Strategies for the Synthesis of Oxetanes as Desirable Fragments for Drug Discovery

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Declaration

I declare that this thesis and the material presented within are my own work. Where other sources of information have been used, work by others has been reported or help was received, appropriate acknowledgement has been given.

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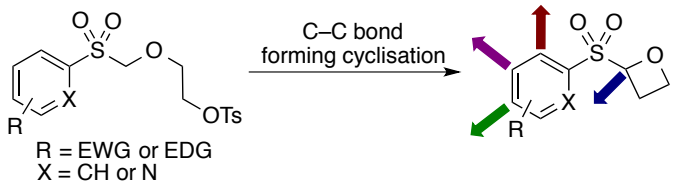
Abstract

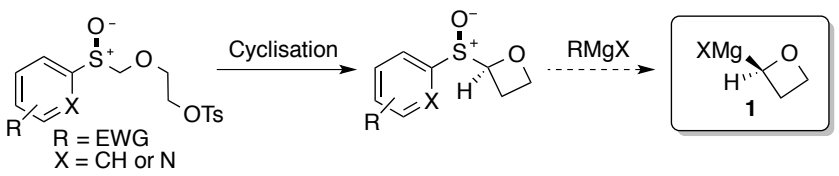
Oxetanes are currently receiving attention as important motifs for drug discovery due to their desirable physicochemical properties. Novel small oxetane containing compounds were designed to access new areas of chemical space and to be suitable motifs for incorporation into drug-like compounds or as fragments appropriate for screening in fragment based drug discovery. Methodology to access oxetanes bearing functional groups was investigated, in particular a novel intramolecular C–C bond forming cyclisation was developed due to the sparcity of synthetic methods for oxetane preparation.

2-Aryl sulfonyl oxetanes, designed with desirable fragment-like properties, were synthesised in excellent yields and could be further derivatised in a variety of directions into more lead-like compounds *via* organometallic intermediates at the intact oxetane and aromatic rings, scheme 1. The oxetane fragments and lead-like derivatives were found to have good half-life values under acidic and basic conditions. In addition, computational analysis determined that there were three possible binding orientations of the fragments.



Scheme 1: Synthesis and directions of functionalisation of 2-sulfonyl oxetanes.

2-Sulfinyl oxetanes were also synthesised as interesting motifs. The sulfoxide-magnesium exchange was explored as a method to access an oxetanyl organometallic species **1** and incorporate the oxetane motif into a wide variety of compounds, scheme 2. This was challenging, however interesting reactivity was observed.



Scheme 2: Synthesis of 2-sufinyl oxetanes and investigated derivatisation *via* sulfoxide-magnesium exchange to access an oxetane organometallic species.

To increase the diversity of oxetane derivatives that could be accessed and the methodology available to incorporate the motif into larger compounds, the synthesis of 2,3-disubstituted oxetanes was explored using an intramolecular epoxide ring opening strategy. More substitution would allow further ways in which to functionalise the oxetane motifs. In addition initial investigation into methodology to incorporate the oxetane motif into a wide array of larger lead-like and drug-like molecules was performed. The 2-oxetanyl sulfinate salt, a potential radical precursor, was not successfully formed. However the 3-oxetanyl radical was obtained by decarboxylation, and successfully reacted with a variety of heterocycles.

Contents

Abbreviations

Å	angstrom
acac	acetylacetone
ADMET	absorption, distribution, metabolism, excretion and toxicity
aq.	aqueous
Ar	aryl
b.p.	boiling point
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthalene
Bn	benzyl
br	broad
Bu	butyl
*s*Bu	*sec*-butyl
*t*Bu	*tert*-butyl
cat.	catalytic
CI	chemical ionisation (MS)
Conc*n*	concentration
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DFT	density functional theory
DMA	dimethylacetamide
DMF	*N,N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
DSF	differential scanning fluorimetry
DTBP	di-*tert*-butyl peroxide
E^+	generic electrophile
EDG	electron-donating group
ee	enantiomeric excess
EI	electron impact (MS)
equiv	molar equivalent(s)
ES	electrospray (MS)
Et	ethyl

EWG	electron-withdrawing group
FBDD	fragment based drug discovery
FDA	Food and Drug Administration
h	hour(s)
HAC	heavy atom count
HBA	hydrogen bond acceptors
HBD	hydrogen bond donors
hCl_{int}	intrinsic clearance in humans
HIV	human immunodeficiency virus
HLM	human liver microsomes
HMDS	hexamethyldisilazane
HRMS	high resolution mass spectrometry
HTS	high-throughput screening
Hz	hertz
IR	infrared
ITC	isothermal titration calorimetry
LA	Lewis acid
LDA	lithium diisopropylamine
LE	ligand efficiency
LG	leaving group
LICKOR	Schlosser's Base – *n*butyl lithium and potassium *tert*-butoxide
LIDAKOR	lithium diisopropylamine and potassium *tert*-butoxide
LiHMDS	lithium hexamethyldisilazane
LLE	lipophilic ligand efficiency
m	*meta*
M	molar
m.p.	melting point
mCL_{int}	intrinsic clearance in mouse
*m*CPBA	*meta*-chloroperbenzoic acid
mg	milligram
min	minute
mL	millilitre
MS	mass spectrometry

MW	molecular weight
µg	microgram
NCS	*N*-chlorosuccinimide
NMR	nuclear magnetic resonance
NMP	*N*-methylpyrrolidine
o	*ortho*
p	*para*
PPI	proton pump inhibitor
ppm	part(s) per million
PPTS	pyridinium *p*-toluenesulfonate
*i*Pr	*iso*-propyl
PSA	polar surface area
R	generic alkyl group
R_f	retention factor
RLi	generic organolithium reagent
RMgX	generic organomagnesium reagent
rt	room temperature
RTB	rotatable bonds
sat.	saturated
SPR	surface plasmon resonance
TBHP	*tert*-butyl hydroperoxide
TBME	*tert*-butyl methyl ether
Temp	temperature
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TMSCN	trimethylsilyl cyanide
Tol	tolyl
TPSA	topological polar surface area
TS	transition state
V	volt(s)

1. Introduction to the Drug Discovery Process and the Oxetane Motif

1.1. The Drug Discovery Process

Drug discovery is the process through which potential new medicines are discovered. The process from initial hit to marketable drug can often take between 10-15 years and in 2014 the average cost to develop a new drug was estimated at US$2.6 billion.[1] The two main approaches to discovering new drugs are phenotypic drug discovery and target-based drug discovery. The general principle of early stage target-based drug discovery is depicted in figure 1.[2] Modern methods for the discovery of new drugs involve rational drug design and often begin with initial target identification. A target is usually a gene or protein which is connected to a particular disease. Identifying a 'drugable' target is important in order to develop a successful drug. A 'drugable' target is one that can be accessed by the potential drug compound and which produces a biological response upon binding of the drug molecule. The identified target must then be validated and shown to be critical in the disease process. As target validation confirms that interaction with the target results in the desired effect on the disease this step is necessary to ensure that during the drug development process there is the potential to access a safe and effective drug and therefore a drug discovery effort can be justified.

Figure 1: General process of the early stages of target-based drug discovery.[2]

The next step, hit identification, is to discover a molecule that binds to and interacts with the chosen target. A library of compounds is screened against the chosen target and any suitable hits can be grown and developed into larger lead-like compounds. There are a variety of screening techniques that can be employed such as high-throughput screening, fragment based screening or a virtual screen. Once a hit series has been defined the 'hit to lead' stage of the development process is performed. Compounds in the hit series are optimised to improve potency and selectivity, often achieved through functional group modification. The identified lead compounds are then modified further to improve the physicochemical and biological properties making the molecules more effective and safe, and therefore viable drug candidates. The optimised compounds are then taken through the drug development process starting with preclinical then clinical testing.[2]

1.1.1. Desirable Drug-like Properties of a Drug Candidate

The discovery of novel potent drug molecules is a major challenge and as described above is a lengthy and expensive process. In the USA only 1 in 1,000 drug candidates which begin preclinical testing advances through the process to clinical trials and only 10% of the drugs in phase 1 clinical trials will be approved by the Food and Drug Administration (FDA) and advanced onto the market.[3] In 1991 adverse bioavailability and pharmacokinetic properties were the main causes of drug attrition within the pharmaceutical industry. However by 2000 the majority of drug candidates failed for reasons including toxicity and efficacy as well as commercial factors, and between 2011 and 2012 the main causes of drug attrition were still safety and efficacy.[4–6] In addition to poor toxicity, safety indirectly causes drug failures by causing the compound dosage in humans to be limited, preventing adequate exposure. In 2014 Hay reported that the majority of drugs that failed in clinical trails between 2003 and 2011 did so in phase 3 or during submission to the national regulatory authority.[3] In addition, Arrowsmith reported that between 2011 and 2012 52% of drugs that failed in phase 3 clinical trials did so due to poor efficacy.[5] For these reasons, the pharmacokinetic and physicochemical properties of a potential drug candidate should be considered alongside biological activity.

1.1.1.1. Guidelines for Desirable Physicochemical Properties

The link between physicochemical properties and aspects of "drug-likeness" of a molecule was first identified in 1997 by Lipinski who reported guidelines for the physicochemical properties of orally available drugs, known as the "rule of 5". These guidelines stated that compounds with a molecular weight less than 500 daltons, lipophilicity (LogP) less than 5 and no more than 5 H-bond donors or 10 H-bond acceptors were more likely to be absorbed within the body and therefore become a marketable drug.[7] Over time these guidelines, intended to predict oral absorption, have been used to define the limits of drug-like space, however they do not identify compounds with toxicological risks. As such, modifications of these guidelines have been reported to identify molecules in more general drug-like space. Gleeson reported that molecules with a clogP < 4 and a molecular weight < 400 daltons (the GSK 4/400 rule) have more favourable ADMET profiles.[8] ADMET refers to absorption, distribution, metabolism, excretion and toxicity. Compounds with issues relating to these pharmacokinetic properties often require further studies before

approval by the national regulatory authority, emphasising the importance of being able to predict these properties. Similarly Hughes reported the Pfizer 3/75 rule which indicated that compounds with clogP < 3 and polar surface area > 75 Å showed less toxicity and therefore greater safety in pre-clinical trials.[9] Polar surface area (PSA) is the sum of the surfaces of polar atoms in a molecule and this measurement has been shown to correlate with molecular transport properties such as intestinal absorption.[10] Calculation of PSA is often time consuming and computationally demanding as the 3-dimensional geometry of the molecule needs to be considered and the surface determined, however in 2000 Ertl developed a method to calculate PSA based on topological information, TPSA.[10] TPSA was based on the summation of surface contributations of the polar fragments within a molecule and allowed for a fast virtual bioavailability screen of a large number of compounds.

1.1.1.2. The Importance of Controlling Physicochemical Properties

Molecular weight (MW) and lipophilicity are two influential properties on the success of a drug compound.[11] Molecular weight is often added during the optimisation stage to increase the potency of a drug, however this may result in reduced solubility and permeability. As the drug must pass through a lipid bilayer in the cell membrane an increased lipophilicity is required to retain desirable permeability. Lipophilicity, logP, is defined as the logarithm of the ratio of concentrations of a solute between immiscible phases, often water and *n*-octanol, at equilibrium.[12] LogP represents the intrinsic lipophilicity of the neutral (unionised) species. The logarithm of the distribution coefficient, logD, considers the ionised and neutral form of the compound when determining the lipophilicity and can be derived from the experimental pK_a and logP, equation 1.[12]

$$For\ Bases:\ \log D = \log P - \log_{10}(1 + 10^{(pK_a - pH)})$$

$$For\ Acids:\ \log D = \log P - \log_{10}(1 + 10^{(pH - pK_a)})$$

Equation 1: Equations to calculate logD, showing the relationship between logP and logD.

In addition to improved permeability an advantage of increased lipophilicity is that binding of the drug compound to the desired target can improve, resulting in increased

potency. However high lipophilicity can also increase the binding of the drug to undesired targets and therefore decrease selectivity and increase the possibility of unwanted toxicology issues. Leeson reported that compounds with a calculated logP < 3 showed decreased promiscuity.[13]

To help determine desirable lead compounds and to quantify molecular properties, including MW, a measure known as Ligand Efficiency (LE) was reported. LE estimates binding efficiency of the drug to the target with respect to the number of heavy atoms, therefore correlating potency with molecular weight, equation 2-A.[14] LE does not consider lipophilicity, instead a Lipophilic Ligand Efficiency (LLE) value can be used, equation 2-B. A value of 5 or greater is suggested to lead to a drug candidate with desirable potency and lipophilicity and a reduced risk of toxicity.[13] These concepts help to identify and control an increase in MW and/or lipophilicity that may become detrimental to the drug compound during optimisation.[15]

A) Ligand Efficiency

$$\mathrm{LE} = \frac{p\mathrm{IC}_{50}}{\text{Number of heavy atoms}}$$

B) Lipophilic Ligand Efficiency

$$\mathrm{LLE} = p\mathrm{IC}_{50} - \mathrm{clogP}$$

Equation 2: Equations of ligand efficiency, $p\mathrm{IC}_{50}$ = binding affinity, logP = lipophilicity, see equation 1.[14,13]

In addition, lipophilicity correlates with aqueous solubility, an important property of a drug compound that is required to achieve the desired concentration essential for pharmacological effect. As lipophilicity increases solubility decreases because higher lipophilicity represents less polar, hydrophobic, poorly soluble molecules.[12] The human body metabolises lipophilic molecules to obtain more polar soluble compounds which can be excreted, therefore lipophilic compounds are required to be metabolically robust.[15] As a result a careful balance between potency, lipophilicity, metabolic stability and solubility is required for a successful drug.

An additional property to consider when designing a drug is complexity. Over the last 5/6 years the desire to synthesise more diverse and architecturally complex molecules has emerged. There is a move away from the many flat sp^2 rich compounds produced in the pharmaceutical industry that could be readily accessed by powerful cross-coupling methods. Complex molecules are likely to be more "natural product like" in structure. As

many potent drugs have been derived from natural products, creating more complex molecules was anticipated to increase the chance of finding appropriate bioactive compounds. Diverse, complex molecules will also allow the exploration of new areas of chemical space.[16] Molecular complexity may be described by analysing saturation and chirality within the molecule. Saturation allows more complex molecules to be created without increasing the molecular weight significantly.[16] Increasing sp^3 character and designing out-of-plane substituents onto the molecule could allow more binding interactions between the drug candidate and target, often not possible with flat molecules, resulting in increased potency and selectivity. Complexity and saturation can be calculated by various methods. Lovering reported using the fraction of saturated carbons within a molecule (Fsp^3) as a descriptor of saturation and therefore complexity, equation 3.[16]

$$Fsp^3 = \frac{\text{Number of } sp^3 \text{ hybridised carbons}}{\text{total carbon count}}$$

Equation 3: Calculating the fraction of sp^3 centres (Fsp^3) as a measure of saturation.[16]

The mean Fsp^3 value for compounds at various stages of the drug development process increases from discovery through clinical trials to approved drug, demonstrating the importance of considering the complexity of a drug compound.[16] In addition to saturation the average number of stereocentres present in compounds during the drug development process increases from discovery to approved drug.[16] This method to improve drugability of a molecule by increasing complexity was employed by Ishikawa who disrupted molecular planarity by increasing the number of sp^3 centres in the molecule and disrupted the symmetry by introducing chirality into a drug candidate, figure 2.[17] An increase in solubility was observed when the number of sp^2 centres present in **2** was reduced, **3**. Similarly, when the amino-piperidine group in compound **4** was modified to afford **5**, an increase in solubility was observed.[17]

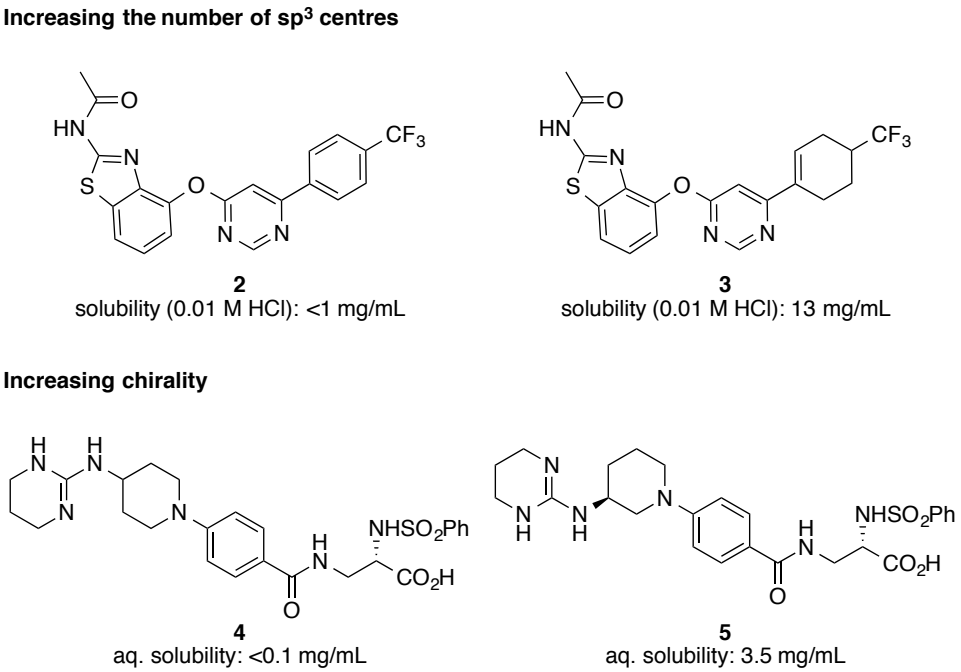


Figure 2: The effect of disrupting molecular planarity and symmetry on solubility.[17]

As demonstrated by Ishikawa the number of sp^2 centres in a drug can be reduced if the number of aromatic rings is decreased.[17] Analysis of 280 compounds in GlaxoSmithKline's pipeline showed that fewer aromatic rings were present in late stage drug candidates compared to pre-clinical compounds.[18] This result suggested that if the number of aromatic rings in a molecule was lower the compound was more likely to progress further through the development process. Aromatic ring count affects physicochemical properties. As aromatic ring count increased a detrimental effect on solubility and lipophilicity was observed, toxicity increased and drug potency was reduced.[18] Ritchie reported that more than three aromatic rings present in a molecule correlated to poor developability of the compound and therefore a higher risk of attrition in development.[18] Ritchie further investigated the effects of aromatic and aliphatic rings on the physicochemical properties and therefore desirability of the drug candidate. The presence of carboaromatics had the most detrimental effect compared to heteroaromatic and carbo- and heteroaliphatic compounds, whilst incorporation of heteroaliphatic moieties improved compound desirability.[19] The presence or absence of certain functional groups is important for identifying drugs with desirable properties. Some groups can increase the risk of toxicity, instability or unwanted biological interactions therefore eliminating these functional groups during the drug development process is beneficial.

1.1.2. Approaches to Identifying Lead Compounds

A key step in finding new drug candidates is the identification of a lead compound. For the final compound to fall within drug-like space it is advantageous for the lead structures to display desirable properties themselves. In 2001 Oprea analysed the average value of a variety of properties for 96 lead and drug compounds to determine how the properties changed during optimisation.[20] The properties analysed included; MW, number of rings, number of rotatable bonds, H-bond acceptors, H-bond donors, clogP and logD. The average value of the physicochemical properties analysed increased when progressing through lead optimisation to a final drug candidate, demonstrating the importance of identifying structures with desirable lead-like properties.

Churcher suggested that desirable lead-like molecules should have cLogP values between –1 and +3, MW of 200–350 daltons and a heavy atom count (HAC) of 14–26.[21] Multiple approaches have been employed to obtain good lead compounds. Nature has been a source of medicinal compounds for centuries, with many drugs developed from lead compounds derived from natural products or the natural ligand of the proposed target.[22] Due to advances in technologies such as X-ray crystallography and nuclear magnetic resonance (NMR), novel approaches to drug discovery have emerged and the focus of drug discovery efforts in the pharmaceutical industry has shifted away from nature to synthetic chemistry. The structure of a new lead compound is often related to an existing drug or lead with a similar structure and so the challenge is to identify a lead compound with significantly improved properties relative to the existing molecule whilst falling into novel intellectual property space.[23]

One of the main methods currently used in the pharmaceutical industry for identifying lead compounds is high-throughput screening (HTS). Large libraries of up to 10^6 compounds are screened against the drug target in an automated fashion. The selected hits are then optimised into lead compounds and potential drug candidates.[24] Maintaining the diversity and quality of these compound libraries is difficult and as a result they contain molecules which are not ‘drug-like’.[24] An alternative approach to lead identification is fragment based drug discovery (FBDD). Contrary to HTS small low molecular weight compounds, known as fragments, are screened against the known drug target. Fragment libraries are often smaller than those screened using HTS and typically contain about

1,000 fragments.[23] This thesis will focus on compounds for use in fragment based drug discovery.

1.1.2.1. The Method of Fragment Based Drug Discovery

In 1981 Jencks reported that although small molecules bind weakly to a target they form high quality interactions.[25] The fragment based methodology was then established by researchers at Abbott who reported the discovery of high-affinity ligands for proteins by linking together small molecules that bound to the target.[26] Subsequently, scientists at Astex Pharmaceuticals developed a pioneering structure guided fragment based approach to drug discovery using X-ray crystallography. This resulted in significant advances in the field and the fragment based approach to drug discovery emerged as a complementary method to high-throughput screening.[27]

An important milestone for FBDD was reached in 2011 when the FDA approved PLX4032, marketed as Zelboraf, as a treatment for late stage melanoma, figure 3.[28] PLX4032 was one of the first drugs approved that was developed using fragment based methodology. Twenty thousand compounds were screened, 7-azaindole **6** was selected for optimisation, leading to the development of PLX4720.[29] Further optimisation by addition of an aryl group led to the development of PLX4032.

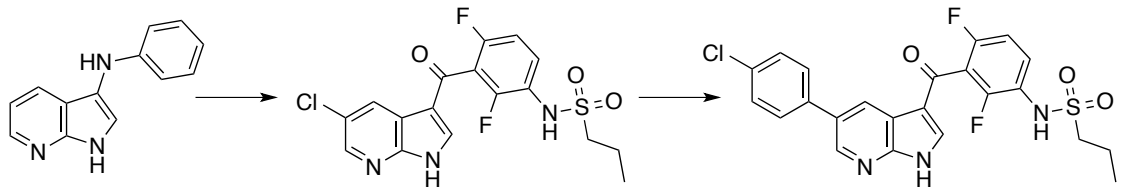


Figure 3: First example of an approved drug which was discovered using fragment based approaches.[28,29]

FBDD involves fragment library design, fragment screening and fragment optimisation. When designing a fragment library it is important that the fragments have desirable physicochemical properties in order to identify a drug in drug-like space. Similar to the "rule of 5" for drug-like compounds researchers at Astex defined guidelines for desirable criteria for fragments, known as the "rule of 3".[30]

The following properties were suggested:

- MW < 300 daltons
- cLogP < 3
- H-bond donors ≤ 3
- H-bond acceptors ≤ 3

In addition, the number of rotatable bonds should be less than three and a polar surface area of less than 60 would be beneficial.[30] These are only recommended guidelines and in fact Klebe suggested that the number of hydrogen bond acceptors should be raised to six or fewer as this can improve solubility and provide additional binding elements.[31]

Having designed a library of fragments they are screened against a known target to identify compounds which show biological activity, these fragments are known as hits. Fragments make high quality interactions with the target but only a small number so exhibit low binding affinity, as such sensitive biophysical techniques and high fragment concentrations are often required.[32] A variety of fragment screening techniques including NMR;[33] X-ray crystallography;[27] surface plasmon resonance (SPR);[34] differential scanning fluorimetry (DSF);[35] virtual screening;[36] isothermal titration calorimetry (ITC);[37] and mass spectrometry;[38] have been developed. In 2011 Erlanson reported that SPR and ligand-observed NMR were the most widely used techniques.[39] Whilst both methods are rapid they require expensive equipment and can produce false positives. Employing a combination of techniques can be beneficial to confirm and validate fragment hits and reduce the number of false positives.[39] In 2013 Abell disclosed a three-stage fragment screening approach. DSF was used for the preliminary screen, any hits were confirmed using ligand-observed NMR, then the validated fragments were further characterised using a low-throughput method such as X-ray crystallography or ITC.[40]

Fragments hits can be optimised into lead-like compounds using methodology such as fragment linking or fragment growing.[24] Fragment linking involves connecting two or more low affinity fragments, which bind to the target in adjacent sites, to form a high affinity lead-like compound, figure 4-A. Fragments that bind to similar sites on the target and partially overlap may also be combined to improve fragment potency. In principle

fragment linking is an appealing method, however in practice developing an appropriate linker to connect the fragments without altering their binding modes or finding synthetic methodology to access the merged fragment without affecting the binding affinity can be challenging.[24]

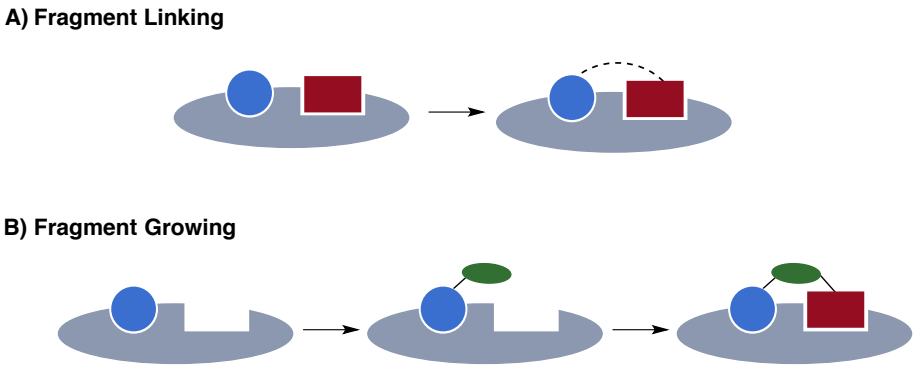


Figure 4: An illustration of fragment optimisation strategies.

Fragment growing is a more general approach which involves the step-wise addition of substituents onto the core fragment hit to improve potency, in addition to pharmacological properties, and grow the fragment into a potent lead compound, figure 4-B.[36] Fragment growing provides more options during optimisation compared to fragment linking as the fragment can be elaborated in a variety of directions.[36] Structural information of the target and fragment binding modes is advantageous when using both methods to facilitate the optimisation process.

FBDD is often compared to the more developed HTS approach in drug discovery, however they are two different approaches. FBDD starts with small, efficiently bound, low molecular weight compounds with low lipophilicities, whilst HTS libraries contain larger more lead-like compounds. Fragments can be optimised for potency and selectivity, which inevitably involves an increase in molecular weight and lipophilicity, whilst maintaining the final compound in desirable "drug-like" space.[23,41] Maintaining desirable physicochemical properties of the drug candidate is more challenging when employing a HTS method. In 2009 Reymond compiled a virtual list of all possible compounds with less than 13 heavy atoms, the number of small drug-like molecules was estimated at 970 million and this number increased exponentially with molecular size.[42] Consequently, small fragment libraries can attain greater chemical diversity and sample a greater

proportion of chemical space than the much larger libraries required for HTS.

When binding to a target a molecule must overcome an entropic barrier. This barrier is independent of the size of the compound and so when normalized with respect to molecular size the barrier is larger for fragments than for drug-like molecules.[41] To have measurable affinity fragments must form higher quality interactions with the target, compared to larger molecules. These interactions may also then be formed by the final drug candidate.

The disadvantages of FBDD are that large amounts of the target are often required and multiple methods are needed to confirm fragment binding. In addition fragment optimisation benefits from more information about the fragment binding modes than is required for optimisation of HTS hits.[23] Despite some disadvantages FBDD has become a well-established and important approach to the development of new drugs and lead compounds.[43,44] As discussed, employing fragments with desirable properties including low MW, low lipophilicity, high solubility and few aromatic rings would be beneficial when developing a drug candidate. Given this, the oxetane motif was considered desirable for use in FBDD and as such the oxetane structure, properties and reactivity are discussed below.

1.2. Oxetanes as Desirable Motifs for Use in Drug Discovery

1.2.1. Properties of the Oxetane Ring

Oxetane is a four-membered cyclic ether with a molecular formula C_3H_6O and a molecular weight of 58. The structure is shown in figure 5.

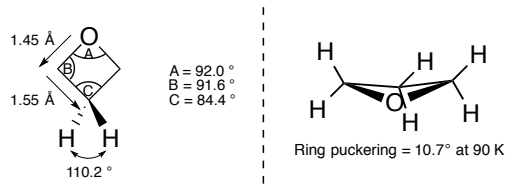


Figure 5: Structural properties of the oxetane ring.[45,46]

The oxetane ring is often compared to the analogous cyclobutane ring in terms of physical properties. The cyclobutane ring is puckered with a puckering angle of 30 º however the oxetane ring is only slightly puckered with a puckering angle of 8.7 º at 140 K and a slightly larger puckering angle of 10.7 º at 90 K, figure 5.[46] There are two competing factors which determine the ring structure; 1) the ring strain and 2) conformation of the hydrogen atoms. To minimise the strain in a four membered ring a planar structure is promoted. Alternatively the hydrogen atoms prefer to be in a staggered conformation, leading to a puckered ring structure. In a cyclobutane ring the eight hydrogen atoms promote the puckered conformation more than the effect of the ring strain. However replacing a methylene group with an oxygen atom in oxetane reduces this effect causing the ring strain to be prominent leading to a more planar conformation.[47] The introduction of substituents onto the oxetane ring increases the unfavourable eclipsed interaction resulting in a more puckered ring conformation.[48]

The carbon-oxygen bond length in an unsubstituted oxetane is 1.45 Å whilst the carbon-carbon bond length is 1.55 Å. This results in bond angles of 84.4 º (C–C–C), 91.6 º (C–C–O) and 92 º (C–O–C), figure 5.[45] The strained C–O–C bond angle exposes the oxygen lone pair of electrons, allowing the oxetane to act as an excellent hydrogen bond acceptor and Lewis base compared to other cyclic ethers.[49] There are two factors which influence hydrogen bonding ability and Lewis basicity; 1) the ring size and 2) hybridisation of the oxygen atom. As ring size decreases the C–O–C bond angle decreases therefore the lone pairs of electrons on oxygen become more accessible for bonding. Alternatively as ring size decreases the s-character of the non-bonding orbital on the oxygen atom increases causing the lone pair of electrons to be less accessible. Only the epoxide experiences a significant change in the hybridisation of the oxygen lone pair, consequently oxetane is the best hydrogen bond acceptor and Lewis base in the cyclic ether series.[50,51] Comparing the ability of oxetane to form hydrogen bonds with that of carbonyl compounds such as aliphatic ketones,[52] aldehydes[52] and esters,[53] only amides provide better hydrogen bond acceptors.[54] The ability of the motif to form hydrogen bonds is important from a pharmaceutical perspective as incorporating an oxetane ring into a potential drug candidate may increase the solubility or potency of the scaffold. Similarly the ability of the oxetane to act as a Lewis base is important in understanding the reactivity of the motif.

Despite the fact that an oxetane can donate electron density from the oxygen atom, oxetane itself can have an electron-withdrawing effect on neighbouring functional groups, altering the pK_a. Carreira showed that the effect on the basicity of an amine was dependent on the distance between the amine and oxetane. The greatest effects were seen when the oxetane was alpha to the amine but interestingly a decrease of 0.3 pK_a units was still observed when the oxetane was delta to the amine, figure 6.[55]

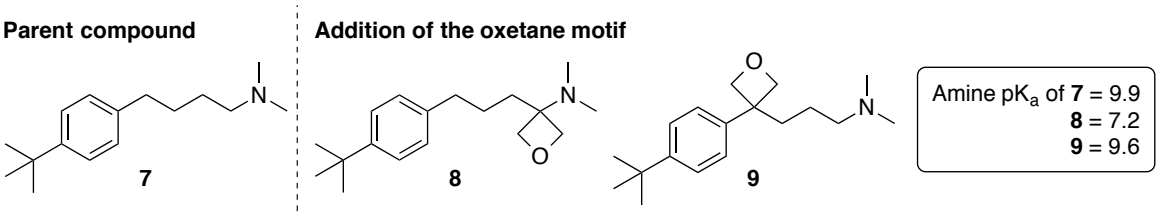


Figure 6: Effect of the oxetane motif on amine basicity.[55]

1.2.2. Oxetanes in Natural Products

Oxetanes are found in a variety of natural products and biologically active compounds. One of the most well known natural products is paclitaxel, Taxol, which was first isolated in 1971 from the stem bark of the western yew (*Taxus brevifolia)* and was used in cancer chemotherapy.[56] The structure of Taxol with the oxetane ring highlighted is shown in figure 7.

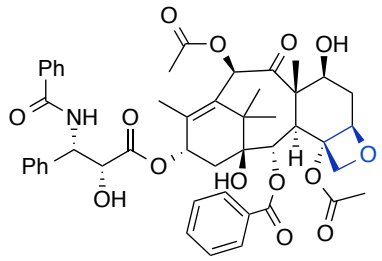


Figure 7: Structure of the well known natural product containing an oxetane ring, Taxol.[56]

Taxol acts by binding to microtubules and stabilising them during cell division, however due to the complex structure the conformation in which Taxol binds has not been confirmed.[57] The oxetane ring is crucial to the bioactivity of Taxol. This was demonstrated by the lower activity exemplified when the oxetane was replaced with an azetidine, thietane or selenetane ring.[57,58] A computational study on Taxol concluded that the

oxetane acted as a conformational lock, rigidifying the structure,[59] alternatively Kingston proposed that the oxetane was important as a hydrogen bond acceptor.[57]

The oxetane motif is found in only a few other natural products, some of which are shown in figure 8. The oxetane ring can be the core of the natural product, for example oxetanocin A and oxetin. Oxetanocin A was first isolated from the soil bacteria *Bacillus megaterium* and inhibits the *in vivo* replication of the HIV virus.[60] Oxetin was isolated from a broth of *Streptomyces* sp. OM-2317 and has antibacterial and herbicidal effects.[61]

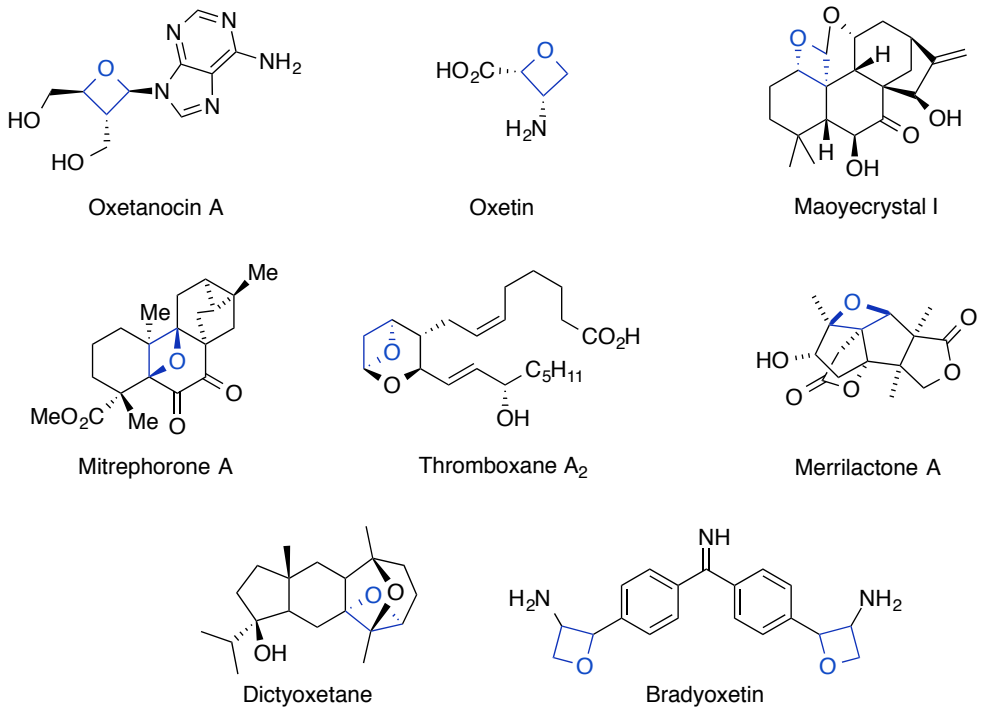


Figure 8: Natural products containing the oxetane motif.

Both Maoyecrystal I and Mitrephorone A were shown to be cytotoxic,[62,63] whilst Thromboxane A_2, synthesised by platelets in the blood, has prothrombotic properties.[64,65] Merrilactone A was first isolated in 2000 from the pericarps of the *Illicium merrillianum* plant and shown to stimulate the growth of rat neurons.[66] Dictyoxetane is a marine diterpene isolated from the brown algae *Dictyota dichotome* whose biological properties are currently not understood.[67] Finally Bradyoxetin, produced by the soil bacteria *Bradyrhizobium japonicum*, has two pendent oxetane rings and is involved in symbiotic gene regulation.[68] Although the oxetane ring was known in natural products the motif was

scarce in industry and academia until recently, largely due to a lack of knowledge about its synthesis, reactivity and properties.

1.2.3. Methods for the Synthesis of Oxetanes

Oxetane building blocks have only become widely commercially available within the last 5/6 years, demonstrating increased interest in this small heterocycle as more knowledge is gained about its structure and properties. There are limited methods for synthesising oxetanes and due to the growing attention this motif is receiving there is a need for robust, versatile synthetic routes to form a wide variety of oxetane derivatives. The first reported synthesis of the 4-membered heterocycle was by Reboul in 1878 *via* the base induced cyclisation of 3-chloro-1-propanol.[69] Since then additional strategies for preparing oxetanes have been reported. The two most widely used methods are the [2+2] Paternò−Büchi cyclisation, resulting in a C–C and C–O bond formation highlighted in figure 9, and the intramolecular Williamson etherification which affords the oxetane *via* formation of a C–O bond. Epoxide ring opening/ring closing has also been exploited as a route to synthesise 2-substituted oxetanes, figure 9.

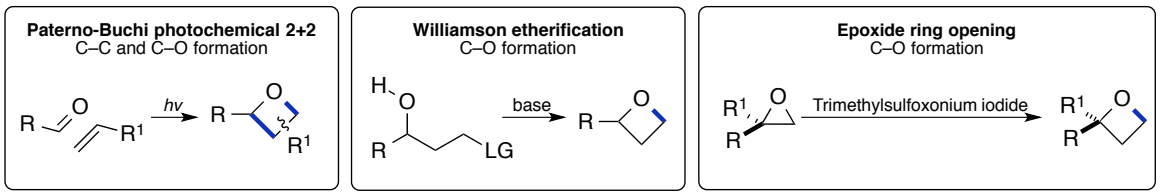
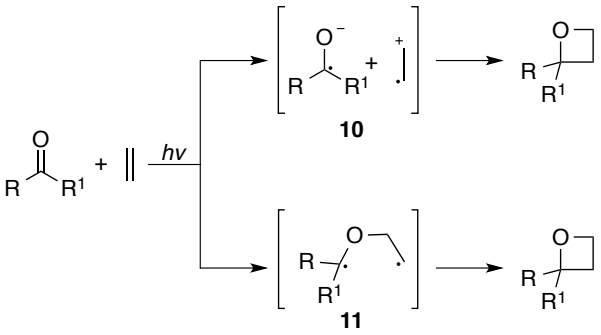


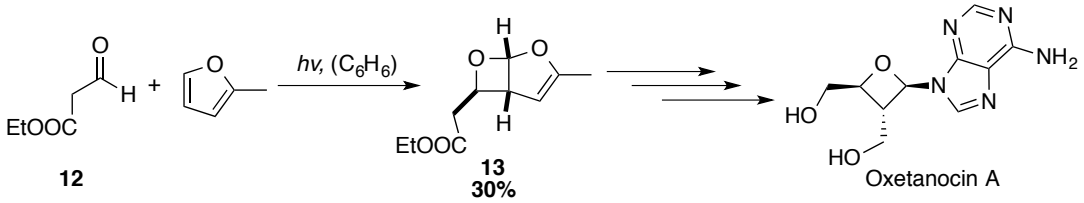
Figure 9: General scheme for synthetic approaches to substituted oxetanes.

The [2+2] Paternò−Büchi cycloaddition is a method frequently used to synthesise the oxetane ring *via* reaction of a carbonyl compound with an alkene in the presence of light.[70] There are two possible mechanisms of this photochemical reaction; either *via* formation of a radical ion pair **10,** generated by photo-induced electron transfer, or formation of a 1,4 biradical **11**, scheme 3. The Paternò−Büchi reaction can result in the formation of substituted oxetanes in good yields, however controlling regio- site- and stereoselectivity can be challenging.[71]



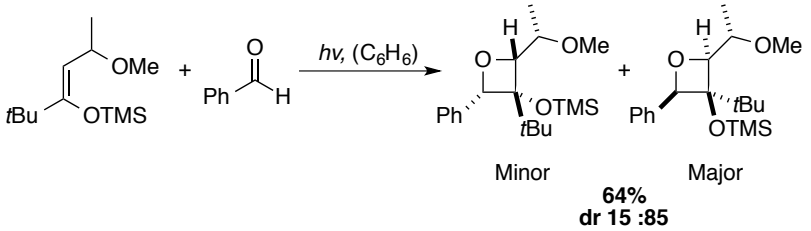
Scheme 3: Two proposed mechanisms of the Paternò−Büchi reaction.[71]

The [2+2] cycloaddition has been employed to synthesise the oxetane ring in a variety of natural products. Hambalek and Just reported the synthesis of the oxetane ring in oxetanocin *via* a Paternò−Büchi reaction.[72] The addition of 2-acyloxy-substituted aldehyde **12** to 2-methylfuran afforded the desired oxetane bicycle **13** as the *exo* isomer, scheme 4. Despite the high stereoselectivity poor regioselectivity was observed accounting for the low yield. In 2005 Greaney reported the construction of the oxetane ring in Merrilactone A *via* an intramolecular Paternò−Büchi photoaddition reaction, emphasising the importance and utility of this cycloaddition reaction.[73]



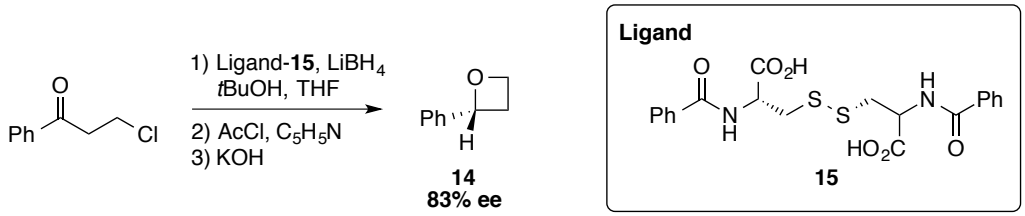
Scheme 4: Formation of the oxetane core of oxetanocin A *via* a Paternò−Büchi [2+2] cycloaddition.[72]

Bach reported the photochemical reaction between benzaldehyde and silyl enol ethers leading to diastereoselective oxetane formation, scheme 5.[74] This facial selectivity was observed when bulky, nucleophilic substituents such as a methoxy group were employed along with small alkyl substituents such as the methyl group shown in scheme 5.



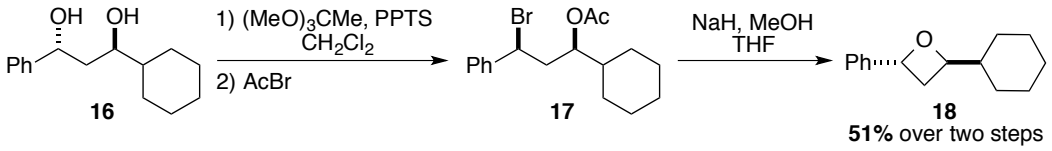
Scheme 5: Diastereoselective formation of the oxetane ring *via* a Paternò−Büchi reaction mechanism.[74]

The Williamson etherification is an alternative method to oxetane synthesis that requires a 1,3 relationship between an alcohol and a leaving group. The oxy-anion, generated from the alcohol, undergoes an intramolecular cyclisation *via* an S_N2-like mechanism to afford the corresponding oxetane by formation of a C–O bond. This methodology was further developed to allow the synthesis of chiral oxetanes as demonstrated by Soai.[75] 2-Aryl substituted oxetanes were synthesised in good enantiomeric excess (79–89% ee) *via* an enantioselective reduction of β-halo-ketones with a chiral reduction catalyst generated *in situ* from lithium borohydride and chiral ligand **15**. Acetylation followed by subsequent ring closure afforded chiral oxetanes such as **14**, scheme 6.[75]



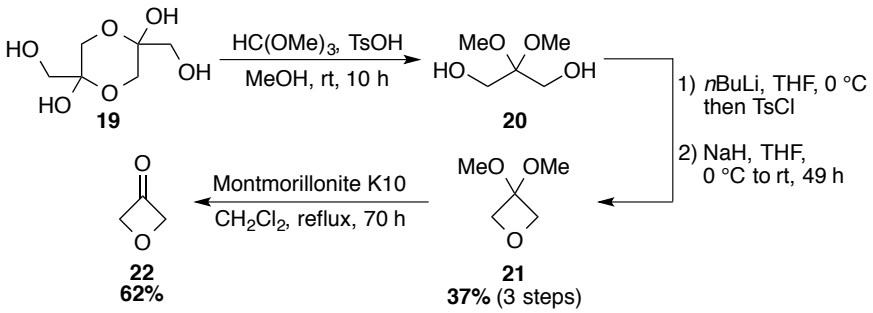
Scheme 6: Asymmetric synthesis of 2-substituted oxetanes using a chiral catalyst. No yield reported.[75]

In addition, Nelson reported the two-pot procedure for the stereocontrolled synthesis of di- and trisubstituted oxetanes from the corresponding 1,3 diols.[76] The starting 1,3 diol **16** was converted into the corresponding acetoxy bromide **17** with inversion of one stereogenic centre. Deacetylation with sodium methoxide followed by cyclisation afforded the desired oxetane **18** as one diastereoisomer, scheme 7.[76] This method involved a stereogenic centre being inverted twice, resulting in overall retention of configuration.



Scheme 7: Synthesis of a chiral 2,4-disubstituted oxetane from the corresponding chiral 1,3 diol.[76]

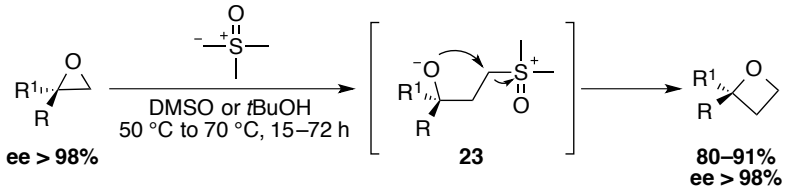
In recent efforts to access diverse oxetanes, particularly by Carreira, oxetan-3-one **22** was the required starting material. Carreira developed a four-step synthesis of the cyclic ketone which involved an intramolecular cyclisation to form the oxetane, scheme 8.[55]



Scheme 8: Synthesis of oxetan-3-one by an intramolecular cyclisation.[55]

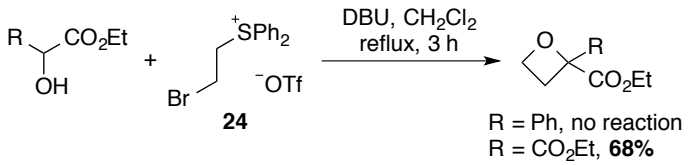
The dihydroxyacetone dimer **19** was converted into the corresponding dimethylketal **20**. Monotosylation with TsCl followed by deprotonation with NaH prompted the intramolecular cyclisation, forming oxetane **21**. Acidic cleavage of the ketal provided oxetan-3-one **22** in a yield of 62%. In general intramolecular cyclisation leads to the desired oxetane products however the yields can be modest due to undesirable side reactions such as the Grob fragmentation of the halo alkoxide into an aldehyde and an alkene.[77] Consequently the intramolecular Williamson etherification as a method for oxetane synthesis is rather substrate dependent.

Similar to the Williamson ether synthesis, epoxide ring opening/ring closing has been exploited as a facile route to access substituted oxetanes. A sulfur ylide, formed *in situ* from trimethyloxosulfonium iodide, acts as a nucleophilic methylene transfer reagent attacking the epoxide to generate **23**. Subsequent ring closing with release of dimethyl sulfoxide affords the oxetane. Okuma first reported the synthesis of 2,2-disubstituted oxetanes using this approach in 1983,[78] since then the epoxide ring opening/ring closing methodology was developed into an asymmetric synthesis by the introduction of a heterobimetallic catalyst[79] or by employing chiral epoxides.[80] During the reaction the substituted chiral centre remained untouched, as a result the stereochemical information of the epoxides was retained in the resulting oxetanes, scheme 9.[80]



Scheme 9: Stereocontrolled ring expansion of chiral epoxides to the corresponding oxetanes.[80]

Krief reported a similar regioselective ring expansion of epoxides to oxetanes employing selenoalkyllithiums, generating hydroxy selenides as the reactive intermediates.[81] In addition to using trimethyloxosulfonium ylide or selenoalkyllithiums Aggarwal disclosed the synthesis of an oxetane ring using a vinylsulfonium salt generated *in situ* from 2-bromoethyl sulfonium triflate **24**, however this reaction was only successful when a diester was used, scheme 10.[82]



Scheme 10: Formation of the oxetane motif using a vinylsulfonium salt.[82]

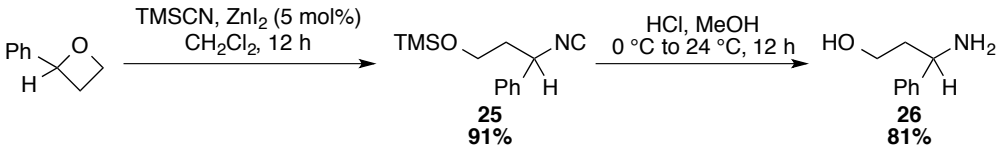
1.2.4. Reactivity of the Oxetane Motif

The oxetane motif was neglected in medicinal chemistry for a long time due to concerns over its chemical and metabolic stability. The small saturated heterocycle has an inherent ring strain of 106 kJ mol^{-1}, compared to 113 kJ mol^{-1} for oxirane and 25 kJ mol^{-1} for THF.[83] The desire to release this strain can cause instability. This property allows oxetane derivatives to be useful synthetic intermediates in addition to interesting motifs. As such the reactivity of the oxetane motif has been explored and a selection of ring opening and ring expansion reactions is discussed below.

1.2.4.1. Ring Opening Reactions of Oxetanes

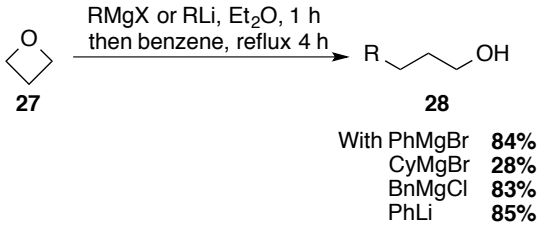
The oxetane ring is hydrolysed under acidic conditions to give 1,3 glycols. The reaction is usually catalysed by sulfuric or perchloric acid in aqueous dioxane and proceeds almost as fast as the hydrolysis of epoxides.[84] Under basic or neutral conditions oxetane hydrolysis is remarkably slow. Similarly the ring opening of an oxetane by reaction with simple nucleophiles proceeds under acidic conditions. Treatment of 2-substituted or 2,2-disubstituted oxetanes with TMSCN in the presence of zinc iodide resulted in ring opening of the oxetane by attack of the isonitrile nucleophile.[85] The most electropositive carbon, when the Lewis acid (LA) was coordinated, was attacked resulting in a regiospecific ring opening of the oxetanes to afford γ-hydroxy isonitriles, including **25**, in

yields of 73–94%. These intermediates were converted into the corresponding γ-amino alcohols such as **26** following deprotection and hydrolysis, scheme 11.[85]



Scheme 11: Ring opening of oxetanes using TMSCN with ZnI_2 as the Lewis acid.[85]

In 1916 Derick and Bissell first explored the reaction of oxetane with a Grignard reagent, affording a ring opened product.[86] To confirm the synthesis of unsubstituted oxetane the product was treated with *n*propyl magnesium bromide and heated at reflux, which resulted in the formation of *n*hexanol in a 49% yield.[86] This prompted the seminal work by Searles on the reaction of oxetane with organometallic compounds. Treatment of **27** with a variety of aromatic and aliphatic Grignard reagents and organolithium compounds resulted in the open chain alcohols **28** in moderate to good yields, scheme 12.[87]

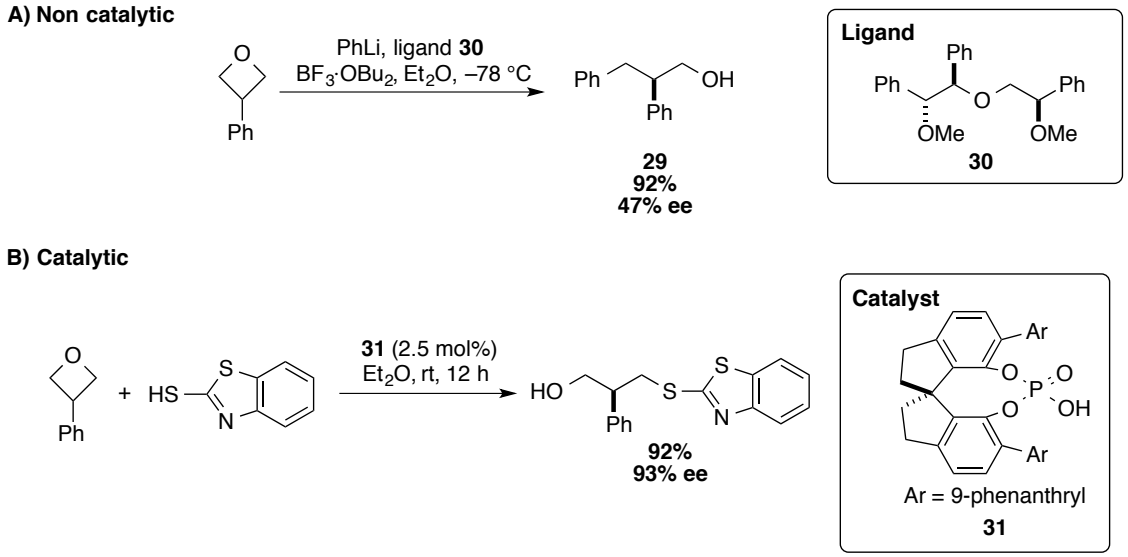


Scheme 12: Reaction of oxetane with organometallic reagents resulting in the corresponding alcohols.[87]

These initial reaction conditions were undesirable as they required refluxing in benzene for 4 h. Huynh reported the more mild reaction conditions of stirring the oxetane and Grignard reagent at room temperature (rt) in the presence of copper iodide (10 mol%), however the products were obtained in lower yields of 50–75%.[88]

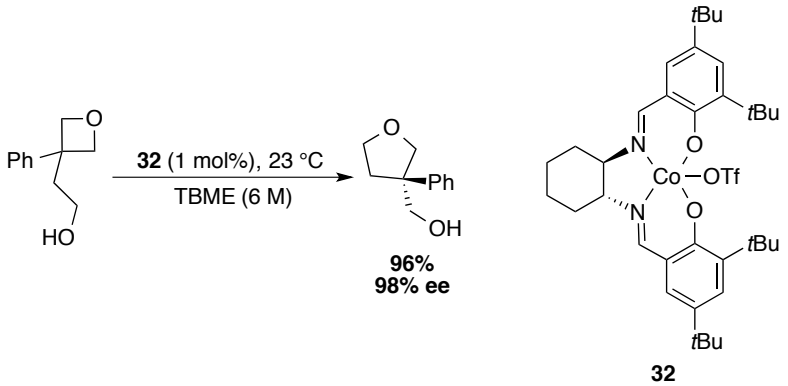
Over the last 20 years the enantioselective ring opening of the oxetane was developed. Tomioka reported the first example of the desymmetrisation of 3-substituted oxetanes by treatment with organolithium reagents.[89] 3-Phenyloxetane was treated with PhLi, $BF_3{\cdot}OBu_2$ and an external chiral tridentate ligand **30** at –78 ºC to afford chiral alcohol **29** in a yield of 92%, scheme 13-A. Unfortunately, stoichiometric quantities of the chiral boron reagent were required and the product was afforded with low enantioselectivity

(47% ee).[89] In 2013 Sun reported the catalytic enantioselective ring opening of 3-substituted oxetanes using a chiral phosphoric acid catalyst, scheme 13-B. Low catalyst loadings of 2.5 mol% were employed and good enantioselectivities of 71–99% were obtained.[90,91]



Scheme 13: Non catalytic and catalytic enantioselective ring opening of 3-substituted oxetanes.[89,90]

The intramolecular ring opening of 3,3-disubstituted oxetanes catalysed by a cobalt salen complex **32** was reported by Jacobsen in 2009, affording the tetrahydrofuran products with excellent enantioselectivities, scheme 14.[92]

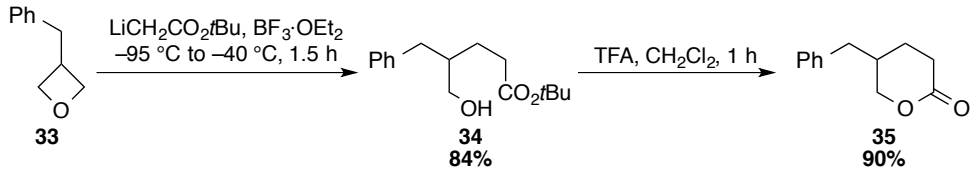


Scheme 14: Enantioselective intramolecular ring opening reaction of 3,3-disubstituted oxetanes.[92]

1.2.4.2. Ring Expansion Reactions of Oxetanes

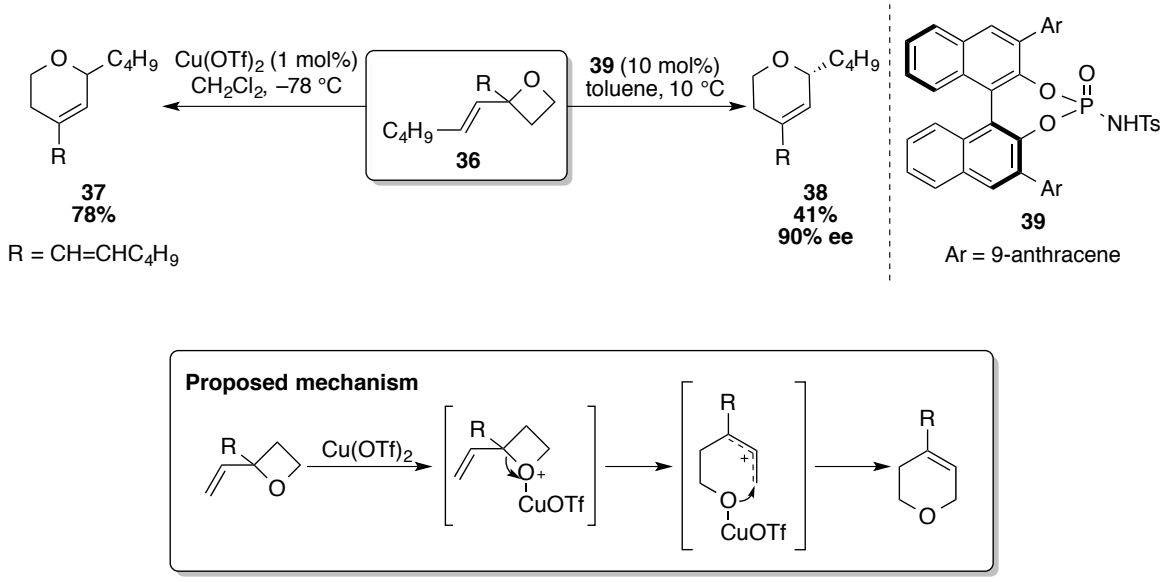
Oxetanes have been employed as synthetic intermediates in the synthesis of a variety of larger heterocycles through ring expansion reactions as shown in scheme 14. In addition to

forming the 5-membered THF ring as described above, the 6-membered δ-lactones were synthesised when substituted oxetanes such as **33** were reacted with esters in the presence of a base.[93] When $BF_3{\cdot}OEt_2$ was employed the lithium enolates, prepared *in situ*, attacked the least sterically hindered position or the most electrophilic carbon on the oxetane prompting the ring to open affording intermediates including **34**. The δ-hydroxyesters were then converted into the corresponding δ-lactones **35** when exposed to acidic conditions, scheme 15.[93]



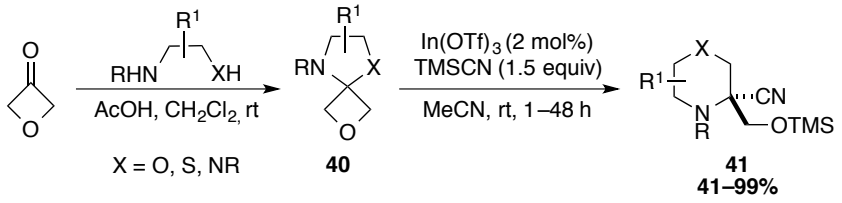
Scheme 15: Ring expansion of the oxetane ring to form δ-lactones.[93]

Njardarson reported the ring expansion of vinyl oxetanes **36** to 3,6-dihydro-2H-pyrans **37** in the presence of 1 mol% of copper triflate or 10 mol% of triflic acid.[94] Njardarson proposed that $Cu(OTf)_2$ coordinated to the oxetane oxygen atom prompting the ring to open, the resulting allylic cation was then captured by the oxygen in a 6-*endo-trig* cyclisation, scheme 16. This methodology was further developed to allow chiral dihydropyrans to be accessed by employing a chiral phosphoric acid catalyst **39**. 3,6-Dihydro-2H-pyran **38** was synthesised with 90% ee but in a low yield of 41%, scheme 16.



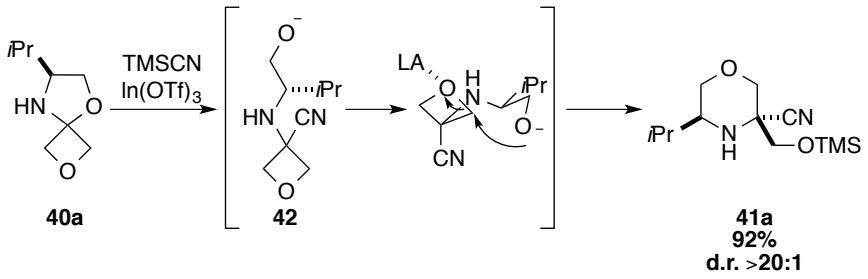
Scheme 16: Ring expansion of vinyl oxetanes to 3,6-dihydro-2H-pyrans.[94]

Over the last 5 years Carreira has reported the ring expansion of oxetan-3-one to a variety of heterocycles such as isoxazoles,[95] morpholines, thiomorpholines and piperazines.[96] Oxetan-3-one was converted into a variety of spirocycles **40** by reaction with β-heteroatom substituted amino compounds. The resulting intermediates were treated with TMSCN in the presence of a Lewis acid to form saturated nitrogen heterocycles, **41**, relevant to drug discovery, scheme 17.



Scheme 17: Conversion of oxetan-3-one into saturated nitrogen heterocycles *via* the formation of intermediate spirocycles.[96]

The proposed mechanism for the formation of a morpholine ring is discussed, scheme 18. Carreira speculated that spirocycles such as **40a** underwent a Strecker reaction with trimethylsilyl cyanide to produce nitrile **42**. An intramolecular cyclisation then occurred, prompted by activation of the oxetane by the Lewis acid, affording morpholine **41a** with an excellent yield and diastereomeric ratio.[96]



Scheme 18: Proposed mechanism for the ring expansion of spirocyclic **40a** to morpholine **41a**.[96]

Oxetanes are involved in a variety of ring opening and ring expansion reactions demonstrating the versatility and utility of the oxetane motif. Despite the ring strain and assumed instability of the oxetane most of the reactions resulting in ring opening or ring expansion required a Lewis acid. With this in mind industry and academia have begun to show interest in the oxetane motif.

1.2.5. Oxetanes in Medicinal Chemistry

1.2.5.1 Desirable Physicochemical Properties of the Oxetane Motif

The pioneering work by Carreira, Rogers-Evans, Müller and coworkers demonstrated oxetanes as desirable low molecular weight motifs for drug discovery.[65] Of particular importance was the desirable physicochemical and pharmacokinetic properties displayed when an oxetane was incorporated into a drug molecule. In recent years Carreira has investigated the properties of the oxetane motif with respect to medicinal chemistry and drug discovery.[65,97] The oxetane can be a beneficial isosteric polar replacement for a *gem*-dimethyl group, imparting improved physicochemical properties to drug-like compounds without a significant increase in molecular weight.[55] Similarly the oxetane ring can be an isosteric replacement for a carbonyl group and recently has been introduced into peptide mimics.[98,99] In addition Carreira has developed a class of spirocyclic oxetanes which can be desirable morpholine replacements, figure 10.[100] These aspects are discussed in more detail below.

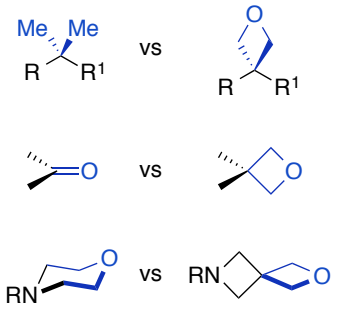


Figure 10: The oxetane motif as a bioisostere for a *gem*-dimethyl, carbonyl and morpholine group.

1.2.5.1.1. Oxetane as a Bioisostere for a gem-Dimethyl Group

A *gem*-dimethyl group is commonly introduced into a biologically active molecule to block a metabolically exposed site, such as a methylene group. Unfortunately this modification often results in an undesirable increase in lipophilicity causing adverse effects on the physicochemical and pharmacokinetic properties, decreasing the desirability of the drug compound.[55] Carreira hypothesised that due to the similar size of an oxetane and *gem*-dimethyl moiety the oxetane motif could be regarded as a polar oxygen bridged

gem-dimethyl group, that could provide a reduction in lipophilicity and metabolic liability, figure 11.[55,65]

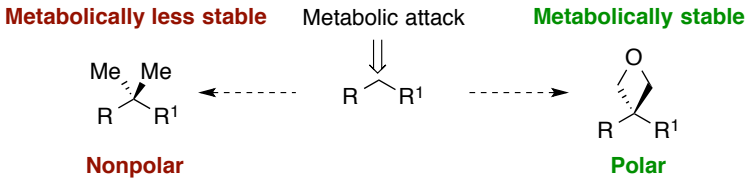


Figure 11: A *gem*-dimethyl and oxetane ring as motifs to block a metabolically liable methylene group.

To probe this hypothesis the *t*-butyl group of a model compound **7** was replaced with a methyl substituted oxetane, highlighted in **43**. A variety of physicochemical and biological properties were investigated including solubility, lipophilicity and intrinsic clearance rates which correlate to metabolic stability, table 1.

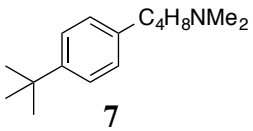
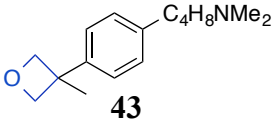
	 **7**	 **43**
Solubility (μg mL^{-1})	<1	4400
Lipophilicity logD (logP)	1.8 (4.3)	0.8 (3.3)
hCL_{int} (min^{-1} mg^{-1} μL)[a]	16	0
mCL_{int} (min^{-1} mg^{-1} μL)[a]	417	43

Table 1: Physicochemical and biological properties demonstrating the effects of replacing a *gem*-dimethyl group with an oxetane. [a] Intrinsic clearance rates measured in human (h) and mouse (m) liver microsomes.[55]

The thermodynamic solubility of **7** and **43** was measured in 50 mM phosphate buffer at pH 9.9 at 22.5 ºC. Compound **7** was essentially insoluble under these basic conditions however when the oxetane was present, in compound **43**, the solubility significantly increased. This solubility data correlated with the lipophilicity data logD and logP, incorporating an oxetane decreased the lipophilicity of the compound by 1 unit. Next the metabolic stability in both human and mouse liver microsomes was examined. The model compound **7** showed medium to high clearance rates for both the human and mouse microsomes whilst in comparison **43** showed much lower clearance rates therefore demonstrating an increase in metabolic stability, table 1. These results confirmed that replacing a *gem*-dimethyl group with an oxetane could result in improved physicochemical and biological properties. For example, Fujishima employed this strategy

to improve the binding affinity of 1,25-dihydroxyvitamin D_3 analogues for the bovine thymus vitamin D receptor.[101]

1.2.5.1.2. Oxetane as a Bioisostere for a Carbonyl Group

Carbonyl moieties such as aldehydes, ketones and esters are common in biological and synthetic chemistry however due to their inherent reactivity they are undesirable moieties for drug discovery. Carbonyl compounds are vulnerable to enzymatic attack and α-deprotonation which can cause stereogenic centres at that position to be susceptible to epimerisation, both unwanted properties in drug candidates.[97] The oxetane motif was predicted to be a desirable surrogate for a carbonyl group due to the similar dipoles and similar hydrogen bonding properties of the two motifs.[65,97] In addition the lone pair of electrons on the oxygen atom in both the oxetane and carbonyl groups have similar spatial arrangements, figure 12.[97] The main difference between an oxetane and carbonyl motif is the length of the group. This may result in incompatibility with targets that cannot accommodate the larger size of the oxetane, however for some targets a larger volume may be beneficial.

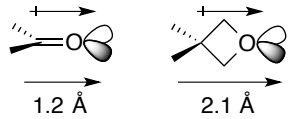


Figure 12: Comparison between the carbonyl and oxetane functional groups.[97]

To investigate this hypothesis Carreira studied the physiochemical and biological properties of spirocycle **45** compared to those of the corresponding carbonyl compound **44**, table 2.

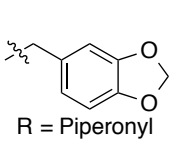
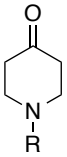
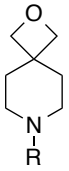
	 R = Piperonyl	 **44**	 **45**
Solubility (μg mL^{-1})		4000	1400
Lipophilicity logD (logP)		1.2 (1.6)	1.0 (2.0)
hCL_{int} (min^{-1} mg^{-1} μL)[a]		120	6
mCL_{int} (min^{-1} mg^{-1} μL)[a]		88	22

Table 2: Physicochemical and biological properties demonstrating the effects of replacing a carbonyl group with an oxetane ring. [a] Intrinsic clearance rates measured in human (h) and mouse (m) liver microsomes.[100]

The incorporation of an oxetane ring decreased the solubility and increased the lipophilicity (logP) of **45** compared to **44**, however the metabolic stability was improved for the oxetane spirocycle compared to **44**.[100] In 2013 Carreira explored the effects of structural modification of thalidomide and lenalidomide. When the imide C=O, highlighted in table 3, was replaced by an oxetane an increase in solubility and decrease in lipophilicity was observed. The results for thalidomide are shown in table 3.[102] While a decrease in metabolic stability was observed, crucially, the susceptibility to racemisation was prevented.

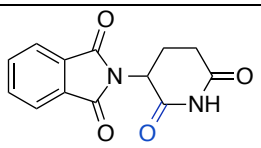
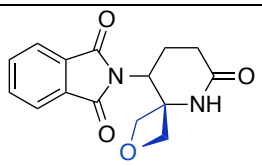
	 Thalidomide	 Oxetano-thalidomide
Solubility (μg mL^{-1})	29	78
Lipophilicity (logD)	0.24	0.00

Table 3: Comparison of the physicochemical properties of thalidomide and oxetano-thalidomide.[102]

1.2.5.1.3. Oxetane as a Bioisostere for a Morpholine Ring

Morpholine rings are often incorporated into drug scaffolds to improve aqueous solubility however they can undergo undesirable oxidative metabolism. Due to similar structural properties the spirocyclic oxetane motif was suggested as a desirable morpholine replacement. When compared to morpholine **46** spirocyclic oxetane **47** had an increased aqueous solubility and decreased lipophilicity whilst remaining metabolically stable

towards oxidation, proving the oxetane motif to be an ideal morpholine replacement, table 4.[100]

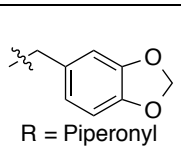
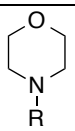
 R = Piperonyl	 **46**	 **47**
Solubility (μg mL^{-1})	8000	24000
Lipophilicity logD (logP)	1.5 (1.6)	0.5 (1.2)
hCL_{int} (min^{-1} mg^{-1} μL)[a]	9	3
mCL_{int} (min^{-1} mg^{-1} μL)[a]	8	7

Table 4: Physicochemical and biological properties demonstrating the effects of replacing a morpholine ring with a spirocyclic oxetane. [a] Intrinsic clearance rates measured in human (h) and mouse (m) liver microsomes.[100]

In addition, 1,6-heteroatom-substituted spiro[3.3]heptanes **49** can be considered as stable alternatives to 1,3-heteroatom-substituted cyclohexanes **48**, figure 13.[103] The instability of heterocycles **48** leads to their limited use in drug discovery however spiro[3.3]heptanes allow similar positioning of the heteroatoms without the associated instability, providing desirable surrogates.

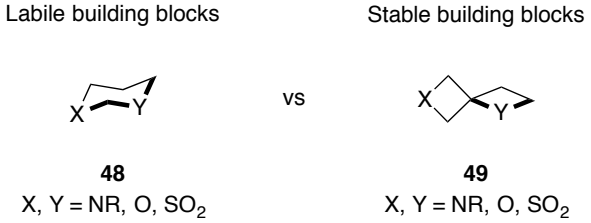


Figure 13: Spiro[3.3]heptanes **49** as alternatives to unstable 1,3 heteroatom-substituted cyclohexanes.[103]

The oxetane motif is an exciting structure in medicinal chemistry as it provides a possibility to increase steric bulk without increasing lipophilicity. Incorporation of an oxetane onto a molecule can also improve solubility in addition to metabolic and chemical stability. As a result of these desirable properties oxetanes have recently received significant interest from the pharmaceutical industry, often being employed to improve the physicochemical properties of drug-like compounds.[104,105]

1.2.5.2. Oxetanes in Drug Discovery Programmes

An early example of an oxetane containing compound demonstrating medicinal properties was in 1959 when 3,3-diethyloxetane was shown to display anticonvulsant activity in rats and 3-ethyloxetane displayed sedative and anaesthetic effects, figure 14.[106]

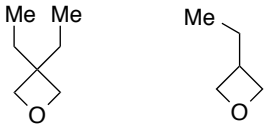


Figure 14: The structures of simple oxetanes displaying medicinal properties.

For much more recent examples, Stepan explored arylsulfonamides as potential γ-secretase inhibitors which are viable treatment options for Alzheimer's disease.[107] Lead compound **50** contained a cyclohexyl substituent and suffered from poor metabolic stability and solubility, but good potency, figure 15. As a method to improve metabolic stability whilst retaining potency the cyclohexyl ring was replaced with cyclic ethers; 6-, 5- and 4-membered rings. The 4-membered oxetane resulted in the greatest improvement in metabolic stability and lipophilicity. Further investigation into the substitution of the oxetane showed that 3-substituted and 2,4,4-trisubstituted analogues were more metabolically stable than the corresponding 2-substituted derivatives. Overall 2,4,4-trisubstituted analogue **51** was the most stable γ-secretase inhibitor of the series.[107,108]

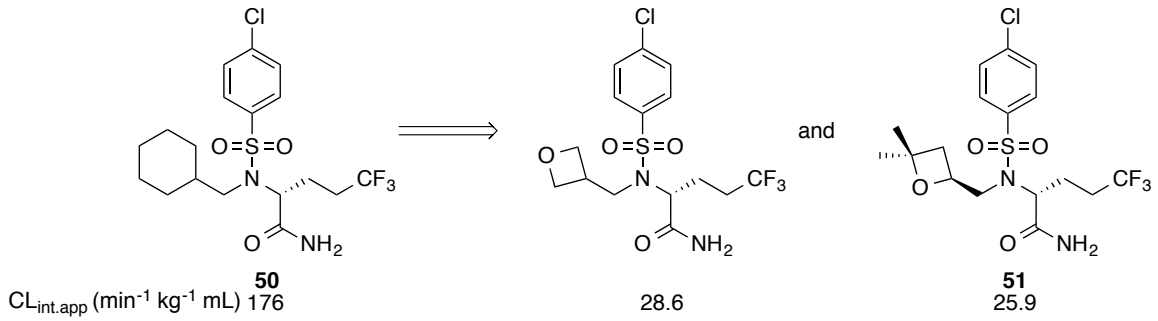
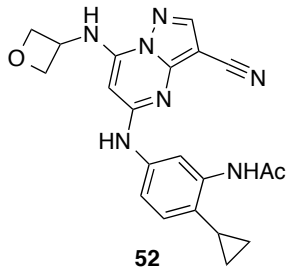


Figure 15: Comparison of the metabolic stability of lead compound **50** compared to oxetane-containing analogues. $CL_{int.app}$ is total intrinsic clearance obtained from scaling *in vitro* HLM half-lives.[107]

Dowling investigated a series of 5-anilinopyrazolo[1,5-a]pyrimidine derivatives as inhibitors of the kinase CK2. Incorporating a 7-oxetane-3-yl amino group onto the drug

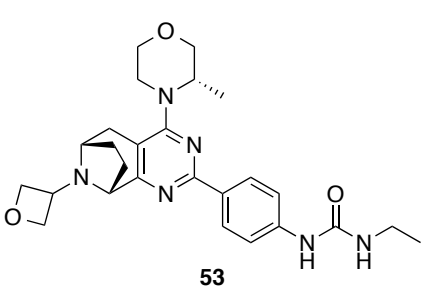
scaffold resulted in reduced lipophilicity and increased metabolic stability whist retaining potency, leading to **52** being identified as the most promising analogue, figure 16.[109]



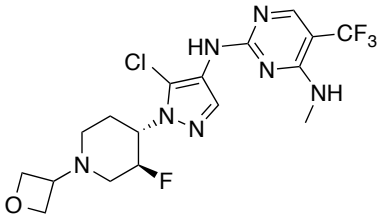
52

Figure 16: Structure of a promising CK2 kinase inhibitor containing the oxetane motif.[109]

Another successful oxetane-containing kinase inhibitor was reported by Pei and Lyssikatos who disclosed a series of tetrahydroquinazolines as inhibitors of mTOR, a therapeutic target for treating cancer. A clinical development candidate was established which contained an oxetane ring that was incorporated to improve the physicochemical properties.[104] Within 6 months the candidate was further developed to reduce the inhibitory concentration required by converting to a pyrimidoaminotropane core, affording drug candidate **53**, figure 17.[105]



53



54

Figure 17: Structure of an inhibitor of mTOR **53** and an inhibitor of LRRK2 **54**.[105,110]

An additional successful drug candidate containing the oxetane motif is **54**, figure 17. Leucine-rich repeat kinase 2 (LRRK2) is a gene related to Parkinson's disease with significant interest within neuroscience research. Estrada reported the development of highly potent, selective and brain-penetrant small molecule inhibitors of LRRK2.[110] The lead compound was optimised to establish compound **54**, with a pendent oxetane motif, as one of the best inhibitor with an IC_{50} value of 19 nM.[110]

1.3. Synthesis of Oxetanes for use in Drug Discovery, in particular FBDD

Fragment based drug discovery has emerged as an important strategy in the development of new drugs. As discussed, when developing new lead and drug compounds employing molecules with desirable properties such as low MW and low lipophilicity is advantageous. Therefore employing fragments with desirable physicochemical properties in FBDD may be benefical in the drug development process. Oxetanes are small heteroaliphatic rings that confer desirable physicochemical properties when incorporated into larger drug-like compounds. As such small oxetane containing compounds based in fragment space were examined as motifs likely to be desirable for medicinal chemistry, particularly for screening in FBDD. Owing to the limited methods available for the synthesis of oxetanes bearing functional groups there was a need to develop novel versatile methods to access oxetanes and their derivatives.

