

Exploring Oxetane Isosteres for Drug Discovery through the Catalytic Generation of Oxetanyl Carbocations

A Thesis Submitted by

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I confirm that the work presented within this document is my own. Clear acknowledgement has been made when referring to the work of others, or where help has been received.

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Abstract

Oxetanes are valuable motifs for modulating the metabolic susceptibility and physicochemical properties of medicinally promising compounds, as well as replacement motifs for carbonyl, *gem*-dimethyl and methylene units. For this reason, development of methodology to synthesise novel oxetane derivatives through efficient and robust routes is highly desirable.

In this thesis, the preparation of novel oxetane scaffolds through the *in situ* generation of oxetanyl carbocations is explored. First, the preparation of 3,3-diaryloxetanes, designed as isosteres for benzophenone and diarylmethane derivatives, through a catalytic Friedel–Crafts reaction is described. Using a lithium catalyst, 3,3-diaryloxetanes and dihydrobenzofuran scaffolds are both selectively prepared in one step by reaction of oxetan-3-ols with phenols. A scope of both scaffolds is exemplified along with further derivatisations of the 3,3-diaryloxetane motif. Studies into the mechanism of the reaction using ^1H NMR spectroscopy to observe oxetane ether intermediates are described.

The same lithium catalyst is applied to the thiol alkylation of oxetanols with sulfides towards a wide range of novel 3-sulfanyloxetanes in excellent yields (up to 91%). The sulfide linker presents a versatile site for further derivatisation leading to novel oxetane-containing structural classes and building blocks such as sulfoxides, sulfones, sodium sulfinates and sulfonyl fluorides. The reactivity of the oxetane-containing sulfinates and sulfonyl fluorides is described. In particular, oxetane-containing sulfonyl fluorides show exciting novel reactivity giving 3-aminooxetanes when reacted with a variety of amines instead of the expected sulfonamides. Studies into this unprecedented reactivity are described and compared to other alkyl sulfonyl fluorides.

The final section of this thesis provides full experimental details and data for all compounds synthesised during the course of this research.

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Abbreviations

AEBSF	4-(2-Aminoethyl)benzenesulfonyl fluoride
ADMET	Absorption, distribution, metabolism, excretion and toxicity
Ar	Aryl
ATP	Adenosine triphosphate
aq	Aqueous
BHO	3,3-Bis(hydroxymethyl)oxetane
Bn	Benzyl
Boc	<i>tert</i> -Butyloxycarbonyl
BPA	Bisphenol A
CCF	Central composite faced
cLogP	Calculated partition coefficient
cLogD	Calculated distribution coefficient
CROP	Cationic ring opening polymerisation
DABSO	1,4-Diazobicyclo[2.2.2]octane bis(sulfur dioxide) adduct
DAST	Diethylaminosulfur trifluoride
DCDMH	1,3-Dichloro-5,5-dimethylhydantoin
DDT	Dichlorodiphenyltrichloroethane
DIPEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMSO	Dimethylsulfoxide
DOE	Design of experiments

dr	Diastereomeric ratio
EC ₅₀	Half maximal effective concentration
EDO	2,2-Bis(4-ethoxyphenyl)-3,3-dimethyloxetane
EHO	3-Ethyl-3-(hydroxymethyl)oxetane
ee	Enantiomeric excess
FSBA	5'-(4-Fluorosulfonylbenzoyl)adenosine
FTIR	Fourier transform infrared spectroscopy
G4	4 th Generation
GBP	Great british pound
GSK	GlaxoSmithKline
h	Hour
HBA	Hydrogen bond acceptor
HBD	Hydrogen bond donor
hERG	Human ether-a-go-go related gene
IC ₅₀	Half maximal inhibitory concentration
IR	Infrared spectroscopy
K _i	Inhibitory Constant
LG	Leaving group
<i>m</i> CPBA	<i>meta</i> -Chloroperoxybenzoic acid
mins	Minutes
MsOH	Methanesulfonic acid
M _w	Molecular weight
NADPH	Nicotinamide adenine dinucleotide phosphate

NCS	<i>N</i> -Chlorosuccinimide
NFSI	<i>N</i> -Fluorobenzenesulfonimide
NMR	Nuclear magnetic resonance spectroscopy
PAMPA	Parallel artificial membrane permeability assay
Ph	Phenyl
PMPMEase	Polyisoprenylated methylated protein methyl esterase
PMSF	Phenylmethane sulfonyl fluoride
ppm	Parts per million
PSA	Polar surface area
RNA	Ribonucleic acid
SF	Sulfonyl fluoride
SM	Starting material
SMOPS	Sodium 3-methoxy-3-oxopropane-1-sulfinate
TBHP	<i>tert</i> -Butyl hydroperoxide
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl ether
WHO	World Health Organisation
X	Halide or heteroatom

1 Introduction

1.1 Drug Discovery

The discovery of innovative and effective drugs to address unmet medical needs remains of vital importance. However, discovery of new drugs is a time-consuming and increasingly costly process. The time for a new drug to reach the market averages over a decade from inception, and the research and development cost per new drug is currently estimated at \$2.6 billion compared to \$0.8 billion in 2000.^{1,2} One of the biggest challenges facing drug discovery, driving up costs and reducing productivity, is late stage failure of drug candidates when substantial investment has already been made. The success rate for drug candidates entering clinical trials (approximately 5 years and \$824 million into the drug development process)³ stands at an incredibly low 10%.⁴ Identifying causes of attrition and ways to identify these in prospective drug candidates earlier in the drug discovery process presents a huge challenge but also an opportunity to significantly increase productivity.

In the early 1990's, the majority of failures (40%) were due to the adverse pharmacokinetic properties and bioavailability of drug candidates.⁵ A deeper understanding of pharmacokinetics and the underlying compound related factors associated helped reduce attrition due to these reasons to just 10% of drug candidates in 2000 as causes of failure shifted towards efficacy and safety related reasons.^{6,7}

1.1.1 Desirable Properties for Drug Candidates

Sufficient potency and selectivity at the desired biological target are basic requirements for a successful drug. However, pharmacological effect at the intended target is alone not sufficient as pharmacokinetic profile and toxicity are also fundamentally important for the ultimate advancement of a candidate compound to marketed drug. Pharmacokinetics refers to the study of the disposition of a drug in the body over time.⁸ Absorption, distribution, metabolism, excretion and toxicity (ADMET) are parameters that provide insight into the interaction between the body and the drug.⁹

Absorption: Refers to how readily a compound passes from the site of administration into the bloodstream. Absorption of a drug is critical for bioavailability. Solubility is a key factor affecting permeability through biological membranes particularly for orally administered drugs.¹⁰

Distribution: Once absorbed, how widely a compound is distributed throughout the body is an important consideration. If concentration at the target is insufficient for a pharmacological

response this is a problem for a drug candidate. Being able to cross the blood-brain barrier is important for drugs targeting the central nervous system.¹¹

Metabolism: *In vivo* conversion of a compound to (typically inactive) metabolites by oxidation, reduction, hydrolysis, hydration, conjugation or isomerisation.¹² Rate of metabolism is critical, with low bioavailability a concern if clearance is too rapid. Cytochromes P450 are important enzymes that catalyse the oxidative metabolism of many drugs.⁹

Excretion: Removal of metabolites from the body usually *via* the kidneys or liver.

Toxicity: Adverse effects of a drug compound on the body. Toxicity problems to avoid include: the inhibition of the voltage gated potassium channel (hERG) which can cause fatal cardiac arrhythmia and cytochrome P450 inhibition as this can cause toxic concentrations of a drug to build up if metabolism *via* these enzymes is blocked.^{13,9}

A compound that has the desired pharmacological effect, is selective for its target, is able to reach the target site at sufficient concentrations and reside in the body long enough to have therapeutic effect can be described as 'drug-like'.⁸

1.1.2 Importance of Controlling Physicochemical Properties

There is an intrinsic link between the physicochemical properties of a molecule and its ADMET profile and therefore its chances of becoming a successful drug (Figure 1.1). Many studies have looked to gain an understanding of simple molecular properties and their influence on the ultimate drug-likeness of a compound.

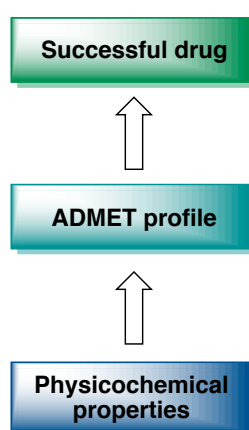


Figure 1.1 Physicochemical properties inform the ADMET profile which in turn has a direct impact on the potential success of a drug.

The term lipophilicity refers to how readily a compound dissolves in non-polar media and is measured by calculating the octanol/water partition coefficient, logP, and/or distribution coefficient, logD. There are numerous computational methods for the calculation of these coefficients, enabling rapid and convenient prediction of lipophilicity for proposed and synthesised structures.¹⁴ Lipophilicity is a highly influential parameter on the ADMET profile of a compound.¹⁵ High lipophilicity is associated with off-target promiscuity as a result of lipophilic molecules favouring the hydrophobic binding pocket over the aqueous bulk environment. In a specific example, Waring (AstraZeneca) found that compounds with high lipophilicity (clogP>3) were more likely to act as inhibitors of the hERG cardiac potassium channel.¹⁶ Rate of metabolism is also affected by lipophilicity with highly lipophilic molecules often targeted by metabolic enzymes and converted to more polar metabolites for removal from the body. Johnson and co-workers (Pfizer), examined the *in vitro* clearance of 47,018 compounds and found a general trend of increasing metabolic stability with decreasing logD.¹⁷ Furthermore, there exists a strong negative correlation between lipophilicity and aqueous solubility.¹⁵ A balance must be achieved between solubility in the aqueous environment and ability to pass through the body's lipophilic membranes, unless additional transport mechanisms are functioning and appropriate.^{18,19}

Molecular weight (M_w) and lipophilicity are inextricably linked. During compound optimisation, M_w and lipophilicity often increase together as medicinal chemists look to maximise potency by introducing additional ligand-protein interactions and by favouring the hydrophobic binding site.²⁰ M_w has a large effect on solubility as Gleeson found that compounds with a M_w <300 had average solubilities of 250 μ M whereas compounds with a M_w >700 saw a reduction in average solubility to just 11 μ M.⁹ Permeability is also impacted, with increased size linked to poorer permeability through biological membranes.⁹ Consideration of these significant effects mean that control of M_w is important for maintaining a favourable pharmacokinetic profile.

Hydrogen bond donors and acceptors can give strong, specific interactions between a compound and the desired target protein. However, too many hydrogen bond acceptor/donor groups can hinder membrane permeability.²¹ This is due to a large unfavourable desolvation enthalpy associated with the compound moving from the aqueous bulk surroundings into the hydrophobic membrane.²² A related property, polar surface area (PSA) describes the amount of molecular surface occupied by polar atoms (oxygen, nitrogen and sometimes sulfur and phosphorus) and can give an indication of aqueous solubility and permeability.²³

A seminal report by Lovering and co-workers in 2009, described how increasing the fraction of sp^3 hybridised carbons in a molecule has a positive correlation to the clinical success of a compound.²⁴ Furthermore, a 2009 study from GSK indicated that compounds with more than

three aromatic rings exhibit increased risk of compound attrition.²⁵ Carboaromatic rings were shown to be most detrimental for compound developability when compared to heteroaromatics and carbo/heteroaliphatic ring systems.²⁶ Highly 3-dimensional scaffolds remain under-represented in compound libraries and therefore methods that access 3-dimensional scaffolds are of high value to the pharmaceutical industry.²⁷

Certain functional groups have inherent reactivity and toxicity that makes them unsuitable for incorporation into pharmaceuticals. Lack of chemical stability can be problematic with respect to ensuring the integrity of the compound and therefore the reliability and reproducibility of any biological data obtained.²⁸ The propensity of electrophilic compounds to undergo hydrolysis and react with nucleophilic species present in the body e.g. DNA or nucleophilic amino acid residues in proteins, can lead to undesirable side effects.²⁸ Additionally, redox active compounds are recognised as problematic due to the potential interference with essential redox processes in the body.^{28,29}

The relationship between physicochemical properties and *in vivo* drug-like behaviour has led to the development of guidelines for prospective drug compounds. In 1997, Lipinski published his 'rule of 5', a set of parameters ($M_w < 500$, $cLogP < 5$, < 5 H-bond donors, < 10 H-bond acceptors) determined to give compounds with suitable solubility and permeability for oral administration in drug discovery.^{21a} Subsequent studies have refined these parameters, particularly at the upper limits, to develop new sets of guidelines to help medicinal chemists design compounds with the greatest probability of successful development. Gleeson (GSK) studied the properties of approximately 30,000 molecules and found that compounds with a molecular weight < 400 and a $cLogP < 4$ were most likely to display favourable ADMET profiles giving rise to GSK's favoured '4/400 rule'.⁹ Pfizer developed an alternative '3/75 rule' as compounds with a polar surface area $< 75 \text{ \AA}^2$ and a $cLogP > 3$ were found to show decreased drug-likeness in their study.³⁰

Churcher and co-workers highlighted the need to consider lipophilicity and M_w at earlier stages of drug discovery.²⁸ Employing hits or leads with lower logP values and M_w ($LogP$ 0–3 and M_w 200–350) offers a degree of flexibility for property modulation during the lead optimisation phase. The synthesis of scaffolds that conform to these 'lead-like' properties are likely to be of value to medicinal chemists as elaboration can provide molecules that remain within drug-like chemical space.

1.1.3 Oxetanes in Drug Discovery

Work by several research groups has validated oxetanes as expedient motifs and scaffolds in medicinal chemistry.³¹ This section will describe: the occurrence of oxetanes in natural products and bioactive compounds, the intrinsic structural features of oxetanes that make them fundamentally attractive modules for drug discovery, and studies that have investigated the benefits and effects of oxetane incorporation within the context of medicinal chemistry. The use of oxetanes as bioisosteres for medicinal chemistry is covered separately in Section 1.1.5 due the particular relevance of this area to the research described in this thesis.

1.1.3.1 Oxetanes in Natural Products and Bioactive Compounds

Taxol (Figure 1.2), isolated from the bark of the western yew, *taxus brevifolia*, is a well known oxetane-containing natural product.³² Following commercial development by Bristol Myers Squibb, taxol was approved for use in cancer chemotherapy in 1993 and remains on the World Health Organisation (WHO) list of essential medicines.^{33,34} Taxol acts by halting cell division through the stabilisation of microtubules.³⁵ Although studies have shown that replacing the oxygen in the oxetane ring with N, S or Se is detrimental to bioactivity,³⁶ recent analyses have indicated that the oxetane motif is not essential for the cytotoxic activity of taxol.³⁷

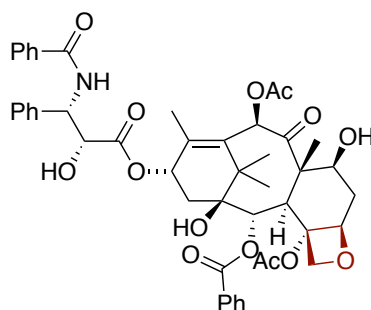


Figure 1.2 The structure of taxol with the oxetane ring highlighted in red.

The biosynthesis of the oxetane ring in taxol is proposed to proceed through enzyme-mediated rearrangement of an epoxy ester. Neutral concerted, acid-catalysed and dissociative pathways have all been considered (Figure 1.3).³⁸ However, computational studies have been unable to definitively confirm the mechanism.³⁹

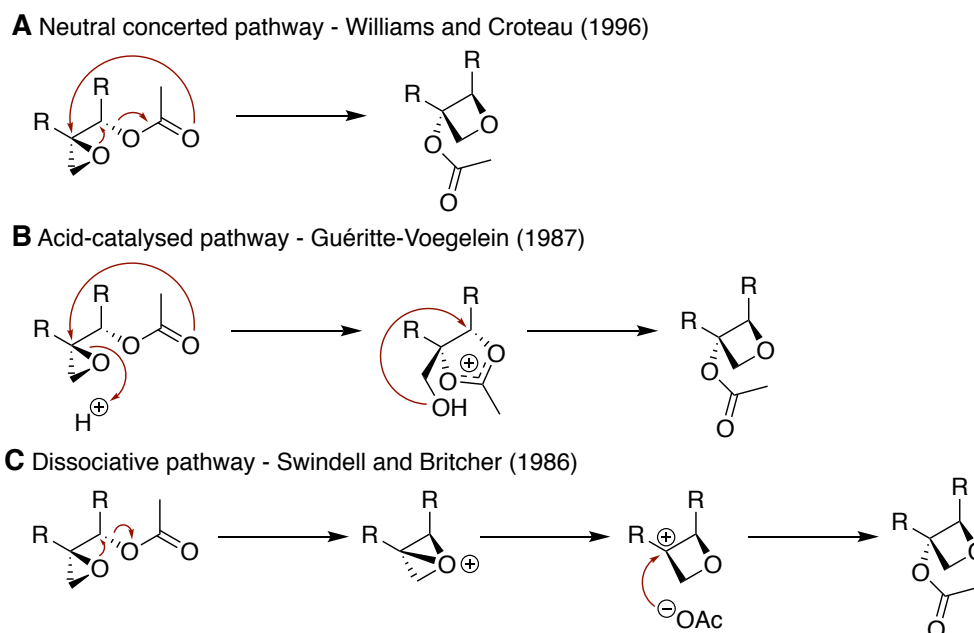


Figure 1.3 Putative pathways for the biosynthesis of the oxetane ring in taxol.

There are few other known examples of oxetanes in natural products. Examples include: oxetin extracted from a broth of the bacterium *Streptomyces*;⁴⁰ oxetanocin from the soil bacterium *Bacillus megaterium*;⁴¹ thromboxane A₂ from activated blood platelets;⁴² mitrephorone A from the plant species *Mitrephora glabra* Scheff;⁴³ merrillactone A isolated from the pericarps of the *Illicium merrillianum* plant species;⁴⁴ and bradyoxetin from the bacterium *Bradyrhizobium japonicum* (Figure 1.4).⁴⁵ Biological activity is varied with cytotoxic, antibacterial, herbicidal, prothrombotic and neurotrophic activity observed across the various examples.

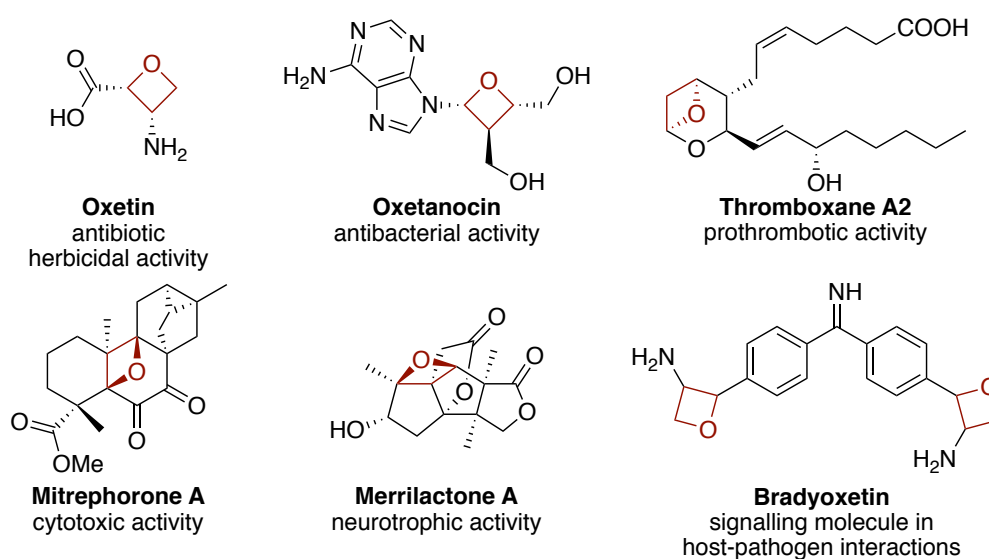


Figure 1.4 Examples of oxetane-containing natural products with the oxetane ring(s) highlighted in red.

The oxetane motif also features in a small number of pesticides (Figure 1.5). Oxetane-containing EDO, is a highly active and biodegradable insecticide that displays significant benefits compared to DDT which is 25x less reactive and is a persistent organic pollutant.⁴⁶ Oxasulfuron, a second example of an oxetane-containing pesticide, was used on soybean crops before being discontinued in 2007 due to the development of resistance.⁴⁷

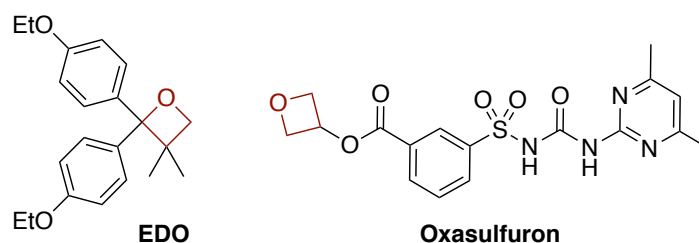


Figure 1.5 Oxetane-containing pesticides with the oxetane motif highlighted in red.

1.1.3.2 Intrinsic Properties of the Oxetane Ring

Oxetanes are 4-membered cyclic ethers featuring a rigid 3-dimensional structure and six defined vectors for potential substitution. With a calculated puckering angle of just 8.7° at 140 K,⁴⁸ oxetane has an effectively planar structure. However, it has been found that substitution around the oxetane ring can lead to an increase in puckering of the ring e.g. in the oxetane-containing insecticide EDO, the calculated puckering angle is 16° almost double that observed for unsubstituted oxetane.⁴⁹ This increase in puckering helps relieve the torsional strain caused by steric clashes between adjacent substituents.

The oxetane oxygen is highly Lewis basic and consequently oxetanes function as excellent hydrogen bond acceptors, an attractive property for bioactive motifs in terms of potential ligand-target interactions. The hydrogen bonding ability of oxetanes compares favourably to other common hydrogen bond acceptors such as aldehydes, esters, lactones, carbonates and ketones (Figure 1.6).⁵⁰ Only carbamates, amides and ureas have been found to possess superior hydrogen bond acceptor ability.⁵¹

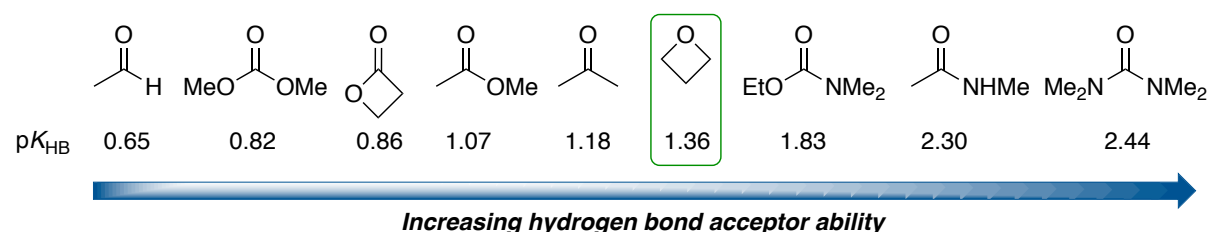


Figure 1.6 The hydrogen bonding ability of various common hydrogen bond acceptors. $pK_{HB} = \log K_f$ where K_f is the equilibrium constant for the formation of 1:1 hydrogen bonded complexes with 4-fluorophenol in CCl_4 at 298 K, determined using FTIR spectrometry.

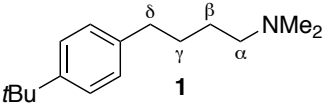
In 1998, Berthelot investigated the hydrogen bonding ability of cyclic ethers using 4-fluorophenol as the model hydrogen bond donor.^{50a} Oxetane was found to have the highest equilibrium constant for the formation of a hydrogen bond complex when compared to 3-, 5- and 6-membered cyclic ethers. The conclusion from this study is that oxetanes present the optimal combination of the two important factors that influence hydrogen bonding ability: ring size and hybridisation. As ring size and the C–O–C bond angle decrease, the oxygen lone pairs become more exposed, increasing hydrogen bonding capability.⁵² A competing effect is the hybridisation of the oxygen atom. The s-character of the non-bonding orbitals increases as ring size decreases, leading to reduced availability of the oxygen lone pairs for smaller ring systems. However, this effect is only significant for epoxides where hydrogen bonding ability is greatly reduced as a result.⁵³

1.1.3.3 Oxetanes as Attractive Motifs for Medicinal Chemistry

Recently, medicinal chemists have looked towards more 3-dimensional, less lipophilic and lower molecular weight compounds for drug discovery in order to access compounds more likely conform to desirable ADMET parameters and become successful drugs. The small, polar nature of the oxetane ring has attracted attention from the medicinal chemistry community for these reasons and has led to the evaluation of their potential benefits and biocompatibility. There are also several examples of their application in drug discovery programmes and selected recent examples are described.

Carreira demonstrated that oxetanes can be used to modify the basicity of proximal amines in a compound even when incorporated at relatively remote sites to the relevant amine (Table 1.1).⁵⁴ Compound **1**, without oxetane substitution, has a pK_aH of 9.9. Installation of an electron-withdrawing oxetane motif at the α -position to the tertiary amine resulted in a reduction in pK_aH to 7.2. As the oxetane was moved further from the site of the amine the pK_aH was reduced to a lesser extent indicating the distance dependence of this effect. However, even when the oxetane was installed at the distant δ -position, a reduction in pK_aH of 0.3 units was observed.

Table 1.1 The effect of oxetane incorporation on the basicity of nearby amines.

				
α	β	γ	δ	pK_{aH}
CH_2	CH_2	CH_2	CH_2	9.9
	CH_2	CH_2	CH_2	7.2
CH_2		CH_2	CH_2	8.0
CH_2	CH_2		CH_2	9.2
CH_2	CH_2	CH_2		9.6

Dunton conducted a study to assess how readily 3-substituted oxetanes form covalent adducts upon bioactivation.⁵⁵ When 3-substituted oxetanes were incubated *in vitro* with human liver microsomes in the presence of glutathione and nicotinamide adenine dinucleotide phosphate (NADPH) cofactor, less than 50% of the oxetanes examined formed conjugates. This study provides evidence that 3-substituted oxetanes don't exhibit inherently unacceptable levels of proclivity to nucleophilic attack, making them potentially attractive and suitable motifs for medicinal chemistry.

Furthermore, Wessel and co-workers (Hoffman Le Roche) investigated a library of over 100 oxetane δ -aminoacids elaborated with oxadiazole and triazole pharmacophores.⁵⁶ Several key physicochemical properties were measured and it was found that the synthesised compounds exhibited desirable ADMET properties for use in medicinal chemistry as discussed in Section 1.1.2 (Figure 1.7).

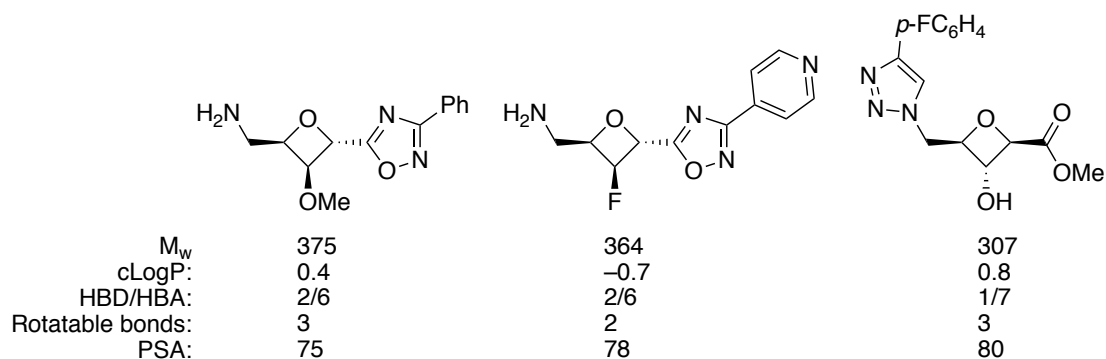
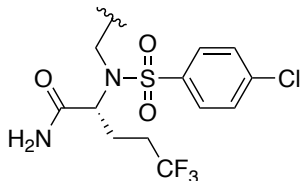
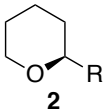
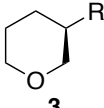
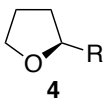
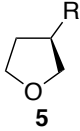
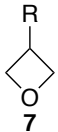
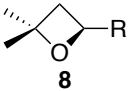


Figure 1.7 Examples from Wessel's oxetane library. HBD = number of hydrogen bond donors; HBA = number of hydrogen bond acceptors; and PSA = polar surface area.

In 2011, Stepan investigated oxetane-containing arylsulfonamide derivatives as potent γ -secretase inhibitors for the treatment of Alzheimer's disease (Table 1.2).⁵⁷ Oxetane substituted compounds (**6–8**) showed increased metabolic stability compared to tetrahydrofuran and tetrahydropyran analogues **2–5**. Oxetane **6** with mono-substitution at the 2-position was more prone to metabolic attack than the 3-monosubstituted oxetane derivative **7**. However, the highest metabolic stability was observed for the 2,4,4-trisubstituted oxetane analogue **8**. Additionally, oxetane **8** gave similarly high potency compared to the other compounds tested, providing evidence that oxetane incorporation into a lead compound has the potential to increase drug-likeness without compromising potency.

Table 1.2 Metabolic stability and potency of arylsulfonamide derivatives. $CL_{int,app}$ is the total intrinsic clearance obtained by scaling *in vitro* human liver microsome half lives. IC_{50} values were obtained in a whole cell assay using human APP_{wt} cells by measuring A β_{1-42} .

R = 		
Compound	$CL_{int,app}$ (mLmin ⁻¹ kg ⁻¹)	IC_{50} (A β_{42} nM)
 2	>300	27.9
 3	136	45.2
 4	210	44.5
 5	69.8	11.2
 6	62.1	7.99
 7	28.6	16.9
 8	25.9	16.5

Within the medicinal chemistry literature, there have been a number of examples of oxetane-containing compounds as promising therapeutic agents. In 2010, Du and co-workers reported the development of 3',4'-oxetane nucleosides as promising Hepatitis C inhibitors.⁵⁸ The oxetane fused ring systems were explored due to their ability to introduce conformational restriction, an approach known to enhance biological activity of nucleosides. Triphosphate

derivative **9** was the most potent inhibitor of HCV NS5B RNA dependent RNA polymerase in the study with an IC_{50} of 31 μ M (Figure 1.8A). Genentech explored oxetane **10** as a potent and selective inhibitor of the mTOR pathway, a promising target for the treatment of cancer (Figure 1.8B).⁵⁹ Oxetane derivative **10** showed favourable free plasma clearance and was not a hERG liability. Due to its desirable overall profile, oxetane **10** was progressed as the drug development candidate. In 2014, Jadhav and co-workers (Eli Lilly) reported the development of cathepsin S inhibitors for the treatment of abdominal aortic aneurysms.⁶⁰ Oxetane derivative **11** was selected for clinical development as it showed excellent nanomolar potency, selectivity for the desired target and efficacy in a $CaCl_2$ -induced *in vivo* model (Figure 1.8C). Gonzalez (Amgen) examined 3-substituted oxetane derivative **12** as an inhibitor of oncogene MDM2 (Figure 1.8D). This target presented an opportunity to selectively target cancer cells by enabling the reactivation of the tumor suppressor p53 pathway in tumor cells.⁶¹ Although oxetane **12** was not selected for further development, nanomolar potency and good stability in human hepatocytes was observed.

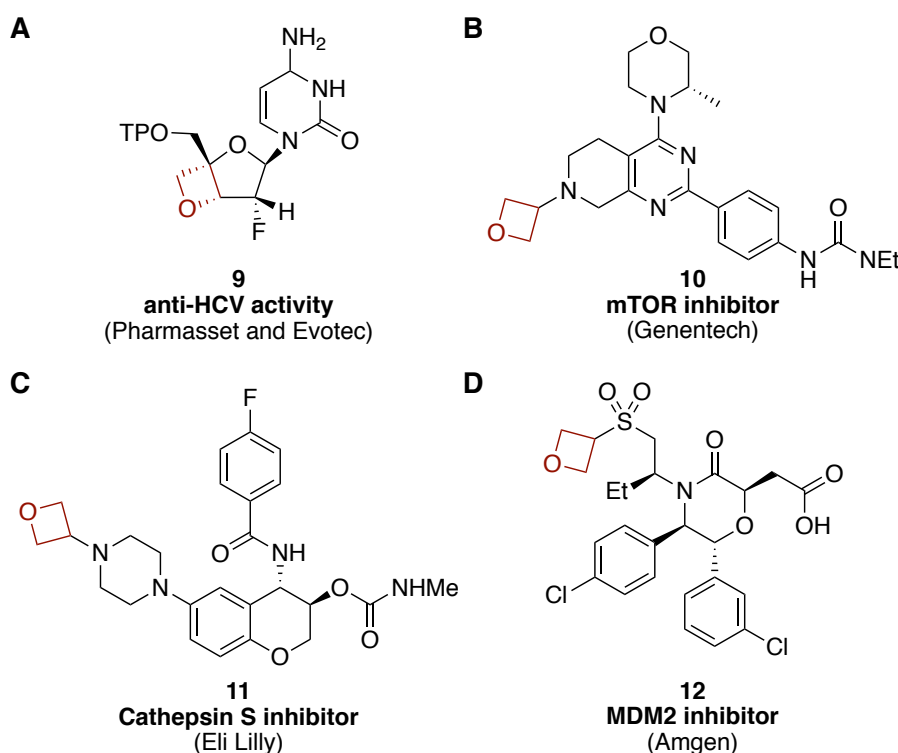


Figure 1.8 Selected examples of the oxetane motif in drug discovery programmes with the oxetane motif highlighted in red.

1.1.4 Bioisosteres as an Important Tool in Drug Discovery

Isosterism is a concept that was introduced by Langmuir in 1919 and initially described compounds that had the same total number and arrangement of electrons.⁶² In 1951, Harris

Friedman introduced the term “bioisostere” to describe compounds eliciting a similar biological effect.⁶³ The concept of bioisosterism has since evolved and now is generally accepted to refer to substituents or groups that exhibit broadly similar shape, electronic distribution and biological activity.⁶⁴

Bioisosteric replacement, the substitution of problematic functionality with a suitable bioisostere, is a well-established strategy in drug discovery.⁶⁵ Bioisosteres are often utilised to reduce toxicity, modulate bioactivity, improve the physicochemical profile of a lead compound and access new intellectual property space.

An important example is the introduction of fluorine as a commonly used bioisostere for hydrogen due to their similar steric requirements (Van der Waal’s radii of 1.47 and 1.20 Å respectively)⁶⁶ but differing electronic properties.⁶⁷ This strategy has been shown to have a beneficial impact on metabolic stability, the basicity of neighbouring groups and molecular conformation.⁶⁸ Oxidative metabolic pathways involving P450 cytochromes often limit bioavailability. Blocking metabolically vulnerable C–H sites through the introduction of fluorine has been a successful strategy in drug discovery.⁶⁹ During the development of the cholesterol absorption inhibitor ezetimibe, blocking two metabolically labile sites with fluorine gave an increase in metabolic stability that proved key for successful development (Figure 1.9).^{69b}

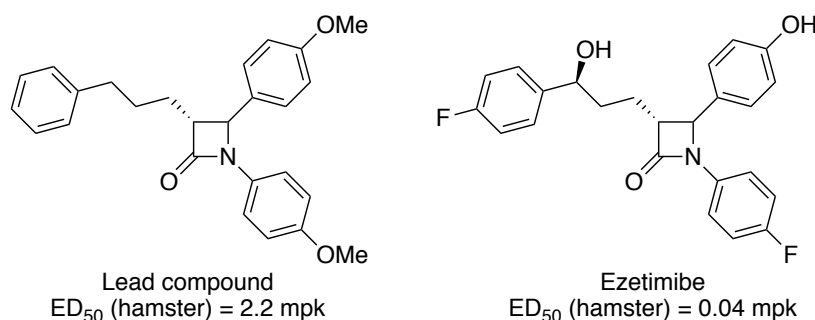


Figure 1.9 Development of the cholesterol absorption inhibitor ezetimibe by introduction of fluorine to block metabolically vulnerable sites.

A further example of bioisosterism is the use of amide bioisosteres to modulate polarity and bioavailability particularly in the field of peptidomimetics.⁷⁰ A noncomprehensive list of amide bioisosteres includes: sulfonamides, trifluoroethylamines, cyclopropylamines, fluoroalkenes, and triazoles (Figure 1.10).^{65b} In general, the geometry of the amide bond is maintained, the NH remains in place and frequently the polarity of the C=O bond is mimicked. However, the differences in structure compared to the amide motif can lead to significant benefits with regards to the pharmacokinetic profile of a compound.

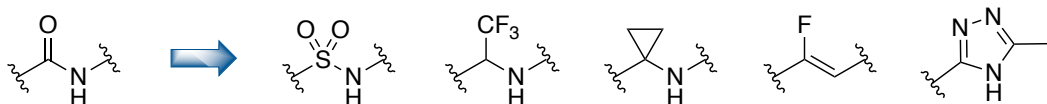


Figure 1.10 Selected examples of amide bioisosteres.

In 2008, Merck reported that during the development of a cathepsin K inhibitor, replacing the amide functionality with a trifluoroethylamine group led to improved potency and selectivity for the desired target (Figure 1.11).⁷¹ Importantly, the trifluoroethylamine bioisostere is capable of reducing the basicity of NH without compromising H-bond donor ability.

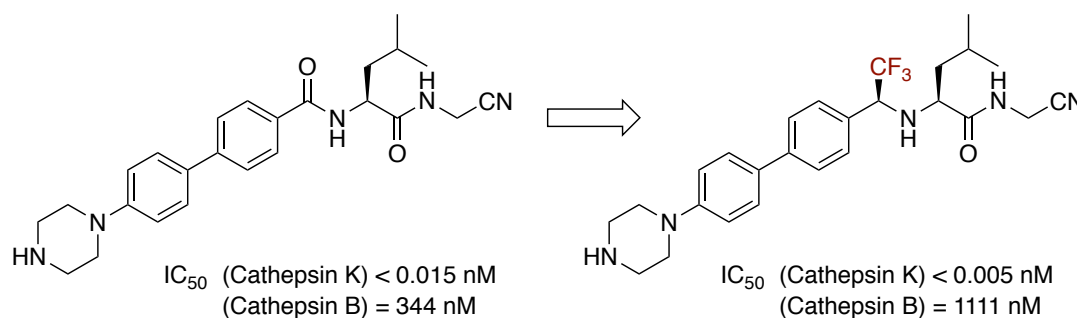


Figure 1.11 Development of a Cathepsin K inhibitor through use of a trifluoroethylamine bioisostere.

Many more bioisosteres are known for a range of different potentially problematic groups such as carboxylic acids, esters, phenyl rings, carbonyls and phosphates, and have been employed as invaluable tools in drug discovery programmes.⁶⁵

1.1.5 Oxetanes as Bioisosteres

Seminal work published by the Carreira group has established the oxetane motif as a valuable bioisosteric replacement for a variety of functional groups.^{54,72} Oxetanes have been introduced as polar replacements for methylene and *gem*-dimethyl motifs and as metabolically stable replacements for carbonyl groups (Figure 1.12).

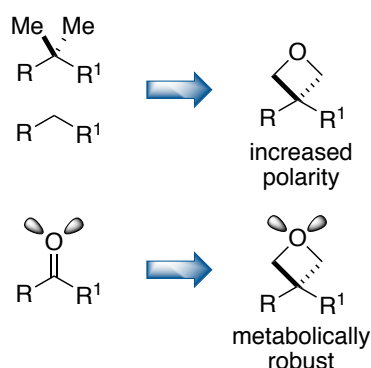
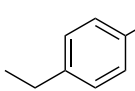
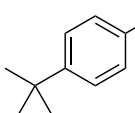
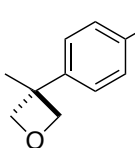


Figure 1.12 Oxetanes are bioisosteres for methylene, *gem*-dimethyl and carbonyl groups.

Metabolically vulnerable methylene sites in biologically active compounds are often blocked through introduction of *gem*-dimethyl groups.⁷³ However, the resultant increase in lipophilicity can potentially have a negative impact on the ADMET profile and therefore developability of a compound.^{74,75} The oxetane motif has a similar molecular volume and arrangement in space when compared to the *gem*-dimethyl group and was therefore proposed by Carreira and Rogers-Evans as a polar alternative.⁷²

The ability of oxetane to act as a favourable replacement group for *gem*-dimethyl and methylene motifs was investigated by comparing several important physicochemical properties of 4-ethyl-phenyl-substituted compound **13**, 4-*tert*-butyl-phenyl substituted compound **14** and oxetane **15**, where the *tert*-butyl group was replaced with a 3-methyloxetane motif (Table 1.3).^{54,72} Oxetane **15** gave a 1 unit decrease in logD and logP compared to compound **13** and a decrease of 1.7 units compared to compound **14**. In both cases oxetane incorporation led to a significant increase in solubility when measured in 50 mM phosphate buffer at pH 9.9 at 22.5 °C. Inhibition of the hERG potassium channel, a vitally important test for *in vitro* safety, was also calculated for oxetane **15** and compound **14**.⁷² As a result of the decrease in lipophilicity, oxetane **15** showed decreased hERG liability compared to compound **14** (hERG IC₅₀ 35 µM for **15** vs 7.5 µM for **14**). As expected, susceptibility to metabolic degradation in human liver microsomes, calculated by the intrinsic clearance rate (CL_{int}), was considerably lower for the oxetane derivative **15** when compared to compounds **13** and **14**. This study indicates that the oxetane group has the potential to act as a beneficial bioisosteric replacement group for *gem*-dimethyl and methylene motifs.

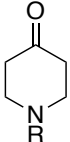
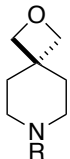
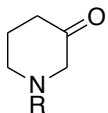
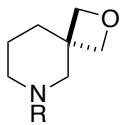
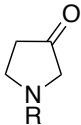
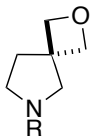
Table 1.3 Comparison of physicochemical properties for compound **13**, compound **14** and oxetane **15**.

Compound	Lipophilicity LogD (LogP)	Solubility (µg mL ⁻¹)	hERG IC ₅₀ (µM)	hCL _{int} (min ⁻¹ mg ⁻¹ µL)
 13	1.8 (4.3)	250	Not calculated	37
 14	2.5 (5.0)	<4	7.5	16
 15	0.8 (3.3)	18000	35	0

Despite the prevalence of the carbonyl group in bioactive compounds, their use in medicinal chemistry programmes is limited due to their inherent susceptibility to nucleophilic attack which presents a chemical and metabolic liability.²⁹ Utilisation of oxetanes as surrogates for carbonyl derivatives has been explored as both motifs exhibit similar spacial arrangement of lone pairs and polarisation. The oxetane motif presents the opportunity to circumvent the limitations associated with the reactive carbonyl functional group whilst maintaining similar polarity and hydrogen bonding ability. A consideration when evaluating the ability of the oxetane motif to act as a bioisostere for carbonyl derivatives is the different lengths of the two groups which may impact binding affinity. The C–O bond distance in carbonyls is approximately 1.2 Å whereas in oxetanes it is slightly longer at 2.1 Å on average.⁷⁶ In some cases, the altered oxygen position may be beneficial; however, in others the added spacial requirement of the oxetane motif may be incompatible with steric restrictions at the target binding site.

Carreira and co-workers have demonstrated that bioisosteric replacement of a carbonyl with an oxetane is advantageous with regards to metabolic stability by comparing matched molecular pairs of oxetane substituted spirocycles and their carbonyl derivatives (for selected results from this study see Table 1.4).⁵⁴ Upon oxetane incorporation, a significant decrease in the intrinsic clearance in human liver microsomes was reported for all the examined pairs of compounds. In general, lipophilicity increased slightly for the oxetane spirocycles compared to the carbonyl derivatives but remained within desirable 'drug-like' space (see Section 1.1.1).

Table 1.4 Comparison of key physicochemical parameters for oxetane spirocycles and their carbonyl analogues. ^aR = piperonyl group.

Compound ^a	Lipophilicity LogD (LogP)	Solubility ($\mu\text{g mL}^{-1}$)	hCL _{int} ($\text{min}^{-1}\text{mg}^{-1}\mu\text{L}$)
	1.2 (1.6)	17000	120
	1.0 (2.0)	5400	6
	0.1 (0.5)	9000	120
	1.7 (2.3)	7700	16
	-0.1 (-0.1)	19000	100
	0.7 (1.5)	3000	2

Carbonyls readily stabilise α -carbanions and so stereogenic centers at the α -position are susceptible to epimerisation.⁵⁴ In 2013, Carreira synthesised the oxetane derivative of the infamous teratogen thalidomide.⁷⁷ The (+)-*R*-enantiomer of thalidomide is a powerful antimimetic whereas the (–)-*S*-enantiomer is teratogenic and led to birth defects in up to 12,000 children in the late 1950's and early 1960's.⁷⁸ In the human body, deprotonation/racemisation occurs rapidly at the stereogenic center α to the imide carbonyl. Critically, this study found that oxetano-thalidomide, unlike the parent compound, was stable to racemisation in human blood plasma demonstrating a potential strategy that would avoid the devastating effects of thalidomide (Figure 1.13). This example gives an indication of the powerful potential benefits of oxetane incorporation into drug discovery programmes.

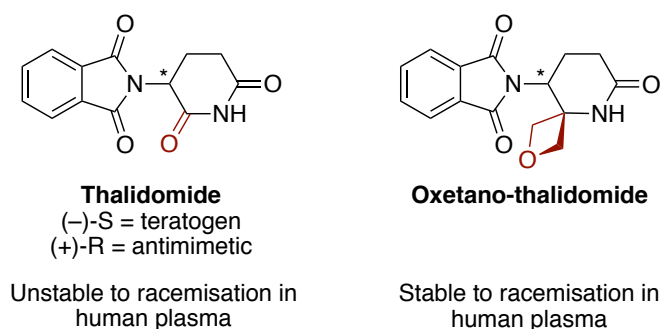
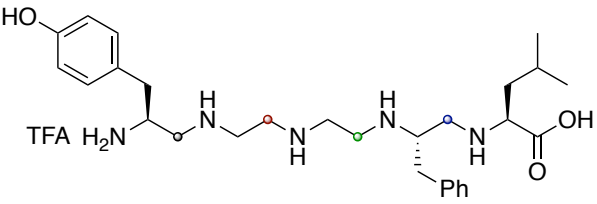


Figure 1.13 Comparison of thalidomide and spirocyclic oxetano-thalidomide.

Peptidomimetics featuring an oxetane as a less easily cleaved surrogate for an amide linkage have recently gained attention as compounds of interest for medicinal chemistry. In 2014, Shipman and Carreira independently published on this idea, outlining the synthesis of a new class of peptidomimetic in which 3-aminooxetane units were used as replacement groups for selected amide bonds.⁷⁹ Half lives in human serum and binding affinities of various oxetane analogues of the δ -opioid receptor agonist Leu-enkephalin, where the oxetane is placed at different positions along the chain, were evaluated and compared to Leu-enkephalin (Table 1.5).⁸⁰ Stability in human serum was measured as an indicator of metabolic profile. Leu-enkephalin rapidly degraded in human serum with a short half life of just 10 minutes. All the oxetane derivatives (**16–19**) showed some increase in stability in human serum compared to the parent compound. This is likely due to oxetane substitution hindering the substrate recognition process of proteases to a greater or lesser degree reflected by the extent of increase in half life. The binding affinities of the oxetane analogues to the δ -opioid receptor in rat brain homogenates were also explored through experimental determination of the inhibitory constant (K_i). The binding affinity for Leu-enkephalin was calculated as 9.2 nM. Oxetane analogues **18** and **19** also showed nanomolar binding affinities indicating that oxetane substitution at certain positions is tolerated without significant loss of potency. Although oxetanes **16** and **17** showed a total loss of binding affinity, the activity and half lives of oxetanes **18** and **19** confirmed that oxetane-containing peptidomimetics present a promising strategy for increasing robustness towards peptidase cleavage whilst maintaining biological activity.

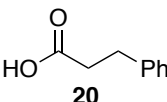
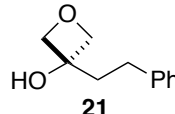
Table 1.5 Comparison of stability in human serum and binding affinity of Leu-enkephalin and oxetane analogues **16–19**. ^aExperiments performed with rat brain homogenates and [³H]-DPDPE as the radioligand.⁸⁰

						
Compound					Serum half life	Binding affinity K _i (nM) ^a
Leu-enkephalin					10 min	9.2 ± 3.2
Oxetane 16					3.2 h	>1000
Oxetane 17					18 h	>1000
Oxetane 18					15 min	157 ± 15
Oxetane 19					26 min	43 ± 9

Furthermore, a recent 2018 study showed that gels formed from oxetane-modified peptidomimetics showed significantly greater resistance to proteolysis compared to the unmodified native dipeptides.⁸¹

During the course of the research detailed in this thesis, oxetan-3-ols have been investigated as carboxylic acid isosteres.⁸² Lipophilicity, permeability, pK_a and hydrogen bonding ability were calculated for compounds **20** and **21** to evaluate the effect of introducing an oxetanol in place of the carboxylic acid motif (Table 1.6). Interestingly, although the oxetane analogue **21** was 8 orders of magnitude less acidic relative to the carboxylic derivative **20**, hydrogen bonding ability was only reduced by half. Additionally, the oxetane derivative **21** gave a slight increase in lipophilicity and was more permeable in a parallel artificial membrane permeability assay (PAMPA).⁸²

Table 1.6 Investigation into oxetan-3-ols as bioisosteric replacements for carboxylic acids.⁸²

	 20	 21
Lipophilicity logD_{7.4}	-0.49 ± 0.19	2.07
Permeability logP_{app}	-5.79 ± 0.10	-5.08
pK_a	4.64	>12
H-Bonding ability ln(K_{eq})	4.31	2.53

Mukherjee and am Ende reported trifluoromethyl oxetanes as bioisosteres for the *tert*-butyl group.⁸³ Investigations found that replacement of a *tert*-butyl group with a trifluoromethyl oxetane motif led to γ -secretase inhibitors with superior metabolic stability and polarity. These recent developments show a continued interest in the area of oxetane bioisosteres for medicinal chemistry.

1.2 Synthesis of Oxetanes

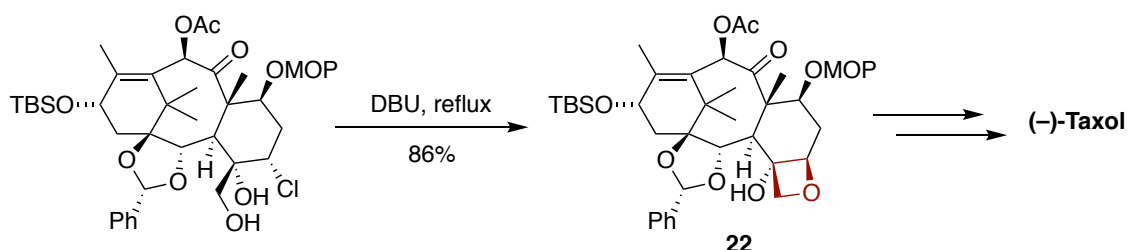
As has been described in the previous section there is significant interest surrounding oxetanes as valuable motifs for medicinal chemistry. There is a particular interest in 3,3-disubstituted oxetanes due to their potential as bioisosteres. As a consequence, there is a continued drive within synthetic chemistry to develop mild, robust and efficient methods for oxetane synthesis. However, the ring strain exhibited by oxetanes makes their formation a fundamental synthetic challenge. The rates of ring closing reactions towards cyclic ethers were studied and 4-membered oxetanes were shown to have a significantly slower rate of formation compared to 3-, 5- and 6-membered analogues.⁸⁴ Despite this, the most common strategy employed for oxetane synthesis is through ring closing methods. However, due to the increasing number of oxetane-containing motifs that are now commercially available, functionalisation directly onto the intact oxetane ring has emerged as an excellent strategy for the divergent synthesis of oxetane derivatives. An overview of both ring closing and direct functionalisation approaches and their limitations are described in the following section.

1.2.1 C–O Bond Forming Approaches

In 1878, Reboul reported the first oxetane synthesis through an intramolecular ring closing etherification to form the C–O bond of the oxetane ring, an approach that remains widely used for the synthesis of both chiral and achiral oxetanes.⁸⁵ Base mediated ring closure of acyclic

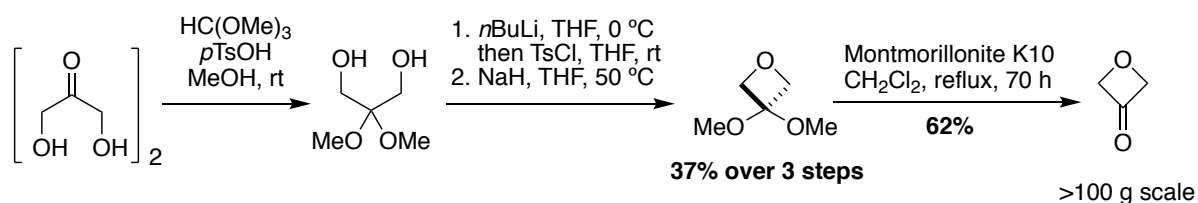
alcohols substituted with a suitable leaving group at the 3-position, furnishes the desired oxetane ring system.

Williamson etherification refers specifically to the intramolecular cyclisation of 1,3-halohydrins and was used in both Wender's and Kuwajima's syntheses of the oxetane-containing natural product taxol.⁸⁶ The desired oxetane motif in intermediate **22** was installed relatively late in the synthetic sequence by selective deprotonation of the primary alcohol by mild base and subsequent S_N2 ring closure (Scheme 1.1).



Scheme 1.1 Williamson etherification for the installation of the oxetane motif in Kuwajima's taxol synthesis.

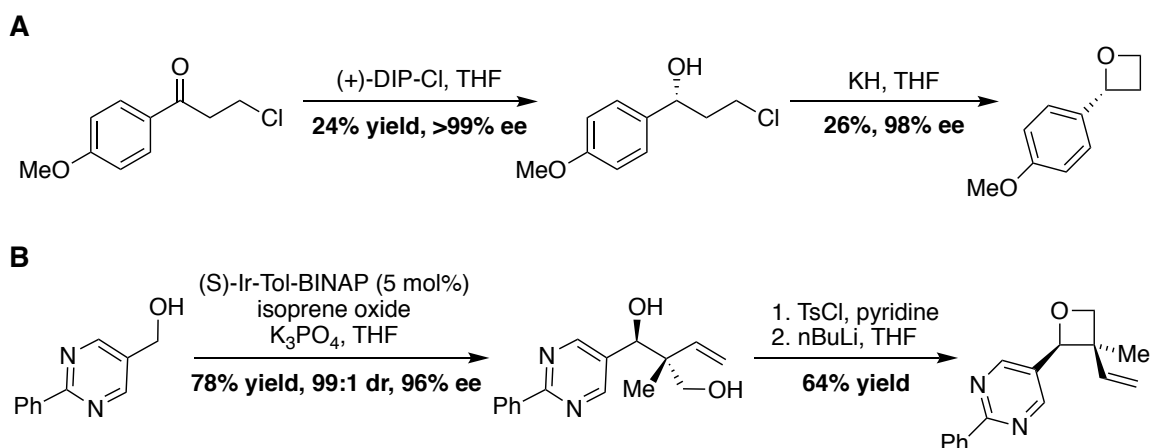
Commonly, 1,3-diols are used as starting materials to give oxetanes in two steps; installation of a leaving group followed by base mediated cyclisation. The first step requires either introduction of a halogen to form a Williamson etherification precursor,⁸⁷ or mono-activation of a single hydroxy group through tosylation or mesylation.^{88,89} This method was employed by Carreira for the first large-scale synthesis of oxetan-3-one, an important oxetane-containing building block (Scheme 1.2).⁹⁰ In the key ring forming step, mono-tosylation is followed by deprotonation of the remaining alcohol using NaH to form an oxyanion which attacks the electrophilic carbon to substitute the tosylate anion and give the cyclised product.



Scheme 1.2 Carreira's large scale synthesis of oxetan-3-one.

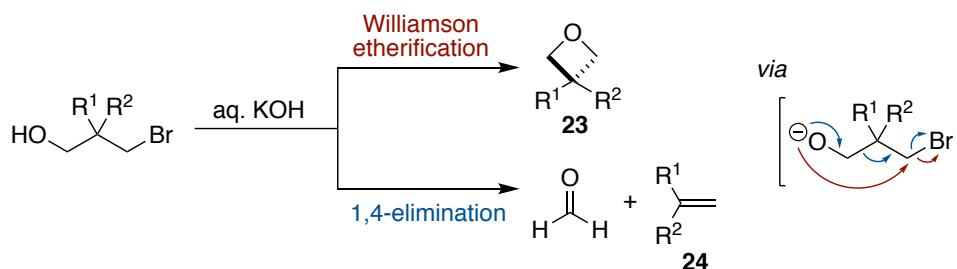
The use of enantiomerically enriched starting materials provides an efficient route to chiral oxetane derivatives. Fu showed that enantioselective reduction of β -haloketones using a (+)-DIP-Cl catalyst led to enantioenriched 1,3-halohydrins in excellent ee's (>89%). Treatment of the cyclisation precursors with KH enabled cyclisation with no loss of ee (Scheme 1.3A).⁹¹ Similarly, synthesis of chiral 1,3-diols and subsequent ring closing etherification has also been

a successful strategy.⁹² In 2017, Krische showed the synthesis of enantioenriched oxetanes with the key step for the introduction of stereochemistry involving an enantioselective iridium catalysed coupling of isoprene oxide with alcohols to give the desired chiral cyclisation precursors (Scheme 1.3B).^{92c}



Scheme 1.3 Synthesis of enantioenriched oxetanes through intramolecular etherification of chiral starting materials.

Yields for the intramolecular etherification process towards oxetane derivatives are often moderate due to competing ring fragmentation processes, particularly for alcohol precursors with further substitution at the 2-position.⁹³ Searles investigated the effects of different 2-substituents on the Williamson etherification reaction of 3-bromo-1-propanol derivatives and found that the extent of fragmentation correlated to the stability of the alkene formed (Table 1.7).⁹⁴ Derivatives with a single alkyl substituent resulted in an approximately 1:1 ratio of oxetane **23**: olefin **24** (entries 1–2). 2,2-Dialkylsubstituted 3-bromo-1-propanols gave the olefin as the major product (entries 4–5) and when a phenyl substituent was introduced at the 2-position, exclusively the 1,4-elimination product was observed (entries 3 and 6). This shows that Williamson etherification would not be a viable approach for the synthesis of 3-aryloxetanes.

Table 1.7 Investigations into the effect of 2-substitution on competing Williamson etherification and 1,4-elimination.

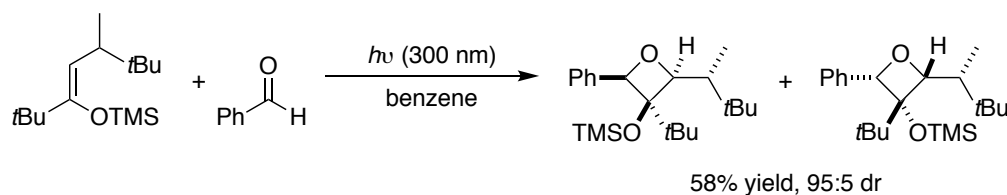
Entry	R ¹	R ²	Yield of Oxetane 23 (%)	Yield of Olefin 24 (%)
1	Et	H	23	19
2	Bu	H	21	24
3	Ph	H	0	26
4	Me	Me	12	60
5	Et	Et	27	54
6	Ph	Et	0	47

1.2.2 Paternò-Büchi [2+2] Photocycloaddition

The [2+2] photocycloaddition reaction between carbonyls and olefins is a well-established method for the synthesis of oxetanes.⁹⁵ This reaction was first reported in 1909 by Paternò.⁹⁶ Benzaldehyde and 2-methylbut-2-ene were exposed to sunlight for over 3 months although the structure of the product was unconfirmed. In 1954, Büchi re-examined the experiment using irradiation with artificial UV light over 48 hours and fully characterised the resultant oxetane product.⁹⁷ The reaction proceeds through an excited state carbonyl which reacts with an alkene in the ground state to form a diradical intermediate.⁹⁵

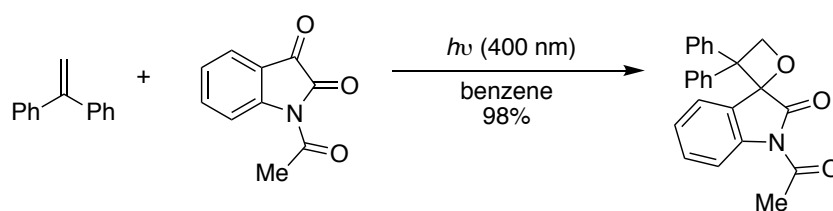
Achieving chemo-, regio- and stereocontrol is a significant challenge for this methodology with selectivity often achieved through strategic substitution on the reactants. Bach, achieved good regio- and diastereoselectivity for the [2+2] photocycloaddition of silyl enol ethers and benzaldehyde.⁹⁸ The reaction showed moderate to excellent regioselectivity for the 3-OTMS oxetane isomer over the 2-OTMS analogue. Ring closure occurred with the phenyl of benzaldehyde and the α -alkyl group of the silyl enol ether approaching in an *anti*-configuration to minimise steric repulsion. Good diastereoselectivity was also achieved for γ -silyl enol ethers

using either a sterically bulky (SiMe₂Ph or *t*Butyl) or polar group (OR) at the γ -position of the silyl enol ether (Scheme 1.4).



Scheme 1.4 Example of high diastereocontrol in the Paternò-Büchi reaction between γ -silyl enol ethers and benzaldehyde.

High levels of substitution are often required to stabilise the reactive intermediates leading to highly functionalised oxetane products. Several research groups have used the Paternò-Büchi photocycloaddition for the synthesis of 3,3-diaryloxetanes with further substitution at the 2- and/or 4-positions (e.g. Scheme 1.5).⁹⁹

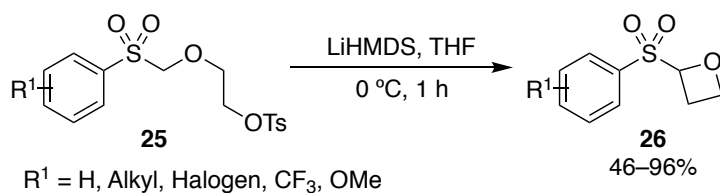


Scheme 1.5 Synthesis of a 3,3-diaryloxetane through a [2+2] photocycloaddition.

1.2.3 C–C Bond Forming Approaches

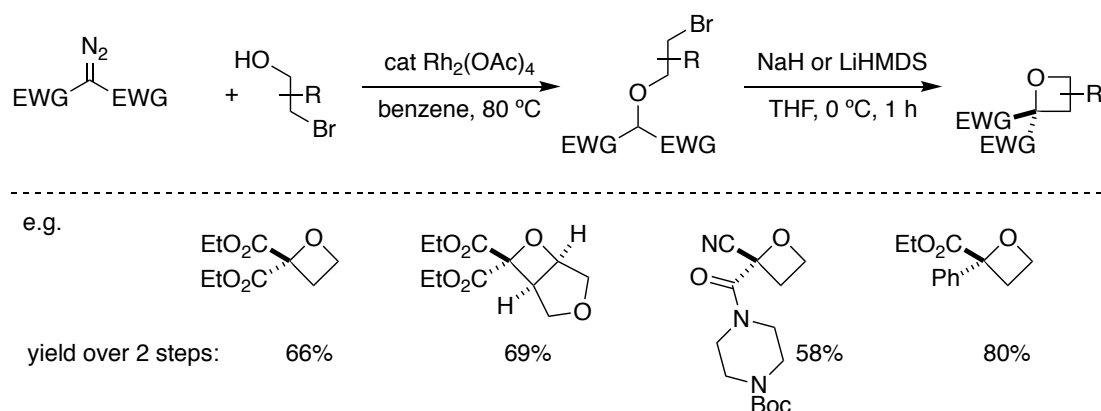
Retrosynthetic disconnection of C–C bonds has proved a valuable complementary option for construction of the oxetane ring, allowing access to a large number of novel oxetane derivatives with substitution at the 2-position.¹⁰⁰

The Bull group reported the synthesis of 2-sulfonyloxetanes through an intramolecular 4-*exo*-tet cyclisation to form the C2–C3 bond.¹⁰¹ Cyclisation was facilitated using LiHMDS to form a carbanion, stabilised by the adjacent sulfonyl group. Intramolecular cyclisation of **25** by nucleophilic displacement of the OTs group delivered the oxetane products **26** in excellent yields (Scheme 1.6). Good stability of the 2-sulfonyloxetane products was observed across a pH range 1–10.^{101b}



Scheme 1.6 Formation of 2-sulfonyl oxetanes through a C–C bond forming strategy.

The Bull group has also developed an efficient C–C bond forming protocol to form 2,2-disubstituted oxetanes in just two steps from easily accessible diazo compounds.¹⁰² Rhodium carbenes were formed from diazos and then underwent O–H insertion with β -bromohydrins. Subsequent base mediated C–C bond forming cyclisation delivered a wide variety of di-, tri- and tetra-substituted oxetanes with desirable properties for drug discovery (Scheme 1.7).

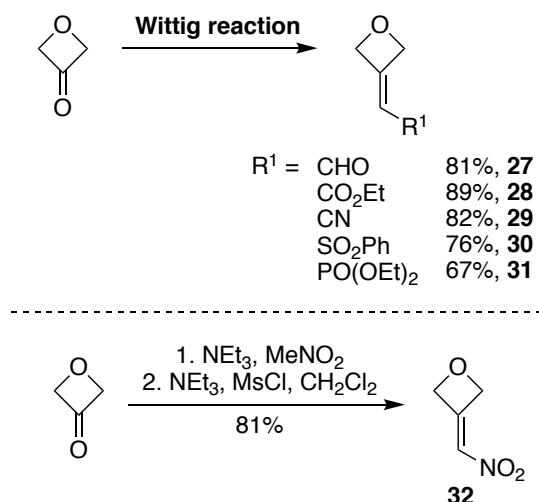


Scheme 1.7 Two step synthesis of 2,2-disubstituted oxetanes from diazos employing a key C–C bond forming cyclisation step.

1.2.4 Conjugate Addition to α,β -Unsaturated Oxetanes

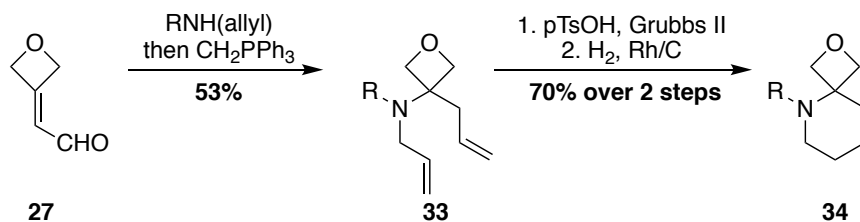
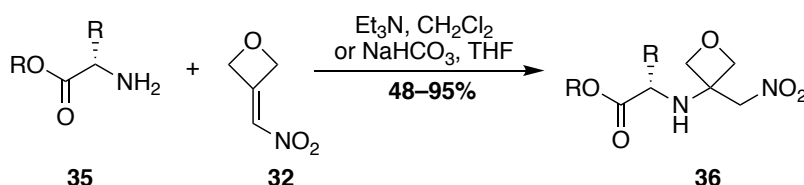
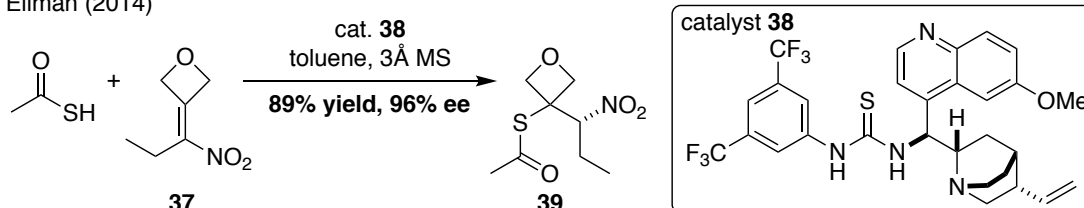
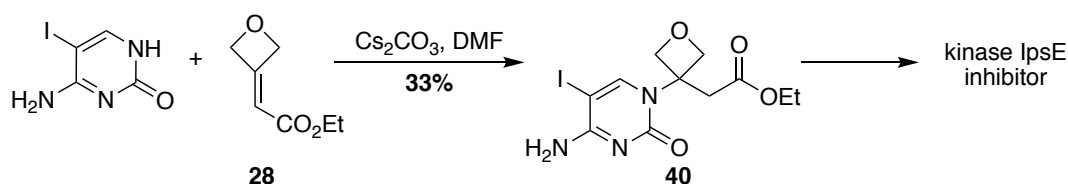
Oxetan-3-one presents a commercially available and inexpensive building block that has enabled the development of several new methodologies for the synthesis of 3,3-disubstituted oxetanes.

Carreira and co-workers have devised the synthesis of α,β -unsaturated oxetanes in a single step from oxetan-3-one through a Wittig reaction (α,β -unsaturated oxetanes **27–31**), or in the case of nitroalkene **32**, in two steps through reaction of oxetan-3-one and nitromethane and subsequent elimination of water (Scheme 1.8).⁷² 1,4-Conjugate addition of nucleophiles to these versatile oxetane-containing Michael acceptors has become an important method for the synthesis numerous 3,3-disubstituted oxetane derivatives with a wide variety of substituents.



Scheme 1.8 Synthesis of α,β -unsaturated oxetanes **27–32**.

Spirocyclic oxetanes have been synthesised using α,β -unsaturated oxetanes substituted with aldehyde and ester groups (**27** and **28**). 1,4-Conjugate nucleophilic addition using amines, malonates or nitromethane followed by further manipulations has provided interesting oxetane spirocyclic structures e.g. spirocycle **34** formed *via* 3,3-disubstituted oxetane **33** (Scheme 1.9A).⁷⁶ As outlined in Section 1.1.5, oxetane-modified peptides are gaining attention as peptidomimetics. The synthesis of the oxetane-modified dipeptide units (**36**) has been achieved through addition of amino esters **35** to nitroalkene **32** (Scheme 1.9B).^{79,103} Reduction of the nitro group in the resultant 3-aminooxetane product **36** enabled controlled extension of the peptide chain. In a further example, Ellman reported the synthesis of enantioenriched 3-sulfanyloxetanes **39** through the 1,4-addition of thioacetic acid to oxetane nitroalkene **37** using a 3,5-bistrifluoromethylphenyl catalyst **38** (Scheme 1.9C).¹⁰⁴ In 2016, this protocol was extended to pyrazolone nucleophiles using a bifunctional *N*-sulfinylurea catalyst.¹⁰⁵ In 2008, Diederich and co-workers, used a Michael addition strategy for the synthesis of kinase IspE inhibitors. 5-Iodocytosine reacted with oxetane-containing Michael acceptor **28** to provide key intermediate **40** (Scheme 1.9D).¹⁰⁶

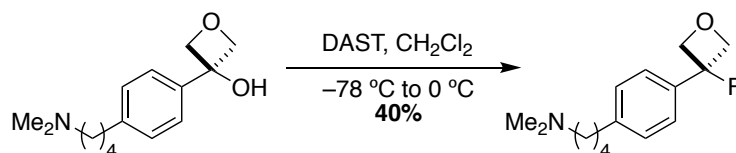
A Carreira (2008)**B** Carreira and Shipman (separately) (2014)**C** Ellman (2014)**D** Diederich (2008)

Scheme 1.9 Selected examples of 1,4-conjugate addition for the synthesis of 3,3-disubstituted oxetanes. A) oxetane spirocycles, R = piperonyl; B) oxetane-modified dipeptide units; C) enantioenriched 3-sulfanyloxetanes; D) Kinase IspE inhibitor.

1.2.5 Substitution Reactions of Oxetan-3-ols

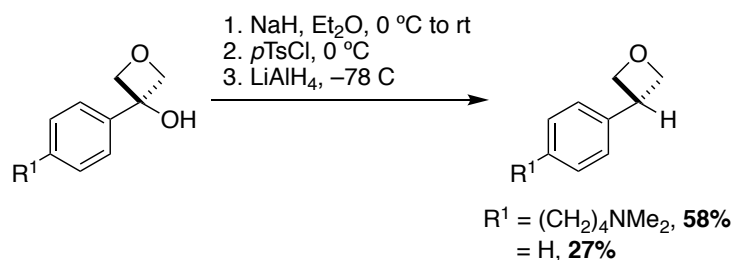
Oxetan-3-ols further substituted at the 3-position with aryl, alkyl, allyl or alkenyl groups are readily accessed from addition of organometallic reagents to oxetan-3-one.^{72,90} The tertiary hydroxy component presents an attractive, but little explored, handle for further reactivity.

In 2006, Carreira reported the synthesis of 3-aryl-3-fluorooxetanes using stoichiometric DAST as a nucleophilic fluoride source (Scheme 1.10).⁷² Subsequently, this reaction has been carried out with a range of different 3-aryloxetan-3-ols and with different nucleophilic fluoride sources e.g. deoxofluor and Xtal-fluor.¹⁰⁷ Additionally, a single example of chlorination of oxetanols has been reported where reaction of 3-phenyl-oxetan-3-ol with methanesulfonyl chloride and triethylamine gave 3-chloro-3-phenyloxetane in a 42% yield.⁹⁰



Scheme 1.10 Fluorination of 3-aryloxetan-3-ols.

Dehydroxylation of the tertiary alcohol has been reported through a three step, one-pot procedure (Scheme 1.11).⁷² Deprotonation of the alcohol using NaH followed by tosylation and subsequent reduction using LiAlH₄ delivered mono-substituted 3-aryloxetanes. Very low temperatures (-78 °C) were required to prevent oxetane ring opening. Wuitschik observed a second oxetane ether product when THF was used as the solvent in the reduction step which was proposed to be formed through addition of THF to a carbocationic intermediate.⁹⁰ Dehydroxylation was achieved directly in one step for 3-anisoleoxetan-3-ol using trifluoroacetic acid (TFA) and triethylsilane as the hydride donor, although it is noted that this approach was not applicable to other oxetanol derivatives.



Scheme 1.11 Dehydroxylation of 3-aryloxetan-3-ols.

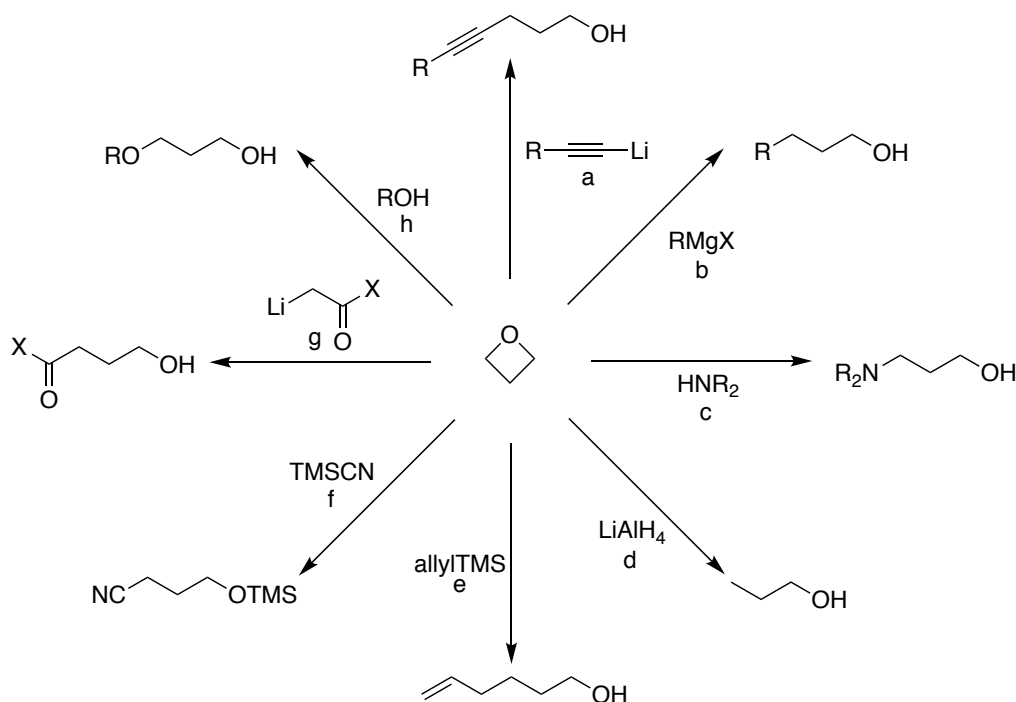
1.3 Oxetanes as Synthetic Intermediates

Oxetanes have an associated ring strain of 25.2 kcal mol⁻¹, only 1.6 kcal mol⁻¹ less than that determined for epoxides.¹⁰⁸ This inherent ring strain has led to the use of oxetanes as valuable synthetic intermediates for the synthesis of numerous achiral and chiral alcohol-containing compounds.¹⁰⁹ The following section gives an overview of ring opening and polymerisation reactions of oxetanes, particularly focusing on their reactivity under acidic conditions.

1.3.1 Ring Opening Reactions of Oxetanes

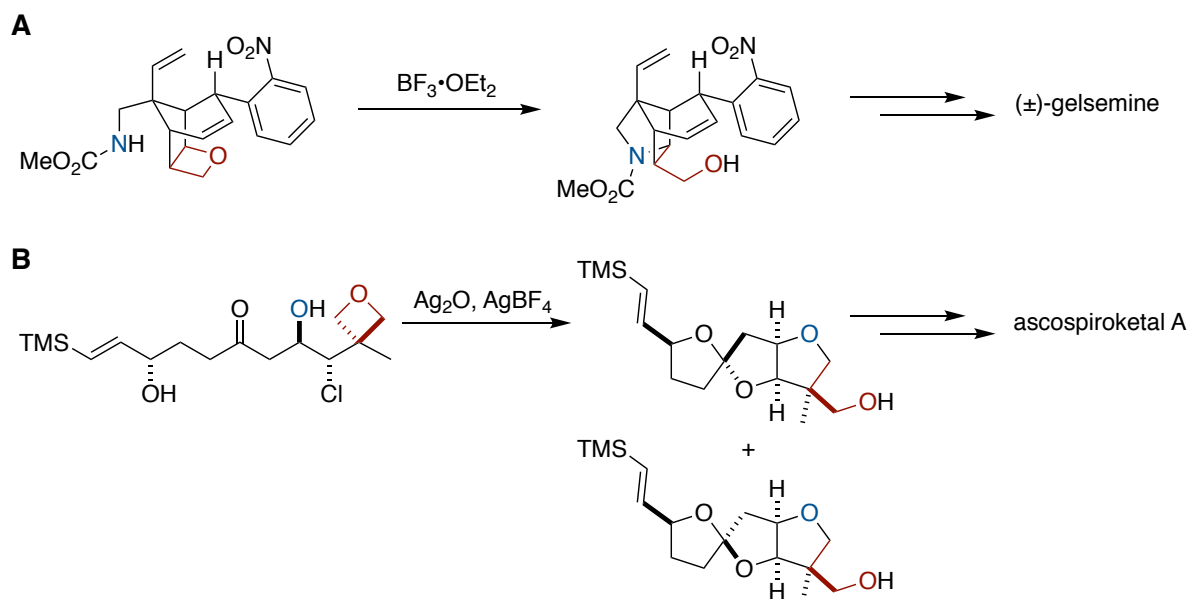
Oxetanes have been shown to undergo intermolecular ring opening with various nucleophiles including: organometallic reagents,¹¹⁰ amines,¹¹¹ LiAlH₄,¹¹² allylTMS,¹¹³ TMSCN,¹¹⁴ lithium enolates,¹¹⁵ hydrogen peroxide,^{116,92a} alkylalcohols¹¹⁷ and aryl borates¹¹⁸ (see Scheme 1.12 for an overview of ring opening processes). High temperatures (in the case of organometallics reagents) or acidic conditions are usually required for ring opening to occur. It has been

observed that 3,3-disubstituted oxetanes display a reduced proclivity for intermolecular ring opening due to steric hinderance at the β -carbon analogous to that observed at neopentyllic centers.¹¹⁹



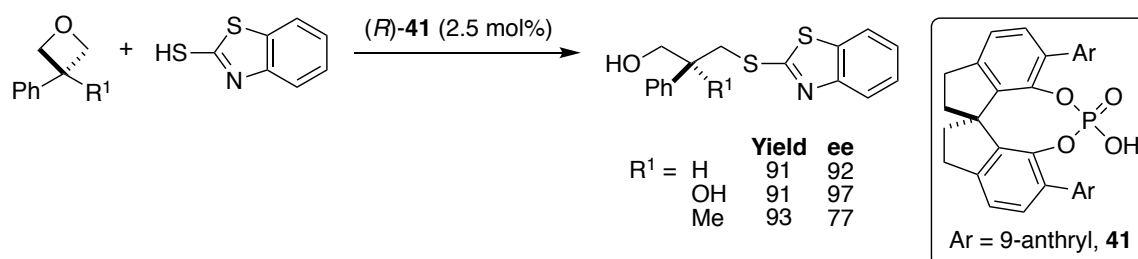
Scheme 1.12 Overview of intermolecular oxetane ring opening reactions. Possible substitution on the oxetane ring is not shown for clarity. Conditions: a) $\text{BF}_3 \cdot \text{OEt}_2$, $-78\text{ }^\circ\text{C}$; b) CuI , rt. or $180\text{ }^\circ\text{C}$, microwave irradiation; c) $\text{Ln}(\text{OTf})_3$ or LiBF_4 , rt.; d) $35\text{ }^\circ\text{C}$; e) TiCl_4 , rt.; f) cat. ZnI_2 , $40\text{ }^\circ\text{C}$; g) $\text{BF}_3 \cdot \text{OEt}_2$, $-95\text{ }^\circ\text{C}$; h) cat. H_2SO_4 , rt.

Intramolecular ring opening of oxetanes provides a successful route for the synthesis of a variety of new ring systems. This approach has been applied to the synthesis of natural products ($\pm$)-gelsemine and ascospiroketal.¹²⁰ For ($\pm$)-gelsemine, Danishefsky used a stoichiometric Lewis acid, $\text{BF}_3 \cdot \text{OEt}_2$, to activate the oxetane oxygen towards ring opening by an intramolecular amine nucleophile (Scheme 1.13A).^{120a,b} Britton, achieved the desired tricyclic structure in ascospiroketal with excellent diastereoselectivity using a combination of Ag(I) salts to initiate oxetane ring opening (Scheme 1.13B).^{120c,d}



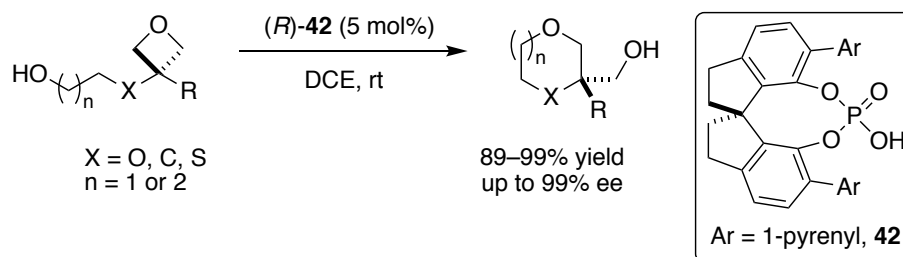
Scheme 1.13 Acid-catalysed ring opening of oxetanes as a key step in the total synthesis of natural products (±)-gelsemine (A) and ascospiroketal A (B).

Sun and co-workers have reported enantioselective intra- and intermolecular ring opening of oxetanes with a variety of S, N and O nucleophiles using chiral phosphoric acid catalysts.¹²¹ An important example is the intermolecular reaction between 3-monosubstituted and 3,3-disubstituted oxetanes, and mercaptobenzothiazoles.^{121c} Use of 2.5 mol% of chiral phosphoric acid catalyst **41** at room temperature gave enantioenriched alcohols in excellent yields and ee (Scheme 1.14).



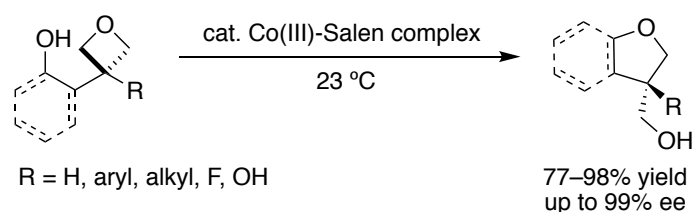
Scheme 1.14 Enantioselective desymmetrisation of 3-substituted oxetanes with sulfur nucleophiles using chiral phosphoric acid catalyst **41**.

A similar chiral phosphoric acid (**42**) promoted the intramolecular ring opening of 3,3-disubstituted oxetanes featuring a pendant hydroxy group to deliver a variety of oxygen-containing heterocycles including dioxanes, tetrahydropyrans and a single example of an oxathiane (Scheme 1.15).^{121e} A variety of functionality including alkyl, hydroxy, vinyl, allyl and alkynyl groups were tolerated at the 3-position of the oxetane with ring opening giving the desired heterocyclic products in excellent yields.



Scheme 1.15 Synthesis of oxygen containing heterocycles *via* an oxetane ring opening strategy.

In 2009, Jacobsen reported the enantioselective ring opening of 3-monosubstituted and 3,3-disubstituted oxetanes using a Co(III)-Salen complex catalyst (Scheme 1.16).¹²² Tetrahydrofurans and dihydrobenzofurans with tertiary and quaternary stereocenters were synthesised in high yields (up to 98%) and ee's (up to 99%).



Scheme 1.16 Enantioselective tetrahydrofuran and dihydrobenzofuran synthesis *via* oxetane ring opening.

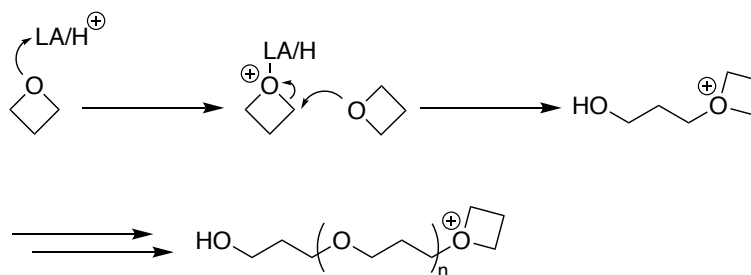
1.3.2 Polymerisation of Oxetanes

The capability of oxetanes to undergo ring opening has led to their widespread application as monomers in polymerisation reactions towards polyethers through either anionic or, much more commonly, cationic ring opening processes.

Anionic ring opening polymerisation is known for oxetanes featuring a pendant hydroxy substituent. Nishikubo reported the synthesis of hyperbranched polymers from 3,3-bis(hydroxymethyl)oxetane (BHO) or 3-ethyl-3-(hydroxymethyl)oxetane (EHO) using *t*BuOK as an initiator, in the presence of 18-crown-6-ether.¹²³ The requirement for a pendant hydroxy group is a significant limitation as only a very limited number of oxetane monomers are suitable for this approach.

Cationic ring opening polymerisation (CROP) occurs through initial coordination of the oxetane oxygen to a suitable acid catalyst, activating the strained ring towards nucleophilic ring opening by a second oxetane monomer (Scheme 1.17). Sequential attack from further oxetane monomers propagates chain growth. Various catalysts have been successfully employed to initiate CROP involving oxetane monomers including: BF₃ complexes,¹²⁴

trialkylaluminium reagents,¹²⁵ PF_5 ,¹²⁶ carboxylic acids,¹²⁷ triflic acid,^{124b} and heteropolyacids (PW_{12}).¹²⁸



Scheme 1.17 Overview of the catalytic ring opening polymerisation of oxetanes (LA = Lewis acid).

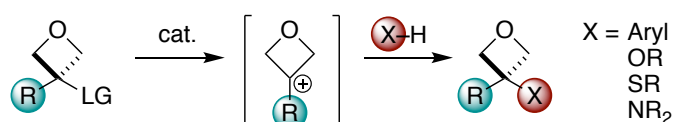
In 2004, Crivello reported photoinitiated CROP of oxetane monomers.¹²⁹ Onium salt photoinitiators (e.g. diaryliodonium or triarylsulfonium salts with PF_6^- or SbF_6^- counterions) were employed as precursors for the *in situ* generation of strong Brønsted acids. The photoinitiator underwent photolysis through irradiation with UV light to generate reactive cations, radicals and cation-radicals. These intermediates reacted with protic species present in the reaction mixture to generate very strong protic acids (H^+X^-) whereby the counterion (X^-) was that associated with the starting photoinitiator. The generated Brønsted acid then initiated CROP of the desired oxetane monomer.

The first commercial oxetane derived polymer, PENTON[®], found wide application as a resin in chemical plants due to its resistance to degradation.¹³⁰ More recently, oxetane derived polymers have found applications in the fields of: electrolytes for lithium batteries, inorganic surface modification, controlled drug release and self-assembling polymeric micelles.¹³¹

2 Project Aims

The research in this thesis looks to develop convenient and general methods for the synthesis of novel oxetane motifs to provide valuable synthetic options for drug discovery as bioisosteres and new building blocks. Oxetanes have physicochemical profiles attractive for medicinal chemistry due to their small and polar nature. Functionalised 3,3-disubstituted oxetanes have potential as new bioisosteres for drug discovery allowing exploration of new chemical and intellectual property space. However, current synthetic strategies have limitations with many, even relatively simple, oxetane motifs not accessible through current methods, e.g. 3,3-diaryloxetanes without further substitution at the 2- and/or 4-position.

Functionalisation directly on an oxetane ring by substitution of a preinstalled leaving group with different nucleophiles presents an intriguing strategy for the synthesis of novel oxetane derivatives (Scheme 2.1).



Scheme 2.1 Functionalisation directly on the oxetane ring through substitution of a suitable leaving group.

Acid-catalysed generation of tertiary oxetanyl carbocations has potential as a versatile approach for the general and mild synthesis of 3,3-disubstituted oxetanes. The lack of literature precedent for oxetanyl carbocations meant that assessing their stability with respect to formation and potential for further reaction would be the first priority. The electron withdrawing nature of the oxetane oxygen and increased p-character of the strained ring bonds highlight interesting questions with regards to the viability and nature of the planned carbocationic intermediate. The electronic properties of the preinstalled 3-substituent were likely to be of vital importance to assist in stabilisation. Ultimately, if oxetanyl carbocation generation was successful, compatibility of the methodology with a wide variety of nucleophiles (e.g. C, O, S and N nucleophiles) would be desirable.

Elaboration of the 3,3-disubstituted scaffolds produced in the alkylation reaction would provide access to further interesting oxetane derivatives suitable as reaction intermediates or as compounds directly for use in medicinal chemistry.

The primary aims of this research were:

- 1) To investigate the feasibility of carbocation generation from oxetanes substituted with a suitable leaving group.
- 2) To develop a scalable set of reaction conditions for the synthesis of 3,3-disubstituted oxetanes that maximise product yields and that are tolerant of a wide variety of functional groups.
- 3) To examine the chemical stability of these scaffolds particularly towards reactions commonly used within drug discovery programmes.
- 4) To assess the suitability of the scaffolds synthesised for medicinal chemistry applications by calculation/experimental determination of key physicochemical properties.

The next chapter will present the synthesis of novel 3,3-diaryloxetanes, the starting point for this investigation. Further functionalisation of the synthesised scaffolds and investigations into the mechanism of formation will also be described. Subsequent chapters will describe the use of sulfur nucleophiles in the alkylation reaction of oxetanols, the synthesis of a novel oxetane-containing sulfonyl fluoride and the synthesis of 3-aminooxetanes.

3 Results and Discussion

3.1 3,3-Diaryloxetanes

Concise accounts of the investigations discussed in this section have been published in *Chemistry A European Journal*¹³² and *Tetrahedron*.¹³³

3.1.1 Diaryloxetanes as a Target Bioisostere

Diarylketones are undesirable scaffolds for medicinal chemistry applications due to the reactive electrophilic carbonyl center which presents a chemical and metabolic liability in the body. Many benzophenone derived compounds act as photosensitisers leading to phototoxicity.¹³⁴ Irradiation of benzophenone generates a triplet biradical species (Figure 3.1) which in the presence of DNA leads to a plethora of photochemical events including: nucleobase modifications, DNA-protein cross links and single strand breaks.¹³⁵ Indeed, the photoactive nature of benzophenone derivatives has led to their application as cross-linkers useful for the study of biomolecular interactions.¹³⁶

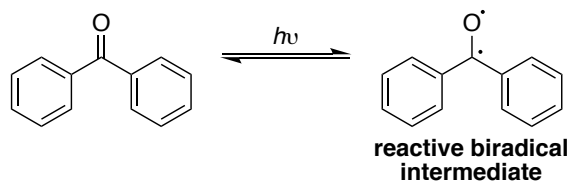


Figure 3.1 Generation of a triplet biradical from benzophenone.

There are over 300 examples of the diarylketone motif in natural products and there are also several further examples of synthetic diarylketones that possess important biological activity (for selected examples see Figure 3.2).¹³⁷ Cariphenone A isolated from *Hypericum carinatum*, a plant in the Guttiferae family, was shown to exhibit antioxidant activity.¹³⁸ A second example, phenstatin, was synthesised by the Pettit group in 1998 as a related analogue of the natural product, combretastatin A4.¹³⁹ Phenstatin acts as a potent inhibitor of tubulin polymerisation and showed excellent anti-cancer activity in human cell lines.

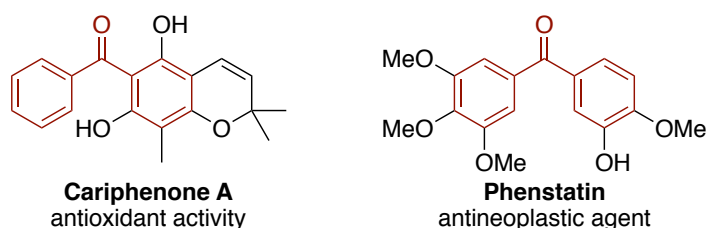


Figure 3.2 Examples of bioactive compounds containing the diarylketone motif (highlighted in red).

Diarylmethanes present a second class of diaryl-containing compounds which also display interesting bioactivity. Important examples include the chemopotentiator tesmilifene, shown to be an effective treatment for metastatic breast cancer,¹⁴⁰ and tofogliflozin, a selective inhibitor of the sodium glucose co-transporter 2 (SGLT2) used for the treatment of type 2 diabetes (Figure 3.3).¹⁴¹ However, the methylene group in diarylmethane derivatives can present a metabolic liability and so incorporation of groups to block this site may be advantageous.¹⁴²

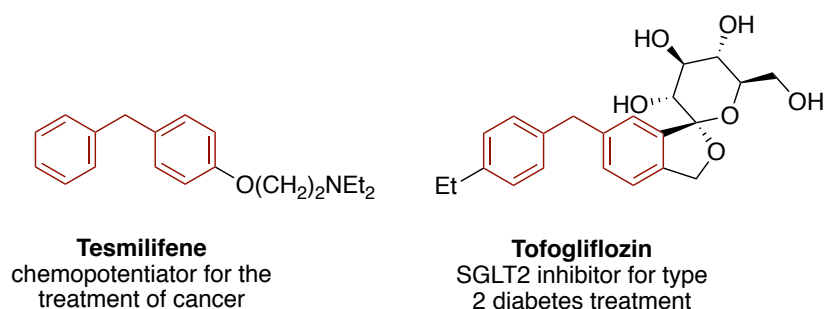


Figure 3.3 Selected examples of diarylmethane analogues in medicinal chemistry with the diarylmethane motif highlighted in red.

The diaryl motif also features in bisphenol A (BPA), a mass-produced monomer for the polymer industry used in the synthesis of polycarbonates and epoxy resins (Figure 3.4).¹⁴³ These BPA derived polymers are useful for the production of various consumer products although concerns exist surrounding potential interactions with the endocrine system *in vivo*.¹⁴⁴ For this reason, BPA is banned in the production of certain consumer goods e.g. baby bottles.¹⁴⁵

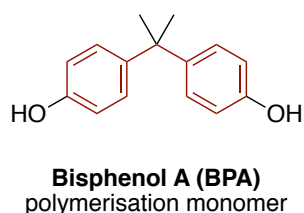


Figure 3.4 Structure of bisphenol A with the diaryl motif highlighted in red.

Bioisosteric replacement of problematic functional groups presents an excellent strategy to combine the original benefits of the group being substituted with an improved physicochemical profile (see Section 1.1.4). In the literature, oxetanes have been shown across various examples to act as beneficial bioisosteres for carbonyl, methylene and *gem*-dimethyl groups particularly with regards to improving metabolic stability (see Section 1.1.5). Therefore, 3,3-diaryloxetanes were designed as intriguing and novel bioisosteres for diarylketones and diarylmethanes. This scaffold was designed to afford improved properties for drug discovery,

whilst retaining important potential binding interactions which may be necessary for conserving biological activity (Figure 3.5).

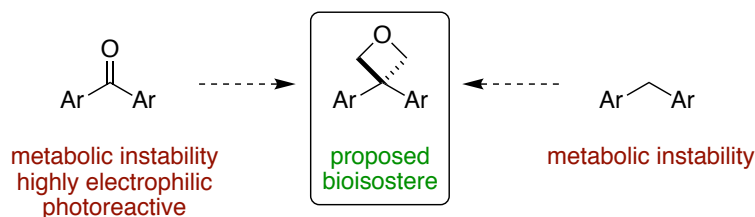
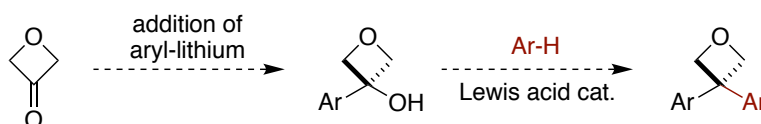


Figure 3.5 3,3-Diaryloxetanes are proposed as bioisosteres for diarylmethanes and diarylketones.

3.1.2 Approach for the Synthesis of 3,3-Diaryloxetanes

3,3-Diaryloxetanes presented a significant synthetic challenge due to their incompatibility with known methods for oxetane synthesis. The only prior example of a disubstituted 3,3-diaryloxetane in the literature was synthesised in a very low 6% yield through a zinc modified ring closing Mitsunobu reaction of a 1,3-diol precursor.¹⁴⁶ Competing degradation processes and requirements for further substitution at the 2- and/or 4-positions make ring closing methods unsuitable for the synthesis of this motif. Therefore, direct functionalisation on the intact oxetane ring presented the most viable strategy.

Inspired by recent developments in the field of catalytic Friedel–Crafts alkylation reactions from tertiary alcohols,¹⁴⁷ a two-step protocol from commercially available oxetan-3-one was envisaged (Scheme 3.1).



Scheme 3.1 Proposed two-step route towards 3,3-diaryloxetanes.

In the key step of our proposal, the acid-catalysed generation of an oxetanyl carbocation from oxetan-3-ol and then addition of an aromatic nucleophile forms the desired C–C bond. The activation of alcohols for substitution reactions has gained popularity as a less toxic alternative to alkyl halides.¹⁴⁷ Additionally, in principle, water is the only by-product from the reaction making alcohols attractive precursors from a green chemistry perspective. The unknown nature and feasibility of the planned carbocation intermediate and stability of the oxetane ring to acidic conditions presented substantial challenges to overcome in the early stages of this research.

3.1.3 Preparation of Oxetan-3-ols

Through the course of this research, nucleophilic addition of aryl-lithium reagents into oxetan-3-one provided a wide range of 3-aryl-oxetan-3-ols. Using a protocol established by Carreira and co-workers,^{72,90} 10 examples of 3-aryl-3-oxetanols were synthesised in isolated yields between 46% and 94% (Table 3.1). The aryl-lithium was generated *in situ* through halogen-lithium exchange between *n*BuLi and the desired arylbromide (or aryl-H for the furan substituted example **51**). The process was scalable with the synthesis of oxetanol **44** achieved on a 20 mmol scale to provide over 3 g of oxetanol **44** in a single reaction. The oxetanol products were generally bench stable crystalline white solids that showed no notable degradation when stored at room temperature making them expedient reaction precursors.

Table 3.1 Oxetanols synthesised through addition of aryl-lithium reagents into oxetan-3-one.

^aSynthesised at Pfizer. ^bSynthesised using the same conditions directly from 2-methylfuran.

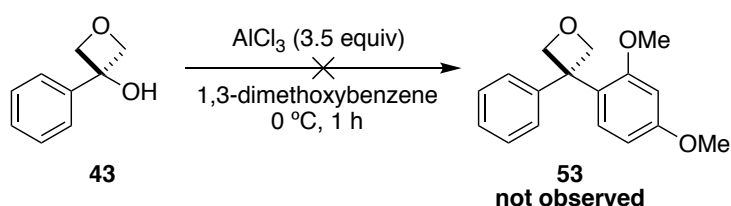
Ar-Br $\xrightarrow[2. \text{oxetan-3-one, } -78^\circ\text{C to rt}]{1. \text{ nBuLi, THF, } -78^\circ\text{C}}$ Ar-CH(OH)-CH₂-CH₂-O **43–52**

	Aryl	Yield (%)		Aryl	Yield (%)
43		83	48^a		73
44		90	49		86
45		70	50		94
46		79	51^{a,b}		47
47^a		46	52		90

3.1.4 Initial Optimisation: Screening of Substrates and Catalysts

An important consideration for the success of the Friedel–Crafts alkylation reaction was the acid catalyst. Judicious choice of acid catalyst and conditions would be required to selectively activate the tertiary alcohol over the oxetane oxygen. It was assumed that coordination of the acid catalyst to the oxetane would occur due to the highly basic nature of the oxygen lone pairs but this process needed to be sufficiently dynamic to allow for the desired Friedel–Crafts alkylation to occur and to minimise acid-catalysed ring opening side reactions.

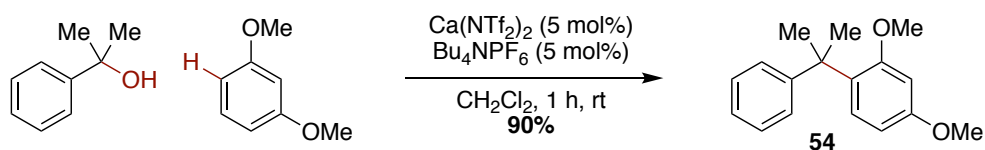
Firstly, oxetanol **43** was submitted to traditional aluminium trichloride Friedel–Crafts conditions using the nucleophile, 1,3-dimethoxybenzene, as solvent (Scheme 3.2). During investigations by the Carreira group, a degree of stability to these conditions was observed as some recovery of starting material was reported when oxetanol **43** was subjected to aluminium trichloride conditions at 75 °C for 60 hours. However, under the tested conditions complete decomposition to a ring opened polymerised species occurred after 1 hour at 0 °C. Therefore, milder catalytic conditions were investigated for this study.



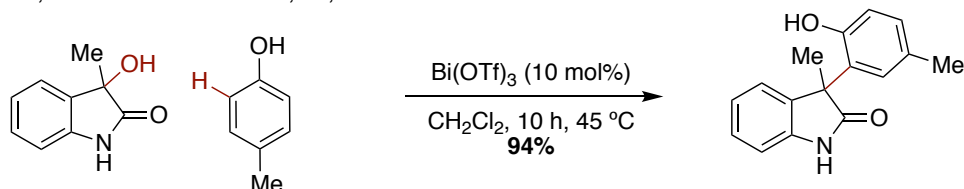
Scheme 3.2 Reaction of oxetanol **43** under traditional Friedel–Crafts alkylation conditions.

In 2010, Niggemann reported the high yielding calcium-catalysed Friedel–Crafts alkylation of tertiary alcohols under mild conditions in just 1 hour (Scheme 3.3A).¹⁴⁸ $\text{Ca}(\text{NTf}_2)_2$ in combination with a hexafluorophosphate additive was indicated as an excellent catalyst system for a variety of transformations invoking tertiary carbocations.¹⁴⁹ Replication of the reaction in Scheme 3.3A proved somewhat difficult as at room temperature only starting material was recovered after 1 hour. However, increasing the reaction temperature to 40 °C enabled the diaryl product **54** to be synthesised in a 91% yield (by ^1H NMR) indicating that these conditions are sensitive to temperature. In a further example from 2012, Bisai and co-workers successfully used $\text{Bi}(\text{OTf})_3$ to catalyse the addition of electron rich phenols to 3-hydroxy-2-oxindoles in high yields at just 45 °C (Scheme 3.3B).¹⁵⁰ During the optimisation stage, other triflates such as $\text{In}(\text{OTf})_3$ and $\text{Cu}(\text{OTf})_2$ as well as FeCl_3 were also shown to be successful catalysts for this transformation giving only slightly reduced yields compared to $\text{Bi}(\text{OTf})_3$.

A Niggemann, *Angew. Chem. Int. Ed.* 2010, 49, 3684



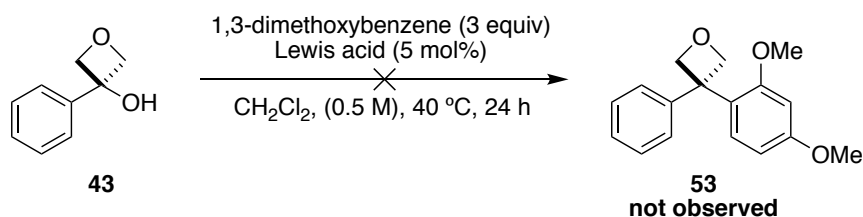
B Bisai, *Chem. Commun.* 2012, 48, 10134



Scheme 3.3 Selected examples of catalytic Friedel–Crafts alkylations of tertiary alcohols.

Initial investigations examined phenyl-substituted oxetanol **43** as a suitable precursor for the Friedel–Crafts reaction (Table 3.2). Lewis acid catalysts were screened using dichloromethane as the solvent at 40 °C over 24 hours. These conditions were chosen based on those most commonly used in the literature.¹⁴⁷ None of the catalysts examined gave any diaryloxetane product **53** and varying amounts of the starting material were recovered. In several cases, the production of an insoluble gel-like substance in the reaction provided evidence of polymerisation. Despite the lack of desired product, the presence of starting material in several cases (Entries 3–9) was encouraging as the oxetanol starting material was not simply undergoing ring opening processes under the acidic conditions.

Table 3.2 Initial screen of Lewis acids with oxetanol **43**. ^aYields calculated by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. ^b5 mol% of Bu₄NPF₆ added.

