 2,2,2-trifluoroethanol to afford λ⁶-sulfanenitrile **169** as a brown oil. **169** Characterised as a mixture with the corresponding sulfonimidamide (88:12). R_f 0.57 (10% MeOH in CH_2Cl_2). IR (film)/cm^{-1} 3064, 2940, 2855, 1446, 1356 (S≡N), 1278, 1159, 1036, 961,

905, 715, 689. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86–7.83 (m, 2H, 2 × Ar-H), 7.55–7.45 (m, 3H, 3 × Ar-H), 4.48 (dq, *J* = 12.6, 8.5 Hz, 1H, OCH_aH$_b$), 4.34 (dq, *J* = 12.6, 8.5 Hz, 1H, OCH$_a$$H_b$), 3.18 (dt, *J* = 11.2, 5.3 Hz, 2H, 2 × NCH_aH$_b$), 3.08 (dt, *J* = 11.8, 5.3 Hz, 2H, 2 × NCH$_a$$H_b$), 1.60–1.51 (m, 6H, 2 × NCH$_2$CH_2 and N(CH$_2$)$_2$CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.5 (Ar-C$_q$), 132.2 (Ar-C), 129.0 (2 × Ar-C), 127.2 (2 × Ar-C), 123.4 (q, $^{1}J_{C-F}$ = 278.0 Hz, CF_3), 58.2 (q, $^{2}J_{C-F}$ = 36.8 Hz, OCH_2), 46.0 (2 × NCH_2), 25.3 (2 × NCH$_2$*C*H$_2$), 23.9 (N(CH$_2$)$_2$*C*H$_2$). ^{19}F NMR (377 MHz, $CDCl_3$) δ −73.0. HRMS (ESI) *m/z*: Calcd for $C_{13}H_{18}N_2OSF_3$ [M+H]: 307.1092; Found: 307.1103.

1-[(2,2-Dimethylpropoxy)(nitrilo)phenyl-λ^6-sulfanyl]piperidine (170)



General procedure E was followed using neopentyl alcohol and toluene (1:1 v/v) to afford λ^6-sulfanenitrile **170** as a brown oil. **170** Characterised as a mixture with the corresponding sulfonimidamide (65:35). R_f 0.54 (10% MeOH in CH_2Cl_2). IR (film)/cm^{-1} 3060, 2937, 2855, 1476, 1446, 1349 (S≡N), 1259, 1215, 1080, 1040, 969, 909, 723, 693. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 8.0, 1.7 Hz, 2H, 2 × Ar-H), 7.49–7.43 (m, 3H, 3 × Ar-H), 3.83 (d, *J* = 9.2 Hz, 1H, OCH_aH$_b$), 3.67 (d, *J* = 9.2 Hz, 1H, OCH$_a$$H_b$), 3.12–3.05 (m, 4H, 2 × NCH_2), 1.59–1.55 (m, 4H, 2 × NCH$_2$CH_2), 1.50–1.43 (m, 2H, N(CH$_2$)$_2$CH_2), 0.99 (s, 9H, 3 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.1 (Ar-C$_q$), 131.5 (Ar-C), 128.7 (Ar-C), 127.2 (Ar-C), 71.8 (OCH_2), 46.5 (2 × NCH_2), 31.8 (*C*(CH$_3$)$_3$), 26.7 (3 × CH_3), 25.6 (2 × NCH$_2$*C*H$_2$), 24.1 (N(CH$_2$)$_2$*C*H$_2$). HRMS (ESI) *m/z*: Calcd for $C_{16}H_{27}N_2OS$ [M+H]: 295.1844; Found: 295.1837.

4.2.4 Accessing New Reactive Warheads for Drug Discovery

4.2.4.1 General Procedures

General procedure G for the synthesis of vinyl sulfides by hydrothiolation of alkynes: Procedure adapted from Love and co-workers.[288] $RhCl(PPh_3)_3$ (5 mol%) and any other solid reagents (thiol (1.1 equiv)/alkyne (1.0 equiv)) were added to a microwave vial and sealed. The flask was evacuated and filled with N_2 three times before adding any liquid reagents (thiol (1.1 equiv)/alkyne (1.0 equiv)) and 1,2-dichloroethane (0.1 M) at 25 °C and stirred for 18 h. The solvent is removed under reduced pressure. Purification by flash column chromatography (SiO_2) afforded the corresponding vinyl sulfides.

General procedure H for the synthesis of sulfoximines by NH and O transfer to sulfides: Procedure adapted from Bull, Luisi and co-workers.[166] Ammonium carbamate (2.0 equiv) and bis(acetoxy)iodobenzene (2.5 equiv) were added to a solution of sulfide (1.0 equiv) in MeOH

(0.5 M) at 25 °C and stirred for 3 h. The solvent was removed under reduced pressure. Purification by flash column chromatography (SiO_2) afforded the corresponding sulfoximines.

General procedure I for the synthesis of terminal vinyl sulfoximines by alcohol mesylation and *in situ* elimination:

Mesyl chloride (1 M in CH_2Cl_2) (1.05 equiv) was added dropwise to a solution of triethylamine (4.0 equiv) and sulfoximine (1.0 equiv) in CH_2Cl_2 (0.1 M) at 0 °C, warmed to room temperature and stirred for 1 h. The solvent was removed under reduced pressure. Purification by flash column chromatography (SiO_2) afforded the corresponding vinyl sulfoximines and in some cases mesylated vinyl sulfoximines.

General procedure J for the synthesis of sulfonimidamides via a sulfenamide intermediate:

Procedure adapted from Bull, Luisi and co-workers.[229] Amine (1.33 equiv), triethylamine (2.0 or 3.5 equiv) and silver nitrate (2.0 equiv) were added to a solution of disulfide (1.0 equiv) in MeOH (0.1 M) at 25 °C, under air, and stirred for 1 h. The reaction mixture was filtered and washed with MeOH (2 × 50 mL). The filtrate solvent was removed under reduced pressure. H_2O (75 mL) was added to the crude mixture and the aqueous mixture extracted with CH_2Cl_2 (3 × 75 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent removed under reduced pressure. Purification by filtration through a basic alumina (activity IV) plug (2 cm thick) afforded the corresponding crude sulfenamide intermediate. Iodosylbenzene (2.5 equiv), ammonium carbamate (2.0 equiv) and acetic acid (1.0 equiv) were added to a strirred solution of crude sulfenamide (1.0 equiv) in *i*PrOH (0.2 M) at 25 °C, under air, for 1 h. The solvent was then removed under reduced pressure and sat. aq. $NaHCO_3$ (20 mL) was added. The aqueous mixture was then extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were dried (Na_2SO_4), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (SiO_2) afforded the corresponding sulfonimidamide products.

General procedure K for the synthesis of vinyl sulfonimidamides by THP deprotection and alcohol elimination:

HCl (37% in H_2O, 1 mL) was added to a solution of sulfonimidamide (1 equiv) in MeOH:THF (1:1, 12 mL) at 25 °C and stirred for 30 min. Sat. aq. $NaHCO_3$ (25 mL) was added and the aqueous mixture was then extracted with EtOAc (3 × 50 mL) and the combined organic layers were dried (Na_2SO_4), filtered and the solvent removed under reduced pressure to afford the crude alcohol intermediate. A solution of MsCl (1 M in CH_2Cl_2, 1.05 equiv) was added dropwise to a solution of the crude alcohol (1.0 equiv) and triethylamine (4.0 equiv) in CH_2Cl_2 (0.1 M) at

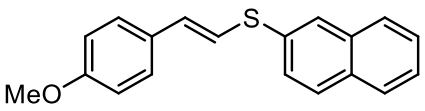
0 °C and left to warm to room temperature for 16 h. The solvent was removed under reduced pressure and purification by flash chromatography (SiO_2) afforded the corresponding vinyl sulfonimidamide products.

General procedure L for the synthesis of *N*-Propargyl sulfonimidamides:

NaH (60% in mineral oil, 1.2 equiv) was added to a solution of the sulfonimidamide (1.0 equiv) in DMF (0.1 M) at 0 °C and stirred for 30 min. Propargyl bromide (80% in toluene, 1.5 equiv) was added and the reaction allowed to warm to room temperature over 3 h. H_2O (10 mL) was added and the aqueous mixture extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (SiO_2) afforded the corresponding *N*-propargyl sulfonimidamide products.

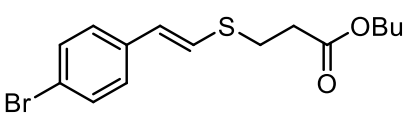
4.2.4.2 Substituted Vinyl Sulfoximines

(*E*)-(4-Methoxystyryl)(naphthalen-2-yl)sulfane (198)



General procedure G was followed using $RhCl(PPh_3)_3$ (46 mg, 0.05 mmol), naphthalene-2-thiol (176 mg, 1.1 mmol) and 1-ethynyl-4-methoxybenzene (129 µL, 1.0 equiv). Purification by flash column chromatography (SiO_2, 5% Et_2O in hexane) afforded vinyl sulfide **198** (227 mg, 78%) as a white solid. R_f 0.40 (5% Et_2O in hexane). mp = 103–105 °C. IR (film)/cm^{-1} 3056, 3004, 1602, 1509, 1252, 1032, 950, 846, 801. ^1H NMR (400 MHz, $CDCl_3$) δ 7.87–7.75 (m, 4H, 4 × Ar-H), 7.53–7.44 (m, 3H, 3 × Ar-H), 7.38–7.32 (m, 2H, 2 × Ar-H), 6.92–6.85 (m, 2H, 2 × Ar-H), 6.83 (s, 2H, HC=CH), 3.83 (s, 3H, OCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5 (Ar-C_q), 133.8 (Ar-C_q), 133.4 (Ar-C_q), 133.1 (S*C*H=CH), 132.1 (Ar-C_q), 129.4 (Ar-C_q), 128.6 (Ar-C), 127.8 (Ar-C), 127.5 (2 × Ar-C), 127.4 (Ar-C), 127.2 (2 × Ar-C), 126.6 (Ar-C), 125.9 (Ar-C), 119.8 (SCH=*C*H), 114.2 (2 × Ar-C), 55.3 (OCH_3). HRMS (+p APCI) m/z: Calcd for $C_{19}H_{17}OS^+$ $[M+H]^+$: 374.0420; Found: 374.0437. Analytical data (NMR, IR) in agreement with those reported in the literature.[334]

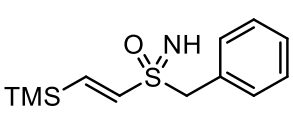
Butyl (*E*)-3-((4-bromostyryl)thio)propanoate (202)



General procedure G was followed using $RhCl(PPh_3)_3$ (92 mg, 0.1 mmol), 1-bromo-4-ethynylbenzene (181 mg, 1.0 mmol) and butyl 3-mercaptopropanoate (178 µL, 1.1 mmol) as well as heating to 65 °C and increasing the catalyst loading to 10 mol%. Purification by flash column chromatography (SiO_2, 5% Et_2O in hexane) afforded vinyl sulfide **202** (185 mg, 53%) as a white solid. R_f 0.14 (5% Et_2O in hexane). mp = 55–57 °C. IR (film)/cm^{-1} 2959, 2870, 1722, 1595, 1487, 1401, 1364, 1241, 1178, 1107, 939, 827. ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.37

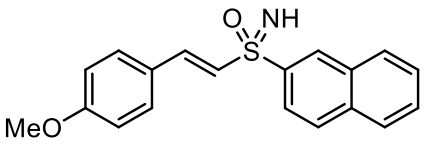
(m, 2H, 2 × Ar-H), 7.19–7.11 (m, 2H, 2 × Ar-H), 6.71 (d, *J* = 15.5 Hz, 1H, SCH=C*H*), 6.43 (d, *J* = 15.6 Hz, 1H, SC*H*=CH), 4.11 (t, *J* = 6.7 Hz, 2H, OCH_2), 3.07 (t, *J* = 7.3 Hz, 2H, SCH_2), 2.71 (t, *J* = 7.3 Hz, 2H, CH_2CO_2Bu), 1.66–1.58 (m, 2H, OCH_2CH_2), 1.46–1.31 (m, 2H, $O(CH_2)_2CH_2$), 0.93 (t, *J* = 7.4 Hz, 3H, $O(CH_2)_3CH_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6 (C=O), 135.7 (Ar-C_q), 131.7 (2 × Ar-C), 127.0 (2 × Ar-C), 126.6 (HC=CH), 125.1 (HC=CH), 120.7 (Ar-C_q), 64.8 (OCH_2), 34.6 (SCH_2), 30.6 (OCH_2CH_2), 27.6 (CH_2CO_2Bu), 19.1 $(CH_2)_2CH_2$), 13.7 ($O(CH_2)_3CH_3$). HRMS (+p APCI) m/z: Calcd for $C_{15}H_{20}O_2SBr^+$ $[M+H]^+$: 343.0362; Found: 343.0370.

(*E*)-Benzyl(imino)(2-(trimethylsilyl)vinyl)-λ^6-sulfanone (197)



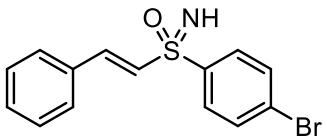
General procedure H was followed using ammonium carbamate (144 mg, 1.84 mmol), bis(acetoxy)iodobenzene (742 mg, 2.30 mmol) and vinyl sulfide **196** (205 mg, 0.92 mmol). Purification by flash column chromatography (SiO_2, 50% EtOAc in hexane) afforded sulfoximine **197** (178 mg, 76%) as a colourless oil. R_f 0.34 (50% EtOAc in hexane). IR (film)/cm^{-1} 2955, 1494, 1453, 1248, 1215, 976, 842. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.32 (m, 5H, 5 × Ar-H), 7.05 (d, *J* = 17.8 Hz, 1H, SC*H*=CH), 6.62 (d, *J* = 17.8 Hz, 1H, SCH=C*H*), 4.30 (d, *J* = 13.2 Hz, 1H, PhC*H*H), 4.20 (d, *J* = 13.2 Hz, 1H, PhCH*H*), 2.63 (s, 1H, NH), 0.14 (s, 9H, $Si(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.0 (S*C*H=CH), 140.7 (SCH=*C*H), 130.9 (2 × Ar-C), 128.6 (Ar-C), 128.5 (2 × Ar-C), 128.3 (Ar-C_q), 62.7 (Ph*C*H_2), -2.1 ($Si(CH_3)_3$). HRMS (ESI) m/z: Calcd for $C_{12}H_{20}NOSSi^+$ [M+H]: 254.1035; Found: 254.1027.

(*E*)-Imino(4-methoxystyryl)(naphthalen-2-yl)-λ^6-sulfanone (199)



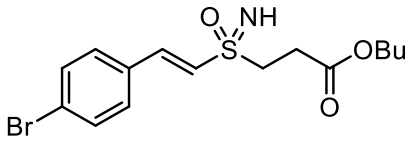
General procedure H was followed using ammonium carbamate (105 mg, 1.34 mmol), bis(acetoxy)iodobenzene (540 mg, 1.68 mmol) and vinyl sulfide **198** (197 mg, 0.67 mmol). Purification by flash column chromatography (SiO_2, 50% EtOAc in hexane) afforded sulfoximine **199** (145 mg, 67%) as a colourless oil. R_f 0.24 (50% EtOAc in hexane). IR (film)/cm^{-1} 3268, 3056, 2840, 1602, 1509, 1256, 1215, 1174, 1066, 976, 864, 813, 757. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64–8.60 (m, 1H, Ar-H), 8.02–7.94 (m, 3H, 3 × Ar-H), 7.92–7.89 (m, 1H, Ar-H), 7.67–7.59 (m, 3H, 2 × Ar-H + SC*H*=CH), 7.46–7.41 (m, 2H, 2 × Ar-H), 6.91–6.83 (m, 3H, 2 × Ar-H + SCH=C*H*), 3.83 (s, 3H, OCH_3), 3.01 (s, 1H, NH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.8 (Ar-C_q), 141.5 (S*C*H=CH), 140.1 (Ar-C_q), 134.8 (Ar-C_q), 132.4 (Ar-C_q), 130.2 (2 × Ar-C), 129.4 (Ar-C), 129.3 (Ar-C), 128.9 (Ar-C), 128.8 (Ar-C), 127.8 (Ar-C), 127.4 (Ar-C), 126.5 (Ar-C), 125.3 (Ar-C_q), 123.1 (SCH=*C*H), 114.4 (2 × Ar-C), 55.4 (OCH_3). HRMS (+p APCI) m/z: Calcd for $C_{19}H_{18}NO_2S^+$ $[M+H]^+$: 324.1053; Found: 324.1046.

(*E*)-(4-Bromophenyl)(imino)(styryl)-λ^6-sulfanone (201)



General procedure H was followed using ammonium carbamate (156 mg, 2.0 mmol), bis(acetoxy)iodobenzene (805 mg, 2.5 mmol) and vinyl sulfide **200** (291 mg, 1.0 mmol). Purification by flash column chromatography (SiO_2, 30% EtOAc in hexane) afforded sulfoximine **201** (263 mg, 82%) as a yellow oil. R_f 0.38 (30% EtOAc in hexane). IR (film)/cm^{-1} 3257, 3056, 1729, 1613, 1572, 1464, 1386, 1237, 965, 790. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94–7.85 (m, 2H, 2 × Ar–H), 7.70–7.60 (m, 3H, 2 × Ar-H + SC*H*=CH), 7.51–7.45 (m, 2H, 2 × Ar-H), 7.44–7.34 (m, 3H, 3 × Ar-H), 6.91 (dd, *J* = 15.2, 1.0 Hz, 1H, SCH=C*H*), 2.98 (s, 1H, NH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.1 (S*C*H=CH), 142.0 (Ar-C_q), 132.4 (3 × Ar-C), 131.0 (SCH=*C*H), 129.5 (2 × Ar-C), 129.0 (2 × Ar-C), 129.0 (Ar-C_q), 128.5 (2 × Ar-C), 128.0 (Ar-C_q). HRMS (+p APCI) m/z: Calcd for $C_{14}H_{13}NOSBr^+$ $[M+H]^+$: 321.9901; Found: 321.9895.

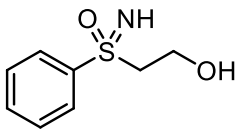
Butyl (*E*)-3-(2-(4-bromophenyl)vinylsulfonimidoyl)propanoate (203)



General procedure H was followed using ammonium carbamate (44 mg, 0.56 mmol), bis(acetoxy)iodobenzene (225 mg, 0.70 mmol) and vinyl sulfide **202** (96 mg, 0.28 mmol). Purification by flash column chromatography (SiO_2, 50% EtOAc in hexane) afforded sulfoximine **203** (84 mg, 80%) as a white solid. R_f 0.23 (50% EtOAc in hexane). mp = 57–59 °C. IR (film)/cm^{-1} 3280, 2959, 2870, 1729, 1617, 1487, 1244, 1211, 1185, 1069, 1006, 857, 801. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.52 (m, 2H, 2 × Ar-H), 7.47 (d, *J* = 15.3 Hz, 1H, SCH=C*H*), 7.41–7.33 (m, 2H, 2 × Ar-H), 6.89 (d, *J* = 15.3 Hz, 1H, SC*H*=CH), 4.04 (t, *J* = 6.7 Hz, 2H, OCH_2), 3.46 (td, *J* = 7.4, 1.7 Hz, 2H, SCH_2), 2.84 (td, *J* = 7.2, 2.2 Hz, 2H, C*H*$_2$$CO_2$Bu), 2.73 (s, 1H, NH), 1.61–1.48 (m, 2H, OCH_2C*H*$_2$), 1.39–1.24 (m, 2H, $O(CH_2)_2C$*H*$_2$), 0.89 (t, *J* = 7.4 Hz, 3H, $O(CH_2)_3C$*H*$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5 (C=O), 142.6 (S*C*H=CH), 132.4 (2 × Ar-C), 131.3 (Ar-C_q), 129.8 (2 × Ar-C), 128.1 (SCH=*C*H), 125.6 (Ar-C_q), 65.2 (OCH_2), 51.6 (SCH_2), 30.4 (OCH_2*C*H$_2$), 28.4 (*C*H$_2$$CO_2$Bu), 19.0 ($CH_2$)$_2$*C*H$_2$), 13.6 ($O(CH_2)_3$*C*H$_3$). HRMS (+p APCI) m/z: Calcd for $C_{15}H_{21}NO_3SBr^+$ $[M+H]^+$: 393.0995; Found: 393.1003.

4.2.4.3 Terminal Vinyl Sulfoximines

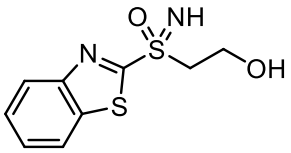
(2-Hydroxyethyl)(imino)(phenyl)-λ^6-sulfanone (211)



General procedure H was followed using ammonium carbamate (156 mg, 2.0 mmol), bis(acetoxy)iodobenzene (805 mg, 2.5 mmol) and sulfide **207** (135 µL, 1.0 mmol). Purification by flash column chromatography (SiO_2, 50% acetone in pentane) afforded sulfoximine **211** (136 mg, 73%) as a colourless oil. R_f 0.29 (50% acetone in pentane). IR (film)/cm^{-1} 3261, 1446, 1215, 1095, 1059, 987, 760, 723, 699.

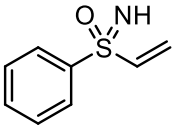
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04–7.98 (m, 2H, 2 × Ar-H), 7.71–7.64 (m, 1H, Ar-H), 7.64–7.57 (m, 2H, 2 × Ar-H), 4.70 (t, *J* = 6.1 Hz, 1H, CH_2OH), 4.08 (ddd, *J* = 12.6, 6.5, 3.8 Hz, 1H, C*H*HOH), 3.90–3.78 (m, 1H, CH*H*OH), 3.32 (dt, *J* = 6.1, 2.9 Hz, 2H, SCH_2), 2.88 (s, 1H, NH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.8 (Ar-C_q), 133.6 (Ar-C), 129.4 (2 × Ar-C), 128.3 (2 × Ar-C), 58.2 (SCH_2), 56.4 (CH_2OH). Analytical data (NMR, IR) in agreement with those reported in the literature.[167]

Benzo[*d*]thiazol-2-yl(2-hydroxyethyl)(imino)-λ^6-sulfanone (213)



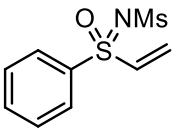
General procedure H was followed using ammonium carbamate (156 mg, 2.0 mmol), bis(acetoxy)iodobenzene (805 mg, 2.5 mmol) and sulfide **209** (135 µL, 1.0 mmol). Purification by flash column chromatography (SiO_2, 40% acetone in pentane) afforded sulfoximine **213** (131 mg, 54%) as a white solid. R_f 0.24 (40% acetone in pentane). mp = 125–127 °C. IR (film)/cm^{-1} 3283, 1468, 1315, 1241, 1212, 1051, 980, 764. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27–8.18 (m, 1H, Ar-H), 8.07–7.98 (m, 1H, Ar-H), 7.69–7.56 (m, 2H, 2 × Ar-H), 4.23–4.09 (m, 3H, CH_2OH), 3.79–3.68 (m, 1H, SC*H*H), 3.66–3.60 (m, 2H, SCH*H* + NH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2 (Ar-C_q), 152.7 (Ar-C_q), 137.5 (Ar-C_q), 127.9 (Ar-C), 127.7 (Ar-C), 125.4 (Ar-C), 122.3 (Ar-C), 57.8 (SCH_2), 56.6 (CH_2OH). HRMS (+p APCI) m/z: Calcd for $C_9H_{11}N_2O_2S_2^+$ $[M+H]^+$: 243.0256; Found: 243.0260.