Thus, the aims of the research are:

1) To synthesise and evaluate a variety of oxetane containing compounds as desirable motifs for use in medicinal chemistry.
2) To develop novel methods to access oxetane containing compounds and their derivatives.

2. Synthesis and Functionalisation of 2-Aryl Sulfonyl Oxetanes Designed as Desirable Fragments for Fragment Based Drug Discovery

Concise summaries of the results discussed below are published in *Chemical Communications* and *Organic and Biomolecular Chemistry*.[111,112]

2.1. 2-Sulfonyl Oxetanes: Interesting Motifs for Drug Discovery?

2-Aryl sulfonyl oxetanes were designed as new chemical motifs to be incorporated into drug-like compounds as well as interesting fragments for use in FBDD. The oxetane was predicted to confer beneficial physicochemical properties whilst the sulfonyl moiety had the potential to form favourable hydrogen bond interactions with the chosen target. Initially four sulfonyl oxetanes were designed as novel and potentially interesting fragments with properties complying to the "rule of 3" modified for the number of hydrogen bond acceptors.[31] The tolyl, phenyl, *para*-chloro phenyl and 2-pyridyl substrates were all considered to have desirable physicochemical properties, figure 18.

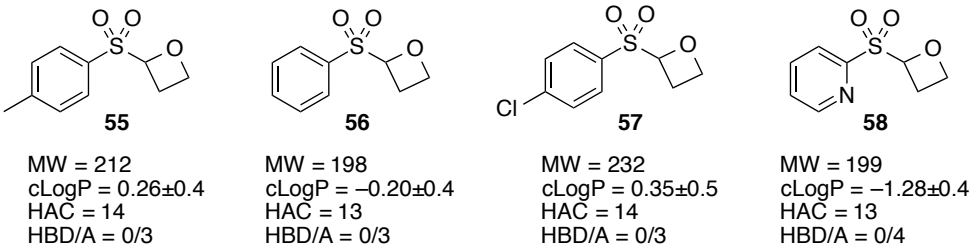


Figure 18: 2-Aryl sulfonyl oxetane targets. MW = molecular weight; cLogP = calculated logP (lipophilicity); HAC = heavy atom count (number of non-H atoms); HBD/A = number of hydrogen bond donors/acceptors.

In addition, the shape of 2-aryl sulfonyl oxetanes was considered as evidence suggests that 3-D fragments are more likely to be developed into successful drug candidates than "flat" molecules.[16,18] To demonstrate the 3-dimensional shape of the 2-sulfonyl oxetane series an energy minimised structure of 2-(benzenesulfonyl)oxetane **56** was calculated,[i] figure 19-A.[113] This structure clearly illustrated the non-planar shape of 2-aryl sulfonyl oxetanes, which resulted in a variety of possible vectors in which the fragments could potentially be elaborated. For example, deprotonation alpha to the sulfone moiety may allow functionalisation directly on the oxetane ring; the sulfone group could be exploited to functionalise in the *ortho* position of the aromatic ring[114] and substituents incorporated

[i] Calculation performed by Dr. James A. Bull at Imperial College London.

onto the aromatic ring, such as a halide, would encourage elaboration in a third direction, figure 19-B.

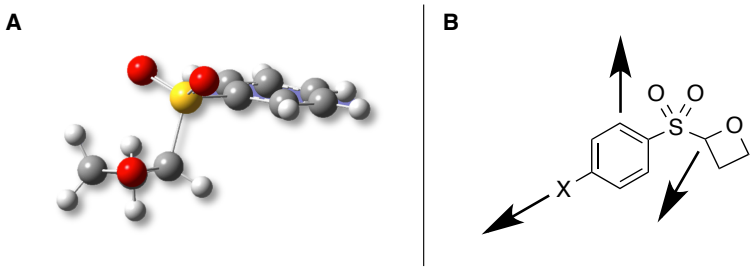
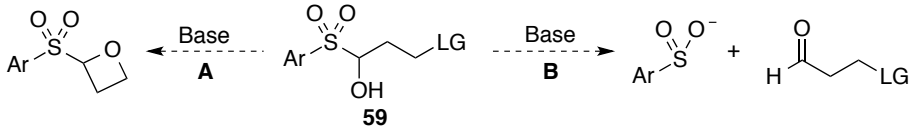


Figure 19: A: DFT calculation of the minimum energy structure of oxetane **56** calculated using Gaussian 09, up to the B3LYP/3-21G level of theory with default implicit solvation in water.[113] B: Illustration of the potential directions in which 2-sulfonyl oxetanes could be functionalise.

2.2. Synthesis of 2-Aryl Sulfonyl Oxetanes

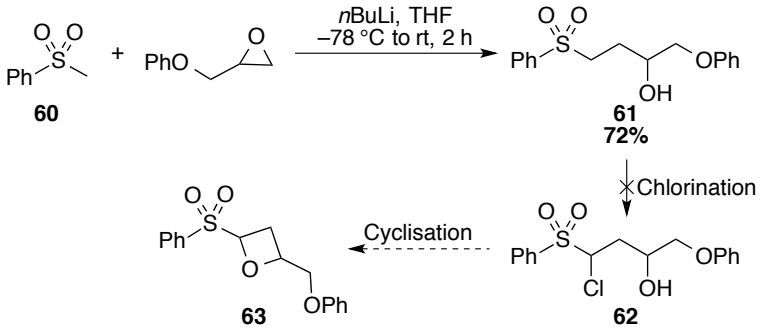
The three most prominent methods for synthesising the oxetane structure are intramolecular Williamson etherification, [2+2] Paternò−Büchi cycloaddition and epoxide ring opening/ring closing, previously discussed in chapter 1. All three approaches involve the construction of the oxetane ring *via* formation of a carbon-oxygen bond and so are not suitable for the synthesis of the proposed 2-aryl sulfonyl oxetanes due to the instability of the required intermediates. The synthesis of 2-aryl sulfonyl oxetanes using a Williamson etherification would require α-hydroxy sulfonyl intermediate **59**, scheme 19 **A**. However, under basic conditions α-hydroxy sulfones undergo a retrocondensation reaction to afford the corresponding carbonyl compound and sulfinate, scheme 19 **B**.[115]



Scheme 19: Desired cyclisation and expected retrocondensation of α-hydroxyl sulfone intermediate **59**. LG = leaving group.

A Williamson etherification approach to synthesise 2-sulfonyl oxetanes without generating an α-hydroxy sulfone was investigated within the Bull group. The reaction of sulfone **60** with 1,2-epoxy-3-phenoxypropane in the presence of *n*BuLi resulted in the formation of product **61**. Subsequent chlorination was required to afford **62** which, upon treatment with a base, was proposed to cyclise affording the 2-aryl sulfonyl oxetane **63**,

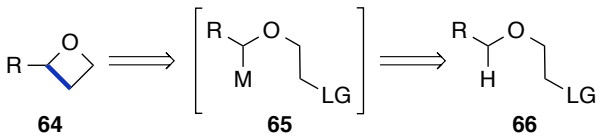
scheme 20. Chlorination with NCS or CCl_4 was unsuccessful as only starting material was observed, so this route could not be progressed and the desired sulfonyl oxetane was not synthesised.[116]



Scheme 20: Previous investigation into 2-sulfonyl oxetane synthesis.[116]

2.2.1. A Novel Approach to Oxetane Synthesis

The synthesis of the oxetane heterocycle is challenging due to the formation of a small strained ring. There is a need for new diverse methods to synthesise oxetanes with wide substrate scope. To overcome the limitations of the current methods and probe a new strategy, synthesis of the oxetane ring *via* a carbon-carbon bond formation was proposed, scheme 21.

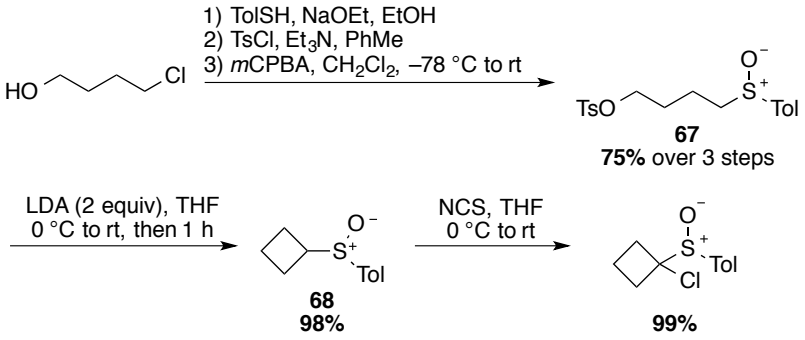


Scheme 21: Proposed retrosynthetic analysis of the oxetane motif.

Accessing the oxetane by formation of the C–C bond highlighted would require the synthesis of precursor **66**. Deprotonation with an appropriate base would result in a metallated immediate, which could undergo an intramolecular cyclisation to afford oxetane **64**. Intermediate **65** would be required to be stable under the reaction conditions to allow the desired cyclisation to occur. The stability could be enhanced if R was an anion stabilising group. The required electron-withdrawing R group may also allow a substituent that could be further functionalised to be incorporated onto the oxetane motif. In the case of 2-aryl sulfonyl oxetanes the aryl sulfone moiety would fulfil the role of the

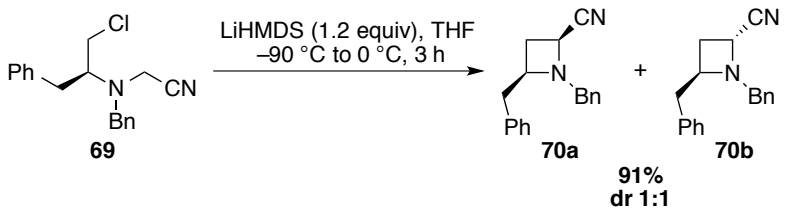
anion stabilising group, stabilising the metallated intermediate and encouraging derivatisation in multiple directions.

A similar C–C bond forming 4-*exo*-*tet* ring closing strategy was exploited for cyclobutane and azetidine formation.[117,118] In 2011 Satoh reported the synthesis of sulfinyl cyclobutane **68** in 4 steps. Alkylation of 4-chlorobutan-1-ol with sodium 4-methylbenzene thiolate resulted in an hydroxyl intermediate which was subsequently converted to the *p*-toluenesulfonate substrate then oxidised with *m*CPBA to afford tosyl sulfoxide **67** in a yield of 75% over the 3 steps. When treated with LDA an intramolecular cyclisation proceeded to afford cyclobutane **68** in a yield of 98%. Chlorination of the resulting cyclobutane with NCS afforded the desired chlorinated derivative in quantitative yield, scheme 22.[117]



Scheme 22: Synthesis of sulfinyl cyclobutane **68** *via* a C–C bond forming cyclisation.[117]

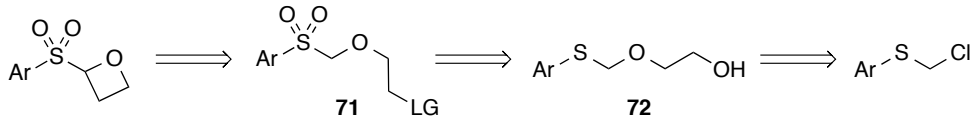
Couty reported a similar C–C bond forming intramolecular cyclisation in the synthesis of 2-cyano azetidines from β-amino-alcohols.[118] α-Amino nitrile **69** was treated with 1.2 equivalents of LiHMDS to afford a mixture of azetidine stereoisomers **70a** and **70b** *via* a 4-*exo*-*tet* cyclisation of the lithiated amino nitrile, scheme 23.



Scheme 23: Azetidine formation *via* a 4-*exo*-*tet* cyclisation.[118]

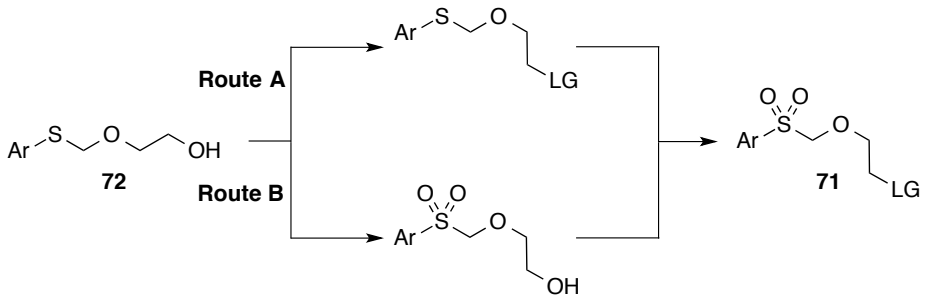
2.2.2. Synthesis of a Suitable Cyclisation Precursor

A retro synthetic analysis of 2-aryl sulfonyl oxetanes was performed, scheme 24. The desired cyclisation precursor **71** could be generated *via* oxidation and incorporation of a leaving group onto sulfide **72**, which could be obtained from the corresponding chloromethyl sulfide. A variety of aryl chloromethyl sulfides were commercially available or could be obtained from the analogous thiols in two steps, providing these as desirable starting materials.



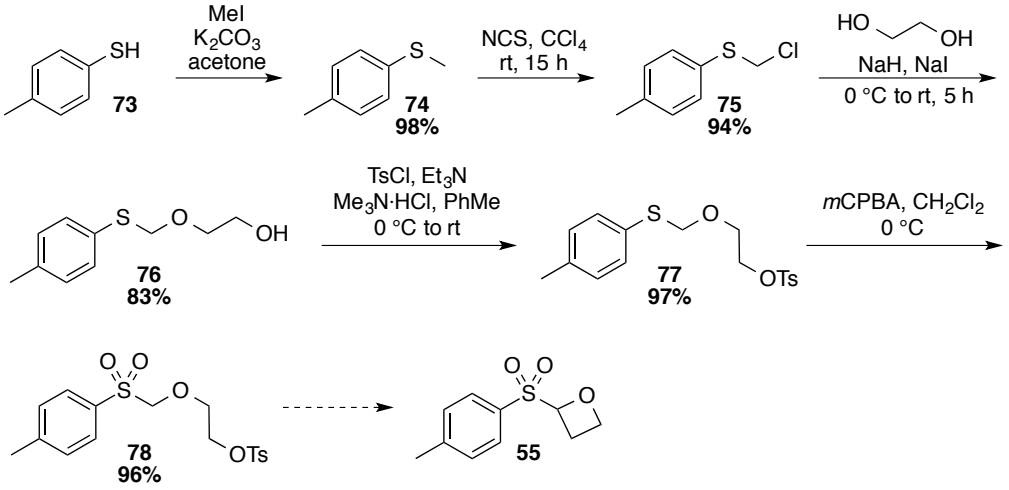
Scheme 24: Retrosynthetic analysis of 2-aryl sulfonyl oxetanes.

Two possible routes were considered for the synthesis of **71** from **72**, scheme 25. A leaving group could be incorporated utilising the free hydroxyl of **72**, then the resulting sulfide oxidised to the sulfone, route A. Alternatively oxidation of **72** followed by incorporation of a leaving group could generate the cyclisation precursor, route B. Both synthetic pathways were reasonable and the success would depend on the stability of the intermediate compounds to the reaction conditions. Initial investigation explored oxidation as the final step (route A) as this would provide the opportunity to access sulfide and sulfoxide derivatives with minimum synthetic effort. In addition successful oxidation of sulfide **72** may require protecting the alcohol first which would increase the number of synthetic steps required.



Scheme 25: Two possible synthetic routes to transform **72** into sulfone **71**.

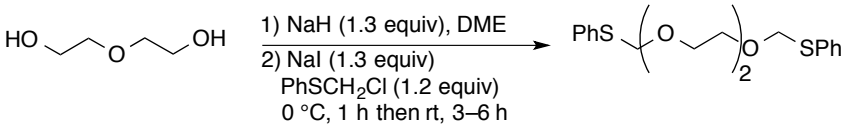
Investigation of the synthetic route was undertaken using 2-(4-methylbenzene)-sulfonyl oxetane **55**, starting with readily available 4-methylbenzenethiol **73**, scheme 26.



Scheme 26: Synthesis of the precursor to 2-(4-methylbenzene)-sulfonyl oxetane **55**.

Methylation with MeI followed by chlorination with 1.1 equiv of NCS resulted in the desired chloromethyl sulfide in a 92% yield over the 2 steps. Only a small excess of chlorinating reagent was employed, to prevent undesired double chlorination. Both reactions proceeded to completion with no side product formation, enabling the products to be filtered through a short pad of silica gel and progressed through the synthesis without further purification. This was advantageous as intermediate **75** was unstable to chromatography on silica gel.

Alkylation of ethylene glycol with chloromethyl sulfide **75** was examined next. Julia reported the alkylation of diethylene glycol with chloromethyl phenyl sulfide in the presence of NaH and NaI affording the corresponding bis-sulfide, scheme 27.[119] The resulting bis-sulfide was oxidised to the corresponding bis-sulfone using hydrogen peroxide to obtain the product in a 56% yield over the two steps.



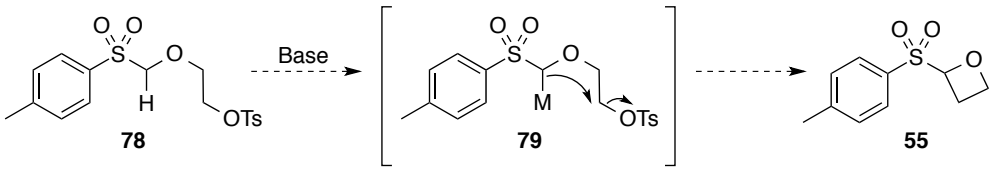
Scheme 27: Alkylation of diethylene glycol with chloromethyl phenyl sulfide.[119]

To promote mono-alkylation, required to synthesise alcohol **76**, and prevent undesirable double alkylation a large excess of ethylene glycol, 100 equivalents, was employed as the solvent. Initially ethylene glycol was deprotonated with NaH (1.1 equiv), then NaI followed by chloromethyl sulfide **75** were added. After 5 h alcohol **76** was formed in a yield of 83%.

Similar to Satoh's approach to cyclobutane synthesis, scheme 22, a *p*-toluenesulfonate group was initially investigated as an appropriate leaving group that could be substituted in the intramolecular cyclisation reaction.[117] Alcohol **76** was reacted with *p*-toluenesulfonyl chloride in the presence of triethylamine and catalytic trimethylamine hydrochloride to afforded intermediate **77** in a yield of 97%.[120] Subsequent oxidation of the sulfide to the corresponding sulfone was performed with 3 equivalents of *m*CPBA to avoid mono-oxidation to the sulfoxide, affording the desired cyclisation precursor **78** in a yield of 96%.

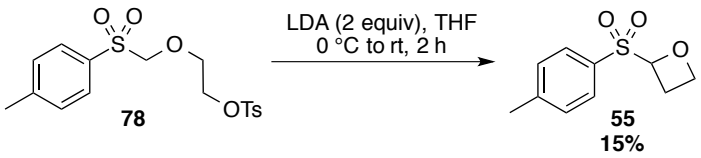
2.2.3. Investigation into the Intramolecular C–C Bond Forming Cyclisation

Deprotonation of **78** alpha to the sulfone moiety would result in the formation of a metallated intermediate which was anticipated to undergo a 4-*exo*-*tet* cyclisation, displacing the leaving group, to generate oxetane **55**, scheme 28. The stability of **79** was crucial, requiring stability to alpha-elimination but sufficient reactivity to cyclise.



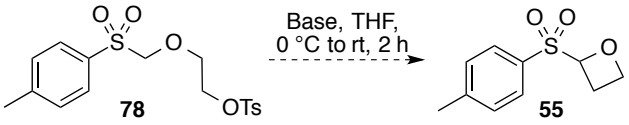
Scheme 28: Proposed mechanism of the cyclisation to form oxetane **55**.

Initially sulfone **78** was added to a solution of LDA in THF at 0 ºC and warmed to rt (cf. Satoh),[117] a yellow colour was observed indicating anion formation. After 2 h the desired 2-sulfonyl oxetane was obtained with a 15% yield following chromatography, scheme 29. This result prompted investigation into the reaction conditions.



Scheme 29: Initial examination of the desired intramolecular ring forming reaction.

A selection of bases was explored to promote cyclisation, table 5. The proton alpha to the sulfone was expected to have a pK_a value around 30 however NaH with an estimated pK_a value of 35 did not deprotonate sulfone **78**, entry 1.[121] Amine bases were examined next; LDA, LiTMP, KHMDS, NaHMDS and LiHMDS all formed sulfonyl oxetane **55** in moderate yields. Comparing entries 5–7 showed that employing the lithium substrate resulted in the highest yield. This increase in yield was thought to be due to the smaller size of the lithium cation which resulted in stronger coordination to the anion, stabilising the intermediate.



Entry	Base	Equiv base	Conc*n* [M]	Order of addition[a]	Yield **55** (%)[b]	Yield **78** (%)[b]
1	NaH	2	0.025	A	0	100
2	LDA[c]	2	0.025	A	12	50
3	LiTMP[c]	2	0.025	A	32	25
4	*n*BuLi[d]	2	0.025	A	68	0
5	KHMDS	2	0.025	A	45	0
6	NaHMDS	2	0.025	A	33	0
7	LiHMDS	2	0.025	A	50	0
8	LiHMDS[c]	2	0.025	A	63	0
9	*n*BuLi[d]	2	0.025	B	52	0
10	LiHMDS[c]	2	0.025	B	89	0
11	LiHMDS[c]	1.2	0.025	B	97	0
12	LiHMDS[c]	1.2	0.05	B	81	0
13	LiHMDS[c]	1.2	0.0125	B	99	0
14	LiHMDS[c,e]	1.2	0.025	B	99	0
15	**LiHMDS[c,e]**	**1.1**	**0.025**	**B**	**99**	**0**
16	LiHMDS[c,e]	1.05	0.025	B	93	7

Table 5: Selected optimisation: intramolecular cyclisation of sulfone **78** to oxetane **55**. [a] Conditions A, addition of the substrate to a solution of the base in THF; Conditions B, addition of the base to a solution of the substrate in THF. [b] Yield determined by ^{1}H NMR with respect to 1,3,5-trimethoxybenzene as an internal standard. [c] Base made immediately prior to use. [d] Reaction run at –78 ºC not 0 ºC. [e] Total reaction time of 1 h.

LiHMDS and *n*BuLi were both selected for progression in the optimisation as they resulted in the highest product yields of 63% and 68%, entries 4 and 8. The low recovery of material was thought to be due to the compounds' instability under basic conditions, prompting investigation into the order of reagent addition. Changing the order to allow addition of the base to a solution of **78** in THF resulted in a decrease in yield when employing *n*BuLi, entries 4 and 9, but a substantial increase in yield of 26% was observed when using LiHMDS, entries 8 and 10. This result demonstrated the disadvantage of employing a large excess of base which led to the number of equivalents of base employed being examined. The amount of LiHMDS could be reduced to 1.2 equiv affording a further increase in yield to 97%, entry 11.

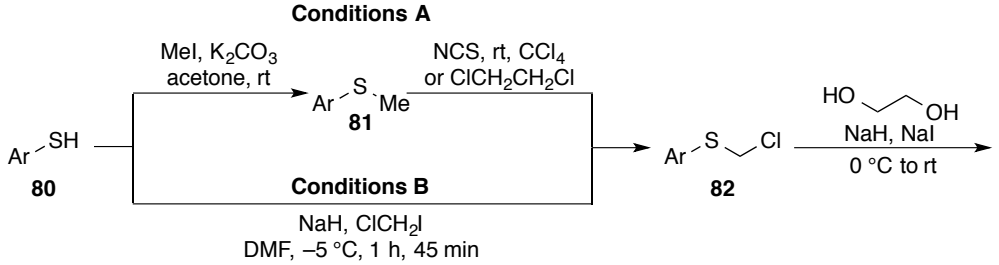
The concentration of the reaction was then investigated. Dilute conditions were preferred to favour intramolecular cyclisation over an intermolecular reaction. As anticipated a notable reduction in yield was observed upon increasing the concentration whilst more dilute conditions gave a marginal increase in yield to 99%, entries 11–13. The reaction could be further improved by reducing the time from 2 h to 1 h, entry 14, and reducing the number of equivalents of base further to 1.1 afforded a quantitative conversion to the oxetane product, entry 15. This provided the optimal reaction conditions as a further decrease in the number of equivalents of LiHMDS did not improve the reaction, entry 16.

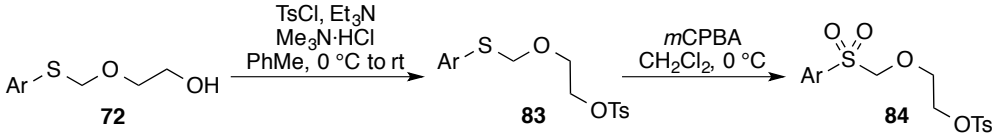
Under these conditions the synthesis was performed on a 6.5 mmol scale to obtain 1.2 g of oxetane **55** with a 93% isolated yield. This gram scale reaction was important when considering the desirability of 2-aryl sulfonyl oxetanes as fragments or motifs to be incorporated into drug candidates. A protocol would be required to produce large quantities of the 2-sulfonyl oxetane were the fragment to be incorporated into a successful drug candidate.

2.2.4. Investigation into the Scope of 2-Aryl Sulfonyl Oxetanes

The optimised cyclisation conditions were employed to a variety of substrates to access a wide range of novel fragments. Synthesis of the initial four fragments designed along with substrates with *meta* and *ortho* substitution on the aromatic ring and an electron-withdrawing and electron-donating example was examined. The diversity was introduced

at the beginning of the synthetic sequence so a variety of sulfone substrates **84** were synthesised before the cyclisation could be investigated, scheme 30.

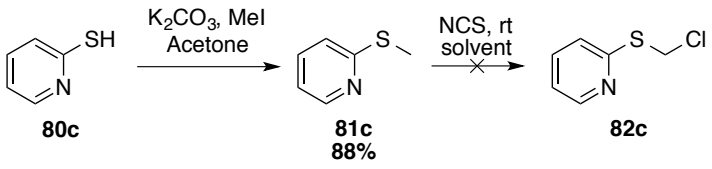




Ar	Yield **82**	Yield **72**	Yield **83**	Yield **84**
a Ar = Ph	**82a** -	**72a** 87%	**83a** 98%	**84a** 93%
b Ar = 4-Cl-(C_6H_4)	**82b** 94%	**72b** 74%	**83b** 98%	**84b** 95%
c Ar = 2-pyridyl	**82c** 91%*	**72c** 63%	**83c** 95%	**84c** 86%
d Ar = 2-Me-(C_6H_4)	**82d** 90%	**72d** 66%	**83d** 91%	**84d** 99%
e Ar = 2-Cl-(C_6H_4)	**82e** 99%	**72e** 71%	**83e** 94%	**84e** 90%
f Ar = 3-Cl-(C_6H_4)	**82f** 95%	**72f** 71%	**83f** 92%	**84f** 99%
g Ar = 4-F-(C_6H_4)	**82g** 94%	**72g** 72%	**83g** 96%	**84g** 97%
h Ar = 4-Br-(C_6H_4)	**82h** 99%	**72h** 79%	**83h** 96%	**84h** 99%
i Ar = 4-F_3C-(C_6H_4)	**82i** 91%	**72i** 61%	**83i** 99%	**84i** 97%
j Ar = 4-OMe-(C_6H_4)	**82j** 99%	**72j** 58%	**83j** 98%	**84j** 88%

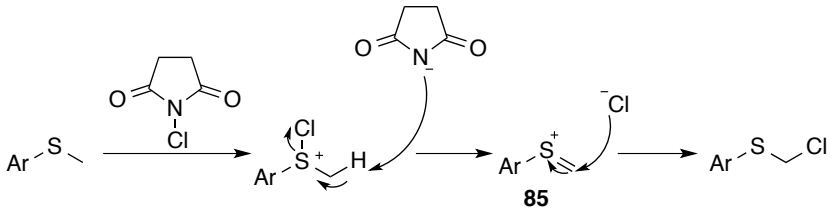
Scheme 30: Synthesis of the cyclisation precursor **84** with a variety of aromatic substituents. *Isolated as a 9:1 mixture with bis(pyridine-2-ylthio)methane.

Chloromethyl phenyl sulfide **82a** was commercially available however all other substrates were prepared from the corresponding aryl methyl sulfides **81** or thiols, following a methylation then chlorination sequence depicted in scheme 30, conditions A. An alternative approach to access the 2-pyridyl substrate was required as 2[(chloromethyl)sulfanyl] pyridine **82c** was not commercially available and could not be synthesised successfully using conditions A, scheme 31.



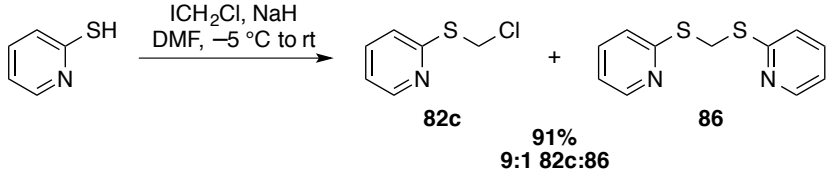
Scheme 31: Initial investigation into the synthesis of chloromethyl sulfide **82c**.

Methylation of 2-mercaptopyridine with MeI provided methyl sulfide **81c** in a yield of 88%, however chlorination with NCS was unsuccessful and only starting material was isolated. In an effort to improve the chlorination a range of solvents was tested; dichloromethane, acetonitrile, carbon tetrachloride and dichloroethane, however no desired product was seen. To explain this observation the proposed chlorination mechanism was considered, scheme 32.



Scheme 32: Proposed mechanism of the chlorination reaction with NCS.

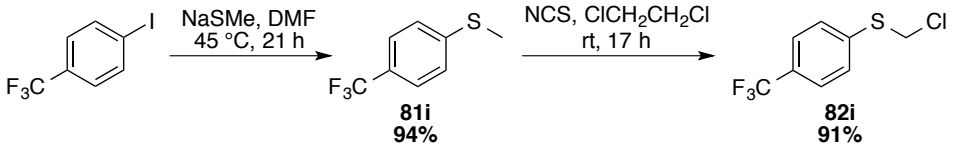
Following initial chlorination of the sulfur atom with NCS the acidity of the methyl group would increase. The resulting succinimide could therefore deprotonate the methyl group to form intermediate **85** which, after attack of a chloride ion, would afford the desired chloromethyl sulfide. The electron poor pyridyl group may reduce the reactivity at the sulfur atom, hindering the initial chlorination and preventing formation of **82c**. Alternatively *N*-chlorination was possible and may have occurred, therefore an alternative route using chloroiodomethane was explored, conditions B (scheme 30).[122]



Scheme 33: Alterative conditions to synthesise 2-((chloromethyl)sulfanyl)pyridine **82c**.

A solution of chloroiodomethane in DMF was added in one portion to a mixture of 2-mercaptopyridine and sodium hydride in DMF to form chloromethyl sulfide **82c** in one step. The rate of addition was crucial to the reaction as slow addition of the chloroiodomethane solution resulted in the formation of disulfide **86** whilst fast addition resulted in a 91% yield as a 9:1 mixture of **82c** to disulfide **86**, scheme 33.

p-Trifluoromethyl phenyl chloromethyl sulfide **82i** was also synthesised *via* an alternative route due to the lack of availability of the corresponding thiol. 4-Iodobenzotrifluoride was treated with sodium thiomethoxide in DMF to form methyl sulfide **81i** which subsequently underwent successful chlorination with NCS to afford the desired chloromethyl sulfide. Both steps proceeded in excellent yields of 94% and 91% respectively, scheme 34.



Scheme 34: Synthetic route to 1-[(chloromethyl)sulfanyl]-4-(trifluoromethyl)benzene **82i**.

The subsequent steps in the synthetic sequence were successful for all substrates investigated and proceeded in excellent yields. The alkylation of ethylene glycol varied between 58–87% depending on the substrate employed. These intermediates were reactive towards tosylation with *p*-toluenesulfonyl chloride affording substrates **83a-j** in greater than 90%. Finally oxidation with *m*CPBA gave the desired sulfones **84a-j** in good yields.

Having synthesised 11 novel aryl sulfones they were exposed to the optimised cyclisation conditions of LiHMDS (1.1 equiv) in THF at 0 ºC for 1 h to form the corresponding 2-aryl sulfonyl oxetane fragments. The wide substrate scope is shown in figure 20.

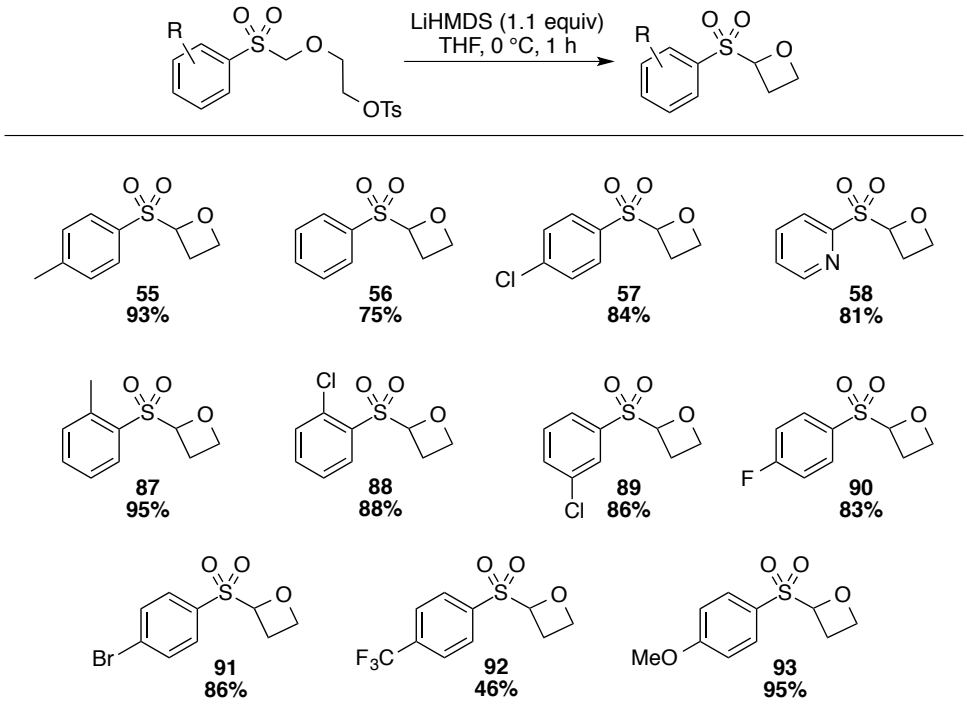


Figure 20: 2-Sulfonyl oxetanes synthesised *via* an intramolecular carbon-carbon bond formation.

The initial four fragments designed incorporating a phenyl, *para*-tolyl, *para*-chloro phenyl and 2-pyridyl ring were successfully synthesised in good yields, **55-58**. The cyclisations to afford **55-57** were performed on a larger scale to give over 1 g of the desired fragments. The aromatic substitution was probed next. The synthesis of oxetanes **87-89** exemplified the successful incorporation of substituents in the *meta* and *ortho* positions of the aromatic ring. Pleasingly the *ortho*-substituted derivatives cyclised to afford the corresponding sulfonyl oxetanes **87** and **88** in yields of 95% and 88%. In addition the fluoro and bromo substrates **90** and **91** were obtained in excellent yields. The introduction of halides on the aromatic ring provided opportunities for further elaboration and derivatisation of the oxetane fragments in a variety of directions. Finally, both electron-withdrawing and electron-donating derivatives were successful, **92** and **93**. Cyclisation to form **92** proceeded in a slightly lower yield than other substrates with no starting material remaining. This may have been due to the electron-withdrawing nature of the aromatic ring inhibiting cyclisation or promoting degradation of the intermediate anion. The electron-donating methoxy substituent may have increased the reactivity of the sulfonyl anion, promoting cyclisation and leading to oxetane **93** in a yield of 95%.

Not all the substrates investigated were successfully synthesised *via* the developed route. The 2-sulfonyl oxetanes that could not be obtained are shown in figure 21 and are discussed below.

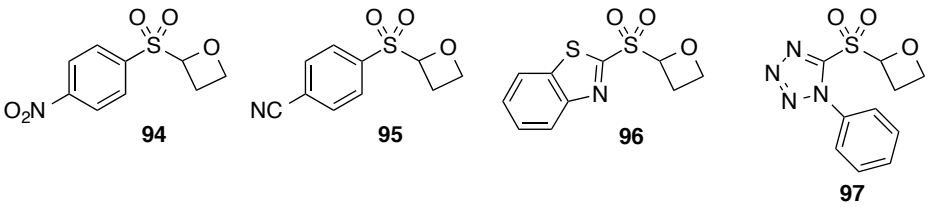
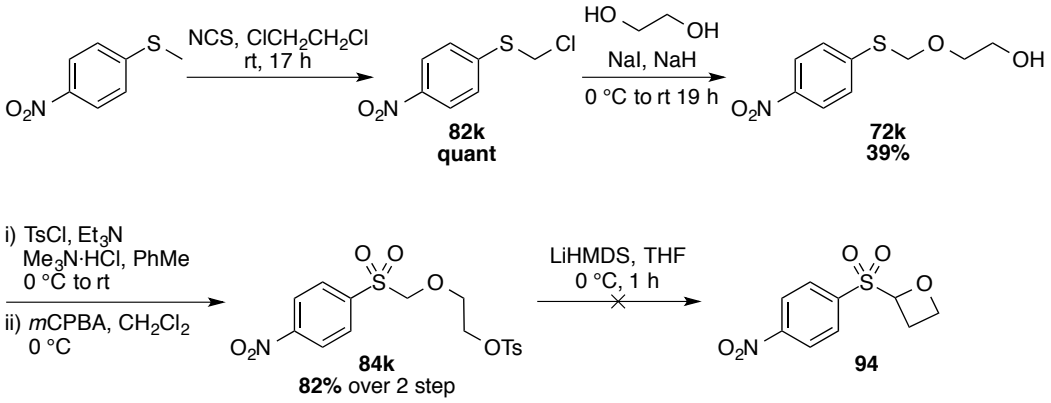


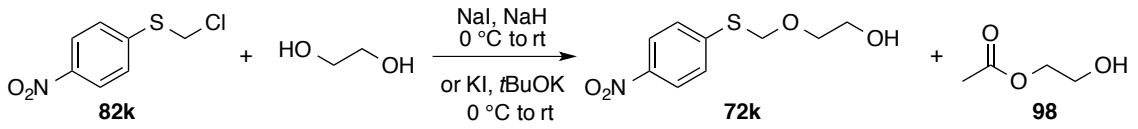
Figure 21: Structure of the 2-sulfonyl oxetane fragments that were not successfully obtained.

2-(4-Nitrobenzenesulfonyl)oxetane **94** was interesting as the nitro group provided a potential handle for further derivatisation, for example by reduction to the aniline which could then undergo subsequent amide bond formation. Chlorination of 4-nitrothioanisole with NCS proceeded in a quantitative yield but unfortunately alkylation of ethylene glycol afforded **72k** in only 39% after 19 h, scheme 35.



Scheme 35: Synthetic route employed to synthesise 2-(4-nitrobenzenesulfonyl)oxetane **94**.

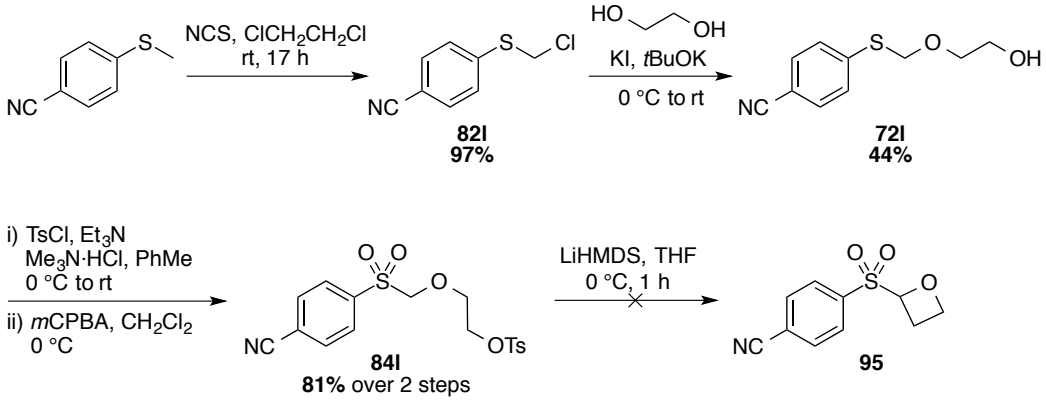
Increasing the reaction time to 48 h resulted in a decrease in yield of **72k** and formation of an additional compound, characterised as 2-hydroxyethyl acetate **98**, scheme 36. To optimise away from this undesired product a second set of reaction conditions was explored. Treatment of chloromethyl sulfide **82k** with KI and *t*BuOK eliminated formation of **98** but unfortunately did not increase the yield of desired product, scheme 36.



Scheme 36: Alkylation of ethylene glycol with 1-[(chloromethyl)sulfanyl]-4-nitrobenzene.

The isolated material was progressed through the synthetic route to afford cyclisation precursor **84k** in an 82% yield over 2 steps, scheme 35. If the cyclisation was successful the alkylation of ethylene glycol would be optimised further. Surprisingly when **84k** was treated with LiHMDS to allow cyclisation no sulfonyl oxetane was formed, only starting material was recovered. The electron-withdrawing effect of the NO_2 substituent may have stabilised the lithiated intermediate generated after deprotonation, hindering the cyclisation. As a result fragment **94** could not be synthesised *via* the developed C–C bond forming cyclisation.

The synthesis of 2-(4-cyanobenzenesulfonyl)oxetane **95** was attractive as the nitrile group is itself an interesting group in medicinal chemistry and would also provide a handle for further functionalisation, for example *via* reduction to an amine or hydrolysis to an amide. The synthetic route is shown in scheme 37.

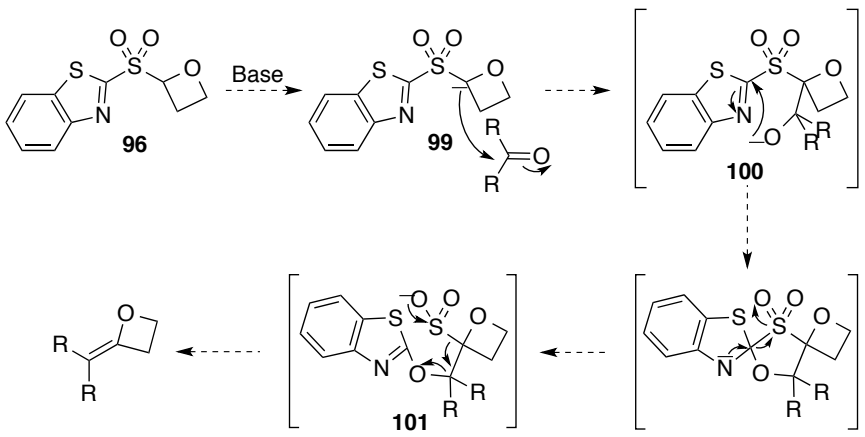


Scheme 37: Attempted synthetic route to synthesise 2-(4-cyanobenzenesulfonyl)oxetane **95**.

When ethylene glycol was alkylated with chloromethyl sulfide **82l** in the presence of NaH and NaI a yield of 13% was observed. This was possibly due to the electron-withdrawing nature of the nitrile group. Employing KI and *t*BuOK allowed the desired product to be isolated in a 44% yield and progressed through the synthetic route to afford the cyclisation precursor. Sulfone **84l** was treated with LiHMDS at 0 ºC of 1 h. Possible oxetane products

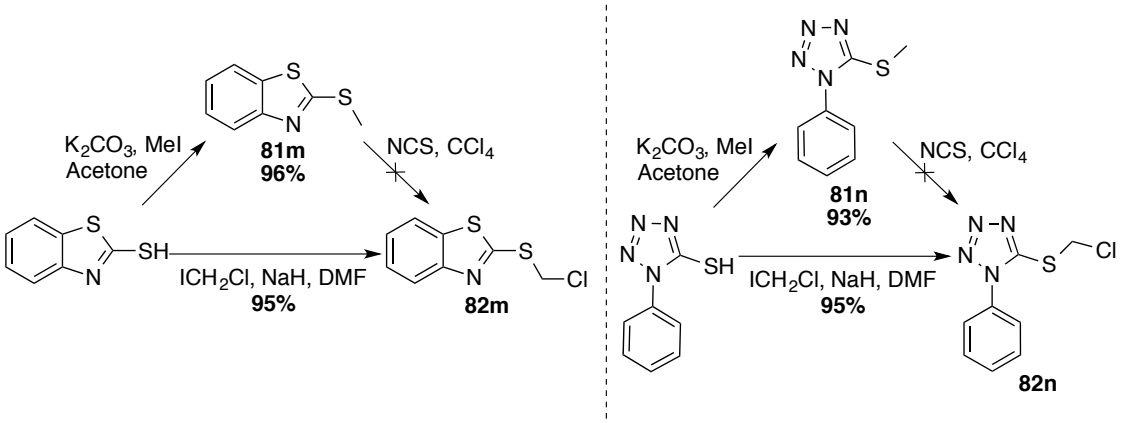
were observed during anaylsis of the crude material by ^{1}H NMR however the desired sulfonyl oxetane could not be isolated from the crude reaction mixture, therefore the outcome of the reaction could not be confirmed.

A desirable property of the 2-sulfonyl oxetanes was the potential to further derivatise and elaborate them. With this in mind the synthesis of oxetanes **96** and **97** was investigated with the aim of exploring their use in the modified Julia olefination reaction, a widely used method for alkene formation that has emerged as a powerful tool for advanced fragment linking.[123] This would allow the synthesis of a variety of vinyl oxetanes. The proposed mechanism of the modified Julia olefination with the heteroaryl sulfonyl oxetane **96** is shown in scheme 38.



Scheme 38: Proposed mechanism of the Julia olefination with 2-(oxetane-2-sulfonyl)-1,3-benzothiazole **96**.

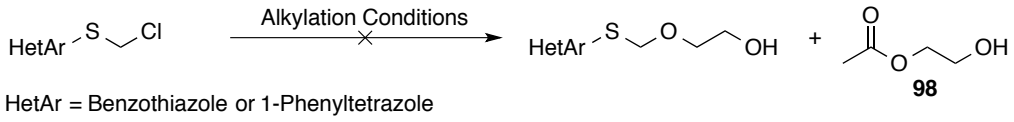
Initial deprotonation of oxetane **96** was expected to afford anion **99** which, following addition to a carbonyl compound, could result in the formation of intermediate **100**. The alkoxysulfone intermediate would be unstable and expected to undergo a Smiles rearrangement to form sulfinate **101**. Elimination of sulfur dioxide and the benzothiazole salt would yield the vinyl oxetane product. Before the Julia olefination could be investigated the heterocyclic sulfonyl oxetanes needed to be synthesised. Starting from the corresponding thiols the synthesis of the required chloromethyl sulfides was examined, scheme 39.



Scheme 39: Synthesis of chloromethyl sulfides **82m** and **82n** required to synthesise oxetanes **96** and **97**.

In general the two-step methylation then chlorination protocol was preferred as the products were pure after work-up removing the need for further purification. For both the benzothiazole and phenyltetrazole substrates methylation proceeded in high yields but subsequent chlorination was unsuccessful, scheme 39. The electron-withdrawing effect of the heterocycles may deactivate the sulfur atom, as discussed previously, preventing chlorination. So the one-step reaction with chloroiodomethane was explored and successfully produced chloromethyl sulfides **82m** and **82n** in excellent yields.

Alkylation of ethylene glycol in the presence of NaH and NaI was unsuccessful. Interestingly, in addition to 2-hydroxyethyl acetate, starting material was observed in the crude reaction mixture for both substrates, scheme 40.



Scheme 40: Unsuccessful alkylation of ethylene glycol with heteroaromatic chloromethyl sulfides.

The developed conditions employed ethylene glycol as the reaction solvent however this introduced problems with the solubility of the chloromethyl sulfides. As poor compound solubility may have prohibited the alkylation of ethylene glycol the reaction was repeated with DMF added to aid sulfide solubility, however still no product formation was observed. Reducing the amount of ethylene glycol to 1.1 equivalents to inhibit formation of **98** resulted in no **98** or product formation, whilst employing alternative alkylation conditions of KI and *t*BuOK did not improve the reaction. These findings suggested that

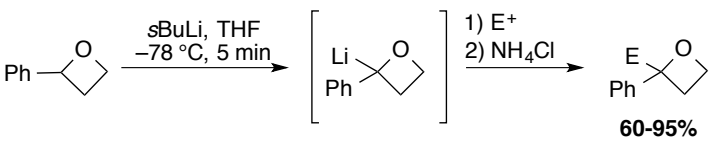
the heterocyclic chloromethyl sulfides were not reactive enough under the current conditions to alkylate ethylene glycol. Due to this observation the synthesis of these fragments was not investigated further and consequently the Julia olefination could not be explored.

2.3. Functionalisation of 2-Aryl Sulfonyl Oxetanes

2-Aryl sulfonyl oxetanes were designed as novel, 3-D fragments for use in FBDD or as interesting motifs to be incorporated into larger drug molecules. An important aspect of the fragment design was the ability to elaborate and derivatise the compounds in multiple directions, allowing the fragments to be developed and optimised towards larger lead-like and drug-like compounds. Similarly the ability to introduce the oxetane motif into drug compounds by a range of methods is important. Investigations into the functionalisation of 2-aryl sulfonyl oxetanes are discussed below.

2.3.1. Lithiation of 2-Aryl Sulfonyl Oxetanes

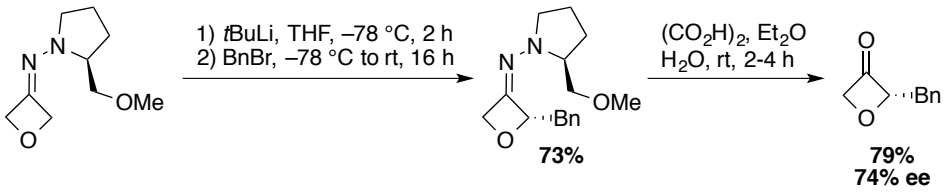
Carbon-carbon bond formation directly on the strained oxetane ring was desirable from a synthetic perspective, as little was known about the reactivity of 2-sulfonyl oxetanes, and from a medicinal chemistry perspective as the potential products may be interesting to incorporate in a drug discovery programme. Initially functionalisation *via* a metallated intermediate was investigated. Capriati reported an efficient route to 2-substituted phenyloxetanes *via* 2-lithio-2-phenyloxetane, formed by deprotonation with *s*BuLi, scheme 41.[124] 2-Sulfonyl oxetanes were predicted to show similar reactivity and undergo regioselective deprotonation on the oxetane ring.



Scheme 41: Functionalisation of 2-phenyloxetane *via* lithiation followed by electrophilic trapping.[124]

A timely publication by Shipman discussed the enantioselective synthesis of 2-substituted oxetan-3-ones by metallation followed by alkylation, scheme 42.[125] This further

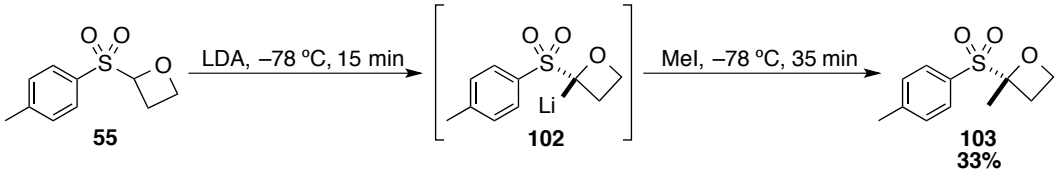
exemplified the viability of functionalising the oxetane motif by lithiation of the heterocycle.



Scheme 42: Enantioselective synthesis of 2-substituted oxetan-3-ones by lithiation then alkylation.[125]

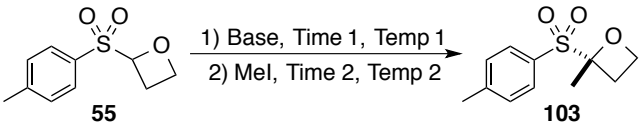
2.3.1.1. Optimisation of Reaction Conditions

2-(4-Methylbenzene)sulfonyloxetane **55** was chosen as the fragment with which to investigate the functionalisation. Initially lithium amide bases were explored for the deprotonation of the oxetane ring. Oxetane **55** was treated with 1.1 equivalents of LDA at –78 ºC to afford metallated oxetane **102** which, following addition of MeI, gave alkylated oxetane **103** in a 33% isolated yield, scheme 43. This result demonstrated that the intact oxetane ring could be functionalised.



Scheme 43: Initial investigation into the functionalisation of sulfonyl oxetanes directly on the oxetane ring.

To probe the reason for the low yield a deuterium quench was performed. Oxetane **55** was treated with LDA then quenched with either MeOD or D_2O after 15 min, analysis of the ^1H NMR spectra showed only 60% deuterium incorporation. This was a surprising result as LDA, with a pK_a of 36, was expected to fully deprotonate the oxetane. A deuterium proton exchange may have occurred between the deuterium source and the excess amine, present in the reaction from the synthesis of LDA, prior to reaction with the oxetanyl anion. As a result the deuterium quench was inconclusive and could not be used to further explore the lithiation reaction. Despite this, the reaction was investigated further to promote product formation. A selection of the optimisation results is shown in table 6.



55 **103**

Entry[a]	Base	Order of addition[b]	Temp 1 (ºC)	Temp 2 (ºC)	Time 1 (min)	Time 2 (min)	Yield[c]
1	LDA	B	–78	–78 to 0	15	45	62
2	*n*BuLi	B	–78	–78 to 0	15	45	49
3	*s*BuLi	B	–78	–78 to 0	15	45	20
4	LiHMDS	B	–78	–78 to 0	15	45	76
5	LiHMDS	B	–78	–78	15	45	22
6	LiHMDS	B	–40	–40	15	60	70
7	LiHMDS	B	–78	–78 to 0	30	45	84
8	LiHMDS[d]	B	–78	–78 to 0	30	45	79
9	LiHMDS[e]	B	–78	–78 to 0	30	45	86
10	LiHMDS	A	–78	–78 to 0	30	45	61
11	**LiHMDS**	**B**	**–78**	**–78 to 0**	**0**	**90**	**90**

Table 6: Selected optimisation results for the functionalisation of 2-sulfonyl oxetane **55** *via* metallation. [a] Conditions: oxetane **55** (0.24 mmol), base (1.1 equiv), at temp 1 for time 1; MeI (2 equiv) added then warmed to temp 2 for time 2. [b] Order of addition. A: addition of the base to a solution of the substrate in THF, B: addition of a solution of substrate **55** in THF to a solution of the base. [c] Yield determined by ^{1}H NMR with respect to 1,3,5-trimethoxybenzene as an internal standard. [d] Reaction performed with 1.3 equiv of LiHMDS, [e] Reaction performed with 1.5 equiv of LiHMDS.

To encourage cyclisation the reaction temperature was raised. 2-Sulfonyl oxetane **55** was deprotonated with LDA at –78 ºC for 15 min then MeI was added and the reaction warmed to 0 ºC for 45 min. These conditions resulted in an increase in yield of alkylated oxetane **103** to 62%, entry 1. A variety of bases was then screened which concluded that LiHMDS was the optimum base, forming the desired product in a 76% yield, entries 1–4. For comparison the reaction with LiHMDS was performed without warming to 0 ºC but this resulted in a decreased yield of 22%, demonstrating the importance of warming the reaction to allow full deprotonation or quench with MeI, entries 4 and 5.

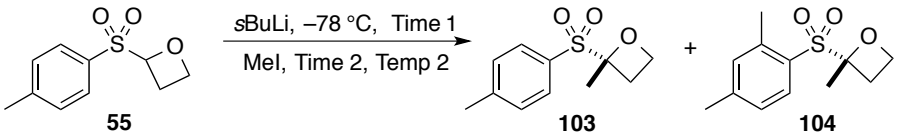
To gain a greater understanding of the reaction between –78 ºC and 0 ºC the reaction was sampled and the progress monitored as it was warmed. Oxetane **55** was treated with LiHMDS at –78 ºC and stirred for 15 min. MeI was added in one portion and stirred at –78 ºC for 10 min before an aliquot was taken for analysis by ^{1}H NMR. The reaction was then sampled at –50 ºC, –30 ºC and 0 ºC at 10 min intervals and continued at 0 ºC for 1 h 30 min before a final sample was taken. The results showed that alkylation predominantly occurred between –50 ºC and –30 ºC with no increase in yield when the reaction was warmed above –30 ºC. So the reaction was performed at –40 ºC for 1 h 15 min. Oxetane

103 was obtained in a 70% yield however this was not an improvement on the previous conditions, entry 6.

To promote deprotonation of the sulfonyl oxetane a longer deprotonation time of 30 min compared to the previous 15 min was examined, this resulted in an increased yield of 84% (comparing entries 4 and 7). The longer deprotonation time was beneficial however a further increased deprotonation time was not examined as the stability of the lithiated intermediate was a concern. Next the number of equivalents of LiHMDS was investigated. Oxetane **55** was treated with 1.1 equiv however increasing the amount to 1.3 or 1.5 equiv did not affect the yield significantly, entries 7–9. This prompted investigation into the order of reagent addition, a solution of substrate **55** in THF was added to a solution of LiHMDS at –78 ºC. Reversing the order of addition so LiHMDS was added to a solution of **55** in THF resulted in a detrimental effect on the yield, reducing the yield from 84% to 61%, entries 7 and 10.

Deprotonation of the sulfonyl oxetane with LiHMDS at –78 ºC was slow and the lithiated intermediate was not expected to be stable for long periods of time. Addition of the electrophile directly after addition of the base would allow the resulting lithiated intermediate to react with the electrophile immediately upon formation, therefore removing the stability concern. Pleasingly this protocol increased the yield of the reaction with MeI to 90% and provided the optimised set of conditions for the regioselective deprotonation of 2-sulfonyl oxetane **55** followed by electrophilic trapping, entry 11.

Addition of the electrophile before full oxetane deprotonation occurred limited the range of electrophiles that could be employed. As such alternative reaction conditions were developed to increase the scope of electrophiles and therefore the variety of functionalised sulfonyl oxetanes that could be formed. Capriati reported the use of *s*BuLi for the lithiation of 2-phenyloxetane and as a stronger base than LiHMDS a shorter deprotonation time was expected to be required, therefore *s*BuLi was investigated further.[124] A summary of the results is shown in table 7.



Entry[a]	Base	Equiv base	Time 1 (min)	Time 2 (min)	Temp 2 (ºC)	Yield[b] 103	104	55
1	*s*BuLi	1.4	5	25	–78 to rt	68	20	0
2	*s*BuLi	1.1	5	25	–78	71	1	27
3	*s*BuLi	1.2	5	25	–78	77	3	4
4	*s*BuLi	1.4	5	25	–78	83	3	6
5	*s*BuLi	1.1	10	25	–78	80	4	6
6	*s*BuLi	1.4	10	25	–78	84	12	4
7	*s*BuLi	1.4	0	35	–78	74	18	3
8	*n*BuLI	1.2	5	25	–78	64	0	21
9	***n*BuLi**	**1.3**	**5**	**25**	**–78**	**86**	**5**	**7**
10	*n*BuLi	1.4	5	25	–78	85	10	3

Table 7: Selected optimisation results for the alkylation with *s*BuLi. [a] Conditions: base added to oxetane **55** (0.24 mmol), at –78 ºC for time 1, MeI (2 equiv) added then warmed to temp 2 for time 2. [b] Yield determined by ^{1}H NMR with respect to 1,3,5-trimethoxybenzene as an internal standard.

Initially a solution of oxetane **55** in THF at –78 ºC was treated with 1.4 equiv of *s*BuLi for 5 min. MeI was added and the reaction warmed to rt for 25 min affording the desired product in 68%, entry 1. Interestingly a second product was observed, isolation and characterisation concluded that the sulfonyl oxetane had also been methylated in the *ortho* position of the aromatic ring to give oxetane **104**. This was a plausible result as Snieckus demonstrated that *t*Bu-aryl sulfones, analogous to aryl sulfonyl oxetanes, were powerful directing groups for *ortho* metallation.[114] Separation of oxetane **103** from oxetane **104** using chromatography was difficult, so *ortho* metallation needed to be minimised.

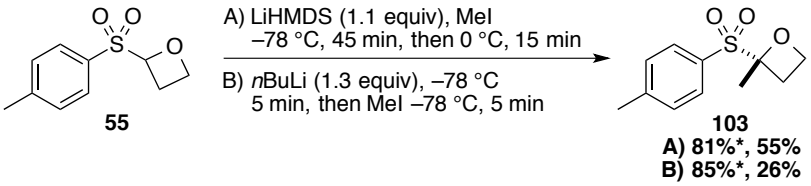
Optimisation was performed with addition of *s*BuLi to a solution of oxetane **55** in THF as this order of reagent addition provided **103** in a higher yield than when **55** was added to a solution of *s*BuLi. The reaction was optimised to decrease the amount of **104** produced and increase the formation of the desired product. Initially the number of equivalents of *s*BuLi employed was decreased to 1.1 equiv and the reaction temperature remained at –78 ºC. The quantity of *ortho*-methylated oxetane **104** decreased from 20% to 1% and pleasingly the yield of the desired oxetane increased to 71%, entry 2. Unfortunately starting material was present, implying that full deprotonation or electrophilic trapping had not occurred. To promote deprotonation the number of equivalents of *s*BuLi were increased slightly to 1.2 and 1.4 equiv, entries 3 and 4. As hoped, the yield of **103**

increased to 83% and the amount of unreacted starting material decreased to 6%. Comparing entries 1 and 4 suggested that the colder reaction temperature inhibited the *ortho* methylation. A longer deprotonation time of 10 minutes was also examined to reduce the amount of starting material remaining, however this did not significantly affect the reaction outcome, entries 5 and 6. When LiHMDS was employed to deprotonate oxetane **55** immediate addition of the electrophile was beneficial, immediate addition of MeI when using *s*BuLi was examined however this did not improve on previous reaction conditions, entry 7.

During optimisation all three oxetane compounds were present simultaneously, implying that the *ortho* methylation occurred before **55** was completely consumed. In addition, *ortho* metallation must have occurred following oxetane metallation as no compound solely alkylated in the *ortho* position of the aromatic ring was observed. The alkyl group on the oxetane may promote *ortho* lithiation on the aromatic ring due to a change in conformation. Interestingly compounds **55**, **103** and **104** were all still observed when oxetane **55** was treated with a large excess of *s*BuLi (2.2 equiv).

As the formation of oxetane **104** could not be eliminated the use of *n*BuLi was investigated. Employing 1.2 equivalents of *n*BuLi resulted in no double methylated oxetane, however 21% unreacted starting material remained, entry 8. Increasing the number of equivalents of *n*BuLi to 1.3 limited the amount of oxetanes **55** and **104** observed whilst improving the yield of the desired product to 86%, entry 9. This allowed **103** to be isolated cleanly and provided the second set of optimised reaction conditions. A further increase in the number of equivalents of *n*BuLi did not improve the reaction outcome, entry 10.

Having optimised two high yielding reaction conditions to functionalise directly on the intact oxetane ring, both reactions were performed on a larger scale in order to obtain isolated yields. The crude reaction material was purified by chromatography on silica gel but unfortunately a loss of material was observed when employing either set of reaction conditions, scheme 44. These results prompted investigation into the stability and purification of the alkylated 2-aryl sulfonyl oxetanes.



Scheme 44: Larger scale functionalisation of sulfonyl oxetane. * Yield determined by ^{1}H NMR with respect to 1,3,5-trimethoxybenzene as an internal standard.

2.3.1.2. Stability and Purification of Alkylated Sulfonyl Oxetanes

When methylated sulfonyl oxetane **103** was purified a drastic decrease in isolated yield was seen when comparing to the yield determined from the ^{1}H NMR of the crude material. The acidic nature of the silica gel may have caused product degradation, so the stability of the sulfonyl oxetane to a variety of stationary phases was investigated. A protocol developed within the Bull group to quantitatively assess the stability of potentially unstable compounds to a variety of stationary phases was used to investigate the stability of methylated oxetane **103**.[126] The product degradation on each stationary phase would be determined relative to the crude material. The yield of oxetane **103** after treatment with various conditions, designed to simulate those employed during chromatography, would be compared to the yield of **103** in the crude material to determine the percentage of expected mass recovered, equation 4.

$$\frac{\text{Yield of product after treatment with purification conditions}}{\text{Yield of product in crude mixture}} \times 100$$

Equation 4: Equation used to determined percentage of expected mass recovered.

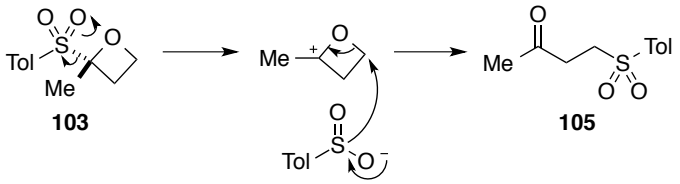
To begin, a yield for the crude sample was required so 1,3,5-trimethoxybenzene was added to the crude mixture as an internal standard and a yield calculated from the ^{1}H NMR spectrum. The crude sample was then separated into 8 batches with each batch being added to a slurry of a different stationary phase in the column solvent system of 30% EtOAc/hexane and stirred for 30 min. After this time the slurry was filtered and the filtrate analysed by ^{1}H NMR to assess the recovery of oxetane **103**. A control experiment was performed to ensure the product did not degrade in the purification solvent system alone, so the sample was stirred for 30 min in 30% EtOAc/hexane with no stationary phase present. The results of the study are shown in table 8.

Entry	Stationary Phase	Oxetane **103** (% of Expected Mass)[a]
1	Crude	100
2	Control	100
3	Silica	66
4	Silica + 1% Et_3N	79
5	Florisil	68
6	Neutral Alumina	20
7	Basic Alumina	21
8	Dry Basic Alumina[b]	39
9	Basic Alumina Activity IV	99

Table 8: Effect of different stationary phases on the stability of **103**. [a] Yield determined by ^{1}H NMR with respect to 1,3,5-trimethoxybenzene then converted to a percentage of the expected yield. [b] Basic alumina (activity I), oven-dried for 24 h prior to use.

No loss of material was seen in the control reaction demonstrating that methylated oxetane **103** was stable at rt for 30 min in 30% EtOAc/hexane, however when employing silica gel 34% of the product was lost. This loss of material was thought to be due to degradation or potential trapping of the oxetane on the stationary phase. A significant loss was also observed when using silica gel treated with Et_3N, florisil, neutral alumina, basic alumina or basic alumina which had been dried in the oven at 160 ºC for 24 hours prior to use. Pleasingly, when basic alumina modified to activity IV was employed little degradation occurred and 99% of the material expected was recovered. All fragments alkylated on the heterocyclic ring were therefore purified using basic alumina modified to activity IV. Commercial basic alumina (activity I) can be deactivated by addition of water. For this study the stationary phase was deactivated to activity IV by addition of water (10% w/v) which was evenly distributed. This was an exothermic reaction so once cooled the alumina could be used for chromatography.

Degradation of alkylated oxetane **103** was also observed when stored at rt for prolonged periods of time. The 2,2-disubstituted oxetane was stable at –20 ºC for >2 months without degrading however the compound underwent a rearrangement when stored at rt for more than 24 hours. Characterisation of the degradation product concluded that this rearrangement occurred cleanly to quantitatively afford β-sulfonyl ketone **105**. A proposed mechanism is shown in scheme 45.

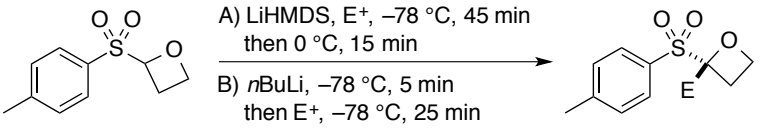


Scheme 45: Proposed mechanism for the rearrangement of oxetane **103** to β-sulfonyl ketone **105** at rt.

The increased steric demands of the α-alkylated derivative over the stable sulfonyl oxetane may have caused loss of the sulfonyl group to afford a tertiary carbocationic intermediate, possibly stabilised by the adjacent oxygen atom. Subsequent ring opening by attack of the sulfonyl group, with release of the ring strain as the driving force, afforded the observed product **105**, scheme 45. Despite this observation the scope of α-alkylated derivatives was explored.

2.3.1.3. Scope of the Lithiation of 2-Aryl Sulfonyl Oxetanes

The scope of electrophiles successfully employed using the 2 sets of optimised conditions is shown in table 9. When using LiHMDS the reactions went to completion with no additional product formation and so the functionalised oxetanes were purified by filtration through a pad of basic alumina activity IV. When employing *n*BuLi the products required purification by flash chromatography, resulting in lower isolated yields.



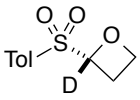
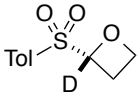
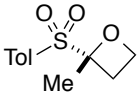
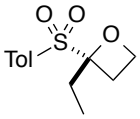
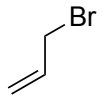
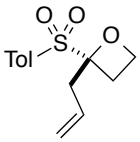
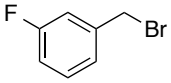
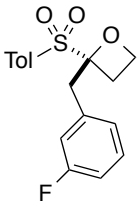
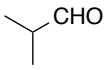
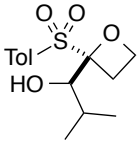
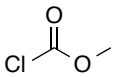
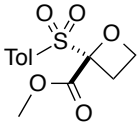
Entry	Electrophile (E^+)	Conditions[a]	Oxetane		Yield (%)
1	MeOD	A		**106**	0
2	D_2O	A		**106**	0
3	D_2O	B			60[b]
4	MeI	A		**103**	93
5	MeI	B			71
6	EtI	A		**107**	85
7		A		**108**	91
8		B		**109**	90
9		A		**110**	0
10		B			69[c] (86[d])
11		B		**111**	0

Table 9: Scope of the lithiation of sulfonyl oxetane **55** and reaction with electrophiles. [a] Conditions A: LiHMDS (1.2 equiv), electrophile (2 equiv), THF, –78 ºC, 90 min; conditions B: *n*BuLi (1.3 equiv), electrophile (2 equiv), THF, –78 ºC, 30 min. [b] Conversion value as product could not be isolated. [c] Isolated as a mixture of diastereoisomers, dr = 1 : 0.9. [d] Conditions B with a longer reaction time of 1 h.

Reaction with a simple deuterium source, MeOD or D_2O, under the optimised conditions with LiHMDS resulted in no deuterium incorporation, entries 1 and 2. The reaction was therefore performed using *n*BuLi. Pleasingly 60% deuterium incorporation was observed by ^{1}H NMR analysis, but as full deuterium incorporation was not observed the deuterated oxetane could not be cleanly isolated from the crude reaction mixture. The reaction was optimised with MeI so methylated oxetane **103** was obtained in good yields under both reaction conditions, entries 4 and 5. Ethyl iodide and allyl bromide were also compatible with LiHMDS to afford alkylated oxetanes **107** and **108** in excellent yields, entries 6 and 7, whilst *m*-fluorobenzyl bromide was successful when using *n*BuLi, entry 8. *iso*-Butyraldehyde was unsuccessful when using LiHMDS due to incompatibility with the base, however when using *n*BuLi the desired product could be obtained in a 69% yield, entries 9 and 10. A longer reaction time of 1 h further increased the yield to 86% for this electrophile. The introduction of an ester onto the oxetane ring was desirable but unfortunately no product was isolated from the reaction with methyl chloroformate, entry 11. Analysis of the crude material by ^{1}H NMR showed formation of the desired product. However degradation, possibly promoted by the presence of the ester group, was observed before the product could be purified or characterised.

A variety of electrophiles were unsuccessful at trapping the lithiated oxetane intermediate despite which optimised conditions were employed, figure 22.

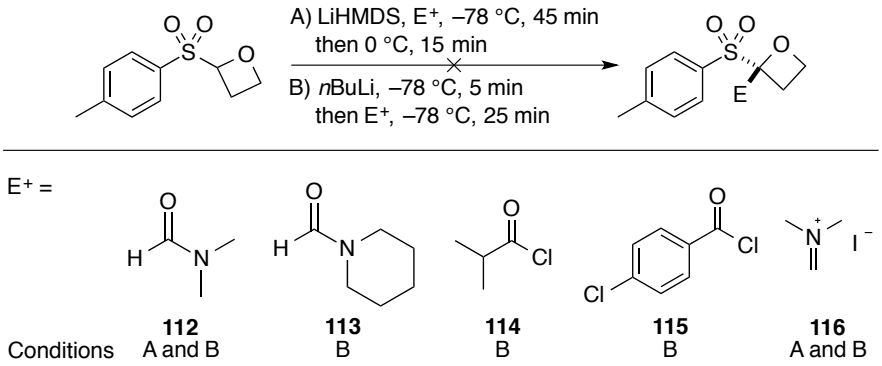


Figure 22: Electrophiles unsuccessful in reaction with the sulfonyl oxetane after lithiation.

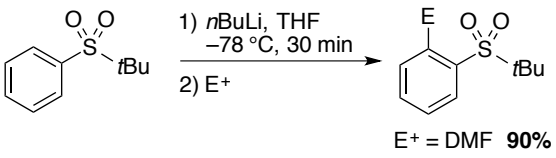
DMF was employed as a readily available electrophile to incorporate an aldehyde onto the oxetane but no product was formed when using LiHMDS or *n*BuLi. 1-Formylpiperidine was investigated as a more reactive electrophile that would afford the same product

however similarly no reaction was observed. This electrophile may have been too bulky to react with the sterically hindered oxetanyl anion. Acid chlorides were investigated next, in order to incorporate a ketone onto the oxetane ring. Reaction with alkyl acid chloride **114** or aromatic acid chloride **115** in the presence of *n*BuLi both resulted in material degradation and no product formation. The degradation may have been caused by the increased steric bulk on the product, or the instability of the lithiated intermediate if reaction with the electrophile was slow. The reaction was also unsuccessful with Eschenmoser's salt **116** using either set of optimised conditions.

Despite the unsuccessful examples functionalisation directly on the intact oxetane ring was possible and provided a route to further derivatise and expand the motifs. However, due to the instability and degradation observed during the study the alkylated products were considered to be less viable as fragments or interesting motifs for use in drug discovery programmes. Instead derivatisation of the 2-aryl sulfonyl oxetanes in an alternative direction was explored.

2.3.2. Ortho-Lithiation of 2-Aryl Sulfonyl Oxetanes

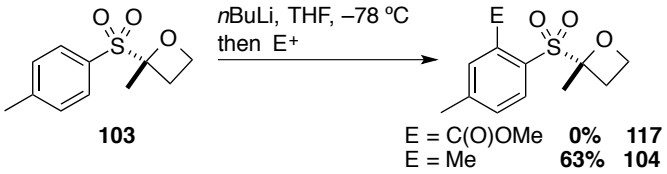
Directed *ortho* metallation has evolved as an effective strategy for selectively functionalising a molecule. A variety of substituents have emerged that direct the metal atom, often lithium, to the *ortho* position on the aromatic ring. In particular aryl sulfones have been shown to be great directing groups due to the increased acidity of the *ortho* C–H bond. Snieckus demonstrated that *t*Bu-aryl sulfones were powerful directing groups for *ortho* metallation, scheme 46, whilst secondary and tertiary sulfonamides have also been highlighted as good *ortho* directing groups.[114,127]



Scheme 46: *t*Bu-aryl sulfones as powerful directing groups for *ortho* metallation.[114]

The sulfone moiety of 2-aryl sulfonyl oxetanes was exploited to perform selective functionalisation on the aromatic ring. Alkylated oxetane **103** was chosen as the substrate

for the investigations to eliminate the competing oxetane lithiation. The 2-sulfonyl oxetane was treated with *n*BuLi and the resulting lithiated intermediate was quenched with an electrophile such as methyl chloroformate, scheme 47.[114] *Ortho*-functionalised oxetane **117** was observed in the ^{1}H NMR spectrum of the crude material but could not be isolated due to the product's instability. When MeI was employed as a small electrophile *ortho*-methylated oxetane **104** was isolated in a yield of 63%.



Scheme 47: Directed *ortho* metallation of oxetane **103** and reaction with methyl chloroformate or MeI.[114]

The initial sulfonyl oxetane fragment had now been elaborated in two different directions. Investigations into derivatising the fragments in alternative directions using cross-coupling methodology are discussed below.

2.3.3. Cross-Coupling of Halo-Substituted 2-Aryl Sulfonyl Oxetanes

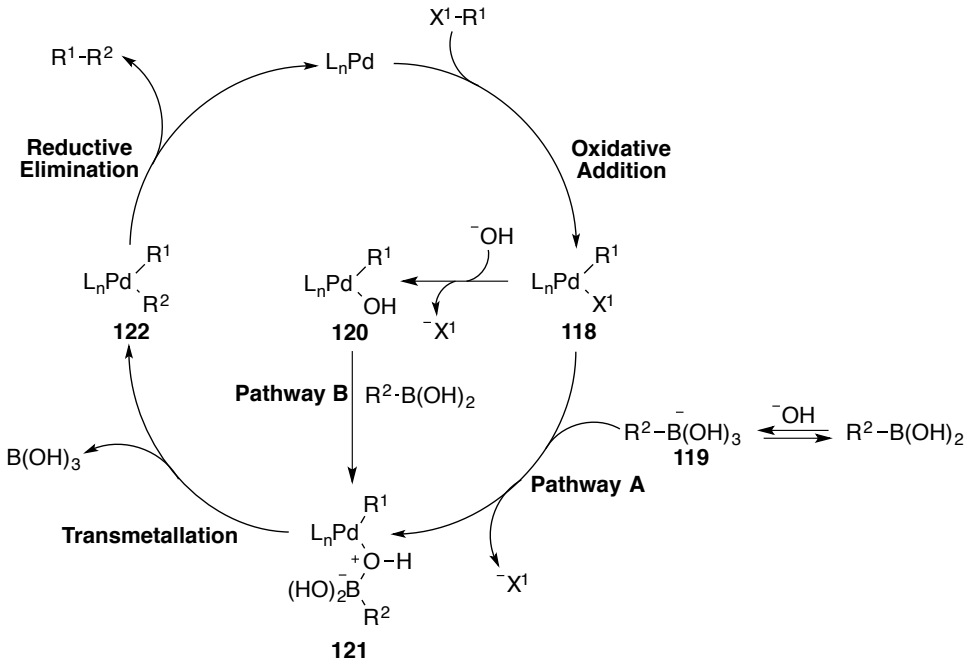
The cross-coupling reaction of an organometallic reagent with an electrophile has emerged as one of the most straightforward, widely used methods for C–C bond formation. Of particular importance is the seminal work by Heck, Negishi and Suzuki on palladium-catalysed cross-coupling reactions which led to them being awarded the Nobel Prize in Chemistry in 2010.[128–133] Employing 2-sulfonyl oxetanes in cross-coupling reactions to form C–C or C–X bonds was of interest.