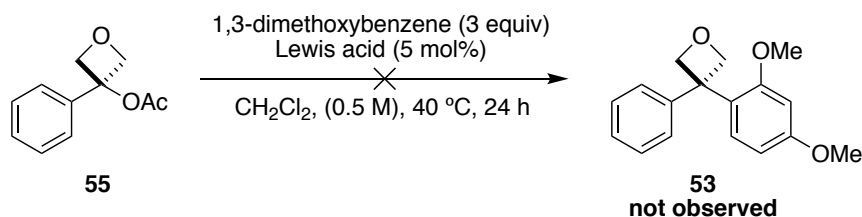


Entry	Lewis Acid Catalyst	Yield of 53 (%) ^a	Recovered SM 43 (%) ^a
1	Hf(OTf) ₃	0	0
2	Bi(OTf) ₃	0	0
3	Sc(OTf) ₃	0	48
4	Ga(OTf) ₃	0	10
5	Yb(OTf) ₃	0	81
6	Zr(OEt) ₄	0	67
7	Zr(O ⁱ Pr) ₄	0	76
8	FeCl ₃	0	68
9 ^b	Ca(NTf ₂) ₂	0	100

The same Lewis acids were investigated in the reaction using toluene as the solvent at 110 °C. Unfortunately, the higher temperature did not lead to the formation of diaryloxetane **53** and starting material was recovered in much lower yields for all the Lewis acids examined (0–38% by ¹H NMR spectroscopy).

The lack of formation of any diaryloxetane product led to the exploration of different leaving groups. The acetate derivative **55** was investigated as it was hoped that the acetate would provide superior coordination to the Lewis acid catalyst. Acetate **55** was readily synthesised from oxetanol **43** in an 86% yield using DMAP and acetic anhydride. Unfortunately, when acetate **55** was submitted to a screen of Lewis acids, no diaryloxetane product **53** was observed after 24 hours (Table 3.3). Additionally, for the majority of Lewis acids (Entries 1–5 and 7) no starting material was recovered suggesting that acetate **55** was unstable under the acidic conditions.

Table 3.3 Screen of Lewis acids with acetate **55**. ^aYields calculated by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. ^b5 mol% of Bu₄NPF₆ added.



Entry	Lewis Acid Catalyst	Yield 53 (%) ^a	Recovered SM 55 (%) ^a
1	Hf(OTf) ₃	0	0
2	Bi(OTf) ₃	0	0
3	Sc(OTf) ₃	0	0
4	Ga(OTf) ₃	0	0
5	Yb(OTf) ₃	0	82
6	FeCl ₃	0	13
7 ^b	Ca(NTf ₂) ₂	0	0

As no diaryloxetane product **53** was observed under any of the conditions tested when using phenyl as the preinstalled aromatic group, more electronically favourable options were explored. It was hoped that use of an electron donating group (OMe or OBn) in the *para*-position would provide sufficient stabilisation of the carbocationic intermediate to allow the reaction to progress.

The Friedel–Crafts alkylation reaction between *p*-methoxyphenyl substituted oxetanol **44** and 1,3-dimethoxybenzene was explored by examining a variety of Lewis acid catalysts (Table 3.4). Pleasingly, use of Ca(NTf₂)₂/Bu₄NPF₆, Yb(OTf)₃ or FeCl₃ successfully led to the formation of diaryloxetane **56** (Entries 5, 8–9). Excellent mass recovery was observed for the reaction with Yb(OTf)₃ although conversion was very low (Entry 5). Further studies that explored increasing the temperature, catalyst loading and equivalents of dimethoxybenzene whilst using this catalyst did not increase the yield of diaryloxetane **56** above 12% and therefore its use in the reaction was not examined further. The highest yield of diaryloxetane **56** (18%) was obtained under the calcium-catalysed conditions (Entry 9), prompting further investigations using this catalyst.

Table 3.4 Screen of Lewis acids for the reaction of oxetanol **44** with 1,3-dimethoxybenzene. ^aYields calculated by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. ^b5 mol% of Bu₄NPF₆ added.

Entry	Lewis Acid Catalyst	Yield 56 (%) ^a	Recovered SM 44 (%) ^a
1	Hf(OTf) ₃	0	0
2	Bi(OTf) ₃	0	0
3	Sc(OTf) ₃	0	48
4	Ga(OTf) ₃	0	10
5	Yb(OTf) ₃	6	70
6	Fe(OTf) ₂	0	0
7	Fe(OTf) ₃	0	0
8	FeCl ₃	14	51
9 ^b	Ca(NTf ₂) ₂	18	29

Different solvents were investigated in the reaction (Table 3.5). Chlorinated solvents gave the best yields (Entries 2–4) with chloroform giving the highest yield of oxetane **56** and recovery of starting material. Non-polar toluene was also a suitable solvent although gave a slightly reduced yield of oxetane **56** (Entry 1). Polar solvents such as nitromethane, ethanol and acetonitrile yielded no desired product probably due to coordination to the catalyst preventing the desired catalytic cycle (Entries 5–7). It was also observed that the same yield and recovery of starting material was achieved at both 1 hour and 24 hour reaction times so the shorter 1 hour reaction time was adopted.

Table 3.5 Screen of solvents for the calcium-catalysed Friedel–Crafts reaction between oxetanol **44** and 1,3-dimethoxybenzene. ^aYields calculated by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. ^b24 h reaction time.

Entry	Solvent	Yield 56 (%) ^a	Recovered SM 44 (%) ^a
1 ^b	toluene	16	0
2	dichloromethane	19	30
3	chloroform	25	34
4	dichloroethane	17	34
5	nitromethane	0	84
6	ethanol	0	94
7	acetonitrile	0	72

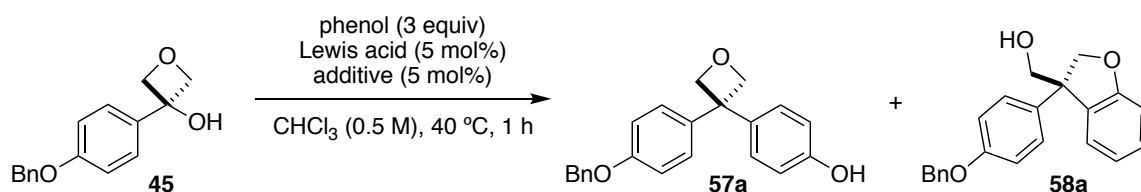
The effect of small increases and decreases in temperature was also investigated with interesting results. Temperatures lower than 40 °C (25 °C, 30 °C and 35 °C) resulted in a 0% conversion of starting material. Temperatures above 40 °C (45 °C, 50 °C, 55 °C) resulted in no further increase in product yield or conversion. Concentrations between 1 M and 0.1 M were also examined and at all concentrations tested the yield of oxetane **56** was the approximately the same. However, lower concentrations showed higher levels of recovered starting material (34% at 0.5 M vs 63% at 0.1 M) suggesting that there may be potential to increase conversion at lower concentrations.

The lack of progression in terms of increasing the yield of the reaction above 25% when using 1,3-dimethoxybenzene led to an examination of alternative electron rich nucleophilic coupling partners. Phenols presented an attractive option as the hydroxy functional handle possesses potential for a wide variety of further reactivity and a large number of derivatives are commercially available. More versatile preinstalled aromatic groups were also explored and pleasingly, *p*-OBn substituted oxetanol **45** displayed very similar reactivity to oxetanol **44**. It was envisaged that deprotection of the benzyl group and further reaction of the revealed phenol would present an opportunity to access further interesting derivatives.

The reaction between oxetanol **45** and phenol in chloroform using a variety of Lewis acids and additives at 40 °C for 1 hour resulted in the isolation of two separable products in an approximately 2.5:1 ratio and combined yield of up to 66% (Table 3.6). This ratio was consistent with the *para:ortho* ratios observed in Friedel–Crafts alkylation reactions with nucleophiles where addition at both *ortho*- and *para*-positions is possible.¹⁴⁸ The major product was the desired diaryloxetane **57a** which was isolated exclusively as the *para*-substituted regioisomer. In the ¹H NMR spectra of the major product, a broad singlet integrating to four protons was observed at 5.21 ppm corresponding to the four oxetane hydrogens. Although there are two proton environments, in this example they are similar enough that the peak appears as a singlet instead of two separate doublets. The ¹H NMR spectra of the minor product contained four doublets between 4.77 ppm and 4.04 ppm each integrating to a single proton. This was not compatible with the expected *ortho*-alkylated diaryloxetane product as in this case there would be only two environments for the oxetane protons *cf.* diaryloxetane **57a**. This observation alongside further analysis using COSY NMR techniques enabled identification of the minor product as 2,3-dihydrobenzofuran **58a**. This product was derived from reaction at the *ortho*-position of the phenol followed by intramolecular oxetane ring opening by the proximal hydroxy group.

The best combined yields of Friedel–Crafts derived products **57a** and **58a** were obtained using either Ca(NTf₂)₂ or Li(NTf₂) as the catalyst in conjunction with Bu₄NPF₆ as an additive (Entries 4 and 5). Other catalysts either gave no desired product (Entries 1, 3 and 9) or vastly reduced yields (Entries 2 and 8). Alternative additives NH₄BF₄ and AgPF₆ were explored in combination with Ca(NTf₂)₂ but neither gave an improvement in yield (Entries 6–7).

Table 3.6 Catalyst and additive screen for reaction between oxetanol **45** and phenol. ^aYields calculated by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. ^b10 mol% of catalyst used.



Entry	Lewis Acid Catalyst	Additive	Yield 57a (%) ^a	Yield 58a (%) ^a	Recovered SM 45 (%) ^a
1	$\text{Yb}(\text{OTf})_3$	-	0	0	100
2	$\text{Fe}(\text{OTf})_3$	-	24	14	0
3	FeCl_3	-	0	0	100
4	$\text{Li}(\text{NTf}_2)_2^b$	Bu_4NPF_6	47	19	0
5	$\text{Ca}(\text{NTf}_2)_2$	Bu_4NPF_6	44	19	0
6	$\text{Ca}(\text{NTf}_2)_2$	NH_4BF_4	13	2	29
7	$\text{Ca}(\text{NTf}_2)_2$	AgPF_6	45	14	0
8	$\text{Ca}(\text{BF}_4)_2$	Bu_4NPF_6	14	7	45
9	$\text{Ca}(\text{OTf})_2$	Bu_4NPF_6	0	0	85

3.1.5 DOE Optimisation: Statistical Analysis

Reaction space describes all combinations of the different variables affecting a reaction.¹⁵¹ For a hypothetical reaction dependent on just three continuous variables this can be imagined as a cube whereby the axes represent the different continuous parameters on which the reaction yield depends e.g. temperature, catalyst loading, reaction time etc (Figure 3.6). Traditionally, exploration of reaction space is conducted through a linear optimisation approach where one parameter is changed at a time whilst the other variables are kept constant. The parameter is then set at the value that gives the optimal reaction outcome and a different parameter is changed. The limitation of this strategy is that synergistic relationships between multiple parameters are not considered and so large areas of potentially optimal reaction space may be left unexplored.

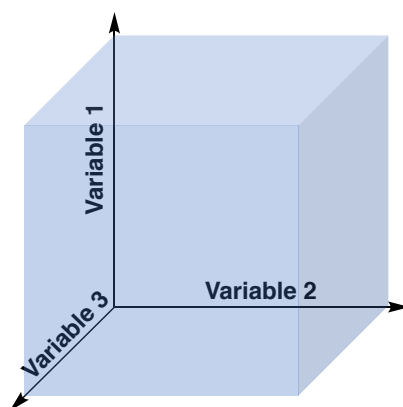


Figure 3.6 Representation of reaction space for a reaction dependent on variables 1, 2 and 3 with reaction space indicated by the blue cube.

Design of experiments (DOE) is a powerful optimisation method that is used to systematically explore reaction space in an efficient manner by using statistical analysis to maximise the amount of information gained from a minimal number of experiments.¹⁵² Multiple factors are changed simultaneously meaning that relationships between different variables and their effect on the outcome of a reaction can be fully investigated. We believed that using a DOE approach would allow efficient optimisation of the continuous factors affecting the Friedel–Crafts alkylation between oxetanol **45** and phenol.

Both $\text{Ca}(\text{NTf}_2)_2$ and $\text{Li}(\text{NTf}_2)_2$ gave similar yields in the Lewis acid screen so it was decided at this stage to progress both to further optimisation using DOE analysis, starting with $\text{Ca}(\text{NTf}_2)_2$. Five factors were selected that were thought to be most significant to the outcome of the reaction: temperature, concentration, catalyst loading, equivalents of nucleophile and reaction time. The area of reaction space to be explored was determined by upper and lower limits for each factor. The values for these limits were selected to allow for reasonable variation whilst aiming to maintain mild reaction conditions.

Table 3.7 Parameters selected for DOE optimisation using $\text{Ca}(\text{NTf}_2)_2/\text{Bu}_4\text{NPF}_6$.

Parameter	Units	Lower Limit	Upper Limit
Temperature	°C	40	55
Concentration	M	0.05	0.5
Catalyst loading	mol%	1	9
Equiv of nucleophile	equiv	1	5
Reaction time	min	30	240

DOE optimisation was carried out using Modde pro 11 software from MKS Umetrics. A central composite faced (CCF) design was employed which used maximum, minimum and midpoint values for each of the parameters and generated 29 combinations of these values to allow effective exploration of the reaction space (see Appendix, Table 7.1). The experiment where the midpoint value of all five parameters was used was repeated three times to verify reproducibility.

Each experiment was conducted using oxetanol **45** and phenol, and the results were analysed using a partial least squares (PLS) modelling method to generate a reaction profile. Pleasingly, the three repeats all gave yields within 1% of each other indicating the reaction was highly reproducible, essential for producing a high-quality model. The model found an excellent correlation between the observed outcomes and those predicted by the PLS model (Figure 3.7).

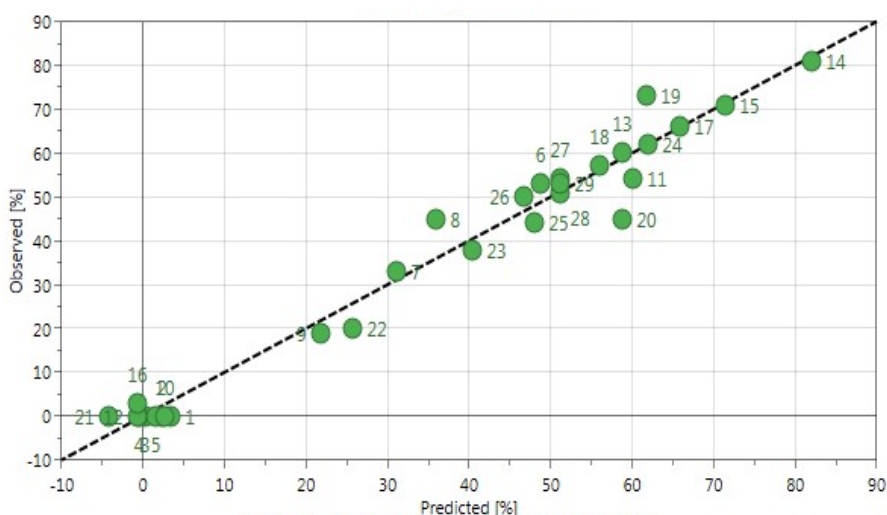


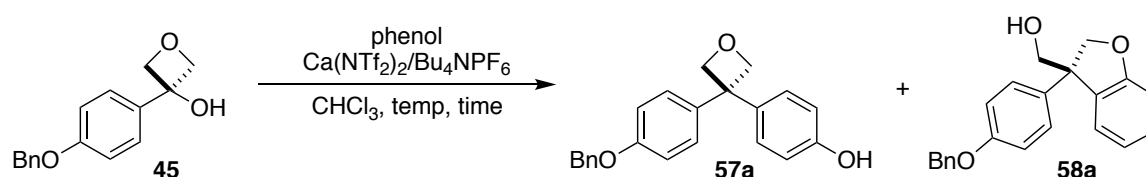
Figure 3.7 A plot of observed vs predicted yields based on the PLS model.

The DOE analysis found that the equivalents of nucleophile and catalyst loading were the most important factors for increasing product yields. Furthermore, a relationship between temperature and concentration was uncovered; at high temperatures, lower concentrations gave improved yields of products whereas at the lower limit for temperature, higher concentrations were favourable. Within the limits studied (30 to 240 min), reaction time did not have a meaningful impact on the product yields.

The highest combined yield of products **57a** and **58a** directly from the DOE study was 81% (cf. 63% from the unoptimised conditions, Table 3.8, Entry 1). This improved yield was achieved using an increased 5 equivalents of nucleophile, 9 mol% loading of $\text{Ca}(\text{NTf}_2)_2/\text{Bu}_4\text{NPF}_6$ and a 0.05 M concentration at 55 °C for 30 min (Table 3.8, Entry 2). Next,

the optimisation function was employed to generate conditions predicted by the PLS model to give the highest yield of oxetane **57a** (Table 3.8, Entry 3). Although under these conditions the same combined yield of oxetane **57a** and dihydrobenzofuran **58a** was observed (81%), there was slightly improved selectivity for the oxetane product. The conditions in Entry 3 were also preferred as they required less catalyst and solvent.

Table 3.8 Key sets of conditions from the DOE optimisation of the reaction between oxetanol **45** and phenol using $\text{Ca}(\text{NTf}_2)_2/\text{Bu}_4\text{NPF}_6$. ^aYields calculated by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard.



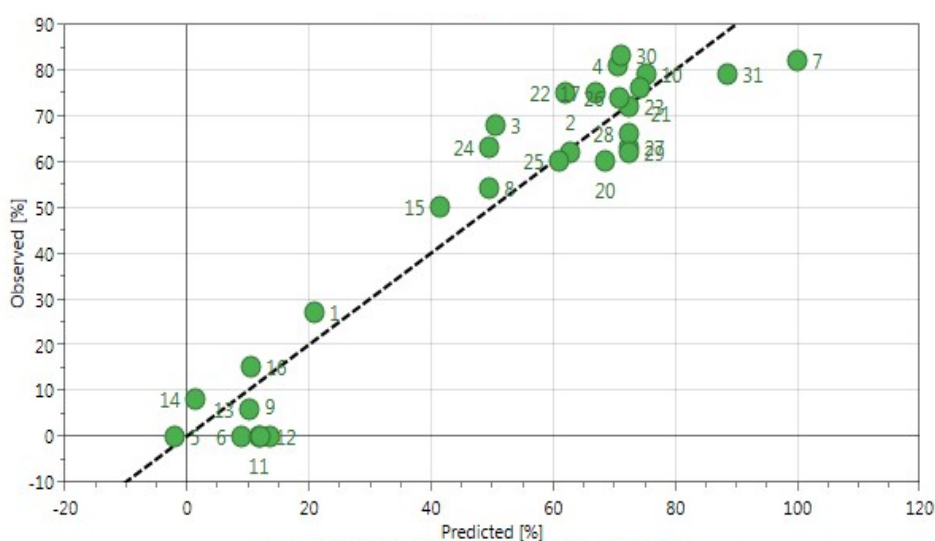
Entry	Conditions	Yield of 57a (%) ^a	Yield of 58a (%) ^a	Combined yield (%) ^a
Unoptimised:				
1	3 equiv phenol 5 mol% $\text{Ca}(\text{NTf}_2)_2/\text{Bu}_4\text{NPF}_6$ CHCl_3 (0.5 M), 40 °C, 1 h	44	19	63
Best conditions from DOE:				
2	5 equiv phenol 9 mol% $\text{Ca}(\text{NTf}_2)_2/\text{Bu}_4\text{NPF}_6$ CHCl_3 (0.05 M), 55 °C, 30 min	54	27	81
Predicted best conditions:				
3	5 equiv phenol 5.5 mol% $\text{Ca}(\text{NTf}_2)_2/\text{Bu}_4\text{NPF}_6$ CHCl_3 (0.5 M), 40 °C, 1 h	59	22	81

A similar DOE optimisation was conducted for the reaction using $\text{Li}(\text{NTf}_2)/\text{Bu}_4\text{NPF}_6$. As before, five continuous factors were selected for investigation. As reaction time had little effect on the reaction when using the calcium catalyst, reaction time was set at 1 hour for this study. However, additionally for the lithium catalyst different combinations of catalyst and additive loading were explored.

Table 3.9 Parameters selected for DOE optimisation using Li(NTf₂)/Bu₄NPF₆.

Parameter	Units	Lower Limit	Upper Limit
Temperature	°C	40	60
Concentration	M	0.05	1
Catalyst loading	mol%	5	15
Additive loading	mol%	2.5	7.5
Equiv of nucleophile	equiv	2	5

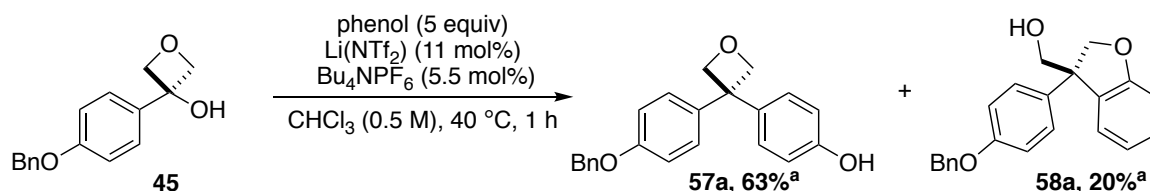
Again, 29 experiments featuring different combinations of the minimum, maximum and midpoint values for each factor were generated using a CCF factorial design (see Appendix, Table 7.2). A PLS modelling method was applied using the results of the 29 experiments and a good correlation was observed between the experimental yields and the yields predicted by the model (Figure 3.8).

**Figure 3.8** A plot of observed vs predicted yields based on the PLS model.

The main finding from the DOE study with Li(NTf₂) was that a <1:1 ratio of catalyst:additive was detrimental to the reaction whereas ratios of 2:1 or greater gave the highest product yields. The highest yield of the diaryloxetane product **57a** (approximately 57%) could be achieved at either 60 °C or 40 °C, at concentrations at the lower and upper limits and also at various different catalyst loadings, indicating that these factors do not independently have a significant effect on the reaction outcome. The optimiser tool was again employed but the

suggested conditions (3.25 equiv nucleophile, 15 mol% Li(NTf₂), 7.5 mol% Bu₄NPF₆, 0.2 M CHCl₃, 40 °C) did not provide improved yields of oxetane **57a**.

The learnings from the two DOE studies were combined and the optimal conditions from the investigation with the calcium catalyst were applied to the lithium catalyst using a 2:1 catalyst:additive ratio. Under these conditions, the highest yield of oxetane **57a** was reproducibly observed (63%) alongside 20% of dihydrobenzofuran **58a** (Scheme 3.4).



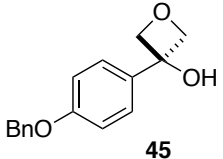
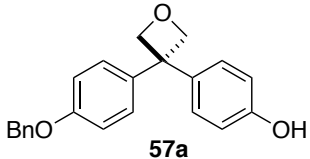
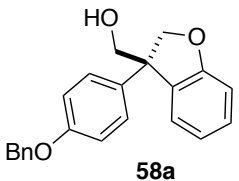
Scheme 3.4 Optimal conditions from the DOE optimisation studies. ^aYields calculated by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard.

3.1.6 Final Optimisation of the Lithium-Catalysed Friedel–Crafts Reaction

Li(NTf₂) was chosen as the catalyst for further studies due to its superior activity in the reaction and considerably cheaper cost compared to Ca(NTf₂)₂ (GBP£1407/mol for Li(NTf₂) and GBP£59076/mol for Ca(NTf₂)₂).¹⁵³ However, Ca(NTf₂)₂ is also considered a suitable catalyst to deliver the desired Friedel–Crafts products in good yields.

A final examination of certain parameters was conducted to confirm the optimal conditions obtained from the DOE study (Table 3.10, see entry 1 for optimal conditions from the DOE study). A 1:1 catalyst:additive ratio gave considerably lower yields of products **57a** and **58a** compared to a 2:1 ratio (Entries 2 and 3). The reason why a 2:1 ratio is preferred is unclear but may relate to the solubilisation and availability of the active catalytic species. With no additive or at a temperature of 25 °C, quantitative recovery of starting material was observed indicating that the additive and temperature are critical to the success of the reaction (Entries 4–5). On addition of the lithium salt, the reaction mixture became a cloudy white suspension. After 10–20 minutes at 40 °C in the presence of the hexafluorophosphate additive, solubilisation occurred to give a clear solution. Without additive or when the reaction was conducted at 25 °C, the reaction mixture remained a cloudy white suspension throughout indicating that the lack of reactivity is perhaps due to lack of solubilisation of the catalyst at lower temperatures or without the additive. The result in the absence of additive suggested that the role of the hexafluorophosphate additive may be to aid catalyst solubilisation through disruption of the tetrahedrally coordinated lattice adopted by Li(NTf₂) in the solid state.¹⁵⁴

Table 3.10 Final optimisation for the reaction of oxetanol **45** and phenol. ^aYields calculated by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard.

 45 $\xrightarrow[\text{'standard' conditions}]{\begin{array}{l} \text{phenol (5 equiv)} \\ \text{Li(NTf}_2\text{)} (11 \text{ mol}\%) \\ \text{Bu}_4\text{NPF}_6 (5.5 \text{ mol}\%) \\ \text{CHCl}_3 (0.5 \text{ M}), 40^\circ\text{C}, 1 \text{ h} \end{array}}$  57a +  58a				
Entry	Change from the 'standard' conditions	Yield of 57a (%) ^a	Yield of 58a (%) ^a	Recovered 45 (%) ^a
1	none	63	20	0
2	5 mol% of Li(NTf ₂) and Bu ₄ NPF ₆	11	4	32
3	11 mol% of Li(NTf ₂) and Bu ₄ NPF ₆	22	6	46
4	No Bu ₄ NPF ₆	0	0	83
5	25 °C reaction temperature	0	0	86
6	15 mol% Li(NTf ₂), 7.5 mol% of Bu ₄ NPF ₆	59	20	0
7	20 mol% Li(NTf ₂), 10 mol% of Bu ₄ NPF ₆	51	20	0
8	10 equivalents of phenol	65	21	0
9	AgPF ₆ instead of Bu ₄ NPF ₆	63	20	0
10	Dichloroethane instead of chloroform	56	19	0
11	Chlorobenzene instead of chloroform	52	13	0
12	Hexane instead of chloroform	58	16	0
13	Toluene instead of chloroform	0	0	87

Higher catalyst loadings were then examined. Employing a 15 mol% catalyst loading gave similar product yields compared to 11 mol% (Entry 6), but at 20 mol% the yield of oxetane **57a** was reduced to 51% possibly due to an increase in acid-catalysed degradation processes (Entry 7). Increasing the equivalents of nucleophile from 5 to 10 led to comparable yields of products so raising the equivalents of nucleophile above 5 was not considered further (Entry 8).

Switching the additive from Bu_4NPF_6 to AgPF_6 gave no difference in the reaction outcome (Entry 9). Different chlorinated solvents, dichloroethane and chlorobenzene, as well as hexane gave only slightly reduced yields compared to chloroform (Entries 10–12). Toluene, was also investigated but no desired reactivity was observed (Entry 13).

As none of the changes that were explored gave a meaningful increase in yield or selectivity, the conditions in entry 1 (11 mol% $\text{Li}(\text{NTf}_2)$, 5.5 mol% Bu_4NPF_6 , 5 equivalents of nucleophile, chloroform, 0.5 M, 40 °C, 1 h) were adopted as optimal for the reaction.

As standard throughout the optimisation, reactions were carried out on a 0.25 mmol scale. To demonstrate the scalability of this reaction, the reaction between oxetanol **45** and phenol was conducted on a 7.5 mmol scale under the optimal conditions. This delivered 1.3 g of oxetane **57a** (51% yield *cf.* 60% on a 0.25 mmol scale) and 0.5 g of dihydrobenzofuran **58a** (19% yield *cf.* 19% on a 0.25 mmol scale).

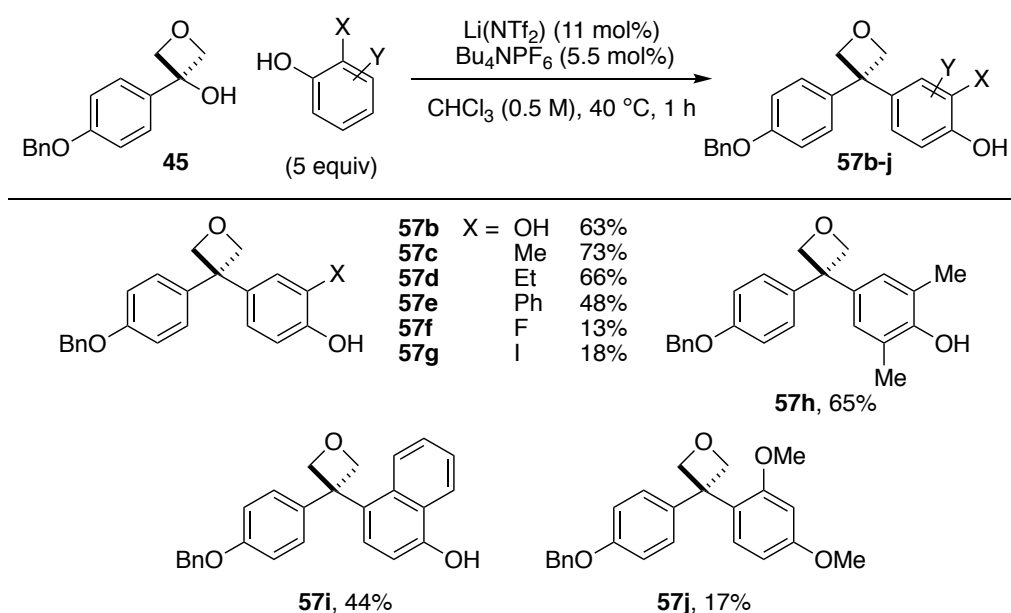
During this study, reactions were conducted using flamedried glassware under an argon atmosphere. When the reaction was conducted without measures being taken to eliminate moisture and air, only a small reduction in yield was observed (54% oxetane **57a** + 19% dihydrobenzofuran **58a**).

3.1.7 Scope of Diaryloxetanes

With optimised conditions in hand, the scope of this methodology for the synthesis of 3,3-diaryloxetanes was explored. Pleasingly, *ortho*-substituted phenols showed excellent selectivity for the diaryloxetane product with the dihydrobenzofuran regioisomer formed in <5% yield in all cases (by ^1H NMR spectroscopy of the crude reaction). This is thought to be due to the steric bulk of the *ortho*-substituent deterring alkylation through the other unsubstituted *ortho*-carbon (where available). Full consumption of starting material was observed after just 1 hour with the loss in mass most likely attributed to degradation of the proposed oxetanyl carbocation intermediate through ring opening or elimination processes.

For phenols substituted with electron rich *ortho*-substituents such as OH, Me and Et, 3,3-diaryloxetanes **57b–57d** were obtained in good yields (63–73%). 2-Phenylphenol gave the 3,3-diaryloxetane **57e** in a 48% yield indicating that electron neutral groups are also compatible with this methodology. Phenols substituted with halides in the *ortho*-position successfully delivered 3,3-diaryloxetane products **57f** and **57g**, although yields were significantly reduced compared to electron rich examples. This could be attributed to the lower rate of addition for these nucleophiles not outcompeting the rate of decomposition of the oxetanyl carbocation intermediate. 2,6-Dimethylphenol and 1-naphthol were also suitable

nucleophiles for the reaction with oxetane derivatives **57h** and **57i** synthesised in 65% and 44% yields respectively. Oxetane **57j** from 1,3-dimethoxybenzene, the only 3,3-diaryloxetane example not featuring phenol, was synthesised in a low 17% yield. No other products were observed in the crude reaction mixture by ^1H NMR suggesting formation of possibly volatile or insoluble degradation products. It was considered that a more electron rich non-phenol derived nucleophile may react more rapidly, leading to less oxetanyl carbocation degradation and higher product yields. Unfortunately, 1,3,5-trimethoxybenzene did not react under the optimised reaction conditions likely due to the added steric bulk of the nucleophile preventing addition to the carbocation.



Scheme 3.5 Different aryl nucleophiles for the lithium-catalysed Friedel–Crafts alkylation reaction to give 3,3-diaryloxetanes.

Certain coordinating groups such as OMe and SMe and TMS were not tolerated at the *ortho*-position with starting material recovered quantitatively from the reaction (Figure 3.9). Chelation to the catalyst preventing the desired coordination to the tertiary alcohol provides a possible explanation for the complete lack of observed activity.

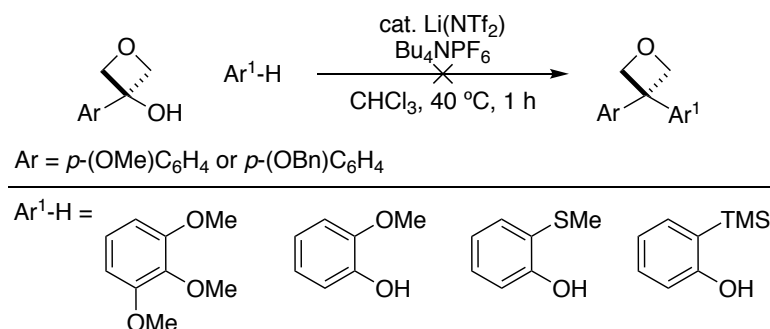


Figure 3.9 Unsuccessful electron rich nucleophiles for the Friedel–Crafts alkylation of oxetanols.

Several other nucleophiles were tested in the reaction including: *N*-methylindole, *N*-methylpyrrole, 2-methylthiophene, anilines and *N*-phenylacetamide (Figure 3.10). Unfortunately, in all cases no Friedel–Crafts alkylation products were observed with 0% conversion of starting material. Strong coordination of the catalyst to the nucleophile is thought to be the reason for the lack of reactivity under these conditions.

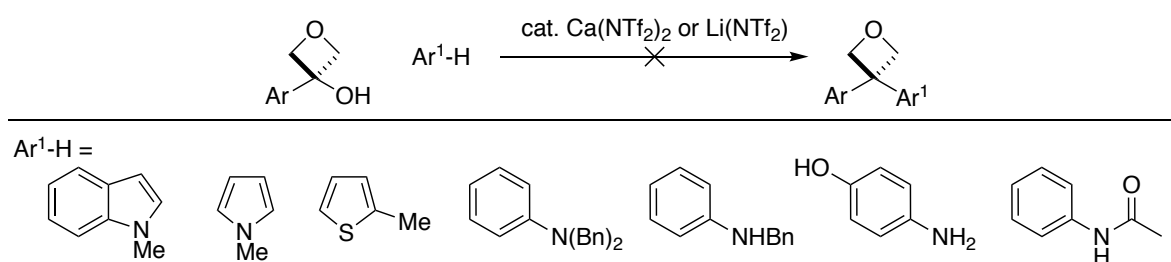
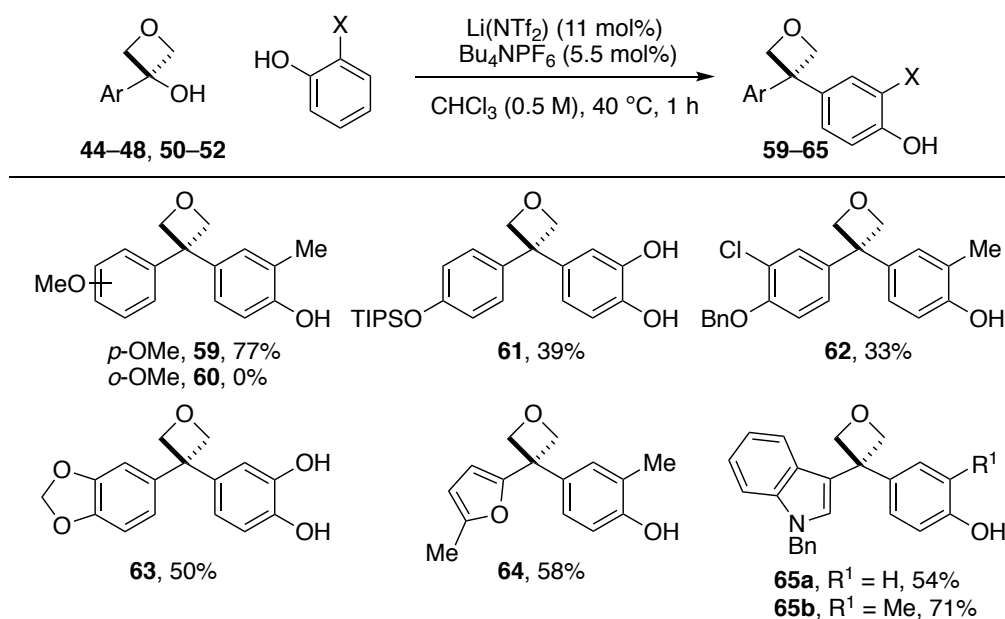


Figure 3.10 Unsuccessful heteroaromatic and nitrogen containing nucleophiles for the Friedel–Crafts alkylation of oxetanols.

Changing the preinstalled aromatic component was also investigated through reaction of different oxetanols with either catechol or *o*-methylphenol (Scheme 3.6). Oxetanols **44** and **46**, substituted with *p*-OMe and *p*-OTIPS groups gave products **59** and **61** in yields of 39% and 77% respectively. Oxetanol **50** featuring an *o*-OMe substituent was also submitted to the optimised conditions. Unfortunately, no desired product (**60**) was observed indicating a sensitivity to increased bulk around the tertiary alcohol. An additional *m*-Cl substituent was tolerated on the preinstalled aromatic group with oxetanol **47** giving the corresponding diaryloxetane product **62** in 33% yield. Benzodioxole functionalised oxetanol **48** reacted with catechol to give oxetane derivative **63** in 50% yield. The poor solubility of catechol in the reaction solvent may account for the slightly lower than expected yields of **61** and **63**.



Scheme 3.6 Variation of the preinstalled aromatic group in the Friedel-Crafts alkylation of 3-aryl-oxetan-3-ols and *ortho*-substituted phenols.

The capacity of electron rich heterocycles to stabilise the carbocationic intermediate was also explored for the reaction. Use of 2-methylfuran as the preinstalled aromatic component led to the synthesis of derivative **64** in 58% yield. Indole containing 3,3-diaryloxetanes **65a** and **65b** were synthesised from oxetanol **52** in 54% and 71% yields respectively. Interestingly, no dihydrobenzofuran was observed even when phenol was used as the nucleophile. This may be due to the increase in steric bulk precluding *ortho*-addition of the phenol to the carbocation intermediate for this example.

A select few *meta*-substituted phenols gave mixtures of 3,3-diaryloxetane and dihydrobenzofuran products with separation of the two regioisomers achieved through flash column chromatography (Table 3.11). The ratio of the two products was found to be dependent on the size of the *meta*-substituent as well as the presence of further substitution in the *ortho*-position. 3-Methylphenol gave dihydrobenzofuran **58k** as the major product in a 59% yield and diaryloxetane **57k** as the minor product in a 27% yield (Entry 1). The higher yield of dihydrobenzofuran **58k** shows the preference for addition *ortho* to the hydroxy group over addition next to the larger methyl group. Interestingly, this preference is reversed when a second methyl group is introduced at the 2-position of the nucleophile; a 2.5:1 ratio of diaryloxetane **57l**: dihydrobenzofuran **58l** was observed when using 2,3-dimethylphenol (Entry 2). This provides further confirmation that the presence of a single *ortho*-substituent drastically reduces the incidence of alkylation at the other available *ortho*-carbon. 3-Fluorophenol showed a slight preference for addition at the 4-position with diaryloxetane **57m** isolated in a

44% yield as the major product (Entry 3). Addition at both *ortho*-positions occurred due to the similar small size of F and H to give a mixture of the 4-F and 6-F dihydrobenzofuran products (**58m/m'**).

Table 3.11 Use of *meta*-substituted phenols in the Friedel–Crafts alkylation reaction to give mixtures of regioisomeric products. ^aIsolated as a mixture of 4-F and 6-F isomers.

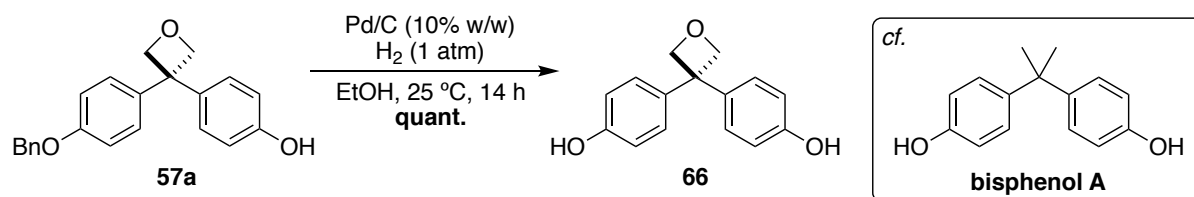
Entry	X	Y	Yield 57 (%)		Yield 58 (%)	
1	Me	H	57k	27	58k	59
2	Me	Me	57l	51	58l	20
3	F	H	57m	44	58m/m'	28 ^a

In conclusion, 20 different 3,3-diaryloxetanes were synthesised through a lithium-catalysed Friedel–Crafts alkylation reaction. The vast majority of the 3,3-diaryloxetane products were bench stable white solids that were stored exposed to air at room temperature for periods >6 months without degradation. A variety of substitution patterns were tolerated and interesting functional handles for further derivatisation could be readily incorporated. Furthermore, variation of the preinstalled aromatic substituent considerably widened the scope of the reaction and enabled access to 3,3-diaryloxetanes featuring heteroaromatic groups.

3.1.8 Further Functionalisation of Diaryloxetanes

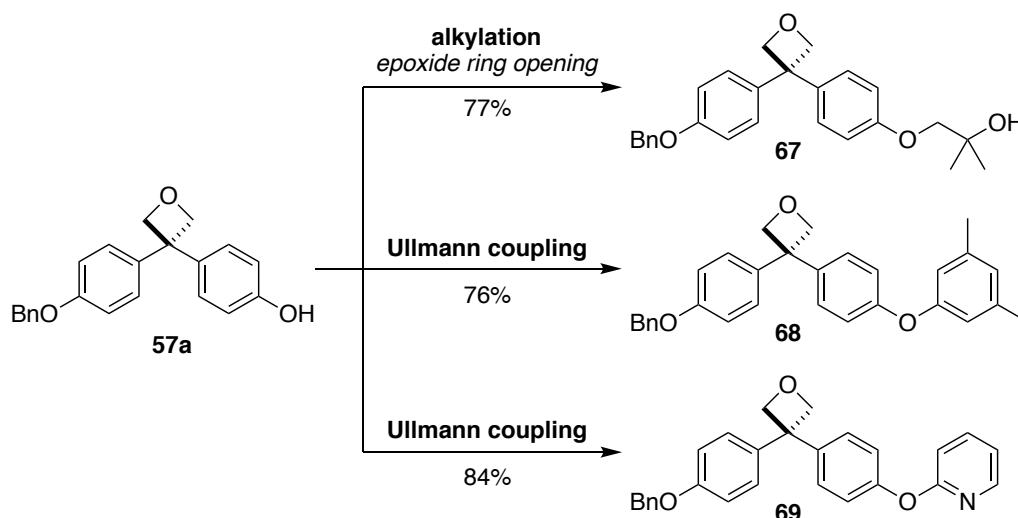
The reactivity and stability of the 3,3-diaryloxetane scaffolds to further derivatisation was investigated particularly towards reactions frequently used in the pharmaceutical industry. These investigations were imperative to establish 3,3-diaryloxetanes as stable, versatile and practical motifs for medicinal chemistry.

Benzyl deprotection of oxetane **57a** to reveal the phenol functional handle was achieved in quantitative yield using Pd/C under H₂ (Scheme 3.7). The product, oxetane **66**, is the oxetane derivative of bisphenol A and may have interesting alternative properties as a monomer for plastic production.



Scheme 3.7 Hydrogenolysis of 3,3-diaryloxetane **57a**.

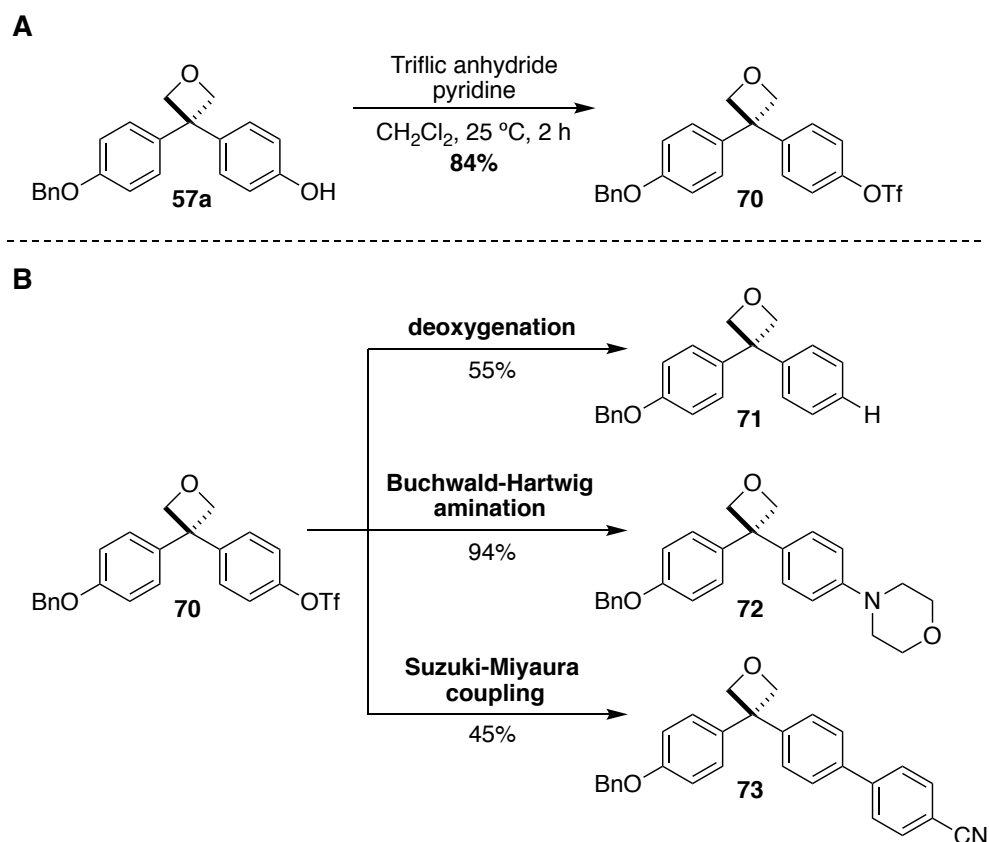
The diverse reactivity of the phenol functional handle was explored. The phenol motif could be functionalised directly through either alkylation or Ullmann cross-coupling reactions (Scheme 3.8). Base mediated ring opening of 1,1-dimethyloxirane gave alkylated oxetane **67** in 77% yield without any observed ring opening of the oxetane by the deprotonated phenol. Oxetane **57a** also successfully underwent copper catalysed Ullmann reactions using 5 mol% of CuI as the catalyst. Both 5-iodo-*m*-xylene and 2-iodopyridine were excellent coupling partners giving oxetanes **68** and **69** in 76% and 84% yields respectively. This demonstrated the considerable stability of the diaryloxetane motif to elevated temperatures (90 °C) and extended reaction times (up to 23 hours). Use of a lower 2 mol% catalyst loading in the reaction with 5-iodo-*m*-xylene resulted in a slightly reduced, 59% yield of oxetane **68**.



Scheme 3.8 Functionalisation directly from the phenol group of oxetane **57a**. Alkylation reaction conditions: 1,1-dimethyloxirane, K_2CO_3 , DMF, 100 °C, 16 h. Ullmann coupling conditions: 5-iodo-*m*-xylene, CuI (5 mol%), *N,N*-dimethylglycine·HCl (18.5 mol%), Cs_2CO_3 , dioxane, 90 °C, 20 h or 2-iodopyridine, CuI (5 mol%), picolinic acid (10 mol%), K_3PO_4 , DMSO, 90 °C, 23 h.

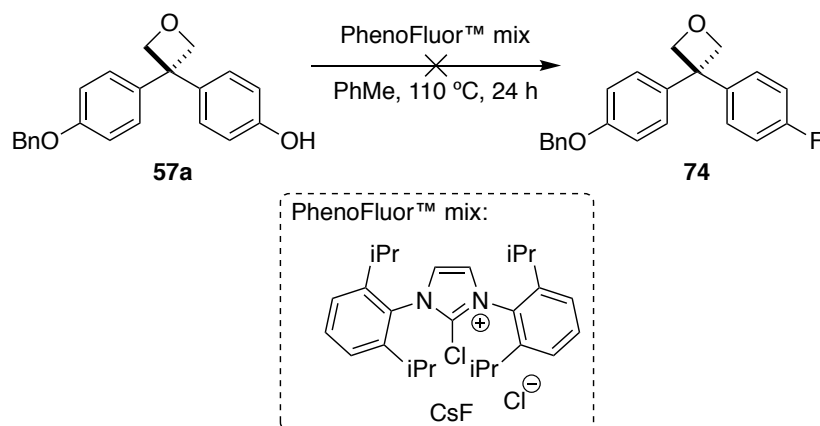
Triflate **70** was synthesised from oxetane **57a** using triflic anhydride and pyridine conditions and provided a useful intermediate for further reactions (Scheme 3.9). The phenol motif could be entirely removed through palladium catalysed deoxygenation to afford oxetane **71** using conditions developed by Ortár and co-workers.¹⁵⁵ Buchwald–Hartwig coupling of triflate **70**

with morpholine was achieved in an excellent 94% yield using just 1 mol% of palladium acetate in combination with Johnphos as the ligand. Additionally, Suzuki–Miyaura cross-coupling successfully delivered biaryl **73** using a combination of palladium acetate and SPhos.



Scheme 3.9 A) Triflation of oxetane **57a**. B) Derivatisation from triflate **70**. Buchwald-Hartwig conditions: morpholine, $\text{Pd}(\text{OAc})_2$ (1 mol%), JohnPhos (2 mol%), K_3PO_4 , THF, 65 °C, 24 h. Deoxygenation conditions: $\text{Pd}(\text{OAc})_2$ (2 mol%), 1,1'-ferrocenediyl-bis(diphenylphosphine) (dppf) (2 mol%), Et_3N , HCO_2H , DMF, 60 °C, 24 h. Suzuki-Miyaura conditions: 4-cyanoboronic acid, $\text{Pd}(\text{OAc})_2$ (5 mol%), SPhos (10 mol%), K_2CO_3 , THF, 65 °C, 18 h.

Ritter and co-workers developed a method to directly synthesise aryl fluorides from phenols using their, now commercialised, PhenoFluor™ mix.¹⁵⁶ Unfortunately, when oxetane **57a** was stirred at 110 °C in toluene with PhenoFluor™ mix, starting material was recovered quantitatively (Scheme 3.10).



Scheme 3.10 Attempted fluorination of oxetane **57a** to deliver oxetane **74** using PhenoFluor™ mix.

3.1.9 2,3-Dihydrobenzofurans as Desirable Scaffolds

The minor dihydrobenzofuran product, obtained in the reaction between oxetanols and phenols presented an interesting alternative diaryl-containing scaffold.¹⁵⁷ The 2,3-dihydrobenzofuran scaffold features in a multitude of bioactive natural products (for selected examples see Figure 3.11). Cedralin A, extracted from the leaves of *Cedrela sinensis* shows weak cytotoxic activity against human leukemia cell lines.¹⁵⁸ Sanggenon C, an ingredient in oriental medicine isolated from the root bark, *Mori Cortex Radicis*, displays some activity as an an inhibitor of the hypoxia-inducible-factor-1 (HIF-1), a key mediator of the body's hypoxic response.¹⁵⁹

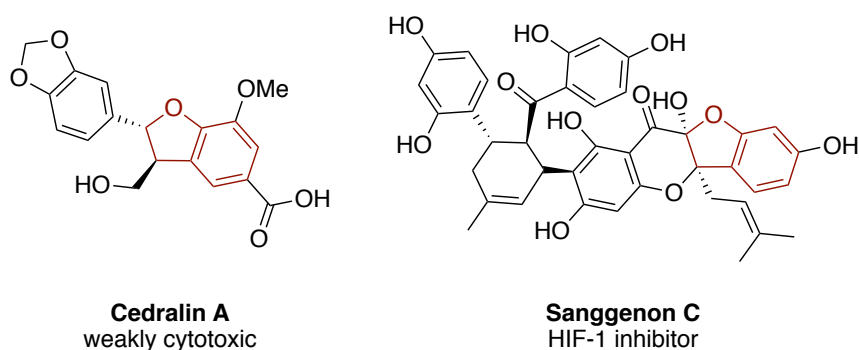


Figure 3.11 Selected examples of 2,3-dihydrobenzofuran-containing natural products with the dihydrobenzofuran motif highlighted in red.

Dihydrobenzofurans also feature in several bioactive synthetic compounds and marketed drugs (Figure 3.12). TAK-875, was developed by Takeda as a potent GPR40 agonist with an EC₅₀ of 0.014 μM and a high binding efficiency of 0.038 μM.¹⁶⁰ GPR40 is a G-protein coupled receptor involved in the regulation of glucose-stimulated insulin secretion and is expressed predominantly in the pancreas. As a result, agonists of GPR40 such as TAK-875 are attractive

as anti-diabetic drugs. TAK-875 was progressed into clinical trials but was withdrawn during stage III due to drug-induced liver injury.¹⁶¹ Dihydrobenzofuran-containing prucalopride (Resolor®) is a highly active serotonin 5-HT₄-receptor agonist, developed by Johnson & Johnson as a treatment for constipation.¹⁶² Another example, Efaroxan, is an established α_2 -adrenoreceptor antagonist.¹⁶³

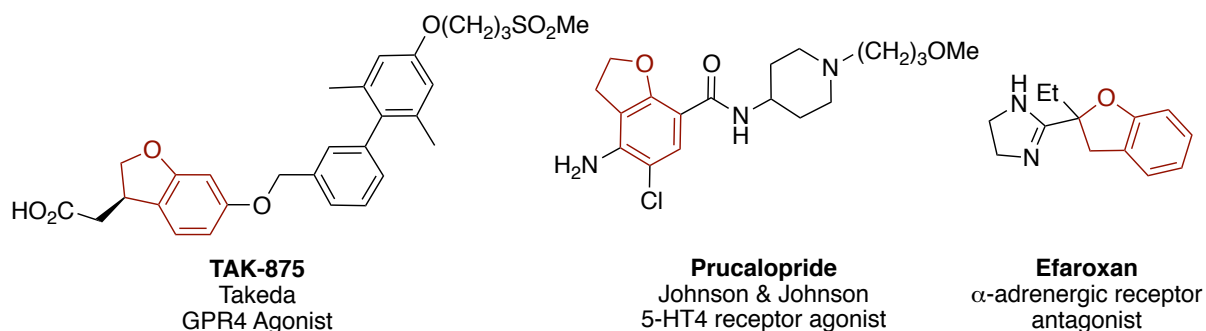
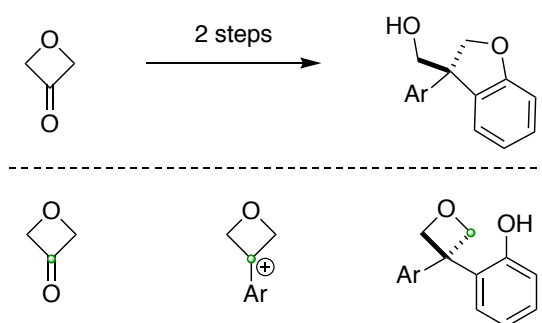


Figure 3.12 Selected examples of 2,3-dihydrobenzofurans in bioactive drugs and drug candidates with the dihydrobenzofuran motif highlighted in red.

Intramolecular ring opening of oxetanes has been established in recent years as a viable method for the synthesis of various heterocycles including dihydrobenzofurans (see Section 1.3.1). Jacobsen reported three examples of dihydrobenzofurans formed through the ring opening of phenol substituted oxetanes using a Co(III)-salen catalyst (Section 1.3.1, Scheme 1.16).¹²² In our method, the dihydrobenzofuran scaffold is formed in just two steps from commercially available oxetan-3-one (Scheme 3.11). Considerable complexity is introduced remarkably rapidly with the oxetane acting as a triple electrophile over the two steps.



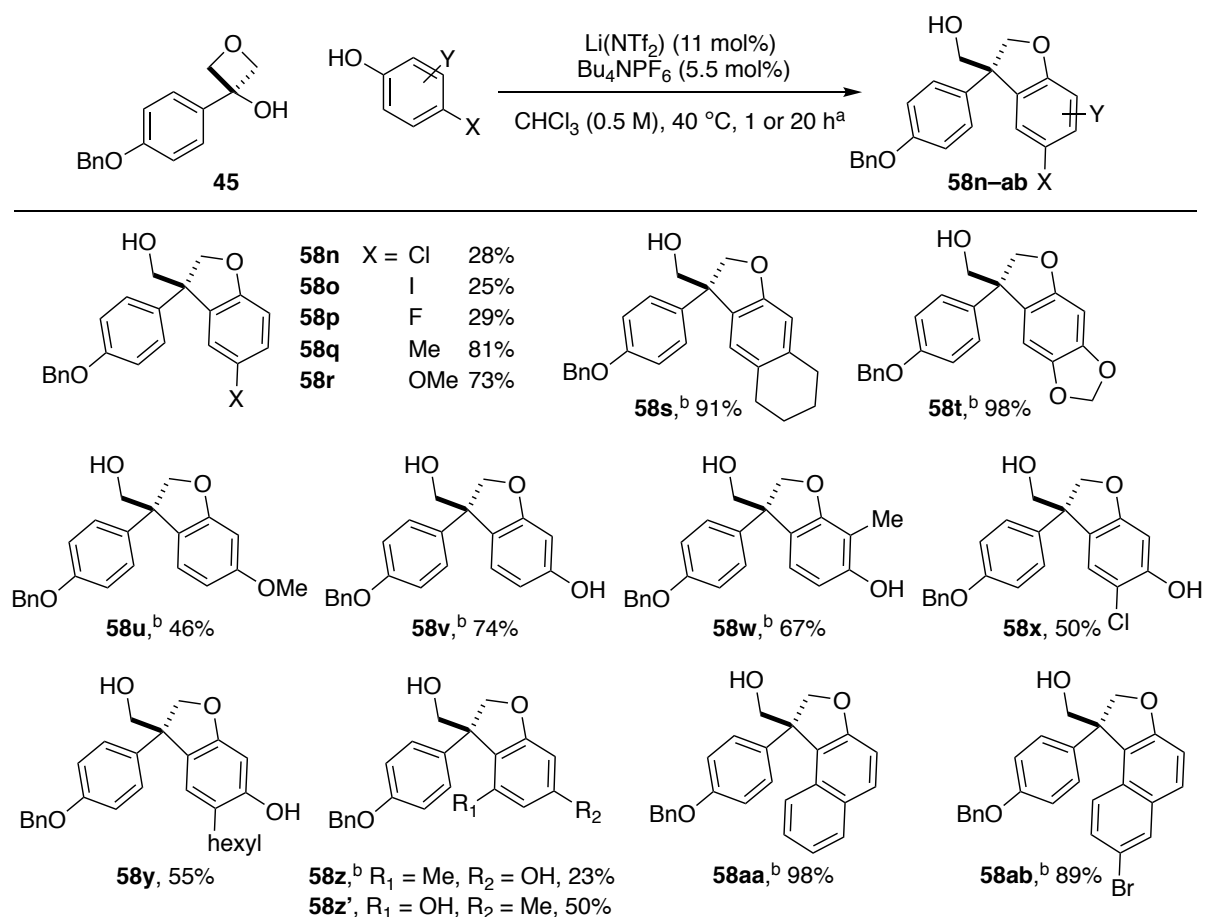
Scheme 3.11 Dihydrobenzofurans are formed in two steps from oxetan-3-one with the three different oxetanyl electrophiles involved the formation of the dihydrobenzofuran motif shown. The electrophilic site that is attacked is indicated by the green spot.

3.1.10 Scope of Dihydrobenzofurans

Due to the interest in dihydrobenzofurans as attractive modules for drug discovery, a number of dihydrobenzofurans were prepared under the same optimised Friedel–Crafts conditions. It was envisaged that *ortho*-selective alkylation to give exclusively the dihydrobenzofuran products could be achieved using *para*-substituted phenols.

Indeed, dihydrobenzofurans **58n–ab** were synthesised as the sole product through the lithium-catalysed Friedel–Crafts reaction of oxetanol **45** with a variety of *para* and *meta*-substituted phenols, resorcinols and 2-naphthols (Scheme 3.12). In no example was any of the proposed *ortho*-phenol substituted oxetane intermediate observed, indicating remarkably rapid intramolecular cyclisation to the dihydrobenzofuran under the optimised conditions. It is also noted that an extended reaction time of 20 hours was required in the majority of cases for the reaction to reach completion. This observation and the reasons for it are discussed in further detail in Section 3.1.11.

Purification of the products by flash column chromatography proved significantly easier on removal of the excess nucleophile following the reaction. Therefore, a basic wash was introduced during the aqueous work-up stage. Aqueous sodium hydroxide (1 M) proved a suitable base enabling selective deprotonation of the remaining phenol starting material without affecting the primary alcohol in the product.

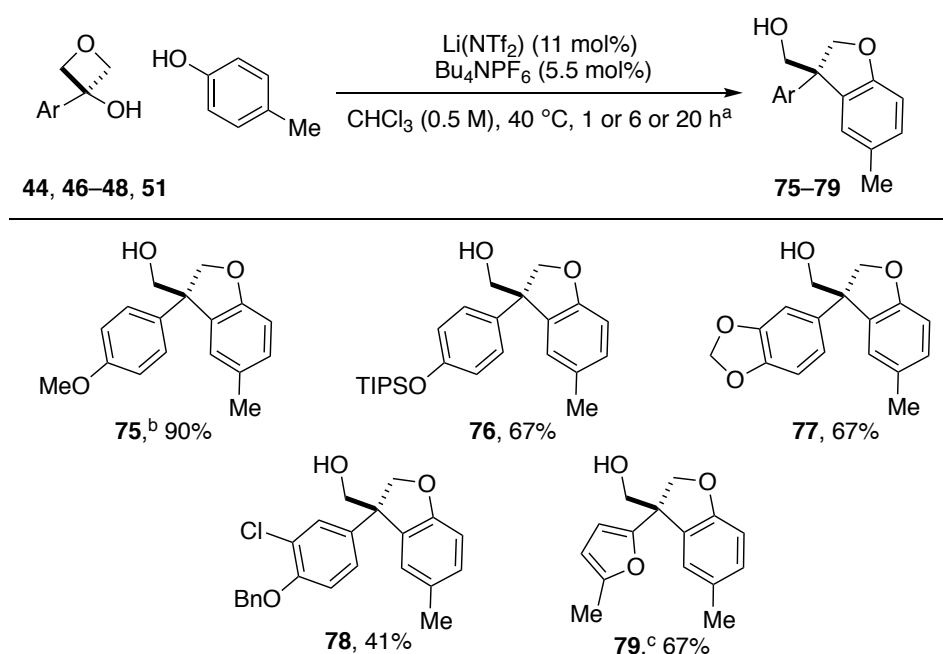


Scheme 3.12 Scope of dihydrobenzofurans using *para*- and *meta*-substituted phenols, resorcinols and naphthols. ^aReaction time 20 h unless otherwise stated. ^bReaction time of 1 h.

Under the optimised conditions, electron rich *para*-methoxyphenol and *para*-methylphenol, gave good yields of the corresponding dihydrobenzofuran products (**58q** and **58r**). Phenols substituted with halides were still successful nucleophiles for the reaction although yields of the dihydrobenzofuran products **58n–p** were much reduced (25–29%). Sesamol and 5,6,7,8-tetrahydro-2-naphthol, substituted at both the *para*- and *meta*-positions, gave the dihydrobenzofuran products **58t** and **58u** in yields >91% as single regioisomers after just 1 hour. When 3-methoxyphenol was employed as the nucleophile dihydrobenzofuran **58u** was synthesised with complete regioselectivity, with the difference in steric bulk between the methoxy and hydroxy groups proving sufficient to prevent addition at the *para*-position of the phenol. Resorcinols reacted under the optimised reaction conditions to deliver dihydrobenzofurans **58v–z** in yields between 50% and 74%. 5-Methylresorcinol gave the two regioisomeric products **58z** and **58z'** in a combined yield of 73%. The steric difference between hydroxy and methyl was evidently not sufficient for complete regioselectivity in this case. 2-Naphthol was an excellent nucleophile for this reaction with derivative **58aa** synthesised in almost quantitative yield. Bromo-substitution at the 6-position of naphthol was tolerated with

derivative **58ab** synthesised in only a slight reduced yield of 89%. Although not explored in this work, it can be anticipated that the bromide handle would be valuable for further functionalisation.

In a similar manner to the 3,3-diaryloxetane derivatives, further examples could be prepared by variation of the preinstalled aromatic component. Oxetanols **44**, **46–48** and **51** reacted with *para*-methylphenol under the optimised conditions to give dihydrobenzofuran derivatives **75–78** in good yields (Scheme 3.13). Furan-substituted oxetanol **51** reacted to give derivative **79** after just 1 hour. Over a longer reaction time of 20 hours, significant hydrolysis of the furan occurred to give the ring opened dicarbonyl derivative.



Scheme 3.13 Scope of dihydrobenzofurans using oxetanols substituted with different aromatic groups.

^aReaction time 20 h unless otherwise stated. ^bReaction time of 6 h. ^cReaction time of 1 h.

Not all nucleophiles were successful. 6-Quinolinol gave no desired product with quantitative starting material recovered. This is likely due to strong coordination of the nitrogen to the lithium catalyst preventing the required activation of the tertiary hydroxy group.

3.1.11 Mechanistic Insights

Whilst exploring the scope of *para*-substituted phenols, it was found that reaction of oxetanol **45** with 4-cyanophenol gave oxetane ether **80ac** resulting from nucleophilic attack through the oxygen atom of the phenol (Scheme 3.14). The O-alkylated product was the only observed product after both 1 hour and 20 hours indicating that C-alkylation to give the dihydrobenzofuran product is prohibited for this electron poor phenol.

In the literature, O-alkylated products in Friedel–Crafts alkylation reactions with phenols are little reported.¹⁶⁴ However, separate studies by Poliakoff and Adam investigated the effects of reaction time and temperature on the extent of ether formation.¹⁶⁵ Poliakoff studied the reaction between phenol and isopropanol and found that higher temperatures favoured C-alkylation over O-alkylation.^{165a} In 2011, Adam corroborated this trend and additionally found that longer reaction times also led to greater selectivity for C-alkylation.^{165b} However, prior to this work, the effect of the electronic nature of the phenol nucleophile on ether formation was unexplored.

The relationship between oxetane ether formation and the electronic nature of the nucleophile was probed by examination of the products from the reaction of oxetanol **45** with different *para*-substituted phenols at 1 hour and 20 hour time points (Figure 3.13). Interesting differences in product distribution were observed after 1 hour and 20 hour reaction times and with changes to the electronic nature of the nucleophile. It was noted that for each reaction, even after just 1 hour only a trace amount of starting material was observed by ¹H NMR spectroscopy of the crude reaction mixture.

First electron-withdrawing and neutral *para*-substituents on the phenol nucleophile were investigated. After 1 hour, O-alkylation predominated for halide substituted phenols (4-Cl, 4-I, 4-F) with oxetane ethers **80n–p** isolated as the major product alongside small amounts of dihydrobenzofurans **58n–p** resulting from C-alkylation and subsequent intramolecular ring opening. However, after 20 hours the exclusive product was the dihydrobenzofuran revealing that the formation of the oxetane ether is reversible. From these reactions, it was concluded that the oxetane ether is formed rapidly and reversibly as the kinetic product with a lower energy barrier for formation compared to thermodynamically preferred dihydrobenzofuran.

Phenols substituted at the *para*-position with either an OMe or Me group displayed increased reactivity for C-alkylation compared to phenols substituted with halogens or CN. The major product observed in the reaction between oxetanol **45** and 4-methylphenol or

4-methoxyphenol after 1 hour was the dihydrobenzofuran product with the oxetane ether product observed in <11% yield. A third product, identified as dimer **81**, was also observed in substantial amounts (up to 38%) at the 1 hour time point and is derived from addition of the primary alcohol of dihydrobenzofuran **58** to the putative oxetanyl carbocation intermediate. The prevalence of products featuring the dihydrobenzofuran motif after just 1 hour indicates that the energy barrier for dihydrobenzofuran formation is lower for more electron rich phenols compared to phenols substituted with electron neutral or electron poor groups. After 20 hours, dihydrobenzofuran **58** was again the single product indicating that formation of dimer **81** is also reversible to some extent.

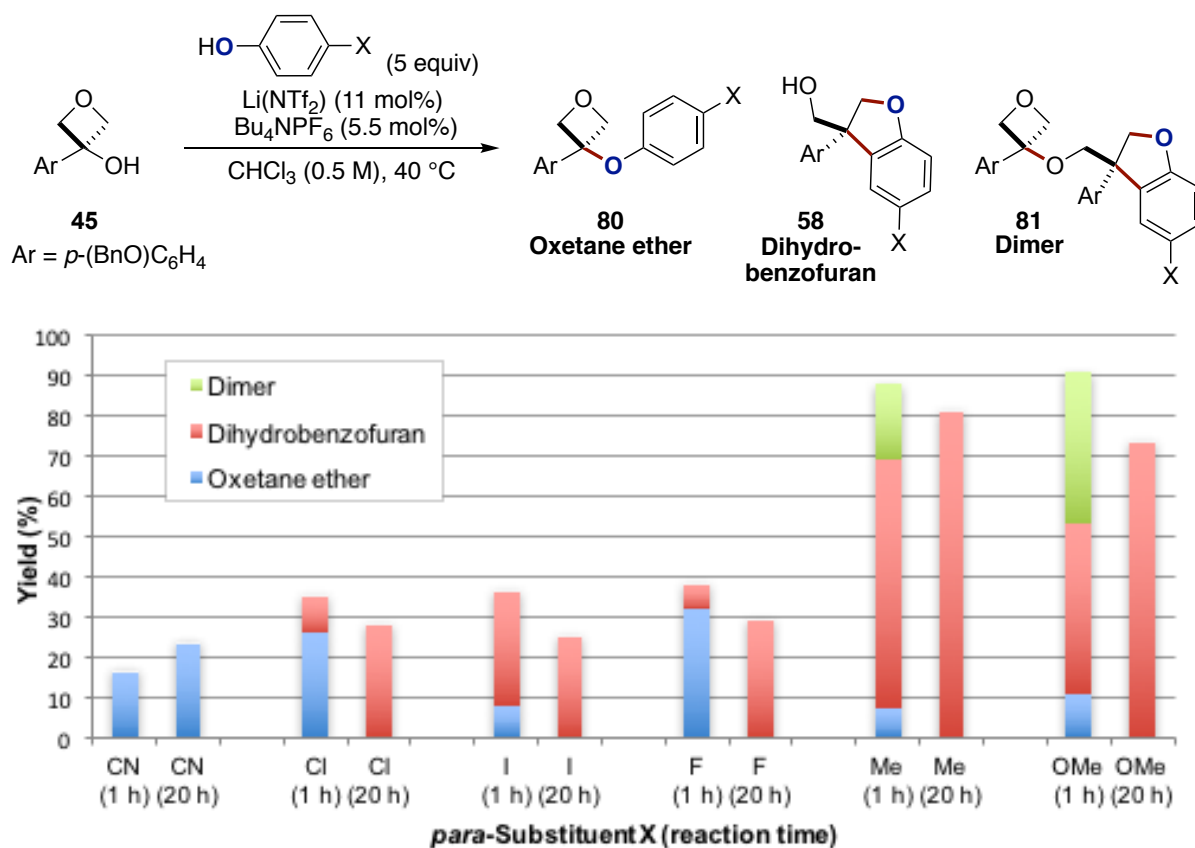


Figure 3.13 Product distribution (isolated yields) in the reaction between oxetanol **45** and different *para*-substituted phenols after 1 h and 20 h. New bonds formed are highlighted in red and the oxygen of the phenol is highlighted in blue for clarity.

Several reactions between oxetanol **45** and selected *para*-substituted phenols with different electronic properties were examined in greater detail by monitoring the progress of the reaction using *in situ* ¹H NMR spectroscopy. The primary aims of this study were the identification of reaction intermediates and to gain further insight into the reaction mechanism. The experiments were conducted in NMR tubes and spectra were generated every 30 seconds for the first hour and then every 5 minutes thereafter. These time gaps were

chosen to generate the maximum amount of information, particularly during the early stages in the reaction when rapid change was expected, within the confines of what was practically possible and whilst keeping the number of spectra requiring analysis to a manageable number.

A known amount of an internal standard in the reaction allowed calculation of *in situ* NMR yields of the starting material and products. Use of these values enabled the generation of reaction profiles showing the formation and depletion of different species in the reaction over time. Mesitylene was selected as the internal standard as a test reaction between oxetanol **45** and phenol showed that mesitylene did not affect the reaction outcome. Furthermore, the signal at 2.26 ppm correlating to the three CH₃ peaks in mesitylene was significantly different to the peaks for the substances being examined. The Ar-H peak at 6.78 ppm could not be used to calculate *in situ* yields as significant deuterium exchange was observed during the course of the reaction.

A solubility difference was observed between reactions conducted in NMR tubes and the same reactions carried out in round bottomed flasks. Upon addition of the catalyst to the reaction mixture, a cloudy white suspension was observed. When the reaction was conducted in NMR tubes solubilisation occurred almost instantaneously to give a clear solution whereas in round bottomed flasks there was a delay of up to 20 minutes for this change. This may be attributed to extra moisture and greater surface to volume ratio associated with the NMR tubes facilitating solubilisation of the catalyst. Ultimately, it meant that reactions proceeded more rapidly in NMR tubes during the early stages of the reactions and this was a consideration when deciding on reaction times for scaled up reactions in round bottomed flasks.

The reaction between oxetanol **45** and 4-fluorophenol was investigated and a reaction profile was generated (Figure 3.14). It was revealed by this experiment that a maximum yield of 64% for oxetane ether **80p** was achieved after just 4 minutes indicating rapid generation of the oxetanyl carbocationic intermediate under the reaction conditions. The quantity of oxetane ether **80p** then decreased until the reaction reached completion. Throughout the reaction, the amount of dihydrobenzofuran **58p** in the reaction mixture increased reaching a plateau at 18 hours where the dihydrobenzofuran was the sole product.

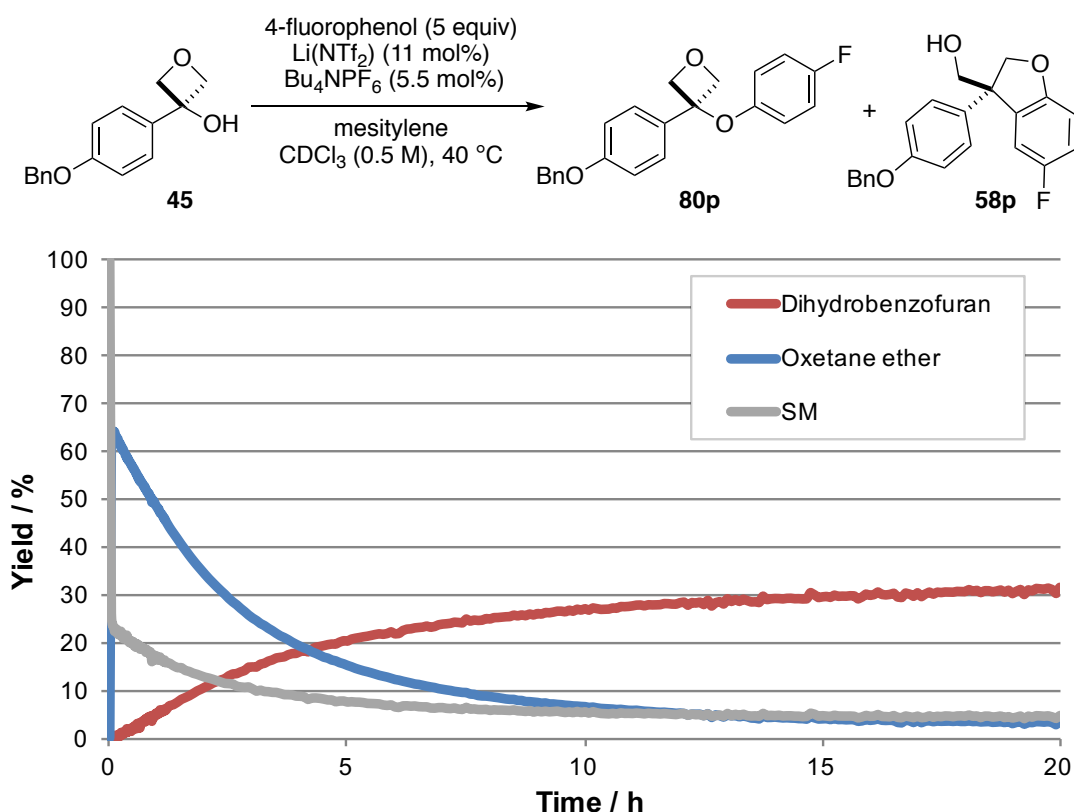


Figure 3.14 Reaction profile for the reaction between oxetanol **45** and 4-fluorophenol.

Similarly, ^1H NMR experiments enabled a reaction profile to be produced for the reaction of oxetanol **45** with 4-methoxyphenol (Figure 3.15). In this case overlap of the starting material peaks with other peaks correlating to reaction species of interest in the ^1H NMR spectra meant that reliable yields could not be calculated for oxetanol **45**. Fortunately, oxetane ether **80r**, dihydrobenzofuran **58r** and dimer **81r** all had sufficiently distinct peaks for the calculation of *in situ* NMR yields and so quantitative information about their formation and disappearance could be determined.

The maximum yield of oxetane ether **80r** (43%) was reached rapidly after only 11 minutes. Subsequently, the amount of oxetane ether **80r** decreased until reaction completion. Likewise, the other O-alkylated product, dimer **81r**, showed a similar pattern, reaching a maximum yield of 29% after 2 hours and then decreasing steadily for the remainder of the reaction. The amount of dihydrobenzofuran **58r** continually increased up to a final yield of 77%. This study presents compelling evidence for the reversible formation of the O-alkylated intermediates to regenerate the oxetanyl carbocationic intermediate. After 11 minutes, the product distribution was 43% oxetane ether **80r**, 10% dihydrobenzofuran **58r** and 6% dimer **81r** (41% unassigned). Even without the yields for starting material which would account for some of the unassigned mass, it is clear that significant amounts of the O-alkylated products are converting to dihydrobenzofuran **58r** in order to achieve the observed 77% yield.

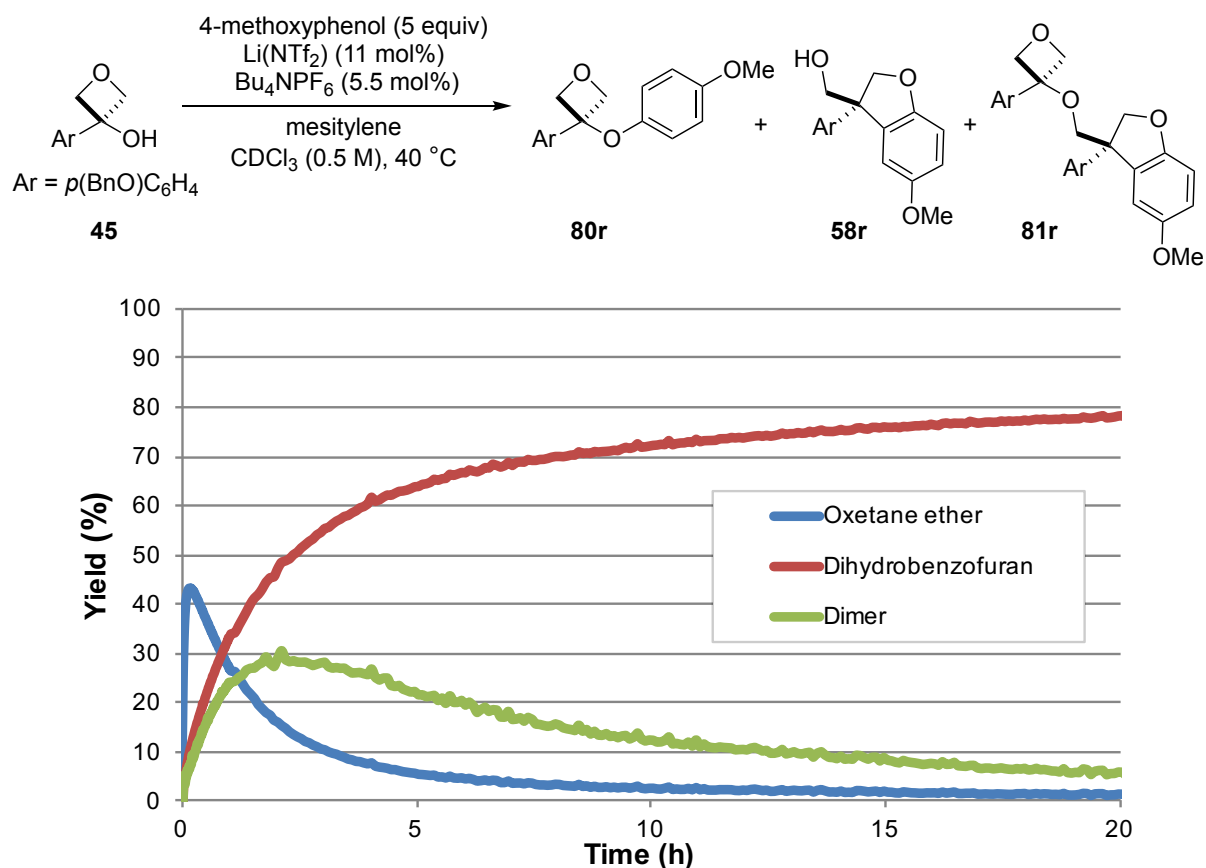
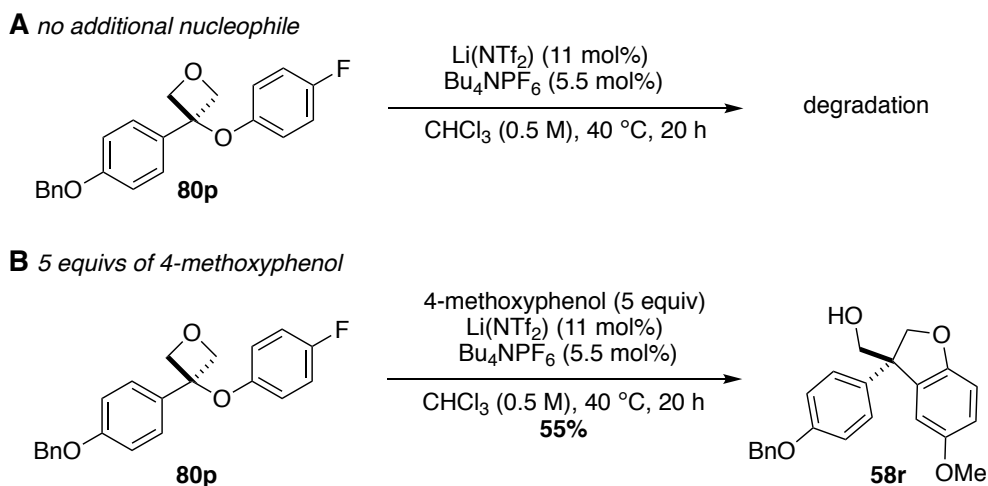


Figure 3.15 Reaction profile for the reaction between oxetanol **45** and 4-methoxyphenol.

To provide further evidence for the reversibility of oxetane ether formation to regenerate the oxetanyl carbocation and proceed to the Friedel–Crafts products, oxetane ether **80p** was resubmitted to the reaction conditions without added nucleophile (Scheme 3.15A) and also in the presence of 5 equivalents of 4-methoxyphenol (Scheme 3.15B). When no nucleophile was added, quantitative degradation occurred over the 20 hour reaction time. However, when the reaction was conducted in the presence of 4-methoxyphenol, dihydrobenzofuran **58r** was isolated in a 55% yield after 20 hours. This provides strong evidence for the regeneration of the oxetanyl carbocation intermediate from oxetane ethers under the lithium catalysed reaction conditions.



Scheme 3.15 Reaction of oxetane ether **80p** under the reaction conditions with no additional nucleophile (A) and in the presence of 5 equivalents of 4-methoxyphenol (B).

Next, the reaction between oxetanol **45** and phenol was studied using *in situ* ^1H NMR spectroscopy (Figure 3.16). The O-alkylated oxetane ether product **80a** formed rapidly and reversibly as the kinetic product reaching a maximum yield of 42% after just 6 minutes and then decreasing throughout the remainder of the reaction. The amounts of C-alkylated products (**58a** and **57a**) increased throughout the reaction as the thermodynamically preferred products eventually reaching a combined yield of 79% after 2 hours. It was hoped that monitoring by NMR spectroscopy might allow identification of the expected *ortho*-alkylated phenol intermediate. However, peaks potentially correlating to this intermediate were not observed in the ^1H NMR spectra indicating that, if formed, this species reacts rapidly. The 3:1 ratio of **57a**:**58a** that was maintained throughout the reaction is consistent with this intermediate being formed prior to ring opening.

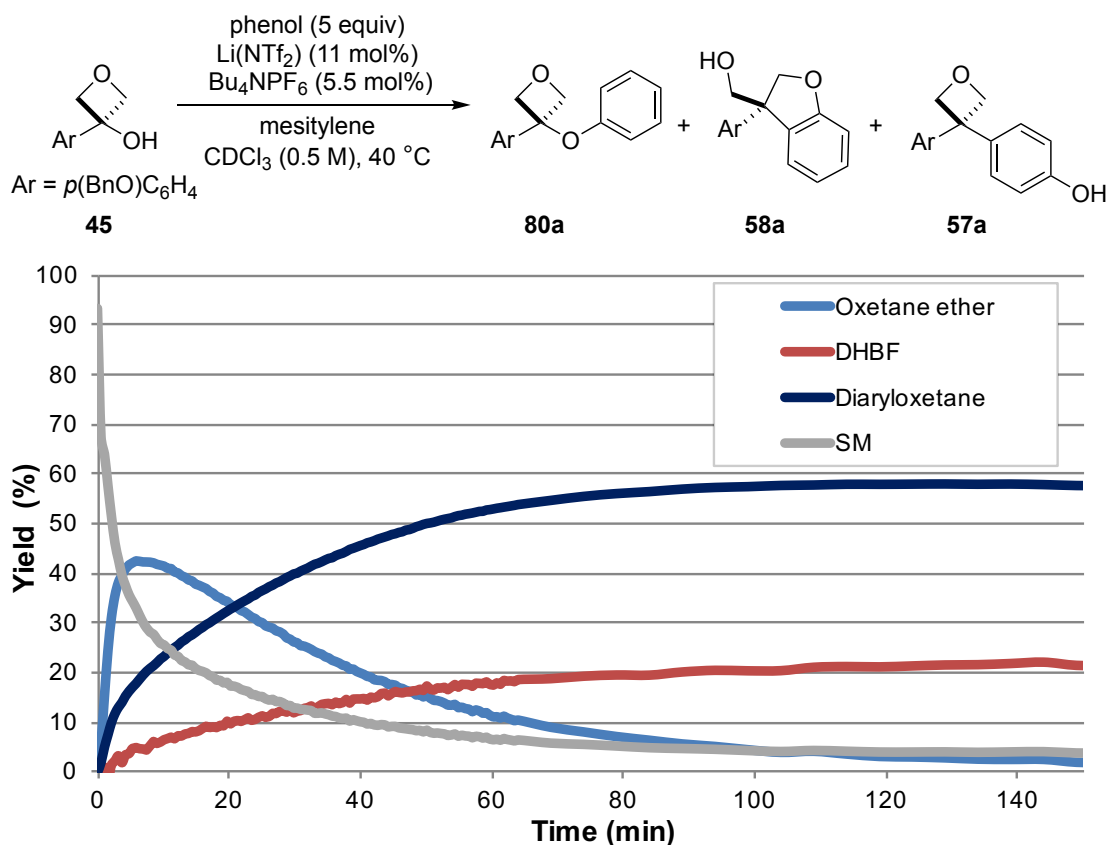
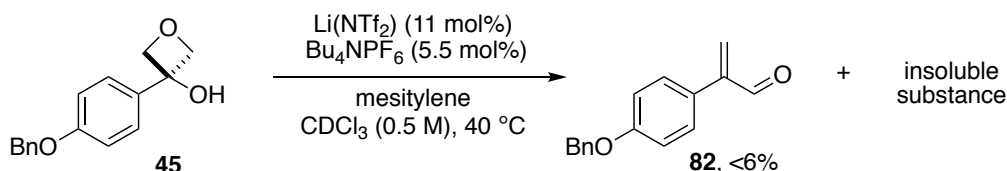


Figure 3.16 Reaction profile for the reaction between oxetanol **45** and phenol.

The reaction between *ortho*-methylphenol and oxetanol **45** was also explored through *in situ* ¹H NMR spectroscopy. Overlap of peaks in the ¹H NMR spectra meant quantitative data and generation of a meaningful reaction profile was not possible. Regardless, some interesting qualitative observations were still made. No intermediates resulting from O-alkylation were observed in the reaction with only formation of the diaryloxetane product observed. The increased steric bulk of the *ortho*-methyl group may prevent O-alkylation of the oxetanyl carbocation for this nucleophile. This may provide an explanation for the lower yields observed in general for the 3,3-diaryloxetanes (Section 3.1.7) compared to the dihydrobenzofurans (Section 3.1.10). For the dihydrobenzofurans, O-alkylation provides stable intermediates in equilibrium with the oxetanyl carbocation, leading to higher product yields. When *ortho*-substituted phenols are employed for the selective synthesis of 3,3-diaryloxetanes, this off-cycle equilibrium is not possible and so the oxetanyl carbocation intermediate is more susceptible to degradation.

In order to investigate possible degradation pathways for the Friedel–Crafts reaction, the reaction of oxetanol **45** under the optimised reaction conditions without nucleophile present was examined using ¹H NMR spectroscopy. In the absence of nucleophile, rapid degradation of the starting material was observed. The majority of the mass was unaccounted for with an

aldehyde side-product (**82**) that was formed in <6% yield, the only identifiable product from the reaction (Scheme 3.16). A dark coloured insoluble substance was observed in the reaction vial, possibly indicating formation of a polymeric species. Ring opening of the oxetane by a second oxetane monomer is feasible under the acidic reaction conditions in the absence of a better nucleophile than the starting oxetanol.



Scheme 3.16 Reaction of oxetanol **45** in the absence of nucleophile.

The learnings from these investigations enabled a putative catalytic cycle to be proposed (Figure 3.17). Activation of the catalyst, possibly through solubilisation of the lithium catalyst aided by the hexafluorophosphate additive occurs. The exact nature of this active catalyst species remains unknown although it is possible that it could be either a solubilised lithium cation or some form of lithium aggregate. When $\text{Ca}(\text{NTf}_2)_2$ is used as the catalyst, activation with the ammonium salt additive occurs through an anion metathesis step to give the more Lewis acidic $\text{Ca}(\text{NTf}_2)(\text{PF}_6)$ complex.¹⁶⁶

The active lithium catalyst coordinates to the tertiary alcohol group, activating it towards the formation of the key oxetanyl carbocation intermediate. Competing O- and C-alkylation then occurs to give either oxetane ether **80** or diaryloxetane species **57** or **83**. O-Alkylation is reversible leading to regeneration of the oxetanyl carbocation which can then react again. Alkylation through the *para*-carbon of the phenol and rearomatisation gives 3,3-diaryloxetane product **57**. Alternatively, C-alkylation at the *ortho*-position of the phenol ultimately gives dihydrobenzofuran **58** following rearomatisation to give **83**, coordination of the catalyst to the oxetane oxygen and intramolecular ring opening by the proximal hydroxy group. Dihydrobenzofuran **58** can react further through the primary alcohol adding to a second equivalent of the oxetanyl carbocation to give dimer **81**. However, this process also appears to be reversible under the reaction conditions to deliver the oxetanyl carbocation which can then proceed to the thermodynamically preferred products.

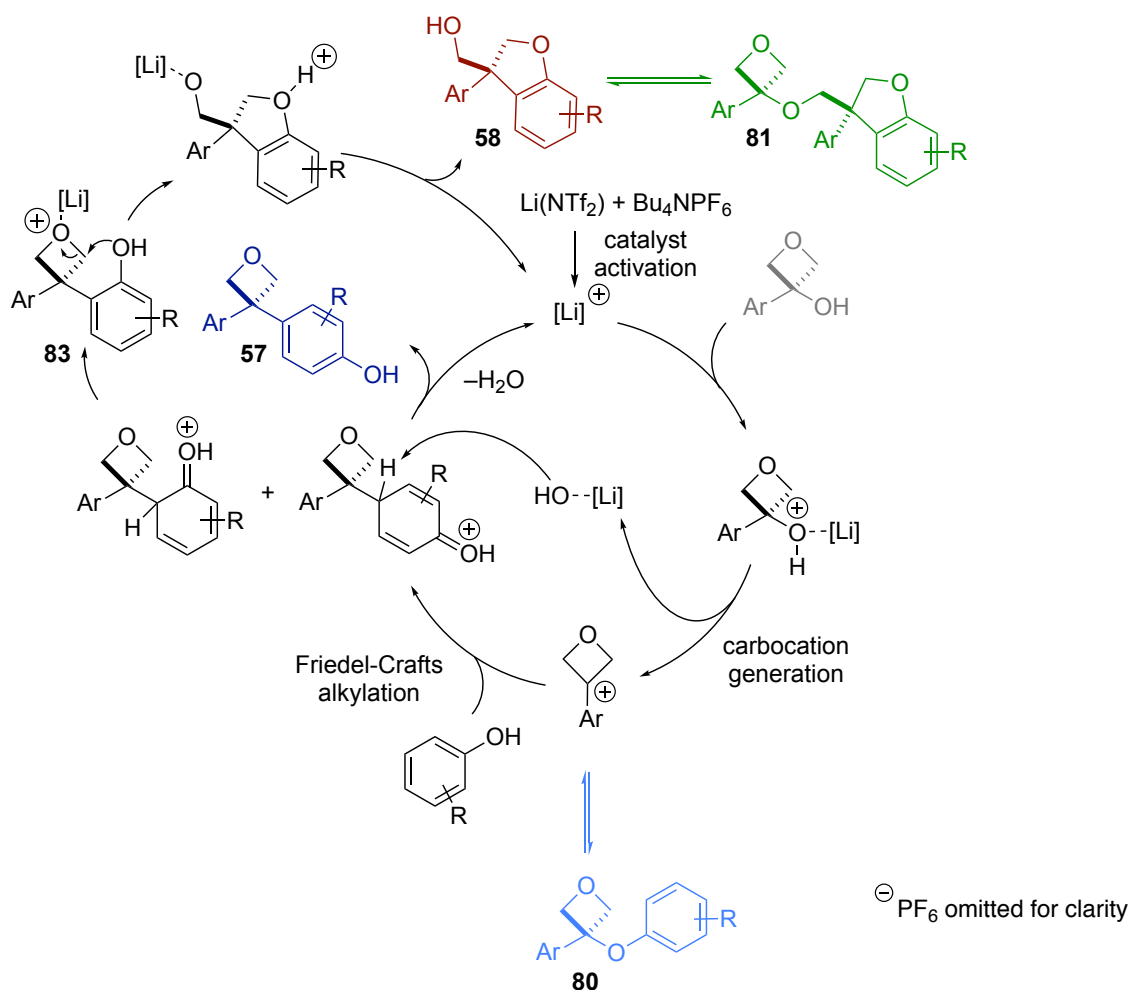


Figure 3.17 Proposed catalytic cycle for the Friedel–Crafts reaction of oxetanols with phenols.

3.1.12 Synthesis of Oxetane Ethers under Optimal Conditions

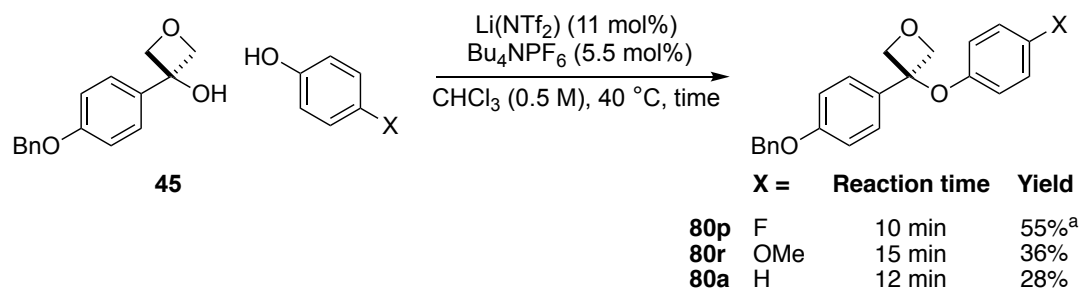
The oxetane ether products were considered interesting as potential bioisosteres for ester groups with the oxetane motif replacing the the carbonyl group (Figure 3.18). For this reason, several examples of the oxetane ethers were isolated.



Figure 3.18 Oxetane ethers as proposed bioisosteres for esters.

Optimal reaction times were selected based on when the peak yield was observed during the *in situ* ^1H NMR studies. The reactions were carried out in NMR tubes on a 0.25 mmol scale. Fluoro-substituted oxetane ether **80p** was isolated in a 55% yield after 10 minutes (*cf.* maximum yield of 64% by ^1H NMR). This reaction was repeated on a larger 1.6 mmol in a round bottomed flask. In this case, the slower solubilisation of the catalyst with this set up

meant an increased reaction time of 20 minutes was required to achieve a similar yield. Oxetane ethers **80r** and **80a** were isolated in 28% and 36% yields respectively, comparing well the the maximum possible yield as determined by the *in situ* ^1H NMR experiments (~43%).



Scheme 3.17 Synthesis of oxetane ethers **80p,r** and **a**. Reactions carried out on a 0.25 mmol scale in NMR tubes. ^a50% yield achieved on a 1.6 mmol scale, conducted in a round bottomed flask with a 20 minute reaction time.

3.1.13 Conclusions

The synthesis of novel 3,3-diaryloxetanes and 2,3-dihydrobenzofurans has been achieved through a divergent lithium-catalysed Friedel–Crafts alkylation reaction (Figure 3.19). This study showed that oxetanyl carbocations can be formed and are sufficiently stable *in situ* to be useful reaction intermediates. Oxetanols serve as excellent precursors for the generation of oxetanyl carbocations which can then react with phenols to deliver the desired diaryl scaffolds. Where *para*-addition of the phenol nucleophile occurs, 3,3-diaryloxetanes result. Conversely, addition at the *ortho*-position leads to 2,3-dihydrobenzofurans following *in situ* ring opening by the proximal hydroxy group. Complete regioselectivity for each class of products has been realised through careful choice of substitution on the phenol ring. In the few examples where mixtures of products were obtained, the two products were entirely separable by flash column chromatography.

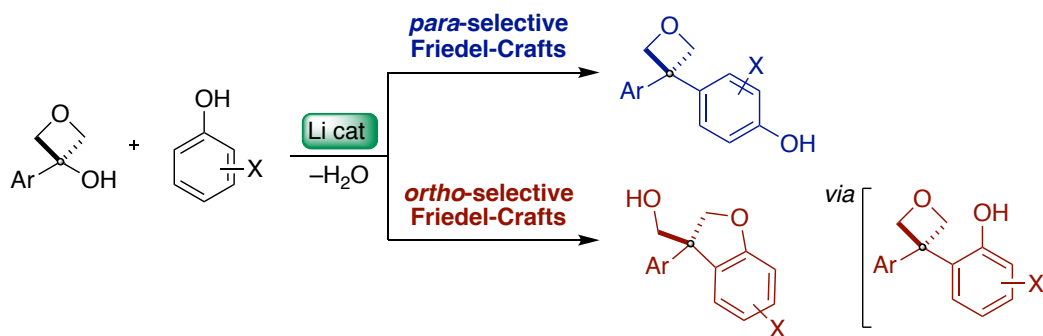


Figure 3.19 Divergent Friedel–Crafts alkylation between oxetanols and phenols to give 3,3-diaryloxetanes or dihydrobenzofurans.

Pleasingly, the optimal lithium catalyst activated the tertiary hydroxy group without detrimental coordination to other oxygen containing species in the reaction mixture. Particularly of concern at the beginning of this research was the potential for coordination of the acid catalyst to initiate oxetane ring opening or polymerisation but this did not made a significant contribution to the observed reactivity.

3,3-Diaryloxetanes, designed as bioisosteric replacement groups for diarylmethanes and benzophenones, were synthesised with excellent selectivity using *ortho*-phenols and related derivatives. Scope of the reaction was good although restricted to electron rich coupling partners. Furthermore, several classes of nucleophiles, particularly nitrogen-containing nucleophiles, were unsuccessful so future work looked to examine other methods for their incorporation. The 3,3-diaryloxetane scaffolds showed excellent stability and desired reactivity towards a wide variety of synthetically useful transformations including functionalisation directly on the phenol handle and also through further reaction of the easily prepared triflate derivative.

Use of *para*-substituted phenols and resorcinols enabled rapid and high yielding synthesis of 2,3-dihydrobenzofuran scaffolds, attractive for medicinal chemistry applications. Under the same lithium-catalysed conditions as used for the 3,3-diaryloxetanes, >20 examples of 2,3-dihydrobenzofurans were synthesised.

Investigations into the reaction mechanism using ^1H NMR spectroscopy to monitor the reaction *in situ* enabled the generation of quantitative reaction profiles and elucidated interesting *O*-alkylated reaction intermediates. An interesting relationship between the electronic nature of the nucleophile and the extent of *O*-alkylation vs *C*-alkylation over the reaction time was revealed. The presence of *O*-alkylation through the primary alcohol of the dihydrobenzofuran to form dimer **81**, indicated that aliphatic alcohols may be suitable nucleophiles and this is the subject of current studies within the Bull group.

The next chapter of this thesis will describe the use of sulfur nucleophiles for the *S*-alkylation of oxetanols.

3.2 3-Oxetane Sulfides, Sulfoxides and Sulfones

A concise account of this work has been published in *Chemistry A European Journal*.¹⁶⁷

3.2.1 Oxetane Sulfides as Desirable Targets in Medicinal Chemistry

Organosulfur compounds have widespread medicinal chemistry applications including as anti-cancer drugs, anti-inflammatories and anti-bacterials.^{168,169} Benzylic sulfides, sulfoxides and sulfones feature in numerous examples of marketed pharmaceuticals including AstraZeneca's blockbuster drug Nexium, a proton pump inhibitor useful for the treatment of gastroesophageal reflux related diseases, and Diltiazem, a calcium channel blocker used to treat heart disease (Figure 3.20).¹⁷⁰

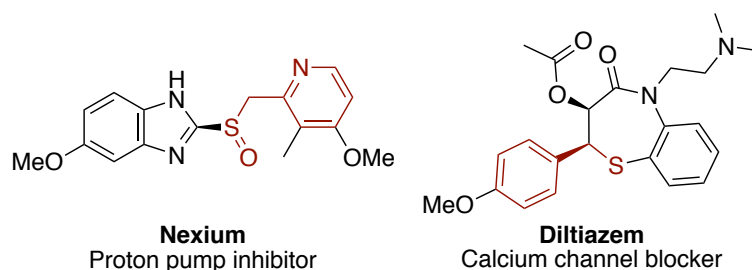


Figure 3.20 Examples of benzylic sulfur compounds in marketed drugs.

Thioester containing bioactive compounds have also been reported but only account for 2% of all sulfur containing pharmaceuticals.^{171,169} Thioesters are often employed as part of pro-drugs due to the high reactivity of the thioester motif towards nucleophilic attack. An example is Zofenopril which undergoes rapid biotransformation in the body to give the active metabolite, Zofenoprilat (Figure 3.21).¹⁷² Prior to the research outlined in this chapter, there were no suitable known bioisosteres for thioesters, limiting the available options for medicinal chemists.

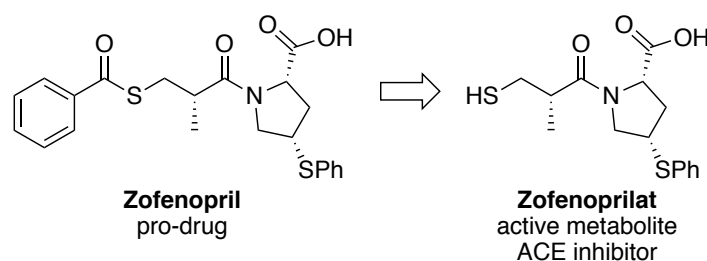


Figure 3.21 Example of a thioester containing pro-drug.

Oxetane-3-sulfide derivatives were considered as intriguing bioisosteres for thioesters and benzylic sulfides (Figure 3.22). The oxetane scaffold would retain certain characteristics of

thioesters, such as lone pair position and dipole, without presenting a highly reactive electrophilic center. Additionally, use of the oxetane motif to block the methylene site of benzylic sulfides, sulfoxides and sulfones may be beneficial for metabolic stability and provide valuable synthetic options for the exploration of new chemical space.

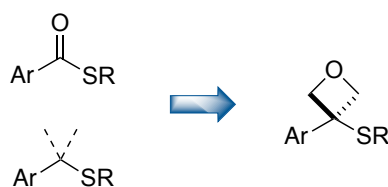


Figure 3.22 3-Sulfanyloxetanes as a potential bioisostere for thioesters and benzylic sulfides.

Computational analysis conducted at Pfizer investigated important selected properties of thioester **84** and oxetane **85a**.¹⁷³ DFT studies indicated that although the C–O bond distance for oxetane **85a** was calculated to be 0.8 Å longer, the electrostatic mapping corresponded well (Figure 3.23).

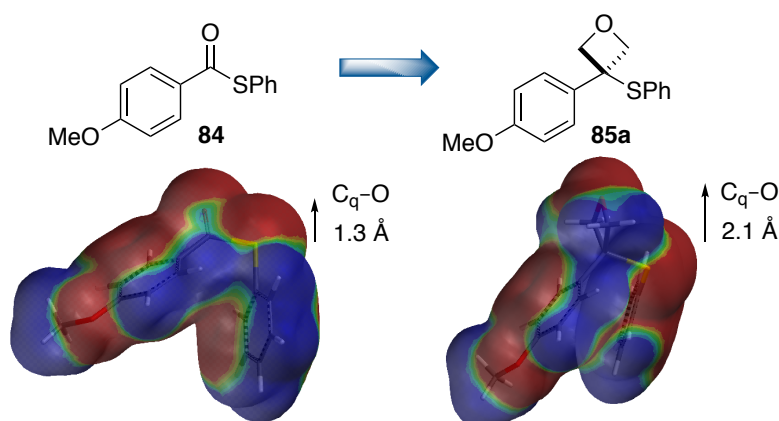


Figure 3.23 Electrostatic mapping for thioester **84** and sulfanyloxetane **85a** (–25 to 25 kJ/mol). DFT calculations conducted at Pfizer by Dr James. J. Mousseau.