Imino(phenyl)(vinyl)-λ^6-sulfanone (206)



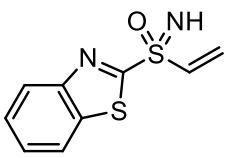
General procedure I was followed using mesyl chloride (1 M in CH_2Cl_2) (800 µL, 0.80 mmol), triethylamine (421 µL, 3.0 mmol) and sulfoximine **211** (141 mg, 0.76 mmol). Purification by flash column chromatography (SiO_2, 50% EtOAc in pentane) afforded vinyl sulfoximine **206** (63 mg, 50%) as a colourless oil and mesylated vinyl sulfoximine **218** (11 mg, 6%) as a colourless oil. Analytical data for vinyl sulfoximine **206**: R_f 0.23 (50% EtOAc in pentane). IR (film)/cm^{-1} 3269, 3064, 1446, 1223, 1129, 977, 731, 693. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04–7.94 (m, 2H, 2 × Ar-H), 7.67–7.58 (m, 1H, Ar-H), 7.57–7.51 (m, 2H, 2 × Ar-H), 6.75 (dd, *J* = 16.4, 9.5 Hz, 1H, SCH), 6.43 (dd, *J* = 16.4, 0.6 Hz, 1H, HC=CH*H*), 5.99 (dd, *J* = 9.5, 0.5 Hz, 1H, HC=C*H*H), 2.88 (s, 1H, NH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.7 (Ar-C_q), 140.5 (S*C*H=CH_2), 133.0 (Ar-C), 129.2 (2 × Ar-C), 128.1 (2 × Ar-C), 126.6 (SC=*C*H_2). Analytical data (NMR, IR) in agreement with those reported in the literature.[164]

_N_-(Oxo(phenyl)(vinyl)-λ⁶-sulfaneylidene)methanesulfonamide (218)



Prepared according to the above procedure for vinyl sulfoximine **206**. Mesylated vinyl sulfoximine **218** afforded as a colourless oil (11 mg, 6%). R_f 0.29 (50% EtOAc in pentane). IR (film)/cm^{-1} 3269, 3060, 1308, 1230, 1140, 1099, 1066, 969, 801, 745. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07–7.96 (m, 2H, 2 × Ar-H), 7.76–7.67 (m, 1H, Ar-H), 7.67–7.57 (m, 2H, 2 × Ar-H), 6.83 (dd, *J* = 16.3, 9.6 Hz, 1H, SCH), 6.52 (dd, *J* = 16.3, 1.3 Hz, 1H, HC=CH*H*), 6.23 (dd, *J* = 9.6, 1.4 Hz, 1H, HC=C*H*H), 3.18 (s, 3H, SCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.5 (S*C*H=CH_2), 137.0 (Ar-C_q), 134.5 (Ar-C), 129.7 (2 × Ar-C), 129.4 (SC=*C*H_2), 128.0 (2 × Ar-C), 45.4 (SCH_3). Analytical data (NMR) in agreement with those reported in the literature.[335]

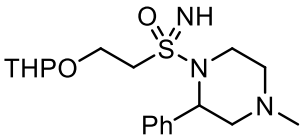
Benzo[*d*]thiazol-2-yl(imino)(vinyl)-λ⁶-sulfanone (216)



General procedure I was followed using mesyl chloride (1 M in CH_2Cl_2) (580 µL, 0.58 mmol), triethylamine (305 µL, 2.2 mmol) and sulfoximine **213** (133 mg, 0.55 mmol). Purification by flash column chromatography (SiO_2, 30% acetone in pentane) afforded vinyl sulfoximine **216** (48 mg, 39%) as a white solid. R_f 0.39 (30% acetone in pentane). mp = 99–101 °C. IR (film)/cm^{-1} 3261, 1468, 1315, 1259, 1237, 1111, 977, 760, 723. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24–8.17 (m, 1H, Ar-H), 8.02–7.95 (m, 1H, Ar-H), 7.66–7.53 (m, 2H, 2 × Ar-H), 7.02 (dd, *J* = 16.4, 9.5 Hz, 1H, SCH), 6.71 (dd, *J* = 16.4, 1.0 Hz, 1H, HC=CH*H*), 6.28 (dt, *J* = 9.5, 0.9 Hz, 1H, HC=C*H*H), 3.56 (s, 1H, NH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5 (Ar-C_q), 153.0 (Ar-C_q), 137.7 (S*C*=CH_2), 137.5 (Ar-C_q), 131.0 (SCH=*C*H_2), 127.7 (Ar-C), 127.4 (Ar-C), 125.3 (Ar-C), 122.2 (Ar-C). HRMS (+p APCI) m/z: Calcd for $C_9H_9N_2OS_2^+$ $[M+H]^+$: 225.0151; Found: 225.0153.

4.2.4.4 Propargylated Terminal Vinyl Sulfonimidamides

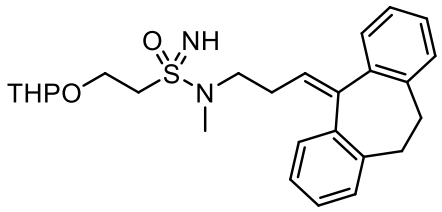
4-Methyl-2-phenyl-1-(2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethylsulfonimidoyl)piperazine (223)



General procedure J was followed using 1-methyl-3-phenylpiperazine (587 mg, 3.33 mmol), triethylamine (693 µL, 5.0 mmol), silver nitrate (849 mg, 5.00 mmol), disulfide **220** (806 mg, 2.50 mmol), ammonium carbamate (390 mg, 5.0 mmol), iodosylbenzene (1.37 g, 6.25 mmol) and acetic acid (143 µL, 2.5 mmol). Purification by flash column chromatography (SiO_2, 70% EtOAc in pentane) afforded sulfonimidamide **223** (292 mg, 32%) as an inseparable 0.6:1 mixture of diastereomers as a brown oil. R_f = 0.11 (70% EtOAc in pentane). IR (film)/cm^{-1} 3272, 2937, 2870, 2791, 1453, 1244, 1148, 1118, 1029, 976, 917. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.64 (m, 4H, 4 × Ar-H_{a+b}), 7.38–7.32 (m, 4H, 4 × Ar-H_{a+b}), 7.31–7.27 (m, 2H, 2 × Ar-H_{a+b}), 5.14

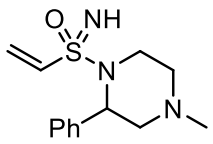
(d, *J* = 3.4 Hz, 1H, Ar-$CH_{a/b}$), 5.10 (d, *J* = 4.3 Hz, 1H, Ar-$CH_{a/b}$), 4.60–4.53 (m, 2H, $CH_{a/b}(OR)_2$), 4.13–4.01 (m, 2H, $OCH_{a+b}H$), 3.89–3.74 (m, 6H, 2 × $OCHH_{a/b}$ + 2 × $OC(H_{a+b})_2$), 3.54–3.45 (m, 2H, $SCHH_{a+b}$), 3.41–3.05 (m, 6H, 2 × $NC(H_{a+b})_2$ + $SCH_{a+b}H$), 2.98–2.78 (m, 4H, 2 × $NC(H_{a+b})_2$), 2.52–2.47 (m, 2H, 2 × $NCHH_{a+b}$), 2.31–2.28 (m, 6H, 2 × $NC(H_{a+b})_3$), 2.30 (s, 2H, 2 × NH), 2.22–2.11 (m, 2H, 2 × $NCH_{a+b}H$), 1.84–1.64 (m, 4H, 2 × $C(H_{a+b})_2$), 1.64–1.45 (m, 8H, 4 × $C(H_{a+b})_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 2 × 139.7 (Ar-$C_{(a+b)q}$), 2 × 128.5 (Ar-C_{a+b}), 128.4 (Ar-C_a), 128.3 (Ar-C_b), 128.13 (Ar-$C_{a/b}$), 128.10 (Ar-$C_{a/b}$), 127.5 (Ar-C_a), 127.4 (Ar-C_b), 99.1 ($C_bH(OR)_2$), 99.0 ($C_aH(OR)_2$), 62.3 (SC_aH_2), 62.2 (S_bCH_2), 61.93 (OC_aH_2), 61.89 (OC_bH_2), 59.1 (OC_aH_2), 58.5 (OC_bH_2), 56.2 (NC_aHPh), 55.9 (NC_bHPh), 55.4 (NC_aH_2), 55.2 (NC_bH_2), 53.64 ($NC_{a/b}H_2$), 53.63 ($NC_{a/b}H_2$), 46.30 (NC_aH_3), 46.27 (NC_bH_3), 42.09 (NC_aH_2), 41.94 (NC_bH_2), 30.4 (C_bH_2), 30.3 (C_aH_2), 2 × 25.2 ($C_{a/b}H_2$), 19.32 ($C_{a/b}H_2$), 19.29 ($C_{a/b}H_2$). HRMS (ESI) m/z: Calcd for $C_{18}H_{30}N_3O_3S$ [M+H]: 368.2008; Found: 368.2006.

N-(3-(10,11-Dihydro-*5*H-dibenzo[*a*,*d*][7]annulen-5-ylidene)propyl)-*N*-methyl-2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethane-1-sulfonimidamide (225)



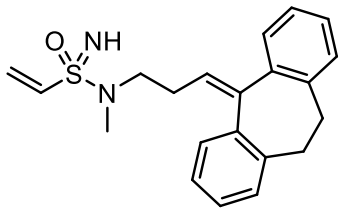
General procedure J was followed using nortriptyline hydrochloride (1.00 g, 3.33 mmol), triethylamine (1.20 mL, 8.75 mmol), silver nitrate (849 mg, 5.00 mmol), disulfide **220** (806 mg, 2.50 mmol), ammonium carbamate (390 mg, 5.0 mmol), iodosylbenzene (1.37 g, 6.25 mmol) and acetic acid (143 μL, 2.5 mmol). Purification by flash column chromatography (SiO_2, 20% acetone in pentane) afforded sulfonimidamide **225** (375 mg, 33%) as a brown oil. R_f = 0.18 (20% acetone in pentane). IR (film)/cm^{-1} 3309, 3015, 2937, 1643, 1483, 1442, 1244, 1121, 1077, 1028, 969, 766. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.25 (m, 1H, Ar-H), 7.23–7.13 (m, 6H, 6 × Ar-H), 7.06–7.03 (m, 1H Ar-H), 5.85 (td, *J* = 7.4, 1.4 Hz, 1H, C=CH), 4.60 (dd, *J* = 4.5, 3.0 Hz, 1H, $CH(OR)_2$), 4.10 (ddt, *J* = 10.9, 9.3, 6.1 Hz, 1H, OCH_aH_b), 3.90–3.80 (m, 2H, OCH_2), 3.65–3.13 (m, 9H, OCH_aH_b, SCH_2, 2 × Ar-CH_2, NCH_2), 2.97 (s, 1H, NH), 2.76 (s, 3H, NCH_3), 2.44–2.34 (m, 2H, NCH_2CH_2), 1.83–1.70 (m, 2H, CH_2), 1.61–1.49 (m, 4H, 2 × CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.1 (*C*=CH), 140.8 (Ar-C_q), 139.7 (Ar-C_q), 139.4 (Ar-C_q), 137.0 (Ar-C_q), 130.1 (Ar-C), 128.5 (Ar-C), 128.1 (Ar-C), 128.0 (Ar-C), 127.6 (Ar-C), 127.3 (C=*C*H), 127.2 (Ar-C), 126.1 (Ar-C), 125.7 (Ar-C), 99.2 ($CH(OR)_2$), 62.6 (SCH_2), 61.8 (OCH_2), 61.6 (OCH_2), 50.5 (Ar-CH_2), 50.3 (Ar-CH_2), 33.7 (NCH_3), 32.0 (NCH_2), 30.5 (CH_2), 28.6 (NCH_2CH_2), 25.2 (CH_2), 19.5 (CH_2). HRMS (ESI) m/z: Calcd for $C_{26}H_{35}N_2O_3S$ [M+H]: 455.2368; Found: 455.2354.

4-Methyl-2-phenyl-1-(vinylsulfonimidoyl)piperazine (224)



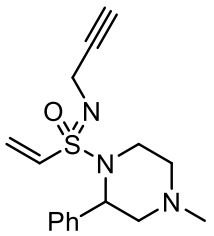
General procedure K was followed using sulfonimidamide **223** (238 mg, 0.65 mmol), 1 M solution of MsCl in CH_2Cl_2 (660 μL, 0.66 mmol) and triethylamine (350 μL, 2.52 mmol). Purification by flash column chromatography (SiO_2, 20% acetone in pentane) afforded sulfonimidamide **224** (70 mg, 42%) as an inseparable 0.5:1 mixture of diastereomers as a brown oil. R_f = 0.27 (20% acetone in pentane). IR (film)/cm^{-1} 3272, 2937, 2795, 1453, 1267, 1244, 1148, 973, 924. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 7.3, 1.9 Hz, 2H, 2 × Ar-H$_a$), 7.63 (dd, *J* = 7.4, 1.8 Hz, 2H, 2 × Ar-H$_b$), 7.36–7.32 (m, 4H, 4 × Ar-H$_{a+b}$), 7.31–7.25 (m, 2H, 2 × Ar-H$_{a+b}$), 6.27–6.09 (m, 4H, 2 × SCH$_{a+b}$ + 2 × C=C*H*$_{a+b}$H), 5.76–5.71 (m, 2H, 2 × C=CH*H*$_{a+b}$), 5.05–5.02 (m, 2H, 2 × Ar-CH$_{a+b}$), 3.72–3.67 (m, 2H, 2 × NC*H*$_{a+b}$H), 3.35–3.13 (m, 4H, 2 × NC*H*$_{a+b}$H + 2 × NCH*H*$_{a+b}$), 2.84–2.77 (m, 2H, 2 × NCH*H*$_{a+b}$), 2.51–2.47 (m, 2H, 2 × NC*H*$_{a+b}$H), 2.33 (s, 2H, 2 × NH), 2.30–2.17 (m, 6H, 2 × NCH$_3$), 2.24–2.13 (m, 2H, 2 × NCH*H*$_{a+b}$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 2 × 139.6 (Ar-C$_{(a+b)q}$), 137.1 (SC$_b$H), 136.4 (SC$_a$H), 2 × 128.6 (Ar-C$_{a+b}$), 2 × 128.4 (Ar-C$_{a+b}$), 2 × 128.3 (Ar-C$_{a+b}$), 2 × 128.2 (Ar-C$_{a+b}$), 2 × 127.5 (Ar-C$_{a+b}$), 125.3 (SCH=*C*$_a$H$_2$), 125.0 (SCH=*C*$_b$H$_2$), 58.8 (NC$_a$HPh), 57.9 (NC$_b$HPh), 56.3 (NC$_a$H$_2$), 56.2 (NC$_b$H$_2$), 54.9 (NC$_b$H$_2$), 54.8 (NC$_a$H$_2$), 2 × 46.3 (NC$_{a+b}$H$_2$), 42.1 (NC$_a$H$_3$), 41.9 (NC$_b$H$_3$). HRMS (ESI) m/z: Calcd for $C_{13}H_{20}N_3OS$ [M+H]: 266.1327; Found: 266.1334.

***N*-(3-(10,11-Dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)propyl)-*N*-methylethenesulfonimidamide (226)**



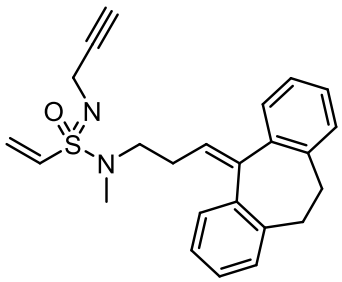
General procedure K was followed using sulfonimidamide **225** (516 mg, 1.13 mmol), 1 M solution of MsCl in CH_2Cl_2 (1.2 mL, 1.2 mmol) and triethylamine (626 μL, 4.5 mmol). Purification by flash column chromatography (SiO_2, 50% EtOAc in pentane) afforded sulfonimidamide **226** (188 mg, 47%) as a brown oil. R_f = 0.33 (50% EtOAc in pentane). IR (film)/cm^{-1} 3309, 3060, 3015, 2914, 1483, 1453, 1267, 1107, 965, 742. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.27 (m, 1H, Ar-H), 7.26–7.09 (m, 6H, 6 × Ar-H), 7.08–7.02 (m, 1H, Ar-H), 6.42 (dd, *J* = 16.6, 9.8 Hz, 1H, SCH), 6.19 (d, *J* = 16.6 Hz, 1H, HC=C*H*H), 5.90 (d, *J* = 9.9 Hz, 1H, HC=CH*H*), 5.85 (t, *J* = 7.5 Hz, 1H, C=CH), 3.46–3.23 (m, 3H, 3 × Ar-CH), 3.17–3.05 (m, 1H, Ar-CH), 3.02–2.92 (m, 1H, NC*H*H), 2.85–2.75 (m, 1H, NCH*H*), 2.71–2.60 (m, 3H, NCH$_3$), 2.44–2.32 (m, 2H, NCH$_2$C*H*$_2$), 2.09 (s, 1H, NH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.2 (*C*=CH), 140.7 (Ar-C$_q$), 139.7 (Ar-C$_q$), 139.4 (Ar-C$_q$), 137.0 (Ar-C$_q$), 133.4 (SCH), 130.1 (SCH=*C*H$_2$), 128.5 (Ar-C), 128.1 (Ar-C), 128.0 (Ar-C), 127.6 (Ar-C), 127.23 (Ar-C), 127.20 (Ar-C), 126.6 (C=*C*H), 126.1 (Ar-C), 125.8 (Ar-C), 50.5 (2 × Ar-CH$_2$), 33.7 (NCH$_3$), 31.9 (NCH$_2$), 28.3 (NCH$_2$*C*H$_2$). HRMS (ESI) m/z: Calcd for $C_{21}H_{25}N_2OS$ [M+H]: 353.1688; Found: 353.1682.

4-Methyl-2-phenyl-1-(*N*-(prop-2-yn-1-yl)vinylsulfonimidoyl)piperazine (231)



General procedure L was followed using NaH (60% in mineral oil, 9.6 mg, 0.24 mmol), sulfonimidamide **224** (53 mg, 0.20 mmol) and propargyl bromide (80% in toluene, 33 μL, 0.30 mmol). Purification by flash column chromatography (SiO_2, 10% acetone in pentane) afforded sulfonimidamide **231** (29 mg, 48%) as an inseparable 0.5:1 mixture of diastereomers as a brown oil. R_f = 0.26 (10% acetone in pentane). IR (film)/cm^{-1} 3287, 2937, 2844, 2795, 1457, 1278, 1230, 1148, 972, 917, 767. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77–7.72 (m, 2H, 2 × Ar-H_a), 7.70 (dd, *J* = 7.4, 1.8 Hz, 2H, 2 × Ar-H_b), 7.37–7.24 (m, 6H, 6 × Ar-H_{a+b}), 6.29 (dd, *J* = 16.5, 9.5 Hz, 1H, SCH_b), 6.16 (d, *J* = 16.5 Hz, 1H, C=CH_bH), 6.00 (dd, *J* = 16.5, 9.6 Hz, 1H, SCH_a), 5.89 (d, *J* = 16.5 Hz, 1H, C=CH_aH), 5.77 (d, *J* = 9.6 Hz, 1H, C=CHH_b), 5.56 (d, *J* = 9.6 Hz, 1H, C=CHH_a), 4.98 (d, *J* = 4.2 Hz, 1H, Ar-CH_b), 4.94–4.90 (m, 1H, Ar-CH_a), 3.89–3.85 (m, 4H, 2 × ($CH_{(a+b)}$)$_2$C≡CH), 3.66–3.57 (m, 2H, 2 × NCH_{a+b}H), 3.29–3.22 (m, 2H, 2 × NCHH_{a+b}), 3.15 (dt, *J* = 11.9, 1.8 Hz, 1H, NCH_bH), 3.10 (dt, *J* = 11.6, 1.8 Hz, 1H, NCH_aH), 2.91–2.87 (m, 1H, NCHH_a), 2.81–2.77 (m, 1H, NCHH_b), 2.56 (dd, *J* = 11.6, 4.5 Hz, 1H, NCH_aH), 2.53–2.44 (m, 1H, NCH_bH), 2.31–2.27 (m, 8H, 2 × NCH_3 + 2 × NCHH_{a+b}), 2.21 (t, *J* = 2.5 Hz, 1H, C≡CH_b), 2.19 (t, *J* = 2.5 Hz, 1H, C≡CH_a). ^{13}C NMR (101 MHz, $CDCl_3$) δ 2 × 139.3 (Ar-$C_{(a+b)q}$), 136.8 (SC_bH), 134.3 (SC_aH), 2 × 129.3 (Ar-C_{a+b}), 2 × 128.5 (Ar-C_{a+b}), 2 × 128.2 (Ar-C_{a+b}), 2 × 128.0 (Ar-C_{a+b}), 2 × 127.7 (Ar-C_{a+b}), 126.1 (SCH=C_aH_2), 124.8 (SCH=C_bH_2), 82.9 (CH_2C_a≡CH), 82.6 (CH_2C_b≡CH), 70.2 (CH_2C≡C_bH), 69.9 (CH_2C≡C_aH), 59.2 (NC_aHPh), 57.2 (NC_bHPh), 56.2 (NC_aH_2), 55.9 (NC_bH_2), 54.8 (NC_aH_2), 54.7 (NC_bH_2), 2 × 46.2 ($NC_{a+b}H_2$), 41.9 (NC_bH_3), 41.5 (NC_aH_3), 30.8 (C_bH_2C≡CH), 30.7 (C_aH_2C≡CH). HRMS (ESI) m/z: Calcd for $C_{16}H_{22}N_3OS$ [M+H]: 304.1484; Found: 304.1497.

***N*-(3-(10,11-Dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)propyl)-*N*-methyl-*N*'-(prop-2-yn-1-yl)ethenesulfonimidamide (232)**



General procedure L was followed using NaH (60% in mineral oil, 9.6 mg, 0.24 mmol), sulfonimidamide **226** (70 mg, 0.20 mmol) and propargyl bromide (80% in toluene, 33 μL, 0.30 mmol). Purification by flash column chromatography (SiO_2, 30% EtOAc in pentane) afforded sulfonimidamide **232** (63 mg, 81%) as a brown oil. R_f = 0.53 (50% EtOAc in pentane). IR (film)/cm^{-1} 3287, 3060, 3019, 2914, 2855, 1483, 1442, 1282, 1230, 1148, 969, 756. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.25 (m, 1H, Ar-H), 7.26–7.09 (m, 6H, 6 × Ar-H), 7.08–7.02 (m, 1H, Ar-H), 6.49–6.38 (m, 1H, SCH), 6.15 (d, *J* = 16.7 Hz, 1H, C=CH_aH_b), 5.92–5.81 (m, 2H, C=CH_aH_b + C=CH), 3.82 (d, *J* = 2.9 Hz, 2H, CH_2C≡CH), 3.51–3.11 (m, 5H, 2 × Ar-CH_2 + C≡CH), 3.03–2.93 (m, 1H, NC*H*H), 2.87–

2.74 (m, 1H, NC*H*H), 2.69 (s, 3H, NCH_3), 2.41 (qd, *J* = 7.3, 1.4 Hz, 2H, $NCH_2C\mathit{H_2}$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.0 (*C*=CH), 140.8 (Ar-C_q), 139.7 (Ar-C_q), 139.3 (Ar-C_q), 137.0 (Ar-C_q), 133.1 (SCH), 130.0 (SCH=CH_2), 128.5 (Ar-C), 128.1 (Ar-C), 128.0 (Ar-C), 127.6 (Ar-C), 2 × 127.2 (Ar-C), 126.4 (C=*C*H), 126.1 (Ar-C), 125.8 (Ar-C), 82.7 ($CH_2\mathit{C}{\equiv}CH$), 70.0 ($CH_2C{\equiv}\mathit{C}H$), 50.4 (2 × Ar-CH_2), 33.7 (NCH_3), 32.0 (NCH_2), 30.6 ($\mathit{C}H_2C{\equiv}CH$), 28.1 ($NCH_2\mathit{C}H_2$). HRMS (ESI) m/z: Calcd for $C_{24}H_{27}N_2OS$ [M+H]: 391.1844; Found: 391.1854.