2.3.3.1. Methods for Carbon-Carbon Bond Formation

In particular the Suzuki cross-coupling of boronic acids with aryl halides along with the iron catalysed cross-coupling of alkyl Grignard reagents with aryl halides were explored.

2.3.3.1.1. Suzuki-Miyaura Cross-Coupling

First the mechanism of the cross-coupling reaction should be considered. The general catalytic cycle is shown in scheme 48.

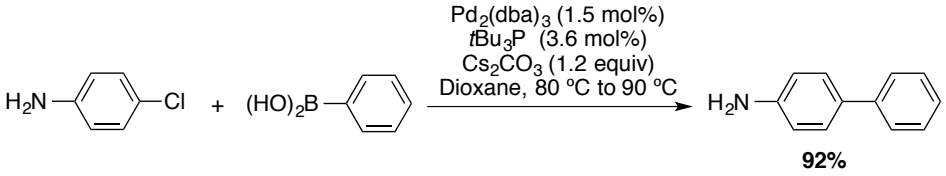


Scheme 48: General mechanism of the Suzuki-Miyaura cross-coupling reaction.[134]

The initial step of the Suzuki reaction involves oxidative addition of the aryl halide to the active Pd^0 catalyst to form the Pd^{II} intermediate **118**. A four-coordinate boronate complex **121** is then required for the transmetallation of the R^2 ligand from an organoboron species to Pd centre. There are two possible pathways to form the activated boron species; boronate **119** can be preformed from the reaction of a boronic acid with a base, then attack Pd species **118** to generate **121** *via* pathway A. Alternatively oxo-palladium species **120** can react with the boronic acid affording four-coordinate boron species **121**, pathway B.[134] Subsequent transmetallation would afford organopalladium species **122** then reductive elimination would generate the desired coupled product and regenerate the Pd^0 complex.[132]

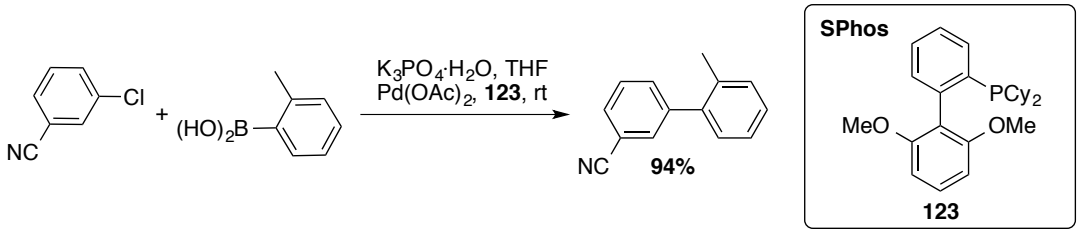
Alkenyl and aryl bromides, iodides and triflates are common reagents employed in the Suzuki cross-coupling reaction however aryl chlorides are often more challenging to employ. The decreased reactivity of aryl chlorides in the palladium catalysed cross-

coupling reaction has been attributed to the slow oxidative addition step.[135] In 1998 Fu disclosed reaction conditions to successfully couple neutral or electron rich aryl chlorides with aryl boronic acids in the presence of $Pd_2(dba)_3$, tBu$_3$P and Cs_2CO_3, scheme 49.[136] Employing *ortho*- or *para*-substituted aryl chlorides resulted in a variety of biaryl compounds in yields of 82–92%.



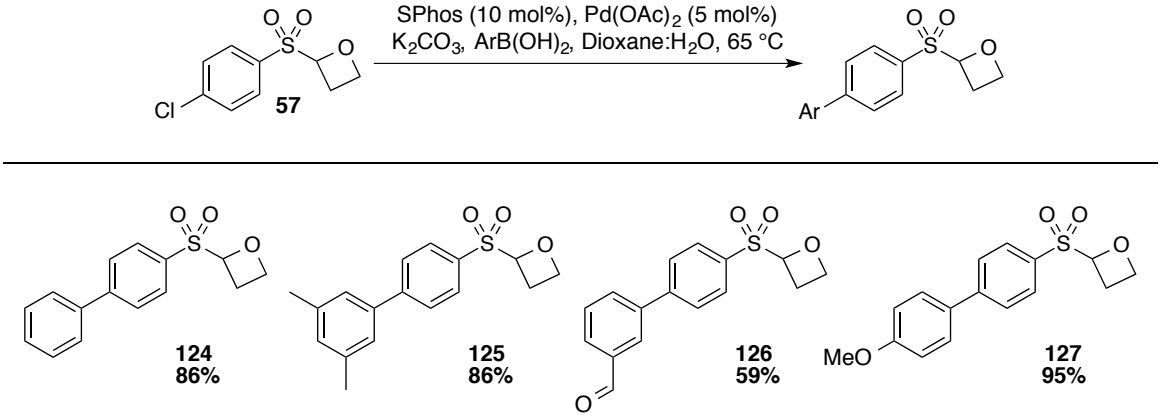
Scheme 49: Suzuki cross-coupling of aryl chloride with aryl boronic acids.[136]

Over the last two decades enormous advances have been made in the area and a wide substrate scope has been developed, with the coupling of hindered substrates now possible.[137] In efforts towards developing a universal catalyst and ligand appropriate for all substrates in the Suzuki cross-coupling, Buchwald developed a new air stable phosphine ligand that could be used, with a suitable Pd source, to couple a wide variety of aryl and heteroaryl halides with aryl-, heteroaryl- and vinylboronic acids.[138] Excellent yields were obtained when the ligand, 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) **123**, was employed with palladium acetate, scheme 50.



Scheme 50: Suzuki cross-coupling of aryl chlorides in the presence of the SPhos ligand.[138]

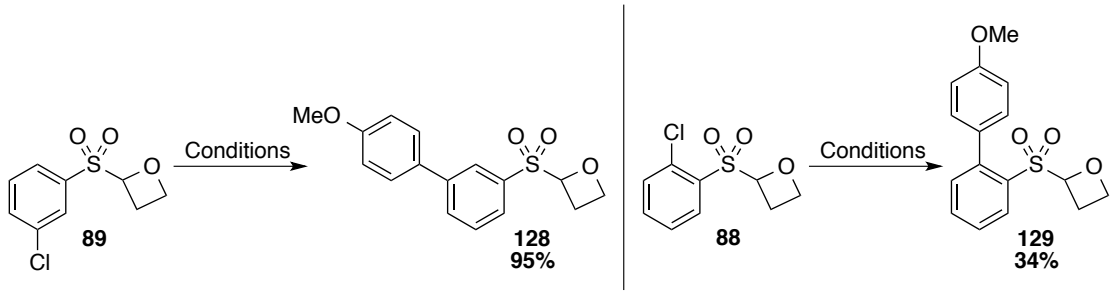
The Suzuki cross-coupling of chloro substituted 2-aryl sulfonyl oxetanes with aryl boronic acids was investigated using Buchwald's SPhos ligand. If successful this reaction would result in the functionalisation of 2-sulfonyl oxetanes *via* the formation of a new aryl-aryl, C–C bond. Phenylboronic acid and 2-(4-chlorobenzene-sulfonyl)oxetane **57** were treated with $Pd(OAc)_2$, SPhos and K_2CO_3 then heated at 65 ºC for 3 h 30 min to afford the desired biaryl sulfonyl oxetane **124** in a yield of 86% following purification, scheme 51.



Scheme 51: Suzuki cross-coupling of oxetane **57** with aryl boronic acids.

A variety of aromatic boronic acids was examined under the reaction conditions, successfully generating biaryls **124–127**, scheme 51. 3,5-Dimethylphenylboronic acid afforded biaryl **125** in a yield of 86%. Both electron poor (3-formylphenylboronic acid) and electron rich (4-methoxyphenylboronic acid) substrates were tolerated. Biaryl **126** was obtained in a yield of 59%, although a longer reaction time of 20 h was required for this electron poor substrate as the electron deficient nature of the boronic acid hindered the transmetallation step. The more electron rich biaryl **127** was isolated in a yield of 95% after 5 h 30 min.

To determine the effect of substitution on the aryl sulfonyl oxetane coupling partner, the *meta*- and *ortho*-substituted derivatives 2-(3-chlorobenzenesulfonyl)oxetane **89** and 2-(2-chlorobenzenesulfonyl)oxetane **88** were exposed to the cross-coupling reaction conditions, scheme 52.

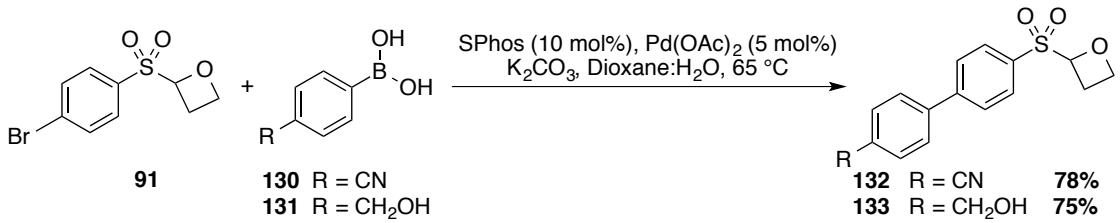


Scheme 52: Cross-coupling with *meta*- and *ortho*-substituted aryl chlorides **89** and **88**. Conditions: SPhos (10 mol%), $Pd(OAc)_2$ (5 mol%), K_2CO_3 (2 equiv), 4-methoxyphenylboronic acid, Dioxane:H_2O, 65 ºC, 20 h.

The reaction with aryl chloride **89** went to completion affording biaryl sulfonyl oxetane **128** in an excellent yield after purification, scheme 52. When employing aryl chloride **88**

the lower reactivity of the *ortho*-substituted derivative, compared to the corresponding *meta*- and *para*-substituted derivatives, along with the increased steric hindrance inhibited the reaction resulting in incomplete conversion after 20 h. As such biaryl oxetane **129** was obtained in a 34% isolated yield. The reaction may require an increased temperature or reaction time to improve the yield further. These reactions demonstrated functionalisation of 2-aryl sulfonyl oxetanes in a variety of directions using cross-coupling methodology.

To enhance the scope of the Suzuki cross-coupling of 2-aryl sulfonyl oxetanes employing 2-(4-bromobenzenesulfonyl)oxetane was investigated. Aryl bromide **91** was treated with $Pd(OAc)_2$, SPhos, K_2CO_3 and **130** or **131** then heated at 65 ºC for 15 h to afford biaryl products **132** and **133** in good yields, scheme 53. 4-Cyanophenylboronic acid and 4-(hydroxymethyl)phenylboronic acid were chosen due to the introduction of the interesting nitrile and hydroxymethyl functional groups onto the products.



Scheme 53: Suzuki cross-coupling of boronic acids with 2-(4-bromobenzenesulfonyl)oxetane.

The success of the Pd catalysed cross-coupling of 2-aryl sulfonyl oxetanes relied on the stability of **57**, **88**, **89** and **91** to heating at 65 ºC in the presence of K_2CO_3. Degradation of the oxetane by possible ring opening could be envisaged under these conditions however no instability was observed, enhancing the attractiveness of the fragments.

2.3.3.1.2. Iron Catalysed Cross-Coupling

Over the last 10-15 years iron has emerged as an alternative metal to palladium or nickel in cross-coupling reactions.[139,140] Iron is an abundant, cheap, non-toxic and environmentally benign element which can catalyse the cross-coupling of a nucleophilic organometallic reagent with an electrophilic organohalide reagent. The first example of iron salts catalysing a coupling reaction of a Grignard reagent with an organic halide was reported in 1970 by Kochi. Vinyl bromides were coupled with alkyl Grignard reagents in

the presence of a soluble iron species to form the cross-coupled products in good yields of above 60%.[141] There is still much debate about the nature of the iron catalytic cycle. Initially Kochi proposed a mechanism, similar to that of a palladium or nickel catalytic cycle, which involved an oxidative addition, transmetallation and reductive elimination.[142] It was not until 30 years later that Bogdanovic questioned this mechanism when reinvestigating the stoichiometric reaction of $FeCl_2$ with alkyl Grignard reagents.[143] Bogdanovic reported that $FeCl_2$ reacted with 4 equivalents of the Grignard reagent to give a reactive Fe^{-2} intermediate, a dark-brown bimetallic cluster of the composition $[Fe(MgX)_2]_n$, figure 23.[143]

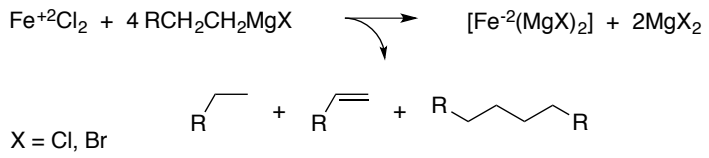
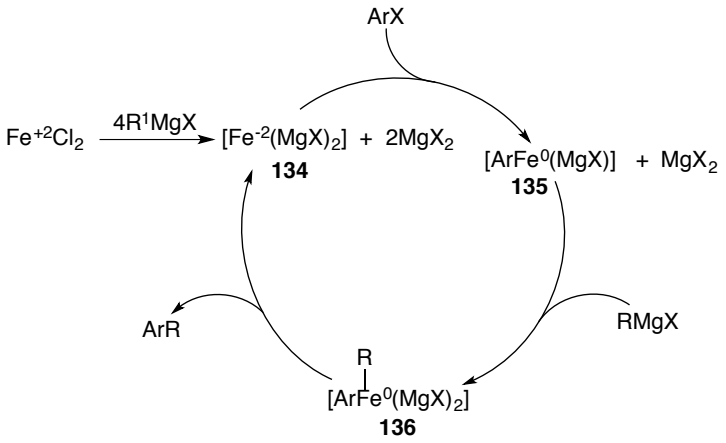


Figure 23: Formation of an active Fe^{-2} complex from $FeCl_2$.[143]

Two years later Fürstner proposed a mechanism for the cross-coupling reaction employing this reduced form of iron, in an Fe^0/Fe^{-2} cycle, scheme 54.[144]

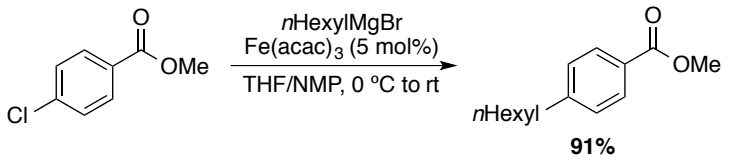


Scheme 54: Proposed catalytic cycle for the Fe catalysed coupling of Grignard reagents and aryl halides.[144]

The reactive inorganic Grignard reagent **134**, with an oxidation state of Fe^{-2}, was proposed to undergo an oxidative addition with the organohalide to give the Fe^0 complex **135**. Alkylation of **135** with the organomagnesium reagent affords complex **136** which undergoes subsequent reductive elimination to afford the desired product whilst regenerating the Fe^{-2} catalytic species.[144] Support for a Fe^0/Fe^{-2} catalytic cycle was

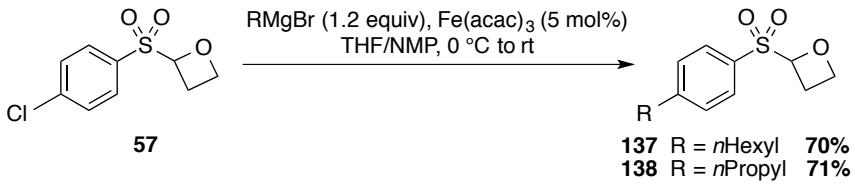
provided when Fürstner disclosed that Fe^0 powder did not participate in the cross-coupling reaction, however upon addition of a Grignard reagent a catalytically active species was formed. In addition, the tetrakis(ethylene)ferrate complex, $[Li(tmeda)]_2[Fe(C_2H_4)_4]$ a well characterised Fe^{-2} complex,[145] was catalytically active in the cross-coupling of aryl or alkyl Grignard reagents with organohalides.[146]

The most common iron salts employed in cross-coupling reactions are $FeCl_2$, $FeCl_3$, Fe(salen)Cl and $Fe(acac)_3$, however the iron source has been shown to have little effect on the rate, yield or selectivity of the reaction.[147] Fürstner reported the catalytic cross-coupling of aryl chlorides and alkyl Grignard reagents in the presence of $Fe(acac)_3$ in a mixed solvent of THF and NMP, scheme 55. These reactions were performed at low temperatures with quick reaction times of 5–10 min, affording the products in yields of 59–95%. Interestingly the ester moiety in methyl 4-chlorobenzoate was untouched.[144]



Scheme 55: Cross-coupling of aryl chloride and alkyl Grignard reagents in the presence of $Fe(acac)_3$.[144]

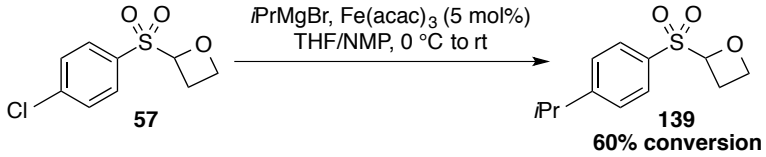
The low reaction temperatures and short reaction times made these attractive conditions to employ to functionalise the 2-sulfonyl oxetanes by the formation of an aryl-alkyl C–C bond. Initially *n*hexyl and *n*propyl magnesium bromide were added to solutions of $Fe(acac)_3$ and oxetane **57** in THF/NMP at 0 ºC then stirred at rt for 10 min to afford compounds **137** and **138** in yields of 70% and 71% after purification, scheme 56.[144]



Scheme 56: Functionalisation of 2-sulfonyl oxetane **57** by cross-coupling with an alkyl Grignard reagent.

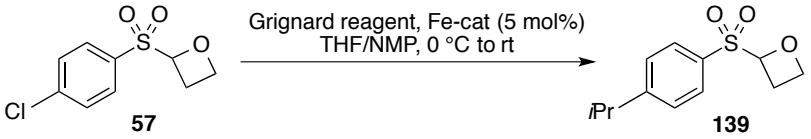
No reaction was observed when sulfonyl oxetane **57** was treated with 1.2 equiv of EtMgBr despite Fürstner reporting the successful coupling of EtMgBr with an aryl chloride to

provide the product with a >95% yield.[144] Employing *i*PrMgBr formed the desired product **139** in 60% conversion but unfortunately **139** could not be isolated from the crude reaction mixture by chromatography as oxetane **57** had the same polarity in multiple solvent systems, scheme 57.



Scheme 57: Iron catalysed cross-coupling of sulfonyl oxetane **57** with *i*PrMgBr. Conversion determined from the ^{1}H NMR spectrum.

If the reaction with *i*PrMgBr went to completion the purification challenge would be removed and **139** could be isolated, the reaction was therefore investigated further, table 10. For ease of analysis the conversion observed by ^{1}H NMR analysis of the crude material was used to determine the outcome of the changes made to the reaction conditions. It should be noted that Fürstner reported a yield of 59% for the coupling of the secondary Grignard reagent, *i*PrMgBr, with an aryl chloride.[144]



Entry	Grignard reagent	Iron catalyst	Time (min)	^{1}H NMR conversion (%)
1	*i*PrMgBr	$Fe(acac)_3$	10	60
2	*i*PrMgBr	$Fe(acac)_3$	100	80
3	*i*PrMgCl	$Fe(acac)_3$	10	42
4	*i*PrMgBr	$Fe(salen)Cl_2$	30	50
5*	*i*PrMgCl	$Fe(acac)_3$	5	56

Table 10: Investigation into the cross-coupling with the secondary Grignard reagent, *i*PrMgBr. * Modified conditions used: TMEDA (10 mol%), $Fe(acac)_3$ (1 mol%), *i*PrMgCl, rt, 5 min in THF.[148]

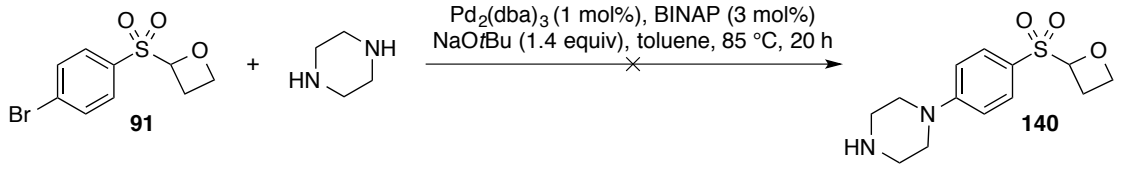
Treating 2-sulfonyl oxetane **57** with *i*PrMgBr in the presence of $Fe(acac)_3$ for 10 min resulted in a 60% conversion to sulfonyl oxetane **139**, entry 1. To increase the amount of product formed the reaction time was increased significantly to 100 min, resulting in an improved conversion of 80% however starting material still remained, entry 2. Employing *i*PrMgCl instead of *i*PrMgBr resulted in a lower conversion of 42%, entry 3. Fürstner

reported the use of Fe(salen)Cl instead of $Fe(acac)_3$ in the cross-coupling of *i*PrMgBr with an aryl chloride.[144] Treating sulfonyl oxetane **57** with *i*PrMgBr in the presence of $Fe(salen)Cl_2$ did not improve the reaction yield as only a 50% conversion was observed, entry 4. In 2013 Fox reported a modified set of cross-coupling conditions using TMEDA, eliminating the need for the amine co-solvent, and decreasing the number of equivalents of $Fe(acac)_3$ to 0.1-1 mol%.[148] Oxetane **57** was exposed to these modified conditions using *i*PrMgBr however no improvement on the initial conditions was observed as only a 56% conversion was seen, entry 5. Unfortunately the reaction conditions could not be optimised to allow product **139** to be isolated.

According to the Fürstner mechanism, β-hydride elimination would be required to form the catalytic iron species **134** (scheme 54) by reduction of $FeCl_2$. Grignard reagents that lacked this hydride such as MeMgBr or PhMgBr could not undergo this pathway. A possible reason why the reactions with *i*PrMgBr and EtMgBr were not as successful as when longer alkyl chains were employed could be that they underwent β-hydride elimination slowly, therefore generated the catalyst at a slower rate than *n*hexylMgBr or *n*PrMgBr.

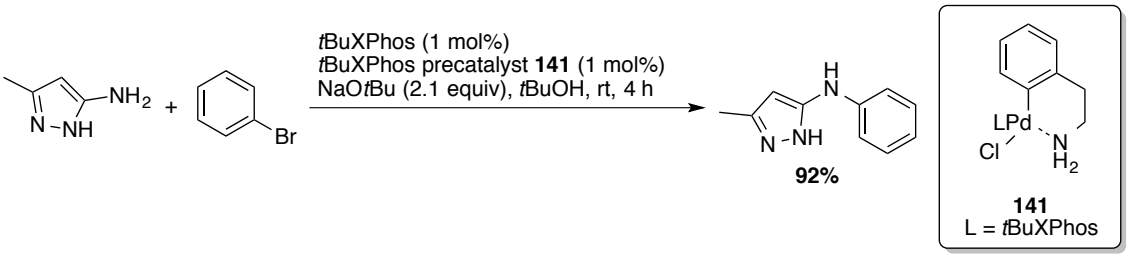
2.3.3.2. Towards Carbon-Nitrogen Bond Formation

The palladium catalysed cross-coupling between aryl halides and primary or secondary amines to form aromatic amines is known as the Buchwald-Hartwig amination. Since the pioneering work of both Buchwald and Hartwig in 1994 this cross-coupling has become a widely used method for creating a carbon-nitrogen bond.[149,150] Despite developments over the last 20 years to improve the reaction conditions and increase the substrate scope this methodology often involves a strong base such as sodium *tert*-butoxide.[151] Additionally, the reactions often require heating at temperatures of 100 ºC for up to 24 h.[152] These reaction conditions were carefully considered when employing the 2-sulfonyl oxetane fragments as degradation or ring opening could be envisaged *via* deprotonation of the acidic proton alpha to the sulfonyl group. Conditions modified from those reported by Morita, were investigated, scheme 58.[153]



Scheme 58: Investigation into the Buchwald-Hartwig amination of 2-sulfonyl oxetane **91** with piperazine.

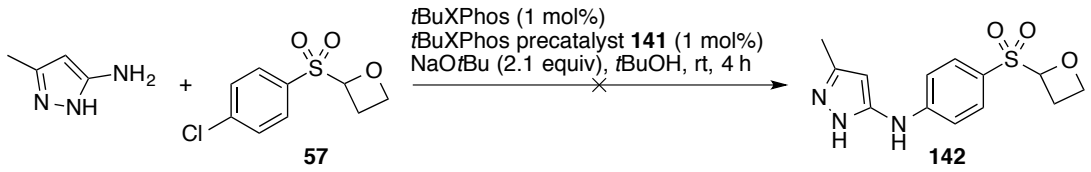
Oxetane **91** was treated with $Pd_2(dba)_3$, BINAP and sodium *tert*-butoxide then heated at 85 ºC for 20 h but no product formation was seen. Complete degradation of the starting material to an unidentified mixture of compounds was observed by ^{1}H NMR analysis of the crude material. Sodium *tert*-butoxide is a stronger base than K_2CO_3, which was successfully employed in the Suzuki cross-coupling of sulfonyl oxetanes, so may have caused compound instability. Similarly the temperature, palladium source or ligand may also have prompted degradation, so milder reaction conditions were investigated. Moss reported a Pd-catalysed coupling of heteroaryl amines with aryl or heteroaryl bromides or chlorides at room temperature using NaO*t*Bu, an example is shown in scheme 59.[154]



Scheme 59: Room temperature conditions reported for the amination of aryl bromides.[154]

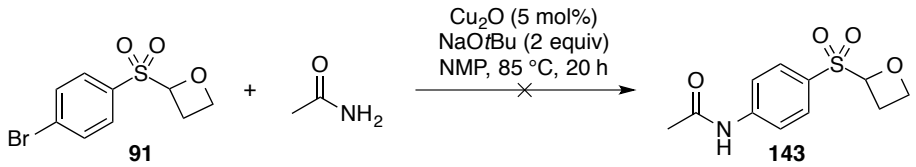
Due to the low temperature, interesting product scope and high yields obtained, these conditions were explored with the 2-sulfonyl oxetanes. The stability of the sulfonyl oxetanes to NaO*t*Bu was a concern so initially oxetane **57** was stirred in the presence of NaO*t*Bu in *t*BuOH at rt for 4 h. The reaction was sampled every 30 min and analysed by LCMS, no degradation was observed after 4 h. With this pleasing result oxetane **57** was treated with 3-methyl-5-aminopyrazole in the presence of NaO*t*Bu, *t*BuXPhos precatalyst and ligand in *t*BuOH, scheme 60. Analysis of the crude reaction material by ^{1}H NMR determined that the reaction was unsuccessful as the oxetane reagent decomposed to give a complex mixture of compounds and no desired product was observed. The stability of the oxetane to NaO*t*Bu had already been examined so the presence of the amine or catalyst

was likely to have caused degradation. As a result the Buchwald-Hartwig amination was not investigated further.



Scheme 60: Unsuccessful Buchwald-Hartwig amination of 2-(4-chlorobenzenesulfonyl)oxetane.

The amidation of 2-(4-bromobenzenesulfonyl)oxetane **91** was briefly investigated. Wolf reported efficient conditions for the copper catalysed C–N bond formation using aryl bromides, chlorides or iodides and an amine in the presence of catalytic copper oxide and sodium *tert*-butoxide.[155] Treatment of oxetane **91** with Cu_2O, NaO*t*Bu and acetamide, chosen as a simple amide with which to examine the reaction conditions, unfortunately did not yield the desired product **143**, scheme 61. The crude reaction mixture contained no oxetane species suggesting that compound degradation had occurred, possibly by ring opening caused by heating in the presence of NaO*t*Bu.



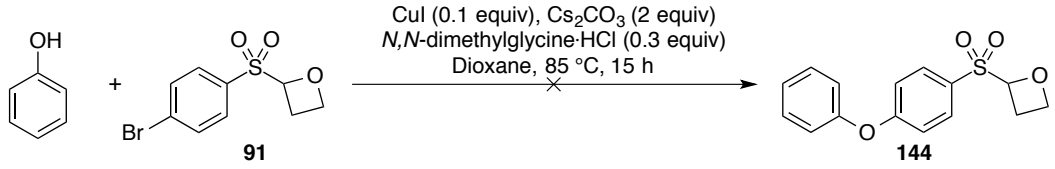
Scheme 61: An unsuccessful amidation reaction of 2-(4-bromobenzenesulfonyl)oxetane **91** with acetamide.

Functionalisation *via* a C–N bond formation was currently unsuccessful. This was most likely due to the strong reaction conditions required to promote the amination or amidation reaction.

2.3.3.3. Towards Carbon-Oxygen Bond Formation

The functionalisation of 2-aryl sulfonyl oxetanes by C–O bond formation was also investigated. Ma and Cai reported the Ullmann-type coupling reaction of phenols and aryl halides in the presence of CuI, Cs_2CO_3 and *N,N*-dimethylglycine·HCl, resulting in a variety of diaryl ethers in high yields.[156] *N,N*-Dimethylglycine·HCl was employed to

increase reaction efficiency and allow the reaction temperature to be lowered to 85 ºC.[156] Heating 2-sulfonyl oxetanes at 85 ºC in the presence of NaO*t*Bu resulted in degradation of the oxetane however employing the weaker base, Cs_2CO_3, was expected to improve oxetane stability. Oxetane **91** was treated with catalytic CuI, Cs_2CO_3, *N,N*-dimethylglycine·HCl and phenol then heated at 85 ºC for 15 h, scheme 62.[156]



Scheme 62: Ullmann-type coupling of 2-(4-bromobenzenesulfonyl)oxetane with phenol.

Analysis of the crude reaction mixture by ^{1}H NMR showed no oxetane derivative present, which suggested that oxetane **91** or **144** degraded under the reaction conditions. Again, exposing the 2-sulfonyl oxetane to high temperatures in the presence of a metal and base caused degradation, therefore this Ullmann-type coupling was not explored further.

The ability to functionalise 2-aryl sulfonyl oxetanes provided ways in which to access oxetane derivatives and increased the sulfonyl oxetanes' desirability and usefulness as fragments. In addition their physicochemical and structural properties were important to consider when evaluating their potential as fragments. As such they are discussed below.

2.4. Investigations into the Physical Properties of 2-Sulfonyl Oxetanes

2.4.1. Calculated Fragment-like and Lead-like Properties

As discussed in chapter 1, guidelines have been suggested for desirable physicochemical properties of compounds at various stages in the drug discovery process. 2-Aryl sulfonyl oxetanes were designed as fragments for use in FBDD. The scope of 2-aryl sulfonyl oxetanes synthesised was analysed against the "rule of 3" guidelines (cf. section 1.1.2.1.) as a method to indicate desirable molecular properties and determine their suitability as fragments and motifs for use in drug discovery, the results are shown in table 11.[30]

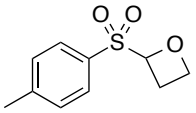
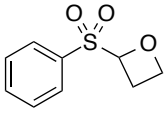
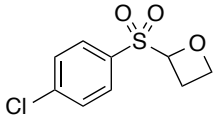
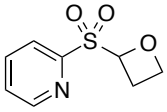
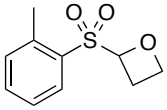
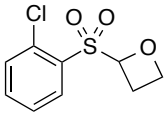
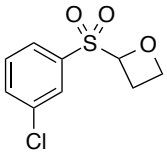
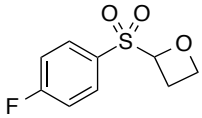
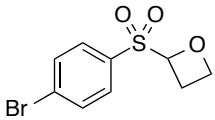
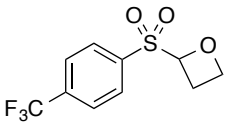
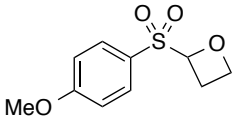
		Molecular Weight	cLogP	HAC	HBD/A	TPSA (Å^2)	NROT
	**55**	212	0.26±0.4	14	0/3	43.4	2
	**56**	198	–0.2±0.4	13	0/3	43.4	2
	**57**	232	0.35±0.5	14	0/3	43.4	2
	**58**	199	–1.28±0.4	13	0/4	56.3	2
	**87**	212	0.26±0.4	14	0/3	43.4	2
	**88**	232	0.42±0.5	14	0/3	43.4	2
	**89**	232	0.76±0.4	14	0/3	43.4	2
	**90**	216	0.11±0.5	14	0/4	43.4	2
	**91**	276	0.54±0.5	14	0/3	43.4	2
	**92**	266	0.77±0.4	17	0/6	43.4	2
	**93**	228	0.05±0.5	15	0/4	52.6	2

Table 11: Physicochemical data calculated for the library of 2-sulfonyl oxetanes prepared. cLogP = calculated log of partition coefficient (lipophilicity);[ii] HAC = heavy atom count; HBD/A = hydrogen bond donors/acceptors; TPSA = topological polar surface area;[iii] NROT = number of rotatable bonds.

[ii] cLogP values were determined using ACDlabs LogP calculator. http://www.acdlabs.com/resources/freeware/chemsketch/logp.

[iii] TPSA values were determined using MarvinSketch version 6.2.0. https://www.chemaxon.com/download/ marvin-suite.

2-Aryl sulfonyl oxetanes **55–58** and **87–93** all had physicochemical properties that complied with the fragment guidelines. The MWs of the oxetanes ranged from 198 to 276 daltons and lipophilicity ranged from –1.28 to 0.76. In addition the heavy atom count was 13–17 atoms whilst the number of HBD and HBA ranged from 0 to 4. Finally the TPSA for all oxetane fragments examined was less than 60 $Å^2$ as recommended and the number of rotatable bonds was 2.[30] These properties suggested that 2-sulfonyl oxetanes would be viable fragments for use in fragment based drug discovery.

Elaboration of 2-sulfonyl oxetanes through palladium or iron catalysed cross-coupling with boronic acids or Grignard reagents resulted in larger more complex molecules that moved away from fragment space into more lead-like and drug-like space. Their physicochemical properties were also analysed to determine the attractiveness of the compounds to the drug discovery process, table 12. The physicochemical properties of sulfonyl oxetanes **124–129**, **132–133** and **137–138** complied with desired drug-like properties proposed by Lipinski,[7] however they also fulfilled the desired requirements for lead-like compounds recently proposed by Churcher (cf. section 1.1.2.).[21] The derivatised oxetanes all had MWs between 240 and 304 daltons; clogP values between 0 and +3; HAC between 16 and 21 atoms and the number of HBD and HBA less than 4, table 12. These properties illustrated that the elaborated 2-aryl sulfonyl oxetanes were attractive motifs to continue through the optimisation process of a drug discovery programme. This conclusion highlighted one of the advantages of starting with small simple molecules that can sample chemical space efficiently then be optimised into larger lead-like compounds with desirable properties.

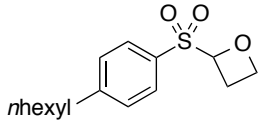
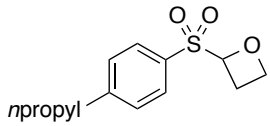
		Molecular Weight	cLogP	HAC	HBD/A
	**137**	282	2.92±0.4	19	0/3
	**138**	240	1.32±0.4	16	0/3

Table 12: Physicochemical data calculated for the 2-sulfonyl oxetane derivatives **137–138**. cLogP = calculated log of partition coefficient (lipophilicity); HAC = heavy atom count; HBD/A = hydrogen bond donors/acceptors. cLogP values were determined using ACDlabs LogP calculator.[ii]

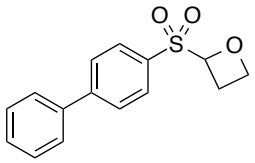
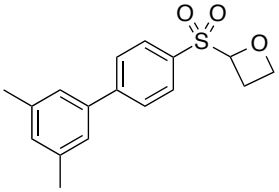
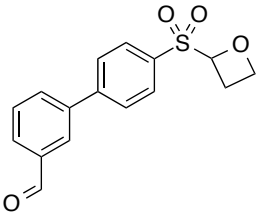
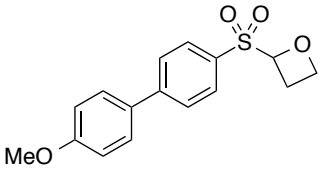
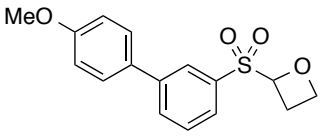
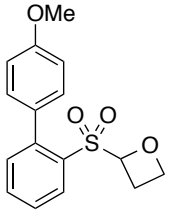
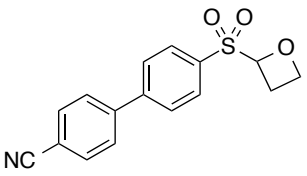
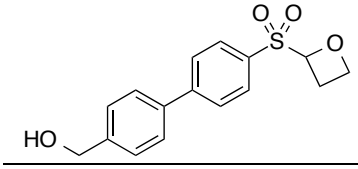
		Molecular Weight	cLogP	HAC	HBD/A
	**124**	274	1.45±0.4	19	0/3
	**125**	302	2.37±0.4	21	0/3
	**126**	302	0.87±0.5	21	0/4
	**127**	304	1.26±0.4	21	0/4
	**128**	304	1.37±0.4	21	0/4
	**129**	304	1.37±0.4	21	0/4
	**132**	299	0.76±0.5	21	0/3
	**133**	304	0.26±0.4	21	0/4

Table 12 continued: Physicochemical data calculated for the 2-sulfonyl oxetane derivatives **124–129** and **132–133**. cLogP = calculated log of partition coefficient (lipophilicity); HAC = heavy atom count; HBD/A = hydrogen bond donors/acceptors. cLogP values were determined using ACDlabs LogP calculator.[ii]

2.4.2. Studies into the Stability of 2-Aryl Sulfonyl Oxetanes

The chemical and biological stability of a compound is important when evaluating the viability and attractiveness of a motif for use in drug discovery. Given this, the overall stability of 2-aryl sulfonyl oxetanes was examined. When stored under argon at –20 ºC all the sulfonyl oxetanes investigated were stable. Oxetanes **55–58** and biaryl oxetanes **124** and **125** were stable for >12 months at –20 ºC and when stored at rt for >24 h no degradation was observed. On the other hand, while 2,2-disubstituted sulfonyl oxetanes **103–107** were stable at –20 ºC for >2 months, upon warming to rt for 24 h they underwent a rearrangement to quantitatively afford the corresponding β-sulfonyl ketones (cf. section 2.3.1.2.). It was also notable that purification of these disubstituted oxetanes **103** and **107-111** required the use of basic alumina (activity IV) in place of silica gel. Consequently these compounds were excluded from additional stability studies and were considered to be less viable fragments.

The instability observed of the 2,2-disubstituted oxetanes to silica gel prompted investigation into the stability of 2-sulfonyl oxetanes under acidic conditions. This was important for stability in the body due to the acidic environment in the stomach. Attractive fragments would also be stable under basic conditions to allow a variety of reaction conditions to be employed during the optimisation process. Seven sulfonyl oxetane derivatives were selected and hydrolytic stability studies performed by Philip MacFaul at AstraZeneca; 2-(phenylsulfonyl)oxetane **56**, a slightly electron rich derivative **55** and an electron poor aryl sulfonyl oxetane **57**. Oxetanes **90** and **93** were also chosen as fluoro- and methoxy- substituents are often incorporated during the optimisation of a potential drug candidate and finally biaryl compounds **124** and **127** were selected to examine more lead-like derivatives. The solution stability of the selected sulfonyl oxetanes was evaluated by incubating 10 μM of each compound in buffer solutions at a variety of pH values at 70 ºC for 15 h. The solutions were analysed at regular intervals by LC-UV-MS to obtain half-lives at 70 ºC. These results were then extrapolated to predict the half-lives at room temperature, 25 ºC, using a reduction in rate of a factor of 2 per 10 degree reduction in temperature. The reduction in rate was determined from the Arrhenius equation and was considered the 'worse case scenario'.[157] The measured and calculated half-lives are shown in table 13.

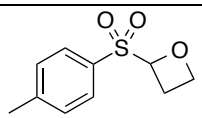
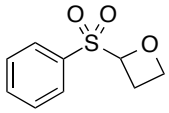
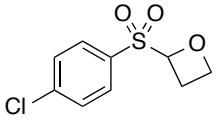
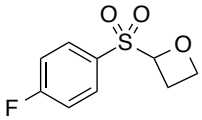
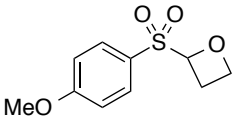
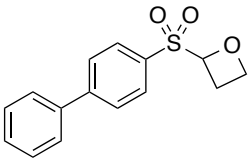
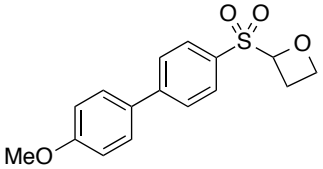
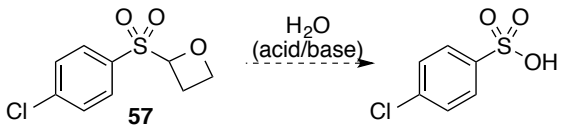
Entry	Compound		Half life (days) (**A** = measured at 70 °C; **B** = predicted at 25 °C)				
				pH 1	pH 4	pH 6	pH 8	pH 10
1		**55**	**A**	0.31	0.45	0.44	0.40	0.41
2			**B**	10.2	9.9	9.9	9.1	9.2
3		**56**	**A**	0.18	0.22	0.23	0.23	0.16
4			**B**	4.0	5.0	5.3	5.3	3.7
5		**57**	**A**	0.07	0.08	0.08	0.08	0.08
6			**B**	1.7	1.9	1.9	1.9	1.8
7		**90**	**A**	0.09	0.12	0.11	0.10	0.16
8			**B**	2.0	2.7	2.4	2.2	3.5
9		**93**	**A**	0.28	0.50	0.51	0.49	0.44
10			**B**	6.3	11.2	11.5	11.1	10.0
11		**124**	**A**	0.17	0.21	0.21	0.02	0.20
12			**B**	3.9	4.7	4.7	4.6	4.6
13		**127**	**A**	0.20	0.25	0.25	0.32	0.23
14			**B**	4.6	5.7	5.7	7.1	5.3

Table 13: Half-lives of selected compounds, showing their stability to acidic and basic conditions. Results obtained by Philip MacFaul at AstraZeneca.

When developing a lead compound a half-life of >60 min (0.04 days) is strived for when the compound is administered intravenously into a rat.[2] In general the 2-sulfonyl oxetanes showed good half-lives across the pH range. A slight decrease in the half-life was observed at pH 1 and pH 10, compared to more neutral conditions, however there was no significant acid or base sensitivity. This was pleasing as possible decomposition pathways could be envisaged under acidic conditions through protonation of the oxetane promoting ring opening, or through protonation of the sulfonyl group resulting in expulsion of the aryl sulfinic acid. The largest effect under acidic conditions was seen for the electron rich derivative **93** which at 25 °C had a half-life of 6.3 days at pH 1 compared to 11.5 days at pH 6, entry 10. The 2-pyridyl substrate, **58,** was also subjected to the hydrolytic stability study but unfortunately results could not be obtained as the compound was not detected by UV or MS, therefore the investigations into substrate **58** were inconclusive.

The fate of the compounds when they decomposed during the stability investigation could not be determined from the MS study. One possible pathway for decomposition was likely to be hydrolysis to the parent sulfonic acid. This would afford a $[M–H]^-$ signal, which was observed during the mass spectrometry studies of chlorinated compound **57**, scheme 63.



Scheme 63: Proposed decomposition pathway of sulfonyl oxetanes to the corresponding sulfonic acid.

By comparing derivatives **56**, **57** and **93** it was concluded that the half-lives increased as the aromatic group became more electron rich indicating that the electron rich substrates were more stable than the electron poor derivatives, (entries 4, 6 and 10). This observation suggested a pathway for decomposition that involved a nucleophilic attack at the sulfur center, as this would be promoted by a more electron poor substituent on the aryl group. Alternatively the decreased stability of the electron poor compounds could be due to the improved leaving group ability of the electron poor substrates compared to the electron rich derivatives. This trend was further demonstrated with biaryl compounds, **124** and **127**. In general the half-lives were comparable to the phenyl derivative however the more electron rich substrate **127** had a longer half-life under acidic, neutral and basic conditions, compared to biphenyl **124,** (entries 4, 12 and 14). Overall these studies demonstrated that the fragments showed good stability under acidic and basic conditions signifying their potential as desirable fragments or motifs for use in drug discovery.

The logD and solubility of the selected sulfonyl oxetane derivatives was also measured by Philip MacFaul at AstraZeneca, however only values for oxetanes **58**, **90** and **93** were obtained, table 14. Lipophilicity is an important parameter to consider in fragment design; surprisingly the measured logD values did not correlate with the calculated clogP values as expected (cf. equation 1), in addition the trend in logD and clogP did not correlate. This discrepancy could not be explained confidently as data for only three sulfonyl oxetanes was obtained. However it should be considered that the data generated during the logD calculations may be subject to significant error on the MSMS readout, this is emphasised by data only being obtained for three of the substrates.

The lipophilicity data could be used to conclude that the sulfonyl oxetanes are polar compounds as all of the logD values are low however clogP suggests that **58** is the most polar compound whilst the logD data suggests that **90** is the most polar sulfonyl oxetane. Interestingly the 2-pyridyl sulfonyl oxetane **58** was expected to have an effect on the logD value due to protonation, however this would have led to a lower logD compared to the clogP value, which was not observed. Unfortunately further investigation was required to further understand these results.

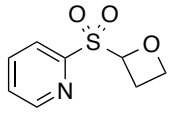
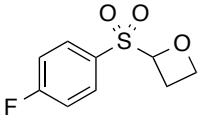
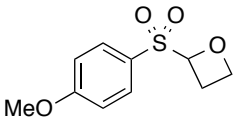
Entry	Compound		Measured LogD[a]	cLogP[b]	Solubility (μM)[c]
1		**58**	–0.3	–1.3	37
2		**90**	<–1.6	0.11	-
3		**93**	<–1.1	1.3	99

Table 14: Solubility and LogD of 2-sulfonyl oxetanes **58**, **90** and **93**. [a] Distribution coefficient between *n*-octanol and aqueous phosphate buffer at pH 7.4 at 25 ºC determined by LCMSMS. [b] cLogP values were determined using ACDlabs LogP calculator.[ii] [c] Determined by LCMSMS following incubation of solid compound in pH 7.4 aqueous phosphate buffer at 25 ºC.

The solubility of **58** and **93** in aqueous phosphate buffer at pH 7.4 after 24 h at 25 ºC was measured. Given the fragments' lipophilicity and MW a solubility value in excess of 100 μM was expected.[iv] The lower solubility observed for 2-pyridyl substrate **58** may have been due to tight crystal packing, however the low melting point of 64–65 ºC contradicted this hypothesis. Further investigation into the possible hydrogen bonding of these fragments would be required to fully explain these observations. Finally the intrinsic clearance of **58** in rat hepatocytes was measured and indicated that there was no inherent metabolic instability. A value of 2.8 μl per min per 1E6 cells was obtained which signified low turnover which was expected for a fragment with low lipophilicity.

[iv] According to Philip MacFaul at AstraZeneca.

2.4.3. Structural and Conformational Analysis of 2-Sulfonyl Oxetanes[v]

In addition to the three-dimensional structure of 2-aryl sulfonyl oxetanes a feature that increased their desirability as fragments was the small number of rotatable bonds present. Rotation around the oxetane-sulfonyl and sulfonyl-aryl bonds, highlighted in figure 24, was possible, however if a symmetrical aromatic group was present then only rotation around the oxetane-sulfonyl bond was possible.

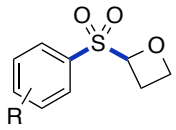


Figure 24: Structure of a 2-aryl sulfonyl oxetane depicting the rotatable bonds present in the molecule.

To determine the potential binding conformation of the 2-sulfonyl oxetane fragments the conformational profiles of selected oxetane derivatives were investigated. 2-(Phenylsulfonyl)oxetane **56** was chosen to represent an unsubstituted sulfonyl oxetane; **58** was examined as the heterocyclic pyridine ring had two distinct conformations which may affect the fragment's overall configuration; and finally *ortho*-tolyl derivative **87** was chosen as a more conformationally constrained substrate. Initially the conformational profile of **56** was investigated by computational methods.[113] To obtain the conformational profile the energy of the possible conformations, accessed by varying the dihedral angle around the C–S–oxetane bond in 10 degree increments between 0 and 360 degrees, was calculated, figure 25.

[v] Calculations performed by Dr. James A. Bull at Imperial College London.

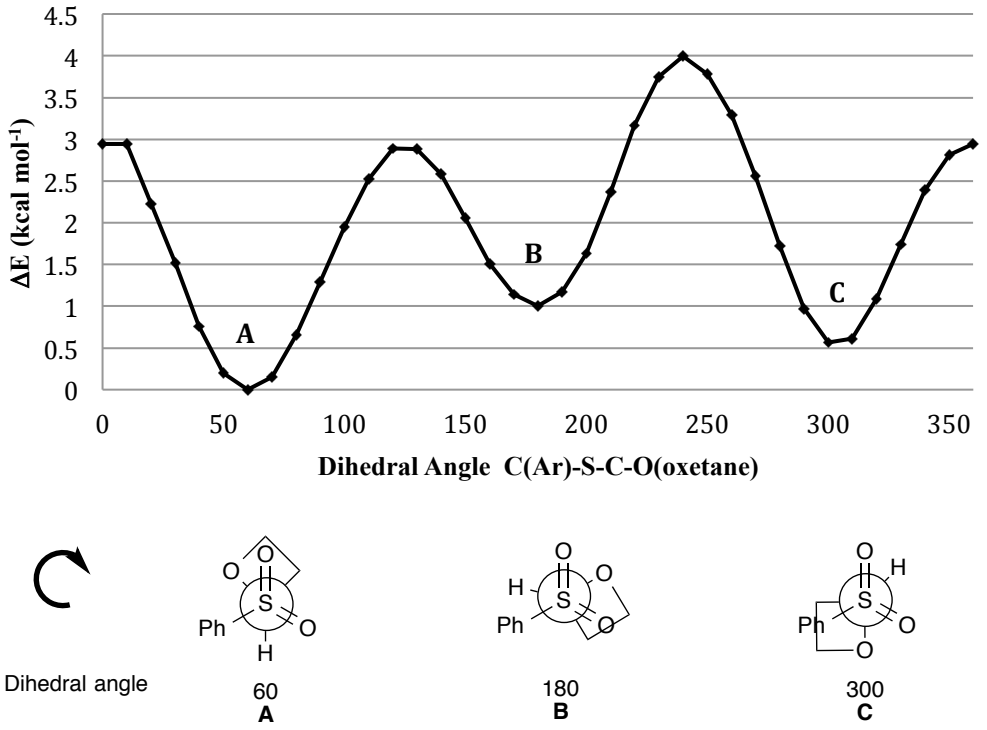


Figure 25: Conformational profile of 2-(phenylsulfonyl)oxetane **56** performed using Gaussian 09 and a DFT relaxed coordinate scan at B3LYP/6-31G(d,p) level of theory, and the three preferred conformations.

Three energy minima were observed with dihedral angles of 60, 180 and 300 degrees, indicating three preferred conformations of sulfonyl oxetane **56**. Representation of these conformations is shown in figure 25. The low energy conformations corresponded to the staggered arrangement of all bonds, whilst the eclipsed arrangement was present in the highest energy conformations. Conformation **A** had the lowest overall energy due to the effects of opposing dipoles of the oxetane C–O bond and the sulfonyl S=O bond, in addition to minimal steric interactions between the oxetane and phenyl ring. Conformation **B** had a slightly higher energy due to the less favourable bisecting dipoles, whilst conformation **C** had undesirable steric interactions. The minimal energy difference between the three staggered conformations of less than 1 kcal mol^{-1} together with the low energy barriers to rotation (maximum 4 kcal mol^{-1}) led to the conclusion that the fragment could adopt any of the three conformations **A**, **B** or **C** when binding to a possible target.

The same calculations and computational analysis were performed for oxetane **58**. There were two possible orientations of the pyridyl ring, **58A** and **58B**, so the conformational

profile for each isomer was determined, figure 26. The results were then analysed to deduce the overall preferred configuration of the sulfonyl oxetane.

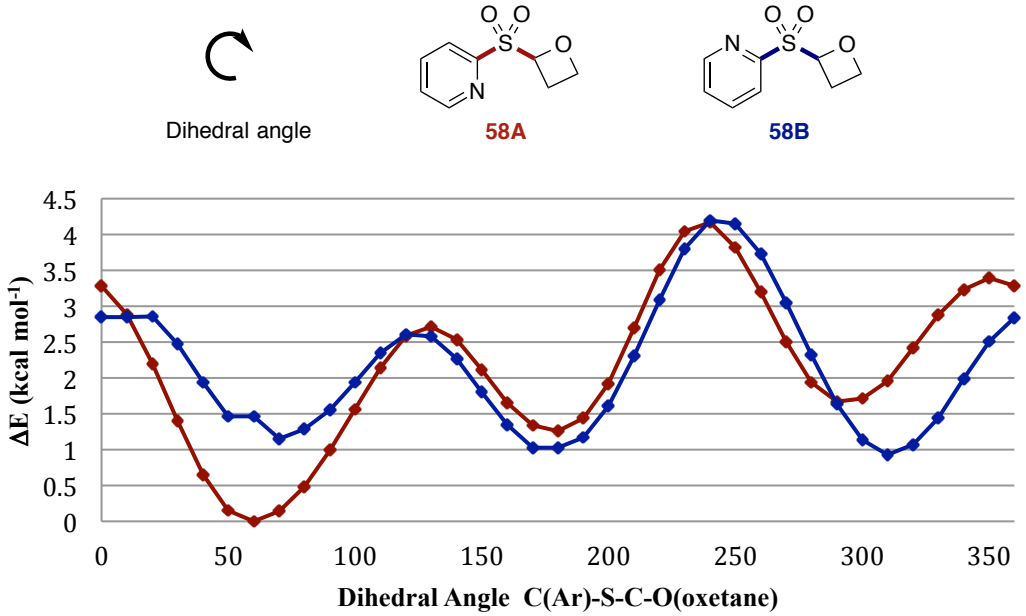


Figure 26: Structure of the 2 possible orientations of the pyridyl group in 2-(oxetane-2-sulfonyl)pyridine and the conformational profile of both configurations; **58A** = red, **58B** = blue. A DFT relaxed coordinate scan was performed at B3LYP/6-31G(d,p) level of theory.

The conformational profiles for **58A** and **58B** both showed three distinct minima corresponding to three low energy conformations. Similar to those calculated for oxetane **56**, the minimal energy conformations for **58A** and **58B** correlated to the staggered conformation of bonds whilst the maximum energy conformations correlated to the eclipsed configuration. Structures of the 3 preferred conformations for each series are shown in figure 27.

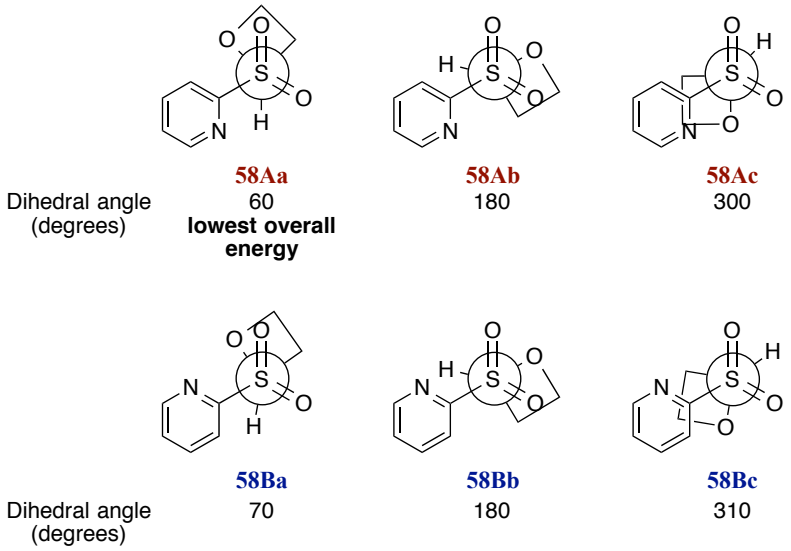


Figure 27: Low energy conformations of 2-(oxetane-2-sulfonyl)pyridine **58**.

Conformation **58Aa** was the overall lowest energy conformation due to opposing dipoles between the oxetane C–O bond and the sulfonyl S=O bond in addition to the opposing pyridine and oxetane dipoles. In addition, there was minimal steric hindrance between the pyridyl and oxetane rings. In series B the corresponding configuration, **58Ba**, had a slightly higher energy due to an unfavourable van der Waals interaction between the oxetane and pyridine ring. Conformations **58Ab** and **58Bb** both had less favourable bisecting dipoles whilst **58Ac** and **58Bc** had unfavourable steric interactions. As the barrier to rotation and the energy differences between all 6 low energy configurations were low, oxetane **58** was proposed to bind to a possible target in any of the staggered conformations.

Finally, the conformational profile of 2-(2-methylbenzenesulfonyl)oxetane **87** was investigated. A distinct favoured conformation was expected due to potential steric interactions of the *ortho*-methyl group. A preferred conformation would facilitate the prediction of how the fragment may bind to a potential drug target and therefore ease the optimisation process, increasing the desirability of employing the conformationally constrained sulfonyl oxetanes in the drug discovery process. There were two possible orientations of the methyl group, **87A** and **87B**, so the conformational profile of each isomer was calculated using the same computational methodology and analysis as for oxetanes **56** and **58**, figure 28.

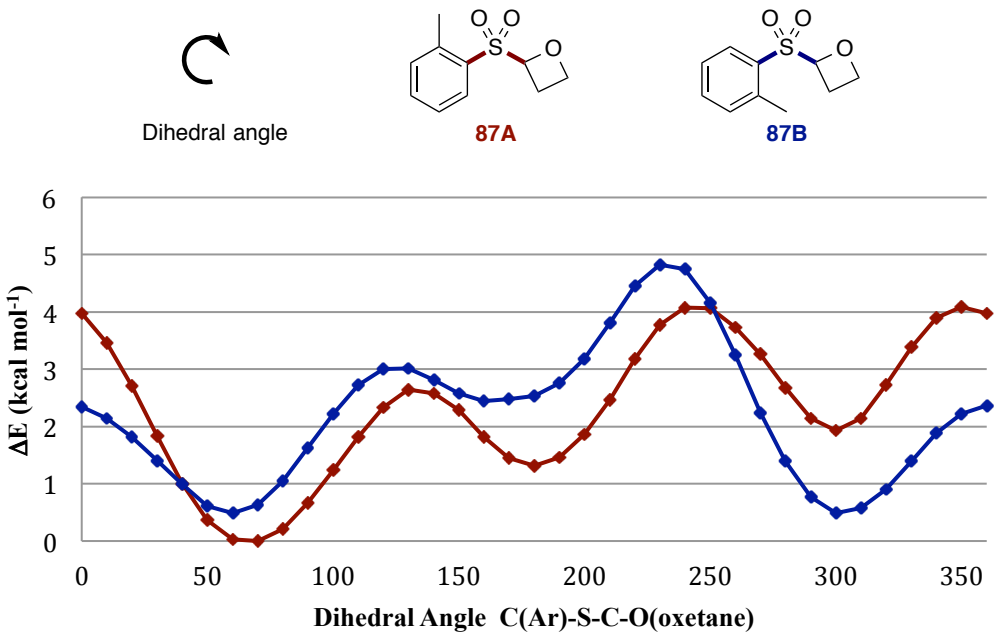


Figure 28: Structure of the 2 possible orientations of the tolyl group in oxetane **87** and the conformational profile of both isomers; **87A** = red, **87B** = blue.

Three minima were observed in the conformational profiles of both **87A** and **87B**. Except for the minima observed for **87B** with a dihedral angel of 180 degrees, these correlated to low energy conformations of the sulfonyl oxetane. The preferred conformations of **87A** had dihedral angles of 70, 180 or 300 degrees resulting in a staggered orientation of bonds, whilst the lowest energy conformations of **87B** had dihedral angles of 60 or 300 degrees. The low energy conformations which the fragment may adopt when bound to a potential target, are shown in figure 29.

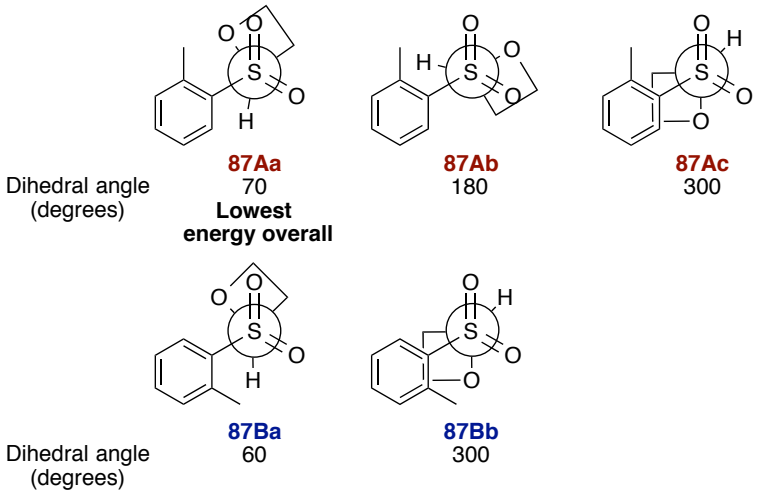


Figure 29: Structures of the low energy conformations of 2-(2-methylbenzenesulfonyl)oxetane **87**.

For isomer **A** the lowest energy conformation was **87Aa**. This configuration was intially hypothesised to be the highest in energy due to the possible steric clash between the oxetane and tolyl methyl group, but instead a favourable intramolecular van der Waals interaction between a proton on the benzylic CH_3 and the oxetane oxygen was observed. **87Ab** had a slightly higher energy due to the absence of this favourable interaction and bisecting dipoles of the oxetane and sulfone moiety. The energy of **87Ac** was raised by 1.9 kcal mol^{-1}, compared to **87Aa**, due to a steric clash between the aromatic and oxetane rings. When the methyl group was in the orientation of isomer **B** conformation **87Ba** resulted in the lowest energy due to opposing dipoles of the oxetane C–O and sulfonyl S=O bonds and no steric hindrance. The energy of conformation **87Bb** increased by 0.006 kcal mol^{-1} compared to **87Ba**. With a dihedral angle of 300 degrees a favourable interaction was present between the oxetane oxygen and a proton on the benzylic CH_3 however there was a steric clash between the oxetane and aromatic rings. Overall the lowest energy conformation was **87Aa** due to the combined effects of opposing dipoles, limited steric clash and favourable van der Waals interactions.

2.5. Conclusions from the Synthesis and Evaluation of 2-Aryl Sulfonyl Oxetanes as Fragments

A novel strategy for oxetane synthesis was developed involving an intramolecular C–C bond forming cyclisation and employed to synthesise a library of 2-sulfonyl oxetanes in yields of 46–95%. Although versatile the oxetane synthesis appeared dependent on the electronics of the substrate as the more electron poor derivatives could not be progressed through the synthetic route. Future work investigating the cyclisation would be to control the absolute stereochemistry of the resulting oxetanes. Deprotonation of sulfone **84** with a combination of *s*BuLi/sparteine or a chiral lithium amide base may result in an asymmetric cyclisation affording chiral 2-sulfonyl oxetanes.[158,159]

Methods to incorporate the motifs into larger compounds and grow any potential fragment hits into lead-like and drug-like compounds were desired. The sulfonyl oxetanes were functionalised by four different methods. 1) The oxetane ring was functionalised directly *via* a lithiated intermediate. Unfortunately the scope of electrophiles was limited due to steric hindrance. 2) The *ortho* directing ability of the sulfone moiety was successfully exploited to derivatise the fragments on the aromatic ring *via* lithiation and electrophilic

trapping. 3) Suzuki cross-coupling of **57**, **88**, **89** and **91** was successful, forming biaryl derivatives in good yields. 4) Fe-catalysed cross-coupling of oxetane **57** with Grignard reagents proceeded in good yields at rt after 5 min. The Grignard reagent employed was required to have a proton in the beta position and so longer chain Grignard reagents were desirable. A summary is shown in figure 30.

Derivatisation by Buchwald-Hartwig amination or Ullmann-type coupling was not successful due to the instability of the oxetane compounds, possibly caused by heating in the presence of a strong base. If mild reaction conditions were developed these reactions could be investigated again as incorporating an amine, amide or ether onto the oxetane fragments would be advantageous.

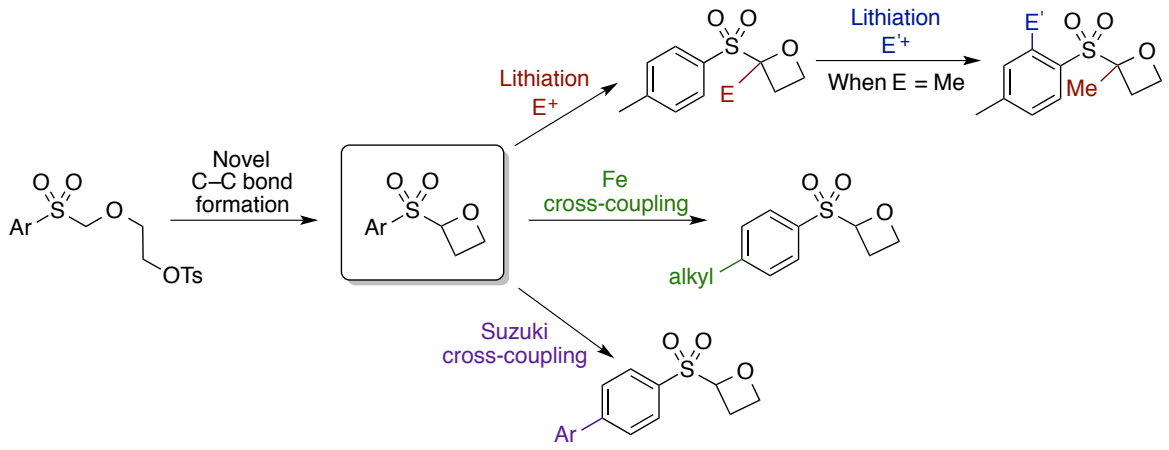


Figure 30: Summary of the synthesis and functionalisation of 2-sulfonyl oxetanes.

The physicochemical and conformational properties of the sulfonyl oxetanes were evaluated as a method to determine their suitability for use in drug discovery. The physicochemical properties of a selection of 2-sulfonyl oxetane derivatives were calculated and analysed against the reported guidelines for fragment and lead-like compounds. Oxetanes **55–58** and **87–93** possessed desirable fragment-like properties whilst the derivatised substrates investigated possessed desirable lead-like properties. This suggested that they would be ideal motifs for use in designing a drug candidate whose properties fall within desirable drug-like space. Additionally, pH stability studies concluded that the sulfonyl oxetanes were stable to acidic and basic conditions with the more electron rich substrates showing increased stability. LogD and solubility of a selection of 2-sulfonyl oxetanes were also measured however LogD did not correlate to

the calculated clogP and the solubility of **58** and **93** was surprisingly low, further investigation is required to explain these observations.

Studies into the conformational profiles of **56**, **58** and **87** provided a greater understanding of how the fragments may bind to a potential target. All three substrates resulted in low energy conformations with small energy differences between them and low energy barriers to rotation, suggesting that the sulfonyl oxetanes may adopt any of the low energy conformations when binding to a potential target. From a drug discovery perspective the potential for the fragment to bind to a possible target would increase if the compound could adopt multiple conformations, however the exact binding conformation would be unknown leading to a more challenging optimisation process.

3. Synthesis of 2-Sulfinyl Oxetanes and Investigations into Functionalisation by Sulfoxide-Metal Exchange

3.1. Introduction to the Sulfoxide Functional Group

In this section, the synthesis of 2-sulfinyl oxetanes and their elaboration is explored. The sulfoxide functional group is scarcely found in natural products but is present in a variety of active pharmaceutical agents, figure 31.[160] Omeprazole is a proton pump inhibitor (PPI) used to treat the symptoms of acid reflux disease, which contains a racemic sulfoxide moiety,[161] Sulindac has shown anti-inflammatory properties whilst Lansoprazole is a PPI used to treat stomach disorders caused by gastric acid.[162,160]

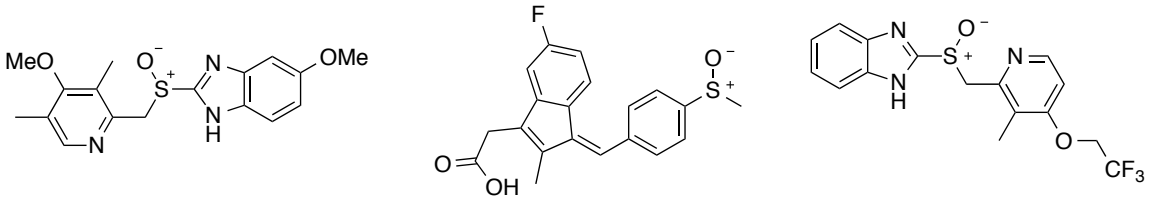


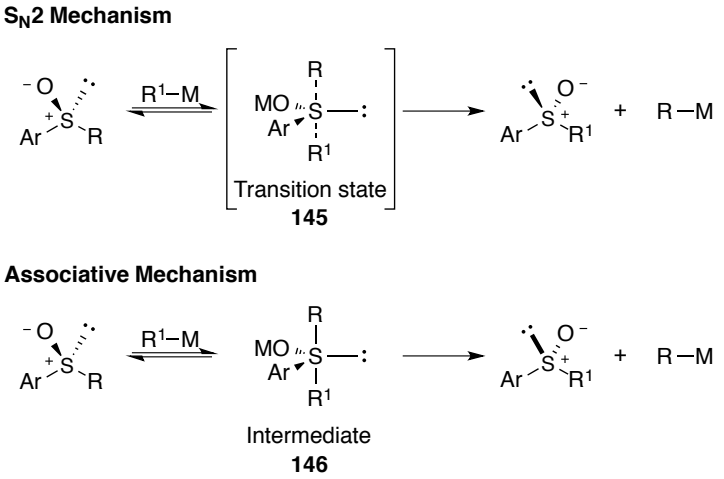
Figure 31: Examples of pharmaceutical compounds containing the sulfoxide functional group.[161,162,160]

In addition the sulfoxide functional group can be employed as a handle for derivatisation and functionalisation of a molecule. Of particular interest is the exchange reaction between an organometallic compound and a sulfoxide group to form a new organometallic reagent.

3.1.1. Sulfoxide-Metal Exchange

3.1.1.1. Mechanistic Discussion of the Sulfoxide-Metal Exchange Reaction

When treated with an organometallic reagent such as *n*BuLi or *i*PrMgCl the sulfoxide moiety can undergo a sulfoxide-metal exchange, resulting in a new organometallic reagent and sulfoxide species. As sulfur can form tetra- or pentacoordinated compounds the exchange reaction may occur *via* an S_N2-type mechanism involving a sulfurane transition state or an associative mechanism resulting in a trigonal bipyramidal sulfurane intermediate, scheme 64.[163,164]



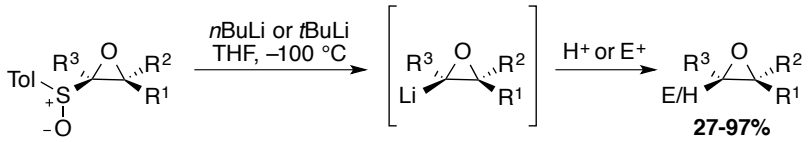
Scheme 64: Proposed mechanisms for the sulfoxide-metal exchange reaction.[163,164]

The reaction proceeds with initial attack of the organometallic reagent on the sulfinyl sulfur atom forming a hypervalent sulfur species **145** or **146** after addition at the axial position.[163] The central sulfur atom of the sulfurane has an expanded valence shell resulting in instability. The sulfurane can regain a preferred 'normal' valence of 8 electrons through loss of a substituent *via* ligand exchange. The ligand displaced is the substituent that results in the most stable anion,[165] corresponding to the most electron poor ligand, R in scheme 64. This results in the formation of a more stable organometallic species and new sulfoxide derivative. The sulfoxide is formed with inversion of configuration if an S_N2 mechanism occurs due to the diaxial relationship of the attacking and displaced ligands, R^1 and R, scheme 64.[163] If the reaction proceeds *via* an associative mechanism the resulting sulfoxide may also have inversion of configuration however the sulfurane intermediate may undergo isomerisation by pseudorotation resulting in retention of configuration.[166,167] The majority of sulfoxide-metal exchange reactions result in inversion of configuration, concluding that either mechanistic pathway is possible.[163,168]

3.1.1.2. Examples of Sulfoxide-Lithium Exchange

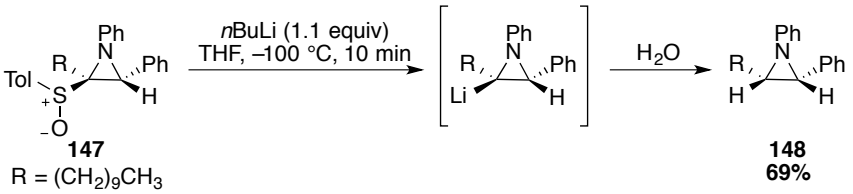
The displacement of a sulfoxide substituent when exposed to an organolithium reagent was initially observed as a side reaction in the synthesis of α-sulfinyl carbanions in 1972.[169] A year later Lockard utilised this reactivity to form dialkyl sulfoxides from aryl alkyl sulfoxides and the sulfoxide-lithium exchange reaction became of great interest.[170] Satoh demonstrated the reaction on small heterocyclic rings, synthesising trisubstituted

epoxides from the corresponding α,β-epoxy sulfides by treatment with *n*BuLi at –100 ºC, followed by a proton quench, scheme 65.[171] This methodology was further developed to allow trapping of the oxiranyllithiums with a variety of electrophiles such as aldehydes, ketones and methylchloroformate.[172]



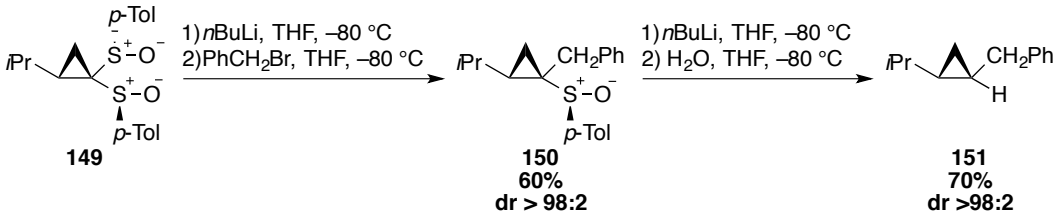
Scheme 65: The sulfoxide-lithium exchange of sulfinyl epoxides to form trisubstituted epoxides.[171]

Desulfinylation by treatment with alkyllithiums was also reported on sulfinylaziridines.[173,174] Treatment of aziridine **147** with *n*BuLi followed by trapping of the resulting lithium intermediate with water formed aziridine **148** in a 69% yield, scheme 66. Only the cis-isomer was generated, demonstrating that the sulfoxide-lithium exchange proceeded in a stereospecific manner and that the intermediate aziridyl lithium species was configurationally stable at –100 ºC.[173]



Scheme 66: Sulfoxide-lithium exchange on sulfinylaziridines.[173]

More recently Marek reported consecutive sulfoxide-lithium exchange as a method to synthesise enantiomerically pure polyalkylated cyclopropane derivatives, scheme 67.[175]



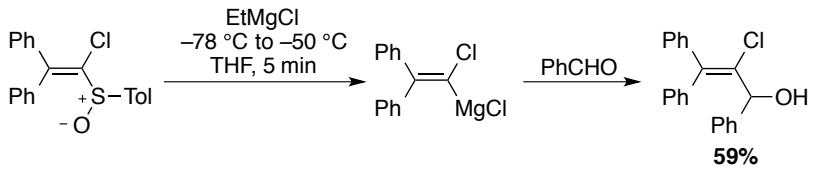
Scheme 67: Consecutive sulfoxide-lithium exchange to functionalise cyclopropanes selectively.[175]

Enantiopure cyclopropane **149** was treated with *n*BuLi at –80 ºC to selectively form the corresponding cyclopropyllithium intermediate. Subsequent reaction with an electrophile such as benzyl bromide afforded sulfinyl cyclopropane **150**. Marek proposed that the more hindered syn-selective sulfoxide-lithium exchange occurred initially due to the release of strain on the cyclopropyl ring.[175] Further treatment of **150** with *n*BuLi followed by a proton quench resulted in the formation of polyalkylated derivative **151** in a yield of 70%. The selectivity of the sulfoxide-lithium exchange and stability of the lithiated intermediates allowed diastereomerically and enantiomerically pure polyalkylated cyclopropanes to be accessed.

Organolithium reagents are successful in sulfoxide-metal exchange reactions however they form very reactive lithium reagents and therefore suffer from functional group compatibility. In addition, by-products are produced as the organolithium intermediates can often deprotonate the alkyl sulfoxides generated during the reaction, so stringent temperature control is required to prevent these competing reactions.[163,172,173] Given this, the use of organomagnesium reagents in sulfoxide-metal exchange has grown and selected examples are discussed below.