The Ar–C–S bond angles were calculated and found to be broadly similar for the two scaffolds (Figure 3.24A). However, the ArC–SAr dihedral angles showed more variation with oxetane **85a** found to have a dihedral bond angle 35° wider than that calculated for thioester **84** (Figure 3.24B).

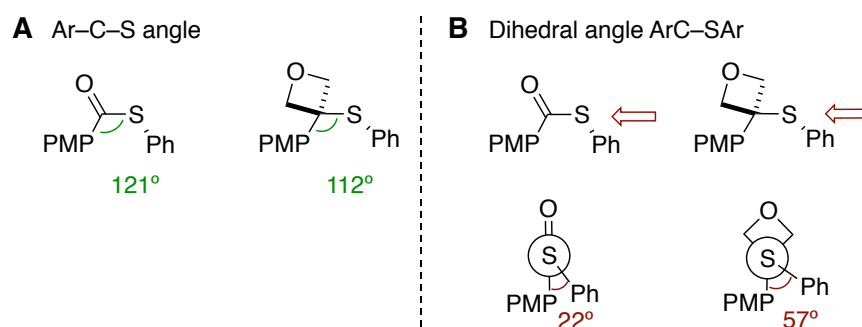
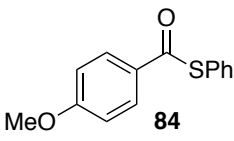
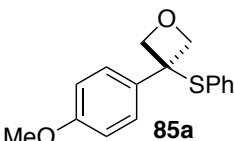


Figure 3.24 Calculated Ar-C-S angles (A) and dihedral ArC-SAr angles (B) for thioester **84** and oxetane **85a**. Angle calculations conducted at Pfizer by Dr James. J. Mousseau.

Several other physicochemical properties were calculated and compared for thioester **84** and oxetane **85a** (Table 3.12). Computationally derived values for LogP, polarisability and volume as well as the number of hydrogen bond donors/acceptors were similar, indicating that 3-sulfanyloxetanes have potential as suitable bioisosteres for thioesters. However, oxetane **85a** had a lower PSA of 13.3 Å² compared to 21.4 Å² for thioester **84**.

Table 3.12 Predicted physicochemical properties for thioester **84** and oxetane **85a**. Calculations conducted at Pfizer by Dr James. J. Mousseau.

		
LogP	3.96	3.54
HBD/HBA	0/3	0/3
Polarisability	59.5	62.1
Volume	248.4 Å ³	281.8 Å ³
PSA	21.4 Å ²	13.3 Å ²

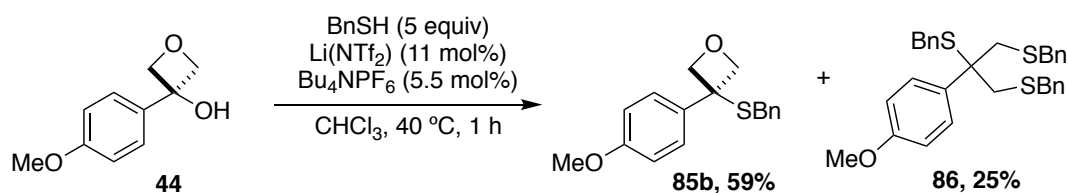
In 2017, Bernardes and co-workers investigated the modification of proteins with oxetanes.¹⁷⁴ As part of their study they found that a protein modified with a mono-substituted 3-S-oxetane motif was stable upon incubation with blood plasma at 37 °C over 24 hours. Excellent stability was also found in the presence of various sulfur and nitrogen based nucleophiles, such as endogenous glutathione, thiobenzene, β-mercaptoethanol and benzylamine, at 37 °C for up to 24 hours. These initial stability studies show that 3-S-oxetanes have potential for *in vivo* applications.

3.2.2 Reaction Optimisation

The synthesis of mono-substituted 3-sulfanyloxetane derivatives is known through substitution directly on the intact oxetane ring by displacing a suitable leaving group with a sulfur nucleophile.¹⁷⁵ Methods for the synthesis of 3,3-disubstituted derivatives are limited to the conjugate addition of sulfur nucleophiles into α,β -unsaturated oxetanes towards 3-alkyl-3-sulfanyloxetanes^{104,121e} and Paternò-Büchi photocycloaddition reactions for the synthesis of highly substituted examples.¹⁷⁶

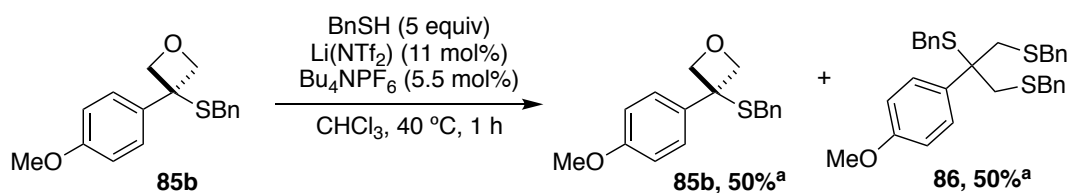
The synthesis of 3-aryl-3-sulfanyloxetanes was envisaged through the reaction of sulfur nucleophiles with oxetanyl carbocations generated *in situ* from 3-aryloxetanols under acidic conditions. There were initial concerns as 3,3-disubstituted oxetanes are known to undergo rapid ring opening under acidic conditions in the presence of sulfur nucleophiles (see Section 1.3.1, Scheme 1.14).^{121c} Furthermore, catalytic thiol alkylation reactions are often perceived as problematic due to the potential for catalyst poisoning by the sulfur nucleophile which often leads to high catalyst loadings being employed.¹⁷⁷ Lower catalyst loadings ($\leq 10\%$) are known although substrate scope is often very limited with functionalised tertiary examples rare.¹⁷⁸

The reaction to form 3-sulfanyloxetane **85b** was attempted under the lithium-catalysed conditions optimised for the Friedel–Crafts reaction between oxetanols and phenols (Scheme 3.18). Under these conditions, 3-sulfanyloxetane **85b** was formed in a 59% yield alongside the tribenzylated side product **86** in 25% yield.



Scheme 3.18 Reaction of oxetanol **44** with benzylmercaptan under the optimised conditions for the Friedel–Crafts alkylation reaction of oxetanols.

Feasibly, the tribenzylated side product **86** could be formed from ring opening of either the starting material or the product. To investigate its formation, oxetane **85b** was resubmitted to the reaction conditions and after 1 hour a 1:1 ratio of oxetane **85b** and side product **86** was observed by ¹H NMR (Scheme 3.19). This showed that the product was susceptible to further reaction under the thiol alkylation conditions.



Scheme 3.19 Reaction of 3-sulfanyloxetane **85b** under the lithium-catalysed Friedel–Crafts conditions.

^aYield calculated by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard.

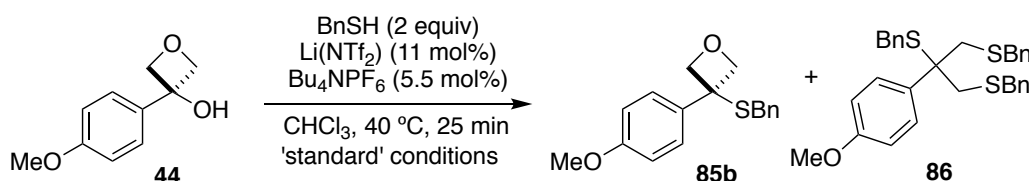
As a strategy to minimise ring opening, shorter reaction times and fewer equivalents of nucleophile were examined (Table 3.13). This appeared to be a successful approach as decreasing the equivalents of nucleophile from 5 to 3 led to a reduced 10% yield of **86** (Entry 2) and when combined with a shorter reaction time of 25 minutes, a higher yield of 71% for oxetane **85b** was obtained (Entry 3). No reaction was observed after a reaction time of 10 minutes suggesting an activation period for the reaction probably related to solubilisation of the catalyst (Entry 4). Further decreasing the equivalents of nucleophile to just 2 equivalents gave the optimal conditions whereby oxetane **85b** was isolated in a 67% yield with almost complete suppression of the ring opening side reaction (Entry 5). Increasing the reaction time to 6 hours and using 6 equivalents of benzylmercaptan led to exclusive formation of the tribenzylated product **86** in a 97% yield (Entry 6).

Table 3.13 Selected optimisation of equivalents of nucleophile and reaction time for the reaction between oxetan-3-ol **44** and benzylmercaptan. ^aYields calculated by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. Isolated yields in parentheses.

Entry	Equiv of nucl.	Reaction time (min)	Yield of 85b (%) ^a	Yield of 86 (%) ^a
1	5	60	(59)	(20)
2	3	60	(60)	(10)
3	3	25	71	18
4	3	10	0	0
5	2	25	81 (67)	<5
6	6	6	0	97

Selected other factors were then investigated to confirm the optimal conditions (Table 3.14). Other catalysts were investigated; however, none of those examined gave an increase in yield. FeCl_3 , $\text{Ga}(\text{OTf})_3$ and $\text{Ca}(\text{NTf}_2)_2/\text{Bu}_4\text{NPF}_6$ gave reduced yields of oxetane sulfide **85b** compared to the lithium catalyst (Entries 2–4) and use of catalytic $\text{Bi}(\text{OTf})_3$ or TsOH led to either minimal or no desired product (Entries 5–6). Toluene was a suitable solvent for the reaction although yield and selectivity were slightly lower than when chloroform was used (Entry 7). In the absence of either catalyst or additive no reaction was observed confirming that both are essential for reactivity (Entries 8–9).

Table 3.14 Selected optimisation for the thiol alkylation reaction of oxetanol **44**. ^aYields calculated by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. Isolated yields in parentheses. ^b45% recovered **44**. ^cTrace amount of recovered **44**. ^d63% recovered **44**.

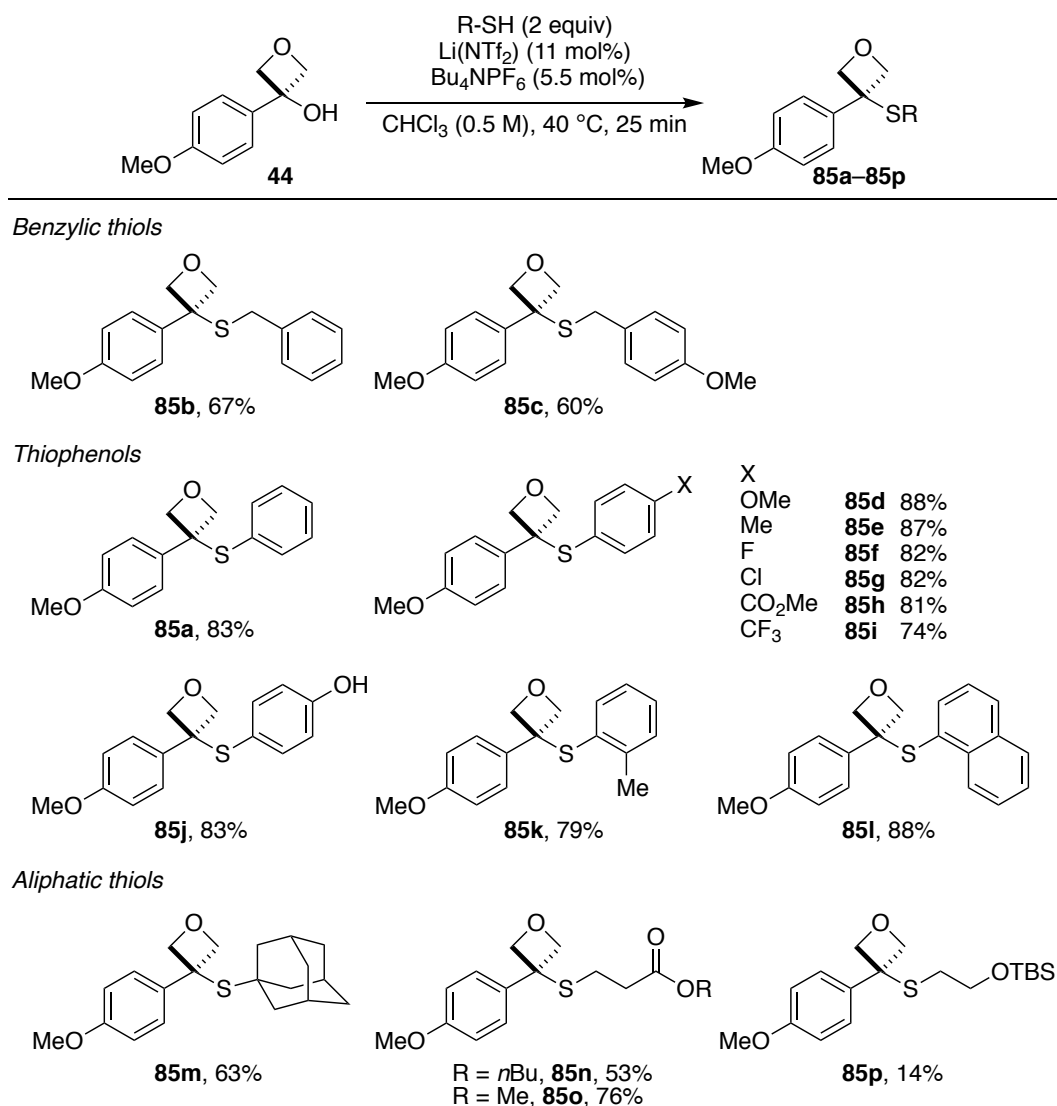


Entry	Change from 'standard' conditions	Yield 85b (%) ^a	Yield 86 (%) ^a
1	none	81 (67)	<5
2	FeCl_3 (5 mol%), instead of $\text{Li}(\text{NTf}_2)/\text{Bu}_4\text{NPF}_6$	18	0
3	$\text{Ca}(\text{NTf}_2)_2$ (5 mol%), Bu_4NPF_6 (5 mol%) instead of $\text{Li}(\text{NTf}_2)$	62	0
4	$\text{Ga}(\text{OTf})_3$ (5 mol%), instead of $\text{Li}(\text{NTf}_2)/\text{Bu}_4\text{NPF}_6$	21	11 ^b
5	$\text{Bi}(\text{OTf})_3$ (5 mol%), instead of $\text{Li}(\text{NTf}_2)/\text{Bu}_4\text{NPF}_6$	4	0 ^c
6	$\text{TsOH} \cdot \text{H}_2\text{O}$ (5 mol%), instead of $\text{Li}(\text{NTf}_2)/\text{Bu}_4\text{NPF}_6$	0	0 ^d
7	Toluene, instead of CHCl_3	61	16
8	No $\text{Li}(\text{NTf}_2)$	0	0
9	No Bu_4NPF_6	0	0

The conditions in entry 1 were taken forward as the optimal conditions and a scope of 3-sulfanyloxetanes was explored to assess the limits of this methodology.

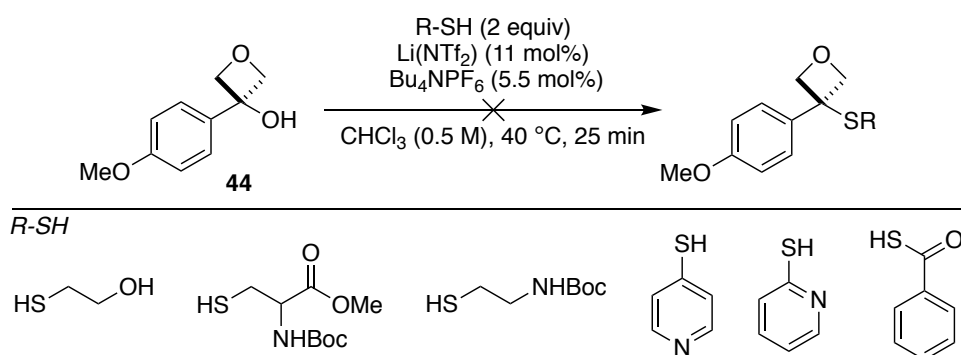
3.2.3 Scope of Oxetan-3-sulfides

Different thiol nucleophiles were examined for the reaction leading to the synthesis of a wide variety of oxetan-3-sulfides (Scheme 3.20). 4-Methoxybenzylmercaptan was successful in the reaction giving oxetane **85c** in a 60% yield. Various thiophenol nucleophiles gave the oxetane products **85a,d–k** in excellent yields (74–88%). Only a small decrease in yield was observed going from electronic rich to electron poor *para*-substituents and *ortho*-methylthiophenol gave only an 8% reduction in yield compared to the *para*-methyl derivative. These results signify that the reaction was not overly sensitive to the steric and electronic nature of the substituents on thiophenol. Interestingly, *para*-hydroxythiophenol gave exclusively sulfanyloxetane **85j** in an 83% yield with no O- or C-alkylation observed. Oxetane **85i** was synthesised in an 88% yield using 1-thionaphthol with this high yield possibly accounted for by the increase in steric bulk helping to suppress ring opening.



Scheme 3.20 Scope of thiols for the lithium-catalysed thiol alkylation reaction of oxetan-3-ol **44**.

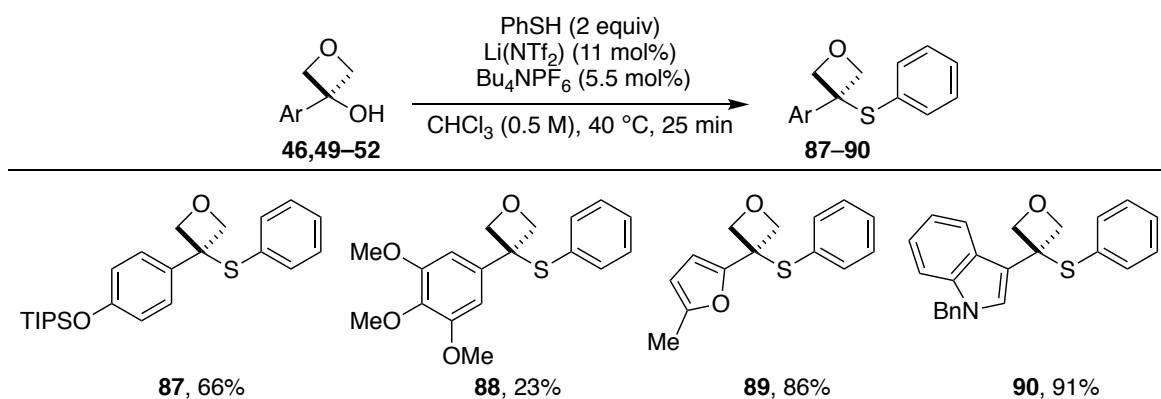
Aliphatic thiol were suitable nucleophiles for the reaction with tertiary thiol, 1-adamantanethiol, and primary thiols, butyl- and methyl-3-mercaptopropionate, giving the desired oxetane sulfides **85m**, **85n** and **85o** respectively. Use of 2-mercaptoethan-1-ol gave no conversion of starting material (Scheme 3.21) although protection of the hydroxyl group with TMS enabled synthesis of oxetane **85p** in a low yield (14%). *N*-Boc-cysteine methyl ester and 2-(Boc-amino)-ethanethiol did not provide the desired oxetane sulfides, with starting material recovered quantitatively for both these nucleophiles (Scheme 3.21). When directly compared to the reactivity of methyl-3-mercaptopropionate, it would appear that the NHBoc group is the cause of this lack of desired reactivity probably due to catalyst deactivation through inhibitory coordination.



Scheme 3.21 Unsuccessful thiols for the lithium-catalysed thiol alkylation of oxetanol **44**.

Furthermore, 4- and 2-pyridinethiol nucleophiles led to no desired product with starting material recovered quantitatively. Thiobenzoic acid was also examined as the nucleophile in the reaction. However, no desired reactivity was observed possibly due to chelation of the catalyst with the nucleophile.

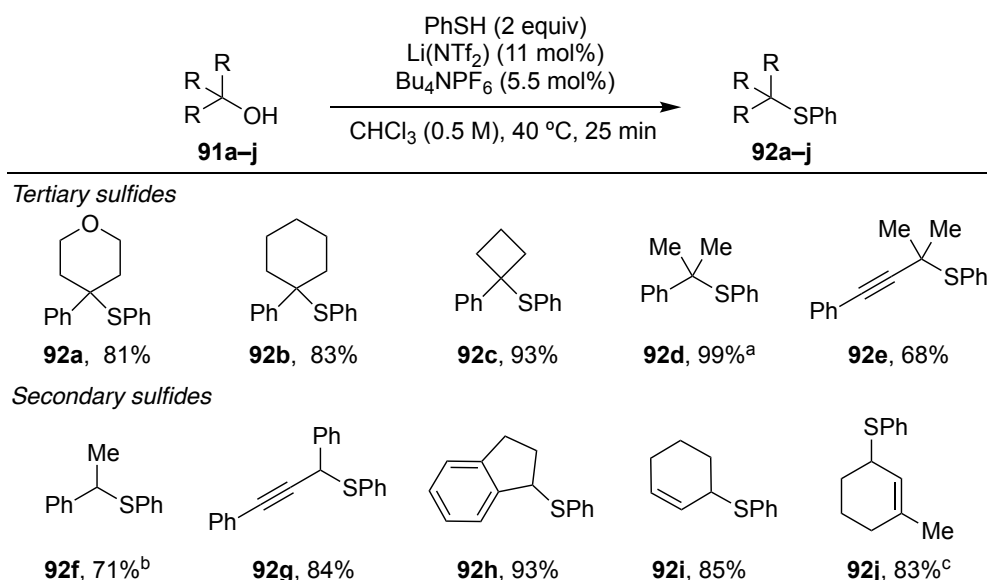
We then investigated the scope of oxetanols (Scheme 3.22). Oxetanol **46**, substituted with an OTIPS group, gave the corresponding oxetane sulfide (**87**) in a 66% yield. 3,4,5-Trimethoxy-substituted oxetanol **49** delivered the oxetane product **88** in a much reduced 23% yield with significant amounts of ring opening observed for this substrate. The highly electron donating nature of the aromatic group increases the reactivity of the 2- and 4-positions of the oxetane towards nucleophilic attack, accounting for this observed reactivity. Heterocycles such as indole and furan were suitable preinstalled aromatic groups for the stabilisation of the proposed oxetanyl carbocationic intermediate with oxetanols **51** and **52** giving oxetanes **89** and **90** in 86% and 91% yields respectively.



Scheme 3.22 Thiol alkylation of different oxetanols with thiophenol.

3.2.4 Application to General Tertiary and Secondary Sulfides

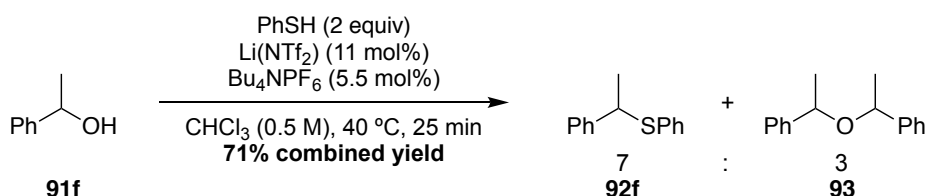
These lithium-catalysed thiol alkylation conditions were also suitable for a more general selection of π -activated secondary and tertiary alcohols (Scheme 3.23). In general, high yields were obtained for the sulfide products from the reaction between different alcohols and thiophenol. Oxygen heterocycles and carbocycles were readily incorporated with tetrahydropyranol **91a**, cyclohexanol **91b** and cyclobutanol **91c** all giving the corresponding sulfide product (**92a–c**) in >80% yield. Additionally, tertiary benzylic and propargylic alcohols (**91d** and **91e**) were also tolerated to provide sulfides **92d** and **92e** in 99% and 68% yields respectively. Sulfide **92d** was also synthesised using heptane as a solvent in only a slightly reduced yield compared to chloroform.



Scheme 3.23 Lithium-catalysed thiol alkylation of secondary and tertiary π -activated alcohols. ^a93% yield when heptane used as a solvent instead of CHCl_3 . ^b5 equivalents of thiophenol. ^c5:1 mixture, 3-methyl:1-methyl

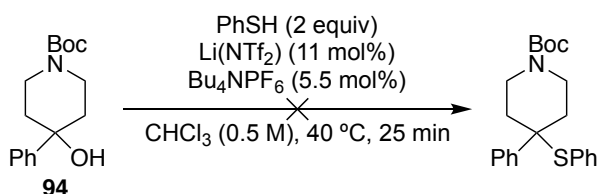
Excellent yields of the sulfide products **92f–92i** were obtained for the secondary benzylic, propargylic, indane and vinylic alcohols that were investigated. Reaction of unsymmetrical tertiary alcohol **91j** gave sulfide **92j** as a 5:1 mixture of the secondary and tertiary regioisomers with attack of the carbocationic intermediate by the nucleophile occurring preferentially at the less hindered 3-position.

A lower yield was achieved for sulfide **92f** due to the formation of dimeric ether side product **93** (Scheme 3.24). Using 2 equivalents of thiophenol, a 7:3 mixture of sulfide **92f** and side product **93** was formed. To limit dimerisation, the equivalents of thiophenol was increased from 2 to 5. At 5 equivalents a reduced amount of side-product formation was observed (approx 8% by ^1H NMR of the crude reaction) enabling successful isolation of sulfide **92f** in a 71% yield.



Scheme 3.24 Thiol alkylation of benzylic alcohol **91f** to give sulfide **92f** and dimerised side product **93**.

Piperidin-4-ol **94** was prepared by reaction of phenyllithium with *N*-Boc-piperidin-4-one. However, when this substrate was submitted to the standard reaction conditions no desired product was observed, only recovered starting material (Scheme 3.25). This is presumably due to coordination of the catalyst to the NBoc group inhibiting the desired catalytic cycle.

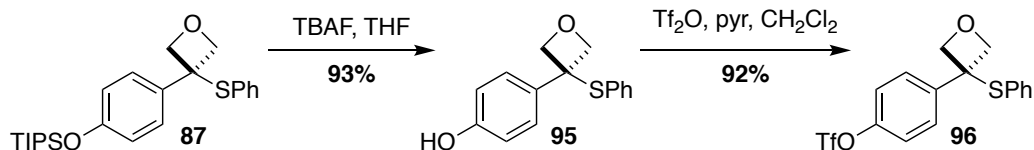


Scheme 3.25 Attempted reaction of piperidin-4-ol **94** with thiophenol.

3.2.5 Further Derivatisation of Oxetane Sulfides

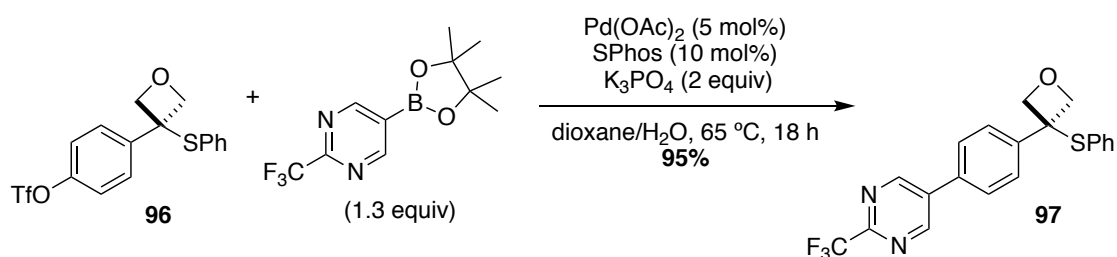
Stability of the oxetane sulfide motif to further derivatisation was essential to establish these scaffolds as building blocks for medicinal chemistry. Treatment of oxetane-3-sulfide **87** with TBAF successfully deprotected the TIPS group to give the unprotected phenol derivative **95** in a 93% yield (Scheme 3.26). Subsequent triflation under standard conditions (triflic

anhydride, pyridine) occurred in excellent yield to give triflate **96** with a useful functional handle for cross-coupling reactions.



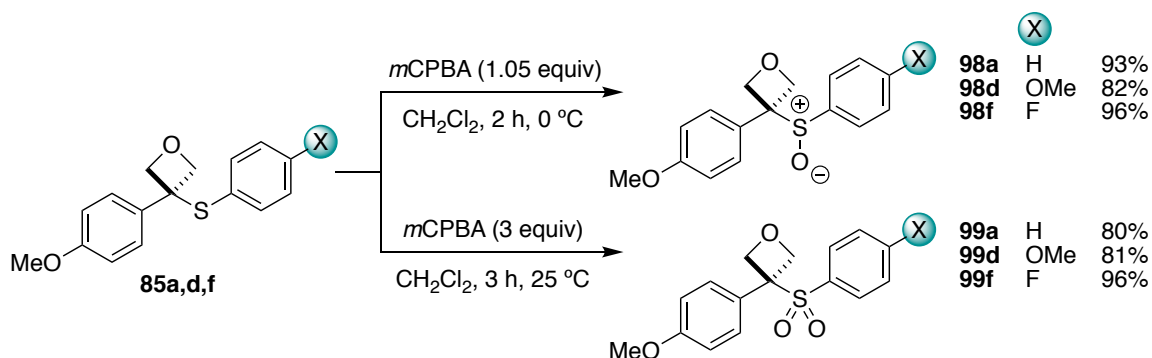
Scheme 3.26 TIPS deprotection of 3-sulfanyloxetane **87** and subsequent triflation.

Suzuki–Miyaura cross-coupling of **96** with a pyrimidine containing boronic ester coupling partner gave biaryl derivative **97** in a 95% yield (Scheme 3.27). Reaction conditions used 5 mol% of Pd(OAc)₂ in combination with 10 mol% of an SPhos ligand.



Scheme 3.27 Suzuki–Miyaura cross-coupling to form biaryl containing 3-sulfanyloxetane **97**.

The oxetane sulfides **85a,d,f** could be readily oxidised to give either sulfoxides **98a,d,f** or sulfones **99a,d,f** in high yields, themselves new classes of oxetane-containing compounds (Scheme 3.28). Control of the equivalents of *m*CPBA and reaction temperature enabled complete selectivity for either single or double oxidation. Use of 1.05 equivalents of the oxidant at 0 °C gave only the sulfoxide analogues whereas 3 equivalents of oxidant at 25 °C gave the corresponding sulfones.

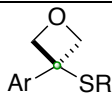
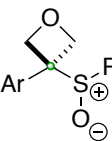
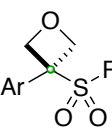
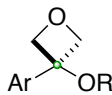
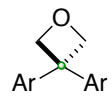
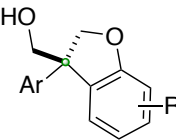
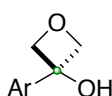


Scheme 3.28 The oxidation of oxetane-3-sulfides to give selectively sulfoxides **98a,d,f** or sulfones **99a,d,f**.

3.2.6 Analysis of Oxetane Quaternary Carbon Peaks in ^{13}C NMR Spectra¹³³

Characterisation of closely related oxetane derivatives was in some cases more complex due to similar ^1H NMR spectra and overlapping absorptions by IR spectroscopy. However, the ^{13}C NMR signal of the quaternary oxetane C-3 atom has proved diagnostic for many examples, enabling preliminary characterisation without needing to wait for mass spectrometry data (Table 3.15). For example, the peak corresponding to the C-3 atom in 3-aryl-oxetan-3-sulfides was observed between 49.8–55.7 ppm across 25 examples whereas for sulfoxides this peak occurs in the range 67.2–67.4 ppm and for sulfones between 68.2–69.3 ppm. However, it is noted that there are significantly fewer examples for the latter two classes of oxetane.

Table 3.15 Comparison of quaternary carbon peaks in ^{13}C NMR spectra of oxetane and dihydrobenzofuran derivatives. ^aThe syntheses of some examples are detailed later in this thesis.

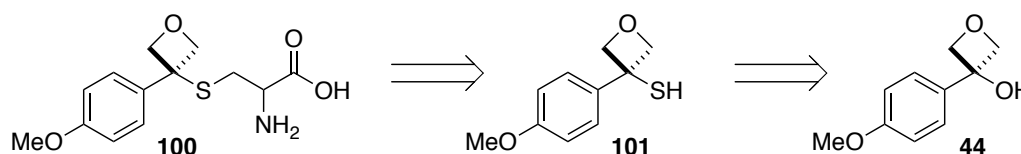
Entry	General Structure	Range for C _q peak in ^{13}C NMR spectra (ppm)	Number of examples ^a
1		49.8–55.7	25
2		67.2–67.4	3
3		68.2–69.3	8
4		80.1–81.2	9
5		46.0–51.0	17
6		53.2–57.1	24
7		72.1–75.8	9

This method for preliminary characterisation was also useful for reliably distinguishing between 3,3-diaryloxetanes and the isomeric oxetane ethers (see Section 3.1). Discriminating

between the two isomers by ^1H NMR spectroscopy was in some cases complicated by overlapping peaks in the aromatic region. For oxetane ethers, the signal in the ^{13}C NMR spectra relating to the oxetane C-3 atom was observed between 80.1 ppm and 81.2 ppm. In contrast, the 3,3-diaryloxetane C-3 peak was consistently observed in the range 46.0–51.0 ppm. Furthermore, the dihydrobenzofuran analogues could also be distinguished from the regioisomeric 3,3-diaryloxetane products as the fully substituted quaternary carbon peak by ^{13}C NMR spectroscopy occurred between 53.2–57.1 ppm across the 24 dihydrobenzofuran examples synthesised in this research. The quaternary carbon peaks in the ^{13}C NMR spectra of the oxetanol starting materials were also significantly different and were observed in the range 72.1–75.8 ppm across the nine examples synthesised in this work.

3.2.7 Synthesis of an Oxetane Containing Cysteine Derivative

The current interest in oxetane modified peptides and presence of alkylated cysteine derivatives in several marketed drugs led to the identification of oxetane cysteine **100** as an attractive target.^{179,174} Unfortunately, the use of protected cysteine as the nucleophile was not successful in the lithium-catalysed thiol alkylation, so an alternative strategy was considered *via* oxetane thiol **101** (Scheme 3.29).



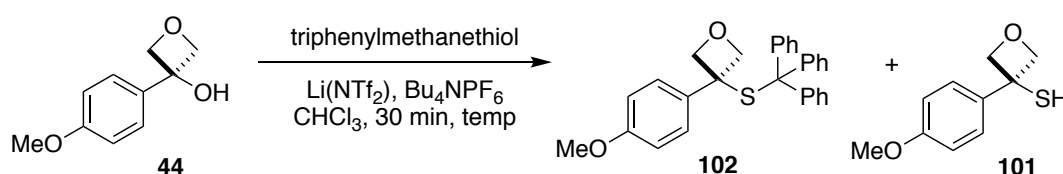
Scheme 3.29 Retrosynthetic analysis of oxetane cysteine derivative **100**.

Several methods for the synthesis of thiols from alcohols are known. Lawesson's reagent is most commonly employed to introduce the thiol motif but heating with thiourea under acidic conditions or alkylation with benzylmercaptan and subsequent deprotection through a Birch reduction are also known strategies.¹⁸⁰ We considered a novel one-pot approach using convenient and non-malodorous reagents. Introduction of triphenylmethanethiol through a lithium-catalysed thiol alkylation then trityl deprotection at room temperature using trifluoroacetic acid in the same reaction pot presented an expedient approach.

Initially, the thiol alkylation step between oxetanol **44** and triphenylmethanethiol was investigated (Table 3.16). Under the previously identified optimal thiol alkylation conditions the desired oxetane sulfide **102** was observed in a 29% yield alongside 13% of deprotected thiol **101** (Entry 2). Different temperatures (25 °C and 60 °C) were considered (Entries 1 and 3). However, although good levels of reactivity were observed in some cases, the results obtained were not reproducible so 40 °C was used as the reaction temperature. Different concentrations

between 0.25 M and 1 M were examined but concentration appeared to have little effect on the overall combined yield (Entries 4–5). A higher catalyst loading of 20 mol% was also investigated but again there was no improvement in yield (Entry 6). Pleasingly, increasing the equivalents of nucleophile from 2 to 5 gave the desired increase in yield with the two products **101** and **102** isolated as a mixture in a 59% yield (Entry 8).

Table 3.16 Selected optimisation for the lithium-catalysed thiol alkylation reaction between oxetanol **44** and triphenylmethanethiol. ^aYields calculated by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. Isolated yields in parentheses.



Entry	Temp (°C)	Conc (M)	Catalyst/additive loading (mol%)	Equiv of nucl	Yield of 102 (%) ^a	Yield of 101 (%) ^a	Total yield (%) ^a
1	25	0.5	11/5.5	2	39	11	50
2	40	0.5	11/5.5	2	29	13	42
3	60	0.5	11/5.5	2	40	5	45
4	40	0.25	11/5.5	2	32	8	40
5	40	1	11/5.5	2	33	8	41
6	40	1	20/10	2	30	7	37
7	40	1	11/5.5	3	36	11	47
8	40	1	11/5.5	5	42	11	53 (59)

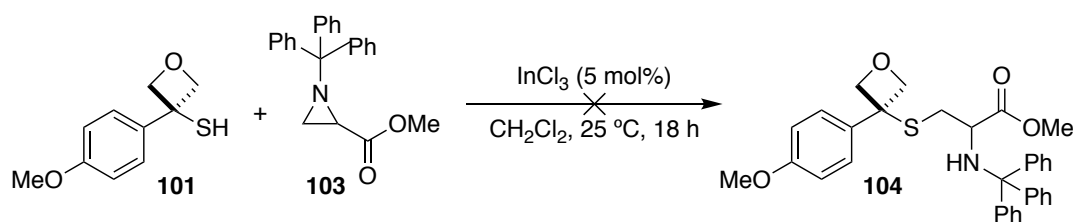
With these optimal conditions in hand, deprotection of the trityl group by adding trifluoroacetic acid (TFA) and triethylsilane into the same reaction pot was explored (Table 3.17). Triethylsilane was employed to prevent the reverse reaction by reacting with the trityl cation produced in the deprotection step. It was important for the reaction to reach completion as the protected and deprotected products proved inseparable by flash column chromatography. Use of 6 equivalents of TFA and 1.2 equivalents of triethylsilane gave the deprotected product **101** in a 51% yield and trityl protected intermediate **102** in a 2% yield. Pleasingly, increasing the

equivalents of triethylsilane from 1.2 to 2 enabled the deprotected derivative **101** to be isolated as the sole product in 53% yield over the two steps.

Table 3.17 Optimisation for the two-step one-pot synthesis of thioxetane thiol **101**. ^aYields calculated by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. Isolated yields in parentheses.

Entry	Equiv of triethylsilane	Yield 102 (%) ^a	Yield 101 (%) ^a
1	1.2	2	51
2	2	0	(53)

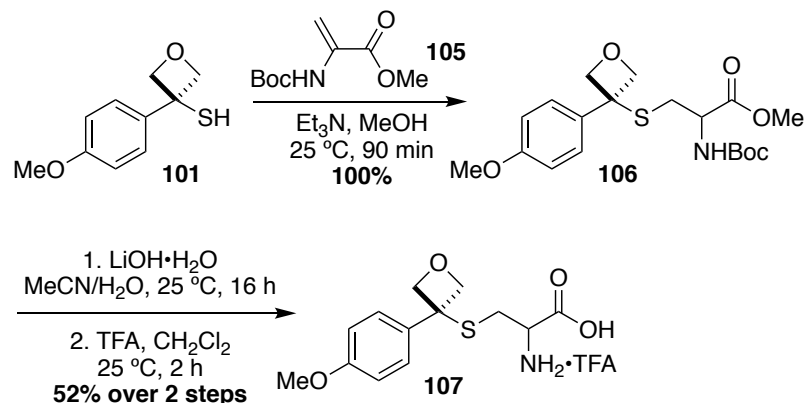
With a convenient and mild method for the synthesis of oxetane thiol **101** in hand, the synthesis of oxetane cysteine **100** was investigated. Initially, incorporation of the cysteine functionality was explored through Lewis acid catalysed ring opening of aziridine derivative **103** (Scheme 3.30).¹⁸¹ Unfortunately, using InCl_3 as the catalyst, only starting material was observed in the crude reaction mixture by ¹H NMR spectroscopy. The lack of desired reaction towards oxetane **104** was most likely due to steric clashes between the tertiary sulfide and large trityl protecting group. Additionally, the presence of an insoluble substance in the crude reaction mixture indicated possible polymerisation under the acidic conditions and so an alternative route for the introduction of the cysteine motif was sought.



Scheme 3.30 Attempted ring opening of an azetidine derivative with oxetane thiol **101**.

Pleasingly, conjugate addition of oxetane thiol **101** to a dehydroalanine derivative gave the protected oxetane cysteine **106** in quantitative yield after 90 minutes at room temperature (Scheme 3.31). Hydrolysis of the ester group using lithium hydroxide then Boc deprotection

using TFA enabled the synthesis of the racemic unnatural amino acid derivative **106** in a 52% yield from oxetane thiol **101**.



Scheme 3.31 Synthesis of oxetane cysteine **107** from thiol **101**.

3.2.8 ADME Studies¹

In order to assess the suitability of the novel oxetane sulfides synthesised in this section for medicinal chemistry applications, several important physicochemical properties were calculated for selected compounds. LogD is a key parameter that is considered by medicinal chemists when assessing the ‘drug-likeness’ of a compound as high lipophilicity can result in poor permeability, target promiscuity and metabolic instability (see Section 1.1.2).

To evaluate the effect of oxetane incorporation on lipophilicity, eLogD values were calculated for thioester **108**, sulfide **85d**, and sulfone **99d** (Figure 3.25). Oxetane sulfide **85d** had a calculated eLogD value of 3.8, a decrease in lipophilicity of approximately 1 log unit compared to thioester **108**. Additionally, oxidation to the sulfone led to a further favourable decrease in eLogD to 2.1. These calculated values for the oxetane derivatives lie in desirable property space for drug discovery making them potentially valuable synthetic options.

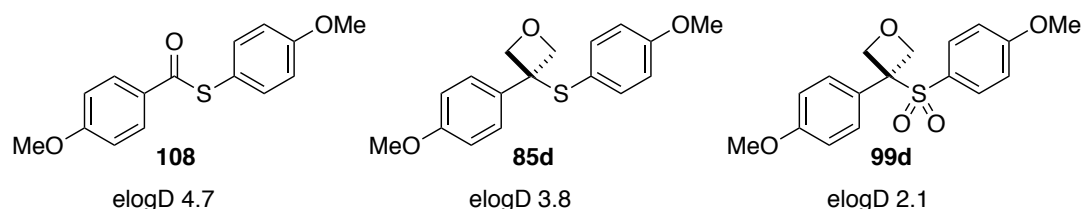
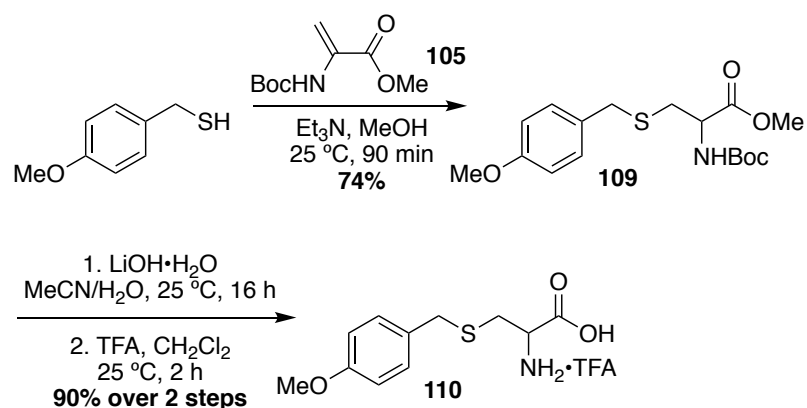


Figure 3.25 Comparison of eLogD values for compounds **108**, **85d** and **99d**. Values determined at Pfizer.

¹ADME properties determined at Pfizer.

Cell permeability and metabolic clearance were explored for oxetane cysteine **107** and the corresponding methylene analogue **110**. The protected methylene derivative **109** was synthesised through addition of commercially available 4-methoxybenzylmercaptan to the same dehydroalanine derivative used in the synthesis of oxetane **106** (Scheme 3.32). Subsequent ester hydrolysis and deprotection of the boc group under standard conditions gave the methylene derivative **110** in a 67% yield over the three steps.



Scheme 3.32 Synthesis of methylene derivative **110**.

Importantly, clearance in human liver microsomes was found to be the same for both compounds **107** and **110** indicating that the oxetane sulfide motif is not a metabolic liability (Figure 3.26). Cell membrane permeability was found to be slightly lower for oxetane **107** compared to the methylene derivative **110**. However, it is likely that for highly polar compounds of this type, active transport mechanisms would be more appropriate for transfer across biological membranes than passive transport.

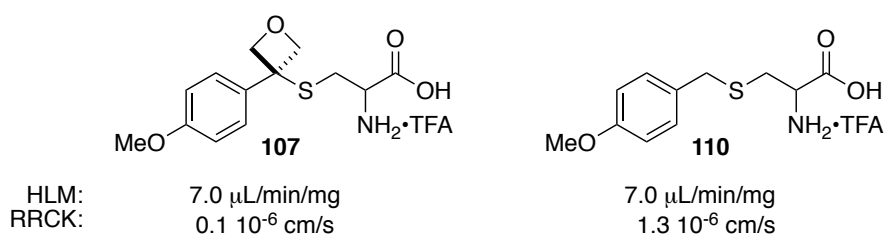


Figure 3.26 Clearance in liver microsomes (HLM) and cell membrane permeability (RRCK) for cysteine containing compounds **107** and **110**. Properties determined at Pfizer.

Measurement of these key physicochemical parameters for the oxetane sulfide and sulfone derivatives and comparison to selected carbonyl and methylene analogues indicated that these motifs are suitable for incorporation into medicinal chemistry programmes and that their inclusion may convey benefits with regards to the physicochemical profile.

3.2.9 Conclusions

To summarise, 3-sulfanyl oxetanes can be readily accessed from oxetanols *via* an oxetanyl-carbocation intermediate. Control of the equivalents of nucleophile and reaction time led to excellent regioselectivity with alkylation strongly preferred over ring opening. Aromatic, benzylic and aliphatic thiols were all suitable nucleophiles with electron poor and electron rich substituents tolerated. Nitrogen-containing thiol nucleophiles such as protected cysteine and pyridinethiol derivatives were not successful when used directly in the thiol alkylation presenting a limitation of this methodology. The lithium-catalysed conditions were also suitable for a variety of other π -activated alcohols to give a more general range of sulfides in good to excellent yields.

The oxetane-3-sulfide derivatives successfully underwent further functionalisation through oxidation, triflation and palladium-catalysed cross-coupling reactions enabling access to a diverse range of analogues. In addition, a thiol alkylation with triphenylmethanethiol and subsequent trityl deprotection enabled access to oxetane-containing thiol **101** which was a suitable nucleophile for conjugate addition with a dehydroalanine derivative to access protected cysteine derivative **106**.

Comparison of important physicochemical properties of selected sulfur-containing oxetane derivatives and their methylene and carbonyl analogues suggested that oxetane sulfides and sulfones may be attractive motifs for application in medicinal chemistry.

The next section of this thesis will describe our efforts towards oxetane sulfinates and oxetane sulfonyl fluorides and investigations into their reactivity.

3.3 Oxetane Containing Sulfonyl Fluorides

3.3.1 Sulfonyl Fluorides as Biological Probes

Sulfonyl fluorides have found application as privileged small molecule biological probes due to their combination of aqueous stability and ability to form covalent bonds with specific protein residues. For an excellent review of this area see Jones (2015).¹⁸² Sulfonyl fluoride derivatives have been shown to react with various protein residues including: serine, threonine, lysine and tyrosine groups. These probes are useful for numerous applications such as target identification and validation, covalent enzyme inhibition and the mapping of active sites.

Many sulfonyl fluorides are now commercially available (for selected examples see Figure 3.27). AEBSF and PMSF have been employed as inhibitors of serine proteases and are used in the preparation of cell lysates to selectively prevent breakdown of certain proteins. Dansyl fluoride also exhibits serine reactivity and is useful for labelling serine proteases with a fluorescent marker for protein identification studies.¹⁸³ FSBA is an ATP analogue first developed by the Colman group in 1975.¹⁸⁴ This sulfonyl fluoride has found application as a covalent probe for ATP-binding proteins through reaction with lysine groups and has been used to study the ATP hydrolysis catalytic cycle.¹⁸⁵ FSBA can also react with tyrosine residues.¹⁸⁶

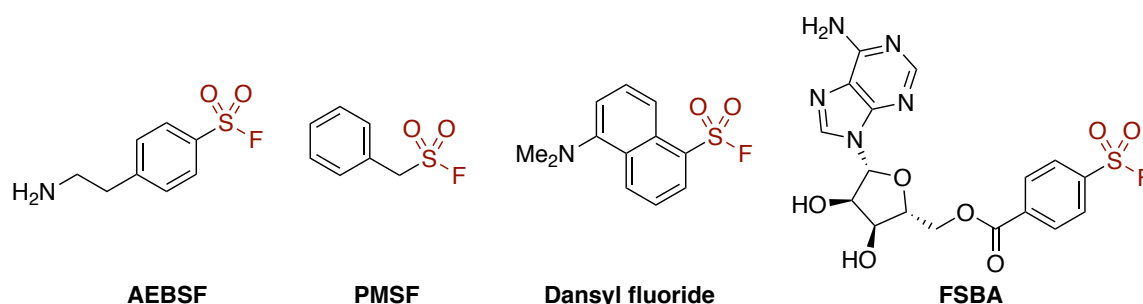


Figure 3.27 Commercially available sulfonyl fluoride containing biological probes with the sulfonyl fluoride motif highlighted in red.

Bespoke sulfonyl fluorides have also been designed and utilised for specific applications. For example, sulfonyl fluoride **111** substituted with a farnesyl group was synthesised to bind covalently to the active site serine in polyisoprenylated methylated protein methyl esterase (PMPMEase) and showed a greater than 35x increase in potency compared to PMSF (Figure 3.28).¹⁸⁷ Information gained using this compound allowed elucidation of the role of PMPMEase in cancers and showed that specific inhibitors of this enzyme may be effective therapeutic agents.

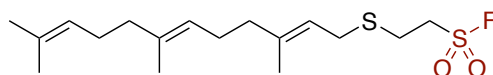
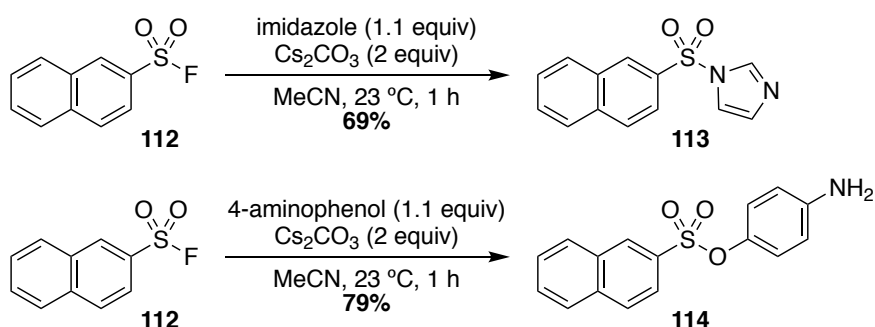
Sulfonyl fluoride **111**

Figure 3.28 Sulfonyl fluoride **111** (sulfonyl fluoride motif highlighted in red) is a potent biological probe for PMPMEase.

3.3.2 Sulfonyl Fluorides as Synthetic Intermediates

Sulfonyl fluorides have emerged as valuable synthetic intermediates as alternative S(VI) electrophiles to more commonly used sulfonyl chlorides.¹⁸⁸ Fluorine is the most electronegative element and as a result cleavage of the S–F bond in sulfonyl fluorides occurs exclusively heterolytically to form fluoride ions. In contrast, homolytic cleavage of S–Cl bonds is widely known. Sulfonyl chlorides also readily undergo reductive cleavage to the sulfinic acid oxidation level in the presence of nucleophiles such as PPh_3 .¹⁸⁹ Hence, reactions using sulfonyl chlorides often give mixtures of products resulting from sulfonylation and chlorination whereas sulfonyl fluorides are less susceptible to reductive attack and so addition only occurs at sulfur. Additionally, sulfonyl fluorides have an advantage over the corresponding chloride derivatives as their higher homolytic S–X bond dissociation energy (81 kcal/mol for $\text{FSO}_2\text{–F}$ ¹⁹⁰ vs 46 kcal/mol for $\text{ClSO}_2\text{–Cl}$)¹⁹¹ makes them more stable to thermolysis.

Reaction of sulfonyl fluorides with amines or alcohols to give sulfonamides or sulfonate esters is known under mild conditions.¹⁹² In a recent example from 2017, Ball demonstrated that treatment of sulfonyl fluoride **112** with different amines or alcohols and 2 equivalents of cesium carbonate gave the desired sulfonylated products in excellent yields after just 1 hour at room temperature (Scheme 3.33).¹⁹³ Interestingly, use of 4-aminophenol gave exclusively the sulfonate ester **114** in a 79% yield.



Scheme 3.33 Reaction of sulfonyl fluoride **112** with imidazole or 4-aminophenol to give sulfonamide **113** or sulfonate ester **114** under basic conditions.

Furthermore, in 2014, Moroz and Mykhailiuk reported a comparison of sulfonyl fluorides and sulfonyl chlorides in the parallel synthesis of 180 sulfonamides through reaction with various amines.¹⁹⁴ Although sulfonyl chlorides showed superior reactivity for sterically hindered amines, sulfonyl fluorides showed excellent reactivity with amines substituted with further functional groups where sulfonyl chlorides frequently failed e.g. amines substituted with aliphatic alcohols, phenols and NH-heteroaromatics.

Oxetane-containing sulfonyl fluoride **115** was targeted as it was considered interesting for potential biological applications and as a versatile reaction intermediate (Figure 3.29).

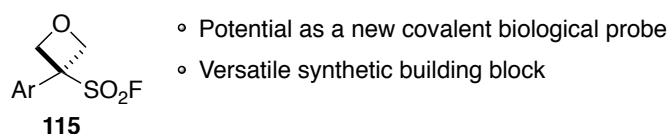
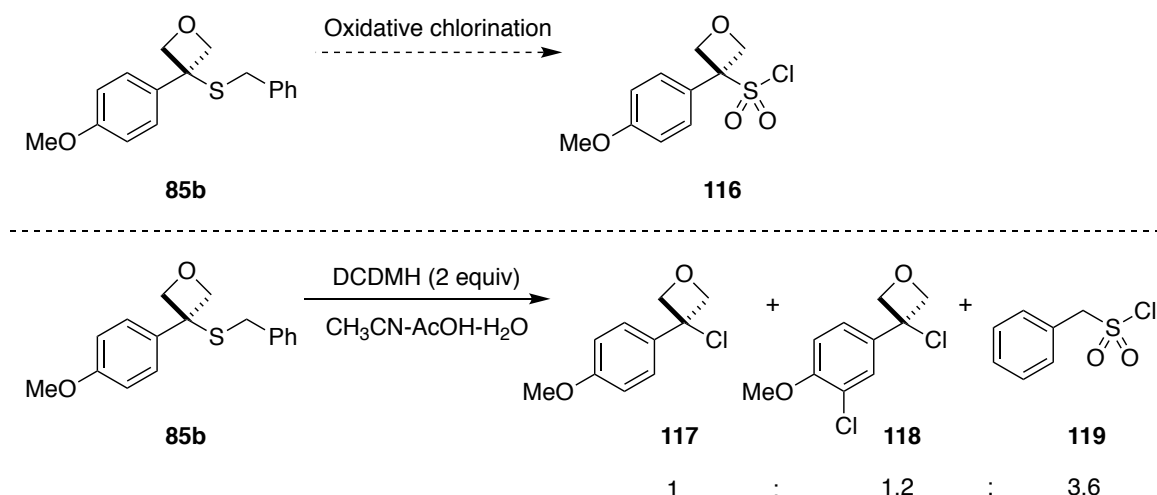


Figure 3.29 Sulfonyl fluoride **115** as a desirable target.

3.3.3 Proposed Synthetic Route to Oxetane Containing Sulfonyl Fluorides

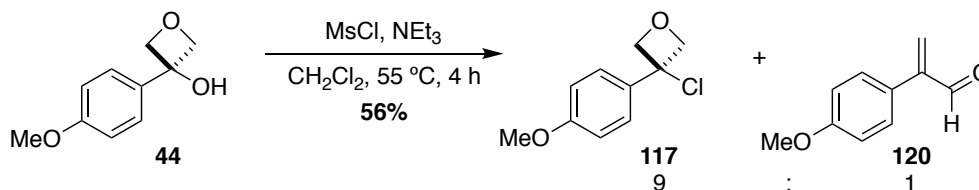
Most commonly, sulfonyl fluorides are accessed from the corresponding sulfonyl chloride using fluoride or bifluoride reagents.¹⁸⁸ In 1931, Davies reported the use of potassium, sodium, ammonium and zinc fluorides for the conversion of sulfonyl chlorides to sulfonyl fluorides in yields of up to 80%.¹⁹⁵ More recent examples often utilise biphasic conditions developed by Sharpless and co-workers where sulfonyl chlorides are treated with potassium bifluoride to give the desired sulfonyl fluoride derivatives.^{188,196}

Based on this precedent, initial studies towards oxetane-containing sulfonyl fluoride **115** focused on synthesising the starting sulfonyl chloride derivative. The synthesis of sulfonyl chloride **116** was attempted from the benzyl sulfide **85b** using an oxidative chlorination protocol (Scheme 3.34). Conditions developed by Pu were tested (1,3-dichloro-5,5-dimethyl hydantoin (DCDMH) in MeCN-HOAc-H₂O)¹⁹⁷ and after 2 hours at 0 °C, three products were observed in the reaction mixture. Isolation of pure samples of the individual products was not achieved; however, analysis of impure samples allowed putative characterisation of each product and confirmed that the desired sulfonyl chloride **116** had not been formed. The major product **119** was identified as benzyl sulfonyl chloride as ¹H and ¹³C NMR spectra matched with data for this compound in literature.¹⁹⁸



Scheme 3.34 Planned and attempted oxidation chlorination of benzyl sulfide **85b**.

Compound **117** was identified as another component of the reaction and its structure was proven by synthesis of an authentic sample. This was achieved by treatment of oxetanol **44** with mesyl chloride and triethylamine which provided a 9:1 mixture of oxetane-3-chloride **117** and α,β -unsaturated aldehyde **120** in a 56% combined yield (Scheme 3.35).



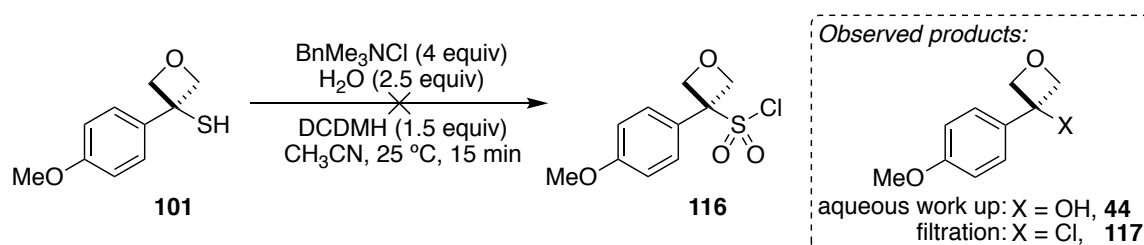
Scheme 3.35 Synthesis of oxetane-3-chloride **117** from oxetanol **44**.

The aromatic peaks in the ^1H NMR spectrum of the third product suggested *meta*-substitution on the anisole ring and led to the putative dichlorinated structure (**118**) shown in Scheme 3.34 being suggested.

Pu's suggested mechanism for the desired reaction to give the sulfonyl chloride proceeds *via* a chlorosulfoxonium intermediate which undergoes cleavage of the benzyl C–S bond through an $\text{S}_{\text{N}}1$ reaction to give a benzyl cation and a sulfinyl chloride intermediate.¹⁹⁷ In the reaction between benzyl sulfide **85b**, preferential cleavage of the oxetane C3–S bond over the benzyl C–S bond accounts for the observed products.

In 2012, Veisi published conditions for the synthesis of sulfonyl chlorides from thiols through treatment with DCDMH, *N*-benzyl-trimethylammonium chloride and water.¹⁹⁹ Oxetane thiol **101** was submitted to these conditions but unfortunately no desired product was observed (Scheme 3.36). Following an aqueous work-up, only oxetanol **44** was observed in the ^1H NMR

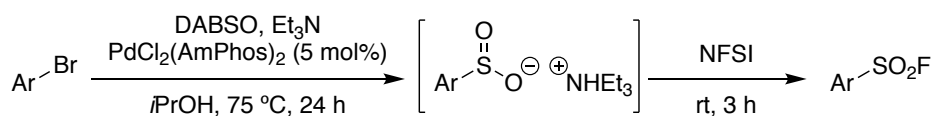
spectrum of the crude product. An alternative work-up was investigated where the reaction was diluted with diethyl ether and filtered through celite but from this reaction only oxetane-3-chloride **117** was formed. As formation of the sulfonyl chloride **116** was unsuccessful through the examined methods, alternative routes to sulfonyl fluoride **115** were considered.



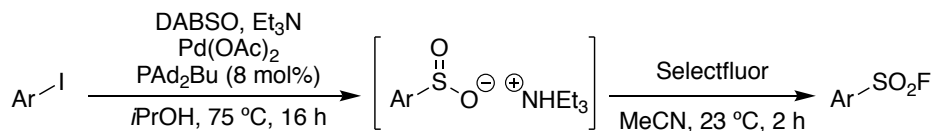
Scheme 3.36 Attempted synthesis of sulfonyl chloride **116** from oxetane thiol **101**.

In 2017, Ball and Willis separately published on the one-pot synthesis of sulfonyl fluorides from aryl halides *via* a sulfinate salt intermediate (Scheme 3.37).^{193,200} In the first step, 1,4-Diazobicyclo[2.2.2]octane bis(sulfurdioxide) adduct (DABSO) was employed as the SO₂ source in a palladium-catalysed sulfonylation reaction to give the aryl sulfinate salt. In the same reaction pot, addition of an electrophilic fluorine source, *N*-fluorobenzenesulfonimide (NFSI) (Willis) or Selectfluor (Ball), delivered the sulfonyl fluoride products in yields between 45% and 93%.

Willis, *Chem. Sci.* **2017**, 8, 1233

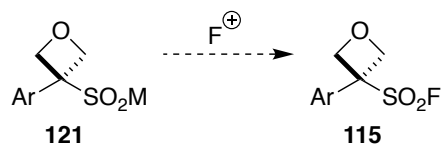


Ball, *J. Org. Chem.* **2017**, 82, 2294



Scheme 3.37 Synthesis of sulfonyl fluorides from aryl halides *via* a sulfinate salt intermediate.

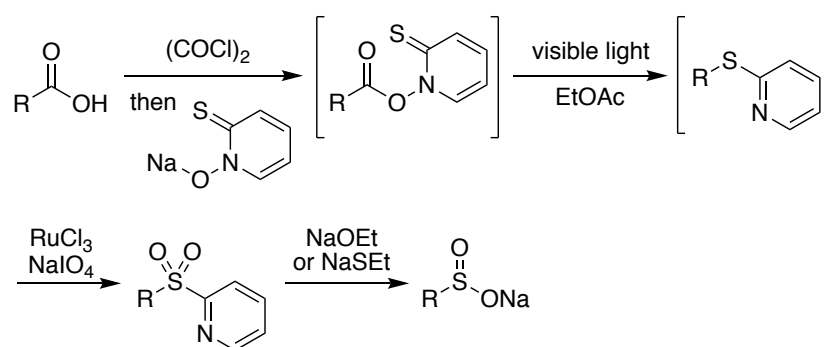
The addition of electrophilic fluorine to a sulfinate salt under mild conditions presented an interesting strategy for the synthesis of oxetane sulfonyl fluoride **115** (Scheme 3.38). Therefore, methods for the synthesis of oxetane sulfinate salt **121** were considered.



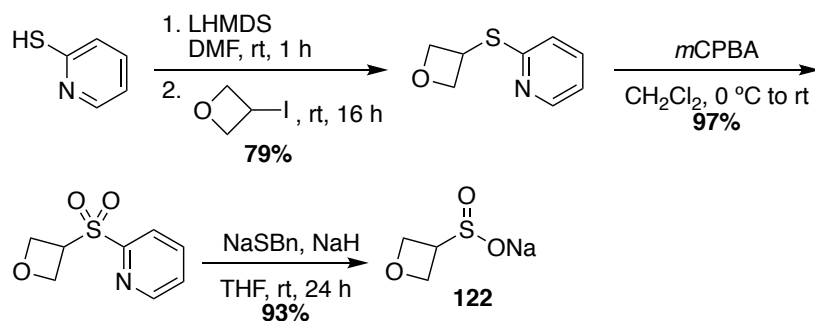
Scheme 3.38 Potential route to sulfonyl fluoride **115** from sulfinate salt **121**.

Sulfinate salts have attracted attention in recent years due to their excellent stability and non-hydroscopic nature.²⁰¹ Sulfonates can be readily prepared by reduction of the corresponding sulfonyl chloride using a combination of sodium sulfite and sodium bicarbonate in water.²⁰² However, the inaccessible nature of the oxetane sulfonyl chloride **116** meant this approach was not feasible for the synthesis of sulfinate salt **121**.

More recently, Baran and co-workers have developed a synthesis of sulfinate salts from carboxylic acids in four steps (Scheme 3.39).²⁰³ The carboxylic acid was converted to a Barton ester which when exposed to visible light underwent radical cleavage and recombination to give a pyridyl sulfide intermediate. Oxidation to the corresponding sulfone using RuCl_3 and sodium periodate followed by cleavage of pyridine by sodium ethoxide or sodium ethanethiolate delivered the desired sulfinate salt product. This method was shown to be applicable for the synthesis of a range of secondary aliphatic sodium sulfinate salts. Furthermore, a single example of a tertiary sulfinate salt (trifluoromethylcyclopropyl sulfinate salt) was synthesised through this method in a 38% yield from the corresponding carboxylic acid. Harrity and co-workers synthesised oxetane sulfinate salt **122** in a high yielding three step sequence from 3-iodooxetane *via* the same pyridyl sulfide intermediate (Scheme 3.40).^{175b}

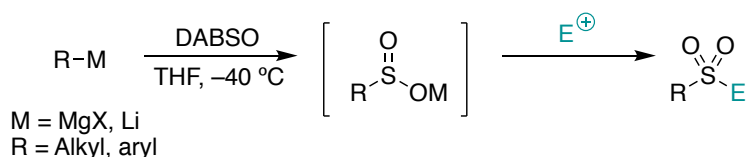


Scheme 3.39 Synthesis of sulfinate salts from carboxylic acids.



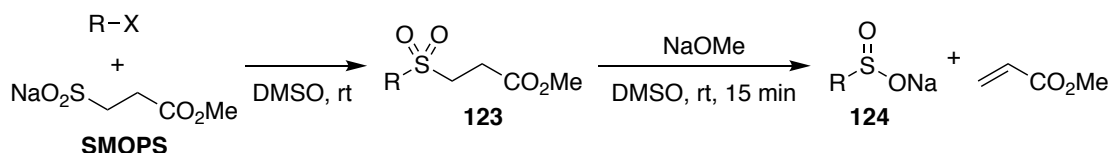
Scheme 3.40 Synthesis of oxetane sulfinate salt **122**.

Willis and co-workers have demonstrated the synthesis of primary and secondary sulfinate salts through the addition of organolithium or Grignard reagents to DABSO (Scheme 3.41).²⁰⁴ The intermediate sulfinate salt can then react with electrophiles to give a diverse range of products. Availability of the starting organometallic substrate makes this strategy not suitable for the synthesis of oxetane sulfinate salt **121**.



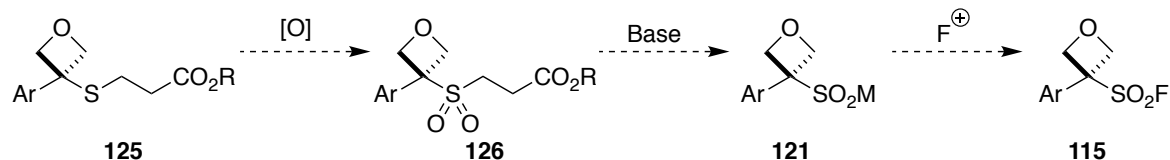
Scheme 3.41 Synthesis of sulfinate salts from organolithium and grignard precursors.

In 2002, Wang published the synthesis of sulfinate salts under mild conditions through an addition and β -elimination strategy (Scheme 3.42).²⁰⁵ Treatment of an alkyl halide with sodium 3-methoxy-3-oxopropane-1-sulfinate (SMOPS) gave sulfone **123** which could undergo base mediated β -elimination of methyl acrylate to give the desired sulfinate salt **124**. Similarly, it has been shown that ethyl-3-(alkylthio)propanoate derivatives can be oxidised to the sulfone and then undergo β -elimination to provide sulfinate salt derivatives.²⁰⁶



Scheme 3.42 Synthesis of sulfinate salts through an elimination protocol.

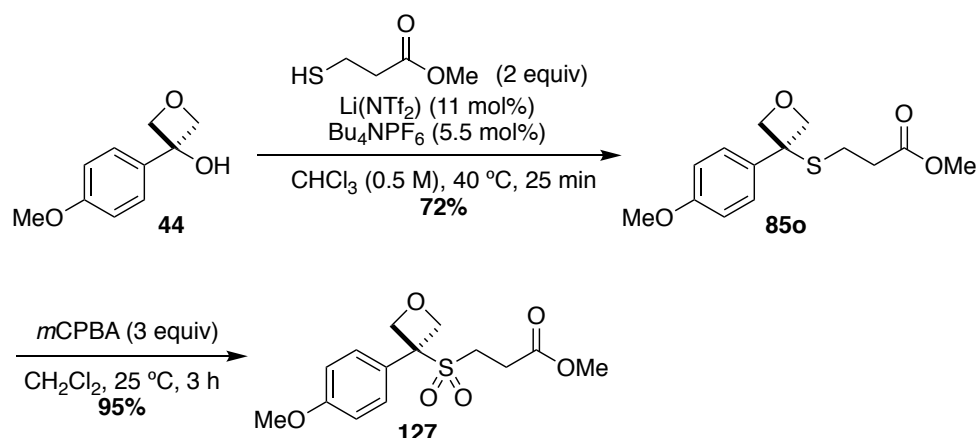
This protocol presented a mild and simple strategy that could be applied to the synthesis of oxetane sulfinate salt **121**. It was anticipated that oxidation of sulfide **125** to sulfone **126** followed by β -elimination would give sulfinate salt **121** which could then be treated by an electrophilic fluorine source to give sulfonyl fluoride **115** (Scheme 3.43).



Scheme 3.43 Proposed synthesis of oxetane sulfonyl fluoride **115**.

3.3.4 Synthesis of Oxetane Sulfinates salts

Sulfide **85o** was synthesised in a 72% yield on a 10 mmol scale through the previously described lithium-catalysed thiol alkylation of oxetanol **44** (see Section 3.2.3). Careful monitoring of the reaction process was required due to significant amounts of oxetane ring opening by the nucleophile under extended reaction times. Oxidation of sulfide **85o** to sulfone **127** was achieved in a 95% yield on an 8.5 mmol scale using 3 equivalents of *m*CPBA. Pleasingly, for this step an aqueous work-up using aq. KOH (3 M) was sufficient for the isolation of pure product without the need for flash column chromatography.



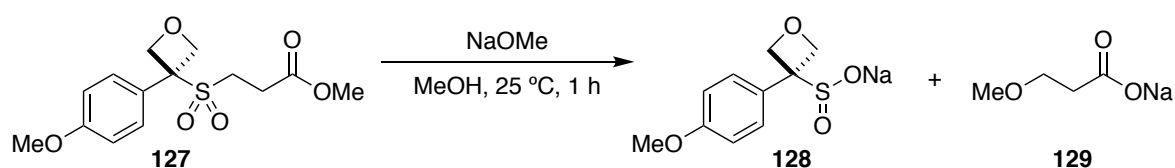
Scheme 3.44 Synthesis of sulfone **127** in 2 steps from oxetanol **44**.

Initial studies for the β -elimination toward sulfinate salt **128** examined sodium methoxide as the base (Table 3.18). Unfortunately, an unseparable side-product resulting from hydrolysis of the methyl acrylate by-product was observed alongside the desired sodium sulfinate salt **128**. Sulfinate salt **128** exhibited low solubility across a range of solvents making aqueous work-up and column chromatography unsuitable. Side-product **129** could not be removed through trituration with an organic solvent in which the sulfinate salt was insoluble (e.g. diethyl ether or ethyl acetate) or evaporation and so conditions were sought to exclude formation of this side-product. In an effort to eliminate water from the reaction and have greater control over the equivalents of base added, a solution of sodium methoxide in anhydrous methanol was freshly prepared. However, only a small increase in selectivity for the sulfinate salt **128**

was observed compared to when using the commercially available solid base and hydrolysed side-product **129** was still obtained in significant quantities (entries 1–2). The effect of different equivalents of sodium methoxide on the formation of this unwanted side-product was then investigated. Use of 1.5 or 2 equivalents of sodium methoxide gave a 3:1 ratio of **128**:**129** (Entries 1 and 3). Reducing the equivalents of base to 1.2 or 1 led to increased selectivity for the sulfinate salt **128** (Entries 4–5). However, in both cases further unseparable reaction intermediates were observed in low quantities.

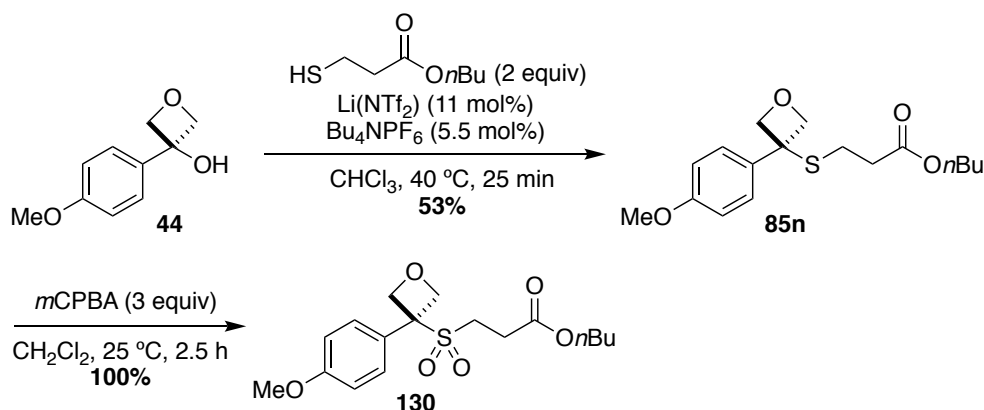
Table 3.18 Examination of sodium methoxide for the formation of sodium sulfinate salt **128**.

^aDetermined from the ¹H NMR spectrum of the crude reaction mixture. ^bOther reaction intermediates observed in low quantities (<5%).



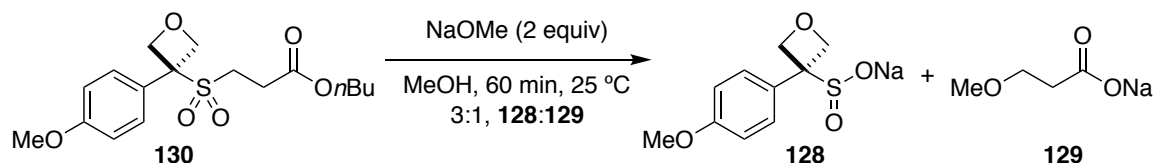
Entry	Source of NaOMe	Equivs of NaOMe	Ratio 128 : 129 ^a
1	Freshly made solution in MeOH	1.5	3:1
2	Commercial solid	1.5	2.5:1 ^b
3	Freshly made solution in MeOH	2	3:1
4	Freshly made solution in MeOH	1.2	4:1 ^b
5	Freshly made solution in MeOH	1	10:1 ^b

To reduce hydrolysis of the acrylate, the synthesis of the more hindered butyl ester **130** was sought (Scheme 3.45). The synthesis of the butyl ester sulfone **130** was achieved in good yield using the same protocol as for the methyl ester analogue **127**.



Scheme 3.45 Synthesis of butyl ester derivative **130**.

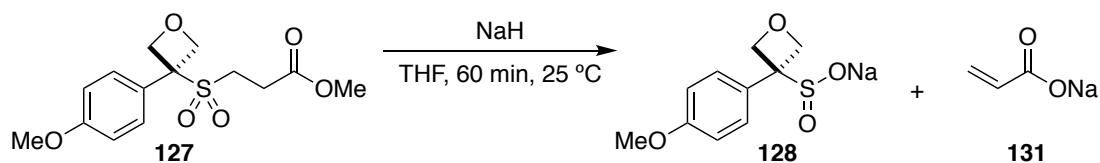
With butyl ester **130** in hand, the synthesis of sulfinate salt **128** was attempted (Scheme 3.46). The desired sulfinate salt **128** was observed as the major product but again hydrolysis of the acrylate by-product occurred to give **129**, making purification difficult. *n*-Butanol was also observed in the reaction mixture providing confirmation of ester hydrolysis.



Scheme 3.46 Synthesis of sulfinate salt **128** from sulfone **130**.

We considered that the water/hydroxide ions in the reaction mixture could be introduced with the sodium methoxide so the use of a different sodium base, sodium hydride, was explored (Table 3.19). Use of 1.1 equivalent of sodium hydride in THF gave a 20:1 ratio of **128**:**131** (Entry 1). Reducing the amount of base further to 1 equivalent gave better selectivity (30:1) although 3% of other reaction intermediates were also observed in the reaction (Entry 2). Pleasing, employing 1.05 equivalents of sodium hydride gave sulfinate salt **128** as the single product in the reaction (Entry 3). Purification was achieved to give pure product through removal of methyl acrylate *in vacuo* and washing the resultant solid with hexane to remove the mineral oil introduced with the sodium hydride. This reaction was conducted on an 8 mmol scale to give sulfinate salt **128** in a 95% yield.

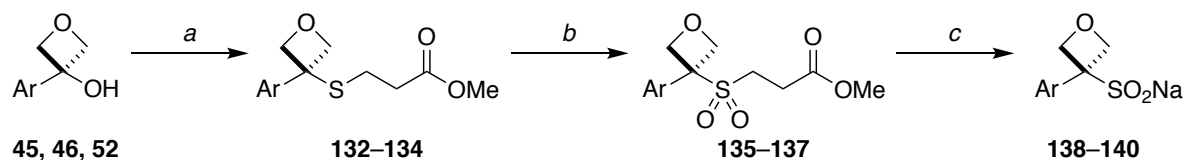
Table 3.19 Synthesis of sulfinate salt **128** using sodium hydride. ^aDetermined from the ¹H NMR spectrum of the crude reaction mixture. ^b3% of other reaction intermediates observed. ^c95% of sulfinate salt **128** isolated on an 8 mmol scale.



Entry	Equivs of NaH	Ratio 128 : 131 ^a
1	1.1	20:1
2	1	30:1 ^b
3	1.05	1:0 ^c

This short 3-step sequence to access oxetane sulfinate salts was successfully applied to other 2-aryl-substituted oxetanols (Table 3.20). Sodium sulfinate salts **138** and **139** substituted with *p*-OBn and *p*-OTIPS groups respectively were synthesised in good overall yields (Entries 1–2). Indole substituted sulfinate salt **140** could also be accessed through this route although there were some differences in reactivity. Indole-containing sulfide **134** required the Ca(NTf₂)₂ catalyst for the thiol alkylation step as the reaction was unsuccessful with Li(NTf₂) (Entry 3). Lower yields were obtained for the oxidation of **134** and this is attributed to the instability of **137** to the basic work-up conditions leading to premature elimination of methyl acrylate. Alternative work-up conditions could be considered in the future but for the purposes of this work sufficient material was obtained.

Table 3.20 Synthesis of sulfinate salts **138–140**. a) For **132** and **133**: methyl 3-mercaptopropionate (2 equiv), Li(NTf₂) (11 mol%), Bu₄NPF₆ (5.5 mol%), CHCl₃ (0.5 M), 40 °C, 25 min; for **134**: methyl 3-mercaptopropionate (2 equiv), Ca(NTf₂)₂ (5 mol%), Bu₄NPF₆ (5 mol%), CHCl₃ (0.5 M), 40 °C, 25 min; b) *m*CPBA (3 equiv), CH₂Cl₂, 25 °C, 3 h; c) NaH (1.05 equiv), THF, 25 °C, 1 h.

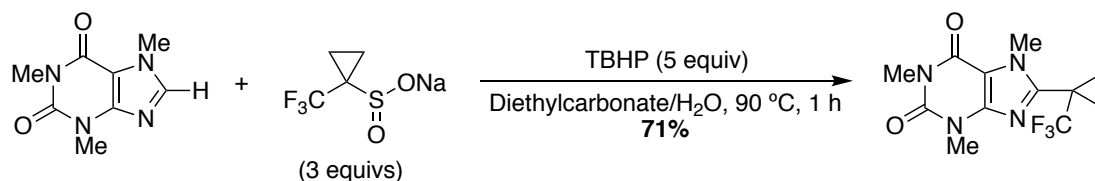


Entry	Ar	Yield for step a (%)	Yield for step b (%)	Yield for step c (%)
1		73	100	100
2		57	99	93
3		90	50	71

3.3.5 Attempted Reactions of Oxetane Sulfinate Salts

With a reliable method for the synthesis of oxetane-containing sulfinate salts in hand, potential reactions of these salts were explored.

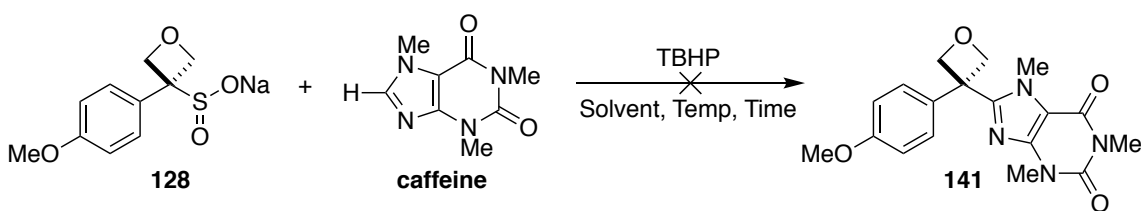
In 2014, Baran and co-workers reported the use of six different sulfinate salts in the C–H functionalisation of four heteroarenes through a radical mediated process using *tert*-butyl hydroperoxide (TBHP) (Scheme 3.47).²⁰³ Examples included coupling of trifluoromethylcyclopropyl sodium sulfinate salt to various heteroarenes, the only examples of couplings using a tertiary sulfinate salt.



Scheme 3.47 Example of C–H functionalisation through the reaction of sulfinate salts with heteroarenes.

In recent years, several other variations of these conditions have been reported using lower temperatures, different solvents and in some cases acidic additives or a catalyst.²⁰⁷ Oxetane-containing sulfinate salt **128** was submitted to these known sets of C–H functionalisation conditions using caffeine as the model heteroaromatic coupling partner (Table 3.21). Unfortunately, in no case was any desired oxetane-containing product **141** observed in the ¹H NMR spectrum of the crude reaction mixture. The sterically bulky nature of sulfinate salt **128** makes this coupling very challenging.

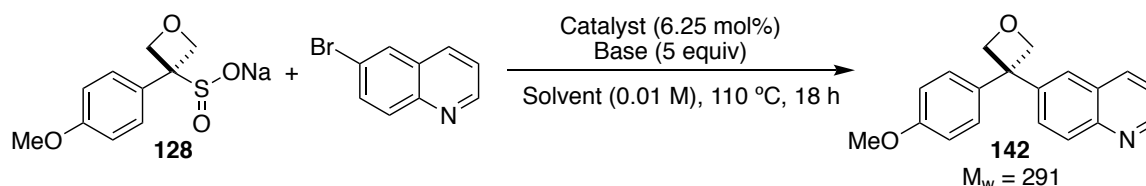
Table 3.21 Examined conditions for the C–H functionalisation of caffeine with sulfinate salt **128**.

							
Entry	Equivs of 128	Equivs of TBHP	Catalyst (mol%)	Solvent	Additive	Temp (°C)	Time (h)
1 ²⁰³	3	5	-	(EtO) ₂ CO/H ₂ O	-	90	1
2 ^{207c}	3	5	-	DMSO	-	50	14
3 ^{207c}	3	5	-	DMSO	TFA	50	14
4 ^{207b}	2	3	-	CH ₂ Cl ₂ /H ₂ O	TFA	25	14
5 ^{207a}	3	5	CuSO ₄ (10)	CH ₂ Cl ₂ /H ₂ O	-	25	14
6 ^{207d}	3	5	-	CH ₂ Cl ₂ /H ₂ O	ZnCl ₂ , TsOH.H ₂ O	25	20

Palladium-catalysed desulfinate cross-coupling of heteroaromatic sulfinates with aryl bromides is known using [Pd(PtBu₃)₂] as the catalyst.²⁰⁸ Furthermore, desulfinate Heck couplings of aryl sulfinate salts have also been reported.²⁰⁹ The possibility of palladium-catalysed cross-couplings using oxetane sulfinate salt **128** was intriguing. Therefore, a screen of different combinations of palladium catalysts, bases and solvents was run at Pfizer for the reaction between oxetane sulfinate salt **128** and 6-bromoquinoline (Table 3.22). A total of 192 reactions were run on a 0.001 mmol scale at a 0.01 M concentration at 110 °C for 18 hours. The reactions were analysed directly using LCMS to identify the product ion at MW292+ve based on ionisation of the quinoline. Selected conditions showed a new product peak at MW292+ve which also showed the expected decrease in polarity compared

to the starting material. However, in all cases yields were very low (<5% by %Area UV). The highest yield was observed using a combination of SPhos Pd 4th generation and cesium fluoride in acetonitrile. Further to the low yields observed, instability of sulfinate salt **128** in the solvents examined was reported which presented a significant problem so investigations were not continued.

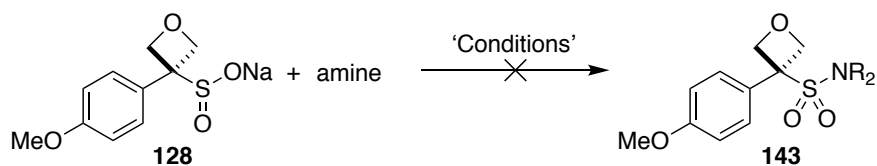
Table 3.22 All the variables screened for the palladium-catalysed coupling of sulfinate salt **128** with 6-bromoquinoline to give **142**. Screen conducted at Pfizer.



Catalyst	Pd(dppf)Cl ₂ , Pd(PtBu ₃) ₂ , Pd(PPh ₃) ₄ , Pd(dtbpf)Cl ₂ , Pd(AmPhos) ₂ Cl ₂ , Pd(OAc) ₂ /CataCXium A, SPhos Pd G4, Pd(P(<i>o</i> -tol) ₃) ₂ Cl ₂ , Pd(P(Cy) ₃) ₂ Cl ₂ , Pd(QPhos) ₂ , Pd(Xantphos)Cl ₂ , Pd(OAc) ₂ /Xphos
Base	NaOH; sat. aq. NaHCO ₃ , aq. CsF, CsF (in EtOH), aq. K ₃ PO ₄
Solvent	MeOH; MeCN; THF; Toluene

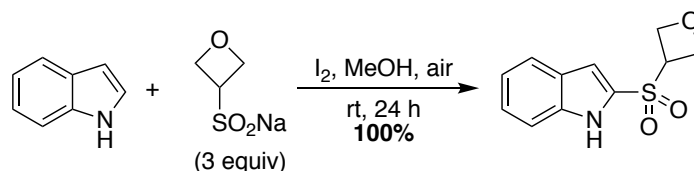
In recent years, sulfinate salts have been reported as precursors to sulfonamides. Oxidative coupling of sodium sulfinate salts with amines has been shown to be successful using: catalytic CuBr₂ and either O₂ or DMSO,²¹⁰ a combination of *tert*-butyl hydroperoxide (TBHP) and *tetra*-*n*butylammonium iodide (TBAI),²¹¹ 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) and diisopropylethylamine (DIPEA),²¹² or *N*-chlorosuccinimide (NCS).²¹³

These literature conditions were examined using oxetane-containing sulfinate salt **128** (Table 3.23). Under the examined conditions using either morpholine or piperidine as the amine, no desired reactivity was observed. In some cases, oxetanol **44** was observed indicating degradation of the starting sulfinate salt **128** (Entries 1–2). When DCDMH was employed only starting material **128** was seen in the ¹H NMR spectrum of the crude reaction mixture (Entries 4–6). Where only starting material **128** was recovered, the lower temperature may account for the lack of reactivity. At this stage, it was decided that other methods to make sulfonamides may be more successful so further conditions to access these scaffolds from sulfinate salt **128** were not examined.

Table 3.23 Conditions screened for the attempted formation of oxetane-containing sulfonamide **143** from sulfinate salt **128**.

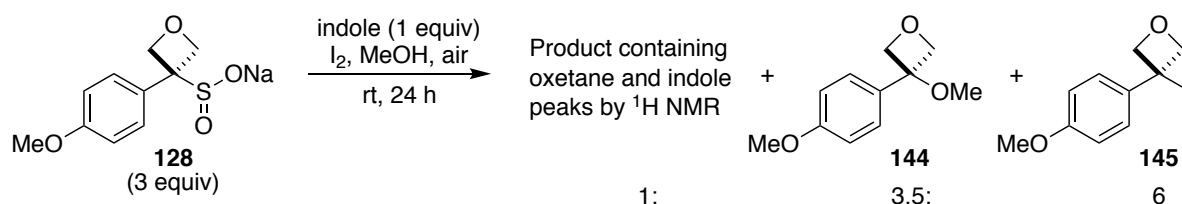
Entry	'Conditions'	Result
1 ²¹⁰	morpholine (1.2 equiv), CuBr ₂ (20 mol%) DMSO, 100 °C, 24 h	oxetanol 44 observed
2 ²¹³	piperidine (2 equiv), NCS (2 equiv), Et ₃ N (33 mol%) DMF, 25 °C, 2 h	oxetanol 44 observed
3 ²¹¹	morpholine (1.5 equiv), TBAI (20 mol%), TBHP (3 equiv) DMSO, 100 °C, 24 h	No products identified
4 ²¹²	piperidine (2 equiv), DCDMH (0.3 equiv) CH ₂ Cl ₂ /heptane, 25 °C, 2 h	SM returned
5 ²¹²	piperidine (2 equiv), DCDMH (0.3 equiv), DIPEA (2 equiv) CH ₂ Cl ₂ /heptane, 25 °C, 2 h	SM returned
6 ²¹²	piperidine (2 equiv), DCDMH (0.3 equiv), TBAI (20 mol%) CH ₂ Cl ₂ /heptane, 25 °C, 2 h	SM returned

Sulfinate salts can undergo coupling reactions with indole through a radical process.²¹⁴ In 2014, Kuhakarn reported conditions for the coupling of sodium sulfinate salts with various indole derivatives using 1.5 equivalents of iodine in methanol at room temperature for 2 hours.²¹⁵ A total of 41 examples were reported in yields between 10% and 96%. Subsequently, Harrity reported the use of these conditions for the coupling of indole derivatives to azetidine sulfinate salts and, importantly in the context of the research detailed in this thesis, sodium oxetane-3-sulfinate (Scheme 3.48).^{175b} Electron rich indoles gave the desired coupled products in excellent yields (up to 100%).



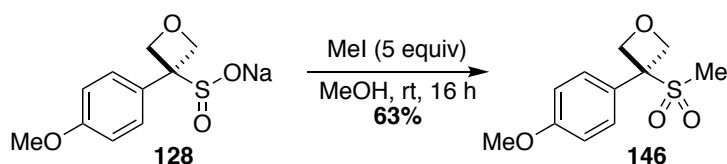
Scheme 3.48 Radical coupling of sodium oxetane-3-sulfinate with indole.

This reaction was attempted using oxetane sulfinate salt **128** and indole (Scheme 3.49). In the ^1H NMR spectrum of the crude product only a small amount of product containing both oxetane and indole functionality was observed (<10%). The major products, tentatively assigned as **144** and **145**, resulted from ionic processes. Unfortunately, the small amount of indole containing product was not separable from 3-iodooxetane **145** preventing full characterisation. The reaction was repeated without indole present and in this case **144** and **145** were observed as the only products in a 71:29 ratio. In comparison to Harrity's successful reaction, the steric requirements of sulfinate salt **128** may prevent the desired radical coupling from proceeding. Alternatively, the stability of sulfinate salt **128** may not be sufficient under the reaction conditions.



Scheme 3.49 Attempted indole coupling using sulfinate salt **128**.

Methylation of sulfinate salt **128** was attempted using conditions from Paras and co-workers (Scheme 3.50).²¹⁶ Pleasingly, treatment of sulfinate salt **128** with 5 equivalents of methyl iodide in methanol at room temperature for 16 hours delivered the desired methylated product **146** in a 63% yield. This successful reaction also demonstrated that sulfinate salt **128** is stable enough at room temperature in methanol to be a useful intermediate.



Scheme 3.50 Methylation of sulfinate salt **128**.

3.3.6 Optimisation of Oxetane Sulfonyl Fluorides

Next, the synthesis of oxetane sulfonyl fluoride **147** was explored through reaction of oxetane sulfinate salt **128** with electrophilic fluorine sources (Table 3.24). Pleasingly, both selectfluor and *N*-fluorobenzenesulfonimide (NFSI) enabled formation of the desired sulfonyl fluoride product in similar yields of approximately 70% by ^1H NMR spectroscopy against an internal standard (Entries 1–2). 3-Methoxyoxetane **144** was also observed in the reaction mixture resulting from reaction with methanol. To confirm the structure of this side-product, a pure sample of **144** was synthesised through methylation of oxetanol **44**. This was achieved in an 88% yield through treatment of oxetanol **44** with sodium hydride then addition of methyl iodide. Full characterisation was carried out and the peaks in the ^1H NMR spectrum of the pure sample matched peaks for the side-product from the fluorination reaction of sulfinate salt **128**.

Table 3.24 Optimisation of the reaction of sulfinate salt **128** to form sulfonyl fluoride **147**. ^a*In situ* yields calculated by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. Isolated yields in parentheses.

Reaction scheme: Sulfinate salt **128** (4-methoxyphenyl oxetane sulfinate sodium salt) reacts with an F^+ Source (1.5 equiv) in a solvent at a certain temperature and time to produce sulfonyl fluoride **147** (4-methoxyphenyl oxetane sulfonyl fluoride) and side-product **144** (3-methoxyoxetane).

Entry	F^+ Source	Solvent	Temp (°C)	Time (h)	Yield 147 (%) ^a	Yield 144 (%) ^a
1	NFSI	MeOH	25	2	70 (45)	17
2	Selectfluor	MeOH	25	2	68 (50)	16
3	Selectfluor	MeCN	25	2	60	n/a
4	Selectfluor	<i>i</i> PrOH	25	2	43	n/a
5	Selectfluor	MeOH	0	2	90	0
6	Selectfluor	MeOH	0	1	89 (85)	0
7	Selectfluor	MeOH	0	0.5	84	0

Different polar solvents, acetonitrile and *iso*-propanol, were explored to preclude side-product formation (Entries 3–4). However, both these alternative solvents gave lower yields of the desired sulfonyl fluoride product **147** so methanol was chosen as the preferred solvent.

Control of the reaction temperature was found to be key for the reaction. Reducing the reaction temperature from 25 °C to 0 °C maximised yield of sulfonyl fluoride **147** and prevented

formation of side-product **144** (Entries 2 and 5). To aid temperature control the set-up of the reaction was optimised. Adding the solid reagents into the reaction vial and then adding precooled methanol gave variable yields particularly for larger scale reactions (>1 mmol). However, precooling the solvent in the reaction vessel and then adding the selectfluor and sulfinate salt reagents led to more reliably reproducible results most likely due to better temperature control.

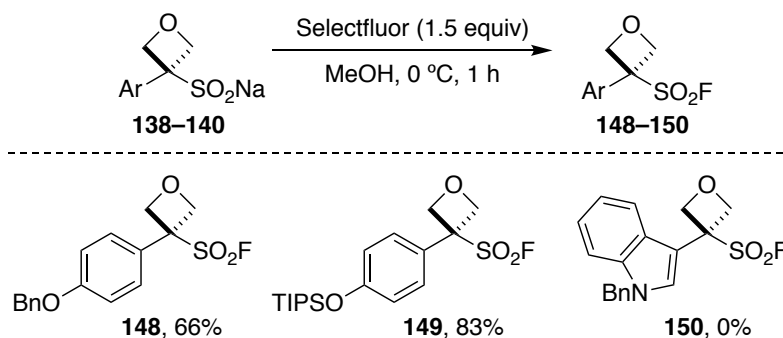
Finally, reducing the reaction time to 1 hour was sufficient for the reaction to reach completion (Entry 6). Further reducing the reaction time to just 30 minutes gave a slightly lower yield of **147** so a 1 hour reaction time was adopted as optimal (Entry 7).

Large discrepancies between the *in situ* yields (by ^1H NMR against an internal standard) and isolated yields of sulfonyl fluoride **147** were noted and were attributed to a degree of instability of the product on silica (Entries 1–2). Pleasingly, under the optimised conditions lack of side-product formation enabled purification by flash column chromatography through a very short plug of silica using dichloromethane as the eluent. This significantly reduced the time sulfonyl fluoride **147** was exposed to silica leading to higher isolated yields that corresponded well with those calculated from the crude reaction mixture using ^1H NMR spectroscopy. The high polarity of the excess selectfluor and selectfluor-derived salt produced as a by-product in the reaction meant that these did not advance through the silica in the eluent system used.

Under the optimal conditions on a 3.5 mmol scale, oxetane sulfonyl fluoride **147** was isolated cleanly in an 85% yield (Entry 6). The product was an easily handled white crystalline solid which required storage <0 °C as rapid degradation was observed when stored at room temperature for longer than 24 hours.

3.3.7 Scope of Oxetane Sulfonyl Fluorides

Sulfinate salts **138–140** were submitted to the optimal conditions to form the corresponding sulfonyl fluorides **148–150** (Scheme 3.51). Replacing the methoxy group with an OBn or OTIPS group was successful with sulfonyl fluorides **148** and **149** synthesised in good yields. Sulfinate salt **140**, substituted with an indole group, was unsuccessful in the reaction and underwent complete degradation under the fluorination conditions indicating a limitation of this methodology.

Scheme 3.51 Scope of oxetane-containing sulfonyl fluorides.

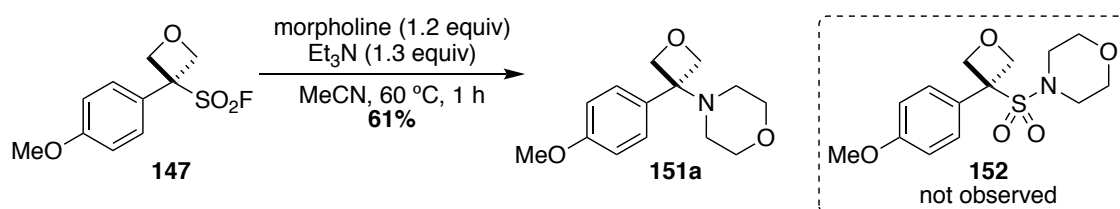
Although this route to oxetane sulfonyl fluorides is five steps from commercially available oxetan-3-one, all the steps are high yielding and relatively simple. For example, oxetane sulfonyl fluoride **147** was synthesised in a high 46% yield over the five steps from oxetan-3-one. In addition to the high yields obtained, neither the oxidation or elimination steps required column chromatography and the fluorination step required minimal purification.

The reactivity of these oxetane sulfonyl fluorides derivatives with amines is discussed in the next section.

3.4 The Synthesis of 3-Aminooxetanes

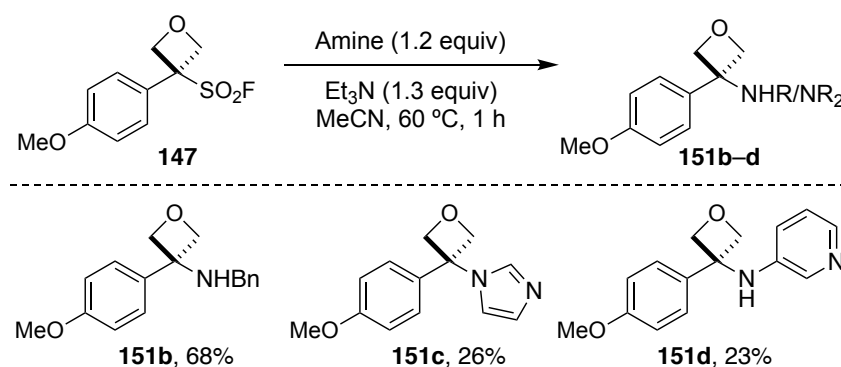
3.4.1 Reactivity of Oxetane Containing Sulfonyl Fluorides

Sulfonamides are ubiquitous motifs in medicinal chemistry and so the synthesis of oxetane-containing sulfonamide analogues was of interest.¹⁶⁹ Oxetane sulfonyl fluoride **147** was reacted with morpholine in the presence of triethylamine in acetonitrile at 60 °C for 1 hour (Scheme 3.52). Based on the precedent in the literature, under these conditions sulfonamide **152** was the expected product (see Section 3.3.2).^{192,193,194} However, sulfonamide **152** was not observed and instead 3-aminooxetane **151a** was isolated in a 61% yield.



Scheme 3.52 Reaction of sulfonyl fluoride **147** with morpholine to give 3-aminooxetane **151a**.

This represented the first example of this reactivity for sulfonyl fluorides and so several different amines were examined to confirm that the reaction of sulfonyl fluoride **147** with morpholine was not an anomalous result (Scheme 3.53). Benzylamine, imidazole and 3-aminopyridine all gave the 3-aminooxetane product (**151b–d**) under these unoptimised conditions and, importantly, none of the corresponding sulfonamide product was observed for any of the examples.



Scheme 3.53 Scope of 3-aminooxetanes under unoptimised conditions.

The ¹H and ¹³C NMR spectra of the sulfonamide and 3-aminooxetane products would be expected to be very similar. Furthermore, complex absorption patterns in the IR spectra led to inconclusive interpretation of this data as the presence or absence of absorptions at frequencies corresponding to S=O stretching in sulfonamides could not be confirmed.

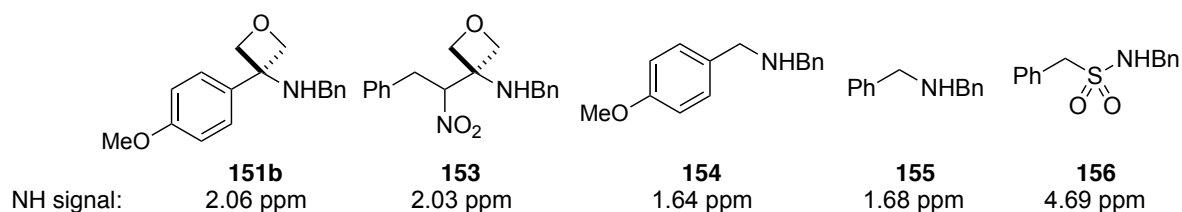
However, for all reactions of sulfonyl fluoride **147** with different amines, mass spectrometry data supported the formation of the 3-aminooxetane product (Table 3.25) leading to the assignment of the products as the 3-aminooxetanes as shown in Scheme 3.52 and Scheme 3.53. The expected mass ion for the sulfonamide product was not observed for any of the examples.

Table 3.25 Expected mass ions for the amines and sulfonamide products and the observed mass ions by mass spectrometry.

Entry	Amine	Expected [M+H] ⁺ ion for 3-aminooxetane	Expected [M+H] ⁺ ion for sulfonamide	Observed mass ion
1	morpholine	250.1443	314.1062	250.1438
2	benzylamine	270.1494	334.4100	270.1495
3	imidazole	231.1134	295.3250	231.1138
4	3-aminopyridine	257.1290	321.3710	257.1283

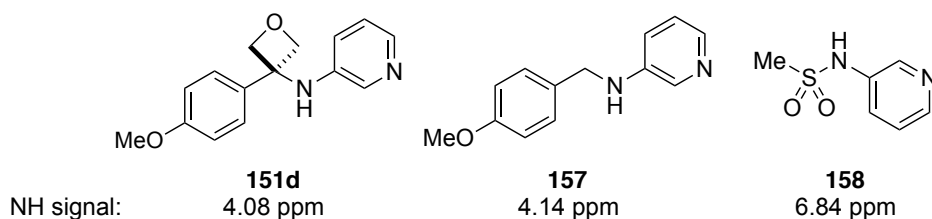
For the reaction with either benzylamine or 3-aminopyridine, the NH signal in the ¹H NMR spectra of the products corresponded to the expected NH signal for the 3-aminooxetane product based on comparisons to related literature compounds. The ¹H NMR spectrum for the oxetane-containing product resulting from the reaction of sulfonyl fluoride **147** with benzylamine showed a broad singlet corresponding to the NH proton at 2.06 ppm (Figure 3.30). This corresponded well to the NH signal for 3-aminooxetane **153**, a known literature compound, which occurs at 2.03 ppm.²¹⁷ Furthermore, literature ¹H NMR data for the NH peaks of methylene compounds **154** and **155** also corresponded well, occurring at 1.64 ppm and 1.68 ppm respectively.²¹⁸ The observed downfield shift for the NH signal of oxetane analogue **151b** compared to these methylene derivatives can be attributed to the electron-withdrawing nature of the oxetane motif. The NH peak in sulfonamide **156** occurs at a significantly higher 4.69 ppm, providing further evidence that the oxetane sulfonamide product is not being formed.²¹⁹

Figure 3.30 Comparison of NH peaks in the ^1H NMR spectra of related amines and sulfonamides containing NHBn.

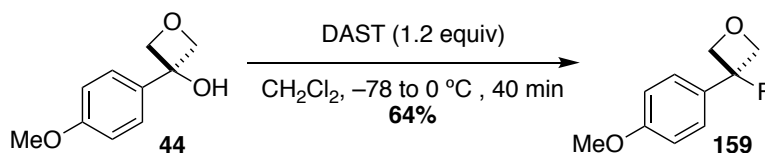


The signal for the NH proton in the ^1H NMR spectrum of the product from the reaction of sulfonyl fluoride **147** with 3-aminopyridine occurred at 4.08 ppm (Figure 3.31). This corresponded well to the methylene amine analogue **157** where the NH peak is reported at 4.14 ppm.²²⁰ For 3-aminopyridine sulfonamide **158** the reported NH signal is shifted significantly downfield at 6.84 ppm and therefore does not closely align with the observed oxetane-containing product.²²¹

Figure 3.31 Comparison of NH peaks in ^1H NMR spectra of related amines and sulfonamides containing a 3-aminopyridine group.