4.2.5 Synthesis of Sulfonimidamides from Sulfonimidoyl Fluorides

4.2.5.1 General Procedures

General procedure M for the synthesis of racemic sulfonimidoyl fluorides:
Selectfluor (1.5 equiv) was added to a solution of sulfinamide salt (1 equiv) in DMF (0.2 M) at 0 °C, warmed to room temperature and stirred for 18 h. H_2O (25 mL) was added and the aqueous mixture extracted with EtOAc (3 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent removed under reduced pressure to afford the sulfonimidoyl fluoride products which were typically used without further purification.

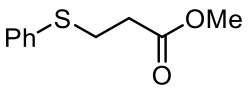
General procedure N for the synthesis of racemic sulfonimidamides:
Amine (2.0 equiv) and triethylamine (2.0 equiv) were added to a solution sulfonimidoyl fluoride (1 equiv) in THF (0.3 M) at room temperature, heated to 80 °C and stirred for 24 h. The solvent was removed under reduced pressure. The resulting residue was then purified by flash chromatography (SiO_2) as described for each entry to afford the sulfonimidamide products.

General Procedure O for the synthesis of enantioenriched sulfonimidoyl fluorides:
Selectfluor (2 equiv) and KOAc (2.0 equiv) was added to a solution of sulfinamide salt (1 equiv) in ethanol (0.2 M) at 0 ºC, warmed to room temperature and stirred for 24 h. H_2O (25 mL) was added and the aqueous mixture extracted with EtOAc (3 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford the sulfonimidoyl fluoride products which were typically used without further purification.

General Procedure P for the synthesis of enantioenriched sulfonimidamides:
Amine (2.0 equiv), triethylamine (2.0 equiv) and LiBr (2.0 equiv) were added to a solution of sulfonimidoyl fluoride (1 equiv) in MeCN (0.3 M) at room temperature, heated to 80 °C and stirred for 24 h. The solvent was removed under reduced pressure. The resulting residue was then purified by flash chromatography (SiO_2) as described for each entry to afford the sulfonimidamide products.

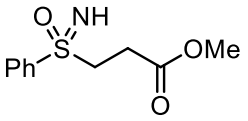
4.2.5.2 Synthesis of Racemic Sulfinamide Salts

Methyl 3-(phenylthio)propanoate (248)



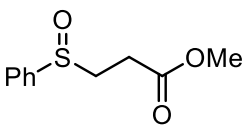
Methyl acrylate (1.35 mL, 15.0 mmol, 1.0 equiv) and sodium acetate (185 mg, 2.25 mmol, 0.15 equiv) were added to a solution of benzenethiol (1.53 mL, 15.0 mmol, 1.0 equiv) in THF:H_2O (1:1, 50 mL, 0.3 M) at 25 °C and stirred for 18 h. Sat. aq. $NaHCO_3$ (50 mL) was added and the aqueous mixture was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (5% EtOAc in pentane) afforded sulfide **248** (2.63 g, 89%) as a colourless oil. R_f 0.25 (5% EtOAc in pentane). IR (film)/cm^{-1} 2951, 1733, 1583, 1481, 1437, 1356, 1243, 1171, 1024, 737, 690. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.35 (m, 2H, 2 × Ar-H), 7.35–7.25 (m, 2H, 2 × Ar-H), 7.24–7.18 (m, 1H, Ar-H), 3.68 (s, 3H, OCH_3), 3.17 (t, *J* = 7.4 Hz, 2H, SCH_2), 2.63 (t, *J* = 7.4 Hz, 2H, SCH_2CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2 (C=O), 135.1 (Ar-C_q), 130.1 (Ar-C), 129.0 (2 × Ar-C), 126.6 (2 × Ar-C), 51.9 (OCH_3), 34.2 (SCH_2), 29.1 (SCH_2CH_2). Analytical data (NMR) in agreement with those reported in the literature.[336]

Methyl 3-(phenylsulfonimidoyl)propanoate (249)



Procedure adapted from Bull, Luisi and co-workers.[164] Bis(acetoxy)iodobenzene (805 mg, 2.5 mmol, 2.5 equiv) and ammonium carbamate (156 mg, 2.0 mmol, 2.0 equiv) was added to a solution of sulfide **248** (196 mg, 1.0 mmol) in MeOH (3.3 mL, 0.3 M) at 25 °C and stirred for 18 h. The solvent was removed under reduced pressure. Purification by flash column chromatography (SiO_2, 50% EtOAc in pentane) afforded sulfoximine **249** (188 mg, 83%) as a colourless oil. R_f 0.18 (50% EtOAc in pentane). IR (film)/cm^{-1} 3283, 2952, 1732, 1476, 1444, 1363, 1217, 675. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.8 Hz, 2H, 2 × Ar-H), 7.64 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.56 (t, *J* = 7.5 Hz, 2H, 2 × Ar-H), 3.63 (s, 3H, OCH_3), 3.51–3.45 (m, 2H, SCH_2), 2.86–2.66 (m, 2H, SCH_2CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8 (C=O), 141.2 (Ar-C_q), 133.4 (Ar-C), 129.3 (2 × Ar-C), 128.5 (2 × Ar-C), 52.7 (SCH_2), 52.3 (OCH_3), 28.3 (SCH_2CH_2). HRMS (ESI) *m/z* Calcd for $C_{10}H_{14}NO_3S$ [M+H]: 228.0694; Found: 228.0693.

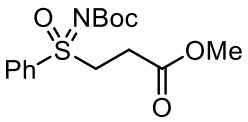
Methyl 3-(phenylsulfinyl)propanoate (250)



*m*CPBA (2.40 g, 13.9 mmol, 1.05 equiv) was added portion wise to a solution of sulfide **248** (2.60 g, 13.2 mmol, 1 equiv) in CH_2Cl_2 (90 mL, 0.15 M) at 0 °C and stirred for 2 h. The reaction mixture was quenched with 3 M aq. KOH (75 mL) and the aqueous mixture was extracted with CH_2Cl_2 (3 × 75 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced

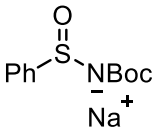
pressure. Purification by flash column chromatography (50% EtOAc in pentane) afforded sulfoxide **250** (2.23 g, 81%) as a colourless oil. R_f 0.17 (50% EtOAc in pentane). IR (film)/cm^{-1} 3316, 3054, 2949, 2901, 1721, 1591, 1440, 1197, 1183, 819, 756. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.60 (m, 2H, 2 × Ar-H), 7.58–7.48 (m, 3H, 3 × Ar-H), 3.67 (s, 3H, OCH_3), 3.25 (ddd, *J* = 13.4, 8.5, 6.7 Hz, 1H, SC*H*H), 2.97 (ddd, *J* = 13.3, 8.3, 5.7 Hz, 1H, SCH*H*), 2.85 (ddd, *J* = 17.2, 8.4, 6.7 Hz, 1H, SCH_2CHH), 2.57 (ddd, *J* = 17.2, 8.5, 5.7 Hz, 1H, SCH_2CHH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8 (C=O), 143.0 (Ar-C_q), 131.3 (Ar-C), 129.4 (2 × Ar-C), 124.1 (2 × Ar-C), 52.3 (OCH_3), 51.2 (SCH_2), 26.1 (SCH_2CH_2). Analytical data (NMR) in agreement with those reported in the literature.[337]

Methyl 3-(*N*-(*tert*-butoxycarbonyl)phenylsulfonimidoyl)propanoate (251)



Procedure adapted from Bull, Luisi and co-workers.[150] Magnesium oxide (71 mg, 1.8 mmol, 4 equiv), *tert*-butyl carbamate (77 mg, 0.66 mmol, 1.5 equiv), bis(acetoxy)iodobenzene (213 mg, 0.66 mmol, 1.5 equiv) and $Rh_2(OAc)_4$ (4.9 mg, 0.011 mmol, 2.5 mol%) were added to a solution of sulfoxide **250** (94 mg, 0.44 mmol, 1 equiv) in CH_2Cl_2 (4.4 mL, 0.1 M) at room temperature, heated to 40 °C and stirred for 18 h. The reaction mixture was cooled to room temperature and filtered through celite and concentrated under reduced pressure. Purification by flash column chromatography (50% EtOAc in pentane) afforded sulfoximine **251** (114 mg, 80%) as a colourless oil. R_f 0.43 (50% EtOAc in pentane). IR (film)/cm^{-1} 2987, 2940, 1738, 1666, 1447, 1408, 1367, 1215, 1153, 1133, 872, 740. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00–7.93 (m, 2H, 2 × Ar-H), 7.73–7.67 (m, 1H, Ar-H), 7.65–7.58 (m, 2H, 2 × Ar-H), 3.73 (ddd, *J* = 14.4, 9.4, 6.0 Hz, 1H, SC*H*H), 3.63 (s, 3H, OCH_3), 3.61–3.54 (m, 1H, SCH*H*), 2.92–2.72 (m, 2H, SCH_2CH_2), 1.37 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3 (C=O), 157.5 (C=O), 137.1 (Ar-C_q), 134.1 (Ar-C), 129.8 (2 × Ar-C), 128.2 (2 × Ar-C), 80.9 ($C(CH_3)_3$), 52.5 (OCH_3), 51.8 (SCH_2), 28.1 ($C(CH_3)_3$), 27.4 (SCH_2CH_2). HRMS (ESI) *m/z* Calcd for $C_{15}H_{22}NO_5S$ [M+H]: 328.1219; Found: 328.1213.

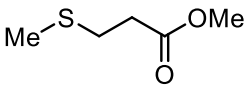
Sodium (*tert*-butoxycarbonyl)(phenylsulfinyl)amide (252)



NaH (60 % in oil, 137 mg, 3.44 mmol, 1.05 equiv) was added to a solution of sulfoximine **251** (1.07 g, 3.27 mmol, 1.0 equiv) in anhydrous THF (33 mL, 0.1 M) at 25 °C and stirred for 1 h. MeOH (100 mL) was added and the solvent removed under reduced pressure. The resulting precipitate was washed with hexane (50 mL) and collected by filtration to afford sulfinamide salt **252** as a white solid (852 mg, 99%). mp = 238–240 °C. IR (film)/cm^{-1} 3344, 2978, 1631, 1582, 1268, 1155, 1004, 993, 829, 747, 697. ^{1}H NMR (400 MHz, D_2O) δ 7.63 (dd, *J* = 6.7, 3.0 Hz, 2H, 2 × Ar-H), 7.54–7.47 (m, 3H, 3 × Ar-H), 1.39 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, D_2O) δ 165.9 (C=O), 146.1 (Ar-C_q), 130.9 (Ar-C), 129.0

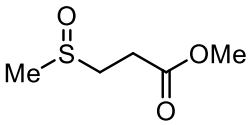
(2 × Ar-C), 124.6 (2 × Ar-C), 79.6 ($C(CH_3)_3$), 27.7 ($C(CH_3)_3$). HRMS (ESI) *m/z*: Calcd for $C_{11}H_{14}NO_3S$ $[M]^-$: 240.0694; Found: 240.0704.

Methyl 3-(methylthio)propanoate (254)



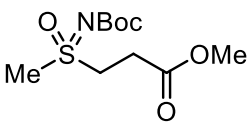
Iodomethane (1.25 mL, 20 mmol, 2 equiv) and K_2CO_3 (1.66 g, 12 mmol, 1.2 equiv) was added to a solution of methyl 3-mercaptopropionate **253** (1.20 mL, 10 mmol, 1 equiv) in acetone (50 mL, 0.2 M) at 25 °C and stirred for 18 h. The reaction mixture was quenched with 1 M aq. K_2CO_3 (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, 5% Et_2O in pentane) afforded sulfide **254** (1.10 g, 82%) as a colourless oil. **Note: due to the volatility of the product, removal of solvent was carried out at pressures no less than 200 mbar at 25 °C** R_f 0.25 (5% Et_2O in pentane). IR (film)/cm^{-1} 2952, 2918, 1733, 1435, 1357, 1245, 1144, 1021. ^1H NMR (400 MHz, $CDCl_3$) δ 3.70 (s, 3H, OCH_3), 2.78 (td, *J* = 7.3, 0.9 Hz, 2H, SCH_2), 2.64 (td, *J* = 7.3, 0.9 Hz, 2H, CH_2), 2.12 (s, 3H, SCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6 (C=O), 51.9 (OCH_3), 34.4 (SCH_2), 29.2 (SCH_2CH_2), 15.6 (SCH_3). Analytical data (NMR and IR) in agreement with those reported in the literature.[338]

Methyl 3-(methanesulfinyl)propanoate (255)



*m*CPBA (934 mg, 5.4 mmol, 1.05 equiv) was added portion wise to sulfide **254** (691 mg, 5.1 mmol, 1 equiv) in CH_2Cl_2 (25 mL, 0.2 M) at 0 °C and stirred for 1 h. The reaction mixture was quenched with 1 M aq. K_2CO_3 (50 mL) and the aqueous mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, 100% acetone) afforded sulfoxide **255** (634 mg, 83%) as a colourless oil. **Note: due to the volatility of the product, removal of solvent was carried out at pressures no less than 1 mbar at 25 °C** R_f 0.28 (100% acetone). IR (film)/cm^{-1} 3000, 2956, 1730, 1439, 1364, 1241, 1178, 1029, 943, 827. ^1H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3H, OCH_3), 3.06 (ddd, J = 13.0, 8.2, 7.1 Hz, 1H, SC*H*H), 2.94–2.87 (m, 1H, SCH*H*), 2.87–2.80 (m, 2H, SCH_2CH_2), 2.59 (s, 3H, SCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9 (C=O), 52.4 (OCH_3), 49.0 (SCH_2), 38.9 (SCH_2CH_2), 26.9 (SCH_3). Analytical data (NMR and IR) in agreement with those reported in the literature.[338]

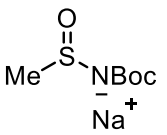
Methyl 3-(*N*-(*tert*-butoxycarbonyl)-*S*-methylsulfonimidoyl)propanoate (256)



Procedure adapted from Bull, Luisi and co-workers.[150] Magnesium oxide (383 mg, 9.51 mmol, 4.0 equiv), *tert*-Butyl carbamate (400 mg, 3.57 mmol, 1.5 equiv), bis(acetoxy)iodobenzene (1.15 g, 3.57 mmol, 1.5

equiv) and $Rh_2(OAc)_4$ (26 mg, 0.06 mmol, 2.5 mol%) was added to a stirred solution of sulfoxide **255** (357 mg, 2.38 mmol, 1.0 equiv) in CH_2Cl_2 (25 mL) at room temperature, heated to 40 °C and stirred for 18 h. The reaction mixture was cooled to room temperature and filtered through celite and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, 50% EtOAc in pentane) afforded sulfoximine **256** (475 mg, 75%) as a colourless oil. R_f 0.28 (50% EtOAc in pentane). IR (film)/cm^{-1} 2978, 2933, 1737, 1655, 1439, 1364, 1275, 1250, 1152, 992, 861, 790. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (dd, J = 14.3, 7.1 Hz, 1H, SC*H*H), 3.74 (s, 3H, OCH_3), 3.65 (dt, J = 14.4, 7.2 Hz, 1H, SCH*H*), 3.24 (s, 3H, SCH_3), 3.10–2.86 (m, 2H, SCH_2CH_2), 1.48 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9 (C=O), 158.5 (C=O), 80.9 ($C(CH_3)_3$), 52.7 (OCH_3), 49.5 (SCH_2), 40.8 (SCH_3), 28.3 ($C(CH_3)_3$), 27.7 (CH_2). HRMS (ESI) m/z Calcd for $C_{10}H_{19}NO_5S$ [M+H]: 266.1060; Found: 266.1062.

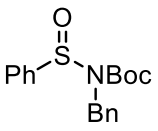
Sodium (*tert*-butoxycarbonyl)(methylsulfinyl)amide (257)



NaH (60 % in oil, 60.8 mg, 1.52 mmol, 1.05 equiv) was added to a solution of sulfoximine **256** (384 mg, 1.45 mmol, 1.0 equiv) in anhydrous THF (15 mL, 0.1 M) at 25 °C and stirred for 1 h. MeOH (1 mL) was added and the solvent removed under reduced pressure. The resulting precipitate was washed with hexane (50 mL) and collected by filtration to afford sulfinamide salt **257** (281 mg, 96%) as a white solid. mp = 170–172 °C. IR (film)/cm^{-1} 2975, 2929, 1611, 1449, 1390, 1364, 1296, 999, 936, 835, 791, 742, 704. ^{1}H NMR (400 MHz, D_2O) δ 2.46 (s, 3H, CH_3), 1.43 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, D_2O) δ 165.6 (C=O), 79.5 ($C(CH_3)_3$), 40.8 (CH_3), 27.8 ($C(CH_3)_3$). HRMS (ESI) *m/z*: Calcd for $C_6H_{12}NO_3S$ $[M]^-$: 178.0543; Found: 178.0547.

4.2.5.3 Sulfinamide Salt Reactions

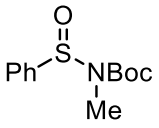
***tert*-Butyl benzyl(phenylsulfinyl)carbamate (258)**



Benzyl bromide (36 μL, 0.30 mmol, 1.5 equiv) was added to a solution of sulfinamide salt **252** (53 mg, 0.20 mmol, 1.0 equiv) in anhydrous DMF (1.33 mL, 0.15 M) at 25 °C and stirred for 2 h. H_2O (10 mL) was added and the aqueous mixture extracted with EtOAc (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash column chromatography (SiO_2, 10% EtOAc/pentane) afforded sulfinamide **258** (39 mg, 59%) as a colourless oil. R_f 0.18 (10% EtOAc in pentane). IR (film)/cm^{-1} 2978, 1711, 1496, 1465, 1367, 1287, 1246, 1155, 1099. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.61 (m, 2H, 2 × Ar-H), 7.48–7.41 (m, 3H, 3 × Ar-H), 7.19–7.10 (m, 3H, 3 × Ar-H), 7.05–7.00 (m, 2H, 2 × Ar-H), 4.36 (d, *J* = 15.8 Hz, 1H, C*H*H), 4.27 (d, *J* = 15.8 Hz, 1H, CH*H*), 1.45 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.7 (C=O), 143.1 (Ar-C_q), 137.4 (Ar-C_q), 131.6 (Ar-C), 129.0 (2 × Ar-C), 128.0 (2 ×

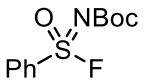
Ar-C), 127.7 (2 × Ar-C), 126.8 (Ar-C), 125.2 (2 × Ar-C), 83.4 (*C*(CH_3)$_3$), 44.4 (CH_2), 28.0 (C(*C*H_3)$_3$). HRMS (ESI) *m/z* Calcd for $C_{18}H_{22}NO_3S$ [M+H]: 332.1320; Found: 332.1318.

tert-Butyl methyl(phenylsulfinyl)carbamate (259)



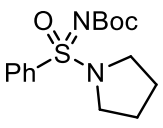
Iodomethane (62 μL, 1.0 mmol, 5.0 equiv) was added to a solution of sulfinamide salt **252** (53 mg, 0.20 mmol, 1.0 equiv) in anhydrous DMF (1.33 mL, 0.15 M) at 25 °C and stirred for 2 h. H_2O (10 mL) was added and the aqueous mixture extracted with EtOAc (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash column chromatography (SiO_2, 10% EtOAc/pentane) afforded sulfinamide **259** (42 mg, 82%) as a colourless oil. R_f 0.35 (10% EtOAc in Pentane). IR (film)/cm^{-1} 2980, 2247, 1710, 1417, 1303, 1145, 1100, 958, 752, 730. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.60 (m, 2H, 2 × Ar-H), 7.58–7.50 (m, 3H, 3 × Ar-H), 2.63 (s, 3H, CH_3), 1.56 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.7 (C=O), 142.9 (Ar-C_q), 131.5 (Ar-C), 129.2 (2 × Ar-C), 125.1 (2 × Ar-C), 83.2 (*C*(CH_3)$_3$), 28.2 (C(*C*H_3)$_3$), 25.4 (CH_3). HRMS (ESI) *m/z* Calcd for $C_{12}H_{18}NO_3S$ [M+H]: 256.1007; Found: 256.1016.

tert-Butyl (fluoro(oxo)(phenyl)-λ^6-sulfaneylidene)carbamate (266)



Selectfluor (81 mg, 0.23 mmol, 1.5 equiv) was added to a solution of sulfinamide salt **252** (40 mg, 0.15 mmol, 1.0 equiv) in DMF (0.75 mL, 0.2 M) at 0 °C and allowed to warm to room temperature and stirred for 18 h. H_2O (25 mL) was added and the aqueous mixture extracted with EtOAc (3 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent removed under reduced pressure. Purification by flash column chromatography (SiO_2, 10% EtOAc in pentane) afforded sulfonimidoyl fluoride **266** (21 mg, 54%) as a colourless oil. R_f 0.51 (20% EtOAc in pentane). IR (film)/cm^{-1} 2980, 1726, 1700, 1325, 1249, 1140, 1095, 744, 697. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16–8.07 (m, 2H, 2 × Ar-H), 7.81–7.73 (m, 1H, Ar-H), 7.68–7.57 (m, 2H, 2 × Ar-H), 1.54 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.3 (d, $^3J_{C\text{-}F}$ = 2.8 Hz, C=O), 135.4 (Ar-C), 133.9 (d, $^2J_{C\text{-}F}$ = 21.4 Hz, Ar-C_q), 129.5 (2 × Ar-C), 128.1 (2 × Ar-C), 82.7 (*C*(CH_3)$_3$), 27.9 (C(*C*H_3)$_3$). ^{19}F NMR (377 MHz, $CDCl_3$) δ 68.54. Analytical data (NMR) in agreement with those reported in the literature.[313]

tert-Butyl (oxo(phenyl)(pyrrolidin-1-yl)-λ^6-sulfaneylidene)carbamate (267)

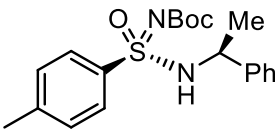


Pyrrolidine (14 μL, 0.17 mmol, 2.0 equiv) and DBU (25 μL, 0.17 mmol, 2.0 equiv) was added to a solution of sulfonimidoyl fluoride **266** (22 mg, 0.09 mmol) in MeCN (0.9 mL, 0.1 M) at room temperature, heated to 60 °C and stirred for 24 h. The solvent was removed under reduced pressure. Purification by flash column chromatography (SiO_2, 25% EtOAc in pentane) afforded sulfonimidamide **267** (13 mg, 49%)

as a white solid. mp = 97–99 °C. R_f 0.14 (20% EtOAc in pentane). IR (film)/cm^{-1} 2973, 2930, 2878, 1668, 1446, 1250, 1147, 1052, 995, 891, 753. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99–7.88 (m, 2H, 2 × Ar-H), 7.65–7.56 (m, 1H, Ar-H), 7.56–7.49 (m, 2H, 2 × Ar-H), 3.40–3.34 (m, 2H, 2 × NC*H*H), 3.32–3.23 (m, 2H, 2 × NCH*H*), 1.89–1.77 (m, 4H, 2 × NCH_2CH_2), 1.41 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7 (C=O), 137.5 (Ar-C_q), 132.8 (Ar-C), 129.0 (2 × Ar-C), 127.5 (2 × Ar-C), 80.0 ($C(CH_3)_3$), 47.9 (2 × NCH_2), 28.0 ($C(CH_3)_3$), 25.4 (2 × NCH_2CH_2). HRMS (ESI) *m/z* Calcd for $C_{15}H_{23}N_2O_3S$ [M+H]: 311.1429; Found: 311.1427.