3.1.1.3. Examples of Sulfoxide-Magnesium Exchange

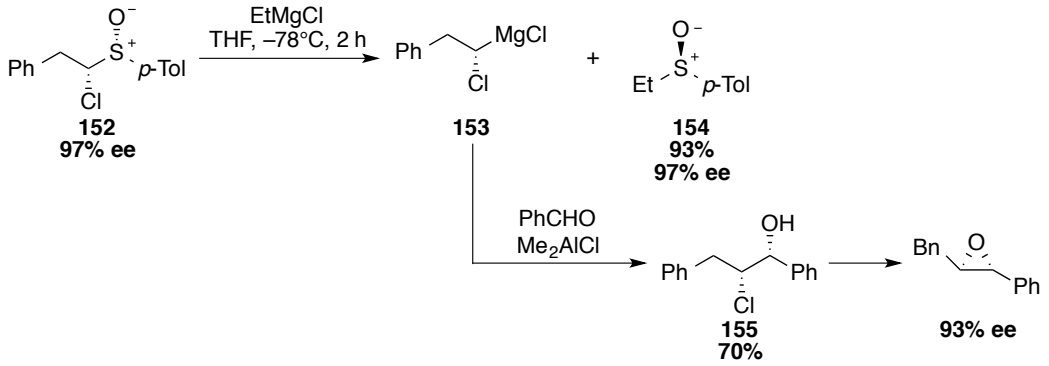
The pioneering research into sulfoxide-magnesium exchange was reported by Satoh in 1995 when he demonstrated that vinyl Grignard reagents were generated from the reaction of α-chloro substituted vinylic sulfoxides with ethyl magnesium chloride, scheme 68.[176]



Scheme 68: Initial generation of a Grignard reagent from a sulfoxide-magnesium exchange reaction.[176]

The magnesium carbenoids generated were shown to be configurationally stable at low temperatures. Hoffman and Satoh both exploited this reactivity generating chiral Grignard reagents with over 90% ee.[177,178] When enantioenriched α-chlorosulfoxide **152** was treated with EtMgCl at –78 ºC for 2 hours chiral Grignard reagent **153** was generated along with

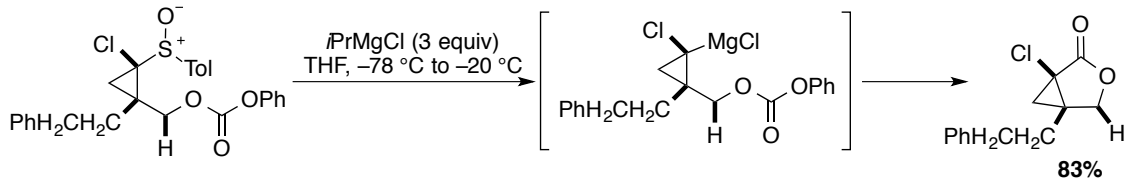
chiral sulfoxide **154**, scheme 69. The sulfoxide-magnesium exchange proceeded with inversion of configuration at the sulfur centre and retention of configuration at the carbon centre of the Grignard reagent.[177–179] The organomagnesium reagent was quenched with benzaldehyde to afford alcohol **155** in a 70% yield with transfer of the enantiomeric purity. This was determined by converting alcohol **155** into the corresponding epoxide, scheme 69.[177]



Scheme 69: Sulfoxide-magnesium exchange of chiral sulfoxides to generate chiral Grignard reagents.[179]

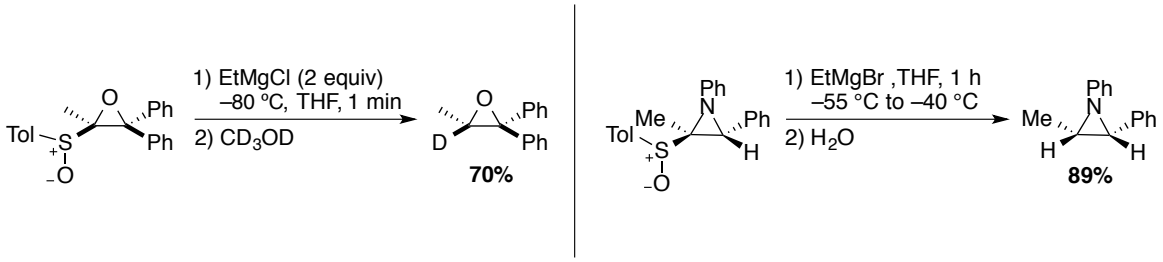
The low temperature was essential for the exchange reaction as the organomagnesium generated was shown to racemise at –60 ºC and the rate of racemisation increased as temperature increased.[177] In 2013 O'Brien reported the synthesis of chiral α-functionalised Grignard reagents by treatment of the corresponding α-alkoxy sulfoxides with *i*PrMgCl at rt for 1 min. The short reaction time helped enable the use of a higher reaction temperature.[180]

Sulfoxide-magnesium exchange has been reported on small rings including cyclobutanes,[117] cyclopropanes,[181,182] epoxides[172] and aziridines.[173] Satoh reported the generation of magnesium cyclopropylidenes from 1-chlorocyclopropyl phenyl sulfoxides *via* sulfoxide-magnesium exchange with alkyl magnesium chlorides and found the organomagnesium intermediates to be stable at low temperatures of –60 ºC for up to 3 h.[183] In 2014 this reactivity was exploited to form cyclopropane-fused α–chlorolactones from the corresponding sulfinyl cyclopropanes by reaction with *i*PrMgCl, scheme 70.[182]



Scheme 70: Synthesis of α–chlorolactones from the corresponding sulfinyl cyclopropanes.[182]

In addition, epoxides and aziridines could be magnesiated when treated with alkyl Grignard reagents and the desulfinated heterocycles were produced in yields of 70–95%, scheme 71. The heterocyclic organomagnesium compounds generated after the ligand exchange were reported to be less reactive towards electrophiles than the corresponding lithiated compounds, resulting in a limited scope.[184,173]

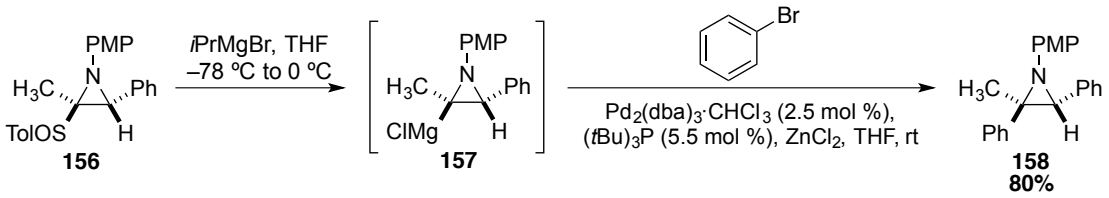


Scheme 71: Sulfoxide-magnesium exchange on 3-membered heterocycles.[184,173]

The scope of functionalised aziridines could be improved by employing cross-coupling methodology. Satoh disclosed the cross-coupling of aziridinylmagnesiums with iodoalkanes in the presence of copper iodide to form alkylated aziridines in yields of 83–94%. The reactions were performed at room temperature and produced diastereomerically pure aziridines due to the magnesiated intermediates being conformationally stable at rt.[185]

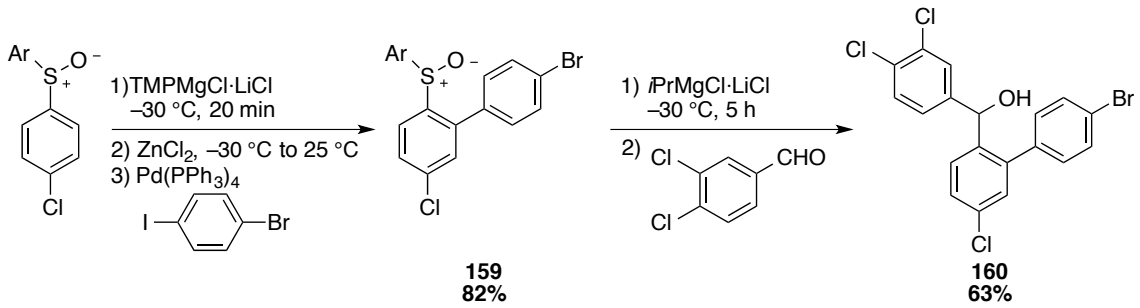
The reactivity of the intermediate organomagnesium compounds, generated from a sulfoxide-magnesium exchange, in cross-coupling reactions was further exploited by Knochel who reported the palladium catalysed cross-coupling of arylmagnesium reagents with aryl iodides following transmetallation with zinc.[186] More recently the use of non-aromatic magnesium reagents in palladium catalysed cross-coupling was disclosed by Bull who developed the reaction of aryl bromides with tertiary organometallic aziridines.[187] Sulfoxide-magnesium exchange between sulfinylaziridine **156** and *i*PrMgBr afforded intermediate **157**. Transmetallation to zinc followed by palladium catalysed

cross-coupling with aryl bromides afforded functionalised aziridines such as **158**, scheme 72. Both electron rich and electron poor aryl bromides were successful in the reaction forming the aziridine as a single diastereoisomer with retention of configuration.[187]



Scheme 72: Sulfoxide-magnesium exchange of sulfinylaziridine **156** followed by palladium catalysed cross-coupling with aryl bromides.[187]

In 2008 Knochel reported the functionalisation of arenes starting from diaryl sulfoxides utilising the reactivity of the sulfoxide functional group.[188] Initially the *ortho* directing ability of the sulfoxide moiety was exploited to regioselectively magnesiate the aromatic ring. The resulting intermediate **159** was treated with *i*PrMgCl·LiCl followed by reaction with an electrophile to afford multi-substituted arenes, including **160**, scheme 73.[188,186]



Scheme 73: Example of the sulfoxide moiety being utilised in the functionalisation of arenes.[188]

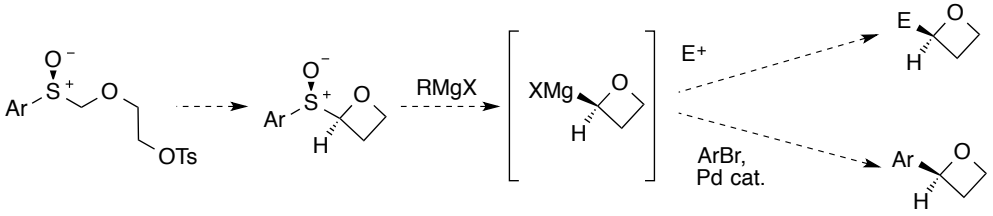
The ability of the sulfoxide moiety to undergo sulfoxide-magnesium exchange when treated with organomagnesium reagents was exploited more recently in the functionalisation of furans,[189] benzofurans,[189] thiophenes,[189] pyridines,[186] 7-azaindoles [190] and imidazoles,[191] demonstrating the utility and versatility of sulfoxide-magnesium exchange methodology in the synthesis of highly functionalised compounds.

3.2. Proposed Synthesis and Derivatisation of 2-Sulfinyl Oxetanes

2-Sulfinyl oxetanes were envisaged as interesting fragments in their own right as well as motifs which may also enable a method for the introduction of a 2-substituted oxetane into a wide variety of compounds *via* an organometallic intermediate. 2-Sulfinyl oxetanes may provide precursors to oxetane organometallic reagents through sulfoxide-metal exchange.

With this in mind the aim of this section was:
1) to investigate the formation of 2-sulfinyl oxetanes and;
2) to investigate the sulfoxide-magnesium exchange as a method to access an oxetanyl organometallic reagent.

Synthesis of 2-sulfinyl oxetanes would initially be explored *via* an intramolecular C–C bond forming cyclisation. If enantiopure cyclisation precursors were employed enantiopure oxetanes may be formed, which were anticipated to produce chiral Grignard reagents and a novel sulfoxide substrate upon treatment with an organomagnesium reagent.[163,179] If successful, functionalisation by electrophilic trapping or cross-coupling could be explored, scheme 74.



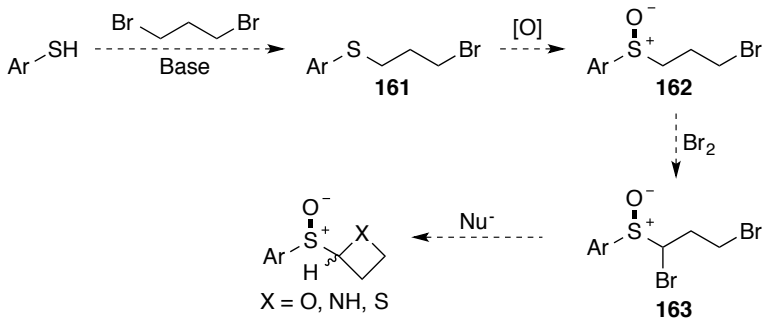
Scheme 74: Proposed synthesis of a chiral oxetane Grignard reagent.

3.3. Investigation into the Synthesis of 2-Sulfinyl Oxetanes

To simplify initial investigations and examine the cyclisation to afford 2-sulfinyl oxetanes a racemic synthesis was explored.

3.3.1. Proposed Synthetic Routes to Access 2-Sulfinyl Oxetanes

Initially a slightly varied synthetic sequence to that developed to synthesise 2-sulfonyl oxetanes was investigated. This route provided the possibility of accessing a variety of heterocyclic compounds, including 2-sulfinyl azetidines and 2-sulfinyl thietanes in addition to 2-sulfinyl oxetanes. The diversity would be incorporated in the latter part of the synthetic sequence to increase the methodology's attractiveness and utility. The synthetic route considered is shown in scheme 75.



Scheme 75: Potential synthetic route to form 2-sulfinyl substituted heterocycles.

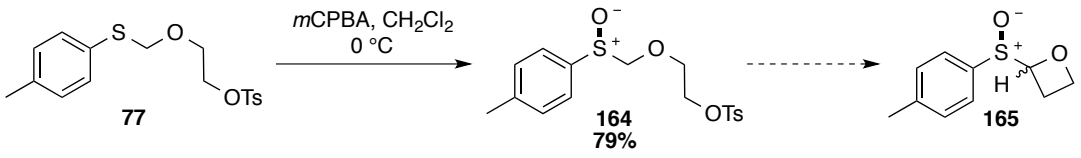
Alkylation of 1,3-dibromopropane with commercially available aromatic thiols was expected to afford brominated compound **161**. Oxidation to the corresponding sulfoxide followed by bromination to incorporate a leaving group would produce cyclisation precursor **163**. Nucleophilic displacement of the bromide followed by treatment with a base to initiate cyclisation could result in the synthesis of a range of 4-membered heterocycles, depending on the nucleophile used. Nucleophiles such as amines or thiols could be employed to obtain 2-sulfinyl azetidines and 2-sulfinyl thietanes respectively.

Alkylation of 1,3-dibromopropane with 4-methylbenzenethiol in the presence of NaH at 0 ºC resulted in sulfide **161** in a 35% yield. Mono-oxidation with *m*CPBA was successful however the product could not be isolated due to instability. Immediately following

purification on silica gel sulfoxide **162** degraded to sulfide **161** and a mixture of unidentified compounds. Given this, the route was not investigated further, instead the synthesis of 2-sulfinyl oxetanes *via* a synthetic route analogous to that previously established to synthesise 2-sulfonyl oxetanes was explored. Initially the synthesis of the *p*-tolyl sulfinyl oxetane substrate **165** was investigated.

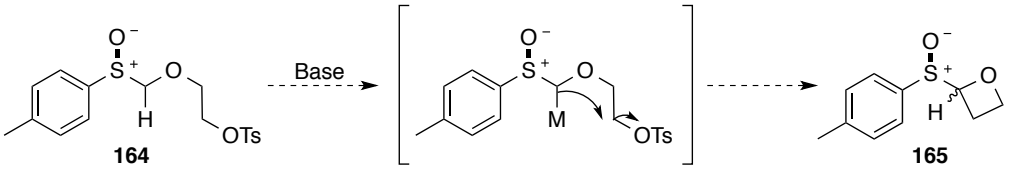
3.3.2. Synthesis of a Suitable Oxetane Cyclisation Precursor

The synthetic route to synthesise 2-sulfinyl oxetanes differed from that to form 2-sulfonyl oxetanes following incorporation of the *p*-toluenesulfonate leaving group. *p*-Toluenesulfonate **77** was a common intermediate however subsequent mono-oxidation to sulfoxide **164**, instead of the corresponding sulfone, was required to form the desired oxetane cyclisation precursor. An oxidation was performed to afford a racemic sulfoxide. Sulfide **77** was treated with 1.1 equiv of *m*CPBA to afford sulfoxide **164** in a 79% yield after purification by chromatography, scheme 76. Once the synthesis and functionalisation through sulfoxide-metal exchange were successfully developed investigation into an asymmetric oxidation to the sulfoxide and therefore chiral Grignard reagent would be performed.[192]



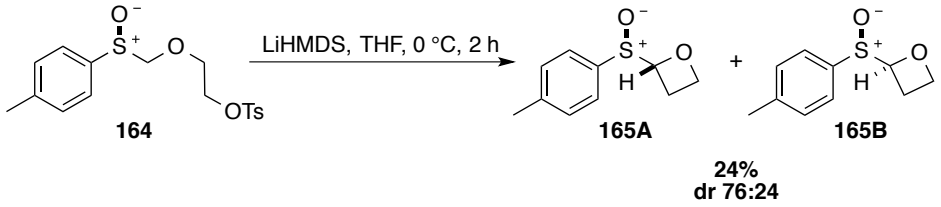
Scheme 76: Synthetic route investigated to afford 2-(4-methylbenzenesulfinyl)oxetane **165**.

The intramolecular cyclisation was investigated next. The required reaction was similar to that reported by Satoh in the synthesis of cyclobutyl *p*-tolyl sulfoxides (cf. scheme 22).[117] Deprotonation alpha to the sulfoxide followed by cyclisation of the resulting metallated intermediate, displacing the *p*-toluenesulfonate moiety, could result in the formation of 2-sulfinyl oxetanes *via* an intramolecular C–C bond formation, scheme 77.



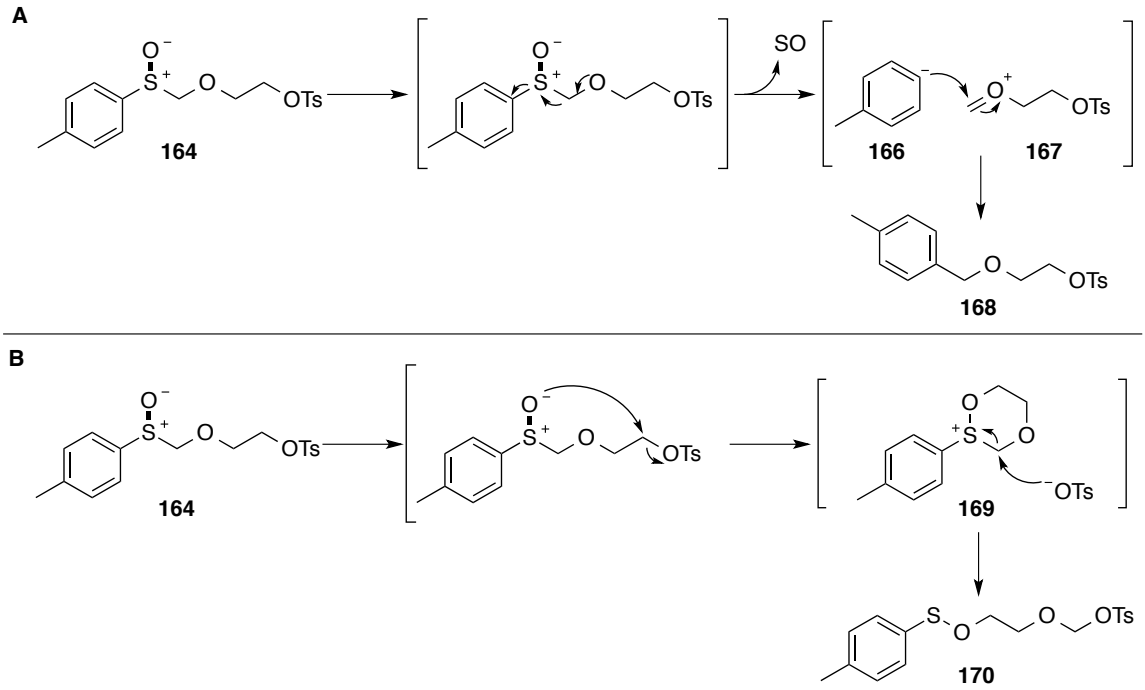
Scheme 77: Proposed mechanism for the formation of 2-sulfinyl oxetanes.

Sulfoxide **164** was treated with 2 equivalents of LDA at 0 ºC but no desired product or starting material was observed in the crude reaction mixture despite the cyclobutyl substrate being isolated in a 98% yield under similar reaction conditions.[117] To confirm the unsuccessful outcome the reaction with **164** was to be repeated however, following oxidation, the sulfoxide could not be isolated efficiently as degradation was observed during purification. A low yield of **164** could be obtained and was treated immediately with LiHMDS to probe the cyclisation reaction. The desired product **165** was formed with a combined 24% yield of the two diastereoisomers, scheme 78. Distinguishing between diastereoisomers **A** and **B** using standard analytical techniques was challenging, therefore the stereochemistry of the major and minor isomers could not be determined and A and B are currently arbitrarily assigned. Although low yielding, due to significant degradation of the sulfoxide starting material **164** at the beginning of the reaction, this result demonstrated that 2-sulfinyl oxetanes could be accessed through an intramolecular C–C bond formation.



Scheme 78: Initial cyclisation of sulfoxide **164** to access 2-sulfinyl oxetanes **165A** and **165B**.

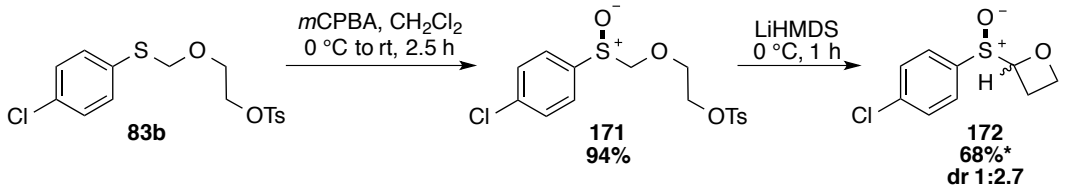
The product obtained following degradation was examined and the mechanism for degradation considered. This proved difficult as the initial degradation product further reacted to give a complicated mixture of compounds. A ^{1}H NMR spectrum was obtained which suggested that no protons were lost following initial degradation however the chiral environment had disappeared. The corresponding sulfone or sulfide were not present, however two alternative products and proposed pathways for degradation are suggested in scheme 79.



Scheme 79: Two proposed pathways for degradation of sulfoxide **164**.

The corresponding cyclisation precursor **67** required to synthesise 2-sulfinyl cyclobutanes was not reported to be unstable,[117] suggesting that the oxygen atom in the chain contributed to the instability of **164**. One possible mechanism for degradation was expulsion of the aromatic group with loss of sulfur monoxide to afford the anionic intermediate **166**. Attack of oxonium **167** may result in formation of *p*-toluenesulfonate **168**, scheme 79-A. Alternatively, sulfoxide **164** may react through the polarised sulfoxide bond to displace the *p*-toluenesulfonate group and form the 6-membered cyclic intermediate **169**. Attack by the *p*-toluenesulfonate anion would result in released ring strain resulting in the formation of *p*-toluenesulfonate **170**, scheme 79-B. Products **168** and **170** were consistent with the observed ^{1}H NMR spectrum, the peaks corresponding to the *p*-toluenesulfonate group did not shift significantly and a singlet corresponding to 2 protons was observed. Due to the instability of sulfoxide **164** the *p*-tolyl substrate was not investigated further.

Altering the electronics of the aromatic ring was anticipated to increase the stability of the cyclisation precursor and allow sulfinyl oxetanes to be accessed successfully and consistently. Degradation *via* alkylation of the sulfoxide was likely to be inhibited by electron poor substrates so the *p*-chloro aryl substrate was synthesised and the cyclisation investigated as shown in scheme 80.

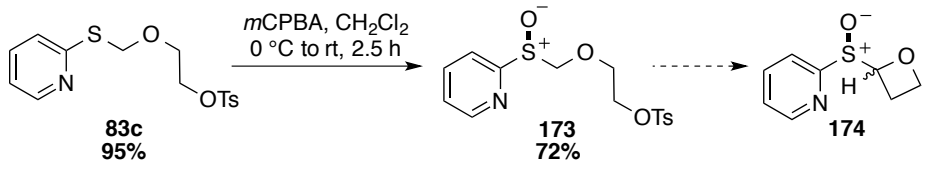


Scheme 80: Synthesis of 2-sulfinyl oxetane **172**. * Yield calculated with respect to 1,3,5-trimethoxybenzene.

Mono-oxidation of *p*-toluenesulfonate **83b** to the corresponding sulfoxide afforded the required oxetane precursor **171** in an excellent yield, scheme 80. As hypothesised the electron poor sulfoxide was more stable than the corresponding *p*-tolyl substrate and could be isolated cleanly, signifying that degradation pathway B (scheme 79) most likely occurred. Although the stability was improved **171** was not stable to storage at rt and required purification by chromatography immediately before cyclisation.

To begin investigations into the intramolecular cyclisation, **171** was treated with 1.2 equivalents of LiHMDS at 0 ºC and stirred for 1 h. Analysis of the crude material by ^{1}H NMR confirmed that the desired 2-sulfinyl oxetane **172** was formed as a mixture of diastereoisomers with a combined yield of 68%, the yield was calculated with respect to 1,3,5-trimethoxybenzene, scheme 80. With this promising result optimisation of the reaction conditions began however sulfoxide **171** was quickly determined to be too unstable to provide a reliable reaction. The cyclisation yields were not consistent or reproducible and ranged from 0 to 80% (22 reactions) due to similar decomposition as observed for the tolyl substrate **164**. These observations prompted investigation into a more electron poor substrate as employing a derivative such as a 2-pyridyl substrate was predicted to improve the stability of the cyclisation precursor further.

p-Toluenesulfonate **83c** was synthesised *via* the synthetic route previously developed (cf. section 2.2.2.). Oxidation of **83c** using 1.1 equiv of *m*CPBA afforded cyclisation precursor **173** in a yield of 72% after purification, scheme 81.

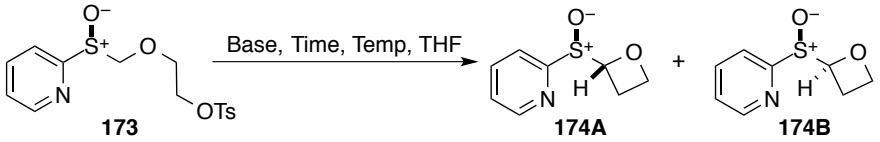


Scheme 81: Synthetic route to form 2-sulfinyl oxetane **174** from **83c**.

The electron-withdrawing 2-pyridyl group improved the stability of the sulfoxide intermediate as hypothesised. No degradation was observed and the compound was successfully stored under argon at –20 ºC for up to 1 year. As **173** was stable the cyclisation to form the corresponding sulfinyl oxetane could be thoroughly investigated.

3.3.3. Optimisation of the Cyclisation to Afford 2-Sulfinyl Oxetanes

Sulfoxide **173** was dissolved in THF and cooled to the required temperature before being treated with a base and stirred for the desired time, scheme 82. Oxetane **174** could be formed successfully as a mixture of diastereoisomers and the two diastereoisomers **A** and **B**, which were arbitrarily assigned, could be separated by chromatography.



Scheme 82: General reaction scheme for the cyclisation to give 2-pyridyl sulfinyl oxetane **174**.

To optimise the reaction, initially a selection of 4 bases was screened. Sulfoxide **173** was treated with 1.5 equiv of the base at 0 ºC and stirred for 90 min before being quenched with sat. aq. NH_4Cl. The results are shown in table 15.

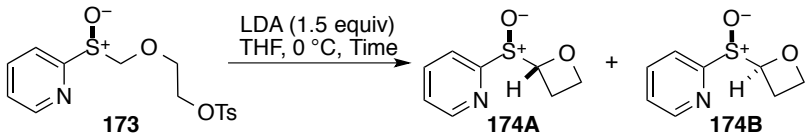
Entry	Base	Equivalents of base	Temp (ºC)	Time (min)	Yield **174A** + **174B** (%)[a]	dr A:B
1	NaH	1.5	0	90	0	-
2	LDA[b]	1.5	0	90	40	1:1
3	LiTMP[b]	1.5	0	90	42	1:1
4	LiHMDS[b]	1.5	0	90	39	3.3:1

Table 15: Optimisation of the base required for intramolecular cyclisation of sulfoxide **173** to oxetane **174**. [a] Yield determined by ^{1}H NMR with respect to 1,3,5-trimethoxybenzene as an internal standard. [b] Base synthesised immediately prior to use.

When NaH was employed no desired oxetane product was observed, instead starting material was recovered in a quantitative yield. Fortunately the amine bases, LDA, LiTMP and LiHMDS successfully deprotonated the sulfoxide which subsequently cyclised to form the desired oxetane, entries 2–4. All three bases gave similar yields and a mixture of oxetane diastereoisomers, LDA and LiTMP gave a 1:1 ratio of diastereoisomers whilst

LiHMDS resulted in a 3.3:1 ratio. A diastereoselective cyclisation may be possible, however this would require further investigation into the conditions, including base, solvent, additives and temperature. LDA was chosen as the base with which to continue optimisation as the oxetane was formed in a good yield with a dr of 1:1. As the diastereoisomers could be separated by chromatography, cyclisation following an enantioselective oxidation could provide both enantiomers of the organometallic reagent by exchange from the two diastereoisomers independently.

The stability of the starting material, intermediates and resulting products was a concern during the cyclisation reaction. A short reaction time was desirable to inhibit any potential degradation so the minimum time required to deprotonate the sulfoxide and for the resulting anion to cyclise was determined. Five parallel reactions were set up, treating **173** with 1.5 equiv of LDA at 0 ºC, and quenched after varying times of 30 min increments in order to monitor the progress of the reaction over time, table 16.

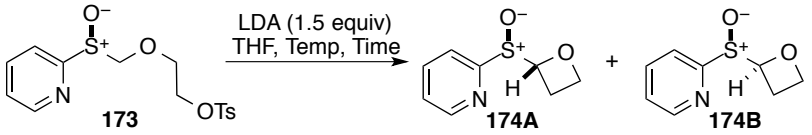


Entry	Base [a]	Equivalents of base	Temp (ºC)	Time (min)	Yield **174A** + **174B** (%)[b]	dr A:B
1	LDA	1.5	0	30	36	1:1
2	LDA	1.5	0	60	40	1:1.1
3	LDA	1.5	0	90	40	1:1
4	LDA	1.5	0	120	31	1:1
5	LDA	1.5	0	180	36	1:1.1

Table 16: Results from varying the time of the cyclisation reaction. [a] Base made immediately prior to use. [b] Yield determined by ^{1}H NMR with respect to 1,3,5-trimethoxybenzene as an internal standard.

The results showed that the highest yield was obtained after 60 min however only a 4% increase was observed when the time was increased from 30 min to 60 min suggesting that the majority of the reaction was complete after 30 min, entries 1 and 2. There was a slight change in yield as the reaction time increased further however this change was not considered significant. The constant yield and dr of the 2-sulfinyl oxetanes suggested that both diastereoisomers were stable under the reaction conditions for up to 3 h. The product was obtained in only a 40% yield and 39% starting material still remained even with the increased reaction time. This indicated that deprotonation or anion cyclisation was

incomplete and that degradation occurred. Reaction temperature was therefore investigated next, table 17.

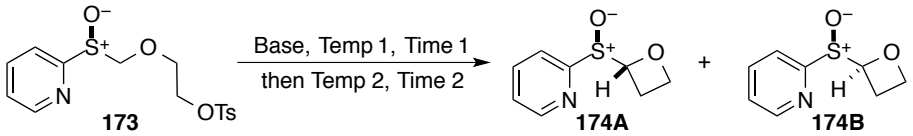


Entry	Base[a]	Equivalents of base	Temp (ºC)	Time (min)	Yield **174A** + **174B** (%)[b]
1	LDA	1.5	–78	120	8
2	LDA	1.5	–40	90	47
3	LDA	1.5	–40	300	35
4	LDA	1.5	–10	90	40

Table 17: Results of varying the temperature of the cyclisation reaction. [a] Base made immediately prior to use. [b] Yield determined by ^{1}H NMR with respect to 1,3,5-trimethoxybenzene as an internal standard.

The reaction temperature was decreased from 0 ºC to –78 ºC to stabilise the metallated intermediate and hinder any possible degradation. Simultaneously a longer reaction time of 2 h was employed to promote cyclisation, which would most likely be inhibited by the colder temperature. Despite these considerations the oxetane was formed in only 8% yield, entry 1. So the reaction was performed at intermediate temperatures of –40 ºC and –10 ºC. When performed at –40 ºC the yield was increased to 47% and the remaining starting material was isolated suggesting that no degradation had occurred, entry 2. As the cyclisation was expected to be slower at –40 ºC than 0 ºC an increased reaction time of 5 h was employed however this did not improve the yield further, entry 3. At –10 ºC a yield of 40% was obtained however only 23% of the starting material was recovered, suggesting that compound degradation had occurred, entry 4.

The reaction temperature must satisfy three requirements; to permit compound deprotonation, to stabilise the resulting anion enough to inhibit degradation, and to promote subsequent cyclisation to afford the 2-sulfinyl oxetane. Given this, performing the reaction at two different temperatures was investigated. A solution of sulfoxide **173** in THF was treated with LDA at temperature 1 and stirred for time 1, after which the reaction was warmed to temperature 2 to encourage cyclisation and stirred for time 2. The results are shown in table 18.



Entry	Base[a]	Equivalents of base	Temp 1 (ºC)	Temp 2 (ºC)	Time 1 (min)	Time 2 (min)	Yield **174A** + **174B** (%)[b]
1	LDA	1.5	–78	0	10	80	61
2	LDA	1.5	–78	0	60	30	63
3	LDA	1.5	–78	–40	60	30	53
4	LDA	1.5	–78	–40	30	60	56
5	LDA	1.5	–78	–20	30	60	67
6	LDA	1.5	–78	–20	20	15	84
7	LDA	1.5	–78	–20	15	15	87
8	**LDA**	**1.5**	**–78**	**–20**	**15**	**20**	**92**

Table 18: Investigation into the optimum reaction temperature. [a] Base made immediately prior to use. [b] Yield determined by ^{1}H NMR with respect to 1,3,5-trimethoxybenzene as an internal standard.

Sulfoxide **173** was deprotonated at –78 ºC for 10 min then warmed to 0 ºC for 80 min, forming oxetane **174A** and **174B** in a combined yield of 61% with no remaining sulfoxide **173** observed, entry 1. Increasing time 1 to 60 min and decreasing time 2 to 30 min in an effort to reduce compound degradation did not improve the yield significantly, entry 2. Temperature 2 was then lowered to –40 ºC to minimise degradation further however this reduction in temperature did not improve the yield despite a longer cyclisation time, entries 3 and 4. The cyclisation, thought to proceed at temperature 2, was hindered at –40 ºC whilst degradation occurred at –10 ºC. Warming the reaction to –20 ºC for 60 min following a 30 min deprotonation time at –78 ºC resulted in an improved yield of 67% and minimal degradation, entry 5. Decreasing the overall reaction time to 35 or 30 min resulted in an increased yield of 84% and 87% respectively, entries 6 and 7. Finally increasing time 2 from 15 min to 20 min resulted in a yield of 92%, entry 8. This result demonstrated the importance of controlling the reaction temperature to balance compound stability with reactivity.

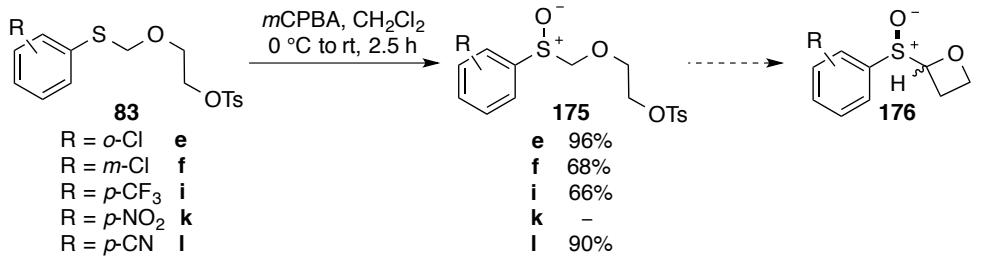
The optimum reaction conditions, entry 8 table 18, gave the desired sulfinyl oxetane in a 92% yield as calculated from the ^{1}H NMR spectrum and an 89% isolated yield. When performed on a larger scale of 2.82 mmol (compared to 0.7 mmol) the isolated yield decreased to 65%. The excess base employed may have caused degradation of the cyclisation precursor resulting in the lower isolated yield. The larger scale reactions are

likely to require fewer equivalents of LDA, due to less adventitious water, but further investigation would be required to confirm this suggestion.

Two purifications were required to separate diastereoisomers **174A** and **174B**. The first purification required an eluent of EtOAc:hexane 4:1 to isolate **174A** from **173** and **174B**, whilst the second column required an eluent of CH_2Cl_2:Et_2O 1:4 to isolate **173** and **174B**. Further optimisation of the reaction to achieve complete conversion would remove the need for two purifications. As mentioned the number of equivalents of base could be investigated, only 1 equiv is required for the deprotonation of **173** so employing fewer then 1.5 equiv may increase the yield when performed on a large scale. Alternatively employing additives such as LiCl or TMEDA which would coordinate to the lithium cation in the metallated intermediate, freeing the anion, may increase the reaction yield. The reaction time could also be explored further with shorter deprotonation times being examined.

3.3.4. Scope of the Cyclisation Affording 2-Sulfinyl Oxetanes

When designing the scope of 2-aryl sulfinyl oxetanes that would be synthesised the electronics of the aromatic group needed to be considered, as earlier investigations concluded that an electron poor aromatic group was required to stabilise the cyclisation precursor. The synthesis of a variety of sulfinyl oxetanes whose aromatic substituents had electron-withdrawing effects, such as an *o*-chloro or *m*-chloro, *p*-trifluoromethyl, *p*-nitro or *p*-nitrile group, was explored. Mono-oxidation of *p*-toluenesulfonates **83e-f**, **83i** and **83k-l** with *m*CPBA cleanly formed the desired sulfoxides **175e-f**, **175i** and **175l**, however **175k** was unstable and could not be isolated, scheme 83. Pleasingly the sulfoxides, **175**, were stable so oxetane formation could be explored.



Scheme 83: Synthesis of a variety of cyclisation precursors **175** required to synthesise 2-sulfinyl oxetanes.

Sulfoxide **175l** was exposed to the optimised cyclisation conditions with LDA and oxetane **176l** was isolated in a yield of 57% following purification, figure 32. The remaining 43% could not be accounted for which suggested that the material had degraded. So substrates **175e**, **175f** and **175i** were cyclised using the conditions developed with LiHMDS (to synthesise 2-sulfonyl oxetanes) as the weaker base was anticipated to be sufficient for deprotonation and reduce the amount of degradation. Sulfinyl oxetanes **176e**, **176f**, **176i** were successfully isolated in yields of 13–82%, figure 32.

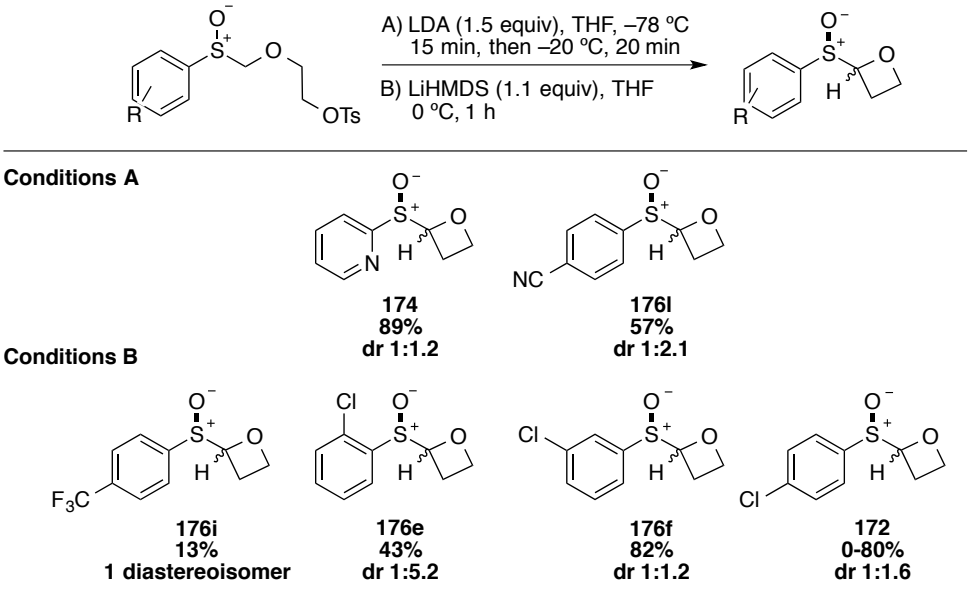


Figure 32: Scope of 2-sulfinyl oxetanes synthesised.

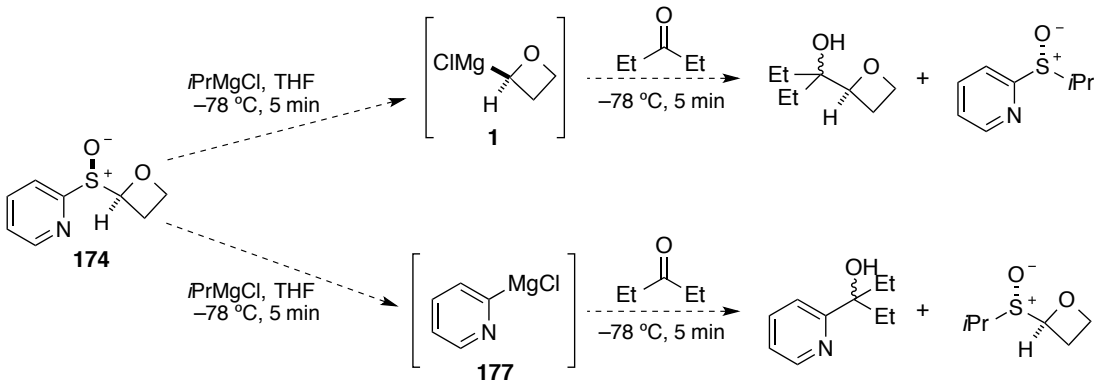
The aromatic substituents were required to be electron-withdrawing during the synthesis limiting the substrate scope, however satisfyingly *para*, *meta* and *ortho* substituents were tolerated in the cyclisation reaction. Both diastereoisomers of **176i** were observed in the ^{1}H NMR spectrum of the crude material however only one diastereoisomer was isolated, implying that degradation occurred during purification. A major diastereoisomer was isolated for substrate **176e**. The cyclisation to form one diastereoisomer may have been promoted over the other diastereoisomer, alternatively one diastereoisomer may have degraded preferentially.

Having synthesised a variety of 2-sulfinyl oxetanes the derivatisation of the oxetane motif *via* sulfoxide-magnesium exchange to afford an oxetanyl organometallic reagent was explored.

3.4. Towards the Functionalisation of 2-Sulfinyl Oxetanes via Sulfoxide-Magnesium Exchange

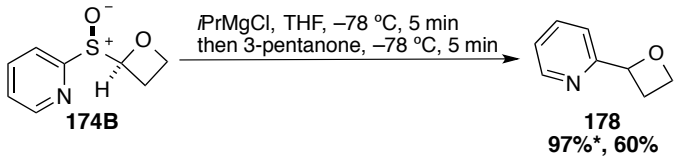
3.4.1. Investigation into the Sulfoxide-Magnesium Exchange

The sulfoxide-magnesium exchange was initially examined with sulfinyl oxetane **174**. When a sulfoxide is treated with an organomagnesium reagent the most electron poor ligand is expelled from the resulting sulfurane to afford the most stable organomagnesium compound.[165,193] Given this, there were two possible outcomes from the reaction with sulfinyl oxetane **174**. The desired oxetanyl magnesium species **1** would be produced if the oxetane was the most electron poor ligand, alternatively magnesium reagent **177** would be produced if the 2-pyridyl ring was more electron poor. This would result in an alcohol and new sulfinyl oxetane species following a quench with 3-pentanone, scheme 84.



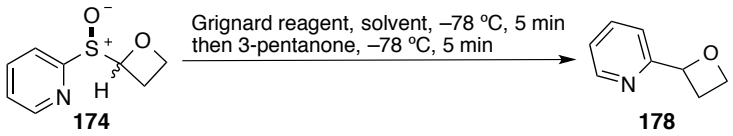
Scheme 84: Two possible outcomes of the sulfinyl-magnesium exchange of 2-(oxetan-2-ylsulfinyl)pyridine.

Sulfoxide-magnesium exchange was investigated on diastereomerically pure 2-sulfinyl oxetanes. 2-Pyridyl sulfoxide **174B** was treated with 2 equiv of *i*PrMgCl at –78 ºC for 5 min then 3-pentanone was added and the reaction stirred for a further 5 min. Interestingly none of the expected products were observed, instead the product was characterised as 2-(oxetan-2-yl)pyridine **178**, scheme 85. This product, resulting from the coupling of the oxetane moiety with the 2-pyridyl ligand, was the only product present in the crude reaction mixture and was isolated in a 60% yield.



Scheme 85: Results of the initial investigation into the sulfoxide-metal exchange on sulfinyl oxetane **174B**. * Yield determined by ^{1}H NMR with respect to 1,3,5-trimethoxybenzene as an internal standard.

Despite this interesting result the formation of **178** indicated that the desired oxetanyl metal species had not been produced or reacted with the electrophile. Therefore the reaction conditions were varied to probe the sulfoxide-magnesium exchange with **174** and to investigate whether the desired oxetanyl species could be formed. The results are shown in table 19.



Entry	Diastereoisomer of **174**	Solvent	Grignard reagent	Yield **178** (%)[a]
1	A	Et_2O	*i*PrMgCl	60
2	A	Toluene	*i*PrMgCl	51
3	A	Hexane	*i*PrMgCl	0
4	A	THF	*i*PrMgCl	60
5	B	THF	*i*PrMgCl	89
6	A	THF	*i*PrMgCl·LiCl	95
7	B	THF	*i*PrMgCl·LiCl	91

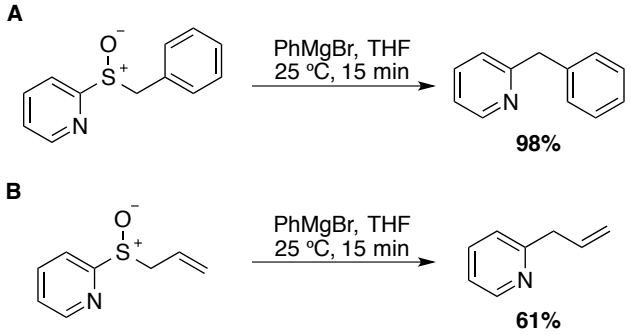
Table 19: Investigation into the effect of solvent and Grignard reagent on the desired sulfoxide exchange reaction. [a] Yield determined by ^{1}H NMR with respect to 1,3,5-trimethoxybenzene as an internal standard. Configuration of diastereoisomer A and B was undetermined.

The effect of different solvents on the outcome of the exchange reaction was investigated. When performed in diethyl ether or toluene (oxetan-2-yl)pyridine **178** was the only product formed but in a slightly lower yield than when THF was employed, entries 1, 2 and 4. No reaction was observed when performed in hexane, this was due to **174** being insoluble in hexane at –78 ºC, entry 3. Diastereoisomer **B** was then employed in the reaction to explore whether a different outcome was observed. Both diastereoisomers resulted in the formation of **178** only, however an increase in yield was observed when employing diastereoisomer **B**, entries 4 and 5. Knochel reported that a Grignard reagent was more reactive when complexed to lithium chloride so the turbo Grignard reagent

*i*PrMgCl·LiCl was employed in the sulfoxide-magnesium exchange reaction with **174A** and **174B**.[194] Both reactions resulted in increased yields of **178** and no ligand exchange products were observed, entries 6 and 7. The observation that ligand coupling consistently occurred as opposed to ligand exchange when 2-(oxetan-2-yl)pyridine **174** was treated with *i*PrMgCl prompted further investigation into the precedent for this transformation.

3.4.1.1. Mechanistic Discussion of the Ligand Coupling Reaction

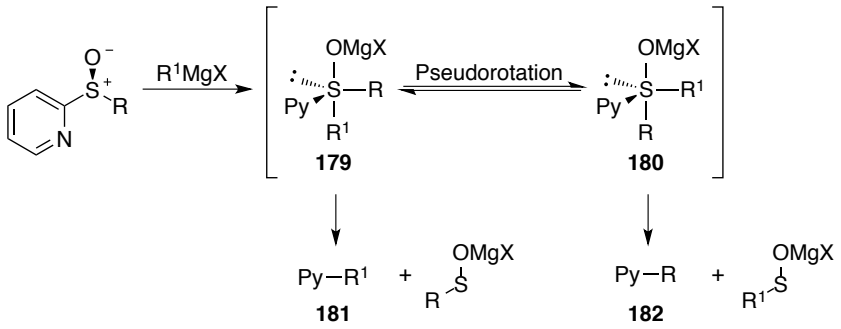
Ligand coupling following attack of a sulfoxide with a Grignard reagent was reported in 1984 by Oae who observed the formation of 2-benzylpyridine in a 98% yield when benzyl 2-pyridyl sulfoxide was treated with PhMgBr, scheme 86-A.[195] Similarly when vinyl 2-pyridyl sulfoxide was treated with PhMgBr the coupled product was isolated, scheme 86-B.[195]



Scheme 86: Examples of ligand coupling reactions when sulfoxides were treated with PhMgBr.[195]

The general consensus in the literature is that when a sulfoxide substrate is treated with a Grignard reagent a tetrasubstituted sulfurane is formed. This unstable species can undergo different pathways, which may occur independently or concurrently, to result in a more stable species with the preferred normal valence shell. The major pathways include ligand exchange (cf. section 3.1.1.), topological transformations and ligand coupling.[166] In general, sulfoxide substrates that were prone to ligand coupling when treated with a Grignard reagent had a 2-pyridyl, quinolinyl, arylsulfonyl or naphthyl substituent, whilst the Grignard reagents used were aryl, benzyl, vinyl, allyl or alkyl.[195,196,193,166] The electron-withdrawing substituents of the sulfoxide were possibly required to stabilise the resulting sulfurane, therefore allowing ligand coupling to proceed or discouraging ligand

exchange. The reported reaction mechanism for ligand coupling when a 2-pyridyl sulfoxide was treated with an organomagnesium reagent is shown in scheme 87.



Scheme 87: Ligand coupling mechanism when a heteroaryl sulfoxide is treated with a Grignard reagent.[193]

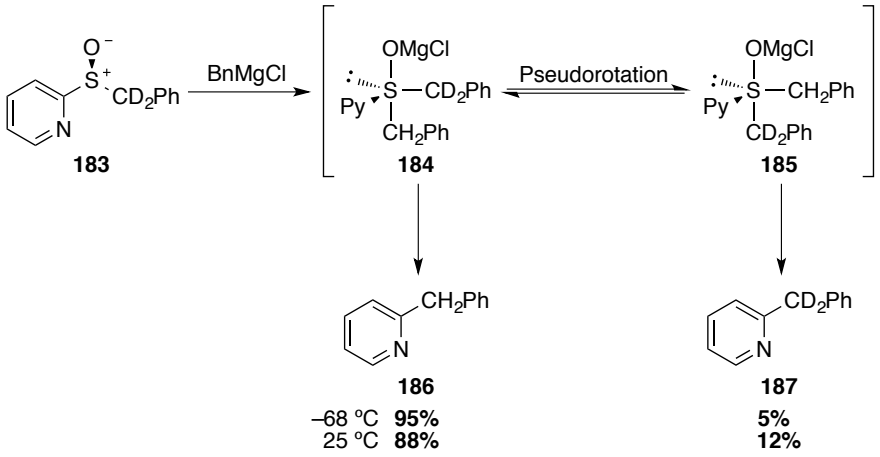
Initial nucleophilic attack of the Grignard reagent on the sulfoxide affords pentacoordinated sulfurane **179** with the nucleophile in an axial position. Ligand coupling can occur if there is a cohesive interaction between two ligands, for example from orbital overlap of an axial and an equatorial ligand, resulting in coupled product **181**. Alternatively **179** can undergo pseudorotation resulting in sulfurane **180** with the R group in the axial position. This ligand may then interact with the equatorial pyridyl ligand affording pyridine **182**.[193] Ligand coupling is an intramolecular, concerted process so when chiral ligands are employed the configuration of both ligands should be retained.[195]

Due to the competing ligand exchange and ligand coupling pathways the reaction outcome is affected by the ability of the ligands to undergo ligand coupling and the rate of pseudorotation. If the ligands on the initial sulfurane, resulting from attack of the Grignard reagent, do not interact sufficiently to allow them to couple then ligand exchange may occur. In addition, if ligand coupling is slower than ligand exchange then the exchange product may be observed. Alternatively the sulfurane may undergo pseudorotation and the resulting axial and equatorial ligands may couple or ligand exchange may proceed. Consequently the rate of pseudorotation and the rate of ligand exchange or ligand coupling affect the reaction outcome.

The rate of pseudorotation is dependent on the apicophilicity of the substituents, that is the tendency of the ligand to occupy an axial position on the trigonal bipyramidal intermediate, which is determined mainly by the electronegativity and electronics of the

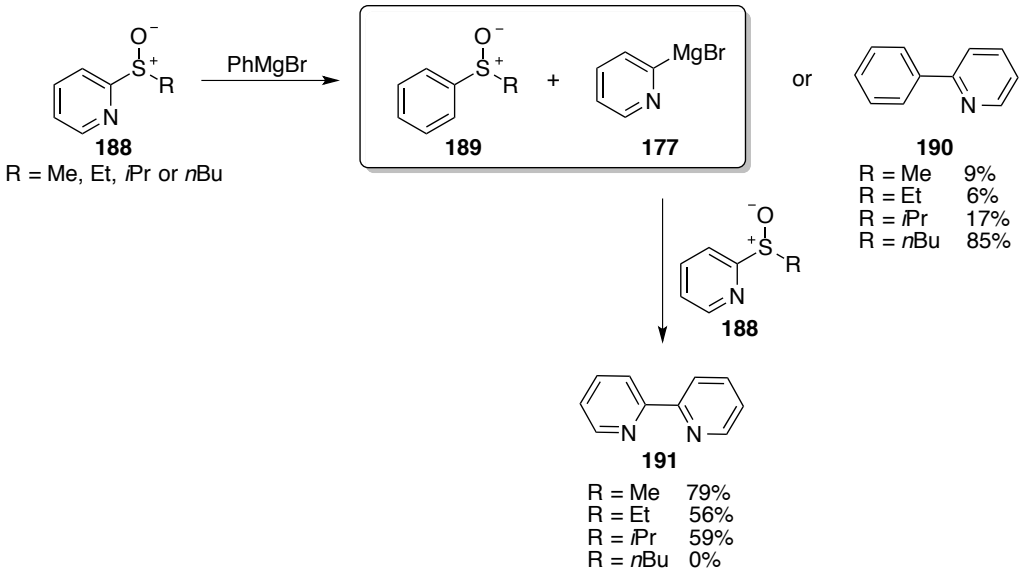
ligand.[197] Oae documented that the axial bonds within the sulfurane species are longer than the equatorial bonds and preferentially accommodate the more electronegative ligands whilst the equatorial positions hold the aromatic and electron-donating ligands.[193,167] However, the 2-pyridyl ligand will always remain in an equatorial position possibly due to a chelation effect with magnesium.[166] When the attacking Grignard possesses the most electronegative group, ligand coupling or exchange proceeds. Whereas if the attacking nucleophile is not the most electronegative ligand pseudorotation may occur followed by ligand coupling or exchange.[166,197]

The rate of pseudorotation is increased as the temperature of the reaction is increased. This was demonstrated by the reaction of benzyl-d_2 2-pyridylsulfoxide **183** with unlabelled BnMgCl. At –68 ºC the coupled product was predominately unlabelled **186** suggesting that the rate of pseudorotation of sulfurane **184** to **185** was slower than that of ligand coupling. When the reaction temperature was raised to 25 ºC the ratio of **186** to **187** decreased, suggesting that the rate of pseudorotation increased, scheme 88.[197]



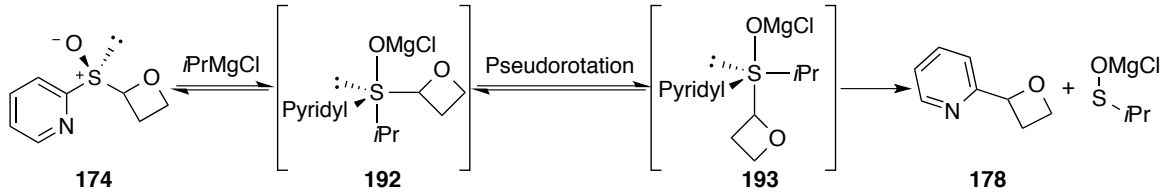
Scheme 88: Example of the effect of temperature on the rate of pseudorotation.[197]

Interestingly a competition between ligand coupling and ligand exchange is observed and consecutive ligand exchange then coupling can occur.[193] Alkyl 2-pyridyl sulfoxides **188** were treated with PhMgBr and ligand exchange to form Grignard reagent **177** competed with ligand coupling to form phenyl pyridyl **190**. Attack of sulfoxide **188** with the new organometallic species resulted in ligand coupling to afford bipyridyl **191**, scheme 89. The ratio of products **190** to **191** varied as ligand R became more sterically hindered. Oae used this methodology to synthesise 6-6'-substituted 2,2'-bipyridyls.[193]



Scheme 89: An example of consecutive ligand exchange then ligand coupling.[193]

For the reaction of 2-pyridyl sulfinyl oxetane with *i*PrMgCl, pyridyl oxetane **178** would have resulted from a ligand coupling mechanism presumably involving pseudorotation of the sulfurane, scheme 90. This would involve initial attack of *i*PrMgCl on sulfinyl oxetane **174** to form sulfurane **192**. Pseudorotation, promoted by the apicophilicity of the electron-withdrawing oxetane ligand, would proceed faster than ligand exchange or ligand coupling between the pyridyl and *i*Pr ligands resulting in sulfurane **193**. Subsequent ligand coupling between the oxetane and pyridyl ligands was observed to be resulting in the formation of 2-(oxetan-2-yl)pyridine **178**, scheme 90.



Scheme 90: Proposed mechanism for the formation of 2-(oxetan-2-yl)pyridine.

Altering the reaction conditions would be unlikely to affect the reaction pathway when 2-pyridyl sulfinyl oxetane **174** was treated with a Grignard reagent. If the rate of pseudorotation could be reduced, potentially by decreasing the reaction temperature, the observed ligand coupling may be inhibited and ligand exchange may be observed. As the reaction was already performed at –78 ºC the sulfoxide-metal exchange was investigated using alternative 2-sulfinyl oxetanes instead.

3.4.2. Investigation into Sulfoxide-Magnesium Exchange with Alternative Sulfinyl Oxetane Substrates

Any cohesive interaction between ligands leading to ligand coupling was postulated to decrease if the 2-pyridyl ligand on **174** was changed for an alternative, non-heteroaromatic ring. The sulfoxide-magnesium exchange was therefore investigated on 2-sulfinyl oxetanes **176e-f**, **176i** and **176l**, figure 33.

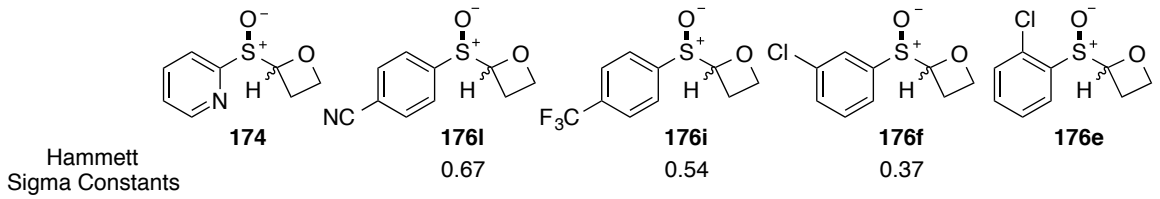
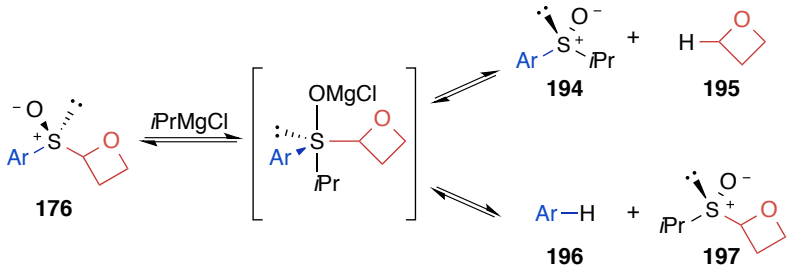


Figure 33: Scope of 2-sulfinyl oxetanes with which the sulfoxide-magnesium exchange was investigated.

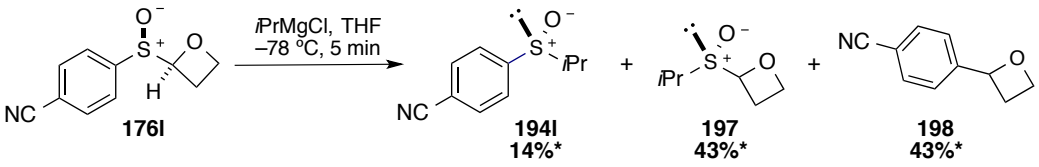
The electronics of the sulfoxide substituents were considered as this would affect the product formed following ligand exchange. The electronics of the aromatic group were altered by changing the substituents on the ring and as such the Hammett sigma constants were used to quantify the overall electronic effects of the aromatic group, figure 33.[198] An appropriate Hammett sigma constant for the 2-pyridyl ring could not be determined however **174** was thought to be the most electron poor substrate. Similarly a Hammett sigma constant for an *ortho* substituent on the phenyl ring could not be used to determine the electronic effects of the *ortho* substitutent relative to a proton due to possible steric effects as well.

The two possible pathways for sulfoxide-magnesium exchange are shown in scheme 91. For ease of analysis the organometallic species produced was quenched with sat. aq. NH_4Cl. The resulting oxetane **195** or aromatic **196** would be lost during work-up, leaving the sulfoxide products **194** or **197** which were analysed to determine the reaction outcome.



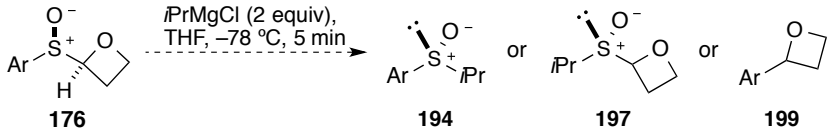
Scheme 91: Two possible outcomes of the reaction of 2-aryl sulfinyl oxetanes with *i*PrMgCl.

To speed up analysis the product conversion observed in the ^{1}H NMR spectrum of the crude reaction material was used to determine which reaction pathway had occurred. The conversion was determined by comparing the product peak integral to that of the combined products and starting material. Diastereomerically pure sulfinyl oxetane **176l** was cooled to –78 ºC, treated with *i*PrMgCl and stirred for 5 min. Both aryl sulfoxide **194l** and alkyl sulfoxide **197** were observed, resulting from ligand exchange, and oxetane **198** was formed which resulted from a ligand coupling mechanism, scheme 92.



Scheme 92: Reaction of 4-(oxetane-2-sulfinyl)benzonitrile **176l** with *i*PrMgCl. * Conversion values.

A 43% conversion of **198** suggested that ligand coupling was a major reaction pathway. Alkyl sulfoxide **197** was also formed with a 43% conversion demonstrating that ligand exchange of the aryl substituent occurred at a similar rate to pseudorotation which was required to form **198**. The presence of both sulfoxides **194l** and **197** indicated that a mixture of aryl organometallic and oxetanyl organometallic intermediates were produced, unfortunately oxetanyl Grignard formation was the minor reaction pathway. To promote the desired reaction employing the 2-sulfinyl oxetanes with less electron poor aromatic groups was investigated. The results are summarised in table 20.



176 194 197 199

Entry	$\sigma_{p/m}$	Ar		Exchange Conversion (Isolated yields %)		
				194	**197**	**199**
1	–	2-pyridyl	**174**			100 (91)
2	0.67	4-CN(C_6H_4)	**176l**	14	43	43
3	0.54	4-CF_3(C_6H_4)	**176i**	38	62	
4	0.37	3-Cl(C_6H_4)	**176f**		100 (86)	
5	–	2-Cl(C_6H_4)	**176e**		100	

Table 20: Results from the sulfoxide-magnesium exchange reaction with a variety of 2-sulfinyl oxetanes.

Entries 1 and 2 have been discussed previously. Changing from an aromatic substrate with a *p*-nitrile group to a *p*-trifluoromethyl substituent was anticipated to increase the amount of aryl *iso*-propyl sulfoxide **194** formed. This increase was observed and no **199** was produced, however alkyl sulfoxide **197** was still formed as the major product with a 62% conversion, entry 3. Employing *m*-chloro and *o*-chloro substituted aryl sulfinyl oxetanes **176f** and **176e** was expected to promote oxetanyl Grignard formation and therefore **194** formation further, however alkyl sulfoxide **197** was the only product observed and was isolated in an 86% yield, entries 4 and 5. This was a surprising result which may reflect a coordination to the chloride lone pairs in the *ortho*-substituted example stabilising the organometallic. Investigating aromatic substrates that were more electron rich was not synthetically possible. As discussed previously the cyclisation precursors to 4-Cl-Ph sulfonyl oxetane **172** (σ_p = 0.22) and 4-tolyl sulfonyl oxetane **165** (σ_p = –0.17) were unstable and so the oxetanes could not be synthesised.

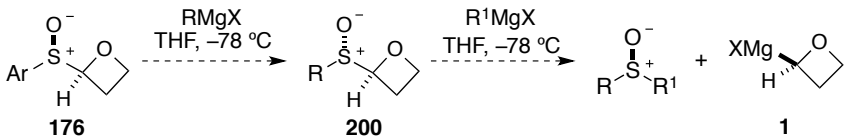
Instead of altering the electronics of the 2-aryl sulfinyl oxetanes the Grignard reagent was varied and the reaction outcome determined. When oxetane **176f** was treated with *i*PrMgCl·LiCl or EtMgCl alkyl sulfoxides analogous to **197** were the only products observed and employing *t*BuMgCl resulted in no reaction, potentially due to the bulky *t*Bu ligand. Finally oxetane **176f** was treated with two equivalents of *n*BuLi at –78 ºC to examine the sulfoxide-lithium exchange, but again the alkyl sulfoxide was the only product observed. These results concluded that the oxetanyl organometallic could not currently be accessed *via* sulfoxide-magnesium exchange of 2-aryl sulfinyl oxetanes with alkyl Grignard reagents.

In the future synthesising 2-sulfinyl oxetanes containing an aromatic group with a Hammett sigma constant between 0.37 and 0.22 would be desirable. If the cyclisation precursors required during the synthesis were stable and the sulfinyl oxetanes isolated, then the reaction with a Grignard reagent would be expected to form the oxetanyl organometallic. Alternatively the investigation of more electron poor substrates in the sulfoxide-magnesium exchange reaction which are not expected to result in ligand coupling, for example the reaction of 4-(oxetane-2-sulfinyl)pyridine or 3-(oxetane-2-sulfinyl)pyridine, would be interesting to confirm the current mechanistic understanding.[166] In addition, examining alternative *ortho*-substituted aromatic substrates may help determine why only sulfoxide **197** was observed when employing *ortho*-chloro substrate **176e**.

3.4.3. Alternative Strategies to Generate the Oxetanyl Organometallic via Sulfoxide-Magnesium Exchange

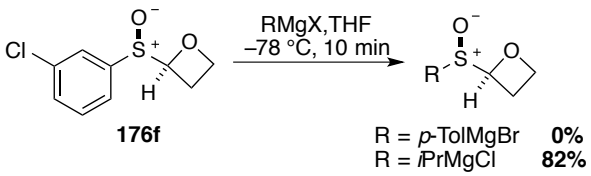
At this stage, the desired oxetanyl organometallic species was not formed efficiently *via* sulfoxide-magnesium exchange of the current 2-sulfinyl oxetanes and more electron rich substrates could not be synthesised due to the instability of the cyclisation precursors. To circumvent this problem two possible strategies were considered; 1) the electronics of the substrate could be altered after oxetane formation and 2) the oxetane could be synthesised without isolating the unstable cyclisation precursor. Both methods are discussed below.

Consecutive sulfoxide-magnesium exchange reactions could be utilised to alter the electronics of the 2-aryl sulfinyl oxetane substrates after oxetane formation. The first exchange would result in a new sulfinyl oxetane with a more electron rich R group, the resulting substrate **200** may then be used to generate the desired oxetanyl metal species **1** *via* a second sulfoxide-magnesium exchange reaction, scheme 93.



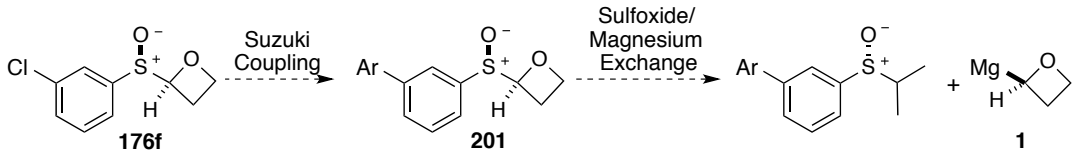
Scheme 93: Alterative route to form oxetanyl Grignard **1** by sequential sulfoxide/Mg exchange reactions.

2-(3-Chlorobenzenesulfinyl)oxetane **176f** was treated with *p*-tolMgBr then stirred at –78 ºC for 10 min. No reaction was observed and the starting material was recovered in a quantitative yield. To determine the reliability of this result oxetane **176f** was treated with *i*PrMgCl and as expected the desired alkyl sulfinyl oxetane was formed cleanly in an 82% yield, confirming the unsuccessful result with *p*-tolMgBr, scheme 94. An alternative approach employing cross-coupling methodology was therefore investigated.



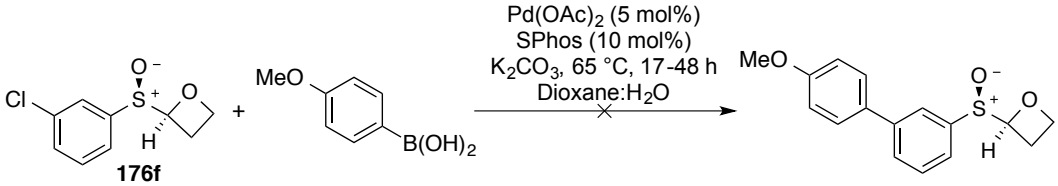
Scheme 94: Initial investigation into consecutive sulfoxide-magnesium exchange reactions.

If 2-sulfinyl oxetane **176f** was coupled with an electron rich aryl boronic acid using palladium catalysis a more electron rich biaryl sulfinyl oxetane **201** could potentially be synthesised. This novel derivative could then be treated with *i*PrMgCl to form the desired oxetanyl organometallic species *via* a sulfoxide-magnesium exchange, scheme 95.



Scheme 95: Proposed route to form **1** by altering the electronics of the 2-aryl sulfinyl oxetane.

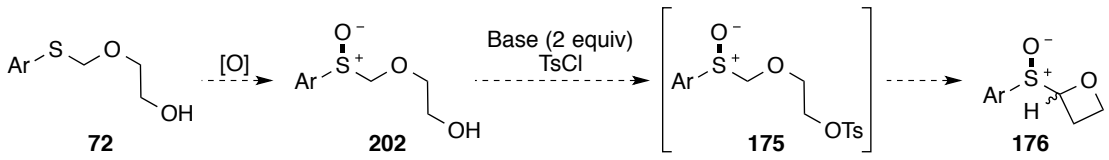
The Suzuki cross-coupling of 2-aryl sulfinyl oxetane **176f** with *p*-methoxyphenyl-boronic acid was performed in the presence of $Pd(OAc)_2$, SPhos and K_2CO_3 at 65 ºC for 17 h, scheme 96.[138]



Scheme 96: Suzuki cross-coupling of oxetane **176f** with *p*-methoxyphenyl-boronic acid.

The Suzuki cross-coupling reaction resulted in no product formation. Increasing the reaction time to 48 h resulted in possible product formation, observed during ^{1}H NMR analysis of the crude reaction material, however the product could not be isolated as degradation occurred during purification. The degradation was possibly due to the acidic nature of the silica gel so in the future alternative stationary phases for purification should be investigated.[126] The cross-coupling of *ortho* or *para* substituted aromatic substrates may afford more stable products if required.

Alternatively, performing the cyclisation without isolating the potentially unstable cyclisation precursor may provide a route to access electron rich 2-aryl sulfinyl oxetanes. Sulfide **72** could be oxidised to sulfoxide **202**, which was anticipated to be more stable than **175** due to the absence of the *p*-toluenesulfonate leaving group however this would need to be investigated. If stable, treatment of **202** with TsCl in the presence of 2 equivalents of base may result in oxetane formation. The first equivalent of base could deprotonate the alcohol and reaction with *p*-toluenesulfonyl chloride may occur, then the second equivalent of base may deprotonate **175** *in situ* and the resulting anion may cyclise to afford oxetane **176**, scheme 97.

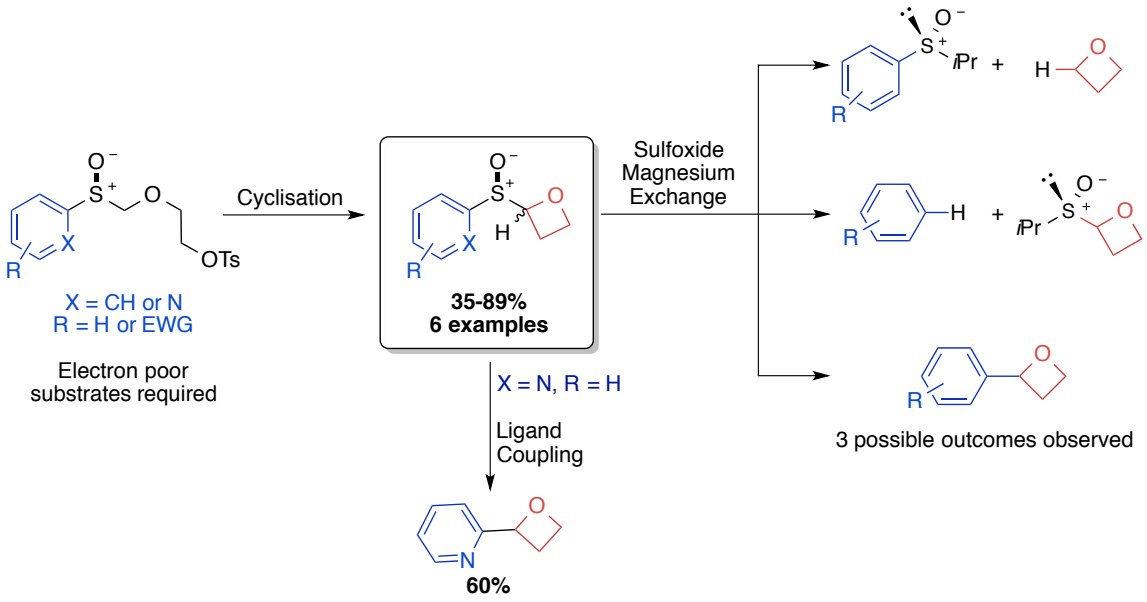


Scheme 97: Proposed route to access sulfinyl oxetanes without isolating the cyclisation precursor.

3.5. Summary of the Investigations into the Synthesis and Reactivity of 2-Sulfinyl Oxetanes

2-Aryl sulfinyl oxetanes were prepared as potentially interesting fragments and reactive motifs. The novel sulfinyl oxetanes were synthesised using a similar synthetic strategy involving an intramolecular C–C bond forming cyclisation to that developed to afford 2-sulfonyl oxetanes. The cyclisation precursor was shown to be unstable for electron rich substrates and therefore electron poor aromatic groups were required. This limited the substrate scope however 6 novel sulfinyl oxetanes were obtained.

The sulfoxide-magnesium exchange was then investigated as a method to access an oxetanyl organometallic reagent and potentially derivatise the motif. When employing oxetane **174** only 2-(oxetan-2-yl)pyridine **178** was obtained which was proposed to result from a ligand coupling mechanism. Investigation of the sulfoxide-magnesium exchange on alternative sulfinyl oxetane derivatives gave a variety of products arising from three different reaction pathways, scheme 98. Currently the oxetanyl metal species cannot be produced as the major product. Electron rich aromatic substrates may promote oxetanyl Grignard formation but the required sulfinyl oxetanes cannot be synthesised due to instability of the cyclisation precursors. To confirm the current conclusions and probe the stability of the cyclisation precursor and sulfoxide-magnesium exchange further, a wider diverse range of substrates should be examined.



Scheme 98: Summary of the synthesis and functionalisation of 2-sulfinyl oxetanes.

Alternative strategies to access electron rich 2-aryl sulfinyl oxetanes with the potential to promote oxetanyl Grignard formation were explored. Altering the electronics of the aromatic group of the sulfinyl oxetanes after cyclisation was not promising. Treating oxetane **176f** with *p*-tolMgBr resulted in no reaction and the biaryl sulfinyl oxetane, potentially formed after Suzuki cross-coupling of substrate **176f** with *p*-methoxyphenyl-boronic acid, was unstable. In the future the cross-coupling of *ortho*- and *para*-substituted aryl sulfinyl oxetanes should be investigated as these substrates may improve the product stability. In addition synthesising sulfinyl oxetanes without isolating the cyclisation precursor may be beneficial.

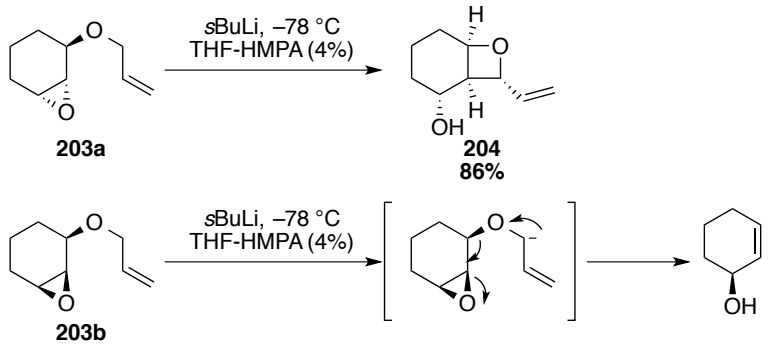
4. Alternative Strategies to Access Functionalised Oxetane Motifs

4.1. Towards the Synthesis of More Highly Substituted Oxetanes

To date work has focused on 2-substituted oxetanes. More highly substituted derivatives could be useful to functionalise the motif in additional directions and access new areas of chemical space, as well as provide additional ways to grow a fragment hit. As such the synthesis of 2,3-disubstituted sulfonyl oxetanes was probed, employing an intramolecular cyclisation/epoxide ring opening.