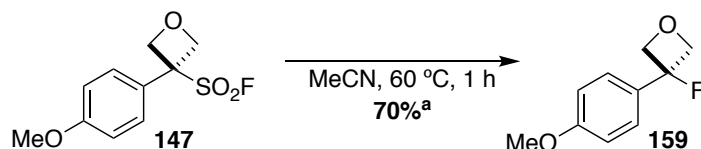


A small amount (approx. 10%) of a volatile side-product was observed in the reaction of sulfonyl fluoride **147** with morpholine (Scheme 3.52). This side-product was difficult to isolate due to its volatility and similar polarity to sulfonyl fluoride **147**. 3-Fluorooxetane **159** was proposed as the most likely structure based on the signals for the side-product in the ^1H and ^{19}F NMR spectra of the crude reaction mixture. In order to confirm the structure, an authentic sample of 3-fluorooxetane **159** was synthesised through treatment of oxetanol **44** with DAST (Scheme 3.54). The signals in the ^1H , ^{13}C and ^{19}F NMR spectra of this pure sample of 3-fluorooxetane **159** matched the signals for the side-product from the reaction of sulfonyl fluoride **147** with morpholine, providing confirmation of the structure.



Scheme 3.54 Synthesis of 3-fluorooxetane **159** from oxetanol **44**.

To investigate the formation of 3-fluorooxetane **159**, sulfonyl fluoride **147** was stirred in acetonitrile at 60 °C for 1 hour without amine or triethylamine (Scheme 3.55). Under these conditions a 70% yield of **159** (by ^1H NMR spectroscopy against an internal standard) was observed alongside 15% of recovered starting material. This result suggested that at 60 °C, fluoride ions are being produced in the reaction and are able to react at the oxetane C3-position. The most likely mechanism is that fluoride and sulfur dioxide are released under the reaction conditions to generate an oxetanyl carbocation intermediate. Subsequent nucleophilic attack by the available fluoride ions in the absence of a more reactive nucleophile leads to the formation of 3-fluorooxetane **159**.



Scheme 3.55 Reaction of sulfonyl fluoride **147** in the absence of amine. ^a*In situ* yield calculated by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

The reactivity of sulfonyl fluoride **147** was studied in greater depth using ^1H NMR spectroscopy to generate reaction profiles. The reactions in this study were conducted in ^1H NMR tubes fitted with a J Young tap due to the high volatility of 3-fluorooxetane. Deuterated acetonitrile was used as the solvent and mesitylene was employed as an internal standard in order to calculate *in situ* yields. The reactions of sulfonyl fluoride **147** with morpholine and TMS-morpholine were studied as well as the reaction in the absence of an amine nucleophile.

In the absence of an amine and triethylamine, the amount of 3-fluorooxetane **159** increased steadily throughout the reaction and was observed in an 82% yield after 2 hours (Figure 3.32). This correlated well to the result obtained from the same reaction when conducted in a round bottomed flask (Scheme 3.55) and confirmed the instability of oxetane sulfonyl fluoride **147** at 60 °C.

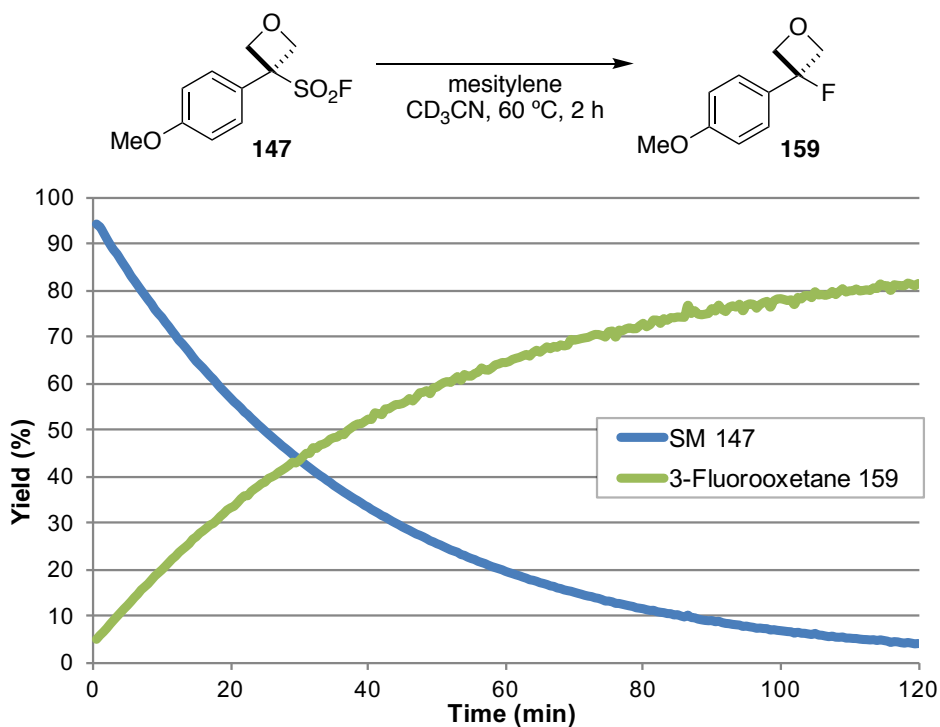


Figure 3.32 Reaction profile for the reaction of sulfonyle fluoride **147** in the absence of nucleophile.

The reaction profile for the reaction of sulfonyle fluoride **147** with morpholine was generated using ¹H NMR spectroscopy and showed 3-aminooxetane **151a** being formed as the major product, reaching a maximum yield of 78% after 2 hours (Figure 3.33). 3-Fluorooxetane **159** was also observed in the reaction in a 10% yield upon reaction completion. Morpholine is clearly a more effective nucleophile in the reaction than fluoride but competition by fluoride ions generated in the reaction is problematic due to the not insignificant amounts side-product formation.

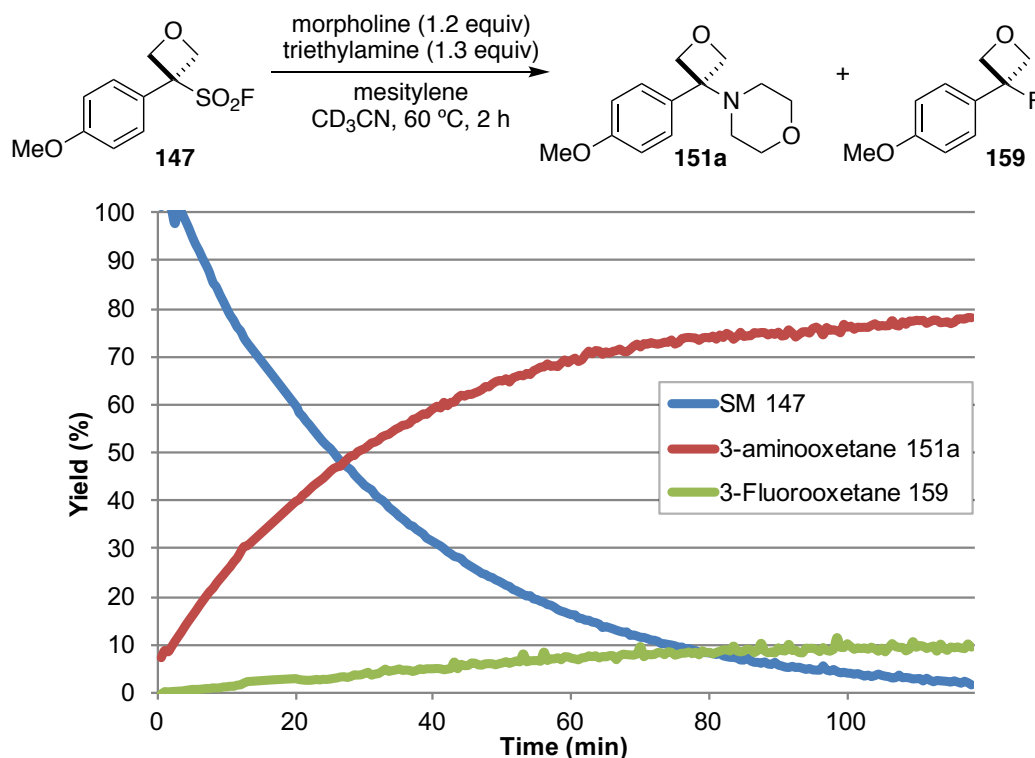


Figure 3.33 Reaction profile for the reaction of sulfonyl fluoride **157** with morpholine.

In 2013, Klumpp reported the use of *N*-silylamines for the preparation of sulfonamides from sulfonyl fluorides, proposing that the formation of a silicon-fluorine bond provided a driving force for the reaction.²²² Therefore, TMS-amines were considered as expedient nucleophiles for the reaction of sulfonyl fluoride **147** towards 3-aminooxetanes as, potentially, the TMS-amine could coordinate to the fluoride produced in the reaction, preventing the formation of 3-fluorooxetane **159**, in addition to its role as the nucleophile. ¹H NMR experiments were conducted to monitor the reaction between sulfonyl fluoride **147** and TMS-morpholine *in situ*. Pleasingly, the generated reaction profile showed that no 3-fluorooxetane **159** was observed over the 2 hour reaction time (Figure 3.34). Furthermore, 3-aminooxetane **151a** was formed in a higher yield of 83% (*cf.* 78% for the reaction with morpholine).

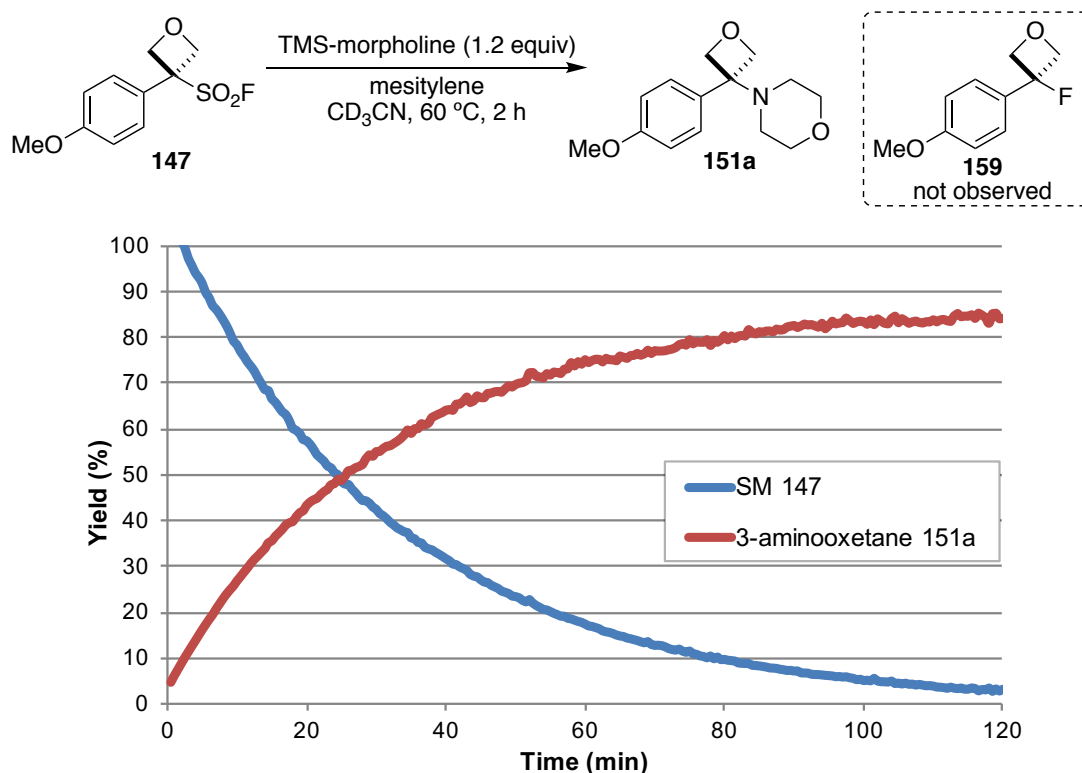
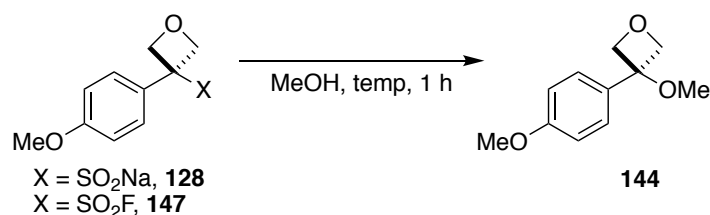


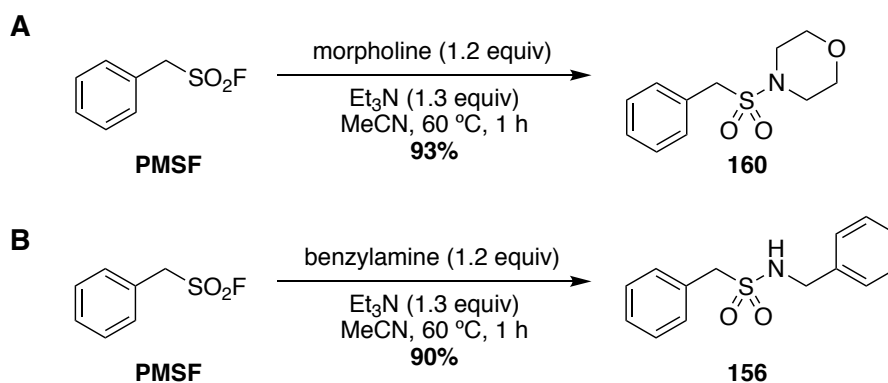
Figure 3.34 Reaction profile for the reaction of sulfonyl fluoride **147** with TMS-morpholine.

To investigate the temperature dependent stability of sulfinate salt **128** and sulfonyl fluoride **147** further, both compounds were stirred in methanol at 25 °C and 60 °C (Table 3.26). Sulfinate salt **128** was stable at both temperatures with starting material recovered quantitatively (Entries 1–2). Sulfonyl fluoride **147** was stable at 25 °C with 97% of starting material recovered and oxetane ether **144** formed in a low 3% yield (Entry 3). However, at 60 °C, a 91% yield of oxetane ether **144** was observed alongside only 6% of the starting material **147**, demonstrating that sulfonyl fluoride **147** lacks stability at this temperature (Entry 4).

Table 3.26 Stability of sulfinate salt **128** and sulfonyl fluoride **147** at 25 °C and 60 °C.

Entry	X	Temperature (°C)	Yield 144 (%)	Recovered SM (%)
1	SO ₂ Na	25	0	100
2	SO ₂ Na	60	0	100
3	SO ₂ F	25	3	97
4	SO ₂ F	60	91	6

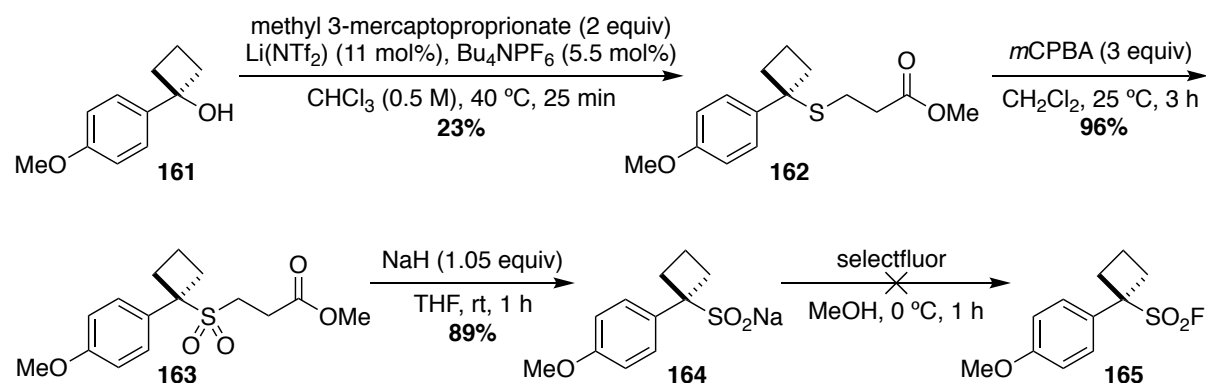
The reactivity of oxetane-containing sulfonyl fluoride **147** was compared to commercially available PMSF. Under the same reaction conditions that were examined for sulfonyl fluoride **147** (triethylamine, 60 °C, 1 hour), PMSF reacted with both morpholine and benzylamine to give the sulfonamide products **160** and **156** in excellent yields (Scheme 3.56). Spectroscopic data for both compounds matched reported values in the literature for the sulfonamide products and categorically did not match reported data for the corresponding amines.²²³

**Scheme 3.56** Reaction of PMSF with morpholine (A) and benzylamine (B) to give sulfonamides **160** and **156** respectively.

In order to gain a deeper understanding of the sulfonamide/amine selectivity when sulfonyl fluorides react with amine nucleophiles, cyclobutane analogues were investigated. Cyclobutane sulfonyl fluorides **165** and **172** were targeted using the same synthetic sequence used for the oxetane sulfonyl fluorides **147–149**. The 1-arylcyclobutan-1-ols **161** and **91c** were

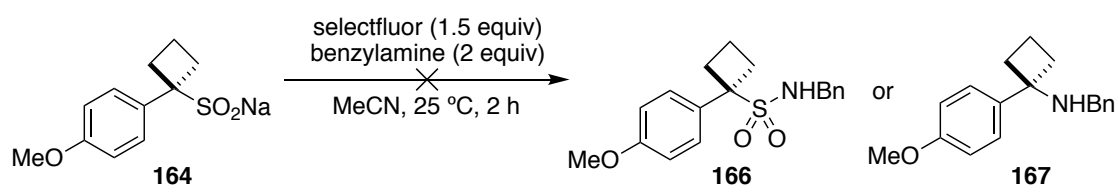
synthesised through addition of aryl-lithium reagents (generated *in situ* from the halogen-lithium exchange between *n*BuLi and the required aryl-bromide) to cyclobutanone.

The thiol alkylation step proved problematic for the synthesis of sulfide **162** from cyclobutanol **161** with a low yield (23%) of sulfide **162** obtained alongside substantial amounts of recovered starting material (Scheme 3.57). Possibly, an unidentified side-product may be forming in the reaction preventing the desired catalytic cycle. Ultimately, for the purposes of this study sufficient sulfide **162** was obtained and so further investigation of alternative thiol alkylation conditions that may have improved the yield were not explored. Oxidation of sulfide **162** to give sulfone **163** and then elimination of methyl acrylate under basic conditions afforded sulfinate salt **164** in excellent yield over the two steps. However, under the developed conditions for forming sulfonyl fluorides from sodium sulfinate salts, degradation of sulfinate salt **164** occurred and no desired sulfonyl fluoride **165** was formed in the reaction.



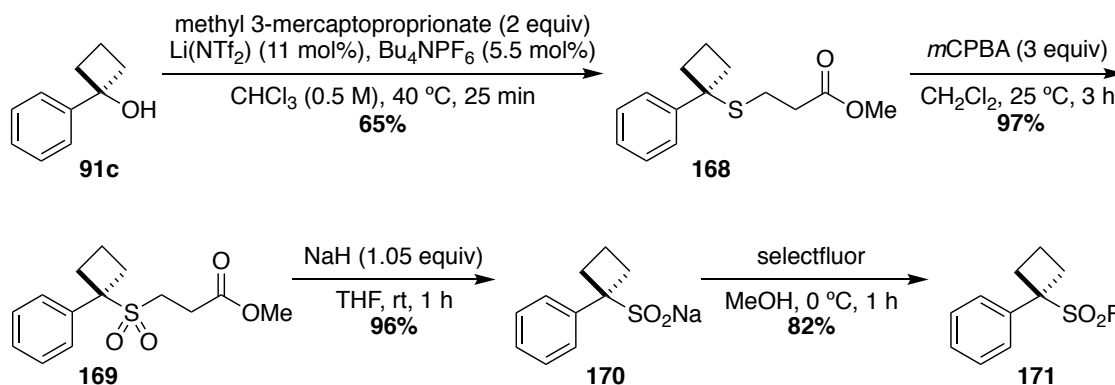
Scheme 3.57 Attempted synthesis of cyclobutane-containing sulfonyl fluoride **165**.

We considered that potentially sulfonyl fluoride **165** was forming *in situ* but rapidly degrading to give an unstable cyclobutane carbocation intermediate. Therefore, reaction of sulfinate salt **164** with selectfluor in the presence of benzylamine was attempted to access the amine or sulfonamide products (**166** and **167**) in a single step (Scheme 3.58). Unfortunately, this was unsuccessful with degradation of the starting material/reaction intermediates. The degradation products were difficult to observe in the ^1H NMR spectrum of the crude reaction mixture indicating possible volatility.



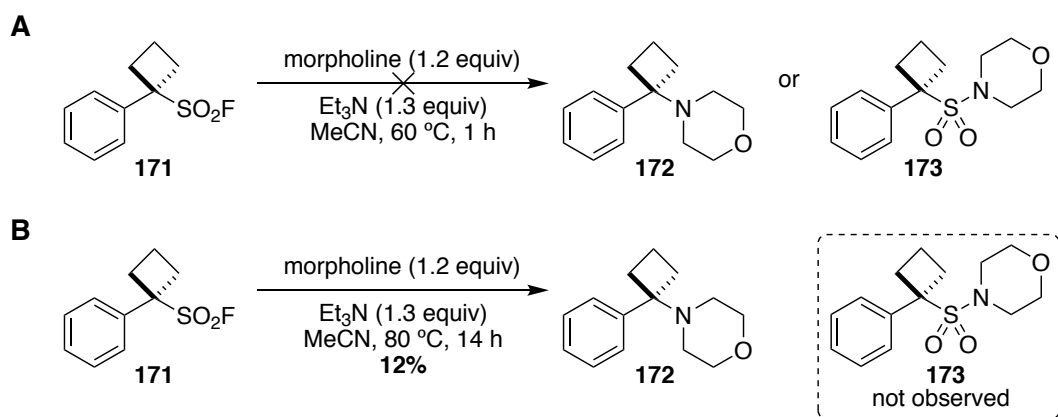
Scheme 3.58 Attempted reaction of sodium sulfinate salt **164** in the presence of selectfluor and benzylamine.

The synthesis of the phenyl-substituted cyclobutane sulfonyl fluoride derivative **171** was more straightforward (Scheme 3.59). All steps proceeded in good yields, comparable to those achieved in the synthesis of oxetane sulfonyl fluoride **147**. Interestingly, unlike the oxetane sulfinate salts **138–140**, cyclobutane sulfinate salt **170** was not stable when stored at room temperature for over 1 week. However, when stored below 0 °C very little degradation occurred over a 3 month period.



Scheme 3.59 Synthesis of cyclobutane sulfonyl fluoride **171**.

Reaction of cyclobutane sulfonyl fluoride **171** with morpholine under the same conditions that were used for oxetane sulfonyl fluoride **147** (triethylamine, 60 °C, 1 hour) gave no reaction (Scheme 3.60A). However, increasing the temperature to 80 °C and the reaction time to 14 hours led to the formation of cyclobutane amine **172** in a low 12% yield (Scheme 3.60B). A large amount of highly volatile 1-fluorocyclobutylbenzene was also formed in the reaction resulting from addition of fluoride to the cyclobutyl carbocationic intermediate. Importantly, no sulfonamide **173** was observed indicating that the unusual reactivity of oxetane-containing sulfonyl fluorides, where the sulfonyl fluoride motif acts as a leaving group, is not limited to oxetanes and may be applicable to other tertiary benzylic sulfonyl fluorides.



Scheme 3.60 Reactions of cyclobutane sulfonyl fluoride **171** with morpholine at 60 °C for 1 h (A) and 80 °C for 14 h (B).

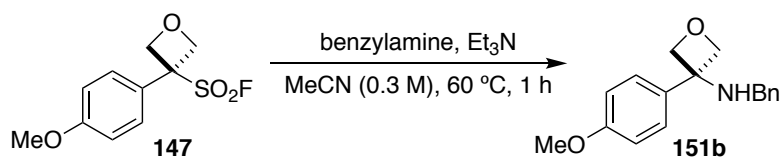
3.4.2 Optimisation of 3-Aminooxetane Forming Protocol

3-Aryl-3-aminooxetanes present a new opportunity to extend the synthetic options available for medicinal chemists enabling access to new chemical and intellectual property space. They have potential application as new bioisosteres for aryl-substituted amides and benzylic amines, both abundant motifs in pharmaceutical drugs.²²⁴ Therefore, optimised conditions were sought for the synthesis of 3-aminooxetane scaffolds from sulfonyl fluorides in maximum yields.

Optimisation of the reaction between oxetane-containing sulfonyl fluorides and amines was investigated using sulfonyl fluoride **147** and benzylamine. In the majority of reactions (except where stated), formation of 3-fluorooxetane **159**, from addition of fluoride at the C3-position of the oxetane, and oxetanol **44**, resulting from the addition of water, were observed in low yields (<10%).

Initially, the effect of using different equivalents of benzylamine and triethylamine was examined (Table 3.27). Use of 1.2 equivalents of benzylamine and 1.3 equivalents of triethylamine delivered 3-aminooxetane **151b** in a 68% yield (Entry 1). Decreasing the equivalents of benzylamine from 1.2 to 1 gave a slightly lower yield of 55% (Entry 2) whereas increasing the equivalents of benzylamine to 2 gave varying yields between 48% and 74% (Entry 3). Keeping the equivalents of benzylamine at 1.2 but increasing the equivalents of triethylamine from 1.3 to 2 gave a reduced yield of 57% (Entry 4). Using equal equivalents of the sulfonamide, amine and triethylamine also led to a lower yield of 3-aminooxetane **151b** (Entry 5). Additionally, use of benzylamine as the limiting reagent and 1.2 equivalents of sulfonyl fluoride **147** did not improved the yield of product (Entry 6).

Table 3.27 Examination of different equivalents of benzylamine and triethylamine for the reaction between sulfonyl fluoride **147** and benzylamine. ^a*In situ* yields calculated by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. Isolated yields in parentheses.



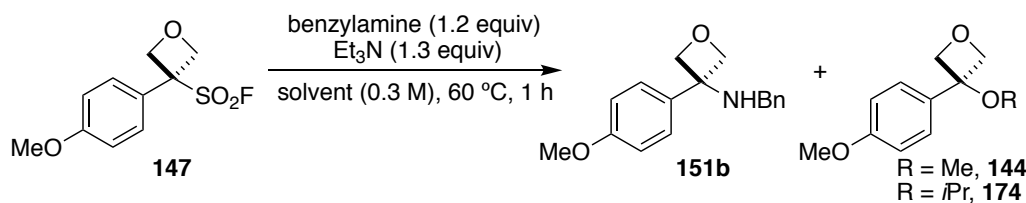
Entry	Equiv of SF 147	Equiv of BnNH ₂	Equiv of Et ₃ N	Yield 151b (%) ^a
1	1	1.2	1.3	68 (68)
2	1	1	1.3	55
3	1	2	1.3	48/62/74
4	1	1.2	2	57
5	1	1	1	53
6	1.2	1	1.3	67

Next, different solvents were investigated for the reaction (Table 3.28). The reaction in dichloromethane gave a substantially lower yield of 3-aminooxetane **151b** (12% yield in dichloromethane *cf.* 68% for the reaction in acetonitrile) with starting material accounting for the rest of the mass (Entry 2). This result indicates that sulfonyl fluoride **147** is much more stable in dichloromethane than in acetonitrile at 60 °C. In 1,4-dioxane, no desired reaction occurred and starting material was recovered quantitatively (Entry 3). When methanol was employed as the solvent, no starting material was observed after 1 hour and the major product was oxetane ether **144** which was formed in an 85% yield (Entry 4). However, when isopropanol was employed as the solvent, 41% of starting material was recovered and the 3-aminooxetane **151b** and oxetane ether **174** were observed in 19% and 28% yields respectively (Entry 5). This result indicates that the larger size and lower nucleophilicity of isopropanol reduces its ability to outcompete benzylamine despite being in large excess. Additionally, the presence of starting material indicates that the solvent may play an important role in the formation of the oxetanyl carbocation intermediate. This was corroborated by the result in neat benzylamine which showed a reduced yield of 34% for 3-aminooxetane **151b** and a 17% yield of remaining starting material (Entry 6). It is possible that polar solvents coordinate to fluorine increasing its leaving group ability and so facilitating the reaction. In the literature, water has been reported to accelerate sulfonyl fluoride reactivity through the

stabilisation of fluoride.¹⁸⁸ The highest yield of 3-aminooxetane **151b** was achieved using acetonitrile so this was continued as the optimal solvent for the reaction.

Table 3.28 Screening different solvents for the reaction between sulfonyl fluoride **147** and benzylamine.

^a*In situ* yields calculated by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. Isolated yields in parentheses.



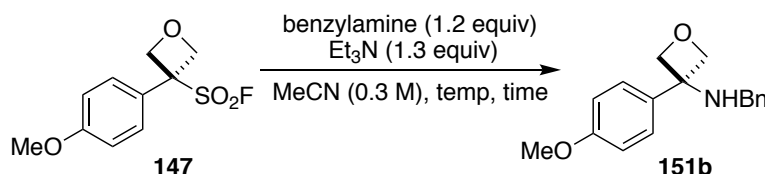
Entry	Solvent	Yield 151b (%) ^a	Yield oxetane ether (%) ^a	Recovered SM (%) ^a
1	MeCN	68 (68)	n/a	0
2	CH ₂ Cl ₂	12	n/a	88
3	1,4-dioxane	0	n/a	98
4	MeOH	8	85	0
5	<i>i</i> PrOH	19	28	41
6	Benzylamine	34	n/a	17

Different concentrations of solvent were also explored. Previous experiments in the optimisation were run at 0.3 M. At a lower concentration of 0.1 M the same yield of 3-aminooxetane **151b** was observed (68%). However, a higher concentration of 1 M led to a lower 54% yield of 3-aminooxetane **151b**. No starting material **147** was observed after 1 hour for any of the concentrations examined.

Experiments were carried out to determine the effect of different temperatures on the reaction towards 3-aminooxetanes (Table 3.29). At 40 °C after 1 hour the yield of 3-aminooxetane **151b** was just 21% (Entry 1). However, due to the near quantitative recovery of material (starting material + 3-aminooxetane **151b**) the reaction was repeated with a longer reaction time of 6 hours (Entry 2). After 6 hours at 40 °C only a 42% yield of 3-aminooxetane **151b** was obtained (*cf.* 68% at 60 °C for 1 hour) alongside just 12% of recovered starting material **147** and so longer reaction times at 40 °C were not explored further. The reaction between sulfonyl fluoride **147** and benzylamine was also conducted at 80 °C and after 1 hour a similar yield to that seen at 60 °C was achieved (Entries 3–4). The reaction was also run at 25 °C for 15 hours

using morpholine as the nucleophile and in this case 3-aminooxetane **151a** was synthesised in a 35% yield as the sole product with 50% of starting material recovered.

Table 3.29 Examining the effect of temperature on the formation of 3-aminooxetane **151**. ^a*In situ* yields calculated by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. Isolated yields in parentheses.



Entry	Temperature (°C)	Reaction time (h)	Yield 151b (%) ^a	Recovered SM (%) ^a
1	40	1	21	76
2	40	6	42	12
3	60	1	68 (68)	0
4	80	1	64	0

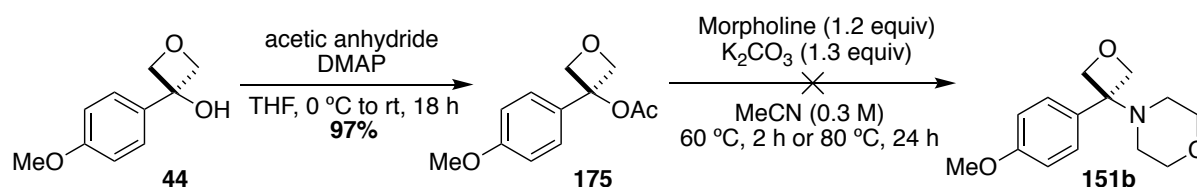
Finally, alternative bases to triethylamine were explored for the reaction (Table 3.30). Potassium carbonate was found to be the optimal base giving 3-aminooxetane **151b** in an 87% yield (Entry 2). Interestingly, for the reaction with potassium carbonate no side-products were observed in the crude reaction mixture. This may be due to a dessicant effect, eliminating water in the reaction mixture and preventing competing nucleophilic addition of water to the oxetanyl carbocation to form oxetanol **44**. Additionally, it is possible that coordination of fluoride by potassium ions may help preclude formation of 3-fluorooxetane **159**. Cesium or sodium carbonate also gave good yields of 3-aminooxetane **151b** although in slightly lower yields compared to potassium carbonate (Entries 3–4). Lithium carbonate and sodium acetate gave reduced yields of 3-aminooxetane **151b** (57–58%) but were still viable bases for the reaction (Entries 5–6).

Table 3.30 Examining the effect of different bases for the reaction between sulfonyl fluoride **147** and benzylamine. ^a*In situ* yields calculated by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. Isolated yields in parentheses.

Entry	Base	Yield 151b (%) ^a	Recovered SM (%) ^a
1	Et ₃ N	68 (68)	0
2	K ₂ CO ₃	87	9
3	Cs ₂ CO ₃	74	8
4	Na ₂ CO ₃	72	5
5	Li ₂ CO ₃	58	6
6	NaOAc	57	4

The reaction with potassium carbonate was repeated with an extended reaction time of 2 hours. After 2 hours, no starting material **147** was observed in the reaction mixture and 3-aminooxetane **151b** was isolated in an excellent 89% yield. Therefore, 2 hours was adopted as the optimal reaction time.

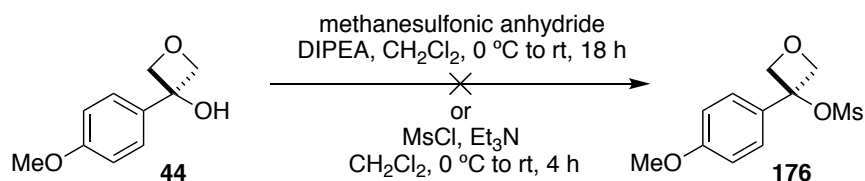
The capacity of different functional groups to act as leaving groups at elevated temperatures and under basic conditions was investigated. Acetate **175** was readily synthesised from oxetanol **44** under standard conditions (acetic anhydride, DMAP) but when submitted to the basic conditions at either 60 °C for 1 hour or 80 °C for 24 hours no desired reactivity was observed (Scheme 3.61).



Scheme 3.61 Synthesis of acetate **175** and attempted reaction with morpholine under basic conditions.

The synthesis of mesylate **176** from oxetanol **44** was also attempted but, under the tested conditions, degradation occurred to give a complex mixture of products (Scheme 3.62). It is

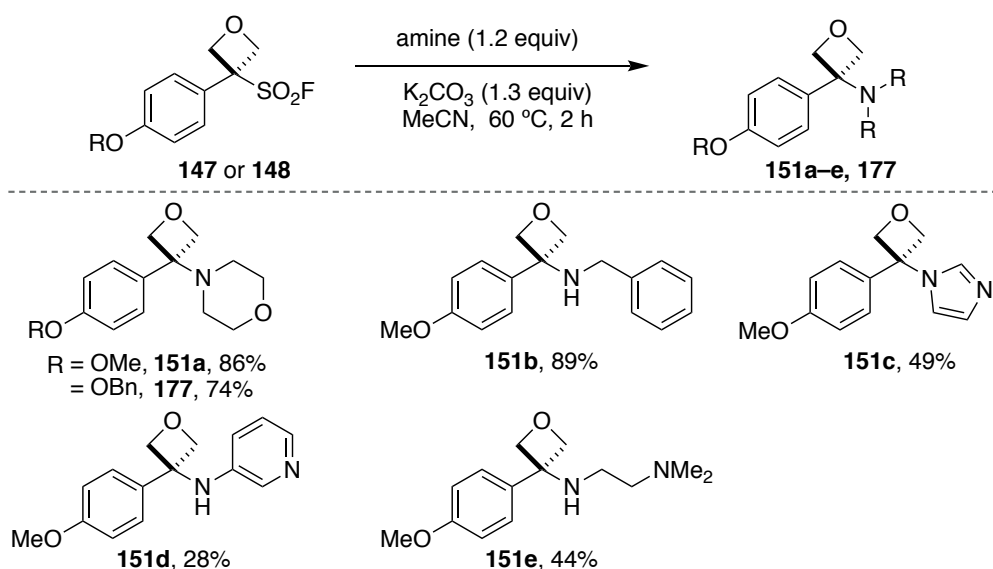
possible that the mesylate was being formed but was unstable under the reaction conditions. The capability of mesylate **176** to act as a useful reaction precursor would be compromised by this lack of stability and so the synthesis of mesylate **176** was not pursued further.



Scheme 3.62 Attempted synthesis of mesylate **176**.

3.4.3 Scope of 3-Aminooxetanes

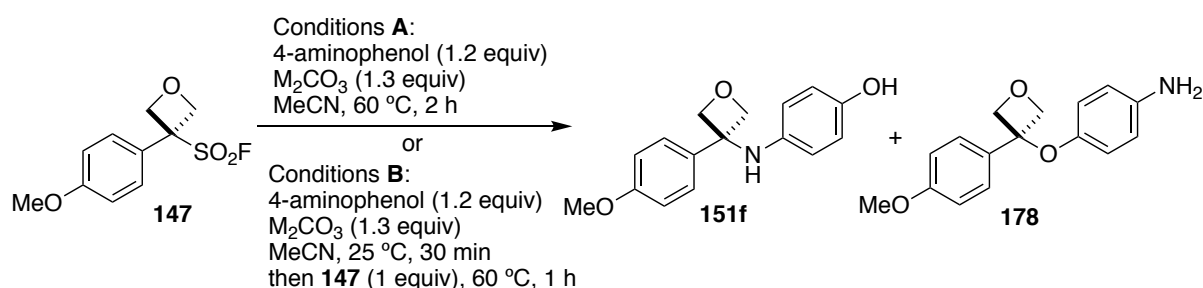
With optimised conditions in hand, a scope of 3-aminooxetanes was investigated (Scheme 3.63). Pleasingly, all the amines examined for the reaction with sulfonyl fluorides gave desired product. Morpholine reacted with both sulfonyl fluorides **147** and **148** to give the corresponding 3-aminooxetanes (**151a** or **177**) in good yields (>74%). Imidazole, 3-aminopyridine and *N,N*-dimethylethylenediamine reacted with sulfonyl fluoride **147** to deliver 3-aminooxetanes **151c**, **151d** and **151e** in yields between 28% and 49%. Additionally, for the reaction with these amines some 3-fluorooxetane **159** was observed. Presumably the lower nucleophilicity of the amine in these examples resulted in a slower reaction towards the 3-aminooxetane meaning that any fluoride ions present in the reaction had greater opportunity to compete with the amine nucleophile.



Scheme 3.63 Scope of 3-aminooxetanes.

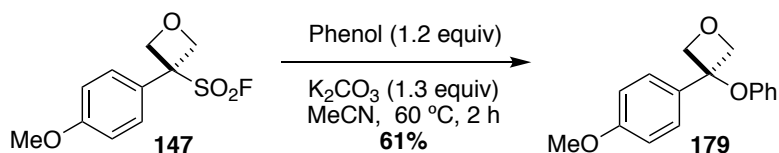
Interestingly, when 4-aminophenol was employed as the nucleophile under the optimised potassium carbonate conditions, alkylation occurred exclusively through nitrogen to give 3-aminooxetane **151f** in an 87% yield with no O-alkylation observed (Table 3.31, Entry 1). However, under a slightly different set-up, whereby the nucleophile and base were prestirred at 25 °C for 30 minutes prior to addition of sulfonyl fluoride **147**, a 70% yield of 3-aminooxetane **151f** was observed alongside 14% of oxetane ether **178** (Entry 2). A greater degree of deprotonation of the O–H group to give a better oxygen nucleophile when potassium carbonate and 4-aminophenol were prestirred, accounts for this difference in selectivity. If cesium carbonate was used instead of potassium carbonate under this same set-up, oxetane ether **178** was isolated in quantitative yield as the exclusive product (Entry 3). The two regioisomers were tentatively assigned based on NH and OH signals in the ^1H NMR spectra. As cesium carbonate and potassium carbonate have similar pK_a values, it is likely that this observed difference in reactivity is a result of greater coordination of the smaller potassium cation to the deprotonated phenol oxygen, reducing its availability for nucleophilic attack.

Table 3.31 Reaction of sulfonyl fluoride and 4-aminophenol using either K_2CO_3 or Cs_2CO_3 .



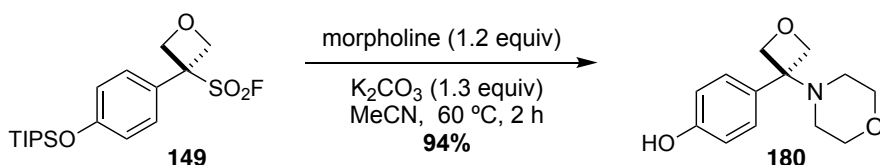
Entry	Conditions	M	Yield 151f (%)	Yield 178 (%)
1	A	K	87	0
2	B	K	70	14
3	B	Cs	0	100

These results indicated that other nucleophiles, such as phenols, would be suitable for reaction with oxetane-containing sulfonyl fluorides to provide 3,3-disubstituted oxetanes. Pleasingly, phenol reacted with sulfonyl fluoride **147** under the optimised conditions to deliver oxetane ether **179** in a 61% yield (Scheme 3.64). Cesium carbonate may give higher yields than potassium carbonate for oxygen nucleophiles based on the observations detailed above for the reaction of 4-aminophenol (Table 3.31) but this was not investigated in this work.



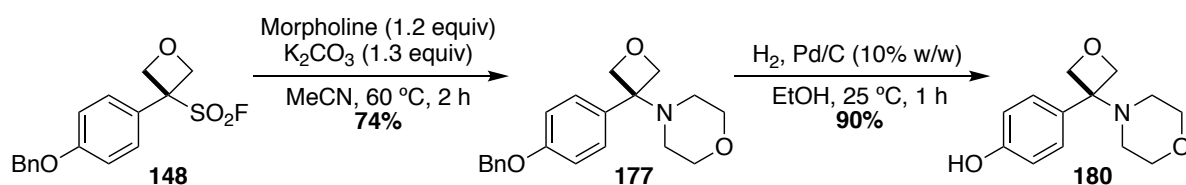
Scheme 3.64 Reaction of sulfonyl fluoride **147** and phenol under the optimised conditions.

When OTIPS-substituted sulfonyl fluoride **149** reacted with morpholine under the optimised conditions, the TIPS groups was entirely deprotected to give 3-aminooxetane **180** with a free O–H group in a 94% yield (Scheme 3.65). Deprotection of the TIPS group was most likely by fluoride ions generated *in situ* during the reaction. Deprotection of the silyl-based protecting group in the same reaction as *N*-alkylation provides a very rapid approach to valuable 3-aminooxetane building blocks featuring a hydroxy handle for further derivatisation.



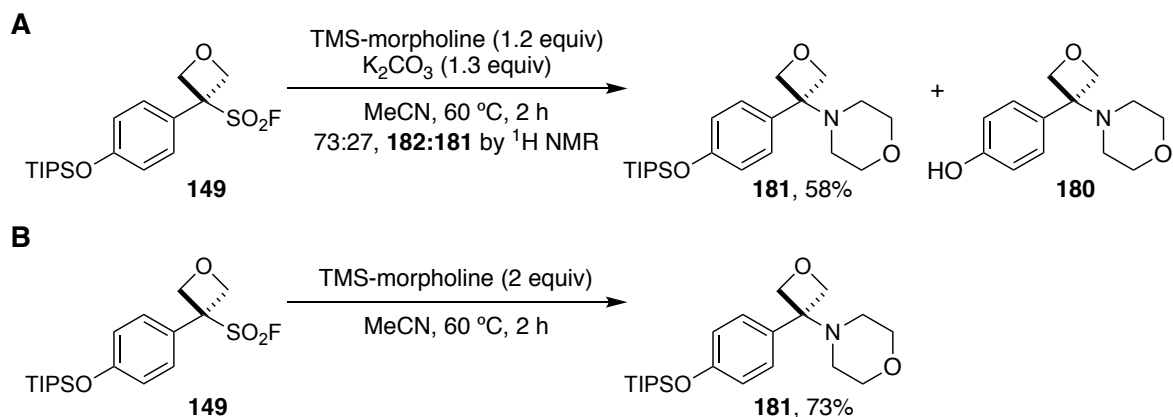
Scheme 3.65 Synthesis of 3-aminooxetane **180** through a one-pot *N*-alkylation and TIPS deprotection.

The reactivity of OTIPS-substituted sulfonyl fluoride **149** was complementary to the observed reactivity of OBn-substituted sulfonyl fluoride **148** where the phenol protecting group was preserved through the amination step (Scheme 3.66). 3-Aminooxetane **180** was accessed in two steps from sulfonyl fluoride **148** via 3-aminooxetane **177** with deprotection of the benzyl group achieved in 90% yield using H_2 and Pd/C in ethanol.



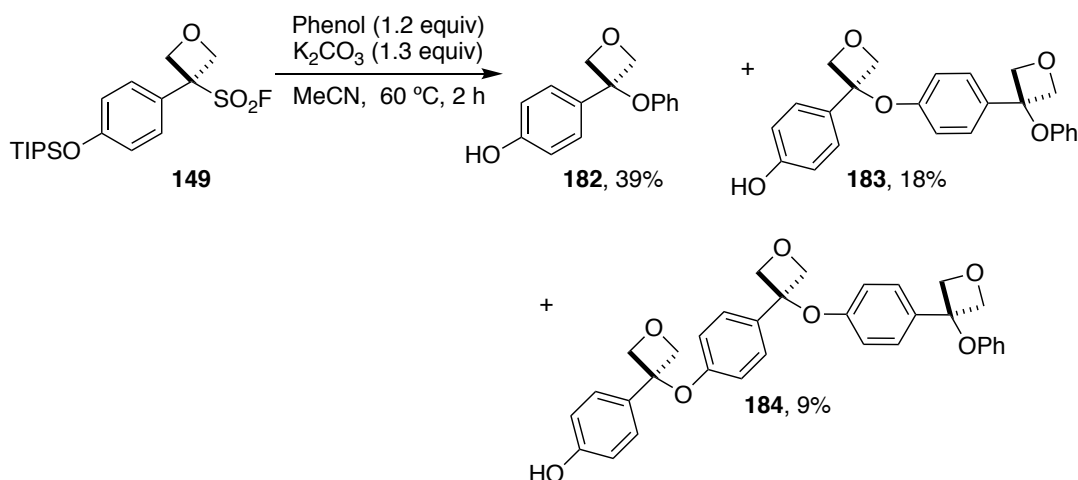
Scheme 3.66 Synthesis of 3-aminooxetane **180** in 2 steps from sulfonyl fluoride **148**.

To prevent the generation of free fluoride ions in the reaction of sulfonyl fluoride **149**, TMS-morpholine was employed. This strategy worked well and under the optimised conditions a 58% yield of the TIPS-protected amino oxetane **181** was isolated (Scheme 3.67A). In the crude reaction mixture, a 73:27 ratio of the TIPS-protected **181**: deprotected 3-aminooxetane **180** was observed by ^1H NMR spectroscopy. Use of 2 equivalents of TMS-morpholine with no base, increased the yield of the 3-aminooxetane **181** to 73% with only trace amounts of the deprotected derivative **180** observed (Scheme 3.67B).



Scheme 3.67 Reaction of sulfonyl fluoride **149** with TMS-morpholine under the previously optimised conditions (A) and using 2 equivalents of nucleophile with no potassium carbonate (B).

The reaction of sulfonyl fluoride **149** with phenol gave a complex mixture of products (Scheme 3.68). Deprotection of the TIPS group under the reaction conditions occurred to provide a free alcohol which was able to compete with phenol to attack the electrophilic oxetanyl carbocationic intermediate. Mono-, di- and tri-products (**182–184**) were all isolated from the reaction indicating that polymerisation will be a consideration for future reactions of sulfonyl fluoride **149** with less reactive nucleophiles.



Scheme 3.68 Reaction of sulfonyl fluoride **149** with phenol.

3.4.4 Synthesis of Medically Relevant 3-Aminooxetane Derivatives

To demonstrate the potential usefulness of this methodology, the oxetane derivatives of two medically relevant compounds were targeted: a H3 receptor antagonist (**185**)²²⁵ and the marketed antihistamine, mepyramine (Figure 3.35).²²⁶

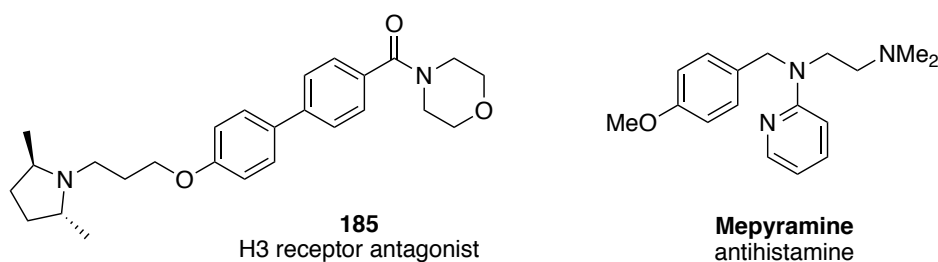
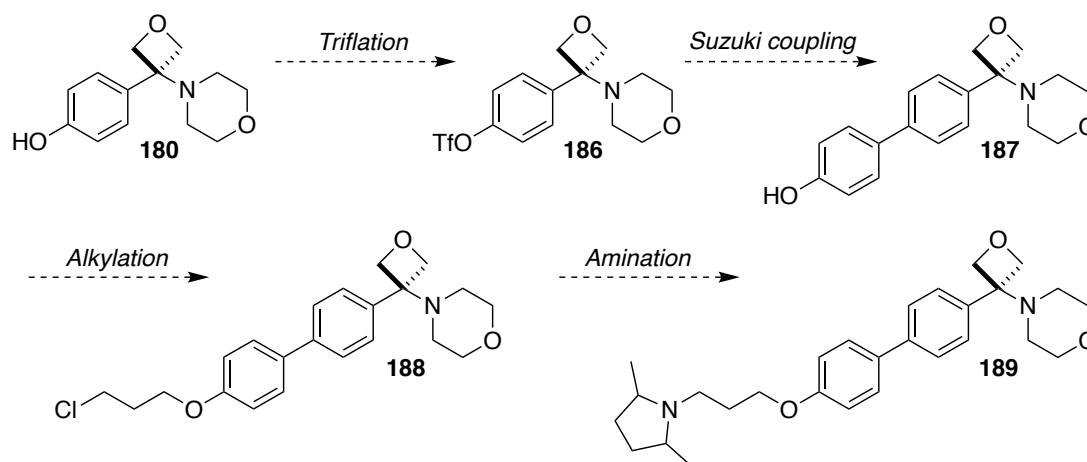


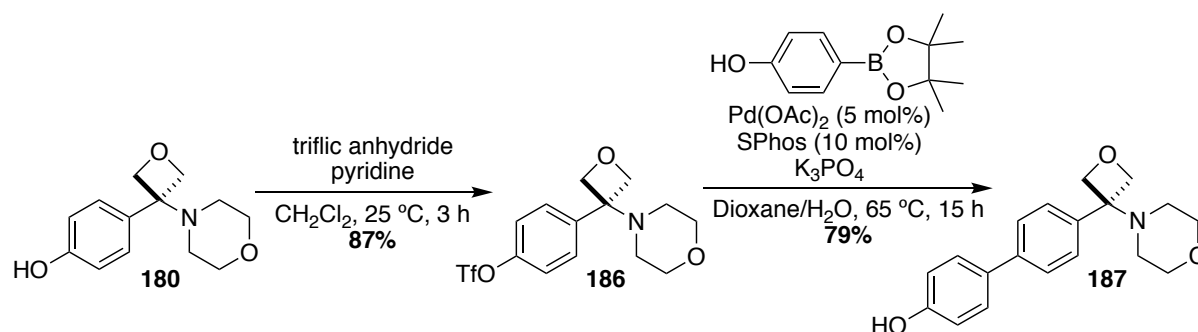
Figure 3.35 Structures of H3 receptor antagonist **185** and mepyramine.

The synthesis of the oxetane derivative of **185** (**189**) was envisaged through a 4-step synthetic sequence from 3-aminooxetane **180** (Scheme 3.69). Triflation and subsequent Suzuki–Miyaura cross-coupling was envisaged as a route to deliver biaryl **187**. Then, based on the literature route for the amide derivative **185**, alkylation with 1-bromo-3-chloropropane and amination would potentially enable the synthesis of oxetane **189**.²²⁵



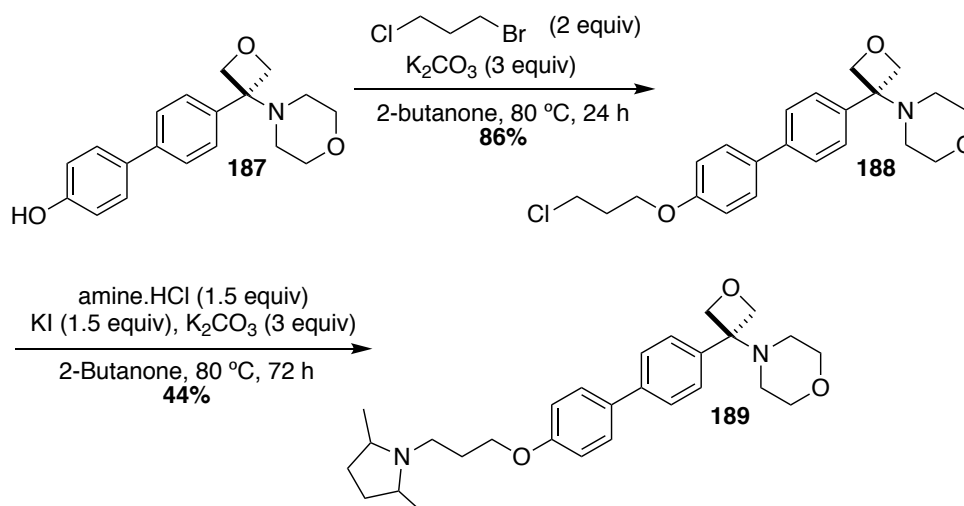
Scheme 3.69 Proposed synthesis of oxetane derivative **189**.

Triflation of 3-aminooxetane **180** occurred under standard conditions (triflic anhydride, pyridine) to deliver triflate **186** in an 87% yield (Scheme 3.70). Different conditions were then examined for the Suzuki–Miyaura cross-coupling of triflate **186** with 4-hydroxyphenylboronic acid pinacol ester. Both tetrakis(triphenylphosphine)palladium and a combination of palladium acetate and SPhos successfully catalysed the reaction to give biaryl **187** in >70% yield. However, triphenylphosphine oxide, which was formed as a side-product when using tetrakis(triphenylphosphine)palladium, was difficult to separate from the desired product **187** meaning that this catalyst was ultimately not suitable. Therefore, the reaction was scaled up using the palladium acetate/SPhos conditions to give 122 mg of biaryl **187** in a 79% yield.



Scheme 3.70 Triflation then Suzuki–Miyaura cross-coupling to deliver biaryl **187** in two steps from 3-aminoxetane **180**.

Alkylation of biaryl **187** with 1-bromo-3-chloropropane successfully delivered chloride **188** in an 86% yield under potassium carbonate conditions at 80 °C for 24 hours (Scheme 3.71). Subsequently, a Finkelstein reaction using potassium iodide, furnished the iodide derivative which underwent amination with 2,5-dimethylpyrrolidine in the same reaction pot to deliver oxetane derivative **189** in a 44% yield.

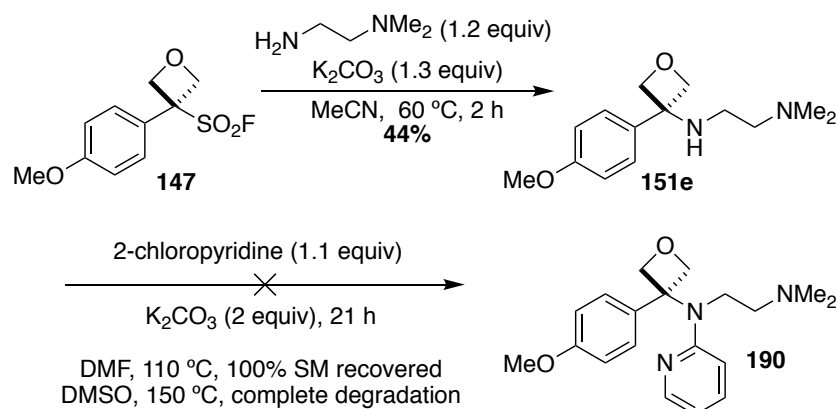


Scheme 3.71 Alkylation of biaryl **187** then amination for the synthesis of oxetane derivative **189**.

The reaction of sulfonyl fluoride **149** with morpholine to give the 3-aminoxetane scaffold was a key step in the successful synthesis of oxetane derivative **189**, indicating that this methodology may allow access to exciting new medically relevant oxetane derivatives. Additionally, the synthesis of oxetane **189** shows that the 3-aminoxetane scaffold is stable to a variety of reaction conditions.

Unfortunately, the synthesis of the oxetane mepyramine derivative **190** was unsuccessful (Scheme 3.72). Synthesis of the oxetane amine **151e** was achieved in a 44% yield; however, the S_NAr reaction to install the pyridine group failed. At 110 °C only starting material was

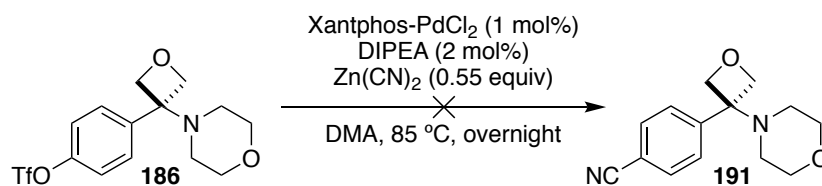
returned and at 150 °C complete degradation of the oxetane motif was observed. Buchwald–Hartwig conditions were not explored in this work but could present a route to access the desired derivative **190** in the future.



Scheme 3.72 Attempted synthesis of the oxetane derivative of mepyramine (**190**).

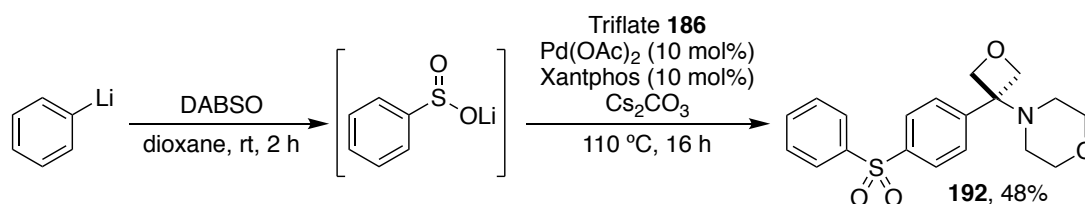
3.4.5 Further Reactions of Triflate **186**

Triflate **186** presented an attractive building block for further reactions. In 2017, Wisniewski published conditions for the cyanation of alkyl bromides utilising the air-stable Xantphos- PdCl_2 precatalyst and catalytic DIPEA.²²⁷ In this study, a single triflate example was also shown to successfully undergo cyanation under the optimised conditions. Unfortunately, when triflate **186** was submitted to the literature conditions, only starting material was recovered and no cyanated product **191** was observed (Scheme 3.73).



Scheme 3.73 Attempted synthesis of **191** from triflate **186**.

In 2013, Willis reported a palladium-catalysed three-component diarylsulfone synthesis *via* an *in situ* generated lithium sulfinatate salt.²²⁸ Pleasingly, when triflate **186** was employed as the coupling partner under the reported conditions (palladium acetate, Xantphos, cesium carbonate) sulfone **192** was synthesised in a 48% yield (Scheme 3.74). This result indicates that further reactions of triflate **186** are possible and there is potential for its use in the preparation of a diverse array of 3-aminooxetane derivatives.



Scheme 3.74 Synthesis of sulfone **192** through a palladium-catalysed coupling with an *in situ* generated lithium sulfinatate salt.

3.4.6 Conclusions

Oxetane sulfonyl fluorides have been shown to be precursors for 3-aryl-3-aminooxetanes *via* a proposed oxetanyl carbocationic intermediate which is generated under basic conditions at elevated temperatures. Formation of this proposed oxetanyl carbocation is further suggested by the formation of 3-fluorooxetanes and oxetanol side-products in the reaction.

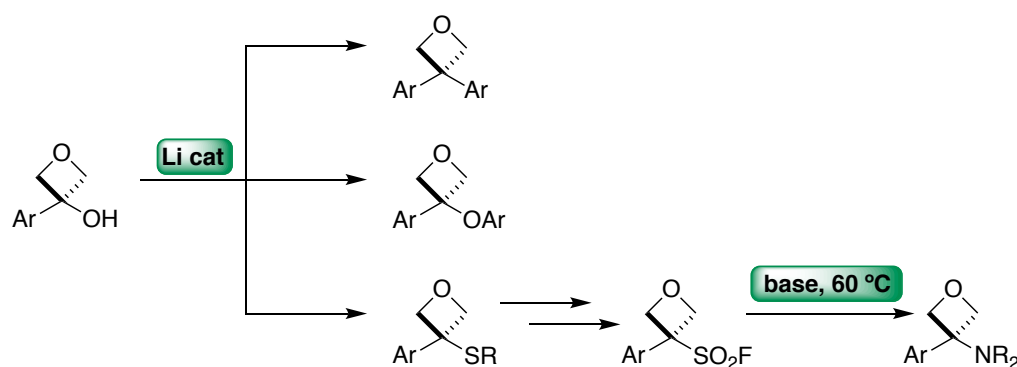
Under optimised conditions, a range of 3-aminooxetanes have been synthesised through the reaction of a variety of sulfonyl fluorides with amines. Additionally, phenols can also be used as substrates to provide the corresponding oxetane ethers. The selectivity for *N* vs *O*-alkylation, when both functional groups are present in the nucleophile, can be controlled by changing the base and this may lead to applications of this methodology in late stage functionalisation.

Deprotection of the TIPS protecting group occurred under the optimised reaction conditions with amine nucleophiles. However, TIPS deprotection could be prevented through the use of TMS-amines. Additionally, this methodology was applied to the synthesis of a medically relevant oxetane derivative indicating that 3-aminooxetanes are stable to a variety of useful synthetic transformations.

4 Conclusion and Future Work

Oxetane-containing scaffolds are valuable modules for drug discovery as they have been shown to convey favourable physicochemical properties to prospective drug candidates and act as advantageous bioisosteres for carbonyl, *gem*-dimethyl and methylene functional groups. There is high demand for new bioisosteres in medicinal chemistry so developing methodology that allows access to novel scaffolds is of high importance.

This research has demonstrated that 3-aryloxetanyl carbocations can be formed directly from 3-aryl-oxetan-3-ols under acidic conditions and from 3-aryloxetane-3-sulfonyl fluorides at elevated temperatures to react with nucleophiles. Invoking this oxetanyl carbocationic intermediate has enabled efficient access to several novel classes of oxetane-containing compounds designed as novel bioisosteres for medicinal chemistry including 3,3-diaryloxetanes, 3-aryl-3-sulfanyl oxetanes and 3-aryl-3-aminooxetanes (Scheme 4.1).



Scheme 4.1 Overview of the synthesis of 3,3-diaryloxetanes, oxetane ethers, 3-sulfanyloxetanes and 3-aminooxetanes.

3,3-Diaryloxetanes were prepared from the reaction of oxetanols with *ortho*-substituted phenols using a cheap and widely available lithium catalyst. Under the same conditions, using para-substituted phenols and resorcinols, 2,3-dihydrobenzofurans were accessed with excellent selectivity. 3,3-Diaryloxetanes were also shown to be suitable scaffolds for a range of further derivatisations with the oxetane ring remaining intact under a variety of conditions commonly used within drug discovery. Unfortunately, electron poor aromatic groups and heteroarenes could not be readily incorporated at the 3-position of the oxetane motif using this methodology. In order to prepare a scope of 3,3-diaryloxetanes featuring electron poor aromatic groups it is likely that different methodology will be required.

The reaction was studied using ^1H NMR spectroscopy to identify oxetane ether intermediates, which are formed reversibly in the reaction. Electron rich phenols showed enhanced reactivity towards C-alkylation compared to more electron poor nucleophiles. The oxetane ethers could be isolated and have potential as interesting new bioisosteres.

The same lithium catalyst was applied to thiol alkylation reactions between oxetanols and a wide range of aryl and aliphatic thiol nucleophiles. Excellent selectivity was observed with minimal oxetane ring opening observed under the optimised conditions. Subsequent derivatisation through cross-coupling and oxidation was achieved and demonstrates the excellent stability of these substrates. Furthermore, promising preliminary ADME data was obtained at Pfizer to indicate that the sulfanyl oxetane group is not a metabolic liability.

Oxetane-containing sulfinate salts were prepared from oxetanols through a thiol alkylation, oxidation and elimination route. Coupling reactions of these sulfinate salts to deliver diaryloxetanes and sulfonamides were not successful. However, coupling with electrophilic fluorine led to novel oxetane-containing sulfonyl fluoride derivatives.

Unprecedented reactivity of aliphatic sulfonyl fluorides was observed for oxetane-containing sulfonyl fluorides: under basic conditions at 60 °C in the presence of amines, 3-aminooxetanes were formed instead of the expected sulfonamides. Investigations into the reaction using ^1H NMR spectroscopy showed formation of 3-fluorooxetane and 3-oxetanol side-products indicating formation of an oxetanyl carbocation under the reaction conditions. It will be important for future work to assess how general this reactivity is through the synthesis of further tertiary alkyl sulfonyl fluorides perhaps incorporating different heterocycles such as azetidines.

Using the developed protocol, a variety of 3-aminooxetanes were synthesised including the oxetane derivative of a known H3 receptor antagonist. Furthermore, selective *N* or *O*-alkylation of 4-aminophenol was achieved through simple variation of the base used in the reaction. The mild conditions, robustness and these preliminary results suggest excellent *N* vs *O* selectivity can be achieved and could make this methodology useful for the late stage functionalisation of amines and alcohols. Examination of this methodology with more complex amines and alcohols featuring a wide variety of functional groups will be important to demonstrate this capability.

One of the key next stages of this work will be the validation of these scaffolds as viable options for drug discovery. Determination of key physicochemical properties such as: metabolic stability, solubility and permeability through biological membranes will give a good

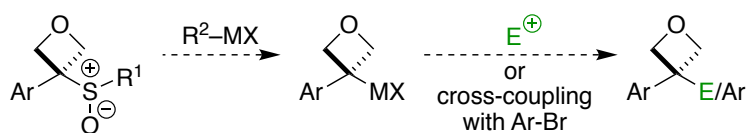
indication of their potential usefulness. A comprehensive pairwise analysis of 3,3-diaryloxetanes with carbonyl, cyclobutane and methylene derivatives to assess 3,3-diaryloxetanes as bioisosteres is ongoing within the Bull group. A full study using 3-aryl-3-sulfanyl oxetanes and 3-aryl-3-aminooxetane scaffolds will also be required to confirm their utility for medicinal chemistry and identify possible advantages compared to the carbonyl and/or methylene derivatives. Ultimately it is hoped that the methodology developed in this research will be taken up by industry and the scaffolds considered in drug discovery programmes.

Several other areas of research have been considered and a brief introduction into possible future projects related to work in this thesis are outlined below.

Future Project 1 – Sulfoxide-Magnesium Exchange using Oxetane-Containing Sulfoxides

Sulfoxide-metal exchange has been used to generate cyclic organometallic reagents.²²⁹ These organometallic intermediates can then react with a wide variety of electrophiles or undergo metal-catalysed cross-coupling reactions to give a diverse range of derivatives.

During the course of this research 6 different sulfoxide derivatives have been synthesised through the oxidation of 3-sulfanyloxetane derivatives. Generation of oxetane organometallic reagents through a sulfoxide-metal exchange protocol would be attractive as a divergent route to a large number of oxetane derivatives (Scheme 4.2). If successful, this could be an excellent method for the introduction of more electron-withdrawing aromatic groups and heteroarenes as well as important functional groups such as aldehydes, amides and ketones. A key consideration would be the electronic nature of the oxetane and its ability to stabilise a negative charge at the 3-position vs the sulfoxide leaving group. This may require functional group manipulations on the aromatic group to increase the electron-withdrawing ability.

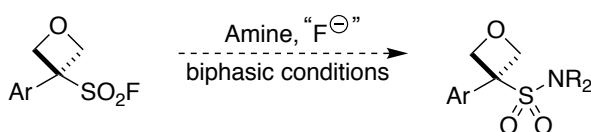


Scheme 4.2 Sulfoxide-metal exchange with 3-aryl-3-sulfoxide oxetane derivatives.

Future Project 2 – Formation of Oxetane Containing Sulfonamides

Due to the importance of sulfonamides in medicinal chemistry, oxetane-containing sulfonamides remain important targets. In this work, 3-aminooxetanes were formed under standard conditions for the formation of sulfonamides from sulfonyl fluorides due to formation

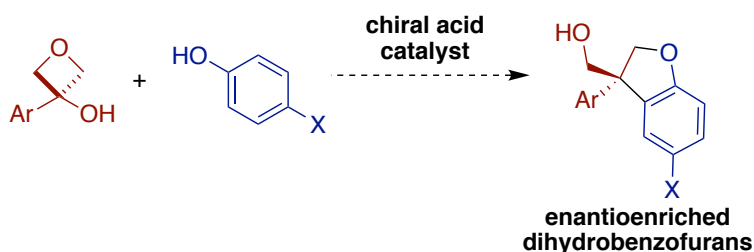
of an oxetanyl carbocationic intermediate (see Section 3.4.1). However, Sharpless has stated that for reactions in which sulfonyl fluorides are made or used, biphasic conditions in which the aqueous phase contains bifluoride (KFHF) may be beneficial with the excess of bifluoride leading to degenerate fluoride exchange until the desired nucleophile reacts.¹⁸⁸ This is an interesting concept in terms of this work, it is possible that in the presence of excess fluoride anions, the oxetane-containing sulfonyl fluoride will be sufficiently stabilised preventing formation of the oxetanyl carbocation and enabling nucleophilic substitution at sulfur to provide sulfonamides (Scheme 4.3). It is possible that other coordinating anionic groups may be able to stabilise the sulfonyl fluoride so a screen of possible anionic additives (e.g. NaBF₄, Bu₄NPF₆, TBAF) is suggested.



Scheme 4.3 Possible conditions for the synthesis of oxetane-containing sulfonamides.

Future Project 3 – Synthesis of Enantioenriched Dihydrobenzofurans

In recent years, ring opening of oxetanes with enantioselective desymmetrisation has been achieved using chiral phosphoric acids.²³⁰ Additionally, Jacobsen used a Co catalyst to catalyse the enantioselective ring opening of oxetanes to form dihydrobenzofurans from a preformed intermediate (see Scheme 1.16).¹²² It would be interesting to explore the use of chiral Brønsted acids for the enantioselective synthesis of dihydrobenzofurans in a one pot procedure from oxetanols (Scheme 4.4). The same chiral Brønsted acid catalyst could activate the hydroxy group of the oxetanol to undergo Friedel–Crafts alkylation with the phenol and then promote oxetane ring opening in an enantioselective manner through association of the chiral counterion to the protonated intermediate.

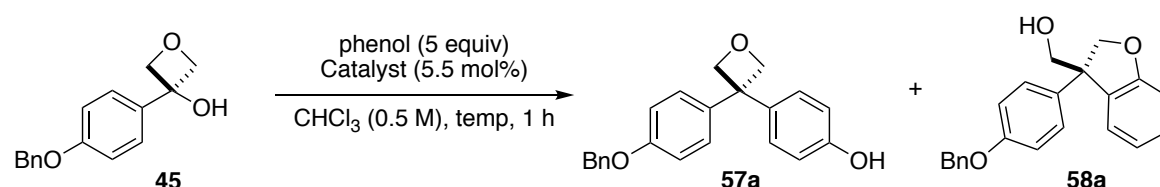


Scheme 4.4 Proposed enantioselective synthesis of dihydrobenzofurans using chiral Brønsted acids.

Initial studies into the viability of this strategy has shown that the racemic reaction can proceed in the presence of Brønsted acid catalysts (Table 4.1). Reaction of oxetanol **45** with phenol

using triflimidic acid or triflic acid gave diaryloxetane **57a** and dihydrobenzofuran **58a** in only slightly lower yields than lithium triflimide (Entries 1–2). Hydrochloric acid and methanesulfonic acid delivered no product and only starting material was recovered (Entries 3–4). Interestingly, triflimidic acid also showed similar reactivity at 25 °C (Entry 5) opening up options for reactions at room temperature and below which may give better ee's.

Table 4.1 Examination of Brønsted acids in the reaction between oxetanol **45** and phenol.

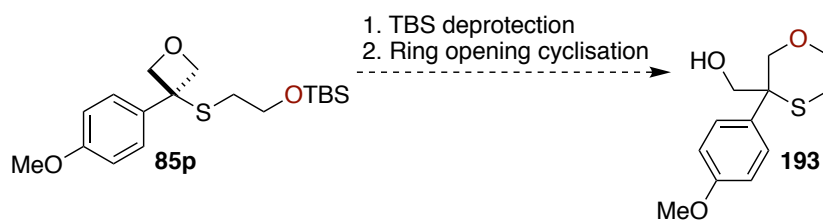


Entry	Catalyst	Temp (°C)	Yield 57a (%)	Yield 58a (%)	Recovered SM (%)
1	NHTf ₂	40	55	18	0
2	TfOH	40	57	18	0
3	HCl	40	0	0	95
4	MsOH	40	0	0	97
5	NHTf ₂	25	57	14	9

To develop the enantioselective methodology a range of chiral Brønsted acids would be examined and suitable conditions developed to obtain dihydrobenzofurans with high ee's.

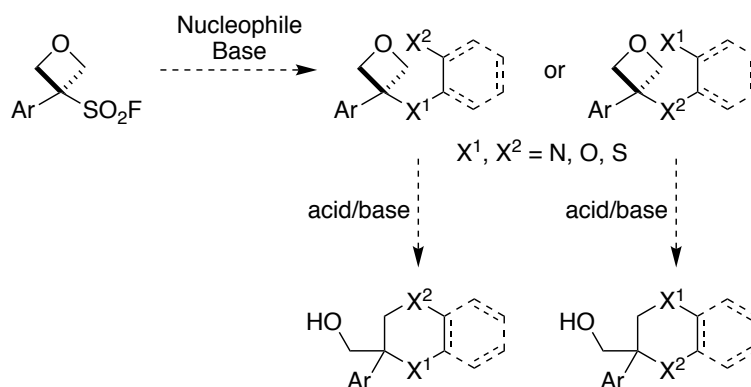
Future Project 4 – Formation of Diverse Heterocyclic Derivatives through Oxetane Ring Opening

Sulfide **85p**, prepared in Section 3.2.3, presents an interesting precursor to oxathiane **193** (Scheme 4.5). Deprotection of the TBS group may promote oxetane ring opening under either acidic or basic conditions to provide this interesting heterocyclic scaffold. Substitution on the thiol nucleophile and different preinstalled aromatic groups can be envisaged towards a diverse range of oxathiane derivatives. Furthermore, the primary alcohol in the products would present a useful handle for further reactions. Aliphatic alcohols have not been explored in this research. However, if they can be used as nucleophiles for the addition to oxetanyl-carbocations, it is possible that dioxanes could also be accessed through a similar ring opening process to that described for 3-sulfanyloxetane **193**.



Scheme 4.5 Proposed synthesis of oxathiane **193**.

Similarly, the use of anilines, phenols and thiophenols substituted with an additional heteroatom in the *ortho*-position in the reaction with sulfonyl fluorides could provide precursors to a variety of interesting heterocyclic derivatives featuring two heteroatoms (Scheme 4.6). In this work, excellent selectivity for either *N* or *O*-alkylation in the reaction of sulfonyl fluorides with 4-aminophenols has been achieved through minor changes to the base and reaction set up. If this selectivity could be realised for *ortho*-substituted anilines, then this could lead to control in the synthesis of different morpholine derivatives. Potentially, this could be further extended to aliphatic nucleophiles featuring two heteroatoms of different chain lengths.



Scheme 4.6 Controlled synthesis of 6-membered heterocyclic derivatives.

5 Experimental

5.1 General Experimental Considerations

All nonaqueous reactions were run under an inert atmosphere (argon) with flame-dried glassware using standard techniques. Anhydrous solvents were obtained by filtration through drying columns (CH₃CN, THF, CH₂Cl₂, MeOH) or used directly from commercial sources (1,4-dioxane, DMF, EtOH, CHCl₃, 2-butanone).

Flash column chromatography was performed using 230-400 mesh silica with the indicated solvent system according to standard techniques. Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel plates. Visualization of the developed chromatogram was performed by UV absorbance (254 nm) and/or stained with aqueous potassium permanganate solution, phosphomolybdic acid or vanillin.

Infrared spectra (ν_{max} , FTIR ATR) were recorded using a Perkin–Elmer Spectrum 100 FT-IR spectrometer and the absorbencies reported in reciprocal centimeters (cm⁻¹).

Nuclear magnetic resonance spectra were recorded on 400 MHz spectrometers. Chemical shifts for ¹H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (CDCl₃, δ = 7.27 ppm, (CD₃)₂SO: 2.50 ppm, CD₃OD: 3.31, D₂O: 4.79 ppm, (CD₃)₂CO: 2.05 ppm). Data is reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, quin = quintet, sep = septet, m = multiplet and br = broad), coupling constant in Hz, integration, assignment]. ¹³C NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard (¹³CDCl₃: 77.0 ppm, (¹³CD₃)₂SO: 39.5 ppm, ¹³CD₃OD: 49.0, (¹³CD₃)₂CO: 29.8 ppm). ¹⁹F 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 ¹H/¹³C spectra were made by the analysis of δ/J values, and COSY, HSQC, and HMBC experiments as appropriate.

Melting points were obtained using Optimelt MPA100 melting point apparatus and are uncorrected.

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

Dihydrobenzofuran OH peak: For several of the dihydrobenzofurans the O–H peak in the ^1H NMR was obscured by the water peak but confirmed by COSY NMR techniques.

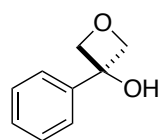
Dihydrobenzofuran notation: When assigning the dihydrobenzofurans, aromatic peaks in the ^1H and ^{13}C NMR spectra related to the dihydrobenzofuran structure are denoted with DHBF.

Sulfinate salt melting points: Sulfinate salts decomposed upon heating ($>200\text{ }^\circ\text{C}$), therefore, melting points have not been determined.

5.2 Experimental Details and Characterisation Data

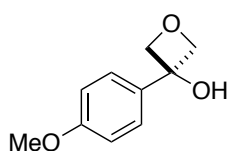
5.2.1 Synthesis of oxetan-3-ols

3-Phenyloxetan-3-ol (**43**)



n-BuLi (2.28 M in hexanes, 2.85 mL, 6.5 mmol) was added dropwise over 5 min to a solution of bromobenzene (0.69 mL, 6.5 mmol) in THF (20 mL) at -78°C . The reaction mixture was stirred at -78°C for a further 10 min. 3-Oxetanone (0.32 mL, 5.0 mmol) was added dropwise as a solution in THF (5 mL) to the reaction mixture. Following a further 10 min at -78°C the reaction mixture was warmed to rt then quenched with water (20 mL). The layers were separated and the aqueous portion extracted with diethylether (3 $\times$ 30 mL). The organic extracts were combined, washed with brine (20 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (30% EtOAc/hexane) afforded oxetanol **43** (623 mg, 83%) as a white solid. R_f = 0.19 (30% EtOAc/hexane); mp = $45\text{--}46^{\circ}\text{C}$ [Lit = $43\text{--}44^{\circ}\text{C}$]²³¹; IR (film)/ cm^{-1} 3332 (br. OH), 2954, 2879, 1605, 1496, 1451, 1427, 1338, 1235, 1178, 1148, 1072, 1058, 1026, 961, 872, 753, 694; ^1H NMR (400 MHz, CDCl_3) δ 7.63–7.58 (m, 2 H, 2 $\times$ Ph-CH), 7.50–7.31 (m, 3 H, 3 $\times$ Ph-CH), 4.97–4.91 (m, 4 H, CH_2OCH_2), 2.46 (s, 1 H, OH); ^{13}C NMR (101 MHz, CDCl_3) δ 142.2 (Ph- C_q), 128.9 (2 $\times$ Ph-CH), 128.2 (Ph-CH), 124.6 (2 $\times$ Ph-CH), 85.6 (CH_2OCH_2), 75.8 (C_q). The spectroscopic data for this compound is consistent with the literature.⁹⁰

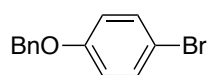
3-(4-Methoxyphenyl)oxetan-3-ol (**44**)



n-BuLi (2.26 M in hexanes, 10.6 mL, 24.0 mmol) was added dropwise over 5 min to a solution of 4-bromoanisole (3.25 mL, 26.0 mmol) in THF (100 mL) at -78°C . The reaction mixture was stirred at -78°C for a further 20 min. Oxetan-3-one (1.28 mL, 20.0 mmol) was added dropwise to the reaction mixture. Following a further 10 min at -78°C the reaction mixture was warmed to rt then quenched with water (100 mL). The layers were separated and the aqueous portion extracted with diethylether (3 $\times$ 100 mL). The organic extracts were combined, washed with brine (100 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (60% Et_2O /pentane) afforded oxetanol **44** (3.25 g, 90%) as a white solid. R_f = 0.23 (50% EtOAc/hexane); mp = $52\text{--}53^{\circ}\text{C}$; IR (film)/ cm^{-1} 3315 (br. OH), 2995, 2950, 2882, 1607, 1581, 1511, 1461, 1439, 1301, 1236, 1179, 1150, 1107, 1053, 1029, 969, 951, 875, 840, 816; ^1H NMR (400 MHz, CDCl_3) δ 7.53–7.51 (m, 2 H, 2 $\times$ Ar-CH), 6.99–6.96 (m, 2 H, 2 $\times$ Ar-CH), 4.95 (d, J = 6.9 Hz, 2 H, CHHOCHH), 4.93 (d, J = 6.9 Hz, 2 H, CHHOCHH), 3.86 (s, 3 H, CH_3), 2.43 (s, 1 H, OH); ^{13}C NMR (101 MHz, CDCl_3) δ 159.3 (Ar- $\text{C}_q\text{-O}$), 134.5

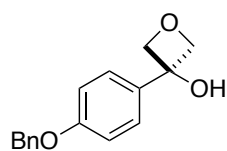
(Ar-C_q-C_q), 125.9 (2 × Ar-CH), 114.0 (2 × Ar-CH), 85.6 (CH₂OCH₂), 75.7 (C_q), 55.4 (CH₃); HRMS (ESI-TOF) *m/z* calcd for C₁₀H₁₁O₂⁺ [M-OH]⁺: 163.0759, Found: 163.0752. Compound was previously reported in the literature but no spectroscopic data was provided.²³²

1-(Benzyloxy)-4-bromobenzene



Potassium carbonate (3.87 g, 28.0 mmol) was added to a solution of 4-bromophenol (3.51 g, 20.0 mmol) in acetonitrile (50 mL) at rt. Benzyl bromide (3.42 g, 20.0 mmol) was added dropwise. The reaction mixture was stirred at rt for 6 h then filtered through celite. The filtrate was concentrated *in vacuo* to afford 1-(benzyloxy)-4-bromobenzene (5.09 g, 97%) as a white solid which was used without further purification. *R_f* = 0.15 (30% EtOAc/hexane); mp = 60–62 °C [Lit = 61 °C]²³³; IR (film)/cm⁻¹ 3089, 3062, 2889, 1884, 1587, 1576, 1486, 1378, 1289, 1243, 1170, 1103, 1041, 1026, 971, 905, 849, 823, 813, 731, 693; ¹H NMR (400 MHz, CDCl₃) δ 7.48–7.31 (m, 7 H, 7 × Ar-CH), 6.90–6.84 (m, 2 H, 2 × Ar-CH), 5.05 (s, 2 H, CH₂); ¹³C NMR (101 MHz, CDCl₃) δ 157.8 (Ar-C_q-O), 136.5 (Ph-C_q), 132.5 (2 × Ar-CH), 128.6 (2 × Ar-CH), 128.1 (Ar-CH), 127.4 (2 × Ar-CH), 116.7 (2 × Ar-CH), 113.1 (Ar-C_q-Br), 70.2 (CH₂). The observed spectroscopic data for this compound was consistent with that previously reported.²³⁴

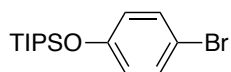
3-[4-(Benzyloxy)phenyl]oxetan-3-ol (45)



n-BuLi (2.24 M in hexanes, 2.90 mL, 6.50 mmol) was added dropwise over 5 min to a solution of 1-(benzyloxy)-4-bromobenzene (1.71 g, 6.50 mmol) in THF (20 mL) at –78 °C. The reaction mixture was stirred at –78 °C for a further 30 min. Oxetan-3-one (0.32 mL, 5.00 mmol) was added dropwise to the reaction mixture. Following a further 45 min at –78 °C the reaction mixture was warmed to rt then quenched with water (20 mL). The layers were separated and the aqueous portion extracted with diethylether (3 × 30 mL). The organic extracts were combined, washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (40% EtOAc/hexane) afforded oxetanol **45** (902 mg, 70%) as a white solid. *R_f* = 0.24 (40% EtOAc/hexane); mp = 114–115 °C; IR (film)/cm⁻¹ 3394 (br. OH), 2974, 2936, 2877, 1609, 1580, 1517, 1458, 1399, 1380, 1318, 1239, 1226, 1179, 1126, 1043, 1008, 958, 892, 843, 822, 756, 733, 701, 656; ¹H NMR (400 MHz, CDCl₃) δ 7.59–7.29 (m, 7 H, 7 × Ar-CH), 7.06–6.99 (m, 2 H, 2 × Ar-CH), 5.12 (s, 2 H, Ph-CH₂), 4.94 (d, *J* = 6.9 Hz, 2 H, CHHOCHH), 4.92 (d, *J* = 6.9 Hz, 2 H, CHHOCHH), 2.44 (s, 1 H, OH); ¹³C NMR (101 MHz, CDCl₃) δ 158.4 (Ar-C_q-O), 136.8 (Ph-C_q), 134.7 (Ar-C_q-C_q), 128.6 (2 × Ar-CH), 128.0 (Ar-CH), 127.4 (2 × Ar-CH), 125.9 (2 × Ar-CH), 115.0 (2 × Ar-CH), 85.5 (CH₂OCH₂), 75.7 (C_q), 70.1 (PhCH₂); HRMS (ESI-TOF) *m/z* calcd for C₁₆H₁₅O₂⁺ [M-OH]⁺: 239.1072, Found: 239.1068. The

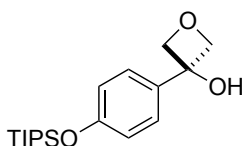
observed spectroscopic data for this compound was consistent with that previously reported.²³⁵

4-Bromophenoxytris(propan-2-yl)silane²³⁶



2,6-Lutidine (1.70 mL, 14.4 mmol) was added dropwise to a solution of 4-bromophenol (2.08 g, 12.0 mmol), triisopropylsilyltrifluoromethane sulfonate (4.05 g, 13.2 mmol) in dichloromethane (16 mL). The reaction mixture was stirred at 0 °C for 2 h then concentrated *in vacuo*. The residue was taken up in EtOAc (30 mL) and water (30 mL) was added. The layers were separated and the organic portion was washed with water (20 mL) then brine (20 mL). The organic extract was dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (100% hexane) afforded the 4-bromophenoxytris(propan-2-yl)silane (3.69 g, 93%) as a colourless oil. *R*_f = 0.5 (100% hexane); IR (film)/cm⁻¹ 2945, 2867, 1586, 1486, 1463, 1261, 1070, 1007, 996, 907, 882, 826, 731, 683; ¹H NMR (400 MHz, CDCl₃) δ 7.35–7.29 (m, 2 H, 2 × Ar-CH), 6.80–6.73 (m, 2 H, 2 × Ar-CH), 1.33–1.18 (m, 3 H, 3 × CH), 1.11 (d, *J* = 7.4 Hz, 18 H, 6 × CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 155.3 (Ar-C_q-O), 132.2 (2 × Ar-CH), 121.7 (2 × Ar-CH), 113.2 (Ar-C_q-Br), 17.9 (6 × CH₃), 12.6 (3 × CH). The observed spectroscopic data for this compound was consistent with that previously reported.²³⁷

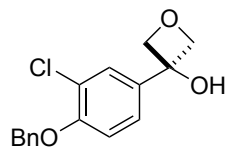
3-(4-{[Tris(propan-2-yl)silyl]oxy}phenyl)oxetan-3-ol (46)



n-BuLi (2.24 M in hexanes, 4.46 mL, 10.0 mmol) was added dropwise over 5 min to a solution of 4-bromophenoxytris(propan-2-yl)silane (3.29 g, 10.0 mmol) in THF (35 mL) at –78 °C. The reaction mixture was stirred at –78 °C for a further 10 min. Oxetan-3-one (0.49 mL, 7.70 mmol) in THF (2.5 mL) was added dropwise to the reaction mixture. Following a further 10 min at –78 °C the reaction mixture was warmed to rt then quenched with water (30 mL). The layers were separated and the aqueous portion extracted with diethylether (3 × 30 mL). The organic extracts were combined, washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (30% EtOAc/hexane) afforded oxetanol **46** (1.96 g, 79%) as a white solid. *R*_f = 0.29 (30% EtOAc/hexane); mp = 63–64 °C; IR (film)/cm⁻¹ 3404 (br. OH), 2945, 2868, 2852, 1605, 1513, 1461, 1421, 1251, 1171, 1104, 1076, 1009, 999, 977, 953, 908, 881, 843, 820, 738, 727, 688; ¹H NMR (400 MHz, CDCl₃) δ 7.44–7.40 (m, 2 H, 2 × Ar-CH), 6.94–6.90 (m, 2 H, 2 × Ar-CH), 4.93 (d, *J* = 7.0 Hz, 2 H, CHHOCHH), 4.90 (d, *J* = 7.0 Hz, 2 H, CHHOCHH), 2.41 (s, 1 H, OH), 1.31–1.22 (m, 3 H, 3 × CH), 1.11 (d, *J* = 7.4 Hz, 18 H, 6 × CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 155.8 (Ar-C_q-O), 134.7 (Ar-C_q-C_q), 125.8 (2 × Ar-CH), 119.9 (2 × Ar-CH), 85.5 (CH₂OCH₂), 75.7 (C_q),

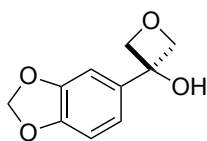
17.9 (6 × CH₃), 12.6 (3 × CH); HRMS (ESI-TOF) m/z calcd for C₁₈H₂₉O₂Si⁺ [M-OH]⁺: 305.1937, Found: 305.1935.

3-[4-(Benzyloxy)-3-chlorophenyl]oxetan-3-ol (47)



n-BuLi (2.50 M in hexanes, 14.8 mL, 37.0 mmol) was added dropwise to a solution of 1-(benzyloxy)-4-bromo-2-chlorobenzene (10.0 g, 33.6 mmol) in THF (100 mL) at -78 °C. The reaction mixture was stirred at -30 °C for 1 h. Oxetan-3-one (2.82 mL, 43.7 mmol) in THF (10 mL) was added dropwise to the reaction mixture at 0 °C. The reaction mixture was warmed to rt and stirred for 16 h. The reaction mixture was filtered through celite, washed with EtOAc (100 mL) and concentrated *in vacuo*. Purification by flash column chromatography (0–20% EtOAc/heptane) afforded oxetanol **47** (4.50 g, 46%) as a white solid. R_f = 0.18 (25% EtOAc/Petroleum ether); mp = 84–87 °C; IR (film)/cm⁻¹ 3363 (br. OH), 2970, 1739, 1606, 1507, 1454, 1430, 1385, 1294, 1264, 1219, 1055, 1005, 956, 906, 888, 853, 833, 809, 741, 722, 694, 654; ¹H NMR (400 MHz, CDCl₃) δ 7.64 (d, J = 2.3 Hz, 1 H, Ar-CH), 7.55–7.17 (m, 6 H, 6 × Ar-CH), 7.00 (d, J = 8.5 Hz, 1 H, Ar-CH), 5.20 (s, 2 H, PhCH₂), 4.88 (d, J = 6.7 Hz, 2 H, CHHOCHH), 4.86 (d, J = 6.7 Hz, 2 H, CHHOCHH), 2.66 (s, 1 H, OH); ¹³C NMR (101 MHz, CDCl₃) δ 153.7 (Ar-C_q-OBn), 136.3 (Ph-C_q), 135.9 (Ar-C_q-C_q), 128.6 (2 × Ar-CH), 128.1 (Ar-CH), 127.0 (2 × Ar-CH), 126.9 (Ar-CH), 123.8 (Ar-CH), 123.6 (Ar-C_q-Cl), 114.0 (Ar-CH), 85.6 (CH₂OCH₂), 75.2 (C_q), 70.9 (PhCH₂); HRMS (ESI-TOF) m/z calcd for C₁₆H₁₅O₃ClNa⁺ [M+Na]⁺: 313.0602, Found: 313.0598. The observed spectroscopic data for this compound was consistent with that previously reported.²³⁵

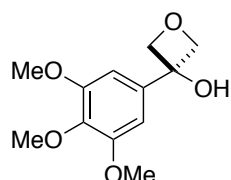
3-(2H-1,3-Benzodioxol-5-yl)oxetan-3-ol (48)



n-BuLi (2.50 M in hexanes, 16.4 mL, 16.4 mmol) was added dropwise over 10 min to a solution of 5-bromo-2H-1,3-benzodioxole (3.00 g, 14.9 mmol) in THF (30 mL) at -70 °C. The reaction mixture was stirred at -70 °C for 1 h. Oxetan-3-one (0.96 mL, 15.0 mmol) in THF (10 mL) was added dropwise to the reaction mixture at -70 °C. The reaction mixture was warmed to rt and stirred for 12 h then quenched with sat. aq. NH₄Cl (10 mL). The layers were separated and the aqueous portion extracted with EtOAc (3 × 50 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (5–50% EtOAc/Petroleum ether) afforded oxetanol **48** (2.10 g, 73%) as a pale yellow solid. R_f = 0.13 (30% EtOAc/hexane); mp = 88–91 °C; IR (film)/cm⁻¹ 3333 (br. OH), 2971, 2875, 1736, 1485, 1435, 1248, 1175, 1099, 1035, 960, 938, 857, 811, 755, 726, 667; ¹H NMR (400 MHz, CDCl₃) δ 7.08–7.02 (m, 2 H, 2 × Ar-CH), 6.84 (d, J = 8.0 Hz, 1 H, Ar-CH), 5.99 (s, 2 H, OCH₂O),

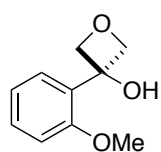
4.88 (s, 4 H, CH₂OCH₂), 2.69 (s, 1 H, OH); ¹³C NMR (101 MHz, CDCl₃) δ 148.1 (Ar-C_q-OCH₂O), 147.3 (Ar-C_q-OCH₂O), 136.4 (Ar-C_q-C_q), 117.9 (Ar-CH), 108.2 (Ar-CH), 105.5 (Ar-CH), 101.2 (OCH₂O), 85.5 (CH₂OCH₂), 75.8 (C_q); HRMS (ESI-TOF) *m/z* calcd for C₁₀H₉O₃⁺ [M-OH]⁺: 177.0552, Found: 177.0550.

3-(3,4,5-Trimethoxyphenyl)oxetan-3-ol (49)



n-BuLi (2.40 M in hexanes, 1.0 mL, 2.4 mmol) was added dropwise over 5 min to a solution of 5-bromo-1,2,3-trimethoxybenzene (642 mg, 2.6 mmol) in THF (10 mL) at -78 °C. The reaction mixture was stirred at -78 °C for a further 10 min. Oxetan-3-one (0.14 mL, 2.0 mmol) was added dropwise to the reaction mixture. Following a further 5 min at -78 °C the reaction mixture was warmed to rt then quenched with water (40 mL). The layers were separated and the aqueous portion extracted with diethylether (3 × 30 mL). The organic extracts were combined, washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (70% EtOAc/hexane) afforded oxetanol **49** (415 g, 86%) as a white solid. *R_f* = 0.23 (70% EtOAc/hexane); mp = 128–130 °C; IR (film)/cm⁻¹ 3429 (br. OH), 2972, 2944, 1739, 1593, 1449, 1412, 1335, 1234, 1092, 1124, 996, 850, 655; ¹H NMR (400 MHz, CDCl₃) δ 6.83 (s, 2 H, 2 × Ar-CH), 4.91 (s, 4 H, CH₂OCH₂), 3.91 (s, 6 H, 2 × OCH₃), 3.87 (s, 3 H, OCH₃), 2.58 (s, 1 H, OH); ¹³C NMR (101 MHz, CDCl₃) δ 153.4 (2 × Ar-C_q-O), 138.1 (Ar-C_q-O), 137.5 (Ar-C_q-C_q), 101.7 (2 × Ar-CH), 85.7 (CH₂OCH₂), 75.8 (C_q), 60.8 (OCH₃), 56.2 (2 × OCH₃); FTMS (+ p NSI) *m/z* calcd for C₁₂H₁₇O₅⁺ [M+H]⁺: 241.1071, Found: 241.1073.

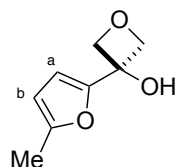
3-(2-Methoxyphenyl)oxetan-3-ol (50)



n-BuLi (2.39 M in hexanes, 5.0 mL, 12.0 mmol) was added dropwise over 5 min to a solution of 2-bromoanisole (1.49 mL, 12.0 mmol) in THF (45 mL) at -78 °C. The reaction mixture was stirred at -78 °C for a further 20 min. Oxetan-3-one (0.64 mL, 10.0 mmol) was added dropwise to the reaction mixture. Following a further 10 min at -78 °C the reaction mixture was warmed to rt then quenched with water (50 mL). The layers were separated and the aqueous portion extracted with diethylether (3 × 50 mL). The organic extracts were combined, washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (60% EtOAc/hexane) afforded oxetanol **50** (1.70 g, 94%) as a white solid. *R_f* = 0.21 (60% EtOAc/hexane); mp = 50–52 °C; IR (film)/cm⁻¹ 3362 (br. OH), 2947, 1601, 1493, 1463, 1437, 1237, 1127, 1024, 968, 879, 751, 668; ¹H NMR (400 MHz, CDCl₃) δ 7.37–7.27 (m, 2 H, 2 × Ar-CH), 7.05–6.99 (m, 1 H, Ar-CH), 6.97–6.92 (m, 1 H, Ar-CH), 5.05 (d, *J* = 6.7 Hz, 2 H, CHHOCHH), 4.88 (d, *J* = 6.7 Hz, 2 H, CHHOCHH), 3.88 (s, 3 H, CH₃), 3.35 (s, 1 H, OH);

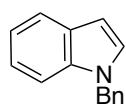
^{13}C NMR (101 MHz, CDCl_3) δ 156.7 (Ar- $\text{C}_q\text{-O}$), 141.7 (Ar- $\text{C}_q\text{-C}_q$), 129.7 (Ar-CH), 129.6 (Ar-CH), 126.2 (Ar-CH), 110.9 (Ar-CH), 82.9 (CH_2OCH_2), 75.7 (C_q), 55.4 (CH_3); HRMS (+ p NSI) m/z calcd for $\text{C}_{10}\text{H}_{12}\text{O}_3\text{Na}^+$ [$\text{M}+\text{Na}$] $^+$: 203.0679, Found: 203.0676.

3-(5-Methylfuran-2-yl)oxetan-3-ol (51)



$n\text{-BuLi}$ (2.50 M in hexanes, 14.0 mL, 35.1 mmol) was added dropwise over 5 min to a solution of 2-methylfuran (3.00 g, 36.5 mmol) in THF (30 mL) at -10°C . The reaction mixture was stirred at 0°C for a further 1 h. Oxetan-3-one (2.04 mL, 31.9 mmol) in THF (15 mL) was added dropwise to the reaction mixture at -10°C . Following a further 15 h at 15°C the reaction mixture was warmed to rt then quenched with sat. aq. NH_4Cl (10 mL). The layers were separated and the aqueous portion extracted with EtOAc (3×50 mL). The organic extracts were combined, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (0–50% EtOAc/Petroleum ether) afforded oxetanol **51** (2.30 g, 47%) as a colourless oil. R_f = 0.64 (50% Petroleum ether/EtOAc); IR (film)/ cm^{-1} 3366 (br. OH), 2951, 2879, 1738, 1565, 1217, 1174, 1140, 1087, 1019, 970. 953, 942, 866, 784, 674; ^1H NMR (400 MHz, CDCl_3) δ 6.29 (d, J = 3.3 Hz, 1 H, Ar- CH_a), 6.01–5.98 (m, 1 H, Ar- CH_b), 4.93 (d, J = 6.5 Hz, 2 H, CHHOCHH), 4.84 (dd, J = 6.5, 1.3 Hz, 2 H, CHHOCHH), 2.74 (s, 1 H, OH), 2.33 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 152.5 (Ar- C_q), 152.4 (Ar- C_q), 106.9 (Ar-CH), 106.4 (Ar-CH), 83.1 (CH_2OCH_2), 72.1 (C_q), 13.5 (CH_3); HRMS (ESI-TOF) m/z calcd for $\text{C}_8\text{H}_9\text{O}_2^+$ [$\text{M}+\text{H}-\text{H}_2\text{O}$] $^+$: 137.0597, Found: 137.0597.

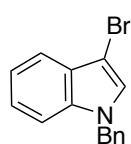
1-Benzyl-1H-indole²³⁸



Indole (1.17 g, 10.0 mmol) in DMF (10 mL) was added to a solution of sodium hydride (60% in mineral oil, 480 mg, 12.0 mmol) in DMF (10 mL) at 0°C . The reaction mixture was stirred at 25°C for 30 min then benzyl bromide (1.80 mL, 15.0 mmol) was added dropwise. The resulting solution was stirred at 25°C for a further 12 h then quenched with water (20 mL). Dichloromethane (15 mL) was added and the layers separated. The organic extract was washed with water (3×20 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (3% EtOAc/hexane) afforded 1-benzyl-1H-indole (1.90 g, 91%) as a pale yellow solid. R_f = 0.32 (3% EtOAc/hexane); mp = $39\text{--}41^\circ\text{C}$ [Lit; 41°C]²³⁹; IR (film)/ cm^{-1} 3025, 1738, 1508, 1485, 1463, 1455, 1440, 1354, 1336, 1316, 1178, 1078, 765, 740, 715, 695; ^1H NMR (400 MHz, CDCl_3) δ 7.70 (d, J = 7.7 Hz, 1 H, Ar-CH), 7.49–7.09 (m, 9 H, $9 \times$ Ar-CH), 6.60 (dd, J = 2.9, 1.7 Hz, 1 H, Ar-CH), 5.37 (CH_2); ^{13}C NMR (101 MHz, CDCl_3) δ 137.5 (Ph- C_q), 136.3 (Ar- C_q), 128.7 ($2 \times$ Ph-CH), 128.4 (Ar- C_q), 128.2 (Ar-CH), 127.6 (Ph-CH), 126.7 ($2 \times$ Ph-CH), 121.7 (Ar-CH),

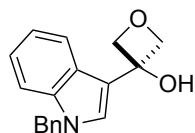
120.9 (Ar-CH), 119.6 (Ar-CH), 109.7 (Ar-CH), 101.7 (Ar-CH), 50.1 (PhCH₂). The observed spectroscopic data for this compound was consistent with that previously reported.²⁴⁰

1-Benzyl-3-bromo-1H-indole²⁴¹



1,3-Dibromo-5,5-dimethylhydantoin (786 mg, 2.75 mmol) was added portionwise over 10 min to a solution of 1-benzyl-1H-indole (1.04 g, 5.00 mmol) in 1,4-dioxane (17 mL) at 10 °C. The resulting solution was stirred for 5 min and then sat. aq. NaHCO₃ (30 mL) was added followed by EtOAc (15 mL). The layers were separated and the aqueous portion was extracted with EtOAc (3 × 15 mL). The organic extract was dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (100% hexane) afforded 1-Benzyl-3-bromo-1H-indole (877 mg, 61%) as a pink oil. *R*_f = 0.27 (30% EtOAc/hexane); IR (film)/cm⁻¹ 3253, 2963, 1739, 1609, 1500, 1464, 1382, 1270, 1252, 1230, 1125, 1062, 1015, 978, 939, 823, 739, 724, 694; ¹H NMR (400 MHz, CDCl₃) δ 7.62 (d, *J* = 6.9 Hz, 1 H, Ar-CH), 7.48–7.02 (m, 9 H, 9 × Ar-CH), 5.31 (s, 2 H, CH₂); ¹³C NMR (101 MHz, CDCl₃) δ 136.7 (Ph-C_q), 135.9 (Ar-C_q), 128.9 (2 × Ph-CH), 127.8 (Ph-CH), 127.5 (Ar-C_q), 127.0 (Ar-CH), 126.9 (2 × Ph-CH), 122.8 (Ar-CH), 120.3 (Ar-CH), 119.4 (Ar-CH), 109.9 (Ar-CH), 90.2 (Ar-C_q-Br), 50.1 (PhCH₂). The observed spectroscopic data for this compound was consistent with that previously reported.²⁴²

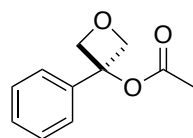
3-(1-Benzyl-1H-indol-3-yl)oxetan-3-ol (52)



n-BuLi (2.45 M in hexanes, 0.97 mL, 2.40 mmol) was added dropwise over 5 min to a solution of 1-benzyl-3-bromo-1H-indole (859 mg, 3.00 mmol) in THF (15 mL) at –78 °C. The reaction mixture was stirred at –78 °C for a further 5 min. Oxetan-3-one (0.13 mL, 2.00 mmol) was added dropwise to the reaction mixture. Following a further 30 min at –78 °C the reaction mixture was warmed to rt then quenched with water (15 mL). The layers were separated and the aqueous portion extracted with diethyl ether (3 × 30 mL). The organic extracts were combined, washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (40% EtOAc/hexane) afforded oxetanol **52** (504 mg, 90%) as a beige solid. *R*_f = 0.19 (40% EtOAc/hexane); mp = 118–120 °C; IR (film)/cm⁻¹ 3278 (br. OH), 2986, 2876, 1739, 1553, 1496, 1467, 1451, 1243, 1198, 1179, 1140, 1087, 1071, 956, 863, 830, 742, 695; ¹H NMR (400 MHz, CDCl₃) δ 7.80 (dt, *J* = 7.9, 1.0 Hz, 1 H, Ar-CH), 7.36–7.14 (m, 9 H, 9 × Ar-CH), 5.34 (s, 2 H, CH₂Ph), 5.09 (d, *J* = 6.9 Hz, 2 H, CHHOCHH), 5.03 (d, *J* = 6.9 Hz, 2 H, CHHOCHH), 2.49 (s, 1 H, OH); ¹³C NMR (101 MHz, CDCl₃) δ 137.4 (Ph-C_q), 136.9 (Ar-C_q), 128.9 (2 × Ar-CH), 127.8 (Ar-CH), 126.9 (2 × Ar-CH), 125.5 (Ar-C_q), 125.2 (Ar-CH), 122.5 (Ar-CH), 120.0 (Ar-CH),

119.9 (Ar-CH), 117.1 (Ar-C_q-C_q), 110.1 (Ar-CH), 84.7 (CH₂OCH₂), 73.1 (C_q), 50.1 (PhCH₂); FTMS (+ p NSI) *m/z* calcd for C₁₈H₁₈O₂N⁺ [M+H]⁺: 280.1332, Found: 280.1330.