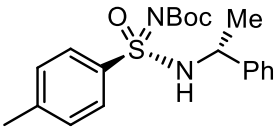
4.2.5.4 Scope of Sulfonimidamide Synthesis

tert-Butyl ((*R*)-oxo(((*S*)-1-phenylethyl)amino)(*p*-tolyl)-λ^6-sulfaneylidene)carbamate (271)



Prepared according to general procedure P using (*S*)-1-phenylethan-1-amine (64 µL, 0.50 mmol), triethylamine (70 µL, 0.50 mmol), LiBr (43 mg, 0.50 mmol) and sulfonimidoyl fluoride **269** (69 mg, 0.25 mmol). Purification by flash column chromatography (SiO_2, 5% Et_2O in CH_2Cl_2) afforded sulfonimidamide **271** (42 mg, 45%) as a single diastereomer as a colourless oil. R_f 0.24 (5% Et_2O in CH_2Cl_2). IR (film)/cm^{-1} 3083, 2978, 1673, 1453, 1367, 1278, 1162, 1118. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.4 Hz, 2H, 2 × Ar-H), 7.15–7.07 (m, 5H, 5 × Ar-H), 7.03–6.96 (m, 2H, 2 × Ar-H), 6.55 (d, *J* = 4.7 Hz, 1H, NH), 4.47–4.44 (m, 1H, NHC*H*), 2.34 (s, 3H, Ar-CH_3), 1.57 (d, *J* = 6.8 Hz, 3H, CHC*H*$_3$), 1.41 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.3 (C=O), 143.5 (Ar-C_q), 141.3 (Ar-C_q), 136.0 (Ar-C_q), 129.3 (2 × Ar-C), 128.4 (2 × Ar-C), 127.8 (2 × Ar-C), 127.4 (Ar-C), 126.2 (2 × Ar-C), 80.4 ($C(CH_3)_3$), 52.6 (NCH), 28.1 ($C(CH_3)_3$), 24.1 (CH(*C*H$_3$)), 21.4 (Ar-CH_3). HRMS (+p APCI) m/z: Calcd for $C_{20}H_{27}N_2O_3S$ [M+H]$^+$: 375.1737; Found: 375.1737. $[\alpha]^{23}_D$ = +4 (c 1.0, $CDCl_3$).

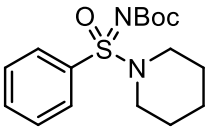
tert-Butyl ((*R*)-oxo(((*R*)-1-phenylethyl)amino)(*p*-tolyl)-λ^6-sulfaneylidene)carbamate (272)



Prepared according to general procedure P using (*R*)-1-phenylethan-1-amine (64 µL, 0.50 mmol), triethylamine (70 µL, 0.50 mmol), LiBr (43 mg, 0.50 mmol) and sulfonimidoyl fluoride **269** (69 mg, 0.25 mmol). Purification by flash column chromatography (SiO_2, 5% Et_2O in CH_2Cl_2) afforded sulfonimidamide **272** (40 mg, 43%) as a single diastereomer as a colourless oil. R_f 0.28 (5% Et_2O in CH_2Cl_2). IR (film)/cm^{-1} 3063, 2978, 1677, 1453, 1367, 1274, 1159, 1118, 969, 909. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.4 Hz, 2H, 2 × Ar-H), 7.34–7.25 (m, 7H, 7 × Ar-C), 6.58 (s, 1H, NH), 4.43 (q, *J* = 6.9 Hz, 1H, NHC*H*), 2.45 (s, 3H, Ar-CH_3), 1.39 (s, 9H, $C(CH_3)_3$), 1.30 (d, *J* = 6.9 Hz, 3H, CHC*H*$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0 (C=O), 143.9 (Ar-C_q), 142.3 (Ar-C_q), 136.8 (Ar-C_q), 129.6 (2 × Ar-C), 128.6 (2 × Ar-C), 127.9 (2 × Ar-C), 127.6 (Ar-C), 126.2 (2 × Ar-C), 80.3 ($C(CH_3)_3$), 52.4 (NHCH), 28.1 ($C(CH_3)_3$), 23.0 (CH*C*H$_3$), 21.5 (Ar-CH_3). HRMS

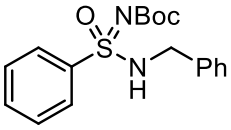
(+p APCI) m/z: Calcd for $C_{20}H_{27}N_2O_3S$ $[M+H]^+$: 375.1737; Found: 375.1725. $[\alpha]^{23}_D$ = +39 (c 1.0, $CDCl_3$).

tert-Butyl (oxo(phenyl)(piperidin-1-yl)-λ⁶-sulfaneylidene)carbamate (273)



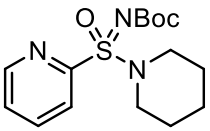
Prepared according to general procedure P using piperidine (50 μL, 0.50 mmol), triethylamine (70 μL, 0.50 mmol), LiBr (43 mg, 0.50 mmol) and sulfonimidoyl fluoride **266** (65 mg, 0.25 mmol). Purification by flash column chromatography (SiO_2, 1% Et_2O in CH_2Cl_2) afforded sulfonimidamide **273** (60 mg, 74%) as a white solid. R_f = 0.12 (1% Et_2O in CH_2Cl_2). mp = 95–97 °C. IR (film)/cm^{-1} 2974, 2937, 2855, 1673, 1446, 1364, 1249, 1148, 928. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88–7.82 (m, 2H, 2 × Ar-H), 7.62–7.56 (m, 1H, Ar-H), 7.55–7.49 (m, 2H, 2 × Ar-H), 3.11 (td, *J* = 5.0, 3.2 Hz, 4H, 2 × NCH_2), 1.63 (p, *J* = 5.8 Hz, 4H, 2 × $NCH_2C\mathit{H}_2$), 1.48–1.41 (m, 2H, $NCH_2CH_2C\mathit{H}_2$), 1.39 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.5 (C=O), 136.5 (Ar-C_q), 132.7 (Ar-C), 128.9 (2 × Ar-C), 127.6 (2 × Ar-C), 80.1 ($\mathit{C}(CH_3)_3$), 46.6 (2 × NCH_2), 28.0 ($C(\mathit{C}H_3)_3$), 25.2 (2 × $NCH_2\mathit{C}H_2$), 23.5 ($NCH_2CH_2\mathit{C}H_2$). HRMS (ESI) m/z: Calcd for $C_{16}H_{25}N_2O_3S$ $[M+H]$: 325.1586; Found: 325.1596.

tert-Butyl ((benzylamino)(oxo)(phenyl)-λ⁶-sulfaneylidene)carbamate (274)



Prepared according to general procedure P using benzylamine (55 μL, 0.50 mmol), triethylamine (70 μL, 0.50 mmol), LiBr (43 mg, 0.50 mmol) and sulfonimidoyl fluoride **266** (65 mg, 0.25 mmol). Purification by flash column chromatography (SiO_2, 5% Et_2O in CH_2Cl_2) afforded sulfonimidamide **274** (62 mg, 72%) as a white solid. R_f = 0.28 (5% Et_2O in CH_2Cl_2). mp = 85–87 °C. IR (film)/cm^{-1} 3063, 2978, 1685, 1278, 1159, 1088, 1062, 909, 752, 689. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00–7.94 (m, 2H, 2 × Ar-H), 7.63–7.58 (m, 1H, Ar-H), 7.54–7.49 (m, 2H, 2 × Ar-H), 7.31–7.21 (m, 5H, 5 × Ar-H), 7.15 (s, 1H, NH), 4.27 (d, *J* = 14.1 Hz, 1H, Ar-C*H*H), 4.00 (d, *J* = 14.1 Hz, 1H, Ar-CH*H*), 1.37 (s, 9H, 3 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.8 (C=O), 138.8 (Ar-C_q), 135.9 (Ar-C_q), 133.0 (Ar-C), 129.0 (2 × Ar-C), 128.6 (2 × Ar-C), 127.9 (4 × Ar-C), 127.8 (Ar-C), 80.5 ($\mathit{C}(CH_3)_3$), 45.3 (Ar-CH_2), 28.0 (3 × CH_3). HRMS (ESI) m/z: Calcd for $C_{18}H_{23}N_2O_3S$ $[M+H]$: 347.1429; Found: 347.1432.

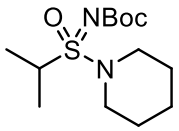
tert-Butyl (oxo(piperidin-1-yl)(pyridin-2-yl)-λ⁶-sulfaneylidene)carbamate (276)



Prepared according to general procedure P using piperidine (50 μL, 0.50 mmol), triethylamine (70 μL, 0.50 mmol), LiBr (43 mg, 0.50 mmol) and sulfonimidoyl fluoride **275** (65 mg, 0.25 mmol). Purification by flash column chromatography (SiO_2, 5% Et_2O in CH_2Cl_2) afforded sulfonimidamide **276** (69 mg, 84%) as a

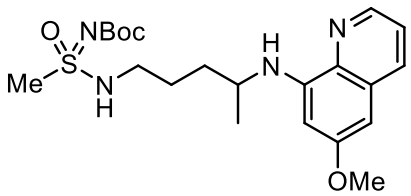
white solid. R_f 0.14 (2% Et_2O in CH_2Cl_2). mp = 123–124 °C. IR (film)/cm^{-1} 2974, 2940, 2855, 1700, 1364, 1278, 1151, 1051, 939. ^1H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, *J* = 7.7 Hz, 1H, Ar-H), 8.08 (d, *J* = 7.9 Hz, 1H, Ar-H), 7.91 (t, *J* = 7.7 Hz, 1H, Ar-H), 7.48 (t, *J* = 7.6 Hz, 1H, Ar-H), 3.38–3.34 (m, 4H, 2 × NCH_2), 1.67–1.62 (m, 4H, 2 × NCH_2CH_2), 1.55–1.46 (m, 2H, $NCH_2CH_2CH_2$), 1.39 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.8 (C=O), 156.5 (Ar-C_q), 149.6 (Ar-C), 137.8 (Ar-C), 126.4 (Ar-C), 124.0 (Ar-C), 80.1 ($C(CH_3)_3$), 47.3 (2 × NCH_2), 28.0 ($C(CH_3)_3$), 25.4 (2 × NCH_2CH_2), 23.7 ($NCH_2CH_2CH_2$). HRMS (+p APCI) m/z: Calcd for $C_{15}H_{24}N_3O_3S$ $[M+H]^+$: 326.1533; Found: 326.1542.

***tert*-Butyl (isopropyl(oxo)(piperidin-1-yl)-λ⁶-sulfaneylidene)carbamate (278)**



Prepared according to general procedure P using piperidine (50 μL, 0.50 mmol), triethylamine (70 μL, 0.50 mmol), LiBr (43 mg, 0.50 mmol) and sulfonimidoyl fluoride **277** (56 mg, 0.25 mmol). Purification by flash column chromatography (SiO_2, 20% EtOAc in pentane) afforded sulfonimidamide **278** (23 mg, 32%) as a white solid. R_f 0.25 (1% Et_2O in CH_2Cl_2). mp = 72–74 °C. IR (film)/cm^{-1} 2929, 2855, 1666, 1453, 1278, 1237, 1162, 1043, 939. ^1H NMR (400 MHz, $CDCl_3$) δ 3.44–3.22 (m, 5H, $CH(CH_3)_2$ + 2 × NCH_2), 1.68–1.60 (m, 6H, 2 × NCH_2CH_2 and $NCH_2CH_2CH_2$), 1.49 (s, 9H, $C(CH_3)_3$), 1.42 (d, *J* = 6.8 Hz, 3H, 1 × $CH(CH_3)_2$), 1.32 (d, *J* = 6.9 Hz, 3H, 1 × $CH(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.6 (C=O), 79.7 ($C(CH_3)_3$), 54.5 ($CHCH_3$), 47.4 (2 × NCH_2), 28.2 ($C(CH_3)_3$), 25.8 (2 × NCH_2CH_2), 23.9 ($NCH_2CH_2CH_2$), 16.2 (1 × $CH(CH_3)_2$), 15.7 (1 × $CH(CH_3)_2$). HRMS (ESI) m/z: Calcd for $C_{13}H_{27}N_2O_3S$ [M+H]: 291.1742; Found: 291.1732.

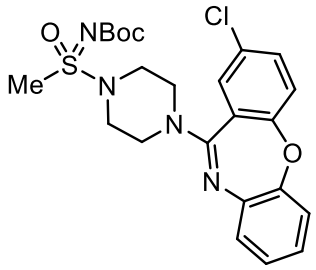
***tert*-Butyl (((4-((6-methoxyquinolin-8-yl)amino)pentyl)amino)(methyl)(oxo)-λ⁶-sulfaneylidene)carbamate (280)**



Prepared according to general procedure N using primaquine bisphosphate (227 mg, 0.50 mmol), triethylamine (210 μL, 1.50 mmol) and sulfonimidoyl fluoride **279** (49 mg, 0.25 mmol). Purification by flash column chromatography (SiO_2, 5% Et_2O in CH_2Cl_2) afforded sulfonimidamide **280** (49 mg, 58%) as a 1:1 mixture of diastereomers as a colourless oil. R_f 0.14 (10% Et_2O in CH_2Cl_2). IR (film)/cm^{-1} 2970, 2933, 1666, 1617, 1520, 1386, 1282, 1162, 977, 824, 790. ^1H NMR (400 MHz, $CDCl_3$) δ 8.53 (dd, *J* = 4.3, 1.7 Hz, 2H, Ar-H_{a+b}), 7.92 (dd, *J* = 8.3, 1.7 Hz, 2H, Ar-H_{a+b}), 7.31 (dd, *J* = 8.2, 4.2 Hz, 2H, Ar-H_{a+b}), 6.34 (d, *J* = 2.5 Hz, 2H, Ar-H_{a+b}), 6.28 (t, *J* = 2.4 Hz, 2H, Ar-H_{a+b}), 5.99 (d, *J* = 8.5 Hz, 2H, NH_{a+b}), 5.70 (s, 2H, NH_{a+b}), 3.89 (s, 6H, $OCH_{3(a+b)}$), 3.68–3.59 (m, 2H, NCH_{a+b}), 3.16 (s, 4H, $NCH_{2(a+b)}$), 3.11 (d, *J* = 1.6 Hz, 6H, $SCH_{3(a+b)}$), 1.79–1.67 (m, 8H, 2 × $CH_{2(a+b)}$), 1.46 (s, 18H, $C(CH_{3(a+b)})_3$), 1.31 (d, *J* = 6.4 Hz, 6H, $CH_{3(a+b)}$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3 (Ar-C_q)$_{a+b}$, 157.7 (C=O)$_{a+b}$, 144.8 (Ar-C_q)$_{a+b}$, 144.3 (Ar-C)$_{a+b}$, 135.2 (Ar-C_q)$_{a+b}$,

134.8 (Ar-C)$_{a+b}$, 129.8 (Ar-C$_q$)$_{a+b}$, 121.9 (Ar-C)$_{a+b}$, 96.8 (Ar-C)$_{a+b}$, 91.7 (Ar-C)$_{a+b}$, 80.4 (*C*(CH$_3$)$_3$)$_{a+b}$, 55.2 (OCH$_3$)$_{a+b}$, 47.7 (NCH$_2$)$_{a/b}$, 47.6 (NCH$_2$)$_{a/b}$, 42.4 (NCH)$_{a/b}$, 42.3 (NCH)$_{a/b}$, 41.0 (SCH$_3$)$_{a+b}$, 33.6 (CH$_2$)$_{a/b}$, 33.5 (CH$_2$)$_{a/b}$, 28.1 (C(*C*H$_3$)$_3$)$_{a+b}$, 26.5 (CH$_2$)$_{a/b}$, 26.4 (CH$_2$)$_{a/b}$, 20.6 (CH*C*H$_3$)$_{a+b}$. HRMS (ESI) m/z: Calcd for $C_{21}H_{33}N_4O_4S$ [M+H]: 437.2223; Found: 437.2225.

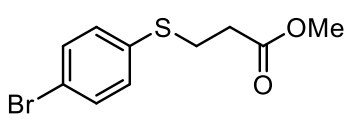
tert-Butyl ((4-(2-chlorodibenzo[*b*,*f*][1,4]oxazepin-11-yl)piperazin-1-yl)(methyl)(oxo)-λ^6-sulfaneylidene)carbamate (281)



Prepared according to general procedure N using amoxipine (157 mg, 0.50 mmol), triethylamine (70 μL, 0.50 mmol) and sulfonimidoyl fluoride **279** (49 mg, 0.25 mmol). Purification by flash column chromatography (SiO_2, 5% Et_2O in CH_2Cl_2) afforded sulfonimidamide **281** (45 mg, 45%) as a colourless oil. R_f 0.26 (5% Et_2O in CH_2Cl_2). IR (film)/cm^{-1} 2978, 2929, 1669, 1602, 1558, 1472, 1282, 1252, 1162, 954. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 8.7, 2.6 Hz, 1H, Ar-H), 7.31 (d, *J* = 2.6 Hz, 1H, Ar-H), 7.20 (d, *J* = 8.6 Hz, 1H, Ar-H), 7.17–7.08 (m, 3H, 3 × Ar-H), 7.06–7.00 (m, 1H, Ar-H), 3.65 (s, 4H, 2 × NCH$_2$), 3.45 (s, 4H, 2 × NCH$_2$), 3.06 (s, 3H, SCH$_3$), 1.49 (s, 9H, C(CH$_3$)$_3$)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3 (Ar-C$_q$), 158.4 (Ar-C$_q$), 156.5 (C=O), 151.7(Ar-C$_q$), 139.6 (Ar-C$_q$), 132.9 (Ar-C), 130.5 (Ar-C$_q$), 128.7 (Ar-C), 127.1 (Ar-C), 125.8 (Ar-C), 125.1 (Ar-C), 124.6 (Ar-C$_q$), 122.8 (Ar-C), 120.1 (Ar-C), 80.5 (*C*(CH$_3$)$_3$), 47.1 (2 × NCH$_2$), 45.5 (2 × NCH$_2$), 38.4 (SCH$_3$), 28.1 (C(*C*H$_3$)$_3$). HRMS (ESI) m/z: Calcd for $C_{23}H_{28}N_4O_4SCl$ [M+H]: 491.1520; Found: 491.1511.

4.2.5.5 Synthesis of Enantioenriched p-Br Sulfonimidamides

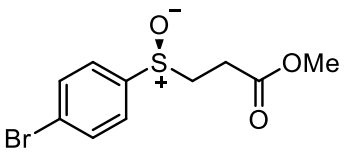
Methyl 3-((4-bromophenyl)thio)propanoate (285)



Methyl acrylate (2.00 mL, 22.0 mmol, 1.1 equiv) and sodium acetate (247 mg, 3.0 mmol, 0.15 equiv) were added to 4-bromobenzenethiol **284** (3.78 g, 20.0 mmol, 1 equiv) in THF:H_2O (1:1, 67 mL, 0.3 M) at 25 °C and stirred for 18 h. Sat. aq. $NaHCO_3$ (50 mL) was added and the aqueous mixture was extracted with EtOAc (3 × 60 mL) before being washed with brine (60 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give sulfide **285** (5.08, 92%) as a white solid. R_f 0.18 (5% Et_2O in pentane). mp = 52–54 °C. IR (film)/cm^{-1} 2997, 2950, 2844, 1737, 1474, 1435, 1359, 1245, 1217, 1195, 1172, 1092, 1008, 811. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.6 Hz, 2H, 2 × Ar-H), 7.23 (d, *J* = 8.6 Hz, 2H, 2 × Ar-H), 3.68 (s, 3H, OCH$_3$), 3.15 (t, *J* = 7.4 Hz, 2H, SCH$_2$), 2.62 (t, *J* = 7.4 Hz, 2H, SCH$_2$C*H*$_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5 (C=O), 134.6 (Ar-C$_q$), 132.2 (2 ×

Ar-C), 131.8 (2 × Ar-C), 120.8 (Ar-C_q), 52.0 (OCH_3), 34.2 (SCH_2), 29.3 (SCH_2CH_2). Analytical data (NMR, IR, mp) in agreement with those reported in the literature.[339]

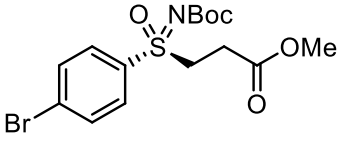
Methyl (*S*)-3-((4-bromophenyl)sulfinyl)propanoate (286)



Procedure adapted from Jackson and co-workers.[211,212] A solution of $VO(acac)_2$ (16 mg, 0.06 mmol, 1 mol%) in $CHCl_3$ (1.5 mL) was added dropwise to a solution of (*S*,*E*)-2-(((1-hydroxy-3,3-dimethylbutan-2-yl)imino)methyl)-4,6-diiodophenol (42 mg, 0.09 mmol, 1.5 mol%) in $CHCl_3$ (1.5 mL) and stirred at 25 °C for 30 min. Sulfide **285** (1.65 g, 6.0 mmol, 1.0 equiv) and $CHCl_3$ (3 mL) were added and the reaction mixture cooled to 0 °C. H_2O_2 (30% in H_2O, 736 µL, 7.2 mmol, 1.2 equiv) was added dropwise and the mixture left to vigorously stir at 0 °C for 72 h. Sat. aq. $Na_2S_2O_3$ (30 mL) was added and the aqueous mixture was extracted with $CHCl_3$ (3 × 30 mL) and washed with brine (40 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (40% EtOAc in pentane) afforded sulfoxide **286** (1.19 g, 68%, 99% *ee*) as a white solid. R_f 0.23 (40% EtOAc in pentane). mp = 79–80 °C. IR (film)/cm^{-1} 3050, 2997, 2948, 2916, 2846, 1728, 1571, 1472, 1435, 1415, 1388, 1239, 1170, 1131, 1060, 1034, 1005, 893, 826, 762, 732, 718. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.5 Hz, 2H, 2 × Ar-H), 7.49 (d, *J* = 8.6 Hz, 2H, 2 × Ar-H), 3.67 (s, 3H, OCH_3), 3.23 (ddd, *J* = 13.2, 8.2, 6.8 Hz, 1H, SC*H*H), 2.94 (ddd, *J* = 13.4, 8.0, 5.7 Hz, 1H, SCH*H*), 2.84 (ddd, *J* = 17.2, 8.1, 6.8 Hz, 1H, SCH_2CHH), 2.56 (ddd, *J* = 17.2, 8.2, 5.7 Hz, 1H, SCH_2CHH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6 (C=O), 142.2 (Ar-C_q), 132.7 (2 × Ar-C), 125.8 (Ar-C_q), 125.8 (2 × Ar-C), 52.3 (SCH_2), 51.3 (OCH_3), 26.1 (SCH_2CH_2). HRMS (Voltage EI+) *m/z* Calcd for $C_{10}H_{11}O_3S^{79}Br$ [M]: 289.9612; Found: 289.9607. $[\alpha]^{23}_D$ = –98 (c 1.0, $CHCl_3$). HPLC conditions: Chiralpak IA column, 90:10 *n*hexane:*i*PrOH, flow rate: 1 mL min^{-1}, 35 °C, UV detection wavelength: 250 nm, **286** retention time: 19 min.