4.1.1. Intramolecular Epoxide Ring Opening to Afford Substituted Oxetanes

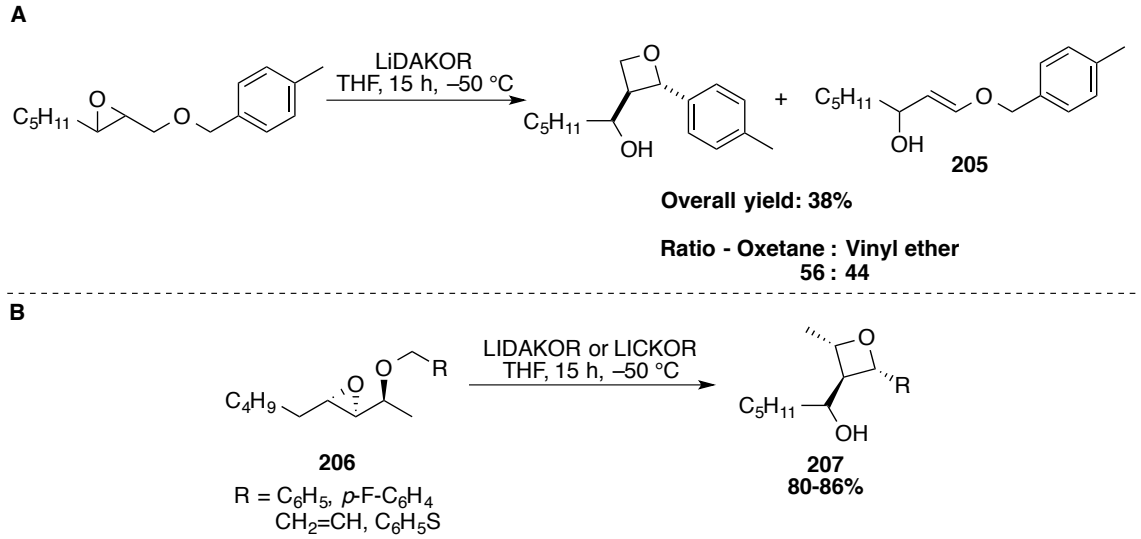
In 1976 Clark Still disclosed the formation of the 4-membered oxetane ring *via* an intramolecular cyclisation resulting in epoxide ring opening.[199] Trans epoxy allylic ether **203a** was treated with *s*BuLi in THF-HMPA to regio- and stereoselectively form vinyl oxetane **204** in a yield of 86%, scheme 99. The trans isomer of **203** was required for the intramolecular epoxide ring opening to proceed as when cis epoxy allylic ether **203b** was treated with *s*BuLi 2-cyclohexenol was formed. This product was presumed to arise from an elimination mechanism shown in scheme 99.[199]



Scheme 99: Synthesis of vinyl oxetane **204** *via* an intramolecular epoxide ring opening.[199]

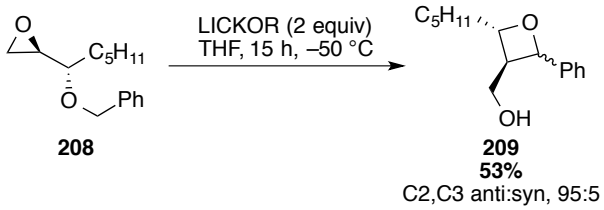
Formation of the more strained 4-membered ring over the isomeric 5- or 6-membered rings was favoured due to the least strain necessary in the transition state to obtain the required alignment of the carbanionic centre and the epoxide carbon-oxygen bond.[199] Bird reported a similar observation when treating allyl glycidyl ethers with *s*BuLi in THF-HMPA at –78 ºC, the oxetane or oxepane products were favoured over the isomeric tetrahydrofuran.[200]

In 1996 Mordini developed a synthesis of 2,3-disubstituted oxetanes from the corresponding chain epoxy ethers, however the oxetane products were obtained in low yields due to a competing elimination reaction to form regioisomeric vinyl ethers **205**, scheme 99-A.[201] This pathway was particularly prominent when electron rich aromatic groups were employed. To prevent the competing reaction Mordini employed α-substituted epoxy ethers **206** which prohibited the elimination, resulting in trisubstituted oxetanes as the sole product, scheme 99-B.[202] Oxetane **207** was formed with complete stereocontrol conferred from the chiral epoxy ether and configuration of the C2 and C3 positions was usually anti due to steric interactions present in the transition state.



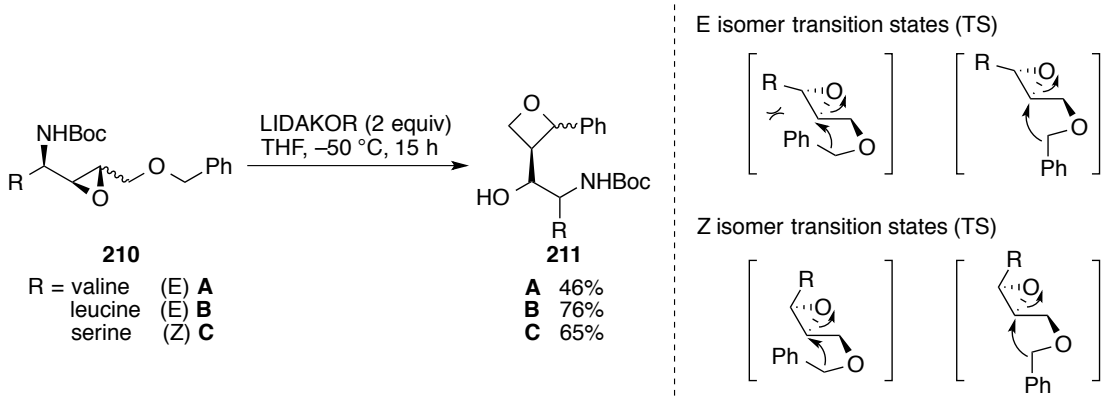
Scheme 100: Synthesis of di- and trisubstituted oxetanes in a stereocontrolled manner.[201,202]

This intramolecular cyclisation was further developed by Mordini to allow the synthesis of chiral trisubstituted oxetanes with an hydroxymethyl substituent. Terminal epoxy α-substituted ether **208** was treated with LiCKOR at –50 ºC for 15 h to afford trisubstituted oxetane **209**.[203] Similarly the relative configuration of the alkyl and hydroxymethyl substituents was anti due to the stereochemistry of the chiral starting material being transferred, and an anti configuration between the C2 and C3 positions was present in the major isomer. A ratio of 95:5 anti:syn isomers was obtained, scheme 101.



Scheme 101: Synthesis of trisubstituted oxetanes from the ring opening of terminal epoxy ether.[203]

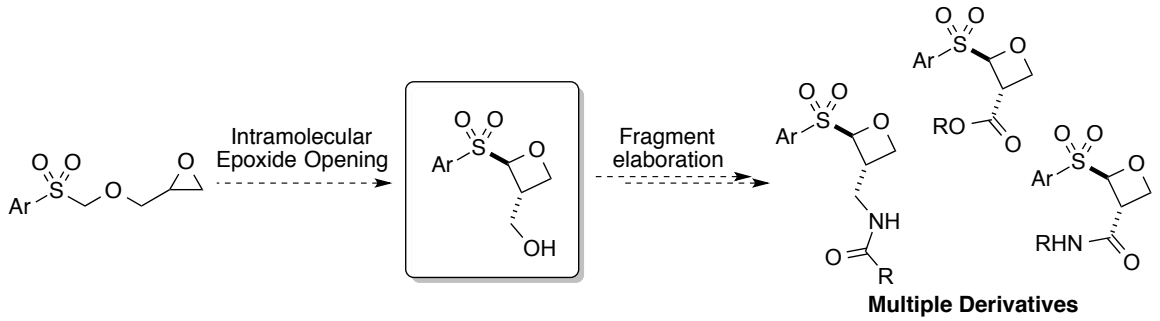
Having developed a stereoselective synthesis to chiral di- and trisubstituted oxetanes with an hydroxymethyl group Mordini successfully prepared amino alcohol substituted oxetanes **211** through ring opening of the corresponding epoxy ethers.[204] The E isomers **210A** and **210B** resulted in the anti configuration of **211** however the Z isomer resulted in a mixture of the syn and anti configuration due to reduced steric repulsion between the R and Ph groups in the cyclisation transition state, scheme 102.



Scheme 102: Synthesis of amino alcohol substituted oxetanes **211** and the proposed TS of the 2 isomers.[204]

4.1.2. Proposed Synthesis of 2,3-Disubstituted Sulfonyl Oxetanes

The synthesis of highly substituted oxetane derivatives would be investigated initially employing an intramolecular epoxide opening strategy, resulting in incorporation of an hydroxymethyl substituent. The additional substituents would allow increased chemical space to be accessed and further ways in which to functionalise the sulfonyl oxetane fragment hits, scheme 103.

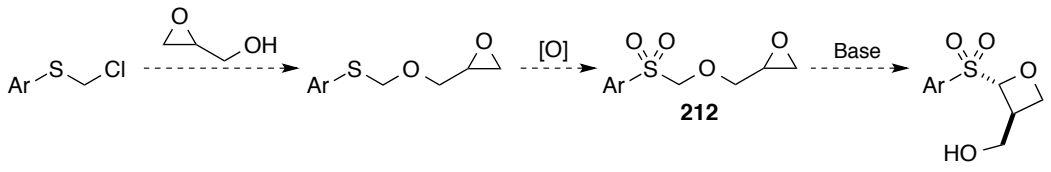


Scheme 103: Proposed route to afford a variety of novel 2,3-disubstituted sulfonyl oxetanes.

The 4-membered oxetane was anticipated to form over the less strained 5-membered cyclic ether due to observations by Clark Still and Bird.[199,200] The cyclisation was predicted to proceed with high diastereoselectivity, resulting in the formation of the anti configuration of the disubstituted oxetane.[202,203] If chiral epoxides were employed enantioenriched sulfonyl oxetanes could be accessed if the reaction proceeded exclusively with inversion.

4.1.3. Towards the Synthesis of 2,3-Disubstituted Sulfonyl Oxetanes

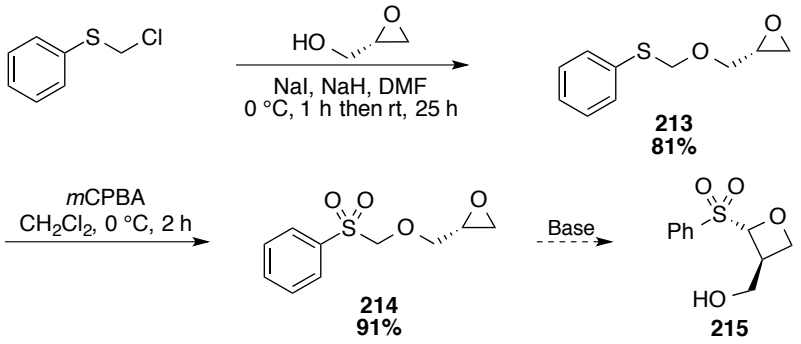
The proposed synthetic route is shown in scheme 104. Similar to the route developed for the synthesis of 2-sulfonyl oxetanes (see chapter 2) aryl chloromethyl sulfides would be employed as accessible starting materials. Alkylation of glycidol followed by oxidation of the sulfide to the corresponding sulfone would afford the required cyclisation precursor **212**. Treatment of **212** with a base was predicted to form the anion alpha to the sulfone moiety. Cyclisation of the anionic intermediate resulting in epoxide opening at the more substituted position would afford the desired 2,3-disubstituted oxetane.



Scheme 104: Proposed synthetic route to 2,3-disubstituted oxetanes.

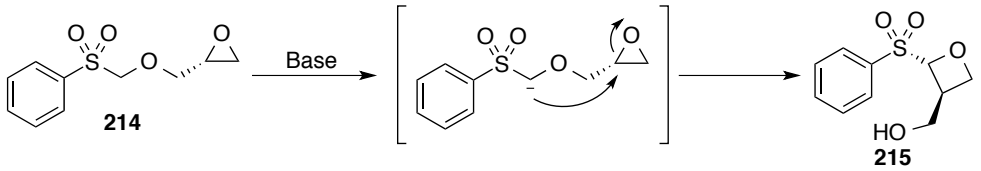
Chloromethyl phenyl sulfide was treated with NaI, NaH and 3 equivalents of (*S*)-(−)-glycidol in DMF at 0 ºC then warmed to rt for 25 h to afford epoxide **213** with an isolated yield of 81%, scheme 105. In an effort to develop more desirable conditions

appropriate for larger scale synthesis, the reaction was performed with glycidol as the limiting reagent however a lower yield of 57% was obtained after 17 h. Increasing the reaction time to 68 h did not improve the yield. Further investigation into more desirable conditions would be required if this route successfully formed the desired 2,3-disubstituted oxetanes.



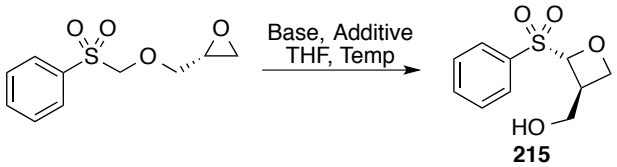
Scheme 105: Synthetic route to afford [2-(benzenesulfonyl)oxetan-3-yl]methanol **215**.

Sulfide **213** was treated with 3 equiv of *m*CPBA to afford sulfone **214** in 91% after purification. Next the intramolecular epoxide ring opening cyclisation was investigated. Cyclisation required deprotonation of **214** alpha to the sulfone to form a carbanionic intermediate which was expected to undergo a cyclisation to afford the desired disubstituted oxetane **215**, scheme 106.



Scheme 106: Proposed mechanism for the cyclisation to afford 2,3-disubstituted sulfonyl oxetanes.

A solution of sulfonyl epoxide **214** in THF was treated with 1.1 equiv of LiHMDS at 0 ºC. Analysis after 4 h showed that no reaction had occurred. The reaction was continued whilst warming to rt to promote cyclisation but after 23 h no product was formed. The resulting carbanionic intermediate may not have been reactive enough to cyclise and open the epoxide ring or the required orbital overlap was not possible. This lack of reactivity prompted further investigation into the reaction conditions, table 21.



215

Entry	Base	Additive	Temp (ºC)	Yield of **215** (%)*
1	LiHMDS	-	0 to rt	0
2	KHMDS	-	0 to rt	0
3	LiHMDS	TMEDA	0 to rt	0
4	LiHMDS	DMPU	0 to rt	0
5	LiHMDS	$BF_3{\cdot}Et_2O$ (1.1 equiv)	0 to rt	0
6	LiHMDS	$BF_3{\cdot}Et_2O$ (3 equiv)	0 to rt	0
7	LiHMDS	-	0 to 40	13[a]

Table 21: Summary of reaction conditions investigated to probe the intramolecular epoxide opening. * Yield determined by ^{1}H NMR with respect to 1,3,5-trimethoxybenzene as an internal standard. [a] Possible product formation but result not confirmed.

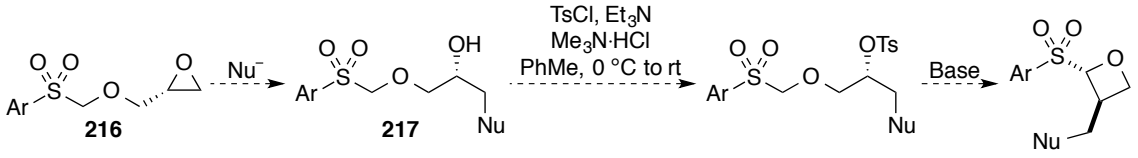
KHMDS was employed as the larger potassium cation would be more weakly coordinating than Li^+ therefore encouraging cyclisation, however no reaction was observed, entry 2. Additives are often used to enhance the reactivity of alkyllithium reagents by coordinating to the lithium ion, releasing the carbanion,[205] however addition of TMEDA or DMPU during the cyclisation did not facilitate the reaction, entries 3 and 4. Addition of a Lewis acid to activate the epoxide was then examined. The oxophilic $BF_3{\cdot}Et_2O$ reagent was introduced, following deprotonation, to weaken the C–O bond of the epoxide and promote ring opening. With 1.1 equiv of $BF_3{\cdot}Et_2O$ no reaction was observed whilst with 3 equiv degradation, possibly of the anionic intermediate, occurred and no desired product was formed, entries 5 and 6. Lastly an increase in temperature was examined to promote cyclisation, heating at 40 ºC for 3.5 h resulted in possible product formation in a 13% yield, entry 7. Analysis of the crude reaction material by ^{1}H NMR suggested formation of oxetane **215** however the compound could not be isolated and therefore the result could not be confirmed during the course of the investigation.

Additional investigation into the reaction conditions is required to confirm the formation of **215** and probe the reaction further. Material degradation occurred at the elevated temperature suggesting that temperatures between rt and 40 ºC may improve the reaction outcome. The addition of an oxophilic Lewis acid at warmer temperatures may promote the epoxide ring opening cyclisation and the incorporation of alternative Lewis acids or additives such as LiCl, HMPA or potassium *tert*-butoxide should be investigated.

4.1.4. Alternative Strategies to Access 2,3-Disubstituted Oxetanes

The conformation of sulfonyl epoxide **214** may not allow the required interaction between the carbanion and the C–O bond of the epoxide, prohibiting the desired cyclisation. Two alternative routes to synthesise 2,3-disubstituted oxetanes are discussed below; 1) opening the epoxide with an external nucleophile and 2) employing substituted diols to eliminate the need to open the epoxide ring.

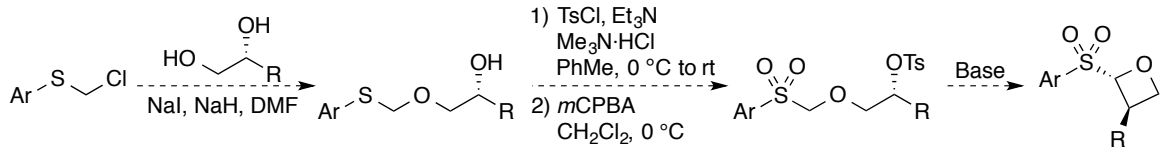
Sulfonyl epoxy ether **216**, synthesised *via* a known synthetic sequence, has the potential to undergo nucleophilic attack by an external nucleophile such as a thiol, an amine or an alkyl alcohol, affording **217**, scheme 107. Subsequently a leaving group could be incorporated *via* tosylation and the resulting *p*-toluenesulfonate may cyclise to form the desired 2,3-disubstituted sulfonyl oxetane upon treatment with a base. Altering the nucleophile could afford a diverse range of oxetane derivatives from a common intermediate **216**.



Scheme 107: Proposed alternative route to form 2,3-disubstituted oxetanes.

The required cyclisation is similar to that already developed to synthesise 2-sulfonyl oxetanes however the intermediate carbanion must attack a secondary as opposed to a primary carbon centre, this may inhibit the cyclisation reaction due to increased steric hindrance.

An alternative approach that would eliminate epoxide ring opening utilises a substituted diol in the initial step. This approach would allow diversity to be introduced into the oxetane fragments however a selective alkylation of the primary hydroxyl over the secondary would be required in the initial step of the synthetic sequence, scheme 108. If successful, subsequent incorporation of the *p*-toluenesulfonate group then oxidation could form the desired cyclisation precursor.

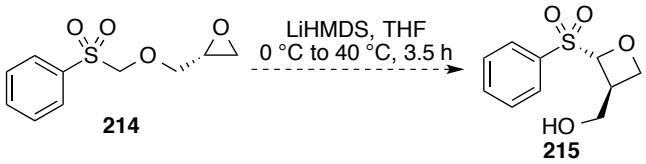


Scheme 108: Alternative approach to 2,3-disubstituted oxetane synthesis employing a substituted diol.

Preliminary results performed within the Bull group during the course of the investigation demonstrated that the selective alkylation was challenging, when R = CH_2OBn a 1:1.2 ratio of regioisomers was observed.[vi] This selectivity may be improved by incorporating a bulky R group to favour alkylation of the primary position due to steric hindrance.

4.1.5. Summary of Investigations into the Synthesis of More Highly Substituted Sulfonyl Oxetane Derivatives.

Methodology to synthesise highly substituted sulfonyl oxetanes was desired to allow additional substituents to be incorporated onto the oxetane core, increasing the variety of sulfonyl oxetane derivatives accessed. An intramolecular cyclisation resulting in epoxide ring opening was examined to incorporate an hydroxymethyl group, scheme 109.



Scheme 109: Formation of a 2,3-disubstituted oxetane *via* an intramolecular epoxide ring opening.

Initial investigation demonstrated that the intramolecular cyclisation was challenging and unfortunately when heated to 40 ºC the reaction outcome was inconclusive. Further examination and optimisation of a range of variables including a stronger base, warmer temperature, addition of additives and reaction time is possible and may facilitate the reaction. In addition a variety of alternative methods, involving epoxide opening with an external nucleophile or alkylation of substituted diols followed by tosylation, oxidation and cyclisation, have been suggested. An alternative strategy to derivatise the oxetane motif and access oxetane containing compounds is discussed below.

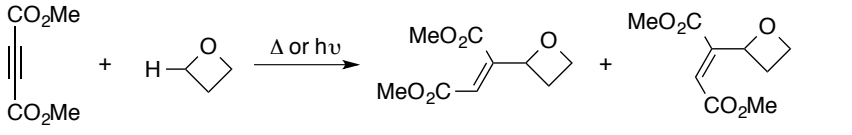
[vi] Reaction performed by UROP student, Aaron Trowbridge.

4.2. Towards a Divergent Route to Oxetane Derivatives via Radical Formation

In the final part of the study, efforts focused on generating oxetane radicals to provide a means to introduce an oxetane motif to a target compound in a divergent manner.

4.2.1. Precedent For Oxetane Radical Formation

Formation of an oxetanyl radical has previously been reported under thermal and photochemical conditions.[206] Ahlgren reported the reaction of oxetane with dimethyl acetylenedicarboxylate to form the 2-substituted oxetanes **218** and **219** involving radical formation, scheme 110.[206]

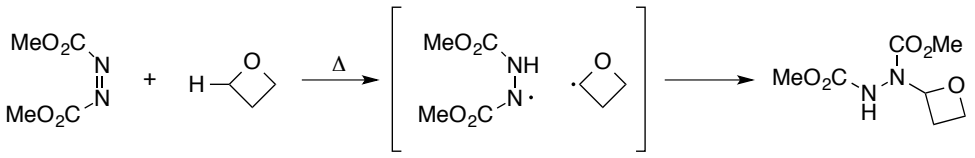


218 **219**

Thermal conditions	**30 %**	**218:219, 2:1**
Photochemical conditions	**80 %**	**218:219, 2:1**

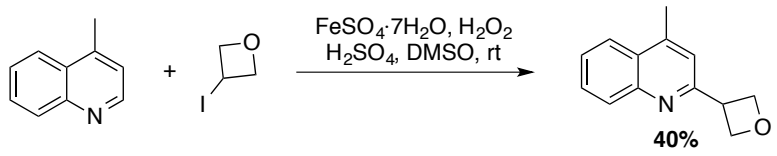
Scheme 110: Formation of an oxetanyl radical under thermal or photochemical conditions.[206]

A similar addition reaction of oxetane to dimethyl azodicarboxylate was also proposed to proceed *via* the formation of an oxetanyl radical under thermal conditions, scheme 111.[207]



Scheme 111: Hydrazination of oxetane under thermal conditions. No yield reported.[207]

More recently Duncton reported the introduction of an oxetan-3-yl substituent onto aryl and heteroaryl groups *via* a radical pathway, scheme 112. Under Minisci reaction conditions a secondary oxetanyl radical was generated in the 3-position from the readily available 3-iodooxetane.[208] Addition of the oxetanyl radical to a range of aryl groups was successful however the products were only formed in low to moderate yields.



Scheme 112: Preparation of heteroaryl oxetanes *via* a radical addition.[208]

4.2.2. Proposed Methods to Access the Oxetanyl Radical

The aim of the investigation was to develop methodology to incorporate the oxetane motif into a wide array of larger lead-like and drug-like molecules. This was envisaged through the formation of oxetanyl radical species either in the 2- or 3- positions.

Radical formation by two different methods would be examined, figure 34:
1) from the appropriate sodium sulfinate substrate, obtained from the corresponding 2-sulfonyl oxetane, to access the radical in the 2-position, and;
2) *via* silver catalysed decarboxylation to form a tertiary radical in the 3-position.
These approaches will be discussed below.

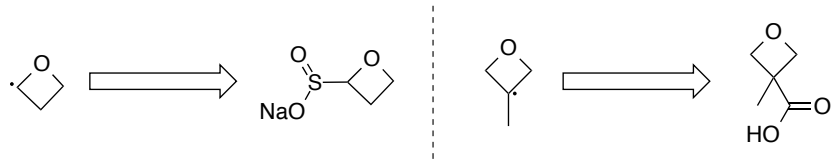


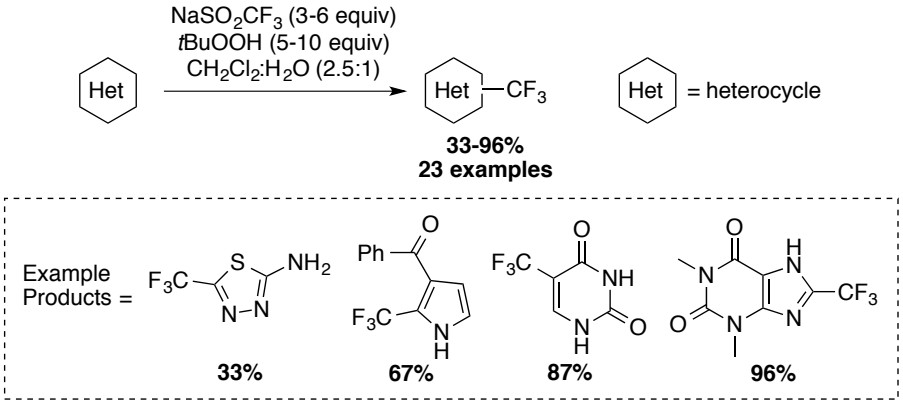
Figure 34: Two potential methods to access the oxetanyl radical.

4.2.3. Towards Oxetane Radical Formation From Oxetanesulfinate Salts

4.2.3.1. Alkyl Sulfinate Salts as Precursors to Generate Alkyl Radicals

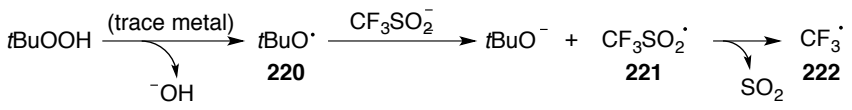
Over the last five years sulfinate salts have emerged as promising reagents for the functionalisation of heterocycles.[209] Previously alkyl and acyl radicals were generated from the corresponding carboxylic acids or boronic acids, however harsh reaction conditions were often required.[210] Due to the weaker C–S bond, compared to the corresponding C–C or C–B bond in carboxylic acids and boronic acids, sulfinates have a lower energy barrier for homolysis and so mild reaction conditions can be employed to generate the radical.

Radical generation from sulfinates was first reported in 1991 when Langlois disclosed the trifluoromethylation of electron rich aromatic rings with a trifluoromethyl radical generated from the corresponding sodium trifluoromethanesulfinate.[211] This discovery prompted the seminal work by Baran on the functionalisation of heterocycles with zinc and sodium sulfinates.[212,210,213,214] Upon investigation into a reagent for the trifluoromethylation of 4-*t*-butylpyridine, Baran found Langlois' reagent CF_3SO_2Na to be the most effective. Optimisation of reaction conditions led to the functionalisation of 23 different heterocycles including pyridines, pyrroles and pyrazines, in moderate to excellent yields, scheme 113.[212]



Scheme 113: Sodium trifluoromethanesulfinate as a reagent for the trifluoromethylation.[212]

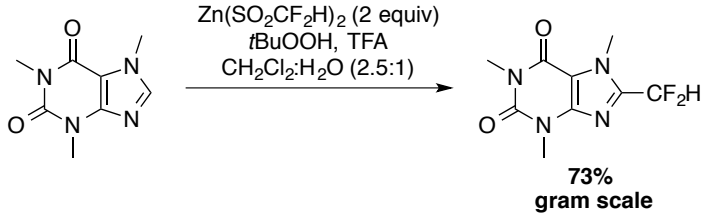
An excess of *tert*-butyl hydroperoxide (TBHP) and sodium trifluoromethanesulfinate were required for the reaction to proceed. The proposed mechanism for radical formation is shown in scheme 114. Trace metal in the reaction, possibly remaining from the sulfinate synthesis, leads to formation of the *t*-butoxy radical **220**. Subsequent reaction with $CF_3SO_2^-$ produces a CF_3SO_2 radical **221** which can afford the desired CF_3 radical **222** following release of sulfur dioxide.[212]



Scheme 114: Proposed mechanism for the formation of a CF_3 radical from the corresponding sulfinate.[212]

Baran also explored the incorporation of a difluoromethyl group onto a variety of heterocycles, including caffeine, using a zinc sulfinate as the radical precursor.[213] The

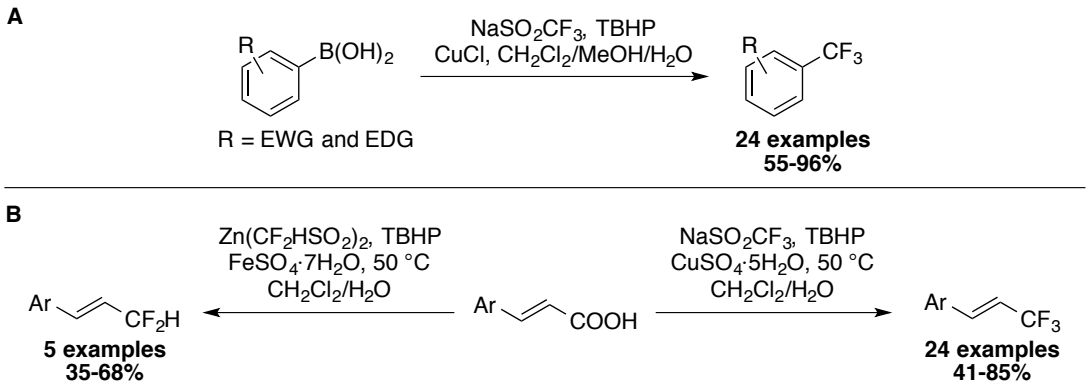
mild reaction conditions were successful on a large scale demonstrating their potential utility within industry, scheme 115.



Scheme 115: Difluoromethylation of caffeine on a gram scale, using zinc difluoromethyl sulfinate.[213]

Due to the increased interest a library of zinc sulfinates was developed including reagents for trifluoromethylation, difluoromethylation and fluoromethylation. In addition sodium difluoroethylsulfinate was synthesised as a reagent for the incorporation of a difluoro ethyl group onto a variety of heterocycles.[210,214] In 2014 Baran reported the synthesis of novel sodium alkanesulfinates including cyclopropane, difluorohexyl, THP, THF, cyclobutane, azetidine and trifluoropropyl substrates, significantly increasing the derivatives available.[209]

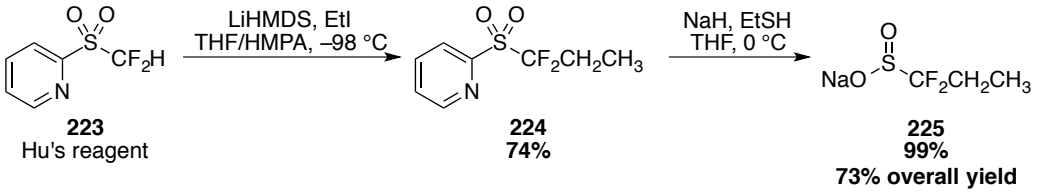
Along with addition into heterocycles, sodium trifluoromethyl sulfinate ($NaSO_2CF_3$) was employed in the trifluoromethylation of aryl and heteroaryl boronic acids in the presence of TBHP at rt, scheme 116-A.[215] The trifluoromethylation of α,β-unsaturated carboxylic acids in the presence of TBHP and a copper (II) catalyst was also reported, scheme 116-B.[216] Similarly $Zn(CF_2HSO_2)_2$ was employed in the difluoromethylation of α,β-unsaturated carboxylic acids forming difluoromethyl substituted alkenes, scheme 116-B.[216]



Scheme 116: Examples of the reactivity of sodium and zinc sulfinates.[215,216]

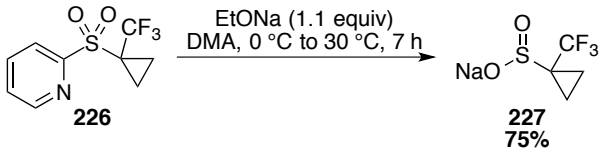
4.2.3.2. Reported Synthesis of Alkyl Sulfinate Salts

Baran disclosed the synthesis of zinc difluoromethanesulfinate from the reaction of zinc dust with difluoromethanesulfonyl chloride, however the corresponding sodium sulfinate could not be synthesised from the same starting material.[213] In 2011 Prakash and Olah developed a novel, two-step synthesis of sodium sulfinates from Hu's reagent **223** involving alkylation followed by aromatic substitution, scheme 117.[217] Sodium sulfinate **225** was generated using this two-step procedure, deprotonation with LiHMDS followed by alkylation afforded sulfone **224**. Subsequent reaction with NaH in EtSH resulted in the desired sulfinate **225** in a good overall yield of 73%, scheme 117.[217]



Scheme 117: Synthesis of a sodium sulfinate reagent in a two step procedure from Hu's reagent.[217]

Baran generated a variety of small heterocyclic, cyclic and acyclic sodium sulfinates from the corresponding 2-pyridyl sulfone substrates, synthesised in 3 steps from the corresponding carboxylic acids, using the conditions reported by Prakash and Olah.[209,214] Alternative reaction conditions were developed for the formation of sodium trifluoromethylcyclopropylsulfinate using NaOEt in DMA to generate the desired sulfinate, scheme 118.[209] These alternative conditions eased the purification of sulfinate **227**.



Scheme 118: Alternative conditions to generate sodium sulfinate **227** from 2-pyridyl sulfone **226**.[209]

4.2.3.3. Towards the Synthesis of Sodium Oxetane-2-sulfinate

2-(Oxetane-2-sulfonyl)pyridine **58**, synthesised as a desirable 2-sulfonyl oxetane fragment (see chapter 2), was analogous to the pyridyl sulfones from which sodium sulfinates were generated, such as **228**, figure 35. Treatment of **58** with NaSEt or NaOEt was anticipated to produce the analogous oxetanyl sodium sulfinate **229**. If successful the formation of the oxetanyl radical and subsequent heterocycle functionalisation could be investigated, figure 35.

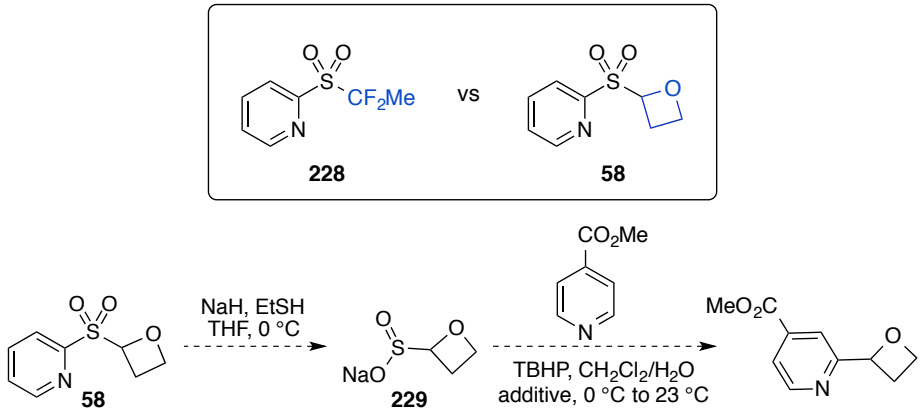
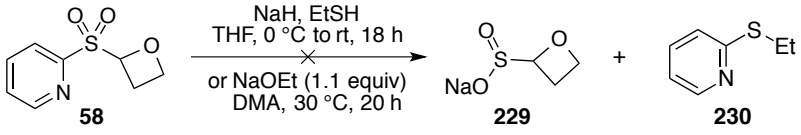


Figure 35: 2-(Oxetane-2-sulfonyl)pyridine **58** as a sulfinate precursor.

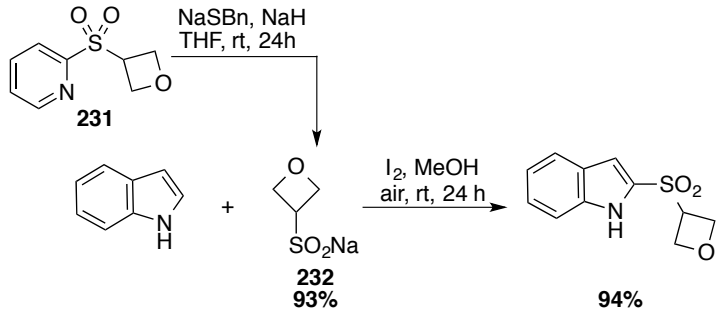
Ethanethiol was added dropwise to a suspension of NaH in THF at 0 ºC and stirred for 5 min to form sodium ethanethiolate. A solution of oxetane **58** in THF was added dropwise and stirred whilst warming to rt for 18 h, scheme 119.[214] No oxetane derivative was observed in the crude material however there was possible formation of 2-(ethylsulfanyl)pyridine **230**. The stability of the novel oxetanyl sulfinate **229** was unknown. Baran reported the majority of sodium and zinc sulfinates as air stable white solids however the oxetane substrate could not be assumed to be stable. At this stage of the investigation it was unclear whether the reaction was successful but the required product unstable, or the starting material decomposed under the reaction conditions.



Scheme 119: Investigation into the synthesis of sodium oxetane-2-sulfinate **229**.

The less reactive ethoxide nucleophile was expected to reduce the possibility of compound degradation. Oxetane **58** was treated with NaOEt and heated at 30 ºC for 20 h, scheme 119. Following removal of the solvent, starting material was recovered indicating that NaOEt was too weak a nucleophile to attack 2-pyridyl oxetane **58**. These results suggested that an alternative nucleophile to NaSEt or NaOEt was required.

In 2015 Harrity reported the synthesis and coupling of oxetane sulfinate salts generated from pyridyl sulfonyl oxetane **231**, which in turn was obtained from 3-iodooxetane, employing NaSBn as the nucleophile, scheme 120.[218]



Scheme 120: Synthesis and indole coupling reactions of oxetane sufinate salts.[218]

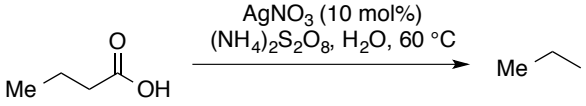
This emphasised that alternative nucleophiles and solvents could be explored to synthesise the isomeric sodium oxetane-2-sulfinate. Different reaction temperatures could also be investigated although the stability of the 2-substituted product could be different to that of **232**. Formation of the corresponding zinc sulfinate may improve stability if required.[210,213] Simultaneously an alternative route to obtain an oxetanyl radical was investigated, *via* decarboxylation.

4.2.4. Oxetanyl Radical Formation via Silver Catalysed Decarboxylation

4.2.4.1. Silver Catalysed Oxidative Decarboxylation to Afford Alkyl Radicals

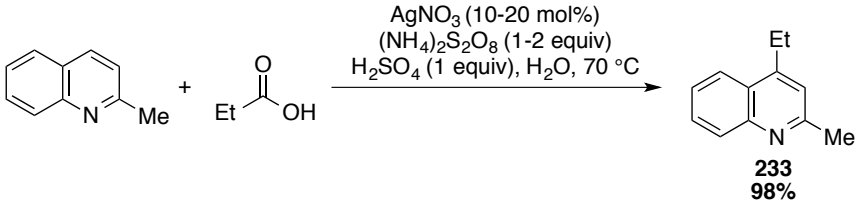
Kochi first reported the silver catalysed oxidative decarboxylation of aliphatic carboxylic acids by peroxydisulfate in 1970.[219] Treating pivalic, *iso*-butyric or *n*-butyric acids with 10 mol% of silver (I) nitrate and stoichiometric ammonium peroxydisulfate resulted in

decarboxylation to afford the corresponding alkane as the major product. The reaction with *n*-butyric acid is shown in scheme 121.[219]



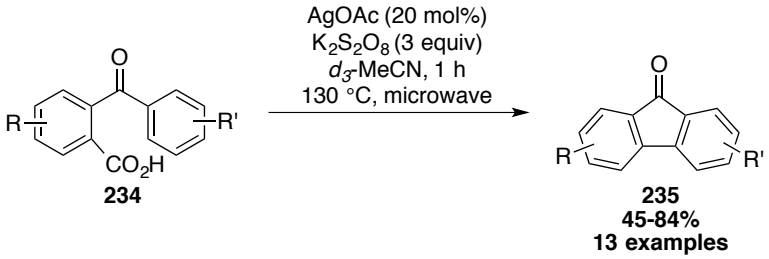
Scheme 121: Silver catalysed decarboxylation of aliphatic carboxylic acids. No yield reported.[219]

Soon after, Minisci used this methodology to substitute electron poor heteroaromatic compounds through addition of an alkyl radical.[220] In 1971 the first example of the well known Minisci reaction was reported using similar conditions to those described by Kochi.[220] Quinoline, 2-methylquinoline, isoquinoline, pyridine, 2-cyanopyridine and acridine were all successfully alkylated with a variety of primary, secondary and tertiary alkyl radicals generated from the corresponding carboxylic acids, an example is shown in scheme 122. The reactions proceeded in good to excellent yields under mild aqueous conditions to afford alkylated heterocycles such as **233**. The alkylation occurred with predicted selectively at the positions with the highest reactivity towards nucleophiles and at the sterically less hindered positions.[220]



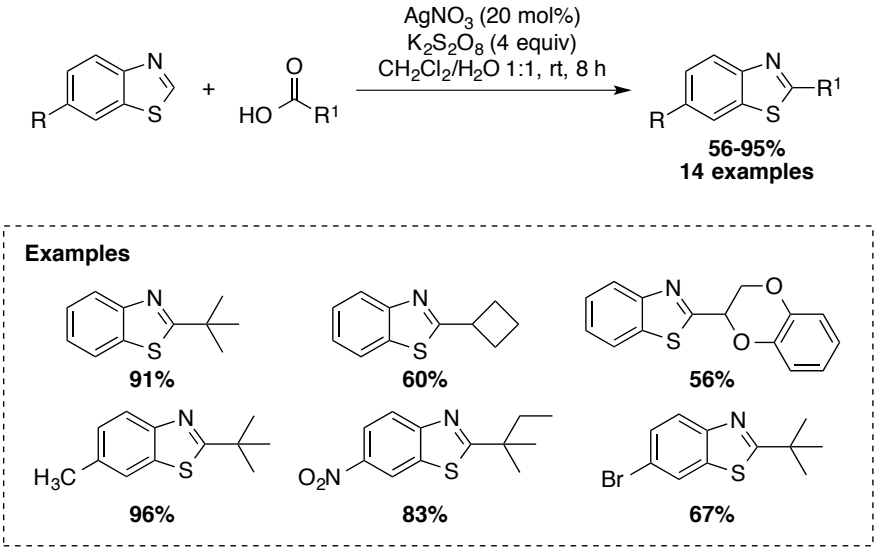
Scheme 122: Alkylation of nitrogen heterocycles with alkyl radicals generated through decarboxylation.[220]

In 2012 Greaney developed a silver catalysed decarboxylative radical cyclisation to form fluorenones **235** in good yields, scheme 123. $K_2S_2O_8$ was employed along with AgOAc to oxidatively decarboxylate acid **234** forming an aryl radical which subsequently underwent an intramolecular cyclisation.[221] Interestingly deuterated solvent was used in order to inhibit the competing protodecarboxylation.



Scheme 123: Decarboxylative C–H arylation forming fluorenones under radical conditions.[221]

In 2014 Zhao reported the decarboxylative C2-alkylation of benzothiazoles with secondary and tertiary alkyl carboxylic acids. The heterocycle and carboxylic acid were treated with silver (I) nitrate and $K_2S_2O_8$ in a mixed solvent of CH_2Cl_2 and H_2O to afford substituted benzothiazoles in good to excellent yields, scheme 124.[222] In comparison to Minisci's reaction conditions this decarboxylation was performed at rt without addition of sulfuric acid.

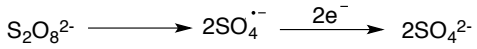


Scheme 124: Silver catalysed decarboxylative C2-alkylation of benzothiazole with carboxylic acids.[222]

These mild conditions were applied to other heterocycles such as thiazoles and benzoxazoles with similar high yields,[222] which prompted investigation into formation of the oxetanyl radical *via* silver catalysed decarboxylation, for the functionalisation of heterocycles.

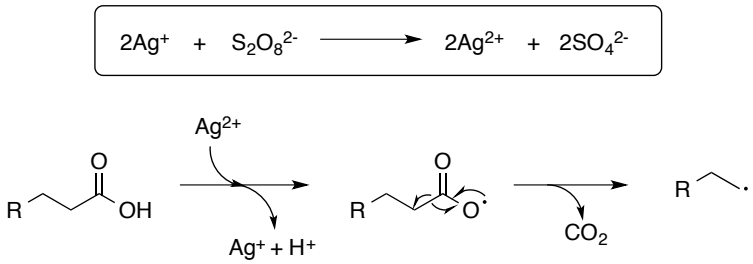
4.2.4.2. Mechanistic Discussion of Silver Catalysed Decarboxylation Followed by Addition into Benzothiazole

The peroxydisulfate ion $S_2O_8^{2-}$ is reduced to $2SO_4^{2-}$ *via* initial decomposition to afford radical anion $2SO_4^{\bullet-}$ which is an efficient electron transfer agent, equation 5.[219]



Equation 5: Reduction of the peroxydisulfate ion.

The reduction of $S_2O_8^{2-}$ to $2SO_4^{2-}$ has a redox potential of 2.01 V, however reactions involving this ion are often slow at room temperature due to the rate limiting step, the formation of the radical anion, having a high activation energy of 30 kcal mol^{-1}.[219] Metal ions have been employed as catalysts to accelerate the decomposition of the peroxydisulfate ion and generation of $2SO_4^{2-}$ and therefore accelerate the rate of decarboxylation.[223] The proposed mechanism for the silver catalysed decarboxylation is shown in scheme 125.

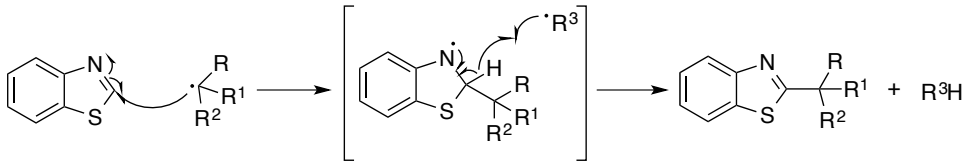


Scheme 125: Proposed mechanism for the silver catalysed decarboxylation.[219,220]

The silver (I) salt is initially oxidized by the peroxydisulfate ion to produce SO_4^{2-} and a reactive silver (II) species. The silver (II) species is then reduced by reaction with the carboxylic acid to regenerate a silver (I) species and a carboxylate radical. This intermediate subsequently decomposes to afford an alkyl radical with loss of carbon dioxide, scheme 125.[220] The combination of a silver (I) catalyst and a peroxydisulfate salt has been exploited for the generation of alkyl and aryl radicals.[220,221]

For the alkylation of benzothiazole with secondary and tertiary radicals Zhao suggested a mechanism that involved the formation of the alkyl radical *via* the pathway shown in

scheme 125, followed by coupling with a benzothiazole radical generated from a hydrogen abstraction.[222] Little experimental evidence for this mechanism was presented. Another plausible mechanism could have involved the addition of the alkyl radical to the benzothiazole followed by hydrogen abstraction, scheme 126.



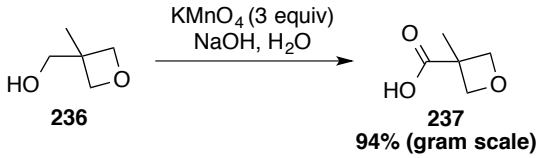
Scheme 126: Alternative proposed mechanism for the decarboxylative C2-alkylation of benzothiazole.

Metal-catalysed decarboxylation is growing as a versatile, efficient method to form new carbon-carbon or carbon-heteroatom bonds due to carboxylic acids usually being non-toxic, inexpensive, stable and structurally diverse. Silver catalysed decarboxylation had the potential to be an efficient method to access the desired oxetanyl radical from an oxetanyl acid. The above system was chosen to assess whether the addition of a 3-oxetanyl radical may be feasible, which could perhaps allow a diverse range of oxetane containing compounds to be accessed quickly.

4.2.4.3. Investigations into the Silver Catalysed Decarboxylation of 3-Methyloxetane-3-carboxylic Acid

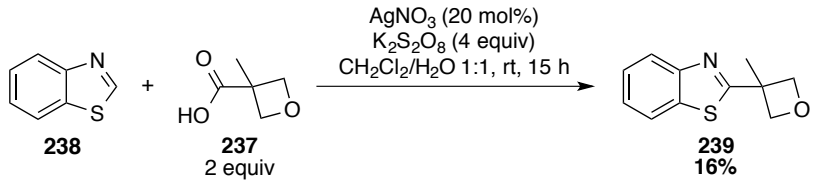
3-Methyloxetane-3-carboxylic acid **237** was selected as the desired substrate with which to examine the decarboxylation. The ease of carboxylic acid decarboxylation increased when going from secondary to tertiary radicals due to the increased stability,[222] so the methyl group in the 3-position was expected to benefit the reaction. 3-Methyloxetane-3-carboxylic acid was synthesised from a readily available, inexpensive alcohol **236**. 3-Methyl-3-oxetanemethanol **236** was oxidised using $KMnO_4$ in the presence of aqueous NaOH to afford **237** in a yield of 94% on a 10 mmol scale, scheme 127.[vii] Following a work-up procedure pure material was provided which required no further purification.

[vii] Conditions developed by Jessica Bevan whilst undertaking MSci research within the Bull group.



Scheme 127: Synthesis of 3-methyloxetane-3-carboxylic acid.

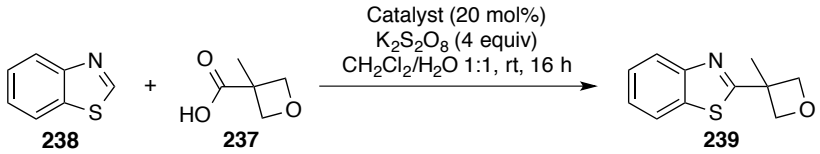
To examine the decarboxylation and radical addition, benzothiazole and carboxylic acid **237** were treated with $AgNO_3$ and $K_2S_2O_8$ at rt.[222] After 8 h no product was seen by TLC analysis however an increased reaction time of 15 h afforded the desired oxetane **239** in a 16% yield, scheme 128. This result indicated that the oxetanyl radical had been formed using silver catalysed decarboxylation methodology and then successfully alkylated benzothiazole, prompting investigation into optimisation of the reaction conditions.



Scheme 128: Initial investigation into the coupling of benzothiazole with carboxylic acid **237**. Yield calculated by ^{1}H NMR analysis of the crude material with respect to 1,3,5-trimethoxybenzene.

4.2.4.3.1. Towards Optimisation of the Decarboxylation/Addition Reaction

The reaction was optimised to increase the formation of the oxetane containing compound **239**. Initially the catalyst employed was investigated and so a variety of silver (I) catalysts were screened. The results are shown in table 22.

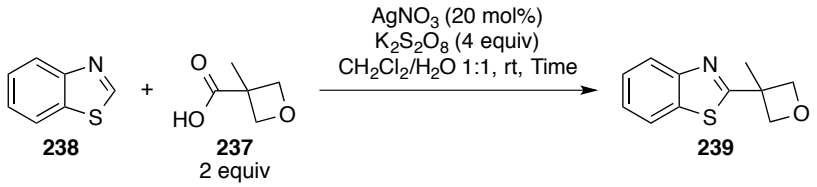


Entry	Catalyst	Catalyst equiv (mol%)	Time (h)	Yield **239** (%)*	Yield **238** (%)*	Total material recovered (%)*a
1	$AgNO_3$	20	16	13	35	48
2	Ag_2CO_3	20	16	18	25	43
3	Ag_3PO_4	20	16	19	42	61
4	AgOAc	20	16	6	34	40

Table 22: Results for the radical addition of 3-methyloxetane-3-carboxylic acid **237** when employing different silver catalysts. * Yield determined by ^{1}H NMR with respect to 1,3,5-trimethoxybenzene as an internal standard. [a] Determined by yield of **238** + yield of **239**.

No significant change in yield was observed when using $AgNO_3$, Ag_2CO_3 or Ag_3PO_4, but a decrease in yield to 6% was obtained when employing AgOAc, entries 1–4. All reactions resulted in less than 100% total recovery of material indicating that material was lost during the reaction possibly through degradation of benzothiazole or product **239**. To investigate the material loss the work-up procedure was examined. The aqueous work-up protocol was eliminated, instead the solvent was removed immediately to determine whether material was lost due to incomplete extraction. Despite no aqueous work-up procedure only 53% of the total material was recovered indicating that material was lost during the reaction. Whether additional material was lost during the aqueous work-up, through partial extraction, could not be concluded. To further investigate the stability of benzothiazole to the reaction conditions, the reaction was performed without addition of oxetane **237**. A significant loss of material occurred concluding that benzothiazole was degrading in the presence of $AgNO_3$ and $K_2S_2O_8$ at rt.

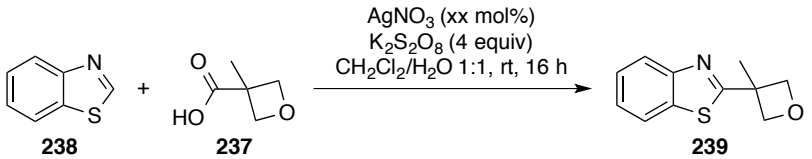
The reaction time was investigated to determine whether there was an optimum time that reduced degradation whilst allowing the reaction to proceed. The reaction was heterogeneous between CH_2Cl_2 and H_2O therefore sampling was not possible to obtain accurate results, so parallel reactions were performed. The results are shown in table 23.



Entry	Catalyst	Catalyst equiv (mol%)	Time (h)	Yield **239** (%)*	Yield **238** (%)*	Total material recovered (%)*a
1	$AgNO_3$	20	2	8	76	84
2	$AgNO_3$	20	4	12	55	67
3	$AgNO_3$	20	8	15	50	65
4	$AgNO_3$	20	12	15	46	61
5	$AgNO_3$	20	16	13	54	67
6	$AgNO_3$	20	24	15	22	37
7	$AgNO_3$	20	48	15	33	48

Table 23: Results investigating the optimum time of the reaction. * Yield determined by ^{1}H NMR with respect to 1,3,5-trimethoxybenzene as an internal standard. [a] Determined by yield of **238** + yield of **239**.

The highest yield of **239** was obtained after 8 h although only a 3% increase was observed between 4 and 8 h indicating that the reaction did not progress further after 4 h. entries 2 and 3. Total recovery of material was only 84% after 2 h and decreased further to 65% after 8 h and 37% after 24 h, entries 1, 3 and 6. These results showed that compound degradation occurred within the first two hours of the reaction and continued even after product formation had stopped. Interestingly the yield of **239** did not decrease significantly over time suggesting that the product was stable and therefore benzothiazole **238** was most likely degrading, entries 3–7. As the product yield or total material recovered did not vary significantly between 8 and 16 h, 16 h was selected for further optimisation due to ease of reaction analysis. The number of equivalents of $AgNO_3$ were investigated next, table 24.



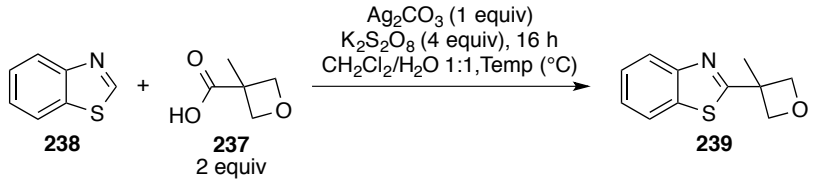
238 **237** 2 equiv **239**

Entry	Catalyst	Catalyst equiv (mol%)	Time (h)	Yield **239** (%)*	Yield **238** (%)*	Total material recovered (%)*a
1	$AgNO_3$	20	16	34	41	75
2	$AgNO_3$	100	16	21	30	51
3	Ag_2CO_3	50	16	25	50	75
4	Ag_2CO_3	100	16	25	25	50
5	Ag_2CO_3	150	16	30	49	79

Table 24: Number of equivalents of silver catalyst. For consistency the reactions were performed for 16 h before being quenched. * Yield determined by ^{1}H NMR with respect to 1,3,5-trimethoxybenzene as an internal standard. [a] Determined by yield of **238** + yield of **239**.

Stoichiometric $AgNO_3$ was expected to increase the product yield however a surprisingly low yield of 21% was obtained, this yield was lower than that observed when employing 20 mol% of catalyst, entries 1 and 2. In addition, the control reactions were not producing consistent results during the investigation so an alternative silver catalyst was employed in an effort to develop a reliable set of reaction conditions. From the initial catalyst screen silver carbonate was selected as an alternative catalyst. Entries 3–5, table 24, show that varying the number of equivalents of Ag_2CO_3 did not significantly improve the reaction outcome and so 100 mol% (1 equiv) of Ag_2CO_3 was chosen as the conditions to progress through the optimisation.

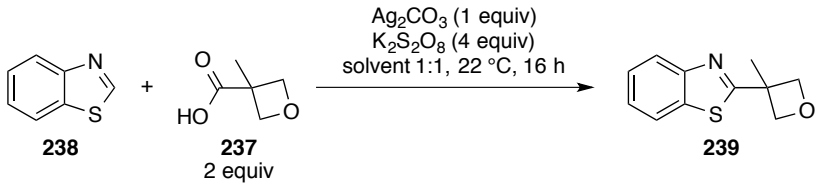
Silver catalysed decarboxylation is often reported at elevated temperatures of 60–130 ºC.[220,221] Reaction temperature was examined next as a higher temperature may increase product formation whilst a lower temperature may reduce benzothiazole degradation. The results are shown in table 25.



Entry	Catalyst	Temperature (ºC)	Yield **239** (%)*	Yield **238** (%)*	Total material recovered (%)*a
1	Ag_2CO_3	0	20	71	91
2	Ag_2CO_3	22	45	35	80
3	Ag_2CO_3	30	29	29	58
4	Ag_2CO_3	40	24	45	69
5	Ag_2CO_3	60	24	27	51

Table 25: Effects of altering the reaction temperature. * Yield determined by ^{1}H NMR with respect to 1,3,5-trimethoxybenzene as an internal standard. [a] Determined by yield of **238** + yield of **239**.

Previous optimisation was performed at 22 ºC, entry 2. Reducing the temperature to 0 ºC hindered the benzothiazole degradation however the desired reaction was also inhibited and only a 20% yield of oxetane **239** was observed, entry 1. A longer reaction time may be required at the lower temperature but as the reaction was performed for 16 h a longer time was deemed undesirable. Conversely heating the reaction to promote product formation resulted in reduced yields along with increased benzothiazole degradation, entries 3–5. This observation was due to the heterogeneous nature of the reaction. Heating above the boiling point of CH_2Cl_2 would alter the concentration of each phase and hinder the radical addition thought to proceed in the organic phase. Employing a higher boiling point solvent system would prevent solvent evaporation and allow increased temperatures to be explored further, as such a solvent screen was run, table 26.



238 **237** 2 equiv **239**

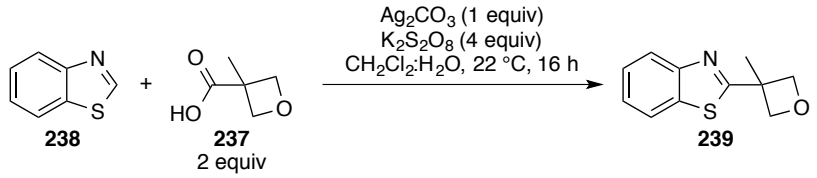
Entry	Catalyst	Solvent	Yield **239** (%)*	Yield **238** (%)*	Total material recovered (%)*a
1	Ag_2CO_3	CH_2Cl_2/H_2O	42	41	83
2	Ag_2CO_3	$CHCl_3/H_2O$	40	11	51
3	Ag_2CO_3	$MeCN/H_2O$	29	71	100
4	Ag_2CO_3	$Toluene/H_2O$	28	37	65
5	Ag_2CO_3	$Dioxane/H_2O$	11	56	67
6	Ag_2CO_3	$2\text{-}MeTHF/H_2O$	0	29	29
7	Ag_2CO_3	DMF/H_2O	10	60	70
8	Ag_2CO_3	H_2O	9	42	51
9	Ag_2CO_3	CH_2Cl_2	0	100	100

Table 26: Effects of changing the reaction solvent system. All reactions performed at 22 ºC to prevent solvent evaporation and allow comparable results to be obtained. * Yield determined by ^{1}H NMR with respect to 1,3,5-trimethoxybenzene as an internal standard. [a] Determined by yield of **238** + yield of **239**.

The highest yield of **239** was obtained when the reaction was performed in a mixed solvent system of CH_2Cl_2 and H_2O, entry 1. Interestingly a combination of $CHCl_3$ and H_2O gave a similar yield of 40%, entry 2, whilst non-chlorinated solvents gave lower yields of 0–29%, entries 3–7, indicating that chlorinated solvents were desired. MeCN and H_2O are miscible so the heterogeneous nature of the reaction would be eliminated and an improved yield was expected, however a surprisingly low yield of 29% was obtained. Performing the reaction under aqueous conditions resulted in a low yield of 9% whilst employing only CH_2Cl_2 resulted in no product formation, entries 8 and 9. These results emphasised the requirement for heterogeneous reaction conditions. The oxetane, oxidant and silver catalyst were proposed to be in the aqueous layer whilst benzothiazole was in the organic phase. Initially decarboxylation was expected to occur in the aqueous phase then the resulting radical would be transferred to the organic layer and radical addition could proceed.

The ratio of CH_2Cl_2 to H_2O was therefore investigated in an attempt to increase the yield of substituted benzothiazole **239**, table 27. Surprisingly increasing the overall reaction concentration to 0.15 M resulted in a lower yield of 34% compared to 45% observed at a

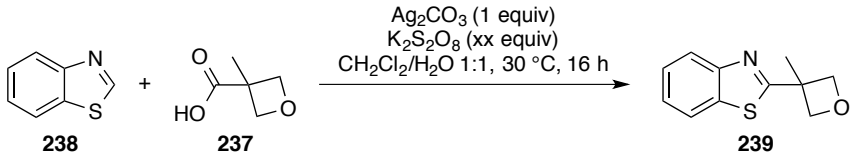
0.1 M concentration, entries 1 and 2. Similarly decreasing the overall reaction concentration to 0.075 M did not improve the yield, entry 3.



Entry	Catalyst	Solvent Ratio CH_2Cl_2:H_2O	Reaction Conc*n* (M)	Yield **239** (%)*	Yield **238** (%)*	Total material recovered (%)*[a]
1	Ag_2CO_3	1:1	0.15	34	43	77
2	Ag_2CO_3	1:1	0.10	45	35	80
3	Ag_2CO_3	1:1	0.075	42	29	71
4	Ag_2CO_3	1:5	0.10	30	34	64
5	Ag_2CO_3	5:1	0.10	13	79	92

Table 27: Effect of changing the overall reaction concentration and solvent ratio. * Yield determined by ^{1}H NMR with respect to 1,3,5-trimethoxybenzene as an internal standard. [a] Determined by yield of **238** + yield of **239**.

Altering the ratio of organic to aqueous solvent did not improve the reaction further. Increasing the volume of either H_2O or CH_2Cl_2 by a factor of 5 resulted in lower yields, emphasising further the requirement for a heterogeneous reaction, compare entries 2, 4 and 5. In the future a wider range of solvent ratios and smaller ratio differences should be examined to confirm the current conclusion. Varying the number of equivalents of carboxylic acid **237** and $K_2S_2O_8$ was briefly explored, table 28.



Entry	Catalyst	Oxetane **237** (equiv)	$K_2S_2O_8$ (equiv)	Yield **239** (%)*	Yield **238** (%)*	Total material recovered (%)*[a]
1	Ag_2CO_3	2	6	30	49	79
2	Ag_2CO_3	2	2.2	23	66	89
3	Ag_2CO_3	3	4	28	37	65
4	Ag_2CO_3	10	4	28	51	79
5	**Ag_2CO_3**	**6**	**8**	**62**	**4**	**66**

Table 28: Number of equivalents of reagent. * Yield determined by ^{1}H NMR with respect to 1,3,5-trimethoxybenzene as an internal standard. [a] Determined by yield of **238** + yield of **239**.

The number of equivalents of reagents were altered in order to obtain a reasonable yield and therefore be able to investigate the scope of the reaction. Increasing the number of equivalents of $K_2S_2O_8$ from 4 to 6 equiv did not improve the reaction as **239** was produced with only a 30% yield, entry 1, compared to 45% yield (table 27 entry 2). Similarly, decreasing the number of equivalents of oxidant to 2.2 equiv hindered the reaction although less material degradation was observed suggesting that $K_2S_2O_8$ contributed to the benzothiazole degradation, entry 2. Increasing the number of equivalents of carboxylic acid **237** to 3 or further to 10 equiv did not improve the reaction, entries 3 and 4. The increase in the number of equivalents of oxidant or carboxylic acid may not have affected the reaction yield if an increase in both $K_2S_2O_8$ and **237** was required. So the number of equivalents of both were increased simultaneously, resulting in a significantly improved yield of 62%, entry 5. Although these were undesirable conditions as a large excess of both oxidant and oxetane were employed and further optimisation, particularly of the number of equivalents of reagent, was required, investigation into the scope of the reaction was performed. Exploring reaction scope would determine if the reaction was versatile and applicable to alternative heterocycles.

4.2.4.3.2. Investigation into the Scope of Heterocycles Functionalised by an Oxetanyl Radical

The silver catalysed decarboxylation to afford the oxetanyl radical followed by radical addition into 8 different heterocycles was investigated, employing the current optimised conditions, figure 36.

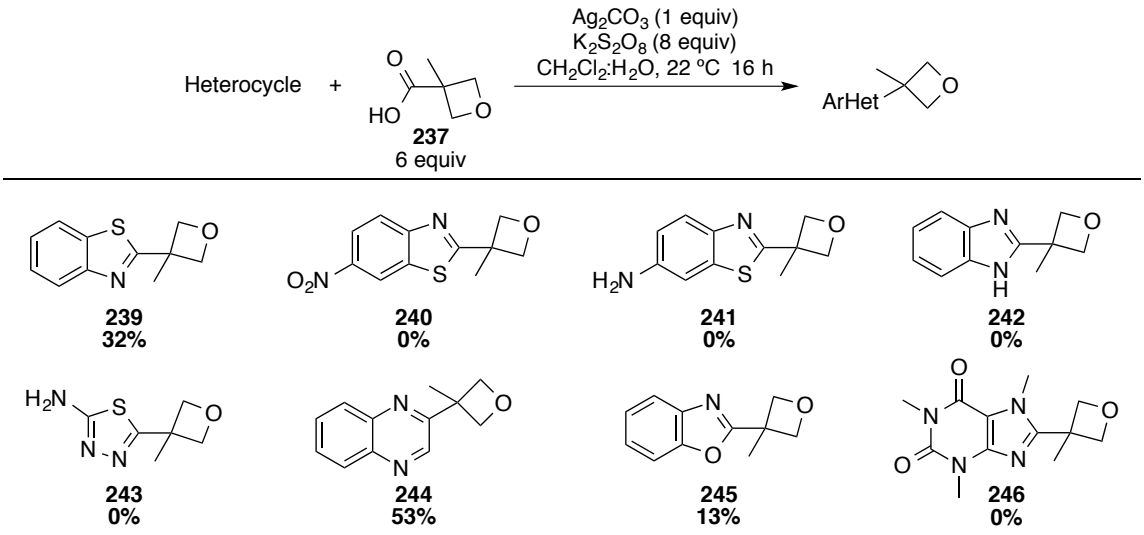


Figure 36: Initial investigation into the substrate scope of the reaction.

The reaction with benzothiazole resulted in a 32% isolated yield of **239**, significantly lower than the 62% yield calculated from the ^{1}H NMR spectrum. This lower yield suggested that **239** was not stable to purification on silica gel and alternative stationary phases should be investigated in the future. The reactions with 6-nitrobenzothiazole and 6-aminobenzothiazole predicted to form **240** and **241** were unsuccessful. When employing 6-aminobenzothiazole, carboxylic acid **237** was the only compound observed in the ^{1}H NMR spectrum of the crude material. A similar result was obtained when employing benzimidazole to afford **242**, or 2-amino-1,3,4-thiadiazole to form **243**. The radical additions into quinoxaline and benzoxazole were successful forming **244** and **245** in 53% and 13% respectively. Oxetane **245** was obtained in a low yield of 13% possibly due to the reaction not going to completion within 16 h, alternatively the stability of **244** and **245** to purification should be investigated. Finally employing caffeine, successful in the radical addition of sodium sulfinates, resulted in no product **246** formation.[210,214,209] In the future a wider variety of heterocycles susceptible to radical addition could be explored.

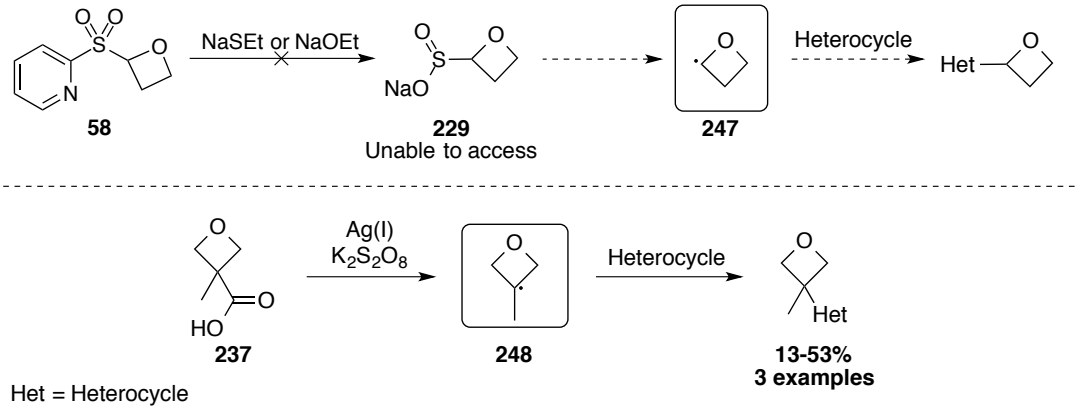
4.2.4.4. Further Investigation into the Decarboxylation Followed by Heterocycle Addition

Initial investigation concluded that the oxetane motif could be incorporated into heterocycles following silver catalysed decarboxylation. Further optimisation of the reaction conditions is required including examination of alternative solvent systems at warmer temperatures to promote the reaction without solvent evaporation. The concentration and ratio of each solvent may be beneficial to investigate, as would a wider

variety of overall reaction concentrations. Additionally, alternative oxidants could be explored including $Na_2S_2O_8$, $NH_4S_2O_8$, H_2O_2, TBHP and DTBP, and a more thorough examination of the number of equivalents of reagent may be beneficial. In addition, employing diphenyl disulfide instead of benzothiazole may determine whether radical formation or radical addition is the cause of the low yields currently observed as diphenyl disulfide would be more reactive towards radicals than benzothiazole.[224]

4.2.5. Summary of the Investigations into Generating an Oxetanyl Radical

The formation of an oxetanyl radical species is an interesting approach to incorporate the oxetane motif into larger molecules and therefore quickly access a variety of compounds containing an oxetane ring, which have the potential to be desirable fragments or lead-like compounds. Unfortunately generating the 2-oxetanyl radical from the corresponding sodium sulfinate was unsuccessful. Further investigation into the use of alternative nucleophiles to displace the sulfinate from the pyridyl sulfone, or the formation of zinc sulfinates would be required before oxetanyl radical **247** could be synthesised, scheme 129.



Scheme 129: Summary of investigations into functionalisation of the oxetane motif *via* radical formation.

Pleasingly formation of the tertiary, 3-oxetanyl radical *via* decarboxylation of the corresponding carboxylic acid was successful and radical addition into medicinally relevant heterocycles was performed. Of the 8 heterocycles investigated 3 successfully afforded the desired product in yields of 13–53%, scheme 129. Additional optimisation of the silver catalysed decarboxylation reaction is required to improve the yield further and increase the reaction scope.

Conclusion of the Investigations into Strategies for the Synthesis of Oxetanes as Desirable Fragments for Drug Discovery

Interest in the oxetane motif is currently growing within medicinal chemistry as more knowledge about the heterocycle and its properties is gained. A novel strategy to synthesise the oxetane ring has been developed and consequently a variety of novel oxetane containing compounds, relevent to drug discovery, have been produced. Initial studies showed these compounds to have desired properties, however further investigation is required to fully understand their potential when incorporated into lead-like or drug-like compounds. Investigation into strategies to derivatise the oxetane motif, for example by sulfoxide-magnesium exchange or radical generation has begun. In addition the synthesis of highly substituted oxetanes was explored however further investigation is required.

5. Experimental

General: All non-aqueous reactions were carried out under an inert atmosphere (argon or nitrogen) with oven-dried (160 ºC) or flame dried glassware using standard techniques. Anhydrous solvents were obtained by filtration through drying columns (Innovative Technology Inc. PureSolv^{TM} Solvent Purification System, model: SPS-400-4, THF, Et_2O, CH_2Cl_2, PhMe) or obtained from commercial suppliers and used without further purification (DMF). H_2O was distilled before use.

Reagents: For the preparation of LDA or LiHMDS solutions, diisopropylamine or hexamethyldisilazane were distilled over potassium hydroxide immediately before use. Unless otherwise stated *m*CPBA was dissolved in CH_2Cl_2, washed with a phosphate buffer (pH 7.5) and dried ($MgSO_4$) then the solvent removed under reduced pressure before use. All commercially available organometallic solutions were titrated against salicylaldehyde phenylhydrazone.[225] All other commercially available reagents were used without further purification.

Chromatography: Flash column chromatography was performed using 230–400 mesh silica gel, 70–290 mesh basic alumina modified to activity IV or ISCO Flash Silica cartridges with the indicated solvent system according to standard techniques. Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel plates. Visualisation of the developed chromatogram was performed by UV absorbance (254 nm) and/or aqueous potassium permanganate stain or phosphomolybdic acid stain.

Melting Points: Melting points are uncorrected.

Infrared spectroscopy: Infrared spectra were recorded using a Perkin-Elmer spectrum 100 FT-IR Spectrometer and the absorbencies were reported in wavenumbers (cm^{-1}). All reported spectra are for neat compounds only.

NMR spectroscopy: Nuclear magnetic resonance spectra were recorded on a Bruker AV 400 (400 MHz) or AV 500 (500 MHz) spectrometer. Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad), coupling constant in Hz and assignment. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as an internal standard (^{1}H NMR spectra: $CDCl_3$: δ = 7.27 ppm, $(CD_3)_2CO$: δ = 2.05 ppm, CD_3OD: δ = 3.31 ppm,

$(CD_3)_2SO$: δ = 2.50 ppm. ^{13}C NMR spectra: $CDCl_3$: δ = 77.00 ppm, $(CD_3)_2CO$: δ = 29.84, 206.26 ppm, CD_3OD: δ = 49.00 ppm, $(CD_3)_2SO$: δ = 39.52 ppm) or using chloroform with 1% tetramethylsilane as the internal standard. ^{13}C NMR spectra were recorded with complete proton decoupling. ^{19}F NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in parts per million referenced to the standard monofluorobenzene: −113.5 ppm. Assignments of ^{1}H and ^{13}C spectra were made by the analysis of *δ*/*J* values and COSY, HSQC and HMBC experiments as appropriate.

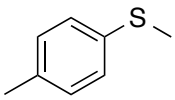
Mass Spectrometry: High resolution mass spectrometry were recorded on VG Platform II, Waters Xevo G2-S, VG Autospec or Thermofisher LTQ Orbitrap XL spectrometers.

General Procedure for the preparation of a 0.61 M solution of LiHMDS: A solution of HMDS (1.26 mL, 6.04 mmol) in THF (5.35 mL) was cooled to –78 ºC for 10 min then *n*BuLi (2.39 mL, 5.49 mmol, 2.3 M in hexane) was added dropwise. Solution stirred at –78 ºC for 30 min then warmed to 0 ºC for 30 min prior to use.

General Procedure for the preparation of a 1 M solution of LDA: A solution of diisopropylamine (0.92 mL, 6.60 mmol) in THF (2.68 mL) was cooled to –78 ºC for 10 min then *n*BuLi (2.40 mL, 6.00 mmol, 2.5 M in hexane) was added dropwise. Solution stirred at –78 ºC for 1 h prior to use.

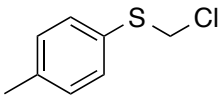
5.1. Synthesis of 2-Sulfonyl Oxetanes

1-Methyl-4-(methylsulfanyl)benzene (74)[226]



Potassium carbonate (122.2 g, 884 mmol) was added to a solution of 4-methyl benzene thiol **73** (100.0 g, 805 mmol) in acetone (1 L) followed by MeI (52.6 mL, 845 mmol) and the reaction stirred at rt for 14 h. The reaction was filtered through Celite® and the solvent removed under reduced pressure. The crude material was dissolved in diethyl ether (300 mL) and washed with 5% NaOH (3 × 150 mL). The combined aqueous layers were extracted with diethyl ether (150 mL) then the combined organics were washed with brine (100 mL), dried (Na_2SO_4) and solvent removed under reduced pressure to afford *p*-tolyl methyl sulfide **74** (109.3 g, 98%) as a yellow liquid which was used without further purification. R_f = 0.44 (10% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (2 H, d, *J* = 8.2 Hz, 2 × Ar-H), 7.11 (2 H, d, *J* = 8.2 Hz, 2 × Ar-H), 2.48 (3 H, s, SCH_3), 2.33 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.0 (Ar-C_q), 134.6 (Ar-C_q), 129.6 (2 × Ar-C), 127.2 (2 × Ar-C), 21.0 (Ar-CH_3), 16.5 (SCH_3). The observed data (^{1}H) was consistent with that reported in the literature.[226]

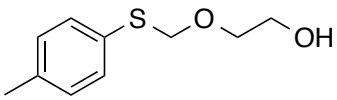
1-[(Chloromethyl)sulfanyl]-4-methylbenzene (75)[227]



N-Chlorosuccinimide (33.4 g, 250 mmol) was added portionwise to a solution of *p*-tolyl methyl sulfide **74** (31.5 g, 228 mmol) in carbon tetrachloride (250 mL). The reaction was stirred at rt for 14.5 h then filtered through a short pad of silica, eluting with CCl_4 (30 mL) and the solvent removed under reduced pressure. Purification by vacuum distillation afforded chloromethyl sulfide **75** (36.9 g, 94%) as an orange oil. b.p. = 98 ºC at 2.1 mbar (lit. b.p. = 88 ºC at 0.2 Torr).[228] R_f = 0.55 (20% EtOAc/hexane). IR (film)/cm^{-1} 3021, 2920, 1490, 1398, 1226, 1091, 854, 802, 719. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (2 H, d, *J* = 8.5 Hz, 2 × Ar-H), 7.21 (2 H, d, *J* = 8.5 Hz, 2 × Ar-H), 4.95 (2 H, s, SCH_2Cl), 2.39 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3 (Ar-C_q), 131.6 (2 × Ar-C), 129.9 (2 ×

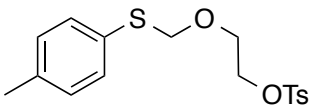
Ar-C), 129.4 (Ar-C_q), 51.9 (CH_2), 21.1 (CH_3). The observed data (^1H, ^{13}C) was consistent with that reported in the literature.[227]

2-{[(4-Methylphenyl)sulfanyl]methoxy}ethan-1-ol (76)



Sodium hydride (60% in mineral oil, 2.57 g, 64.25 mmol) was added to ethylene glycol (400 mL) at 0 ºC and stirred for 1 h 15 min. Sodium iodide (9.62 g, 64.18 mmol) was added followed by a solution of sulfide **75** (10.04 g, 58.37 mmol) in ethylene glycol (5 mL). The resulting solution was stirred at 0 ºC for 1 h then warmed to rt for 4 h. Water (300 mL) was added and the product was extracted with ethyl acetate (10 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (50% EtOAc/hexane) afforded alcohol **76** (9.60 g, 83%) as a yellow oil. R_f = 0.34 (50% EtOAc/hexane). IR (film)/cm^{-1} 3449 (OH), 2926, 2872, 1734, 1493, 1461, 1373, 1250, 1052, 1017, 806, 734. ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (2 H, d, *J* = 8.1 Hz, 2 × Ar-H), 7.13 (2 H, d, *J* = 8.1 Hz, 2 × Ar-H), 5.00 (2 H, s, SCH_2O), 3.78–3.72 (4 H, m, OCH_2CH_2OH), 2.34 (3 H, s, CH_3), 1.94 (1 H, s, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2 (Ar-C_q), 131.5 (Ar-C_q), 131.1 (2 × Ar-C), 129.8 (2 × Ar-C), 77.0 (SCH_2O), 69.7 (OCH_2), 61.7 (OCH_2), 21.1 (CH_3). HRMS (ESI) *m/z* Calculated for $C_{10}H_{14}NaO_2S^+$ $[M+Na]^+$: 221.0607; Found: 221.0607 $[M+Na]^+$, Δ 0 ppm.