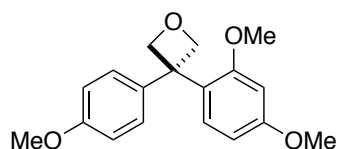
3-Phenyloxetan-3-yl acetate (**55**)



Acetic anhydride (0.71 mL, 7.5 mmol) was added dropwise at 0 °C to a solution of oxetanol **43** (751 mg, 5.0 mmol), 4-dimethylaminopyridine (916 mg, 7.5 mmol) in THF (100 mL). The reaction mixture was heated to 25 °C and stirred for 17 h. Water (100 mL) was added and the layers were separated. The aqueous portion was extracted with ethyl acetate (3 × 30 mL). The organic extracts were combined, washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% Et₂O/pentane) afforded oxetane **55** (826 mg, 86%) as a white solid. *R*_f = 0.23 (20% Et₂O/pentane); mp = 28–29 °C; IR (film)/ cm⁻¹ 2971, 2882, 1737, 1497, 1449, 1370, 1232, 1163, 1115, 1013, 977, 904, 864, 758, 697; ¹H NMR (400 MHz, CDCl₃) δ 7.50–7.46 (m, 2 H, 2 × Ph-CH), 7.42 (ddd, *J* = 7.8, 6.7, 1.3 Hz, 2 H, 2 × Ph-H), 7.37–7.30 (m, 1 H, Ph-CH), 5.12–5.02 (m, 2 H, CHHOCHH), 5.00–4.93 (m, 2 H, CHHOCHH), 2.16 (s, 3 H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 169.5 (C=O), 139.6 (Ph-C_q), 128.8 (2 × Ph-CH), 128.3 (Ph-CH), 124.9 (2 × Ph-CH), 82.3 (CH₂OCH₂), 80.3 (C_q), 21.3 (CH₃); HRMS (ESI-TOF) *m/z* calcd for C₁₁H₁₃O₃⁺ [M+H]⁺: 193.0865, Found: 193.0868.

5.2.2 Synthesis of 3,3-Diaryloxetanes and 2,3-Dihydrobenzofurans

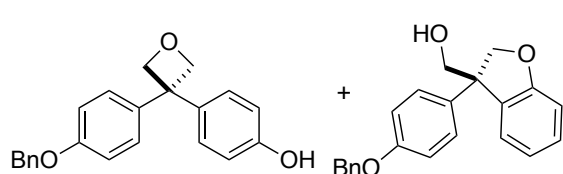
3-(2,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)oxetane (**56**)



Calcium bis(trifluoromethanesulfonimide) (15 mg, 0.025 mmol) and tetrabutylammonium hexafluorophosphate (9.6 mg, 0.025 mmol) were added to a solution of oxetanol **4** (90 mg, 0.5 mmol) and dimethoxybenzene (0.2 mL, 1.5 mmol) in chloroform (1.0 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. NaHCO₃ (15 mL) was added followed by dichloromethane (5 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 × 15 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (30% Et₂O/pentane) afforded oxetane **56** (21 mg, 14%) as a colourless oil. *R*_f = 0.24 (30% Et₂O/pentane); IR (film)/ cm⁻¹ 2954, 2877, 2836, 1610, 1584, 1508, 1463, 1417, 1304, 1288, 1247, 1207, 1182, 1158, 1141, 1030, 982, 913, 829, 805; ¹H NMR (400 MHz, CDCl₃) δ 7.35–7.29 (m, 2 H, 2 × Ar-CH), 6.96 (d, *J* = 8.3 Hz, 1 H, Ar-CH), 6.91–6.77 (m, 2 H, 2 × Ar-CH), 6.55 (dd, *J* = 8.3, 2.4 Hz, 1 H, Ar-CH), 6.48 (d, *J* = 2.4 Hz, 1 H, Ar-CH), 5.32 (d, *J* = 5.8 Hz, 2 H, CHHOCHH), 4.97 (d, *J* = 5.8 Hz, 2 H, CHHOCHH), 3.85

(s, 3 H, OCH₃), 3.79 (s, 3 H, OCH₃), 3.67 (s, 3 H, OCH₃); ¹³C NMR (101 MHz, CDCl₃) δ 159.9 (Ar-C_q-OMe), 158.0 (Ar-C_q-OMe), 157.8 (Ar-C_q-OMe), 138.8 (Ar-C_q-C_q), 127.9 (Ar-CH), 126.9 (Ar-CH), 125.4 (Ar-C_q-C_q), 113.6 (Ar-CH), 104.1 (Ar-CH), 99.1 (Ar-CH), 84.5 (CH₂OCH₂), 55.4 (OCH₃), 55.3 (OCH₃), 55.24 (OCH₃), 49.0 (C_q); HRMS (ESI-TOF) *m/z* calcd for C₁₈H₂₁O₄⁺ [M+H]⁺: 301.1440, Found: 301.1440.

4-{3-[4-(Benzyloxy)phenyl]oxetan-3-yl}phenol (**57a**) and {3-[4-(benzyloxy)phenyl]-2,3-dihydro-1-benzofuran-3-yl}methanol (**58a**)



Lithium bis(trifluoromethanesulfonyl)imide (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution

of oxetanol **45** (64 mg, 0.25 mmol) and phenol (117 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. NaHCO₃ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (3 × 15 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (30% EtOAc/hexane) afforded dihydrobenzofuran **58a** (16 mg, 19%) as a colourless gum followed by oxetane **57a** (50 mg, 60%) as a white solid.

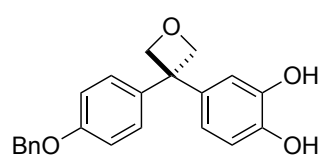
Oxetane **57a**: *R_f* = 0.23 (25% EtOAc/hexane); mp = 164–166 °C; IR (film)/cm⁻¹ 3325 (br. OH), 2881, 2045, 1608, 1591, 1511, 1455, 1433, 1384, 1269, 1228, 1207, 1176, 1111, 1015, 973, 930, 836, 806, 741, 696; ¹H NMR (400 MHz, CDCl₃) δ 7.49–7.30 (m, 5 H, 5 × Ar-CH), 7.17–7.11 (m, 2 H, 2 × Ar-CH), 7.11–7.05 (m, 2 H, 2 × Ar-CH), 7.01–6.94 (m, 2 H, 2 × Ar_(phenol)-CH), 6.85–6.78 (m, 2 H, 2 × Ar_(phenol)-CH), 5.21 (s, 4 H, CH₂OCH₂), 5.15 (s, 1 H, OH), 5.07 (s, 2 H, CH₂Ph); ¹³C NMR (101 MHz, CDCl₃) δ 157.4 (Ar-C_q-OBn), 154.3 (Ar-C_q-OH), 138.4 (Ar_(phenol)-C_q-C_q), 138.2 (Ar_(p-OBn)-C_q-C_q), 136.9 (Ph-C_q), 128.6 (2 × Ar-CH), 128.0 (Ar-CH), 127.8 (2 × Ar-CH), 127.6 (2 × Ar-CH), 127.5 (2 × Ar-CH), 115.3 (2 × Ar_(phenol)-CH), 114.8 (2 × Ar_(phenol)-CH), 85.0 (CH₂OCH₂), 70.1 (CH₂Ph), 50.3 (C_q); HRMS (CI⁺) *m/z* calcd for C₂₂H₂₄NO₃⁺ [M+NH₄]⁺: 350.1756, Found: 350.1772.

Dihydrobenzofuran **58a**: *R_f* = 0.30 (25% EtOAc/hexane); IR (film)/cm⁻¹ 3462 (br. OH), 2882, 1609, 1511, 1481, 1458, 1382, 1239, 1184, 1123, 1017, 973, 827, 753, 698; ¹H NMR (400 MHz, CDCl₃) δ 7.48–7.30 (m, 5 H, 5 × Ar-CH), 7.30–7.17 (m, 4 H, 4 × Ar-CH), 7.00–6.84 (m, 4 H, 4 × Ar-CH), 5.06 (s, 2 H, PhCH₂), 4.77 (d, *J* = 8.9 Hz, 1 H, OCHHC_q), 4.58 (d, *J* = 8.9 Hz, 1 H, OCHHC_q), 4.12 (d, *J* = 11.1 Hz, 1 H, CHHOH), 4.04 (d, *J* = 11.1 Hz, 1 H, CHHOH); ¹³C NMR (101 MHz, CDCl₃) δ 160.8 (Ar_(DHBf)-C_q-OCH₂), 157.8 (Ar-C_q-OBn), 136.9 (Ph-C_q), 134.9

(Ar-C_q-C_q), 130.1 (Ar_(DHBf)-C_q-C_q), 129.3 (Ar-CH), 128.6 (2 × Ar-CH), 128.1 (2 × Ar-CH), 128.0 (Ar-CH), 127.5 (2 × Ar-CH), 125.2 (Ar-CH), 120.8 (Ar-CH), 115.1 (2 × Ar-CH), 110.2 (Ar-CH), 81.3 (OCH₂C_q), 70.0 (PhCH₂), 67.7 (CH₂OH), 55.8 (C_q); HRMS (CI⁺) *m/z* calcd for C₂₂H₂₄NO₃⁺ [M+NH₄]⁺: 350.1756, Found: 350.1767.

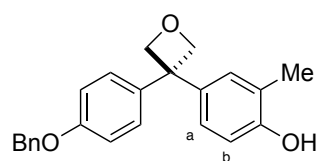
Reaction was also conducted on a 7.50 mmol scale (1.92 g of oxetanol **45**). Purification by flash column chromatography (3% EtOAc/CH₂Cl₂) afforded oxetane **57a** (1.41 g, 57%) and dihydrobenzofuran **58a** (524 mg, 21%).

4-{3-[4-(Benzyloxy)phenyl]oxetan-3-yl}benzene-1,2-diol (**57b**)



Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **45** (64 mg, 0.25 mmol) and 1,2-dihydroxybenzene (138 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. NaHCO₃ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with EtOAc (3 × 15 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (45% EtOAc/hexane) afforded oxetane **57b** (55 mg, 63%) as a white solid. *R_f* = 0.10 (40% EtOAc/hexane); mp = 204–207 °C; IR (film)/cm⁻¹ 3453 (br. OH), 2971, 1737, 1609, 1533, 1513, 1437, 1384, 1289, 1264, 1237, 1206, 1180, 1119, 1011, 968, 934, 864, 843, 811, 787, 741, 697; ¹H NMR (400 MHz, (CD₃)₂SO) δ 8.84 (s, 2 H, 2 × OH), 7.46–7.32 (m, 5 H, 5 × Ar-CH), 7.16 (d, *J* = 8.2 Hz, 2 H, 2 × Ar-CH), 6.99 (d, *J* = 8.5 Hz, 2 H, 2 × Ar-CH), 6.68 (d, *J* = 8.2 Hz, 1 H, Ar-CH), 6.60 (d, *J* = 2.5 Hz, 1 H, Ar-CH), 6.51 (dd, *J* = 8.5, 2.5 Hz, 1 H, Ar-CH), 5.09 (s, 2 H, PhCH₂), 5.04 (d, *J* = 6.0 Hz, 2 H, CHHOCHH), 5.02 (d, *J* = 6.0 Hz, 2 H, CHHOCHH); ¹³C NMR (101 MHz, (CD₃)₂SO) δ 157.1 (Ar-C_q-OBn), 145.6 (Ar-C_q-OH), 144.1 (Ar-C_q-OH), 139.5 (Ar_(p-OBn)-C_q-C_q), 137.9 (Ar_(catechol)-C_q-C_q), 137.6 (Ph-C_q), 128.9 (2 × Ar-CH), 128.3 (Ar-CH), 128.1 (2 × Ar-CH), 127.8 (2 × Ar-CH), 117.3 (Ar-CH), 115.8 (Ar-CH), 115.1 (2 × Ar-CH), 114.2 (Ar-CH), 83.8 (CH₂OCH₂), 69.7 (PhCH₂), 50.5 (C_q); FTMS (+ p NSI) *m/z* calcd for C₂₂H₂₄O₄N⁺ [M+NH₄]⁺: 366.1700, Found: 366.1700.

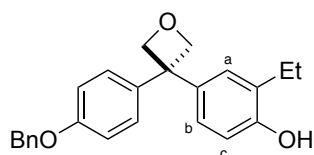
4-{3-[4-(Benzyloxy)phenyl]oxetan-3-yl}-2-methylphenol (**57c**)



Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **45** (64 mg, 0.25 mmol) and 2-methylphenol (135 mg, 1.25 mmol) in chloroform

(0.5 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. NaHCO₃ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 × 15 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc/hexane) afforded oxetane **57c** (63 mg, 73%) as a white solid. *R*_f = 0.11 (20% EtOAc/hexane); mp = 179–181 °C; IR (film)/cm⁻¹ 3307 (br. OH), 1738, 1609, 1511, 1455, 1382, 1298, 1236, 1181, 1120, 1013, 972, 933, 910, 842, 810, 737, 695; ¹H NMR (400 MHz, CDCl₃) δ 7.49–7.29 (m, 5 H, 5 × Ar-CH), 7.21–7.10 (m, 2 H, 2 × Ar-CH), 7.04–6.91 (m, 3 H, 3 × Ar-CH), 6.88 (dd, *J* = 8.3, 2.4 Hz, 1 H, Ar-CH_a), 6.75 (d, *J* = 8.3 Hz, 1 H, Ar-CH_b), 5.21 (d, *J* = 5.6 Hz, 2 H, CHHOCHH), 5.18 (d, *J* = 5.6 Hz, 2 H, CHHOCHH), 5.07 (s, 2 H, PhCH₂), 4.70 (s, 1 H, OH), 2.25 (s, 3 H, CH₃). ¹³C NMR (101 MHz, (CD₃)₂SO) δ 157.1 (Ar-C_q-OBn), 154.2 (Ar-C_q-OH), 139.8 (Ar_(phenol)-C_q-C_q), 137.6 (Ar_(p-OBn)-C_q-C_q), 137.2 (Ph-C_q), 128.9 (2 × Ar-CH), 128.8 (Ar-CH), 128.3 (Ar-CH), 128.1 (2 × Ar-CH), 127.7 (2 × Ar-CH), 124.8 (Ar-CH_a), 124.2 (Ar-C_q-CH₃), 115.1 (2 × Ar-CH), 114.8 (Ar-CH_b), 83.8 (CH₂OCH₂), 69.7 (PhCH₂), 50.6 (C_q), 16.7 (CH₃); FTMS (+ p NSI) *m/z* calcd for C₂₃H₂₆O₃N⁺ [M+NH₄]⁺: 364.1907, Found: 364.1913.

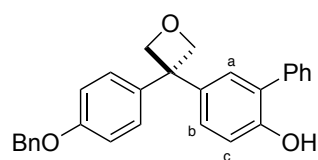
4-{3-[4-(Benzyloxy)phenyl]oxetan-3-yl}-2-ethylphenol (**57d**)



Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **45** (64 mg, 0.25 mmol) and 2-ethylphenol (0.15 mL, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. NaHCO₃ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 × 15 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (25% EtOAc/hexane) afforded oxetane **57d** (60 mg, 66%) as a white solid. *R*_f = 0.29 (30% EtOAc/hexane); mp = 152–153 °C; IR (film)/cm⁻¹ 3343 (br. OH), 2972, 2889, 1608, 1509, 1455, 1422, 1382, 1276, 1235, 1181, 1157, 1120, 1011, 970, 930, 842, 811, 735, 695; ¹H NMR (400 MHz, CDCl₃) δ 7.49–7.29 (m, 5 H, 5 × Ar-CH), 7.18–7.11 (m, 2 H, 2 × Ar-CH), 7.02 (d, *J* = 2.4 Hz, 1 H, Ar-CH_a), 7.00–6.93 (m, 2 H, 2 × Ar-CH), 6.85 (dd, *J* = 8.2, 2.4 Hz, 1 H, Ar-CH_b), 6.73 (d, *J* = 8.2 Hz, 1 H, Ar-CH_c), 5.22 (d, *J* = 5.6 Hz, 2 H, CHHOCHH), 5.19 (d, *J* = 5.6 Hz, 2 H, CHHOCHH), 5.07 (s, 2 H, PhCH₂), 4.71 (s, 1 H, OH), 2.63 (q, *J* = 7.6 Hz, 2 H, CH₂CH₃), 1.22 (t, *J* = 7.6 Hz, 3 H, CH₂CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 157.4 (Ar-C_q-OBn), 152.1 (Ar-C_q-OH), 138.6 (Ar_(phenol)-C_q-C_q), 138.0 (Ar_(p-OBn)-C_q-C_q), 136.9 (Ph-C_q), 130.2 (Ar-C_q-CH₂CH₃), 128.6 (2 × Ar-CH), 128.0 (Ar-CH), 127.6 (2 × Ar-CH), 127.48 (Ar-CH_a),

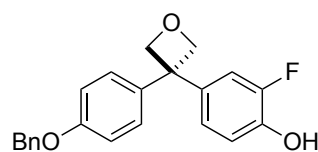
127.45 (2 × Ar-CH), 125.1 (Ar-CH_b), 115.0 (Ar-CH_c), 114.8 (2 × Ar-CH), 85.1 (CH₂OCH₂), 70.1 (PhCH₂), 50.3 (C_q), 23.2 (CH₂CH₃), 15.7 (CH₃); FTMS (+ p NSI) *m/z* calcd for C₂₄H₂₈O₃N⁺ [M+NH₄]⁺: 378.2064, Found: 378.2062.

4-{3-[4-(Benzyloxy)phenyl]oxetan-3-yl}-2-phenylphenol (57e)



Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **45** (64 mg, 0.25 mmol) and 2-phenylphenol (213 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. NaHCO₃ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with EtOAc (3 × 15 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (25% EtOAc/hexane) afforded oxetane **57e** (49 mg, 48%) as a white solid. *R*_f = 0.17 (25% EtOAc/hexane); mp = 175–178 °C; IR (film)/cm⁻¹ 3307 (br. OH), 2964, 2888, 1739, 1608, 1579, 1511, 1492, 1454, 1406, 1379, 1294, 1273, 1235, 1119, 1009, 971, 930, 810, 748, 734, 696; ¹H NMR (400 MHz, (CD₃)₂SO) δ 9.49 (s, 1 H, OH), 7.55–7.44 (m, 2 H, 2 × Ar-CH), 7.47–7.26 (m, 8 H, 8 × Ar-CH), 7.26–7.21 (m, 2 H, 2 × Ar-CH), 7.14 (d, *J* = 2.4 Hz, 1 H, Ar-CH_a), 7.06 (dd, *J* = 8.3, 2.4 Hz, 1 H, Ar-CH_b), 6.98 (m, 2 H, 2 × Ar-CH), 6.91 (d, *J* = 8.3 Hz, 1 H, Ar-CH_c), 5.14 (d, *J* = 6.0 Hz, 2 H, CHHOCHH), 5.10–5.08 (m, 4 H, CHHOCHH + PhCH₂); ¹³C NMR (101 MHz, (CD₃)₂SO) δ 157.1 (Ar-C_q-OBn), 153.1 (Ar-C_q-OH), 139.6 (Ar(_p-OBn)-C_q-C_q), 139.0 (Ar-C_q-Ph), 138.0 (Ar(_{phenol})-C_q-C_q), 137.6 (Ph-C_q-CH₂), 129.6 (2 × Ar-CH), 128.9 (2 × Ar-CH), 128.5 (Ar-CH_a), 128.4 (2 × Ar-CH), 128.3 (Ar-CH), 128.1 (2 × Ar-CH), 127.7 (2 × Ar-CH), 127.0 (Ar-CH), 126.7 (Ar-CH_b), 116.4 (Ar-CH_c), 115.2 (2 × Ar-CH), 83.8 (CH₂OCH₂), 69.7 (PhCH₂), 50.7 (C_q); FTMS (+ p NSI) *m/z* calcd for C₂₈H₂₈O₃N⁺ [M+NH₄]⁺: 426.2064, Found: 426.2063.

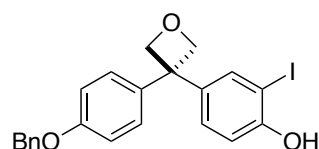
4-{3-[4-(Benzyloxy)phenyl]oxetan-3-yl}-2-fluorophenol (57f)



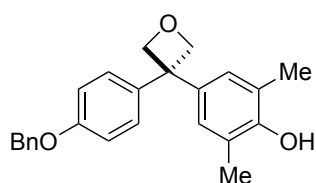
Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **45** (64 mg, 0.25 mmol) and 2-fluorophenol (140 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. NaHCO₃ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with EtOAc (3 × 15 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography

(30% EtOAc/hexane) afforded oxetane **57f** (12 mg, 13%) as a white solid. R_f = 0.26 (30% EtOAc/hexane); mp = 153–156 °C; IR (film)/cm⁻¹ 3244 (br. OH), 2885, 1609, 1512, 1455, 1382, 1297, 1243, 1180, 1119, 1011, 831, 740, 697; ¹H NMR (400 MHz, CHCl₃) δ 7.50–7.30 (m, 6 H, 6 × Ar-CH), 7.11 (d, J = 8.7 Hz, 2 H, 2 × Ar-CH), 7.04–6.87 (m, 4 H, 4 × Ar-CH), 5.29 (d, J = 3.9 Hz, 1 H, OH), 5.22 (d, J = 5.7 Hz, 2 H, CHHOCHH), 5.14 (d, J = 5.7 Hz, 2 H, CHHOCHH), 5.08 (s, 2 H, PhCH₂); ¹³C NMR (101 MHz, CHCl₃) δ 157.6 (Ar-C_q-OBn), 150.6 (d, J_{C-F} = 237.9 Hz, Ar-C_q-F), 142.1 (d, J_{C-F} = 14.3 Hz, Ar-C_q-OH), 139.2 (d, J_{C-F} = 4.8 Hz, Ar_(phenol)-C_q-C_q), 137.5 (Ar_(p-OBn)-C_q-C_q), 136.9 (Ph-C_q), 128.6 (2 × Ar-CH), 128.0 (Ar-CH), 127.6 (2 × Ar-CH), 127.5 (2 × Ar-CH), 122.8 (d, J_{C-F} = 3.4 Hz, Ar-CH), 117.2 (Ar-CH), 115.0 (2 × Ar-CH), 114.4 (d, J_{C-F} = 18.5 Hz, Ar-CH), 84.7 (CH₂OCH₂), 70.1 (PhCH₂), 50.4 (C_q); FTMS (+ p NSI) m/z calcd for C₂₂H₂₃FO₃N⁺ [M+NH₄]⁺: 368.1656, Found: 368.1654.

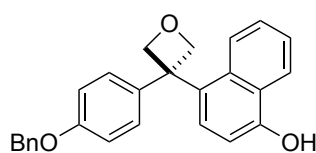
4-{3-[4-(Benzyloxy)phenyl]oxetan-3-yl}-2-iodophenol (**57g**)



Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **45** (64 mg, 0.25 mmol) and 2-iodophenol (275 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. NaHCO₃ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 × 15 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (30% EtOAc/hexane) afforded oxetane **57g** (21 mg, 18%) as a white solid. R_f = 0.24 (30% EtOAc/hexane); mp = 190–194 °C; IR (film)/cm⁻¹ 3249 (br. OH), 3030, 2971, 1739, 1609, 1511, 1366, 1230, 1218, 1182, 1025, 829, 735, 697; ¹H NMR (400 MHz, CDCl₃) δ 7.51 (d, J = 2.3 Hz, 1 H, Ar-CH), 7.48–7.30 (m, 5 H, 5 × Ar-CH), 7.13–7.07 (m, 3 H, 3 × Ar-CH), 7.02–6.94 (m, 3 H, 3 × Ar-CH), 5.31 (s, 1 H, OH), 5.19 (d, J = 5.7 Hz, 2 H, CHHOCHH), 5.14 (d, J = 5.7 Hz, 2 H, CHHOCHH), 5.08 (s, 2 H, PhCH₂); ¹³C NMR (101 MHz, CDCl₃) δ 157.6 (Ar-C_q-OBn), 153.5 (Ar-C_q-OH), 140.4 (Ar_(p-OBn)-C_q-C_q), 137.6 (Ph-C_q), 136.9 (Ar_(phenol)-C_q-C_q), 136.1 (Ar-CH), 128.61 (2 × Ar-CH), 128.55 (Ar-CH), 128.0 (Ar-CH), 127.6 (2 × Ar-CH), 127.5 (2 × Ar-CH), 114.96 (2 × Ar-CH), 114.94 (Ar-CH), 85.9 (Ar-C_q-I), 84.6 (CH₂OCH₂), 70.1 (PhCH₂), 50.0 (C_q); FTMS (+p NSI) m/z calcd for C₂₂H₂₃O₃NI⁺ [M+NH₄]⁺: 476.0717, Found: 476.0711.

4-{3-[4-(Benzyloxy)phenyl]oxetan-3-yl}-2,6-dimethylphenol (57h)

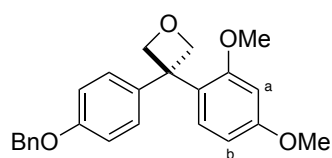
Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **45** (64 mg, 0.25 mmol) and 2,5-dimethylphenol (153 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. NaHCO₃ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with EtOAc (3 × 15 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc/hexane) afforded oxetane **57h** (64 mg, 74%) as a white solid. *R*_f = 0.21 (20% EtOAc/hexane); mp = 166–167 °C; IR (film)/cm⁻¹ 3291 (br. OH), 2960, 2886, 1607, 1579, 1509, 1489, 1456, 1381, 1290, 1320, 1310, 1243, 1226, 1178, 1121, 1014, 976, 952, 900, 864, 834, 814, 732, 967, 747, 600; ¹H NMR (400 MHz, CHCl₃) δ 7.47–7.29 (m, 5 H, 5 × Ar-CH), 7.18–7.09 (m, 2 H, 2 × Ar-CH), 6.98–6.92 (m, 2 H, 2 × Ar-CH), 6.80 (s, 2 H, Ar-CH), 5.21 (d, *J* = 5.6 Hz, 2 H, CHHOCHH), 5.16 (d, *J* = 5.6 Hz, 2 H, CHHOCHH), 5.07 (s, 2 H, PhCH₂), 4.60–4.55 (m, 1 H, OH), 2.24 (s, 6 H, 2 × CH₃); ¹³C NMR (101 MHz, CHCl₃) δ 157.3 (Ar-C_q-OBn), 150.8 (Ar-C_q-OH), 138.7 (Ar_(phenol)-C_q-C_q), 137.5 (Ar_(p-OBn)-C_q-C_q), 136.9 (Ph-C_q), 128.6 (2 × Ar-CH), 128.0 (Ar-CH), 127.6 (2 × Ar-CH), 127.5 (2 × Ar-CH), 126.7 (2 × Ar-CH), 123.1 (2 × Ar-C_q-CH₃), 114.8 (2 × Ar-CH), 85.0 (CH₂OCH₂), 70.1 (PhCH₂), 50.3 (C_q), 16.1 (2 × CH₃); FTMS (+ p NSI) *m/z* calcd for C₂₄H₂₈O₃N⁺ [M+NH₄]⁺: 378.2064, Found: 378.2060.

{3-[4-(Benzyloxy)phenyl]-2H,3H-naphtho[1,2-b]furan-3-yl}methanol (57i)

Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **45** (64 mg, 0.25 mmol) and 1-naphthol (180 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. NaHCO₃ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 × 15 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (30% EtOAc/hexane) afforded oxetane **57i** (42 mg, 44%) as a cream solid. *R*_f = 0.13 (30% EtOAc/hexane); mp = 221–224 °C; IR (film)/cm⁻¹ 3223 (br. OH), 2967, 1887, 1625, 1605, 1588, 1507, 1467, 1454, 1373, 1251, 1282, 1236, 1183, 1151, 1121, 1053, 1027, 1014, 981, 949, 918, 864, 833, 813, 762, 743, 713, 698; ¹H NMR (400 MHz, (CD₃)₂SO) δ

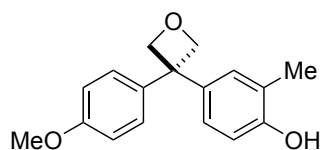
10.21 (s, 1 H, OH), 8.20, (dd, $J = 8.3, 1.4$ Hz, 1 H, Ar-CH), 7.45–7.21 (m, 10 H, 10 × Ar-CH), 6.99–6.87 (m, 4 H, 4 × Ar-CH), 5.31 (d, $J = 5.6$ Hz, 2 H, CHHOCHH), 5.07 (d, $J = 5.6$ Hz, 2 H, CHHOCHH), 5.04 (s, 2 H, PhCH₂). ¹³C NMR (101 MHz, (CD₃)₂SO) δ 157.4 (Ar-C_q-OBn), 152.9 (Ar-C_q-OH), 139.1 (Ar(_p-OBn)-C_q-C_q), 137.6 (Ph-C_q), 131.6 (Ar(_{naphthol})-C_q-C_q), 131.3 (Ar(_{naphthol})-C_q), 128.9 (2 × Ar-CH), 128.3 (Ar-CH), 128.1 (2 × Ar-CH), 127.4 (2 × Ar-CH), 126.7 (Ar-CH), 126.1 (Ar-CH), 125.8 (Ar(_{naphthol})-C_q), 125.0 (Ar-CH), 124.7 (Ar-CH), 123.4 (Ar-CH), 115.0 (2 × Ar-CH), 107.6 (Ar-CH), 84.1 (CH₂OCH₂), 69.6 (PhCH₂), 50.6 (C_q); FTMS (+ p NSI) m/z calcd for C₂₆H₂₆O₃N⁺ [M+NH₄]⁺: 400.1907, Found: 400.1905.

3-[4-(Benzyloxy)phenyl]-3-(2,4-dimethoxyphenyl)oxetane (57j)



Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **45** (64 mg, 0.25 mmol) and dimethoxybenzene (0.16 mL, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. NaHCO₃ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 × 15 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (30% EtOAc/hexane) afforded oxetane **57j** (16 mg, 17%) as a colourless oil. $R_f = 0.35$ (30% EtOAc/hexane); IR (film)/cm⁻¹ 2954, 2876, 2836, 1609, 1583, 1509, 1454, 1438, 1417, 1381, 1287, 1241, 1207, 1180, 1157, 1140, 1118, 1076, 1056, 1026, 981, 945, 911, 827, 732, 696; ¹H NMR (400 MHz, CDCl₃) δ 7.53–7.28 (m, 7 H, 7 × Ar-CH), 7.04–6.87 (m, 3 H, 3 × Ar-CH), 6.55 (dd, $J = 8.3, 2.4$ Hz, 1 H, Ar-CH_a), 6.49 (d, $J = 2.4$ Hz, 1 H, Ar-CH_b), 5.32 (d, $J = 5.9$ Hz, 2 H, CHHOCHH), 4.97 (d, $J = 5.9$ Hz, 2 H, CHHOCHH), 3.84 (s, 3 H, OCH₃), 3.67 (s, 3 H, OCH₃). ¹³C NMR (101 MHz, CDCl₃) δ 159.9 (Ar-C_q-OMe), 157.7 (Ar-C_q-OMe), 157.3 (Ar-C_q-OBn), 139.0 (Ar(_{OMe})-C_q-C_q), 137.1 (Ph-C_q), 128.5 (2 × Ar-CH), 127.9 (Ar-CH), 127.8 (Ar-CH), 127.4 (2 × Ar-CH), 126.9 (2 × Ar-CH), 125.4 (Ar(_{OBn})-C_q-C_q), 114.4 (2 × Ar-CH), 104.1 (Ar-CH_b), 99.1 (Ar-CH_a), 84.5 (CH₂OCH₂), 70.0 (PhCH₂), 55.4 (OCH₃), 55.2 (OCH₃), 49.0 (C_q); HRMS (ESI-TOF) m/z calcd for C₂₄H₂₅O₄⁺ [M+H]⁺: 377.1752, Found: 377.1753.

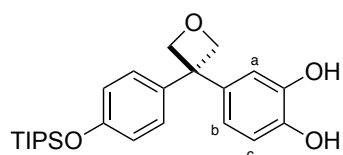
4-[3-(4-Methoxyphenyl)oxetan-3-yl]-2-methylphenol (59)



Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **44** (45 mg, 0.25 mmol) and 2-methylphenol (135 mg, 1.25 mmol) in chloroform

(0.5 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. NaHCO₃ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 × 15 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (25% EtOAc/hexane) afforded oxetane **59** (52 mg, 77%) as a white solid. *R*_f = 0.20 (25% EtOAc/hexane); mp = 141–143 °C; IR (film)/cm⁻¹ 3236 (br. OH), 2963, 1739, 1610, 1579, 1507, 1461, 1413, 1365, 1294, 1242, 1217, 1179, 1117, 1030, 976, 941, 901, 833, 819, 766, 727; ¹H NMR (400 MHz, CDCl₃) δ 7.19–7.10 (m, 2 H, 2 × Ar-CH), 7.00 (d, *J* = 2.4 Hz, 1 H, Ar-CH), 6.94–6.82 (m, 3 H, 3 × Ar-CH), 6.73 (d, *J* = 8.3 Hz, 1 H, Ar-CH), 5.22 (d, *J* = 5.6 Hz, 2 H, CHHOCHH), 5.20 (d, *J* = 5.6 Hz, 2 H, CHHOCHH), 5.06 (s, 1 H, OH), 3.82 (OCH₃), 2.25 (s, 3 H, ArCH₃); ¹³C NMR (101 MHz, (CD₃)₂SO) δ 158.0 (Ar-C_q-OMe), 154.2 (Ar-C_q-OH), 139.5 (Ar_(OMe)-C_q-C_q), 137.2 (Ar_(phenol)-C_q-C_q), 128.8 (Ar-CH), 127.7 (2 × Ar-CH), 124.8 (Ar-CH), 124.2 (Ar-C_q-CH₃), 114.8 (Ar-CH), 114.2 (2 × Ar-CH), 83.8 (CH₂OCH₂), 55.5 (OCH₃), 50.5 (C_q), 16.6 (ArCH₃); FTMS (+ p NSI) *m/z* calcd for C₁₇H₁₉O₃⁺ [M+H]⁺: 271.1329, Found: 271.1331.

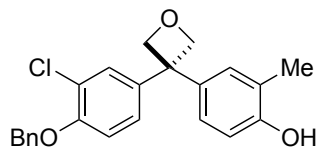
4-[3-(4-[[Tris(propan-2-yl)silyl]oxy]phenyl)oxetan-3-yl]benzene-1,2-diol (**61**)



Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **46** (81 mg, 0.25 mmol) and 2-hydroxyphenol (138 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. NaHCO₃ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with EtOAc (3 × 15 mL). The organic extract was dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (25% EtOAc/hexane) afforded oxetane **61** (41 mg, 39%) as a white solid. *R*_f = 0.12 (25% EtOAc/hexane); mp = 162–163 °C; IR (film)/cm⁻¹ 3384 (br. OH), 2945, 2866, 1741, 1606, 1508, 1462, 1382, 1263, 1174, 1122, 914, 882, 843, 811, 787, 755, 735, 707, 687; ¹H NMR (400 MHz, (CD₃)₂SO) δ 8.84 (s, 1 H, OH), 8.83 (s, 1 H, OH), 7.14–7.08 (m, 2 H, 2 × Ar-CH), 6.86–6.79 (m, 2 H, 2 × Ar-CH), 6.67 (d, *J* = 8.1 Hz, 1 H, Ar-CH_c), 6.59 (d, *J* = 2.2 Hz, 1 H, Ar-CH_a), 6.46 (dd, *J* = 8.1, 2.2 Hz, 1 H, Ar-CH_b), 5.01 (s, 4 H, CH₂OCH₂), 1.30–1.16 (m, 3 H, 3 × CH(CH₃)₂), 1.05 (d, *J* = 7.3 Hz, 18 H, 3 × CH(CH₃)₂); ¹³C NMR (101 MHz, (CD₃)₂SO) δ 154.1 (Ar-C_q-OTIPS), 145.6 (Ar-C_q-OH), 144.1 (Ar-C_q-OH), 139.8 (Ar_(p-OTIPS)-C_q-C_q), 137.8 (Ar_(catechol)-C_q-C_q), 127.9 (2 × Ar_(p-OTIPS)-CH), 119.7 (2 × Ar_(p-OTIPS)-CH), 117.4 (Ar_(catechol)-CH), 115.8 (Ar_(catechol)-CH), 114.3 (Ar_(catechol)-CH), 83.9 (CH₂OCH₂), 50.5 (C_q), 18.2 (2 × CH(CH₃)₂),

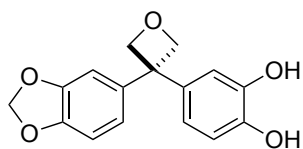
12.5 ($3 \times \text{CH}(\text{CH}_3)_2$); FTMS (+ p NSI) m/z calcd for $\text{C}_{24}\text{H}_{35}\text{O}_4\text{Si}^+$ $[\text{M}+\text{H}]^+$: 415.2299, Found: 415.2302.

4-{3-[4-(Benzyloxy)-3-chlorophenyl]oxetan-3-yl}-2-methylphenol (**62**)



Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **47** (73 mg, 0.25 mmol) and 2-methylphenol (135 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. NaHCO_3 (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2×15 mL). The organic extracts were combined, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (30% EtOAc/hexane) afforded oxetane **62** (32 mg, 33%) as a white solid. R_f = 0.27 (30% EtOAc/hexane); mp = 151–152 °C; IR (film)/ cm^{-1} 3253 (br. OH), 2963, 1739, 1609, 1500, 1464, 1382, 1270, 1252, 1230, 1125, 1062, 1015, 978, 939, 823, 739, 724, 694; ^1H NMR (400 MHz, $(\text{CD}_3)_2\text{SO}$) δ 9.25 (s, 1 H, OH), 7.51–7.28 (m, 6 H, 6 $\times$ Ar-CH), 7.22–7.13 (m, 2 H, 2 $\times$ Ar-CH), 6.98 (d, J = 1.6 Hz, 1 H, Ar-CH), 6.87 (d, J = 8.3 Hz, 1 H, Ar-CH), 6.72 (dd, J = 8.3, 1.6 Hz, 1 H, Ar-CH), 5.19 (s, 2 H, PhCH_2), 5.05 (d, J = 6.1 Hz, 2 H, CHHOCHH), 5.02 (d, J = 6.1 Hz, 2 H, CHHOCHH), 2.09 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $(\text{CD}_3)_2\text{SO}$) δ 154.3 (Ar- C_q -OBn), 152.3 (Ar- C_q -OH), 141.1 (Ar_(phenol)- C_q - C_q), 137.1 (Ar_(p-OBn)- C_q - C_q), 136.5 (Ph- C_q), 129.0 (2 $\times$ Ar-CH), 128.8 (Ar-CH), 128.4 (Ar-CH), 128.1 (Ar-CH), 127.9 (2 $\times$ Ar-CH), 126.3 (Ar-CH), 124.8 (Ar-CH), 124.4 (Ar- C_q - CH_3), 121.9 (Ar- C_q -Cl), 114.9 (Ar-CH), 114.7 (Ar-CH), 83.5 (CH_2OCH_2), 70.5 (PhCH_2), 50.6 (C_q), 16.6 (CH_3); FTMS (+ p NSI) m/z calcd for $\text{C}_{23}\text{H}_{25}\text{O}_3\text{N}^{35}\text{Cl}^+$ $[\text{M}+\text{NH}_4]^+$: 398.1517, Found: 398.1517.

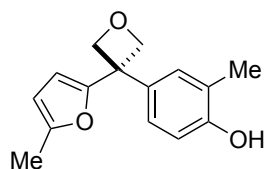
4-[3-(2H-1,3-Benzodioxol-5-yl)oxetan-3-yl]benzene-1,2-diol (**63**)



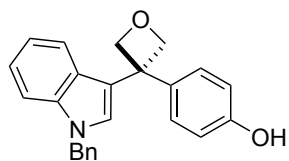
Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **48** (49 mg, 0.25 mmol) and 2-hydroxyphenol (138 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. NaHCO_3 (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with EtOAc (3×15 mL). The organic extracts were combined, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (40% EtOAc/hexane) afforded oxetane **63** (36 mg, 50%) as a light brown solid. R_f = 0.19 (40% EtOAc/hexane); mp = 176–180 °C; IR (film)/ cm^{-1} 3473 (br. OH), 3187, 1737, 1610, 1532, 1499,

1433, 1363, 1269, 1231, 1200, 1175, 1116, 1033, 971, 930, 893, 806, 755; ^1H NMR (400 MHz, $(\text{CD}_3)_2\text{SO}$) δ 8.85 (s, 1 H, OH), 8.84 (s, 1 H, OH), 6.89–6.79 (m, 2 H, 2 $\times$ Ar-CH), 6.67 (dd, J = 8.1, 2.2 Hz, 2 H, 2 $\times$ Ar-CH), 6.61 (d, J = 2.2 Hz, 1 H, Ar-CH), 6.52 (dd, J = 8.1, 2.2 Hz, 1 H, Ar-CH), 5.98 (s, 2 H, OCH_2O), 5.02 (d, J = 5.9 Hz, 2 H, CHHOCHH), 4.98 (d, J = 5.9 Hz, 2 H, CHHOCHH); ^{13}C NMR (101 MHz, $(\text{CD}_3)_2\text{SO}$) δ 147.8 (Ar- C_q - OCH_2O), 145.9 (Ar- C_q - OCH_2O), 145.6 (Ar- C_q -OH), 144.2 (Ar- C_q -OH), 141.2 (Ar_(catechol)- C_q), 137.9 (Ar_(benzodioxole)- C_q), 119.7 (Ar-CH), 117.3 (Ar-CH), 115.8 (Ar-CH), 114.2 (Ar-CH), 108.4 (Ar-CH), 107.5 (Ar-CH), 101.3 (OCH_2O), 83.7 (CH_2OCH_2), 51.0 (C_q); FTMS (+ p NSI) m/z calcd for $\text{C}_{16}\text{H}_{18}\text{NO}_5^+$ [$\text{M}+\text{NH}_4$] $^+$: 304.1179, Found: 304.1179.

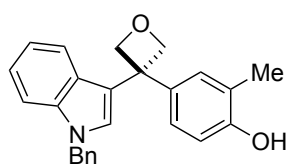
2-Methyl-4-[3-(5-methylfuran-2-yl)oxetan-3-yl]phenol (**64**)



Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **51** (39 mg, 0.25 mmol) and 2-methylphenol (135 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. NaHCO_3 (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 $\times$ 15 mL). The organic extracts were combined, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc/hexane) afforded oxetane **64** (35 mg, 58%) as a yellow gum. R_f = 0.17 (20% EtOAc/hexane); IR (film)/ cm^{-1} 3307 (br. OH), 2956, 2886, 1739, 1612, 1559, 1509, 1457, 1416, 1355, 1257, 1217, 1124, 977, 949, 907, 814, 785, 729; ^1H NMR (400 MHz, CDCl_3) δ 6.99 (d, J = 2.4 Hz, 1 H, Ar_(phenol)-CH), 6.91 (dd, J = 8.1, 2.4 Hz, 1 H, Ar_(phenol)-CH), 6.75 (d, J = 8.1 Hz, 1 H, Ar_(phenol)-CH), 5.88 (dd, J = 3.1, 1.1 Hz, 1 H, Ar_(furan)-CH), 5.69 (d, J = 3.1 Hz, 1 H, Ar_(furan)-CH), 5.58 (s, 1 H, OH), 5.25 (d, J = 5.6 Hz, 2 H, CHHOCHH), 5.15 (d, J = 5.6 Hz, 2 H, CHHOCHH), 2.32 (d, J = 1.0 Hz, 3 H, Ar_(furan) CH_3), 2.26 (s, 3 H, Ar_(phenol) CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 155.7 (Ar_(furan)- C_q - C_q), 153.0 (Ar- C_q -OH), 151.9 (Ar_(furan)- C_q - CH_3), 134.7 (Ar_(phenol)- C_q - C_q), 129.1 (Ar_(phenol)-CH), 125.1 (Ar_(phenol)-CH), 124.0 (Ar_(phenol)- C_q - CH_3), 114.7 (Ar_(phenol)-CH), 107.6 (Ar_(furan)-CH), 106.0 (Ar_(furan)-CH), 82.2 (CH_2OCH_2), 46.9 (C_q), 15.9 (Ar_(phenol) CH_3), 13.6 (Ar_(furan) CH_3); FTMS (+ p NSI) m/z calcd for $\text{C}_{15}\text{H}_{16}\text{O}_3\text{Na}^+$ [$\text{M}+\text{Na}$] $^+$: 267.0992, Found: 267.0992.

4-[3-(1-Benzyl-1H-indol-3-yl)oxetan-3-yl]phenol (65a)

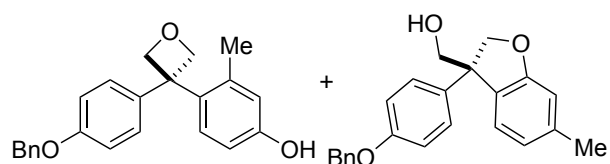
Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **52** (70 mg, 0.25 mmol) and phenol (118 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. NaHCO₃ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 × 15 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (30% EtOAc/hexane) afforded oxetane **65a** (48 mg, 54%) as a light brown solid. *R*_f = 0.19 (30% EtOAc/hexane); mp = 180–182 °C; IR (film)/cm⁻¹ 3278 (br. OH), 2957, 1738, 1611, 1509, 1480, 1467, 1449, 1351, 1268, 1232, 1175, 972, 919, 837, 741, 712, 700; ¹H NMR (400 MHz, CDCl₃) δ 7.67 (dt, *J* = 8.0, 1.0 Hz, 1 H, Ar-CH), 7.37–7.18 (m, 7 H, 7 × Ar-CH), 7.16–7.08 (m, 3 H, 3 × Ar-CH), 6.87–6.80 (m, 2 H, 2 × Ar-CH), 6.70 (s, 1 H, Ar-CH), 5.82 (s, 1 H, OH), 5.46 (d, *J* = 5.6 Hz, 2 H, CHHOCHH), 5.34 (d, *J* = 5.6 Hz, 2 H, CHHOCHH), 5.29 (s, 2 H, PhCH₂); ¹³C NMR (101 MHz, CDCl₃) δ 154.4 (Ar-C_q-OH), 137.32 (Ph-C_q), 137.25 (Ar_(phenol)-C_q and Ar_(indole)-C_q), 128.7 (2 × Ar-CH), 127.8 (2 × Ar-CH), 127.6 (Ar-CH), 126.6 (2 × Ar-CH), 126.5 (Ar-CH), 126.4 (Ar_(indole)-C_q), 122.1 (Ar-CH), 120.2 (Ar_(indole)-C_q-C_q), 120.1 (Ar-CH), 119.5 (Ar-CH), 115.2 (2 × Ar-CH), 110.1 (Ar-CH), 84.5 (CH₂OCH₂), 50.0 (PhCH₂), 46.0 (C_q); FTMS (+ p NSI) *m/z* calcd for C₂₄H₂₂NO₂⁺ [M+H]⁺: 356.1645, Found: 356.1644.

4-[3-(1-Benzyl-1H-indol-3-yl)oxetan-3-yl]-2-methylphenol (65b)

Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **52** (70 mg, 0.25 mmol) and 2-methylphenol (135 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. NaHCO₃ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 × 15 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (30% EtOAc/hexane) afforded oxetane **65b** (66 mg, 71%) as a white solid. *R*_f = 0.29 (30% EtOAc/hexane); mp = 189–191 °C; IR (film)/cm⁻¹ 3196 (br. OH), 2961, 1738, 1612, 1513, 1465, 1451, 1376, 1354, 1334, 1268, 1237, 1194, 1177, 1125, 966, 940, 817, 768, 729, 693; ¹H NMR (400 MHz, CDCl₃) δ 7.67 (dt, *J* = 8.0, 1.0 Hz, 1 H, Ar-CH), 7.37–7.23 (m, 4 H, 4 × Ar-CH), 7.23–7.13 (m, 2 H, 2 × Ar-CH), 7.14–7.05 (m, 3 H, 3 × Ar-CH), 6.99 (dd, *J* = 8.0, 2.4 Hz, 1 H,

Ar-CH), 6.74 (d, $J = 8.0$ Hz, 1 H, Ar-CH), 6.66 (s, 1 H, Ar-CH), 5.39 (d, $J = 5.5$ Hz, 2 H, CHHOCHH), 5.33–5.21 (m, 4 H, PhCH₂ + CHHOCHH), 4.76 (s, 1 H, OH), 2.26 (s, 3 H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 152.4 (Ar-C_q-OH), 137.7 (Ar_(phenol)-C_q-C_q), 137.4 (Ph-C_q), 137.3 (Ar_(indole)-C_q), 129.1 (Ar-CH), 128.7 (2 $\times$ Ar-CH), 127.6 (Ar-CH), 126.6 (2 $\times$ Ar-CH), 126.52 (Ar-CH), 126.50 (Ar_(indole)-C_q), 125.3 (Ar-CH), 123.7 (Ar-C_q-CH₃), 122.1 (Ar-CH), 120.5 (Ar_(indole)-C_q-C_q), 120.2 (Ar-CH), 119.5 (Ar-CH), 114.7 (Ar-CH), 110.0 (Ar-CH), 84.4 (CH₂OCH₂), 50.0 (PhCH₂), 46.1 (C_q), 16.0 (CH₃); FTMS (+ p NSI) m/z calcd for C₂₅H₂₄NO₂⁺ [M+H]⁺: 370.1802, Found: 370.1802.

4-{3-[4-(Benzyloxy)phenyl]oxetan-3-yl}-3-methyl phenol (57k) and {3-[4-(benzyloxy)phenyl]-6-methyl -2,3-dihydro-1-benzofuran-3-yl}methanol (58k)



Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a

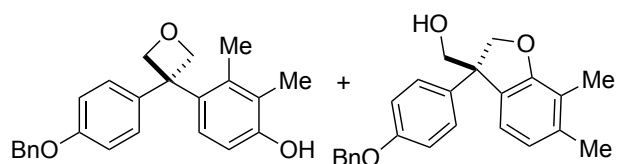
solution of oxetanol **45** (64 mg, 0.25 mmol) and 3-methylphenol (0.13 mL, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. NaHCO₃ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 $\times$ 15 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc/hexane) afforded dihydrobenzofuran **58k** (51 mg, 59%) as a white solid followed by oxetane **57k** (24 mg, 27%) as a white solid.

Oxetane **57k**: $R_f = 0.14$ (20% EtOAc/hexane); mp = 151–154 °C; IR (film)/cm⁻¹ 3297 (br. OH), 3031, 2960, 1877, 1608, 1580, 1507, 1455, 1380, 1295, 1243, 1182, 1116, 1010, 977, 927, 860, 830, 735, 697; ¹H NMR (400 MHz, CDCl₃) δ 7.49–7.25 (m, 7 H, 7 $\times$ Ar-CH), 6.99–6.86 (m, 3 H, 3 $\times$ Ar-CH), 6.73 (dd, $J = 8.3, 2.7$ Hz, 1 H, Ar-CH), 6.69 (d, $J = 2.7$ Hz, 1 H, Ar-CH), 5.41 (d, $J = 5.5$ Hz, 2 H, CHHOCHH), 5.10 (s, 1 H, OH), 5.06 (s, 2 H, PhCH₂), 4.92 (d, $J = 5.5$ Hz, 2 H, CHHOCHH), 1.80 (s, 3 H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 157.6 (Ar-C_q-OBn), 154.5 (Ar-C_q-OH), 138.2 (Ar_(p-OBn)-C_q-C_q), 137.6 (Ar-C_q-CH₃), 136.9 (Ph-C_q), 134.5 (Ar_(phenol)-C_q-C_q), 128.6 (2 $\times$ Ar-CH), 128.4 (Ar-CH), 128.0 (Ar-CH), 127.5 (2 $\times$ Ar-CH), 126.9 (2 $\times$ Ar-CH), 118.0 (Ar-CH), 114.7 (2 $\times$ Ar-CH), 112.6 (Ar-CH), 84.7 (CH₂OCH₂), 70.0 (PhCH₂), 50.6 (C_q), 19.7 (CH₃); FTMS (+ p NSI) m/z calcd for C₂₃H₂₆O₃N⁺ [M+NH₄]⁺: 364.1907, Found: 364.1908.

Dihydrobenzofuran **58k**: $R_f = 0.23$ (20% EtOAc/hexane); mp = 80–82 °C; IR (film)/cm⁻¹ 3427 (br. OH), 3034, 2923, 1608, 1590, 1509, 1497, 1454, 1425, 1380, 1294, 1242, 1182, 1129,

1115, 1080, 1009, 972, 911, 861, 828, 807, 731, 696; ^1H NMR (400 MHz, CHCl_3) δ 7.52–7.31 (m, 5 H, 5 $\times$ Ar-CH), 7.29–7.20 (m, 2 H, 2 $\times$ Ar-CH), 7.13–7.05 (m, 1 H, Ar-CH), 7.02–6.92 (m, 2 H, 2 $\times$ Ar-CH), 6.83–6.77 (m, 1 H, Ar-CH), 6.77–6.71 (m, 1 H, Ar-CH), 5.08 (s, 2 H, PhCH_2), 4.78 (d, J = 8.9 Hz, 1 H, OCHHC_q), 4.58 (d, J = 8.9 Hz, 1 H, OCHHC_q), 4.09 (dd, J = 11.2, 4.0 Hz, 1 H, CHHOH), 4.02 (dd, J = 11.2, 7.3 Hz, 1 H, CHHOH), 2.38 (s, 3 H, CH_3) 1.65 (br. s, 1 H, OH); ^{13}C NMR (101 MHz, CHCl_3) δ 161.0 ($\text{Ar}_{(\text{DHBf})}\text{-C}_q\text{-OCH}_2$), 157.7 ($\text{Ar-C}_q\text{-OBn}$), 139.5 ($\text{Ar}_{(\text{DHBf})}\text{-C}_q\text{-CH}_3$), 136.9 (Ph-C_q), 135.1 ($\text{Ar}_{(\text{p-OBn})}\text{-C}_q\text{-C}_q$), 128.6 (2 $\times$ Ar-CH), 128.0 (2 $\times$ Ar-CH), 127.9 (Ar-CH), 127.4 (2 $\times$ Ar-CH), 127.0 ($\text{Ar}_{(\text{DHBf})}\text{-C}_q\text{-C}_q$), 124.7 (Ar-CH), 121.6 (Ar-CH), 115.0 (2 $\times$ Ar-CH), 110.8 (Ar-CH), 81.4 (OCH_2C_q), 70.0 (PhCH_2), 67.7 (CH_2OH), 55.5 (C_q), 21.5 (CH_3); FTMS (+ p NSI) m/z calcd for $\text{C}_{23}\text{H}_{26}\text{O}_3\text{N}^+$ [$\text{M}+\text{NH}_4$] $^+$: 364.1907, Found: 364.1906.

4-{3-[4-(Benzyloxy)phenyl]oxetan-3-yl}-2,3-di methylphenol (57I) and {3-[4-(benzyloxy)phenyl]-6,7-dimethyl-2,3-dihydro-1-benzofuran-3-yl} methanol (58I)



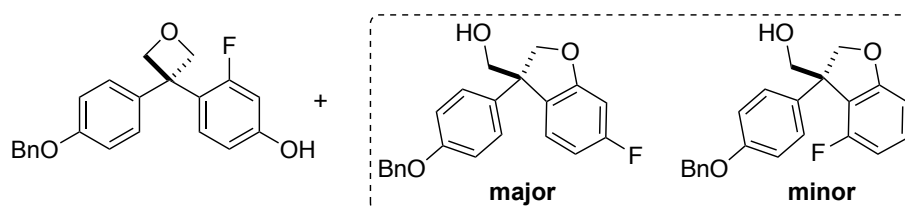
Lithium bis(trifluoromethanesulfonyl)imide (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a

solution of oxetanol **45** (64 mg, 0.25 mmol) and 2,3-dimethylphenol (153 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. NaHCO_3 (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 $\times$ 15 mL). The organic extracts were combined, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (3% EtOAc/ CH_2Cl_2) afforded dihydrobenzofuran **58I** (18 mg, 20%) as a yellow gum followed by oxetane **57I** (46 mg, 51%) as a white solid.

Oxetane **57I**: R_f = 0.16 (3% EtOAc/ CH_2Cl_2); mp = 185–187 °C; IR (film)/ cm^{-1} 3306 (br. OH), 1587, 1507, 1457, 1382, 1281, 1242, 1182, 1064, 1017, 970, 919, 864, 834, 813, 748, 736, 698; ^1H NMR (400 MHz, $(\text{CD}_3)_2\text{SO}$) δ 9.21 (s, 1 H, OH), 7.50–7.27 (m, 5 H, 5 $\times$ Ar-CH), 7.27–7.17 (m, 2 H, 2 $\times$ Ar-CH), 7.01–6.89 (m, 2 H, 2 $\times$ Ar-CH), 6.73 (q, J = 8.3 Hz, 1 H, Ar-CH), 5.16 (d, J = 5.7 Hz, 2 H, CHHOCHH), 5.07 (s, 2 H, PhCH_2), 4.80 (d, J = 5.7 Hz, 2 H, CHHOCHH), 2.03 (s, 3 H, CH_3), 1.62 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $(\text{CD}_3)_2\text{SO}$) δ 157.4 ($\text{Ar-C}_q\text{-OBn}$), 154.2 ($\text{Ar-C}_q\text{-OH}$), 139.2 ($\text{Ar}_{(\text{p-OBn})}\text{-C}_q\text{-C}_q$), 137.6 (Ph-C_q), 135.5 ($\text{Ar-C}_q\text{-CH}_3$), 133.7 ($\text{Ar}_{(\text{phenol})}\text{-C}_q\text{-C}_q$), 128.9 (2 $\times$ Ar-CH), 128.3 (Ar-CH), 128.1 (2 $\times$ Ar-CH), 127.2 (2 $\times$ Ar-CH), 125.2 (Ar-CH), 123.8 ($\text{Ar-C}_q\text{-CH}_3$), 115.0 (2 $\times$ Ar-CH), 112.4 (Ar-CH), 84.1 (CH_2OCH_2), 69.7 (PhCH_2), 50.9 (C_q), 16.8 (CH_3), 12.3 (CH_3); FTMS (+ p NSI) m/z calcd for $\text{C}_{24}\text{H}_{28}\text{O}_3\text{N}^+$ [$\text{M}+\text{NH}_4$] $^+$: 378.2064, Found: 378.2063.

Dihydrobenzofuran **58l**: $R_f = 0.30$ (3% EtOAc/CH₂Cl₂); IR (film)/cm⁻¹ 3381 (br. OH), 3035, 2920, 1608, 1589, 1510, 1454, 1381, 1242, 1182, 1079, 1021, 976, 908, 828, 805, 730, 696; ¹H NMR (400 MHz, CHCl₃) δ 7.52–7.15 (m, 7 H, 7 $\times$ Ar-CH), 7.02–6.87 (m, 3 H, 3 $\times$ Ar-CH), 6.79 (d, $J = 7.6$ Hz, 1 H, Ar-CH), 5.07 (s, 2 H, PhCH₂), 4.78 (d, $J = 8.9$ Hz, 1 H, OCHHC_q), 4.60 (d, $J = 8.9$ Hz, 1 H, OCHHC_q), 4.09 (d, $J = 11.1$ Hz, 1 H, CHHOH), 4.02 (d, $J = 11.1$ Hz, 1 H, CHHOH), 2.30 (s, 3 H, CH₃), 2.19 (s, 3 H, CH₃); ¹³C NMR (101 MHz, CHCl₃) δ 159.4 (Ar_(DHBf)-C_q-OCH₂), 157.7 (Ar-C_q-OBn), 138.0 (Ar-C_q-CH₃), 136.9 (Ph-C_q), 135.3 (Ar_(p-OBn)-C_q-C_q), 128.6 (2 $\times$ Ar-CH), 128.1 (2 $\times$ Ar-CH), 128.0 (Ar-CH), 127.4 (2 $\times$ Ar-CH), 126.6 (Ar_(DHBf)-C_q-C_q), 122.2 (Ar-CH), 121.6 (Ar-CH), 119.1 (Ar-C_q-CH₃), 115.0 (2 $\times$ Ar-CH), 81.1 (OCH₂C_q), 70.0 (PhCH₂), 67.7 (CH₂OH), 56.1 (C_q), 19.4 (CH₃), 11.7 (CH₃); FTMS (+ p NSI) m/z calcd for C₂₄H₂₅O₃⁺ [M+H]⁺: 361.1798, Found; 361.1800.

4-{3-[4-(Benzyloxy)phenyl]oxetan-3-yl}-3-fluorophenol (57m) and {3-[4-(benzyloxy)phenyl]-6-fluoro-2,3-dihydro-1-benzofuran-3-yl}methanol (58m major) and {3-[4-(benzyloxy)phenyl]-4-fluoro-2,3-dihydro-1-benzofuran-3-yl}methanol (58m' minor)



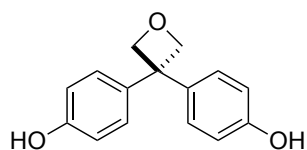
Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **45** (64 mg, 0.25 mmol) and 3-fluorophenol (0.11 mL, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. NaHCO₃ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 $\times$ 15 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (30% EtOAc/hexane) afforded a mixture dihydrobenzofurans **58m/m'** (24 mg, 28%, 85:15) as a colourless gum followed by oxetane **57m** (39 mg, 44%) as a white solid.

Dihydrobenzofurans **58m/m'** (**a**, **major**) and (**b**, **minor**): $R_f = 0.37$ (30% EtOAc/hexane); IR (film)/cm⁻¹ 3422 (br. OH), 3034, 2875, 1608, 1510, 1491, 1454, 1437, 1294, 1183, 1133, 1107, 1085, 1018, 982, 908, 829, 806, 731, 697; ¹H NMR (400 MHz, CHCl₃) δ 7.51–7.29 (m, 5 H^a + 5 H^b, 5 $\times$ Ar-CH^a + 5 $\times$ Ar-CH^b), 7.24–7.17 (m, 2 H^a + 3 H^b, 2 $\times$ Ar-CH^a + 3 $\times$ Ar-CH^b), 7.13 (dd, $J = 8.2, 5.7$ Hz, 1 H^a, Ar-CH^a), 7.03–6.84 (m, 2 H^a + 2 H^b, 2 $\times$ Ar-CH^a + 2 $\times$ Ar-CH^b), 6.76–6.50 (m, 2 H^a + 2 H^b, 2 $\times$ Ar-CH^a + 2 $\times$ Ar-CH^b), 5.06 (s, 2 H^a + 2 H^b, PhCH₂^a + PhCH₂^b),

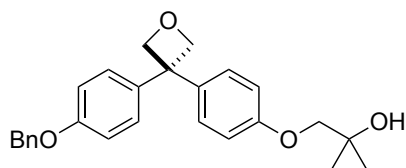
4.86 (d, $J = 9.0$ Hz, 1 H^b, OCHHC_q^b), 4.80 (d, $J = 9.0$ Hz, 1 H, OCHHC_q^a), 4.64 (d, $J = 9.0$ Hz, 1 H^b, OCHHC_q^b), 4.64 (d, $J = 9.0$ Hz, 1 H^a, OCHHC_q^a), 4.26 (d, $J = 11.0$ Hz, 1 H, CHHOH^b), 4.15 (dd, $J = 11.0, 4.2$ Hz, 1 H, CHHOH^b), 4.09 (d, $J = 10.8$ Hz, 1 H, CHHOH^a), 4.01 (dd, $J = 10.8, 5.8$ Hz, 1 H, CHHOH^a), 1.65 (s, 1 H, OH^b); ¹³C NMR (101 MHz, CHCl₃) δ 163.8 (d, $J_{C-F} = 244.8$ Hz, Ar-C_q-F), 161.9 (d, $J_{C-F} = 13.3$ Hz, Ar_(DHBf)-C_q-OCH₂), 157.9 (Ar-C_q-OBn), 136.8 (Ph-C_q), 134.6 (Ar_(p-OBn)-C_q-C_q), 128.6 (2 $\times$ Ar-CH), 128.1 (Ar-CH), 128.0 (2 $\times$ Ar-CH), 127.5 (2 $\times$ Ar-CH), 125.9 (d, $J_{C-F} = 2.4$ Hz, Ar_(DHBf)-C_q-C_q), 125.6 (d, $J_{C-F} = 10.8$ Hz, Ar-CH), 115.1 (2 $\times$ Ar-CH), 107.6 (d, $J_{C-F} = 22.8$ Hz, Ar-CH), 98.6 (d, $J_{C-F} = 26.5$ Hz, Ar-CH), 82.4 (OCH₂C_q), 70.1 (PhCH₂), 67.7 (CH₂OH), 55.1 (C_q); ¹⁹F NMR (377 MHz, CDCl₃) δ -112.6 (a, major), -117.1 (b, minor); FTMS (+ p NSI) m/z calcd for C₂₂H₂₃O₃NF⁺ [M+NH₄]⁺: 368.1656, Found: 368.1656.

Oxetane **57m**: $R_f = 0.27$ (30% EtOAc/hexane); mp = 185–187 °C; IR (film)/cm⁻¹ 3276 (br. OH), 2954, 2882, 1738, 1623, 1610, 1599, 1511, 1455, 1388, 1348, 1298, 1280, 1245, 1188, 1161, 1116, 1013, 968, 942, 846, 834, 816, 746; ¹H NMR (400 MHz, CDCl₃) δ 7.49–7.24 (m, 7 H, 7 $\times$ Ar-CH), 7.02–6.87 (m, 3 H, 3 $\times$ Ar-CH), 6.66 (dd, $J = 8.3, 2.5$ Hz, 1 H, Ar-CH), 6.58 (dd, $J = 11.6, 2.5$ Hz, 1 H, Ar-CH), 5.36 (dd, $J = 5.6, 1.3$ Hz, 2 H, CHHOCHH), 5.30 (s, 1 H, OH), 5.06 (s, 2 H, PhCH₂), 5.06 (d, $J = 5.6$ Hz, 4 H, CHHOCHH + PhCH₂); ¹³C NMR (101 MHz, CDCl₃) δ 160.8 (d, $J_{C-F} = 246.8$ Hz, Ar-C_q-F), 157.7 (Ar-C_q-OBn), 156.0 (d, $J_{C-F} = 11.6$ Hz, Ar-C_q-OH), 137.7 (Ar_(p-OBn)-C_q-C_q), 136.9 (Ph-C_q), 128.6 (2 $\times$ Ar-CH), 128.5 (d, $J_{C-F} = 6.7$ Hz, Ar-CH), 128.0 (Ar-CH), 127.4 (2 $\times$ Ar-CH), 126.8 (2 $\times$ Ar-CH), 124.0 (d, $J_{C-F} = 14.5$ Hz, Ar_(phenol)-C_q-C_q), 114.8 (2 $\times$ Ar-CH), 111.3 (d, $J_{C-F} = 2.8$ Hz, Ar-CH), 103.8 (d, $J_{C-F} = 24.7$ Hz, Ar-CH), 84.1 (CH₂OCH₂), 70.1 (PhCH₂), 48.0 (C_q); ¹⁹F NMR (377 MHz, CDCl₃) δ -113.1; FTMS (+ p NSI) m/z calcd for C₂₂H₂₃O₃NF⁺ [M+NH₄]⁺: 368.1656, Found: 368.1657.

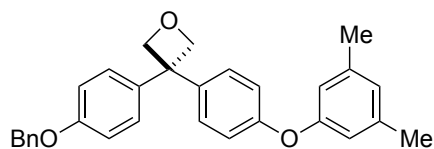
4-[3-(4-Hydroxyphenyl)oxetan-3-yl]phenol (**66**)



Palladium on carbon (10% w/w, 17 mg) was added to a solution of oxetane **57a** (166 mg, 0.5 mmol) in ethanol (4.5 mL). The reaction mixture was stirred under an atmosphere of hydrogen at 25 °C overnight. The reaction mixture was filtered through celite, washed through with ethanol and then concentrated *in vacuo* to afford oxetane **66** (121 mg, 100%) as a white solid. $R_f = 0.35$ (50% EtOAc/hexane); mp = 237–239 °C; IR (film)/cm⁻¹ 3183 (br. OH), 2953, 2880, 2506, 2365, 1611, 1514, 1438, 1266, 1182, 1111, 969, 929, 841, 818, 752; ¹H NMR (400 MHz, CD₃OD) δ 7.11–7.00 (m, 4 H, 4 $\times$ Ar-CH), 6.83–6.73 (m, 4 H, 4 $\times$ Ar-CH), 5.18 (s, 4 H, CH₂OCH₂); ¹³C NMR (101 MHz, CD₃OD) δ 155.6 (2 $\times$ Ar-C_q-OH), 137.2 (2 $\times$ Ar-C_q-C_q), 127.2 (4 $\times$ Ar-CH), 114.8 (4 $\times$ Ar-CH), 84.8 (CH₂OCH₂), 50.2 (C_q); FTMS (+ p NSI) m/z calcd for C₁₅H₁₈O₃N⁺ [M+NH₄]⁺: 260.1281, Found: 260.1283.

1-(4-{3-[4-(Benzyloxy)phenyl]oxetan-3-yl}phenoxy)-2-methylpropan-2-ol (67)

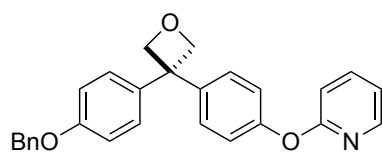
1,1-Dimethyloxirane (44 μ L, 0.50 mmol) was added to a solution of oxetane **57a** (83 mg, 0.25 mmol), K_2CO_3 (48 mg, 0.35 mmol) in DMF (0.5 mL). The reaction mixture was stirred at 100 $^{\circ}C$ for 40 h then water (20 mL) was added followed by diethylether (20 mL). The layers were separated and the aqueous portion was extracted with diethylether (20 mL). The organic extracts were combined, washed with brine (2 $\times$ 15 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (30% EtOAc/hexane) afforded oxetane **67** (77 mg, 77%) as a white solid. R_f = 0.13 (30% EtOAc/hexane); mp = 115–117 $^{\circ}C$; IR (film)/ cm^{-1} 3377 (br. OH), 2974, 1739, 1609, 1509, 1227, 1179, 1041, 1011, 977, 939, 833, 817, 745, 698; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49–7.30 (m, 5 H, 5 $\times$ Ar-CH), 7.21–7.09 (m, 4 H, 4 $\times$ Ar-CH), 7.01–6.94 (m, 2 H, 2 $\times$ Ar-CH), 6.94–6.88 (m, 2 H, 2 $\times$ Ar-CH), 5.20 (s, 4 H, CH_2OCH_2), 5.07 (s, 2 H, $PhCH_2$), 3.80 ($CH_2C_q(CH_3)_2$), 2.24 (s, 1 H, OH), 1.36 (s, 6 H, 2 $\times$ CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.5 (Ar- C_q -O), 157.4 (Ar- C_q -O), 138.6 (Ar- C_q - C_q), 138.4 (Ar- C_q - C_q), 137.0 (Ph- C_q), 128.6 (2 $\times$ Ar-CH), 128.0 (Ar-CH), 127.7 (2 $\times$ Ar-CH), 127.6 (2 $\times$ Ar-CH), 127.5 (2 $\times$ Ar-CH), 114.8 (2 $\times$ Ar-CH), 114.6 (2 $\times$ Ar-CH), 84.9 (CH_2OCH_2), 76.1 ($C_q(CH_3)_2$), 70.1 ($PhCH_2$), 50.4 ($CH_2C_q(CH_3)_2$), 26.2 (2 $\times$ CH_3); FTMS (+ p NSI) m/z calcd for $C_{26}H_{32}O_4N^+$ [$M+NH_4$] $^+$: 422.2326, Found: 422.2323.

3-[4-(Benzyloxy)phenyl]-3-[4-(3,5-dimethylphenoxy)phenyl]oxetane (68)

Using conditions developed by Ma,²⁴³ oxetane **57a** (99.7 mg, 0.30 mmol), *N,N*-dimethylglycine.HCl (7.9 mg, 0.055 mmol), CuI (2.9 mg, 0.015 mmol) and Cs_2CO_3 (196 mg, 0.60 mmol) were added to a reaction vial. The reaction vial was evacuated and then refilled with nitrogen ($\times$ 3). 5-Iodo-*m*-xylene (65 μ L, 0.45 mmol) then 1,4-dioxane (0.6 mL) were added *via* syringe. The reaction mixture was stirred at 90 $^{\circ}C$ for 20 h then cooled to rt. Brine (20 mL) was added and the layers separated. The aqueous portion was extracted with EtOAc (3 $\times$ 15 mL). The organic extracts were combined, washed with brine (15 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (15% EtOAc/hexane) afforded oxetane **68** (99 mg, 76%) as a white solid. R_f = 0.26 (15% EtOAc/hexane); mp = 154–157 $^{\circ}C$; IR (film)/ cm^{-1} 2881, 1586, 1504, 1295, 1232, 1219, 1167, 1026, 1013, 989, 833, 743, 696, 688; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52–7.28 (m, 5 H, 5 $\times$ Ar-CH), 7.23–7.11 (m, 4 H, 4 $\times$ Ar-CH), 7.03–6.92 (m, 4 H, 4 $\times$ Ar-CH), 6.81–6.73 (m, 1 H, Ar-CH), 6.72–6.64 (m, 2 H, 2 $\times$ Ar-CH), 5.23 (s, 4 H,

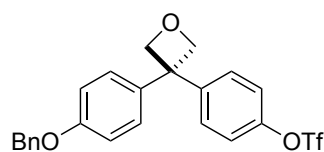
CH₂OCH₂), 5.08 (s, 2 H, PhCH₂), 2.31 (s, 6 H, 2 × CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 157.5 (Ar-C_q-OBn), 156.9 (Ar_(m-ylene)-C_q-O), 156.1 (Ar_(p-OAr)-C_q-O), 140.5 (Ar-C_q-C_q), 139.6 (2 × Ar-C_q-CH₃), 138.2 (Ar-C_q-C_q), 136.9 (Ph-C_q), 128.6 (2 × Ar-CH), 128.0 (Ar-CH), 127.8 (2 × Ar-CH), 127.6 (2 × Ar-CH), 127.5 (2 × Ar-CH), 125.1 (Ar-CH), 118.6 (2 × Ar-CH), 116.7 (2 × Ar-CH), 114.8 (2 × Ar-CH), 84.8 (CH₂OCH₂), 70.1 (PhCH₂), 50.5 (C_q), 21.3 (2 × CH₃); FTMS (+ p NSI) m/z calcd for C₃₀H₃₂O₃N⁺ [M+NH₄]⁺: 454.2377, Found: 454.2368.

2-(4-{3-[4-(Benzyloxy)phenyl]oxetan-3-yl}phenoxy)pyridine (69)



Using Ullmann conditions developed by Buchwald,²⁴⁴ oxetane **57a** (99.7 mg, 0.30 mmol), picolinic acid (3.7 mg, 0.03 mmol), CuI (2.9 mg, 0.015 mmol) and K₃PO₄ (127 mg, 0.60 mmol) were added to a reaction vial. The reaction vial was evacuated and then refilled with nitrogen (× 3). 2-Iodopyridine (38 μL, 0.36 mmol) then DMSO (0.6 mL) were added *via* syringe. The reaction mixture was stirred at 90 °C for 23 h then cooled to rt. Water (20 mL) was added followed by EtOAc (15 mL). The layers were separated and the aqueous portion was extracted with EtOAc (2 × 15 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc/hexane) afforded oxetane **69** (103 mg, 84%) as a white solid. R_f = 0.35 (25% EtOAc/hexane); mp = 93–95 °C; IR (film)/cm⁻¹ 2961, 2885, 1581, 1506, 1464, 1425, 1231, 1213, 1187, 1010, 987, 855, 750, 735, 702; ¹H NMR (400 MHz, CDCl₃) δ 8.24–8.20 (m, 1 H, Ar_(py)-CH), 7.74–7.66 (ddd, *J* = 8.2, 7.2, 2.0 Hz, 1 H, Ar_(py)-CH), 7.48–7.31 (m, 5 H, 5 × Ar-CH), 7.30–7.22 (m, 2 H, 2 × Ar-CH), 7.20–7.10 (m, 4 H, 4 × Ar-CH), 7.04–6.91 (m, 4 H, 4 × Ar-CH), 5.24 (s, 4 H, CH₂OCH₂), 5.09 (s, 2 H, PhCH₂); ¹³C NMR (101 MHz, CDCl₃) δ 163.5 (Ar_(py)-C_q), 157.5 (Ar-C_q-OBn), 152.7 (Ar-C_q-OPy), 147.7 (Ar_(py)-CH), 142.2 (Ar-C_q-C_q), 139.4 (Ar_(py)-CH), 138.0 (Ar-C_q-C_q), 136.9 (Ph-C_q), 128.6 (2 × Ar-CH), 128.0 (Ar-CH), 127.8 (2 × Ar-CH), 127.7 (2 × Ar-CH), 127.5 (2 × Ar-CH), 121.0 (2 × Ar-CH), 118.5 (Ar_(py)-CH), 114.9 (2 × Ar-CH), 111.7 (Ar-CH), 84.8 (CH₂OCH₂), 70.1 (PhCH₂), 50.6 (C_q); FTMS (+ p NSI) m/z calcd for C₂₇H₂₄O₃N⁺ [M+H]⁺: 410.1751, Found: 410.1745.

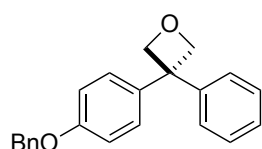
4-{3-[4-(Benzyloxy)phenyl]oxetan-3-yl}phenyl trifluoromethanesulfonate (70)



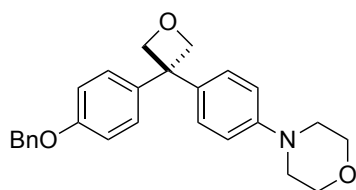
Pyridine (0.24 mL, 3.0 mmol) then triflic anhydride (0.30 mL, 1.8 mmol) were added to a solution of oxetane **57a** (499 mg, 1.5 mmol) in dichloromethane (3.0 mL). The reaction mixture was stirred at 25 °C for 3 h then water (20 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 × 15 mL). The organic extracts were combined, dried over Na₂SO₄,

filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc/hexane) afforded oxetane **70** (584 mg, 84%) as a white solid. R_f = 0.36 (20% EtOAc/hexane); mp = 103–104 °C; IR (film)/cm⁻¹ 2960, 2871, 1610, 1516, 1499, 1423, 1250, 1207, 1182, 1136, 1017, 897, 884, 845, 743, 696; ¹H NMR (400 MHz, CDCl₃) δ 7.49–7.30 (m, 7 H, 7 × Ar-CH), 7.30–7.20 (m, 2 H, 2 × Ar-CH), 7.12–7.04 (m, 2 H, 2 × Ar-CH), 7.04–6.96 (m, 2 H, 2 × Ar-CH), 5.27 (d, J = 5.8 Hz, 2 H, CHHOCHH), 5.15 (d, J = 5.8 Hz, 2 H, CHHOCHH), 5.09 (s, 2 H, PhCH₂); ¹³C NMR (101 MHz, CDCl₃) δ 157.4 (Ar-C_q-OBn), 148.1 (Ar-C_q-OTf), 146.8 (Ar-C_q-C_q), 136.81 (Ar-C_q-C_q or Ph-C_q), 136.77 (Ar-C_q-C_q or Ph-C_q), 128.6 (2 × Ar-CH), 128.4 (2 × Ar-CH), 128.0 (Ar-CH), 127.6 (2 × Ar-CH), 127.5 (2 × Ar-CH), 121.4 (2 × Ar-CH), 118.7 (q, J_{C-F} = 319.3 Hz, CF₃), 115.1 (2 × Ar-CH), 84.4 (CH₂OCH₂), 70.1 (PhCH₂), 50.7 (C_q); ¹⁹F NMR (377 MHz, CDCl₃) δ -72.8; FTMS (+ p NSI) m/z calcd for C₂₃H₂₃O₅NF₃S⁺ [M+NH₄]⁺: 482.1244, Found: 482.1232.

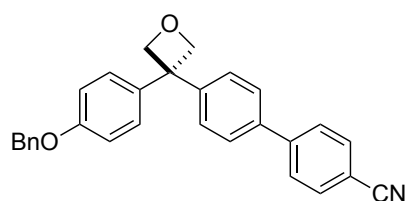
3-[4-(Benzyloxy)phenyl]-3-phenyloxetane (**71**)



Using conditions developed by Ortar,¹⁵⁵ Triethylamine (105 μL, 0.75 mmol) then formic acid (19 μL, 0.50 mmol) were added to a solution of oxetane **70** (116 mg, 0.25 mmol), Pd(OAc)₂ (1.1 mg, 0.005 mmol), 1,1'-bis(diphenylphosphino)ferrocene (2.8 mg, 0.005 mmol) in dimethylformamide (3.0 mL). The reaction mixture was stirred at 60 °C for 1 h then brine (20 mL) was added followed by diethylether (15 mL). The layers were separated and the aqueous portion was extracted with diethylether (2 × 15 mL). The organic extracts were combined, washed with brine (2 × 15 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (15% EtOAc/hexane) afforded oxetane **71** (44 mg, 55%) as a white solid. R_f = 0.29 (15% EtOAc/hexane); mp = 130–132 °C; IR (film)/cm⁻¹ 2953, 2938, 2874, 1509, 1497, 1383, 1239, 1184, 1009, 988, 832, 784, 763, 745, 699; ¹H NMR (400 MHz, CDCl₃) δ 7.41–7.22 (m, 7 H, 7 × Ar-CH), 7.23–7.11 (m, 3 H, 3 × Ar-CH), 7.11–7.04 (m, 2 H, 2 × Ar-CH), 6.93–6.85 (m, 2 H, 2 × Ar-CH), 5.16 (d, J = 5.6 Hz, 2 H, CHHOCHH), 5.14 (d, J = 5.6 Hz, 2 H, CHHOCHH), 4.99 (s, 2 H, PhCH₂); ¹³C NMR (101 MHz, CDCl₃) δ 157.4 (Ar-C_q-OBn), 145.9 (Ar-C_q-C_q), 138.2 (Ar-C_q-C_q), 136.9 (Ph-C_q), 128.6 (2 × Ar-CH), 128.5 (2 × Ar-CH), 128.0 (Ar-CH), 127.6 (2 × Ar-CH), 127.4 (2 × Ar-CH), 126.6 (Ar-CH), 126.5 (2 × Ar-CH), 114.8 (2 × Ar-CH), 84.7 (CH₂OCH₂), 70.0 (PhCH₂), 50.9 (C_q); FTMS (+ p NSI) m/z calcd for C₂₂H₂₄O₂N⁺ [M+NH₄]⁺: 334.1802, Found: 334.1804.

4-(4-{3-[4-(Benzyloxy)phenyl]oxetan-3-yl}phenyl)morpholine (72)

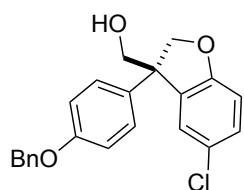
Using conditions developed by Buchwald,²⁴⁵ oxetane **70** (232 mg, 0.50 mmol), Pd(OAc)₂ (1.1 mg, 0.005 mmol), JohnPhos (3.0 mg, 0.010 mmol) and K₃PO₄ (149 mg, 0.70 mmol) were added to a reaction vial. The reaction vial was evacuated and then refilled with nitrogen ($\times$ 3). Morpholine (53 μ L, 0.60 mmol) then THF (1.0 mL) were added *via* syringe. The reaction mixture was stirred at 65 °C for 24 h then cooled to rt. Diethylether (15 mL) was added and the crude mixture was filtered through celite and then concentrated *in vacuo*. Purification by flash column chromatography (30% EtOAc/hexane) afforded oxetane **72** (189 mg, 94%) as a white solid. R_f = 0.14 (30% EtOAc/hexane); mp = 131–133 °C; IR (film)/cm⁻¹ 2955, 2188, 1736, 1609, 1513, 1451, 1380, 1229, 1183, 1119, 1017, 981, 921, 817, 749, 697; ¹H NMR (400 MHz, CDCl₃) δ 7.54–7.28 (m, 5 H, 5 $\times$ Ar-CH), 7.22–7.07 (m, 4 H, 4 $\times$ Ar-CH), 7.00–6.86 (m, 4 H, 4 $\times$ Ar-CH), 5.22 (d, J = 5.7 Hz, 2 H, CHHOCHH), 5.20 (d, J = 5.7 Hz, 2 H, CHHOCHH), 5.07 (s, 2 H, PhCH₂), 3.97–3.82 (m, 4 H, CH₂CH₂OCH₂CH₂), 3.25–3.09 (m, 4 H, CH₂NCH₂); ¹³C NMR (101 MHz, CDCl₃) δ 157.4 (Ar-C_q-OBn), 145.9 (Ar-C_q-N), 138.5 (Ar-C_q-C_q), 137.3 (Ar-C_q-C_q), 136.9 (Ph-C_q), 128.6 (2 $\times$ Ar-CH), 128.0 (Ar-CH), 127.6 (2 $\times$ Ar-CH), 127.5 (2 $\times$ Ar-CH), 127.3 (2 $\times$ Ar-CH), 115.5 (2 $\times$ Ar-CH), 114.8 (2 $\times$ Ar-CH), 84.9 (CH₂OCH₂), 70.1 (PhCH₂), 66.9 (CH₂CH₂OCH₂CH₂), 50.3 (C_q), 49.2 (CH₂NCH₂); FTMS (+ p NSI) m/z calcd for C₂₆H₂₈O₃N⁺ [M+H]⁺: 402.2064, Found: 402.2055.

4-(4-{3-[4-(Benzyloxy)phenyl]oxetan-3-yl}phenyl)benzonitrile (73)

Oxetane **70** (139 mg, 0.30 mmol), 4-cyanoboronic acid (58.8 mg, 0.40 mmol), Pd(OAc)₂ (3.4 mg, 0.015 mmol), SPhos (12.3 mg, 0.03 mmol) and K₂CO₃ (82.9 mg, 0.60 mmol) were added to a reaction vial. The reaction vial was evacuated and then refilled with nitrogen ($\times$ 3). Dioxane/water (4:1, 3.0 mL) was added *via* syringe. The reaction mixture was stirred at 65 °C for 18 h then cooled to rt. Diethylether (15 mL) was added and the crude mixture was filtered through celite[®] and then concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc/hexane) afforded oxetane **73** (57 mg, 45%) as a white solid. R_f = 0.12 (20% EtOAc/hexane); mp = 169–172 °C; IR (film)/cm⁻¹ 2871, 2224 (CN), 1738, 1607, 1517, 1492, 1256, 1239, 1178, 1028, 982, 856, 824, 737; ¹H NMR (400 MHz, CDCl₃) δ 7.76–7.66 (m, 4 H, 4 $\times$ Ar-CH), 7.62–7.55 (m, 2 H, 2 $\times$ Ar-CH), 7.49–7.31 (m, 7 H, 7 $\times$ Ar-CH), 7.21–7.12 (m, 2 H, 2 $\times$ Ar-CH), 7.03–6.96 (m, 2 H, 2 $\times$ Ar-CH), 5.28 (d, J = 5.8 Hz, 2 H, CHHOCHH), 5.26 (d,

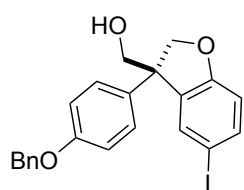
$J = 5.8$ Hz, 2 H, CHHOCHH), 5.08 (s, 2 H, PhCH₂); ¹³C NMR (101 MHz, CDCl₃) δ 157.6 (Ar-C_q-OBn), 146.7 (Ar-C_q-C_q), 145.1 (Ar-C_q-C_q), 137.7 (Ar-C_q-Ar), 137.5 (Ar-C_q-Ar), 136.9 (Ph-C_q), 132.6 (2 $\times$ Ar-CH), 128.6 (2 $\times$ Ar-CH), 128.0 (Ar-CH), 127.60 (2 $\times$ Ar-CH), 127.59 (2 $\times$ Ar-CH), 127.5 (2 $\times$ Ar-CH), 127.4 (2 $\times$ Ar-CH), 127.3 (2 $\times$ Ar-CH), 118.9 (CN), 114.9 (2 $\times$ Ar-CH), 113.2 (Ar-C_q-CN), 84.5 (CH₂OCH₂), 70.1 (PhCH₂), 50.9 (C_q); FTMS (+ p NSI) m/z calcd for C₂₉H₂₇O₂N₂⁺ [M+H]⁺: 435.2067, Found: 435.2063.

{3-[4-(Benzyloxy)phenyl]-5-chloro-2,3-dihydro-1-benzofuran-3-yl}methanol (**58n**)



Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **45** (64 mg, 0.25 mmol) and 4-chlorophenol (161 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 20 h then sat. aq. NaHCO₃ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 $\times$ 15 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc/hexane) afforded dihydrobenzofuran **58n** (26 mg, 28%) as a colourless gum. $R_f = 0.18$ (20% EtOAc/hexane); IR (film)/cm⁻¹ 3420 (br. OH), 2880, 1609, 1512, 1479, 1381, 1297, 1244, 1183, 1025, 975, 827, 736, 696; ¹H NMR (400 MHz, CDCl₃) δ 7.48–7.30 (m, 5 H, 5 $\times$ Ar-CH), 7.27–7.13 (m, 4 H, 4 $\times$ Ar-CH), 7.02–6.94 (m, 2 H, 2 $\times$ Ar-CH), 6.86–6.79 (m, 1 H, Ar-CH), 5.07 (s, 2 H, PhCH₂), 4.77 (d, $J = 9.0$ Hz, 1 H, OCHHC_q), 4.59 (d, $J = 9.0$ Hz, 1 H, OCHHC_q), 4.11 (dd, $J = 11.2, 4.6$ Hz, 1 H, CHHOH), 4.03 (dd, $J = 11.2, 7.1$ Hz, 1 H, CHHOH); ¹³C NMR (101 MHz, CDCl₃) δ 159.3 (Ar_(DHBf)-C_q-OCH₂), 157.9 (Ar_(p-OBn)-C_q-OBn), 136.8 (Ph-C_q), 134.1 (Ar-C_q-C_q), 132.4 (Ar-C_q-C_q), 129.1 (Ar-CH), 128.6 (2 $\times$ Ar-CH), 128.1 (Ar-CH), 128.0 (2 $\times$ Ar-CH), 127.5 (2 $\times$ Ar-CH), 125.5 (Ar-C_q-Cl), 125.4 (Ar-CH), 115.2 (2 $\times$ Ar-CH), 111.2 (Ar-CH), 81.9 (OCH₂C_q), 70.1 (PhCH₂), 67.5 (CH₂OH), 55.9 (C_q); FTMS (+ p NSI) m/z calcd for C₂₂H₂₃ClO₃N⁺ [M+NH₄]⁺: 384.1361, Found: 384.1356.

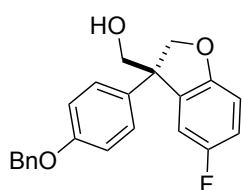
{3-[4-(Benzyloxy)phenyl]-5-iodo-2,3-dihydro-1-benzofuran-3-yl}methanol (**58o**)



Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **45** (64 mg, 0.25 mmol) and 4-iodophenol (275 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 20 h then sat. aq. NaHCO₃ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with

dichloromethane (2 × 15 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (30% EtOAc/pentane) afforded dihydrobenzofuran **58o** (27 mg, 25%) as a colourless gum. *R*_f = 0.26 (20% EtOAc/hexane); IR (film)/cm⁻¹ 3429 (br. OH), 3032, 2880, 1609, 1582, 1476, 1456, 1382, 1293, 1238, 1183, 1130, 1025, 971, 909, 827, 811, 734, 697, 669; ¹H NMR (400 MHz, CDCl₃) δ 7.55–7.30 (m, 7 H, 7 × Ar-CH), 7.24–7.15 (m, 2 H, 2 × Ar-CH), 7.02–6.92 (m, 2 H, 2 × Ar-CH), 6.73–6.62 (m, 1 H, Ar-CH), 5.07 (s, 2 H, PhCH₂), 4.75 (d, *J* = 9.0 Hz, 1 H, OCHHC_q), 4.57 (d, *J* = 9.0 Hz, 1 H, OCHHC_q), 4.09 (d, *J* = 11.1 Hz, 1 H, CHHOH), 4.02 (d, *J* = 11.1 Hz, 1 H, CHHOH); ¹³C NMR (101 MHz, CDCl₃) δ 160.6 (Ar_(DHBf)-C_q-OCH₂), 157.9 (Ar-C_q-OBn), 137.9 (Ar-CH), 136.8 (Ph-C_q), 134.1 (Ar-C_q-C_q), 133.9 (Ar-CH), 133.6 (Ar-C_q-C_q), 128.6 (2 × Ar-CH), 128.01 (ArCH), 127.97 (2 × Ar-CH), 127.4 (2 × Ar-CH), 115.2 (2 × Ar-CH), 112.5 (Ar-CH), 82.1 (Ar-C_q-I), 81.7 (OCH₂C_q), 70.0 (PhCH₂), 67.5 (CH₂OH), 55.7 (C_q); FTMS (+ p NSI) *m/z* calcd for C₂₂H₂₃O₃NI⁺ [M+NH₄]⁺: 476.0717, Found: 476.0709.

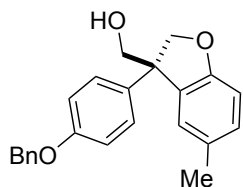
{3-[4-(Benzyloxy)phenyl]-5-fluoro-2,3-dihydro-1-benzofuran-3-yl}methanol (**58p**)



Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **45** (64 mg, 0.25 mmol) and 4-fluorophenol (140 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 20 h then sat. aq. NaHCO₃ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 × 15 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (25% EtOAc/hexane) afforded dihydrobenzofuran **58p** (25 mg, 29%) as a colourless gum. *R*_f = 0.11 (20% EtOAc/hexane); mp = 92–94 °C; IR (film)/cm⁻¹ 3439 (br. OH), 2875, 1609, 1501, 1511, 1485, 1382, 1296, 1246, 1183, 1025, 978, 863, 828, 813, 775, 738, 697; ¹H NMR (400 MHz, CDCl₃) δ 7.47–7.29 (m, 5 H, 5 × Ar-CH), 7.26–7.19 (m, 2 H, 2 × Ar-CH), 7.01–6.87 (m, 4 H, 4 × Ar-CH), 6.83–6.75 (m, 1 H, 1 × Ar-CH), 5.07 (s, 2 H, PhCH₂), 4.76 (d, *J* = 9.0 Hz, 1 H, OCHHC_q), 4.58 (d, *J* = 9.0 Hz, 1 H, OCHHC_q), 4.12 (dd, *J* = 11.1, 4.9 Hz, 1 H, CHHOH), 4.03 (dd, *J* = 11.1, 7.6 Hz, 1 H, CHHOH); ¹³C NMR (101 MHz, CDCl₃) δ 157.9 (Ar-C_q-OBn), 157.5 (d, *J*_{C-F} = 240.5 Hz, Ar-C_q-F), 156.5 (Ar_(DHBf)-C_q-OCH₂), 136.8 (Ph-C_q), 134.2 (Ar_(p-OBn)-C_q-C_q), 131.8 (d, *J*_{C-F} = 7.8 Hz, Ar_(DHBf)-C_q-C_q), 128.6 (2 × Ar-CH), 128.01 (2 × Ar-CH), 127.97 (Ar-CH), 127.4 (2 × Ar-CH), 115.5 (d, *J*_{C-F} = 23.9 Hz, Ar-CH), 115.2 (2 × Ar-CH), 112.4 (d, *J*_{C-F} = 25.4 Hz, Ar-CH), 110.3 (d, *J*_{C-F} = 8.2 Hz, Ar-CH), 81.8 (OCH₂C_q),

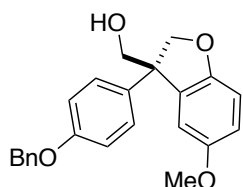
70.0 (PhCH₂), 67.5 (CH₂OH), 56.0 (C_q); ¹⁹F NMR (377 MHz, CDCl₃) δ –123.5; FTMS (+ p NSI) *m/z* calcd for C₂₂H₂₃O₃NF⁺ [M+NH₄]⁺: 368.1656, Found: 368.1659.

{3-[4-(Benzyloxy)phenyl]-5-methyl-2,3-dihydro-1-benzofuran-3-yl}methanol (58q)



Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutyl-ammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **45** (64 mg, 0.25 mmol) and 4-methylphenol (135 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 20 h then sat. aq. NaHCO₃ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 × 15 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (30% EtOAc/hexane) afforded dihydrobenzofuran **58q** (61 mg, 81%) as a colourless gum. *R*_f = 0.33 (30% EtOAc/hexane); IR (film)/cm⁻¹ 3420 (br. OH), 3034, 2868, 1608, 1580, 1489, 1454, 1381, 1295, 1241, 1182, 1127, 1037, 1024, 971, 827, 809, 732, 696; ¹H NMR (400 MHz, CDCl₃) δ 7.52–7.32 (m, 5 H, 5 × Ar-CH), 7.29–7.21 (m, 2 H, 2 × Ar-CH), 7.10–6.94 (m, 4 H, 4 × Ar-CH), 6.81 (d, *J* = 8.1 Hz, 1 H, 1 × Ar-CH), 5.09 (s, 2 H, PhCH₂), 4.77 (d, *J* = 8.8 Hz, 1 H, OCHHC_q), 4.58 (d, *J* = 8.8 Hz, 1 H, OCHHC_q), 4.12 (dd, *J* = 11.1, 3.9 Hz, 1 H, CHHOH), 4.04 (dd, *J* = 11.1, 7.5 Hz, 1 H, CHHOH), 2.35 (s, 3 H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 158.6 (Ar_(DHBf)-C_q-OCH₂), 157.6 (Ar-C_q-OBn), 136.8 (Ph-C_q), 135.0 (Ar-C_q-C_q), 130.1 (Ar_(DHBf)-C_q-C_q), 130.0 (ArC_q-CH₃), 129.6 (Ar-CH), 128.5 (2 × Ar-CH), 128.0 (2 × Ar-CH), 127.9 (Ar-CH), 127.4 (2 × Ar-CH), 125.5 (Ar-CH), 115.0 (2 × Ar-CH), 109.7 (Ar-CH), 81.3 (OCH₂C_q), 69.9 (PhCH₂), 67.5 (CH₂OH), 55.7 (C_q), 20.9 (CH₃); FTMS (+ p NSI) *m/z* calcd for C₂₃H₂₆O₃N⁺ [M+NH₄]⁺: 364.1907, Found: 364.1909.

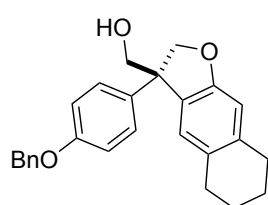
{3-[4-(Benzyloxy)phenyl]-5-methoxy-2,3-dihydro-1-benzofuran-3-yl}methanol (58r)



Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **45** (64 mg, 0.25 mmol) and 4-methoxyphenol (155 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 20 h then sat. aq. NaHCO₃ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 × 15 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (30% EtOAc/hexane) afforded dihydrobenzofuran **58r** (66 mg, 73%) as a colourless gum. *R*_f = 0.18 (30% EtOAc/hexane); IR

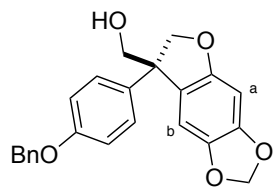
(film)/cm⁻¹ 3442 (br. OH), 3034, 2941, 1608, 1510, 1486, 1466, 1381, 1242, 1199, 1179, 1025, 974, 907, 828, 804, 727, 696; ¹H NMR (400 MHz, CDCl₃) δ 7.50–7.31 (m, 5 H, 5 × Ar-CH), 7.31–7.21 (m, 2 H, 2 × Ar-CH), 7.02–6.92 (m, 2 H, 2 × Ar-CH), 6.86–6.76 (m, 3 H, 3 × Ar-CH), 5.08 (s, 2 H, PhCH₂), 4.75 (d, *J* = 8.8 Hz, 1 H, OCHHC_q), 4.56 (d, *J* = 8.8 Hz, 1 H, OCHHC_q), 4.13 (dd, *J* = 11.1, 3.6 Hz, 1 H, CHHOH), 4.05 (dd, *J* = 11.1, 7.0 Hz, 1 H, CHHOH), 3.79 (s, 3 H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 157.8 (Ar-C_q-OBn), 154.8 (Ar_(DHBf)-C_q-OCH₂), 154.3 (Ar-C_q-OMe), 136.9 (Ph-C_q), 134.7 (Ar_(p-OBn)-C_q-C_q), 131.2 (Ar_(DHBf)-C_q-C_q), 128.6 (2 × Ar-CH), 128.1 (2 × Ar-CH), 128.0 (Ar-CH), 127.4 (2 × Ar-CH), 115.1 (2 × Ar-CH), 114.2 (Ar-CH), 111.2 (Ar-CH), 110.1 (Ar-CH), 81.5 (OCH₂C_q), 70.0 (PhCH₂), 67.4 (CH₂OH), 56.1 (C_q), 56.0 (CH₃); FTMS (+ p NSI) *m/z* calcd for C₂₃H₂₆O₄N⁺ [M+NH₄]⁺: 380.1856, Found: 380.1857.

{3-[4-(Benzyloxy)phenyl]-2H,3H,5H,6H,7H,8H-naphtho[2,3-b]furan-3-yl} methanol (**58s**)



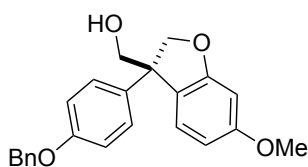
Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **45** (64 mg, 0.25 mmol) and 5,6,7,8-tetrahydro-2-naphthol (185 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. NaHCO₃ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 × 15 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc/hexane) afforded dihydrobenzofuran **58s** (88 mg, 91%) as a yellow gum. *R*_f = 0.17 (20% EtOAc/hexane); IR (film)/cm⁻¹ 3469 (br. OH), 2930, 1739, 1609, 1510, 1487, 1242, 1182, 1024, 975, 905, 855, 828, 726, 696; ¹H NMR (400 MHz, CHCl₃) δ 7.51–7.33 (m, 5 H, 5 × Ar-CH), 7.32–7.24 (m, 2 H, 2 × Ar-CH), 7.04–6.93 (m, 2 H, 2 × Ar-CH), 6.91 (s, 1 H, Ar-CH), 6.64 (s, 1 H, Ar-CH), 5.09 (s, 2 H, PhCH₂), 4.74 (d, *J* = 8.8 Hz, 1 H, OCHHC_q), 4.56 (d, *J* = 8.8 Hz, 1 H, OCHHC_q), 4.10 (dd, *J* = 11.1, 4.8 Hz, 1 H, CHHOH), 4.02 (dd, *J* = 11.1, 7.5 Hz, 1 H, CHHOH), 2.86–2.77 (m, 2 H, 2 × ArCHHCH₂), 2.77–2.66 (m, 2 H, 2 × ArCHHCH₂), 1.88–1.76 (m, 4 H, 2 × ArCH₂CH₂), 1.75–1.64 (m, 1 H, OH); ¹³C NMR (101 MHz, CHCl₃) δ 158.7 (Ar_(DHBf)-C_q-OCH₂), 157.7 (Ar-C_q-OBn), 138.3 (Ar-C_q-CH₂CH₂), 136.9 (Ph-C_q), 35.1 (Ar_(p-OBn)-C_q-C_q), 129.4 (Ar-C_q-CH₂CH₂), 128.6 (2 × Ar-CH), 128.1 (2 × Ar-CH), 128.0 (Ar-CH), 127.7 (Ar_(DHBf)-C_q-C_q), 127.4 (2 × Ar-CH), 125.3 (Ar-CH), 114.9 (2 × Ar-CH), 110.0 (Ar-CH), 81.2 (OCH₂C_q), 70.0 (PhCH₂), 67.7 (CH₂OH), 55.6 (C_q), 29.9 (ArCH₂CH₂), 29.2 (ArCH₂CH₂), 23.4 (ArCH₂CH₂), 23.1 (ArCH₂CH₂); FTMS (+ p NSI) *m/z* calcd for C₂₆H₃₀O₃N⁺ [M+NH₄]⁺: 404.2220, Found: 404.2217.

{12-[4-(Benzyloxy)phenyl]-4,6,10-trioxatricyclo[7.3.0.0³,7]dodeca-1(9),2,7-trien-12-yl} methanol (58t)



Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **45** (64 mg, 0.25 mmol) and sesamol (173 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. NaHCO₃ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 × 15 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc/hexane) afforded oxetane **58t** (89 mg, 94%) as a white solid. *R*_f = 0.06 (20% EtOAc/hexane); mp = 110–111 °C; IR (film)/cm⁻¹ 3441 (br. OH), 2885, 1609, 1580, 1510, 1474, 1452, 1382, 1291, 1244, 1182, 1151, 1034, 1012, 938, 861, 828, 769, 735, 698; ¹H NMR (400 MHz, CHCl₃) δ 7.48–7.29 (m, 5 H, 5 × Ar-CH), 7.24–7.16 (m, 2 H, 2 × Ar-CH), 6.98–6.92 (m, 2 H, 2 × Ar-CH), 6.65 (s, 1 H, Ar-CH_a), 6.47 (s, 1 H, Ar-CH_b), 5.95 (s, 2 H, OCH₂O), 5.06 (s, 2 H, PhCH₂), 4.73 (d, *J* = 8.9 Hz, 1 H, OCHHC_q), 4.54 (d, *J* = 8.9 Hz, 1 H, OCHHC_q), 4.06 (dd, *J* = 11.1, 4.5 Hz, 1 H, CHHOH), 3.99 (dd, *J* = 11.1, 7.8 Hz, 1 H, CHHOH), 1.61 (dd, *J* = 7.8, 4.5 Hz, 1 H, OH); ¹³C NMR (101 MHz, CHCl₃) δ 157.8 (Ar-C_q-OBn), 155.6 (Ar_(DHBf)-C_q-OCH₂C_q), 148.3 (Ar_(DHBf)-C_q-OCH₂O), 141.8 (Ar_(DHBf)-C_q-OCH₂O), 136.9 (Ph-C_q), 135.1 (Ar_(p-OBn)-C_q-C_q), 128.6 (2 × Ar-CH), 128.0 (3 × Ar-CH), 127.5 (2 × Ar-CH), 121.0 (Ar_(DHBf)-C_q-C_q), 115.1 (2 × Ar-CH), 105.0 (Ar-CH_a), 101.4 (OCH₂O), 93.5 (Ar-CH_b), 82.0 (OCH₂C_q), 70.0 (PhCH₂), 67.5 (CH₂OH), 55.7 (C_q); FTMS (+ p NSI) *m/z* calcd for C₂₃H₂₁O₅⁺ [M+H]⁺: 377.1384, Found: 377.1380.