Synthesis of racemic sample for HPLC analysis prepared by *m*CPBA oxidation to afford sulfoxide ***rac*-286** (5.09 g, 87%) as a white solid with characterisation data in accordance with the above. HPLC conditions: Chiralpak IA column, 90:10 *n*hexane:*i*PrOH, flow rate: 1 mL min^{-1}, 35 °C, UV detection wavelength: 250 nm, ***rac*-286** retention times: 19 & 21 min.

Methyl (*S*)-3-(4-bromo-*N*-(*tert*-butoxycarbonyl)phenylsulfonimidoyl)propanoate (287)

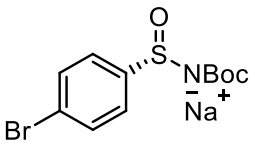


Procedure adapted from Bull, Luisi and co-workers.[150] Magnesium oxide (659 mg, 16.4 mmol, 4.0 equiv), *tert*-butyl carbamate (720 mg, 6.2 mmol, 1.5 equiv), bis(acetoxy)iodobenzene (1.98 g, 6.2 mmol, 1.5 equiv) and $Rh_2(OAc)_4$ (45 mg, 0.10 mmol, 2.5 mol%) were added to a solution of sulfoxide **286** (1.19 g,

4.1 mmol, 1 equiv) in CH_2Cl_2 (40 mL, 0.1 M) at room temperature, heated to 40 °C and stirred for 18 h. The reaction mixture was cooled to room temperature and filtered through celite and concentrated under reduced pressure. Purification by flash column chromatography (25% EtOAc in pentane) afforded sulfoximine **287** (1.45 g, 87%, 99% *ee*) as a white solid. R_f 0.15 (25% EtOAc in pentane). mp = 100–101 °C. IR (film)/cm^{-1} 2978, 1740, 1699, 1669, 1390, 1274, 1252, 1155, 1110. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.78 (m, 2H, 2 × Ar-H), 7.77–7.73 (m, 2H, 2 × Ar-H), 3.76–3.65 (m, 1H, SC*H*H), 3.63 (s, 3H, OCH_3), 3.58 (dd, *J* = 6.3, 5.5 Hz, 1H, SCH*H*), 2.81 (qdd, *J* = 17.3, 8.9, 6.2 Hz, 2H, SCH_2CH_2), 1.38 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0 (C=O), 157.3 (C=O), 136.0 (Ar-C_q), 133.0 (Ar-C_q), 129.6 (2 × Ar-C), 129.4 (2 × Ar-C), 81.0 ($C(CH_3)_3$), 52.4 (OCH_3), 51.6 (SCH_2), 27.9 ($C(CH_3)_3$), 27.1 (SCH_2CH_2). HRMS (ESI) m/z: Calcd for $C_{15}H_{21}NO_5S^{81}Br$ [M+H]: 408.0303; Found: 408.0296. $[\alpha]^{23}_D$ = +44 (c 1.0, $CHCl_3$). HPLC conditions: Chiralpak IA column, 93:7 *n*hexane:*i*PrOH, flow rate: 1 mL min^{-1}, 35 °C, UV detection wavelength: 250 nm, **287** retention time: 22 min.

Synthesis of racemic sample for HPLC analysis prepared by using the above procedure using sulfoxide ***rac*-286** to afford sulfoximine ***rac*-287** (6.24 g, 95%) as a white solid with characterisation data in accordance with the above. HPLC conditions: Chiralpak IA column, 93:7 *n*hexane:*i*PrOH, flow rate: 1 mL min^{-1}, 35 °C, UV detection wavelength: 250 nm, ***rac*-287** retention times: 22 & 37 min.

Sodium (*S*)-((4-bromophenyl)sulfinyl)(*tert*-butoxycarbonyl)amide (288)

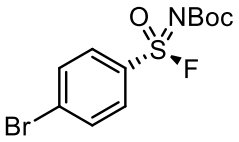


5 M NaOH in MeOH (718 µL, 3.6 mmol, 1.05 equiv) was added to a solution of sulfoximine **287** (1.39 g, 3.4 mmol, 1.0 equiv) in CH_2Cl_2 (25 mL, 0.1 M) at 25 °C and stirred for 1 h. The suspension was then filtered to collect the white precipitate and washed with CH_2Cl_2 (100 mL). Excess solvent was removed under reduced pressure to afford sulfinamide salt **288** as a white solid (1.05 g, 90%, 99% *ee*). mp = 227–229 °C. IR (film)/cm^{-1} 2981, 1640, 1468, 1390, 1271, 1162, 998, 834, 760; ^{1}H NMR (400 MHz, D_2O) δ 7.71–7.65 (m, 2H, 2 × Ar-H), 7.56–7.50 (m, 2H, 2 × Ar-H), 1.40 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, D_2O) δ 165.9 (C=O), 145.6 (Ar-C_q), 132.0 (2 × Ar-C), 126.5 (2 × Ar-C), 124.6 (Ar-C_q), 79.7 ($C(CH_3)_3$), 27.7 ($C(CH_3)_3$). HRMS (ESI) m/z: Calcd for $C_{11}H_{13}NO_3S^{79}Br$ $[M]^-$: 317.9800; Found: 317.9806. Further characterisation was carried out after washing ~20 mg with sat. aq. NH_4Cl. Sulfinamide: $[\alpha]^{23}_D$ = +88 (c 1.0, $CDCl_3$). HPLC conditions: Chiralpak IA column, 95:5 *n*hexane:*i*PrOH, flow rate: 1 mL min^{-1}, 35 °C, UV detection wavelength: 250 nm, **288** retention time: 21 min.

Synthesis of racemic sample for HPLC analysis prepared by using the above procedure using sulfoximine ***rac*-287** to afford sulfinamide salt ***rac*-288** (786 mg, 89%) as a white solid with characterisation data in accordance with the above. HPLC conditions: Chiralpak IA column,

95:5 *n*hexane:*i*PrOH, flow rate: 1 mL min^{-1}, 35 °C, UV detection wavelength: 250 nm, ***rac*-288** retention times: 19 & 21 min.

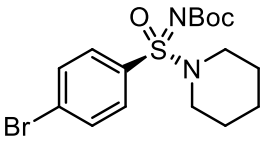
***tert*-Butyl ((4-bromophenyl)fluoro(oxo)-λ^6-sulfaneylidene)carbamate (289)**



Prepared according to general procedure O using selectfluor (850 mg, 2.4 mmol), potassium acetate (235 mg, 2.4 mmol) and sulfinamide salt **288** (411 mg, 1.2 mmol) affording sulfonimidoyl fluoride **289** (175 mg, quant., 92% *ee*) as a colourless oil. IR (film)/cm^{-1} 3093, 2982, 1707, 1573, 1331, 1252, 1148, 1069, 1010, 909, 857, 756. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01–7.94 (m, 2H, 2 × Ar-H), 7.79–7.74 (m, 2H, 2 × Ar-H), 1.53 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.7 (C=O), 132.5 (2 × Ar-C), 132.3 (Ar-C_q), 130.8 (Ar-C_q), 129.2 (2 × Ar-C), 82.7 ($C(CH_3)_3$), 27.5 ($C(CH_3)_3$). ^{19}F NMR (377 MHz, $CDCl_3$) δ 69.8. $[\alpha]^{23}_D$ = –15 (c 1.7, $CDCl_3$). HPLC conditions: Chiralpak IA column, 98:2 *n*hexane:*i*PrOH, flow rate: 1 mL min^{-1}, 35 °C, UV detection wavelength: 250 nm, **289** retention time: 12 min.

Synthesis of racemic sample for HPLC analysis prepared by using the above procedure using sulfinamide salt ***rac*-288** to afford sulfonimidoyl fluoride ***rac*-289** (175 mg, quant.) as a colourless oil with characterisation data in accordance with the above. HPLC conditions: Chiralpak IA column, 98:2 *n*hexane:*i*PrOH, flow rate: 1 mL min^{-1}, 35 °C, UV detection wavelength: 250 nm, ***rac*-289** retention times: 11 & 12 min.

***tert*-Butyl ((4-bromophenyl)(oxo)(piperidin-1-yl)-λ^6-sulfaneylidene)carbamate (290)**

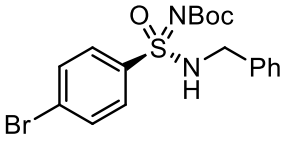


Prepared according to general procedure P using piperidine (50 μL, 0.50 mmol), triethylamine (70 μL, 0.50 mmol), LiBr (43 mg, 0.50 mmol) and sulfonimidoyl fluoride **289** (85 mg, 0.25 mmol). Purification by flash column chromatography (SiO_2, 2% Et_2O in CH_2Cl_2) afforded sulfonimidamide **290** (88 mg, 87%, 90% *ee*) as a white solid. R_f = 0.36 (2% Et_2O in CH_2Cl_2). mp = 171–172 °C. IR (film)/cm^{-1} 2974, 2937, 2855, 1674, 1572, 1275, 1151, 931, 745. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75–7.71 (m, 2H, 2 × Ar-H), 7.69–7.65 (m, 2H, 2 × Ar-H), 3.20–3.05 (m, 4H, 2 × NCH_2), 1.67–1.59 (m, 4H, 2 × NCH_2CH_2), 1.51–1.44 (m, 2H, $NCH_2CH_2CH_2$), 1.42 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4 (C=O), 135.8 (Ar-C_q), 132.3 (2 × Ar-C), 129.2 (2 × Ar-C), 127.9 (Ar-C_q), 80.4 ($C(CH_3)_3$), 46.6 (2 × NCH_2), 28.0 ($C(CH_3)_3$), 25.2 (2 × NCH_2CH_2), 23.5 ($NCH_2CH_2CH_2$). HRMS (ESI) m/z: Calcd for $C_{16}H_{24}N_2O_3S^{79}Br$ [M+H]: 403.0691; Found: 403.0703. $[\alpha]^{23}_D$ = –8 (c 0.5, CH_2Cl_2). HPLC conditions: Chiralpak IA column, 95:5 *n*hexane:*i*PrOH, flow rate: 1 mL min^{-1}, 35 °C, UV detection wavelength: 250 nm, **290** retention time: 25 min.

Synthesis of racemic sample for HPLC analysis prepared by using the above procedure on a 0.1 mmol scale using sulfonimidoyl fluoride ***rac*-289** to afford sulfonimidamide ***rac*-290** (20 mg,

50%) as a white solid with characterisation data in accordance with the above. HPLC conditions: Chiralpak IA column, 95:5 *n*hexane:*i*PrOH, flow rate: 1 mL min^{-1}, 35 °C, UV detection wavelength: 250 nm, ***rac*-290** retention times: 16 & 25 min.

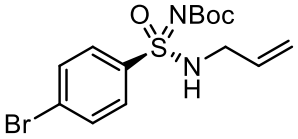
tert-Butyl (*R*)-((benzylamino)(4-bromophenyl)(oxo)-λ⁶-sulfaneylidene)carbamate (291)



Prepared according to general procedure P using benzylamine (55 μL, 0.50 mmol), triethylamine (70 μL, 0.50 mmol), LiBr (43 mg, 0.50 mmol) and sulfonimidoyl fluoride **289** (85 mg, 0.25 mmol). Purification by flash column chromatography (SiO_2, 2% Et_2O in CH_2Cl_2) afforded sulfonimidamide **291** (66 mg, 62%, 92% *ee*) as a white solid. R_f = 0.23 (2% Et_2O in CH_2Cl_2). mp = 154–156 °C. IR (film)/cm^{-1} 3086, 1684, 1572, 1282, 1159, 1088, 909. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79–7.75 (m, 2H, 2 × Ar-H), 7.63–7.60 (m, 2H, 2 × Ar-H), 7.30–7.25 (m, 3H, 3 × Ar-H), 7.23–7.17 (m, 2H, 2 × Ar-H), 6.89 (s, 1H, NH), 4.25 (d, *J* = 14.1 Hz, 1H, NHC*H*H), 3.99 (d, *J* = 14.1 Hz, 1H, NHCH*H*), 1.38 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.8 (C=O), 138.0 (Ar-C_q), 135.6 (Ar-C_q), 132.3 (2 × Ar-C), 129.4 (2 × Ar-C), 128.7 (2 × Ar-C), 128.2 (Ar-C_q), 128.0 (3 × Ar-C), 80.9 (*C*$(CH_3)_3$), 45.5 ($NHCH_2$), 28.0 ($C(CH_3)_3$). HRMS (ESI) m/z: Calcd for $C_{18}H_{22}N_2O_3S^{79}Br$ [M+H]: 425.0535; Found: 425.0531. $[\alpha]^{23}_D$ = +6 (c 0.5, CH_2Cl_2). HPLC conditions: Chiralpak ID column, 90:10 *n*hexane:*i*PrOH, flow rate: 1 mL min^{-1}, 35 °C, UV detection wavelength: 254 nm, **291** retention time: 15 min.

Synthesis of racemic sample for HPLC analysis prepared by using the above procedure on half the scale using sulfonimidoyl fluoride ***rac*-289** to afford sulfonimidamide ***rac*-291** (20 mg, 47%) as a white solid with characterisation data in accordance with the above. HPLC conditions: Chiralpak ID column, 90:10 *n*hexane:*i*PrOH, flow rate: 1 mL min^{-1}, 35 °C, UV detection wavelength: 254 nm, ***rac*-291** retention times: 15 & 20 min.

tert-Butyl (*R*)-((allylamino)(4-bromophenyl)(oxo)-λ⁶-sulfaneylidene)carbamate (292)

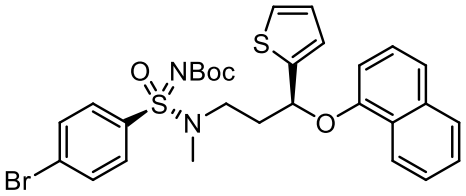


Prepared according to general procedure P using allylamine (38 μL, 0.50 mmol), triethylamine (70 μL, 0.50 mmol), LiBr (43 mg, 0.50 mmol) and sulfonimidoyl fluoride **289** (85 mg, 0.25 mmol). Purification by flash column chromatography (SiO_2, 5% Et_2O in CH_2Cl_2) afforded sulfonimidamide **292** (70 mg, 75%, 90% *ee*) as a white solid. R_f = 0.31 (5% Et_2O in CH_2Cl_2). mp = 86–88 °C. IR (film)/cm^{-1} 3243, 2981, 1677, 1572, 1390, 1282, 1159, 1088, 905. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.81 (m, 2H, 2 × Ar-H), 7.70–7.66 (m, 2H, 2 × Ar-H), 6.36 (s, 1H, NH), 5.73 (dddd, *J* = 17.1, 10.2, 6.1, 5.5 Hz, 1H, NCH_2CH), 5.22 (dq, *J* = 17.1, 1.5 Hz, 1H, NCH_2CHCHH), 5.15 (dq, *J* = 10.2, 1.3 Hz, 1H, NCH_2CHCHH), 3.68 (dd, *J* = 15.1, 5.5 Hz, 1H, NC*H*H), 3.46 (dd, *J* = 15.0, 6.1 Hz, 1H, NCH*H*), 1.41 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (101 MHz,

$CDCl_3$) δ 156.7 (C=O), 138.0 (Ar-C_q), 132.4 (2 × Ar-C), 132.3 ($NCH_2CH{=}CH_2$), 129.5 (2 × Ar-C), 128.2 (Ar-C_q), 118.2 (NCH_2CHCH_2), 80.8 ($C(CH_3)_3$), 43.9 (NCH_2), 28.0 ($C(CH_3)_3$). HRMS (ESI) m/z: Calcd for $C_{14}H_{20}N_2O_3SBr$ [M+H]: 375.0378; Found: 375.0380. $[\alpha]^{23}_D$ = +8 (c 0.5, CH_2Cl_2). HPLC conditions: Chiralpak IA column, 97:3 *n*hexane:*i*PrOH, flow rate: 1 mL min^{-1}, 35 °C, UV detection wavelength: 250 nm, **292** retention time: 21 min.

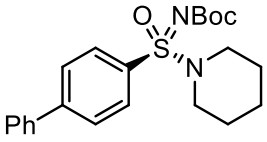
Synthesis of racemic sample for HPLC analysis prepared by using the above procedure on half the scale using sulfonimidoyl fluoride ***rac*-289** to afford sulfonimidamide ***rac*-292** (18 mg, 48%) as a white solid with characterisation data in accordance with the above. HPLC conditions: Chiralpak IA column, 97:3 *n*hexane:*i*PrOH, flow rate: 1 mL min^{-1}, 35 °C, UV detection wavelength: 250 nm, ***rac*-292** retention times: 21 & 29 min.

tert-Butyl ((*R*)-(4-bromophenyl)(methyl((*S*)-3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propyl)amino)(oxo)-λ^6-sulfaneylidene)carbamate (293)



Prepared according to general procedure P using duloxetine hydrochloride (167 mg, 0.50 mmol), triethylamine (140 μL, 1.0 mmol), LiBr (43 mg, 0.50 mmol) and sulfonimidoyl fluoride **289** (85 mg, 0.25 mmol). Purification by flash column chromatography (SiO_2, 5% Et_2O in CH_2Cl_2) followed by (SiO_2, 10% acetone in pentane) afforded sulfonimidamide **293** (124 mg, 80%) as a single diastereomer as a white solid. R_f 0.15 (10% acetone in pentane). mp = 57–60 °C. IR (film)/cm^{-1} 2978, 1744, 1673, 1572, 1461, 1394, 1263, 1151, 1088, 775. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 6.9, 3.0 Hz, 1H, Ar-H), 7.82–7.76 (m, 1H, Ar-H), 7.70 (d, *J* = 8.6 Hz, 2H, 2 × Ar-H), 7.56–7.46 (m, 4H, 4 × Ar-H), 7.41 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.32–7.24 (m, 1H, Ar-H), 7.22 (dd, *J* = 5.1, 1.2 Hz, 1H, Ar-H), 7.10 (d, *J* = 3.4 Hz, 1H, Ar-H), 6.94 (dd, *J* = 5.0, 3.5 Hz, 1H, Ar-H), 6.83 (d, *J* = 7.7 Hz, 1H, Ar-H), 5.74 (dd, *J* = 8.3, 4.3 Hz, 1H, OC*H*Ar), 3.52 (ddd, *J* = 13.7, 8.2, 5.3 Hz, 1H, NC*H*H), 3.37 (dt, *J* = 14.2, 7.4 Hz, 1H, NCH*H*), 2.87 (s, 3H, NCH_3), 2.51 (dtd, *J* = 13.5, 8.0, 5.2 Hz, 1H, NCH_2CHH), 2.40–2.28 (m, 1H, NCH_2CHH), 1.45 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.3 (C=O), 152.8 (Ar-C_q), 144.3 (Ar-C_q), 136.6 (Ar-C_q), 134.5 (Ar-C_q), 132.3 (2 × Ar-C), 128.9 (2 × Ar-C), 128.0 (Ar-C_q), 127.6 (Ar-C), 126.7 (Ar-C), 126.3 (Ar-C), 125.9 (Ar-C_q), 125.7 (Ar-C), 125.3 (Ar-C), 124.98 (Ar-C), 124.97 (Ar-C), 121.8 (Ar-C), 120.9 (Ar-C), 107.0 (Ar-C), 80.5 ($C(CH_3)_3$), 73.4 (O*C*HAr), 47.0 (NCH_2), 37.4 (NCH_3), 35.4 (NCH_2CH_2), 28.1 ($C(CH_3)_3$). HRMS (ESI) m/z: Calcd for $C_{29}H_{31}N_2O_4S_2{}^{79}BrNa$ [M+Na]: 637.0806; Found: 637.0815. $[\alpha]^{23}_D$ = +10 (c 0.5, CH_2Cl_2).

***tert*-Butyl (*R*)-([1,1'-biphenyl]-4-yl(oxo)(piperidin-1-yl)-λ^6-sulfaneylidene)carbamate (294)**

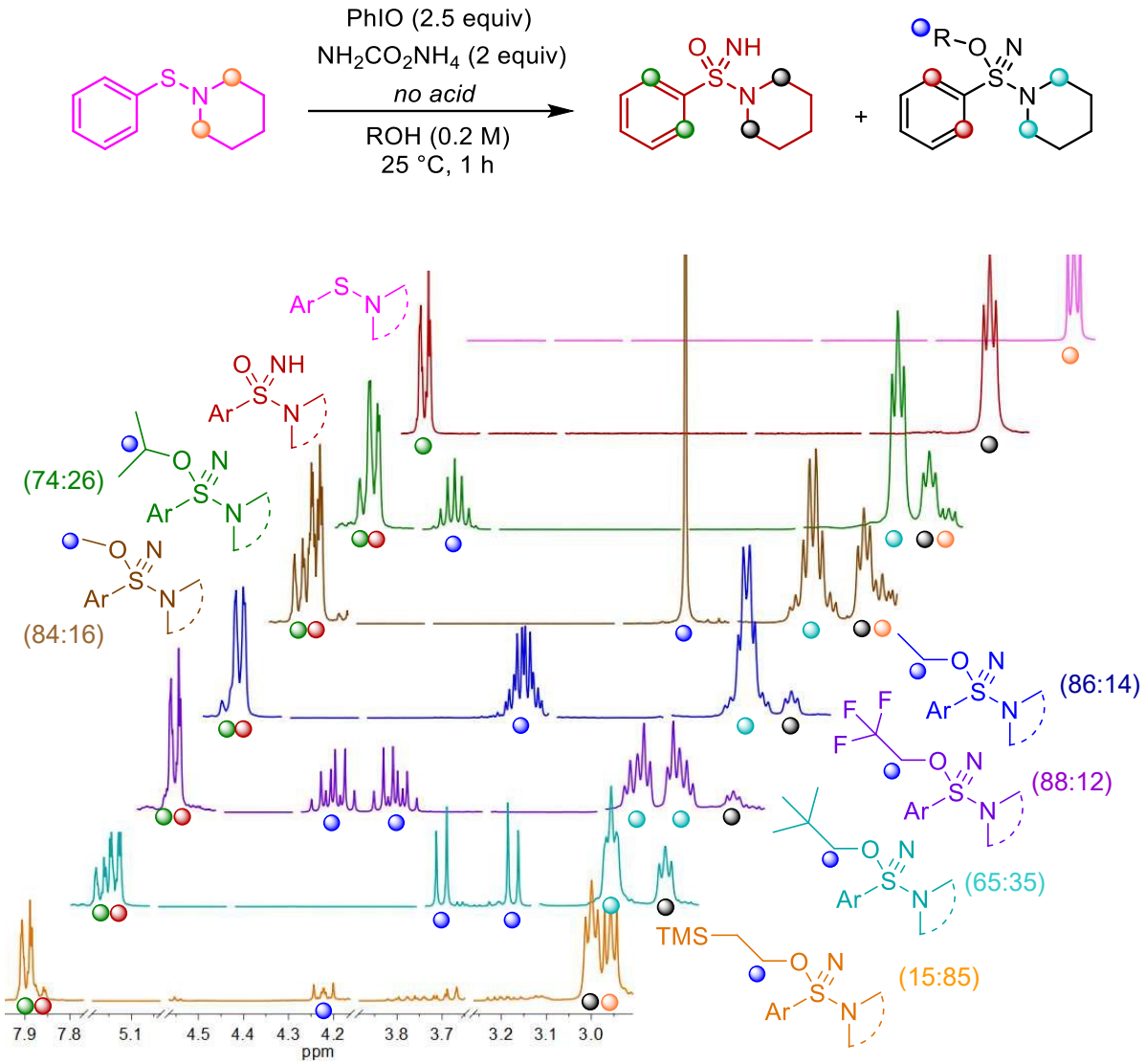


Procedure adapted from Pemberton and co-workers.[133] Sulfonimidamide **290** (40 mg, 0.10 mmol, 1 equiv), phenylboronic acid (18 mg, 0.15 mmol, 1.5 equiv), potassium carbonate (28 mg, 0.20 mmol, 2 equiv) and 1,1'-bis(di-*tert*-butylphosphino)ferrocene palladium dichloride (6.5 mg, 0.01 mmol, 10 mol%) was added to a glass vial with MeCN:H_2O (1:1, 0.5 mL, 0.2 M) and was degassed before being stirred and heated to 80 °C for 2 h. Aq. sat. NH_4Cl (10 mL) was added and the aqueous mixture extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, 3% Et_2O in CH_2Cl_2) afforded sulfonimidamide **294** (37 mg, 91%, 90% *ee*) as a colourless oil. R_f 0.38 (3% Et_2O in CH_2Cl_2). IR (film)/cm^{-1} 2974, 2937, 2855, 1669, 1595, 1453, 1394, 1248, 1148, 928, 760. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95–7.90 (m, 2H, 2 × Ar-H), 7.76–7.70 (m, 2H, 2 × Ar-H), 7.64–7.60 (m, 2H, 2 × Ar-H), 7.52–7.46 (m, 2H, 2 × Ar-H), 7.45–7.39 (m, 1H, Ar-H), 3.17 (q, *J* = 4.9 Hz, 4H, 2 × NCH_2), 1.67 (p, *J* = 5.6 Hz, 4H, 2 × NCH_2CH_2), 1.52–1.46 (m, 2H, $NCH_2CH_2CH_2$), 1.43 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7 (C=O), 145.7 (Ar-C_q), 139.2 (Ar-C_q), 135.1 (Ar-C_q), 129.0 (2 × Ar-C), 128.5 (Ar-C), 128.2 (2 × Ar-C), 127.6 (2 × Ar-C), 127.3 (2 × Ar-C), 80.1 ($C(CH_3)_3$), 46.6 (2 × NCH_2), 28.1 ($C(CH_3)_3$), 25.2 (2 × NCH_2CH_2), 23.6 ($NCH_2CH_2CH_2$). HRMS (ESI) m/z: Calcd for $C_{22}H_{29}N_2O_3S$ [M+H]: 401.1893; Found: 401.1906. $[\alpha]^{23}_D$ = –7 (c 1.0, $CDCl_3$). HPLC conditions: Chiralpak IA column, 95:5 *n*hexane:*i*PrOH, flow rate: 1 mL min^{-1}, 35 °C, UV detection wavelength: 250 nm, **294** retention time: 32 min.