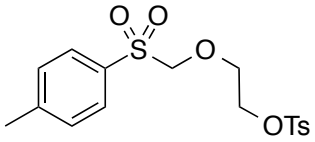
2-{[(4-Methylphenyl)sulfanyl]methoxy}ethyl-4-methylbenzene-1-sulfonate (77)



Triethylamine (3.14 mL, 22.34 mmol) and trimethylamine hydrochloride (70 mg, 0.75 mmol) were added to a solution of sulfide **76** (1.50 g, 7.56 mmol) in toluene (10 mL) at 0 ºC and stirred for 10 min. A suspension of 4-toluenesulfonyl chloride (2.86 g, 15.00 mmol) in toluene (10 mL) was added dropwise. The mixture was stirred at 0 ºC for 30 min then allowed to warm to rt slowly over 40 min and stirred for a further 1 h 20 min.

Water (100 mL) was added to the reaction and the product was extracted with EtOAc (4 × 50 mL). The combined organic layers were washed with brine (50 mL) and H_2O (30 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (40% EtOAc/hexane) afforded *p*-toluenesulfonate **77** (2.52 g, 97%) as a yellow oil. R_f = 0.34 (40% EtOAc/hexane). IR (film)/cm^{-1} 2984, 2891, 1734, 1596, 1499, 1362, 1237, 1175, 1095, 1011, 915, 807. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (2 H, d, *J* = 8.2 Hz, 2 × Ts-H), 7.34–7.30 (4 H, m, 2 × Ts-H + 2 × Tol-H), 7.10 (2 H, d, *J* = 8.2 Hz, 2 × Tol-H), 4.90 (2 H, s, SCH_2O), 4.22–4.18 (2 H, m, $TsOCH_2$), 3.83–3.78 (2 H, m, CH_2OCH_2), 2.45 (3 H, s, Ts-CH_3), 2.33 (3 H, s, Tol-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8 (Ts-C_q), 137.1 (Tol-C_q), 132.9 (Ts-C_q), 131.4 (Tol-C_q), 131.0 (2 × Ar-C), 129.8 (2 × Ar-C), 129.7 (2 × Ar-C), 127.9 (2 × Ar-C), 76.8 (SCH_2O), 68.7 (SCH_2OCH_2), 65.5 ($TsOCH_2$), 21.6 (Ts-CH_3), 21.0 (Tol-CH_3). HRMS (ESI) *m/z* Calculated for $C_{17}H_{24}NO_4S_2^+$ $[M+NH_4]^+$: 370.1141; Found: 370.1134 $[M+NH_4]^+$, Δ 1.9 ppm.

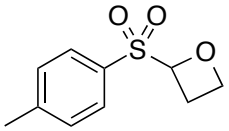
1-Methyl-4-({2-[4-methylbenzenesulfonyl)oxy]ethoxy}methanesulfonyl)benzene (78)



meta-Chloroperbenzoic acid (1.47 g 8.52 mmol) was added to a solution of sulfide **77** (1.00 g, 2.84 mmol) in dichloromethane (15 mL) at 0 ºC and the mixture stirred at 0 ºC for 4 h. The reaction was quenched with sat. aq. Na_2SO_3 (25 mL) and extracted with dichloromethane (6 × 20 mL). The combined organic layers were washed with 1 M NaOH (3 × 15 mL) and sat. aq. NH_4Cl (50 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (50% EtOAc/hexane) afforded sulfone **78** (1.04 g, 96%) as a white solid; m.p. = 73–79 ºC. R_f = 0.65 (EtOAc). IR (film)/cm^{-1} 2992, 2926, 2885, 1599, 1461, 1350, 1327, 1300, 1170, 1130, 1080, 813. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (2 H, d, *J* = 8.2 Hz, 2 × Ts-H), 7.77 (2 H, d, *J* = 8.2 Hz, 2 × Ar-H), 7.38 (2 H, d, *J* = 8.2 Hz, 2 × Ar-H), 7.34 (2 H, d, *J* = 8.2 Hz, 2 × Ts-H), 4.52 (2 H, s, SCH_2O), 4.19–4.15 (2 H, m, $TsOCH_2$), 4.12–4.08 (2 H, m, CH_2OCH_2), 2.49 (3 H, s, Ts-CH_3), 2.48 (3 H, s, Tol-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4 (Ar-C_q), 145.0 (Ar-C_q), 133.9 (Ar-C_q), 132.7 (Ar-C_q), 130.0 (2 × Ar-C), 129.9 (2 × Ar-C), 128.9 (2 × Ar-C), 127.9 (2 × Ar-C), 86.2 (SCH_2O), 70.6 (SCH_2OCH_2), 68.5

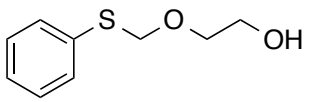
(TsO*C*H$_2$), 21.7 (CH$_3$), 21.7 (CH$_3$). HRMS (ESI) *m/z* Calculated for $C_{17}H_{24}NO_6S_2^+$ $[M+NH_4]^+$: 402.1040; Found: 402.1040 $[M+NH_4]^+$, Δ 0 ppm.

2-(4-Methylbenzenesulfonyl)oxetane (55)



A solution of LiHMDS (0.61 M in THF, 11.73 mL, 7.16 mmol) was added dropwise to a solution of sulfone **78** (2.50 g, 6.50 mmol) in THF (250 mL) at 0 ºC and stirred for 1 h. Reaction quenched with sat. aq. NH_4Cl (200 mL) and extracted with $CHCl_3$ (8 × 30 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (40% EtOAc/hexane) afforded oxetane **55** (1.28 g, 93%) as a white solid; m.p. = 106–108 ºC. R_f = 0.26 (40% EtOAc/hexane). IR (film)/cm^{-1} 2977, 2901, 1596, 1447, 1406, 1310, 1147, 1089, 1030, 984, 909, 816, 717. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (2 H, d, *J* = 8.2 Hz, 2 × Ar-H), 7.39 (2 H, d, *J* = 8.2 Hz, 2 × Ar-H), 5.37 (1 H, dd, *J* = 7.4, 5.6 Hz, OCHS), 4.80–4.74 (1 H, m, OCH*H*), 4.67–4.61 (1 H, m, OC*H*H), 3.17–3.05 (2 H, m, OCH$_2$C*H*$_2$), 2.47 (3H, s, CH$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4 (Ar-C$_q$), 132.2 (Ar-C$_q$), 129.9 (2 × Ar-C), 129.5 (2 × Ar-C), 94.0 (OCHS), 71.3 (OCH$_2$), 22.4 (OCH$_2$*C*H$_2$), 21.7 (CH$_3$). HRMS (APCI) *m/z* Calculated for $C_{10}H_{13}O_3S^+$ $[M+H]^+$: 213.0580; Found: 213.0580 $[M+H]^+$, Δ 0 ppm.

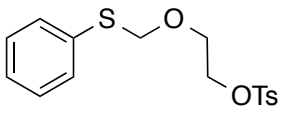
2-[(Phenylsulfanyl)methoxy]ethan-1-ol (72a)



Sodium hydride (60% in mineral oil, 0.70 g, 17.60 mmol) was added to ethylene glycol (100 mL) at 0 ºC and stirred for 1 h 15 min. Sodium iodide (2.60 g, 17.35 mmol) was added followed by sulfide **82a** (2.50 g, 15.76 mmol). The resulting solution was stirred at 0 ºC for 1 h then warmed to rt for 5 h. Water (100 mL) was added and the product was extracted with ethyl acetate (6 × 40 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash

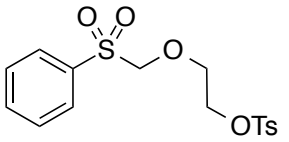
chromatography (30% EtOAc/heptane) afforded alcohol **72a** (2.54 g, 87%) as a colourless oil. R_f = 0.42 (50% EtOAc/heptane). IR (film)/cm^{-1} 3402 (OH), 2927, 1583, 1480, 1438, 1370, 1304, 1102, 1053, 887, 823, 690, 673. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.46 (2 H, m, 2 × Ar-H), 7.33–7.27 (2 H, m, 2 × Ar-H), 7.26–7.21 (1 H, m, Ar-H), 5.03 (2 H, s, SCH_2O), 3.74–3.69 (4 H, m, OCH_2CH_2OH), 2.32 (1 H, br s, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5 (Ar-C_q), 130.4 (2 × Ar-C), 129.0 (2 × Ar-C), 126.9 (Ar-C), 76.4 (SCH_2O), 69.9 (OCH_2), 61.6 (OCH_2). HRMS (EI) *m/z* Calculated for $C_9H_{12}O_2S^+$ $[M]^+$: 184.0553; Found: 184.0550 $[M]^+$, Δ 1.6 ppm.

2-[(Phenylsulfanyl)methoxy]ethyl-4-methylbenzene-1-sulfonate (83a)



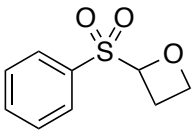
Triethylamine (5.54 mL, 39.42 mmol) and trimethylamine hydrochloride (127 mg, 1.32 mmol) were added to a solution of sulfide **72a** (2.44 g, 13.24 mmol) in toluene (20 mL) at 0 ºC and stirred for 20 min. A suspension of 4-toluenesulfonyl chloride (5.05 g, 26.49 mmol) in toluene (15 mL) was added dropwise. The mixture was stirred at 0 ºC for 35 min then allowed to warm to rt slowly over 40 min and stirred for a further 1 h 30 min. Water (150 mL) was added to the reaction and the product was extracted with EtOAc (5 × 20 mL). The combined organic layers were washed with H_2O (20 mL) and brine (10 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (20% EtOAc/heptane) afforded *p*-toluenesulfonate **83a** (4.40 g, 98%) as a colourless oil. R_f = 0.49 (40% EtOAc/heptane). IR (film)/cm^{-1} 2952, 1596, 1583, 1480, 1439, 1354, 1189, 1173, 1095, 1001, 913, 814, 773, 738, 661. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (2 H, d, J = 8.3 Hz, 2 × Ts-H), 7.43–7.39 (2 H, m, 2 × Ph-H), 7.30 (2 H, d, J = 8.3 Hz, 2 × Ts-H), 7.29–7.19 (3 H, m, 3 × Ph-H), 4.93 (2 H, s, SCH_2O), 4.21–4.18 (2 H, m, $TsOCH_2$), 3.81–3.79 (2 H, m, CH_2OCH_2), 2.43 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8 (Ts-C_q), 135.3 (Ph-C_q), 133.0 (Ts-C_q), 130.3 (2 × Ph-C), 129.8 (2 × Ts-C), 128.9 (2 × Ph-C), 127.9 (2 × Ts-C), 126.9 (Ph-C), 76.3 (SCH_2O), 68.7 (SCH_2OCH_2), 65.7 ($TsOCH_2$), 21.6 (CH_3). HRMS (CI) *m/z* Calculated for $C_{16}H_{22}NO_4S_2^+$ $[M+NH_4]^+$: 356.0990; Found: 356.0997 $[M+NH_4]^+$, Δ 2.0 ppm.

1-({2-[(Phenylsulfonyl)methoxy]ethoxy}sulfonyl)-4-methylbenzene (84a)



meta-Chloroperbenzoic acid (77%, 8.34 g, 37.23 mmol) was added to a solution of sulfide **83a** (4.20 g, 12.41 mmol) in dichloromethane (65 mL) at 0 ºC and the mixture stirred at 0 ºC for 4 h. The reaction was quenched with sat. aq. Na_2SO_3 (60 mL) and extracted with dichloromethane (5 × 30 mL). The combined organic layers were washed with 2 M NaOH (3 × 30 mL) and sat. aq. NH_4Cl (60 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (50% EtOAc/heptane) afforded sulfone **84a** (4.27 g, 93%) as a white solid; m.p. = 82–83 ºC. R_f = 0.19 (40% EtOAc/heptane). IR (film)/cm^{-1} 3071, 1594, 1445, 1357, 1323, 1294, 1251, 1149, 1127, 1080, 1016, 927, 939, 893, 818, 803, 705. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93–7.90 (2 H, m, 2 × Ts-H), 7.77 (2 H, d, *J* = 8.3 Hz, 2 × Ph-H), 7.70 (1 H, dddd, *J* = 7.5, 7.3, 1.3, 1.2 Hz, Ph-H), 7.61–7.56 (2 H, m, 2 × Ph-H), 7.33 (2 H, d, *J* = 8.5 Hz, 2 × Ts-H), 4.52 (2 H, s, SCH_2O), 4.18–4.15 (2 H, m, $TsOCH_2$), 4.10–4.08 (2 H, m, CH_2OCH_2), 2.45 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0 (Ar-C_q), 137.0 (Ar-C_q), 134.2 (Ph-C), 132.8 (Ar-C_q), 129.9 (2 × Ts-C), 129.3 (2 × Ph-C), 128.8 (2 × Ph-C), 127.9 (2 × Ts-C), 86.2 (SCH_2O), 70.7 (SCH_2OCH_2), 68.4 ($TsOCH_2$), 21.6 (CH_3). HRMS (ESI) *m/z* Calculated for $C_{16}H_{18}O_6S_2Na^+$ $[M+Na]^+$: 393.0442; Found: 393.0451 $[M+Na]^+$, Δ 2.3 ppm.

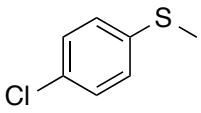
2-(Phenylsulfonyl)oxetane (56)



A solution of LiHMDS (0.61 M in THF, 12.20 mL, 7.44 mmol) was added dropwise to a solution of sulfone **84a** (2.50 g, 6.75 mmol) in THF (240 mL) at 0 ºC and stirred for 1 h. Reaction quenched with sat. aq. NH_4Cl (150 mL) and extracted with CH_2Cl_2 (5 × 50 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (20% EtOAc/heptane) afforded

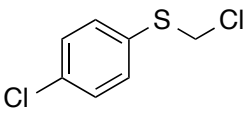
oxetane **56** (1.01 g, 75%) as a white solid; m.p. = 87–88 ºC. R_f = 0.23 (40% EtOAc/heptane). IR (film)/cm^{-1} 2996, 2980, 2908, 1583, 1478, 1445, 1301, 1288, 1266, 1144, 1084, 1026, 977, 901, 762, 730. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01–7.97 (2 H, m, 2 × Ar-H), 7.70 (1 H, dddd, *J* = 7.6, 7.4, 1.4, 1.2 Hz, Ar-H), 7.62–7.56 (2 H, m, 2 × Ar-H), 5.39 (1 H, dd, *J* = 7.1, 6.0 Hz, OCHS), 4.79 (1 H, ddd, *J* = 8.2, 8.0, 5.4 Hz, OCH*H*), 4.67–4.62 (1 H, m, OC*H*H), 3.16–3.07 (2 H, m, OCH_2CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5 (Ar-C_q), 134.2 (Ar-C), 129.5 (2 × Ar-C), 129.2 (2 × Ar-C), 94.1 (OCHS), 71.4 (OCH_2), 22.4 (OCH_2CH_2). HRMS (APCI) *m/z* Calculated for $C_9H_{11}O_3S^+$ $[M+H]^+$: 199.0423; Found: 199.0423 $[M+H]^+$, Δ 0 ppm.

1-Chloro-4-(methylsulfanyl)benzene (81b)[226]



Potassium carbonate (109.7 g, 794 mmol) was added to a solution of 4-chloro benzene thiol **80b** (95.0 g, 657 mmol) in acetone (1.1 L) followed by MeI (50.5 mL, 811 mmol) and the reaction stirred at rt for 4 h. The reaction was filtered through Celite® and the solvent removed under reduced pressure. The crude material was dissolved in diethyl ether (300 mL) and washed with 5% NaOH (3 × 150 mL). The combined aqueous layers were extracted with diethyl ether (2 × 100 mL) then the combined organics were washed with brine (100 mL), dried (Na_2SO_4) and solvent removed under reduced pressure to afford 4-chlorophenyl methyl sulfide **81b** (96.5 g, 93%) as a yellow liquid which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.25 (2 H, m, 2 × Ar-H), 7.22–7.18 (2 H, m, 2 × Ar-H), 2.49 (3 H, s, SCH_3). The observed data (^{1}H) was consistent with that reported in the literature.[226]

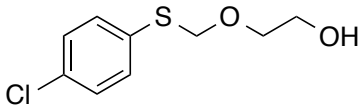
1-Chloro-4-[(chloromethyl)sulfanyl]benzene (82b)[229]



N-Chlorosuccinimide (9.26 g, 69.35 mmol) was added portionwise to a solution of 4-chloro phenyl methyl sulfide **81b** (10.00 g, 63.04 mmol) in carbon tetrachloride

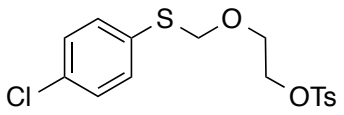
(65 mL). The reaction was stirred at rt for 19 h then filtered through a short pad of silica, eluting with CCl_4 (30 mL), and the solvent removed under reduced pressure to afford chloromethyl 4-chlorophenyl sulfide **82b** (11.52 g, 94%) as a colourless oil. R_f = 0.76 (30% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (2 H, d, *J* = 8.9 Hz, 2 × Ar-H), 7.36 (2 H, d, *J* = 8.9 Hz, 2 × Ar-H), 4.94 (2 H, s, SCH_2Cl). The observed data (^{1}H) was consistent with that reported in the literature.[229]

2-{[(4-Chlorophenyl)sulfanyl]methoxy}ethan-1-ol (72b)



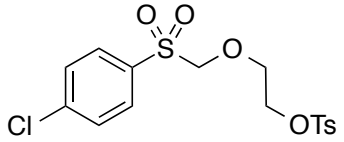
Sodium hydride (60% in mineral oil, 1.56 g, 39.01 mmol) was added to ethylene glycol (200 mL) at 0 ºC and stirred for 30 min. Sodium iodide (5.83 g, 38.90 mmol) was added followed by chloromethyl sulfide **82b** (6.26 g, 32.42 mmol) using DMF (5 mL) to aid transfer. The resulting solution was stirred at 0 ºC for 3 h then warmed to rt for 12 h. The reaction was quenched by the addition of sat. aq. NH_4Cl (200 mL) and the mixture extracted with EtOAc (4 × 75 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (50% EtOAc/hexane) afforded alcohol **72b** (5.27 g, 74%) as a colourless oil. R_f = 0.31 (50% EtOAc/hexane). IR (film)/cm^{-1} 3388 (OH), 2934, 2872, 1481, 1392, 1313, 1095, 1059, 1013, 816, 683. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (2 H, d, *J* = 8.6 Hz, 2 × Ar-H), 7.27 (2 H, d, *J* = 8.6 Hz, 2 × Ar-H), 5.01 (2 H, s, SCH_2O), 3.80–3.69 (4 H, m, OCH_2CH_2OH), 2.08 (1 H, s, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.9 (Ar-C_q), 133.0 (Ar-C_q), 131.6 (2 × Ar-C), 129.1 (2 × Ar-C), 76.4 (SCH_2O), 69.8 (OCH_2), 61.5 (OCH_2). HRMS (ESI) *m/z* Calculated for $C_9H_{11}{}^{35}ClNaO_2S^+$ $[M+Na]^+$: 241.0060; Found: 241.0060 $[M+Na]^+$, Δ 0 ppm.

2-{[(4-Chlorophenyl)sulfanyl]methoxy}ethyl-4-methylbenzene-1-sulfonate (83b)



Triethylamine (6.19 mL, 44.04 mmol) and trimethylamine hydrochloride (141 mg, 1.48 mmol) were added to a solution of alcohol **72b** (3.24 g, 14.82 mmol) in toluene (40 mL) at 0 ºC and stirred for 20 min. 4-Toluenesulfonyl chloride (5.65 g, 29.64 mmol) was added portionwise. The mixture was stirred at 0 ºC for 30 min then at rt for 2h. The reaction was quenched by the addition of sat. aq. $NaHCO_3$ (200 mL) and the mixture extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with sat. aq. NH_4Cl (100 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (40% EtOAc/hexane) afforded *p*-toluenesulfonate **83b** (5.39 g, 98%) as a colourless oil. R_f = 0.24 (20% EtOAc/hexane). IR (film)/cm^{-1} 2920, 1601, 1482, 1358, 1180, 1095, 1093, 1017, 922, 820, 776, 668, 559. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (2 H, d, *J* = 8.3 Hz, 2 × Ts-H), 7.38–7.31 (4 H, m, 2 × Ts-H + 2 × Ar-H), 7.26–7.20 (2 H, m, 2 × Ar-H), 4.92 (2 H, s, SCH_2O), 4.23–4.19 (2 H, m, $TsOCH_2$), 3.84–3.80 (2 H, m, CH_2OCH_2), 2.45 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9 (Ts-C_q), 133.7 (Ar-C_q), 133.0 (Ts-C_q), 132.8 (Ar-C_q), 131.7 (2 × Ar-C), 129.8 (2 × Ts-C), 129.0 (2 × Ar-C), 127.9 (2 × Ts-C), 76.3 (SCH_2O), 68.6 (SCH_2OCH_2), 65.6 ($TsOCH_2$), 21.7 (CH_3). HRMS (ESI) *m/z* Calculated for $C_{16}H_{21}{}^{35}ClNO_4S_2{}^+$ $[M+NH_4]^+$: 390.0595; Found: 390.0595 $[M+NH_4]^+$, Δ 0 ppm.

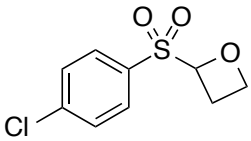
1-Chloro-4-({2-[(4-methylbenzenesulfonyl)oxy]ethoxy}methanesulfonyl)benzene (84b)



meta-Chloroperbenzoic acid (7.50 g 43.46 mmol) was added to a solution of sulfide **83b** (5.39 g, 14.46 mmol) in dichloromethane (75 mL) at 0 ºC and the mixture stirred at 0 ºC for 5 h. The reaction was quenched with sat. aq. Na_2SO_3 (125 mL) and extracted with dichloromethane (6 × 35 mL). The combined organic layers were washed with 1 M NaOH (3 × 25 mL) and sat. aq. NH_4Cl (100 mL) then dried ($MgSO_4$), filtered and the solvent

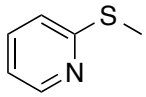
removed under reduced pressure. Purification by flash chromatography (50% EtOAc/hexane) afforded sulfone **84b** (5.58 g, 95%) as a white solid; m.p. = 87–88 ºC. R_f = 0.19 (40% EtOAc/hexane). IR (film)/cm^{-1} 3130, 2892, 1578, 1474, 1397, 1357, 1323, 1291, 1135, 1108, 1040, 1017, 948, 804, 728, 701, 686. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (2 H, d, *J* = 9.0 Hz, 2 × Ts-H), 7.77 (2 H, d, *J* = 7.8 Hz, 2 × Ar-H), 7.54 (2 H, d, *J* = 9.0 Hz, 2 × Ts-H), 7.35 (2 H, d, *J* = 7.8 Hz, 2 × Ar-H), 4.53 (2 H, s, SCH_2O), 4.18–4.10 (4 H, m, OCH_2CH_2), 2.46 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1 (Ts-C_q), 141.1 (Ar-C_q), 135.2 (Ts-C_q), 132.6 (Ar-C_q), 130.4 (2 × Ar-C), 129.9 (2 × Ts-C), 129.6 (2 × Ar-C), 127.9 (2 × Ts-C), 86.0 (SCH_2O), 70.6 (SCH_2OCH_2), 68.4 ($TsOCH_2$), 21.7 (CH_3). HRMS (ESI) *m/z* Calculated for $C_{16}H_{17}{}^{35}ClNaO_6S_2^+$ $[M+Na]^+$: 427.0047; Found: 427.0044 $[M+Na]^+$, Δ 0.7 ppm.

2-(4-Chlorobenzenesulfonyl)oxetane (57)



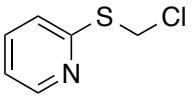
A solution of LiHMDS (0.61 M in THF, 4.45 mL, 2.72 mmol) was added dropwise to a solution of sulfone **84b** (0.99 g, 2.45 mmol) in THF (100 mL) at 0 ºC and stirred for 1 h. Reaction quenched with sat. aq. NH_4Cl (100 mL) and extracted with $CHCl_3$ (8 × 20 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (40% EtOAc/hexane) afforded oxetane **57** (0.48 g, 84%) as a white solid; m.p. = 91–93 ºC. R_f = 0.36 (40% EtOAc/hexane). IR (film)/cm^{-1} 3092, 2977, 2927, 1654, 1581, 1474, 1393, 1312, 1273, 1144, 1087, 1010, 976, 940, 897, 843, 712. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (2 H, d, *J* = 8.6 Hz, 2 × Ar-H), 7.56 (2 H, d, *J* = 8.6 Hz, 2 × Ar-H), 5.37 (1 H, dd, *J* = 7.6, 5.4 Hz, OCHS), 4.83–4.77 (1 H, m, OCH*H*), 4.66 (1 H, ddd, *J* = 8.5, 6.1, 5.4 Hz, OC*H*H), 3.18–3.05 (2 H, m, OCH_2CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2 (Ar-C_q), 133.7 (Ar-C_q), 130.9 (2 × Ar-C), 129.5 (2 × Ar-C), 94.0 (OCHS), 71.5 (OCH_2), 22.2 (OCH_2CH_2). HRMS (APCl) *m/z* Calculated for $C_9H_{10}{}^{35}ClO_3S^+$ $[M+H]^+$: 233.0034; Found: 233.0034 $[M+H]^+$, Δ 0 ppm.

2-(Methylsulfanyl)pyridine (81c)[230]



Potassium carbonate (4.17 g, 30.18 mmol) was added to a solution of pyridine-2-thiol **80c** (3.05 g, 27.44 mmol) in acetone (43 mL) followed by MeI (1.80 mL, 28.81 mmol) and the reaction stirred at rt for 26 h. The reaction was filtered through Celite® and the solvent removed under reduced pressure. The crude material was dissolved in diethyl ether (30 mL) and washed with 2 M NaOH (3 × 20 mL). The combined aqueous layers were extracted with diethyl ether (2 × 20 mL) then the combined organics were washed with brine (20 mL), dried (Na_2SO_4) and solvent removed under reduced pressure to afford methyl sulfide **81c** (3.01 g, 88%) as a yellow oil, which was used without further purification. R_f = 0.68 (50% EtOAc/heptane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46–8.43 (1 H, m, Py-H), 7.47 (1 H, ddd, *J* = 8.1, 7.4, 1.9 Hz, Py-H), 7.19–7.16 (1 H, m, Py-H), 6.97 (1 H, ddd, *J* = 7.4, 5.0, 1.0 Hz, Py-H), 2.57 (3 H, s, SCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0 (Py-C_q), 149.4 (Py-C), 135.7 (Py-C), 121.5 (Py-C), 119.0 (Py-C), 13.2 (SCH_3). The observed data (^{1}H, ^{13}C) was consistent with that reported in the literature.[230]

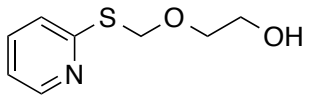
2-[(Chloromethly)sulfanyl]pyridine (82c)[231]



Sodium hydride (60% in mineral oil, 0.79 g, 19.76 mmol) was added to a solution of 2-mercaptopyridine **81c** (2.0 g, 17.99 mmol) in DMF (50 mL) at –5 ºC and stirred for 10 min. A solution of chloroiodomethane (1.96 mL, 26.91 mmol) in DMF (7 mL) was added in one portion and stirred for 1 h 45 min at rt. The reaction was quenched by the addition of sat. aq. NH_4Cl (100 mL) and diluted with EtOAc (30 mL) then extracted with EtOAc (4 × 40 mL). The combined organic layers were washed with H_2O (3 × 20 mL) and brine (20 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to give an orange oil. The crude product consisting of a 9:1 mixture of pyridine **82c** and bis(pyridine-2-ylthio)methane (2.60 g, 91%, 9:1) was used without further purification. R_f = 0.80 (40% EtOAc/heptane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56–8.54 (1 H, m, Py-H), 7.58 (1 H, ddd, *J* = 8.0, 7.4, 1.9 Hz, Py-H), 7.27 (1 H, ddd, *J* = 8.0, 1.0,

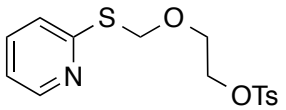
0.9 Hz, Py-H), 7.11 (1 H, ddd, *J* = 7.4, 4.9, 1.0 Hz, Py-H), 5.38 (2 H, s, SCH_2Cl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7 (Py-C_q), 149.9 (Py-C), 136.6 (Py-C), 122.9 (Py-C), 120.8 (Py-C), 45.3 (SCH_2Cl). The observed data (^1H) was consistent with that reported in the literature.[231]

2-[(Pyridin-2-ylsulfanyl)methoxy]ethan-1-ol (72c)



Sodium hydride (60% in mineral oil, 0.55 g, 13.78 mmol) was added to ethylene glycol (120 mL) at 0 ºC and stirred for 55 min. Sodium iodide (2.06 g, 13.78 mmol) was added followed by chloromethyl sulfide **82c** (2.00 g, 12.53 mmol) using ethylene glycol (1 mL) to aid transfer. The resulting solution was stirred at 0 ºC for 25 min then warmed to rt for 19 h 20 min. Water (150 mL) was added to the reaction and the product was extracted with EtOAc (10 × 35 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (0–80% EtOAc/heptane) afforded alcohol **72c** (1.46 g, 63%) as a colourless oil. R_f = 0.59 (80% EtOAc/heptane). IR (film)/cm^{-1} 3344 (OH), 2925, 1656, 1577, 1454, 1416, 1281, 1102, 1060, 908, 824, 758, 721, 678. ^1H NMR (400 MHz, $CDCl_3$) δ 8.46–8.44 (1 H, m, Py-H), 7.52 (1 H, ddd, *J* = 8.0, 7.3, 1.9 Hz, Py-H), 7.29 (1 H, ddd, *J* = 8.0, 1.0, 0.9 Hz, Py-H), 7.04 (1 H, ddd, *J* = 7.3, 5.0, 1.0 Hz, Py-H), 5.38 (2 H, s, SCH_2O), 3.77–3.72 (4 H, m, OCH_2CH_2OH), 2.95 (1 H, br s, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4 (Py-C_q), 149.5 (Py-C), 136.5 (Py-C), 123.2 (Py-C), 120.4 (Py-C), 71.9 (SCH_2O), 70.5 (OCH_2), 61.6 (OCH_2). HRMS (ESI) *m/z* Calculated for $C_8H_{12}NO_2S^+$ $[M+H]^+$: 186.0583; Found: 186.0582 $[M+H]^+$, Δ 0.5 ppm.

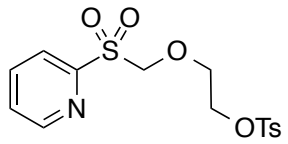
2-[(Pyridin-2-ylsulfanyl)methoxy]ethyl-4-methylbenzene-1-sulfonate (83c)



Triethylamine (4.06 mL, 28.89 mmol) and trimethylamine hydrochloride (93 mg, 0.97 mmol) were added to a solution of alcohol **72c** (0.90 g, 4.86 mmol) in toluene (30 mL) at 0 ºC and stirred for 30 min. A solution of 4-toluenesulfonyl chloride (3.71 g,

19.46 mmol) in toluene (10 mL) was added and the mixture was stirred at 0 ºC for 35 min then at rt for 2 h 35 min. Water (50 mL) was added to the reaction and the product was extracted with EtOAc (7 × 30 mL). The combined organic layers were washed with H_2O (30 mL) and brine (30 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (0–40% EtOAc/heptane) afforded *p*-toluenesulfonate **83c** (1.57 g, 95%) as a colourless oil. R_f = 0.36 (40% EtOAc/heptane). IR (film)/cm^{-1} 2924, 1610, 1533, 1494, 1453, 1419, 1353, 1281, 1216, 1172, 1119, 1032, 1009, 916, 816, 767, 680. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43–8.41 (1 H, m, Py-H), 7.76 (2 H, d, *J* = 8.3 Hz, 2 × Ts-H), 7.50 (1 H, ddd, *J* = 8.0, 7.4, 1.9 Hz, Py-H), 7.31 (2 H, d, *J* = 8.3 Hz, 2 × Ts-H), 7.24 (1 H, d, *J* = 8.0 Hz, Py-H), 7.02 (1 H, ddd, *J* = 7.4, 4.9, 1.0 Hz, Py-H), 5.32 (2 H, s, SCH_2O), 4.18–4.16 (2 H, m, OCH_2CH_2), 3.79–3.76 (2 H, m, OCH_2CH_2), 2.42 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2 (Py-C_q), 149.4 (Py-C), 144.7 (Ts-C_q), 136.4 (Py-C), 133.0 (Ts-C_q), 129.7 (2 × Ts-C), 127.8 (2 × Ts-C), 122.8 (Py-C), 120.3 (Py-C), 71.8 (SCH_2O), 68.7 (OCH_2CH_2), 66.2 (OCH_2CH_2), 21.5 (CH_3). HRMS (NSI) *m/z* Calculated for $C_{15}H_{18}NO_4S_2^+$ $[M+H]^+$: 340.0672; Found: 340.0674 $[M+H]^+$, Δ 0.6 ppm.

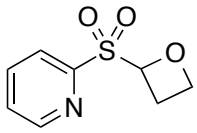
2-({2-[(4-Methylbenzenesulfonyl)oxy]ethoxy}methanesulfonyl)pyridine (84c)



meta-Chloroperbenzoic acid (70%, 3.05 g 12.37 mmol) was added to a solution of sulfide **83c** (1.40 g, 4.12 mmol) in dichloromethane (25 mL) at 0 ºC and the mixture stirred at 0 ºC for 2 h then at rt for a further 2 h 30 min. The reaction was quenched with sat. aq. Na_2SO_3 (20 mL) and extracted with dichloromethane (5 × 20 mL). The combined organic layers were washed with 2 M NaOH (3 × 10 mL) and sat. aq. NH_4Cl (20 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (50% EtOAc/heptane) afforded sulfone **84c** (1.31 g, 86%) as a white solid; m.p. = 95–97 ºC. R_f = 0.46 (40% EtOAc/heptane). IR (film)/cm^{-1} 3069, 1598, 1454, 1431, 1358, 1323, 1238, 1173, 1127, 1104, 1032, 990, 926, 836, 824, 808, 736, 663. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79–8.77 (1 H, m, Py-H), 8.11 (1 H, d, *J* = 7.9 Hz, Py-H), 8.00 (1 H, ddd, *J* = 7.9, 7.7, 1.7 Hz, Py-H), 7.73 (2 H, d, *J* = 8.3 Hz, 2 × Ts-H), 7.59 (1 H,

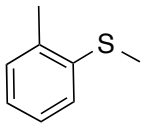
ddd, J = 7.7, 4.7, 1.3 Hz, Py-H), 7.33 (2 H, d, J = 8.3 Hz, Ts-H), 4.87 (2 H, s, SCH_2O), 4.10–4.08 (2 H, m, CH_2OCH_2), 4.05–4.03 (2 H, m, $TsOCH_2$), 2.45 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6 (Py-C_q), 150.4 (Py-C), 145.0 (Ts-C_q), 138.2 (Py-C), 132.7 (Ts-C_q), 129.8 (2 × Ts-C), 127.8 (2 × Ts-C), 127.6 (Py-C), 123.8 (Py-C), 82.9 (SCH_2O), 70.5 ($TsOCH_2$), 68.4 (CH_2OCH_2), 21.6 (CH_3). HRMS (ESI) *m/z* Calculated for $C_{15}H_{18}NO_6S_2^+$ $[M+H]^+$: 372.0570; Found: 372.0576 $[M+H]^+$, Δ 1.6 ppm.

2-(Oxetane-2-sulfonyl)pyridine (58)



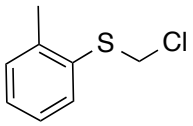
A solution of LiHMDS (0.61 M in THF, 5.67 mL, 3.46 mmol) was added dropwise to a solution of sulfone **84c** (1.07 g, 2.88 mmol) in THF (90 mL) at 0 ºC and stirred for 1 h. Reaction quenched with sat. aq. NH_4Cl (75 mL) and extracted with CH_2Cl_2 (5 × 20 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (40% EtOAc/heptane) afforded oxetane **58** (0.47 g, 81%) as a white solid; m.p. = 64–65 ºC. R_f = 0.16 (40% EtOAc/heptane). IR (film)/cm^{-1} 3101, 3051, 2974, 2904, 1580, 1426, 1415, 1311, 1272, 1230, 1161, 1108, 1040, 1024, 991, 906, 792, 734, 682. ^1H NMR (400 MHz, $CDCl_3$) δ 8.77–8.75 (1 H, m, Py-H), 8.17 (1 H, d, J = 7.8 Hz, Py-H), 7.97 (1 H, ddd, J = 7.8, 7.7, 1.8 Hz, Py-H), 7.56 (1 H, ddd, J = 7.7, 4.7, 1.2 Hz, Py-H), 5.96 (1 H, dd, J = 8.0, 5.2 Hz, OCHS), 4.93–4.87 (1 H, m, OCH*H*), 4.69 (1 H, ddd, J = 8.6, 5.7, 5.4 Hz, OC*H*H), 3.31–3.15 (2 H, OCH_2CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1 (Py-C_q), 150.4 (Py-C), 138.0 (Py-C), 127.6 (Py-C), 124.3 (Py-C), 91.9 (OCHS), 72.0 (OCH_2), 21.9 (OCH_2CH_2). HRMS (ESI) *m/z* Calculated for $C_8H_{10}NO_3S^+$ $[M+H]^+$: 200.0386; Found: 200.0389 $[M+H]^+$, Δ 1.5 ppm.

1-Methyl-2-(methylsulfanyl)benzene (81d)[232]



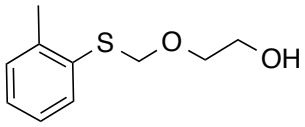
Potassium carbonate (3.07 g, 22.21 mmol) was added to a solution of *o*-tolyl thiol (2.40 mL, 20.36 mmol) in acetone (25 mL) followed by MeI (1.3 mL, 21.20 mmol) and the reaction stirred at rt for 18 h. The reaction was filtered through Celite® and the solvent removed under reduced pressure. The crude material was dissolved in diethyl ether (30 mL) and washed with 1 M NaOH (3 × 20 mL). The combined aqueous layers were extracted with diethyl ether (30 mL) then the combined organics were washed with brine (20 mL), dried (Na_2SO_4), filtered and solvent removed under reduced pressure to afford sulfide **81d** (2.66 g, 95%) as a yellow oil which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.16 (3 H, m, 3 × Ar-H), 7.12–7.07 (1 H, m, Ar-H), 2.50 (3 H, s, CH_3), 2.38 (3 H, s, CH_3). The observed data (^{1}H) is consistent with that reported in the literature.[232]

1-[(Chloromethyl)sulfanyl]-2-methylbenzene (82d)



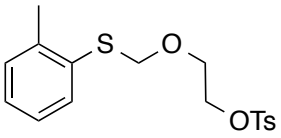
N-Chlorosuccinimide (2.83 g, 21.19 mmol) was added portionwise to a solution of sulfide **81d** (2.66 g, 19.24 mmol) in dichloroethane (32 mL). The reaction was stirred at rt for 17 h then filtered through a short pad of silica, eluting with dichloromethane (50 mL) and the solvent removed under reduced pressure to afford chloromethyl sulfide **82d** as a yellow oil (3.03 g, 90%). Sulfide **82d** was taken on without further purification. R_f = 0.70 (40% EtOAc/hexane). IR (film)/cm^{-1} 3061, 3014, 1718, 1589, 1470, 1455, 1380, 1278, 1227, 1149, 1062, 1046, 908, 850, 739, 677. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61–7.57 (1 H, m, Ar-H), 7.30–7.25 (3 H, m, 3 × Ar-H), 5.00 (2 H, s, SCH_2Cl), 2.46 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0 (C_q), 132.5 (C_q), 130.5 (2 × Ar-C), 127.9 (Ar-C), 126.8 (Ar-C), 50.3 (SCH_2Cl), 20.5 (CH_3). HRMS (EI) *m/z* Calculated for $C_8H_9{}^{35}ClS$ [M]: 172.0113; Found: 172.0121 [M], Δ 4.7 ppm.

2-{[(2-Methylphenyl)sulfanyl]methoxy}ethan-1-ol (72d)



Sodium hydride (60% in mineral oil, 0.64 g, 16.00 mmol) was added to ethylene glycol (150 mL) at 0 ºC and stirred for 1 h. Sodium iodide (2.40 g, 16.01 mmol) was added followed by chloromethyl sulfide **82d** (2.51 g, 14.54 mmol). DMF (2 mL) was added to aid solubility. The resulting solution was stirred at 0 ºC for 1 h then warmed to rt for 18 h. Water (100 mL) was added and the product was extracted with ethyl acetate (10 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (30% EtOAc/hexane) afforded alcohol **72d** (1.91 g, 66%) as a colourless oil. R_f = 0.19 (30% EtOAc/hexane). IR (film)/cm^{-1} 3389 (OH), 3058, 2928, 1589, 1470, 1456, 1379, 1308, 1265, 1094, 1047, 1016, 888, 824, 735, 696, 668. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.54 (1 H, m, Ar-H), 7.21–7.12 (3 H, m, 3 × Ar-H), 5.05 (2 H, s, SCH_2O), 3.80–3.70 (4 H, m, OCH_2CH_2OH), 2.41 (3 H, s, CH_3), 2.24–2.15 (1 H, br m, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1 (C_q), 134.8 (C_q), 130.1 (Ar-C), 129.8 (Ar-C), 126.7 (Ar-C), 126.6 (Ar-C), 75.5 (SCH_2O), 69.9 (OCH_2), 61.5 (OCH_2), 20.5 (CH_3). HRMS (NSI) *m/z* Calculated for $C_{10}H_{18}O_2NS^+$ $[M+NH_4]^+$: 216.1053; Found: 216.1054 $[M+NH_4]^+$, Δ 0.5 ppm.

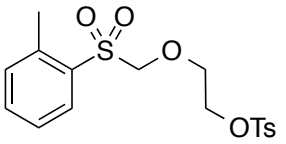
2-{[(2-Methylphenyl)sulfanyl]methoxy}ethyl-4-methylbenzene-1-sulfonate (83d)



Triethylamine (3.45 mL, 24.75 mmol) and trimethylamine hydrochloride (79 mg, 0.83 mmol) were added to a solution of sulfide **72d** (1.63 g, 8.22 mmol) in toluene (30 mL) at 0 ºC and stirred for 30 min. 4-Toluenesulfonyl chloride (3.14 g, 16.47 mmol) was added portionwise. The mixture was stirred at 0 ºC for 30 min then warmed to rt and stirred for a further 1 h 30 min. Water (75 mL) was added to the reaction and the product was extracted with EtOAc (5 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (20% EtOAc/hexane) afforded *p*-toluenesulfonate **83d** (2.65 g, 91%) as a

white solid; m.p. 46–47 ºC. R_f = 0.27 (20% EtOAc/hexane). IR (film)/cm^{-1} 2919, 2875, 1596, 1468, 1424, 1358, 1310, 1278, 1175, 1122, 1088, 1016, 922, 817, 780, 758, 696, 662. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (2 H, d, *J* = 8.2 Hz, 2 × Ts-H), 7.49–7.45 (1 H, m, Tol-H), 7.32 (2 H, d, *J* = 8.2 Hz, 2 × Ts-H), 7.19–7.12 (3 H, m, 3 × Tol-H), 4.95 (2 H, s, SCH_2O), 4.22–4.18 (2 H, m, $TsOCH_2$), 3.83–3.79 (2 H, m, CH_2OCH_2), 2.45 (3 H, s, Ts-CH_3), 2.37 (3 H, s, Tol-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8 (Ts-C_q), 137.9 (Tol-C_q), 134.7 (Tol-C_q), 132.8 (Ts-C_q), 130.0 (Tol-C), 129.7 (2 × Ts-C + Tol-C), 127.8 (2 × Ts-C), 126.7 (Tol-C), 126.6 (Tol-C), 75.4 (SCH_2O), 68.7 (OCH_2), 65.7 (OCH_2), 21.6 (Ts-CH_3), 20.5 (Tol-CH_3). HRMS (ES) *m/z* Calculated for $C_{17}H_{20}NaO_4S_2$ [M+Na]: 375.0701; Found: 375.0725 [M+Na], Δ 6.4 ppm.

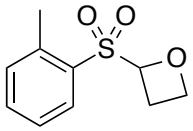
1-Methyl-2-({2-[(4-methylbenzenesulfonyl)oxy]ethoxy}methanesulfonyl)benzene (84d)



meta-Chloroperbenzoic acid (2.21 g, 12.81 mmol) was added to a solution of sulfide **83d** (1.55 g, 4.39 mmol) in dichloromethane (60 mL) at 0 ºC and the mixture stirred at 0 ºC for 1 h then stirred at rt for 3 h 45 min. The reaction was quenched with sat. aq. Na_2SO_3 (100 mL) and extracted with dichloromethane (5 × 20 mL). The combined organic layers were washed with 1 M NaOH (2 × 15 mL) and sat. aq. NH_4Cl (25 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (40% EtOAc/hexane) afforded sulfone **84d** (1.67 g, 99%) as a white solid; m.p. 78–79 ºC. R_f = 0.17 (40% EtOAc/hexane). IR (film)/cm^{-1} 2925, 1597, 1574, 1457, 1357, 1319, 1289, 1247, 1235, 1189, 1174, 1120, 1096, 1080, 1021, 950, 844, 813, 707. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (1 H, dd, *J* = 8.0, 1.3 Hz, Tol-H), 7.74 (2 H, d, *J* = 8.3 Hz, 2 × Ts-H), 7.58–7.53 (1 H, m, Tol-H), 7.41–7.31 (4 H, m, 2 × Ts-H + 2 × Tol-H), 4.57 (2 H, s, SCH_2O), 4.14–4.10 (2 H, m, $TsOCH_2$), 4.07–4.03 (2 H, m, CH_2OCH_2), 2.67 (3 H, s, Tol-CH_3), 2.45 (3 H, s, Ts-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0 (Ts-C_q), 138.8 (Tol-C_q), 135.3 (Tol-C_q), 134.2 (Tol-C), 132.8 (Tol-C), 132.7 (Ts-C_q), 131.1 (Tol-C), 129.9 (2 × Ts-C), 127.9 (2 × Ts-C), 126.7 (Tol-C), 86.0 (SCH_2O),

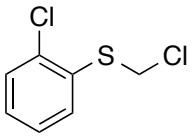
70.9 (OCH_2), 68.4 (OCH_2), 21.7 (Ts-CH_3), 20.5 (Tol-CH_3). HRMS (NSI) *m/z* Calculated for $C_{17}H_{24}NO_6S_2^+$ $[M+NH_4]^+$: 402.1040; Found: 402.1029 $[M+NH_4]^+$, Δ 2.7 ppm.

2-(2-Methylbenzenesulfonyl)oxetane (87)



A solution of LiHMDS (0.61 M in THF, 3.52 mL, 2.15 mmol) was added dropwise to a solution of sulfone **84d** (0.75 g, 1.95 mmol) in THF (60 mL) at 0 ºC and stirred for 1 h 30 min. The reaction was quenched with sat. aq. NH_4Cl (30 mL) and extracted with CH_2Cl_2 (5 × 20 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (40% EtOAc/hexane) afforded oxetane **87** (0.39 g, 95%) as a colourless oil. R_f = 0.36 (40% EtOAc/hexane). IR (film)/cm^{-1} 2973, 2901, 1595, 1568, 1471, 1444, 1309, 1290, 1270, 1232, 1198, 1148, 1128, 1065, 1026, 936, 908, 840, 763, 716, 694, 665. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (1 H, dd, *J* = 7.6, 1.5 Hz, Ar-H), 7.53 (1 H, ddd, *J* = 7.6, 7.5, 1.4 Hz, Ar-H), 7.41–7.32 (2 H, m, 2 × Ar-H), 5.46 (1 H, dd, *J* = 7.7, 5.5 Hz, OCHS), 4.88–4.80 (1 H, m, OCH*H*), 4.67 (1 H, ddd, *J* = 8.3, 6.1, 5.6 Hz, OC*H*H), 3.22–3.07 (2 H, m, OCH_2CH_2), 2.72 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0 (C_q), 134.1 (Ar-C), 133.8 (C_q), 132.8 (Ar-C), 131.5 (Ar-C), 126.5 (Ar-C), 94.2 (OCHS), 71.6 (OCH_2), 22.4 (OCH_2CH_2), 20.9 (CH_3). HRMS (APCI) *m/z* Calculated for $C_{10}H_{13}O_3S^+$ $[M+H]^+$: 213.0580; Found: 213.0579 $[M+H]^+$, Δ 0.5 ppm.

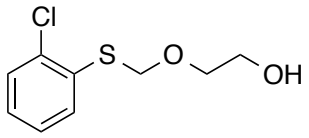
2-Chlorophenyl chloromethyl sulfide (82e)



N-Chlorosuccinimide (4.55 g, 34.07 mmol) was added portionwise to a solution of 2-chlorothioanisole (4.10 mL, 31.01 mmol) in dichloroethane (50 mL). The reaction was stirred at rt for 70 h then filtered through a short pad of silica, eluting with CH_2Cl_2 (50 mL). The solvent was removed under reduced pressure to afford chloromethyl sulfide **82e** (6.00 g, 99%) as a yellow oil, which was used without further purification. R_f = 0.10

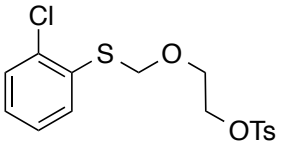
(40% EtOAc/hexane). IR (film)/cm^{-1} 1576, 1452, 1432, 1226, 1117, 1035, 935, 851, 736, 663. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (1 H, dd, *J* = 7.8, 1.6 Hz, Ar-H), 7.44 (1 H, dd, *J* = 7.8, 1.5 Hz, Ar-H), 7.32 (1 H, ddd, *J* = 9.1, 7.8, 1.5 Hz, Ar-H), 7.25 (1 H, ddd, *J* = 9.1, 7.8, 1.6 Hz, Ar-H), 5.02 (2 H, s, SCH_2Cl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.5 (C_q), 132.4 (C_q), 130.4 (Ar-C), 130.0 (Ar-C), 128.5 (Ar-C), 127.4 (Ar-C), 48.3 (SCH_2Cl). HRMS (EI) *m/z* Calculated $C_7H_6S^{35}Cl_2$ [M]: 191.9567; Found 191.9572 [M], Δ 0.5 ppm.

2-(((2-Chlorophenyl)thio)methoxy)ethanol (72e)



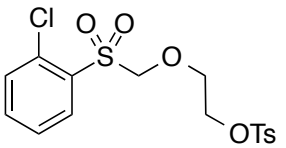
Sodium hydride (60% in mineral oil, 1.60 g, 40.01 mmol) was added to ethylene glycol (350 mL) at 0 ºC and stirred for 1 h 30 min. Sodium iodide (6.01 g, 40.10 mmol) was added followed by sulfide **82e** (6.88 g, 35.63 mmol). The resulting solution was stirred at 0 ºC for 2 h then warmed to rt for 17 h. Water (175 mL) was added and the product was extracted with ethyl acetate (10 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (30% EtOAc/hexane) afforded alcohol **72e** (5.60 g, 71%) as a pale yellow oil. R_f = 0.42 (100% EtOAc). IR (film)/cm^{-1} 3380 (OH), 2927, 1575, 1454, 1431, 1309, 1253, 1100, 1055, 1033, 1018, 887, 824, 745, 656. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (1 H, dd, *J* = 7.8, 1.6 Hz, Ar-H), 7.38 (1 H, dd, *J* = 7.8, 1.5 Hz, Ar-H), 7.23 (1 H, ddd, *J* = 9.1, 7.8, 1.5 Hz, Ar-H), 7.16 (1 H, ddd, *J* = 9.1, 7.8, 1.6 Hz, Ar-H), 5.10 (2 H, s, SCH_2O), 3.75 (4 H, br s, SCH_2CH_2OH), 2.05 (1 H, br s, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.8 (C_q), 134.0 (C_q), 130.2 (Ar-C), 129.7 (Ar-C), 127.5 (Ar-C), 127.3 (Ar-C), 74.8 (SCH_2O), 70.0 (OCH_2), 61.5 (OCH_2). HRMS (EI) *m/z* Calculated for $C_9H_{15}NO_2S^{35}Cl$ [M+NH_4]: 236.0512; Found: 236.0521 [M+NH_4], Δ 3.8 ppm.

2-{[(2-Chlorophenyl)sulfanyl]methoxy}ethyl-4-methylbenzene-1-sulfonate (83e)



Triethylamine (9.59 mL, 68.24 mmol) and trimethylamine hydrochloride (0.22 g, 2.29 mmol) were added to a solution of sulfide **72e** (5.02 g, 22.93 mmol) in toluene (100 mL) at 0 ºC and stirred for 1 h. 4-Toluenesulfonyl chloride (8.74 g, 45.87 mmol) was added portionwise. The mixture was stirred at 0 ºC for 50 min then allowed to warm to rt and stirred for a further 1 h 30 min. Water (75 mL) was added to the reaction and the product was extracted with EtOAc (5 × 25 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (20% EtOAc/hexane) afforded *p*-toluenesulfonate **83e** (8.03 g, 94%) as a white solid; m.p. = 40–42 ºC. R_f = 0.15 (20% EtOAc/hexane). IR (film)/cm^{-1} 3069, 2876, 1596, 1573, 1450, 1357, 1314, 1230, 1175, 1123, 1085, 1018, 924, 835, 759, 730, 661. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (2 H, d, *J* = 8.0 Hz, 2 × Ts-H), 7.55 (1 H, dd, *J* = 7.9, 1.7 Hz, Ar-H), 7.37 (1 H, dd, *J* = 7.9, 1.6 Hz, Ar-H), 7.32 (2 H, d, *J* = 8.0 Hz, 2 × Ts-H), 7.25–7.14 (2 H, m, 2 × Ar-H), 5.00 (2 H, s, SCH_2O), 4.23–4.18 (2 H, m, $TsOCH_2$), 3.80–3.80 (2 H, m, CH_2OCH_2), 2.45 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9 (C_q), 134.6 (C_q), 133.8 (C_q), 132.9 (C_q), 130.3 (Ar-C), 129.8 (2 × Ts-C), 129.6 (Ar-C), 127.9 (2 × Ts-C), 127.5 (Ar-C), 127.4 (Ar-C), 74.6 (SCH_2O), 68.6 (OCH_2), 65.8 (OCH_2), 21.6 (CH_3). HRMS (ES) *m/z* Calculated $C_{18}H_{21}NO_4S_2{}^{35}Cl$ [M+H+CH_3CN]: 414.0601; Found: 414.0605 [M+H+CH_3CN], Δ 1.0 ppm.

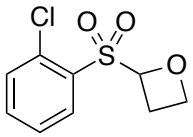
2-(((2-Chlorophenyl)sulfonyl)methoxy)ethyl-4-methylbenzenesulfonate (84e)



meta-Chloroperbenzoic acid (70%, 10.23 g, 41.52 mmol) was added to a solution of sulfide **83e** (5.16 g, 13.84 mmol) in dichloromethane (185 mL) at 0 ºC and the mixture stirred at 0 ºC for 2 h 30 min, then warmed to rt and stirred for a further 1 h. Another equivalent of *m*CPBA was added (3.30 g) and the reaction stirred at rt for 2 h. The

reaction was quenched with sat. aq. Na_2SO_3 (50 mL) and extracted with dichloromethane (5 × 25 mL). The combined organic layers were washed with 1 M NaOH (2 × 20 mL) and sat. aq. NH_4Cl (20 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (40% EtOAc/hexane) afforded sulfone **84e** (5.03 g, 90%) as a white solid; m.p = 113–114 ºC. R_f = 0.16 (40% EtOAc/hexane). IR (film)/cm^{-1} 2996, 1597, 1575, 1429, 1373, 1358, 1325, 1296, 1250, 1190, 1175, 1126, 1093, 1036, 915, 844, 769, 728, 663. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (1 H, dd, *J* = 7.9, 1.6 Hz, Ar-H), 7.72 (2 H, d, *J* = 8.1 Hz, 2 × Ts-H), 7.64–7.55 (2 H, m, 2 × Ar-H), 7.52–7.47 (1 H, m, Ar-H), 7.33 (2 H, d, *J* = 8.1 Hz, 2 × Ts-H), 4.83 (2 H, s, SCH_2O), 4.11–4.07 (2 H, m, OCH_2CH_2), 4.06–4.03 (2 H, m, OCH_2CH_2), 2.45 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0 (Ts-C_q), 135.3 (Ar-C), 134.6 (Ar-C_q), 132.9 (Ar-C), 132.9 (Ts-C_q), 132.6 (Ar-C_q), 131.8 (Ar-C), 129.9 (2 × Ts-C), 127.9 (2 × Ts-C), 127.6 (Ar-C), 84.7 (SCH_2O), 70.8 (OCH_2), 68.4 (OCH_2), 21.7 (CH_3). HRMS (ES) *m/z* Calculated $C_{16}H_{18}O_6S_2{}^{35}Cl$ [M+H]: 405.0233; Found 405.0237 [M+H], Δ 1.0 ppm.

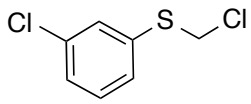
2-((2-Chlorophenyl)sulfonyl)oxetane (88)



A solution of LiHMDS (0.61 M in THF, 4.45 mL, 2.71 mmol) was added dropwise to a solution of sulfone **84e** (1.00 g, 2.47 mmol) in THF (75 mL) at 0 ºC and stirred for 1 h 30 min. The reaction was quenched with sat. aq. NH_4Cl (40 mL) and extracted with CH_2Cl_2 (5 × 20 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (40% EtOAc/hexane) afforded oxetane **88** (0.50 g, 88%) as a white solid; m.p = 70–71 ºC. R_f = 0.24 (40% EtOAc/hexane). IR (film)/cm^{-1} 3065, 2918, 1574, 1435, 1311, 1274, 1146, 1107, 1066, 1028, 980, 894, 748, 710, 684. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (1 H, dd, *J* = 7.9, 1.5 Hz, Ar-H), 7.63–7.53 (2 H, m, 2 × Ar-H), 7.52–7.47 (1 H, m, Ar-H), 5.95 (1 H, dd, *J* = 8.1, 5.1 Hz, OCHS), 5.01–4.93 (1 H, m, OCH*H*), 4.71 (1 H, ddd, *J* = 8.5, 5.8, 5.4 Hz, OC*H*H), 3.32–3.15 (2 H, m, OCH_2CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.2 (Ar-C), 133.5 (C_q), 133.4 (Ar-C), 133.2 (C_q), 131.9 (Ar-C), 127.4 (Ar-C), 92.9 (OCHS),

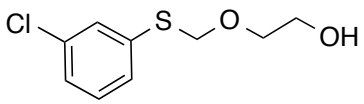
72.3 (OCH_2), 21.9 (OCH_2CH_2). HRMS (CI) *m/z* Calculated $C_9H_{10}O_3S^{35}Cl$ [M+H]: 233.0039; Found: 233.0043 [M+H], Δ 1.7 ppm.

1-Chloro-3-[(choromethyl)sulfanyl]benzene (82f)



N-Chlorosuccinimide (1.00 g, 7.49 mmol) was added portionwise to a solution of 3-chlorothioanisole (0.90 mL, 6.81 mmol) in dichloroethane (10 mL). The reaction was stirred at rt for 17 h then filtered through a short pad of silica, eluting with CH_2Cl_2 (25 mL). The solvent was removed under reduced pressure to afford chloromethyl sulfide **82f** (1.24 g, 95%) as a pale yellow oil, which was used without further purification. R_f = 0.73 (40% EtOAc/hexane). IR (film)/cm^{-1} 1576, 1462, 1402, 1227, 1119, 1085, 852, 777, 720, 677. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.49 (1 H, m, Ar-H), 7.42–7.37 (1 H, m, Ar-H), 7.34–7.28 (2 H, m, 2 × Ar-H), 4.97 (2 H, s, SCH_2Cl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.2 (C_q), 135.0 (C_q), 130.2 (Ar-C), 130.2 (Ar-C), 128.5 (Ar-C), 128.1 (Ar-C), 50.1 (SCH_2Cl). HRMS (ES) *m/z* Calculated $C_7H_7{}^{35}Cl_2S^+$ $[M+H]^+$: 192.9640; Found: Accurate mass could not be obtained.

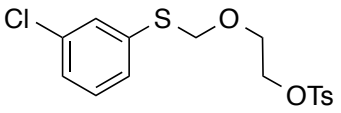
2-{[(3-Chlorophenyl)sulfanyl]methoxy}ethan-1-ol (72f)



Sodium hydride (60% in mineral oil, 0.27 g, 6.87 mmol) was added to ethylene glycol (55 mL) at 0 ºC and stirred for 1 h 20 min. Sodium iodide (1.03 g, 6.87 mmol) was added followed by chloromethyl sulfide **82f** (1.20 g, 6.25 mmol). The resulting solution was stirred at 0 ºC for 1 h then warmed to rt and stirred for a further 17 h. Water (30 mL) was added and the product was extracted with ethyl acetate (10 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (30% EtOAc/hexane) afforded alcohol **72f** (0.97 g, 71%) as a colourless oil. R_f = 0.10 (30% EtOAc/hexane). IR (film)/cm^{-1} 3381 (OH), 2929, 1576, 1562, 1460, 1400, 1307, 1052, 1017, 886, 823, 773, 677. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.46 (1 H, m, Ar-H), 7.35 (1 H, ddd, *J* = 6.6, 1.9, 1.7 Hz,

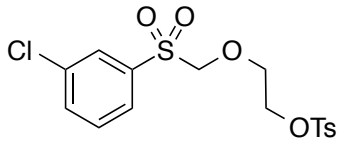
Ar-H), 7.26–7.19 (2 H, m, 2 × Ar-H), 5.07 (2 H, s, SCH_2O), 3.83–3.73 (4 H, m, OCH_2CH_2OH), 1.87 (1 H, br s, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6 (C_q), 134.5 (C_q), 129.9 (Ar-C), 129.4 (Ar-C), 127.9 (Ar-C), 126.8 (Ar-C), 75.9 (SCH_2O), 69.9 (OCH_2), 61.4 (OCH_2). HRMS (CI) *m/z* Calculated $C_9H_{12}O_2S^{35}Cl$ [M+H]: 219.0247; Found: 219.0253 [M+H], Δ 2.7 ppm.

2-{[(3-Chlorophenyl)sulfanyl]methoxy}ethyl-4-methylbenzene-1-sulfonate (83f)



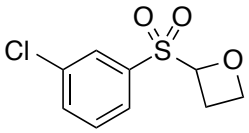
Triethylamine (1.66 mL, 11.83 mmol) and trimethylamine hydrochloride (38 mg, 0.39 mmol) were added to a solution of sulfide **72f** (0.86 g, 3.94 mmol) in toluene (18 mL) at 0 ºC and stirred for 30 min. 4-Toluenesulfonyl chloride (1.50 g, 7.87 mmol) was added portionwise. The mixture was stirred at 0 ºC for 20 min then allowed to warm to rt and stirred for a further 1 h 30 min. Water (20 mL) was added to the reaction and the product was extracted with EtOAc (5 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (20% EtOAc/hexane) afforded *p*-toluenesulfonate **83f** (1.35 g, 92%) as a colourless oil. R_f = 0.15 (20% EtOAc/hexane). IR (film)/cm^{-1} 2921, 1576, 1453, 1431, 1251, 1117, 1034, 954, 907, 735, 658. ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (2 H, d, *J* = 8.2 Hz, 2 × Ts-H), 7.40 (1 H, br s, Ar-H), 7.33 (2 H, d, *J* = 8.2 Hz, 2 × Ts-H), 7.31–7.26 (1 H, m, Ar-H), 7.23–7.18 (2 H, m, 2 × Ar-H), 4.95 (2 H, s, SCH_2O), 4.24–4.18 (2 H, m, $TsOCH_2$), 3.84–3.78 (2 H, m, CH_2OCH_2), 2.44 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9 (Ts-C_q), 137.4 (Ar-C_q), 134.6 (Ar-C_q), 132.8 (Ts-C_q), 129.9 (Ar-C), 129.8 (2 × Ts-C), 129.4 (2 × Ar-C), 127.9 (2 × Ts-C), 126.9 (Ar-C), 75.8 (SCH_2O), 68.6 (OCH_2), 65.8 (OCH_2), 21.6 (CH_3). HRMS (APCI) *m/z* Calculated $C_{16}H_{21}{}^{35}ClNO_4S_2^+$ $[M+NH_4]^+$: 390.0595; Found: 390.0587 $[M+NH_4]^+$, Δ 2.1 ppm.

1-Chloro-3-({2-[(4-methylbenzenesulfonyl)oxy]ethoxy}methanesulfonyl)benzene (84f)



meta-Chloroperbenzoic acid (0.41 g, 2.38 mmol) was added to a solution of sulfide **83f** (0.29 g, 0.78 mmol) in dichloromethane (12 mL) at 0 ºC and the mixture stirred at 0 ºC for 2 h. The reaction was quenched with sat. aq. Na_2SO_3 (20 mL) and extracted with dichloromethane (5 × 10 mL). The combined organic layers were washed with 1 M NaOH (2 × 10 mL) and sat. aq. NH_4Cl (15 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (40% EtOAc/hexane) afforded sulfone **84f** (0.32 g, 99%) as an off white solid; m.p. = 110–111 ºC. R_f = 0.30 (40% EtOAc/hexane). IR (film)/cm^{-1} 2956, 2256, 1598, 1458, 1416, 1356, 1327, 1294, 1175, 1153, 1096, 1020, 908, 814, 774, 727, 660. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (1 H, br s, Ar-H), 7.81 (1 H, d, *J* = 7.8 Hz, Ar-H), 7.76 (2 H, d, *J* = 8.4 Hz, 2 × Ts-H), 7.66 (1 H, d, *J* = 8.0 Hz, Ar-H), 7.53 (1 H, dd, *J* = 8.0, 7.8 Hz, Ar-H), 7.33 (2 H, d, *J* = 8.4 Hz, 2 × Ts-H), 4.54 (2 H, s, SCH_2O), 4.18–4.07 (4 H, m, OCH_2CH_2OH), 2.45 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1 (Ts-C_q), 138.6 (Ar-C_q), 135.5 (Ar-C_q), 134.4 (Ar-C), 132.6 (Ts-C_q), 130.6 (Ar-C), 129.9 (2 × Ts-C), 128.6 (Ar-C), 127.9 (2 × Ts-C), 127.1 (Ar-C), 86.1 (SCH_2O), 70.8 (OCH_2), 68.4 (OCH_2), 21.6 (CH_3). HRMS (ES) *m/z* Calculated $C_{16}H_{18}O_6S_2{}^{35}Cl$ [M+H]: 405.0233; Found: 405.0234 [M+H], Δ 0.2 ppm.

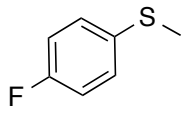
2-(3-Chlorobenzenesulfonyl)oxetane (89)



A solution of LiHMDS (0.61 M in THF, 5.58 mL, 3.40 mmol) was added dropwise to a solution of sulfone **84f** (1.25 g, 3.09 mmol) in THF (90 mL) at 0 ºC and stirred for 1 h 30 min. The reaction was quenched with sat. aq. NH_4Cl (50 mL) and extracted with CH_2Cl_2 (5 × 25 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (40%

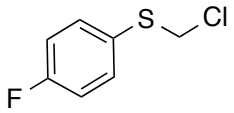
EtOAc/hexane) afforded oxetane **89** (0.62 g, 86%) as an off white solid; m.p. = 82–83 ºC. R_f = 0.26 (40% EtOAc/hexane). IR (film)/cm^{-1} 3090, 2912, 1579, 1460, 1439, 1409, 1312, 1263, 1232, 1148, 1119, 1075, 1026, 976, 928, 897, 797, 700, 662. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (1 H, dd, *J* = 1.7, 1.5 Hz, Ar-H), 7.87 (1 H, d, *J* = 7.7 Hz, Ar-H), 7.67 (1 H, d, *J* = 8.0 Hz, Ar-H), 7.53 (1 H, dd, *J* = 8.0, 7.7 Hz, Ar-H), 5.40 (1 H, dd, *J* = 7.3, 6.0 Hz, OCHS), 4.88–4.81 (1 H, m, OCH*H*), 4.68 (1 H, ddd, *J* = 8.2, 6.1, 5.6 Hz, OC*H*H), 3.21–3.09 (2 H, m, OCH_2CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1 (C_q), 135.5 (C_q), 134.4 (Ar-C), 130.4 (Ar-C), 129.4 (Ar-C), 127.5 (Ar-C), 94.1 (OCHS), 71.6 (OCH_2), 22.2 (OCH_2CH_2). HRMS (APCI) *m/z* Calculated $C_9H_{10}{}^{35}ClO_3S^+$ $[M+H]^+$: 233.0034; Found: 233.0032 $[M+H]^+$, Δ 0.9 ppm.

1-Fluoro-4-(methylsulfanyl)benzene (81g)[226]



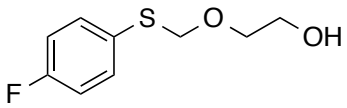
Potassium carbonate (11.84 g, 85.67 mmol) was added to a solution of 4-fluorobenzene thiol (10.00 g, 78.02 mmol) in acetone (100 mL) followed by MeI (5.10 mL, 81.92 mmol) and the reaction stirred at rt for 2 h 30 min. The reaction was filtered through Celite® and the solvent removed under reduced pressure. The crude material was dissolved in diethyl ether (50 mL) and washed with 5% NaOH (3 × 150 mL). The combined aqueous layers were extracted with diethyl ether (2 × 50 mL) then the combined organics were washed with brine (50 mL), dried ($MgSO_4$) and solvent removed under reduced pressure to afford sulfide **81g** (10.90 g, 98%) as a pale yellow oil which was used without further purification. R_f = 0.72 (40% EtOAc/hexane). IR (film)/cm^{-1} 2921, 1589, 1488, 1437, 1396, 1223, 1157, 1092, 1013, 968, 817, 723. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.24 (2 H, m, 2 × Ar-H), 7.02 (2 H, dd, *J* = 8.7, 8.6 Hz, 2 × Ar-H), 2.48 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0 (C_q, d, J_{CF} = 244.1 Hz, Ar-C_q-F), 133.3 (C_q, d, J_{CF} = 3.1 Hz, Ar-C_q), 129.1 (d, J_{CF} = 7.9 Hz, 2 × Ar-C), 115.8 (d, J_{CF} = 21.5 Hz, 2 × Ar-C), 16.9 (CH_3). ^{19}F NMR (400 MHz, $CDCl_3$) δ –117.29 (Ar-F). HRMS (APCI) *m/z* Calculated $C_7H_8FS^+$ $[M+H]^+$: 143.0325; Found: 143.0322 $[M+H]^+$, Δ 2.1 ppm. The observed data (^{1}H) is consistent with that reported in the literature.[226]

1-[(Chloromethyl)sulfany]-4-fluorobenzene (82g)[233]



N-Chlorosuccinimide (10.33 g, 77.36 mmol) was added portionwise to a solution of sulfide **81g** (10.00 g, 70.33 mmol) in carbon tetrachloride (65 mL). The reaction was stirred at rt for 19 h then filtered through a short pad of silica, eluting with CH_2Cl_2 (40 mL). The solvent was removed under reduced pressure to afford chloromethyl sulfide **82g** (11.47 g, 94%) as a pale yellow oil, which was used without further purification. R_f = 0.74 (40% EtOAc/hexane). IR (film)/cm^{-1} 2985, 1734, 1590, 1491, 1226, 1173, 1157, 1091, 1044, 916, 826, 732. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.52 (2 H, m, 2 × Ar-H), 7.09 (2 H, dd, *J* = 8.7, 8.6 Hz, 2 × Ar-H), 4.90 (2 H, s, SCH_2Cl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0 (C_q, d, J_{CF} = 249.5 Hz, Ar-C_q-F), 134.3 (d, J_{CF} = 7.8 Hz, 2 × Ar-C), 128.1 (C_q, d, J_{CF} = 2.7 Hz, Ar-C_q), 116.4 (d, J_{CF} = 22.1 Hz, 2 × Ar-C), 52.0 (SCH_2Cl). ^{19}F NMR (400 MHz, $CDCl_3$) δ –112.57 (Ar-F). HRMS (APCI) *m/z* Calculated $C_7H_6{}^{35}ClFS^+$ $[M]^+$: 175.9857; Found: 175.9855 $[M]^+$, Δ 1.1 ppm. The observed data (^{1}H, ^{13}C, IR) is consistent with that reported in the literature.[233]

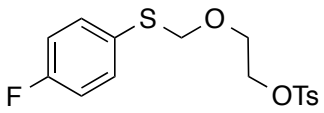
2-{[(4-Fluorophenyl)sulfanyl]methoxy}ethan-1-ol (72g)



Sodium hydride (60% in mineral oil, 0.36 g, 9.00 mmol) was added to ethylene glycol (65 mL) at 0 ºC and stirred for 1 h. Sodium iodide (1.35 g, 9.01 mmol) was added followed by chloromethyl sulfide **82g** (1.44 g, 8.18 mmol). DMF (2 mL) was added to aid solubility. The resulting solution was stirred at 0 ºC for 45 min then warmed to rt and stirred for a further 16 h 30 min. Water (50 mL) was added and the product was extracted with ethyl acetate (10 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (30% EtOAc/hexane) afforded alcohol **72g** (1.19 g, 72%) as a colourless oil. R_f = 0.16 (30% EtOAc/hexane). IR (film)/cm^{-1} 3379 (OH), 2927, 1589, 1489, 1458, 1397, 1308, 1219 (CF), 1087, 1053, 1013, 887, 823, 676. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.43 (2 H, m, 2 × Ar-H), 7.04–6.97 (2 H, dd, *J* = 8.8, 8.5 Hz, 2 × Ar-H), 4.97 (2 H,

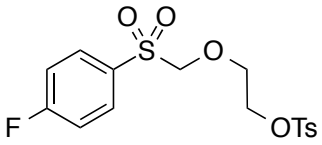
s, SCH_2O), 3.79–3.71 (4 H, m, SCH_2CH_2OH), 2.11 (1 H, br s, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3 (C_q, d, J_{CF} = 247.7 Hz, Ar-C_q-F), 133.2 (d, J_{CF} = 8.5 Hz, 2 × Ar-C), 130.3 (C_q, d, J_{CF} = 2.8 Hz, Ar-C_q), 116.1 (d, J_{CF} = 21.2 Hz, 2 × Ar-C), 77.2 (SCH_2O), 69.8 (OCH_2), 61.5 (OCH_2). ^{19}F NMR (400 MHz, $CDCl_3$) δ –114.53 (CF). HRMS (APCI) *m/z* Calculated $C_9H_{15}FNO_2S^+$ $[M+NH_4]^+$: 220.0802; Found: 220.0799 $[M+NH_4]^+$, Δ 1.4 ppm.

2-(((4-Fluorophenyl)thio)methoxy)ethyl-4-methylbenzenesulfonate (83g)



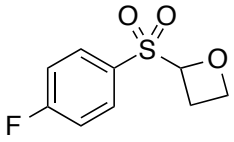
Triethylamine (2.08 mL, 14.82 mmol) and trimethylamine hydrochloride (46 mg, 0.49 mmol) were added to a solution of sulfide **72g** (1.00 g, 4.94 mmol) in toluene (21 mL) at 0 ºC and stirred for 50 min. 4-Toluenesulfonyl chloride (1.88 g, 9.86 mmol) was added portionwise. The mixture was stirred at 0 ºC for 30 min then allowed to warm to rt and stirred for a further 1 h 30 min. Water (40 mL) was added to the reaction and the product was extracted with EtOAc (5 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (20% EtOAc/hexane) afforded *p*-toluenesulfonate **83g** (1.71 g, 96%) as a colourless oil. R_f = 0.22 (20% EtOAc/hexane). IR (film)/cm^{-1} 2977, 2910, 1588, 1485, 1458, 1433, 1355, 1307, 1216, 1169, 1120, 1020, 912, 806, 781, 662. ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (2 H, d, *J* = 8.4 Hz, 2 × Ts-H), 7.45–7.39 (2 H, m, 2 × Ar-H), 7.33 (2 H, d, *J* = 8.4 Hz, 2 × Ts-H), 7.01–6.95 (2 H, dd, *J* = 8.9, 8.6 Hz, 2 × Ar-H), 4.88 (2 H, s, SCH_2O), 4.23–4.19 (2 H, m, OCH_2), 3.84–3.80 (2 H, m, OCH_2), 2.45 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3 (C_q, d, J_{CF} = 237.8 Hz, Ar-C_q), 144.9 (Ts-C_q), 133.3 (d, J_{CF} = 8.2 Hz, 2 × Ar-C), 132.9 (Ts-C_q), 130.0 (Ar-C_q), 129.8 (2 × Ts-C), 127.9 (2 × Ts-C), 116.1 (d, J_{CF} = 20.3 Hz, 2 × Ar-C), 70.7 (SCH_2O), 68.6 (OCH_2CH_2), 65.6 (OCH_2CH_2), 21.6 (CH_3). ^{19}F NMR (400 MHz, $CDCl_3$) δ –114.50 (CF). HRMS (NSI) *m/z* Calculated $C_{16}H_{21}FNO_4S_2^+$ $[M+NH_4]^+$: 374.0891; Found: 374.0891 $[M+NH_4]^+$, Δ 0 ppm.