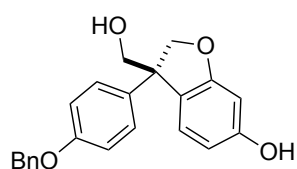
{3-[4-(Benzyloxy)phenyl]-6-methoxy-2,3-dihydro-1-benzofuran-3-yl} methanol (58u)



Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **45** (64 mg, 0.25 mmol) and 3-methoxyphenol (0.14 mL, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. NaHCO₃ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 × 15 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (40% EtOAc/hexane) afforded oxetane **58u** (41 mg, 46%) as a pale yellow gum. *R*_f = 0.18 (40% EtOAc/hexane); IR (film)/cm⁻¹ 3451 (br. OH), 2943, 2836, 1739, 1619, 1595, 1510, 1496, 1466, 1454, 1444, 1379, 1332, 1278, 1241, 1183, 1147, 1085, 1024, 980, 910, 827, 697; ¹H

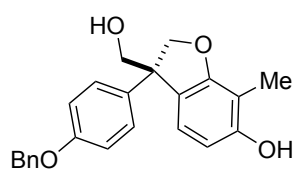
NMR (400 MHz, CHCl_3) δ 7.47–7.30 (m, 5 H, 5 $\times$ Ar-CH), 7.26–7.18 (m, 2 H, 2 $\times$ Ar-CH), 7.11–7.05 (m, 1 H, Ar-CH), 6.99–6.91 (m, 2 H, 2 $\times$ Ar-CH), 6.52 (dd, J = 8.2, 2.2 Hz, 1 H, Ar-CH), 6.49 (d, J = 2.2 Hz, 1 H, Ar-CH), 5.06 (s, 2 H, PhCH_2), 4.79 (d, J = 8.8 Hz, 1 H, OCHHC_q), 4.58 (d, J = 8.8 Hz, 1 H, OCHHC_q), 4.06 (d, J = 11.1, 1 H, CHHOH), 3.99 (d, J = 11.1 Hz, 1 H, CHHOH), 3.81 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, CHCl_3) δ 162.1 ($\text{Ar}_{(\text{DHBf})}\text{-C}_q\text{-OCH}_2$), 161.2 ($\text{Ar}_{(\text{DHBf})}\text{-C}_q\text{-OMe}$), 157.7 ($\text{Ar-C}_q\text{-OBn}$), 136.9 (Ph-C_q), 135.2 ($\text{Ar}_{(\text{p-OBn})}\text{-C}_q\text{-C}_q$), 128.6 (2 $\times$ Ar-CH), 128.0 (3 $\times$ Ar-CH), 127.4 (2 $\times$ Ar-CH), 125.3 (Ar-CH), 121.9 ($\text{Ar}_{(\text{DHBf})}\text{-C}_q\text{-C}_q$), 115.0 (2 $\times$ Ar-CH), 106.7 (Ar-CH), 96.5 (Ar-CH), 82.0 (OCH_2C_q), 70.0 (PhCH_2), 67.8 (CH_2OH), 55.5 (CH_3), 55.2 (C_q); FTMS (+ p NSI) m/z calcd for $\text{C}_{23}\text{H}_{23}\text{O}_4^+$ $[\text{M}+\text{H}]^+$: 363.1591, Found: 363.1591.

3-[4-(Benzyloxy)phenyl]-3-(hydroxymethyl)-2,3-dihydro-1-benzofuran-6-ol (**58v**)



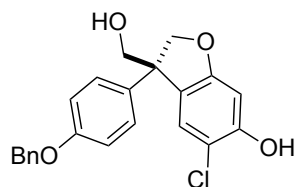
Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **45** (64 mg, 0.25 mmol) and resorcinol (138 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. NaHCO_3 (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 $\times$ 15 mL). The organic extracts were combined, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (35% EtOAc/hexane) afforded oxetane **58v** (64 mg, 74%) as a white solid. R_f = 0.09 (35% EtOAc/hexane); mp = 185–187 °C; IR (film)/ cm^{-1} 3356 (br. OH) 3045, 2874, 1611, 1514, 1479, 1453, 1386, 1286, 1243, 1173, 1189, 1152, 1121, 1094, 1080, 1039, 1014, 1005, 987, 916, 834, 810, 748, 698; ^1H NMR (400 MHz, $(\text{CD}_3)_2\text{SO}$) δ 9.34 (s, 1 H, Ar-OH), 7.52–7.28 (m, 5 H, 5 $\times$ Ar-CH), 7.27–7.19 (m, 2 H, 2 $\times$ Ar-CH), 6.99–6.87 (m, 3 H, 3 $\times$ Ar-CH), 6.35–6.25 (m, 1 H, Ar-CH), 6.25–6.19 (m, 1 H, Ar-CH), 5.07 (s, 2 H, PhCH_2), 5.03 (m, 1 H, CH_2OH) 4.68 (d, J = 8.9 Hz, 1 H, OCHHC_q), 4.46 (d, J = 8.9 Hz, 1 H, OCHHC_q), 3.84 (dd, J = 10.5, 5.0 Hz, 1 H, CHHOH), 3.75 (dd, J = 10.5, 5.0 Hz, 1 H, CHHOH); ^{13}C NMR (101 MHz, $(\text{CD}_3)_2\text{SO}$) δ 161.5 ($\text{Ar}_{(\text{DHBf})}\text{-C}_q\text{-OCH}_2$), 158.6 ($\text{Ar}_{(\text{DHBf})}\text{-C}_q\text{-OH}$), 157.2, ($\text{Ar-C}_q\text{-OBn}$), 137.7 (Ph-C_q), 137.2 ($\text{Ar}_{(\text{p-OBn})}\text{-C}_q\text{-C}_q$), 128.9 (2 $\times$ Ar-CH), 128.6 (2 $\times$ Ar-CH), 128.2 (Ar-CH), 128.1 (2 $\times$ Ar-CH), 125.8 (Ar-CH), 122.6 ($\text{Ar}_{(\text{DHBf})}\text{-C}_q\text{-C}_q$), 114.9 (2 $\times$ Ar-CH), 107.7 (Ar-CH), 97.6 (Ar-CH), 81.5 (OCH_2C_q), 69.6 (PhCH_2), 66.8 (CH_2OH), 54.9 (C_q); FTMS (+ p NSI) m/z calcd for $\text{C}_{22}\text{H}_{21}\text{O}_4^+$ $[\text{M}+\text{H}]^+$: 349.1434, Found: 349.1436.

3-[4-(Benzyloxy)phenyl]-3-(hydroxymethyl)-7-methyl-2,3-dihydro-1-benzofuran-6-ol (58w)



Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) or calcium bis(trifluoromethanesulfonimide) (8.3 mg, 0.0138 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **45** (64 mg, 0.25 mmol) and 2-methylresorcinol (155 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. NaHCO₃ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 × 15 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (30% EtOAc/hexane) afforded dihydrobenzofuran **58w** (61 mg, 67%) as a pale orange solid. *R*_f = 0.15 (30% EtOAc/hexane); mp = 150–152 °C; IR (film)/cm⁻¹ 3467 (br. OH), 1738, 1597, 1511, 1468, 1454, 1431, 1383, 1241, 1217, 1183, 1137, 1124, 1078, 1056, 1015, 983, 840, 816, 799, 745, 696; ¹H NMR (400 MHz, (CD₃)₂SO) δ 9.20 (s, 1 H, Ar-OH), 7.49–7.27 (m, 5 H, 5 × Ar-CH), 7.26–7.17 (m, 2 H, 2 × Ar-CH), 6.97–6.86 (m, 2 H, 2 × Ar-CH), 6.75 (d, *J* = 8.0 Hz, 1 H, Ar-CH), 6.34 (d, *J* = 8.0 Hz, 1 H, Ar-CH), 5.06 (s, 2 H, PhCH₂), 4.99 (t, *J* = 5.1 Hz, 1 H, CH₂OH), 4.67 (d, *J* = 8.9 Hz, 1 H, OCHHC_q), 4.47 (d, *J* = 8.9 Hz, 1 H, OCHHC_q), 3.84 (dd, *J* = 10.7, 5.1 Hz, 1 H, CHHOH), 3.74 (dd, *J* = 10.7, 5.1 Hz, 1 H, CHHOH), 1.95 (s, 3 H, CH₃); ¹³C NMR (101 MHz, (CD₃)₂SO) δ 159.8 (Ar_(DHBF)-C_q-OCH₂), 157.1 (Ar-C_q-OBn), 156.3 (Ar_(DHBF)-C_q-OH), 137.7 (Ph-C_q), 137.3 (Ar_(p-OBn)-C_q-C_q), 128.8 (2 × Ar-CH), 128.6 (2 × Ar-CH), 128.2 (Ar-CH), 128.0 (2 × Ar-CH), 122.2 (Ar-CH), 122.0 (Ar_(DHBF)-C_q-C_q), 114.8 (2 × Ar-CH), 107.3 (Ar-CH), 106.2 (Ar-C_q-CH₃), 81.2 (OCH₂C_q), 69.6 (PhCH₂), 66.9 (CH₂OH), 55.4 (C_q), 9.1 (CH₃); FTMS (+ p NSI) *m/z* calcd for C₂₃H₂₃O₄⁺ [M+H]⁺: 363.1591, Found: 363.1581.

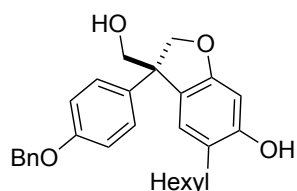
3-[4-(Benzyloxy)phenyl]-5-chloro-3-(hydroxymethyl)-2,3-dihydro-1-benzofuran-6-ol (58x)



Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **45** (64 mg, 0.25 mmol) and 4-chlororesorcinol (181 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 20 h then sat. aq. NaHCO₃ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 × 15 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (30% EtOAc/hexane) afforded dihydrobenzofuran **58x** (48 mg, 50%) as a pale brown solid. *R*_f

= 0.10 (30% EtOAc/hexane); mp = 140–141 °C; IR (film)/cm⁻¹ 3427 (br. OH), 2946, 2901, 1739, 1600, 1583, 1510, 1490, 1468, 1456, 1428, 1378, 1286, 1245, 1223, 1185, 1139, 1091, 1041, 1012, 987, 873, 837, 801, 765, 747, 727, 695, 684; ¹H NMR (400 MHz, (CD₃)₂SO) δ 10.09 (s, 1 H, Ar-OH), 7.48–7.27 (m, 5 H, 5 × Ar-CH), 7.26–7.16 (m, 2 H, 2 × Ar-CH), 7.08 (s, 1 H, Ar-CH), 7.00–6.90 (m, 2 H, 2 × Ar-CH), 6.44 (s, 1 H, Ar-CH), 5.09 (t, *J* = 5.0 Hz, 1 H, CH₂OH), 5.08 (s, 2 H, PhCH₂), 4.69 (d, *J* = 8.9 Hz, 1 H, OCHHC_q), 4.50 (d, *J* = 8.9 Hz, 1 H OCHHC_q), 3.84 (dd, *J* = 10.9, 5.0 Hz, 1 H, CHHOH), 3.80 (dd, *J* = 10.9, 5.0 Hz, 1 H, CHHOH); ¹³C NMR (101 MHz, (CD₃)₂SO) δ 160.0 (Ar_(DHBf)-C_q-OCH₂), 157.3 (Ar-C_q-OBn), 153.7 (Ar_(DHBf)-C_q-OH), 137.6 (Ph-C_q), 136.5 (Ar_(p-OBn)-C_q-C_q), 128.9 (2 × Ar-CH), 128.4 (2 × Ar-CH), 128.3 (Ar-CH), 128.1 (2 × Ar-CH), 126.2 (Ar-CH), 124.1 (Ar_(DHBf)-C_q-C_q), 115.0 (2 × Ar-CH), 111.3 (Ar-C_q-Cl), 98.6 (Ar-CH), 81.8 (OCH₂C_q), 69.6 (PhCH₂), 66.4 (CH₂OH), 55.3 (C_q); FTMS (+ p NSI) *m/z* calcd for C₂₂H₂₃O₄NCl⁺ [M+NH₄]⁺: 400.1310, Found: 400.1300.

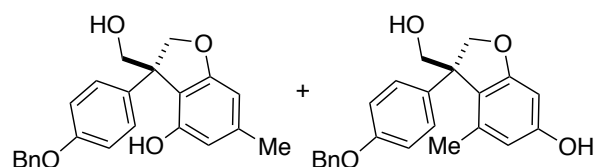
3-[4-(Benzyloxy)phenyl]-5-hexyl-3-(hydroxymethyl)-2,3-dihydro-1-benzofuran-6-ol (58y)



Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **45** (64 mg, 0.25 mmol) and 4-hexylresorcinol (243 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 20 h then sat. aq. NaHCO₃ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 × 15 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (25% EtOAc/hexane) afforded dihydrobenzofuran **58y** (60 mg, 55%) as a dark red gum. *R*_f = 0.18 (30% EtOAc/hexane); IR (film)/cm⁻¹ 3400 (br. OH), 2927, 2858, 1739, 1610, 1510, 1497, 1455, 1379, 1296, 1243, 1180, 1023, 905, 829, 726, 697; ¹H NMR (400 MHz, CHCl₃) δ 7.54–7.29 (m, 5 H, 5 × Ar-CH), 7.30–7.14 (m, 2 H, 2 × Ar-CH), 7.02–6.85 (m, 3 H, 3 × Ar-CH), 6.35 (s, 1 H, Ar-CH), 5.26 (s, 1 H, Ar-OH), 5.06 (s, 2 H, PhCH₂), 4.74 (d, *J* = 8.8 Hz, 1 H, OCHHC_q), 4.53 (d, *J* = 8.8 Hz, 1 H, OCHHC_q), 4.06 (d, *J* = 11.1 Hz, 1 H, CHHOH), 4.00 (d, *J* = 11.1 Hz, 1 H, CHHOH), 2.54 (sep, *J* = 7.2 Hz, 2 H, CH₂), 1.56 (quin, *J* = 7.2 Hz, 2 H, CH₂), 1.45–1.20 (m, 6 H, CH₂CH₂CH₂), 0.97–0.81 (m, 3 H, CH₃); ¹³C NMR (101 MHz, CHCl₃) δ 159.9 (Ar_(DHBf)-C_q-OCH₂), 157.7 (Ar-C_q-OBn), 154.5 (Ar_(DHBf)-C_q-OH), 136.8 (Ph-C_q), 135.3 (Ar_(p-OBn)-C_q-C_q), 128.6 (2 × Ar-CH), 128.0 (2 × Ar-CH), 128.0 (Ar-CH), 127.4 (2 × Ar-CH), 125.8 (Ar-CH), 121.2 (Ar_(DHBf)-C_q-Hexyl), 121.1 (Ar_(DHBf)-C_q-C_q), 115.0 (2 × Ar-CH), 97.8 (Ar-CH), 81.8 (OCH₂C_q), 70.0 (PhCH₂), 67.7 (CH₂OH), 55.4 (C_q), 31.7 (CH₂), 30.0 (CH₂), 29.8 (CH₂), 29.2

(CH₂), 22.7 (CH₂), 14.1 (CH₃); FTMS (+ p NSI) *m/z* calcd for C₂₈H₃₃O₄⁺ [M+H]⁺: 433.2373, Found: 433.2371.

3-[4-(Benzyloxy)phenyl]-3-(hydroxymethyl)-6-methyl-2,3-dihydro-1-benzofuran-4-ol (58z) and 3-[4-(benzyloxy)phenyl]-3-(hydroxymethyl)-4-methyl-2,3-dihydro-1-benzofuran-6-ol (58z')



Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a

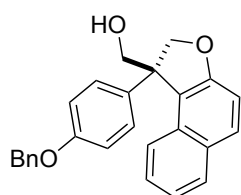
solution of oxetanol **45** (64 mg, 0.25 mmol) and orcinol (155 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. NaHCO₃ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 × 15 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (30% EtOAc/hexane) afforded dihydrobenzofuran **58z** (21 mg, 23%) as a white solid followed by dihydroxybenzofuran **58z'** (46 mg, 50%) as a white solid.

Dihydrobenzofuran **58z** (minor): *R_f* = 0.22 (30% EtOAc/hexane); mp = 162–164 °C; IR (film)/cm⁻¹ 3429 (br. OH), 2928, 1630, 1588, 1511, 1387, 1363, 1292, 1244, 1214, 1182, 1108, 1065, 1013, 996, 934, 831, 816, 747, 699, 668; ¹H NMR (400 MHz, CDCl₃) δ 8.23 (s, 1 H, Ar-OH), 7.48–7.29 (m, 5 H, 5 × Ar-CH), 7.16–7.06 (m, 2 H, 2 × Ar-CH), 7.00–6.90 (m, 2 H, 2 × Ar-CH), 6.40 (d, *J* = 1.4 Hz, 1 H, Ar-CH), 6.26 (d, *J* = 1.4 Hz, 1 H, Ar-CH), 5.04 (s, 2 H, PhCH₂), 4.46 (d, *J* = 8.8 Hz, 1 H, OCHHC_q), 4.34 (dd, *J* = 10.6, 3.2 Hz, 1 H, CHHOH), 4.29 (d, *J* = 8.8 Hz, 1 H, OCHHC_q), 4.10 (dd, *J* = 10.6, 7.7 Hz, 1 H, CHHOH), 2.50 (dd, *J* = 7.7, 3.2 Hz, 1 H, CH₂OH), 2.32 (s, 3 H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 161.7 (Ar_(DHBf)-C_q-OCH₂), 158.0 (Ar-C_q-OBn), 154.0 (Ar_(DHBf)-C_q-OH), 141.4 (Ar_(DHBf)-C_q-CH₃), 136.8 (Ph-C_q), 133.4 (Ar_(p-OBn)-C_q-C_q), 128.6 (2 × Ar-CH), 128.0 (3 × Ar-CH), 127.5 (2 × Ar-CH), 115.5 (2 × Ar-CH), 112.9 (Ar_(DHBf)-C_q-C_q), 110.2 (Ar-CH), 102.9 (Ar-CH), 106.2 (Ar-C_q-CH₃), 80.9 (OCH₂C_q), 70.1 (PhCH₂), 68.8 (CH₂OH), 56.4 (C_q), 21.6 (CH₃); FTMS (+ p NSI) *m/z* calcd for C₂₃H₂₃O₄⁺ [M+H]⁺: 363.1591, Found: 363.1593.

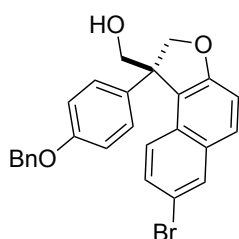
Dihydrobenzofuran **58z'** (major): *R_f* = 0.05 (30% EtOAc/hexane); mp = 173–175 °C; IR (film)/cm⁻¹ 3484 (br. OH), 3293, 2956, 2898, 1739, 1608, 1597, 1510, 1476, 1453, 1381, 1251, 1186, 1176, 1133, 1055, 1044, 1024, 996, 978, 831, 809, 741, 696; ¹H NMR (400 MHz, (CD₃)₂SO) δ 9.21 (s, 1 H, Ar-OH), 7.51–7.26 (m, 5 H, 5 × Ar-CH), 7.24–7.11 (m, 2 H, 2 × Ar-CH), 7.02–6.86 (m, 2 H, 2 × Ar-CH), 6.07 (d, *J* = 2.1 Hz, 1 H, Ar-CH), 6.03 (d, *J* = 2.1 Hz,

1 H, Ar-CH), 5.12 (t, $J = 5.1$ Hz, 1 H, CH₂OH), 5.07 (s, 2 H, PhCH₂), 4.73 (d, $J = 8.8$ Hz, 1 H, OCHHC_q), 4.24 (d, $J = 8.8$ Hz, 1 H, OCHHC_q), 4.07 (dd, $J = 11.0, 5.1$ Hz, 1 H, CHHOH), 3.81 (dd, $J = 11.0, 5.1$ Hz, 1 H, CHHOH), 1.76 (s, 3 H, CH₃); ¹³C NMR (101 MHz, (CD₃)₂SO) δ 161.8 (Ar_(DHBf)-C_q-OCH₂), 158.4 (Ar_(DHBf)-C_q-OH), 157.1 (Ar-C_q-OBn), 137.6 (Ph-C_q), 137.1 (Ar_(p-OBn)-C_q-C_q), 135.8 (Ar_(DHBf)-C_q-CH₃), 128.9 (2 $\times$ Ar-CH), 128.7 (2 $\times$ Ar-CH), 128.3 (Ar-CH), 128.2 (2 $\times$ Ar-CH), 121.0 (Ar_(DHBf)-C_q-C_q), 114.9 (2 $\times$ Ar-CH), 110.0 (Ar-CH), 95.3 (Ar-CH), 82.5 (OCH₂C_q), 69.6 (PhCH₂), 64.3 (CH₂OH), 55.4 (C_q), 18.8 (CH₃); FTMS (+ p NSI) m/z calcd for C₂₃H₂₃O₄⁺ [M+H]⁺: 363.1591, Found: 363.1593.

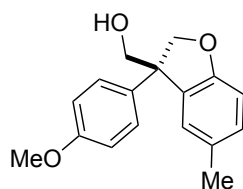
{1-[4-(Benzyloxy)phenyl]-1H,2H-naphtho[2,1-b]furan-1-yl}methanol (**58aa**)



Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **45** (64 mg, 0.25 mmol) and 2-naphthol (180 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. NaHCO₃ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with EtOAc (2 $\times$ 15 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (25–30% EtOAc/hexane) afforded dihydrobenzofuran **58aa** (94 mg, 98%) as a pale yellow gum. $R_f = 0.31$ (30% EtOAc/hexane); IR (film)/cm⁻¹ 3431 (br. OH), 3063, 2887, 1626, 1609, 1598, 1579, 1510, 1455, 1374, 1294, 1244, 1183, 1063, 1012, 967, 909, 828, 811, 779, 698; ¹H NMR (400 MHz, CHCl₃) δ 7.87–7.83 (m, 1 H, Ar-CH), 7.81 (d, $J = 8.9$ Hz, 1 H, Ar-CH), 7.49–7.32 (m, 6 H, 6 $\times$ Ar-CH), 7.32–7.24 (m, 4 H, 4 $\times$ Ar-CH), 7.22 (d, $J = 8.8$ Hz, 1 H, Ar-CH), 7.00–6.92 (m, 2 H, 2 $\times$ Ar-CH), 5.07 (s, 2 H, PhCH₂), 4.98 (d, $J = 8.9$ Hz, 1 H, OCHHC_q), 4.61 (d, $J = 8.9$ Hz, 1 H, OCHHC_q), 4.51 (d, $J = 11.0$ Hz, 1 H, CHHOH), 4.32 (dd, $J = 11.0, 7.3$ Hz, 1 H, CHHOH), 1.52 (d, $J = 7.3$ Hz, 1 H, OH); ¹³C NMR (101 MHz, CHCl₃) δ 159.4 (Ar_(DHBf)-C_q-OCH₂), 157.6 (Ar-C_q-OBn), 136.8 (Ph-C_q), 135.4 (Ar_(p-OBn)-C_q-C_q), 131.0 (Ar-CH), 130.6 (Ar_(naphthol)-C_q), 130.0 (Ar_(naphthol)-C_q), 129.2 (Ar-CH), 128.6 (2 $\times$ Ar-CH), 128.2 (2 $\times$ Ar-CH), 128.0 (Ar-CH), 127.5 (2 $\times$ Ar-CH), 126.8 (Ar-CH), 122.9 (Ar-CH), 122.5 (Ar-CH), 119.6 (Ar_(DHBf)-C_q-C_q), 115.0 (2 $\times$ Ar-CH), 112.5 (Ar-CH), 83.4 (OCH₂C_q), 70.0 (PhCH₂), 66.4 (CH₂OH), 57.1 (C_q); FTMS (+ p NSI) m/z calcd for C₂₆H₂₆O₃⁺ [M+H]⁺: 400.1907, Found: 400.1898.

{1-[4-(Benzyloxy)phenyl]-7-bromo-1H,2H-naphtho[2,1-b]furan-1-yl}methanol (58ab)

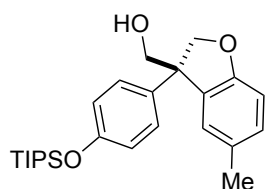
Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **45** (64 mg, 0.25 mmol) and 6-bromo-2-naphthol (279 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. NaHCO₃ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with EtOAc (2 × 15 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc/hexane) afforded dihydrobenzofuran **58ab** (102 mg, 89%) as a white solid. *R*_f = 0.15 (20% EtOAc/hexane); mp = 115–117 °C; IR (film)/cm⁻¹ 3456 (br. OH), 3060, 3033, 2937, 2863, 1840, 1618, 1580, 1506, 1453, 1376, 1354, 1297, 1182, 1127, 1072, 1015, 1004, 963, 880, 827, 802, 747, 727, 697; ¹H NMR (400 MHz, CHCl₃) δ 7.98 (d, *J* = 2.0 Hz, 1 H, Ar-CH), 7.70 (d, *J* = 8.8 Hz, 1 H, Ar-CH), 7.49–7.30 (m, 6 H, 6 × Ar-CH), 7.29–7.18 (m, 4 H, 4 × Ar-CH), 6.99–6.89 (m, 2 H, 2 × Ar-CH), 5.06 (s, 2 H, PhCH₂), 4.95 (d, *J* = 9.0 Hz, 1 H, OCHHC_q), 4.59 (d, *J* = 9.0 Hz, 1 H, OCHHC_q), 4.46 (dd, *J* = 11.1, 4.3 Hz, 1 H, CHHOH), 4.30 (dd, *J* = 11.1, 7.7 Hz, 1 H, CHHOH), 1.53 (dd, *J* = 7.7, 4.3 Hz, 1 H, OH); ¹³C NMR (101 MHz, CHCl₃) δ 159.6 (Ar_(DHBf)-C_q-OCH₂), 157.7 (Ar-C_q-OBn), 136.8 (Ph-C_q), 135.0 (Ar_(p-OBn)-C_q-C_q), 131.2 (Ar_(naphthol)-C_q), 131.1 (Ar-CH), 130.1 (Ar-CH), 130.0 (Ar-CH), 129.1 (Ar_(naphthol)-C_q), 128.6 (2 × Ar-CH), 128.2 (2 × Ar-CH), 128.0 (Ar-CH), 127.5 (2 × Ar-CH), 124.3 (Ar-CH), 120.5 (Ar_(DHBf)-C_q-C_q), 116.4 (Ar-C_q-Br), 115.1 (2 × Ar-CH), 113.5 (Ar-CH), 83.4 (OCH₂C_q), 70.0 (PhCH₂), 66.4 (CH₂OH), 56.9 (C_q); FTMS (+ p NSI) *m/z* calcd for C₂₆H₂₅BrO₃⁺ [M+NH₄]⁺: 478.1012, Found: 478.0999.

[3-(4-Methoxyphenyl)-5-methyl-2,3-dihydro-1-benzofuran-3-yl]methanol (75)

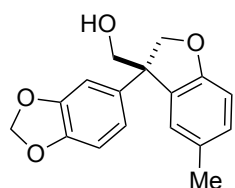
Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) or calcium bis(trifluoromethanesulfonimide) (8.3 mg, 0.0138 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **44** (45 mg, 0.25 mmol) and 4-methylphenol (135 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 6 h then sat. aq. NaHCO₃ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 × 15 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (30% EtOAc/hexane) afforded dihydrobenzofuran **75** (61 mg, 90%) as a pale yellow gum. *R*_f = 0.25 (30% EtOAc/hexane); IR (film)/cm⁻¹ 3433 (br. OH), 2934,

2837, 1610, 1581, 1512, 1489, 1464, 1297, 1247, 1183, 1127, 1078, 1033, 973, 829, 810, 794, 768, 731; ^1H NMR (400 MHz, CDCl_3) δ 7.35–7.21 (m, 2 H, 2 $\times$ Ar-CH), 7.05 (dt, J = 8.1, 1.2 Hz, 1 H, Ar-CH), 7.00 (d, J = 1.8 Hz, 1 H, Ar-CH), 6.93–6.85 (m, 2 H, 2 $\times$ Ar-CH), 6.81 (d, J = 8.1 Hz, 1 H, 1 $\times$ Ar-CH), 4.75 (d, J = 8.9 Hz, 1 H, OCHHC_q), 4.57 (d, J = 8.9 Hz, 1 H, OCHHC_q), 4.11 (dd, J = 11.2, 4.5 Hz, 1 H, CHHOH), 4.03 (dd, J = 11.2, 7.2 Hz, 1 H, CHHOH), 3.82 (s, 3 H, OCH_3), 2.33 (s, 3 H, CH_3), 1.69 (br. s, 1 H, OH); ^{13}C NMR (101 MHz, CDCl_3) δ 158.6 (Ar- C_q -OMe), 158.4 ($\text{Ar}_{(\text{DHBf})}$ - C_q - OCH_2), 134.7 ($\text{Ar}_{(\text{p-OMe})}$ - C_q - C_q), 130.2 ($\text{Ar}_{(\text{DHBf})}$ - C_q - C_q), 130.0 (Ar- C_q - CH_3), 129.6 (Ar-CH), 128.0 (2 $\times$ Ar-CH), 125.5 (Ar-CH), 114.1 (2 $\times$ Ar-CH), 109.7 (Ar-CH), 81.3 (OCH_2C_q), 67.5 (CH_2OH), 55.7 (C_q), 55.2 (OCH_3), 20.9 (CH_3); FTMS (+ p NSI) m/z calcd for $\text{C}_{17}\text{H}_{22}\text{O}_3\text{N}^+$ [$\text{M}+\text{NH}_4$] $^+$: 288.1594, Found: 288.1596.

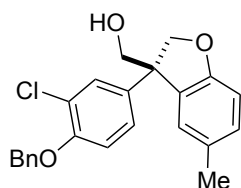
[5-Methyl-3-(4-{[tris(propan-2-yl)silyl]oxy}phenyl)-2,3-dihydro-1-benzofuran-3-yl] methanol (76)



Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **46** (81 mg, 0.25 mmol) and 4-methylphenol (135 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 20 h then sat. aq. NaHCO_3 (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 $\times$ 15 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc/hexane) afforded dihydrobenzofuran **76** (70 mg, 67%). R_f = 0.19 (20% EtOAc/hexane); IR (film)/ cm^{-1} 3436 (br. OH), 2944, 2867, 1606, 1510, 1491, 1463, 1264, 1177, 1040, 975, 912, 882, 835, 808, 749, 725, 682; ^1H NMR (400 MHz, CDCl_3) δ 7.20–7.11 (m, 2 H, 2 $\times$ Ar-CH), 7.06–6.96 (m, 2 H, 2 $\times$ Ar-CH), 6.91–6.83 (m, 2 H, 2 $\times$ Ar-CH), 6.79 (d, J = 8.1 Hz, 1 H, Ar-CH), 4.75 (d, J = 8.8 Hz, 1 H, OCHHC_q), 4.56 (d, J = 8.8 Hz, 1 H, OCHHC_q), 4.06 (d, J = 11.0 Hz, 1 H, CHHOH), 4.00 (dd, J = 11.0, 5.1 Hz, 1 H, CHHOH), 2.32 (Ar- CH_3), 1.58 (d, J = 5.1 Hz, 1 H, OH), 1.26 (ddd, J = 13.6, 10.1, 6.5 Hz, 3 H, 3 $\times$ $\text{CH}(\text{CH}_3)_2$), 1.11 (d, J = 7.3 Hz, 18 H, 3 $\times$ $(\text{CH}_3)_2$); ^{13}C NMR (101 MHz, CDCl_3) δ 158.7 ($\text{Ar}_{(\text{DHBf})}$ - C_q - OCH_2), 155.0 (Ar- C_q -OTIPS), 134.9 ($\text{Ar}_{(\text{p-OTIPS})}$ - C_q - C_q), 130.1 ($\text{Ar}_{(\text{DHBf})}$ - C_q - CH_3), 130.0 ($\text{Ar}_{(\text{DHBf})}$ - C_q - C_q), 129.6 ($\text{Ar}_{(\text{DHBf})}$ -CH), 127.9 (2 $\times$ $\text{Ar}_{(\text{p-OTIPS})}$ -CH), 125.6 ($\text{Ar}_{(\text{DHBf})}$ -CH), 120.0 (2 $\times$ $\text{Ar}_{(\text{p-OTIPS})}$ -CH), 109.7 ($\text{Ar}_{(\text{DHBf})}$ -CH), 81.4 (OCH_2C_q), 67.7 (CH_2OH), 55.8 (C_q), 20.9 (Ar- CH_3), 17.9 (3 $\times$ $\text{CH}(\text{CH}_3)_2$), 12.6 (3 $\times$ $\text{CH}(\text{CH}_3)_2$); FTMS (+ p NSI) m/z calcd for $\text{C}_{25}\text{H}_{40}\text{O}_3\text{NSi}^+$ [$\text{M}+\text{NH}_4$] $^+$: 430.2759, Found: 430.2765.

[3-(2H-1,3-Benzodioxol-5-yl)-5-methyl-2,3-dihydro-1-benzofuran-3-yl]methanol (77)

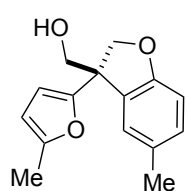
Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **48** (49 mg, 0.25 mmol) and 4-methylphenol (135 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 20 h then sat. aq. NaHCO₃ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 × 15 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (25% EtOAc/hexane) afforded dihydrobenzofuran **77** (55 mg, 78%) as a white solid. *R_f* = 0.19 (25% EtOAc/hexane); IR (film)/cm⁻¹ 3410 (br. OH), 2885, 1610, 1504, 1485, 1435, 1234, 1202, 1125, 1110, 1035, 1065, 972, 933, 807, 728; ¹H NMR (400 MHz, CDCl₃) δ 7.03 (dd, *J* = 8.3, 1.8 Hz, 1 H, Ar-CH), 6.98 (d, *J* = 1.8 Hz, 1 H, Ar-CH), 6.83–6.73 (m, 4 H, 4 × Ar-CH), 5.95 (s, 2 H, OCH₂O), 4.71 (d, *J* = 8.9 Hz, 1 H, OCHHC_q), 4.53 (d, *J* = 8.9 Hz, 1 H, OCHHC_q), 4.07 (dd, *J* = 11.3, 3.5 Hz, 1 H, CHHOH), 3.99 (dd, *J* = 11.3, 6.8 Hz, 1 H, CHHOH), 2.32 (s, 3 H, CH₃), 1.64 (br. s, 1 H, OH); ¹³C NMR (101 MHz, CDCl₃) δ 158.6 (Ar_(DHBf)-C_q-OCH₂), 148.0 (Ar-C_q-OCH₂O), 146.4 (Ar-C_q-OCH₂O), 136.7 (Ar_(benzodioxole)-C_q-C_q), 130.1 (Ar-C_q-CH₃), 129.9 (Ar_(DHBf)-C_q-C_q), 129.8 (Ar-CH), 125.5 (Ar-CH), 120.0 (Ar-CH), 109.8 (Ar-CH), 108.2 (Ar-CH), 107.8 (Ar-CH), 101.1 (OCH₂O), 81.4 (OCH₂C_q), 67.6 (CH₂OH), 56.2 (C_q), 20.9 (CH₃); FTMS (+ p NSI) *m/z* calcd for C₁₇H₁₇O₄⁺ [M+H]⁺: 285.1121, Found: 285.1118.

{3-[4-(Benzyloxy)-3-chlorophenyl]-5-methyl-2,3-dihydro-1-benzofuran-3-yl}-methanol (78)

Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **47** (73 mg, 0.25 mmol) and 4-methylphenol (135 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 20 h then sat. aq. NaHCO₃ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 × 15 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (30% EtOAc/hexane) afforded dihydrobenzofuran **78** (39 mg, 41%) as a yellow gum. *R_f* = 0.28 (30% EtOAc/hexane); IR (film)/cm⁻¹ 3423 (br. OH), 3032, 2926, 1739, 1603, 1490, 1454, 1381, 1293, 1255, 1240, 1125, 1061, 1023, 975, 907, 809, 731, 695; ¹H NMR (400 MHz, CDCl₃) δ

7.52–7.29 (m, 6 H, 6 × Ar-CH), 7.13 (dd, $J = 8.7, 2.4$ Hz, 1 H, Ar-CH), 7.05 (dd, $J = 8.2, 1.8$ Hz, 1 H, Ar-CH), 6.98–6.87 (m, 2 H, 2 × Ar-CH), 6.80 (d, $J = 8.2$ Hz, 1 H, Ar-CH), 5.16 (s, 2 H, PhCH₂), 4.72 (d, $J = 9.0$ Hz, 1 H, OCHHC_q), 4.52 (d, $J = 9.0$ Hz, 1 H, OCHHC_q), 4.09 (d, $J = 11.1$, 1 H, CHHOH), 4.00 (d, $J = 11.1$ Hz, 1 H, CHHOH), 2.32 (s, 3 H, CH₃), 1.59 (s, 1 H, OH) ¹³C NMR (101 MHz, CDCl₃) δ 158.6 (Ar_(DHBf)-C_q-OCH₂), 153.0 (Ar-C_q-OBn), 136.4 (Ph-C_q + Ar-C_q-C_q), 130.4 (Ar-C_q-CH₃), 129.9 (Ar-CH), 129.6 (Ar_(DHBf)-C_q-C_q), 129.0 (Ar-CH), 128.6 (2 × Ar-CH), 128.0 (Ar-CH), 127.0 (2 × Ar-CH), 126.3 (Ar-CH), 125.3 (Ar-CH), 123.4 (Ar-C_q-Cl), 114.0 (Ar-CH), 109.9 (Ar-CH), 81.2 (OCH₂C_q), 70.8 (PhCH₂), 67.3 (CH₂OH), 55.6 (C_q), 20.9 (CH₃); FTMS (+ p NSI) m/z calcd for C₂₃H₂₅O₃N³⁵Cl⁺ [M+NH₄]⁺: 398.1517, Found: 398.1515.

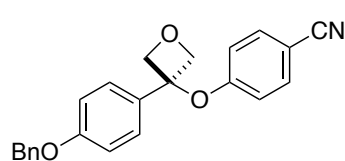
[5-Methyl-3-(5-methylfuran-2-yl)-2,3-dihydro-1-benzofuran-3-yl]methanol (**79**)



Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **51** (39 mg, 0.25 mmol) and 4-methylphenol (135 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. NaHCO₃ (15 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 × 15 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc/hexane) afforded dihydrobenzofuran **79** (40 mg, 66%) as a colourless gum. $R_f = 0.25$ (20% EtOAc/hexane); IR (film)/cm⁻¹ 3409 (br. OH), 2921, 1739, 1611, 1560, 1490, 1380, 1217, 1043, 1021, 972, 809, 783; ¹H NMR (400 MHz, CDCl₃) δ 7.07 (d, $J = 1.8$ Hz, 1 H, Ar_(DHBf)-CH), 7.01 (dd, $J = 8.1, 1.8$ Hz, 1 H, Ar_(DHBf)-CH), 6.76 (d, $J = 8.1$ Hz, 1 H, Ar_(DHBf)-CH), 6.05 (d, $J = 3.1$ Hz, 1 H Ar_(furan)-CH), 5.92 (m, 1 H, Ar_(furan)-CH), 4.73 (d, $J = 9.0$ Hz, 1 H, OCHHC_q), 4.68 (d, $J = 9.0$ Hz, 1 H, OCHHC_q), 3.99 (dd, $J = 11.2, 6.3$ Hz, 1 H, CHHOH), 3.92 (dd, $J = 11.2, 6.3$ Hz, 1 H, CHHOH), 2.31 (s, 3 H, Ar_(DHBf)CH₃), 2.29 (d, $J = 1.0$ Hz, 3 H, Ar_(furan)CH₃), 1.80 (t, $J = 6.3$ Hz, 1 H, OH); ¹³C NMR (101 MHz, CDCl₃) δ 158.1 (Ar_(DHBf)-C_q-OCH₂), 153.2 (Ar_(furan)-C_q-C_q), 152.1 (Ar_(furan)-C_q-CH₃), 130.0 (Ar_(DHBf)-C_q-CH₃), 129.9 (Ar_(DHBf)-CH), 128.4 (Ar_(DHBf)-C_q-C_q), 125.0 (Ar_(DHBf)-CH), 109.7 (Ar_(DHBf)-CH), 107.5 (Ar_(furan)-CH), 106.2 (Ar_(furan)-CH), 78.0 (OCH₂C_q), 67.0 (CH₂OH), 53.2 (C_q), 20.8 (Ar_(DHBf)CH₃), 13.6 (Ar_(furan)CH₃); FTMS (+ p NSI) m/z calcd for C₁₅H₁₆O₃Na⁺ [M+Na]⁺: 267.0992, Found: 267.0993.

5.2.3 Studies into the Formation of Oxetane Ethers

4-({3-[4-(Benzyloxy)phenyl]oxetan-3-yl}oxy)benzonitrile (**80ac**)

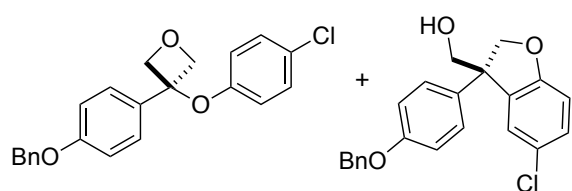


Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **45** (64 mg, 0.25 mmol) and 4-cyanophenol (149 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. NaHCO₃ (10 mL) was added followed by dichloromethane (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (2 × 10 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash chromatography (30% EtOAc/hexane) afforded oxetane ether **80ac** (14 mg, 16%) as a white solid.

After 20 h the same procedure afforded oxetane ether **80ac** (21 mg, 23%) as a white solid.

Oxetane ether **80ac**: R_f = 0.37 (30% EtOAc/hexane); mp = 164–166 °C; IR (film)/cm⁻¹ 2948, 2879, 2226 (CN stretch), 1605, 1582, 1505, 1455, 1297, 1247, 1172, 1112, 1010, 987, 900, 832, 737, 698; ¹H NMR (400 MHz, CDCl₃) δ 7.52–7.35 (m, 9 H, 9 × Ar-CH), 7.05–7.00 (m, 2 H, 2 × Ar-CH), 6.63–6.59 (m, 2 H, 2 × Ar-CH), 5.09 (d, J = 7.0 Hz, 2 H, CHHOCHH), 5.08 (s, 2 H, PhCH₂), 4.96 (d, J = 7.0 Hz, 2 H, CHHOCHH); ¹³C NMR (101 MHz, CDCl₃) δ 158.7 (Ar-C_q-O), 158.4 (Ar-C_q-O), 136.6 (Ph-C_q-CH₂), 133.9 (2 × Ar-CH), 130.8 (Ar-C_q-C_q), 128.7 (2 × Ar-CH), 128.2 (Ar-CH), 127.5 (2 × Ar-CH), 125.9 (2 × Ar-CH), 118.9 (CN), 117.1 (2 × Ar-CH), 115.4 (2 × Ar-CH), 104.8 (Ar-C_q-CN), 82.5 (CH₂OCH₂), 81.2 (C_q), 70.1 (PhCH₂); FTMS (+ p NSI) m/z calcd for C₂₃H₁₉NO₃Na⁺ [M+Na]⁺: 380.1257, Found: 380.1256.

3-[4-(Benzyloxy)phenyl]-3-(4-chlorophenoxy)oxetane (**80n**) and {3-[4-(benzyloxy)phenyl]-5-chloro-2,3-dihydro-1-benzofuran-3-yl}methanol (**58n**)



Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **45** (64 mg, 0.25 mmol) and 4-chlorophenol (161 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. NaHCO₃ (10 mL) was added followed by dichloromethane (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (2 × 10 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na₂SO₄, filtered and concentrated *in*

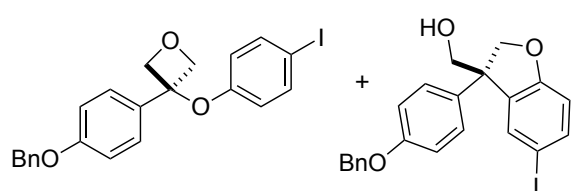
vacuo. Purification by flash chromatography (20% EtOAc/hexane) afforded oxetane ether **80n** (24 mg, 26%) as a white solid followed by dihydrobenzofuran **58n** (8 mg, 9%) as a colourless gum.

After 20 h the same procedure afforded dihydrobenzofuran **58n** (26 mg, 28%).

Oxetane ether **80n**: R_f = 0.47 (20% EtOAc/hexane); mp = 120–125 °C; IR (film)/cm⁻¹ 2950, 2876, 1610, 1582, 1487, 1455, 1382, 1283, 1283, 1235, 1179, 1112, 1091, 1008, 987, 899, 824, 736, 697, 667; ¹H NMR (400 MHz, CDCl₃) δ 7.49–7.34 (m, 7 H, 7 $\times$ Ar-CH), 7.16–7.11 (m, 2 H, 2 $\times$ Ar-CH), 7.03–6.98 (m, 2 H, 2 $\times$ Ar-CH), 6.49–6.44 (m, 2 H, 2 $\times$ Ar-CH), 5.08 (d, J = 6.9 Hz, 2 H, CHHOCHH), 5.07 (s, 2 H, PhCH₂), 4.91 (d, J = 6.9 Hz, 2 H, CHHOCHH); ¹³C NMR (101 MHz, CDCl₃) δ 158.5 (Ar-C_q-OBn), 153.4 (Ar(*p*-Cl)-C_q-O), 136.7 (Ph-C_q), 131.7 (Ar-C_q-C_q), 129.3 (2 $\times$ Ar-CH), 128.6 (2 $\times$ Ar-CH), 128.0 (Ar-CH), 127.5 (2 $\times$ Ar-CH), 126.10 (Ar-C_q-Cl), 126.06 (2 $\times$ Ar-CH), 117.6 (2 $\times$ Ar-CH), 115.2 (2 $\times$ Ar-CH), 82.7 (CH₂OCH₂), 80.5 (C_q), 70.1 (PhCH₂); HRMS (ESI-TOF) m/z calcd for C₂₂H₂₀O₃Cl⁺ [M+H]⁺: 367.1101, Found: 367.1096.

Dihydrobenzofuran **58n**: See page 181.

3-[4-(Benzyloxy)phenyl]-3-(4-iodophenoxy)oxetane (**80o**) and {3-[4-(benzyloxy)phenyl]-5-iodo-2,3-dihydro-1-benzofuran-3-yl}methanol (**58o**)



Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **45** (64 mg, 0.25 mmol) and 4-iodophenol (275 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. NaHCO₃ (10 mL) was added followed by dichloromethane (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (2 $\times$ 10 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash chromatography (20% EtOAc/hexane) afforded oxetane ether **80o** (10 mg, 8%) as a white solid followed by dihydrobenzofuran **58o** (32 mg, 28%) as a colourless gum.

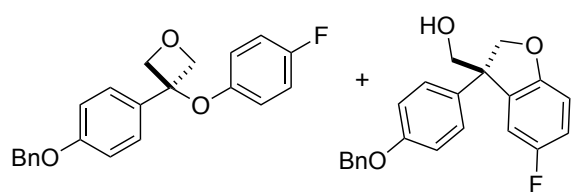
After 20 h the same procedure afforded dihydrobenzofuran **58o** (27 mg, 25%).

Oxetane ether **80o**: R_f = 0.54 (20% EtOAc/hexane); mp = 112–114 °C; IR (film)/cm⁻¹ 2872, 1612, 1578, 1511, 1482, 1456, 1385, 1301, 1279, 1234, 1176, 1113, 1058, 1025, 1001, 986,

958, 899, 831, 813, 745, 698, 679; ^1H NMR (400 MHz, CDCl_3) δ 7.48–7.32 (m, 9 H, 9 $\times$ Ar-CH), 7.01–6.97 (m, 2 H, 2 $\times$ Ar-CH), 6.35–6.29 (m, 2 H, 2 $\times$ Ar-CH), 5.07 (d, J = 7.4 Hz, 2 H, CHHOCHH), 5.06 (s, 2 H, PhCH_2), 4.90 (d, J = 7.4 Hz, 2 H, CHHOCHH); ^{13}C NMR (101 MHz, CDCl_3) δ 158.6 (Ar- C_q -OBn), 154.8 (Ar(p -I)- C_q -O), 138.3 (2 $\times$ Ar-CH), 136.7 (Ar- C_q - C_q), 131.6 (Ph- C_q), 128.6 (2 $\times$ Ar-CH), 128.1 (Ar-CH), 127.5 (2 $\times$ Ar-CH), 126.0 (2 $\times$ Ar-CH), 118.7 (2 $\times$ Ar-CH), 115.2 (2 $\times$ Ar-CH), 83.5 (Ar- C_q -I), 82.7 (CH_2OCH_2), 80.5 (C_q), 70.1 (PhCH_2); FTMS (+ p NSI) m/z calcd for $\text{C}_{22}\text{H}_{23}\text{O}_3\text{NI}^+$ [$\text{M}+\text{NH}_4$] $^+$: 476.0717, Found: 476.0714.

Dihydrobenzofuran **58o**: See page 181.

[4-(Benzyloxy)phenyl]-3-(4-fluorophenoxy)oxetane (80p) and {3-[4-(benzyloxy)phenyl]-5-fluoro-2,3-dihydro-1-benzofuran-3-yl}methanol (48p)



Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution

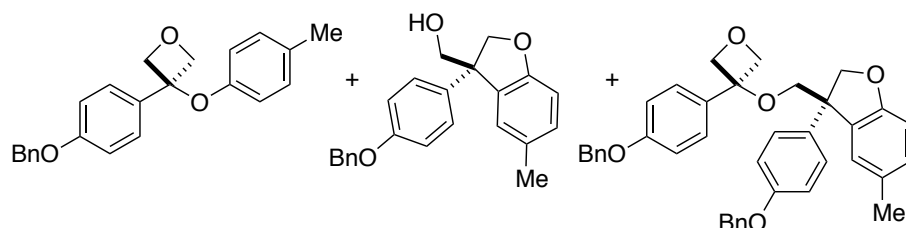
of oxetanol **45** (64 mg, 0.25 mmol) and 4-fluorophenol (140 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. NaHCO_3 (10 mL) was added followed by dichloromethane (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (2 $\times$ 10 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash chromatography (20% EtOAc/hexane) afforded oxetane ether **80p** (28 mg, 32%) as a white solid followed by dihydrobenzofuran **58p** (5 mg, 6%) as a white solid.

After 20 h the same procedure afforded dihydrobenzofuran **58p** (25 mg, 29%).

Oxetane ether **80p**: R_f = 0.37 (20% EtOAc/hexane); mp = 100–102 °C; IR (film)/ cm^{-1} 2950, 2876, 1609, 1500, 1455, 1382, 1294, 1241, 1207, 1179, 1112, 1098, 1009, 986, 900, 826, 744, 697; ^1H NMR (400 MHz, CDCl_3) δ 7.51–7.32 (m, 7 H, 7 $\times$ Ar-CH), 7.03–6.97 (m, 2 H, 2 $\times$ Ar-CH), 6.91–6.81 (m, 2 H, 2 $\times$ Ar-CH), 6.51–6.44 (m, 2 H, 2 $\times$ Ar-CH), 5.08 (d, J = 6.9 Hz, 2 H, CHHOCHH), 5.07 (s, 2 H, PhCH_2), 4.91 (d, J = 6.9 Hz, 2 H, CHHOCHH); ^{13}C NMR (101 MHz, CDCl_3) δ 158.5 (Ar- C_q -OBn), 157.3 (d, $J_{\text{C-F}}$ = 240.5, Ar- C_q -F), 150.9 (Ar(p -F)- C_q -O), 136.7 (Ph- C_q), 132.0 (Ar- C_q - C_q), 128.6 (2 $\times$ Ar-CH), 128.1 (Ar-CH), 127.5 (2 $\times$ Ar-CH), 126.1 (2 $\times$ Ar-CH), 117.3 (d, $J_{\text{C-F}}$ = 8.3 Hz, 2 $\times$ Ar-CH), 115.8 (d, $J_{\text{C-F}}$ = 23.1 Hz, 2 $\times$ Ar-CH), 115.1 (2 $\times$ Ar-CH), 82.6 (CH_2OCH_2), 80.5 (C_q), 70.1 (PhCH_2); ^{19}F NMR (377 MHz, CDCl_3) δ –123.3; FTMS (+ p NSI) m/z calcd for $\text{C}_{22}\text{H}_{23}\text{O}_3\text{FNa}^+$ [$\text{M}+\text{Na}$] $^+$: 373.1210, Found: 373.1216.

Dihydrobenzofuran **58p**: See page 182.

3-[4-(Benzyloxy)phenyl]-3-(4-methylphenoxy)oxetane (80q), **{3-[4-(benzyloxy)phenyl]-5-methyl-2,3-dihydro-1-benzofuran-3-yl}methanol (58q)** and **3-[4-(benzyloxy)phenyl]-3-[[{3-[4-(benzyloxy)phenyl]oxetan-3-yl}oxy)methyl]-5-methyl-2,3-dihydro-1-benzofuran (81q)**



Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **45** (64 mg, 0.25 mmol) and 4-methylphenol (135 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. NaHCO₃ (10 mL) was added followed by dichloromethane (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (2 × 10 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash chromatography (30% EtOAc/hexane) afforded oxetane ether **80q** (6 mg, 3 %) as a white solid followed dimer **81q** (12 mg, 8%) as a yellow gum followed by dihydrobenzofuran **58q** (54 mg, 62%) as a colourless gum.

After 20 h the same procedure using 0.22 mmol of oxetanol **45** afforded dihydrobenzofuran **58q** (61 mg, 81%).

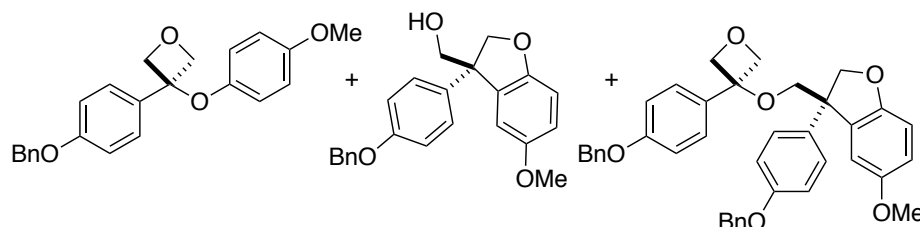
Oxetane ether **80q**: R_f = 0.57 (30% EtOAc/hexane); mp = 101–104 °C; IR (film)/cm⁻¹ 2951, 2875, 1611, 1508, 1455, 1291, 1231, 1179, 1112, 987, 813, 740, 698; ¹H NMR (400 MHz, CDCl₃) δ 7.52–7.30 (m, 7 H, 7 × Ar-CH), 7.01–6.95 (m, 4 H, 4 × Ar-CH), 6.46–6.40 (m, 2 H, 2 × Ar-CH), 5.09 (d, J = 7.3 Hz, 2 H, CHHOCHH), 5.06 (s, 2 H, PhCH₂), 4.90 (d, J = 7.3 Hz, 2 H, CHHOCHH), 2.24 (s, 3 H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 158.4 (Ar-C_q-OBn), 152.6 (Ar-(*p*-Me)-C_q-O), 136.8 (Ph-C_q), 132.6 (Ar-C_q-C_q), 130.3 (Ar-C_q-CH₃), 129.8 (2 × Ar-CH), 128.6 (2 × Ar-CH), 128.0 (Ar-CH), 127.5 (2 × Ar-CH), 126.10 (2 × Ar-CH), 116.0 (2 × Ar-CH), 115.0 (2 × Ar-CH), 82.9 (CH₂OCH₂), 80.0 (C_q), 70.1 (PhCH₂), 20.4 (CH₃); HRMS (TOF-ASAP+) m/z calcd for C₂₃H₂₃O₃⁺ [M+H]⁺: 347.1647, Found: 347.1650.

Dimer **81q**: R_f = 0.42 (30% EtOAc/hexane); IR (film)/cm⁻¹ 3034, 2872, 1610, 1511, 1490, 1455, 1382, 1299, 1243, 1182, 1130, 1025, 982, 830, 812, 735, 698; ¹H NMR (400 MHz, CDCl₃) δ

7.48–7.32 (m, 10 H, 10 × Ar-CH), 7.29–7.20 (m, 4 H, 4 × Ar-CH), 7.00–6.97 (m, 3 H, 3 × Ar-CH), 6.94–6.90 (m, 2 H, 2 × Ar-CH), 8.86–6.83 (m, 1 H, Ar-CH), 6.79–6.67 (m, 1 H, Ar-CH), 5.09 (s, 2 H, PhCH₂), 5.06 (s, 2 H, Ph-CH₂), 4.91–4.69 (m, 5 H, CH₂OCH₂ + OCHHC_q), 4.55 (d, *J* = 9.0 Hz, 1 H, OCHHC_q), 3.63 (d, *J* = 9.2 Hz, 1 H, C_qOCHHC_q), 3.51 (d, *J* = 9.2 Hz, 1 H, C_qOCHHC_q), 2.27 (s, 3 H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 158.5 (Ar-C_q-OBn), 158.0 (Ar-C_q-O_(DHBf)), 157.5 (Ar-C_q-OBn), 137.0 (Ph-C_q), 136.7 (Ph-C_q), 135.6 (Ar_(p-OBn)-C_q-C_{q(DHBf)}), 131.7 (Ar-C_q-C_q), 131.6 (Ar-C_q-C_q), 129.8 (Ar-C_q-CH₃), 129.3 (Ar-CH), 128.62 (2 × Ar-CH), 128.58 (2 × Ar-CH), 128.3 (2 × Ar-CH), 128.1 (Ar-CH), 128.0 (Ar-CH), 127.46 (2 × Ar-CH), 127.45 (2 × Ar-CH), 127.44 (2 × Ar-CH), 125.8 (Ar-CH), 114.9 (2 × Ar-CH), 114.6 (2 × Ar-CH), 109.5 (Ar-CH), 81.8 (O_(DHBf)CH₂C_q), 81.1 (C_{q(oxetane)}), 80.5 (CH₂OCH₂), 80.3 (CH₂OCH₂), 70.1 (PhCH₂), 70.0 (PhCH₂), 68.3 (C_qOCH₂C_q), 54.0 (C_{q(DHBf)}), 20.9 (CH₃); FTMS (+ p NSI) *m/z* calcd for C₃₉H₄₀O₅N⁺ [M+NH₄]⁺: 602.2901, Found: 602.2894.

Dihydrobenzofuran **58q**: See page 183.

3-[4-(Benzyloxy)phenyl]-3-(4-methoxyphenoxy)oxetane (80r), **{3-[4-(benzyloxy)phenyl]-5-methoxy-2,3-dihydro-1-benzofuran-3-yl}methanol (58r)** and **3-[4-(benzyloxy)phenyl]-3-[(3-[4-(benzyloxy)phenyl]oxetan-3-yl)oxy)methyl]-5-methoxy-2,3-dihydro-1-benzofuran (81r)**



Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **45** (64 mg, 0.25 mmol) and 4-methoxyphenol (155 mg, 1.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. NaHCO₃ (10 mL) was added followed by dichloromethane (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (2 × 10 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash chromatography (30% EtOAc/hexane) afforded oxetane ether **80r** (10 mg, 11%) as a white solid followed by dimer **81r**, (17 mg, 19%) as a yellow gum followed by dihydrobenzofuran **58r** (38 mg, 42%) as a colourless gum.

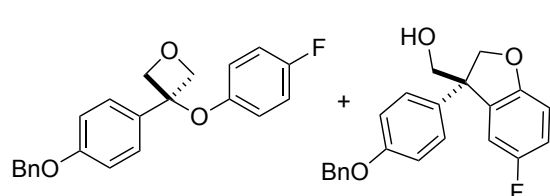
After 20 h the same procedure afforded dihydrobenzofuran **58r** (66 mg, 73%).

Oxetane ether **80r**: R_f = 0.43 (30% EtOAc/hexane); mp = 100–102 °C; IR (film)/ cm^{-1} 2952, 2876, 1610, 1504, 1455, 1381, 1295, 1223, 1178, 1111, 1035, 985, 906, 825, 730, 698; ^1H NMR (400 MHz, CDCl_3) δ 7.51–7.33 (m, 7 H, 7 $\times$ Ar-CH), 7.02–6.96 (m, 2 H, 2 $\times$ Ar-CH), 6.74–6.70 (m, 2 H, 2 $\times$ Ar-CH), 6.50–6.44 (m, 2 H, 2 $\times$ Ar-CH), 5.08 (d, J = 6.9 Hz, 2 H, CHHOCHH), 5.06 (s, 2 H, PhCH_2), 4.89 (d, J = 6.9 Hz, 2 H, CHHOCHH), 3.72 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 158.4 (Ar- C_q -OBn), 154.0 (Ar- C_q -OMe), 148.7 (Ar- C_q -O- C_q), 136.8 (Ph- C_q), 132.6 (Ar- C_q - C_q), 128.6 (2 $\times$ Ar-CH), 128.0 (Ar-CH), 127.5 (2 $\times$ Ar-CH), 126.2 (2 $\times$ Ar-CH), 117.2 (2 $\times$ Ar-CH), 115.0 (2 $\times$ Ar-CH), 114.6 (2 $\times$ Ar-CH), 82.8 (CH_2OCH_2), 80.2 (C_q), 70.1 (PhCH_2), 55.6 (CH_3); FTMS (+ p NSI) m/z calcd for $\text{C}_{23}\text{H}_{22}\text{O}_4\text{Na}^+$ $[\text{M}+\text{Na}]^+$: 385.1410, Found: 385.1412.

Dimer **81r**: R_f = 0.33 (30% EtOAc/hexane); IR (film)/ cm^{-1} 3034, 2946, 2875, 1738, 1609, 1582, 1511, 1487, 1455, 1381, 1301, 1242, 1201, 1179, 1026, 982, 908, 830, 734, 698; ^1H NMR (400 MHz, CDCl_3) δ 7.50–7.34 (m, 10 H, 10 $\times$ Ar-CH), 7.30–7.21 (m, 4 H, 4 $\times$ Ar-CH), 7.05–7.00 (m, 2 H, 2 $\times$ Ar-CH), 6.96–6.92 (m, 2 H, 2 $\times$ Ar-CH), 6.82–6.77 (m, 2 H, 2 $\times$ Ar-CH), 6.72–6.69 (m, 1 H, Ar-CH), 5.11 (s, 2 H, PhCH_2), 5.08 (s, 2 H, PhCH_2), 4.87 (dd, J = 9.3, 6.7 Hz, 2 H, CHHOCHH), 4.79 (d, J = 6.7 Hz, 2 H, CHHOCHH), 4.71 (d, J = 9.0 Hz, 1 H, $\text{OCHHC}_{q(\text{oxetane})}$), 4.53 (d, J = 9.0 Hz, 1 H, $\text{OCHHC}_{q(\text{oxetane})}$), 3.76 (s, 3 H, CH_3), 3.61 (d, J = 9.3 Hz, 1 H, C_qOCHHC_q), 3.56 (d, J = 9.3 Hz, 1 H, C_qOCHHC_q); ^{13}C NMR (101 MHz, CDCl_3) δ 158.5 (Ar- C_q -OBn), 157.6 (Ar- C_q -OBn), 154.2 (Ar- C_q -O), 154.1 (Ar- C_q -O), 136.9 (Ph- C_q), 136.7 (Ph- C_q), 135.3 (Ar(p -OBn)- C_q - $\text{C}_q(\text{DHBf})$), 131.6 (Ar- C_q - C_q), 131.5 (Ar- C_q - C_q), 128.62 (2 $\times$ Ar-CH), 128.58 (2 $\times$ Ar-CH), 128.3 (2 $\times$ Ar-CH), 128.1 (Ar-CH), 128.0 (Ar-CH), 127.5 (2 $\times$ Ar-CH), 127.4 (4 $\times$ Ar-CH), 114.9 (2 $\times$ Ar-CH), 114.6 (2 $\times$ Ar-CH), 114.1 (Ar-CH), 111.4 (Ar-CH), 109.9 (Ar-CH), 82.0 ($\text{O}(\text{DHBf})\text{CH}_2\text{C}_q$), 81.2 ($\text{C}_{q(\text{oxetane})}$), 80.3 (CH_2OCH_2), 70.1 (2 $\times$ PhCH_2), 68.2 ($\text{C}_q\text{OCH}_2\text{C}_q$), 56.0 (CH_3), 54.4 ($\text{C}_q(\text{DHBf})$); FTMS (+ p NSI) m/z calcd for $\text{C}_{39}\text{H}_{40}\text{O}_6\text{N}^+$ $[\text{M}+\text{NH}_4]^+$: 618.2850, Found: 618.2843.

Dihydrobenzofuran **58r**: See page 183.

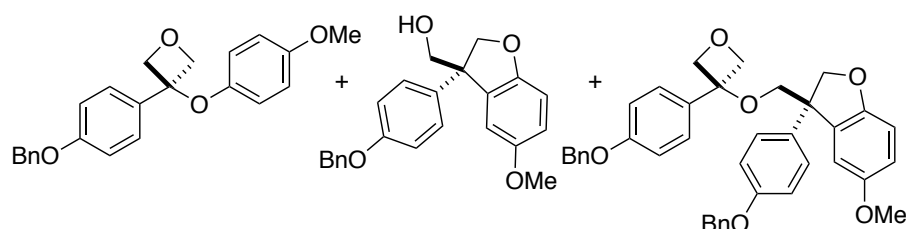
[4-(Benzyloxy)phenyl]-3-(4-fluorophenoxy)oxetane (80p) and {3-[4-(benzyloxy)phenyl]-5-fluoro-2,3-dihydro-1-benzofuran-3-yl}methanol (58p)



^1H NMR study: Oxetanol **45** (64 mg, 0.25 mmol), 4-fluorophenol (140 mg, 1.25 mmol), tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol), mesitylene (12.8 mg, 0.10 mmol) and lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) were added into a ^1H NMR tube. Immediately prior to starting the ^1H NMR experiments, CDCl_3 (0.5 mL)

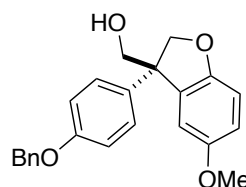
was added and the ^1H NMR tube inverted 3 times to mix the reagents. Nuclear magnetic resonance spectra were recorded on a 400 MHz spectrometer at 40 °C with a spectrum recorded every 30 seconds for the first hour and then every 5 minutes for a further 19 h. *In situ* ^1H NMR yields were calculated using the following signals: mesitylene (2.26 ppm, 9 H), oxetanol **45** (4.90, 2 H) oxetane ether **80p** (6.51–6.44 ppm, 2 H) and dihydrobenzofuran **58p** (4.58 ppm, 1 H). For full data see page 197 for oxetane ether **80p** and page 182 for dihydrobenzofuran **58p**.

3-[4-(Benzyloxy)phenyl]-3-(4-methoxyphenoxy)oxetane (80r), {3-[4-(benzyloxy)phenyl]-5-methoxy-2,3-dihydro-1-benzofuran-3-yl}methanol (58r) and 3-[4-(benzyloxy)phenyl]-3-[(3-[4-(benzyloxy)phenyl]oxetan-3-yl)oxy)methyl]-5-methoxy-2,3-dihydro-1-benzofuran (81r)



^1H NMR study: Oxetanol **45** (64 mg, 0.25 mmol), 4-methoxyphenol (155 mg, 1.25 mmol), tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol), mesitylene (12.5 mg, 0.10 mmol) and lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) were added into a ^1H NMR tube. Immediately prior to starting the ^1H NMR experiments, CDCl_3 (0.5 mL) was added and the ^1H NMR tube inverted 3 times to mix the reagents. Nuclear magnetic resonance spectra were recorded on a 400 MHz spectrometer at 40 °C with a spectrum recorded every 30 seconds for the first hour and then every 5 minutes for a further 19 h. *In situ* ^1H NMR yields were calculated using the following signals: mesitylene (2.26 ppm, 9 H), oxetane ether **45** (6.50–6.44 ppm, 2 H), dimer **81r** (4.71 ppm, 1 H) and dihydrobenzofuran **58r** (4.56 ppm, 1 H). For full data see page 200 for oxetane ether **80r** and dimer **81r** and page 183 for dihydrobenzofuran **58r**.

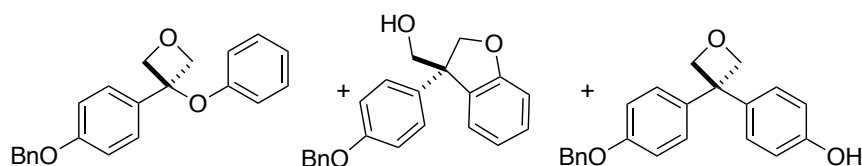
Synthesis of **58r** from **80p**



Lithium bis(trifluoromethanesulfonimide) (6.3 mg, 0.022 mmol) and tetrabutylammonium hexafluorophosphate (4.3 mg, 0.011 mmol) were added to a solution of oxetane ether **80p** (70 mg, 0.20 mmol) and 4-methoxyphenol (124 mg, 1.00 mmol) in chloroform (0.4 mL). The reaction mixture was stirred at 40 °C for 20 h then sat. aq. NaHCO_3 (10 mL) was added followed by dichloromethane (10 mL). The layers were separated and the aqueous portion

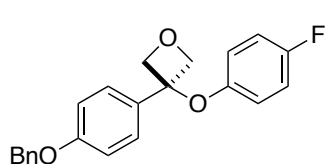
extracted with dichloromethane (2 × 10 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na₂SO₄, filtered and concentrated in vacuo. Purification by flash chromatography (50% Et₂O/pentane) afforded dihydrobenzofuran **58r** (50 mg, 55%) as a white solid. For full data see page 183.

3-(4-(Benzyloxy)phenyl)-3-phenoxyoxetane (80a), 4-{3-[4-(benzyloxy)phenyl]oxetan-3-yl}phenol (57a) and {3-[4-(benzyloxy)phenyl]-2,3-dihydro-1-benzofuran-3-yl}methanol (58a)

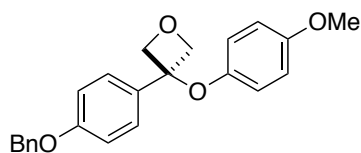


¹H NMR study: Oxetanol **45** (64 mg, 0.25 mmol), phenol (118 mg, 1.25 mmol), tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol), mesitylene (12.8 mg, 0.10 mmol) and lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) were added into a ¹H NMR tube. Immediately prior to starting the ¹H NMR experiments, CDCl₃ (0.5 mL) was added and the ¹H NMR tube inverted 3 times to mix the reagents. Nuclear magnetic resonance spectra were recorded on a 400 MHz spectrometer at 40 °C with a spectrum recorded every 30 seconds for the first hour and then every 5 minutes for a further 90 min. *In situ* ¹H NMR yields were calculated using the following signals: mesitylene (2.26 ppm, 9 H), oxetanol **45** (4.90, 2 H) oxetane ether **80a** (6.56–6.50 ppm, 2 H), dihydrobenzofuran **58a** (4.58 ppm, 1 H) and diaryloxetane **57a** (5.25, 4 H). For full data see page 203 for oxetane ether **80a** and pages 162–163 for diaryloxetane **57a** and dihydrobenzofuran **58a**.

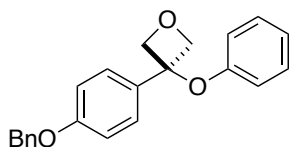
[4-(Benzyloxy)phenyl]-3-(4-fluorophenoxy)oxetane (80p)



Oxetanol **45** (64 mg, 0.25 mmol), 4-fluorophenol (140 mg, 1.25 mmol), tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol), lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and CHCl₃ (0.5 mL) were added into a ¹H NMR tube. The reaction mixture was stirred at 40 °C for 10 min then sat. aq. NaHCO₃ (10 mL) was added followed by dichloromethane (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (2 × 10 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash chromatography (15% Et₂O/pentane) afforded oxetane ether **80p** (49 mg, 55%) as a white solid. For data see page 197.

3-[4-(Benzyloxy)phenyl]-3-(4-methoxyphenoxy)oxetane (80r)

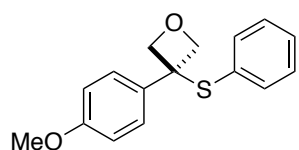
Oxetanol **45** (64 mg, 0.25 mmol), 4-methoxyphenol (155 mg, 1.25 mmol), tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol), lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and CHCl_3 (0.5 mL) were added into a ^1H NMR tube. The reaction mixture was stirred at 40 °C for 15 min then sat. aq. NaHCO_3 (10 mL) was added followed by dichloromethane (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (2 × 10 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash chromatography (15% EtOAc/hexane) afforded oxetane ether **80r** (43 mg, 47%) as a white solid. For data see page 200.

3-(4-(Benzyloxy)phenyl)-3-phenoxyoxetane (80a)

Oxetanol **45** (64 mg, 0.25 mmol), phenol (118 mg, 1.25 mmol), tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol), lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and CHCl_3 (0.5 mL) were added into a ^1H NMR tube. The reaction mixture was stirred at 40 °C for 12 min then sat. aq. NaHCO_3 (10 mL) was added followed by dichloromethane (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (2 × 10 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash chromatography (10% EtOAc/hexane) afforded oxetane ether **80a** (23 mg, 28%) as a white solid. R_f = 0.24 (10% EtOAc/hexane); mp = 113–114 °C; IR (film)/ cm^{-1} 3036, 2950, 2877, 1611, 1587, 1512, 1489, 1455, 1382, 1297, 1232, 1179, 1113, 1076, 1025, 987, 831, 752, 694; ^1H NMR (400 MHz, CDCl_3) δ 7.52–7.33 (m, 7 H, 7 × Ar-CH), 7.21–6.15 (m, 2 H, 2 × Ar-CH), 7.02–6.98 (m, 2 H, 2 × Ar-CH), 6.94–6.90 (m, 1 H, Ar-CH), 6.56–6.50 (m, 2 H, 2 × Ar-CH), 5.11 (d, J = 7.4 Hz, 2 H, CHHOCHH), 5.06 (s, 2 H, PhCH_2), 4.92 (d, J = 7.4 Hz, 2 H, CHHOCHH); ^{13}C NMR (101 MHz, CDCl_3) δ 158.4 (Ar- C_q -OBn), 154.8 (Ph- C_q -O), 136.8 (Ph- C_q - CH_2), 132.4 (Ar- C_q - C_q), 129.4 (2 × Ar-CH), 128.6 (2 × Ar-CH), 128.0 (Ar-CH), 127.5 (2 × Ar-CH), 126.1 (2 × Ar-CH), 121.0 (Ar-CH), 116.2 (2 × Ar-CH), 115.1 (2 × Ar-CH), 82.9 (CH_2OCH_2), 80.1 (C_q), 70.1 (PhCH_2); HRMS (ESI-TOF) m/z calcd for $\text{C}_{22}\text{H}_{21}\text{O}_3^+$ [$\text{M}+\text{H}$] $^+$: 333.1491, Found: 333.1497.

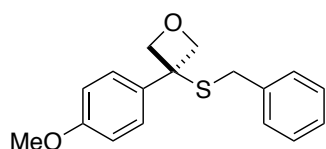
5.2.4 Synthesis of Sulfides, Sulfoxides and Sulfones

3-(4-Methoxyphenyl)-3-(phenylsulfanyl)oxetane (**85a**)



Lithium bis(trifluoromethanesulfonimide) (47.4 mg, 0.165 mmol) and tetrabutylammonium hexafluorophosphate (32.0 mg, 0.0825 mmol) were added to a solution of oxetanol **44** (270 mg, 1.5 mmol) and thiophenol (0.31 mL, 3.0 mmol) in chloroform (3.0 mL). The reaction mixture was stirred at 40 °C for 25 min then quenched with sat. aq. NaHCO₃ (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (3 × 5 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (15% Et₂O/pentane) afforded oxetane **85a** (340 mg, 83%) as a white solid. *R*_f = 0.15 (15% Et₂O/pentane); mp = 97–99 °C; IR (film)/cm⁻¹ 2959, 1739, 1609, 1513, 1252, 1175, 1022, 982, 818, 756, 695; ¹H NMR (400 MHz, CDCl₃) δ 7.32–7.19 (m, 5 H, 5 × Ph-CH), 6.98–6.93 (m, 2 H, 2 × Ar_(p-OMe)-CH), 6.84–6.79 (m, 2 H, 2 × Ar_(p-OMe)-CH), 5.13 (d, *J* = 6.4 Hz, 2 H, CHHOCHH), 4.96 (d, *J* = 6.4 Hz, 2 H, CHHOCHH), 3.81 (s, 3 H, OCH₃); ¹³C NMR (101 MHz, CDCl₃) δ 158.6 (Ar-C_q-OMe), 135.2 (2 × Ph-CH), 134.7 (Ar-C_q-C_q), 132.1 (Ar-C_q-S), 128.7 (3 × Ph-CH), 127.7 (2 × Ar_(p-OMe)-CH), 113.6 (2 × Ar_(p-OMe)-CH), 82.6 (CH₂OCH₂), 55.3 (OCH₃), 54.8 (C_q); HRMS (TOF-ASAP+) *m/z* calcd for C₁₆H₁₅SO⁺ [M+H-H₂O]⁺: 255.0844, Found: 255.0845.

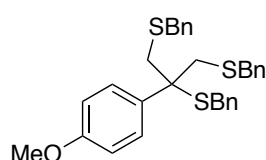
3-(Benzylthio)-3-(4-methoxyphenyl)oxetane (**85b**)



Lithium bis(trifluoromethanesulfonimide) (31.6 mg, 0.11 mmol) and tetrabutylammonium hexafluorophosphate (21.3 mg, 0.055 mmol) were added to a solution of oxetanol **44** (180 mg, 1.0 mmol) and benzylmercaptan (0.23 mL, 2.0 mmol) in chloroform (2.0 mL). The reaction mixture was stirred at 40 °C for 25 min then quenched with sat. aq. NaHCO₃ (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (3 × 5 mL). The organic extracts were combined then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (15% Et₂O/pentane) afforded oxetane **85b** (191 mg, 67%) as a colourless oil. *R*_f = 0.17 (15% Et₂O/pentane); IR (film)/cm⁻¹ 2948, 2870, 1739, 1610, 1511, 1495, 1453, 1301, 1244, 1179, 1026, 982, 829, 697; ¹H NMR (400 MHz, CDCl₃) δ 7.34–7.23 (m, 5 H, 5 × Ph-CH), 7.22–7.13 (m, 2 H, 2 × Ar_(p-OMe)-CH), 7.00–6.87 (m, 2 H, 2 × Ar_(p-OMe)-CH), 5.09 (d, *J* = 6.4 Hz, 2 H, CHHOCHH), 4.80 (d, *J* = 6.4 Hz, 2 H, CHHOCHH), 3.85 (s, 3 H, OCH₃), 3.61 (s, 2 H, CH₂Ph); ¹³C NMR (101 MHz, CDCl₃) δ 158.7 (Ar-C_q-OMe), 137.6 (Ph-C_q), 134.3 (Ar-C_q-C_q), 129.0 (2 ×

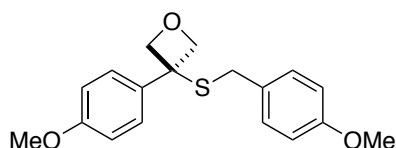
Ph-CH), 128.5 (2 × Ph-CH), 127.7 (2 × Ar_(p-OMe)-CH), 127.1 (Ph-CH), 113.9 (2 × Ar_(p-OMe)-CH), 82.9 (CH₂OCH₂), 55.3 (OCH₃), 52.6 (C_q), 35.1 (CH₂Ph); HRMS (TOF-ASAP+) *m/z* calcd for C₁₇H₁₇SO⁺ [M+H-H₂O]⁺: 269.1000, Found: 269.1004.

(2-(4-Methoxyphenyl)propane-1,2,3-triyl)tris(benzylsulfane) (86)



Lithium bis(trifluoromethanesulfonimide) (7.9 mg, 0.0275 mmol) and tetrabutylammonium hexafluorophosphate (5.3 mg, 0.0138 mmol) were added to a solution of oxetanol **44** (45 mg, 0.25 mmol) and benzylmercaptan (0.18 mL, 1.5 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at 40 °C for 6 h then quenched with sat. aq. NaHCO₃ (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (3 × 5 mL). The organic extracts were combined then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (15% Et₂O/pentane) afforded trisulfide **86** (126 mg, 97%) as a white solid. *R_f* = 0.37 (15% Et₂O/pentane); IR (film)/cm⁻¹ 3060, 3025, 2909, 2837, 1510, 1454, 1258, 1182, 1035, 826, 817, 696; ¹H NMR (400 MHz, CDCl₃) δ 7.43–7.38 (m, 2 H, 2 × Ar-CH), 7.35–7.18 (m, 13 H, 13 × Ar-CH), 7.12–7.07 (m, 2 H, 2 × Ar-CH), 6.91–6.84 (m, 2 H, 2 × Ar-CH), 3.83 (s, 3 H, OCH₃), 3.62–3.52 (m, 4 H, 2 × CH₂SCH₂Ph), 3.32 (s, 2 H, C_qSCH₂Ph), 3.30–3.21 (m, 4 H, 2 × C_qCH₂SCH₂Ph); ¹³C NMR (101 MHz, CDCl₃) δ 158.6 (Ar-C_q-OMe), 138.4 (2 × Ph-C_q), 137.2 (Ph-C_q), 133.8 (Ar-C_q-C_q), 129.0 (2 × Ar-CH), 128.9 (6 × Ar-CH), 128.5 (4 × Ar-CH), 128.3 (2 × Ar-CH), 127.0 (2 × Ar-CH), 126.9 (Ar-CH), 113.5 (2 × Ar-CH), 56.7 (C_q), 55.3 (OCH₃), 40.5 (2 × C_qCH₂SCH₂Ph), 37.7 (CH₂SCH₂Ph) 34.4 (C_qSCH₂Ph); HRMS (TOF-ASAP+) *m/z* calcd for C₃₁H₃₃S₃O⁺ [M+H-H₂O]⁺: 517.1694, Found: 517.1693.

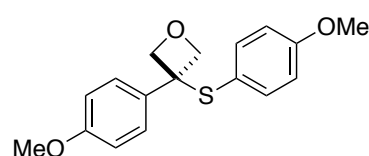
3-((4-Methoxybenzyl)thio)-3-(4-methoxyphenyl)oxetane (85c)



Lithium bis(trifluoromethanesulfonimide) (47.4 mg, 0.165 mmol) and tetrabutylammonium hexafluorophosphate (32.0 mg, 0.0825 mmol) were added to a solution of oxetanol **44** (270 mg, 1.5 mmol) and (4-methoxyphenyl)methanethiol (0.42 mL, 3.0 mmol) in chloroform (3.0 mL). The reaction mixture was stirred at 40 °C for 25 min then quenched with sat. aq. NaHCO₃ (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (3 × 5 mL). The organic extracts were combined then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% pentane/CH₂Cl₂) afforded oxetane **85c** (190 mg, 60%) as a colourless oil. *R_f* = 0.31 (20% pentane/CH₂Cl₂); IR (film)/cm⁻¹ 2870, 2950, 2835, 1739, 1609, 1509, 1241, 1175, 1027, 982, 827; ¹H NMR (400 MHz, CDCl₃) δ 7.20–7.14 (m, 4 H, 4 × Ar-CH),

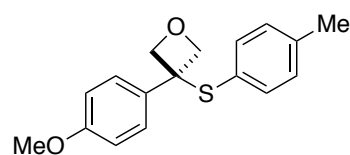
6.96–6.90 (m, 2 H, 2 × Ar-CH), 6.85–6.80 (m, 2 H, 2 × Ar-CH), 5.09 (d, $J = 6.4$ Hz, 2 H, CHHOCHH), 4.81 (d, $J = 6.4$ Hz, 2 H, CHHOCHH), 3.85 (s, 3 H, OCH₃), 3.79 (s, 3 H, OCH₃), 3.56 (s, 2 H, CH₂Ph); ¹³C NMR (101 MHz, CDCl₃) δ 158.64 (Ar-C_q-OMe), 158.55 (Ar-C_q-OMe), 134.3 (Ar-C_q-C_q), 130.0 (2 × Ar-CH), 129.3 (Ar-C_q-CH₂), 127.7 (2 × Ar-CH), 113.9 (4 × Ar-CH), 82.9 (CH₂OCH₂), 55.3 (OCH₃), 55.2 (OCH₃), 52.5 (C_q), 34.4 (SCH₂); HRMS (TOF-ASAP+) m/z calcd for C₁₈H₁₉SO₂⁺ [M+H-H₂O]⁺: 299.1106, Found: 299.1108.

3-(4-Methoxyphenyl)-3-[(4-methoxyphenyl)sulfanyl]oxetane (85d)



Lithium bis(trifluoromethanesulfonimide) (47.4 mg, 0.165 mmol) and tetrabutylammonium hexafluorophosphate (32.0 mg, 0.0825 mmol) were added to a solution of oxetanol **44** (270 mg, 1.5 mmol) and 4-methoxythiophenol (0.37 mL, 3.0 mmol) in chloroform (3.0 mL). The reaction mixture was stirred at 40 °C for 25 min then quenched with sat. aq. NaHCO₃ (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (3 × 5 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (25% Et₂O/pentane) afforded oxetane **85d** (400 mg, 88%) as a white solid. $R_f = 0.18$ (25% Et₂O/pentane); mp = 113–116 °C; IR (film)/cm⁻¹ 2956, 2882, 2837, 1740, 1611, 1585, 1511, 1492, 1456, 1440, 1298, 1284, 1237, 1171, 1021, 976, 823, 810; ¹H NMR (400 MHz, CDCl₃) δ 7.20–7.16 (m, 2 H, 2 × Ar-CH), 6.91–6.90 (m, 2 H, 2 × Ar-CH), 6.87–6.76 (m, 4 H, 4 × Ar-CH), 5.11 (d, $J = 6.5$ Hz, 2 H, CHHOCHH), 4.94 (d, $J = 6.5$ Hz, 2 H, CHHOCHH), 3.81 (s, 3 H, OCH₃), 3.80 (s, 3 H, OCH₃); ¹³C NMR (101 MHz, CDCl₃) δ 160.6 (Ar-C_q-OMe) 158.4 (Ar-C_q-OMe), 137.9 (2 × Ar-CH), 135.0 (Ar-C_q-C_q), 127.6 (2 × Ar-CH), 122.5 (Ar-C_q-S), 114.2 (2 × Ar-CH), 113.5 (2 × Ar-CH), 82.2 (CH₂OCH₂), 55.3 (2 × OCH₃), 54.9 (C_q); HRMS (TOF-ASAP+) m/z calcd for C₁₇H₁₇SO₂⁺ [M+H-H₂O]⁺: 285.0949, Found: 285.0952.

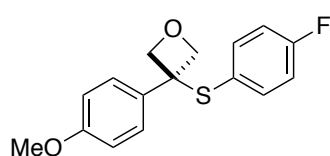
3-(4-Methoxyphenyl)-3-[(4-methylphenyl)sulfanyl]oxetane (85e)



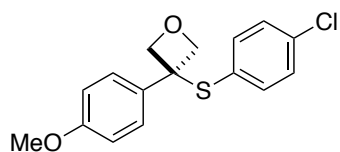
Lithium bis(trifluoromethanesulfonimide) (31.6 mg, 0.11 mmol) and tetrabutylammonium hexafluorophosphate (21.3 mg, 0.055 mmol) were added to a solution of oxetanol **44** (180 mg, 1.0 mmol) and 4-methylthiophenol (248 mg, 2.0 mmol) in chloroform (2.0 mL). The reaction mixture was stirred at 40 °C for 25 min then quenched with sat. aq. NaHCO₃ (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (3 × 5 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash

column chromatography (15% Et₂O/pentane) afforded oxetane **85e** (250 mg, 87%) as a white solid. R_f = 0.21 (15% Et₂O/pentane); mp = 98–100 °C; IR (film)/cm⁻¹ 2947, 2877, 1615, 1515, 1454, 1308, 1258, 1175, 1025, 978, 814; ¹H NMR (400 MHz, CDCl₃) δ 7.14–7.11 (m, 2 H, 2 × Ar_(p-Me)-CH), 7.07–7.04 (m, 2 H, 2 × Ar_(p-Me)-CH), 6.98–6.92 (m, 2 H, 2 × Ar_(p-OMe)-CH), 6.84–6.81 (m, 2 H, 2 × Ar_(p-OMe)-CH), 5.11 (d, J = 6.4 Hz, 2 H, CHHOCHH), 4.96 (d, J = 6.4 Hz, 2 H, CHHOCHH), 3.82 (s, 3 H, OCH₃), 2.33 (CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 158.5 (Ar-C_q-OMe), 139.1 (Ar-C_q-CH₃), 135.7 (2 × Ar_(p-Me)-CH), 135.0 (Ar-C_q-C_q), 129.6 (2 × Ar_(p-Me)-CH), 128.4 (Ar-C_q-S), 127.7 (2 × Ar_(p-OMe)-CH), 113.6 (2 × Ar_(p-OMe)-CH), 82.5 (CH₂OCH₂), 55.3 (OCH₃), 54.8 (C_q), 21.2 (CH₃); HRMS (TOF-ASAP+) m/z calcd for C₁₇H₁₇SO₂⁺ [M+H-H₂O]⁺: 269.1000, Found: 269.1000.

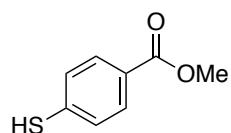
3-[(4-Fluorophenyl)sulfanyl]-3-(4-methoxyphenyl)oxetane (**85f**)



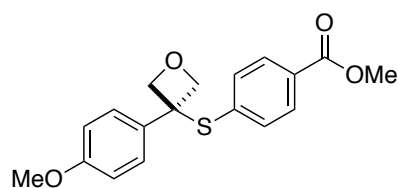
Lithium bis(trifluoromethanesulfonimide) (47.4 mg, 0.165 mmol) and tetrabutylammonium hexafluorophosphate (32.0 mg, 0.0825 mmol) were added to a solution of oxetanol **44** (270 mg, 1.5 mmol) and 4-fluorothiophenol (0.32 mL, 3.0 mmol) in chloroform (3.0 mL). The reaction mixture was stirred at 40 °C for 25 min then quenched with sat. aq. NaHCO₃ (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (3 × 5 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (15% Et₂O/pentane) afforded oxetane **85f** (358 mg, 82%) as a white solid. R_f = 0.25 (15% Et₂O/pentane); mp = 69–71 °C; IR (film)/cm⁻¹ 2959, 2882, 1740, 1611, 1588, 1512, 1484, 1459, 1305, 1245, 1223, 1177, 1026, 983, 825; ¹H NMR (400 MHz, CDCl₃) δ 7.20–7.14 (m, 2 H, 2 × Ar_(p-F)-CH), 6.97–6.89 (m, 2 H, 2 × Ar_(p-F)-CH), 6.88–6.85 (m, 2 H, 2 × Ar_(p-OMe)-CH), 6.84–6.80 (m, 2 H, 2 × Ar_(p-OMe)-CH), 5.13 (d, J = 6.5 Hz, 2 H, CHHOCHH), 4.94 (d, J = 6.5 Hz, 2 H, CHHOCHH), 3.81 (s, 3 H, OCH₃); ¹³C NMR (101 MHz, CDCl₃) δ 163.5 (d, J = 253.8 Hz, Ar-C_q-F), 158.6 (Ar-C_q-OMe), 137.9 (d, J_{C-F} = 8.4 Hz, 2 × Ar_(p-F)-CH), 134.5 (Ar-C_q-C_q), 127.6 (2 × Ar_(p-OMe)-CH), 127.1 (d, J_{C-F} = 3.4 Hz, Ar-C_q-S), 115.9 (d, J_{C-F} = 21.7 Hz, 2 × Ar_(p-F)-CH), 113.6 (2 × Ar_(p-OMe)-CH), 82.4 (CH₂OCH₂), 55.3 (OCH₃), 55.1 (C_q); ¹⁹F NMR (377 MHz, CDCl₃) δ -111.7; HRMS (TOF-ASAP+) m/z calcd for C₁₆H₁₅SFO⁺ [M+H-H₂O]⁺: 273.0749, Found: 273.0751.

3-[(4-Chlorophenyl)sulfanyl]-3-(4-methoxyphenyl)oxetane (85g)

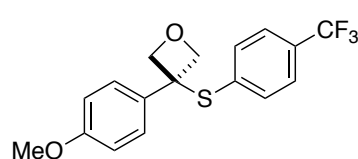
Lithium bis(trifluoromethanesulfonimide) (47.4 mg, 0.165 mmol) and tetrabutylammonium hexafluorophosphate (32.0 mg, 0.0825 mmol) were added to a solution of oxetanol **44** (270 mg, 1.5 mmol) and 4-chlorothiophenol (434 mg, 3.0 mmol) in chloroform (3.0 mL). The reaction mixture was stirred at 40 °C for 25 min then quenched with sat. aq. NaHCO₃ (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (3 × 5 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (15% Et₂O/pentane) afforded oxetane **85g** (378 mg, 82%) as a white solid. *R*_f = 0.21 (15% Et₂O/pentane); mp = 103–105 °C; IR (film)/cm⁻¹ 2947, 2878, 1739, 1514, 1454, 1366, 1230, 1217, 1176, 1092, 1024, 1013, 974, 823; ¹H NMR (400 MHz, CDCl₃) δ 7.23–7.18 (m, 2 H, 2 × Ar_(p-Cl)-CH), 7.12–7.09 (m, 2 H, 2 × Ar_(p-Cl)-CH), 6.96–6.90 (m, 2 H, 2 × Ar_(p-OMe)-CH), 6.85–6.80 (m, 2 H, 2 × Ar_(p-OMe)-CH), 5.13 (d, *J* = 6.5 Hz, 2 H, CHHOCHH), 4.94 (d, *J* = 6.5 Hz, 2 H, CHHOCHH), 3.82 (s, 3 H, OCH₃); ¹³C NMR (101 MHz, CDCl₃) δ 158.7 (Ar-C_q-OMe), 136.5 (2 × Ar_(p-Cl)-CH), 135.3 (Ar-C_q-Cl), 134.3 (Ar-C_q-C_q), 130.5 (Ar-C_q-S), 128.9 (2 × Ar_(p-Cl)-CH), 127.7 (2 × Ar_(p-OMe)-CH), 113.7 (2 × Ar_(p-OMe)-CH), 82.5 (CH₂OCH₂), 55.3 (OCH₃), 55.1 (C_q); HRMS (TOF-ASAP+) *m/z* calcd for C₁₆H₁₄SOCI⁺ [M+H-H₂O]⁺: 289.0454, Found: 289.0451.

Methyl-4-mercaptobenzoate

Concentrated H₂SO₄ (2 drops) was added to a stirred solution of 4-mercaptobenzoic acid (771 mg, 5.0 mmol) in MeOH (4.0 mL). The reaction mixture was stirred for 6 h at reflux then cooled to rt and concentration *in vacuo*. The residue was taken up in EtOAc (15 mL) and washed with water (2 × 15 mL) then sat. aq. NaHCO₃ (15 mL). The organic portions was then dried over Na₂SO₄ and concentrated *in vacuo*. Purification by flash column chromatography (60% Et₂O/pentane) afforded methyl-4-mercaptobenzoate (553 mg, 66%) as a pale yellow solid. *R*_f = 0.42 (60% Et₂O/pentane); mp = 53–55 °C; IR (film)/cm⁻¹ 2960, 2553, 1717 (C=O), 1595, 1433, 1278, 1179, 1111, 1014, 952, 842, 829, 757, 690; ¹H NMR (400 MHz, CDCl₃) δ 7.92–7.86 (m, 2 H, 2 × Ar-CH), 7.32–7.25 (m, 2 H, 2 × Ar-CH), 3.90 (s, 3 H, CH₃), 3.61 (s, 1 H, SH); ¹³C NMR (101 MHz, CDCl₃) δ 166.6 (C(O)OMe), 138.3 (Ar-C_q-C(O)OMe), 130.2 (2 × Ar-CH), 128.1 (2 × Ar-CH), 127.1 (Ar-C_q-SH), 52.1 (CH₃). The observed spectroscopic data for this compound was consistent with that previously reported.²⁴⁶

Methyl 4-((3-(4-methoxyphenyl)oxetan-3-yl)thio)benzoate (85h)

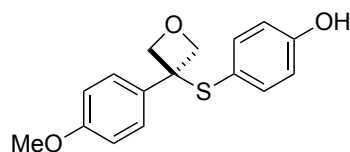
Lithium bis(trifluoromethanesulfonimide) (31.6 mg, 0.11 mmol) and tetrabutylammonium hexafluorophosphate (21.3 mg, 0.055 mmol) were added to a solution of oxetanol **44** (180.2 mg, 1.0 mmol) and methyl-4-mercaptobenzoate (336.4 mg, 2.0 mmol) in chloroform (2.0 mL). The reaction mixture was stirred at 40 °C for 25 min then quenched with sat. aq. NaHCO₃ (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (3 × 5 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (31:65:4 Et₂O/pentane/Et₃N) afforded oxetane **85h** (267 mg, 81%) as a pale yellow solid. *R*_f = 0.30 (31:65:4 Et₂O/pentane/Et₃N); mp = 106–108 °C; IR (film)/cm⁻¹ 2951, 1719 (C=O), 1615, 1516, 1425, 1300, 1259, 1175, 1115, 1017, 980, 817, 764, 697; ¹H NMR (400 MHz, CDCl₃) δ 7.89–7.85 (m, 2 H, 2 × Ar_(p-CO₂Me)-CH), 7.19–7.09 (m, 4 H, 2 × Ar_(p-CO₂Me)-CH + 2 × Ar_(p-OMe)-CH), 6.87–6.81 (m, 2 H, 2 × Ar_(p-OMe)-CH), 5.16 (d, *J* = 6.5 Hz, 2 H, CHHOCHH), 4.99 (d, *J* = 6.5 Hz, 2 H, CHHOCHH), 3.90 (C(O)OCH₃), 3.81 (s, 3 H, ArOCH₃); ¹³C NMR (101 MHz, CDCl₃) δ 166.5 (C(O)OMe), 158.8 (Ar-C_q-OMe), 139.0 (Ar-C_q-C(O)OMe), 133.8 (Ar-C_q-C_q), 132.4 (2 × Ar_(p-CO₂Me)-CH), 129.7 (2 × Ar_(p-CO₂Me)-CH), 129.3 (Ar-C_q-S), 127.6 (2 × Ar_(p-OMe)-CH), 113.8 (2 × Ar_(p-OMe)-CH), 83.1 (CH₂OCH₂), 55.3 (OCH₃), 54.7 (C_q), 52.2 (C(O)OCH₃); HRMS (TOF-ASAP+) *m/z* calcd for C₁₈H₁₇SO₃⁺ [M+H-H₂O]⁺: 313.0898, Found: 313.0894.

3-(4-Methoxyphenyl)-3-((4-(trifluoromethyl)phenyl)thio)oxetane (85i)

Lithium bis(trifluoromethanesulfonimide) (47.4 mg, 0.165 mmol) and tetrabutylammonium hexafluorophosphate (32.0 mg, 0.0825 mmol) were added to a solution of oxetanol **44** (270 mg, 1.5 mmol) and 4-(trifluoromethyl)thiophenol (0.41 mL, 3.0 mmol) in chloroform (3.0 mL). The reaction mixture was stirred at 40 °C for 25 min then quenched with sat. aq. NaHCO₃ (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (3 × 5 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% Et₂O/pentane) afforded oxetane **85i** (378 mg, 74%) as a colourless oil. *R*_f = 0.26 (20% Et₂O/pentane); IR (film)/cm⁻¹ 2953, 2874, 1739, 1607, 1512, 1321, 1245, 1164, 1120, 1100, 1088, 1062, 827; ¹H NMR (400 MHz, CDCl₃) δ 7.48–7.44 (m, 2 H, 2 × Ar_(p-CF₃)-CH), 7.24–7.20 (m, 2 H, 2 × Ar_(p-CF₃)-CH), 7.11–7.05 (m, 2 H, 2 × Ar_(p-OMe)-CH), 6.87–6.82 (m, 2 H, 2 × Ar_(p-OMe)-CH), 5.17 (d, *J* = 6.6 Hz, 2 H, CHHOCHH), 4.97 (d, *J* = 6.6

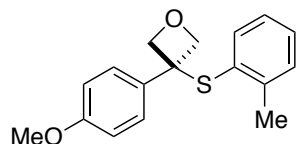
Hz, 2 H, CHHOCHH), 3.81 (s, 3 H, OCH₃); ¹³C NMR (101 MHz, CDCl₃) δ 158.8 (Ar-C_q-OMe), 137.5 (Ar-C_q-C_q), 133.7 (Ar-C_q-S), 133.4 (2 × Ar_(p-CF₃)-CH), 130.0 (q, J_{C-F} = 32.9 Hz, Ar-C_q-CF₃), 127.6 (2 × Ar_(p-OMe)-CH), 125.5 (q, J_{C-F} = 3.9 Hz, 2 × Ar_(p-CF₃)-CH), 123.9 (q, J_{C-F} = 271.7 Hz, CF₃), 113.8 (2 × Ar_(p-OMe)-CH), 82.9 (CH₂OCH₂), 55.3 (OCH₃), 54.8 (C_q); ¹⁹F NMR (377 MHz, CDCl₃) δ -62.7; HRMS (TOF-ASAP+) *m/z* calcd for C₁₇H₁₄SO₃⁺ [M+H-H₂O]⁺: 323.0717, Found: 323.0725.

3-(4-Methoxyphenyl)-3-((4-methoxyphenyl)thio)oxetane (85j)



Lithium bis(trifluoromethanesulfonimide) (15.8 mg, 0.055 mmol) and tetrabutylammonium hexafluorophosphate (10.6 mg, 0.0275 mmol) were added to a solution of oxetanol **44** (90 mg, 0.5 mmol) and 4-hydroxythiophenol (126 mg, 1.0 mmol) in chloroform (1.0 mL). The reaction mixture was stirred at 40 °C for 25 min then quenched with sat. aq. NaHCO₃ (10 mL). The layers were separated and the aqueous portion extracted with EtOAc (5 × 10 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo* affording oxetane **85j** (90 mg, 62%) as a white solid. R_f = 0.22 (40% EtOAc/hexane); mp = 226–228 °C; IR (film)/cm⁻¹ 3221 (br. OH), 2944, 1611, 1597, 1575, 1512, 1444, 1267, 1246, 1216, 1179, 1164, 1024, 968, 929, 833, 818, 773; ¹H NMR (400 MHz, (CD₃)₂SO) δ 9.82 (s, 1 H, OH), 7.15–7.10 (m, 2 H, 2 × Ar-CH), 7.00–6.95 (m, 2 H, 2 × Ar-CH), 6.89–6.84 (m, 2 H, 2 × Ar-CH), 6.73–6.68 (m, 2 H, 2 × Ar-CH), 4.98 (d, J = 6.6 Hz, 2 H, CHHOCHH), 4.82 (d, J = 6.6 Hz, 2 H, CHHOCHH), 3.75 (s, 3 H, OCH₃); ¹³C NMR (101 MHz, (CD₃)₂SO) δ 159.2 (Ar-C_q-OH) 158.5 (Ar-C_q-OMe), 138.3 (2 × Ar-CH), 135.0 (Ar_(p-OMe)-C_q-C_q), 128.2 (2 × Ar-CH), 120.5 (Ar-C_q-S), 116.4 (2 × Ar-CH), 114.0 (2 × Ar-CH), 81.6 (CH₂OCH₂), 55.6 (OCH₃), 54.9 (C_q); HRMS (TOF-ASAP+) *m/z* calcd for C₁₆H₁₇SO₃⁺ [M+H]⁺: 289.0898, Found: 289.0896.

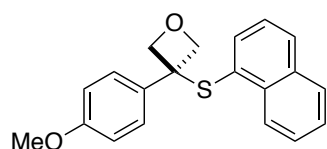
3-(4-Methoxyphenyl)-3-[(2-methylphenyl)sulfanyl]oxetane (85k)



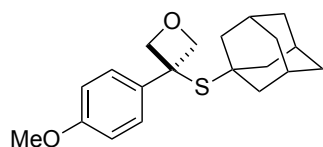
Lithium bis(trifluoromethanesulfonimide) (47.4 mg, 0.165 mmol) and tetrabutylammonium hexafluorophosphate (32.0 mg, 0.0825 mmol) were added to a solution of oxetanol **44** (270 mg, 1.5 mmol) and 2-methylthiophenol (0.35 mL, 3.0 mmol) in chloroform (3.0 mL). The reaction mixture was stirred at 40 °C for 25 min then quenched with sat. aq. NaHCO₃ (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (3 × 5 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (15% Et₂O/pentane) afforded oxetane **85k** (340 mg, 79%) as a white solid. R_f = 0.28 (15%

Et₂O/pentane); mp = 90–91 °C; IR (film)/cm⁻¹ 2952, 1739, 1509, 1455, 1366, 1230, 1217, 1177, 1022, 977, 804, 777; ¹H NMR (400 MHz, CDCl₃) δ 7.22–7.15 (m, 3 H, 3 × Ar_(o-Me)-CH), 7.09–7.05 (m, 1 H, Ar_(o-Me)-CH), 7.04–6.99 (m, 2 H, 2 × Ar_(p-OMe)-CH), 6.85–6.79 (m, 2 H, 2 × Ar_(p-OMe)-CH), 5.14 (d, *J* = 6.4 Hz, 2 H, CHHOCHH), 5.04 (d, *J* = 6.4 Hz, 2 H, CHHOCHH), 3.82 (s, 3 H, OCH₃), 2.16 (CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 158.6 (Ar-C_q-OMe), 141.9 (Ar-C_q-CH₃), 134.8 (Ar_(o-Me)-CH), 134.7 (Ar-C_q-C_q), 131.8 (Ar-C_q-S), 130.4 (Ar_(o-Me)-CH), 128.4 (Ar_(o-Me)-CH), 127.5 (2 × Ar_(p-OMe)-CH), 126.2 (Ar_(o-Me)-CH), 113.6 (2 × Ar_(p-OMe)-CH), 83.1 (CH₂OCH₂), 55.3 (OCH₃), 54.8 (C_q), 20.7 (CH₃); HRMS (TOF-ASAP+) *m/z* calcd for C₁₇H₁₈SO⁺ [M+H-H₂O]⁺: 269.1000, Found: 269.0998.