Synthesis of racemic sample for HPLC analysis prepared by using the above procedure on a 0.05 mmol using racemic sulfonimidamide ***rac*-290** scale to afford sulfonimidamide ***rac*-294** (~10 mg) as a colourless oil with characterisation data in accordance with the above. HPLC conditions: Chiralpak IA column, 95:5 *n*hexane:*i*PrOH, flow rate: 1 mL min^{-1}, 35 °C, UV detection wavelength: 250 nm, ***rac*-294** retention times: 27 & 32 min.

4.2.6 Selected Spectra

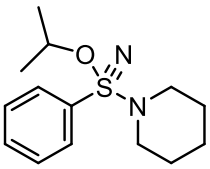
4.2.6.1 Isolated ^{1}H NMR of Alkoxy-amino-λ^6-sulfanenitrile Species



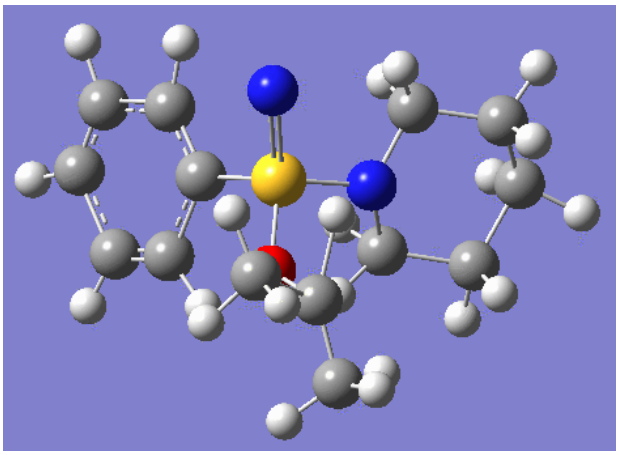
Scheme 4.1: Comparison of ^{1}H NMR spectra (400 MHz in $CDCl_3$) of the starting sulfenamide and product sulfonimidamide and λ^6-sulfanenitriles. Numbers in brackets indicate the ratio between λ^6-sulfanenitrile and sulfonimidamide

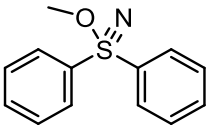
4.2.6.2 Gaussian 09 Calculations of Alkoxy-amino-λ^6-sulfanenitrile Species

The assignment of the experimentally observed vibrational stretch of both compound **112** and **165** at 1363 cm^{-1} and 1331 cm^{-1} respectively was confirmed as being the S≡N triple bond stretch.[1] DFT (density functional theory) calculations for lowest energy structure optimisation and vibrational frequency at the B3LYP level of theory using the 6-31G d,p basis set was undertaken. The computed S≡N bond stretch was shown to occur at 1368 cm^{-1} and 1332 cm^{-1} for compounds **112** and **165** respectively, showing good agreement with that obtained in this study and as reported by Yoshimura.[262]

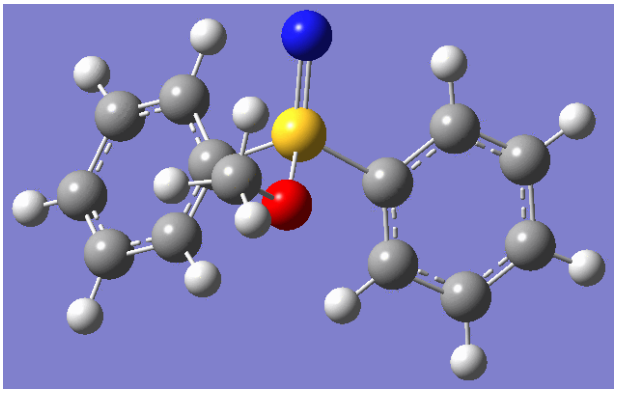


112



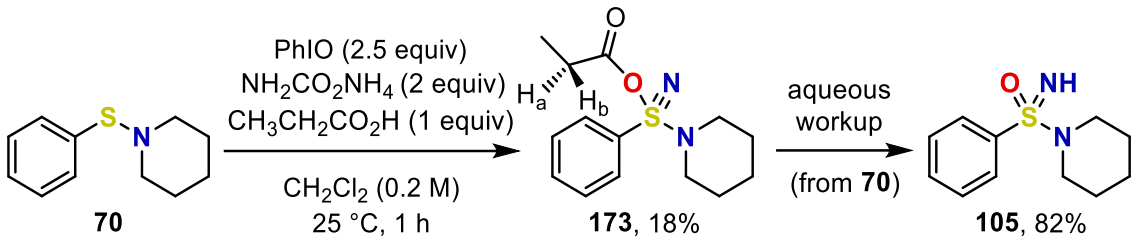


165



[1]Gaussian 09, Revision A.02, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2016.

*4.2.6.3 Spectra of Acetoxy-amino-λ^6-sulfanenitrile **173***



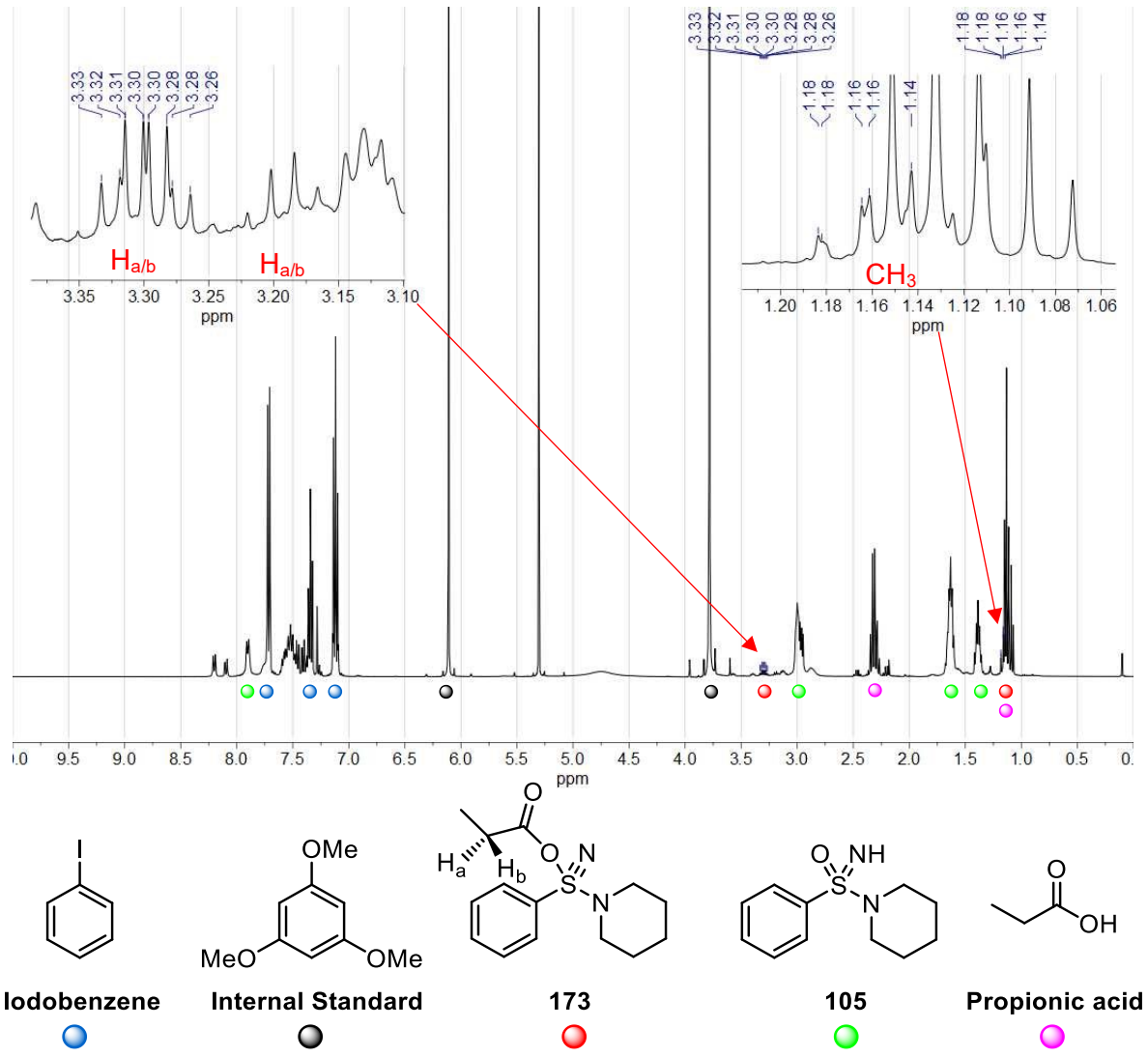


Figure 4.1: ^{1}H NMR (400 MHz, $CDCl_3$) analysis of **173** with signals attributed to the CH_2 and CH_3 protons expanded.

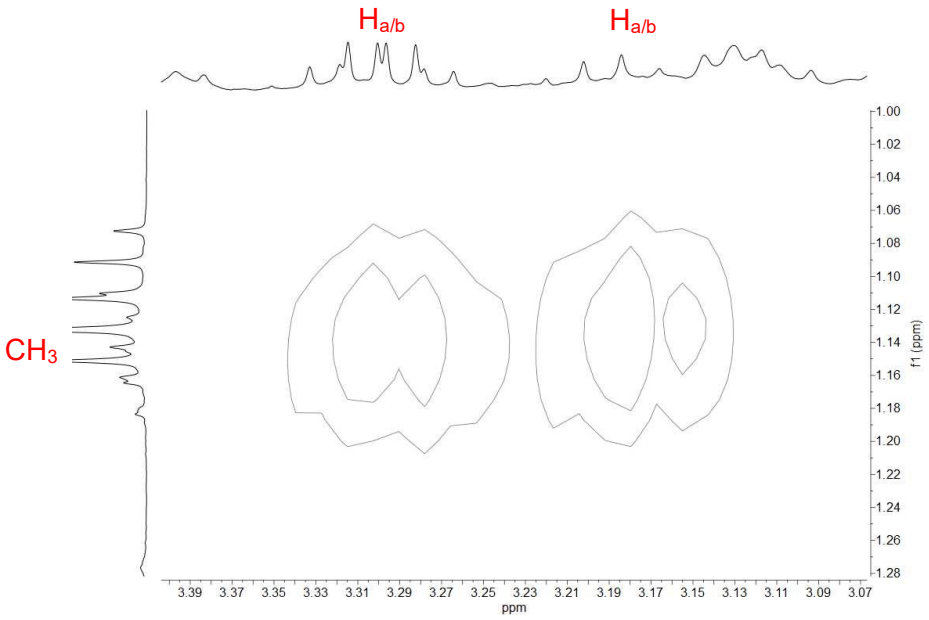


Figure 4.2: COSY (400 MHz, $CDCl_3$) analysis of **173** with signals attributed to the CH_2 and CH_3 showing correlation.

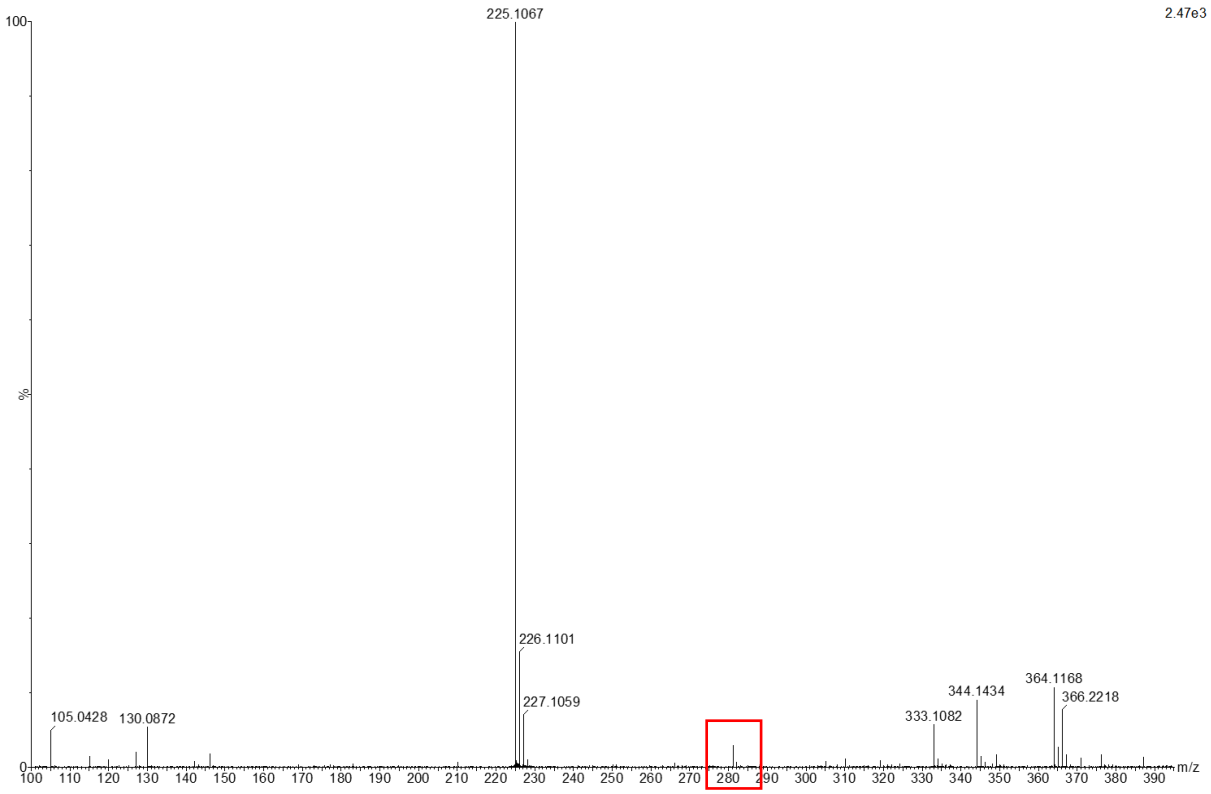


Figure 4.3: HRMS experiment on the crude sample of **173**.

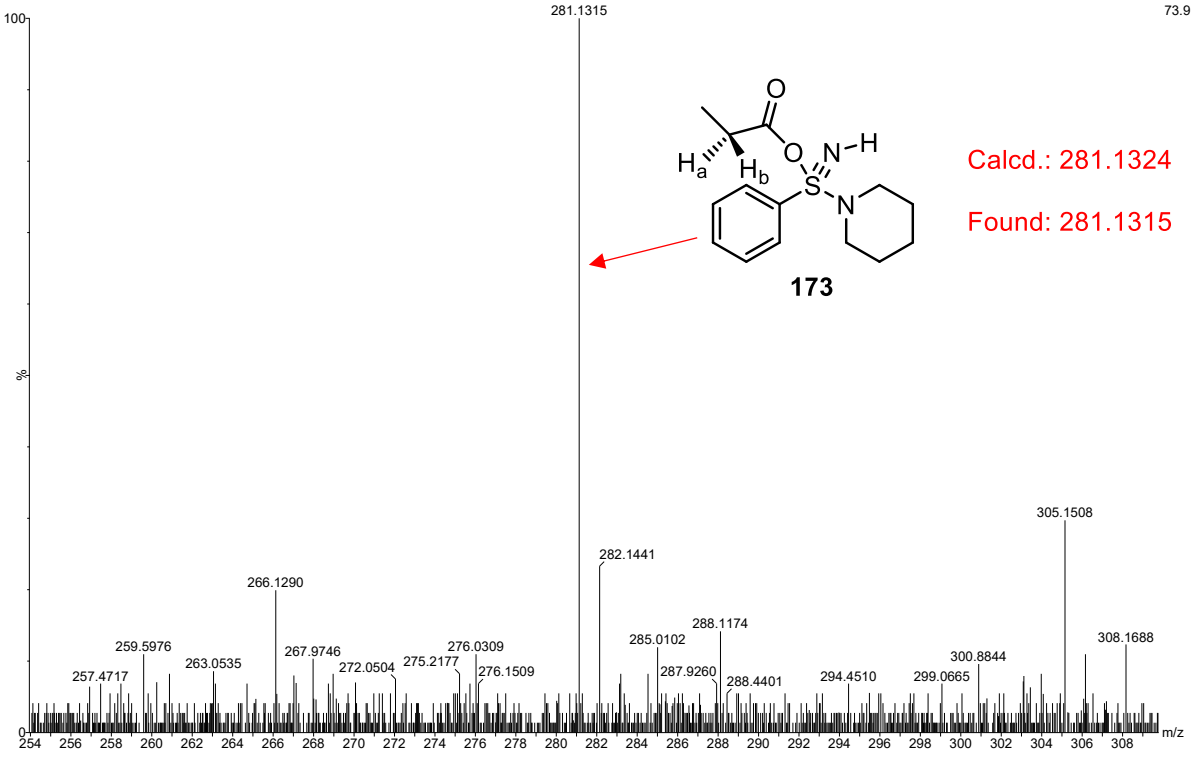


Figure 4.4: HRMS experiment on the crude sample of **173**. – inside red box of Figure 4.3.

4.2.6.4 Evidence of ^{18}O Incorporation in ***105***

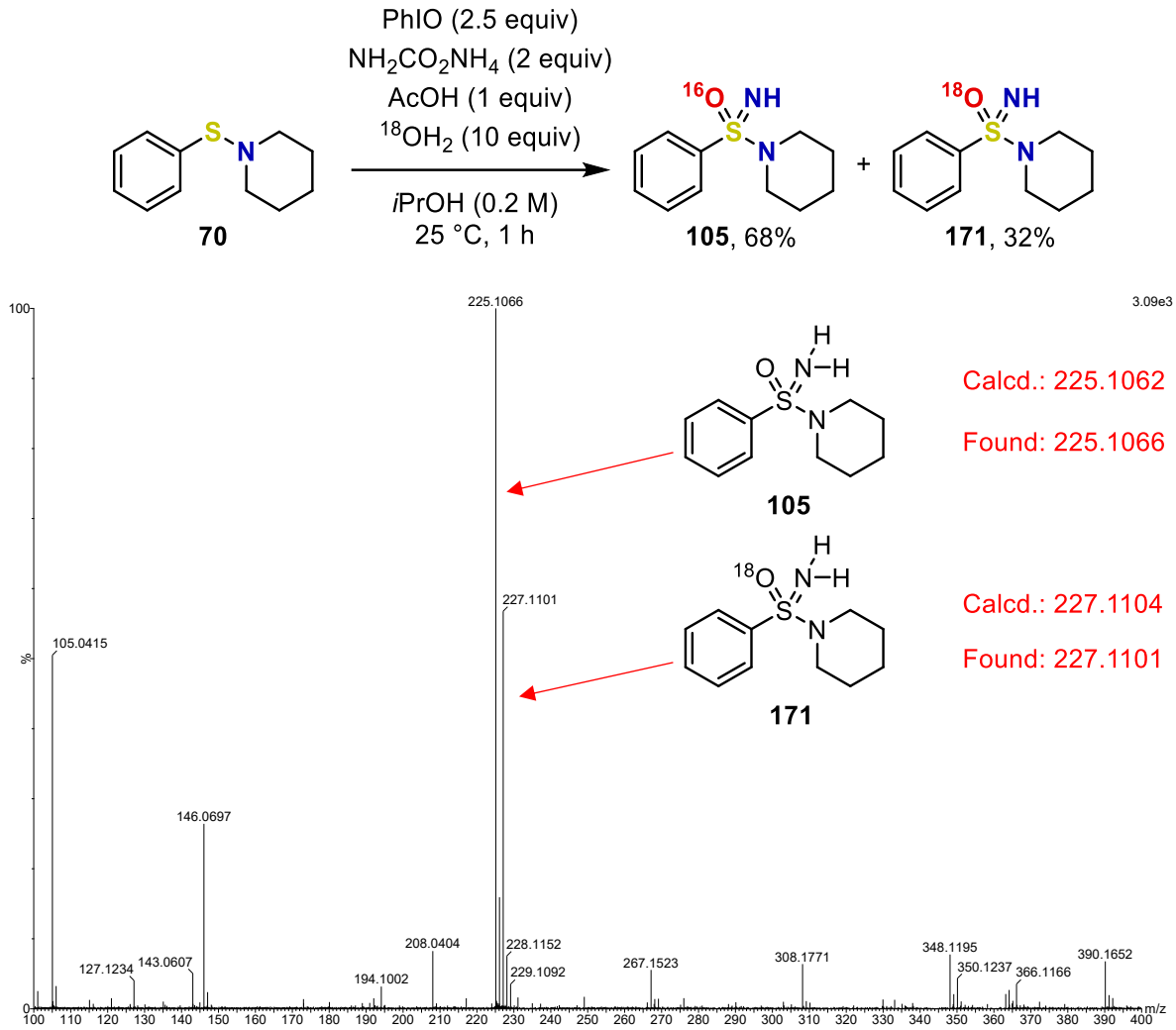


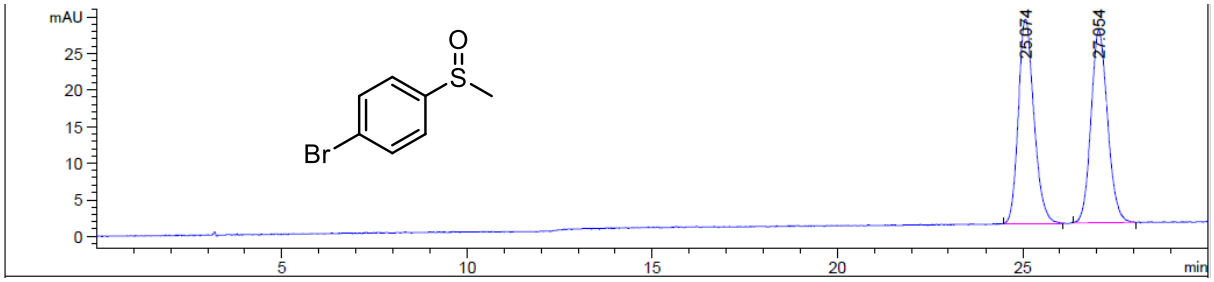
Figure 4.5: HRMS experiment on the mixture of **105** and **171** showing ^{18}O incorporation (68:32; ^{16}O:^{18}O).