2-(((4-Fluorophenyl)sulfonyl)methoxy)ethyl-4-methylbenzenesulfonate (84g)



meta-Chloroperbenzoic acid (70%, 2.07 g, 8.41 mmol) was added to a solution of sulfide **83g** (1.00 g, 2.80 mmol) in dichloromethane (38 mL) at 0 ºC and the mixture stirred at 0 ºC for 2 h then warmed to rt and stirred for a further 3 h. The reaction was quenched with sat. aq. Na_2SO_3 (20 mL) and extracted with dichloromethane (5 × 20 mL). The combined organic layers were washed with 1 M NaOH (2 × 10 mL) and sat. aq. NH_4Cl (10 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (40% EtOAc/hexane) afforded sulfone **84g** (1.07 g, 97%) as a white solid; m.p = 73–74 ºC. R_f = 0.25 (40% EtOAc/hexane). IR (film)/cm^{-1} 2947, 1590, 1494, 1459, 1359, 1322, 1289, 1230, 1175, 1134, 1078, 1018, 916, 835, 770, 703, 665. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96–7.90 (2 H, m, 2 × Ar-H), 7.76 (2 H, d, J = 8.3 Hz, 2 × Ts-H), 7.34 (2 H, d, J = 8.3 Hz, 2 × Ts-H), 7.27–7.21 (2 H, m, 2 × Ar-H), 4.52 (2 H, s, SCH_2O), 4.17–4.09 (4 H, m, OCH_2CH_2OTs), 2.45 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2 (C_q, d, J_{CF} = 254.6 Hz, Ar-C_q-F), 145.1 (Ts-C_q), 132.7 (C_q, d, J = 2.7 Hz, Ar-C_q), 132.5 (Ts-C_q), 131.8 (d, J_{CF} = 9.7 Hz, 2 × Ar-C), 129.9 (2 × Ts-C), 127.9 (2 × Ts-C), 116.6 (d, J_{CF} = 22.6, 2 × Ar-C), 86.0 (SCH_2O), 70.6 (OCH_2), 68.4 (OCH_2), 21.6 (CH_3). ^{19}F NMR (400 MHz, $CDCl_3$) δ –102.50 (CF). HRMS (ES) *m/z* Calculated for $C_{16}H_{18}O_6FS_2$ [M+H]: 389.0529; Found: 389.0521 [M+H], Δ 2.1 ppm.

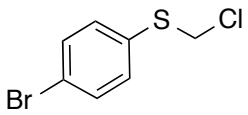
2-((4-Fluorophenyl)sulfonyl)oxetane (90)



A solution of LiHMDS (0.61 M in THF, 2.32 mL, 1.42 mmol) was added dropwise to a solution of sulfone **84g** (0.50 g, 1.29 mmol) in THF (40 mL) at 0 ºC and stirred for 1 h 15 min. The reaction was quenched with sat. aq. NH_4Cl (40 mL) and extracted with CH_2Cl_2 (5 × 30 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (20%

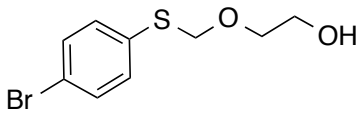
EtOAc/hexane) afforded oxetane **90** (0.23 g, 83%) as a white solid; m.p = 74–75 ºC. R_f = 0.18 (20% EtOAc/hexane). IR (film)/cm^{-1} 2986, 2914, 1588, 1494, 1405, 1312, 1292, 1234, 1144, 1085, 1027, 982, 905, 846, 819, 723, 690. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04–7.96 (2 H, m, 2 × Ar), 7.30–7.23 (2 H, m, 2 × Ar), 5.38 (1 H, dd, *J* = 7.8, 5.5 Hz, OCHS), 4.80 (1 H, ddd, *J* = 8.6, 7.7, 5.5 Hz, OCH*H*), 4.67 (1 H, ddd, *J* = 8.6, 6.2, 5.5 Hz, OC*H*H), 3.20–3.05 (2 H, m, OCH_2CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3 (C_q, d, J_{CF} = 253.8 Hz, C_q-F), 132.3 (d, J_{CF} = 9.9 Hz, 2 × Ar-C), 131.3 (C_q), 116.5 (d, J_{CF} = 22.8 Hz, 2 × Ar-C), 94.1 (OCHS), 71.4 (OCH_2), 22.3 (OCH_2CH_2). ^{19}F NMR (400 MHz, $CDCl_3$) δ –102.50 (CF). HRMS (CI) *m/z* Calculated for $C_9H_{10}O_3FS$ [M+H]: 217.0335; Found: 217.0339 [M+H], Δ 1.8 ppm.

1-Bromo-4-[(chloromethyl)sulfanyl]benzene (82h)



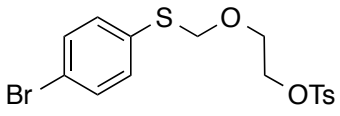
N-Chlorosuccinimide (3.75 g, 28.11 mmol) was added portionwise to a solution of 4-bromothioanisole (5.19 g, 25.56 mmol) in dichloroethane (40 mL). The reaction was stirred at rt for 18 h then filtered through a short pad of silica, eluting with dichloroethane (20 mL) and the solvent removed under reduced pressure to afford chloromethyl sulfide **82h** as a yellow oil (6.03 g, 99%). Product was taken on without further purification. R_f = 0.65 (40% EtOAc/hexane). IR (film)/cm^{-1} 1636, 1565, 1472, 1386, 1334, 1226, 1175, 1144, 1090, 1067, 1007, 906, 854, 808, 731, 715. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (2 H, d, *J* = 8.6 Hz, 2 × Ar-H), 7.39 (2 H, d, *J* = 8.6 Hz, 2 × Ar-H), 4.94 (2 H, s, SCH_2Cl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1 (C_q), 132.5 (2 × Ar-C), 132.3 (2 × Ar-C), 122.3 (C_q), 50.6 (SCH_2Cl). HRMS (APCI) *m/z* Calculated for $C_7H_6{}^{80}Br^{35}ClS^+$ $[M]^+$: 237.9033; Found: 237.9031 $[M]^+$, Δ 0.8 ppm.

2-{[(4-Bromophenyl)sulfanyl]methoxy}ethan-1-ol (72h)



Sodium hydride (60% in mineral oil, 1.03 g, 25.76 mmol) was added to ethylene glycol (200 mL) at 0 ºC and stirred for 1 h. Sodium iodide (3.85 g, 25.69 mmol) was added followed by chloromethyl sulfide **82h** (5.51 g, 23.20 mmol). DMF (2 mL) was added to aid solubility. The resulting solution was stirred at 0 ºC for 30 min then warmed to rt for 18 h. Water (100 mL) was added and the product was extracted with ethyl acetate (10 × 25 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (30% EtOAc/hexane) afforded alcohol **72h** (4.83 g, 79%) as a pale yellow oil. R_f = 0.14 (30% EtOAc/hexane). IR (film)/cm^{-1} 3348 (OH), 2926, 1473, 1426, 1387, 1308, 1263, 1105, 1087, 1052, 1019, 1006, 940, 915, 887, 727, 674. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (2 H, d, *J* = 8.4 Hz, 2 × Ar-H), 7.35 (2 H, d, *J* = 8.4 Hz, 2 × Ar-H), 5.03 (2 H, s, SCH_2O), 3.79–3.72 (4 H, m, OCH_2CH_2OH), 1.85 (1 H, br s, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.7 (C_q), 132.0 (2 × Ar-C), 131.8 (2 × Ar-C), 121.0 (C_q), 76.3 (SCH_2O), 69.8 (OCH_2), 61.6 (OCH_2). HRMS (APCI) *m/z* Calculated for $C_9H_{15}{}^{79}BrNO_2S^+$ $[M+NH_4]^+$: 280.0001; Found: 280.0000 $[M+NH_4]^+$, Δ 0.4 ppm.

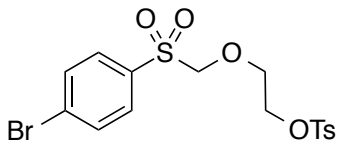
2-{[(4-Bromophenyl)sulfanyl]methoxy}ethyl-4-methylbenzene-1-1sulfonate (83h)



Triethylamine (6.59 mL, 46.89 mmol) and trimethylamine hydrochloride (0.15 g, 1.57 mmol) were added to a solution of sulfide **72h** (4.12 g, 15.66 mmol) in toluene (55 mL) at 0 ºC and stirred for 30 min. 4-Toluenesulfonyl chloride (6.01 g, 31.52 mmol) was added portionwise. The mixture was stirred at 0 ºC for 30 min then warmed to rt and stirred for a further 1 h 30 min. Water (100 mL) was added to the reaction and the product was extracted with EtOAc (5 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (20% EtOAc/hexane) afforded *p*-toluenesulfonate **83h** (6.31 g, 96%) as a white solid; m.p. = 54–55 ºC. R_f = 0.19 (20% EtOAc/hexane). IR (film)/cm^{-1} 1598, 1473,

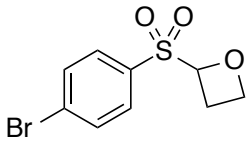
1368, 1346, 1297, 1280, 1191, 1171, 1120, 1099, 1085, 1015, 1006, 949, 923, 809, 796, 784, 725, 680, 661. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (2 H, d, *J* = 8.3 Hz, 2 × Ts-H), 7.38 (2 H, d, *J* = 8.5 Hz, 2 × Ar-H), 7.33 (2 H, d, *J* = 8.3 Hz, 2 × Ts-H), 7.28 (2 H, d, *J* = 8.5 Hz, 2 × Ar-H), 4.92 (2 H, s, SCH_2O), 4.23–4.19 (2 H, m, $TsOCH_2$), 3.84–3.80 (2 H, m, CH_2OCH_2), 2.46 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9 (Ts-C_q), 134.5 (Ar-C_q), 132.9 (Ts-C_q), 132.0 (2 × Ar-C), 131.8 (2 × Ar-C), 129.8 (2 × Ts-C), 127.9 (2 × Ts-C), 121.0 (Ar-C_q), 76.1 (SCH_2O), 68.5 (OCH_2), 65.7 (OCH_2), 21.7 (CH_3). HRMS (ESI) *m/z* Calculated for $C_{16}H_{17}O_4{}^{79}BrNaS_2$ [M+Na]: 438.9644; Found: 438.9622 [M+Na], Δ 5.0 ppm.

1-Bromo-4-({2-[(4-methylbenzenesulfonyl)oxy]ethoxy}methanesulfonyl)benzene (84h)



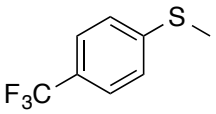
meta-Chloroperbenzoic acid (3.85 g, 22.31 mmol) was added to a solution of sulfide **83h** (3.10 g, 7.45 mmol) in dichloromethane (100 mL) at 0 ºC and the mixture stirred at 0 ºC for 3 h. The reaction was quenched with sat. aq. Na_2SO_3 (75 mL) and extracted with dichloromethane (5 × 30 mL). The combined organic layers were washed with 1 M NaOH (2 × 25 mL) and sat. aq. NH_4Cl (25 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (50% EtOAc/hexane) afforded sulfone **84h** (3.34 g, 99%) as a white solid; m.p. = 88–89 ºC. R_f = 0.42 (50% EtOAc/hexane). IR (film)/cm^{-1} 3099, 2953, 1574, 1458, 1358, 1323, 1290, 1247, 1175, 1135, 1107, 1078, 1008, 949, 916, 815, 715, 665. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.73 (4 H, m, 2 × Ar-H + 2 × Ts-H), 7.70 (2 H, d, *J* = 8.7 Hz, 2 × Ar-H), 7.35 (2 H, d, *J* = 8.0 Hz, 2 × Ts-H), 4.52 (2 H, s, SCH_2O), 4.18–4.13 (2 H, m, $TsOCH_2$), 4.12–4.08 (2 H, m, CH_2OCH_2), 2.46 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1 (Ts-C_q), 135.8 (Ar-C_q), 132.6 (Ts-C_q), 132.6 (2 × Ts-C), 130.4 (2 × Ts-C), 129.9 (2 × Ar-C), 129.8 (Ar-C_q), 127.9 (2 × Ar-C), 86.0 (SCH_2O), 70.6 (OCH_2), 68.3 (OCH_2), 21.7 (CH_3). HRMS (ES) *m/z* Calculated for $C_{16}H_{17}{}^{79}BrNaO_6S_2$ [M+Na]: 470.9548; Found: 470.9576 [M+Na], Δ 5.9 ppm.

2-(4-Bromobenzenesulfonyl)oxetane (91)



A solution of LiHMDS (0.61 M in THF, 4.03 mL, 2.46 mmol) was added dropwise to a solution of sulfone **84h** (1.01 g, 2.25 mmol) in THF (70 mL) at 0 ºC and stirred for 1 h 30 min. The reaction was quenched with sat. aq. NH_4Cl (30 mL) and extracted with CH_2Cl_2 (5 × 20 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (40% EtOAc/hexane) afforded oxetane **91** (0.54 g, 86%) as a white solid; m.p. = 99–100 ºC. R_f = 0.38 (40% EtOAc/hexane). IR (film)/cm^{-1} 3089, 2979, 2909, 1571, 1468, 1441, 1387, 1313, 1272, 1144, 1067, 1007, 975, 939, 895, 818, 769, 707, 681. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (2 H, d, *J* = 8.6 Hz, 2 × Ar-H), 7.73 (2 H, d, *J* = 8.6 Hz, 2 × Ar-H), 5.37 (1 H, dd, *J* = 7.7, 5.5 Hz, OCHS), 4.85–4.77 (1 H, m, OCH*H*), 4.67 (1 H, ddd, *J* = 8.2, 5.8, 5.6 Hz, OC*H*H), 3.20–3.05 (2 H, m, OCH_2CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.3 (C_q), 132.5 (2 × Ar-C), 131.0 (2 × Ar-C), 129.9 (C_q), 94.1 (OCHS), 71.6 (OCH_2), 22.3 (OCH_2CH_2). HRMS (NSI) *m/z* Calculated for $C_9H_9{}^{79}BrNaO_3S^+$ $[M+Na]^+$: 298.9348; Found: 298.9349 $[M+Na]^+$, Δ 0.3 ppm.

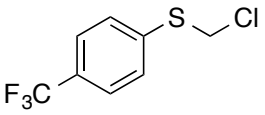
1-(Methylsulfanyl)-4-(trifluoromethyl)benzene (81i)[234]



4-Iodobenzo-trifluoride (1.08 mL, 7.35 mmol) was added to a solution of sodium thiomethoxide (0.57 g, 8.08 mmol) in DMF (18 mL) and the resulting solution was heated at 45 ºC for 21 h. The reaction was quenched with sat. aq. NaCl (10 mL) and extracted with Et_2O (6 × 10 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (100% hexane) afforded methyl sulfide **81i** (1.32 g, 94%) as a white solid. R_f = 0.65 (100% hexane). IR (film)/cm^{-1} 2926, 1605, 1436, 1404, 1322, 1196, 1157, 1091, 1011, 949, 817, 779, 725, 698. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (2 H, d, *J* = 8.2 Hz, 2 × Ar-H), 7.31 (2 H, d, *J* = 8.2 Hz, 2 × Ar-H), 2.52 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8

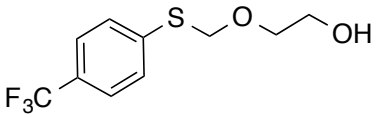
(C_q), 126.7, (C_q, q, J_{CF} = 31.8 Hz, *C*-CF_3), 125.6 (4 × Ar-C), 124.2, (C_q, q, J_{CF} = 270.5 Hz, CF_3), 15.0 (CH_3). ^{19}F NMR (400 MHz, $CDCl_3$) δ –62.33 (CF_3). HRMS (EI) *m/z* Calculated for $C_8H_7F_3S$ [M]: 192.0221; Found: 192.0228 [M], Δ 3.6 ppm. The observed data (^{1}H and ^{13}C) is consistent with that reported in the literature.[234]

1-[(Chloromethyl)sulfanyl]-4-(trifluoromethyl)benzene (82i)



N-Chlorosuccinimide (0.53 g, 3.97 mmol) was added portionwise to a solution of *p*-trifluoromethyl methyl sulfide **81i** (0.73 g, 3.81 mmol) in dichloroethane (8 mL). The reaction was stirred at rt for 17 h then filtered through a short pad of silica, eluting with CH_2Cl_2 (15 mL). The solvent was removed under reduced pressure to afford chloromethyl sulfide **82i** (0.78 g, 91%) as a pale yellow oil. R_f = 0.27 (10% Et_2O/hexane). IR (film)/cm^{-1} 1607, 1500, 1405, 1321, 1228, 1165, 1119, 1094, 1061, 1013, 824, 734, 700. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (2 H, d, *J* = 8.6 Hz, 2 × Ar-H), 7.58 (2 H, d, *J* = 8.6 Hz, 2 × Ar-H), 5.03 (2 H, s, SCH_2Cl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5 (Ar-C_q), 129.3 (C_q, q, J_{CF} = 32.1 Hz, *C*-CF_3), 129.0 (2 × Ar-C), 125.9 (q, J_{CF} = 3.1 Hz, 2 × Ar-C), 123.9 (C_q, q, J_{CF} = 272.9 Hz, CF_3), 48.8 (SCH_2Cl). ^{19}F NMR (400 MHz, $CDCl_3$) δ –62.66 (CF_3). HRMS (EI) *m/z* Calculated for $C_8H_6{}^{35}ClF_3S$ [M]: 225.9831; Found: 225.9831 [M], Δ 0 ppm.

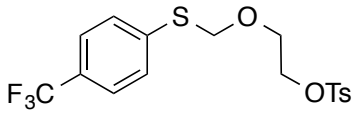
2-({[4-(Trifluoromethyl)phenyl]sulfanyl}methoxy)ethan-1-ol (72i)



Sodium hydride (60% in mineral oil, 76 mg, 1.92 mmol) was added to ethylene glycol (16 mL) at 0 ºC and stirred for 40 min. Sodium iodide (0.29 g, 1.95 mmol) was added followed by chloromethyl sulfide **82i** (0.40 g, 1.77 mmol). The resulting solution was stirred at 0 ºC for 2 h then warmed to rt for 15 h. Water (20 mL) was added and the product was extracted with ethyl acetate (10 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by

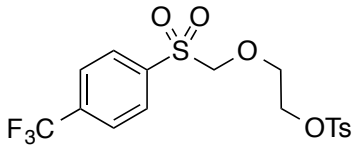
flash chromatography (30% EtOAc/hexane) afforded alcohol **72i** (0.28 g, 61%) as a pale yellow oil. R_f = 0.10 (30% EtOAc/hexane). IR (film)/cm^{-1} 2927, 2296, 1607, 1403, 1321, 1162, 1060, 1013, 888, 825, 779, 677. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.52 (4 H, m, 4 × Ar-H), 5.12 (2 H, s, SCH_2O), 3.83–3.75 (4 H, m, OCH_2CH_2OH), 2.03 (1 H, br s, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0 (Ar-C_q), 128.7 (2 × Ar-C), 128.2 (C_q, q, J_{CF} = 32.9 Hz, *C*-CF_3), 125.5 (q, J_{CF} = 3.3 Hz, 2 × Ar-C), 123.9 (C_q, q, J_{CF} = 272.0 Hz, CF_3), 75.0 (SCH_2O), 69.9 (OCH_2), 61.2 (OCH_2). ^{19}F NMR (400 MHz, $CDCl_3$) δ –62.57 (CF_3). HRMS (CI) *m/z* Calculated $C_{10}H_{15}NF_3O_2S$ $[M+NH_4]^+$: 270.0770; Found: 270.0770 $[M+NH_4]^+$, Δ 0 ppm.

2-({[4-(Trifluoromethyl)phenyl]sulfanyl}methoxy)ethyl-4-methylbenzene-1-sulfonate (83i)



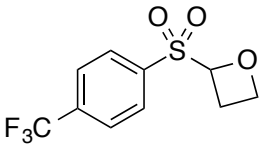
Triethylamine (0.33 mL, 2.37 mmol) and trimethylamine hydrochloride (7 mg, 0.07 mmol) were added to a solution of sulfide **72i** (0.20 g, 0.79 mmol) in toluene (4 mL) at 0 ºC and stirred for 30 min. 4-Toluenesulfonyl chloride (0.31 g, 1.61 mmol) was added portionwise. The mixture was stirred at 0 ºC for 20 min then allowed to warm to rt and stirred for a further 1 h 30 min. Water (20 mL) was added to the reaction and the product was extracted with EtOAc (5 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (20% EtOAc/hexane) afforded *p*-toluenesulfonate **83i** (0.32 g, 99%) as an off white solid; m.p. = 70–71 ºC. R_f = 0.15 (20% EtOAc/hexane). IR (film)/cm^{-1} 2926, 1603, 1317, 1161, 1097, 1083, 1028, 996, 909, 826, 811, 759, 683. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (2 H, d, *J* = 8.3 Hz, 2 × Ts-H), 7.52–7.48 (4 H, m, 4 × Ar-H), 7.33 (2 H, d, *J* = 8.3 Hz, 2 × Ts-H), 5.02 (2 H, s, SCH_2O), 4.26–4.29 (2 H, m, $TsOCH_2$), 3.86–3.81 (2 H, m, CH_2OCH_2), 2.45 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9 (Ts-C_q), 140.7 (Ar-C_q), 132.9 (Ts-C_q), 129.8 (2 x Ts-C), 129.0 (2 × Ar-C), 128.5 (C_q, q, J_{CF} = 32.1 Hz, *C*-CF_3), 127.9 (2 x Ts-C), 125.6 (q, J_{CF} = 3.5 Hz, 2 × Ar-C), 124.0 (C_q, q, J_{CF} = 272.6 Hz, CF_3), 75.1 (SCH_2O), 68.5 (OCH_2), 65.8 (OCH_2), 21.6 (CH_3). ^{19}F NMR (400 MHz, $CDCl_3$) δ –62.5 (CF_3). HRMS (APCI) *m/z* Calculated $C_{17}H_{21}F_3NO_4S_2^+$ $[M+NH_4]^+$: 424.0859; Found: 424.0854 $[M+NH_4]^+$, Δ 1.2 ppm.

1-({2-[(4-Methylbenzenesulfonyl)oxy]ethoxy}methanesulfonyl)-4-(trifluoromethyl)benzene (84i)



meta-Chloroperbenzoic acid (0.12 g, 0.72 mmol) was added to a solution of sulfide **83i** (95 mg, 0.23 mmol) in dichloromethane (4 mL) at 0 ºC and the mixture stirred at 0 ºC for 2 h. The reaction was quenched with sat. aq. Na_2SO_3 (10 mL) and extracted with dichloromethane (5 × 10 mL). The combined organic layers were washed with 1 M NaOH (2 × 10 mL) and sat. aq. NH_4Cl (15 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (40% EtOAc/hexane) afforded sulfone **84i** (99 mg, 97%) as a white solid; m.p. = 86–87 ºC. R_f = 0.26 (40% EtOAc/hexane). IR (film)/cm^{-1} 2927, 1598, 1453, 1403, 1357, 1320, 1295, 1172, 1129, 1083, 1060, 1016, 915, 842, 815, 755, 695, 662. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (2 H, d, *J* = 8.2 Hz, 2 × Ar-H), 7.83 (2 H, d, *J* = 8.2 Hz, 2 × Ar-H), 7.77 (2 H, d, *J* = 8.3 Hz, 2 × Ts-H), 7.34 (2 H, d, *J* = 8.3 Hz, 2 × Ts-H), 4.57 (2 H, s, SCH_2O), 4.20–4.09 (4 H, m, OCH_2CH_2OTs), 2.45 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, (Ts-C_q), 140.4 (Ar-C_q), 135.8 (C_q, q, J_{CF} = 32.0 Hz, *C*-CF_3), 132.6 (Ts-C_q), 129.9 (2 x Ts-C), 129.6 (2 × Ar-C), 127.9 (2 x Ts-C), 126.3 (q, J_{CF} = 3.5 Hz, 2 x Ar-C), 123.1 (C_q, q, J_{CF} = 263.9 Hz, CF_3), 85.9 (SCH_2O), 70.7 (OCH_2), 68.3 (OCH_2), 21.6 (CH_3). ^{19}F NMR (400 MHz, $CDCl_3$) δ –63.2 (CF_3). HRMS (ES) *m/z* Calculated $C_{17}H_{16}O_6F_3NaS_2$ [M+Na]: 461.0316; Found 461.0328 [M+Na], Δ 2.6 ppm.

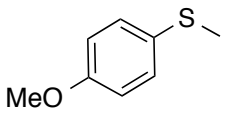
2-[4-(Trifluoromethyl)benzenesulfonyl]oxetane (92)



A solution of LiHMDS (0.61 M in THF, 0.15 mL, 0.09 mmol) was added dropwise to a solution of sulfone **84i** (37 mg, 0.08 mmol) in THF (3 mL) at 0 ºC and stirred for 1 h 30 min. The reaction was quenched with sat. aq. NH_4Cl (20 mL) and extracted with CH_2Cl_2 (5 × 10 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent

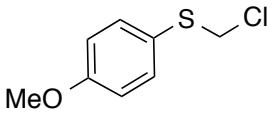
removed under reduced pressure. Purification by flash chromatography (20% EtOAc/hexane) afforded oxetane **92** (10 mg, 46%) as a white solid. R_f = 0.24 (20% EtOAc/hexane). IR (film)/cm^{-1} 2977, 2907, 1403, 1319, 1130, 1107, 1061, 1029, 984, 909, 844, 787, 715, 679. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (2 H, d, *J* = 8.0 Hz, 2 × Ar-H), 7.86 (2 H, d, *J* = 8.0 Hz, 2 × Ar-H), 5.41 (1 H, dd, *J* = 6.7, 6.0 Hz, OCHS), 4.90–4.82 (1 H, m, OCH*H*), 4.73–4.65 (1 H, m, OC*H*H), 3.22–3.11 (2 H, m, OCH_2CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1 (Ar-C_q), 135.9 (C_q, q, J_{CF} = 33.0 Hz, *C*-CF_3), 130.1 (2 × Ar-C), 126.2 (q, J_{CF} = 3.6 Hz, 2 × Ar-C), 123.1 (C_q, q, J_{CF} = 272.6 Hz, CF_3), 94.1 (OCHS), 71.7 (OCH_2), 22.1 (OCH_2CH_2). ^{19}F NMR (400 MHz, $CDCl_3$) δ –63.3 (CF_3). HRMS (ASAP) *m/z* Calculated for $C_{10}H_{10}F_3O_3S$ [M+H]: 267.0303; Found: 267.0303 [M+H], Δ 0 ppm.

1-Methoxy-4-(methylthio)-benzene (81j)[235]



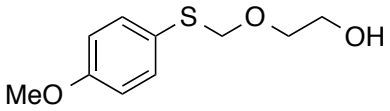
Potassium carbonate (5.42 g, 39.23 mmol) was added to a solution of 4-methoxythiophenol (5.00 g, 4.39 mL, 35.66 mmol) in acetone (45 mL) followed by MeI (2.33 mL, 37.43 mmol) and the reaction stirred at rt for 70 h. The reaction was filtered through Celite® and the solvent removed under reduced pressure. The crude material was dissolved in diethyl ether (30 mL) and washed with 1 M NaOH (3 × 25 mL). The combined aqueous layers were extracted with diethyl ether (20 mL) then the combined organics were washed with brine (20 mL), dried ($MgSO_4$) and solvent removed under reduced pressure to afford sulfide **81j** (5.45 g, 99%) as a yellow oil which was used without further purification. R_f = 0.43 (40% EtOAc/hexane). IR (film)/cm^{-1} 2919, 2834, 1592, 1492, 1462, 1438, 1282, 1238, 1175, 1105, 1029, 967, 818. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (2 H, d, *J* = 8.7 Hz, 2 × Ar-H), 6.87 (2 H, d, *J* = 8.7 Hz, 2 × Ar-H), 3.80 (3 H, s, OCH_3), 2.46 (3 H, s, SCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1 (C_q), 130.2 (2 × Ar-C), 128.7 (C_q), 114.6 (2 × Ar-C), 55.3 (OCH_3), 18.1 (SCH_3). The observed data (^{1}H) is consistent with that reported in the literature.[235]

4-(Chloromethyl)thioanisole (82j)[229]



N-Chlorosuccinimide (5.10 g, 38.19 mmol) was added portionwise to a solution of sulfide **81j** (5.34 g, 34.63 mmol) in dichloroethane (55 mL). The reaction was stirred at rt for 16 h 30 min then filtered through a short pad of silica, eluting with CH_2Cl_2 (40 mL). The solvent was removed under reduced pressure to afford chloromethyl sulfide **82j** (6.52 g, 99%) as a pale yellow oil, which was used without further purification. R_f = 0.45 (40% EtOAc/hexane). IR (film)/cm^{-1} 2836, 1723, 1589, 1492, 1462, 1288, 1245, 1172, 1138, 1026, 823, 716. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (2 H, d, *J* = 8.9 Hz, 2 × Ar), 7.51 (2 H, d, *J* = 8.9 Hz, 2 × Ar), 5.46 (2 H, s, SCH_2Cl), 4.42 (3 H, s, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2 (C_q), 134.7 (2 × Ar-C), 123.3 (C_q), 114.7 (2 × Ar-C), 55.3 (OCH_3), 53.0 (SCH_2Cl). HRMS (CI) *m/z* Calculated for $C_8H_9{}^{35}ClOS^+$ $[M]^+$: 188.0057; Found: 188.0052 $[M]^+$, Δ 2.7 ppm. The observed data (^{1}H) is consistent with that reported in the literature.[229]

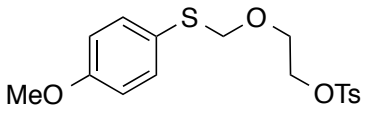
2-(((4-Methoxyphenyl)thio)methoxy)ethanol (72j)



Sodium hydride (60% in mineral oil, 1.40 g, 35.09 mmol) was added to ethylene glycol (300 mL) at 0 ºC and stirred for 1 h 30 min. Sodium iodide (5.26 g, 35.09 mmol) was added followed by chloromethyl sulfide **82j** (6.00 g, 31.80 mmol). The resulting solution was stirred at 0 ºC for 2 h then warmed to rt for 16 h. Water (150 mL) was added and the product was extracted with ethyl acetate (10 × 25 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (30% EtOAc/hexane) afforded alcohol **72j** (3.95 g, 58%) as a colourless oil. R_f = 0.10 (30% EtOAc/hexane) IR (film)/cm^{-1} 3403 (OH), 2937, 1591, 1493, 1461, 1440, 1284, 1240, 1174, 1053, 1025, 887, 822, 676. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (2 H, d, *J* = 8.7 Hz, 2 × Ar-H), 6.86 (2 H, d, *J* = 8.7 Hz, 2 × Ar-H), 4.93 (2 H, s, SCH_2O), 3.80 (3 H, s, OCH_3), 3.78–3.71 (4 H, m, OCH_2CH_2OH), 2.07 (1 H, br s,

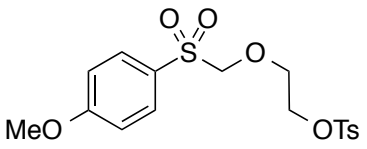
OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4 (C_q), 133.8 (2 × Ar-C), 125.4 (C_q), 114.6 (2 × Ar-C) 77.8 (SCH_2O), 69.7 (CH_2OCH_2), 61.6 (CH_2OH), 55.3 (OCH_3). HRMS (EI) *m/z* Calculated for $C_{10}H_{14}O_3S$ [M]: 214.0664; Found: 214.0665 [M], Δ 0.5 ppm.

2-(((4-Methoxyphenyl)thio)methoxy)ethyl-4-methylbenzenesulfonate (83j)



Triethylamine (6.87 mL, 48.93 mmol) and trimethylamine hydrochloride (0.15 g, 1.63 mmol) were added to a solution of sulfide **72j** (3.53 g, 16.47 mmol) in toluene (70 mL) at 0 ºC and stirred for 1 h. 4-Toluenesulfonyl chloride (6.22 g, 32.63 mmol) was added portionwise. The mixture was stirred at 0 ºC for 50 min then allowed to warm to rt and stirred for a further 1 h 30 min. Water (75 mL) was added to the reaction and the product was extracted with EtOAc (5 × 25 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (20% EtOAc/hexane) afforded *p*-toluenesulfonate **83j** (5.93 g, 98%) as a yellow oil. R_f = 0.23 (20% EtOAc/hexane). IR (film)/cm^{-1} 2954, 1595, 1493, 1353, 1286, 1245, 1172, 1095, 1003, 912, 814, 771, 661. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (2 H, d, *J* = 7.9 Hz, 2 × Ts-H), 7.37 (2 H, d, *J* = 8.8 Hz, 2 × Ar-H), 7.31 (2 H, d, *J* = 7.9 Hz, 2 × Ts-H), 6.82 (2 H, d, *J* = 8.8 Hz, 2 × Ar-H), 4.81 (2 H, s, SCH_2O), 4.21–4.17 (2 H, m, $TsOCH_2$), 3.82–3.76 (5 H, m, OCH_3 + CH_2OCH_2), 2.43 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4 (Ar-C_q), 144.8 (Ts-C_q), 133.8 (2 × Ar-C), 132.9 (Ts-C_q), 129.8 (2 × Ts-C), 128.0 (2 × Ts-C), 125.3 (Ar-C_q), 114.6 (2 × Ar-C), 77.7 (SCH_2O), 68.7 (CH_2OCH_2), 65.5 ($TsOCH_2$), 55.3 (OCH_3), 21.6 (CH_3). HRMS (ES) *m/z* Calculated for $C_{17}H_{20}O_5S_2$ $[M]^+$: 368.0747; Found: Accurate mass not found due to degradation.

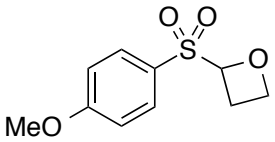
2-(((4-Methoxyphenyl)sulfonyl)methoxy)ethyl-4-methylbenzenesulfonate (84j)



meta-Chloroperbenzoic acid (5.62 g, 32.57 mmol) was added to a solution of sulfide **83j** (4.00 g, 10.86 mmol) in dichloromethane (150 mL) at 0 ºC and the mixture stirred at 0 ºC

for 2 h then warmed to rt and stirred for a further 3 h. The reaction was quenched with sat. aq. Na_2SO_3 (30 mL) and extracted with dichloromethane (5 × 25 mL). The combined organic layers were washed with 1 M NaOH (2 × 20 mL) and sat. aq. NH_4Cl (15 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (40% EtOAc/hexane) afforded sulfone **84j** (3.81 g, 88%) as a white solid; m.p. = 85–87 ºC. R_f = 0.12 (40% EtOAc/hexane). IR (film)/cm^{-1} 3013, 2981, 1594, 1498, 1456, 1287, 1255, 1174, 1135, 1081, 1009, 994, 957, 815, 755, 658. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (2 H, d, *J* = 9.2 Hz, 2 × Ar-H), 7.77 (2 H, d, *J* = 7.8 Hz, 2 × Ts-H), 7.34 (2 H, d, *J* = 7.8 Hz, 2 × Ts-H), 7.04 (2 H, d, *J* = 9.2 Hz, 2 × Ar-H), 4.48 (2 H, s, SCH_2O), 4.17–4.13 (2 H, m, OCH_2CH_2), 4.09–4.06 (2 H, m, OCH_2CH_2), 3.90 (3 H, s, OCH_3), 2.46 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2 (Ar-C_q), 145.0 (Ts-C_q), 132.7 (Ts-C_q), 131.1 (2 × Ar-C), 129.9 (2 × Ts-C), 128.2 (Ar-C_q), 127.9 (2 × Ts-C), 114.6 (2 × Ar-C), 86.2 (SCH_2O), 70.5 (OCH_2CH_2), 68.5 (OCH_2CH_2), 55.7 (OCH_3), 21.6 (CH_3). HRMS (ES) *m/z* Calculated for $C_{17}H_{21}O_7S_2$ [M+H]: 401.0729; Found: 401.0724. [M+H], Δ 1.2 ppm.

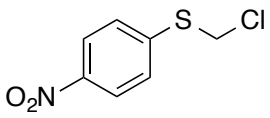
2-((4-Methoxyphenyl)sulfonyl)oxetane (93)



A solution of LiHMDS (0.61 M in THF, 3.38 mL, 2.06 mmol) was added dropwise to a solution of sulfone **84j** (0.75 g, 1.87 mmol) in THF (58 mL) at 0 ºC and stirred for 1 h 30 min. The reaction was quenched with sat. aq. NH_4Cl (40 mL) and extracted with CH_2Cl_2 (5 × 25 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (40% EtOAc/hexane) afforded oxetane **93** (0.40 g, 95%) as a white solid; m.p = 65–66 ºC. R_f = 0.12 (40% EtOAc/hexane). IR (film)/cm^{-1} 2973, 2929, 1594, 1497, 1448, 1302, 1262, 1136, 1090, 1058, 1027, 976, 896, 828, 801, 726, 696. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (2 H, d, *J* = 9.7 Hz, 2 × Ar-H), 7.02 (2 H, d, *J* = 9.7 Hz, 2 × Ar-H), 5.33 (1 H, dd, *J* = 7.8, 5.5 Hz, OCHS), 4.74–4.67 (1 H, m, OCH*H*), 4.61 (1 H, ddd, *J* = 8.3, 6.0, 5.5 Hz, OC*H*H), 3.87 (3 H, s, OCH_3), 3.13–2.97 (2 H, m, OCH_2CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3 (C_q), 131.7 (2 × Ar-C), 126.4 (C_q), 114.5 (2 × Ar-C), 94.0 (OCHS), 71.2 (OCH_2), 55.7

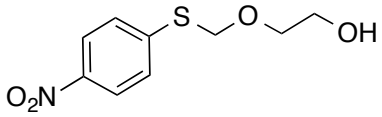
(OCH_3), 22.5 (OCH_2CH_2). HRMS (APCI) *m/z* Calculated for $C_{10}H_{16}NO_4S^+$ $[M+NH_4]^+$: 246.0795; Found: 246.0793 $[M+NH_4]^+$, Δ 0.8 ppm.

1-[(Chloromethyl)sulfanyl]-4-nitrobenzene (82k)[229]



N-Chlorosuccinimide (2.17 g, 16.25 mmol) was added portionwise to a solution of 4-nitroanisole (2.50 g, 14.78 mmol) in dichloroethane (25 mL). The reaction was stirred at rt for 17 h then filtered through a short pad of silica, eluting with dichloromethane (25 mL). The solvent was removed under reduced pressure to afford chloromethyl sulfide **82k** (3.04 g, quant) as a pale yellow solid, which was used without further purification; m.p. = 58–59 ºC (lit m.p. 63–64 ºC)[236]. R_f = 0.81 (100% EtOAc). IR (film)/cm^{-1} 3098, 3022, 2964, 2829, 1593, 1575, 1500 (NO_2), 1479, 1401, 1319 (NO_2), 1235, 1186, 1110, 1089, 964, 836, 735, 720. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (2 H, d, *J* = 9.0 Hz, 2 × Ar-H), 7.57 (2 H, d, *J* = 9.0 Hz, 2 × Ar-H), 5.07 (2 H, s, SCH_2Cl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7 (C_q), 141.3 (C_q), 127.5 (2 × Ar-C), 123.9 (2 × Ar-C), 47.1 (SCH_2Cl). HRMS (CI) *m/z* Calculated for $C_7H_7{}^{35}ClNO_2S^+$ $[M+H]^+$: 203.9881; Found: 203.9879 $[M+H]^+$, Δ 1.0 ppm. The observed data (^{1}H) was consistent with that reported in the literature.[229]

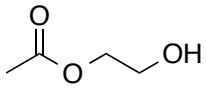
2-{[(4-Nitrophenyl)sulfanyl]methoxy}ethan-1-ol (72k)



Sodium hydride (60% in mineral oil, 0.11 g, 2.70 mmol) was added to ethylene glycol (25 mL) at 0 ºC and stirred for 1 h 30 min. Sodium iodide (0.41 g, 2.71 mmol) was added followed by chloromethyl sulfide **82k** (0.50 g, 2.46 mmol). DMF (1 mL) was added to aid solubility. The resulting solution was stirred at 0 ºC for 30 min then warmed to rt for 15 h 30 min. Water (50 mL) was added and the product was extracted with ethyl acetate (10 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (50%

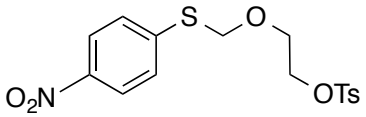
EtOAc/hexane) afforded alcohol **72k** (0.22 g, 39%) as a pale yellow solid; m.p. = 40–41 ºC. R_f = 0.15 (50% EtOAc/hexane). IR (film)/cm^{-1} 2923, 1595, 1578, 1510 (NO), 1479, 1338 (NO), 1109, 1080, 1062, 888, 853, 742, 683. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (2 H, d, *J* = 8.9 Hz, 2 × Ar-H), 7.57 (2 H, d, *J* = 8.9 Hz, 2 × Ar-H), 5.18 (2 H, s, SCH_2O), 3.82–3.75 (4 H, m, OCH_2CH_2OH), 1.84 (1 H, br s, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.0 (C_q), 145.8 (C_q), 127.8 (2 × Ar-C), 124.0 (2 × Ar-C), 74.5 (SCH_2O), 70.2 (OCH_2), 61.5 (OCH_2). HRMS (APCI) *m/z* Calculated for $C_9H_{15}N_2O_4S^+$ $[M+NH_4]^+$: 247.0747; Found: 247.0749 $[M+NH_4]^+$, Δ 0.8 ppm.

2-Hydroxyethyl acetate (98)[237]



Above procedure afforded alcohol **98** (0.13 g, 1.28 mmol) as a colourless liquid. R_f = 0.13 (50% EtOAc/hexane). IR (film)/cm^{-1} 3358 (OH), 2928, 1575, 1454, 1431, 1309, 1253, 1056, 1018, 888, 825, 745, 656. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19–4.15 (2 H, m, OCH_2), 3.81–3.77 (2 H, m, OCH_2), 2.50 (1 H, br s, OH), 2.07 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4 (C=O), 65.9 (OCH_2), 60.8 (OCH_2), 20.8 (CH_3). HRMS (CI) *m/z* Calculated for $C_4H_{12}NO_3^+$ $[M+NH_4]^+$: 122.0812; Found: 122.0827 $[M+NH_4]^+$. The observed data (^{1}H) was consistent with that reported in the literature.[237]

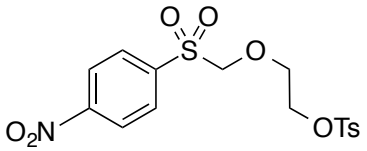
2-{[(4-Nitrophenyl)sulfanyl]methoxy}ethyl-4-methylbenzene-1-sulfonate (83k)



Triethylamine (0.24 mL, 1.71 mmol) and trimethylamine hydrochloride (6 mg, 0.06 mmol) were added to a solution of sulfide **72k** (0.13 g, 0.57 mmol) in toluene (2 mL) at 0 ºC and stirred for 30 min. 4-Toluenesulfonyl chloride (0.22 g, 1.15 mmol) was added portionwise. The mixture was stirred at 0 ºC for 30 min then allowed to warm to rt slowly over 30 min and stirred for a further 1 h 30 min. Water (20 mL) was added to the reaction and the product was extracted with EtOAc (4 × 20 mL). The combined organic layers were washed with brine (25 mL) and H_2O (20 mL) then dried ($MgSO_4$), filtered and the

solvent removed under reduced pressure. Purification by flash chromatography (40% EtOAc/hexane) afforded *p*-toluenesulfonate **83k** (0.19 g, 90%) as a white solid; m.p. = 82–83 ºC. R_f = 0.29 (40% EtOAc/hexane). IR (film)/cm^{-1} 2925, 1593, 1577, 1505 (NO), 1454, 1345 (NO), 1332, 1280, 1188, 1172, 1103, 1085, 1013, 946, 852, 837, 810, 781, 739, 682. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (2 H, d, *J* = 8.7 Hz, 2 × Ar-H), 7.78 (2 H, d, *J* = 8.2 Hz, 2 × Ts-H), 7.50 (2 H, d, *J* = 8.7 Hz, 2 × Ar-H), 7.34 (2 H, d, *J* = 8.2 Hz, 2 × Ts-H), 5.08 (2 H, s, SCH_2O), 4.25–4.21 (2 H, m, $TsOCH_2$), 3.88–3.84 (2 H, m, CH_2OCH_2), 2.46 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.9 (Ar-C_q), 145.6 (Ar-C_q), 145.1 (Ts-C_q), 132.8 (Ts-C_q), 129.8 (2 × Ts-C), 128.0 (2 × Ts-C), 127.9 (2 × Ar-C), 123.9 (2 × Ar-C), 74.3 (SCH_2O), 68.3 ($TsOCH_2$), 66.0 (CH_2OCH_2), 21.6 (CH_3). HRMS (NSI) *m/z* Calculated for $C_{16}H_{21}N_2O_6S_2^+$ $[M+NH_4]^+$: 401.0836; Found: 401.0834 $[M+NH_4]^+$, Δ 0.5 ppm.

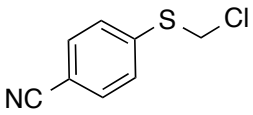
1-({2-[(4-Methylbenzenesulfonyl)oxy]ethoxy}methanesulfonyl)-4-nitrobenzene (84k)



meta-Chloroperbenzoic acid (0.13 g 0.75 mmol) was added to a solution of sulfide **83k** (96 mg, 0.25 mmol) in dichloromethane (4 mL) at 0 ºC and the mixture stirred at 0 ºC for 2 h 30 min. The reaction was quenched with sat. aq. Na_2SO_3 (10 mL) and extracted with dichloromethane (6 × 20 mL). The combined organic layers were washed with 1 M NaOH (3 × 10 mL) and sat. aq. NH_4Cl (20 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (50% EtOAc/hexane) afforded sulfone **84k** (95 mg, 91%) as a white solid. R_f = 0.18 (50% EtOAc/hexane). IR (film)/cm^{-1} 3107, 1598, 1532 (NO), 1453, 1350 (NO), 1301, 1248, 1175, 1154, 1133, 1081, 1019, 916, 854, 816, 772, 740, 664. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (2 H, d, *J* = 8.7 Hz, 2 × Ar-H), 8.12 (2 H, d, *J* = 8.7 Hz, 2 × Ar-H), 7.77 (2 H, d, *J* = 8.2 Hz, 2 × Ts-H), 7.36 (2 H, d, *J* = 8.2 Hz, 2 × Ts-H), 4.61 (2 H, s, SCH_2O), 4.19–4.12 (4 H, m, OCH_2CH_2OTs), 2.46 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2 (Ar-C_q), 145.3 (Ts-C_q), 142.4 (Ar-C_q), 132.6 (Ts-C_q), 130.5 (2 × Ar-C), 130.0 (2 × Ts-C), 127.9 (2 × Ts-C), 124.4 (2 × Ar-C), 85.9 (SCH_2O), 70.8 (OCH_2), 68.2 (OCH_2), 21.7

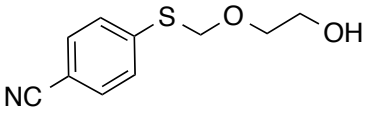
(CH_3). HRMS (ESI) *m/z* Calculated for $C_{16}H_{17}NNaO_8S_2^+$ $[M+Na]^+$: 438.0288; Found: 438.0272 $[M+Na]^+$, Δ 3.7 ppm.

4-[(Chloromethyl)sulfanyl]benzonitrile (82l)[238]



N-Chlorosuccinimide (2.46 g, 18.42 mmol) was added portionwise to a solution of 4-(methylthio)benzonitrile (2.50 g, 16.75 mmol) in dichloroethane (25 mL). The reaction was stirred at rt for 18 h then filtered through a short pad of silica, eluting with dichloromethane (50 mL). The solvent was removed under reduced pressure to afford chloromethyl sulfide **82l** (3.00 g, 97%) as an off white solid, which was used without further purification; m.p. = 146–147 ºC. R_f = 0.51 (40% EtOAc/hexane). IR(film)/cm^{-1} 3034, 2224 (CN), 1590, 1486, 1403, 1224, 1140, 1123, 1085, 1016, 831, 811, 736. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.65 (2 H, d, *J* = 8.6 Hz, 2 × Ar-H), 7.55–7.52 (2 H, d, *J* = 8.6 Hz, 2 × Ar-H), 5.04 (2 H, s, SCH_2Cl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6 (Ar-C_q), 132.6 (2 × Ar-C), 128.4 (2 × Ar-C), 118.4 (CN), 110.5 (Ar-C_q), 47.8 (SCH_2Cl). HRMS (EI) *m/z* Calculated for $C_8H_6NS_2{}^{35}Cl$ [M]: 182.9909; Found: 182.9908 [M], Δ 0.5 ppm. The observed data (^{1}H and ^{13}C) is consistent with that reported in the literature.[238]

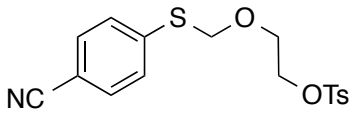
4-{[(2-Hydroxyethoxy)methyl]sulfanyl}benzonitrile (72l)



Potassium *t*-butoxide (1.01 g, 9.00 mmol) was added to a solution of ethylene glycol (4.6 mL, 82.50 mmol) in DMF (67 mL) at 0 ºC and stirred for 1 h. Potassium iodide (1.49 g, 8.98 mmol) was added followed by sulfide **82l** (1.50 g, 8.17 mmol). DMF (2 mL) was added to aid solubility. The resulting solution was stirred at 0 ºC for 1 h then warmed to rt for 14 h. Water (100 mL) was added and the product was extracted with ethyl acetate (7 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (40%

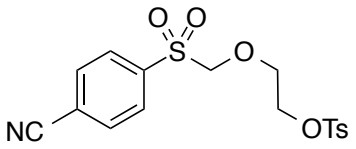
EtOAc/hexane) afforded alcohol **72l** (0.76 g, 44%) as a colourless oil. R_f = 0.09 (40% EtOAc/hexane). IR (film)/cm^{-1} 3411 (OH), 2925, 2226 (CN), 1592, 1457, 1432, 1402, 1316, 1303, 1273, 1181, 1106, 1085, 1058, 1016, 975, 888, 822, 778, 760, 680. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (2 H, d, *J* = 8.7 Hz, 2 × Ar-H), 7.54 (2 H, d, *J* = 8.7 Hz, 2 × Ar-H), 5.16 (2 H, s, SCH_2O), 3.83–3.76 (4 H, m, OCH_2CH_2OH), 1.77 (1 H, br s, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4 (Ar-C_q), 132.3 (2 × Ar-C), 128.4 (2 × Ar-C), 118.7 (CN), 109.5 (Ar-C_q), 74.7 (SCH_2O), 70.1 (OCH_2), 61.5 (OCH_2). HRMS (CI) *m/z* Calculated for $C_{10}H_{12}NO_2S^+$ $[M+H]^+$: 210.0583; Found: 210.0579 $[M+H]^+$, Δ 1.9 ppm.

2-{[(4-Cyanophenyl)sulfanyl]methoxyethyl-4-methylbenzene-1-sulfonate (83l)



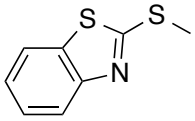
Triethylamine (2.52 mL, 17.93 mmol) and trimethylamine hydrochloride (57 mg, 0.60 mmol) were added to a solution of sulfide **82l** (1.26 g, 6.03 mmol) in toluene (20 mL) at 0 ºC and stirred for 30 min. 4-Toluenesulfonyl chloride (2.30 g, 12.06 mmol) was added portionwise. The mixture was stirred at 0 ºC for 35 min then allowed to warm to rt slowly and stirred for a further 3 h. Water (75 mL) was added to the reaction and the product was extracted with EtOAc (4 × 25 mL). The combined organic layers were washed with brine (25 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (30% EtOAc/hexane) afforded *p*-toluenesulfonate **83l** (1.79 g, 82%) as an off white solid; m.p. = 86–87 ºC. R_f = 0.18 (30% EtOAc/hexane). IR (film)/cm^{-1} 2221 (CN), 1590, 1487, 1430, 1317, 1292, 1240, 1188, 1171, 1118, 1081, 1029, 995, 907, 822, 761, 683. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (2 H, d, *J* = 8.4 Hz, 2 × Ts-H), 7.54–7.46 (4 H, m, 4 × Ar-H), 7.34 (2 H, d, *J* = 8.4 Hz, 2 × Ts-H), 5.04 (2 H, s, SCH_2O), 4.24–4.20 (2 H, m, $TsOCH_2$), 3.85–3.82 (2 H, m, CH_2OCH_2), 2.46 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0 (Ts-C_q), 143.0 (Ar-C_q), 132.8 (Ts-C_q), 132.3 (2 × Ar-C), 129.8 (2 × Ts-C), 128.5 (2 × Ar-C), 127.9 (2 × Ts-C), 118.6 (CN), 109.5 (Ar-C_q), 74.5 (SCH_2O), 68.4 (OCH_2), 65.9 (OCH_2), 21.7 (CH_3). HRMS (NSI) *m/z* Calculated for $C_{17}H_{21}N_2O_4S_2^+$ $[M+NH_4]^+$: 381.0937; Found: 381.0940 $[M+NH_4]^+$, Δ 0.8 ppm.

4-({2-[(4-Methylbenzenesulfonyl)oxy]ethoxy)methanesulfonyl)benzonitrile (84l)



meta-Chloroperbenzoic acid (0.71 g 4.14 mmol) was added to a solution of sulfide **83l** (0.50 g, 1.38 mmol) in dichloromethane (20 mL) at 0 ºC and the mixture stirred at 0 ºC for 5 h. The reaction was quenched with sat. aq. Na_2SO_3 (30 mL) and extracted with dichloromethane (5 × 15 mL). The combined organic layers were washed with 1 M NaOH (2 × 15 mL) and sat. aq. NH_4Cl (15 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (60% EtOAc/hexane) afforded sulfone **84l** (0.54 g, 99%) as a white solid; m.p. = 97–98 ºC. R_f = 0.33 (60% EtOAc/hexane). IR (film)/cm^{-1} 3097, 2233 (CN), 1598, 1451, 1400, 1352, 1306, 1286, 1251, 1174, 1133, 1115, 1079, 1000, 910, 816, 772, 664. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (2 H, d, *J* = 8.3 Hz, 2 × Ar-H), 7.85 (2 H, d, *J* = 8.3 Hz, 2 × Ar-H), 7.76 (2 H, d, *J* = 8.2 Hz, 2 × Ts-H), 7.35 (2 H, d, *J* = 8.2 Hz, 2 × Ts-H), 4.59 (2 H, s, SCH_2O), 4.17–4.10 (4 H, m, OCH_2CH_2OTs), 2.45 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2 (Ts-C_q), 140.9 (Ar-C_q), 132.9 (2 × Ar-C), 132.5 (Ts-C_q), 129.9 (2 × Ts-C), 129.6 (2 × Ar-C), 127.8 (2 × Ts-C), 117.9 (CN), 117.1 (Ar-C_q), 85.7 (SCH_2O), 70.6 (OCH_2), 68.3 (OCH_2), 21.6 (CH_3). HRMS (ES) *m/z* Calculated for $C_{17}H_{17}NNaO_6S_2$ [M+Na]: 418.0395; Found: 418.0410 [M+Na], Δ 3.6 ppm.

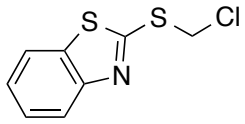
2-(Methylthio)benzothiazole (81m)[239]



Potassium carbonate (0.91 g, 6.58 mmol) was added to a solution of 2-mercaptobenzothiazole (1.00 g, 5.98 mmol) in acetone (100 mL) followed by MeI (0.39 mL, 6.26 mmol) and the reaction stirred at rt for 64 h. The reaction was filtered through Celite® and the solvent removed under reduced pressure. The crude material was dissolved in diethyl ether (50 mL) and washed with 1 M NaOH (3 × 20 mL). The combined aqueous layers were extracted with diethyl ether (20 mL) then the combined

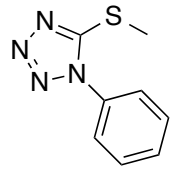
organics were washed with brine (40 mL), dried ($MgSO_4$) and solvent removed under reduced pressure to afford methyl sulfide **81m** (1.04 g, 96%) as a yellow solid, which was used without further purification. R_f = 0.75 (100% EtOAc). IR (film)/cm^{-1} 3052, 2990, 2927, 1454 (C=N), 1423, 1307, 1272, 1162, 1153, 1073, 1019, 1003, 959, 889, 852, 721, 705, 678. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (1 H, ddd, *J* = 8.2, 1.2, 0.6 Hz, Ar-H), 7.77 (1 H, ddd, *J* = 8.2, 1.2, 0.6 Hz, Ar-H), 7.43 (1 H, ddd, *J* = 8.2, 7.3, 1.2 Hz, Ar-H), 7.30 (1 H, ddd, *J* = 8.2, 7.3, 1.2 Hz, Ar-H), 2.81 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1 (C_q), 153.3 (C_q), 135.1 (C_q), 126.0 (Ar-C), 124.1 (Ar-C), 121.4 (Ar-C), 120.9 (Ar-C), 15.9 (CH_3). HRMS (CI) *m/z* Calculated for $C_8H_8NS_2$ [M+H]: 182.0098; Found: 182.0103 [M+H], Δ 2.7 ppm. The observed data (^{1}H and ^{13}C) was consistent with that reported in the literature.[239]

(2-Chloromethylthio)benzothiazole (82m)[240]



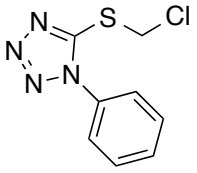
Sodium hydride (60% in mineral oil, 0.53 g, 13.26 mmol) was added to a solution of 2-mercaptobenzothiazole (2.00 g, 11.96 mmol) in DMF (35 mL) at –5 ºC and stirred for 10 min. A solution of chloroiodomethane (1.30 mL, 17.85 mmol) in DMF (5 mL) was added dropwise and stirred for 2 h at rt. The reaction was quenched by the addition of sat. aq. NH_4Cl (100 mL) and diluted with EtOAc (30 mL) then extracted with EtOAc (4 × 30 mL). The combined organic layers were washed with H_2O (3 × 20 mL) and brine (20 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to give chloromethyl sulfide **82m** (2.46 g, 95%) as an orange oil, which was used without further purification. R_f = 0.74 (100% EtOAc). IR (film)/cm^{-1} 3061, 3021, 2924, 1662, 1598, 1490, 1456 (C=N), 1423, 1310, 1234, 1077, 1033, 992, 851, 752, 721, 658. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (1 H, d, *J* = 8.2 Hz, Ar-H), 7.82 (1 H, d, *J* = 8.2 Hz, Ar-H), 7.50–7.46 (1 H, m, Ar-H), 7.39–7.34 (1 H, m, Ar-H), 5.39 (2 H, s, SCH_2Cl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7 (C_q), 152.4 (C_q), 135.3 (C_q), 126.4 (Ar-C), 125.0 (Ar-C), 122.1 (Ar-C), 121.2 (Ar-C), 46.6 (SCH_2Cl). HRMS (CI) *m/z* Calculated for $C_8H_7{}^{35}ClNS_2$ [M+H]: 215.9708; Found: 215.9717 [M+H], Δ 4.2 ppm. The observed data (^{1}H, IR) was consistent with that reported in the literature.[240]

5-Methylsulfanyl-1-phenyl-5H-1,2,3,4-tetrazol-1-ium (81n)



Potassium carbonate (0.88 g, 6.37 mmol) was added to a solution of 1-phenyl-1H-tetrazole-5-thiol (1.03 g, 5.78 mmol) in acetone (100 mL) followed by MeI (0.38 mL, 6.07 mmol) and the reaction stirred at rt for 64 h. The reaction was filtered through Celite® and the solvent removed under reduced pressure. The crude material was dissolved in diethyl ether (50 mL) and washed with 1 M NaOH (3 × 20 mL). The combined aqueous layers were extracted with diethyl ether (20 mL) then the combined organics were washed with brine (40 mL), dried ($MgSO_4$) and solvent removed under reduced pressure to afford methyl sulfide **81n** (1.02 g, 93%) as a white solid, which was used without further purification; m.p. = 82–83 ºC. R_f = 0.68 (100% EtOAc). IR (film)/cm^{-1} 3059, 2935, 1597, 1498, 1417, 1399, 1314, 1279, 1244, 1077, 1012, 979, 694. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.50 (5 H, m, 5 × Ar-H), 2.83 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9 (S-C_q), 133.6 (C_q), 130.1 (Ar-C), 129.8 (2 × Ar-C), 123.6 (2 × Ar-C), 15.4 (CH_3). HRMS (ES) *m/z* Calculated for $C_{10}H_{12}N_5S$ [M+H+CH_3CN]: 234.0813; Found: 234.0822 [M+H+CH_3CN], Δ 3.8 ppm.

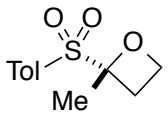
5-Chloromethylsulfanyl-1-phenyl-5H-1,2,3,4-tetrazol-1-ium (82n)



Sodium hydride (60% in mineral oil, 0.49 g, 12.30 mmol) was added to a solution of 5-methylsulfanyl-1-phenyl-5H-1,2,3,4-tetrazol-1-ium (2.00 g, 11.22 mmol) in DMF (35 mL) at –5 ºC and stirred for 10 min. A solution of chloroiodomethane (1.22 mL, 16.83 mmol) in DMF (5 mL) was added dropwise and stirred for 3 h at rt. The reaction was quenched by the addition of sat. aq. NH_4Cl (100 mL) and diluted with EtOAc (30 mL) then extracted with EtOAc (4 × 30 mL). The combined organic layers were washed with H_2O (3 × 20 mL) and brine (20 mL) then dried ($MgSO_4$), filtered and the

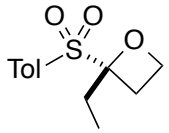
solvent removed under reduced pressure to give chloromethyl sulfide **82n** (2.42 g, 95%) as an orange solid, which was used without further purification, m.p. = 92–93 ºC. R_f = 0.73 (100% EtOAc). IR (film)/cm^{-1} 3044, 1594, 1500, 1419, 1392, 1241, 1092, 1014, 977, 918, 845, 758, 727, 685, 660. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.53 (5 H, m, 5 × Ar-H), 5.38 (2 H, s, SCH_2Cl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4 (S-C_q), 133.1 (C_q), 130.6 (Ar-C), 130.0 (2 × Ar-C), 124.0 (2 × Ar-C), 45.4 (SCH_2Cl). HRMS (ES) *m/z* Calculated for $C_8H_8{}^{35}ClN_4S$ [M+H]: 227.0158; Found: 227.0168 [M+H], Δ 4.4 ppm.

2-Methyl-2-(4-methylbenzenesulfonyl)oxetane (103)



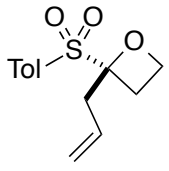
A solution of oxetane **55** (50 mg, 0.24 mmol) in THF (1 mL) was added dropwise to a solution of LiHMDS (1 M in THF, 0.25 mL, 0.25 mmol) in THF (0.95 mL) at –78 ºC. Methyl iodide (0.03 mL, 0.47 mmol) was added immediately and the reaction stirred at –78 ºC for 1 h, before being warmed to 0 ºC in an ice bath for 15 min. The reaction was quenched by the addition of sat. aq. NH_4Cl (6 mL) and extracted with $CHCl_3$ (5 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by filtration through a pad of basic alumina (activity IV) eluting with Et_2O (15 mL) afforded oxetane **103** (51 mg, 93%) as a yellow solid. R_f = 0.27 (20% EtOAc/hexane). IR (film)/cm^{-1} 3064, 2978, 2906, 1602, 1444, 1375, 1287, 1141, 1113, 1075, 973, 941, 864, 749. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (2 H, d, *J* = 8.2 Hz, 2 × Ar-H), 7.37 (2 H, d, *J* = 8.2 Hz, 2 × Ar-H), 4.56–4.51 (1 H, m, OCH*H*), 4.45 (1 H, ddd, *J* = 8.5, 5.5, 5.4 Hz, OC*H*H), 3.25 (1 H, ddd, *J* = 12.4, 8.5, 5.4 Hz, OCH_2CH*H*), 2.76 (1 H, ddd, *J* = 12.4, 8.5, 7.6 Hz, OCH_2C*H*H), 2.45 (3 H, s, Ar-CH_3), 1.64 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1 (Ar-C_q), 130.9 (Ar-C_q), 130.3 (2 × Ar-C), 129.6 (2 × Ar-C), 100.3 (C_q), 67.3 (OCH_2), 28.6 (OCH_2CH_2), 22.1 (CH_3), 21.7 (Ar-CH_3). HRMS (APCI) *m/z* Calculated for $C_{11}H_{15}O_3S^+$ $[M+H]^+$: 227.0736; Found: 227.0736 $[M+H]^+$, Δ 0 ppm.

2-Ethyl-2-(4-methylbenzenesulfonyl)oxetane (107)



A solution of oxetane **55** (50 mg, 0.24 mmol) in THF (1 mL) was added dropwise to a solution of LiHMDS (1 M in THF, 0.25 mL, 0.25 mmol) in THF (0.95 mL) at –78 ºC. Ethyl iodide (0.04 mL, 0.46 mmol) was added immediately and the reaction stirred at –78 ºC for 1 h, before being warmed to 0 ºC in an ice bath for 15 min. The reaction was quenched by the addition of sat. aq. NH_4Cl (6 mL) and extracted with $CHCl_3$ (5 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by filtration through a pad of basic alumina (activity IV) eluting with Et_2O (15 mL) afforded oxetane **107** (47 mg, 85%) as a white solid. R_f = 0.44 (40% EtOAc/hexane). IR (film)/cm^{-1} 2971, 2899, 1596, 1460, 1309, 1299, 1288, 1237, 1113, 1076, 1035, 967, 952, 931, 853, 813, 707. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (2 H, d, *J* = 8.2 Hz, 2 × Ar-H), 7.37 (2 H, d, *J* = 8.2 Hz, 2 × Ar-H), 4.55–4.50 (1 H, m, OCH*H*), 4.38 (1 H, ddd, *J* = 8.7, 5.6, 5.4 Hz, OC*H*H), 3.11 (1 H, ddd, *J* = 12.7, 8.7, 5.6 Hz, OCH_2CH*H*), 2.87 (1 H, ddd, *J* = 12.7, 8.7, 7.3 Hz, OCH_2C*H*H), 2.45 (3 H, s, Ar-CH_3), 2.00–1.91 (1 H, m, CCH*H*CH_3), 1.76–1.65 (1 H, m, CC*H*HCH_3), 1.17 (3 H, t, *J* = 7.6 Hz, CCH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0 (Ar-C_q), 131.5 (Ar-C_q), 130.4 (2 × Ar-C), 129.5 (2 × Ar-C), 103.5 (C_q), 67.8 (OCH_2), 26.2 (CCH_2CH_3), 24.1 (OCH_2CH_2), 21.6 (Ar-CH_3), 7.1 (CH_2CH_3). HRMS (ESI) *m/z* Calculated for $C_{12}H_{17}O_3S^+$ $[M+H]^+$: 241.0893; Found: 241.0894 $[M+H]^+$, Δ 0.4 ppm.

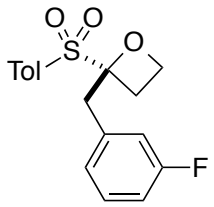
2-Allyl-2-(4-methylbenzenesulfonyl)oxetane (108)



A solution of oxetane **55** (50 mg, 0.24 mmol) in THF (1 mL) was added dropwise to a solution of LiHMDS (1 M in THF, 0.25 mL, 0.25 mmol) in THF (0.95 mL) at –78 ºC. Allyl bromide (0.04 mL, 0.48 mmol) was added immediately and the reaction stirred at –78 ºC for 1 h, before being warmed to 0 ºC in an ice bath for 15 min. The reaction was

quenched by the addition of sat. aq. NH_4Cl (6 mL) and extracted with $CHCl_3$ (5 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by filtration through a pad of basic alumina (activity IV) eluting with Et_2O (15 mL) afforded oxetane **108** (54 mg, 91%) as an orange solid. R_f = 0.28 (20% EtOAc/hexane). IR (film)/cm^{-1} 2970, 2899, 1641, 1597, 1403, 1300, 1288, 1235, 1156, 1106, 1070, 944, 857, 814, 710. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (2 H, d, *J* = 8.2 Hz, 2 × Ar-H), 7.38 (2 H, d, *J* = 8.2 Hz, 2 × Ar-H), 6.08–5.89 (1 H, m, C*H*=), 5.33–5.24 (2 H, m, =C*H*$_2$), 4.46 (1 H, ddd, *J* = 8.6, 7.5, 5.5 Hz, OCH*H*), 4.32 (1 H, ddd, *J* = 8.9, 5.7, 5.5 Hz, OC*H*H), 3.06 (1 H, ddd, *J* = 12.7, 8.6, 5.7 Hz, OCH_2CH*H*), 2.87 (1 H, ddd, *J* = 12.7, 8.9, 7.5 Hz, OCH_2C*H*H), 2.61 (1 H, dd, *J* = 14.6, 8.8 Hz, C*H*HCH=CH_2), 2.47–2.41 (4 H, m, CH_3 + CH*H*CH=CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2 (Ar-C_q), 131.0 (Ar-C_q), 130.4 (2 × Ar-C), 130.1 (CH=), 129.6 (2 × Ar-C), 121.0 (=CH_2), 101.9 (C_q), 67.7 (OCH_2), 37.5 (*C*H_2CH=CH_2), 24.3 (OCH_2*C*H_2), 21.7 (CH_3). HRMS (ESI) *m/z* Calculated for $C_{13}H_{17}O_3S^+$ $[M+H]^+$: 253.0893; Found: 253.0899 $[M+H]^+$, Δ 2.4 ppm.

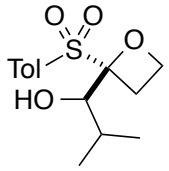
2-(3-Fluorobenzyl)-2-(4-methylbenzenesulfonyl)oxetane (109)



*n*BuLi (1.60 M in hexane, 0.18 mL, 0.28 mmol) was added dropwise to a solution of oxetane **55** (50 mg, 0.24 mmol) in THF (1.2 mL) at –78 ºC and stirred at –78 ºC for 5 min. 3-Fluorobenzyl bromide (0.06 mL, 0.48 mmol) was added and the reaction stirred at –78 ºC for 25 min. The reaction was quenched by the addition of sat. aq. NH_4Cl (6 mL) and extracted with $CHCl_3$ (5 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography on basic alumina (activity IV) (10–50% EtOAc/hexane) afforded oxetane **109** (68 mg, 90%) as a white solid. R_f = 0.26 (40% EtOAc/hexane). IR (film)/cm^{-1} 2970, 2899, 2255, 1616, 1590, 1487, 1449, 1301, 1255, 1155, 1104, 952, 941, 906, 861, 725, 703. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (2 H, d, *J* = 8.3 Hz, 2 × Tol-H), 7.40 (2 H, d, *J* = 8.3 Hz, 2 × Tol-H), 7.33–7.27 (1 H, m, Ar-H), 7.09–6.98 (3 H, m, 3 × Ar-H), 4.28–4.23 (1 H, m, OCH*H*), 3.83 (1 H, ddd, *J* = 9.0, 5.8, 5.6 Hz, OC*H*H), 3.14 (1 H, d, *J* = 14.3 Hz,

CC*H*H), 3.00 (1 H, ddd, *J* = 12.7, 8.6, 5.8 Hz, OCH_2CH*H*), 2.93 (1 H, d, *J* = 14.3 Hz, CCH*H*), 2.54–2.47 (1 H, m, OCH_2C*H*H) 2.48 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6 (d, $J_{C\text{-}F}$ = 245.0 Hz, Ar-C_q), 145.3 (Tol-C_q), 136.7 (d, $J_{C\text{-}F}$ = 7.0 Hz, Ar-C_q), 131.1 (Tol-C_q), 130.4 (2 × Tol-C), 129.8 (d, $J_{C\text{-}F}$ = 8.2 Hz, Ar-C), 129.7 (2 × Tol-C), 126.3 (d, $J_{C\text{-}F}$ = 2.6 Hz, Ar-C), 117.4 (d, $J_{C\text{-}F}$ = 21.3 Hz, Ar-C), 114.3 (d, $J_{C\text{-}F}$ = 21.3 Hz, Ar-C), 102.1 (C_q), 67.5 (OCH_2), 38.1 (CCH_2Ar), 24.2 (OCH_2CH_2), 21.7 (CH_3). HRMS (ESI) *m/z* Calculated for $C_{17}H_{18}FO_3S^+$ $[M+H]^+$: 321.0955; Found: 321.0978 $[M+H]^+$, Δ 7.2 ppm.

2-Methyl-1-(2-tosyloxetan-2-yl)propan-1-ol (110)



*n*BuLi (1.60 M in hexane, 0.18 mL, 0.28 mmol) was added dropwise to a solution of oxetane **55** (50 mg, 0.24 mmol) in THF (1.2 mL) at –78 ºC and stirred at –78 ºC for 5 min. *iso*-Butyraldehyde (0.04 mL, 0.48 mmol) was added and the reaction stirred at –78 ºC for 1 h. The reaction was quenched by the addition of sat. aq. NH_4Cl (6 mL) and extracted with $CHCl_3$ (5 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by filtration through a pad of basic alumina (activity IV) eluting with Et_2O (15 mL) afforded oxetane **110** (57 mg, 86%, dr 1:0.9) as a colourless oil. R_f = 0.28 (20% EtOAc/hexane). IR (film)/cm^{-1} 3504 (OH), 2966, 2905, 1596, 1493, 1448, 1365, 1311, 1299, 1287, 1154, 1134, 1067, 935, 815, 713.

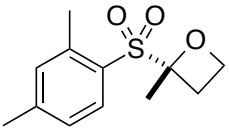
Major Diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (2 H, d, *J* = 8.0 Hz, 2 × Ar-H), 7.39 (2 H, d, *J* = 8.0 Hz, 2 × Ar-H), 4.30 (1 H, dt, *J* = 9.0, 5.7 Hz, OCH*H*), 4.14–4.03 (1 H, m, OC*H*H), 3.72–3.67 (1 H, m, HOC*H*), 3.24 (1 H, dt, *J* = 12.4, 8.6 Hz, OCH_2CH*H*), 2.92–2.85 (1 H, m, OCH_2C*H*H), 2.48 (3 H, s, Ar-CH_3), 2.42–2.36 (1 H, m, $(CH_3)_2C$*H*), 1.59 (1 H, br s, OH), 1.02 (3 H, d, *J* = 6.6 Hz, CHC*H*$_3$), 0.97 (3 H, d, *J* = 6.6 Hz, CHC*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3 (Ar-C_q), 132.6 (Ar-C_q), 130.4 (2 × Ar-C), 129.5 (2 × Ar-C), 104.5 (C_q), 74.4 (HOCH), 69.0 (OCH_2), 29.0 $(CH_3)_2$*C*H, 23.9 (OCH_2*C*H_2), 21.7 (Ar-CH_3), 20.8 (CH_3), 15.5 (CH_3).

Minor Diastereoisomer ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (2 H, d, *J* = 8.0 Hz, 2 × Ar-H), 7.39 (2 H, d, *J* = 8.0 Hz, 2 × Ar-H), 4.50–4.38 (2 H, m, OCH_2), 3.72–3.68 (1 H, m,

HOC*H*), 3.19–2.98 (3 H, m, OCH_2CH_2 + $(CH_3)_2CH$), 2.48 (3 H, s, Ar-CH_3), 1.59 (1 H, br s, OH), 1.03 (3 H, d, *J* = 6.6 Hz, $CHCH_3$), 0.94 (3 H, d, *J* = 6.6 Hz, $CHCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4 (Ar-C_q), 132.6 (Ar-C_q), 130.5 (2 × Ar-C), 129.5 (2 × Ar-C), 103.7 (C_q), 74.4 (HOCH), 68.7 (OCH_2), 29.8 $(CH_3)_2CH$, 23.8 (OCH_2CH_2), 21.7 (Ar-CH_3), 20.9 (CH_3), 17.5 (CH_3).

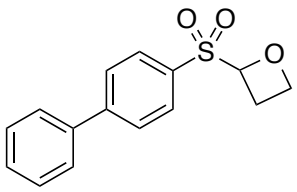
HRMS (ESI) *m/z* Calculated for $C_{14}H_{21}O_4S^+$ $[M+H]^+$: 285.1161; Found: 285.1179 $[M+H]^+$, Δ 6.3 ppm.

2-((2,4-Dimethylphenyl)sulfonyl)-2-methyloxetane (104)



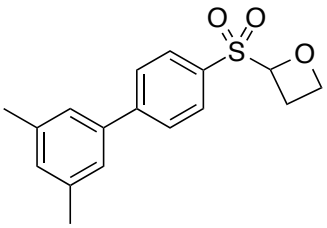
*n*BuLi (1.60 M in hexane, 0.16 mL, 0.26 mmol) was added dropwise to a solution of oxetane **103** (50 mg, 0.23 mmol) in THF (1.2 mL) at –78 ºC and stirred at –78 ºC for 30 min. MeI (0.03 mL, 0.44 mmol) was added and the reaction stirred at –78 ºC for 2 h. The reaction was quenched by the addition of sat. aq. $NaHCO_3$ (6 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography on basic alumina (activity IV) (25% Et_2O/hexane) afforded oxetane **104** (33 mg, 63%) as a colourless oil. R_f = 0.28 (20% EtOAc/hextane). IR (film)/cm^{-1} 2974, 2931, 2900, 1602, 1567, 1440, 1373, 1294, 1212, 1174, 1107, 1050, 973, 948, 865, 744, 675. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (1 H, d, *J* = 8.7 Hz, Ar-H), 7.19–7.14 (2 H, m, 2 × Ar-H), 4.57–4.50 (1 H, m, OCH*H*), 4.49–4.43 (1 H, m, OC*H*H), 3.27, (1 H, ddd, *J* = 12.6, 8.6, 5.6 Hz, OCH_2CHH), 2.83–2.75 (1 H, m, OCH_2CHH), 2.73 (3 H, s, Ar-CH_3), 2.39 (3 H, s, Ar-CH_3), 1.65 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9 (Ar-C_q), 141.3 (Ar-C_q), 133.6 (Ar-C), 132.6 (Ar-C), 129.6 (Ar-C_q), 126.8 (Ar-C), 101.6 (C_q), 67.3 (OCH_2), 29.0 (OCH_2CH_2), 22.1 (CH_3), 21.4 (Ar-CH_3), 21.3 (Ar-CH_3). HRMS (ESI) *m/z* Calculated for $C_{12}H_{17}O_3S^+$ $[M+H]^+$: 241.0893; Found: 241.0927 $[M+H]^+$, Δ 14.1 ppm.