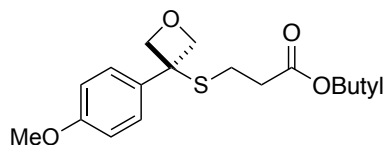
3-(4-Methoxyphenyl)-3-(naphthalen-1-ylsulfanyl)oxetane (**85I**)



Lithium bis(trifluoromethanesulfonimide) (47.4 mg, 0.165 mmol) and tetrabutylammonium hexafluorophosphate (32.0 mg, 0.0825 mmol) were added to a solution of oxetanol **44** (270 mg, 1.5 mmol) and 1-naphthalenethiol (0.42 mL, 3.0 mmol) in chloroform (3.0 mL). The reaction mixture was stirred at 40 °C for 25 min then quenched with sat. aq. NaHCO₃ (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (3 × 5 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (25% Et₂O/pentane) afforded oxetane **85I** (424 mg, 88%) as a colourless oil. *R*_f = 0.35 (25% Et₂O/pentane); IR (film)/cm⁻¹ 2951, 2870, 1739, 1610, 1511, 1299, 1244, 1179, 1026, 983, 827, 799, 771, 729; ¹H NMR (400 MHz, CDCl₃) δ 8.42–8.39 (m, 1 H, Ar_(naphthyl)-CH), 7.85–7.80 (m, 2 H, 2 × Ar_(naphthyl)-CH), 7.51–7.37 (m, 3 H, 3 × Ar_(naphthyl)-CH), 7.36–7.30 (m, 1 H, Ar_(naphthyl)-CH), 6.93–6.87 (m, 2 H, 2 × Ar_(p-OMe)-CH), 6.75–6.70 (m, 2 H, 2 × Ar_(p-OMe)-CH), 5.11 (d, *J* = 6.4 Hz, 2 H, CHHOCHH), 5.04 (d, *J* = 6.4 Hz, 2 H, CHHOCHH), 3.76 (s, 3 H, OCH₃); ¹³C NMR (101 MHz, CDCl₃) δ 158.6 (Ar-C_q-OMe), 135.6 (Ar_(naphthyl)-C_q), 135.1 (Ar_(naphthyl)-CH), 134.6 (Ar_(p-OMe)-C_q-C_q), 134.0 (Ar_(naphthyl)-C_q), 129.9 (Ar_(naphthyl)-CH), 129.7 (Ar-C_q-S), 128.3 (Ar_(naphthyl)-CH), 127.6 (2 × Ar_(p-OMe)-CH), 126.6 (Ar_(naphthyl)-CH), 126.1 (Ar_(naphthyl)-CH), 125.9 (Ar_(naphthyl)-CH), 125.3 (Ar_(naphthyl)-CH), 113.6 (2 × Ar_(p-OMe)-CH), 82.6 (CH₂OCH₂), 55.7 (C_q), 55.3 (OCH₃); HRMS (TOF-ASAP+) *m/z* calcd for C₂₀H₁₇SO⁺ [M+H-H₂O]⁺: 305.1000, Found: 305.1007.

3-(((3s,5s,7s)-Adamantan-1-yl)thio)-3-(4-methoxyphenyl)oxetane (85m)

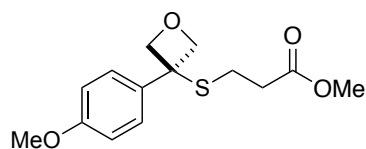
Lithium bis(trifluoromethanesulfonimide) (15.8 mg, 0.055 mmol) and tetrabutylammonium hexafluorophosphate (10.7 mg, 0.0275 mmol) were added to a solution of oxetanol **44** (90.1 mg, 0.5 mmol) and 1-adamantane thiol (168.3 mg, 2.0 mmol) in chloroform (1.0 mL). The reaction mixture was stirred at 40 °C for 25 min then quenched with sat. aq. NaHCO₃ (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (3 × 5 mL). The organic extracts were combined then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (10% Et₂O/pentane) afforded oxetane **85m** (104 mg, 63%) as a white solid; *R_f* = 0.40 (10% Et₂O/pentane); mp = 126–128 °C; IR (film)/cm⁻¹ 2914, 2850, 1607, 1509, 1455, 1248, 1175, 1040, 1024, 986, 830, 815; ¹H NMR (400 MHz, CDCl₃) δ 7.35–7.29 (m, 2 H, 2 × Ar-CH), 6.92–6.86 (m, 2 H, 2 × Ar-CH), 5.14 (d, *J* = 6.1 Hz, 2 H, CHHOCHH), 4.96 (d, *J* = 6.1 Hz, 2 H, CHHOCHH), 3.84 (s, 3 H, OCH₃), 1.92–1.81 (m, 3 H, 3 × CH), 1.64–1.45 (m, 12 H, 6 × CH₂); ¹³C NMR (101 MHz, CDCl₃) δ 158.4 (Ar-C_q-OMe), 136.7 (Ar-C_q-C_q), 128.0 (2 × Ar-CH), 113.6 (2 × Ar-CH), 84.6 (CH₂OCH₂), 55.3 (OCH₃), 51.7 (C_q(oxetane)), 48.7 (C_q(adamantyl)), 43.7 (3 × CH₂), 36.1 (3 × CH₂), 29.6 (3 × CH); HRMS (TOF-ASAP+) *m/z* calcd for C₂₀H₂₆SO₂⁺ [M+H]⁺: 331.1732, Found: 331.1724.

Butyl 3-((3-(4-methoxyphenyl)oxetan-3-yl)thio)propanoate (85n)

Lithium bis(trifluoromethanesulfonimide) (79.0 mg, 0.275 mmol) and tetrabutylammonium hexafluorophosphate (53.3 mg, 0.138 mmol) were added to a solution of oxetanol **44** (451 mg, 2.5 mmol) and butyl 3-mercaptopropionate (0.81 mL, 5.0 mmol) in chloroform (5 mL). The reaction mixture was stirred at 40 °C for 25 minutes then quenched with sat. aq. NaHCO₃ (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (3 × 5 mL). The organic extracts were combined then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (40% Et₂O/pentane) afforded oxetane **85n** (473 mg, 53%) as a colourless oil; *R_f* = 0.33 (40% Et₂O/pentane); IR (film)/cm⁻¹ 2957, 2872, 1731 (C=O), 1512, 1244, 1178, 1027, 985, 830; ¹H NMR (400 MHz, CDCl₃) δ 7.16–7.12 (m, 2 H, 2 × Ar-CH), 6.93–6.88 (m, 2 H, 2 × Ar-CH), 5.19 (d, *J* = 6.4 Hz, 2 H, CHHOCHH), 4.90 (d, *J* = 6.4 Hz, 2 H, CHHOCHH), 4.08 (t, *J* = 6.7 Hz, 2 H, CO₂CH₂), 3.82 (s, 3 H, ArOCH₃), 2.66 (t, *J* = 7.4 Hz, 2 H, SCH₂), 2.41 (t, *J* = 7.4 Hz, 2 H, SCH₂CH₂), 1.67–1.53 (m, 2 H, CH₂CH₂CH₃), 1.44–1.29 (m, 2 H, CH₂CH₂CH₃), 0.93 (t, *J* = 7.4 Hz, CH₂CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 171.7 (C=O),

158.6 (Ar-C_q-OMe), 134.3 (Ar-C_q-C_q), 127.5 (2 × Ar-CH), 114.0 (2 × Ar-CH), 83.2 (CH₂OCH₂), 64.6 (CO₂CH₂), 55.3 (Ar-OCH₃), 52.1 (C_q), 34.3 (SCH₂CH₂), 30.6 (CH₂CH₂CH₃), 25.3 (SCH₂), 19.1 (CH₂CH₂CH₃), 13.7 (CH₂CH₃); HRMS (TOF-ASAP+) *m/z* calcd for C₁₇H₂₈NSO₄⁺ [M+NH₄]⁺: 342.1737, Found: 342.1733.

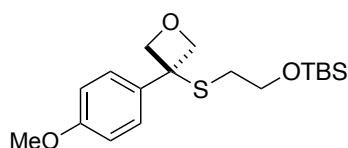
Methyl 3-((3-(4-methoxyphenyl)oxetan-3-yl)thio)propanoate (**85o**)



Lithium bis(trifluoromethanesulfonimide) (47.4 mg, 0.0165 mmol) and tetrabutylammonium hexafluorophosphate (32.0 mg, 0.0825 mmol) were added to a solution of oxetanol **44** (270.3 mg, 1.5 mmol) and methyl 3-mercaptopropionate (0.33 mL, 3.0 mmol) in chloroform (3 mL). The reaction mixture was stirred at 40 °C for 25 min then quenched with sat. aq. NaHCO₃. The layers were separated and the aqueous portion extracted with dichloromethane (3 × 10 mL). The organic extracts were combined then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (60% Et₂O/pentane) afforded oxetane **85o** (321 mg, 76%) as a white solid; *R*_f = 0.20 (60% Et₂O/pentane); mp = 45–47 °C; IR (film)/cm⁻¹ 2952, 2884, 1732, 1610, 1514, 1436, 1420, 1369, 1298, 1250, 1208, 1178, 1146, 1022, 980, 839, 819, 803; ¹H NMR (400 MHz, CDCl₃) δ 7.17–7.10 (m, 2 H, 2 × Ar_(p-OMe)-CH), 6.95–6.86 (m, 2 H, 2 × Ar_(p-OMe)-CH), 5.19 (d, *J* = 6.5 Hz, 2 H, CHHOCHH), 4.90 (d, *J* = 6.5 Hz, 2 H, CHHOCHH), 3.83 (s, 3 H, ArOCH₃), 3.68 (s, 3 H, C(O)OCH₃), 2.67 (t, *J* = 7.4 Hz, 2 H, SCH₂), 2.42 (t, *J* = 7.4 Hz, 2 H, CH₂C(O)OMe); ¹³C NMR (101 MHz, CDCl₃) δ 172.0 (C=O), 158.7 (Ar-C_q-OMe), 134.2 (Ar-C_q-C_q), 127.5 (2 × Ar-CH), 114.0 (2 × Ar-CH), 83.2 (CH₂OCH₂), 55.3 (Ar-OCH₃), 52.2 (C_q), 51.8 (C(O)OCH₃), 34.1 (CH₂CO₂Me), 25.2 (SCH₂); HRMS (TOF-ASAP+) *m/z* calcd for C₁₄H₂₂NSO₄⁺ [M+NH₄]⁺: 300.1270, Found: 300.1266.

Reaction was also conducted on a 12.0 mmol scale (2.16 g of oxetanol **44**). During the aqueous work-up the organic portions were washed with aq. NaOH (1 M, 100 mL) prior to drying over Na₂SO₄. Purification by flash column chromatography (60% Et₂O/pentane) afforded oxetane **85o** (2.43 g, 72%).

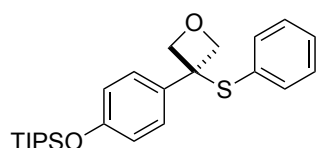
tert-Butyl(2-((3-(4-methoxyphenyl)oxetan-3-yl)thio)ethoxy)dimethylsilane (**85p**)



Lithium bis(trifluoromethanesulfonimide) (32 mg, 0.11 mmol) and tetrabutylammonium hexafluorophosphate (21 mg, 0.055 mmol) were added to a solution of oxetanol **44** (180 mg, 1.0 mmol) and 2-((TBS)oxy)ethane-1-thiol (385 mg, 2.0 mmol) in chloroform (2 mL). The reaction mixture was stirred at 40 °C for 25 min then quenched with sat. aq.

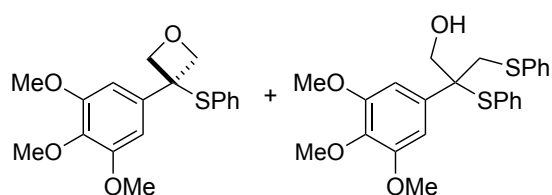
NaHCO₃ (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (2 × 10 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (10% EtOAc/hexane) afforded oxetane **85p** (49 mg, 14%) as a colourless oil. *R*_f = 0.69 (10% EtOAc/hexane); IR (film)/cm⁻¹ 2953, 2929, 2857, 1513, 1246, 1086, 1029, 987, 831, 775; ¹H NMR (400 MHz, CDCl₃) δ 7.17–7.11 (m, 2 H, 2 × Ar-CH), 6.93–6.87 (m, 2 H, 2 × Ar-CH), 5.18 (d, *J* = 6.3 Hz, CHHOCHH), 4.90 (d, *J* = 6.3 Hz, CHHOCHH), 3.82 (s, 3 H, OCH₃), 3.57 (t, *J* = 7.0 Hz, 2 H, CH₂OTBS), 2.58 (t, *J* = 7.0 Hz, 2 H, SCH₂), 0.87 (s, 9 H, (CH₃)₃), 0.02 (s, 6 H, Si(CH₃)₂); ¹³C NMR (101 MHz, CDCl₃) δ 158.6 (Ar-C_q-OMe), 134.7 (Ar-C_q-C_q), 127.5 (2 × Ar-CH), 113.9 (2 × Ar-CH), 83.5 (CH₂OCH₂), 62.7 (CH₂OTBS), 55.3 (OCH₃), 51.9 (C_q), 32.8 (CH₂S), 25.9 (CH₃)₃, 18.3 (C(CH₃)₃), 5.3 (Si(CH₃)₂); HRMS (TOF-ASAP+) *m/z* calcd for C₁₈H₃₄NO₃SiS⁺ [M+NH₄]⁺: 372.2029, Found: 372.2022.

Triisopropyl(4-(3-(phenylthio)oxetan-3-yl)phenoxy)silane (**87**)



Lithium bis(trifluoromethanesulfonimide) (54.0 mg, 0.188 mmol) and tetrabutylammonium hexafluorophosphate (36.4 mg, 0.094 mmol) were added to a solution of oxetanol **46** (551 mg, 1.7 mmol) and thiophenol (0.35 mL, 3.4 mmol) in chloroform (3.4 mL). The reaction mixture was stirred at 40 °C for 25 min then quenched with sat. aq. NaHCO₃ (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (3 × 5 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (10% Et₂O/pentane) afforded oxetane **87** (470 mg, 66%) as a colourless oil. *R*_f = 0.22 (10% Et₂O/pentane); IR (film)/cm⁻¹ 2944, 2866, 1606, 1510, 1462, 1262, 988, 909, 882, 835, 748, 689; ¹H NMR (400 MHz, CDCl₃) δ 7.33–7.27 (m, 1 H, Ph-CH), 7.23–7.15 (m, 4 H, 4 × Ph-CH), 6.85–6.75 (m, 4 H, 4 × Ar_(p-OTIPS)-CH), 5.14 (d, *J* = 6.4 Hz, 2 H, CHHOCHH), 4.97 (d, *J* = 6.4 Hz, 2 H, CHHOCHH), 1.31–1.20 (s, 3 H, CH(CH₃)₂), 1.11 (d, *J* = 7.3 Hz, 18 H, CH(CH₃)₂); ¹³C NMR (101 MHz, CDCl₃) δ 155.1 (Ar-C_q-OTIPS), 135.5 (2 × Ph-CH), 135.1 (Ar-C_q-C_q), 132.0 (Ph-C_q-S), 128.8 (Ph-CH), 128.7 (2 × Ph-CH), 127.6 (2 × Ar_(p-OTIPS)-CH), 119.6 (2 × Ar_(p-OTIPS)-CH), 82.7 (CH₂OCH₂), 55.0 (C_q), 17.9 (CH(CH₃)₂), 12.7 (CH(CH₃)₂); HRMS (TOF-ASAP+) *m/z* calcd for C₂₄H₃₅O₂SSi⁺ [M+H]⁺: 415.2127, Found: 415.2126.

3-(Phenylthio)-3-(3,4,5-trimethoxyphenyl)oxetane (88**) and 2,3-bis(phenylthio)-2-(3,4,5-trimethoxyphenyl)propan-1-ol (**88'**)**

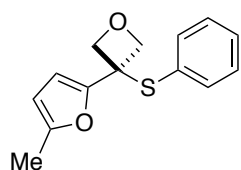


Lithium bis(trifluoromethanesulfonimide) (15.6 mg, 0.055 mmol) and tetrabutylammonium hexafluorophosphate (10.7 mg, 0.0275 mmol) were added to a solution of oxetanol **49** (120 mg, 0.5 mmol) and thiophenol (0.10 mL, 1.0 mmol) in

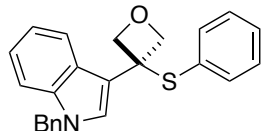
chloroform (1.0 mL). The reaction mixture was stirred at 40 °C for 25 min then quenched with sat. aq. NaHCO₃ (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (3 × 5 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (25% EtOAc/hexane) afforded oxetane **88** (39 mg, 23%) as a yellow oil followed by alcohol **88'** (54 mg, 25%).

Oxetane **88**: *R_f* = 0.16 (20% EtOAc/hexane); IR (film)/cm⁻¹ 2940, 1588, 1509, 1456, 1414, 1349, 1243, 1127, 1006, 986, 752; ¹H NMR (400 MHz, CDCl₃) δ 7.35–7.30 (m, 1 H, Ph-CH), 7.27–7.19 (m, 4 H, 4 × Ph-CH), 6.12–6.07 (m, 2 H, 2 × Ar-CH), 5.14 (d, *J* = 6.4 Hz, 2 H, CHHOCHH), 4.97 (d, *J* = 6.4 Hz, 2 H, CHHOCHH), 3.83 (s, 3 H, OCH₃), 3.72 (s, 6 H, 2 × OCH₃); ¹³C NMR (101 MHz, CDCl₃) δ 152.9 (2 × Ar-C_q-O), 138.2 (Ar-C_q-O), 137.0 (Ar-C_q-C_q), 135.6 (2 × Ph-CH), 131.8 (Ar-C_q-S), 129.0 (Ph-CH), 128.7 (2 × Ph-CH), 103.7 (2 × Ar-CH), 82.5 (CH₂OCH₂), 60.9 (OCH₃), 56.1 (2 × OCH₃), 55.5 (C_q); HRMS (TOF-ASAP+) *m/z* calcd for C₁₈H₂₁SO₄⁺ [M+H]⁺: 333.1161, Found: 333.1160.

Alcohol **88'**: *R_f* = 0.16 (20% EtOAc/hexane); IR (film)/cm⁻¹ 3493 (br. OH), 2935, 1588, 1511, 1464, 1327, 1439, 1415, 1128, 749, 693; ¹H NMR (400 MHz, CDCl₃) δ 7.38–7.14 (m, 10 H, 10 × Ph-CH), 6.59–6.52 (m, 2 H, 2 × Ar-CH), 4.10 (d, *J* = 11.6 Hz, 1 H, CHHOH), 4.04 (d, *J* = 11.6 Hz, 1 H, CHHOH), 3.85 (s, 3 H, OCH₃), 3.74 (s, 6 H, 2 × OCH₃), 3.67 (d, *J* = 13.1 Hz, 1 H, CHHSPH), 3.57 (d, *J* = 13.1 Hz, 1 H, CHHSPH), 2.42 (s, 1 H, OH); ¹³C NMR (101 MHz, CDCl₃) δ 152.7 (2 × Ar-C_q-O), 137.5 (Ar-C_q-C_q), 136.7 (2 × Ph-CH), 136.5 (Ar-C_q-O), 134.5 (Ar-C_q-S), 130.5 (2 × Ph-CH), 129.7 (Ar-C_q-S), 129.4 (Ph-CH), 128.8 (4 × Ph-CH), 126.6 (Ph-CH), 105.5 (2 × Ar-CH), 63.9 (CH₂OH), 61.5 (C_q), 60.8 (OCH₃), 56.1 (2 × OCH₃), 42.3 (CH₂SPh); HRMS (+ p NSI) *m/z* calcd for C₂₄H₂₆S₂O₄Na⁺ [M+Na]⁺: 465.1165, Found: 465.1159.

2-Methyl-5-(3-(phenylthio)oxetan-3-yl)furan (89)

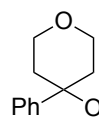
Lithium bis(trifluoromethanesulfonimide) (47.4 mg, 0.165 mmol) and tetrabutylammonium hexafluorophosphate (32.0 mg, 0.0825 mmol) were added to a solution of oxetanol **51** (231 mg, 1.5 mmol) and thiophenol (0.31 mL, 3.0 mmol) in chloroform (3.0 mL). The reaction mixture was stirred at 40 °C for 25 min then quenched with sat. aq. NaHCO₃ (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (3 × 5 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (5% Et₂O/pentane) afforded oxetane **89** (316 mg, 86%) as a colourless oil. *R_f* = 0.19 (5% Et₂O/pentane); IR (film)/cm⁻¹ 2950, 2875, 1739, 1476, 1439, 1366, 1350, 1217, 1021, 985, 906, 783, 748, 691; ¹H NMR (400 MHz, CDCl₃) δ 7.30–7.21 (m, 5 H, 5 × Ph-CH), 6.01 (d, *J* = 3.1 Hz, 1 H, Ar_(furan)-CH), 5.90–5.87 (m, 1 H, Ar_(furan)-CH), 5.05 (d, *J* = 6.3 Hz, 2 H, CHHOCHH), 4.87 (d, *J* = 6.3 Hz, 2 H, CHHOCHH), 2.31 (d, *J* = 1.0 Hz, 3 H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 152.3 (Ar_(furan)-C_q-CH₃), 151.7 (Ar-C_q-C_q), 133.8 (2 × Ph-CH), 132.0 (Ar-C_q-S), 128.8 (2 × Ph-CH), 128.3 (Ph-CH), 109.0 (Ar_(furan)-CH), 106.4 (Ar_(furan)-CH), 81.2 (CH₂OCH₂), 49.8 (C_q), 13.6 (CH₃); HRMS (TOF-ASAP+) *m/z* calcd for C₁₄H₁₃SO⁺ [M+H-H₂O]⁺: 229.0687, Found: 229.0691.

1-Benzyl-3-(3-(phenylthio)oxetan-3-yl)-1H-indole (90)

Lithium bis(trifluoromethanesulfonimide) (18.9 mg, 0.07 mmol) and tetrabutylammonium hexafluorophosphate (12.8 mg, 0.03 mmol) were added to a solution of oxetanol **52** (168 mg, 0.6 mmol) and thiophenol (0.12 mL, 1.2 mmol) in chloroform (1.2 mL). The reaction mixture was stirred at 40 °C for 25 min then quenched with sat. aq. NaHCO₃ (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (3 × 5 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% Et₂O/pentane) afforded oxetane **90** (203 mg, 91%) as a colourless oil. *R_f* = 0.17 (20% Et₂O/pentane); IR (film)/cm⁻¹ 2971, 2866, 1739, 1468, 1455, 1438, 1366, 1229, 1217, 983, 741, 695; ¹H NMR (400 MHz, CDCl₃) δ 7.75–7.71 (m, 1 H, Ar_(indole)-CH), 7.31–7.14 (m, 11 H, 11 × Ar-CH), 7.03–6.98 (m, 2 H, 2 × Ar-CH), 6.78 (s, 1 H, Ar_(indole)-CH), 5.25 (d, *J* = 6.3 Hz, 2 H, CHHOCHH), 5.23 (s, 2 H, CH₂), 5.13 (d, *J* = 6.3 Hz, 2 H, CHHOCHH); ¹³C NMR (101 MHz, CDCl₃) δ 137.1 (Ar-C_q), 137.0 (Ar-C_q), 134.3 (2 × Ar-CH), 133.0 (Ar-C_q-S), 128.7 (2 × Ar-CH), 128.5 (2 × Ar-CH), 128.1 (Ar-CH), 127.6 (Ar-CH), 126.71 (Ar_(indole)-CH), 126.65 (2 × Ar-CH), 125.6 (Ar_(indole)-C_q), 122.3 (Ar-CH), 120.4 (Ar_(indole)-CH), 119.6 (Ar_(indole)-CH), 116.3 (Ar_(indole)-C_q), 110.0

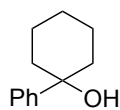
(Ar_(indole)-CH), 83.3 (CH₂OCH₂), 50.9 (C_q), 49.9 (CH₂); HRMS (TOF-ASAP+) *m/z* calcd for C₂₄H₂₂NSO⁺ [M+H]⁺: 372.1422, Found: 372.1420.

4-Phenyloxan-4-ol (91a)



n-BuLi (2.4 M in hexanes, 2.7 mL, 6.5 mmol) was added dropwise over 5 min to a solution of bromobenzene (0.69 mL, 6.5 mmol) in THF (20 mL) at -78°C . The reaction mixture was stirred at -78°C for a further 10 min. Oxan-4-one (0.46 mL, 5 mmol) was added dropwise as a solution in THF (5 mL) to the reaction mixture. Following a further 10 min at -78°C the reaction mixture was warmed to rt and water (20 mL) was added. The layers were separated and the aqueous portion extracted with diethylether (3 $\times$ 30 mL). The organic extracts were combined, washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (50% EtOAc/hexane) afforded 4-phenyloxan-4-ol **91a** (780 mg, 87%) as a white solid. *R*_f = 0.35 (50% EtOAc/hexane); mp = 99–100 $^{\circ}\text{C}$ (Lit. mp = 100.0–100.5 $^{\circ}\text{C}$)²⁴⁷; IR (film)/ cm⁻¹ 3375 (br. OH), 3026, 2970, 2956, 2923, 2889, 1739, 1491, 1446, 1408, 1366, 1310, 1218, 1140, 1126, 1089, 1071, 1039, 1024, 1016, 1007, 965, 916, 834, 660, 759, 693; ¹H NMR (400 MHz, CDCl₃) δ 7.54–7.47 (m, 2 H, 2 $\times$ Ph-CH), 7.47–7.35 (m, 2 H, 2 $\times$ Ph-CH), 7.35–7.27 (m, 1 H, Ph-CH), 4.04–3.85 (m, 4 H, 2 $\times$ CH₂O), 2.21 (ddd, *J* = 13.6, 11.9, 5.4 Hz, 2 H, 2 $\times$ CHHC_q), 1.77–1.65 (m, 2 H, 2 $\times$ CHHC_q); ¹³C NMR (101 MHz, CDCl₃) δ 148.0 (Ph-C_q), 128.5 (2 $\times$ Ph-CH), 127.2 (Ph-CH), 124.4 (2 $\times$ Ph-CH), 70.7 (C_q), 63.9 (2 $\times$ CH₂O), 38.8 (2 $\times$ C_qCH₂). The spectroscopic data for this compound is consistent with the literature.²⁴⁷

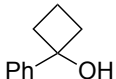
1-Phenylcyclohexan-1-ol (91b)



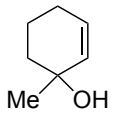
n-BuLi (2.3 M in hexanes, 2.8 mL, 6.5 mmol) was added dropwise over 5 min to a solution of bromobenzene (0.69 mL, 6.5 mmol) in THF (20 mL) at -78°C . The reaction mixture was stirred at -78°C for a further 10 min. Cyclohexanone (0.52 mL, 5 mmol) was added dropwise as a solution in THF (5 mL) to the reaction mixture. Following a further 10 minutes at -78°C the reaction mixture was warmed to rt and water (20 mL) was added. The layers were separated and the aqueous portion extracted with diethylether (3 $\times$ 30 mL). The organic extracts were combined, washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% Et₂O/pentane) afforded 1-phenylcyclohexan-1-ol **91b** (735 mg, 83%) as a white solid. *R*_f = 0.26 (20% Et₂O/pentane); mp = 62–64 $^{\circ}\text{C}$ (Lit. mp = 61 $^{\circ}\text{C}$)²⁴⁸; IR (film)/ cm⁻¹ 3321 (br. OH), 3062, 3033, 2923, 2854, 1494, 1444, 1381, 1351, 1259, 1210, 1176, 1146, 1135, 1032, 1015, 974, 897, 849, 831, 754, 694; ¹H NMR (400 MHz, CDCl₃) δ 7.61–7.44 (m, 2 H, 2 $\times$ Ph-CH), 7.43–7.30 (m, 2 H, 2 $\times$ Ph-CH), 7.30–7.18 (m, 1 H, Ph-CH), 1.93–1.71 (m,

7 H, 2 × C_qCH₂ + CHHCHHCHH), 1.71–1.61 (m, 2 H, 2 × CHHCH₂CHH), 1.58 (s, 1 H, OH), 1.39–1.23 (m, 1 H, 1 × CH₂CHHCH₂); ¹³C NMR (101 MHz, CDCl₃) δ 149.4 (Ph-C_q), 128.2 (2 × Ph-CH), 126.7 (Ph-CH), 124.6 (2 × Ph-CH), 73.1 (C_q), 38.8 (CH₂C_qCH₂), 25.5 (CH₂CH₂CH₂), 22.2 (CH₂CH₂CH₂). The spectroscopic data for this compound is consistent with the literature.²⁴⁹

1-Phenylcyclobutan-1-ol (91c)

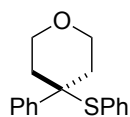
 *n*-BuLi (2.4 M in hexanes, 2.7 mL, 6.5 mmol) was added dropwise over 5 min to a solution of bromobenzene (0.69 mL, 6.5 mmol) in THF (20 mL) at –78 °C. The reaction mixture was stirred at –78 °C for a further 10 min. Cyclobutanone (0.32 mL, 5.0 mmol) was added dropwise as a solution in THF (5 mL) to the reaction mixture. Following a further 10 minutes at –78 °C the reaction mixture was warmed to rt and water (20 mL) was added. The layers were separated and the aqueous portion extracted with diethylether (3 × 30 mL). The organic extracts were combined, washed with brine (20 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (30% EtOAc/hexane) afforded 1-phenylcyclobutan-1-ol **91c** (574 mg, 78%) as a white solid. *R*_f = 0.3 (25% EtOAc/hexane); mp = 40 °C (lit. mp = 40–41 °C)²⁵⁰; IR (film)/ cm^{–1} 3303 (br. OH), 2989, 2940, 2869, 1495, 1446, 1423, 1246, 1185, 1132, 1110, 1074, 1026, 959, 913, 825, 760, 697; ¹H NMR (400 MHz, CDCl₃) δ 7.57–7.47 (m, 2 H, 2 × Ph-CH), 7.46–7.35 (m, 2 H, 2 × Ph-CH), 7.35–7.22 (m, 1 H, Ph-CH), 2.67–2.50 (m, 2 H, 2 × C_qCHH), 2.50–2.28 (m, 2 H, 2 × C_qCHH), 2.11–1.98 (m, 1 H, C_qCH₂CHH), 1.93 (br. s, 1 H, OH), 1.71 (dt, *J* = 11.3, 8.8, 7.5 Hz, 1 H, C_qCH₂CHH); ¹³C NMR (101 MHz, CDCl₃) δ 146.2 (Ph-C_q), 128.4 (2 × Ph-CH), 127.2 (Ph-CH), 125.0 (2 × Ph-CH), 36.8 (2 × C_qCH₂), 13.0 (C_qCH₂CH₂). The spectroscopic data for this compound is consistent with the literature.²⁵¹ Quaternary carbon peak obscured by CDCl₃ peak in ¹³C NMR but presence confirmed by HMBC.

1-Methylcyclohex-2-en-1-ol (91j)

 MeLi (1.6 M, 2.9 mL, 4.5 mmol) was added dropwise to 2-cyclohexen-1-one (0.29 mL, 3 mmol) in THF (5 mL) at 78 °C. The reaction mixture was stirred at –78 °C for 10 min then warmed to 0 °C and stirred for a further 3 h. The reaction mixture was quenched with sat. aq. NH₄Cl (15 mL). The aqueous portion was extracted with EtOAc (3 × 50 mL). The organic portions were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (40% Et₂O/pentane) afforded oxetane **91j** (337 mg, 54%) as a colourless oil; *R*_f = 0.23 (40% Et₂O/pentane); IR (film)/cm^{–1} 3366 (br. OH), 2933, 1368, 1180, 1122, 1101, 1017, 997, 963, 905, 728; ¹H NMR (400 MHz, CDCl₃) δ 5.75 (ddd, *J* = 10.0, 4.2, 3.1 Hz, 1 H, C_qCH=CH), 5.68–5.58 (m, 1 H,

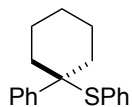
$C_qCH=CH$), 2.11–1.99 (m, 1 H, $CH=CHCHH$), 1.99–1.85 (m, 1 H, $CH=CHCHH$), 1.81–1.56 (m, 5 H, $C_qCH_2CH_2 + OH$), 1.29 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.7 ($C_qCH=CH$), 129.0 ($C_qCH=CH$), 67.9 (C_q), 37.9 (C_qCH_2), 29.3 (CH_3), 25.0 ($CH=CHCH_2$), 19.5 ($CH_2CH_2CH_2$). The observed spectroscopic data for this compound was consistent with that previously reported.²⁵²

4-Phenyl-4-(phenylthio)tetrahydro-2H-pyran (**92a**)



Lithium bis(trifluoromethanesulfonimide) (47.4 mg, 0.165 mmol) and tetrabutylammonium hexafluorophosphate (32.0 mg, 0.0825 mmol) were added to a solution of 4-phenyltetrahydro-2H-pyran-4-ol **91a** (267 mg, 1.5 mmol) and thiophenol (0.31 mL, 3.0 mmol) in chloroform (3.0 mL). The reaction mixture was stirred at 40 °C for 25 min then quenched with sat. aq. $NaHCO_3$ (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (3×5 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (5% EtOAc/hexane) afforded sulfide **92a** (328 mg, 81%) as a white solid. R_f = 0.18 (5% EtOAc/hexane); mp = 66–68 °C; IR (film)/ cm^{-1} 2955, 2909, 2861, 1245, 1106, 1027, 1019, 749, 694, 655; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.10 (m, 8 H, $8 \times Ph-CH$), 7.02–6.93 (m, 2 H, $2 \times Ph-CH$), 4.12 (ddd, J = 11.5, 8.6, 2.9 Hz, 2 H, $CHHOCHH$), 3.76 (ddd, J = 11.5, 5.6, 3.7 Hz, 2 H, $CHHOCHH$), 2.27 (ddd, J = 12.4, 8.6, 3.7 Hz, 2 H, $CHHC_qCHH$), 2.22–2.11 (m, 2 H, $CHHC_qCHH$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.5 ($Ph-C_q-C_q$), 137.1 ($2 \times Ph-CH$), 130.9 ($Ph-C_q-S$), 128.8 ($Ph-CH$), 128.2 ($2 \times Ph-CH$), 128.0 ($2 \times Ph-CH$), 126.7 ($Ph-CH$), 126.6 ($2 \times Ph-CH$), 64.2 (CH_2OCH_2), 52.6 (C_q), 35.9 ($CH_2C_qCH_2$); HRMS (TOF-ASAP+) m/z calcd for $C_{16}H_{21}NO_5S^+$ $[M+H]^+$: 340.1219, Found: 340.1210.

Phenyl(1-phenylcyclohexyl)sulfane (**92b**)



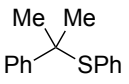
Lithium bis(trifluoromethanesulfonimide) (47.4 mg, 0.165 mmol) and tetrabutylammonium hexafluorophosphate (32.0 mg, 0.0825 mmol) were added to a solution of 1-phenylcyclohexan-1-ol **91b** (264 mg, 1.5 mmol) and thiophenol (0.31 mL, 3.0 mmol) in chloroform (3.0 mL). The reaction mixture was stirred at 40 °C for 25 min then quenched with sat. aq. $NaHCO_3$ (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (3×5 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (2% EtOAc/hexane) afforded sulfide **92b** (403 mg, 83%) as a white solid. R_f = 0.28 (2% EtOAc/hexane); mp = 65–67 °C; IR (film)/ cm^{-1} 3062, 2928, 2853, 1443, 745, 704, 691; ^1H NMR (400 MHz, $CDCl_3$) δ

7.30–7.18 (m, 6 H, 6 × Ph-CH), 7.18–7.11 (m, 2 H, 2 × Ph-CH), 7.04–6.99 (m, 2 H, 2 × Ph-CH), 2.30–2.19 (m, 2 H, CHHC_qCHH), 2.11–2.01 (m, 2 H, CHHC_qCHH), 1.92–1.80 (m, 2 H, CH₂CHHCH₂CHHCH₂) 1.59–1.39 (m, 4 H, CH₂CHHCH₂CHHCH₂ + CH₂CH₂CH₂CH₂CH₂); ¹³C NMR (101 MHz, CDCl₃) δ 144.4 (Ph-C_q-C_q), 137.0 (2 × Ph-CH), 131.7 (Ph-C_q-S), 128.4 (Ph-CH), 128.0 (2 × Ph-CH), 127.8 (2 × Ph-CH), 127.0 (2 × Ph-CH), 126.2 (Ph-CH), 55.3 (C_q), 36.4 (CH₂CH₂CH₂CH₂CH₂), 25.9.0 (CH₂CH₂CH₂CH₂CH₂), 22.9 CH₂CH₂CH₂CH₂CH₂); HRMS (TOF-ASAP+) *m/z* calcd for C₁₆H₂₁NO₅S⁺ [M+H]⁺: 340.1219, Found: 340.1210.

Phenyl(1-phenylcyclobutyl)sulfane (92c)

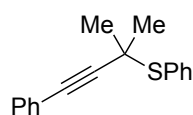
 Lithium bis(trifluoromethanesulfonimide) (47.4 mg, 0.165 mmol) and tetrabutylammonium hexafluorophosphate (32.0 mg, 0.0825 mmol) were added to a solution of 1-phenylcyclobutan-1-ol **91c** (222 mg, 1.5 mmol) and thiophenol (0.31 mL, 3.0 mmol) in chloroform (3.0 mL). The reaction mixture was stirred at 40 °C for 25 min then quenched with sat. aq. NaHCO₃ (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (3 × 5 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (2% EtOAc/hexane) afforded sulfide **92c** (337 mg, 93%) as a white solid. *R*_f = 0.21 (2% EtOAc/hexane); mp = 46–48 °C; IR (film)/cm⁻¹ 2978, 2930, 1473, 1445, 1436, 774, 752, 692, 655; ¹H NMR (400 MHz, CDCl₃) δ 7.34–7.10 (m, 8 H, 8 × Ph-CH), 7.05–6.99 (m, 2 H, 2 × Ph-CH), 2.71–2.60 (m, 2 H, CHHC_qCHH), 2.57–2.35 (m, 3 H, CHHC_qCHH + CH₂CHHCH₂), 1.98–1.86 (m, 1 H, CH₂CHHCH₂); ¹³C NMR (101 MHz, CDCl₃) δ 147.3 (Ph-C_q-C_q), 135.9 (2 × Ph-CH), 133.2 (Ph-C_q-S), 128.3 (Ph-CH), 128.2 (2 × Ph-CH), 127.7 (2 × Ph-CH), 126.1 (2 × Ph-CH), 126.0 (Ph-CH), 56.5 (C_q), 34.5 (CH₂C_qCH₂), 16.4 (CH₂CH₂CH₂); HRMS (EI⁺) *m/z* calcd for C₁₆H₁₆S⁺ [M]⁺: 240.0967, Found 240.0965.

Phenyl(2-phenylpropan-2-yl)sulfane (92d)

 Lithium bis(trifluoromethanesulfonimide) (47.4 mg, 0.165 mmol) and tetrabutylammonium hexafluorophosphate (32.0 mg, 0.0825 mmol) were added to a solution of 2-Phenylpropan-2-ol (210 μL, 1.5 mmol) and thiophenol (0.31 mL, 3.0 mmol) in chloroform (3.0 mL). The reaction mixture was stirred at 40 °C for 25 min then quenched with sat. aq. NaHCO₃ (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (3 × 5 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (5% EtOAc/hexane) afforded sulfide **92d** (340 mg, 99%) as a colourless oil. *R*_f = 0.34 (5% EtOAc/hexane); IR (film)/cm⁻¹ 2955, 2909, 2861, 1245, 1106, 1027, 1019, 749, 694, 655; ¹H NMR (400 MHz, CDCl₃) δ 7.47–7.42 (m, 2 H, 2 × Ph-CH),

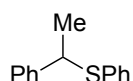
7.34–7.15 (m, 8 H, 8 × Ph-CH), 1.72 (s, 6 H, 2 × CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 146.3 (Ph-C_q-C_q), 136.5 (2 × Ph-CH), 132.8 (Ph-C_q-S), 128.5 (Ph-CH), 128.2 (2 × Ph-CH), 127.9 (2 × Ph-CH), 126.53 (2 × Ph-CH), 126.50 (Ph-CH), 51.0 (C_q), 29.7 (2 × CH₃). The observed spectroscopic data for this compound was consistent with that previously reported.²⁵³

(2-Methyl-4-phenylbut-3-yn-2-yl)(phenyl)sulfane (92e)



Lithium bis(trifluoromethanesulfonimide) (47.4 mg, 0.165 mmol) and tetrabutylammonium hexafluorophosphate (32.0 mg, 0.0825 mmol) were added to a solution of 2-methyl-4-phenylbut-3-yn-2-ol (240 mg, 1.5 mmol) and thiophenol (0.31 mL, 3.0 mmol) in chloroform (3.0 mL). The reaction mixture was stirred at 40 °C for 25 min then quenched with sat. aq. NaHCO₃ (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (3 × 5 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (10% dichloromethane/pentane) afforded sulfide **92e** (259 mg, 68%) as a colourless oil. *R*_f = 0.35 (10% dichloromethane/pentane); IR (film)/cm⁻¹ 2971, 1739, 1490, 1474, 1439, 1360, 1121, 750, 705, 690; ¹H NMR (400 MHz, CDCl₃) δ 7.73–7.69 (m, 2 H, 2 × Ph-CH), 7.44–7.28 (m, 8 H, 8 × Ph-CH), 1.65 (6 H, s, 2 × CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 136.9 (2 × Ph-CH), 132.5 (Ph-C_q-C_q), 131.5 (2 × Ph-CH), 129.1 (Ph-CH), 128.4 (2 × Ph-CH), 128.2 (2 × Ph-CH), 127.9 (Ph-CH), 123.2 (Ph-C_q-S), 93.9 (C_(alkyne)C(CH₃)₂), 83.3 (PhC_(alkyne)), 42.5 (C_q), 30.5 (2 × CH₃). HRMS (TOF-ASAP+) *m/z* calcd for C₁₇H₁₇S⁺ [M+H]⁺: 253.1051, Found: 253.1053.

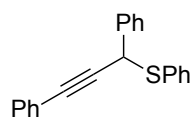
Phenyl(1-phenylethyl)sulfane (92f)



Lithium bis(trifluoromethanesulfonimide) (47.4 mg, 0.165 mmol) and tetrabutylammonium hexafluorophosphate (32.0 mg, 0.0825 mmol) were added to a solution of 1-phenylethan-1-ol (181 μL, 1.5 mmol) and thiophenol (0.31 mL, 3.0 mmol) in chloroform (3.0 mL). The reaction mixture was stirred at 40 °C for 25 min then quenched with sat. aq. NaHCO₃ (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (3 × 5 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (10% dichloromethane/pentane) afforded sulfide **92f** (227 mg, 71%) as a colourless oil. *R*_f = 0.25 (10% dichloromethane/pentane); IR (film)/cm⁻¹ 3059, 3028, 2924, 1739, 1492, 1480, 1451, 1438, 1372, 1217, 1025, 763, 739, 691; ¹H NMR (400 MHz, CDCl₃) δ 7.37–7.18 (m, 10 H, 10 × Ph-CH), 4.37 (q, *J* = 7.0 Hz, 1 H, CH), 1.66 (s, 3 H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 143.2 (Ph-C_q-C_q), 135.1 (Ph-C_q-S), 132.5 (2 × Ph-CH), 128.6 (2 × Ph-CH), 128.4 (2 × Ph-CH), 127.2 (2 × Ph-CH), 127.1 (2 × Ph-CH), 48.0 (CH), 22.3 (CH₃). The

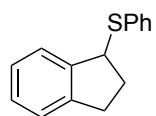
observed spectroscopic data for this compound was consistent with that previously reported.²⁵⁴

(1,3-Diphenylprop-2-yn-1-yl)(phenyl)sulfane (92g)



Lithium bis(trifluoromethanesulfonimide) (47.4 mg, 0.165 mmol) and tetrabutylammonium hexafluorophosphate (32.0 mg, 0.0825 mmol) were added to a solution of 1,3-diphenylprop-2-yn-1-ol (90% pure, 316 μ L, 1.5 mmol) and thiophenol (0.31 mL, 3.0 mmol) in chloroform (3.0 mL). The reaction mixture was stirred at 40 °C for 25 min then quenched with sat. aq. NaHCO_3 (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (3×5 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (2% Et_2O /pentane) afforded sulfide **92g** (403 mg, 84%) as a yellow oil. $R_f = 0.19$ (2% Et_2O /pentane); IR (film)/ cm^{-1} 3057, 2030, 1739, 1490, 1439, 1025, 753, 689; ^1H NMR (400 MHz, CDCl_3) δ 7.51–7.45 (m, 4 H, 4 $\times$ Ph-CH), 7.43–7.38 (m, 2 H, 2 $\times$ Ph-CH), 7.37–7.27 (m, 9 H, 9 $\times$ Ph-CH), 5.24 (1 H, s, CH); ^{13}C NMR (101 MHz, CDCl_3) δ 138.0 (Ph- C_q -S), 134.5 (2 $\times$ Ph-CH), 133.4 (Ph- C_q), 131.6 (2 $\times$ Ph-CH), 128.7 (2 $\times$ Ph-CH), 128.5 (2 $\times$ Ph-CH), 128.4 (Ph-CH), 128.3 (Ph-CH), 128.2 (2 $\times$ Ph-CH), 127.8 (2 $\times$ Ph-CH), 122.9 (Ph-CH), 87.3 ($\text{C}_{\text{(alkyne)}}$ CH), 86.9 (Ph $\text{C}_{\text{(alkyne)}}$), 44.3 (CH). The observed spectroscopic data for this compound was consistent with that previously reported.^{178a}

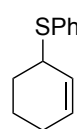
(2,3-Dihydro-1H-inden-1-yl)(phenyl)sulfane (92h)



Lithium bis(trifluoromethanesulfonimide) (47.4 mg, 0.165 mmol) and tetrabutylammonium hexafluorophosphate (32.0 mg, 0.0825 mmol) were added to a solution of 2,3-dihydro-1H-inden-1-ol (201.3 mg, 1.5 mmol) and thiophenol (0.31 mL, 3.0 mmol) in chloroform (3.0 mL). The reaction mixture was stirred at 40 °C for 25 min then quenched with sat. aq. NaHCO_3 (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (3×5 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (2% Et_2O /pentane) afforded sulfide **92h** (340 mg, 93%) as a white solid. $R_f = 0.25$ (2% Et_2O /pentane); mp = 29–31 °C; IR (film)/ cm^{-1} 3023, 2935, 2849, 1737, 1581, 1568, 1476, 1458, 1436, 1021, 756, 735, 699, 688; ^1H NMR (400 MHz, CDCl_3) δ 7.46–7.37 (m, 2 H, 2 $\times$ Ar-CH), 7.37–7.14 (m, 7 H, 7 $\times$ Ar-CH), 4.80 (dd, $J = 7.3, 4.0$ Hz, 1 H, CHSPh), 3.06 (dt, $J = 15.7, 7.8$ Hz, 1 H, Ar-CHH), 2.89 (ddd, $J = 15.7, 8.4, 4.3$ Hz, 1 H, Ar-CHH), 2.57 (ddt, $J = 13.4, 8.4, 7.3$ Hz, 1 H, CHHCH), 2.24 (ddt, $J = 13.4, 8.4, 4.0$ Hz, 1 H, CHHCH); ^{13}C NMR (101 MHz, CDCl_3) δ 143.8 (Ar- C_q -CH $_2$),

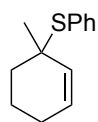
142.8 (Ar-C_q-CH), 136.0 (Ph-C_q-S), 131.3 (2 × Ph-CH), 128.8 (2 × Ph-CH), 127.7 (Ph-CH), 126.7 (Ar-CH), 126.5 (Ar-CH), 124.9 (Ar-CH), 124.7 (Ar-CH), 51.9 (CH), 33.6 (CH₂CH), 30.8 (Ar-CH₂). The observed spectroscopic data for this compound was consistent with that previously reported.²⁵⁵

Cyclohex-2-en-1-yl(phenyl)sulfane (92i)



Lithium bis(trifluoromethanesulfonimide) (47.4 mg, 0.165 mmol) and tetrabutylammonium hexafluorophosphate (32.0 mg, 0.0825 mmol) were added to a solution of cyclohex-2-en-1-ol (147 μL, 1.5 mmol) and thiophenol (0.31 mL, 3.0 mmol) in chloroform (3.0 mL). The reaction mixture was stirred at 40 °C for 25 min then quenched with sat. aq. NaHCO₃ (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (3 × 5 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 15 mL) then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (1% Et₂O/pentane) afforded sulfide **92i** (285 mg, 85%) as a colourless oil. *R*_f = 0.39 (1% Et₂O/pentane); IR (film)/cm⁻¹ 3026, 2935, 1739, 1479, 1438, 1204, 1089, 870, 723, 690, 736; ¹H NMR (400 MHz, CDCl₃) δ 7.47–7.42 (m, 2 H, 2 × Ph-CH), 7.35–7.28 (m, 2 H, 2 × Ph-CH), 7.27–7.21 (m, 1 H, Ph-CH), 5.91–5.84 (m, 1 H, CHCH=CH), 5.84–5.75 (m, 1 H, CHCH=CH), 3.96–3.82 (m, 1 H, CHCH=CH), 2.16–2.02 (m, 2 H, CH=CHCH₂), 2.02–1.86 (m, 2 H, CHCHHCH₂ + CHCH₂CHH), 1.86–1.74 (m, 1 H, CHCHHCH₂), 1.71–1.55 (m, 1 H, CHCH₂CHH); ¹³C NMR (101 MHz, CDCl₃) δ 135.8 (Ph-C_q-S), 131.2 (2 × Ph-CH), 130.4 (CH=CH), 128.8 (2 × Ph-CH), 126.8 (CH=CH), 126.5 (Ph-CH), 43.8 (CHCH=CH), 28.7 (CH=CHCH₂), 24.9 (CHCH₂CH₂), 19.4 (CHCH₂CH₂). The observed spectroscopic data for this compound was consistent with that previously reported.²⁵⁶

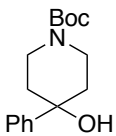
(1-Methylcyclohex-2-en-1-yl)(phenyl)sulfane (92j) and (3-methylcyclohex-2-en-1-yl)(phenyl)sulfane (92j')



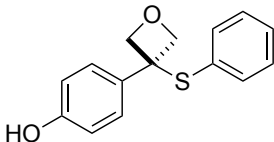
Lithium bis(trifluoromethanesulfonimide) (32 mg, 0.11 mmol) and tetrabutylammonium hexafluorophosphate (21 mg, 0.055 mmol) were added to a solution of alcohol **91j** (112 mg, 1.0 mmol) and benzenethiol (0.21 mL, 2.0 mmol) in chloroform (2.0 mL). The reaction mixture was stirred at 40 °C for 25 min then quenched with sat. aq. NaHCO₃ (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (3 × 5 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (2% EtOAc/hexane) afforded a mixture of sulfide **92j** (minor) and sulfide **92j'** (major) (169 mg, 83%) in a 1:5 ratio as a colourless oil. *R*_f = 0.28 (2% EtOAc/hexane); IR (film)/cm⁻¹ 2930, 1739, 1479, 1438, 873, 749, 736, 690; ¹H NMR (400 MHz, CDCl₃) δ

7.43–7.39 (m, 2 H, 2 × Ph-CH), 7.32–7.26 (m, 2 H, 2 × Ph-CH), 7.25–7.19 (m, 1 H, Ph-CH), 5.52 (dq, $J = 3.3, 1.6$ Hz, 1 H, $C_q=CH$), 3.90 (dt, $J = 5.4, 3.3, 1.6$ Hz, 1 H, CHSPh), 2.00–1.84 (m, 4 H, $C_qCH_2 + CH_2CHHCH_2 + CHHCH$), 1.78–1.73 (m, 1 H, CH_2CHHCH_2), 1.70 (s, 3 H, CH_3), 1.65–1.59 (m, 1 H, $CHHCH$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.3 ($CH=C_qCH_3$), 136.3 (Ph- C_q-S), 131.0 (2 × Ph-CH), 128.8 (2 × Ph-CH), 126.4 (Ph-CH), 121.0 ($CH=CCH_3$), 44.5 (CHSPh), 30.0 ($C_q(CH_3)CH_2$), 28.4 ($CH_2CH_2CH_2$), 23.9 (CH_3), 19.6 (CH_2CH); HRMS (CI^+) m/z calcd for $C_{13}H_{15}S^+$ [$M-2H+H$] $^+$: 203.0889, Found: 203.0893.

***tert*-Butyl 4-hydroxy-4-phenylpiperidine-1-carboxylate (94)**

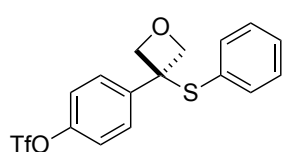
 *n*-BuLi (2.4 M in hexanes, 2.5 mL, 6.0 mmol) was added dropwise over 5 min to a solution of bromobenzene (0.69 mL, 6.5 mmol) in THF (20 mL) at -78 °C. The reaction mixture was stirred at -78 °C for a further 10 min. *tert*-Butyl-4-oxopiperidine-1-carboxylate (996 mg, 5.0 mmol) was added dropwise to the reaction mixture. Following a further 5 min at -78 °C the reaction mixture was warmed to rt then quenched with water (40 mL). The layers were separated and the aqueous portion extracted with diethylether (3 × 30 mL). The organic extracts were combined, washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (10% EtOAc/dichloromethane) afforded alcohol **94** (763 g, 55%) as a white solid. $R_f = 0.15$ (10% EtOAc/dichloromethane); mp = $118-120$ °C; IR (film)/ cm^{-1} 3451 (br. OH), 2947, 2929, 1737, 1667, 1366, 1354, 1219, 1166, 1137, 1099, 759, 699; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52–7.47 (m, 2 H, 2 × Ar-CH), 7.41–7.35 (m, 2 H, 2 × Ar-CH), 7.32–7.28 (m, 1 H, Ar-CH), 4.10–3.98 (m, 2 H, $CHHNCHH$), 3.32–3.18 (m, 2 H, $CHHNCHH$), 2.08–1.98 (m, 2 H, $CHHC_qCHH$), 1.78–1.70 (m, 2 H, $CHHC_qCHH$), 1.49 (s, 9 H, 3 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.9 (Ar- C_q-O), 148.0 (Ar- C_q-C_q), 128.5 (2 × Ar-CH), 127.2 (Ar-CH), 124.4 (2 × Ar-CH), 79.5 ($C(O)OC_q$), 71.5 (C_qOH), 39.9 (CH_2NCH_2), 38.1 ($CH_2C_qCH_2$), 28.5 (3 × CH_3); FTMS (+ p NSI) m/z calcd for $C_{16}H_{24}NO_3^+$ [$M+H$] $^+$: 278.1751, Found: 278.1755.

4-(3-(Phenylthio)oxetan-3-yl)phenol (95)

 TBAF (1 M in THF, 1.5 mL, 1.5 mmol) was added dropwise to a solution of oxetane sulfide **87** (415 mg, 1.0 mmol) in THF (3.3 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 3 h then quenched with sat. aq. NH_4Cl (15 mL). The layers were separated and the aqueous portion extracted with EtOAc (3 × 15 mL). The organic extracts were combined, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (50% Et₂O/pentane) afforded oxetane **95** (239 mg, 93%) as a white solid. $R_f = 0.27$ (50% Et₂O/pentane); mp = $169-171$ °C; IR (film)/ cm^{-1} 3269 (br. OH), 2940, 2879, 1515, 1438, 1209,

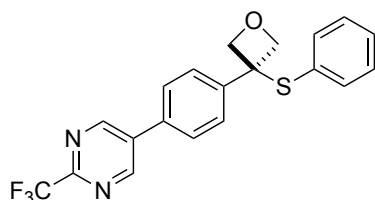
1170, 1108, 965, 825, 748, 691; ^1H NMR (400 MHz, CDCl_3) δ 7.34–7.29 (m, 1 H, Ph-CH), 7.27–7.18 (m, 4 H, 4 $\times$ Ph-CH), 6.93–6.87 (m, 2 H, 2 $\times$ Ar(p -OH)-CH), 6.77–6.71 (m, 2 H, 2 $\times$ Ar(p -OH)-CH), 5.13 (d, J = 6.4 Hz, 2 H, CHHOCHH), 4.98 (d, J = 6.4 Hz, 2 H, CHHOCHH), 4.93 (s, 1 H, OH); ^{13}C NMR (101 MHz, CDCl_3) δ 154.6 (Ar- C_q -OH), 135.3 (2 $\times$ Ph-CH), 134.9 (Ar- C_q - C_q), 132.0 (Ph- C_q -S), 128.77 (Ph-CH), 128.75 (2 $\times$ Ph-CH), 127.9 (2 $\times$ Ar(p -OH)-CH), 115.1 (2 $\times$ Ar(p -OH)-CH), 82.7 (CH_2OCH_2), 54.8 (C_q); HRMS (TOF-ASAP+) m/z calcd for $\text{C}_{15}\text{H}_{15}\text{SO}_2^+$ $[\text{M}+\text{H}]^+$: 259.0793, Found: 259.0793.

4-(3-(Phenylthio)oxetan-3-yl)phenyl trifluoromethanesulfonate (**96**)



Pyridine (0.13 mL, 1.6 mmol) then triflic anhydride (0.16 mL, 0.96 mmol) were added to a solution of oxetane **95** (207 mg, 0.8 mmol) in dichloromethane (1.6 mL). The reaction mixture was stirred at 25 °C for 3 h then water (15 mL) was added followed by dichloromethane (10 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 $\times$ 10 mL). The organic extracts were combined, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% Et_2O /pentane) afforded oxetane **96** (287 mg, 92%) as a white solid. R_f = 0.42 (30% Et_2O /pentane); mp = 58–60 °C; IR (film)/ cm^{-1} 2957, 2884, 1501, 1419, 1249, 1229, 1214, 1202, 1140, 1130, 987, 884, 840, 829, 749, 693; ^1H NMR (400 MHz, CDCl_3) δ 7.36–7.30 (m, 1 H, Ph-CH), 7.26–7.20 (m, 2 H, 2 $\times$ Ph-CH), 7.19–7.11 (m, 4 H, 2 $\times$ Ph-CH + 2 $\times$ Ar(p -OTf)-CH), 7.03–6.99 (m, 2 H, 2 $\times$ Ar(p -OTf)-CH), 5.14 (d, J = 6.6 Hz, 2 H, CHHOCHH), 5.02 (d, J = 6.6 Hz, 2 H, CHHOCHH); ^{13}C NMR (101 MHz, CDCl_3) δ 148.2 (Ar- C_q - C_q), 143.3 (Ar- C_q -OTf), 135.5 (2 $\times$ Ph-CH), 131.0 (Ph- C_q -S), 129.3 (Ph-CH), 129.0 (2 $\times$ Ar-CH), 128.3 (2 $\times$ Ar-CH), 121.1 (2 $\times$ Ar-CH), 118.7 (q, $J_{\text{C-F}}$ = 320.0 Hz, CF_3), 82.2 (CH_2OCH_2), 54.6 (C_q); ^{19}F NMR (377 MHz, CDCl_3) δ -72.7; HRMS (TOP-ASAP+) m/z calcd for $\text{C}_{16}\text{H}_{14}\text{F}_3\text{O}_4\text{S}_2^+$ $[\text{M}+\text{H}]^+$: 391.0286, Found: 391.0283.

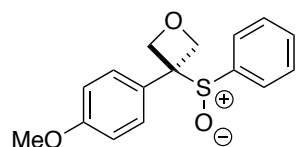
5-(4-(3-(Phenylthio)oxetan-3-yl)phenyl)-2-(trifluoromethyl)pyrimidine (**97**)



Oxetane **96** (98 mg, 0.25 mmol), 5-(4,4,5,5-tetramethyl 1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl) pyrimidine (91 mg, 0.33 mmol), $\text{Pd}(\text{OAc})_2$ (2.8 mg, 0.0125 mmol), SPhos (10.2 mg, 0.025 mmol) and K_3PO_4 (106 mg, 0.5 mmol) were added to a reaction vial. The reaction vial was evacuated and then refilled with nitrogen ($\times$ 3). Degassed dioxane/water (4:1, 2.5 mL) was added *via* syringe. The reaction mixture was stirred at 65 °C for 18 h then cooled to rt. Diethylether (15 mL) was added and the crude mixture was filtered through celite[®] and then concentrated *in vacuo*.

Purification by flash column chromatography (30% Et₂O/pentane) afforded oxetane **97** (92 mg, 95%) as a white solid. R_f = 0.15 (30% Et₂O/pentane); mp = 110–112 °C; IR (film)/cm⁻¹ 3053, 2950, 2865, 1357, 1185, 1138, 1118, 986, 829, 748, 692; ¹H NMR (400 MHz, CDCl₃) δ 9.10 (s, 2 H, 2 × Ar_(pyridyl)-CH), 7.59–7.54 (m, 2 H, 2 × Ar-CH), 7.38–7.31 (m, 1 H, Ph-CH), 7.30–7.19 (m, 6 H, 6 × Ar-CH), 5.19 (d, J = 6.5 Hz, 2 H, CHHOCHH), 5.07 (d, J = 6.5 Hz, 2 H, CHHOCHH); ¹³C NMR (101 MHz, CDCl₃) δ 155.6 (2 × Ar_(pyridyl)-CH), 155.4 (q, J_{CF} = 36.8 Hz, Ar_(pyridyl)-C_q-CF₃), 144.7 (Ar-C_q-C_q), 135.4 (Ar-C_q-C_q), 135.2 (2 × Ph-CH), 131.0 (Ph-C_q-S), 131.4 (Ar-C_q-C_q), 129.1 (Ph-CH), 128.9 (2 × Ph-CH), 127.8 (2 × Ar-CH), 127.1 (2 × Ar-CH), 119.6 (q, J_{CF} = 275.2 Hz, CF₃), 82.2 (CH₂OCH₂), 54.7 (C_q); ¹⁹F NMR (377 MHz, CDCl₃) δ -70.1; FTMS (+ p NSI) m/z calcd for C₂₀H₁₆F₃OSN₂⁺ [M+H]⁺: 389.0930, Found: 389.0931.

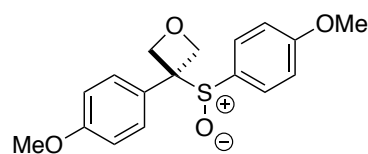
3-(4-Methoxyphenyl)-3-(phenylsulfinyl)oxetane (98a)



m-CPBA (45.3 mg, 0.26 mmol) was added in 3 portions over 30 min to a solution of 3-(4-methoxyphenyl)-3-(phenylsulfonyl)oxetane **85a** (68.1 mg, 0.25 mmol) in dichloromethane (2.5 mL). The reaction mixture was stirred at 0 °C for 2.5 h then aq. KOH (3 M, 5 mL) was added.

The layers were separated and the aqueous portion extracted with dichloromethane (5 × 5 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (70% EtOAc/pentane) afforded sulfoxide **98a** (67 mg, 93%) as a white solid; R_f = 0.21 (70% EtOAc/pentane); mp = 85–87 °C; IR (film)/cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.46–7.40 (m, 1 H, 1 × Ph-CH), 7.33–7.27 (m, 2 H, 2 × Ph-CH), 7.05–6.99 (m, 2 H, 2 × Ph-CH), 6.83–6.78 (m, 2 H, 2 × Ar_(p-OMe)-CH), 6.61–6.55 (m, 2 H, 2 × Ar_(p-OMe)-CH), 5.37 (d, J = 7.1 Hz, 1 H, CHHOCH₂), 5.33 (d, J = 7.1 Hz, 1 H, CHHOCH₂), 5.00 (d, J = 7.1 Hz, 1 H, CH₂OCHH), 4.87 (d, J = 7.1 Hz, 1 H, CH₂OCHH), 3.82 (s, 3 H, OCH₃); ¹³C NMR (101 MHz, CDCl₃) δ 159.7 (Ar-C_q-OMe), 138.7 (Ph-C_q-SO), 131.5 (Ph-CH), 129.0 (2 × Ar_(p-OMe)-CH), 128.2 (2 × Ph-CH), 126.2 (Ar-C_q-C_q), 125.4 (2 × Ph-CH), 113.7 (2 × Ar_(p-OMe)-CH), 73.5 (CH₂OCH₂), 67.3 (C_q), 55.3 (OCH₃); HRMS (TOF-ASAP+) m/z calcd for C₁₆H₁₇SO₃⁺ [M+H]⁺: 289.0898, Found: 289.0895.

3-(4-Methoxybenzenesulfinyl)-3-(4-methoxyphenyl)oxetane (98d)

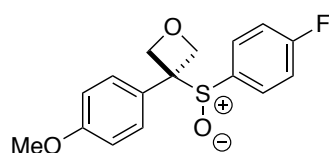


m-CPBA (90.6 mg, 0.525 mmol) was added in 3 portions over 30 min to a solution of 3-(4-methoxyphenyl)-3-[(4-methoxyphenyl)sulfonyl]oxetane **85d** (151.2 mg, 0.5 mmol) in dichloromethane (5.0 mL). The reaction mixture

was stirred at 0 °C for 2.5 h then aq. KOH (3 M, 10 mL) was added. The layers were separated and the aqueous portion extracted with dichloromethane (5 × 10 mL). The organic extracts

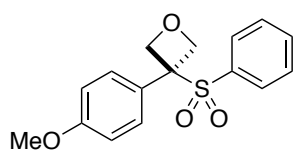
were combined, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (70% EtOAc/pentane) afforded sulfoxide **98d** (131 mg, 82%) as a white solid; R_f = 0.07 (70% Et₂O/pentane); mp = 130–132 °C; IR (film)/cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.98–6.92 (m, 2 H, 2 × Ar-CH), 6.85–6.78 (m, 4 H, 4 × Ar-CH), 6.62–6.57 (m, 2 H, 2 × Ar-CH), 5.36 (d, J = 7.0 Hz, 1 H, CHHOCH₂), 5.28 (d, J = 7.0 Hz, 1 H, CHHOCH₂), 4.99 (d, J = 7.0 Hz, 1 H, CH₂OCHH), 4.88 (d, J = 7.0 Hz, 1 H, CH₂OCHH), 3.83 (s, 3 H, OCH₃), 3.81 (s, 3 H, OCH₃); ¹³C NMR (101 MHz, CDCl₃) δ 162.3 (Ar-C_q-OMe), 159.6 (Ar-C_q-OMe), 129.4 (Ar-C_q-SO), 129.0 (2 × Ar-CH), 127.2 (2 × Ar-CH), 126.3 (Ar-C_q-C_q), 113.8 (2 × Ar-CH), 113.6 (2 × Ar-CH), 73.7 (CH₂OCH₂), 67.2 (C_q), 55.44 (OCH₃), 55.35 (OCH₃); HRMS (TOF-ASAP+) m/z calcd for C₁₇H₁₉SO₄⁺ [M+H]⁺: 319.1004, Found: 319.0998.

3-(4-Fluorobenzenesulfinyl)-3-(4-methoxyphenyl)oxetane (**98f**)



m-CPBA (90.6 mg, 0.525 mmol) was added in 3 portions over 30 min to a solution of 3-[(4-fluorophenyl)sulfonyl]-3-(4-methoxyphenyl)oxetane **85f** (145.2 mg, 0.5 mmol) in dichloromethane (5.0 mL). The reaction mixture was stirred at 0 °C for 2.5 h then aq. KOH (3 M, 10 mL) was added. The layers were separated and the aqueous portion extracted with dichloromethane (5 × 10 mL). The organic extracts were combined, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (70% EtOAc/pentane) afforded sulfoxide **98f** (131 mg, 82%) as a white solid; R_f = 0.12 (70% Et₂O/pentane); mp = 95–97 °C; IR (film)/cm⁻¹ 2938, 2875, 1609, 1586, 1513, 1488, 1253, 1223, 1179, 1160, 1042 (strong, SO stretch), 1023, 994, 838, 825, 813, 800; ¹H NMR (400 MHz, CDCl₃) δ 7.04–6.99 (m, 4 H, 4 × Ar_(p-F)-CH), 6.87–6.82 (m, 2 H, 2 × Ar_(p-OMe)-CH), 6.64–6.58 (m, 2 H, 2 × Ar_(p-OMe)-CH), 5.35 (d, J = 7.2 Hz, 1 H, CHHOCH₂), 5.31 (d, J = 7.2 Hz, 1 H, CHHOCH₂), 5.01 (d, J = 7.2 Hz, 1 H, CH₂OCHH), 4.90 (d, J = 7.2 Hz, 1 H, CH₂OCHH), 3.84 (s, 3 H, OCH₃); ¹³C NMR (101 MHz, CDCl₃) δ 164.7 (d, J = 252.5 Hz, Ar-C_q-F), 159.8 (Ar-C_q-OMe), 134.2 (d, J = 2.8 Hz, Ar-C_q-SO), 129.0 (2 × Ar_(p-OMe)-CH), 127.7 (d, J = 8.9 Hz, 2 × Ar_(p-F)-CH), 125.9 (Ar-C_q-C_q), 115.6 (d, J = 22.6 Hz, 2 × Ar_(p-F)-CH), 113.8 (2 × Ar_(p-OMe)-CH), 73.3 (CH₂OCH₂), 67.4 (C_q), 55.4 (OCH₃); ¹⁹F NMR (377 MHz, CDCl₃) δ -107.5; HRMS (TOF-ASAP+) m/z calcd for C₁₆H₁₆SO₃F⁺ [M+H]⁺: 307.0804, Found: 307.0796.

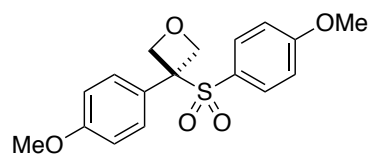
3-(4-Methoxyphenyl)-3-(phenylsulfonyl)oxetane (**99a**)



m-CPBA (129.4 mg, 0.75 mmol) was added to a solution of 3-(4-methoxyphenyl)-3-(phenylsulfonyl)oxetane **85a** (68.1 mg, 0.25 mmol) in dichloromethane (12.5 mL). The reaction mixture was stirred at 25 °C for 3 h then aq. KOH (3 M, 5 mL) was added. The

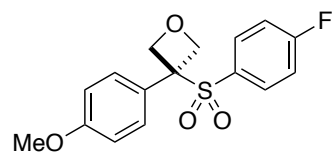
layers were separated and the aqueous portion extracted with dichloromethane (4 × 5 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (55% Et₂O/pentane) afforded sulfone **99a** (61 mg, 80%) as a white solid; *R_f* = 0.19 (55% Et₂O/pentane); mp = 145–148 °C; IR (film)/cm⁻¹ 2962, 1719, 1615; 1516, 1447, 1303 (S-O), 1265, 1173, 1146 (S-O), 1019, 980, 928, 766, 724, 692; ¹H NMR (400 MHz, CDCl₃) δ 7.63–7.57 (m, 1 H, Ph-CH), 7.46–7.38 (m, 4 H, 4 × Ph-CH), 6.81–6.74 (m, 4 H, 4 × Ar-CH), 5.20 (d, *J* = 7.0 Hz, 2 H, CHHOCHH), 5.04 (d, *J* = 7.0 Hz, 2 H, CHHOCHH), 3.82 (s, 3 H, OCH₃); ¹³C NMR (101 MHz, CDCl₃) δ 159.9 (Ar-C_q-OMe), 134.8 (Ph-C_q-SO₂), 134.0 (Ph-CH), 129.73 (2 × Ar-CH), 129.68 (2 × Ar-CH), 128.7 (2 × Ar-CH), 126.5 (Ar-C_q-C_q), 113.7 (2 × Ar-(*p*-OMe)-CH), 76.6 (CH₂OCH₂), 69.2 (C_q), 55.3 (OCH₃); HRMS (TOF-ASAP+) *m/z* calcd for C₁₆H₂₀NSO₄⁺ [M+NH₄]⁺: 322.1113, Found: 322.1108.

3-(4-Methoxyphenyl)-3-((4-methoxyphenyl)sulfonyl)oxetane (**99d**)



m-CPBA (129.4 mg, 0.75 mmol) was added to a solution of 3-[(4-methoxyphenyl)-3-[(4-methoxyphenyl)sulfonyl]oxetane **85d** (75.6 mg, 0.25 mmol) in dichloromethane (12.5 mL). The reaction mixture was stirred at 25 °C for 3 h then aq. KOH (3 M, 5 mL) was added. The layers were separated and the aqueous portion extracted with dichloromethane (4 × 5 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (70% Et₂O/pentane) afforded sulfone **99d** (68 mg, 81%) as a white solid; *R_f* = 0.11 (55% Et₂O/pentane); mp = 158–160 °C; IR (film)/cm⁻¹ 2961, 1720, 1514, 1297 (S-O), 1257, 1138 (S-O), 1111, 1025, 825, 800, 725, 660; ¹H NMR (400 MHz, CDCl₃) δ 7.37–7.33 (m, 2 H, 2 × Ar-CH), 6.87–6.83 (m, 2 H, 2 × Ar-CH), 6.83–6.77 (m, 4 H, 4 × Ar-CH), 5.46 (d, *J* = 6.9 Hz, 2 H, CHHOCHH), 5.02 (d, *J* = 6.9 Hz, 2 H, CHHOCHH), 3.86 (s, 3 H, OCH₃), 3.82 (s, 3 H, OCH₃); ¹³C NMR (101 MHz, CDCl₃) δ 164.1 (Ar-(*p*-S)-C_q-OMe), 159.8 (Ar-C_q-OMe), 131.9 (2 × Ar-CH), 129.7 (2 × Ar-CH), 126.8 (Ar-C_q-C_q), 126.2 (Ar-C_q-SO₂), 113.9 (2 × Ar-CH), 113.6 (2 × Ar-CH), 76.7 (CH₂OCH₂), 69.1 (C_q), 55.7 (OCH₃), 55.4 (OCH₃); HRMS (TOF-ASAP+) *m/z* calcd for C₁₇H₂₂NSO₅⁺ [M+NH₄]⁺: 352.1219, Found: 352.1215.

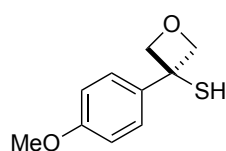
3-((4-Fluorophenyl)sulfonyl)-3-(4-methoxyphenyl)oxetane (**99f**)



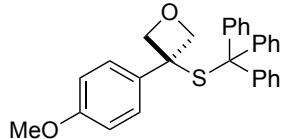
m-CPBA (129.4 mg, 0.75 mmol) was added to a solution of 3-[(4-fluorophenyl)sulfonyl]-3-(4-methoxyphenyl)oxetane **85f** (75.6 mg, 0.25 mmol) in dichloromethane (12.5 mL). The reaction mixture was stirred at 25 °C for 3 h then aq. KOH (3 M, 5 mL) was added. The layers were separated and the aqueous portion extracted with dichloromethane (4 ×

5 mL). The organic extracts were combined, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (70% Et_2O /pentane) afforded sulfone **99f** (68 mg, 81%) as a white solid; $R_f = 0.11$ (55% Et_2O /pentane); mp = 129–130 °C; IR (film)/ cm^{-1} 2953, 1740, 1588, 1291 (S-O), 1251, 1227, 1146 (S-O), 832, 722, 664; ^1H NMR (400 MHz, CDCl_3) δ 7.47–7.40 (m, 2 H, $2 \times \text{Ar}_{(\text{p-F})}\text{-CH}$), 7.11–7.04 (m, 2 H, $2 \times \text{Ar}_{(\text{p-F})}\text{-CH}$), 6.83–6.76 (m, 4 H, $4 \times \text{Ar}_{(\text{p-OMe})}\text{-CH}$), 5.47 (d, $J = 7.0$ Hz, 2 H, CHHOCHH), 5.04 (d, $J = 7.0$ Hz, 2 H, CHHOCHH), 3.82 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 166.1 (d, $J = 257.6$ Hz, $\text{Ar-C}_q\text{-F}$), 160.0 ($\text{Ar-C}_q\text{-OMe}$), 132.5 (d, $J = 9.6$ Hz, $2 \times \text{Ar}_{(\text{p-F})}\text{-CH}$), 130.8 (d, $J = 3.4$ Hz, $\text{Ar-C}_q\text{-SO}_2$), 129.7 ($2 \times \text{Ar}_{(\text{p-OMe})}\text{-CH}$), 126.3 ($\text{Ar-C}_q\text{-C}_q$), 116.2 (d, $J = 22.6$ Hz, $2 \times \text{Ar}_{(\text{p-F})}\text{-CH}$), 113.8 ($2 \times \text{Ar}_{(\text{p-OMe})}\text{-CH}$), 76.6 (CH_2OCH_2), 69.3 (C_q), 55.4 (OCH_3); ^{19}F NMR (377 MHz, CDCl_3) δ -102.4; HRMS (TOF-ASAP+) m/z calcd for $\text{C}_{16}\text{H}_{19}\text{NSFO}_4^+ [\text{M}+\text{NH}_4]^+$: 340.1019, Found: 340.1019.

3-(4-Methoxyphenyl)oxetane-3-thiol (**101**)



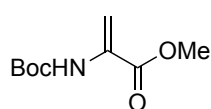
Lithium bis(trifluoromethanesulfonimide) (15.8 mg, 0.055 mmol) and tetrabutylammonium hexafluorophosphate (10.6 mg, 0.028 mmol) were added to a solution of oxetanol **44** (90.1 mg, 0.50 mmol) and triphenylmethanethiol (691 mg, 2.5 mmol) in chloroform (1.0 mL). The reaction mixture was stirred at 40 °C for 30 minutes then cooled to 20 °C. Dichloromethane (1.5 mL), triethylsilane (0.16 μL , 1.0 mmol) then trifluoroacetic acid (0.23 mL, 3.0 mmol) were added dropwise. The reaction mixture was stirred at 20 °C for 30 min then quenched with sat. aq. NaHCO_3 (20 mL). The aqueous portion extracted with dichloromethane (3×10 mL). The organic extracts were combined then dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (15% Et_2O /pentane) afforded thiol **101** (52 mg, 53%) as a white solid; $R_f = 0.21$ (15% Et_2O /pentane); mp = 59–61 °C; IR (film)/ cm^{-1} 2966, 2884, 2544, 1610, 1513, 1458, 1297, 1245, 1179, 1024, 974, 949, 840, 818, 799; ^1H NMR (400 MHz, CDCl_3) δ 7.25–7.20 (m, 2 H, $2 \times \text{Ar-CH}$), 6.94–6.89 (m, 2 H, $2 \times \text{Ar-CH}$), 5.25 (d, $J = 6.4$ Hz, 2 H, CHHOCHH), 4.95 (d, $J = 6.4$ Hz, 2 H, CHHOCHH), 3.83 (s, 3 H, OCH_3), 2.81 (s, 1 H, SH); ^{13}C NMR (101 MHz, CDCl_3) δ 158.8 ($\text{Ar-C}_q\text{-OMe}$), 135.9 ($\text{Ar-C}_q\text{-C}_q$), 126.7 ($2 \times \text{Ar-CH}$), 114.1 ($2 \times \text{Ar-CH}$), 86.7 (CH_2OCH_2), 55.3 (OCH_3), 49.2 (C_q); HRMS (TOF ASAP+) m/z calcd for $\text{C}_{10}\text{H}_{11}\text{SO}^+ [\text{M}-\text{H}_2\text{O}+\text{H}]^+$: 179.0531, Found: 179.0535.



Intermediate 3-(4-methoxyphenyl)-3-(tritylthio)oxetane **102**: mp = 134–136 °C; IR (film)/ cm^{-1} 2930, 1509, 1488, 1443, 1305, 1242, 1178, 1029, 983, 773, 745, 706, 698, 676; ^1H NMR (400 MHz, CDCl_3) δ 7.44–7.38 (m, 6 H, $6 \times \text{Ph-CH}$), 7.26–7.12 (m, 9 H, $9 \times \text{Ph-CH}$),

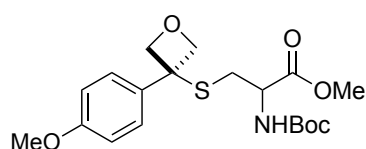
7.00–6.94 (m, 2 H, 2 × Ar_(p-OMe)-CH), 6.77–6.72 (m, 2 H, 2 × Ar_(p-OMe)-CH), 4.64 (d, J = 6.4 Hz, 2 H, CHHOCHH), 4.43 (d, J = 6.4 Hz, 2 H, CHHOCHH), 3.79 (s, 3 H, OCH₃); ¹³C NMR (101 MHz, CDCl₃) δ 158.4 (Ar-C_q-OMe), 144.1 (3 × Ph-C_q), 136.0 (Ar_(p-OMe)-C_q-C_q), 129.7 (6 × Ph-CH), 128.0 (2 × Ar_(p-OMe)-CH), 127.7 (6 × Ph-CH), 126.6 (3 × Ph-CH), 113.6 (2 × Ar_(p-OMe)-CH), 82.1 (CH₂OCH₂), 68.8 (S-C_q-C_q), 55.4 (OCH₃), 54.7 (C_q(oxetane)); HRMS (TOF-ASAP+) m/z calcd for C₂₉H₂₇SO₂⁺ [M+H]⁺: 439.1732, Found: 439.1729.

Methyl 2-((*tert*-butoxycarbonyl)amino)acrylate (**105**)



MsCl (0.77 mL, 10 mmol) was added dropwise to a solution of methyl (*tert*-butoxycarbonyl)serinate (1.01 g, 5 mmol), triethylamine (2.8 mL, 20 mmol) in dichloromethane (30 mL). The reaction mixture was stirred at 25 °C for 3 h then quenched with sat. aq. NaHCO₃ (20 mL). The layers were separated and the aqueous portion extracted with dichloromethane (3 × 15 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (15% Et₂O/pentane) afforded acrylate **105** (950 mg, 94%) as a pale yellow oil. R_f = 0.49 (15% Et₂O/pentane); IR (film)/cm⁻¹ 3424, 2980, 1714 (C=O), 1508, 1440, 1368, 1238, 1202, 1323, 1154, 1065, 884; ¹H NMR (400 MHz, CDCl₃) δ 7.02 (s, 1 H, NH), 6.16 (s, 1 H, CHH), 5.73 (d, J = 1.5 Hz, 1 H, CHH), 3.84 (s, 3 H, OCH₃), 1.49 (s, 9 H, C(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ 164.4 (C(O)OMe), 152.5 (C(O)C(CH₃)₃), 131.3 (C=CH₂), 105.2 (C=CH₂), 80.7 (C(CH₃)₃), 52.9 (OCH₃), 28.2 (C(CH₃)₃). The observed spectroscopic data for this compound was consistent with that previously reported.²⁵⁷

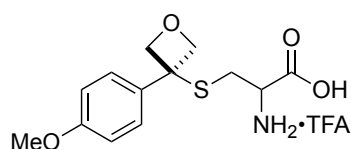
Methyl *N*-((*tert*-butoxycarbonyl)-S-(3-(4-methoxyphenyl)oxetan-3-yl)cysteinate (**106**)



Methyl 2-((*tert*-butoxycarbonyl)amino)acrylate **105** (121 mg, 0.6 mmol) was added to a stirring solution of thiol **101** (98 mg, 0.5 mmol) and triethylamine (209 μL, 1.5 mmol) in methanol (2.0 mL). The reaction mixture was stirred at 25 °C for 90 minutes then quenched with sat. aq. NH₄Cl (10 mL). The aqueous portion was extracted with EtOAc (3 × 15 mL). The organic portions were combined, washed with water (25 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (50% Et₂O/pentane) afforded oxetane **106** (190 mg, 100%) as a colourless oil; R_f = 0.22 (50% Et₂O/pentane); IR (film)/cm⁻¹ 2953, 1745 (C=O), 1709 (C=O), 1513, 1246, 1162, 909, 729; ¹H NMR (400 MHz, CDCl₃) δ 7.17–7.11 (m, 2 H, 2 × Ar-CH), 6.94–6.89 (m, 2 H, 2 × Ar-CH), 5.21–5.16 (m, 3 H, CHHOCHH + NH), 4.88 (dd, J = 6.4, 4.2 Hz, 2 H, CHHOCHH), 4.51–4.41 (m, 1 H, SCH₂CH), 3.84 (s, 3 H, ArOCH₃), 3.74 (s, 3 H, C(O)OCH₃), 2.85 (dd, J = 13.2, 5.0 Hz, 1 H, SCHH), 2.80 (dd, J = 13.2, 5.6 Hz, 1 H, SCHH), 1.46 (s, 9 H,

$C(CH_3)_3$; ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.6 ($C(O)OC(CH_3)_3$), 171.2 ($C(O)OMe$), 158.8 ($Ar-C_q-OMe$), 133.8 ($Ar-C_q-C_q$), 127.6 ($2 \times Ar-CH$), 114.0 ($2 \times Ar-CH$), 83.1 (CH_2OCH_2), 80.3 ($C(CH_3)_3$), 55.3 ($ArOCH_3$), 53.0 (SCH_2CH), 52.6 ($C(O)OCH_3$), 52.2 (C_q), 32.7 (SCH_2), 28.3 ($C(CH_3)_3$); FTMS (+ p NSI) m/z calcd for $C_{19}H_{31}N_2O_6S^+$ $[M+NH_4]^+$: 415.1897, Found: 415.1898.

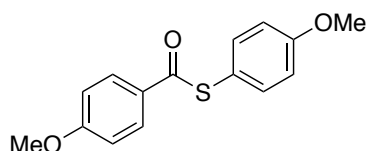
S-(3-(4-Methoxyphenyl)oxetan-3-yl)cysteine trifluoroacetate salt (**107**)



Methyl *N*-(*tert*-butoxycarbonyl)-*S*-(3-(4-methoxyphenyl)-oxetan-3-yl)cysteinate **106** (99 mg, 0.25 mmol) and lithium hydroxide monohydrate (12 mg, 0.275 mmol) in MeCN (1.25 mL) and water (1.25 mL) was stirred at 25 °C for 16 h. Water (10 mL) was

added and the aqueous layer washed with EtOAc (2×10 mL). The aqueous layer was acidified to pH 2 with 4 M HCl and the product was extracted with EtOAc (3×10 mL). The organic extracts were combined then dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude product was then dissolved in dichloromethane (1 mL) and trifluoroacetic acid (0.19 mL, 2.5 mmol) was added. The reaction mixture was stirred at 25 °C for 2 h then concentrated *in vacuo* to afford oxetane **107** (52 mg, 52%) as a beige solid. IR (film)/ cm^{-1} 2953 (br. OH), 1737 (C=O), 1667, 1610, 1513, 1247, 1178, 1134, 830, 796, 721; ^1H NMR (400 MHz, CD_3OD) δ 7.26–7.20 (m, 2 H, $2 \times Ar-CH$), 6.99–6.96 (m, 2 H, $2 \times Ar-CH$), 5.26 (d, $J = 6.8$ Hz, 1 H, $CHHOCH_2$), 5.18 (d, $J = 6.8$ Hz, 1 H, CH_2OCHH), 4.91 (dd, $J = 6.7, 2.1$ Hz, 2 H, $CHHOCHH$), 3.82 (s, 3 H, OCH_3), 3.74 (dd, $J = 7.8, 4.3$ Hz, 1 H, SCH_2CH), 3.05 (dd, $J = 14.3, 4.4$ Hz, 1 H, $SCHH$), 2.91 (dd, $J = 14.3, 7.9$ Hz, 1 H, $SCHH$); ^{13}C NMR (101 MHz, CD_3OD) δ 168.7 ($C(O)OH$), 161.2 (q, $J_{C-F} = 34.7$ Hz, $C(O)CF_3$), 159.2 ($Ar-C_q-OMe$), 133.4 ($Ar-C_q-C_q$), 127.6 ($2 \times Ar-CH$), 116.5 (q, $J_{C-F} = 285.4$ Hz, $C(O)CF_3$), 113.9 ($2 \times Ar-CH$), 82.9 (CH_2OCH_2), 82.8 (CH_2OCH_2), 54.4 ($ArOCH_3$), 52.5 (SCH_2CH), 52.1 (C_q), 30.0 (SCH_2); FTMS (+ p NSI) m/z calcd for $C_{13}H_{17}NO_4SNa^+$ $[M+Na]^+$: 306.0769, Found: 306.0770.

S-(4-Methoxyphenyl) 4-methoxybenzothioate (**108**)

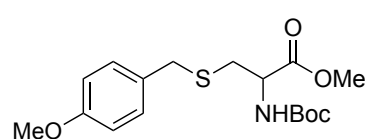


4-Methoxybenzoyl chloride (256 mg, 1.5 mmol) in MeCN (2 mL) then pyridine (0.24 mL, 3 mmol) were added dropwise to a solution of 4-methoxythiophenol (0.18 mL, 1.5 mmol) in MeCN (3.0 mL) at 0 °C. The reaction mixture was stirred at 25 °C for

2 h then concentrated *in vacuo*. Water (10 mL) was added and the product was extracted with EtOAc (2×10 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 10 mL), water (10 mL) and brine (10 mL) then dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (30% Et_2O /pentane) afforded thioester **108** (342 mg, 83%) as a white solid. $R_f = 0.30$ (20% Et_2O /pentane); mp = 133–135 °C; IR (film)/ cm^{-1}

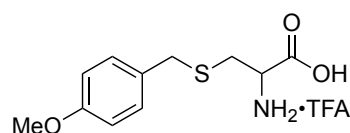
2969, 1662 (C=O), 1593, 1251, 1213, 1166, 1023, 905, 824, 792; ^1H NMR (400 MHz, CDCl_3) δ 8.03–7.98 (m, 2 H, 2 $\times$ Ar-CH), 7.44–7.39 (m, 2 H, 2 $\times$ Ar-CH), 7.03–6.94 (m, 4 H, 4 $\times$ Ar-CH), 3.89 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 188.9 (C=O), 163.9 (Ar- C_q -C(O)S), 160.6 (2 $\times$ Ar- C_q -OMe), 136.7 (2 $\times$ Ar(p -OMe)-CH), 129.7 (2 $\times$ Ar(p -OMe)-CH), 129.5 (Ar- C_q -S), 114.9 (2 $\times$ Ar(p -OMe)-CH), 113.9 (2 $\times$ Ar(p -OMe)-CH), 55.5 (OCH_3), 55.4 (OCH_3); HRMS (TOF-ASAP+) m/z calcd for $\text{C}_{15}\text{H}_{15}\text{SO}_3^+$ $[\text{M}+\text{H}]^+$: 275.0742, Found: 275.0742.

Methyl *N*-(*tert*-butoxycarbonyl)-*S*-(4-methoxybenzyl)cysteinate (**109**)



Methyl 2-((*tert*-butoxycarbonyl)amino)acrylate (604 mg, 3.0 mmol) was added to a stirring solution of 4-Methoxybenzyl mercaptan (0.35 mL, 2.5 mmol) and triethylamine (1.0 μL , 7.5 mmol) in methanol (10 mL). The reaction mixture was stirred at 25 $^\circ\text{C}$ for 90 min then quenched with sat. aq. NH_4Cl (50 mL). The aqueous portion was extracted with EtOAc (3 $\times$ 50 mL). The organic portions were combined, washed with water (50 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (40% Et_2O /pentane) afforded methyl *N*-(*tert*-butoxycarbonyl)-*S*-(4-methoxybenzyl)cysteinate **109** (660 mg, 74%) as a white solid; R_f = 0.30 (40% Et_2O /pentane); mp = 81–83 $^\circ\text{C}$; IR (film)/ cm^{-1} 3366 (NH), 2971, 1732 (C=O), 1680 (C=O), 1512, 1234, 1293, 1249, 1163, 1031, 1011, 832, 824; ^1H NMR (400 MHz, CDCl_3) δ 7.26–7.20 (m, 2 H, 2 $\times$ Ar-CH), 6.89–6.83 (m, 2 H, 2 $\times$ Ar-CH), 5.30 (d, J = 8.1 Hz, 1 H, NH), 4.56 (m, 1 H, CHNH), 3.82 (s, 3 H, ArOCH_3), 3.77 (s, 3 H, C(O)OCH_3), 3.70 (Ar- CH_2S), 2.70 (m, 2 H, SCH_2CH), 1.48 (s, 9 H, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (101 MHz, CDCl_3) δ 171.6 (C(O)OMe), 158.8 (Ar- C_q -OMe), 155.0 ($\text{C(O)OC}(\text{CH}_3)_3$), 130.0 (2 $\times$ Ar-CH) 129.6 (Ar- C_q - C_q), 114.0 (2 $\times$ Ar-CH), 80.1 ($\text{C}(\text{CH}_3)_3$), 55.3 (ArOCH_3), 53.1 (SCH_2CH), 52.5 (C(O)OCH_3), 36.0 (Ar- CH_2S), 33.5 (SCH_2CH), 28.3 ($\text{C}(\text{CH}_3)_3$); FTMS (+ p NSI) m/z calcd for $\text{C}_{17}\text{H}_{26}\text{NO}_5\text{S}^+$ $[\text{M}+\text{H}]^+$: 356.1526, Found: 356.1530.

S-(4-Methoxybenzyl)cysteine trifluoroacetate salt (**110**)

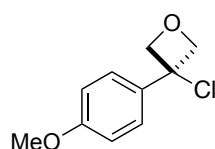


Methyl *N*-(*tert*-butoxycarbonyl)-*S*-(4-methoxybenzyl)-cysteinate **109** (356 mg, 1.0 mmol) and lithium hydroxide monohydrate (46 mg, 1.1 mmol) in MeCN (5 mL) and water (5 mL) was stirred at 25 $^\circ\text{C}$ for 16 h. Water (15 mL) was added and the aqueous layer washed with EtOAc (2 $\times$ 15 mL). The aqueous layer was acidified to pH 2 with 4 M HCl and the product was extracted with EtOAc (3 $\times$ 15 mL). The organic extracts were combined then dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude product was then dissolved in dichloromethane (4 mL) and trifluoroacetic acid (0.77 mL, 10 mmol) was added. The reaction mixture was stirred at 25 $^\circ\text{C}$ for 2 h then concentrated *in vacuo* to afford cysteine derivative **110** (305 mg, 86%) as

a white solid. IR (film)/cm⁻¹ 2906 (br. OH), 1744 (C=O), 1654, 1612, 1512, 1431, 1135, 1243, 1032, 819; ¹H NMR (400 MHz, CD₃OD) δ 7.32–7.28 (m, 2 H, 2 × Ar-CH), 6.92–6.88 (m, 2 H, 2 × Ar-CH), 4.07 (dd, *J* = 8.1, 4.2 Hz, 1 H, SCH₂CH), 3.82–3.78 (m, 5 H, ArCH₂ + OCH₃), 3.06 (dd, *J* = 14.9, 4.2 Hz, 1 H, SCHH), 2.91 (dd, *J* = 14.9, 8.1 Hz, 1 H, SCHH); ¹³C NMR (101 MHz, CD₃OD) δ 169.3 (C(O)OH), 159.1 (Ar-C_q-OMe), 129.9 (2 × Ar-CH), 129.1 (Ar-C_q-C_q), 113.7 (2 × Ar-CH), 54.3 (ArOCH₃), 52.0 (SCH₂CH), 34.9 (ArCH₂), 30.9 (SCH₂); FTMS (+ p NSI) *m/z* calcd for C₁₁H₁₅NO₃SNa⁺ [M+Na]⁺: 264.0665, Found: 264.0667.

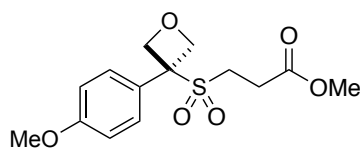
5.2.5 Synthesis of Oxetane Containing Sulfonyl Fluorides

3-Chloro-3-(4-methoxyphenyl)oxetane (117)



Methanesulfonyl chloride (77 μL, 1.0 mmol) and triethylamine (0.14 mL, 1.0 mmol) were added to oxetanol **44** (45 mg, 0.25 mmol) in dichloromethane (2 mL). The reaction mixture was stirred at 55 °C for 4 h then water (10 mL) was added followed by dichloromethane (10 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 × 10 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (30% Et₂O/pentane) afforded a mixture of oxetane **117** and aldehyde **120** (9:1, oxetane **117**: aldehyde **120**) 28 mg, 50 %) as an orange oil; *R*_f = 0.46 (30% Et₂O/pentane); IR (film)/cm⁻¹ 2957, 1727, 1601, 1512, 1462, 1247, 1179, 1027, 978, 829; Oxetane **117**: ¹H NMR (400 MHz, CDCl₃) δ 7.40–7.35 (m, 2 H, 2 × Ar-CH), 6.96–6.91 (m, 2 H, 2 × Ar-CH), 5.22 (dd, *J* = 6.9, 0.9 Hz, 2 H, CHHOCHH), 5.18 (dd, *J* = 6.9, 0.9 Hz, 2 H, CHHOCHH), 3.84 (s, 3 H, ArOCH₃); ¹³C NMR (101 MHz, CDCl₃) δ 133.5 (Ar-C_q-C_q), 126.9 (2 × Ar-CH), 114.1 (2 × Ar-CH), 85.9 (CH₂OCH₂), 65.5 (C_q), 55.3 (ArOCH₃); FTMS (+ p NSI) *m/z* calcd for C₁₀H₁₂O₂Cl⁺ [M+H]⁺: 199.0520, Found: 199.0520.

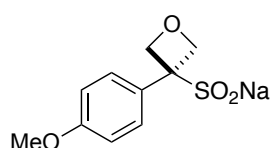
Methyl 3-((3-(4-methoxyphenyl)oxetan-3-yl)sulfonyl)propanoate (127)



m-CPBA (4.40 g, 25.5 mmol) was added to a solution of methyl 3-((3-(4-methoxyphenyl)oxetan-3-yl)thio)propanoate **85o** (2.40 g, 8.5 mmol) in dichloromethane (350 mL). The reaction mixture was stirred at 25 °C for 3 h then aq. KOH (3 M, 60 mL) added and the phases separated. The aqueous portion was extracted with dichloromethane (3 × 50 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford sulfone **127** (2.54 g, 95%) as a white solid; *R*_f = 0.59 (75% EtOAc/hexane); mp = 79–82 °C; IR (film)/cm⁻¹ 2939, 1741 (C=O), 1512, 1309, 1302 (strong, SO), 1269, 1248, 1183, 1143 (strong, SO), 1019, 987, 836; ¹H NMR (400 MHz, CDCl₃) δ

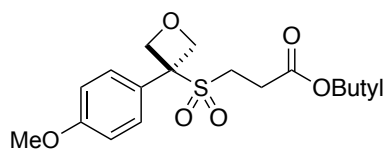
7.25–7.20 (m, 2 H, 2 × Ar-CH), 7.00–6.95 (m, 2 H, 2 × Ar-CH), 5.40 (d, $J = 7.2$ Hz, 2 H, CHHOCHH), 5.12 (d, $J = 7.2$ Hz, 2 H, CHHOCHH), 3.84 (s, 3 H, ArOCH₃), 3.70 (s, 3 H, CO₂CH₃), 3.08 (dd, $J = 8.2, 7.1$ Hz, 2 H, SO₂CH₂), 2.71 (dd, $J = 8.2, 7.1$ Hz, 2 H, CH₂CO₂Me); ¹³C NMR (101 MHz, CDCl₃) δ 170.8 (C=O), 160.3 (Ar-C_q-OMe), 129.4 (2 × Ar-CH), 125.5 (Ar-C_q-C_q), 114.5 (2 × Ar-CH), 76.3 (CH₂OCH₂), 68.3 (C_q), 55.4 (Ar-OCH₃), 52.4 (CO₂CH₃), 43.2 (SO₂CH₂), 25.9 (CH₂CO₂Me); HRMS (TOF-ASAP+) m/z calcd for C₁₄H₁₉SO₆⁺ [M+H]⁺: 315.0902, Found: 315.0898.

Sodium 3-(4-methoxyphenyl)oxetane-3-sulfinate (**128**)



Sulfone **127** (2.43 g, 7.74 mmol) was added to a solution of NaH (60% in mineral oil, 325 mg, 8.13 mmol, 1.05 equiv) in THF (45 mL). The reaction mixture was stirred at 25 °C for 1 h then quenched with anhydrous methanol (15 mL) and concentrated *in vacuo*. The resultant solid was washed with hexane and filtered to afford sulfinate salt **128** (1.95 g, 95%). $R_f = 0.12$ (20% MeOH/CH₂Cl₂); Melting point not determined, degradation observed at 250 °C; IR (film)/cm⁻¹ 2926, 2873, 1738, 1513, 1243, 1177, 1038, 989, 973, 928, 829, 661; ¹H NMR (400 MHz, D₂O) δ 7.11–7.00 (m, 4 H, 4 × Ar-CH), 5.12 (d, $J = 7.2$ Hz, 2 H, CHHOCHH), 5.01 (d, $J = 7.2$ Hz, 2 H, CHHOCHH), 3.86 (s, 3 H, OCH₃); ¹³C NMR (101 MHz, D₂O) δ 158.2 (Ar-C_q-OMe), 128.7 (Ar-C_q-C_q), 128.5 (2 × Ar-CH), 113.9 (2 × Ar-CH), 76.6 (CH₂OCH₂), 67.0 (C_q), 55.3 (OCH₃); FTMS (– p NSI) m/z calcd for C₁₀H₁₁SO₄[–] [M–Na][–]: 227.0384, Found: 227.0385.

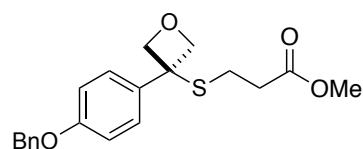
Butyl 3-((3-(4-methoxyphenyl)oxetan-3-yl)sulfonyl)propanoate (**130**)



m-CPBA (388 mg, 2.25 mmol) was added to a solution of oxetane sulfide **85n** (267 mg, 0.82 mmol) in dichloromethane (37.5 mL). The reaction mixture was stirred at 25 °C for 3 h then aq. KOH (3 M, 20 mL) added and the phases separated. The aqueous portion was extracted with dichloromethane (3 × 30 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (60% Et₂O/pentane) afforded sulfone **130** (292 mg, 100%) as a white solid; $R_f = 0.13$ (60% Et₂O/pentane); mp = 56–58 °C; IR (film)/cm⁻¹ 2965, 1729, 1514, 1204, 1250 (strong, S=O), 1184, 1138 (strong, S=O), 1022, 986, 924, 832; ¹H NMR (400 MHz, CDCl₃) δ 7.25–7.20 (m, 2 H, 2 × Ar-CH), 6.99–6.94 (m, 2 H, 2 × Ar-CH), 5.40 (dd, $J = 7.3, 1.4$ Hz, 2 H, CHHOCHH), 5.12 (dd, $J = 7.3, 1.4$ Hz, 2 H, CHHOCHH), 4.09 (t, $J = 6.7$ Hz, 2 H, CO₂CH₂), 3.84 (s, 3 H, ArOCH₃), 3.06 (dd, $J = 8.4, 7.0$ Hz, 2 H, SO₂CH₂), 2.71 (ddd, $J = 8.4, 7.0, 1.7$ Hz, 2 H, CH₂CO₂Bu), 1.65–1.54 (m, 2 H, CH₂CH₂CH₃), 1.40–1.32 (m, 2 H,

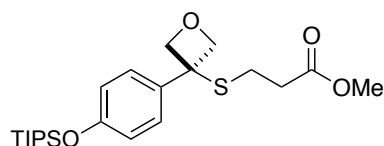
$\text{CH}_2\text{CH}_2\text{CH}_3$), 0.93 (td, $J = 7.4, 1.2$ Hz, 3 H, CH_2CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 170.4 (C=O), 160.3 (Ar-C_q-OMe), 129.4 (2 × Ar-CH), 125.6 (Ar-C_q-C_q), 114.5 (2 × Ar-CH), 76.3 (CH_2OCH_2), 68.3 (C_q), 65.4 (CO_2CH_2), 55.4 (Ar-OCH₃), 43.3 (SO_2CH_2), 30.5 ($\text{CH}_2\text{CH}_2\text{CH}_3$), 26.0 ($\text{CH}_2\text{CO}_2\text{Bu}$), 19.0 ($\text{CH}_2\text{CH}_2\text{CH}_3$), 13.6 (CH_2CH_3); HRMS (TOF-ASAP+) m/z calcd for $\text{C}_{17}\text{H}_{28}\text{NSO}_6^+ [\text{M}+\text{NH}_4]^+$: 374.1637, Found: 374.1637.

Methyl 3-((3-(4-(benzyloxy)phenyl)oxetan-3-yl)thio)propanoate (**132**)



Lithium bis(trifluoromethanesulfonimide) (316 mg, 1.1 mmol) and tetrabutylammonium hexafluorophosphate (213 mg, 0.55 mmol) were added to a solution of oxetanol **45** (2.56 g, 10 mmol) and methyl 3-mercaptopropionate (2.2 mL, 20 mmol) in chloroform (20 mL). The reaction mixture was stirred at 40 °C for 25 min then quenched with sat. aq. NaHCO_3 (25 mL). The layers were separated and the aqueous portion extracted with dichloromethane (3 × 10 mL). The organic extracts were combined then dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (30% EtOAc/hexane) afforded oxetane **132** (2.63 g, 73%) as a white solid; $R_f = 0.4$ (35% EtOAc/hexane); mp = 61–63 °C; IR (film)/ cm^{-1} 2947, 2868, 1736 (s, C=O), 1606, 1513, 1435, 1352, 1247, 1179, 1134, 1011, 983, 837, 823, 751, 738, 697; ^1H NMR (400 MHz, CDCl_3) δ 7.47–7.31 (m, 5 H, 5 × Ph-CH), 7.17–7.12 (m, 2 H, 2 × Ar_(p-OBn)-CH), 7.00–6.95 (m, 2 H, 2 × Ar_(p-OBn)-CH), 5.19 (d, $J = 6.5$ Hz, 2 H, CHHOCHH), 5.08 (s, 2 H, PhCH_2), 4.90 (d, $J = 6.5$ Hz, 2 H, CHHOCHH), 3.68 (s, 3 H, CO_2CH_3), 2.68 (t, $J = 7.4$ Hz, 2 H, SCH_2), 2.43 (t, $J = 7.4$ Hz, 2 H, $\text{CH}_2\text{CO}_2\text{Me}$); ^{13}C NMR (101 MHz, CDCl_3) δ 172.0 (C=O), 157.8 (Ar-C_q-OBn), 136.7 (Ph-C_q-CH₂), 134.5 (Ar-C_q-C_q), 128.6 (2 × Ph-CH), 128.0 (Ph-CH), 127.5 (2 × Ar-CH), 127.4 (2 × Ph-CH), 114.9 (2 × Ar-CH), 83.1 (CH_2OCH_2), 70.0 (PhCH_2), 52.1 (C_q), 51.8 (CO_2CH_3), 34.0 ($\text{CH}_2\text{CO}_2\text{Me}$), 25.1 (SCH_2); FTMS (+ p NSI) m/z calcd for $\text{C}_{20}\text{H}_{22}\text{O}_4\text{SNa}^+ [\text{M}+\text{Na}]^+$: 381.1131, Found: 381.1136.