4.2.6.5 HPLC Spectra

(*S*)-(–)-*p*-Bromophenyl methyl sulfoxide ((*S*)-12)

Conditions: Chiralpak IE column, 90:10 *n*hexane:*i*PrOH, flow rate: 1 mL min^{-1}, 35 °C, UV detection wavelength: 250 nm.

12

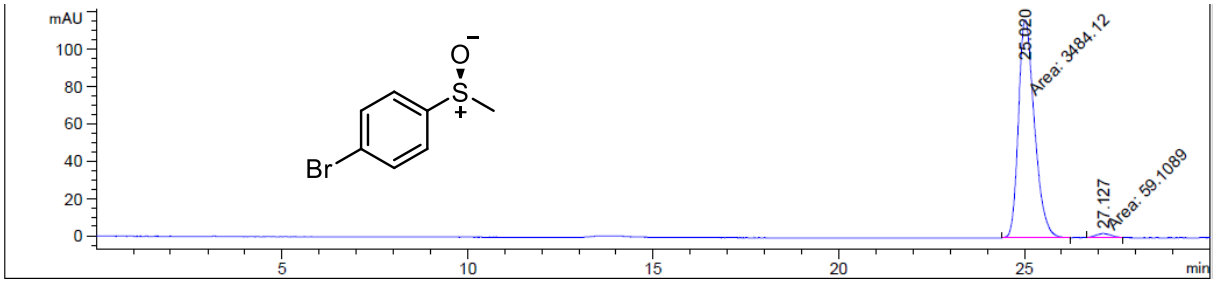


Signal 1: DAD1 A, Sig=250,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.074	BB	0.4455	816.78119	27.90198	50.0515
2	27.054	BB	0.4750	815.10089	26.34421	49.9485
Totals :				1631.88208	54.24619	

(*S*)-12

$[\alpha]^{23}_{D}$ = –95 (c 1.8, acetone).



Signal 1: DAD1 A, Sig=250,10 Ref=360,100

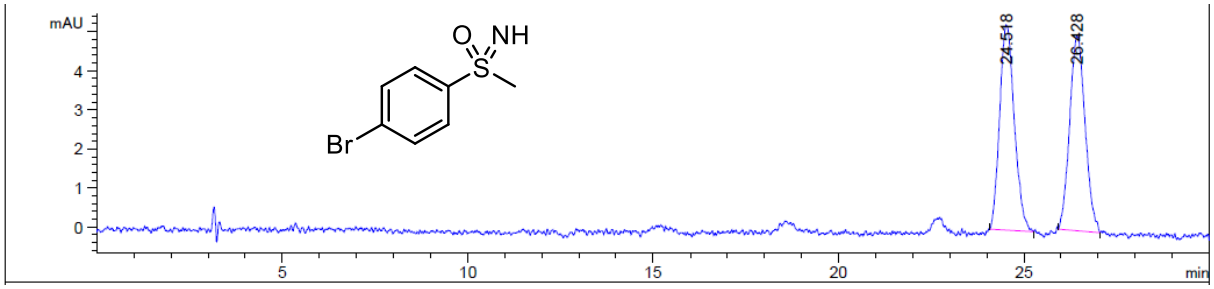
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.020	MM	0.4981	3484.12158	116.57963	98.3318
2	27.127	MM	0.4619	59.10894	2.13265	1.6682
Totals :				3543.23052	118.71228	

***ee* = 97%**

(*S*)-(4-Bromophenyl)(imino)(methyl)-λ^6-sulfanone ((*S*)-13)

Conditions: Chiralpak IE column, 90:10 *n*hexane:*i*PrOH, flow rate: 1 mL min^{-1}, 35 °C, UV detection wavelength: 254 nm.

13

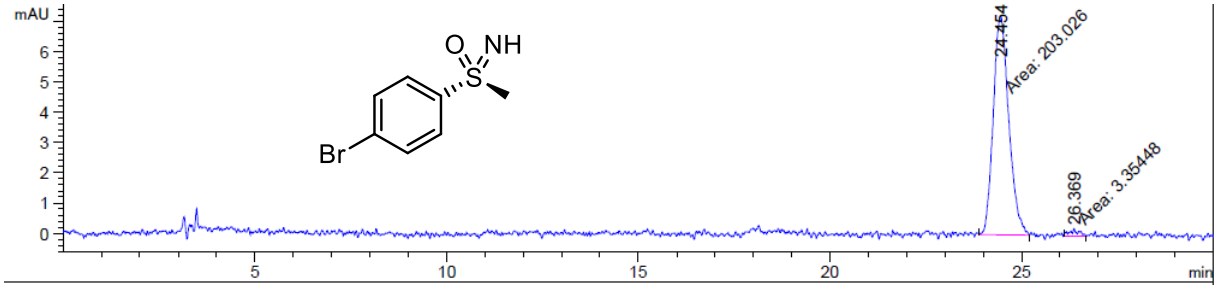


Signal 2: DAD1 B, Sig=254,10 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.518	BB	0.3349	144.67506	5.26026	50.1330
2	26.428	BB	0.3655	143.90746	4.97417	49.8670
Totals :				288.58252	10.23444	

(*S*)-13

$[\alpha]^{23}_D$ = +15 (c = 0.93, $CHCl_3$).



Signal 2: DAD1 B, Sig=254,10 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.454	MM	0.4683	203.02577	7.22577	98.3746
2	26.369	MM	0.2579	3.35448	2.16758e-1	1.6254
Totals :				206.38025	7.44253	

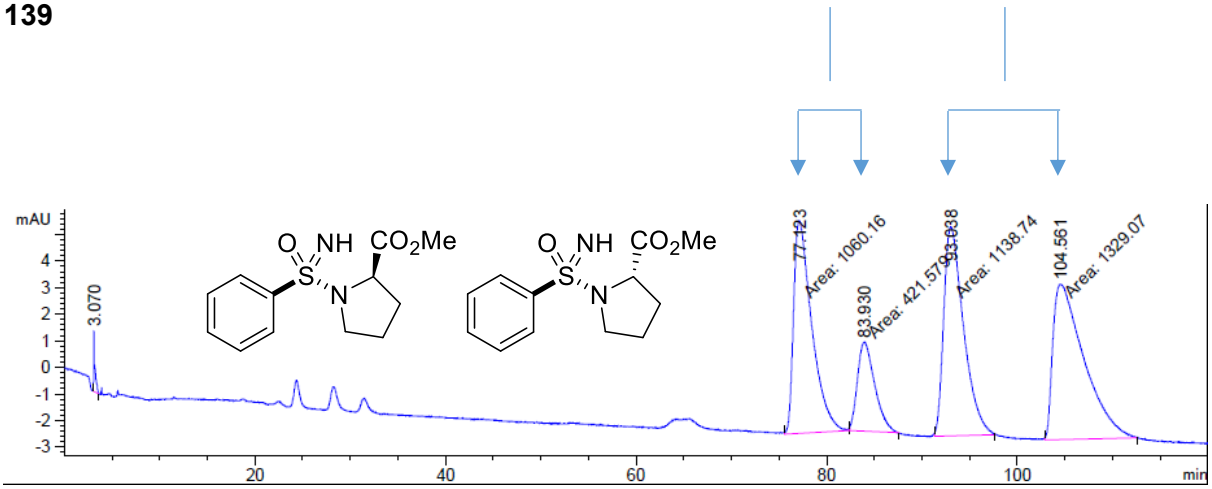
***ee* = 97%**

Methyl (phenylsulfonimidoyl)prolinate (139)

Conditions: Chiralpak IA column, 97:3 *n*-hexane:*i*PrOH, flow rate: 1 mL min-1, 35 °C, UV detection wavelength: 250 nm.

Diastereoisomers

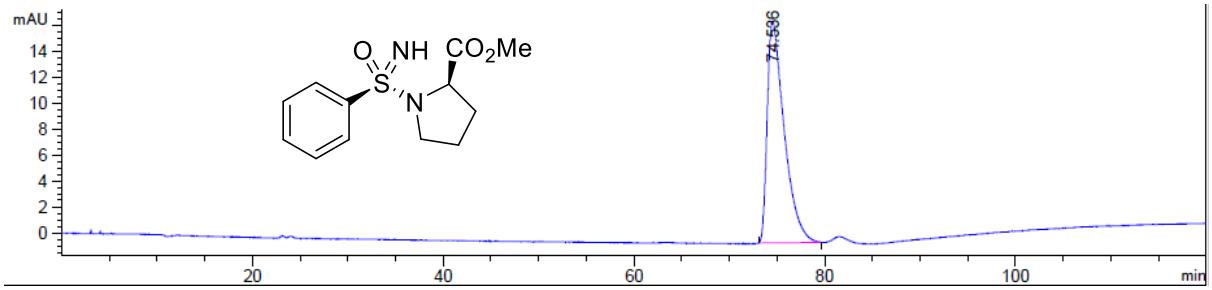
139



Signal 1: DAD1 A, Sig=250,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.070	BB	0.1186	20.79201	2.27564	0.5237
2	77.123	MM	2.2061	1060.15686	8.00923	26.7019
3	83.930	MM	2.0963	421.57919	3.35184	10.6182
4	93.038	MM	2.4125	1138.74487	7.86691	28.6812
5	104.561	MM	3.7867	1329.07336	5.84980	33.4750
Totals :				3970.34630	27.35342	

Methyl ((*R*)-phenylsulfonimidoyl)-*D*-prolinate (139c)

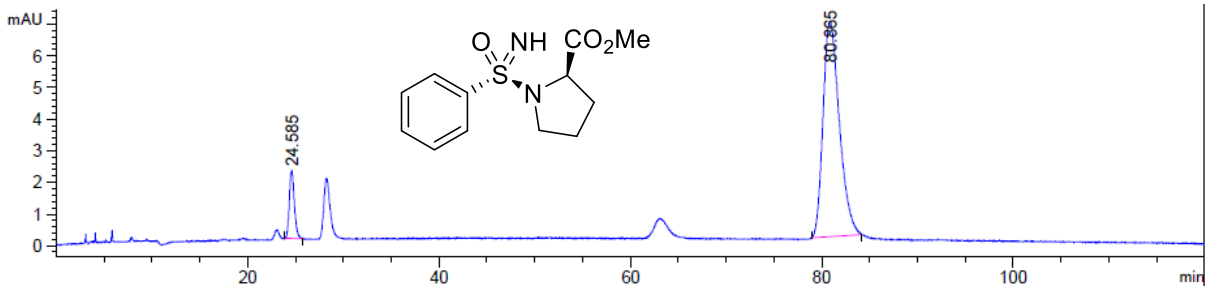


Signal 1: DAD1 A, Sig=250,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	74.536	BB	1.4607	2115.78564	17.08560	100.0000
Totals :				2115.78564	17.08560	

***ee* = >99%**

Methyl ((*S*)-phenylsulfonimidoyl)-*D*-prolinate (139d)

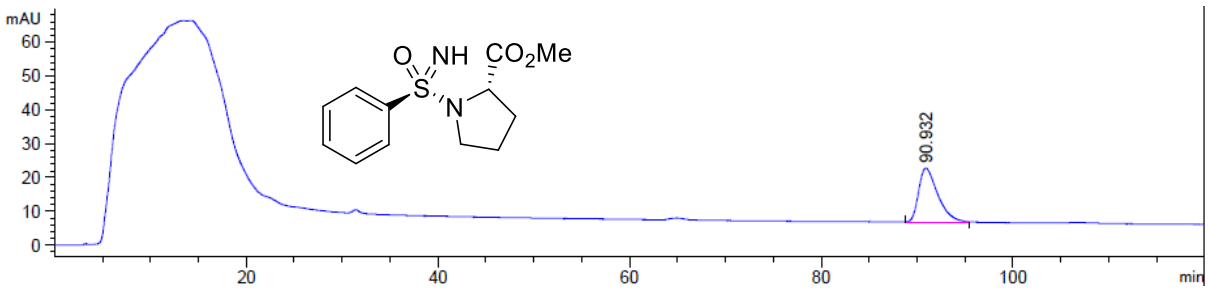


Signal 1: DAD1 A, Sig=250,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.585	BB	0.4554	78.63645	2.14655	8.8955
2	80.865	BB	1.3860	805.36920	6.80871	91.1045
Totals :				884.00565	8.95526	

***ee* = >99%**

Methyl ((*R*)-phenylsulfonimidoyl)-*L*-prolinate (139a)

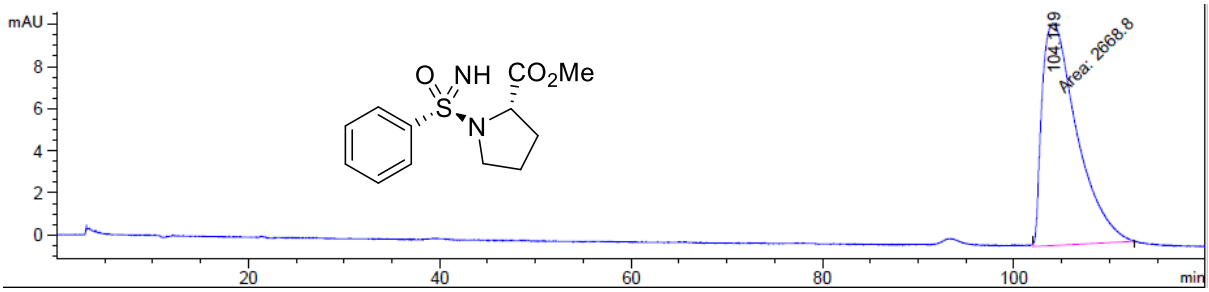


Signal 1: DAD1 A, Sig=250,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	90.932	BB	1.6191	2183.67578	15.87166	100.0000
Totals :				2183.67578	15.87166	

***ee* = >99%**

Methyl ((S)-phenylsulfonimidoyl)-L-prolinate (139b)



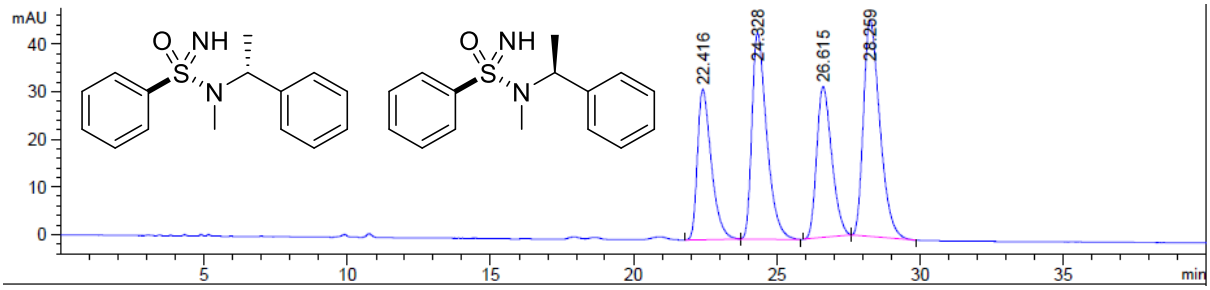
Signal 1: DAD1 A, Sig=250,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	104.149	MM	4.2128	2668.79541	10.55825	100.0000
Totals :				2668.79541	10.55825	

***ee* = >99%**

N-Methyl-*N*-(1-phenylethyl)benzenesulfonimidamide (140)

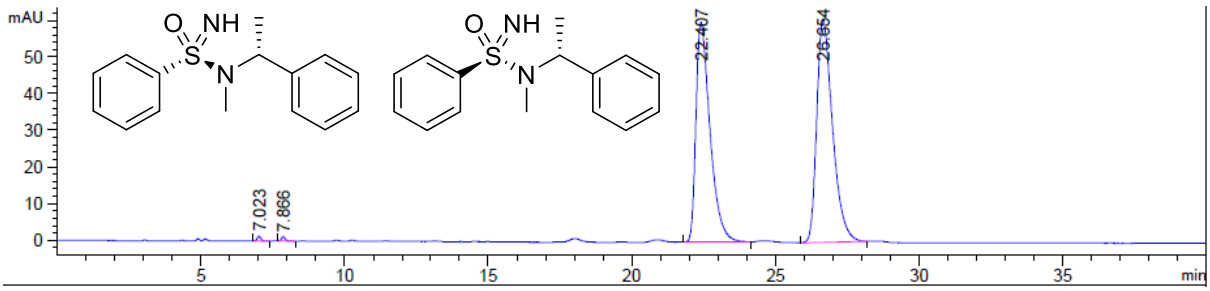
Conditions: Chiralpak IA column, 93:7 *n*-hexane:*i*PrOH, flow rate: 1 mL min-1, 35 °C, UV detection wavelength: 250 nm.



Signal 1: DAD1 A, Sig=250,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.416	BB	0.5106	1060.33118	31.51244	19.0016
2	24.328	BB	0.5409	1552.28735	43.23514	27.8177
3	26.615	BB	0.5566	1158.20898	31.67783	20.7556
4	28.259	BB	0.6060	1809.38391	45.49650	32.4250
Totals :				5580.21143	151.92190	

N-Methyl-*N*-((*R*)-1-phenylethyl)benzenesulfonimidamide (140c and 140d)

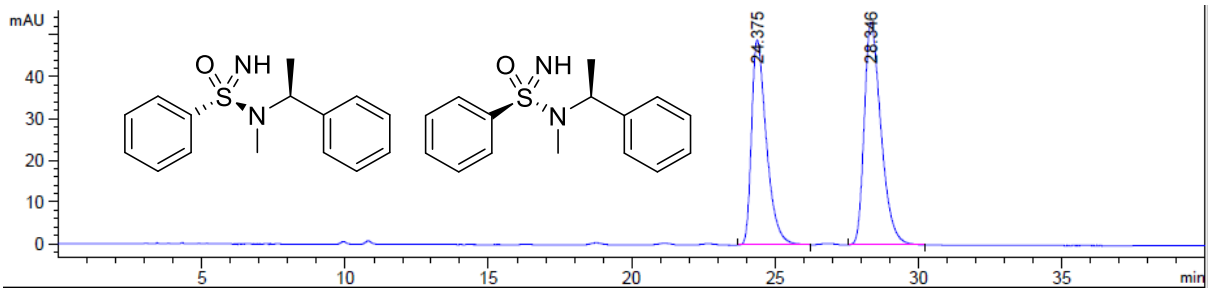


Signal 1: DAD1 A, Sig=250,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.023	BB	0.1324	12.02993	1.37104	0.2745
2	7.866	BB	0.1454	10.92052	1.14394	0.2492
3	22.407	BB	0.5086	2033.92236	59.82642	46.4138
4	26.654	BB	0.5780	2325.27686	60.82158	53.0625
Totals :				4382.14968	123.16297	

***ee* = >99%**

N-Methyl-*N*-((*S*)-1-phenylethyl)benzenesulfonimidamide (140a and 140b)



Signal 1: DAD1 A, Sig=250,10 Ref=360,100

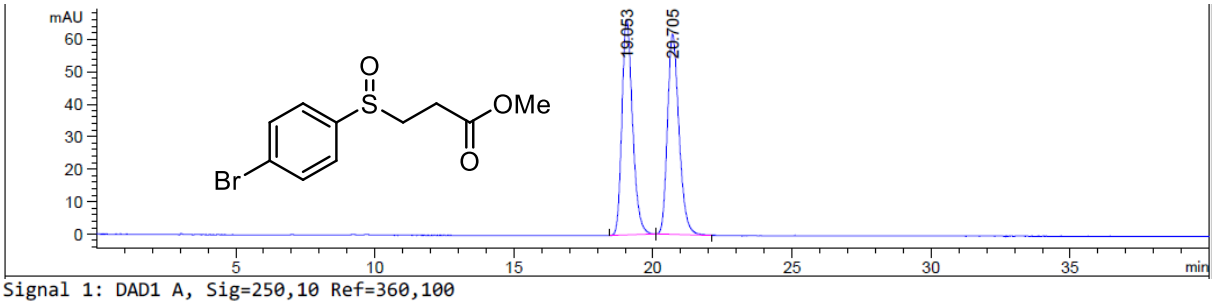
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.375	BB	0.5438	1766.48157	49.09108	44.9271
2	28.346	BB	0.6117	2165.40405	53.33170	55.0729
Totals :				3931.88562	102.42278	

***ee* = >99%**

Methyl (*S*)-3-((4-bromophenyl)sulfinyl)propanoate (286)

Conditions: Chiralpak IA column, 90:10 *n*hexane:*i*PrOH, flow rate: 1 mL min^{-1}, 35 °C, UV detection wavelength: 250 nm.

***rac*-286**

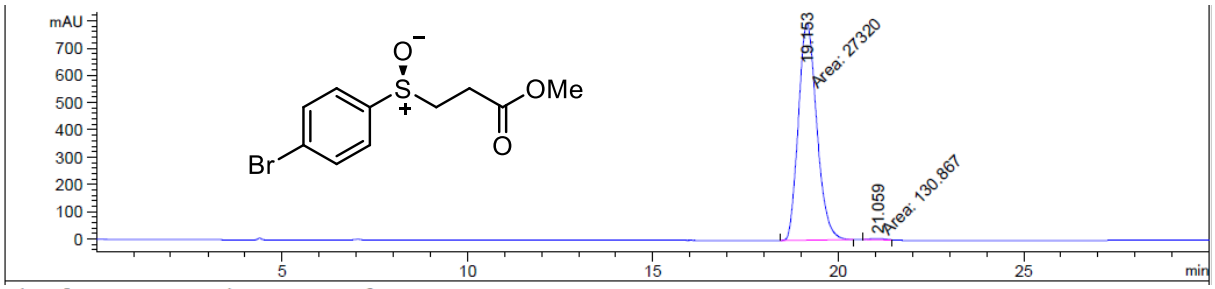


Signal 1: DAD1 A, Sig=250,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.053	BB	0.4091	1772.47925	66.46956	49.9404
2	20.705	BB	0.4420	1776.70703	61.69768	50.0596
Totals :				3549.18628	128.16724	

286

$[\alpha]^{23}_{D}$ = –98 (c 1.0, $CHCl_3$).