2-([1,1'-Biphenyl]-4-ylsulfonyl)oxetane (124)



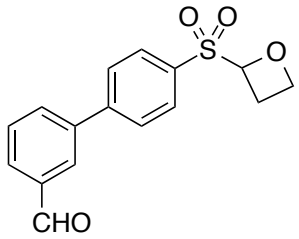
A flask was charged with $Pd(OAc)_2$ (3 mg, 0.012 mmol), S-Phos (9 mg, 0.023 mmol), K_2CO_3 (64 mg, 0.46 mmol), phenylboronic acid (38 mg, 0.31 mmol) and 2-(4-chlorobenzenesulfonyl)oxetane **57** (54 mg, 0.23 mmol) then flushed with N_2. The mixture was dissolved in dioxane:water (4:1, 2.5 mL) and heated at 65 ºC for 3 h 30 min. The crude mixture was filtered through Celite® and the solvent removed under reduced pressure. The residue was partitioned between EtOAc (20 mL) and H_2O (10 mL). The aqueous layer was extracted with EtOAc (2 × 15 mL) and the combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (0–100% EtOAc/heptane) afforded oxetane **124** (55 mg, 86%) as a white solid. R_f = 0.39 (40% EtOAc/heptane). IR (film)/cm^{-1} 3066, 2980, 2909, 1592, 1563, 1479, 1446, 1396, 1302, 1144, 1091, 900, 838, 762, 720, 657. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (2 H, d, *J* = 8.7 Hz, 2 × Ar-H), 7.79 (2 H, d, *J* = 8.7 Hz, 2 × Ar-H), 7.64–7.59 (2 H, m, 2 × Ar-H), 7.52–7.42 (3 H, m, 3 × Ar-H), 5.43 (1 H, dd, *J* = 7.0, 6.5 Hz, OCHS), 4.84 (1 H, ddd, *J* = 8.0, 7.9, 5.5 Hz, OCH*H*), 4.68 (1 H, ddd, *J* = 7.3, 7.0, 5.5 Hz, OC*H*H), 3.18–3.12 (2 H, m, OCH_2CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3 (C_q), 139.2 (C_q), 133.9 (C_q), 130.0 (2 × Ar-C), 129.1 (2 × Ar-C), 128.7 (Ar-C), 127.8 (2 × Ar-C), 127.4 (2 × Ar-C), 94.1 (OCHS), 71.4 (OCH_2), 22.4 (OCH_2CH_2). HRMS (APCI) *m/z* Calculated for $C_{15}H_{18}NO_3S^+$ $[M+NH_4]^+$: 292.1002; Found: 292.1001 $[M+NH_4]^+$, Δ 0.3 ppm.

2-([3',5'-Dimethylbiphenyl]-4-ylsulfonyl)oxetane (125)



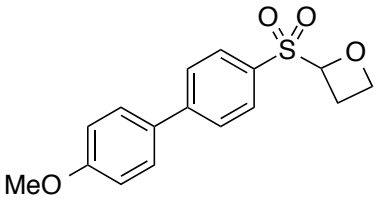
A flask was charged with $Pd(OAc)_2$ (4 mg, 0.016 mmol), S-Phos (12 mg, 0.032 mmol), K_2CO_3 (88 mg, 0.64 mmol), 3,5-dimethylbenzeneboronic acid (60 mg, 0.42 mmol) and 2-(4-chlorobenzenesulfonyl)oxetane **57** (75 mg, 0.32 mmol) then flushed with Ar. The mixture was dissolved in dioxane:water (4:1, 3.1 mL) and heated at 65 ºC for 5 h. The crude mixture was filtered through Celite® and the solvent removed under reduced pressure. The residue was partitioned between EtOAc (20 mL) and H_2O (10 mL). The aqueous layer was extracted with EtOAc (2 × 15 mL) and the combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (30% EtOAc/hexane) afforded oxetane **125** (83 mg, 86%) as a colourless oil. R_f = 0.53 (40% EtOAc/hexane). IR (film)/cm^{-1} 2972, 2903, 1593, 1443, 1389, 1314, 1270, 1231, 1185, 1064, 1029, 982, 908, 829, 737, 722, 697. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (2 H, d, *J* = 8.4 Hz, 2 × Ar-H), 7.77 (2 H, d, *J* = 8.4 Hz, 2 × Ar-H), 7.23 (2 H, br s, 2 × Ar-H), 7.09 (1 H, br s, Ar-H), 5.43 (1 H, dd, *J* = 7.4, 6.0 Hz, OCHS), 4.81 (1 H, ddd, *J* = 8.2, 7.9, 5.4 Hz, OCH*H*), 4.70–4.63 (1 H, m, OC*H*H), 3.19–3.08 (2 H, m, OCH_2CH_2), 2.40 (6 H, s, 2 × CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5 (C_q), 139.0 (C_q), 138.6 (2 × C_q), 133.4 (C_q), 130.3 (Ar-C), 129.8 (2 × Ar-C), 127.7 (2 × Ar-C), 125.2 (2 × Ar-C), 94.0 (OCHS), 71.4 (OCH_2), 22.4 (OCH_2CH_2), 21.3 (2 × CH_3). HRMS (EI) *m/z* Calculated for $C_{17}H_{18}O_3S^+$ $[M]^+$: 302.0971; Found: 302.0973 $[M]^+$, Δ 0.7 ppm.

2-([1,1'-Biphenyl]-3-carboxaldehyde-4-ylsulfonyl)oxetane (126)



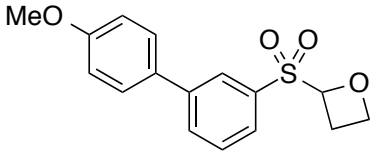
A flask was charged with $Pd(OAc)_2$ (4 mg, 0.016 mmol), S-Phos (12 mg, 0.032 mmol), K_2CO_3 (88 mg, 0.64 mmol), 3-formylphenylboronic acid (60 mg, 0.42 mmol) and 2-(4-chlorobenzenesulfonyl)oxetane **57** (75 mg, 0.32 mmol) then flushed with Ar. The mixture was dissolved in dioxane:water (4:1, 3.1 mL) and heated at 65 ºC for 20 h. The crude mixture was filtered through Celite® and the solvent removed under reduced pressure. The residue was partitioned between EtOAc (20 mL) and H_2O (10 mL). The aqueous layer was extracted with EtOAc (2 × 15 mL) and the combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (20% EtOAc/hexane) afforded oxetane **126** (57 mg, 59%) as a colourless oil. R_f = 0.13 (40% EtOAc/hexane). IR (film)/cm^{-1} 2973, 2902, 2827, 1694, 1595, 1585, 1442, 1398, 1380, 1314, 1232, 1180, 1090, 1064, 1028, 937, 868, 843, 769, 761, 660. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.09 (1 H, s, C*H*O), 8.13–8.11 (1 H, m, Ar-H), 8.06 (2 H, d, *J* = 8.5 Hz, 2 × Ar-H), 7.93 (1 H, d, *J* = 7.5 Hz, Ar-H), 7.87 (1 H, d, *J* = 7.7 Hz, Ar-H), 7.81 (2 H, d, *J* = 8.5 Hz, 2 × Ar-H), 7.67 (1 H, dd, *J* = 7.7, 7.5 Hz, Ar-H), 5.43 (1 H, dd, *J* = 7.2, 5.5 Hz, OCHS), 4.85–4.79 (1 H, m, OCH*H*), 4.70–4.64 (1 H, m, OC*H*H), 3.21–3.07 (2 H, m, OCH_2CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8 (C=O), 145.6 (C_q), 140.0 (C_q), 137.0 (C_q), 134.5 (C_q), 133.1 (Ar-C), 130.1 (2 × Ar-C), 130.0 (Ar-C), 129.8 (Ar-C), 128.1 (Ar-C), 127.8 (2 × Ar-C), 94.0 (OCHS), 71.5 (OCH_2), 22.3 (OCH_2CH_2). HRMS (APCI) *m/z* Calculated for $C_{16}H_{18}NO_4S^+$ $[M+NH_4]^+$: 320.0951; Found: 320.0951 $[M+NH_4]^+$, Δ 0 ppm.

2-([4'-Methoxybiphenyl]-4-ylsulfonyl)oxetane (127)



A flask was charged with $Pd(OAc)_2$ (4 mg, 0.016 mmol), S-Phos (12 mg, 0.032 mmol), K_2CO_3 (88 mg, 0.64 mmol), 4-methoxyphenylboronic acid (64 mg, 0.42 mmol) and 2-(4-chlorobenzenesulfonyl)oxetane **57** (75 mg, 0.32 mmol) then flushed with Ar. The mixture was dissolved in dioxane:water (4:1, 3.1 mL) and heated at 65 ºC for 5 h 30 min. The crude mixture was filtered through Celite® and the solvent removed under reduced pressure. The residue was partitioned between EtOAc (20 mL) and H_2O (10 mL). The aqueous layer was extracted with EtOAc (2 × 15 mL) and the combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (20% EtOAc/hexane) afforded oxetane **127** as a white solid (92 mg, 95%). R_f = 0.34 (40% EtOAc/hexane). IR (film)/cm^{-1} 2980, 2909, 2839, 1591, 1523, 1485, 1396, 1294, 1203, 1136, 1091, 1012, 982, 907, 819, 751, 712, 682. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (2 H, d, *J* = 8.6 Hz, 2 × Ar-H), 7.75 (2 H, d, *J* = 8.6 Hz, 2 × Ar-H), 7.58 (2 H, d, *J* = 8.6 Hz, 2 × Ar-H), 7.02 (2 H, d, *J* = 8.6 Hz, 2 × Ar-H), 5.42 (1 H, dd, *J* = 7.0, 6.4 Hz, OCHS), 4.82 (1 H, ddd, *J* = 8.2, 8.0, 5.5 Hz, OCH*H*), 4.67 (1 H, ddd, *J* = 7.5, 7.1, 5.5 Hz, OC*H*H), 3.88 (3 H, s, CH_3), 3.19–3.09 (2 H, m, OCH_2CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3 (C_q), 146.8 (C_q), 133.0 (C_q), 131.4 (C_q), 130.0 (2 × Ar-C), 128.6 (2 × Ar-C), 127.2 (2 × Ar-C), 114.5 (2 × Ar-C), 94.1 (OCHS), 71.4 (OCH_2), 55.4 (CH_3), 22.4 (OCH_2CH_2). HRMS (EI) *m/z* Calculated for $C_{16}H_{16}O_4S^+$ $[M]^+$: 304.0769; Found: 304.0744 $[M]^+$, Δ 8.2 ppm.

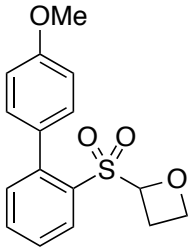
2-[3-(4-Methoxyphenyl)benzenesulfonyl]oxetane (128)



A flask was charged with $Pd(OAc)_2$ (2 mg, 0.008 mmol), S-Phos (9 mg, 0.021 mmol), K_2CO_3 (58 mg, 0.42 mmol), 4-methoxyphenylboronic acid (41 mg, 0.28 mmol) and

2-(3-chlorobenzenesulfonyl)oxetane **89** (50 mg, 0.21 mmol) then flushed with Ar. The mixture was dissolved in dioxane:water (4:1, 1.9 mL) and heated at 65 ºC for 20 h. The crude mixture was filtered through Celite® and the solvent removed under reduced pressure. The residue was partitioned between EtOAc (20 mL) and H_2O (10 mL). The aqueous layer was extracted with EtOAc (2 × 15 mL) and the combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (20% EtOAc/hexane) afforded oxetane **128** (62 mg, 95%) as a white solid; m.p. 67–68 ºC. R_f = 0.24 (20% EtOAc/hexane). IR (film)/cm^{-1} 2966, 2898, 1607, 1518, 1470, 1431, 1304, 1256, 1184, 1148, 1020, 983, 904, 833, 794, 771, 699. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16–8.13 (1 H, m, Ar-H), 7.90 (1 H, ddd, *J* = 7.9, 1.7, 1.0 Hz, Ar-H), 7.86 (1 H, ddd, *J* = 7.7, 1.7, 1.0 Hz, Ar-H), 7.62 (1 H, dd, *J* = 7.9, 7.7 Hz, Ar-H), 7.56 (2 H, d, *J* = 8.9 Hz, 2 × Ar-H), 7.01 (2 H, d, *J* = 8.9 Hz, 2 × Ar-H), 5.43 (1 H, dd, *J* = 6.8, 6.6 Hz, OCHS), 4.82 (1 H, ddd, *J* = 8.2, 8.0, 5.5 Hz, OCH*H*), 4.67 (1 H, ddd, *J* = 7.3, 7.0, 5.5 Hz, OC*H*H), 3.87 (3 H, s, OCH_3), 3.18–3.11 (2 H, m, OCH_2CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0 (C_q), 142.2 (C_q), 135.9 (C_q), 132.3 (Ar-C), 131.4 (C_q), 129.6 (Ar-C), 128.4 (2 × Ar-C), 127.4 (Ar-C + Ar-C), 114.5 (2 × Ar-C), 94.1 (OCHS), 71.5 (OCH_2), 55.4 (OCH_3), 22.4 (OCH_2CH_2). HRMS (ES) *m/z* Calculated $C_{18}H_{19}NNaO_4S$ [M+CH_3CN+Na]: 368.0932; Found: 368.0948 [M+CH_3CN+Na], Δ 4.3 ppm.

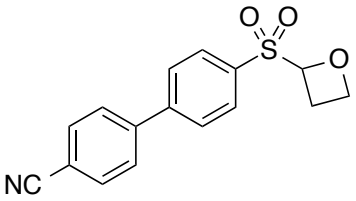
2-[2-(4-Methoxyphenyl)benzenesulfonyl]oxetane (129)



A flask was charged with $Pd(OAc)_2$ (2 mg, 0.008 mmol), S-Phos (9 mg, 0.021 mmol), K_2CO_3 (58 mg, 0.42 mmol), 4-methoxyphenylboronic acid (41 mg, 0.28 mmol) and 2-((2-chlorophenyl)sulfonyl)oxetane **88** (53 mg, 0.22 mmol) then flushed with Ar. The mixture was dissolved in dioxane:water (4:1, 1.9 mL) and heated at 65 ºC for 20 h. The crude mixture was filtered through Celite® and the solvent removed under reduced pressure. The residue was partitioned between EtOAc (20 mL) and H_2O (10 mL). The aqueous layer was extracted with EtOAc (2 × 15 mL) and the combined organic layers

were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (10% EtOAc/hexane) afforded oxetane **129** (24 mg, 34%) as a white solid; m.p. 109–110 ºC. R_f = 0.13 (10% EtOAc/hexane). IR (film)/cm^{-1} 2968, 1609, 1516, 1465, 1442, 1309, 1244, 1147, 982, 906, 834, 755, 693. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (1 H, dd, *J* = 7.8, 1.4 Hz, Ar-H), 7.63 (1 H, ddd, *J* = 8.9, 7.4, 1.4 Hz, Ar-H), 7.55 (1 H, ddd, *J* = 8.9, 7.8, 1.4 Hz, Ar-H), 7.38–7.32 (3 H, m, 3 × Ar-H), 6.96 (2 H, d, *J* = 8.9 Hz, 2 × Ar-H), 4.86 (1 H, dd, *J* = 8.2, 5.0 Hz, OCHS), 4.85–4.79 (1 H, m, OCH*H*), 4.54 (1 H, ddd, *J* = 8.7, 5.7, 5.4 Hz, OC*H*H), 3.88 (3 H, s, OCH_3), 3.10–3.00 (1 H, m, OCH_2CH*H*), 2.94–2.83 (1 H, m, OCH_2C*H*H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5 (C_q), 142.4 (C_q), 134.7 (C_q), 133.4 (Ar-C), 132.9 (Ar-C), 131.2 (2 × Ar-C), 130.8 (Ar-C), 130.6 (C_q), 127.7 (Ar-C), 113.1 (2 × Ar-C), 93.0 (OCHS), 71.8 (OCH_2), 55.2 (OCH_3), 21.7 (OCH_2CH_2). HRMS (ES) *m/z* Calculated $C_{18}H_{19}NNaO_4S$ [M+CH_3CN+Na]: 368.0932; Found: 368.0948 [M+CH_3CN+Na], Δ 4.3 ppm.

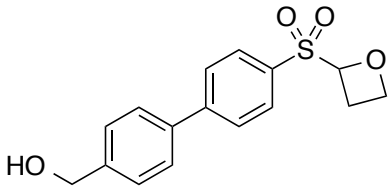
4-[4-(Oxetane-2-sulfonyl)phenyl]benzonitrile (132)



A flask was charged with $Pd(OAc)_2$ (2 mg, 0.009 mmol), S-Phos (7 mg, 0.017 mmol), K_2CO_3 (47 mg, 0.36 mmol), 4-cyanophenylboronic acid (35 mg, 0.24 mmol) and 2-(4-bromobenzenesulfonyl)oxetane **91** (51 mg, 0.18 mmol) then flushed with Ar. The mixture was dissolved in dioxane:water (4:1, 1.6 mL) and heated at 65 ºC for 15 h. The crude mixture was filtered through Celite® and the solvent removed under reduced pressure. Purification by flash chromatography (30% EtOAc/hexane) afforded oxetane **132** (43 mg, 78%) as a white solid; m.p. 156–157 ºC. R_f = 0.36 (30% EtOAc/hexane). IR (film)/cm^{-1} 2976, 2915, 2222, 1592, 1392, 1323, 1310, 1274, 1151, 1091, 1031, 981, 905, 873, 821, 734, 675. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (2 H, d, *J* = 8.2 Hz, 2 × Ar-H), 7.81–7.76 (4 H, m, 4 × Ar-H), 7.72 (2 H, d, *J* = 8.2 Hz, 2 × Ar-H), 5.43 (1 H, dd, *J* = 6.7, 6.4 Hz, OCHS), 4.90–4.83 (1 H, m, OCH*H*), 4.72–4.65 (1 H, m, OC*H*H), 3.20–2.13 (2 H, m, OCH_2CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1 (Ar-C_q), 143.5 (Ar-C_q), 135.4 (Ar-C_q), 132.9 (2 × Ar-C), 130.3 (2 × Ar-C), 128.1 (2 × Ar-C), 128.0 (2 × Ar-C), 118.4

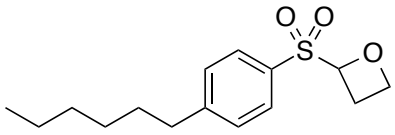
(CN), 112.5 (Ar-C_q), 94.2 (OCHS), 71.7 (OCH_2), 22.3 (OCH_2CH_2). HRMS (ES) *m/z* Calculated $C_{16}H_{14}NO_3S$ [M+H]: 300.0694; Found: 300.0708 [M+H], Δ 4.7 ppm.

{4-[4-Oxetane-2-sulfonyl)phenyl]phenyl}methanol (133)



A flask was charged with $Pd(OAc)_2$ (2 mg, 0.009 mmol), S-Phos (7 mg, 0.017 mmol), K_2CO_3 (47 mg, 0.36 mmol) 4-(hydroxymethyl)phenylboronic acid (36 mg, 0.24 mmol) and 2-(4-bromobenzenesulfonyl)oxetane **91** (50 mg, 0.18 mmol) then flushed with Ar. The mixture was dissolved in dioxane:water (4:1, 1.6 mL) and heated at 65 ºC for 15 h. The crude mixture was filtered through Celite® and the solvent removed under reduced pressure. Purification by flash chromatography (40–100% EtOAc/hexane) afforded oxetane **133** (41 mg, 75%) as a white solid; m.p. 136–137 ºC. R_f = 0.06 (40% EtOAc/hexane). IR (film)/cm^{-1} 3505 (OH), 2913, 1593, 1392, 1302, 1272, 1146, 1025, 978, 901, 804, 756, 688. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (2 H, d, *J* = 8.5 Hz, 2 × Ar-H), 7.76 (2 H, d, *J* = 8.5 Hz, 2 × Ar-H), 7.60 (2 H, d, *J* = 8.1 Hz, 2 × Ar-H), 7.49 (2 H, d, *J* = 8.1 Hz, 2 × Ar-H), 5.42 (1 H, dd, *J* = 7.0, 6.3 Hz, OCHS), 4.86–4.79 (1 H, m, OCH*H*), 4.77 (2 H, s, CH_2OH), 4.67 (1 H, ddd, *J* = 7.5, 6.9, 5.5 Hz, OC*H*H), 3.19–2.09 (2 H, m, OCH_2CH_2), 1.99 (1 H, br s, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8 (C_q), 141.6 (C_q), 138.3 (C_q), 133.7 (C_q), 130.0 (2 × Ar-C), 127.7 (2 × Ar-C), 127.6 (2 × Ar-C), 127.5 (2 × Ar-C), 94.1 (OCHS), 71.5 (OCH_2), 64.8 (CH_2OH), 22.4 (OCH_2CH_2). HRMS (ES) *m/z* Calculated $C_{18}H_{19}NO_4S$ [M+CH_3CN+Na]: 368.0932; Found: 368.0936 [M+CH_3CN+Na], Δ 1.1 ppm.

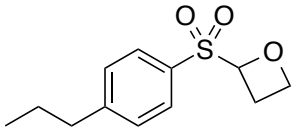
2-(4-Hexylbenzenesulfonyl)oxetane (137)



*n*Hexylmagnesium bromide (1.50 M in Et_2O, 0.16 mL, 0.25 mmol) was added dropwise to a solution of 2-(4-chlorobenzenesulfonyl)oxetane **57** (48 mg, 0.21 mmol) and $Fe(acac)_3$

(3.6 mg, 0.01 mmol) in THF/NMP (9:1, 2 mL). The reaction was stirred at rt for 15 min. The reaction mixture was diluted with Et_2O (10 mL) and quenched with 1 M HCl (10 mL) then extracted with Et_2O (5 × 7 mL). Combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (0–20% EtOAc/heptane) afforded oxetane **137** (41 mg, 70%) as a colourless oil. R_f = 0.18 (20% EtOAc/heptane). IR (film)/cm^{-1} 2928, 2858, 2257, 1596, 1465, 1408, 1309, 1232, 1148, 1089, 1029, 984, 908, 816, 727. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (2 H, d, *J* = 8.5 Hz, 2 × Ar-H), 7.38 (2 H, d, *J* = 8.5 Hz, 2 × Ar-H), 5.37 (1 H, dd, *J* = 6.7, 6.2 Hz, OCHS), 4.77 (1 H, ddd, *J* = 8.1, 7.8, 5.4 Hz, OCH*H*), 4.66–4.61 (1 H, m, OC*H*H), 3.13–3.08 (2 H, m, OCH_2CH_2), 2.70 (2 H, t, *J* = 7.6 Hz, Ar-CH_2CH_2), 1.64 (2 H, qn, *J* = 7.6 Hz, Ar-CH_2CH_2), 1.36–1.28 (6 H, m, 3 × CH_2), 0.89 (3 H, t, *J* = 6.9 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3 (C_q), 132.5 (C_q), 129.5 (2 × Ar-C), 129.2 (2 × Ar-C), 94.1 (OCHS), 71.3 (OCH_2), 36.0 (CH_2), 31.6 (CH_2), 30.9 (CH_2), 28.9 (CH_2), 22.5 (CH_2), 22.4 (OCH_2CH_2), 14.0 (CH_3). HRMS (APCI) *m/z* Calculated for $C_{15}H_{26}NO_3S^+$ $[M+NH_4]^+$: 300.1628; Found: 300.1627 $[M+NH_4]^+$, Δ 0.3 ppm.

2-(4-Propylbenzenesulfonyl)oxetane (138)

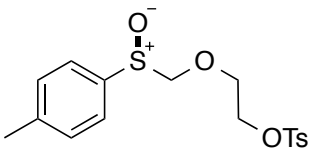


*n*Propylmagnesium chloride (1 M in MeTHF, 0.25 mL, 0.25 mmol) was added dropwise to a solution of 2-(4-chlorobenzenesulfonyl)oxetane **57** (50 mg, 0.21 mmol) and $Fe(acac)_3$ (4 mg, 0.01 mmol) in THF/NMP (9:1, 2 mL). The reaction was stirred at rt for 15 min. The reaction mixture was diluted with Et_2O (10 mL) and quenched with 1 M HCl (10 mL) then extracted with Et_2O (5 × 7 mL). Combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (20% EtOAc/hexane) afforded oxetane **138** (37 mg, 71%) as a colourless oil. R_f = 0.19 (20% EtOAc/hexane). IR (film)/cm^1 2962, 2932, 2872, 1596, 1444, 1408, 1307, 1274, 1232, 1184, 1146, 1090, 1065, 1029, 939, 910, 843, 804, 768, 694. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (2 H, d, *J* = 8.3 Hz, 2 × Ar-H), 7.38 (2 H, d, *J* = 8.3 Hz, 2 × Ar-H), 5.38 (1 H, dd, *J* = 6.9, 6.0 Hz, OCHS), 4.78 (1 H, ddd, *J* = 8.3, 7.8, 5.5 Hz, OCH*H*), 4.67–4.62 (1 H, m, OC*H*H), 3.16–3.07 (2 H, m, OCH_2CH_2), 2.69 (2 H, t, *J* = 7.5 Hz, Ar-CH_2CH_2), 1.68 (2 H,

tq, J = 7.5, 7.4 Hz, Ar-CH_2CH_2), 0.96 (3 H, t, J = 7.4 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0 (C_q), 133.3 (C_q), 129.5 (2 × Ar-C), 129.3 (2 × Ar-C), 94.0 (OCHS), 71.4 (OCH_2), 38.0 (CH_2), 24.1 (CH_2), 22.4 (OCH_2CH_2), 13.7 (CH_3). HRMS (APCI) *m/z* Calculated for $C_{12}H_{20}NO_3S^+$ $[M+NH_4]^+$: 258.1158; Found: 258.1158 $[M+NH_4]^+$, Δ 0 ppm.

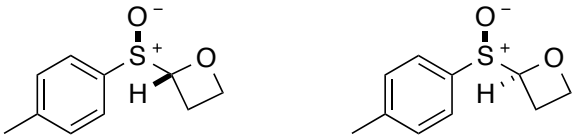
5.2. Synthesis of 2-Sulfinyl Oxetanes and Investigations into Functionalisation

1-Methyl-4-({2-[(4-methylbenzenesulfonyl)oxy]ethoxy}methanesulfinyl)benzene (164)



meta-Chloroperbenzoic acid (70%, 1.18 g, 4.80 mmol) was added to a solution of sulfide **77** (1.54 g, 4.37 mmol) in dichloromethane (20 mL) at 0 ºC and the mixture stirred at 0 ºC for 3 h. The reaction was quenched with sat. aq. Na_2SO_3 (20 mL) and extracted with dichloromethane (7 × 20 mL). The combined organic layers were washed with 5% NaOH (3 × 10 mL) and sat. aq. NH_4Cl (50 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (60% EtOAc/hexane) afforded sulfoxide **164** (1.27 g, 79%) as pale yellow oil. R_f = 0.30 (60% EtOAc/hexane). IR (film)/cm^{-1} 2970, 1599, 1496, 1355, 1189, 1175, 1142, 1096, 1004, 915, 810. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (2 H, d, J = 8.5 Hz, 2 × Ts-H), 7.50 (2 H, d, J = 8.2 Hz, 2 × Ar-H), 7.37–7.32 (4 H, m, 2 × Ts-H + 2 × Ar-H), 4.43 (1 H, d, J = 10.6 Hz, SC*H*HO), 4.36 (1 H, d, J = 10.6 Hz, SCH*H*O), 4.24–4.15 (2 H, m, OCH_2), 4.13–3.97 (2 H, m, OCH_2), 2.46 (3 H, s, CH_3), 2.43 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0 (Ts-C_q), 142.1 (Ar-C_q), 137.1 (Ar-C_q), 132.7 (Ts-C_q), 130.1 (2 × Ar-C), 129.9 (2 × Ts-C), 128.0 (2 × Ts-C), 124.4 (2 × Ar-C), 93.0 (SCH_2O), 70.9 (OCH_2), 68.7 (OCH_2), 21.7 (CH_3), 21.5 (CH_3). HRMS (NSI) *m/z* Calculated for $C_{17}H_{21}O_5S_2^+$ $[M+H]^+$: 369.0825; Found: 369.0831 $[M+H]^+$, Δ 1.6 ppm.

2-(4-Methylbenzenesulfinyl)oxetane (165)



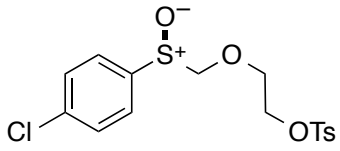
A **B**

A solution of LiHMDS (1 M in THF, 1.36 mL, 1.36 mmol) was added dropwise to a solution of sulfoxide **164** (0.25 g, 0.68 mmol) in THF (25 mL) at 0 ºC and stirred for 2 h. Reaction quenched with sat. aq. NH_4Cl (25 mL) and extracted with $CHCl_3$ (4 × 25 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (60% EtOAc/hexane) afforded the oxetane as a mixture of two diastereoisomers **165B** (24 mg, 18%) followed by **165A** (7 mg, 6%), both as colourless oils.

Major Diastereoisomer 165B: R_f = 0.21 (60% EtOAc/hexane). IR (film)/cm^{-1} 2971, 2896, 1730, 1599, 1493, 1448, 1259, 1179, 1088, 1050, 1014, 973, 920, 810. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (2 H, d, *J* = 8.0 Hz, 2 × Ar-H), 7.34 (2 H, d, *J* = 8.0 Hz, 2 × Ar-H), 5.37 (1 H, dd, *J* = 7.5, 5.7 Hz, OCHS), 4.64–4.54 (2 H, m, OCH_2), 3.07–2.91 (2 H, m, OCH_2CH_2), 2.42 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9 (C_q), 135.5 (C_q), 129.8 (2 × Ar-C), 125.1 (2 × Ar-C), 96.9 (OCHS), 70.9 (OCH_2), 22.6 (OCH_2CH_2), 21.5 (CH_3).

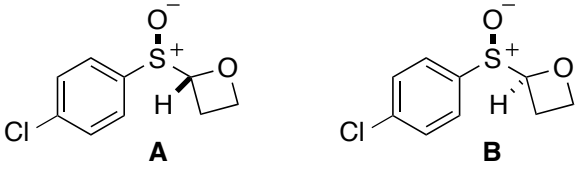
Minor Diastereoisomer 165A: R_f = 0.20 (60% EtOAc/hexane). IR (film)/cm^{-1} 2971, 2896, 1730, 1599, 1493, 1448, 1259, 1179, 1088, 1050, 1014, 973, 920, 810. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (2 H, d, *J* = 8.0 Hz, 2 × Ar-H), 7.32 (2 H, d, *J* = 8.0 Hz, 2 × Ar-H), 5.26 (1 H, dd, *J* = 7.4, 5.3 Hz, OCHS), 4.78 (1 H, ddd, *J* = 8.8, 6.7, 5.3 Hz, OCH*H*), 4.66 (1 H, ddd, *J* = 8.2, 6.2, 5.3 Hz, OC*H*H), 3.20–3.21 (1 H, m, OCH_2CH*H*), 2.68–2.58 (1 H, m, OCH_2CH*H*), 2.40 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7 (C_q), 135.7 (C_q), 129.9 (2 × Ar-C), 124.1 (2 × Ar-C), 99.6 (OCHS), 71.1 (OCH_2), 21.4 (OCH_2CH_2), 19.3 (CH_3).

2-(((4-Chlorophenyl)sulfinyl)methoxy)ethyl-4-methylbenzenesulfonate (171)



meta-Chloroperbenzoic acid (1.11 g, 6.43 mmol) was added slowly to a solution of sulfide **83b** (2.00 g, 5.36 mmol) in dichloromethane (50 mL) at 0 ºC and the mixture stirred at 0 ºC for 1 h then warmed to rt for 1 h. The reaction was quenched with sat. aq. Na_2SO_3 (80 mL) and $NaHCO_3$ (80 mL) then extracted with dichloromethane (4 × 40 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (80 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (70% EtOAc/hexane) afforded sulfoxide **171** (1.95 g, 94%) as a colourless oil. R_f = 0.19 (70% EtOAc/hexane). IR (film)/cm^{-1} 3060, 2954, 2932, 1597, 1475, 1452, 1391, 1353, 1244, 1174, 1086, 1010, 909, 815, 772, 740. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (2 H, d, *J* = 8.5 Hz, 2 × Ts-H), 7.54 (2 H, d, *J* = 8.6 Hz, 2 × Ar-H), 7.49 (2 H, d, *J* = 8.6 Hz, 2 × Ar-H), 77.33 (2 H, d, *J* = 8.5 Hz, 2 × Ts-H), 4.45 (1 H, d, *J* = 10.5 Hz, SC*H*HO), 4.38 (1 H, d, *J* = 10.5 Hz, SCH*H*O), 4.18–4.16 (2 H, m, OCH_2), 4.10–3.89 (2 H, m, OCH_2), 2.44 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1 (Ts-C_q), 138.9 (Ar-C_q), 137.6 (Ar-C_q), 132.5 (Ts-C_q), 129.9 (2 × Ts-C), 129.5 (2 × Ar-C), 127.8 (2 × Ts-C), 125.8 (2 × Ar-C), 91.7 (SCH_2O), 71.0 (OCH_2CH_2O), 68.5 (OCH_2CH_2O), 21.6 (CH_3). HRMS (ESI) *m/z* Calculated for $C_{16}H_{18}{}^{35}ClO_5S_2^+$ $[M+H]^+$: 389.0279; Found: Accurate mass could not be found due to compound degradation.

2-(4-Chlorobenzenesulfinyl)oxetane (172)



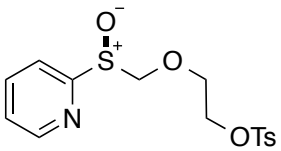
A solution of LiHMDS (1 M in THF, 0.16 mL, 0.16 mmol) was added dropwise to a solution of sulfoxide **171** (50 mg, 0.13 mmol) in THF (5 mL) at 0 ºC and stirred for 1 h. Reaction quenched with sat. aq. NH_4Cl (10 mL) and extracted with CH_2Cl_2 (5 × 6 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed under

reduced pressure. Purification by flash chromatography (70% EtOAc/hexane) afforded the oxetane as a mixture of two diastereoisomers **172A** (10 mg, 36%) followed by **172B** (12 mg, 44%) both as colourless oils.

Major Diastereoisomer 172B: R_f = 0.13 (70% EtOAc/hexane). IR (film)/cm^{-1} 3079, 2965, 2897, 1574, 1475, 1391, 1256, 1235, 1176, 1090, 1079, 1052, 975, 931, 913, 822, 741, 702. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (2 H, dt, *J* = 8.4, 2.0 Hz, 2 × Ar-H), 7.51 (2 H, dt, *J* = 8.4, 2.0 Hz, 2 × Ar-H), 5.38 (1 H, dd, *J* = 7.4, 5.7 Hz, OCHS), 4.65–4.55 (2 H, m, OCH_2), 3.07–3.98 (2 H, m, OCH_2CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7 (Ar-C_q), 137.4 (Ar-C_q), 129.3 (2 × Ar-C), 126.5 (2 × Ar-C), 96.8 (OCHS), 71.1 (OCH_2), 22.5 (OCH_2CH_2).

Minor Diastereoisomer 172A: R_f = 0.30 (70% EtOAc/hexane). IR (film)/cm^{-1} 3079, 2965, 2897, 1574, 1475, 1391, 1256, 1235, 1176, 1090, 1079, 1052, 975, 931, 913, 822, 741, 702. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.49 (4 H, m, 4 × Ar-H), 5.26 (1 H, dd, *J* = 7.6, 5.2 Hz, OCHS), 4.80 (1 H, ddd, *J* = 9.0, 6.8, 5.4 Hz, OCH*H*), 4.68 (1 H, ddd, *J* = 8.4, 6.0, 5.4 Hz, OC*H*H), 3.26–3.18 (1 H, m, OCH_2CH*H*), 2.73–2.63 (1 H, m, OCH_2C*H*H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7 (Ar-C_q), 137.4 (Ar-C_q), 129.3 (2 × Ar-C), 126.5 (2 × Ar-C), 96.8 (OCHS), 71.1 (OCH_2), 22.5 (OCH_2CH_2). HRMS (ESI) *m/z* Calculated for $C_9H_{10}{}^{35}ClO_2S^+$ $[M+H]^+$: 217.0085; Found: Accurate mass could not be obtained.

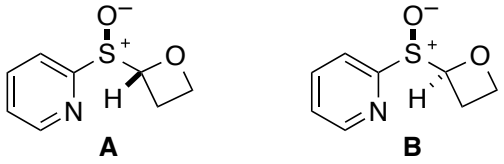
2-({2-[(4-Methylbenzenesulfonyl)oxy]ethoxy}methanesulfinyl)pyridine (173)



meta-Chloroperbenzoic acid (2.06 g, 11.93 mmol) was added portionwise to a solution of sulfide **83c** (3.37 g, 9.93 mmol) in dichloromethane (150 mL) at 0 ºC and the mixture stirred whilst warming to rt for 2 h 30 min. The reaction was quenched with sat. aq. Na_2SO_3 (40 mL) and sat. aq. $NaHCO_3$ (40 mL) then extracted with dichloromethane (5 × 40 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (50 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (90–100% EtOAc/hexane) afforded sulfoxide **173** (2.54 g, 72%) as a yellow solid, m.p. = 81–83 ºC. R_f = 0.30 (100% EtOAc). IR (film)/cm^{-1} 1577, 1445, 1421, 1347, 1240, 1172, 1145, 1110, 1035, 1009, 947, 914, 805, 770, 664. ^{1}H NMR

(400 MHz, $CDCl_3$) δ 8.62–8.59 (1 H, m, Py-H), 7.99–7.90 (2 H, m, Py-H), 7.75 (2 H, d, *J* = 8.3 Hz, 2 × Ts-H), 7.38 (1 H, ddd, *J* = 7.0, 4.7, 1.8 Hz, Py-H), 7.32 (2 H, d, *J* = 8.3 Hz, 2 × Ts-H), 4.85 (1 H, d, *J* = 10.8 Hz, SC*H*HO), 4.57 (1 H, d, *J* = 10.8 Hz, SCH*H*O), 4.17–3.99 (4 H, m, OCH_2CH_2O), 2.42 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6 (Py-C_q), 149.6 (Py-C), 145.0 (Ts-C_q), 138.0 (Py-C), 132.7 (Ts-C_q), 129.8 (2 × Ts-C), 127.9 (2 × Ts-C), 124.7 (Py-C), 120.8 (Py-C), 91.1 (SCH_2O), 71.1 (OCH_2), 68.6 (OCH_2), 21.6 (CH_3). HRMS (ES) *m/z* Calculated for $C_{15}H_{17}NNaO_5S_2$ [M+Na]: 378.0446; Found: 378.0457 [M+Na], Δ 2.9 ppm.

2-(Oxetan-2-ylsulfinyl)pyridine (174)



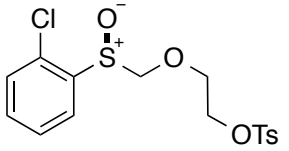
A solution of LDA (1 M in THF, 1.08 mL, 1.08 mmol) was added dropwise to a solution of sulfoxide **173** (0.26 g, 0.71 mmol) in THF (28 mL) at –78 °C and stirred for 15 min. Reaction transferred to a –20 ºC bath and stirred for a further 20 min. Reaction quenched with sat. aq. NH_4Cl (50 mL) and extracted with CH_2Cl_2 (5 × 30 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography afforded the oxetane as a mixture of two diastereoisomers **174A** (50 mg, 38%) (20% EtOAc/hexane) followed by **174B** (68 mg, 51%) (20% CH_2Cl_2/Et_2O) both as white solids.

Major Diastereoisomer 174B: M.p. = 71–73 ºC. R_f = 0.15 (20% CH_2Cl_2/Et_2O). IR (film)/cm^{-1} 3398, 2956, 1573, 1564, 1447, 1418, 1332, 1222, 1113, 1083, 1042, 988, 764, 712. ^1H NMR (400 MHz, $CDCl_3$) δ 8.63–8.61 (1 H, d, *J* = 4.6 Hz, Py-H), 7.98–7.90 (2 H, m, 2 × Py-H), 7.38 (1 H, ddd, *J* = 6.8, 4.8, 2.2 Hz, Py-H), 5.82 (1 H, dd, *J* = 7.4, 5.3 Hz, OCHS), 4.80 (1 H, ddd, *J* = 12.0, 6.8, 5.4 Hz, OCH*H*), 4.69 (1 H, ddd, *J* = 11.4, 6.0, 5.4 Hz, OC*H*H), 3.58–3.47 (1 H, m, OCH_2CHH), 3.22–3.12 (1 H, m, OCH_2CHH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0 (Py-C_q), 149.7 (Py-C), 137.9 (Py-C), 124.6 (Py-C), 120.5 (Py-C), 100.0 (OCHS), 71.5 (OCH_2), 18.7 (OCH_2CH_2). HRMS (CI) *m/z* Calculated for $C_8H_{10}NO_2S$ [M+H]: 184.0432; Found: 184.0430 [M+H], Δ 1.1 ppm.

Minor Diastereoisomer 174A: M.p. = 71–73 ºC. R_f = 0.10 (20% CH_2Cl_2/Et_2O). IR (film)/cm^{-1} 3502, 2970, 2912, 1575, 1449, 1421, 1240, 1088, 1053, 1009, 975, 915, 774,

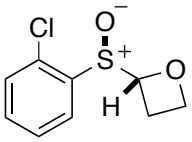
739. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (1 H, d, *J* = 4.7 Hz, Py-H), 8.04 (1 H, d, *J* = 7.8 Hz, Py-H), 7.94 (1 H, ddd, *J* = 7.8, 7.5, 1.7 Hz, Py-H), 7.37 (1 H, ddd, *J* = 7.5, 4.7, 1.1 Hz, Py-H), 5.78 (1 H, dd, *J* = 7.9, 5.6 Hz, OCHS), 4.82 (1 H, ddd, *J* = 8.8, 6.9, 5.4 Hz, OCH*H*), 4.65 (1 H, ddd, *J* = 8.4, 6.0, 5.4 Hz, OC*H*H), 3.39–3.28 (1 H, m, OCH_2CH*H*), 3.17–3.05 (1 H, m, OCH_2C*H*H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0 (Py-C_q), 149.5 (Py-C), 137.7 (Py-C), 124.6 (Py-C), 121.4 (Py-C), 97.2 (OCHS), 71.4 (OCH_2), 22.7 (OCH_2*C*H_2). HRMS (CI) *m/z* Calculated for $C_8H_{10}NO_2S$ [M+H]: 184.0432; Found: 184.0430 [M+H], Δ 1.1 ppm.

1-Chloro-2-({2-[(4-methylbenzenesulfonyl)oxy]ethoxy}methanesulfinyl)benzene (175e)

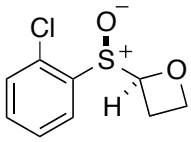


meta-Chloroperbenzoic acid (0.26 g, 1.51 mmol) was added portionwise to a solution of sulfide **83e** (0.51 g, 1.37 mmol) in dichloromethane (20 mL) at 0 ºC and the mixture for 1 h 45 min. The reaction was quenched with sat. aq. Na_2SO_3 (20 mL) and sat. aq. $NaHCO_3$ (20 mL) then extracted with dichloromethane (3 × 15 mL). The combined organic layers were washed with sat. aq. Na_2SO_3 (2 × 10 mL) and sat. aq. $NaHCO_3$ (10 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (70% EtOAc/hexane) afforded sulfoxide **175e** (0.51 g, 96%) as a colourless oil. R_f = 0.30 (70% EtOAc/hexane). IR (film)/cm^{-1} 2953, 1598, 1448, 1355, 1175, 1095, 1018, 910, 814, 733, 661. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (1 H, dd, *J* = 7.6, 1.7 Hz, Ar-H), 7.89 (2 H, d, *J* = 8.4 Hz, 2 × Ts-H), 7.55 (1 H, ddd, *J* = 9.0, 7.6, 1.3 Hz, Ar-H), 7.48 (1 H, ddd, *J* = 9.0, 7.9, 1.7 Hz, Ar-H), 7.41 (1 H, dd, *J* = 7.9, 1.3 Hz, Ar-H), 7.35 (2 H, d, *J* = 8.4 Hz, 2 × Ts-H), 4.79 (1 H, d, *J* = 10.8 Hz, SC*H*HO), 4.39 (1 H, d, *J* = 10.8 Hz, SCH*H*O), 4.23–4.19 (2 H, m, OCH_2), 4.14–4.09 (2 H, m, OCH_2), 2.45 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0 (Ts-C_q), 135.9 (Ar-C_q), 132.8 (Ts-C_q), 130.1 (Ar-C_q), 129.9 (2 × Ts-C), 129.4 (Ar-C), 128.0 (2 × Ts-C), 127.4 (Ar-C), 126.9 (Ar-C), 122.8 (Ar-C), 101.7 (SCH_2O), 68.8 (OCH_2), 67.4 (OCH_2) 21.7 (CH_3). HRMS (ES) *m/z* Calculated for $C_{16}H_{18}{}^{35}ClO_5S_2^+$ $[M+H]^+$: 389.0279; Found: Accurate mass could not be obtained.

2-(2-Chlorobenzenesulfinyl)oxetane (176e)



A



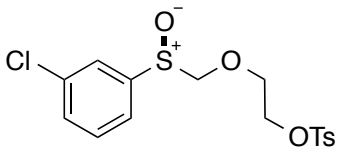
B

A solution of LiHMDS (1.0 M in THF, 0.94 mL, 0.94 mmol) was added dropwise to a solution of sulfoxide **175e** (0.30 g, 0.78 mmol) in THF (30 mL) at 0 ºC and stirred for 1 h 15 min. Reaction quenched with sat. aq. NH_4Cl (20 mL) and extracted with CH_2Cl_2 (5 × 15 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (40% EtOAc/hexane) afforded the sulfinyl oxetane as a mixture of two diastereoisomers **176eA** (12 mg, 6%) followed by **176eB** (62 mg, 37%) both as colourless oils.

Major Diastereoisomer 176B: R_f = 0.15 (40% EtOAc/hexane). IR (film)/cm^{-1} 2965, 1724, 1573, 1433, 1357, 1248, 1176, 1103, 1026, 914, 815, 752, 660. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (1 H, dd, *J* = 7.7, 1.7 Hz, Ar-H), 7.50 (1 H, ddd, *J* = 9.0, 7.7, 1.3 Hz, Ar-H), 7.43 (1 H, ddd, *J* = 9.0, 7.9, 1.7 Hz, Ar-H), 7.36 (1 H, dd, *J* = 7.9, 1.3 Hz, Ar-H), 5.75 (1 H, dd, *J* = 7.7, 5.5 Hz, OCHS), 4.79 (1 H, ddd, *J* = 8.8, 6.9, 5.2 Hz, OCH*H*), 4.64 (1 H, ddd, *J* = 8.3, 5.9, 5.2 Hz, OCH*H*), 3.31–3.23 (1 H, m, OCH_2CH*H*), 3.13–3.04 (1 H, m, OCH_2C*H*H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8 (C_q), 132.1 (Ar-C), 129.9 (C_q), 129.5 (Ar-C), 128.0 (Ar-C), 127.5 (Ar-C), 94.5 (SCHO), 71.5 (OCH_2), 22.7 (OCH_2*C*H_2). HRMS (ES) *m/z* Calculated $C_9H_{10}{}^{35}ClO_2S$ [M+H]: 217.0090; Found: 217.0104, [M+H], Δ 6.5 ppm.

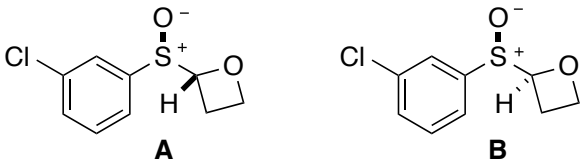
Minor Diastereoisomer 176A: R_f = 0.22 (40% EtOAc/hexane). IR (film)/cm^{-1} 2965, 1724, 1573, 1433, 1357, 1248, 1176, 1103, 1026, 914, 815, 752, 660. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (1 H, dd, *J* = 7.3, 1.8 Hz, Ar-H), 7.50 (1 H, ddd, *J* = 8.9, 7.3, 1.3 Hz, Ar-H), 7.44 (1 H, ddd, *J* = 8.9, 7.8, 1.8 Hz, Ar-H), 7.39 (1 H, dd, *J* = 7.8, 1.3 Hz, Ar-H), 5.79 (1 H, dd, *J* = 7.4, 5.3 Hz, OCHS), 4.81 (1 H, ddd, *J* = 8.9, 6.7, 5.3 Hz, OCH*H*), 4.68 (1 H, ddd, *J* = 8.3, 6.1, 5.3 Hz, OC*H*H), 3.27–3.18 (1 H, m, OCH_2CH*H*), 2.56–2.47 (1 H, m, OCH_2C*H*H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9 (C_q), 132.2 (Ar-C), 130.3 (C_q), 129.8 (Ar-C), 127.9 (Ar-C), 126.4 (Ar-C), 97.5 (SCHO), 71.5 (OCH_2), 18.2 (OCH_2*C*H_2). HRMS (ES) *m/z* Calculated $C_9H_{10}{}^{35}ClO_2S$ [M+H]: 217.0090; Found: 217.0104, [M+H], Δ 6.5 ppm.

1-Chloro-3-({2-[(4-methylbenzenesulfonyl)oxy]ethoxy}methanesulfinyl)benzene (175f)



meta-Chloroperbenzoic acid (0.36 g, 2.09 mmol) was added to a solution of sulfide **83f** (0.71 g, 1.91 mmol) in dichloromethane (28 mL) at 0 ºC and the mixture stirred at 0 ºC for 2 h. The reaction was quenched with sat. aq. Na_2SO_3 (25 mL) and extracted with dichloromethane (5 × 20 mL). The combined organic layers were washed with 1 M NaOH (2 × 10 mL) and sat. aq. NH_4Cl (15 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (70% EtOAc/hexane) afforded sulfoxide **175f** (0.50 g, 68%) as a white solid, m.p. = 81–82 ºC. R_f = 0.30 (70% EtOAc/hexane). IR (film)/cm^{-1} 3060, 2957, 1597, 1588, 1457, 1406, 1352, 1249, 1186, 1172, 1121, 1041, 1015, 937, 915, 887, 775, 664. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (2 H, d, *J* = 8.3 Hz, 2 × Ts-H), 7.63–7.60 (1 H, m, Ar-H), 7.51–7.44 (3 H, m, 3 × Ar-H), 7.34 (2 H, d, *J* = 8.3 Hz, 2 × Ts-H), 4.49 (1 H, d, *J* = 10.6 Hz, SC*H*HO), 4.39 (1 H, d, *J* = 10.6 Hz, SCH*H*O), 4.23–3.99 (4 H, m, OCH_2CH_2O), 2.44 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1 (Ts-C_q), 142.6 (Ar-C_q), 135.7 (Ar-C_q), 132.6 (Ts-C_q), 131.5 (Ar-C), 130.5 (Ar-C), 129.9 (2 × Ts-C), 127.9 (2 × Ts-C), 124.3 (Ar-C), 122.5 (Ar-C), 92.1 (SCH_2O), 71.1 (OCH_2), 68.8 (OCH_2), 21.6 (CH_3). HRMS (ES) *m/z* Calculated $C_{17}H_{18}O_5S_2{}^{35}Cl$ [M+H]: 389.0284; Found 389.0300 [M+H], Δ 4.1 ppm.

2-(3-Chlorobenzenesulfinyl)oxetane (176f)



A **B**

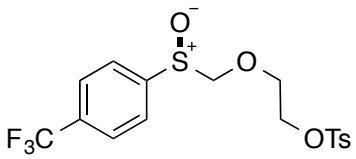
A solution of LiHMDS (1.0 M in THF, 5.04 mL, 5.04 mmol) was added dropwise to a solution of sulfoxide **175f** (1.78 g, 4.58 mmol) in THF (175 mL) at 0 ºC and stirred for 1 h 25 min. Reaction quenched with sat. aq. NH_4Cl (50 mL) and extracted with CH_2Cl_2 (5 × 15 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (50% EtOAc/hexane)

afforded the oxetane as a mixture of two diastereoisomers **176fA** (0.45 g, 45%) followed by **176fB** (0.37 g, 37%) both as off white solids.

Major Diastereoisomer 176fA: M.p. = 65–66 ºC. R_f = 0.17 (50% EtOAc/hexane). IR (film)/cm^{-1} 3025, 2970, 2937, 1756, 1738, 1438, 1336, 1228, 1217, 1208, 914, 650. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.58 (1 H, m, Ar-H), 7.49–7.41 (3 H, m, 3 × Ar-H), 5.31 (1 H, dd, *J* = 7.5, 5.0 Hz, OCHS), 4.81 (1 H, ddd, *J* = 8.8, 6.7, 5.4 Hz, OCH*H*), 4.68 (1 H, ddd, *J* = 8.5, 6.2, 5.4 Hz, OC*H*H), 3.28–3.16 (1 H, m, OCH_2CH*H*), 2.74–2.62 (1 H, m, OCH_2C*H*H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3 (C_q), 135.7 (C_q), 131.4 (Ar-C), 130.4 (Ar-C), 124.2 (Ar-C), 122.2 (Ar-C), 99.9 (SCHO), 71.3 (OCH_2), 19.5 (OCH_2*C*H_2). HRMS (ES) *m/z* Calculated $C_9H_{10}{}^{35}ClO_2S^+$ $[M+H]^+$: 217.0085; Found: 217.0079, $[M+H]^+$, Δ 2.8 ppm.

Minor Diastereoisomer 176fB: M.p. = 65–66 ºC. R_f = 0.09 (50% EtOAc/hexane). IR (film)/cm^{-1} 3025, 2970, 2937, 1756, 1738, 1438, 1336, 1228, 1217, 1208, 914, 650. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.67 (1 H, m, Ar-H), 7.55–7.44 (3 H, m, 3 × Ar-H), 5.42 (1 H, dd, *J* = 7.6, 5.6 Hz, OCHS), 4.67–4.59 (2 H, m, OCH_2), 3.10–2.99 (2 H, m, OCH_2C*H*$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1 (C_q), 135.5 (C_q), 131.5 (Ar-C), 130.2 (Ar-C), 125.2 (Ar-C), 123.2 (Ar-C), 97.0 (SCHO), 71.2 (OCH_2), 22.6 (OCH_2*C*H_2). HRMS (ES) *m/z* Calculated $C_9H_{10}{}^{35}ClO_2S^+$ $[M+H]^+$: 217.0085; Found: 217.0079, $[M+H]^+$, Δ 2.8 ppm.

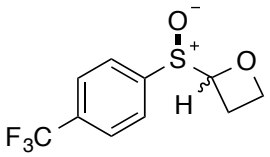
1-({2-[(4-Methylbenzenesulfonyl)oxy]ethoxy}methanesulfinyl)-4-(trifluoromethyl)benzene (175i)



meta-Chloroperbenzoic acid (79 mg, 0.46 mmol) was added to a solution of sulfide **83i** (0.17 g, 0.42 mmol) in dichloromethane (6 mL) at 0 ºC and the mixture stirred at 0 ºC for 2 h 15 min. The reaction was quenched with sat. aq. Na_2SO_3 (10 mL) and extracted with dichloromethane (5 × 10 mL). The combined organic layers were washed with 1 M NaOH (2 × 10 mL) and sat. aq. NH_4Cl (10 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (70% EtOAc/hexane) afforded sulfoxide **175i** (0.12 g, 66%) as a colourless oil. R_f = 0.21 (70%

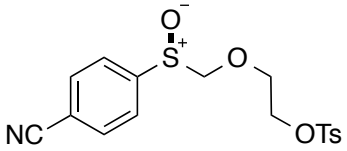
EtOAc/hexane). IR (film)/cm^{-1} 2914, 1599, 1452, 1404, 1359, 1322, 1170, 1102, 1037, 1013, 946, 811, 700, 659. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.70 (6 H, m, 4 × Ar-H + 2 × Ts-H), 7.34 (2 H, d, J = 8.3 Hz, 2 × Ts-H), 4.53 (1 H, d, J = 10.4 Hz, SC*H*HO), 4.44 (1 H, d, J = 10.4 Hz, SCH*H*O), 4.22–4.00 (4 H, m, OCH_2CH_2O), 2.44 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2 (Ts-C_q), 133.6 (Ar-C_q), 132.6 (Ts-C_q), 131.9 (C_q, q, J_{CF} = 31.2 Hz, *C*-CF_3), 129.9 (2 × Ts-C), 127.9 (2 × Ts-C), 126.3 (q, J_{CF} = 3.6 Hz, 2 × Ar-C), 124.9 (2 × Ar-C), 123.5 (C_q, q, J_{CF} = 248.9 Hz, CF_3), 91.8 (SCH_2O), 71.3 (OCH_2), 68.5 (OCH_2), 21.6 (CH_3). ^{19}F NMR (400 MHz, $CDCl_3$) δ –62.5 (CF_3). HRMS (ES) *m/z* Calculated $C_{17}H_{17}O_5F_3NaS_2$ [M+Na]: 445.0367; Found 445.0373 [M+Na], Δ 1.3 ppm.

2-[4-(Trifluoromethyl)benzenesulfinyl]oxetane (176i)



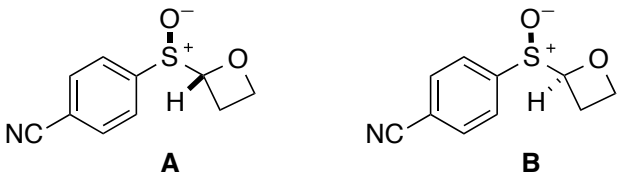
A solution of LiHMDS (1 M in THF, 0.21 mL, 0.21 mmol) was added dropwise to a solution of sulfoxide **175i** (74 mg, 0.17 mmol) in THF (7 mL) at 0 ºC and stirred for 1 h 45 min. Reaction quenched with sat. aq. NH_4Cl (20 mL) and extracted with CH_2Cl_2 (5 × 10 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (50% EtOAc/hexane) afforded oxetane **176i** (6 mg, 13%) as a colourless oil. Only one diastereoisomer isolated. R_f = 0.22 (50% EtOAc/hexane). IR (film)/cm^{-1} 2929, 1730, 1605, 1402, 1321, 1169, 1128, 1102, 1061, 1014, 952, 836, 698, 666. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (2 H, d, J = 7.7 Hz, 2 × Ar), 7.72 (2 H, d, J = 7.7 Hz, 2 × Ar), 5.32 (1 H, dd, J = 7.4, 5.2 Hz, SCHO), 4.84 (1 H, ddd, J = 8.8, 6.8, 5.4 Hz, OCH*H*), 4.70 (1 H, ddd, J = 8.8, 6.2, 5.4, Hz, OC*H*H), 3.28–3.18 (1 H, m, OCH_2CH*H*), 2.75–2.64 (1 H, m, OCH_2C*H*H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7 (Ar-C_q), 133.2 (C_q, q, J_{CF} = 32.3 Hz, *C*-CF_3), 126.2 (q, J_{CF} = 4.2 Hz, 2 × Ar-C), 124.7 (2 × Ar-C), 123.5 (q, J_{CF} = 274.4 Hz, CF_3), 99.9 (OCHS), 71.4 (OCH_2), 19.8 (OCH_2CH_2). ^{19}F NMR (400 MHz, $CDCl_3$) δ –62.9 (CF_3). HRMS (EI) *m/z* Calculated $C_{10}H_9F_3O_2S$ [M]: 250.0275; Found 250.0287 [M], Δ 4.8 ppm.

4-({2-[(4-Methylbenzenesulfonyl)oxy]ethoxy)methanesulfinyl)benzonitrile (175l)



meta-Chloroperbenzoic acid (0.26 g, 1.51 mmol) was added to a solution of sulfide **83l** (0.50 g, 1.38 mmol) in dichloromethane (20 mL) at 0 ºC and the mixture stirred at 0 ºC for 2 h 30 min. The reaction was quenched with sat. aq. Na_2SO_3 (30 mL) and extracted with dichloromethane (5 × 15 mL). The combined organic layers were washed with 1 M NaOH (2 × 15 mL) and sat. aq. NH_4Cl (15 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (70% EtOAc/hexane) afforded sulfoxide **175l** (0.47 g, 90%) as pale yellow solid, m.p. = 85–87 ºC. R_f = 0.20 (70% EtOAc/hexane). IR (film)/cm^{-1} 2929, 2231, 1596, 1487, 1445, 1397, 1351, 1309, 1295, 1247, 1189, 1120, 1080, 1042, 939, 834, 811, 775, 719, 704, 663. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86–7.73 (6 H, m, 4 × Ar-H + 2 × Ts-H), 7.37 (2 H, d, *J* = 8.4 Hz, 2 × Ts-H), 4.56 (1 H, d, *J* = 10.6 Hz, SC*H*HO), 4.47 (1 H, d, *J* = 10.6 Hz, SCH*H*O), 4.24–4.03 (4 H, m, OCH_2CH_2O), 2.47 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5 (Ar-C_q), 145.2 (Ts-C_q), 132.9 (2 × Ar-C), 132.9 (Ts-C_q), 130.0 (2 × Ts-C), 127.9 (2 × Ts-C), 125.2 (2 × Ar-C), 117.7 (CN), 115.2 (Ar-C_q), 91.4 (SCH_2O), 71.4 (OCH_2), 68.5 (OCH_2), 21.7 (CH_3). HRMS (ES) *m/z* Calculated for $C_{17}H_{18}NO_5S_2^+$ $[M+H]^+$: 380.0621; Found: 380.0624 $[M+H]^+$, Δ 0.8 ppm.

4-(Oxetane-2-sulfinyl)benzonitrile (176l)



A **B**

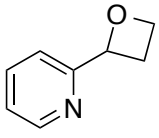
A solution of LDA (1 M in THF, 0.40 mL, 0.40 mmol) was added dropwise to a solution of sulfoxide **175l** (0.10 g, 0.26 mmol) in THF (10.5 mL) at –78 ºC and stirred for 15 min. Reaction transferred to a –20 ºC bath and stirred for a further 20 min. Reaction quenched with sat. aq. NH_4Cl (10 mL) and extracted with CH_2Cl_2 (5 × 10 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure.

Purification by flash chromatography (70% EtOAc/hexane) afforded the oxetane as a mixture of two diastereoisomers, **176lA** (10 mg, 18%) followed by **176lB** (22 mg, 39%); both as white solids.

Major Diastereoisomer 176lB: M.p. = 75–76 ºC. R_f = 0.21 (70% EtOAc/hexane). IR (film)/cm^{-1} 3090, 2967, 2881, 2229, 1731, 1589, 1483, 1397, 1338, 1245, 1177, 1144, 1073, 1015, 953, 828, 778, 715, 663. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (2 H, d, *J* = 8.3 Hz, 2 × Ar-H), 7.78 (2 H, d, *J* = 8.3 Hz, 2 × Ar-H), 5.44 (1 H, dd, *J* = 7.6, 5.4 Hz, OCHS), 4.66–4.60 (2 H, m, OCH_2), 3.18–3.02 (2 H, m, OCH_2CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9 (C_q), 132.5 (2 × Ar-C), 125.8 (2 × Ar-C), 117.8 (CN), 115.0 (C_q), 97.1 (OCHS), 71.5 (OCH_2), 22.7 (OCH_2CH_2). HRMS (ASAP) *m/z* Calculated for $C_{10}H_{10}NO_2S$ [M+H]: 208.0432; Found: 208.0432 [M], Δ 0 ppm.

Minor Diastereoisomer 176lA: M.p. = 76–76 ºC. R_f = 0.20 (70% EtOAc/hexane). IR (film)/cm^{-1} 3090, 2967, 2881, 2229, 1731, 1589, 1483, 1397, 1338, 1245, 1177, 1144, 1073, 1015, 953, 828, 778, 715, 663. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (2 H, d, *J* = 8.5 Hz, 2 × Ar-H), 7.72 (2 H, d, *J* = 8.5 Hz, 2 × Ar-H), 5.31 (1 H, dd, *J* = 7.3, 5.0 Hz, OCHS), 4.84 (1 H, ddd, *J* = 8.8, 7.0, 5.5 Hz, OCH*H*), 4.71 (1 H, ddd, *J* = 8.5, 5.9, 5.5 Hz, OC*H*H), 3.25–3.15 (1 H, m, OCH_2CHH), 2.78–2.68 (1 H, m, OCH_2CHH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2 (C_q), 132.8 (2 × Ar-C), 124.9 (2 × Ar-C), 117.6 (CN), 115.0 (C_q), 99.9 (OCHS), 71.5 (OCH_2), 20.1 (OCH_2CH_2). HRMS (ASAP) *m/z* Calculated for $C_{10}H_{10}NO_2S$ [M+H]: 208.0432; Found: 208.0432 [M], Δ 0 ppm.

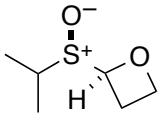
2-(Oxetan-2-yl)pyridine (178)



*i*PrMgCl·LiCl (1.3 M in THF, 0.35 mL, 0.46 mmol) was added dropwise to a solution of 2-(oxetan-2-ylsulfinyl)pyridine **174** (41 mg, 0.23 mmol) in THF (4.5 mL) at –78 ºC and stirred for 5 min. 3-Pentanone (75 μL, 0.69 mmol) was added and the reaction stirred at –78 ºC for a further 5 min. Reaction quenched with sat. aq. NH_4Cl (10 mL) and extracted with CH_2Cl_2 (5 × 10 mL). Combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (100% EtOAc) afforded oxetane **178** (18 mg, 60%) as a colourless oil. R_f = 0.48 (100% EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (1 H, d, *J* = 4.7 Hz, Py-H), 7.78 (1 H, ddd, *J* = 9.4, 7.7, 1.6 Hz, Py-H), 7.62 (1 H, d, *J* = 7.7 Hz, Py-H), 7.23 (1 H, dd, *J* = 7.2, 4.7 Hz, Py-H), 5.87 (1 H, t, *J* = 7.5 Hz, OCHPy), 4.91–4.85 (1 H, m, OCH*H*), 4.72 (1 H, dt, *J* = 9.2, 5.9 Hz, OC*H*H), 3.19–3.08 (1 H, m, OCH_2CH*H*), 2.80–2.69 (1 H, m, OCH_2C*H*H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4 (C_q), 149.3 (Py-C), 136.8 (Py-C), 122.5 (Py-C), 119.8 (Py-C), 83.0 (OCHPy), 69.0 (OCH_2), 28.9 (OCH_2*C*H_2). HRMS (EI) *m/z* Calculated for $C_8H_{10}NO^+$ $[M+H]^+$: 136.0757; Found: Accurate mass could not be obtained.

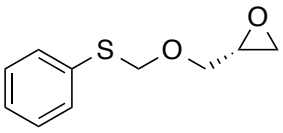
2-(Propane-2-sulfinyl)oxetane (197)



*i*PrMgCl (2 M in Et_2O, 0.13 mL, 0.26 mmol) was added dropwise to a solution of 2-(3-chlorobenzenesulfinyl)oxetane **176f** (28 mg, 0.13 mmol) in THF (1.5 mL) at –78 ºC and stirred for 5 min. Reaction quenched with sat. aq. NH_4Cl (10 mL) and extracted with CH_2Cl_2 (5 × 10 mL). Combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (100% EtOAc) afforded oxetane **197** (16 mg, 86%) as a colourless oil. R_f = 0.14 (100% EtOAc). IR (film)/cm^{-1} 2967, 1646, 1471, 1368, 1241, 1051, 1009, 975, 916, 764. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57 (1 H, dd, *J* = 8.1, 6.0 Hz, SCHO), 4.84–4.77 (1 H, m, OCH*H*), 4.76–4.70 (1 H, m, OC*H*H), 3.30–3.22 (1 H, m, OCH_2CH*H*), 3.19 (1 H, sept, *J* = 7.0 Hz, (SC*H*$(CH_3)_2$), 3.06–2.95 (1 H, m, OCH_2C*H*H), 1.42 (3 H, d, *J* = 7.0 Hz, CH_3), 1.14 (3 H, d, *J* = 7.0 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 91.3 (SCHO), 71.6 (OCH_2), 46.0 (S*C*H$(CH_3)_2$), 22.2 (OCH_2*C*H_2), 16.7 (CH_3), 15.9 (CH_3).

5.3. Alternative Strategies to Access Functionalised Oxetane Motifs

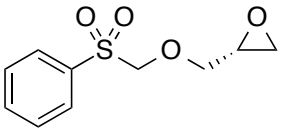
(2R)-2-{[(Phenylsulfanyl)methoxy]methyl}oxirane (213)



Sodium hydride (9 mg, 0.38 mmol) was added to a solution of (*R*)-oxiran-2-ylmethanol (0.06 mL, 0.95 mmol) in DMF (2 mL) at 0 ºC and stirred for 50 min. Sodium iodide

(52 mg, 0.35 mmol) and chloromethyl phenyl sulfide (0.04 mL, 0.32 mmol) were added and the reaction was stirred at 0 ºC for 1 h then warmed to rt and stirred for a further 25 h. The reaction was quenched with H_2O (10 mL) and extracted with EtOAc (6 × 7 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (0–10% EtOAc/heptane) afforded epoxide **213** (50 mg, 81%) as a colourless oil. R_f = 0.13 (10% EtOAc/heptane). IR (film)/cm^{-1} 3057, 2909, 1583, 1479, 1438, 1305, 1256, 1064, 890, 841, 740, 689. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.46 (2 H, m, 2 × Ar-H), 7.33–7.28 (2 H, m, 2 × Ar-H), 7.24 (1 H, tt, *J* = 7.3, 1.3, Hz, Ar-H), 5.08 (1 H, d, *J* = 11.6 Hz, SC*H*HO), 5.04 (1 H, d, *J* = 11.6 Hz, SCH*H*O), 3.92 (1 H, dd, *J* =11.4, 3.1 Hz, CH_2OCHH), 3.61 (1 H, dd, *J* = 11.4, 5.8 Hz, CH_2OCHH), 3.21–3.16 (1 H, m, $OCHCH_2$), 2.81 (1 H, dd, *J* = 5.0, 4.1 Hz, OC*H*H), 2.63 (1 H, dd, *J* = 5.0, 2.7 Hz, OCH*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.6 (C_q), 130.3 (2 × Ar-C), 129.0 (2 × Ar-C), 126.8 (Ar-C), 76.3 (SCH_2O), 68.7 (CH_2OCH_2), 50.4 ($OCHCH_2$), 44.3 (OCH_2). HRMS (EI) *m/z* Calculated for $C_{10}H_{12}O_2S^+$ $[M]^+$: 196.0553; Found: 196.0545 $[M]^+$, Δ 4.1 ppm.

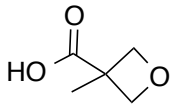
(2R)-2-{[(Benzenesulfonyl)methoxy]methyl}oxirane (214)



meta-Chloroperbenzoic acid (77%, 6.89 g, 30.72 mmol) was added to a solution of sulfide **213** (2.01 g, 10.24 mmol) in CH_2Cl_2 (50 mL) at 0 ºC and stirred for 2 h at 0 ºC. Reaction quenched with sat. aq. Na_2SO_3 (25 mL) and extracted with CH_2Cl_2 (5 x 40 mL). Combined organics were washed with 2 M NaOH (3 x 35 mL) and sat. aq. NH_4Cl (40 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (0–40% EtOAc/heptane) afforded epoxide **214** (2.12 g, 91%) as a colourless oil. R_f = 0.19 (40% EtOAc/heptane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95–7.90 (2 H, m, 2 × Ar-H), 7.67 (1 H, tt, *J* = 7.4, 1.3 Hz, Ar-H), 7.60–7.55 (2 H, m, 2 × Ar-H), 4.62 (2 H, s, SCH_2O), 4.16 (1 H, dd, *J* =11.8, 2.6 Hz, CH_2OCHH), 3.75 (1 H, dd, *J* = 11.8, 6.3 Hz, CH_2OCHH), 3.13–3.08 (1 H, m, $OCHCH_2$), 2.76 (1 H, dd, *J* = 4.9, 4.2 Hz, OC*H*H), 2.56 (1 H, dd, *J* = 4.9, 2.7 Hz, OCH*H*). ^{13}C NMR (100 MHz,

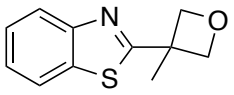
$CDCl_3$) δ 137.2 (C_q), 134.1 (Ar-C), 129.2 (2 × Ar-C), 128.7 (2 × Ar-C), 86.1 (SCH_2O), 73.5 (CH_2OCH_2), 50.1 ($OCHCH_2$), 43.7 (OCH_2). HRMS (EI) *m/z* Calculated for $C_6H_5O_2S^+$ $[M\text{-}C_4H_7O_2]^+$: 141.0005; Found: 140.9999 $[M\text{-}C_4H_7O_2]^+$, Δ 4.3 ppm.

3-Methyloxetane-3-carboxylic acid (237)



$KMnO_4$ (4.74 g, 29.99 mmol) was added to a solution of NaOH (0.30 g, 7.50 mmol) in H_2O (10 mL) at 0 ºC. The resulting purple solution was stirred at 0 ºC for 15 min. 2-Methyloxetane methanol (1.00 mL, 10.00 mmol) was added dropwise and the reaction stirred at 0 ºC for 1 h 45 min. The reaction was quenched with sodium metabisulfite, and H_2O was added to aid stirring. The reaction was then acidified to pH 2 with 4 M HCl. Once acidified, the product was extracted with EtOAc (7 × 20 mL) and the combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to afford oxetane **237** (1.06 g, 92%) as a white solid, which was taken on without further purification; m.p. = 56–57 ºC. R_f = 0.02 (100% EtOAc). IR (film)/cm^{-1} 2963, 2896, 2568, 1712, 1450, 1381, 1294, 1182, 926, 873, 817, 713. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.00 (1 H, br s, OH), 5.00 (2 H, d, *J* = 6.1 Hz, OC*H*HCC*H*H), 4.46 (2 H, d, *J* = 6.1 Hz, OCH*H*CCH*H*), 1.66 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.0 (C=O), 79.4 (2 × OCH_2), 44.3 (C_q), 21.5 (CH_3). HRMS (CI) *m/z* Calculated for $C_5H_{12}NO_3$ $[M+NH_4]$: 134.0817; Found: 134.0815 $[M+NH_4]$, Δ 1.5 ppm.

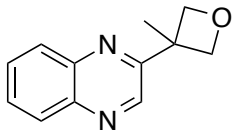
2-(3-Methyloxetan-3-yl)-1,3-benzothiazole (239)



Benzothiazole (50 mg, 0.37 mmol), 3-methyloxetane-3-carboxylic acid **237** (0.26 g, 2.24 mmol), Ag_2CO_3 (0.10 g, 0.37 mmol) and $K_2S_2O_8$ (0.80 g, 2.96 mmol) were added to a flame dried vial. The vial was flushed with argon then degassed before H_2O (1.87 mL) and CH_2Cl_2 (1.87 mL) were added. The vial was sealed and the reaction stirred at 22 ºC for 16 h. Reaction was quenched with brine (2 mL) then extracted with CH_2Cl_2 (4 × 10 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed

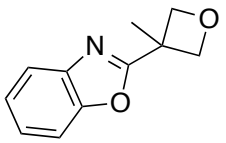
under reduced pressure. Purification by flash chromatography (10% EtOAc/hexane) afforded oxetane **239** (24 mg, 32%) as a colourless oil. R_f = 0.15 (10% EtOAc/hexane). IR (film)/cm^{-1} 2961, 2872, 1513, 1438, 1313, 1080, 1033, 985, 839, 760, 730. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (1 H, ddd, *J* = 8.3, 1.2, 0.6 Hz, Ar-H), 7.90 (1 H, ddd, *J* = 8.3, 1.2, 0.6 Hz, Ar-H), 7.50 (1 H, ddd, *J* = 8.3, 7.3, 1.2 Hz, Ar-H), 7.40 (1 H, ddd, *J* = 8.3, 7.3, 1.2 Hz, Ar-H), 5.17 (2 H, d, *J* = 5.9 Hz, OC*H*HCC*H*H), 4.72 (2 H, d, *J* = 5.9 Hz, OCH*H*CCH*H*), 1.94 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1 (NC_qS), 153.1 (Ar-C_q), 135.0 (Ar-C_q), 126.2 (Ar-C), 125.1 (Ar-C), 123.0 (Ar-C), 121.7 (Ar-C), 82.7 (2 × OCH_2), 44.5 (C_q), 25.0 (CH_3). HRMS (CI) *m/z* Calculated for $C_{11}H_{12}NOS$ [M+H]: 206.0640; Found: 206.0649 [M+H], Δ 4.4 ppm.

2-(3-Methyloxetan-3-yl)|quinoxaline (244)



Quinoxaline (50 mg, 0.38 mmol), 3-methyloxetane-3-carboxylic acid **237** (0.26 g, 2.28 mmol), Ag_2CO_3 (0.10 g, 0.39 mmol) and $K_2S_2O_8$ (0.82 g, 3.04 mmol) were added to a flame dried vial. The vial was flushed with argon then degassed before H_2O (1.93 mL) and CH_2Cl_2 (1.93 mL) were added. The vial was sealed and the reaction stirred at 22 ºC for 16 h. Reaction was quenched with brine (2 mL) then extracted with CH_2Cl_2 (4 × 10 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (10% EtOAc/hexane) afforded oxetane **244** (41 mg, 53%) as a colourless oil. R_f = 0.10 (10% EtOAc/hexane). IR (film)/cm^{-1} 2963, 2872, 1558, 1492, 1452, 1159, 1091, 979, 841, 762. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (1 H, s, NCHC), 8.14–8.04 (2 H, m, 2 × Ar-C), 7.81–7.72 (2 H, m, 2 × Ar-C), 5.27 (2 H, d, *J* = 6.0 Hz, OC*H*HCC*H*H), 4.80 (2 H, d, *J* = 6.0 Hz, OCH*H*CCH*H*), 1.89 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1 (N-C_q), 143.0 (N*C*HC_q), 141.5 (Ar-C_q), 141.2 (Ar-C_q), 130.2 (Ar-C), 129.5 (Ar-C), 129.1 (Ar-C), 129.1 (Ar-C), 81.7 (2 × OCH_2), 44.6 (C_q), 25.7 (CH_3). HRMS (NSI) *m/z* Calculated for $C_{12}H_{13}N_2O^+$ $[M+H]^+$: 201.1022; Found: 201.1021 $[M+H]^+$, Δ 0.5 ppm.

2-(3-Methyloxetan-3-yl)-1,3-benzoxazole (245)



Benzoxazole (49 mg, 0.41 mmol), 3-methyloxetane-3-carboxylic acid **237** (0.29 g, 2.50 mmol), Ag_2CO_3 (0.11 g, 0.40 mmol) and $K_2S_2O_8$ (0.90 g, 3.36 mmol) were added to a flame dried vial. The vial was flushed with argon then degassed before H_2O (2.14 mL) and CH_2Cl_2 (2.14 mL) were added. The vial was sealed and the reaction stirred at 22 ºC for 16 h. Reaction was quenched with brine (2 mL) then extracted with CH_2Cl_2 (4 × 10 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (100% hexane) afforded oxetane **245** (10 mg, 13%) as a colourless oil. R_f = 0.17 (100% hexane). IR (film)/cm^{-1} 2968, 2878, 1613, 1568, 1455, 1350, 1243, 1122, 1097, 989, 934, 824, 708. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76–7.71 (1 H, m, Ar-H), 7.58–7.52 (1 H, m, Ar-H), 7.39–7.33 (2 H, m, 2 × Ar-H), 5.21 (2 H, d, *J* = 6.0 Hz, OC*H*HCC*H*H), 4.67 (2 H, d, *J* = 6.0 Hz, OCH*H*CCH*H*), 1.93 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0 (NC_qO), 150.9 (Ar-C_q), 141.1 (Ar-C_q), 125.1 (Ar-C), 124.5 (Ar-C), 120.0 (Ar-C), 110.6 (Ar-C), 80.7 (2 × OCH_2), 40.2 (C_q), 22.7 (CH_3). HRMS (APCI) *m/z* Calculated for $C_{11}H_{12}NO_2^+$ $[M+H]^+$: 190.0863; Found: 190.0860 $[M+H]^+$, Δ 1.6 ppm.

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