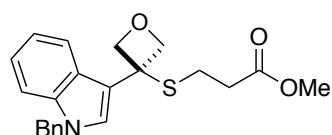
Methyl 3-((3-(4-((triisopropylsilyl)oxy)phenyl)oxetan-3-yl)thio)propanoate (**133**)



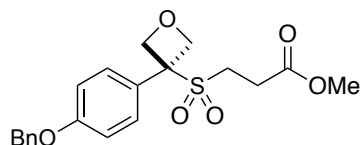
Lithium bis(trifluoromethanesulfonimide) (94.7 mg, 0.33 mmol) and tetrabutylammonium hexafluorophosphate (63.9 mg, 0.165 mmol) were added to a solution of oxetanol **46** (968 mg, 3.0 mmol) and methyl 3-mercaptopropionate (0.66 mL, 6.0 mmol) in chloroform (6 mL). The reaction mixture was stirred at 40 °C for 25 min then quenched with sat. aq. NaHCO_3 (15 mL). The layers were separated and the aqueous portion extracted with dichloromethane (3 × 30 mL). The organic extracts were combined then dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column

chromatography (20% EtOAc/hexane) afforded oxetane **133** (721 mg, 57%) as a colourless oil; $R_f = 0.33$ (20% EtOAc/hexane); IR (film)/ cm^{-1} 2945, 2867, 1739, 1510, 1262, 987, 910, 883, 681; ^1H NMR (400 MHz, CDCl_3) δ 7.08–7.05 (m, 2 H, $2 \times \text{Ar-CH}$), 6.90–6.86 (m, 2 H, $2 \times \text{Ar-CH}$), 5.19 (d, $J = 6.3$ Hz, 2 H, CHHOCHH), 4.89 (d, $J = 6.3$ Hz, 2 H, CHHOCHH), 3.66 (s, 3 H, CO_2CH_3), 2.65 (t, $J = 7.4$ Hz, 2 H, SCH_2), 2.37 (t, $J = 7.4$ Hz, 2 H, $\text{CH}_2\text{CO}_2\text{Me}$), 1.31–1.19 (m, 3 H, $3 \times \text{CH}(\text{CH}_3)_2$), 1.10 (d, $J = 7.3$ Hz, 18 H, $3 \times \text{CH}(\text{CH}_3)_2$); ^{13}C NMR (101 MHz, CDCl_3) δ 172.1 (C=O), 155.2 (Ar- C_q -OTIPS), 134.5 (Ar- C_q - C_q), 127.4 ($2 \times \text{Ar-CH}$), 120.0 ($2 \times \text{Ar-CH}$), 83.3 (CH_2OCH_2), 52.2 (C_q), 51.8 (CO_2CH_3), 34.1 ($\text{CH}_2\text{CO}_2\text{Me}$), 25.2 (SCH_2), 17.9 ($3 \times \text{CH}(\text{CH}_3)_2$), 12.6 ($\text{CH}(\text{CH}_3)_2$); HRMS (Cl^+) m/z calcd for $\text{C}_{22}\text{H}_{40}\text{O}_4\text{SNSi}^+$ $[\text{M}+\text{NH}_4]^+$: 442.2452, Found: 442.2442.

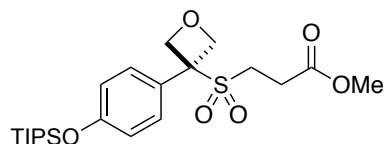
Methyl 3-((3-(1-benzyl-1H-indol-3-yl)oxetan-3-yl)thio)propanoate (**134**)



Calcium bis(trifluoromethanesulfonimide) (66.0 mg, 0.11 mmol) and tetrabutylammonium hexafluorophosphate (42.6 mg, 0.11 mmol) were added to a solution of oxetanol **52** (614 mg, 2.2 mmol) and methyl 3-mercaptopropanoate (0.49 mL, 4.4 mmol) in chloroform (4.4 mL). The reaction mixture was stirred at 40 °C for 25 min then quenched with sat. aq. NaHCO_3 (20 mL). The layers were separated and the aqueous portion extracted with dichloromethane (3×10 mL). The organic extracts were combined then washed with aq. NaOH (1 M, 15 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (30% EtOAc/hexane) afforded oxetane **134** (761 mg, 90%) as a yellow gum; $R_f = 0.20$ (30% EtOAc/hexane); IR (film)/ cm^{-1} 1736 (C=O), 1680, 1548, 1467, 1454, 1439, 1360, 1249, 1197, 1180, 983, 906, 725, 698; ^1H NMR (400 MHz, CDCl_3) δ 7.64–7.61 (m, 1 H, Ar-CH), 7.36–7.28 (m, 4 H, $4 \times \text{Ar-CH}$), 7.26–7.20 (m, 1 H, Ar-CH), 7.16–7.11 (m, 3 H, $3 \times \text{Ar-CH}$), 7.10 (s, 1 H, Ar-CH), 5.34 (s, 2 H, CH_2Ph), 5.25 (d, $J = 6.1$ Hz, 2 H, CHHOCHH), 5.05 (d, $J = 6.1$ Hz, 2 H, CHHOCHH), 3.63 (s, 3 H, CO_2CH_3), 2.62 (t, $J = 7.4$ Hz, 2 H, SCH_2), 2.40 (t, $J = 7.4$ Hz, 2 H, $\text{CH}_2\text{CO}_2\text{Me}$); ^{13}C NMR (101 MHz, CDCl_3) δ 172.0 (C=O), 137.3 (Ar- C_q), 137.1 (Ar- C_q), 128.8 ($2 \times \text{Ar-CH}$), 127.7 (Ar-CH), 126.7 ($2 \times \text{Ar-CH}$), 126.2 (Ar-CH), 125.5 (Ar- C_q), 122.5 (Ar-CH), 120.4 (Ar-CH), 119.6 (Ar-CH), 115.8 (Ar- C_q), 110.1 (Ar-CH), 84.0 (CH_2OCH_2), 51.7 (CO_2CH_3), 50.6 (CH_2Ph), 48.2 (C_q), 34.3 ($\text{CH}_2\text{CO}_2\text{Me}$), 25.6 (SCH_2); FTMS (+ p NSI) m/z calcd for $\text{C}_{22}\text{H}_{23}\text{NSO}_3\text{Na}^+$ $[\text{M}+\text{Na}]^+$: 404.1291, Found: 404.1287.

Methyl 3-((3-(4-(benzyloxy)phenyl)oxetan-3-yl)sulfonyl)propanoate (135)

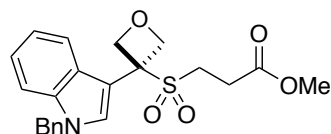
m-CPBA (3.37 g, 21.0 mmol) was added to a solution of oxetane sulfide **132** (2.33 g, 6.5 mmol) in dichloromethane (325 mL). The reaction mixture was stirred at 25 °C for 3 h then 3 M KOH_(aq) (200 mL) added and the phases separated. The aqueous portion was extracted with dichloromethane (4 × 200 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford sulfone **135** (2.31 g, 91%) as a white solid; *R*_f = 0.54 (75% EtOAc/hexane); mp = 129–131 °C; IR (film)/cm⁻¹ 2953, 1744 (C=O), 1516, 1435, 1306 (S=O), 1271, 1248, 1190, 1134 (S=O), 1095, 1011, 998, 934, 841, 824, 740, 693; ¹H NMR (400 MHz, CDCl₃) δ 7.47–7.33 (m, 5 H, 5 × Ph-CH), 7.25–7.21 (m, 2 H, 2 × Ar_(p-OBn)-CH), 7.07–7.03 (m, 2 H, 2 × Ar_(p-OBn)-CH), 5.40 (d, *J* = 7.2 Hz, 2 H, CHHOCHH), 5.13 (d, *J* = 7.2 Hz, 2 H, CHHOCHH), 5.10 (s, 2 H, PhCH₂), 3.71 (s, 3 H, CO₂CH₃), 3.09 (dd, *J* = 8.2, 7.1 Hz, 2 H, SO₂CH₂), 2.72 (dd, *J* = 8.2, 7.1 Hz, 2 H, CH₂CO₂Me); ¹³C NMR (101 MHz, CDCl₃) δ 170.8 (C=O), 159.5 (Ar-C_q-OBn), 136.3 (Ph-C_q), 129.5 (2 × Ar_(p-OBn)-CH), 128.7 (2 × Ph-CH), 128.2 (Ph-CH), 127.5 (2 × Ph-CH), 125.8 (Ar-C_q-C_q), 115.4 (2 × Ar_(p-OBn)-CH), 76.3 (CH₂OCH₂), 70.2 (PhCH₂), 68.3 (C_q), 52.4 (CO₂CH₃), 43.2 (SO₂CH₂), 25.9 (CH₂CO₂Me); FTMS (+ p NSI) *m/z* calcd for C₂₀H₂₆O₆NS⁺ [M+NH₄]⁺: 408.1475, Found: 408.1479.

Methyl 3-((3-(4-((triisopropylsilyl)oxy)phenyl)oxetan-3-yl)sulfonyl)propanoate (136)

m-CPBA (800 mg, 5.1 mmol) was added to a solution of oxetane sulfide **133** (722 mg, 1.7 mmol) in dichloromethane (85 mL). The reaction mixture was stirred at 25 °C for 3 h then aq. KOH (3 M, 75 mL) added and the phases separated. The aqueous portion was extracted with dichloromethane (4 × 100 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford sulfone **136** (769 mg, 99%) as a white solid; *R*_f = 0.26 (40% EtOAc/hexane); mp = 95–97 °C; IR (film)/cm⁻¹ 2944, 2866, 1740, 1513, 1317 (S=O), 1266, 1249, 1179, 1137 (S=O), 986, 913, 882, 680; ¹H NMR (400 MHz, CDCl₃) δ 7.18–7.14 (m, 2 H, 2 × Ar-CH), 6.96–6.92 (m, 2 H, 2 × Ar-CH), 5.40 (d, *J* = 7.1 Hz, 2 H, CHHOCHH), 5.12 (d, *J* = 7.1 Hz, 2 H, CHHOCHH), 3.69 (s, 3 H, CO₂CH₃), 3.05 (dd, *J* = 8.4, 7.0 Hz, 2 H, SO₂CH₂), 2.66 (dd, *J* = 8.4, 7.0 Hz, 2 H, CH₂CO₂Me), 1.33–1.21 (m, 3 H, 3 × CH(CH₃)₂), 1.11 (d, *J* = 7.4 Hz, 18 H, 3 × CH(CH₃)₂); ¹³C NMR (101 MHz, CDCl₃) δ 170.7 (C=O), 157.1 (Ar-C_q-OTIPS), 129.3 (2 × Ar-CH), 125.8 (Ar-C_q-C_q), 120.4 (2 × Ar-CH), 76.3 (CH₂OCH₂), 68.3 (C_q), 52.4 (CO₂CH₃), 43.4 (SO₂CH₂), 26.0 (CH₂CO₂Me), 17.9 (3 ×

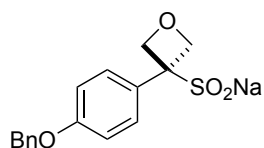
CH(CH₃)₂), 12.6 (CH(CH₃)₂); HRMS (Cl⁺) *m/z* calcd for C₂₂H₄₀O₆NSi⁺ [M+NH₄]⁺: 474.2340, Found: 474.2343.

Methyl 3-((3-(1-benzyl-1*H*-indol-3-yl)oxetan-3-yl)sulfonyl)propanoate (**137**)

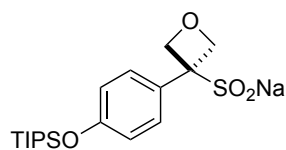


m-CPBA (957 mg, 5.55 mmol) was added to a solution of Methyl 3-((3-(1-benzyl-1*H*-indol-3-yl)oxetan-3-yl)thio) propanoate **134** (705 mg, 1.85 mmol) in dichloromethane (93 mL). The reaction mixture was stirred at 25 °C for 3 h then aq. KOH (3 M, 20 mL) added and the phases separated. The aqueous portion extracted with dichloromethane (4 × 30 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (50% EtOAc/hexane) afforded sulfone **137** (385 mg, 50%) as a colourless gum; *R*_f = 0.31 (50% EtOAc/hexane); IR (film)/cm⁻¹ 2950, 2884, 1735 (C=O), 1453, 1438, 1360, 1302 (S=O), 1246, 1199, 1178, 1131 (S=O), 1094, 996, 738; ¹H NMR (400 MHz, CDCl₃) δ 7.48–7.44 (m, 1 H, Ar-CH), 7.38–7.30 (m, 4 H, 4 × Ar-CH), 7.28–7.22 (m, 2 H, 2 × Ar-CH), 7.23–7.17 (m, 1 H, Ar-CH), 7.17–7.13 (m, 2 H, 2 × Ar-CH), 5.54 (d, *J* = 6.9 Hz, 2 H, CHHOCHH), 5.36 (s, 2 H, CH₂Ph), 5.24 (d, *J* = 6.9 Hz, 2 H, CHHOCHH), 3.67 (s, 3 H, CO₂CH₃), 3.14 (dd, *J* = 8.1, 7.1 Hz, 2 H, SO₂CH₂), 2.70 (dd, *J* = 8.1, 7.1 Hz, 2 H, CH₂CO₂Me); ¹³C NMR (101 MHz, CDCl₃) δ 170.8 (C=O), 136.7 (Ar-C_q), 136.4 (Ar-C_q) 129.0 (2 × Ar-CH), 128.5 (Ar-CH), 128.0 (Ar-CH), 126.8 (2 × Ar-CH), 125.9 (Ar-C_q), 123.0 (Ar-CH), 120.9 (Ar-CH), 120.0 (Ar-CH), 110.6 (Ar-CH), 108.5 (Ar-C_q), 76.7 (CH₂OCH₂), 65.1 (C_q), 52.3 (CO₂CH₃), 50.5 (CH₂Ph), 43.3 (SO₂CH₂), 26.0 (CH₂CO₂Me); HRMS (EI⁺) *m/z* calcd for C₂₂H₂₃ NSO₅⁺ [M]⁺: 413.1291, Found: 413.1290.

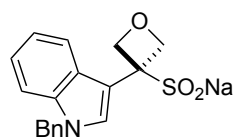
Sodium 3-(4-(benzyloxy)phenyl)oxetane-3-sulfinate (**138**)



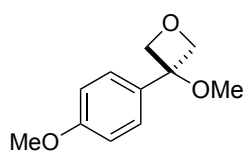
Sulfone **135** (2.15 g, 5.5 mmol) was added to a solution of NaH (60% in mineral oil, 231 mg, 5.8 mmol) in THF (35 mL). The reaction mixture was stirred at 25 °C for 1 h then quenched with anhydrous methanol (15 mL) and concentrated *in vacuo*. The resultant solid was washed with hexane and filtered to afford sulfinate salt **138** (1.80 g, 100%) as a white solid. *R*_f = 0.15 (15% MeOH/CH₂Cl₂); Melting point not determined, degradation observed at 250 °C; IR (film)/cm⁻¹ 2889, 1511, 1250, 1029, 960, 753; ¹H NMR (400 MHz, D₂O) δ 7.54–7.36 (m, 5 H, 5 × Ph-CH), 7.12–7.02 (m, 2 H, 2 × Ar-CH), 7.02–6.96 (m, 2 H, 2 × Ar-CH), 5.17 (s, 2 H, PhCH₂), 5.09 (d, *J* = 7.1 Hz, 2 H, CHHOCHH), 4.97 (d, *J* = 7.1 Hz, 2 H, CHHOCHH); ¹³C NMR (101 MHz, D₂O) δ 157.1 (Ar-C_q-OBn), 136.5 (Ph-C_q-CH₂), 129.5 (Ar-C_q-C_q), 128.8 (2 × Ph-CH), 128.5 (2 × Ar-CH), 128.4 (Ph-CH), 128.1 (2 × Ph-CH), 115.1 (2 × Ar-CH), 76.6 (CH₂OCH₂), 70.3 (PhCH₂), 67.0 (C_q); FTMS (– p NSI) *m/z* calcd for C₁₆H₁₅SO₄[–] [M–Na][–]: 303.0697, Found: 303.0701.

Sodium 3-(4-((triisopropylsilyl)oxy)phenyl)oxetane-3-sulfinate (139)

Sulfone **136** (685 mg, 1.5 mmol) was added to a solution of NaH (60% in mineral oil, 63 mg, 1.6 mmol) in THF (8.8 mL). The reaction mixture was stirred at 25 °C for 1 h then quenched with anhydrous methanol (5 mL) and concentrated *in vacuo*. The resultant solid was washed with hexane and filtered to afford sulfinate salt **139** (545 gm, 93%) as a white solid. R_f = 0.20 (15% MeOH/CH₂Cl₂); Melting point not determined, degradation observed at 250 °C; IR (film)/cm⁻¹ 2944, 2867, 1509, 1260, 1034, 984, 971, 912, 882, 834, 740, 685; ¹H NMR (400 MHz, (CD₃)₂SO) δ 6.79–6.71 (m, 4 H, 4 × Ar-CH), 4.89 (d, J = 5.6 Hz, 2 H, CHHOCHH), 4.47 (d, J = 5.6 Hz, 2 H, CHHOCHH), 1.29–1.18 (m, 3 H, 3 × CH(CH₃)₂), 1.07 (d, J = 7.3 Hz, 18 H, 3 × CH(CH₃)₂); ¹³C NMR (101 MHz, (¹³CD₃)₂SO) δ 153.4 (Ar-C_q-OTIPS), 128.0 (2 × Ar-CH), 124.6 (Ar-C_q-C_q), 118.7 (2 × Ar-CH), 76.7 (CH₂OCH₂), 67.2 (C_q), 18.3 (3 × CH(CH₃)₂), 12.6 (CH(CH₃)₂); FTMS (– p NSI) m/z calcd for C₁₈H₂₉O₄SSi[–] [M-Na][–]: 369.1561, Found: 369.1561.

Sodium 3-(1-benzyl-1H-indol-3-yl)oxetane-3-sulfinate (140)

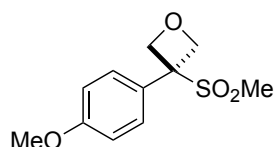
Sulfone **137** (354 mg, 0.86 mmol) was added to a solution of NaH (60% in mineral oil, 36 mg, 0.90 mmol, 1.05 equiv) in THF (6 mL). The reaction mixture was stirred at 25 °C for 1 h then quenched with anhydrous methanol (10 mL) and concentrated *in vacuo*. The resultant solid was washed with hexane and filtered to afford sulfinate salt **140** (212 mg, 71%). R_f = 0.17 (25% MeOH/CH₂Cl₂); Melting point not determined, degradation observed at 200 °C; IR (film)/cm⁻¹ 2923, 2877, 1356, 1026, 970, 956, 742, 720, 691; ¹H NMR (400 MHz, D₂O) δ 7.27–7.23 (m, 1 H, Ar-CH), 7.22–7.10 (m, 5 H, 5 × Ar-CH), 7.08–7.00 (m, 3 H, 3 × Ar-CH), 6.98–6.92 (m, 1 H, Ar-CH), 5.17 (d, J = 6.8 Hz, 2 H, CHHOCHH), 5.14 (s, 2 H, CH₂Ph), 4.88 (d, J = 6.8 Hz, 2 H, CHHOCHH); ¹³C NMR (101 MHz, D₂O) δ 137.8 (Ar-C_q), 136.2 (Ar-C_q), 128.7 (2 × Ar-CH), 127.6 (2 × Ar-CH), 126.9 (2 × Ar-CH), 126.3 (Ar-C_q), 122.1 (Ar-CH), 119.8 (Ar-CH), 119.6 (Ar-CH), 111.3 (Ar-C_q), 110.6 (Ar-CH), 76.4 (CH₂OCH₂), 63.7 (C_q), 49.6 (CH₂Ph); FTMS (– p NSI) m/z calcd for C₁₈H₁₆NSO₃[–] [M-Na][–]: 326.0856, Found: 326.0853.

3-Methoxy-3-(4-methoxyphenyl)oxetane (144)

Oxetanol **44** (90 mg, 0.5 mmol) was added to a solution of NaH (60% in mineral oil, 22 mg, 0.55 mmol) in DMF (2 mL) at 0 °C and the reaction mixture stirred at 0 °C for 1 h. MeI (93 μ L, 1.5 mmol) was added and the reaction mixture stirred for a further 15 h at 25 °C. Water (10 mL) was

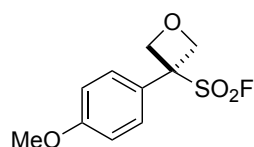
added followed by diethylether (10 mL) and the phases separated. The aqueous portion was extracted with diethylether (2 × 10 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (40% Et₂O/pentane) afforded oxetane **144** (86 mg, 88%) as a white solid. *R*_f = 0.39 (40% Et₂O/pentane); mp = 42–44 °C, IR (film)/cm⁻¹ 2954, 2880, 1512, 1249, 1181, 1172, 1042, 1027, 973, 828, 819, 808; ¹H NMR (400 MHz, CDCl₃) δ 7.37–7.31 (m, 2 H, 2 × Ar-CH), 6.98–6.92 (m, 2 H, 2 × Ar-CH), 4.90 (d, *J* = 6.8 Hz, 2 H, CHHOCHH), 4.84 (d, *J* = 6.8 Hz, 2 H, CHHOCHH), 3.84 (s, 3 H, ArOCH₃), 3.10 (s, 3 H, C_qOCH₃); ¹³C NMR (101 MHz, CDCl₃) δ 159.3 (Ar-C_q-OMe), 131.5 (Ar-C_q-C_q), 127.3 (2 × Ar-CH), 114.0 (2 × Ar-CH), 80.9 (CH₂OCH₂), 80.6 (C_q), 55.3 (ArOCH₃), 51.5 (C_qOCH₃); HRMS (TOF-ASAP+) *m/z* calcd for C₁₁H₁₁O₂⁺ [M-OCH₃]⁺: 163.0759, Found: 163.0757.

3-(4-Methoxyphenyl)-3-(methylsulfonyl)oxetane (**146**)



CH₃I (62 μL, 1.0 mmol) was added to a solution of sodium sulfinate salt **128** (53 mg, 0.21 mmol) in methanol (0.6 mL) and the reaction mixture was stirred at 25 °C for 14 h then concentrated *in vacuo*. Dichloromethane (15 mL) and water (15 mL) were added and the layers separated. The aqueous portion was extracted with dichloromethane (2 × 15 mL). The organic extracts were combined then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (50% EtOAc/hexane) afforded oxetane **146** (31 mg, 60%) as a white solid; *R*_f = 0.14 (50% EtOAc/hexane); mp = 151–153 °C; IR (film)/cm⁻¹ 2932, 2892, 1611, 1516, 1289 (S=O), 1248, 1187, 1138 (S=O), 1099, 993, 929, 841; ¹H NMR (400 MHz, CDCl₃) δ 7.20–7.14 (m, 2 H, 2 × Ar-CH), 6.99–6.92 (m, 2 H, 2 × Ar-CH), 5.36 (d, *J* = 7.2 Hz, 2 H, CHHOCHH), 5.14 (d, *J* = 7.2 Hz, 2 H, CHHOCHH), 3.84 (s, 3 H, OCH₃), 2.72 (s, 3 H, SO₂CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 160.2 (Ar-C_q-OMe), 129.3 (2 × Ar-CH), 125.6 (Ar-C_q-C_q), 114.4 (2 × Ar-CH), 76.3 (CH₂OCH₂), 68.2 (C_q), 55.4 (OCH₃), 35.3 (SO₂CH₃); FTMS (+ p NSI) *m/z* calcd for C₁₁H₁₈NO₄S⁺ [M+NH₄]⁺: 260.0951, Found: 260.0951.

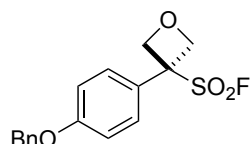
3-(4-Methoxyphenyl)oxetane-3-sulfonyl fluoride (**147**)



Sulfinate salt **128** (876 mg, 3.5 mmol) and selectfluor (1.86 g, 5.25 mmol) were added to MeOH (17.5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h then concentrated *in vacuo*. Purification by flash column chromatography (100% CH₂Cl₂) through a short plug of silica afforded sulfonyl fluoride **147** (731 mg, 85%). *R*_f = 0.47 (20% pentane/dichloromethane); mp = 115–117 °C, IR (film)/cm⁻¹ 2969, 2903, 1738, 1615, 1517, 1393 (S=O), 1308, 1263, 1210 (S=O), 1174, 1021, 997, 928; ¹H NMR (400 MHz, CDCl₃) δ 7.24–7.20 (m, 2 H, 2 × Ar-CH),

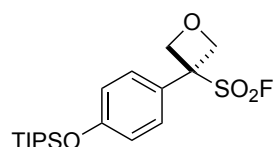
7.03–6.98 (m, 2 H, 2 × Ar-CH), 5.45 (d, $J = 7.6$ Hz, 2 H, CHHOCHH), 5.25 (dd, $J = 7.6, 1.5$ Hz, 2 H, CHHOCHH), 3.87 (s, 3 H, OCH₃); ¹³C NMR (101 MHz, CDCl₃) δ 160.9 (Ar-C_q-OMe), 129.5 (2 × Ar-CH), 123.3 (Ar-C_q-C_q), 114.7 (2 × Ar-CH), 77.1 (CH₂OCH₂), 68.1 (d, $J_{C-F} = 14.4$ Hz, C_q), 55.5 (OCH₃); ¹⁹F NMR (377 MHz, CDCl₃) δ 34.3; HRMS (TOF-ASAP+) m/z calcd for C₁₀H₁₁O₂⁺ [M-SO₂F]⁺: 163.0759, Found: 163.0761.

3-(4-(Benzyloxy)phenyl)oxetane-3-sulfonyl fluoride (148)



Sulfinate salt **138** (1.30 g, 4.0 mmol) and selectfluor (2.13 g, 6.0 mmol) were added to MeOH (20 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h then concentrated *in vacuo*. Purification by flash column chromatography (100% CH₂Cl₂) through a short plug of silica afforded sulfonyl fluoride **148** (854 mg, 66%) as a white solid. $R_f = 0.46$ (CH₂Cl₂); mp = 112–114 °C, IR (film)/cm⁻¹ 2895, 2361, 1513, 1397 (S=O), 1249, 1211 (S=O), 1185, 1007, 1000, 830, 781, 755, 700; ¹H NMR (400 MHz, CDCl₃) δ 7.50–7.33 (m, 5 H, 5 × Ph-CH), 7.25–7.17 (m, 2 H, 2 × Ar-CH), 7.10–7.03 (m, 2 H, 2 × Ar-CH), 5.43 (d, $J = 7.6$ Hz, 2 H, CHHOCHH), 5.23 (dd, $J = 7.6, 1.5$ Hz, 2 H, CHHOCHH), 5.11 (s, 2 H, PhCH₂); ¹³C NMR (101 MHz, CDCl₃) δ 160.0 (Ar-C_q-OBn), 136.2 (Ph-C_q), 129.6 (2 × Ar-CH), 128.7 (2 × Ph-CH), 128.2 (Ph-CH), 127.4 (2 × Ph-CH), 123.5 (Ar-C_q-C_q), 115.5 (2 × Ar-CH), 77.1 (CH₂OCH₂), 70.2 (PhCH₂), 68.1 (d, $J_{C-F} = 14.5$ Hz, C_q); ¹⁹F NMR (377 MHz, CDCl₃) δ 34.4; HRMS (CI⁺) m/z calcd for C₁₆H₁₉O₄SNF⁺ [M+NH₄]⁺: 340.1013, Found: 340.1019.

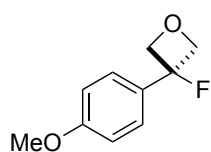
3-(4-((Triisopropylsilyl)oxy)phenyl)oxetane-3-sulfonyl fluoride (149)



Sulfinate salt **139** (510 mg, 1.30 mmol) and selectfluor (691 mg, 1.95 mmol) were added to MeOH (6.5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h then concentrated *in vacuo*. Purification by flash column chromatography (100% CH₂Cl₂) through a very short plug of silica afforded sulfonyl fluoride **149** (383 mg, 83%) as a white solid. $R_f = 0.71$ (CH₂Cl₂); mp = 63–64 °C, IR (film)/cm⁻¹ 2948, 2868, 1607, 1510, 1270, 1268, 901, 881, 836, 795, 684, 653; ¹H NMR (400 MHz, CDCl₃) δ 7.15–7.10 (m, 2 H, 2 × Ar-CH), 6.98–6.93 (m, 2 H, 2 × Ar-CH), 5.42 (d, $J = 7.6$ Hz, 2 H, CHHOCHH), 5.23 (d, $J = 7.6$ Hz, 2 H, CHHOCHH), 1.33–1.21 (m, 3 H, 3 × CH(CH₃)₂), 1.12 (d, $J = 7.4$ Hz, 18 H, 3 × CH(CH₃)₂); ¹³C NMR (101 MHz, CDCl₃) δ 157.5 (Ar-C_q-OTIPS), 129.3 (2 × Ar-CH), 123.3 (Ar-C_q-C_q), 120.3 (2 × Ar-CH), 76.6 (CH₂OCH₂), 68.0 (d, $J_{C-F} = 14.9$ Hz, C_q), 17.7 (3 × CH(CH₃)₂), 12.5 (CH(CH₃)₂); ¹⁹F NMR (377 MHz, CDCl₃) δ 34.3; HRMS (CI⁺) m/z calcd for C₁₆H₁₉O₄SNF⁺ [M+NH₄]⁺: 340.1013, Found: 340.1019.

5.2.6 Synthesis of 3-Aminooxetanes and Derivatives

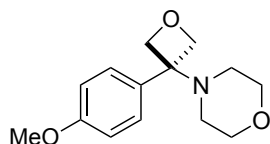
3-Fluoro-3-(4-methoxyphenyl)oxetane (**159**)



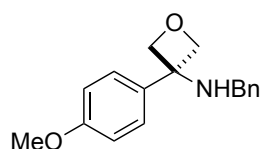
DAST (40 μ L, 0.3 mmol) was added dropwise to a solution of oxetanol **44** (45 mg, 0.25 mmol) in dichloromethane (3.8 mL) at -78 $^{\circ}$ C. The reaction was stirred at -78 $^{\circ}$ C for 30 mins then warmed to 0 $^{\circ}$ C using an ice bath.

After 10 min at 0 $^{\circ}$ C the reaction was quenched with aq. NaOH (1 M, 10 mL) and the layers separated. The aqueous portion was extracted with dichloromethane (3×10 mL). The organic extracts were combined, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (15% Et_2O /pentane) afforded oxetane **159** (46 mg, 64%) as a clear oil. $R_f = 0.5$ (15% Et_2O /pentane); IR (film)/ cm^{-1} 3949, 2879, 1615, 1517, 1304, 1249, 1180, 1029, 978, 875, 830; ^1H NMR (400 MHz, CDCl_3) δ 7.48–7.43 (m, 2 H, $2 \times \text{Ar-CH}$), 7.00–6.93 (m, 2 H, $2 \times \text{Ar-CH}$), 5.10 (ddd, $J = 21.5, 7.7, 1.2$ Hz, 2 H, CHHOCHH), 4.89 (ddd, $J = 21.5, 7.7, 1.2$ Hz, 2 H, CHHOCHH), 3.84 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 159.7 ($\text{Ar-C}_q\text{-OMe}$), 130.3 (d, $J_{\text{C-F}} = 24.0$ Hz, $\text{Ar-C}_q\text{-C}_q$), 125.5 (d, $J_{\text{C-F}} = 8.1$ Hz, $2 \times \text{Ar-CH}$), 114.0 ($2 \times \text{Ar-CH}$), 95.2 (d, $J_{\text{C-F}} = 206.1$ Hz, C_q), 83.0 (d, $J_{\text{C-F}} = 25.7$ Hz, CH_2OCH_2), 55.3 (OCH_3); ^{19}F NMR (377 MHz, CDCl_3) δ -145.9 ; HRMS (Cl^+) m/z calcd for $\text{C}_{10}\text{H}_{11}\text{O}_2^+$ [$\text{M}+\text{H}-\text{HF}$] $^+$: 163.0754, Found: 163.0756.

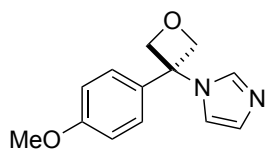
4-((3-(4-Methoxyphenyl)oxetan-3-yl)sulfonyl)morpholine (**151a**)



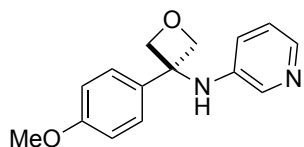
K_2CO_3 (36 mg, 0.26 mmol) was added to a solution of sulfonyl fluoride **147** (49 mg, 0.20 mmol) and morpholine (21 μ L, 0.24 mmol) in acetonitrile (0.7 mL). The reaction mixture was stirred at 60 $^{\circ}$ C for 2 h then water (10 mL) and dichloromethane (10 mL) were added. The layers were separated and the aqueous portion extracted with dichloromethane (2×10 mL). The organic extracts were combined, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (80% EtOAc /hexane) afforded aminooxetane **151a** (43 mg, 86%) as a white solid. $R_f = 0.21$ (80% EtOAc /hexane); mp = 97 – 99 $^{\circ}$ C, IR (film)/ cm^{-1} 2950, 2855, 1610, 1513, 1453, 1296, 1246, 1179, 1114, 1029, 988, 929; ^1H NMR (400 MHz, CDCl_3) δ 7.00–6.96 (m, 2 H, $2 \times \text{Ar-CH}$), 6.94–6.88 (m, 2 H, $2 \times \text{Ar-CH}$), 4.90 (d, $J = 5.9$ Hz, 2 H, CHHOCHH), 4.87 (d, $J = 5.9$ Hz, 2 H, CHHOCHH), 3.83 (s, 3 H, OCH_3), 3.74 (t, $J = 4.6$ Hz, 4 H, $\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2$), 2.31 (t, $J = 4.6$ Hz, 4 H, CH_2NCH_2); ^{13}C NMR (101 MHz, CDCl_3) δ 158.8 ($\text{Ar-C}_q\text{-OMe}$), 129.4 ($\text{Ar-C}_q\text{-C}_q$), 128.4 ($2 \times \text{Ar-CH}$), 113.3 ($2 \times \text{Ar-CH}$), 79.3 (CH_2OCH_2), 67.1 ($\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2$), 66.4 (C_q), 55.3 (OCH_3), 46.4 (CH_2NCH_2); HRMS (TOF-ASAP+) m/z calcd for $\text{C}_{14}\text{H}_{19}\text{NO}_3^+$ [$\text{M}+\text{H}$] $^+$: 250.1443, Found: 250.1438.

N-Benzyl-3-(4-methoxyphenyl)oxetan-3-amine (151b)

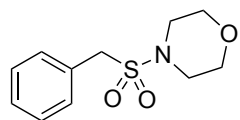
K_2CO_3 (36 mg, 0.26 mmol) was added to a solution of sulfonyl fluoride **147** (49 mg, 0.20 mmol) and benzylamine (26 μL , 0.24 mmol) in acetonitrile (0.7 mL). The reaction mixture was stirred at 60 $^\circ\text{C}$ for 2 h then water (10 mL) and dichloromethane (10 mL) were added. The layers were separated and the aqueous portion extracted with dichloromethane (2×10 mL). The organic extracts were combined, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (40% EtOAc/hexane) afforded aminooxetane **151b** (48 mg, 89%) as a white solid. $R_f = 0.25$ (40% EtOAc/hexane); mp = 53–55 $^\circ\text{C}$, IR (film)/ cm^{-1} 2949, 2869, 2836, 1610, 1513, 1454, 1245, 1177, 1027, 980, 829, 733, 698; ^1H NMR (400 MHz, CDCl_3) δ 7.44–7.39 (m, 2 H, $2 \times \text{Ar}_{(\text{p-OMe})}\text{-CH}$), 7.36–7.30 (m, 4 H, $4 \times \text{Ph-CH}$), 7.29–7.23 (m, 1 H, Ph-CH), 6.99–6.94 (m, 2 H, $2 \times \text{Ar}_{(\text{p-OMe})}\text{-CH}$), 4.97 (d, $J = 6.4$ Hz, 2 H, CHHOCHH), 4.77 (d, $J = 6.4$ Hz, 2 H, CHHOCHH), 3.85 (s, 3 H, OCH_3), 3.56 (s, 2 H, CH_2Ph), 2.05 (br. s, 1 H, NH); ^{13}C NMR (101 MHz, CDCl_3) δ 158.7 ($\text{Ar-C}_q\text{-OMe}$), 140.1 (Ph-C_q), 134.1 ($\text{Ar-C}_q\text{-C}_q$), 128.4 ($2 \times \text{Ph-CH}$), 128.1 ($2 \times \text{Ph-CH}$), 127.4 ($2 \times \text{Ar}_{(\text{p-OMe})}\text{-CH}$), 127.1 (Ph-CH), 113.9 ($2 \times \text{Ar}_{(\text{p-OMe})}\text{-CH}$), 82.7 (CH_2OCH_2), 63.2 (C_q), 55.3 (OCH_3), 47.9 (CH_2Ph); HRMS (ES^+) m/z calcd for $\text{C}_{17}\text{H}_{20}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$: 270.1494, Found: 270.1495.

1-(3-(4-Methoxyphenyl)oxetan-3-yl)-1H-imidazole (151c)

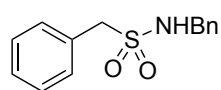
K_2CO_3 (36 mg, 0.26 mmol) was added to a solution of sulfonyl fluoride **147** (49 mg, 0.20 mmol) and imidazole (16 mg, 0.24 mmol) in acetonitrile (0.7 mL). The reaction mixture was stirred at 60 $^\circ\text{C}$ for 2 h then water (10 mL) and dichloromethane (10 mL) were added. The layers were separated and the aqueous portion extracted with dichloromethane (2×10 mL). The organic extracts were combined, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (100% EtOAc) afforded aminooxetane **151c** (23 mg, 49%) as a colourless oil. $R_f = 0.22$ (100% EtOAc); IR (film)/ cm^{-1} 2960, 2884, 1613, 1515, 1492, 1463, 1301, 1250, 1184, 1076, 1027, 987, 905, 830, 730, 663; ^1H NMR (400 MHz, CDCl_3) δ 7.42 (s, 1 H, $\text{Ar}_{(\text{imidazole})}\text{-CH}$), 7.18 (s, 1 H, $\text{Ar}_{(\text{imidazole})}\text{-CH}$), 7.11–7.05 (m, 3 H, $\text{Ar}_{(\text{imidazole})}\text{-CH} + 2 \times \text{Ar}_{(\text{p-OMe})}\text{-CH}$), 6.97–6.91 (m, 2 H, $2 \times \text{Ar}_{(\text{p-OMe})}\text{-CH}$), 5.23 (s, 4 H, CH_2OCH_2), 3.83 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 159.8 ($\text{Ar-C}_q\text{-OMe}$), 136.2 ($\text{Ar}_{(\text{imidazole})}\text{-CH}$), 131.9 ($\text{Ar-C}_q\text{-C}_q$), 130.0 ($\text{Ar}_{(\text{imidazole})}\text{-CH}$), 126.9 ($2 \times \text{Ar}_{(\text{p-OMe})}\text{-CH}$), 117.6 ($\text{Ar}_{(\text{imidazole})}\text{-CH}$), 114.4 ($2 \times \text{Ar}_{(\text{p-OMe})}\text{-CH}$), 83.5 (CH_2OCH_2), 63.1 (C_q), 55.4 (OCH_3); HRMS (ES^+) m/z calcd for $\text{C}_{13}\text{H}_{15}\text{N}_2\text{O}_2^+$ $[\text{M}+\text{H}]^+$: 231.1134, Found: 231.1138.

***N*-(3-(4-Methoxyphenyl)oxetan-3-yl)pyridin-3-amine (151d)**

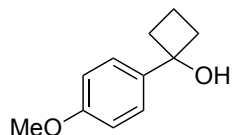
K_2CO_3 (36 mg, 0.26 mmol) was added to a solution of sulfonyl fluoride **147** (49 mg, 0.20 mmol) and 2-aminopyridine (23 mg, 0.24 mmol) in acetonitrile (0.6 mL). The reaction mixture was stirred at 60 °C for 2 h then water (10 mL) and dichloromethane (10 mL) were added. The layers were separated and the aqueous portion extracted with dichloromethane (2 × 10 mL). The organic extracts were combined, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (80% EtOAc/hexane) afforded aminooxetane **151d** (14 mg, 28%) as a pale yellow solid. R_f = 0.13 (80% EtOAc/hexane); mp = 121–123 °C, IR (film)/ cm^{-1} 3222 (NH), 3032, 2949, 2877, 1578, 1513, 1479, 1309, 1274, 1248, 1176, 1023, 987, 832, 816, 795, 705; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, J = 4.8, 1.3 Hz, 1 H, $Ar_{(pyridine)}-CH$), 7.89 (d, J = 2.9 Hz, 1 H, $Ar_{(pyridine)}-CH$), 7.57–7.52 (m, 2 H, 2 × $Ar_{(p-OMe)}-CH$), 6.99 (dd, J = 8.3, 4.8 Hz, 1 H, $Ar_{(pyridine)}-CH$), 6.97–6.91 (m, 2 H, 2 × $Ar_{(p-OMe)}-CH$), 6.47 (ddd, J = 8.3, 2.9, 1.3 Hz, 1 H, $Ar_{(pyridine)}-CH$), 5.01 (d, J = 6.4 Hz, 2 H, $CHHOCHH$), 4.89 (d, J = 6.4 Hz, 2 H, $CHHOCHH$), 4.80 (br. s, 1 H, NH), 3.83 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1 ($Ar-C_q-OMe$), 140.9 ($Ar-C_q-NH$), 139.4 ($Ar_{(pyridine)}-CH$), 137.1 ($Ar_{(pyridine)}-CH$), 132.7 ($Ar-C_q-C_q$), 126.5 (2 × $Ar_{(p-OMe)}-CH$), 123.5 ($Ar_{(pyridine)}-CH$), 119.9 ($Ar_{(pyridine)}-CH$), 114.3 (2 × $Ar_{(p-OMe)}-CH$), 83.9 (CH_2OCH_2), 59.9 (C_q), 55.3 (OCH_3); HRMS (ES^+) m/z calcd for $C_{15}H_{17}N_2O_2^+$ [$M+H$] $^+$: 257.1290, Found: 257.1283.

4-(Benzylsulfonyl)morpholine (160)

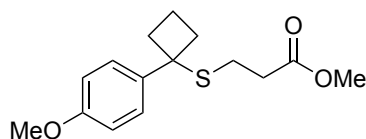
Triethylamine (36 μ L, 0.26 mmol) was added to a solution of PMSF (36 mg, 0.20 mmol) and morpholine (21 μ L, 0.24 mmol) in acetonitrile (0.7 mL). The reaction mixture was stirred at 60 °C for 1 h then water (10 mL) was added followed by dichloromethane (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (2 × 10 mL). The organic extracts were combined, dried over Na_2SO_4 then filtered. Concentration *in vacuo* afforded sulfonamide **160** (45 mg, 93%) as a white solid. R_f = 0.41 (50% EtOAc/hexane); mp = 173–175 °C [Lit. mp = 174–176 °C (ethanol)]²⁵⁸; IR (film)/ cm^{-1} 2857, 1451, 1345 (S=O), 1318, 1258, 1152 (S=O), 1111, 1068, 944 923, 785, 746, 705; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46–6.38 (m, 5 H, 5 × Ph-CH), 4.25 (s, 2 H, $PhCH_2$), 3.63 (t, J = 4.6 Hz, 4 H, $CH_2CH_2OCH_2CH_2$), 3.12 (t, J = 4.6 Hz, 4 H, CH_2NCH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 130.7 (2 × Ph-CH), 128.89 (Ph-CH), 128.85 (2 × Ph-CH), 128.5 ($Ar-C_q-CH_2$), 66.7 (CH_2OCH_2), 56.7 ($PhCH_2$), 46.1 (CH_2NCH_2). The observed spectroscopic data for this compound was consistent with that previously reported.²⁵⁹

N-Benzyl-1-phenylmethanesulfonamide (156)

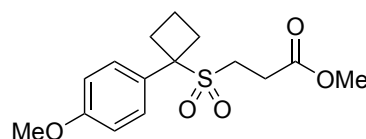
Triethylamine (36 μ L, 0.26 mmol) was added to a solution of PMSF (36 mg, 0.20 mmol) and benzylamine (26 μ L, 0.24 mmol) in acetonitrile (0.7 mL). The reaction mixture was stirred at 60 $^{\circ}$ C for 1 h then water (10 mL) was added followed by dichloromethane (10 mL). The layers were separated and the aqueous portion extracted with dichloromethane (2 $\times$ 10 mL). The organic extracts were combined, dried over Na_2SO_4 then filtered. Concentration *in vacuo* afforded sulfonamide **156** (47 mg, 90%) as a white solid. R_f = 0.26 (50% Et_2O /pentane); mp = 145–147 $^{\circ}$ C [Lit. mp = 144–145 $^{\circ}$ C (ethanol)]²⁶⁰; IR (film)/ cm^{-1} 3284 (NH), 1454, 1308 (S=O), 1136 (S=O), 1084, 1063, 1025, 847, 780, 727; ^1H NMR (400 MHz, CDCl_3) δ 7.41–6.27 (m, 10 H, 10 $\times$ Ph-CH), 4.38 (t, J = 6.0 Hz, 1 H, NH), 4.23 (s, 2 H, PhCH_2SO_2), 4.16 (d, J = 6.0 Hz, 2 H, CH_2NH); ^{13}C NMR (101 MHz, CDCl_3) δ 136.8 (Ph- C_q - CH_2NH), 130.7 (2 $\times$ Ph-CH), 129.2 (Ar- C_q - CH_2SO_2), 128.9 (2 $\times$ Ph-CH), 128.82 (2 $\times$ Ph-CH), 128.78 (Ph-CH), 128.1 (Ph-CH), 128.0 (2 $\times$ Ph-CH), 59.4 (PhCH_2SO_2), 47.7 (PhCH_2NH). The observed spectroscopic data for this compound was consistent with that previously reported.²⁶¹

1-(4-Methoxyphenyl)cyclobutan-1-ol (161)

n -BuLi (2.3 M in hexanes, 5.22 mL, 12 mmol) was added dropwise over 5 min to a solution of 4-bromoanisole (1.6 mL, 13 mmol) in THF (50 mL) at -78°C . The reaction mixture was stirred at -78°C for a further 20 min then cyclobutanone (0.75 mL, 10 mmol) was added dropwise to the reaction mixture. Following a further 5 min at -78°C the reaction mixture was warmed to rt then quenched with water (50 mL). The layers were separated and the aqueous portion extracted with diethylether (3 $\times$ 50 mL). The organic extracts were combined, washed with brine (50 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (35% Et_2O /pentane) afforded cyclobutanol **161** (1.49 g, 84%) as a white solid. R_f = 0.20 (35% Et_2O /pentane); mp = 66–68 $^{\circ}$ C; IR (film)/ cm^{-1} 3397 (br. OH), 2938, 2836, 1611, 1563, 1512, 1464, 1442, 1426, 1299, 1243, 1177, 1132, 1108, 1068, 1029, 962, 957, 908, 828, 792, 731; ^1H NMR (400 MHz, CDCl_3) δ 7.47–7.41 (m, 2 H, 2 $\times$ Ar-CH), 6.94–6.59 (m, 2 H, 2 $\times$ Ar-CH), 3.83 (s, 3 H, OCH_3), 2.57–2.51 (m, 2 H, CHHC_qCHH), 2.39–2.34 (CHHC_qCHH), 2.05–1.93 (m, 2 H, $\text{CH}_2\text{CHHCH}_2$ + OH), 1.71–1.58 (m, 1 H, $\text{CH}_2\text{CHHCH}_2$); ^{13}C NMR (101 MHz, CDCl_3) δ 158.8 (2 $\times$ Ar- C_q -O), 138.5 (Ar- C_q - C_q), 126.3 (2 $\times$ Ar-CH), 113.7 (2 $\times$ Ar-CH), 55.3 (C_q), 36.9 (2 $\times$ CH_2), 12.9 (CH_2). The observed spectroscopic data for this compound was consistent with that previously reported.²⁶² Melting point not previously reported.

Methyl 3-((1-(4-methoxyphenyl)cyclobutyl)thio)propanoate (162)

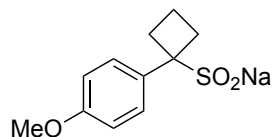
Lithium bis(trifluoromethanesulfonimide) (158 mg, 0.55 mmol) and tetrabutylammonium hexafluorophosphate (107 mg, 0.275 mmol) were added to a solution of cyclobutanol **161** (891 mg, 5.0 mmol) and methyl 3-mercaptopropionate (1.11 mL, 10.0 mmol) in chloroform (10 mL). The reaction mixture was stirred at 40 °C for 25 min then sat. aq. NaHCO₃ (40 mL) was added followed by dichloromethane (40 mL). The layers were separated and the aqueous portion extracted with dichloromethane (2 × 40 mL). The organic extracts were combined then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (10% Et₂O/pentane) afforded cyclobutane **162** (321 mg, 23%) as a white solid; *R*_f = 0.15 (10% Et₂O/pentane); mp = 69–71 °C; IR (film)/cm⁻¹ 2985, 2956, 1736 (s. C=O), 1509, 1249, 1236, 1211, 1176, 1153, 1038, 833, 813; ¹H NMR (400 MHz, CDCl₃) δ 7.20–7.15 (m, 2 H, 2 × Ar-CH), 6.88–6.83 (m, 2 H, 2 × Ar-CH), 3.81 (s, 3 H, ArOCH₃), 3.64 (s, 3 H, CO₂CH₃), 2.68–2.56 (m, 2 H, CHHC_qCHH), 2.49 (t, *J* = 7.4 Hz, 2 H, SCH₂), 2.44–2.34 (m, 3 H, CHHC_qCHH + CH₂CHHCH₂), 2.30 (t, *J* = 7.4 Hz, 2 H, CH₂CO₂Me), 2.34–2.27 (m, 1 H, CH₂CHHCH₂); ¹³C NMR (101 MHz, CDCl₃) δ 172.5 (C=O), 157.9 (Ar-C_q-OMe), 139.3 (Ar-C_q-C_q), 127.0 (2 × Ar-CH), 113.5 (2 × Ar-CH), 83.2 (CH₂OCH₂), 55.3 (Ar-OCH₃), 52.9 (C_q), 51.6 (CO₂CH₃), 35.2 (2 × CH₂), 34.1 (CH₂CO₂Me), 24.9 (SCH₂), 16.6 (CH₂CH₂CH₂); HRMS (TOF-ASAP+) *m/z* calcd for C₁₅H₁₉SO₃⁺ [M-H]⁺: 279.1055, Found: 279.1056.

Methyl 3-((1-(4-methoxyphenyl)cyclobutyl)sulfonyl)propanoate (163)

m-CPBA (518 mg, 3.0 mmol) was added to a solution of cyclobutane **162** (280 mg, 1.0 mmol) in dichloromethane (50 mL). The reaction mixture was stirred at 25 °C for 3 h then aq. KOH (3 M, 40 mL) added and the phases separated. The aqueous portion was extracted with dichloromethane (4 × 30 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (50% EtOAc/hexane) afforded sulfone **163** (301 mg, 96%) as a white solid; *R*_f = 0.15 (10% Et₂O/pentane); mp = 67–71 °C; IR (film)/cm⁻¹ 2946, 1735 (C=O), 1516, 1287, 1250, 1131, 1093, 1018, 840, 828; ¹H NMR (400 MHz, CDCl₃) δ 7.38–7.34 (m, 2 H, 2 × Ar-CH), 6.95–6.91 (m, 2 H, 2 × Ar-CH), 3.83 (s, 3 H, ArOCH₃), 3.67 (s, 3 H, CO₂CH₃), 3.16–3.09 (m, 2 H, CHHC_qCHH), 2.90 (t, *J* = 7.6 Hz, 2 H, SO₂CH₂), 2.69–2.58 (m, 4 H, CHHC_qCHH + CH₂CO₂Me), 2.33–2.23 (m, 1 H, CH₂CHHCH₂), 2.04–1.95 (m, 1 H, CH₂CHHCH₂); ¹³C NMR (101 MHz, CDCl₃) δ 171.0 (C=O), 159.7 (Ar-C_q-OMe), 129.6 (2 × Ar-CH), 129.0 (Ar-C_q-C_q),

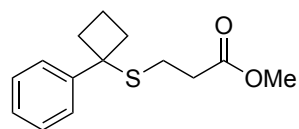
114.0 (2 × Ar-CH), 67.8 (C_q), 55.3 (Ar-OCH₃), 52.2 (CO₂CH₃), 41.7 (SO₂CH₂), 29.3 (2 × CH₂), 25.7 (CH₂CO₂Me), 15.8 (CH₂CH₂CH₂); HRMS (TOF-ASAP+) *m/z* calcd for C₁₅H₂₁SO₅⁺ [M+H]⁺: 313.1110, Found: 313.1107.

Sodium 1-(4-methoxyphenyl)cyclobutane-1-sulfinate (**164**)

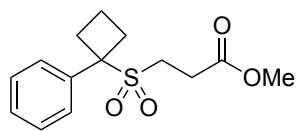


Sulfone **163** (250 mg, 0.8 mmol) was added to a solution of NaH (60% in mineral oil, 34 mg, 0.84 mmol) in THF (5 mL). The reaction mixture was stirred at 25 °C for 1 h then quenched with anhydrous methanol (5 mL) and concentrated *in vacuo* to afford sulfinate salt **164** (176 mg, 89%). *R_f* = 0.13 (20% MeOH/CH₂Cl₂); mp = 214–216 °C; IR (film)/cm⁻¹ 3271, 2954, 1610, 1510, 1458, 1442, 1299, 1249, 980, 953, 829; ¹H NMR (400 MHz, D₂O) δ 7.10–7.01 (m, 2 H, 2 × Ar-CH), 6.94–6.88 (m, 2 H, 2 × Ar-CH), 3.74 (s, 3 H, OCH₃), 2.55–2.47 (m, 2 H, CHHC_qCHH), 2.28–2.20 (m, 2 H, CHHC_qCHH), 1.92–1.73 (m, 2 H, CH₂CH₂CH₂); ¹³C NMR (101 MHz, D₂O) δ 157.5 (Ar-C_q-OMe), 133.9 (Ar-C_q-C_q), 128.9 (2 × Ar-CH), 113.5 (2 × Ar-CH), 67.7 (C_q), 55.3 (OCH₃), 27.0 (2 × C_qCH₂), 15.1 (CH₂CH₂CH₂); FTMS (+ p NSI) *m/z* calcd for C₁₁H₁₄SO₃Na⁺ [M+H]⁺: 249.0556, Found: 249.0558.

Methyl 3-((1-phenylcyclobutyl)thio)propanoate (**168**)

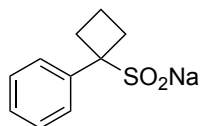


Lithium bis(trifluoromethanesulfonimide) (158 mg, 0.55 mmol) and tetrabutylammonium hexafluorophosphate (107 mg, 0.275 mmol) were added to a solution of cyclobutanol **91c** (741 mg, 5.0 mmol) and methyl 3-mercaptopropionate (1.11 mL, 10.0 mmol) in chloroform (10 mL). The reaction mixture was stirred at 40 °C for 25 min then sat. aq. NaHCO₃ (40 mL) was added followed by dichloromethane (40 mL). The layers were separated and the aqueous portion extracted with dichloromethane (2 × 40 mL). The organic extracts were combined then dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (15% Et₂O/pentane) afforded cyclobutane **168** (819 mg, 65%) as a white solid; *R_f* = 0.50 (15% Et₂O/pentane); mp = 42–43 °C; IR (film)/cm⁻¹ 2960, 2921, 1733 (s. C=O), 1438, 1358, 1244, 1190, 1167, 779, 743, 705; ¹H NMR (400 MHz, CDCl₃) δ 7.36–7.29 (m, 2 H, 2 × Ph-CH), 7.25–7.17 (m, 3 H, 3 × Ph-CH), 3.64 (s, 3 H, CO₂CH₃), 2.71–2.59 (m, 2 H, CHHC_qCHH), 2.50 (t, *J* = 7.6 Hz, 2 H, SCH₂), 2.45–2.35 (m, 3 H, CHHC_qCHH + CH₂CHHCH₂), 2.28 (t, *J* = 7.6 Hz, 2 H, CH₂CO₂Me), 2.31–2.23 (m, 1 H, CH₂CHHCH₂); ¹³C NMR (101 MHz, CDCl₃) δ 172.4 (C=O), 147.3 (Ph-C_q-C_q), 128.1 (2 × Ph-CH), 126.2 (Ph-CH), 125.8 (2 × Ph-CH), 53.1 (C_q), 51.7 (CO₂CH₃), 34.9 (2 × C_qCH₂), 34.0 (CH₂CO₂Me), 24.9 (SCH₂), 16.7 (CH₂CH₂CH₂); FTMS (+ p NSI) *m/z* calcd for C₁₄H₂₂NSO₂⁺ [M+NH₄]⁺: 268.1366, Found: 268.1368.

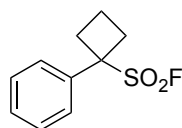
Methyl 3-((1-phenylcyclobutyl)sulfonyl)propanoate (169)

m-CPBA (518 mg, 3.0 mmol) was added to a solution of cyclobutane **168** (280 mg, 1.0 mmol) in dichloromethane (50 mL).

The reaction mixture was stirred at 25 °C for 3 h then aq. KOH (3 M, 40 mL) added and the phases separated. The aqueous portion was extracted with dichloromethane (4 × 30 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (50% EtOAc/hexane) afforded sulfone **169** (301 mg, 96%) as a white solid; *R*_f = 0.15 (10% Et₂O/pentane); mp = 67–71 °C; IR (film)/cm⁻¹ 2958, 1743 (C=O), 1300, 1270, 1242, 1193, 1176, 1137, 1094, 793, 702; ¹H NMR (400 MHz, CDCl₃) δ 7.47–7.34 (m, 5 H, 5 × Ar-CH), 3.66 (s, 3 H, CO₂CH₃), 3.19–3.13 (m, 2 H, CHHC_qCHH), 2.98–2.86 (m, 2 H, SCH₂), 2.77–2.62 (m, 2 H, CHHC_qCHH), 2.62–2.53 (m, 2 H, CH₂CO₂Me), 2.40–2.22 (m, 1 H, CH₂CHHCH₂), 2.07–1.92 (m, 1 H, CH₂CHHCH₂); ¹³C NMR (101 MHz, CDCl₃) δ 171.0 (C=O), 137.5 (Ph-C_q-C_q), 128.6 (2 × Ph-CH), 128.5 (Ph-CH), 128.3 (2 × Ph-CH), 68.3 (C_q), 52.2 (CO₂CH₃), 41.9 (SO₂CH₂), 29.4 (2 × C_qCH₂), 25.7 (CH₂CO₂Me), 15.9 (CH₂CH₂CH₂); HRMS (TOF-ASAP+) *m/z* calcd for C₁₄H₂₂NSO₄⁺ [M+NH₄]⁺: 300.1270, Found: 300.1267.

Sodium 1-phenylcyclobutane-1-sulfinate (170)

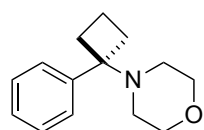
Sulfone **169** (705 mg, 2.5 mmol) was added to a solution of NaH (60% in mineral oil, 105 mg, 2.63 mmol) in THF (15 mL). The reaction mixture was stirred at 25 °C for 1 h then quenched with anhydrous methanol (15 mL) and concentrated *in vacuo* to afford sulfinate salt **170** (523 mg, 96%). *R*_f = 0.17 (20% MeOH/CH₂Cl₂); mp = 210–212 °C; IR (film)/cm⁻¹ 3294, 2946, 1682, 1598, 1445, 1206, 1034, 1019, 982, 772, 697; ¹H NMR (400 MHz, D₂O) δ 7.35–7.30 (m, 2 H, 2 × Ph-CH), 7.25–7.18 (m, 1 H, Ph-CH), 7.14–7.08 (m, 2 H, 2 × Ph-CH), 2.61–2.51 (m, 2 H, CHHC_qCHH), 2.38–2.25 (m, 2 H, CHHC_qCHH), 1.92–1.75 (m, 2 H, CH₂CH₂CH₂); ¹³C NMR (101 MHz, D₂O) δ 140.5 (Ph-C_q-C_q), 127.9 (2 × Ph-CH), 127.5 (2 × Ph-CH), 126.6 (Ph-CH), 68.3 (C_q), 27.1 (2 × C_qCH₂), 15.2 (CH₂CH₂CH₂); FTMS (+ p NSI) *m/z* calcd for C₁₀H₁₂SO₂Na⁺ [M+H]⁺: 219.0450, Found: 219.0451.

1-Phenylcyclobutane-1-sulfonyl fluoride (171)

MeOH (1.5 mL) at 0 °C was added to sodium sulfinate salt **170** (66 mg, 0.3 mmol) and selectfluor (159 mg, 0.45 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h then concentrated *in vacuo*. Purification by filtering through a short plug of silica, washing with dichloromethane (150 mL) and concentration *in*

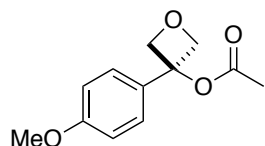
vacuo afforded sulfonyl fluoride **171** (54 mg, 82%). R_f = 0.78 (100% CH_2Cl_2); mp = 60–62 °C; IR (film)/ cm^{-1} 1386 (S=O), 1192 (S=O), 989, 947, 789, 772, 742, 695; ^1H NMR (400 MHz, CDCl_3) δ 7.49–7.38 (m, 5 H, 5 $\times$ Ph-CH), 3.29–3.20 (m, 2 H, CHHC_qCHH), 2.99–2.87 (m, 2 H, CHHC_qCHH), 2.55–2.39 (m, 1 H, $\text{CH}_2\text{CHHCH}_2$), 2.13–2.00 (m, 1 H, $\text{CH}_2\text{CHHCH}_2$); ^{13}C NMR (101 MHz, CDCl_3) δ 135.6 (Ar- C_q - C_q), 129.1 (Ar-CH), 128.5 (2 $\times$ Ar-CH), 128.3 (2 $\times$ Ar-CH), 68.3 (C_q , d, $J_{\text{C-F}}$ = 12.3 Hz), 31.2 (2 $\times$ C_qCH_2), 15.8 ($\text{CH}_2\text{CH}_2\text{CH}_2$); ^{19}F NMR (377 MHz, CDCl_3) δ 32.4; HRMS (EI $^+$) m/z calcd for $\text{C}_{10}\text{H}_{15}\text{NSO}_2\text{F}^+$ [$\text{M}+\text{NH}_4$] $^+$: 232.0834, Found: 232.0804.

4-(1-Phenylcyclobutyl)morpholine (172)



Triethylamine (36 μL , 0.26 mmol) was added to a solution of sulfonyl fluoride **171** (43 mg, 0.20 mmol) and morpholine (21 μL , 0.24 mmol) in acetonitrile (0.7 mL). The reaction mixture was stirred at 80 °C for 14 h then water (10 mL) was added followed by dichloromethane (10 mL). The layers separated and the aqueous portion was extracted with dichloromethane (2 $\times$ 10 mL). The organic extracts were combined, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (30% Et_2O /pentane) afforded sulfonamide **172** (5 mg, 12%) as a white solid. R_f = 0.21 (30% Et_2O /pentane); mp = 55–57 °C, IR (film)/ cm^{-1} 2934, 2819, 1264, 1151, 1109, 966, 913, 769, 709; ^1H NMR (400 MHz, CDCl_3) δ 7.41–7.35 (m, 2 H, 2 $\times$ Ph-CH), 7.31–7.23 (m, 3 H, 3 $\times$ Ph-CH), 3.69 (t, J = 4.6 Hz, 4 H, CH_2OCH_2), 2.48–2.31 (m, 4 H, $\text{CH}_2\text{C}_q\text{CH}_2$), 2.27 (s, 4 H, CH_2NCH_2), 1.97 (ddd, J = 11.0, 9.2, 4.7 Hz, 1 H, $\text{CH}_2\text{CHHCH}_2$), 1.75–1.63 (m, 1 H, $\text{CH}_2\text{CHHCH}_2$); ^{13}C NMR (101 MHz, CDCl_3) δ 139.5 (Ph- C_q - C_q), 127.6 (2 $\times$ Ph-CH), 127.3 (2 $\times$ Ph-CH), 126.6 (Ph-CH), 67.5 (CH_2OCH_2), 66.5 (C_q), 45.8 (CH_2NCH_2), 31.1 ($\text{CH}_2\text{C}_q\text{CH}_2$), 14.0 ($\text{CH}_2\text{CH}_2\text{CH}_2$); HRMS (ES $^+$) m/z calcd for $\text{C}_{14}\text{H}_{20}\text{NO}^+$ [$\text{M}+\text{H}$] $^+$: 218.1545, Found: 218.1540.

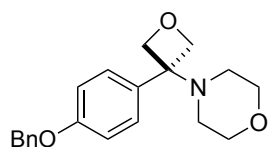
3-(4-Methoxyphenyl)oxetan-3-yl acetate (175)



Acetic anhydride (0.14 mL, 1.5 mmol) was added dropwise at 0 °C to a solution of oxetanol **44** (180 mg, 1.0 mmol) and 4-dimethylaminopyridine (183 mg, 1.5 mmol) in THF (5 mL). The reaction mixture was stirred at 25 °C for 15 h then water (15 mL) was added followed by ethyl acetate (15 mL). The layers were separated and the aqueous portion was extracted with ethyl acetate (2 $\times$ 15 mL). The organic extracts were combined, washed with brine (15 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (40% Et_2O /pentane) afforded oxetane **175** (217 mg, 97%) as a white solid. R_f = 0.28 (40% Et_2O /pentane); mp = 102–104 °C; IR (film)/ cm^{-1} 2975, 2899, 2840, 1733, 1519, 1291, 1247, 1186, 1163, 1117, 1029, 969, 911, 839, 816; ^1H NMR (400 MHz, CDCl_3) δ 7.42–7.36 (m, 2 H, 2 $\times$ Ar-CH), 6.97–6.90 (m, 2 H, 2 $\times$ Ar-CH), 5.05 (d, J = 7.5 Hz, 2 H,

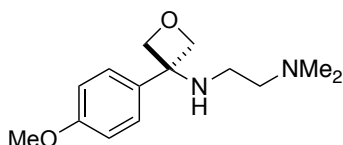
CHHOCHH), 4.95 (d, $J = 7.5$ Hz, 2 H, CHHOCHH), 3.82 (OCH₃), 2.16 (s, 3 H, C(O)CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 169.4 (C=O), 159.3 (Ar-C_q-OMe), 131.5 (Ar-C_q-C_q), 126.4 (2 $\times$ Ar-CH), 113.9 (2 $\times$ Ar-CH), 82.0 (CH₂OCH₂), 80.0 (C_q), 55.3 (OCH₃), 21.2 (C(O)CH₃); HRMS (Cl⁺) m/z calcd for C₁₁H₁₃O₃⁺ [M+H]⁺: 223.0965, Found: 223.0967.

4-(3-(4-(Benzyloxy)phenyl)oxetan-3-yl)morpholine (177)



Acetonitrile (12.5 mL) was added to a reaction vial containing sulfonyl fluoride **148** (1.21 g, 3.8 mmol), K₂CO₃ (674 mg, 4.9 mmol) and morpholine (0.39 mL, 4.5 mmol). The reaction mixture was stirred at 60 °C for 2 h then water (50 mL) was added followed by dichloromethane (50 mL). The layers were separated and the aqueous portion extracted with dichloromethane (2 $\times$ 50 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (80% EtOAc/hexane) afforded aminooxetane **177** (905 mg, 74%) as a white solid. $R_f = 0.41$ (80% EtOAc/hexane); mp = 154–156 °C, IR (film)/cm⁻¹ 2938, 2863, 1509, 1236, 1177, 1121, 1112, 1009, 986, 924, 914, 810, 704; ¹H NMR (400 MHz, CDCl₃) δ 7.48–7.32 (m, 5 H, 5 $\times$ Ph-CH), 7.02–6.95 (m, 4 H, 4 $\times$ Ar-CH), 5.09 (s, 2 H, PhCH₂), 4.90 (d, $J = 6.0$ Hz, 2 H, CHHOCHH), 4.87 (d, $J = 6.0$ Hz, 2 H, CHHOCHH), 3.74 (t, $J = 4.5$ Hz, 4 H, CH₂CH₂OCH₂CH₂), 2.32 (t, $J = 4.5$ Hz, 4 H, CH₂NCH₂); ¹³C NMR (101 MHz, CDCl₃) δ 158.0 (Ar-C_q-OBn), 136.8 (Ph-C_q-CH₂), 129.6 (Ar-C_q-C_q), 128.6 (2 $\times$ Ph-CH), 128.4 (2 $\times$ Ar-CH), 128.0 (Ph-CH), 127.4 (2 $\times$ Ar-CH), 114.2 (2 $\times$ Ar-CH), 79.3 (CH₂OCH₂), 70.1 (PhCH₂), 67.1 (CH₂CH₂OCH₂CH₂), 66.4 (C_q), 46.3 (CH₂NCH₂); HRMS (TOF- ASAP+) m/z calcd for C₂₀H₂₄NO₃⁺ [M+H]⁺: 326.1756, Found: 326.1750.

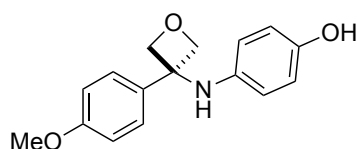
N-(3-(4-Methoxyphenyl)oxetan-3-yl)-N',N'-dimethylethane-1,2-diamine (151e)



K₂CO₃ (359 mg, 2.6 mmol) was added to a solution of sulfonyl fluoride **147** (493 mg, 2.0 mmol) and *N,N*-dimethylethylenediamine (0.26 mL, 2.4 mmol) in acetonitrile (7.0 mL). The reaction mixture was stirred at 60 °C for 2 h then water (20 mL) and dichloromethane (20 mL) were added. The layers were separated and the aqueous portion extracted with dichloromethane (2 $\times$ 20 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (90:8:2, CH₂Cl₂: MeOH: Et₃N) afforded aminooxetane **151e** (201 mg, 40%) as a yellow gum. $R_f = 0.41$ (90:8:2, CH₂Cl₂: MeOH: Et₃N); IR (film)/cm⁻¹ 3287 (br. NH), 2945, 2864, 2820, 2771, 1611, 1514, 1458, 1243, 1178, 1029, 980, 831; ¹H NMR (400 MHz, CDCl₃) δ 7.31–7.27 (m, 2 H, 2 $\times$ Ar-CH), 6.95–6.88 (m, 2 H, 2 $\times$ Ar-CH), 4.94 (d, $J = 6.3$ Hz, 2 H, CHHOCHH), 4.74

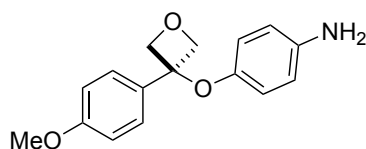
(d, $J = 6.3$ Hz, 2 H, CHHOCHH), 3.82 (s, 3 H, OCH₃), 2.43–2.33 (m, 5 H, NHCH₂CH₂), 2.17 (s, 6 H, N(CH₃)₂); ¹³C NMR (101 MHz, CDCl₃) δ 158.6 (Ar-C_q-OMe), 134.5 (Ar-C_q-C_q), 127.3 (2 $\times$ Ar-CH), 113.8 (2 $\times$ Ar-CH), 82.7 (CH₂OCH₂), 62.7 (C_q), 59.1 (N(CH₃)₂), 55.3 (OCH₃), 45.3 (NHCH₂), 40.7 (CH₂N(CH₃)₂); FTMS (+ p NSI) m/z calcd for C₁₄H₂₃N₂O₂⁺ [M+H]⁺: 251.1754, Found: 251.1754.

4-((3-(4-Methoxyphenyl)oxetan-3-yl)amino)phenol (**151f**)



K₂CO₃ (36 mg, 0.26 mmol) was added to a solution of sulfonyl fluoride **147** (49 mg, 0.20 mmol) and 4-aminophenol (26 mg, 0.24 mmol) in acetonitrile (0.6 mL). The reaction mixture was stirred at 60 °C for 2 h then water (10 mL) and dichloromethane (10 mL) were added. The layers were separated and the aqueous portion extracted with dichloromethane (2 $\times$ 10 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (60% Et₂O/pentane) afforded aminooxetane **151f** (47 mg, 87%) as a cream solid. $R_f = 0.22$ (60% Et₂O/pentane); mp = 154–156 °C, IR (film)/cm⁻¹ 3396 (NH), 3272 (br, OH), 2953, 2892, 1615, 1509, 1304, 1255, 1214, 1175, 1032, 944, 817; ¹H NMR (400 MHz, CDCl₃) δ 7.60–7.53 (m, 2 H, 2 $\times$ Ar_(p-OMe)-CH), 6.95–6.87 (m, 2 H, 2 $\times$ Ar_(p-OMe)-CH), 6.64–6.58 (m, 2 H, 2 $\times$ Ar_(p-OH)-CH), 6.23–6.18 (m, 2 H, 2 $\times$ Ar_(p-OH)-CH), 4.96 (d, $J = 6.3$ Hz, 2 H, CHHOCHH), 4.85 (d, $J = 6.3$ Hz, 2 H, CHHOCHH), 4.45 (br. s, 2 H, NH + OH), 3.82 (s, 3 H, OCH₃); ¹³C NMR (101 MHz, CDCl₃) δ 158.8 (Ar-C_q-OMe), 148.1 (Ar-C_q-OH), 138.6 (Ar-C_q-NH), 134.1 (Ar-C_q-C_q), 126.8 (2 $\times$ Ar_(p-OMe)-CH), 116.1 (2 $\times$ Ar_(p-OH)-CH), 115.7 (2 $\times$ Ar_(p-OH)-CH), 114.0 (2 $\times$ Ar_(p-OMe)-CH), 84.3 (CH₂OCH₂), 60.3 (C_q), 55.3 (OCH₃); HRMS (ES⁺) m/z calcd for C₁₆H₁₈NO₃⁺ [M+H]⁺: 272.1287, Found: 272.1284.

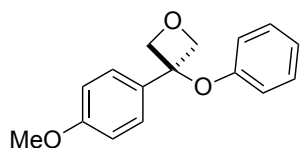
4-((3-(4-Methoxyphenyl)oxetan-3-yl)oxy)aniline (**178**)



Cesium carbonate (130 mg, 0.40 mmol) and 4-aminophenol (26 mg, 0.24 mmol) in acetonitrile (0.7 mL) were stirred at 25 °C for 30 min then sulfonyl fluoride **147** (49 mg, 0.20 mmol) was added in one portion. The reaction mixture was stirred at 60 °C for 1 h then water (10 mL) and dichloromethane (10 mL) were added. The layers were separated and the aqueous portion extracted with dichloromethane (2 $\times$ 10 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (70% EtOAc/hexane) afforded ether **178** (55 mg, 100%) as a cream solid. $R_f = 0.47$ (70% EtOAc/hexane); mp = 146–148 °C, IR (film)/cm⁻¹ 3485 (NH₂), 2973, 1516, 1506, 1339, 1263, 1199, 1146, 1022, 1000, 866, 830; ¹H NMR (400 MHz, CDCl₃) δ 7.31–7.25 (m,

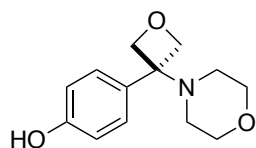
2 H, 2 × Ar_(p-OMe)-CH), 7.02–6.97 (m, 2 H, 2 × Ar_(p-OMe)-CH), 6.91–6.86 (m, 2 H, 2 × Ar_(p-NH₂)-CH), 6.63–6.57 (m, 2 H, 2 × Ar_(p-NH₂)-CH), 5.52 (d, *J* = 7.2 Hz, 2 H, CHHOCHH), 5.22 (d, *J* = 7.2 Hz, 2 H, CHHOCHH), 3.87 (s, 3 H, OCH₃), 3.70 (br. s, 2 H, NH₂); ¹³C NMR (101 MHz, CDCl₃) δ 160.2 (Ar-C_q-OMe), 145.4 (Ar-C_q-O), 140.8 (Ar-C_q-NH₂), 129.8 (2 × Ar_(p-OMe)-CH), 125.8 (Ar-C_q-C_q), 122.7 (2 × Ar_(p-NH₂)-CH), 115.5 (2 × Ar_(p-NH₂)-CH), 114.2 (2 × Ar_(p-OMe)-CH), 77.4 (CH₂OCH₂), 67.5 (C_q), 55.4 (OCH₃); HRMS (ES) *m/z* calcd for C₁₆H₁₈NO₃⁺ [M+H]⁺: 272.1287, Found: 272.1286.

3-(4-Methoxyphenyl)-3-phenoxyoxetane (179)



K₂CO₃ (27 mg, 0.20 mmol) was added to a solution of sulfonyl fluoride **147** (37 mg, 0.15 mmol) and phenol (17 mg, 0.18 mmol) in acetonitrile (0.5 mL). The reaction mixture was stirred at 60 °C for 2 h then water (10 mL) and dichloromethane (10 mL) were added. The layers were separated and the aqueous portion extracted with dichloromethane (2 × 10 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (40% Et₂O/pentane) afforded oxetane ether **179** (23 mg, 61%) as a white solid. *R*_f = 0.29 (40% Et₂O/pentane); mp = 84–86 °C, IR (film)/cm⁻¹ 2958, 2899, 1488, 1362, 1250, 1200, 1178, 1142, 1021, 989, 862, 834, 760, 746, 733; ¹H NMR (400 MHz, CDCl₃) δ 7.39–7.31 (m, 2 H, 2 × Ar-CH), 7.30–7.24 (m, 3 H, 3 × Ar-CH), 7.12–7.07 (m, 2 H, 2 × Ar-CH), 7.02–6.95 (m, 2 H, 2 × Ar-CH), 5.53 (d, *J* = 7.2 Hz, 2 H, CHHOCHH), 5.24 (d, *J* = 7.2 Hz, 2 H, CHHOCHH), 3.86 (s, 3 H, OCH₃); ¹³C NMR (101 MHz, CDCl₃) δ 160.3 (Ar-C_q-OMe), 149.1 (Ar-C_q-OC_q), 129.8 (4 × Ar-CH), 127.0 (Ar-CH), 125.5 (Ar-C_q-C_q), 121.8 (2 × Ar-CH), 114.2 (2 × Ar-CH), 77.4 (CH₂OCH₂), 67.9 (C_q), 55.4 (OCH₃); HRMS (CI⁺) *m/z* calcd for C₁₆H₂₀NO₃⁺ [M+NH₄]⁺: 274.1438, Found: 274.1437.

4-(3-Morpholinooxetan-3-yl)phenol (180)

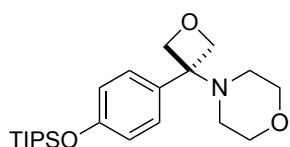


K₂CO₃ (438 mg, 3.2 mmol) was added to a solution of sulfonyl fluoride **149** (950 mg, 2.4 mmol) and morpholine (0.26 mL, 2.9 mmol) in acetonitrile (8.0 mL). The reaction mixture was stirred at 60 °C for 2 h then water (40 mL) and dichloromethane (40 mL) were added. The layers were separated and the aqueous portion extracted with dichloromethane (2 × 50 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (80–100% EtOAc/hexane) afforded aminooxetane **180** (574 mg, 94%) as a white solid. *R*_f = 0.21 (80% EtOAc/hexane); mp = 172–174 °C, IR (film)/cm⁻¹ 3282 (br. OH), 2938, 2866, 1612, 1518, 1263, 1224, 1115, 1104, 1062, 982, 928, 912, 841; ¹H NMR (400 MHz, (CD₃)CO) δ 8.40 (s, 1 H, OH), 7.03–6.98 (m,

2 H, 2 × Ar-CH), 6.89–6.83 (m, 2 H, 2 × Ar-CH), 4.83–4.71 (m, 4 H, CH₂OCH₂), 3.61 (t, *J* = 4.6 Hz, 4 H, CH₂CH₂OCH₂CH₂), 2.24 (s, 4 H, CH₂NCH₂); ¹³C NMR (101 MHz, (CD₃)CO) δ 157.3 (Ar-C_q-OH), 129.6 (2 × Ar-CH), 129.1 (Ar-C_q-C_q), 115.2 (2 × Ar-CH), 81.1 (CH₂OCH₂), 67.6 (CH₂CH₂OCH₂CH₂), 66.8 (C_q), 47.2 (CH₂NCH₂); FTMS (+ p NSI) *m/z* calcd for C₁₃H₁₈NO₃⁺ [M+H]⁺: 236.1281, Found: 236.1283.

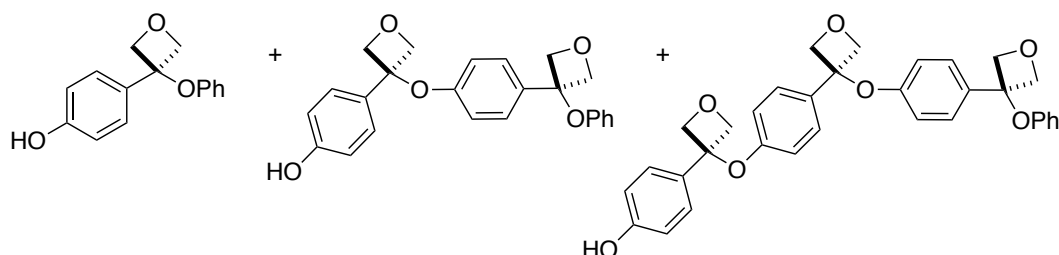
Alternatively, aminooxetane **180** can be synthesised through the benzyl deprotection of aminooxetane **177**: Palladium on carbon (10% w/w, 72 mg) was added to a solution of aminooxetane **177** (716 mg, 2.2 mmol) in ethanol (17.5 mL). The reaction mixture was stirred under an atmosphere of hydrogen at 25 °C for 1 h. The reaction mixture was filtered through celite, washed through with ethanol and then concentrated *in vacuo* to afford aminooxetane **180** (465 mg, 90%) as a white solid.

4-(3-(4-((Triisopropylsilyl)oxy)phenyl)oxetan-3-yl)morpholine (**181**)



Acetonitrile (0.7 mL) was added to a reaction vial containing sulfonyl fluoride **149** (78 mg, 0.20 mmol) and TMS-morpholine (71 μL, 0.40 mmol). The reaction mixture was stirred at 60 °C for 2 h then water (10 mL) and dichloromethane (15 mL) were added. The layers were separated and the aqueous portion extracted with dichloromethane (2 × 15 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (80% EtOAc/hexane) afforded aminooxetane **181** (58 mg, 73%) as a white solid. *R_f* = 0.39 (80% EtOAc/hexane); mp = 87–89 °C, IR (film)/cm⁻¹ 2938, 2863, 1509, 1236, 1177, 1121, 1112, 1009, 986, 924, 914, 810, 704; ¹H NMR (400 MHz, CDCl₃) δ 6.90–6.86 (m, 4 H, 4 × Ar-CH), 4.90 (d, *J* = 6.0 Hz, 2 H, CHHOCHH), 4.86 (d, *J* = 6.0 Hz, 2 H, CHHOCHH), 3.74 (t, *J* = 4.5 Hz, 4 H, CH₂CH₂OCH₂CH₂), 2.29 (t, *J* = 4.5 Hz, 4 H, CH₂NCH₂), 1.32–1.21 (m, 3 H, 3 × CH(CH₃)₂), 1.11 (d, *J* = 7.3 Hz, 18 H, 3 × CH(CH₃)₂); ¹³C NMR (101 MHz, CDCl₃) δ 155.3 (Ar-C_q-OTIPS), 129.4 (Ar-C_q-C_q), 128.3 (2 × Ar-CH), 119.2 (2 × Ar-CH), 79.4 (CH₂OCH₂), 67.1 (CH₂CH₂OCH₂CH₂), 66.3 (C_q), 46.4 (CH₂NCH₂), 17.9 (3 × CH(CH₃)₂), 12.6 (3 × CH(CH₃)₂); HRMS (Cl⁺) *m/z* calcd for C₂₂H₃₈NO₃Si⁺ [M+H]⁺: 392.2615, Found: 392.2614.

4-(3-Phenoxyoxetan-3-yl)phenol (182), 4-(3-(4-(3-phenoxyoxetan-3-yl)phenoxy)oxetan-3-yl)phenol (183) and 4-(3-(4-(3-(4-(3-phenoxyoxetan-3-yl)phenoxy)oxetan-3-yl)phenoxy)oxetan-3-yl)phenol (184)



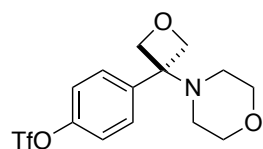
K_2CO_3 (36 mg, 0.26 mmol) was added to a solution of sulfonyl fluoride **149** (78 mg, 0.20 mmol) and phenol (23 mg, 0.24 mmol) in acetonitrile (0.7 mL). The reaction mixture was stirred at 60 °C for 2 h then water (15 mL) and dichloromethane (15 mL) were added. The layers were separated and the aqueous portion extracted with dichloromethane (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (40% EtOAc/hexane) afforded oxetane ether **182** (19 mg, 39%) followed by dimer product **183** (7.1 mg, 18%) followed by trimer product **184** (3.3 mg, 9%) all as colourless oils.

Oxetane ether **182**: R_f = 0.38 (40% EtOAc/hexane); IR (film)/ cm^{-1} 3323 (br. OH), 2876, 1588, 1516, 1488, 1231, 1174, 971, 827, 748, 685; ^1H NMR (400 MHz, CDCl_3) δ 7.47–7.43 (m, 2 H, 2 × Ar-CH), 7.20–7.14 (m, 2 H, 2 × Ar-CH), 6.94–6.88 (m, 1 H, Ar-CH), 6.87–6.82 (m, 2 H, 2 × Ar-CH), 6.55–6.50 (m, 2 H, 2 × Ar-CH), 5.10 (d, J = 7.4 Hz, 2 H, CHHOCHH), 4.93 (s, 1 H, OH), 5.91 (d, J = 7.4 Hz, 2 H, CHHOCHH); ^{13}C NMR (101 MHz, CDCl_3) δ 155.2 (Ar- C_q -O), 154.8 (Ar- C_q -O), 132.3 (Ar- C_q - C_q), 129.4 (2 × Ar-CH), 126.3 (2 × Ar-CH), 121.1 (Ar-CH), 116.3 (2 × Ar-CH), 115.6 (2 × Ar-CH), 83.0 (CH_2OCH_2), 80.1 (C_q); FTMS (– p NSI) m/z calcd for $\text{C}_{15}\text{H}_{13}\text{O}_3^-$ [$\text{M}-\text{H}$] $^-$: 241.0870, Found: 241.0872.

Dimer **183**: R_f = 0.23 (40% EtOAc/hexane); IR (film)/ cm^{-1} 3309 (br. OH), 2953, 2881, 1612, 1594, 1508, 1489, 1276, 1232, 1173, 992, 982, 904, 828, 734; ^1H NMR (400 MHz, CDCl_3) δ 7.44–7.41 (m, 2 H, 2 × Ar-CH), 7.39–7.35 (m, 2 H, 2 × Ar-CH), 7.19–7.13 (m, 2 H, 2 × Ar-CH), 6.93–6.82 (m, 3 H, 3 × Ar-CH), 6.54–6.46 (m, 4 H, 4 × Ar-CH), 5.08–5.04 (m, 4 H, 2 × CHHOCHH), 5.01 (s, 1 H, OH), 4.91–4.83 (m, 4 H, 2 × CHHOCHH); ^{13}C NMR (101 MHz, CDCl_3) δ 155.3 (Ar- C_q -O), 154.7 (Ar- C_q -O), 154.4 (Ar- C_q -O), 132.0 (Ar- C_q - C_q), 129.4 (2 × Ar-CH), 126.3 (2 × Ar-CH), 126.0 (2 × Ar-CH), 125.0 (Ar- C_q - C_q), 121.0 (Ar-CH), 116.4 (2 × Ar-CH), 116.1 (2 × Ar-CH), 115.7 (2 × Ar-CH), 82.9 (CH_2OCH_2), 82.8 (CH_2OCH_2), 80.3 (2 × C_q); FTMS (– p NSI) m/z calcd for $\text{C}_{24}\text{H}_{21}\text{O}_5^-$ [$\text{M}-\text{H}$] $^-$: 389.1394, Found: 389.1396.

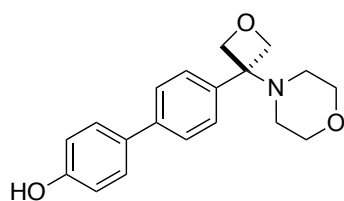
Trimer **184**: R_f = 0.08 (40% EtOAc/hexane); IR (film)/ cm^{-1} 3352 (br. OH), 2954, 2882, 1611, 1509, 1236, 904, 832, 726; ^1H NMR (400 MHz, CDCl_3) δ 7.42–7.38 (m, 2 H, 2 $\times$ Ar-CH), 7.36–7.31 (m, 4 H, 4 $\times$ Ar-CH), 7.19–7.13 (m, 2 H, 2 $\times$ Ar-CH), 6.95–6.91 (m, 1 H, Ar-CH), 6.84–6.79 (m, 2 H, 2 $\times$ Ar-CH), 6.54–6.43 (m, 6 H, 6 $\times$ Ar-CH), 5.14 (s, 1 H, OH), 5.10–5.06 (m, 4 H, 2 $\times$ CHHOCHH), 5.03 (d, J = 7.0 Hz, 2 H, CHHOCHH), 4.93–4.88 (m, 2 H, CHHOCHH), 4.88–4.82 (m, 4 H, 2 $\times$ CHHOCHH); ^{13}C NMR (101 MHz, CDCl_3) δ 156.5 (2 $\times$ Ar- C_q -O), 155.3 (Ar- C_q -O), 154.4 (Ar- C_q -O), 132.2 (2 $\times$ Ar- C_q - C_q), 129.4 (2 $\times$ Ar-CH), 126.4 (2 $\times$ Ar-CH), 126.0 (2 $\times$ Ar-CH), 125.9 (2 $\times$ Ar-CH), 125.0 (Ar- C_q - C_q), 121.1 (Ar-CH), 116.7 (2 $\times$ Ar-CH), 116.6 (2 $\times$ Ar-CH), 116.2 (2 $\times$ Ar-CH), 115.7 (2 $\times$ Ar-CH), 82.9 (CH_2OCH_2), 82.8 (CH_2OCH_2), 82.6 (CH_2OCH_2), 80.5 (C_q), 80.3 (C_q), 79.9 (C_q); FTMS (– p NSI) m/z calcd for $\text{C}_{33}\text{H}_{29}\text{O}_7^-$ [$\text{M}-\text{H}$] $^-$: 537.1919, Found: 537.1922.

4-(3-Morpholinooxetan-3-yl)phenyl trifluoromethanesulfonate (**186**)



Pyridine (0.21 mL, 2.6 mmol) then triflic anhydride (0.24 mL, 1.4 mmol) were added to a solution of aminooxetane **180** (306 mg, 1.3 mmol) in dichloromethane (2.6 mL). The reaction mixture was stirred at 25 °C for 3 h then sat. aq. NaHCO_3 (20 mL) was added followed by dichloromethane (15 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (2 $\times$ 15 mL). The organic extracts were combined, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (80% EtOAc/hexane) afforded oxetane **186** (417 mg, 87%) as a yellow gum. R_f = 0.39 (80% EtOAc/hexane); IR (film)/ cm^{-1} 2951, 2858, 1501, 1421, 1205, 1136, 1115, 883, 845; ^1H NMR (400 MHz, CDCl_3) δ 7.35–7.28 (m, 2 H, 2 $\times$ Ar-CH), 7.22–7.15 (m, 2 H, 2 $\times$ Ar-CH), 4.91 (d, J = 6.2 Hz, 2 H, CHHOCHH), 4.85 (d, J = 6.2 Hz, 2 H, CHHOCHH), 3.73 (t, J = 4.5 Hz, 4 H, $\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2$), 2.31 (t, J = 4.5 Hz, 4 H, CH_2NCH_2); ^{13}C NMR (101 MHz, CDCl_3) δ 148.6 (Ar- C_q -OTf), 138.2 (Ar- C_q - C_q), 128.9 (2 $\times$ Ar-CH), 121.0 (2 $\times$ Ar-CH), 118.7 (q, $J_{\text{C-F}}$ = 320.9 Hz, CF_3), 78.5 (CH_2OCH_2), 66.8 ($\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2$), 66.5 (C_q), 46.4 (CH_2NCH_2); ^{19}F NMR (377 MHz, CDCl_3) δ –72.8; FTMS (+ p NSI) m/z calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_5\text{SF}_3^+$ [$\text{M}+\text{H}$] $^+$: 368.0774, Found: 368.0775.

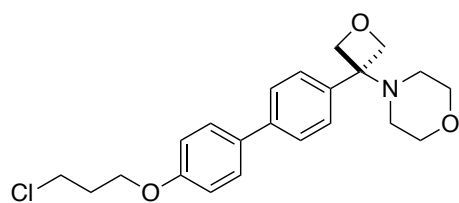
4'-(3-Morpholinooxetan-3-yl)-[1,1'-biphenyl]-4-ol (**187**)



Triflate **186** (184 mg, 0.5 mmol), 4-hydroxyphenylboronic acid pinacol ester (147 mg, 0.7 mmol), $\text{Pd}(\text{OAc})_2$ (5.6 mg, 0.025 mmol), SPhos (20.5 mg, 0.05 mmol) and K_3PO_4 (213 mg, 1.0 mmol) were added to a reaction vial. The reaction vial was evacuated and then refilled with nitrogen ($\times$ 3). Dioxane/water (4:1, 5.0 mL) was added *via* syringe. The reaction mixture was stirred at 65 °C for 18 h then

cooled to rt. Diethylether (15 mL) was added and the crude mixture was filtered through celite and then concentrated *in vacuo*. Purification by flash column chromatography (80% EtOAc/hexane) afforded biaryl **187** (122 mg, 79%) as a white solid. $R_f = 0.19$ (80% EtOAc/hexane); mp = 194–196 °C; IR (film)/cm⁻¹ 3287 (br. OH), 2823, 1497, 1268, 1172, 1107, 968, 929, 806, 723, 716; ¹H NMR (400 MHz, CDCl₃) δ 7.58–7.53 (m, 2 H, 2 × Ar-CH), 7.49–7.44 (m, 2 H, 2 × Ar-CH), 7.13–7.07 (m, 2 H, 2 × Ar-CH), 6.93–6.88 (m, 2 H, 2 × Ar-CH), 5.09 (s, 1 H, OH), 4.97 (d, $J = 6.1$ Hz, 2 H, CHHOCHH), 4.93 (d, $J = 6.1$ Hz, 2 H, CHHOCHH), 3.77 (t, $J = 4.5$ Hz, 4 H, CH₂CH₂OCH₂CH₂), 2.38 (t, $J = 4.5$ Hz, 4 H, CH₂NCH₂); ¹³C NMR (101 MHz, CDCl₃) δ 155.4 (Ar-C_q-OH), 140.0 (Ar_(phenol)-C_q-C_q), 135.3 (Ar-C_q-C_{q(phenol)}), 133.1 (Ar-C_q-C_{q(oxetane)}), 128.3 (2 × Ar-CH), 127.6 (2 × Ar-CH), 126.2 (2 × Ar-CH), 115.7 (2 × Ar-CH), 79.2 (CH₂OCH₂), 67.1 (CH₂CH₂OCH₂CH₂), 66.7 (C_q), 46.4 (CH₂NCH₂); FTMS (+ p NSI) m/z calcd for C₁₉H₂₂NO₄S⁺ [M+H]⁺: 360.1264, Found: 360.1262.

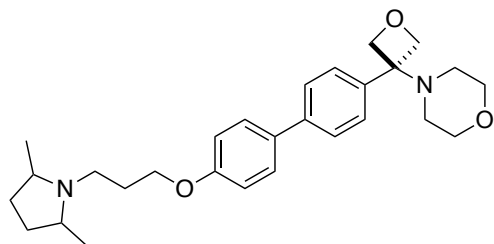
4-(3-(4'-(3-Chloropropoxy)-[1,1'-biphenyl]-4-yl)oxetan-3-yl)morpholine (**188**)



1-Bromo-3-chloropropane (20 μ L, 0.2 mmol) was added to a solution of biaryl **187** (31 mg, 0.1 mmol) and K₂CO₃ (42 mg, 0.3 mmol) in 2-butanone (0.7 mL). The reaction mixture was stirred at 80 °C for 24 h then cooled to rt.

Water (10 mL) and dichloromethane (10 mL) were added and the layers separated. The aqueous portion was extracted with dichloromethane (4 × 10 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography (60% EtOAc/hexane) afforded aminooxetane **188** (33 mg, 86%) as a white solid. $R_f = 0.22$ (60% EtOAc/hexane); mp = 108–111 °C; IR (film)/cm⁻¹ 2946, 2867, 1740, 1513, 1270, 1139, 911, 883; ¹H NMR (400 MHz, CDCl₃) δ 7.60–7.50 (m, 4 H, 4 × Ar-CH), 7.13–7.07 (m, 2 H, 2 × Ar-CH), 7.04–6.97 (m, 2 H, 2 × Ar-CH), 4.97 (d, $J = 6.1$ Hz, 2 H, CHHOCHH), 4.92 (d, $J = 6.1$ Hz, 2 H, CHHOCHH), 4.18 (t, $J = 6.1$ Hz, 2 H, ArOCH₂), 3.83–3.72 (m, 6 H, CH₂CH₂OCH₂CH₂ + CH₂Cl), 2.37 (t, $J = 4.5$ Hz, 4 H, CH₂NCH₂), 2.28 (p, $J = 6.1$ Hz, 2 H, CH₂CH₂CH₂); ¹³C NMR (101 MHz, CDCl₃) δ 158.4 (Ar-C_q-O), 139.9 (Ar-C_q-C_q), 135.4 (Ar-C_q-C_{q(oxetane)}), 133.2 (Ar-C_q-C_q), 128.1 (2 × Ar-CH), 127.6 (2 × Ar-CH), 126.2 (2 × Ar-CH), 114.8 (2 × Ar-CH), 79.2 (CH₂OCH₂), 67.1 (CH₂CH₂OCH₂CH₂), 66.6 (C_q), 64.3 (ArOCH₂), 46.4 (CH₂NCH₂), 41.5 (CH₂Cl), 32.2 (CH₂CH₂CH₂); HRMS (Cl⁺) m/z calcd for C₂₂H₂₇NO₃Cl⁺ [M+H]⁺: 388.1674, Found: 388.1674.

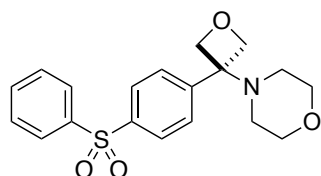
4-(3-(4'-(3-(2,5-Dimethylpyrrolidin-1-yl)propoxy)-[1,1'-biphenyl]-4-yl)oxetan-3-yl)morpholine (189)



2,5-Dimethylpyrrolidine (20.3 mg, 0.15 mmol) was added to a solution of aminooxetane **188** (29.1 mg, 0.075 mmol), K_2CO_3 (31.1 mg, 0.225 mmol), potassium iodide (24.9 mg, 0.15 mmol) in 2-butanone (0.4 mL). The reaction mixture was stirred at 80 °C

for 72 h then cooled to rt then water (10 mL) and dichloromethane (10 mL) were added. The layers were separated and the aqueous portion was extracted with dichloromethane (3 × 10 mL). The organic extracts were combined, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (2% $Et_3N/EtOAc$) afforded aminooxetane **189** (14.8 mg, 44%) as a white solid. R_f = 0.21 (2% $Et_3N/EtOAc$); mp = 89–91 °C; IR (film)/ cm^{-1} 2956, 2870, 1739, 1608, 1498, 1247, 1186, 1115, 825; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60–7.50 (m, 4 H, 4 × Ar-CH), 7.11–7.07 (m, 2 H, 2 × Ar-CH), 7.02–6.97 (m, 2 H, 2 × Ar-CH), 4.96 (d, J = 6.0 Hz, 2 H, CHHOCHH), 4.91 (d, J = 6.0 Hz, 2 H, CHHOCHH), 4.06 (t, J = 6.1 Hz, 2 H, $ArOCH_2$), 3.76 (t, J = 4.5 Hz, 4 H $CH_2CH_2OCH_2CH_2$), 2.79 (t, J = 7.4 Hz, 2 H, $CH_2CH_2CH_2N$), 2.64 (q, J = 6.0 Hz, 2 H, 2 × CHCH₃), 2.37 (t, J = 4.5 Hz, 4 H, CH_2NCH_2), 2.01–1.94 (m, 2 H, $CH_2CH_2CH_2$), 1.86–1.79 (m, 2 H, CHCHHCHHCH), 1.43–1.35 (m, 2 H, CHCHHCHHCH), 1.14 (d, J = 6.0 Hz, 6 H, 2 × CH₃); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8 ($Ar-C_q-O$), 140.0 ($Ar-C_q-C_q$), 135.4 ($Ar-C_q-C_q(oxetane)$), 132.2 ($Ar-C_q-C_q$), 128.0 (2 × Ar-CH), 127.6 (2 × Ar-CH), 126.2 (2 × Ar-CH), 114.8 (2 × Ar-CH), 79.2 (CH_2OCH_2), 67.1 ($CH_2CH_2OCH_2CH_2$), 66.7 (C_q), 66.5 ($ArOCH_2$), 60.4 (2 × CHCH₃), 48.1 ($CH_2CH_2CH_2N$), 46.4 (CH_2NCH_2), 31.4 (CHCH₂CH₂CH), 27.4 ($CH_2CH_2CH_2$), 20.9 (2 × CH₃); FTMS (+ p NSI) m/z calcd for $C_{28}H_{39}N_2O_3^+$ $[M+H]^+$: 451.2955, Found: 451.2

4-(3-(4-(Phenylsulfonyl)phenyl)oxetan-3-yl)morpholine (192)



Phenyllithium (1.82 M, 0.11 mL, 0.2 mmol) was added dropwise to a solution of DABSO (24 mg, 0.1 mmol) in degassed dioxane (0.77 mL). The reaction was stirred at 25 °C for 2 h. Triflate **186** (49 mg, 0.13 mmol), $Pd(OAc)_2$ (3.0 mg, 0.013 mmol), Cs_2CO_3

(65 mg, 0.2 mmol) and Xantphos (7.7 mg, 0.013 mmol) were added to a separate microwave vial. The reaction vial was evacuated and then refilled with nitrogen (× 3). The dioxane suspension was then added *via* syringe. The reaction was stirred at 110 °C for 16 h then cooled to rt. Dichloromethane (10 mL) was added and the reaction was filtered through celite and then concentrated *in vacuo*. Purification by flash column chromatography (50% $EtOAc/CH_2Cl_2$) afforded aminooxetane **192** (21 mg, 58%) as a colourless oil. R_f = 0.24 (50%

EtOAc/CH₂Cl₂); IR (film)/cm⁻¹ 2957, 2856, 1447, 1319 (S=O), 1309, 1290, 1266, 1157 (S=O), 1110, 990, 932, 912, 729; ¹H NMR (400 MHz, CDCl₃) δ 8.01–7.94 (m, 4 H, 4 × Ph-CH), 7.64–7.58 (m, 1 H, Ph-CH), 7.58–7.51 (m, 2 H, 2 × Ar-CH), 7.25–7.18 (m, 2 H, 2 × Ar-CH), 4.90 (d, *J* = 6.4 Hz, 2 H, CHHOCHH), 4.83 (d, *J* = 6.4 Hz, 2 H, CHHOCHH), 3.72 (t, *J* = 4.5 Hz, 4 H, CH₂CH₂OCH₂CH₂), 2.29 (t, *J* = 4.5 Hz, 4 H, CH₂NCH₂); ¹³C NMR (101 MHz, CDCl₃) δ 143.1 (Ar-C_q-SO₂), 141.3 (Ar-C_q-SO₂), 140.8 (Ar-C_q-C_q), 133.4 (Ph-CH), 129.4 (2 × Ar-CH), 128.0 (2 × Ar-CH), 127.7 (2 × Ph-CH), 127.4 (2 × Ph-CH), 78.4 (CH₂OCH₂), 67.0 (CH₂CH₂OCH₂CH₂), 66.7 (C_q), 46.3 (CH₂NCH₂); HRMS (Cl⁺) *m/z* calcd for C₁₉H₂₂NO₃⁺ [M+H]⁺: 312.1594, Found: 312.1597.

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Table 7.2 DOE optimisation experiments for study with Li(NTf₂)/Bu₄NPF₆. ^aYields calculated by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard.

Entry	Temp / °C	Catalyst loading / mol%	Additive loading / mol%	Conc / M	Equiv of nucl	Yield 57a (%) ^a	Yield 58a (%) ^a	Recovery of 45 (%) ^a
1	40	5	2.5	0.05	5	20	7	66
2	60	5	2.5	0.05	2	41	21	62
3	40	15	2.5	0.05	2	45	23	68
4	60	15	2.5	0.05	5	49	32	81
5	40	5	7.5	0.05	2	0	0	100
6	60	5	7.5	0.05	5	0	0	82
7	40	15	7.5	0.05	5	53	29	82
8	60	15	7.5	0.05	2	35	19	54
9	40	5	2.5	1	2	0	0	90
10	60	5	2.5	1	5	56	23	79
11	40	15	2.5	1	5	0	0	99
12	60	15	2.5	1	2	0	0	0
13	40	5	7.5	1	5	0	6	33
14	60	5	7.5	1	2	0	8	20
15	40	15	7.5	1	2	35	15	50
16	60	15	7.5	1	5	3	12	15
17	40	10	5	0.525	3.5	57	18	75
18	60	10	5	0.525	3.5	0	0	0
19	50	5	5	0.525	3.5	6	2	17
20	50	15	5	0.525	3.5	37	23	60
21	50	10	2.5	0.525	3.5	53	23	76
22	50	10	7.5	0.525	3.5	53	22	75
23	50	10	5	0.05	3.5	44	28	72
24	50	10	5	1	3.5	41	22	63
25	50	10	5	0.525	2	39	21	60
26	50	10	5	0.525	5	51	23	74
27	50	10	5	0.525	3.5	45	18	63
28	50	10	5	0.525	3.5	42	24	66
29	50	10	5	0.525	3.5	41	21	62