Signal 1: DAD1 A, Sig=250,10 Ref=360,100

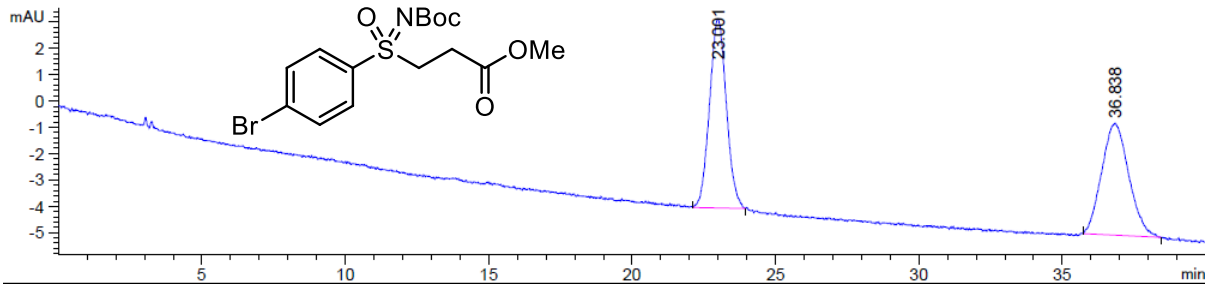
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.153	MM	0.5728	2.73200e4	794.92761	99.5233
2	21.059	MM	0.4381	130.86740	4.97806	0.4767
Totals :				2.74509e4	799.90567	

***ee* = 99%**

Methyl (*S*)-3-(4-bromo-*N*-(*tert*-butoxycarbonyl)phenylsulfonimidoyl)propanoate (287)

Conditions: Chiralpak IA column, 93:7 *n*hexane:*i*PrOH, flow rate: 1 mL min^{-1}, 35 °C, UV detection wavelength: 250 nm.

***rac*-287**

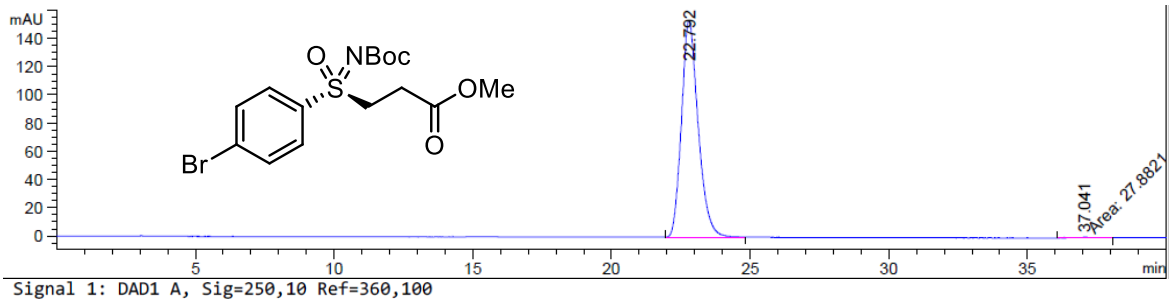


Signal 1: DAD1 A, Sig=250,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.001	BB	0.5177	292.65317	7.17716	51.1008
2	36.838	BB	0.7778	280.04456	4.25531	48.8992
Totals :				572.69772	11.43247	

287

$[\alpha]^{23}_{D}$ = +44 (c 1.0, $CHCl_3$)



Signal 1: DAD1 A, Sig=250,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.792	BB	0.6193	6407.31689	153.39117	99.5667
2	37.041	MM	0.9987	27.88206	4.65299e-1	0.4333
Totals :				6435.19896	153.85647	

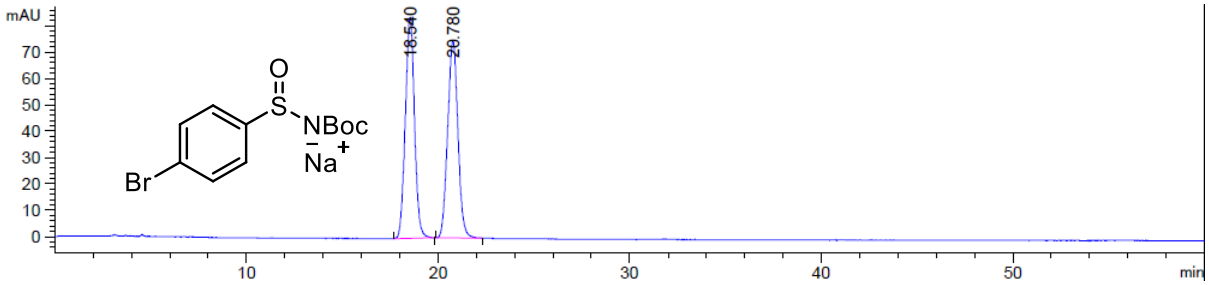
***ee* = 99%**

Sodium (*S*)-((4-bromophenyl)sulfinyl)(*tert*-butoxycarbonyl)amide (288)

The ee of the sulfinamide salt was tested by reprotonation to the sulfinamide with sat. aq. NH_4Cl.

Conditions: Chiralpak IA column, 95:5 *n*hexane:*i*PrOH, flow rate: 1 mL min^{-1}, 35 °C, UV detection wavelength: 250 nm.

***rac*-288**

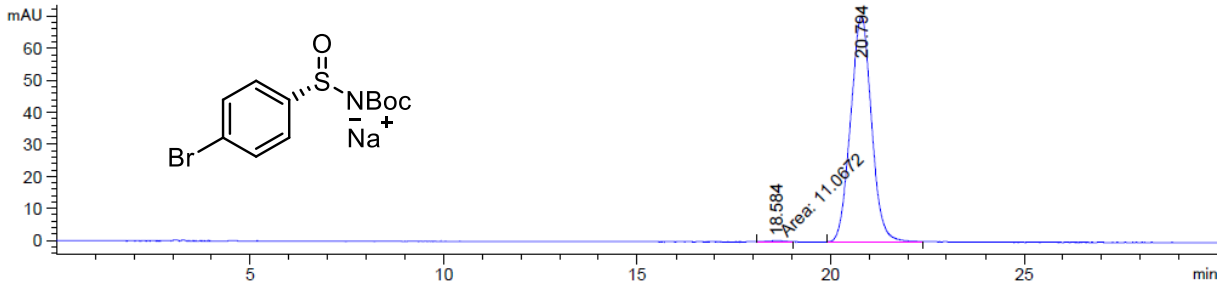


Signal 1: DAD1 A, Sig=250,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.540	BB	0.5101	2789.14917	83.83952	50.0487
2	20.780	BB	0.5762	2783.71631	74.80299	49.9513
Totals :				5572.86548	158.64250	

288

$[\alpha]^{23}_D$ = +88 (c 1.0, $CDCl_3$)



Signal 1: DAD1 A, Sig=250,10 Ref=360,100

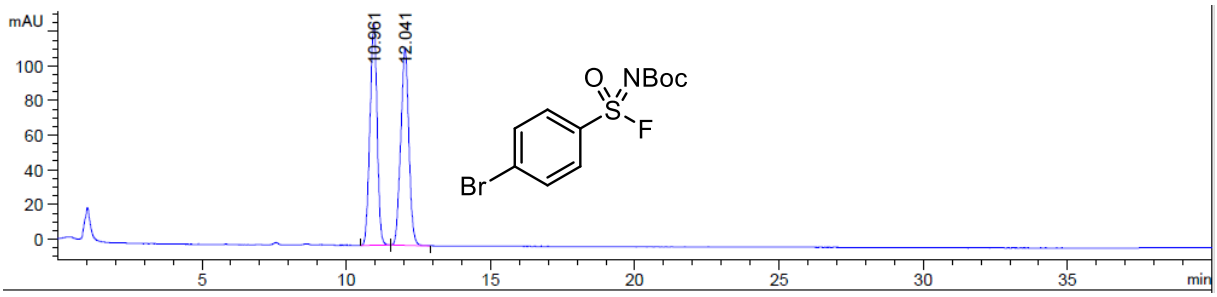
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.584	MM	0.4719	11.06724	3.90911e-1	0.4186
2	20.794	BB	0.5750	2633.01880	70.30122	99.5814
Totals :				2644.08604	70.69213	

***ee* = 99%**

***tert*-Butyl (*R*)-((4-bromophenyl)fluoro(oxo)-λ^6-sulfaneylidene)carbamate (289)**

Conditions: Chiralpak IA column, 98:2 *n*hexane:*i*PrOH, flow rate: 1 mL min^{-1}, 35 °C, UV detection wavelength: 250 nm.

***rac*-289**

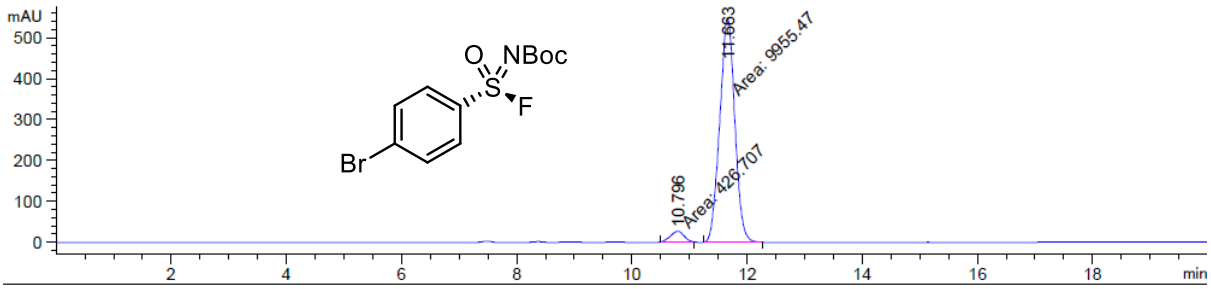


Signal 1: DAD1 A, Sig=250,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.961	BB	0.2623	2229.76563	128.59897	50.0398
2	12.041	BB	0.2921	2226.22266	113.86397	49.9602
Totals :				4455.98828	242.46294	

289

$[\alpha]^{23}_D$ = –15 (c 1.7, $CDCl_3$)



Signal 1: DAD1 A, Sig=250,10 Ref=360,100

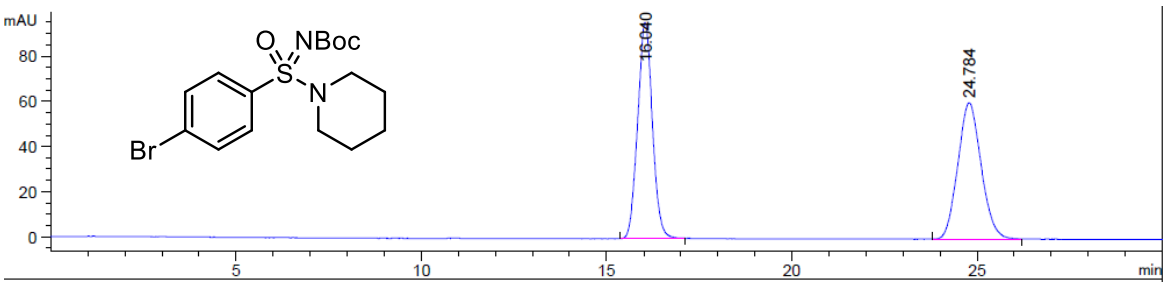
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.796	MM	0.2715	426.70654	26.19217	4.1100
2	11.663	MM	0.3022	9955.47168	549.06299	95.8900
Totals :				1.03822e4	575.25516	

***ee* = 92%**

***tert*-Butyl (*R*)-((4-bromophenyl)(oxo)(piperidin-1-yl)-λ^6-sulfaneylidene)carbamate (290)**

Conditions: Chiralpak IA column, 95:5 *n*hexane:*i*PrOH, flow rate: 1 mL min^{-1}, 35 °C, UV detection wavelength: 250 nm.

***rac*-290**

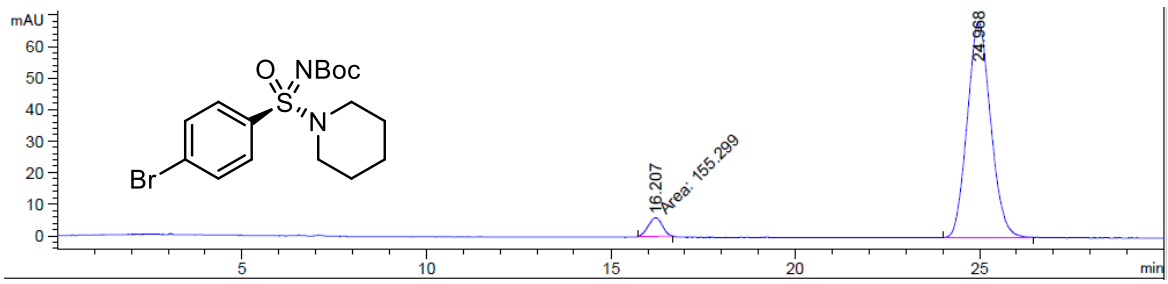


Signal 1: DAD1 A, Sig=250,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.040	BB	0.4242	2639.59253	95.57035	50.0593
2	24.784	BB	0.6478	2633.33691	60.26088	49.9407
Totals :				5272.92944	155.83123	

290

$[\alpha]^{23}_D$ = –8 (c 0.5, CH_2Cl_2)



Signal 1: DAD1 A, Sig=250,10 Ref=360,100

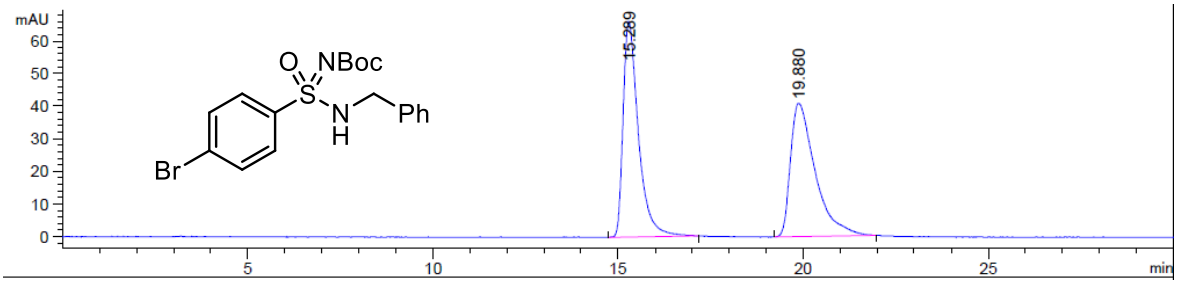
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.207	MM	0.4393	155.29939	5.89220	4.9157
2	24.968	BB	0.6367	3003.94165	68.35349	95.0843
Totals :				3159.24104	74.24569	

***ee* = 90%**

***tert*-Butyl (*R*)-((benzylamino)(4-bromophenyl)(oxo)-λ^6-sulfaneylidene)carbamate (291)**

Conditions: Chiralpak ID column, 90:10 *n*hexane:*i*PrOH, flow rate: 1 mL min^{-1}, 35 °C, UV detection wavelength: 254 nm.

***rac*-291**

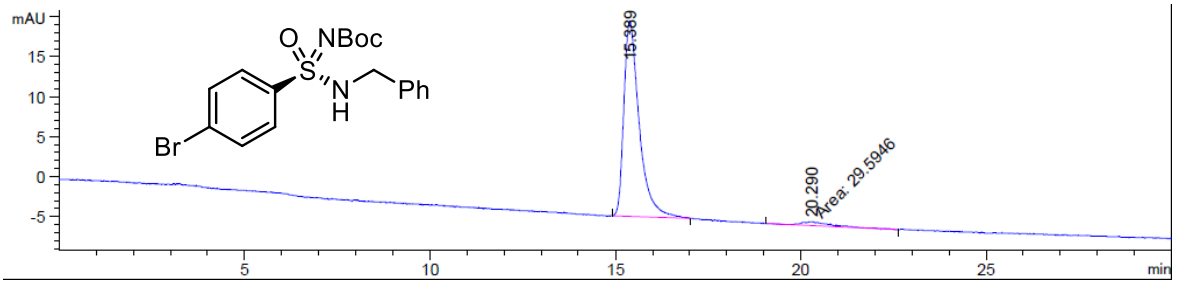


Signal 2: DAD1 B, Sig=254,10 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.289	BB	0.4308	1897.99060	66.13738	49.9878
2	19.880	BB	0.6643	1898.91638	40.85403	50.0122
Totals :				3796.90698	106.99141	

291

$[\alpha]^{23}_D$ = +6 (c 0.5, CH_2Cl_2)



Signal 2: DAD1 B, Sig=254,10 Ref=off

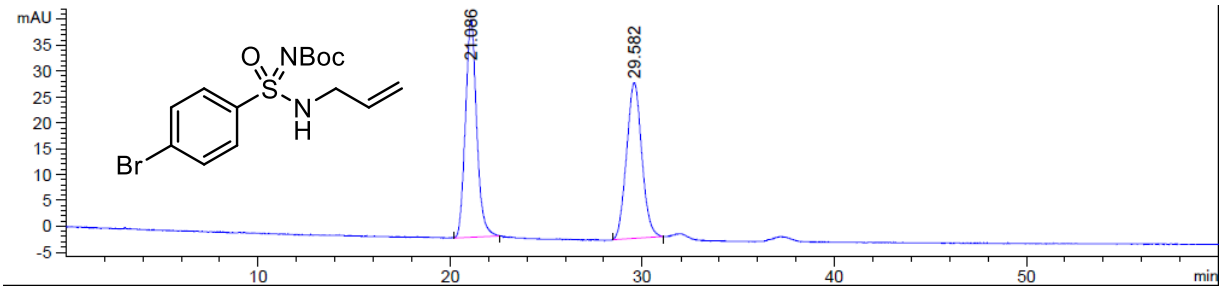
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.389	BB	0.4214	703.08716	24.45546	95.9608
2	20.290	MM	1.0244	29.59464	4.81516e-1	4.0392
Totals :				732.68180	24.93698	

***ee* = 92%**

***tert*-Butyl (*R*)-((allylamino)(4-bromophenyl)(oxo)-λ^6-sulfaneylidene)carbamate (292)**

Conditions: Chiralpak IA column, 97:3 *n*hexane:*i*PrOH, flow rate: 1 mL min^{-1}, 35 °C, UV detection wavelength: 250 nm.

***rac*-292**

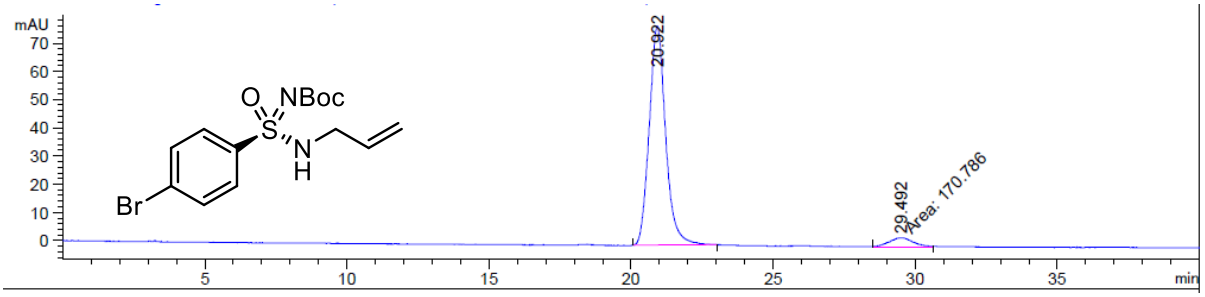


Signal 1: DAD1 A, Sig=250,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.086	BB	0.5924	1710.61499	42.06887	50.7446
2	29.582	BB	0.7395	1660.41260	30.10318	49.2554
Totals :				3371.02759	72.17204	

292

$[\alpha]^{23}_{D}$ = +8 (c 0.5, CH_2Cl_2)



Signal 1: DAD1 A, Sig=250,10 Ref=360,100

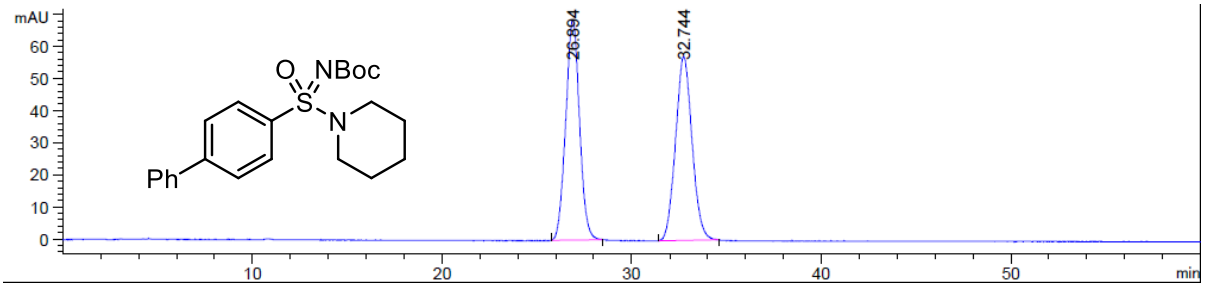
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.922	BB	0.5810	3122.61719	77.67725	94.8143
2	29.492	MM	0.9223	170.78593	3.08615	5.1857
Totals :				3293.40312	80.76340	

***ee* = 90%**

***tert*-Butyl (*R*)-([1,1'-biphenyl]-4-yl(oxo)(piperidin-1-yl)-λ^6-sulfaneylidene)carbamate (294)**

Conditions: Chiralpak IA column, 95:5 *n*hexane:*i*PrOH, flow rate: 1 mL min^{-1}, 35 °C, UV detection wavelength: 250 nm.

***rac*-294**

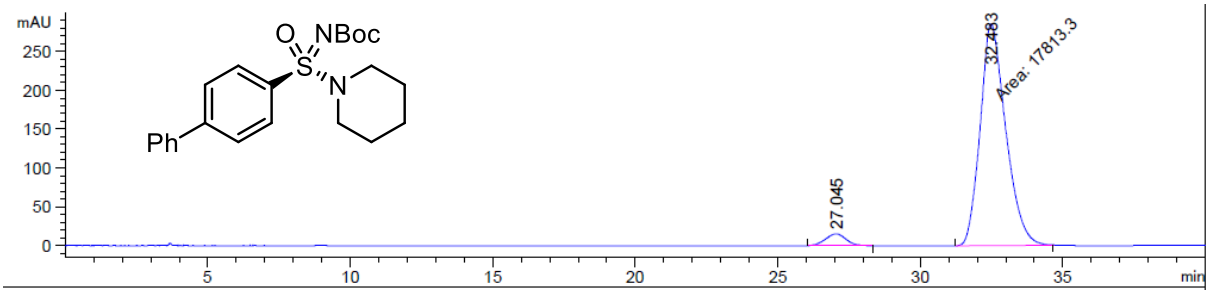


Signal 1: DAD1 A, Sig=250,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.894	BB	0.7426	3461.90698	68.61781	49.9489
2	32.744	BB	0.8816	3468.99438	57.19546	50.0511
Totals :				6930.90137	125.81327	

294

$[\alpha]^{23}_D = -7$ (c 1.0, $CDCl_3$).



Signal 1: DAD1 A, Sig=250,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.045	BB	0.6254	763.23010	15.26192	4.1086
2	32.483	MM	1.0390	1.78133e4	285.74695	95.8914
Totals :				1.85765e4	301.00886	

***ee* = 92%**

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